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Preface

It is approximately ten years since the modern era of fluorous chemistry began. A historical perspective on the development of this field is provided in Chapter 2. During this period, over 500 publications on fluorous chemistry have appeared. Although there has been a steady stream of review articles and other compendia, in our view it was time for a Monograph or Handbook. This idea found resonance among many others in the fluorous community, who either contributed chapters or offered valuable counsel.

Our goal was to create a Handbook that would supply both the necessary entry-level information for beginners and advanced reference material for experienced practitioners. With respect to the former objective, Chapters 1 through 8 constitute a cohesive pedagogical introduction to the fundamentals of fluorous chemistry. In Chapter 10, a number of reviews that highlight specific synthetic applications are provided. The companion Chapters 12 and 13 similarly treat selected materials and biomedical applications of fluorous chemistry. While it was not possible to comprehensively cover all of the diverse synthetic and materials applications that have appeared, references to most of the fluorous synthesis literature up to mid-2003 can be found in this Handbook.

Chapter 9 provides lead references to the “fluorous pool”, or simple monofunctional compounds that are the starting points for most synthetic sequences. About 50 experimental procedures, in many cases representing optimized versions of those in the literature, have been collected in Chapter 11. Chapter 14 details several experimental “divertissements” that showcase some of the unusual properties of fluorous molecules. These are particularly suitable for lecture demonstrations, helping to attract new students to the field, or piquing the interest of the lay person.

We wish to express our sincere thanks to the many authors who have written chapters or subchapters for their hard work, engagement, and patience. We would also like to acknowledge here the granting agencies that supported the preparation of our sections (JAG, DFG; GL 300-3/1; DPC, NIH).

Fluorous chemistry continues to be a dynamic and evolving discipline. Indeed, the many intrinsic challenges associated with synthesis and catalysis – yield, selectivity, reactivity, overall cost, recoverability, etc. – are never-ending. One long-term mandate of fluorous chemists is to build a new world or “parallel universe” encompassing fluorous versions of all basic organic molecules, building blocks, reagents, homogeneous catalysts, macromolecules, supramolecular assemblies, etc. The following chapters illustrate that substantial progress has been made. However in constructing this parallel universe, the many fluorous...
pioneers have in fact created an expanded universe, with a diverse palette of unusual phenomena and exploitable properties that have no counterparts in old-world chemistry.

Future generations of researchers will put their mark on this discipline. If this Handbook can help to catalyze these efforts, we and the other authors will feel that this undertaking has been successful. Regardless, the call to all readers is to “take a dive into the fluorous pool”: given the high oxygen solubility, no special breathing apparatus is required, and the high density makes it difficult to sink. As is evident in the following chapters, there are a lot of good things swimming around.

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Fluorous Chemistry: Scope and Definition

István T. Horváth, Dennis P. Curran, and J. A. Gladysz

1.1 The Birth of a Term

The title of this Handbook features a word, fluorous, which was not in the chemists vocabulary ten years ago. It was introduced in a classic 1994 paper by Horváth and Rábai, who envisioned a term that could be used analogously to “aqueous” or “aqueous media” [1]. Although there were earlier studies of reactions in “fluorous media” (defined below) [2], the general concept remained unarticulated, almost like parallel worlds unaware of each other.

Why not simply refer to fluorous solvents as non-aqueous? Importantly, fluorous solvents do not mix with most common organic solvents at room temperature. Bilayers or liquid/liquid biphase systems form, with the more dense fluorous solvent on the bottom. Given this orthogonality, a special term is clearly justified. The word “oleophobic” can be found in the older patent literature [3], and fluorous media can be defined as simultaneously oleophobic and hydrophobic. However, this expression is cumbersome and lacks pizzazz or showroom appeal. Would you be attracted to a symposium with the title “Recent Advances in the Chemistry of Oleophobic and Hydrophobic Molecules”?

Importantly, fluorous and organic solvents usually mix at elevated temperatures. This allows the facile switching of reactions between heterogeneous and homogeneous conditions. Temperature-dependent miscibility represents one of many types of thermomorphic behavior. The adjective thermomorphic is applied in such broad contexts that a precise definition becomes problematic, but a physical property that is temperature dependent is always involved.

The 1994 paper also introduced the concept of a “ponytail”. These are most commonly fluoroalkyl moieties of the formula \((\text{CH}_2)_m(\text{CF}_2)_n\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\•
This broad concept was expanded almost immediately to the separation of products and (spent) reagents, and to the use of ponytails of varying fluorine content to label or tag libraries of compounds. New separation techniques of fluorous solid-phase extraction and fluorous chromatography sprouted to disentangle tagged molecules from non-tagged molecules and from each other. The field now extends from fluorous nanoparticles on the materials side to fluorous peptides and enzymatic reactions on the biological side. It has evolved so far beyond its original incarnation that a review and reassessment of its working vocabulary is needed, as is provided in the following two sections.

1.2 The Definition of Fluorous Today

As noted above, it was initially envisioned that fluorous would be used analogously to aqueous or aqueous media. However usage dictates definitions, and early researchers soon expanded the term to include fluoroalkyl-labeled species, and this sense dominates in current practice. Accordingly, we propose the following definition of the adjective fluorous [4]: “of, relating to, or having the characteristics of highly fluorinated saturated organic materials, molecules or molecular fragments.” Or, more simply (but less precisely), “highly fluorinated” or “rich in fluorines” and based on sp³-hybridized carbon.

This liberal definition subsumes the original definition as well as newer uses involving such diverse subjects as organic synthesis with fluorous tags, fluorous chromatography, fluorous materials, various types of analytical measurements, and societal and sociological extensions such as “fluorous chemists” and “the fluorous community”. Astute readers will recognize that it also renames existing fields – for example, fluorocarbon surfactants are now fluorous surfactants. In the same vein, fluorocarbon blood substitutes are now fluorous blood substitutes, and Teflon becomes a fluorous polymer. The term fluorous is already creeping into the vocabulary of researchers in many of these established areas. Whether or not it is broadly accepted in these allied circles, the liberal definition does recognize that both the established and new fields build in different ways on the same unique properties of polyfluorinated molecules or fragments.

All that glitters is not gold, and everything with fluorines is not fluorous. But where should the line be drawn between fluorous and non-fluorous molecules or groups? We have
heard researchers call a single fluorine atom in a molecule a “fluorous substituent”. This is way over the line. “Fluorine” is a perfectly clear noun, and it obfuscates to replace it with a vague adjective (fluorous) modifying a vague noun (substituent). So 5-fluorouracil (5-FU) is not a fluorous molecule even though the unique properties of fluorine are in play. Perfluorohexane obviously is a fluorous molecule. In between is a vast continuum where properties and to some extent individual researchers will dictate what is or is not fluorous. Said another way, we don’t know exactly how to define a fluorous molecule or group, but we know one when we see one, as will you after you have read this book!

1.3 Other Definitions within the Fluorous Repertoire

Within the above framework, we offer the following definitions for corollary concepts that are important to this Handbook [4]:

1. “a fluorous medium is any phase of a perfluoroalkane, perfluorodialkylether, perfluorotrialkylamine, or similar non-polar species, or any similarly-composed micro-environment within a non-fluorous medium that shares key physical properties with these species.”

   Fluorous media can include greases and coated phases, and are treated further in Chapter 3. It is worth emphasizing that perfluoroarenes, such as hexafluorobenzene, are not fluorous under the above definitions. They are significantly more polar than perfluoroalkanes, and preferentially partition into organic media.

   Fluorophilic molecules, materials or fragments show an affinity for fluorous media under a given set of conditions, while fluorophobic ones do not. Fluorophilicity may be used interchangeably with fluorous phase affinity and is quantified by a fluorous/organic liquid/liquid partition coefficient, as described in Chapter 6.

2. “a fluorous separation technique is any method that separates fluorous or fluorous-labeled molecules from other types of molecules, or from each other, based primarily on the structure of the fluorous domain of the molecule(s).”

   As detailed in Chapter 7, fluorous separation techniques are often (but not always) based on the interactions between a fluorous medium and a fluorous portion of a molecule, and include liquid–liquid extraction with organic and fluorous solvents, and solid–liquid extraction and chromatography with fluorous solid phases. Fluorous separation techniques can also involve interactions of fluorous molecules with each other (for example, precipitation).

3. “a fluorous label or tag is a portion or domain of a molecule that is rich in sp³ carbon–fluorine bonds and exerts primary control over the separability characteristics of the molecule in fluorous separation techniques.”

   A ponytail contains at least six fully fluorinated sp³ carbons, stemming from the goal in much early fluorous research of compounds with very high fluorous/organic partition coefficients. Both tags and ponytails are (phase) labels. Many authors use label and tag and ponytail almost interchangeably. Others view a ponytail as being permanently affixed to a molecule (for example, as part of the carbon skeleton), and a tag as being removable (for example, as part of a protecting group).
It is sometimes convenient to speak of “light fluorous” and “heavy fluorous” substances. Almost always, the former contain only a single tag or ponytail, which, as detailed further in Chapter 8, should contain no more than 21 fluorine atoms. We suggest that the latter be reserved for cases where two or more ponytails emerge from a shared atom or molecular fragment.

4. “a fluorous reaction component is any participant in a reaction (catalyst, pre-catalyst, reagent, reactant/educt, product, scavenger, etc.) to which a fluorous label has been deliberately affixed.”

The labeling can be permanent (ponytail) or temporary (tag). This terminology also encompasses “fluorous reaction intermediates”.

5. “a fluorous reaction involves at least one fluorous reaction component, which afterwards can be separated from the non-fluorous or other fluorous components of the reaction mixture by a fluorous separation technique.”

6. “fluorous chemistry is the study of the structure, composition, properties and reactions of fluorous molecules, molecular fragments, materials and media.”

We believe that standardization of the field to the definitions provided above will greatly help its continued advancement. On the other hand, there are other practices that have not yet converged to a common standard, and perhaps never will. Partition coefficients provide one example. These are sometimes expressed as logarithmic values, and at other times as ratios normalized to 100 (for example, 98.3:1.7), and also as ratios with the less populated phase set to 1 (for example, 57.8:1). Symbols for ponytails and tags are another example. Some authors in this Handbook utilize “Rfn” for (CF₂)nCF₃ or (CF₂)nF, and others eschew abbreviations altogether. However, it should be noted that IUPAC has authorized the prefix F- for perfluoro, enabling “F-alkyl” to denote “perfluoroalkyl” (F-surfactant = perfluorosurfactant, etc.).

### 1.4 Present Scope of Fluorous Chemistry

The definitions associated with fluorous chemistry in the preceding sections are so broad (as they should be) that further introductory classifications would be of little use. Rather, readers are directed to Chapters 3–8 for structured treatments of various aspects and protocols. Although Figure 1-1 is pedagogically appealing as a point of introduction, it now represents just one of countless ways to conduct fluorous reactions, and one of several main strategies for the recovery of fluorous catalysts or reagents. Since recovery can present diverse challenges, a portfolio of methodologies is normally desirable, and these variations and extensions are detailed in Chapter 4.

### References

4. These definitions are adapted from an earlier treatment: Gladysz, J. A.; Curran, D. P. Tetrahedron 2002, 58, 3823.
2
A Personal View of the History of Fluorous Chemistry

István T. Horváth

The fluorous story probably began with the synthesis of the first few drops of a liquid perfluoroalkane. The high density and many other unique properties were immediately apparent upon isolation [1]. The systematic development of the chemistry of perfluorocarbons actually began with the US Atomic Energy Program at Columbia University and other universities in the fall of 1941. The observation of separate liquid/liquid phases must have been the reason for the statement by Groose and Cady that “the liquid saturated fluorocarbons are substantially insoluble in water, alcohols, and hydrocarbons” [2]. Although the temperature dependent phase separation of perfluorinated alkanes – even from hydrocarbons – had already been established by Hildebrand in 1949 [3], the tremendous potential of the liquid/liquid phase separation was only recognized 50 years later [4].

The original fluorous biphase concept was developed on paper at Exxon Corporate Research Laboratories during the search for a novel approach for the selective oxidation of methane to methanol utilizing supported [5] (or stationary [6]) liquid phase catalysis, an attractive immobilization technique for transition metal complexes developed in the late 1980s. Perfluorotributyl amine was selected as the supported or stationary liquid phase due to its intriguing properties including the high solubility of methane and, in particular, of oxygen [7], the low miscibility with methanol at ambient conditions, and a remarkable stability under air even at higher temperatures. Thus, the use of a two-phase system, consisting of a perfluorotributyl amine phase containing the oxidation catalyst and a product phase being methanol itself, was proposed. To avoid the oxidation of the catalyst and to achieve high solubility in the perfluorotributyl amine phase, perfluoralkyl chains were to be attached to the ligand core of the catalyst (Figure 2-1). The idea of using perfluoroalkylated ligands was also in line with the successful application of electron deficient perhalogenated iron porphyrins for isobutane oxidation by Ellis and Lyons in the late 1980s [8]. However, it was later clearly established that these iron prophyrins are not stable in oxidative environments [9]. Although the fluorous approach has not resulted in a new methane oxidation catalyst, it led to the development of a much broader concept.

In terms of the personal dynamics of the fluorous story, important contributions were made by Dr. Andrew Kaldor, Director of Resource Chemistry Laboratory at Exxon Corporate Research Laboratories, who continually emphasized the necessity for thinking "outside the
box”. He had asked his research staff to develop new concepts for methane conversion and to present them at a meeting. At the same time, I had asked Dr. József Rábai, an organic chemist and a visiting scientist at Exxon (from Eötvös University, Budapest, Hungary) to help me in various projects and indeed he was instrumental in transferring the idea from the drawing-board to actual experiments.

When the limited miscibility of perfluoroalkanes, perfluorodialkyl ethers, and perfluorotrialkyl amines with common organic solvents such as toluene, THF, and acetone was recognized, a general concept, the fluorous biphase concept [4], was born which led to the development of fluorous biphase chemistry [10]. The term fluorous was introduced, as the analog to the term aqueous, to emphasize the fact that a chemical transformation is primarily controlled by a reagent or a catalyst designed to dissolve preferentially in the fluorous phase. The fluorous phase was originally defined as the perfluoroalkane, perfluorodialkyl ether, or perfluorotrialkyl amine rich phase of a biphase system. Thus, a fluorous biphase system consisted of a fluorous phase containing a preferentially fluorous soluble reagent or catalyst, and a second product phase, which may be any organic or nonorganic solvent with limited solubility in the fluorous phase. Reagents and catalysts can be made fluorous soluble by attaching fluorocarbon moieties to ligands in appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms (the “fluorous ponytails”). It was also recognized at the early stages of the development [4], that the possibility of dipole–dipole interactions render perfluoroaryl-containing [11] reagents and catalysts more soluble in common organic solvents and therefore less useful as part of fluorous biphase systems.

Because of the well-known electron-withdrawing properties of the fluorine atom, the attachment of fluorous ponytails could change the electronic properties significantly and consequently the reactivity of fluorous reagents and catalysts. Therefore, the insertion of insulating groups before the fluorous ponytail may be necessary to decrease the strong electron-withdrawing effects [12]. It should be noted that tails “consisting of perfluoroalkyl and

![Fig. 2-1. The original drawing of the stationary liquid phase catalyst for methane oxidation to methanol showing the fluorous ponytails](image-url)
insulating methylene groups” were first introduced by Husted and Ahlbrecht of the 3M Company around 1953 [13].

Convincing evidence that such systems can be constructed was disclosed more than 40 years ago [14]. Researchers at the 3M Company faced the challenging question of how to develop dye pigments that can be employed for coloring perfluoroalkanes and Teflon, because ordinary oil or water soluble dyes were not compatible with perfluorinated materials, e.g., they form separate phases. Perfluoroalkylation of a Cu-phthalocyanine yielded a blue dye, which was soluble in perfluorotributyl amine and could be used to prepare a Teflon compatible ink.

It was recognized from the beginning that a fluorous biphase catalyst system could become a one-phase system by increasing the temperature, which was originally demonstrated for fluorous biphase hydroformylation [4, 12]. Thus, a fluorous catalyst could combine the advantages of one-phase catalysis with biphase product separation by running the reaction at higher temperatures and separating the products at lower temperatures (Figure 2-2). The application of hydrocarbon soluble phosphine-modified rhodium catalysts for the hydroformylation of higher olefins such as decene-1 is limited by catalyst degradation during distillation of the aldehyde from the catalysts. While the use of water-soluble catalysts could provide easy separation for heavy aldehydes, the low solubility of the higher olefins in water could limit the application of aqueous catalysts. In contrast, a fluorous soluble phosphine-modified rhodium catalyst appeared very attractive for the hydroformylation of high molecular weight olefins, as their solubility is high in fluorous media and the catalyst could be separated from the product aldehydes. The facile separation of high molecular weight aldehydes was first demonstrated for the hydroformylation of decene-1 in the presence of the fluorous soluble P(CH2CH2(CF2)5CF3)3-modified rhodium catalyst. It was also shown that the solution structure of HRh(CO)(P(CH2CH2(CF2)5CF3)3)3, the key rhodium species in solution, in c-C6F11CF3 is similar to HRh(CO)(PPh3)3 in toluene and HRh(CO)(P(m-C6H4SO3Na)3)3 in water. The fluorous biphase catalyst recovery was tested in a semicontinuous hydroformylation of decene-1 with the Rh/P(CH2CH2(CF2)5CF3)3 catalyst. During nine consecutive reactions/separations a total turnover of more than 35 000 was achieved with a loss of 1.18 ppm of Rh/mol of undecanals. The Rh/P(CH2CH2(CF2)5CF3)3 catalyst

![Fig. 2-2. The temperature-dependent fluorous-liquid/liquid biphase concept](image-url)
was also used for the continuous hydroformylation of ethylene. The long-term (60 days) stability of the Rh/P(\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3)_3 catalyst was better than that of the Rh/P\text{Ph}_3 catalyst. Thus, the Rh/P(\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3)_3 catalyst was the first catalyst system that could be used for the hydroformylation of both low and high molecular weight olefins and provides facile catalyst separation for both low and high molecular weight aldehydes [12].

Another key player in fluorous chemistry has been Prof. John A. Gladysz, University of Erlangen, Germany. He was a consultant to Exxon and became familiar with the development of fluorous chemistry from the beginning. In fact, that is why I suggested that Science should ask him to write a short article [15] along with the first publication of the fluorous biphasic concept [4]. We have also collaborated for a number of years, work which was co-supported by Exxon and NSF. Our joint research program led to the synthesis of a fluorous analog of Wilkinson’s catalyst, ClRh[\text{P(CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3)]_3, which was used as a catalyst for hydrogenation [16], hydroboronation [17], and hydroisilylation [18] reactions.

As frequently happens in science, when a new direction is emerging in a given field, one consequence is that the same discovery is made independently in different laboratories practically at the same time. The application of perfluorinated polyalkyl ether soluble transition metal complexes in catalytic oligomerization of ethylene, oxidation of cyclohexene, and polymerization and telomerization of butadiene was described in the Ph.D. thesis of Vogt in 1991 [19]. Despite the potential springboard that these preliminary observations offered, no patents were filed and the first paper was only published in 1999 [20]. In addition, the thesis could not be accessed by any literature search methods (except through a personal pilgrimage to the library of the RWTH in Aachen). Cornils, one of the leading authorities on biphasic organometallic catalysis, has observed that “German theses which do not lead to publications do not become internationally known” [21]. After the first public disclosure of the fluorous biphasic concept at the NATO Advanced Research Workshop on Aqueous Organometallic Chemistry and Catalysis in Debrecen, Hungary in the fall of 1993, Cornils published a synopsis of the meeting including the fluorous biphasic concept with no mention of Vogt’s thesis, indicating that it was unknown even to an established expert [22].

A liquid fluorocarbon as a solvent was first used in the separation of uranium isotopes in 1940 [23]. Although the remarkable chemical inertness, thermal stability, and non-flammability of fluorous solvents make them particularly attractive reaction media, they were used sparingly in the following half century. One of the first examples of the use of fluorous solvents in chemical reactions was the photodegradation of fluorous extracts of PCB-contaminated solid- or liquid-phase wastes [24]. The first systematic application of perfluoroalkanes and perfluorotrialkyl amines as inert media for organic reactions was published by Zhu of the 3M Company in 1993 [25].

Perfluoro-cis-2,3-dialklyloxadiziridines are to my knowledge the first fluorous reagents, although their capability for reagent separation was not recognized at the time [26]. Interestingly, in this paper it is stated that good results could be obtained despite the fact that the reactions became two-phase systems. Perfluoro-cis-2,3-dialklyloxadiziridines can be prepared from commercially available perfluorotrialkyl amines and can be used for mild and selective hydroxylation of unactivated tertiary C–H bonds in alkanes, as well as for oxidation of alkenes, alcohols, ethers, sulfides, and silanes. The application of the first fluorous tin reagent was reported by Prof. Dennis Curran in 1996, which exhibited similar reactivity to that of...
the parent organic reagents but offered the facile separation of the product from the spent reagent [27].

Because of the extremely apolar nature of the fluorous media, the application of fluorous reagents is limited to apolar substrates; e.g., reactions of polar substrates in a fluorous biphasic mode could be too slow for practical applications. Curran recognized this limitation and developed a new protocol for the use of fluorous reagents [28]. The reaction of a polar substrate and a fluorous reagent is performed in a single liquid phase using a common solvent for both. Benzotrifluoride (BTF, C₆H₅CF₃) has been found to have the suitable properties for several fluorous reagents. After the reaction is completed all liquids are removed in vacuum and the residue is treated with an organic-fluorous two-phase system to dissolve the product in the organic phase and the spent fluorous reagent in the fluorous phase. For reactions producing water-soluble side products a three-phase liquid system consisting of an organic solvent, water, and a fluorous solvent is used to separate simultaneously the organic products, the water soluble side products, and the spent fluorous reagent. Curran has in addition extended the application of the fluorous biphasic concept for multistep organic synthesis [28], which also provided a new approach to liquid-phase combinatorial synthesis [29]. Finally, the separation of fluorous compounds from each other and from non-fluorous components of various reaction systems was developed by Curran using fluorous silica gel as the sorbent [30]. It is important to note that Curran has been the major force in the introduction of fluorous chemistry to organic chemists – and they have been listening!

Finally, Wende and Gladysz [31] and Yamamoto et al. [32] have independently demonstrated that the temperature-dependent solubility of solid fluorous catalysts in liquid substrates or in conventional solvents containing the substrates could eliminate the need for fluorous solvents (Figure 2-3), an important new direction for commercial applications of fluorous chemistry.

As reflected by the contents of this handbook, fluorous chemistry has grown into a well-established area and provides a complementary approach to the chemistries performed in water, ionic liquids, supercritical carbon dioxide, and in their various combinations. Since each chemical reaction could have its own perfectly designed environment, the possibility.

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![Fig. 2-3. The temperature-dependent fluorous-solid/liquid biphasic concept](image-url)
of selecting from biphase systems ranging from fluorous to aqueous systems provides a powerful portfolio for molecular designers. My association with this field, as outlined above, has been the personally most rewarding aspect of my career and I take particular enjoyment in watching the ongoing collective history that the many contributors to this handbook are helping to write.

References

3 Fluorous Solvents and Related Media

J. A. Gladysz and Charlotte Emnet

3.1 Introductory Remarks

Most applications of fluorous chemistry involve a partnership of fluorous and non-fluorous solvents. The success of these applications is often critically dependent upon the exact physical properties of both solvents. For this reason, general compendia of solvent data represent useful desk references. There are several excellent choices, and the most recent also provide some data on fluorous solvents [1]. Some general physical attributes of perfluorinated molecules are summarized in Chapter 13.2, which also contains much information on biocompatibility and medical applications.

3.2 Commercial Fluorous Solvents

As summarized in Table 3-1, numerous fluorous solvents are commercially available. Perfluorinated alkanes [2] are the most common, followed by perfluorinated dialkyl ethers and polyethers and then perfluorinated trialkyl amines. Importantly, the lone pairs in such ethers and amines are extremely low in energy. There is no residual basicity, or any other basis for appreciable intermolecular interactions. All major vendors now sell fluorous solvents. Oakwood Products, ABCR, Fluorochem, Lancaster, ACROS, and Apollo offer the largest selections.

The densities of the fluorous solvents in Table 3-1 are much greater than those of common organic solvents, including CCl$_4$ (1.589 g mL$^{-1}$). A wide selection of boiling points is available. The $n$-perfluoroalkanes are always slightly more volatile than the corresponding $n$-alkanes, and the boiling points correlate linearly [3]. Technical solvent grades often have distinct CAS numbers and trade names, as well as lower melting points. Some of these solvents are used in the electronics industry, for example in the manufacture of printed circuits.

The most common solvent for fluorous chemistry is perfluorohexane or FC-72 (entry 1, Table 3-1). However, like “hexanes”, FC-72 is a mixture of isomers, and minor amounts of other fluorous molecules can be present [4]. For preparative chemistry this is of no consequence [4]. However, for physical measurements or mechanistic studies, CF$_3$C$_6$F$_{11}$...
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Formula</th>
<th>bp (°C)</th>
<th>mp (°C)</th>
<th>Density (g/mL)</th>
<th>Common name</th>
<th>CAS #</th>
<th>2003 Vendors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>perfluorohexane</td>
<td>C₆F₁₄</td>
<td>57.1</td>
<td>-90</td>
<td>1.669</td>
<td>FC-72 (Fluorinert)</td>
<td>[355-42-0]</td>
<td>a-e,g,h,m</td>
</tr>
<tr>
<td>2</td>
<td>perfluoroheptane</td>
<td>C₇F₁₆</td>
<td>82.4</td>
<td>-78</td>
<td>1.745</td>
<td>–</td>
<td>[335-57-9]</td>
<td>a-d,g,h,m</td>
</tr>
<tr>
<td>3</td>
<td>perfluorooctane</td>
<td>C₈F₁₈</td>
<td>103–104</td>
<td>-25</td>
<td>1.766</td>
<td>–</td>
<td>[307-34-6]</td>
<td>a-e,g,m</td>
</tr>
<tr>
<td>4</td>
<td>perfluoromethylcyclohexane</td>
<td>CF₃C₆F₁₁</td>
<td>76.1</td>
<td>-37</td>
<td>1.787</td>
<td>PFMC</td>
<td>[355-02-2]</td>
<td>a-e,g,i,m</td>
</tr>
<tr>
<td>5</td>
<td>perfluoro-1,2-dimethylcyclohexane</td>
<td>C₉F₁₆</td>
<td>101.5</td>
<td>-56</td>
<td>1.867</td>
<td>PP3 (Fluotec(R))</td>
<td>[306-98-9]</td>
<td>a-d,g,m</td>
</tr>
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<td>6</td>
<td>perfluoro-1,3-dimethylcyclohexane</td>
<td>C₉F₁₆</td>
<td>101–102</td>
<td>-53</td>
<td>1.828</td>
<td>–</td>
<td>[335-27-3]</td>
<td>a-e,g,h,m</td>
</tr>
<tr>
<td>7</td>
<td>perfluoro-1,3,5-trimethylcyclohexane</td>
<td>C₉F₁₈</td>
<td>125–128</td>
<td>-68</td>
<td>1.888</td>
<td>–</td>
<td>[374-76-5]</td>
<td>a-d,m</td>
</tr>
<tr>
<td>8</td>
<td>perfluorodecalin</td>
<td>C₁₀F₁₈</td>
<td>142</td>
<td>-10</td>
<td>1.908</td>
<td>–</td>
<td>[306-94-5]</td>
<td>a-e,g,i,m</td>
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<tr>
<td>9</td>
<td>1-bromoperfluoroctane</td>
<td>C₈F₁₇Br</td>
<td>142</td>
<td>6</td>
<td>1.930</td>
<td>–</td>
<td>[423-55-2]</td>
<td>a-e,g,h</td>
</tr>
<tr>
<td>10</td>
<td>perfluoro-2-butyltetrahydrofuran</td>
<td>C₁₀F₁₈O</td>
<td>99–107</td>
<td>-88</td>
<td>1.77</td>
<td>FC-75 (Fluorinert)</td>
<td>[335-36-4]</td>
<td>a-e,h,m</td>
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<td>11</td>
<td>perfluoropolyether</td>
<td>MW ≈ 340</td>
<td>57</td>
<td>–</td>
<td>1.65</td>
<td>HT55 (Galden)</td>
<td>–</td>
<td>l</td>
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<tr>
<td>12</td>
<td>perfluoropolyether</td>
<td>MW ≈ 410</td>
<td>70</td>
<td>–</td>
<td>1.68</td>
<td>HT70 (Galden(R))</td>
<td>[69991-67-9]</td>
<td>c,l,m</td>
</tr>
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<td>perfluoropolyether</td>
<td>MW ≈ 460</td>
<td>90</td>
<td>–</td>
<td>1.69</td>
<td>HT90 (Galden(R))</td>
<td>–</td>
<td>c,l,m</td>
</tr>
<tr>
<td>14</td>
<td>perfluoropolyether</td>
<td>MW ≈ 580</td>
<td>110</td>
<td>–</td>
<td>1.72</td>
<td>HT110 (Galden(R))</td>
<td>–</td>
<td>c,l,m</td>
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<td>15</td>
<td>perfluorotributylamine</td>
<td>C₁₂F₂₇N</td>
<td>178</td>
<td>–</td>
<td>1.883</td>
<td>FC-43 (Fluorinert)</td>
<td>[311-89-7]</td>
<td>a-e,g,h,k,m</td>
</tr>
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<td>16</td>
<td>perfluorotripentylamine</td>
<td>C₁₅F₃₃N</td>
<td>212–218</td>
<td>–</td>
<td>1.93</td>
<td>FC-70 (Fluorinert(R))</td>
<td>[338-84-1]</td>
<td>a-e,k,m</td>
</tr>
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<td>17</td>
<td>perfluorotrihexylamine</td>
<td>C₁₈F₃₉N</td>
<td>250–260</td>
<td>33</td>
<td>1.90</td>
<td>FC-71 (Fluorinert(R))</td>
<td>[432-08-6]</td>
<td>a-e,m</td>
</tr>
</tbody>
</table>

*Codes for vendors are as follows: a = Oakwood Products (http://www.oakwoodchemical.com); b = ABCR (http://www.abcr.de); c = Fluorochem (http://www.fluorochem.co.uk/index2_ns.asp); d = Lancaster (http://www.lancastersynthesis.com); e = Acros Organics (http://www.acros.be); f = 3M (http://www.3m.com); g = Aldrich (http://www.sigmaaldrich.com/Brands/Aldrich.html); h = Fluka (http://www.sigmaaldrich.com/Brands/Fluka___Riedel_Home.html); i = Merck (http://www.merck.de/en/support/technicaldata/1001723/index.html); j = Oxychem (http://www.oxychem.com); k = Sigma (http://www.sigmaaldrich.com/Brands/Sigma.html); l = Solvay Solexis (http://www.solvaysolexis.com); m = Apollo Scientific Ltd. (http://www.apolloscientific.co.uk).** Several fluorous solvents are available in technical grades that have distinct CAS numbers and/or common names. 1 [86508-42-1], FC-72 [Fluorinert(R)], PP1 [Flutec(R)], a, c, f, m. 2 [86508-42-1], FC-84 [Fluorinert(R)], a, c, f, m. 3 [86508-42-1], FC-77 [Fluorinert(R)], a, c, e, f, h, k, m. 4 General formula CF₃[(OCF(CF₃)CF₂)m]OCF₃. 5 [86508-42-1], FC-43 [Fluorinert(R)], a, c, f, m. 6 [86508-42-1].
[perfluoro(methylcyclohexane) or PFMC], a more expensive but homogeneous solvent, is often favored (entry 4). This ensures a higher level of reproducibility.

Most commercial perfluoropolyethers (e.g., entries 11–14) [5] contain multiple stereocenters, and are therefore mixtures of diastereomers. Perfluorodecalin is sometimes described as a mixture of cis/trans diastereomers, a potential that also exists for the poly-methylated cyclohexanes in entries 5–7, and at other times is implied to be the more stable trans isomer. Substituted perfluorodecalins as well as higher homologs with additional fused rings are similarly available (not listed).

Brominated organic solvents are seldom employed in organic synthesis, but 1-bromoperfluorooctane (entry 9, Table 3-1) is commonly applied in fluorous chemistry. The availability of this compound derives in part from its use in artificial blood (e.g., Oxygent™, a product of the Alliance Pharmaceutical Company) [6]. There are also ongoing efforts to develop and bring new fluorous solvents to the market.

### 3.3 Related Solvents and Media

#### 3.3.1 Amphiphilic or Hybrid Solvents

Some solvents are able to dissolve appreciable quantities of both fluorous and non-fluorous solutes, and can hence be termed “hybrid”, “universal” or “amphiphilic”. The most familiar example is CF₃C₆H₅, which is known by a variety of names such as (trifluoromethyl)-benzene, α,α,α-trifluorotoluene, and benzotrifluoride (BTF) [7]. This solvent, which has convenient melting and boiling points of −29 and 102 °C, is not fluorous according to the definition given in Chapter 1. Another example is the ether CF₃(CF₂)₅CH₂CH₂OCH(CH₃)−CH₂CH(CH₃)₂ (F-626) [8], mp/bp < −78/214 °C, which contains a fluorous segment. Such solvents or additives offer unique possibilities for certain types of processes and/or workups, as detailed in Chapter 4.

#### 3.3.2 Fluorous Ionic Liquids

The fluorous ionic liquids shown in Figure 3-1 have recently been reported [9]. Solvents 1a–d act as surfactants in conventional ionic liquids, facilitating their emulsification with fluoroalkanes. Solvent 2 exhibits a polarity comparable to those of acetone and diethyl ether, is highly miscible with apolar solvents such as alkenes, and resembles fluorous solvents in its phase behavior with organic solvents [9c].

#### 3.3.3 “Faux Fluorous” Solvents

Certain solvents are often mistakenly assumed to be fluorous, but are not. Of these, the most important are perfluoroarenes such as hexafluorobenzene. The arene π cloud and sp² carbon–fluorine bonds lead to significant intermolecular bond dipole, induced dipole,
and quadrupolar interactions with non-fluorous molecules [10, 11]. However, such solvents can exhibit amphiphilic properties. Quantitative polarity data are provided in the following section.

### 3.3.4 Fluorous Greases

Another possible medium for recycling fluorous materials is a low-melting fluorous solid or grease. There is an extensive technical literature of high-performance lubricants containing only fluorine, oxygen, and saturated carbon. These have long-term operating ranges of >300 °C under extreme conditions, and are extensively applied in the aerospace, automotive, semiconductor, and paper/textile industries. For interested researchers, the Krytox® family of products from DuPont constitutes a good starting point [12].

### 3.3.5 Bonded Fluorous Phases

Chapter 7 will detail the use of fluorous silica gel for preparative and analytical separations. However, solid supports that carry bonded fluorous moieties represent attractive and fluorous-solvent-free media for recycling. Several recently published protocols are further described in Chapters 10.8.2.4, and 10.8.2.5 [13, 14].

### 3.4 Polarities of Fluorous Solvents

Perfluorinated solvents exhibit extremely low polarities. There are many ways to quantify polarity, ranging from familiar parameters such as dielectric constant and dipole moment to kinetic, equilibrium, and solventochromic measurements. As analyzed elsewhere [3, 15],

**Fig. 3-1.** Fluorous ionic liquids [9]
one of the best scales involves the shift of the absorption maximum of a perfluoroheptyl-
substituted dye. This models the ability of a solvent to solvate or complex a solute or transition state particularly well. The dye was optimized to be soluble in both fluorocarbons and very polar solvents such as DMSO. Over 100 solvents were assayed [15], and some of the resulting “Spectral Polarity Index” or $P_S$ values are given in Table 3-2.

The data in Table 3-2 confirm that perfluoroalkanes are much less polar than the corresponding alkanes (first five entries in each column; $P_S$ 0.00–0.99 vs. 2.56–4.07). They also show that perfluorinated trialkylamines exhibit similar polarities, but those of fluorinated arenes are higher. Nonetheless, hexafluorobenzene remains less polar than benzene ($P_S$ 4.53 vs. 6.95). Interestingly, highly fluorinated alcohols such as CF$_3$CF$_2$CF$_2$CH$_2$OH and (CF$_3$)$_2$CHOH exhibit $P_S$ values higher than those of similar non-fluorinated alcohols (9.76 and 11.08 vs. 7.62 and 7.85). This has been attributed to strong hydrogen bonding [16]. Applications of the latter solvent are highlighted in Chapter 10.17

3.5 Solubilities of Solutes in Fluorous Solvents

3.5.1 General Aspects

It is important to distinguish between the absolute solubility of a solute, which is defined by a $K_{sp}$ value (solubility constant) or similar parameter, and the relative solubility, which reflects the equilibrium distribution of the solute between two solvents and is defined by a partition coefficient. Absolute solubilities are treated in this section, and relative solubilities in Chapter 6. Theoretical approaches to predicting both types of solubilities are also discussed in Chapter 6 [17].

Solubilities in fluorous solvents are largely determined by two parameters: solute polarity and size. The first is an extension of the familiar “like dissolves like” paradigm. The second is uniquely important to perfluorinated solvents, which because of low intermolecular forces have large cavities (free volumes) that can accommodate small molecules. There is an extensive literature involving gas solubilities in fluorocarbons. Importantly, the data correlate with the isothermal compressibility of the solvent [18], supporting the cavity-based solubility model.

Unfortunately, quantitative solubility data for the types of solutes that would be of greatest interest to fluorous chemists, such as representative monofunctional fluorous and non-fluorous molecules, are scarce. There is some literature on solubilities of small non-fluorous molecules [19]. For example, a solution of perfluoroheptane that is saturated with octane contains 11.2 mol% octane at 27.5 °C, 31.8 mol% octane at 60.0 °C, and 45.1 mol% octane at 65.8 °C [19e]. This nicely documents the strong temperature dependences of solubilities in fluorous phases. The smaller hydrocarbon heptane is approximately twice as soluble as octane (21.4 mol%, 27.3 °C), in accord with the above generalization. Chloroform is similar (22.4 mol%, 24.6 °C). The solubilities of several fluorous arylphosphines in CF$_3$C$_6$F$_{11}$ have been measured [20], and there is a growing body of computational data [17].

It should be emphasized that some fluorous compounds are poorly soluble in fluorous solvents at room temperature. This is most often observed with, but not limited to,
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Formula</th>
<th>Ps</th>
<th>Solvent</th>
<th>Formula</th>
<th>Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>perfluoromethylcyclohexane (PFMC)</td>
<td>CF₃C₆F₁₁</td>
<td>0.46</td>
<td>methylcyclohexane</td>
<td>C₆H₁₁</td>
<td>3.34</td>
</tr>
<tr>
<td>perfluoro-1,3-dimethylcyclohexane</td>
<td>C₆F₁₆</td>
<td>0.58</td>
<td>1,3-dimethylcyclohexane</td>
<td>C₆H₁₆</td>
<td>3.31</td>
</tr>
<tr>
<td>perfluorohexane</td>
<td>C₆F₁₄</td>
<td>0.00</td>
<td>n-hexane</td>
<td>C₆H₁₄</td>
<td>2.56</td>
</tr>
<tr>
<td>perfluoroocane</td>
<td>C₆F₁₈</td>
<td>0.55</td>
<td>n-octane</td>
<td>C₆H₁₈</td>
<td>2.86</td>
</tr>
<tr>
<td>perfluorodecalin</td>
<td>C₁₀F₁₈</td>
<td>0.99</td>
<td>decalin</td>
<td>C₁₀H₁₈</td>
<td>4.07</td>
</tr>
<tr>
<td>perfluorotributylamine</td>
<td>(C₄F₉)N</td>
<td>0.68</td>
<td>tri-n-butylamine</td>
<td>(C₄H₉)N</td>
<td>3.93</td>
</tr>
<tr>
<td>hexafluorobenzene</td>
<td>C₆F₆</td>
<td>4.53</td>
<td>benzene</td>
<td>C₆H₆</td>
<td>6.95</td>
</tr>
<tr>
<td>2,2,2-trifluorotoluene (BTF)</td>
<td>CF₃C₆H₆</td>
<td>7.03</td>
<td>toluene</td>
<td>C₆H₆</td>
<td>6.58</td>
</tr>
<tr>
<td>2,2,2-trifluoroethyl trifluoroacetate</td>
<td>CF₃CO₂CH₂CF₃</td>
<td>7.74</td>
<td>ethyl acetate</td>
<td>CH₃CO₂CH₂CH₃</td>
<td>6.96</td>
</tr>
<tr>
<td>1H,1H-perfluoro-1-butanol</td>
<td>CF₃(CF₂)₂CH₂OH</td>
<td>9.76</td>
<td>1-butanol</td>
<td>CH₃(CH₂)₂CH₂OH</td>
<td>7.62</td>
</tr>
<tr>
<td>1,1,1,3,3,3-hexafluoroisopropanol</td>
<td>(CF₃)₂CHOH</td>
<td>11.08</td>
<td>2-propanol</td>
<td>(CH₃)₂CHOH</td>
<td>7.85</td>
</tr>
</tbody>
</table>
molecules with longer $R_n$ segments ($n > 8$). Such species are even less soluble in organic solvents. Representative examples include the fluorous sulfoxides O=S(CH$_2$)$_m$R$_f$ ($m = 2, 3$) [21], and certain fluorous palladacycles [22]. Also, solubilities in all solvents dramatically decrease in the series of fluorous phosphines $P[(CH_2)_2R_6]_3$, $P[(CH_2)_3R_8]_3$, and $P[(CH_2)_2R_10]_3$ [23, 24].

One way to conceptualize this phenomenon is to view the ponytails as short pieces of teflon, which does not dissolve in any common fluorous or non-fluorous solvent. As the ponytails become longer, many physical properties of the molecule approach those of teflon. However, just as the miscibilities of fluorous liquid phases and organic liquid phases are highly temperature dependent, so are the solubilities of fluorous solids in fluorous or non-fluorous liquid phases highly temperature dependent [24]. Hence, much higher solubilities can be achieved at elevated temperatures. This phenomenon can be used to conduct homogeneous reactions at elevated temperatures, with catalyst or reagent recovery by solid/liquid phase separation at lower temperatures [24–26].

3.5.2
Gas Solubilities

Some specific data on gas solubilities are provided in Table 3-3. Literature values are normally compiled as mole fractions, a unit not commonly employed by preparative chemists or kineticists. These constitute the origin of the widespread statement that “gases are much more soluble in fluorocarbons than other solvents”. This generalization is indeed appropriate with reference to water, where a strong hydrogen bonding network must be disrupted, but is much less so for organic solvents [27].

As shown in Table 3-3, the solubilities of O$_2$ in the fluorous solvent CF$_3$C$_6$F$_{11}$ and the organic solvent THF differ by a factor of five when expressed as mol fractions (0.00456...
Since the mole fractions are so small, the mol ratios are essentially identical (0.00453 vs. 0.000815). When the denominators of the mol ratios are replaced by the molecular weights of the solvents, molal concentrations can be calculated (mol gas/kg solvent). Importantly, the molecular weights of fluorocarbons tend to be higher than those of organic solvents, and those of CF$_3$C$_6$F$_{11}$ and THF differ by a factor of ca. five. Substitution gives (0.00453 mol O$_2$)/(350.05 g CF$_3$C$_6$F$_{11}$) and (0.000815 mol O$_2$)/(72.11 g THF), or nearly equal molal concentrations (Table 3-3).

The densities of fluorocarbons are also higher than those of common organic solvents, and CF$_3$C$_6$F$_{11}$ is twice as dense as THF. This translates the preceding concentrations into (0.00453 mol O$_2$)/(195.9 mL CF$_3$C$_6$F$_{11}$) and (0.000815 mol O$_2$)/(81.1 mL THF), resulting in molarities that differ by a factor of slightly more than 2 (Table 3-3). The solubility of H$_2$ in CF$_3$C$_6$F$_{11}$ and THF is slightly lower (0.0012 vs. 0.000274 as mol fractions). However, the relationships between molal and molar concentrations turn out to be nearly the same as with O$_2$ (Table 3-3).

Understandably, fluorous solvents are often proposed as good media for reactions of gases. However, the above data clearly show that relative to organic solvents, any solubility-based rate accelerations must by necessity be modest. Furthermore, the addition of oxygen to the square planar iridium complex in Scheme 3-1 is much slower in CF$_3$C$_6$F$_{11}$ than THF, despite a 2.3-fold higher oxygen concentration in the former [28]. The transition state of the rate determining step is thought to be more polar than the reactants – a very common situation in chemical reactions. This creates a rate-constant-based disadvantage for the fluorous solvent that more than counteracts the solubility-based advantage. The analogous addition of H$_2$ to iridium is also slower in CF$_3$C$_6$F$_{11}$ than THF.

![Scheme 3-1](image)

Scheme 3-1. Slower reaction of oxygen in a fluorous solvent, despite a higher concentration [28]

### 3.6 Fluorous/Non-fluorous Solvent Miscibilities

Although fluorous chemistry can be conducted under heterogeneous liquid/liquid biphasic conditions, homogeneous monophasic conditions as in Figure 1-1 will normally give faster reactions. Towards this end, it is important to know the temperatures at which various fluorous and non-fluorous solvents become miscible. Literature data and some qualitative observations of the authors’ coworkers are summarized in Table 3-4 [19c, 29, 30].
With binary solvent systems, it is common to determine a “consolute” or “upper critical solution” temperature, above which phase separation cannot occur, whatever the composition [31]. As would be intuitively expected, consolute temperatures are usually found for ca. 50:50 (mol/mol) mixtures. Representative consolute temperatures are given in Table 3-4. However, as is evident from the full phase diagrams, solvents can become miscible in other proportions at much lower temperatures. For example, the phase diagram for toluene and the fluorous ionic liquid $\text{[9c]}$ is given in Figure 3-2. This system has a consolute temperature of 62°C, but one-phase conditions can often be achieved at 55°C or lower.

Importantly, consolute temperatures can be strongly affected by solutes or dissolved species, including impurities. It is well known that homogeneous mixtures of aqueous and certain organic solvents can often be induced to “salt out” or phase separate by adding a suitable material. Thus, researchers quickly learn that Table 3-4 provides at best a rough guide to a property that is a function of many parameters. Lighter organic solvents such as pentane and ether are the most likely to give one phase reaction conditions at room temperature.

The mixing of two liquid phases is of course entropically favorable. From an enthalpic standpoint, intermolecular attractive interactions will always be greater within the pure non-fluorous phase (which has a much greater polarity) than the pure fluorous phase (which has a much lower polarity). Upon mixing, the stronger intermolecular interactions in the former will be markedly diluted, and the intermolecular interactions felt by the fluorous molecules will only slightly increase. Hence, no enthalpic gain is to be expected. The Hildebrand-Scatchard Theory, alternatively termed Regular Solution Theory, provides a quantitative framework for this qualitative picture [32]. In principle, the consolute temperature can be related to the Hildebrand solubility parameters of the two liquids.

One aspect of this situation deserves emphasis: despite the “like dissolves like” paradigm, it is misleading to view fluorous solvents as capable of highly attractive or repulsive intermolecular interactions. Rather, they facilitate what might be viewed as a “molecular

<table>
<thead>
<tr>
<th>Solvent system</th>
<th>Two phases at (°C)</th>
<th>One phase at (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{CCl}_4$</td>
<td>RT</td>
<td>≥26.7$^b$</td>
<td>19c</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{CHCl}_3$</td>
<td>RT</td>
<td>≥50.1$^b$</td>
<td>19c</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{C}_4\text{H}_6$</td>
<td>RT</td>
<td>≥84.9$^b$</td>
<td>19c</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{CH}_3\text{C}_6\text{H}_5$</td>
<td>RT</td>
<td>≥88.6$^b$</td>
<td>19c</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{CIC}_6\text{H}_5$</td>
<td>RT</td>
<td>≥126.7$^b$</td>
<td>19c</td>
</tr>
<tr>
<td>$\text{C}<em>6\text{F}</em>{12}\text{Br}/\text{CH}_3\text{C}_6\text{H}_5$</td>
<td>RT</td>
<td>50–60$^c$</td>
<td>30a</td>
</tr>
<tr>
<td>$\text{C}<em>{10}\text{F}</em>{18}^d/\text{CH}_3\text{C}_6\text{H}_5$</td>
<td>RT</td>
<td>64$^c$</td>
<td>30a</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{hexane}/\text{CH}_3\text{C}_6\text{H}_5$</td>
<td>RT</td>
<td>36.5$^c$</td>
<td>29</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{hexane}$</td>
<td>0</td>
<td>RT$^c$</td>
<td>30b</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{pentane}$</td>
<td>−16</td>
<td>RT$^c$</td>
<td>30b</td>
</tr>
<tr>
<td>$\text{CF}_3\text{C}<em>6\text{F}</em>{11}/\text{ether}$</td>
<td>0</td>
<td>RT$^c$</td>
<td>30b</td>
</tr>
</tbody>
</table>

$^a$ All data for a 1:1 volume ratio unless otherwise stated. $^b$ Consolute temperature. $^c$ Experimental observation; not a consolute temperature.

3.6 Fluorous/Non-fluorous Solvent Miscibilities

With binary solvent systems, it is common to determine a “consolute” or “upper critical solution” temperature, above which phase separation cannot occur, whatever the composition [31]. As would be intuitively expected, consolute temperatures are usually found for ca. 50:50 (mol/mol) mixtures. Representative consolute temperatures are given in Table 3-4. However, as is evident from the full phase diagrams, solvents can become miscible in other proportions at much lower temperatures. For example, the phase diagram for toluene and the fluorous ionic liquid $\text{[9c]}$ is given in Figure 3-2. This system has a consolute temperature of 62°C, but one-phase conditions can often be achieved at 55°C or lower.

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One aspect of this situation deserves emphasis: despite the “like dissolves like” paradigm, it is misleading to view fluorous solvents as capable of highly attractive or repulsive intermolecular interactions. Rather, they facilitate what might be viewed as a “molecular
xenophobia” – the separation of non-fluorous molecules capable of stronger intermolecular interactions from fluorous molecules capable of only feeble ones.

Molecules from both phases of a liquid/liquid biphasic system are commonly found in each phase. This is termed solvent leaching. One familiar example is ether/water, where drying agents are needed to render the ether layer anhydrous after separating the aqueous layer. Also, the phase diagram in Figure 3-2 does not extend across the entire x-axis because small amounts of the fluorous ionic liquid \(2\) remain completely dissolved in the non-fluorous toluene solvent at room temperature (\(\leq 2\%\) by volume), and a rather sizeable amount of toluene remains dissolved in \(2\) (ca. 35% by volume at 10 °C).

In the specific case of toluene/\(\text{CF}_3\text{C}_6\text{F}_{11}\) at 25 °C (50:50 v/v), the authors’ coworkers have measured ratios of 98.4:1.6 (molar), 94.2:5.8 (mass), and 97.1:2.9 (volume) in the upper organic layer, and 3.8:96.2, 1.0:99.0, and 2.0:98.0 in the lower fluorous layer [33]. Thus, some leaching of the fluorous solvent into the non-fluorous solvent occurs under the conditions of Figure 1-1. Solvent leaching represents an intrinsic disadvantage of liquid/liquid biphasic recovery protocols. Although engineering solutions exist, this provides an impetus for alternative fluorous recovery protocols as described in Chapter 4.

Interestingly, it has recently been shown that \(\text{CO}_2\) pressure can function as a “miscibility switch” for fluorous and organic solvents [34]. This may, for certain applications, have advantages over temperature, such as with thermally labile substrates or catalysts. The compatibility of \(\text{CO}_2\) with both fluorinated solutes and organic solvents is well known, and its
role is thought to be essentially that of a cosolvent. The pressures necessary to mix 1:1 volumes of perfluorohexane and various organic solvents are summarized in Table 3-5. Strongly associating solvents, such as ethanol and methanol, have some of the highest miscibility pressures. Acetic and propionic acid, which form dimers in solution, have lower miscibility pressures. Additional trends have been rationalized by the investigators, and other fluorous solvents gave similar data.

### Tab. 3-5. CO₂ Pressures at which 1:1 volumes of perfluorohexane and various organic solvents mix at 25 °C [34]

<table>
<thead>
<tr>
<th>Organic solvent</th>
<th>Miscibility pressure (bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethyl acetate</td>
<td>16.3</td>
</tr>
<tr>
<td>THF</td>
<td>18.8</td>
</tr>
<tr>
<td>chloroform</td>
<td>19.4</td>
</tr>
<tr>
<td>acetone</td>
<td>21.9</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>26.3</td>
</tr>
<tr>
<td>propionic acid</td>
<td>27.5</td>
</tr>
<tr>
<td>acetic acid</td>
<td>27.5</td>
</tr>
<tr>
<td>toluene</td>
<td>32.5</td>
</tr>
<tr>
<td>decane</td>
<td>36.3</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>40.0</td>
</tr>
<tr>
<td>DMF</td>
<td>44.4</td>
</tr>
<tr>
<td>nitromethane</td>
<td>44.4</td>
</tr>
<tr>
<td>ethanol</td>
<td>44.4</td>
</tr>
<tr>
<td>methanol</td>
<td>45.6</td>
</tr>
<tr>
<td>decahydronaphthalene</td>
<td>53.8</td>
</tr>
</tbody>
</table>

3.7 Special Reactivity Phenomena in Fluorous Solvents

As shown in Scheme 3-1, the low polarities of fluorous solvents can lead to lower reactivities. To balance the picture, it would seem appropriate to close this chapter with a counterexample that illustrates some of the physical principles discussed above [35]. Diels-Alder reactions have negative volumes of activation. Rates are often dramatically accelerated in aqueous relative to organic media, partly due to hydrophobic interactions. Analogous fluorophobic interactions might provide similar driving forces, and an impressive effect has been found for the cycloaddition of 9-methoxyanthracene (3) in Scheme 3-2. Rate constants were determined in several non-fluorous solvents, as well as C₆F₁₄ and FC-75 to which a small amount of isoctane had been added (2% v/v) to solubilize the educts.

As summarized in Scheme 3-2, cycloadditions in C₆F₁₄ and FC-75 are 50–42 times faster than in acetonitrile, and 6–7 times faster than in the most favorable organic solvents (CF₃CH₂OH, n-hexane). Cycloadditions are still faster in water, but this can be attributed to additional hydrogen-bond stabilization of the transition state. Importantly, 3 (the more fluorophobic educt) exhibits the lowest solubilities in C₆F₁₄, FC-75, and water. It can be computed that roughly 25% of the surface area of 3 is removed from the solvent in the
transition state. Hence, the chemical potential of the transition state is raised to a lesser extent in fluorous and aqueous media. Faster rates result, and there is a parabolic dependence of the logarithm of the rate constant on the Hildebrand solubility parameter.

\[ \text{Scheme 3-2. Acceleration of a cycloaddition in fluorous solvents [35]} \]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( k_{\text{rel}} (45^\circ \text{C})^a )</th>
<th>Saturation solubility, [3] (mM)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(<em>6)F(</em>{14})</td>
<td>49.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FC-75</td>
<td>42.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>( n)-C(<em>6)H(</em>{14})</td>
<td>7.2</td>
<td>1.24 ± 0.1</td>
</tr>
<tr>
<td>([n-C_6H_{14}]_2)O</td>
<td>2.3</td>
<td>20.9 ± 0.5</td>
</tr>
<tr>
<td>C(_6)F(_6)</td>
<td>1.4</td>
<td>11.22 ± 0.4</td>
</tr>
<tr>
<td>CH(_3)CN</td>
<td>1.0</td>
<td>29.5 ± 0.7</td>
</tr>
<tr>
<td>CH(_3)OH</td>
<td>3.1</td>
<td>29.9 ± 1.3</td>
</tr>
<tr>
<td>CF(_3)CH(_2)OH</td>
<td>7.8</td>
<td>18.1 ± 1.9</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>206</td>
<td>0.027 ± 0.005</td>
</tr>
</tbody>
</table>

\( ^a \) Rations of second order rate constants. \( ^b \) 25°C

References

10 (a) Filler, R. In Fluorine-Containing Molecules, Liebman, J. F.; Greenberg, A.; Dolbier, W. R. Jr., Eds.; VCH:
References
4

Strategies for the Recovery of Fluorous Catalysts and Reagents: Design and Evaluation

J. A. Gladysz and Rosenildo Corrêa da Costa

4.1

Introduction; Basic Recycling Concepts

This chapter summarizes various approaches to recovering and recycling fluorous catalysts and reagents. A “process chemistry” standpoint is emphasized, as opposed to a “discovery chemistry” standpoint, where the rapid screening of a library of fluorous catalysts might be a goal. In addition, methods by which catalyst recovery can be quantified are analyzed. For exploratory work on recyclable catalysts and reagents to be meaningful, some type of recovery data are essential. Too frequently, only product yields are provided, which can be very misleading as exemplified below.

Chemists often only loosely distinguish between a catalyst precursor and the active catalyst. The former is introduced at the beginning of a reaction, and one or more steps are often needed to enter the catalytic cycle. This is particularly true for transition metal-based catalysts, for which initial ligand dissociation would be typical. Some catalyst precursors exhibit induction periods. This generally reflects some fundamental and irreversible change that must occur before entering the cycle. Regardless, it is always the catalyst rest state that is being recycled. Only in certain cases, such as for some simple Brønsted or Lewis acid/base catalysts, will this be identical with the catalyst precursor.

Thus, any property being exploited for catalyst recovery must be associated with the rest state. This can make for a “moving target”. Just like an equilibrium mixture of keto/enol tautomers, catalysts may have a distribution of rest states. Furthermore, the rest state present after the limiting reactant has been consumed, such as in a batch reactor, may be different from the rest state present in a continuous reactor. Thus, the partition coefficient, solubility, or other key property of the catalyst precursor may be substantially different from that of the species being recovered. Accordingly, rational design can carry an investigator only so far, and intuition and luck play intrinsic roles.

The situation is analogous but experimentally simpler for recoverable reagents. Here, the properties of the spent reagent or coproduct are critical to recycling. In most cases, these can be measured directly. Since a spent reagent or coproduct would be recovered analogously to a catalyst, most of the examples in the following sections involve catalysts.
4.2 Fluorous/Non-Fluorous Liquid/Liquid Biphase Catalysis

This protocol, introduced in Chapter 1 and Figure 1-1 [1], is represented in slightly expanded form in Figure 4-1, sequence A. The non-fluorous solvent is nearly always an organic solvent. Reaction can be conducted at the high-temperature one-phase limit (sequence A-I), or if sufficiently rapid, at the lower temperature two-phase limit (sequence A-II). In the early days of fluorous chemistry, it was not uncommon for researchers to design for the former, only to find that reactions were rapid below the mixing temperature of the solvents [2].

Fluorous/non-fluorous liquid/liquid biphase catalysis has also been used in an inverse sense. In this case a non-fluorous catalyst is employed to effect conversions of molecules with high fluorous phase affinities [3]. The catalyst is then recovered from the upper organic layer, and the products from the lower fluorous layer. In either variant, the use of CO₂ pressure as a non-thermal “miscibility switch” (Chapter 3.6 and Table 3-5) [4] is certain to see use in the future. In all cases, some knowledge of the partition coefficients is necessary to optimize product isolation and catalyst recovery.

4.3 Fluorous Catalysis in Amphiphilic or Hybrid Solvents

As described in Chapter 3, there are a few amphiphilic solvents that can dissolve appreciable quantities of both fluorous and organic solutes. In these cases, reactions can be run under homogeneous, one-solvent conditions as shown in Figure 4-1, sequence B. However, additional manipulations are required to effect catalyst/product separation. One approach is to remove the amphiphilic solvent and add an organic or fluorous solvent to extract the product or catalyst (sequences B-1 and B-2). In many cases, the direct addition of an organic and a fluorous solvent to the reaction mixture will give a biphasic system that can be worked up as in sequence A.

The fluorous tin hydride HSn[(CH₂)₂R₆]₃ has been used to showcase these protocols [5]. Reactions with adamantyl bromide in CF₃C₆H₅ give adamantane and the tin bromide BrSn[(CH₂)₂R₆]₃, which is easily recovered and recycled. A catalytic variant that uses NaCNBH₃ and the cosolvent t-BuOH has been developed. Not all of the NaCNBH₃ dissolves, but the reaction mixture becomes homogeneous and a triphasic aqueous/CH₂Cl₂/CF₃C₆F₁₁ workup efficiently separates the inorganic products, adamantane, and fluorous tin hydride catalyst.

4.4 Fluorous Catalysis Without Non-Fluorous Solvents

There is intense current interest in reducing and/or eliminating the need for reaction solvents. In this context, several variations on sequence A of Figure 4-1 deserve emphasizing. As shown in sequence C, the non-fluorous solvent can be omitted in the case of liquid
Fig. 4-1. Strategies for the recovery of fluorous catalysts $R_f$–catalyst–$R_f$
reactants and products. The product is simply decanted or removed by syringe. Traces of product that adhere to or remain dissolved in the fluorous phase can be carried through subsequent cycles. In cases where an exact yield for each cycle is required, an organic solvent can be added to extract the residual product.

Photographs of a specific example, an alkene hydroboration catalyzed by the fluorous rhodium complex ClRh{P[(CH₂)₂Rf₆]}₃ [1; Rf₆ = (CF₂)₅CF₃] and conducted under two-phase conditions, are shown in Figure 4-2 [2]. This catalyst system exhibits an induction period on the first cycle, but not on subsequent cycles [6]. ICP-AES (inductively coupled plasma atomic emission spectrometry) measurements indicate rhodium losses of 0.4% per cycle, or (under the conditions employed) 4.5 rhodium atoms per million product molecules. For the still more fluorophilic catalyst with Rf₈ ponytails, rhodium losses decrease to 0.2% per cycle or 2.2 rhodium atoms per million product molecules.
4.5 Fluorous Catalysis Without Fluorous Solvents

4.5.1 Thermomorphic Catalysts

An obvious counterpart to sequence C in Figure 4-1 is to eliminate the fluorous solvent, which is commonly much more expensive than the non-fluorous solvent. Many fluorous compounds with \( R_{10} \) and \( R_{10} \) ponytails are low melting solids or waxes with little or no solubilities in non-fluorous solvents at room temperature. Accordingly, it was proposed that the same factors that give rise to highly temperature dependent fluorous/organic liquid/liquid phase miscibilities might also give rise to highly temperature dependent fluorous/organic solid/liquid phase miscibilities [7]. A catalyst or reagent with a highly temperature-dependent property, such as solubility, is said to be **thermomorphic**. However, above the
melting point of the catalyst or reagent, the issue again becomes one of liquid/liquid miscibility.

These considerations led to the development of the one-liquid-phase protocol in sequence D-I of Figure 4-1 [7]. Here a fluorous catalyst is simply suspended in an organic solvent containing the reactants. The system is warmed, dissolving the fluorous catalyst to achieve one-phase reaction conditions. Subsequent cooling precipitates the catalyst, and catalyst/product separation is achieved by a simple solid/liquid phase separation. Analogously to sequence A of Figure 4-1, there is also the possibility that reaction can proceed rapidly at the low temperature biphasic limit (sequence D-II), where only traces of the catalyst might be dissolved.

Since this newer protocol is only treated in one other chapter (10.18), the current literature is briefly reviewed here. One of the first applications involved phosphine-catalyzed conjugate additions of the type shown in Scheme 4-1A [7]. Good evidence was available that the dominant catalyst rest state for such additions was the starting phosphine. The fluorous phosphines \( P[(CH_2)_2R_{18}]_3 \) (2a) and \( P[(CH_2)_1R_{18}]_3 \) (2b) were utilized, and solubilities as a function of temperature in the reaction solvent \( n \)-octane are shown in Figure 4-3. Note that
Scheme 4-1. Examples of sequence D in Figure 4-1; recovery of fluorous catalysts via liquid/solid phase separations [7–11]
Photographs of a typical cycle are given in panels A–C of Figure 4-4. After reaction under homogeneous conditions at 65 °C (panel B), catalyst/product separation was effected by syringe at −30 °C. From the solubility data in Figure 4-3, less than 0.33% of the catalysts 2a,b should leach under the workup conditions. Some catalyst discoloration is evident (panel C). The rates decrease by ca. 10%/cycle, and recovery data are presented in Section 4-7 below.

The solubilities of 2a,b increase less dramatically with temperature in the more polar solvents toluene, chlorobenzene, and dioxane. Nonetheless, concentrations identical to those used in Scheme 4-1A and Figure 4-4 can be achieved at 65 °C. The critical point for this recovery protocol is not a high solubility at the high-temperature limit, but a miniscule solubility at the low-temperature limit. When solubility does prove to be limiting, an obvious fix is to employ a more active catalyst. For example, 2b is much more active than 2a due to electronic effects, which are treated in Chapter 5.

Similar protocols have been applied to other classes of catalytic reactions, and representative examples are shown in Scheme 4-1B–E. Examples B–D involve simple transformations of organic carbonyl compounds, and fluorous Brønsted (3, 5) or Lewis (4) acids that could logically represent catalyst rest states [8–10]. Example E involves the novel polyoxometalate salt [[Rf8(CH2)3]12NCH3]12[WZn3(H2O)2(ZnW9O34)2] (6), which features twelve fluorous ammonium cations [11]. The salt is insoluble in ethyl acetate (and toluene) at room temperature, but dissolves at 80 °C to give an effective catalyst system for the oxidation of al-
kenes and alcohols by 30% aqueous H₂O₂. Cooling precipitates the catalyst, which is reused. No ponytails are detected by ¹⁹F NMR (nuclear magnetic resonance) in the product phase.

The fluorous stannyl hydride HSn[(CH₂)₂Rf₁₀]₃ has also been used as a catalyst in a radical chain addition and recovered via a solid/liquid phase separation [12]. This process used the amphiphilic solvent CF₃C₆H₅ and a stoichiometric amount of NaCNBH₃, as described for a similar reaction in Section 4.3. Microwave heating was also employed. This is probably the earliest example of fluorous catalyst removal from a reaction mixture via precipitation.

In one case in Scheme 4-1, a fluorous solvent was used to extract the precipitated catalyst, and any residual dissolved species (reaction C). This leads to the question of how such catalysts might be efficiently recovered from smaller-scale reactions when loadings are modest and/or only a few milligrams of catalyst are involved. One solution is to use supports. This is treated in Section 4.7, together with additional fluorous catalysts that are probably thermomorphic but have only been applied in the presence of supports.

The absolute solubilities of fluorous molecules can be tailored by varying the length of the Rᵣᵣ segments [13]. As these become longer, the poor solubility characteristics of Teflon are increasingly imparted. Hence, this protocol promises to have broad applicability. In the case of fluorous reagents, the solubility of the spent reagent or coproduct is the critical factor.

Fig. 4-3. Solubilities of fluorous phosphines in n-octane as a function of temperature. ◆ P[(CH₂)₂Rf₆]₃ (2a); ■ P[(CH₂)₃Rf₈]₃ (2b) [7]
for recovery. The catalytic sequence is best suited for reactions normally conducted at elevated temperatures, and insoluble byproducts such as inorganic salts potentially complicate workup. Several types of polymer-bound catalysts with temperature dependent solubilities have been developed. However, fluorous compounds are the first broad class of nonmacromolecular catalysts for which this strategy appears to be generally applicable.
4.5.2 Other Approaches

Fluorous compounds have recently been shown to have greatly enhanced solubilities in hydrocarbons when pressurized with 20–70 bar (atm) of CO₂ gas [14a], as exemplified by the procedure in Chapter 11.45. This phenomenon is conceptually related to the superior solubilities of fluorinated solutes in liquid and supercritical CO₂. Some compounds that are absolutely insoluble (for example, deeply colored species) dissolve readily. One example is the dirhodium tetracarboxylate \( \text{Rh}_2(\text{O}_2\text{C}R_9\text{C})_4(\text{MeOH})_2 \). At least 64 mg can dissolve in 5 mL of cyclohexane under 43–59 bar. In the absence of gas expansion of the solvent volume, which is considerable, the solution would be 0.0055 M. When the pressure is released, quantitative precipitation occurs.

This procedure constitutes a non-thermal solubility “switch”, and could obviously be applied to a catalyst recovery protocol analogous to that in sequence D of Figure 4-1. It would be possible to conduct reactions at room temperature, and thermally labile educt, products, or catalysts could be employed. Progress towards these ends has been reported at conferences, and it is only a matter of time before a successful demonstration appears in the literature [14b].

As this book was going to press, the fluorous nickel acac complex \( \text{Ni}[R_{16}\text{C(O)}\text{CHC(O)}R_{16}]_2 \) was reported to catalyze the condensation of \( \beta \)-diketones with ethyl cyanoformate [15]. This complex is soluble in dichloromethane, and could be used under homogeneous conditions at room temperature and 1 mol% loadings. It could be recovered by a solid phase extraction using fluorous silica gel and dichloromethane as the eluent. This technique, which is often implemented on a column, is detailed in Chapter 7. Within the hierarchy of Figure 4-1, this protocol most closely resembles sequence B, since the fluorous catalyst must have reasonable solubility in an organic or amphiphilic medium. However, the recovery method is unique.

4.6 Fluorous Catalysis Without Solvents

One holy grail in chemistry is to eliminate solvents altogether. In principle, solvent-free protocols should be possible with fluorous catalysts as illustrated in sequence E of Figure 4-1. The organic reactants and product must be liquids, analogous to sequence C. The fluorous catalyst must be essentially insoluble at the low temperature limit, analogous to sequence D. Either higher temperature one-phase conditions, or lower-temperature two-phase conditions, can in theory be employed.

This protocol has so far been applied (in the absence of supports as described in the following section) to a single reaction, the phosphine catalyzed addition in Scheme 4-1A. The results were excellent, surpassing those obtained with sequence D-I [7]. However, since an exact yield for each cycle was sought, the product was extracted from the catalyst residue with \( n \)-octane. In principle, the residual product could have equally well been carried through the next cycle. Such material would ultimately be recaptured in the final cycle (if not earlier).
4.7 Recovery of Fluorous Catalysts using Supports

An ongoing goal in catalysis research is to minimize the amount of catalyst required. How might very small quantities of fluorous catalysts be efficiently recovered from sequences D and E of Figure 4-1? One approach is to use a solid support to increase the mass, as shown schematically in sequence F-I of Figure 4-1. At one extreme, the support could be inert, with only a mechanical function. At another level, the support might provide physical adhesion—for example, for a waxy or gum-like catalyst. At yet another level, the support might provide attractive interactions that would enhance recovery. As noted in Chapter 3, attractive interactions between saturated fluorocarbons are small, but could nonetheless be brought into play.

This support-based approach was first tested with the phosphine catalyzed reaction in Scheme 4-1A, using Teflon shavings [7]. A picture of the reaction sequence is shown in panels D–F of Figure 4-4. Importantly, the catalyst residues became more firm and compact, suggestive of physical adhesion. The total phosphorus recovery was 97.4%, as assayed by $^{31}$P NMR. This corresponded to an 85.2% recovery of 2a, and 12.2% of other species, some of which may represent alternative rest states. The total ponytail recovery was 97.9%, as assayed by $^{19}$F NMR. Examination of the product fraction showed 2.3% ponytail leaching (100.2% mass balance). In the absence of Teflon shavings, this increased to 7.1%.

Supports were next applied to Suzuki and Sonogashira coupling reactions with the palladium fluorous phosphine catalyst precursors 7a,b and 8 depicted in Scheme 4-2A [16]. Complexes 7a,b and 8, which are soluble in ether/C$_6$F$_6$ and CHCl$_3$/C$_6$F$_6$ mixtures, were first absorbed onto the fluorous silica gel supports 9 or 10. Owing to the presence of both fluorous and non-fluorous domains, such supports are probably capable of stronger attractive interactions with many fluorous molecules than Teflon. Reactions were conducted at 80–100°C in dimethoxyethane with 0.001–2 mol% palladium. The mixtures were cooled to 0°C and the support was removed and further extracted. Palladium leaching was as little as 1.9–1.6% per cycle. Additional details are provided in Chapters 10.8.2.4 and 10.8.2.5, and experimental procedures are detailed in Chapters 11.7 and 11.8. It is not yet known whether the active catalyst desorbs from the support and reacts in solution (sequence F-I of Figure 4-1), or remains bound (sequence F-II). The latter is conceptually similar to the biphasic reaction conditions in sequences A-II, C-II, and D-II. However, the former scenario has recently been demonstrated for a fluorous rhodium catalyst under CO$_2$ pressure [14b].

As shown in Scheme 4-2B, the fluorous dirhodium tetracarboxylate 11 has been absorbed from a hot toluene solution onto fluorous silica gel [17]. ICP-AES analysis of the supernatant and washings (room temperature) showed only 14% of the original rhodium charge in unbound form. This system catalyzes the silylation of alcohols by trialkylsilanes. The authors suggested that the catalyst remains embedded in the fluorous silica gel, and termed the procedure “bonded fluorous phase catalysis”. Importantly, the best results were obtained under solvent-free conditions. The rhodium loss was 2.5–2.6% per cycle, and the activity loss about 10%, as determined by turnover frequency (TOF) measurements. A homolog of 11 with R$_{f1}$ groups was also prepared and studied.

Similar protocols have also been applied to stoichiometric syntheses of fluorous molecules. As depicted in Scheme 4-3, the fluorous benzylic alcohol 12 was absorbed onto
fluorous silica gel, and used as a protecting group for parallel syntheses of quinazoline-2,4-diones [18]. The detached protecting group remained absorbed and could be recycled. The overall procedure was termed “fluorous solid-phase organic synthesis” (FSPOS). Although control experiments clearly established the importance of the fluorous interactions, the data do not seem to exclude the reactions from occurring in solution. However, this point is only
of importance with respect to the classification of this successful methodology. As practiced, the individual steps conceptually resemble fluorous solid phase extractions, and this subject is treated in Chapter 7.

### 4.8 Criteria for Recoverability

The quantitative evaluation of recycling efficiency is critically important for all recyclable catalysts. Unfortunately, there is much substandard work in the literature. The following sections illustrate some of the more common pitfalls, as well as tips that can help with fluorous catalysts.

#### 4.8.1 Yield as a Function of Cycle

Almost without exception, papers describing recyclable catalysts report these values, and/or equivalent turnover numbers (TON). However, product yield as a function of cycle is a poor criterion for recoverability. The time selected for the cycles is often arbitrary. Suppose each cycle is allowed to run overnight (16 h). Consider a case where the reaction is in fact complete after 0.5 h. Also, assume that half the catalyst is lost in the first recycling operation. Product formation in cycle 2 would then be complete after 1.0 h (given reasonable rate law assumptions, no higher-order catalyst effects, etc.). Suppose that half the catalyst is lost in each succeeding cycle. No major yield deterioration would be noted until cycle 7, despite the recurring losses! However, if reaction rates or turnover frequencies (TOF) are assayed, the loss of activity becomes glaringly apparent in the second cycle.

#### 4.8.2 TOF as a Function of Cycle

As mentioned in the preceding example, this is a telling measurement but is absent in the majority of papers involving catalyst recycling. Rate data or conversion vs. time plots which
are constant or nearly so as a function of cycle represent good evidence for efficient catalyst recovery. With systems that give induction periods, comparisons between the second and third (and subsequent) cycles are more meaningful than between the first and second cycles. In any event, a high retention of activity requires a high level of catalyst recovery. A high maintenance of yield levels is a necessary but not sufficient criterion for retention of activity.

4.8.3 Catalyst Inventory

In the next level of analysis, the challenge is to “inventory” the fate of the initial catalyst charge. Key quantities include the amounts of: (1) catalyst rest state recovered; (2) catalyst precursor recovered; (3) decomposed catalyst recovered; (4) catalyst rest state leached; (5) catalyst precursor leached; (6) decomposed catalyst leached.

These measurements can be experimentally demanding, as very small quantities are often involved. Also, the spectroscopic properties of the catalyst rest state may not match those of the well-characterized catalyst precursor. Furthermore, consider atomic absorption/emission spectroscopies, which are frequently used to quantify total metal recovery and leaching. Such techniques do not distinguish between quantities such as leached catalyst rest states and leached decomposed catalysts. Subsequent catalyst optimization depends very much upon which of these two pathways dominates: the former requires a more fluorophilic catalyst, and the latter a more stable catalyst.

With some metal-based fluorous catalyst precursors, a fluorous ligand must dissociate before the system can enter the catalytic cycle. In a good number of these cases, this sacrificial ligand has no further role, but might leach to some degree and be detected in certain analyses; further complicating interpretation. With regard to such questions, $^{19}$F NMR can very easily be used to measure “total ponytail” leaching or recovery, as described for experiments associated with Scheme 4-1A above. All ponytails that terminate in an $R_f$ group with $n \geq 4$ give identical chemical shifts for the terminal CF$_3$ group (Chapter 5.3). The $^{19}$F nucleus is easy to detect at low concentrations, and the signal can be integrated against an internal standard [7b].

4.9 Slanting Data: How to Make a Non-recoverable Catalyst Appear Recoverable

An example from the authors’ laboratory records shows how easy it is to obtain an incorrect picture of catalyst recoverability from yield data. The fluorous palladacycle 13 in Scheme 4-4 was evaluated as a catalyst in the Heck reaction, with recovery by sequence D in Figure 4-1, or variations thereof [19]. Screening experiments were conducted at somewhat high catalyst loadings for a Heck reaction (0.5 mol%). Good yields were maintained over eight cycles, an impressive number, and in two separate runs as summarized in Scheme 4-4. Fortunately, there was not a rush to publish this data immediately.

The exceptionally talented graduate student involved was well aware of the pitfalls outlined above. Experiments were next conducted at lower loadings, and yields deteriorated over just 2–3 cycles. Rate measurements confirmed the loss of activity, and showed induction periods for every cycle (not just the first). Additional experiments showed that the palladacycle 13 simply acted as a slow steady state-source of palladium nanoparticles (unfortunately,
non-fluorous), which were the active catalysts. Only the remaining palladacycle was recycled, and when it was exhausted, activity ceased.

In conclusion, many projects involving recoverable catalysts have an “all or nothing” success aspect. A grant renewal or Dissertation may hang in the balance, and there may in some cases be a tendency not to probe the catalytic system or data such as in Scheme 4-4 too deeply. A higher catalyst loading for a reaction that is feasible at much lower catalyst loadings can be a danger sign [20]. Thus, experienced researchers maintain a skeptical eye, and one that is also appropriately focused upon claims in fluorous catalysis.

4.10 Prospects

Consider in retrospect the various recycling protocols in Figure 4-1. Excellent catalyst recoveries have been obtained with sequence A, which utilizes a fluorous solvent, for commodity chemical processes [21]. However, from solvent cost considerations alone, large scale commercial applications are not likely to be developed. Nonetheless, smaller scale applications of fluorous/non-fluorous liquid/liquid biphasic catalysis have a bright future, as exemplified in other Chapters in this Handbook.

Sequences D–F of Figure 4-1, which do not rely on fluorous solvents, are poised for rapid growth. Furthermore, the variants in Figure 4-2 and Schemes 4-2 and 4-3 emphasize that homogeneous conditions are by no means essential for fluorous chemistry. The key point is that the reaction should be rapid, high-yielding, and convenient to execute, and not whether

Scheme 4-4. A non-recyclable catalyst made to appear recyclable

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conversion (%)</td>
<td>yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>98</td>
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<tr>
<td>4</td>
<td>94</td>
<td>83</td>
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<tr>
<td>5</td>
<td>91</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>56</td>
</tr>
</tbody>
</table>

(recovered as bridging iodide by precipitation/C8F17Br extraction)
one- or two-phase conditions apply. Finally, the use of fluorous greases or low-melting fluorous solids or polymers, which were briefly mentioned in Chapter 3, appear to present highly attractive non-liquid phases for the reversible entrainment and release of catalysts.

Process development has been an extremely active theme during the first decade of fluorous chemistry. This chapter has systematized the diverse strategies that have been applied to the recovery of fluorous catalysts and reagents, and helped to standardize the methods by which they are evaluated. The upcoming decade is certain see the continued refinement of the protocols outlined above, such as the use of CO2 pressure as a miscibility and solubility switch [4, 14], as well as the development of new approaches.

References

1 Horváth, I. T.; Rábai, J. Science 1994, 266, 72.
20 Although many possible examples could be given, a relevant recent report is as follows: Lin, C.-A.; Luo, F.-T. Tetrahedron Lett. 2003, 44, 4565 (2% loadings were used to test the recoverability of a polystyrene-supported palladacycle).
5
Ponytails: Structural and Electronic Considerations

J. A. Gladysz

5.1 Introduction

The loose distinction between ponytails, fluorous tags, and fluorous labels was discussed in Chapter 1. All of these can be viewed as tuning elements. Their primary function is to control the fluorous phase affinity of the parent molecule. In some cases a very high fluorous phase affinity is sought, and in others only a moderate one. Partition coefficients help guide ponytail design, and are presented in Chapter 6. The key variables are the length and number of the perfluoroalkyl or Rfn segments \([Rfn = (CF_2)_{n-1}CF_3]\).

Ponytails are permanently affixed. Therefore, they can serve a secondary function of modulating the electronic properties of the fluorous catalyst or reagent, which often acts as a Lewis base or acid. Consider a ponytail of the formula \((CH_2)_mRfn\). By adjusting the number of methylene groups or spacers, \((CH_2)_m\), the Lewis basicity or acidity of the active site can be tuned. High m values will give properties similar to those of non-fluorous analogs, whereas low m values will give reduced Lewis basicities or enhanced Lewis acidities. Phenyl rings or heteroatoms can also be used, alone or in combination with methylene groups, to insulate the active site from the perfluoroalkyl groups. The tuning of these electronic effects represents a major theme of this chapter.

However, other tuning functions of ponytails are certain to become of increasing importance. For example, how are solubilities, melting points, and other physical properties affected by the ponytail structure? Are there motifs that promote biodegradability? Such issues are of both fundamental and practical interest, and extend into materials applications of fluorous compounds (liquid crystals, gelators, etc.).

5.2 Structural Aspects of Ponytails

The overwhelming majority of ponytails in current use have the formula \((CH_2)_mRfn\). The Rfn segment should consist of at least six carbons (Rf6). Smaller segments (particularly trifluoromethyl groups) are sometimes called pigtails. These can, in the presence of Rf6 or longer segments, have appreciable affects upon fluorophilicities. Examples are provided in Chapter 6. In principle, heteroatoms such as oxygen can be incorporated within the Rfn seg-
ment. Although only a few such systems are known [1], this represents an attractive direction for future research.

Assemblies in which branching occurs in the aliphatic segment have been reported [2–4]. Some examples are collected in Figure 5-1 (1–7). A group of the formula (CH₂)ₙCH[(CH₂)ₘRᶠₙ]₂ (see 1–4) is “doubly branched” and is sometimes termed a “split ponytail”. However, it is probably better viewed as consisting of two ponytails. A “tripyly branched” group of the formula (CH₂)ₙC[(CH₂)ₘRᶠₙ]₃ (see 6–7) would normally be viewed as consisting of three ponytails. There is not yet enough data to know whether such systems have any special or superior properties, but there are interesting possibilities. More work needs to be done on general synthetic routes to such compounds.

Ponytails in which branching occurs in the perfluoroalkyl segment would similarly be of interest. Such systems are extremely rare, but the triarylpophile 8 in Figure 5-2 constitutes one example [5]. The C(CF₃)₂CF₂CF₄ unit is conveniently generated via the addition of CsF to the alkene (CF₃)₂C=CFCF₂CF₃, which gives a carbanion that reacts with benzyl bromides. Heteroatoms can also serve as branch points, such as silicon in the benzyl protecting group 9 [6] or the phosphines 10b,c [7]. Most workers would regard the silicon substituent in 9 and 10c as having three ponytails, but the branched C₆F₁₃ moiety in 8 as one.

The “spacer” consists of the entire sequence of atoms between the Rᶠₙ moiety and the chemically active site of the reagent or catalyst. Therefore, this includes the arene rings in 8.
and 10, as well as the additional methylene groups in benzyl bromides 7 and 9. Spacers may contain heteroatoms such as oxygen and nitrogen, or the silicon atoms in 9 and 10. Ponytails that contain alternating spacer/fluorous/spacer/fluorous segments, involving moieties such as -C(CF₃)₂OCH₂Rf₇ and -C(CF₃)₂O(CH₂)₃Rf₈, are beginning to appear (raccoon tails?) [8]. Other directions for the design of novel pony tails, as well as classification systems, have been proposed [8].

If ponytails have an “Achilles’ heel”, it is a tendency for HF elimination across CH₂CF₂ junctions [9]. Thus, strong bases are avoided in certain series of compounds. Alternatively, the spacer or perfluoroalkyl segment can be modified so that HF elimination is impossible, as exemplified by 8.

5.3 NMR Characterization of Ponytails

When the characterization of fluorous molecules is reported in the literature, it is not uncommon to find NMR data for the non-fluorous portion, but no NMR data for the fluorous portion. Typically there are a multitude of ¹³C and ¹⁹F signals that are not, individually at least, very informative. Table 5-1 summarizes assignments that were carefully made for the fluorous phosphine P[₃₃₃₃₃₃p₃₄₅₆₇₈₉]ₙₐₖ, a lower homolog of 10a in Figure 5-2 [7a], and the fluorous tertiary amine N[(CH₂)₃Rf₈]ₙₐₖ [10]. Extensive series of 2D NMR experiments were necessary.

In both cases, all ¹⁹F NMR signals except for those for the two carbons at the end of the ponytail (CF₂CF₂) and the one at the beginning (CH₂CF₂) are clustered in a narrow 1–2 ppm range. The corresponding ¹³C NMR signals are spread over a 1 ppm range. When such data are critical for a structure proof, ¹³C NMR spectra that are simultaneously ¹H– and ¹⁹F– decoupled (i.e., ¹³C(¹H,¹⁹F) spectra) can be especially informative [10]. Such experiments require an appropriately configured triple-resonance probe.

5.4 Electronic Effects: Introduction

From the standpoint of fluorous catalyst and reagent design, it is important to know how to insulate the reactive center from the electron withdrawing perfluoroalkyl groups. With
ponytails of the formula \((\text{CH}_2)_n\text{R}_\text{f}\), this becomes a question of the number of methylene groups. There are many sensitive probes of electronic effects, and as described in the following sections, a surprisingly large number of methylene groups are required.

There is a parallel question of the length of an \(\text{R}_\text{f}\) segment needed to exert a maximum electron withdrawing effect. Computational studies with \(\text{P}[(\text{CH}_2)_2\text{CF}_3]_3\) and

---

### Tab. 5-1. Representative \(^{19}\text{F}\) and \(^{13}\text{C}\) NMR data for \((\text{CH}_2)_n\text{R}_\text{f}\) groups [7a, 10]

<table>
<thead>
<tr>
<th>(^{19}\text{F}) ((\delta))</th>
<th>(^{13}\text{C}) ((\delta))</th>
<th>(J_{\text{X,Y}}) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2C</td>
<td>5.62</td>
<td></td>
</tr>
<tr>
<td>CH2</td>
<td>26.6 (t)</td>
<td></td>
</tr>
<tr>
<td>(\varepsilon) F2C</td>
<td>-115.8 (qm)</td>
<td>119.3 (tt)</td>
</tr>
<tr>
<td>(\beta) CF2</td>
<td>-123.3 (m)</td>
<td>112.3 (tquint)</td>
</tr>
<tr>
<td>(\gamma) CF2</td>
<td>-122.2 (m)</td>
<td>112.1 (tquint)</td>
</tr>
<tr>
<td>(\delta) CF2</td>
<td>-123.2 (m)</td>
<td>111.3 (tquint)</td>
</tr>
<tr>
<td>(\epsilon) F2C</td>
<td>-126.5 (m)</td>
<td>109.4 (tm)</td>
</tr>
<tr>
<td>(\zeta) CF3</td>
<td>-81.4 (t)</td>
<td>118.1 (qt)</td>
</tr>
</tbody>
</table>

\(J_{\text{F,F}} > J_{\text{F,H}}\) in accord with much precedent; the \(\text{R}_\text{f}\) homolog 10a gives (1) additional \(^{19}\text{F}\) signals that are not resolved from the \(\gamma\)-CF2 signal (122.2 (m)) (2) additional \(^{13}\text{C}\{-^{19}\text{F}\}\) signals at \(\delta\) 111.8 and 111.7

<table>
<thead>
<tr>
<th>(^{19}\text{F}) ((\delta))</th>
<th>(^{13}\text{C}) ((\delta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53.5</td>
</tr>
<tr>
<td>CH3</td>
<td>19.0</td>
</tr>
<tr>
<td>CH2</td>
<td>29.4</td>
</tr>
<tr>
<td>F2C</td>
<td>-113.9</td>
</tr>
<tr>
<td>CF2</td>
<td>-123.5</td>
</tr>
<tr>
<td>F2C</td>
<td>-121.2</td>
</tr>
<tr>
<td>CF2</td>
<td>-122.5</td>
</tr>
<tr>
<td>F2C</td>
<td>-122.5</td>
</tr>
<tr>
<td>CF2</td>
<td>-122.3</td>
</tr>
<tr>
<td>F2C</td>
<td>-125.8</td>
</tr>
<tr>
<td>CF3</td>
<td>-80.8</td>
</tr>
</tbody>
</table>

---
P[(CH2)2CF2CF3]3 indicate only a very slight increase in the vertical ionization potential (VIP) associated with the phosphorus lone pair (9.38 vs. 9.39 eV), and a similarly slight difference in the proton affinity (PA; 207.2 vs 207.8 kcal mol\(^{-1}\)) [11]. Hence, electronic saturation in such systems is probably achieved with only two perfluorinated carbons. Accordingly, the Hammett \(\sigma\) constants associated with CF3, CF2CF3, and CF2CF2CF2CF3 groups are all very close (\(\sigma_p\) 0.53–0.54, 0.52, 0.52; \(\sigma_m\) 0.43–0.46, 0.47–0.50, 0.47–0.52) [12].

However, it is important to pick appropriate model compounds for such comparisons. For example, ionizations become thermodynamically more favorable in the series P(CF3)3/P(CF2CF3)3 (VIP 11.67, 11.37 eV) and P(CH2CF3)3/P(CH2CF2CF3)3/P(CH2CF2CF2CF3)3 (VIP 10.07, 10.02, 10.01 eV). This is presumably due to lone pair/F or Rf/C0 hyperconjugation effects, as discussed elsewhere [11].

5.5 Electronic Effects: IR Data

The fluorous trialkylphosphines P[(CH2)mRf8]3 \((m = 2–5, 12–15)\) have been converted into the iridium carbonyl complexes shown in Table 5-2 (Ir-12 through Ir-15) [13]. An adduct of tri(\(n\)-octyl)phosphine, P[(CH2)7CH3]3, which lacks fluorine atoms, was prepared for reference (Ir-16). IR spectra were measured under identical conditions. As the number of methylene groups \((m)\) increases from two to five, the \(v_{\text{CO}}\) values decrease from 1973.9 to 1946.1 cm\(^{-1}\) (Table 5-2). This indicates progressively more backbonding, consistent with phosphine ligands that are more Lewis basic and less Lewis acidic. However, the values never reach the limit of the non-fluorinated phosphine complex Ir-16 (1942.3 cm\(^{-1}\)), or converge to an alternative limit.

These data show that the electron withdrawing effect of the perfluoroalkyl groups is still felt through five methylene groups, as well as the intervening phosphorus–iridium and

<table>
<thead>
<tr>
<th>Complex</th>
<th>R</th>
<th>IR (v_{\text{CO}}) (cm(^{-1}))</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ir-11</td>
<td>(CH2)2Rf8</td>
<td>1973.6</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-12</td>
<td>(CH2)2Rf8</td>
<td>1973.9</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-13</td>
<td>(CH2)2Rf8</td>
<td>1956.7</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-14</td>
<td>(CH2)3Rf8</td>
<td>1949.2</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-15</td>
<td>(CH2)3Rf8</td>
<td>1946.1</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-16</td>
<td>(CH2)3Rf3</td>
<td>1942.3</td>
<td>C6H5CF3</td>
</tr>
<tr>
<td>Ir-17</td>
<td>p-C6H4(CH2)2Rf8</td>
<td>1958</td>
<td>Nujol</td>
</tr>
<tr>
<td>Ir-18</td>
<td>C6H5</td>
<td>1952</td>
<td>Nujol</td>
</tr>
</tbody>
</table>

Tab. 5-2. IR data for fluorous-phosphine-analogs of Vaska’s complex [13, 14]
iridium–carbonyl bonds. Graphical analyses, such as in Figure 5-3, suggest that seven to eight methylene groups are required for essentially complete insulation (limiting value 1943.7 cm$^{-1}$) [13]. Importantly, the IR (infrared) data reflect the combined effect of six ponytails, affording more resolution than experiments involving compounds with one ponytail. Note also that Ir-$^{11}$ and Ir-$^{12}$, which are identical except in the lengths of the R$_{f_{\alpha}}$ segments, give virtually the same IR $v_{CO}$ value.

A triphenylphosphine complex is included in Table 5-2 (Ir-$^{18}$; Vaska’s complex), together with a fluorous analog with a (CH$_2$)$_3$R$_{f_{8}}$ substituent in the para position of each ring (Ir-$^{17}$) [14]. The latter features seven carbon atoms between the phosphorus and the R$_{f_{8}}$ segment. Nonetheless, the IR $v_{CO}$ value is noticeably higher (1958 vs. 1952 cm$^{-1}$), indicating incomplete insulation. Similar trends have been observed for related rhodium complexes of fluorous triarylphosphines [15, 16].

5.6 Electronic Effects: Gas Phase Ionization Data

The photoelectron spectra of the fluorous phosphines 12–15 have been measured, and the VIP values associated with the phosphorus lone pairs are summarized in Table 5-3 [11]. These exhibit a monotonic decrease from 9.22 to 8.49 eV, indicating progressively more facile ionizations. As indicated by the IR data, the effect of the perfluoroalkyl group is clearly decreasing, but the asymptotic limit is by no means at hand. A graph, which includes computational data described below, is provided in Figure 5-4.

Experimental VIP values of other phosphines are given in Table 5-4, together with computational data described below. That of 14 (8.59 eV) is close to P(CH$_3$)$_3$ (8.58 eV), whereas 15 (8.49 eV) is less readily ionized than P(CH$_2$CH$_3$)$_3$ (8.34–8.28 eV) and P((CH$_2$)$_3$CH$_3$)$_3$ (8.14–8.00 eV). Both 12 and 13 (9.22 and 8.85 eV) are much less readily ionized than any simple trialkylphosphine, with the former between PH(CH$_3$)$_2$ and PH$_2$CH$_3$ (9.08 and 9.70 eV). Hence, 12 and 13 are particularly feeble electron donors.
### 5.6 Electronic Effects: Gas Phase Ionization Data

<table>
<thead>
<tr>
<th>Molecule</th>
<th>VIP (expt)</th>
<th>VIP (calc)</th>
<th>PA (calc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P((CH₂)₂Rf₈)₃ (12)</td>
<td>9.22</td>
<td>9.38</td>
<td>207.2</td>
</tr>
<tr>
<td>P((CH₂)₃Rf₈)₃ (13)</td>
<td>8.85</td>
<td>8.92</td>
<td>217.5</td>
</tr>
<tr>
<td>P((CH₂)₄Rf₈)₃ (14)</td>
<td>8.59</td>
<td>8.67</td>
<td>222.2</td>
</tr>
<tr>
<td>P((CH₂)₅Rf₈)₃ (15)</td>
<td>8.49</td>
<td>8.48</td>
<td>226.5</td>
</tr>
<tr>
<td>P((CH₂)₆CF₃)₃ (12⁻)</td>
<td>9.38</td>
<td>8.38</td>
<td>229.0</td>
</tr>
<tr>
<td>P((CH₂)₇CF₃)₃ (13⁻)</td>
<td>8.92</td>
<td>8.28</td>
<td>231.2</td>
</tr>
<tr>
<td>P((CH₂)₈CF₃)₃ (14⁻)</td>
<td>8.67</td>
<td>8.22</td>
<td>231.2</td>
</tr>
<tr>
<td>P((CH₂)₉CF₃)₃ (15⁻)</td>
<td>8.48</td>
<td>8.17</td>
<td>231.2</td>
</tr>
<tr>
<td>NH₂CH₂CF₂CF₃ (26)</td>
<td>8.38</td>
<td>201.4</td>
<td></td>
</tr>
<tr>
<td>NH₂(CH₂)₂CF₂CF₃ (27)</td>
<td>8.28</td>
<td>207.7</td>
<td></td>
</tr>
<tr>
<td>NH₂(CH₂)₃CF₂CF₃ (28)</td>
<td>8.17</td>
<td>212.1</td>
<td></td>
</tr>
<tr>
<td>NH₂(CH₂)₄CF₂CF₃ (29)</td>
<td>8.08</td>
<td>214.1</td>
<td></td>
</tr>
<tr>
<td>NH₂(CH₂)₅CF₂CF₃ (30)</td>
<td>8.00</td>
<td>215.8</td>
<td></td>
</tr>
<tr>
<td>NH(CH₂)₃(CH₂)₃CF₂CF₃ (31)</td>
<td>8.00</td>
<td>219.5</td>
<td></td>
</tr>
<tr>
<td>N(CH₂)₃(CH₂)₃CF₂CF₃ (32)</td>
<td>8.00</td>
<td>223.8</td>
<td></td>
</tr>
<tr>
<td>NH(CH₂)₃CF₂CF₃ (33)</td>
<td>8.00</td>
<td>218.4</td>
<td></td>
</tr>
<tr>
<td>N(CH₂)(CH₂)₃CF₂CF₃ (34)</td>
<td>8.00</td>
<td>222.6</td>
<td></td>
</tr>
<tr>
<td>N(CH₂)₃CF₂CF₃ (35)</td>
<td>8.00</td>
<td>221.6</td>
<td></td>
</tr>
</tbody>
</table>

*a alternative formatting: CF₃ = R₁₁; CF₂CF₃ = R₁₂.*

---

**Fig. 5-4.** Relationship between VIP (eV) and \( m \) for P((CH₂)ₘRf₈)₃ (12–15, ◇) and P((CH₂)ₘCF₃)₃ (12⁻–19⁻, ▲) as well as extrapolated values for 20⁻–21⁻ (○) [11]
5. Electronic Effects: Calorimetry

The enthalpies of reaction of many amines and phosphines with triflic acid (CF₃SO₃H) have been measured in dichloromethane [17]. The values correlate well with Brønsted basicities in water. The fluorous phosphines 12–15 were similarly studied, but for solubility reasons trifluoromethylbenzene (CF₃C₆H₅) was employed. The resulting enthalpies of protonation are summarized in Scheme 5-1 [11]. The reactions become more exothermic with increasing numbers of methylene groups, in accord with the VIP values.

Experiments with other phosphines show a close correlation between values in CF₃C₆H₅ and CH₂Cl₂ [11]. On this basis (and neglecting standard deviations), the enthalpy of protonation of 12 [−25.5(0.5) kcal mol⁻¹] is between that of P(CH₃)(C₆H₅)₂ and P(CH₃)₂(C₆H₅) [−24.7(0) and −28.4(2) kcal mol⁻¹]. The enthalpies of protonation of 14 and 15 [−31.9(6) and −32.0(3) kcal mol⁻¹] are between those of P(CH₃)₃ and P(CH₂CH₃)₃ [−31.6(2) and

\[
\begin{align*}
\text{P(CH}_2\text{)}_n\text{R}_{\text{Rf8}} \text{H} & + \text{CF}_3\text{C}_6\text{H}_5 \rightarrow \text{[HP(CH}_2\text{)}_n\text{R}_{\text{Rf8}}\text{]}^+ \text{CF}_3\text{SO}_3^- \\
\Delta H_p & (\text{kcal/mol}^{-1}) \\
12 & = -25.5 \pm 0.5 \\
13 & = -31.0 \pm 0.3 \\
14 & = -31.9 \pm 0.6 \\
15 & = -32.0 \pm 0.3
\end{align*}
\]

Scheme 5-1. Enthalpies of protonation of fluorous phosphines [11]

---

Tab. 5-4. Calculated and observed vertical ionization potentials (VIP, eV) for reference non-fluorous phosphines [11]

<table>
<thead>
<tr>
<th></th>
<th>VIP (calc)</th>
<th>VIP (expt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(CH₃)₃</td>
<td>8.57</td>
<td>8.58</td>
</tr>
<tr>
<td>PH₃</td>
<td>10.56</td>
<td>10.85</td>
</tr>
<tr>
<td>PH(CH₃)₂</td>
<td>9.04</td>
<td>9.08</td>
</tr>
<tr>
<td>PH₂CH₃</td>
<td>9.69</td>
<td>9.70</td>
</tr>
<tr>
<td>P(C(CH₃)₃)₂</td>
<td>7.51</td>
<td>7.70, 7.72</td>
</tr>
<tr>
<td>P(CH₂CH₃)₁</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>P(CH₂CH₃)₂</td>
<td>8.27</td>
<td>8.28, 8.34</td>
</tr>
<tr>
<td>P(CH₂CH₃)₃</td>
<td>8.16</td>
<td>8.08</td>
</tr>
<tr>
<td>P(CH₂CH₃)₄</td>
<td>8.04</td>
<td>8.00, 8.14</td>
</tr>
<tr>
<td>P(CH₂CH₃)₅</td>
<td>8.03</td>
<td>8.00</td>
</tr>
<tr>
<td>P(CH₂CH₃)₆</td>
<td>8.01</td>
<td>8.00</td>
</tr>
<tr>
<td>P(CH₂CH₃)₇</td>
<td>7.98</td>
<td>7.98</td>
</tr>
<tr>
<td>P(CH₂CH₃)₈</td>
<td>7.98</td>
<td>7.98</td>
</tr>
</tbody>
</table>

VIP (calc) and VIP (expt) values for reference phosphines.
The $pK_a$ (BH$_+^+$, H$_2$O) values of 12–15 can also be extrapolated from calibration graphs (5.05, 8.08, 8.57, 8.63). That of 15 is close to P(CH$_2$CH$_3$)$_3$ (8.69). In all comparisons, the two methylene groups in 12 again provide a distinctly inferior level of insulation [18].

5.8 Electronic Effects: Solution Equilibria

Substituent effects upon the $pK_a$ values of carboxylic acids have played an immense role in the history of physical organic chemistry. Surprisingly, extensive series of measurements involving fluorous carboxylic acids R$_n$(CH$_2$)$_m$CO$_2$H have not yet been made [19]. Phosphine substitution reactions involving rhodium complexes could be used to show that 13 has a higher Lewis basicity than 12, paralleling other data above [11]. However, better equilibrium data could be obtained with proton transfer reactions of analogous fluorous tertiary amines, N[(CH$_2$)$_m$R$_8$]$_3$(m = 3–5, 23–25) [20]. The results, obtained from NMR chemical shift measurements in CDCl$_3$, are summarized in Table 5-5.

Competitions between N(CH$_2$CH$_3$)$_3$ and 23–25 show progressively increasing protonation of the fluorous amine, consistent with a diminishing inductive influence of the perfluoroalkyl group. Nonetheless, there remains a $\Delta pK_a$(CDCl$_3$) of 1.5–1.9 between the con-

<table>
<thead>
<tr>
<th>$N[R']_3$/$N[R''']_3$</th>
<th>$^+HN[R']_3$ + $N[R''']_3$ + CF$_3$CO$_2$H</th>
<th>$K_{eq}$</th>
<th>$\Delta pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(CH$_2$CH$_3$)$_3$/$N[(CH$_2$)$_3$R$_8$]_3$</td>
<td>100:0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>N(CH$_2$CH$_3$)$_3$/$N[(CH$_2$)$_4$R$_8$]_3$</td>
<td>&gt;95:&lt;5</td>
<td>&gt;361</td>
<td>&gt;2.6</td>
</tr>
<tr>
<td>N(CH$_2$CH$_3$)$_3$/$N[(CH$_2$)$_5$R$_8$]_3$</td>
<td>85–90:10–15</td>
<td>32–81</td>
<td>1.5–1.9</td>
</tr>
<tr>
<td>N[(CH$_2$)$_3$]$_3$/$N[(CH$_2$)$_4$R$_8$]_3$</td>
<td>&gt;95:&lt;5</td>
<td>&gt;361</td>
<td>&gt;2.6</td>
</tr>
<tr>
<td>N[(CH$_2$)$_3$]$_3$/$N[(CH$_2$)$_5$R$_8$]_3$</td>
<td>85–90:10–15</td>
<td>32–81</td>
<td>1.5–1.9</td>
</tr>
<tr>
<td>N[(CH$_2$)$_4$]$_3$/$N[(CH$_2$)$_3$R$_8$]_3$</td>
<td>70–75:30–25</td>
<td>9.0–16</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>N[(CH$_2$)$_4$]$_3$/$N[(CH$_2$)$_5$R$_8$]_3$</td>
<td>40:60</td>
<td>0.44</td>
<td>0.3</td>
</tr>
<tr>
<td>N[(CH$_2$)$_5$]$_3$/$N[(CH$_2$)$_4$R$_8$]_3$</td>
<td>&lt;5:&lt;95</td>
<td>&lt;0.0028</td>
<td>&gt;2.6</td>
</tr>
<tr>
<td>N[(CH$_2$)$_5$]$_3$/$N[(CH$_2$)$_5$R$_8$]_3$</td>
<td>10–15:85–90</td>
<td>0.012–0.031</td>
<td>1.9–1.5</td>
</tr>
</tbody>
</table>
jugate acids of N(CH₂CH₃)₃ and 25, which has five methylene groups. The fluorous amines compete slightly more effectively with the n-dodecyl amine N[(CH₂)₁₁CH₃]₃, which is a better reference base due to the similar number of carbons. Still, a ΔpKₐ(CDCl₃) of 0.9–1.2 remains for 25.

Pairs of fluorous amines were also compared. Competitions between 23 and 24, 23 and 25, and 24 and 25 (Table 5-5) show the expected order for Bronsted basicity. However, an asymptotic limit is clearly not at hand. Counter-intuitively, a greater difference is found between 24 and 25 as compared with 23 and 24. Note that for measurements made in solution, there is always the possibility that some fluorous substances (but not others) might aggregate, giving structures with enhanced thermodynamic stabilities (micelles, gels, etc.). Such non-ideal behavior could lead to non-linear responses to certain probes, non-classical means for transmitting inductive effects, etc. One way to minimize interpretive problems is to conduct measurements over a range of concentrations, and extrapolate to infinite dilution.

5.9 Electronic Effects: Computational Data

The above data clearly indicate that more than five methylene groups are required to insulate the heteroatom in tertiary phosphines or amines of the formula E[(CH₂)mRf₈]₃ from the electron withdrawing perfluoroalkyl groups. The author’s coworkers viewed it as more productive to probe the asymptotic limit via DFT theory than to engage in additional synthesis [11, 21]. Calculations with non-fluorinated reference phosphines were first required. Key results are summarized in Table 5-4, and are in good agreement with experimental data where available. Interestingly, the VIP values of trialkyl phosphines P[(CH₂)mCH₃]₃ show small changes even for m = 7–9, when effective saturation is reached (<0.01 eV or <0.23 kcal mol⁻¹ difference, nonyl vs. decyl).

The fluorous phosphines were modeled with the trifluoromethyl (Rf₁) analogs P[(CH₂)mCF₃]₃ (12’–15’). As summarized in Table 5-3, the calculated VIP values agree very well with those of 12–15, and are depicted on the same graph in Figure 5-4. A good linear relationship (R = 0.98; plotted elsewhere) [11] allows the values computed for the higher model compounds 16’–19’ to be confidently extrapolated to those of the unknown fluorous phosphines 16–19 (predicted, eV: 16, 8.35; 17, 8.27; 18, 8.21; 19, 8.17).

The VIP values for 17’, 18’, and 19’ show differences of 0.06 and 0.05 eV. These are larger than those between P[(CH₂)₆CH₃]₃, P[(CH₂)₇CH₃]₃, and P[(CH₂)₈CH₃]₃, which have the same number of non-fluorinated carbon atoms (0.02 and 0.01 eV; Table 5-4). This indicates a residual inductive effect of the fluorinated segment. The graphical analysis in Figure 5-4 suggests that an effective limit is almost reached with m = 10 (8.14 eV), with further incremental decreases for m = 11 and 12 to a limit of ca. 8.12–8.11 eV. However, the non-fluorinated phosphines in Table 5-4 converge to a still lower limit (7.98 eV). That in Figure 5-4 is between the computed VIP values of P[(CH₂)₆CH₃]₃ and P[(CH₂)₇CH₃]₃ (8.16 and 8.08 eV).

The apparent difference in limiting VIP values crystallizes the question as to what constitutes the best reference molecules for fluorous phosphines P(CH₂)mR₆₈ in which the perfluoroalkyl group is “completely” insulated from phosphorus. This issue can be framed in a different, but perhaps simpler, context: are the electronic properties of a fluorous aryl system
It is possible to sidestep this problem with an alternative probe, homodesmotic exchange reactions [22]. Two series are given in Scheme 5-2. The left side of each equation features a molecule with $\text{CH}_3$ and $\text{CF}_3$ endgroups that are separated by $m$ methylene groups. The right side of each equation features a molecule with phosphorus-atom and $\text{CF}_3$ endgroups that are separated by $m$ methylene groups. The other molecules in the equilibria remain constant. The enthalpies approach a limiting value as $m$ becomes large enough to block out endgroup–endgroup interactions.

With both $\text{P(CH}_2\text{CH}_3)_3$ [Eq. (1)] and $\text{P((CH}_2)_n\text{CF}_3)_3$ [Eq. (2)], the computed enthalpies indicate that seven methylene groups effectively screen the phosphorus atom from the $\text{CF}_3$ moiety. Continuing to eight methylene groups would make a difference of at most 0.1 kcal mol$^{-1}$ (0.0043 eV), a quantity that has a small effect upon equilibrium constants at room temperature. The limiting enthalpies are close to zero, and would be expected to become even closer to zero as the $n$-alkyl group of the phosphine utilized is lengthened.

DFT calculations have also been reported for fluorous amines with $(\text{CH}_2)_m\text{CF}_2\text{CF}_3$ substituents ($m = 1–5$) [10]. The $PA$ values given in Table 5-3 for the primary amines 26–30 show the expected monotonic trend, but as with the analogous tertiary phosphines, an asymptotic limit is clearly not at hand. The $\Delta PA$ values for amines that differ by one meth-
ylene group are one-half to one-third of those of the corresponding tertiary phosphines, which feature three ponytails per heteroatom (e.g., for \( m = 4 \) and 5: 1.7 kcal mol\(^{-1} \) for 29 and 30 vs. 4.3 kcal mol\(^{-1} \) for 14 and 15\(^\dagger \)). Interestingly, the PA value of the fluorous tertiary amine \( \text{N}[\text{(CH}_2\text{)}_3\text{CF}_2\text{CF}_3]_3 \) \((35, 221.6 \text{ kcal mol}\(^{-1} \)) indicates a higher gas phase basicity than the corresponding primary amine \( \text{28} \) (212.1 kcal mol\(^{-1} \)). In other words, a \( \text{(CH}_2\text{)}_3\text{CF}_2\text{CF}_3 \) substituent can stabilize a positively charged ammonium salt more than a proton in the gas phase. However, the basicity is lower than that of the fluorous dimethyl amine \( \text{N}\text{(CH}_3\text{)}_2\text{(CH}_2\text{)}_3\text{CF}_2\text{CF}_3 \) \((32, \text{ PA} 223.8 \text{ kcal mol}\(^{-1} \)).

Computational studies of fluorous triarylphosphines have also been reported [15]. Consistent with the IR data in Table 5-2, the phosphorus lone pair energies calculated with \( p^-\text{(CH}_2\text{)}_3\text{Rf}_{16} \) groups are much lower than those with \( p^-\text{(CH}_2\text{)}_2\text{CH}_3 \) groups (\(-9.2 \text{ vs. } -8.7 \text{ eV}\)).

5.10 Electronic Effects: Reactivity

Effects of ponytails upon reactivity are frequently observed. One example especially relevant to the above data is the phosphine-catalyzed addition in Scheme 5-3 [23]. The first step is a nucleophilic attack of the phosphine on the alkyne linkage of methyl propiolate to give the zwitterion \( \text{I} \). Under standard conditions (n-octane, 65 °C), the fluorous phosphine 12, with two insulating methylene groups, required 1.5 h for complete reaction. The phosphine 13, which with three methylene groups should be more nucleophilic, required less than 15 min. In the same vein, phosphines 12–15 become progressively more air sensitive [14, 24]. Whereas 15 requires rigorous inert atmosphere conditions, 12 survives for several hours as a solid in air.

The primary fluorous iodides I(\( \text{CH}_2\text{)}_m\text{Rf}_{18} \) and similar electrophiles become progressively more reactive in \( S\text{N}2 \) reactions as \( m \) is increased from one to two to three [9b, 13, 24]. The fluorous tin allyls \( \text{H}_2\text{C}=\text{CHCH}_2\text{Sn}[(\text{CH}_2\text{)}_m\text{Rf}_{16}]_3 \) afford much cleaner free radical and platinum-catalyzed allylations when \( m \) is increased from two to three [25]. However, in cases where the fluorous catalyst or reagent functions as a Lewis or Brønsted acid, longer methylene segments decrease reactivity. The same trend is expected for the rates of certain

![Scheme 5-3. Phosphine catalyzed addition of alcohols to methyl propiolate [23]](image-url)
hydrogen-atom-transfer reactions of fluorous tin hydrides [26]. In any event, such rate effects pervade fluorous chemistry. Many reflect the difficulty in fully insulating active sites from the electron-withdrawing perfluoroalkyl segments.

5.11 Electronic Effects: Additional Probes

One recent study featured several probes that are complementary to those described above, and systems in which arene rings help to insulate the perfluoroalkyl groups from the active site [27]. The fluorous and non-fluorous dppe nickel, palladium, and platinum complexes shown in Figure 5-5 were synthesized. The XPS (X-ray photoelectron spectroscopy) spectra were measured, and both the phosphorus [P(2p)] and metal [e.g., Pd(3d5/2), Pd(3d3/2)] binding energies were very similar. Those of the non-fluorous and fluorous silicon-substituted palladium complexes 37b,c and 40b,c which contain the same number of carbon atoms, differed by only 0.0–0.2 eV. This indicates that a \( p-C_6H_4Si(CH_3)_2(CH_2)_2 \) moiety provides a very high degree of insulation.

Cyclic voltammograms of the cationic complexes 39 and 40 showed only irreversible reductions, precluding quantitative comparisons [27]. However, in principle electrochemical \( E^0 \) values represent excellent probes for the electronic effects of ponytails. NMR spectra of the platinum complexes 38a,c exhibited essentially identical \( ^{195}\text{Pt} \) chemical shifts (−4573, −4570 ppm) and \( ^1J_{\text{PP}} \) values (3612, 3604 Hz). Analogous compounds with non-chelating triarylphosphine ligands behaved similarly.

5.12 Electronic Effects: Conclusions

The above data show that it is very challenging to “completely” insulate a reactive site from a perfluoroalkyl group in a fluorous molecule. With ponytails of the formula \( (\text{CH}_2)_mR_{6n} \), there are still readily detectable effects upon lengthening the spacer from four to five methylene groups. The magnitudes are such that solution equilibria can be significantly affected. The computational data in Scheme 5-2 indicate that the asymptotic limit is reached with seven to eight methylene groups, in accord with estimates from the IR data in Table 5-2.

The gas phase ionization potentials in Figure 5-4 suggest a somewhat higher limit. However, it is well known that gas-phase processes in which charge is created are subject to tre-
mendous substituent effects, in which polarizability and size play roles. This is evidenced by the stabilizing effect of a (CH$_2$)$_3$CF$_2$CF$_3$ group relative to a proton upon the basicities of the fluorous amines in Table 5-3. In solution, this substituent-based stabilization is to a significant extent replaced by solvent-based stabilization, dampening certain effects of the ponytail relative to others.

Computational studies have virtually infinite resolution. Thus, a line must be drawn somewhere, i.e., when the calculated difference would no longer have reactivity implications. Even in monofunctional fluorinated compounds of the formula $X(CH_2)_m$CH$_3$ ($m = 4, 5, 11; X = F, CF_3, \text{and non-fluorinated groups}$), there is a clear influence of $X$ upon properties such as atomic charge polarizations, carbon 1s orbital energies, and atomic dipole vectors over the entire carbon chain [28].

Many practicing fluorous chemists roughly calibrate themselves with respect to one or more of the experimental probes summarized above, and fine-tune the ponytails in their systems somewhat intuitively. The bottom line is that the fluorous catalyst or reagent should be convenient and practical, i.e., “reactive enough”, and a small residual electronic effect is for many applications of no significant consequence.

References

1 One recent example and potential building block would be the fluorous primary alcohol CF$_3$(CF$_2$)$_2$OCF(CF$_3$)-CF$_2$OCF(CF$_3$)-CF$_2$OH: Paleta, O.; Paleček, J.; Michálek, J. J. Fluorine Chem. 2002, 114, 51.
9 (a) This point is often masked in the literature because published procedures are optimized to avoid the problem. For example, in Wittig condensations developed in the author’s laboratory that lead to alkenes ArCH$_2$CH$_2$CHR$_n$,$K_2$CO$_3$ is preferred to n-BuLi for generating the ylide. However, excessive reaction times with either base can give detectable HF elimination. (b) Rocaboy, C.; Rutherford, D.; Bennett, B. L.; Gladysz, J. A. J. Phys. Org. Chem. 2000, 13, 596.
References

21 For earlier probes of this point at lower levels of theory, see Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rábai, J.; Mozefiessi, E. J. J. Am. Chem. Soc. 1998, 120, 3133.
22 Georg, P.; Trachtman, M.; Bock, C. W.; Bret, A. M. J. Chem. Soc., Perkin Trans. 2, 1976, 1222. The term homodesmotic denotes reactions in which there are equal numbers of (1) each type of bond in reactants and products, and (2) each type of atom with the same connections in reactants and products.
6
Partition Coefficients Involving Fluorous Solvents

J. A. Gladysz, Charlotte Emnet, and József Rábai

6.1 Introduction

Partition coefficients quantify the equilibrium distribution of a solute between two immiscible phases, which are most often but not necessarily liquids. They see extensive use throughout chemistry, and their thermodynamic nuances have been analyzed in detail [1].

In order to rationally extract non-fluorous products from reactions involving fluorous solvents, partition coefficients for fluorous/non-fluorous liquid/liquid biphasic systems are necessary. The design and optimization of fluorous catalysts and reagents require analogous data. Such partition coefficients constitute a direct measure of fluorophilicity, a term that is used interchangeably with fluorophase affinity.

By 1999, only a few partition coefficients involving fluorous and organic phases had been measured [2, 3]. Now there is a wealth of data, to which sophisticated analysis and parameterization methods have been applied [4–6]. The primary aim of this chapter is to summarize the literature reports, and qualitatively interpret the principal trends. Representative procedures for the determination of partition coefficients are also given.

6.2 Literature Data

Some investigators prefer to express partition coefficients as ratios that have been normalized to 100 (e.g., 98.3:1.7), others as ratios with either the less populated phase or the non-fluorous phase set to 1 (e.g., 57.8:1), and still others as logarithmic values. The abbreviation $P$ indicates a concentration ratio with the non-fluorous phase in the denominator. The natural logarithm of the $\text{CF}_3\text{C}_6\text{F}_{11}$/toluene concentration ratio, $\ln\left(\frac{[c(\text{CF}_3\text{C}_6\text{F}_{11})]}{[c(\text{toluene})]}\right)$, has been given the abbreviation $f$, for fluorophilicity [4].

All partition coefficients measured in the authors’ laboratories can be found in Table 6-1. Most of these involve the solvent system $\text{CF}_3\text{C}_6\text{F}_{11}$/toluene. Many data from other research groups are also included. However, there are undoubtedly inadvertent omissions, for which the authors express their regrets. Since the entries are sorted by functional group, the placement of difunctional molecules is arbitrary. At the end of some sections, cross refer-
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<td>C&lt;sub&gt;10&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;</td>
<td>62.1:37.9</td>
<td>GLC 5</td>
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<td>(P = 1.64)</td>
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<td>II-12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;9&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;9&lt;/sub&gt;Br:C&lt;sub&gt;10&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;</td>
<td>67.5:32.5</td>
<td>GLC 5</td>
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<td>II-13&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;9&lt;/sub&gt;Br:C&lt;sub&gt;10&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;</td>
<td>72.6:27.4</td>
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<td>(P = 2.65)</td>
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<td>II-14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>E-R&lt;sub&gt;15&lt;/sub&gt;CH=CHC&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;</td>
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<td>42.58</td>
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<td>C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;9&lt;/sub&gt;Br:C&lt;sub&gt;10&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;</td>
<td>49.51</td>
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<td>II-16&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>50.0:50.0 (P = 1.00)</td>
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<td>II-18&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>53.1:46.9 (P = 1.13)</td>
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<td>II-19&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>60.0:40.0 (P = 1.50)</td>
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<td>II-20&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>20.80</td>
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<td>44.56 (P = 0.74)</td>
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<td>II-23&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
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<td>II-24&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>40.60 (P = 0.88)</td>
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<td>II-25&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>47.53 (P = 0.38)</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>79.8:20.2 (P = 0.68)</td>
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<td>II-27&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>86.0:14.0 (P = 0.68)</td>
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<td>II-28&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>86.4:13.6 (P = 0.74)</td>
<td>GLC</td>
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<td>II-29&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>77.2:22.8 (P = 0.80)</td>
<td>GLC</td>
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<td>II-30&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>82.0:18.0 (P = 0.80)</td>
<td>GLC</td>
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<td>II-31&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>83.6:16.4 (P = 0.88)</td>
<td>GLC</td>
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<td>II-32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>E-R&lt;sub&gt;6&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>72.5:27.5 (P = 0.95)</td>
<td>GLC</td>
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<td>II-33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;9&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;):C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>76.7:23.3 (P = 0.95)</td>
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<td>II-34&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>79.2:20.8 (P = 0.95)</td>
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<td>II-35&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>71.5:28.5 (P = 1.00)</td>
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<td>78.6:21.4 (P = 1.00)</td>
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<td>E-R&lt;sub&gt;6&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;21&lt;/sub&gt;</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;F&lt;sub&gt;18&lt;/sub&gt;:C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;</td>
<td>54.8:45.2 (P = 1.00)</td>
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<td>II-39&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>63.1:36.9 (P = 1.00)</td>
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<td>Entry</td>
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<td>II-41[^c]</td>
<td>Z-RC=CH⁻:C₁₆H₃₄ 54.1:45.9</td>
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<td>II-42[^c]</td>
<td>(C₄F₉CH⁺)₂⁻:C₁₆H₃₄ 56.7:43.3</td>
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<td>II-43[^c]</td>
<td>C₈F₁₇Br:C₁₆H₃₄ 65.5:34.5</td>
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<td>II-44[^c]</td>
<td>C₆F₁₄([CH₂]₄):CH₃C₆H₅ 55.45</td>
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<td>II-45[^c]</td>
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<td>II-46[^c]</td>
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<td>II-47[^c]</td>
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<td>II-48[^c]</td>
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<td>II-49[^c]</td>
<td>C₆F₁₄([CH₂]₁₀):[(CH₂)₂]₁₀ 86.14</td>
<td>GLC</td>
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for further compounds see XII and XIII

III Ketones and Aldehydes

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<td>cyclohexanone</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>2.2:97.8 (P = 0.022)</td>
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<td>III-2</td>
<td>2-cyclohexen-1-one</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>1.7:98.3 (P = 0.017)</td>
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<td>III-3</td>
<td>R₉(CH₂)₃-C(O)(CH₂)₉</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>84:6:15.4 (P = 5.49)</td>
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<td>R₉(CH₂)₅-CHO</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>98.6:1.4 (P = 73.0[^d])</td>
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IV Alcohols

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<td>CF₃CH₂OH</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>14.5:85.5 (P = 0.170[^d])</td>
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<td>IV-3[^c]</td>
<td>(CF₃)₂CHOH</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>26.7:73.3 (P = 0.364[^d])</td>
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<td>R₉(CH₂)₉OH</td>
<td>CF₃C₆H₅:CH₃C₆H₅</td>
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<td>IV-5[^c]</td>
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<td>CF₃C₆H₅:CH₃C₆H₅</td>
<td>44:56 (P = 0.79[^d])</td>
<td>GLC</td>
<td>8</td>
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<tr>
<td>Entry</td>
<td>Solute$^b$</td>
<td>Solvent system</td>
<td>Partitioning fluorous: organic (P)</td>
<td>Method</td>
<td>Ref.</td>
</tr>
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<td>IV-6$^c$</td>
<td>R$_2$(CH$_2$)$_2$OH</td>
<td>CF$_3$C$_6$F$_5$:CH$_3$C$_6$H$_5$</td>
<td>73.5:26.5 ($P = 2.77$)$^d$</td>
<td>GLC</td>
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<td>IV-7$^c$</td>
<td>R$_2$(CH$_2$)$_2$OH</td>
<td>CF$_3$C$_6$F$_5$:CH$_3$C$_6$H$_5$</td>
<td>64:36 ($P = 1.8$)$^d$</td>
<td>GLC</td>
<td>8</td>
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<tr>
<td>IV-8$^c$</td>
<td>R$_{10}$(CH$_2$)$_3$OH</td>
<td>CF$_3$C$_6$F$_5$:CH$_3$C$_6$H$_5$</td>
<td>80.5:19.5 ($P = 4.14$)$^d$</td>
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<td>8</td>
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<td>IV-9$^c$</td>
<td>[R$_6$(CH$_2$)$_3$]COH</td>
<td>C$<em>6$F$</em>{14}$:THF</td>
<td>90.9:9.1 ($P = 10.0$)</td>
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<td>IV-10$^b$</td>
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<td>C$<em>6$F$</em>{14}$:THF</td>
<td>95.8:4.2 ($P = 23.0$)</td>
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<td>IV-11$^c$</td>
<td>R$_2$(CH$_2$)$_3$OH</td>
<td>CF$_3$C$_6$F$_5$:CH$_3$C$_6$H$_5$</td>
<td>97.4:2.6 ($P = 38.1$)$^d$</td>
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<td>4a</td>
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<td>IV-12$^c$</td>
<td>[R$_6$(CH$_2$)$_3$]COH</td>
<td>C$<em>6$F$</em>{14}$:THF</td>
<td>19:81 ($P = 0.24$)</td>
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<td>IV-13$^c$</td>
<td>(R$_6$(CH$_2$)$_3$)CNC$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$CN</td>
<td>88:12 ($P = 7.3$)</td>
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<td>IV-14$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>59:41 ($P = 1.4$)</td>
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<td>IV-15$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>38:62 ($P = 0.61$)</td>
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<td>IV-16$^c$</td>
<td>(R$_6$(CH$_2$)$_3$)SiCNC$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$CN</td>
<td>82:18 ($P = 4.6$)</td>
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<td>IV-17$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>48:52 ($P = 0.92$)</td>
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<td>IV-18$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>25:75 ($P = 0.33$)</td>
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<td>IV-19$^c$</td>
<td>(R$_6$(CH$_2$)$_3$)NC$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$CN</td>
<td>97:3 ($P = 32$)</td>
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<td>IV-20$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>97:3 ($P = 32$)</td>
<td>gravimet</td>
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<td>IV-21$^c$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_2$Cl$_2$</td>
<td>94:6 ($P = 16$)</td>
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for further compounds see VII

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**Tab. 6-1.** (continued)
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<tr>
<th>Entry</th>
<th>Solute(^b)</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic ((P))</th>
<th>Method</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>V-1(^c)</td>
<td>(R_n)</td>
<td>CF(_3)C(<em>6)F(</em>{13}):CH(_3)C(_6)H(_5)</td>
<td>98.3:1.7 ((P = 56.8))(^d)</td>
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<td>V-2(^i)</td>
<td>(R_{n})</td>
<td>CF(_3)C(<em>6)F(</em>{13}):CH(_3)CN</td>
<td>88:12 ((P = 7.3))</td>
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<td>V-3(^i)</td>
<td>CF(_3)F(_2):CH(_3)OH</td>
<td>79:21 ((P = 3.8))</td>
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<td>V-4(^i)</td>
<td>CF(_3)F(_2):CH(_3)OH</td>
<td>78:22 ((P = 3.6))</td>
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<td>V-5(^i)</td>
<td>CF(_3)F(_2):C(_6)H(_6)</td>
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<td>V-6(^i)</td>
<td>CF(_3)F(_2):C(_6)F(_14):CH(_3)Cl</td>
<td>57:43 ((P = 1.3))</td>
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<td>V-7(^i)</td>
<td>CF(_3)F(_2):C(_6)F(_14):CH(_3)CO(_2)C(_2)H(_5)</td>
<td>46:54 ((P = 0.85))</td>
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<td>V-8(^i)</td>
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<td>46:54 ((P = 0.85))</td>
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for further compounds see IV, VII and VIII

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<th>Carboxylic Acids and Derivatives</th>
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<td>VI-1(^c)</td>
<td>(R_n)C(O)OC(_6)H(_5)</td>
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<tr>
<td>VI-2(^c)</td>
<td>(R_n)C(O)OCH(_2)C(_6)H(_5)</td>
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<tr>
<td>VI-3(^c)</td>
<td>(R_n)OOC(_6)F(_3)</td>
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<td>VI-4(^c)</td>
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<td>VI-5(^c)</td>
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<td>VI-6(^c)</td>
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<td>VI-7(^c)</td>
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### Tab. 6-1. (continued)

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<tr>
<th>Entry</th>
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<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
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<td>VI-8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;8&lt;/sub&gt; O&lt;sup&gt;0&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
<td>89.0:11.0 (P = 8.10)</td>
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<td>VI-9&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>90.3:9.5 (P = 9.58)</td>
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<td>VI-10&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>88.6:11.4 (P = 7.75)</td>
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<td>VI-11&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>86.6:13.4 (P = 6.46)</td>
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<td>VI-12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>90.1:9.9 (P = 9.08)</td>
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<td>93.8:6.2 (P = 15.4)</td>
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<td>75.4:24.6 (P = 3.06)</td>
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<td>85.6:14.4 (P = 5.93)</td>
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<td>VI-16&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>76.5:23.5 (P = 3.25)</td>
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<td>VI-18&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
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<td>91.5:8.5 (P = 10.8)</td>
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<sup>a</sup> Partition Coefficients Involving Fluorous Solvents
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<td>C₆F₁₄:C₆H₅CO₂C₂H₅</td>
<td>22:78</td>
<td>(P = 0.29)</td>
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<td>VI-77&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>37:63</td>
<td>(P = 0.58)</td>
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<td>VI-78&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆F₁₄:THF</td>
<td>27:73</td>
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<td>VI-79&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆F₁₄:F₆C₆H₅THF</td>
<td>35:65</td>
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<td>VI-80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆F₁₄:C₆H₅CO₂CH₃</td>
<td>20:80</td>
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<td>VI-81&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>VI-82&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆F₁₄:CH₂CN</td>
<td>77:23:6</td>
<td>(P = 3.42)</td>
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<td>VI-83&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>VI-113&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Partitioning fluorous: organic (P)</td>
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<td>VI-116&lt;sup&gt;i&lt;/sup&gt;</td>
<td>R = H, R' = O</td>
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<td>55:45 (P = 1.2)</td>
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<td>[(R&lt;sub&gt;6&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;]</td>
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for further compounds see XIV, XV, XVII, and Table 6-2
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<th>Partitioning&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>HO-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>20:80&lt;sup&gt;d&lt;/sup&gt;</td>
<td>GLC</td>
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<sup>a</sup>Partitions were expressed as the log<sub>10</log> of the ratio of the solute concentration in the fluorous phase to its concentration in the organic phase.}<sup>b</sup>Abbreviation: R<sub>2</sub>={CH<sub>2</sub>CH<sub>2</sub>}.<sup>c</sup>Method: GLC 1-4a. I = H and 1<sup>19</sup>F NMR.
<table>
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<th>Partitioning fluorous: organic (P)</th>
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<th>Ref.</th>
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<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>12.88 ((P = 0.14))</td>
<td>(^1)H and (^{19})F NMR</td>
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<td>VII-21</td>
<td>HO(CH(_2)(_n))R(_n)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-22(^c)</td>
<td>Cl(CH(_2)(_n))R(_n)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-23(^c)</td>
<td>Cl(CH(_2)(_n))R(_n)</td>
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<td>VII-24(^c)</td>
<td>Cl(CH(_2)(_n))R(_n)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-25(^c)</td>
<td>Cl(CH(_2)(_n))R(_n)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-26(^c)</td>
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<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-27(^c)</td>
<td>Br(CH(_2)(_n))R(_n)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>VII-30(^c)</td>
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<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
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for further compounds see III, IV, VI, VII, X, XI, XIII, XIV, XV, XVI and XVII
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| VIII-1<sup>c</sup> | \[
\begin{array}{c}
\text{N} \\
\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 63:37 \((P = 1.7)^{d}\) | GLC | 4a |
| VIII-2<sup>c</sup> | \[
\begin{array}{c}
\text{N} \\
\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 71:29 \((P = 2.4)^{d}\) | GLC | 4a |
| VIII-3<sup>c</sup> | \[
\begin{array}{c}
\text{N} \\
\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 69:31 \((P = 2.2)^{d}\) | GLC | 4a |
| VIII-4 | \[
\begin{array}{c}
\text{R}_{18}(\text{CH}_2)_{12}\text{N} \\
\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 93.8:6.2 \((P = 15.1)\) | GLC | 21 |
| VIII-5 | \[
\begin{array}{c}
\text{R}_{18}(\text{CH}_2)_{12}\text{N} \\
\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 90.4:9.6 \((P = 9.42)\) | GLC | 21 |
| VIII-6 | \[
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\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 93.9:6.1 \((P = 15.4)\) | GLC | 21 |
| VIII-7 | \[
\begin{array}{c}
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\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | \(>99.7:<0.3\) \((P > 332)\) | GLC | 21 |
| VIII-8 | \[
\begin{array}{c}
\text{R}_{18}(\text{CH}_2)_{12}\text{N} \\
\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 93.6:6.4 \((P = 14.6)\) | GLC | 21 |
| VIII-9 | \[
\begin{array}{c}
\text{R}_{18}(\text{CH}_2)_{12}\text{N} \\
\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 79.3:20.7 \((P = 3.83)\) | GLC | 21 |
| VIII-10<sup>c</sup> | \[
\begin{array}{c}
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\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | C<sub>6</sub>F<sub>18</sub>:CH<sub>3</sub>Cl<sub>2</sub> | 82.18 \((P = 4.7)\) | gravimet | 22 |
| VIII-11<sup>c</sup> | \[
\begin{array}{c}
\text{R}_{18}(\text{CH}_2)_{12}\text{N} \\
\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | C<sub>6</sub>F<sub>18</sub>:CH<sub>3</sub>CN | 94.6:5.4 \((P = 17.5)\) | gravimet | 22 |
| VIII-12<sup>c</sup> | \[
\begin{array}{c}
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\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | C<sub>6</sub>F<sub>14</sub>:CH<sub>3</sub>Cl<sub>2</sub> | 14.86 \((P = 0.16)\) | - | 23 |
| VIII-13<sup>c</sup> | \[
\begin{array}{c}
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\text{R}_{18}(\text{CH}_2)_{12}\text{R}_{18}
\end{array}
\] | C<sub>6</sub>F<sub>14</sub>:CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> | 20.80 \((P = 0.25)\) | - | 23 |
### Tab. 6-1. (continued)

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<td>40:60&lt;sup&gt;(P = 0.67)&lt;/sup&gt;</td>
<td>–</td>
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for further compounds see XIV

### IX Aliphatic Halides

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<td>4a</td>
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for further compounds see VII

### X Amines, Imines and related Compounds

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<tr>
<td>X-2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>R&lt;sub&gt;8&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>63.2:36.8&lt;sup&gt;(P = 1.72)&lt;/sup&gt;</td>
<td>GLC</td>
<td>26</td>
</tr>
</tbody>
</table>

for further compounds see VII

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<sup>a</sup> For further details see [25].
<sup>b</sup> For further details see [26].
<sup>c</sup> For further details see [27].
<sup>d</sup> For further details see [28].

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**6 Partition Coefficients Involving Fluorous Solvents**
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solute$^b$</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic ($P$)</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-3</td>
<td>Rf$_3$(CH$_2$)$_6$NH$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>56.9:43.1 ($P = 1.32$)</td>
<td>GLC</td>
<td>26</td>
</tr>
<tr>
<td>X-4$^c$</td>
<td>R$_2$CH$_2$NH(CH$_3$)</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>74.5:25.5 ($P = 2.92$)</td>
<td>GLC</td>
<td>4a</td>
</tr>
<tr>
<td>X-5$^c$</td>
<td>R$_7$CH$_2$N</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>30:70 ($P = 0.42$)</td>
<td>GLC</td>
<td>24</td>
</tr>
<tr>
<td>X-6$^c$</td>
<td>R$_7$(CH$_2$)$_3$NH(CH$_3$)</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>71:29 ($P = 2.4$)</td>
<td>GLC</td>
<td>4b</td>
</tr>
<tr>
<td>X-7</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$NH</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>96.5:3.5 ($P = 27.6$)</td>
<td>GLC</td>
<td>4b, 26</td>
</tr>
<tr>
<td>X-8</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$NH</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>95.1:4.9 ($P = 19.4$)</td>
<td>GLC</td>
<td>26</td>
</tr>
<tr>
<td>X-9</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$NH</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>93.0:7.0 ($P = 13.3$)</td>
<td>GLC</td>
<td>26</td>
</tr>
<tr>
<td>X-10$^c$</td>
<td>R$_7$CH$_2$N(CH$_3$)$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>82.2:17.8 ($P = 4.62$)</td>
<td>GLC</td>
<td>24</td>
</tr>
<tr>
<td>X-11$^c$</td>
<td>R$_7$(CH$_2$)$_3$N(CH$_3$)$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>79.8:20.2 ($P = 3.94$)</td>
<td>GLC</td>
<td>4b</td>
</tr>
<tr>
<td>X-12$^c$</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$N(CH$_3$)</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>97.4:2.6 ($P = 37.7$)</td>
<td>GLC</td>
<td>4b</td>
</tr>
<tr>
<td>X-13</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$N</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>&gt;99.7:&lt;0.3 ($P &gt; 332$)</td>
<td>GLC</td>
<td>4b, 26</td>
</tr>
<tr>
<td>X-14</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$N</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>&gt;99.7:&lt;0.3 ($P &gt; 332$)</td>
<td>GLC</td>
<td>26</td>
</tr>
<tr>
<td>X-15</td>
<td>[R$_7$(CH$_2$)$_3$]$_2$N</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>99.5:0.5 ($P = 199$)</td>
<td>GLC</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>[(R$_7$(CH$_2$)$_3$)$_2$Si(CH$_2$)$_3$]NR$R'$</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>X-16$^j$</td>
<td>R = H, R' = O$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CHCl$_3$</td>
<td>42.58 ($P = 0.71$)</td>
<td>gravimet</td>
<td>15</td>
</tr>
<tr>
<td>X-17$^j$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$CN</td>
<td>27.73 ($P = 0.37$)</td>
<td>gravimet</td>
<td>15</td>
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</tr>
<tr>
<td>X-18$^j$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$OH</td>
<td>67.33 ($P = 2.0$)</td>
<td>gravimet</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>X-19$^j$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>5.95 ($P = 0.05$)</td>
<td>gravimet</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>X-20$^j$</td>
<td>R = CH$_3$, R' = O$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CHCl$_3$</td>
<td>17.83 ($P = 0.20$)</td>
<td>gravimet</td>
<td>15</td>
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<tr>
<td>X-21$^j$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$CN</td>
<td>44.56 ($P = 0.77$)</td>
<td>gravimet</td>
<td>15</td>
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<tr>
<td>Entry</td>
<td>Solute&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solvent system</td>
<td>Partitioning fluorous: organic (P)</td>
<td>Method</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>X-22&lt;sup&gt;e&lt;/sup&gt;</td>
<td>C₆F₁₄:CH₃OH 87:13</td>
<td>87.13</td>
<td>gravimet or HPLC</td>
<td>15</td>
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<tr>
<td>X-23&lt;sup&gt;e&lt;/sup&gt;</td>
<td>C₆F₁₄:THF 9:91</td>
<td>9.91</td>
<td>gravimet</td>
<td>15</td>
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for further compounds see IV

### XI Phosphorus Compounds

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<tr>
<th>Entry</th>
<th>Solute&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI-1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>98.8:1.2</td>
<td>GLC</td>
<td>28</td>
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<tr>
<td>XI-2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>&gt;99.7:&lt;0.3</td>
<td>GLC</td>
<td>28</td>
</tr>
<tr>
<td>XI-3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[R₁₀(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>&gt;99.7:&lt;0.3</td>
<td>GLC</td>
<td>28</td>
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<tr>
<td>XI-4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>98.8:1.2</td>
<td>GLC</td>
<td>28</td>
</tr>
<tr>
<td>XI-5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>98.9:1.1</td>
<td>GLC</td>
<td>28</td>
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<tr>
<td>XI-6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₂]₃P</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>98.9:1.1</td>
<td>GLC</td>
<td>28</td>
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<tr>
<td>XI-7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₁]₃P=O</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>&gt;99.7:&lt;0.3</td>
<td>GLC</td>
<td>28</td>
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<tr>
<th>Entry</th>
<th>Solute&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI-8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₁]₂−P=O</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>78.4:21.6</td>
<td>GLC</td>
<td>30</td>
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<table>
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<th>Entry</th>
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<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>XI-9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Rf₆(CH₂)₁]₂−P=O</td>
<td>CF₃C₆F₁₁:CH₃C₆H₅</td>
<td>93.7:6.3</td>
<td>GLC</td>
<td>30</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solute&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI-10</td>
<td>(C₆H₅)₃P</td>
<td>C₆F₁₄:C₅H₁₀</td>
<td>&lt;0.5:&lt;99.5</td>
<td>–</td>
<td>31</td>
</tr>
<tr>
<td>XI-11</td>
<td>(4-Rf₆C₆H₅)₃P</td>
<td>1,3(CF₃)₃C₆F₁₈:CH₃C₆H₅</td>
<td>81.19</td>
<td>gravimet</td>
<td>32</td>
</tr>
<tr>
<td>XI-12</td>
<td>(4-Rf₆C₆H₅)₃P</td>
<td>1,3(CF₃)₃C₆F₁₈:THF</td>
<td>69.31</td>
<td>gravimet</td>
<td>32</td>
</tr>
<tr>
<td>XI-13</td>
<td>(4-Rf₆(CH₂)₂C₆H₄)₃P</td>
<td>1,3(CF₃)₃C₆F₁₈:CH₃C₆H₅</td>
<td>47.53</td>
<td>gravimet</td>
<td>32</td>
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<tr>
<td>Entry</td>
<td>Solute</td>
<td>Solvent system</td>
<td>Partitioning fluorous: organic (P)</td>
<td>Method</td>
<td>Ref.</td>
</tr>
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<tr>
<td>XI-14</td>
<td>1,3-(CF&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;10&lt;/sub&gt;:THF</td>
<td>17.83 (P = 0.2)</td>
<td>gravimet</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>XI-15</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
<td>96.8:3.2 (P = 30.03)</td>
<td>HPLC</td>
<td>33</td>
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<tr>
<td>XI-16</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>7.93 (P = 0.08)</td>
<td>HPLC</td>
<td>33</td>
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<tr>
<td>XI-17</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>43.57</td>
<td>HPLC</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>XI-18</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>19.5:80.5 (P = 0.242)</td>
<td>GLC</td>
<td>34</td>
</tr>
<tr>
<td>XI-19</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>66.6:33.4 (P = 1.99)</td>
<td>GLC</td>
<td>34</td>
</tr>
<tr>
<td>XI-20</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P→BH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>37.3:62.7 (P = 0.595)</td>
<td>31P NMR</td>
<td>17</td>
</tr>
<tr>
<td>XI-21</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P→BH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>96.6:3.4 (P = 28.4)</td>
<td>19F NMR</td>
<td>17</td>
</tr>
<tr>
<td>XI-22</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>65.0:35.0 (P = 1.86)</td>
<td>HPLC</td>
<td>33</td>
</tr>
<tr>
<td>XI-23</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>5.95 (P = 0.05)</td>
<td>HPLC</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>XI-24</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>5.95 (P = 0.05)</td>
<td>HPLC</td>
<td>33</td>
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<tr>
<td>XI-25</td>
<td>4-R&lt;sub&gt;f&lt;/sub&gt;3(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;P(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>11.89 (P = 0.12)</td>
<td>HPLC</td>
<td>33</td>
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<td>XI-26</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>2.98 (P = 0.02)</td>
<td>HPLC</td>
<td>33</td>
<td></td>
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<tr>
<td>XI-27</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>5.95 (P = 0.05)</td>
<td>HPLC</td>
<td>33</td>
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<tr>
<td>XI-28</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CF&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CCH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>94.9:5.1 (P = 18.48)</td>
<td>HPLC</td>
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<tr>
<td>XI-29</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>34.66 (P = 0.51)</td>
<td>HPLC</td>
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<td>XI-30</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>87.2:12.8 (P = 6.84)</td>
<td>HPLC</td>
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<td>XI-31</td>
<td>[4-R&lt;sub&gt;f&lt;/sub&gt;3(CF&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CCH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;P</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>77.0:23.0 (P = 3.34)</td>
<td>HPLC</td>
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<td>XI-32</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>51.2:48.8 (P = 1.05)</td>
<td>HPLC</td>
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<td>XI-33</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>15.85 (P = 0.18)</td>
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<td>XI-34</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>8.92 (P = 0.09)</td>
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<td>XI-35</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:THF</td>
<td>1.99 (P = 0.01)</td>
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<td>XI-36</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>Entry</td>
<td>Solute</td>
<td>Solvent system</td>
<td>Partitioning fluorous: organic (P)</td>
<td>Method</td>
<td>Ref.</td>
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<td>XI-37</td>
<td>[4-(CH₃)₃SiC₆H₄]₃P</td>
<td>C₆F₁₄:C₅H₁₂</td>
<td>&lt;4:1:96 (P &lt; 0.004)</td>
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<td>XI-38</td>
<td>C₆F₁₄:n-C₆H₁₄</td>
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<td>&lt;1:1:99 (P &lt; 0.01)</td>
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<td>XI-39</td>
<td>x = 1, n = 6</td>
<td>C₆F₁₄:n-C₆H₁₄</td>
<td>21:79 (P = 0.26)</td>
<td>ICP-AAS⁹</td>
<td>35, 36</td>
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<td>XI-40</td>
<td>CF₃C₆F₁₁:n-C₆H₁₈</td>
<td>52:48 (P = 1.1)</td>
<td>ICP-AAS⁹</td>
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<td>XI-41</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>60:40 (P = 1.5)</td>
<td>ICP-AAS⁹</td>
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<td>XI-42</td>
<td>x = 1, n = 8</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>69:31 (P = 2.2)</td>
<td>ICP-AAS⁹</td>
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<td>XI-43</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>82:18 (P = 2.2)</td>
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<td>C₆F₁₄:n-C₆H₁₂</td>
<td>43:55:6:5 (P = 0.77)</td>
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<td>XI-47</td>
<td>x = 2, n = 6</td>
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<td>89:11 (P = 7.8)</td>
<td>ICP-AAS⁹</td>
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<td>XI-48</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
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<td>XI-49</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>85:15 (P = 5.7)</td>
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<td>XI-50</td>
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<td>89:11 (P = 7.8)</td>
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<td>XI-51</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>97:3 (P = 28)</td>
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<td>XI-52</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>90:10 (P = 9.2)</td>
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<td>XI-53</td>
<td>x = 3, n = 6</td>
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<td>81:19 (P = 4.3)</td>
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<td>90:10 (P = 9.4)</td>
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<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
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<td>XI-56</td>
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<td>68:32 (P = 2.1)</td>
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<td>XI-57</td>
<td>CF₃C₆F₁₁:n-C₆H₁₂</td>
<td>92:8 (P = 12)</td>
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<td>Entry</td>
<td>Soluteb</td>
<td>Solvent system</td>
<td>Partitioning fluorous: organic (P)</td>
<td>Method</td>
<td>Ref.</td>
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<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:n-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;</td>
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<td>62:38</td>
<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>96.1:3.9</td>
<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>XI-62&lt;sup&gt;mn&lt;/sup&gt;</td>
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<td>Galden D-100:THF</td>
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<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>91.2:8.8</td>
<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>94.9:5.1</td>
<td>gravimet or ICP-AES&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>XI-71&lt;sup&gt;gn&lt;/sup&gt;</td>
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<td>Galden D-100:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>74:26</td>
<td>HPLC</td>
<td>20</td>
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**Notes:**
- **Entry:** identifies each row in the table.
- **Soluteb:** describes the solute being partitioned.
- **Solvent system:** lists the solvent system used.
- **Partitioning fluorous: organic (P):** indicates the partitioning ratio of fluorous to organic components.
- **Method:** specifies the method used for analysis.
- **Ref.:** references the source of the data.

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**Diagrams:**
- **XI-58:** shows a diagram of the solute structure.
- **XI-62:** shows a similar diagram with a different solute structure.

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**Table:**
- The table contains entries for various solutes and solvent systems, each with a partitioning ratio and the method of analysis.
- The table is sorted by entry number, with entries from XI-58 to XI-71.
- For each entry, the solute and solvent system are listed, followed by the partitioning ratio and the method of analysis.
- The table includes additional details such as the reference number for each entry.
### Tab. 6-1. {continued}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solute&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent system</th>
<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
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<td>XI-76&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(R&lt;sub&gt;n&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>95:5 (P = 19)</td>
<td>GLC</td>
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<td>99:1 (P = 19)</td>
<td>GLC</td>
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<td>92:8 (P = 12)</td>
<td>¹H and ¹⁹F NMR</td>
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<td>XII-3&lt;sup&gt;g&lt;/sup&gt;</td>
<td>[R&lt;sub&gt;4&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;]&lt;sub&gt;j&lt;/sub&gt;SnH</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>85:15 (P = 5.8)</td>
<td>gravimet</td>
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<td>XII-4&lt;sup&gt;g&lt;/sup&gt;</td>
<td>[R&lt;sub&gt;4&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;]&lt;sub&gt;j&lt;/sub&gt;SnH</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>91.3:8.7 (P = 10.5)</td>
<td>gravimet</td>
<td>40</td>
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<td>XII-5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>97.8:2.2 (P = 44.5)</td>
<td>gravimet</td>
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<td>XII-6&lt;sup&gt;g&lt;/sup&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>97.0:3.0 (P = 32.3)</td>
<td>gravimet</td>
<td>41</td>
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<td>XII-7&lt;sup&gt;g&lt;/sup&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>95.3:4.7 (P = 20.3)</td>
<td>gravimet</td>
<td>41</td>
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<td>XII-8&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>89.6:10.4 (P = 8.62)</td>
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<td>41</td>
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<td>XII-9&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>85.9:14.1 (P = 6.09)</td>
<td>gravimat</td>
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<td>XII-10&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>XII-11&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>98.2 (P = 45)</td>
<td>gravimat</td>
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<td>XII-12&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>70.30 (P = 12.3)</td>
<td>gravimat</td>
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<td>XII-13&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>55.45 (P = 1.2)</td>
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<td>Entry</td>
<td>Solute&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solvent system</td>
<td>Partitioning</td>
<td>Method</td>
<td>Ref.</td>
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<td>fluorous:</td>
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<td>XII-14&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>86.14</td>
<td>gravimet</td>
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<td>XII-15&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>90.9:9.1</td>
<td>gravimet</td>
<td>40</td>
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<td>XII-16&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>71.29</td>
<td>GLC</td>
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<td>XII-17&lt;sup&gt;10&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
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<td>GLC</td>
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<td>XII-18&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>93.7</td>
<td>GLC</td>
<td>40</td>
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<td>XII-19&lt;sup&gt;10&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
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<td>GLC</td>
<td>40</td>
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<td>XII-20&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>98.2</td>
<td>GLC</td>
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<td>XII-21&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>GLC</td>
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<td>XII-22&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>86.14</td>
<td>gravimet</td>
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<td>XII-23&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>gravimet</td>
<td>42</td>
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<td>99.1</td>
<td>gravimet</td>
<td>42</td>
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<td>XII-25&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>gravimet</td>
<td>42</td>
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<td>XII-26&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>93.7</td>
<td>gravimet</td>
<td>42</td>
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<td>XII-27&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>gravimet</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>98.2</td>
<td>gravimet</td>
<td>42</td>
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<td>42</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>63.0:37.0</td>
<td>–</td>
<td>43</td>
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<td>XII-31&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>22.78</td>
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<td>43</td>
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<td>65.5:34.5</td>
<td>–</td>
<td>43</td>
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<td>XII-33&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>99.1</td>
<td>–</td>
<td>44</td>
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<td></td>
<td>99.1</td>
<td>–</td>
<td>44</td>
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<td>XII-35&lt;sup&gt;10&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
<td></td>
<td>98.2</td>
<td>–</td>
<td>44</td>
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<td>Entry</td>
<td>Solute</td>
<td>Solvent system</td>
<td>Partitioning</td>
<td>Method</td>
<td>Ref.</td>
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<td>XIII</td>
<td>Silicon Compounds</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>3.6:96.4</td>
<td>GLC</td>
<td>45a</td>
</tr>
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<td>XIII-1</td>
<td>Rf$_i$(CH$_2$)$_3$Se(CH$_3$)$_2$Cl</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>66:34</td>
<td>ICP-AAS$^a$</td>
<td>46</td>
</tr>
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<td>XIII-2$^m$</td>
<td>Rf$_i$(CH$_2$)$_3$Se(CH$_3$)$_2$Cl</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>83:17</td>
<td>gravimet</td>
<td>46</td>
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<td>XIII-3$^m$</td>
<td>Rf$_{10}$(CH$_2$)$_3$Si(CH$_3$)$_2$Cl</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>95:5</td>
<td>gravimet</td>
<td>46</td>
</tr>
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<td>XIII-4</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$Cl</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>74:26</td>
<td>ICP-AAS$^a$</td>
<td>46</td>
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<td>XIII-5$^m$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$Cl</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>83:17</td>
<td>ICP-AAS$^a$</td>
<td>46</td>
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<tr>
<td>XIII-6$^m$</td>
<td>Rf$_i$(CH$_2$)$_3$SiCl$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>0.6:99.4</td>
<td>GLC</td>
<td>45a</td>
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<td>XIII-7</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>0.8:99.2</td>
<td>GLC</td>
<td>45b</td>
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<td>XIII-8</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$C$_6$H$_5$</td>
<td>3.6:96.4</td>
<td>GLC</td>
<td>45a</td>
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<td>XIII-9$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>48:52</td>
<td>HPLC</td>
<td>47</td>
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<td>XIII-10$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>48:52</td>
<td>HPLC</td>
<td>47</td>
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<td>XIII-11$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$CN</td>
<td>43:57</td>
<td>HPLC</td>
<td>47</td>
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<td>XIII-12$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:DMF</td>
<td>28:72</td>
<td>HPLC</td>
<td>47</td>
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<td>XIII-13$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$Cl$_2$</td>
<td>12:88</td>
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<td>XIII-14$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:THF</td>
<td>3:97</td>
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<td>XIII-15$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>73:27</td>
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<td>XIII-16$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>28:72</td>
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<td>XIII-17$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>11:89</td>
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<td>XIII-18$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
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<td>60:40</td>
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<td>XIII-19$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
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<td>57:43</td>
<td>HPLC</td>
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<td>XIII-20$^o$</td>
<td>Rf$_i$(CH$_2$)$_3$Si(CH$_3$)$_2$</td>
<td>C$<em>6$F$</em>{14}$:CH$_3$OH</td>
<td>42:58</td>
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### Tab. 6-1. (continued)

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<th>Partitioning fluorous: organic (P)</th>
<th>Method</th>
<th>Ref.</th>
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<td>XIII-21&lt;sup&gt;p&lt;/sup&gt;</td>
<td>R = CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;11&lt;/sub&gt;; R' = R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
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<td>XIII-22&lt;sup&gt;p&lt;/sup&gt;</td>
<td>R = cholestanyl; R' = R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
<td>83:17</td>
<td>HPLC</td>
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<td>XIII-23&lt;sup&gt;p&lt;/sup&gt;</td>
<td>R = 2-adamantylethyl; R' = R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
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<td>XIII-24&lt;sup&gt;p&lt;/sup&gt;</td>
<td>R = 2-adamantylethyl; R' = R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
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<td>XIII-25&lt;sup&gt;p&lt;/sup&gt;</td>
<td>R = mappicine; R' = R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
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<td>XIII-26&lt;sup&gt;mn&lt;/sup&gt;</td>
<td>R&lt;sub&gt;f&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si(OCH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;14&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>52:48</td>
<td>gravimet</td>
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for further compounds see IV, VI, VII, X, XI, XV and XVI

### XIV Sulfur Compounds

<p>| XIV-1&lt;sup&gt;c&lt;/sup&gt; | H&lt;sub&gt;5&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;c&lt;/sub&gt;C(O)OCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt; | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 0.5:99.5                           | GLC        | 24   |
| XIV-2&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;d&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;HC&lt;sub&gt;3&lt;/sub&gt;F&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 56:44                           | GLC        | 4a   |
| XIV-3&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;S(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;c&lt;/sub&gt;C(O)OCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt; | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 34:66                              | GLC        | 4a   |
| XIV-4&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;S(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;c&lt;/sub&gt;C(O)OCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt; | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 50:50                              | GLC        | 24   |
| XIV-5&lt;sup&gt;c&lt;/sup&gt; | CF&lt;sub&gt;3&lt;/sub&gt;SCH&lt;sub&gt;3&lt;/sub&gt;                                                   | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 8:92                               | GLC        | 4a   |
| XIV-6&lt;sup&gt;c&lt;/sup&gt; | CF&lt;sub&gt;3&lt;/sub&gt;S(3-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CF&lt;sub&gt;3&lt;/sub&gt;)                           | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 17:1:82.9                           | GLC        | 4a   |
| XIV-7&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;SC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;                                             | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 64:36                              | GLC        | 4a   |
| XIV-8&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;C(O)SCH&lt;sub&gt;3&lt;/sub&gt;                                               | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 76:123.9                           | GLC        | 24   |
| XIV-9&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;C(S)OCH&lt;sub&gt;3&lt;/sub&gt;                                               | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 74:6:25.4                           | GLC        | 24   |
| XIV-10&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;f&lt;/sub&gt;C(S)N(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;                                       | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 34:66                              | GLC        | 24   |
| XIV-11&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;r&lt;/sub&gt;(\text{S}^\text{N}\text{O})\text{R}&lt;sub&gt;r&lt;/sub&gt;                     | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 17:4:82.6                           | GLC        | 24   |
| XIV-12&lt;sup&gt;c&lt;/sup&gt; | R&lt;sub&gt;r&lt;/sub&gt;(\text{S}^\text{N}^\text{B}^\text{N})\text{R}&lt;sub&gt;r&lt;/sub&gt;          | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 13:7:86.3                           | GLC        | 24   |
| XIV-13&lt;sup&gt;c&lt;/sup&gt; | [R&lt;sub&gt;f&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;]\text{S}                                 | CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;11&lt;/sub&gt;:CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; | 98:7:1.3                           | GLC        | 48   |</p>
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<th>Solvent system</th>
<th>Partitioning (P)</th>
<th>Method</th>
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<td>XIV-14</td>
<td>[(R_{18}(CH_2)_{13})](_2)S</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>96.6:3.4 ((P = 28.4))</td>
<td>GLC</td>
<td>48</td>
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<tr>
<td>XIV-15</td>
<td>[(R_{16}(CH_2)_{13})](_2)S</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>99.5:0.5 ((P = 199))</td>
<td>GLC</td>
<td>7</td>
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<td>XIV-15</td>
<td>(R_{16}(CH_2)_{13})</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>99.5:0.5 ((P = 199))</td>
<td>GLC</td>
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<td>XV</td>
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<td>XV-1(^c)</td>
<td>(n = 6)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>11.6:88.4 ((P = 0.131)) (^d)</td>
<td>GLC</td>
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<td>XV-2(^c)</td>
<td>(n = 8)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>24.4:75.6 ((P = 0.323)) (^d)</td>
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<td>XV-3(^c)</td>
<td>(n = 10)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>39.61 ((P = 0.63)) (^d)</td>
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<tr>
<td>XV-4(^e)</td>
<td>(n = 6)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>21.6:78.4 ((P = 0.275)) (^d)</td>
<td>GLC</td>
<td>19</td>
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<td>XV-5(^e)</td>
<td>(n = 8)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>46.54 ((P = 0.36)) (^d)</td>
<td>GLC</td>
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<td>XV-6(^e)</td>
<td>(n = 10)</td>
<td>CF(_3)C(<em>6)F(</em>{11}):CH(_3)C(_6)H(_5)</td>
<td>76.1:23.9 ((P = 3.19)) (^d)</td>
<td>GLC</td>
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<td>XV-7(^f)</td>
<td>(R_{16}(CH_2)_{13})Si(_3)</td>
<td>FC-77:CH(_3)CN</td>
<td>93.0:7.0 ((P = 13.3))</td>
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<td>XV-8(^f)</td>
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<td>FC-77:CH(_2)O(_2)</td>
<td>88.3:11.7 ((P = 7.53))</td>
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<td>XV-9(^f)</td>
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<td>FC-77:CHCl(_3)</td>
<td>84.4:15.6 ((P = 5.43))</td>
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<td>XV-10(^f)</td>
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<td>FC-77:C(_4)H(_4)</td>
<td>86.7:13.3 ((P = 6.50))</td>
<td>–</td>
<td>49</td>
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<tr>
<td>XV-11(^f)</td>
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<td>FC-77:C(_4)O(_2)C(_2)H(_5)</td>
<td>47.53 ((P = 0.88))</td>
<td>–</td>
<td>49</td>
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<td>XV-12(^f)</td>
<td></td>
<td>FC-77:C(_4)OCH(_3)</td>
<td>73.2:26.8 ((P = 2.73))</td>
<td>–</td>
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Tab. 6-1. (continued)

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<td>XVI-13(^1)</td>
<td>FC-77:CH(_3)C(_6)H(_5)</td>
<td>88.5:11.5</td>
<td>–</td>
<td>49</td>
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<td>XVI-14(^1)</td>
<td>FC-77:THF</td>
<td>74.4:25.6</td>
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for further compounds see XI and XVI

### XVI Transition Metal Compounds

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<th>Partitioning fluorous: organic (P)</th>
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<th>Ref.</th>
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<td>XVI-1(^i)</td>
<td>Rh(_2)(O(_2)C(_Rf_7))(_4)</td>
<td>CF(_3)C(_6)F(_11):Et(_2)O</td>
<td>83:17</td>
<td>gravim</td>
<td>50</td>
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<td>XVI-2(^i)</td>
<td>CF(_3)C(_6)F(_11):CH(_3)Cl</td>
<td>94.9:5.1</td>
<td>–</td>
<td>gravim</td>
<td>50</td>
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<tr>
<td>XVI-3(^i)</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>96.7:3.3</td>
<td>–</td>
<td>gravim</td>
<td>50</td>
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<tr>
<td>XVI-4(^i)</td>
<td>CF(_3)C(_6)F(_11):CH(_3)C(_6)H(_5)</td>
<td>95.0:5.0</td>
<td>–</td>
<td>gravim</td>
<td>50</td>
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<tr>
<td>XVI-5(^i)</td>
<td>Rh(_2)(O(_2)C(_2)H(_2))(_4)</td>
<td>CF(_3)C(_6)F(_11):Et(_2)O</td>
<td>38:62</td>
<td>gravim</td>
<td>50</td>
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<td>XVI-6(^i)</td>
<td>CF(_3)C(_6)F(_11):CH(_3)Cl</td>
<td>89:11</td>
<td>–</td>
<td>gravim</td>
<td>50</td>
</tr>
<tr>
<td>XVI-7(^i)</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>96.6:3.4</td>
<td>–</td>
<td>gravim</td>
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<tr>
<td>XVI-8(^i)</td>
<td>CF(_3)C(_6)F(_11):CH(_3)C(_6)H(_5)</td>
<td>96.3:3.7</td>
<td>–</td>
<td>gravim</td>
<td>50</td>
</tr>
<tr>
<td>XVI-9(^i)</td>
<td>[(R(_f_6)(CH(_2))(_2))(_3)P](_3)RhCl</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>99.86:0.14</td>
<td>ICP-AES(^a)</td>
<td>51</td>
</tr>
<tr>
<td>XVI-10(^i)</td>
<td>[(R(_f_8)(CH(_2))(_2))(_3)P](_3)RhCl</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>99.88:0.12</td>
<td>ICP-AES(^a)</td>
<td>51</td>
</tr>
<tr>
<td>XVI-11(^i)</td>
<td>[(R(_f_6)(CH(_2))(_2))(_3)P](_3)Rh(H(_2))(CO)</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>99.5:0.5</td>
<td>GLC</td>
<td>4a, 52a</td>
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<td>XVI-12(^m)</td>
<td>Ar = 4-C(_6)H(_4)Si(CH(_3))(_2)(CH(_2))(_2)R(_f_6)</td>
<td>CF(_3)C(_6)F(_11):n-C(_6)H(_18)</td>
<td>99.7:0.3</td>
<td>ICP-AAS(^n)</td>
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<tr>
<td>XVI-13(^i)</td>
<td>CF(_3)C(_6)F(_11):n-C(_6)H(_18)</td>
<td>98.7:1.3</td>
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<td>ICP-AAS(^n)</td>
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<td>XVI-14(^m)</td>
<td>Ar = 4-C(_6)H(_4)Si(CH(_3))(_2)(CH(_2))(_2)R(_f_8)</td>
<td>CF(_3)C(_6)F(_11):n-C(_6)H(_18)</td>
<td>99.9:0.1</td>
<td>ICP-AAS(^n)</td>
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<td>XVI-15(^i)</td>
<td>[R(_{10})(CH(_2))(_2)C(_6)H(_4)](_n)Rh(CO)(_2)</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>44:56</td>
<td>ICP-AES(^a)</td>
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<td>XVI-16(^i)</td>
<td>[R(_{10})(CH(_2))(_2)C(_6)H(_4)](_n)Rh(CO)[P(C(_6)H(_2))(R(_f_6))(_2)]</td>
<td>CF(_3)C(_6)F(_11):C(_6)H(_14)</td>
<td>96.7:3.3</td>
<td>ICP-AES(^a)</td>
<td>52a</td>
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<tr>
<td>([\text{Rh(COD)[(Ar}_n P(C(_6)H(_2))_n PAr}_n)]^+)X(^-)</td>
<td>CF(_3)C(_6)F(_11):THF</td>
<td>&lt;1:99</td>
<td>ICP-AAS(^n)</td>
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<tr>
<td>XVI-17(^m)</td>
<td>Ar = C(_6)H(_4)</td>
<td>CF(_3)C(_6)F(_11):THF</td>
<td>&lt;1:99</td>
<td>ICP-AAS(^n)</td>
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<tr>
<td>X(^-) = [B(3,5-C(_6)H(_3))(R(_f_6))(_2)]^+; n = 4</td>
<td>41:59</td>
<td>ICP-AAS(^n)</td>
<td>53</td>
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\(^{a}\) ICP-AES = Inductively Coupled Plasma-Atomic Emission Spectroscopy

\(^{n}\) ICP-AAS = Inductively Coupled Plasma-Atomic Absorption Spectroscopy
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<th>Entry</th>
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<th>Solvent system</th>
<th>Partitioning fluores: organic (P)</th>
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<td>XVI-19$^{m}$</td>
<td>Ar = 4-C$_6$H$_4$[Si(CH$_3$)$_2$(CH$_2$)$_2$Rf$_6$]</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>68:32 $(P = 2.1)$</td>
<td>ICP-AAS$^a$</td>
<td>53</td>
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<tr>
<td>XVI-20$^{m}$</td>
<td>X$^-$ = [B(3,5-C$_6$H$_3$(Rf$_6$)$_2$)$_4$] ; n = 2</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>97:1:9.2 $(P = 34)$</td>
<td>ICP-AAS$^a$</td>
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<tr>
<td>XVI-21$^{m}$</td>
<td>Ar = 4-C$_6$H$_4$[Si(CH$_3$)$_2$(CH$_2$)$_2$Rf$_6$]</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>89:11 $(P = 8.1)$</td>
<td>ICP-AAS$^a$</td>
<td>53</td>
</tr>
<tr>
<td>XVI-22$^{m}$</td>
<td>X$^-$ = BF$_4$ $^-$ ; n = 2</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>98:4:1.6 $(P = 61)$</td>
<td>ICP-AAS$^a$</td>
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<td>XVI-23$^{m}$</td>
<td>Ar = 4-C$_6$H$_4$[Si(CH$_3$)$_2$(CH$_2$)$_2$Rf$_6$]</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>86:14 $(P = 6.4)$</td>
<td>ICP-AAS$^a$</td>
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<tr>
<td>XVI-24$^{m}$</td>
<td>X$^-$ = BF$_4$ $^-$ ; n = 2</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>98:5:1.5 $(P = 65)$</td>
<td>ICP-AAS$^a$</td>
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<tr>
<td>XVI-25$^{m}$</td>
<td>Ar = 4-C$_6$H$_4$[Si(CH$_3$)$_2$(CH$_2$)$_2$Rf$_6$]</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>97:1:2.9 $(P = 34)$</td>
<td>ICP-AAS$^a$</td>
<td>53</td>
</tr>
<tr>
<td>XVI-26$^{m}$</td>
<td>X$^-$ = BF$_4$ $^-$ ; n = 2</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>98:5:1.5 $(P = 66)$</td>
<td>ICP-AAS$^a$</td>
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<tr>
<td>XVI-27$^i$</td>
<td>[R$_{10}$(CH$_2$)$_2$C$_6$H$_4$]Mn(CO)$_3$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>64:36 $(P = 1.8)$</td>
<td>IR</td>
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<tr>
<td>XVI-28$^i$</td>
<td>[(CH$_3$(CH$_2$)$_2$)$_3$P]$_2$Ir(Cl)(CO)</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>$&lt;0.3$:$&gt;99.7$ $(P &lt; 0.003)$</td>
<td>$^{31}$P NMR</td>
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<td>XVI-29$^i$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>$&lt;0.3$:$&gt;99.7$ $(P &lt; 0.003)$</td>
<td>$^{31}$P NMR</td>
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<td>XVI-30$^i$</td>
<td>[(R$_6$(CH$_2$)$_2$)$_3$P]$_2$Ir(Cl)(CO)</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>$&gt;99.7$:$&lt;0.3$ $(P &gt; 332)$</td>
<td>$^{31}$P NMR</td>
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<tr>
<td>XVI-31$^i$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$COCH$_3$</td>
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<td>$^{31}$P NMR</td>
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<td>XVI-32$^i$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_2$Cl$_2$</td>
<td>$&gt;99.7$:$&lt;0.3$ $(P &gt; 332)$</td>
<td>$^{31}$P NMR</td>
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<tr>
<td>XVI-33$^i$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:THF</td>
<td>$&gt;99.7$:$&lt;0.3$ $(P &gt; 332)$</td>
<td>$^{31}$P NMR</td>
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<td></td>
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<tr>
<td>XVI-34$^i$</td>
<td>[(R$_6$(CH$_2$)$_2$)$_3$P]$_2$NiCl$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>98:8:1.2 $(P = 83)$</td>
<td>ICP-AES$^a$</td>
<td>52a</td>
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<tr>
<td>NiCl$_2$[Ar$_2$P(CH$_2$)$_2$PAR$_2$]</td>
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<td>XVI-35$^m$</td>
<td>Ar = 4-C$_6$H$_4$Si(CH$_3$)$_3$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
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<tr>
<td>XVI-36$^m$</td>
<td>Ar = 4-C$_6$H$_4$Si(CH$_3$)$_2$(CH$_2$)$_2$Rf$_6$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>62:38 $(P = 1.6)$</td>
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<td>XVI-37$^m$</td>
<td>Ar = 4-C$_6$H$_4$Si(CH$_3$)$_2$(CH$_2$)$<em>2$Rf$</em>{8}$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>79:21 $(P = 3.7)$</td>
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<td>XVI-38$^m$</td>
<td>Ar = 4-C$_6$H$_4$Si(CH$_3$)$_2$(CH$_2$)$<em>2$Rf$</em>{10}$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>89:11 $(P = 8)$</td>
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<td>XVI-39$^m$</td>
<td>Ar = 4-C$_6$H$_4$Si(CH$_2$)$<em>2$Rf$</em>{10}$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>95:8:4.2 $(P = 23)$</td>
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<td>XVI-40$^i$</td>
<td>Fe(C$_5$H$_4$(CH$_2$)$<em>2$Rf$</em>{10}$)$_2$</td>
<td>C$<em>7$F$</em>{16}$:CH$_3$C$_6$H$_5$</td>
<td>95:2:4.8 $(P = 20)$</td>
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<td>XVI-41</td>
<td>Fe($C_6H_4$[($CH_2$)$<em>2$R$</em>{f4}$]$_2$)$_3$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
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<td>ICP-AAS$^a$</td>
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<td>XVI-42</td>
<td>Fe($C_6H_4$[($CH_2$)$<em>2$R$</em>{f6}$]$_2$)$_3$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>98.6:1.4</td>
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<tr>
<td>XVI-43</td>
<td>Fe($C_6H_4$[($CH_2$)$<em>2$R$</em>{f5}$][($CH_2$)$<em>2$R$</em>{f6}$])$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>94.4:5.6</td>
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<td>XVI-44</td>
<td>Fe($C_6H_4$[($CH_2$)$<em>2$R$</em>{f5}$][($CH_2$)$<em>2$R$</em>{f8}$])$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
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<td>XVI-45</td>
<td>Fe($C_6H_4$[($CH_2$)$<em>2$R$</em>{f6}$][($CH_2$)$<em>2$R$</em>{f8}$])$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
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<td>XVI-46</td>
<td>[R$_{f6}$($CH_2$)$_2$C$_6$H$_4$]ZrCl$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
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<td>[R$_{f6}$($CH_2$)$_2$C$_6$H$_4$]Zr(Ch$_3$)$_2$</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>87.5:12.5</td>
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<td>XVI-48</td>
<td>R$_{f6}$($CH_2$)$<em>2$N$</em>{2}$PdAc</td>
<td>CF$_3$C$<em>6$F$</em>{11}$:CH$_3$C$_6$H$_5$</td>
<td>95.5:4.5</td>
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<td>XVI-49</td>
<td>C$_4$F$_7$Br:DMF</td>
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<td>91.4:8.6</td>
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### XVII Supramolecular Complexes and Polymers

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<th>Solvent system</th>
<th>Partitioning</th>
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<td>XVII-1</td>
<td>[R$_{f6}$($CH_2$)$_2$NHCONHCH$<em>2$][[$H_2$]$C_6$F$</em>{14}$:CH$_2$Cl$_2$</td>
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<td>XVII-2</td>
<td>[[$C_6$F$_7$NH$_2$]$<em>2$CO]:[$H_2$]$C_6$F$</em>{14}$:CH$_2$Cl$_2$</td>
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<td>XVII-3</td>
<td>[[$C_6$F$_7$NH$_2$]$<em>2$CO]:[$H_2$]$C_6$F$</em>{14}$:CH$_2$Cl$_2$</td>
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<td>XVII-4</td>
<td>[R$_{f6}$($CH_2$)$_2$NH$<em>2$]CO]:[$H_2$]$C_6$F$</em>{14}$:CH$_2$Cl$_2$</td>
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<td>XVII-5</td>
<td>[R$_{f6}$($CH_2$)$_2$NH$<em>2$]CO]:[$H_2$]$C_6$F$</em>{14}$:CH$_2$Cl$_2$</td>
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<td>XVII-6</td>
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### Tab. 6-1. (continued)

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<td>XVII-7(^c)</td>
<td>C(_6)F(_14):CH(_3)CN</td>
<td>90:10 ((P = 9.0))</td>
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<td>XVII-8(^c)</td>
<td>C(_6)F(_14):CH(_2)Cl(_2)</td>
<td>98:2 ((P = 49))</td>
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<td>XVII-9(^c)</td>
<td>C(_6)F(_14):CH(_2)Cl(_2)</td>
<td>95:5 ((P = 19))</td>
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<td>XVII-10</td>
<td>1,3-(CF(_3))(_3)C(_6)F(_10):CH(_3)C(_6)H(_5)</td>
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\(^{a}\) All measurements obtained at 24 °C unless otherwise stated.  
\(^{b}\) R\(_{RF}\) = (CF\(_2\))\(_n\):CF\(_3\). *25 °C.  
\(^{c}\) Calculated from ln \(P\). *Perfluorodecalin.  
\(^{d}\) Mixture of isomers. *Ambient temperature implied.  
\(^{e}\) 5–20 °C.  
\(^{f}\) 20 °C.  
\(^{g}\) 45 °C.  
\(^{h}\) 10 °C.  
\(^{i}\) 0 °C.  
\(^{j}\) Inductively coupled plasma – atomic absorption spectrometry.  
\(^{k}\) Inductively coupled plasma – atomic emission spectrometry.  
\(^{l}\) 23 °C.  
\(^{m}\) Mixture of regioisomers.

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**References to Tab. 6-1**

Tab. 6-1 (continued)

ences to other sections are given. The abbreviation \( R_{\text{f}} \) \([(\text{CF}_2)_n\text{CF}_3] \) is used throughout, except for trifluoromethyl groups (formally \( R_{\text{f}1} \)).

The partition coefficients are listed both as ratios normalized to 100, and as \( P \) values. As some rounding is necessary, the value originally reported in the literature is indicated in bold type. When a \( P \) value has been calculated from an \( \ln P \) or \( f \) value, this is indicated by a footnote. All data from the authors’ groups are believed to be correctly represented with respect to the number of significant digits.

GLC (gas-liquid chromatography), HPLC (high-performance liquid chromatography), and ICP-AAS/AES measurements are generally the most reliable. Gravimetric determinations where only a very small amount of the solute is present in one phase are subject to greater errors. Importantly, ICP methods give the total amount of a given element in a given phase. Hence, the decomposition of a solute to a species with a different partition coefficient (e.g., by oxidation), even to a small extent, can introduce error. Since GLC and HPLC assay a molecular characteristic, they are not subject to this problem.

Partition coefficients are temperature dependent, as illustrated by entries IV-9/IV-10 and XVI-12/XVI-13 of Table 6-1. The fluorous phase affinity of a fluorous solute is enhanced at lower temperature. However, most of the values in Table 6-1 were determined between 20 and 27 °C, as specified in the footnotes, and should not vary substantially within this range. In the most rigorous work, partition coefficients are determined over a range of concentrations and extrapolated to infinite dilution [1]. However, the concentrations used in the authors’ experiments are close to those encountered in “real-life” fluorous/organic liquid/liquid biphasic separations, and the values for various classes of molecules are believed to have excellent cross-comparability.
6.3 Trends with Respect to Functional Groups

6.3.1 Non-Aromatic Hydrocarbons

Entries I-1 to I-6 in Table 6-1 give partition coefficients (CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene) for n-alkanes (decane through hexadecane), and entries II-1 to II-6 give data for the corresponding terminal alkenes. The alkanes, although very non-polar, show high affinities for the toluene phase. These increase monotonically with alkane size (5.4:94.6 for decane to 1.1:98.9 for hexadecane). This is in accord with the general trends for absolute solubilities in fluorous solvents, as discussed in Chapter 3.5. Non-fluorous solutes are thought to occupy cavities, and smaller guests are always better accommodated.

The n-alkenes have slightly higher toluene phase affinities, consistent with their slightly greater polarities. A comparable monotonic size trend is found (4.8:95.2 for 1-decene to 0.9:99.1 for 1-hexadecene). When the side-chain of 1-decene is perfluorinated to give R<sub>f</sub>CH=CH<sub>2</sub>, the partition coefficient nearly reverses, to 93.5:6.5 (entry II-7). A variety of hemifluorinated disubstituted alkenes, R<sub>f</sub>nCH=CH(CH<sub>2</sub>)mCH<sub>3</sub>, have been analyzed (entries II-8 to II-43). As would be expected, they exhibit intermediate fluorophilicities.

6.3.2 Non-Aromatic Monofunctional Compounds

Entries III-1 and III-2 give partition coefficients (CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene) for the ketones cyclohexanone and 2-cyclohexen-1-one – species more polar than alkanes and alkenes but somewhat “smaller” than specific examples discussed above. Their toluene phase affinities are also high (2.2:97.8 and 1.7:98.3). The toluene phase affinity of cyclohexanol (entry IV-1, 1.6:98.4) is higher than that of cyclohexanone, and the corresponding dimethylphenyl silyl ether is higher still (entry XIII-8, 0.8:99.2).

Section IV of Table 6-1 contains several simple fluorous alcohols. The short-chain species in entries IV-2 and IV-3 show poor fluorophilicities [7]. As the perfluoroalkyl segment lengthens in the series R<sub>f</sub>6(CH<sub>2</sub>)3OH, R<sub>f</sub>8(CH<sub>2</sub>)3OH, and R<sub>f</sub>10(CH<sub>2</sub>)3OH (entries IV-5, IV-7, IV-8), the fluorophilic phase affinities increase from 44:56 to 64:36 to 80:5:19.5 (CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene). As would be expected, when a methylene group is removed from the first two compounds, the fluorophilicities also increase (52:48 and 73.5:26.5; entries IV-4 and IV-6). Similar trends are found with all other functional groups in Table 6-1.

The thiol R<sub>f</sub>6(CH<sub>2</sub>)3SH (entry XIV-2), iodide R<sub>f</sub>6(CH<sub>2</sub>)3I (entry IX-4), and primary amine R<sub>f</sub>6(CH<sub>2</sub>)3NH<sub>2</sub> (entry X-1) exhibit CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene partition coefficients (56:44, 50:7:49.3, and 70:0:30.0) roughly comparable to that of the corresponding alcohol (64:36). Thus, more than one R<sub>f</sub>-containing ponytail is clearly needed to achieve higher fluorophilicities with simple monofunctional organic compounds.

The effect of the number of ponytails is clearly seen in amines of the formula ([R<sub>f</sub>6(CH<sub>2</sub>)3]xNH<sub>1-x</sub> (entries X-1, X-7, and X-13). As x increases from one to three, the fluorophilic phase affinities increase monotonically from 70:0:30:0 to 96:5:3.5 to the point where no GLC-detectable concentration in toluene remains (>99.7:<0.3). Thus, [R<sub>f</sub>6(CH<sub>2</sub>)3]3N repre-
sents a highly immobilized fluorous base. When the number of the methylene groups in each ponytail is increased to five, a small amount of the amine can again be detected in the toluene phase (99.5:0.5; entry X-15).

Similar trends are observed with fluorous trialkylphosphines. Here, the lengths of the \( R_f \) as well as the \( (CH_2)_m \) segments have been varied (entries XI-1 to XI-6), and very high fluorous phase affinities can be achieved \( >99.7:<0.3 \) for \( [R_f^8(CH_2)_2]P \) and \( [R_f^{10}(CH_2)_2]P \). Where comparisons are possible, fluorophilicities are slightly lower than for analogous amines. Counter-intuitively from a polarity standpoint, oxidation to a phosphine oxide slightly increases the fluorous phase affinity (entry XI-7 vs. XI-1).

As shown in Section XII of Table 6-1, appropriately designed trialkyltin hydrides can also be highly fluorophilic. Although the solvent systems used are slightly different, partition coefficients for the compounds \( [R_f^n(CH_2)_2]_3SnH \) are comparable to those of the corresponding phosphines (entries XII-5 and XII-11 for \( n = 6; n = 10 \) is still more fluorophilic but due to solubility limitations an accurate value could not be determined) [8]. Another triply-branched system is the tertiary alcohol \( [(R_f^6(CH_2)_2)COH] \). The \( CF_3C_6F_{14}/THF \) partition coefficient is 90.9:9.1 at ambient temperature or 95.8:4.2 at \(-45^\circ C\) (entries IV-9 and IV-10).

Thioethers, which can only accommodate two ponytails around the central heteroatom, possess fluorous phase affinities slightly lower than those of comparable amines and phosphines. For example, the \( CF_3C_6F_{11}/toluene \) partition coefficients for \( [R_f^8(CH_2)_2]_2S \) and \( [R_f^8(CH_2)_3]_2S \) are 98.7:1.3 and 96.6:3.4 (entries XIV-13 and XIV-14).

6.3.3 Simple Monoarenes

Data for simple arenes are collected in Section VII of Table 6-1, and the \( CF_3C_6F_{11}/toluene \) partition coefficients can be analyzed as follows. Both pentafluorobenzene and hexafluorobenzene preferentially partition into toluene \( (22.4:77.6 \) and \( 28.0:72.0; \) entries VII-2 and VII-3), consistent with their non-fluorous nature as described in Chapter 3.2.2. Benzene exhibits an even greater toluene phase affinity \( (6.9; \) entry VII-1). However, the introduction of a single ponytail of formula \( R_f^8(CH_2)_3 \) evens the playing field, and a partition coefficient of 49.5:50.5 is obtained (entry VII-18). This value is similar to those obtained when an \( R_f^8(CH_2)_3 \) moiety is capped with an iodide or thiol. The compound \( R_f^8C_6H_5 \) (entry VII-16), which lacks methylene spacers, is more fluorophilic still \( (77.5:22.5) \), but the electronic properties of the arene ring are strongly perturbed.

As shown in entries VII-43, VII-45, and VII-46, benzenes with two ponytails of formula \( R_f^8(CH_2)_3 \) exhibit appreciable fluorophilicities, with partition coefficients of 91.2:8.8 to 90.7:9.3. The substitution pattern has little influence. As seen with other compounds above, when the perfluoroalkyl segment of the ponytail is shortened, the fluorous phase affinity decreases \( (73.7:26.3 \) for \( R_f^6(CH_2)_3; \) entry VII-42), and when it is lengthened the fluorous phase affinity increases \( (97.4:2.6 \) for \( R_f^{10}(CH_2)_3; \) entry VII-44). Importantly, benzenes with three ponytails of formula \( R_f^8(CH_2)_3 \) partition (within detection limits) completely into \( CF_3C_6F_{11} \), at least when arrayed in a 1,3,5-pattern (entry VII-61).

Entries VII-49 through to VII-54, as well as VII-62 and VII-63, feature moniodide derivatives of some of the preceding fluorous benzenes. In all cases, the fluorophilicities decrease. Only for entry VII-62, a triply ponytailed compound, is a highly biased \( CF_3C_6F_{11}/\)
toluene partition coefficient maintained (98.0:2.0). When the more polar non-fluorous solvent methanol is employed, relative fluorous phase affinities increase. Regardless, it is clear that with monofunctional benzenes, at least three ponytails of the formula \(R_f8(CH_2)_3\) are required for high degrees of fluorous phase immobilization. Entries III-4, IV-11, and VI-7 – a benzaldehyde, benzyl alcohol, and methyl benzoate – show that two ponytails of formula \(R_f8\) (i.e., without spacers) are essentially as effective (\(CF_3C_6F_{11}/toluene\) partition coefficients 98.6:1.4, 97.4:2.6 and 98.8:1.2).

6.3.4 Triarylphosphines

These points are further illustrated by some of the \(para\)-substituted fluorous triarylphosphines in Section XI of Table 6-1. With one ponytail of the formula \(R_f6(CH_2)_3\) per ring, the \(CF_3C_6F_{11}/toluene\) partition coefficient is 19.5:80.5 (entry XI-18). When the perfluoroalkyl segment is lengthened, giving \(R_f8(CH_2)_3\), the fluorophilicity increases (66.6:33.4; entry XI-19). When the methylene segment is shortened, giving \(R_f6(CH_2)_2\), the fluorophilicity should also increase. Accordingly, the \(C_6F_{14}/toluene\) partition coefficient is 43:57 (entry XI-17). When toluene is replaced by the much more polar solvent methanol, the fluorous phase affinity becomes much higher (96.8:3.2, entry XI-15).

Entries XI-30 and XI-28 provide analogous data for a phosphine with a single methylene spacer and a branched \(R_f6\) moiety. In \(C_6F_{14}/toluene\), the fluorous phase affinity is lower (87.2:12.8), but in \(C_6F_{14}/methanol\), slightly higher (94.9:5.1). When the phenyl groups bear only \(p-R_f6\) substituents (no methylene spacers), the partition coefficient in \(1,3-(CF_3)_2C_6F_{10}/toluene\) is 81:19 (entry XI-11).

It has proved problematic to attach additional ponytails directly onto the aryl moieties of fluorous triarylphosphines. Thus, there are no readily available compounds of the formula \(\{[R_f6(CH_2)_m]_xC_6H_{5-x}\}_3P\ (m > 0)\) with truly high fluorous phase affinities. However, a clever way around this dilemma has been developed [9]. Namely, silicon-based ponytails of the formula \([R_f6(CH_2)_2]_xSi(CH_3)_{3-x}\) have been used as anchors for as many as three \(R_f6\) or \(R_f8\) groups per ring [10]. As summarized in entries XI-47 through to XI-58, this gives triarylphosphines with much higher fluorous phase affinities (up to 95:5 for \(x = 3\) and \(n = 8\) in \(CF_3C_6F_{11}/n-C_6H_{12}\)). When the exact values are carefully analyzed, some non-monotonic trends are obvious, and this point is treated further below.

Note that the analogous dppe derivative in entry XI-62, which contains two fluorous arenes on each phosphorus atom, gives a \(CF_3C_6F_{11}/toluene\) partition coefficient of \(>98:<2\). The related BINAP derivative in entries XI-72 through to XI-75 features only a single fluorous arene on each phosphorus atom, and the \(C_6F_{14}/C_6H_6\) partition coefficient is only 74:26 (HPLC).

6.3.5 Pyridines

The \(R_f8\)-monosubstituted pyridines in entries VIII-1 through to VIII-3, which are \(ortho\), \(meta\), and \(para\) isomers, give \(CF_3C_6F_{11}/toluene\) partition coefficients in the narrow range of
63:37 to 71:29. The R₈(CH₂)₃-disubstituted pyridine in entry VIII-5 is rigorously comparable to the benzenoid analog in entry VII-45 (N/CH exchange), and gives an essentially identical partition coefficient (90.4:9.6 vs. 90.7:9.3). Hence, the polar pyridine nitrogen has little influence. Entry VIII-7 shows that three ponytails of the formula R₈(CH₂)₂ provide essentially complete fluorous phase immobilization (>99.7:<0.3). The hydrogenation of the pyridine in entry VIII-5 to the piperidine in entry VIII-8 slightly increases fluorophilicity (90.4:9.6 vs. 93.6:6.4). This secondary amine can in turn be compared to HN[(CH₂)₅Rf₈]₂ (entry X-9) which has one less CH₄ group and a very similar fluorous phase affinity (93.0:7.0).

6.3.6 Metal Complexes

Section XVI of Table 6-1 features a variety of metal complexes, the majority of which have been engineered to have high fluorophilicities. As illustrated by entries XVI-40 through to XVI-45, a ferrocene appears slightly more difficult to immobilize than a benzene ring. Two ponytails of the formula R₈(CH₂)₂ or four ponytails of the formula R₄(CH₂)₂ suffice for CF₃C₆F₁₁/toluene partition coefficients of >91:<9. The fluoruous zirconocenes (η⁵-C₅H₄(CH₂)₂Rf₈)₂ZrX₂ exhibit CF₃C₆F₁₁/toluene partition coefficients of 95.4:4.6 (X = Cl, entry XVI-46) and 87.5:12.5 (X = CH₃, entry XVI-47).

Compounds that are catalyst precursors are of particular interest. The neutral rhodium complexes in entries XVI-9 and XVI-10, which feature three phosphine ligands of the formula P[(CH₂)₃Rf₈]₃, exhibit very high fluorophilicities (CF₃C₆F₁₁/toluene partition coefficients 99.86:0.14, n = 6, and 99.88:0.12, n = 8). Those of similar square planar iridium and nickel complexes with two such phosphate ligands are slightly lower (entries XVI-30 through to XVI-34). Salts should normally have higher polarities and poorer fluorous phase affinities. However, entries XVI-20 and XVI-24 show that when appropriate cationic fluoruous rhodium complexes and fluorous anions are combined, CF₃C₆F₁₁/toluene partition coefficients of 97.1:2.9 to 98.5:1.5 can be achieved. Although partition coefficients have not yet been reported, polyoxometalate salts with fluoruous tetralkylammonium cations can exhibit similar fluorophilicities [11].

Entry XVI-12 illustrates an interesting effect. The central rhodium is surrounded by three fluoruous triarylphosphines that have only one ponytail per ring, and a CF₃C₆F₁₁/n-C₆H₁₄ partition coefficient of 52:48 at 0 °C (entry XI-40). Nonetheless, the rhodium complex is highly fluorophilic, with a partition coefficient of 99.7:0.3 under analogous conditions. Similar phenomena, in which the “sum is greater than the parts”, have been observed with other compounds that are aggregates of fluoruous building blocks. Two effects are probably at work. Firstly, the ponytails are deployed in a maximally efficient way around the periphery of the molecule. Secondly, the molar volume increases, the influence of which is discussed in Section 6.5 below.

Dirhodium tetracarboxylates Rh₂[O₂C(CH₃)₃nRf₈]₄ with very high fluoruous phase affinities are also available (entries XVI-1 through to XVI-8), although for some reason CF₃C₆F₁₁/ether gives much less biased partition coefficients than /CH₂Cl₂, /C₆H₁₄, or /toluene mixtures. The fluoruous nitrogen and sulfur palladacycles in entries XVI-48 through to XVI-51 contain three ponytails of the formula R₈(CH₂)₃m (m = 2 or 3) per arene ring. The
CF$_3$C$_6$F$_{11}$/toluene partition coefficients (95.5:4.5 and 90.7:9.3) indicate fluorophilicities somewhat lower than those of the free non-palladated ligands (98.7:1.3 and 99.5:0.5, entries X-24 and XIV-15).

6.4 General Trends and Special Situations

Table 6-1 shows that, with only a very few exceptions, the introduction of longer ponytails or additional ponytails leads to higher fluorous phase affinities. When additional methylene spacers are introduced, while keeping the perfluoroalkyl segments constant, fluorous phase affinities decrease. In the authors’ view, compounds with CF$_3$C$_6$F$_{11}$/toluene partition coefficients of $>90$:9 have high fluorophilicities, and those with partition coefficients of $>99$:1 possess very high fluorophilicities. When the ratio exceeds $>99.7$:0.3, the compounds can be viewed as “immobilized”.

In general, simple monofunctional organic compounds, including arenes, require two ponytails of the formula (CH$_2$)$_m$R$_{f8}$ ($m = 2, 3$) for high fluorophilicities. Three such ponytails lead to very high fluorophilicities, and often essentially complete immobilization. An early rule of thumb stated that for a molecule to be preferentially soluble in a fluorous liquid phase (partition coefficient $>50$:50), 60% of the molecular weight should be fluorine-derived [12]. However, Table 6-1 contains exceptions to all of these generalizations, and selected cases are now examined in turn.

In compounds that already contain a long perfluoroalkyl segment, the introduction of a CF$_3$ group or a “pigtail” sometimes imparts a fluorophilicity significantly greater than might be expected. For example, the R$_{f8}$/CF$_3$ in entry VII-16 can be compared with the R$_{f8}$/CF$_3$ and R$_{f8}$/R$_{f8}$-disubstituted benzenes in entries VII-37 through VII-40 and the R$_{f8}$/CF$_3$/CF$_3$-trisubstituted benzene in entry VII-60. Although the CF$_3$C$_6$F$_{11}$/toluene partition coefficients for the R$_{f8}$/CF$_3$ compounds [91.5:8.5 (meta), 89.4:10.6 (para), 81.8:18.2 (ortho)] indicate fluorophilicities less than that of the R$_{f8}$/R$_{f8}$ compound (99.3:0.7), they are in two cases distinctly greater than that of the R$_{f8}$/monosubstituted compound (77.5:22.5). The R$_{f8}$/CF$_3$/CF$_3$ compound (98.3:1.7) is nearly as fluorophilic as the R$_{f8}$/R$_{f8}$ compound. Thus, although trifluoromethylbenzene itself has a very poor fluorous phase affinity (entry VII-6, 12.4:87.6), CF$_3$ groups represent legitimate design elements for enhancing fluorophilicities once a ponytail is in place. Other compounds that appear to show similar effects can be found in entries VII-33 through VII-36 and VII-55 through VII-59.

A possibly related effect, already noted in Section 6.3.6, is as follows. Some compounds that can be viewed as aggregates of fluorous building blocks give partition coefficients distinctly higher than the individual building blocks. For example, the fluorophilicity of the rhodium tris(phosphine) complex in entry XVI-12 is much greater than that of the phosphine ligand (entry XI-40). A good example involving fluorous tin complexes appeared after this chapter had been sent to the publisher [13]. Another manifestation of this phenomenon, but in a supramolecular context, is illustrated in Scheme 6-1 [14]. The fluorous N,N'-dialkyl urea 1 is not very fluorophilic (C$_6$F$_{14}$/CH$_2$Cl$_2$ partition coefficient 30:70). However, the addition of an equivalent of the fluorous carboxylic acid 2 gives a highly fluorophilic 1:1 complex (partition coefficient 99:1). Although the partition coefficient of 2 is not known, it could well be somewhat lower due to the polar acidic functional group. In this event, two
more polar solutes combine to give a less polar and more fluorophilic complex. Additional examples are provided in entries XVII-1 through to XVII-9 of Table 6-1.

In such compounds or complexes, three main effects are probably operating. Firstly, polar acidic and basic sites (either Brønsted or Lewis) combine to give less polar moieties. Secondly, the ponytails are directed around the outer perimeter of the molecule in an efficient manner such that solvation in non-fluorous media is impeded. One wonders whether a “Maginot line” (or perhaps more accurately, a “Maginot sphere”) of CF₃-pigtails, accompanied by a smattering of ponytails, might constitute a particularly staunch defender of the fluorous character. Thirdly, the molar volume increases, the effect of which is discussed in the following section.

The most puzzling exceptions to the generalizations regarding ponytail length and quantity and fluorous phase affinities involve silicon-substituted triarylphosphines of the formula $\text{P}\{p$-C₆H₄Si(CH₃)$_3\}_{1-3}$ ([CH₂$_2$]$_x$Rf$_n$)$_3$ (entries XI-39 through XI-58). The partition coefficients were carefully measured in several solvent systems [9a]. The values in CF₃C₆F₁₁/n-pentane show the expected monotonic trend, with fluorophilicities increasing in the order $x/n = 1/6 < 1/8 < 3/6 < 2/6 < 3/8$. However, in CF₃C₆F₁₁/n-octane the phosphines with three ponytails show lower fluorophase affinities than those with two ponytails ($x/n = 1/6 < 1/8 < 3/6 < 2/6 < 2/6$). The situation is similar in CF₃C₆F₁₁/toluene, but now with some of compounds with Rf₆ ponytails showing fluorophase affinities equal to or greater than the homologs with Rf₈ ponytails ($x/n = 1/6 < 1/8 < 3/8 < 3/6 < 2/8$).

The preceding trends cannot be rationalized by any of the qualitative fluorophilicity models, but yet are real and must have an explanation. Apart from questioning the models, it should be noted that for measurements made in solution, there is always the possibility that certain fluorous solutes, but not others, might aggregate in some way. Gel formation is not uncommon, and micelles are certainly conceivable. As noted in Section 6.2, in the most rigorous studies, the concentration dependences of partition coefficients are determined.
The data are then extrapolated to infinite dilution, where aggregates become impossible. Perhaps some of these non-monotonic trends reflect non-ideal solution behavior.

For many compounds in Table 6-1, partition coefficients were measured with more than one non-fluorous solvent. Although there are a few curious exceptions (e.g., ether vs. toluene or hexane in entries XVI-1 through to XVI-8), the more polar the non-fluorous solvent, the greater the fraction of the fluorous solute in the fluorous phase. In contrast, only a few compounds have been probed with more than one fluorous solvent. Naturally, it is of interest to know which ones give the most biased partition coefficients. This has been investigated with two test solutes and toluene as summarized in Table 6-2 [15]. The best results were obtained with perfluorodecalin, and all cyclic solvents tested were superior to $n$-C$_6$F$_{14}$. Entries of VI-8 through VI-107 of Table 6-1 also feature many parallel measurements involving CF$_3$C$_6$F$_{11}$ and $n$-C$_6$F$_{14}$. In nearly all cases, the former gives the more biased partition coefficient.

### 6.5 Quantitative Analysis and Prediction of Partition Coefficients

There have been several efforts to parameterize the above data such that fluorophilicities can be predicted [4–6]. One approach makes use of 3D QSAR descriptors and neural networks [4]. A host of parameters was considered: percent fluorine, molecular volume, molecular surface, globularity, solvent accessible surface, solvent extended surface, solvent extended volume, calculated polarizability, calculated dipole moment, calculated Hildebrand parameter, degree of chemical bond rotational freedom, and others. In the end, very good agreement between measured and predicted partition coefficients in the test group of 60 molecules was realized.

Another parameterization effort involving a test group of 90 molecules found fluorine content, dispersion, and hydrogen bond acidity factors to be most important [5a]. Polarity, hydrogen bond basicity, and size effects played much smaller roles.
The most definitive work to date involves Mobile Order and Disorder (MOD) theory [6, 16]. This has been applied to other types of liquid/liquid partition coefficients, using a five-term expression. With aprotic fluorous biphasic systems, the expression reduces to two terms. One involves the molar volumes of the fluorous and organic solvents and the solute. The other involves the corresponding cohesion parameters. Once the solvent properties have been measured, the partition coefficients are a function of only two solute variables, one of which (the molar volume) is easily calculated from group increments. The investigators use a small amount of the data in Table 6-1 to back-calculate the solute cohesion parameter and derive a second set of group increments. This allows the partition coefficients of approximately 50 additional compounds to be predicted with good accuracy.

6.6 Future Directions

On the computational side, the prediction of partition coefficients is certain to attract further attention. To better interpret raw data, fluorous solutes will be increasingly scrutinized for non-ideal behavior in solution. Naturally, there will be many new entries for Table 6-1, as well as increased focus on supramolecular assemblies. However, there are some likely directions for future research that are not straightforward extensions of themes discussed above.

For example, partition coefficients for fluorous liquid/non-fluorous solid biphasic systems are of interest from several standpoints. Recently, the partitioning of small organic molecules from both fluorous and non-fluorous solvents as well as mixtures into highly cross-linked, macroporous, and insoluble organic polymers has been studied [17]. One goal is to enhance access of organic substrates to imbedded catalyst sites. Presumably due to a flu-orophobic effect, fluorous/organic solvent mixtures give up to 200-fold increases in local concentrations relative to pure organic solvents. Under catalytic conditions, turnover frequencies are greatly enhanced.

6.7 Sample Experimental Determinations

The following procedures illustrate recommended procedures for determining partition coefficients by GLC, HPLC, and $^{19}$F NMR. All correspond to entries in Table 6-1.

A [18]. A 10 mL vial was charged with 3,4-(Rf8 CH2CH2CH2)2C6H3I (entry VII-50; 0.0156 g, 0.0138 mmol), CF3C6F11 (2.000 mL), and MeOH (2.000 mL), fitted with a mini-nert valve, vigorously shaken (2 min), and immersed (cap-level) in a 35 °C oil bath. After 12 h, the bath was removed. After 12–24 h, a 0.500 mL aliquot of each layer was added to 0.250 mL of a standard 0.0244 M solution of eicosane in hexane. The samples were diluted with ether and GLC analysis (average of 7–8 injections) showed that 0.00325 mmol of 3,4-(Rf8 CH2CH2CH2)2C6H3I was in the CF3C6F11 aliquot and 0.000101 mmol in the MeOH aliquot (97.0:3.0; a 2.000/0.500 scale factor gives a total mass recovery of 0.0150 g, 97%).

B [19]. A 10 mL vial was charged with the imine palladacycle from entry XVI-48; (0.0104 g, 0.0031 mmol), CF3C6F11 (2.000 mL), and toluene (2.000 mL), fitted with a mininert valve,
and vigorously shaken (2 min). After 2 h (24 °C), a 0.250 mL aliquot of the fluorous phase and a 0.750 mL aliquot of the non-fluorous phase were removed. The solvents were evaporated and the residues dried by oil pump vacuum (1 h). Each residue was taken up in CF₃C₆H₅/EtOH (9:1 v/v; 0.500 mL) and analyzed by HPLC (average of 5 injections, 200 x 4 mm Nucleosil 100-5 column, UV/visible detector). The relative peak intensities were (after normalization to the aliquot volumes) 95.5:4.5.

C [20]. A 5 mL flask was charged with H₃B·P[p-C₆H₄(CH₂)₃CH(CH₂Rf₈)]₃ (entry XI-21; 0.0368 g, 0.0121 mmol) and CF₃C₆F₁₁ (2.00 mL). After complete dissolution, toluene (2.00 mL) was added and the mixture was vigorously shaken (20 min). The flask was kept at 25 °C for 48 h. Then aliquots (each of 0.500 mL) were taken from both phases. The CF₃C₆F₁₁ aliquot was evaporated to dryness. A solution of the internal standard C₆F₆ (0.0738 g, 0.397 mmol) in CF₃C₆H₅ (12.7016 g) was prepared. Portions of this standard solution were added gravimetrically to the above aliquots (CF₃C₆F₁₁: 0.6413 g solution, 0.0199 mmol C₆F₆; toluene: 0.0596 g solution, 0.00185 mmol C₆F₆). Then C₆D₆ was added (0.05 mL each) and the samples were analyzed by ¹⁹F NMR (integration of CF₃ signal against C₆F₆). The procedure was repeated, giving an average partition coefficient of 96.6:3.4 (0.00840 g of H₃B·P[p-C₆H₄(CH₂)₃CH(CH₂Rf₈)]₃ in 0.500 mL of CF₃C₆F₁₁; 0.000292 g of H₃B·P[p-C₆H₄(CH₂)₃CH(CH₂Rf₈)]₃ in 0.500 mL of toluene). A 2.00/0.500 scale factor gives a total mass recovery of 0.0348 g (95%).

References

7 It should be emphasized in passing that an appreciable amount of the very polar solute methanol can be found in the fluorous phase of CF₃C₆F₁₁/toluene mixtures. However, the authors are not aware of any quantitative measurements.
This dramatically illustrates the effect of the sizes of non-fluorous solutes on solubilities and partition coefficients.
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Separations with Fluorous Silica Gel and Related Materials

Dennis P. Curran

7.1 Introduction

Early work in the fluorous field relied on liquid/liquid separations to bifurcate reaction mixtures into organic and fluorous fractions [1]. However, limitations quickly arose due to the large numbers of fluorines needed to entice otherwise organic molecules to partition into a fluorous phase. The high molecular weights associated with heavy fluorous molecules are not a detraction in catalysis provided that the fluorous catalysts are efficient and can therefore be used in small quantities. In the late 1990s, the high molecular weights and attendant low organic solubilities and other unusual properties of heavy fluorous molecules posed a significant hurdle for budding chemical discovery techniques such as synthesis with fluorous reagents and protecting groups [2]. This hurdle can be surmounted by the design of appropriate heavy fluorous tags and identification of reliable reaction and separation conditions for tagged compounds [3]. Alternatively, and often more conveniently, this hurdle can be bypassed by switching from a heavy fluorous approach to a light fluorous approach that uses a solid/liquid separation in place of a liquid/liquid one. Fluorous solid phase extractions were first reported in a Note in J. Org. Chem. by He, Hadida and Curran in 1997 [4]. Related techniques of fluorous chromatography soon followed [5], and separations with fluorous solid phases have rapidly progressed to complement and supplement the liquid phase approaches.

7.1.1 Fluorous Silica Gel

Silica gel with a fluorocarbon bonded phase, hereafter called fluorous silica gel, is by far the most common material used for solid-based fluorous separations. The material predates the fluorous field, but for nearly two decades fluorous silica gel was like a material not matched with its natural analyte – like an ice hockey player asked to play soccer. Early reviews provide much useful information on the features of fluorous silica in separation of organic molecules without fluorines or with only a stray fluorine or two (that is, not enough fluorines to be fluorous) [6]. However, just as an ice hockey player’s natural game is ice hockey, fluorous silica gel’s natural game is separating fluorous molecules from non-fluorous molecules and from each other.
Outside its natural element, fluorous silica gel is a cousin of standard reverse phase silica gels such as C₁₈; however, it is much less retentive for organic molecules so very high water contents must be used in elution solvents when non-fluorous molecules are being separated. Polarity is a factor in separations of organic compounds on fluorous silica, but it is not the sole factor since there are many examples of reversed order of elution of non-fluorous molecules on regular reverse phase and fluorous silica. Molecular size may also be important, with larger molecules tending to be retained less well on fluorous silica. In addition to the reviews cited above and company “product notes”, recent papers by Monde et al. of the NEOS Company (makers of Fluofix®) highlight attractive features of fluorous silica separations including the separation of geometrical isomers of various sorts [7].

It quickly became apparent after 1997 that the unique feature of fluorous silica is its ability to separate fluorous molecules from non-fluorous molecules and from each other due to the selective retention of the fluorous molecules. A 2001 review highlights early work [8], but applications have advanced quickly and this chapter provides an overview of work from 1997 through to early 2003. Additional examples of fluorous silica separations can be found in Chapter 8 on “Light Fluorous Chemistry”.

7.1.2 Types and Sources of Fluorous Silica Gel Materials and Products

Fluorous silica gel has been prepared in ways that are generally analogous to standard reverse phase silica gels by bonding silanes to prepared silica. Most products have the general structure silica–O–Si(Me)₂(CH₂)ₙRƒ where n is 2 or 3 and Rƒ is C₆F₁₃ or C₈F₁₇; these materials are prepared from silylating reagents of the general structure XSi(Me)₂(CH₂)ₙRƒ. A few materials are prepared from reagents X₃Si(CH₂)ₙRƒ that lack methyl groups and these materials are interlinked at silicon by condensation to each other and to the support. Also, products can be made with and without endcapping, though without seems more common. Methods of preparation and even sometimes content of these materials can be trade secrets. Fortunately, all sources of fluorous silicas provide the structure of the Rƒ group, an important factor that can dictate choice since longer Rƒ chains retain fluorous compounds more strongly. This is typically an advantage, especially in solid phase extraction applications. Names for fluorous silica gel can be ambiguous with terms such as an “octyl bonded phase” meaning “CH₂(CH₂)₃(CH₂CH₂)₃H₂(CH₂CH₂)₃H₂(CH₂CH₂)₃H₂H₂(CH₂CH₂)₃H₂-perfluorooctyl, or perfluorohexylethyl” to some and “C₆F₁₇” (perfluorooctyl) to others. We avoid terms like “octyl” here entirely because it is unclear whether they include the spacer.

Silica gel sold under the name FluoroFlash™ by Fluorous Technologies, Inc. bears a perfluorooctylethyl bonded phase: Si(CH₂CH₂C₆F₁₃) [9]. This is available as TLC plates and loose for flash chromatography. It is also packed in assorted cartridges for SPE (solid phase extraction) and in Biotage [10] cartridges and Samplets™ for use with popular flash chromatography instruments. At this writing, the only other provider of loose fluorous silica gel appears to be Silicycle [11], whose less fluorous “Tridecafluoro-2” [Si(CH₂CH₂C₆F₁₃)] bonded phase is not as attractive as FluoroFlash™ for SPE and flash chromatographic applications since higher water content is needed to retain fluorous materials.

In addition to these commercial grade silica gels, there are several more or less similar materials described in the literature. All of our early work was conducted on so-called “homemade” fluorous silica gel prepared by a standard procedure from silica and
ClSi(Me)$_2$CH$_2$CH$_2$C$_8$F$_{17}$ [12]. We no longer recommend the use of this material since the commercial grade is superior in both loading capacity and separation ability. Bannwarth describes a silica made from (EtO)$_3$SiCH$_2$CH$_2$C$_6$F$_{13}$ in recent work [13]. We made fluorous silica some time ago from ClSi(Me)$_2$CH$_2$CH$_2$C$_6$F$_{13}$, and found that this was inferior in SPE applications to the longer C$_8$F$_{17}$ homolog. Recently, Bannwarth and coworkers have described a branched tris-perfluorohexylethylsilyl silica represented as 1 and Tsang and coworkers have described a perfluoroether material 2 [14]. Whether these materials have significant differences from other silicas is not yet apparent.

There is more selection with HPLC columns. Perfluorohexylethyl bonded phases are featured in Fluophase™, PrincetonSPHER Fluoroctyl and FluoSep™ RP Octyl columns (note that ‘octyl’ and “fluoroctyl” in these products seem to refer to the total carbon chain length, that is perfluorohexylethyl not perfluoroctyl). These products also appear to be dimethylsilanes with ethylene spacers bridging the silicon and the C$_6$F$_{13}$ group. Fluofix®, in contrast, has a well defined branched bonded phase: Si([Me]$_2$(CH$_3$)$_2$C(CF$_3$)CF$_2$CF$_2$CF$_3$ [7]. Although it differs by having an extra methylene group in the spacer and a branched instead of linear perfluorohexyl group, its HPLC performance is essentially indistinguishable from a similarly prepared linear material [7]. A simple web search turns up a number of US suppliers of HPLC columns with linear and branched C$_6$F$_{13}$ bonded phases including Keystone Scientific [15], ES Industries [16] and Princeton Chromatography [17], among others. FluoroFlash™ silica packed into HPLC columns of assorted sizes appears to be the only C$_8$F$_{17}$ bonded phase product on the market. We have tested a number of commercial and non-commercial HPLC columns in our group and most have performed admirably, exhibiting good separations and long lifetimes in the face of heavy use. However, we favor the increased retention times that FluoroFlash™ provides for tight separations and especially for demixing applications in fluorous mixture synthesis (see Section 7.4.2.3).

In short, there are now a range of excellent commercially available products that can be used for applications from SPE through flash chromatography to HPLC. While the existing materials have been optimized well for performance by their manufacturers, there is still much room for research on new fluorous silica materials with capabilities different from currently marketed products.

### 7.2 Fluorous Solid Phase Extraction (FSPE)

First described by Curran and coworkers in 1997 [4], fluorous solid phase extraction has quickly become the most common separation technique that is used in conjunction with light fluorous molecules.
7.2.1 Fluorous Solid Phase Extraction and its Relationship to Chromatography and Liquid/Liquid Extraction

Long a popular technique in chemical analysis [18], solid phase extraction is increasingly used in chemical synthesis due to its relative simplicity and separation power [19]. Solid phase extraction (SPE) has a resolution capability in between that of liquid/liquid extraction and chromatography, and it is productive to build analogies between SPE and both of these techniques.

Figure 7-1 shows a diagram of an idealized fluorous solid phase extraction. A mixture of a fluorous and an organic compound is loaded onto fluorous silica gel and eluted in a first-pass with a “fluorophobic” solvent. The fluorous material adsorbs onto the column while the organic material elutes with or near the solvent front. A second-pass elution with a “fluorophilic” solvent now elutes the fluorous compound with or near the solvent front. During each pass, only a single fraction is collected so this simple process resembles a filtration more than a chromatography. Unlike SPE techniques of chemical analysis where the target product or fraction is usually in the second-pass of the SPE, the fluorous SPE techniques of chemical synthesis may produce the target product in the first-pass, the second-pass or even both passes (for example, when a fluorous catalyst is being separated from an organic product and both are targeted for recovery).

Like fluorous SPEs, the uses of polar/non-polar SPEs and ion exchange SPEs are also increasing [19]. Each type of commonly used SPE process has an analogy in liquid/liquid extractions. Ion exchange processes are the solid/liquid equivalents of acid/base extractions while polar/non-polar SPEs on regular or (more typically) reverse phase silica gel are analogs of hexane/acetonitrile, hexane/methanol and related extractions. Fluorous SPEs are of
course the analogs of fluorous/organic liquid/liquid extractions. The SPE process resembles a liquid/liquid extraction in that one of the compounds is extracted out of the initial liquid phase (the fluorophobic solvent) and onto the solid phase (the fluorous silica), and in that the purified product fractions from the separation are in two volatile liquid phases from which the products are recovered by evaporation. Conveniently for parallel synthesis, SPE fractions can typically be analyzed directly by LC or LC-MS (liquid chromatography mass spectrometry).

The relationship between SPE and chromatography is analogous to the relationship between evaporation and distillation. A mixture of two compounds of widely differing boiling points can easily be separated by evaporating one away from the other. As the respective boiling points of the mixture components approach each other, distillations must be conducted with increasing care. Likewise, the ideal SPE is a “chromatography” wherein one component or sub-set of components has an $R_f$ (retention factor) of 1 while the others have an $R_f$ of zero. As the $R_f$ values of the respective components approach each other, the separation must be done with increasing care and the SPE mutates to a chromatography. Asking when does an SPE become a chromatography is something like asking when does an evaporation become a distillation; there is a healthy grey zone where either term might be appropriate. SPEs feature high loading levels (sometimes 10% or more) and generally only two fractions – organic and fluorous – are collected. The transition to a chromatography entails decreased loading (or, more accurately, the use of more support) with attendant increased resolution, and collection of multiple fractions.

### 7.2.2 Examples of Fluorous Solid Phase Extractions

Figure 7-2 summarizes the first fluorous solid phase extraction (FSPE), which involved the use of a fluorous tin reagent [4, 20]. SPE was used to bifurcate the crude reaction mixtures resulting from the thermal alkylation of aryl aldehydes 3 with fluorous allyl stannane 4. A first-pass elution with acetonitrile provided the pure alkylation product 5 while a second-pass with hexane provided a fluorous tin fraction. Tin reagents 4 are best classed as heavy fluorous reagents because their byproducts can also be removed by liquid/liquid extraction. In a series of seven alkylation experiments, both liquid/liquid and SPE separations were conducted.

![Fig. 7-2. SPE separations of heavy fluorous tin reagents and byproducts](image-url)
ducted and the results (yields and purities) were comparable. Related SPE separations were conducted in reactions involving homologous tin reagents with propylene spacers [20].

Subsequent to this initial work, the uses of fluorous SPE quickly shifted to light fluorous chemistry. This is understandable given that the SPE in effect enables light fluorous chemistry. However, the potential advantages of SPE have been largely overlooked in heavy fluorous chemistry, where liquid/liquid separations provide a viable option. In addition to its simplicity, the SPE procedure is attractive because no fluorous solvent is needed for either reaction or separation and because the fluorous silica is robust and reusable. Finally, SPEs of heavy fluorous compounds are attractive relative to light ones because water-free fluorophobic solvents can often be used to obtain the organic fraction.

The concept of using fluorous SPE to enable light fluorous synthesis was introduced in a pair of complementary papers in 1999 and 2000 [5, 21]. In the first [5], fluoroacyl-tagged amino acids like 6 were coupled under standard conditions with excess amines such as 7 in a reaction promoted by EDCI and HOBt (Figure 7-3). Loading of the crude mixture onto fluorous silica and first-pass elution with 80% methanol/water provided an organic fraction of excess and spent organic reagents and reactants. Second-pass elution with acetonitrile provided the pure fluorous-tagged amide 8 and related products in excellent yields and purities. Because of their relatively low fluorine content, compounds like 8 have little or no solubility in FC-72, so using liquid/liquid separation techniques for reactions such as these is pointless.

In the second paper [21], fluorous phosphines were prepared and tested as ligands and reagents. Among the six phosphines, three linear 9a–c and three branched 10a–c, shown in Figure 7-4, only those with three fluororous phenyl rings showed partition coefficients ($K_p$) sufficiently high for use in liquid/liquid extractions. Even these high partition coefficients were limited to highly fluorophbic solvents such as methanol. In contrast, HPLC experiments showed that all of these phosphines were well retained on fluorous silica gel com-
pared with typical organic compounds. As an example of how these phosphines can be used as ligands, platinum complex 11 was prepared and used to promote allylation of aldehydes with fluorous stannane 12. SPE with 90% methanol/water provided a pure product fraction free from fluorous ligand-derived products and also free from tin products. In this application, the catalyst was apparently not stable to the reaction conditions since the fluorous fraction was not pure catalyst but a complex mixture of products. Nonetheless, the simple isolation of pure alcohols is valuable. This work “rescued” a large number of light fluorous phosphines and other reagents that had been made by others and discarded as reaction partners because they were found to exhibit partition coefficients too low for liquid/liquid extractions; such reagents can now routinely be separated by SPE instead.

Figure 7-5 summarizes representative recent uses of fluorous SPE techniques, including one example each from the classes of fluorous reagents (the Mitsunobu reaction [22]), fluorous scavengers [23], and fluorous protecting groups [24]. In the reagent application, the target product is in the organic fraction, while the fluorous fraction contains spent reagents that can be recovered for reuse. In the scavenger application, the target product is again in the organic fraction, but this time the fluorous fraction is a mixture of scavenged product

Fig. 7-4. Light fluorous phosphines with FC-72/MeOH partition coefficients (Kp)
Fluorous Reagent

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{Et} + \text{O}_2\text{N}-\text{Ph} - \text{CO}_2\text{H} \\
& \quad \xrightarrow{\text{FDAD, TPP}} \quad \text{THF} \\
& \quad \xrightarrow{\text{FDCEH, TPP}} \quad \text{THF} \\
& \quad \xrightarrow{\text{FDCEH, TPP}} \quad \text{THF}
\end{align*}
\]

1) react 2) fspe

\[
\begin{align*}
\text{FDAD} & \quad \text{C}_8\text{F}_{13}(\text{CH}_2)_2\text{CN}=\text{NCO}_2(\text{CH}_2)_3\text{C}_6\text{F}_{13} \\
& \quad \text{FDCEH} \quad \text{C}_8\text{F}_{13}(\text{CH}_2)_2\text{CO}_2\text{NH}_2\text{CO}_2(\text{CH}_2)_3\text{C}_6\text{F}_{13}
\end{align*}
\]

Fluorous Scavenger

\[
\begin{align*}
\text{O} & \quad \text{OPMP} + \quad \text{NH}_2\text{Ph} \\
& \quad \xrightarrow{1\text{ equiv}} \quad \text{2 equiv} \\
& \quad \xrightarrow{1) 60^\circ C, CH}_2\text{Cl}_2} \quad \text{2) FITA} \\
& \quad \xrightarrow{3) \text{fspe}} \quad \text{organic} \\
& \quad \xrightarrow{\text{PMP is p-methoxyphenyl}} \quad \text{MeOH}
\end{align*}
\]

\[
\begin{align*}
\text{FITA is fluorous isatoic anhydride}
\end{align*}
\]

Fluorous Protecting Group

\[
\begin{align*}
\text{N} \quad \text{CO}_2\text{H} & \quad \text{H}_2\text{N} - \text{Ph} \\
& \quad \xrightarrow{\text{Boc}} \quad \text{Et}_3\text{N} \\
& \quad \xrightarrow{\text{EDCI, HOBt}} \quad \text{THF} \\
& \quad \xrightarrow{\text{EDCI, EDCI, HOBt, excess amine}} \quad \text{organic}
\end{align*}
\]

\[
\begin{align*}
\text{Boc} & \quad \text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{O}
\end{align*}
\]

Fig. 7-5. Examples of light fluorous reactions with SPE separations
and unreacted scavenger and is generally discarded. In the protecting group application, it is the organic fraction with the excess and spent reagents that is generally discarded (or occasionally, recovered) and the fluorous fraction now contains the target product. Additional examples of uses of fluorous SPE in the context of light fluorous synthesis are highlighted in Chapter 8.

In addition to the primary literature cited herein, practical aspects of conducting fluorous solid phase reactions including solvent choices and loading levels can be found in a recent review [8], in several of the Procedures in Chapter 11 of this Handbook, and in an information sheet provided by Fluorous Technologies, Inc. [25]. Fluorous TLC plates are useful for selecting conditions for solid phase extractions. By spotting authentic or model light fluorous products in aqueous methanol or acetonitrile of varying water content (typical 0–25%), one can quickly identify the minimum water content that still holds the fluorous product at or near the baseline. Even with water contents of 25% and above, most organic compounds have $R_f$ values well above 0.5 and often not far from 1. Even better is to use fluorous HPLC columns as predictors of successful SPEs; this is covered in Section 7.4.2.2 below.

7.2.3 Reverse Fluorous Synthesis with Solid Phase Extractions

A general theme in most fluorous reactions to date is that the final target products are not fluorous, even when fluorous protecting groups or tags are used, these are only in place at intermediate stages and are removed at the end. The synthesis of highly fluorinated molecules is itself a specialized field of significant importance [26], and such molecules lend themselves to the logical reversal of standard fluorous synthesis. In other words, the precursors and target products are themselves fluorous, so organic (or inorganic) reagents, catalysts, scavengers, etc. are used to allow easy separation of the target products from the other remaining or spent reaction components.

A powerful separation tool in the “reverse fluorous synthesis” approach is solid phase extraction. This was introduced by Ryu, Curran and coworkers in 2000 with allylation of perfluoroalkyl iodides, as summarized in Figure 7-6 [27, 28]. In a reversal of reaction of organic precursors with a fluorous allyl tin reagent (see Figure 7-3), perfluoroalkyl iodides such as 13

![Fig. 7-6. Reverse fluorous synthesis: the use of organic reagents to make fluorous target products with SPE separation](image-url)
were reacted with the standard organic tin reagents such as alkyl tributyltin 14. First-pass solid phase extraction with acetonitrile provided an organic fraction containing the tin reagent and byproducts, while second-pass elution with ether provided the fluorous target product 15. For heavy fluorous compounds with suitable partition coefficients, fluorous/organic liquid/liquid extraction provides a viable alternative to SPE in reverse fluorous synthesis [28].

In the past, traditional organic separations have been routinely applied for the synthesis of fluorous molecules. Looking forward, reverse fluorous synthesis provides a powerful synthesis and separation strategy that is naturally suited to fluorous target molecules and will be widely applicable.

7.3 Fluorous Flash Chromatography

Bridging the large gulf between fluorous SPE and fluorous HPLC are intermediate chromatographic methods. These have only recently been exploited, and generally this has been at the SPE end of the continuum where speed is an important feature, hence the term “fluorous flash chromatography”. Compared with SPE, loading levels in fluorous flash chromatography are lower but resolution is higher. Typically, several fractions are collected and analyzed.

Perhaps the first fluorous flash chromatography resulted from a collaboration of our group and Leitner’s in 1998 [29]. For a time in the late 1990s, the best synthesis of fluorous aryl bromide 18 – a key intermediate for making phosphines and other fluorous reagents – involved the copper catalyzed coupling of Grignard reagent 16 and iodide 17. This gave target product 18 contaminated with dimer 19. Having similar boiling points and polarities, these two compounds were not easy to separate by distillation or silica gel chromatography. However separation on homemade fluorous silica gel was straightforward because of the large differences in fluorine content. Loading of a mixture followed by elution with acetonitrile provided initial fractions containing pure 18, while subsequent elution with THF provided fractions with the dimer 19. Recovery was generally close to quantitative in this process, which is on the borderline between an SPE and a flash chromatography.

![Fluorous Flash Chromatography Diagram](image.png)

Fig. 7-7. The first fluorous flash chromatography
Until very recently, the use of fluorous flash chromatographic methods has been limited by the lack of suitable commercial silica products. However, the FluoroFlash™ line of products, including SPE and Biotage cartridges and loose silica, now fills this need and flash chromatographic methods can be considered on the one hand for separations that have been conducted by SPE (if higher resolution is needed) or on the other hand for separations that have been done by HPLC (if higher loading levels or speed are needed). As an early illustration of the potential, fluorous quasiracemate derivatives of amino acids have recently been preparatively demixed by fluorous flash chromatography [30].

7.4
Fluorous HPLC

Fluorous HPLC is the separation of fluorous compounds over silica gel with a fluorocarbon bonded phase (fluorous silica gel) in a high pressure/performance liquid chromatography mode. As mentioned in Section 7.1.2, an assortment of fluorous HPLC columns is now available in sizes from analytical to semi-preparative. These columns predate the fluorous field, and early uses were primarily for chemical analysis of organic or biological molecules [6, 7]. Among the organic molecules separated were lightly fluorinated ones, and fluorous columns were generally superior at separating these molecules compared with standard reverse phase columns. For example, a Fluofix® column separates all ten fluorinated benzenes from each other, except for 1,2-difluorobenzene and 1,3-difluorobenzene, which coeluted [7]. Other fluorous HPLC columns probably behave similarly.

7.4.1
Structure/Retention Trends in Fluorous Chromatography

A utilitarian if simplistic analysis of structure/retention trends in fluorous HPLC considers the fluorous and organic parts of a molecule separately. The fluorous part of the molecule exerts the “primary” effect, with separation by fluorine content being the signature of fluorous HPLC, while the organic part of the molecule exerts a significant but “secondary” effect. The primary organofluorine effect arises because the partitioning of isolated CF₂ groups from solvents such as MeOH or acetonitrile into fluorous silica gel is considerably more favorable than the same partitioning into reverse phase silica gel and is likewise higher than the partitioning of CH₂ groups to either fluorous or reverse phase silica gel [6, 7]. In short, fluorine content rules.

The facile separation of a homologous set of fluorous-tagged amides 20 over fluorous silica gel is shown in Figure 7-8. The solvent gradient starts at 80% MeOH/water and increases linearly to 100% MeOH over the 8 min. The compounds emerge in order of tag size from C₃F₇ to C₁₀F₂₁. The analog bearing the C₅F₉ tag is absent from this mixture, and its absence is readily spotted by the large gap between the C₄F₉ and C₆F₁₃ analogs.

Of special importance in this separation experiment is the behavior of molecules like the standard Boc analog of 20 (not shown) that do not bear any fluorines; these molecules emerge at or near the solvent front. Indeed in our experience, essentially all non-fluorinated organic molecules elute at or within 1 min of the solvent front with both 80% MeOH/water and 80% acetonitrile/water. This big difference in retention between fluorous and non-
fluorous molecules is the basis for the fluorous/organic solid phase extractions described above. Indeed, to chromatograph non-fluorous organic molecules on fluorous silica gel requires water contents of 50% or more due to the low affinity of the compounds for the support [6, 7].

The organic part of a fluorous molecule can exert significant secondary effects on its retention, and the early work on chromatography of organic and lightly fluorinated molecules provides guidelines on what types of secondary effects to expect [6, 7]. Polarity is clearly important, with salts and highly polar functional groups decreasing retention times and lipophilic groups (especially compact ones) increasing retention times. However, the retention orders of a series of compounds on fluorous and reverse phase silica gel are not always identical so the simple notion that the behavior of organic molecules or molecular fragments on fluorous silica can be predicted from reverse phase behavior is not always appropriate. Other factors that may be important are molecular size and shape (smaller being retained better) as well as the presence of specific groups such as H-bond donors or acceptors.

Figure 7-9 shows retention times on a FluoroFlash™ analytical column for a series of fluorous Diels-Alder adducts bearing C₆F₁₃ or C₈F₁₇ tags along with related non-fluorous controls [31]. Conditions are isocratic (80% MeOH/water) to maximize the separations. As expected, the controls from the non-fluorous N-phenylmaleimide emerge very close to the solvent front, while fluorous maleimide adducts with the C₆F₁₃ tags generally emerge before other adducts with the C₈F₁₇ tags. However, there is also a significant secondary separation and the first of the C₈F₁₇ adducts (fluorous triazoline dione adduct with anthracene)
emerges at 14.8 min, which is very close to the last of the C₆F₁₃ adducts (fluorous maleimide adduct with pentamethyl cyclopentadiene) at 14.3 min. This raises a caution flag for fluorous mixture synthesis applications, where secondary effects could cause crossing of tagged molecules and complicate separation and analysis (see Section 7.4.2.3, below). Within the tag families, the adducts from pentamethyl cyclopentadiene are particularly well retained. This effect of compact lipophilic groups has already been observed with t-butyl and trimethylsilyl groups [32, 33]. Likewise, adducts of the more polar triazoline dione emerge before adducts of the N-benzylmaleimides with the same dienes. Finally, the power of the fluorous compounds to separate stereoisomers is also evident: in all three pairs of fluorous adducts

**Fig. 7-9.** Retention times (min) of selected fluorous and non-fluorous Diels-Alder adducts, (separation on a FluoroFlash™ HPLC column, 15 x 150 mm, isocratic, 80% MeOH/H₂O, solvent front is at about 1.7 min)
with pentamethyl cyclopentadiene, the syn adduct (methyl group on the same side as dienophile) elutes well before its anti isomer. These isomers could be separated in preparative fluorous HPLC experiments, but could not be separated over regular or reverse phase silica gel.

7.4.2
Uses of Fluorous HPLC

The potential utility of fluorous HPLC columns in fluorous chemistry runs the gamut of applications from the separation of molecules by differing fluorine content, through the separation of molecules with the same fluorine content by structure of the organic fragment, to separation of diastereomers bearing identical organic and fluorous components. In short, if you are making or working with fluorous molecules, you need a fluorous HPLC column. Here we present representative highlights of examples showing how and when to use fluorous HPLC.

7.4.2.1 Analysis and Purification of Organofluorine Compounds

The strength of fluorous HPLC columns in analyzing and purifying fluorinated compounds of all sorts is still not widely appreciated. For molecules bearing from one to a handful of fluorines (that is, fluorinated but not fluorous), fluorous columns should routinely be evaluated alongside regular and reverse phase silica gel columns. While the primary (fluorine content) effect is at its minimum for these lightly fluorinated compounds, the unique features of the fluorous materials can still make fluorous HPLC the method of choice [6, 7]. Fluorous HPLC should be considered for typical fluorination reactions where separation of unfluorinated and lightly fluorinated products is desired, or for separation of stereoisomers of organofluorine compounds.

In the fluorous area, the unique features of fluorous columns are useful for both the purification and analysis of fluorous molecules, and we routinely analyze and sometimes purify our fluorous reagents and intermediates by fluorous HPLC. In the light fluorous area, solvents such as methanol or acetonitrile with 0–20% water are typical. As molecules move towards the heavy end, more powerfully eluting solvents are needed, and we typically begin to introduce THF at a suitable rate. Fluorous columns are readily used in both LC-MS and LC-NMR experiments, and each provides an extremely powerful tool for identification and analysis.

The recent peptide synthesis work of van Boom and coworkers nicely shows the power of fluorous HPLC when coupled with solid phase peptide synthesis (Figure 7-10) [34]. They synthesized protected heptapeptide 21 on a resin by using the standard Fmoc protection approach with HATU for coupling and Ac₂O for endcapping. Exposure of the resin to HATU in each coupling was deliberately limited to 5 min to enhance the amount of truncated, endcapped products. The final sequence 21 was then tagged with 5-Cbz reagent 22, then the products were removed from the resin and purified by fluorous HPLC (Fluophase column, MeOH/water gradient with a trace of TFA). The retention provided by the fluorous tag on the target product allowed isolation of pure protected heptamer 23 even though non-optimized coupling conditions were used since the truncated, endcapped products do not bear fluorous tags. Final deprotection gave the target heptapetide 24.
7.4.2.2 Method Development for Preparative Fluorous Chromatographies and SPEs
Fluorous TLC plates provide simple tools to identify solvent systems and methods for preparative fluorous chromatographies and SPEs, but the quantitative information provided by fluorous HPLC columns is often appreciated. For example, we often inject samples onto a 4.6 × 150 mm FluoroFlash™ HPLC column with a linear gradient of 80% MeOH water to 100% MeOH over 30 min (a similar gradient with MeCN can also be used). Organic compounds elute at or near the solvent front under these conditions. Fluorous compounds with retention times of 20 min or more are highly suitable for simple SPE separations with high loading levels using 80% MeOH/water in the first-pass followed by 100% MeOH or THF in the second-pass. As retention times increase, the water content in the first-pass solvent can be decreased. Retention times of 15–20 min are still suitable for SPE, but lower loading levels are recommended, more careful loading is needed to prevent breakthrough, and higher water content in the first-pass solvent may be beneficial. Compounds with retention times of 10 min or more are well suited for simple flash chromatographic separations from organic compounds at or near the solvent front. Using different columns and conditions will doubtless change these absolute values, but it is nonetheless not difficult to build a small yet powerful knowledge base of HPLC data as references points for SPEs and chromatographies. For example, Lindsley’s group at Merck in West Point recommends a fast analysis of fluorous compounds on reverse phase silica gel as a basis for a “go/no go” decision on fluorous SPE, and this succeeds in many instances because of the non-polar nature of the typical fluorous tags (see below) [35].

7.4.2.3 Demixing in Fluorous Mixture Synthesis
In the general strategy for solution phase mixture synthesis that we have recently introduced, compounds are tagged with different “separation tags” and then the tagged compounds are mixed [36]. As desired, the mixtures are resolved into their individual components based on the structure of the tags in a process called “demixing”. In fluorous mixtures synthesis, demixing is typically conducted by chromatography over fluorous silica gel. In a recent synthesis of 560 analogs of the natural product mappicine, 80 seven-compound mix-
tures were prepared and demixed by serial preparative fluorous HPLC experiments. A typical chromatogram for one of these preparative experiments is shown in Figure 7-11. In each of the 80 chromatograms, the seven components were widely separated and emerged in order of tag.

Demixing is also used at intermediate stages of fluorous mixture syntheses to follow the progress of reactions, to ascertain the structures of products and to determine if any by-products are formed. In both analytical and preparative demixing experiments, the combination of the primary and secondary separation becomes important and something resembling “two chromatographies in one” results. This is best illustrated with an example. The N-propargylation of a seven compound mixture of pyridones 25a–g under standard conditions provides a mixture of not seven but 14 products: seven major N-propargylated products 26a–g and 7 minor O-propargylated products 27a–g. The fluorous HPLC chromatogram of this mixture is shown in Figure 7-12. The primary separation is reflected in the emerging of the compounds in pairs in order by tag size. Within each pair the major (and more polar) N-propargyl isomer 26 emerges before the minor (and less polar) O-propargyl isomer 27 and the structures of all 14 components in the mixtures as well as the ratios of N/O-propargylation for each pyridone precursor are readily determined.

This is two chromatographies in one because embedded within the primary separation by tag is a secondary separation by structure of the organic compound. In other words, the experiment in Figure 7-12 is something like the sum of seven chromatographies of each of
the components with the different tags all piggybacked into one. If the samples are cut and combined based on tags, then a demixing is accomplished. Then if the samples are cut and combined based on N/O-propargylation, two pure mixtures result will from one impure mixture. Finally, if the samples are cut and not combined, both demixing and purification are accomplished.

25a-g, Rf/RD coding same as Figure 7-11

26a-g, major 87% after purification

27a-g, minor

Top: The 26a-g/27a-g crude mixture; arrows highlight the minor products 27
Bottom: Pure 26a-g mixture after silica gel flash chromatography

Both hplcs are on a FluoroFlash™ analytical column, gradient 95% MeOH/water for 15 min, then 100% MeOH

Fig. 7.12. Obtaining pure mixtures from impure mixtures by silica gel chromatography
However, the mixture can be resolved into its two underlying N-propargylation 26a–g and O-propargylation 27a–g sub-mixtures without the demixing that attends fluorous chromatography. Simple flash chromatography on standard silica gel results in a less polar fraction containing all seven O-propargylated products 27a–g followed by a more polar fraction containing all seven N-propargylated compounds 26a–g. The fluorous HPLC chromatogram of this latter mixture is also shown in Figure 7-12. This ability to purify mixtures of fluorous-tagged compounds without demixing relies on the inherent differences between fluorous silica gel and regular silica gel. On regular silica gel, the structure of the organic functionality dominates and there is a profound reordering of the elutions of the components. In this example, the reordering is so profound that the O-propargylation product with the longest (that is, least polar) tag still comes off far before the N-propargylation product with the shortest (that is, least non-polar) tag! Experiments like this clearly show that fluorous silica deserves its own classification and is not a standard “reverse phase” of regular silica gel [37].

7.4.2.4 Derivatization for Chemical Analysis
Derivatization of chemical samples followed by SPE clean-up and HPLC analysis is common practice in analytical chemistry [18]. To date, the use of fluorous derivatizing agents coupled with SPE and/or HPLC analysis seems to have escaped the attention of the analytical community, but there is clear potential for widespread application. Take for example the fluorous triazoline dione shown in Figure 7-9. This is an excellent dienophile and could be used to derivatize mixtures containing suitable dienes for clean-up by SPE followed by HPLC analysis. The possibilities are limited only by the available derivatizing reagents.

7.5 Separation of Fluorous Compounds on Non-Fluorous Media

The unique features of separation of fluorous compounds over fluorous silica gel have generated confusion about the roles of standard media such as silica gel and reverse phase silica gel in fluorous separations. Some seem to think that these traditional media are not useful, but this is a mistaken assumption. Others seem to think that standard media can be substituted for fluorous media with no effect, and this is equally mistaken. Indeed, one of the strengths of light fluorous synthesis techniques is that regular silica, reverse phase silica and fluorous silica are all useful and in many respects complementary separation media. Here we provide guidelines on when to use and when not to use other media in place of fluorous media.

When the target mixture to be separated contains components with the same fluorous tag, all types of separation media should be considered. This type of separation is very common in the synthesis and purification of new fluorous reagents, reactants, catalysts, etc. For example, many procedures to prepare fluorous phosphines in the literature result in products contaminated with greater of lesser quantities of the phosphine oxides bearing the same fluorous group. While these phosphine/phosphine oxide mixtures can be separated by fluorous chromatography, their separation on standard silica gel is equally easy and is more cost efficient. Fluorous-tagged intermediates prepared on a large scale have also frequently been purified by flash chromatography on standard silica gel.
In short, when the separation targets differences in the organic domains of molecules with identical fluorous domains, regular silica gel is a material of first choice due to its low cost, while fluorous silica gel and possibly reverse phase silica gel are viable backups when performance is not satisfactory. However, even when we use regular silica gel for preparative separations, we almost always use fluorous silica gel for the analysis because it often provides superior separations of products with the same tag, especially when these are isomers. Then as we scale up syntheses of new fluorous reagents, reactants and catalysts, we almost always look to replace chromatographic separations with crystallizations or precipitations.

*When the target mixture to be separated contains fluorous-tagged compounds and non-fluorous-tagged compounds, we highly recommend fluorous silica gel as the first choice separation medium.* This is the case in the standard use of fluorous catalysts, reagents, reactants and scavengers in organic small molecule synthesis. This is not because regular or reverse phase silica gel cannot ever be used. Indeed in some cases they clearly can because fluorous tags are non-polar and have a tendency to behave like “lipophilic tags” that can be used in polar non-polar fractionations by SPE. Indeed, in these separations, fluorous tags $R_f$ should be better retained than alkyl tags $R$ of the same length since CF$_2$ groups are more hydrophobic than CH$_2$ groups. However, the selective retention of fluorous materials on fluorous silica gel still makes this pairing the first choice. Fluorous/non-fluorous separations will be larger on fluorous silica. This provides for more robust methods that work better across diverse members of a library and are more easily translated into other settings. Compared with an SPE with standard reverse phase silica gel, higher loading levels will be possible with fluorous silica gel and first-pass solvents will have considerably lower water content.

We have observed the superiority of fluorous silica gel in separating fluorous-tagged and non-tagged compounds many times, and this can be illustrated even by simple TLC experiments, as shown in Figure 7-13 [38]. The targeted mixture for separation comprises organic alcohol A, a model for an organic reaction product, and fluorous alcohol B, a model for a fluorous reagent or scavenger. TLC separations are shown on standard silica gel in two different solvent systems (hexane/EtOAc, 9/1 and 2/1), on reverse phase silica gel (MeOH/...
water, 70/30), and on fluorous silica gel (MeOH/water, 80/20). The solvent system for the reverse phase TLC was chosen such that the better retained fluorous alcohol had about the same retention factor \( R_f = 0.08 \) on both reverse phase and fluorous TLC plates.

Visual inspection shows the clear superiority of the fluorous silica gel to effect this separation. The separation on regular silica gel would require a very careful chromatography. The C8F17 group of B is much more lipophilic than the phenyl group of A, yet B is only slightly better retained, presumably because of the strong interaction of the alcohol with the silica gel. Although obviously inferior to fluorous silica gel, the separation provided by reverse phase silica gel does not look unpromising at first glance. However, consider a library experiment where B is being separated from organic products of diverse structures. On both regular silica gel and reverse phase silica gel, these products could potentially span the whole range of the TLC plate from top to bottom. On the fluorous silica, all the organic products are expected to have retention factors of 0.5 or above. In a simple view, the fluorous silica gel provides a general “fluorous/organic” separation but the regular and reverse phase silica gels do not.

In summary, moving away from fluorous silica gel for a fluorous/non-fluorous separation eliminates one of the principle features of the fluorous methods – the selective retention of fluorous compounds on fluorous silica. This does not mean that fluorous/non-fluorous separation are not possible, it simply means that they may not be as robust or reliable and that it may take more time to identify suitable general conditions, especially in library synthesis. If you want to get it right the first time, then just use fluorous silica gel.

When the target mixture to be separated contains isomers or analogs bearing different fluorous tags, fluorous silica is again the first choice because of its ability to separate by fluorine content. This is the case in demixing at the end of a fluorous mixture synthesis. Again, it might be possible to use other media in some applications, but fluorous media will be superior. This point is illustrated in Figures 7-14 a and b, which show attempted demixings of the mappicine mixture FTI 7,6,2 \( \{28a-g\} \) on standard “C18” reverse phase column, on a “PFP” column [PFP is “pentafluorophenyl” in the bonded phase silica–OSi(Me)2CH2CH2C6F5], and on a FluoroFlash™ column.

Depending on your point of view, the demixings on the C18 and PFP columns are partially successful, no doubt because hydrophobicity increases as CF2 groups are added to the fluorous tag. But they are clearly not optimal for at least three reasons: (1) the compounds elute

**Tagged mappicines 28a-g**

![Tagged mappicines 28a-g](image)

**Fig. 7-14a.** Structure and tag coding of mixture FTI 7,5,6 \( \{28a-g\} \)
Fig. 7-14b. Comparison of reverse phase (C\textsubscript{18}), pentafluorophenyl (PFP) and fluorous HPLC columns in demixing of FTI 7,5,6 (28a–g, 80/20, MeOH/water to 100%, MeOH over 8 min, then 100% MeOH)
in a narrower range (that is, there is more chance for overlapping peaks), (2) accumulated organic (non-tagged) impurities are expected to elute at or near the solvent front on the fluorous column but may elute across the chromatogram of the other two columns (notice how some of the minor peaks are intersperse with the target peaks, especially in the C_{18} chromatogram), and (3) sacrificing the selective fluorine–fluorine interaction increases the likelihood that secondary separations will overwhelm the tag effects and peaks will overlap or even swap places. This is readily seen by comparing the compounds with the C_{8}F_{17} and C_{9}F_{19} tags, which are well resolved in the fluorous chromatogram (top), are barely resolved (could not be preparatively separated) in the PFP chromatogram (middle), and overlap in the C_{18} chromatogram (bottom). Even worse, the C_{4}F_{9} and C_{6}F_{13} tagged compounds nearly overlap in the C_{18} chromatogram; there is no room for a prospective analog with a C_{5}F_{11} tag (which was omitted only because the required precursor was not available when the synthesis was started.) These problems were induced by a deliberate mismatching of tag and side-chain substituents, and so could have been avoided. However in many mixture applications, side chain effects on chromatography cannot be predicted in advance, so the best possible tag-based separation medium, fluorous silica gel, is needed.

Recently, Matsuzawa and Mikami have recommended that β-cyclodextrin columns be used for demixing of fluorous-tagged compounds [39]. They propose a selective inclusion of the fluorous tags into the cyclodextrin as the basis for a separation of homologous esters of fluorous alcohols and conclude that cyclodextrin columns are superior to fluorous columns. Mikami appears to conclude that the cyclodextrin columns are superior because demixings are faster on these columns. We believe that this conclusion is premature, and that there are pitfalls to be avoided here. Mikami’s model compounds are derived from the same organic unit and differ only in the fluorous tag. Compounds differing only in their fluorous tags must separate to some extent on virtually any standard column due to their differences in polarity. For example, had we tagged any single compound in Figure 7-14a with different fluorous tags and analyzed only by reverse phase HPLC, we could easily have concluded that this would be an appropriate demixing media. However the results in Figure 7-14b clearly show that fluorous silica gel is superior. The reverse phase columns in Figure 7-14b and perhaps the cyclodextrin columns in Mikami’s work provide inherently faster separations because the compounds elute closer together. We view this as a disadvantage, not an advantage. Optimization of the speed of any demixing is easily done by adjusting the solvent gradient.

Nonetheless, the cyclodextrin columns are a promising lead and more work to evaluate their merits relative to regular, reverse phase and fluorous silica is warranted. As with the other materials above, cyclodextrin columns do not have to be universally superior to fluorous ones to be useful. This point is nicely illustrated by recent work from the Takeuchi group [40]. They reduced a mixture of ketones M-29 bearing the same homologous tag with chiral and achiral reducing agents, and recorded the chromatograms of the resulting alcohol mixtures M-30 on a β-cyclodextrin column. The chromatogram from the chiral reduction product is shown in Figure 7-15. Since only the tags vary, the sample can be demixed to its tag components by any type of medium, but the chiral cyclodextrin column provides a secondary separation of the enantiomers so the ee of each product can be quantified. The chromatogram also shows that tags do not affect the stereoselective reduction, since all of the products are formed in about the same ee.
7.6 Biphasic Reactions with Fluorous Silica Gel

Recently, fluorous solid materials have been added directly to reaction mixtures in methods that parallel fluorous liquid/liquid biphasic reactions and fluorous thermomorphic reactions (Chapter 4). Gladysz first added Teflon® to conjugate addition reactions of benzyl alcohol 29 to methyl propiolate 32 catalyzed by the fluorous phosphine 33 (Figure 7-16) [41]. After heating to promote reaction, cooling and decantation, the product 34 was isolated from the

\[
\begin{align*}
\text{M-29} & \quad \text{10% chiral borane} \quad \text{BH}_3 \quad \text{M-30} \\
\text{contains Rf} & \\
c & \text{C}_4\text{F}_9 & \text{b} & \text{C}_8\text{F}_{13} & \text{c} & \text{C}_9\text{F}_{17} & \text{d} & \text{C}_{10}\text{F}_{21} \\
\end{align*}
\]

\(a\) separation on SUMICHIRAL OA-7500 cycloextrin column; acetonitrile/water, 55/45; minor enantiomers are highlighted with arrows; Chromatogram provided by Prof. S. Takeuchi and Dr. Y. Nakamura, Niigata University of Pharmacy and Applied Life Sciences

Fig. 7-15. Analysis of a non-racemic fluorous alcohol mixture from chiral reduction
hexane phase in high yield contaminated by only 0.4% of the catalyst. Extraction of the Teflon® shavings provided about 98% recovery of the fluorous material which was mostly (89.5%) phosphine 33 along with two other species that were postulated to be unspecifiededucts on the reaction pathway. One of the strengths of this work is that the ability to recover the catalyst intact is clearly demonstrated. However, it is not entirely clear whether the fluorous nature of Teflon® is essential for the removal of the catalyst in this reaction. This phosphine has a low solubility in hexane at room temperature or below, and can also be conveniently used in thermomorphic reactions without any added support.

More recently, the groups working with Bannwarth and Tsang have reported similar techniques with fluorous silica gel [13, 14]. Bannwarth and coworkers have conducted biphasic Heck and Suzuki reactions with catalyst 35 deposited on fluorous silica gel [13] (Figure 7-17). After heating, cooling and filtration, the product is isolated from the liquid phase and the fluorous solid phase is used directly in additional cycles. In one experiment, only about 2% of the originally introduced Pd was found in the organic product. However, the recovered catalyst on the silica gel was not analyzed, and the catalyst itself is heavily fluorous and is highly insoluble in organic solvents. So the experiments still leave unclear whether the fluorous silica gel functions as a passive support (in other words, non-fluorous materials or no materials at all could also be used) or an active support (the catalyst does not just precipitate but actively partitions onto the support). Unfortunately, the possibility that some
active palladium species simply leaches from the support and catalyzes successive reactions
must also be considered, since this has been shown to occur with solid-supported palladium
catalysts [42]. Going forward, it will be important to sort out these possibilities with appro-
priate experiments. However the convenience of having a support to hold the catalyst, espe-
cially on a small scale, is already evident.

In a somewhat different approach, Bannwarth and coworkers also reported the synthesis
of quinazoline diones by using a heavy fluorous Cbz tag and supporting intermediates
on silica (Figure 7-18) [43]. For example, supported intermediate 36 is treated with a primary
amine, TBTU and Hunig’s base in THF. Since THF is an excellent solvent for fluorous
compounds, the tagged intermediates and products will partition predominately into the
THF phase during the reaction. Then the solvent is removed to redeposit the residual ma-
terials, and the non-fluorous compounds are washed away with 80% MeOH/water to give a
pure supported product 37 ready for the next reaction.

This process very closely resembles the fluorous solid phase extractions described above.
Indeed, one of the standard SPE procedures is to add fluorous silica gel to a reaction mixture
and then to evaporate the solvent to deposit the residue on the silica. This material is then
washed with MeOH/H2O in the first-pass of the SPE. The difference here is that the second-
pass of the SPE is omitted. Instead, the solid-supported fluorous material is simply added to
the next reaction, where the reaction solvent for the next step extracts it off. The convenience
of having a free-flowing powder of a supported product is clear, and the use of the heavy
fluorous tags as opposed to light ones no doubt helps to minimize the amount of fluorous
silica that is needed to support the intermediates.

7.7 Conclusion

Originally called silica gel with a fluorocarbon bonded phase, fluorous silica gel predates the
fluorous field. However for almost two decades, it was like a separation medium without
its natural analyte. While it found and still finds important niche roles in analysis of non-
fluorinated or lightly fluorinated organic or biological molecules, its natural calling is in the
analytical and preparative separation of fluorous compounds either from non-fluorous compounds or from each other. From modest beginnings in a simple solid phase extraction of a heavy fluorous tin derivative, fluorous silica gel has emerged to facilitate whole new branches of fluorous chemistry, including all light fluorous synthesis techniques and fluorous mixture synthesis. In turn, the increased use of fluorous silica gel in its natural element is generating a better understanding of its properties, and this has engendered new applications in analytical and preparative separations. As awareness of the power and properties of fluorous silica gel continues to increase, so will its use both in and beyond the fluorous field.

Acknowledgements

I warmly thank present and former students and coworkers at both Pitt and FTI for their many contributions to our work with fluorous silica gel, and I also thank Professors Ilhyong Ryu and Seiji Takeuchi for their friendly collaborations. I thank the National Institutes of Health, Bayer and Merck for funding. In addition, I thank Christine H.-T. Chen and Wei Zhang of Fluorous Technologies, Inc. for providing material for several figures.

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37 Early on, we and others used the term “fluorous reverse phase silica gel”; however, we no longer recommend this term since fluorous silica gel is so different from reverse phase silica gel.

38 Dr. Stefan Werner, University of Pittsburgh, unpublished experiments.


8
Light Fluorous Chemistry – A User’s Guide

Dennis P. Curran

8.1 Introduction

After a brief induction period, the field of heavy fluorous chemistry prospered rapidly following Horváth and Rábai’s 1994 paper introducing “fluorous biphasic catalysis” [1]. The original focus on catalysis was soon complemented by fluorous protecting groups, reagents, scavengers and so on as the broader potential of fluorous chemistry began to be recognized (see the reviews in Chapter 9). Underpinning all this work was the need for high or at least moderate partition coefficients into fluorous solvents for the fluorous component of any reaction. Indeed, much of the early work in the field focused on making ligands, especially phosphines, of differing fluorine content to answer the central question: how many fluorines are needed to make a molecule fluorous? An early guideline advanced independently by both Horváth and our group is still handy – molecules require about 60% fluorine by molecular weight to be useful in liquid/liquid separations. Recently, more sophisticated and correspondingly more useful treatments of solubility have emerged [2].

Researchers apparently underestimated the number of fluorines needed to make a molecule fluorous, since many of the early molecules that were made did not exhibit high partition coefficients into fluorous solvents. Increasing the fluorine content of a large organic molecule to the region of 60% requires hefty fluorous tags since fluoroalkyl groups themselves are only about 75% fluorous. In 1997, we proposed what has quickly proven to be a general solution to the problem of what to do when partition coefficients are too low for liquid/liquid extractions. We replaced the liquid/liquid extraction with a solid phase extraction (SPE) over fluorous silica gel [3]. This procedure and subsequent fluorous flash chromatography and HPLC (see Chapter 7) enabled the field of light fluorous chemistry to develop.

The names “light” and “heavy” refer qualitatively to the weight of the fluorous tags involved in the techniques [4]. Representative light and heavy fluorous molecules along with their molecular weights are shown in Figure 8-1 [5, 6]. Heavy fluorous molecules typically contain at least 39 fluorines, and often many more, adorned on one or more tags (or sometimes termed “ponytails’’). At the low end, molecular weights can be over 1 000 mu, while catalysts with multiple ligands each in turn having multiple fluoroalkyl groups can weigh 3 000 mu or more. Heavy fluorous molecules must full their weight by virtue of ease of
recovery and reuse. Many heavy fluorous applications involve catalysts, where the mass of fluorous material is not a major concern since so little is being used in the first place. Heavy fluorous molecules can be separated from reaction mixtures by both liquid/liquid and solid/liquid techniques. While liquid/liquid techniques are far more prevalent, the convenience of fluorous solid phase extractions, especially on a small scale, should not be overlooked.

Light fluorous molecules typically contain 21 fluorines or fewer, and molecular weights can range from 400 to about 900 mu (or more for catalysts containing multiple light ligands). They may exhibit little or even no solubility in fluorous solvents, so separations with fluorous solid phases are often the only practical methods. In addition to their lower molecular weights and decreased cost, light fluorous molecules typically have far better solubilities in organic solvents than their heavy siblings, so identifying suitable reaction solvents and conditions is not difficult. Often, conditions for traditional organic reactions with no fluorous reaction components can simply be hijacked and used directly.

Between light fluorous chemistry and heavy fluorous chemistry lies a continuum (bantam weight fluorous chemistry, middle weight fluorous chemistry, welter weight fluorous chemistry, etc.) exhibiting features intermediate between the two ends of the spectrum.

Within the broad confines of “separation strategy”, both light and heavy fluorous synthe-
sis involve molecules with separation tags [7]. The most common separation tags to date have been polymers [8], so a comparison of traditional solution phase methods and polymer-bound methods to light fluorous methods is instructive (Figure 8-2). Traditional solution phase methods are strong in reaction, analysis and identification features, but separation is a major bottleneck. In addition, mixture synthesis is not practical if individual products are targeted.

Attachment of a reagent or intermediate to a resin makes the transition from the chemistry of molecules to the chemistry of materials [9]. Separation of insoluble polymer-bound materials by filtration is exceptionally easy, and the commercially important techniques of peptide and oligonucleotide synthesis attest to the value of solid phase synthesis. Split-mix synthesis is also a powerful technique that is facilitated by the simple feature that one bead can easily be separated from another [10].

With these advantages come disadvantages. Finding suitably general reaction conditions can be time consuming, and large excesses of reagents and reactants are typically required to drive reactions to completion. Despite the excesses, reaction times can be long. Near-quantitative yields are essential since there are no general ways to purify resin-bound compounds. Swelling characteristics and backbone functionalities of polymers limit their applications. Despite major advances, analysis and identification are not nearly as straightforward.

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<th>Traditional Solution Phase</th>
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mmol/g of reactants 2-3 0.1-1 1-2

**Fig. 8-2.** Qualitative comparison of traditional solution phase, solid phase and fluorous methods
for materials as they are for molecules. Some of these limitations can be bypassed by using polymer-bound reagents (sometimes called polymer-assisted solution phase synthesis) [11], but the slow reactions, the need for large excesses and the swelling limitations remain. Despite these limitations, solid phase techniques have added major new options for many reactions and chemistries.

In contrast to solid phase methods, light fluorous methods involve molecules and not materials. Reaction chemistry typically occurs in solution, so light fluorous chemistry is best considered solution phase synthesis with separation tagging. The fluorous tag enables a simple SPE separation, not unlike the filtrations of solid phase synthesis. However reactions are often rapid and clean and large excesses of reagents are neither required nor even beneficial in many cases. The full complement of small-molecule analytical (TLC, HPLC, and in many cases even GC) and identification (NMR, MS, IR, etc.) techniques are routinely in play. Also, using fluorous-tagged molecules actually expands rather than contracts separation options since in addition to all the standard methods (distillation, crystallization/precipitation, chromatography over regular or reverse phase silica gel), separations over fluorous silica gel are viable and often uniquely powerful added options. Molecular masses of light fluorous molecules (indicated by the polymer standard of mmol g$^{-1}$ in Figure 8-2) are typically closer to traditional non-tagged molecules than to polymers.

Heavy fluorous methods share most of the features and advantages of their lighter cousins, except for one – the ready identification of suitable reaction conditions and solvents. In our experience, finding suitable reaction solvents for heavy fluorous molecules is more analogous to solid phase synthesis than to light fluorous synthesis. The direct porting of traditional conditions is only occasionally successful and case-by-case optimization is needed. Generally, the problem is finding solvents in which both the heavy fluorous and non-fluorous reaction components are soluble, and many potential solutions, including the use of hybrid (partially fluorinated) solvents are now available [12].

Some observations by Takeuchi and coworkers nicely illustrate the qualitative differences between light and heavy fluorous molecules (Figure 8-3) [13]. Heavy fluorous amino alcohol 1a (MW = 2436) bears 78 fluorines and exhibits excellent partition coefficients (>95/5) out of several organic solvents into FC-72. However these same properties that are so favorable

![Fig. 8-3. Yield and selectivity differences in asymmetric ethylations with heavier and lighter fluorous ligands](image-url)
in separation cause problems in reaction. Attempted asymmetric ethylation of benzaldehyde with diethyl zinc in toluene/hexane was not successful, presumably because 1a is not soluble in toluene. Substituting the partially fluorinated benzotrifluoride (C₆H₅CF₃) [12b] for toluene produced alcohol 2 in 24% yield and 54% ee. This result is still inferior though to the 93% yield and 83% ee obtained with the lighter (39 fluorines, MW = 1308) amino alcohol 1b. Amino alcohol 1b is more a “middle-weight” fluorous compound than a light one, since it can be recovered and recycled by liquid/liquid extraction. But multiple extractions are needed, and separation by solid phase extraction is more convenient.

It is not appropriate to conclude from these experiments that heavy fluorous ligand 1b is inferior across the board to middle-weight ligand 1a in both yield and ee. It is more likely that middle-weight amino alcohol 1a is more similar to the standard organic amino alcohol, so standard conditions may be used. While not certain, it is possible that with further optimization of conditions, amino alcohol 1a could provide similar yields and ee to 1a. However time is money, and middle-weight and especially light fluorous reagents and catalysts can save both by obviating the lengthy process of optimization of reaction conditions.

8.2 Sources of Light Fluorous Compounds and Products

Most light fluorous techniques involve the use of fluorous silica gel (silica gel with a fluorocarbon bonded phase), and varieties and sources of this material are covered in detail in Chapter 7. Fluorous triphasic reactions are currently the only light techniques that use fluorous solvents, and the types and sources of these solvents are covered in Chapter 4.

When possible, the examples in the following sections will feature commercial light fluorous compounds. Fluorous Technologies, Inc. currently offers by far the broadest selection of light fluorous compounds, including assorted reagents, reactants, scavengers, protecting groups, tags, ligands and catalysts [14]. Although the selection is increasing rapidly, it is still not large when compared with traditional or resin-bound reaction components, and the synthesis and study of new light fluorous reaction components is a lively research enterprise. For those so-inclined to make their own reagents, a diverse array of building blocks are available from many suppliers including Aldrich, Fluka, Ozark, Gelest, Matrix and Fluorochem, to name a few. Representative key building blocks are shown in Figure 8-4, and chemistries to incorporate these building blocks into both heavy and light fluorous molecules are featured throughout this Handbook. So the balance of this chapter will focus on the use of light fluorous molecules rather than their synthesis.

![Representative commercial or readily available fluorous building blocks](image_url)
Light fluorous synthesis techniques were introduced by Curran and coworkers in a pair of papers 1999 [4] and 2000 [15]; the first paper demonstrated the principles in a fluorous protecting group setting and the second in the setting of fluorous reagents and ligands (phosphines). Today, reactions of light fluorous molecules are frequently coupled with SPE separations over fluorous silica gel, and the resulting methods have broad general applicability in the synthesis of many classes of organic molecules. Early work in the area is covered in several reviews and overviews [16]; however, the recent review of Zhang is recommended as timely overview [17].

Here we give a high level treatment and highlight by way of example the different ways that light fluorous synthesis methods are being used. The framework is that of “strategy-level separations” with separation tags, introduced first in 1996 [18] and then laid out in more detail in 1998 [5] and thereafter [19]. Reactions are organized based on the phase behavior of their precursors and products into five broad categories: (1) organic precursors and products (fluorous reagents, reactants, catalysts, scavengers are used); (2) fluorous precursors and products (fluorous tags or protecting groups are used with standard non-fluorous reagents); (3) fluorous precursors and organic products (a “phase-switch” is conducted by removing a fluorous tag); (4) organic precursors and fluorous products (a “phase switch” is conducted by adding a fluorous tag); and (5) combinations of solid-phase and fluorous methods. The division is for organizational purposes only. In practice, all of the methods can be mixed and matched not only with each other but with other strategy separation methods such as polymer-assisted solution phase synthesis.

8.3.1 Organic Precursors and Organic Products

The separation goal of “product purification by workup” [5] dictates that traditional solution phase synthesis of small organic molecules be modified such that, ideally, the only “organic molecules” left at the end of a simple workup are the target molecules [16]. Here “organic molecules” are defined more narrowly as molecules partitioning into organic solvents. Workup level separation techniques include extraction (liquid/liquid or solid/liquid), evaporation and filtration. The traditional approach of converting small organic molecule precursors into products is popular in medicinal chemistry and natural products settings because target molecules need not be tagged in any way. Reagents, reactants, catalysts and scavengers can be inorganic or volatile molecules, but more typically bear separation tags including polymers, ionizable and other chemical tags, or fluorous tags. The relative merits of the fluorous tagging approach have been summarized in the Introduction (Section 8.1). An assortment of fluorous reaction components are now commercially available and reaction conditions are typically taken directly from related non-fluorous examples. So this is not only one of the most powerful but also surely the simplest of light fluorous techniques. If you are new to fluorous methods, then here is the place to start.

In Figures 8.5–8.7, representative examples are selected from recent work to highlight the broad potential applications of fluorous reagents, fluorous catalysts and fluorous scavengers.
The reagent application involves fluorous triarylphosphine \textsuperscript{2}. Many olefination and other reactions rely on the conversion of triphenylphosphine to its derived phosphine oxide as a driving force. Separation of the phosphine oxide from target products is notoriously difficult, and careful chromatography is often the method of choice. Lindsley and coworkers at Merck \cite{20} have introduced a simple yet general protocol for conducting parallel solution phase Staudinger reactions, and Figure 8-5 shows a representative example. Reduction of \textsuperscript{3} with fluorous phosphine \textsuperscript{2} in THF, followed by rapid solid phase extraction over Fluoro\textsuperscript{Flash} TM silica gel with 85\% MeOH/water, provides amine \textsuperscript{5} in excellent yield and purity. This reaction is typical of light fluorous synthesis techniques that use a standard organic solvent for reaction and replace a chromatography with an SPE, and it shows excellent functional group tolerance and generality \cite{20}. Since organic compounds are not retained with 85\% MeOH/water, these SPE conditions should be translatable to essentially any reaction producing phosphine oxide \textsuperscript{4}. In head-to-head comparisons with resin-bound phosphines, fluorous phosphine \textsuperscript{2} promoted a much faster reaction, and provided products in better yields and purities. Consumption of reactants and formation of products was readily monitored by TLC.

The pace of development of heavy fluorous catalysts has far exceeded light fluorous catalysts to date, but work with light fluorous catalysts is accelerating. Figure 8-6 shows recent examples of reactions of fluorous palladium catalysts. Heck reactions mediated by catalysts \textsuperscript{6} and \textsuperscript{10} can be conducted under traditional or microwave \cite{21} conditions, and the catalyst-derived products can be removed by simple fluorous SPE \cite{22, 23}. Fluorous dppp analog \textsuperscript{6} shares with its non-fluorous counterpart the ability to promote the unusual \(\alpha\)-addition pathway in the addition of triflate \textsuperscript{8} to \textsuperscript{7} to give enamide \textsuperscript{9}. Catalyst \textsuperscript{10} shares with it non-fluorous counterpart high stability. After addition of iodobenzene \textsuperscript{11} to isoprene \textsuperscript{12} to give \textsuperscript{13}, catalyst \textsuperscript{10} can be recovered after the fluorous SPE, recrystallized, and reused. We project...
that the use of light fluorous catalysts coupled with SPE should be a general way to solve the problem of catalyst separation and recovery from small scales and upwards.

In parallel synthesis work, when target products will be contaminated with excess reagents or reactants or their byproducts, the technique of scavenging is often used to switch the phase preference of these undesired product components from organic to another phase for rapid separation. Although introduced at about the same time as polymer scavenging [24], fluorous scavenging is only now starting to catch on as its favorable features begin to attract attention. Early leaders in this area are Lindsley and coworkers at Merck [25] and Zhang and coworkers at FTI [26], and Figure 8-7 shows one example from each of these groups. In each case, the target reaction is conducted with one of the reagents in modest excess. Addition of the fluorous scavengers 14 and 15, followed by rapid reaction and then fluorous SPE serves to retain the scavenged adduct and the excess scavenger while allowing the target product to pass.

The usefulness of these techniques expands proportionately as more and more fluorous reagents, catalysts, ligands and scavengers are introduced and commercialized. Additional information on currently available compounds, including phosphines, tin reagents and catalysts, and fluorous diethylazodicarboxylates (DEAD reagents), selenium and sulfur reagents, hypervalent iodine reagents, a large assortment of transition metal and lanthanide catalysts, and assorted scavengers and scavenging techniques can be found in various reviews in Chapter 10.

Fig. 8-6. Microwave fluorous palladium reactions: representative uses of light fluorous catalysts
8.3.2 Fluorous Precursors and Fluorous Products

Although it has since been broadened to encompass essentially all fluorous techniques, the term “fluorous synthesis” was originally introduced by analogy to solid phase synthesis to describe the conversion of fluorous-tagged precursors to fluorous-tagged products. The concepts of this type of fluorous tagging were introduced in 1997 [24], and early implementations employed heavy fluorous molecules [27]. Recently, heavy fluorous tags and liquid/liquid separations have shown excellent potential in carbohydrate and peptide synthesis [28]. However, the majority of applications in this area shifted to the light fluorous mode following its introduction in 1999 [5]. Protecting group and tag applications are covered in this Handbook in more detail by W. Zhang (see review in Chapter 10); here we briefly provide features, concepts, and two representative applications.

Fluorous tagging applications of substrates and products can loosely be classified into one
of two groups based on the secondary role of the tag (the primary role is to facilitate separation): (1) fluorous protecting groups, and (2) fluorous traceless or displaceable tags. Fluorous tagging of target products is advantageous because the majority of commercially available reagents, reactants, catalysts and scavengers are not fluorous and therefore can easily be separated from fluorous-tagged target products following reactions. For parallel synthesis, a single protecting group can make a whole library of compounds fluorous. The predictable separations enable fluorous tagging to provide a combination of speed and high purity not matched by methods with other types of tags or without tags. Finally, recovery of the residual tag at the end of a sequence of reactions is frequently possible, so there is potential to reuse the tags another day.

Figure 8-8 shows a representative application of a fluorous protecting group along with a selection of known fluorous protecting groups. In the application, a fluorous carbobenzyloxy (F-\text{Cbz}) group is attached with reagent 16 to phenylalanine 17 by standard chemistry [29]. Then, the remaining acid of 18 is coupled with excess amounts of amines such as 19 under typical peptide coupling conditions with EDCI, HOBt and Et\text{3}N. Following the coupling, rapid fluorous solid phase extraction provides an organic fraction containing excess and spent reagents and reactants followed by a fluorous fraction containing the target product 20.

Reagent 16 is commercially available along with fluorous Boc (F-Boc) reagent 21 for nitrogen protection [30]. For oxygen protection, commercially available silane 22 can be converted \textit{in situ} into either a halide or triflate for subsequent silylation. So-called “FluoMar\textsuperscript{TM} reagent” (named after the solid phase analog, the "Marshall resin") can be acylated to make esters, and this group serves doubly for protection and later diversification by displacement [31]. A selection of other fluorous protecting groups that are suitable for light fluorous synthesis, including the F-alkoxydiphenylsilyl group 23 and the F-THP group 24, can be prepared from commercial fluorous building blocks in two or three steps [32].

Figure 8-9 shows an example of a displaceable fluorous tag from the work of Zhang at Fluorous Technologies, Inc [33]. Addition of thiol 25 to dichloropyrimidine 26 provides two regiosiomerically tagged scaffolds 27 and 28. Unlike polymer tagging where separation of such regioisomers cannot be contemplated, 27 and 28 are readily separated by standard flash chromatography and are isolated in 69 and 23% yields, respectively. Moving ahead with the major isomer 27, displacement with excess imidazole 29 followed by SPE separation provides 30. Oxidation of the thiol to the sulfone with Oxone\textsuperscript{TM}, followed by tag displacement and final SPE gives product 31 in 79% yield and 90% purity. An assortment of interesting and unusual heterocycles can be made by this powerful solution phase sequence.

8.3.3 Fluorous Precursors and Organic Products

When target compounds bear fluorous protecting groups or tags, a late (often the final) step in the synthetic sequence is the removal of the fluorous tag. This is illustrated by the displacement reaction of 30 to give 31 in Figure 8-9. Tag removal is an example of a ‘phase switch’, because the phase preference of the target molecules changes from fluorous to organic. In practice, this means that the target fraction of a fluorous SPE changes from the second to the first.
Since the residual tag in any detagging reaction will always be fluorous, its separation from detagged products by SPE is built in. Standard deprotection offers little beyond that, but well planned phase switches allow synthetic chemistry to dictate separation features. Consider the simple hydantoin synthesis in Figure 8-10 [34]. Reaction of fluorous amino ester 32 with isocyanate 33 provides adduct 34, which can be separated from excess isocyanate and other non-fluorous byproducts by SPE. However unreacted starting material 32 would presumably not be separated from 34 by SPE since it bears the same fluorous tag. Now, “cyclative cleavage” of crude 34 occurs with tag removal and attendant phase switch to give target hydantoin 35 which is present in the first pass of the SPE [35]. The original

![Chemical structures](image)
precursor 32 does not react under these conditions and it is retained on the column during the first pass. In short, well planned phase switches like this can serve as separation ‘check points’ for one or more prior steps of a synthetic sequence by allowing molecules that pass the test [that is, that have successfully reacted in the prior step(s)] to switch from fluorous to organic and preventing molecules that fail the test from switching.

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**Fig. 8-9.** A displaceable fluorous tag in action

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**Fig. 8-10.** Phase switching in a fluorous hydantoin synthesis
8.3.4 Organic Precursors and Fluorous Products

The phase switching of an organic precursor to a fluorous target product occurs each time a fluorous tag is introduced, and this always permits facile separation of tagged products from untagged starting materials. However the potential for separation goes beyond this in well-planned applications. An innovative sequence that makes this point is shown in Figure 8-11. Wipf, Reeves and coworkers added an equimolar mixture of six aryl- and heteroaryllithium reagents to aldehyde 36. The alcohol products of this reaction were then captured for removal from starting aldehyde 36, protonated heteroaromatics and other byproducts by reaction with fluorous vinyl ether 37 to give purified mixture 38. This early application is best considered as on the low end of heavy fluorous synthesis, and liquid/liquid extraction proved practical provided that water was added to help drive the fluorous products 38 out of methanol and into FC-72. Today, tag 37 or even a lighter variant could be used in combination with SPE to effect this unique type of purification of a mixture by phase-switching (or not) a subset of components based on the presence (or absence) of a target functional group (here, an alcohol).

8.3.5 Combinations of Solid Phase and Fluorous Methods

Phase tagging methods are not mutually exclusive and can be beneficially combined, as illustrated by a number of recent studies that unite fluorous and solid phase methods. The first work in this area was probably done by Wipf and Rover, and is summarized in Figure 8-12. Resin-bound precursor 39 prepared over several steps (not shown) was deprotected and oxidized, and ethyl magnesium bromide was added. Next, the resulting resin-bound alcohols 40 were tagged with the fluorous BPFOS group to give 41. Left untagged were by-
products resulting from the failure of the prior steps. Now, the crude product was removed from the resin and partitioned by SPE into an untagged fraction of impurities and a tagged fraction of \( \text{42} \), which was isolated in 11% yield and in good purity over 11 total steps. Subsequent transformations provided the target oxazoles and thiazoles \( \text{43} \), which are analogs of the natural product curacin.

The Wipf work nicely illustrates how fluorous tagging can be used in combination with solid phase synthesis to give pure products in complex, multi-step reaction sequences where quantitative yields cannot reasonably be expected. The recent elegant work of van Boom and coworkers [38], featured in Chapter 7, shows the potential for fluorous tagging in peptide synthesis and also shows that fluorous chromatography can play a powerful role in this setting.

Fluorous tags can also be used to mark undesired rather than desired products for subsequent SPE separation in a solid phase synthesis. This type of “fluorous end capping” has been deployed by Seeberger and coworkers in automated solid phase carbohydrate synthesis [39], and a representative example of a coupling/capping sequence with a fluorous silyl triflate is illustrated in Figure 8-13. Resin-bound acceptor saccharide \( \text{44} \) is coupled with solution phase donor \( \text{45} \) with associated coupling reagents. After separation of the reagent-derived products from the resin by filtration, unreacted acceptor saccharide \( \text{44} \) is endcapped.
with fluorous silyl triflate to give 47. Deprotection of 46 prepares the resin-bound material for the next coupling cycle. After cleavage of the crude product from the resin, SPE bifurcation then gives a non-fluorous target fraction containing 48 followed by a fluorous fraction containing truncated, endcapped products. The usefulness of the method was validated by the synthesis of several di- and trisaccharides.

8.4 Fluorous Mixture Synthesis

The speed and efficiency of mixture methods compel their consideration for synthesis of chemical libraries. However problems with analysis, separation and identification of mixture components can be formidable. Split-mix synthesis is a powerful technique that is typically
used to make small quantities of large numbers of compounds [8]. This solid phase technique mixes beads, not compounds, so separation is easy. As with other solid phase techniques, on-bead analysis of mixtures is limited, but the identification problem has been solved by the introduction of a number of ingenious encoding methods. Solution phase mixture synthesis without any separation tags has been used for some time to make large mixture libraries [40]. Little effort is made to analyze, separate or identify members of these libraries. Instead, various methods of deconvolution are used to interrogate mixtures and to identify features or even structures of active components.

Introduced in 2001 [41], fluorous mixture synthesis is the first and (to date) the only mixture synthesis method based on solution phase chemistry with separation tags that provides for the analysis, isolation and identification of individual pure products. Fluorous tags are used for target precursors and products. The use of individual tagged compounds as described above expedites synthesis by increasing speed and purity. Mixing tagged compounds also leverages synthesis by producing more compounds per unit effort. Fluorous mixture synthesis complements existing mixture techniques well since its strength is making larger quantities of smaller numbers of compound. (The largest fluorous mixture library reported to date is 560 members, although libraries an order of magnitude larger than this appear practical with existing technology.)

The diagram in Figure 8-14 illustrates the steps of a fluorous mixture synthesis for a simple three component mixture. Each of the initial three building blocks is coded by attachment to one of three homologous compounds, and then the tagged compounds are mixed. During the mixture synthesis phase, three-times more compounds are produced per reaction or separation compared with individual samples. The saving is proportional to the number of mixture steps – the more steps you do, the more work you save. This means that fluorous mixture synthesis is especially valuable in longer synthetic exercises, such as natural products synthesis, or in parallel synthesis exercises with late splits (the later the split and the larger the split, the more work saved). Before the final detagging step, the mixtures are “demixed” into their underlying pure components.

**Fig. 8-14.** The steps of fluorous mixture synthesis
Demixing is a separation based on the tag structure, and fluorous HPLC is used here because it separates primarily by fluorine content so components are expected to elute in order of tag size [42]. This expectation is confirmed by LC-MS or other traditional means. Finally, the individual products are detagged to give the final products. This detagging reaction should be simple and clean; simple because after the demixing there are now three times as many reactions to conduct (now the same number as a traditional parallel synthesis), and clean because the demixing is also an HPLC so highly pure final products can be generated simply by residual tag removal by evaporation or SPE.

Although preparative demixing is typically left until the end of a synthesis, analytical demixing can be done at any time and thus the mixture components can be separated, analyzed and identified on demand. For example, has a given reaction gone to completion and are there any byproducts? An LC-MS or even better LC-NMR experiment can answer such questions for each and every component of the mixture. While we give here a high level treatment, the implementation of fluorous mixture synthesis has induced us to evaluate and deploy a number of new techniques for analysis and characterization, and our papers (see below) contain more details on the practice of fluorous mixture synthesis in the laboratory. Fluorous mixture synthesis methods have been used to code enantiomers, diastereomers and analogs, and examples of each are provided.

8.4.1 Coding of Enantiomers – Fluorous Quasiracemic Synthesis

If you are an organic chemist, you have probably done a mixture synthesis without giving it a second thought. Racemic synthesis, or synthesis with an equal mixture of two enantiomers, was standard practice for decades and is still often used. Analysis of racemates poses no problems since enantiomers exhibit identical properties in many experiments (TLC, NMR, etc.). However separation and identification problems are non-trivial; at the end of a synthesis, how do you separate the two enantiomers and how do you know which enantiomer is which? These questions cannot usually be answered at a strategic level at the beginning of a synthesis, and instead research is needed at the end (finding a suitable chiral column, crystallizing a derivative, etc.).

Today, when both enantiomers of a compound are needed, they might well be made individually by asymmetric synthesis. However this takes up to twice as many steps as racemic synthesis. The new technique of fluorous quasiracemic synthesis unites the efficiency of racemic synthesis with the selectivity of asymmetric synthesis [31, 43]. Enantiomeric (ideally, enantiopure) precursors are tagged with different fluorous tags to make quasienantiomers (“quasi” because they are not isomers), which are then mixed to make a quasiracemate. Despite differing only by one or two CF2 groups, the quasienantiomeric components of the mixture can be demixed on demand with fluorous silica gel. However this is generally not necessary during a synthesis since, like enantiomers, quasienantiomers effectively exhibit identical spectroscopic properties so product analysis is routine. Preparative demixing at the end followed by detagging provides the two enantiomeric products of known absolute configuration as coded by the tag.

Quasiracemic synthesis was introduced with syntheses of mappicine and pyridovericin highlighted in Figure 8-15. To prepare mappicine, synthesis of enantiomers R-50 and S-50 by asymmetric reduction of 49 was followed by tagging (C6F13 to R and C8F17 to S) and
Mixing to give M-51. Four step quasiracemic synthesis with a cascade radical annulation as the key step then gave tagged mappicine quasiracemate M-52. This was demixed into its quasienantiomeric components, which were detagged to give natural S-mappicine 53 and its enantiomer R-mappicine.

**Fig. 8-15.** Summaries of fluorous quasiracemic syntheses of mappicine and pyridovericin
Pyridovericin’s absolute configuration was unknown, and both enantiomers were produced over a seven-step synthesis that started by mixing quasienantiomers. A completion of the synthesis, demixing and detagging gave R- and S-pyridovericin, and the S-enantiomer proved to be the natural product. A shortcoming of this synthesis was that the final products were not enantiopure due to partial epimerization during the synthesis. Traditional racemic synthesis is immune to racemization, so quasiracemic synthesis shares its susceptibility to this nasty disease with asymmetric synthesis.

Quasiracemates of most of the naturally occurring amino acids and their enantiomers have recently been produced with FCbz tags [26]. Natural L-enantiomers were given C₈F₁₇ tags, while D-enantiomers got the shorter C₆F₁₃ tags. Nucleophiles can be derivatized with these quasiracemates to provide both possible enantiomers (or diastereomers, if the nucleophile is chiral) in a single reaction and separation. In the example shown in Figure 8-16, coupling of tetrahydroisoquinoline with the quasiracemate of phenylalanine (Cbz-Phe) M-56 gives a crude reaction product that is subjected to rapid fluorous flash chromatography. An initial fraction containing unreacted and spent reactants is discarded. This is followed by a first fluorous fraction containing the (D)-57 and later a second fluorous fraction containing (L)-57. The fractions are well separated and there is no detectable cross-contamination. In short, two derivatives are obtained for the work of one.

### 8.4.2 Coding of Diastereomers

At the next level up, fluorous tags can be used to encode diastereomers for mixture synthesis. This can of course be done in combination with enantiomers to provide a general scheme for isomeric tagging. There is an additional level of complexity here since tagged
diastereomers could have different reaction and separation properties, but so far such problems have been surmountable.

We have made all 16 possible isomers of the insect pheromone 64 by a combination of fluorous mixture synthesis (four encoding elements) and splitting (four encoding elements) [44]. All four isomers of 58a–d were prepared with suitable fluorous para-methoxyphenylacetal tags. After mixing, PMP cleavage and oxidation, the quasiisomer mixture M-59a–d was divided in half for Kocienski-Julia olefination with either R or S sulfone 60 to give two mixtures of M-61. Deprotection, oxidation and a second split and pair of Julia olefinations with the same enantiomeric sulfones 60 gave 62 as four mixtures of four compounds. Deprotection, Wittig reaction and careful reduction with diimide then gave four mixtures of four compounds M-63a–d with each mixture containing one of the four possible sets of configurations at C7 and C11, and all four of the possible sets at C2 and C3. Demixing of each of the four mixtures followed by simple detagging and acylation provided all 16 of the pheromone isomers 64 in individual pure form at about the 20 mg scale.

More recently, we have completed a more ambitious synthesis of all 16 dihydroxy THF isomers of the natural product acetogenin murisolin 66, starting from the tagged diastereomers 65 and using a similar “4-mix/4-split” strategy, and we have been able to confirm the structure of murisolin [45]. Workers in the acetogenin area have long recognized that stereoisomers of these compounds can have very similar spectroscopic properties [46]. Although just how similar are they? The 16 murisolin isomers 66 exhibit only six unique sets of ¹H and ¹³C NMR spectra at 600 MHz! Every isomer shares an identical spectrum with at least one and sometimes three other diastereoisomers. Clearly, high field NMR spectroscopy cannot provide all the answers in structure assignments of these compounds, even when all the authentic samples are on hand for comparison. Fluorous mixture synthesis is a great aid for difficult stereostructure problems such as murisolin. With all the candidate isomers on hand for a given compound, other methods such as derivatization, chromatography and optical rotation can then be assessed to differentiate similar candidate structures.

8.4.3 Coding of Analogs

Increasing the level of difficulty one more notch, a series of analogs can be coded with fluorous tags. Now the risk of the secondary separation dominating over the primary tag-based separation in fluorous HPLC increases (see Chapter 7), but the problem is far from unmanageable and can be minimized by intelligent choice of tag coding scheme. In the longest linear fluorous mixture synthesis to date, four truncated analogs of the complex natural product discodermolide have been made over eight steps [47]. Figure 8-18 illustrates the power of splitting in a 7-mix/8-split/10-split exercise to make 560 analogs of the natural product mappicine conducted by Fluorous Technologies, Inc. (FTI) [48].

Seven alcohols 67 bearing different R⁰ substituents were coded with seven different fluorous tags and the tagged compounds 68 were mixed and taken through a four-step sequence with splitting in the last two steps. The product mixture M-69 after iododesilylation and de-methylation was divided into eight for reactions with eight different propargyl bromides. Each of these eight products M-70 was divided into ten for reaction with ten different isonitriles. The result was 80 individual mixtures M-71, each of which contained one of the 80
Pheromones

\[ \text{C}_6\text{H}_4(\text{CH}_2)_3\text{C}_4\text{F}_9 + \text{C}_6\text{H}_4(\text{CH}_2)_3\text{C}_6\text{F}_{13} + \text{C}_6\text{H}_4(\text{CH}_2)_3\text{C}_7\text{F}_{15} + \text{C}_6\text{H}_4(\text{CH}_2)_3\text{C}_8\text{F}_{17} \]

1) mix
2) cleave acetal
3) oxidize

\[ \text{FPMB} \text{ is } \text{Rf(CH}_2)_3\text{OC}_6\text{H}_4\text{CH}_2 \text{, where Rf is C}_4\text{F}_9, \text{C}_6\text{F}_{13}, \text{C}_7\text{F}_{15}, \text{or C}_8\text{F}_{17} \]

Acetogenins

\[ \text{FPMB} \text{ is } \text{Rf(CH}_2)_3\text{OC}_6\text{H}_4\text{CH}_2 \]

configuration coded to \text{FPMB} group

Fig. 8-17. Fluorous mixture synthesis approaches to pheromone and acetogenin isomers
possible combinations of \( R^A \) and \( R^B \) and all seven possible combinations of \( R^D \). Eighty demixings by serial fluorous HPLC followed by 560 detaggings with HCl and SPE through reverse phase silica gel (tag is retained, product passes) provide all 560 mappicines 72.

This synthesis began with about 15 g of the first mixture M-68 and produced about 1 g total weight of the 560 analogs 72. Thus fluorous mixture synthesis is scalable. The mixture part of the synthesis required only 90 steps \((1 + 1 + 8 + 80)\) compared with the 630 steps \((7 + 7 + 56 + 560)\) needed for the equivalent parallel synthesis, for a saving of 540 steps. The efficiency is also evident in the demixings, where 560 pure compounds were obtained from only 80 HPLC separations. The exercise proved to be more than a technology validation, since several of the mappicines in this library have shown promising activity in Rnase-H screens [49]. The best of these are being evaluated as potential lead compounds for the development of new AIDS chemotherapies.

While there are only a handful of papers on fluorous mixture synthesize to date, the results in these papers auger very well for future applications in natural products chemistry, drug discovery and other areas.

Fig. 8.18. FTI's fluorous mixture synthesis of 560 mappicine analogs
8.5 Fluorous Triphasic Reactions

As with fluorous mixture synthesis, fluorous triphasic reactions are nascent techniques with a potentially big future; however, triphasic applications are likely to be more on the process and production end of the chemical spectrum than on the discovery end. Fluorous biphasic reactions and fluorous triphasic reactions share an analogous name and both use fluorous reaction solvents. However the similarities end there. Fluorous biphasic reactions involve a reaction first and then a separation. They rely on heavy fluorous molecules and strive for homogenous reaction media. In contrast, fluorous triphasic reactions involve a reaction and a separation simultaneously with the reaction driving the separation. Light fluorous molecules are used, and homogeneity is verboten. We summarize here two types of applications: triphasic detagging and phase-vanishing reactions.

8.5.1 Triphasic Detagging Reactions

Fluorous triphasic reactions were introduced in 2001 in a setting of detagging of silyl ethers, and proof-of-principle experiments showed the viability of triphasic reactions as well as their ability to separate doped, non-tagged impurities from tagged compounds simultaneous with detagging [50]. The need to separate tagged from untagged compounds arises frequently in the real world during multi-step synthesis with fluorous tags (Section 8.3.2), and during kinetic resolution of racemates.

Figure 8-19 shows a recent coupling of an enzyme kinetic resolution and fluorous triphasic reaction to efficiently resolve 2-naphthyl ethanol [51]. Deacylation of racemic ester derivative rac-73 occurs with high enantioselectivity to provide alcohol \( R\)-74 and ester \( S\)-73 [52]. These can be separated by chromatography or repeated fluorous/organic liquid/liquid extraction and the recovered ester can be cleaved. However this is a two step process (separation followed by reaction), and the separation step is solvent-intensive. The coupling of the kinetic resolution with a fluorous triphasic detagging condenses the separation and reaction steps into one and dramatically reduces solvent use.

After filtration of the enzyme preparation and evaporation, the crude mixture of \( R\)-74 and \( S\)-73 is added to the source side of a U-tube containing MeOH. The receiving side of the U-tube contains MeOH/MeONa, and these two phases are separated by FC-72, which behaves like a liquid membrane regulating the exchange between the two organic phases. After 2 days, the contents of the two organic phases were recovered and analyzed. Remarkably, \( S\)-74 was recovered from the source side and the \( R\)-74 was recovered from the receiving side, while the transesterified tag was recovered from the fluorous phase. The results show that FC-72 permits the diffusion of the tagged enantiomer \( R\)-73 through the fluorous phase to the receiving side where it is detagged to \( R\)-74 and then stranded. The \( S\)-74 enantiomer has no tag in the first place so it remains in the source phase, while the residual tag is now quite fluorous and it heads for the FC-72.

Here a chemical reaction–transesterification–provides the energy to drive a non-equilibrium separation. At equilibrium, both organic phases must contain racemic alcohol 74, but reaching this equilibrium is agonizingly slow because of the low solubility of the
alcohol in the fluorous solvent. In short, these early results suggest that fluorous triphasic reactions have excellent potential for use in detagging, and resolutions loom as an important application.

8.5.2 Phase-Vanishing Reactions

At the upper end, light fluorous chemistry merges into heavy fluorous chemistry as the number of fluorine atoms increases. At the lower end, fluorous chemistry vanishes entirely as the number of fluorine atoms decreases. The natural conclusion is that it is impossible to do fluorous chemistry without fluorinated reaction components. However this conclusion is wrong! In phase-vanishing reactions, not only does a phase vanish, but so do all the fluorinated reaction components. The only thing fluorinated is the solvent, which again serves as a barrier to regulate the passing of a non-fluorinated reaction component.

An assortment of small molecules, especially halogenated or polyhalogenated ones, have
some solubility in perfluorinated solvents yet are not miscible. When such molecules can also be used as reagents or reactants in organic transformations, the requirements are met for a phase-vanishing reaction. Such reactions control addition rates chemically rather than mechanically, and should be especially convenient for exothermic reactions or any other reactions where a low-tech (or basic) yet effective regulation of addition rate is needed. In some cases, the vanishing of the reagent phase also provides a visual indication that the reaction is at or near completion.

Reagents for phase-vanishing reactions can be more or less dense than the fluorinated solvent, and an example of the former is shown in Figure 8-20. Ryu and coworkers have demethylated aryl methyl ethers 75 with BBr3 ($d = 2.65$) separated from an ether phase containing the substrate by perfluorohexane ($d = 1.7$) [53]. Gradual diffusion of the BBr3

---

**Single Reaction with More Dense Reagent**

![Diagram](image1)

**Three Reactions with Less Dense Reagent**

![Diagram](image2)

---

**Fig. 8-20.** Phase-vanishing reactions with reagents more (top) and less (bottom) dense than FC-72
through the perfluorohexane followed by demethylation forms the phenol 76 in the ether phase. When BBr₃ is used stoichiometrically, its phase vanishes towards the end of the reaction, hence the name. Cooling or mechanical means to limit an addition or control the heat evolution are not used in this low-tech reaction.

With reagents less dense than the fluorous solvent, Nakamura and coworkers showed that a U-tube setup can be used with the substrate on one side, the reagent on the other, and the fluorous solvent in the middle [54]. When used stoichiometrically, the reagent phase again vanishes near the end of the reaction. Figure 8-20 illustrates this system in a simple and convenient parallel setup for simultaneous chlorination of three alcohols. The top part of a test tube was divided into four compartments by glass slits, while the bottom was left open. FC-72 was added to a level above the lower end of the slits, then toluene solutions of three different alcohols were added to three of the compartments and thionyl chloride (d = 1.63) was added to the fourth. After 1 day, the thionyl chloride phase had vanished and the three chlorides were isolated from their corresponding compartments in 70–80% yields. Cross contamination could not be detected.

Clearly, any number of parallel reactions can be conducted in this way with suitably compartmentalized vessels. The same vessel design can also be used for parallel reactions with more dense reagents with the proviso that even one more substrate can be used since the reagent sits on the bottom and does not require its own compartment [53b].

### 8.6 Conclusion

Now about four years old, light fluorous techniques are already supplementing heavy fluorous techniques in catalytic and other important applications. However more importantly, they are complementing heavy fluorous techniques by opening up powerful new options. Many light fluorous techniques are enabled by fluorous silica gel separation methods. Uses of light fluorous reagents, catalysts and scavengers have almost no learning curve and are well within the comfort zone for the majority of practicing bench chemists. For some important reactions, everything that is needed is now commercially available, and basic fluorous SPE techniques are so similar to traditional methods that they can be learned easily without any difficulties. A step above this, fluorous tagging techniques reward a small time investment devoted to learning with significant potential time savings and purity gains in expedited parallel synthesis. The nascent technique of fluorous mixture synthesis leverages the effort of tagging by producing even more compounds, and mixture synthesis can be used to make enantiomers, diastereomers or analogs. Finally, fluorous triphasic reactions are liquid-based methods that show that light fluorous chemistry is not limited to silica techniques. As with mixture synthesis, the triphasic class has just been introduced and not only practical but probably also conceptual advances are still ahead.

### Acknowledgements

I warmly thank present and former students and coworkers at both Pitt and FTI for their many contributions to our work with fluorous silica gel, and I also thank Professors Hiro-yuki Nakamura, Ilhyong Ryu, and Seiji Takeuchi for their friendly collaborations. I thank
the National Institutes of Health, Bayer and Merck for funding. In addition I thank Christine H.-T. Chen and Wei Zhang of Fluorous Technologies, Inc. for providing material for several figures.

References

14 Fluorous Technologies, Inc. is on the web at www.fluorous.com. DPC is the Founder of this company and holds an equity interest.
17 W. Zhang, Tetrahedron, 2003, 59, 4475–89. I thank Dr. Zhang for a preprint of this review.
For the first example of cyclative cleavage

W. Zhang, Y. Lu,

W. Zhang,


P. Wipf, J. Reeves, S. Rover, US Patent 6,673,539.


Information on the potential limits of demixing is found in Chapter 7, Section 7.3.4.


Unpublished results of Prof. M. Parhiak, University of Pittsburgh, and Dr. W. Zhang and Ms. Christine Chen, Fluorous Technologies, Inc.


9
Getting Started in Synthesis: A Tabular Guide to Selected Monofunctional Fluorous Compounds

József Rábai

9.1 Introduction

The first steps when beginning a fluorous project are to purchase the necessary fluorous starting materials and synthesize the target molecules. The vendors of fluorous solvents listed in Table 3-1 also provide a number of fluorous building blocks, as does Fluorous Technologies Inc. (FTI, http://fluorous.com/index2.html). This chapter, augmented by the references to the table of partition coefficients in Chapter 6 (Table 6-1), is intended as a guide to the synthesis of simple fluorous molecules. It is by no means comprehensive, but does provide many useful leads for researchers just beginning in this field.

Looking first backwards to Table 6-1, it is easy to visually scan various families of functional groups and locate lead references. However, if the partition coefficient has not been measured, the molecule is not included. Furthermore, superior syntheses may have been developed after the initial literature report.

Recognizing this gap, this chapter summarizes a wide range of monofunctional “heavy” fluorous compounds and selected “light” fluorous compounds in a tabular form. In most cases, abbreviated synthetic details are indicated (“⇒” symbol), followed by the literature reference. In some cases, particularly useful reactions are indicated (“●+” symbol). More complex target molecules can then be assembled from perfluoroalkyl- and organic groups of appropriate topologies, sometimes inserting “insulator” groups between these constituents (cf. Chapters 4 and 5).

The latter strategy or modular synthesis calls for an “F-tool-kit” suitable for the most diverse applications. At one extreme, various target F-entities with linear perfluoroalkyl groups exhibit good organic solubilities under reaction conditions at higher temperatures, but quantitatively precipitate at lower temperatures (thermomorphism). At the other extreme F-derivatives with flexible and branched perfluoropolyether type substituents could have rather wide fluid temperature ranges (high-tech lubricants).

Syntheses involving highly fluorinated compounds will certainly provide simultaneous feelings of frustration and pleasure for those so engaged. This derives from differences in reactivity and solubility patterns from those experienced in traditional organic chemistry. The high electronegativity of fluorine atoms and perfluoroalkyl-groups strongly affect reac-
tion centers, unless appropriately positioned (cf. Chapter 5). Moreover, macroscopic properties, such as solubility, fluorophilicity, volatility, melting and boiling point, transition enthalpies, etc. are all governed by the composition and structure of the molecules. The higher their fluorous character, the more unique properties will be expressed.

The trifluoromethyl group, which can be regarded as the shortest F-ponytail, appears in the Beilstein database with a frequency one order of magnitude greater than all longer R₂₄GH*/R₂₅₋₂₄GH* = 205 000:24 000. Hence, some prototype chemistries known only for CF₃-compounds are also displayed in the Tables. In the first series of Tables, molecules without hydrogen atoms are collected. In the second, hydrogen atoms of all descriptions are allowed.

**Series I [no hydrogen included]**

9.1.1 Perfluoroalkanes, perfluoroalkenes and perfluoroalkynes
9.1.2 Perfluoroalkyl halides and related compounds
9.1.3 Perfluoroethers, perfluoroalkanones and perfluoroalkanecarboxylic acid halides
9.1.4 Perfluoroalkylsulfides and disulfides, perfluoroalkanesulfonyl halides and anhydrides
9.1.5 Tris(perfluoroalkyl)amines, perfluoroazomethines, perfluoroalkanenitriles, tris(perfluoroalkyl)triazines and perfluoroalkyl isocyanates
9.1.6 Perfluoroalkylmagnesium-, zinc-, copper(I)-, lithium-, and caesium intermediates.

**Tab. 9.1-1. Perfluoroalkanes, perfluoroalkenes and perfluoroalkynes**

<table>
<thead>
<tr>
<th>Compound [C,F]</th>
<th>Remarks (‘‘=‘‘ for synthesis of; ‘‘+‘‘ for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CₙF₂n+2, cyclo-CₙF₂n, etc.</td>
<td>⇒ + Disclosure of a ‘‘Secret World’: Properties of Fluorocarbons</td>
<td>1</td>
</tr>
<tr>
<td>Perfluoroalkanes</td>
<td>⇒ • + Synthesis and Chemistry of Perfluoroalkanes.</td>
<td>2</td>
</tr>
<tr>
<td>CF₃CF₂CF–C(CF₃)₂</td>
<td>• + KF + ROCH₂Cl/PTC, rt. → ROCH₂C(CF₃)₂CF₂CF₂CF₃ (82%)</td>
<td>3</td>
</tr>
<tr>
<td>CF₃(CF₂)₃CF–CF₂</td>
<td>⇒ R₂₄CO₂Na/heating → R₂₄CF–CF₂ + isomers, in a 73:27 ratio</td>
<td>4</td>
</tr>
<tr>
<td>RₙCF–CF₂, n = 1, 2, 3, 5, 7 (CF₁)₂C–CF₂</td>
<td>⇒ Prepared by the pyrolysis of the salts of Rₙ₋₁₂CO₂H’s</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>⇒ cyclo-CₙF₆/25 s at 710–730 °C/ → yield: 45%, bp = 6–9 °C</td>
<td>6</td>
</tr>
<tr>
<td>RₙC≡CRₘ, n = 2, 4, 8; m = 4, 6, 8</td>
<td>⇒ RₙC≡CH + RₘCl/220 °C → RₙC≡CHRₘ/base-PTC → overall yield: 40–59%</td>
<td>7</td>
</tr>
</tbody>
</table>
### Tab. 9.1-2. Perfluoroalkyl halides and related compounds

<table>
<thead>
<tr>
<th>Compound ([\text{C,F,X}])</th>
<th>Remarks (“⇒” for synthesis of; “●+” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RₙI, n = 1, 3</td>
<td>⇒ RₙCO₂Na + I₂/DMF, reflux → yield: 70–80%</td>
<td>8</td>
</tr>
<tr>
<td>RₙI, n = 1–12</td>
<td>⇒ Ref. 9. Uses and reactions of: Ref. 10</td>
<td>9, 10</td>
</tr>
<tr>
<td>(CF₂)ₙCF(CF₂CF₂)ₙI</td>
<td>⇒ (CF₂)ₙCFI + CF₂=CF⁻/175 °C → mix of telomers; n = 1 (major) &gt; n = 2–4 (minor)</td>
<td>11</td>
</tr>
<tr>
<td>Cl(CF₂)ₙI, n = 2, 4, 6</td>
<td>● + CH₂–CHR/acid treated Fe catalyst → Cl(CF₂)ₙCH₂CH[I]R</td>
<td>12</td>
</tr>
<tr>
<td>C₃F₇Br</td>
<td>⇒ C₃F₇H + CBr₄/300 °C, 24 h → yield: 40%</td>
<td>13</td>
</tr>
<tr>
<td>C₃F₇Cl</td>
<td>⇒ C₃F₇H + CCl₄/350 °C, 24 h → yield: 31%</td>
<td>13</td>
</tr>
<tr>
<td>X(CF₂)ₙCl</td>
<td>● + CH₂–CHR/(NH₄)₂S₂O₈-HCO₂Na → X(CF₂)ₙ(CH₂)ₙR (70–80%)</td>
<td>14</td>
</tr>
<tr>
<td>R₆Cl₂</td>
<td>⇒ R₆Cl₂ + CCl₄/Zn, EtCO₂H, CH₂Cl₂,2h → yield: 51%</td>
<td>15</td>
</tr>
<tr>
<td>R₉Cl₃</td>
<td>⇒ R₉Cl₂ + AlCl₃/~115 °C, 28 h → yield: 55%</td>
<td>16</td>
</tr>
<tr>
<td>(CF₃)₂CF(O)CF(CF₂)Cl₃</td>
<td>⇒ (CF₃)₂CFO(CF₂)Cl₃ + AlCl₃/100 °C, 63 h → yield: 43%</td>
<td>16</td>
</tr>
<tr>
<td>CCl₃(CF₂)ₙN–N(CF₂)ₙCl₃</td>
<td>● + SO₃/H₂SO₄/Hg²⁺ → HO₂(CF₂)ₙN–N(CF₂)ₙH₂O, yield: 95%</td>
<td>17</td>
</tr>
<tr>
<td>(CF₂)₉CF₂NCF₂CF₂I</td>
<td>⇒ (CF₂)₉CF₂NCF₂CF₂COF/LiI, 180 °C, 18 h → yield: 72%</td>
<td>18</td>
</tr>
<tr>
<td>C₁₀(CF₂)ₙOCF₂CF₂I</td>
<td>⇒ C₁₀(CF₂)ₙOCF₂CF₂N(CF₂)ₙCF₂ + CF₂=CF₂/KF, diglyme, –196 °C, 7 d → yield: 46%</td>
<td>19</td>
</tr>
<tr>
<td>C₁₁F₂OCF(CF₂)ₙOCF₂CF₂CF₂CF₃</td>
<td>● + PhI/Cu, bipy, DMSO → C₁₁F₂OCF(CF₂)ₙOCF₂CF₂CF₂CF₃ (73%)</td>
<td>20</td>
</tr>
<tr>
<td>(CF₂)₉CF₂CFO(CF₂)ₙCF₂I</td>
<td>⇒ (CF₂)₉CF₂CFO(CF₂)ₙCF₂Ag + I₂/heating → yield: 54%</td>
<td>21</td>
</tr>
<tr>
<td>F₃SCF₄</td>
<td>⇒ F₃SCF₄CO₂Ag + I₂/heating → yield: 54%</td>
<td>22</td>
</tr>
<tr>
<td>F₅SCF₆CF₂I</td>
<td>⇒ F₅SCF₆CF₂I + ICl₂/CH₃CN → bp = 86–87 °C</td>
<td>23</td>
</tr>
<tr>
<td>F₅SCF₆CF₂Cl</td>
<td>⇒ F₅SCF₆CF₂Cl + ICl₂/CH₃CN → bp = 86–87 °C</td>
<td>24</td>
</tr>
<tr>
<td>C₁₄OCF₂CF₂Cl</td>
<td>⇒ C₁₄OCF₂CF₂Cl + ICl₂/CH₃CN → bp = 86–87 °C</td>
<td>25</td>
</tr>
<tr>
<td>(CF₂)₉GeI</td>
<td>⇒ Ref. 26. Commercially available</td>
<td>26</td>
</tr>
</tbody>
</table>

### Tab. 9.1-3. Perfluoroethers, perfluoroalkanones and perfluoroalkanecarboxylic acid halides

<table>
<thead>
<tr>
<th>Compound ([\text{C,F,O(X)}])</th>
<th>Remarks (“⇒” for synthesis of; “●+” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₆CF(CF₂)ₙCF₂O, n = 2, 3</td>
<td>● + AlCl₃, heating → R₆CCl(CF₂)ₙCCl₂O (51%)</td>
<td>27</td>
</tr>
<tr>
<td>R₆OR₆</td>
<td>● + AlCl₃/185 °C, 14 h → R₆CO₂Cl (63%) + R₆Cl₃ (16%)</td>
<td>28</td>
</tr>
<tr>
<td>R₉(CO)CF(CF₂)ₖ</td>
<td>⇒ R₉CO/Fa/CaF-catalyst + CF₂=CF⁻ → CF₂=CF₂ → yield: 39–75%, R₉ = (CF₂)ₖCF; C₃F₇; C₂F₆; etc.</td>
<td>29</td>
</tr>
<tr>
<td>C₁₂F₆OCF(CF₂)ₖOCF₂(CF₂)ₖOCOF₂</td>
<td>⇒ C₁₂F₆OCF(CF₂)ₖOCF₂(CF₂)ₖOCOF₂ + CF₂SnMe₃/140 °C, 20 h, sealed tube → yield: 49%</td>
<td>30</td>
</tr>
<tr>
<td>C₁₃F₇OCOCl</td>
<td>⇒ C₁₃F₇CO₂H + SOCl₂/DMF, heating, 4 h → yield: 90%</td>
<td>31</td>
</tr>
<tr>
<td>C₁₃F₇OCF(CF₂)ₖCF₂OₖCF(CF₂)ₖCOF</td>
<td>⇒ C₁₃F₇OCF(CF₂)ₖCF₂OₖCF(CF₂)ₖCOF + CF₂SnMe₃/140 °C, 20 h, sealed tube → yield: 49%</td>
<td>32</td>
</tr>
<tr>
<td>C₁₄F₈COF</td>
<td>⇒ C₁₄F₈CO₂H + HCF₂CF₂N(CH₃)₂/0–25 °C, 2 h → yield: 75%</td>
<td>33</td>
</tr>
</tbody>
</table>
### Tab. 9.1-4. Perfluoroalkylsulfides and disulfides, perfluoroalkanesulfonyl halides and anhydrides

<table>
<thead>
<tr>
<th>Compound [C,F,S(O,X)]</th>
<th>Remarks (*&quot;⇒&quot; for synthesis of; &quot;●+&quot; for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C₃F₇)₂S</td>
<td>⇒ C₃F₇I + S₆/300 °C, 10 h → yield: 11%, bp = 88 °C</td>
<td>34</td>
</tr>
<tr>
<td>(C₇F₁₅)₂S₂</td>
<td>⇒ C₂F₁₅I + S₆/255 °C, 17 h → yield: 60%, mp = 39 °C,</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>bp = 247 °C</td>
<td></td>
</tr>
<tr>
<td>C₆F₁₃SO₂Cl</td>
<td>● + C₆H₁₂/RuCl₂[PPh₃]₁₁ → C₆H₃C₆F₁₃, yield: 44%</td>
<td>35</td>
</tr>
<tr>
<td>C₆F₁₃SO₂X, X = F, Cl</td>
<td>⇒ Title compounds were obtained in ~98% purity from a</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>mixture containing branched isomers by cooling to −20 °C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and filtration of the crystalline linear isomers</td>
<td></td>
</tr>
<tr>
<td>R₆SO₂Cl and/or (R₆SO₂)₂O</td>
<td>⇒ R₆SO₂K + PCl₅ 2ZnCl₂ → “high yield and purity”.</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>When PCl₅ reacted with perfluoroalkanesulfonic acids,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yields anhydrides</td>
<td></td>
</tr>
<tr>
<td>(cyclo-C₂F₃C₆F₁₀SO₂)₂O</td>
<td>● Used for the thermal perfluoroalkylation of dyes (e.g.,</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>pyranthrone, Cu phthalocyanine) to yield fluoruous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>derivatives for staining PTFE</td>
<td></td>
</tr>
</tbody>
</table>

### Tab. 9.1-5. Tris(perfluoroalkyl)amines, perfluoroazomethines, perfluoroalkanenitriles, tris(perfluoroalkyl)triazines and perfluoroalkyl isocyanates

<table>
<thead>
<tr>
<th>Compound [C,F,N(O)]</th>
<th>Remarks (*&quot;⇒&quot; for synthesis of; &quot;●+&quot; for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C₄F₉)₃N</td>
<td>● An inert medium for organic reactions</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>⇒ Prepared by the defluorination of undecafluoropiperidine</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>with steel wool at 500 °C/1 atm, yield: 40%</td>
<td></td>
</tr>
<tr>
<td>CF₃CF₂CF₂CF₂N</td>
<td>⇒ (C₄F₉)₃N + SbF₅ catalyst/120 °C, 4 h, (−C₄F₁₀) →</td>
<td>41</td>
</tr>
<tr>
<td>C₇F₁₅CN</td>
<td>yield: 67%</td>
<td></td>
</tr>
<tr>
<td>2,4,6-(C₇F₁₅)₃-1,3,5-triazine</td>
<td>⇒ C₇F₁₅CONH₂ + P₂O₅/200 °C → yield: 84%, bp = 103–104 °C</td>
<td>42</td>
</tr>
<tr>
<td>R₃NCO</td>
<td>⇒ R₃N=NR₃ + CO/300 °C, 800 atm, 8 h → yield: 11% + C₆F₁₄</td>
<td>43</td>
</tr>
<tr>
<td>R₇NCO</td>
<td>⇒ R₇COCl + Me₃SiN₁ → yield: 82%</td>
<td>44</td>
</tr>
</tbody>
</table>

9.1 Introduction
### Tab. 9.1-6. Perfluoroalkylmagnesium- and perfluoroalkylzinc halides; perfluoroalkyl copper(I)-, perfluoroalkyl-lithium-, and perfluoroalkyl-caesium intermediates

<table>
<thead>
<tr>
<th>Compound [C,F,Mg/Zn/Cu/Li-Cs]</th>
<th>Remarks (“⇒” for synthesis of; “• +” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₈MgBr/THF</td>
<td>⇒ C₄F₁₇I + PhMgBr or C₂H₅MgBr/THF at −70°C → R₈MgBr → R₈(CH₂)₂OH or R₈C(CF₃)₂OH, in 90 or 64% yields, resp.</td>
<td>46</td>
</tr>
<tr>
<td>R₆MgBr/ether, n = 4, 6, 8, 10</td>
<td>⇒ C₄F₂₄₋₄I + C₂H₅MgBr/ether at −35 to −40°C → R₆MgBr/ether; quenched by PhCH₂CH=O to yield PhCH₂CH(OH)R₆.</td>
<td>47</td>
</tr>
<tr>
<td>(CF₃)₂CF₂ZnI/THF</td>
<td>• + PhCOF/py → PhCOCF(CF₃)₂, yield: ~100%</td>
<td>48</td>
</tr>
<tr>
<td>R₆Cu.solv</td>
<td>⇒ R₆I + 2Cu/DMSO, 110–120°C, 2 h → R₆Cu, yield &gt; 80%</td>
<td>49</td>
</tr>
<tr>
<td>“C₈F₁₇Li”/ether (−78 °C)</td>
<td>⇒ Generated in situ: C₄F₁₇I + CH₃Li-LiBr/ether, −78°C</td>
<td>50</td>
</tr>
<tr>
<td>CF₃CF₂CF₂(CF₃)₂ “Ca”</td>
<td>• + ArCH₂Br → ArCH₂C(CF₃)₂R₆, 10 examples, yields: ~60%</td>
<td>51</td>
</tr>
<tr>
<td>Miscellaneous F-organometallics</td>
<td>⇒ • + Synthesis and reactivity of F-organometallics.</td>
<td>52</td>
</tr>
</tbody>
</table>

### Series II [hydrogen included]

9.2.1 Hydroperfluoroalkanes, perfluoroalkylalkanes/cycloalkanes, perfluoroalkylalkenes and perfluoroalkylalkynes, perfluoroalkylarenes, (perfluoroalkyl)alkylarenes and related compounds

9.2.2 (Perfluoroalkyl)alkyl halides; perfluoroalkyl- and (perfluoroalkyl)alkyl aryl/benzyl halides

9.2.3 Perfluoroalkylalkanols and ethers

9.2.4 Fluorous mercaptanes, sulfides, sulfoxides, sulfonates, sulfonimides and selenides

9.2.5 Fluorous amines, anilines, pyridines; phosphines and phosphites

9.2.6 Fluorous boron-, silicon-, tin-, lithium-, zinc-, and magnesium compounds

9.2.7 Fluorous aldehydes and ketones

9.2.8 Fluorous carboxylic acids

9.2.9 Fluorous esters and carboxylic acid derivatives

### Acknowledgements

The author thanks the Hungarian Scientific Research Foundation (OTKA T 034871) and the European Contract of Research Training Network (‘Fluorous Phase’ HPRN-CT-2000-00002) for financial support.
Tab. 9.2-1. Hydroperfluoroalkanes, perfluoroalkylalkanes/cycloalkanes, perfluoroalkylalkenes and perfluoroalkylalkynes, perfluoroalkylarenes, (perfluoroalkyl)alkylarenes and related compounds

<table>
<thead>
<tr>
<th>Compound ([C,F,H])</th>
<th>Remarks (“⇒” for synthesis of; “++” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R_\text{f}n)CF(_2)H ((n = 2–4))</td>
<td>(⇒ R_\text{f}n)CF(_2)I + H(_2)/Raney Ni, 60 atm, 350 °C → yield: 80%</td>
<td>9a</td>
</tr>
<tr>
<td>(CF(_3))(_2)CH</td>
<td>+ Prepared as described and its thermodynamic acidity studied</td>
<td>53</td>
</tr>
<tr>
<td>F(CF(<em>2))(</em>{10})CH(_2)H</td>
<td>(⇒ R_\text{f}I + CH(_2)=CHC(_6)H(<em>4)AIBN → R(</em>\text{f}3)CH(_2)I</td>
<td>C(_6)H(_4); + Zn/HCl in CH(_3)OH → title product, its gel formation from alcohols studied</td>
</tr>
<tr>
<td>CF(_3)-cyclo-C(_6)H(_11)</td>
<td>++ As a new solvent? Limits of use</td>
<td>55</td>
</tr>
<tr>
<td>(R_\text{f}n)CH–CH(_2), (n = 4, 6, 8, 10)</td>
<td>(⇒ R_\text{f}I + CH(_2)=CHSi(CH(_3))(<em>3) → R(</em>\text{f}n)CHCH=ISi(CH(_3))(_3); + Bu(_4)NF → overall yield: 58–86%</td>
<td>56</td>
</tr>
<tr>
<td>(R_\text{f}n)CH–CH(_2)bCHC(_6)H(_13)/AIBN</td>
<td>(⇒ R_\text{f}n)CH–CH(I)C(_6)H(_13); title product, its gel formation from alcohols studied</td>
<td>57</td>
</tr>
<tr>
<td>(R_\text{f}n)CH–CH(_2), (n = 4, 6, 8, 10)</td>
<td>(⇒ R_\text{f}I + CH(_2)=CHCH2I/diglyme</td>
<td>58</td>
</tr>
<tr>
<td>(R_\text{f}n)CH–CH(_2)bCH2CH(_3)Br</td>
<td>(⇒ R_\text{f}n)CH–CHCH2Br/CH(_3)CN, reflux</td>
<td>59</td>
</tr>
<tr>
<td>(R_\text{f}n)Ph–Ph</td>
<td>(⇒ R_\text{f}n)I + CH(_2)=CHPh/Et(_2)NH or Br(_2) for several weeks, by m-chloroperbenzoic acid</td>
<td>60</td>
</tr>
<tr>
<td>(R_\text{f}n)CH–CH(_2), (n = 4, 6)</td>
<td>(⇒ R_\text{f}n)I + CH(_2)=CHSi(CH(_3))(<em>3) → R(</em>\text{f}n)CHCH=ISi(CH(_3))(_3); + Cu, DMSO/130–135 °C, 6 h</td>
<td>61</td>
</tr>
<tr>
<td>(C_4F(_7))C(_2)H(_5), etc.</td>
<td>(⇒ C_4F(_7))I + C(_2)H(_4)/K(_2)CO(_2), 2% Ru–C, 30 h, 170 °C → yield: 89%</td>
<td>62</td>
</tr>
<tr>
<td>(R_\text{f}n)Ph</td>
<td>(⇒ PhH + R(<em>\text{f}n)N=NR(</em>\text{f}n)/CF(_3)Cl/CFCl(_2), hv, 2 h → yield: 70%</td>
<td>63</td>
</tr>
<tr>
<td>(R_\text{f}n)R, ((R = Ar, Het))</td>
<td>(⇒ 2R_\text{f}n)I + ArH/(~250 °C, 15 h → R(<em>\text{f}n)Ar + R(</em>\text{f}n)H + I(_2); yield: 60–65%</td>
<td>64</td>
</tr>
<tr>
<td>F(_5)S(CF(_2))(_6)C(_6)H(_5)</td>
<td>(⇒ F_5S(CF(_2))(_6)I + C(_6)H(_6)(160–165 °C/14 d) → yield: 51% by GC</td>
<td>65</td>
</tr>
<tr>
<td>(R_\text{f}n)Ph–Ph</td>
<td>(⇒ Ph(<em>2)I + R(</em>\text{f}n)CH2CH(_2)I/CuBr–THF, 18 h, r.t. → yield: 89%</td>
<td>66</td>
</tr>
<tr>
<td>(R_\text{f}n)R, ((R = Ar, Het))</td>
<td>(⇒ 2R_\text{f}n)I + ArH/(~250 °C, 15 h → R(<em>\text{f}n)Ar + R(</em>\text{f}n)H + I(_2); yield: 60–65%</td>
<td>67</td>
</tr>
<tr>
<td>(R_\text{f}n)R, ((R = Ar, Het))</td>
<td>(⇒ 2R_\text{f}n)I + ArH/(~250 °C, 15 h → R(<em>\text{f}n)Ar + R(</em>\text{f}n)H + I(_2); yield: 40–95%</td>
<td>68</td>
</tr>
<tr>
<td>(R_\text{f}n)CH2CH2Cl</td>
<td>(⇒ PhCl + R(_\text{f}n)CH2CH2I/CuBr–THF, 18 h, r.t. → yield: 89%</td>
<td>69</td>
</tr>
<tr>
<td>(R_\text{f}n)CH2CH2Ph</td>
<td>(⇒ Ph_OH(<em>2) + R(</em>\text{f}n)CH2CH2I/Pd[PPh(_3)](_4), NaHCO(_3), H(_2)O–CH(_3)OCH2CH2OCH(_3), 5 h → yield: 89%</td>
<td>70</td>
</tr>
<tr>
<td>Compound ([C,F,H])</td>
<td>Remarks (&quot;=&quot; for synthesis of; &quot;(+)&quot; for reaction of; etc.)</td>
<td>Ref.</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>(Rf_nAr)</td>
<td>(\Rightarrow) (ArBr + Rf_nI/Cu,DMSO) → good yields</td>
<td>72</td>
</tr>
<tr>
<td>(Rf_nCH_2CH_2Ar) via (Rf_nCH=CHAr)</td>
<td>(\Rightarrow) (ArX + CH_2=CHRf_n/Pd-cat) → (ArCH=CHRf_n); (+) (H_2/Pd-C) → overall yield: 70–90%</td>
<td>73</td>
</tr>
<tr>
<td>(Rf_nCH_2CH_2CH_2Ar, n = 6, 8, 10) (\Rightarrow) ([Rf_nCH_2CH_2PPh_3]^+I^- + Ar(CHO)_x) → ((Rf_nCH_2CH=CH)_xAr; (+) (H_2/cat) → overall yield: 68–90%</td>
<td>74</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound ([C,F,H,X])</th>
<th>Remarks (&quot;=&quot; for synthesis of; &quot;(+)&quot; for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rf_3CH_2I)</td>
<td>(\Rightarrow) (Rf_3CH_2OTs + KI/diethylene glycol, T &gt; 190 °C) → yield: 84%</td>
<td>75</td>
</tr>
<tr>
<td>(Rf_nCH_2CH_2I)</td>
<td>(\Rightarrow) (Rf_nI + CH_2–CH_2/290–390 °C) for (n = 4, 6, 8, 10) → yield: (\sim95%) (72% conversion)</td>
<td>76, 77</td>
</tr>
<tr>
<td>(Rf_8CH_2CH_2CH_2I)</td>
<td>(\Rightarrow) (Rf_8(CH_2)_3OH + KI, P_2O_5/H_3PO_4) → yield: 88%</td>
<td>56</td>
</tr>
<tr>
<td>(Rf_8CH_2CH_2CH_2I)</td>
<td>(\Rightarrow) (Rf_8(CH_2)_3OH + KI, P_2O_5/H_3PO_4; P_2O_5/SiO_2) → yield: 70–85%</td>
<td>78</td>
</tr>
<tr>
<td>(Rf_8CH_2CH_2CH_2CH_2I)</td>
<td>(\Rightarrow) (Rf_8(CH_2)_3OH + KI, P_2O_5/H_3PO_4 (120 °C/4 h)) → yield: 92%</td>
<td>79</td>
</tr>
<tr>
<td>(F_5S(CF_2CF_2)_3CH_2CH_2I)</td>
<td>(\Rightarrow) (CH_2–CH_2 + F_5S(CF_2CF_2)_3/I^+/Bu_2O_2) → yield: 28%</td>
<td>80</td>
</tr>
<tr>
<td>(1,3,5-BrC_6H_3(Rf_8)_2)</td>
<td>(\Rightarrow) (1,3,5-BrC_6H_3 + 2 Rf_8I + 4 Cu/DMF, 120 °C, 18 h) → yield: 60%</td>
<td>81</td>
</tr>
<tr>
<td>(1,3,5-BrC_6H_3[Rf_{10}]_2)</td>
<td>(\Rightarrow) (m-(Rf_{10})_2C_6H_4 + NBS/H_2SO_4-CF_3CO_2H, 50 °C, 8 h) → yield: 94%</td>
<td>82</td>
</tr>
<tr>
<td>(1,2,4,6-tC_6H_3[(CH_2)_3Rf_8]_3; 1,2,4-, 1,2,5-, 1,3,4-, 1C_6H_3[(CH_2)_3Rf_8]_2)</td>
<td>(\Rightarrow) (C_6H_3((CH_2)_3CH_2Rf_8)_3) or (C_6H_4((CH_2)_3CH_2CH_2Rf_8)_2) + (1/2H_2IO_6) in (AcOH, H_2SO_4/H_2O) → yields of respective iodoarenes: 61–97%</td>
<td>83</td>
</tr>
<tr>
<td>(3,5-(Rf_8)_2C_6H_3CH_3Br)</td>
<td>(\Rightarrow) (3,5-(Rf_8)C_6H_5CH_3OH + PBr_3/THF) → yield: 62%</td>
<td>84</td>
</tr>
</tbody>
</table>
Table 9.2-3. Perfluoroalkylalkanols and ethers

<table>
<thead>
<tr>
<th>Compound [C,F,H,O]</th>
<th>Remarks (*=&gt;&quot; for synthesis of; **+&quot; for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{12}F_{20}OCF(CF_{3})CF_{2}OCF(CF_{3})CH_{2}OH</td>
<td>(\Rightarrow) C_{12}F_{20}OCF(CF_{3})CF_{2}OCF(CF_{3})CO_{2}CH_{3} + NaBH_{4}/ether \rightarrow (81%)</td>
<td>85</td>
</tr>
<tr>
<td>(CF_{3})<em>{2}CH</em>{2}OH</td>
<td>(\Rightarrow) (CF_{3})<em>{2}CH + CH</em>{2}O/Et_{3}N, 100 °C, 55 h \rightarrow no yield data given</td>
<td>86</td>
</tr>
<tr>
<td>R_{n}CH_{2}CH_{2}CH_{2}OH, n = 6, 8, 10</td>
<td>(\Rightarrow) One pot synthesis from R_{n}I and triallyl borate, yield: 74–79%</td>
<td>87</td>
</tr>
<tr>
<td>(C_{6}F_{13})<em>{2}CH</em>{2}OH</td>
<td>(\Rightarrow) Preparation of and use for acetylation</td>
<td>88</td>
</tr>
<tr>
<td>(C_{6}F_{13})<em>{2}CH</em>{2}OH</td>
<td>(\Rightarrow) C_{6}F_{13}CH_{2}I + Mg/ultrasound; (\Rightarrow) HCO_{2}Et \rightarrow yield: 93%</td>
<td>89</td>
</tr>
<tr>
<td>(C_{6}F_{13})<em>{2}CH</em>{2}OH, R_{n}(CH_{2})<em>{2}C(CH</em>{3})_{2}OH, n = 2, 3</td>
<td>(\Rightarrow) Conveniently prepared by the reaction of appropriate Grignard reagents with acetone and ethyl acetate, respectively</td>
<td>90</td>
</tr>
<tr>
<td>R_{6}CH_{2}CH_{2}C(CH_{3})_{2}OH</td>
<td>(\Rightarrow) R_{6}I + CH_{2}CHCH_{2}OAc/Cu, 120 °C \rightarrow R_{6}CH_{2}CH(I)CH_{2}OAc; R_{6}CH_{2}CH(OAc)CH_{2}I \rightarrow yield: 67%;</td>
<td>91</td>
</tr>
<tr>
<td>R_{6}CH_{2}CH_{2}C(CH_{3})_{2}OH</td>
<td>(\Rightarrow) R_{6}CH_{2}CH_{2}CH_{2}OH, n = 4, 6, 8;</td>
<td>92</td>
</tr>
<tr>
<td>R_{6}CH_{2}CH_{2}C(CH_{3})_{2}OH</td>
<td>(\Rightarrow) R_{6}CH_{2}CH_{2}CH_{2}OH, n = 4, 6, 8</td>
<td>93</td>
</tr>
<tr>
<td>(C_{6}F_{13})<em>{2}CH</em>{2}OH</td>
<td>(\Rightarrow) (C_{6}F_{13})<em>{2}CH</em>{2}CH(OAc)CH_{2}I; (\Rightarrow) KOH/hexane \rightarrow yield: 94–96%</td>
<td>94</td>
</tr>
<tr>
<td>3,5-(C_{6}F_{13})<em>{2}C</em>{6}H_{3}CH_{2}OH</td>
<td>(\Rightarrow) 3,5-(C_{6}F_{13})<em>{2}C</em>{6}H_{3}CO_{2}CH_{3} + LiAlH_{4}/Et_{2}O, 5 h reflux \rightarrow yield: 90%</td>
<td>95</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) CH_{3}COS(C_{6}F_{13})<em>{3} + (CF</em>{3})_{3}CHMgBr, (\rightarrow) 45 °C to r.t. \rightarrow yield: 45%, mp = 29 °C</td>
<td>96</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) (CF_{3})<em>{3}COCH</em>{3}, (CF_{3})<em>{3}CO</em>{2}CH_{3}</td>
<td>97</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) (CF_{3})<em>{3}CO</em>{2}CH_{3} + (CF_{3})_{3}CHCl</td>
<td>98</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) (CF_{3})<em>{3}CO</em>{2}CH_{3} + (CF_{3})<em>{3}CHCl/CsF, diglyme, 70 °C \rightarrow yield: 90%; (\Rightarrow) SO</em>{3}/H_{2}SO_{4}; r.t., 1 h \rightarrow (CF_{3})<em>{3}CH</em>{2}OH, yield: 45%</td>
<td>99</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) (CF_{3})<em>{3}CO</em>{2}CH_{3} + (CF_{3})_{3}CHCl/CsF, diglyme, 70 °C \rightarrow yield: 90%</td>
<td>100</td>
</tr>
<tr>
<td>(CF_{3})<em>{3}CHOCH</em>{3}</td>
<td>(\Rightarrow) (CF_{3})<em>{3}CO</em>{2}CH_{3} + (CF_{3})_{3}CHCl/CsF, diglyme, 70 °C \rightarrow yield: 90%</td>
<td>100</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>$\text{R}_6\text{CH}_2\text{SH}, n = 2, 3$</td>
<td>$\Rightarrow \text{R}_6\text{COX} (X = \text{H, Cl}) + \text{H}_2\text{S}, 200 ^\circ\text{C}, 3000 \text{ atm} \rightarrow$ yield: 39–54%</td>
<td>101</td>
</tr>
<tr>
<td>$\text{R}_6\text{CH}_2\text{SH}$</td>
<td>$\Rightarrow \text{R}_6(\text{CH}_2)_2\text{I} + \text{H}_2\text{NCSNH}_2$/dioxane $\rightarrow$ yield: 94%, unlike alcohol type solvents no foul-smelling byproducts are formed in dioxane!</td>
<td>102</td>
</tr>
<tr>
<td>$\text{R}_8\text{CH}_2\text{CH}_2\text{SH}$</td>
<td>$\Rightarrow \text{[(C}_6\text{H}_7)_2\text{Na}]\text{AuCl}_4/\text{CF}_3\text{Ph} + \text{NaBH}_4/H_2\text{O} \rightarrow \text{(Au}_x\text{[HS(CH}_2)_3\text{R}_8])_y}$ Example for an isolable and fluorous soluble gold nanocluster</td>
<td>103</td>
</tr>
<tr>
<td>$\text{F}_3\text{S}(\text{CF}_2)_6\text{CH}_2\text{CH}_2\text{SH}$</td>
<td>$\Rightarrow \text{F}_3\text{S}(\text{CF}_2)_6(\text{CH}_2)_2\text{I} + \text{NaH}/\text{AcSH-THF}$ $\rightarrow \text{F}_3\text{S}(\text{CF}_2)_6(\text{CH}_2)_2\text{SAc}; + \text{LiAlH}_4/\text{THF} \rightarrow$ overall yield: 90%</td>
<td>104</td>
</tr>
<tr>
<td>$\text{R}_6\text{CH}_2\text{SCH}_3$</td>
<td>$\Rightarrow \text{HO(CH}_2)_2\text{SH} + \text{R}_6\text{I}/\text{Na}_2\text{SO}_3, \text{HCO}_2\text{Na, DMF-H}_2\text{O},$ r.t. $\rightarrow$ yield: 64–71%</td>
<td>105</td>
</tr>
<tr>
<td>$\text{R}_8\text{CH}_2\text{CH}_2\text{SCH}_3$</td>
<td>$\Rightarrow \text{NO}_{\text{CH}_3}, \text{C}_6\text{H}_4\text{I} \rightarrow$ yield: 94%</td>
<td>106</td>
</tr>
<tr>
<td>$\text{R}_6\text{SCH}_2\text{CH}_2\text{OH}; n = 4, 6$</td>
<td>$\Rightarrow \text{HO(CH}_2)_2\text{SH} + \text{R}_6\text{I}/\text{Na}_2\text{SO}_3, \text{HCO}_2\text{Na, DMF-H}_2\text{O},$ r.t. $\rightarrow$ yield: 64–71%</td>
<td>107</td>
</tr>
<tr>
<td>$[\text{R}_8(\text{CH}_2)_2\text{S}]_2, n = 2, 3$</td>
<td>$\Rightarrow \text{R}_8(\text{CH}_2)_2\text{I} + \text{Li}_2\text{S}/\text{THF} \rightarrow$ yields: 67–71%</td>
<td>108</td>
</tr>
<tr>
<td>$\text{ArSR}_{\text{R}_8}, n = 3$</td>
<td>$\Rightarrow \text{ArSH} + \text{R}_8\text{I} + \text{NaOH, PhCH}_3\text{NEt}_3\text{Cl}$</td>
<td>109</td>
</tr>
<tr>
<td>$\text{ArSR}_{\text{R}_8}, \text{e.g.: Ar} =$ p-$\text{CH}_3\text{C}_6\text{H}_4, n = 6$</td>
<td>(a) $\Rightarrow \text{ArSH} + \text{N}([\text{C}_6\text{H}_5])_3 + \text{R}_8\text{Br}/\text{DMF, hv}$ $\rightarrow$ yield: 52%; (b) $\Rightarrow \text{ArSK} + \text{R}_8\text{Br}/\text{DMF} \sim 3 \text{ atm} \rightarrow$ yield: 77%</td>
<td>110, 111</td>
</tr>
<tr>
<td>$\text{R}_8(\text{CH}_2)_2\text{S}(\text{O})(\text{CH}_2)_n\text{R}_8, n = 2, 3$</td>
<td>$\Rightarrow \text{HO(CH}_2)_2\text{SH} + \text{R}_8\text{I}/\text{Na}_2\text{SO}_3, \text{HCO}_2\text{Na, DMF-H}_2\text{O},$ r.t. $\rightarrow$ yield: 64–71%</td>
<td>108</td>
</tr>
<tr>
<td>$\text{R}_6\text{CH}_2\text{S(OF)}_2(\text{CH}_2)_n\text{R}_8, n = 4, 6$</td>
<td>$\Rightarrow \text{HO(CH}_2)_2\text{SH} + \text{R}_6\text{I}/\text{Na}_2\text{SO}_3, \text{HCO}_2\text{Na, DMF-H}_2\text{O},$ r.t. $\rightarrow$ yield: 64–71%</td>
<td>108</td>
</tr>
<tr>
<td>$\text{R}_8(\text{CH}_2)_2\text{CH}_2\text{OTs}$</td>
<td>$\Rightarrow \text{R}_8\text{CH}_2\text{CH}_2\text{OH} + \text{TsCl/CH}_2\text{Cl}_2$-aq.$\text{NaOH} \rightarrow$ yield: 72%</td>
<td>112</td>
</tr>
<tr>
<td>$\text{(R}_6\text{SO}_2)_2\text{NH}, n = 2, 4, 8$</td>
<td>$\Rightarrow$ Products were obtained after high-vacuum sublimation or short-path distillation from conc. $\text{H}_2\text{SO}_4$</td>
<td>116</td>
</tr>
<tr>
<td>$2,4-\text{(R}_8\text{)}_2\text{C}_6\text{H}_3\text{SeC}_4\text{H}_9$</td>
<td>$\Rightarrow \text{2,4-Li}_2\text{C}_6\text{H}_3\text{NH}_2 + \text{R}_8\text{I}/\text{Cu, DMSO, 120 }^\circ\text{C} \rightarrow 2,4-\text{(R}_8\text{)}_2\text{C}_6\text{H}_3\text{NH}_2 + \text{NaNO}_2, \text{HBr, CuBr} \rightarrow 2,4-\text{(R}_8\text{)}_2\text{C}_6\text{H}_3\text{Br; + C}_6\text{H}_3\text{SeLi/THF, –80 to –25 }^\circ\text{C} \rightarrow 2,4-(\text{R}_8\text{)}_2\text{C}_6\text{H}_3\text{SeC}_4\text{H}_9$, overall yield: 36%</td>
<td>117</td>
</tr>
<tr>
<td>$3,5-\text{(R}_8\text{)}_2\text{C}_6\text{H}_3\text{SeC}_4\text{H}_9$</td>
<td>$\Rightarrow$ Prepared by multiple step synthesis from $3,5-\text{Li}_2\text{C}_6\text{H}_3\text{NH}_2$ and used as a catalyst in Bayer-Villiger oxidation</td>
<td>118</td>
</tr>
</tbody>
</table>
### 9.1 Introduction

#### Tab. 9.2.5. Fluorous amines, anilines, pyridines; phosphines and phosphites

<table>
<thead>
<tr>
<th>Compound [C,F,H,N/P(O)]</th>
<th>Remarks (&quot;•&quot; for synthesis of; &quot;•÷&quot; for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf7CH2NH2, (Rf7CH2)2NH</td>
<td>⇒ Precursors of tetrasubstituted ureas, thermally stable fluids, recoverable in 99% after a 63 h at 270 °C test</td>
<td>119</td>
</tr>
<tr>
<td>(Rf8CH2)2NH</td>
<td>⇒ (Rf8CO2)NH + LiAlH4 → no yield data reported, mp = 85–86 °C</td>
<td>120</td>
</tr>
<tr>
<td>[CF3]3C2NH</td>
<td>⇒ multistep synthesis/bp = 100–101 °C/C</td>
<td>121</td>
</tr>
<tr>
<td>Rf7CH2N(CH3)2</td>
<td>⇒ Rf7CSN(CH3)2; + BH3/diglyme → yield: 59%, GC purity: 99%</td>
<td>122</td>
</tr>
<tr>
<td>(CF3)2NCH2CF2CF3</td>
<td>⇒ CF2CF2CF2CF2N + KF + CF3CF2CH2OSO2CF3 → yield: 71%</td>
<td>123</td>
</tr>
<tr>
<td>CF3CF2(CF3)NCH3</td>
<td>⇒ CF3CF = NCF3 + CsF + (CH3)2SO4/CH3CN → yield: 46%</td>
<td>124</td>
</tr>
<tr>
<td>[(CF3)3CCH2]3N</td>
<td>⇒ (CF3)3C–CF2 + CsF + (ClCH2)3N/diglyme → yield: 32%</td>
<td>97</td>
</tr>
<tr>
<td>Rf8CH2CH2NH2, n = 2, 4, 6, 8</td>
<td>⇒ Rf8CH2CH2I + NaN3 → Rf8CH2CH2N3; H2/Pt →</td>
<td>125</td>
</tr>
<tr>
<td>NH3−[(CH2)mRf8]x, m = 3–5, x = 1.2 N[(CH2)mRf8] = N(Rf8)3</td>
<td>⇒ Rf8(CH2)m−1CHO + NH(Rf8)2 or H2NCH2Ph/Na(AcO)2/BH4 → N(N(Rf8)3) or NH2−(CH2)Ph][(CH2)mRf8]x; + H2/Pd-C → 78–91%</td>
<td>126</td>
</tr>
<tr>
<td>[(Rf8CH2CH2)3SiCH2CH2CH2]2NH</td>
<td>⇒ [(Rf8CH2CH2)3SiCH2CH2CH2]2NCOCF3 + LiAlH4/ether → yield: 97%</td>
<td>127</td>
</tr>
<tr>
<td>• + RNCO → fluorous soluble ureas, easy to remove by extraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rf8CH2CH2CH2)2NCH3</td>
<td>⇒ Rf8(CH2)2NH(CH3) + Rf8(CH2)3I/THF, 60 °C, 24 h → yield: 84%</td>
<td>128</td>
</tr>
<tr>
<td>[(Rf8CH2CH2CH2)3NCH3]++CH3SO3− = Rf8CH3OSO3−</td>
<td>⇒ • + Na12[[WZnM2(H2O)2][ZnW9O34]2]</td>
<td></td>
</tr>
<tr>
<td>2,4,6-[(Rf8)3C6F13]2NCH2NH2</td>
<td>⇒ C6H5N(CH3)2, 4-CCF3C6H4NH2 or Me7CC6H4NH2 + Rf8I/CuO, DMSO, 130 °C, 1 to 3 d → yield: 45, 65, and 27%, resp.</td>
<td>130</td>
</tr>
<tr>
<td>2,4,6-[(Me7)3C6F13]2NCH2NH3</td>
<td>⇒ C6F17CH2N3/THF + Br2/Py/Cl2/Pd(PPh3)2 → yield: 31–85%</td>
<td>131</td>
</tr>
<tr>
<td>s−[Rf8(CH2)3]py, 2,6-[Rf6(CH2)1]2py</td>
<td>⇒ py(CHO) → (Rf8CH2CH−CH=)py; + H2/Pd-C → yield: 93%</td>
<td>132</td>
</tr>
<tr>
<td>2,6-(Rf8)2py</td>
<td>⇒ 2,6-Br2-py + C6F13I/Cu, DMSO, 125 °C → yield: 89%</td>
<td>133, 134</td>
</tr>
<tr>
<td>P[(CH2)2Rf8]1, y = 2, n = 6, 8, 10; y = 3, 4, n = 8</td>
<td>⇒ PH2 + CH2−CH−CH=−Rf8/AIBN or VAZO → yield: 63–81%</td>
<td>133</td>
</tr>
<tr>
<td>Rf8(CH2)mPH2; Rf8(CH2)mP[(CH2)m−Rf8]2</td>
<td>⇒ LiPH2 + Rf8(CH2)mI → Rf8(CH2)mPH2; + Rf8(CH2)m−2CH−CH2/AIBN or VAZO → good yields: m = 2–4, m/m′ = 3/2, 2/3, 3/4</td>
<td>79</td>
</tr>
<tr>
<td>(Rf8CH2CH2O)3P</td>
<td>⇒ Rf8CH2CH2OH + PCl5/py-ether → yield: 55%</td>
<td>133</td>
</tr>
</tbody>
</table>
Tab. 9.2-6. Fluorous boron-, silicon-, tin-, lithium-, zinc-, and magnesium compounds

<table>
<thead>
<tr>
<th>Compound [C,F,H,B/Si/Sn/Metal]</th>
<th>Remarks (“=” for synthesis of; “•”+” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rf10)2C6H3B(OH)2</td>
<td>⇒ Multistep synthesis: 1,3-C6H4I2 → 1,3-C6H4(Rf10)2 → 1,3,5-BrC6H3(Rf10)2 → 1,3,5(RO)2BC6H3(Rf10)2 → overall yield: 35–40%</td>
<td>82</td>
</tr>
<tr>
<td>Na[B(C6H4(SiMe2CH2CH2C6F13)-p]4, Na[B(C6H4C6F13-p]4 ArBr + iBuLi/ether, –78 °C → ArLi/ether; + BF3·O(C2H5)2; → LiB[Ar]4/ether; + NaCl–H2O → overall yield: 70–80%</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Na[B(C6H4F11-3,5)]4</td>
<td>⇒ Multistep synthesis starting from 1,3-C6H4I2 and C6F13I.</td>
<td>137</td>
</tr>
<tr>
<td>[Rf6CH2CH2]3SiH</td>
<td>• + (CH2=CHCH2)2NCOCF3/H2PtCl6, 80 °C, 12 h → [Rf6CH2CH2]3SiCH2CH2CH2NCOCF3, yield: 33–37%</td>
<td>127</td>
</tr>
<tr>
<td>Rf6(CH2)2Si(i-Pr)2Br, n = 6, 8</td>
<td>+ Cl3SnPh + Rf6 CH2MgI → (Rf6 CH2)3SnBr; + Br2 → (Rf6 CH2)3SnBr; + LiAlH4 → overall yield: 65%</td>
<td>143</td>
</tr>
<tr>
<td>[Rf8CH2CH2Si(CH3)2]2O</td>
<td>⇒ [Rf8 (CH2)2]3SiBr + [CH2=CHSi(CH3)2]2O/AIBN → [Rf8 CH2CHSi(CH3)2]2O; + Bu3SnH, 80 °C, 2 h → overall yield: 65%</td>
<td>147</td>
</tr>
<tr>
<td>SiO2(-O)3Si(CH2)3NH2-O(CF3)2OCF3 CF3CF2OCF3CF3OCF3F7</td>
<td>⇒ Silica(-O)3Si(CH2)3NH2 + R1 OR1 C(O)F →</td>
<td>148</td>
</tr>
<tr>
<td>[Rf8CH2CH2]3SnCH2CH2CH2</td>
<td>• + Useful fluorous allyl-transfer reagent</td>
<td>149</td>
</tr>
<tr>
<td>4-Rf6CH2Si(CH2)3Rf6</td>
<td>⇒ Cl3SnPh + Rf6CH2CH2MgI → (Rf6CH2CH2)3SnPh; + Br2 → (Rf6CH2CH2)3SnBr; + LiAlH4 → overall yield: 65%</td>
<td>151</td>
</tr>
<tr>
<td>(Rf6CH2CH2)3SnR, R = Ph, Br, H</td>
<td>⇒ Cl3SnPh + Rf6CH2CH2MgI → (Rf6CH2CH2)3SnPh; + Br2 → (Rf6CH2CH2)3SnBr; + LiAlH4 → overall yield: 65%</td>
<td>151</td>
</tr>
<tr>
<td>(Rf6CH2CH2)3SnCl, n = 6, 8</td>
<td>⇒ Cl3SnPh + Rf6CH2CH2MgI → (Rf6CH2CH2)3SnPh; + Br2 → (Rf6CH2CH2)3SnBr; + LiAlH4 → overall yield: 65%</td>
<td>151</td>
</tr>
<tr>
<td>Sn[N(SO2C8F17)2]4</td>
<td>⇒ Catalyst for Bayer-Villiger oxidation</td>
<td>153</td>
</tr>
<tr>
<td>Rf6CH2CH2Li/EtO, n = 6, 8</td>
<td>⇒ Rf6CH2CH2I/’BuLi, ether; + HSi(’Pr)2Cl → Rf6(CH2)3Si(’Pr)2H</td>
<td>143</td>
</tr>
<tr>
<td>Rf6CH2CH2ZnI/THF</td>
<td>⇒ Rf6CH2CH2I + Zn/THF, BrCH2CH2Br, (CH3)2CCl → yield: &gt;70%</td>
<td>131</td>
</tr>
<tr>
<td>Rf6CH2CH2MgI</td>
<td>• Precursor for the synthesis of the first fluorous tin hydride/azide: [(R6fCH2CH2)SnX, X = H, N3] applied in “Fluorous Synthesis”</td>
<td>151, 154</td>
</tr>
<tr>
<td>Compound $[C,F,H,O]$</td>
<td>Remarks (<em>“</em> for synthesis of; “+” for reaction of; etc.)</td>
<td>Ref.</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>$C_{8}F_{17}COH$</td>
<td>$\Rightarrow C_{8}F_{17}I + (CH_{3})<em>{2}NCHO/Al-PbBr</em>{2}, \text{r.t.} \rightarrow \text{yield: 95%}$</td>
<td>155</td>
</tr>
<tr>
<td>$R_{6}CHO, n = 1, 2, 3, 7$</td>
<td>$\Rightarrow R_{6}CO_{2}R + \text{LiAlH}_{4}/\text{ether}, \text{–78 °C, ”inverse addition”} \rightarrow 70–76%$</td>
<td>156</td>
</tr>
<tr>
<td>$R_{6}CH_{2}CHO$</td>
<td>$\Rightarrow R_{6}I + CH_{2}–CHO\text{OAc}/\text{AIBN}, 4 \text{ h, 80 °C} \rightarrow R_{6}CH_{2}CH\text{IOAc}; \text{+ CH}<em>{2}–\text{CHO}</em>{2}H/\text{C}<em>{2}H</em>{2}\text{Cl}_{4}, \text{reflux, 12 h} \rightarrow \text{aldehyde yield: 85%}$</td>
<td>157</td>
</tr>
<tr>
<td>$R_{6}CH(\text{CH}_{3})CHO$</td>
<td>$\Rightarrow R_{6}CH–\text{CH}<em>{2} + CO/H</em>{2}\text{-cat} \rightarrow 78% \text{ ee at 21% conversion;} \text{cat: a polymer supported (R,S)-BINAPHOS-Rh(I) complex}$</td>
<td>158</td>
</tr>
<tr>
<td>$C_{n}F_{2n+1}(\text{CH}<em>{2})</em>{m}CHO, m = 1–4$</td>
<td>$\Rightarrow$ Oxidation of $C_{n}F_{2n+1}(\text{CH}<em>{2})</em>{m}\text{CH}<em>{2}OH$ by (a), (b) or (c) methods: (a) Swern, (b) $\text{PyH}^{+}\text{CrO}</em>{3}\text{Cl}^{-}$, (c) Dess-Martin periodinane</td>
<td>159, 126</td>
</tr>
<tr>
<td>$3.5(C_{8}F_{17})<em>{2}C</em>{6}H_{5}CHO$</td>
<td>$\Rightarrow 3.5[R_{6}I_{2}C_{8}H_{3}\text{CH}<em>{2}OH + \text{PyH}^{+}\text{CrO}</em>{3}\text{Cl}^{-}/\text{CH}<em>{2}\text{Cl}</em>{2} \rightarrow \text{yield: 85%}$</td>
<td>68</td>
</tr>
<tr>
<td>$R_{6}COCH_{3}, R_{6}CO\text{CH}<em>{2}COR</em>{1m}$</td>
<td>$\Rightarrow R_{6}CO_{2}H + \text{CH}<em>{3}\text{MgBr} \rightarrow R</em>{6}\text{COCH}<em>{3}; \text{+ R}</em>{1m}\text{CO}<em>{2}\text{C}</em>{2}H_{5}; \text{NaOC}<em>{2}H</em>{4} \rightarrow \text{good overall yields: (a) } n = m = 6, \text{(b) } n, m = 6, 1; \text{ } n = m = 6, 7$</td>
<td>160</td>
</tr>
<tr>
<td>$R_{6}CH_{2}CH_{2}COCF_{3}$</td>
<td>$\Rightarrow R_{6}\text{CH}<em>{2}CH</em>{2}I + \text{Mg}/\text{ether, CF}<em>{3}\text{CO}</em>{2}\text{CH}_{3} \rightarrow \text{yield: 32%}$</td>
<td>161</td>
</tr>
<tr>
<td>$F[CF(CF_{3})O]<em>{n}CF(CF</em>{3})–\text{COCH}<em>{2}\text{COCH}</em>{3}, n = 1–4$</td>
<td>$\Rightarrow F[CF(CF_{3})O]<em>{n}CF(CF</em>{3})\text{CO}<em>{2}\text{CH}</em>{3} + \text{CH}<em>{3}\text{COCH}</em>{3}/\text{NaH} \rightarrow \text{no yield data reported}$</td>
<td>162</td>
</tr>
<tr>
<td>Compound [C,F,H,O]</td>
<td>Remarks (&quot;=&quot; &quot;for synthesis of; &quot;•+&quot; for reaction of; etc.)</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>R(_n)CO(_2)H</td>
<td>⇒ R(_n)CF(_2)I + XSO(_3)H (X = Cl, F) → R(_n)CF(_2)OSO(_2)X; + H(_2)O → overall yield: &gt;70%</td>
<td>163</td>
</tr>
<tr>
<td>R(_n)CO(_2)H, n = 2, 3, 5, 6, 7, 11</td>
<td>⇒ R(_{n+1})I(Br) + Rongalite-NaHCO(_3)/DMF-H(_2)O → yield: 51–86%</td>
<td>164</td>
</tr>
<tr>
<td>C(<em>n)F(</em>{2n+1})CO(_2)H, n = 4, 6, 8</td>
<td>⇒ C(<em>n)F(</em>{2n+1})I + Zn-Cu/CO(_2), (CH(_3)O)(_3)PO, –20 °C → yield: 91%</td>
<td>165</td>
</tr>
<tr>
<td>(CF(_3))(_2)CFOCF(CF(_3))CO(_2)H</td>
<td>⇒ (+)-PIPA and (-)-PIPA have been prepared from CF(_3)COF(_3) and CF(_3)CF(_2)O precursors by a multistep synthesis</td>
<td>166</td>
</tr>
<tr>
<td>R(_{n})(CH(_2))(_m)OCH(_2)CO(_2)H, n/m = 7/1, 8/2, 10/2</td>
<td>⇒ R(_{n})(CH(_2))(_m)OH + CrO(_3)/H(_2)SO(_4), acetone-ether → yield: 98%  + Rh(<em>2)OAc/toluene, 110 °C [–4 AcOH] → (R(</em>{n})CH(_2)CO(_2))(_n)Rh(_2)</td>
<td>167, 168</td>
</tr>
<tr>
<td>(CF(_3))(_2)COCH(_2)CO(_2)H</td>
<td>⇒ (CF(_3))(_2)CCF(_2)O + HF → (CF(_3))(_2)COH; + Cl(_2)CO(_2)R → No yield data in Chem. Abstr.</td>
<td>169</td>
</tr>
<tr>
<td>R(_{in})(CH(_2))(_m)OCH(_2)CO(_2)H, n/m = 6, 8, 10</td>
<td>⇒ R(_{in})(CH(_2))(_m)OH + BrCH(_2)CO(_2)H/NaH, THF, r.t. → yield: 70–96%  + BH(<em>3)/THF, 0 °C to r.t. → R(</em>{in})(CH(_2))(_m)O(CH(_2))(_2)OH, yield: 79–96%</td>
<td>170</td>
</tr>
<tr>
<td>(C(<em>8)F(</em>{17}))(_2)CH(_2)CH(_2)CH(_2)CH(_2)CH(_2)CH(_2)CH(_2)CH(_2)CH(_2)CO(_2)H</td>
<td>⇒ R(_{8})(CH(_2))(_2)I + CH(_2)(CO(_2)C(_2)H(_5))(_2) → → → overall yield: 58%</td>
<td>171</td>
</tr>
<tr>
<td>C(<em>8)F(</em>{17})CH(_2)CH(_2)CON(CH(_2)CH(_2)CH(_2)-C(<em>8)F(</em>{17}))CH(_2)CH(_2)CH(_2)CH(_2)CO(_2)H</td>
<td>⇒ Used as a protective group for oligosaccharide synthesis  + Precursor for new fluorous supports for peptide synthesis</td>
<td>172</td>
</tr>
<tr>
<td>3,4,5-[C(<em>8)F(</em>{17})(CH(_2))(_2)O]CC(_6)H(_2)CO(_2)H</td>
<td>⇒ Preparation and use for Mitsunobu-inversion of chiral sec-alcohols</td>
<td>173</td>
</tr>
</tbody>
</table>

Tab. 9.2-8. Fluorous carboxylic acids
Tab. 9.2.9  Fluorous esters and carbonic acid derivatives

<table>
<thead>
<tr>
<th>Compound [C,F,H,O]</th>
<th>Remarks (“−” for synthesis of; “+” for reaction of; etc.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R8fCO2C2H5, n = 4, 6, 8</td>
<td>⇒ R8fI + ClCO2C2H5 + [C2H5O]2CO + Zn-Cu − yield: 50–70%</td>
<td>175</td>
</tr>
<tr>
<td>Br(CF2)4CO2C2H5</td>
<td>⇒ Br(CF2)4CCl + SO3/H2SO4 + C2H5OH − yield: 67%</td>
<td>176</td>
</tr>
<tr>
<td>C3F7OCF(CF3)CF2OCF(CF3)CO2CH3</td>
<td>⇒ C3F7OCF(CF3)CF2OCF(CF3)COF + CH3OH/Na2CO3 + MgSO4, silica gel − yield: 86%</td>
<td>85</td>
</tr>
<tr>
<td>R8fCH2CH2CH(CO2CH3)2</td>
<td>⇒ R8fCH2CH2I + CH2(ClCO2CH3)/NaH or K2CO3 in THF − high yields (~85%) with negligible elimination and dialkylation</td>
<td>177</td>
</tr>
<tr>
<td>R8f(CH2)4CO2CH2CF3, n = 1, 2</td>
<td>⇒ R8fCH2CH2OH − ~CH2OTs − ~CH2Br − ~CH2MgBr − ~CH2CO2H − ~CH2COCl − title ester, overall yield: 55%</td>
<td>178</td>
</tr>
<tr>
<td>(CF3)3CCO2C2H5</td>
<td>⇒ (CF3)3C−C−CF2/CsF + ClC(O)OC2H5 − yield: 76%, bp = 106 °C</td>
<td>179</td>
</tr>
<tr>
<td>4-R8fCH2CH2C6H4CO2CH3</td>
<td>⇒ 4-BrC6H4CO2CH3 + R8fCH2−CH2/Pd-cat, NaOAc, DMF, 125 °C, 14 h, − R8fCH2−CH2C6H4CO2CH3 (72%); + H2/Pd-C − (88%)</td>
<td>180</td>
</tr>
<tr>
<td>(CF3)1CCCH2CH2CO2CH3</td>
<td>⇒ (CF3)1CH + CH22−CHCO2CH3/(C2H5)3N − yield: 30%</td>
<td>181</td>
</tr>
<tr>
<td>3,5-(C8F17)2C6H3CO2CH3</td>
<td>⇒ R8fI + 3,5-Br2C6H4CO2CH3 + Cu/DMSO, 135 °C − yield: 79%</td>
<td>68</td>
</tr>
<tr>
<td>R8fCH2CH2OCOCl</td>
<td>⇒ R8fCH2CH2OH + COCl2/toluene, reflux 24 h − yield: ~95%</td>
<td>182</td>
</tr>
<tr>
<td>(CF3)1COCOCl</td>
<td>⇒ (CF3)1KOCl + COCl2/mesitylene − yield: 54%</td>
<td>183</td>
</tr>
<tr>
<td>R8fCH2NCO</td>
<td>⇒ R8fCH2NH2 + COCl2 − yield: 78%, bp = 166–168 °C</td>
<td>42</td>
</tr>
<tr>
<td>R8fCH2NCO</td>
<td>⇒ R8fCH2NH2 + COCl2/dioxane − mp = 46–47 °C</td>
<td>184</td>
</tr>
<tr>
<td>(C7F15CH2)2NCOCl</td>
<td>⇒ (C7F15CH2)2NH + excess COCl2/autogenous pressure, 140 °C, 14 h − yield: 100%, mp = 22 °C, bp = 70 °C/0.1 mmHg</td>
<td>119</td>
</tr>
<tr>
<td>R8fCH2CH2N−C−NCH3CH2R8f, n = 4, 6, 8</td>
<td>⇒ R8f(CH2)2N+PPh3/THF, &lt; r.t. −⇒ R8f(CH2)2N−PPh3 + CS2 −⇒ R8f(CH2)2NH2+Ph3PBr2 + N(C2H5)3 in CH2Cl2/C6F14 −</td>
<td>185, 186</td>
</tr>
<tr>
<td>R8f(CH2)n-CH2CNHCO2(CH2)mR8f, n/m = 3/1, 4/2, 6/2, 6/3</td>
<td>⇒ NBS or Br2/py, CH2Cl2 −⇒ R8f(CH2)nO2CN−NCO2(CH2)mR8f; yield: 79–100%; used for fluorous Mitsunobu reaction</td>
<td>182, 187</td>
</tr>
</tbody>
</table>
References

References

38 Tiers, G. V. D. J. Fluorine Chem. 1998, 90, 49–51.
References

10
Highlights of Applications in Synthesis and Catalysis

10.1
Synthetic Applications of Fluorous Reagents

Sivaraman Dandapani

10.1.1
Introduction

The widespread practice of combinatorial chemistry has raised new challenges for synthetic organic chemists. There is a need to synthesize a large number of compounds with high purity in a short time. In many cases separation of the desired product from the crude reaction mixture is the rate limiting process. Solid phase organic synthesis came along to rescue the separation problems. In polymer supported solid phase organic synthesis, a tedious chromatographic separation is replaced with a simple filtration. However, the time saved in separation comes with a price tag – longer reaction time due to heterogeneity of the reaction medium. Also, it is hard to use regular analytical methods for characterizing polymer bound intermediates or monitoring the progress of reactions. Use of a fluorous phase in synthetic organic chemistry has provided a pathway to carry out easy separation without sacrificing time at the reaction stage [1]. This section will focus on several families of fluorous reagents including fluorous phosphines, fluorous tin reagents, fluorous iodo arenes, fluorous sele
nides and fluorous carbodiimides.

10.1.2
Fluorous Phosphines

Phosphines are popular ligands in organometallic chemistry and prevalent reagents in organic synthesis. The pioneering work of Horváth with fluorous trialkyl phosphines as ligands in hydroformylation reactions marked the beginning of Fluorous Biphasic Catalysis (FBC) [2]. Subsequently a wide assortment of phosphine ligands have been successfully employed as ligands in a number of different chemical transformations under FBC conditions. These developments have been reviewed in other chapters of this book [3] and elsewhere [4]. The utility of fluorous phosphines as reagents in organic reactions will be discussed here [5].

Sinou and coworkers have used a heavy fluorous phosphine for carrying out Wittig reactions with stabilized ylides [6]. Fluorous phosphine 1 was treated with ethyl bromoace-
tate to form the corresponding fluorous phosphonium salt (Scheme 10.1-1). The salt was deprotonated with triethylamine to form the ylide, which was reacted with benzaldehyde to form the alkene. The crude reaction mixture was subjected to a liquid/liquid/liquid extraction with a fluorous solvent (D-100 containing mainly perfluorooctane), organic solvent (ether) and water. The desired organic product, i.e., the alkene (along with unreacted benzaldehyde), triethyl ammonium bromide and fluorous phosphine oxide partitioned into the organic, aqueous and fluorous layers respectively. Fluorous phosphine oxide recovered from the fluorous layer was reduced to fluorous phosphine using trichlorosilane. Ten different Wittig reactions were carried out with this protocol and in all the cases pure alkene was isolated directly after liquid-liquid-liquid extraction.

Fluorous phosphines have also been employed in Staudinger reactions by groups working with Bannwarth [7] and Lindsley [8]. Both of these groups used fluorous solid phase extraction (FSPE) to purify the crude reaction mixture.

### 10.1.3 Fluorous Tin Reagents

Tin reagents bring about vital transformations in organic chemistry and they continue to be central to the discipline of organic synthesis [9]. Trialkyltin reagents are very popular in reductive radical chemistry in spite of the accompanying problems of separation, toxicity and disposal of tin byproducts. These problems are reduced to a significant extent with tin hydrides by employing a catalytic procedure [10]. Purification problems associated with tin hydride chemistry have been addressed by traditional strategies [11] and by the introduction of fluorous tin hydrides [12]. In addition to fluorous tin hydrides, fluorous tin azides [13], fluorous tin oxides [14], fluorous allyl tin reagents [15] and Stille reactions with fluorous aryl tin compounds [16] have also been developed (Table 10.1-1).

The reduction of adamantyl bromide by fluorous tin hydride is illustrated here in Scheme 10.1-2. Initial attempts to reduce adamantyl bromide 2 to adamantane 3 using fluorous tin hydride 4 and AIBN in typical organic solvents (such as benzene, toluene and tert-butyl alcohol) or a fluorous solvent (perfluoromethylcyclohexane, PFMC) or biphasic solvent mixtures proved to be disappointing. In all these cases, the reaction mixture was non-homogeneous. However, the reaction mixture became homogeneous when benzo trifluoride (BTF) was used as the solvent, and the reduction was complete in 3 h at 80 °C in this solvent. At the end of the reaction, most of the BTF was removed and the crude reaction mixture was partitioned between dichloromethane and PFMC. The layers were separated and evaporated. Pure adamantane 3 was isolated in 90% yield from the dichloromethane layer and the fluorous tin bromide 5 was isolated in 95% yield from the PFMC layer.

![Scheme 10.1-1. Heavy fluorous Wittig reactions](image-url)
Fluorous tin hydride 4 also undergoes hydrostannylation reactions with alkenes and alkyynes. This reaction was taken advantage of in scavenging excess dienophile (dimethyl acetylene dicarboxylate) present at the end of a Diels-Alder reaction (Scheme 10.1-2). The desired cycloadduct was obtained by evaporation of the organic phase and was free of the starting alkene.

10.1.4 **Fluorous Hypervalent Iodine Reagents**

Gladysz and coworkers have developed a family of fluorous diacetoxy iodo arenes and evaluated them for oxidation of hydroquinones to quinones [17]. Oxidation of hydroquinone 6 with iodoarene 7 is illustrative of the utility of this reagent (Scheme 10.1-3). Hydroquinone 6 was dissolved in MeOH and treated with fluorous iodo arene 7. After 3 h PFMC was added to give a biphasic system MeOH/PFMC. The phases were separated and quinone 8 was isolated in 96% yield from the MeOH layer while the reduced fluorous aryl iodide (not shown) was isolated in quantitative yield from the fluorous layer. The aryl iodide obtained from

**Tab. 10.1-1. Fluorous tin reagents**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Applications</th>
<th>Mode of purification employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R(CH₂CH₃)ₘSnMe₃-H</td>
<td>Reduction of alkyl halides, radical cyclizations, Giese reactions and hydrostannylationss</td>
<td>Rᵣ = C₆F₁₃, m = 3, liq/liq extraction</td>
</tr>
<tr>
<td>(R(CH₂CH₃CH₂)ₘSnCH₂CH₂CH₂</td>
<td>Thermal allylation of aldehydes, Barbier and Keck allylations</td>
<td>Rᵣ = C₆F₁₃ liq/liq extraction</td>
</tr>
<tr>
<td>(C₄F₁₃CH₂CH₂)₃SnN₃</td>
<td>Synthesis of tetrozones</td>
<td>Liq/liq extraction</td>
</tr>
<tr>
<td>(C₄F₁₃CH₂CH₂)₃SnAr; Ar = aryl</td>
<td>Stille reactions</td>
<td>Liq/liq extraction</td>
</tr>
<tr>
<td>[(C₆F₁₃CH₂CH₂)₂(Cl)Sn]₂O</td>
<td>Trans-esterifications</td>
<td>Liq/liq extraction and FSPE</td>
</tr>
</tbody>
</table>

**Scheme 10.1-2. Reactions of fluorous tin hydride**

Fluorous tin hydride 4 also undergoes hydrostannylation reactions with alkenes and alkyynes. This reaction was taken advantage of in scavenging excess dienophile (dimethyl acetylene dicarboxylate) present at the end of a Diels-Alder reaction (Scheme 10.1-2). The desired cycloadduct was obtained by evaporation of the organic phase and was free of the starting alkene.
the fluorous phase was reoxidized to a diacetoxy iodo compound for reuse in hydroquinone oxidation.

Lindsley and coworkers have used the light fluorous diacetoxy iodo arene 9 to access unnatural carpanone analogs [19]. Styrene phenol 10 on reaction with iodo arene 9 gives carpanone analog 11. FSPE was used to separate 11 from the crude reaction mixture.

10.1.5 Fluorous Diaryl Diselenides

One of the side reactions in stannane mediated radical reduction of alkyl halides, is the rearrangement of the alkyl radical. This undesirable radical rearrangement pathway can be avoided to a considerable extent by using benzeneselenol. Primary alkyl radicals can abstract hydrogen atoms about 500 times faster from benzene selenol compared with that of a trialkyl stannane. Benzeneselenol can be conveniently generated in situ by reduction of diphenyldiselenide with stannanes. Crich and coworkers have developed a fluorous diaryl diselenide for catalyzing stannane mediated radical reactions which not only suppressed the radical rearrangements but also facilitated separation [20].

Fluorous diselenide 12 carrying two perfluoro hexyl chains showed sufficient solubility in organic solvents for applications in radical chemistry, but was not sufficiently fluorous to be extracted into the fluorous layer in a simple organic liquid/fluorous liquid biphasic extraction. Crich and coworkers solved this problem by designing a suitable continuous extractor.
Details of this continuous extraction procedure are described by Crich elsewhere in this book [21]. We expect FSPE to work equally well for the separation of this light fluorous selenide.

Fluorous diselenide 12 was then applied for the inhibition of stannane mediated rearrangements (Scheme 10.1-4). The initial 5-exo radical cyclization of vinyl radicals was not interrupted but the product radical did not undergo undesired homoallyl rearrangement, instead it was efficiently reduced by fluorous selenol. The crude reaction mixtures from these reactions were treated with benzoyl peroxide (to regenerate fluorous diselenide) and subjected to continuous extraction which allowed ready purification of the reaction mixture and recovery of fluorous diselenide 12.

Crich and coworkers extended the utility of fluorous diaryl diselenides by developing a protocol for efficient conversion of vicinal dimesylates into alkenes by a catalytic amount of fluorous diaryl diselenides and sodium borohydride [22].

10.1.6 Fluorous Carbodiimide

Fluorous ureas are sparingly soluble in organic solvents and fluorous solvents. Palomo and coworkers found that the solubility of fluorous ureas in fluorous solvents can be dramatically increased by the addition of stoichiometric amounts of fluorous alkanoic acids [23]. Fluorous urea forms a stable complex with fluorous acid and the complex has a preferential solubility in fluorous solvents (Scheme 10.1-5).
Ureas are byproducts of a number of important reactions, such as the preparation of amides and esters. It was envisioned that the light fluorous ureas present in the reaction mixture could be removed by liquid/liquid extraction by complexing the fluorous urea with fluorous acid. This phenomenon of complex formation has fundamental advantages. Light fluorous reagents are preferred at the reaction stage since they are more soluble in organic solvents and their behavior is usually closer to the organic analog. The light fluorous by-products are usually not sufficiently fluorous to be separated using liquid/liquid extraction. However the light fluorous byproduct can be made into a heavy fluorous one by complexing it with another fluorous domain, hence facilitating removal by a typical biphasic extraction.

Palomo and coworkers have demonstrated the application of switching a light fluorous byproduct into heavy fluorous complex using fluorous urea. Fluorous carbodiimide 13 was used to prepare ester 14 (Scheme 10.1-5). The reaction was carried out in a biphasic solvent system consisting of dichloromethane and FC-72. The crude reaction mixture was washed twice with a 0.4 M solution of perfluoroheptanoic acid in perfluorohexane and once with perfluorohexane. This was followed by a 1 M aqueous HCl wash, presumably to extract DMAP. The crude product 14 obtained directly after this workup procedure was free from the fluorous urea (0.2% or less was detected by GC) and the purity as assayed by $^1$H NMR spectroscopy was excellent.

10.1.7

Conclusions

Fluorous synthesis and separation procedures cater to the needs of combinatorial chemists who are not only interested in high throughput synthesis but also the purity of the products. Three different separation procedures have gained prominence for separating fluorous

---

**Scheme 10.1-5.** Fluorous carbodiimide and fluorous urea
compounds from organics. Fluorous liquid/organic liquid extraction, which started the ball rolling, continues to remain prevalent in heavy fluorous arena. Crich’s modified continuous extraction procedure allows light fluorous compounds to be extracted using a minimum amount of fluorous liquid. Separations over a fluorous solid phase (FSPE) are not only easy to conduct in parallel, but also amenable to automation. These FSPE procedures are gaining acceptance by medicinal chemists.

The full utility of the fluorous methods can be realized only with the availability of a large collection of reagents and protecting groups. It is now possible to make an educated guess about the retention behavior of new fluorous compounds based on previously studied examples [24]. This helps in designing new fluorous compounds suitable for the specific separation technique of interest. Given the considerable interest in solution phase combinatorial chemistry in and beyond medicinal chemistry, we are optimistic that more and more chemists will find fluorous chemistry attractive in the years to come.

References

3 E. G. Hope, A. M. Stuart, see Chapter 10.7.
Radical carbonylations using fluorous tin reagents: convenient workup and facile recycle of the reagents

Ilhyong Ryu

10.2 Introduction

Radical carbonylation is emerging as a promising method for the introduction of carbon monoxide into organic molecules [1–5]. A key step is the addition of carbon radicals to carbon monoxide to give acyl radicals [6], which can be sequenced in a number of inter- and intramolecular addition processes [2] and atom and group transfer processes [7]. The first report on efficient synthesis of aldehydes by radical carbonylation used tributyltin hydride as a hydrogen transfer reagent [8]. Shortly thereafter the radical carbonylation step was sequenced with the addition to allyltin to give β,γ-unsaturated ketones [9]. The purpose of this chapter is to give an overview of radical carbonylation reactions using fluorous tin reagents, with an emphasis on the advantageous workup procedure, compared with that for conventional tin reagents, as well as on the reactivity differences between traditional and fluorous tin reagents. Since tin hydrides and allyltin reagents have been widely used as chain carriers for a number of synthetically useful radical reactions, we believe that the features contained in this chapter have a broad scope for application to many tin-mediated radical reactions [10].

10.2.2 Radical Carbonylations Using Fluorous Tin Hydrides

The evolution of fluorous methods in the 1990s has greatly influenced the way that preparative organic chemistry is carried out [11–14], and tin-mediated radical chemistry is no ex-
Radical Carbonylations Using Fluorous Tin Reagents: Convenient Workup and Facile Recycle of the Reagents

Ilhyong Ryu

10.2

Radical Carbonylations Using Fluorous Tin Reagents: Convenient Workup and Facile Recycle of the Reagents

Introduction

Radical carbonylation is emerging as a promising method for the introduction of carbon monoxide into organic molecules [1–5]. A key step is the addition of carbon radicals to carbon monoxide to give acyl radicals [6], which can be sequenced in a number of inter- and intramolecular addition processes [2] and atom and group transfer processes [7]. The first report on efficient synthesis of aldehydes by radical carbonylation used tributyltin hydride as a hydrogen transfer reagent [8]. Shortly thereafter the radical carbonylation step was sequenced with the addition to allyltin reagents to give \( \beta,\gamma \)-unsaturated ketones [9]. The purpose of this chapter is to give an overview of radical carbonylation reactions using fluorous tin reagents, with an emphasis on the advantageous workup procedure, compared with that for conventional tin reagents, as well as on the reactivity differences between traditional and fluorous tin reagents. Since tin hydrides and allyltin reagents have been widely used as chain carriers for a number of synthetically useful radical reactions, we believe that the features contained in this chapter have a broad scope for application to many tin-mediated radical reactions [10].

10.2.2

Radical Carbonylations Using Fluorous Tin Hydrides

The evolution of fluorous methods in the 1990s has greatly influenced the way that preparative organic chemistry is carried out [11–14], and tin mediated radical chemistry is no ex-
ception. Having the invention of fluorous tin hydride [15, 16] and allyltin [17] available for radical chain reactions from the Curran group, we jointly set out to develop “fluorous versions” of radical carbonylation reactions. Radical reactions using fluorous tin reagents have the great advantage of easy separation of products and reagents by fluorous/organic liquid/liquid extraction or fluorous/solid phase extraction, which also ensures the facile recycling of tin reagents. The first equation in Scheme 10.2-1 demonstrates a typical workup procedure to separate the tin reagent and product associated with the use of traditional tributyltin hydride. Treatment with aqueous potassium fluoride forms insoluble tributyltin fluoride, which is then filtered off. The filtrate was next partitioned into organic and aqueous layers. The second equation in Scheme 10.2-1 refers to the case of a fluorous radical reaction, which can employ organic/fluorous biphasic workup to separate the product and fluorous tin halide. The fact that tin fluoride is difficult to reduce to the parent tin hydride in the former case is a disadvantage of the traditional workup, whereas tin halides other than fluoride, whether fluorous or triorganyl, are easily reduced to the corresponding tin hydride, allowing for the recycling of tin reagents in the latter case.

To compare the relative reactivity of fluorous tin hydride with a conventional triorganyltin hydride [18], the radical formylation of nonyl bromide was examined at 70 atm of CO pressure (Scheme 10.2-2). Tributyltin hydride gave a good yield of decanal (84%), which is a reflection of a higher formylation/reduction ratio, whereas ethylene-spaced fluorous tin hydride gave an inferior result under identical conditions (70%). Fine tuning of reaction conditions by increasing CO pressure to 90 atm effectively pushed the efficiency of the fluorous tin hydride to a level comparable to that of tributyltin hydride. This difference is well understood in terms of a slightly higher ability of ethylene-spaced fluorous tin hydride to deliver hydrogen to the radical center, which is consistent with the fact that the rate constant for primary alkyl radical trapping by fluorous tin hydride is about twice that for tributyltin hydride at 20 °C [19].

As a model study for tin hydride mediated radical carbonylation, fluorous hydroxymethylation of organic halides was examined using a catalytic quantity of a fluorous tin hy-
dride. While a similar hydroxymethylation, which is based on radical formylation and in situ reduction, was previously examined using a catalytic amount of triphenylgermyl hydride and an excess amount of sodium cyanoborohydride [20], the reaction conditions had not been optimized for tin hydride reagents. We found that the hydroxymethylation reaction of alkyl bromides works well when a catalytic amount of fluorous tin hydride was used together with 1.2 mol equivalent of sodium cyanoborohydride [21], and some results are shown in Scheme 10.2-3 [18]. The catalytic cycle is given in Scheme 10.2-4. The product isolation was easily carried out by a triphasic (aqueous/organic/fluorous) extractive workup and the fluorous tin hydride was recovered from the FC-72 layer by evaporation.

For the cases in Schemes 10.2-3 and 10.2-4, benzotrifluoride (BTF) is used as an amphilic solvent to dissolve both organic substrates and fluorous reagents in order to create a homogeneous reaction medium. Recently we have reported that F-626, 1\(\text{H}\),1\(\text{H}\),2\(\text{H}\),2\(\text{H}\)-perfluoroctyl 1,3-dimethylbutyl ether [22], is a useful high boiling solvent for both fluorous and non-fluorous reactions [23]. Thus, we tested F-626 in place of BTF and found that it works equally well (Scheme 10.2-5). Judging from its partition coefficient (1/3.6 in EtOH/FC-72), F-626 is more fluorophilic than BTF (1/0.18 in EtOH/FC-72). Thus, through tripha-

**Scheme 10.2-2.** Slightly higher reactivity of fluorous tin hydride

\[
\begin{align*}
n-C_9H_{19}Br & + CO + \text{Bu}_3\text{SnH} & & \text{AIBN (10 mol%)} & & n-C_9H_{19}CHO \\
0.02 \text{ M} & & 70 \text{ atm} & & \text{C}_6\text{H}_6, 80 ^\circ \text{C}, 2 \text{ h} & & 84% \\
n-C_9H_{19}Br & + CO + (C_6F_{13}CH_2CH_2)_3\text{SnH} & & \text{AIBN (10 mol%)} & & n-C_9H_{19}CHO \\
0.02 \text{ M} & & 90 \text{ atm (70 atm)} & & \text{BTF (benzotrifluoride)} & & 82\% \text{(70\%)}
\end{align*}
\]

**Scheme 10.2-3.** Hydroxymethylation of \(\text{RBr}\) using a catalytic amount of fluorous tin hydride

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{RBr} & + CO + \text{NaB} & & \text{H}_3\text{CN} & & \text{AIBN (10 mol%)} & & \text{H}_2\text{O} \\
0.5 \text{ M} & & 1.2 \text{ mol equiv} & & \text{BTF, t-BuOH} & & \text{RCH}_2\text{OH}
\end{align*}
\]
sic workup, F-626 remained in the FC-72 together with the fluorous tin hydride. Evaporation of the FC-72 layer gave an F-626 solution containing fluorous tin hydride. The solution is reused conveniently for the second run experiment without adding additional F-626 solvent (Scheme 10.2-5). F-626, fluorous-tagged solvent, has a relatively high boiling point (80 °C at 9 Torr), nevertheless its facile removal by biphasic workup ensures its use without worrying about the general dilemma of how to remove a high-boiling solvent from a reaction mixture.

Among the stannylcarbonylation reactions [24–26], which constitute a useful variant of tin mediated radical carbonylations, the reaction with azaenynes is particularly useful for synthesizing lactams having a wide range of ring sizes [26]. The following example demonstrates the synthesis of a β-lactam by stannylcarbonylation of an azaenyne with a fluorous tin hydride [27]. The crude α-stannylmethylene lactam was subjected to Stille coupling reaction
with iodobenzene without isolation. After the reaction, a fluorous/organic biphasic workup allows for the separation of the \(\alpha\)-phenylmethylene lactam and fluorous tin iodide (Scheme 10.2-6).

**10.2.3 Radical Carbonylations Using Fluorous Allyltin Reagents**

Allyltin compounds are powerful UMCT (unimolecular chain transfer) [28] players in radical chemistry. We have reported that a four-component coupling reaction consisting of alkyl halides, carbon monoxide, electron-deficient alkenes, and allyltin tributyltin [29] is a particularly efficient process leading to \(\beta\)-functionalized \(\delta\),\(\epsilon\)-unsaturated ketones. To ascertain the potential of propylene-spaced fluorous allyltin [17] in such a carbonylative four-component coupling reaction, we carried out a competitive experiment using a system containing an equimolar amount of conventional allyltin tributyltin. This revealed that the conventional allyltin tributyltin is three times more reactive toward the \(S_{\Pi}^2\) reaction than the fluorous allyltin (Scheme 10.2-7) [30].

We offset the modest reactivity of a propylene-spaced fluorous allyltin by employing a higher concentration to ensure an effective chain propagation. To separate coupling products and fluorous tin halides, fluorous/organic biphasic workup (method A) and fluorous solid phase extraction (FSPE) with fluorous reverse phase silica (FRPS) (method B) [31] were carried out, as outlined in Scheme 10.2-8. Thus, after the reaction, BTF (benzotrifluoride) was removed by vacuum evaporation and the resulting oil was partitioned into acetonitrile and FC-72 (method A). Evaporation of the acetonitrile layer, followed by short column chromatography on silica gel, gave the pure four-component coupling product.

Scheme 10.2-9 lists the results of four-component coupling reactions, where alkyl halides, CO, electron-deficient alkenes and fluorous allyl- and methallyltin compounds are coupled in the given sequence [30]. The isolation of the final example was carried out using FRPS (method B).

An attempted four-carbon component reaction using perfluoroalkyl iodides in place of alkyl iodides was unsuccessful, and gave simply allylated perfluoroalkanes in good yields [32]. Apparently, the highly electrophilic perfluoroalkyl radicals prefer to react with electron-
Scheme 10.2-7. Competitive experiments using a mixture of fluorous and conventional allyltin compounds

Scheme 10.2-8. Fluorous allyltin mediated four-component coupling reaction and two types of separation methods A and B
rich allyltin rather than carbon monoxide and electron-deficient alkenes. Thus, we tested a simple synthetic procedure of perfluorinated allylic compounds starting from perfluoroalkyl iodides and allylttributyltin compounds. FRPS is conveniently used for the separation of fluororous products and organic reagents (Scheme 10.2-10). The simplified workup procedures to isolate products will allow for the easy implementation of the parallel synthesis using an

Scheme 10.2-9. Fluorous allyltin mediated four-component coupling reaction

Scheme 10.2-10. Synthesis of perfluoroalkanes by radical addition and isolation by FRPS
automated reaction apparatus. Gladysz and coworkers reported that fluorous/organic bi-
phase workup is also useful for isolating allylated perfluorooctane, which was obtained by
the photolysis of perfluoroocetyl iodide and allyltributyltin [33].

10.2.4
Conclusion

Fluorous tin reagents can be used successfully for radical carbonylation reactions with a
slight modification to the original reaction conditions established for conventional tributyltin
reagents. Catalytic hydroxymethylation of organic halides works well with a fluorous tin hy-
dride, where the triphasic workup is conveniently used for the separation of fluorous tin hydride, inorganic salts, and products. The usefulness of fluorous allyltin and methallyltin
reagents for the cascade type free-radical carbonylation was also established. Using fluorous/
organic liquid/liquid extraction or fluorous-solid phase extraction (FSPE) with fluorous re-
verse phase silica, the tedious procedure of removing organotin reagents and/or byproducts
can be circumvented. These results suggest that fluorous tin reagents have the potential to
be applicable to a wide range of tin-based radical reactions.

Acknowledgements

I wish to acknowledge Professor Dennis P. Curran for giving me the excellent opportunity
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oration on this project.

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Approaches to the Fluorous Mitsunobu Reaction

Roman Dembinski

10.3

Introduction

The Mitsunobu protocol (Scheme 10.3-1) involves the reaction of an alcohol 1 and an acidic pronucleophile 2 (NuH), promoted usually by stoichiometric amounts of diethyl or diisopropyl azodicarboxylate 3 (DEAD or DIAD) and triphenylphosphine 4 (TPP) [1]. This reaction yields product 5 with formation of a C–O, C–N, C–S, C–X or C–C bond, along with dicarboalkoxyhydrazine 6 and triphenylphosphine oxide 7 (TPPO).

The Mitsunobu reaction has been widely used in organic synthesis, often for the inversion of configuration in secondary alcohols or the synthesis of aryl ethers. Synthetic advances
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The Mitsunobu reaction has been widely used in organic synthesis, often for the inversion of configuration in secondary alcohols or the synthesis of aryl ethers. Synthetic advances

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have been summarized in various reviews [1, 2]. Recently, new coupling reagents have been introduced [2h, 3] and the mechanistic features have received additional clarification [4]. Although the lack of material conservation hindered larger scale applications, the reaction is popular in small scale and automated parallel synthesis [5] due to its stereoselectivity, compatibility with a wide range of functional groups, and mild reaction conditions. However, separation of the desired product from the spent and excess reagents consumes time and resources.

To simplify workup, the reaction can be carried out on a polymer support [6–11] or in the presence of separation-friendly Mitsunobu reagents. Polymer-bound phosphines [12–14] and azodicarboxylates [15] have been introduced, though their large excesses are inevitable. Appropriately substituted reagents can be removed by acid–base extractions [16–19] or by decomposition to volatile products [16]. Furthermore, “impurity annihilation” may simplify removal of residual reagents and byproducts [20]. These reagents allow solution-phase reactions, but they require extra reaction chemistry to effect the separation. This potentially adds time, limits the scope, and hampers recycling of the reagents. It can be assumed that laborious isolations affect the yields, which are usually reported to be in the range of 60–90%. The fluororous approach offers appealing solutions to the separation problems of the Mitsunobu reaction by simplifying the isolation protocol, and improving the yields.

10.3.2
Fluorous Azodicarboxylate and Fluorous Phosphine

The most common approach to transforming the Mitsunobu reaction into fluororous conditions includes construction of fluorophilic participating reagents, thus allowing phase separation of fluorous byproducts from organic products. This has led to the synthesis of fluorous azodicarboxylates and the application of fluorous phosphines.

10.3.2.1 Preparation of Fluorous Azodicarboxylate
The fluorous DEAD reagent has been synthesized concurrently by Dandapani and Curran [21], and Dobbs and McGregor-Johnson [22] (Scheme 10.3-2). 1H,1H,2H,2H-perfluoro-1-octanol is treated with 1,1'-carbonyldimidazole in THF, or phosgene in ether to give the fluorous imidazolide or chloroformate. Without further purification, both compounds are reacted with hydrazine hydrochloride/triethylamine in THF or hydrazine hydrate in ethanol. The fluorous hydrazine is isolated as a white solid after chromatography or
recrystallization from methanol. Oxidation of 6a with bromine/pyridine in dichloromethane or N-bromosuccinimide in pyridine is superior to treatment by other reagents such as iodosobenzene diacetate, lead tetraacetate, or manganese dioxide [22]. The fluorous azodicarboxylate 3a (FDEAD) is obtained in 85–63% overall yield. The FDEAD reagent (molecular weight 810), a pale cream/yellow solid that can be recrystallized from ethanol, is stable as a solid at ambient temperature for several months, and in solution (CDCl3) for at least two weeks. Preparation of fluorous phosphines is reviewed in Chapter 10.7.

10.3.2.2 Reactions with Fluorous Azodicarboxylate and Fluorous Phosphine

To explore the efficiency of modified reagents, the Mitsunobu reaction has been examined with fluorous DEAD and regular phosphine [21, 22], or regular DEAD and fluorous phosphine [21]. Concurrent traditional reactions have also been conducted. The reactions take longer times but have comparable yields to those with non-fluorous Mitsunobu reagents. The protocol for isolation requires both reagents to be fluorous for facile separation by solid phase or liquid/liquid extraction. Accordingly, a fully fluorous reaction has been developed.

Dandapani and Curran have established an elegant separation of the organic product from fluorous byproducts allowing regeneration of the latter (Scheme 10.3-3) [21]. When ethanol 1a, 3,5-dinitrobenzoic acid 2a, FDEAD 3a, and fluorous phosphine PhP[C6H4-p-(CH2)2]6F 4a (TPP, molecular weight 954) react in the Mitsunobu reaction, the solvent is removed and the crude reaction mixture is subjected to solid phase extraction (SPE) on fluorous silica. Elution with MeOH/H2O (8:2) gives the organic Mitsunobu adduct 5a in 92% yield. Further elution with ether gives a mixture of the fluorous phosphine oxide 7a and the fluorous hydrazine 6a (DCEH). This mixture of fluorous byproducts is readily separated on regular silica gel by eluting with hexane/EtOAc (3:2). The less polar hydrazine 6a is eluted first and isolated in 80% yield; the more polar phosphine oxide 7a follows in 86% yield. Both the reduction of the fluorous phosphine oxide 7a with AlH3 to regenerate 4a, and
the oxidation of the fluorous hydrazine 6a to reconstitute 3a (also a step on the synthetic route to the FDEAD, cf. Scheme 10.3-2), are quantitative reactions. Thus, effective recycling of the fluorous reagent-based byproducts 6a and 7a is possible.

The order of addition of reagents may affect the course of the Mitsunobu reaction [2c]. A solution of phosphine and the alcohol can be added to the solution of azodicarboxylate and nucleophile (procedure A). Since DEAD is a strong oxidant, Michael acceptor, and dienophile, it is advantageous to avoid an excess. In the classical way, the phosphine, the alcohol, and the nucleophile are dissolved in the solvent and the azodicarboxylate is added dropwise to the solution (procedure B). Alternatively, azodicarboxylate and phosphine are reacted first to form an adduct, followed by addition of the alcohol and the nucleophile (procedure C). These three procedural variations have been investigated in reactions of simple alcohols and nucleophiles (Scheme 10.3-4) with FDEAD 3a and FTPP 4a [Table 10.3-1] [21].

Procedure A has been used with 3,5-dinitrobenzoic acid 2a and 4-nitrobenzoic acid 2b, and procedure C has been used for the 4-(4-nitrophenyl)butyric acid 2c. For nitrogen nucleophiles, such as phthalimide 2d and N-(t-butoxycarbonyl)-p-toluene sulfonamide 2e, procedure B has been examined for both and procedure C for the latter. All of the procedures provide examples of quantitative conversions and very good yields, although for the sulfonamide 2e procedure C is advantageous over procedure B [21].

The stereochemistry of the Mitsunobu reaction has been confirmed with the use of the lighter fluorous phosphine Ph2PC6H4-p-(CH2)2(CF2)2F 4b [21]. The anti-3-hydroxy-2-methylbutyric acid ethyl ester yields the expected syn (inverted) products with nitrobenzoic acids 2a or 2b. Similarly, 5α-cholestan-3α-ol dinitrophenyl ester is obtained with inversion of configuration when 5α-cholestan-3β-ol reacts with 2a. Although the hydrophobicity of

Scheme 10.3-3. Separation and recycling of fluorous byproducts in the fluorous Mitsunobu reaction (SPE = solid phase extraction) [21]
the cholestanol ester affects the fluorous solid phase extraction, a good yield is achieved by chromatography on regular silica gel. An examination of the stereochemistry for reactions of 
S-(+)-2-octanol with benzoic acid, and R-(+)-1-phenylbutanol with phthalimide 2d, in the presence of 6DEAD and regular phosphine 4, has also revealed complete inversion [22].

The fluorous phosphines have been selected based upon a correlation of fluorophilicity with HPLC retention times on a fluorous column [23, see Chapter 7]. The preferred phosphine for the fluorous Mitsunobu reaction is Ph2PC6H4-\(p\)-(CH2)2(CF2)8F 4b (molecular weight 698). Fluorous phosphines with longer chains or with three fluorous phenyl rings are also available, but the longer retentions and added molecular weight of these analogs offer no distinct advantage for SPE separations.

To explore the effect of a reduction in the fluorous content, other fluorous azodicarboxylates 3 that differ in the length of the spacer or perfluoroalkyl group \([R'] = F(CF2)\_4(CH2)\_2, F(CF2)\_6(CH2)\_2; F(CF2)\_8(CH2)\_2]\) have also been synthesized by the same reaction sequence as is shown in Scheme 10.3-2 [21]. Of those tested the one with the same amount of fluorine as 3a gives similar results. When the fluorous content is reduced, as for \(R' = F(CF2)\_4(CH2)\_2\), the precursor hydrazine partitions between the organic and fluorous fractions during SPE. The 6DEAD 3a with 60.9% fluorine content and an ethylene spacer group has been the most extensively examined and is the most popular.

### 10.3.3 Synthesis and Separation of Fluorophilic Compounds

Fluorine-containing compounds have been used in the Mitsunobu reaction, either as the alcohol [24–27] or pronucleophilic component [28–31]. Fluorous esters have also been synthesized by other methods and isolated by fluorous liquid/liquid extraction [32–34, see...
Chapter 10.15]. This chapter presents advances in which the combination of both the Mitsunobu reaction and fluorous separation have been applied.

10.3.3.1 Esters

The fluorous phase labeling is based on the introduction of a fluorous “ponytail” into the product (see Chapter 5) subsequent exploitation for separation, then followed by “detagging” to yield a final product. This concept suits the Mitsunobu reaction well, and allows for efficient separation without column chromatography.

The synthesis of fluorous-tagged esters via the Mitsunobu reaction has been reported by Markowicz and Dembinski [35]. For the best fluorous partitioning, the total fluorine content of the fluorous phase-compatible molecule should equal or exceed 60%. The number of perfluoroalkyl groups is also an important factor, as appropriate shielding of the hydrocarbon domain leads to better fluorous solubility and partition. Accordingly, a tagging unit has been developed from inexpensive gallic acid. The 3,4,5-tris(4-perfluorooctyl-1-butoxy)benzoic acid 2f (Scheme 10.3-4) is obtained by etherification of gallic acid methyl ester with 4-perfluorooctyl butyl iodide or bromide, and subsequent base hydrolysis [36]. The three perfluoroalkyl ponytails provide appropriate shielding, and a fluorine content of 60.9% for the ArCOO unit [Nu, molecular weight 1592], thus exceeding the requirements for good fluorous partitioning.

The use of fluorous tagged nucleophile 2f in the Mitsunobu reaction offers two other advantages: (i) the fluorous esters are solids and can be easily isolated by simple crystallization, eliminating the need to use fluorous solvents; (ii) the fluorous tagged nucleophile (Nu) can be readily cleaved from the organic products by saponification with excellent yield [33, 36], thereby providing recycling opportunities.

The reactions of several representative alcohols with various functional groups and different carbon skeletons have been investigated (Table 10.3-2). All reactions are carried out with TPP 4, in homogeneous conditions as THF provides good solubility for 2f. Since the literature does not provide support for any advantage in using DEAD over diisopropyl azodicarboxylate (DIAD) [2, 10, 37, 38], the less expensive i-Pr derivative is preferred. After reaction by procedure B, separation is carried out according to the organic liquid/fluorous solid principle [39]. The THF is replaced by chloroform/methanol and the mixture is cooled to −10 °C. The highly fluorous products are immiscible with the organic phase and precipitate readily. The analytically pure esters are separated from the organic byproducts by simple filtration, avoiding a chromatographic step. Most alcohols afford complete reaction and the almost quantitative, with respect to the fluorous tagging group, isolation of esters. Such an approach eliminates the use of fluorous solvents, and complements SPE especially for the separation of fluorous esters with large organic parts, such as cholestanol [21, 40].

Hydrolysis of the fluorinated ester allows high yield isolation of the alcohol and recovery of the fluorous tag. A selected alcohol, 5α-cholestan-3α-ol, is isolated in 94% yield after saponification of the fluorous ester obtained from 2f and 5α-cholestan-3β-ol. This example also confirms the expected inversion of configuration. The tagging acid 2f is recovered in 78% yield. Thus, the highly fluorinated carboxylic acid 2f is a useful acyl donor for the acylation of alcohols in the Mitsunobu reaction, with a simple, chromatography- and fluorous solvent-free separation protocol and excellent yields. This example demonstrates the effectiveness of fluorous tags for liquid/solid partition and develops a new aspect of fluorous chemistry.
### Tab. 10.3-1. Products of the Mitsunobu reaction with $^3$DEAD 3a and $^3$TPP 4a (or 4b) reagents [21]

<table>
<thead>
<tr>
<th>Alcohol 1</th>
<th>NuH 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Procedure&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product 5 (NuR)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$OH</td>
<td>2a</td>
<td>A</td>
<td>3,5(NO$_2$)$_2$C$_6$H$_4$COOCH$_3$</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>C</td>
<td>4-NO$_2$C$_6$H$_4$(CH$_2$)$_3$COOCH$_3$</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>2d</td>
<td>B</td>
<td><img src="image" alt="Structure" /></td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>2e</td>
<td>C</td>
<td>4-CH$_3$C$_6$H$_4$SO$_2$-N-CH$_3$</td>
<td>90</td>
</tr>
<tr>
<td>CH$_3$CH$_2$OH</td>
<td>2a</td>
<td>A</td>
<td>3,5(NO$_2$)$_2$C$_6$H$_4$COOCH$_2$CH$_3$</td>
<td>92</td>
</tr>
<tr>
<td>CH$_2$=CHCH$_2$OH</td>
<td>2a</td>
<td>A</td>
<td>3,5(NO$_2$)$_2$C$_6$H$_4$COOCH$_2$CH=CH$_2$</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>C</td>
<td>4-NO$_2$C$_6$H$_4$(CH$_2$)$_3$COOCH$_2$CH=CH$_2$</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>2d</td>
<td>B</td>
<td><img src="image" alt="Structure" /></td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>2e</td>
<td>C</td>
<td>4-CH$_3$C$_6$H$_4$SO$_2$-N-CH$_2$CH=CH$_2$</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>COO-t-Bu</td>
<td></td>
</tr>
<tr>
<td>F-CH$_2$OH</td>
<td>2a</td>
<td>A</td>
<td>3,5(NO$_2$)$_2$C$_6$H$_4$COOCH$_2$C$_6$H$_4$-4-F</td>
<td>75&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>C</td>
<td>4-NO$_2$C$_6$H$_4$(CH$_2$)$_3$COOCH$_2$C$_6$H$_4$-4-F</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>2d</td>
<td>B</td>
<td><img src="image" alt="Structure" /></td>
<td>75</td>
</tr>
</tbody>
</table>
For structures see Schemes 10.3-3 and 10.3-4.

Procedures: A. Addition of $^1$TPP and the alcohol in ether to the $^1$DEAD and NuH in ether. B. Addition of a solution of $^1$DEAD in THF to a solution of NuH, $^1$TPP, and the alcohol. C. $^1$DEAD in THF was added to a solution of $^1$TPP in THF, followed by the alcohol, and the NuH. *91% purity. d With Ph$_2$PC$^6$H$_4$-p(Ch)$(C_{F_2})_9$F 4b.
<table>
<thead>
<tr>
<th>Alcohol 1</th>
<th>$\text{NaH}$ 2$^a$</th>
<th>Product 5 (NuR)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{OH}$</td>
<td>2f$^b$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COOCH$_2$CH$_3$</td>
<td>95</td>
</tr>
<tr>
<td>$\text{C}=$CH-CH$_2$OH</td>
<td>2f$^b$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>83</td>
</tr>
<tr>
<td>$\text{C}=$C-CH$_2$OH</td>
<td>2f$^b$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>93</td>
</tr>
<tr>
<td>$\text{O}$=$\text{O}$</td>
<td>2f$^b$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>96</td>
</tr>
<tr>
<td>$\text{C}$-C-CH$_2$OH</td>
<td>2f$^b$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>92</td>
</tr>
<tr>
<td>$\text{F}$(CF$_2$)$_7$CH$_2$OH</td>
<td>2g$^c$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>94</td>
</tr>
<tr>
<td>$\text{F}$(CF$_2$)$_8$(CH$_2$)$_2$OH</td>
<td>2g$^c$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>0</td>
</tr>
<tr>
<td>$\text{F}$(CF$_2$)$_8$(CH$_2$)$_3$OH</td>
<td>2g$^c$</td>
<td>3,4,5-[$\text{F}$(CF$_2$)$_3$(CH$_2$)$_3$O]$_2$C$_6$H$_2$COO</td>
<td>11$^d$</td>
</tr>
</tbody>
</table>

Highlights of Applications in Synthesis and Catalysis

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[35, 41]
For structures see Scheme 10.3-4. Reaction conducted with DIAD in THF by procedure B. Reaction conducted with DEAD in benzotrifluoride by procedure B. Mixture of isomers: F(CF₂)₈CH₂CH₂ONu and F(CF₂)₈CH(O Nu)CH₃ ~ 10:1.
10.3.3.2 Ethers
Substituted hexafluoropropanols are readily accessible by the reaction of aromatic hydrocarbons and hexafluoroacetone. 2-Phenyl hexafluoropropanol can be used, due to its reactivity, as a protecting group for alcohols [30]. Rábai et al. [41] have shown that the Mitsunobu reaction can be applied effectively for the synthesis of fluorous ethers from either fluorine-containing component. The reaction of the 2-aryl hexafluoropropanols \( 2g-i \) in the presence of DEAD and TPP with aliphatic perfluoroalcohols containing different spacers has been examined (Table 10.3-2). Reaction is sensitive to the electron-withdrawing effect. The \( 1H,1H,2H,2H,3H,3H \)-perfluoro-1-undecanol can be used as the alcohol component with commendable yields, however, the conversion to an ether drops significantly for \( 1H,1H,2H,2H \)-perfluoro-1-decanol due to competing dehydration. The three methylene groups in \( 1H,1H,2H,2H,3H,3H \)-perfluoro-1-undecanol provide sufficient insulation, while no ether formation is observed with \( 1H,1H \)-perfluoro-1-octanol. The additional nucleophiles, 3-trifluoromethylphenol and perfluoro-tert-butanol have also been examined. These reactions are carried out by procedure B in benzotrifluoride, which provides acceptable solubility for all reaction components. After removal of the solvent, the fluorophilic ethers are efficiently separated from the reagent-driven organic byproducts by partition in the two-phase solvent system, methanol and perfluorohexanes (FC-72) or perfluoromethylcyclohexane. Thus, the Mitsunobu reaction offers a complementary method to the Williamson synthesis [37] for the preparation of highly fluorophilic ethers [41].

10.3.4 Conclusion
The fluorous Mitsunobu reaction offers convenient procedures for the synthesis and separation of organic or fluorophilic esters. When fluorous DEAD and fluorous phosphines are used, solvent evaporation followed by solid phase extraction over fluorous silica gel affords the products. An alternative workup can probably be achieved by liquid/liquid extraction. The depleted fluorous reagents can be readily recovered by the SPE column, separated by standard flash chromatography, and recycled. DEAD and fluorous phosphines are commercially available.

The use of highly fluorinated carboxylic acids or alcohols as pronucleophiles for the acylation or etherification of alcohols also offers separation advantages (chromatography-free procedures). In addition, organic liquid/fluorous solid separation eliminates the need for fluorous solvents.

Fluorous isolation and/or reagents compliment existing methods for the chromatography-free separation of esters, amides, or ethers from byproducts in the Mitsunobu reaction. These fluorous Mitsunobu reactions and reagents will probably find applications in chemical discovery or natural product synthesis, and are particularly convenient for solution phase parallel synthesis. The ability to recover and regenerate the reagents encourages larger scale applications. It could be anticipated that the combination of existing methods of the preparation of fluorophilic and non-fluorophilic compounds via the Mitsunobu reaction, or other procedures employing fluorous separations, will lead to increased synthetic efficiency.
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References

10.4 Recyclable Oxidation Reagents

David Crich* and Yekui Zou

10.4.1 Introduction

Oxidations are some of the most widespread transformations in chemistry, both in the research laboratory and in industrial scale production: many are also notoriously wasteful and environmentally harmful when the stoichiometric generation of reduced reagents, often transition metal based, is taken into account. It is not surprising therefore that the development of catalytic and/or more environmentally benign oxidation processes has long provided a fertile ground for the imagination of the organic chemist [1]. The fluorous approach to waste management offers several advantages in the design of oxidation systems. Paramount among these are the obvious ease of separation and recyclability but, and perhaps equally important in the long run, is the issue of enhanced catalyst/reagent longevity resulting from minimization of self-oxidation. This chapter focuses on the synthesis and application of recyclable fluorous oxidation reagents, be they stoichiometric or catalytic. It does not include the use of fluorous ligands to support transition metal catalyzed reactions [2] as these are covered elsewhere in this volume. Similarly, the use of trifluoroethanol and
10.4 Recyclable Oxidation Reagents

David Crich* and Yekui Zou

10.4.1 Introduction

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References:

hexafluoroisopropanol as solvents capable of promoting oxidation reactions with hydrogen peroxide is covered elsewhere in this handbook and not here [3].

10.4.2
Organoselenium Based Oxidations

Selenium based reagents have long provided a paradox for organic chemists with their ability to effect mild, functional group tolerant oxidations being offset by their toxicity and, frequently, problems associated with their complete removal from organic products. Selenium dioxide, the archetypical reagent in the field, set the standard in all senses and was consequently one of the earlier oxidants to be successfully targeted for incorporation in a catalytic cycle [2, 4]. The discovery of the selenoxide syn-elimination [5] and the recognition of its potential in synthesis [6–8], followed rapidly by the advent of oxidation processes based on areneselenenic and areneseleninic acids (Se II and Se IV, respectively) [9–11], and peroxo versions of the same [12] firmly established organoselenium reagents as powerful, versatile oxidants for use in organic synthesis. These extremely useful reagents, capable of bringing about a wide variety of oxidative processes, nevertheless continue to suffer from the perceived problem of toxicity and occasionally from purification problems. The introduction of sequences employing catalytic quantities of areneseleninic acids and their anhydrides [9, 13] alleviated this problem somewhat but as catalyst loadings are often relatively high these methods still fall short of the ideal. The purification problem alluded to above arises from the disproportionation of the selenenic acid, the immediate product of the syn-elimination, into the diselenide and the selenenic acid (Scheme 10.4-1) thereby multiplying the number of byproducts for separation. Obviously, the problem can be minimized by working in the presence of excess oxidant, resulting in the conversion of all species into the seleninic acid, but in many instances this is not desirable. Moreover, the high polarity and insolubility of the areneseleninic acids does little to facilitate their recycling.

\[3 \text{ ArSeOH} \rightarrow \text{ArSeSeAr} + \text{ArSeO}_2\text{H} + \text{H}_2\text{O}\]

Scheme 10.4-1. Disproportionation of areneseleninic acid

Polymer-bound diphenylselenoxide and phenylseleninic acid are both known and have been employed in catalytic oxidations but neither have been widely employed [14–17], perhaps because they predate the 1990s explosion [18] in field of supported reagents and their use in combinatorial chemistry. More recently polymer-supported benzeneselenenyl halides, selenocyanates, and selenosulfonates have been reported and successfully applied in a number of typical transformations, including oxidative syn-eliminations. The issue of recyclability of these reagents is, however, rarely addressed and never quantified [19].

Several groups have responded to the challenge of presenting the chemical advantages of organoselenium based oxidants in a more environmentally acceptable format with the design and synthesis of fluorous derivatives.

Diselenides containing a single fluorous chain were prepared as illustrated in Scheme 10.4-2 [20, 21]. These compounds nicely illustrate one of the chief paradoxes in the area of so-called heavy fluorous reagents, namely the compromise between the desire for high fluorne content to ensure preferential solubility in a fluoruous phase and the high molecular
weight that is thereby imparted to the molecule. The bis(perfluorodecylphenyl) diselenide was completely insoluble in all solvents assayed, fluorous and non-fluorous; whereas the perfluorooctyl analog, with its lower melting point and molecular weight, was more soluble. The perfluorohexyl series and were, as expected, the most soluble with the less crystalline m-isomer [22] having the highest solubility of the series [23]. Unfortunately, at only 52% fluorine by weight both and were below the threshold for efficient extraction into an organic phase by simple partitioning. This problem was readily overcome by use of a continuous extractor which was modified by incorporation of a cooling jacket around the extraction chamber to prevent co-solubility of the two phases in the hot apparatus [21]. This device proved to be very effective and enabled efficient extraction of fluorous compounds with as little as 38% fluorine in a matter of hours. The diselenide was converted into the selenenyl chloride quantitatively by exposure to sulfuryl chloride, whereas the corresponding selenenyl bromide was obtained by treatment of the intermediate selenocyanate with bromine (Scheme 10.4-2) [24].

Compounds with two fluorous chains were prepared by an alternative protocol involving nucleophilic aromatic substitution of fluorous aryl bromides by lithium butylselenide (Scheme 10.4-3) [25, 26]. In the case of the symmetric 3,5-disubstituted system it was specifically noted that an approach similar to that of Scheme 10.4-2 for the introduction of selenium via a modified Sandmeyer reaction using selenocyanate as nucleophile did not function [26]. The butylselenides and were subsequently converted into the seleninic acids 9 and 10 in situ by oxidation with hydrogen peroxide. Although neither of these seleninic acids were isolated and characterized, it was reported that, in contrast to the reagents of Scheme 10.4-2, both were readily extracted into fluorous solvents under standard conditions, thereby underlining the influence of the degree of fluorine incorporation.

Trifluoromethylseleninic acid has been prepared but, apparently, not applied as an ox-
dant in organic systems [27, 28]. Similarly, the preparation of a series of perfluoroaryl seleninic acids 12 has been reported but, so far, without application [29]. It is doubtful whether either of these latter compounds contain sufficient fluorine to be considered “fluorous”.

A convenient preparation of a series of perfluoroalkylselenyl halides has recently been reported (Scheme 10.4-4) and it is possible that these compounds will find application as fluorous selenium-based oxidants in the near future [30].

The fluorous selenenyl chloride 5 has been used in the dehydrogenation of ketones to their \( \alpha,\beta \)-unsaturated derivatives in direct analogy to the use of benzeneselenenyl chloride. This chemistry was predicated on the early work of Sharpless with benzeneselenenyl chloride itself [31] and involved stirring the ketone with 5 in THF at room temperature to give the \( \alpha \)-selenenyl ketone, doubtless via an acid catalyzed enolization, followed by addition of hydrogen peroxide, resulting in oxidative syn-elimination and formation of the enone (Scheme 10.4-5). After completion, sodium metabisulfite was added to the reaction mixture to reduce the selenenic and seleninic acid byproducts to the fluorous diselenide 3, which was then recovered for reuse by continuous fluorous extraction. In each of the examples
studied the overall process was high yielding and the diselenide was recovered in very high yield (Table 10.4-1). Esters could be converted into their \( \alpha,\beta \)-unsaturated congeners by treatment of the lithium enolate with the fluorous selenenyl chloride 5 followed by the oxidative syn-elimination, then recovery of the diselenide 3 by metabisulfite reduction and continuous fluorous extraction (Table 10.4-1). Overall, the isolated yields of enones compare favorably with those obtained by analogous non-fluorous processes, especially when the ease and high yield recovery of the organoselenium moiety is taken into account. It should be noted that Barton and coworkers, in their dehydrogenation of ketones to enones with catalytic diphenyl

**Scheme 10.4-5.** Dehydrogenation of carbonyl compounds with a fluorous selenenyl chloride

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product (% yield)</th>
<th>% Yield</th>
<th>% Recovered 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="substrate1" /></td>
<td><img src="image2" alt="product1" /></td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td><img src="image3" alt="substrate2" /></td>
<td><img src="image4" alt="product2" /></td>
<td>81</td>
<td>92</td>
</tr>
<tr>
<td><img src="image5" alt="substrate3" /></td>
<td><img src="image6" alt="product3" /></td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td><img src="image7" alt="substrate4" /></td>
<td><img src="image8" alt="product4" /></td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td><img src="image9" alt="substrate5" /></td>
<td><img src="image10" alt="product5" /></td>
<td>86</td>
<td>95</td>
</tr>
</tbody>
</table>
diselenide and \textit{m}-iodoxybenzoic acid as oxidant, reported a recovery of diphenyl diselenide with yields as high as 95% following treatment with sodium dithionite \cite{13}. However, that process required multiple extractions between aqueous and organic phases and was not as convenient as the single extraction set out in Scheme 10.4-5.

Following on from the work of Hori and Sharpless \cite{9}, and Grieco et al. \cite{12} with catalytic benzeneseleninic acid and hydrogen peroxide, Knochel and coworkers have employed the fluorous butylselenide \textit{7} as a precursor to an active catalyst in the epoxidation of alkenes (Scheme 10.4-6) \cite{25}. In this system the selenide first undergoes oxidation to the selenoxide followed by \textit{syn}-elimination to the selenenic acid. Further oxidation gives the seleninic acid \textit{9} and, possibly, the perseleninic acid. These species, which were not characterized, catalyze the epoxidations which were conducted at 70 °C in a biphasic mixture of benzene and perfluoroocetyl bromide. It was noted that the use of 60% hydrogen peroxide was critical for the success of the operation as the more dilute 30% solutions caused the formation of emulsions. After completion the fluorous phase, containing either the seleninic acid or the perseleninic acid, was separated off for reuse whereas the epoxide was obtained from the organic phase in the usual manner. Control experiments indicated that <0.1% of the catalyst was lost to the organic phase and that the recycled fluorous solution of catalyst could be employed for at least ten cycles with no loss of activity, indicating excellent catalyst stability. The examples in Table 10.4-2 show that the process is high yielding and tolerant of esters and the more robust silyl ethers. The yields are generally somewhat superior to those conducted with benzeneseleninic acid itself \cite{12}, and approach those obtained, albeit for a limited range of examples, by catalysis with 2-nitro- and 2,4-dinitrobenzeneseleninic acid \cite{9} and other electron deficient benzeneseleninic acids \cite{32}. In two cases (Table 10.4-2) the isolated product was the \textit{trans}-diol resulting from opening of an intermediate epoxide and this is reminiscent of the results observed on attempted epoxidation with catalytic amounts of the polymer-supported seleninic acid and hydrogen peroxide when it was typically the major pathway \cite{16}.

Sheldon and coworkers have employed the regioisomeric butylselenide \textit{8} as a catalyst precursor in the hydrogen peroxide mediated oxidation of aldehydes and ketones \cite{26}. As with the Knochel epoxidation sequence the true catalyst, the perseleninic acid, is generated \textit{in situ} from \textit{8} by oxidation, \textit{syn}-elimination, and further oxidation. In a biphasic system comprised of the perfluorohexane and trifluoroethanol, cyclobutanone underwent Baeyer-Villiger oxidation to \textit{\gamma}-butyrolactone with 1 mol% of \textit{8} in excellent yield in 2 h at room temperature (Scheme 10.4-7). It was noted, however, that under these conditions the persele-
ninic acid formed on oxidation of 8 provoked the formation of emulsions. Oxidations could be conducted in a monophasic system using hexafluoroisopropanol, which satisfactorily dissolved the catalyst and hydrogen peroxide, but the optimum system was a triphasic one comprised of perfluorodecalin, 1,2-dichloroethane and 60% hydrogen peroxide (Table 10.4-3).

The perseleninic acid derived from 8 was found to have a partition coefficient of >100

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H15</td>
<td>C6H15</td>
<td>92</td>
</tr>
<tr>
<td>C4H9</td>
<td>C4H9</td>
<td>93</td>
</tr>
<tr>
<td>O</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>C9H19</td>
<td>C9H19</td>
<td>93</td>
</tr>
<tr>
<td>OSi(i-Pr3)3</td>
<td>OSi(i-Pr3)3</td>
<td>97 (1:1 isomeric mixture)</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>(1:1 isomeric mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>68</td>
</tr>
</tbody>
</table>

Scheme 10.4-7. Catalysis of a Baeyer-Villiger reaction by a fluorous selenium reagent

Table 10.4-2. Epoxidation with hydrogen peroxide catalyzed by 7

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H15</td>
<td>C6H15</td>
<td>92</td>
</tr>
<tr>
<td>C4H9</td>
<td>C4H9</td>
<td>93</td>
</tr>
<tr>
<td>OSi(i-Pr3)3</td>
<td>OSi(i-Pr3)3</td>
<td>97 (1:1 isomeric mixture)</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>(1:1 isomeric mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>68</td>
</tr>
<tr>
<td>(4:1 isomeric mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>63</td>
</tr>
<tr>
<td>OAc</td>
<td>OAc</td>
<td>68</td>
</tr>
</tbody>
</table>
between perfluorohexanes and 1,2-dichloroethane at room temperature thereby ensuring its facile recovery. Unlike the case of the above epoxidation system of Knochel, however, there was a gradual diminution in yield with extended recycling of the catalyst solution (Table 10.4-4) and it was suggested that this might be the result of mechanical losses or catalyst decomposition.

The oxidations reported in Scheme 10.4-6 and in Table 10.4-3 closely parallel those obtained with typical electron deficient areneseleninic acids and hydrogen peroxide [33–36], and with polystyrene-bound benzeneseleninic acid and hydrogen peroxide [16], over which they nevertheless possess the obvious advantage of facile catalyst separation.

**Tab. 10.4-3.** Oxidation of carbonyl compounds with hydrogen peroxide catalyzed by 2 mol% of 8

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂N—CHO</td>
<td>O₂N—CO₂H</td>
<td>90</td>
</tr>
<tr>
<td>F₃C—CHO</td>
<td>F₃C—CO₂H</td>
<td>90</td>
</tr>
<tr>
<td>CHO</td>
<td>CO₂H</td>
<td>75</td>
</tr>
<tr>
<td>CH₃—CHO</td>
<td>CH₃—CO₂H</td>
<td>80</td>
</tr>
<tr>
<td>MeO—CHO</td>
<td>MeO—OH</td>
<td>70</td>
</tr>
<tr>
<td>MeO—CH₂—CHO</td>
<td>MeO—CH₂—CO₂H</td>
<td>75</td>
</tr>
<tr>
<td>MeO—CH₂—CHO</td>
<td>MeO—CH₂—OH</td>
<td>80</td>
</tr>
<tr>
<td>C₆H₄—O</td>
<td>C₆H₄—CO₂H</td>
<td>80</td>
</tr>
</tbody>
</table>

**Tab. 10.4-4.** Diminishing yields in the oxidation of p-nitrobenzaldehyde to p-nitrobenzoic acid with recycled catalyst

<table>
<thead>
<tr>
<th>Cycle</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>
10.4.3 Organosulfur-Based Oxidations

The oxidation of aldehydes and ketones based on the activated dimethyl sulfoxide and dimethyl sulfide are extremely well known and in very widespread use in organic research laboratories. The popularity of these methods stems from a combination of the mildness of the reaction conditions, the ready availability of the reagents, the exceptional functional group compatibility, and the metal-free nature of the oxidations [37–39]. Nevertheless, a considerable disadvantage of these methods, which portends against their use on an industrial scale, is the release of stoichiometric quantities of volatile, malodorous dimethyl sulfide. The problem has been addressed by the use of extractable non-volatile (13) and both insoluble (14) and soluble (15) polymer-supported and sulfoxides [40, 41].

\[ \text{Scheme 10.4-8. Synthesis of fluorous sulfides and sulfoxides for oxidation reactions} \]

Two sulfides, odor-free 16 and 17, were prepared by the protocol of Scheme 10.4-8, and then converted into the corresponding, equally odor-free sulfoxides 18 and 19 by oxidation with hydrogen peroxide in methanol [45]. No over-oxidation to the sulfones was observed in this process, it having been previously determined that more forceful conditions are required for the exhaustive oxidation of such perfluoroalkylethyl sulfides [46]. Evidently, the ability to oxidize the sulfides to the sulfoxides with cheap, clean hydrogen peroxide without concerns of over-oxidation both in the initial preparation and in subsequent recycling reactions represents a considerable advantage of the method. The more highly fluorous sulfoxide 19 was found to be insufficiently soluble in dichloromethane at low temperatures, which prevented its use in the Swern type oxidations, but the lower homolog 18 proved ideal.
for the purpose. A number of Swern oxidations were conducted using 3 equiv of 18. After the oxidation, the excess of 18 and the reduced sulfide byproduct 16 were recovered by a process which included aqueous washing then replacement of the dichloromethane by toluene and brief continuous extraction. The organic product was then obtained from the toluene layer in the usual manner whereas the fluorous layer afforded a mixture of 16 and 18, which was simply reoxidized with hydrogen peroxide to afford pure recovered 18 (Scheme 10.4-9). The somewhat polar 18 did not partition efficiently between dichloromethane and perfluorohexanes but did so between the less polar toluene and perfluorohexanes, hence the switch in organic solvents prior to the fluorous extraction. As is seen from Table 10.4-5, a number of oxidations were conducted in the presence of a wide variety of functional groups, thereby demonstrating the broad generality of the method. In each case (Table 10.4-5) the sulfoxide 18 was recovered for reuse in high yield.

When deuteriosoborneol was subjected to the fluorous Swern reaction with sulfoxide 19, and the oxidative recycling step omitted from the workup, it was possible to isolate the fluorous sulfide 17 by silica gel chromatography. A combination of $^1$H- and $^2$H-NMR spectroscopy revealed that deuterium had been incorporated into the S-methylene group of 16, indicating that the oxidation falls into the category of true Swern oxidations and proceeds via a sulfur ylid with subsequent intramolecular hydrogen transfer (Scheme 10.4-10) [47, 48]. The strongly electron-withdrawing nature of the fluorous chain and its effect on acidity of neighboring C–H bonds accounts for the highly regioselective deprotonation, from the S-methylene rather than the S-methyl group.

The application of fluorous sulfides in the Corey-Kim reaction [49] was also investigated [43] with the aid of the fluorous sulfide 17 (Scheme 10.4-11, Table 10.4-6). As the sulfide is
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
<th>% Recovered 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{OH} )</td>
<td>( \text{O} )</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>( \text{N} )</td>
<td>( \text{Tsoc} )</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>( \text{Br} )</td>
<td>( \text{OTBDMS} )</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>( \text{NO}_2 )</td>
<td>( \text{OH} )</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>( \text{HO} )</td>
<td>( \text{N} )</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>( \text{OH} )</td>
<td>( \text{O} )</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>( \text{O} )</td>
<td>( \text{H} )</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>( \text{HO} )</td>
<td>( \text{BnO} )</td>
<td>81</td>
<td>86</td>
</tr>
<tr>
<td>( \text{OH} )</td>
<td>( \text{DAM} )</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>( \text{MeO} )</td>
<td>( \text{MeO} )</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>( \text{BnO} )</td>
<td>( \text{BnO} )</td>
<td>79</td>
<td>85</td>
</tr>
</tbody>
</table>

Tab. 10.4-5. Fluorous Swern oxidations with sulfoxide \( \text{18} \) (DAM = dianisylmethyl)
Scheme 10.4-10. Mechanism of the fluorous Swern reaction

Scheme 10.4-11. The fluorous Corey-Kim protocol

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
<th>% Recovered 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>OH</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>NO₂</td>
<td>NO₂</td>
<td>86</td>
<td>73</td>
</tr>
<tr>
<td>HO</td>
<td>HO</td>
<td>78</td>
<td>73</td>
</tr>
<tr>
<td>OH</td>
<td>OH</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>OH</td>
<td>OH</td>
<td>88</td>
<td>75</td>
</tr>
</tbody>
</table>
the reagent in this oxidation no oxidative step was necessary in the workup, however, it is important to note that in order to obtain high recoveries of fluorous sulfide it was necessary to work with as near stoichiometric sulfide as possible. This results from the oxidation of any excess sulfide by the excess NCS thereby preventing its recovery, at least in the form of the sulfide.

Overall, fluorous versions of the Swern and Corey-Kim reactions closely parallel those conducted with the more familiar dimethyl sulfoxide and dimethyl methyl sulfide in terms of practicality, yield and functional group tolerance. They offer the obvious advantage of recovery of the fluorous reagents and elimination of obnoxious sulfur-based odors.

10.4.4

Fluorous Ketone-Mediated Oxidations

Dimethyl dioxirane is a powerful reagent, generated from acetone and Oxone, for the transformation of alkenes into epoxides and for a variety of other oxidations [50–53]. A more active version is trifluoromethyl methyl dioxirane (21), derived from trifluoromethylacetone (20), and this reagent has been widely applied in epoxidation and other oxidation sequences whether preformed or generated in situ [50–59]. Hexafluoroacetone (22) is converted into 2-hydroperoxyhexafluoro-2-propanol (23) with concentrated hydrogen peroxide and this reagent has also been shown to effect epoxidation of alkenes under stoichiometric and catalytic conditions [60–62]. Recycling these trifluoromethyl based dioxiranes is, however, impractical owing to a combination of their low molecular weight and high volatility with their instability [52, 53, 63, 64]. The problem of instability has been addressed by the preparation of the silica gel-supported reagent 24 [65]. This substance was reported to be an efficient catalyst for the epoxidation of alkenes with Oxone, with activity comparable to the freely diffusing analog 25. Unlike 25 however, which was 85% decomposed after a single run, 24 was found to retain most of its activity for up to ten cycles. The difference in stability between 24 and 25 was attributed to the isolation of molecules on the support preventing decomposition.

\[
\begin{align*}
20 & : \text{MW: 66, } \%F: 51 \\
21 & : \text{MW: 88, } \%F: 44 \\
22 & : \text{MW: 150, } \%F: 68 \\
23 & : \text{MW: 180, } \%F: 57 \\
24 & : \text{MW: 648, } \%F: 73 \\
25 & : \text{MW: 524, } \%F: 73 \\
26 & : \text{MW: 264, } \%F: 58 \\
27 & : \text{MW: 866, } \%F: 75, \text{mp 110 °C} \\
28 & : \text{MW: 412, } \%F: 69, \text{oil} \\
29 & : \text{MW: 516, } \%F: 73, \text{mp 38 °C}
\end{align*}
\]
via 1,2,4,5-tetroxane formation and to the suppression of Baeyer-Villiger decomposition pathways by the support. Ketone 24 was readily recycled by simple filtration but it was noted that there was an unquantified loss in each cycle owing to the partial solubility in the reaction medium [65].

Fluorous solutions to the problem have been reported. Thus, the epoxidation of cyclooctene with anhydrous hydrogen peroxide in ethyl acetate with catalytic quantities of 22, 26 and 27 was investigated by Sheldon and coworkers. These investigators reported an initial rate with 27 some four times that with 22, whereas oxidation with 26 proceeded at half the initial rate of that with 22 [66]. In subsequent studies, 5 mol% of perfluoroheptadecan-9-one (27), presumably converted into the peroxyhydrate in situ, was demonstrated to bring about effective epoxidation of a range of alcohols in conjunction with anhydrous hydrogen peroxide in a 10:1 mixture of 1,2-dichloroethane and ethyl acetate at reflux (Scheme 10.4-12). All but the most acid sensitive substrates were successfully epoxidized in high yield under these conditions. Success was obtained in the cases of x-pinene and camphene by buffering the reaction mixture with a small amount of base (Table 10.4-7). The choice of a mixed solvent resulted from the insufficient solubility of 27 in halogenated solvents alone. The low solubility of 27 presented a considerable advantage in so far as on cooling the reaction mixtures, it crystallized from solution thereby permitting recycling by simple filtration: 80–92% of the catalyst could be recovered in this manner and this was shown to have no loss of activity in subsequent experiments. The identical transformations could be conducted with 27 and 60% hydrogen peroxide in trifluoroethanol at reflux (Scheme 10.4-12, Table 10.4-7). Ketone 27 could also be recovered by crystallization from these reaction mixtures although not as efficiently as from dichloroethane owing to its higher solubility in trifluoroethanol.

Crousse, Delpon, and coworkers investigated fluorous ketones 28 and 29 as catalysts for the epoxidation of dodecene and cyclooctene with Oxone as the stoichiometric oxidant in both acetonitrile/water and hexafluoropropionic acid/water mixtures, invoking the corresponding dioxiranes as the reactive intermediates [67, 68]. Ketones 28 and 29 both catalyzed epoxidation under these conditions, but unfortunately the most reactive of the pair (28) was found to be subject to Baeyer-Villiger oxidation and could not be recycled. A compromise was reached with the trifluoromethyl perfluoroethylketone 30, readily prepared as shown in Scheme 10.4-13. In these compounds the ethylene spacer group attenuates the electron withdrawing effect of the second perfluoroalkyl group, thereby permitting greater reactivity in epoxidation, yet the proximity of this second perfluoroalkyl group is sufficient to prevent Baeyer-Villiger oxidation of the ketone group.

This ketone (30) effectively promotes epoxidation of alkenes by Oxone in hexafluoropropionic acid/water mixtures, buffered by sodium bicarbonate, at 25 ºC (Scheme 10.4-14, Table 10.4-8). Two higher homologs, 31 and 32 were also prepared and investigated with 31 being
less active than 30 and 32 completely inactive under the standard conditions. Unfortunately, the recovery of ketone 30 from these reaction mixtures by fluorous extraction or by fluorous chromatography was not efficient (<50%), even if GC analysis of the crude reaction mixtures indicated no decomposition [67, 68].

The use of ketone 30 in hydrogen peroxide mediated epoxidations, analogous to those of Scheme 10.4-12 (Table 10.4-7) was also assayed. Thus, cyclooctene underwent 50% con-

\[
\begin{array}{cccc}
\text{Substrate} & \text{Product} & \% \text{Yield in } C_{2}H_{4}Cl_{2}/EtOAc & \% \text{Yield in } CF_{3}CH_{2}OH \\
\hline
\text{O} & \text{O} & 100 & 100 \\
\text{O} & \text{O} & 92 & 89 \\
C_{8}H_{17} & C_{8}H_{17} & 96 & 63^a \\
\text{b} & \text{b} & 72 & \\
\text{b} & \text{b} & 55^a & - \\
\text{b} & \text{b} & 49^a & - \\
\hline
\end{array}
\]

\[^a\text{reactions conducted in the presence of 5 mol\% Na}_{2}HPO_{4}\]
\[^b\text{stereochemistry undefined}\]

Scheme 10.4-13. Synthesis of an optimized fluorous ketone for epoxidation with Oxone

\[
\text{C}_{8}\text{F}_{13}\text{I} \xrightarrow{i) \text{t-BuLi}, -78 ^\circ\text{C}} \xrightarrow{\text{ii)} R_{1} \text{CO}_{2}\text{Et}, -78 ^\circ\text{C}} \text{R}_{1}\text{R}_{2} \text{O}
\]

30: \(R_{1} = \text{CF}_{3}\), MW: 444; %F: 68, oil
31: \(R_{1} = \text{C}_{3}\text{F}_{7}\), MW: 544; %F: 70, oil
32: \(R_{1} = \text{C}_{7}\text{F}_{15}\), MW: 744; %F: 71, Mp 54 ^\circ\text{C}

Scheme 10.4-14. Fluorous ketone catalysis of epoxidation with Oxone
version into the epoxide in acetonitrile with 10 mol% of 30, while 100% conversion was achieved with only 1 mol% of 30 in 1:1 hexafluoroisopropanol/acetonitrile. Unfortunately, even with 10 mol% of 30 the less reactive dodecene only furnished a 20% yield of the epoxide even in the mixed solvent, suggesting that 30 is a much less effective catalyst under the hydrogen peroxide conditions.

Overall, it is clear that the combination of 27 and hydrogen peroxide in hot dichloroethane/ethyl acetate, passing via the peroxyhydrate, is a superior system for the epoxidation of alkenes than the combination of 30 and Oxone, invoking an intermediate dioxirane. The reasons for this superiority are simple and center on the use of the less expensive oxidant, hydrogen peroxide, and the very facile, highly efficient recovery of the catalyst by simple cooling and filtration. The use of hydrogen peroxide rather than Oxone also gives 27 the edge over the silica supported ketone 24 even if the recovery conditions are very similar.

10.4.5 Fluorous Sensitizers for Singlet Oxygenation

Porphyrrins are often employed as sensitizers in the singlet oxygenation of alkenes. Yet they are far from ideal, being themselves subject to competitive degradation by the singlet oxygen they serve to generate. A solution to this problem has been provided in the form of the tetrakis[heptafluoropropyl]porphyrin 33 [69], whose synthesis was described earlier [70]. In a biphasic mixture of perfluorohexane and deuterioacetonitrile this sensitizer enables the photo-initiated singlet oxygenation of cyclohexene in excellent yield with only minimal self-degradation (Scheme 10.4-15). In a preparative scale oxygenation, 2Z-dec-ene-4-ol, a substrate whose tetraphenylporphyrin-sensitized singlet oxygenation was reported to be both difficult
and accompanied by considerable degradation of the sensitizer, was converted into 3-hydroperoxy-1-decene-4-ol in 59% yield in a perfluorohexane/acetonitrile system; analysis of the fluorous layer revealed 57% residual sensitizer after 10 days irradiation.

A related porphyrin to 33 is the chloroperfluoropolyether modified system 34 which, interestingly, is highly soluble in scCO₂ [71]. A series of porphyrins bearing fluorous chains on the pyrrole rings (35) has also been synthesized [72]. However, neither the solubility of these substances in fluorous solvents nor their ability to act as sensitizer have yet been described.

The known propensity of C₆₀ to act as a powerful sensitizer for singlet oxygenation [73–75], coupled with the use of 33 in singlet oxygenations prompted the development of a C₆₀ derivative (36) bearing a fluorous chain. This substance was found to effect singlet oxygenation of alkenes very rapidly with catalyst loadings as low as 0.05 mol%, especially when the reactions were conducted in hexafluorobenzene (Table 10.4-9) as opposed to toluene [76]. A particularly noteworthy example is that of the oxygenation of the difficult case of 2-decene-4-ol when a yield of 91% was obtained, albeit after 24 h irradiation. The use of C₆₀ in this last oxygenation, or that of 36 in toluene, resulted in very much diminished yields, pointing to the importance of the combination of 36 with the employment of hexafluorobenzene as the solvent. A more highly fluorous C₆₀ derivative was subsequently prepared and used to sensitize the formation of singlet oxygen in perfluorohexane [77]. Although no actual oxidations were performed with this latter reagent it was used to establish that the lifetime of singlet oxygen in perfluorohexane was 7 ms, some two orders of magnitude greater than in benzene or toluene [77, 78].

For comparison, a soluble poly(ethylene glycol)supported tetraphenylporphyrin (37) has been synthesized and shown to be effective in photooxygenation reactions [79]. Moreover the catalyst was readily recovered from solution by precipitation with ether and the recycled substance was reported to be as active as the virgin material: quite how 35 is protected from reaction with singlet oxygen is unclear.

Thus, it appears that the appendage of fluorous chains to both porphyrins and C₆₀ leads to superior sensitizers for the generation of singlet oxygen, resulting in both more efficient and less readily oxidized catalysts, especially when employed in perfluoroalkane or perfluoroarene solvents. A caveat arises though in light of the work of Chambers, who showed

![Scheme 10.4-15. Allylic oxygenation sensitized by a fluorous porphyrin](image)
Tab. 10.4-9. Singlet oxygenations sensitized by 36 hexafluorobenzene

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Mo% 36</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.05</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>94 (87:13 mixture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5</td>
<td>91</td>
</tr>
</tbody>
</table>
that simple tetraphenylporphyrin-sensitized singlet oxygen reactions can be carried out very effectively when a catalytic quantity of the porphyrin is suspended in either perfluorohexanes or perfluorooctanes [80]. These latter reactions owe their success to the high solubility of oxygen in the fluorous hydrocarbons and to the extended lifetime of singlet oxygen in fluorous hydrocarbons [77, 78], and perhaps also to the insoluble nature of the sensitizer, which should limit its oxidation by singlet oxygen. This prompts the question as to the true importance of 33 and 36 in the above sequences when compared with the increased solubility of oxygen in the fluorous media employed. It also has to be noted that in none of the above cases, with the exception of the polymer-supported system 37, was actual catalyst recovery described leading one to wonder if the best solution might simply be the use of inexpensive tetraphenylporphyrin in a perfluorohydrocarbon as reported by Chambers [80].

Acknowledgments

We thank the NSF (CHE 9986200) for support of the work in our laboratory on fluorous, recyclable oxidants.

References

In addition to the oxidations covered here the diselenide 3 has been employed as a recyclable catalyst in a number of reductive processes: [20, 21], D. Crich, S. Neelamkavil, F. Sartillo-Piscil, Org. Lett. 2002, 4, 4175–4177.

The intermediate fluorous sulfides have also enjoyed use as ligands for borane when they have the added advantage of also suppressing flammability: D. Crich, S. Neelamkavil, Org. Lett. 2000, 2, 4029–4031.


Fluorous Protecting Groups and Tags

Wei Zhang

10.5 Introduction

Protecting group chemistry is an important sub-discipline of organic synthesis [1]. In traditional solution-phase synthesis, as the structure complexity increases, the control of diverse reactivity can be achieved by the introduction of protecting groups to block undesired reaction sites and allow chemical transformations to take place elsewhere within a molecule. In solid-phase synthesis, however, protecting groups usually serve as a linker to anchor substrates onto the solid support [2]. Linkers for solid-phase synthesis have bifunctional moieties; one of the functionalities is permanently bound to a solid support while the other one is temporarily attached to a starting material so that it can be cleaved to release the product from the support at the end of the synthesis. A spacer between the linker and the support is also used to give attached-substrates more mobility and better reaction kinetics. Linkers and...
10.5 Fluorous Protecting Groups and Tags

Wei Zhang

10.5.1 Introduction

Protecting group chemistry is an important sub-discipline of organic synthesis [1]. In traditional solution-phase synthesis, as the structure complexity increases, the control of diverse reactivity can be achieved by the introduction of protecting groups to block undesired reaction sites and allow chemical transformations to take place elsewhere within a molecule. In solid-phase synthesis, however, protecting groups usually serve as a linker to anchor substrates onto the solid support [2]. Linkers for solid-phase synthesis have bifunctional moieties; one of the functionalities is permanently bound to a solid support while the other one is temporarily attached to a starting material so that it can be cleaved to release the product from the support at the end of the synthesis. A spacer between the linker and the support is also used to give attached-substrates more mobility and better reaction kinetics. Linkers and...
their associated techniques play a key role in the solid-phase combinatorial chemistry (Scheme 10.5-1).

The recent development of fluorous synthesis has provided a solution-phase alternative to solid-phase synthesis [3]. Functionalized perfluoroalkyl groups (R_f), instead of polymer supports (PS), are employed as the “phase tag” to facilitate the separation process. Compared with solid-phase synthesis, fluorous synthesis has some unique features: (1) good solubility of fluorous compound in many organic solvents; (2) favorable solution-phase reaction kinetics; (3) easy intermediate analysis and purification by conventional tools such as NMR, MS, and HPLC, (4) easy adaptation of literature reaction conditions; and (5) flexibility of reaction scale and scope. As an important part of fluorous synthesis, fluorous protecting groups and related tags have been developed and applied in numerous solution-phase syntheses. Similar to their polymer-supported counterparts, the fluorous protecting groups are attached to a perfluoroalkyl chain through a spacer (Scheme 10.5-1). The spacer in fluorous protecting groups is used to separate the functional group from the strong electron-withdrawing R_f group to minimize its effect in the reactivity of the functional group. Each fluorous protecting group has a definite molecular weight, while polymer-supported protecting groups are usually expressed by resin loading (mmol g\(^{-1}\)) in a certain range. With the use of fluorous protecting groups, chemists can have accurate control of stoichiometry and do not have to worry about the swelling properties associated with the resin. Scheme 10.5-1 shows the structures of a normal \(p\)-methoxybenzyl (PMB) group along with its polymer-supported (PS-PMB) and fluorous (F-PMB) versions.

Fluorous protecting groups can be classified into two categories based on their fluorine content and associated separation methods. The “heavy” fluorous protecting groups usually contain greater than 60% of fluorine by molecular weight. The “light” ones contain less than 40% of fluorine. Reactions involving “heavy” fluorous protecting groups usually require a certain amount of fluorous solvent for the reactions, and product purifications are conducted by liquid extraction in an organic/fluorous biphasic system or an aqueous/organic/fluorous triphasic system. With “light” fluorous protection groups, reactions can be performed without fluorous solvent and the separations are accomplished by fluorous silica gel-based solid-phase extraction (FSPE) or fluorous HPLC (FHPLC). FSPE can efficiently separate fluorous molecules from non-fluorous molecules, while FHPLC can separate a mixture of fluorous compounds based on their fluorine content (see Chapter 8). This chapter reviews the progress on fluorous protecting group chemistry. Its application in solution-phase parallel and mixture syntheses for small molecules, peptides, and oligosaccharides will be discussed.
<table>
<thead>
<tr>
<th>Protecting group</th>
<th>Structure</th>
<th>Functional group protected</th>
<th>Conditions for protection</th>
<th>Conditions for de-protection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-Benzyl (F-Bn)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Alcohols</td>
<td>NaH, TBAI</td>
<td>H₂/Pd(OH)₂</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DMF, BTF</td>
<td>FC-72</td>
<td></td>
</tr>
<tr>
<td>F-Silyl</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Alcohols</td>
<td>NEt₃, DMAP</td>
<td>TBAF, THF</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CH₂CH₂, rt</td>
<td>3 h, rt</td>
<td></td>
</tr>
<tr>
<td>F-Alkoxo ethyl</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Alcohols</td>
<td>cat. CSA</td>
<td>CSA</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Et₂O, rt or</td>
<td>Et₂O, MeOH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF, 65 °C</td>
<td>3 h, rt</td>
<td></td>
</tr>
<tr>
<td>F-Carbobenzyloxy</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Amines</td>
<td>DIEPA or</td>
<td>NEt₃, DMF</td>
<td>7a</td>
</tr>
<tr>
<td>(F-Cbz)</td>
<td></td>
<td></td>
<td>NEt₃,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-t-Butoxy</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Carboxylic acids</td>
<td>DCC, DMAP</td>
<td>TFA</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CH₂CH₂, rt</td>
<td>15 h, rt</td>
<td></td>
</tr>
</tbody>
</table>
F-p-Methoxybenzyl (F-PMB)

F-Trialkoxybenzhydryl (F-Rink-type)

F-Carbonyl (Bpf)

*Hfb is a fluorous support containing six C<sub>8</sub>F<sub>17</sub> groups.
10.5.2

“Heavy” Fluorous Protecting Groups

“Heavy” fluorous protecting groups usually contain two, three or even more $R_f$ chains. “Heavy” fluorous protection agents have been reported in the literature including F-benzyl bromide [4], F-alkyloxysilylchloride [5], F-vinyl ether [6], F-carbobenzyloxy chloride (F-CbzCl) [7], F-t-butyl alcohol [8], F-p-methoxybenzyl (F-PMB or F-Wang-type) bromide [9], F-trialkoxybenzhydryl Fmoc amine (F-Rink-type) [9], F-carboxylic acid [10]. Their structures, utilities, and general conditions for protection and deprotection are summarized in Table 10.5-1.

The Curran group reported the synthesis of fluorous benzyl bromide 1 [4]. It was prepared by the reaction of $p$-tolyl magnesium bromide with readily available tris(perfluorohexylethyl)silyl bromide 10 followed by bromination of the intermediate 11 (Scheme 10.5-2). The utility of F-BnBr as an alcohol protecting agent was demonstrated in the synthesis of disaccharide 12 (Scheme 10.5-3). The hydroxyl group of D-glucal 13 was protected with 4 equiv of F-BnBr using NaH as a base and BTF as the solvent. The crude tribenzyl glucal derivative 14 was purified by triphasic ($H_2O/CH_2CH_2/FC-72$) extraction to remove organic and inorganic materials followed by flash silica gel chromatography to remove the excess benzylating agent and other impurities. The fluorous glucal 14 was then coupled with excess diacetone galactose 15 under standard reaction conditions in BTF to give pure fluorous disaccharide 16 after triphasic extraction. The fluorous compound 16 was debenzylated by catalytic hydrogenation with $H_2$ and Pd(OH)$_2$ in FC-72. After another triphasic extraction,
the product 17 in the organic phase was acylated to give disaccharide 12. The deprotected F-Bn can be recovered from the FC-72 layer as 11.

F-alkyloxyisilylchloride 2 and F-vinyl ether 3 were both developed by the Wipf group for alcohol and amine protections [5, 6]. F-CbzCl 4 was developed by Bannwarth and coworkers, who have applied it in fluorous biphasic synthesis of quinazoline-2,4-diones (Scheme 10.5-4) [7a]. Amidation of fluorous protected anthranlic acid 19 followed by cyclative deprotection of 20 led to the formation of quinazoline-2,4-dione 21. This chemistry has been modified by absorption of the fluorous chains onto the fluorous silica gel via strong fluorine–fluorine interactions to eliminate the use of fluorous solvents for the reaction and separations [7b].

Cobas and coworkers prepared several F-t-butyl alcohols bearing one or two R_f chains [8]. Only those with two R_f chains such as 5 were found to have a strong affinity for fluorous liquid extraction. The Inazu group recently reported the preparation of F-t-butyl alcohol 6, which is attached to a much bigger fluorous tag Hfb that contains six C_8F_{17} chains [9]. The same fluorous support Hfb was used in the preparation of F-PMB 7 and F-trialkoxybenzhydryl-type protecting group 8 [9]. Inazu and coworkers developed Bfp tagged-fluorous carboxylic acid 9 [10]. Application of Hfb and Bfp tagged protection agents in peptide and oligosaccharide synthesis will be discussed in Section 10.5.6.

10.5.3 “Light” Fluorous Protecting Groups

The disadvantage of being costly and environmentally persistent when using “heavy” tags and fluorous solvents has been addressed by using “light” fluorous tags which not only gave “heavy” fluorous pony tails a big hair cut but also eliminated the use of a fluorous solvent at both the reaction and separation steps (see Chapter 8). Improved solubility and hence the reactivity of “light” fluorous-tagged molecules in organic solvents is a bonus. The combination of “light” fluorous tags with FSPE and FHPLC has become a trend in the development of new fluorous synthesis [11]. “Light” fluorous protecting agents listed in Table 10.5.2 include F-tetrahydropyranyl (F-THP) iodide and its sulfide analog [12], F-silylbromide [5], F-silane [13], F-PMB bromide [14], F-t-butyl alcohol [8], F-primary alcohol [15], F-BocOSu [16], F-CbzCl [17], and F-CbzOSu [18].

Wipf and coworkers reported the synthesis of two types of F-THP protection groups, 22 and 23, both containing a single C_8F_{17} chain [12]. These two compounds were used to protect alcohols and the purification was carried out by SPE over fluorous silica gel. The Wipf group also prepared the single R_f chain silylbromide 24 [5]. The purification of protected substrates was done by liquid/liquid extraction with FC-72/CH_3CN. An alternative F-silyl
## Tab. 10.5-2. “Light” fluorous protecting groups

<table>
<thead>
<tr>
<th>Protecting group</th>
<th>Structure</th>
<th>Functional group protected</th>
<th>Conditions for Protection</th>
<th>Deprotection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
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<td>F-THP</td>
<td><img src="image1" alt="Structure" /></td>
<td>Alcohols</td>
<td>C₅₂ZrCl₂, AgClO₄, CH₂Cl₂, 4 Å MS</td>
<td>TsOH, MeOH, THF, 70 °C</td>
<td>12</td>
</tr>
<tr>
<td>F-Silyl</td>
<td><img src="image2" alt="Structure" /></td>
<td>Alcohols</td>
<td>NEt₃, DMAP, CH₂CH₂, rt</td>
<td>TBAF, THF</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Structure" /></td>
<td>Alcohols</td>
<td>TiOH, 2,6-lutidine, CH₂Cl₂</td>
<td>HF-Py, THF</td>
<td>13</td>
</tr>
<tr>
<td>F-t-Butyloxy</td>
<td><img src="image4" alt="Structure" /></td>
<td>Carboxylic acids</td>
<td>DCC, DMAP, CH₂CH₂, rt</td>
<td>TFA</td>
<td>8</td>
</tr>
<tr>
<td>F-Alkoxo</td>
<td><img src="image5" alt="Structure" /></td>
<td>Carboxylic acids</td>
<td>DIC, HOBT, DMAP, DMF</td>
<td>cyclative deprotection</td>
<td>15</td>
</tr>
<tr>
<td>F-PMB</td>
<td><img src="image6" alt="Structure" /></td>
<td>Alcohols</td>
<td>t-BuOK, THF</td>
<td>DDQ</td>
<td>14</td>
</tr>
<tr>
<td>Protecting Group</td>
<td>Structure</td>
<td>Conditions</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>------------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-Boc</td>
<td><img src="image" alt="F-Boc Structure" /></td>
<td>Amines, THF, TFA, CH$_2$Cl$_2$</td>
<td>16</td>
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</tr>
<tr>
<td>F-Cbz</td>
<td><img src="image" alt="F-Cbz Structure" /></td>
<td>Amines, DIPEA, TFA, H$_2$O (98/2)</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="F-Cbz Structure" /></td>
<td>Amines, NEt$_3$, THF/H$_2$O, H$_2$, Pd-C, MeOH</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Homologs with different R$_f$ groups are also prepared.*
group 25 and its homologs with a different fluorine content \([R_f = C_3F_7 \text{ to } C_{10}F_{21}]\) prepared by the Curran group has been employed in the fluorous mixture synthesis of mappicines [13] as well as quasiracemic synthesis of enantiomers of pyridovericin [19] (Section 10.5.5). PMB bromide 28 with a \(C_6F_{17}\) chain and its homologs have been applied to the mixture synthesis of truncated analogs of discodermolide [14] (Section 10.5.5). A \(\text{t}-\text{butyl alcohol} 26\) with a \(C_6F_{13}\) chain prepared by the Cobas group was found to have the best reactivity compared with its analogs containing two \(C_6F_{13}\) or \(C_8F_{17}\) chains [8]. However, a protected substrate with the single \(C_6F_{13}\) chain did not have sufficient affinity for fluorous liquid extraction. The use of FSPE is expected to improve the separation efficiency dramatically.

Curran and coworkers have prepared a series of F-BocON compounds containing different \(R_f\) chains [16]. The BocON 29 with a single \(C_8F_{17}\) chain was used in the parallel synthesis of isonipecotic acid derivatives 32 (Scheme 10.5-5). The amino group of the isonipecotic acid was first protected by the F-Boc. The fluorous intermediate 33 was then coupled with eight amines \((R^1NHR^2)\) to give 34. After deprotection of F-Boc with TFA, the resulting compounds were further reacted with 12 electrophiles \((R^3X)\) to give a 96-compound library.

F-CbzCl 30 and F-CbzOsu 31 have been prepared by the van Boom and the Curran groups, respectively. The F-CbzCl has been employed in the purification of synthetic peptides [17] (Section 10.5.6). F-CbzOsu compounds with a \(C_6F_{13}\) or \(C_8F_{17}\) chain have been used to attach to 18 natural (L)-amino acids as well as 18 synthetic (D)-amino acids [18]. These protected amino acids could be useful building blocks for fluorous synthesis of small molecules and peptides.

Using primary fluorous alcohol 27 protected amino acids as the starting material, Zhang and Lu at FTI recently prepared a 120-member hydantoin and thiohydantoin library by parallel synthesis (Scheme 10.5-6) [15]. Two fluorous amino esters 35 \((R^1 = \text{t-Bu} \text{ and } \text{Bz})\) underwent reductive amination with six aldehydes. Each of the 12 intermediates 36 was further reacted with ten aryl isocyanates or aryl isothiocyanates. In situ cyclization of the resulting ureas or thioureas 37 displaced the fluorous tag and afforded the heterocyclic products 38.
The average yield for this two-step synthesis was around 50% and purities of the final products after FSPE were between 85 and 95%. This work shows the power of fluorous tags to effect the speedy synthesis of high quality libraries in solution.

10.5.4 Other Fluorous Tags

In addition to fluorous protecting groups, other fluorous moieties can also be used as “phase tags” attached to starting materials for parallel synthesis. For example, fluorous thiol was used as a nucleophile to displace the chlorine in a pyrimidine ring (Scheme 10.5-7) [20]. The tagged substrate 39 was further displaced with a 3-(trifluoromethyl)-pyrazole to give 40. The thiol tag was then activated by oxidation to a sulfone and displaced by a set of nucleophiles to afford disubstituted pyrimidines 41. The purities of final products after the FSPE were greater than 90%.

The Marshall resin is well-known in solid-phase synthesis. FTI recently introduced FluoMar™ as a fluorous version of the Marshall resin for solution-phase synthesis (Scheme 10.5-8) [21]. In the preparation of a demonstration library, carboxylic acids were coupled with FluoMar™ under standard conditions using diisopropylcarbodiimide (DIC) and dimethylaminopyridine (DMAP). The fluorous tag in compound 42 was then displaced with a set of amines to give amides 43.

Scheme 10.5-6. Synthesis of a substituted hydantoin and thiohydantoin library

Scheme 10.5-7. Synthesis of disubstituted pyrimidines with a fluorous thiol tag
10.5.5
Fluorous Protecting Groups in Mixture Synthesis

In the fluorous mixture synthesis (see Chapter 7), a set of starting materials is individually tagged with a corresponding set of homologous fluorous protecting groups. The tagged substrates are then mixed and taken through a multi-step mixture synthesis. The tagged final products are demixed by FHPLC and deprotected to give individually pure products.

The utility of F-silyl groups has been demonstrated in the mixture synthesis of a 560-member mappicine library (Scheme 10.5-9) [13b]. Seven pyridines 44 with different R_1 groups were protected with seven F-silyl groups with different R_f chains and underwent a multi-step mixture synthesis. The tagged final products are demixed by FHPLC and deprotected to give individually pure products.

Scheme 10.5-8. FluoMar™ tag in the parallel synthesis of amides

Scheme 10.5-9. F-Silyl tags in mixture synthesis of mappicine analogs

\[ \text{Scheme 10.5-8. FluoMar™ tag in the parallel synthesis of amides} \]

\[ \text{Scheme 10.5-9. F-Silyl tags in mixture synthesis of mappicine analogs} \]
four-step mixture synthesis including reactions with eight $N$-propargylbromides and ten isonitriles to give 80 tagged product mixtures $47$. Each mixture sample of $47$ was demixed by FHPLC and then detagged by HF-pyridine to give a 560-member mappicine library.

Four F-PMB bromides ($R_f = C_4F_9, C_6F_{13}, C_8F_{17}, C_{10}F_{21}$) have been used to protect the hydroxyl group of four starting materials with different $R$ groups (H, CH$_2$, Et, Ph) in the synthesis of four truncated analogs of natural product $(+)$-discodermolide at the C22 position (Scheme 10.5-10) [14].

Different fluorous group protected enantiomers can be mixed, undergo quasiracemic synthesis, and lead to the formation of two enantiomeric products. In a synthesis of two enantiomers of pyridovericin (Scheme 10.5-11), the $(S)$- and $(R)$-tagged starting materials with two different fluorous silanes ($R_f = C_6F_{13}$ and $C_8F_{17}$). The mixture was then taken through a multi-step synthesis to give a tagged product mixture. FHPLC demixing of two quasienantiomers followed by deprotection released $(S)$- and $(R)$-enantiomers of pyridovericin [19].

10.5.6 Fluorous Protecting Groups in Peptide and Oligosaccharide Synthesis

The van Boom group reported the use of fluorous protection strategy in solid-phase peptide synthesis (Scheme 10.5-12) [17]. The unreacted free amino groups at each condensation step were capped with an acetyl group. The amino group of the final product was tagged with F-Cbz. Cleavage of oligomers from the resin provided a mixture of the desired F-Cbz-tagged
product and acetyl-capped non-fluorous truncated sequences. The F-Cbz tagged product was separated from the non-fluorous material by FHPLC and then detagged to provide the desired product. Peptides containing 7 to 20 amino acids were prepared by this method.

Inazu and coworkers employed a fluorous Rink-type protecting group with an Hfb tag as the fluorous support in a tripeptide synthesis (Scheme 10.5-13) [9]. At each coupling step, a four-fold excess of amino acid derivative was used. The excess reagent and coupling agents were removed by extraction with MeCN from the FC-72 layer. Product 48 in the FC-72 layer was deprotected and purified by HPLC to give a pure tripeptide.

Fluorous protecting groups have also been used in oligosaccharide synthesis. The Inazu group employed a fluorous propanoyl (Bfp) containing two C8F17 chains to protect three hydroxyl groups of a mannose derivative (Scheme 10.5-14) [10a]. The triphenylmethyl (Trt) group of 49 was selectively removed by treatment with 10-camphorsulfonic acid (CSA). The deprotected hydroxyl group was coupled with galactose derivative 50 to give fluorous disaccharide 51. Deprotection of both the acetyl and Bfp groups followed by FC-72/MeOH extraction gave disaccharide 52 in the MeOH layer in 93%. The protection group was re-
covered from the FC-72 layer as a methyl ester 53 in 92%. A tetrasaccharide was also prepared in the same manner.

Seeberger and coworkers reported a different approach [22]. A fluorous silyl protection group \([Si(i-Pr)_2CH_2CH_2C_6F_{13}]\) was used to cap the hydroxyl group of the undesired sequence, while the desired oligomeric species were non-fluorous. HPLC was used for the separation of the desired oligosaccharide from the fluorous byproduct. Since the final product was the untagged species, no detagging step was needed.

10.5.7 Conclusion

The use of a protecting group in fluorous synthesis is a “one stone hits two birds” strategy. The functional group protection and the “phase tag” introduction can be accomplished by a single operation. Traditional solution-phase reaction conditions can be used for fluorous protections as well as deprotections. Liquid extraction with fluorous solvents can be used for purification of “heavy” fluorous compounds. FSPE and FHPLC can be used to separate “light” fluorous compounds without the use of fluorous solvents. Similar to the linkers used in solid-phase synthesis, the fluorous protecting groups can be used as the phase tag for solution-phase parallel and combinatorial synthesis. The current demands for higher purity, larger quantity, and more diversified molecules have shifted the drug discovery effort from solid-phase synthesis towards solution-phase synthesis. Such a change in the pharmaceutical mentality presents many opportunities to the development of fluorous protecting group and related technologies in the synthesis of small molecule, peptide and oligosaccharide libraries for lead generation and optimization programs.

References

7 (a) D. Schwinn, W. Bannwarth, Helv.
Fluorous Scavengers
Craig W. Lindsley* and William H. Leister

10.6.1 Introduction

During the early 1990s, most research under the rubric of combinatorial chemistry employed solid-phase organic synthesis (SPOS) to generate large libraries of small molecules [1]. SPOS was an attractive strategy in that reaction work-up and purification involved only simple filtration and resin washing. Despite this key advantage, SPOS failed to deliver an increase in drug candidates and never received wide acceptance due to a number of practical issues that have been discussed at length elsewhere [2]. By the end of the decade, a complimentary approach emerged under the moniker “solution-phase parallel synthesis” (SPPS) [3]. This homogeneous solution phase approach was hampered, not by conducting the reactions themselves, but by the time-consuming workup and purification procedures [4]. As more interest was focused on SPPS, researchers from both academia and industry quickly developed an arsenal of practical tools for expedient purification based on simple phase-separation methods, which have gained general acceptance by both organic and medicinal chemists.

Key to the success of this SPPS was the development of “scavenging reagents” [5]. Scavenging (quenching) reagents are highly effective tools for the rapid purification and isolation of the desired product(s) from a solution phase reaction by forming either covalent or ionic bonds with excess reactants and/or reaction byproducts. In general terms, scavenging can be
Fluorous Scavengers
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10.6
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considered a “phase switching” technique wherein a chemoselective reaction is employed to switch the phase of one product relative to another by virtue of a “tag” attached to the scavenging reagent. There are three major classes of scavenging reagents categorized by the nature of the phase tag: solid-phase polymers, ionizable functional groups and fluoroalkyl chains. In a typical scenario, an excess of reactant A is combined with B to provide product P along with A and other reaction byproducts X in a homogeneous solution phase reaction. Then, A and X are chemoselectively removed from solution in a subsequent “scavenging” step with a scavenging reagent 1 linked to a phase tag. After separation of the resulting phases, the product, P, is obtained in high purity simply by evaporation of the solvent (Scheme 10.6-1).

The most commonly used tags are solid-phase polymers, and hence, a wealth of literature centers on the applications of polymer-supported scavenger reagents to transfer a captive species from the organic liquid phase to the solid phase for removal by filtration [5, 6]. Indeed, this approach has gained wide-spread acceptance due to the commercial availability of a diverse array of electrophilic and nucleophilic polymer-supported scavenging reagents [7]. However, polymer-supported scavengers do have limitations. Firstly, hindered access to pendant functionality, especially in higher-loading resins, and the biphasic, heterogeneous nature of the reaction system results in slower overall kinetics. Secondly, solvent selection and volume is dictated by the swelling requirements of the resin matrix and is critical for effective scavenging. Finally, reactions employing polymer-supported reagents are not readily scalable (for example, increasing from 0.1 mol to 10 mmol) for the resynthesis of active compounds.

Another commonly used tagging strategy involves linking a scavenger to an ionizable functional group, such as a COOH (pK<sub>a</sub> < 5) or an NR<sub>2</sub> (pK<sub>a</sub> > 25) [8]. In this instance, the captured species can be selectively phase transferred by either pH adjusted liquid/liquid extraction or by solid-phase extraction (SPE) on an ion-exchange cartridge leaving the desired product either in the organic liquid phase or in the SPE cartridge eluent. SPE is a very attractive method for purification as a crude reaction is simply applied to a disposable silica plug, grafted with either a sulfonic acid (SCX – strong cation exchange) or a tertiary amine (SAX – strong anion exchange), and neutral molecules are eluted off with methanol while ionizable functional groups are retained on the SPE cartridge. Unfortunately, this strategy impacts the diversity of a library by limiting the presence of ionizable groups to either neutral or orthogonally charged library members.
Concurrently, Curran and coworkers were developing new methodologies that extended the generality of the fluorous phase as a strategic alternative to the aqueous, organic liquid and solid phase [9]. Relying on the affinity that fluoroalkyl chains have for each and the phobia they exhibit towards both organic molecules/solvents and aqueous solvents, researchers began examining fluorous tags as a means of phase switching. Initially, efforts centered on “heavy” fluorous tags (60% or more fluorine content by molecular weight, i.e., 18 or more difluoromethylene, CF$_2$, groups) that utilized liquid/liquid phase separation to isolate fluorous-tagged molecules from untagged organics. Typically, a three-phase liquid/liquid extraction, requiring an organic layer, aqueous layer, and a fluorous layer (a per-fluorohexane such as FC-72) delivers pure material. More recently, fluorous solid phase extraction (FSPE) employing fluorous silica gel (reverse-phase silica gel with a fluoro-carbon bonded phase) has been developed to effectively separate both “heavy” fluorous-tagged molecules as well as “light” fluorous-tagged molecules (4–10 CF$_2$ groups) from untagged organics [10]. The FSPE columns, referred to as FluoroFlash™ columns, retain the fluorous-tagged material when eluted with a fluorophobic solvent, such as 80/20 MeOH/H$_2$O, allowing the untagged organic molecule to rapidly elute from the column [11]. Homogeneous reaction kinetics, generality with respect to charged and neutral functional groups and a variety of efficient phase separation options, have spurred a dramatic increase in the development of fluorous scavenging reagents and protocols.

### 10.6.2 Heavy Fluorous Scavenging

The concept of fluorous scavenging was introduced by Curran in 1996 and only a few applications of heavy fluorous scavenging have been reported to date [12]. These heavy fluorous scavengers contain two or more fluoroalkyl chains and depend on liquid/liquid extraction for purification and include a fluorous trialkyltin hydride 2 for scavenging excess alkenes, a fluorous amine 3 for scavenging isocyanates and a fluorous vinyl ether 4 that served as a “catch and release” agent to separate excess alcohols from reaction mixtures (Scheme 10.6-2) [13]. Importantly, these heavy fluorous reagents were not commercially available and had to be prepared and partitioning coefficients optimized prior to use.

![Scheme 10.6-2. Heavy fluorous scavengers](image)

In both catalytic and stoichiometric quantities, 2 was shown to be generally useful for reductive radical and hydrostannation reactions with easy separation from the organic products by liquid/liquid extraction. In Giese reactions, catalytic 2 delivered high yields of product 7 with various alkyl halides 5 when excess alkene 6 (5.0 equiv) was used (Scheme 10.6-3). When the alkene component was volatile, the product 7 was afforded in >95% purity. However, if the excess alkene was not volatile, purity would be poor for this protocol. Since
all of the fluorous products partition into the fluorous phase preferentially, hydrostannation, with excess 2, was reasoned to be a method for removing excess alkene. This hypothesis introduced the technique of “fluorous quenching (scavenging)” whereby a residual undesired organic component at the end of a reaction can be removed by switching to the fluorous phase during workup. In the event, excess, non-volatile benzyl acrylate 8 was first treated with adamantyl iodide 9 and catalytic 2. When the reaction was judged complete, six equivalents of 2 were added to hydrostannate the excess 8 (Scheme 10.6-4).

After three-phase (FC-72/dichloromethane/water) extractive workup, the organic phase yielded the desired adduct 10 in 82% yield and free from 8. The application of fluorous scavenging with 2 was further extended to standard Diels-Alder [Eq. (1)] and nitrile oxide cycloadditions [Eq. (2)] with excellent results (Scheme 10.6-5) [13a].

The next heavy fluorous scavenger, amine 3, was developed specifically with automated SPPS in mind, and proved to be effective for the general scavenging of excess isocyanites in the SPPS of aryl ureas (Scheme 10.6-6). In a generic reaction sequence, excess isocyanate 17 is treated with an amine 18 in THF to generate the aryl urea 19 along with the excess 17. The reaction is then quenched with fluorous scavenger 3 in FC-72, followed by liquid/liquid extraction to afford pure aryl urea 13 in the organic phase and excess 3 and the scavenged urea adduct 20 in the FC-72 layer. Utilizing an HP 7686 synthesizer, this scavenging protocol could be completely automated to produce several 3 x 4 and 3 x 3 aryl urea libraries with HPLC purities and yields averaging >97% and 86%, respectively. For every library member produced in this fully automated procedure, the organic layer contained less than 0.5 mol% F as determined by 19F NMR. Several library members were found to be more...
potent Cl\textsuperscript{−} secretion inhibitors in the human T84 colon cancer cell line than existing inhibitors [13b].

The next application of heavy fluorous scavenging involved a “catch and release” purification strategy for the mixture synthesis of curacin A analogs using vinyl ether 4 [13c]. In a prototypical example (Scheme 10.6-7), Wipf and coworkers prepared mixtures of up to 18 compounds by exposure of three aldehydes, 21–23, to an excess of a 1:1:1:1:1:1 ratio of organolithium reagents (Nu-H) to ensure complete 1,2-addition. The resulting mixture of alcohols, 24–26mix, was quenched (“caught”) with 4 to provide a mixture of fluorous-tagged adducts 27–29mix contaminated with excess Nu-H. After liquid/liquid extraction with FC-72/CH\textsubscript{3}CN/H\textsubscript{2}O, 27–29mix were transferred into the FC-72 layer. The alcohols 30–32mix were “released” from the fluorous tag by methanolation and delivered to the organic phase in pure form by another fluorous/organic/aqueous extraction. Following this “catch and release” scavenging protocol, six mixture libraries of analogs were prepared and screened. Despite their simplified structures, this approach identified, in short order, the most potent curacin A analogs identified to date.

Scheme 10.6-5. Application of 2 to Diels-Alder and nitrile oxide cycloaddition reactions

Scheme 10.6-6. Heavy fluorous isocynate scavenging with 3
Two additional examples of heavy fluorous “catch and release” scavenging in conjunction with liquid/liquid extraction have been reported. In 1997, Curran and coworkers employed a fluorous silane to “catch” alkoxydes, generated by the addition of Grignard reagents to carbonyl compounds, and subsequently “released” by treatment with fluoride [9]. In 1999, Curran’s lab disclosed the application of a fluorous tin azide for the “catch and release” purification of functionalized tetrazoles [13d].

10.6.3 “Light” Fluorous Scavenging

The concept of “light” fluorous scavenging was simultaneously introduced in 2002 by researchers from Fluorous Technologies and Merck Research Laboratories and in less than one year multiple applications have been reported based on the paradigm illustrated in Scheme 10.6-8 [14].
As opposed to the “heavy” scavengers described earlier, these new “light” fluorous reagents contain a single fluorous chain (usually less than 19 F atoms) in the phase tag (molecular weight is significantly reduced), the liquid/liquid extraction has been replaced with a solid-phase extraction over fluorous silica gel (FSPE on FluoroFlash™ SPE cartridges), and both the reagents and the separation media are commercially available [11, 15]. From the beginning, the goal was to develop a “toolkit” of fluorous-tagged equivalents of known polymer-supported scavenging reagents, and thus far, a dozen light fluorous-tagged scavengers have been described (Table 10.6-1) with applications for quenching excess electrophiles (entries 1–5) and nucleophiles (entries 6–12) in SPPS [14, 16].

Every application of these scavengers in concert with FSPE has provided the desired products in excellent isolated yields and with purities exceeding 94%. Some representative examples of light fluorous scavengers for SPPS are illustrated in Scheme 10.6-9 [14].

All of the scavengers depicted in Table 10.6-1 provided rapid quenching as compared with their polymer-supported congeners due to homogeneous reaction kinetics. Indeed, in a critical study, fluorous thiol 42 required only 5 min to achieve >95% quenching of bromide 41 as opposed to 50 min for the analogous polymer-supported thiol 43 (Scheme 10.6-10) [14a]. Quenching rates could be further accelerated to less than 1 min for a number of fluorous scavengers by the application of microwave heating [16]. In general, a 10–20 fold decrease in reaction time was observed with light fluorous scavengers versus the analogous polymer-supported scavenger.

Key to the success of the light fluorous scavengers was the ease of rapid purification, in parallel, by FSPE. Significantly, both Merck and FTI have reported that the FluoroFlash™ SPE columns can be reused up to ten times without loss of efficiency and several sizes (2–10 g) are commercially available [14, 16]. Moreover, multi-gram separations of fluorous-tagged from untagged organics are possible employing fluorous silica gel in Biotage™ cartridges with aqueous methanol gradients on a Horizon™ High Performance FLASH chromatography unit affording excellent results [11, 16, 17].

Based on the reaction conditions and the nature of the fluorous scavenger employed, there are three major variations to the standard “light” fluorous scavenging paradigm depicted in Scheme 10.6-8 [14]. Often times, a solution-phase tertiary amine base may be employed in a fluorous scavenging reaction to either deprotonate the scavenger or to sequester acid generated during the reaction. Since the amine base will co-elute with the desired organic product resulting in contamination, the base must be removed prior to SPE. The first variation [Eq. (1), Scheme 10.6-11] to address this issue required a mildly acidic aqueous workup.
prior to FSPE to reprotonate excess 42 and remove solution-phase tertiary amine base 46. Then, standard FSPE of the organic layer provided the desired product 47 in high yield and purity [14a]. A second common variation [Eq. (2), Scheme 10.6-11] involves the replacement of the solution-phase tertiary amine base 46 with an excess of a polymer-supported tertiary amine base 48. Under this protocol, the aqueous workup could be avoided and the FSPE step also removed the polymer-supported base affording 47 in similar yield and purity [14b].

The third variation centers on the properties of the fluorous reagent/scavenger. During the course of a scavenging reaction, the fluorous reagent/scavenger can be converted into a charged species such as a salt. When this occurs, the scavenger may co-elute with the organics during the FSPE step, as the salt will have reasonable solubility in aqueous methanol, leading to impure products. Therefore, when employing a polar, basic scavenger such as 52 and/or a fluorous-tagged tertiary amine base 51 [Eq. (3), Scheme 10.6-11] a mixed sorbent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fluorous scavenger</th>
<th>Scavenger for...</th>
<th>Functional groups scavenged</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₃N–CH₂C₈F₁₇</td>
<td>electrophiles</td>
<td>acid chlorides, isocyanates, sulfonyl chlorides</td>
<td>14b</td>
</tr>
<tr>
<td>2</td>
<td>HS–CH₂CH₂C₆F₁₃</td>
<td>electrophiles</td>
<td>6′-bromocarbonyl compounds, epoxides, activated halides, michael acceptors</td>
<td>14a,b</td>
</tr>
<tr>
<td>3</td>
<td>Ph₂P–C₆F₁₃</td>
<td>electrophiles</td>
<td>activated halides</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>H₂N–C₆F₁₃</td>
<td>electrophiles</td>
<td>acid chlorides, isocyanates, sulfonyl chlorides, acidic phenols, carboxylic acids</td>
<td>14c</td>
</tr>
<tr>
<td>5</td>
<td>HO–CH₂CH₂C₆F₁₃</td>
<td>electrophiles</td>
<td>trialkylsilyl chlorides/triflates</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>OHC–C₈F₁₇</td>
<td>nucleophiles</td>
<td>organometallics, reducing agents</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>ClO₂S–C₇F₁₅</td>
<td>nucleophiles</td>
<td>1°,2°-amines, alcohols, alkoxides</td>
<td>14b</td>
</tr>
<tr>
<td>8</td>
<td>HO₃S–C₆F₁₇</td>
<td>nucleophiles</td>
<td>1°,2°-amines, anilines</td>
<td>14b</td>
</tr>
<tr>
<td>9</td>
<td>ClO₃C–C₆F₁₅</td>
<td>nucleophiles</td>
<td>1°,2°-amines, alcohols, alkoxides</td>
<td>14b</td>
</tr>
<tr>
<td>10</td>
<td>O–C₆F₁₃</td>
<td>nucleophiles</td>
<td>1°,2°-amines, thiols, thiophenols, organometallic reagents</td>
<td>14b</td>
</tr>
<tr>
<td>11</td>
<td>OCN–CH₂CH₂C₆F₁₇</td>
<td>nucleophiles</td>
<td>1°,2°-amines</td>
<td>14d</td>
</tr>
<tr>
<td>12</td>
<td>O–N(CH₂)₃C₈F₁₇</td>
<td>nucleophiles</td>
<td>1°,2°-amines</td>
<td>14d</td>
</tr>
</tbody>
</table>
SPE cartridge [an ion exchange column (SCX or SAX) fitted inside a FluoroFlash™ SPE cartridge] served to neutralize amine hydrochloride salts and cleanly separate fluorous-tagged from untagged organics. Under this protocol, the crude reaction could be applied directly to the mixed sorbent SPE cartridge and thereby avoid both an aqueous workup and the diminished kinetics of polymer-supported reagents [14c].

10.6.4

Summary

The future for fluorous scavenging to impact on the way in which both organic and medicinal chemistry are conducted looks very promising. These solution-phase tools overcome the
major limitations of polymer-supported and ionic phase tags while providing economic and environmental benefits. Importantly, fluorous scavenging technology has several noteworthy advantages: (1) inexpensive and commercially available reagents and separations media; (2) homogeneous solution-phase kinetics; (3) liquid/liquid and solid-phase extraction protocols for maximum workup flexibility; and (4) both the reactions and the purification strategies are readily scalable. As additional reagents and protocols are developed, fluorous scavenging technology will no doubt occupy a prominent position in the fields of organic and solution-phase parallel synthesis.
Acknowledgement

The authors would like to thank Professor Dennis Curran (University of Pittsburgh) and Dr. Phil Yeske (FTI) for helpful conversations.

References


7 Polymer-supported reagents and scavengers are available from Aldrich, Fluka, Argonaut Technologies, Advanced ChemTech and NovaBiochem to list just a few of the suppliers.


15 Fluorous reagents are commercially available from a number of vendors including: Aldrich, Lancaster, TCI America and Fluorous Technologies Incorporated (FTI). Fluorous separation media is available from FTI and Silicycle.

16 Lindsley, C. W.; Zhao, Z. unpublished results from Merck Research Laboratories.

10.7 Synthesis of Perfluoroalkylated Phosphines

Eric G. Hope and Alison M. Stuart

10.7.1 Introduction

Since Horváth and Rábai’s seminal paper on fluorous biphase catalysis [1] much of the subsequent work in this field has focused on the synthesis of fluorous-soluble phosphines. Phosphines are ubiquitous in homogeneous catalysis and perfluoroalkylated phosphines have already been applied successfully to a range of applications in the fluorous biphase system, such as hydroformylation, hydrogenation, hydroboration, hydrosilylation as well as carbon–carbon bond forming reactions. Generally, the rule of thumb is that \( >60\% \) fluorine is required for preferential fluorous phase solubility, but there are also reports of using the more lightly fluorinated phosphines for catalysis in supercritical carbon dioxide. Some of these applications are described in detail in other chapters (hydroformylation and hydrogenation in Chapter 10.9 and carbon–carbon bond forming reactions in Chapter 10.8) and so the aim of this chapter is to review the synthesis of perfluoroalkylated phosphines used for both fluorous biphase catalysis and for homogeneous catalysis in supercritical carbon dioxide.

10.7.2 Monodentate Phosphines

10.7.2.1 Trialkylphosphines

The first phosphine prepared specifically for its application in fluorous biphase catalysis was the trialkylphosphine, \( \text{P}(\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13})_3 \) (1) [1]. Although this ligand had been synthesized previously [2], Horváth and Rábai developed an alternative route by the radical addition of \( \text{PH}_3 \) to 1,1,2,2-perfluoro-1-octene. This reaction is carried out in two steps in a glass-lined autoclave in the presence of the radical initiator, azobis(isobutyronitrile) (AIBN), to give the fluorous phosphine (1) in 26% yield. Subsequently, this route was improved by Gladysz to give much better yields (Scheme 10.7-1) and to synthesize ligands (2) and (3) which contain the longer perfluoroalkyl chains [3]. Not surprisingly, as the length of the perfluoroalkyl group increases, the partition coefficient of the phosphine in a perfluoromethylcyclohexane/toluene biphase increases (Table 10.7-1), but their absolute solubilities in perfluorocarbon solvents decrease with increasing chain length.

In order to avoid using the highly toxic phosphine, \( \text{PH}_3 \), we and others have developed

$$
\text{PH}_3 + \text{H}_2\text{C} = \text{CHRf} \rightarrow \text{PH}_3(\text{CH}_2\text{CH}_2\text{Rf})_3 \rightarrow \text{P}(\text{CH}_2\text{CH}_2\text{Rf})_3
$$

Scheme 10.7-1. (i) AIBN, 85 °C; (ii) \( \text{H}_2\text{C} = \text{CHRf} \), VAZO, 90 °C

(1) \( \text{Rf} = \text{C}_6\text{F}_{13} \), 75 % yield
(2) \( \text{Rf} = \text{C}_8\text{F}_{17} \), 70 % yield
(3) \( \text{Rf} = \text{C}_{10}\text{F}_{21} \), 63 % yield
alternative routes to phosphine (1) from 1H,1H,2H,2H-perfluorohexyl iodide and phosphorus trichloride. In its original synthesis, the ligand was prepared by the reaction of F13C6CH2CH2ZnI with PCl3 [2]. Knochel and coworkers have also reacted the dialkylzinc reagent, (F13C6CH2CH2)2Zn, with PCl3 and then BH3.SMe2 to give the stable borane adduct, (F13C6CH2CH2)3P.BH3 in 75% yield [4]. Alternatively, the Grignard reagent, F13C6CH2CH2MgI, can be synthesized and it has been reacted with a series of phosphorus chloride reagents (Ph2PCl, PhPCl2 and PCl3) [5, 6]. Unfortunately, however, we were unable to extend the Grignard route to derivatives with longer perfluoroalkyl substituents [7].

Two trialkylphosphines with longer hydrocarbon spacer units, P(CH2CH2C6F13)3 and P(CH2CH2CH2CH2C8F17)3, were synthesized by Gladysz’s radical addition of PH3 to C8F17CH2CH2CH2C8F17 and C8F17CH2CH2CH2C8F17, respectively [3], and a series of unsymmetrically substituted fluorous trialkylphosphines has also been synthesized (Scheme 10.7-2) [8]. Initially, the efficiency of the spacer units was probed by examining the variation in $\text{u}_{\text{CO}}$ values for a series of trans-[IrCl(CO)L2] complexes [8]. Even with five methylene units the electron-withdrawing inductive effect of the fluorous ponytails was still apparent. Further experimental and computational studies on the fluorous phosphines predicted that between eight and ten methylene groups would be needed to insulate effectively a phosphorus lone pair from a perfluoroalkyl segment [9].

![Scheme 10.7-2](image_url)

Tab. 10.7-1. Partition coefficients (P) of trialkylphosphines in perfluoromethylcyclohexane/toluene

<table>
<thead>
<tr>
<th>Ligand</th>
<th>log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(CH2CH2C6F13)3</td>
<td>1.915</td>
</tr>
<tr>
<td>P(CH2CH2C8F17)3</td>
<td>&gt;2.52</td>
</tr>
<tr>
<td>P(CH2CH2C10F21)3</td>
<td>&gt;2.52</td>
</tr>
<tr>
<td>P(CH2CH2CH2C8F17)3</td>
<td>1.915</td>
</tr>
<tr>
<td>P(CH2CH2CH2CH2C8F17)3</td>
<td>1.954</td>
</tr>
</tbody>
</table>

10.7.2.2 Triarylphosphines

Since triphenylphosphine is probably the most widely used ligand in homogeneous catalysis, many different approaches have been developed by groups all over the world to synthesize a range of perfluoroalkylated analogs of triphenylphosphine. In 1997 there were two independent reports [5, 10] on the synthesis of the first fluorous-soluble triarylphosphine (6) and both groups used the same copper coupling methodology, developed by McLoughlin and Thrower [11], to introduce the perfluoroalkyl group directly onto the aromatic ring (Scheme 10.7-3) to form (5). Our selective copper coupling reaction between bromoiodobenzene and perfluoroiodo benzene has also been used to synthesize a series of meta-derivatized triarylphosphines [12], but when 2-bromo-perfluorohexyl benzene was lithiated with n-BuLi and then reacted with PCl3, the tri-derivatized phosphine was not formed [13]. The main product was (F13C6C6H4-2)2PCl, which was air- and moisture-stable due to the two ortho-perfluoroalkyl units protecting the phosphorus atom from attack by incoming nu-
cleophilic reagents. More recently, Chen and Xiao [14] carried out the copper coupling reaction between tris(4-bromophenyl)phosphine oxide and perfluorohexyl iodide (Scheme 10.7-3) and then reduced the resulting triarylphosphine oxide to form the perfluoroalkylated triarylphosphine (6). This method has also been used to introduce the perfluorooctyl group in good yields, whereas, although the copper coupling reaction between perfluoroctyl iodide and 4-bromoiodobenzene proceeds well, only poor yields of the desired phosphine are obtained in the second step because of the poor solubility of the 4-bromoperfluoroctylbenzene in ether at low temperature.

A number of different methods have been developed to synthesize fluorous-derivatized triarylphosphines containing two "CH₂" spacer groups between the aromatic ring and the perfluoroalkyl group. Leitner and coworkers synthesized triarylphosphine (8) for the rhodium-catalyzed hydroformylation of 1-octene in supercritical CO₂ [15, 16]. The first step is a Cu¹ catalyzed coupling of the Grignard reagent, 4-BrC₆H₄MgBr, with 1H,1H,2H,2H-perfluoroocyle iodide to form the bromoaromatic (7) (Scheme 10.7-4), but significant amounts of the Wurtz coupled product, F₁₃C₆CH₂CH₂CH₂CH₂C₆F₁₃, are also produced. Initially, it was impossible to purify the crude reaction mixture by either column chromatography or distillation, but fluororous reverse phase silica gel provided a straightforward separation giving poor yields of bromoaromatic (7) [17]. Curran developed a much cleaner route to (7) by the palladium-catalyzed coupling of F₁₃C₆CH₂CH₂ZnI with 4-bromiodobenzene and found that the use of t-BuLi in the lithiation step led to better yields of the triarylphosphine (8) [18]. An alternative route involved the Heck reaction to form the triarylphosphine oxide (9), which was then hydrogenated to form the (CH₂)₂ spacer group and, finally, reduced to form the triarylphosphine (8) [19]. Similarly, a Heck reaction between 1H,1H,2H-perfluoroalkenes and arendiazonium salts, as well as aryl iodides, followed by a straightforward hydrogenation provided good access to perfluoroalkylated bromoaromatics such as (7) [20]. An alternative efficient route to aromatics containing a (CH₂)₂Rf group that
seems to have been overlooked is the palladium catalyzed Suzuki cross-coupling reaction of $1H,1H,2H$-perfluoroalkenes with aryl boronic acids [21].

Curran and coworkers [18] synthesized the first triarylphosphine that contains a branched fluorous ponytail (Scheme 10.7-5) and more recently, Gladysz’s group [22] has increased the hydrocarbon “spacer” between the aromatic ring and the fluorous ponytails to three methylene units. Here, they carried out a Wittig reaction between 4-bromobenzaldehyde and $[\text{Ph}_3\text{PCH}_2\text{CH}_2\text{Rf}]^+$ to give $4$-$\text{BrC}_6\text{H}_4\text{CH}_2\text{Rf}$ in excellent yields. After hydrogenating the double bond, the bromoaromatic was subjected to the usual low temperature lithiation with $n$-$\text{BuLi}$ and condensation with phosphorus trichloride allowed the formation of a series of perfluoroalkylated triarylphosphines $[\text{P}([4-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{CH}_2\text{Rf}])_3, \text{Rf}=\text{C}_6\text{F}_{13}, \text{C}_8\text{F}_{17}, \text{C}_{10}\text{F}_{21}]$. An alternative spacer unit, $O(\text{CH}_2)_n\text{Rf} (n = 1$ or 3), was prepared by the O-alkylation of para-hydroxy-arylphosphines or -arylphosphine oxides (Scheme 10.7-6) and the extension to ortho- and meta-derivative ligands is straightforward [23, 24]. Finally, van Koten has introduced a silyl spacer group in the para-position of triarylphosphines to attach between three and nine perfluoroalkyl groups, $[4-\text{C}_6\text{H}_4\text{SiMe}_3-n(\text{CH}_2\text{CH}_2\text{Rf})_n]_3$ [25]. Two different methods were used to synthesize this series of fluorous triarylphosphines, but the most efficient method was route B where the expensive perfluoroalkylated silyl group was introduced in the last step (Scheme 10.7-7).

---

**Scheme 10.7-4.** (i) Mg, Et₂O; (ii) $\text{F}_3\text{C}, \text{C}_2\text{H}_4\text{I}, [(\text{Ph}_4\text{Cu})\text{CuCl}]_n$ (10 mol %), Et₂O, 0 °C to RT; (iii) $n$-$\text{BuLi}, \text{EtO}$; (iv) $\text{PCl}_3$; (v) Zn, THF, 25 °C; (vi) 4-$\text{BrC}_6\text{H}_4\text{I}, \text{Pd}(\text{Ph}_3\text{P})_4, 45$ °C; (vii) $\text{H}_2\text{C}^\text{b} \text{CHC}_6\text{F}_{13}$, palladacycle, NaOAc, DMF, 125 °C; (viii) 10 bar $\text{H}_2$, 10 % $\text{Pd/C}$, EtOAc, RT; (ix) $\text{HSiCl}_3, \text{EtN}$, toluene, 120 °C

---

**Scheme 10.7-5.** (i) CsF, DMF, 45 °C; (ii) 4-$\text{BrC}_6\text{H}_4\text{CH}_2\text{Br}$; (iii) $\text{t-BuLi}$; (iv) $\text{PCl}_3$
Both the $\nu_{\text{CO}}$ data for trans-[MCl(CO)L$_2$] complexes and $^1J_{\text{PtP}}$ coupling constants of cis-[PtCl$_2$L$_2$] complexes have been used to gain an insight into the electronic effects of the perfluoroalkyl substituents on triarylphosphines (Table 10.7-2) [26]. Clearly, the additional spacer units between the aromatic ring and the perfluoroalkyl group provide much better insulation of the electronic effect than when the fluorous ponytail is attached directly to the aryl ring. The downside, however, is that these phosphines normally have lower partition coefficients between perfluorocarbon and organic solvents than P(4-C$_6$H$_4$C$_6$F$_{13}$)$_3$ (Table 10.7-3). In the series of silyl-derivatized phosphines containing three, six or nine fluorous ponytails, the triaryl phosphines that contain six perfluoroalkyl groups gave the

![Scheme 10.7-6](image)

Scheme 10.7-6. (i) H$_2$O$_2$, acetone; (ii) BBr$_3$, CH$_2$Cl$_2$; (iii) F$_8$C$_2$H$_2$OTf or F$_8$C$_2$(CH$_2$)$_2$I, Cs$_2$CO$_3$, DMF, 65 °C; (iv) HSiCl$_3$, Et$_3$N, toluene, 130 °C

![Scheme 10.7-7](image)

Scheme 10.7-7. (i) X = I, n-BuLi, 0 °C; (ii) XSiMe$_3$-(CH$_2$CH$_2$Rf)$_n$, $-78$ °C to RT; (iii) t-BuLi, $-78$ °C then RT; (iv) PCl$_3$, $-78$ °C to RT; (v) X = Br, n-BuLi, RT; (vi) PCl$_3$, $78$ °C to RT; (vii) t-BuLi, $-78$ °C; (viii) XSiMe$_3$-(CH$_2$CH$_2$Rf)$_n$, $-78$ °C to RT

Tab. 10.7-2. Selected spectroscopic data of metal complexes containing perfluoroalkylated triarylphosphines

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\nu_{\text{CO}}$ (cm$^{-1}$) of trans-[IrCl(CO)L$_2$]</th>
<th>$\nu_{\text{CO}}$ (cm$^{-1}$) of trans-[RhCl(CO)L$_2$]</th>
<th>$^1J_{\text{PtP}}$ (Hz) of cis-[PtCl$_2$L$_2$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP$_3$</td>
<td>1952</td>
<td>1965</td>
<td>3672</td>
</tr>
<tr>
<td>P(4-C$_6$H$_4$H$_2$CH$_2$H$_2$C$<em>6$F$</em>{17}$)$_3$</td>
<td>1958</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>P(4-C$_6$H$_4$CH$_2$CH$_2$C$<em>6$F$</em>{15}$)$_3$</td>
<td>–</td>
<td>1972</td>
<td>3679</td>
</tr>
<tr>
<td>P(4-C$_6$H$_4$C$<em>6$F$</em>{13}$)$_3$</td>
<td>1979</td>
<td>1993</td>
<td>3631</td>
</tr>
<tr>
<td>P(4-C$_6$H$_4$OCH$_3$)$_3$</td>
<td>1961</td>
<td>1958</td>
<td>3703</td>
</tr>
<tr>
<td>P(4-C$_6$H$_4$OCH$_2$C$<em>7$F$</em>{15}$)$_3$</td>
<td>1967</td>
<td>1977</td>
<td>3680</td>
</tr>
</tbody>
</table>
optimum result, but, even then, all of the triarylphosphines have lower partition coefficients than the fluorous trialkylphosphines. However, triarylphosphines are much easier to handle since they are less air sensitive and in some catalytic applications the electron-withdrawing characteristics can provide an advantage.

Both Bergbreiter [27] and Xiao [28] independently designed a completely different approach to anchoring arylphosphines in fluorous solvents by synthesizing fluorous-soluble polymer-supported alkylarylphosphines and triarylphosphines, respectively (Scheme 10.7-8). Both fluoroacrylate polymers were prepared by the radical copolymerization of \(1H,1H,2H,2H\)-perfluorodecylacrylate in benzotrifluoride in the presence of AIBN and Xiao’s triarylphosphine (11) was shown to have a better partition coefficient in perfluoro-1,3-dimethylcyclohexane than either P(4-C\(_6\)H\(_4\)C\(_6\)F\(_{13}\))\(_3\) or P(4-C\(_6\)H\(_4\)CH\(_2\)CH\(_2\)C\(_6\)F\(_{13}\))\(_3\). Bergbreiter synthesized the direct analog of Wilkinson’s catalyst with phosphine (10) and not only was it shown to have comparable rates of hydrogenation to the traditional homogeneous catalyst, but it was also recycled successfully seven times without loss of activity under an inert atmosphere [27]. Xiao, on the other hand, examined the application of his fluorous soluble polymer ligands in the hydroformylation of olefins and acrylates under fluorous biphasic conditions and in supercritical carbon dioxide [28, 29].

![Scheme 10.7-8](image)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>(\log P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(4-C(_6)H(_4)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.865(^a)</td>
</tr>
<tr>
<td>P(4-C(_6)H(_4)CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.125(^b)</td>
</tr>
<tr>
<td>P(4-C(_6)H(_4)CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.615</td>
</tr>
<tr>
<td>P(4-C(_6)H(_4)SiMe(_2)(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.300</td>
</tr>
<tr>
<td>P(4-C(_6)H(_4)SiMe(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.615</td>
</tr>
<tr>
<td>P(4-C(_6)H(_4)Si(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.300</td>
</tr>
<tr>
<td>P[4-C(_6)H(_4)SiMe(_2)(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.585</td>
</tr>
<tr>
<td>P[4-C(_6)H(_4)SiMe(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.892</td>
</tr>
<tr>
<td>P[4-C(_6)H(_4)Si(CH(_2)CH(_2)C(<em>6)F(</em>{13}))(_3)</td>
<td>0.633</td>
</tr>
</tbody>
</table>

\(\(^a\)\text{Perfluorocarbon solvent is perfluoro-1,3-dimethylcyclohexane.}\)

\(\(^b\)\text{Perfluorocarbon solvent is perfluorohexane.}\)

Tab. 10.7-3. Partition coefficients (P) of triarylphosphines in perfluoromethylcyclohexane/toluene
10.7.3 Bidentate Phosphines

10.7.3.1 Perfluoroalkylated Analogs of 1,2-Bis(diphenylphosphino)ethane
Although chelating ligands normally enhance catalyst stability, only one class of achiral per-
fluoroalkylated bidentate phosphines have been reported and they are all straightforward
analogs of 1,2-bis(diphenylphosphino)ethane (Scheme 10.7-9). All of these ligands have
been synthesized using known methodology developed in the synthesis of either the trialkyl-
or triaryl-phosphines. The advantage of Deelman’s diphosphines (17) are that more than one
perfluoroalkyl group can be attached to each aromatic ring and he has demonstrated that
the ligands containing either eight or twelve perfluorohexyl groups are extremely soluble in
perfluoromethylcyclohexane [31]. However, only the bidentate ligands (14) and (17) have
actually been investigated in fluorous biphase catalysis [32, 33].

![Chemical structures of phosphines](image)

**Scheme 10.7-9**

10.7.3.2 Chiral Phosphines
The concept of synthesizing a chiral fluorous ligand that can be recycled is particu-
larly attractive since most chiral ligands for asymmetric catalysis are expensive and time-
consuming to prepare. A number of perfluoroalkylated chiral phosphines have now been
synthesized (Scheme 10.7-10), but there are no successful reports of their effective recycle.
In fact, only phosphines (18) and (24) have reasonable partition coefficients between per-
fluorocarbon and organic solvents and phosphine (25) can be extracted into the fluorous
phase with multiple extractions. All of the other phosphines, (19)–(23), are only “lightly
fluorinated” and have been used for catalysis in supercritical carbon dioxide.
Apart from Ojima's BINAPHOS analog (20), all of the chiral ligands were synthesized using known methodology to introduce the perfluorinated chains. The enantiopure fluorous BINOL derivative (29) was used to synthesize (20) and was prepared by the palladium-catalyzed addition of perfluorohexyl iodide to (27), followed by reduction of the diiodide (28) with LiAlH₄ and, finally, deprotection with TBAF to give (29) in 37% overall yield from (26) (Scheme 10.7-11).

10.7.4 Outlook

There are two main areas for development: (1) new synthetic methodologies to existing perfluoroalkylated phosphine ligands and (2) the synthesis of novel perfluoroalkylated ligands driven by their potential catalytic applications in the fluorous biphase system, in organic solvents using the novel thermomorphic approach [41] or in supercritical CO₂.

(1) As indicated above, a diverse range of synthetic approaches have already been exploited for phosphine synthesis and, although alternative coupling reactions are available in the
synthetic chemists armory, it is unlikely that these will bring significant advances. To date, Suzuki coupling reactions have found least widespread application and, perhaps, improved reaction yields may be possible using this approach.

(2) The synthesis of novel phosphine ligands will be driven by academic and commercial expediency. At this stage, commercially-viable applications of catalysis using fluorous techniques have not been realized, and novel ligand synthesis must be directed to afford even better catalyst/product separation. There has been relatively little work on triarylphosphines with more than one perfluoroalkyl group per arene ring or using branched perfluoroalkyl chains and work in this area could lead to important developments. However, for fluorous solvent applications, there would be concerns over the absolute solubility of the ligand/catalyst if the total number of fluorous ponytails is increased substantially. In these cases, perhaps mixed systems incorporating both long (C_{6}F_{13}) and short (CF_{3}) or alkyl (C_{6}H_{13}) functional groups might warrant evaluation.

References

10 Highlights of Applications in Synthesis and Catalysis

10.8
Metal Catalyzed Carbon–Carbon Bond Forming Reactions in Fluorous Biphasic Systems

Siegfried Schneider, Carl Christoph Tzschucke, and Willi Bannwarth

10.8.1
Introduction

Metal catalyzed cross coupling reactions are one of the most prominent reaction types in synthetic organic chemistry. They are employed in various areas such as synthesis of natural products, supramolecular chemistry, material science and medicinal chemistry and have been reviewed in numerous articles and monographs [1]. Specifically, the search for new chemical entities in medicinal chemistry requires the synthesis of increasing numbers of compounds in shorter periods of time. To meet this demand, not only do parallel synthesis formats need to be employed, but also the simplification of workup procedures becomes increasingly important. In catalytic processes this can be accompanied by the recovery and reuse of the catalyst.

Recently, several concepts have been developed to simplify workup procedures and to avoid time-consuming purification steps such as column chromatography or distillation [2, 3]. They consist in essence in the use of polymer-supported catalysts [4], the use of molten salts (or ionic liquids) as reaction media [5, 6], reactions in scCO2 or water [7, 8], and the use of fluorous biphasic systems (FBS) [9–14]. In the FBS concept, perfluorinated ligands mediate the solubility of the pertinent catalyst in fluorous solvents. According to Scheme 10.8-1 the reaction is carried out in a two-phase mixture consisting of a perfluorinated and an organic solvent. Such two-phase systems often become homogeneous at elevated temperatures. Lowering the temperature after reaction leads to reformation of the two phases. The organic phase contains the product and the fluorous phase the catalyst to be reused.

In this chapter we describe the evolution of metal catalyzed carbon–carbon bond formations under FBS conditions over the past eight years. The actual synthesis of catalysts and aspects of coordination chemistry of catalysts will not be discussed.

Scheme 10.8-1
10.8.2 C–C Couplings with Perfluoro-Tagged Palladium Complexes

Palladium catalyzed cross-coupling reactions often require relatively large amounts of catalysts, which have to be removed from the reaction product. Perfluoro-labelled Pd complexes offer a solution to this problem, since the perfluoro-labelled catalysts are soluble in fluorous solvents and can be separated from the organic product very easily by liquid/liquid extractions. There are numerous examples in the literature demonstrating the power of this methodology.

10.8.2.1 Negishi Reaction
Betzemeier and Knochel performed cross-couplings of aryl iodides with arylzinc bromides in a toluene/1-bromoperfluorooctane (C₈F₁₇Br) mixture in the presence of a Pd catalyst derived from perfluoro-tagged phosphane 1a and Pd₂(dba)₃ (Scheme 10.8-2) [15]. The reaction was carried out at 60 °C for 30 min with 0.15 mol% of catalyst yielding the desired coupling products in excellent yields (87–99%; 9 examples). By using 1.5 mol% of catalyst it was possible to reuse the catalyst up to four times yielding biphenyl-derivative 2. This cross-coupling reaction could be extended to benzyl- and alkenyl-zinc bromides forming compounds 3 (76%) and 4 (92%).

10.8.2.2 Heck Reaction
The first Heck reaction in perfluorinated solvents was described by Moineau et al. with either Pd₂(dba)₃ or Pd(OAc)₂ as the palladium source and the perfluorinated phosphanes 1a–1c as the ligands (Scheme 10.8-3) [16]. Reactions between iodo benzene and methyl acrylate were conducted with 0.5 mol% of catalyst in an acetonitrile/D-100 (mainly n-per...
fluorooctane) mixture at 80 °C for 4 h. The expected products were formed quantitatively and good selectivity (88–93%) was observed. Recycling of the catalyst was possible, but resulted in lower conversions of the iodobenzene in the second and third runs, respectively.

Rocaboy and Gladysz prepared a fluorous Schiff base, which was converted into palladacycle 5. This represents a phosphane-free Pd catalyst which additionally shows a thermomorphic behavior (Scheme 10.8-4) [17]. Reactions were performed under homogeneous conditions (DMF, 100–140 °C) without fluorous solvents using 0.68–1.83 mol% of the palladacycle. After workup the Heck coupling products were obtained in 49–100% yield. Recycling experiments were done with 0.02 mol% of 5 using C₈F₁₇Br as the “carrier”, which forms a biphasic mixture with DMF. After phase separation and removal of C₈F₁₇Br the catalyst was charged with fresh starting materials and DMF. The results revealed a gradual loss of conversion and yield. The authors assumed that loss of activity is either due to limited stability of the catalyst or that the catalyst is stable but the recycling is not as efficient as anticipated. Reaction rate and transmission electron microscopy indicated the presence of soluble Pd nanoparticles as the active catalyst.

Stabilized Pd nanoparticles of compounds featuring perfluorinated chains 6–10 were described by Moreno-Mañas et al. (Scheme 10.8-5) [18, 19]. The Pd nanoparticles were obtained by the reduction of PdCl₂ with methanol in the presence of 6–10, respectively. The presence of such nanoparticles was confirmed by transmission electron microscopy. Owing to the stabilization by the perfluorinated ligand the palladium colloids are soluble in perfluorinated solvents. Pd nanoparticles stabilized by 1,5-bis[4-bis(perfluorooctyl)phenyl]-1,4-pentadien-3-one (6) were active in Heck and Suzuki couplings [18].
Nakamura et al. prepared a fluorous BINAP [(R)-F13BINAP] ligand and applied it to the asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate (Scheme 10.8-6) [20]. Results showed that (R)-F13BINAP 11 is soluble in fluorinated solvents, but easily oxidized during the reaction. A similar enantioselectivity to that of the original reaction (91% ee) published by Hayashi was obtained in BTF (90% ee) and an even higher enantiomeric excess was achieved in a benzene/FC-72 (93% ee) solvent mixture [21]. Because of the instability of the (R)-F13BINAP towards oxygen, recovery and reuse of the ligand was not efficient.

10.8.2.3 Stille Couplings
Schneider and Bannwarth reported the synthesis of fluorous bis(triphenylphosphane)-palladium dichloride complexes (12a–c) and their application in Stille couplings (Scheme 10.8-7) [22]. The reactions were performed in DMF/perfluoromethylcyclohexane (PFMCH) (1:1) with 1 equiv of LiCl as additive at 80 °C for 3 to 24 h. From the organic phase the C–C
Coupling products (13) were obtained in good yields while the fluorous phase containing the catalyst was used as such for the next cycle. The catalysts could be used up to six times without significant decrease in yield.

Curran and coworkers reported the cross coupling reaction between perfluoro-tagged stannanes (14) and aryl halides under FBS conditions (Scheme 10.8-8) [23, 24]. The perfluoro-tagged tin byproduct (15) and the excess of the tin substrate (14) were removed by simple extraction.

The Stille couplings were performed in DMF/THF (1:1) with 2 mol% of PdCl2(PPh3)2 at 80°C for 22 h with LiCl as an additive. Yields of the coupling products (13) were generally high (>80%) and the recovery of the fluorous byproduct (15) was efficient (80–90%). The workup was performed as outlined in Scheme 10.8-9 by extraction in a three-phase system consisting of water, DCM and FC-72. The fluorous byproduct (15) remained in the fluorous phase and could be recycled, whereas the crude product was in the DCM phase which was further purified by preparative TLC yielding the desired cross coupling product (13). In contrast to common Stille coupling reactions the use of LiCl as an additive was crucial, even with aryl halides as the substrates, probably because an interaction between the chloride ion and the fluorous tin reagent promotes the transmetallation step. Without LiCl low reaction rates, long reaction times and incomplete conversions were observed.

Curran, Hallberg and coworkers also performed Stille coupling reactions with fluorous tin reagents under microwave irradiation [25, 26]. It was possible to reduce the reaction time dramatically from 22 h with conventional heating to less than 6 min with microwave heat-
The workup was similar to that outlined before with fair to good yields (50–96%) of the coupling products.

**10.8.2.4 Suzuki Couplings**

Schneider and Bannwarth applied fluorous bis(triphenylphosphane)palladium dichloride complexes 12a–d as catalyst precursors to Suzuki reactions [27]. The reactions took place in an H₂O/DME/PFMCH tri-phase mixture at 75 °C for 2 h with 1.5 mol% of the Pd complex. It could be demonstrated that perfluoro-tagged complexes 12a–d are highly effective precatalysts for Suzuki couplings under FBS conditions with either electron-rich or electron-deficient bromoarenes and arylboronic acids. The catalysts could be recycled and reused after phase separation up to six times without significant decrease in coupling yields. It could be shown in one example that the amount of catalyst could be reduced from 1.5 mol% to 0.1 mol% still resulting in a high yield (>86%) in the first run but considerable loss of activity in repetitive cycles.

Rocaboy and Gladysz prepared perfluoro-tagged dialkylsulfides [R\(\text{F}(\text{CH}_2)\_n\)]\_2S (\(n = 2\) 16; \(n = 3\) 17) which are soluble in most fluorous and organic solvents with a CF₃C₆F₁₃/toluene partition coefficient of 98.7:1.3 for 16 and 96.6:3.4 for 17 at 24 °C (Scheme 10.8-10) [28]. Reaction of 16 or 17 with Na₂PdCl₄ gave Pd complexes 18 and 19, respectively, which are soluble in only a limited range of fluorinated solvents at room temperature. With 18 and 19 as the catalyst they were able to achieve turnover numbers (TON) of 4500–5000 in Suzuki couplings of aryl bromides and phenylboronic acid in CF₃C₆F₁₃/DMF/H₂O in the presence of K₃PO₄. Under fluorous recycling conditions decreased activities of the catalysts were observed. For this loss of activity the following reasons could be responsible:

1. inefficient recycling of the perfluoro-tagged catalyst;
2. gradual deactivation of the catalyst;
3. slow generation of an active non-recyclable heterogeneous catalyst from a homogeneous precursor and recycling of the remaining precursor;
4. generation of a heterogeneous catalyst which is not stable but efficiently recycled.
The appearance of palladium black in recycling experiments and recent reports on heterogeneous or metallic palladium species lead the authors to favor possibilities (3) and (4) [18, 19, 29, 30].

In accordance with Curran’s work on Stille reactions with perfluoro-tagged organostannane compounds, Chen et al. prepared a series of perfluoro-tagged boronic acid esters (20) and applied them to Suzuki reactions (Scheme 10.8-11) [31]. The reaction was performed with 2 mol% of Pd(PPh$_3$)$_4$ in aqueous dioxane. The desired biaryl derivative was obtained by extraction and chromatographic workup in 76% yield, but no further examples were given.

In examples employing perfluoro-tagged catalysts in FBC, separation of the catalyst followed by its reapplication was usually achieved by liquid/liquid extraction between a fluorous and an organic solvent. Fluorous solvents have the disadvantage of being relatively expensive and environmentally persistent. Bannwarth and coworkers have developed new protocols, which allow for the separation and recycling of perfluoro-tagged catalysts without the need of fluorous solvents [32]. They have employed Pd complexes 12c, 12d and 21, immobilized by adsorption on fluorous reverse phase silica gels (FRPSG) 22 and 23, and demonstrated the application to Suzuki couplings in organic solvents (Scheme 10.8-12). Silica with coarse grain of 100–300 μm particle size was used with loadings of between 0.1 and 100 mg complex per g FRPSG. The coupling of para-nitromonobenzene and phenylboronic acid was carried out using 10 mg Pd complex per g FRPSG with 0.1 mol% palladium. Complete conversions were obtained and recycling was possible by filtration or decantation.
without significant decrease of activity (yield over four cycles with three different immobilized complexes 98–91%). With 0.001 mol% of catalyst, a TON of 131 000 was observed. ICP-MS measurements indicated a leaching of 1.9% of catalyst when adsorbed onto FRPSG 22 and 1.6% when adsorbed onto FRPSG 23, respectively. Suzuki couplings with catalyst 12c on support 22 were performed with different substrates giving high yields for electron-deficient aryl bromides and for aryl iodides.

10.8.2.5 Sonogashira Coupling
Markert and Bannwarth employed the Pd complexes 12c, 12d and 21 as catalyst precursors for the coupling of bromoarenes with alkynes (Scheme 10.8-13) [33]. The reactions were carried out in a mixture of DMF and perfluorodimethylcyclohexane at 100 °C for 4 h with 2 mol% of 12c, 12d or 21 and 5 mol% of CuI as the co-catalyst in the presence of 2 equiv of Bu₂NH.

After the reaction, the phases were separated at 0 °C and the fluorous phase containing the catalyst was washed several times with DMF and was reused as such for the next run. As is known for Sonogashira couplings, electron-deficient bromoarenes proved to be good substrates, whereas the coupling of donor-substituted bromoarene resulted in lower yields. Recycling and reuse of the catalyst was possible in most cases but no influence of the product yield being dependent on the position of the perfluoro-tag in the phosphane or the nature of the spacer group was observed.
Perfluoro-tagged Pd complexes 12c, 12d and 21 adsorbed on FRPSG 22 (2 mol%) were also used for Sonogashira couplings of phenyl acetylene and p-nitrobromobenzene, without the need for fluorous solvents, similar to the protocol outlined for Suzuki couplings [32]. High yields were obtained for three successive experiments. By reducing the amount of catalyst down to 0.2 mol%, conversion was still complete, but a significant drop of product yield was observed in the second run.

10.8.2.6 Allylic Substitutions
Leitner and coworkers described Pd catalyzed nucleophilic substitutions of allylic substrates with different nucleophiles (Scheme 10.8-14) [34]. They used Pd$_2$(dba)$_3$ as the palladium source and phosphane 24 as the perfluoro-tagged ligand. Reaction between cinnamyl methyl carbonate (25) and various nucleophiles (Nu-H) were performed in a THF/C$_7$F$_{14}$ biphasic mixture at 25 °C or 50 °C for 15 to 80 min. A decrease in conversion was observed only after the ninth run (with a 5 mol% Pd complex). By reducing the amount of Pd complex to 1 mol%, five quantitative recyclings were possible. The standard protocol was also applied to the condensation of dimethyl malonate with allyl methyl carbonate, (2-vinyl)butyl carbonate and cyclohex-2-enyl carbonate. In each case two recyclings were performed without any decrease in conversion (100%).

10.8.2.7 Cyclodimerization
Cyclodimerizations of conjugated enynes 26a–e in the presence of perfluoro-tagged Pd catalyst were reported by Saito et al. (Scheme 10.8-15) [35]. Reactions of enynes 26a–e were carried out in toluene/hexane/perfluorodecaline with 1 mol% of Pd$_2$(dba)$_3$ as the palladium source and 8 mol% of perfluoro-tagged phosphane 1 at 65–80 °C for 1–4 h giving the desired products (27a–e) in moderate to good yield (43–78%).

Recovery of the perfluoro-tagged catalyst was possible up to four times. However, ICP atomic emission analysis of the fluorous phase indicated that the concentration of the palladium species decreased significantly.

10.8.3 Fluorous BINOL-Titanium Catalyzed Diethylzinc Additions to Aromatic Aldehydes
Curran and coworkers and Chan and coworkers independently described the asymmetric addition of diethylzinc to aldehydes mediated by chiral perfluoro-tagged BINOL-Ti-catalysts
Whereas Curran tagged the BINOL ligands (28a/b) with perfluoro-silyl ponytails, Chan attached perfluoroalkyl residues directly to the BINOL core (29a–c) (Scheme 10.8-16). The approximate partition coefficients of the perfluoro-tagged BINOLS 28 and 29 are shown in Table 10.8-1.

<table>
<thead>
<tr>
<th>BINOL</th>
<th>Solvent system</th>
<th>Organic-/fluorous-solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>28a</td>
<td>toluene/FC-72</td>
<td>2/98</td>
</tr>
<tr>
<td>28b</td>
<td>toluene/FC-72</td>
<td>1/99</td>
</tr>
<tr>
<td>29a</td>
<td>hexane/perfluoro-(methyldecaline)</td>
<td>1/2</td>
</tr>
<tr>
<td>29b</td>
<td>hexane/perfluoro-(methyldecaline)</td>
<td>1/15</td>
</tr>
<tr>
<td>29c</td>
<td>hexane/perfluoro-(methyldecaline)</td>
<td>1/53</td>
</tr>
</tbody>
</table>
With BINOLs \(28a\) and \(28b\) reactions were performed in a biphasic solvent system according to Scheme 10.8-17.

High yields (81–97%) were obtained with enantioselectivities (78–84%) comparable to reactions in non-fluorous uniphase systems. Furthermore, it was possible to recycle and reuse the fluorous-tagged BINOLs \((28a/b)\) by solid phase extraction on FRPSG giving nearly the same yield and enantioselectivity as in the first run.

Reactions with Ti complexes of \(29a–c\) were performed at 45 °C in a perfluoro-(methyldecalin)/hexane biphasic mixture. Lower enantioselectivities were obtained than with \(28a/b\), which was possibly due to the higher reaction temperature employed. Enantioselectivity in consecutive runs strongly depended on the fluorine content of the BINOL ligand. With \(29a\) high yield (99%) and good enantioselectivity (ee 70%) were obtained for the diethylzinc addition to benzaldehyde in the first run, which significantly dropped in the second cycle (ee 28%), whereas with \(29c\) enantioselectivity was somewhat lower (ee 54–60%), but did not decrease during nine runs. The \(29c\)-Ti complex was also used as a catalyst for the triethyl aluminum addition to benzaldehyde, where good yields and ee values were obtained up to the sixth run (yield 82%; ee 80%) [39].

The zinc-catalysts \(30–32\) were introduced by van Koten and coworkers for enantioselective additions of diethylzinc to benzaldehyde under FBS conditions (Scheme 10.8-18) [40].

Reactions were performed with 2.5 mol% of \(30–32\) in a monophasic (hexane) or a biphasic (octane/PFMCH) system, respectively. In the monophasic system conversions (90–100%) and enantiomeric excesses (82–94%) were higher than with the untagged complex \(33\) (conversion 81%; ee 72%). In the biphasic system the initial enantioselectivity was high but dropped in consecutive runs [\(30\) (ee drop from 72% in second run to 37% in the third run); \(31\) (61%, third to 36%, fourth); \(32\) (76%, third to 43%, fourth)]. The experiments indicated that an increase in length of the perfluoroalkyl chain does not necessarily have a positive effect on the number of runs for which the catalyst can be reused.
Endres and Maas prepared dimeric rhodium(II) carboxylate complexes 34a–c from the sodium salts 35a–c and rhodium(III) chloride hydrate in ethanol (Scheme 10.8-19) [41, 42].

Reactions were performed in CH₂Cl₂ with 34a or in the fluorous/organic hybrid solvent FC-113 (CCl₂F₂CClF₂) with 34b–c. Recovery of the catalyst was achieved by extraction into PFMCH (with 34a) or by replacement of FC-113 with PFMCH/CH₂Cl₂ (with 34b–c) and phase separation, respectively. Yields remained high over four cycles with 34a (70–71%) or five cycles with 34b–c (67–70% with 34b and 75–76% with 34c), respectively. Nevertheless, a total loss of 56% of 34a (after four cycles), 51% and 38% of 34b and 34c, respectively, after five cycles, as shown by gravimetric determination, was observed. The authors attributed this to a partial destruction of the complex.

Intramolecular carbenoid C–H insertions of α-diazo-β-keto ester 36 [Eq. (2); Scheme 10.8-20] were catalyzed by 34c with good selectivity for 37a and good yield [67% (37a):3% (37b)] [42]. By extraction with PFMCH/CH₂Cl₂, 96% of the catalyst could be recycled.
10.8.5 Miscellaneous

10.8.5.1 Kharash Addition

The addition reaction of CCl₄ to methylmethacrylate in DCM was catalyzed by perfluoro-tagged nickel compound 38 as described by Kleijn et al. (Scheme 10.8-21) [43].

Unfortunately, 38 did not have an improved affinity for fluorous solvents which prevented its efficient recycling.

10.8.5.2 Friedel-Crafts Acylation

The Friedel-Crafts acylation of arenes with acetic anhydride was efficiently catalyzed by ytterbium tris(perfluoroalkanesulfonyl)methides 39a–c (Scheme 10.8-22) [44]. It was dem-
onstrated that catalyst 39c could be recovered in 96% yield by extraction of the reaction mixture with hot perfluoromethyldecaline and could be reused in a second run.

The reaction of perfluoro-tagged allyltin compounds with aldehydes catalyzed by PtCl2(PPh3)2 (40a) and PtCl2[PPPh3]/Co(C6H4-4-Rf)n2 (40b–f), where Rf represents a linear or branched perfluoro alkyl chain, was described by Curran and coworkers (Scheme 10.8-23) [45, 46]. The reactions were performed using 5 to 10 mol% of catalyst 40a–f without perfluorinated solvents. Purifications were done by solid phase extraction on FRPSG. All products were obtained in good yields (56–100%) and excellent purities (95–100%). By using catalysts 40b–c and 40e–f neither fluorous phosphane nor the fluorous tin compounds could be detected by NMR. Recovery and reuse of either phosphane or Pt-complexes by solid phase extraction was not successful.

\[
\begin{align*}
\text{Cl}_2\text{Pt} & \left[ \text{Ph}_3\text{P} \left( \text{R}_1 \right) \right]_n \\
40a-f
\end{align*}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Rf Chain</th>
<th>n Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40a</td>
<td>CH2CH2C6F13</td>
<td>0</td>
</tr>
<tr>
<td>40b</td>
<td>CH2CH2C6F13</td>
<td>3</td>
</tr>
<tr>
<td>40c</td>
<td>CH2CH2C6F13</td>
<td>2</td>
</tr>
<tr>
<td>40d</td>
<td>CH2CH2C6F13</td>
<td>1</td>
</tr>
<tr>
<td>40e</td>
<td>CH2(CF3)2C3F7</td>
<td>3</td>
</tr>
<tr>
<td>40f</td>
<td>CH2(CF3)2C3F7</td>
<td>2</td>
</tr>
</tbody>
</table>

References


References

10.9
Hydroformylation and Hydrogenation Catalyzed by Perfluoroalkylated Phosphine/Metal Complexes

**Eric G. Hope and Alison M. Stuart**

10.9.1
Introduction

Although homogeneous catalytic systems, typically discrete soluble metal complexes, offer a number of significant advantages (such as enhanced chemo-, regio- and enantio-selectivity, and/or milder reaction conditions) over comparable heterogeneous catalytic systems, many have not been and will not be industrially commercialized because of one major issue: the separation of the metal catalyst from the reaction product(s). This arises from the relative, thermal instability of many homogeneous catalysts, which are typically unstable above ca. 150 °C, linked with the easiest and most commonly employed separation procedure on an industrial scale – distillation. Consequently, there has been significant interest in the design of processes that draw upon the principle advantages of both homogeneous and heterogeneous catalysts, including supported systems, supercritical fluids and alternative solvent systems such as ionic liquids, aqueous biphasic and fluoruous solvents. In this contribution, we highlight the applications of fluoruous solvents and perfluoroalkylated phosphine ligands/metal catalysts in two, industrially important, processes: hydroformylation and hydrogenation. In a subsequent contribution, closely related work on hydroformylation with perfluoroalkylated phosphite ligands is discussed (see Chapter 10.10).

10.9.2
Hydroformylation

The hydroformylation of alkenes, essentially the addition of syngas (CO + H₂) across the double bond (Scheme 10.9-1), has been extensively investigated and was exploited commercially for the first time in the 1950s using cobalt-carbonyl catalysts [1]. Enhanced hydrogenation to give alcohols coupled with improved selectivity to the linear (n-) product has been accomplished by the introduction of phosphine ligands [2] and these technologies are still in use today for the hydroformylation of long-chain alkenes. In the hydroformylation of propene, where the volatile butanal product can be readily distilled directly from the reactor, more selective rhodium-triphenylphosphine catalysts operating under milder reaction con-
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10.9.2 Hydroformylation

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ditions have replaced the cobalt-based catalysts in continuous processes operating at 3.5 million tonnes per annum [3]. However, the thermal instability of these rhodium catalysts has precluded their widespread adoption and has led to the evaluation of a number of alternative approaches including fluorous chemistry. In fact, Horváth and Rábai highlighted the potential for fluorous technologies for the hydroformylation of long chain alkenes in their original disclosure on the fluorous biphase [4].

10.9.2.1 Alternative Systems

10.9.2.1.1 Aqueous Biphase

The relative instability of the rhodium-based catalysts has already been overcome, and the technique exploited commercially, in the Ruhrchemie-Rhône Poulenc hydroformylation of propene where the sodium salt of a sulfonated triphenylphosphine ligand (1) (Scheme 10.9-2) is used to solubilize the rhodium catalyst in the aqueous phase [5]. In this process, the second phase is toluene and the reaction is carried out in a batch process with rapid stirring to ensure that the two immiscible phases are intimately mixed. After reaction, the system is allowed to separate and the organic product phase is simply decanted from the aqueous catalyst phase. However, this approach has not been extended to the hydroformylation of longer chain alkenes because of their very low aqueous solubility leading to commercially prohibitive low reaction rates. A potential solution to this problem was reported five years ago in which the sulfonated triphenylphosphine ligand has been replaced with triphenyl phosphine functionalized with a single, very long, polyethylene glycol ponytail (2) [6]. Here, although the rhodium-phosphine catalyst is exclusively soluble in water at room temperature, on heating the ponytail undergoes a phase transition rendering the catalyst preferentially soluble in the organic phase. Consequently, the catalyst acts on the substrate under classical homogeneous conditions but, on cooling, reversal of the phase transition returns the catalyst to the aqueous phase allowing the product to be separated by a simple decantation.

10.9.2.1.2 Ionic Liquids

Ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate (3), are salts that are (1) liquid at room temperature, (2) have extremely low vapor pressures, (3) can be tuned to dissolve organic compounds and (4) can dissolve ionic catalysts or, in specific examples, the liquid may act as a catalyst as well as the solvent. Consequently, there has been considerable interest in their potential application as alternative solvents for organic synthesis and catalysis. In initial work on the rhodium-catalyzed hydroformylation of 1-pentene, using the sulfonated phosphine ligand (1) to solubilize the catalyst in the ionic liquid, conversions were disappointingly low [7]. More recently, two groups have reported highly active and regioselective rhodium-catalyzed hydroformylation of 1-octene with Xantphos-type ligands in ionic liquids, ([4] n:i 21:1 and <0.07% rhodium
leaching \[8\]; (5) \(n:i 49:1\) and \(<5\) parts per billion rhodium loss \[9\]}, where separation of the 1-nonanal product can be achieved again by a simple decantation.

10.9.2.1.3 Supported Catalysts Rhodium catalysts for hydroformylation supported on both insoluble (for example inorganic oxides or polymers) and soluble (for example dendrimers) materials have been reported. Work on insoluble solid supports has been dogged by loss of activity and high levels of catalyst leaching as a consequence of bonds breaking between the catalyst and support during catalysis. However, acceptable catalyst leaching \(<100\) parts per billion rhodium) coupled with reasonable activity and excellent regioselectivity \(n:i 40:1\)
has been demonstrated for a sol-gel solution incorporating a triethoxysilyl-functionalized Xantphos-type ligand (6) [10]. Dendrimers are large tree-like soluble molecules with a globular shape making them suitable for ultrafiltration in which the solvent and reaction product(s) pass through whilst the dendrimer is retained. Rhodium for hydroformylation can be supported on the “surface” of the dendrimer functionalized with phosphines, and such a system shows enhanced regioselectivity but loss of activity on recycling [11].

10.9.2.1.4 Supercritical Carbon Dioxide

Most metal-containing complexes, particularly rhodium-based hydroformylation catalysts incorporating aryl-phosphine ligands, are virtually insoluble in apolar scCO₂. Solubility can be enhanced by the incorporation of the perfluoroalkyl groups characteristic of fluorous chemistry and reaction rates and regioselectivities for the hydroformylation of long chain alkenes, comparable to those observed under fluorous biphasic conditions, have been reported using derivatized rhodium catalysts [12, 13]. In two reports, significantly enhanced rates of reaction have been reported in scCO₂ in comparison with those in toluene for the rhodium-catalyzed hydroformylation of acrylic esters using the perfluoroalkylated phosphine (7) [14], or a fluoropolymer ligand [15]. However, although there has been considerable interest in scCO₂ as an environmentally friendly solvent for homogeneous catalysis [16, 17], for which removal of the solvent just requires decompression back to the gaseous phase, this does not per se overcome the principle issue for homogeneous catalysis outlined above; that is the separation of product from catalyst. In theory, since solubility in supercritical fluids is pressure dependent, with careful control of the catalyst/substrate/product system it should be feasible to accomplish the desired separation, and this has been achieved with moderate success (< 170 parts per billion rhodium leaching) in the hydroformylation of 1-octene using the perfluoroalkylated triphenylphosphine (8) [12]. Alternative approaches to the catalyst/product separation problem have combined scCO₂ with a supported catalyst [for example (6)] [18] and scCO₂ with an ionic liquid [19], both of which are potentially very powerful systems but, in both cases the reaction rates are relatively low.

10.9.2.2 Fluorous Systems

In the earliest reports of the application of perfluorocarbon solvents and perfluoroalkylated ligands/metal catalysts, Horváth and Rábai outlined the hydroformylation of 1-octene in a toluene/CF₃C₆F₁₄(P2) two-phase system at 100 °C under 10 atm CO/H₂ (1:1) using a catalyst generated in situ from [Rh(CO)₂(acac)] and P(C₂H₄C₆F₁₃)₃ (9) (1:40), which gave an 85% conversion into aldehydes with an n/i ratio of 2.9 [4, 20]. In the following full paper [21], an in-depth analysis of hydroformylation under fluorous biphasic conditions generated a series of important conclusions. Here, the hydroformylation of 1-decene and ethylene were investigated with the same rhodium catalyst (generated in situ) under both batch and semi-continuous conditions at 100 °C and 1.1 MPa CO/H₂ (1:1) in a 50/50 vol% toluene/P2 bi-phase. The long-term stability of this catalyst under these conditions is significantly greater than that for the catalyst based on triphenylphosphine, the regioselectivity is similar, but the catalytic activity is an order of magnitude lower. The reaction, as expected, is first-order in both rhodium and alkene and is inhibited by excess phosphine, whereas the regioselectivity increases with phosphine concentration such that the best n/i ratio (7.84) is obtained at a P:Rh ratio of approximately 100:1 ([ligand] = 0.3 mol dm⁻³). The semi-continuous experi-
ments were highly successful with total turnovers of up to 35 000 during nine cycles with only 1.18 parts per million (4.2%) loss of rhodium per mol of product(s), which arises from the low solubility of the catalyst in the organic phase.

It is well established that triarylphosphines give much better regioselectivity in rhodium-catalyzed hydroformylation reactions than trialkylphosphines [3, 22], so we have evaluated rhodium catalysts based upon (7) [23, 24]. Initial screening of the hydroformylation of 1-hexene in a toluene/1,3-(CF₃)₂C₆F₁₄ (PP₃) two-phase system at 70 °C under 20 atm CO/H₂ (1:1) using a catalyst generated in situ from [Rh(CO)₂(acac)] and (7) (1:3) gave a 98% conversion into aldehydes with an n/i ratio of 3.8. Visual inspection of the solvent system under 20 atm syngas in high pressure sapphire NMR tubes indicated that the alkene starting materials are miscible with the fluorous solvent at the reaction temperature whilst the more polar aldehyde products are immiscible, and this work led to an evaluation of the perfluoroalkylated rhodium hydroformylation catalyst in the absence of the second organic phase. Here, thorough investigation of the hydroformylation of 1-octene in PP₂ between 70 and 90 °C under 20 atm CO/H₂ (1:1) using the same rhodium catalyst with metal:ligand ratios of 1:3 and 1:10 gave 95−98% conversions with n/i ratios of 3.0−6.3. Crucially, rhodium leaching levels, detected at the best regioselectivity (n/i 6.3; conditions rhodium:phosphine 1:10; 70 °C), were excellent (80 parts per billion) indicating that the omission of toluene from the solvent system has enabled the development of a process which is nearing the rigorous retention of rhodium, whilst maintaining both the high reaction rate and good regioselectivity, which are required for commercial application.

Table 10.9-1 summarizes the key catalytic data for these hydroformylation reactions under fluorous biphasic conditions alongside data for representative examples from the alternative solvent systems outlined above. In general, the results are comparable: in some cases better regioselectivities, in others better reaction rates, in yet others better catalyst retention. In at-
tempts to improve regioselectivity and catalyst retention under fluorous biphase conditions, we and others have been investigating perfluoroalkylated bidentate ligands based upon Xantphos, for example (10) [25], and BIPHEPHOS [26, 27]. Unfortunately, the introduction of perfluoroalkyl units onto biphenol has, to-date, prevented the synthesis of fluorous BIPHEPHOS-type bisphosphite ligands whilst (10) with only four perfluoroalkyl groups, although it is active in the rhodium-catalyzed hydroformylation of 1-octene (n:i 23:1), is not soluble in fluorous solvents and attempts to increase the number of perfluoroalkyl substituents has not yet been successful. These latest results appear to suggest that the future development of fluorous chemistry in hydroformylation probably rests with simpler, monodentate, ligand systems.

10.9.3
Hydrogenation

The hydrogenation of unsaturated organic compounds represents one of the most environmentally benign processes in that it produces virtually no waste. Since heterogeneous catalysts (for example Raney nickel, palladium on carbon) are highly effective and efficient, homogeneous hydrogenation catalysts will only find application when other factors (for example, substrate incompatibility, enantioselectivity, transfer hydrogenation to avoid the need to use gaseous hydrogen) are important [28]. The classic industrial example is the rhodium-catalyzed homogeneous enantioselective hydrogenation of dehydroamino acids in the synthesis of L-dopa [29]. In these cases, as for the homogeneous hydroformylation catalysts outlined above, product/catalyst separation is a major issue that has led to the synthesis and evaluation of homogeneous catalysts under a variety of alternative regimes.

10.9.3.1 Alternative Systems

10.9.3.1.1 Aqueous Biphase So far, no industrial process for hydrogenation under aqueous biphase conditions has been commercialized. In the research laboratories, the biphasic hydrogenation of a wide variety of substrates has been investigated using mainly sulfonated ligands, for example (1), for solubilizing the catalyst [30, 31], leading to the biphasic hydrogenation of CO$_2$ to formic acid [32]. Enantioselective hydrogenation has also been extensively studied, but reaction rates and enantiomeric excesses have usually been lower than those obtained in conventional media [30].

10.9.3.1.2 Ionic Liquids Early work on the hydrogenation of 1-pentene in (3) used cationic rhodium(I) species, for example [Rh(nbd)(PPh$_3$)$_2$][PF$_6$] that did not require functionalized ligands, offered acceptable reactivities, that were anion dependent, with low (<0.02%) rhodium leaching levels [7]. Similarly, up to 90% ee and quantitative conversions have been reported for up to five recycles of conventional ruthenium-BINAP catalysts in the asymmetric hydrogenation of tiglic acid in (3) followed by extraction of the 2-methylbutanoic acid product with scCO$_2$ [33]. In a recent development, [Rh(COD)(PPh$_3$)$_2$][BF$_4$] has been used for the hydrogenation of water-soluble alkenes in a water:ionic liquid system that is monophasic at the reaction temperature (80 °C) but phase separates at room temperature for the facile separation of the water-soluble product and reuse of the catalyst phase [34].
10.9.3.1.3 **Supercritical Carbon Dioxide** Since permanent gases are fully miscible with supercritical fluids, hydrogenation in scCO$_2$ is particularly attractive and work in this area has been reviewed [16, 17]. Of particular interest are enhanced reactivities in ruthenium-catalyzed hydrogenation of CO$_2$ to formic acid in the presence of base [35, 36], and highly enantioselective hydrogenation of prochiral $\alpha,\beta$-unsaturated carboxylic acids [37, 38]. Catalyst/product separation remains a key issue that has been elegantly overcome in an iridium-catalyzed enantioselective (ee up to 81%) hydrogenation of imines using the perfluoroalkylated phosphine-imine ligand (11), where the catalyst is soluble in scCO$_2$ in the presence of the substrate, but precipitates once all the substrate has been used up. This allows the catalyst to be recycled several times without significant loss of either activity or enantioselectivity [39].

10.9.3.2 **Fluorous Systems**
In contrast with the research into hydroformylation under FBS conditions that has been directed towards a commercially important process, publications on hydrogenation under FBS conditions have been focused upon the physical and chemical consequences of using perfluoroalkylated phosphine ligands and fluorous solvents and the ability to recover and recycle the metal catalyst. Horváth and coworkers [40], using the analog of Wilkinson’s catalyst, [RhCl(L)$_3$], where L = P(C$_2$H$_4$C$_6$F$_{13}$)$_3$ (9), studied the hydrogenation of a series of alkenes (2-cyclohexen-1-one, 1-dodecene, cyclododecene and 4-bromostyrene) in a toluene:PP$_2$ biphase under 1 atm H$_2$ at 45°C affording the hydrogen addition products in 87–98% yields. Although the catalyst activity is significantly poorer than those for conventional homogeneous catalysts, recovery and reuse of the catalyst was illustrated by re-charging the fluorous phase with second and third aliquots of substrate and obtaining comparable conversions, but some catalyst decomposition was also observed. It is well known that alkyl phosphines give much less effective analogs of Wilkinson’s catalyst than aryl phosphines, and perfluoroalkylated aryl phosphines have been evaluated by other groups. A soluble fluropolymer supported alkylidiphenyl phosphine is active for the hydrogenation of 1-octene and cyclohexene in a THF:perfluoroctane biphase under 2 atm H$_2$ at 25°C, where reuse seven times shows no loss in activity although rhodium leaching levels have not been measured [41]. Using styrene as a substrate, we have directly compared the catalytic activities of the analogs of Wilkinson’s catalyst containing perfluoroalkylated phosphines, for example (7), with those of their protio-parents in toluene/hexane:PP$_3$ or fluorobenzene:PP$_3$ biphases under 1 atm H$_2$ at 63.5 or 75°C, respectively, where just the introduction of the fluorous phase had a significant impact upon the rates of reaction, but <1 ppm rhodium leaching was observed [42]. In line with well-established trends, the incorporation of the electron withdrawing perfluoroalkyl groups caused a reduction in rate relative to those for the protio-parents and this effect is most pronounced for the trialkyl phosphine with the C$_2$H$_4$ spacer unit, indicating that it is a poorer electronic insulator than the C$_6$H$_4$ group. The most promising results were obtained for a C$_6$H$_4$OCH$_2$ spacer group although, even with this unit, complete electronic insulation of the phosphorus atom was not possible. The most effective insulation is reported in a direct comparison of the aryl-silyl spacer ligand (12; TOF 870 h$^{-1}$) with Wilkinson’s catalyst (TOF 960 h$^{-1}$) in the hydrogenation of 1-octene in $\alpha,\alpha,\alpha$-trifluorotoluene under 1 atm H$_2$ at 80°C [43]. In PP$_2$ [using (12), 1-octene at 80°C] the TOF drops to 177 h$^{-1}$, but on cooling to 0°C a biphase forms that allows separation of the
octane product and the catalyst phase to be recycled nine times with just 3 ppm (0.12%) rhodium leaching per cycle. The reactivity appears to increase during the subsequent cycles, although this can be ascribed to loss of the perfluorocarbon solvent (ca. 12% per cycle) during phase separation and the non-zero miscibility of PP2 with the product phase. The best catalyst retention (> 99.92%) has been reported following hydrogenation of 1-octyne under 1 atm H₂ at 40 °C with the cationic \([\text{Rh} (\text{COD})(\text{13})][\text{BF}_4]\) in a FC-75/hexane biphase, where the chelating bidentate phosphine ligand (13) has 12 fluorous ponytails [44].

It is rather difficult, and not particularly informative, to make a detailed comparison between these data for hydrogenation in fluorocarbon solvents and those for hydrogenation in alternative media since the studies have employed a wide range of metals, types of catalyst, pressures of hydrogen and substrates, but in most cases reactivities are poorer than those reported in conventional organic solvents. Perfluoroalkylated chiral ligands have been prepared [45, 46], but they are not preferentially soluble in fluorous solvents and to achieve this would require considerable further modification. Therefore, although enantioselective hydrogenation in aqueous systems and in supercritical CO₂ has been investigated, the likely application of fluorous chemistry in this area appears remote.

10.9.4
Outlook

In just nine years, considerable advances have been made in the understanding of fluorous chemistry. Research on hydroformylation under FBS conditions has turned full-circle and attention in the future must focus on improving catalyst stability with simple, readily prepared ligands and chemical engineering process design directed towards guaranteeing solvent and catalyst losses at commercially acceptable levels.

At this point in time, the question about whether fluorous or these other alternative approaches to the heterogenization of homogeneous hydroformylation or hydrogenation catalysts can be commercialized cannot be answered. All of these processes have one or more disadvantages (expensive ligand and/or solvent, environmental compatibility, high catalyst leaching, high pressures, low rates) and for most the complicated process of the transfer of the technology from the academic laboratory to larger scales or, indeed, pilot plant has not been attempted. Until these issues and a full cost analysis for the complete process have been undertaken, commercialization of any of these alternative technologies cannot be contemplated.

References

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10.10 Hydroformylation Catalyzed by Rhodium/Fluorinated Triarylphosphite Complexes in Fluorous Biphasic Media

Eric Monflier, André Mortreux, and Yves Castanet

10.10.1 Introduction

Hydroformylation of higher olefins is an important industrial process where less selective cobalt-based catalysts have to be employed because the more reactive and selective rhodium-based catalysts cannot be separated from the long chain aldehyde products without decomposition [1]. To circumvent this problem, five major strategies have been developed: (1) anchoring of rhodium catalysts to resins, polymeric, dendrimeric or inorganic materials [2–4]; (2) immobilization of the catalyst in a thin liquid film supported on inorganic materials [5–7]; (3) the use of amphiphilic ligands which allow the extraction of the rhodium catalyst into another phase at the end of the reaction [8–9]; (4) the use of supercritical fluids as reaction media [10–15]; and (5) the use of two-phase systems where the catalyst is dissolved in a phase which contains neither the substrate nor the products. In the biphasic approach, the rhodium catalyst can be dissolved in a molten salt [16, 17], in a fluorocarbon phase [18–31] or in an aqueous phase. Owing to the low solubility of higher olefins in water, the use of aqueous media requires the presence of a mass-transfer promoter [32–34], a surface-active phosphine [35, 36] or a thermoregulated phase transfer phosphine [37].

Among these different approaches, the fluorous biphasic catalysis is a particularly elegant concept as the two phases are generally readily separated at room temperature and can become homogeneous at higher temperatures [38, 39]. Obviously, this behavior allows combination of the activity of homogeneous catalysts with the simplicity of product isolation. The hydroformylation of olefins in a fluorocarbon phase was first reported by Horváth and Rábai in 1994 [18, 19]. The rhodium catalyst was dissolved in the fluorous phase by using a trialkylphosphine \( P(CH_2CH_2CF_2CF_2)_3 \) prepared by hydrophosphinylation of the corresponding fluorinated alkene. This catalyst displays satisfactory activities in a perfluoromethylcyclohexane/toluene solvent system and the normal to branched aldehyde ratio \( l/b \) was comparable to that obtained in a conventional solvent with \( HRh(CO)(PPh_3)_3 \), \( l/b = 2.9 \). Since this pioneering work, the attention of research groups has been focused on the synthesis of new fluorinated ligands showing a better affinity for the fluorous phase and a better \( l/b \) ratio. With the aim of maintaining the high selectivities and activities observed in classical organic solvents, three classes of ligands have been rapidly developed for
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hydroformylation under fluorous biphasic conditions: triarylphosphines [13] and triarylphosphites [23, 40–43] bearing one or two perfluoroalkyl groups per aromatic ring and more recently, chiral phosphine–phosphite ligands with fluorous ponytails [30].

We will describe here, firstly, the general routes used to synthesize these new phosphites and, secondly, the behavior of catalysts generated in situ from these phosphites and Rh(acac)(CO)₂. The results obtained with fluorous ponytailed triarylphosphines will not be discussed.

10.10.2 Synthesis

Scheme 10.10-1 summarizes the fluorous phosphites synthesized and tested in hydroformylation under fluorous biphasic conditions. The first approach developed to synthesize fluorous phosphites consists of attaching one perfluoroalkyl group directly onto the aromatic ring (phosphites 1 to 4). These compounds were prepared in 20–66% overall yield in two steps. The first step involves a copper mediated coupling reaction between halophenol derivatives and 1-iodoperfluoroalkane [40–42], and the second step is the reaction of the corresponding phenol with phosphorus chloride. The partition coefficients (pKₐ) of the 2b and 3b phosphites in a 1-decene/C₆F₁₃/H (50:50, v/v) mixture were determined at room temperature and were found to be 2.7/97.3 for both phosphites. The above two step synthetic sequence was also successfully used to synthesize phosphites bearing two fluorous ponytails
per ring (phosphites 5 and 6) [43]. As expected, it was found that phosphites 5 and 6 are more fluorophilic than ligands 1–4 [pKₐ of 6 = 0.9/99.1; 1-decene/C₈F₁₇H (50:50); rt].

In order to minimize the strong electron withdrawing effect of the perfluoroalkyl group, the synthesis of fluoruous analogs of P(OPh)₃ where aromatic rings are separated from the perfluoroalkyl groups by two methylene groups has also been performed (phosphites 7 and 8) [23, 27]. The route developed for the synthesis of these phosphites was based on the reaction of Grignard reagents derived from monobromoanisoles with 1H,1H,2H,2H-perfluorodecanyl iodide in the presence of copper catalysts, followed by cleavage of the methoxy group by BBr₃ and reaction of the corresponding phenol with PCl₃. Using this route, phosphites 7 and 8 were easily obtained with overall isolated yields of 35–45%. Owing to the presence of methylene groups, their partition coefficients [pK₂ₐ of 7 and 8 = 5/95; 1-decene/C₈F₁₇ (50:50); rt] were logically lower than those found for phosphites 2b or 3b. The synthesis of phosphite 9 by applying the above method was more tedious (overall isolated yield of 3%). Although phosphite 9 contains insulating methylene groups, its solubility was similar to that of 5 [pKₐ of 9 = 1/99; 1-decene/C₈F₁₇H (50:50); rt], suggesting that this phosphite is also a good candidate for fluoruous biphasic hydroformylation reaction. Although their use in rhodium catalyzed hydroformylation has not been reported to date, it must be pointed out that Gladysz et al. have recently described a more convenient synthesis of a highly fluorocarbon-soluble phosphite of formula P[OC₆H₃(CH₂)₃C₈F₁₇]₃ [overall isolated yield of 60% – pKₐ of this phosphite = 8/92; toluene/CF₃C₆F₁₁ (50:50); rt] [44].

The synthesis of fluoruous analogs of BINAPHOS was initially reported by Leitner et al. [11], but the first use as a ligand in hydroformylation under fluoruous biphasic conditions was described by Ojima et al. in 2001 [30]. In contrast with Leitner’s approach which allows the introduction of a (1H,1H,2H,2H-perfluorohexyl) group at the meta-position of the diphenylphosphinyl moiety, Ojima et al. chose to substitute the peripheral naphthyl moieties with 1H,1H,2H,2H,3H,3H-perfluorononyl groups (overall isolated yield 30% – ligand 10). Although the fluorine content of ligand 10 was low, the authors reported that 10 was very soluble in perfluorotoluene. However, it was found that this ligand was preferentially soluble in toluene over perfluoromethylcyclohexane, which will clearly prevent an efficient recovery of the catalyst.

10.10.3 Hydroformylation Under Fluorous Biphasic Conditions

10.10.3.1 Activity and Selectivity of Catalysts

10.10.3.1.1 Phosphites Without Spacer Groups Phosphites 1 to 6 induce high activity in hydroformylation of terminal alkenes in comparison with the classical ligands PPh₃ and P(OPh)₃ (Table 10.10-1). Nevertheless, considerable differences in activity and selectivity exist according to the nature, the position and the number of substituents on the aromatic ring of the phosphite. For instance, bulky ortho-substituted phosphites lead to catalytic systems that are much more active than those resulting from their meta- or para-counterparts. However, these ortho-phosphites give lower l/b ratios. Indeed, the l/b ratios are found to be
between 2 and 3, i.e., greatly inferior to those observed with the meta- and para-phosphites (ca. 5–8) and slightly inferior or similar to those obtained with ligands PPh$_3$ or P(OPh)$_3$.

Typically the reactivity decreases with the size of the substrate and, more unexpectedly, the $l/b$ ratio and aldehyde selectivity vary in the same way. Interestingly, internal alkenes are also hydroformylated with significant activity with these catalytic systems. Another interesting feature of the process is that better reaction rates and $l/b$ ratios are obtained when the reaction is carried out in the absence of an organic solvent.

10.10.3.1.2 Phosphites With Spacer Groups

This class of phosphites showed little difference compared with phosphites 1–6 (see Table 10.10-2). Indeed, the ortho-substituted phos-
phites 7 and 9 differ from the para-substituted 8 by much higher activities (TOF > 10 000 versus 3900 h⁻¹, respectively), a lower \( l/b \) ratio (2 versus 3.5) and a lower aldehyde selectivity. The main difference lies in the fact that the \( l/b \) ratio with the para-substituted phosphite 8 is much lower than that obtained with phosphites 2 or 3 and close to that obtained with P(OPh)₃.

Experiments performed with different fluorous solvents proved that the nature of the fluorous phase has practically no effect on the \( l/b \) ratio or on the aldehyde selectivity. On the other hand, this factor greatly influences the activity since the TOF dropped from 3900 h⁻¹ when using \( ^{1}H \)-perfluorooctane to 3800, 2500 and 2300 h⁻¹ with perfluoromethylcyclohexane (PFMC), perfluoromethyldecaline (PFMD) and perfluoroalkylcyclohexene (PFPP), respectively. These observations are explained by the fact that at the reaction temperature (80 °C), PFMD and PFPP are not totally miscible with 1-decene, in contrast to the 1-decene–C₈F₁₇H and 1-decene–PFMC combinations [24].

Other heavy terminal olefins behave similarly to 1-decene (Table 10.10-2) giving, for example, with phosphite 8, an \( l/b \) ratio of about 3.0 and an aldehyde selectivity of 95%. However, the activity drops markedly on going from 1-decene to 1-dodecene, presumably again due to its partial solubility with the fluorous solvent C₈F₁₇H.

### Fluous Analog of BINAPHOS

The asymmetric hydroformylation of styrene catalyzed by the (S,R)-10/Rh complex was briefly investigated in various fluorous solvents with or without toluene. The nature of the solvent has no significant effect on the catalytic

### Table 10.10-2. Hydroformylation of higher alkenes under fluorous biphasic conditions with fluorous phosphites with spacer groups [24]

<table>
<thead>
<tr>
<th>Phosphite</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Timea (min)</th>
<th>TOFb (h⁻¹)</th>
<th>l/b</th>
<th>Aldehyde selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1-decene</td>
<td>C₈F₁₇H</td>
<td>15</td>
<td>10000</td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>1-decene</td>
<td>C₈F₁₇H</td>
<td>30</td>
<td>3900</td>
<td>3.5</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>1-decene</td>
<td>C₈F₁₇H</td>
<td>12</td>
<td>11000</td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>1-decene</td>
<td>C₈F₁₇H/Tol.</td>
<td>60</td>
<td>3500</td>
<td>3.0</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>1-decene</td>
<td>PFMC</td>
<td>60</td>
<td>3800</td>
<td>3.0</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>1-decene</td>
<td>PFMD</td>
<td>90</td>
<td>2500</td>
<td>3.3</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1-decene</td>
<td>PFPP</td>
<td>90</td>
<td>2300</td>
<td>3.6</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1-octene</td>
<td>C₈F₁₇H/Tol.</td>
<td>60</td>
<td>3600</td>
<td>3.0</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1-dodecene</td>
<td>C₈F₁₇H/Tol.</td>
<td>60</td>
<td>2600</td>
<td>3.0</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>2-dodecene</td>
<td>C₈F₁₇H/Tol.</td>
<td>90</td>
<td>1200</td>
<td>–</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>4-dodecene</td>
<td>C₈F₁₇H/Tol.</td>
<td>150</td>
<td>440</td>
<td>–</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>cyclolhexene</td>
<td>C₈F₁₇H/Tol.</td>
<td>–</td>
<td>45</td>
<td>–</td>
<td>100</td>
</tr>
</tbody>
</table>

Conditions: [Rh(acac)(CO)₂] (10 mg, 0.039 mmol), phosphite (0.194 mmol), alkene (77.4 mmol), solvent (15 cm³: pure fluorous solvent or 10 cm³ C₈F₁₇H and 10 cm³ toluene), undecane (1.21 g), 80 °C, 40 bar CO/H₂ (1:1).

a Time required to reach 100% conversion. b TOF = initial turn over frequency: moles of alkene converted per mole Rh per hour.
activity of the catalyst. While the regioselectivity was slightly higher than that observed in an organic solvent (l/b ratio: 6/94 versus 12/88), the enantioselectivity was lower (87 versus 94%) and an apparent racemization was observed in the course of the reaction [30].

10.10.3.2 Mechanistic Aspect

The results obtained with ortho-substituted phosphites differ from those of meta- or para-counterparts through a remarkably higher initial rate under the same conditions. At the same time, they lead to a more modest l/b ratio and aldehyde selectivity. This difference is probably related to the fact that with the former bulky phosphites, only one phosphite coordinates to the Rh center to give the active species HRhLf(CO)\(_3\) (Lf = fluorous phosphite) [45]. In contrast with the latter phosphites that are less sterically demanding, two phosphites are bonded to rhodium [HRhLf\(_2\)(CO)\(_2\)] as in the classical triphenyl phosphine modified catalyst. Complex HRhLf(CO)\(_3\) is more prone to CO dissociation than HRhLf\(_2\)(CO)\(_2\), resulting in a much higher reaction rate. Owing to the large space available with the HRhLf(CO)\(_3\) system in comparison with HRhLf\(_2\)(CO)\(_2\), the reactions giving the branched aldehyde as well as the \(\beta\)-H elimination proceed with relative ease, resulting in modest linearity and aldehyde selectivity.

An other important finding is the high l/b ratio observed with meta- and para-phosphites 2 and 3. Electron withdrawing groups attached to the aryl rings of these phosphites afford less basic ligands. Consequently, the electron density on complex HRhLf\(_2\)(CO)\(_2\) decreases, which promotes the olefin insertion on its terminal carbon, giving a linear alkylrhodium intermediate leading to the linear aldehyde. On the other hand, a decrease in the electronic density on the metal also favors the CO dissociation and hence the formation of low coordinated alkylrhodium species, which induce easier \(\beta\)-H elimination and thus olefin isomerization [46].

In the case of phosphites 5 and 6, the combination of the steric and electron withdrawing effects significantly promotes the \(\beta\)-H elimination, leading to a very low aldehyde selectivity.

10.10.3.3 Stability of the Catalyst and Reuse

Investigations on the recovery and reuse of the catalytic system have been made with phosphites 1b, 2b and 6 on the one hand and with phosphites 7, 8 and 9 on the other.

Figure 10.10-1 shows the evolution of the conversion for four reaction cycles with phosphites 1b, 2b and 6. With each phosphite, the activity decreased after each reuse but whereas the decrease was moderate in the case of ortho-substituted phosphites 1b and 6, in the case of 2b, the activity fell dramatically after the second cycle and practically no activity was observed during the fourth run. Concomitantly, the l/b ratio and the aldehyde selectivity decreased after the first run with phosphite 2b whilst they remained practically unchanged with 1b and 6.

In the case of phosphites with spacer groups (Figure 10.10-2), the activity was maintained or even slightly increased (with phosphite 8) during the three first cycles. On the other hand, the conversion dramatically dropped during the course of the fourth cycle with ortho-substituted phosphate 7.

The decrease in activity is more significant than could be expected according to the high partition coefficient of the phosphates, and the variations of the l/b ratio observed during the recovery experiments have been interpreted by considering that the phosphites are not stable
in the reaction medium. Various methods of decomposition could be envisaged for the fluorous phosphites. The main modes include hydrolysis by water produced by aldehyde condensation, nucleophilic attack on the aldehyde and oxidative cyclization with aldehydes [47, 48].

Aldol condensation of aldehydes could give traces of water that could react with phosphate, but no evidence of formation of the expected aldol products was found by GC-MS [25].

To estimate the extent of the other modes of decomposition, the stability of various fluorous phosphites has been studied under hydroformylation reaction conditions. A sample of each phosphite was heated in a mixture of 1-decene/C₈F₁₇H (1/1, v/v) or in a mixture of 1-
decene/undecanal/C8F17H (1/1/1, v/v/v). 31P NMR analyses of the fluorous phase after 1 h showed that in the absence of aldehyde, all phosphites remained unchanged. In contrast, in the presence of undecanal, a large portion of the para- and meta-substituted phosphites 2b and 8 were converted into oxidation products (30% and 50% of the decomposition, respectively) whereas bulky ortho-substituted phosphites 1b, 7 and 9 appeared more stable (3%, 20% and 20% of the decomposition, respectively) [24].

The decrease in the ligand concentration due to the attack of the phosphites by aldehydes explains the change in l[b] ratios and the aldehyde selectivity observed with some phosphites. Nevertheless, owing to the good stability in particular of phosphites 1b and 6, other parameters can be taken into account to explain the decrease in activity observed with these ligands [23, 24].

10.10.4
Conclusion

Although the rhodium complexes associated with phosphites can catalyze the hydroformylation of higher olefins in a fluorocarbon/hydrocarbon biphasic medium, the stability and recovery studies indicates undoubtedly that “simple” fluorinated analogs of P(OPh)3 are not stable in hydroformylation conditions. If the objective is to provide an industrial process for hydroformylation of higher olefins, the development of more fluorous-soluble phosphites. The development of more fluorosoluble and stable phosphazines should be envisaged.

References

Fluorous Nitrogen Ligands for Oxidation Reactions

Gianluca Pozzi and Silvio Quici

10.11.1 Introduction

Selective oxidation reactions catalyzed by transition-metal complexes of organic ligands under homogeneous conditions have been the subject of intense investigations throughout the last three decades [1]. A wealth of theoretical and experimental data is now available and some impressive results have been achieved, as in the case of titanium-mediated asymmetric epoxidation of allylic alcohols [2]. Nevertheless, two major issues still prevent the widespread application of most of these homogeneous catalytic systems: (a) considerable synthetic efforts are often required for the preparation of suitable organic ligands and (b) the corresponding catalytically active complexes suffer from limited stability in the oxidative environment. Immobilization onto organic polymers or inorganic supports represents the most obvious and explored strategy for increasing the lifetime of homogeneous oxidation catalysts and possibly recycling them after completion of the reaction [3]. In addition, water-soluble organometallic oxidation catalysts have been tested under aqueous/organic biphasic conditions [4, 5], and evidence for some positive effects related to the use of alternative reaction media such as ionic liquids [6], supercritical CO$_2$ or CO$_2$-expanded solvents [7] has recently been presented.

Fluorous biphasic (FB) techniques are particularly suited to oxidation reactions, where the substrates are converted into products of greater polarity and these are then very easily expelled from the fluorous phase [8]. This fact, together with the thermal and chemical inertness of perfluorocarbons and the possible improvement of the catalyst stability due to its confinement in the fluorous phase, made catalytic oxidation reactions one of the first and most appealing targets for fluorous chemistry [9]. In this short chapter, complementary to the contribution by J.-M. Vincent et al. (see Chapter 10.12), attempts at using the FB approach in the case of oxidation reactions catalyzed by metal complexes of bi- and polydentate nitrogen ligands will be highlighted, with emphasis on the epoxidation of alkenes, the aerobic oxidation of alcohols to carbonyl compounds and the oxidation of organic sulfides to sulfoxides and/or sulfones. Unfortunately, a direct, fair comparison of the results obtained with those reported using related homogeneous catalysts immobilized onto solids or dissolved in alternative reaction media is seriously hampered by the very different conditions employed (nature of substrates and oxidants, molar ratio of the oxidant/substrate/catalyst, temperature and so forth). Therefore, in this limited space the pros and cons of the different approaches will not be discussed.

10.11.2 Oxidation of Alkenes

Metal complexes of fluorous tetraarylporphyrins 1–5 (Scheme 10.11-1) have been used as catalysts in the epoxidation of alkenes under FB [9] or more traditional conditions.
depending on their affinity for perfluorocarbons. Free base porphyrins 1–5 were readily metalated with transition metal cations under standard conditions normally employed for their non-fluorous counterparts. In particular, porphyrins 1–4 were metalated with Mn(OAc)₂·4H₂O in boiling DMF to give their respective MnⅢ complexes Mn-1–Mn-4 [10], whereas the perfluorocarbon-soluble porphyrin 5 was similarly converted into the CoⅡ complex Co-5 by treatment with Co(OAc)₂·4H₂O [9].

Complexes Mn-1–Mn-4 (% F < 60%) were investigated under aqueous/organic biphasic conditions by using NaOCl or 30% H₂O₂ as oxygen donors [10]. Cyclooctene and 1-dodecene were used as models of reactive and poorly reactive alkenes, respectively, whereas the robust complex [MnⅢ-[5,10,15,20-tetrakis-(2,6-dichlorophenyl)porphyrin]]chloride (Mn-6) was used as a reference catalyst (Table 10.11-1). Computational studies taking into account electronic effects, indicated that the introduction of Rf substituents on the meso-phenyl rings should improve the ligand stability under oxidizing conditions [11]. The experimental results did not confirm this hypothesis: Mn-1–Mn-4 underwent extensive decomposition and only poor yields in epoxide were obtained. Apparently, factors not considered in computational studies, such as solvation effects and the steric protection provided by the bulky chlorine atoms in the 2,6-positions of the meso-aryl rings, prevailed in determining the catalytic activity. Nevertheless, the introduction of Rf substituents coupled with steric protection had a definite positive effect on the course of the epoxidation of terminal alkenes catalyzed by Mn-4, which gave consistently higher epoxide yields than the reference catalyst Mn-6. This effect was particularly marked in reactions carried out in CH₂Cl₂ as the solvent and using aqueous NaOCl as the oxygen donor [10].

The perfluorocarbon-soluble complex Co-5 (% F = 65%) proved to be an efficient catalyst for the FB epoxidation of alkenes with molecular oxygen and 2-methylpropanal as the reducing agent (Table 10.11-2) [9]. Reactions were carried out at room temperature under O₂.
at atmospheric pressure, by adding a solution of the catalyst in perfluorohexane to a solution of the substrate in CH$_3$CN containing an excess of 2-methylpropanal and vigorously stirring the resulting biphasic mixture. The epoxide yields varied from 95% for cyclic substrates to 52% for terminal alkenes, and the fluorous phase containing the catalyst could be easily separated and reused at least three times in the case of the oxidation of cyclooctene. Rather interestingly, the FB approach allowed the use of a much higher substrate/catalyst ratio (1000/1) than that reported for the oxidation of (other) alkenes with O$_2$/aldehyde catalyzed by cobalt complexes of standard tetraarylporphyrins (20/1) \[12\]. Moreover, epoxide yields were higher than those obtained in reactions catalyzed by Mn-4 under optimized aqueous/organic conditions, except for 1-dodecene (entry 2, Table 10.11-2, versus entry 10, Table 10.11-1).

**Tab. 10.11-1.** Catalytic epoxidation of alkenes by aqueous NaOCl at pH = 10$^a$

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Selectivity$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn-6</td>
<td>cyclooctene$^c$</td>
<td>3</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>Mn-1</td>
<td>cyclooctene$^c$</td>
<td>1</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>Mn-2</td>
<td>cyclooctene$^c$</td>
<td>1</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Mn-3</td>
<td>cyclooctene$^c$</td>
<td>3</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>Mn-4</td>
<td>cyclooctene$^c$</td>
<td>3</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>Mn-6</td>
<td>1-dodecene</td>
<td>4</td>
<td>33</td>
<td>69</td>
</tr>
<tr>
<td>Mn-6</td>
<td>1-decene</td>
<td>3</td>
<td>54</td>
<td>80</td>
</tr>
<tr>
<td>Mn-6</td>
<td>hexadec-1-ene</td>
<td>3</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Mn-4</td>
<td>1-dodecene</td>
<td>3</td>
<td>67</td>
<td>96</td>
</tr>
<tr>
<td>Mn-4</td>
<td>1-decene</td>
<td>3</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>Mn-4</td>
<td>hexadec-1-ene</td>
<td>3</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Mn-4</td>
<td>2-methylundec-1-ene</td>
<td>3</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Mn-4</td>
<td>1-methycyclohexene</td>
<td>4</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Mn-4</td>
<td>norbornene</td>
<td>4</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: $T = 0$ °C; solvent = CH$_2$Cl$_2$; molar ratio alkene/oxidant/catalyst = 1/2/0.001. $^b$ Selectivity = (moles of epoxide)/(moles of substrate converted). $^c$ Solvent = AcOEt.

at atmospheric pressure, by adding a solution of the catalyst in perfluorohexane to a solution of the substrate in CH$_3$CN containing an excess of 2-methylpropanal and vigorously stirring the resulting biphasic mixture. The epoxide yields varied from 95% for cyclic substrates to 52% for terminal alkenes, and the fluorous phase containing the catalyst could be easily separated and reused at least three times in the case of the oxidation of cyclooctene. Rather interestingly, the FB approach allowed the use of a much higher substrate/catalyst ratio (1000/1) than that reported for the oxidation of (other) alkenes with O$_2$/aldehyde catalyzed by cobalt complexes of standard tetraarylporphyrins (20/1) \[12\]. Moreover, epoxide yields were higher than those obtained in reactions catalyzed by Mn-4 under optimized aqueous/organic conditions, except for 1-dodecene (entry 2, Table 10.11-2, versus entry 10, Table 10.11-1).

**Tab. 10.11-2.** FB catalytic epoxidation of alkenes with O$_2$/2-methylpropanal catalyzed by Co-5$^a$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Selectivity$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclooctene</td>
<td>3</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>1-Dodecene$^c$</td>
<td>14</td>
<td>52</td>
<td>87</td>
</tr>
<tr>
<td>2-Methylundec-1-ene</td>
<td>5</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>1-Methycyclohexene</td>
<td>4</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Norbornene</td>
<td>5</td>
<td>90</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ In CH$_3$CN/perfluorooctane 1/1 v/v. Reaction conditions: $T = 25$ °C; molar ratio alkene/aldehyde/catalyst = 1/2/0.001. $^b$ Selectivity = (moles of epoxide)/(moles of substrate converted). $^c$ Using 3-methylbutanal instead of 2-methylpropanal.
Tetraazamacrocycle 7 (Scheme 10.11-2) was developed as an alternative to the synthetically demanding porphyrin ligands [13]. At the same time, the triazamacrocycle 8 (Scheme 10.11-2) bearing three \( R_f \) substituents was independently introduced by Fish and coworkers [14]. Metal complexes of these ligands provided new FB catalysts for the oxidative functionalization of hydrocarbons in the presence of \( t\)-BuOOH and \( O_2 \). In particular, oxidation of cyclohexene afforded mixtures of 2-cyclohexen-1-one and 2-cyclohexen-1-ol.

Perfluoroalkylated bipyridines 9–11 (Scheme 10.11-3) are readily soluble in some organic solvents, for instance \( CH_2Cl_2 \), and were tested in the ruthenium-catalyzed epoxidation of trans-stilbene with \( NaIO_4 \) under aqueous/organic biphasic conditions [15], as previously described for 2,2'-bipyridine [16]. In the presence of this ligand, oxidative cleavage of the carbon–carbon double bond strongly affected epoxidation yields at room temperature. The use of perfluoro bipyridines 9–11 reduced the incidence of the side reaction and trans-stilbene epoxide was obtained in good yields (70–87%) [15]. Since the fluorous affinity of the ruthenium catalysts generated \textit{in situ} from 9–11 was found to be higher than that of the free ligands, trans-stilbene epoxidation was also studied in an aqueous/organic/fluorous triphasic system at 0 °C. Higher epoxide yields (92–96%) were obtained and the fluorous phase could be reused without addition of RuCl\(_3\) for at least three further runs before the epoxide yields decreased significantly.
Oxidation of Alcohols

Primary and benzylic alcohols were oxidized smoothly to the corresponding aldehydes by \( \text{O}_2 \) in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO, 3.5%) and a \( \text{Cu}^1 \) complex (2%) generated \textit{in situ} from \( \text{CuBr}_2 \cdot \text{Me}_2\text{S} \) and bipyridine. Reactions were carried out at 90 °C in a biphasic \( \text{C}_8\text{F}_{17}\text{Br} / \text{C}_6\text{H}_5\text{Cl} \) system affording analytically pure aldehydes in 73–96% isolated yield. The recyclability of the catalyst was demonstrated by the case of the oxidation of 4-nitrobenzyl alcohol to give 4-nitrobenzaldehyde: the fluorous phase was reused eight times with a slight decrease in aldehyde yield (from 93% to 86%) and no apparent decrease in reaction rate. Secondary alcohols also underwent oxidation to the corresponding ketones under fluorous biphasic conditions. Reaction rates and yields were comparable to those observed with primary alcohols in the case of benzylic, allylic and cyclic substrates, but in general secondary alcohols were less easily oxidized and higher amounts of TEMPO (up to 10%) were required in order to achieve fast reactions. Sterically hindered secondary alcohols were particularly difficult to oxidize and incomplete conversions were observed even using 10% TEMPO. This allowed the selective oxidation of the less sterically hindered isomer in \( \text{cis} - \text{trans} \) mixtures of 2-, 3- and 4-substituted cyclohexanols and the easy separation of the unreacted isomer by column chromatography.

Oxidation of Organic Sulfides

The first example of FB oxidation of sulfides dates back to 1995: dibenzothiophene and diphenylsulfide gave the corresponding sulfoxides in low yields (1.4% and 10%, respectively) upon treatment with \( \text{O}_2 \) at 100 °C in the presence of a not fully characterized perfluorocarbon-soluble iron-phthalocyanine.

Following this earlier report, \( \text{Co}^{\text{II}} \)-tetraarylporphyrin \( \text{Co-5} \) and \( \text{Co}^{\text{II}} \)-phthalocyanine \( \text{Co-12} \) (Scheme 10.11-4) were tested as catalysts for the FB oxidation of methyl phenyl sulfide and \( \text{para} \)-substituted aryl methyl sulfides with \( \text{O}_2 \) and a sacrificial aldehyde (Table 10.11-3).

Turnover numbers comparable to those obtained in similar FB oxidations catalyzed by nickel complexes of fluorinated 1,3-diketones were observed. Sulfoxides were usually obtained in good yields (50–100%) and selectivities (>90%) together with variable amounts of aldehydes and ketones.
of sulfones. The latter were the major products both in the oxidation of \( p \)-nitrophenyl methyl sulfide and \( p \)-methoxyphenyl methyl sulfide catalyzed by Co-5. The absence of any definite relationship between the electronic properties of the para-substituents and selectivity ruled out the hypothesis of a heterolytic reaction mechanism involving the formation of high-valent oxometal species. Moreover, the addition of a free-radical scavenger was found to inhibit the oxidation process, thus suggesting that acyl and peroxyacyl radicals generated by the action of the cobalt complexes on the sacrificial aldehyde were the true oxidizing agents. As a consequence of the peculiar reaction environment, both Co-5 and Co-12 were progressively bleached and the effectiveness of their recycling was limited.

Formation of high-valent oxometal species from (salen)metal complexes and iodosyl-benzene (PhIO) and the mechanism of the oxygen transfer from these species to alkyl aryl sulfides have been investigated in detail [22]. Fluorous salen ligands 13 and 14 (Scheme 10.11-5) were synthesized and the corresponding (salen)manganese(III) complexes Mn-13 and Mn-14 were evaluated in the oxidation of alkyl aryl sulfides with PhIO under homogeneous and FB conditions, respectively [23].

Both complexes were able to catalyze the oxidation of \( p \)-substituted methyl phenyl sulfides at a substrate/catalyst molar ratio = 100, with good sulfoxide selectivities (\( \geq 90\% \)). It should

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Conversion (%)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sulfoxide (%)</td>
</tr>
<tr>
<td>Co-5</td>
<td>PhSCH(_3)</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Co-5</td>
<td>( p )-CH(_3)OPhSCH(_3)</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Co-5</td>
<td>( p )-CH(_3)PhSCH(_3)</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Co-5</td>
<td>( p )-ClPhSCH(_3)</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>Co-5</td>
<td>( p )-FPhSCH(_3)</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Co-5</td>
<td>( p )-NO(_2)PhSCH(_3)</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Co-12</td>
<td>PhSCH(_3)</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>Co-12</td>
<td>( p )-CH(_3)OPhSCH(_3)</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>Co-12</td>
<td>( p )-CH(_3)PhSCH(_3)</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Co-12</td>
<td>( p )-ClPhSCH(_3)</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>Co-12</td>
<td>( p )-FPhSCH(_3)</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>Co-12</td>
<td>( p )-NO(_2)PhSCH(_3)</td>
<td>100</td>
<td>15</td>
</tr>
</tbody>
</table>

*In CH\(_2\)Cl\(_2\)/perfluorooctane 1/1 v/v. Reaction conditions: \( T = 20 \) °C; \( t = 4 \) h; molar ratio sulfide/aldehyde/catalyst = 1/1/0.001.
be noted that FB reactions catalyzed by Mn-14 consistently afforded higher sulfoxide yields than homogeneous reactions catalyzed by Mn-13 (Table 10.11-4). Moreover, three consecutive recyclings of the fluororous layer were performed with no appreciable loss of catalytic activity and selectivity.

10.11.5 Dye-Sensitized Photooxidation Reactions

Oxidation of unsaturated compounds with singlet oxygen ($^1\text{O}_2$) has been extensively studied because of its considerable synthetic interest [24]. Dye-sensitized photooxidation of triplet oxygen is a practical method for generation of the labile $^1\text{O}_2$ reagent on the laboratory scale. However, the presence of the dye and/or of its decomposition derivatives in the final reaction mixture can complicate the purification of the desired organic products. Another point to be considered is the choice of solvent, which must readily dissolve $^1\text{O}_2$, ensure a relatively long lifetime to the generated $^1\text{O}_2$ and be inert to this reagent. Perfluorocarbons fulfill all of these requirements and have been used as alternative media for the photooxidation of alkenes to give hydroperoxides, in the presence of tetraphenylporphyrin (TPP) dissolved in pyridine as a sensitizer [25]. The biphasic mixture was irradiated while maintaining a constant supply of $\text{O}_2$. After completion of the reaction the two layers were separated to give an organic phase containing the hydroperoxide (plus TPP and its decomposition products) and a fluororous phase free from organic compounds.

The issues of sensitizer degradation and purification of the oxidation products were taken into account by DiMaggio et al. who used the electron-deficient fluororous porphyrin 15 (Scheme 10.11-6) as a sensitizer in the photooxidation of cyclohexene and allylic alcohols in CH$_3$CN/perfluorohexanes [26].

In a CH$_4$ solution, porphyrin 15 showed increased chemical stability toward $^1\text{O}_2$ and hydroperoxides with respect to TPP. However, physical segregation into the fluororous phase was found to be the most important factor in reducing the incidence of degradation processes. In addition, the FB approach ensured the easy separation of the hydroperoxides from

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Conversion (%)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sulfoxide (%)</td>
<td>Sulfone (%)</td>
</tr>
<tr>
<td>Mn-13$^b$</td>
<td>PhSCH$_3$</td>
<td>70</td>
<td>91</td>
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<td>Mn-13$^b$</td>
<td>p-BrPhSCH$_3$</td>
<td>59</td>
<td>91</td>
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<tr>
<td>Mn-13$^b$</td>
<td>p-NO$_2$PhSCH$_3$</td>
<td>64</td>
<td>88</td>
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<td>Mn-14$^c$</td>
<td>PhSCH$_3$</td>
<td>95</td>
<td>95</td>
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<tr>
<td>Mn-14$^c$</td>
<td>p-BrPhSCH$_3$</td>
<td>87</td>
<td>96</td>
</tr>
<tr>
<td>Mn-14$^c$</td>
<td>p-NO$_2$PhSCH$_3$</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: $T = 25^\circ C$; $t = 5$ h; molar ratio sulfide/oxidant/catalyst = 1/1/0.01. $^b$ Homogeneous conditions (CH$_2$Cl$_2$/CH$_3$CN 1/1 v/v). $^c$ FB conditions (CH$_3$CN/perfluorooctane 1/1 v/v).
at the end of the reaction. The fluorous layer containing the sensitizer (57–94% of the starting material depending on reaction conditions) could be reused without further treatments.

10.11.6

Outlook

Most catalytic FB oxidation reactions reported so far are based on the use of metal complexes of perfluoroalkylated nitrogen ligands. The inherent stability and recyclability problems of such oxidation catalysts have yet to be fully solved by the FB approach (or any other immobilization technique or alternative reaction media for that matter). However, some advantages over standard homogeneous conditions, especially the ease of separation of the catalysts from reaction products, have been proved. More importantly, fundamental information on the behavior of fluorous compounds has been obtained through the design, synthesis and use of perfluoroalkylated nitrogen ligands.

Catalytic systems based on metal-free organic molecules (organocatalysts) have been actively investigated in the last few years and their use in organic synthesis is likely to increase in the future. Indeed, organocatalysts are often easier to prepare, less expensive and more stable compared with organometallic complexes performing the same catalytic function. Development of fluorous nitrogen-based organocatalysts for selective oxidative processes, including asymmetric reactions, could eliminate some drawbacks associated with the use of fluorous organometallic catalysts, including leaching of metals into the organic phase. As pointed out by Dalko and Moisan, a large array of ligands originally designed for metal-mediated catalytic reactions are among the most effective organocatalysts [27]. Some of the fluorous ligands discussed here could thus find new application in metal-free oxidation reactions. On the other hand, the basic knowledge acquired while developing those ligands will certainly be helpful for the efficient design and synthesis of new fluorous organocatalysts such as imines, iminium salts, (poly)aminoacids and \( \alpha \)-amidoketones.

References

Synthesis of Fluorous Nitrogen Ligands and Their Metal Complexes as Precatalysts for Applications in Alkane, Alkene, and Alcohol Oxidation, and Atom Transfer Radical Reactions

Jean-Marc Vincent, Dominique Lastécouères, Maria Contel, Mariano Laguna, and Richard H. Fish

10.12 Synthesis of Fluorous Nitrogen Ligands and Their Metal Complexes as Precatalysts for Applications in Alkane, Alkene, and Alcohol Oxidation, and Atom Transfer Radical Reactions

Introduction

Since the seminal paper in 1994 by Horváth and Rábai that introduced the fluoruous biphasic catalysis concept (FBC), as first applied to rhodium(I) catalyzed hydroformylation of...
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Introduction

Since the seminal paper in 1994 by Horváth and Rábai that introduced the fluoruous biphasic catalysis concept (FBC), as first applied to rhodium(I) catalyzed hydroformylation of...
alkenes [1], numerous examples of this methodology for many classical organic reactions have been demonstrated [2]. Unlike the more classical aqueous/hydrocarbon biphasic systems, water sensitive reactants can also be employed, with the solubility of organic substrates being higher in the perfluorocarbons than in water; therefore, more favorable reaction kinetics could be expected. Moreover, because of the unique thermomorphic properties of the perfluorocarbon solvents, it is possible under FBC reaction conditions, by judiciously choosing the solvent system, to obtain a homogeneous monophasic solution when elevating the temperature of the reaction mixture, while reformation of the biphasic system occurs at room temperature. In 1996, we initiated an FBC program at the Lawrence Berkeley National Laboratory, with the objective of developing new catalytic systems for alkane/alkene oxidation chemistry. Thus, the FBC process appeared as a very attractive procedure for alkane and alkene functionalization reactions, not only for the ability to recycle the catalyst, but also because of the chemical inertness of the fluorocarbon solvents, and their unique characteristic of solubilizing O2 in large concentrations.

In this chapter, we will scrutinize a number of fluoroponytailed nitrogen ligand structures and discuss their synthesis for use in our FBC reactions as ligands for precatalyst, fluoroponytailed metal complexes. In other aspects of our FBC studies, we will describe the results obtained in the two main fields of application for these fluoroponytailed, ligated metal complexes as precatalysts, which encompass alkane, alkene, and alcohol oxidations, as well as atom transfer radical reactions. In addition, we will place our results in perspective relative to those of other colleagues’ contributions to the FBC field, in these same areas of research.

10.12.2 Fluorous Nitrogen Ligand Synthesis

Nitrogen ligands are widely used in coordination chemistry, particularly in the field of oxidation catalysis [3]. Relatively simple synthetic procedures are available for the introduction of the fluoroponytails, making the nitrogen ligands valuable targets for the development of fluorous catalysis with transition metal complexes. Representative examples of fluorous nitrogen ligands that have been prepared and, for most of them, applied to fluorous catalysis chemistry, are presented in Scheme 10.12-1.

One of the most successful synthetic strategies used to obtain fluorous nitrogen ligands was the direct alkylation of secondary amines (R2NH) with perfluoroalkyl iodide derivatives, such as RF8(CH2)3I (RF8 = C8F17) [4, 5]. The three methylene spacer was necessary not only to insulate the nitrogen ligating atom from the strong electron withdrawing effect of the perfluoroalkyl chain, but also to avoid a facile elimination reaction of HI, which predominantly occurs during the alkylation step when a two methylene spacer was used. Ligands 1, 2, and 3 were synthesized in fair to good yields (50, 60 and 40%, respectively) by reaction of the corresponding secondary amines with RF8(CH2)3I in DMSO/K2CO3 at 90 °C [4, 5]. Interestingly, amongst the three ligands mentioned, the 1,4,7-triazacyclononane (TACN) derivative, 1, with a fluorine content of 64.2%, was the only ligand found that was soluble in perfluorocarbons at room temperature.

Furthermore, tosylate derivatives have also been shown to be effective alkylation agents. The fluorous peralkylated cyclam, 4, was obtained in 60% yield by refluxing...
RfCH2O(CH2)2OTs in CH3CN/Na2CO3 for 24 h [6]. The tosylate, Rf(CH2)3OTs, was recently used in our group in Bordeaux for the preparation of the fluorous, peralkylated polyamine ligands, 5 and 6 [7]. The alkylation were conducted by refluxing a CH3CN/K2CO3 solution of the diethylenetriamine or tris-aminoethylamine with the tosylate (1.1 equiv per amine group) for 48 h; the ligands 5 and 6 being obtained in 65 and 55% yields, respectively. Interestingly, more recently we have shown that using Rf(CH2)3I, instead of the corresponding tosylate, enables one to not only increase the yield of 5 from 65 to 79%, but also to isolate the ligand as a powder rather than an oil. Moreover, an aromatic nucleophilic substitution on the N-pentafluorophenyl TACN derivatives was used for the preparation of the fluorous TACN, 7 [5]. This reaction proceeds efficiently (yield 80%) by reacting Rf(CH2)3OH in a 50% NaOH/trifluorotoluene mixture at 85°C in the presence of a phase transfer agent. Rather surprisingly, this ligand with three fluoroponytails and a fluorine content of 58.6% was found not to be soluble in perfluorocarbons at room temperature.

Bipyridines are another important class of nitrogen ligands in coordination chemistry and transition metal catalysis. The fluorous bipyridine ligand, 8, was conveniently prepared in 40% yield by reacting the dianion, obtained from 4,4′-dimethyl-2,2′-bipyridine, with Rf(CH2)3I at low temperature (−78°C) [8a]. Recent studies at Zaragoza/Berkeley provided full synthetic details and spectroscopic characterization of ligand 8 [8b]. The fluorine pyridine ligand, 9, was synthesized in moderate yield (26%) by reacting the 3,5-diacylchloride pyridine with the alcohol Rf(CH2)3OH, while the pyridine ligand, 10, was prepared in excellent yield (94%) from pyridine-3-carbaldehyde and Rf(CH2)3OH in the presence of trifluoromethanesulfonic acid [9].
10.12.2.1 Synthesis of Fluorous Soluble Metal Complexes as Precatalysts

In the previous section, we established the parameters necessary to solubilize important nitrogen ligands in fluorocarbon media. In a concomitant manner, important metal complexes that are required as precatalysts for many classical catalytic reactions require special attention with regards to fluorocarbon solubility, simply because of the polar nature of these complexes. Thus, in our experience we found that, in many cases, the counter anion also needed fluoroponytails to ensure fluorocarbon solubility, even if the metal ion was coordinated to a fluorous soluble ligand such as 1 (Scheme 10.12-1). Therefore, we [4, 5] and Pozzi et al. [6] addressed this critical aspect by using fluoroponytailed carboxylate ligands as counter ions for the metal ions of interest [4, 5].

When the above mentioned fluoroponytailed metal carboxylates, such as the complexes 11 [Eq. (1)], were reacted with fluorous soluble ligand 1, either in situ (Mn²⁺ and Co²⁺ complexes in perfluoroheptane) [4, 5], or via isolation and characterization (Cu²⁺ complex, CH₂Cl₂) [8b], to provide precatalysts 12 for alkene, alkane, and alcohol FBC oxidation, the complexes formed were fully fluorocarbon soluble [Eq. (1)].

In another example, the reaction of a Cu¹ complex, [CuCl], with ligand R₈-Th-ACN 1, provided a fully fluorocarbon soluble complex 13 (fully characterized) [8b], without appended fluoroponytails on the Cu¹ metal ion [Eq. (2), isolated from trifluoromethylbenzene]. This appears to be a general phenomena with Cu¹ complexes and fluoroponytailed ligands, and apparently is predicated on their hydrophobic properties, which engender their solubility in hydrophobic solvents, such as fluorocarbons.
10.12.3.1 Alkane and Alkene FBC Oxidation Chemistry

In 1997 we demonstrated unequivocally, possibly for the first time, that this novel FBC approach for separation of the Rf-Mn$^{2+}$ and -Co$^{2+}$ precatalysts from the substrates was indeed viable for oxidation of alkanes and alkenes in the presence of the necessary oxidants, TBHP and O$_2$ gas [4]; shortly after, Pozzi et al. also verified this FBC oxidation chemistry [6]. The Rf-TACN complexes 12 [Eq. (1)] were found to be particularly effective for allylic oxidation of alkenes; the Cu$^{2+}$ analog [Eq. (1)] and the Cu$^1$ complex 13 [Eq. (2)] gave comparable results [8b]. We also provided clear evidence that these FBC oxidation reactions occurred via classical autoxidation mechanisms [4, 5]. The limited scope of the substrates studied also showed that allylic oxidation, for example cyclohexene to cylohexenol and cyclohexenone, was more favorable than alkane functionalization with cyclohexane as the substrate, based on thermodynamic grounds.

10.12.3.2 Alcohol Oxidation Chemistry

The selective oxidation of alcohols to ketones or aldehydes is a very important transformation in organic chemistry. Using the bipyridine ligand, 8 (2 mol%), CuBr-Me$_2$S (2 mol%), and TEMPO (3.5–10 mol%) under O$_2$ (1 atm) in biphasic perfluorooctyl bromide/chlorobenzene at 90 °C, various primary and secondary alcohols (aromatic and aliphatic) were oxidized to the corresponding aldehydes and ketones in good to excellent yields [10, 11]. The stability of the catalyst was found to be excellent, with no observed decrease in yield and reaction rate during the oxidation of 4-nitrobenzyl alcohol to the corresponding aldehyde, after eight reaction cycles. Furthermore, the fluoruous biphasic system consisting of Pd(OAc)$_2$ (5 mol%)/10 (20 mol%), in perfluorodecalin/toluene, under O$_2$ (1 atm) at 80 °C, was another effective catalytic process for the oxidation of primary and secondary alcohols (aliphatic and aromatic) to aldehydes and ketones [9]. Recycling efficiency was also excellent, the yield of isolated acetophenone after five cycles still being 74%, compared with 98% for the first run.

The Zaragoza/Berkeley groups have recently studied the mechanism of the FBC oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde at 90 °C (single phase) with the precatalyst, Rf-TACN-Rf-Cu$^{2+}$ 12 [Eq. (2)], TEMPO, and O$_2$, by using EPR techniques [8b]. The EPR spectra clearly defined a Cu$^{1+}$ to Cu$^1$ redox reaction, and the role of TEMPO and O$_2$ in this selective conversion to aldehyde from alcohol. Precatalyst Rf-TACN-Rf-Cu$^{2+}$ [Eq. (2)] was solubilized in perfluorohexane, and then chlorobenzene, TEMPO, and 4-nitrobenzyl alcohol were added to the reaction mixture. The reaction started at 90 °C in the presence of O$_2$, and after 30 min, followed by cooling to room temperature, an aliquot was removed from the perfluorohexane phase and immediately frozen at 77 K in an EPR tube. The EPR spectrum is shown in Figure 10.12-1 (spectrum a, at LNT). The spectrum shows a narrow central signal at about $g = 2.006$, which could be associated with the TEMPO radical. This was further demonstrated by measuring this radical in perfluorohexane at 77 K, together with a Cu$^{1+}$ signal, with $g\parallel = 2.26(1)$ and $g\perp = 2.06(1)$, $A\parallel = 520(5)$ MHz and $A\perp < 50$ MHz. After 3.5 h, both signals decrease (spectrum b), and after 6 h the signals have decreased further (spectrum c). After 8 h we observed a recovery of the signal corresponding to the Cu$^{1+}$ spe-
cies (spectrum d). What was clear was that the initial Cu II was reduced to the Cu I complex by virtue of a silent EPR spectrum after 3.5 h (Figure 10.12-1, spectrum c), and then was regenerated to the CuII complex (spectrum d). This was in accordance with a mechanism proposed by Semmelhack et al. [12]. After 4 h, a 65% yield of aldehyde had been obtained; however, by leaving the reaction for longer periods of time, an ~100% yield of aldehyde was formed, concomitant with a full recovery of the initial Rf-CuII complex.

10.12.3.3 Atom Transfer Radical Reactions

10.12.3.3.1 Additions Atom transfer radical additions (ATRA) is a particularly useful radical process for the preparation of lactones and lactams through metal-catalyzed cyclization of unsaturated trichloro esters or amides [13]. One of the most efficient catalysts for both ATRA and ATRP reactions is the copper(I)/pentamethyldiethylenetriamine complex [14]. The fluorous polyamino ligands, 5 or 6, associated with copper(I) chloride (1 mol%) and iron powder (10 mol%) catalyzed the intramolecular cyclization of the pent-4-enyl trichloroacetate in almost quantitative yields under FBC conditions [Eq. (3)] [7]. By using a ternary solvent system (perfluoroheptane/trifluorotoluene/1,2-dichloroethane), the reaction was carried out under homogeneous conditions at 80 °C, while phase separation occurred at room temperature enabling facile recycling of the catalyst and recovery of the substrate, with only 1–2% of the copper(I) leaching into the organic phase. Ensuring that no oxygen was introduced during the recycling procedure, the yield of lactone, after the fourth run, was still 91%, making the CuCl/5, and CuCl/6 complexes highly efficient and recoverable catalysts for atom transfer radical reactions.
10.12.3.3.2 Polymerizations Atom transfer radical polymerization (ATRP) is a transition metal mediated living radical polymerization of vinyl monomers that is closely related to ATRA, facilitating the synthesis of well-defined and complex macromolecular architectures. The major limitation of ATRP is that the polymer is usually contaminated by the colored transition metal catalyst, thus requiring purification steps such as column chromatography or precipitation of the polymer. Catalysts grafted onto insoluble supports have been developed to lower the copper content of the final product and for recycling [15]. However, heterogeneous supported catalysts are less efficient than their homogeneous analogs leading to broader polydispersity \( (P_{Di} = 1.4–1.5) \) and lower initiator efficiency. Lower polydispersity and higher recycling efficiency were observed using copper(I) catalysts immobilized on poly(ethylene)-block-poly(ethyleneglycol), a polymer soluble in toluene above 70 °C, but insoluble at room temperature [16]. Using the catalytic system, CuBr/5, and ethyl 2-bromoisobutyrate as the polymerization initiator, Haddleton et al. have shown that living radical polymerization of methyl methacrylate can be carried out very efficiently under FBC conditions [Eq. (4)] [17]. Interestingly, PMMA was also obtained as a colorless solid after separation of the upper hydrocarbon phase and removal of the volatiles. The catalyst was recycled twice with similar results, in terms of kinetics and polydispersity, making this FBC system very attractive for further applications.

10.12.4 Conclusion

In this chapter in this Handbook of Fluorous Chemistry, we have attempted to place our fluorous synthesis of nitrogen ligands and metal complexes that have fluorocarbon solubility, and subsequent applications in alkane, alkene, and alcohol oxidation chemistry, as well as those in ATRA and ATRP, in perspective with FBC contributions from other colleagues. We have also focused on understanding the mechanisms of these FBC reactions, along with developing new FBC applications, to ascertain any similarities or differences in comparison
with their non-fluorous reaction pathways. The major theme in all these FBC studies is still
the separation factor of precatalysts from substrates and products, in comparison with the
non-fluorous solvent equivalent. This separation factor, we believe, will be the seminal char-
acteristic of all FBC contributions in this Handbook of Fluorous Chemistry.

While FBC chemistry has not been fully accepted by the industrial chemistry community,
principally due to economic factors, future directions in a Green Chemistry environment
will provide new opportunities for selective industrial applications, particularly specialty
chemicals, as well as gas-to-liquid technology, where the gases are fluorous soluble, but the
liquid, polar products are not.

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10.13
Enantioselective Catalysis: Biphasic Conditions

Denis Sinou

10.13.1
Introduction

Over the last 20 years there have been very important advances in asymmetric synthesis via the use of a soluble chiral organometallic catalyst [1]. Although homogeneous organometallic catalysts have many advantages over their heterogeneous counterparts (higher activities and selectivities, mild reaction conditions), one of the major problems is the separation of the products from the soluble catalyst, which is generally an expensive and toxic transition metal; this is particularly important for industrial applications. A possible solution to this problem is the heterogenization of the chiral homogeneous catalyst on an inorganic or organic support [2]. Another approach is the use of a liquid/liquid two-phase system, the chiral catalyst being immobilized in one phase, the reactants and the products of the reaction being in the other phase. Aqueous/organic systems have been successfully applied [3], and this is due to the easy and quantitative recovery of the catalyst in the active form by simple phase separation, and also to the environmentally attractive use of water. Other two-phase systems such as ionic liquids [4] or perfluorohydrocarbons [5] in combination with an organic phase have also been proposed.

This section will focus on enantioselective catalysis performed under biphasic conditions, one phase being a fluorous solvent. Catalytic reactions performed in fluorous biphasic systems can effectively show several advantages over classical homogeneous systems or even two-phase systems. One of them is the easy product separation by simple workup techniques of liquid/liquid extraction, due to the low miscibility of fluorous solvents with common organic solvents, and hence the recycling of the catalyst. Moreover, warming the mixture renders the organic and fluorous phases miscible allowing the reaction to occur under homogeneous conditions [5], and so solving the problems of mass transfer between the two phases. Some examples performed in homogeneous systems, followed by separation of the fluorous catalyst or ligand via extraction with a fluorous solvent will also be presented, although separation of organic and fluorous compounds by solid-phase extraction with fluorous silica gel is excluded.

10.13.2
Reduction of Unsaturated Substrates

The catalytic asymmetric reduction of unsaturated compounds is now a well-used methodology in organic synthesis. Enantioselectivities higher than 95% have been obtained using molecular hydrogen or hydrogen donors in the presence of various chiral organometallic complexes [1]. If the asymmetric hydrogenation has been successfully extended to the two-phase water/organic solvent system using water-soluble catalysts [3], the observed enantioselectivities are generally lower than those obtained in normal homogeneous systems. As phosphorous-based ligands have been extensively used in catalytic hydrogenation,
many efforts have been devoted to the synthesis of their fluorous analogs. Klose and Gladysz [6] described the synthesis of the chiral ligand 1 derived from menthol (Scheme 10.13-1), without any applications in catalysis. More recently, a fluorous analog of BINAP 2a (Scheme 10.13-1) was synthesized by the group working with Hope [7], which was used as a ligand of ruthenium in the asymmetric hydrogenation of dimethyl itaconate. Although an enantioselectivity of up to 95% ee was obtained, quite similar to that observed using the original Ru-BINAP complex, recycling of the catalyst was not possible.

Asymmetric transfer hydrogenation of ketones in the presence of soluble transition metal catalysts was developed several years ago [8–10], enantioselectivities of up to 99% ee being obtained using a ruthenium catalyst bearing mono N-tosylated diphenylethylenediamine as the ligand. Iridium complexes associated with fluorous chiral diimines 3a–c or diamines 4a–b (Scheme 10.13-2) have also been shown to be effective catalysts in hydrogen transfer reduction of ketones [11, 12].

Enantioselectivities of up to 56% ee were obtained using [Ir(COD)Cl] 2 associated with fluorous diimines 3a–c at 70 °C in the reduction of acetophenone with isopropanol as the hydride source in the presence of Galden D-100 (mainly n-perfluorooctane, bp 102 °C) as the fluorous solvent (Scheme 10.13-3). The hydrogen transfer reduction was extended to other ketones, an enantioselectivity of 60% ee being obtained for ethyl phenyl ketone for example. However recycling of the catalyst gave lower activity and enantioselectivity, iridium leaching being very high. In order to circumvent the problem of the recycling of the fluorous catalyst, the chiral fluorous diamines 4a–b, obtained by reduction of 3a and 3c, were used as ligands.
of [Ir(COD)Cl]_2 in the reduction of acetophenone in the two-phase system isopropanol/Galden D-100. Whereas ligand 3a gave low enantioselectivity (23% ee) and a very high iridium leaching (51%) in the organic phase, ligand 3b gave an enantioselectivity of up to 69, 79, 59, and 58% ee for the first, second, third, and fourth cycles, respectively, the iridium leaching being very low (less than 4%).

10.13.3 Carbon–Carbon Bond Formation

Carbon–carbon bond formation is one of the most important reactions in organic chemistry. Various approaches concerning the asymmetric carbon–carbon bond formation in a fluorous biphasic system have appeared in the literature.

The asymmetric 1,2-addition of diethylzinc to aromatic aldehydes catalyzed by a BINOL-Ti complex occurs with an enantioselectivity of up to 97% ee [13, 14]. Different groups reported the enantioselective carbon–carbon bond formation in a fluorous biphasic system using a titanium fluorous–BINOL complex. Various chiral fluorous BINOL 5, 6, and 7 complexes, bearing two −Si(C_2H_4C_6F_{13})_3 or −Si(C_2H_4C_8F_{17})_3 chains [15–17], four C_6F_5 or C_8F_{13} chains [18, 19], or two −C_2H_4C_6F_{13} or −C_2H_4C_8F_{17} chains [20], respectively, have been used in this reaction (Scheme 10.13-4).

Takeuchi and collaborators reported the condensation of benzaldehyde with Et_2Zn at 0 °C in the presence of the complex prepared in situ by mixing Ti(O-i-Pr)_4 and fluorous BINOL 5.

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>L*</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3</td>
<td>H</td>
<td>3a</td>
<td>1</td>
<td>0.5</td>
<td>94</td>
<td>15</td>
</tr>
<tr>
<td>CH_3</td>
<td>H</td>
<td>3b</td>
<td>2</td>
<td>0.5</td>
<td>95</td>
<td>13</td>
</tr>
<tr>
<td>C_2H_5</td>
<td>H</td>
<td>3b</td>
<td>1</td>
<td>24</td>
<td>84</td>
<td>56</td>
</tr>
<tr>
<td>CH(CH_3)_2</td>
<td>H</td>
<td>3b</td>
<td>1</td>
<td>24</td>
<td>97</td>
<td>60</td>
</tr>
<tr>
<td>CH_3</td>
<td>H</td>
<td>3c</td>
<td>1</td>
<td>24</td>
<td>93</td>
<td>47</td>
</tr>
<tr>
<td>CH_3</td>
<td>Br</td>
<td>3c</td>
<td>1</td>
<td>24</td>
<td>99</td>
<td>52</td>
</tr>
<tr>
<td>CH_3</td>
<td>NO_2</td>
<td>3c</td>
<td>1</td>
<td>24</td>
<td>98</td>
<td>32</td>
</tr>
<tr>
<td>CH_3</td>
<td>OCH_3</td>
<td>3c</td>
<td>1</td>
<td>24</td>
<td>92</td>
<td>11</td>
</tr>
<tr>
<td>CH_3</td>
<td>CN</td>
<td>3c</td>
<td>1</td>
<td>24</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>CH_3</td>
<td>H</td>
<td>4a</td>
<td>1</td>
<td>5</td>
<td>95</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>CH_3</td>
<td>H</td>
<td>4b</td>
<td>1</td>
<td>0.5</td>
<td>92</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>90</td>
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<td></td>
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<td></td>
<td>3</td>
<td>86</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>69</td>
</tr>
</tbody>
</table>

Scheme 10.13-3. Asymmetric transfer reduction of various ketones
When the reaction was performed in a system toluene/hexane/FC-72, the enantioselectivity in the alcohol obtained was 80% ee, quite similar to that obtained using non-fluorous titanium-BINOL, and remained constant throughout five consecutive runs, the chemical yield being 80–89%. However, about 10% of the fluorous BINOL was recovered from the organic phase after acidic workup of the reaction mixture. Since the partial solubilization of the fluorous catalyst in the organic phase was due to the presence of hexane, the use of the fluorous biphasic system toluene/FC-72 gave enantioselectivities of up to 78% ee (85% yield) and 79% ee (82% yield) using ligands 5a and 5b, respectively; the enantioselectivity was constant during three consecutive runs, as was the chemical yield, the leaching of ligand in the organic phase being negligible (less than 1%).

The condensation of Et\textsubscript{2}Zn with other aromatic aldehydes in the presence of ligand 5a or 5b gave the corresponding alcohols with high enantioselectivity (76–85%) and chemical yields (73–97%).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield (%) (cycle)</th>
<th>ee (%) (cycle)</th>
<th>Ligand recovery (%) (cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>toluene/hexane/FC-72 (3:3:5)</td>
<td>81 (1), 89 (2), 87 (3), 87 (4), 87 (5)</td>
<td>83 (1), 82 (2), 82 (3), 81 (4), 80 (5)</td>
<td>10 (1), 12 (2), 12 (3), 11 (4), 10 (5)</td>
</tr>
<tr>
<td>5a</td>
<td>toluene/FC-72 (3:5)</td>
<td>85 (1), 85 (2), 80 (3)</td>
<td>78 (1), 78 (2), 77 (3)</td>
<td>&lt;1 (1), &lt;1 (2), &lt;1 (3)</td>
</tr>
<tr>
<td>5b</td>
<td>toluene/hexane/FC-72 (1:1:2)</td>
<td>82 (1), 82 (2), 77 (3)</td>
<td>79 (1), 78 (2), 78 (3)</td>
<td>1 (1), 1 (2), 1 (3)</td>
</tr>
<tr>
<td>6a</td>
<td>C\textsubscript{11}F\textsubscript{29}/hexane (1:0.7)</td>
<td>98 (1), 99 (2), 99 (3), 95 (4), 76 (5)</td>
<td>41 (1), 53 (2), 31 (3), 15 (4), 7 (5)</td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>C\textsubscript{11}F\textsubscript{29}/hexane (1:0.7)</td>
<td>69 (1), 80 (2), 79 (3), 76 (4), 80 (5), 79 (6), 80 (7), 79 (8), 79 (9)</td>
<td>54 (1), 57 (2), 58 (3), 55 (4), 60 (5), 58 (6), 57 (7), 56 (8), 55 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 10.13-4. Chiral fluorous BINOL

Scheme 10.13-5. Asymmetric condensation of benzaldehyde with Et\textsubscript{2}Zn
A similar approach was devised by Chan and collaborators [18, 19], who condensed Et₂Zn with benzaldehyde at 45 °C using the fluorous biphasic system hexane/perfluoro-methyl-decalin (or C₁₁F₂₀) in the presence of the catalyst obtained by mixing Ti(O-i-Pr)₄ and fluorous BINOL 6 (Scheme 10.13-5). When the ligand 6a was used, the corresponding alcohol was obtained with 98% conversion and 41% ee; however, the enantioselectivity of the reaction decreased slowly with the reaction runs, and was lost after six runs. Fortunately, when ligand 6b, which contains 32 fluorocarbons, was used, the enantiomeric excess of the product (55–60% ee) as well as the chemical yields (76–80%) were maintained constant after nine reaction runs. The lower enantioselectivity observed using 6 as the ligand instead of 5 (55–60% ee versus 78–79% ee) is probably due to the reaction temperature; in the last case, the critical temperature was 45 °C, lower chemical yield and enantioselectivity being obtained at the lower temperature due to the heterogenization of the catalytic system. Similar enantioselectivities as well chemical yields were obtained in the condensation of Et₂Zn with other aromatic aldehydes in the presence of these ligands 6, with the enantioselectivities remaining constant over three consecutives runs (51–54% ee for 4-chlorobenzaldehyde, and 37–40% ee for 4-methoxybenzaldehyde).

Chan and collaborators [19] used ligand 6b in association with Ti(O-i-Pr)₄ in the condensation of aromatic aldehydes with Et₃Al in the biphasic system hexane/perfluoromethylcyclohexane/hexane at 53 °C (Scheme 10.13-6). Enantioselectivities in the range of 76–88% ee and chemical yields of 77–82% were obtained during six consecutives runs when fresh titanium was added. When the reaction was extended to the electron-deficient 4-chlorobenzaldehyde, the yield was the same (59–88% for three runs) and the enantioselectivity a little lower (63–79% ee for three runs); for the electron-rich 4-methoxybenzaldehyde, only 10% of the product was obtained with an enantioselectivity of 38%.

Zhao and collaborators [20] performed the condensation of allyltributyltin with benzaldehyde in the presence of the catalyst Ti(O-i-Pr)₄/BINOL 7 in various fluorous biphasic systems (Scheme 10.13-7). The highest enantioselectivities, up to 90% ee, were obtained using the hexane/FC-72 system, the yield being 85%. The ligand was recovered by continuous liquid/liquid extraction and can be reused in further experiments. The reaction was extended to other aromatic aldehydes; however only substrates with strong withdrawing groups showed good yields and enantioselectivities, when aldehydes bearing halides or electron donating groups gave rather poor yields and enantioselectivities.

van Koten and coworkers [21] synthesized fluorous chiral ethylzinc arene thiolates 8a–c (Scheme 10.13-8). These organometallic complexes are active in the 1,2-addition of diethyl-

<table>
<thead>
<tr>
<th>X</th>
<th>Cycles</th>
<th>Yield (%) (time)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>6</td>
<td>59–82 (0.5 h)</td>
<td>63–62</td>
</tr>
<tr>
<td>Cl</td>
<td>2</td>
<td>66, 67 (0.5 h)</td>
<td>48, 52</td>
</tr>
<tr>
<td>OMe</td>
<td>2</td>
<td>10, 13 (2 h)</td>
<td>38, 37</td>
</tr>
</tbody>
</table>

Scheme 10.13-6. Asymmetric condensation of benzaldehyde with Et₃Al
zinc to benzaldehyde in hexane, the activity and enantioselectivity being even better than that of the non-fluorous catalyst. Moreover, further experiments showed that they are also active in a two-phase medium of perfluoromethylcyclohexane/hexane. The catalyst could be recycled, although a drop in enantioselectivity was generally observed after two runs: enantioselectivities of up to 92, 92, 76, and 43% ee were obtained using ligand 1c for four consecutive runs.

Among the organometallic catalysts used for alkylation and coupling reactions, palladium has a predominant role. Palladium catalysts are effectively used in a large number of useful transformations in organic chemistry [22]. Surprisingly there are few examples of applications of chiral palladium complexes in the literature. Nakamura et al. [23] carried out the Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate in the presence of Pd(OAc)$_2$ associated with ligand 2b in the two-phase system benzene/FC-72 (Scheme 10.13-9); an enantioselectivity of up to 93% was obtained, the yield being 39%. Unfortunately recycling of the catalyst was not possible, due probably to its inactivation by ligand oxidation.

![Chemical structure](..)

**Scheme 10.13-7. Asymmetric alkylation of benzaldehyde**

<table>
<thead>
<tr>
<th>Solvents (2:1)</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$<em>2$Cl$<em>2$/C$</em>{10}$F$</em>{18}$</td>
<td>7a</td>
<td>27 (24 h)</td>
<td>76</td>
</tr>
<tr>
<td>hexane/C$<em>{10}$F$</em>{18}$</td>
<td>7a</td>
<td>76 (12 h)</td>
<td>83</td>
</tr>
<tr>
<td>hexane/C$<em>{6}$F$</em>{17}$CF$_3$</td>
<td>7a</td>
<td>78 (10 h)</td>
<td>88</td>
</tr>
<tr>
<td>hexane/FC-72</td>
<td>7a</td>
<td>85 (10 h)</td>
<td>90</td>
</tr>
<tr>
<td>hexane/FC-72</td>
<td>7b</td>
<td>83 (5 h)</td>
<td>90</td>
</tr>
<tr>
<td>toluene/FC-72</td>
<td>7a</td>
<td>52 (12 h)</td>
<td>48</td>
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</table>

**Scheme 10.13-8. Asymmetric condensation of benzaldehyde and Et$_2$Zn**

<table>
<thead>
<tr>
<th>Cat.</th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
<th>Run 5</th>
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<tr>
<td>8a</td>
<td>84</td>
<td>72</td>
<td>37</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>8b</td>
<td>79</td>
<td>78</td>
<td>61</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>8c</td>
<td>92</td>
<td>92</td>
<td>76</td>
<td>43</td>
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</tbody>
</table>

10.13 Enantioselective Catalysis: Biphasic Conditions | 311
Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with carbonucleophiles occurred using fluorous bisoxazolines as the ligands in benzotrifluoride or CH$_2$Cl$_2$ as the solvent with ee values of up to 95% [24]; although recycling of the catalyst was not possible, extraction of the ligand allowed the recycling of the latter with the same enantioselectivity.

**10.13.4 Oxidation**

Pozzi's group has shown that asymmetric epoxidation of prochiral alkenes occurred under fluorous biphasic conditions using various chiral fluorous (salen)manganese complexes 9 (Scheme 10.13-10) [25, 26]. The chiral (salen)manganese complexes 9a and 9b, bearing fluorous alkyl substituents in the 3,3'- and 5,5'-positions in the ligand, were used in the epoxidation of indene in the two-phase system CH$_2$Cl$_2$/D-100 in the dark at 20 °C under atmospheric pressure of oxygen, giving the corresponding epoxide with 83 and 77% yield, and 92 and 90% ee, respectively (Table 10.13-1). Recycling of the catalyst was possible without loss of the enantioselectivity: ee values of up to 89 and 92% were obtained, respectively, in a second run. However, very low enantioselectivities were achieved in the epoxidation of other alkenes, such as dihydronaphthalene and benzosuberene, whose structures are very close to indene, whatever the oxidant used.

More recently, chiral fluorous second-generation Mn(salen) complexes 9c and 9d have been prepared [27, 28]. These complexes took into account the fact that the low ee values observed were probably due to the low steric hindrance as a result of the fluorous substituents at the 3,3'- and 5,5'-positions, as well as their electronic effects. These catalysts...
were successfully used in the asymmetric epoxidation of dihydronaphthalene system at 100 °C in CH$_2$CN/perfluorooctane in the presence of PhIO/PNO (pyridine N-oxide) as the oxidant (Table 10.13-1). For example, in the case of 9d, the highest yield was obtained above 40 °C (76% yield), although the ee increased with increasing temperature, the highest value (50% ee) was obtained at 100 °C.

The epoxidation reaction using complexes 9c and 9d as the catalysts was extended to other alkenes: benzosuberene, 1-methylindene, 1-methylcyclohexene, and triphenylethylene, affording the corresponding epoxides in 68–98% yields, and 50–92% enantioselectivities, very close to the values obtained by Regen and Janda [29] using an Mn(salen) supported onto a gel-type resin. The fluorous catalysts could be efficiently recycled, the same activities and enantioselectivities being maintained for three consecutives runs. The lower activity generally observed for the fourth run was mainly due to the oxidative decomposition of the catalyst.

It should be noted that the corresponding Co(salen) complexes have also been used in the hydrolytic kinetic resolution of terminal epoxides, enantioselectivities up to 99% being obtained; however these complexes were never used in a two-phase system [30].

### 10.13.5 Other Reactions

The catalytic enantioselective protonation of a samarium enolate using a C$_2$-symmetric chiral diol as the catalyst and trityl alcohol as the proton source afforded the corresponding ketone with an ee of up to 93% [31]. The use of (S)-2-bis[(perfluorohexyl)ethyl-2-methoxy-1-
phenylethanol (R$_2$H$_2$-MPE) and (C$_6$F$_{13}$C$_2$H$_4$)$_3$OH (or R$_3$COH) in a biphasic system THF/FC-72 (3:4) at \(-45^\circ\text{C}\) gave the ketone in 59% yield and 60% ee, although the use of \(10a\) as the chiral proton source increased the enantioselectivity to 89% ee (Scheme 10.13-11) [32].

This enantioselective protonation was extended to a samarium enolate derived from cyclohexanone (Scheme 10.13-11) in THF using fluorous alcohol \(10b\) as the proton source [15]; enantioselectivities of up to 89% have been obtained. The fluoroalcohol was quantitatively recovered by a simple extraction with FC-72 and reused in five consecutives runs without loss of enantioselectivity.

Fache et al. used fluorous cinchona derivatives in an asymmetric Diels-Alder reaction in CHCl$_3$/C$_6$F$_{14}$ (1:1); low enantioselectivity (13%) was obtained [33]. Moreover, due to the low fluorine content of the catalyst (45 wt% F), the reaction probably occurred in the non-fluorous phase.

10.13.6
Conclusion

In recent years, there has been rapidly increasing interest in asymmetric catalysis in fluorinated media. Although some remarkable progress has been achieved in this field, one problem is the lack of available chiral fluorous ligands. Another problem is the recycling of the catalyst, due probably to the low fluorous content of the chiral complex itself. In order to switch successfully from the homogeneous asymmetric catalytic reaction to its fluorous analog, many factors have to be studied: location as well as the number of fluorous ponytails,
presence of an appropriate spacer in order to insulate completely the metal site from the
electron effect of these substituents, the nature of the counteranion, and the proper choice
of the two-phase system. It is obvious that this technique will become more and more pop-
ular in the future.

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Chiral ligands that contain fluorine atoms which constitute more than 60% by weight are usually sufficiently fluorous to ensure immobilization of the catalysts in a fluorous phase. However, when the fluorous contents of the ligands are much lower than 60%, the solubilities of the ligands and/or catalysts in fluorous solvents decrease significantly. In such cases, asymmetric reactions cannot be carried out in organic and fluorous biphasic conditions but are conducted in common organic solvents or amphiphilic solvents such as BTF. The products and the ligands and/or catalysts are separated from the products for reuse by fluorous liquid/liquid extraction or solid phase extraction with a fluorous reverse phase (FRP) silica gel column [1], depending on the partition coefficients of the ligands or catalysts. Another option for such ligands is to carry out the reactions in supercritical carbon dioxide (scCO₂). The catalysts are recycled successfully by separating the products with an scCO₂ extraction method.

Reactions in Organic Solvents or Amphiphilic Solvents

Takeuchi, Curran and coworkers synthesized a fluorous chiral diol, \((R)-2,2\prime\)-bis\([(S)-2-hydroxy-2-phenylethoxy]-6,6\prime\)-bis\[tris(1\,H,1\,H,2\,H,2\,H-perfluoroctyl)silyl\]-1,1\prime\)-binaphthyl \((R,S)\)-FDHPEB \((F\,\text{content} = 56\%, \text{partition coefficient: benzene/FC-72} = 1/32, \text{THF/FC-72} = 19/1) and applied it to an SmI₂-mediated enantioselective protonation of 2-methoxy-2-phenyl-cyclohexanone [2]. The reaction was carried out under the same reaction conditions as those of the original non-fluorous reaction [3]. In the original reaction, the product was separated from the non-fluorous chiral proton source (2 equiv to the substrate) with preparative TLC to give the product in 70% chemical yield and 87% ee. In the fluorous version, the product and the fluorous chiral proton source were separated by FC-72 extraction (six times) and more simply by fluorous solid phase extraction with an FRP silica gel column. The recovered \((R,S)\)-FDHPEB was used for the next reaction and the reaction was repeated five times. The average chemical yield and enantioselectivity were 78% and 86% ee, respectively (Scheme 10.14-1). The recovery of \((R,S)\)-FDHPEB was quantitative in each run and the recovered \((R,S)\)-FDHPEB after fifth reaction showed the same \(^1\text{H}\) NMR spectrum as that of the pure compound. When the crude product which was obtained by FRP silica gel separation was analyzed by HPLC with CD and UV detectors, the enantioselectivity was found to reach 95% ee. The enantiomeric excess was reduced to 87% ee owing to partial racemization during purification of the crude product by preparative TLC. The quick separation of the product from \((R,S)\)-FDHPEB by FRP silica gel confirmed this fact.

Nakamura and coworkers reported an enantioselective addition of diethylzinc to benzaldehyde using a fluorous chiral \(\beta\)-amino alcohol, \((1R,2S)-N\)-4-tris(1\,H,1\,H,2\,H,2\,H-perfluoro-
octyl)silyl]benzylephedrine (FBE) (F content = 56%, partition coefficient: CH₃CN/FC-72 = 12/88, toluene/FC-72 = 41/59), as a catalyst. The reaction was carried out in toluene by using Et₂Zn in hexane at room temperature [4]. The product was separated from the catalyst by an FRP silica gel column and the recovered chiral catalyst was used for the next reaction. The reaction was repeated ten times and the average chemical yield and enantioselectivity were 88% and 83% ee, respectively (Scheme 10.14-2). The recovery of the chiral catalyst was almost quantitative in each run and the enantioselectivity and chemical yield did not change significantly throughout the experiments. As for an alternative system, Soai and coworkers reported that N-benzylephedrine, the original of the fluorous catalysts, and the corresponding polymer supported compound at the para-position of the benzyl substituent gave the product in 92% ee and 89% ee, respectively [5]. They recovered another polymer-supported ephedrine catalyst and used it again without any loss in catalytic activity and enantioselectivity (using the catalyst twice).

In the two reactions described above, the chiral fluorous ligands were recovered quantitatively by FRP silica gel and reused repeatedly for the reactions. Since no significant drop was observed in chemical yield, enantioselectivity and recovery throughout the experiments, the reactions can be repeated any number of times until the chiral ligands have been consumed through mechanical losses.
Pozzi and coworkers used their fluorous chiral salen compounds for the ligands of cobalt(III) complexes in a catalytic hydrolytic kinetic resolution of terminal epoxides [6]. Among them, (1\(R\),2\(R\),2\(N\),N\(0\)-bis(3,3\(0\)-di-tert-butyl-5,5\(\prime\)-diheptadecfluorooctyl)salicyliden-1,2-cyclo-hexanediamine)cobalt(III) (F content = 49\%) was most effective for the reaction in the presence of counter ion C\(_8\)F\(_{17}\)COO\(^-\). The complex was soluble in neat 1-hexene oxide as well as in common organic solvents such as CH\(_2\)Cl\(_2\) and toluene but insoluble in perfluorocarbons at room temperature. Therefore, the reactions were carried out at room temperature without addition of any co-solvent with a sub-stoichiometric amount of H\(_2\)O under aerobic conditions. In the case of 1-hexene oxide, 1,2-hexanediol and unreacted 1-hexene oxide were isolated by fractional distillation in 47\% and 51\% chemical yields, respectively, and in enantioselectivities higher than 99\% ee (in the original non-fluorous reaction, 98\% ee for both products at 50\% conversion [7]). The non-volatile residue obtained after the distillation was taken up in toluene and treated with C\(_8\)F\(_{17}\)COOH in air. The recovered and reactivated catalyst was used for the next reaction and the reaction was repeated four times. Activity of the recovered catalyst was somewhat decreased at the fourth reaction, although the chemical yield and enantioselectivity of the diol were still higher than 46\% and 97\% ee, respectively (Scheme 10.14-3). Next, they tried to recycle the catalyst by using fluorous separation methods, liquid/liquid extraction and solid phase extraction. n-Perfluorooctane, BTF and CH\(_3\)CN were used for the liquid/liquid extraction and solid phase extraction. n-Perfluorooctane, BTF and CH\(_3\)CN were used for the liquid/liquid extraction and the recovered catalyst resulted in 99\% ee for 1,2-hexanediol although the reaction time was four times longer than the first one. The recovered catalyst by FRP silica gel provided the product in 99\% ee but the reaction rate was reduced to 1/8 that of the first run.

Pozzi, Sinou and coworkers prepared a fluorous chiral phosphine, (R)-2-{bis[4-(1\(H\),1\(H\)-perfluorooctyloxy)phenyl]phosphino}-2′-(1\(H\),1\(H\)-perfluorooctyloxy)-1,1′-binaphthyl (F content = 52\%, partition coefficient: n-perfluorooctane to toluene or CH\(_3\)OH, 0.23 and 7.42, respectively), which was used as the chiral ligand of a palladium complex in an asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate [8]. The reaction was carried out at room temperature in BTF or toluene and gave the corresponding product in 99\% and 88\% chemical yields and 81\% ee and 87\% ee enantioselectivities, respectively (a non-fluorous MOP complex gave the product in 95\% yield and 99\% ee in toluene at 0 °C [9]) (Scheme 10.14-4). When toluene was used as a solvent, the simple extraction of the reaction mixture with n-perfluorooctane (twice) allowed the complete removal of the ligand and of the palladium
complex. However, the recovered palladium complex did not have catalytic activity for the reaction.

Stuart and coworkers reported the first synthesis of a “light” fluorous BINAP, \((R)-6,6'\text{-bis}(1H,1H,2H,2H\text{-perfluoroctyl})-2,2'\text{-bis(diphenylphosphino)-1,1'\text{-binaphthyl}}\) (F content = 38%), and application of it to a Ru-complex catalyzed asymmetric hydrogenation of dimethylitaconate [10]. The reaction was carried out at ambient temperature under the same reaction conditions as those reported by Noyori et al. [11]. The chemical yield (83%) and enantioselectivity (95.7% ee) were similar to those reported (88% and 95.4% ee, respectively) (Scheme 10.14-5). However, there was no description of the recovery of the catalyst or ligand.

Nakamura and coworkers synthesized a heavily fluorinated chiral BINAP, \((R)-6,6'\text{-bis}[\text{tris}(1H,1H,2H,2H\text{-perfluoroctyl})\text{silyle})-2,2'\text{-bis(diphenylphosphino)-1,1'\text{-binaphthyl}}\] \([((R)-F_{13}\text{BINAP})\] (F content = 54%, partition coefficient: benzene/FC-72 = 26/74, CH₃CN/FC-72 = 2/98) and applied it to an asymmetric Heck reaction [12]. The reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate was carried out under the same conditions as those of the original non-fluorous reaction by using F_{13}\text{BINAP} in BTF or benzene to provide the corresponding product, 2-(4-chlorophenyl)-2,3-dihydrofuran in 59% chemical yields and in 90% ee and 92% ee, respectively (71% chemical yield and 91% ee in the original reaction in benzene [13]) (Scheme 10.14-6). The reaction rate was about one third of that in the original reaction. The products and the fluorous chiral ligand were separated by FRP silica.
gel and about 70% of the chiral ligand was recovered. However, the recovered compound was almost all dioxide of F\textsubscript{13}BINAP (F\textsubscript{13}BINAP\textsubscript{O}) and could not be reused for the next reaction.

The three examples of fluorous chiral phosphine ligands described above showed that finding a chiral phosphine ligand that can be effectively recycled by fluorous techniques is still an important challenge.

10.14.3 Reactions in Supercritical Carbon Dioxide

The next two examples are suggestions from the viewpoint of a recyclable fluorous chiral phosphine ligand, because the fluorous complexes led to recyclable systems in supercritical CO\textsubscript{2} (scCO\textsubscript{2}).

Leitner, Pfaltz and coworkers synthesized (4S)-2-[bis[4-(1H,1H,2H,2H-perfluoroctyl)phenylphosphanyl]phenyl]-4-isopropyl-4,5-dihydrooxazole (FPIDO) (F content = 46%) and used it as the ligand in an Ir complex that contained a “CO\textsubscript{2}-philic” counter ion, such as tetrakis-3,5-bis(trifluoromethyl)phenylborate (BARF) (Ir-FPIDO) [14]. Asymmetric hydrogenation of N-(1-phenylethylidene)aniline was carried out under 0.75 g mL\textsuperscript{-1} CO\textsubscript{2} density and 30 bar of hydrogen partial pressure at 40 °C for 20 h by using Ir-FPIDO and the original non-fluorous phosphinodihydrooxazole (PIDO) Ir complex that contained BARF (Ir-PIDO).

The corresponding product was obtained quantitatively in both cases and in 80% ee and 81% ee, respectively (87% ee in CH\textsubscript{2}Cl\textsubscript{2} for Ir-PIDO) (Scheme 10.14-7). The substrate and also H\textsubscript{2} rendered the Ir-PIDO soluble in scCO\textsubscript{2} but the hydrogenated product did not have such an effect. Therefore, the catalyst became insoluble in scCO\textsubscript{2} after the reaction and the product was collected quantitatively in a cold trap by purging the reactor with compressed CO\textsubscript{2}. The catalyst remained in the reactor and the reaction was performed by recharging the substrate and H\textsubscript{2}. Almost identical levels of reaction rate and enantioselectivity were observed in four subsequent experiments (75–80% ee).

(R,S)-FBINAPHOS 4-[2'-{bis-[3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl]phenyl]phosphanyl}]-[1,1']-(R)-binaphthyl-2-yl]oxy]3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']-(S)-dininaphthalene (F content = 34%) was synthesized by Leitner and coworkers and used as a chiral ligand of Rh complexes for the asymmetric hydroformylation of styrene analogs in...
The reaction of styrene using an Rh(acac)(R,S)-FBINAPHOS complex under 0.8 g mL⁻¹ CO₂ density and 40 bar H₂/CO partial pressure at 31 °C for 62 h provided the corresponding products in quantitative conversion and in 96% branched aldehyde selectivity and 92% ee (Scheme 10.14-8).

\[ R = \text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13} \quad \text{(Ir-FPIDO)} \quad (0.09 \text{ mol%}) \]

\[ R = \text{H} \quad \text{(Ir-PIDO)} \]

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Products</th>
<th>Enantiomeric Excess (ee)</th>
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<td>Scheme 10.14-7</td>
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<tr>
<td>H₂, scCO₂, 40 °C, 20 h</td>
<td></td>
<td>quant., 80% ee</td>
</tr>
<tr>
<td>R = CH₂CH₂C₆F₁₃ (Ir-FPIDO) (0.09 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = H (Ir-PIDO)</td>
<td></td>
<td>quant., &gt;75% ee</td>
</tr>
</tbody>
</table>

**Scheme 10.14-7**

scCO₂ [15]. The reaction of styrene using an Rh(acac)(R,S)-FBINAPHOS complex under 0.8 g mL⁻¹ CO₂ density and 40 bar H₂/CO partial pressure at 31 °C for 62 h provided the corresponding products in quantitative conversion and in 96% branched aldehyde selectivity and 92% ee (Scheme 10.14-8). p-tert-Butyl styrene, the precursor for the hydroformylation.

\[ \text{H}_{2}/\text{CO} \ (40 \text{ bar}), \text{scCO}_2, \ 31 \degree \text{C}, \ 62 \text{ h} \]

\[ \text{[Rh(acac)(R,S)-FBINAPHOS]} \quad (0.1 \text{ mol%}) \]

**Scheme 10.14-8**

<table>
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<th>Reaction Conditions</th>
<th>Products</th>
<th>Enantiomeric Excess (ee)</th>
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<td>Scheme 10.14-8</td>
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</tr>
<tr>
<td>H₂/CO (40 bar), scCO₂, 31 °C, 62 h</td>
<td></td>
<td>scCO₂ extraction</td>
</tr>
<tr>
<td>[Rh(acac)(R,S)-FBINAPHOS] (0.1 mol%)</td>
<td></td>
<td>scCO₂ extraction</td>
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</table>
route to ibuprofen, was hydroformylated with an excellent enantioselectivity of up to 93% ee and an unprecedented high regioselectivity of 96% for the branched product. However, the very high regioselectivity was mainly due to the ligand substitution pattern rather than the reaction medium. They tried to recycle the Rh(CO)$_2$[(R,S)-FBINAPHOS] complex in the asymmetric reaction of styrene. After the reaction the reaction mixture was cooled and CO$_2$ was partly vented to reduce the density of the solvent. Re-heating of the mixture resulted in a two-phase system consisting of a liquid phase and a compressed gas phase. The product was distributed between both phases but the complex was contained in the liquid phase. Purging the reactor from the bottom with CO$_2$ at constant temperature and pressure stripped away the product and left the catalyst behind for subsequent use. Eight successive runs were performed and no apparent loss in selectivity or activity occurred up to the third run. The next three runs saw a slow decrease in enantioselectivity, but regioselectivity and conversion remained uniformly high. As for an alternative system, Nozaki and coworkers reported that the reaction using an Rh(acac) complex of polymer-supported BINAPHOS in benzene at 60 °C under 20 atm pressure of CO and H$_2$ (1:1) gave the product in 85% branched aldehyde selectivity and 90% ee [16]. The catalyst was recycled three times without significant loss of regioselectivity and enantioselectivity but with a gradual decrease of catalytic activity.

References

Combining Lipase-Catalyzed Kinetic Resolutions of Racemic Alcohols with Fluorous Phase Labeling

Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

10.15.1 Introduction

In organic synthesis, isolation of pure products is very often the bottleneck of the whole process due to time-consuming and waste-producing separation and purification procedures such as chromatography. In an ideal case an isolation strategy of the desired product(s) should be included in the synthetic plan [1].

Fluorous phase techniques are excellent examples of the easy extractive recovery or isolation of homogeneous catalysts [2], reagents and products [3] equipped with perfluorinated auxiliary groups from non-fluorinated compounds, based on partitioning between organic and fluorous phases and avoiding chromatography.

Biocatalytic methods, particularly the lipase-catalyzed kinetic resolution of racemic alcohols and their esters either by esterification, hydrolysis, or alcoholysis, are well established access routes to enantiomerically pure or enriched building blocks [4]. Lipases are inexpensive and robust biocatalysts; reactions are highly selective in many cases and can be run without any special equipment. However, there is one major drawback to this type of reaction that yields one of the enantiomers as an alcohol and the other one as a carboxylic ester: usually the products must be separated by chromatography, and therefore, on a large scale in the pharmaceutical industry or in high-throughput kinetic resolutions, the required chromatography might be the reason lipase-catalyzed resolution is not to be regarded as being useful.

To circumvent the need for chromatography, several techniques have been reported. For example, lipase-catalyzed esterification of racemic alcohols with succinic anhydride followed by an acid–base extraction separates the acidic ester from the neutral alcohol. However, acidic compounds decrease the lipase activity [5]. Transesterification of racemic esters with poly(ethylene glycol) in the presence of porcine pancreatic lipase in some cases forms crystalline poly(ethylene glycol) esters from the fast reacting enantiomer, which can be simply separated from the unreacted “normal” ester by filtration [6]. On a large scale, there are examples of the separation of esters from alcohols by distillation [7]. Finally, alcohols have been separated from esters by reaction with a polymeric acid chloride [8].

From the progress made running reactions in fluorous phases and/or improving work-up procedures by the introduction of the fluorous phase, the following question arises: is it possible to combine lipase-catalyzed acylation or deacylation reactions with the fluorous phase technique in order to replace chromatography by extraction?

To answer this question we need a fluorinated acylating reagent that fulfills the following tasks: lipase-mediated enantiomer-selective acylation of the fast reacting enantiomer and, simultaneously tagging it in order to be recognized by a fluorous phase that finally allows the separation of the fast reacting fluorinated from the non-fluorinated slow reacting enan-
Enantiomer-selective acylation and deacylation using fluorous labels. \( R^1_f \) = highly fluorinated residue

### 10.15.2 Results and Discussion

Initially, a useful highly fluorinated acyl donor that meets all requirements with regard to reactivity, stability and fluorine content was designed and synthesized. From the point of view of reactivity, it was necessary to introduce a non-fluorinated spacer between the fluorinated alkyl and the carboxylate residue. Otherwise, acyl donors without a spacer would react non-biocatalytically in competition with the enzyme-mediated reaction, yielding products with no or with low enantiomeric excess [11].

From the commercially available highly fluorinated decanol 1 the ester 4 was synthesized as an esterification agent according to Scheme 10.15-2 [12].

After the screening of lipases and solvents *Candida antarctica* B lipase (CAL-B) in acetonitrile turned out to be a useful biocatalyst employing 1.5 equiv of the ester 4 as an ideal acylating agent by resolving rac-5a into its enantiomers \((R)-6a\) and \((S)-5a\) with high efficacy (Scheme 10.15-3) [12].

In contrast, the corresponding fluorinated ester having only one methylene group as a spacer, synthesized by oxidation of 1 to the corresponding acid and subsequent esterification
Scheme 10.15-2. Synthesis of the fluorous label. (a) TsCl, (b) LiBr, (c) Mg, (d) CO₂, (e) PCl₅, (f) HOCH₂CF₃/pyridine, (g) HOCH₂CF₃/H⁺

1.5 equiv. 4,
CAL-B
MeCN, rt
rac-
5a

Scheme 10.15-3. Kinetic resolution of rac-
5a by enantiomer-selective fluorous labeling. \( R_f = (\text{CH}_2)_{12}(\text{CF}_2)_{7}\text{CF}_3 \)
with 2,2,2-trifluoroethanol in analogy to a published procedure [13], was not useful. This ester was rather unstable and did not react in the appropriate manner with 1-phenylethanol (rac-5a) in the presence of lipases [12b].

Enantiomeric excess and yield of the products were determined after conventional workup by flash chromatography to be >99% for both enantiomers, proving that the fluorinated ester 4 is an excellent acyl donor for lipase-catalyzed esterification. In comparison, in the literature the resolution of rac-5a has been reported using vinyl acetate in tert-butyl methyl ether in the presence of Pseudomonas sp. lipase showing similar results [14], demonstrating that the perfluoroester 4 exhibits the same enantioselectivity as vinyl acetate.

For the separation of the products we intended to use liquid/liquid extraction as a quick and simple method. Consequently, the next step was to identify a suitable fluorous/organic biphasic system for the extractive separation of the alcohol 5a from the fluorinated ester 6a. Therefore, as a model substance the ester rac-6a was synthesized in a conventional non-enzymatic way from the alcohol rac-5a and the acid chloride 3. After screening of several biphasic systems consisting of perfluoro-n-hexane and various organic solvents, methanol/n-C6F14 turned out to be the system of choice. Distribution experiments with an equimolar mixture of rac-5a and rac-6a in methanol showed that at least five extractions with perfluoro-n-hexane were required for a total separation of the fluorinated from the non-fluorinated enantiomer. The remaining organic phase was contaminated with less than 1% of rac-6a and the combined fluorous phases with less than 1% of rac-5a, whereby separation was carried out in ordinary separating funnels.

Having identified the appropriate biphasic solvent system, the products (R)-6a and (S)-5a were isolated after a lipase-mediated acylation reaction as follows (Scheme 10.15-3): removal of the enzyme by filtration, evaporation of acetonitrile, and partition between perfluoro-n-hexane and methanol. After extraction the organic phase contains (S)-5a with 99% ee and a trace of not more than 1% of (R)-6a, whereas (R)-6a with an ee of 98% [determined after hydrolysis to (R)-5a] and the excess of the fluoroester 4 remain in the combined fluorous phases. The ee of 98% for (R)-5a represents an impurity of at most 1% of (S)-5a in the fluorous phase.

Saponification of the mixture of the fluorinated esters (R)-6a and 4 with lithium hydroxide yielding (R)-5a allows the almost quantitative recovery of the fluorinated carboxylic acid as its lithium salt in solid form.

In order to prove the general usefulness of this newly developed separation methodology, it was applied to the racemic alcohols rac-5b, c and d (Scheme 10.15-4). These racemic alcohols and their enantiomers, known as versatile building blocks, were resolved utilizing the acylating agent 4 in the presence of CAL-B in acetonitrile (rac-5b, rac-5d) or tert-butyl methyl ether (rac-5c) as solvents and methanol/perfluoro-n-hexane as the fluorous/organic biphasic system for the extractive separation of the fluorinated from the non-fluorinated enantiomer [12b].

Independently of the constitution of the products, the extractive separation of the fluorinated from the non-fluorinated enantiomer was very efficient in all cases, demonstrating that the highly fluorinated ester 4 is an efficient acyl donor and tagging agent establishing sufficient fluorine content in the fast reacting enantiomers.

The results summarized in Table 10.15-1 show that the newly developed separation principle could be applied successfully to substrates of different constitution that have already
been resolved in the literature by lipase-catalysis using conventional non-fluorinated acyl donors and separation techniques. For example, the enantiomers of the silylated butynol rac-\(5b\) have been resolved with a comparable high enantioselectivity by using vinyl acetate in the presence of \(Pseudomonas\) sp. lipase \(\text{[15a]}\) or with \(S\)-ethylthio octanoate in the presence of \(C.\) antarctica B lipase \(\text{[15b]}\). Furthermore, the resolution of the monosilylated cyclopentenol rac-\(5c\) with isopropenyl acetate in the presence of \(Candida\) antarctica B lipase as reported by T. T. Curran et al. \(\text{[16]}\) also proceeded with low enantioselectivity \((E = 15)\). The bicyclic \(C_2\)-symmetric diol rac-\(5d\) has been resolved in our laboratory with either 2,2,2-trichloroethyl acetate in the presence of pancreatin \(\text{[17a]}\) or more efficiently with vinyl acetate in the presence of lipase from \(Pseudomonas\) cepacia \(\text{[17b]}\).
After having demonstrated that lipase-catalyzed acylation under kinetic resolution simultaneously labels the fast reacting enantiomer with a fluorous tag very efficiently, our next aim was to investigate the possibility of an enantiomer-selective detagging procedure by subjecting highly fluorinated esters of racemic alcohols to a lipase-catalyzed alcoholysis under deacylation of the fast reacting enantiomer, and leaving the slow reacting enantiomer attached to the fluorous tag \[18\].

The racemic fluorinated esters rac-6a–c and rac-8a–c were prepared by acylation of the corresponding alcohols rac-5a–c and rac-7a–c with the acid chloride 3 (Scheme 10.15-5), which has already been used for the synthesis of the fluorous acyl donor 4 depicted in Scheme 10.15-2.

The racemic esters rac-6a–c and rac-8a–c were subjected to a lipase-catalyzed alcoholysis in acetonitrile or tert-butyl methyl ether for rac-6c in the presence of *Candida antarctica* B lipase (CAL-B) and four equivalents of n-butanol. Except for the non-reacting bromoindanol derivative rac-8b the other substrates were resolved yielding the fluorinated esters (S)-6a, b, (S)-8a, c or (15,4R)-6c and the non-fluorinated alcohols (R)-5a, b, (R)-7a, c or (1R,4S)-5c, respectively (Scheme 10.15-6). For rac-6c, due to the higher rate of conversion, tert-butyl methyl ether was used instead of acetonitrile as the solvent. After removal of the lipase by filtration and evaporation of the solvent under reduced pressure, the ester and the alcohol were separated by partition between perfluoro-n-hexane and methanol. As expected the extractive separation of the esters 8 from the alcohols 7 also works very well.

The results of the kinetic resolutions are summarized in Table 10.15-2. The outcomes from these reactions confirm that apart from rac-8b the other fluorinated esters were accepted as substrates for CAL-B and resolved with excellent enantiomer selectivity. For all conversions the \(E\)-value of the reaction was \(>200\). In a control experiment (S)-8c and (R)-7c were separated conventionally by flash chromatography, showing almost identical results compared with the extractive separation. Remarkably, the alcoholysis of rac-6c shows a much higher selectivity than the acylation of rac-5c where the \(E\)-value was only 7.6 (Table 10.15-1).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (h)</th>
<th>Ester Config.</th>
<th>ee (%)</th>
<th>Alcohol Config.</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-5a</td>
<td>19</td>
<td>R</td>
<td>98 (&gt;99)</td>
<td>S</td>
<td>&gt;99 (&gt;99)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rac-5b</td>
<td>64</td>
<td>R</td>
<td>97 (99)</td>
<td>S</td>
<td>65</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rac-5c</td>
<td>48</td>
<td>1R,4S</td>
<td>38 (39)</td>
<td>1S,4R</td>
<td>96</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rac-5d</td>
<td>23</td>
<td>1R,2R,5R,6R</td>
<td>96 (99)</td>
<td>1R,2R,5R,6R</td>
<td>99</td>
<td>43</td>
</tr>
</tbody>
</table>

\(a\) Enantiomeric ratio. \(b\) Conversion. \(c\) Assigned on the basis of the known \([\alpha]_D\)-values of the free alcohols. \(d\) The numbers in parentheses correspond to the ee values determined after separation by flash-chromatography. \(e\) The \(E\)-value calculation according to Chen and Sih [4a] is not applicable because it is a sequence of two enantioselective reactions.

After having demonstrated that lipase-catalyzed acylation under kinetic resolution simultaneously labels the fast reacting enantiomer with a fluorous tag very efficiently, our next aim was to investigate the possibility of an enantiomer-selective detagging procedure by subjecting highly fluorinated esters of racemic alcohols to a lipase-catalyzed alcoholysis under deacylation of the fast reacting enantiomer, and leaving the slow reacting enantiomer attached to the fluorous tag [18].
This result demonstrates once more that lipase-catalyzed acylation and deacylation, which are enantiocomplementary, can proceed with a significantly different selectivity. The reason for the resistance of rac-8b towards alcoholysis in the presence of CAL-B is very probably the steric hindrance at the reacting stereogenic center preventing the formation of the necessary transition state, leading to the formation of the acyl-enzyme intermediate which finally must be attacked by n-butanol. Changing of the standard conditions (acetonitrile, room temperature) by using other solvents such as chloroform, toluene, diisopropyl ether and tert-butyl methyl ether at room temperature, or in some cases at 50 °C, did not affect the conversion of rac-8b.

The fluororous phases contain, besides the esters (S)-6a, (S)-8a, c or (1S,4R)-6c, butyl 2H,2H,3H,3H-perfluoroundecanoate, which was removed by saponification with lithium hydroxide and subsequent partition of the reaction mixture in an organic/aqueous biphasic system affording the alcohols (S)-5a and (S)-7a, c or (1S,4R)-5c in the organic and lithium 2H,2H,3H,3H-perfluoroundecanoate in the aqueous phase, respectively. Owing to the instability of silylalkynes under alkaline conditions, cleavage of the ester (S)-6b was performed by acid-catalyzed methanolysis and subsequent partition between methanol containing (S)-5b and perfluoro-n-hexane containing the fluorinated species.

The fluorine content of the fluorinated esters determines the partition properties of this enantiomer between the fluorous and the organic phase. By taking the ratio of fluorine/
workup: filtering off the lipase, evaporation of the solvent, partition between \( n\)-\( C_6F_{14} \) and MeOH

Scheme 10.15-6. Kinetic resolution of rac-6a–c and rac-8a, c by enantiomer-selective fluorous delabeling. \( R_f = (\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3 \)

Tab. 10.15-2. Lipase-catalyzed kinetic resolution of the esters rac-6a–c and rac-8a–c by alcoholysis with \( n\)-butanol

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time/d</th>
<th>Ester Config.</th>
<th>ee (%)</th>
<th>Yield (%)</th>
<th>Alcohol Config.</th>
<th>ee (%)</th>
<th>Yield (%)</th>
<th>( E^a )</th>
<th>( \epsilon^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-6a</td>
<td>0.8</td>
<td>( S^d )</td>
<td>97</td>
<td>43</td>
<td>( R^d )</td>
<td>99</td>
<td>48</td>
<td>&gt;200</td>
<td>0.49</td>
</tr>
<tr>
<td>rac-6b</td>
<td>8</td>
<td>( S^e )</td>
<td>68</td>
<td>25</td>
<td>( R^e )</td>
<td>99</td>
<td>17</td>
<td>&gt;200</td>
<td>0.41</td>
</tr>
<tr>
<td>rac-6c</td>
<td>4</td>
<td>( 1\text{S},4\text{R}^r )</td>
<td>74</td>
<td>42</td>
<td>( 1\text{R},4\text{S}^r )</td>
<td>99</td>
<td>41</td>
<td>&gt;200</td>
<td>0.43</td>
</tr>
<tr>
<td>rac-8a</td>
<td>8</td>
<td>( S^d )</td>
<td>90</td>
<td>41</td>
<td>( R^d )</td>
<td>99</td>
<td>44</td>
<td>&gt;200</td>
<td>0.48</td>
</tr>
<tr>
<td>rac-8b</td>
<td>no conversion</td>
<td>( S^d )</td>
<td>no conversion</td>
<td>no conversion</td>
<td>( R^d )</td>
<td>99 (99%)</td>
<td>44</td>
<td>&gt;200</td>
<td>0.49</td>
</tr>
<tr>
<td>rac-8c</td>
<td>7</td>
<td>( S^d )</td>
<td>94 (96%)</td>
<td>43</td>
<td>( R^d )</td>
<td>99 (99%)</td>
<td>44</td>
<td>&gt;200</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Enantiomeric ratio. \(^b\)Conversion. \(^c\)Determined after saponification or transesterification. \(^d\)Assigned by comparison with one of the commercially available enantiomers. \(^e\)Assigned on the basis of the known \([\alpha]_D\)-values of the free alcohols cf. Ref. [15a] for 5b and Ref. [16b] for 5c. \(^f\)The yields are low due to the high volatility of the alkynol 5b. \(^g\)The numbers in parentheses correspond to the ee values determined after separation by flash-chromatography.

1. workup: filtering off the lipase, evaporation of the solvent, partition between \( n\)-\( C_6F_{14} \) and MeOH

**Scheme 10.15-5.** Kinetic resolution of rac-6a–c and rac-8a, c by enantiomer-selective fluorous delabeling.
hydrogen in the molecule as a very rough measure for the fluorophilicity of an organic compound, it was calculated to be in the region of 1.70, as the maximum for the bicyclic diester 6d, and 0.68 for the cyclopentenol ester 6c as the minimum. The comparison of these ratios illustrates that the extractive separation is efficient even in the case when there is a shortage of fluorine compared with hydrogen, as in the case of the cyclopentenol derivative 6c. In addition, the selectivity of the partition of the fluorinated esters and alcohols between perfluoro-n-hexane and methanol may be increased as a result of the formation of hydrogen bonds between the enantiomeric alcohols and methanol. Alternatively, for the isolation of compounds with low fluorine content solid/liquid extraction is a useful separation technique [1b].

With regard to price and availability, the highly fluorinated acyl donors 3 and 4 at present cannot compete with the frequently used inexpensive vinyl acetate, but the fluorous label can be recycled. On the other hand, perfluoro-n-hexane, FC-72, is a technical product. Its improper use on large scale can cause environmental problems, which could be avoided by using an appropriate extraction technique as opposed to the separatory funnels that are typical for laboratory workup.

10.15.3 Conclusion

Kinetic resolution of racemic alcohols or their corresponding esters has been performed by either enantiomer-selective fluorous phase labeling or delabeling. The highly fluorinated carboxylic ester 4 is an extremely useful and selective acyl donor for the lipase-catalyzed enantiomer-selective acylation of alcohols, whereby the fast reacting enantiomer is equipped with a fluorous tag in order to be recognized selectively by a fluorous phase. Furthermore, if highly fluorinated racemic esters, prepared from the acid chloride 3 and racemic alcohols, were subjected to lipase-catalyzed alcoholysis, the fluorous tag was selectively removed from the fast reacting enantiomer leaving the slow reacting enantiomer equipped with the fluorous label. The enantiomer-selective tagged mixture of ester and alcohol representing the two enantiomers were separated very efficiently by partition in the two-phase solvent system perfluoro-n-hexane/methanol, avoiding a chromatographic step. Hydrolysis of the fluorinated enantiomer allows the recovery of the fluorous tag.

These results are an example of the successful combination of fluorous techniques with lipase-catalyzed kinetic resolutions where the final separation procedure is already integrated into the initial chemical transformation. This newly developed method accomplishes existing methods for the non-chromatographic separation of enantiomeric esters from the corresponding alcohols.

In addition, the fluorous/organic liquid/liquid extractive separation can be replaced by a fluorous triphasic reaction using a U-shaped separation/reaction vessel affording both enantiomers as alcohols on the two different sides of the U-tube [19]. Typical experimental procedures can be found in a separate chapter within this book (see Chapter 11.19–21).

The kinetic resolution of racemic carboxylic acids by enantiomer-selective esterification in fluorous/organic systems with highly fluorinated alcohols can be found in the contribution by D. O’Hagan and P. Beier [20] (see Chapter 10.16).
References


5. Ref. 4f, pp. 44–47.


Enantiomeric Partitioning Using Fluorous Biphase Methodology in Lipase-mediated (Trans)esterifications

Petr Beier and David O’Hagan

10.16.1 Introduction

It is an extraordinary feature of lipase enzymes that they have good catalytic activity when suspended in organic solvents [1]. The catalytic efficiency of an enzyme is highly dependent on its 3D structure and the consequences of removing an enzyme from water into a hydrophobic environment are predicted to unravel the protein and destroy its catalytic prowess. However, lipases have evolved to operate between the aqueous environment of the cell and at lipid membranes and do not unravel in this destructive manner. They control this amphiplicity by opening a “flap” when in a hydrophobic environment and exposing the active site of the protein. In water this flap closes to re-establish a hydrophobic surface [2].

This feature of lipases has resulted in their widespread utility in biotransformation reactions and in transesterifications (esters and alcohols) to generate ester products. The inherent asymmetry of lipase has offered a good strategy for the preparation of enantiomerically enriched esters and secondary alcohols [3]. The non-aqueous environment using lipases in dry organic solvents has also allowed “reverse hydrolysis” strategies to be explored. This has involved very successful esterification (carboxylic acid and alcohol) reactions to be carried out as well as condensation polymerization reactions between long chain ω-hydroxy acids or esters [4] and also diacids and diols. These condensation reactions are generally carried out with an in situ drying agent added, such as molecular sieves or a dehydrated inorganic salt, both of which can absorb the water released from the condensation process [5]. The more free water that accumulates compromises the efficiency of the condensation process as the enzyme begins to catalyze the reverse hydrolytic reaction.

Another feature of such lipase reactions is that they can be carried out at much higher temperatures than enzyme reactions in an aqueous medium. Generally enzymes become less efficient above 40 °C, largely due to water burrowing through the enzyme and disrupting important intramolecular H-bonding interactions. In organic solvents, where competition for hydrogen bonding is not so significant, reactions are generally optimal at about 50 °C and reactions have been recorded in high boiling organic solvents [6] up to 100 °C.

With this background we became interested in the prospect of carrying out lipase mediated reactions in perfluorocarbon solvents, the most hydrophobic solvents available [7]. For example, hexane is a better solvent than THF or ether and acetone, acetonitrile or DMF are very poor solvents for such reactions [8]. It has been argued that this is due to the enzyme retaining “essential water” hydrated to its surface, holding the protein in a catalytically competent structure, and protecting the enzyme from being attacked by the solvent. The more polar the solvent then the greater its ability to strip the “essential water” from the surface of the protein and therefore hexane has emerged as a widely used solvent for such reactions. Perfluorocarbons are more hydrophobic than hydrocarbons [7] and thus it was tempting to speculate that this would offer a more optimal medium for lipase mediated
chemistry. Of course the prospect of carrying out lipase mediated reactions in perfluoro-
carbon/hydrocarbon solvent mixtures was an attractive one too as this offered a potential
method for separating products after completion of a transesterification. Lipase reactions in
perfluorocarbon/hydrocarbon solvent systems are rendered homogenous at temperatures
which are optimal (~50 °C) for lipase activity in organic solvents and clearly filtering of the
enzyme and subsequent cooling of the resultant solution would repartition the solvents for
product separation. For these types of processes to be successful, the product esters and al-
cohols clearly have to be either fluorous or hydrocarbon soluble. It was particularly exciting
to envisage a reaction system starting with a racemic acid or ester, which could result in a
product mixture where the two enantiomeric series partitioned differentially into the hydro-
carbon and fluorous phases.

In order to develop a lipase mediated enantiomeric partitioning system a number of cri-
teria had to me met.

(1) Identification of an enzyme with good catalytic activity in a hydrocarbon/perfluoro-
carbon solvent system.

(2) Identification a carboxylic acid/ester series which resolves well during transesterification
with a fluorous alcohol mediated by the lipase.

(3) Identification of suitable fluorous alcohols or esters to ensure partitioning of the prod-
ucts between the two liquid phases after reaction.

In this study “organic” acids/esters were (trans)esterified using “fluorous” alcohols. Pre-
liminary results of our investigation have been reported [9]. Another recently published
study has taken the alternative approach using lipase-mediated transesterifications of “or-
ganic” alcohols with a “fluorous” ester and is discussed elsewhere [10].

10.16.2
Results and Discussion

10.16.2.1 The Efficiency and Stability of Lipase in Perfluorocarbon Media

From the outset of this study it was important to establish whether certain lipases are
compatible with perfluorocarbon and perfluorocarbon/hydrocarbon solvent systems. Three
different lipase-mediated reactions were tested. The degree of conversion versus
time for the esterification of 2-methylpentanoic acid with butanol and separately with
CF3(CF2)7(CH2)2OH catalyzed by the \textit{Candida rugosa} lipase (CRL) was explored. Also a
transesterification reaction between hexanol and 2,2,2-trichloroethyl butanoate catalyzed by
the lipase from porcine pancreas (PPL) was studied and the collected data are shown in
Figure 10.16-1 and Scheme 10.16-1. It can be seen that the reaction rate increased with the
proportion of the perfluorinated solvent.

It emerged from these trial experiments that the mixed solvent systems provided an
excellent medium in which to carry out lipase-mediated reactions.

The thermostability of the CRL in “fluorous” and “organic” solvents was investigated. The
lipase was suspended in perfluorohexane or hexane and stirred at 40 °C. After a given time
the enzyme was filtered off, air dried and the activity was determined at room temperature
with hexane as the solvent. It emerged that the lipase from \textit{Candida rugosa} is more thermo-
stable in the “fluorous” solvent than in hexane (Figure 10.16-2), however the rate of deactivation is similar for both systems over several days.

10.16.2.2 Transesterification Reactions with Perfluoroalkylated Substrates
In order to test the ability of lipases to mediate a reaction between a “fluorous” tagged ester and hexanol the following system was explored. A reaction between dihydroperfluorododecyl butyrate and 1-hexanol was catalyzed by CRL in a homogeneous mixed solvent system of PFD and hexane, Scheme 10.16-2. Typically reactions were run for 3–4 days to reach full conversion. After filtration of the enzyme and washing with hexane, the liquid phases separated on cooling. The hexane phase was washed with PFD to remove all “fluorous” substrates and hexyl butyrate isolated in excellent yield (98%). Contamination with “fluorous”
products was less than 0.2%. In these trials there was no reaction observed without added enzyme. It was shown that these “fluorous” esters are suitably activated substrates for lipase catalyzed transesterifications and the reverse reaction is very slow as the “fluorous” alcohol is a poor nucleophile.

Conversely (trans)esterifications were explored between “organic” esters, acids or anhydrides and “fluorous” alcohols and some data are presented in Table 10.16-1. It is clear from the relatively short time required to achieve a high percentage of conversion that the perfluoroalkyl alcohol, despite its poor nucleophilicity, can intercept the acylated enzyme intermediate in the lipase mediated process. This renders the method particularly attractive.

\[ \text{OCH}_2(\text{CF}_2)_{10}\text{CF}_3 + \text{CH}_3(\text{CH}_2)_3\text{OH} \rightarrow \text{O}(\text{CH}_3)_2\text{CH}_3 + \text{CF}_3(\text{CF}_2)_{10}\text{CH}_2\text{OH} \]

Scheme 10.16-2. Transesterification reaction catalyzed by CRL in PFD/hexane system at 40 °C

Fig. 10.16-2. Activity of CRL after treatment in PFH (●) or (○) hexane at 40 °C (μmol of converted hexanol into hexyl acetate using 3 equiv of vinyl acetate per hour and 1 mg of enzyme powder) versus time. The activity is the average of three runs in each case.

10.16.2.3 Partitioning of the Products Between the Liquid Phases

The success of the approach to lipase mediated (trans)esterification reactions for product and/or stereochemical separation relies on an efficient partitioning of the reaction products between the perfluorocarbon and hydrocarbon solvents on cooling the reaction medium (−10 °C for 1 h). In order to assess this, partitioning between hexane and some perfluorocarbon solvents was evaluated for a series of alcohols, esters and carboxylic acids (Table 10.16-2).

Recent insights have revealed that the most important factors that influence miscibility of a compound in the fluorous phase are the solvent extended surface and Hildebrand solubility parameter [11], \( \delta \). From the data in Table 11.16-2 it is apparent that the more fluorine
Tab. 10.16-1. Lipase (CRL) catalyzed (trans)esterification reactions between “organic” esters, acid or anhydride and “fluorous” alcohols

<table>
<thead>
<tr>
<th>Acylating agent</th>
<th>Alcohol</th>
<th>Retention time (h)</th>
<th>Conversion (%)</th>
<th>Yield of ester (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl acetate</td>
<td>CF$_3$(CF$_2$)$_3$CH$_2$OH</td>
<td>28</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>2,2,2-Trifluoroethyl butanoate</td>
<td>CF$_3$(CF$_2$)$_7$CH$_2$CH$_2$OH</td>
<td>23</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>Butanoic anhydride</td>
<td>CF$_3$(CF$_2$)$_7$CH$_2$CH$_2$OH</td>
<td>9</td>
<td>99.8</td>
<td>97</td>
</tr>
<tr>
<td>Pentanoic acid</td>
<td>CF$_3$(CF$_2$)$_7$CH$_2$CH$_2$OH</td>
<td>15</td>
<td>95</td>
<td>84</td>
</tr>
</tbody>
</table>

Typical conditions: acylating agent (2 mmol), alcohol (1 mmol), hexane (5 mL), PFH (5 mL) and the catalyst (CRL, 200 mg) were shaken at 300 rpm at 40 °C. *Determined by GC-MS. †The enzyme was filtered off, washed with hexane (5 mL) and PFH (5 mL) and liquid phases were partitioned after cooling (0 °C, 1 h). The hexane phase was washed with PFH (10 mL) and the combined fluorous phases were evaporated give the “fluorous” ester.

Tab. 10.16-2. Partitioning for some alcohols, esters and acids in the system hexane/perfluorohexane (PFH) and hexane/perfluorodecalin (PFD) determined at −10 °C

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent system</th>
<th>Partitioning (%) organic:fluorous</th>
<th>Partitioning coefficient $P = c_{oh}/c_{or}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_3$(CF$_2$)$_3$CH$_2$OH</td>
<td>hexane/PFH</td>
<td>11 ± 1.89 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>8 ± 2.92 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>CF$_3$(CF$_2$)$_7$CH$_2$CH$_2$OH</td>
<td>hexane/PFH</td>
<td>20 ± 1.80 ± 1</td>
<td>4 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>10 ± 1.90 ± 1</td>
<td>9 ± 0.1</td>
</tr>
<tr>
<td>EtMeCHCOOCH$_2$CF$_3$</td>
<td>hexane/PFH</td>
<td>74 ± 1.26 ± 1</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>80 ± 1.20 ± 1</td>
<td>0.25 ± 0.01</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CH$_2$COOCH$_2$(CF$_2$)$_6$CF$_3$</td>
<td>hexane/PFH</td>
<td>15 ± 1.85 ± 1</td>
<td>6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>13 ± 4.67 ± 4</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>EtMeCHCOOCH$_2$(CF$_2$)$_8$CF$_3$</td>
<td>hexane/PFH</td>
<td>30 ± 2.70 ± 2</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>20 ± 1.80 ± 1</td>
<td>4 ± 0.2</td>
</tr>
<tr>
<td>EtMeCHCOOCH$_2$CH$_2$(CF$_2$)$_7$CF$_3$</td>
<td>hexane/PFH</td>
<td>40 ± 1.60 ± 1</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>43 ± 1.57 ± 1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>PrMeCHCOOCH$_2$(CF$_2$)$_8$CF$_3$</td>
<td>hexane/PFH</td>
<td>30 ± 1.70 ± 1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>36 ± 1.64 ± 1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>PrMeCHCOOCH$_2$CH$_2$(CF$_2$)$_7$CF$_3$</td>
<td>hexane/PFH</td>
<td>49 ± 1.51 ± 1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>49 ± 1.51 ± 1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>2-Methylbutyric acid</td>
<td>hexane/PFH</td>
<td>&gt;99.9: &lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>&gt;99.9: &lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-Methylpentanoic acid</td>
<td>hexane/PFH</td>
<td>&gt;99.9: &lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>&gt;99.9: &lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-Methylhexanoic acid</td>
<td>hexane/PFH</td>
<td>99 ± 0.5:1 ± 0.5</td>
<td>0.01 ± 0.001</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>&gt;99.9: &lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-Hexanol</td>
<td>hexane/PFH</td>
<td>98 ± 0.5:2 ± 0.5</td>
<td>0.02 ± 0.001</td>
</tr>
<tr>
<td></td>
<td>hexane/PFD</td>
<td>95 ± 0.5:5 ± 0.5</td>
<td>0.05 ± 0.001</td>
</tr>
</tbody>
</table>
atoms within a molecule, the better the partitioning into the fluorous phase. There is some improvement of partitioning (increase of $P$ for “fluorous” tagged molecules and decrease of $P$ for “organic” molecules) when switching from PFH to PFD and from hexane to more polar solvents such as methanol (data not shown). However, the more polar solvents do not form a homogenous solution at lower temperatures (≤50°C) appropriate to the enzymatic reactions. It was also found that non-halogenated esters, acids and alcohols partition almost only to the organic phase. If a “fluorous” tagged molecule partitions 65% into the fluorous solvent, then at least four extractions of the “organic” phase are required to remove 99% of the fluorous tagged enantiomer. Conversely, if a non-tagged molecule partitions 99.8% to an “organic” phase and four extractions are performed with the same volume of the fluorous solvent, then about 1% of total mass of non-tagged molecules leaks into the combined “fluorous” phase. Clearly it is important for the success of this new lipase methodology to design substrates and products that will achieve good partitioning.

10.16.2.4 Enantiomeric Partitioning After Lipase-Mediated Reactions

To exemplify enantiomeric partitioning in the mixed solvent systems the esterification reaction of racemic 2-methylalkanoic acids 1–3, transesterification reactions of vinyl 4–5 and “fluorous” 6 esters with a range of “fluorous” and “organic” alcohols 7–9 were explored (Scheme 10.16-3). The reactions were carried out in a hexane/PFH solvent mixture and catalyzed by CRL lipase and the data are presented in Table 10.16-3.

In all of these reactions no (trans)esterification was observed without added enzyme, however after adding lipase from Candida rugosa (CRL) the reactions proceeded smoothly. The CRL lipase has previously been shown to mediate a kinetic resolution of 2-methylbranched carboxylic acids and reacts faster with the $S$-enantiomer [12, 13]. The same stereochemical outcome was confirmed in this study by reference to commercially available compounds.

Activated vinyl and fluorous esters proved to be much more reactive than the corresponding acids, but the esterifications proceeded with higher enantioselectivities than the transesterifications. The longer the alkyl chain of the 2-methyl branched carboxylic acid, the slower the esterification reaction, but the better the enantiomeric discrimination. The resul-

\begin{align*}
R_1^1 &\quad O \quad R_2^1 + R_3^1 &\rightarrow& R_1^1 O R_3^1 + R_1^2 R_2^2 + R_3^2 \\
1 &\quad R_1 = &\text{Me}, &\quad R_2 = &\text{H}, \\
2 &\quad R_1 = &\text{Et}, &\quad R_2 = &\text{H}, \\
3 &\quad R_1 = &\text{Pr}, &\quad R_2 = &\text{H}, \\
4 &\quad R_1 = &\text{Me}, &\quad R_2 = &\text{CH} = \text{CH}_2, \\
5 &\quad R_1 = &\text{Et}, &\quad R_2 = &\text{CH} = \text{CH}_2, \\
6 &\quad R_1 = &\text{Me}, &\quad R_2 = &\text{CH}_2(\text{CF}_2)_2\text{CF}_3. \\
7 &\quad R_1 = &\text{CH}_2\text{CH}_2(\text{CF}_2)_2\text{CF}_3, \\
8 &\quad R_1 = &\text{CH}_2(\text{CF}_2)_2\text{CF}_3, \\
9 &\quad R_1 = &\text{(CH}_2)_2\text{CH}_2.
\end{align*}

Scheme 10.16-3. Enantioselective esterification and transesterification reactions catalyzed by CRL in hexane/perfluorohexane solvent mixture.
tant enantiomeric purity of the products from each liquid phase emerges as a consequence
of the inherent stereoselectivity of the enzyme with the substrate, the level of conversion of
the reaction and the partitioning of the unreacted ester and the product ester between the
two phases, Scheme 10.16-4.

These fluoruous phase lipase-mediated reactions interestingly improved the enantioselec-
tivity of both product and unreacted substrates compared with the reported values [13]. In
that particular study, esterification reactions between acids 1–3 and various “organic” alco-

Tab. 10.16-3. Lipase-catalyzed (CRL) kinetic resolution of acids and esters 1–6 by reaction with alcohols
7–9 in hexane/perfluorohexane solvent mixture

| Ester/acid | Alcohol | Reaction time (h),
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>(temperature °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>25 (40)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>95 (40)</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>149 (40)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>50 (30)</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>44 (40)</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Conversion (%) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>50</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>53</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>52</td>
<td>53</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S-product ester, ee (%)</th>
<th>R-unreacted ester/acid, ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60b</td>
<td>45b (N = 5)</td>
</tr>
<tr>
<td>95b</td>
<td>79b (N = 5)</td>
</tr>
<tr>
<td>95b</td>
<td>95b (N = 5)</td>
</tr>
<tr>
<td>44b</td>
<td>40b (N = 1)</td>
</tr>
<tr>
<td>72b</td>
<td>44b (N = 2)</td>
</tr>
<tr>
<td>77b</td>
<td>33b (N = 2)</td>
</tr>
<tr>
<td>46c (N = 2)</td>
<td>42b</td>
</tr>
</tbody>
</table>

Conditions: ester/acid (1 mmol), alcohol (1 mmol), hexane (10 mL),
PFH (10 mL) and the catalyst (CRL 200 mg) were shaken at 250 rpm.
* Determined by GC-MS. The enzyme was filtered off, washed with 5
mL of hexane and 5 mL of PFH and liquid phases were partitioned
after cooling (−10 °C, 1 h). The hexane phase was washed with PFH
(N times with 10 mL) and the combined fluorous phases were
evaporated to yield the fluorous ester. The ee values were determined
by chiral GC-MS of the corresponding acid obtained by hydrolysis of:
*combined fluorous phase, *washed hexane phase.

Scheme 10.16-4. A scheme showing the enantioselective partitioning in
a lipase-mediated esterification reaction using fluoruous biphase
methodology.
hols in heptane at room temperature were reported. The same enzyme (CRL) was used to catalyze the reaction and the resulting esters were separated from unreacted acids by chromatography on silica gel. Our approach of introducing or removing the fluorous tag in a mixed solvent system leads to a much more straightforward separation of enantiomers. However, prolonged reaction time is needed when using less nucleophilic “fluorous” alcohols such as 7 and 8.

To illustrate the preparative utility, a kinetic resolution of 2, catalyzed by CRL, was conducted on a multigram (6 g) scale. Racemic 2 was esterified with 7 using a hexane/perfluorohexane solvent system and the CRL. At around 50% conversion (96 h) the enzyme was filtered off and the liquids were separated after cooling. The hexane phase was washed five times with perfluorohexane to yield unreacted (R)-2 (57%, ee 79%). The product (S)-ester (ee 94%), together with unreacted 7, was recovered from the combined fluorous washings and subjected to enzymatic hydrolysis in an aqueous phosphate (pH 7.0) buffer of CRL. After completion of the enzymatic hydrolysis the aqueous solution was washed with PFH to recover 7 (62%) and the residual was then acidified and extracted into ether to yield the product (S)-2 (66%, ee 96%). This compound has been converted by us, using standard methods, into a natural pheromone [14].

10.16.3

Conclusion

We have demonstrated that lipases operate efficiently not only in hydrophobic organic solvents, such as hexane, but also in super hydrophobic perfluorocarbons [9], such as perfluodecalin. Owing to the extreme hydrophobicity of the perfluorocarbons with their inactivity to dehydrate the enzyme, lipases have been shown to be particularly active in these unnatural media. “Fluorous” alcohols and esters can act as substrates in the enzymatic reactions and it is possible to isolate the products using fluorous biphasic methodology.

Lipase-catalyzed kinetic resolutions of 2-methyl branched alkanoic acids have allowed products of opposite enantiomeric series to be separated by liquid/liquid “fluorous”/“organic” extraction. One of the main limiting factors for efficient separation of enantiomers by fluorous biphasic extraction is inefficient partitioning and care must be taken when designing good systems. The methodology was successfully applied to the multigram production of both enantiomers of 2-methylpentanoic acid. Industrial applications of this methodology will require efficient recycling protocols of the perfluorous solvents and reagents, in order to become cost effective.

References

2 M. Cygler, J. D. Schrag, Methods Enzymol. 1997, 284, 3.
Selective and Clean Reactions in Fluorinated Alcohols

Jean-Pierre Bégué, Danièle Bonnet-Delpou, and Benoit Crousse

Introduction

A large number of the useful applications of fluorous media in organic synthesis concern reactions and separation processes using perfluoroalkanes, perfluoroalkylethers or any parent non-polar solvent. Fluorinated alcohols such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) are not considered *stricto sensu* as fluorous media [1]. However, the presence of one or more fluoroalkyl groups introduces specific properties to fluorinated alcohols compared with those that are non-fluorinated. They have a high ionizing power (\(Y = 1.80\) for TFE and 3.82 for HFIP) [2], and an “acidic” character (\(pK_a = 12.4\) for TFE and 9.3 for HFIP) [3]. They are strong hydrogen-bond-donors [4] and poor nucleophiles [5].

While the properties of fluorinated alcohols have been exploited in physical organic chemistry (solvolysis [5], stabilization of radical cations [6]) and for their effect on the conformation of proteins and peptides [7], it is quite surprising that they have not been exploited to any great extent for synthetic purposes. Indeed, their specific properties could induce changes in reaction courses. The objectives of our projects were thus to investigate reactions where fluorinated alcohols, used as solvents, were expected to significantly improve reaction conditions. We report here some typical examples from our investigations on oxidation reactions in fluorinated alcohols.

Activation of Hydrogen Peroxide

Bearing in mind that fluorinated alcohols can be hardly oxidized [8], we initiated this project with various oxidation reactions, using hydrogen peroxide as the oxidant, with the hypothe-
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10.17.1 Introduction

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10.17.2 Activation of Hydrogen Peroxide

Bearing in mind that fluorinated alcohols can be hardly oxidized [8], we initiated this project with various oxidation reactions, using hydrogen peroxide as the oxidant, with the hypothe-
sis that the electrophilic activation of H$_2$O$_2$ through a hydrogen bond could facilitate O–O bond cleavage (Scheme 10.17-1).

10.17.2.1 Selective Oxidation of Sulfides

Among the numerous oxidizing reagents able to convert sulfides into sulfoxides, aqueous hydrogen peroxide is the cheapest and the simplest. In order to facilitate the loss of the hydroxyl group in the transition state, the reaction requires acidic conditions or the use of catalysts [9]. Conditions have to be controlled to avoid over oxidation to sulfones.

We showed that when sulfides were treated with 1 or 2 equiv of hydrogen peroxide (30%) in HFIP at room temperature, oxidation was very fast (5–15 min) and sulfoxides were obtained in quantitative yields, without any trace of sulfone [10]. The same reactions conducted in TFE were also effective and selective, but reaction times were longer.

These results clearly demonstrated the significant activation of hydrogen peroxide by fluorinated alcohols, probably due to both their high hydrogen bond donor ability and their high ionizing power. More striking is the selectivity of reactions: even when sulfoxides were again placed in the presence of 2 equiv of hydrogen peroxide (30%) in HFIP, they were recovered unchanged. This is due to the hydrogen bond between HFIP and the oxygen atom of the sulfoxide, which greatly decreases the nucleophilicity of the second available electron pair of the sulfur atom (Scheme 10.17-2) [5].

Besides the selectivity, the other great advantage of the process is the absence of any metal catalyst or salt. The reaction proceeds smoothly at room temperature, under neutral conditions and without strict control. The only effluent is water, and the solvent can be recovered by distillation. Under these conditions, a wide range of sulfides (allyl and vinyl sulfides, di-tert-butyl sulfide) could be selectively oxidized in high yield. The N atom of the pyridinyl group and C=C double bonds are not affected by the reagent system. Interestingly, these
neutral conditions allowed the oxidation of the glycosyl sulfides to glycosyl sulfoxides, which was achieved in very high yield at room temperature, even when acid sensitive protecting groups are present (Scheme 10.17-3) [10b].

10.17.2.2 Oxidation of Thiols to Disulfides
A large number of oxidative reagents are able to oxidize thiols to disulfides. Most of the existing methods involve the use of metal catalysts or reagents such as halogens [11]. Hydrogen peroxide is also known to oxidize some thiols to disulfides, but this requires a long reaction time and proceeds only under strong acidic or basic conditions [12].

We found that thiols were also cleanly oxidized into disulfides in quantitative yields with H$_2$O$_2$, 30% in HFIP or in TFE, without any catalyst (Scheme 10.17-4) [13]. The method presents the same advantages as for oxidation of sulfides (Scheme 10.17-4).

The oxidation reactions of sulfides to sulfoxides and of thiols to disulfides can be performed on a large scale. Fluorinated alcohols (HFIP and TFE) can be recycled by simple distillation and reused [14].
10.17.3

**Epoxidation**

10.17.3.1 **With Aqueous Hydrogen Peroxide**

We have been interested in the epoxidation reaction by activation of hydrogen peroxide by HFIP. To our knowledge the first reports of the use of hexafluoroisopropanol as a solvent in the epoxidation reaction with H$_2$O$_2$ 60%, are patents [15]. A transition metal catalyst (W, As, Sh, Bi) was required.

Since then, other examples of epoxidation reactions in HFIP or TFE with hydrogen peroxide in the presence of metal catalysts have been reported (H$_3$AsPhO$_3$ [16], HReO$_4$ [16], MeReO$_3$ [17, 18]) or non metal catalysts such as perfluoroketones [19, 20].

More recently, Neumann and Neumann [21] and Sheldon and coworkers [22] took advantage of the activation of hydrogen peroxide by fluorinated alcohols to perform epoxidation reactions in HFIP or TFE without any catalyst. In most of these examples the reaction required H$_2$O$_2$ 60% and were sometimes conducted under solvent reflux.

10.17.3.2 **With Urea–Hydrogen Peroxide (UHP): H$_2$O$_2$ 100%**

From a synthetic point of view, a search for safer conditions appeared to be essential. The urea–hydrogen peroxide complex (UHP) has been reported to be easy to handle and a safe source of anhydrous hydrogen peroxide [23]. It is a white crystalline solid, formed by strong hydrogen bonds between urea and hydrogen peroxide in a 1:1 stoichiometry (Scheme 10.17-5). However, such high stability could be a drawback to its potential chemical reactivity towards substrates. Indeed additions of anhydrides or catalysts to UHP are required to achieve oxidation reactions [23, 24]. The results described above prompted us to investigate the effect of fluorinated alcohols on the activation of hydrogen peroxide from UHP.

![Scheme 10.17-5. UHP complex](image)

As a preliminary study, epoxidation of the highly reactive cyclooctene was evaluated and performed using UHP in various solvents (Table 10.17-1) [25].

Among all of the solvents used, UHP was soluble only in HFIP and MeOH, and HFIP was the sole solvent where epoxidation was efficient, with a 100% conversion after 10 h at room temperature. UHP was not soluble in other commonly used reaction solvents (CH$_2$Cl$_2$, MeCN and AcOEt) and when reactions were carried out, cyclooctene remained unchanged even after 24 h. In addition, UHP was not soluble in TFE, and cyclooctene af-
forded only 4% of the epoxide after 24 h, whilst it could undergo epoxidation with aqueous H₂O₂ in this solvent [21]. Conversely with methanol, despite the complete dissolution of UHP, cyclooctene remained unchanged, confirming that although methanol is able to disassociate the complex, it is not able to catalyze cleavage the covalent O-O bond.

HFIP has the unique ability of combining the two requirements for efficient epoxidation with UHP: solubility of the UHP complex and activation of hydrogen peroxide. Under these conditions di- and trisubstituted olefins underwent epoxidation in high yields under safe and mild conditions without a catalyst (Scheme 10.17-6) [25].

### Scheme 10.17-6

This ability of fluorinated alcohols to cleave the O-O bond of peroxide could be applied to the activation of dioxiranes, which are excellent oxidizing reagents for the epoxidation of olefins. They are generated most often \textit{in situ} from the parent ketone with Oxone® under basic conditions (Scheme 10.17-7) [26].

Following along these lines, fluoro analogs of acetone have been shown to be precursors of very efficient epoxidation reagents [26].

We initially designed new models of fluorketones [27] as precursors of dioxiranes and found that the most efficient ketone for epoxidation is CF₃CO(CH₂)₂C₆F₁₃. Epoxidation re-

### Tab. 10.17-1. The effect of solvent on the epoxidation of cyclooctene with UHP

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Solublity of UHP</th>
<th>Time (h)</th>
<th>Conversion (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UHP</td>
<td>HFIP</td>
<td>yes</td>
<td>10</td>
<td>100c</td>
</tr>
<tr>
<td>2</td>
<td>H₂O₂ 30%</td>
<td>HFIP</td>
<td>–</td>
<td>24</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>UHP</td>
<td>TFE</td>
<td>no</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>UHP</td>
<td>CH₂Cl₂</td>
<td>no</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>UHP</td>
<td>MeCN</td>
<td>no</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>UHP</td>
<td>AcOEt</td>
<td>no</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>UHP</td>
<td>MeOH</td>
<td>yes</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

*Conditions: cyclooctene (1 mmol), UHP or H₂O₂ 30% aq. (3 mmol), HFIP (3 mL), 25 °C. ²Epoxide; measured by GC. ³Yield isolated: 91%.
actions are usually conducted in an acetonitrile/water system [28], and have been investigated in this study using HFIP instead of acetonitrile as the solvent.

Both systems (HFIP/water and MeCN/water) were evaluated in epoxidation reactions of cyclooctene and the poorly reactive dodecene with this new perfluoro ketone \([\text{CF}_3\text{CO(CH}_2\text{)}_2\text{C}_6\text{F}_{13}]\) as the catalyst (Scheme 10.17-8) [27]. With the use of HFIP we found new conditions where the reactions were largely improved.

HFIP introduced the following advantages: a decreased reaction rate, and a smaller amount of Oxone\(^{\text{a}}\) was required (1.5 equiv instead of 10 equiv in MeCN). Since under these new conditions the fluoro ketone is very stable towards Baeyer-Villiger decomposition, the catalytic amount required could be decreased to 1% for reactive olefins and 5% for poorly reactive ones. A number of olefin substrates provided epoxides in good yields (Table 10.17-2).

Besides the activation of the O–O bond cleavage by strong hydrogen bonding with HFIP, the enhanced solubility of the ketone can also be evoked to explain the efficiency of the system (Scheme 10.17-9).

10.17.3.4 With Oxygen
Fluorous solvents are known to solubilize molecular oxygen. With this in mind we investigated the influence of fluorinated solvents on aerobic epoxidation, with the hypothesis that the high solubility of molecular oxygen in fluorocarbons should favor reactions. In the course of that study, epoxidation reactions were carried out, for comparison, in various fluorinated solvents with Mn(OAc)\(_3\) as the catalyst, oxygen as the oxidant, and pivalaldehyde as the co-reductant [29].

In all of the solvents used, but most efficiently in the perfluorinated tetrahydrofuran FC-75, the electron-rich di- and trisubstituted olefins readily underwent epoxidation reactions,
while terminal olefins were poorly reactive. The most striking result of this study was the opposite reactivity that olefins exhibited when aerobic epoxidation was performed in hexafluoroisopropanol: terminal olefins easily reacted to provide high yields of epoxides, while dis- and trisubstituted olefins were fairly unreactive (Scheme 10.17-10).

In addition to the synthetic significance of this result for selective epoxidations, it clearly indicates that, compared with other solvents, HFIP induces a change in the mechanism of epoxidation. However, unlike the role of fluorinated alcohols on O–O bond cleavage, in this case the role of HFIP has not been elucidated.
Conclusion

We have reported that HFIP and TFE are excellent solvents that have enabled new efficient and selective processes for oxidation reactions to be developed. Their specific properties, with the combination of high hydrogen bonding donor ability, low nucleophilicity, and high ionizing power, allowed reactions to proceed under neutral and mild conditions, where the use of additive reagents or metal catalysts is usually required. Providing they are used as solvents, HFIP and, to a lesser extent TFE, are able to facilitate O–O bond cleavage of peroxides. In this way new clean processes could be described: selective oxidation reactions with oxygen, aqueous hydrogen peroxide, hydrogen peroxide complexed with urea (UHP), and Oxone. These systems were used for oxidation of sulfides to sulfoxides, of thiols to disulfides and for epoxidation reactions.

The procedures offer several advantages, such as mild and neutral reaction conditions, operational simplicity and ease of isolation of products along with good yields of the products. In most cases there are no effluents after reaction, and the fluorinated alcohols can be recovered and reused for other reactions.

Acknowledgements

The authors thank all participants in these studies: F. Barbier, J. Bourdon, U. Das, J. Iskra, V. Kesavan, J. Legros, M. Ourêvitch, K. S. Ravikumar. We thank the CEFIPRA (French Indian collaborative program), the European Community Human Potential program Marie Curie Fellowship under contract number HPMF-CT-1999-00097, the European Contract of Research Training Network (“Fluorous Phase” HPRN CT 2000-00002) and the COST-Action “Fluorous Medium” D12/98/0012. Central Glass Co. Ltd. is acknowledged for a kind gift of HFIP.

References

1 According to a definition proposed by: J. A. Gladysz, D. P. Curran, Tetrahedron 2002, 58, 3823–3825.
References


15 For the first examples of HFIP used as co-solvent in catalyzed hydrogen peroxide epoxidation, see: (a) T. M. Shriver, US 4024165 (1977) (Shell); (b) M. G. Romanelli, EP 0096130 (1983) (Exxon).


Liquid/Solid Catalyst-Recycling Method without Fluorous Solvents

Kazuaki Ishihara and Hisashi Yamamoto

10.18.1 Introduction

Over the past 5 years or more, fluorous biphasic catalysis has emerged as an environmentally attractive alternative to traditional catalysis methods [1]. Fluorous techniques take advantage of the temperature-dependent miscibility of organic and perfluorocarbon solvents to provide easier isolation of products and recovery of a fluorinated catalyst. The large-scale use of fluorous solvents, however, has drawbacks: cost and concern over environmental persistence.

The fluorous biphasic technique involves dissolving a catalyst with long fluorinated alkyl chains in a perfluorocarbon. The reactants are added to an organic solvent that is immiscible with the perfluorocarbon at room temperature, forming a second phase. On heating, the two phases mix and the reaction occurs; on cooling, the fluorinated and organic layers separate. The organic phase can be removed and the product isolated, while the fluorinated catalyst/solvent phase can be reused.

In 2001, we [2] and Gladysz’s group [3] independently reported that the fluorous solvent can be bypassed by designing fluorinated catalysts that themselves have a temperature-dependent phase miscibility, that is, solubility, in ordinary organic solvents.

10.18.2 Fluorous Catalysis without Fluorous Solvents

We have developed a direct amide condensation catalyst, 3,5-bis(perfluorodecyl)phenylboronic acid (1), which can be recovered without using any fluorous solvents [2]. Arylboronic acids bearing electron-withdrawing substituents at the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. 3,5-bis-(Trifluoromethyl)phenylboronic acid (2) and 3,4,5-trifluorophenylboronic acid (3) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1
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To the best of our knowledge, this is the first example of a catalytic and direct amide condensation which does not require excess amounts of the substrates. Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1–20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This hampers the application of this methodology to large-scale syntheses. Therefore, we have designed phenylboronic acids 1 and 4 bearing perfluorinated ponytails based on the direct coupling of fluoroalkyl iodides with halobenzenes. Their fluorous boronic acids can be easily recovered by the fluorous biphasic technique (Scheme 10.18-1) [2].

The catalytic activities of arylboronic acids 1–4 (5 mol%), which promote the model reaction of 4-phenylbutyric acid (1 equiv) with 3,5-dimethylpiperidine (1 equiv) in toluene at azeotropic reflux with removal of water (4 Å molecular sieves in a Soxhlet thimble) for 1 h, and their recoverabilities by extraction with perfluoromethylcyclohexane are shown in Table 10.18-1. As expected, 1 is more active than 4, and is recovered in quantitative yield by ex-

### Scheme 10.18-1. Amide condensation catalysts

<table>
<thead>
<tr>
<th>ArB(OH)₂</th>
<th>Yield of amide (%)ᵃ</th>
<th>Recovery of ArB(OH)₂ (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>57</td>
</tr>
<tr>
<td>1</td>
<td>47 (95)ᶜ</td>
<td>&gt;99</td>
</tr>
<tr>
<td>PhB(OH)₂</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>-ᵈ</td>
<td>&lt;2</td>
<td>–</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield.ᵇ Extraction with perfluoromethylcyclohexane.ᶜ Yield after heating at azeotropic reflux for 15 h is indicated in parenthesis.ᵈ No catalyst was added.

Another example

99% yield, >99% recovery of 1
[Reaction conditions: 1 (2 mol%), toluene, azeotropic reflux for 4 h]

### Tab. 10.18-1. Catalytic activities and recovery of arylboronic acid for the direct amide condensation
traction with perfluoromethylcyclohexane. Although 2 and 3 are more active than 4, they cannot be recovered by extraction with any of the fluorous solvents. The amide condensation proceeds cleanly in the presence of 5 mol% of 1, the desirable amide has been obtained in 95% yield by azeotropic reflux for 15 h. In addition, the corresponding N-benzylamide has been obtained in quantitative yield by heating 4-phenylbutyric acid with benzylamine in the presence of 2 mol% of 1 under azeotropic reflux conditions for 4 h.

Based on the above results, the reuse of 1 has been examined for the direct amide condensation reaction of cyclohexanecarboxylic acid and benzylamine in a 1:1:1 mixture of o-xylene, toluene, and perfluorodecalin under azeotropic reflux conditions with removal of water for 12 h (Table 10.18-2 and Figure 10.18-1) \[5\]. After completion of the reaction, the homogeneous solution is cooled to ambient temperature to be separated in the biphasic mode of o-xylene/toluene or perfluorodecalin. The corresponding amide is obtained in quantitative yield from the organic phase. Catalyst 1 can be completely recovered from the fluorous phase and reused in the recyclable fluorous immobilized phase.

Catalyst 1 is insoluble in toluene and o-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by 1 proceeds homogeneously under reflux conditions. To demonstrate this advantage of 1 with respect to solubility, we have attempted to reuse 1 (5 mol%) ten times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine (Table 10.18-3 and Figure 10.18-2) \[6\]. After heating the reaction mixture at reflux with removal of water for 3 h, the mixture is allowed to stand at ambient temperature for 1 h to precipitate 1. The liquid phase of the resultant mixture is decanted and the residual solid catalyst 1 is reused without isolation. No loss of activity has been observed for the recovered catalyst, and 26% of 1 remains in the flask in the tenth reaction. This means that 88% of 1 has been retained in each cycle. The total isolated yield of the amide which is obtained in ten reactions is 96%. Moreover, pure compound 1 can be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene \[6\].

Gladysz’s group has also reported the temperature-dependent solubility of the solid phosphine catalyst 5 in octane \[3\]. Between 20–80 and 20–100 °C, 5 exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dis-

---

**Table 10.18-2.** Recovery and reuse of 1 in the recyclable fluorous immobilized phase

<table>
<thead>
<tr>
<th>Cyclea</th>
<th>Conversion (%)b</th>
<th>1 (3 mol%)</th>
<th>o-xylene–toluene-perfluorodecalin (1:1:1) azotropic reflux, 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;99 (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;99 (98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>&gt;99 (99)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[a\] Reaction conditions: o-xylene (2.5 mL), toluene (2.5 mL), and perfluorodecaline (2.5 mL). After the reaction, a solution of the amide in the upper phase was decanted and 1 in the lower phase was recycled successively. \[b\] Values in parenthesis refer to the isolated yields. \[c\] Catalyst 1 was recovered in 98% yield from the perfluorodecalin phase.
solving nonpolar fluorous compounds, little 5 can be detected at 0 °C by GC (0.31 mM) or $^{31}$P NMR. At 20 °C, millimolar concentration levels are present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility has been observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C).

Such a dramatic solubility/temperature dependence suggests an obvious catalyst method. The method has been tested by carrying out a series of additions of alcohols to methyl pro-

Fig. 10.18-1. Recycling system of 1 in the recyclable fluorous immobilized phase

Tab. 10.18-3. Reuse of catalyst 1 for amide condensation of cyclohexanecarboxylic acid with benzylamine

<table>
<thead>
<tr>
<th>Use of 1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

$^a$Reaction conditions: 1 (0.05 mmol), cyclohexanecarboxylic acid (1 mmol), benzylamine (1 mmol), xylene (5 mL). After the reaction, the solution was decanted and the residual catalyst 1 was reused without isolation (see, Figure 9.3). $^b$Recovered catalyst 1 was used successively (Use 2, 3, 4, ...).
piolate (6) in octane. Catalyst 5 (10 mol%), benzyl alcohol (2 equiv), and 6 are combined in octane (65 mM in 6). The sample is kept at 65 °C (8 h) and cooled to −30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) is isolated by decantation. GC analysis of the supernatant indicates an 82% yield of 7. The recovered catalyst has been used for four further cycles without deterioration in yield, as summarized in Figure 10.18-3.

In a further refinement, Gladysz’s group has shown that the above reaction of benzyl alcohol with 6 can be made even greener by not using a solvent at all [3]. Raising the temperature of a mixture of the neat reactants and solid catalyst above the catalyst’s melting point of 47 °C yields the addition product. The solid catalyst can be recovered at room temperature and is recyclable with yields consistently above 95%.

We have developed a fluorous super Brønsted acid catalyst, 4-(1H,1H-perfluorotetradecanoyl)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonfyl)methane (8), which can be recycled by applying liquid/solid phase separation without fluorous solvents [8] and an organic-solvent-swellable resin-bound super Brønsted acid, polystyrene-bound tetrafluorophenylbis(trifluoromethanesulfonfyl)methane (9) [9]. These super Brønsted acids can be synthesized by using the para-substitution reaction of pentafluorophenylbis(trifluoromethanesulfonfyl)methane (10) with nucleophiles such as sodium alkoxide and alkyl lithium as a key step (Scheme 10.18-2).

Pentafluorophenylbis(trifluoromethanesulfonfyl)methane 10 (47 wt% F) is soluble in most organic and fluorous solvents. However, it is possible to achieve high fluorous-phase affinity for 4-alkoxy-
The addition of PhCH2OH to 6:

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>82</td>
<td>82</td>
<td>80</td>
<td>81</td>
<td>75</td>
</tr>
</tbody>
</table>

Fig. 10.18-3. Recovery of 5 by decantation and its reuse without isolation

Scheme 10.18-2. Preparation of 8 and 9 from 10 via nucleophilic para-substitution reactions
2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane by appending “a fluorous ponytail”, OCH$_2$(CF$_2$)$_n$CF$_3$ group, to the para-position of 10 via the nucleophilic para-substitution reaction. In preliminary experiments, the preparation of 4-hexanoxy- and 4-trifluororoethanoxy-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methanes, 11 and 12, have been examined by reacting a lithium salt of 10 with the corresponding sodium alkoxides in pyridine at room temperature [Eq. (1)] [9]. As expected, 11 and 12 have been obtained in respective yields of 83% and 93%. Fluorous Brønsted acid 13 (59 wt% F) has been also prepared in 97% yield from a lithium salt of 10 and sodium 1H,1H-perfluorodecanoxide.

\[
\begin{align*}
\text{ROH} & \quad (3 \text{ equiv}) \\
\text{NaH (3 equiv)} & \quad \text{pyridine} \\
0 \degree C & \quad \text{rt, 2 h} \\
1. \text{C}_6\text{F}_5\text{CTf}_2\text{Li (1 equiv)} & \quad 2.4 \text{ M HCl} \\
& \quad \text{rt, 1 day} \\
& \quad 4 \text{ M HCl} \\
& \quad \text{83% yield} \\
\end{align*}
\]

Their pK$_a$ values in glacial acetic acid have been measured by the $^1$H NMR method of Schantl et al. (Table 10.18-4) [8, 10]. The Brønsted acidity of 11 is less than that of conc. H$_2$SO$_4$, while 12 is a superacid like 10.

To obtain a higher fluorinated Brønsted acid, 3d (62 wt% F) has been prepared in 84% yield by heating a lithium salt of 1 and sodium 1H,1H-perfluorotetradecanoxide in a 2:1 mixed solvent of pyridine and perfluorotributylamine at 70 °C [Eq. (2)]. Perfluorotributylamine has been added to partially dissolve sodium 1H,1H-perfluorotetradecanoxide.

\[
\begin{align*}
\text{CF}_3(\text{CF}_2)_8\text{CH}_2\text{OH} & \quad (3 \text{ equiv}) \\
\text{NaH (3 equiv)} & \quad \text{pyridine}/(\text{CF}_3\text{CF}_2)_3\text{N}
=2:1 \\
& \quad \text{rt to 70 °C, 1 h} \\
1. \text{C}_6\text{F}_5\text{CTf}_2\text{Li (1 equiv)}, \text{70 °C, 1 day} & \quad 2.4 \text{ M HCl} \\
& \quad 84\% \text{ yield} \\
& \quad 62 \text{ wt% F} \\
\end{align*}
\]

The acetalization of benzaldehyde with 1,3-propanediol has been examined in the presence of 1 mol% of a fluorous super Brønsted acid, 13 or 8, at azeotropic reflux in cyclohexane with the removal of water for 3 h [Eq. (3)]. Both solid acids are soluble in cyclo-

Tab. 10.18-4. Bronsted acidities of arylbis(trifluoromethanesulfonyl)methanes

<table>
<thead>
<tr>
<th></th>
<th>11</th>
<th>conc. H$_2$SO$_4$</th>
<th>12</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR (ppm)$^a$</td>
<td>6.19</td>
<td>–</td>
<td>6.23</td>
<td>6.21$^b$</td>
</tr>
<tr>
<td>pK$_a$ in AcOH</td>
<td>11</td>
<td>7.5$^b$ (7.0)$^c$</td>
<td>6.6</td>
<td>1.5$^b$</td>
</tr>
</tbody>
</table>

$^a$ $^1$H NMR chemical shift observed for an acidic proton of ArCHTF$_2$ in CDCl$_3$ is indicated. $^b$ Reference 8a. $^c$ Reference 10.
hexane under reflux conditions, and promote the reaction well to give the desired acetal in good yields. Post-reaction, 13 has been recovered in 96% yield by precipitation at room temperature. However, 13 can not be recovered in the same manner. Besides this acetalization, 8 is also effective as a fluorous catalyst for the acylation of 1-menthol with benzoic anhydride [Eq. (4)] and esterification of 3-phenylpropionic acid in methanol [Eq. (5)] [11].

\[
\text{PhCHO} + \text{HO-}\text{OH} \rightarrow \overset{13 \text{ or } 8 \text{ (1 mol%)}}{\text{cyclohexane azeotropic reflux, 3 h}} \overset{\text{Acetal: 74% yield; recovery of 13: failed}}{\text{Ph}}{\text{Ph}}{\text{O}}
\]

The use of 13: Acetal: 74% yield; recovery of 13: failed
The use of 8: Acetal: 86% yield; recovery of 8: 96%

\[
\overset{8 \text{ (3 mol%)}}{\text{toluene 70 °C; 14 h}} \overset{>99\% \text{ yield; recovery of 8: 70%}}{\text{Ph}}{\text{OBz}}
\]

\[
\overset{8 \text{ (1 mol%)}}{\text{MeOH 70 °C; 7 h}} \overset{>99\% \text{ yield; recovery of 8: 68%}}{\text{Ph}}{\text{CO}_2}\text{Me}
\]

Fluorous solid catalyst 8 is highly effective for the Mukaiyama aldol reaction [Eq. (6)] and the Sakurai-Hosomi allylation reaction [Eq. (7)]. These reactions have been performed at −78 °C and rt, respectively, under heterogeneous conditions. Post-reaction, 8 has been recovered in high yield by decanting the liquids at room temperature.

\[
\text{PhCHO} + \text{OSiMe}_3 \rightarrow \overset{1. \text{ 8 (3 mol%), toluene } -78 \ ^\circ \text{C; 3 h}}{\text{Ph}}{\text{OH}}{\text{O}}
\]

1. 8 (1 mol%), CH$_2$Cl$_2$, rt, 0.5 h
2. Addition of PhCHO (1 equiv) at rt over 30 min
3. Stirred at rt, 1 h

82% yield
Recovery of 8: 92%

84% yield
Recovery of 8: 97%

Pentafluorophenylbis(trifluoromethanesulfonyl)methane 10 offers a great advantage over other analogous super Brønsted acids such as tris(trifluoromethanesulfonyl)methane, trifluoromethanesulfonimide, and trifluoromethanesulfonic acid from the perspective of synthetic modification. Barrett’s group [12] and Mikami’s group [13] have independently re-
ported metal tris(perfluoroalkanesulfonyl)methides as fluorous Lewis acids. Similarly, it may be possible to design pentafluorophenylbis(perfluoroalkanesulfonyl)methanes. However, it is synthetically more concise and practical to append 1H,1H-perfluoroalkoxy groups to 10 by a para-substitution reaction. In addition, solid acids 8 and 9 are more active catalysts than perfluorosulfonic acids such as Nafion® [8].

Mikami’s group has also demonstrated the advantage of the fluorous super Lewis acids such as lanthanide tris(perfluorooctanesulfonyl)methide and perfluorooctanesulfonimide complexes with respect to temperature-dependent solubility [13b]. For example, these complexes can be reused for the Friedel-Crafts acylation reaction without fluorous solvents [Eq. (8)]. After heating the reaction mixture of anisole with acetic anhydride in 1,2-dichloroethane in the presence of ytterbium perfluorooctanesulfonimide (10 mol%) at 80 °C for 6 h, the mixture is allowed to stand at −20 °C for 30 min to precipitate the ytterbium complex. The liquid phase is decanted and the residual lanthanide complex is reused without isolation. No loss of activity is observed for the catalyst recovered. The total isolated yield of the product, which is combined from the three runs, is 78%.

\[
\begin{align*}
\text{OMe} & \quad + \quad \text{Ac}_2\text{O} \\
1 \text{ mmol} & \quad 2 \text{ mmol} \\
\text{Yb}[\text{N(SO}_2\text{C}_8\text{F}_{17})_2]\text{Cl, 80 °C, 6 h} & \quad \text{Total isolated yield: 78\%}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Use of catalyst</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Conversion</td>
<td>&gt;85</td>
<td>&gt;85</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

10.18.3

**Outlook**

One-solvent protocols of the type described above may be applicable to a wide variety of fluorous catalysts. It is probably not always necessary to traverse a melting point to achieve a sufficient solubility gradient. Nonetheless, one would expect that melting points of fluorous compounds can be engineered by shortening, lengthening, or branching the ponytails and by increasing/decreasing their numbers. The phase properties of a catalyst family could be optimized and tailored to a broad portfolio of solvents.

**References**

4. Ishihara, K.; Ohara, S.; Yamamoto,
Microwave-Assisted Fluorous Chemistry

Kristofer Olofsson and Mats Larhed

10.19.1 Introduction

Despite the fact that most of the time chemistry can be a fascinating and intellectually stimulating choice of occupation, it is no secret to the initiated that many reactions can be both time-consuming and involve tedious workup procedures. In particular, in the context of applying small-scale reactions in modern drug discovery and lead identification and optimization projects, the process of making chemical reactions faster and easier to purify is of paramount importance [1].

Microwave chemistry is a powerful and effective means of meeting the challenge to increase the speed of reactions [1–5]. The number of reports on microwave-assisted chemistry has increased rapidly during recent years [4] and as the understanding of the in situ superheating mechanisms behind the success of microwave heating has been clarified [6], this new technique has reached a level of acceptance in the chemical community that would have been difficult to foresee ten years ago. These achievements are followed hand in hand by the development of commercially available microwave reactors designed especially for
Microwave-Assisted Fluorous Chemistry

Kristofer Olofsson and Mats Larhed

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chemical synthesis, which are thus very different from the domestic microwave ovens used in the infancy of microwave chemistry. Computer controlled single-mode applicators have greatly increased the efficiency, safety and reproducibility of reactions conducted under microwave heating [7] even though the limited reaction scale is a constraint to the methodology [4]. Modern multi-mode reactors have also been applied in parallel synthesis [8].

Our own interest in homogeneous catalysis has revealed that microwave heating is advantageous in many areas of transition metal-catalyzed organic chemistry and the recent advances in this field have been reviewed [2, 5].

Having established that focused microwave heating is a reliable tool for increasing the speed of performing chemistry, we, together with Prof. Curran’s group, undertook to investigate the combination of fluorous [9] and microwave chemistry with the aim of introducing new protocols for both fast organic transformations and uncomplicated workup procedures. The importance of having easy and reliable separation protocols should not be underestimated as today it is easy, not only in microwave chemistry but also in combinatorial and parallel synthesis, to generate vast amounts of crude products in a short time.

10.19.2 Introducing Fluorous Groups in Microwave-Assisted Organometallic Chemistry

Following the rationale presented by Curran of using fluorous tags to ease the separation of organic reactions [10], a number of fluorous tags, with a varying degree of fluoricity, were evaluated in Stille- and radical mediated-reactions. These tags were introduced with the aim of inserting a fluorous handle that could be taken advantage of in the reaction phase of the synthesis and then easily cleaved or disposed of by other means in the separation phase. In the special applications of Stille-couplings [11] and stannous radical mediated reactions [12], special tin-containing fluorous reactants and reagents were designed to ease the otherwise often tedious workup procedures associated with these reactions. The fluorinated stannous compounds were envisioned to partition to a fluorous phase under workup and thus ensure a quick and reliable method of removing and isolating the tin-containing reagents from the rest of the reaction mixture.

However, the design of fluorous ligands is not without problems. It has been found that, when fluorous tags are used, the inductive power of the fluorine atoms can influence the reactivity of the tagged molecule. A spacer is often introduced between the fluorous kernel and the rest of the substrate in order to prevent inductive effects [13] (Scheme 10.19-1). The ideal length of the spacers has been the subject of several papers [14–16]. The use of longer spacers than the propylene tether does not seem to be of value and may increase the risk of micelle creation [13].

![Scheme 10.19-1. A fluorous tin reactant](image-url)
Fluorous Reaction Systems in Microwave Chemistry

The first report on microwave-heated fluorous palladium-catalyzed reactions was published in 1997 [17]. These Stille-couplings were performed in septa-sealed microwave transparent Pyrex vessels utilizing diverse reagents substituted with the \( \text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13} \) (F-13) tag and with reaction times as short as 1.5–2.0 min (Scheme 10.19-2). A wide selection of substrates and stannous reagents could be used. The unprotected aldehyde in example a) and the pyridine in example b) both constitute reactants that have been known to present problems in palladium-catalyzed Stille cross-coupling reactions. Vinyl triflates as in example c) could be used although the yields tended to be lower, as was the case with one reported allyl substrate [example d)]. The workup procedures were simple with three-phase extractions between a perfluorinated solvent (FC-84), an organic phase (dichloromethane) and water. Almost full partitioning of the fluorinated tin compounds to the fluorous phase was achieved and only traces of fluorous reagents and byproducts could be found in the organic phase after workup.

For a few applications it was recognized that the fluorous content of the F-13 tag was not sufficient to ensure a full partitioning of the tagged compound to the liquid fluorous phase. Large compounds with a high molecular weight need a higher fluorine content in the attached tag in order to be fully distributed. Indeed, the mass percentage of fluorine atoms compared with the total amount of non-fluorous atoms can usually give a good approxima-
tion of the solubility in fluorous media. Horváth recommended a fluorine content of at least 60% in order to ensure a good partitioning to a fluorous phase [13].

The most obvious solution to the problem of poor partitioning was to further enrich the tags with fluorine. This strategy was investigated and the tag \( \text{CH}_2\text{CH}_2\text{C}_{10}\text{F}_{21} \) (F-21) was duly introduced by Curran. However, efforts to use this ligand in oil bath heated Stille-reactions were met with disappointing and irreproducible results, plausibly caused by the insolubility of the F-21 ligand in both organic as well as perfluorinated or partly fluorinated solvents [18]. When microwave heating was applied to this reaction system it was soon evident that palladium-catalyzed couplings and radical mediated reactions could easily be carried out in single-mode reactors [18] (Scheme 10.19-3). Stille-couplings with the heavier F-21 tag were brought to full conversion within 6 min of microwave heating at 50 W power [example a)]. The radical reactions induced by AIBN in examples b) and c) also proceeded smoothly and in the case of example c) only catalytic amounts of the stannous hydride had to be used in combination with sodium cyanoborohydride. Example c) also presented an exceptionally straightforward workup procedure. The stannous byproducts that were dissolved under the high temperatures of the microwave reaction participated when brought back to room temperature and could thus easily be removed by silica filtration. No contamination of fluorous species in the organic phase was seen.

From this presentation it is possible to reach the conclusion that in order for a successful fluorous synthetic strategy to be realized, the fluorous content of the tags must be controlled. Too high a degree of fluorination may result in insoluble fluorous reactants that cannot react efficiently with non-fluorinated substrates; and a too low degree may, on the other hand, give leaching of the fluorinated content into the organic phase under a liquid/liquid separation. A different approach to exploiting fluoricity and an important and interesting application of fluorous chemistry has been developed by Curran in the use of fluorous reverse phase (FRP) chromatography [19]. Molecules with a low degree of fluorination are in this context beneficial as a good separation can be fulfilled by eluting non-fluorous com-
pounds with methanol and water and the fluorous compounds with acetonitrile [16, 19]. Lightly fluorinated phosphine bidentate ligands have very recently been investigated in microwave promoted and palladium-catalyzed regioselective Heck vinylations [20] (Scheme 10.19-4).

One attractive possibility when using fluorous ligands in metal catalysis is the option of recycling the often expensive ligands and catalysts used [21]. With that aim, the recyclability of the catalytic system with lightly to moderately fluorinated ligands 1a–c was studied [20] (Scheme 10.19-5).

Three different fluorous 1,3-bis(diphenylphosphino)propane (dppp) analogues (F-dppp) were prepared and their reactivities evaluated in an internal Heck-vinylation reaction. The para-substituted ligands 1a and 1c were found to be more widely applicable than the meta-substituted 1b. The lightly fluorinated 1a was also observed to react faster in DMSO than the more fluororous 1c: a finding that is reminiscent of the earlier results where the more heavily fluorinated tags reacted more sluggishly [17, 18]. The reactivities of dppp versus F-dppp (1a) under classic (18 h at 60 °C) as well as microwave (15 min at 90 °C) reaction conditions were compared. The isolated yields and the regioselectivities turned out to be in large identical, but there was a trend for a slightly lower regioselectivity when the fluorous ligand was used or when microwave heating was applied (Scheme 10.19-4).

### Scheme 10.19-4. Heck-coupling with fluorous and non-fluorous ligands under oil-bath or controlled microwave heating

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Method of Heating</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Selectivity (α/β)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dppp</td>
<td>Standard</td>
<td>60</td>
<td>18 h</td>
<td>96/4</td>
<td>53</td>
</tr>
<tr>
<td>dppp</td>
<td>MW</td>
<td>90</td>
<td>15 min</td>
<td>91/9</td>
<td>57</td>
</tr>
<tr>
<td>F-dppp (1a)</td>
<td>Standard</td>
<td>60</td>
<td>18 h</td>
<td>94/6</td>
<td>46</td>
</tr>
<tr>
<td>F-dppp (1a)</td>
<td>MW</td>
<td>90</td>
<td>15 min</td>
<td>90/10</td>
<td>46</td>
</tr>
</tbody>
</table>

### Scheme 10.19-5. Fluorous bidentate ligands (F-dppp)

1a = \(p\)-CH\(_2\)CH\(_2\)C\(_4\)F\(_9\)

1b = \(o\)-CH\(_2\)CH\(_2\)C\(_4\)F\(_9\)

1c = \(p\)-CH\(_2\)CH\(_2\)C\(_6\)F\(_{13}\)
The same methodology was also applied on a cyclic enamide as the olefin and, in another coupling, with a steroidal vinyl triflate as the substrate [20]. All traces of fluorous reagents were handily removed from the reaction medium by direct solid fluorous phase separation using a 90% methanol/10% water eluting system. However, attempts to reuse the isolated catalyst from the reaction did not result in a productive coupling: a fact that, as the authors suggest, may implicate breakdown of the catalytic system during the course of the reaction.

All in all, the outcome of the protocols has given very positive indications of the use and applicability of microwave-heated fluorous chemistry. The reactivity of Stille- and radical mediated-reactions are maintained in the fluorous procedures and the regioselectivity in Heck-couplings have been shown to be preserved.

10.19.4

Outlook

Microwave and fluorous chemistry are both new and up-and-coming techniques that have yet to reach their full potential. To predict the exact direction that the combination of these two methodologies will take is thus likely to be a challenge. However, a few themes could be brought up for discussion.

Fluorous chemistry can be used to good effect in synthetic strategies if the reaction conditions and choice of reagents can be controlled to ensure a smooth separation. This has been proven to work both with heavily fluorinated tags and more recently with more lightly fluorinated tags in combination with fluorous reverse phase chromatography (FRP). These convenient separation procedures in combination with the speed of microwave-assisted chemistry have the potential to reduce the time necessary for both synthesis and separation in modern high throughput applications [5].

When toxic compounds, for example the tin reagents used in the palladium-catalyzed Stille-reactions, have to be used; it would not only be convenient but also environmentally advantageous if the toxic compounds could be easily contained and separated from the reaction mixture. It has been shown that fluorous chemistry fulfills this need and that microwave-assisted reactions ensure short reaction times. One further benefit of this strategy is the potential possibility of recycling expensive ligands and metal catalysts.

Despite the drawbacks of the cost of equipment and the limited availability of some reagents and solvents, the outlook for microwave-heated, fluorous chemistry is bright, especially in the field of small-molecule drug discovery. Some keywords that easily could be associated with these techniques include High-speed synthesis, Convenient chromatography and Environmental benefits: all of which should be of great interest for industrial applications. As the number of groups and companies interested in these areas increase there is a promise for the introduction of further accomplishments and novel applications of microwave and fluorous chemistry in the future.

Acknowledgment

We thank Knut and Alice Wallenberg’s Foundation, PersonalChemistry AB and Biolipox.
References

11 Preparations

11.1 (R)-6,6'-Diperfluorobutyl-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluorobutylation of Dibromobinaphthol

*Kin Shing Chan and Yuan Tian*

**Reaction 11.1-1**

![Chemical structure](image)

**Experimental Procedure**

A mixture of enantiomerically pure (R)-6,6'-dibromo-1,1'-binaphthol (1) [1] (2.22 g, 5.0 mmol), copper bronze (3.2 g, 50 mmol) [2] and perfluorobutyl iodide (6.92 g, 3.44 mL, 20 mmol) in anhydrous DMSO (50 mL) is degassed three times with the freeze-pump-thaw cycles using liquid nitrogen, and is then heated to 90 °C for 5 days. After cooling to room temperature, ethyl acetate (150 mL) is added and the mixture is filtered through Celite. The filtrate is washed with 10% HCl, water, brine and dried over MgSO4. After removal of the solvent, the residue is purified by column chromatography eluting with ethyl acetate/hexane (1/6) to give the product (1.25 g, 52%) as a white solid [3]: mp 65–66 °C; $[\alpha]_D^{20} = -25.7$ (c 1.0, CHCl3); $^1$H NMR (300 MHz, CDCl3) δ 5.30 (brs, 2 H), 7.22 (d, 2 H, $J = 8.9$ Hz), 7.45 (d, 2 H, $J = 8.8$ Hz), 7.51 (d, 2 H, $J = 9.0$ Hz), 8.11 (d, 2 H, $J = 9.0$ Hz), 8.18 (s, 2 H); $^{13}$C NMR (75.5 MHz, CDCl3) δ 110.62, 115.80 (q, $J = 31.7$ Hz), 119.29, 124.53, 124.61, 124.77, 128.33, 132.69, 135.05, 154.73; EIMS m/z (relative intensity) 723 ([M + H]+, 82), 704 (7), 553 (100), 525 (7), 485 (3), 333 (12); FABMS m/z (relative intensity) 722 (M+ , 100), 704 (8), 694 (2), 584 (2), 569 (2), 553 (59); HRMS (M+). Calc. for C38H12O2F18 722.0544. Found 722.0513; >99% ee.
Discussion

The copper is activated by adding to a suspension of copper bronze (3.18 g, 50 mmol) in acetone (20 mL) a few crystals of iodine [2]. After 30 min, the solvent is removed and the copper is washed sequentially with HCl in acetone and then acetone.

The copper mediated perfluoroalkylations of dibromobinaphthol in other polar aprotic solvents, such as DMF, HMPA and NMP, are not successful. The temperature of the reaction in DMSO needs to be well-controlled. Higher reaction temperature erodes the enantiopurity of the product.

Enantiomerically pure (S)-6,6'-diperfluorobutyl-1,1'-binaphthyl-2,2'-diol [3] is also obtained in the same way; mp 60–63 °C; [a]_D^20 = +26.1° (c: 0.5, CHCl_3). The enantiomeric purities of both isomers are determined by HPLC using a chiral Daicel OD-H column (0.46 × 15 cm). Solvent system: hexane/2-propanol = 9:1; flow rate: 1.0 mL min⁻¹. For R-isomer: T_R = 5.51 min; for S-isomer: T_R = 3.61 min.

References


11.2 (R)- and (S)-4,4',6,6'-Tetrafluoroocycty-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluoroalkylation of Tetrabromobinaphthol and Resolution

Kin Shing Chan and Yuan Tian

Reaction 11.2-1
Experimental Procedures

**Step A. Racemic-4,4′,6,6′-tetaperfluoro-octyl-1,1′-binaphthyl-2,2′-diole 2** [1] A mixture of 4,4′,6,6′-tetrabromo-1,1′-binaphthol 1 [2] (1.0 g, 1.66 mmol), copper bronze [3] (1.6 g, 25 mmol) and perfluoroctyl iodide (5.46 g, 2.6 mL, 10 mmol) in anhydrous DMSO (15 mL) is degassed three times by the freeze-pump-thaw cycles using liquid nitrogen and is then heated to 160 °C for 3 days. After cooling to room temperature, ethyl acetate (50 mL) is added and the mixture is filtered through Celite. The filtrate is washed with 10% HCl, water, brine and dried over MgSO₄. After removal of the solvent, the residue is purified by column chromatography eluting with ethyl acetate/hexane (1/10) to give 2 (1.48 g, 46%) as a yellow oil: Rₐ = 0.17 (ethyl acetate/hexane = 1/10); ¹H NMR (300 MHz, CDCl₃) δ 5.86 (brs, 2 H), 7.27 (d, 2 H, J = 7.6 Hz), 7.56 (d, 2 H, J = 8.9 Hz), 7.87 (s, 2 H), 8.55 (s, 2 H); FABMS m/z (relative intensity) 1159 ([M + H]⁺, 85), 1141 (17), 990 (100), 853 (3), 820 (19), 772 (18); SIMS m/z 1959 ([M + H]⁺). Anal. calc. for C₅₂H₁₀F₆₈O₂: C, 31.89; H, 0.89. Found: C, 32.02; H, 0.73.

**Step B. Diastereomers 2,2′-Di-[(1S)-camphor-10-sulfonyl]-4,4′,6,6′-tetaperfluoro-octyl-1,1′-binaphthyl (R)- and (S)-2-(S)-CS** To a solution of 4,4′,6,6′-tetaperfluoro-octyl-BINOL 2 (1.18 g, 0.60 mmol) at 0 °C, (1S)-camphor-10-sulfonyl chloride (605 mg, 2.4 mmol) in dry CCl₄ (20 mL) and triethylamine (304 mg, 0.57 mL, 3.0 mmol) are added. The yellow solution is refluxed for 2 days. After cooling to room temperature, water (15 mL) is added and the mixture is extracted with CCl₄. The combined organic layer is washed with brine and dried over MgSO₄. After evaporation of the solvents, the residue is purified by column chroma-
tography using a solvent mixture of ethyl acetate/hexane (1/6) to give a mixture of diasteromers \((\pm)-2-(S)\)-CS (1.1 g, 76%) as a white solid. Further careful column chromatography (hexane/dichloromethane \(= 10/7\)) gives a less polar diastereomer \((S)-2-(S)-CS\): mp 127–128 °C; \(R_f = 0.25\) (hexane/dichloromethane = 10/7); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 0.60\) (s, 6 H), \(0.81\) (s, 6 H), \(1.27\)–\(1.30\) (m, 4 H), \(1.80\) (d, 2 H, \(J = 18.6\) Hz), \(1.85\)–\(2.02\) (m, 6 H), \(2.22\) (dd, 2 H, \(J = 18.6, 2.9\) Hz), \(2.77\) (d, 2 H, \(J = 14.9\) Hz), \(3.17\) (d, 2 H, \(J = 14.9\) Hz), \(7.43\) (d, 2 H, \(J = 8.9\) Hz), \(7.65\) (t, 2 H, \(J = 9.1\) Hz), \(8.29\) (s, 2 H); \(^13\)C NMR (75.5 MHz, CDCl\(_3\)) \(19.11, 19.18, 24.72, 26.58, 42.06, 42.63, 47.71, 49.77, 57.65, 107.76, 110.94, 114.87, 124.89, 125.34, 127.50, 127.94, 128.85, 129.23, 135.18, 145.86, 212.57. Anal. calcd. for C\(_{72}\)H\(_{38}\)F\(_{68}\)S\(_2\)O\(_8\): C, 36.23; H, 1.60. Found: C, 36.12; H, 1.86. A second fraction of the more polar diastereomer \((R)-2-(S)-CS\) is also isolated: mp 109–110 °C; \(R_f = 0.19\) (hexane/dichloromethane = 3/5); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 0.58\) (s, 6 H), \(0.68\) (s, 6 H), \(1.23\)–\(1.34\) (m, 4 H), \(1.80\) (d, 2 H, \(J = 18.6\) Hz), \(1.78\)–\(1.81\) (m, \(J = 14.9\) Hz), \(3.49\) (d, 2 H, \(J = 15.0\) Hz), \(7.40\) (d, 2 H, \(J = 8.9\) Hz), \(7.63\) (t, 2 H, \(J = 9.1\) Hz), \(8.30\) (s, 2 H), \(8.64\) (s, 2 H). Anal. calc. for C\(_{72}\)H\(_{38}\)F\(_{68}\)S\(_2\)O\(_8\): C, 36.11; H, 1.52.

**Step C.** \((S)-4,4'\)-Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol (S)-2 To a suspension of \((S)-2-(S)-CS\) (239 mg, 0.10 mmol) in methanol (10 mL) and CCl\(_4\) (10 mL), NaOH (1 M, 5 mL) is added. The resulting yellow solution is stirred at 60 °C for 24 h. After cooling to room temperature, 10% HCl is added to neutralize the solution to pH 7. Methanol is removed in vacuo and the residue is extracted with CCl\(_4\). The combined organic layer is washed with brine and dried over MgSO\(_4\). After removal of the solvent, the product is purified by column chromatography eluting with ethyl acetate/hexane (1/10) to give \((S)-2\) (167 mg, 85%) as a yellow oil: \([\alpha]_{D}^{20} = -15.7\) (c 0.15, ethyl acetate). The \(^1\)H NMR spectrum is the same as the racemic compound.

\((R)-4,4',6,6'-\)Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol (R)-2 The same procedure is used to saponify \((R)-2-(S)-CS\). \((R)-2\) is obtained as a yellow oil in 79% yield: \([\alpha]_{D}^{20} = +15.6\) (c 0.96, ethyl acetate).

**Discussion**

The copper is activated by adding a few crystals of iodine to a suspension of copper bronze (3.18 g, 50 mmol) in acetone (20 mL) [3]. After 30 min, the solvent is removed and the copper is washed sequentially with HC1 in acetone and then acetone. The high reaction temperature (160 °C) gives good yield in the perfluorooctylation; however, the binaphthyl chiral axis racemizes if the enantiopure precursor is used. At lower reaction temperature, little perfluoroctylation occurs. Therefore, enantiomerically pure products have to be prepared by resolution.

Commercially available (1\(S\))-camphor-10-sulfonyl chloride is only 97% pure and is not pure enough for resolution. \((1S)\)\(+\)-Camphor-10-sulfonyl chloride is prepared from the reaction of \((1S)\)\(+\)-camphor-10-sulfonic acid with phosphorus pentachloride [4].

The absolute configuration of the camphorsulfonates is assigned based on proton NMR and CD spectra and the X-ray structure of the perfluorobutyl analog [1]. The enantiopurities of \((S)-2\) and \((R)-2\) are determined by the proton NMR spectra of their corresponding camphorsulfonates.
11 Preparations

4-Aminobenzoic Acid. The Staudinger Reduction with a Fluorous Phosphine Reagent

Craig W. Lindsley and Zhijian Zhao

Reaction 11.3-1

\[
\begin{align*}
\text{N}_3 & \quad \text{COOH} \\
\downarrow & \quad \downarrow \\
\text{Ph}_2\text{P} & \quad \text{H}_2\text{N} \quad \text{COOH} \\
\text{THF, 1 h, RT} & \quad \text{H}_2\text{O, 3 h, 60 }^\circ\text{C}
\end{align*}
\]

93%

Reagents

Diphenyl-[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phosphine [462996-04-9] is commercially available from Fluorous Technologies, Inc. (www.fluorous.com) or can be prepared according to the literature procedure [1]. FluoroFlash™ silica gel from Fluorous Technologies, Inc. was used for the solid phase extraction.

Experimental Procedure

In a 10 mL round-bottomed flask is placed 4-azidobenzoic acid (82 mg, 0.50 mmol) and diphenyl-[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phosphine (389 mg, 0.55 mmol) in dry THF (3 mL). Immediately, gas evolution is observed. After 1 h, water (500 μL) is added, and the reaction vessel is warmed to 60 °C for 3 h, when the solvent is then evaporated and the residue is loaded onto a 5 g FluoroFlash™ SPE cartridge using 5% aqueous methanol. Elution with 15% aqueous methanol (10 mL) and evaporation of the solvent provides analytically pure 4-aminobenzoic acid (64 mg, 93%). A second elution with THF (20 mL) provides the corresponding fluorous phosphine oxide.

Discussion

The Staudinger reaction is a mild, chemoselective method for the reduction of functionalized azides to the corresponding amine [2]. While the reaction itself is operationally very simplistic, developing a Staudinger protocol amenable to solution phase parallel synthesis,
free from triphenylphosphine byproducts is not. Indeed, polymer-supported triphenylphosphine has been employed, but reaction and conversion rates are very poor [3, 4].

Recently, a fluorous variant of the Staudinger reduction appeared [4]. In this variant, a solution phase, homogeneous fluorous-tagged phoshine is used. Reduction rates are the same as with traditional triphenylphosphine, and 10-fold faster than with polymer-supported congeners. Solid phase extraction over FluoroFlash™ silica gel allows for the general and rapid separation of the desired amine from the spent fluorous reagents [5].

References


11.4 1,2-Diethyl-6a,10-dimethoxy-1,6a,11b,11c-tetrahydro-2H-benzo[k]xanthen-4-one

11.4 1,2-Diethyl-6a,10-dimethoxy-1,6a,11b,11c-tetrahydro-2H-benzo[k]xanthen-4-one. β,β-Phenolic Coupling Reactions to Access Unnatural Carpanone Analogs with a Fluorous Diacetoxy Iodobenzene (F-DAIB) Reagent

Craig W. Lindsley and Zhijian Zhao

Reaction 11.4-1

Reagents

4-(1H,1H,2H,2H-Perfluorodecyl)-1-(diacetoxyiodo)benzene (F-DAIB) 2 is commercially available from Fluorous Technologies, Inc. (www.fluorous.com). FluoroFlash™ silica gel from Fluorous Technologies, Inc. was used for the solid phase extraction.

Experimental Procedure

In a 10 mL round-bottomed flask is placed styrenyl phenol 1 (53.4 mg, 0.3 mmol) and CH₂Cl₂ (3 mL). To this solution is than added F-DAIB 2 (230 mg, 0.3 mol). The solution quickly changes from a pale yellow to a deep orange hue. After 20 min, the solvent is evaporated and the residue is loaded onto a 5 g FluoroFlash™ SPE cartridge in 5% aqueous
methanol. Elution with 20% aqueous methanol (10 mL) and evaporation of the solvent delivers unnatural carpanone analog 3 (46 mg, 86%). A second elution with THF (20 mL) gives a mixture of F-DAIB 2 and the reduced fluorous-tagged iodobenzene. The iodide can be converted back into 2.

Discussion

Diacetoxy iodobenzene (DAIB) is a mild, yet powerful one electron oxidant that facilitates a number of chemical transformations [1]. Often times, chromatographic separation of the desired products from excess DAIB and the iodobenzene byproduct is problematic. In short order, both “heavy” and “light” fluorous-tagged DAIB derivatives have been prepared to facilitate purification by liquid/liquid or solid phase extraction protocols, respectively [2].

Recently, DAIB has been shown to effect hetero- and homo-β,β-phenolic couplings to access unnatural carpanone analogs on the solid phase [3]. A complimentary, solution phase parallel synthesis approach for the diversity-oriented synthesis of unnatural carpanone analogs takes advantage of fluorous-tagged DAIB congeners, such as 2, to generate the carpanone core through a homo-β,β-phenolic coupling reaction followed by an inverse electron demand Diels-Alder reaction. In this instance, solid phase extraction on FluoroFlash™ SPE cartridges has proven to be a general method for the purification of diverse, unnatural carpanone-like molecules such as 3, with clean separation from the fluorous reagent [4].

References


11.5

4-Nitro-1,1′-biphenyl. Suzuki Coupling in Liquid/Liquid FBS

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

Reaction 11.5-1

\[
\begin{align*}
\text{Br} & \quad + \quad \text{B(OH)}_2 \\
\text{NO}_2 & \quad \xrightarrow{1, \text{PFMCH, DME, aq. Na}_2\text{CO}_3} \quad \xrightarrow{2 \, \text{h, } 75 \, ^\circ\text{C}} \quad \text{NO}_2
\end{align*}
\]

\[\left(\text{C}_8\text{F}_{17}\right)_{\text{P}}\] \[\text{PdCl}_2\]
Reagents

Dichlorobis[tris(4-(3,3,4,4,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-phenyl]phosphane]palladium 1 [326475-46-1] is commercially available from Fluka [1] or can be prepared according to the literature procedure [2, 3]. Perfluoromethylcyclohexane (PFMCH) [355-02-2] is available from Fluka.

Experimental Procedure

A 20 mL Schlenktube with magnetic stir-bar is charged with complex 1 (10 mg, 3 μmol, 0.015 equiv). Under argon, perfluoromethylcyclohexane (1.5 mL), stock solutions of 4-nitro-bromobenzene (0.2 M in dimethoxyethane [DME], 1.0 mL, 0.2 mmol, 1.00 equiv) and phenylboronic acid (0.44 M in DME, 0.5 mL, 0.22 mmol, 1.10 equiv) and aq. Na₂CO₃ (2 M, 1.0 mL, 2 mmol, 10 equiv) are added. The mixture is heated to 75°C for 2 h. After cooling to rt, the aqueous and organic phases are separated from the fluorous phase. The fluorous phase is sequentially extracted with DME (2 × 1 mL), H₂O (2 × 1 mL) and DME (2 × 1 mL). The fluorous phase containing the catalyst can be used as such for the next run. The combined aqueous and organic phases are diluted with H₂O (4 mL) and extracted with diethyl ether (4 × 1 mL). The combined extracts are concentrated in vacuo, the residue taken up in diethyl ether (1 mL) and passed through a plug of neutral alumina (activity 2–3, 2 mL) and silica gel (4 mL). The filtrate is concentrated to dryness, yielding the product as a pale yellow solid (36 mg, 0.18 mmol, 91%).

Discussion

The Suzuki reaction is one of the most attractive possibilities for the formation of biaryls [4]. This is because a variety of functional groups are tolerated and substrates are stable, readily available and of low toxicity.

This fluorous protocol simplifies the isolation of the product significantly and offers the possibility of reusing the catalyst. The procedure was applied to several substrates, and Pd complexes with different fluororous tags were employed. The catalysts were recycled up to five times. In all cases high yields were obtained and no difference in the reactivity of the catalyst precursors was apparent [2].

References

1 Fluka Chemie GmbH, CH-9471 Buchs, Switzerland.
3 S. Schneider, W. Bannwarth, Angew.
11.6  
1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling in Liquid/Liquid FBS

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

Reaction 11.6-1

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \\
\text{Br} & \quad \text{PdCl}_2
\end{align*}
\]

1. FC-72, CuI, nBu₂NH, DMF

4 h, 55 °C

98%

Reagents

FC-72 is a mixture of perfluorohexane isomers [355-42-0] and can be obtained from Fluka.

Experimental Procedure

A dry 20 mL Schlenktube with magnetic stir-bar is charged with complex 1 (20 mg, 0.02 equiv) and 4-nitro-bromobenzene (62 mg, 0.30 mmol, 1.0 equiv). The flask is evacuated and refilled with argon (3 ×). A solution of CuI (2.9 mg, 0.05 equiv) and di-n-butylamine (102 µl, 0.6 mmol, 2.0 equiv) in DMF (0.4 mL) is prepared in a second Schlenktube under argon. To the reaction flask are added FC-72 (0.7 mL), phenylacetylene (40 µl, 0.36 mmol, 1.2 equiv) and the CuI solution. The reaction mixture is heated to 55 °C for 4 h. After cooling to 0 °C, the organic phase is separated and the fluorous phase is extracted with DMF (3 × 2 mL). The fluorous phase can be used as such for the next run. The combined organic phases are diluted with brine (40 mL) and aqueous HCl (0.5 M, 10 mL) and extracted with CHCl₃ (4 × 2 mL). The combined extracts are washed with saturated aqueous NaHCO₃ (4 mL), the NaHCO₃ solution is back-extracted with CHCl₃ (5 mL) and the combined CHCl₃ phases are evaporated. To completely remove the DMF, the residue is taken up in diethyl ether (5 mL), washed with brine (4 mL) and passed through a plug of silica gel (4 mL) and neutral alumina (activity 2–3, 2 mL). Removal of the solvent in vacuo yields the product together with excess alkyne as a brown oil. After column chromatography (silica gel, cyclohexane/ethyl acetate 20:1) yellow crystals (67 mg, 0.3 mmol, 98%) are obtained.

Discussion

The Sonogashira reaction is an efficient reaction for the catalytic coupling of aryl halides with terminal alkynes [1]. A drawback is that high catalyst loadings in the range of 5 to 10
mol% are usually used. This highlights the necessity of an efficient protocol for the separation of the catalyst. The present procedure has been applied to different alkynes and aryl halides. The yields depend very much on the reactivity of the aryl halide. While reactive substrates such as aryl iodides or electron-deficient aryl bromides gave high yields and recycling of the catalyst was possible, electron rich aryl bromides gave lower yields and catalyst recycling was not successful. Different Pd complexes were used, but no significant differences in the reactivity were observed.

During the reaction, oxygen has to be rigorously excluded to avoid homocoupling of the alkyne. Therefore all solvents have to be carefully degassed prior to use. It is also possible to use perfluoromethylcyclohexane as the fluorous phase in order to allow for higher reaction temperatures. The elaborate extraction sequence during workup is necessary to obtain the products free of DMF [2].

References


11.7 4-Nitro-1,1′-biphenyl. Suzuki Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

Reaction 11.7-1

\[
\begin{align*}
\text{NO}_2 & \quad \text{B(OH)}_2
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{1 on FRPSG, DME, aq. Na}_2\text{CO}_3
\end{align*}
\]

\[
\begin{align*}
15 \text{ h, } 80 \degree \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{95%}
\end{align*}
\]

Reagents

The supported complex is prepared as mentioned below. Fluorous reverse phase silica gel (FRPSG) suited for this application can be prepared according to the literature procedure [1].
Immobilization of Pd-complexes on FRPSG

In a round-bottomed flask, complex 1 (29.8 mg) is dissolved in a sufficient amount of diethyl ether (~200 mL) and FRPSG (2945 mg) is added. The solvent is removed by rotary evaporation. To the dry FRPSG is added diethyl ether (~200 mL) and the solvent is again removed by rotary evaporation. Drying in vacuo gives the FRPSG-supported complex 1 as a pale yellow free flowing solid.

Experimental Procedure

A 50 mL Schlenktube is charged with FRPSG-supported complex 1 (100 mg, containing 1 mg complex, 0.3 μmol, 0.001 equiv), evacuated and refilled with argon (3×). Stock solutions of 4-nitrobromobenzene (0.3 M in DME, 1.0 mL, 0.3 mmol, 1.00 equiv) and phenylboronic acid (0.33 M in DME, 1.0 mL, 0.33 mmol, 1.10 equiv) and aqueous Na₂CO₃ (2 M, 1.0 mL, 2.0 mmol, 6.7 equiv) are added. The tube is sealed with a screw cap and shaken at 80 °C for 15 h. The reaction mixture is cooled to 0 °C and the liquid phase is removed under argon with a pipette. The FRPSG is washed with DME (2×2 mL), water (2×2 mL) and DME (2×2 mL). The combined liquid phases are diluted with water (40 mL) and brine (20 mL) and are extracted with tert-butylmethylether (3×20 mL). The combined extracts are concentrated in vacuo, the residue is taken up in diethyl ether (2 mL), put on a plug of neutral alumina (activity 2–3, 3 mL) and eluted with diethyl ether (~14 mL). Evaporation of the solvent gives the product (57 mg, 0.29 mmol, 95%). The immobilized catalyst can be reused as such in further experiments.

Discussion

The present protocol is particularly suited for automated combinatorial synthesis, since the solid support is easily separated by decantation or filtration. The dilution of the precatalyst allows for the accurate weighing of very small amounts of catalysts, which simplifies the miniaturization of the reaction setup for parallel synthesis.

With 4-nitrobromobenzene and phenylboronic acid, different Pd complexes were employed and were recycled three times without apparent loss of activity or differences between the catalysts. A maximal turnover number of 131 000 was achieved when the catalyst loading was lowered to 0.001 mol%.

The procedure has been used for a number of different aryl bromides. With electron-deficient substrates, high yields were achieved and the catalyst was successfully recycled. With electron-rich aryl bromides, conversion was often not complete and yields dropped significantly upon recycling of the catalyst [2].

References

11.8

1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

Reaction 11.8-1

\[
\begin{align*}
\text{Br} & \quad + \quad \text{I} \\
\text{Br} & \quad \text{I} \\
\text{C}_8\text{F}_{17} & \quad \text{PdCl}_2
\end{align*}
\]

1 on FRPSG, CuI, nBu\textsubscript{2}NH, DMF

14 h, 100 °C

100%

Reagents

see previous procedure.

Experimental Procedure

A dry 50 mL Schlenktube is charged with FRPSG supported complex 1 (200 mg, containing 2 mg complex, 0.6 μmol, 0.002 equiv), CuI (1.0 mg, 5 μmol, 0.02 equiv) and 4-nitro bromobenzene (62 mg, 0.30 mmol, 1.0 equiv). The flask is evacuated and refilled with argon (3 ×). To the reaction flask are added DMF (2.0 mL), di-n-butylamine (102 μl, 0.6 mmol, 2.0 equiv) and phenylacetylene (40 μl, 0.36 mmol, 1.2 equiv). The tube is sealed with a screw cap and shaken in an oil bath at 100 °C for 14 h. After cooling to 0 °C, the liquid phase is removed under argon with a pipette and the FRPSG is washed with DMF (3 × 2 mL). The combined organic phases are diluted with brine (40 mL) and aqueous HCl (0.5 M, 15 mL) and extracted with CHCl\textsubscript{3} (4 × 4 mL). The combined extracts are washed with saturated aqueous NaHCO\textsubscript{3} (4 mL), the NaHCO\textsubscript{3} solution is back-extracted with CHCl\textsubscript{3} (4 × 4 mL) and the combined CHCl\textsubscript{3} phases are evaporated. To remove the DMF completely, the residue is taken up in diethyl ether (5 mL), washed with brine (4 mL) and the aqueous phase is back-extracted with diethyl ether (4 × 4 mL). The combined ether phases are passed through a plug of silica gel (4 mL) and neutral alumina (activity 2–3, 2 mL), and washed down with additional diethyl ether (~10 mL). Removal of the solvent in vacuo yields the product together with excess alkyne as a brown oil. The immobilized catalyst can be reused as such in further experiments.

Discussion

The procedure offers similar opportunities to those mentioned previously for the Suzuki coupling [1].
Tris(4-perfluorohexylphenyl)phosphine. Synthesis of Perfluoroalkyl Aryl Phosphines by Copper-mediated Cross Coupling

Weiping Chen and Jianliang Xiao

Reaction 11.9-1

Reagents

Step A. Tris(4-perfluorohexylphenyl)phosphine Oxide (3) A mixture of 1 (515 mg, 1.0 mmol), 2 (1.405 g, 3.2 mmol), copper powder (450 mg, 7.1 mmol), 2,2'-bipyridine (34 mg, 0.2 mmol), DMSO (1.0 mL), and benzotrifluoride (10 mL) is refluxed with stirring for 24 h under nitrogen in a two-necked flask. The mixture is then cooled to room temperature, filtered through a ca. 1 cm long pad of Celite. The flask is washed with CHCl₃ (2 x 20 mL) and each washing is filtered through the Celite. The combined filtrates are washed successively with 1 n HCl (2 x 50 mL), water (50 mL) and brine (30 mL), dried over anhydrous MgSO₄, and evaporated on a rotary evaporator. The resulting solid is crystallized from hot EtOH to give tris(4-perfluorohexylphenyl)phosphine oxide 3 as colorless needles (1.133 g, 92%), mp 136–138 °C: ¹H NMR (CDCl₃, 400 MHz) δ 7.77 (dd, 6 H, J = 8.3, 2.1 Hz), 7.84 (dd, 6 H, J = 11.4, 8.3 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 127.5 (dt, 3 J₇C = 16.6 Hz, 6 JCF = 6.6 Hz), 132.3 (d, 3 JCP = 10.2 Hz), 133.4 (td, 2 JCF = 21.1, 4 JCP = 2.4 Hz), 135.6 (d, 1 JCP = 101.7 Hz) (the ¹³C signals of the fluorocarbon chains were too weak to be assigned); ³¹P NMR (CDCl₃, 101 MHz) δ 25.6 (s). Anal. calc. for C₃₆H₁₂F₃₉PO: C, 35.09; H, 0.98. Found: C, 35.35; H, 0.97.

Step B. Tris(4-perfluorohexylphenyl)phosphine (4) To a mixture of 3 (2.465 g, 2.0 mmol), triethylamine (4.554 g, 45 mmol), and toluene (20 mL) in a three-necked flask is injected...
trichlorosilane (4.064 g, 30 mmol) under nitrogen. The mixture is stirred at 120 °C for 6 h under nitrogen. The mixture is cooled to room temperature and further cooled with an ice bath for 10 min, to which is then added degassed, saturated NaHCO3 aqueous solution (1 mL). Under nitrogen, the mixture is stirred for 10 min and filtered through a short alumina column. The flask is washed with hexane and the washings are filtered through the alumina. The combined filtrates are then concentrated on a rotary evaporator to afford tris(4-perfluorohexylphenyl)phosphine 4 as a white solid (2.384 g, 98%), mp 66–68 °C: 1H NMR (CDCl3, 200 MHz) δ 7.42 (dd, 6 H, JPH = 8.2, JHH = 7.7), 7.61 (d, 6 H, JHH = 7.7); 31P NMR (CDCl3, 101 MHz) δ −6.1 (s). For other analytical details on this compound, see reference [2].

Discussion

Perfluoroalkyl-derivatized triarylphosphines can be prepared by lithiation of perfluoroalkyl bromobenzenes followed by reaction with PAr3Cln [2, 3]. This methodology involves using moisture-sensitive and pyrophoric reagents and low temperatures, and gives low yields of product relative to the perfluoroalkyl reagents used. The current method centers on copper-mediated cross coupling of bromoarylphosphine oxide 1 with a perfluoroalkyl iodide 2 and is simpler and higher yielding [4, 5]. Phosphine oxide 1 can be easily prepared from 1,4-dibromobenzene and phosphorus chloride [1]. Since the perfluoroalkylation of 1 reduces its solubility in normal organic solvents, the choice of solvent is important to ensure rapid coupling rates and high yields of 3. For instance, longer reaction times and lower yields resulted when the reaction was performed in DMSO compared with a mixture of perfluoro-1,3-dimethylcyclohexane and DMSO (10:1, v/v). Benzotrifluoride in the presence of DMSO (10:1, v/v) is even better. This medium dissolves both the starting materials and products under the reaction conditions, and BTI is inexpensive with low toxicity and favorable environmental properties [6]. With this solvent mixture, the workup is also simpler. Thus, the pure product can be easily obtained by filtering off the excess copper and copper salts followed by washing with HCl and water to remove the remaining copper salts and DMSO prior to drying. The phosphine 4 was readily released from the oxide by reduction with trichlorosilane following normal procedures. The method described herein can be extended to the synthesis of mono-, bis-, and tris-perfluoroalkyl-substituted arylphosphines with either short or long fluorous chains and with an overall yield usually close to 90% [4].

References

11.10
Tris[4-(1H,2H,2H-perfluorooctyl)phenyl]phosphine. Synthesis of Fluoroalkyl Arylphosphines by the Heck Reaction

Weiping Chen and Jianliang Xiao

Reaction 11.10-1

Step A

\[
\begin{align*}
O=P\left(\begin{array}{c}
\text{Br} \\
\text{Br} \\
\text{Br}
\end{array}\right) \quad \text{palladacycle} & \quad \text{DMF, 125 °C} & \quad 3, 91% \\
& \quad 24 h
\end{align*}
\]

Step B

\[
\begin{align*}
O=P\left(\begin{array}{c}
\text{C}_2\text{H}_4\text{C}_6\text{F}_{13} \\
\text{C}_2\text{H}_4\text{C}_6\text{F}_{13}
\end{array}\right) \quad \text{Pd/C} & \quad \text{EtOAc, rt} & \quad 4, 100%
\end{align*}
\]

Step C

\[
\begin{align*}
O=P\left(\begin{array}{c}
\text{C}_2\text{H}_4\text{C}_6\text{F}_{13} \\
\text{C}_2\text{H}_4\text{C}_6\text{F}_{13}
\end{array}\right) \quad \text{Pd/C} & \quad \text{EtOAc, rt} & \quad \text{Pd/C} \quad \text{EtOAc, rt}
\end{align*}
\]

Reagents

Tris(4-bromophenyl)phosphine oxide 1 [1] and the Herrmann-Beller palladacycle [2] were prepared according to published procedures. The palladacycle is also available from Strem (46-0290). 1H,1H,2H-Perfluoro-1-octene 2 was purchased from Aldrich or Apollo Scientific Ltd. and used without further purification. The Pd/C (10%) catalyst was obtained from Aldrich (20,569-9). Toluene and triethylamine were distilled over CaH₂ under nitrogen prior to use. DMF, NaOAc, ethylacetate, chloroform, and trichlorosilane were used as received.

Experimental Procedures

Step A. Tris[4-(1H,2H-perfluorooct-1-ethyl)phenyl]phosphine Oxide (3) A mixture of 1 (1.03 g, 2.0 mmol), 2 (2.284 g, 6.6 mmol), palladacycle (56 mg, 0.06 mmol), NaOAc (656 mg, 8.0 mmol), and DMF (10 mL, degassed by bubbling through nitrogen for 10 min prior to use) is stirred at 125 °C under nitrogen for 24 h. After cooling to room temperature, most of the DMF is removed under reduced pressure. The residue is dissolved in CHCl₃ (100 mL) and water (100 mL). The organic layer is separated, washed with water (100 mL) and brine...
(50 mL), dried (MgSO₄), and evaporated under reduced pressure. The residue is purified by flash chromatography (SiO₂, EtOAc-CHCl₃, 1:8) to give tris[4-(1H,2H-perfluorooctyl)phenyl]phosphine oxide 3 as a pale yellow oil (2.385 g, 91%): ¹H NMR (CDCl₃, 300 MHz) δ 6.31 (dt, 3 H, J = 16.2, 12.0 Hz), 7.22 (d, 3 H, J = 16.2 Hz), 7.60 (dd, 6 H, J = 8.2, 2.5 Hz), 7.73 (dd, 6 H, J = 11.6, 8.2 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 117.6 (t, 2 JCF = 23.5 Hz), 127.4 (d, 3 JCP = 12.5 Hz), 132.8 (d, 2 JCP = 10.4 Hz), 133.9 (d, 1 JCP = 103.7 Hz), 137.5, 138.5 (t, 3 JCF = 9.2 Hz) (the ¹³C signals of the fluorocarbon chains were too weak to be assigned); ³¹P NMR (CDCl₃, 101 MHz) δ 26.8 (s). Anal. calc. for C₄₂H₁₈F₃₉PO: C, 38.49; H, 1.38. Found: C, 38.24; H, 1.00; MS (CI, m/z) 1311 (M⁺ + 1), 1041, 967, 926, 890, 873.

Step B. Tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine Oxide (4) In a fume hood, a mixture of 3 (2.611 g, 2.0 mmol), 10% Pd/C (50 mg), and EtOAc (40 mL) in a glass liner-equipped autoclave is pressurized with 10 bar of hydrogen, which is then carefully released. After repeating this process three times, the autoclave is pressurized with 10 bar of hydrogen and the mixture is stirred for 5 h at room temperature. The hydrogen is carefully released, and the mixture is filtered through a short pad of Celite. The filtrate is evaporated under reduced pressure to give tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine oxide 4 as a pale yellow oil (2.630 g, 100%): ¹H NMR (CDCl₃, 300 MHz) δ 2.39 (m, 6 H), 2.98 (t, 6 H, J = 7, 8 Hz), 7.33 (dd, 6 H, J = 8.1, 2.4 Hz), 7.63 (dd, 6 H, J = 11.7, 8.1 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 26.5, 32.5 (t, 2 JCF = 29.9 Hz), 128.6 (d, 3 JCP = 12.0 Hz), 131.2 (d, 1 JCP = 104.8 Hz), 132.6 (d, 2 JCP = 9.8 Hz), 143.6; ³¹P NMR (CDCl₃, 101 MHz) δ 28.0 (s). Anal. calc. for C₄₂H₂₄F₃₉PO: C, 38.32; H, 1.84. Found: C, 38.46; H, 1.52; MS (CI, m/z): 1317 (M⁺ + 1), 1000, 971, 909, 893, 876.

Step C. Tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine (5) To a mixture of 4 (666 mg, 0.5 mmol), triethylamine (380 mg, 3.75 mmol), and toluene (10 mL) in a three-necked flask is added trichlorosilane (339 mg, 2.5 mmol) under nitrogen. The mixture is stirred at 120 °C under nitrogen for 5 h. After cooling to room temperature, degassed, saturated NaHCO₃ aqueous solution (0.5 mL) is added. The mixture is stirred under nitrogen for 5 min at room temperature, and then filtered through a pad of alumina. The flask is washed with toluene (3 × 15 mL) and the washings are filtered through the alumina. Finally, the combined filtrates are evaporated under reduced pressure to give tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine 5 as a white solid (630 mg, 96%): ¹H NMR (CDCl₃, 400 MHz) δ 2.37 (m, 6 H), 2.92 (m, 6 H), 7.19 (d, 6 H, J = 7.9), 7.26 (d, 6 H, J = 7.9); ¹³C NMR (CDCl₃, 100 MHz) δ 26.6, 33.1 (t, 2 JCF = 22.1 Hz), 128.9 (d, 2 JCP = 7.0 Hz), 134.5 (d, 1 JCP = 19.8 Hz), 133.9 (d, 1 JCP = 10.8 Hz), 140.3; ³¹P NMR (CDCl₃, 101 MHz) δ -7.6 (s) [3]. For other analytical details on this compound, see reference [4b].

Discussion

Fluoroalkyl-derivatized aryl phosphines that contain an insulating spacer between the aryl group and the electron-withdrawing fluorous fragments can be prepared by lithiation of fluoroalkyl-substituted bromobenzens followed by reaction with PAr₃Clₙ [3, 4]. Various methods have been developed for the synthesis of fluoroalkyl bromobenzens; these include coupling with Grignard reagents [4a], Negishi-type coupling [4b], Wittig reactions [4c], and
the Heck reaction [5]. The method presented herein is based on the Heck coupling of 1 and provides an alternative that is easy to perform, high yielding and versatile, provided that a suitable fluorous olefin is available [6]. Thus, the olefination of 1 with 2 by the palladacycle catalyst afforded 3 in 91% isolated yield and, as with normal Heck reactions, substitution of the vinylic protons by the arylphosphine oxide occurred at the less substituted side of the C–C double bond leading to a trans-olefin. The reaction did not proceed with the less-activated tris(4-bromophenyl)phosphine and the borane protected tris(4-bromophenyl)-phosphine, however. To obtain the free phosphine 5, the substituted phosphine oxide 3 was first subjected to hydrogenation and then reduced by treatment with trichlorosilane by normal procedures; 5 was isolated in 87% overall yield. Mono-, bis- and other tris-fluoroalkylated arylphosphines have been obtained in similar yields by the same method [6], and this method has also been used to prepare 6,6'-fluoroalkylated BINAP [7].

References


11.11
3,5-bis(Perfluorodecyl)phenylboronic Acid. An Easily Recyclable Direct Amide Condensation Catalyst

Kazuaki Ishihara and Hisashi Yamamoto

Reaction 11.11-1

**Step A**

1

\[ \text{I} \]

\[ \text{C}_{10}\text{F}_{21} \] 2 (2.2 equiv) 

\[ \text{Cu} \] (3.3 equiv) 

\[ \text{H}_{2}SO_{4}\text{CF}_{3}CO_{2}H \] (3:7.5 (v:v)) 

\[ \text{Br} \]

\[ \text{I} \]

2 (57%)

**Step B**

\[ \text{C}_{10}\text{F}_{21} \]

\[ \text{H}_{2}SO_{4}\text{CF}_{3}CO_{2}H \] (3:7.5 (v:v)) 

\[ \text{Br} \]

\[ \text{I} \]

2 (57%)

\[ \text{C}_{10}\text{F}_{21} \]
the Heck reaction [5]. The method presented herein is based on the Heck coupling of 1 and provides an alternative that is easy to perform, high yielding and versatile, provided that a suitable fluorous olefin is available [6]. Thus, the olefination of 1 with 2 by the palladacycle catalyst afforded 3 in 91% isolated yield and, as with normal Heck reactions, substitution of the vinylic protons by the arylphosphine oxide occurred at the less substituted side of the C=C double bond leading to a trans-olefin. The reaction did not proceed with the less-activated tris(4-bromophenyl)phosphine and the borane protected tris(4-bromophenyl)-phosphine, however. To obtain the free phosphine 5, the substituted phosphine oxide 3 was first subjected to hydrogenation and then reduced by treatment with trichlorosilane by normal procedures; 5 was isolated in 87% overall yield. Mono-, bis- and other tris-fluoroalkylated arylphosphines have been obtained in similar yields by the same method [6], and this method has also been used to prepare 6,6'-fluoroalkylated BINAP [7].

References


11 Preparations

3,5-bis(Perfluorodecyl)phenylboronic Acid. An Easily Recyclable Direct Amide Condensation Catalyst

Kazuaki Ishihara and Hisashi Yamamoto

Reaction 11.11-1

\[ \text{Step A} \]

\[ \begin{align*}
\text{1} & \quad \text{C}_{10} \text{F}_{21} \quad \text{Cu (3.3 equiv)} \\
& \quad \text{DMSO, 120 °C, 68 h} \\
& \quad \text{2,2'-dipyridyl (40 mol%)} \\
& \quad \text{H}_{2}\text{SO}_{4}/\text{CF}_{3}\text{CO}_{2} \text{H} \quad \text{NBS (1.5 equiv)} \\
& \quad \text{50 °C, 8 h} \\
& \quad \text{3 (94%)}
\end{align*} \]

\[ \text{Step B} \]

11.11

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Copyright © 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
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1-Iodoperfluorodecane [423-62-1] is commercially available from Lancaster Synthesis Ltd.

**Experimental Procedure**

**Step A. 1,3-Bis(perfluorodecyl)benzene (2)**  [1] A mixture of 1,3-diiodobenzene (1) (5.0 g, 15.2 mmol), 1-iodoperfluorodecane (21.6 g, 33.4 mmol), copper (powder, 3.2 g, 50.2 mmol), 2,2'-dipyridyl (940 mg, 6.0 mmol) [2] and DMSO (100 mL) is stirred at 120 °C for 68 h. After cooling to room temperature, the reaction mixture is diluted with chloroform (250 mL) and water (250 mL), filtered through a pad of Celite and washed with chloroform (100 mL). The organic layer is separated, washed with 1 M HCl (100 mL), water (100 mL), and brine (100 mL), dried over MgSO₄, and evaporated under reduced pressure (ca. 20 Torr) to give the crude product. Recrystallization from chloroform yields pure compound (2) (9.6 g, 8.6 mmol, 57% yield) as colorless needles: mp 78 °C; IR (KBr) 1210, 1152 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz, 50 °C) δ 7.69 (t, J = 7.8 Hz, 1 H), 7.82 (s, 1 H), 7.83 (d, J = 7.8 Hz, 2 H); ¹³C NMR (CDCl₃, 282 MHz, 55 °C) δ -16.64 (s, 6 F), -123.25 (s, 4 F), -122.63 (s, 4 F), -122.25 (s, 16 F), -121.63 (s, 4 F), -111.69 (t, J = 12.1 Hz, 4 F), -81.82 (t, J = 9.3 Hz, 4 F). Anal. calc. for C₂₆H₄F₄₂: C, 28.03; H, 3.62. Found: C, 27.98; H, 3.67.

**Step B. 1-Bromo-3,5-bis(perfluorodecyl)benzene (3)**  [3] In a 100 mL round-bottomed flask, equipped with powerful magnetic stirrer, is placed trifluoroacetic acid (7.5 mL), 2 (2.0 g, 1.78 mmol), and concentrated sulfuric acid (3 mL). The mixture is stirred vigorously, and N-bromosuccinimide (475 mg, 2.67 mmol) is added in portions over an 8 h period. After the reaction mixture is stirred at 50 °C for 8 h, it is poured into ice water (50 mL). The reaction mixture is then stirred at room temperature for several hours, and the solid is separated by filtration. Washing with water (20 mL), drying by air and recrystallization from chloroform gives pure compound (3) with 94% yield (1.99 g, 1.67 mmol) as colorless needles: mp 109 °C,
Step C. 3,5-Bis(perfluorodecyl)phenylboronic Acid Pinacol Ester (4) The flask is charged with PdCl₂(dppf) (32.6 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), KOAc (196.3 mg, 2 mmol), 3 (800 mg, 0.67 mmol), and bis(pinacolato)diboron (188 mg, 0.74 mmol), and flushed with argon. DMSO (10 mL) is added, and the resulting mixture is then stirred at 100°C for 12 h. The reaction mixture is diluted with hot chloroform and hot water, then the organic layer is separated, dried over MgSO₄, filtered through glass filter (40–100 μm) and evaporated under reduced pressure (ca. 20 Torr). Recrystallization from hot CHCl₃ yields pure compound 4 (490 mg, 59% yield) as colorless needles: mp 112°C; IR (KBr) 1341, 1240, 1220, 1200, 1152 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz, 50°C) δ 1.38 (s, 12 H), 7.87 (s, 1 H), 8.21 (s, 2 H); ¹⁹F NMR (CDCl₃, 282 MHz, 55°C) δ 126.67 (s, 6 F), 123.23 (s, 4 F), 122.32 (s, 20 F), 121.67 (s, 4 F), 111.56 (t, J = 15.2 Hz, 4 F), –81.82 (t, J = 9.3 Hz, 4 F). Anal. calc. for C₃₂H₁₅F₄₂BO₂: C, 30.99; H, 1.22. Found: C, 30.97; H, 1.28.

Step D. 3,5-Bis(perfluorodecyl)phenylboronic Acid (5) To a stirred suspension of 4 (430 mg, 0.35 mmol) in dichloromethane (10 mL) is added boron tribromide (94.5 μL, 1.05 mmol) at −78°C. The reaction mixture is stirred at 0°C for 2 h and additionally at room temperature for 0.5 h. After water is added to the reaction mixture at 0°C, the resulting mixture is diluted with chloroform (10 mL) and stirred vigorously for 1 h. The white solid is separated by filtration, washed with water (20 mL) and dichloromethane (20 mL), and dried under vacuum (1 Torr) to give pure 5 in 74% yield (301 mg, 0.26 mmol): mp 166°C; IR (KBr) 1375, 1841, 1293, 1225, 1150, 1096, 899 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz, 55°C) δ 7.90 (s, 1 H), 8.12 (s, 2 H); ¹⁹F NMR (CDCl₃, 282 MHz, 55°C) δ −127.09 (s, 6 F), −123.70 (s, 4 F), −122.78 (s, 20 F), −121.15 (s, 4 F), −112.04 (t, J = 15.2 Hz, 4 F), −81.96 (t, J = 9.0 Hz, 4 F). Anal. calc. for C₂₆H₁₅F₄₂BO₂: C, 26.97; H, 0.44. Found: C, 27.01; H, 0.35.

Step E. N-Benzyl-4-phenylbutyramide A dry, 10-mL round-bottomed flask fitted with a stir bar and a 5 mL pressure-equalized addition funnel [containing a cotton plug and ca. 2 g of 4 A molecular sieves (pellets) and functioning as a Soxhlet extractor] surmounted by a reflux condenser is charged with cyclohexanecarboxylic acid (128.2 mg, 1.0 mmol), benzylamine (109.2 μL, 1.0 mmol), and 5 (37.9 mg, 0.05 mmol) in o-xylene (5 mL). The mixture is heated at azotropic reflux with removal of water to provide a homogeneous solution. After 3 h, the resulting mixture is cooled to ambient temperature to precipitate 5. After 1 h, the liquid phase of the resultant mixture is decanted and the residual solid catalyst 5 is reused without isolation. Catalyst 5 remains in the flask up to the tenth reaction. Liquid phases which are obtained in each of the reactions are combined, concentrated under reduced pressure, and the residue is purified by column chromatography on silica gel (eluant: hexane–ethyl acetate = 3:1) to give the corresponding amide (2.08 g, 9.6 mmol, 96% yield) [5].

Typical Procedure for Recovery of 5 After completing the above reaction (one cycle), the resulting mixture is cooled to ambient temperature to precipitate 5. After 1 h, the resultant
mixture is diluted with toluene (3 mL), and 5 is separated by filtration, washed with toluene (2 mL), and dried under vacuum (1 Torr) to recover 5 (56.0 mg, 97% yield) as a pure white solid.

Discussion

Arylboronic acids bearing electron-withdrawing substituents at the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. Ishihara et al. have found that 3,5-bis(trifluoromethyl)phenylboronic acid (6) and 3,4,5-trifluorophenylboronic acid (7) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1 equiv) [5]. This is the first example of a catalytic and direct amide condensation which does not require excess amounts of substrates. Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1~20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This has hampered the application of this methodology to large scale syntheses.

Catalyst 5 is insoluble in toluene and o-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by 5 proceeds homogeneously under reflux conditions. To demonstrate this advantage of 5 with respect to solubility, Ishihara et al. have reused 5 (5 mol%) ten times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine. After heating the reaction mixture at reflux with removal of water for 3 h, the mixture is allowed to stand at ambient temperature for 1 h to precipitate 5. The liquid phase of the resultant mixture is decanted and the residual solid catalyst 5 is reused without isolation. No loss of activity is observed for the recovered catalyst, and 26% of 5 remains in the flask after the tenth reaction. This means that 88% of 5 is retained in each cycle. The total isolated yield of the amide which is obtained in ten reactions is 96%. Moreover, pure compound 5 can be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene [6].
References


11.12 Fluorous-tagged Tetrafluorophenylbis(triflyl)methane. An Organic Solvent-swellable and Strong Brønsted Acid Catalyst

\textit{Kazuaki Ishihara and Hisashi Yamamoto}

\textbf{Reaction 11.12-1}

\begin{align*}
\text{Step A} & \quad \text{Step B} & \quad \text{Step C} \\
\text{CF}_3\text{SO}_2\text{Na} \quad \text{EtCN, reflux} & \quad \text{BuLi (1 equiv), } \text{Et}_2\text{O}, -78^\circ \text{C}, 0.5 \text{ h} & \quad \text{LiOH•H}_2\text{O} \quad \text{Et}_2\text{O} \\
(1.3 \text{ equiv}) & \quad \text{CF}_3\text{Br} \quad 2 \quad (91\%) & \quad \text{CF}_3\text{CHTf}_2 \quad 3 \quad (95\%) \\
\text{Step D} & \quad \text{Step E} \\
\text{CF}_3(\text{CF}_2)_{12}\text{CH}_2\text{OH} \quad \text{NaH (3 equiv), } \text{Et}_2\text{O} \quad \text{70}^\circ \text{C, 1 day} & \quad \text{CF}_3(\text{CF}_2)_{12}\text{CH}_2\text{OH} \quad 4 \quad (>99\%) \\
(3 \text{ equiv}) & \quad \text{C}_6\text{F}_5\text{CH}_2\text{Br} \quad \text{pyridine/(CF}_3\text{CH}_2\text{CN} \quad = 2:1 & \quad \text{1. } \text{4 (1 equiv), } \\
\text{rt to } 70^\circ \text{C, 1 h} & \quad \text{70}^\circ \text{C, 1 day} & \quad \text{2. } 4 \text{ M HCl} \\
\text{PhCHO} + \quad \text{O} & \quad \text{6 (1 mol\%)} & \quad \text{CF}_3(\text{CF}_2)_{12}\text{CH}_2\text{OH} \quad 6 \quad (84\%, 62 \text{ wt } \%\text{F}) \\
\text{8 (1.2 equiv)} & \quad \text{cyclohexane azeotropic reflux, 3 h} & \quad \text{Ph} \\
\text{9 (86\%); recovery of 6, 96\%} 
\end{align*}
Reagents

Sodium sulfinate is commercially available from Central Glass Co., Ltd., Japan. 1H,1H-Perfluoro-1-tetradecanol [15622-57-8] is commercially available from Fluorochem Ltd., UK. Pentafluorophenylbis(triflyl)methane (3) is sold by TCI Co., Ltd.

Experimental Procedures

**Step A. Pentafluorophenylmethyl Triflone (2)**  [1] A solution of 2,3,4,5,6-pentafluorobenzyl bromide (1) (2.6 g, 10 mmol) and sodium triflinate (2.0 g, 13 mmol) in propionitrile (30 mL) is heated at reflux. After one day, the mixture is cooled, the salts are filtered and the solvent is evaporated under reduced pressure. The residue is purified by column chromatography using a linear EtOAc gradient in hexane to give 2 as a solid (2.9 g, 91% yield): IR (KBr) 1509, 1374, 1210, 1121, 995 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.64; ¹³C NMR (CDCl₃, 125 MHz) δ 44.3, 100.0 (dt, JCF = 4, 17 Hz, 1 C, ipso-C), 119.5 (q, JCF = 326 Hz, 1 C, CF₃), 137.9 (d, JCF = 251 Hz, 2 C, 2m-C), 142.8 (d, JCF = 258 Hz, 1 C, p-C), 145.9 (d, JCF = 252 Hz, 2 C, 2o-C); ¹⁹F NMR (CDCl₃, 282 MHz) δ -160.0 (d, J = 15.2 Hz, 2 F, 2m-F), -149.0 (s, 1 F, p-F), 139.4 (d, J = 15.2 Hz, 2 F, 2o-F), -78.3 (s, 3 F, CF₃). Anal. calc. for C₈H₁₂O₂F₈S: C, 30.59; H, 0.64; F, 48.38; S, 10.21. Found C, 30.49; H, 0.73; F, 48.37; S, 10.18.

**Step B. Pentafluorophenylbis(triflyl)methane (3)**  [2] To a solution of 2 (157 mg, 0.5 mmol) in dry Et₂O (3 mL) is added BuLi (0.34 mL, 0.5 mmol, 1.6 M solution in hexanes) dropwise at -78 °C, and the resulting mixture is stirred for 10 min. Triflic anhydride (42 µL, 0.25 mmol) is then added, and the resulting mixture is allowed to warm to room temperature over a period of 1 h, before the reaction is quenched with water. The resultant mixture is neutralized and washed with hexane. The aqueous phase is acidified with 4 M aqueous HCl and extracted with ether twice. The organic layers are dried over magnesium sulfate, filtrated and concentrated under reduced pressure to give 3 as a solid, which is purified by vacuum sublimation (0.3 Torr, 100 °C): mp 86–87 °C; IR (KBr) 1522, 1501, 1347, 1321, 1198, 1127, 1024, 988, 613 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.21 (brs, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 70.4, 98.0 (s, 1 C, ipso-C), 119.2 (q, JCF = 330 Hz, 2 C, 2CF₃), 137.8 (d, JCF = 258 Hz, 1 C, m-C), 138.6 (d, JCF = 257 Hz, 1 C, m-C), 144.7 (d, JCF = 264 Hz, 1 C, p-C), 145.4 (d, JCF = 262 Hz, 1 C o-C), 142.4 (d, JCF = 262 Hz, 1 C), 117.2 (d, JCF = 294 Hz, 1 C, o-C); ¹³C NMR (CD₂OD (δ 49.0), 125 MHz) δ 70.4, 98.0 (s, 1 C, ipso-C), 119.2 (q, JCF = 330 Hz, 2 C, 2CF₃), 137.8 (d, JCF = 258 Hz, 1 C, m-C), 138.6 (d, JCF = 257 Hz, 1 C, m-C), 144.7 (d, JCF = 264 Hz, 1 C, p-C), 145.4 (d, JCF = 262 Hz, 1 C o-C), 142.4 (d, JCF = 262 Hz, 1 C), 142.4 (d, JCF = 294 Hz, 1 C, o-C), 19F NMR (CDCl₃, 282 MHz) δ -157.9 (dt, J = 6.2, 21.5 Hz, 1 F, m-F), -156.8 (dt, J = 6.2, 21.5 Hz, 1 F, m-F), -152.6 (dt, J = 5.9, 21.5 Hz, 1 F, p-F), -140.3 (br, 1 F, o-F), -127.7 (dd, J = 5.9, 15.2, 21.5 Hz, 1 F, o-F), -75.2 (s, 6 F, 2CF₃); HRMS (EI) calc. for C₉H₁₄O₄F₁₄S₂ [M]⁺ 445.9141, found 445.9137.

**Step C. Preparation of Lithium Pentafluorophenylbis(triflyl)methide (4)**  A solution of 3 (1.36 g, 3.05 mmol) in diethyl ether (20 mL) is neutralized by addition of lithium hydroxide monohydrate (0.13 g, 3.05 mmol). Diethyl ether is evaporated under reduced pressure and the residual salt was dried at 80 °C under vacuum (ca. 1 Torr) for 12 h (quantitative yield): ¹³C
NMR (CD$_3$OD, 125 MHz) $\delta$ 56.1, 109.0 (dt, $J = 4$, 19 Hz, 1 C, ipso-C), 122.3 (q, $J_{CF} = 324$ Hz, 2 C, 2CF$_3$), 138.5 (d, $J_{CF} = 247$ Hz, 2 C, 2m-C), 143.0 (d, $J_{CF} = 251$ Hz, 1 C, p-C), 149.5 (d, $J_{CF} = 245$ Hz, 2 C, 2o-C).

**Step D. 4-(1H,1H-Perfluorotetradecanoyl)-2,3,5,6-tetrafluorophenylbis(triflyl)methane (6)** To a mixture of sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol) and 1H,1H-perfluoro-1-tetradecanol (5) (0.53 g, 0.75 mmol) is added pyridine (4 mL) [3] and perfluorotributylamine (2 mL) at room temperature. The resulting mixture is heated to 70 °C and stirred at the same temperature for 1 h. Lithium salt 4 (0.11 g, 0.25 mmol) is then added at 70 °C, and the resulting mixture is stirred for an additional 1 day at the same temperature. After cooling to 0 °C, the reaction is quenched with 4 M aqueous HCl (40 mL) at 0 °C. The resultant acidified mixture is extracted with diethyl ether (40 mL). The organic layers are dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a brown solid. Furthermore, excess 5 which is contained in the solid is removed by vacuum sublimation (120 °C, 0.06 Torr). The residual dark-brown solid is dissolved in diethyl ether (20 mL) or perfluoromethylcyclohexane (20 mL), and some insoluble impurities are then removed by filtration. The filtrate is concentrated under reduced pressure to give 6 (0.238 g, 0.21 mmol, 84% yield) as a white solid: mp 95–96 °C; IR (KBr) 1503, 1406, 1397, 1213, 1154, 1111, 984, 646, 625, 550, 527 cm$^{-1}$; $^1$H NMR (toluene-$d_8$ þ perfluorotoluene, 80 °C, 300 MHz) $\delta$ 4.06 (t, $J = 12.5$ Hz, 2 H), 6.21 (s, 1 H). Anal. calc. for C$_{23}$H$_3$O$_5$F$_{37}$S$_2$: C, 24.53; H, 0.27. Found: C, 24.51; H, 0.31.

**Step E. 2-Phenyl-1,3-dioxane (9)** To a solution of 6 (33.8 mg, 0.03 mmol) in cyclohexane (6 mL) are added benzaldehyde (7) (0.30 mL, 3.0 mmol) and 1,3-propanediol (8) (0.24 mL, 3.3 mmol), and the resulting mixture is heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 3 h, the reaction mixture is cooled to ambient temperature to precipitate 6, which is filtered and washed with cyclohexane (2 mL) to recover 6 (32.4 mg, 0.029 mmol, 96% yield). The filtrate is concentrated under reduced pressure. The purity of the recovered catalyst is checked by $^1$H and $^{19}$F NMR analyses. The crude oil is purified by column chromatography on silica gel (eluent: hexane–EtOAc = 20:1 to 5:1) to afford the corresponding acetal 9 (0.425 g, 2.6 mmol, 86% yield).

**Discussion**

Pentafluorophenylbis(triflyl)methane 3 (47 wt% F) is soluble in most organic and fluorous solvents [4]. Fluorous-phase affinity for arylbis(triflyl)methane is increased by appending, “fluorous ponytails,” OCH$_2$(CF$_2$)$_n$CF$_3$ groups to 3. For example, 4(1H,1H-perfluoro-1-tetradecanoyl)-2,3,5,6-tetrafluorophenylbis(triflyl)methane 6 (62 wt% F) can be recycled by using a fluorous biphasic technique [5]. Fluorous solid catalyst 6 is a more active catalyst than perfluoresinsulfonic acids such as Nafion®.

Fluorous solid catalyst 6 is soluble in cyclohexane under reflux conditions, and promotes the acetalization of 7 with 8 well to give the desired acetal 9 in 86% yield. After the reaction, 6 is recovered in 96% yield by precipitation at room temperature [6]. Besides this acetalization, 6 is also effective as a fluorous catalyst for the acylation of l-menthol with benzoic anhydride [Eq. (1)] and esterification of 3-phenylpropionic acid in methanol [Eq. (2)] [7]. Fluorous solid catalyst 6 was also used in the Mukaiyama aldol reaction [Eq. (3)] and the Sakurai-Hosomi allylation reaction [Eq. (4)]. These reactions are performed at $-78$ °C and rt.
respectively, under heterogeneous conditions. After the reaction, 6 is recovered in high yield by decanting the liquids at room temperature.

\[
\text{PhCHO} + \text{OSiMe}_3 \xrightarrow{\text{PhCHO (1 equiv), \text{CH}_2\text{Cl}_2, rt, 0.5 h, 1 M \text{HCl-THF (1:1) 84%}} \text{ recapture of 6, 97%}}
\]

References


3. D. J. Byron, A. S. Matharu, R. C. Wilson, Liquid Crystals 1995, 19, 39. Pyridine is more effective as a solvent in the para-substitution reaction of 4 with sodium alkoxides. In contrast, this reaction does not occur smoothly in diethyl ether which is effective in the para-substitution reaction with alkyllithiums.


7. In the case of the esterification, the resultant solution is concentrated under reduced pressure, and the crude compounds are diluted in hexane to precipitate 6. Thus, 6 is recovered by filtration.
11.13 Tetrakis[μ-3,5-bis(perfluorooctyl)benzoato-O,O'] Dirhodium. Application as a Recyclable Catalyst for a Carbenoid Cyclopropanation Reaction

Gerhard Maas and Andreas Endres

Reaction 11.13-1

Step A

\[
\text{I} \quad \text{C}_8\text{F}_{17}\text{I}, \text{Cu powder} \rightarrow \quad \text{COOMe} \\
\text{DMSO, 125 °C, 6 h} \quad \text{F}_{17}\text{C}_8 \quad \text{F}_{17}\text{C}_8 \quad \text{COOMe} \\
1 \quad 2, 56\% \\
\]

Step B

\[
\text{NaOH, H}_2\text{O}, \text{MeOH} \rightarrow \quad \text{COOH} \\
\text{rfx, 15 h} \quad \text{F}_{11}\text{C}_8 \quad \text{C}_8\text{F}_{17} \\
3, 82\% \\
\]

Step C

\[
1, \text{NaOH, EtOH} \\
2. \text{RhCl}_3\cdot3\text{H}_2\text{O, EtOH, rfx, 7 h} \\
\text{R:} \\
\text{C}_8\text{F}_{17} \\
4, 63\% \\
\]

Step D

\[
\text{Ph} \quad \text{N}_2=\text{CH–COOMe} \quad \text{5} \\
\text{FC-113, rt, 12 h} \\
\text{4 (1 mol%)} \\
\text{6, 76%} \\
\]

Reagents

Perfluoroocetyl iodide and perfluoro(methylcyclohexane) (PFMC) were purchased from Lancaster, 1,1,2-trichloro-1,2,2-trifluoroethane (FC-113) from Riedel-de-Haen.

Experimental Procedure [1]

Step A. Methyl 3,5-Bis(perfluorooctyl)benzoate (2) A mixture of a few iodine crystals and copper dust (3.00 g) in acetone (20 mL) is stirred for 30 min. After removal of the solvent, the copper is washed with aq. HCl (6 N) in acetone (20 mL, 2:3 v/v) and acetone (2 x 10 mL) and dried in vacuo. The activated copper powder (819 mg, 12.89 mmol) is mixed with methyl 3,5-diiodobenzoate 1 (500 mg, 1.29 mmol), perfluoroocetyl iodide (1.48 g, 2.71 mmol) and dry DMSO (9 mL). The suspension is stirred for 6 h at 125 °C. After cooling to rt, water and
ether (10 mL each) are added. The mixture is stirred for 10 min, then filtered with suction. The solid residue is washed with ether (2 x 20 mL). The filtrate (ether, water, DMSO) and the ether washings are combined, the ethereal layer is separated and kept, and the DMSO–water phase is extracted with ether (2 x 20 mL). All ether phases are combined, dried (Na₂SO₄), and evaporated. The resulting pale-brown solid is purified by chromatography on silica gel [eluent: petroleum ether/diethyl ether (7:3)] to give colorless crystals (702 mg, 56% yield), mp 62–63°C: 1H NMR (400.1 MHz, CDCl₃/FC-113) δ 4.01 (s, 3 H, OMe), 7.98 (s, 1 H, 4-Hₐ), 8.49 (s, 2 H, 2,6-Hₐ); 13C NMR (CDCl₃, FC-113) δ 53.7 (OMe), 113.5–131.5 (several m, C F), 129.4 (2,6-Cₐ), 130.9 (3,5-Cₐ), 131.6 (4-Cₐ), 132.3 (C-1ₐ), 164.4 (C-8); 19F NMR (376 MHz, CDCl₃) δ -82.2 (t, 3J = 10.8 Hz, 6 F, CF₃), -112.38 (t, 3J = 14.3 Hz, 4 F), -122.45 (m, 4 F), -123.15 (m, 16 F), -124.05 (m, 2 F), -127.45 (m, 2 F).

Step B. 3,5-Bis(perfluorooctyl)benzoic Acid (3) Ester 2 (250 mg, 0.26 mmol) is suspended in a mixture of methanol (2 mL) and water (4 mL), and potassium hydroxide (130 mg, 2.32 mmol) is added. A clear solution forms upon heating at reflux. After 15 h at reflux, most of the methanol is evaporated and the remaining solution is neutralized with 6 N hydrochloric acid. After extraction with ether (3 x 20 mL), drying of the combined ether phases (Na₂SO₄) and evaporation of the solvent, the residue is recrystallized from toluene to give a white solid (205 mg, 82% yield), mp 117°C: 1H NMR (400.1 MHz, CDCl₃) δ 7.97 (s, 1 H, 4-Hₐ), 8.49 (s, 2 H, 2,6-Hₐ); IR (KBr) ν = 3650–2700 (several broad absorptions, OH), 1712 (s, C=O), 1204 (vs, CF), 1149 (vs, CF); 19F NMR (376 MHz, CDCl₃) δ -82.5 (t, 3J = 10.3 Hz, 24 F, CF₃), -112.3 (m, 16 F, CF₂), -122.5 (m, 16 F, CF₂), -122.7 (m, 16 F, CF₂), -123.3 (m, 32 F, CF₂), -124.1 (m, 16 F, CF₂), -127.7 (m, 16 F, CF₂); IR (KBr) ν = 3650–2700 (several broad absorptions, OH), 1712 (s, C=O), 1204 (vs, CF), 1149 (vs, CF) cm⁻¹.

Step C. Complex 4 A solution of acid 3 (100 mg, 0.104 mmol) and sodium hydroxide (4.1 mg, 0.104 mmol) in ethanol (10 mL) is added to a stirred solution of rhodium trichloride trihydrate (RhCl₃·3H₂O) (9.0 mg, 34.6 mmol) in refluxing ethanol (3 mL). The color of the solution changes from red to yellow, yellow brown, and green. After 7 h a green waxy solid precipitates. Half of the solvent is removed at 40°C/120 mbar and after cooling to 4°C, the remaining solvent is decanted completely. The dark-green residue, which contains some rhodium powder, is dried at 50°C/1 mbar, then dissolved in PFMC (2 mL). After filtration and liquid/liquid extraction with THF (2 x 1.5 mL), the fluorous layer yields a solid which is subjected to flash chromatography on silica gel [eluent petroleum ether/diethyl ether (7:3); Rf of 4 = 0.97] to remove left-overs of the sodium salt of 3. Complex 4 is obtained as a dark-green waxy solid (44 mg, 63% yield): 1H NMR (400.1 MHz, CDCl₃/FC-113) δ 7.83 (s, 1 H, 4-Hₐ); 13C NMR (CDCl₃, FC-113) δ 129.4 (2,6-Cₐ), 130.9 (3,5-Cₐ), 131.6 (4-Cₐ), 132.3 (C-1ₐ), 164.4 (C=O); 19F NMR (376 MHz, CDCl₃) δ -82.2 (t, 3J = 10.8 Hz, 6 F, CF₃), -112.38 (t, 3J = 14.3 Hz, 4 F), -122.45 (m, 4 F), -123.15 (m, 16 F), -124.05 (m, 2 F), -127.45 (m, 2 F).

Step D. Cyclopropanation of Styrene with Methyl Diazoacetate (5) Catalyzed by 4 A solution of methyl diazoacetate (5) (100 mg, 1.00 mmol) in FC-113 (0.5 mL) is added via a syringe pump over 8 h to a stirred solution of catalyst 4 (40.3 mg, 1 mol%) and a ten-fold excess of styrene (1.13 mL, 10.0 mmol) in FC-113 (1.5 mL). After 4 h at 20°C, most of the volatiles are removed at 20°C/1 mbar and the residue is stirred with PFMC (0.8 mL) and dichloromethane (2.5 mL) for 20 min. After phase separation, methyl 2-phenylcyclopropane-1-carboxylate 6 is found in the CH₂Cl₂ phase (yield: 76.4%; E:Z = 0.88; all values determined by GC). Preparative isolation and purification of 6 can be achieved by column chro-
matography (silica gel, ether–pentane) followed by bulb-to-bulb distillation (162–168 °C/16 mbar). The dark-green fluorous phase is evaporated, and the recovered catalyst so obtained is used in a subsequent reaction cycle. A series of five subsequent reaction cycles gave the following results for yield of cyclopropane 6 and percentage of recovered catalyst relative to the amount used in the first cycle (in parentheses): 76.4% (98%), 75.9 (88), 76.1 (77), 75.6 (68), 75.1 (62). The evaporated fluorous solvents can be collected in a cold trap and can be reused after vacuum distillation.

Discussion

Metal-catalyzed inter- and intramolecular carbenoid reactions of diazo compounds are powerful tools in contemporary organic synthesis because they allow chemical transformations that often cannot be readily realized by other means [3]. Besides some copper-based catalysts, dinuclear rhodium(II) carboxylates and amidates currently represent the most effective and versatile catalysts for such carbenoid reactions. For various different reasons, it may be desirable to recover and to reuse the rhodium catalyst. As an alternative to polymer-supported catalysts, we investigated the fluoruous approach and found [1] that rhodium complex 4 and the related 3,5-bis(perfluorohexyl)benzoate complex serve the purpose much better than highly fluorinated rhodium(II) alkanoate complexes [4]. Owing to the insolubility of 4 in common organic solvents applicable for carbenoid reactions, the cyclopropanation reaction described above was run in the hybrid solvent [5] 1,1,2-trichloro-1,2,2-trifluoroethane in which both 4 and the organic reactants and products are soluble, in order to provide homogeneous catalysis conditions. Separation of the fluoruous catalyst from the reaction mixture was achieved by a biphase extraction (CH2Cl2-PFMC), and the catalyst could be reused through several subsequent reaction cycles with only a slight decrease in efficiency. The observed loss after each cycle is not caused by leaching into the organic phase but appears to be due mainly to partial degradation.

The preparation of the highly fluorinated free ligand 3 and of the rhodium complex 4 (F contents are 67.4 and 64%, respectively) does not require fluorous solvents, since the fluorinated reactants are soluble in the hydroxylic solvents at the given reaction temperatures. However, a liquid/liquid extraction using the PFMC/THF biphasic system is a convenient step in the purification procedure of fluorous complex 4, due to its good solubility in the fluorous solvent.

References

11.14 1,4,7-Tris-N-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoroundecyl)-1,4,7-triazacyclononane [R$_f$–TACN]. A Fluorous Soluble Nitrogen Ligand via Alkylation with a Fluoroponytail, C$_{8}$F$_{17}$(CH$_{2}$)$_{3}$I

Jean-Marc Vincent* and Richard H. Fish*

Reaction 11.14-1

<table>
<thead>
<tr>
<th>Step A</th>
<th>Step B</th>
<th>Step C</th>
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<tr>
<td>R$_f$I</td>
<td>Bu$_3$SnH, AIBN</td>
<td>KI, P$_2$O$_5$</td>
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<tr>
<td>75 °C, 14 h</td>
<td>C$_6$H$_5$CF$_3$</td>
<td>85% H$_3$PO$_4$</td>
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<td>1, 75%</td>
<td>R$_f$OH</td>
<td>120 °C, 3 h</td>
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<tr>
<td>R$<em>f$ = C$</em>{8}$F$_{17}$</td>
<td>R$_f$OH</td>
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<tr>
<td>R$_f$I(3, 85%)</td>
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<tr>
<td>120 °C, 22 h</td>
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</table>

Reagents

R$_f$I (R$_f$ = C$_{8}$F$_{17}$) and perfluorohexane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene, phosphorous pentaoxide, 85%, phosphoric acid, potassium iodide, and 1,4,7-triazacyclononane (TACN) were purchased from Aldrich Chemical Company.

Experimental Procedures

Step A. 2-Iodo-1-perfluorooctyl-3-propanol (1) The R$_f$I (R$_f$ = C$_{8}$F$_{17}$, 7 g, 12.8 mmol), allyl alcohol (1 mL, 14.7 mmol), and AIBN (84 mg, 0.51 mmol) are heated at 70–75 °C under an inert atmosphere for 14 h. Every 2 h, a new portion of AIBN is added to the reaction mixture. The pale yellow solid obtained is recrystallized from refluxing hexane (40 mL), and 1 is obtained in 75% yield, mp 93–94 °C. EIMS [M$^+$] 604. Elemental anal. calc. for C$_{11}$H$_{6}$F$_{17}$I: C, 21.87; H, 1.00. Found: C, 22.06; H, 0.97. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) δ 4.45 (m, 1 H, -CHI-), 3.79 (m, 2H, -CH$_2$-OH), 2.9 (2m, 2 H, R$_f$-CH$_2$), 2.04 (t, -OH).

Step B. 3-Perfluorooctyl-1-propanol (2) Compound 1, R$_f$CH$_2$CHI$\cdot$CH$_2$OH (8 g, 13.2 mmol), and AIBN (52 mg, 0.31 mmol) are partially dissolved in dry trifluorotoluene (40 mL). Tributyltin hydride (4.2 mL, 15.8 mmol) is then added dropwise and the reaction mixture is heated at 80 °C under an inert atmosphere for 4 h (reaction followed by GC analysis). After removing the solvent under vacuum, the resulting residue is partitioned between per-
fluoroheptane and toluene. After decantation, the lower phase is separated from the upper one, which mainly contains (Bu)_3SnI. By removing the perfluoroheptane, compound 2 is isolated as a white powder in 75% yield. Compound 2 can be recrystallized from hexane: EIMS [M^+] 477. Elemental anal. calc. for C_{11}H_{7}F_{17}O: C, 27.63; H, 1.46. Found: C, 27.72; H, 1.63. 1H NMR (400 MHz, CDCl_3, 25 °C) δ 3.75 (m, 2 H, -CH_2-OH), 2.20 (m, 2 H, Rf-CH_2), 1.88 (m, 2 H, -CH_2-CH_2-CH_2), 1.57 (s, -OH).

**Step C. 3-Perfluorooctyl-1-iodopropane (3)** Phosphorous pentaoxide (3.4 g) is added to phosphoric acid (85%, 7.1 mL) in a 50 mL round-bottomed flask and then the mixture is cooled to 0 °C. The KI (1.39 g, 8.2 mmol) is added, followed immediately by RfCH_2CH_2CH_2OH (1.5 g, 3.1 mmol). The mixture is heated at 120 °C for 3.5 h. At ambient temperature, 10 mL of water are added, and the resulting brown solution is extracted four times with 25 mL of diethyl ether. The organic layer is washed twice with 25 mL thiosulfate (0.1 M), then dried over Na_2SO_4. After removing the solvent, the iodo derivative is obtained as an oil, which solidifies at 4 °C. Compound 3 is used without further purification (yield 85%); however, 3 can be recrystallized from methanol: EIMS [M^+] 588. Elemental anal. calc. for C_{11}F_{17}H_{6}I: C, 22.47; H, 1.02. Found: C, 22.80; H, 1.26. 1H NMR (400 MHz, CDCl_3, 25 °C) δ 3.26 (t, 2 H, I-CH_2), 2.16 (2m, 4 H, -CH_2-CH_2-Rf).

**Discussion**

The alkylation of aliphatic amines is a very convenient reaction for the fluorocarbon solubilization of these important ligands that are utilized with fluorponytailed metal complexes as precatalysts in fluorous biphasic catalysis (FBC) systems [1]. Thus, by specifically using the necessary three carbon spacer, fluorponytailed synthon, 3-perfluorooctyl-1-iodopropane, 3, a wide variety of fluorponytailed amine ligands, such as 4, are now readily accessible [1b, 1c].

**Reference**


11.15 Precatalysts for FBC Alkane, Alkene, and Alcohol Oxidation Chemistry

Jean-Marc Vincent*, Maria Contel, Mariano Laguna, and Richard H. Fish*

Reaction 11.15-1

\[
\begin{align*}
\text{MX} & + \text{RfCH}_2\text{CH}_2\text{CO}_2\text{H} \rightarrow (\text{RfCH}_2\text{CH}_2\text{CO}_2)_2\text{M} \\
\text{MX} = \text{Mn(ClO}_4)_2\cdot6\text{H}_2\text{O} & \quad \text{Rf} = \text{C}_8\text{F}_{17} \\
\text{MX} = \text{Co(ClO}_4)_2\cdot6\text{H}_2\text{O} & \\
\text{MX} = \text{CuSO}_4\cdot5\text{H}_2\text{O} & \\
\end{align*}
\]

Steps A-C

11.15

\[
\begin{align*}
\text{MX} & + \text{RfCH}_2\text{CH}_2\text{CO}_2\text{H} \rightarrow (\text{RfCH}_2\text{CH}_2\text{CO}_2)_2\text{M} \\
\text{MX} = \text{Mn(ClO}_4)_2\cdot6\text{H}_2\text{O} & \quad \text{Rf} = \text{C}_8\text{F}_{17} \\
\text{MX} = \text{Co(ClO}_4)_2\cdot6\text{H}_2\text{O} & \\
\text{MX} = \text{CuSO}_4\cdot5\text{H}_2\text{O} & \\
\end{align*}
\]

Reagents

\(\text{RfI} (\text{Rf} = \text{C}_8\text{F}_{17})\) and perfluoroheptane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene (benzotri fluoride), phosphorous pentaoxide, 85%, phosphoric acid, potassium iodide, 1,4,7-triazacyclononane (TACN), triethylamine, diethyl malonate, sodium hydride, potassium hydroxide were purchased from Aldrich Chemical Company. \(\text{CF}_3(\text{CF}_2)_{7}\text{CH}_2\text{CH}_2\text{CO}_2\text{H}\) was a gift from Elf Atochem, France, but is now available from Strem Chemical Co. The non-fluorous metal complexes were purchased from Strem Chemical Co.

Experimental Procedures

Step A. Manganese bis(2-(2-Perfluoroocetyl)-3-perfluoroocyl Propanoate Dihydrate \(\{\text{Mn[C}_4\text{F}_{17}(\text{CH}_2)_{2}\text{CO}_2\text{H}(\text{H}_2\text{O})_2}\}\) (1) \(\text{CF}_3(\text{CF}_2)_{7}\text{CH}_2\text{CH}_2\text{CO}_2\text{H}\) (1.35 g, 2.80 mmol) is dissolved in acetone (15 mL) and triethylamine is added (380 mL, 2.80 mmol). This resulting solution is added dropwise to \(\text{Mn(ClO}_4)_2\cdot6\text{H}_2\text{O}\) (500 mg, 1.37 mmol) dissolved in acetone (30 mL). The sticky precipitate that forms is vigorously stirred for 2 h. After filtration, 1 is obtained
as a white powder in 75% yield. Elemental anal. calc. for C_{22}F_{34}H_{12}O_{6}Mn: C, 24.61; F, 60.19; H, 1.12; Mn, 5.12. Found: C, 25.37; F, 59.77; H, 0.94; Mn, 5.50.

Step B. Cobalt bis(2-(2-Perfluorooctylethyl)-3-perfluorooctyl Propanoate Dihydrate Co[C_{8}F_{17}(CH_{2})_{2}CO_{2}]_{2}(H_{2}O)_{2} (2) The same procedure, as conducted with complex 1, was used for the synthesis of 2, except with Co(ClO_{4})_{2}·6H_{2}O. A pink precipitate formed immediately, and after filtration, a pink powder is obtained in 100% yield. Elemental anal. calc. for C_{22}H_{12}F_{34}CoO_{6}: C, 24.53; H, 1.11; F, 59.98; Co, 5.46. Found: C, 25.05; H, 1.27; F, 60.15; Co, 5.35.

Step C. Copper bis(2-(2-Perfluorooctylethyl)-3-perfluorooctyl Propanoate Dihydrate {Cu[C_{8}F_{17}(CH_{2})_{2}CO_{2}]_{2}}(CF_{3}(CF_{2})_{7}CH_{2}CH_{2}CO_{2}H (1.35 g, 2.80 mmol) was dissolved in acetone (15 mL), and to this solution is added triethylamine (0.39 mL, 2.80 mmol). This solution is added dropwise to a suspension of CuSO_{4}·5H_{2}O (0.342 g, 1.37 mmol) in acetone (30 mL). After 24 h stirring at room temperature, the complex 3 precipitates as a blue powder, which is collected by filtration and washed with Et_{2}O. This complex is obtained in 69% yield (0.098 g). Elemental anal. calc. for C_{22}H_{8}F_{34}O_{4}Cu: C, 25.27; H, 0.77. Found: C, 25.44; H, 0.81. IR: carboxylate bands ν = 1573 and 1420 cm⁻¹. UV-vis spectrum (diffuse reflectance): λ 666 nm (28%). This complex is totally soluble in trifluorotoluene, partly soluble in dichloromethane, and insoluble in acetone, Et_{2}O, n-hexane, MeOH, H_{2}O, and perfluoroheptane.

Step D. Mn[C_{8}F_{17}(CH_{2})_{2}CO_{2}](RF-TACN) (5a), Co[C_{8}F_{17}(CH_{2})_{2}CO_{2}](RF-TACN) (5b), and Cu[C_{8}F_{17}(CH_{2})_{2}CO_{2}](RF-TACN) (5c) The complexes 5a and 5b are prepared [1a, 1b] in situ, while 5c is isolated as follows: R_{f}-TACN (0.218 g, 0.14 mmol) is added to a suspension of {Cu[C_{8}F_{17}(CH_{2})_{2}CO_{2}]_{2}} (0.15 g, 0.14 mmol) in 10 mL of dichloromethane. A green solid precipitates immediately and is collected by filtration. After drying under vacuum, 4 is obtained as a green powder in 80% yield (0.255 g). Elemental anal. calc. for C_{61}H_{38}F_{85}O_{4}N_{3}Cu: C, 28.67; H, 1.49; N, 1.64. Found: C, 29.01; H, 1.60; N, 1.70. LSIMS-MS: m/z 2063 (75%, [M/Cu[C_{8}F_{17}(CH_{2})_{2}CO_{2}]+]), m/z 1572 (30%, [M/Cu[C_{8}F_{17}(CH_{2})_{2}CO_{2}]_{2}]+), m/z 1508 (58%, RF-TACN⁺). IR carboxylate bands = 1632 and 1403 cm⁻¹; UV-vis spectra (perfluoroheptane): λ 272 nm, (diffuse reflectance): λ 1013 nm (62%), 700 nm (48%). This complex was totally soluble in trifluorotoluene and in perfluoroheptane, while being insoluble in acetone, acetone, n-hexane, MeOH, H_{2}O, and perfluoroheptane.

Step E. [Cu(R_{f}-TACN)Cl] (6) R_{f}-TACN (0.151 g, 0.1 mmol) is added to a suspension of excess [CuCl] (0.050 g, 0.5 mmol) in 5 mL of trifluorotoluene. After 3 h at room temperature, the suspension was filtered through Celite (to remove the excess of CuCl), and the colorless solution was evaporated to 1 mL. The addition of n-hexane affords an off white powder 6 in 78% yield (0.125 g). Elemental anal. calc. for C_{39}H_{30}F_{51}N_{3}ClCu: C, 29.12; H, 1.88; N 2.61. Found: C, 29.45; H, 1.97; N, 2.43; LSIMS-MS m/z 1573 (88%, [M – Cl]⁺), m/z 1095 (100%, [M – Cl – (CH_{2})_{2}C_{8}F_{17} – F]⁺); ¹H NMR (CDCl_{3}, 25 °C), δ 2.25 (m, 6 H, -CH_{2}-CH_{2}-CH_{2}-C_{8}F_{17}), 2.10 (s, 12 H, -N-CH_{2}-CH_{2}-N), 1.57 (m, 6 H, -CH_{2}-CH_{2}-CH_{2}-C_{8}F_{17}), 1.20 (m, 6 H, -CH_{2}-CH_{2}-CH_{2}-C_{8}F_{17}); ¹⁹F[¹H] NMR (CDCl_{3}, 25 °C) δ = −80.5, −100.8, −111.2, −121.1, −121.7, −122.6 and −125.9 ppm. The ¹⁹F[¹H] NMR spectrum in CDCl_{3} of R_{f}-TACN 4
shows the signals at δ -81.7, -115.2, -122.9, -123.9, -124.7 and -127.3. UV-vis spectrum (perfluoroheptane) λ 212, 260 nm (diffuse reflectance). This complex was totally soluble in trifluorotoluene and perfluoroheptane, partly soluble in dichloromethane and chloroform, and insoluble in acetone, Et₂O, n-hexane, MeOH, and H₂O.

Discussion

The use of metal complexes as precatalysts in fluorous biphasic catalysis (FBC) reactions has led to the discovery that the ligands for the central metal ion needed to have appended fluoro-R-ponytails to enhance their perfluorocarbon solubility [1]. We also found that fluoro-R-ponytailed metal carboxylates, such as complexes 1–3, were not totally soluble in perfluoro-carbons, but were solubilized via reaction with a fluorous soluble, fluoro-R-ponytailed organic ligand, such as ligand 4, to synthesize complexes, such as 5a–c, where M²⁺ is Mn²⁺, Co²⁺, or Cu²⁺ [1, 2]. Interestingly, the Cu²⁺ complex 6 was found to be fluorous soluble, without the [CuCl] complex having appended fluoro-R-ponytails [2]. Complexes 1–3, 5a–c, and 6 were used as precatalysts in the FBC oxidation of alkanes, alkenes, and alcohols [1, 2].

References


11.16 A Fluorous Soluble Carboxylic Acid Ligand for Metal Complexes

Jean-Marc Vincent* and Richard H. Fish*

Reaction 11.16-1

Step A

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{NaH, } R_f(\text{CH}_2)_3 & \quad \text{KOH, EIOH, } 90^\circ C \\
\text{CO}_2\text{Et} & \quad \text{DMF, } 80^\circ C & \quad \text{R}_f(\text{CH}_2)_3 & \quad \text{R} \\
\text{R}_f & = \text{C}_8\text{F}_{17} & \quad & \text{2. } R = \text{CO}_2\text{H, } 80\% \\
\text{1. } 76\% & & & \text{3. } R = \text{H, } 86\% \\
\end{align*}
\]
Reagents

Rf(CH2)3I, RfI (Rf = C8F17) and perfluoroheptane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene (benzotrifluoride), phosphorous pentaoxide, 85%, phosphoric acid, and potassium iodide were purchased from Aldrich Chemical Company. Diethyl malonate, sodium hydride, and potassium hydroxide were purchased from Strem Chemical Co.

Experimental Procedures

Step A. 2,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)malonic Acid Diethyl Ester (1)

Diethyl malonate (0.72 g, 4.5 mmol) dissolved in anhydrous DMF (15 mL) is added dropwise to an NaH suspension (95%, 0.324 g, 13.5 mmol) in anhydrous DMF (30 mL) at 0 °C. After 1 h at ambient temperature, Rf(CH2)3I (6 g, 10.2 mmol) dissolved in anhydrous DMF (15 mL) is slowly added, and the mixture is stirred at 80 °C for 12 h. After cooling to room temperature, perfluorohexane (20 mL) is added to extract 1. The perfluorohexane solvent is removed under reduced pressure leading to 1, as a beige oil in 76% yield: 1H NMR (CDCl3) δ 4.20 (q, 4 H), 1.91–2.05 (m, 8 H); 13C NMR δ 170.6, 61.3, 56.9, 31.9, 30.7, 15.2, 13.5; MS (m/z, I%) 1080, <1, M+; 1061, 2, M+; 1035, 4, M+; 1007, 23, M–; 620, 39, M–.

Step B. 2,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-Heptadecafluoroundecyl)malonic Acid (2)

The diester 1 (7 g, 6.5 mmol) is refluxed in a mixture of absolute ethanol (70 mL) and aqueous potassium hydroxide (50%, 70 mL) for 6 h. The mixture is acidified at 0 °C (pH 2–3) with concentrated HCl leading to the precipitation of 2 as a yellow powder; yield, 5.3 g (80%), mp 150–151 °C: 1H NMR (THF-d8) δ 2.35–2.08 (m, 8 H), 1.91–2.05 (m, 8 H), 1.50–1.53 (m, 4 H), 1.23 (t, 6 H); 13C NMR δ 170.6, 61.3, 56.9, 31.9, 30.7, 15.2, 13.5; MS (m/z, I%) 1080, <1, M+; 1061, 2, M–; 1035, 4, M–.

Step C. 6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoroundecyl)tridecanoic Acid (3)

The diacid 2 is heated at 180 °C until the CO2 evolution ceases. The monoacid 3 was recrystallized in hot toluene; yield 86%, mp 91–92 °C; 1H NMR (THF-d8) δ 2.1–2.4 (m, 5 H), 1.55–1.72 (m, 8 H); 13C NMR (THF-d8)
Step D. bis[6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoroundecyl)tridecanoyl] Manganese and Cobalt (4a,b) A mixture of the monoacid 3 (0.2 g, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in THF (5 mL) is added to a solution of Mn(ClO₄)₂ or Co(ClO₄)₂ (0.1 mmol) in THF (2 mL) at room temperature. After 12 h, 4a,b are recovered by filtration, the triethylammonium salt being eliminated in the filtrate. Anal. calcd. for C₄₈H₂₆O₄F₆₈Mn: C, 28.61; H, 1.29; Mn, 2.73. Found: C, 28.63; H, 1.35; Mn, 2.75%. Anal. calcd. for C₄₈H₂₆O₄F₆₈Co: C, 28.57; H, 1.29; Co, 2.92. Found: C, 28.39; H, 1.29; Co, 3.15%.

Step E. tetrakis[6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-heptadecafluoroundecyl)tridecanoyl] Dicopper (5) A solution of carboxylic acid 3 (0.2 g, 0.2 mmol) and triethylamine (30.5 μL, 0.22 mmol) in acetone (5 mL) is added to a stirred solution of Cu(OTf)₂ (36.9 mg, 0.1 mmol) in acetone (2 mL). After 3 h, an insoluble blue oil forms. After decanting off the acetone solution, the resulting oil is washed with cold acetone. The oil is dissolved in hot toluene/trifluorotoluene and the blue solution is left to stand at –18 °C. After 24 h, the precipitated complex 5 is collected by filtration and washed with toluene (0.194 g, 96%): FTIR (cm⁻¹, KBr) 1592 (νasymCO₂), 1420 (νsymCO₂); UV-vis (perfluorodecalin) [λmax, nm (ε, M⁻¹ cm⁻¹)] 680 (300). Anal. calcd. for C₉₆F₁₃₆H₅₂O₈Cu: C, 28.50; F, 63.90; H, 1.29; Cu, 3.14. Found: C, 28.29; F, 62.57; H, 1.21; Cu, 3.14.

Discussion

The use of metal complexes as precatalysts in fluorous biphasic catalysis (FBC) reactions has led to the discovery that the ligands for the central metal ion needed to have appended fluoroponytails to enhance their perfluorocarbon solubility [1]. More importantly, it was found that the fluoroponytailed carboxylate ligands could themselves be made fluorous soluble by appending two fluoroponytails to the carboxylic acid backbone, compound 3, enabling their metal complexes to be concomitantly soluble in fluorous media, 4a,b and 5 [2, 3].

References


170.3, 45.3, 32.2, 31.4, 19.0; MS (m/z, %, M – X): 980, <1; M; 961, I, M – 19; 520, 31, M – 460. Anal. calc. for C₄₄H₁₄O₂F₃₄: C, 29.39; H, 1.43. Found: C, 29.31; H, 1.50.
11.17
1H,1H,2H,2H-Heptadecafluorodecyl Nicotinate (1) and Bis(1H,1H,2H,2H-Heptadecafluorodecyl)pyridine-3,5-dicarboxylate (2). Esterification of Nicotinic Acid with a Fluoroalcohol

Takahiro Nishimura and Sakae Uemura

Reaction 11.17-1

\[
\begin{align*}
\text{Step A} & \\
\text{Step B} & 
\end{align*}
\]

Reagent


Experimental Procedures

Step A. 1H,1H,2H,2H-Heptadecafluorodecyl Nicotinate (1)  To a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are charged nicotinic acid (1.23 g, 10.0 mmol) and thionyl chloride (5 mL) and the mixture is stirred at 90 °C under nitrogen. After 6 h, excess thionyl chloride is removed on a rotary evaporator under reduced pressure and the resulting yellow-white solid is dissolved in CH₂Cl₂ (10 mL). The mixture is cooled to 0 °C and triethylamine (1 mL) is added. 1H,1H,2H,2H-Heptadecafluorodecanol (2.32 g, 5.0 mmol) is then added portion-wise to the mixture with stirring at 0 °C, and the resulting mixture is allowed to warm to room temperature and stirred for 12 h. After the solvent is removed on a rotary evaporator under reduced pressure, the resulting white solid is washed with water (30 mL) and dried under vacuum at room temperature. The pure compound is obtained after column chromatography on Merck silica gel 60 with hexane/ethyl acetate (6/1) as an eluent (2.48 g, 4.35 mmol, 87%) as a white solid; ¹H NMR (300 MHz, CDCl₃) δ 2.63 (tt, J₅H = 18.2 Hz, J₃H = 6.3 Hz, 2 H), 4.67 (t, J = 6.3 Hz, 2 H), 7.41 (dd, J = 7.9, 5.0 Hz, 1 H), 8.29 (d, J = 7.9 Hz, 1 H), 8.81 (d, J = 5.0 Hz, 1 H), 9.23 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 30.7 (t, ¹JC₅ = 22 Hz), 57.4, 105–122 (m), 123.5, 125.7, 137.2, 151.1, 153.9, 165.0 [1].
Step B. bis(1H,1H,2H,2H-Heptadecafluorodecyl)pyridine-3,5-dicaboxylate (2) To a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are charged 3,5-pyridinedicarboxylic acid (0.33 g, 2.0 mmol) and thionyl chloride (2.2 mL) and the mixture is stirred at 90 °C under nitrogen. After 6 h, excess thionyl chloride is removed on a rotary evaporator under reduced pressure and the resulting yellow-white solid is dissolved in CH₂Cl₂ (10 mL). The mixture is cooled to 0 °C and triethylamine (1 mL) is added. 1H,1H,2H,2H-Heptadecafluorodecanol (2.04 g, 4.4 mmol) is then added portion-wise to the mixture with stirring at 0 °C, and the resulting mixture is allowed to warm to room temperature with stirring. After 12 h, water (10 mL) is added and the mixture is dissolved in CHCl₃ (400 mL). The organic layer is washed with water (50 mL) and dried over MgSO₄. After the solvent is removed on a rotary evaporator under reduced pressure, the resulting orange solid is washed with acetone (30 mL) and dried under vacuum at room temperature. The pure compound is obtained (1.60 g, 1.52 mmol, 76%) as a white solid after recrystallization from hexane/ethyl acetate; ¹H NMR (270 MHz, CDCl₃) δ 2.65 (tt, JHF = 18.1 Hz, JHH = 6.2 Hz, 4 H), 4.71 (t, J = 6.2 Hz, 4 H), 8.84 (s, 1 H), 9.50 (br s, 2 H) [1].

Discussion

The reaction of carboxylic acids with alcohols is widely used for preparation of the corresponding esters. In particular, the method of preparation of esters via acid chlorides using thionyl chloride [2] is most widely employed because of high yields of products. In the case of step B, the extraction of the product with CHCl₃ is recommended. If the solvent is removed after the reaction and the resulting orange solid is washed with water, as in the case of step A, jelly-like solids appear and the filtration becomes quite difficult.

References


11.18 Pyridine-3-carbaldehyde Bis(1H,1H,2H,2H-heptadecafluorodecyl) Acetal. Acetalization of Pyridine-3-carbaldehyde with a Fluoroalcohol

Takahiro Nishimura and Sakae Uemura

Reaction 11.18-1
Reagent


Experimental Procedure

A mixture of pyridine-3-carbaldehyde (0.32 g, 3.0 mmol), 1H,1H,2H,2H-heptadecafluorodecanol (4.18 g, 9.0 mmol) and trifluoromethanesulfonic acid (TfOH; 0.3 ml, 3.3 mmol) in 1,2-dichloroethane (30 mL) is stirred at reflux (bath temperature: 90 °C) in a 50 ml two-necked round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel (30 mL), the top of which is attached with a reflux condenser. The 1,2-dichloroethane that condenses in the dropping funnel during the reaction is added occasionally to the reaction mixture. After 6 h, the mixture is cooled to room temperature and then triethylamine (2 mL) is added to the solution, and the mixture is diluted with diethyl ether (100 mL). The ether solution is washed with water and dried over MgSO₄. The solvent is removed on a rotary evaporator under vacuum and the residue is subjected to column chromatography on Merck silica gel 60 with hexane/ethyl acetate (4/1) as an eluent to give pyridine-3-carbaldehyde bis(1H,1H,2H,2H-heptadecafluorodecyl) acetal (2.85 g, 2.81 mmol, 94%) as a colorless oil: $^1$H NMR (400 MHz, CDCl₃) $\delta$ 2.46 (tt, $J_{HF} = 18.6$ Hz, $J_{HH} = 6.4$ Hz, 4 H), 3.77–3.81 (m, 4 H), 5.67 (s, 1 H), 7.34 (dd, $J = 7.8$, 4.9 Hz, 1 H), 7.77 (d, $J = 7.8$ Hz, 1 H), 8.62 (d, $J = 4.9$ Hz, 1 H), 8.70 (s, 1 H); $^{13}$C NMR (75.5 MHz, CDCl₃) $\delta$ 31.4 (t, $J_{CF} = 21$ Hz), 57.4, 100.0, 105–122 (m), 123.3, 132.5, 134.3, 148.5, 150.3 [1].

Discussion

Acetalization is one of the most popular protection methods of carbonyl compounds. Acetals are formed by treatment of the aldehydes or ketones with alcohols in the presence of acid catalyst. Generally, $p$-toluenesulfonic acid is used as a catalyst for this reaction, but the protection of pyridine-3-carbaldehyde with 1H,1H,2H,2H-heptadecafluorodecanol failed using this acid. In this case, the use of a small excess amount of TfOH to the substrate is efficient in giving the corresponding acetal in excellent yield [2].

References

2,2,2-Trifluoroethyl 2H,2H,3H,3H-perfluoroundecanoate. A Highly Fluorinated Acyl Donor Useful for the Lipase Catalyzed Labeling of Racemic Alcohols [1]

Fritz Theil*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

**Reaction 11.19-1**

```
Step A
C_{8}F_{17}(CH_{2})_{2}OH \overset{TsCl, Et_{3}N}{\rightarrow} C_{8}F_{17}(CH_{2})_{2}OTs \overset{THF, 10 h, 67 \degree C}{\rightarrow} C_{8}F_{17}(CH_{2})_{2}Br
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1, 2, 2H, 2H, 3H, 3H-perfluorodecane-1-ol (1) [678-39-7], 2,2,2-trifluoroethanol [75-89-8] and all other chemicals used are commercially available.

**Experimental Procedures**

**Step A. 1H,1H,2H,2H-Perfluorodecane-1-ol Tosylate (2)** To a solution of 1H,1H,2H,2H-perfluorodecane-1-ol (400 g, 0.862 mol) and p-toluenesulfonyl chloride (TsCl, 207.0 g, 1.086 mol) in dry THF (800 mL) is added triethylamine (110.0 g, 151.3 mL, 1.086 mol) at rt within 10 min. The reaction mixture is refluxed under argon until 1 is completely consumed (~10 h). The precipitate is filtered off and washed with tert-butyl methyl ether (500 mL). The filtrate is evaporated under reduced pressure and the remaining residue is partitioned between a mixture of tert-butyl methyl ether (1000 mL)/ethyl acetate (500 mL) and 2 N HCl (500 mL). The organic phase is washed with 2 N K_{2}CO_{3} (2 × 100 mL), brine (100 mL) and dried (Na_{2}SO_{4}). Evaporation under reduced pressure (up to 95 °C bath temperature/10 mbar) yields the crude product still containing p-toluenesulfonyl chloride that is distilled off by rotatory evaporation (140–154 °C bath temperature, 0.08 mbar). The slightly brown oily residue crystallizes on cooling affording toluene-4-sulfonic acid 1H,1H,2H,2H-perfluorodecylester (2, 470.6 g, 88%), which is used in the next step without further purification: 1H NMR (CDCl_{3}) δ 2.47 (s, 3 H), 2.51 (m, 2 H), 4.31 (t, 3 H, J = 6.9 Hz), 7.37 (d, 2 H, J = 7.8 Hz), 7.81 (d, 2 H, J = 7.8 Hz).

**Step B. 1-Bromo-1H,1H,2H,2H-perfluorodecane (3)** A suspension of the above described toluene sulfonate 2 (470.0 g, 0.76 mol) and dry LiBr (132.0 g, 1.52 mol) in acetone (380 mL)
is refluxed for 7 h turning into a fluffy suspension. After this time a complete conversion of
the starting material takes place [3]. The reaction mixture is cooled down to rt, cyclohexane
(1000 mL) is added and the precipitate is filtered off, washed with a mixture of cyclohexane
(100 mL) and acetone (20 mL) and finally with pure cyclohexane (3 × 100 mL). The filtrate
is concentrated under reduced pressure and the oily residue is distilled affording 1-bromo-
H,2H,2H,2H-perfluorodecane [3, 371.8 g, 93%, bp 68–72 °C at 0.1 mbar] as a colorless
liquid that crystallized at ~6 °C. 1H NMR (CDCl3) δ 2.70 (tt, 2 H, J1 = 8.1 Hz, J2 = 8.4 Hz),
3.51 (t, 2 H, J = 8.4 Hz). 13C NMR (CDCl3) δ 43.7 g, 88.8 mmol) in dry THF (150 mL) is slowly added over 1.25 h keeping
the reaction under gentle reflux. The mixture is refluxed for another 4.5 h and cooled down
in an ice/NaCl bath to ~6 °C. Dry carbon dioxide is bubbled through the reaction mixture
whereby the temperature rises up to 24 °C and a brown solid precipitates (15 min). 2 N HCl
(75 mL) is added slowly at 0 °C. The aqueous mixture is extracted with tert-butyl methyl
ether (1 × 200 mL, 2 × 50 mL). The combined organic layers are washed with brine (50 mL),
dried (Na2SO4) and concentrated under reduced pressure affording crude 2H,2H,2H,2H-
perfluoroundecanoic acid (4, 42.9 g, 88%) as a brown solid that is used in the next step
without further purification. (If required, 4 can be recrystallized from CHCl3). 1H NMR
(CD2COCD2) δ 2.57 (m, 2 H), 2.69 (t, 2 H, J = 8.1 Hz), 11.0 (broad s, 1 H).

**Step D. 2H,2H,2H,2H-Perfluoroundecanonyl chloride (5)** A solution of 4 (43.7 g, 88.8 mmol) in dry diethyl ether (150 mL) is treated with PCl5 (37.0 g, 177.6 mmol) and refluxed under argon (4 h). After cooling with an ice bath the reaction mixture is filtered and the filter cake
(excess PCl5) is washed with n-hexane (100 mL). The filtrate is concentrated under reduced
pressure and the resulting brown oily residue is distilled under reduced pressure affording
2H,2H,2H,2H-perfluoroundecanonyl chloride (5, 38.0 g, 84%, bp 95–97 °C at 0.5 mbar) as a colorless liquid: 1H NMR (CDCl3) δ 2.53 (m, 2 H), 3.24 (t, 2 H, J = 7.8 Hz); 19F NMR [CDCl3; δ (CFCl3) = 0] δ = −80.5, −113.7, −120.9, −121.2 (2 signals), −122.0, −122.6, −125.4.

**Step E. 2,2,2-Trifluoroethyl 2H,2H,2H,2H-Perfluoroundecanoate (6)** To an ice-cold solution of the above described acid chloride 5 (25.5 g, 50.0 mmol) and 2,2,2-trifluoroethanol (5.2 g, 3.7
mL, 52.5 mmol) in dry THF (50 mL) containing a catalytic amount of DMAP (200 mg) is
added dry pyridine (4.15 g, 4.24 mL, 52.5 mmol) dropwise within 5 min. The cooling bath
is removed and the solution is allowed to reach rt. After stirring for 1 h at rt, the precipitate
is filtered off. The filtrate is concentrated under reduced pressure and the remaining residue is partitioned between tert-butyl methyl ether (100 mL) and 2 N HCl (25 mL). The organic layer is washed with water (25 mL), dried (Na2SO4), concentrated under reduced pressure and distilled under reduced pressure affording 2,2,2-trifluoroethyl 2H,2H,2H,2H-perfluoroundecanoate (6, 26.2 g, 91%, bp 58–60 °C at 1 × 10⁻¹ mbar) as a colorless liquid that crystallized at 4 °C [5, 6]: 1H NMR (CDCl3) δ 2.51 (tt, 2 H, J1 = 8.4 Hz, J2 = 8.0 Hz), 2.77 (t, 2 H, J = 8.4 Hz), 4.52 (t, 2 H, J = 8.4 Hz); 19F NMR [CDCl3; δ (CFCl3) = 0] δ = −73.7, −80.5, −114.1, −120.9, −121.1 (2 signals), −121.9, −122.7, −125.3.
Discussion

A highly fluorinated acyl donor is obtained in a five step synthesis starting from \( \text{H}_1\text{H}_1\text{H}_2\text{H}_2\text{H}-\text{perfluoro-decane-1-ol} \). Two of the four intermediates of the synthesis are already, as the crude product, of sufficient purity and can be used in the next step without further purification.

References and Notes

2. Caution: The obtained bromide is a lachrymator.
3. The progress of the reaction was followed by \(^1\text{H}-\text{NMR}\).
4. All reagents and glassware are dried rigorously.
5. Prior to use of the substance in enzymatic reactions, the pH of \( \text{6} \) should be tested on wet pH paper after waiting for 5 min. If necessary, traces of acid that decrease enzyme activity are to be removed by simple silica gel filtration (80.0 g of \( \text{6} \) through a layer of 4 cm in height, 13 cm in diameter with cyclohexane/ethyl acetate, 10:1).
6. An alternative procedure to obtain \( \text{6} \) directly from \( \text{4} \) is conducted as follows: to a solution of the acid \( \text{4} \) (11.8 g, 24 mmol) in \( 2,2,2\)-trifluoroethanol (30 mL) is added sulfuric acid (2 mL) and the mixture is refluxed for 6 h. The solvent is distilled off under reduced pressure and the residue is partitioned between tert-butyl methyl ether (60 mL) and water (20 mL). The aqueous layer is re-extracted with tert-butyl methyl ether (60 mL). The combined organic layers are washed with water (10 mL), 5% aqueous NaHCO\(_3\) (10 mL) and dried (Na\(_2\)SO\(_4\)). Evaporation yields a crude liquid that is distilled by Kugelrohr distillation (oven temperature: \( 88 \ ^\circ\text{C}/1 \times 10^{-3} \text{ mbar} \)) affording pure \( \text{6} \) (10.2 g, 74%). The reaction also works with the dry crude lithium salt \( \text{4a} \) obtained as a byproduct of resolution of racemic alcohols by use of \( \text{6} \) (see reaction described in Section 11.20 in connection with the resolution of racemic 1-phenylethanol).

11.20 (R)- and (S)-1-Phenylethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Labeling

*Fritz Theil*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

**Reaction 11.20-1**

- **Step A**
  - rac-2
  - 1) 1, CAL-B, CH\(_3\)CN, 19 h, rt
  - 2) MeOH/C\(_6\)F\(_{14}\), extraction

- **Step B**
  - LiOH, THF/H\(_2\)O, 3 h, 67 \(^\circ\text{C}\)

\( \text{(S)-2} \) 48%, 99% ee, \( \text{(R)-3} \) 47%, 99% ee

1. Is \( \text{CF}_3\text{CH}_2\text{OCO(CH}_2\text{)}_2\text{R}_i \) where \( \text{R}_i \) is \( \text{C}_8\text{F}_{17} \)

\( \text{(S)-2} \) 99%, 99% ee, \( \text{(R)-3} \) 99%, 99% ee

\( \text{+ LiO}_2\text{C(CH}_2\text{)}_2\text{R}_i \) \( \text{4} \), 98%
Reagents

The synthesis of 2,2,2-trifluoroethyl 2H,2H,3H,3H-perfluoro-undecanoate (1) [1, 2] is described in the preceding procedure (Section 11.19). Candida antarctica B lipase (CAL-B, Chirazyme L-2, c.-f., lyo., Roche Diagnostics, Mannheim), 1-phenyl-ethanol [98-85-1] and the other chemicals used are commercially available. The enantiomeric excess of the enantiomeric alcohols was determined by HPLC on Chiralcel OJ® (250 × 4.6 mm); mobile phase: n-heptane/n-propanol (95:5); flow rate: 1 mL/min; temperature: 22 °C; detection: UV at 254 nm [1].

Experimental Procedures

Step A. (S)-1-Phenylethanol ([(S)-2]) and (R)-1-Phenylethyl 2H,2H,3H,3H-Perfluoroundecanoate [(R)-3] A solution of (R,S)-1-phenylethanol (rac-2, 1.22 g, 10 mmol) in acetonitrile (65 mL) is treated with 2,2,2-trifluoroethyl 2H,2H,3H,3H-perfluoro-undecanoate [2] (1, 8.61 g, 15 mmol) and CAL-B (2.00 g). The reaction mixture is stirred at ambient temperature until the conversion reaches about 50% (19 h). The enzyme is filtered off and the solid residue is washed with acetone (2 × 40 mL). The combined filtrates are evaporated under reduced pressure. The residue is dissolved in MeOH (25 mL). The resulting solution is extracted with n-C6F14 (6 × 25 mL). The organic phase is concentrated to dryness yielding (S)-2 (0.59 g, 48%) with an ee of 99% containing ca. 1% of (R)-3. From the fluorous phase a mixture (8.50 g) of (R)-3 (ee 98%) [1] and the excess of 1 is obtained.

Step B. (R)-1-Phenylethanol [(R)-2] For saponification of (R)-3 to (R)-2 the mixture of (R)-3 and 1 obtained in step A is dissolved in a 1:1 mixture of THF/water (40 mL) containing LiOH (0.64 g, 26.7 mmol) and refluxed for 3 h. Subsequently, the reaction mixture is diluted with cyclohexane (100 mL), cooled to 0 °C and filtered. The filter cake is washed with a mixture of cyclohexane (100 mL) and tert-butyl methyl ether (30 mL). The filtrate is concentrated to dryness yielding (R)-2 (0.57 g, 47% related to rac-2) with an ee of 98%.

The solid filter cake (7.35 g, 98%) consists of the lithium salt of 2H,2H,3H,3H-perfluoroundecanoic acid 4 [3].

Discussion

The highly fluorinated carboxylic ester 1 is an extremely useful and selective acyl donor for the lipase-catalyzed enantiomer-selective acylation of alcohols, thus the faster reacting enantiomer is equipped with a fluoruous tag in order to be recognized selectively by a fluoruous phase. The enantiomer-selective labeled mixture of ester and alcohol representing the two enantiomers can be separated very efficiently by partition in the two-phase solvent system perfluoro-n-hexane/methanol avoiding a chromatographic step. Hydrolysis of the fluorinated enantiomer allows the quantitative recovery of the fluorous tag.

Kinetic resolutions by use of the highly fluorinated ester 1 are a useful alternative to existing methods for the non-chromatographic separation of enantiomeric esters from the corresponding alcohols [4–9].
(R)- and (S)-1-Naphthalen-2-yl-ethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Delabeling of a Corresponding Highly Fluorinated Ester

Fritz Theil*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

Reaction 11.21-1

Step A

\[
\text{rac-2} \xrightarrow{1, \text{pyridine, THF}} \text{rac-3}, 82 \%
\]

Step B

\[
1) \text{BuOH, CAL-B} \\
2) \text{CH}_3\text{OH/C}_8\text{F}_{14} \text{ extraction}
\]

1 is CICO(CH_2)_2R_i where R_i is C_8F_{17}

\[
\text{(R)-2, 44%, 99% ee} + \text{(S)-3, 43%, 94% ee}
\]
(R)- and (S)-1-Naphthalen-2-yl-ethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Delabeling of a Corresponding Highly Fluorinated Ester

Fritz Theil*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

Reaction 11.21-1

**Step A**

\[
\text{rac-2} \xrightarrow{1, \text{pyridine, THF}, 3h, 0 \, ^\circ \text{C-rt}} \text{rac-3, 82 \%}
\]

1 is CI\text{CO(CH}_2\text{)}\text{)_2R}_i where \text{R}_i is \text{C}_8\text{F}_{17}

**Step B**

1) BuOH, CAL-B

\[
\text{CH}_3\text{CN, 7 d, rt}
\]

2) CH\text{3OH}/C\text{6F}_{14} extraction

\[
\begin{align*}
\text{(R)-2, 44\%, 99\% ee} & \quad + \quad \text{(S)-3, 43\%, 94\% ee} & \quad + \quad \text{BuO} & \quad \text{O} & \quad \text{(CH}_2\text{)}\text{)_2R}_i}
\end{align*}
\]

References and Notes

2 The pH of 6 should be tested on wet pH paper after waiting for 5 min. If necessary, traces of acid that decrease enzyme activity are to removed on a large scale by simple silica gel filtration [see synthesis of 2,2,2-trifluoroethyl 2H,2H,3H,3H-perfluoroundecanoate (11.19)].
3 Before its use in esterification, the salt 4a has to be dried under reduced pressure over P\text{2O}_5.
OH
LiOH, THF, H2O
3 h, 67 °C
(S)-3 →
OH
(S)-2, 99%, 94%ee
LiO
CH2)2Rf
5

Reagents

The synthesis of 2H,2H,3H,3H-perfluoroundecanoyl chloride (1) [1] is described above in connection with the preparation of 2,2,2-trifluoroethyl 2H,2H,3H,3H-perfluoro-undecanoate (Section 11.19). Candida antarctica B lipase (CAL-B, Chirazyme L-2, c.-f., lyo., Roche Diagnostics, Mannheim), (R,S)-1-naphthalen-2-yl-ethanol [52193-85-8] and the other chemicals used are commercially available. The enantiomeric excess of the alcohols was determined by HPLC on Chiracel OJ® (250 × 4.6 mm); mobile phase: n-heptane/2-propanol (90:10); flow rate: 1.5 mL/min; detection: UV at 254 nm [2].

Experimental Procedures

**Step A. (rac)-1-Naphthalen-2-yl-ethyl 2H,2H,3H,3H-perfluoroundecanoate (3)** To an ice-cold solution of the 2H,2H,3H,3H-perfluoroundecanoyl chloride (1; 5.10 g, 10.0 mmol) and the (R,S)-1-naphthalen-2-yl-ethanol (rac-2, 1.81 g, 10.5 mmol) in anhydrous THF (10 mL) containing a catalytic amount of DMAP (20 mg) is added dropwise anhydrous pyridine (0.83 g, 10.5 mmol) within 5 min. The cooling bath is then removed. After reaching rt, the mixture is stirred for another 2 h. The precipitate is filtered off, the filtrate is concentrated under reduced pressure and the residue is partitioned between tert-butyl methyl ether (20 mL) and 2 N HCl (5 mL). The organic layer is washed with water (5 mL), dried with Na2SO4 and concentrated under reduced pressure. Flash chromatography [cyclohexane/ethyl acetate (10:1)] of the residue on silica gel yields the pure 2H,2H,3H,3H-perfluoroundecanoic acid-1-naphthalen-2-yl-ethylester (rac-3, 5.30 g, 82%) as a white powder with a melting point of 66–67 °C [2].

**Step B. (R)-1-Naphthalen-2-yl-ethanol ([R]-2) and (S)-1-Naphthalen-2-yl-ethyl 2H,2H,3H,3H-perfluoroundecanoate ([S]-3)** A solution of the ester rac-3 (3.23 g, 5 mmol) in acetonitrile (120 mL) is treated with n-butanol (1.48 g, 1.83 mL, 20 mmol) and CAL-B (8.0 g). The reaction mixture is stirred at ambient temperature until the conversion reaches ca. 50% (7 days, estimated by TLC). The lipase is removed by filtration and washed with acetone (2 × 40 mL). The combined filtrates are evaporated under reduced pressure. The residue is dissolved in MeOH (25 mL). The resulting solution is extracted with n-C6F14 (6 × 25 mL). The organic phase is concentrated to dryness yielding pure (R)-2 (0.379 g, 44%) with an ee of 99%. From
the fluorous phase a mixture (2.97 g) of (S)-3 and the butylester of 2H,2H,3H,3H-perfluoroundecanoic acid (4) is obtained.

**Step C. (S)-1-Naphthalen-2-yl-ethanol [(S)-2]** For saponification of (S)-3 to (S)-2 the mixture, obtained from the fluorous phase of step B [2.97 g, (S)-3 and 4] is dissolved in a 1:1 mixture of THF/water (40 mL) containing LiOH (0.36 g, 15 mmol) and refluxed for 3 h. Subsequently, the reaction mixture is diluted with cyclohexane (70 mL) and tert-butyl methyl ether (30 mL), and the two distinct phases are separated. The aqueous phase containing S is washed with a mixture of cyclohexane (7 mL) and tert-butyl methyl ether (3 mL). The combined organic phases are dried (Na$_2$SO$_4$) and concentrated to dryness to yield the alcohol (S)-2 (0.367 g, 99%, ee 94%).

**Discussion**

The example demonstrates that highly fluorinated carboxylic esters of racemic alcohols are substrates for lipase B from *Candida antarctica*. The enantiomer-selective alcoholysis of 2H,2H,3H,3H-perfluoroundecanoic acid-1-naphthalen-2-yl-ethyl ester selectively cleaves the fluorous label from the fast-reacting enantiomer affording a mixture of an alcohol and the corresponding enantiomeric fluorinated ester. The products can be separated very efficiently by partition in the biphasic solvent system methanol/perfluoro-n-hexane avoiding chromatography. These results represent an example for the successful combination of fluorous techniques with lipase catalyzed kinetic resolutions where the final separation procedure is already integrated into the initial chemical transformation.

This technique is a useful alternative to existing methods for the non-chromatographic separation of enantiomeric alcohols [3–8].

**References**

Tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane

Denis Sinou and David Maillard

Reaction 11.22-1

Reagents

Nonafluorobutane sulfonyl fluoride $C_{4}F_{9}SO_{2}F$ [375-72-4], and tris(4-methoxyphenyl)-phosphane $2$ [855-38-9] are commercially available from Aldrich, and $1H,1H$-pentadecafluoroctan-1-ol [307-30-2] is from Fluka.

Experimental Procedures

Step A. $1H,1H$-Pentadecafluorooctyl Nonafluorobutanesulfonate ($3$) $C_{4}F_{9}SO_{2}F$ (3.4 g, 11 mol) is slowly added under argon to a solution of $1H,1H$-pentadecafluoroctan-1-ol (4 g, 10 mmol) and $Et_{3}N$ (1.55 mL, 11 mmol) in $Et_{2}O$ (20 mL). After stirring for 24 h at room temperature, the solution is treated with $H_{2}O$ (10 mL) and $Et_{2}O$ (20 mL). Evaporation of the solvent affords butaflate $3$ as a solid (6.2 g, 95%).

Step B. Tris(4-hydroxyphenyl)phosphane Oxide ($2$) A solution of $BBBr_{3}$ (1 M in $CH_{2}Cl_{2}$, 67 mmol, 67 mL) is slowly added at −10 °C to a solution of the methoxyphosphane oxide $1$ (4.9 g, 13.3 mmol) in $CH_{2}Cl_{2}$ (50 mL) under argon. After stirring for 20 h at room temperature, the solution is slowly poured into cold water (200 mL). After partial evaporation of the solvent, the aqueous phase is filtered and extracted with ethyl acetate ($3 \times 120$ mL). The combined organic phases are washed with a saturated aqueous solution of $NaCl$ ($2 \times 80$ mL) and
dried over Na$_2$SO$_4$. Evaporation of the solvent gives a solid which is recrystallized from ethyl acetate to give hydroxyphosphane oxide 2 (3.69 g, 85%).

**Step C. Tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane Oxide (4)** A mixture of hydroxyphosphane oxide 2 (653 mg, 2 mmol), 1H,1H-pentadecafluorooctyl nonafluorobutanesulfonate 3 (5.45 g, 8 mmol), and Cs$_2$CO$_3$ (1.63 g, 10 mmol) in DMF (25 mL) is stirred at 80 °C under N$_2$ for 18 h. The suspension is then cooled to 25 °C and poured into H$_2$O (30 mL). The aqueous solution is extracted with Et$_2$O (3 x 50 mL), the combined organic phases are washed with a saturated aqueous solution of NaCl (2 x 50 mL) and dried over Na$_2$SO$_4$. Evaporation of the solvent gives a residue which is purified by column chromatography over silica eluting with Et$_2$O/CH$_2$Cl$_2$ (1:1) to give fluorous phosphane oxide 3 as a white solid (1.91 g, 65%): $R_f = 0.55$ (diethyl ether/CH$_2$Cl$_2$ 1:1); mp 103–104 °C; $^1$H NMR (CDCl$_3$) δ 4.51 (t, $^3$J$_{HF}$ = 12 Hz, 6 H, CH$_2$), 7.03 (dd, $^3$J$_{HH}$ = 8 Hz, 4 $^4$J$_{HP}$ = 1.8 Hz, 6 H, H$_{arom}$), 7.62 (dd, $^3$J$_{HH}$ = 8.8, $^3$J$_{HF}$ = 11.4 Hz, 6 H, H$_{arom}$); $^{13}$C NMR (CDCl$_3$, partial) δ 65.0 (t, $^2$J$_{CF}$ = 27 Hz, CH$_2$), 114.9 (d, $^3$J$_{CP}$ = 13.6 Hz, C$_{arom}$), 127.1 (d, $^3$J$_{CP}$ = 110.2 Hz, C$_{arom}$), 134.1 (d, $^2$J$_{CP}$ = 11.6 Hz, C$_{arom}$), 160.1 (s, C$_{arom}$); $^{19}$F NMR (CDCl$_3$) δ −126.7 (s, 6 F), −123.6 (s, 6 F), −123.3 (s, 6 F), −122.5 (s, 12 F), −119.9 (s, 6 F), −81.3 (t, $^3$J$_{FF}$ = 9.5 Hz, 9 F); $^{31}$P NMR (CDCl$_3$) δ 27.9 (s).

**Step D. Tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane (5)** HSiCl$_3$ (832 µL, 8.24 mmol) is cautiously added under argon at room temperature to a mixture of phosphane oxide 4 (3.1 g, 2.1 mmol), and freshly distilled triethylamine (1.24 mL, 8.9 mmol) in dry toluene (15 mL). The mixture is warmed to 130 °C and stirred for 5 h. After being cooled to 5 °C, the solution is treated with precooled deaerated 2 N NaOH (50 mL). The aqueous layer is extracted with deaerated Et$_2$O (3 x 50 mL), and the combined organic layers are washed with deaerated water (2 x 40 mL) and then dried over Na$_2$SO$_4$. Evaporation of the solvent gives the corresponding fluorous phosphane 5 as a white solid (2.72 g, 89%), mp 82–83 °C: $^1$H NMR (CDCl$_3$) δ 4.46 (t, $^3$J$_{HF}$ = 12.9 Hz, 6 H, CH$_2$), 6.93 (dd, $^3$J$_{HH}$ = 8.8, $^4$J$_{HP}$ = 0.7 Hz, 6 H, H$_{arom}$), 7.25 (dd, $^3$J$_{HH}$ = 8.8, $^3$J$_{HF}$ = 7.0 Hz, 6 H, H$_{arom}$); $^{19}$F NMR (CDCl$_3$) δ −126.6 (s, 6 F), −123.6 (s, 6 F), −123.2 (s, 6 F), −122.5 (s, 12 F), −119.9 (s, 6 F), −81.3 (t, $^3$J$_{FF}$ = 10 Hz, 9 F); $^{31}$P NMR (CDCl$_3$) δ −9.5 (s).

**Discussion**

Organometallic complexes containing phosphanes are now commonly used as homogeneous catalysts in organic transformations. One of the major problems is the separation of the organometallic catalyst from the product(s) of the reaction. Although chromatography can be used as a standard purification method, another approach is the use of a non-miscible two-phase system of organic solvent/fluorous solvent, the organometallic complex being immobilized in the fluorous phase by association with fluorous phosphanes.

Several fluorous phosphanes have recently been prepared [1–5]. In our case [6], tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane is conveniently obtained from commercially available tris[4-methoxyphenyl]phosphane. The fluorous organometallic catalyst can be very easily separated by simple decantation and the fluorous phase eventually recycled. This
fluorous phosphane has been successfully used in hydrogenation [7], alkylation reactions [8], as well as non-catalyzed reactions such as the Wittig reaction [9]

References


11.23
Bis(1H,1H,2H,2H-perfluoroctyl) Tin Oxide and 1,3-Dichloro-tetra(1H,1H,2H,2H-perfluoroctyl)distannoxane. Synthesis and Applications of Fluorous Distannoxanes

Junzo Otera

Reactions 11.23-1 [1]

\[
\begin{align*}
\text{Step A} & \\
\text{Step B} & \\
\text{Step C} & \\
\text{Step D} & \\
\end{align*}
\]

Reagents

Ph\(_2\)SnCl\(_2\) and \(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\)I (R\(_I\)) are commercially available.
Experimental Procedures

**Step A. Bis(1H,1H,2H,2H-perfluorooctyl)diphenyltin (1)** A flask containing Mg turnings (1.27 g, 52.5 mmol) is heated by flame in vacuo. Dry Et₂O (30 mL) is added and the mixture is stirred at ambient temperature for 1 h to activate the surface of the Mg turnings. An Et₂O solution (30 mL) of 1H,1H,2H,2H-perfluorooctyl iodide (Rf₁) (21.33 g, 45 mmol) is slowly added at 0°C. The mixture is stirred at ambient temperature for 3 h, and Et₂O (20 mL) is added. A THF solution (30 mL) of Ph₂SnCl₂ (5.15 g, 15 mmol) is slowly added and the mixture is stirred at ambient temperature for 24 h. Water is added and the mixture is filtered through a Celite pad and the pad is washed with hexane. The combined filtrate is extracted with ethyl acetate. The organic layer is washed with water and brine. After drying (MgSO₄) and evaporation, the residue is subjected to column chromatography on silica gel (hexane) to give pure Rf₂SnPh₂ (1) (13.3 g, 92%) [2].

**Step B. Bis(1H,1H,2H,2H-perfluorooctyl)tin Dichloride (2)** To a CCl₄ solution (15 mL) containing 1 (4.83 g, 5 mmol) and dry MeOH (1.0 mL, 25 mmol) is added TMSCl (1.45 mL, 11.5 mmol) at 0°C and the solution is stirred at ambient temperature overnight. The reaction mixture is evaporated and the residue is subjected to column chromatography on silica gel (hexane) to give pure Rf₂SnCl₂ (2) (4.15 g, 94%) as a white solid [3]: mp 90–92°C; ¹H NMR δ 1.96 (t, 4 H, 2J_SnH = 64 Hz), 2.62 (t, 4 H, J_FH = 16 Hz, 3J_SnH = 111 Hz); ¹¹⁹Sn NMR δ −42.7; ¹⁹F NMR δ −82.00 (m, 6 F), −116.71 (m, 4 F), −123.10 (m, 4 F), −124.10 (m, 4 F), −124.56 (m, 4 F), −127.39 (m, 4 F).

**Step C. Bis(1H,1H,2H,2H-perfluorooctyl)tin Oxide (3)** To a THF solution (70 mL) of 2 (8.82 g, 10 mmol) is added 4 N NaOH solution (7.5 mL, 30 mmol) and the solution is stirred at ambient temperature for 6 h. The solution is evaporated and acetone (20 mL) is added to the residue. Heating with a heatgun results in homogeneous solution. Upon addition of water (40 mL), a viscous oil separates on the bottom of the flask. After decantation of the water, the residue is pumped in vacuo. The resulting oil is washed with water and pumped again. These operations are repeated until the pH of the water becomes 7 [4]. Then, the oil is washed with CH₂Cl₂ and pumped to give a white solid of (Rf₂SnO)n (3) (7.2 g, 88%) [2]. In case the oil does not solidify however, the oil is dissolved in a small amount of FC-72 and evaporation of this solution under reduced pressure affords a solid: ¹H NMR (75 MHz, acetone-d₆) δ 10.0–14.0 (br, 2 C), 25.0–27.0 (br, 2 C); 104.0–123.0 (12 C); ¹¹⁹Sn NMR (112 MHz, acetone-d₆) δ −168–−233 (complex pattern).

**Step D. 1,3-Dichloro-tetra(1H,1H,2H,2H-perfluorooctyl) distannoxane (4)** An acetone solution (25 mL) of 2 (8.83 g, 10 mmol) and 3 (8.29 g, 10 mmol) is heated under reflux for 8 h. The solution is evaporated and the residue was recrystallized from 2:1 FC-72/hexane to give (ClRf₂SnOSnRf₂Cl)₂ (4) (16.2 g, 95%): mp 71–72°C; ¹H NMR (300 MHz, FC-72
with CDCl₃ as external lock) δ 1.87–2.35 (m, 16 H), 2.65–3.05 (m, 16 H); ¹³C NMR (75 MHz, acetone-d₆) δ 13.7 (4 C), 15.2 (4 C), 25.8 (²J_{CF} = 23.2 Hz, 4 C), 26.0 (²J_{CF} = 23.2 Hz, 4 C), 106.3–122.3 (complex pattern, 48 C); ¹¹⁹Sn NMR (112 MHz, acetone-d₆) δ -178.3, -202.5.

Discussion

Distannoxane 4 can also be prepared by treating 3 with aqueous HCl solution at ambient temperature [5], but this procedure suffers from some problems arising from the difficulty in adjusting the amount of HCl. Thus, occasionally the yield of 3 is not satisfactory. However, this route must be invoked for synthesis of the 1,3-dibromo derivative, (Br₂SnOSnBr₂)₂ (5) because treatment of R₂SnBr₂ with 3 does not give rise to a satisfactory outcome [5]. Reaction of 4 with AgSCN results in replacement of non-bridging chlorines exclusively to give (ClR₂SnOSnR₂NCS)₂ (6).

Reaction 11.23-2

\[
\begin{align*}
4/n (R_2SnO)_n + 4HBr & \rightarrow (BrR_2SnOSnR_2Br)_2 \\
(ClR_2SnOSnR_2Cl)_2 + AgSCN & \rightarrow (ClR_2SnOSnR_2NCS)_2
\end{align*}
\]

These distannoxanes catalyze (trans)esterification under fluorous biphasic conditions [6–8]. Of particular interest is attainment of the 100% yield of the desired esters even by use of equimolar amounts of reactants. Apparently, the equilibrium is completely shifted to the product side by virtue of the biphasic reaction conditions.

References

4. The neutrality of 3 is crucial for the next reaction. When the washing is not sufficient, no smooth reaction occurs between 2 and 3.
Gb3 Oligosaccharide Derivative. Fluorous Synthesis of an Oligosaccharide

Tsuyoshi Miura and Toshiyuki Inazu

Reaction 11.24-1

Reagents

Compounds 1 [1] and 2 [2] can be prepared according to the literature procedure. EtOC₄F₉ is a commercially available fluorocarbon solvent (Novec HFE-7200™) from 3M Tokyo.

Experimental Procedure

A molecular sieve (4 Å) powder (2 g) is added to a solution of compound 1 (510 mg, 0.11 mmol) and compound 2 (530 mg, 0.77 mmol) in dry ether (12 mL)/EtOC₄F₉ (12 mL) under an argon atmosphere. After stirring for 3 h at room temperature, TMS-OTf (60 µL, 0.33 mmol) is slowly added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, saturated NaHCO₃ (5 mL) is added. The reaction mixture is filtered. The filtrate is added to water, and extracted three times with AcOEt. The AcOEt layers are washed with brine, dried over anhydrous Na₂SO₄, and evaporated. Methanol is added to the residue, and this is extracted three times with FC-72. The FC-72 layers are evaporated to give compound 3 (540 mg, 95%) as colorless oil, Rₘ = 0.6 (hexane/AcOEt = 2:1): 1H-NMR (400 MHz, CDCl₃) δ 1.68–2.07 (16 H, m), 2.35–2.69 (24 H, m), 3.20–3.90 (21 H, m), 4.08 (5 H, m), 4.28 (4 H, m), 4.40 (1 H, m), 4.52 (4 H, m), 4.70–4.98 (10 H, m), 5.17 (4 H, m), 5.80 (1 H, m), 7.22 (18 H, m).
Discussion

The oligosaccharides on cell surfaces play important roles in biological processes such as cell–cell interaction, cell adhesion, and immunogenic recognition; however, the synthesis of an oligosaccharide is not easy. Although the solid phase synthesis of oligosaccharides has been actively studied, the usual solid phase method suffers from some serious disadvantages, such as the difficulty of large scale synthesis, reduced reactivity, and the inability to monitor the reaction by TLC, NMR, and MS. The use of the Bfp (bisfluorous chain type propanoyl) group as a fluorous protective group made possible the rapid synthesis of the Gb3 oligosaccharide derivative by a fluorous/organic extraction purification without column chromatography [1]. Because synthetic intermediates containing the Bfp group can be monitored by TLC, NMR, and MS, the reaction conditions are optimized rapidly. The fluorous intermediates can also be purified by silica gel column chromatography if necessary. Therefore, fluorous oligosaccharide synthesis using the Bfp group is an excellent strategic alternative to solid phase oligosaccharide synthesis, and removes some of the disadvantages of the solid phase method. Recently, oligosaccharide synthesis on the fluorous support Hfb (hexakisfluorous chain type butanoyl group) has also been developed [3].

References


11.25


*Mamoru Mizuno, Kohtaro Goto, Tsuyoshi Miura, and Toshiyuki Inazu*

**Reaction 11.25-1**

![Reaction Diagram](image-url)
**Step B. Coupling**

\[
\text{PyBOP, DIEA} \quad \text{Fmoc-Pro-OH} \quad \text{CH}_2\text{Cl}_2-\text{EtOC}_4\text{F}_9 \quad \text{rt, 1 h} \quad \text{Fmoc-Pro-N-Linker-Hfb} \quad \text{Repeat} \quad \text{Deprotection (A)} \quad \text{and Coupling (B)} \quad \text{pGlu-His(Trt)-Pro-N-Linker-Hfb} \quad 3 \quad 4
\]

**Step C**

\[\text{TFA, H}_2\text{O, 1,4-butanedithiol} \quad \text{rt, 2 h} \quad \text{pGlu-His-Pro-NH}_2 \quad \text{TRH, 5} \quad 62\% \text{ from 1} \]

---

**Reagents**

Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) is commercially available from Novabiochem. EtOC\textsubscript{4}F\textsubscript{9} is a commercially available fluorocarbon solvent (Novec HFE-7200\textsuperscript{TM}) from 3 M Tokyo.

**Experimental Procedures**

**Step A. Deprotection of Fmoc Group** To a solution of Fmoc protected fluorous support 1 [2] (575 mg, 0.15 mmol) in FC-72 (10 mL) is added 10\% piperidine in DMF (10 mL). After stirring for 30 min at room temperature, MeOH (30 mL) is added and the mixture is extracted with FC-72 (3×30 mL). The combined FC-72 layer is washed with 5\% citric acid and saturated NaHCO\textsubscript{3}, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated to provide the compound 2.

**Step B. Coupling Reaction** Fmoc-Pro-OH (202 mg, 0.60 mmol) and 2 are dissolved in a mixed solution of CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and EtOC\textsubscript{4}F\textsubscript{9} (5 mL). PyBOP (344 mg, 0.66 mmol) and DIEA (0.16 mL, 0.90 mmol) are added, and the mixture is stirred at room temperature for 1 h. The reaction mixture is concentrated to approximately 1/3 volume, and MeOH (30 mL) is added. The mixture is extracted with FC-72 (3×30 mL), and concentrated to give compound 3 in 97\% (two steps: deprotection and coupling). Repeating the coupling reaction and the deprotection for Fmoc-His(Trt)-OH and pGlu-OH, the peptide with a fluorous support is obtained 4 (518 mg, 83\% over six steps).
Step C. Deprotection and Tag Removal The peptide derivative 4 is treated with TFA (19 mL), H₂O (0.5 mL), and 2.5% 1,4-butanedithiol (0.5 mL) at room temperature for 2 h. After concentration, FC-72 (50 mL), H₂O (50 mL), and toluene (50 mL) are added to the residue, and the layers are separated. The water layer is washed with EtOC₄F₉, and lyophilized to give the crude peptide (65 mg). This is purified by RP-HPLC [3] [0.1% TFA/H₂O–0.1% TFA/MeCN 98:2–60:40 (40 min)] to yield TRH [4] (5) (53 mg, 76 μmol, 62% from 1) after lyophilization. MALDI-TOF MS calc. for C₁₆H₂₃N₆O₄ [M + H]⁺: 363.39. Found [M + H]⁺: 363.41.

Discussion

Normally peptides are easily prepared by solid phase synthesis, which allows for a very simple product isolation by filtration. However, the solid phase method suffers from some serious disadvantages, such as reduced reactivity and the inability to monitor the reaction progress by TLC, NMR, or mass spectrometry. Similarly to solid phase synthesis, fluorous synthesis does not resort to chromatography. Since a fluorous compound is soluble not only in fluorous solvents but also in common organic solvents, the fluorous reaction can be carried out in such organic solvents [5]. Therefore, the strategy of “fluorous synthesis” is designed to combine the advantages of solid phase synthesis with those of traditional organic synthesis in the liquid phase. Thus fluorous synthesis is very useful in peptide synthesis, and has become an excellent strategic alternative to solid phase synthesis.

References

2 (a) M. Mizuno, T. Miura, K. Goto, D. Hosaka, T. Inazu, Peptide Science 2002: Proceedings of the 39th Japanese Peptide Symposium, T. Yamada, Ed.; The Japanese Peptide Society (2003), pp. 147–150. (b) M. Mizuno, K. Goto, T. Miura, D. Hosaka, T. Inazu, Chem. Commun. 2003, 972. Compound 1: amorphous solid, ¹H NMR (600 MHz, CDCl₃), δ = 1.81–1.90 (m, 10 H), 2.06–2.17 (m, 15 H), 2.32–2.78 (m, 17 H), 3.37–3.44 (m, 20 H), 3.57–3.67 (m, 8 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.23 (br, 1 H), 4.41 (d, 1 H, 6.9 Hz), 4.46 (s, 2 H), 5.91 (m, 1 H), 6.03 (m, 1 H), 6.47 (m, 2 H), 6.84 (m, 2 H), 7.09 (m, 1 H), 7.16 (m, 3 H), 7.30 (m, 2 H), 7.39 (m, 3 H), 7.58 (d, 2 H, J = 6.9 Hz), 7.76 (d, 2 H, J = 6.9 Hz). MALDI-TOF MS: calc. for C₁₂₁H₉₈F₁₁₀N₁₀NaO₁₄ [M + Na]⁺: 3876.96. Found [M + Na]⁺: 3875.05.
3 RP-HPLC was performed on Inertsil ODS-3 (20 × 250 mm) (GL Sciences Inc., Tokyo). Flow rate, 10.0 mL min⁻¹.
4 The yield of 5 was calculated by amino acid analysis. Compound 5: amino acid analysis of Glu 1.02 (1), Pro 1.00 (1), His 0.98 (1).
11.26 Perfluoroctylpropyl Alcohol. Radical Addition of Perfluoroctyl Iodide to Triallyl Borate, Followed by Reductive Dehalogenation and Aqueous Deprotection

József Rábai, István Kövesi, and Ana-Maria Bonto

Reaction 11.26-1

Reagents

Perfluoroctyl iodide 1 [507-63-1], tributyltin hydride [668-73-3], silica gel 60, azobisisobutyronitrile (AIBN) [78-67-1] are commercially available, while triallyl borate [1693-71-6] can be prepared according to the literature procedure [1].

Experimental Procedure

Step A. tris(3-Perfluoroctyl-2-iodopropyl)borate (2) A 500 mL three-necked flask with a teflon-coated magnetic stirrer bar is equipped with a pressure equalizing dropping funnel, a thermometer and a reflux condenser connected to an argon bypass. The assembled glassware is carefully dried in a flow of argon using a hot air gun and allowed to cool to room temperature. It is then charged with isooctane (125 mL), 1 (100 g, 183 mmol) and triallyl borate (11.1 g, 61 mmol) [1]. Powdered AIBN (0.25 g) is added and the mixture is heated to 80 °C for 3.5 h. The addition of AIBN is repeated three times (0.25 g, with further heating at 80 °C for 3 h) for complete conversion of 1 to 2. The reaction mixture solidifies at room temperature.

Step B. 3-Perfluoroctyl-2-iodo-1-propanol (3) Borate 2 is refluxed in water (100 mL) for 15 min. Evaporation of the separated organic phase and recrystallization of the crude product from benzene (1.3 mL g⁻¹) gives pale yellow crystals, mp 93 °C, lit. mp 93–94 °C [4]: ¹H NMR (250 MHz, CDCl₃) δ 4.11–4.49 (m, 1 H, C₃H), 3.75–3.89 (m, 2 H, CH₂OH), 2.65–3.14 (m, 2 H, C₈F₁₇CH₂), 2.08 (t, 1 H, OH).
Step C. tris(3-Perfluorooctylpropyl)borate (4) AIBN (0.25 g) is added in one portion to the above melted borate and the mixture is stirred at 70–73 °C, with dropwise addition of tributyltin hydride (53 g, 182 mmol) over 2 h. The addition of AIBN and the heating process is repeated three times (0.25 g at 80 °C for 3 h) to complete the reduction.

Step D. 3-Perfluorooctylpropyl alcohol (5) After addition of water (100 mL) the mixture is stirred and heated to reflux for 15 min using an 120 °C oil bath. This results in the complete hydrolysis of ester 4. The mixture is cooled in an ice–water bath and the resulting crystalline product is isolated by suction filtration on a medium porosity glass funnel. The filter cake is pressed well and washed with ice-cold isooctane (2/50 mL) and dried on filter paper sheets in a stream of air under the hood. Then the crude product (70 g, GC: 88%) is recrystallized from isooctane (500 mL) to afford 57.0 g (65% from C₈F₁₇I, GC: 98%) of alcohol 5 as white crystals with characteristic “tin” odour, mp 40–41 °C; selected spectral data [2]: 1H NMR (300 MHz, CD₃OD) δ 3.64 (t, 2 H, 3JHH = 6.0 Hz, H₂-1), 2.15–2.37 (m, 2 H, H₂-3), 1.76–1.86 (m, 2 H, H₂-2); 19F NMR −81.3 (CF₃), −114.2, −121.7, −122.5, −123.3, −126.1; FT-IR (CCl₄) ν (cm⁻¹) 3640.3 (OH). HRMS (m/z) calc. for C₁₁H₇F₁₇O, M⁺ = 478.0225. Found M⁺ = 478.0224. Last traces of tin can be removed from this product (1 g, 98%) by boiling it with a mixture of 50% aqueous NaOH (2 mL) and ether (20 mL) for 5 h, then filtering the separated and dried (Na₂SO₄) ether phase over SiO₂ (2 g).

Discussion

The addition of perfluoroalkyl iodides to alkenes is a valuable method for the introduction of linear perfluoroalkyl groups into organic molecules [1]. The best procedures for the synthesis of perfluoroalkylated iodohydrins rely on the use of protected unsaturated alcohols [2]. These radical reactions can be initiated by different means, including but not restricted to azobisisobutyronitrile, organic peroxides and transition metals, the synthetic utility of which has been commented on [3]. Furthermore, perfluoroalkyl substituted iodohydrins are versatile synthetic intermediates, for example they can be used for the synthesis of fluorous oxiranes [4, 5]. Although tributyltin hydride used above allows the selective reduction of carbon–iodine bonds, the toxicity of the organotin compounds involved calls for appropriate measures to be taken during procedures for the reaction, the workup and the disposal of side products [6].

References

Perfluorooctylpropyl Amine. Use of Perfluorooctylpropyl Iodide for a Gabriel Synthesis of a Fluorophilic Amine

József Rábai, Abudurexiti Abulikemu, and Dénes Szabó

Reaction 11.27-1

Reagents

Perfluorooctylpropyl alcohol 1 [1651-41-8], perfluorooctylpropyl iodide 2 [200112-75-0] and the title perfluorooctylpropyl amine 4 [139175-50-1] are commercially available from Fluorous Technologies, Inc. (www.fluorous.com) or can be prepared according to literature procedures [1–3].

Experimental Procedures

Step A. Perfluorooctylpropyl Iodide (2) Under an N₂ atmosphere, P₂O₅ (115 g, 0.81 mol) is added first at room temperature to a stirred mixture of 85% H₃PO₄ (240 mL, 3.33 mol) and sulfolane (40 mL), followed by powdered potassium iodide (47 g, 0.283 mol) and 1 (50.2 g, 0.105 mol) at 0 °C. The mixture is heated and stirred at 120 °C for 6 h then cooled to room temperature and extracted with water (300 mL) and ether (4 × 100 mL). The combined ether phases are washed consecutively with 5% NaHSO₃ solution (2 × 100 mL) and water (2 × 50 mL) and dried (Na₂SO₄). Distillation yields 51.5 g (83%) of the crude product of bp 95 °C/0.1 mmHg. It is a mixture of 94% 2 and 6% 1 (GC), and difficult to separate by distillation. The unreacted 1 can be scavanged with P₂O₅/SiO₂. Thus, a solution of the crude iodide (50 g) in ether (80 mL) is mixed with SicaPent® (8 g, Merck) and kept at room temperature for 2
days. It is filtered and washed with ether and the solvent is removed by atmospheric distillation. The residue is distilled in vacuo from Raschig rings to yield the pure iodide as a colorless liquid, 42 g (GC: 99.5%), bp 111°C/14 mmHg, or shining crystals at room temperature, mp 33–34°C. 1H NMR (250 MHz, CDCl3) δ 3.24 (t, 2 H, CH2I), 2.08–2.33 (2 m, 4 H, C8F17CH2CH2); 19F NMR δ −81.9 (t, 3 F), −114.5 (2 F), −122.7 (6 F), −123.5 (2 F), −124.2 (2 F), −127.0 (2 F); 13C NMR δ 32.30 (t, C8F17C); 24.66 (t, CH2CH2I); 3.65 (s, CH2CH2I).

Step B. N-(3-Perfluorooctylpropyl)phthalimide (3) To a stirred suspension of potassium phthalimide (11.8 g, 64.0 mmol) in DMF (100 mL), 2 (18.8 g, 32.0 mmol) is added and the mixture heated at 100°C for 7 h. The mixture is poured into 0.5 n Na2CO3 (400 mL), extracted with CH2Cl2 (3 × 100 mL) and the combined organic phases are filtered through Celite, washed with water (3 × 200 mL) and dried (Na2SO4). After evaporation of the solvent, the residue is recrystallized from methanol (140 mL) to yield 15.4 g (80%) of pure 3 as pale yellow needles, mp 93.0–93.8°C (GC: 99.4%): 1H NMR (500 MHz, CDCl3) δ 7.72–7.84 (m, 4 H, ArH's), 3.77 (t, 2 H, J = 7.0 Hz, N-C2H5), 2.02 (qi, 2 H, J = 7.0 Hz, NCH2C8H17), 2.16 (m, 2 H, CH2C8F17). HRMS (m/z) calc. for C19H10F17NO2, [M+H]+ = 607.0440. Found [M+H]+ = 607.0449.

Step C. Perfluorooctylpropyl Amine (4) Hydrazine hydrate (98%, 1.20 mL, 24 mmol) is added to a stirred solution of 3 (13.4 g, 22 mmol) in methanol (50 mL) and the mixture is refluxed for 1 h. This results in the formation of a voluminous crystalline precipitate. After addition of 6 N hydrochloric acid (50 mL), the mixture is refluxed for 1 h and filtered at room temperature. Then the filter cake is stirred with a mixture of 1 N NaOH (100 mL) and ether (100 mL) for 3 h to afford a clear solution of phthalylhydrazide in the water phase, while 4 is in the ether layer. The phases are separated and the water phase washed with more ether (2 × 50 mL). The ether solution is dried (Na2SO4) and distilled to yield 8.1 g (77%) of pure amine 4 as a colorless liquid (GC: 98+%), bp 140–141°C/100 mmHg: 1H NMR (500 MHz, CDCl3) δ 1.19 (s, br, 2 H, NH2), 1.71–1.78 (m, 2 H, CH2CH2NH2), 2.09–2.21 (m, 2 H, C8F17CH2); 2.80 (t, 2 H, CH2CH2NH2); 19F NMR δ −81.3 (F-11), −114.6 (F-4), −122.1 (F-6), −122.4 (F-7 and F-8), −123.2 (F-9), −123.9 (F-5), −126.6 (F-10). HRMS (m/z) calc. for C19H18F17N, [M+H]+ = 476.0307. Found [M+H]+ = 476.0302. This is a fluorophilic amine, since its fluorophilicity is larger than zero: f = ln PFBs = 0.79 [3b].

Discussion

Perfluorooctylpropyl amine is a nucleophilic scavanger, which has been prepared by multiple step syntheses using perfluorooctylpropyl alcohol as a precursor [3]. In the former procedure this alcohol is first oxidized to the corresponding aldehyde, which is then used for N-monooalkylation of benzylamine and the obtained intermediate on hydrogenolysis affords the title amine in excellent yield [3a]. The latter procedure relies on the conversion of this alcohol into the corresponding alkyl iodide, which on reaction with excess liquid ammonia/THF under pressure, yields a separable mixture of the primary amine and the corresponding secondary amine [2, 3b]. However, the substitution of potassium phthalimide for ammonia...
results in an improved procedure, which increases the yield since only primary amine is formed, and eliminates the hazards associated with the use of pressurized ammonia solutions [3c].

References


11.28 Cyclohexyl Acetate. The Acylation Reaction with a Fluorous Lanthanide Catalyst in Supercritical Carbon Dioxide with or without a Fluorous Solvent

Koichi Mikami, Hiroshi Matsuzawa, Joji Nishikido, and Mayumi Kamishima

Reaction 11.28-1

\[
\text{Step A} \quad 1 \text{ (1 mol%)} \quad \text{scCO}_2, 20 \text{ MPa} \\
\begin{array}{c}
\text{OH} \\
\text{C}_8\text{F}_{18}\text{, 15 min} \\
\text{40 °C, 99%}
\end{array}
\]

\[
\begin{array}{ccc}
\text{OH} & + & \text{Ac}_2\text{O} \\
\text{Step B} & 1 \text{ (1 mol%)} & \text{scCO}_2, 10 \text{ MPa} \\
\text{1} = \text{Yb[N(SO}_2\text{C}_8\text{F}_{17}]_3}
\end{array}
\]

\[
\begin{array}{ccc}
\text{OAc} \\
10 \text{ min} \\
\text{40 °C, 98%}
\end{array}
\]

Reagents

Perfluorooctane is commercially available (Aldrich). Ytterbium(III) bis(perfluoroocatanesulfonylamide) 1 is prepared by the published procedure [1].
Experimental Procedures

Step A. Acylation of Cyclohexanol with Acetic Anhydride by Using scCO\(_2\) and Fluorous Solvent

A 20 mL stainless steel autoclave equipped with magnetic stirring bar is charged with cyclohexanol (0.20 g, 2 mmol), acetic anhydride (0.22 g, 2.2 mmol), and the ytterbium(III) complex \(1\) (1 mol\% based on cyclohexanol) as a Lewis acid catalyst in perfluorooctane (5 mL). Carbon dioxide is added and a pressure of 20 MPa is applied to the autoclave. The reaction mixture is stirred for 15 min at 40 °C. After cooling below 0 °C, the pressure in the autoclave is slowly released. The autoclave is opened at room temperature, and dichloroethane (5 mL) is added. After stirring for 15 min and standing for 5 min, the mixture separates into an upper organic phase and a lower fluorous phase. Cyclohexyl acetate is obtained from the dichloroethane layer after evaporation under reduced pressure and silica gel chromatography (0.280 g, 98% isolated yield). After removing the dichloroethane layer, fresh cyclohexanol (0.20 g, 2 mmol) and acetic anhydride (0.22 g, 2.2 mmol) are added. Carbon is added and the reaction and separation cycle is repeated with similar results. The cycle is repeated a further three times, and the yields of cyclohexyl acetate are 99%, 99% and 99%, respectively.

Step B. Acylation of Cyclohexanol with Acetic Anhydride Using scCO\(_2\) without Fluorous Solvent

A 20 mL stainless steel autoclave equipped with magnetic stirring bar is charged with cyclohexanol (0.20 g, 2 mmol), acetic anhydride (0.22 g, 2.2 mmol), and the ytterbium(III) complex \(1\) (1 mol\% based on cyclohexanol) as a Lewis acid catalyst. After adding carbon dioxide and applying a pressure of 10 MPa to the autoclave, the reaction mixture is stirred for 10 min at 40 °C. After cooling to −20 °C, liquid carbon dioxide is successively introduced at a flow rate of 1 mL min\(^{-1}\) for 1 h under 6 MPa. The product is extracted with dichloroethane (5 mL). Cyclohexyl acetate is obtained from the dichloroethane layer after evaporation under reduced pressure and silica gel chromatography (0.279 g, 98% isolated yield). After successive introduction of liquid carbon dioxide, the pressure in the autoclave is released to give the catalyst, to which cyclohexanol (0.20 g, 2 mmol) and acetic anhydride (0.22 g, 2.2 mmol) were added for a second and a third cycle with similar results (98% yields).

Discussion

We have developed the strong Lewis acids lanthanide(III) tris(perfluorooctanesulfonyl)methide and bis(perfluorooctanesulfonyl)amide in order to decrease the amount of a Lewis acid complex used in a reaction and to enable recycling to be utilized. Thus, numerous and sufficiently long (perfluoroctyl, C\(_8\)F\(_{17}\)) perfluoroalkyl ligands [2] can be attached directly without any hydrocarbon spacers to increase the Lewis acidity. These lanthanide catalysts can be employed for fluorous biphasic catalysis (FBC) to be solubilized in fluorous solvent [3]. FBC has the features of an environmentally benign reaction system, having the advantage that fluorous catalysts are immobilized in the fluorous solvent and recycled. However, the FBC method is not a completely green reaction system because organic solvents such as 1,2-dichloroethane and toluene are present. To solve this drawback, we investigated the use of supercritical carbon dioxide (scCO\(_2\)) in place of an organic solvent. The replacement of conventional liquid solvents by supercritical fluids as the reaction media for homogeneous
catalysis provides the opportunity to control a reaction in terms of the reactivity and selectivity, because of high gas miscibilities, greater diffusivities, clustering effects, and tunable solvent power by changing their densities along with the pressure [4]. Supercritical fluids have been employed as an environmentally benign reaction media in late transition metal catalysis for hydroformylation [5] and hydrogenation [6]. By contrast, the design and immobilization of strong Lewis acid catalysts have remained a challenging problem in this unorthodox non-polar media [7]. Since fluororous compounds are soluble in scCO$_2$ [5a, 5f, 6c, 6e, 7a, 7e], a homogeneous phase with a fluororous solvent immobilizes fluororous lanthanide catalysts. After the reaction, the fluororous solvent remains in the reaction vessel, the liquid carbon dioxide being released with the product. In addition, we tried to reuse the lanthanide catalysts by changing from scCO$_2$ to liquid carbon dioxide. Lanthanide catalysts are insoluble in liquid carbon dioxide even in the presence of the reaction substrate or product. Our procedure features the completely recyclable use of lanthanide(III) tris(perfluorooctanesulfonyl)methide and bis(perfluorooctanesulfonyl)amide complexes in scCO$_2$ with or without fluororous solvent.

References

2 Koppel and Taft et al. have reported the gas phase acidities of a variety of super acids: bis(trifluoromethanesulfonyl)amine is stronger than trifluoromethanesulfonic acid by $\Delta G = 7.7$ kcal mol$^{-1}$ and tris(trifluoromethanesulfonylmethyl)ane is stronger than bis(trifluoromethanesulfonic)amine by $\Delta G = 2.8$ kcal mol$^{-1}$. They have also reported that bis(perfluorobutanesulfonate)amine is stronger than bis(trifluoromethanesulfonic)amine by $\Delta G = 7.7$ kcal mol$^{-1}$. J. Am. Chem. Soc. 1994, 116, 3047.
11.29

p-Methoxyacetophenone. The Friedel-Crafts Acylation with a Fluorous Lanthanide Catalyst

Koichi Mikami, Hiroshi Matsuzawa, and Joji Nishikido

Reaction 11.29-1

\[
\begin{align*}
\text{Step A} & : \text{OMe} + \text{Ac}_2\text{O} \xrightarrow{\text{Sc} \left[ \text{C(SO}_2\text{C}_8\text{F}_{17}\text{)}_3\right]} \text{AcOMe} \\
& \quad \text{CF}_3\text{C}_6\text{F}_{11}/(\text{CH}_2\text{Cl}_2) \\
& \quad 70 \degree \text{C}, 6 \text{ h}, 87-93% \\
\text{Step B} & : \text{OMe} + \text{Ac}_2\text{O} \xrightarrow{\text{Yb} \left[ \text{N(SO}_2\text{C}_8\text{F}_{17}\text{)}_2\right]} \text{AcOMe} \\
& \quad \text{(CH}_2\text{Cl}_2) \\
& \quad 80 \degree \text{C}, 6 \text{ h}, 78%
\end{align*}
\]

Reagents

Perfluoromethylcyclohexane is commercially available (Aldrich). Scandium(III) tris(perfluorooctanesulfonyl)methide 1 and ytterbium(III) bis(perfluorooctanesulfonyl)amide 2 are made by literature procedures [1–3].

Experimental Procedures

Step A. The Friedel-Crafts Acylation of Anisole with Acetic Anhydride under Biphasic Conditions

Anisole (0.22 mL, 0.22 g, 2 mmol) and acetic anhydride (0.38 mL, 0.41 g, 4 mmol) are added to a mixture of perfluoromethylcyclohexane (6 mL) and 1,2-dichloroethane (6 mL). To the resultant mixture is added 10 mol% of scandium(III) complex 1 (0.89 g, 0.2 mmol). The solution is stirred at 70 °C for 6 h. After cooling to room temperature (20 °C), the mixture separates into an upper 1,2-dichloroethane phase and a lower...
perfluoromethylcyclohexane phase. Each phase is individually analyzed by GC. *p*-Methoxyacetophenone is obtained from the upper phase after evaporation under reduced pressure and silica gel chromatography (0.261 g, 87% isolated yield). To the lower phase containing the catalyst is again added 1,2-dichloroethane (6 mL), anisole (0.22 mL, 0.22 g, 2 mmol), and acetic anhydride (0.38 mL, 0.41 g, 4 mmol) following by stirring at 70 °C for 6 h. Two phases again separate on cooling, and each phase is analyzed by GC. The overall yield of *p*-methoxyacetophenone is 93%. Substantially the same procedure as mentioned above was repeated twice. The overall yields of *p*-methoxyacetophenone were 93% and 92%, respectively.

**Step B. The Friedel-Crafts Acylation Catalyzed by Ytterbium bis(Perfluorooctanesulfonyl)amide as a Solid**

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reaction</td>
<td>10 mol% of ytterbium(III) complex 2 (0.31 g, 0.1 mmol), anisole (0.11 mL, 0.11 g, 1 mmol) and acetic anhydride (0.19 mL, 0.20 g, 2 mmol) are added to 1,2-dichloroethane (5 mL). The solution is stirred at 80 °C for 6 h. The resultant mixture is allowed to stand at −20 °C to precipitate the ytterbium complex. After 30 min, the liquid phase of the resultant mixture is decanted and the residual solid catalyst is reused without isolation. The catalyst still remains in the vessel after the third reaction. Liquid phases are combined, and concentrated under reduced pressure. <em>p</em>-Methoxyacetophenone is purified by silica gel chromatography (0.354 g, 78% isolated yield).</td>
</tr>
</tbody>
</table>

**Discussion**

In fluororous biphasic catalysis (FBC), phospine or phosphite ligands with fluororous ponytails and hydrocarbon spacers have been developed to immobilize late transition metal catalysts for hydroformylation [4], hydrogenation [5], alkene epoxidation [6], and hydroboration [7] in non-polar fluororous media. However, the design and immobilization of strong Lewis acid catalysts have remained as challenging problems in this unorthodox non-polar media. Numerous (nine) and sufficiently long (perfluoroctyl, C₈F₁₇) fluororous ponytails can be attached directly without any hydrocarbon spacer to increase the Lewis acidity of lanthanide catalysts and for fluororous phase immobilization. The key to the success is the powerful electron-withdrawing effect of the perfluoroalkanesulfonyl)methide or -amide group [8] without any hydrocarbon spacers. The lanthanide tris(perfluoroalkanesulfonyl)methide and bis(perfluoroalkanesulfonyl)amide complexes are insoluble in organic solvents such as toluene and 1,2-dichloroethane at room temperature or below, even in the presence of reaction substrates. However, these complexes are soluble in organic solvents at high temperatures. We have thus reported the reuse of these fluororous lanthanide complexes as solids for the F–C acylation reaction without a fluororous solvent.

**References**

4. (a) I. T. Horváth, G. Kiss, R. A. Cook, J. E. Bond, P. A. Stevens, J. Rábai, E. J.
11.30 Tris(4-tridecafluorohexylphenyl)phosphine. Versatile Ligand Synthesized via Copper Catalyzed Cross Coupling with a Perfluoroalkyl Iodide, Lithiation and Condensation Reactions

Dave J. Adams, Eric G. Hope, Alison M. Stuart, and Andrew J. West

Reaction 11.30-1

\[
\begin{align*}
\text{Br} &\quad \text{C}_6\text{F}_{13}\text{I}, \text{Cu} \\
&\quad 2,2'-\text{bipyridine} \\
&\quad \text{DMSO, } \text{C}_6\text{H}_5\text{F} \\
&\quad 120 \text{ h, } 70 ^\circ \text{C} \\
&\quad \text{Br} &\quad \text{C}_6\text{F}_{13} \\
\end{align*}
\]

**Step A**

1) \(n\)-BuLi, ether
-78 °C, 6 h

2) 0.33 equiv PCl₃, ether
-78 °C to rt, 18 h

**Step B**

1) 0.33 equiv PCl₃, ether
-78 °C to rt, 18 h

Reagents

All starting reagents were purchased from Aldrich Chemical Company or Fluorochem. Perfluoro-n-hexyl iodide [355-43-1] was stored in a fridge upon receipt before use. Anhydrous diethyl ether was prepared by distillation under dinitrogen from sodium benzophenone ketyl and was freeze/pump/thaw degassed three times before use. Phosphorus trichloride was heated at reflux for 3 h and then distilled under dinitrogen before use.
Experimental Procedure

Step A. 4-(Tridecafluorohexyl)bromobenzene [149068-56-4] A 500 mL, three-necked round-bottomed flask is equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, thermometer and condenser and purged for 10 min with dinitrogen. The flask is charged with 4-bromiodobenzene (25.0 g, 88.34 mmol), copper bronze (12.36 g, 193.13 mmol) [1], 2,2'-bipyridine (0.98 g, 6.36 mmol), DMSO (200 mL) and fluorobenzene (150 mL). The pressure-equalizing dropping funnel is charged with perfluoro-n-hexyl iodide (39.42 g, 88.39 mmol) and fluorobenzene (50 mL). The flask is purged with dinitrogen for a further 20 min whilst the suspension is stirred vigorously. The mixture is then heated to exactly 70 °C and the perfluoro-n-hexyl iodide added dropwise over 7 h, with the temperature of the mixture being maintained at exactly 70 °C throughout. The mixture is then stirred for a further 120 h at 70 °C. After cooling the reaction mixture to room temperature, it is added to water (250 mL) and diethyl ether (500 mL) in a 1 L conical flask. The solids that precipitate are removed by filtration through a Buchner funnel and are washed with two 50 mL portions of diethyl ether. The organic layer is separated in a 1 L separating funnel and washed five times with 250 mL water, dried over magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to give a brown oil. This oil is heated in a Kugelrohr oven at 65 °C at 0.01 mmHg to remove residual 4-bromoiodobenzene and, subsequently, the temperature of the oven is increased to 100 °C to distill the 4-(tridecafluoro)bromobenzene and 1,4-bis(tridecafluoro)benzene as a clear oil away from the residual copper complexes, which remain in the base bulb as a dark brown tar. The clear oil is then distilled in a microfine distillation apparatus to give 28.56 g (68%) of 4-(tridecafluoro)bromobenzene as a colorless oil (bp 89–92 °C at 10 mbar). NMR analysis showed that this sample is >98% pure and contained less than 2% of 1,4-bis(tridecafluoro)bromobenzene. Material of this purity is acceptable for use in step B. 1H NMR (250 MHz, CDCl3) δ 7.90 (2 H, d, JHH = 8.5 Hz, ArH), 7.70 (2 H, d, JHH = 8.5 Hz, ArH); 19F NMR (235 MHz, CDCl3) δ /C0 81.80 (3 F, t, JFF = 9.3 Hz, CF3), /C0 111.72 (2 F, t, JFF = 14.6 Hz, α-CF2), /C0 122.10 (2 F, m, CF2), /C0 122.63 (2 F, m, CF2), /C0 123.63 (2 F, m, CF2), /C0 126.90 (2 F, m, CF2); m/z (EI) 474/6 (M+). Anal. calc. for C12H4BrF13: C, 30.3; H, 0.8; F, 52.0. Found C, 30.2; H, 0.8; F, 51.7.

Step B. tris(4-Tridecafluorohexylphenyl)phosphine [193197-68-1] [2] A 500 mL, three-necked round-bottomed flask is equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, low-temperature thermometer, and Rotaflo stopcock adaptor and attached to a Schlenk line. After flame-drying under high vacuum, the flask is cooled and filled with dinitrogen. The flask is charged with 4-(tridecafluoroxy)bromobenzene (24.0 g, 50.53 mmol) and degassed again under high vacuum for 20 min. The apparatus is again filled with nitrogen before adding dry diethyl ether (300 mL) to the main flask. Dry diethyl ether (30 mL) and a 1.6 M hexane solution of n-butyllithium (31.5 mL, 50.40 mmol) are both added to the dropping funnel and the flask is cooled to −78 °C using a dry ice/acetone bath. The n-butyllithium solution is added dropwise over 60 min with the internal temperature never allowed to warm above −75 °C. The mixture is then stirred for 5 h at −78 °C. The dropping funnel is rinsed with a 10 mL portion of dry diethyl ether and then charged with dry diethyl ether (30 mL) and phosphorus trichloride (2.29 g, 16.72 mmol). The phosphorus trichloride solution is added dropwise over 60 min with the internal temperature never al-
allowed to warm above \(-75\ ^\circ\text{C}\). The solution is then allowed to warm to room temperature and stirred overnight. A 10% ammonium hydroxide solution (100 mL) is then added [3] and the mixture is stirred for 20 min. The organic solution is then transferred into a flame-dried Schlenk flask under dinitrogen containing magnesium sulfate via a cannula. After stirring for 20 min, the solution is transferred to a flame-dried Schlenk flask under dinitrogen and the solvent removed \textit{in vacuo} to give a yellow oil. This oil is distilled in a Kugelrühr oven to give a clear oil (bp \(210\ ^\circ\text{C}\) at \(0.01\ \text{mmHg}\)). This is transferred to a glove box where it slowly solidifies to give a white solid (10.98 g, 56%). NMR analysis showed that this sample is \(>98\%\) pure, mp \(63–64\ ^\circ\text{C}\). ¹H NMR (250 MHz, CDCl₃) \(\delta\) 7.53 (6 H, d, \(J_{HH} = 8.0\ Hz\), 3-C₆H₄), 7.35 (6 H, vt, \(J_{HH} \approx J_{HF} = 8.0\ Hz\), 2-C₆H₄); ¹⁹F NMR (235 MHz, CDCl₃) \(\delta\) −81.32 (9 F, t, \(J_{FF} = 9.6\ Hz, \text{CF}_3\)), −111.48 (6 F, t, \(J_{FF} = 14.2\ Hz, \alpha\text{-CF}_2\)), −121.90 (6 F, m, CF₂), −122.24 (6 F, m, CF₂), −123.24 (6 F, m, CF₂), −126.59 (6 F, m, CF₂); ³¹P{¹H} NMR (101 Hz, CDCl₃) \(\delta\) −6.3; \(m/z\) (FAB) 1216 (M⁺). Anal. calc. for C₃6H₁₂F₃₉P: C, 35.5; H, 1.0; P, 2.5. Found C, 35.8; H, 0.9; P, 2.5.

Discussion

Reaction A is also suitable for the preparation of ortho- [4], meta- [5], and bis-meta-perfluoroalkylated bromobenzenes [6]. tris(4-Tridecafluorohexylphenyl)phosphine was first reported in the patent literature as a potentially useful oil additive in 1970 [7] and, more recently, has been successfully used as a modifying ligand for the hydroformylation of long chain alkenes under fluorous biphasic conditions [8] and in perfluorinated solvents [9]. It is commercially available from Fluka and Fluorous Technologies Inc. The ligand partitions 88:12 in a perfluoro-1,3-dimethylcyclohexane:toluene biphasic system and, although sensitive to oxidation in solution, can be handled as a solid in the open laboratory. Reaction B is also suitable for the preparation of tris(4-Heptadecafluorooctylphenyl)phosphine via 4-(heptadecafluorooctyl)bromobenzene. However, the yield for stage B is only 26% due to the low solubility of the bromobenzene in ether at \(-78\ ^\circ\text{C}\). This tris(4-heptadecafluorooctyl)-phosphine has been used successfully as a modifying ligand for palladium-catalyzed Stille [10] and Suzuki [11] coupling reactions under fluorous biphasic conditions. This procedure is also suitable for the preparation of other perfluoroalkylated aryl phosphine ligands by the replacement of phosphorous trichloride by other phosphorus-chloride reagents, e.g., 1,2-bis(dichlorophosphino)ethane [12] or diethylphosphoramic dichloride [4].

References

1. It is essential that copper bronze is used for this stage, not copper powder.
3. The ammonium hydroxide solution was degassed prior to addition by stirring under vacuum for a few seconds and then backfilling with dinitrogen. This procedure was repeated six times. Alternatively, the aqueous ammonium hydroxide solution is degassed by bubbling dinitrogen through the solution for 20 min.
11.31 \((R)-6,6'\text{-Bis(tridecafluoro-n-hexyl)}\)-2,2'\text{-bis(diphenylphosphino)}\)-1,1'\text{-binaphthyl} ((R)-Rf-BINAP).

A Multi-Step Sequence to a Chiral Perfluoroalkylated Bidentate Phosphine Ligand

Dave J. Adams, Eric G. Hope, Alison M. Stuart*, and Andrew J. West

Reaction 11.31-1

\(\text{Step A}\)  \(\text{Step B}\)

\(\text{Step C}\)  \(\text{Step D}\)

\(\text{Step E}\)

1) Ph\(_2\)PH, [NiCl\(_2\)(dppe)]
   DMF, 100 °C, 30 min
2) DABCO, 110 °C, 2 h
3) Ph\(_2\)PH, 110 °C, 72 h

D. J. Adams, J. Bennett, E. G. Hope, J. L. Kite, A. M. Stuart, unpublished work.

6
7
8
9

11.31 (R)-6,6′-Bis(tridecafluoro-n-hexyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (((R)-Rf-BINAP)). A Multi-Step Sequence to a Chiral Perfluoroalkylated Bidentate Phosphine Ligand

Dave J. Adams, Eric G. Hope, Alison M. Stuart*, and Andrew J. West

Reaction 11.31-1

Step A

\[
\text{Br} \quad \text{OH} \quad \text{OH} \quad \text{Br} \\
\text{NEt}_3, \text{Ac}_2\text{O} \\
\text{DMAP, DCM} \quad \text{reflux, 1 h} \\
\text{77%}
\]

Step B

\[
\text{Br} \quad \text{OH} \quad \text{OH} \\
\text{C}_6\text{F}_{13} \quad \text{Cu} \\
\text{2,2′-bipyridine} \\
\text{C}_6\text{H}_5\text{N}, 0^\circ\text{C}, 4 \text{ h} \\
\text{95%}
\]

Step C

\[
\text{NaOEt, EtOH} \quad \text{rt, 60 min} \\
\text{90%}
\]

Step D

\[
\text{NaOEt, EtOH} \quad \text{rt, 60 min} \\
\text{(CF}_3\text{SO}_2)_2\text{O} \\
\text{80 ^\circ C, 72 h} \\
\text{95%}
\]

Step E

1) \( \text{Ph}_2\text{PH, [NiCl}_2\text{(dppe)]} \) \\
DMF, 100° C, 30 min \\
2) \( \text{DABCO, 110 ^\circ C, 2 h} \) \\
3) \( \text{Ph}_2\text{PH, 110 ^\circ C, 72 h} \) \\
41%
Reagents

Perfluoro-n-hexyl iodide [355-43-1] was purchased from Fluorochem Ltd., stored in a refrigerator and used without further purification. All solvents were dried under dinitrogen. Dry dichloromethane was prepared by refluxing 1 L of the solvent over calcium hydride (approximately 15 g) for 3 days, followed by distillation from calcium hydride and transfer of the solvent to a 1 L ampoule sealed with a Youngs tap. Dry pyridine was prepared by refluxing 150 mL of the reagent over calcium hydride (approximately 10 g) for 1 day, followed by distillation from calcium hydride and transfer to a flame-dried 200 mL ampoule sealed with a Youngs tap. Anhydrous DMF was transferred from a SureSeal™ bottle to a dried ampoule containing 4 Å molecular sieves. The dichloromethane, DMF and pyridine were all freeze/pump/thaw degassed until no bubbles of gas were visible during thawing. The [NiCl2(dppe)] can be prepared easily by stirring equimolar quantities of [NiCl2]·6H2O and 1,2-bis(diphenylphosphino)ethane for 30 min in methanol followed by filtration of the suspension. The red-orange solid can then be used in the preparation. Storage of the material leads to degradation of the catalyst and unsuccessful reaction, and so the material should be freshly prepared before each synthesis. All other chemicals in this synthesis were obtained and used as supplied from Aldrich Chemical Company Inc.

Experimental Procedures

Step A. (R)-6,6'-Dibromo-2,2'-diacetoxy-1,1'-binaphthyl [179866-78-5] A 250 mL, round-bottomed flask is equipped with a magnetic stirrer bar and charged with (R)-6,6'-dibromo-1,1'-bi-2,2'-naphthol (5.0 g, 11.2 mmol) [65283-60-5] [1], triethylamine (9.4 mL, 66.6 mmol), (4-N,N-dimethylamino)pyridine (DMAP; 100 mg, 10 mmol), acetic anhydride (2.1 mL, 22.4 mmol) and dichloromethane (100 mL). A reflux condenser is fitted to the flask and the mixture is heated to reflux for 1 h with vigorous stirring. Upon cooling, 1 M hydrochloric acid (100 mL) is slowly added and the mixture transferred to a separating funnel. The organic layer is separated and washed with saturated sodium carbonate solution (100 mL), brine (100 mL) and water (100 mL) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to yield the crude product as a yellow semi-solid. Recrystallization from ethanol yields 8.4 g (77%) of (R)-6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthyl as white needles: 1H NMR (250 MHz, CDCl3) δ 1.84 (6 H, s, COCH3), 7.05 (2 H, d, 3JHH = 9.0 Hz, ArH), 7.49 (2 H, d, 3JHH = 9.0 Hz, 3JHH = 1.8 Hz, ArH), 7.64 (2 H, d, 3JHH = 9.0 Hz, ArH), 8.14 (2 H, d, 3JHH = 9.0 Hz, ArH), 8.32 (2 H, d, 3JHH = 1.8 Hz, ArH); 13C{1H} NMR (63 MHz, CDCl3) δ 20.91, 120.48, 123.50, 123.62, 128.15, 129.24, 130.50, 130.69, 132.11, 133.01, 147.44, 169.53, m/z (FAB) 529 (MH)⁺ (14%), 486 (MH-COCH3)⁺ (14%). [α]D 33.8 (CDCl3, c 6.4).

Step B. (R)-6,6'-Bis(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl [410523-70-5] A 250 mL, round-bottomed flask is equipped with a magnetic stirrer bar, thermometer and condenser and purged for 10 min with dinitrogen. The flask is charged with (R)-6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthyl (3.5 g, 6.6 mmol), perfluoro-n-hexyl iodide (8.9 g, 20 mmol), cop-
per bronze (2.6 g, 39.7 mmol) [2], 2,2'-bipyridine (0.2 g, 1.5 mmol), fluorobenzene (50 mL) and DMSO (100 mL). The flask is purged with dinitrogen for a further 15 min before heating the resulting mixture at 80 °C for 72 h with constant stirring. The mixture is then transferred to a 1 L conical flask and diethyl ether (300 mL) and water (200 mL) added. The suspension is filtered using a Buchner funnel and the solids are washed with two 25 mL portions of diethyl ether. The filtrate is transferred to a 1 L separating funnel and the organic layer is separated. This is washed with 1 M hydrochloric acid (100 mL) and five portions of water (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to give 4.4 g (66%) of (R)-6,6'-bis(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl as a yellow oil. The sample was shown to be >95% pure by 1H NMR spectroscopy. Material of this purity is acceptable for use in the third step. The yellow oil can be solidified by addition of hexane (30 mL) followed by removal of the solvent under reduced pressure using a rotary evaporator three times, followed by prolonged drying under high vacuum: 1H NMR (250 MHz, CDCl 3) δ 1.81 (6 H, s, COCH 3), 6.93 (2 H, d, J HHH = 9.0 Hz, ArH), 7.24 (2 H, d, J HHH = 9.0 Hz, ArH), 7.41 (2 H, d, J HHH = 9.0 Hz, ArH), 7.85 (2 H, d, J HHH = 9.0 Hz, ArH), 8.08 (2 H, s, ArH); 19F NMR (235 MHz, CDCl 3) δ –81.31 (6 F, t, J FF = 10.6 Hz, CF 3), –110.70 (4 F, m, x-CF 2), –121.89 (4 F, m, CF 2), –121.95 (4 F, m, CF 2), –123.17 (4 F, m, CF 2), –126.52 (4 F, m, CF 2); 13C{1H} NMR (63 MHz, CDCl 3) δ 12.19, 125.13, 128.69, 129.40, 129.85, 133.63, 147.69, 168.07; m/z (FAB) 1007 (MH+) (8%). Anal. calc. for C 36H 16F 26O 4: C, 42.9; H, 1.6. Found: C, 42.8; H, 1.75; [α] D 2.7 (CHCl 3, c 0.6).

Step C. (R)-6,6'-Bis(tridecafluorohexyl)-1,1'-bi-2,2'-napthol [410523-71-6] A 100 mL, round-bottomed flask, equipped with a magnetic stirrer bar, is charged with (R)-6,6'-bis-(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl (2.1 g, 2 mmol) and ethanol (65 mL). The resulting suspension is stirred rapidly and sodium ethoxide (0.34 g, 5 mmol) is added. The resulting brown solution is stirred for 1 h at room temperature. The magnetic stirrer bar is removed from the mixture and the ethanol is then removed under reduced pressure using a rotary evaporator. Dichloromethane (50 mL) is added to the brown oil and the liquid is transferred into a 250 mL separating funnel. The organic solution is washed with 1 M hydrochloric acid (100 mL) and water (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to yield a yellow-brown oil. Methanol (30 mL) is added to the oil and the solution is filtered. The solvent is removed again using a rotary evaporator to yield a yellow oil. This oil is triturated with hexane and recrystallized from hexane to give 1.6 g (90%) of (R)-6,6'-bis(tridecafluorohexyl)-1,1'-bi-2,2'-napthol as a yellow solid, mp 81–83 °C: 1H NMR (250 MHz, CDCl 3) δ 5.21 (2 H, s, OH), 7.18 (2 H, d, J HHH = 9.0 Hz, ArH), 7.37 (2 H, d, J HHH = 9.2 Hz, ArH), 7.44 (2 H, d, J HHH = 9.0 Hz, ArH), 8.11 (2 H, d, J HHH = 9.0 Hz, ArH), 8.24 (2 H, s, ArH); 19F NMR (235 MHz, CDCl 3) δ –81.22 (6 F, t, J FF = 10.2 Hz, CF 3), –110.98 (4 F, m, x-CF 2), –121.88 (8 F, m, 2 x CF 2), –123.21 (4 F, m, CF 2), –126.59 (4 F, m, CF 2); 13C{1H} NMR (63 MHz, CDCl 3) δ 110.96, 119.69, 124.95 (t, J CF = 6.1 Hz), 125.13, 125.15 (t, J CF = 24.4 Hz), 128.69 (t, J CF = 7.1 Hz), 128.74, 133.10, 135.41, 155.13; m/z (ES+) 922 (M+) (33%), 921 (M-H)– (100%). Anal. calc. for C 36H 16F 26O 4: C, 41.65; H, 1.3. Found: C, 41.7; H, 1.3; [α] D
The 13C{1H} NMR analysis reports no carbon signals for the perfluoroalkyl groups as these are coupled extensively to the fluorine nuclei and so are not distinguishable.

Step D. (R)-6,6′-Bis(tridecafluorohexyl)-2,2′-di-trifluoromethanesulfonyloxy-1,1′-binaphthyl [410523-72-7] A 100 mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer and flame-dried under high vacuum. Once cool, the flask is filled with dinitrogen. (R)-6,6′-bis(tridecafluorohexyl)-1,1′-bi-2,2′-napthol (2.0 g, 2.2 mmol) is added to the flask against a positive flow of dinitrogen and the removed glass stopper is replaced with a rubber septum. Dry dichloromethane (50 mL) is added to the flask through the septum via a cannula and dry pyridine (0.15 mL, 3.2 mmol) is added via syringe. The mixture is cooled in an ice bath to 0 °C and trifluoromethanesulfonic anhydride (0.44 mL, 2.6 mmol) is added dropwise via syringe through the septum. The resulting orange solution containing a white precipitate is allowed to warm to room temperature over 4 h under nitrogen. 1 M Hydrochloric acid (50 mL) is added and the mixture transferred to a separating funnel. The organic layer is separated, washed with saturated sodium carbonate solution (50 mL) followed by water (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator. The crude brown product is recrystallized from hexane to yield 1.2 g (95%) of (R)-6,6′-bis(tridecafluorohexyl)-2,2′-di-trifluoromethanesulfonyloxy-1,1′-binaphthyl as a white crystalline solid, mp 120–122 °C: 1H NMR (250 MHz, CDCl3) δ 7.29 (2 H, d, 3JHH = 9.0 Hz, ArH), 7.51 (2 H, d, 3JHH = 9.2 Hz, ArH), 7.70 (2 H, d, 3JHH = 9.2 Hz, ArH), 8.24 (2 H, d, 3JHH = 9.0 Hz, ArH); 19F NMR (235 MHz, CDCl3) δ 74.92 (6 F, s, OSO2CF3), 81.24 (6 F, t, 4JFF = 10.7 Hz, CF2CF3), 111.00 (4 F, m, a-CF2), 121.88 (4 F, m, CF2), 121.93 (4 F, m, CF2), 123.18 (4 F, m, CF2), 126.54 (4 F, m, CF2); 13C{1H} NMR (63 MHz, CDCl3) δ 121.34, 123.45, 125.11, 126.54 (4 F, m, CF2); 19F NMR (235 MHz, CDCl3) δ 74.92 (6 F, s, OSO2CF3), 81.24 (6 F, t, 4JFF = 10.7 Hz, CF2CF3), 111.00 (4 F, m, a-CF2), 121.88 (4 F, m, CF2), 121.93 (4 F, m, CF2), 123.18 (4 F, m, CF2), 126.54 (4 F, m, CF2); 13C{1H} NMR (63 MHz, CDCl3) δ 121.34, 123.45, 125.11, 126.54 (4 F, m, CF2); 13C{1H} NMR (63 MHz, CDCl3) δ 121.34, 123.45, 125.41 (t, 3JCF = 6.2 Hz), 127.70, 128.73 (t, 3JCF = 7.1 Hz), 128.96 (m), 131.68, 133.79, 134.80, 147.35; m/z (FAB) 1186 (M)+ (82%). Anal. calc. for C34H10F32O6S2: C, 34.4; H, 0.8. Found: C, 34.4; H, 0.8; [α]D 5.7 (CHCl3, c 2.3). The 13C{1H} NMR analysis reports no carbon signals for the perfluoroalkyl groups as these are coupled extensively to the fluorine nuclei and so are not distinguishable.

Step E. (R)-6,6′-Bis(tridecafluorohexyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [410523-73-8] A 100 mL, three-necked, round-bottomed flask is fitted with a magnetic stirrer bar and reflux condenser and flame-dried under high vacuum. Once cool, the flask is filled with dinitrogen. A freshly prepared [NiCl2(dppe)] (44 mg, 8.3 × 10-5 mol) is added to the flask against a positive flow of dinitrogen and the removed glass stopper is replaced with a rubber septum. A 100 mL Schlenk flask is equipped with a magnetic stirrer bar and flame dried under high vacuum. Upon cooling, this flask is also filled with dinitrogen. (R)-6,6′-bis(tridecafluorohexyl)-2,2′-di-trifluoromethanesulfonyleoxy-1,1′-binaphthyl (0.84 mmol) is added to the Schlenk flask against a positive flow of dinitrogen and a rubber septum is placed in the mouth of the flask. Dry DMF (50 mL) is then added to each flask via a cannula. To the round-bottomed flask, diphenylphosphine (120 μL, 1.1 mmol) is added through the septum via syringe and the mixture of phosphine and nickel stirred at 100 °C.
°C for 30 min. The solution of \((R)-6,6'-\text{bis(tridecafluorohexyl)-2,2'}\)-di-trifluoromethanesulfonloxy-1,1'-binaphthyl in the Schlenk flask is then added to the phosphine via a cannula. The septum is removed and 1,4-diazabicyclo[2,2,2]octane (DABCO; 0.4 g, 3.3 mmol) is added against a positive flow of dinitrogen and the septum is replaced. The resulting green solution is stirred at 110 °C for 2 h. An additional portion of diphenylphosphine (120 μL, 1.1 mmol) is then added via syringe, the septum is replaced with a stopper and the solution stirred at 110 °C for a further 72 h. Upon cooling, the DMF is removed under high dynamic vacuum at 70 °C by trap-to-trap distillation using a round-bottomed flask trap cooled in liquid nitrogen. The resulting dark brown solid is stirred in methanol (50 mL) for 30 min and filtered to yield an off-white crude product. This is recrystallized from dichloromethane/methanol to yield 0.4 g (41%) of \((R)-6,6'-\text{bis(tridecafluorohexyl)-2,2'}\)-bis(diphenylphosphino)-1,1'-binaphthyl as a white powder, mp 241–244 °C: 1H NMR (250 MHz, CDCl3) δ 6.69 (2 H, d, 3JHH = 9.1 Hz, ArH), 6.85 (2 H, d, 3JHH = 8.9 Hz, ArH), 7.02 (8 H, m, ArH), 7.25 (12 H, m, ArH), 7.59 (2 H, d, 3JHH = 8.5 Hz, ArH), 7.60 (2 H, d, 3JHH = 8.5 Hz, ArH), 8.00 (2 H, d, 3JHH = 8.5 Hz, ArH), 8.05 (2 H, s, ArH); 19F NMR (235 MHz, CDCl3) δ −81.18 (6 F, t, 4JFF = 10.2 Hz, CF3), −110.68 (4 F, m, a-CF2), −121.77 (8 F, m, 2× CF2), −123.15 (4 F, m, CF2), −126.49 (4 F, m, CF2); 31P{1H} NMR (101 MHz, CDCl3) δ −13.6 (s); m/z (ES+) 1259 [MH]+ (5%). Anal. calc. for C56H30F26P2: C, 53.4; H, 2.4. Found: C, 53.3; H, 2.3; [x]D 104.2 (C 6H6, c 0.1).

Discussion

This perfluoroalkylated ligand is insoluble in perfluorinated cycloalkane solvents, e.g., perfluoro-1,3-dimethylcyclohexane, but has been used in the ruthenium-catalyzed asymmetric hydrogenation of dimethyl itaconate in methanol and supercritical CO2. In methanol, the perfluoroalkylated BINAP gave similar enantioselectivity but slightly lower conversion than the non-fluorous parent BINAP [3], but in supercritical CO2 both the reaction rates and enantioselectivity were lower than those obtained in methanol [4]. The \(-C_8F_{17}\) analog can be prepared by a similar route using perfluoro-octyl iodide in place of perfluoro-n-hexyl iodide.

References

1. (R)-6,6'-Bis(tridecafluoro-n-hexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((R)-Rf-BINAP)

2. It is essential that copper bronze is used for this stage, not copper powder.
11.32
4-Fluorobenzyl 4-(4-Nitrophenyl)butyrate. The Mitsunobu Reaction with a Fluorous Phosphine and a Fluorous Dead Reagent

Dennis P. Curran and Sivaraman Dandapani

Reaction 11.32-1

\[
\text{C}_6\text{F}_{13}\text{ON} \quad \text{O} \quad \text{NO C}_6\text{F}_{13} \quad \text{O} \\ 1, 2, \text{THF} \quad 14 \text{ h, RT} \\
\]

88%

Reagents

Bis(1\(H\),1\(H\),2\(H\),2\(H\)-perfluoroctyl) azodicarboxylate (\(\text{FDEAD}\)) 1 [452912-11-7] and bis[4-(1\(H\),1\(H\),2\(H\),2\(H\)-perfluoroctyl)phenyl] phenylphosphine 2 [290827-94-0] are commercially available from Fluorous Technologies, Inc. [1] (www.fluorous.com) or can be prepared according to the literature procedure [2]. Fluorous silica gel can be made by the literature procedure [3], but commercially available FluoroFlash™ silica gel from Fluorous Technologies, Inc. is recommended for higher loading and better reproducibility.

Experimental Procedure

A solution of \(\text{FDEAD}\) 1 (85 mg, 0.105 mmol) in THF (0.5 mL) is slowly added to a solution of fluorous phosphine 2 (100 mg, 0.105 mmol) in THF (0.5 mL) at 0 °C. 4-Fluorobenzyl alcohol (12 \(\mu\)L, 0.105 mmol) is added neat. Then 4-(4-nitrophenyl) butyric acid (15 mg, 0.07 mmol) is added. After stirring overnight, the solvent is evaporated and the residue is loaded on to 2 g of fluorous silica [4] using methanol. Elution with 80% MeOH (10 mL) and evaporation of the solvent provides 4-fluorobenzyl 4-(4-nitrophenyl) butyrate (20 mg, 88%). A second elution with ether (20 mL) gives a mixture of the fluorous phosphine oxide and the fluorous hydrazine.

Discussion

The Mitsunobu reaction is frequently used for substitution because of its generality and because its precursors, alcohols, are readily available and can be displaced without a separate activation step [5]. While conducting Mitsunobu reactions is easy, purifying the products often is not. Chromatography is the standard purification method, but all too often one of the spent Mitsunobu reagents is difficult to separate from the target product.
Several fluorous variants of the Mitsunobu reaction have recently appeared [2, 6]. In this variant [2], a standard alcohol and nucleophile are used, and both of the reagents are fluorous. Solid phase extraction [7] over FluoroFlash silica gel allows rapid separation of the target products from the spent fluorous reagents. If desired, the spent fluorous reagents can be separated and reconverted into the starting reagents for reuse. The procedure is especially convenient for small scale reactions such as those used in natural products synthesis, medicinal chemistry or solution phase parallel synthesis.

References

1 DPC holds an equity interest in Fluorous Technologies, Inc.
4 Homemade fluorous silica was used for this experiment. However, subsequent control experiments showed that FluoroFlash™ cartridges were superior in terms of loading and separation.

Seiji Takeuchi and Yutaka Nakamura

Reaction 11.33-1

\[
\begin{align*}
(R)-6,6'-\text{Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silyl]}-1,1'-\text{binaphthalene-2,2'-dil} & \\
(R)-6,6'-\text{Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silyl]}-2,2'-\text{bis(diphenylphosphino)}-1,1'-\text{binaphthalene} & \\
\end{align*}
\]
Reagents

(R)-6,6'-Dibromo-2,2'-bis(methoxymethoxy)-1,1' -binaphthalene 1 [179866-74-1] and bromo tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silane 2 [201740-57-0] can be prepared according to the literature procedures [1].

Experimental Procedures

Step A. (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silyl]-2,2'-bis(methoxymethoxy)-1,1' -binaphthalyl (3) (R)-6,6'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene 1 (2.00 g, 3.76 mmol) is dissolved in THF (20 mL) and cooled to −78 °C under argon. n-BuLi (1.55 M in hexane, 5.4 mL, 8.3 mmol) is added dropwise, and the resulting solution is stirred at that temperature for 50 min. A solution of bromo tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silane 2 (10.6 g, 9.22 mmol) in ether (50 mL) is added via a cannula to the reaction mixture. The reaction mixture is allowed to warm to room temperature, stirred for 1.5 h, and then quenched with a saturated aqueous NH₄Cl solution (50 mL). The volatiles are removed in vacuo and CH₂Cl₂ (80 mL) is added. The mixture is extracted with FC-72 (30 mL x 5) and the combined FC-72 layer is concentrated in vacuo. The resulting syrup is purified by flash column chromatography on silica gel (400 g, hexane-EtOAc = 20/1) to afford fluorous BINOL bis MOM ether 3 as a colorless syrup (8.6 g, 91%) [2].

Step B. (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silyl]-1,1'-binaphthalene-2,2'-diol (4)  A mixture of fluorous BINOL bis MOM ether 3 (399 mg, 0.159 mmol), concent-
trated HCl (4 mL) and THF (8 mL) is stirred vigorously at 60 °C for 3 h. After addition of CH2Cl2 (10 mL), the cloudy biphase is extracted with FC-72 (10 mL × 5). The combined FC-72 layer is concentrated in vacuo to give a syrup, which is purified by flash column chromatography on silica gel (30 g, hexane/EtOAc = 10/1) to afford (R)-FBINOL 4 as a colorless syrup that gradually crystallizes (379 mg, 98%, >99% ee); mp 80–81 °C; IR (KBr) cm⁻¹: 3500, 2946, 1614, 1470, 1207, 1144, 1071, 1019, 900, 844, 746, 708; ¹H NMR (200 MHz, CDCl₃) δ 1.10–1.30 (m, 12 H), 1.80–2.20 (m, 12 H), 5.14 (s, 2 H), 7.22 (d, 2 H, J = 8.3 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 7.47 (d, 2 H, J = 8.3 Hz), 7.99 (s, 2 H), 8.04 (d, 2 H, J = 9.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 1.6, 25.5 (t, J_FC = 24.0 Hz), 105.6–121.5 (m), 110.4, 118.7, 124.6, 126.5, 129.2, 130.8, 132.0, 134.5, 135.6, 154.1; MS (EI) m/z 2422 (M⁺). Anal. calc. for C₆₈H₃₆F₇₈O₂Si₂: C, 33.71; H, 1.50; F, 61.16. Found: C, 33.12; H, 1.25; F, 60.93; [α]D²⁰ = −16.9° (c 0.463, FC-72).

Step C. (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1'-binaphthalene (5) A solution of (R)-FBINOL 4 (1.0 g, 0.41 mmol) and pyridine (0.10 mL, 1.24 mmol) in BTF (10 mL) is treated with trifluoromethanesulfonic anhydride (280 mg, 0.991 mmol) at 0 °C under argon. The reaction mixture is allowed to warm to room temperature and stirred for 2 h. The mixture is diluted with ether (30 mL) and washed with water (20 mL), saturated aqueous NaHCO₃ solution (20 mL), and brine (20 mL). The organic layer is dried over anhydrous MgSO₄ and then concentrated in vacuo. The residual syrup is purified by flash column chromatography on silica gel (50 g, hexane/ether = 20/1) to afford fluorous BINOL bis Tf₅ as a colorless syrup (1.12 g, quantitative) [3, 4].

Step D. (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphinyl)-1,1'-binaphthyl (6) A mixture of [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (133 mg, 0.245 mmol) in BTF (3 mL) is treated with diphenylphosphine (65 mg, 0.349 mmol) at 100 °C under argon. After stirring for 1 h, a solution of fluorous BINOL bis Tf₅ 5 (1.12 g, 0.417 mmol) and DABCO (187 mg, 1.67 mmol) in BTF (5 mL) is added via a cannula to the reaction mixture. The green suspension is stirred at 100 °C and two additional portions of diphenylphosphine (65 mg, 0.349 mmol each) are added after 3 h and 6 h. After stirring at that temperature for 3 days, the reaction mixture is diluted with ether (50 mL). The mixture is washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO₄. After the solvent is removed in vacuo, the residue is dissolved with BTF (20 mL). 30% H₂O₂ (0.5 mL) is added and the mixture is stirred vigorously at room temperature for 30 min, and then excess H₂O₂ is decomposed with MnO₂ (ca. 0.1 g). The mixture is dried over anhydrous MgSO₄ and concentrated in vacuo. The resulting syrup is purified by flash column chromatography on silica gel (50 g, hexane/ether = 20/1) to afford fluorous BINAP oxide 6 as a white powder (1.0 g, 86%, >99% ee) [3].

Step E. (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7) A solution of fluorous BINAP oxide 6 in 1,2-dimethoxyethane (DME) (2 mL) is treated with methyl trifluoromethanesulfonate (MeOTf) (35 mg, 0.21
mmol) at ambient temperature for 2 h under argon. To the solution is added a solution of LiAlH₄ (0.5 M in DME, 0.72 mL, 0.36 mmol) at 0 °C and then the reaction mixture is stirred at that temperature for 3 h. The reaction mixture is quenched with a few drops of saturated aqueous Na₂SO₄ solution. The mixture is loaded on a column of silica gel (5 g) and then eluted with hexane-THF (20/1) [5] to afford fluorous BINAP 7 as a colorless viscous syrup which gradually crystallizes (134 mg, 68%); mp 98–101 °C; IR (KBr) cm⁻¹: 3056, 2947, 1438, 1363, 1144, 1120, 1070, 906, 813, 745, 698; ¹H NMR (400 MHz, CDCl₃) δ 1.08–1.18 (m, 12 H), 1.95–2.11 (m, 12 H), 6.79 (d, 2 H, J = 9.0 Hz), 6.81 (d, 2 H, J = 9.0 Hz), 7.01–7.36 (m, 20 H), 7.52 (d, 2 H, J = 8.5 Hz), 7.91 (s, 2 H), 7.92 (d, 2 H, J = 8.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 1.6, 25.5 (t, J.FC = 24.0 Hz), 107.2–120.8 (m), 127.5–138.1 (m), 128.0, 128.4, 128.6, 129.4, 144.0 (d, J.P = 20.0 Hz); ³¹P NMR (162 MHz, CDCl₃) δ −14.1. HRMS (ESI-TOF) calc. for C₉₂H₅₅F₇₈Si₂P₂ ([M + H]⁺): 2759.2066. Found: 2759.1995; [α]D²⁵ +21.2° (c 0.897, THF).

Discussion

(R)-FBINOL 4 is prepared in two steps in good yield by using Curran’s tagging method [6] and the procedures are applicable to a preparation of a 6,6'-bis(C₈F₁₇CH₂CH₂)₃Si-tagged analog [7]. The FBINOL synthetic method has a benefit that the fluorous products in each step are easily separable from organic and inorganic byproducts by FC-72/organic solvent/water three phase extraction. Fluorous BINAP [(R)-FBINAP] 7 is prepared in four steps from (R)-FBINOL 4 in moderate yield. However, operations under nitrogen or argon should be carried out carefully in order to avoid an oxidation of (R)-FBINAP, for example, during a column chromatography purification.

References

5 All purification steps were carried out under argon in a glove bag. The eluent was degassed prior to use.
11.34 5α-Cholestan-3α-ol. Inversion of Configuration via the Mitsunobu Reaction with a Fluorous Gallic Acid

Roman Dembinski and Marcin W. Markowicz

Reagents

[CAS Registry Number]: 5α-Cholestan-3β-ol (dihydrocholesterol) [80-97-7], diisopropyl azodicarboxylate [2446-83-5], and triphenylphosphine [603-35-0] are commercially available. 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoic acid [172701-34-7] was prepared from methyl 3,4,5-trihydroxybenzoate (methyl gallate) [99-24-1] and 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12-heptadecafluorododecyl bromide [99324-99-9] or iodide [38565-62-7] by a literature method [1]. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone.

Experimental Procedures

Step A. 5α-Cholestan-3α-yl 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12-heptadecafluorododecan-1-yloxy)benzoate (3) [477935-28-7] A round-bottomed flask (100 mL) is charged under nitrogen atmosphere with fluorous benzoic acid 1 (0.478 g, 0.300 mmol), triphenylphosphine (0.213 g, 0.812 mmol), and tetrahydrofuran (10 mL). The mixture is stirred at room temperature. 5α-Cholestan-3β-ol 2 (0.155 g, 0.399 mmol) is added, followed by diiso-
propyl azodicarboxylate (0.15 mL, 0.76 mmol). The stirring is continued for 40 h. The solvent is removed by rotary evaporation [2] and the residue is recrystallized from chloroform/methanol (1:1 v/v, ca. 15 mL). The white solid of ester 3 is isolated by filtration (medium porosity frit) and dried over phosphorus pentoxide under an oil pump vacuum (0.556 g, 0.283 mmol, 94%), mp 117–119°C. IR (cm⁻¹, KBr) νc=O 1712 s; MS (EI, 70 eV) 1962 (M⁺, 100%), 1591 [(M–C₂₇H₄₇)⁺, 24%], 1118 [(M–C₁₂F₁₇H₈–C₁₂F₁₇H₈ + 2)⁺, 21%]; no other peaks above 200 of >7%; ¹H NMR (CDCl₃) 7.29 (s, 2 H, C₆H₂COO), 5.23 (m, 1 H, OC₆H), 4.20–3.90 (m, 6 H, C₆H₂OC₆H₂), 2.30–0.65 (m, 64 H, remaining hydrogens); ¹³C NMR 165.6 (COO), 152.7 (m-C₆H₂COO), 141.9 (p-C₆H₂COO), 126.6 (i-C₆H₂COO), 108.3 (o-C₆H₂COO), 72.9 (4-CH₂OC₆H₂), 71.3 (COOCH), 68.6 (3,5-CH₂OC₆H₂), 56.9, 56.6, 55.1, 42.8, 40.9, 40.3, 39.7, 36.3, 36.13, 36.06, 35.7, 33.6, 33.2, 32.4, 30.8 (t, J = 22.0 Hz, CF₂CH₂), 29.9 (4-CH₂CH₂OC₆H₂), 28.9 (3,5-CH₂CH₂OC₆H₂), 28.6, 28.4, 28.2, 26.5, 24.3, 24.1, 23.0, 22.7, 21.1, 18.8, 17.6 (m, CF₂CH₂CH₂), 12.3, 11.7.

Step B. 5α-Cholestan-3α-ol (4) (Epidihydrocholesterol) [516-95-0] A round-bottomed flask (100 mL) is charged with ester 3 (0.500 g, 0.255 mmol), tetrahydrofuran/methanol (1:1 v/v, 30 mL), and 10 M potassium hydroxide (0.6 mL). The mixture is refluxed for 1.5 h, cooled, and acidified with 5% hydrochloric acid (ca. 2 mL). The solvent is removed by rotary evaporation [2]. The solid residue is extracted with methylene chloride (2 x 25 mL) and filtered through a silica gel pad (3 cm). The solvent is removed from the filtrate by rotary evaporation to give 5α-cholestan-3α-ol 4 as a white solid that was dried over phosphorus pentoxide under an oil pump vacuum (0.093 g, 0.24 mmol, 94%). The silica gel pad with the remaining solid is washed with tetrahydrofuran (2 x 15 mL). The solvent is removed from the filtrate by rotary evaporation and the residue is crystallized from chloroform/methanol (1:1 v/v, ca. 15 mL). The white solid is isolated by filtration (medium porosity frit) and dried over phosphorus pentoxide under an oil pump vacuum to recover the fluorous benzoic acid 1 (0.317 g, 0.199 mmol, 78%) [3].

Discussion

The conversion of asymmetric secondary alcohols into esters, with inversion of configuration, is of considerable importance in synthesis. The Mitsunobu reaction is well suited to accomplish this transformation [4]. In this reaction an alcohol is treated with dialkyl azodicarboxylate, triphenylphosphine and a carboxylic acid to provide an ester with inversion of configuration.

Inversion of configuration on C-3 of the cholestanol can be achieved by several methods and/or reagents. These include, among others, classical [5] and fluorous [6] Mitsunobu protocols, treatment with (chloromethylene)dimethylammonium chloride [7], Pd/benzquinone [8], a Ni catalyst [9], reaction of isourea ethers with carboxylic acids [10], or reaction of sulfonates with cesium acetate [11]. Synthesis of 5α-cholestan-3α-ol 4 by other methods also includes a large number of references and patents. Stereocontrolled reduction of the carbonyl precursor is one of the most common approaches [12].

The side products of the Mitsunobu reaction, triphenylphosphine oxide and dialkyl hydrazinedicarboxylate are of substantial mass and may cause isolation of the product to be tedious. Several fluorous approaches addressing this issue have been recently reported (short review in Chapter 10.3). The present fluorous variant of the Mitsunobu reaction pro-
vides for facile, chromatography-free separation of the ester 3 [13] and due to the hydrophobicity of cholestanol esters has an advantage over solid phase extraction [6]. Saponification of 3 with retention of configuration gives, after workup, an alcohol 4, and a fluorous gallic acid 1 that can be reused without any additional treatment. Other esters can also be synthesized by this method (Table 10.3-2 in Chapter 10.3).

References

2 Solutions containing fluorous compounds tend to bump during rotary evaporation. An anti-splash adapter and pressure monitoring is recommended.
4 See references 1–3 in Chapter 10.3.
8 B. M. Choudary, Polyhedron 1986, 5, 2117–2118.

11.35 1,3-Bis(heptadecafluorooctyl)-5-chlorobenzene. Synthesis of Perfluoroalkylarenes from Aryl Bromides

Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson

Reaction 11.35-1

\[
\begin{align*}
\text{Cl} & \quad \text{Cu, C}_8\text{F}_{17}\text{l} (2) \\
\text{Br} & \quad \text{DMF, 120 °C, 18 h} \\
1 & \quad \text{Cl, C}_8\text{F}_{17} \\
& \quad 3, 77\%
\end{align*}
\]
Reagents

1,3-Dibromo-5-chlorobenzene 1 [14862-52-3] and 1-heptadecafluoro-1-iodooctane 2 [507-63-1] are available from commercial sources. Copper powder 99% for organic synthesis, commercially available from Aldrich, is used as obtained.

Experimental Procedure

Copper powder (2.42 g, 38.1 mmol) and solid 1,3-dibromo-5-chlorobenzene 1 (1.03 g, 3.8 mmol) are suspended under nitrogen in 20 mL of dry, degassed DMF in a flame-dried Schlenk tube stopped with a rubber septum. The mixture is vigorously stirred at 70 °C and the first portion of 1-heptadecafluoro-1-iodooctane 2 (1.11 mL, 4.2 mmol) is added dropwise with a syringe. The temperature is then increased to 120 °C and the reaction stirred for 1 h before adding the second portion of 2 (1.11 mL, 4.2 mmol). After 18 h, the reaction mixture is cooled to room temperature. Water (20 mL) and diethyl ether (50 mL) are added and the mixture is filtered using a Büchner funnel to remove insoluble inorganic compounds. The solid is then washed on the filter with diethyl ether (5 × 30 mL). The filtrate is poured into a separatory funnel, the aqueous layer is separated and extracted with diethyl ether (2 × 20 mL). The combined ethereal extracts are washed with water (40 mL), dried over Na2SO4, and the solvent and volatile byproducts are removed at reduced pressure. The crude product is washed with boiling dichloromethane (3 × 10 mL) affording pure 3 (2.70 g, 77%) as a white solid [1], mp 51–52 °C. 1H NMR (300 MHz, CDCl3/CCl2FCF2Cl) δ 7.69 (br s, 1 H), 7.81 (br s, 1 H). GC analysis: column HP-5 (5% phenyl methyl siloxane), carrier He = 2.7 mL min⁻¹, split ratio = 50:1, detector T = 280 °C, injector T = 180 °C, oven T = 50 °C (5 min) to 70 °C (rate = 5 °C min⁻¹) (1 min) to 220 °C (rate = 15 °C min⁻¹), retention time = 15.4 min.

Discussion

A discussion of copper coupling procedures accompanies the following preparation (11.36): 3-tert-butyl-5-heptafluoroctyl-2-hydroxybenzaldehyde.

Reference

1 While compound 3 has never been reported, a similar method has been used to synthesize 1,3-bis[heptadecafluoro-octyl]-5-bromobenzene: M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi, Eur. J. Org. Chem. 2001, 4639–4649.
3-tert-Butyl-5-heptadecafluorooctyl-2-hydroxybenzaldehyde. Synthesis of Perfluoroalkylarenes from Aryl Bromides

Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson

Reaction 11.36-1

\[
\begin{array}{c}
\text{CHO} \\
\text{Br} \\
\text{OH} \\
\text{Cu, C}_8\text{F}_{17}\text{I} (2) \\
\text{DMF, 125} \, ^\circ\text{C, 5 h}
\end{array}
\quad
\begin{array}{c}
\text{CHO} \\
\text{C}_8\text{F}_{17} \\
\text{OH}
\end{array}
\]

Reagents

5-Bromo-3-tert-butyl-2-hydroxybenzaldehyde 1 [153759-58-1] is prepared by bromination of 3-tert-butyl-2-hydroxybenzaldehyde [24623-65-2] according to a literature procedure [1]. 1-Heptadecafluoro-1-iodooctane 2 [507-63-1] is available from commercial sources. Copper powder 99% for organic synthesis (Aldrich) is used as obtained.

Experimental Procedure

Copper powder (1.91 g, 30.0 mmol) is added under nitrogen to a solution of bromosalicylaldehyde 1 (1.54 g, 6.0 mmol) in dry, degassed DMF (30 mL) in a flame-dried Schlenk tube stoppered with a rubber septum [1]. The suspension is heated at 125 °C under stirring. 1-Heptadecafluoro-1-iodooctane 2 (3.2 mL, 12.1 mmol) is added dropwise with a syringe in four equal portions (0.80 mL each); the reaction is stirred for 40 min after each addition and then left for a further 2 h. The suspension is allowed to cool to room temperature, treated with water (30 mL) and diethyl ether (40 mL), and filtered using a Büchner funnel. The solid residue is washed with diethyl ether (3 × 20 mL). The aqueous phase is extracted with diethyl ether (3 × 15 mL). The combined organic layers are washed with brine (20 mL), dried over Na₂SO₄ and the solvent removed under reduced pressure. The residue is purified by column chromatography (silica gel, petroleum ether/diethyl ether 9/1), affording 3 (2.72 g, 76%) as a white solid, mp 54 °C: 1H NMR (CDCl₃) δ 1.43 [s, 9 H, C(CH₃)₃], 7.57 (d, J = 2.5 Hz, 1 H), 7.66 (br s, 1 H), 9.93 (s, 1 H, CHO), 12.13 (s, 1 H, OH); 19F NMR (CDCl₃) δ −81.1 (t, J = 10 Hz, 3 F), −111.2 (t, J = 13 Hz, 2 F), −121.8 (br s, 2 F), −122.3 (br s, 6 F), −123.0 (br s, 2 F), −126.4 (br s, 2 F); 13C NMR (CDCl₃) δ 28.9, 35.2, 104–119 (m, C₈F₁₇), 120.1, 131.0, 131.5, 139.8, 163.7, 196.5.

Discussion

Perfluoroalkyl-substituted aromatic compounds are useful intermediates in the synthesis of more complex fluorous molecules. Several methods have been developed to introduce one
or more perfluoroalkyl (R_f) groups into aromatic substrates, among which are free-radical reactions promoted by light, heat or various initiators [2], the use of electrophilic perfluoroalkylating agents [3] and coupling reactions of perfluoroalkyl organometallic reagents [4]. The coupling reaction of perfluoroalkylcopper reagents with aromatic halides is particularly useful for the preparation of fluorous building-blocks because it occurs exclusively at the halogen site(s) and is compatible with the presence of a wide range of functional groups [5].

Perfluoroalkylcopper reagents are easily obtained when perfluoroalkyl iodides are heated with finely divided copper metal in coordinating solvents such as DMF or DMSO. The coupling reactions can be conveniently carried out by using perfluoroalkylcopper species generated in situ when a mixture of R_fI, Cu and aromatic halide in the appropriate solvent is heated to 110–130 °C. Since reactivity of aromatic halides follows the order ArCl < ArBr < ArI, the iodides are often chosen as starting materials for the preparation of fluorous aromatic building-blocks [6]. However, aryl (poly)iodides bearing additional functional groups are often expensive or not commercially available and the preparation of these compounds can be non-trivial. They can be usefully replaced by the corresponding, more easily accessible aryl (poly)bromides as exemplified here and in literature reports [1, 7]. Longer, but still reasonable, reactions times are required to bring the coupling to completion, as expected on the basis of the reactivity order. A slight excess of R_fI is necessary, and its addition is staggered so that there is full conversion of the aryl (poly)bromides into the corresponding perfluoroalkyl derivative. When more than one bromine atom is present in the aromatic substrate, a careful choice of the reaction conditions allows introduction of the desired number of perfluoroalkyl substituents, as in the case of the copper-mediated coupling reaction between 1,3,5-tribromobenzene and 2 equiv of 2 to give 3,5-bis(heptadecafluorooctyl)-1-bromobenzene as the main product in 60% yield [1]. The presence of substituents other than halides (e.g. -COOR, -R, -OR, OCOR, COR) is well-tolerated, but aromatic aldehydes usually give perfluoroalkylation products in very low yields because of extensive decomposition under the reaction conditions [8]. When the carbonyl group is both sterically hindered and hydrogen bonded to an ortho-substituent, as in the case of aldehyde 3, the reaction proceeds in good yields and selectivities.

References

The Immobilization of Boronic Acids with a Fluorous Diol

Feng-Ling Qing

Reaction 11.37-1

Step A

\[(C_6F_{13}CH_2CH_2)_3SiBr \rightarrow (C_6F_{13}CH_2CH_2)_3Si\]  
\[\text{Et}_2O, 20^\circ C, \text{NH}_4\text{Cl}\]  
\[2, 98\%\]

Step C

\[(C_6F_{13}CH_2CH_2)_3Si\]  
\[\text{Et}_2O/\text{pentane}, 4 \text{ Å MS, rt}\]  
\[4, 90\%\]

Reagents

Bromotris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane 1 [201740-57-0] can be prepared according to the literature procedure [1]. FC-77 [86508-42-1] (mainly perfluoro-2-n-butyltetrahydrofuran) is commercially available from 3 M.

Experimental Procedure

Step A. 2-Propenyltris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane (2) To a freshly prepared allyl Grignard reagent (30 mmol) in ether (40 mL), a solution of fluorous bromosilane 1 (9.1 g, 7.4 mmol) in ether (30 mL) is slowly added at 20 °C under nitrogen atmosphere. The reaction mixture is allowed to reflux overnight, cooled to room temperature, and quenched with aqueous NH_4Cl. The aqueous phase is further extracted with ether, and the combined organic layer is dried over MgSO_4, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, hexane) afford pure fluorous allylsilane 3 (8.6 g, 98%): 1H NMR (CDCl_3, 300 MHz) δ 5.73 (m, 1 H), 4.97 (m, 2 H), 2.08 (m, 6 H), 1.70 (d, J = 8.1 Hz, 2 H), 0.9 (m, 6 H); 19F NMR (CDCl_3, CF_3COOH, 282 MHz) δ −81.43 (s, 9 F), −116.69 (m, 6 F), −122.52 (s, 6 F), −123.48 (s, 6 F), −123.84 (s, 6 F), −126.77 (m, 6 F); IR (thin film) 1635, 1363, 1240, 1208, 1146, 1074, 908 cm\(^{-1}\); MS (EI, 70 eV, m/z) 639, 309, 289, 239. Anal. calc. for C_{27}H_{17}F_{39}Si: C 28.19; H 1.53; F 66.76. Found: C 28.61; H 1.61; F 66.28.
**Step B. 3-[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoroctyl)silyl]-1,2-propanediol (3)**

In a three-necked flask, NMNO (1.48 g, 11 mmol) and compound 2 (8.5 g, 7.7 mmol) are dissolved in acetone (20 mL) and H₂O (2 mL). The mixture is cooled to 0–5 °C, and a 4% aqueous solution of OsO₄ (0.64 mL) is added via a syringe. After stirring for 1 h, the mixture is warmed to room temperature, and the stirring is continued until TLC indicated complete conversion of 2 into 3. Saturated aqueous NaHSO₄ (5 mL) was added. The mixture is extracted with FC-77 (3 x 10 mL). The combined fluorous layer is washed with H₂O and evaporated to give pure compound 3 (8.7 g, 99%): ¹H NMR (CDCl₃, 300 MHz) δ 3.88 (m, 1 H), 3.68 (dd, J₁ = 10.5 Hz, J₂ = 10.5 Hz, 1 H), 3.38 (dd, J₁ = 10.5 Hz, J₂ = 8.0 Hz, 1 H), 2.13 (m, 6 H), 1.93 (br, 2 H), 0.95 (m, 6 H), 0.82 (m, 2 H); IR (thin film) 3383, 2949, 1443, 1240, 1208, 1145, 904, 707 cm⁻¹; MS (EI, 70 eV, m/z) 721, 289, 239, 69. Anal. calc. for C₂₇H₁₉O₂F₃₉Si: C 28.32; H 1.66; F 64.77. Found: C 28.43; H 1.72; F 65.72.

**Step C. 2-Phenyl-4-[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)silyl]methyl]-1,3,2-dioxaborole (4)**

A solution of compound 3 (0.46 g, 0.40 mmol) in anhydrous ether (2 mL) is added to a mixture of 4 Å molecular sieve (0.3 g) and phenylboronic acid (55 mg, 0.45 mmol). Then anhydrous pentane (8 mL) is added, and the mixture is stirred at room temperature. When the reaction is complete, as detected by TLC, the mixture is filtered, concentrated in vacuo, and dissolved in FC-77 (5 mL). The fluorous solution is washed with anhydrous acetonitrile (1 mL), and evaporated to afford the fluorous boronates 4 (0.44 g, 90%): ¹H NMR (CDCl₃, 300 MHz) δ 7.73 (d, J = 8.1 Hz, 2 H), 7.46 (m, 1 H), 7.36 (t, J = 8.1 Hz, 2 H), 4.72 (m, 1 H), 4.54 (t, J = 8.1 Hz, 1 H), 3.92 (t, J = 8.1 Hz, 1 H), 2.14 (m, 6 H), 1.17 (m, 2 H), 1.02 (m, 6 H); IR (thin film) 2908, 1605, 1502, 1443, 1240, 1212, 1145, 1096, 904, 746 cm⁻¹; MS (EI, 70 eV, m/z) 1230 (M⁺), 527, 367, 227. Anal. calc. for C₃₃H₂₂O₂F₃₉SiB: C 32.02; H 1.79; F 60.24. Found: C 31.84; H 1.60.

**Discussion**

Boronic acids are important intermediates in organic synthesis. For example, boronic acids are widely used in Suzuki cross-coupling reactions [2]. However, the isolation and purification compounds containing a boronic acid functionality by conventional methods can prove to be notoriously troublesome, as a result of their amphiphilic character. To facilitate the synthesis and separation of functionalized boronic acids, several groups have recently reported the preparation of several types of polymer-bound diols that can be used as linkers to immobilize boronic acids [3]. Fluorous phase synthesis is developing into a viable alternative to solid-phase techniques in organic synthesis. The synthesis performed in homogeneous media overcomes some drawbacks of heterogeneous reactions associated with solid-phase synthesis. In principle, any solid-phase synthetic technology has a counterpart in fluorous synthesis. Thus, we have prepared the fluorous diol 3. A series of boronic acids are attached to a fluorous diol 3 by esterification. We have carried out the Suzuki reaction of fluorous boronates 4 as a detagging process. Although normal boronic acids or esters were replaced by fluorous boronates, we do not find any retarding effect for the Suzuki-coupling reaction from perfluoroalkyl chains. The fluorous diol 3, which partitions into FC-77, is completely recovered from repeated FC-77/CH₂Cl₂ extractions. The coupling product is obtained by the concentration of the CH₂Cl₂ layer followed by flash chromatography.
Ytterbium(III) Tris(trifluoromethylsulfonyl)methide. Preparation of a Highly Active Lanthanide Catalyst

Anthony G. M. Barrett, D. Christopher Braddock, and Jérôme J.-P. Peyralans

Reaction 11.38-1

Step A

\[ \text{Me}_3\text{SiCH}_2\text{Li} \xrightarrow{\text{Ti}_2\text{O}, 0{^\circ}\text{C}} \text{Ti} \xrightarrow{\text{Tf}} \text{Tf}_2\text{O}, -78{^\circ}\text{C} \xrightarrow{\text{Et}_2\text{O}} \text{CsCTf}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{Yb(CTf}_3)_3 \]

1. 51%

Step B

2. 65%

Step C

3. ca 98%

Reagents

[Trimethylsilylmethyl]lithium [1822-00-0] solution in hexane can be prepared according to the literature procedure [1] or is commercially available typically as a 1.0 M solution. Methylene ditriflone [428-76-2] is prepared according to the procedure reported below but can also be purchased from ABCR GmbH (www.abcr.de).

Experimental Procedure [2]

Step A. Methylene Ditriflone (1) [428-76-2] 3 By means of a syringe pump, freshly distilled (from P_2O_5) triflic anhydride (7.9 mL, 46.9 mmol) is added over 1 h to a solution of (trimethylsilylmethyl)lithium (0.78 M, 120 mL, 93.8 mmol) in hexane at 0{^\circ}\text{C} taking care not to let the internal temperature rise above 5{^\circ}\text{C}. After stirring a further 1 h at 0{^\circ}\text{C}, the solution is allowed to warm to room temperature, stirred for 2 h and quenched with saturated aqueous NaHCO_3 solution (100 mL). The organic layer is separated and the aqueous layer is extracted with CH_2Cl_2 (3 × 75 mL), acidified with concentrated HCl (12 M, 50 mL) and re-
extracted with CH₂Cl₂ (3 × 75 mL). The latter combined CH₂Cl₂ extracts are dried over anhydrous MgSO₄, filtered and concentrated under vacuum. The residual yellow oil (crystals may appear) is sublimed (0.1 mmHg, water cooled cold finger, heating ~70 °C) to give methyleneditriflone 1 (3.4 g, 11.8 mmol, 51%) as a white solid, mp 33–35 °C (lit. [3b] 35 °C); 1H NMR (300 MHz; CDCl₃) δ 4.98 (br s, 2 H); 13C NMR (75 MHz; CDCl₃) δ 118.7 (q, J ¼ 327 Hz), 64.0; 19F (376 MHz; CDCl₃) δ −75.1.

Step B. Cesium(I) tris(Trifluoromethylsulfonyl)methide (2) [114395-68-5] [4] A solution of t-butyl lithium (8.1 mL, 1.82 M, 14.7 mmol) in hexanes is added over 40 min to a solution of methyleneditriflone 1 (2.0 g, 7.0 mmol) in Et₂O (55 mL) at −78 °C to make the dianion. After stirring for 30 min at −78 °C, freshly distilled triflic anhydride (1.8 mL, 10.5 mmol) is added dropwise over 40 min. After 40 min at −78 °C, the solution is allowed to warm to room temperature over 2 h. The solution is concentrated under vacuum and saturated aqueous NaHCO₃ solution (60 mL) is added to the residue. The aqueous layer is extracted with CH₂Cl₂ (3 × 60 mL), acidified with concentrated HCl (12 M, 50 mL) and re-extracted with CH₂Cl₂ (3 × 75 mL). The aqueous layer is further extracted with Et₂O (3 × 60 mL), and the combined extracts are dried over anhydrous MgSO₄, filtered and concentrated to give a yellow oil consisting of lithium triflate and lithium tris(trifluoromethylsulfonyl)methide. The oil is taken up in water (4 mL) and a solution of CsCl (2.1 g, 12.3 mmol) in water (3 mL) is added to precipitate cesium(I) tris(trifluoromethylsulfonyl)methide 2. The beige precipitate obtained is isolated by filtration and concentrated sulfuric acid (98%, 4 mL) is added. Sublimation of the resultant slurry (0.1 mmHg, acetone/dry-ice cooling, heating 100–110 °C) gives free acid tris(trifluoromethylsulfonyl)methane, HCTf₃, [60805-12-1] as a low melting white solid. The solid is taken up in H₂O (4 mL) and a solution of CsCl (2.1 g, 12.3 mmol) in water (3 mL) is added. The precipitate obtained is isolated by filtration and recrystallized from water (~10 mL) to obtain cesium(I) tris(trifluoromethylsulfonyl)methide 2 (2.5 g, 4.6 mmol, 65%) as white platelets, mp 324–326 °C; 13C NMR (75 MHz; CD₃CN) δ 121.7 (q, J = 326 Hz), 83.8; 19F (376 MHz; CD₃CN) δ −76.6; MS (electrospray, negative ions) 410.9 (Tf₃C⁻).

Step C. Ytterbium(III) Tris(trifluoromethylsulfonyl)methide (3) [224317-61-7] [2] Concentrated H₂SO₄ (sp. gr. 1.835, 0.7 mL, approx. 10 equiv) is added to cesium salt 2 (0.744 g, 1.37 mmol) in a sublimation pot and the slurry is sublimed (1.5 mmHg, 100 °C rising to 160 °C). The liberated free acid is taken up in H₂O (2 mL) and treated with a saturated aqueous solution of BaCl₂ (6 mL) to remove sulfate impurities. The resulting white precipitate in a colorless solution is extracted with Et₂O (3 × 50 mL) and the aqueous component is saturated with solid NaCl and re-extracted with Et₂O (50 mL). The combined ethereal extracts are concentrated and the residue is sublimed (1.5 mmHg, 100 °C). The resultant purified free acid is taken up in H₂O (25.00 mL) and titrated (4 × 0.2 mL aliquots) against a standard NaOH solution (0.9995 M, phenolphthalein indicator). In a series of separate experiments the titrations reveal that aqueous solutions of the free acid are produced in 88–98% yield from 2.

Solid Yb₂O₃ (100 mg, 0.25 mmol) is added in one portion to a titrated aqueous solution of tris(trifluoromethylsulfonyl)methane (0.057 M, 1.27 mmol, 22.4 mL). The milky suspension is heated at reflux for 24 h and the resultant colorless solution is filtered [to remove traces of
unreacted ytterbium(III) oxide]. The filtrate is concentrated and the white solid obtained dried under vacuum (0.1 mmHg, 24 h) to give ytterbium(III) tris(trifluoromethylsulfonyl)methide \(3(0.59 \text{ g}, 0.42 \text{ mmol}, 100\%)\) as a white powder: \(^{13}\text{C} \text{NMR (100 MHz; } \text{D}_2\text{O)} \delta 122.7 (q, J = 325 \text{ Hz}), 84.1; ^{19}\text{F} \text{NMR (376 MHz; CD}_3\text{CN)} \delta -76.5.\)

Discussion

The described procedure allows for the gram scale preparation of ytterbium(III) tris(trifluoromethylsulfonyl)methide (referred to as ytterbium “triflide”). Scandium triflide may also be prepared by substituting \(\text{Sc}_2\text{O}_3\) for \(\text{Yb}_2\text{O}_3\) in the last step \[2\]. It is to be expected that this methodology could also be applied to the synthesis of all the remaining lanthanide(III) triflides. A bismuth(III) salt has also been prepared \[5\]. Ytterbium and scandium triflides have been used as catalysts (10 mol% loading) for the nitration of electron deficient aromatics (e.g., \(\text{o-nitrotoluene}\)) using 1 equiv of nitric acid where the only side product is water \[2\]. In these instances, the related ytterbium and scandium triflates are essentially ineffective under the same conditions where the relative \(pK_a\)’s of the conjugate acids (ca. –18 \[6\] versus –12, respectively) are held to be ultimately responsible \[7\]. This superior activity is expected to translate to all reactions where the triflate salts have been employed. Additionally, the triflide catalysts may be recovered from the nitration reactions and re-used by a simple evaporative procedure. They have also been applied to the nitration of fluoroaromatics where problems of HF liberation (via \(\text{SNAr}\) displacement of fluoride) do not arise, and again recycling and re-use was demonstrated \[8\]. Ytterbium triflide is the parent compound of perfluorinated homologs \([\text{Yb}(\text{SO}_2\text{C}_8\text{F}_{17})_3: n = m = 4; n = m = 6; n = 6, m = 8]\) which are prepared by modification of the above procedure \[9\]. These compounds have been employed for the first fluororous biphasic catalytic Friedel-Crafts acylation reactions \[10\], and (in benzotrifluoride) at catalyst loadings as low as 1% \[11\]. The ytterbium and scandium salts, \(\text{M}(\text{SO}_2\text{C}_8\text{F}_{17})_3\) (\(\text{M} = \text{Yb, Sc}\)), have been reported as recyclable fluororous catalysts for the acetylation of alcohols, Diels-Alder cycloadditions and the Mukaiyama aldol reaction \[12\, 13\]. The scandium salt has also been employed for the same reactions in supercritical carbon dioxide with recycling by tuning the supercritical versus liquid phase \[14\].

References

Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)cyclopenta-1,3-diene. Preparation from Cyclopenta-1,3-diene, 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-iodooctane and 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Triflate

Tomaš Bríza, Jaroslav Kvičala, and Oldřich Paleta

Reaction 11.39-1

**Step A**

1) BuLi, diethyl ether

-80 °C to rt, 10 min

2) 1, rt overnight

**Step B**

1) BuLi, dimethoxyethane

-80 °C to -10 °C, 10 min

2) 3, reflux, 30 min

<table>
<thead>
<tr>
<th>Step</th>
<th>Reagents</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BuLi, diethyl ether</td>
<td>C₆F₁₃</td>
</tr>
<tr>
<td>B</td>
<td>BuLi, dimethoxyethane</td>
<td>C₆F₁₃</td>
</tr>
</tbody>
</table>

2. 84%

3. 58%

Reagents

Cyclopentadiene [542-92-7] is prepared by distillation of commercially available (Aldrich) dicyclopentadiene [77-73-6] [1]. 1.1.1.2,2.3,3,4,4,5,5,6,6-Tridecafluoro-8-iodooctane [1] [2043-57-4] is commercially available from Aldrich or Fluorochem. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl triflate [3] [78522-69-7] can be prepared according to the literature procedure [2] from commercially available (Aldrich, Fluorochem) 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-octan-1-ol [647-42-7] and triflic anhydride [358-23-6].
Experimental Procedures

**Step A.** 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Cyclopenta-1,3-diene (2) A flask equipped with a magnetic stirbar is charged with THF (50 mL), freshly distilled cyclopentadiene (1.00 g, 15.1 mmol) and cooled to −80 °C, followed by the addition of butyllithium solution (6.85 mL, 2.2 M in hexanes, 15.1 mmol) by a syringe. The reaction mixture is then allowed to warm to rt while stirring and polyfluoroiodooctane 1 (7.20 g, 18.2 mmol) in THF (10 mL) are added. The mixture is then stirred overnight at rt. The reaction is quenched by dropwise addition of ammonium chloride solution (20%, 20 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers are dried with anhydrous magnesium sulfate. The drying agent is filtered and the dissolved salts are removed on a chromatographic column (silica, 10 × 2.5 cm, eluent hexane). Removal of solvents on a rotary vacuum evaporator affords mono(fluoroalkylated) cyclopentadiene 2 (5.27 g, 84.2%, light-yellow liquid).

**Step B.** bis(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)cyclopenta-1,3-diene (4) A flask is charged with fluorocyclopentadiene 2 (1.50 g, 3.63 mmol) and 1,2-dimethoxyethane (50 mL). The mixture is cooled to −80 °C while stirring and butyllithium solution (1.78 M in hexanes, 2.2 ml, 3.9 mmol) is added by syringe. The mixture is then warmed to 0 °C, and stirred for 10 min. Then it is cooled again to −80 °C and a solution of fluoroalkyl triflate 3 (2.30 g, 4.63 mmol) in 1,2-dimethoxyethane (10 mL) is added dropwise. The mixture is then heated to reflux for 30 min and cooled to room temperature. Solvents are removed on a vacuum rotary evaporator, followed by a removal of salts on a chromatographic column (10 × 2.5 cm, eluent hexane). After evaporation of the solvent on a vacuum rotary evaporator, bis(polyfluoroalkylated) cyclopentadiene 4 (1.59 g, 58.0%, colorless liquid) is obtained by column chromatography (15 × 2.5 cm, eluent hexane) as a mixture of four regioisomers (1,2-, 1,3-, 1,4- and 2,3-disubstituted) in the 21:40:23:16 ratio (1D and 2D 1H NMR): IR (neat) 2937, 1460, 1365, 1317, 1239, 1202, 1145 cm⁻¹; 1H NMR (300.1 MHz, CDCl₃) regioisomer 4A (1,2-) 2.23 (4 H, m), 2.56 (4 H, m), 2.88 (2 H, t, 3JHH = 1:2 Hz), 6.26 (1 H, d, 3JHH = 5:5 Hz), 6.28 (1 H, d, 3JHH = 5:5 Hz, J = 1.2 Hz); regioisomer 4B (1,3-) 2.23 (4 H, m), 2.56 (4 H, m), 2.84 (2 H, quintet, 3JHH = 1:8 Hz), 5.87 (1 H, sextet, J = 1.6 Hz), 6.04 (1 H, m); regioisomer 4C (1,4-) 2.23 (4 H, m), 2.56 (4 H, m), 2.83 (2 H, sextet, J = 1.8 Hz), 6.04 (2 H, m); 13C NMR (100.6 MHz, CDCl₃) regioisomer 4A (1,2-) 17.9 (s), 21.3 (s), 30.4 (2 C, m), 43.2 (s), 108.3–121.5 (12 C, m), 131.7 (s), 133.7 (s), 138.1 (s), 143.9 (s); regioisomer 4B (1,3-) 20.6 (s), 21.3 (s), 30.4 (2 C, m), 42.9 (s), 108.3–121.5 (12 C, m), 125.0 (2 C, s), 143.9 (s), 147.2 (s); regioisomer 4C (1,4-) 21.3 (2 C, s), 30.4 (2 C, m), 44.7 (s), 108.3–121.5 (12 C, m), 127.3 (2 C, s), 143.9 (2 C, s); 19F NMR (376.5 MHz, CDCl₃) δ −81.5 (6 F, t, 3JFF = 10 Hz), −115.2 (4 F, m), −122.4 (4 F, m), −124.0 (4 F, m), −126.7 (m, 4 F). Anal. calc. for C₂₁H₁₂F₂₆: C, 33.62%; H, 1.60%. Found: C, 33.80%; H, 1.76%.

**Discussion**

Although cyclopentadienes belong to the most common ligands employed in organometallic chemistry, surprisingly little attention has been paid to the preparation of fluorous cyclo-
pentadienes. The first such ligands synthesized were cyclopentadienes directly substituted by an electron-attracting perfluoroalkyl chain, which results in poor ligand properties [3, 4]. Cyclopentadienes containing one polyfluorinated ring with an insulating spacer between the ring and perfluorinated chain displayed insufficient fluorophilic properties due to the low content of fluorine, which should exceed 60% [5].

Bis(polyfluorinated) cyclopentadienes [2, 6] which display both sufficient complexing and fluorophilic properties [7], can be synthesized by the stepwise nucleophilic substitution of polyfluorinated compounds with cyclopentadienide anions. Whereas commercially available 2-(perfluoroalkyl)ethyl iodides are preferably employed in the preparation of mono-substituted cyclopentadienes [3, 4], more reactive building blocks, 2-(perfluoroalkyl)ethyl triflates [6], are essential for successful second polyfluoroalkylation [2]. The bis(polyfluorinated) cyclopentadienes thus synthesized consist of four regioisomers and efficiently complex iron or rhodium cations [7].

References

4 V. Herrera, P. J. F. de Rege, I. T.

11.40

5,5,6,6,7,8,8,9,9,10,10-Tridecafluorodec-1-yne. Preparation from Ethynyldimethylphenylsilane and 3,3,4,4,5,5,6,6,7,7,8,8-Tridecafluoroctyl Triflate

Jaroslav Kvíčala, Tomáš Bříza, and Oldřich Paleta

Reaction 11.40-1

\[
\begin{align*}
\text{Step A} & \\
1) \text{BuLi, Et}_2\text{O} & -80^\circ\text{C} \text{ to rt, } \text{20 min} \\
2) \text{-10}^\circ\text{C} \text{ to reflux, } & \text{3h} \\
\text{Step B} & \\
\text{KF, methanol} & \text{reflux, 2h} \\
\end{align*}
\]

\[
\begin{align*}
1 & \text{Me} \text{Si-} \equiv \text{H} \\
2 & \text{Me} \text{Si-} \equiv \text{C}_6\text{F}_{13} \\
3 & \text{Me} \text{Si-} \equiv \text{C}_6\text{F}_{13} \\
4 & \text{H} \equiv \text{C}_6\text{F}_{13} \\
\end{align*}
\]
Reagents

Ethynyldimethylphenylsilane (1) [17156-64-8] is synthesized from commercially available (Aldrich) ethynylmagnesium bromide [4301-14-8] (0.5 M solution in THF) and chlorodimethylphenylsilane [768-33-2] [1]. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl triflate (2) [78522-69-7] can be prepared according to the literature procedure [2] from commercially available (Aldrich, Fluorochem) 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctan-1-ol [647-42-7] and triflic anhydride [358-23-6].

Experimental Procedures

Step A. 1-(Dimethylphenylsilyl)-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-1-yne (3)

A 25 mL flask equipped with magnetic stirrer bar is charged with ethynyldimethylphenylsilane (1, 6.00 g, 37.4 mmol) and diethyl ether (20 mL). After cooling the mixture to −78 °C, butyllithium solution (16.5 mL, 2.63 g, 41.1 mmol, 2.5 M solution in hexanes) is slowly added by syringe. The mixture is then allowed to warm to room temperature while stirring for about 20 min. The second 500 mL flask equipped with a magnetic stirrer bar and reflux condenser fitted with a septum is charged with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl triflate (2, 14.3 g, 28.8 mmol) and diethyl ether (150 mL). Solutions in both flasks are cooled to −10 °C and the contents of the first flask are transferred into the second flask by a capillary. After the mixing is completed, the mixture is refluxed for 3 h. After cooling the mixture it is extracted with water (100 mL). The water layer is separated and extracted with diethyl ether (3 × 50 mL). The combined organic layers are dried with anhydrous magnesium sulfate, then the drying agent is filtered and solvents are removed on a vacuum rotary evaporator. From the residue, unreacted ethynyl silane 1 and fluoro triflate 2 are distilled off (fraction boiling at 50–80 °C/200 Pa). The product, silylated fluoroalkyne 3, is isolated as the main fraction (6.1 g, 42%, bp 106–115 °C/200 Pa, colorless liquid): IR (CHCl 3) 3073, 2964, 2928, 2186, 1430, 1238, 1145, 1118, 1074 cm⁻¹; ¹H NMR (300.1 MHz, CDCl 3) δ 0.41 (s, 6 H), 2.40 (m, 2 H), 2.60 (t, 2 H, ³JHH = 7.2), 7.39 (m, 3 H), 7.62 (m, 2 H); ¹³C NMR (75.5 MHz, CDCl 3) δ 1.0 (s, 2 C), 12.0 (s, 1 C), 30.6 (t, 1 C, ³JCF = 21.2), 84.4 (s, 1 C), 104.8 (s, 1 C), 108.2–120.9 (bm, 6 C), 127.9 (s, 1 C), 129.4 (s, 2 C), 133.6 (s, 2 C), 137.0 (s, 1 C); ¹⁹F NMR (282.4 MHz, CDCl 3) δ –81.3 (t, 3 F, ³JFF = 10.5), –115.7 (t, 2 F, ³JFF = 15.4), –122.4 (m, 2 F), –123.3 (m, 2 F), –124.1 (m, 2 F), –126.6 (m, 2 F). Anal. calc. for C 18H15F13Si: C, 42.70%; H, 2.96%. Found: C, 42.30%; H, 3.14%.

Step B. 5,5,6,6,7,7,8,8,9,9,10,10-Tridecafluorodec-1-yn e (4)

A 250 mL flask equipped with a reflux condenser is charged with silylated polyfluorodecyne 3 (12.2 g, 24.0 mmol), methanol (150 mL) and anhydrous potassium fluoride (4.20 g, 72.3 mmol). The reaction mixture is then refluxed for 2 h. After cooling to rt, the mixture is diluted with water (100 mL). The aqueous layer is separated and extracted with pentane (2 × 50 mL). The combined organic layers are dried with anhydrous magnesium sulfate and the drying agent is filtered. The solvents are carefully removed on a vacuum rotary evaporator (40 °C/80 kPa). Deprotected fluorodecyne 4 is isolated by fractional distillation of the residue (4.5 g, 50%, bp 126–129 °C/200 Pa).
70 kPa, colorless liquid): IR (CHCl$_3$) 3320, 2964, 1451, 1241, 1146, 1113, 1075 cm$^{-1}$; $^1$H NMR (300.1 MHz, CDCl$_3$) $\delta$ 2.02 (t, 1 H, $^3$$J_{HH}$ = 2.5), 2.36 (m, 2 H), 2.52 (m, 2 H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 10.6 (s, 1 C), 30.5 (t, 1 C, $^2$$J_{CF}$ = 21.2), 69.7 (s, 1 C), 80.8 (s, 1 C), 108.2–120.9 (bm, 6 C); $^{19}$F NMR (282.4 MHz, CDCl$_3$) $\delta$ −81.3 (t, 3 F, $^3$$J_{FF}$ = 10.5), −115.7 (t, 2 F, $^3$$J_{FF}$ = 15.4), −122.4 (m, 2 F), −123.3 (m, 2 F), −124.1 (m, 2 F), −126.6 (m, 2 F); GC-MS (EI, $m/z$) 372 (4, M$^+$), 134 (5), 133 (5), 131 (5), 104 (52), 103 (100), 83 (21), 77 (8), 69 (14), 57 (5), 53 (28), 51 (7), 39 (37), 27 (5). Satisfactory elemental analysis could not be obtained due to the high volatility of the product.

Discussion

To preserve the electronic character of alkynes, at least a two carbon spacer has to connect the triple bond and the perfluoroalkyl group [3]. Internal alkynes containing a phenyl and a (perfluoroalkyl)ethyl group have been prepared by palladium catalyzed coupling of alkynylstannanes with (perfluoroalkyl)ethyl iodides [4]. Neither coupling of ethynyltributylstannane, nor reaction of ethynylmagnesium bromide or ethynyllithium with 2-(perfluoroalkyl)ethyl iodides can be employed for the preparation of analogous terminal alkynes [5]. On the other hand, the lithium salt of 2-(dimethylphenylsilyl)ethynyllithium (1) reacts with a more reactive fluorinated electrophile, 2-(perfluorohexyl)ethyl triflate (2) [6], to afford silylated polyfluoroalkyne 3, which can be deprotected by the standard desilylation protocol using potassium fluoride in methanol [7] to form the target polyfluorinated terminal alkyne 4 [5]. Polyfluoroalkyne 4 is a highly volatile compound and all manipulations with this compound have to be conducted with great care to prevent loss of material.

Terminal polyfluoroalkyne 4 is a useful fluorous building block, which can be employed in various cyclization reactions forming, for example, polyfluorinated cyclohexadienes, cyclopentadienes, arenes, or carboranes.

References

11.41

\[ \text{N,N'-Bis(1H,1H,2H,2H-perfluorooctyl)carbodiimide} \]

\text{Jesús M. Aizpurua, Claudio Palomo, and Iraida Loinaz}

\text{Reaction 11.41-1}

\text{Reagents}

\text{1H,1H,2H,2H-Perfluorooctyl iodide} [2043-57-4] was purchased from Fluka A. G. and perfluorohexane [355-42-0] from Fluorochem Ltd. \text{Methyltrioctylammonium chloride (Aliquat}^\text{2336}) [1] [5137-55-3] was available from Acros Chemical Company. \text{Triethylamine} was distilled over calcium hydride prior to use. All reagents and solvents were used without purification.

\text{Experimental Procedures}

\text{Step A. 1H,1H,2H,2H-Perfluorooctyl Amine} \quad \text{A 50 mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer and reflux condenser is charged with sodium azide (2.60 g, 40 mmol), water (6.00 mL), 1H,1H,2H,2H-perfluorooctyl iodide (4.89 mL, 20 mmol) and methyltrioctylammonium chloride (Aliquat}^\text{2336}) (0.40 g, 1 mmol). The mixture is heated overnight to 90–100 \degree \text{C (oil bath)} under stirring and then is cooled to 0 \degree \text{C. The lower phase, consisting of pure 1H,1H,2H,2H-perfluorooctyl azide, is separated by decantation using a pipette (7.70 g, 99\%)} [2] and used without purification in the next step. A high pressure hydrogenator [3] equipped with a mechanical stirrer and temperature controller is charged with diethyl ether (150 mL), 10\% Pd-C (150 mg) and 1H,1H,2H,2H-perfluorooctyl azide (7.70 g, 19.8 mmol). Hydrogen pressure is set at 150 psi and the mixture is hydrogenated over 1 h at 25 \degree \text{C.} The hydrogenation is slowly depressurized, purged with fresh hydrogen [4] and the hydrogenation is continued at 150 psi and 25 \degree \text{C for 16 h.} The reactor is...
depressurized again and the resulting ethereal solution is filtered through a pad of Celite in a funnel. The Celite is washed with dried diethyl ether (20 mL) and the solvent is carefully evaporated under reduced pressure (20 °C/20 mmHg) to afford the product as a colorless liquid; yield, 9.59 g (88%); 1H NMR (CDCl3) δ 1.30–1.21 (s, 2 H), 2.34–2.17 (m, 2 H), 3.04 (t, 2 H, J = 7 Hz); 13C NMR (CDCl3) δ 34.3 (s), 34.7 (t, JCF = 21 Hz), 125–140 (m).

Step B. N,N’-Bis(1H,1H,2H,2H-perfluorooctyl)urea  A solution of triphosgene (2.60 g, 8.80 mmol) in CH2Cl2 (13 mL) is added dropwise to a stirred cold (0 °C) mixture of the corresponding 2,2,2-trifluoroethylamine (9.59 g, 26.4 mmol), CH2Cl2 (20 mL) and 6 M NaOH (26 mL). Stirring of the mixture to room temperature is continued for 5 h, while a white precipitate is observed. The CH2Cl2 is evaporated directly from the mixture (rotavapor, carefully because of the foam) and the solid is dissolved in diethyl ether (30 mL) and washed with brine (5 × 35 mL) until neutrality. The organic layer is dried (MgSO4), evaporated and the product crystallized from methanol (50 mL); yield, 9.03 g (91%); 1H NMR (CDCl3) δ 2.48 (m, 4 H), 3.70 (s, 4 H), 6.48 (s, 2 H); 13C NMR (CDCl3) δ 32.8 (t, JCF = 21 Hz), 33.9, 159.

Step C. N,N’-Bis(1H,1H,2H,2H-perfluorooctyl)carbodiimide  A suspension of N,N’-bis(1H,1H,2H,2H-perfluorooctyl)urea (9.03 g, 12.0 mmol) in perfluorohexane (45 mL) is stirred in a dried flask under nitrogen at 0 °C and a solution of triphenylphosphine (9.44 g, 36.0 mmol) in CH2Cl2 (90 mL) is added. Then, bromine (1.84 mL, 5.75 g, 36.0 mmol) is added dropwise until a drop gives a persistent yellow color to the upper CH2Cl2 solution. Finally, triethylamine (8.36 mL, 60 mmol) is added dropwise and the reaction is vigorously stirred at 0 °C for 15 min and at room temperature for 16 h. The lower fluorous colorless solution is separated with a syringe and placed in another flask under nitrogen. The remaining CH2Cl2 brown suspension is extracted twice with perfluorohexane (2 × 8 mL) and the combined fluorous solution is evaporated in the rotavapor to afford pure carbodiimide as a colorless liquid [5]; yield, 8.72 g (99%); 1H NMR (CDCl3) δ 2.29–2.5 (m, 2 H) and the combined fluorous solution is extracted twice with perfluorohexane (2 × 8 mL) and the combined fluorous solution is evaporated in the rotavapor to afford pure carbodiimide as a colorless liquid [5]; yield, 8.72 g (99%); 1H NMR (CDCl3) δ 2.29–2.5 (m, 2 H), 3.59 (t, 2 H, J = 7 Hz); 13C NMR (CDCl3) δ 32.3 (t, JCF = 21 Hz), 38.5 (s), 105–125 (m), 139.0 (s).

Discussion

N,N’-Dialkylcarbodiimides are among the most popular dehydrating reagents, widely used despite the purification difficulties often met in separating the byproduct N,N’-dialkylureas from the polar reaction products (typically, peptides). A chromatography-free fluorous version of the peptide synthesis, based on the use of N,N’-bis(1H,1H,2H,2H-perfluorooctyl)carbodiimide, has been described recently as an alternative to the existing methods [6]. Although a different synthesis of N,N’-bis(1H,1H,2H,2H-perfluorooctyl)carbodiimide has been reported [7, 8] in 86% yield from 1H,1H,2H,2H-perfluorooctyl azide and 1H,1H,2H,2H-perfluorooctyl isocyanate by means of triphenyliminophosphorane intermediates, the method requires a careful final distillation to purify the product. The use of N,N’-bis(1H,1H,2H,2H-perfluorooctyl)urea as the carbodiimide source [9], combined with a fluorous protocol consisting of phase separation and evaporation, circumvents such a problem and ensures the reuse of spent fluorous materials [10].
References

1 Phase transfer-catalyst presented as a liquid mixture of C₈ and C₁₀ chains with C₈ predominant.
2 ¹H NMR (CDCl₃): 3.62 (t, 2 H, J = 7.0), 2.5–2.3 (m, 2 H). The presence of trace amounts of Aliquat® 336 in the product is irrelevant for subsequent reactions.
3 Model Parr-4842 from Parr Instrument Company, Volume: 350 mL, max. pressure 3000 psi.
4 An increase of pressure may be observed due to the nitrogen evolved during the reaction. To attain a complete transformation to the amine it is necessary to purge the nitrogen formed during the reaction periodically.
5 Storable under nitrogen for several months at −20 °C.
8 H. Trabelsi, F. Szönyi, N. Michel-Angeli, A. Cambon, J. Fluorine Chem. 1994, 69, 115–117. 1H,1H,2H,2H-Perfluorooctyl amine has been previously prepared in 83% yield by reduction of 1,1H,2H,2H-Perfluorooctyl azide with 98% hydrazine and Raney nickel at 60 °C.
10 Several runs of reaction C using recovered N,N’-bis(1,1H,2H,2H-perfluorooctyl) urea afforded carbodiimide yields above 95%.

11.42 tert-Butoxycarbonyl-α-aminoisobutyryl-α-aminoisobutyric Acid Benzyl Ester (Boc-Aib-Aib-OBn). Peptide Synthesis with a Fluorous Carbodiimide Reagent

 Jesús M. Aizpurua, Claudio Palomo, and Iraida Loinaz

Reaction 11.42-1
Reagents

N,N'-bis[1H,1H,2H,2H-Perfluorooctyl]carbodiimide [133600-23-4] is prepared from urea following the method described in the accompanying procedure and z-aminoisobutyric acid benzyl ester (H-Aib-OBn) [55456-01-1] is prepared according to the literature procedure [1]. Perfluoroheptanoic acid [375-85-9] and perfluorohexane [355-42-0] are commercially available from Fluorochem Ltd. All compounds are used without purification.

Experimental Procedure

A flame-dried 50 mL round-bottomed flask equipped with a magnetic stirrer is charged with dry CH2Cl2 (10 mL), benzyl z-aminoisobutyrate (0.48 g, 2.5 mmol) and z-tert-butoxycarbonylaminoisobutyric acid (0.51 g, 2.5 mmol) under a nitrogen atmosphere. A solution of bis[1H,1H,2H,2H-perfluorooctyl]carbodiimide 1 (1.97 g, 2.7 mmol) in perfluorohexane (10 mL) is added and the biphasic mixture is vigorously stirred for 24 h at room temperature. Perfluoroheptanoic acid (0.91 g, 2.5 mmol) is added to the resulting suspension, the mixture is stirred for 5 min [2], and the fluorous phase (lower) is separated with a syringe. The washing is repeated using successively a solution of perfluoroheptanoic acid (0.36 g, 1.0 mmol) in perfluorohexane (5 mL) and perfluorohexane (5 mL). Evaporation of the dichloromethane solution provides the pure product, yield: 0.70 g (74%): $^1$H NMR (CDCl3) $\delta$ 1.42 (s, 12 H), 1.55 (s, 9 H), 4.97 (s, 1 H), 5.15 (s, 2 H), 7.33 (m, 5 H). $^{13}$C NMR (CDCl3): 24.5, 25.4, 28.2, 56.2, 56.7, 67.0, 72.1, 128.0, 128.1, 128.4, 135.7, 154.8, 173.8, 174.3.

Recovery of Urea 2 The fluorous solutions are combined and evaporated in a 20 mL flask to give a syrup consisting of the impure urea/perfluorohexanoic complex 3. Kugelrohr distillation is carried out cooling the collecting bulb tubes with an acetone/dry ice bath (−78 °C). After 3 h heating at 110 °C/0.02 Torr, perfluoroheptanoic acid is separated (1.16 g, 91% recovery). The solid residue in the oven flask is crystallized from methanol to afford pure urea, yield: 1.76 g (87% recovery).

Discussion

The noncoded peptide sequence -Aib-Aib- occurring, for example, in peptaibol antibiotics [3] is a prototypical case of a difficult coupling between hindered z-z-disubstituted z-amino acids [4].

Dehydration reactions using fluorous carbodiimide 1 [5] are conducted under standard peptide synthesis conditions, as exemplified by the preparation of building block Boc-Aib-Aib-OBn [4, 6]. An important advantage of the method is the easy removal of the urea byproduct by the simple addition of perfluoroheptanoic acid to the reaction mixture, followed by perfluorohexane/dichloromethane phase separation. Under these conditions, hydrogen bonded complex 3, and the subsequent traces of the starting carbodiimide, partition
with great preference into the fluorous phase, leaving almost pure peptide in the dichloromethane layer.

References

2. A white precipitate of \( N,N' \)-bis\([1H,1H,2H,2H\)-perfluorooctyl\]urea 2 is gradually formed during the reaction, which dissolves immediately in the presence of perfluoroheptanoic acid to form the fluorous-soluble complex 3.

11.43

*N-Methyl-N-[1-(20-oxopregna-3,5-dien-3-yl)vinyl]acetamide*. Regioselective Heck Coupling Reactions with a Fluorous Tagged Bidentate Ligand to Make 2-Acylamino-1,3-butadienes

*Karl S. A. Vallin*

**Reaction 11.43-1**

![Reaction Diagram](attachment:image.png)

**Reagents**

17-\(\beta\)-Acetylandrosta-3,5-dien-3-yl triflate 1a [95667-43-9], 4-tert-butylcyclohex-1-enyl triflate 1b [77412-96-5] and 1,3-bis\(\{4-(3,3,4,4,5,5,6,6,6\)-nonafluorohexyl\}phenyl\}-phosphino)pro-
pane 3 (F-dppp) can be prepared according to literature procedures [1–3]. N-methyl-N-vinyl acetamide 2a [3195-78-6], 1-vinyl-2-pyrrolidone 2b [88-12-0], the triethylamine, Pd(OAc)$_2$ and dry DMSO are obtained from commercial sources and used without further purification. Fluorous silica gel can be prepared by the literature procedure [4], but commercially available FluoroFlash™ silica gel from Fluorous Technologies, Inc. is recommended for higher loading and better reproducibility (www.fluorous.com) [5]. Controlled microwave heating is performed with a Smith Synthesizer from Personal Chemistry (the Biotage group).

**Experimental Procedure**

A mixture of the vinyl triflate 1a (1.0 mmol), enamide 2a (2.5 mmol), triethylamine (0.121 g, 1.2 mmol), Pd(OAc)$_2$ (0.0067 g, 0.030 mmol) and ligand 3 (0.090 mmol) is stirred in 4.0 mL dry DMSO under N$_2$ in a sealed 2.0–5.0 mL process vial at 60 °C for 18 h. After complete conversion of the starting vinyl triflate, as analyzed by GC/MS or LC/MS, the reaction mixture is allowed to cool. The reaction mixture is then charged directly on to the fluorous reverse phase silica gel and the organic mixture is eluted with 200 mL, 90% methanol/10% water, to give an organic fraction. Resonances from the phosphine-based ligand could not be detected in either $^{31}$P or $^1$H NMR spectra of the crude product. The methanol is thereafter removed under reduced pressure and the salts are removed by water/ether extraction. The combined ether layers are washed with brine, dried over potassium carbonate and concentrated. A second elution of the fluorous silica gel with 50 mL 100% methanol provided some of the homocoupled byproducts and subsequent elution with THF provided a complicated phosphine mixture according to $^{31}$P NMR analysis. The α-vinylated product 4a is finally purified by column chromatography (hexane/ethyl acetate).

**Discussion**

The carbon–carbon bond forming Heck coupling is a powerful tool in both organic and medicinal chemistry and new applications and protocols are being reported continuously [6–9]. Thus, the Heck coupling of vinyl halides (or pseudohalides) with olefins, to provide 1,3-dienes, comprise a convenient approach in the synthesis of functionalized cyclohexane derivatives by cycloaddition reactions [6, 10, 11]. The described highly regioselective Heck route from vinyl triflates and enamides constitutes a valuable new method to form 2-acylamino-1,3-butadienes [3]. In addition, controlled heating by microwave irradiation [12, 13] accelerates these palladium-catalyzed internal vinylations, and full conversions were achieved after reaction times of only 15 min.

The vinylations of 1b with enamides 2a and 2b [Eqs. (1) and (2)] show that these reactions can be performed equally well with conventional heating (ΔC) or in a microwave oven (ΔMw). The microwave method is much speedier (15 min versus 18 h). The α-vinylations of the enamides 2a and 2b with the F-dppp ligand 3 (with a fluorine content of 49%) rendered essentially the same α-selectivity and catalytic activity as in those vinylations where non-fluorous dppp ligands were employed. Furthermore fluorous solid phase purification
completely removed the fluorous-tagged phosphine ligand before subsequent product isolation. This conventional and microwave-heated procedure is convenient for rapid small-scale reactions such as those used in medicinal chemistry or solution phase parallel synthesis.

\[
\begin{align*}
\text{1b} & + \text{2a} \xrightarrow{\text{Et}_3\text{N, DMSO}} \text{Et}_3\text{N, DMSO} \xrightarrow{\Delta C, 60 \degree C, 18 \text{ h}} \text{4b} \\
\text{1b} & + \text{2b} \xrightarrow{\text{Et}_3\text{N, DMSO}} \text{Et}_3\text{N, DMSO} \xrightarrow{\Delta Mw, 15 \text{ min}, 90 \degree C} \text{4b}
\end{align*}
\]

References

11.44

Marc Wende and J. A. Gladysz* 

Reaction 11.44-1

\[
\begin{align*}
\text{Step A} & \quad \text{Step B} \\
R_{\text{f8}} \text{I} \quad \text{hv} & \quad R_{\text{f8}} \text{I} \quad \text{VAZO} \\
\text{Bu}_3\text{Sn} & \quad 3.8 \text{ bar, } 110 \, ^\circ \text{C} \\
\text{1, } 78\% & \quad \text{2, } 71\%
\end{align*}
\]

Reagents

\(R_{\text{f8}}\text{I}\) (Lancaster, 97%), allyl tri(n-butyl)tin (Lancaster, 97%), and VAZO (1,1'-azobis(cyclohexanecarbonitrile); Fluka, ≥97%) were used as received.

Experimental Procedure

**Step A.** 1H,1H,2H,3H,3H-Perfluoroundec-1-ene (1)  
[1] A UV-photolysis apparatus (immersion well, Pyrex glass) [2] is charged with allyltributyltin (17.5 mL, 18.9 g, 57.0 mmol), \(R_{\text{f8}}\text{I}\) \([\text{CF}_3\text{(CF}_2)\text{I}]; 10.0 \text{ mL, 20.7 g, 37.9 mmol}\] and \(\text{CH}_2\text{Cl}_2\) (100 mL) [3], and wrapped with protective aluminum foil. The mixture is irradiated with an Original Hanau TNN 15/32 lamp for 4 h [2], and then stirred overnight. The volatiles are removed by rotary evaporation, giving a cloudy or biphasic mixture. Subsequent Vigreux distillation (0.020 bar, 54–56 °C) gives 1 as a clear liquid (13.5 g, 29.4 mmol, 78% based upon \(R_{\text{f8}}\text{I}\)) [4]: NMR (\(\delta\), \(\text{CDCl}_3\)) 1H 5.81 (ddt, \(J_{HH} = 17, 11, 7 \text{ Hz, } \text{CH}_2\text{CH}^-\)), 5.35 (dm, \(J_{HH} = 11 \text{ Hz, } \text{CH}_2\text{H}^-\)), 5.33 (dm, \(J_{HH} = 17 \text{ Hz, } \text{CH}_2\text{H}^-\)), 2.85 (dtm, \(J_{HF} = 18 \text{ Hz, } \text{CH}_2\text{H}^-\)), 36.1 (td, \(J_{CF} = 22 \text{ Hz})); 13C (\(\delta\), \(\text{CDCl}_3\)), partial 125.4 (d, \(J_{CH} = 158 \text{ Hz})), 122.6 (dt, \(J_{CH} = 160 \text{ Hz})), 36.1 (td, \(J_{CH} = 130 \text{ Hz})), 2.85 (dtm, \(J_{HF} = 18 \text{ Hz, } \text{CH}_2\text{H}^-\)), \(19\text{F NMR} (\delta, \text{CDCl}_3) - 81.5 \text{ (t, } J_{FF} = 8 \text{ Hz, CF}^-\)), -113.8 \text{ (pseudopentet, } 2 \text{ F), -122.4 (m, } 6 \text{ F), -123.3 (m, } 2 \text{ F), -123.6 (m, } 2 \text{ F), -126.8 (m, } 2 \text{ F); IR (cm}^{-1}, \text{CHCl}_3) \nu_{\text{C=C}} 1649 \text{ m.}

**Step B.** 10-iodo-9H,9H,10H,11H,11H-perfluorononadecane (2)  
[5] A Fisher-Porter bottle is charged with 1 (12.00 g, 26.08 mmol), \(R_{\text{f8}}\text{I}\) (14.24 g, 26.08 mmol) and VAZO (1,1'-azobis(cyclohexanecarbonitrile) (0.510 g, 2.09 mmol), briefly evacuated and refilled with nitrogen (3×), and then pressurized with nitrogen (3.8 bar or 55 psig). The mixture is stirred at 110 °C for 4 h and allowed to cool. The bottle is vented and the off-white solid is dissolved in refluxing hexane (ca. 75 mL). The solution is cooled to 0 °C and gels. The gel is filtered and dried by oil pump vacuum to give 2 as soft, sublimable white flakes (18.60 g, 18.49
mmol, 71%), mp 55.7 °C. In some cases, a second gel precipitation from acetone is required for purification. Although the solid product is light-stable, solutions show decomposition after several hours: NMR (δ, 1:4 v/v CF_3C_6F_5/CDCl_3) 1H 4.63 (quint, J_HH = 6.6 Hz, CHI), 3.01 (m, 2 CH_2); 13C{1H} (partial) 36.6 (t, J_CF = 23.0 Hz, CH_2), −1.2 (s, ICH). Calc. for C_{19}H_{5}F_{3}I: C, 22.68; H, 0.50. Found: C, 22.99; H, 0.37.

Discussion

There is an extensive literature on free radical chain reactions of fluorous primary alkyl iodides [6]. As illustrated by the above two procedures, one a substitution and the other an addition, many types of carbon–carbon bond forming reactions can be effected. Both photochemical and thermal initiation can be employed. Starting from R_f8I and H_2C=CHCH_2CH_2OH, an addition/reduction/iodination sequence has been used to prepare R_f8CH_2CH_2CH_2I on a 40 gram scales [7].

The first reaction works equally well with the fluorous alkyl iodides R_f6I [1], R_f10I [1], R_f8CH_2I [1], (CF_3)2CF(CF_2)6I [6c], and (CF_3)2CF(CF_2)8I [6c]. This provides a family of olefins, which can be elaborated in free radical chain reactions with PH_3 to various fluorous phosphines [1, 7]. The product of the second reaction, 2, is an example of a branched fluorous building block. This can be employed in coupling reactions to give products with “split ponytails” [5].

References

2 A quartz immersion well may also be used, and equivalent results are obtained with a Hannovia 450 W lamp or a Rayonet reactor.
3 Reactants and solvents can normally be employed without purification.
4 The product may be used directly in the next procedure. However, the rates of free radical chain reactions with PH_3 [1, 7] are more sensitive to reactant purity. Before such additions, a CF_3C_6F_11 solution of the alkene should be passed through a silica gel plug.
11.45
Tris(1,1,5,5,5-hexafluoroacetylacetonate)chromium(III). Crystallization of A Highly Fluorinated Compound from a CO2-Expanded Liquid Solvent

Philip G. Jessop, Christopher D. Ablan, Charles A. Eckert, and Charles L. Liotta

Reaction 11.45-1

Reagents and Equipment

Carbon dioxide (at least 99.9% purity) in a full-size pressurized cylinder with a full-length dip tube is available from Praxair, Nellcor, Air Products and other sources. CO2 cylinders at room temperature typically have a pressure of 57 bar (830 psi). A fluororous solid which is to be crystallized is required; commercially available Cr(hfacac)3 (hfacac = 1,1,5,5,5-hexafluoroacetylacetonate) is used here as an example.

The procedure requires a pressure vessel that (a) does not contain a stirring rotor, (b) is large enough to take at least one and preferably several uncapped glass vials, (c) is safe to use at pressures of 60–70 bar, and (d) is equipped with a rupture disk (to rupture at 100 to 200 bar), a pressure gauge, and an inlet/outlet valve capable of fine control rather than simply switching between open and closed. An acceptable vessel is the 160 mL Parr Model 4773 equipped with a 4316 gauge block assembly, a needle valve, and a 136 bar (2000 psi) rupture disk. Blast shields should be located between the vessel (when pressurized) and the operator. Blast shields should be made of polycarbonate or other impact-resistant material, and not glass or acrylic. Shields can be fabricated to match the size of the operator’s equipment or can be purchased from I2R (Instruments for Research and Industry).

The CO2 cylinder can be connected to the pressure vessel via a high pressure regulator (e.g., Matheson Model 3030-320), a fitting adapter, and a length of 1/16” stainless-steel tubing (HPLC type, available from Supelco or Alltech). The fitting adapter is required to allow the connection from the exit of the fine valve on the regulator to the 1/16” tubing; an appropriate choice is a high pressure steel 1/4” female pipe thread to 1/16” Swagelok adapter. There is no need for any pump, gas compressor, or back-pressure regulator.
Vials (4 mL, 1 dram), microstir bars (7–8 mm length), a constant-temperature water bath, and a magnetic stirrer are also required. The constant-temperature water bath can be as simple as an acrylic bath (e.g., Fisher Isotemp Model 13-873-14) fitted with an immersion circulator such as the Fisher Isotemp Model 2100. The magnetic stirrer should be sufficiently powerful to couple to the stir bars inside the steel vessel; powerful models are available from IKA.

SAFETY WARNINGS

Operators of high-pressure equipment such as that required for these experiments should take proper precautions, including but not limited to the use of blast shields and pressure relief mechanisms, to minimize the risk of personal injury. Never heat a CO2 cylinder or raise the temperature of an already-pressurized vessel. Do not perform this procedure if the CO2 cylinder is at or exposed to a temperature ≥ 30 °C.

Experimental Procedure

Place as many uncapped vials into the vessel as possible, so that they cannot fall over. Thirteen of the 4 mL vials will fit into the Model 4773 vessel at one time. Place into each vial a stir bar, a quantity of the fluorous solid [e.g., Cr(hfacac)3, 200 mg], and a quantity of an organic solvent (e.g., decane, 40, 100, or 200 μL) insufficient to completely dissolve the fluorous solid. The volume of liquid should not exceed one eighth of the volume of the vials, to allow for volumetric expansion of the liquid under CO2 pressure. Do not cap the vials. Close the vessel, place it in the water bath (prewarmed to 35 °C) over the magnetic stirrer, and turn on the magnetic stirrer. Place blast shields around the vessel to protect the operator and passers-by. After 30 min, open the connection between the vessel and the CO2 cylinder. Open up the CO2 regulator such that the vessel is exposed to the full pressure of the CO2 cylinder; when the pressure in the vessel becomes constant, close the connection to the CO2 cylinder. Allow the system to stir for 30 min and then turn off the stirrer and water bath immersion circulator. Disconnect the vessel from the CO2 cylinder and open the fine valve on the vessel slightly so that the CO2 gas escapes at a rate of approximately 1–2 mL per min. The flow rate of CO2 gas can be measured with a flow meter or an upturned, water-filled graduated cylinder in a large beaker of water. Adjust the valve twice daily to maintain this rate. After the vessel has completely depressurized (approx. 1 week), open the vessel to look for crystals in the vials. Alternatively, vent the CO2 at a much greater rate (40–60 mL min−1, taking around 4 h), open the vessel, cap the vials and leave them undisturbed at 1 bar for 1 week.

Discussion

The preparation of crystals of solid fluorous compounds (i.e., having a fluorine content of greater than 50% by mass) can be very problematic, in that the compounds often precipitate as oils rather than crystals or powders. However, the described method allows one to prepare crystals of sufficient quality for X-ray crystallography [1, 2]. The method is based upon the...
observation that the dissolution of CO\textsubscript{2} into an organic liquid increases the fluorophilicity of the liquid so that it becomes more capable of dissolving fluorinated compounds. Removing the CO\textsubscript{2} pressure removes the fluorophilicity, causing the complex to precipitate or creating a supersaturated solution. Variants of this method can be used for water sensitive compounds [3], for reaction and crystallization in one step [4], and for use and recovery of fluororous homogeneous catalysts [5].

References


3 If the fluorous solid is air- or moisture-sensitive, then the procedure must be modified in the following manner. The organic solvents must be dried and degassed before use. The CO\textsubscript{2} must have <10 ppm of O\textsubscript{2} and H\textsubscript{2}O. The loading of the vials and vessel and the unloading of the vessel should take place under a dry and inert atmosphere in a glove box. The entire exterior of the vessel should be dried before it is brought into the glove box again for unloading.

4 The crystallization can be combined with an in situ reaction by adding a liquid or soluble reagent in addition to the liquid solvent and fluorous compound. For example, put Rh\textsubscript{2}[O\textsubscript{2}C(CF\textsubscript{2})\textsubscript{3}F]\textsubscript{4} (30 mg, prepared by the published method [6]), dimethylformamide (10 \mu L) and toluene (0.4 mL) in a vial, and then follow the procedure above to obtain crystals of Rh\textsubscript{2}[O\textsubscript{2}C(CF\textsubscript{2})\textsubscript{3}F]\textsubscript{4}(DMF)\textsubscript{2} [1, 2].

5 Use a fluorous homogeneous catalyst that is soluble in the CO\textsubscript{2}-expanded solvent. Place fluorous silica, the catalyst, the organic solvent and the reagents for the reaction to be catalyzed in a vial in a vessel. Expand the solvent with CO\textsubscript{2}, as described above, for enough time for the reaction to proceed, then release the CO\textsubscript{2} pressure over 30 min. After depressurization, filter the catalyst-bearing fluorous silica from the product-bearing liquid phase. One can then re-use the catalyst/silica combination for further cycles [1].


11.46

trans-1,2-Dibromocyclohexane. The Phase Vanishing Bromination with FC-72 as a Screen Phase

Ilhyong Ryu, Hiroshi Matsubara, Hiroyuki Nakamura, and Dennis P. Curran

Reaction 11.46-1
Reagents

All reagents including perfluorohexane (FC-72) are commercially available.

Experimental Procedure

Bromine (2.1 mmol, 335 mg) was added slowly to FC-72 (1.5 mL) in a test tube (13 mm φ x 105 mm) with a septum by using a glass pipette and then cyclohexene (2 mmol, 164 mg) in hexane (1.5 mL) was added slowly, forming three layers. The test tube was covered with aluminum foil in order to shield the reaction from light and kept at room temperature. Gentle stirring of the bromine layer using a magnetic stirrer was carried out, taking care not to mix the three layers. After 4 h, the bromine layer disappeared leaving two colorless layers. The upper hexane layer was taken up with a pipette. Then, additional hexane (2 mL x 4) was placed on the residual FC-72 layer, followed by decanting off. The combined hexane layer was washed with aqueous 2% Na₂S₂O₃ (30 mL) and water (30 mL), dried over MgSO₄, and concentrated. Purification by a short column chromatography on silica gel with hexane gave trans-1,2-dibromocyclohexane (1.8 mmol, 435 mg) in 90% yield.

Discussion

Generally, the bromination of alkenes requires careful slow addition of bromine and cooling to avoid heat evolution, which can cause undesirable side reactions [2]. The PV bromination method, which relies upon a diffusion of reagent through a fluorous “liquid membrane” regulator to adjust the addition, can circumvent such a tedious reaction procedure. The PV bromination can be performed without any stirring, although it takes 2 days to finish.

The concept of the “phase-vanishing” (PV) method is applicable to other exothermic reactions, such as demethylation of aryl methyl ethers by boron tribromide [1], Friedel-Crafts acylation using tin tetrachloride [3], and bromination of alcohols by phosphorous tribromide and thionyl bromide [4]. While the original PV reaction takes advantage of the triphasic system based on the density of three layers (organic (top), fluorous (middle), and heavier reagents (bottom)), recent efforts enabled us to apply reagents even lighter than FC-72 (d = 1.67) by using a triphasic U-tube system [5, 6]. A U-tube holds a lower fluorous phase that serves as a phase screen to separate the upper reagent and organic phases (d < 1.67). The substrate added in the organic phase reacts with the reagent regularly transported through the fluorous phase to afford a product, and the reagent phase vanishes as it is consumed. The chlorination of alcohols using thionyl chloride (d = 1.63) and phosphorous trichloride (d = 1.57) as a lighter reagent has been accomplished using the triphasic U-tube system [4]. It is now possible to conduct reactions with controlled addition rates of various unfluorinated reagents by the fluorous phase-screen, independent of whether the reagent is more or less dense than the phase screen.
1-Hydroxymethyladamantane. Radical Hydroxymethylation with a Fluorous Tin Hydride

Ilhyong Ryu, Hiroshi Matsubara, and Dennis P. Curran

Reaction 11.47-1

\[ \text{I} \xrightarrow{\text{AIBN (10 mol%), 90}^\circ \text{C, 3 h}} \text{F-626, t-BuOH} \]

\[ \text{NaBH}_3\text{CN (1.5 equiv.), CO (80 atm)} \]

\[ \text{85\% (first run)} \]

\[ \text{80\% (second run)} \]

\[ \text{1 \text{is} (C}_6\text{F}_{13})_3\text{SnHCH}_2\text{CH}_2 \]

Reagents

\[ \text{1H,1H,2H,2H-Perfluorooctyl-1,3-dimethylbutyl ether (F-626) can be prepared according to the literature procedure [1].} \]

\[ \text{tris(1H,1H,2H,2H-Perfluorooctyl)stannane (fluorous tin hydride, \text{1}) is commercially available from Fluorous Technologies, Inc. (www.fluorous.com) or can be prepared according to the literature procedure [2].} \]

\[ \text{Perfluorohexane (FC-72) is commercially available.} \]

Experimental Procedure

\textbf{Caution:} Carbon monoxide is highly poisonous and all operations should be carried out in a fume hood; high pressure experiments should be carried out with suitable precautions. 1-Iodoadamantane (262 mg, 1.0 mmol), fluorous tin hydride \text{1} (68 mg, 0.05 mmol), sodium cyanoboroxydride (94 mg, 1.5 mmol), \text{a,a'-azobisisobutyronitrile} (17 mg, 0.1 mmol), F-626 (1 mL), and t-butyl alcohol (1 mL) were placed in a 30 mL stainless-steel autoclave lined with a glass liner. The autoclave was closed and purged two times with 10 atm of carbon monoxide, pressurized with 80 atm of carbon monoxide and stirred for 3 h at 90 \degree \text{C}. After cooling, excess CO was discharged and the mixture was diluted with CH}_2\text{Cl}_2 (20 mL), washed twice with H}_2\text{O} and then three times with FC-72 (30 mL total). The CH}_2\text{Cl}_2 layer was dried over MgSO}_4, and concentrated \textit{in vacuo}. The residue was purified by column chromatography on
silica gel (8 mm × 40 mm) eluting with hexane/ethyl acetate (2:1) to afford 1-hydroxymethyladamantane (142 mg, 85%) [3]. The FC-72 solution was dried over MgSO\(_4\) and evaporated to give 1.45 g of F-626 solution containing fluorous tin hydride 1, which was reused for the second run to give 133 mg (80%) of 1-hydroxymethyladamantane.

**Discussion**

Many useful radical carbonylations of organic halides [4] employ tin reagents, such as tributyltin hydride and allyltributyltin, as radical mediators [5]. In many tin-mediated radical processes, separation of products and triorganyltin residues is often tedious. In the present case, since a catalytic amount of fluorous tin hydride is used in combination with an excess amount of NaBH\(_3\)CN, the three-phase workup procedure [aqueous/organic/fluorous], which was originally used for catalytic “Giese type” addition [2], is applicable.

BTF (benzotrifluoroide) is an amphiphilic solvent available for hydroxymethylation of organic halides using a fluorous tin hydride [6]. The above procedure using a high boiling fluorous solvent F-626 [bp 80 °C (9 Torr)] has an advantage of convenient reuse of the solution containing fluorous tin hydride for the second experiment. The method of recycling of both fluorous solvents and reagents can be generalized to other fluorous reactions.

**References**


**11.48**

5,5-Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroocetyl)-2-(4-formylphenyl)-1,3-dioxane. Selective Acetal Formation with Fluorous 1,3-Diol Reagents and its Use in Multistep Synthesis

*Roger W. Read and Chutian Zhang*

**Reaction 11.48-1**
Reagents

2,2-Bis(3,4,5,6,7,8,8,9,9-tridecafluorooctyl)-1,3-propanediol 1 can be prepared according to the literature procedure [1, 2]. Fluorous silica gel can be prepared by the literature procedure [3], but commercially available FluoroFlash™ silica gel from Fluorous Technologies, Inc. (www.fluorous.com) is recommended for higher loading and better reproducibility.

Experimental Procedure

Diol 1 (1.101 g, 1.43 mmol), Amberlyst® 15 ion exchange resin (0.150 g) and 4 Å molecular sieves (6.1 g) are added sequentially to a solution of terephthalaldehyde (0.385 g, 2.87 mmol) in benzotrifluoride (BTF) (25 mL) and the mixture is stirred vigorously for 20 h at ambient temperature. The mixture is filtered under suction, the solid residue is washed well with Et2O (ca. 300 mL), and the combined filtrate and washings are evaporated to dryness under vacuum. The resulting solid is loaded on to a FluoroFlash silica gel column (10 g). Elution with 70:30 MeOH/H2O (200 mL) gives unreacted dialdehyde, while further elution with pure MeOH (200 mL) gives 5,5-bis(3,4,5,6,7,8,8,9,9-tridecafluorooctyl)-2-(4-formylphenyl)-1,3-dioxane 2 (1.036 g, 82%). Elution with Et2O (200 mL) gives 1,4-bis[5,5-bis(3,4,5,6,7,8,8,9,9-tridecafluorooctyl)-1,3-dioxane]benzene (0.144 g, 12%).

Discussion

Acetal (used here to include the older term ketal) formation is frequently used in organic synthesis in the protection of alcohols and, in a reciprocal sense, of aldehydes and ketones [4]. The acetal group is generally stable to basic conditions, but is prone to cleavage under a variety of acidic conditions, and can in some cases be partly cleaved to yield useful intermediates for further transformations. In its fluorous modification, in addition to protection, acetal formation can provide a means of tagging appropriate substrates with fluorous groups that can then be used in efficient fluorous solid phase extraction. Normally, 1,3-alkanediols react more rapidly with aldehydes than with ketones to form 1,3-dioxanes, and this is also observed in the reactions with fluorous 1,3-diols, as for example the selective reaction of the aldehyde group in 4-formylacetophenone [2b, 2c].

In this procedure a two-fold excess of terephthalaldehyde is reacted with fluorous diol to selectively tag one aldehyde group, leaving the remaining aldehyde group to undergo further reaction. Solid phase extraction over FluoroFlash silica gel allows rapid separation of the fluorous acetal from excess dialdehyde and other organic contaminants. Subsequent chemistry has provided a route to 4-formylacetophenone and various ketone derivatives through sequential Grignard reaction, pyridinium dichromate oxidation, ketone modification (as appropriate, including hydrazone formation and aldol condensation), and acetal cleavage [2c,5].
Fluorous diols have not been used previously as reagents in acetal formation.

References


11.49

1-(4-Methoxyphenoxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol. The Amination Reaction

Using a Fluorous Isatoic Anhydride Scavenger to Remove Excess Amine

Weizhang and Christine Hiu-Tung Chen

Reaction 11.49-1

![Reaction diagram]

\[ \text{MeO} \begin{array}{c} \text{O} \\ \text{MeO} \end{array} + \begin{array}{c} \text{HN} \\ \text{N} \end{array} \xrightarrow{1.5 \text{ equiv}} \begin{array}{c} \text{O} \\ \text{MeO} \end{array} \xrightarrow{1} \text{CH}_2\text{Cl}_2, 60 \degree \text{C}, 6 \text{ h} \xrightarrow{2} 1, 2.5 \text{ h} \xrightarrow{3} \text{spe} \]

scavenger 1 is
Reagents and Materials

Fluorous isatoic anhydride 1 \([1\{1H,1H,2H,2H,3H,3H\text{-perfluoroundecyl}\}1H\text{-benzo[d]-}[1,3]\text{o}xazine-2,4-dione]\) is commercially available from Fluorous Technologies, Inc. (www.fluorous.com) or can be prepared by N-alkylation of isatoic anhydride with 1\(H,1H,2H,2H,3H,3H\text{-perfluoroundecyl iodide}\) using sodium hydride as a deprotonation agent. FluoroFlash™ cartridges from Fluorous Technologies, Inc. are used for solid-phase extraction (SPE).

Experimental Procedure

To a solution of glycidyl 4-methoxyphenyl ether (18 mg, 0.10 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL) is added 1-(2-pyridyl)piperazine (23 mg, 0.15 mmol) [1]. After stirring at 60 °C for 6 h, fluorous isatoic anhydride 1 (43 mg, 0.07 mmol) is added and the reaction mixture is stirred at 60 °C for an additional 2.5 h. The reaction mixture is concentrated to ~0.3 mL and loaded onto a 5 g FluoroFlash™ cartridge pre-conditioned with 80:20 MeOH/H\(_2\)O on an SPE manifold. Initial elution with 80:20 MeOH/H\(_2\)O (10 mL) and evaporation of the solvent provides 1-(4-methoxyphenoxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol (34 mg, 100%). Further elution with MeOH (20 mL) gives a mixture fluorous compounds containing the scavenged amine species.

Discussion

Unwanted species can be quenched with fluorous scavengers and removed from a reaction mixture by fluorous solid-phase extraction [2]. Both the reaction and the scavenging process are performed in a homogeneous solution-phase environment. The scavenged species can be recovered from the fluorous silica gel if necessary. In addition to fluorous isatoic anhydride 1, other fluorous scavengers such as 1\(H,1H,2H,2H\text{-perfluorodecyl isocyanate}\) [1] (electrophilic scavenger) and 1\(H,1H,2H,2H\text{-perfluorodecane-1-thiol}\) [3] (nucleophilic scavenger) have been developed. This technique has a potential utility in the solution-phase parallel synthesis of small molecules and natural products.

References

Borane-(1H,1H,2H,2H-Perfluorodecyl) Methyl Sulfide Adduct. Preparation of a Borane-Fluorous Dialkyl Sulfide and its Application to the Hydroboration of β-Pinene

David Crich, Mitesh Patel, and Santhosh Neelamkavil

Reaction 11.50-1

\[ \text{Step A}\]

\[ \text{Step B}\]

\[ \text{Step C}\]

\[ \text{Step D}\]

Reagents

(1H,1H,2H,2H-Perfluorodecyl) Iodide 1 [2043-53-0] and perfluorohexane [355-42-0] are widely available commercially.

Experimental Procedures

**Step A. S-(1H,1H,2H,2H-Perfluorodecyl) Thioacetate (2)** A dry 1 L round-bottomed flask is charged with a stir bar, potassium thioacetate (4.0 g, 35.1 mmol), and DMF (400 mL). The mixture is stirred at room temperature until a homogeneous solution is obtained before 1 (20.0 gm, 34.8 mmol) is added. After stirring at room temperature for 3 h, diethyl ether (400 mL) is added and stirring is continued for 15 min. The reaction mixture is then transferred into a separating funnel, and is washed successively with saturated aqueous NH₄Cl (120 mL), brine (100 mL), water (100 mL), and again with brine (50 mL). The ethereal solution is dried over Na₂SO₄, then concentrated at room temperature by rotary evaporation. Purification of the residue by chromatography over silica gel (EtOAc/hexane, 1:40) gives 1 (14.6 g,
80%) as a colorless solid [1], mp 31 °C: $^1$H NMR (CDCl$_3$) $\delta$ 3.11–3.06 (m, 2 H), 2.47–2.29 (m, 2 H), 2.36 (s, 3 H).

**Step B. (1H,1H,2H,2H-Perfluorodecyl) Methyl Sulfide (3)** Thioacetate 2 (10.0 g 19.1 mmol) is dissolved under a nitrogen atmosphere in dry MeOH (100 mL) in a 250 mL round-bottomed flask, then cooled to 0 °C in an ice bath. Freshly prepared NaOMe in MeOH (20 mL of 2.4 M) is then added over 5 min. Stirring is maintained for 45 min then methyl iodide (3.0 mL, 47.9 mmol) in dry MeOH (15 mL) is added over 10 min while the temperature is maintained at 0 °C. The reaction mixture is allowed to warm to room temperature and is then stirred for 2 h before ice water (100 mL) is added. The reaction mixture is extracted with CH$_2$Cl$_2$ (200 mL), and the extracts are washed with brine (100 mL), then dried over Na$_2$SO$_4$ before concentration by rotary evaporation at water aspirator vacuum below 30 °C [2]. Purification of the concentrate by chromatography over silica gel (hexane) provides 3 (8.7 g, 91%) as a colorless oil [1]: $^1$H NMR (C$_6$D$_6$) $\delta$ 2.28 (m, 2 H), 2.10–1.95 (m, 2 H), 1.55 (s, 3 H).

**Step C. Borane-(1H,1H,2H,2H-perfluorodecyl) Methyl Sulfide Adduct (4)** A steady stream of diborane gas [generated by dropwise addition at room temperature of BF$_3$-OEt$_2$ (10.3 mL, 81 mmol) to a stirred solution of NaBH$_4$ (2.7 g, 71 mmol) in 2-methoxyethyl ether (20 mL)] is passed, over 15 min, into neat 3 (5.0 g, 10.2 mmol) in a two-necked pear-shaped flask, that had been well flushed with nitrogen, until complete solidification is achieved. Excess diborane is purged with nitrogen to give a white solid (5.1 g) comprised of a mixture of adduct 4 and the sulfide 3, which may be manipulated in air and which is best stored under nitrogen in the refrigerator [1]. Analysis of this mixture by $^1$H NMR spectroscopy in C$_6$D$_6$ shows it to be a 1:1 mixture of 3 and 4: $^1$H NMR of 4 (C$_6$D$_6$) $\delta$ 2.10–1.90 (m, 4 H), 1.29 (s, 3 H).

**Step D. Hydroboration of β-pinene** A 1:1 solid mixture of 3 and 4 (0.64 g, 0.64 mmol of 4) is added over 5 min under nitrogen to a stirred solution of β-pinene (0.20 mL, 1.3 mmol) in a biphasic mixture of dry CH$_2$Cl$_2$ (9.0 mL) and dry perfluorohexane (9.0 mL) at 0 °C. The reaction mixture is then stirred at 0 °C for 3 h, before it is allowed to warm to room temperature. The lower perfluorohexane layer is removed with a pipette and fresh perfluorohexane (9.0 mL) is added, followed by stirring for 10 min. After separation of the phases, the perfluorohexane layers are combined and concentrated by rotary evaporation at water aspirator vacuum below 30 °C [2] to give recovered 3 (0.55 g, 88%). 3 M NaOH (0.24 mL) and 30% H$_2$O$_2$ (0.12 mL) are added to the CH$_2$Cl$_2$ phase followed by stirring at room temperature for 12 h. The reaction mixture is then diluted with water (10 mL) and stirred for a further 1 h. The organic layer is then run off and the aqueous layer is extracted with CH$_2$Cl$_2$ (20 mL). The combined organic layers are washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated at room temperature [2]. Purification of the concentrate by chromatography on silica gel (0–15% ethyl acetate in hexane) gave further recovered 3 (0.03 g, 5%), trans-myrtanol 6 (0.01 g, 6%), and cis-myrtanol 5 (0.15 g, 76%).

**Discussion**

The solid mixture of 3 and 4 presents numerous advantages over the familiar borane-dimethyl sulfide complex [1]. Firstly, the white solid shows no tendency to ignite sponta-
neously and only deliquesces slowly over a matter of days in air; it may, therefore, be readily handled and weighed in the open laboratory. Secondly, the mixture is readily assayed by integration of the $^1$H NMR spectrum recorded in deuteriobenzene solution; the ability to accurately weigh the mixture coupled with the convenient NMR assay greatly facilitates the dispensation of accurate amounts of borane. Thirdly, in addition to hydroborations, the mixture of 3 and 4 performs all the standard reductions typically conducted with borane/dimethyl sulfide, including those of ketones catalyzed by oxazaborolines. Fourthly, the sulfide carrier 3 is easily recovered in high yield, ready for reuse. Last, but not least, thioacetate 2, sulfide 3, and sulfide-borane 4 are all completely odorless.

References

2 Care should be taken in the concentration of solutions of 3 to avoid evaporation. At room temperature with a water aspirator vacuum losses are minimal.
12
Applications of Fluorous Compounds in Materials Chemistry

12.1
Basic Principles and Recent Advances in Fluorinated Self-Assemblies and Colloidal Systems

Marie Pierre Krafft

12.1.1
Introduction

A clear understanding of the basic properties of fluorinated self-assembled systems and interfaces should be valuable to chemists using fluorous phases for syntheses as these properties determine phase separations, the development of large size interfaces and the possible constitution of micro- or nanoreactors and templates. Many reagents, catalysts and substrates used in fluorous chemistry, once fitted with perfluorinated chains (F-chains [1]), are likely to become amphiphilic or to experience enhanced amphiphilic character (Scheme 12.1-1). Hence, they become susceptible to adsorption at interfaces and to self-association into colloidal systems, including spherical and worm-like micelles, vesicles and hollow fibers, emulsions, microemulsions or other more or less complex self-assemblies. In addition, fluorinated compounds (F-compounds), due to their combined hydro- and lipophobia and consequent tendency to phase separate from both aqueous and hydrocarbon media, can generate compartmentalization in molecular systems. These phenomena may often account

Scheme 12.1-1. Grafting one or more F-chains on essentially any (non-fluorinated) molecule endows that molecule with amphiphilic character. This means that the molecule consists of at least two parts that have low affinity for each other. Beware of possible modifications of the microstructure and, hence, the properties of their solutions.
for unexpected kinetics or reaction pathways when \( F \)-amphiphilic reactants, products or even byproducts are involved. Interface-driven parameters, which depend largely on the length of the \( F \)-chain, can then complicate apparently simple chemistry.

Molecular and macromolecular compounds with \( F \)-chains have distinctive properties [2–4]. They are chemically and thermally more stable, and have lower intermolecular interactions, hence display lower surface tensions and higher vapor pressures than their \( H \) counterparts. The unique properties of their colloidal systems are the basis of a wealth of applications [5]. In both materials and biological sciences, a key objective has become the design and development of materials and devices based on multiscaled subunits. \( F \)-compounds provide valuable tools for generating organization and segregation of molecular systems into nano- to meso-scale phases with controlled sizes and specific properties. Examples of such systems include arrangements mimicking living organisms or nano-patterned surfaces destined for microfluidics, nanolubrication and molecular sensing. Another exciting field in which fluorinated surfactants (\( F \)-surfactants) are instrumental is the development of biphasic reactions and industrial processes in liquid or supercritical CO\(_2\). Polymers with \( F \)-moieties have found new potential applications in wastewater treatment, oil recovery, control of surface erosion, and antibacterial activity.

In the biomedical area, injectable microbubbles stabilized by gaseous fluorocarbons (FC) have recently provided new contrast agents for effective diagnosis of disease by ultrasound imaging [6, 7]. Therapeutic uses of such microbubbles are also being investigated. Direct and reverse \( F \)-emulsions are being developed as oxygen carriers and drug delivery systems [8, 9].

After a brief reminder of the basic physicochemical properties of FC and \( F \)-surfactants, this review will focus on the most recent advances on self-assemblies and colloidal systems, e.g., micelles, vesicles, tubules, monolayers, emulsions and polymers that comprise \( F \)-chemicals. Their present and potential applications, primarily in materials science, will also be mentioned; their biomedical applications are reviewed by Riess in Chapter 13 of this Handbook [10]. The more classical, highly diverse industrial uses of \( F \)-surfactants and \( F \)-polymers, such as in textile and plastic manufacturing, fire fighting, surface cleaning, emulsion polymerization, etc., will generally not be considered here.

### 12.1.2 Basic Physicochemical Properties

#### 12.1.2.1 Fluorocarbons

Fluorine is the most electronegative of all elements, has a high ionization potential and a very low polarizability [2, 4]. This relatively small atom is, nevertheless, significantly larger than hydrogen (van der Waals radius 1.47\( \text{Å} \) versus 1.20\( \text{Å} \)) [11]. Consequently, \( F \)-chains (\( C_nF_{2n+1} \)) are bulkier than \( H \)-chains (cross sections: 30\( \text{Å}^2 \) versus 20\( \text{Å}^2 \)) [12]. Another consequence of the large size of the fluorine atom is the greater stiffness of \( F \)-chains as compared with \( H \)-chains [13], which is accompanied by a loss of gauche/trans freedom. The gauche/trans energy differences are of ca. 2.0 kJ mol\(^{-1}\) and 4.6 kJ mol\(^{-1}\) for \( H \)- and \( F \)-chains, respectively [12]. In order to minimize steric hindrance, \( F \)-chains adopt a helical conformation.

Owing to effective overlapping of orbitals, the C–F bond is the most stable single bond
found in organic chemistry (~485 kJ mol⁻¹ as compared with ~425 kJ mol⁻¹ for a standard C–H bond) [2]. As a consequence, FCs are thermally and chemically very stable. Furthermore, the dense electron cloud of the fluorine atoms provides a repellent sheath that protects F-chains against reagents [14]. FCs are also inert biologically.

The low polarizability of fluorine results in low van der Waals interactions between F-chains and low cohesive energy densities in liquid FCs [4, 14, 15]. These low intermolecular interactions are responsible for many of the most valuable properties of FCs, such as very low surface tensions, excellent spreading properties, high fluidity, low dielectric constant, high vapor pressure, high compressibilities and high gas solubilities [3, 14, 16]. The weak interactions between FCs also explain that they usually do not mix with hydrocarbons (HCs) that have a higher cohesive energy density. In fact, FCs are surface active in HCs both at the air/oil and the water/oil interfaces (Figure 12.1-1) [17]. The larger surface presented by the F-chains, in conjunction with the low polarizability of the fluorine atoms results in enhanced hydrophobicity. F-chains thus combine two characteristics that are commonly considered antinomic: they are extremely hydrophobic and in addition have a pronounced lipophobic character.

Fig. 12.1-1. Interfacial tensions of mixtures of hexane and F-hexane against water at 25 °C (X = mole fraction of C₆F₁₄). Very pronounced deviations from ideal behavior have been observed. The experimental data (circles) indicate a reciprocal interfacial activity of FCs as dilute solutions in HCs and of HCs as dilute solutions in FCs. In model a, the solution is assumed to be ideal. In model b, the solution is assumed to be regular. In model c, volume fractions have been used to calculate the activity coefficients, as the molar volumes of HCs and FCs are very different. In model d, an approach based on a monolayer at the surface has been used, as the partial molar areas of FCs and HCs are different. In model e, the activity coefficients have been calculated directly from vapor pressure data. From [17].
Fluorinated Surfactants

The strong hydrophobic interactions and low van der Waals interactions displayed by \(F\)-chains dramatically increase the tendency for \(F\)-amphiphiles to self-assemble in water and to collect at interfaces \([3, 4]\). \(F\)-surfactants can decrease the superficial tension of water down to values \(15–20 \text{ mN m}^{-1}\) that cannot be reached by \(H\)-surfactants \(30–40 \text{ mN m}^{-1}\) \([18]\). The interfacial tensions between an aqueous solution of an \(F\)-surfactant and an \(F\)-phase are usually extremely low (typically \(0–5 \text{ mM m}^{-1}\)). The incremental changes in the free energy of adsorption for the transfer of a \(\text{CF}_2\) group from water to the air/water interface are about twice those of a \(\text{CH}_2\) group \((-5.1 \text{ versus } -2.6 \text{ kJ mol}^{-1})\) \([19]\). The free energies of transfer of a \(\text{CH}_2\) group from an \(HC\) phase to an \(FC\) phase and of a \(\text{CF}_2\) from an \(FC\) phase to an \(HC\) phase are 1.1 and 1.4 \(\text{ kJ mol}^{-1}\), respectively \([20]\). These values are about one third of the energy needed to transfer a \(\text{CH}_2\) from an \(HC\) phase to water.

Owing to their increased hydrophobic character, \(F\)-surfactants have lower critical micellar concentrations (cmc) than \(H\)-surfactants, with cmc values being roughly equivalent to those of \(H\)-surfactants with a 50% longer chain. For example, the contribution of a \(\text{CF}_2\) group toward micellization of metal salts of \(F\)-carboxylic acids or \(F\)-sulfonates \([21]\), or of \(F\)-alkylated poly(oxyethylene) surfactants \([22]\) is roughly equivalent to 1.6 times that of a \(\text{CH}_2\) group. However, it was shown that this “1 \(\text{CF}_2\) \(\cong\) 1.5 \(\text{CH}_2\)” rule is not necessarily valid when the chains are only partially fluorinated. In this case, the \(H\)-spacer inserted between the polar head and the \(F\)-chain does not contribute fully to the micellization and adsorption processes, which are essentially controlled by the \(F\)-chain length \([23]\). Replacing the terminal \(\text{CF}_1\) group of an \(F\)-surfactant by a \(\text{CF}_3\) group strongly reduces its surface activity properties \([22, 24]\).

Among the notions that provide tools to chemists using \(F\)-surfactants one should mention the hydrophilic lipophilic balance (HLB), which, for example, is a useful index for selecting a suitable surfactant for emulsification \([18]\). Phase diagrams are also basic to the understanding of \(F\)-surfactant behavior \([22, 25]\).

\(F\)-surfactants cannot, however, be simply considered as more hydrophobic analogs of \(H\)-surfactants; they have specific properties of their own. Their self-assembly behavior is characterized by a strong tendency to form vesicles and lamellar phases rather than micelles, primarily due to the bulkiness of the \(F\)-chain that tends to decrease the curvature of the aggregates they form in solution. Thus, micelles of \(F\)-surfactants tend to be rod-shaped at concentrations where they are spherical for \(H\)-surfactants \([12]\). Single-chain \(F\)-phosphocholines readily form stable, heat-sterilizable vesicles while their \(H\)-analogs form micelles \([26, 27]\). Further examples of bilayer aggregates and vesicles from single chain \(F\)-surfactants have been reported \([28]\). The phase diagrams of \(F\)-surfactants tend to exhibit larger domains of the fluid lamellar phase \((L_0)\) and more restrained domains of the micellar phase \((L_\alpha)\) than \(H\)-surfactants, which also supports their strong proclivity to form vesicles \([22, 29]\). Vesicles made from \(F\)-amphiphiles are characterized by higher organization of their bilayer and improved stability (see Section 12.1.3.1).

Fluorinated cationic gemini surfactants were shown to exhibit a slow exchange rate of the molecule between the monomeric and the micellar states on the NMR time scale \([30]\). In addition, \(F\)-surfactants are characterized by slower kinetics of dissolution from the solid state while forming aggregates in solution, and longer residence times in micelles as compared with \(H\)-surfactants \([31]\).
The hydrophobic effect is not the only driving force that can lead to \( F \)-self-assemblies. Halogen molecules (\( I_2, Br_2, \ldots \)), alkyl(aryl) halides, and more recently \( F \)-alkyl(aryl) halides can act as electron acceptors and form complexes with atoms that have lone pairs. This non-covalent interaction has been named a “halogen bond” by analogy with the hydrogen bond with which it has similarities. The attractive \( N \cdots I \cdots F \)-alkyl(aryl) chain interaction was shown to be specific, directional and strong enough to overcome the low affinity that exists between \( F \)- and \( H \)-modules and to drive their self-assembly into oligomeric structures in the liquid phase, as well as into crystalline networks [32]. Halogen bonding thus adds a novel assembling element to the toolbox of supramolecular engineers.

12.1.2.3 Semifluorinated Alkanes: a Class of Special Amphiphiles

Semifluorinated alkanes \( C_nF_{2n+3}C_{m+1}H_{2m+1} \) (\( FnHm \) diblocks) consist of a lipophobic \( F \)-alkyl block (\( F \)-block) and an \( H \)-alkyl block (\( H \)-block). The mutual antipathy of these blocks results in a tendency for them to demix, which can lead \( FnHm \) diblocks to self-organize both in the bulk and in solutions. In the bulk, \( FnHm \) diblocks crystallize in a variety of smectic phases, depending on block lengths and temperature [33]. This complex phase behavior is still a matter of debate [34]. At high temperatures, solid \( FnHm \) form a lamellar structure with ordered \( F \)-blocks, while the \( H \)-blocks are in a liquid-like state [34]. In suitable solvents, \( FnHm \) form gels made of long networked fibers [35]. In solutions \( FnHm \) form micelles in both HCs and FCs [36]. Their aggregation number is, however, lower than in the case of conventional micelle-forming surfactants in water [20]. \( FnHm \) diblocks exhibit a “surface freezing” phenomenon, that is, the formation of a crystalline monolayer at their free surface melts a few degrees above the freezing point of the bulk material [37].

\( FnHm \) diblocks thus constitute a new class of non-conventional surfactants that are active at the interface between a \( F \)-phase and an \( H \)-phase. \( FnHm \) diblocks were recently used in combination with phospholipids in vesicles, monolayers and emulsion films (Sections 12.1.3.1 and 12.1.5.1). They also allowed stable HC-in-FC emulsions to be obtained.

12.1.3 Self-Assembly Behavior of \( F \)-Amphiphiles

\( F \)-amphiphiles have a much stronger tendency to self-assemble into supramolecular aggregates when dispersed in water and other solvents than their \( H \)-analogs (Figure 12.1-2).

12.1.3.1 Vesicles

The first examples of \( F \)-bilayers and vesicles were reported by the groups of Kunitake [38] and Ringsdorf [39]. Stable, often heat-sterilizable \( F \)-vesicles have since been elaborated from numerous single, double and triple-chain amphiphiles [40, 41]. The amphiphiles used include a large variety of non-ionic, cationic, anionic, or zwitterionic head groups. Liposomes made from \( F \)-phospholipids have been extensively investigated and reviewed by Riess and coworkers [40, 41]. \( F \)-phospholipids are characterized by higher gel-to-fluid transition temperatures, as compared with \( H \)-analogs, which indicate increased ordering of the bilayer membrane. The strongly hydrophobic and lipophobic \( F \)-chains form an internal \( F \)-film within the bilayer that decreases the permeability of the vesicles and slows down the
release of an encapsulated probe, as compared with \(H\)-vesicles. Additional \(F\)-vesicles were prepared from further examples of \(F\)-phospholipids [42] as well as from various glycolipids and glycophospholipids [43]. See Chapter 13 for the biological properties of such vesicles.

\(F\)-colloids can be used as templates for reactions. For example, \(F\)-vesicles allowed polymerization of hydrophobic monomers within their bilayer [44], while, in the case of \(H\)-vesicles, a phase separation between the polymer chain and the lipid matrix occurred, which led to the formation of a latex bead.

\(F\)-gemini surfactants form unilamellar vesicles, while the coexistence of unilamellar vesicles and threadlike micelles was observed in the case of mixed \(F\)-alkyl/\(H\)-alkyl gemini surfactants [30]. Spontaneously forming vesicles were also obtained from mixtures of an \(F\)-propylether surfactant and \(n\)-dodecylbetaine [45].

Additionally, \(F\)-vesicles have been obtained by combining standard phospholipids and \(FnHm\) diblocks. These \(F\)-vesicles are more stable and less permeant than vesicles made from the phospholipid alone [46]. The \(Ca^{2+}\)-induced fusion kinetics of these vesicles were slowed down as compared with those of \(H\)-vesicles [47]. Direct experimental evidence for the diblock’s presence and organization within the bilayer has recently been provided [48].
12.1.3.2 Tubules and Fibers

Hollow nano- and microtubules made from rolled-up bilayers of amphiphiles have received substantial attention since the 1990s because of their potential applications [49]. Recently, nanotubules are being investigated as nanocontainers for the elaboration of metal nanowires [50] and as templates for molecular recognition-driven protein controlled self-assembly [51].

Prior to using F-amphiphiles, the presence of a chiral center and/or the ability to form hydrogen bonds between polar heads were deemed necessary for the inception of the rolling-up process that leads to the tubular structures. However, very stable and sturdy rigid microtubules and flexible fibers were obtained from non-chiral, non-hydrogen bound single-chain F-amphiphiles derived from dimorpholinophosphate in water and other polar solvents, leading to the formation of gels [52, 53]. Nanotubules have also been obtained from mixed F-alkyl/H-alkyl double-chain anionic F-gluco lipids [54]. The introduction of an F-chain had a significant impact on tubule diameter. Examples of tubules and fibers formed by F-surfactants in polar solvents are depicted in Figure 12.1-3. Amphiphiles with two F-chains and one H-chain grafted on the chiral L-glutamate residue were reported to form very viscous turbid dispersions in organic solvents [55]. Optical and electron microscopy studies revealed the presence of fibers (Figure 12.1-3).

Fig. 12.1-3. Examples of tubules and fibers formed by F-amphiphiles in various media. Formation of a, aligned rods and b, tube-like aggregates from a glutamate derivative containing two F-chains and one H-chain, in benzene and chlorocyclohexane, respectively (negative staining electron microscopy) from [55]. c, Formation of hollow tubules from a partially fluorinated derivative of dimorpholinophosphate (optical microscopy); the insert d shows the hollow core of a tubule (freeze fracture electron microscopy) from [53]. e, Fibers formed by a partially fluorinated alcohol in methanol (scanning electron microscopy; courtesy Dr. F. Giulieri, University of Nice).
12.1.4

Bi-dimensional Films

12.1.4.1 Langmuir and Gibbs Monolayers
Langmuir films (spread monolayers that are compressed with a barrier in a trough) and 
Gibbs monolayers (spontaneously adsorbed monolayers at an air/liquid or liquid/liquid 
interface) are valuable tools for studying chain–chain interactions and the formation and 
structure of interfacial films. Monolayers of F-amphiphiles present specific structures and 
properties, due to differences in chain cross-section, stiffness and molecular interactions 
between the F- and H-amphiphiles [56]. A stable Langmuir monolayer was formed from a 
non-amphiphilic F-alkane, C_{20}F_{42}, at room temperature [57], while such behavior was only 
seen, subsequently, for alkanes one and a half times longer. A specific feature of monolayers 
of F-amphiphiles having a polar head smaller than the chain cross section of the hydro-
phobic chain (e.g., F-acids and F-alcohols, or acids and alcohols with short, one or two CH_{2} 
group H-spacers between the polar head and the F-chains) is that, due to the stiffness of the 
F-chain, they undergo a direct transition from the gas phase to an untilted liquid condensed 
(crystalline) phase upon compression, without occurrence of the liquid expanded phase 
usually found for H-analogs [58]. In the liquid condensed phase, F-surfactant molecules are 
vertical and packed in a well-organized 2D hexagonal lattice [59]. The introduction of an H- 
spacer in carboxylic F-acids results in a decrease in the ordering due to the combined effects 
of the F-chain and H-spacer cross-sections mismatch and of repulsive interactions between 
the dipoles associated with the CF_{2}–CH_{2} linkage. This leads then to the appearance of a 
liquid phase in addition to the gas and liquid condensed phases [58].

Precise control of the shape, size and molecular organization of colloids is necessary to 
master the construction of supramolecular 2D architectures. Patterned surfaces with lateral 
phase separations were achieved by mixing F- and H-surfactants that form liquid condensed 
and liquid expanded monolayers, respectively [59], or two liquid condensed phases [60]. 
Monolayers can also be compartmentalized vertically. This was achieved by compressing 
mixed Langmuir monolayers of a phospholipid and an FnHm diblock, resulting in the ex-
pulsion of the diblock molecule at high surface pressures and the formation of segregated 
layers of lipid and diblock [61]. Monodisperse two-dimensional surface micelles were 
formed in monolayers of partially fluorinated carboxylic acids [62], as well as from nonpolar 
FnHm diblocks [63], after transfer onto solid substrates.

12.1.4.2 Self-Assembled Monolayers
Thin F-films have been proposed as alternative materials for coatings in order to compen-
sate for certain inherent drawbacks of F-polymers that are related to the cost of F-
omomers, certain processing difficulties and poor stability against UV radiation. Since the 
first studies of films of adsorbed partially fluorinated acids pioneered by Zisman and co-
workers [64], extensive research has focused on self-assembled monolayers (SAM) of F-
alkanethiols and partially fluorinated alkanethiols adsorbed on gold and, particularly, on the 
relations between the structure of the hydrophobic chain and the corresponding interfacial 
properties [65]. The lattice spacing of F-SAMs and partially fluorinated SAMs with a short 
H-spacer is larger than that of H-SAMs and the former adopt more ordered structures [66]. 
The tail chain lattice is tilted by 30° with respect to the underlying gold lattice [67]. Increas-
ing the length of the H-spacer increases disorder. The wettability of totally and partially fluorinated SAMs appears to be dictated primarily by the interactions of the dipoles orientated along the CF₃–CH₂ axis with the molecular dipoles of the solvent [68]. As a consequence, replacing the terminal CH₃ group of an H-SAM by a CF₃ group increases the wettability of the monolayer by polar solvents [69]. Likewise, the wettability of a partially fluorinated SAM decreases, for a given H-spacer, with decreasing degree of fluorination due to the progressive burying of the CF₃–CH₂ dipole within the SAM. The frictional properties of F-SAMs appear to be primarily controlled by the size of the terminal group.

12.1.5

Emulsions and Microemulsions Containing a Fluorocarbon or a Fluorinated Surfactant

12.1.5.1 Fluorocarbon Emulsions and Microemulsions

FC-in-water emulsions are the focus of extensive research and development efforts with a view to providing injectable oxygen carriers and for other biomedical applications, including diagnostic [9]. They have been extensively reviewed [8] along with the basic properties of FCs relevant to oxygen transport. Details on emulsion engineering have also been provided [70]. Efforts have focused on the protection of concentrated emulsions against aging, that is, primarily molecular diffusion (Ostwald ripening). Ostwald ripening was successfully reduced by adding to the primary FC small amounts of an FC that is slightly heavier, which lowers the solubility of the F-phase in water [70]. Particle size increase was slowed down even more effectively by adding small amounts of an F-alkyl/H-alkyl diblock. The latter was shown to have a synergetic interfacial activity with phospholipids at the FC/water interface [71] in addition to their potential contribution to lowering the solubility of the F-phase. Use of diblocks also allowed smaller-sized F-emulsions to be obtained. Such F-emulsions could be used as reservoirs for gases other than O₂, for example NO and Xe. F-emulsions offer large interfaces for reactivity. Water-in-FC emulsions and non-polar HC-in-FC emulsions can also be obtained using F-surfactants.

Microemulsions of FCs and F-polyethers stabilized by F-alkanoic surfactants [72] or F-polyether surfactants [73] have been widely investigated. Depending on composition, these microemulsions consist either of discrete droplets dispersed in a continuous phase or of bicontinuous phases. F-microemulsions have been used for the production of polyfluoroolefins [74] and of magnetic oxide particles of controlled characteristics in aqueous dispersions. The effect of pressure on the phase behavior of microemulsions of an F-olefin in water, stabilized by an F-alkanoate and an F-alcohol has been reported [75]. F-microemulsions have also been used to control chemical reactivity. Thus, the microstructure of microemulsions based on C₆F₁₇CH=CHR (R = H or C₁₀H₂₁) and formamide has been reported to control the yield and regioselectivity of photoamidation [76]. Some mixed F-alkyl/H-alkyl catanionic surfactants, i.e., C₆F₂₄₊₁COO⁻ NR(CₙH₂₃m₊₁)₃, were shown to form microemulsion phases with hydrofluoroethers, and to form an acid/soap complex that can easily be recovered and recycled [77, 78]. These compounds may provide an alternative to F-alkanoyl surfactants.

12.1.5.2 Water-in-CO₂ Microemulsions

The scope of industrial processes using supercritical or liquid CO₂ is rapidly expanding. Indeed, CO₂ provides a cheap, non-toxic, non-flammable and bio-recyclable solvent alternative
to conventional volatile organic compounds. Commercial processes include decaffeination of coffee, supercritical fluid chromatography, and fluoropolymer synthesis. The challenge was to identify surfactants that are capable of stabilizing water-in-CO₂ microemulsions to replace the water-in-HC microemulsions stabilized by aerosol-OT (sodium bis-2-ethylhexyl sulfosuccinate, AOT) that are widely used for chemical synthesis and extraction processes. F-surfactants (and, to a lesser extent, silicone surfactants) were shown to be the best candidates for this purpose, due to the favorable solubility of F-chains in CO₂. F-surfactants able to form water-in-CO₂ microemulsions include F-polyether carboxylates [79], F-analogs of AOT [80], F-phosphates [81], and surfactants with mixed F-alkyl and H-alkyl chains [82]. The structure of the resulting microemulsions has been determined, and the effects of the F-surfactant’s chain structure (terminal CF₂H group versus CF₃, in particular) on the formation of water-in-CO₂ microemulsions have been investigated [83]. The relations established between the aqueous surface tension of F-surfactants and their ability to stabilize CO₂ microemulsions should facilitate the rational design of highly efficient, low cost CO₂-philic surfactants [84].

12.1.5.3 Fluorocarbon Microbubbles
Injectable aqueous dispersions of FC-stabilized gaseous micron-size bubbles, most of which can be considered as emulsions of gases in water, have recently been developed as contrast agents for ultrasound imaging [6, 7]. By providing a more accurate and reliable diagnosis at relatively low cost with respect of other imaging techniques, these agents are likely to play a significant role in patient care. The role of FCs in these products was to oppose the rapid dissolution of the gaseous microbubbles in the blood due to the combined action of Laplace pressure, arterial pressure, oxygen metabolism, and ultrasound waves. FCs provide the unique combination of low solubility in water and high vapor pressure that was needed to achieve bubble stabilization.

12.1.6 Fluorocarbon Polymers
Fluorine-containing polymers are widely used for their uniquely low friction, high thermal and electrical insulation properties and chemical inertness. They can be applied to a variety of surfaces or manufactured into thin films. In order to improve the solubility of F-polymers in solvents or to promote their self-association, as well as for cost-effectiveness reasons, hybrid polymers with non-fluorinated moieties have been synthesized. The most recent investigations on the rheological and colloidal properties of a variety of fluorinated homopolymers and block copolymers have been reported [85, 86]. The synthesis, self-assembly and rheological properties in aqueous solutions of F-side-chain and F-end-capped associative polymers have also been recently reviewed [87].

A range of fluorinated dendrimers has recently been developed [88]. These “molecular colloids” have potential applications as nanoreactors, in catalysis and for biomedical applications. One particular dendrimer has been used to extract a polar ionic dye from water into supercritical CO₂ [89].

The behavior of living organisms, proteins, cell organelles and cells is based on the cooperation of specialized and miniaturized functional subunits. The concept of multicompart-
ment polymerized micelles was devised in the mid-1980s by Ringsdorf as a simple model of complex natural systems. The various approaches to these multicompartment polymerized micelles have recently been analyzed [90].

12.1.7
Conclusions and Perspectives

Highly fluorinated compounds provide behavior that is not seen and performances that are not reached by H-analogs. Most unique is the antipathy between FC and HC molecules or moieties that allows phase separation (macro, micro and nano) and endows colloidal systems with special properties. These properties may be exploited to control syntheses in fluorous phases. The presence of F-amphiphiles in a medium, including in the form of F-alkylated substrates, reagents or byproducts can significantly alter the structure of this medium, hence its properties.

Further fundamental work in F-colloid chemistry is needed in order to improve control of the properties of self-assemblies and adaptation of them to specific applications. Despite unmatched performances, the obstacles on the path to the development of highly fluorinated materials are numerous. They include a number of economical and environmental issues and, when use in living organisms is contemplated, a perceived alien character. The still limited knowledge of the in vivo behavior of F-surfactants and lipids certainly hinders the development of fluorinated micelles, liposomes, emulsions, emulsions or dendrimers for therapeutic uses. The approval by health authorities of injectable FC-based microbubbles for diagnosis may help change this situation. Minimizing the number of fluorine atoms needed to achieve the targeted material properties, such as for applications related to self-assembled monolayers or chemistry in supercritical CO$_2$, is a definite trend as it reduces cost.

Fluorine chemistry provides unique building blocks and components for materials and biomedical sciences, whether for research or applications in industry and medicine. Conversely, F-self-assemblies and F-colloids represent for fluorine chemistry a logical and inescapable step towards increased complexity, thus participating in the evolution of chemistry from molecules to molecular assemblies, from designing structures to seeking specialized functions.

References

1 For the extended use of the F-symbol and, conversely, of the H-symbol for the hydrocarbon analog, see reference [4].
References

12 Applications of Fluorous Compounds in Materials Chemistry

64 E. F. Hare, E. G. Shafрин, W. A. Zisman, J. Colloid Interf. Sci. 1954, 58, 236.
12.2 Fluorous Nanoparticles

Marcial Moreno-Manás and Roser Pleixats

12.2.1 Introduction

The preparation, structure determination, and possible applications of metallic nanoparticles have attracted a great deal of attention in the last ten years [1]. In general metallic nanoparticles are defined as having: (1) a diameter of 1 to 50 nm, and (2) a surrounding shell of a suitable agent that prevents their agglomeration [1b]. Nanoparticles are in the size realm where metals and their oxides, halides, and chalcogenides can show size-dependent properties. Thus, physicists wonder what is the minimal size of a fragment of metal (e.g., how many atoms) necessary for the metal to lose its known bulk properties, and which new properties are to be found. On the other hand, the smaller the cluster of atoms, the higher is the percentage of atoms in the surface (high specific surface), and this renders nanoparticles very interesting in catalysis [1f, k].

Two key issues arise when thinking about nanoparticles. The first is how nanoparticles are formed and the second is why they do not agglomerate to form higher aggregates with bulk metal properties. Metal nanoparticles, not binary combinations, can be formed by: (1) chemical reduction of a metal salt; (2) thermal, photochemical, or sonochemical decomposition of a metal(0) complex; (3) hydrogenation of an unsaturated ligand, the metal being liberated upon saturation of the coordinating olefinic moiety; and (4) vapor phase deposition. To this list proposed by Bradley [1b] should be added (5), electrochemical reduction of higher valence species of the metal [1i, 2].

Nanoparticles are formed by a process consisting of the following steps: (1) generation of atoms; (2) nucleation to form a cluster of atoms; (3) growing of the cluster to reach a certain volume; and (4) surrounding by a protecting shell that prevents agglomeration.

Of course size and dispersity are significant properties, which are usually determined by transmission electron microscopy (TEM).

Therefore, the nanoparticles ought to be generated in the presence of one such protecting agent. The protecting agents can be broadly divided into two categories: those that provide electrostatic and those that provide steric stabilization. The electrostatic stabilization is based upon the double electric layer formed when some ions of the same sign are adsorbed at the nanoparticle surface (the charges in Figure 12.2-1 could be inverted). The counterions form a second layer that repels the neighboring nanoparticle; for example sodium citrate acts by this mechanism. In other cases protecting molecules of considerable length interact in an attractive manner with the surface of the nanoparticle. The volume of the surrounding molecules prevents mutual approximation of metal surfaces at bonding distance. Popular protecting agents are polymers [for example polyvinylpyrrolidone, (PVP)], cyclodextrines, dendrimers, and so forth. Particularly well known is the mechanism of stabilization by large molecules possessing a functional group with high affinity for the metal: thiols, sulfides, amines, phosphanes. Other common stabilizers are some cationic and anionic surfactants,
for example, lauryltrimethylammonium chloride and sodium dodecylsulfate. They protect nanoparticles by both electrostatic and steric mechanisms (Figure 12.2-1).

Organic compounds heavily or totally (per) fluorinated can also stabilize metallic nanoparticles. This is intriguing since perfluorinated carbon chains are reputable because of their low affinity towards many materials and towards themselves. Thus, non-stick pans are often coated with poly(tetrafluoroethylene) (PTFE) commonly known as Teflon®. As another example it should be recalled that the boiling point of perfluorohexane (82 °C) is lower than the boiling point of heptane (92 °C) [3].

Examples have been reported of metallic nanoparticles (pure metal or binary combinations) stabilized by heavily fluorinated compounds. In some cases the fluorinated compounds also possess a functional group with high affinity for the metal (for example, thiols). In these cases the stabilization probably takes place mainly by attractive interaction of the sulfur atom with the metal surface, the poly- or perfluorinated chains playing a steric role as well as contributing repulsive interactions with the surroundings. In cases in which the ancillary functional group, thiol or others, are absent, it is more difficult to understand how the protecting agent sticks to the metal surface. This chapter deals with such a curious situation of metal (and binary combinations) nanoparticles being protected by heavily fluorinated compounds. By heavily we mean something more than a simple CF₃ group in a molecule or in a polymer.

This chapter deals with a multidisciplinary field; papers frequently focus on many different topics but not specifically on the protecting fluorine-containing shell. Therefore, it is possible that the “less chemical papers” could have escaped our attention. A prudent “and references cited therein” should be added to the cited works. Small clusters with well-defined stoichiometry, such as, Ru₃(CO)₁₂, Au₅₅(PPh₃)₁₂Cl₆, and the like will not be considered.

12.2.2 Metal Nanoparticles

Table 12.2-1 contains examples found in our literature search dealing, in one form or another, with “perfluor”, “fluoro” or “fluorinated” “nanoparticle”, “cluster”, or “colloid”.

**Fig. 12.2-1.** Possible mechanisms of nanoparticle stabilization
Nafion®. 1a, (Scheme 12.2-1) has been extensively used as a stabilizer of metal nanoparticles. Nafion® is a strong sulfonic acid made of a polymer of perfluoropropylene oxide. It forms ionomeric films that permit protons to cross through. Some examples are in entries 1–7 of Table 12.2-1.

Evolution of hydrogen by oxidation of chromium(II) with protons can be achieved under catalysis by colloidal silver anchored in Nafion® resin (entry 1 in Table 12.2-1) [4]. The silver nanoparticles were formed by hydrogenation of Ag⁺ in the presence of water.

In 1993 Mills and coworkers reported the preparation of silver nanoparticles by reduction of silver nitrate with isopropanol in basic media (entry 2) [5]. If Nafion® is present in the preparation procedure the particles were deposited on it. This silver is oxidized to Ag₂O in the presence of air and upon exposure to UV light. The same group described the preparation of gold nanoparticles on Nafion® by reduction of chloroaurate (AuCl₄⁻) with basic methanol (entry 3) [6].
<table>
<thead>
<tr>
<th>Entry</th>
<th>Main author</th>
<th>Ref.</th>
<th>Catalyzed reaction</th>
<th>Metal (diameter nm)</th>
<th>Generation. Protecting shell</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lee, Meisel</td>
<td>[4]</td>
<td>Cr^{2+} + H^+ → Cr^{3+} + ½H_2</td>
<td>Ag (7)</td>
<td>Hydrogenation of Ag(I). Nafion®, 1a</td>
<td>Non-electrochemical production of hydrogen</td>
</tr>
<tr>
<td>2</td>
<td>Mills</td>
<td>[5]</td>
<td>none</td>
<td>Ag (7.4)</td>
<td>Reduction. Nafion®, 1a (MW 1100)</td>
<td>Cubic silver. It is oxidized to Ag_2O by air/h_2O 290 nm</td>
</tr>
<tr>
<td>4</td>
<td>Aberdam</td>
<td>[7]</td>
<td>CO → CO_2</td>
<td>Pt_5Ru_20 (2)/C</td>
<td>Electrochemical reduction. Nafion®</td>
<td>Bimetallic composite deposited over Nafion® to prepare working electrodes</td>
</tr>
<tr>
<td>5</td>
<td>Antoine, Durand, Gloaguen</td>
<td>[8–10]</td>
<td>O_2 → H_2O methanol oxidation</td>
<td>Pt/C (1.2–4.4)</td>
<td>Electrochemical reduction. Nafion®</td>
<td>Composite of Pt/C deposited over Nafion® to modify electrodes</td>
</tr>
<tr>
<td>7</td>
<td>Sun</td>
<td>[12]</td>
<td>none</td>
<td>Ag (13)</td>
<td>Reduction Nafion®, 1a (MW 1100), 1a, and 1b</td>
<td>Silver hosted in the structural cavities of Nafion®</td>
</tr>
<tr>
<td>8</td>
<td>Foss</td>
<td>[14]</td>
<td>none</td>
<td>Au</td>
<td>Reduction C_12H_22SH</td>
<td>Thiol-protected nanoparticles embedded in PTFE</td>
</tr>
<tr>
<td>9</td>
<td>Smirnov</td>
<td>[15]</td>
<td>isomerization of dichlorobutenes</td>
<td>Fe</td>
<td>Thermal decomp. of Fe(CO)_5. PTFE</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dalacu, Martinu</td>
<td>[16]</td>
<td>none</td>
<td>Au</td>
<td>Gold sputtering, 3, polymer from 4</td>
<td>Spectroellipsometric characterization. Plasma polymerization of ε-C_4F_8, 4</td>
</tr>
<tr>
<td>12</td>
<td>Torsi, Convertino</td>
<td>[18]</td>
<td>none</td>
<td>Au</td>
<td>Gold and PTFE sputtering</td>
<td>Analysis of chemical composition of shell</td>
</tr>
<tr>
<td>Entry</td>
<td>Author(s)</td>
<td>Nanoparticles</td>
<td>Reagents</td>
<td>Reaction</td>
<td>Note</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>13</td>
<td>Wai</td>
<td>none</td>
<td>Ag (5–15)</td>
<td>Reduction</td>
<td>Nanoparticles in the water core of a water-in-CO₂ emulsion</td>
<td></td>
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<tr>
<td>14</td>
<td>Wai</td>
<td>none</td>
<td>Ag (5–15)</td>
<td>Reduction</td>
<td>Nanoparticles in the water core of a water-in-CO₂ emulsion</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Wai</td>
<td>Hydrogenation of alkenes and of nitrobenzene to aniline</td>
<td>Pd (5–10)</td>
<td>Hydrogenation</td>
<td>Nanoparticles in the water core of a water-in-CO₂ emulsion</td>
<td></td>
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<tr>
<td>16</td>
<td>Johnston, Korgel</td>
<td>none</td>
<td>Ag (5.5)</td>
<td>Reduction</td>
<td>Careful description of the purification procedure</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Yonezawa, Kimizuka</td>
<td>none</td>
<td>Ag (2.5)</td>
<td>Reduction</td>
<td>As for entry 17.</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Yonezawa, Kimizuka</td>
<td>none</td>
<td>Au (2.5)</td>
<td>Reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Kim</td>
<td>none</td>
<td>Ag (5)</td>
<td>Thermal decomp. of ( R_f \text{COOAg(C}<em>{12}\text{–C}</em>{18}) )</td>
<td>See text</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Crooks</td>
<td>Hydrogenation of alkene</td>
<td>Pd</td>
<td>Reduction</td>
<td>Recovered 12 times in a biphasic solvent system toluene/FC75 (fluorinert, 10)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Crooks</td>
<td>Heck reaction</td>
<td>Pd (2.1)</td>
<td>Reduction</td>
<td>Recovered in a biphasic solvent system heptane/FC75 (fluorinert, 10)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Crooks</td>
<td>Hydrogenation of alkene; Heck reaction</td>
<td>Pd</td>
<td>Reduction</td>
<td>Review articles covering also non-fluorous nanoparticles</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Klabunde</td>
<td>none</td>
<td>Au (3.4–5)</td>
<td>Metal atom vapor deposition on ( \text{N(C}<em>n\text{F}</em>{2n+1}) )</td>
<td>Precursors for thin films</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Moreno-Manas</td>
<td>Heck reaction</td>
<td>Pd (4–5)</td>
<td>Reduction</td>
<td>Recovery in biphasic solvent systems</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Moreno-Manas</td>
<td>Suzuki coupling</td>
<td>Pd (see text)</td>
<td>Reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Gladysz</td>
<td>Heck reaction</td>
<td>Pd</td>
<td>Formation from 19. Possibly ( \text{R}_3\text{NH}^+ )</td>
<td>Full paper in entry 27</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Gladysz</td>
<td>Heck reaction</td>
<td>Pd</td>
<td>Formation from 19 and from 20. Possibly ( \text{R}_3\text{NH}^+ )</td>
<td>Remarkable high TON values</td>
<td></td>
</tr>
</tbody>
</table>
Owing to its ionomeric character Nafion® has found extensive application in the stabilization of metal nanoparticles used in the construction of electrodes for electrochemical reactions requiring the transfer of protons. Thus, Aberdam et al. reported the preparation of working electrodes made from carbon-supported Pt₅₀Ru₅₀ nanoparticles deposited in Nafion® for the electro-oxidation of carbon monoxide (entry 4) [7].

Electrochemical reduction of platinum(IV) [8] produced nanoparticles supported on carbon and inside Nafion® that have been used for the electrochemical reduction of oxygen [9] and for the electrocatalytic oxidation of methanol [10] at the metal/ionomer interface (entry 5). The last studies have implications in the construction of methanol fuel cells.

Ruthenium nanoparticles prepared by thermal decomposition of Ru₃(CO)₁₂ were deposited on Nafion® and the thin layer so prepared was deposited on a glassy carbon rotating disk electrode for studies on the electrochemical four-electron reduction of oxygen (entry 6) [11].

Owing to the beneficial properties of electrodes modified by nanoparticles embedded in Nafion®, it is important to know how metal nanoparticles are bound to Nafion® membranes. The answer can be found in a paper by Sun et al. who have prepared silver nanoparticles by reduction of silver nitrate with sodium borohydride (NaBH₄) as well as silver sulfide nanoparticles (vide infra) (entry 7) [12]. They reported that structural cavities in ionomer membranes serve as excellent templates for the formation of nanoparticles, or, in other words, nanoscale silver particles are hosted in the structural cavities of Nafion® membranes. The related sulfonimide ionomer 1b behaves similarly.

A patent related to noble metal-containing nanoparticles deposited in ionomeric fluorinated polymers for producing membrane electrode assemblies has been published [13].

Poly(tetrafluoroethylenes) (PTFE) 2 (Scheme 12.2-1), have been used for stabilization or deposition of metal nanoparticles. Thus, Foss et al. have reported that dodecylthiol (C₁₂H₂₅–SH) stabilized gold nanoparticles can be embedded in PTFE (entry 8) [14]. In this case the SH termination of the thiol is responsible of the particle stabilization rather than the perfluorinated support. The gold particles were prepared by the classical reduction of chloroauric acid (HAuCl₄) with sodium borohydride.

Smirnov et al. have reported iron-containing composites made by the thermal decomposition of Fe(CO)₅ on a solution-melt of PTFE. The resulting metallopolymeric material was tested as a catalyst for the isomerization of dichlorobutenes (entry 9, Scheme 12.2-2) [15].

Dalacu and Martinu have used another perfluoro-stabilizer for gold. It can be better described as −(CF₂)ₙ−, 3, or −(CF₂)₄n− since it is formed by plasma polymerization of perfluorocyclobutane, 4 (Scheme 12.2-1). The composite films are formed by simultaneous plasma polymerization of 4 and gold sputtering onto glass substrates [16]. The authors described an ellipsometric characterization of the material as an alternative to the classical transmission electron microscopy (TEM) for determining the size and dispersion of the nanoparticles.

Cobalt or aluminum clusters can be formed in plasma polymerized fluorocarbon films by co-sputtering the metal and a mixture of perfluoropropane and argon (entry 11) [17]. The size of the particles depends on the [C₃F₈]/[argon] ratio. At higher ratios cobalt(II) fluoride particles are also formed together with cobalt.

Torsi and Convertino et al. have prepared another example of gold–PTFE nanocomposite [18]. CF₆Au samples were deposited on silicon substrates by co-sputtering PTFE and gold
targets with Ar\(^{+}\) ion beams at room temperature and a pressure of 10\(^{-4}\) mbar (entry 12). The X-ray photoelectron spectroscopy of the fluorocarbon polymer revealed that it contains not only CF\(_2\) and CF\(_3\) groups but also CF, C=C, CF, and C=C in a fluorinated environment. Therefore, a PTFE target can suffer alterations on co-sputtering with a gold target with Ar\(^{+}\) ion beams.

A review on the properties of metal nanoparticle–polymer composites, including PTFE has been published [19].

Wai and coworkers have reported an interesting method for stabilization of metal nanoparticles in liquid and supercritical CO\(_2\). The particles are kept in the water core of a water-in-CO\(_2\) microemulsion. The stabilizing shell is made of two surfactants, the conventional sodium bis(2-ethylhexyl)sulfosuccinate, 5, and the polyfluorinated polyether-phosphate 6 (Scheme 12.2-1). The role of 6 seems to be two-fold: it renders the system soluble in CO\(_2\), and it provides the nanoparticles with a shell that reduces the interdroplet attractive interactions. This method has permitted the preparation of silver (entries 13 and 14) [20, 21] and copper [21] (entry 14) nanoparticles by reduction of silver nitrate with modified sodium borohydrides [NaBH(OAc)\(_3\) or NaBH\(_3\)CN] or N,N,N,N-tetramethyl-p-phenylenediamine (TMPD) and of copper nitrate with TMPD.
The group of Wai has also reported the preparation of palladium nanoparticles in the same water-in-CO$_2$ system by hydrogenation of palladium(II). The formed nanoparticles catalyze the hydrogenation of several olefins such as $p$-methoxycinnamic acid, trans-stilbene and maleic acid as well as the hydrogenation of nitrobenzene to aniline (entry 15, Scheme 12.2-2) [22].

Thiols are classical stabilizers of transition-metal nanoparticles [23]. Brust and co-workers have determined by $^1$H NMR the fate of the sulfur-bound hydrogen in dodecylthiol-stabilized gold particles and concluded that intact thiols are adsorbed to the gold clusters [24].

Fluorinated thiols C$_8$F$_{17}$CH$_2$CH$_2$SH and C$_6$F$_{13}$CH$_2$CH$_2$SH have been successfully applied to the preparation of silver (entries 16 and 17) [25, 26] and gold (entry 18) [27] nanoparticles. The description of the careful purification procedure by the group of Yonezawa and Kimizuka is noteworthy [26, 27]. The same group recommended the use of HCFC-225 or AK-225 (mixture of CF$_3$CF$_2$CHCl$_2$ and CF$_3$ClCF$_2$CHFCl, 7), fluid of low surface tension, as dispersal medium for TEM determinations. In the three cases the metal(0) was generated by reduction of silver nitrate [25] or perchlorate [26] and of chloroauroic acid [27] with sodium borohydride.

The thermal decomposition of silver perfluoroalkanecarboxylates [AgOCO(CF$_2$)$_n$CF$_3$, $n + 2 = 12, 14, 16, 18$] produced silver nanoparticles. The exact nature of the silver/shell interface is not clear although the authors suggested that carboxylate groups are symmetrically bound to the surface of silver via their two oxygen atoms (entry 19) [28].

The high specific surface of nanoparticles renders these materials potentially useful in catalysis [1f, k]. Two examples of catalysis by nanoparticles have already been mentioned in this chapter [15, 22]. More have been reported by Crooks and coworkers, who have encapsulated palladium nanoparticles, generated by reduction of palladium(II) with sodium borohydride, in the interior of fourth-generation amine-terminated poly(amidoamine) PAMAM dendrimers [29, 30]. The metal is simply entrapped within the branches of the dendrimer. Moreover, this fourth generation dendrimer has 32 amino groups in periphery and it is soluble in toluene and in heptane containing dodecanoic acid since an acid–base self-assembly is formed featuring the dodecanoic acid lipophilic moiety. This material is active in the hydrogenation of olefins [31] although recovery was not mentioned. The recovery problem was addressed by proton transfer between the PAMAM dendrimer and perfluoronic acid (Scheme 12.2-3). The palladium nanoparticles entrapped inside assembly 8 catalyze hydrogenation of olefins and were recovered in the fluorous layer of a biphasic solvent system toluene/perfluoro-2-butyltetrahydrofuran, 10 (Fluoroinert FC-75) and reused 12 times (entry 20) [32, 33].

A further step by the group of Crooks is the modification of 4th and 5th generation of poly(propylene imine) PPI dendrimers (32 and 64 amino groups in periphery) as amides with perfluoronic acid 9 to give structure 11 (Scheme 12.2-3), fully covalent as opposed to 8 (entry 21) [34]. Structure 11 encapsulates palladium nanoparticles and the assembly catalyzes Heck reactions of iodoarenes with butyl acrylate. The palladium-in-dendrimer was recovered in the fluorous layer of the biphasic solvent system heptane/10, but the recovered material showed decreased catalytic activity upon successive recovery/catalysis cycles. Reviews on the palladium-in-dendrimer work by Crooks’ group, both fluorous and non-fluorous, have been published (entry 22) [35].
Klabunde et al. reported the clustering of gold atoms in perfluorotributylamine (entry 23) [36]. The method is conceptually very simple. It consists of the thermal vaporization of the metal and depositing the atoms in the perfluoroamine at 77 K. The infrared and the 19F NMR spectra of the particles revealed that the perfluorotributyl amine had been altered despite the mild method of preparation. These particles are soluble in acetone and when recovered the elemental analysis showed that the solvent had been incorporated into the protecting shell, together with the amine.

Our group reported the generation of palladium nanoparticles stabilized by ketone 12 by reduction of PdCl₂ with methanol (entry 24, Scheme 12.2-4) [37]. This method, when
applied to bis(dibenzylidene)acetone (H instead of C₈F₁₇ in 12), produces a discrete palladium(0) complex \([\text{Pd(dba)}_{2}]\) that is used as a precatalyst in many palladium-catalyzed reactions. The nanoparticles catalyzed Suzuki-type couplings and Heck reactions and could be recovered and reused without loss of activity in the biphasic solvent systems benzene/1-bromoperfluorooctane (Suzuki coupling) or acetonitrile/Galden HT 135 (Heck reactions).

Compounds 13–16 also stabilized palladium nanoparticles (entry 25) [38]. Although stabilization by 15 and 16 can be attributed to the functional groups, this is not possible for 13 and especially for 14. It is noteworthy that the ortho- and meta-isomers of 13 did not stabilize nanoparticles under identical experimental conditions for palladium(II) reduction. No clear explanation for these observations can be offered so far. The same type of compounds also stabilize gold nanoparticles [39].

Gladysz et al. have investigated the use of complexes of palladium(II) with fluorous dialkyl sulfides [40] as well as fluorous imine [41] and thioether [40, 42] palladacycles 18 and 19 as precatalysts for the Suzuki coupling and Heck reaction (entries 26 and 27, Scheme 12.2-5). They presented evidence that palladium nanoparticles are the actual catalysts, but these nanoparticles are soluble in DMF rather than in fluorous solvents. Therefore, 18 acts mainly as a steady-state source of extremely reactive, soluble-in-DMF palladium nanoparticles, plausibly non-fluorous in nature and stabilized by ammonium ions during the Heck reactions. The high TON are remarkable.
12.2.3 Nanoparticles of Metal Oxides, Halides, and Chalcogenides

Many of the fluorinated agents discussed above for the protection of metal nanoparticles are useful also for metallic oxides, halides, and chalcogenides. The methods of preparation of these new particles are, of course, different.

Thus, Nafion® has been used extensively. Sun and coworkers, in a paper already commented upon [12], described the formation of silver sulfide (Ag₂S) nanoparticles hosted in the structural cavities of Nafion®. They were formed by immersion of the Nafion® film first in aqueous silver nitrate and, after drying, in aqueous sodium sulfide (entry 1 in Table 12.2-2, Scheme 12.2-6).

The same preparation technique was adopted by Nagamura et al. to prepare cadmium sulfide (CdS) nanoparticles by immersion of the Nafion® film in cadmium chloride, drying, and immersion in sodium sulfide in the indicated order. Alternatively, the sodium sulfide immersion can by replaced by exposure to ammonia and hydrogen sulfide [43]. The authors found size-dependence in the ultra-fast dynamics of transient photobleaching upon excitation with a femtosecond laser at 400 nm (entry 2).

Size-dependence was also observed in photoetching with CdS nanoparticles made by immersion of Nafion® in Cd(ClO₄)₂ solution, drying, and exposure to SH₂ (entry 3) [44].
Mauritz et al. have described the growth of SiO$_2$ by the sol–gel procedure within or over Nafion$^\text{®}$ films (entry 4) [45]. This method consists of hydrolysis of tetraethyl orthosilicate (TEOS) to form the network of SiO$_2$ in situ. The peripheral silicon contains free OH groups that by reaction with excess diethoxydimethylsilane [(CH$_3$)$_2$Si(OEt)$_2$] or ethoxytrimethylsilane (CH$_3$)$_3$SiOEt are capped as silicon ethers. The uncapped free OH groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>Main author</th>
<th>Ref.</th>
<th>Metal (diameter nm)</th>
<th>Protecting shell</th>
<th>Observations</th>
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<tr>
<td>1</td>
<td>Sun</td>
<td>[12]</td>
<td>Ag$_2$S (10.5)</td>
<td>Nafion® (MW 1100), 1a, and 1b</td>
<td>Silver sulfide hosted in the structural cavities of Nafion®</td>
</tr>
<tr>
<td>2</td>
<td>Nagamura</td>
<td>[43]</td>
<td>CdS (2.7–4.9)</td>
<td>Nafion® (MW 1100), 1a</td>
<td>Ultra-fast dynamics of transient bleaching of CdS nanoparticles</td>
</tr>
<tr>
<td>3</td>
<td>Yoneyama</td>
<td>[44]</td>
<td>CdS (8.9–24)</td>
<td>Nafion®, 1a</td>
<td>Size-selective photoetching for particles of &lt;12 nm</td>
</tr>
<tr>
<td>4</td>
<td>Mauritz</td>
<td>[45]</td>
<td>SiO$_2$</td>
<td>Nafion®, 1a</td>
<td>Sol–gel preparation by hydrolysis of Si(OEt)$_4$ (TEOS)</td>
</tr>
<tr>
<td>5</td>
<td>Mauritz</td>
<td>[46]</td>
<td>SiO$_2$–TiO$_2$ and SiO$_2$–Al$_2$O$_3$</td>
<td>Nafion®, 1a</td>
<td>Simultaneous or successive hydrolysis of TEOS and Ti(OBu)$_4$ or Al(O–s-Bu)$_3$</td>
</tr>
<tr>
<td>6</td>
<td>Several</td>
<td>[47–49]</td>
<td>Several metal oxides</td>
<td>PTFE, 2</td>
<td>PTFE filled with metal oxides shows modified mechanical and other properties</td>
</tr>
<tr>
<td>7</td>
<td>Kim</td>
<td>[50]</td>
<td>TiO$_2$</td>
<td>Copolymer of CH$_2$=CF$_2$/CF$_3$CF=CF$_2$</td>
<td>Microwave Plasma Process of nanoparticle generation</td>
</tr>
<tr>
<td>8</td>
<td>Lamparth, Szabó</td>
<td>[51]</td>
<td>Several metal oxides</td>
<td>Compounds in Scheme 12.2-7 or derived polymers</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Wai</td>
<td>[52, 53]</td>
<td>AgCl, AgBr, AgI, ZnS, CdS</td>
<td>5 + 6 or 20</td>
<td>Nanoparticles in a water-in-CO$_2$ emulsion</td>
</tr>
<tr>
<td>10</td>
<td>Johnston, Korgel</td>
<td>[54]</td>
<td>CdS (1.8–3.6)</td>
<td>21</td>
<td>Semiconductor nanoparticles have size-dependent properties. Nanoparticles in a water-in-CO$_2$ emulsion</td>
</tr>
<tr>
<td>11</td>
<td>Johnston</td>
<td>[55]</td>
<td>TiO$_2$ (9–18)</td>
<td>21 and 22</td>
<td>Sol–gel preparation by hydrolysis of Ti(O-isoPr)$_4$</td>
</tr>
</tbody>
</table>
give hydrophilicity to the surface whereas the capped ones confer hydrophobicity (Scheme 12.2-6).

The simultaneous or consecutive sol–gel process can be applied to TEOS and a second alkoxide of a different metal. This is the method of Mauritz to prepare perfluorosulfonate ionomer/[SiO$_2$–TiO$_2$] or [SiO$_2$–Al$_2$O$_3$] nanocomposites (entry 5) [46].

Composites of PTFE, 2, with metal oxides have been described. The materials are considered as PTFE filled with the metal oxide and in general, they are prepared by mechanical mixing. Thus, PTFEs filled with the following oxides have been prepared for studying the indicated properties: with zinc oxide powder (50 nm) for their friction and anti-wear properties [47]; with Al$_2$O$_3$, and with SiO$_2$, TiO$_2$, Al$_2$O$_3$, and ZrO$_2$ for their mechanical properties [48]; with TiO$_2$ for their exceptional diffuse reflectivity (entry 6) [49].

A related polymer, poly(vinilydenefluoride-co-hexafluoropropylene) (from CH$_2$CF$_2$ and CF$_3$CF=CF$_2$) has been filled with TiO$_2$ and its properties pertinent for application to rechargeable lithium batteries have been studied (entry 7) [50].

A different method for coating nanoparticles with polymers is the Karlsruhe Microwave Plasma Process. This consists of introducing a vaporized metal precursor into an argon/oxygen microwave plasma where metal oxide particles are formed. The coating is achieved by introducing the coating or coating precursor after the plasma zone [51]. This method has been successful in preparing nanoparticles of ZnO, ZrO$_2$, HfO$_2$, Al$_2$O$_3$, TiO$_2$, SnO$_2$, and WO$_3$ coated by the fluorinated products indicated in Scheme 12.2-7 or derived polymers. Enhanced thermal and chemical stabilities, fluorescence, and permittivity of these materials have been measured (entry 8).

Two different groups have made halides and chalcogenide nanoparticles in the water-in-CO$_2$ medium. Thus, Wai and coworkers have prepared silver iodide (3.4 nm), bromide (3.0 nm), and chloride (size not determined) nanoparticles by mixing two water-in-CO$_2$
emulsions, one containing silver nitrate and the other sodium halide [52]. The mixture of surfactants made with 5 and 6 stabilizes the system (entry 9).

In a related work Wai et al. reported the preparation of zinc and cadmium sulfide nanoparticles by mixing emulsions containing zinc or cadmium nitrate and sodium sulfide [53]. An interesting novelty is the use of fluorous surfactant 20 (Scheme 12.2-1) for stabilization of the system (entry 9).

Korgel, Johnston et al. have described cadmium sulfide semiconductor nanoparticles (1.8–3.6 nm) by injecting aqueous sodium sulfide into a water-in-CO2 emulsion containing cadmium nitrate [54]. The stabilizing surfactant is the ammonium salt 21 (Scheme 12.2-8). The exciton energies of these materials are size-dependent (entry 10).

Johnson and coworkers have prepared TiO2 nanoparticles (9–18 nm) by hydrolysis of titanium tetraisopropoxide [Ti(OCH(CH3)2)4] (sol–gel method) in the presence of either 21 or the fluorinated polymer 22 (Scheme 12.2-8) (entry 11) [55].

Finally, stabilization of nanoparticles of metal binary combinations has been the subject of some patents. Those not specifically mentioned above can be found in the last reference [56].

Acknowledgements

Financial support was obtained from the “Ministerio de Ciencia y Tecnología” of Spain (Project BQU2002-04002) and from Generalitat de Catalunya (Project 2001SGR00181).
33 For the principles of recovery of catalysts by biphasic fluororous solvent systems see other contributions to this Handbook.
47 F. Li, K. Hu, J. Li, B. Zhao, Wear 2002, 249, 877.
48 (a) C. He, H. Gu, W. Ding, Goucheng Suliao Yingyong 2000, 28, 1; Chem. Abstr. 135:345077. (b) C. He, W. Ding, H. Gu, Suliao Gongyi 2001, 29, 16; Chem. Abstr. 136:217553.
12.3 Self-Assembly of Hybrid Fluorous Materials

Pierangelo Metrangolo*, Tullio Pilati, and Giuseppe Resnati*

12.3.1 Introduction

Perfluorocarbon (PFC) derivatives show a unique combination of physical properties and chemical reactivities, which account for some of their useful applications. Enthalpies of interaction between PFCs and hydrocarbons (HCs) are smaller than interaction enthalpies between HCs. For this reason, PFCs usually have a very low affinity for their analogous HC parents [1]. Specifically tailored patterns of intermolecular interactions are thus required if the PFC-HC recognition process is pursued to the point of triggering the intermolecular recognition and self-assembly of the two species into stable hybrid materials.

An attractive interaction occurs between halogen atoms, which work as electron acceptor sites (Lewis acids, halogen bond donors) and lone-pair possessing atoms, which work as electron donor sites (Lewis bases, halogen bond acceptors). This interaction was first recognized as early as two centuries ago [2]. The term “halogen bond” has been proposed for this interaction in order to stress the numerous analogies between its properties and those of the hydrogen bond [3]. Carbon-bound iodine, bromine, and chlorine atoms C–X (X = I, Br, Cl) effectively work as electron acceptor motifs and give rise to halogen bonded complexes C–X···B (X = I, Cl, Br; B = O, N, S, Se, I–, Br–,...) with a wide variety of neutral or anionic electron donor motifs [4]. Recently, fluorine atoms of perfluoroalkanes have also been reported to work as electron acceptors when amines are used as bases [5]. The tendency to form strong complexes (I > Br > Cl > [F]) usually parallels the order of halogen atom polarizabilities, consistent with a key role for halogen polarization in the interaction [6].

The presence of electron withdrawing groups on halocarbon modules promotes the acidity of halogen atoms and, consequently, their tendency to form strong halogen bonds [6a, 7]. Fluorine atoms and perfluorinated residues are among the most powerful electron withdrawing groups [8] so that halo-PFCs form halogen bonds definitively stronger than the corresponding halo-HC. According to quantum chemical calculations (DFT and MP2), the interaction energies for the halogen bond between trimethylamine and iodomethane and between 4,4′-bipyridyl and 1,4-diiodobenzene are 2.8 and 3.3 kcal mol⁻¹, respectively [9]. The
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interaction energies for the corresponding halogen bonds involving trifluoriodomethane and tetrafluorodiodobenzene are 7.1 and 5.8 kcal mol$^{-1}$, respectively. From the experimental point of view, the shortening of the van der Waals distances between the halogen bonded nuclei are much greater for halo-PFCs than for the corresponding halo-HC.

The halogen bond involving halo-PFCs proved to be strong enough to effectively overcome the low affinity between PFC and HC derivatives or inorganic salts (IS) [10]. A wide variety of hybrid materials were obtained where heteroatom substituted HC or anions self-assemble with mono- and di-ido-PFCs or their bromo-analogs. While both aliphatic and aromatic PFCs give self-assembled systems with equal success, we will discuss here only the hybrid materials formed starting from the former derivatives (i.e., fluorous compounds), occasional discussions also being included for the latter. Discrete aggregates, 1D infinite chains, helical structures have been obtained where fluorous modules alternate with HC modules.

### 12.3.2 Neutral Two-Component PFC-HC Materials

When difunctional electron donors interact with monofunctional acceptors, or when monofunctional donors interact with difunctional acceptors, the halogen bond forms well defined trimeric adducts and starting modules are present in a 2:1 ratio in the resulting co-crystals [11]. When difunctional electron acceptors and difunctional donors are used, the interaction is doubled at either end of the modules and one dimensional (1D) infinite networks are formed where the starting modules are present in a 1:1 ratio [12]. The effectiveness of the protocol is shown by the fact that a wide diversity of highly crystalline supramolecular architectures has been obtained starting from differently sized diiodoperfluoroalkanes (acid modules) and from pyridine derivatives or dialkyl- or trialkyl-amines (basic modules) (Scheme 12.3-1).

Halogen bonded co-crystals obtained starting from iodoperfluoroalkanes and nitrogen substituted HC are typically crystalline solids stable in the air at room temperature. They usually melt definitively higher than pure starting modules. For instance, the non-covalent co-polymer formed by 1,2-diiodotetrafluoroethane and tetramethylethylenediamine (1:1 co-crystal) melts at 105 °C, while pure starting modules melt at $-27$ and $-55$ °C, respectively. Dramatic melting point increases are observed not only when non-covalent co-polymers are formed but also when the halogen bond affords discrete adducts. 1-Iodoperfluoroheptane melts at $-8$ °C and the trimeric adduct it gives with tetramethylethylenediamine (2:1 co-crystal) melts at 52 °C. While the correlation between intermolecular interaction strength and melting point cannot be quantified, this thermal behavior is consistent with the formation of well defined molecular aggregates due to interaction of the starting modules. It is also indirect proof of the strength that the halogen bond is responsible for such an interaction. The melting point of the co-crystals obtained starting from bromo-PFCs is usually slightly higher than or in between those of pure starting modules, consistent with bromo-PFCs being weaker acids than iodo-PFCs. Theoretical calculations [9a], experiments of competitive co-crystal formation, and different analytical techniques ($^{19}$F NMR, IR, Raman, single crystal X-ray analyses) [13] all confirm this relative acidity of halo-PFCs.
In solid hybrid materials, vibrational spectroscopies (IR and Raman) are effective techniques to check whether the PFC and HC modules are halogen bonded \[12a–12c, 14\]. The co-crystals spectra are the sum of the starting modules spectra, some diagnostic band shifts and band intensity changes revealing the halogen bond occurrence. Consistent with the \(n \rightarrow \sigma^*\) electron donation from the lone-pair possessing atoms to the iodine, or bromine, atoms \[15\], the \(v_{\text{CH}}\) IR stretching frequencies (2900–3100 cm\(^{-1}\) region) of the basic modules show a blue shift and an intensity decrease while the \(v_{\text{CF}}\) stretchings (1100–1250 cm\(^{-1}\) re-
The N···I interactions give larger changes than the N···Br ones, consistent with the relative strength of the two interactions.

\(^{19}\)F NMR spectroscopy is the best tool to detect the halogen bond formation in liquid hybrid materials, or in solution. The technique is a simple, powerful, and versatile method to rank the relative acidities of different halo-PFCs and the relative basicities of different lone-pair possessing motifs [13]. Signals invariably shift upfield on halogen bond formation and shift values decrease with increasing distance from the iodine, or bromine, atoms. The stronger the halogen bond is, the larger the shifts are and shift values up to 20 ppm have been observed for fluoride atoms geminal to secondary iodine atoms. Iodo-PFCs give larger shifts than Br-PFCs and secondary halo-PFCs give larger shifts than primary halo-PFCs, consistent with the greater electron withdrawing ability of a perfluoroalkyl chain with respect to a fluorine atom.

Owing to the strong tendency of long perfluorinated chains to form waxes and act as lubricants [16], few reports exist on the single crystal X-ray structure of perfluoroalkyl substituted compounds and in most cases low temperatures were used in these studies [17]. Often, the co-crystals obtained starting from diiodo-PFCs and dinitrogen-HCs can be studied through single crystal X-ray analyses, even at room temperature. The halogen bond driven formation of PFC-HC or PFC-HC-IS hybrid materials (see later) can thus be considered as a general and reliable strategy to readily obtaining halo-PFC derivatives that are suitable for X-ray studies (Figure 12.3-1).

X-Ray structures of numerous supramolecular architectures assembled via the N···I–RF (RF = perfluoroalkyl chain) halogen bond have been obtained so that the geometric characteristics of the interaction were determined in detail. Nitrogen atoms approach iodine atoms roughly along the elongated C–I bond axis, consistent with the n → σ* electron donation from nitrogen to iodine (Figure 12.3-1). The N···I–RF distance spans the range 2.75–2.87 Å, and is clearly longer than the average covalent N–I bond length (2.07), and approximately 0.8 times the sum of van der Waals radii (1.55 Å for nitrogen, 1.98 Å for iodine). These contractions are greater, with a single exception [18], than those reported in the Cambridge Crystallography Data Centre for intermolecular N···I interactions, consistent with the ability of iodo-PFCs to form particularly strong halogen bonds. Also the N···Br interactions develop along the elongated C–Br bond axis, and the N···Br distances are usually 0.85 times the sum of van der Waals radii of involved atoms, this smaller shortening being consistent with the N···Br halogen bond being weaker than that for N···I. The C–X (X = Br, I) covalent bond lengthens in the halogen bonded co-crystals compared with the pure halo-PFCs. Furthermore, the stronger the halogen bond, the greater the lengthening, once again consistent with an electron donation from the lone-pair possessing atoms to the iodine, or bromine, atoms [4c].

These geometric characteristics of the halogen bonds involving iodo- and bromo-PFCs are exactly analogous to those of the halogen bonds involving iodine and bromine [4a, 4b, 6]. The use of iodine for the formation of halogen bonded co-crystals has recently witnessed a renewed interest [19] as iodine easily works as a removable structural template and allows polymorphs to be isolated and interconverted. Halo-PFCs are notorious as particularly volatile compounds and they can be easily removed from their co-crystals. They could therefore function as effective alternatives for iodine as removable templates in polymorphism studies. Their removal from the co-crystal could afford nanoporous materials.
In many PFC-HC co-crystals the perfluoroalkyl chains show dramatic rotational disorder not only at room temperature, but also in the cold. This disorder increases in the perfluoroalkyl chain with increasing distance from the iodine, or bromine, atoms which, on the contrary, never show any disorder. Halo-PFC molecules are clearly pinned in their position in the co-crystals through the halogen bond involving the iodine, or bromine, atoms and the perfluoroalkyl chains, reminiscent of their poor tendency to be involved in any interaction, flip as much as possible.
Single crystal X-ray analyses allowed the structural details of co-crystals to be established. For instance, with very few exceptions the perfluorinated chains adopt an all-trans and twisted conformation. In the hybrid materials, the halo-PFCs are present as rigid and parallel bars aligned and segregated into PFC layers alternating with HC layers (Figure 12.3-2) [13]. This arrangement persists independently of the nature and shape of the HC module, and by simply changing the metric dimensions of the PFC or HC modules, differently sized PFC-HC layer-like hybrid materials can be rationally designed and prepared (Figure 12.3-3).

12.3.3 Anionic Three-Component PFC-HC-IS Materials

The ability of halide anions to act as donors to electron-poor carbon-bound halogens may be developed as a general protocol for halide-centered supramolecular chemistry. Both PFCs and HCs have a very low affinity for inorganic salts, and it can thus be expected that three-component heteromeric architectures where PFCs, HCs, and ISs self-assemble are endowed with unique structures and useful properties.

Fig. 12.3-2. Layer-like PFC-HC domains in the crystal matrix of the complex between 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (Kryptofix® K.2.2.) and 1,8-diodoperfluorooctane. Dashed lines represent halogen bonds.

Fig. 12.3-3. Alternating PFC-HC layers characterizing the crystal matrix of the halogen-bonded complex obtained from 1,3-di(4-pyridyl)propane and 1,8-diodoperfluorooctane. Dashed lines represent halogen bonds.
Crystalline organic iodides represent a special group of halogen-doped organic crystals. The presence of polyiodide chains in organic materials noticeably influences their electrical properties. Polyiodides have been extensively studied in the solid and liquid state as constituents of a large number of molecular conductors and superconductors [20]. They are characterized by a strong tendency to concatenation [21] and give rise to solid structures that may contain small and discrete polyiodides or extended networks of interconnected units [22]. These important applications produced a great demand for new crystalline organic materials containing polyiodide chains [23].

We have already discussed the ability of diiodoperfluoroalkanes to mimic iodine [12c] and pseudo- or interhalogens in the halogen bond driven formation of adducts with neutral electron donors. Telechelic iodoperfluoroalkanes are also reminiscent of iodine in their tendency to self-assemble with $I^-$ anions. In fact, fluorous polyiodide networks of different lengths and different fluorine-contents have been synthesized by varying the metric parameters of the $x, o$-diiodoperfluoroalkane utilized.

When 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane (K.2.2.2.) is crystallized from a methanol solution of KI, the solid cryptate K.2.2.2. $\subset$ Ba1 1 is isolated. If 1 is crystallized from methanol in the presence of 1,2-diidoctetrafluoroethane (2a), the naked iodide of the cryptate K.2.2.2. $\subset$ Ba2 functions as a strong electron donor towards the iodine atoms of 2a, causing the precipitation of the three-component PFC-HC-IS architecture [Ba(K.2.2.2.)$^2 \cdot$][C$_2$F$_4$I$_4$]$^2$ - 3a as colorless crystals (Scheme 12.3-2).

![Scheme 12.3-2. Diagram showing the formation of fluorous polyiodide networks starting from cryptate 1 and differently-sized telechelic diiodoperfluoroalkanes 2. The 2/1 modules ratio in the complexes is reported for each structure as derived from single crystal X-rays analyses and $^1$H/$^{19}$F NMR experiments. For polyiodides 3a,d the concatenation is reported as found in the crystal structures]
The structural details of 3a were established through single crystal X-ray analysis. Barium cations are embedded in the cryptand and two molecules of water are also present and complete the co-ordination sphere of the alkaline-earth metal. Diiodotetrafluoroethane works as a bidentate and telechelic electron acceptor as two distinct iodide ions are halogen bonded at either ends of the molecule. Iodide anions behave as monodentate electron donors and are located at the surface of the cryptate with a distance from the cation of 5.845 Å. This concatenation gives rise to the fluorinated polyiodide network \([\text{C}_2\text{F}_4\text{I}_4]\)^{2-}. The I\(^-\)⋯I–C– angle is 177.3(1)° and the I\(^-\)⋯I–PFC halogen bond length is 3.391(1) Å, longer than the average covalent I–I bond (2.666 Å) but approximately 0.8 times the sum of the van der Waals radii for an iodine atom (1.98 Å) and iodide ion (2.20 Å). A strictly related crystalline organization has recently been described by Pantenburg et al. \([24]\) for the complex [Ba(benzo-15-crown-5)]^2I\(^-\)). This confirms the suggestion that the supramolecular synthon \(\cdots\text{I(CF}_2)\_2\text{I} \cdots\text{I}^\text{\scriptsize{I}}\) functions as a fluorous analog of the triiodide building block (Figure 12.3-4).

Naked iodide anions have been demonstrated to be strong templating agents for iodo-PFCs. This behavior, along with the great tendency of perfluoroalkyl chains to behave as rigid rod-like modules, allows one to predict the formation of higher fluorine-content polyiodide networks when using iodo-PFCs longer than 2a. Co-crystals 3b–d were obtained starting from \(\_\text{o, o-diiodoperfluorobutane (2b), -hexane (2c), and -octane (2b, 2c, and 2d, respectively), as confirmed by thermal and IR analyses. Microanalyses and }^{1}H/^{19}F\text{ NMR revealed the PFC/cryptate ratios are 1.5:1.0, 2.0:1.0, and 3.0:1.0, in 3b–d, respectively [25].}

Fig. 12.3-4. Ortep III view of the crystal packing of 3a. I\(^-\)⋯I halogen bonds are dashed lines. For the sake of clarity hydrogen atoms have been omitted.
Single crystals of 3d suitable for X-ray analysis were grown from methanol. Barium cations are again embedded in the cryptand and two molecules of methanol, rather than of water as in 3a, complete the co-ordination sphere. Two different iodide ions are present in the asymmetric unit of the crystal. One of these iodide ions is tridentate, bridges two distinct and well-ordered all-trans diiodoperfluorooctane molecules in a linear manner, and gives rise to infinite and linear fluorous polyiodide chains (Figure 12.3-5). A third molecule of diiodoperfluorooctane is bound, with an angle of 127°, to the iodide ions of the infinite chains and is connected to a linear, discrete, and disordered \( \cdots I^- \cdots I \) unit. The overall lattice organization of the true polyiodide network thus obtained reminds one closely of the structure of a comb-like co-polymer. Each “monomer” consists of a perfluorinated octaiodide which can be described as a V-shaped pentaïodide unit \( C_{16}F_{12}I_5^- \) \( \{I_{1B} \cdots I_1 = 3.531(1) \, \text{Å}, I_1 \cdots I_{1A} = 3.584(1) \, \text{Å}, I_{1B} \cdots I_{1A} = 126.96(2)^\circ \} \), connected to a triiodide unit \( C_8F_{16}I_3^- \) unit \( \{I_{12A}(x, y, -1 + z) \cdots I_{12} = 3.464(1) \, \text{Å}, I_{12} \cdots I_{11}(1 + x, y, z) = 3.442(1) \, \text{Å}, I_{12A}(x, y, -1 + z) \cdots I_{12} \cdots I_{11}(1 + x, y, z) = 174.5(2)^\circ \} \) of the same type found in 3a. The single fluorous monomers are then connected head-to-head by \( \cdots I^- \cdots I \) secondary interactions of 4.167–3.999 Å with angles of 60–65.6°. The packing of the fluorous and comb-like polymeric poly-
iodides in the crystal matrix is characterized by a strong segregation of the perfluoroalkyl chains and alternating PFC-HC layers are present as usual (Figure 12.3-5).

To the best of our knowledge, this is the first example of a comb-like fluorous polymer constructed exclusively by means of non-covalent interactions. This is also the first report of the syntheses of fluorine-rich polyiodide networks. Their formation is driven by the strength of the $I^{-} \cdots I^{-}\text{PFC}$ halogen bond, which gives rise to single comb-like co-polymer chains, and by the fluorophobic effect, which packs the single chains into a nano-segregated crystal matrix.

Fluorous polyiodide networks are a virtually unknown class of materials, but remembering the technological importance of PFCs in general, and of PFC-halides in particular, interesting properties can be anticipated for the new systems described in this section.

12.3.4 Polymeric PFC-HC Comb-shaped Complexes

Comb-like polymers with perfluoroalkyl side chains have recently received interest because of their unique surface behavior [26]. Random copolymers containing fluorinated segments are much more common than graft copolymers because of the greater difficulties encountered in the synthesis of a two-phase graft copolymer.

We have demonstrated above how the halogen bond is a powerful tool in crystal engineering. Owing to its high strength and specificity, this interaction also effectively drives the self-assembly of long chain halo-PFCs with HC polymers carrying appropriate electron-donor sites. This approach has been applied in the coating of surfaces with fluorinated materials [27]. The halogen bond is thus confirmed as an effective intermolecular interaction for the design of new comb-like complexes.

Poly(4-vinylpyridine) 4 (P4VP) gives 2:1 halogen-bonded comb-shaped complexes with $\alpha,\omega$-diiodoperfluoroalkanes 2a–d (Scheme 12.3-3). The complexes 5a–d have been fully characterized by FT-IR, Raman, $^1$H and $^{19}$F-NMR, CP-MAS $^{13}$C-NMR, DSC and thermogravimetric analyses (TGA).

IR and Raman spectroscopies effectively show the occurrence of the halogen bond on both the HC and PFC modules. The observed blue shift and intensity decrease in the 3100–
2900 cm\(^{-1}\) region of the IR of P4VP is highly diagnostic of halogen bond formation, and the same holds for the blue-shift to 1001 cm\(^{-1}\) of the absorption at 993 cm\(^{-1}\) in pure 1 [28]. As to the acidic module, the C–I bond Raman vibration (at 277 cm\(^{-1}\) in pure 2a) underwent the typical red-shift on complex formation [14a].

TGA-FTIR experiments on complexes 5 having different stoichiometries were very informative as to the relationship between their stoichiometry and single module properties. The halogen bond dramatically decreases the volatility of the perfluorinated compound and bonded PFCs show quite different behaviors from unbonded PFCs. With this technique it was possible to establish that the 1:1 N/I stoichiometry is favored in the complexes and these results are confirmed by titration experiments with IR and Raman measurements.

While 5d had a paste-like morphology, the complexes 3a–c were dense oils. The features typical for a smectic-type liquid crystallinity were confirmed in complex 3c with polarized light. The macroscopic organization also remained unchanged upon heating to 70 °C, thus suggesting the lyotropic character of this LC system (Figure 12.3-6).

Studies in which shear stress was applied to the molten complex showed a behavior typical of the lamellar organization, distinctly similar to related literature systems [29].

Thanks to the high strength and directionality of the halogen bond, and the rigid, rod-like structure of perfluoroalkyl residues, materials with a nice comb-like structure have been obtained starting from P4VP 4 and halo-PFCs 2. The high tendency of PFCs to segregate from HCs contribute to the LC properties of such materials. The self-assembly of halo-PFCs
with polymers carrying suitable electron-donor residues can be an alternative route to fluoro-
inated graft co-polymers, easier and more convenient than the covalent synthesis. These
non-covalent approaches could be successfully pursued as a new method to the deposition of
fluorinated coatings.

12.3.5 Conclusion

It has been proven how the halogen bond can be considered as a first choice intermolecular
interaction to rationally design the self-assembly of PFCs with HCs and ISs both reliably and
effectively. In the resulting hybrid materials, the single modules are arranged by the halogen
bond into well-defined discrete aggregates or infinite networks. The packing of these self-
assembled units into the supramolecular structure of the material is heavily influenced by
the low affinity which exists between PFCs and HCs or ISs. As HC and IS derivatives are
fluophobic, segregation of the different modules into separated nanodomains occurs and
the halogen bond holds together the alternating layers of PFC and HC, or IS, modules. This
nanodomain formation is largely independent of the molecular structure of single modules.

Physical and chemical properties of bulk materials are not simply the sum of the molec-
ular properties of the constituting compound(s) and this becomes particularly true when
multi-component materials are considered. Very few systems (e.g., PFC-HC emulsions or
diblock and triblock compounds R$_F$–R$_H$ and R$_F$–R$_H$–R$_F$, respectively) can be considered
in an attempt to anticipate the properties of mixed PFC-HC supramolecular architectures.
Nevertheless, also remembering the unique and useful properties of PFC materials (e.g.,
Nafion®, Teflon®, . . .), the few precedents cited above allow one to state that the properties
of mixed PFC-HC supramolecular architectures, while difficult to anticipate, are expected to
be of great interest. Similar considerations hold for PFC-HC-IS hybrid materials.

In synthetic chemistry, the halogen bond can drag hydrocarbon reagents/catalysts into
fluorous solvents thus offering an alternative to the “perfluorinated ponytail” approach in
fluorous based technology [30]. The formation of PFC-HC co-crystals can also be used as a
low cost and large scale approach to the separation of mixtures of PFC-halides, a class of
compounds of great technological relevance.

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17 More than 4000 substances containing perfluorinated chains as long as eight carbon atoms are reported in the Beilstein Abstracts Database, but the X-ray crystal structures of only 13 compounds have been determined.


25 To establish the 1/2 ratio in co-crystals 3a–d, their $^1$H and $^{19}$F NMR spectra were determined in the presence of 2,2,2-trifluoroethyl ether as an internal standard. On calibrating integration parameters so that in the $^1$H NMR spectrum the CH$_2$O quartet of 2,2,2-trifluoroethyl ether corresponded with four and in the $^{19}$F NMR spectrum the CF$_3$ triplet of 2,2,2-trifluoroethyl ether corresponded to six, the ratio of the NCH$_2$CH$_2$O signal area (deriving from 1) and the CF$_3$ signal area (deriving from 2) revealed the 1:2 ratio in the co-crystals 3.


13
Fluorous Materials for Biomedical Uses

Jean G. Riess

13.1
Introduction

This chapter reviews the uses, present and potential, of highly fluorinated compounds (F-compounds) and colloids with fluorous components (F-colloids) in medicine and biology (Figure 13-1). The IUPAC-authorized italicized prefixal symbol F-, meaning perfluoro, as in F-alkyl = perfluoroalkyl, will, by extension, be used to designate entities (F-chains, F-amphiphiles, F-surfactants, F-vesicles and F-colloids) that comprise a highly fluorinated moiety or phase, responsible for significant effects, different from those found for hydrocarbon (HC) analogs. Mirroring this representation, the prefix H- (as in H-alkyl) will be used for unambiguous designation of HC counterparts [1].

Several perfluorocarbon (or fluorocarbon, FC)-based contrast agents for ultrasound diagnostic imaging have recently been commercialized. Fluids for ophthalmologic applications and a magnetic resonance image enhancement device are also available. An injectable oxygen-carrier (blood substitute) is undergoing advanced clinical evaluation, while others are in the early investigation stages. Various F-compounds and F-colloids have potential for the detection of diseases by molecular imaging, and for the delivery of drugs, genes and other bioactive agents or markers. Other F-compounds and F-colloids provide valuable research tools and processing aids for the manufacture of drug delivery vehicles.

The simultaneously hydrophobic and lipophobic character of F-chains is a powerful driving force for FCs to phase separate and for F-amphiphiles to self-assemble in aqueous media as well as in standard organic solvents. FCs and F-amphiphiles can thus allow the formulation of an array of multicomponent, multiphase nano- and micro-compartmentalized colloidal systems and nano-objects that comprise confinement and exclusion zones with differential solubility and diffusibility characteristics, responses to sound waves, etc. These colloids have potential as gas carriers, targetable drug vehicles and microreservoirs, sound reflectors and sound-triggered cavitators, diffusion barriers and templates, useful for biomedical applications and beyond [2]. Fluorinated colloids thus participate in the ineluctable movement towards increased, yet increasingly controlled complexity that characterizes the evolution of science.

Selection of fluorous components and formulations for biomedical applications is largely determined by the target properties and constraints appropriate to their specific uses. These
criteria and constraints include pharmacokinetic and side effect profiles, especially when intravascular administration is intended. Further selection criteria are dictated by the need for large-scale manufacture, extended shelf-life, user friendliness, need to abide by current Good Manufacturing Practices and strict regulatory rules, and numerous other practical considerations, including cost-effectiveness.

The scope of this chapter embraces all biomedical applications of molecular F-compounds. However, FC-in-water emulsions for oxygen delivery will only be briefly summarized here, as they have recently been reviewed extensively [3–6]. Likewise for F-component-containing gels [7] and vesicles [8]. Research directed at developing pharmaceuticals has generated numerous novel F-compounds, self-assemblies and other colloidal
systems, as well as a wealth of data on these compounds and systems. These data have been analyzed from the perspective of the formation, structure and behavior of fluorous nano- and microphases in colloidal systems [2]. Fluorinated colloids and self-assemblies are reviewed in Chapter 12.1 of this Handbook [9], while F-colloids and interfaces are the topic of a section in Current Opinion in Colloid and Interface Science, edited by Krafft [10]. Fluorinated polymers and copolymers (including, for example, the Goretex® materials used in reconstructive surgery), liquid crystals and mesophases in general are excluded from the scope of this review. The reference selection is primarily intended to provide background information, illustration and literature sources, rather than exhaustiveness.

13.2 Specific Properties of Highly Fluorinated Materials That Are the Basis for Their Uses in Medicine and Biology

The potential of FCs in medicine results from a unique set of strongly interrelated properties that will be briefly discussed as a reminder here (see also [5, 8, 11, 12]). The components discussed include FCs and F-amphiphiles, as well as F-alkyl/H-alkyl diblocks. All are characterized by extensive fluorine content, typically in the form of linear or cyclic FCs or of linear F-alkyl moieties.

It must be emphasized that the properties and behavior of FCs and F-alkylated amphiphiles are nothing mysterious. They are in essence of the same nature as those of HC-derived compounds and derive directly from the electronic and dimensional characteristics of the component atoms in a generally well understood and predictable manner [2, 12]. However, swapping a substantial number (typically 7 to 20) of hydrogen atoms for fluorines in a molecule can hardly be inconsequential. The fluorine atom is larger, more electronegative and less polarizable than the hydrogen atom. F-chains are bulkier, stiffer, less cohesive, more hydrophobic and more electroattractive than H-chains. The impact of these differences on macroscopic properties can be of such amplitude that it can generate behavior that is not observed, or reach a level of effectiveness in their performances that cannot be attained, by H-compounds [2].

Moreover, certain combinations of properties can lead to technological feats that just cannot be achieved with non-fluorinated materials, making the fluorinated ones irreplaceable. Superior O2 solubilities would not suffice to make FCs good candidate in vivo O2 carriers; it is the combination of O2 solubilities and biological inertness that creates the potential. Likewise, it is the combination of high volatility and water solubilities lower than those of any other volatile compound that allows use of FCs to stabilize injectable microbubbles for ultrasound imaging.

13.2.1 Perfluoroalkyl Chains: Bulkier, Stiffer, Hydrophobic and Lipophobic

The element fluorine has extremely high ionization potential (just after Ne and before Ar), electroaffinity and electronegativity, and low polarizability (second to Ne). Fluorine is larger than hydrogen (van der Waals radii estimated at 1.47 Å versus 1.20 Å, respectively) and comparable in size to oxygen, but less polarizable [13, 14].
Because fluorine atoms fill more space than hydrogens, F-alkyl chains are bulkier and more rigid than alkyl chains (H-chains). Their cross-section is around 30 Å² (compared with 20 Å² for H-chains) and they have a helical structure rather than the planar “zigzag” structure of H-chains. The mean volumes of CF₂ and CF₃ groups are estimated to be 38 Å³ and 92 Å³ versus 27 Å³ and 54 Å³ for CH₂ and CH₃, respectively [15, 16]. CF₃ is substantially larger than CH(CH₃)₂ and only marginally smaller than C(CH₃)₃ [17]. The larger trans/gauche interchange energy of 4.6 versus 2.0 kJ mol⁻¹ for F- and H-chains, respectively, strongly reduces the conformational freedom of the former. Consequently, the occurrence of gauche defects at equilibrium is also reduced in F-chains which, along with enhanced stiffness, favors their ordered stacking [18]. On the other hand, F-chain stiffness is a likely cause for slower dissolution and equilibration and slower exchange kinetics, as between different types of aggregates or aggregates and monomer [19–21].

On a hydrophobicity scale (Figure 13-2), F-alkyl chains are located on the hydrophobic side, well beyond H-chains of similar length and are, therefore, not only more hydrophobic than H-alkyl chains, but lipophobic as well. Enhanced hydrophobicity has been related primarily to larger molecular surface area for F-chains as compared with H-chains [22, 23]. These features promote self-aggregation, molecular organization, phase separation and the exclusion of non-highly fluorinated solutes [2, 9]. Hydrophobic interactions are well known to influence the availability, distribution and activity of biologically active molecules.

The powerful electron-withdrawing character of F-alkyl chains can generate or amplify an electric dipole, locally increase the polarity of the molecules to which they belong, and modify the surface potential of molecules adsorbed on water. F-alkanoic acids are more extensively dissociated in water than H-alkanoic acids, F-alcohols are substantially more acidic than H-alcohols, while F-alkyl diethers and F-alkyl tertiary amines generally lose all base character.

The thermal stability and chemical inertness of FCs and F-chains reflect a combination of the strength of the C–F bond, low polarizability and strong electroattracting character of fluorine (which reinforces the C–C backbone), and of the compact, repellent electron shield provided by the fluorine atoms. Resistance of F-chains to metabolism may be advantageous when enzymatic material is present.

**Fig. 13-2.** A hydrophobicity scale. FCs are both more hydrophobic and lipophobic than HC, as reflected by their surface tensions γ_s and their interfacial tensions with water γ_i.
13.2.2 Perfluorocarbons: Inert Liquids with Gas-like Behavior

In sharp contrast with strong intramolecular covalent bonds, FCs display very low intermolecular cohesiveness. This originates from the low polarizability of fluorine, which results in lower van der Waals interactions between F-chains than between H-chains, hence in lesser cohesive energy density. Consequently, liquid FCs behave as nearly ideal, gas-like fluids [2, 16, 24]. Lesser chain flexibility is reflected by higher melting points than for HCs, and lesser van der Waals interactions by lower boiling points (barely higher than those of noble gases with comparable MW), translating into a narrower liquid phase domain. As compared with HCs, FCs are also characterized by much higher vapor pressures relative to their MW, exceptional chemical and biological inertness, higher gas solubilities, density, fluidity, spreading coefficients and compressibility, lower surface tensions, water solubility, refractive index and dielectric constant, and a magnetic susceptibility comparable to that of water. For example, the boiling points of \( n\)-F-octane (MW = 438) and \( n\)-octane (MW = 114) are 104 °C and 126 °C, respectively and their surface tensions are 13.6 and 21.6 mN m\(^{-1}\), respectively.

The mixing of FCs and HCs is highly non-ideal [25–27], which is the basis for fluorous biphasic chemistry [28]. The Hildebrand parameter \( \delta \), which is related to the cohesive energy density of fluids and reflects their similarity, ranges as follows: \( \delta \) FCs < \( \delta \) HCs < \( \delta \) water. In order for two fluids to be mutually soluble, they need to have similar \( \delta \) values. The \( \delta \) values of FCs are typically close to 6 hildebrands (cal\(^{1/2}\) cm\(^{-3/2}\)), as compared with 5.7 for O\(_2\), 7 to 9 for HCs, and 23.4 for water. FCs and HCs with seven carbon atoms or more are not miscible at room temperature. The calculated Hildebrand solubility parameter was used for a rough estimation of fluorophilicities within a given family of compounds [29].

The large solubility of gases in liquid FCs is well documented (Figure 13-3) [5, 30, 31]. Indeed it takes less energy to create a hole in a lesser cohesive material and also less energy to introduce a molecule of comparable cohesive energy into that hole. The large solubility of gaseous CO\(_2\) in FCs, and the enhanced solubility of FCs in liquid and supercritical
CO₂ further indicate the likeness of the two media. The solubility of O₂ in F-n-hexane and n-hexane has recently been measured precisely (51.8 and 36.8% v/v, respectively, at 37 °C) and compared with computer simulations [32].

High hydrophobicity translates into low water solubility. The solubility of FCs in water, as estimated from Ostwald ripening rate measurements in emulsions, is indeed very low (e.g., 3.8 × 10⁻⁹ mol L⁻¹ for n-C₄F₁₈) [33]. It decreased by a factor of ~8 for each added CF₂ in a homologous series, while it increased upon cyclization and branching, in correlation with the decreasing solvent cavity surface [29, 33]. This solubility correlates well with the surface or the volume of the cavity created in water by the FC molecule [34]. The solubility of short F-alkanes in water has been determined experimentally as well as calculated by molecular simulation [35]. Molecular simulation of this solubility of O₂, CO₂ and H₂O in some F-alkyl/H-alkyl compounds and in F-octyl bromide has also been carried out [35a].

Biological constraints, especially excretion rates, have limited the number of liquid FCs that have actually undergone any significant pharmaceutical development for intravascular use. These include primarily F-decalin 1, F-tripropylamine 2, bis(F-butyl)ethene 3, F-octyl bromide 4, and F-x,α-dichlorooctane 5. Volatile F-chemicals, including the light F-alkanes CₙF₂ₙ₊₂ (n = 3 to 6) and SF₆, are being used in injectable gaseous microbubbles (Section 13.3).

The biological inertness of FCs is well documented. Clinical research on liquid ventilation involving installation of liter-size amounts of F-octyl bromide in the lungs uncovered no significant side effects [36–40]. Oral ingestion of liter-size doses of F-octyl bromide was approved by the FDA for X-ray imaging of the gastrointestinal tract. Intravascular administration of FCs in dispersed form and excretion characteristics are discussed in Sections 13.3 and 13.4.

13.2.3
Fluorinated Amphiphiles: a Predilection for Self-Assembly

Fitting molecules with F-alkyl chains exacerbates the amphiphilic character of these molecules. Fluorosurfactants are particularly valuable when extreme surface activity, extreme hydrophobicity, high fluorophilicity or lipophobicity, and resistance to high temperatures, aggressive environments and detergent activity are needed [41].

A large diversity of well-defined F-surfactants has been synthesized with a view to providing highly surface-active components usable in pharmaceuticals and to determining the impact of F-chains on the structure and properties of colloids. Hydrophilic, lipophilic and fluorophilic characters, size and shape, chemical functions available for derivatization, etc. were varied extensively [11, 42, 43]. Further examples of F-surfactants that may provide components for biomedical applications include F-amphiphiles derived from carbohydrates and polyols [44–46], aminoacids and peptides [47], lipids [48], dimeric (gemini) surfactants [49], surfactants with two polar heads for one F-chain [50], surfactants with a “reverse” HC-
FC-polar head sequence [51–53], bolaamphiphiles with a central F-segment [54], amphiphilic fluorinated copolymers [55], and gel-forming amphiphilic polymers with F-alkyl-ends or side-chains [21, 56–58].

F-surfactants are both more effective and more efficient than their H-counterparts. They can decrease the surface tension of water from 72 mN m⁻¹ to typically 15–20 mN m⁻¹ versus 25–40 mN m⁻¹ for H-analogs. They can reduce the FC/water interfacial tension to values as low as 1 mN m⁻¹ or less. Efficiency is illustrated by critical micellar concentrations (CMC) in water that are typically one to two orders of magnitude lower than for HC analogs. The CMC of a surfactant is indeed related to the water solubility of its hydrophobic moiety [22]. Therefore, F-surfactants can usually be used in much smaller amounts, partially compensating for higher cost and possibly reducing any physiological burden associated with the surfactant. The CMC values for F-alkylated surfactants are generally considered to be roughly equivalent to those of H-alkylated analogs with a 50–70% longer chain [15, 34]. This rule may, however, not be applicable when the chains are only partially fluorinated, as F-chains tend to reduce the contribution of H-spacers to the adsorption and micellization energies [59]. It is also worth noting that the presence of a single hydrogen atom at the end of the hydrophobic chain (as in HCF₂− versus CF₃−) results in a considerable increase in surface tension and CMC [34, 60].

Despite substantially higher surface activity, F-surfactants were consistently found to be less hemolytic than their H-counterparts. Hemolytic activity was often fully suppressed [8, 46, 61]. The introduction of F-alkyl chains into a molecule apparently does not increase its acute toxicity. Acute lethal doses, LD₅₀, of several grams per kg body weight (b.w.) have been reported for certain F-alkylated phosphatidylcholines of type 6 and F-alkylated telomers 7 in mice [8, 42, 62]. The cytotoxicity of the F-alkylated dimorpholinophosphates 8 on mouse fibroblast or human lung epithelial cells was noted to decrease with increasing F-chain length [63]. However, contrary to FCs, the pharmacology of F-surfactants is still largely unknown. With few exceptions [64], their absorption, distribution, metabolism and excretion characteristics remain to be determined, as well as their sub-acute and chronic toxicity. F-surfactants can influence protein adsorption onto particles and phagocytic uptake of particles by macrophages [65, 66]. The many unknowns that remain relating to their toxicity and pharmacology certainly hinders the acceptance of F-surfactants in pharmaceuticals.

When co-dispersed in water, F- and H-amphiphiles tend to form two types of micelles, rich in one or other of the amphiphiles [67–71]. When present simultaneously in bilayer membranes, they form phase-separated domains [72, 73]. Poor mixing also commonly leads to phase separations within Langmuir and Langmuir-Blodgett films [72, 74–76]. Application to the preparation of associative polymers [55, 77] and terpolymers [78] with mutually incompatible F- and H-domains has also been reported.
The extreme hydrophobic character and, additionally, the lipophobic character of F-alkyl chains generate a powerful driving force for F-amphiphiles with F-chains longer than four carbon atoms to collect at interfaces, and to self-assemble into discrete compartmentalized organized molecular systems when dispersed at low concentrations in water and other solvents [2, 8]. F-amphiphiles display a stronger tendency to form bilayer membranes than H-analogs, generating well-organized stable films, bilayers, vesicles, tubules and fibers, with stability and properties generally unmatched by H-analogs.

The enhanced tendency for F-amphiphiles to self-assemble into Lₐ (fluid lamellar) rather than L₁ (micellar) phases (Figure 13-4) and the powerful structuring and stabilizing effect provided by F-chains is remarkably illustrated by the formation of highly stable F-vesicles from single-chain, short (typically 10 C atoms) F-amphiphiles (e.g., 9), without the need for any co-surfactant or any supplementary associative interaction, while their hydrogenated analogs only form micelles [79–81]. Such F-vesicles withstood heat sterilization and showed only little changes in particle size distribution after 3 months at 40 °C. This finding has since been confirmed in other systems [82, 83]. The differences in aggregation behavior of F- versus H-amphiphiles are in line with the difference in their packing parameter (which relates to the tail cross section to polar head area ratio) [80, 84–86]. The larger tail cross section of F-amphiphiles tends to favor formation of aggregates with lesser surface curvature; their stiffness tends to slow down aggregation kinetics.

Likewise, F-amphiphiles have been reported to readily form hollow microtubules made of rolled-up bilayers [8, 62, 87]. While the presence of a chiral center is generally deemed necessary for the inception of the rolling-up of tubules, and hydrogen bonds are also usually involved in their formation, robust fluorinated tubules were obtained from non-chiral, non-hydrogen bonding single-chain F-amphiphiles such as 8 [87–89]. Helical fibers, several
microns in length, were obtained from F-alkylated glycolipids [90, 91]. F-tubules and fibers were also grown in ethanol, dimethylsulfoxide, formamide and dimethylformamide [50, 92] and supercritical CO₂ [93].

13.2.4 Fluorocarbon–Hydrocarbon Diblocks: Fluorophilic/Lipophilic Amphiphiles

Linear F-alkyl/H-alkyl diblock compounds, such as 10 and 11 constitute a set of

\[ C_n F_{2n+1} C_m H_{2m+1} \quad (\text{FnHm}) \quad 10 \quad C_n F_{2n+1} CH=CCH_{m} H_{2m+1} \quad (\text{FnHmE}) \quad 11 \]

F-amphiphiles that have mutually incompatible fluorophilic and lipophilic moieties, but are devoid of the hydrophilic polar head present in standard surfactants. These diblocks can play, with respect to fluorous and hydrocarbonous phases, a role similar to that played by standard surfactants at a water/HC interface. They represent simple and valuable building blocks for producing and stabilizing colloids with fluorous phases, and provide an effective means of modulating the properties of these colloids.

The synthesis of F-alkyl/H-alkyl diblocks is straightforward [94]. These diblocks can have dipole moments (primarily due to the CH₂–CF₂ dipole), surface tensions and dielectric constants higher than those of both their totally fluorinated and totally hydrogenated analogs, and physical properties quite different from those of these analogs [2, 16, 27, 95]. F-alkyl/H-alkyl diblocks form micelles, although with low aggregation numbers, when dispersed in an HC and reverse micelles in an FC [96, 97]. They form gels in organic solvents, including FCs and HCs [98, 99]. They can reduce the surface tension of HCs [100, 101], lower the interfacial tension between an FC and water, and act as a co-surfactant that further reduces the FC/water interfacial tension in the presence of a phospholipid monolayer [102]. Langmuir films made from combinations of phospholipids and F-alkyl/H-alkyl diblocks display a unique reversible, vertical segregation phenomenon upon compression [103]. Novel, highly monodisperse, stable non-polar surface hemimicelles were obtained when a monolayer of FnHm was transferred onto a silicon wafer. The radius of the micelles was determined by the length of the F-chain and H-chain, demonstrating the possibility of decorating surfaces with molecular clusters of predetermined size in the nanometer range [104].

From the biological viewpoint, the still limited data that are available indicate a behavior close to that of FCs, including absence of hemolytic activity and effect on cell cultures, very low acute toxicity, absence of metabolism, and excretion rate dependent on block length [8, 105]. Diblocks thus appear to benefit from simplified pharmacology, which may facilitate their pharmaceutical development.

F-alkyl/H-alkyl diblocks have provided effective emulsifiers for the preparation of HC-in-FC emulsions and strong stabilization of FC-in-water emulsions when used in conjunction with an appropriate surfactant (Section 13.4.5). They have also been used as the dispersed phase of microemulsions in water [106]. Addition of diblocks to a fluorous phase may help increase the solubility of lipophilic material. When present in a liposomal membrane, F-alkyl/H-alkyl diblocks impart to this membrane some of the properties obtained with complete F-surfactants (Section 13.6).
Contrast Agents for Diagnostic Imaging

Recent approval by the European or American health authorities of several contrast agents for ultrasound imaging has propelled FC-stabilized injectable microbubbles into the limelight. These agents constitute the first large market-size FC-based medical products to have become commercially available, which explains the tremendous activity that is currently focused on FC-based microbubbles. Targeted FC microbubbles and FC-in-water emulsions are now being investigated for molecular imaging, that is identifying the molecular signature (rather than anatomical signs) of disease by ultrasound or magnetic resonance (MR) imaging (Section 13.3.2).

13.3.1 Gaseous Fluorocarbon-Loaded Microbubbles as Sound Reflectors for Ultrasound Imaging

13.3.1.1 Needs and Challenges

Worldwide echography is the most frequently used imaging modality. It is a non-invasive, portable (e.g., bedside), widespread, low-cost technique that allows diagnosis of numerous pathological conditions. However, as for any imaging technique, there are instances when contrast between tissues is not large enough to allow reliable, conclusive diagnosis. For instance, in the absence of a contrast agent, ultrasound imaging provides only limited information on the cardiovascular system, blood flow and organ perfusion. The availability of effective ultrasound contrast agents is having a considerable impact on diagnostic ultrasound imaging [107–114].

The optimal injectable sound scatterer is a tiny gas bubble, which is highly compressible and reflects sound waves several orders of magnitude more effectively than red blood cells. In the circulation this gas bubble needs to be stable long enough to provide an adequate imaging time window. It must also have minimal side effects. Its diameter, in the 1–5 μm range, must be large enough to provide effective scattering intensity (which shows dependence to the sixth power of the bubble radius), yet small enough to easily cross capillary beds. Particle size needs to be well controlled and should not grow in the circulation. The microbubbles should preferably have a highly deformable soft shell, so as not to damp sound scattering. Their components obviously need to be safe and readily excretable, and should preferably not include proteinous material of human or animal origin.

13.3.1.2 Principles of In Vivo Microbubble Stabilization: a Key Role for Perfluorochemicals

When micron-size air bubbles are injected into the circulation, they dissolve rapidly in the blood under the combined actions of the blood pressure and the Laplace pressure ($\Delta P = 2\sigma/r$) generated by surface tension (Figure 13-5). Additional contributors to bubble dissolution include oxygen metabolism and ultrasound energy. In order to hinder bubble dissolution, the gas inside the bubble must be less soluble in the blood than air. Perfluorochemical gases are obvious candidates for this role, as their water solubility is at least an order of magnitude lower than for HC analogs of similar volatility. The in vivo behavior of a microbubble filled only with an FC gas is depicted in Figure 13-6a. It first expands because the gases dissolved in the blood will be drawn into the bubble until the FC is diluted to
Fig. 13-5. Simulation of the dissolution of air-filled microbubbles in the blood under the combined action of surface tension and arterial blood pressure. From reference [117], with permission.

Fig. 13-6. Simulations of microbubble size changes in the circulation. a) Bubbles containing only an FC gas first expand as blood gases diffuse into the bubble, until an osmotic equilibrium is reached (stage 1); they then slowly shrink at a rate that depends on the solubility of the FC (stage 2); eventually the FC may condense and the bubble collapse if the Laplace pressure exceeds the saturated vapor pressure of the FC (stage 3). b) In osmotically stabilized bubbles, the partial pressure of the FC gas counterbalances surface pressure and blood pressure, thus stabilizing the bubble at a predetermined size; the expansion phase is prevented. From reference [117], with permission.
an osmotic equilibrium composition [115–117]. Such droplet growth in the circulation can
be prevented by loading the bubble with just the amount of insoluble FC vapor needed to
counterbalance the surface tension and blood pressure forces that push the gases inside
the bubble towards dissolution (Figure 13-6b) [113, 117, 118]. Once osmotic equilibrium is
reached, the rates of diffusion of the water-soluble gases in and out of the bubble are equal.
The concentration of FC required to stabilize a microbubble at a given target diameter in
the circulation (Figure 13-6b or Figure 13-7) can be calculated. The optimal FC osmotic
stabilizing agent combines low water solubility and high saturated vapor pressure at
body temperature [117]. An in vitro study indicated that \( n-C_6F_{14}, CF_3(OCF_2)OCF_3 \) and
\( CF_3(OCF_2CF_2)OCF_3 \) are among the most effective FCs in this respect [119]. A further study
of the effect of filling gases on the backscatter from microbubbles in vitro can be found in
[120].

The bubble wall consists typically of 2–3 nm thick, highly expandable phospholipid mono-
layers or somewhat thicker membranes made from a heat-denaturated protein or a biode-
gradable polymer. The properties of the bubble wall can significantly influence resonance
frequency; the stiffer the shell, the higher the resonance frequency. Microbubbles a few mi-
crons in size are normally restricted to the vascular spaces, hence are essentially blood pool
agents, i.e., agents that, when submitted to ultrasound, "light up" the blood, hence the
blood vessels and chambers of the heart. Substantial negative surface charge (such as ob-
tained by including palmitic acid or dipalmitoylphosphatidic acid in the lipid shell) can re-

![Fig. 13-7. Phospholipid-coated nitrogen microbubble osmotically
stabilized by F-hexane vapor. At equilibrium, the rates of diffusion of the
water-soluble blood gases in and out of the bubble are equal. The added
partial pressure of the FC vapor counterbalances blood pressure and
Laplace pressure](image-url)
sult in bubble retention within pulmonary and myocardial capillaries via complement-mediated attachment to the endothelium [121]. Such retention may be useful when delayed imaging is sought; it may, however, also raise some safety issues. The presence of poly-(ethylene glycol) (PEG) on the bubble’s surface markedly reduced such attachment [121].

Because gas bubbles provide extremely high scattering intensity, the total dose of gas that is injected intravenously to patients is minuscule, typically 250 μL, containing in the order of 10⁸ microbubbles of a few μm in diameter. Peak blood concentrations of FC are then in the order of 10 ng mL⁻¹. The total amount of material needed for effective diagnosis is in the order of milligrams as compared with grams for the contrast agents currently used in MR or X-ray imaging. The light F-chemicals used ultimately leave the body with the expired air. A pharmacokinetic study in humans indicated, for example, that diagnostic doses of F-pentane, administered in the form of an emulsion, had an elimination half-life of around 2 min; recovery of the FC in the expired air was almost complete after 2 h [122].

13.3.1.3 **Bubble-Specific Imaging – Harmonics and Pulse Inversion Techniques**

A unique feature of contrast echosonography as compared with any other imaging modality is that the contrast agent interacts with the sound waves [123–130]. Microbubbles rapidly expand and contract under the action of ultrasound. At a critical frequency, which depends primarily on bubble size, they resonate and become transmitters themselves. By chance, microbubbles a few microns in size resonate within the range of ultrasound frequencies used for diagnostic imaging. Moreover, when the acoustic pressure is sufficient, the microbubbles behave differently during the positive and negative pressure of the sound wave. Their oscillations being asymmetric generate non-linear echoes and a significant amount of super- and sub-harmonics of the incident sound wave [123, 129, 131]. “Harmonic imaging” can be performed by using broadband transducers that transmit between 1.3 and 3 MHz and receive at twice that frequency, while filtering the incident frequency. This way, the signals from red blood cells and tissues (which are poor resonators and do not generate much harmonics) are largely suppressed, leaving the signals at the second harmonic frequency, which originate essentially from the microbubbles. Harmonic imaging thus enhances the contrast between microbubble-containing and non-microbubble-containing tissues, hence is a microbubble-specific imaging mode [123, 129, 131–136].

The resolution and sensitivity of harmonic imaging have been further enhanced by using appropriate pulse sequences. In pulse inversion techniques [137, 138], two ultrasound pulses are emitted in close sequence, the second 180° out of phase with the first (Figure 13-8). When the received signals of the two pulses are added, the echoes from linear reflectors essentially cancel out since they are equal and opposite. On the contrary, the signals from the microbubbles, which are non-linear reflectors, do not cancel out, yielding a highly contrasted image (Figure 13-9). This technique is particularly effective at producing high contrast, high resolution imaging of blood vessels [139]. Its sensitivity is so high that a single microbubble can be monitored [140].

13.3.1.4 **Controlled Bubble Destruction: Monitoring Tissue Perfusion**

Another unique property of microbubble contrast agents is that the bubbles can be destroyed in a controlled fashion by ultrasound, especially at resonance. When the bubble shell is disrupted, the scattering level increases sharply for a short period of time and the scat-
Fig. 13-8. Phase inversion harmonic imaging. Early second harmonic imaging used band pass filters that allowed the generation of images from frequencies mostly reflected by microbubbles. However, these images still contained some signal from the tissues. The much more efficient pulse inversion modes use a pulse cancellation technique: two pulses are sent out close together in time. The second pulse is an inverted replica (180° phase shift) of the first. Because tissues do not distort sound, the reflections from tissues, when added, cancel each other (panel a). The distortions produced when sound is reflected by microbubbles affect the two transmitted pulses differently. When added, these pulses do not cancel, producing an image that is highly sensitive to the presence of microbubbles (panel b). Highly contrasted high resolution images are produced.

Fig. 13-9. *In vitro* images of a “phantom” (model) vessel containing the FC bubble contrast agent Optison surrounded by tissue-mimicking material. a) conventional, non-contrasted image; b) harmonic image with improved contrast between agent and tissue; c) pulse inversion harmonic image; contrast is further improved by suppressing linear echoes from tissue. From reference [110], with permission.
tered signal becomes highly nonlinear, hence well suited for harmonic imaging [129, 141].
This effect is irreversible and lasts until the shell-free gas microbubble is dissolved in the 

blood.

Controlled bubble destruction (“bleaching”) by intermittent high power pulses in a region 
of interest, and monitoring of bubble reappearance in the field also provides a very effective 
tool for kinetic studies [138, 142–145]. This technique allows the assessment of tissue blood 
flow velocity and fractional blood volume. Accurate determination of blood velocity supposes 
that the vast majority of the bubbles within the region of interest will be destroyed by an 
ultrasonic pulse of sufficient intensity. Different contrast agents displayed significant differ-
ences in sensitivity to acoustic pressure [146]. A phantom that mimics the microcirculation 
allowed standardized analysis of contrast replenishment kinetics after acoustic destruction 
of the microbubbles at velocities comparable to those found in capillary beds [147]. Bubble 
destruction depends on frequency and intensity of the ultrasound waves. At very high en-
ergy (as expressed by a “mechanical index”) destruction of microbubble-containing phag-
ocytic cells can occur [128]. Bubble destruction can be limited by use of low acoustic power 
and/or intermittent insonation and increasing the time interval between pulses. The possi-
ble effects of microbubble destruction on tissues have also been investigated [148, 149]. The 
extremely localized, transient heating of a liquid shell of micrometer thickness around a 
bubble as a result of acoustic heat deposition was not deemed likely to cause severe biologi-
cal damage [150].

13.3.1.5 The Products
The initial commercial ultrasound contrast agents Albunex (Molecular Biosystems Inc., San 
Diego, CA, USA) and Echovist (Schering AG, Berlin, Germany) that were developed in the 
early 1990s did not contain FCs. Their intravascular persistence was limited and they did not 
withstand repeated passage through the pulmonary capillary beds. When injected intrave-
nously they could not reach the left cardiac ventricle, and hence had little utility.

The first FC-based agent, Optison® (developed by Molecular Biosystems; now marketed 
by Amersham Health Corp., Little Chalford, UK) was launched in 1998. It consists of an 
aqueous suspension of F-propane microspheres, 2.0 to 4.5 μm in diameter, whose shells are 
made of heat-denatured human albumin. The agent effectively improves ultrasound 
imaging and displays minimal side effects [143, 151–155]. Definity®, developed by ImaRx 
(Tucson, AZ, USA) and DuPont Pharmaceutical Co. (North Billerica, MA, USA) [156–158] 
was licensed in the United States in 2001 and is now marketed by Bristol-Myers-Squibb 
(New York, USA). It is also a dispersion of F-propane microbubbles, 1 to 3.3 μm in diameter, 
but with a phospholipid monolayer coating consisting of dipalmitoylphosphatidylcholine 
(DPPC), a methylPEG dipalmitoylphosphatidylethanolamine (MPEG5000 DPPE) and a mi-
nor amount of negatively charged dipalmitoylphosphatidic acid. The product comes as a vial 
containing the precursor components that, upon agitation by the sonographer in a calibrated 
mechanical shaker, yields the injectable microbubble dispersion. Both Optison and Definity 
have a shelf life of two years under refrigerated storage conditions.

SonoVue® (Bracco, Milan, Italy) [159–164] has been licensed in Europe. It uses SF₆ as 
the poorly water soluble F-chemical and a phospholipids/PEG/palmitic acid membrane. It 
comes as a lyophilized powder stored under SF₆, which upon addition of a saline solution, 
yields the injectable agent.
Imagent™, which is based on the osmotic stabilization concept developed by Alliance Pharmaceutical Corp. (San Diego, CA, USA) and has been approved in the United State in 2002, is formulated as a heat-sterilized spray-dried powder comprising hollow, amorphous and porous microspheres under a nitrogen/F-hexane atmosphere. The microspheres are made of dimyristoylphosphatidylcholine (DMPC), hydroxyethylstarch (as a wall-forming agent), a poloxamer (as a wetting agent), sodium chloride and a phosphate buffer (for tonicity and pH control). Upon addition of water, a phospholipid monolayer forms that traps the gas mixture present in the headspace inside a microbubble. The amount of FC in the gas mixture was calculated to provide bubbles about 3 μm in diameter in the circulation, and ensure that these bubbles could not grow in vivo, but rather shrink slowly over time. The persistence of the microbubbles in the blood is controlled by their eventual dissolution rather than by clearance by the reticuloendothelial system [119]. Recent reports on the product’s use and efficacy include [111, 135, 136, 165–167]. Imagent has now been licensed to and is being marketed by IMCOR Pharmaceutical Co. (San Diego, CA).

All of the above commercial agents appear to benefit from satisfactory side effect profiles. With several million injections given, no death has been reported that is attributable to the agent, nor has there been any clinically significant side effects.

A phase change from liquid at room temperature to gaseous at body temperature was the basis for an injectable F-pentane emulsion stabilized by an F-surfactant (Sonus Pharmaceuticals, Bothel, WA, USA) [122, 168, 169]. This product was, however, abandoned, possibly because bubble formation and growth in the circulation were difficult to control, and/or because of side-effects [170]. A negatively charged variant of this agent was briefly investigated [171].

Further agents and formulations under investigation include PFC-exposed sonicated dextrose albumin (PESDA) [172–175]; Acusphere’s AI-700, which has a biodegradable synthetic polymer shell [176]; BR14 (Bracco), a lipid-coated F-butane microbubble [177–179]; Sonazoid® (Amersham Health), which consists of lipid-stabilized F-butane microbubbles, but whose development appears to have been interrupted [180]; and MP1950 (Mallinckrodt, St. Louis, MO, USA), a sonicated dispersion of F-butane in an aqueous micellar dispersion of phospholipids, pegylated phospholipid and PEG stearate [181]. Targeted microbubbles are also being developed (Section 13.3.2).

13.3.1.6 Medical Imaging Applications

Being restricted to the vascular space, the present FC-based ultrasound contrast agents are ideal for echocardiography and vascular imaging. Echocardiography is extensively used to assess ischemic heart disease. The approved contrast agents have all demonstrated left ventricular opacification, significant improvement in endocardial border delineation (Figure 13-10) and assessment of wall motion during systolic contraction, hence allowing improved detection of structural and functional abnormalities, as compared with non-contrast ultrasound procedures [108–110, 112]. For example, harmonic ultrasound imaging at the bedside with Optison allowed determination of left ventricular wall motion and ejection fraction (the percentage of the blood in the left ventricle that is ejected during a heart beat), hence ventricular function, in 91% of patients, as compared with 56% with standard imaging, and prevented misinterpretations in 44% of studies [182]. Contrast-echocardiography during stress is even more effective than imaging at rest [109]. Improved image quality
results in increased diagnostic accuracy, a reduction in downstream testing, and possible improvement in patient outcome. Use of contrast agents may therefore have a significant impact on patient management in the intensive care setting [107].

Vascular imaging is another important goal for contrast echosonography. Filling a blood vessel with a contrast agent allows detecting vessel occlusions, wall abnormalities such as atherosclerotic plaques, and assessment of their effects on blood flow. Clear visualization of blood clots can be obtained and even, because of the ability of ultrasound to monitor single microbubbles, of the tiny open channels that form as a clot begins to recanalize [183]. Accurate demonstration of plaques and plaque ulceration was reported [166, 184]. Unstable plaques are susceptible to rupture and microthrombus formation that often precede myocardial infarction, ischemic attacks and strokes. Their timely detection may allow early therapeutic intervention.

Controlled microbubble destruction (bleaching) by a high energy pulse, followed by imaging with a non-destructive pulse allows accurate imaging of tissue perfusion and detection of vascular insufficiencies, hence of vascular occlusion [135, 144, 185]. Assessment of myocardial perfusion, hence of microvascular integrity, is a key to diagnosing coronary artery disease and myocardial infarction, determining infarct area during coronary occlusion and the area at risk of necrosis, assessing coronary stenosis, and monitoring the success of thrombolytic treatment, hence guide subsequent patient management [109, 164, 167, 186–189]. Assessment of perfusion differentiated between stunning and necrosis and accurately predicted recovery of left ventricular function in patients after acute myocardial infarction [190]. Further recent papers demonstrating the utility of PFC microbubbles to assess myocardial perfusion and viability include [153, 157, 173, 174, 191]. Accuracy of myocardial
perfusion quantification was similar or superior to that provided by $^{99}$Tc single-photon emission computed tomography, a much more cumbersome and costly technique [112, 175]. Contrast-specific ultrasound of the myocardium may thus provide results equivalent to perfusion imaging with radionuclides with the advantages of providing real-time, direct information on both heart function and perfusion at lower cost and of eliminating the handling of radioactive materials [152, 175].

By visualizing the arterial tree and filling pattern within an organ, contrast-specific sonography can allow detection of abnormal regions. It can also improve characterization of the disease, i.e., infection versus infarction versus trauma versus cancer [155, 192], and detection and assessment of angiogenesis consequent to tumor growth [193]. Regional cerebral blood flow mapping was achieved in newborn piglets [194]. Analysis of microbubble refill kinetics in human cerebral microcirculation after bubble destruction by transcranial ultrasound allowed quantitative evaluation of cerebral blood flow [195]. Similar techniques allowed visualization and quantification of kidney [153, 196], liver [153] and tumor microvascularity [136, 197, 198]. Renal perfusion and perfusion defects in animal models were depicted [135, 199, 200]. The detection of liver lesions, including carcinoma and metastasis were substantially enhanced when contrast agent was present [201, 202]. Contrast-echosonography may help monitor the microvascular changes associated with the growth of malignant tumors and with tumor response to treatment more easily than CT or MR imaging [203]. A clinical study indicated that sonographic contrast may help identify prostate cancer based on differences in vasculature between malignant and normal tissue (Figure 13-11) [165].

Finally, contrast imaging can facilitate guidance in therapeutic procedures such as biopsies, cryo- and radiofrequency ablation of malignant tissue and metastasis, assessment of tissue destruction and detection of any residual viable tumor [204]. It can also provide a non-invasive means of monitoring the outcome of surgical intervention or drug treatment. Furthermore, microbubbles may constitute effective tools for drug development to determine the pharmacokinetics and pharmacodynamics of new molecules, establish therapeutic efficacy, dose regimen, etc.

![Fig. 13-11. Prostate echography a) before and b) after administration of Imagent. The presence of an abnormal mass is clearly seen, which was not the case in the absence of contrast agent. From reference [165], with permission](image-url)
13.3.2 Targeted Fluorinated Colloids for Molecular Imaging – Molecular Markers for Specific Pathologies

Substantial efforts are now being devoted to designing FC microbubbles [205–207] and FC emulsion droplets [208] that seek the unique molecular signature of a given pathology, making diseased tissues detectable by ultrasound or MR imaging. Molecular imaging (the detection of specific molecular markers such as proteins or other cellular receptors associated with a given pathology) extends the basis for diagnosis of pathology from anatomic description to detection of biochemical changes. Site-targeted particles (Figure 13-12) that are retained by specific diseased tissues, are expected to provide higher sensitivity and specificity than standard blood pool agents, hence earlier and safer assessment of pathology. Because microbubbles and emulsion droplets normally do not escape the circulation, targeting is essentially restricted to pathologies that express specific ligands within the vascular lumen, typically endothelial cells, leukocytes and thrombi. Targeting of activated endothelial cells may thus be used to signal thrombi, areas of inflammation, atherosclerotic plaques and angiogenesis in solid tumors. Additionally, particles targeted to specific cell-surface epitopes can provide site-specific drug and gene delivery (Section 13.6).

Fig. 13-12. Schematic representation of FC microbubble and emulsion droplet targeting strategies for molecular imaging and drug delivery. a) Passive targeting using the intrinsic ability of certain shell components (e.g., albumin or phosphatidylserine) to bind to receptors expressed on the target cell’s surface. b) Binding of the particle, through avidin–biotin interactions, to biotinylated antibody or other ligands that recognize specific disease-related antigens. c) Covalent binding of such ligands, usually through a PEG spacer, to a microparticle shell component. d) Simultaneous binding to a targeted microparticle of stealth-providing elements, drugs and markers (e.g., a Gd$^{3+}$ chelate). Adapted from references [205, 208], with permission.
13.3.2.1 “Passive” Targeting of Microbubbles

Certain microbubbles provide a late phase of enhancement when, after initial enhancement of the blood pool, they highlight liver and spleen parenchyma. This can occur when bubbles are cleared from the bloodstream and taken up by the reticuloendothelial system (RES) or are mechanically slowed down within the sinusoidal network [209]. Passive targeting of microbubbles relies essentially on size and shell characteristics. It allows detection of very small size liver lesions, including carcinoma and metastasis, as microbubbles highlight normal tissue, but not tumors [210]. RES accumulation also allowed evaluation of hemorrhage within the liver and spleen in dogs [180], providing potential benefit for the assessment of trauma victims.

Assessment of inflammation is another important goal for microbubble-enhanced imaging. Both albumin- and lipid-coated PFC microbubbles were found to be retained in inflamed tissue, for example after myocardial ischemia-reperfusion injury, because of \( \beta_2 \)-integrin- and complement-mediated attachment to and phagocytosis by activated leukocytes that adhere to vascular endothelium [211, 212]. The phagocytosed microbubbles remained acoustically active well after microbubbles had been cleared from the blood pool [212]. These non-specific leukocyte/microbubble interactions may thus provide a means of imaging inflammation, in which leukocyte adhesion plays an important part, and monitoring treatment. Retention of F-butane microbubbles in areas of inflammation has been further increased by incorporating phosphatidylserine into the lipid shell [213]. This targeting procedure was used to assess the severity of myocardial inflammation after ischemia/reperfusion [214]. Phagocytosed microbubbles experience a viscous damping that increases the frequency of their echo as compared with free microbubbles [128]. The distinct signals from microbubbles inside of activated neutrophils may thus provide a unique tool for selective identification of sites of inflammation.

13.3.2.2 Active Site-Directed Targeting of Microbubbles

Active targeting supposes attachment to the microbubbles’ surface of receptor ligands, including monoclonal antibodies, polysaccharides and peptides, which recognize disease antigens. Binding can be achieved through covalent or non-covalent (hydrophobic, avidin/biotin pairing) interactions [215]. The strength of receptor–ligand mediated adhesion between pegylated phospholipid-coated microbubbles and coated glass beads was shown to depend on bubble surface architecture [216]. Strong attachment required that the ligand be attached to the shell via an extended PEG spacer (i.e., a spacer that is longer than the PEG chains that were used as a shell stabilizer), thus projecting the ligand away from the bubble’s surface and enhancing its availability.

Active targeting to inflammation sites can be achieved with FC microparticles that have antibodies to endothelium cell adhesion molecules attached on their surface. Such adhesion molecules (which are expressed on endothelial cells activated during the inflammatory response) include P-selectin, intercellular adhesion molecule-1 (ICAM-1) and certain integrins. An anti-ICAM-1 monoclonal antibody has been covalently bound to a lipid component of the shell of F-butane microbubbles through amide bonds [217]. These microbubbles demonstrated selective binding to activated cultured endothelial cells overexpressing ICAM-1 \textit{in vitro}. In another approach, conjugation, via a biotin/avidin system, of antibodies against P-selectin to F-butane/lipid microbubbles through a PEG spacer increased their re-
tention in inflamed tissue, allowing early detection of ischemia-reperfusion injury of the kidney [218]. The binding and detachment kinetics of such microbubbles when exposed to shear stress have been investigated [218a].

Detection of blood clots is another clinically important goal. Targeting of vascular clots has been achieved with a FC microbubble (e.g., MRX-408, ImaRx Pharmaceutical Corp., Tucson, AZ, USA) having a peptide with an Arg-Gly-Asp sequence covalently attached via a PEG spacer to a lipid membrane component [219, 220]. The peptide binds selectively to the GPIIb/IIIa fibrinogen receptor on activated platelets that attach to thrombi. Detection of thrombus was demonstrated in dog and mouse models using such targeted microbubbles [221, 220].

F-butane/lipid microbubbles targeted to α-integrins (which are overexpressed in neo-vascular endothelium) allowed assessment of regions of angiogenesis in mice [222]. Such agents may improve tumor imaging, as tumors promote angiogenesis for their growth, and hence help diagnose cancer at earlier stages [203]. They may also help monitor promotion of angiogenesis in chronically ischemic tissue.

13.3.2.3 Targeted Fluorocarbon Emulsions for Diagnosis by Ultrasound or Magnetic Resonance Imaging

Targeted FC emulsions also provide a very interesting approach to molecular imaging of pathology [208, 223, 224]. The target pathologies are the same as for microbubbles and include inflammation, thrombi, atherosclerosis and tumor-related angiogenesis, each having its specific molecular signature. Detection of these targets and differentiation from normal tissue likewise involves binding onto the droplet’s surface of ligands that specifically bind to cellular epitopes and receptors characteristic of the target pathology.

While enhancement of ultrasonic scattering by an untargeted emulsion is poor, the scattering observed when the droplets attach collectively in adequate density to a surface is remarkable. This phenomenon has been accounted for by a simple acoustic transmission line model [224, 225]. In this model, a thin, contiguous layer of ligand-bound emulsion droplets, which has essentially the properties of the neat FC, creates an acoustically reflective interface between the targeted surface and its surrounding. In vitro acoustic reflectivity enhancement of a nitrocellulose membrane or plasma thrombi targets was inversely correlated with the acoustic impedance of the FC. The greatest enhancement, in the series investigated, was obtained for F-hexane. An advantage of FC emulsions over FC microbubbles may reside in their longer intravascular persistence.

Specific detection of thrombi in a canine model demonstrated the concept of molecular imaging with targeted FC emulsions [223]. In a first step, a biotinylated monoclonal antifibrin antibody was administered that accumulated at the target. Avidin, which attaches to the biotinylated ligand, was then infused. In a third step, an FC emulsion that had a biotinylated phosphatidylethanolamine incorporated in its lipid membrane was administered, which attached to the avidin–biotin complex, and hence to the target site. The time course of binding of site-targeted FC emulsions to human thrombi incubated with a biotinylated monoclonal antifibrin antibody and then exposed to avidin has been investigated in vitro [226]. The same biotin/avidin binding strategy allowed visualization of carotid artery overstretch inflammation injury in pigs after balloon angioplasty using a tissue factor-targeted emulsion (tissue factor is a transmembrane glycoprotein responsible for initiating the coag-
ulation cascade) [227]. Subsequently, a more realistic approach, from a practical and product development standpoint, used an emulsion with antibodies covalently bound to a component of the interfacial film, allowing single step administration [228, 229].

Incorporation of paramagnetic material (e.g., a gadolinium chelate-phosphatidylethanolamine) into the membrane of ligand-targeted FC emulsion droplets provided contrast agents useful with both ultrasound and MR imaging modalities [208]. For example, paramagnetic fibrin-specific FC emulsion droplets provided sensitive detection and localization of clots \emph{in vitro} and \emph{in vivo} (dogs), which may allow early identification of fibrin deposits in unstable atherosclerotic plaques [228]. The lipid coating of the emulsion droplets used for the \emph{in vivo} studies had both an anti-fibrin monoclonal antibody and gadolinium diethylamine-triaminepentaacetic acid (DTPA)-phosphatidylethanolamine attached. A similar Gd-FC emulsion, with an \(x\_5\beta_3\) integrin (a molecular marker of angiogenic endothelium) antibody attached, allowed localization of the molecular epitopes of neovasculature in rabbits [230]. Such agents may improve detection of tumors and metastasis, and monitoring of therapy.

Further ligand-targeted FC emulsions are being investigated that combine site-directed ultrasound or MR imaging and drug delivery capacity (Section 13.6).

13.3.3 Further Uses of Fluorocarbons in Diagnosis

Neat \(F\)-octyl bromide has gained approval in the United States for oral use as a bowel marker during MR imaging of the gastrointestinal tract. In this case it is the absence of protons, hence of the signal, that creates the desired contrast, improving stomach and bowel wall delineation, thus facilitating the detection of pathology [231]. Fast \emph{in vivo} \(^{19}\text{F}\) NMR imaging was used to monitor clearance of \(F\)-octyl bromide from the liver and spleen of rats, based on the reduction of the \(^{19}\text{F}\) spin-lattice relaxation parameter \(T_1\) by the paramagnetic \(O_2\) molecule [232]. The same technique allowed measurement of partial \(O_2\) pressure in the RES organs using bis(\(F\)-butyl)ethene [233]. FC emulsions allowed quantitative mapping of \(O_2\) partial pressure by NMR in organs [234] and tumors [235]. Myocardial \(pO_2\) monitoring with \(^{19}\text{F}\) MR imaging demonstrated changes with global and regional ischemia [236]. Aerosolized \(F\)-tributylamine was investigated as a means of analyzing lung structure and oxygenation patterns using \(^{19}\text{F}\) NMR [237]. An emulsion of \(F\)-15-crown-5-ether (20 magnetically equivalent \(^{19}\text{F}\) nuclei) was used to map \(O_2\) tension in tumors by analyzing \(^{19}\text{F}\) relaxation rates [238, 239]. The same emulsion, when directly infused into the interstitial/ventricular space in the rat brain, allowed investigation of the effect of hyperoxia, hypoxia, and \(CO_2\) concentration on cerebral interstitial \(O_2\) tension [240]. Recently, such an emulsion was used as a “gold standard” to validate a \(^{1}\text{H}\) MR imaging method to assess changes in tumor oxygenation in carbogen (95% \(O_2/5\%\ CO_2\))-breathing rats [241]. In another example, neat \(F\)-benzene was directly deposited in the tumor, providing the local \(O_2\) sensor that allowed mapping of tumor \(O_2\) tension by \(^{19}\text{F}\) MR imaging techniques [242]. An \(F\)-octyl bromide emulsion allowed intravenous delivery of laser-polarized xenon, making \emph{in vivo} \(^{129}\text{Xe}\) NMR studies possible [243]. However, such use appears limited by the rapid exchange of \(Xe\) with the water environment. Externally applied FC-filled pads are available commercially (SatPad®) which improve magnetic homogeneity, hence image quality, when fat saturation techniques are used during \(^{3}\text{H}\) MR imaging [244].
X-ray radiography allowed monitoring of FC distribution during liquid ventilation of patients with the radiopaque FC F-octyl bromide [36, 38, 245, 246]. Percutaneous computed tomography after subcutaneous injection of an FC emulsion effectively depicted intranodal distribution of macrophages in lymph nodes, which is important for cancer staging [247].

13.4

In Vivo Oxygen Delivery: Fluorocarbon-in-Water Emulsions

Considerable research and development efforts have focused on engineering and investigating FC-in-water emulsions for in vivo oxygen delivery (blood substitutes). These efforts have recently been analyzed in detail, including the context of blood transfusion issues: basic principles of in vivo O2 delivery by injectable FC emulsions; formulation, engineering and characterization issues; in vivo behavior; potential indications and clinical development status [3–5, 248]. For recent updates on FC emulsion development see [6, 248a]. Therefore, this topic will only be briefly surveyed here. Reports on blood substitute research in Russia can be found in references [249, 250].

13.4.1

Objectives and Challenges

In short, reasons for developing “blood substitutes” include: the reluctance that has developed against allogeneic (donor) blood transfusion through fear of infectious risks; the realization that banked blood is less effective than fresh blood; evidence that donor blood may reduce the immune responsiveness of the organism; shortages in blood collection to meet the augmenting needs of an aging population; and the possibility of providing the developing countries with an alternative to blood banking. Examples of recent papers on these issues include: those dealing with the change in the physicians’ attitude vis-à-vis blood transfusion [251]; the transmission of prion by blood transfusion [252]; transfusion-related acute lung injury [253]; transfusion mortality due to clerical errors [254]; and a review of immunological aspects of blood transfusions [255]. An analysis of the perceived risks of transfusion in the UK shows that, given a choice, anesthetists would more likely accept a blood substitute than donor blood [256]. Another paper concludes that mass appeal to blood donation is not an appropriate response in the case of a disaster [257].

Use of O2-carrying injectable FC emulsions during surgery is expected to provide effective O2 delivery (thus preventing tissue ischemia) and reduction in exposure of patients to donor blood. Consequently, O2 carriers could help mitigate the increasingly frequent blood shortages. FC emulsions could also help bridge the time gap between the moment when a critical need for increased tissue oxygenation is determined and transfusion of compatible blood becomes possible, or the time between transfusion and full effectiveness of the transfused banked blood. Trauma is one such situation. Further potential applications for FC-based O2 carriers include use during cardiopulmonary bypass surgery, treatment of acute myocardial infarction and stroke, use for cardioplegia and reperfusion. Oxygenation of hypoxic tumors may improve the response of tumor cells to radio- and chemotherapy. Use of FC-enriched perfusates may help increase the availability and quality of organs suitable for transplantation. FC emulsions are also being investigated for treatment of sickle cell disease, treat-
ment of decompression sickness, as research tools for stabilizing and controlling animal models, organs and tissues, in cell culture technology, and as drug delivery systems [5, 258, 259]. Targeted FC emulsions offer potential for molecular imaging and drug delivery (Sections 13.3.2 and 13.6.1).

The principal challenges in the development of injectable FC-in-water emulsions included: selecting an FC that is readily excretable, easy to manufacture and to emulsify; preparing small-sized heat-sterilizable emulsions using a surfactant well accepted in the pharmaceutical industry; controlling particle size and counteracting molecular diffusion, which is responsible for particle size growth over time; understanding the *in vivo* behavior of the emulsion and minimizing its side effects; and defining conditions of use for clinical evaluation and optimal benefit to the patient. Also important are cost-effectiveness, user-friendliness, and compliance with current Good Manufacturing Practices and regulations from health authorities.

13.4.2 Selecting a Fluorocarbon with Lipophilic Character: Perfluorooctyl Bromide

The most critical criterion for selecting an FC for intravascular use turned out to be its fluorophilic/lipophilic balance, as it largely determines the rate of excretion of the FC (unchanged, with the expired air) from the body [3, 5]. This is because the rate-determining step in the elimination process is dissolution of the FC into lipid carriers in the blood. Lipid solubility also largely determines tissue distribution and accumulation. The solubility of FCs in lipids is therefore an essential parameter for FC selection. The lipophilicity of an FC is reflected by its critical solution temperature in *n*-hexane (*CST*$_{\text{hex}}$, the temperature at which equal volumes of the FC and hexane form a single isotropic phase; Figure 13-13b).

The organ retention half-time of regular FCs turned out to be primarily an exponential function of MW, and *CST*$_{\text{hex}}$ a linear function of MW) reflecting the decreasing lipid solubility generally attached to the increasing molecular volume of the solute (Figure 13-13). Neither cyclization nor branching, or the presence of heteroatoms had any significant effect on organ retention [260–262]. On the other hand, the presence of lipophilic elements, such as Cl, Br or a CH$_2$CH$_3$ moiety, causes a definite lowering of the CST and increase in excretion rate [3]. F-Octyl bromide was selected as an injectable O$_2$ carrier primary because its organ half-life was shorter than that of other FCs of similar MW and vapor pressure. The lipophilic character induced by the well-exposed, polarizable terminal bromine atom in C$_8$F$_{17}$Br translates into a *CST*$_{\text{hex}}$ of around –20 °C, i.e., about 25 °C lower than that of C$_8$F$_{18}$ (in spite of higher MW) and about 50 °C lower than that of F-N-methyldecahydroisoquinoline (C$_{10}$F$_{19}$N), an earlier candidate O$_2$ carrier with a similar MW to C$_8$F$_{17}$Br. The effect of one Br on the solubility of an FC in olive oil was essentially equivalent to that of two Cl and almost comparable to that of two C$_2$H$_5$ groups, and the effect of two terminal Br was equivalent to that of one terminal I [263]. A too high vapor pressure was observed to cause a so-called increased pulmonary residual volume effect due to retention of air in the alveoli in certain animal species [264]. Although this phenomenon, which depends on airways size has never been reported with humans, the vapor pressure of the FC phase should probably not exceed around 10 torr.
Fig. 13.13.  a) Organ retention of regular FCs in vivo is an exponential function of molecular weight. Lipophilic FCs are excreted faster than regular FCs of similar MW (FDC, F-decalin; FTPA, F-tripropylamine; FTBA, F-tributylamine; PFDCO, F-3,3,3-trichloroocatane; PFDB, F-decyl bromide; F-44E, bis(F-butyl)ethene; FMIQ, F-N-methyldecahydroisoquinoline; PFDB, F-decyl bromide; FMCP, F-N-methylcyclohexylpiperidine.

b) Assessing the lipophilicity of FCs: correlation between CST_{hex} and MW for a variety of regular (△ acyclic, ○ monocyclic, □ bicyclic, △ tricyclic) and lipophilic (▲) FCs. A lower CST corresponds to higher lipophilicity; dotted lines indicate trends observed for the more lipophilic FCs (taken from reference [3]).
13.4.3

Stabilizing Fluorocarbon Emulsions: Counteracting Molecular Diffusion

Formulating FCs as fine (< 0.2 μm) emulsions for intravascular administration requires a surfactant system capable of reproducibly ensuring homogenous dispersion, stability and biocompatibility. Phospholipids, which are commonly used in pharmaceuticals, including the fat emulsions routinely used for parenteral nutrition, are capable of fulfilling these requirements. Emulsions, however, undergo particle size growth over time, ultimately leading to phase separation. The principal mechanism for irreversible particle growth in FC-in-water emulsions was determined to be molecular diffusion (Ostwald ripening). Particle growth by molecular diffusion essentially obeys the Lifshits-Slezov theory, which states that particle volume increase is directly proportional to interfacial tension, and to solubility and diffusibility of the dispersed phase into the continuous phase [265]. Such growth can be counteracted by lowering the FC/water interfacial tension and by reducing the solubility and diffusibility of the dispersed FC phase in the aqueous phase. In the case of F-octyl bromide, unexpectedly low interfacial tension could be achieved using phospholipids [266]. Solubility and diffusibility of the fluorour phase in water was reduced by adding a secondary, higher molecular weight FC. F-decyl bromide was selected for this purpose because it is slightly lipophilic, which mitigates the increase in organ retention that normally accompanies an increase in MW (Figure 13-14) [267]. Processing conditions were optimized to produce fine and narrowly dispersed emulsions. Particle size is indeed known to affect both intravascular persistence and side effect profile. Large particles are cleared more rapidly from the circulation than smaller ones and tend to stimulate macrophage activation, resulting in “flu-like” side effects [264].

![Graph showing the reduction in droplet growth rate by adding F-decyl bromide](image)

**Fig. 13-14.** Repressing Ostwald ripening in an F-octyl bromide emulsion by addition of the higher, less water soluble homolog F-decyl bromide. A few percent of F-decyl bromide suffice to reduce the rate of droplet growth by a factor of about 6. From reference [267] with permission.
Extensive research and development efforts led to Oxygent™ AF0144 (Alliance Pharmaceutical Corp.), a submicronic (about 0.16 μm in average diameter) 60% weight/volume-concentrated FC emulsion consisting principally of F-octyl bromide, emulsified with egg yolk phospholipids and stabilized against particle growth with a few percent of F-decyl bromide. The product is terminally heat sterilized, has a shelf life of two years at standard refrigeration temperatures (5–10 °C) and is ready for use [5].

13.4.4 Fluorocarbon Emulsion Physiology and Clinical Trials

Extensive pre-clinical experimentation has investigated Oxygent’s pharmacology and safety, and demonstrated O₂ delivery efficacy [5, 268].

During Phase I clinical safety studies in conscious volunteers with the Oxygent formulation AF0144, fever frequency (~15% of patients) and amplitude (seldom exceeding 1 °C) was not significantly different from the controls, and platelet count, although temporarily depressed with respect to the base line, remained within normal range. There were no effects on platelet function and coagulation parameters, no complement activation, immunogenic or allergic reactions, vasoconstriction or microcirculatory disturbances, abnormal changes in liver, lung or kidney function, or clinically meaningful effects on blood chemistry at the doses administered [269, 270].

Phase II trials have demonstrated that the emulsion was more effective than fresh blood in reversing the need for transfusion (transfusion triggers) during surgery [271] and led to a reduction in the number of patients who reached a transfusion trigger during surgery [272].

The recently published results of a Phase III clinical trial conducted in Europe in general surgery patients have established the ability of the emulsion to significantly reduce and avoid red blood cell transfusion during general surgery [273]. The trials were conducted using an augmented acute normovolemic hemodilution with FC emulsion protocol. In the protocol-defined target population (330 subjects with blood loss ≥ 20 mL kg⁻¹ b.w.), significantly greater avoidance of any red blood cell transfusion (including predonated blood), as compared with controls, was gained and maintained through day 21 or day of hospital discharge (Figure 13-15, \( p < 0.05 \)). There was also a significant reduction in the number of blood units transfused (\( p < 0.001 \)). The latter result is not negligible, as each unit of blood transfused carries the same risks. The added O₂-delivering capacity provided by administration of a dose of FC emulsion has been described in terms of a “hemoglobin equivalent” value [273, 274]. Using data from clinical trials, the hemoglobin (Hb) equivalent of a 1.8 g kg⁻¹ b.w. dose of F-octyl bromide was calculated to be about 2.7 g Hb (i.e., about 1.5 g Hb per g FC) at an inspired O₂ fraction of 1. The intended clinical dose (4.5 mL kg⁻¹ b.w. of the 60% w/v emulsion, i.e., 2.7 g of FC) would then provide an Hb equivalent of around 4 g dL⁻¹, comparable to that of four units of fresh blood. Another Phase III study, conducted in cardiopulmonary bypass surgery patients was suspended because of adverse effects that were traced to protocol-related, overly aggressive autologous blood harvesting in the treatment group prior to bypass [275]. Clinical development is being pursued through a partnership between Alliance and Nycomed (Copenhagen, Denmark).

The gastric tonometric variables (which are markers of proper tissue perfusion) were preserved in surgical patients administered Oxygent [276]. FC emulsions also appear to
attenuate neutrophil activation and reduce inflammation during extracorporeal circulation [277]. A further study indicated that the emulsion was effective in reducing sickle cell vasocclusion caused by human sickle cells in a rat mesocecum vasculature preparation [278]. Sickle cell anemia is due to a mutation (b6, Glu → Val) in the Hb molecule that causes Hb to polymerize and the sickling of red blood cells under deoxygenated conditions. Blockage of blood vessels by the non-deformable sickle cells leads to painful vaso-occlusive crises and multiple organ damage. The FC emulsion was capable of unsickling trapped red cells in partially occluded vessels, thus decreasing peripheral resistance, probably as a result of effective O2 delivery.

13.4.5 Further Research on Fluorocarbon Emulsions for Oxygen Delivery

Objectives for additional emulsion improvement include further increasing emulsion stability, achieving smaller size particles and prolonging intravascular persistence. These improvements are likely to require modification of the interfacial film. Use of F-surfactants allowed the shelf stability of an F-decalin emulsion to be increased from days to years [3]. However, the physiological effects of large doses of an F-surfactant are, at this point, largely unknown.

F-alkyl/H-alkyl diblocks, when used in combination with phospholipids, provide a highly effective means of stabilizing small-size FC emulsions (Figure 13-16) [105, 279]. The fit between emulsifier and diblock is then critical. Thus, while incorporation of F-alkyl/H-alkyl diblocks provided very effective stabilization of an F-octyl bromide emulsion when phospholipids were the emulsifier, combination of diblocks with poloxamers (e.g., Pluronic® F68) was insufficient to effectively stabilize an F-decalin emulsion [3]. Additionally, FnHm/phospholipid mixtures allowed close control of particle size (i.e., of fluorous microdomain size) over a wide range of sizes [280].
The mechanism of emulsion stabilization by F-alkyl/H-alkyl diblocks is not yet fully established. The stabilization effect could a priori result from a modification of the interfacial film, resulting in a reduction in interfacial tension, and/or from the effect on water solubility of less water-soluble diblock molecules homogeneously dispersed in the bulk of the FC phase (in which the diblocks may, however, also form micelles), or from an increased local concentration of the heavier, molecular diffusion-repressing material in the neighborhood of the lipidic interface.

Increasing evidence supports an involvement of the FnHm diblocks at the FC/water interface. Thus, incorporation of diblock F6H10 into an F-octyl bromide-in-water emulsion emulsified with egg phospholipids upon addition of the heavier FC C16F34, or of diblock F6H10 (C6F13C10H21) to the formulation. The stabilizers and EYP were in equimolar amounts; note that the two additives have about the same boiling point. From reference [279], with permission.

The mechanism of emulsion stabilization by F-alkyl/H-alkyl diblocks is not yet fully established. The stabilization effect could a priori result from a modification of the interfacial film, resulting in a reduction in interfacial tension, and/or from the effect on water solubility of less water-soluble diblock molecules homogeneously dispersed in the bulk of the FC phase (in which the diblocks may, however, also form micelles), or from an increased local concentration of the heavier, molecular diffusion-repressing material in the neighborhood of the lipidic interface.

Increasing evidence supports an involvement of the FnHm diblocks at the FC/water interface. Thus, incorporation of diblock F6H10 into an F-octyl bromide-in-water emulsion emulsified with egg phospholipids increased the proportion of phospholipids associated with the FC droplets relative to that present in the form of free vesicles dispersed in the aqueous phase; it also reduced the area occupied by the phospholipids’ head groups at the surface of the FC droplets [281]. Reduced surface area of the polar heads reflects tighter packing of the phospholipid film. A dramatic reduction in FC/water interfacial tension (typically from about 24 to ~2 mN m⁻¹; pendant drop method) between an FC and an aqueous phospholipids solution was measured when increasing amounts of a diblock were added to the FC phase (Figure 13-17) [282]. The observation that the emulsion stabilization effect of a given diblock depended on the length of the lipid’s fatty acid chains, while this was not so when a heavier FC (that simply reduces the solubility of the FC phase in the aqueous phase) was used as a stabilizer, further demonstrated that the diblocks were involved at the interface. On the contrary, when the fit between lipid and diblock alkyl chain length was inadequate, a droplet coalescence mechanism set in that actually led to emulsion destabilization [282]. Of course, involvement of part of the diblocks at the interface does not exclude the presence of diblocks in the bulk of the droplet and vice versa. Even a relatively small proportion of diblocks at the interface can result in a substantial reduction in interfacial tension, while the diblocks present in the bulk can contribute to increasing emulsion stability by reducing the water solubility of the dispersed FC.
Evaluation of a diblock-stabilized emulsion is in progress. Successful long-term preservation of intestine has been reported [283]. Improved tissue oxygenation was demonstrated in a rabbit model of resuscitation from acute hemorrhagic shock [284]. No perturbation of the hemodynamic or rheological parameters was induced, even at very large doses [285].

Droplet coalescence in FC and HC emulsions stabilized by water-soluble poloxamers and a bis(F-alkylated) PEG has been thoroughly investigated [286]. It was found that the interfacial adsorption layers of surfactant can provide an effective structural-mechanical barrier against coalescence, depending on the nature of the dispersed phase and its interaction with the hydrophobic tail of the surfactant. Droplet resistance to coalescence was enhanced by a “deficiency in affinity” between the hydrophobic moiety of the surfactant and the dispersed hydrophobic phase, which pushes the surfactant to aggregate into a compact, mechanically resistant structure. An H-surfactant is in this respect more effective in stabilizing an FC emulsion against coalescence than an F-surfactant, whose F-tails would tend to dissolve loosely in the FC rather than form a mechanically strong structure [286]. Phospholipids, which are used in the FC emulsions in development, are essentially insoluble in both polar and non-polar phases, and provide an effective barrier against coalescence.

An F-octyl bromide emulsion stabilized by phospholipids and an F-surfactant, and surface-modified with a distearoylphosphatidylethanolamine-poly(ethylene glycol) (DSPE-PEG) has been described briefly [287]. Its ability to deliver O₂ in a cardiopulmonary bypass with hemodilution canine model was demonstrated. Phagocytosis of an FC emulsion by macrophages in vitro was reportedly slowed down when an F-alkylated PEG emulsifier was used [288].

Assays that allow detection of FCs in blood by headspace solid-phase microextraction combined with gas chromatography/mass spectrometry have been developed as part of efforts towards anti-doping in sport [289, 290].

Interestingly, the so-called “phase-shift” emulsion of F-pentane (bp 29 °C) that turns into
gaseous microbubbles at body temperature and was initially intended as a contrast agent for ultrasound imaging, is now being investigated for O₂ delivery. The theory underlying the use of FC-stabilized microbubbles for in vivo O₂ transport had been developed earlier [291, 292]. As indicated in Section 13.3.1 the fast permeating gases inside the bubble, i.e., O₂ and CO₂, equilibrate rapidly with the gases dissolved in the plasma and surrounding tissues, allowing O₂ to be carried from the lungs to the tissues. The role of the FC (a slowly permeating gas) is then no longer to dissolve O₂, but to stabilize O₂ microbubbles in vivo. Experimental proof of the concept includes survival of normovolemic erythrocyte-depleted rats and pigs, and of pigs with potentially lethal hemorrhagic shock and with severe right-to-left shunt [293]. Administration of the F-pentane emulsion, along with carbogen breathing, led to suppression of resistance to radiation of a hypoxic cell in a rat tumor model [294]. However, the mechanism for prolonged O₂ delivery over at least 2 h remains unclear in view of the short intravascular life of F-pentane [122]. A depot effect and possible bubble stabilization by serum proteins may contribute to prolonged circulation times. Emulsion formulation and stability, and in vivo bubble size control also warrants further research.

13.5 Fluorocarbons as Therapeutic Aids and Tissue-Sustaining Devices

The combination of FCs for fluidity, easy spreading (F-octyl bromide spreads spontaneously on a saline solution), density and biological inertness provides opportunities for a number of atypical biomedical uses.

13.5.1 Pulmonary Applications – an Anti-Inflammatory Effect?

Total or partial liquid ventilation (PLV) with FCs have been investigated as a treatment of acute respiratory distress syndrome (ARDS) and other acute lung injuries. Improved oxygenation and lung function have been achieved, usually with F-octyl bromide, in animal models of lung injury [295–299], as well as in clinical trials with ARDS patients [36, 245, 300, 301]. Use of PLV in conjunction with high frequency ventilation improved gas exchange, decreased pulmonary vascular resistance and reversed acidosis in preterm lambs with respiratory distress syndrome and may represent an effective approach to the management of preterm infants with respiratory distress syndrome [302]. Lung lavage with FCs can help remove edema fluids while improving gas exchange and lung mechanics [303]. Bronchoscopic lavage with F-octyl bromide was found to be advantageous in the treatment of smoke inhalation injury in an ovine model [304]. PLV may help treat meconium aspiration [305] and may have been critical in managing a case of acute verapamil poisoning with respiratory failure [306]. Liquid ventilation with an FC may reduce lung injury associated with neonatal cardiopulmonary bypass [307].

Moreover, PLV with FCs was repeatedly reported to have an anti-inflammatory effect and to reduce oxidative damage to lipids and proteins during experimental acute lung injury [37, 308–311]. Thus, PLV with F-octyl bromide reduced production of oxygen free radicals and concomitant pulmonary oxidative damage, and reduced mortality in piglets with acute lung injury caused by oleic acid [310] or systemic endotoxemia [311]. FCs were shown to protect lung epithelial cells from inflammatory cell-mediated injuries and to reduce the release of
inflammatory mediators (leukotriene B4 and interleukin-6) [312, 313]. They may protect the lung from acute inflammation more effectively than conventional ventilation procedures [312]. Pre-exposure to F-octyl bromide attenuated neutrophil adhesion to activated endothelial cells in vitro; infiltration of activated neutrophils into the lung is a key component of inflammation in acute lung injury [314]. Intranasal administration of F-octyl bromide reduced lung cellular inflammation and the expression of chemokines in mice infected with respiratory syncytial virus, the major etiologic agent of bronchiolitis in infancy [315].

More recently, delivery of vaporized or aerosolized rather than liquid FC to the bronchial tree has been investigated. Treatment of sheep with ARDS with vaporized F-hexane (18% vaporized F-hexane carried in the inspiratory gas flow during ventilation) resulted in significant and sustained improvement of gas exchange and lung compliance, possibly due to a surfactant effect [316, 317]. Exposure to F-hexane vapor attenuated the proinflammatory and procoagulatory responses of human activated mononuclear blood cells and isolated alveolar macrophages in vitro, as indicated by a reduction of expression and release of interleukin-1β, tumor necrosis factor α and tissue factor [318]. A simpler treatment of lung surfactant-depleted pigs with aerosolized FC77 (primarily F-octane, from 3M) resulted in sustained improvement of oxygenation and lung mechanics, lasting for hours after the end of the intervention [319]. The treatment also suppressed an early pulmonary response in lung surfactant-depleted piglets, as indicated by reduced gene expression of proinflammatory cytokines [320].

Pulmonary infusion of cold FCs is being investigated as a means of rapidly cooling the body core and protecting the brain [321a, b]. Rapid body core and brain cooling has become an important goal of resuscitation research. It could be extremely valuable in the treatment of cardiac arrest, myocardial infarction and stroke, as well as doing neurosurgery, cardiac surgery and for organ preservations.

13.5.2 Cardiovascular Uses: Thrombolysis

FC-loaded microbubbles, in conjunction with ultrasound, have been investigated for breaking up blood clots that cause myocardial infarction. Thrombolysis was enhanced in vitro, with or without the presence of a thrombolytic agent (urokinase), probably as a result of cavitation [321]. Greater efficacy was found with FC- versus air-filled lipid microbubbles [321] or polymer microspheres [322]. Thrombolysis with a tissue plasminogen activator was improved by ultrasound irradiation and further improved in the presence of microbubbles [323–326].

Ultrasound was used to vaporize an F-pentane emulsion, of average radius 1.5 μm, producing large microbubbles, around 100 μm in diameter, which were suggested to have potential for tissue occlusion in cancer treatment [327].

13.5.3 Topical Applications: Fluorocarbon Gels

Fluorocarbon-based gels have recently been reviewed [7] as have concentrated emulsions in general [328]. Elastic gel-emulsions with a high water content were obtained that consisted of water in a swollen reverse water-in-FC micellar phase [34]. Investigation of the changes in rheological behavior of such a concentrated reverse emulsion [F-decalin emulsified with
over time determined that coalescence was the mechanism of aging in these emulsions [329]. Complex gel-emulsion formulations also containing decane and both $H$- and $F$-surfactants have been reported [330].

Gels with a continuous FC phase have also been obtained from associations of $F$-alkyl/$H$-alkyl diblocks, phospholipids and water in FCs [331]. Generation of worm-like entangled micelles of hydrated surfactants within the continuous fluororous phase is a likely mechanism for their formation. An $F$-alkylated gelator consisting of a bis-benzamide with two $F$-alkyl chains attached provided an $F$-tributylamine gel [332]. Gels containing twisted lamellae have been observed to form from $F$-alkylated gluconamides in formamide [50].

On the other hand, clear, highly stable high internal phase ratio emulsions (HIPRE), consisting of up to 99% FC have been produced from a wide range of FCs, from low-boiling hydrofluoroalkanes to high-boiling polycyclic FCs, using an $F$-alkylated amine oxide surfactant [333]. Structurally, these gels consist of micron-sized polyhedral fluororous compartments enclosed within a thin hydrated film of the surfactant. Dispersion in water (the continuous phase) generates a standard FC-in-water emulsion.

PEGs with $F$-alkyl chains at both ends provided hydrogels with controlled surface erosion characteristics [334]. Phase behavior could be modulated by varying $F$-alkyl chain length relative to PEG chain length, resulting in single-phase behavior, sol-gel coexistence, or precipitation. Mechanical and erosion properties of the hydrogels could thus be tailored for use as implantable drug-release depots. $F$-alkyl end-capped polyacrylamides with pendant betaine groups provided gels that combine the surface active properties imparted by $F$-chains and the antibacterial activity of quaternary ammonium moieties [58, 335]. The enhanced hydrophobicity provided by $F$-alkylated end caps leads to larger relaxation times and higher activation energies, hence to rheological behavior that is unusual with non-fluorinated associative polymers [21].

$F$-gels may have applications in topical delivery, wound healing, and as low friction, gas-permeant, repellant protective barrier creams against toxic or aggressive media, and in cosmetic applications. A gel-emulsion of Fomblin® (a mixture of $F$-polymers) in water showed protective efficacy against irritants such as sodium lauryl sulfate, sodium hydroxide, lactic acid and toluene [336]. Water soluble $F$-polyether PEG phosphates, when incorporated into aqueous gels, also provided prevention of irritant contact dermatitis [337].

### 13.5.4 Ophthalmologic Applications

Diverse gaseous ($F$-propane, SF$_6$) and liquid ($F$-octane, $F$-decalin, $F$-perhydrophenanthrene) $F$-compounds are being used as ocular tamponades, vitreous substitutes, intraocular washes to remove silicone oil, etc. [338, 339]. More recently investigated compounds include fluoroelastomers [340], ($F$-alkyl)alkanes [341], and semifluorinated diethers of type [(CF$_3$CH$_2$O)$_n$(CH$_2$)$_n$-4] [342].

### 13.5.5 Organ and Tissue Preservation, Cell Cultures

Neat liquid FCs are being investigated for the preservation of transplants using the so-called “two layer” method in which the organ lays on an $O_2$-providing FC layer, while it is overlaid
by a nutrient-rich aqueous solution [343]. Clinical transplantation of pancreas preserved by
this method achieved results at least equivalent or superior to those obtained without the FC
layer [344, 345]. FC emulsions allowed preservation of organ blocks from rats [346].

Both neat FCs and FC-in-water emulsions provide effective means for facilitating and
regulating the supply of O2 and CO2 to prokaryotic and eukariotic (including human) cells
in culture [347]. Neat FCs enhanced mitosis of isolated cells of diverse plants, thus increas-
ing biomass production. The metabolic responses of cultured cells to oxygenated FCs has
been investigated [348]. An underlying layer of oxygenated F-decalin stimulated cellular O2
consumption, mitochondrial function and the intracellular activity of the enzymes super-
oxide dismutases and catalases (which scavenge deleterious oxygen radicals, thus affording
protection against oxidative cell damage). Cryopreservation of agronomically important plant
cells is an important storage procedure; there is evidence that FCs can improve the post-
thaw viability and biomass production of frozen cultured plant cells; synergistic effects of F-
decalin and Pluronic F-68 were also observed [349]. Use of neat F-decalin to supply CO2 to
cultured shoots of roses enhanced biomass and root production [350]. FCs have also been
used to provide CO2 to algae and remove excess O2 from closed bioreactors, resulting in sig-
nificantly enhanced growth rates (accumulation of O2, a photosynthetic byproduct of micro-
algae culture, severely inhibits algae growth) [351].

13.6 Delivery of Bioactive Agents

F-colloids provide a variety of microreservoirs for drug delivery. The active components
can be incorporated in aqueous or lipidic compartments inside particles, within their walls,
or attached to their surface. Targeted delivery with F-colloids is being actively pursued. For a
recent review, see [351a].

Additionally, certain F-amphiphiles may have biological activity by themselves. Anti-
thrombogenic activity [352] and anti-HIV activity [48, 353] have, for example, been observed.

13.6.1 The Parenteral Route

13.6.1.1 Microbubbles and Ultrasound

Microbubbles, combined with ultrasound, offer wide possibilities in terms of carrying, tar-
geting, delivering or facilitating and monitoring the delivery and efficacy of drugs and genes
to specific tissues. Bubble destruction in a chosen tissue can facilitate local delivery of an
independently administered drug; alternatively, the bubbles themselves can be loaded with
the active agent; ultrasound can help trace the delivery of the active cargo; finally, ultrasound
can provide the external trigger that commands bubble destruction and local release. Ad-
vantages of ultrasound include deep penetration into body tissues and the capacity to be fo-
cused into a narrow beam. However, the cargo space offered by microbubbles is generally
small, as it usually only concerns the bubble shell, meaning that only potent drugs can be
delivered effectively. Microbubbles with thicker walls can be considered, the downside being
that thicker, hence more rigid walls tend to dampen the scattering efficacy of the bubbles.

Delivery of colloidal particles and red blood cells through microvessel ruptures created
by ultrasound-triggered microbubble destruction has been demonstrated [324]. The acoustic
power required to induce sonoporation, i.e., generation of transient ultrasound-induced
perforations in cell membranes, is significantly reduced when microbubbles are present
[356]. In vitro experiments on lymphocytes indicated that sonoporation was directly related
to the microbubble-to-cell ratio and to the bubble-to-cell spacing, r, and that the effects decay
as $r^{-3}$ [356].

Paclitaxel, packaged in F-butane microbubbles that contain soybean oil and are believed to
comprise an oil layer inside a pegylated phospholipids shell, was released in vitro when suf-
ficiently high-energy ultrasound was applied [357]. A prodrug of dexamethasone, with fatty
chains attached for insertion into the lipid membrane of microbubbles, has been synthe-
sized [358]. Interestingly, F-butane-exposed, but not air-containing, sonicated dextrose albu-
mim microbubbles preserved albumin’s ability to bind synthetic antisense oligonucleotides,
indicating that the FC may have prevented albumin denaturation during sonication [359].
These oligonucleotides could be released by insonation in a target organ, in this case the
kidney of a dog.

Targeted delivery of the thrombolytic agent urokinase was achieved in vitro using micro-
bubbles fitted with a surface ligand that binds to the GPIIB/IIIA receptors expressed on ac-
tivated platelets present in thrombi [219]. Ultrasound thrombolysis efficiency was signifi-
cantly increased.

Gene delivery is another important goal for ultrasound-manipulated microbubbles. Ultra-
sound alone can facilitate gene transfection [360]. The presence of microbubbles signifi-
cantly enhanced acoustically-induced cell transfection, probably due to enhanced sonopora-
tion [361, 362]. Ultrasound exposure in the presence of microbubbles achieved 300-fold
higher transgene expression in vascular cells in vitro than with naked plasmid DNA alone,
and a 3000-fold increase when a polyamide transfection agent was used [363]. Intrauterine
injection of naked DNA, in combination with FC microbubble-enhanced ultrasound, pro-
duced protein expression in fetal mice [364]. Luciferase expression increased $\sim 10^3$-fold
in comparison with expression after injection of naked DNA alone or with naked DNA and
ultrasound. In vitro ultrasound-mediated gene expression and transfection efficiency were
enhanced when DNA was incorporated into albumin-coated F-propane microbubbles, as
compared with unloaded bubbles mixed with plasmid [365]. Adenovirus delivery in rats
has been promoted using an albumin-coated FC microbubble; ultrasound was used to image
the delivery and disrupt the microbubbles, leading to increased myocardial gene expression
[366]. Positively charged microbubbles that bind DNA have also been produced [367, 367a].

Transgene expression of β-galactosidase in the myocardium of rats was achieved by infu-
sion of albumin-coated F-propane microbubbles having a β-galactosidase-containing recom-
binant adenoviral gene vector attached, followed by insonation of the heart [368].

13.6.1.2 Targeted Fluorocarbon Emulsions
Targeted FC-in-water emulsions (Section 13.3.2.3) were designed that provide site-directed
drug delivery. For example, site-directed doxorubicin and paclitaxel was delivered to vascular
smooth muscle cells in vitro using a Gd chelate- and drug-loaded, smooth muscle-adherent
F-octyl bromide emulsion [369]. The targeted drug inhibited proliferation and migration of vascular smooth muscle cells and prevented restenosis after angioplasty; simultaneously, MR could allow visualization of delivery.

13.6.1.3 Fluorinated Vesicles and Other Self-Assembled Fluoro-Colloids

A range of F-vesicles has been elaborated for the purpose of determining the impact of F-chains on the formation, structure and properties of such F-colloids and to provide novel delivery vehicles for bioactive agents [2, 8, 42, 62]. At this point, however, the potential of these F-colloids as drug delivery systems remains largely unexploited.

The salient structural characteristic of F-vesicles is the presence of a well-organized highly hydrophobic, Teflon-like fluorinated core within their bilayer membrane. This modifies the thermotropic and lyotropic behavior of such vesicles, usually providing improved thermal resistance and shelf stability as compared with vesicles made from H-analogs, and lower membrane permeability. The ability of F-liposomes for withstanding heat sterilization, efficiently loading and slowly releasing diverse hydrophilic, lipophilic and amphipathic drugs, drug models and dyes has been demonstrated [8, 42, 62].

Alternatively, F-vesicles have been obtained by combining standard H-amphiphiles, in particular phospholipids, with mixed F-alkyl/H-alkyl diblocks [105, 370]. The diblocks confer to F-liposomes increased stability and reduced permeability. Thus, liposomes made from DMPC and diblock F4H10E 11 became heat sterilizable. Slower fusion kinetics were illustrated by the initial rates of Ca\(^{2+}\)-induced fusion of F-vesicles made from phosphatidylserine (PS) and F6H10, being an order of magnitude slower than when PS was alone, and reduced membrane permeability by a 40-fold slower release of encapsulated carboxyfluoresceine [371]. Mixtures of F-alkylated phosphocholine 8 and F8H2 yielded vesicles with dramatically reduced membrane permeability than when 8 was alone [372].

The intra-bilayer F-film can also have repercussions on the vesicle’s behavior in vivo or in a biological milieu, possibly by affecting the conformation and orientation of the polar groups, hence in vivo particle recognition and phagocytosis, leading, for example to prolonged, dose-independent intravascular persistence [373]. The presence of diblocks of type 10 in the bilayer membrane of liposomes made from DMPC or DPPC dramatically reduced the rate of hydrolysis of the phospholipid by pancreatic phospholipase A\(_2\) [374]. The dependence of the effect on H-alkyl chain length in the diblock and the absence of effect when there is no F-chain present demonstrated a key role of the latter in structuring the bilayer membrane. These observations indicate that interactions with peptides and proteins and in vivo recognition could be modulated by changes made inside the liposomal membrane.

13.6.2 The Pulmonary Route – Dispersions of Particles within a Fluorous Phase

Administration of F-systems through the respiratory tract deserves a special mention as FCs provide a fluid, rapidly spreading inert vehicle that may allow uniform delivery of drugs, lung surfactant, vaccines, genes and other bioactive agents. However, very few agents (besides gases and highly fluorinated compounds) are soluble in FCs; hence the interest of colloidal systems with a fluorous continuous phase incorporating aqueous, oily or solid dispersed phases (Figure 13-1, h–m) thus allowing homogeneous dispersion of both hydro-
philic and lipophilic materials within the FC carrier. Objectives include treatment of ARDS, pneumonia and pulmonary hypertension and gene delivery.

Fluorous phases are particularly apt at carrying gases. Several papers report that PLV with an FC, usually F-octyl bromide, combined with nitric oxide inhalation, led to augmented oxygenation, improved lung mechanics and decreased pulmonary hypertension in various models of lung injury [301, 375–378]. Halothane, CF3CHBrCl, a fluorophilic inhalation anesthetic, can also be delivered with liquid ventilation [379].

Simple suspensions of solid drugs, for example in nanocrystalline form, usually in F-octyl bromide or F-decalin have been investigated. Combination of lung surfactant treatment with PLV with F-octyl bromide improved gas exchange and lung mechanics in preterm lambs with surfactant deficiency [299, 380]. Intratracheal administration of prostaglandin E1 during PLV of rabbits with oleic acid-induced lung injury resulted in sustained improvement in oxygenation and reduction in pulmonary artery pressure [381]. The feasibility of pulmonary delivery of the vasoactive drugs acetylcholine, epinephrine and priscoline during liquid ventilation was demonstrated [382]. Combination treatment of rats infected by lethal pneumococcal pneumonia with penicillin and FC liquid ventilation led to significantly improved survival as compared with treatment with penicillin alone [383]. Intratracheal delivery of a nanocrystal suspension of the antibiotic gentamycin provided effective pulmonary delivery while maintaining safe serum levels [384].

Other strategies for improving incorporation of drugs into FCs for pulmonary delivery consist in synthesizing FC-soluble prodrugs [354] or in using an F-alkylated solubilizing agent capable of forming hydrogen bonds with the drug [385]. In both cases, F-chains provide the required increase in FC solubility. As an example, FC-soluble nicotinic acid esters with F-chains have been synthesized [386].

Use of FCs as a vehicle could improve distribution of genes throughout the lung and facilitate their access to binding sites on distal target cells [387]. Intratracheal instillation of viral and nonviral gene transfer vectors along with neat F-octyl bromide resulted in increased, earlier and more uniformly distributed gene expression, including in animal models of acute lung injury [388, 389].

Reverse water-in-FC emulsions and “apolar” HC-in-FC emulsions also have potential for the delivery of bioactive material through the pulmonary route [8]. Producing reverse (i.e., water-in-FC) emulsions supposes the stabilization of a dispersion of water droplets in an extremely water-repellent medium. Highly stable water-in-FC emulsions and microemulsions (i.e., thermodynamically stable reverse emulsions), ranging from ca. 10 to ca. 500 nm in diameter, have been obtained using strongly fluorophilic surfactants such as the (F-alkyl)alkyldimorpholinophosphates 8 [390, 391]. These reverse emulsions could be loaded with a range of drugs, including antibacterial, bronchodilating, mucolytic, tuberculostatic, cholinergic, and antineoplastic agents, without loss of stability. Slower release of carboxyfluoresceine than from water-in-HC oil emulsions was obtained [392]. The cytotoxicity towards mouse fibroblast and human lung epithelial cell cultures, of 8 dissolved in F-octyl bromide or as part of a reverse emulsion, was lower than with an H-analog of 8 and decreased with increasing F-chain length [63]. Reverse emulsions stabilized by 8 (n = 8 or 10, m = 11) were assessed as non-cytotoxic. Pulmonary delivery of a water-in-F-octyl bromide emulsion was investigated using pressurized metered-dose inhalers with light hydrofluorocarbons (e.g., H2CFCF3, HFA 134a) as the propellant [393]. Homogeneous and re-
producible delivery of caffeine was demonstrated. Studies of mixed monolayers of 8 with DPPC (the main constituent of lung surfactant) in contact with F-octyl bromide (or of water-in-F-octyl bromide emulsions formulated with 8) indicated that 8 was miscible with DPPC, which may facilitate the spreading of DPPC in the lung and the delivery of drugs [394, 395].

Water-in-HFA 134a microemulsions suitable for aerosolized delivery of water-soluble drugs have been prepared using either combinations of nonionic F-alkylated PEG surfactants and short-chain H-alcohols [396], or of F-acid surfactants with short-chain F- or H-alcohols [397]. Terbutaline sulfate was solubilized in such microemulsions.

Stable apolar HC-in-FC emulsions (i.e., emulsions of one hydrophobic phase dispersed in another hydrophobic phase) have also been produced [398]. The amphiphiles used for emulsification and stabilization included the F-alkyl/H-alkyl diblocks 10. Dodecane has, for example, been dispersed in F-octyl bromide using F6H10 as the emulsifier. Antibiotics, corticosteroids and antitumor agents have been incorporated in these emulsions.

Multiple emulsions including three distinct, non-miscible phases (fluorous, hydrocarbonous and aqueous), the continuous phase being fluororous, have also been obtained [8]. Such systems allow simultaneous loading of fluorophilic, lipophilic and hydrophilic agents.

Finally, novel hollow and porous microparticles (PulmoSpheres™, developed by Alliance Pharmaceutical Corp. and licensed to Nektar Therapeutics (San Carlos, CA formerly Inhale Therapeutic Systems) have been devised that have small aerodynamic diameters, which facilitate their uniform delivery throughout the lung. These particles can be delivered to the respiratory tract as dry powders or as suspensions in non-aqueous solvents, including propellants for metered dose inhalers (e.g., hydrofluoroalkanes, HFAs) and liquid FCs (e.g., F-octyl bromide). The particles can release their active content when reaching an aqueous environment such as a mucosa. Excellent aerosolization efficiency and dose uniformity were obtained for albuterol sulfate, cromolyn sodium, and formoterol fumarate microspheres [399]. Functional integrity of immunoglobulins formulated in PulmoSpheres for local and systemic delivery via the respiratory mucosa has been demonstrated [400]. Inhaleable tobramycin and budesonide [400a] formulations (as dry powders) and an albuterol formulation (suspended in an HFA) in PulmoSpheres are presently in clinical trials (Nektar Therapeutics) [401]. Instillation in the lungs of a gentamicin/PulmoSphere formulation in F-octyl bromide is also being investigated [402].

13.7

Highly Fluorinated Materials as Research Tools, Processing Aids, etc.

13.7.1

Research Tools

FC-in-water emulsions have been used to preserve or prolong and control the viability of cells, organs, tissues and animal models for physiological experimentation [346, 351, 403]. Exchange transfusion of rats with an FC emulsion allowed the interfering hemoglobin signal to be reduced in a study of the functional organization of the brain, by analyzing optical signals evoked by peripheral nerve simulation in the cortex [404]. Likewise, replacement of hemoglobin by a FC emulsion allowed demonstration that the response, as observed by near-infrared spectroscopy, of a mitochondrial cytochrome oxidase to anoxia was not a spectral artifact due to the presence of hemoglobin [405].
\(F\)-surfactants with an \(F\)-alkyl segment inserted between a retinoid receptor ligand and a lipidic tail have been designed for the purpose of promoting two-dimensional crystallization of membrane proteins at an air/water interface [406]. The \(F\)-alkyl segments stabilize the monolayer against solubilization by the detergent used for protein solubilization. The fluidity necessary for crystallization to occur is provided by branched terminal HC chains or by the presence of both \(H\)- and \(F\)-chains. The \(F\)-alkyl segment also forces a lipophilic ligand to stay exposed on the aqueous side of the monolayer, while its natural tendency would be to bury itself in the lipidic region of the monolayer [407].

\(F\)-alkylation was used to immobilize biomolecules (e.g., proteins) onto FC surfaces for applications in affinity chromatography, enzyme immobilization for bioprocessing and analytical and clinical chemistry, biosensors, immunodiagnostic and other assays [408]. Monolayers of steroidal \(F\)-alkylated amphiphiles with cellobiose or maltose hydrophilic heads exhibited pressure-area behavior related to, respectively, specific and nonspecific interactions with the enzyme cellulase present in the sub-phase [409].

Phase separation of \(F\)- and \(H\)-amphiphiles within bilayer membranes has been used to "drill" holes in liposomes, thus simulating a process that is believed to take place when an activated macrophage attacks a tumor cell [410]. Formation of phase-separated microdomains of \(F\)-alkylated crown ethers within an HC membrane resulted in faster transport of \(K^+\) through the membrane than with \(H\)-alkylated crown ethers; contrary to the HC carrier, transport was nearly completely suppressed below the membrane's phase transition temperature, \(T_c\), thus providing temperature-regulation for \(K^+\) transport [411].

Although most compounds are excluded from fluororous domains, diffusion of small molecules and ions remains possible, offering a means for diffusion control. On the other hand, the HC shells that flank the \(F\)-core within the bilayer of an \(F\)-vesicle can dissolve and confine lipophilic material. Reverse water-in-FC microemulsions provide size-controlled insulated zones for confinement within a highly hydrophobic external medium. This feature allowed evaluation of the perturbation of water dynamics as a function of confining size [412]. This confinement system could also be used for investigation of individual proteins and other material. The apolar HC-in-FC emulsions may prove useful for confining, protecting and delivering water-sensitive lipophilic material.

Possible applications evoked for tubular self-assemblies include the elaboration of models of enzyme clefts, and of microcontainers for the controlled release of active agents [413, 414]. More recently, nanotubules have been used as templates for the molecular recognition–driven self-assembly of proteins [415] and the preparation of insulated nanowires [416].

A fluorocarbon affinity emulsion has been used for extracting proteins [417], and fluorinated gel-like network structures for electrophoretic DNA sequencing in capillary columns [418].

13.7.2 Fluorocarbons and Fluorinated Colloids as Processing Aids

FC-colloids also provide tools for the engineering of other particulate-based delivery systems. For example, segregation within the lipophilic shells that flank the \(F\)-core of \(F\)-vesicles made of phospholipid 11 provided an appropriate confinement microreactor for the polymerization of a lipophilic monomer into spherical microcapsules, a goal that had not been achieved with \(H\)-vesicles [419].
FC-in-water emulsions allowed production of hollow porous microparticles for delivery of bioactive agents to the respiratory tract [399, 400]. The process involved spray-drying of an F-octyl bromide-in-water/phospholipid emulsion along with a solution of the active component to be delivered. Evaporation of water first leaves a shell containing the bioactive agent and phospholipid on the FC droplets’ surface; subsequent vaporization of the FC “blows” holes in this shell. The free-flowing powder obtained consists of amorphous microparticles, about 4–7 μm in diameter with pore diameters in the order of 50–300 nm. They form very stable “homodispersions” in HFAs and FCs where the dispersed and continuous phases are identical, thus reducing the attractive forces between particles and the difference in density between particles and carrier medium.

13.8 Summary and Perspectives

FCs and F-colloids have potential in medicine and biology that includes contrast agents for diagnostic imaging, in vivo oxygen delivery systems, systems for controlled delivery of other bioactive material, diverse therapeutic aids, and tools for research and particle engineering.

FC-based micron-size injectable gaseous bubbles constitute effective contrast agents for ultrasound imaging and are the first major product to reach the market. These highly echogenic agents provide improved diagnostic of structural and functional cardiac abnormalities. Assessment of myocardial perfusion, blood flow and blood flow abnormalities and solid tumors has also been demonstrated. Better images enable patients to be diagnosed sooner and more accurately, thus increasing the physician’s confidence in the diagnosis and reducing downstream testing. Use of ultrasound contrast agents thus provides both added clinical and economical value, which is of paramount importance in the present times of health care cost constraints. A shift from the more expensive testing modalities to ultrasound imaging can be expected, which could position echosonography as the leading diagnostic modality of the decade. Research in the field is moving rapidly towards molecular imaging, i.e., detection of molecular markers characteristic of a given pathology, using targeted microbubbles. Fine-tuning of microbubble/ultrasound interaction is also being pursued. Membrane and surface engineering are therefore likely to play a key role in optimizing control over bubble targeting and response to ultrasound waves.

FC-based injectable O₂ carriers stand a good chance of providing another major application for F-colloids. An O₂ carrying, heat-sterilized phospholipid-based emulsion of a rapidly excreted, slightly lipophilic fluorocarbon, perfluorooctyl bromide is being developed to serve as a temporary blood substitute. A Phase III clinical trial in Europe has demonstrated that use of the emulsion resulted in avoidance and reduction of blood transfusion in surgery patients. Such O₂ carriers are expected to reduce exposure of patients to donor blood, thereby helping reduce blood shortages, and to provide an emergency blood substitute. Improving the understanding of FC emulsion “physiology” should allow optimization of the conditions of use of such products.

Drug delivery with F-colloid appears promising, both where the parenteral and pulmonary routes are concerned. It may rely on microbubbles, emulsions, vesicles and other systems. Targeting of F-colloids sounds particularly attractive and is rapidly progressing. As yet, this potential remains largely untapped.

F-amphiphiles (including F-alkyl/H-alkyl diblocks) provide unique and versatile compo-
ments for delivery systems. Their highly hydrophobic (and lipophobic) F-alkyl chains largely determine the ordering of molecules at interfaces and promote their self-assembly into stable F-vesicles and other organized molecular systems with distinctive properties. F-amphiphiles also allow preparation of direct, reverse, apolar and multiple FC emulsions and gels. Because F-chains offer the ultimate in terms of hydrophobicity, they tend to phase-separate, thereby promoting micro- and nanocompartmentation and segregation between fluororous, hydrocarbonous and aqueous compartments. FCs and F-colloids, can thus play a decisive role in the formulation, dispersion, encapsulation, segregation and exclusion of diverse material, thereby providing microreservoirs, microreactors, confinement zones, templates, control over reaction kinetics, etc. The diversity of components and structures available allows manipulation of the physical and biological characteristics of F-colloids over a wide range.

As for other colloids, F-colloids may, as needed, be fitted with targeting devices, or rendered pH-, pressure-, temperature-, or stimuli-sensitive, or be surface modified, as with PEG strands to hinder their in vivo recognition and clearance from circulation. Goals for targeted F-colloids include molecular imaging and drug and gene delivery. Triggering of drug release from microbubbles using ultrasound is an additional appealing feature of microbubbles.

The unique and intriguing characteristics of F-compounds and F-colloids (a fertile emerging branch of fluorine chemistry) will undoubtedly continue to inspire original research, providing novel research tools and engineering solutions, probably leading to novel uses in the medical field and beyond. Pharmaceutical development, however, involves many disciplines, extreme complexity and innumerable constraints. It requires bringing together a wide diversity of complementary skills, considerable resources, and time. Managing such complexity is a key factor in the equation for success, while advancing basic research is paramount to tomorrow’s pharmaceuticals.

Acknowledgements

My favorite nitpickers: Marie Pierre Krafft and Jolene Shorr.

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Fluorous Materials for Biomedical Uses


Fun and Games with Fluorous Chemistry

József Rábai

14.1 Introduction: Where Does the Fun Come From?

Much of the fun emanates from the unique phase properties of fluorocarbons, which are governed by thermodynamics. The extraordinary solvent properties of fluorocarbons came to light in the late 1940s, as illustrated by the following citation [1]: “The large molal volumes of the fluorocarbons compared with the corresponding hydrocarbons leads to unusually low ‘internal pressures’ or ‘cohesive energy densities’, while their high molecular weights aid in maintaining them in the liquid state; the net result of which is to make many of their solutions with ordinary liquid hydrocarbons deviate from Raoult’s law to such an extent as to form two liquid phases, a state of affairs comparatively rare among non-polar liquids.”

The thermodynamic theory of non-electrolyte solutions, as developed by van Laar, Hildebrand, and Scatchard, in its simplest form uses solubility parameters ($\delta$), molal volumes ($V$), temperature, mole fractions and volume fractions to account for the molal free energy of a component in a mixture of two non-polar liquids. Furthermore, this theory allows the estimation of liquid/liquid miscibilities and critical solution (consolute) temperatures ($T_c$), using Eq. (1) [2]:

$$4RT_c = (V_1 + V_2)(\delta_1 - \delta_2)^2$$

Increasing differences in solubility parameters will result in higher critical solution temperatures, or in other words bring about lower miscibility. Thus, C$_6$F$_{11}$CF$_3$ and CCl$_4$ yield a one-phase system at 27 °C, while the more polar non-fluorous solvents benzene and chlorobenzene afford single phases at 85 °C and 127 °C, respectively. All systems were assayed easily and precisely in sealed glass tubes, as reported (Table 14-1) [2].

The above theory also predicts that the best solubility or miscibility is observed for components with similar molal volumes, provided their solubility parameters are equal. This is a simplified thermodynamic expression of the “like dissolves like” principle [3]. Conciously or not, synthetic and separation chemists make frequent use of this theory of regular solutions in selecting solvents for reactions and workups.

This chapter will describe some experiments in which three liquid phase systems are converted into two-phase systems, and with further temperature increases into one-phase systems. Since the liquid layers in these systems can be colored independently according to the wish of the person who performs the experiments, many other variations are possible.
The experiments included here are the author’s favorites, because they call attention to keywords and concepts such as solubility [4], extraction [4], partition [4, 5], solvatochromism [4], fluorophilicity [5], fluorous gold nanoclusters [6], temperature dependent miscibility [7], density [8], volatility [8], polarizability [8], lipophilicity [8], fluorine substituent effects [8] and perfluoroalkylation [9]. Owing to space limitations, experiments are described in the most compact way and references given for more detailed analyses.

This chapter also features the preparation of fluorous and organic dyes, as well as a three-component three-phase system and a four-component three-phase system. Two-phase systems are incorporated in the experiments with the four-component three-phase systems \((3 \rightarrow 2 \rightarrow 1 \text{ or } 1 \rightarrow 2 \rightarrow 3)\), which equilibrate with one-phase systems upon heating and reform three-phase systems upon cooling.

14.2 Synthesis of Dyes for Fluorous and Organic Phases

14.2.1 How to Make the “Blue Dye”: The Taming of Aromatic Perfluoroalkylations

The story of the fluorocarbon soluble blue dye is recalled by the author after a personal talk with Tiers [10], who invented the first perfluoroalkylation method for aromatic compounds [9]:

\[
\text{ArH}_m + 2x \text{Rf}_n \text{I} \rightarrow \text{ArH}_{m-x}(\text{Rf}_n)_x + x \text{I}_2 + x \text{Rf}_n \text{H}
\] (2)

Accordingly, an aromatic compound is mixed with an excess of perfluoroalkyl iodide, sealed in a Carius tube, and heated at high temperature within a bronze protecting tube for several hours. The Carius tube is subsequently cooled in an acetone–dry ice bath, still within the bronze safety container, and then the tip is inserted into rubber tubing and cracked with the aid of a hammer (Figure 14-1). Tiers refers to this sequence as a “brutal perfluoroalkylation”.

In the early 1950s it was thought that perfluorocarbon based hydraulic fluids used in submarines should be colored to improve on-board safety by making them more easily distinguishable from liquid fuels. A dye had been prepared from copper phthalocyanine and perfluorohexyl iodide under the above conditions. Since the byproducts of the above equation, \(\omega\)-hydroperfluoroalkanes and iodine, are more volatile than the educts, a significant

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(V (\text{cm}^3 \text{ mol}^{-1}))</th>
<th>(T_c, \text{obs (K)})</th>
<th>(\delta_2 (\text{cal cm}^{-3})^{1/2})</th>
<th>(\delta_{1,\text{solid (cal cm}^{-3})^{1/2}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(<em>6)F(</em>{11})CF(_3)</td>
<td>195</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCl(_4)</td>
<td>97</td>
<td>300</td>
<td>8.6</td>
<td>5.8</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>81</td>
<td>323.5</td>
<td>9.0</td>
<td>6.0</td>
</tr>
<tr>
<td>C(_6)H(_6)</td>
<td>89</td>
<td>358.5</td>
<td>9.15</td>
<td>6.0</td>
</tr>
<tr>
<td>C(_6)H(_5)CH(_3)</td>
<td>102</td>
<td>362.0</td>
<td>8.9</td>
<td>5.8</td>
</tr>
<tr>
<td>C(_6)H(_5)Cl</td>
<td>107</td>
<td>400.0</td>
<td>9.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>

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\[
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pressure increase is expected at higher conversions. Accordingly, this procedure is not only brutal but hazardous.

The product obtained forms brilliant blue solutions in fluorocarbons and benzotrifluoride, and is suitable for staining Teflon® at higher temperatures, near its glass transition point [9].

Other methods disclosed later provide lower reaction temperatures and higher yields based on perfluoroalkyl iodides [11–13]. However, in one of these [11] the increased yields are at the expense of the use of a peroxide reagent in stoichiometric amounts, which limits applications due to the explosion hazards associated with this compound family. The other two methods are easy to apply under standard laboratory conditions. The addition of sodium acetate or potassium carbonate to the aromatic hydrocarbon and perfluoroalkyl iodide mixture suppresses or eliminates the formation of ω-hydroperfluoroalkanes and iodine side products, resulting in less pressure increase [12, 13].

The “blue dye” of the initial FBS paper [14] was made analogously to the original Tiers procedure. However, for the benefit of the readers a milder, safer and “less brutal” method is elaborated [15b]. Here melting point capillary tubes are substituted for the Carius tube, and household aluminum wrapping foil is used instead of the protecting bronze tube of Figure 14-1.

**Perfluorodecyl Cobalt(II)phthalocyanines. Direct Alkylation with Perfluorodecyl Iodide**

**Reaction 14-1**

![Chemical reaction diagram]

Fig. 14-1. Safe opening of a Carius tube. Redrawn from a sketch by George van Dyke Tiers [10].
Reagents

Perfluorodecyl iodide [423-62-1], cobalt(II)phthalocyanine [3317-67-7], and ruthenium, 5 wt.% on carbon are commercially available.

Experimental Procedure

Cobalt(II)phthalocyanine (0.088 g, 0.154 mmol), C₁₀F₂₁I (1.0 g, 1.5 mmol), K₂CO₃ (0.12 g, 0.87 mmol) and 5% Ru/C (0.026 g) were mixed in a mortar. Then five melting point capillary tubes (approximately 10 cm long and 1 mm inner diameter) were filled with this mixture to a height of ca. 2 cm and sealed in a Bunsen flame. The capillaries were bunched together and wrapped with ten turns of aluminum foil. The ends of the foil were folded back from the capillary tips. This package was heated in the oven of a “retired” gas chromatograph at 200 °C for two days. The bundle was cooled to room temperature and broken into two halves by bending at the middle. The colored pieces of the capillaries were ground in a mortar and extracted with a few mL of benzotrifluoride. The resulting blue solution was filtered through a cotton plug in a Pasteur pipette. The filtrate was treated at room temperature with an excess of NaBH₄ (0.05 g) dissolved in methanol (0.5 mL) to convert the unreacted C₁₀F₂₁I (bp ~200 °C) into C₁₀F₂₁H (bp ~160 °C), which is easier to remove on evaporation. The mixture was evaporated to dryness and the residue extracted with hot FC-84. Filtration and evaporation yields approximately 0.1 g of the fluorous soluble “blue dye”. About 1 mg of this product is used to color the bottom layer of the system shown in Figure 14-2A.

14.2.2 Preparation of a Fluorophilic “Gold Dye”: (Auₘ)(HS(CH₂)₃Rf₈)ₙ

Reaction 14-2

\[ \text{AuCl₄}^-(aq) + (C₈H₁₇)₄N^+ (\text{BTF}) \rightarrow (C₈H₁₇)₄N^+ \text{AuCl₄}^- (BTF) \]  
(3)

\[ m\text{AuCl₄}^- (\text{BTF}) + nC₈F₁₇(CH₂)₃SH(\text{BTF}) + 3m^- \rightarrow 4m\text{Cl}(aq) + (\text{Au}_m)(C₈F₁₇(CH₂)₃SH)_n(\text{BTF}) \]  
(4)

Reagents

Hydrogen tetrachloroauroate(III) trihydrate [16961-25-4] and tetraoctylammonium bromide [63462-99-7] are commercially available, whereas perfluoroctylpropyl mercaptan can be prepared according to the literature procedure [16].

Experimental Procedure

A solution of HAuCl₄·3H₂O (0.178 g, 0.457 mmol) in water (15 mL) was mixed with a solution of (C₈H₁₇)₂NBr (1.09 g, 2.0 mmol) in benzotrifluoride (40 mL). The two-phase mixture was shaken at room temperature until all the tetrachloroauroate was transferred into the organic layer. The water phase separated, and then the perfluoroctylpropyl mercaptan (0.21 g, 0.42 mmol) was added to the organic phase. A freshly prepared solution of NaBH₄...
(0.19 g, 5 mmol) in water (12.5 mL) was added slowly (~10 min) with vigorous stirring. After further stirring for 3 h, the organic phase was separated and washed with water (3 × 5 mL). Then it was evaporated in vacuum using a rotavap and a water bath for heating (50–60 °C). The dark residue was treated with dioxane (40–50 mL) at room temperature for 1 h to dissolve all components but the solid fluorous-thiol protected the gold nanoparticles. The latter product was isolated by suction filtration, washed with dioxane (2 × 5 mL) and dried in a vacuum desiccator over phosphorous pentoxide. Yield: 140 mg of a glittering black solid, stable to air, soluble in benzotrifluoride and fluorous solvents, insoluble in most organic solvents.

Discussion

Using a two-phase (water/toluene) reduction of AuCl₄⁻ by sodium borohydride in the presence of an alkanethiol results in the formation of solutions of 1–3 nm gold particles bearing a surface coating of thiol, as described by Brust et al. [17]. The above synthesis of fluorous thiol-protected gold nanoparticles, disclosed by Rábai et al., adopted the same strategy [6a].

14.2.3 Preparation of an Organophilic “Gold Dye” (Auₘ)(HS(CH₂)₁₁CH₃)ₙ

Reaction 14-3

Prepared according to the literature procedure [17]. For the equations, see 14.2.2 and substitute toluene for BTF, and CH₃(CH₂)₁₁SH for nC₈F₁₇(CH₂)₃SH.

Reagents

Dodecanethiol [112-55-0] is commercially available.

Experimental Procedure

This preparation is conducted analogously to that in 14.2.2, but substituting toluene for BTF and 1-dodecanethiol (0.085 g, 0.42 mmol) for the fluorous thiol. The workup was altered as follows. The solvent (toluene) was evaporated in vacuum, and the residue was consecutively treated with dioxane (30 mL) and benzene (3 × 30 mL), with the evaporation of each solvent portion before the next was added. The dark residue was finally treated with acetone (50 mL), and the precipitate formed was isolated by filtration and washed with acetone (3 × 5 mL). Yield: 100 mg of glittering black solid, stable to air, soluble in benzotrifluoride and most organic solvents, insoluble in fluorocarbons.

14.3 Fluorous Phase Systems for the Games

Any of the solvent systems displayed in Table 14-2 are easy to assemble, however, appropriate chemical safety should be practiced during demonstrations. Although these experiments were designed to be as safe as possible, eye protection is a must in all cases. To avoid overheating the systems, and as a consequence of sudden boiling (splashes) in open vials or
excess pressure development in closed systems, one should check the physical properties of the solvents considered for the Games (Table 14-3). When capped vials or sealed glass tubes are warmed, the safest heat source is a water bath of ca. 60 °C.

Entries 5 and 8 in Table 14-2 constitute particularly amusing systems, since all their phase transitions can be triggered by ice water and with bare hands. All phase transitions can be observed either in warming or in cooling modes. During the experiments with entries 4 and 8, the transition temperatures can differ significantly from those listed if the experiments are performed in static mode (i.e., no rocking or shaking applied to the vials). This is caused by the screening effect of the middle phase, since the top and bottom phases should merge or equilibrate on warming. The latter unstable systems immediately merge on turning the vials. In some cases, heavy emulsions can be observed over narrow temperature ranges (not shown on Figure 14-4, but possible).

Tab. 14-2. Selected solvent miscibility data*\textsuperscript{b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent system</th>
<th>Phase</th>
<th>Temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FC-72/(CF\textsubscript{3})\textsubscript{2}CHOH</td>
<td>One phase</td>
<td>RT</td>
</tr>
<tr>
<td>2</td>
<td>FC-72/CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>Two phase</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>on boiling</td>
</tr>
<tr>
<td>3</td>
<td>FC-72/\textit{n}-heptane</td>
<td>Two phase</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>47\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>FC-72/\textit{n}-heptane/CH\textsubscript{3}NO\textsubscript{2}\textsuperscript{d}</td>
<td>Three phase</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two phase</td>
<td>on warming\textsuperscript{b}</td>
</tr>
<tr>
<td>5</td>
<td>FC-84/\textit{n}-hexane</td>
<td>Two phase</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>34\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>FC-84/\textit{n}-heptane</td>
<td>Two phase</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>54\textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>FC-84/(CF\textsubscript{3})\textsubscript{2}CHOH/CF\textsubscript{3}CH\textsubscript{2}OH\textsuperscript{e}</td>
<td>Two phase</td>
<td>0–RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>26\textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td>FC-84/\textit{n}-hexane/(CF\textsubscript{3})\textsubscript{2}CHOH/CF\textsubscript{3}CH\textsubscript{2}OH\textsuperscript{f}</td>
<td>Three phase</td>
<td>0°</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two phase</td>
<td>~15–30\textsuperscript{c}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One phase</td>
<td>~33\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>\textit{n}-hexane/(CF\textsubscript{3})\textsubscript{2}CHOH/CF\textsubscript{3}CH\textsubscript{2}OH\textsuperscript{g}</td>
<td>Two phase</td>
<td>T &lt; 60°</td>
</tr>
</tbody>
</table>

*Reference [15a]. \textsuperscript{b}All data for a 1:1 volume ratio unless otherwise stated. \textsuperscript{c}Experimental observation; not a consolute temperature. \textsuperscript{d}Volume ratio 1:1:1. \textsuperscript{e}Volume ratio 3:1:1. \textsuperscript{f}Volume ratio 3:3:1:1.

Tab. 14-3. Some physical properties of selected solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>\textit{Mp} (°C)</th>
<th>\textit{Bp} (°C)</th>
<th>Density (g mL\textsuperscript{−1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC-72</td>
<td>−90</td>
<td>56</td>
<td>1.68</td>
</tr>
<tr>
<td>FC-84</td>
<td>−95</td>
<td>80</td>
<td>1.73</td>
</tr>
<tr>
<td>\textit{n}-Hexane</td>
<td>−95</td>
<td>69</td>
<td>0.659</td>
</tr>
<tr>
<td>\textit{n}-Heptane</td>
<td>−91</td>
<td>98</td>
<td>0.684</td>
</tr>
<tr>
<td>(CF\textsubscript{3})\textsubscript{2}CHOH</td>
<td>−4</td>
<td>59</td>
<td>1.596</td>
</tr>
<tr>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>−43.5</td>
<td>77–80</td>
<td>1.373</td>
</tr>
<tr>
<td>CH\textsubscript{3}NO\textsubscript{2}</td>
<td>−29</td>
<td>101.2</td>
<td>1.127</td>
</tr>
</tbody>
</table>
14.4
Name of the Games

All Games are displayed in Figures 14-2 to 14-7. The standing vials shown in the photographs correspond to 30% of actual size. Figures 14-2 to 14-5 display Games with System 3 \( \rightarrow \) 2 \( \rightarrow \) 1; Figure 14-6 with System 3 \( \rightarrow \) 2, middle \( \rightarrow \) up version; and Figure 14-7 with System 3 \( \rightarrow \) 2, middle \( \rightarrow \) down version. Each vial is charged with appropriate amounts of the solvent mixtures shown below. Then the dyes are added and the vials sealed. More details are given under the names of the appropriate Games.

**System 3 \( \rightarrow \) 2 \( \rightarrow \) 1 (cf.: Entry 8, Table 14-2)**

A mixture of \( n \)-hexane (8.0 mL), trifluoroethanol (2.5 mL), 1,1,1,3,3,3-hexafluoro-2-propanol (2.5 mL) and FC-84 (8.0 mL) is made at room temperature. This mixture forms three layers at ice temperature, two layers at room temperature, and a one-phase system at body temperature (Table 14-2, Figures 14-2 to 14-5).

**System 3 \( \rightarrow \) 2, middle \( \rightarrow \) up version (cf.: Entry 4, Table 14-2)**

A mixture of \( n \)-heptane (5.75 mL), nitromethane (5.75 mL) and FC-72 (5.75 mL) is made at room temperature. The top and bottom phases merge on heating, facilitated by gentle shaking, while the nitromethane layer goes up (Table 14-2, Figure 14-6).

**System 3 \( \rightarrow \) 2, middle \( \rightarrow \) down version (cf.: Entry 4, Table 14-2)**

A mixture of \( n \)-heptane (10.5 mL), nitromethane (5.75 mL) and FC-72 (10.5 mL) is made at room temperature. The top and bottom phases merge on heating, facilitated by gentle shaking, while the nitromethane layer goes down (Table 14-2, Figure 14-7).

14.4.1
Make Them Blue!

---

**Fig. 14-2.** Make Them Blue!
14.4 Name of the Games

This Game features stages of System 3 → 2 → 1 in the warming cycle (cf. entry 8, Table 14-2). The FC-84 rich layer is colored with the “blue dye”, while the middle and top ones are clear and colorless (Figure 14-2A). Slight warming merges the lower layers, the blue color becomes lighter, while the hexane rich layer remains colorless (Figure 14-2B). The one-phase system formed at higher temperature is evenly dyed blue: thus the job is done (Figure 14-2C)!

14.4.2
Purple Empire

This Game is a variant of the above (14.4.1), since besides the “blue dye” some iodine is added to make different colors at the three-phase condition: purple, orange-red and blue. At the two-layer stage, much of the iodine is still in the hexane rich top phase, while the color of the fluorous cobalt phthalocyanine is shaded or augmented by iodine (Figure 14-3B). Finally, all space is evenly dyed purple by iodine (Figure 14-3C).

14.4.3
Which Phase to Winter?

This Game features the stages of System 3 → 2 → 1 in a cooling cycle (cf. entry 8, Table 14-2). One series of vials contains the organophilic \( \text{Au}_{m}(\text{HS(CH}_2\text{)}_n\text{CH}_3)_n \) dye (Figure 14-4A,B,C); the other series contains the fluorophilic \( \text{Au}_{m}(\text{HS(CH}_2\text{)}_n\text{Rf}_8)_n \) dye (Figure 14-5A,B,C). No one can tell which is which until the three-phase stage of both series arrives. At the warm side or high temperature limit the gold nanoparticles are evenly distributed through the whole liquid volume (Figures 14-4A and 14-5A); however, at lower temperature they are completely withdrawn to the fluorine rich lower layers of the intermediate biphasic

---

**Fig. 14-3.** Purple Empire.
Neither type of thiol protected gold nanoparticles remain in the hexane rich upper layer, an unexpected event for the organophilic dye (Figure 14-4B). The splitting of the bottom phases on further cooling yields the three-phase systems shown, and gives the solution to the puzzle: the gold particles select phases for wintering according to their coats (Figures 14-4C and 14-5C)!
14.4.4
Up and Down

This Game features the stages of System 3 → 2, middle → up (C\textsubscript{7}H\textsubscript{16}:CH\textsubscript{3}NO\textsubscript{2}:FC-72 = 5.75:5.75:10.5 v/v) and System 3 → 2, middle → down (C\textsubscript{7}H\textsubscript{16}:CH\textsubscript{3}NO\textsubscript{2}:FC-72 = 10.5:5.75:5.75 v/v) in their warming cycles (Figure 14-6A,B,C and Figure 14-7A,B,C, cf. entry 4, Table 14-2). The density of the merged heptane/FC-72 phases is tuned by volume ratios to be higher/lower than that of CH\textsubscript{3}NO\textsubscript{2}. This results in the up and down movements of
the CH$_3$NO$_2$ layers upon phase transitions. The partition and the extent of solvation of the iodine used for dying the layers improves the beauty of the Game. Moreover, in an undisturbed cooling cycle special phenomena can be observed. The top phase releases small droplets, which penetrate through the screening CH$_3$NO$_2$ phase to the bottom, until an equilibrium is established; at the same time, the droplets from the bottom phase move in the opposite direction (Figure 14-7B). A magic “F-fun” can be observed if the tubes are kept with two hands in a horizontal position and smooth waves generated by minute up and down movements (not shown).

14.5 Epilogue

In the closing pages of this book, the author wishes to pay tribute to the many pioneers of organofluorine chemistry. Their contributions, brought to fruition in both academic and in industrial research laboratories, established the vast knowledge base available today and made the advances described in this book possible [18–20].

Acknowledgements

The author thanks Ana-Maria Bonto and Dr. Peter Ivanko for their careful experimental assistance, László T. Mika for the drawings and photographs, and the European Contract of Research Training Network (“Fluorous Phase” HPRN-CT-2000-00002) for financial support.

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