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FTI PRIMER:

A SHORT INTRODUCTION TO FLUOROUS TECHNIQUES FOR THE SYNTHESIS AND SEPARATION OF ORGANIC MOLECULES

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Summary: The yield of every chemical step is limited both by the efficiency of the reaction and the ability to recover the pure product from the reaction mixture. However, most traditional solution phase synthesis methods are concerned only with conversion of starting materials to products (reactions) and not with product separations. Fluorous techniques provide strategic new options for conducting solution phase organic reactions and for separating the resulting reaction mixtures. Fluorous molecules typically contain at least one highly fluorinated domain attached to an organic domain. The fluorinated domain can be an integral part of the molecule (permanent attachment) if the intended use is as a reagent, reactant or catalyst. A temporary attachment of a removable fluorous group is required to render a reaction substrate or product fluorous. Fluorous compounds can be separated from standard organic compounds by simple workup techniques of liquid-liquid extraction (two- or three-phase) or solid-liquid extraction. Fluorous compounds can also be separated from each other based on fluorine content by fluorous chromatography.

Five different types of techniques are summarized: fluorous biphasic catalysis, fluorous triphasic reactions, fluorous reagents and reactants, fluorous substrates (fluorous synthesis), and fluorous mixture synthesis. The techniques differ in the size and nature of the fluorous tag, in the reaction conditions and in the separation method. Fluorous techniques are applicable to both green chemical process development and chemical discovery research. Many of these new techniques are especially suited to the preparation of combinatorial libraries by solution phase parallel synthesis.

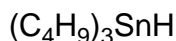
Fluorous Molecules

Fluorous molecules are designed to mimic organic molecules in terms of reactivity yet to still be readily separable from other organic molecules. In the technique of fluorous mixture synthesis, fluorous molecules are also separated from each other. Fluorous molecules typically have two domains. The organic domain resembles a standard organic parent molecule and dictates the reactivity of the molecule. The fluorous domain is a highly fluorinated group that controls the separation features of the molecule. Fluorous domains are often perfluoroalkyl groups.

Shown below are two simple examples of fluorous molecules designed after common organic parents. Fluorous tin hydrides have similar reactivity to the classical reagent tributyltin hydride. But unlike tributyltin compounds, the fluorous tin compounds are readily separable from organic compounds by simple fluorous separation techniques like liquid-liquid extraction or solid-liquid extraction. The fluorous domain of the tin hydride is permanently attached because there is never any need to separate it from the organic domain. The tin compounds are simply recovered at the end of the reaction and recycled. Although only one tin hydride is shown below, a whole family is now available whose members differ from each other by the length and number of the fluorinated chains and the length of the spacer. This allows the separation properties and (sometimes) the reactivity properties to be tuned for particular needs.

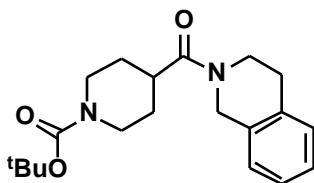
The fluorous Boc group is a typical example of a fluorous protecting group that is designed to be attached and removed by analogy with the standard Boc group. Such fluorous protecting groups are also called “fluorous tags”, and they allow rapid separation of all tagged molecules from non-tagged molecules by fluorous solid phase extractions. A growing assortment of fluorous tags is now available.

Organic Compound



a typical organic tin hydride

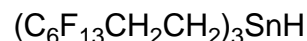
- mediates diverse radical reactions, but...
- is difficult to separate from organic products



a typical Boc protected amide

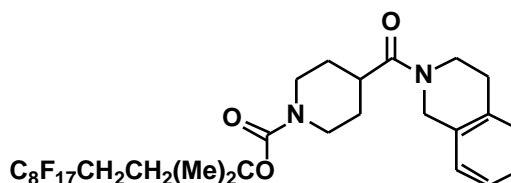
- is easy to prepare by amide coupling, but...
- is difficult to separate from the coupling reagents

Fluorous Compound



a typical fluorous tin hydride

- mimics the reactivity of its organic parent, and...
- is easy to separate from organic products by liquid-liquid extraction
- recovery and reuse are routine



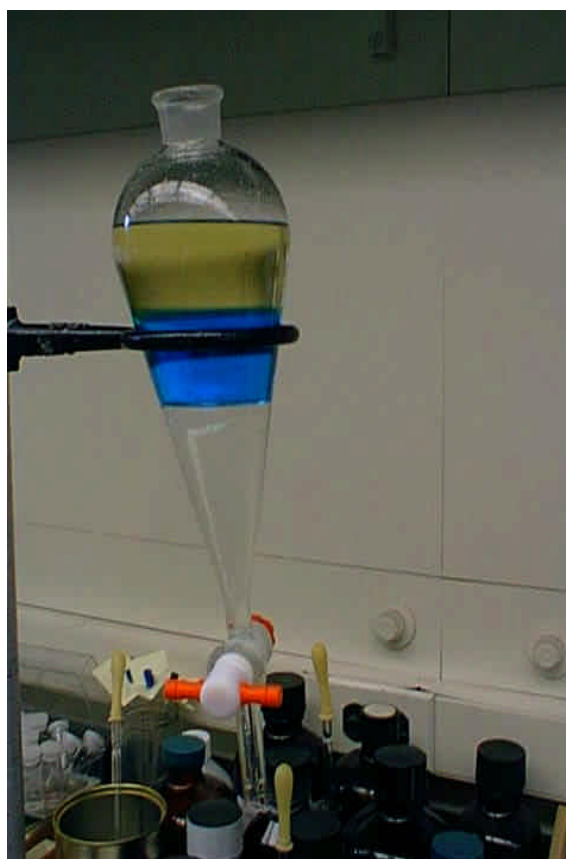
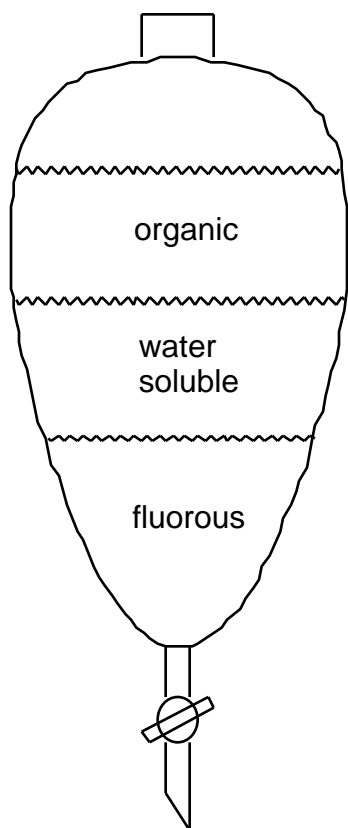
a fluorous Boc protected amide

- prepared by the same methods as the standard Boc-amide, and...
- is easy to separate from the coupling reagents by solid-liquid extraction

Fluorous Separation Methods: Liquid-Liquid Extraction

Perfluorinated or very highly fluorinated solvents are called “fluorous solvents” and they are typically immiscible with organic solvents and water. They are used in liquid-liquid extractions to quickly separate fluorous compounds from organic compounds in a two phase liquid-liquid extraction, or from organic and inorganic (or water soluble organic) compounds in a three-phase liquid-liquid extraction. The most popular fluorous solvent is 3M’s FC-72™, but a number of related solvents are available and these are all comparably priced.

A photograph of a typical three-phase liquid-liquid extraction is shown below. Such extractions are readily automated, and can be used to quickly partition reaction mixtures into organic (yellow), inorganic (blue) and fluorous (clear) fractions. In many cases, the crude organic products are pure enough to be taken on to the next reaction, and the fluorous products can usually be recycled, if desired.

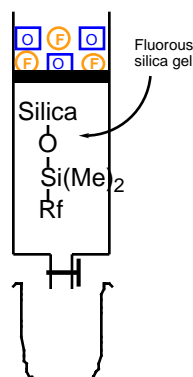


Liquid-liquid extractions work well when fluorous domains are relatively large. In the best cases, only a single separation is needed. With lower partition coefficients, the organic fraction is washed several times with the fluorous solvent. Thanks to the exceedingly low solubilities of organic compounds in fluorous solvents, the washing process can be conducted repeatedly without extractive loss of the organic product. Liquid-liquid extractive methods are typically used when the desired product is organic and some other reaction component (reactant, reagent, catalyst, scavenged product) is fluorous.

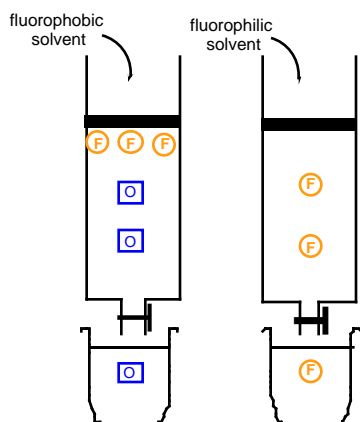
Fluorous Separation Methods: Solid-Liquid Extraction

FTI sells a complete line of fluorous reverse phase silica gel products under the *FluoroFlash*TM name. In addition to loose silica with a $\text{SiCH}_2\text{CH}_2\text{C}_8\text{F}_{17}$ bonded phase, *FluoroFlash*TM TLC plates, solid phase extraction and flash chromatography cartridges and HPLC columns are available. Silica gel with a fluorocarbon-bond phase can be used to adsorb fluorous molecules and free them from non-absorbed organic molecules by the simple process of solid-liquid extraction illustrated below. In the separation stage, a crude reaction mixture is charged to a suitable amount of fluorous silica gel and the silica is eluted first with a “fluorophobic” solvent to remove the organic compounds while leaving the fluorous compounds adsorbed. In cases where the fluorous products are desired, a second elution with a “fluorophilic” solvent then provides this material. These fluorous solid phase extractions are different from traditional chromatographies, and this is advantageous in a parallel setting. In solid phase extractions relatively high loadings of substrate/silica are used, and all of the mixtures in the synthesis behave identically. No fractionation is needed. In traditional chromatographies, each mixture behaves differently and lower loadings and carefully monitoring of fractions are needed.

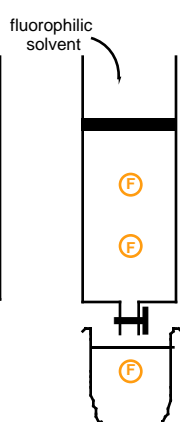
1) Charge reaction mixture containing organic (O) and fluorous (F) components



2) elute organic fraction



3) elute fluorous fraction



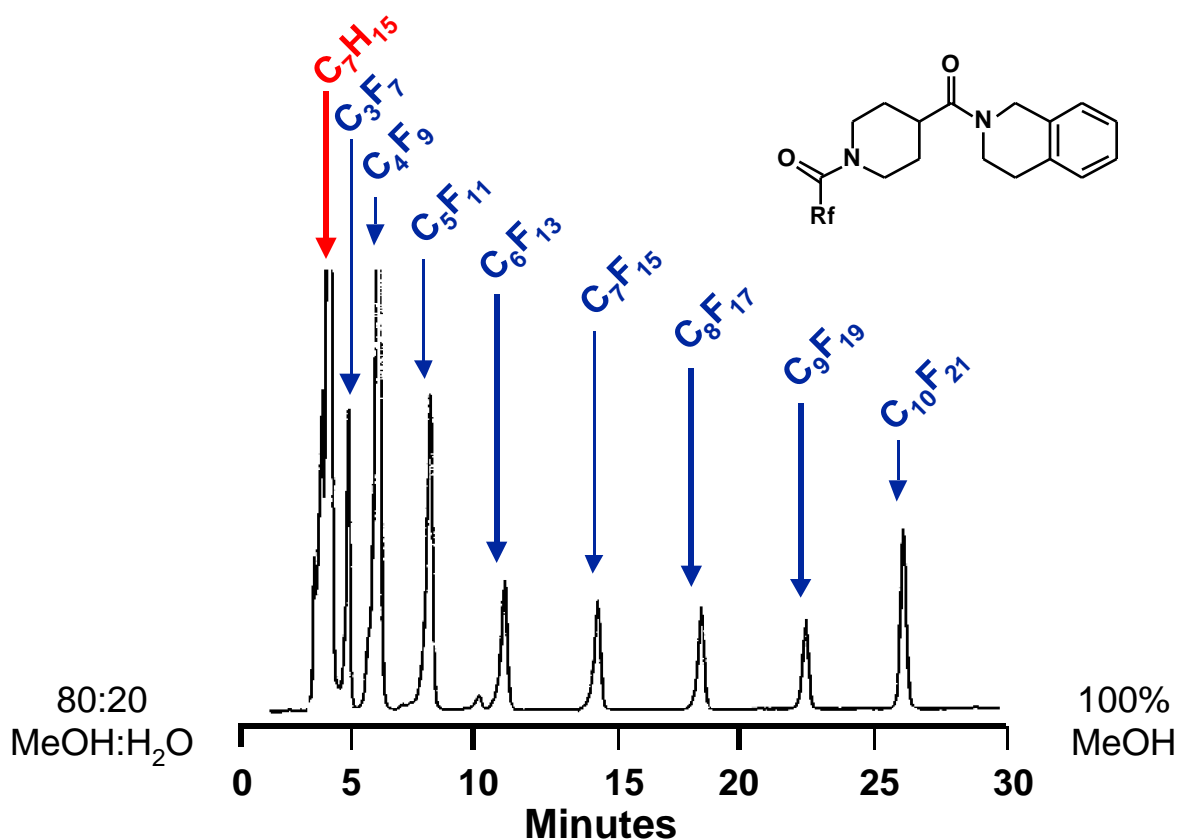
The cartoon shows the separation of an organic (blue) compound from a fluorous (orange) compound by SPE over *FluoroFlash*TM silica. The photo shows duplicate completed experiments conducted with an organic dye (Solvent Blue) and a fluorous dye (F-Orange-I, C_7F_{15} tag). These aminoanthraquinone dyes have about the same polarity and cannot be separated by regular or reverse phase silica gel. The cartridges can be reused.

The solid-liquid extractions are operationally filtrations and they are easy to conduct in parallel either manually (see the manual solid-phase extraction apparatus above) or by using various automated techniques. In addition to the operational convenience, solid-liquid extractions succeed with many fewer fluorines in the fluorous domain compared to liquid-liquid extractions. For this reason, solid-liquid extractions are especially useful when the desired product of the reaction bears a fluorous tag. The solid phase extraction is applicable in essentially all areas from traditional synthesis through parallel synthesis, and is especially useful for parallel synthesis of intermediates.

Solid-liquid extraction over *FluoroFlash*TM silica is currently the most general and most easily implemented fluorous-organic phase separation technique. It is useful for the gamut of fluorous methods. Fluorous solvents are rarely needed for the extractions, and they are used only to wash the silica prior to reuse, if desired.

Fluorous Separation Methods: Fluorous Chromatography

The separation of fluorous molecules from each other can sometimes be accomplished by standard chromatographic techniques, including traditional or reverse phase chromatography. However, the best way to separate fluorous compounds from each other is usually by chromatography over *FluoroFlash*TM fluorous silica. These separations capitalize on the unique feature of fluorous solid phases, which is their ability to separate molecules primarily by fluorine content. An illustrative example of this is shown below with a family of fluoroacyl-tagged amides. The control compound lacking the fluorous tag (C_7H_{15}) comes off with the solvent front, as do most other non-fluorinated organic compounds under these conditions. The fluorinated homologs then emerge strictly in order of fluorine content, and a solvent gradient is needed to push the more highly fluorinated members of the series off the column.

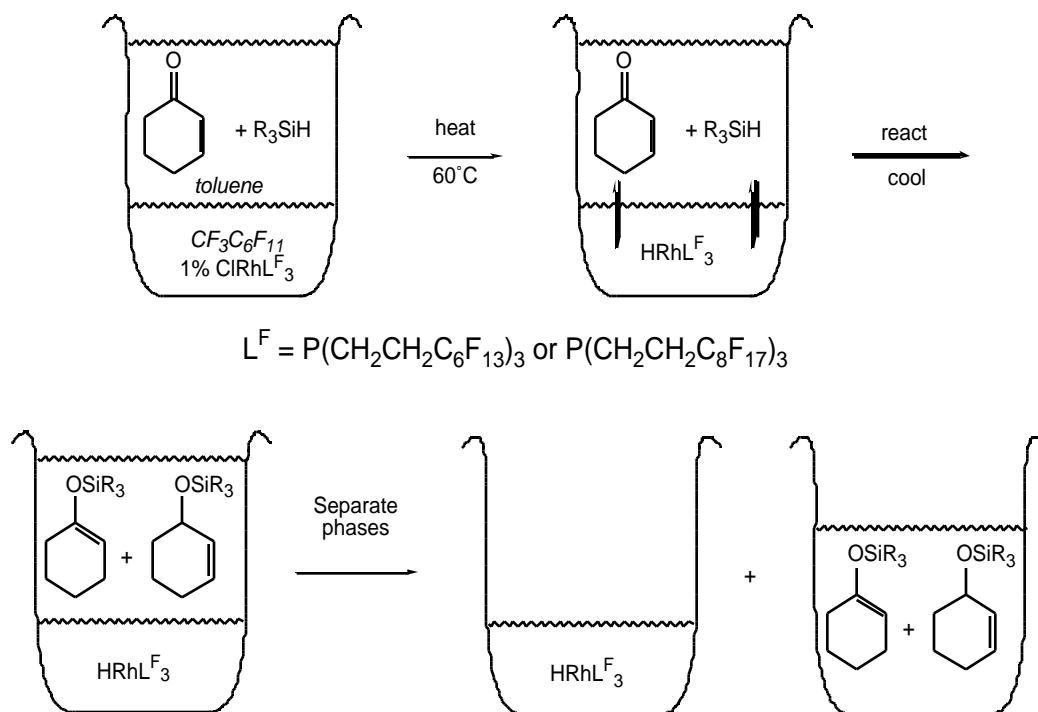


Many popular fluorous techniques involve fluorous-organic separations, so preparative fluorous chromatography is not needed. However, fluorous chromatography still has two major uses. First, it can be used in methods development experiments to select suitable solvents for fluorous-organic solid phase extractions, thereby ensuring in advance that separation conditions are suitable. Second, it can be used to analyze the purity of essentially any kind of fluorous component, and it provides information that is largely complementary to traditional chromatographic analyses. In contrast to other methods, fluorous mixture synthesis techniques rely heavily on fluorous chromatography for the separation of tagged compounds by the fluorine content of the tag.

Fluorous Biphasic Catalysis

Introduction: What we now call “Fluorous Biphasic Catalysis” (FBC) was first introduced in the thesis of Dr. M. Vogt in Aachen in 1991. A seminal paper by Horváth and Rábai in 1994 introduced new concepts and results along with today’s terminology. Since that time, fluorous biphasic catalytic methods have advanced rapidly, and a large number of fluorous catalysts and ligands (especially phosphines) are known. The defining feature of FBC is the use of a fluorous reaction solvent, and the technique is best viewed as a liquid phase catalyst immobilization method.

Example: Hydroformylation with a fluorous variant of Wilkinson’s catalyst provides a typical example of fluorous biphasic catalysis. A toluene solution of an enone and a silane is heated with a perfluoromethylcyclohexane solution of the catalyst. After the reaction is complete, the mixture is cooled and the two phases are separated to provide the organic hydrosilylation products and the recovered catalyst immobilized in the fluorous phase. In an important variant of fluorous biphasic catalysis, an organic solvent is chosen such that on warming a homogeneous (one phase) solution results. After the reaction is complete, the mixture is cooled to induce the phases to separate once again. In the hydrosilylation example, the replacement of toluene by hexane allows for one phase reaction and two phase separation.

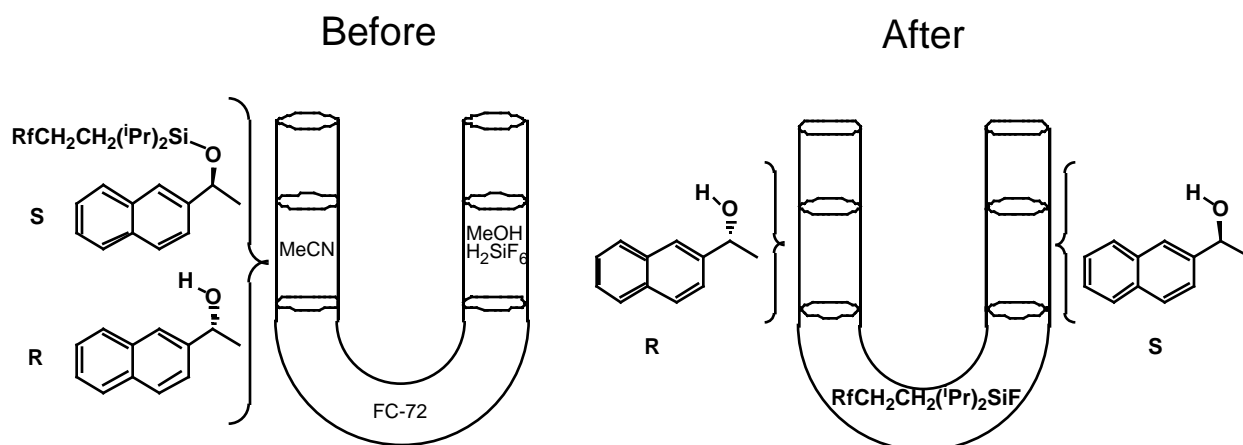


Features: FBC and related methods are ideally suited for economical and green chemical processes. A single liquid-liquid separation provides both the product and the recovered catalyst. The safety of fluorous solvents is also an attractive feature. For the single separation to succeed, high partition coefficients are needed, so the catalysts generally have large numbers of fluorines. Fluorous catalysts have advantages over solid-supported catalysts since they can be soluble in the reaction medium. Water-based biphasic catalysis reactions are also used, but are obviously limited to water-tolerant processes. Fluorous catalysts do not share this limitation. In an important recent advance, the thermomorphic (temperature dependent solubility) properties of fluorous compounds have been used—reactions are heated to dissolve a catalyst and cooled to precipitate it. No fluorous solvent is needed. If needed, spe through fluorous silica can remove last traces of the dissolved catalyst from the product.

Fluorous Triphasic Reactions

Introduction: Triphasic reactions consist of two organic phases that are separated from each other by a fluorous phase. Accordingly, exchange between the two organic phases is only possible for molecules that can pass through the fluorous phase. This innovative technique intimately couples a separation with a reaction—the reaction in one of the organic phases is used to drive the separation through the fluorous phase in a non-equilibrium fashion.

Example: Consider the U-tube reaction of a 1/1 mixture of fluorous-tagged (*S*)-2-naphthylethanol and free (*R*)-2-naphthylethanol shown below. To start, the mixture is added to the left side of a U-tube containing organic solvents (both top sides) bridged by FC-72 (bottom). A detagging reagent (here, H_2SiF_6) is added to the right side of the U-tube. Over time, the tagged (*S*)-enantiomer migrates through the fluorous phase to the right side, where it is detagged. The resulting free (*S*)-enantiomer lacks the tag and is now stranded on the right side, whereas the residual tag is highly fluorophilic and migrates back to the FC-72. The (*R*)-enantiomer lacks the tag in the first place, so it cannot migrate away from the left side. At the end of the reaction, the (*R*)-enantiomer remains on the left side, the residual tag is in the middle, and the (*S*)-enantiomer has migrated to the right side and been detagged.



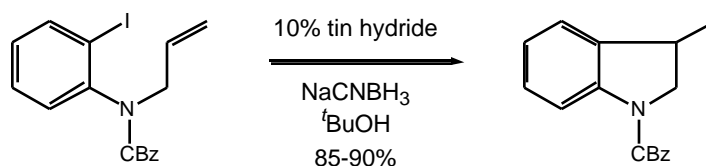
tagged enantiomer migrates from left organic phase through fluorous phase to right organic phase, where it is stranded by detagging

Features: Fluorous triphasic reactions are especially useful for removal of fluorous tags because such reactions occur with separation of the tagged product from all untagged impurities. The pairing of an efficient enzymatic or chemical kinetic resolution reaction with a triphasic detagging reaction can result in a rapid and practical separation of enantiomers that does not require any chromatography. As usual, the technique allows for ready recovery of the fluorous tag in a form suitable for reuse. Like fluorous biphasic reactions, volumes of fluorous solvent used are small. However, many fewer fluorines are needed relative to biphasic reactions since the fluorous tagged molecules only need to transiently pass through the fluorous phase.

Fluorous Reagents, Reactants, Catalysts

Introduction: For many types of organic reactions, it is desirable to use fluorous reaction components (reagents, reactants, catalysts) with fewer fluorines. Such molecules have advantages of lower molecular weight and increased solubility in organic solvents. With these types of molecules, fluorous reaction solvents are not used, and the fluorous phase (either solid or liquid) is used only in the separation stage.

Example: The reductive radical cyclizations with the family of fluorous tin hydrides shown below illustrate many of the features of this branch of fluorous chemistry. In general, the substrate and the product are organic molecules and one of the other reaction components (in this case, the tin hydride) is fluorous. The fluorous component can be used either catalytically or stoichiometrically and the reaction and separation stages are decoupled. After standard reactions, members of the tin hydride family with more fluorines can be separated either by liquid-liquid extraction or by solid-liquid extraction, while the solid-liquid extraction is preferred for members with fewer fluorines. For the most highly fluorinated member of the series, a fluorinated reaction co-solvent like benzonitrile (C_6H_5CN) is needed. Benzonitrile is not a “fluorous” solvent since it is miscible in all organic solvents (and indeed dissolves many types of organic compounds as well), but it still aids in the solubilization of fluorous compounds in the reaction medium.



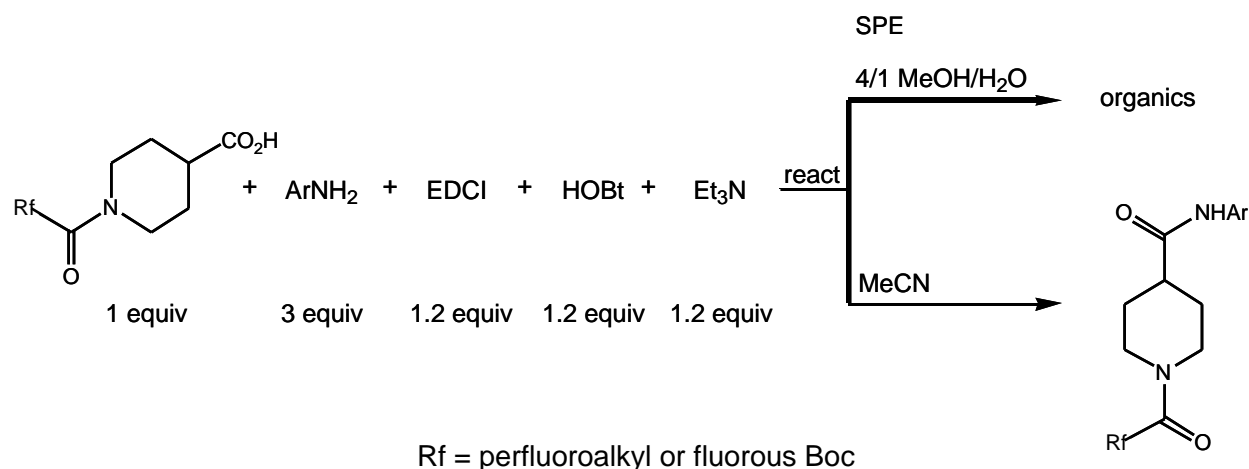
tin hydride	I-I extraction (# of extractions)	s-l extraction	fluorinated rxn cosolvent?
$(C_6F_{13}CH_2CH_2)_3SnH$	yes (3)	yes	yes
$(C_4F_9CH_2CH_2)_3SnH$	yes (8-10)	yes	no
$(C_6F_{13}CH_2CH_2CH_2)_3SnH$	yes (5-8)	yes	no
$(C_4F_9CH_2CH_2CH_2)_3SnH$	yes (10-12)	yes	no
$C_{10}F_{21}CH_2CH_2SnMe_2H$	yes (3)	yes	no
$C_8F_{17}CH_2CH_2SnMe_2H$	no	yes	no

Features: These methods are broadly useful for all types of organic synthesis from process chemistry (fluorous catalysts preferred) through traditional synthesis to solution phase parallel synthesis and combinatorial chemistry. Tuning of preferred reaction solvents and separation methods is accomplished by selecting a reagent with an appropriate fluorine content. The reagents with fewer fluorines are especially attractive since they often have excellent solubility in organic solvents, yet can still be separated from standard organic compounds by solid-liquid extraction. Fluorous compounds are also soluble in supercritical CO_2 , and can be used in green chemical reactions in that solvent. The general solubility of the fluorous reaction components is an attractive feature in comparison to reagents, quenchers, and catalysts that are immobilized on insoluble polymers.

Fluorous Substrates, Products

Introduction: The term “fluorous synthesis” is often used to describe techniques in which the substrates and/or desired products are rendered fluorous. This technique is a phase tagging strategy that is conceptually analogous to “solid phase synthesis”, but with major operational differences. Making substrates and products fluorous necessarily involves cleavable tags (since the final product will not be tagged), and fluorous protecting groups or traceless tags can be used. Fluorous synthesis concepts were introduced with liquid-liquid separation methods coupled with very large fluorous tags (60-120 fluorines). These early “heavy” fluorous techniques are quickly being superseded by “light” techniques where tags with many fewer fluorines are used coupled with solid-liquid extraction.

Example: Amino acids are readily coupled to make amides by first tagging the amine with a fluorous acyl group or a fluorous Boc group and then coupling the acids with amines under standard conditions. In general, only about 15-19 fluorines are needed, and the resulting tagged molecules have solubility properties that are largely dominated by the organic domain. In other words, they are soluble in organic not fluorous solvents. However, the solid phase extraction properties of the molecule are still dominated by the fluorous domain. The protected acids are coupled with amines under standard conditions. The desired tagged products are then retained on the column in the first pass of the solid phase extraction (MeOH/water) while all the coupling reagents, reactants and byproducts are eluted off. The coupled fluorous products are then eluted off in a second pass (MeCN) and are obtained in excellent purity.

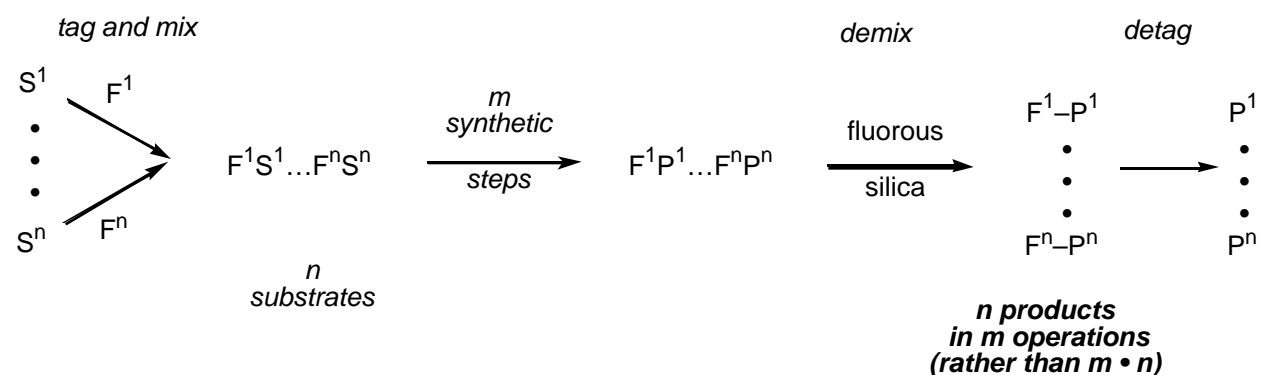


Features: Fluorous synthesis is attractive because a single protecting group or tag can be used to render a library of organic molecules fluorous. The resulting library of soluble molecules can then be separated from broad classes of organic and inorganic reagents, reactants, side products, etc. by solid phase extraction. Unlike polymer-bound molecules, the fluorous-tagged compounds are small molecules that can be analyzed and characterized by standard small molecule techniques. The tagging methods are ideal for expedited parallel synthesis and for the gram-scale preparation of chemical intermediates in parallel. Because the tagged compounds have relatively few fluorines, they can be reacted under typical conditions for non-tagged molecules and the solid phase extraction gives a fast yet substantive separation. In the final detagging step, solid phase extraction can again be used to separate the organic product from the remnant of the fluorous tag. The tag can often be recovered in a form suitable for reuse, if desired. In addition to fluorous acyl and Boc groups, there are now a number of fluorous silyl groups, fluorous THP groups, fluorous benzyl groups, etc.

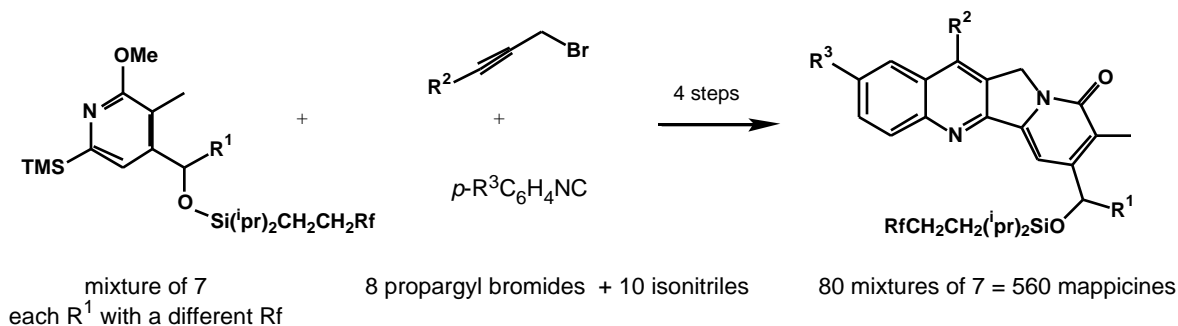
Fluorous Mixture Synthesis

Introduction: The synthesis of compound mixtures economizes time, effort and money since many fewer operations are required compared to standard serial or parallel synthesis. However, solution mixture synthesis is not used because it is not possible to ensure that the final mixture can be resolved into its individual pure components. Fluorous mixture synthesis is the first technique that captures the economy inherent in solution phase synthesis of mixtures yet still allows the predictable isolation of individual pure products at the end of the exercise.

Concepts: The concepts of fluorous mixture synthesis are shown in the cartoon below. Members of series of substrates (S^1 - S^n) are tagged with a corresponding series of fluorous tags (F^1 - F^n). Each fluorous tag bears the same basic functionality, but the tags differ in fluorine content. This crucial difference controls the final separation. The tagged substrates (S^1F^1 - S^nF^n) are mixed and then taken through a series of synthetic reactions where the economy of the mixture techniques is harvested (the number of operations required at each stage is divided by the number of tags, n). Just prior to detagging, the final products (P^1F^1 - P^nF^n) are “demixed” (separated) by fluorous chromatography. This separates the molecules, which elute in order of increasing fluorine content of the tag. The compounds are simultaneously identified in the demixing simply by comparison to the original tag/substrate pairings.



Example: Based on preliminary work in Prof. Curran's group, FTI has prepared a 560-member library of mappicine analogs on ~2 mg scale. A mixture of seven pyridines shown below was taken through four steps with splitting into 8 in the penultimate step and 10 in the final step. This provides 80 mixtures of tagged mappicine analogs, each containing 7 analogs.

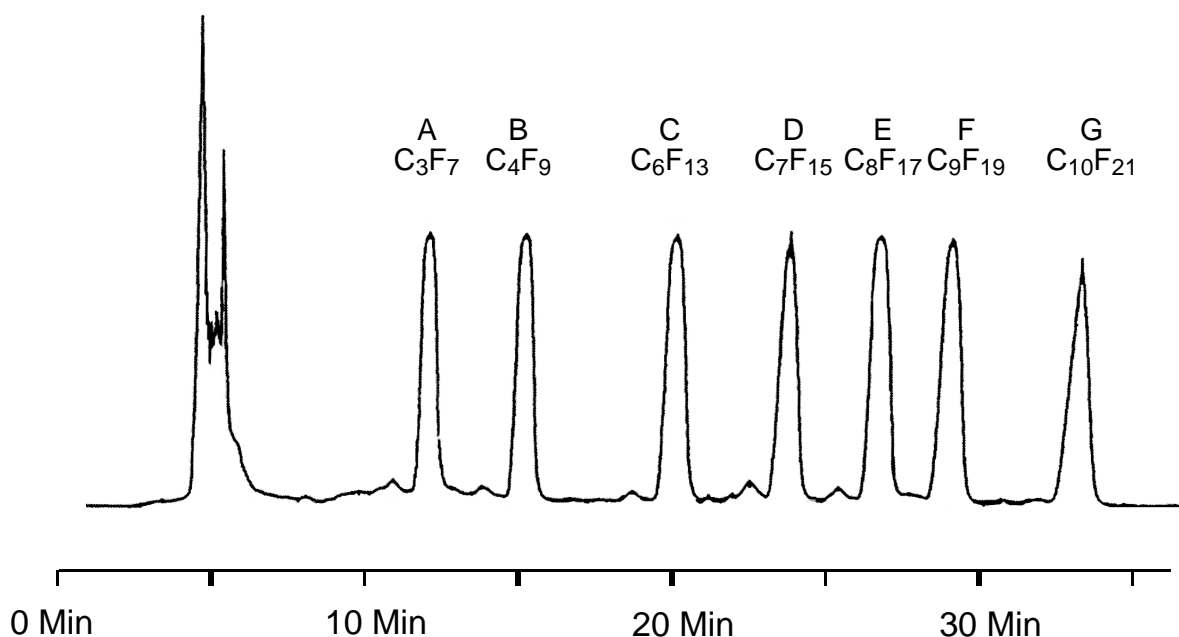


Each final mixture was then demixed by fluorous chromatography to give the seven individual components in order of increasing fluorine content from the C_3F_7 -tag up to the $C_{10}F_{21}$ -tag (the C_5F_{11} -tag was missing from the exercise). A representative HPLC trace of the demixing is shown below (the absence of the C_5F_{11} -tag is readily seen by the gap between the second and third peaks in each of the 80 chromatograms). A steep solvent gradient is needed to elute all the compounds

within 35 min. All 560 tagged mappicines were identified by LCMS analysis and were isolated from serial preparative runs. Finally, the tags were removed with HF followed by a simple spe to remove the residual tag from the final mappicine analogs.

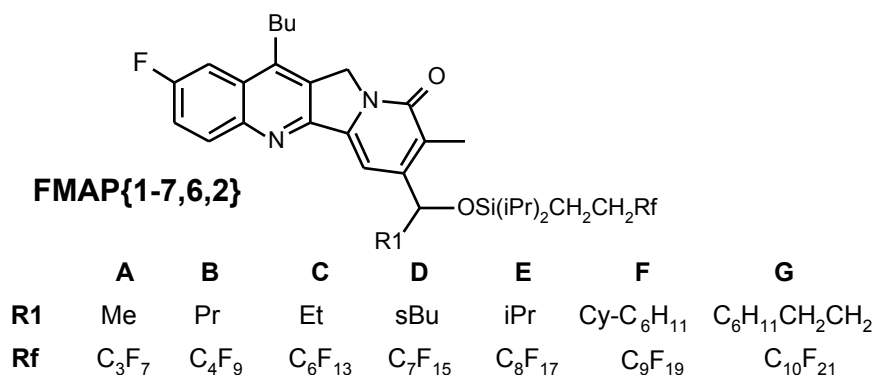
Features: Fluorous mixture synthesis techniques are ideal for leveraging either serial or parallel synthesis discovery efforts since more compounds are produced without a proportional increase in effect. The analytical power of the fluorous silica gel allows one to follow reactions and identify products in mixtures almost as easily as with individual pure compounds. This technique is especially useful for making analog libraries or for making multiple stereoisomers in a single synthetic sequence.

Representative Demixing of One Seven Component Mixture {1-7,6,2} of the Fluorous Mappicine Library: Analogs elute in order determined by the fluorous tag.^a



^agradient of 85% MeOH/water to 100% MeOH. Following the large solvent front and some organic impurities, the tagged mappicine analogs elute in order of tag size: C₃F₇, C₄F₉, (C₅F₁₁ not used), C₆F₁₃, C₇F₁₅, C₈F₁₇, C₉F₁₉, C₁₀F₂₁.

Structures of Tagged Molecules from the Illustrated Mixture



Summary

By directly addressing the separation problems inherent in the synthesis of small organic molecules, fluorous techniques provide an array of powerful solutions that span the discipline of organic synthesis from large scale chemical processes through traditional fine synthesis to modern chemical discovery by combinatorial methods.

The following Table summarizes the five main fluorous methods outlined in this overview and compares and contrasts them.

Technique	Fluorine Content	Rxn Solvent	Separation	Uses
Fluorous Biphasic Catalysis	high	fluorous and organic	single liquid-liquid separation	green chemical processes
Fluorous Triphasic Reactions	low-medium	fluorous and organic	built into reaction, synthesis drives separation	resolution of racemates, detagging
Fluorous Reagents	low-medium	organic or hybrid	liquid-liquid or solid-liquid extraction	universal
Fluorous Substrates	low	organic	solid-liquid extraction	chemical discovery, intermediate synthesis
Fluorous Mixture Synthesis	low, variable	organic	fluorous chromatography	leveraged chemical discovery

Fluorous methods are attractive and easy to apply because the experimental techniques (solution phase reactions, liquid-liquid extractions, solid phase extractions) are familiar to practicing organic chemists. What differs from standard organic techniques are the fluorous components that are used. The application of fluorous techniques has been limited to a few specialized laboratories due to the lack of availability of fluorous reagents, reactants, tags, solvents, silica, etc. Fluorous Technologies intends to change this by providing laboratories worldwide with both the materials and the expertise that are needed to integrate fluorous methods into their ongoing discovery and production projects.

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