Fluorous Synthesis: A Fluorous-Phase Strategy for Improving Separation Efficiency in Organic Synthesis

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Recovery and purification difficulties can limit the yield and utility of otherwise successful organic synthesis strategies. A "fluorous synthesis" approach is outlined in which organic molecules are rendered soluble in fluorocarbon solvents by attachment of a suitable fluorocarbon group. Fluorocarbon solvents are usually immiscible in organic solutions, and fluorous molecules partition out of an organic phase and into a fluorous phase in a standard liquid-liquid extraction. Simple yet substantive separations of organic reaction mixtures are achieved without resorting to chromatography. Because fluorous synthesis combines in many respects the favorable purification features of solid-phase synthesis with the favorable reaction, identification, and analysis features of traditional organic synthesis, it should prove valuable in the automated synthesis of libraries of individual pure organic compounds.

The practical synthesis of organic compounds is limited not only by the yield of specific reactions but also by the ability to recover the desired product in pure form. Traditionally, chemists have relied on phase separation to recover products; under favorable conditions, crystallization, distillation, or solvent partitioning (extraction) of the product or a derivative are effective, but more often the physical properties of the product and by-products are so similar that chromatographic methods must be used to effect a separation.

More recently, a solid support, such as the polymer resins used in peptide and oligonucleotide synthesis, has been used to "hold on" to the substrate while it reacts in solution, thereby allowing the product to be purified before it is cleaved from its support (*1*). Solid-phase synthesis is well suited for conducting multiple synthetic steps in succession, so the combinatorial synthesis of numerous products can be effected in a few steps (*2, 3*). An advantage of solid-phase methods is that they add another phase to the reaction that in principle is available only to the product molecule. In practice, both the functionality of the polymer and its general insolubility pose problems that limit the choice of synthetic methods. These problems are now being addressed by solution chemistry, both with (*4*) and without (*5*) polymers.

We have pursued an approach (*6*–*8*) that takes advantage not of the insolubility of polymers in liquids but instead of the insolubility (immiscibility) of fluorocarbon fluids (or fluorous solvents) in both aqueous and organic solvents (*9*). The use of the fluorous phase in organic synthesis has been spurred by recent papers by Zhu (*10*), who used fluorous solvents in an organic reaction, and by Horváth and Rábai, who introduced the concept of fluorous biphasic catalysis (*11*). Here, we outline three approaches: (i) fluorous synthesis, (ii) the fluorous-phase switch, and (iii) fluorous multiphase condensations, which take advantage of labeling the substrate (starting molecule) of the synthesis with a perfluorinated segment that is large enough to force partitioning of the resulting molecule into the fluorous phase.

These fluorous synthesis strategies combine in many respects the favorable reaction and characterization features of traditional organic synthesis (solution-phase reactions, easy identification and analysis of products) with the purification features of solid-phase synthesis. Because fluorous synthesis is not a solid-phase method, it cannot be used to conduct "split syntheses," which rely on solid-solid separations (*2, 3*). In this respect, it resembles solution synthesis with soluble polymer-bound substrates (*4*). However, the fluorous substrates are not polymers but single molecules, so all standard spectroscopic, analytical, and even chromatographic techniques can be used.

As a test reaction for fluorous synthesis, we chose nitrile oxide cycloadditions (*12*) to labeled derivatives of simple unsaturated alcohols. These reactions occur in high yields with terminal alkenes and alkynes, and an interesting class of heterocycles is produced; however, the two common ways to produce nitrile oxides use different reagents and thus provide differing purification challenges. These two methods—the Huisgen method and the Mukaiyama method—are summarized in Fig. 1 (*12*). If the nitrile oxide precursor is used in excess, then both methods require that the product be separated from the nitrile oxide dimer (a furoxan). The two reagents (RCH_2NO_2 and PhNCO, where R = alkyl or aryl and Ph = phenyl), the furoxan dimer, and the obligatory *sym*-diphenyl urea (PhNHCONHPh) by-product of the Mukaiyama method are all organic compounds, and chromatographic procedures for separation are usually used.

The protocol for the nitrile oxide cycloaddition reactions (*13*) is shown in Fig. 2 with allyl alcohol as an example. Each reaction stage is followed by an extractive purification stage. Although each of the steps has been studied separately in the traditional way for a dozen compounds (with purification of each intermediate), we describe here only five examples of the overall process (without intermediate chromatographies or characterizations) as designed for library synthesis.

The phase labeling reagent **1** was designed after the popular trialkylsilyl class of protecting groups commonly used in organic synthesis (*14*), and it is readily available in multigram quantities (*15*). Silylations were performed with the use of excess alcohol **2** [2 to 4 equivalents (equiv)] in tetrahydrofuran (THF) under standard conditions. After removal of the THF, a three-phase liquid extraction was performed with water (top), CH_2Cl_2 (middle), and FC-72 (bottom; FC-72 is a mixture of perfluorohexanes, C_6F_{14}, boiling point 56°C). The organic phase containing the unreacted alcohol and the water phase containing the amine hydrobromide (and probably also some alcohol in the case of these small substrates) were discarded, and the fluorous phase was concentrated to provide the desired fluorous-labeled silyl ethers **3**. At this stage, the strategy allows for ready separation of unreacted organic substrates **2** from

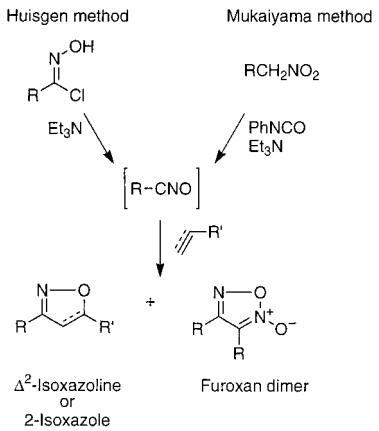

Fig. 1. In situ methods of nitrile oxide generation and cycloaddition.

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labeled products **3**, as demonstrated by the intentional use of excess alcohol.

Nitrile oxide cycloadditions were then conducted under standard Mukaiyama [R = propyl (Pr) or methyl (Me)] or Huisgen [R = *tert*-butyl (*t*-Bu) or Ph] conditions (*12*). All of the reagents were used in four- to tenfold excesses to mimic the need to drive reactions to completion and to deliberately generate impurities for separation. The Huisgen reactions were conducted in CH_2Cl_2, a solvent in which the fluorous substrate **3** was not completely soluble (as determined visually), whereas the Mukaiyama reactions were conducted in benzotrifluoride (*7*) (trifluoromethylbenzene, $C_6H_5CF_3$), a solvent in which the substrates **3** appear to fully dissolve. After the reactions, three-phase extractions were conducted with benzene as the organic solvent. Evaporation of the fluorous phase provided the cycloadducts **4** substantially free from organic (and inorganic) impurities.

The fluorous label was then removed by desilylation of the products **4** with HF•pyridine in diethyl ether (Et_2O) at room temperature. The organic phase now contained the desired product in the final three-phase extraction between aqueous ammonium chloride (top), CH_2Cl_2 (middle), and FC-72 (bottom). Evaporation of the CH_2Cl_2 phase then provided the final products **5**, which were analyzed for yield and purity without any additional purification. Overall isolated yields of **5a** through **5e** for the three-step sequence are shown under each of the final products in Fig. 2. The isolated yields are reasonable (in the case of **5d**, material loss from evaporation contributes to a lower yield) and the gas chromatography (GC) purities are quite acceptable by present standards, especially considering that deliberate stoichiometry mistakes generated large amounts of by-products. Interestingly, the anti/syn ratio obtained in **5e** is virtually identical to the ratio obtained in nitrile oxide cycloadditions with normal (nonfluorous) trialkylsilyl ethers (*16*).

Although only one step (nitrile oxide cycloaddition) was conducted in Fig. 2, we envision that fluorous synthesis will be used like solid-phase synthesis with multiple steps between attachment and detachment of the label. As in solid-phase synthesis, excess reagents and reactants can be used to drive the reaction to completion. Indeed, it is crucial that the substrate be completely consumed because it has the same phase as the product. Herein lies the potential downfall of all "one-phase" techniques: the substrate, the desired product derived from the substrate, and any by-products derived from the substrate all will partition into the same phase. This problem is especially acute in combinatorial synthesis because general classes of reactions that occur in quantitative yield on a diverse collection of organic substrates are still the exception rather than the rule.

A solution to the one-phase problem is to conduct a selective "phase switch." In this process, the phase into which one product (or a subset of products) partitions is temporarily switched from that of the other products. After separation, the phase is switched back. Acid-base extractions are a classic example, and switches from the organic liquid phase to the solid (polymer) phase and back have recently been introduced as a means of purification (*17*).

"Organic-fluorous" switches are a potentially general method to purify organic reaction mixtures. The reaction of a given functional group in an organic molecule with a fluorous label "triggers" the phase switch. The technique is illustrated by the simple sequence shown in Fig. 3. A standard Grignard reaction of an aldehyde with 1.5 equiv of a Grignard reagent is followed by addition of excess fluorous label **1**. The fluorous ether products **6** are then separated by three-phase extraction. Treatment of the crude products from the fluorous phase with cesium fluoride followed by a second three-phase extraction provides the 10 organic alcohol products **7** in the yields and purities indicated in Fig. 3.

The main purpose of these reactions was to demonstrate that the products could be labeled and extracted into the fluorous layer. However, the purification features of the technique are also apparent. For example, when the aldehyde is used in excess instead of the Grignard reagent, then the unreacted aldehyde is left in the organic phase after the first extraction. In the standard procedure where excess Grignard reagent is used, the residual reagent presumably reacts with an equivalent amount of the silylating agent to form a silane $RSi(CH_2CH_2C_6F_{13})_3$. This silane is extracted into the fluorous phase with the desired silyl ether in the first extraction; however, it does not react with CsF, so it is left in the fluorous phase during the second extraction when the alcohol switches back to the organic phase. There are thus two different triggers that can be manipulated: one into and one out of the fluorous phase. Reactions can also be designed so that the by-product rather than the desired product is left in the fluorous phase (*18*).

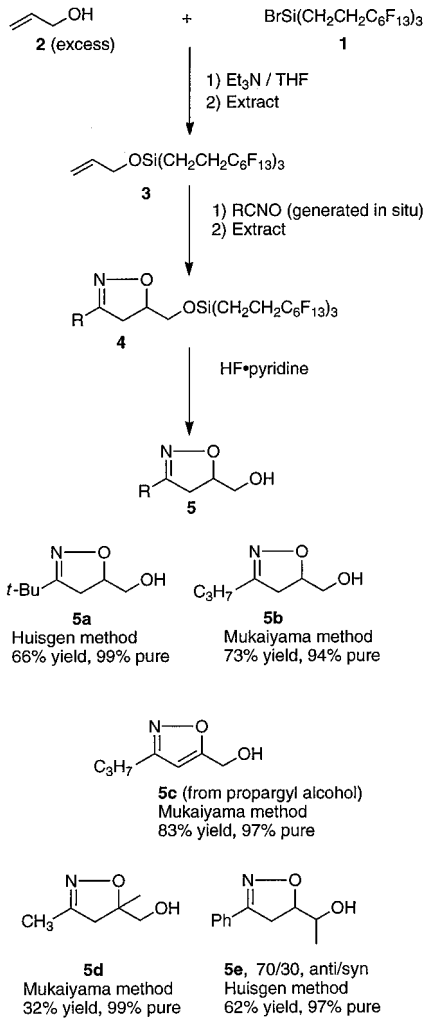

Fig. 2. Nitrile oxide cycloadditions with fluorous-labeled allyl alcohols. The RCNO intermediate is generated as in Fig. 1; here R′ would be CH_2OH labeled with the fluorous tag at the oxygen.

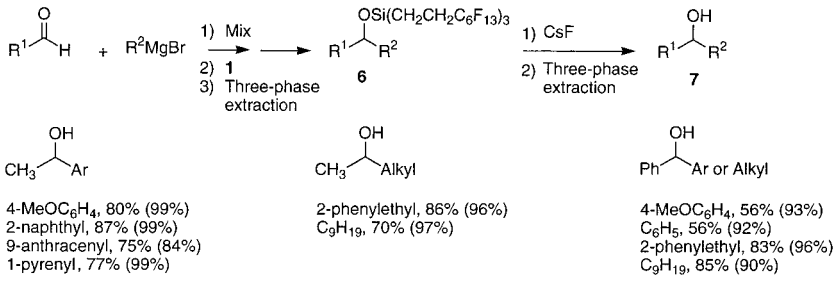

Fig. 3. Purification of Grignard products by fluorous-phase switch, and yields and GC purities (in parentheses) for reactions with $R^2 = CH_3$ and Ph. Ar, aryl.

The desired transformation of substrate and the fluorous-phase switch can also be directly coupled, as illustrated by the reactions of tin azide **8** shown in Fig. 4. This is the fluorous analog of tributyltin azide, a reagent for making tetrazoles from nitriles (*19*). Reaction of an organic nitrile **9** used in twofold excess (to simulate incomplete conversion) with fluorous azide **8** in benzotrifluoride at 80°C for 12 hours provides the fluorous tetrazoles **10** after organic and fluorous extraction (benzene and FC-72) to remove unreacted nitrile and any other organic by-products. Brief exposure of the fluorous tetrazoles **10** to ethereal HCl, followed by organic and fluorous extraction (acetonitrile and FC-72) and evaporation of the organic (acetonitrile) phase, then provides the pure tetrazoles **11** in the indicated yields. The examples show that the fluorous-phase switch can provide pure organic products even in reactions that do not occur in quantitative yield, and can be used to remove fluorous reagents and by-products from organic products. The final fluorous product **12** can be retrieved in high yield from the fluorous layer and reused (*8*). The more usual way to conduct these reactions would be to use excess fluorous tin azide, and indeed the treatment of one equivalent of *p*-tolunitrile with three equivalents of tin azide **8** under the standard conditions provided tolyl tetrazole **11** (R = tolyl) in almost quantitative yield.

The phase switching method can also be used to rectify problems in prior steps of a sequence of synthetic steps. Because nitriles are commonly prepared from halides, we doped 1 equiv of *p*-tolunitrile with an additional equivalent of 4-bromotoluene (called "impurities" in Fig. 4) and then carried out the reaction and extraction sequence. The 4-bromotoluene does not react with the tin azide **8**, and it partitions into the organic layer in the first extraction. In the end, the desired tetrazole **11** (R = tolyl) was isolated in about the same yield and purity as in the experiment without the bromide.

The experiments described thus far suffice to illustrate the fluorous techniques, but the final organic products of the reactions are too small to be of much interest (most have molecular weights of <150). The preparation of very small organic molecules glosses over crucial features on which the success of these fluorous strategies will hinge: What are the structural requirements for fluorous labels, and will it be possible to render important large classes of organic molecules fluorous with appropriate labels and still retain some semblance of normal solution reactivity?

Multicomponent reactions bring together a substrate and two or more reactants to provide products in a single step (*20–22*). The Ugi and Biginelli reactions (*23*) are two important classes of multicomponent condensations that have recently been adapted to the solid phase (*21, 22*). The standard solution phase forms and fluorous variants of these two reactions are shown in Fig. 5.

In a fluorous variant of the Ugi reaction, acid **13** bearing 63 F atoms in the label (the previous labels had 39 F atoms) was reacted with a large excess (17 equiv) of the other three components: benzyl amine ($PhCH_2NH_2$), cyclohexane carboxaldehyde ($c\text{-}C_6H_{11}CHO$), and cyclohexyl isonitrile ($c\text{-}C_6H_{11}NC$). Methanol is the usual solvent for Ugi reactions, but the preferred solvent for this fluorous Ugi reaction was trifluoroethanol, presumably because this solvent has the ability to solubilize both the organic and fluorous components of the reaction mixture.

Purification by two-phase extraction (benzene and FC-72) and evaporation of the fluorous phase provided a fluorous Ugi product (not shown). The unreacted or partially reacted components were left in the organic phase. Without further purification, the fluorous Ugi product was desilylated with tetrabutylammonium fluoride (TBAF). Standard organic and fluorous extraction separated the label and any other fluorous compounds from the organic Ugi product **14**, which was isolated by evaporation of the final organic phase in 84% yield (>95% pure by GC analysis), even though it represented only 6 weight % of the reaction mixture.

The Biginelli reaction started with attachment of hydroxyethyl urea to the acyl bromide analog of acid **13**. Fluorous urea **15** was purified as usual by fluorous and organic extraction. The Biginelli reaction was also conducted with large excesses of keto ester and aldehyde reactants (10 equiv) both to drive the reaction to completion and to deliberately generate large amounts of organic reaction components to separate. The components were heated for 3 days at 50°C in 2:1 THF–benzotrifluoride (BTF) containing HCl. The fluorous Biginelli product (not shown) was then isolated by three-phase extraction. Desilylation with TBAF followed by extractive purification provided the pure organic Biginelli product **16** in 60% yield.

These transformations illustrate the power of the fluorous approach for conducting and purifying multicomponent reac-

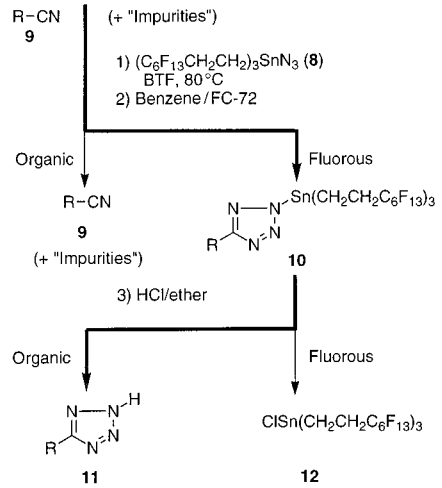

Fig. 4. Combining a fluorous reagent and label. Yields: R = CH_3, 83%; *i*-Bu, 87%; $PhCH_2$, 77%; *p*-$CH_3C_6H_4$, 61%; *p*-$MeOC_6H_4$, 72%; Ph, 59%; *p*-$NO_2C_6H_4$, <10%.

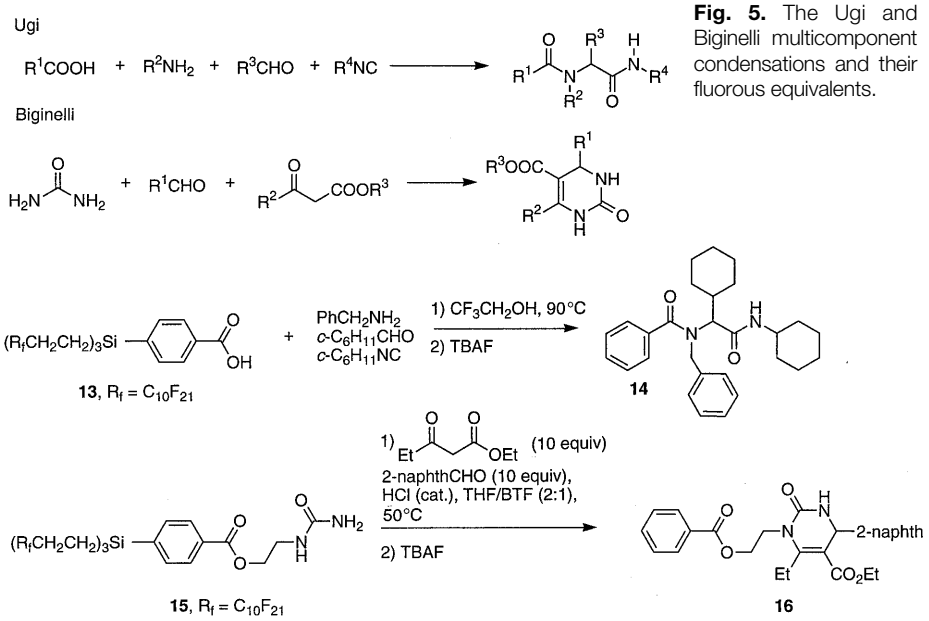

Fig. 5. The Ugi and Biginelli multicomponent condensations and their fluorous equivalents.

tions. The final organic products of these multicomponent reactions have molecular weights of 432 (**14**) and 472 (**16**), yet the fluorous-labeled precursors of these products were successfully extracted into the fluorous phase for purification. These and related fluorous-labeled products have molecular weights in the range of 2000, of which roughly three-fifths is fluorine, one-fifth is other atoms in the label (C, H, Si), and one-fifth is the labeled substrate itself. In these examples, the fluorous label has a role roughly analogous to that of the "traceless linkers" recently introduced in solid-phase synthesis (*3*).

In light of the increased demand for combinatorial and parallel synthesis of libraries of small organic molecules, the issue of purification is no longer a technical concern but needs to be addressed at the strategy level in synthetic planning. Reactions should be designed such that the desired product has a different phase from all of the other components of the final reaction mixture. The fluorous synthesis techniques outlined here introduce new strategic options to meet this goal.

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Recharge in Volcanic Systems: Evidence from Isotope Profiles of Phenocrysts

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Strontium isotope ratios measured from core to rim across plagioclase feldspar crystals can be used to monitor changes in the isotope composition of the magma from which they grew. In samples from three magma systems from convergent margin volcanoes, sudden changes in major element composition, petrographic features, and strontium isotope composition were found to correspond to discrete magmatic events, most likely repeated recharge of more mafic magma with lower ratios of strontium-87 to strontium-86 into a crustally contaminated magma.

Mineral assemblages and individual crystal phases from magmatic suites record differentiation processes in magmatic systems. Compositional zoning, textural discontinuities, inclusion zones, and reaction rims in crystals all reflect changes in magmatic conditions. Compositional changes may be produced either by changes in intrinsic variables (such as changes in water content, temperature, or pressure, reflecting eruptive or convective cycles from a magma chamber) or by open system processes such as recharge (the introduction of a fresh batch of generally hotter and less evolved magma into the chamber) and contamination (the assimilation of country rock and its incorporation into the magma).

Plagioclase feldspar can serve as a recorder of differentiation processes in many volcanic rocks (*1*). In mafic to intermediate volcanic rocks of subduction-related suites, it typically occurs as large (2 to 20 mm) phenocrysts. Growth zones within plagioclase crystals form an effective stratigraphy reflecting changes through time in the magma from which it grows. Dissolution surfaces preserved in the crystals, and revealed by petrographic and Nomarski interferometry analysis (*2*), reveal rapid changes in the magmatic environment. We show that Sr isotope profiling of plagioclase phenocrysts is a potentially powerful tool in elucidating differentiation processes and discuss three examples that underscore the importance of repeated mafic recharge in subduction-related volcanic systems. We studied plagioclase from Chaos Crags in California, Purico-Chascon in Chile, and El Chichón in Mexico. In the first two systems, the presence of mafic magmatic inclusions provides direct evidence that recharge occurred, whereas at El Chichón, the phenocrysts themselves provide the most compelling evidence for recharge by a mafic magma.

We obtained the crystal isotope stratigraphy by mechanically drilling polished, thick sections. Drill sites were planned to sample discrete zones within the crystal, which may be bounded by dissolution surfaces. This objective was rarely achieved, however, because the width of distinct zones is typically similar to, or less than, the drill diameter. Furthermore, adjacent zones may also be penetrated in the vertical dimension. Thus, individual drill sites commonly include mixtures of two or more adjacent growth zones, but careful overlap-

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