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CBS Reductions with a Fluorous Prolinol Immobilized in a Hydrofluoroether Solvent

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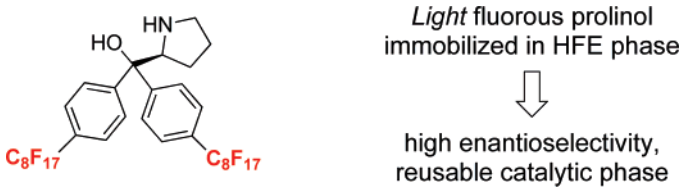
ABSTRACT



A fluorous prolinol precatalyst bearing only 34 fluorine atoms has been immobilized in the hydrofluoroether solvent HFE-7500. The CBS reduction of acetophenone proceeded rapidly, in high yield and in high ee in the absence of any organic solvent. The organic product was stripped from the HFE-7500 phase with a polar solvent, and the HFE-7500 phase was reused "as is" with satisfactory results through eight runs. This process is an attractive prototype for the large-scale use, recovery, and reuse of fluorous organocatalysts.

As the field of organocatalysis expands,[1−3] the efficient separation of such catalysts from reaction products becomes an increasingly important aim.[4] The high loading levels typically used with organocatalysts (often 10−20 mol %) make them inherently less atom economical than many transition metal catalysts, but this potential disadvantage can be offset to a degree on large scale by efficient protocols for recovery and reuse.[5] Consequently, a variety of recyclable analogues of organocatalysts have been synthesized and studied. Most of these catalysts have phase tags[6] (polymer,[7] ionic liquid,[8] other[9]), but it can be difficult to identify tagged catalysts whose reactivity and selectivity levels match those of their parents.

Light fluorous reagents and reactants often show similar selectivities to their non-fluorous analogues,[10] and indeed several promising light fluorous organocatalysts have recently

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been introduced by us and others.[11] Representative structures are shown in Figure 1. These catalysts are typically recovered

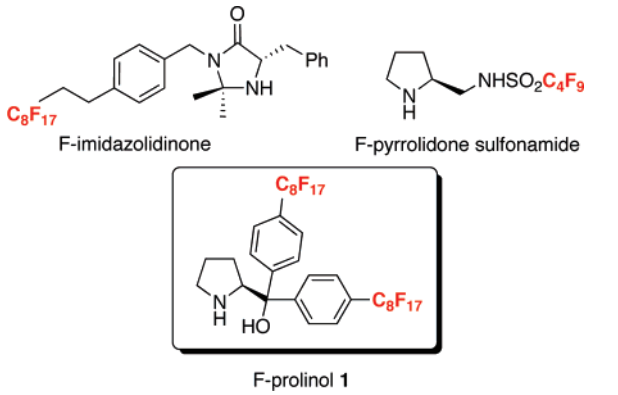

Figure 1. Selected organocatalysts with fluorous tags.

by fluorous solid-phase extraction,[12] a process that is well suited for small-scale reactions, but less so for large-scale ones.

Liquid−liquid biphasic separations (fluorous biphasic reactions) are convenient for large-scale chemical processes, but very large fluorous phase tags are usually used.[13] These tags bear at least 50 fluorines, often many more, so the catalysts have high molecular weights and can be complex and costly to make. This may not be a problem for organometallic catalysts, provided that the catalyst levels are low. However, it is a problem for organocatalysts, which are commonly used in high-loading levels. Also, perfluoroalkane solvents are usually used for fluorous biphasic reactions, but the environmental persistence of these solvents detracts from their use on large scale.

Several groups have recently shown that hydrofluoroethers (HFEs, RfOR) have favorable reaction and separation properties, and can often be used to replace traditional perfluoroalkane solvents with considerable advantage in fluorous/organic liquid−liquid processes.[14,15] A systematic study of mutual solubilities of HFEs with organic solvents[16] suggested that solvents like HFE-7500 ($C_3F_7CF(OC_2H_5)CF(CF_3)_2$, Figure 2) might be able to immobilize organocatalysts

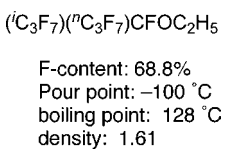

Figure 2. Structure and selected properties of HFE-7500.

with only two fluorous tags. HFE-7500 is commercially available[17] and has many attractive features for industrial use.[18]

Enantioselective borane reductions of ketones in the presence of chiral proline-derived oxazaborolides (Corey−Bakshi−Shibata or CBS catalysts) are commonly used to make chiral secondary alcohols.[19] Beyond CBS catalysts, there are now many organocatalysts that feature a proline derivative as a central element.[1,2] On the heels of the introduction of fluorous prolinols by Bolm,[11a] Soós and coworkers used **1** (Figure 1) as a catalyst in CBS reductions.[11b] Like reactions of other light fluorous catalysts, these reactions were conducted in an organic solvent (THF), and the precatalyst was recovered by a workup process that included fluorous solid-phase extraction. Yields and selectivities were comparable to the non-fluorous precatalyst. With this backdrop, we set out to develop conditions for reaction and recovery of **1** that involved only liquid−liquid separations.

Fluorous prolinol **1** was prepared according to the reported five-step procedure and was obtained in gram quantities in 35% overall yield.[11a,b,20] With 34 fluorine atoms and 56% fluorine by molecular weight, the prolinol is not expected to be applicable to traditional biphasic processes that use perfluorocarbons as the fluorous phase. Indeed, **1** is soluble in typical organic solvents (THF, Et_2O, CH_2Cl_2) and is not expected to have high partition coefficients into FC-72.[11a]

As a prelude to biphasic reactions, we first conducted a standard reduction with **1** in THF, followed by extractive workup with HFE-7500 (Scheme 1, Procedure A). According to the usual procedure, BH_3 (1 equiv) in THF was added to prolinol **1** (0.1 equiv) in THF at room temperature. After 1

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(17) HFE-7500 is a product of the 3M Novotec line of engineering fluids: http://products3.3m.com/catalog/. Current list prices for HFE fluids range from $50 to $90/L.

(18) According to the 3M Product Information Sheet, HFE-7500 is not flammable, does not cause ozone depletion, has much lower global warming potential than perfluorocarbons or perfluoroethers, and is not expected to be classified as a volatile organic chemical (VOC) by the U.S. EPA.

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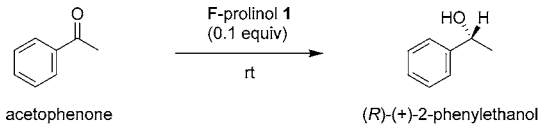
(20) (a) Intermediates for this synthesis are commercially available from Fluorous Technologies, Inc. (b) D.P.C. owns an equity interest in this company.

Scheme 1. Fluorous CBS Reductions of Acetophenones, Procedures A−C, 0.5 mmol scale



acetophenone (*R*)-(+)-2-phenylethanol

	borane (conc.)	reaction solvent	cycles	extraction solvent[a]	wash solvent[b]	results
Procedure A	BH_3·THF (1 M)	THF	single	NA	NA	96% yld 92% ee
Procedure B	BH_3·THF (1 M)	HFE-7500	multiple	CH_3CN	H_2O	Tables 1,2
Procedure C	BH_3·DMS (10 M)	HFE-7500	multiple	DMSO	none	Table 3

[a] Removes the product from the HFE-7500 phase prior to recycle. [b] Wash solvent for the HFE-7500 phase prior to recycle.

h, acetophenone (0.5 mmol, 1 equiv) in THF was added. Reaction progress was followed by GC, and after 1 h, the reaction was quenched with methanol, and the solvents were evaporated.

The residue was partitioned between acetonitrile and HFE-7500, and the two phases were separated and analyzed by GC. The acetonitrile phase contained 98% of the (+)-2-phenylethanol product and no detectable prolinol **1**. Evaporation of the acetonitrile provided 2-phenylethanol in 96% yield, 97% GC purity, and 92% ee. The HFE-7500 phase contained the remaining 2% of the 2-phenylethanol along with all of the fluorous prolinol **1**. Evaporation of this phase and vacuum drying (removes the residual 2-phenylethanol) provided **1** in 99% yield in comparable purity (GC, ^{1}H NMR) to that of the starting sample.

Encouraged by the results with traditional liquid−liquid extraction, we next explored a procedure where HFE-7500 was used as the primary reaction solvent in place of THF (Scheme 1, Procedure B). Borane·THF (1 M in THF, 0.6 equiv) was added to a solution of fluorous prolinol **1** (54.5 mg, 0.1 equiv) in HFE-7500 (2 mL). The resulting solvent blend is about 90% HFE-7500/10% THF. After 1 h, neat acetophenone (0.5 mmol) was added. Two hours later, the reaction was quenched with MeOH (0.1 mL). The HFE-7500 phase was extracted with acetonitrile to strip away the product, then washed with water, dried, and evaporated.

The acetonitrile layer contained 87% of the (+)-2-phenylethanol product in 93% ee and was free of fluorous prolinol **1** (Table 1, entry 1). The remaining 13% of 2-phenylethanol was in the HFE-7500 phase along with the prolinol **1**. The decreased partitioning of 2-phenylethanol in this experiment compared to that in the previous one is presumably due to the presence of THF (the reaction solvent is evaporated in Procedure A but not in Procedure B). In principle, the presence of small amounts of the product in the catalyst phase is not a problem, and this phase can be reused without further processing.

Similar experiments were then conducted at lower precatalyst loadings, as summarized in Table 1, entries 2−4. When the loading was reduced to 5% (0.05 equiv), the ee

Table 1. Fluorous CBS Reduction of Acetophenone in HFE-7500/THF with Different Precatalyst Loadings, Procedure B

entry	precatalyst (equiv)	conversion[a] (%)	ee[b] (%)
1	0.1	>99	93
2	0.05	>99	84
3	0.025	>99	83
4	0.005	42	54

[a] Determined by GC analysis on a Hewlett-Packard 5890 instrument with split mode (column: 30 m x 0.32 mm x 0.25 mm HP-1 methyl siloxane). [b] Determined by HPLC analysis on a Chiracel OD column (hexane/isopropanol, 98:2; flow, 1 mL/min; λ = 210 nm).

eroded to 84%, while at 0.5 mol % (0.005 equiv), it was only 54%. These results suggest that any recycle process starting with 10% precatalyst will begin to suffer decreased selectivity when half of the precatalyst has decomposed or leached, if not before.[21] Further, because high precatalyst loading is essential, recovery and reuse is especially important.

To test the recycling possibilities for Procedure B, we began by repeating the experiment with 10% precatalyst loading and obtained comparable results (compare entries 1 in Tables 1 and 2). Now, the HFE-7500 phase was not

Table 2. Fluorous CBS Reduction of Acetophenone in HFE-7500/THF with Acetonitrile Extraction, Procedure B

run	borane (equiv)	conversion[a] (%)	ee[b] (%)
1	0.6	>99	92
2	1.2	>99	92
3	1.2	>99	89
4	1.2	>99	76
5	1.2	>99	63
6	1.2	>99	45

[a] Determined by GC analysis on a Hewlett-Packard 5890 instrument with split mode (column: 30 m x 0.32 mm x 0.25 mm HP-1 methyl siloxane). [b] Determined by HPLC analysis on a Chiracel OD column (hexane/isopropanol, 98:2; flow, 1 mL/min; λ = 210 nm).

evaporated, but simply dried over molecular sieves and reused. The same process was repeated five more times, each time adding the HFE-7500 phase from the prior reaction cycle to the next reaction cycle along with fresh BH_3·THF (now 1.2 equiv) and acetophenone. The conversions for all six reactions were >99% (Table 1), but the high ee was only maintained through the first three runs. After the sixth run, the final HFE-7500 phase was concentrated, and the fluorous prolinol **1** was recovered in 46% yield and about 90% purity. This corresponds to an average recovery of 88% per run.

To improve this process, we next decided to remove the THF entirely by using BH_3·DMS (DMS is dimethylsulfide)

(21) These experiments to test for breakdown in ee are important because the recyclability of catalysts in multiple run experiments can be made to look artificially high simply by overloading the initial charge. See: Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319−1324.

in place of BH_3·THF, and to replace the acetonitrile extraction solvent with the more fluorophobic DMSO (Scheme 1, Procedure C). These changes should favor the partitioning of both organic and fluorous components into their respective phases. To simplify the recycling, we also omitted the water wash and drying of the HFE-7500 phase. Thus, after stripping the product into DMSO, the HFE-7500 phase was used directly in the next run.

A cycle of nine runs was conducted by Procedure C, and the results are shown in Table 3. Even though the reaction solvent is now only HFE-7500 (there is no THF cosolvent), the reaction was still complete in 2 h, and the ee of the product was even marginally increased to 94%. This time, the ee was much more satisfactory on recycle, remaining essentially constant through the first five runs, then slowly dropping down to 88% by the eighth run.

Table 3. Fluorous CBS Reduction of Acetophenone in Neat HFE-7500 with DMSO Extraction, Procedure C

run	borane (equiv)	conversion[a] (%)	ee[b] (%)
1	0.6	>99	94
2	1.2	>99	95
3	1.2	99	94
4	1.2	>99	93
5	1.2	98	93
6	1.2	>99	90
7	1.2	>99	91
8	1.2	98	88
9	1.2	>99	74

[a] Determined by GC analysis on a Hewlett-Packard 5890 instrument with split mode (column: 30 m x 0.32 mm x 0.25 mm HP-1 methyl siloxane). [b] Determined by HPLC analysis on a Chiracel OD column (hexane/isopropanol, 98:2; flow, 1 mL/min; $\lambda = 210$ nm).

In run 9, the first large decrease in ee was observed (74%), and the process was terminated. The HFE-7500 phase was concentrated, and fluorous prolinol **1** was recovered in 54% yield (average 94% yield per cycle) and about 90% purity. The recovered catalyst was purified by flash chromatography and later reused for other experiments. The nine DMSO phases were combined and diluted with brine, and this phase was extracted with ether. After concentration and flash chromatography, (+)-2-phenylethanol was isolated in 84% combined yield with 99% CG purity. In total, 0.05 mmol of prolinol **1** (54.5 mg) was used to completely reduce 4.5 mmol of acetophenone, providing 3.9 mmol (474 mg) of (+)-2-phenylethanol in >90% ee.

It is interesting to compare and contrast these new processes with related fluorous reactions and separations. Funabiki and co-workers very recently described CBS reductions with a fluorous prolinol related to **1**, but with ethylene spacers to insulate the C_6F_{13} groups.[11d] Reactions in toluene with BH_3 gave moderate ees, but high ees were obtained if the initial CBS reagent was made with $B(OMe)_3$. Pretreatment of **1** with $B(OMe)_3$ is not needed. The ethylene-spacer fluorous prolinol could be recovered by low-temperature precipitation, but its reuse provided a product with low ee.

More generally, the convenient procedures in this work differ from most other fluorous biphasic processes in that there is no thermomorphic component (heating or cooling).[22] The reaction and separation processes both take place at ambient temperatures.

Further, Procedure C is a rare example of fluorous catalysis without organic solvents,[23] a type of process that has high potential in sustainable chemistry applications. Gladysz and co-workers have described a hydroboration reaction catalyzed by a fluorous rhodium complex immobilized in perfluoromethylcyclohexane.[24] This catalyst has 117 fluorine atoms compared to the 34 fluorine atoms of **1**. Ryu and co-workers immobilized a palladium species bearing 21 fluorines in F-626 (a high-boiling perfluoroalkyl alkyl ether).[14a]

Ryu's results and those herein show the potential performance advantage of the hydrofluoroether solvents over perfluorocarbons in fluorous catalysis; they are more polar and hence better reactions solvents, and they allow the use of catalysts with lower fluorine content. Accordingly, while Procedure C uses an organic solvent (DMSO) to strip the product from the catalyst phase, we propose that it will be possible to develop other processes—with either organic or organometallic catalysts—in which the precursor is added directly to the HFE phase and later the product is harvested by simple phase separation. Such processes are attractive because they have no organic solvent at either the reaction or separation.

In summary, a fluorous prolinol precatalyst bearing only two fluorous chains has been effectively immobilized in the hydrofluoroether solvent HFE-7500. The CBS reduction of acetophenone proceeded rapidly and in high yield in this medium, in the absence of any organic solvent. The organic product was readily recovered by stripping it from the HFE-7500 phase with a polar solvent. The catalyst phase was directly reused with satisfactory results through eight runs. This process is an attractive prototype for the large-scale use, recovery, and reuse of fluorous organocatalysts.

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Supporting Information Available: Complete experimental procedures. This material is available free of charge via the Internet at www.pubs.acs.org.

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