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Recoverable Fluorous CBS Methodology for Asymmetric Reduction of Ketones

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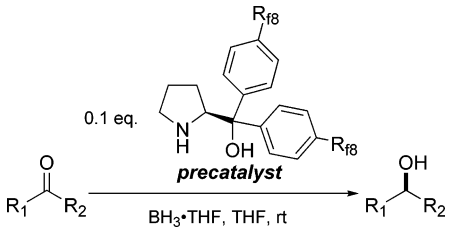
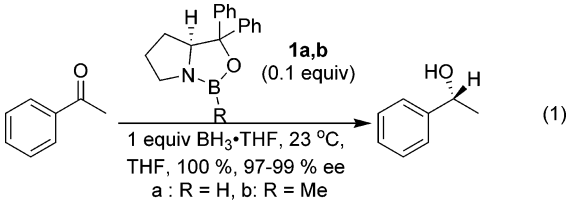
ABSTRACT



An operationally simple and recoverable fluorous CBS methodology was developed. The in situ-generated fluorous oxazaborolidine efficiently catalyzed the reduction of ketones with high enantioselectivity and reactivity. The subsequent recycling of the fluorous prolinol precatalyst was achieved by fluorous solid-phase extraction.

Enantioselective borane reduction of ketones in the presence of chiral oxazaborolidines has emerged as a standard method for the synthesis of chiral secondary alcohol.[1] Among the several catalysts which have been disclosed in the literature, the system devised by Corey, Bakshi, and Shibata, known as CBS catalyst (**1**),[2] excels in enantioselectivities and chemical yields eq 1.



(1)

To facilitate the recovery of this useful catalyst and simplify reaction conditions, various polymer-bound heterogeneous analogues were synthesized and studied.[3−5] However, these challenges have generally appeared to be associated with reduced enantioselectivity and reactivity. These experiences indicated that the diffusional limitation inside the polymer support slowed the rate of catalyzed reduction so that the competing, nonselective reduction in the bulk phase decreased the overall enantioselectivity. To avoid the diminished kinetics of the biphasic, resin-mediated reactions, a homogeneous, soluble polymer was used instead of a heterogeneous support.[6] However, application of ultra- and nanofiltration was necessary for catalyst retention or recovery.

To develop an operationally simple methodology for CBS catalyst immobilization for which no special instruments and

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(1) Reviews with extensive literature background: (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (b) Singh, V. K. *Synthesis* **1992**, 605. (c) Srebnik, M.; Deloux, L. *Chem. Rev.* **1993**, *93*, 763. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (e) Itsuno, S. In *Organic Reactions*; John Wiley: New York, 1998; Vol. 52, p 395.

(2) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(3) Catalysts are bound via the boronic acid: (a) Franot, C.; Stone, G. B.; Engeli, P.; Spöndlin, C.; Waldvogel, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2755.

(4) Catalysts are bound via the phenyl residue: (a) Price, M. D.; Sui, J. K.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2002**, *67*, 8086. (b) Kell, R. J.; Hodge, P.; Snedden, P.; Watson, D. *Org. Biomol. Chem.* **2003**, *1*, 3238. (c) Degni, S.; Wilén, C.-E.; Rosling, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1495.

(5) Microgel-support bound via the boronic acid: Schunicht, C.; Biffis, A.; Wulff, G. *Tetrahedron* **2000**, *56*, 1693.

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techniques are required, we turned our attention to fluorous chemistry as a promising option for catalyst recovery.[7] This recently introduced methodology is an alternative solution-phase tagging approach in catalysis[8] and high-throughtput synthesis.[9] Highly hydrophobic perfluoroalkyl phase-tags, instead of polymers, are used to facilitate the separation of the fluorous compounds from a reaction mixture using fluorous liquid−liquid or solid−liquid extraction.

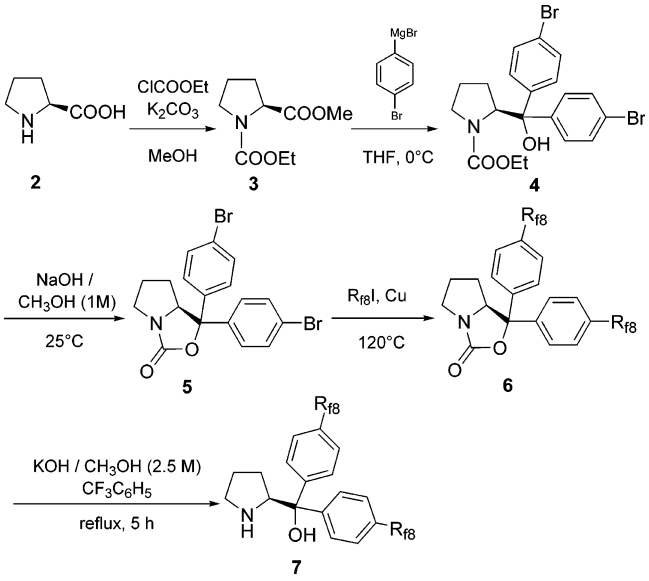
Inspired by the achievements of the fluorous chemistry, we reasoned that it might be possible to prepare the fluorous analogue of CBS catalyst (**1a** or **1b**) and employ it in enantioselective reduction of ketones. To minimize the interference with the catalyst active site, we envisaged a fluorous analogue that has the perfluorinated tags in the para position of the phenyl residue.

We built upon the sequence described by Kanth and Periasamy[10] to synthesize **1** and applied similar methodology for the preparation of **7**. Moreover, our synthetic path is basically the same as the one Bolm and Kim developed recently for the synthesis of fluorous prolinol derivatives.[11]

We converted L-proline (**2**) into its N-protected methyl ester derivative **3** in a one-pot procedure, followed by addition of 4-bromophenylmagnesium bromide to afford **4**. Subsequent treatment with NaOH gave cyclic carbamate **5** quantitatively. To access the fluorous derivative **6**, we made use of the Ullmann-type reaction between perfluorooctyl iodide and cyclic carbamate **5** in the presence of freshly activated copper powder. Contrary to a recent report,[11] this coupling step worked well in our hands, providing easy access to fluorous proline derivative **6**. Finally, the hydrolysis of **6** gave the free amino alcohol **7** in an excellent yield. In performing asymmetric reduction with diphenyl prolinol **7**, it is essential to prepare and use its oxazaborolidine derivative prior to the catalytic application (Figure 1).

Following established procedures, the fluorous analogue **8a** was formed by the addition of trimethylboroxine to a solution of **7** in toluene. However, NMR analysis (^{1}H and DOSY experiments) of the oxazaborolidine product **8a** indicated the formation of unidentified fluorous impurities. This catalyst, although not pure, was tested in asymmetric reduction, since our aim was to determine whether it was catalytically efficient and also establish the catalyst endurance under recycling conditions. To comparatively evaluate our catalyst, acetophenone (**9**) was reduced with BH_3·THF

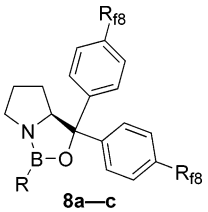
Scheme 1. Synthesis of Fluorous Prolinol **7**



complex in tetrahydrofuran at room temperature. The result showed that fluorous catalyst **8a** perfomed as efficiently as the original catalyst **1b** (Table 1, entry 1). Once a reduction was complete, it was worked up using fluorous SPE methodology.[12] Unfortunately, the catalyst **8a** did not remain intact under the recycling conditions, hydrolysis of the oxazaborolidine catalyst to fluorous prolinol **7** occurred. Although we were glad that the catalyst **8a** performed as well as the original catalyst **1b** and that it could be easily separated from the reaction products, the recovery of this fluorous catalyst is not viable in this way because of its hydrolysis.

As the above protocol returned the catalyst **8a** in the form of fluorous prolinol **7**, we reasoned that the utilization of in situ-generated oxazaborolidine might be the key to the development of recoverable CBS reduction methodology. Furthermore, the in situ formation of catalyst eliminates the necessity of isolating the catalyst as a discrete step, providing a simple method for asymmetric ketone reduction. The in situ preparation and usage of chiral oxazaborolidines is a known procedure[13] that was employed successfully even on an industrial scale.[14]

To demonstrate the ability of fluorous prolinol **7** to serve as a catalyst precursor, first we generated the B−OMe



(a: R = Me, b: R = MeO, c: R = H)

Figure 1. Fluorous oxazaborolidine catalysts.

(6) Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. *Tetrahedron: Asymmetry* **1998**, *9*, 691.

(7) (a) Curran, D. P. In *Stimulating Concepts in Chemistry*; Stoddard, F., Reinhoud, D., Shibasaki, M., Eds.; Wiley-VCH: New York, 2000; p 25. (b) Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823 and the following articles in this special issue entitled "Fluorous Chemistry". (c) *The Handbook on Fluorous Chemistry*; Gladysz, J. A., Horváth, I. T., Curran, D. P., Eds.; Wiley-VCH: New York, 2004.

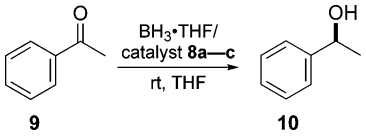
(8) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.

(9) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y. Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.

(10) Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

(11) Park, J. K.; Lee, H. G.; Bolm, C.; Kim, B. M. *Chem. Eur. J.* **2005**, *11*, 945. During the preparation of this manuscript, we became aware of the presence of this recent paper closely related to our work. Compounds **4**, **5**, and **6** are also intermediates in their synthetic path. However, their target was a fluorous N-Me diphenylprolinol derivative that was used in asymmetric diethyl- and diphenylzinc addition.

Table 1. Catalytic Asymmetric Reduction of Acetophenone (**9**) with BH_3·THF Complex



9 **10**

entry	catalyst	catalyst load	BH_3 excess	% yield[a]	% ee[b]
1	**8a**	18	2[c]	99	97
2	**8b**	10	1	99	92
3	**8c**	10	2	99	92
4	**8c**	20	2	99	95
5	**8c**	10	0.6	99	95
6	**8c**	10	2[c]	99	86
7	**8c**	10[d]	0.6	99	95
8	**8c**	10[e]	0.6	99	95
9	**8c**	10	0.6	89[f]	95

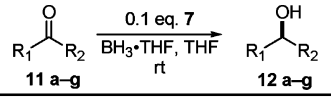
[a] Determined either by GC or HPLC in 0.5 mmol scale reactions. [b] Determined either by chiral GC (Cyclosil-B) or chiral HPLC (Chiralcel OD). [c] Performed with 0.005 M $NaBH_4$-stabilized BH_3·THF. [d] Second cycle of **7**. [e] Third cycle of **7**. [f] Isolated yield in a 5.0 mmol scale reaction.

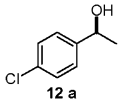
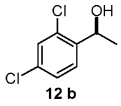
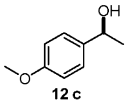
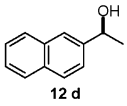
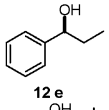
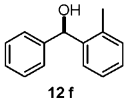
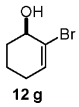
oxazaborolidine **8b** in situ. Combination of **7** with a stoichiometric quantity of trimethyl borate ester in THF at ambient temperature generated the oxazaborolidine **8b** in 30 min. Addition of acetophenone (**9**) to this solution of oxazaborolidine containing 1 equiv borane afforded the alcohol product **10** with high enantioselectivity (Table 1, entry 2). Moreover, recovery of the fluorous amino alcohol **7** over 98% yield was achieved by fluorous SPE methodology.[12]

To simplify this fluorous in situ procedure further, we attempted to employ BH_3·THF complex as a boron source to inititate the formation of oxazaborolidine **8c**. Although the preparation of oxazaborolidine **1a** from its diphenylprolinol precursor requires extended heating with excess BH_3 under increased pressure,[2a] quite suprisingly this reaction seemed to proceed smoothly (ambient temperature, atmospheric pressure, 60 min) in the case of the fluorous prolinol **7**. This was suggested by the facts that comparable enantioselectivity was achieved in acetophenone (**9**) reduction (entry 3) and that oxazaborolidines **8c** and its borane adduct were detected in MS experiments.[15] We assume that this difference in reactivity of the diphenylprolinols may stem from the electron-withdrawing nature of the perfluoroalkyl tags.

As might be expected, the application of a higher catalyst load resulted in higher enantioselectivity (entry 4). Furthermore, we found that even 0.6 equiv of borane was sufficient for complete reduction of acetophenone (**9**) with better enantioselectivity (entry 3 vs entry 5). Finally, it is important to note that the usage of $NaBH_4$-stabilized BH_3·THF resulted

Table 2. Catalytic Asymmetric Reduction of Ketones with BH_3·THF Complex



entry	product	BH_3THF equiv	% yield[a]	% ee[b]
1		2	93	91
2		0.6	92	93
3		2	92	76
4		0.6	90	88
5		2	81	90
6		0.6	83	91
7		2	82	90
8		0.6	82	95
9		2	74	71
10		0.6	73	71
11		2	85	90
12		0.6	81	73
13		2	67	90
14		0.6	72	90

[a] Isolated yields after fluorous SPE workup. [b] Determined by chiral HPLC (Chiracel OD or OJ).

in lower enantioselectivity (entry 6). This detrimental effect of the stabilizer is known in the literature[16] and could be avoided by employing nonstabilized BH_3·THF complex.

Next, the recycling of the precatalyst **7** was tested. On consumption of the acetophenone (**9**), the reaction mixture was quenched with MeOH and worked up using the fluorous SPE protocol.[12] The recovery of the precatalyst **7** was almost quantitative (99% recovery) when it was washed from the fluorous silica gel. The fluorous prolinol **7** proved to be sufficiently chemically robust to withstand reaction cycles, since it was recycled two more times without any deleterious effect on enantioselectivity (entries 7, 8). Parallel with this, the purity of the recycled catalyst was also checked by NMR and MS experiments. Finally, when the reaction was run in a small preparative scale, we obtained the same enantioselectivity for the reduction and isolated the pure alcohol **10** as a volatile colorless liquid with 89% yield (entry 9).

Having developed a one-pot procedure for fluorous CBS-mediated asymmetric ketone reduction, the in situ-generated oxazaborolidine catalyst **8c** was applied to a number of

(12) See Supporting Information.
(13) (a) Masui, M.; Takayuki, S. *Synlett* **1997**, 273. (b) Gilmore, N. J.; Jones, S.; Muldowney, M. P. *Org. Lett.* **2004**, *6*, 2805.
(14) Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285.
(15) EI, *m/z* for **8c** is [1099], *m/z* for **8c** + BH_3 [1113].
(16) Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970.

ketone reductions (Table 2). No attempt was made to optimize reaction enantioselectivity; however, in all cases, the selectivities were high. In general, the excess of borane had a slight influence on enantioselectivities and 0.6 equiv of borane was sufficient for complete reduction of ketones. It is worth mentioning that the enantioselectivity was surprisingly higher when we used 2.0 equiv of BH_3 in the case of biaryl ketone **11f** reduction (entries 11, 12). This can be explained if the rate-limiting step of the catalytic cycle was not the complexation of the ketone **11f** to catalyst or the hydrid transfer but rather the regeneration of the catalyst via addition of BH_3 to oxazadiboretane intermediate.[17]

In summary, we have synthesized fluorous diphenyl prolinol derivative **7** and generated a procedure where the active catalytic species was prepared in situ. This methodology has several practical advantages: it eliminates the necessity of prior synthesis of the catalyst, works in homogeneous conditions, and affords high levels of enantioselectivities, and the precatalyst **7** can be easily separated from the reaction mixture using fluorous SPE and recycled in almost quantitative yield.

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Supporting Information Available: Complete experimental procedures and characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051024J

(17) Recent paper with extensive literature background: Alagona, G.; Ghio C.; Persico, M.; Tomasi, S. *J. Am. Chem. Soc.* **2003**, *125*, 10027.