Role of $NaBH_4$ Stabilizer in the Oxazaborolidine-Catalyzed Asymmetric Reduction of Ketones with BH_3–THF

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When stabilized BH_3–THF (BTHF) was added to a mixture of ketone and tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (MeCBS-ozaxaborolidine, MeCBS) catalyst **1**, low enantioselectivities resulted. Several relative rate experiments showed that a borohydride species in BTHF catalyzed the nonselective borane reduction of ketones, effectively competing with enantioselective MeCBS reduction of ketones, lowering the overall selectivity of the reaction. Improved enantioselectivities in the reaction are obtained by reversing the mode of addition (ketone to BTHF and catalyst), lowering the concentration of $NaBH_4$ stabilizer in the BTHF solution (87−95% ee) and increasing the concentration or addition rate of BTHF. Decreased reaction temperature and increased catalyst loading only slightly improved the selectivity of the reaction. Upon reaction parameter optimization, simultaneous addition of substrate and BTHF to MeCBS catalyst stabilizer resulted in the highest overall enantioselectivities (96% ee) and diminished the effect of the borohydride. Alternatively, the addition of Lewis acids such as BF_3–THF to the reaction mixture effectively destroyed the $NaBH_4$ stabilizer in BTHF solutions, restoring the enantioselectivity to acceptable levels.

Introduction

Borane−tetrahydrofuran complex (BTHF) is a very good reducing agent for aldehydes, ketones, amides, carboxylic acids, and other functional groups.[1] Due to the commercial availability of BTHF along with its selectivity and cleanliness as reducing agent (only easily removed borate byproduct is produced), BTHF is a very useful reagent for pharmaceutical and industrial applications.[2]

The enantioselective reduction of prochiral ketones with BTHF catalyzed by tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole [(*R*)- or (*S*)-MeCBS-oxazaborolidine reagent, (*R*)- or (*S*)-MeCBS] catalyst **1** is an excellent tool for the synthesis of alcohols in high enantiomeric excess.[3] This process has been successfully applied to the asymmetric synthesis of various natural products and pharmaceuticals such as (*R*)-denopamine,[4] (*S*)-α-damascone,[5] (*R*)-fluoxetine,[6] and ginkgolide B.[7]

Early in the examination of this catalyst, Jones and co-workers reported variable results when they utilized commercial BTHF as the borane source together with the MeCBS catalyst to synthesize the anhydrase inhibitor MK-0417.[8] They attributed the erratic selectivities to the propensity of BTHF to decompose in the presence of air and/or moisture. Corey and Helal also promoted the advantages of other borane sources over BH_3–THF for this asymmetric reduction due to the sensitivity of BTHF to moisture and oxygen.[3]

Another problem with BTHF in the CBS reaction is the reduction of other functional groups within the ketonic substrate, especially when the substrate is added to the borane/catalyst mixture. Recently, King and co-workers reported hydroboration byproducts (3−10%) when they carried out the oxazaborolidine-catalyzed borane reduction of LTD4 antagonist L-699,392 used for asthma treatment. Due to the over-reduction problems with the CBS process, they changed the process to employ chlorodiisopinocampheylborane for the reduction.[9]

The variable results and potential over-reduction problems when BTHF is used for these CBS reductions represent serious limitations for potential applications of this chemistry. Therefore, we chose to find optimal conditions for this process that would give consistently high enantioselectivities with BTHF as the borane source.

Results and Discussion

A way to decrease or eliminate substrate over-reduction is by adding the borane to the substrate and catalyst. Through this mode of addition, borane is not in excess, thus lowering the chance for reduction of other functional groups. Borane addition would also be required in cases of low substrate solubility.

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(1) Brown, H. C.; Zaidlewics, M. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol 1, p 638.
(2) (a) Wilkerson, W. W.; Rodgers, J. D. US Patent 5,508,400. (b) Sohar, P.; Mathre, D. J.; Blacklock, T. J. EP 617037.
(3) Corey, E. J.; Helal, C. J. *Angew Chem. Int. Ed.* **1998**, *37*, 1986.
(4) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442.
(5) Mori, K.; Amaike, M.; Itou, M. *Tetrahedron* **1988**, *29*, 3423.
(6) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.
(7) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201.
(8) Jones, T. K.; Mohar, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, T. T.; Reamer, R. A.; Roberts, F. G.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763.
(9) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731.

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Table 1. Ketone Reduction with BTHF and (*R*)-MeCBS

entry	ketone	% ee[a,b]	% ee[b,c]
1	acetophenone	65	95
2	3-methyl-2-butanone	33	61
3	cyclohexyl methyl ketone	37	61
4	α-tetralone	66	81
5	3,3-dimethylbutanone	46	91

[a] Commercial 1 M BTHF in THF was added to a mixture of ketone and (*R*)-MeCBS. [b] Enantiomeric excess was measured with chiral column J & W 30 m × 0.25 mm CDX-B. [c] Nonstabilized 1 M BTHF in THF was added to a mixture of ketone and (*R*)-MeCBS.

To determine general reaction conditions to minimize over-reduction byproducts, we studied the reduction of acetophenone with commercial 1 M BTHF (stabilized with ~0.005 M $NaBH_4$, >98% purity)[10] and MeCBS catalyst. We were greatly disappointed that the addition of commercial 1 M BTHF to a mixture of acetophenone and the MeCBS catalyst (5 mol % relative to ketone) at ambient temperature gave 1-phenethanol with low enantioselectivity (60% ee). Similar low enantioselectivities were obtained when commercial 1 M BTHF was used in the MeCBS reduction of other ketones (see Table 1).[11]

Since others have attributed such low selectivities to the purity of the borane, we chose to address this issue.[8] For the reductions summarized in Table 1, we used commercial BTHF solution (>98% purity by ^{11}B NMR spectroscopy) that had been stored cold (0−5 °C). Under these storage conditions, ^{11}B NMR analysis has revealed its stable nature for periods of at least 1 year. However, if 1 M BTHF solutions are left at ambient temperature, degradation by about 10% occurs in 40−50 d. The degradation products are di-*n*-butoxyborane, $(n\text{-BuO})_2BH$, and tri-*n*-butylborate ($(n\text{-BuO})_3B$).[12]

To evaluate the effect of these degradation products on selectivity, commercial BTHF kept at room temperature for 99 days (84% hydride activity) was tested under the same ketone reduction conditions. A higher selectivity (82% ee compared to 65% ee) was observed in the acetophenone reduction. The increased selectivity could be related to (1) borate species, (2) alkoxyborane species, or (3) borohydride species generated or destroyed during the degradation process.

To better understand the increased selectivity with degraded BTHF, we spiked commercial BTHF with dibutoxyborane (10 mol % relative to BTHF) and carried out the CBS reduction. The enantioselectivity using this spiked BTHF solution was 66% ee, essentially the same as unspiked BTHF. Therefore, we eliminated this species as a contributor to the observed selectivity employing commercial BTHF.

Recently, Jockel and Schmidt demonstrated that the borohydride concentration in commercial BTHF[13] solutions accelerated the BTHF reduction of ketones.[14] They found that the use of commercial BTHF for ketone reduction resulted in ~300 times faster reaction than with freshly prepared BTHF solution. In a related paper, they determined the kinetics of the borane reduction of pinacolone catalyzed by phenyl oxazaborolidine derivatives.[15] Although they found that the presence of $NaBH_4$ stabilizer in commercial BTHF solutions accelerated the direct borane reduction and oxazaborolidine-catalyzed reduction, the enantioselectivity of the reduction was not discussed.[16]

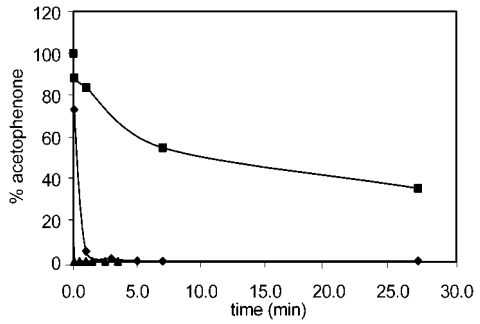

Figure 1. Reduction of acetophenone with ■ nonstabilized BTHF, ◆ $NaBH_4$-stabilized BTHF, and ▲ nonstabilized BTHF and (*R*)-MeCBS. The disappearance of acetophenone was monitored by GC.

To further investigate the role of borohydride in CBS-catalyzed reductions, we prepared and used a 1 M BTHF solution without the $NaBH_4$ stabilizer. Higher enantioselectivities were obtained in the MeCBS-catalyzed reduction of the same ketones with this unstabilized BTHF solution (see Table 1).

Evidently, a borohydride species present in commercial BTHF is participating in nonselective ketone reduction or interacting with oxazaborolidine catalyst to lower the enantioselectivity of the CBS reduction. To rationalize the lower selectivity, one must learn more about the mechanisms involved and the relative rate of reduction of the pathways. Since Jockel's experiments were with a higher amount of borohydride and under different conditions, we decided to study the relative rate of reduction of acetophenone with (1) nonstabilized BTHF; (2) $NaBH_4$-stabilized commercial BTHF; and (3) nonstabilized BTHF/MeCBS (5 mol % relative to ketone) mixture.

In each experiment, the BTHF solution was rapidly added to a solution of acetophenone in THF at 0 °C. A slight exotherm of approximately 6 °C was noted when the nonstabilized BTHF was added to the ketone. On the contrary, a very large exotherm was observed upon addition of either commercial BTHF (to approximately 25 °C) or BTHF/MeCBS catalyst (to approximately 35 °C) to the ketone.

A plot of acetophenone disappearance versus time for the three kinetic experiments showed that the MeCBS reduction is the fastest (see Figure 1). In the absence of MeCBS or borohydride, 50% of the acetophenone had reacted with unstabilized BTHF in ~8 min. The reduction in the presence of borohydride stabilizer was much

(10) For the experiments, 1 and 2 M borane−tetrahydrofuran solutions (>98% pure) were supplied from Callery Chemical Co. These solutions are prepared by bubbling 99.5% pure diborane gas into tetrahydrofuran, followed by addition of the required amounts of $NaBH_4$ stabilizer. This preparation eliminates any traces of boron trifluoride in the solution, preventing the partial destruction of stabilizer.

(11) In all experiments, the addition rate of borane to ketone was kept uniform at 0.11 mL/min (0.11 mmol/min for 1 M and 0.22 mmol/min for 2 M BTHF) using a syringe pump. The ratio of borane to ketone was 0.67 to 1. MeCBS prepared in toluene was 5 mol % relative to ketone. The percent enantiomeric excess (% ee) of product alcohol was determined via chiral gas chromatography.

(12) Burkhardt, E. R.; Corella, J. A. US Patent 6,048,985.

(13) The commercial source was Aldrich Chemical Co.

(14) Jockel, H.; Schmidt, R. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2719.

(15) Schmidt, R.; Jockel, H.; Schmalz, H.-G.; Jope, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2125.

(16) Jockel, H.; Schmidt, R.; Jope, H.; Schmalz, H.-G. *J. Chem. Soc., Perkin Trans. 2* **2000**, 69.

Table 2. Ketone Reduction with $NaBH_4$-Stabilized BTHF and (*R*)-MeCBS

entry	sodium borohydride concentration[a] (M)	% ee[b] acetophenone reduction	% ee[b] pinacolone reduction
1	none[c]	95	91
2	0.0005	91	88
3	0.0025	85	
4	0.0035		66
5	0.004	63	62
6	0.005	65	46

[a] $NaBH_4$-stabilized 1 M BTHF in THF was added to a mixture of ketone and (*R*)-MeCBS (5 mol % relative to ketone). [b] Enantiomeric excess was measured with chiral column J & W 30 m × 0.25 mm CDX-B. [c] Nonstabilized 1 M BTHF in THF was added to a mixture of ketone and (*R*)-MeCBS.

faster, with a $t_{1/2}$ estimated at ~0.3 min. However, in the presence of MeCBS catalyst, the $t_{1/2}$ could not be estimated accurately, since the initial sample at 5 s showed only 0.23% acetophenone remaining unreduced. The exotherm and the rapid decrease in ketone with stabilized BTHF solution suggests that a species in the stabilized BTHF solution is playing a catalytic role in the nonselective acetophenone reduction.

The kinetic measurements of Jockel et al. using stopflow techniques demonstrated that the borohydride-catalyzed ketone reduction is 300 times faster than the uncatalyzed reduction.[13] Although a direct comparison of our data with Jockel's data cannot be made, even very small amounts of borohydride in BTHF participate in nonselective reduction and compete with the enantioselective MeCBS-catalyzed process, thus lowering the overall enantioselectivity of the reduction.

To investigate the borohydride species in BTHF solution responsible for the drop in selectivity, we analyzed the commercial 1 M BTHF by ^{11}B NMR spectroscopy. The spectrum revealed the presence of only NaB_3H_8 (^{11}B NMR δ −28.0) as a minor component in the BTHF solution. Presumably, this NaB_3H_8 is produced from $NaBH_4$ and 2 equiv of borane after loss of hydrogen. Addition of ~0.7 mol % of NaB_3H_8 to nonstabilized BTHF prior to acetophenone reduction in the presence of 5 mol % MeCBS gave an enantioselectivity of only 69% ee. This result clearly demonstrates that a soluble anionic $B-H^-$ species in THF such as NaB_3H_8 can negatively impact the overall selectivity of the MeCBS reduction.

In another experiment, $NaBH_4$ (5 mol % relative to ketone) was added to ketone and MeCBS in THF followed by addition of unstabilized BTHF. The enantioselectivity of the reduction (89% ee) correlates to nonselective reduction of ketone by two hydrides of the added $NaBH_4$, but the effect here was apparently not catalytic.

Throughout this paper, we will refer to sodium borohydride ($NaBH_4$) rather than NaB_3H_8, because $NaBH_4$ is the added stabilizing agent. Since NaB_3H_8 is the only borohydride species observed, we assume that the "borohydride" concentration is directly related to $NaBH_4$ added.

Borohydride Concentration. To determine the minimum concentration of $NaBH_4$ that could be utilized to stabilize 1 M BTHF and still achieve a high enantioselectivity in the MeCBS reduction, we reduced pinacolone and acetophenone with 1 M BTHF solutions containing increasing amounts of $NaBH_4$ (see Table 2). A plot of selectivity versus concentration of $NaBH_4$ in BTHF showed a linear, inverse relationship between the amount of $NaBH_4$ stabilizer present in BTHF and the enantioselectivity (see Figure 2).

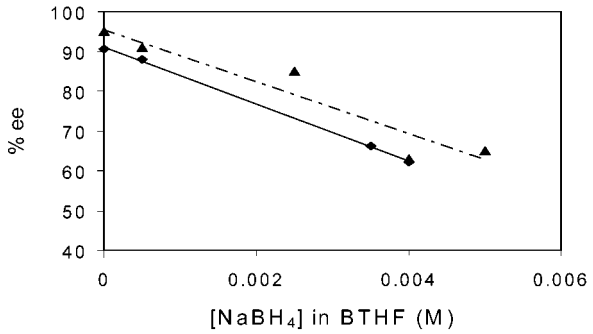

Figure 2. Addition of 1 M BTHF with increasing amounts of $NaBH_4$ to ▲ acetophenone or ◆ pinacolone.

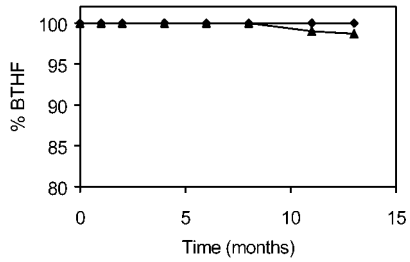

Figure 3. Shelf life of unstabilized 1 M BTHF: ▲ 1 M BTHF at 0 °C and ◆ 1 M BTHF at −20 °C.

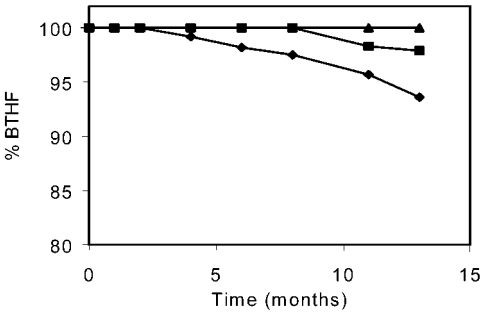

Figure 4. Shelf life of unstabilized 2 M BTHF: ◆ 2 M BTHF at 0 °C, ▲ 2 M BTHF at −20 °C, and ■ 2 M BTHF at 0 °C with 0.0035 M $NaBH_4$.

The higher selectivities obtained with no stabilizer or lower concentrations of borohydride point toward commercialization of these BTHF solutions, provided the shelf life is adequately long. Refrigerated storage shelf life studies on these BTHF solutions, as well as unstabilized BTHF, indicated very little decomposition over 1 year at 0 °C. The decomposition was further suppressed at −20 °C, indicating a shelf life longer than 1 year (see Figures 3 and 4).

Mode of Addition. The mode of addition can have a dramatic effect on the overall enantioselectivity of a reduction. The preferred mode of addition, studied and rationalized by Merck co-workers, is ketone to BH_3/MeCBS.[17] Their mechanistic investigation pointed to several reaction intermediates capable of chiral reduction but at a lower enantioselectivity than the MeCBS−borane complex **2** (see Scheme 1). In the absence of borohydride, these competing pathways can also lower

(17) King, A. O.; Mathre, D. J.; Tschaen, D. M.; Shinkai, I. *ACS Symp. Ser.* **1996**, *641*, 98.

Scheme 1

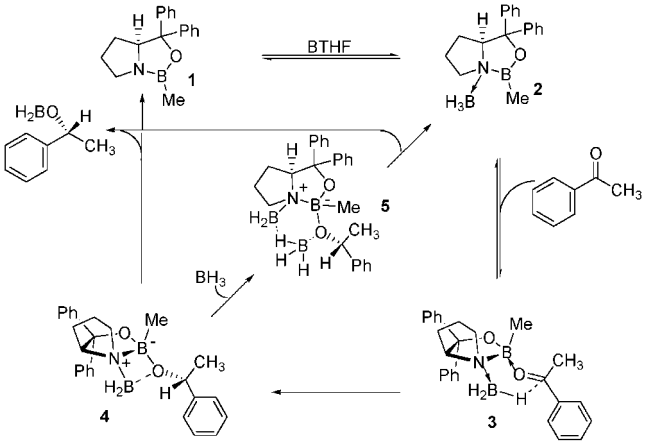

Table 3. Ketone Reduction with $NaBH_4$-Stabilized BTHF and (*R*)-MeCBS

entry	sodium borohydride concentration[a] (M)	% ee[b] acetophenone reduction	% ee[b] pinacolone reduction
1	none[c]	95	95
2	0.0005	94	93
3	0.0025		87
4	0.0035	92	
5	0.004	91	83
6	0.005	90	82

[a] Ketone was added to a mixture of $NaBH_4$-stabilized 1 M BTHF in THF and (*R*)-MeCBS (5 mol % relative to ketone). [b] Enantiomeric excess was measured with chiral column J & W 30 m × 0.25 mm CDX-B. [c] Ketone was added to a mixture of nonstabilized 1 M BTHF in THF and (*R*)-MeCBS.

the enantioselectivity, especially with ketones of specific structural types that react slower.

As expected, higher enantioselectivities in the MeCBS reduction were obtained when acetophenone (89% ee) or pinacolone (82% ee) was slowly added to a mixture of commercial BTHF and MeCBS (see Table 3 and Figure 5).[18]

Following the trend observed, even better selectivities were obtained when acetophenone or pinacolone was added to MeCBS catalyst and BTHF solutions with lower concentrations of $NaBH_4$ (see Table 3 and Figure 5).

During the ketone addition, excess BTHF in the reaction solution may play a role in the MeCBS catalytic cycle by driving the intermediates in the catalytic cycle back to active MeCBS−borane complex **2** through a six-membered-hydride bridged complex **5** (see Scheme 1). Comparison of the two modes of addition strongly suggests that the equilibration between the intermediate complexes and borane (BH_3) was critical to minimize the nonselective reduction presumably catalyzed by borohydride species.

We noticed the slope is steeper for pinacolone than acetophenone, showing that some steric and/or electronic factors are involved in the reduction pathways. Researchers at Merck were able to observe intermediates in the catalytic cycle (see Scheme 1) by ^{11}B NMR and showed evidence for ketone structure effecting catalyst turnover.[19] A number of other researchers have also observed a substrate dependence on the stereoselectivity. As the rate of catalyst turnover slows, the opportunity for nonselective ketone reduction by "borohydride" increases.

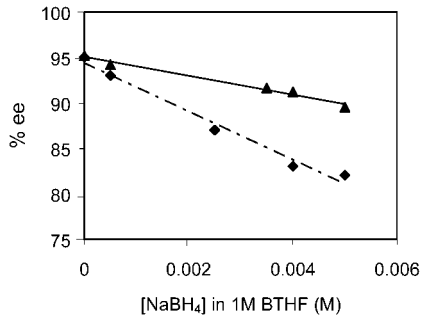

Figure 5. Addition of ▲ acetophenone or ◆ pinacolone to 1 M BTHF with increasing $NaBH_4$ concentrations and (*R*)-MeCBS at 23 °C.

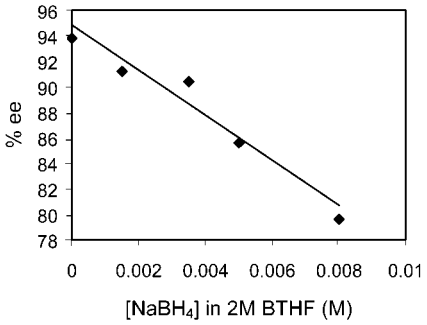

Figure 6. Addition of 2 M BTHF with increasing $NaBH_4$ concentrations to acetophenone and (*R*)-MeCBS at 23 °C.

Concentration of BTHF Complex. We found that the enantioselectivities of the MeCBS reduction of acetophenone with commercial 2 M BTHF (80% ee) were superior to that of commercial 1 M BTHF (65% ee). Commercial 2 M BTHF solutions are stabilized with ~0.008 M $NaBH_4$, which is close to the same relative amount per borane, "BH_3", as in 1 M BTHF. The higher selectivity appears related to the actual addition rate of borane. For 2 M BTHF, the addition rate was 0.22 mmol/min compared to 0.11 mmol/min for 1 M BTHF.

Our correlation between enantioselectivity and increasing BTHF concentration agrees very well with Jockel's results.[16] They found that the reaction was first-order in catalyst and the rate of the catalytic reaction increases with increasing borane concentration. On the basis of Jockel's and our results, the higher concentration of BTHF is presumably contributing to a more rapid turnover of the MeCBS catalyst.

The data shown in Figure 6 for reduction of acetophenone using 2 M BTHF also confirms the linear trend seen with 1 M BTHF of higher enantioselectivity with lower borohydride concentration.

The optimum conditions for high enantioselective ketone reductions were demonstrated with simultaneous addition experiments. Recently, Tillyer and co-workers reported better selectivities in the synthesis of cyclic amino alcohols using simultaneous addition of the ketone and BH_3–SMe_2 as the borane source to the catalyst.[20] Under these reaction conditions, the MeCBS to ketone

(18) The BTHF and MeCBS catalyst were stirred for 10 min before ketone addition to ensure equilibration of the MeCBS−borane complex, since a control experiment where ketone addition was immediately added gave 84% ee.

(19) Douglas, A. W.; Tschaen, D. M.; Reamer, R. A.; Shi, Y.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 1303.

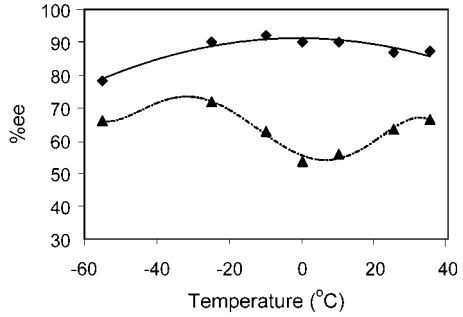

Figure 7. Effect of temperature on the % ee: ▲ commercial 1 M BTHF added to mixture of acetophenone and (*R*)-MeCBS and ◆ acetophenone added to a mixture of commercial 1 M BTHF and (*R*)-MeCBS.

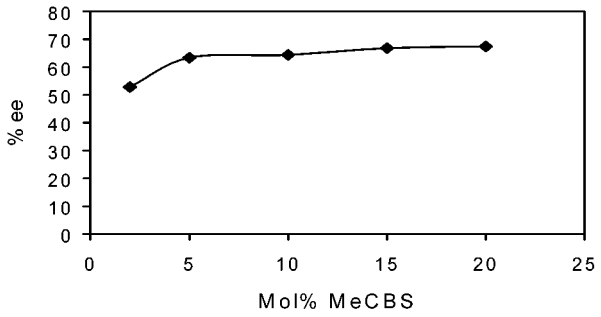

Figure 8. Effect of the catalyst concentration on % ee: commercial 1 M BTHF added to mixture of acetophenone and (*R*)-MeCBS (mol % relative to ketone).

ratio is probably near 1:1, which may help to minimize the influence of the borohydride species on the overall selectivity.[21] Indeed, we found that by simultaneously adding commercial 1 M BTHF and acetophenone to MeCBS in THF, high enantioselectivity was obtained (95% ee).[22] Addition of the acetophenone two times faster than BTHF, or vice versa, gave equally high enantioselectivities (both 96% ee), demonstrating that equal rates were not critical. Simultaneous addition of BTHF and ketone to a continuous reactor with supported oxazaborolidine catalyst, as reported by BASF using borane−dimethyl sulfide complex,[23] would be advantageous for reducing costs and environmental impact.

Reaction Temperature. Because other groups had observed temperature effects on enantioselectivity,[24] we explored the effect of this variable on the selectivity of MeCBS-catalyzed reduction. When commercial BTHF was added to ketone, the results showed decreasing enantioselectivity as the temperatures was lowered from 35 to 0 °C and then increasing selectivity below 0 °C to about −25 °C (see Figure 7). As reported by several groups,[25] the selectivity dropped below −25 °C. The higher enantioselectivity at temperatures between 0 to −25 °C may reflect the faster regeneration of active catalyst (BH_3/MeCBS) or a slowing in the rate of ketone reduction by the BTHF/"$NaBH_4$" system.

Although higher enantioselectivities were observed when acetophenone was added to a mixture of commercial BTHF and MeCBS, the effect of temperature was less dramatic (see Figure 7).

Catalyst Loading. We also investigated the MeCBS-catalyzed reduction while changing the catalyst-loading variable. When commercial BTHF was added to ketone and MeCBS, higher enantioselectivity was obtained with 5% loading over 2.5%, but >5% MeCBS did not significantly increase the selectivity (see Figure 8). Stone also reported a similar nonlinear effect with 1−10 mol % of PhCBS using borane−1,4-thioxane complex.[24]

With this mode of addition, the MeCBS catalytic system is borane (BH_3) starved, resulting in only a small amount of MeCBS actually participating in the catalytic cycle. As a consequence, the higher amounts of MeCBS do not overcome the nonselective "borohydride" pathway.

Since temperature and catalyst-load optimization did not sufficiently increase the enantioselectivity, an alternative process to increase the selectivity in the MeCBS with commercial BTHF was sought, especially in the case where the ketone substrate has limited solubility, ruling out simultaneous addition techniques.

Addition of Lewis Acids. Researchers at Merck have used additives to achieve a high degree of enantioselectivity in the oxazaborolidine-catalyzed ketone reduction.[21] Triethylamine was used with stoichiometric methyloxazaborolidine−borane complex to trap the monoalkoxyborane product as an amine complex, thus inhibiting less selective reduction of ketone by the monoalkoxyborane. 2-Propanol was also used to intercept the monoalkoxyborane, yielding a mixed dialkoxyborane that is very slow to reduce ketones.[26] Both of these additives make less than efficient use of the borane source.

If simultaneous addition mode is not feasible, the borohydride species in BTHF solutions must be removed or deactivated to improve the overall enantioselectivity of the MeCBS-catalyzed reduction. The initial observation that degraded BTHF gives a higher selectivity is not a viable option for commercial utility. The reaction of Lewis acids with $NaBH_4$ is a well-known process to make diborane, *but would a Lewis acid react with the* NaB_3H_8 *observed or other trace "borohydrides"*?

Upon screening several Lewis acids as additives, we found that the selectivity of the MeCBS reduction was effectively restored (see Table 4). Of the Lewis acids investigated, BF_3–THF complex proved to be the best, with an enantioselectivity of 90% ee for the 1-phenylethanol product.

Further optimization of the conditions to utilize BF_3-THF in the reaction by adding the BTHF solution to a mixture of ketone, MeCBS, and BF_3-THF gave a slightly

(20) Tillyer, R. D.; Boudreau, C.; Tschaen, D.; Dolling, U.-H.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 4337.

(21) Cai and co-workers reported very high enantioselectivities in the reduction of representative ketones using oxazaborolidine−BH_3 complex as the stoichiometric reducing agent: Cai, D.; Tschaen, D.; Shi, Y.-J.; Verhoeven, T. R.; Reamer, R. A.; Douglas, A. W. *Tetrahedron Lett.* **1993**, *34*, 3243.

(22) 3 mmol of 1 M BTHF and 5 mmol of ketone were added over 30 min.

(23) (a) Woltinger, J.; Bommarius, A. S.; Drauz, K.; Wandrey, C. *Org. Process Res. Dev.* **2001**, *5*, 241. (b) Giffels, G.; Felder, M.; Kragl, U.; Wandrey, C.; Bommarius, A.; Bolm, C.; Derrien, N.; Drauz, K. US Patent 6,180,837.

(24) Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465.

(25) Literature reports have shown that, depending on the borane source, the selectivity of the MeCBS reduction is influenced by the reaction temperature. See: (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carrol, J. D.; Corley, E. G.; Grabowski, J. *J. Org. Chem.* **1993**, *58*, 2880; (c) Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465; (d) Jiang, Y. Z.; Qin, Y.; Mi, A. Q. *Chin. Chem. Lett.* **1995**, *6*, 9.

(26) (a) Shi, Y.-J.; Cai, D.; Dolling, U.-H.; Douglas, A. W.; Tschaen, D. M.; Verhoeven, T. R. *Tetrahedron Lett.* **1994**, *35*, 6409. (b) Tschaen, D. M.; Abrahamson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Krady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

Table 4. Effect of Lewis Acids on the Enantioselectivity of the (*R*)-MeCBS Reduction of Acetophenone with Commercial 1 M BTHF Solutions

entry	Lewis acid	% ee[a,b]
1	$ZrCl_4$	85.6
2	$AlCl_3$	83.0
3	$FeCl_3$	86.0
4	BF_3	90.4
5	$TiCl_4$	82.6

[a] Commercial 1 M BTHF solution (~0.005 M $NaBH_4$) in THF and the Lewis acid (~3−8 mol %) was added to a mixture of ketone and (*R*)-MeCBS. [b] Enantiomeric excess was measured with chiral column J & W 30 m × 0.25 mm CDX-B.

better selectivity of 93% ee. The flexibility of where the BF_3-THF additive can be introduced into the reaction shows the utility of this Lewis acid additive to increase the selectivity of the MeCBS reaction.

To demonstrate that the Lewis acid, BF_3–THF, was not enhancing the selectivity of the reduction, we carried out the MeCBS reduction of acetophenone with nonstabilized 1 M BTHF in the presence of 8 mol % of BF_3–THF complex. The selectivity observed under these reaction conditions was 95% ee.[27] Evidently, the BF_3–THF serves to remove the borohydride and not to catalyze the reduction.

The addition of $NaBF_4$, a byproduct of the reaction,[28] did not significantly affect the enantioselectivity of the reduction (93% ee).[29] This result does not rule out the possibility that other byproducts from the BF_3 addition may slightly lower the enantioselectivity as compared to the reduction with nonstabilized BTHF solutions (95% ee).

Conclusion

In conclusion, a soluble borohydride species in BTHF solution was detrimental to the enantioselective reduction of ketones using the oxazaborolidine catalyst. From the relative rate studies, the MeCBS-catalyzed reduction pathway is much faster than the "borohydride"-catalyzed pathway. However, the borohydride participates in a nonselective reduction, effectively competing with the enantioselective process, resulting in an overall drop in enantioselectivity.

Upon reaction parameter optimization, the nonselective borohydride reduction pathway was dramatically minimized via simultaneous addition of substrate and BTHF to MeCBS catalyst. During the simultaneous addition, the ketone/MeCBS catalyst ratio is close to stoichiometric, as opposed to during BTHF addition to ketone and 5 mol % MeCBS, where the catalytic cycle may be deficient in borane.

When the ketonic substrate has limited solubility, requiring BTHF addition, the use of BF_3 as an additive proved very effectively to restore the enantioselectivity to acceptable levels. On the basis of our control experiments, the BF_3 additive was reacting with the borohydride species and not catalyzing the enantioselective process.

(27) The mode of addition for this experiment was acetophenone added to the BTHF/MeCBS/BF_3-THF mixture.

(28) Sodium tetrafluoroborate is also a byproduct of in situ generated borane from sodium borohydride and boron trifluoride.

(29) The mode of addition for this experiment was acetophenone added to unstabilized 1 M BTHF/MeCBS/$NaBF_4$ mixture.

The mechanistic implications of this work merit further study of this important asymmetric reduction process.

Experimental Section

General Considerations. All reactions were carried out in predried glassware (1 h, 150 °C) under a dry nitrogen atmosphere. Tetrahydrofuran (THF) and ketones were dried over 4 Å molecular sieves. BF_3–THF was distilled under vacuum prior to use. Sodium octahydrotriborate (NaB_3H_8) was prepared according to a literature method.[30] BTHF solution (>98% pure containing ~0.005 M $NaBH_4$ for 1 M and ~0.008 M for 2 M), 99.5% pure diborane gas, and (*R*)-MeCBS (1 M in toluene) were used directly as obtained from commercial sources unless otherwise noted. Unstabilized BTHF solutions were prepared by bubbling pure diborane into tetrahydrofuran. BTHF solutions containing <0.005 M $NaBH_4$ were prepared by addition of pure diborane gas followed by addition of the required amounts of $NaBH_4$. Chiral alcohol products were analyzed via gas chromatography techniques.

Reduction of Acetophenone, BTHF Added to Acetophenone/THF/MeCBS. To a solution of acetophenone (2.1 g, 17.1 mmol) in THF (17 mL) was added (*R*)-MeCBS in toluene (0.86 mL of 1.0 M, 0.86 mmol). A BTHF solution in THF (10.3 mL of 1.0 M, 10.3 mmol) was then slowly added at ambient temperature over 30 min. After completing the addition of BTHF, the reaction mixture was allowed to stir for 10 min before quenching with a solution of HCl in H_2O (10 mL of 2 M, 20 mmol). Diethyl ether (20 mL) was added, and the organic phase was washed with saturated aqueous solutions of KCl (3 × 8 mL), $NaHCO_3$ (3 × 12 mL), and KCl (3 × 8 mL). The organic phase was then dried over Na_2SO_4, filtered, and analyzed by chiral GC to determine optical purity of the 1-phenylethanol product.

Reduction of Acetophenone, Acetophenone/THF Added to BTHF/MeCBS. To a BTHF solution in THF (10.3 mL of 1.0 M, 10.3 mmol) was added (*R*)-MeCBS in toluene (0.86 mL of 1.0 M, 0.86 mmol). After stirring the BTHF/MeCBS reaction mixture for 10 min, acetophenone (2.1 g, 17.1 mmol) in THF (17 mL) was then slowly added to the reaction flask at ambient temperature over 30 min. After completing the addition of acetophenone in THF, the reaction solution was allowed to stir for 10 min before quenching with a solution of HCl in H_2O (10 mL of 2 M, 20 mmol). Diethyl ether (20 mL) was added, and the organic phase was washed with saturated aqueous solutions of KCl (3 × 8 mL), $NaHCO_3$ (3 × 12 mL), and KCl (3 × 8 mL). The organic phase was then dried over Na_2SO_4, filtered, and analyzed by chiral GC to determine the optical purity of the 1-phenylethanol product.

Reduction of Acetophenone, Simultaneous Addition of BTHF/Ketone to MeCBS. To a solution of (*R*)-MeCBS in toluene (0.25 mL of 1.0M, 0.25 mmol) were added simultaneously BTHF solution in THF (3.2 mL of 0.94 M, 3 mmol) and acetophenone (0.60 g, 5 mmol) in THF (4.4 mL) at ambient temperature over 30 min. After completing the addition of the BTHF and ketone solutions, the reaction solution was allowed to stir for 10 min before quenching with a HCl solution in H_2O (10 mL of 2 M, 20 mmol). Diethyl ether (20 mL) was added, and the organic phase was washed with saturated aqueous solutions of KCl (3 × 8 mL), $NaHCO_3$ (3 × 12 mL), and KCl (3 × 8 mL). The organic phase was then dried over Na_2SO_4, filtered, and analyzed by chiral GC to determine the optical purity of the 1-phenylethanol product.

Reduction of Acetophenone, BTHF/BF_3–THF Added to Acetophenone/THF/MeCBS. To a solution of acetophenone (2.0 g, 16.6 mmol) and THF (14.7 mL) was added (*R*)-MeCBS in toluene (0.83 mL of 1.0 M, 0.83 mmol). BF_3–THF (0.1 g, 0.81 mmol) was then added to the BTHF solution. A BTHF solution in THF (10.0 mL of 1.0 M, 10.0 mmol) solution

(30) Dewkett, W. J.; Grace, M.; Beall, H. *Inorg. Synth.* **1974**, *15*, 111.

was then slowly added at ambient temperature over 30 min. After completing the addition of the BTHF solution, the reaction solution was allowed to stir for 10 min before quenching with a HCl solution in H_2O (10 mL of 2 M, 20 mmol). Diethyl ether (20 mL) was added, and the organic phase was washed with saturated aqueous solutions of KCl (3×8 mL), $NaHCO_3$ (3×12 mL), and KCl (3×8 mL). The organic phase was then dried over Na_2SO_4, filtered, and analyzed by chiral GC to determine the optical purity of the 1-phenylethanol product.

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