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Highly Enantioselective Reduction of Prochiral Ketones with *N,N*-Diethylaniline·borane (DEANB) in Oxazaborolidine-catalyzed Reductions

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Abstract: *A variety of prochiral ketones including phenyl, aralkyl, cycloalkyl, alkyl and tertiary alkyl are enantioselectively reduced with an oxazaborolidine catalyst (5 mol% of the Me-CBS) and N,N-diethylaniline·borane as the borane source. The enantioselectivity of the reduction produced secondary alcohols in the range of 90 to ≥99% ee.*

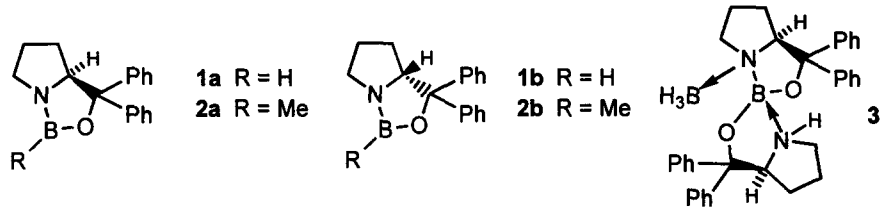
The synthesis of enantiomerically pure compounds has become an important area of research for pharmaceutical industries,[1] because studies have demonstrated that two enantiomers of a chiral drug usually display different biological activities. Oxazaborolidine-catalyzed reduction (CBS reduction)[2] of prochiral ketones is an extremely important methodology for the synthesis of chiral secondary alcohols. Since Corey's article in 1987,[2a] oxazaborolidine-catalyzed reductions have been studied extensively.[3,2c,e]

The most commonly employed borane reductants for oxazaborolidine-catalyzed reduction of prochiral ketones are borane·tetrahydrofuran, borane·dimethyl sulfide, borane·1,4-thioxane,[4] diborane,[5] and catechol borane.[6] However, these borane carriers suffer from drawbacks to commercial application such as thermal decomposition, low concentration, noxious odor, or expense. Thus, the growing importance of oxazaborolidine-catalyzed reduction for the large-scale synthesis of pharmaceuticals create a need for an easy to handle, stable, concentrated borane carrier for this type of asymmetric catalytic reduction of prochiral ketones.

Although amine borane complexes have been rarely used as the borane source in oxazaborolidine-catalyzed reduction, amines have been added to reaction mixtures to enhance the enantioselectivity.[7] M. Periasamy[8] and coworkers have used *N,N*-diethylaniline·borane (DEANB) as a reductant in asymmetric reduction of prochiral ketones and obtained the corresponding chiral alcohols in good enantioselectivity (91.4% ee)[8a] using the parent CBS catalyst (**1a**, (*S*) HCBS, 0.25 equiv.). However, only aromatic ketones were studied and the enantioselectivity observed was lower than that reported using other borane sources. Therefore, we repeated the reduction under optimized reaction conditions[9] and obtained (*R*)-*sec*-phenethyl alcohol with high enantioselectivity (97.2% ee) using DEANB and catalyst generated *in situ* from (*S*)-diphenyl prolinol (5 mole percent (*S*) DPP, 0.05 equivalents based on ketone).

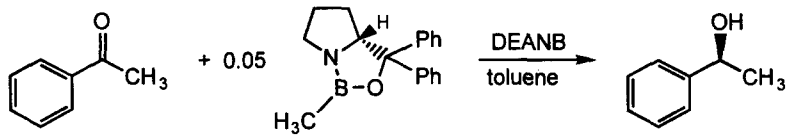
Closer inspection of the catalyst prepared by Periasamy's procedure showed some (*S*) HCBS monomer and dimer at δ 27 and δ 7 respectively as broad peaks in the ^{11}B NMR spectrum. However, the major component of the catalyst mixture was a compound comprised of two (*S*) DPP molecules, first isolated by researchers at Merck.[10] This compound (**3**) contains an amine·borane functionality (δ -13, broad) and a borate (δ 10.8, s). Since we have observed compound **3** when HCBS catalyst is generated *in situ* from THFB or DMSB,[5] the

concentration of the active catalyst for this type of reduction is questionable. In any event, the actual amount of "HCBS" in our experiment, estimated at 2 mol% relative to the ketone as determined by ^{11}B NMR spectroscopy, provided excellent selectivity. Efforts to use compound **3** as a catalyst gave a low enantioselectivity in the range of 20-40% ee for the reduction of acetophenone. Therefore, compound **3** can not be responsible for the high enantioselectivity described above. Compound **3** is very robust[11] and not easily converted to the parent (*S*) HCBS.



Because "HCBS" generated *in situ* is a mixture and may not always give reproducible results, we used MeCBS (either **2a** or **2b**) of known structure and purity for the evaluation of asymmetric ketone reductions with *N,N*-diethylaniline·borane as the borane source. In this communication, we describe excellent enantioselectivities in ketone reductions using this reagent (DEANB) and MeCBS catalyst combination, see Table 1.

Reduction of acetophenone with DEANB in the presence of 5 mol% (*R*) MeCBS, (**2b**, Equation 1) gave 94.7% ee (*S*)-*sec*-phenethyl alcohol. In contrast to observations in the preceeding study[12] with *N,N*-diethylaniline·borane, the reduction of acetophenone with "HCBS" or MeCBS was complete within 30 minutes at room temperature. A ^{11}B NMR spectrum taken about 15 minutes after the ketone addition showed the presence of dialkoxyborane, [$(RO)_2BH$ at δ 27, d, J = 135 Hz], unreacted DEANB (δ -11, q, J = 99 Hz), and



small peaks attributed to $(RO)_3B$ and the catalyst[13] (broad peak at δ 34). The slight reduction in the enantioselectivity of MeCBS versus "HCBS" under identical conditions may be attributed to temperature effects since at 30 °C the reduction of acetophenone with 5 mol% MeCBS gave 98.7% ee (entry 3).

The reaction temperature,[14] rate of ketone addition and other factors influence the enantioselectivity in the CBS reduction, therefore the reductions were conducted under isothermal conditions at 20 ± 2 °C with a 1 to 1.5 h ketone addition. The effects of several reaction parameters such as ratio of DEANB to acetophenone and percent of catalyst were briefly investigated. Using a 1:0.66 ratio of acetophenone to DEANB, the chiral alcohol was obtained in 94.3% ee. When the reduction of acetophenone was carried out with 10 mol% catalyst, the enantioselectivity was slightly higher (96.4% ee) than with 5 mol% catalyst. Contrary to literature reports,[3b] the water content of acetophenone (0.068% measured by Karl Fischer titration) did not have a severe effect on the outcome of the enantioselectivity. As indicated in the table, pinacolone, cyclohexyl methyl ketone, 2-chloroacetophenone, and α-tetralone were reduced to the corresponding alcohols in excellent enantioselectivity.

For the aliphatic ketone of entry 8, we were pleasantly surprised to obtain excellent selectivity under these reaction conditions.

Table 1. Asymmetric Reduction of Prochiral Ketones with Oxazaborolidine Catalysts and *N,N*-Diethylaniline·Borane (DEANB) as the Borane Source[a]

Entry	Prochiral Ketone[b]	Catalyst	% ee[c]	Alcohol Configuration
1	$PhCOCH_3$	"(*S*) HCBS"	97.2	*R*
2	$PhCOCH_3$	(*R*) MeCBS	94.7 (96.4)[d]	*S*
2	$PhCOCH_3$	(*S*) MeCBS	98.7[e]	*R*
2	$PhCOCH_3$	(*S*) MeCBS	94.3[f]	*R*
3	α-Tetralone	(*R*) MeCBS	≥99	*S*
4	$C_6H_{11}COCH_3$	(*R*) MeCBS	≥99	*S*
5	*t*-$BuCOCH_3$	(*S*) MeCBS	97.4	*R*
6	$PhCOCH_2Cl$	(*R*) MeCBS	90[g] (98.3)[h]	*R*
7	$PhCOCH_2Br$	(*R*) MeCBS	90[g]	*R*
8	*i*-$PrCOCH_3$	(*R*) MeCBS	91	*S*

[a]All reactions were carried out using 5 mol% MeCBS with DEANB and ketone in 1:1 ratio in toluene unless otherwise mentioned. [b]In all cases ketone was dissolved in 5 mL of toluene and added slowly to the mixture of MeCBS and DEANB in 10 mL of toluene. [c]Percent ee was determined by chiral GC. [d]Reaction was carried out using 10 mol% of catalyst. [e]Reduction was carried out at 30±2 °C. [f]The ratio of ketone to DEANB was 1:0.66. [g] Percent ee determined by converting the 2-halo hydrins to styrene oxide with tetrabutylammonium bromide and sodium hydroxide. [h]Reaction was carried out using 10 mol% of catalyst, ketone dried with molecular sieves overnight, and temperature of the reaction mixture was 31-32 °C.

The described asymmetric reduction procedure does not require any special efforts to remove the borane carriers. Both amine precursors, DPP from the MeCBS and *N,N*-diethylaniline from the borane carrier can be easily extracted from the product by washing with 1.0 N HCl.

In conclusion, we have demonstrated the general applicability and successful utilization of *N,N*-diethylaniline·borane as a borane source in MeCBS catalyzed reduction of prochiral ketones. The enantioselectivities achieved with this combination of borane reagent and catalyst were at least as high as the literature reports using combinations of other borane reagents and oxazaborolidine catalysts. The high selectivity observed with "HCBS" and DEANB merits further study, especially in light of the low amounts of this parent catalyst in the solution. We are pursuing the preparation of pure HCBS in our effort to supply affordable oxazaborolidine catalysts for commercial applications.

The following procedure for the asymmetric reduction of acetophenone is representative. A dry 100 mL two-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, thermocouple, and septum inlet was charged with (*R*) MeCBS (0.84 mmols) in 10 mL of toluene. DEANB (16.8 mmols, 2.74 gms) was added to the catalyst and the flask was immersed in a water bath to moderate the temperature. Acetophenone (16.6 mmols, 2.00 mL) in 5 mL of toluene was placed in the additional funnel and then slowly added to the reaction flask over 1 to 1.5 hrs. After the ketone addition, the reaction mixture was stirred for an additional hour. The reaction mixture was then carefully quenched with 5 mL of MeOH (hydrogen evolution), followed by addition of 1.0 N HCl (10 mL) and stirred for 15-20 minutes. The organic layer was separated and the aqueous layer was extracted with fresh toluene or diethyl ether (3 x 10 mL). The combined

organic layers were washed with 1.0 N HCl (2 x 10 mL), water, brine, and dried over anhydrous magnesium sulfate. At this stage the organic layer was analyzed for the optical purity by GC with a CDX-B 30 m x 0.25 mm column (J and W Scientific) and found to be 94.7% ee (*S*)-*sec*-phenethyl alcohol. Solvent was then removed by distillation and the residue distilled under vacuum to get an 85% yield of (*S*)-1-phenethyl alcohol. Spectral data matched with an authentic sample.

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