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Diphenyloxazaborolidine
A New Catalyst For Enantioselective Reduction Of Ketones

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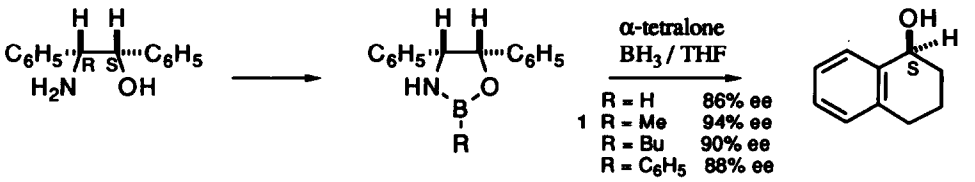
ABSTRACT: A variety of ketones can be reduced in high enantioselectivity with the oxazaborolidines derived from commercially available erythro aminodiphenylethanol.

Since the discovery of oxazaborolidines as catalysts (CBS catalysts)[1] for the enantioselective reduction of prochiral ketones in high ee and predictable absolute stereochemistry, numerous applications have appeared.[2] Improved procedures for the preparation of diphenylprolinols and subsequent condensation to afford oxazaborolidines have been reported,[3] and a review of reagents for enantioselective ketone reduction including CBS has been published.[4] We have recognized the importance of catalytic oxazaborolidine reduction and employed it to generate chiral alcohols for subsequent higher order cuprate displacements.[5] In addition, these catalysts are compatible with some ketones containing heteroatoms, particularly nitrogen, which can competitively coordinate borane.[6]

A number of new oxazaborolidines have been reported which provide varying enantioselectivities in prochiral ketone reductions, but none have offered an improvement from the proline derived oxazaborolidines.[7] Comparing the stoichiometric reducing agent *B*-chlorodiisopinocampheylborane (DIP-Chloride) with CBS catalysts, both enantiomers of α-pinene are commercially available for preparation of DIP-Chloride, but unnatural D-proline is costlier than L-proline for the CBS catalysts.[8,9] To this end, we sought to identify a catalyst which would be readily available in both enantiomeric forms, provide high enantiomeric excess of predictable absolute stereochemistry, and be a catalytic reagent for the enantioselective reduction of prochiral ketones.

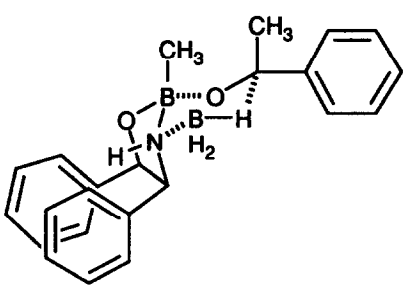
During this study we developed the operating hypothesis that *the primary requirement of a good oxazaborolidine catalyst to obtain high enantiomeric excess in prochiral ketone reductions was to completely block one face of the oxazaborolidine.* This tenet was based on the proposed mechanism of the reduction which entailed a double docking on the oxazaborolidine by borane and the carbonyl oxygen atom.[10] Thus blocking one face of the oxazaborolidine in conjunction with the double docking mechanism was envisioned to afford high enantioselective reduction. Our best catalyst precursor, erythro 2-amino-1,2-diphenylethanol, had been investigated four decades earlier as a potential analgesic agent,[11] and is commercially available.[12] Conversion of the (1S, 2R)-(+)-2-amino-1,2-diphenylethanol into the B-H, B-Me, B-Bu, and B-phenyl catalysts was achieved with borane,[13] trimethylboroxine,[3a] butaneboronic acid,[14] and triphenylboroxine[3a]

respectively under conditions previously reported for oxazaborolidine formation. At 5 mole%, the methyl version of the catalyst **1** provided the highest enantiomeric excess in the reduction of α-tetralone, although all of the substitutions on boron provided good ee's.[15]



A broad survey of ketones employed with the methyl catalyst enantiomers, **1** and **2**, is compiled in Table 1. High enantiomeric excess is secured when the groups flanking the ketone are of significantly different size, compare entry A and E. A variety of heteroatom containing ketones are compatible with the reduction conditions, entries C, D, G, N, P. 1,2-Aminoalcohols can be prepared with good enantiomeric excess employing 1.7 equivalents of borane as required with any substrate containing a basic nitrogen.[6] Dimethylaminoacetone, entry M, afforded a good ee comparable to that obtained in the carbon analogue, 4,4-dimethyl-2-pentanone entry, L. By contrast, in the case of dimethylaminoacetophenone, entry I, the low ee was a result of two groups of comparable steric demand flanking the ketone (phenyl verses the equivalent of a "methylene t-butyl" group). This catalyst provides high ee in the reduction of 1,3-aminoalcohols, entry P, and offers an alternative to the use of Chirald® with Mannich bases.[16] Oxazaborolidines **1** and **2**, are compatible with oxygen, sulfur, halogen, nitriles, amines, and other nitrogen containing compounds. Of particular note is the higher ee obtained with catalyst **2** relative to the CBS catalyst in the reduction of acetylpyridines (entries N, O).[6] Other than the acetylpyridines, diphenyloxazaborolidines and the CBS catalysts give quite similar selectivities.

As mentioned earlier, these catalysts operate by a double docking of borane and the carbonyl oxygen atom on the oxazaborolidine. The absolute stereochemistry of the alcohol is predicted by the six membered ring transition state working model depicted below. This model illustrates the reduction of acetophenone by **2**. The diphenyl substituents must be orthogonal to the oxazaborolidine ring, otherwise their ortho protons would contact the other aromatic ring. Because of this orthogonal arrangement, which is within π-overlap stabilization distance, the phenyl groups synergistically augment each others steric requirements effectively shielding one face of the oxazaborolidine. The 1,3-diaxial interaction of the methyl group on boron and the small group flanking the ketone is then responsible for enantiospecific delivery of hydride.



Predictable absolute stereochemistry of the product alcohols results from the preceeding transition state model and is graphically illustrated below. The data in Table 1 substantiates this premise.

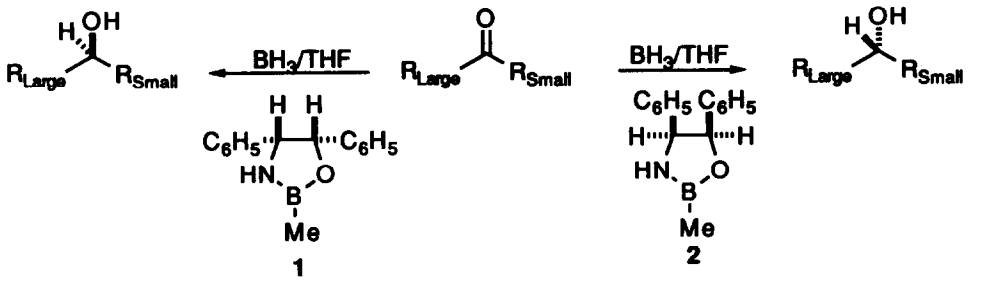


Table 1[17]

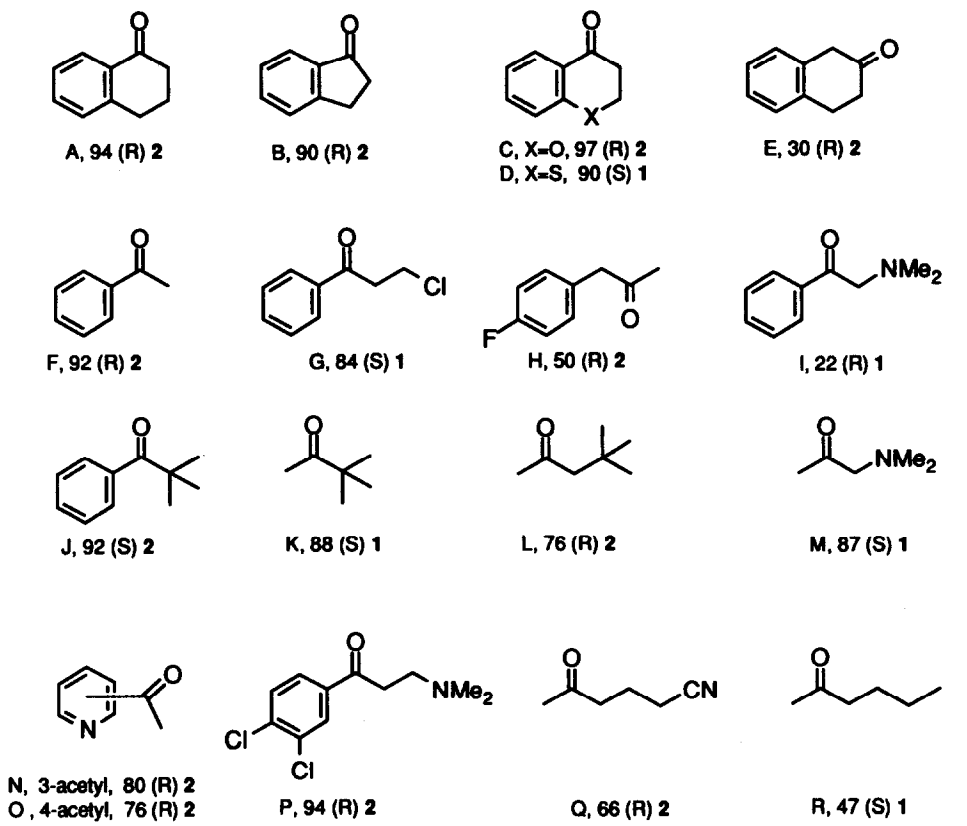


Table code: entry letter, % enantiomeric excess, (product configuration), catalyst enantiomer used in **bold**.

In summary, the enantioselective reduction of ketones catalyzed by diphenyloxazaborolidines provides high enantiomeric excess in the production of chiral secondary alcohols of predictable absolute stereochemistry. Use of this reagent is often applicable to compounds which contain heteroatoms including nitrogen. Both enantiomers of the erythro aminodiphenylethanol are commercially available[12] and are comparably priced. It is anticipated in the case where the CBS catalyst derived from D-proline is required that the diphenyloxazaborolidine **1** will be less expensive.

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[14] Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275-78.

[15] In some cases, use of 10 mole% catalyts in reduction of aliphatic ketones did improve enantioselectivity while higher levels of catalyst did not improve enantioselectivity with aromatic ketones.

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[17] Preparation of **1** is as follows: (1S,2R)-(+)-2-amino-1,2-diphenylethanol (4.9g, 22.9mmol) was suspended in toluene (150mL) and heated to 80°C to afford a colorless solution. The reaction mixture was treated all at once with trimethylboroxine (2.13mL, 15mmol) and the heating bath removed. The reaction mixture was stirred for 18 h, the toluene and excess trimethylboroxine and water were distilled off until only 65mL remained. The reaction was chased with toluene (3X60mL) each time distilling until 65mL remained. After the third time the remaining toluene was distilled off at atmospheric pressure and then under high vacuum to yield an off-white solid mp 69-70°C α_D = -65 (c=2, toluene). ^{1}H NMR (C_6D_6) δ 7.21-6.68 (m, 10H), 5.54 (d, J = 8 Hz, 1H), 4.48 (d, J = 8 Hz, 1H), 3.02 (bs, 1H), 0.46 (s, 3H).
All reductions were performed at 25°C, on a 20mmole ketone scale, 0.25M in tetrahydrofuran, by adding 0.7 equivalents of borane dimethylsulfide complex (2M in tetrahydrofuran) via syringe pump over 1hr except in the cases where the ketone contains a basic nitrogen atom in which cases 1.7 equivalents of borane were employed. Isolated yields of products were all >90% and typically >95%. Enantiomeric excesses were determined by HPLC with a chiral support. Product configurations were assigned by the sign of rotation as reported in the literature and/or by comparison with an authentic sample on HPLC.

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