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cis-1-Amino-2-indanol in Asymmetric Synthesis. Part I. A Practical Catalyst System for the Enantioselective Borane Reduction of Aromatic Ketones

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Abstract: *A new class of oxazaborolidine catalysts has been prepared from optically pure cis-1-amino-2-indanols which are available in large quantities. The asymmetric borane reduction of aromatic ketones using these catalysts has been studied.*

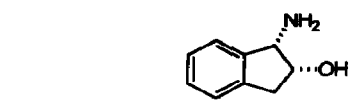
The design and development of cost-effective catalysts that exhibit high reactivity and enantioselectivity is a challenging endeavor in organic chemistry. Over the past decade, the asymmetric borane reduction of prochiral ketones using chiral oxazaborolidine catalysts has emerged as a useful tool for synthetic chemists.[1] So far, a large number of β-aminoalcohols have been synthesized, mostly from natural sources, and utilized in the preparation of the corresponding oxazaborolidine catalysts. Some of these catalysts have been extensively studied and achieved great success. However, a major drawback in using these oxazaborolidine catalysts is that unnatural amino acids are frequently required as the starting materials to make the desired chiral β-aminoalcohols. In contrast to L-α-amino acids, D-α-amino acids are often difficult to obtain,[2] which severely limits the applications of these oxazaborolidine catalysts in large scale preparation.

In this communication, we describe a new class of chiral oxazaborolines prepared from optically pure *cis*-1-amino-2-indanols (**1a,b**) and their use as catalysts in the enantioselective borane reduction. Both enantiomers of *cis*-1-amino-2-indanol have been prepared by diastereomeric resolution[3] and by enzymatic resolution.[4] More recently, we have developed a four-step industrial process for the manufacture of optically pure *cis*-1-amino-2-indanols *via* the Jacobsen epoxidation starting from inexpensive indene.[5]

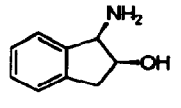
Optically pure *cis*-1-amino-2-indanols have been used in asymmetric transformations.[3,4] For instance, Didier and co-workers have reported the asymmetric borane reduction of acetophenone using stoichiometric amounts of 1,3,2-oxazaborolidine B-H compounds formed *in situ* from some chiral β-aminoalcohols, including (1S,2R)-1-amino-2-indanol.[4] However, on the basis of their observations, the authors concluded that "no system was found to be efficient with catalytic amounts of ligands [studied]".

According to the previous mechanistic studies on the asymmetric borane reduction catalyzed by chiral oxazaborolidines and structural investigation of the oxazaborolidine catalysts, one essential prerequisite for a good catalyst is to have one face of the catalyst completely blocked in order to attain high enantioselectivity in the asymmetric borane reduction.[1,6] Model study on the oxazaborolidine derived from chiral *cis*-1-amino-2-indanol reveals that one face of the oxazaborolidine is totally blocked by the indanyl moiety. To test the catalytic efficiency, oxazaborolidine **2** was prepared *in situ* from **1a** following a literature procedure.[7] Oxazaborolidine **3a** or **3b** was prepared from the reaction of **1a** or **1b** with trimethylboroxine in toluene and was

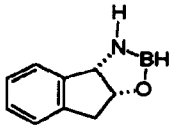
used as the toluene solution.[8] α-Chloroacetophenone was chosen as a model substrate for the study because the resulting chlorohydrin is a versatile synthon in organic synthesis.[9]



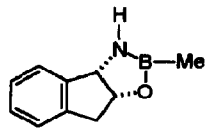
1a
(1S, 2R)



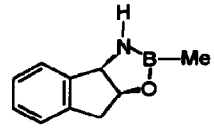
1b
(1R, 2S)



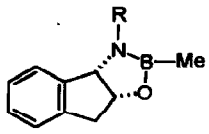
2

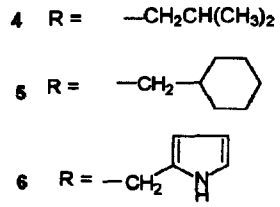


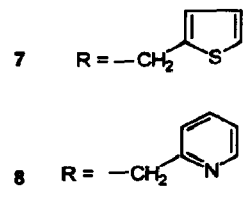
3a



3b



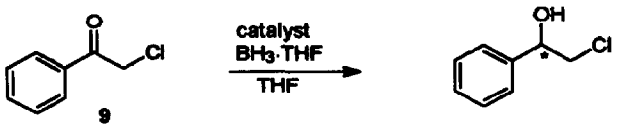




The reduction was performed by slow addition of the substrate solution and borane reagent to a preformed solution containing the oxazaborolidine-BH_3 complex in THF.[10] The results are summarized in Table 1, entries 1-4. At ambient temperature using 5-10 mol% of catalyst **2** or **3a** (or **3b**), enantiomeric excess over 90% can be achieved. In contrast to catalyst **2** which is less reactive at low temperature, catalyst **3** is effective even at -20 °C, and ee's up to 96% was obtained (entries 3,4). Although CH_2Cl_2 and toluene are favored solvents for the proline-derived oxazaborolidine catalyst,[10] the reductions with catalyst **3** in these solvents gave lower enantioselectivities than that in THF.

A limited study was conducted on the variation of the catalyst structure (see Table 1, entries 5-9). So far we have only tried to modify **1a** by varying the substituents on the nitrogen atom. The precursors for catalysts **4-8** were prepared in good yields by the reductive alkylation of **1a** with a variety of aldehydes.[11] As a general trend, oxazaborolidines **4-7** displayed lower reactivities and stereoselectivities than their parent compound **3a** (entries 5-8). The data suggest that the substituent on the nitrogen increases the steric hindrance of the nitrogen and thereby weakens the complexation of the nitrogen with borane, resulting in a less reactive system. Introduction of one additional strong coordinating atom in the catalyst system decreases the enantioselectivities drastically as illustrated in the cases of oxazaborolidines **7** and **8** (entries 8, 9).

Table 1. Catalyst Comparison in the Asymmetric Reduction of α-Chloroacetophenone 9[a,b]



9

entry	catalyst (mol%)	ee (%)[c] (temperature)	config.[d]
1	**2** (10)	91.7 (rt); 89.1(0 °C)	S
2	**2** (5)	91.0 (rt)	S
3	**3a** (10)	92.0 (rt); 94.0 (0 °C); 96.0 (-20 °C)	S
4	**3b** (10)	92.0 (rt); 96.0 (-20 °C)	R
5	**4** (10)	90.0 (rt)	S
6	**5** (10)	82.3 (rt)	S
7	**6** (10)	89.0 (rt)	S
8	**7** (10)	40.0 (rt))	S
9	**8** (10)	rac (rt)	

a. The reaction was performed by slow addition of the ketone **9** and borane reagent to the the catalyst solution over 2 to 3 h at desired temperature. b. Isolated yields >95%. c. Ee's were determined by HPLC on a Chiralcel OJ column; mobile phase: hexane/isopropanol (95:5); flow rate: 0.6 mL/min; detector: UV 220 nm. d. Absolute configuration was assigned by comparison of the optical rotation with that reported in the literature.

We then extended our investigation to other aromatic ketones using oxazaborolidine **3a**. The results are shown in Table 2. For more reactive ketone substrates such as α-halogenated ketones (**9-12**), the reduction proceeded smoothly at -20 °C, affording the alcohols in high ee's (up to 96.8%, entries 1-4). However, for those less reactive ketones, namely acetophenone (**13**) and its analogs **14-17**, the reductions did not proceed to completion at -20 °C, and the reactions were carried out at 0 °C.

Table 2. Enantioselective Reduction of Prochiral Ketones Using 10 mol% of **3a** in THF[a,b]

entry	ketone	temperature	ee (%)	config.[c]
1	**9** $C_6H_5COCH_2Cl$	-20 °C	96.0[d]	S
2	**10** 4-$MeOC_6H_4COCH_2Br$	-20 °C	96.5[e]	S[f]
3	**11** 4-$BrC_6H_4COCH_2Br$	-20 °C	96.8[d]	S[f]
4	**12** 4-$NO_2C_6H_4COCH_2Br$	-20 °C	89.0[e]	S[f]
5	**13** $C_6H_5COCH_3$	0 °C	86.0[d]	R
6	**14** $C_6H_5COCH_2CH_3$	0 °C	80.3[d]	R
7	**15** 4-$MeOC_6H_4COCH_3$	0 °C	90.0[e]	R
8	**16** 4-$NO_2C_6H_4COCH_3$	0 °C	87.0[e]	R
9	**17** α-tetralone	0 °C	83.2[d]	R

a. For the reaction procedure, see References and Notes 12. b. Isolated yields >95%. c. Absolute configurations were assigned by comparison of the optical rotations with these of authentic compounds except as stated. d. Ee's determination, see footnote c of Table 1, except flow rate: 0.4-1.0 mL/min. e. Ee's were determined by HPLC on a Chiralpak AS column; mobile phase: hexane/isopropanol (85:15); flow rate: 0.6-1.0 mL/min; detector: UV 220 nm. f. Absolute configration was tentatively assigned by comparison with the reduction product of ketone **9**.

In conclusion, we have developed a new, practical system of oxazaborolidine catalysts for the enantioselective borane reduction of prochiral ketones. Both enantiomers of *cis*-1-amino-2-indanol used for preparing these catalysts can be obtained equally in a cost-effective manner. Studies aimed to improve the enantioselectivity and catalytic efficiency are currently underway.

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5. The asymmetric synthesis of optically pure *cis*-1-amino-2-indanols will be addressed in a separate paper. (1S,2R)-1-amino-2-indanol and its enantiomer are commercially available from Sepracor in gram to hundred-kilogram quantities. Also see: Stinson, S. *Chemical & Engineering News* **1994**, *May 16*, 6.
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11. All compounds derived from (1S,2R)-1-amino-2-indanol were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses.
12. **Experimental procedure using oxazaborolidine 3a**: A solution of **3a** (0.3 mL, 1.0 M in toluene, 0.3 mmol, 10 mol%) was added to the reaction flask containing 6 mL of dry THF. To the solution at rt was added a BH_3·THF solution (0.6 mL, 1.0 M in THF, 0.6 mmol, 0.2 eq). The resulting mixture was stirred at rt for 30 min and was then cooled to 0 or -20 °C. A solution of 3.0 mmol of ketone in 3 mL of anhydrous THF and a solution of BH_3·THF (2.4 mL, 1.0 M, 2.4 mmol, 0.8 eq) in 0.6 mL of THF were added simultaneously into the flask via a syringe pump over 2-3 h at 0 or -20 °C. After the addition, the mixture was stirred for 30 min at that temperature. The reaction was then quenched with 3 mL of 2 wt% H_2SO_4 aqueous solution and followed by the addition of 20 mL of EtOAc. Normal workup provided the crude product which could be further purified by either flash chromatography on silica gel or distillation under reduced pressure.

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