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LETTERS

Enantioselective Reduction of Ketones. Examination of Bifunctional Ligands

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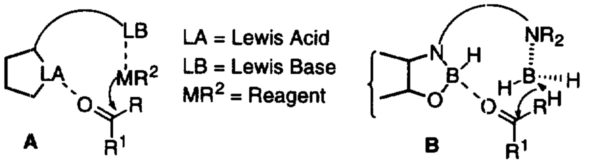
Abstract: New bifunctional ligands based on a *cis*-amino indanol framework have been evaluated in the reduction of prochiral ketones. These reductions proceed with high chemical efficiency and good-to-excellent enantioselectivity using borane and 10 mol% of an oxazaborolidine derived from *cis*-2-amino indanol ligand containing a 2-sulfonylpyridyl tether attached to the amino group.

Keywords: Enantioselective reduction; Oxazaborolidines; Bifunctional ligands

Development of new ligands for the enantioselective addition of nucleophilic reagents to carbonyl compounds is an important synthetic goal. In this context, bifunctional catalysts[1] containing both Lewis acidic and basic sites could offer advantages over their mono functional counterparts in that they provide an environment for coordination of the substrate as well as the reagent. This organization may lead to intramolecular delivery of the reagent to the substrate in a highly selective manner (see structure A, eqn 1). Prototypical examples of bifunctional catalysts are oxazaborolidines that transfer hydrides through a six-membered transition state to carbonyl compounds with high selectivity.[2] As a preliminary model for more complex reactions using bifunctional ligands, we report here carbonyl reductions and evaluate ligands with basic nitrogen tethers (structure B, eqn 1) which also contain functionalities for specific incorporation of a Lewis acid.



(1)

The rigid platform we chose for our study was the *cis*-2-amino indanol skeleton, since oxazaborolidines derived from this ligand have shown good selectivity in reduction of prochiral ketones.[3] We have modified this basic framework and introduced tethers containing the Lewis basic site (**2**, **3**, **4** and **6**, Figure 1) as well as prepared ligands for control experiments (**5**, **7**, and **8**, Figure 1) to assess the effect of the additional coordination site in ketone reductions.[4]

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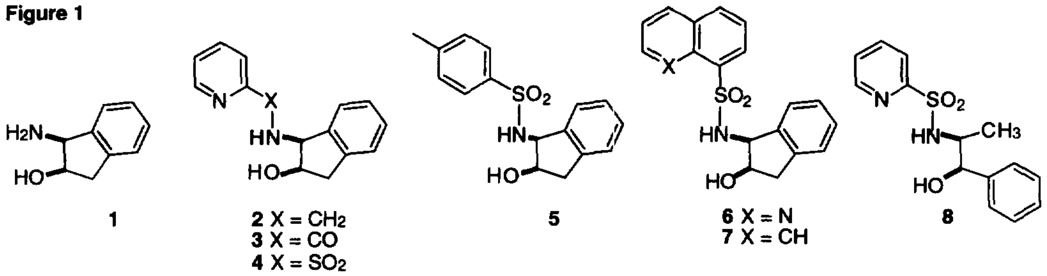
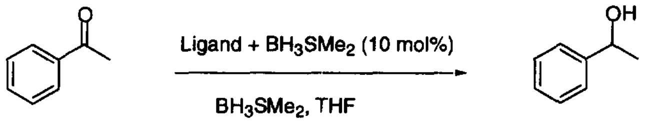
Figure 1



The reduction of acetophenone using ligands (**2-8**)[5] as well as the parent amino alcohol **1** are tabulated in the table below (eqn 2). In this study, the catalysts were prepared by treating the ligand with 4 equivalents of BH_3•DMS in the appropriate solvent at 40 °C for 4 hours. To this was added the borane reagent followed by the ketone over 2 hours and reaction monitored by TLC for completion. Several interesting trends emerge. The reduction using the parent amino indanol **1** was carried out as a reference[6] and showed high selectivity (entries 1 and 2). Use of ligand **2**, a modification of **1** containing a 2-pyridylmethyl group, led to a large decrease in ee as compared to the parent ligand **1** (compare entry 3 with entry 1).[7] Ligand **3**, with an sp^2 carbonyl as an attach point to the tether, gave similar levels of selectivity as **2** (entry 4). In contrast, incorporation of a 2-pyridylsulfonyl group, ligand **4**, led to much improved selectivity (entries 5 and 6). A brief optimization of the reduction by changing solvent, reducing agent, and temperature showed that the use of BH_3•DMS in THF at 40 °C provided for the highest selectivity (entry 6).[8] A control experiment using ligand **5** lacking an additional Lewis basic site, indicated that the pyridyl-nitrogen in **4** is important for obtaining selectivity (compare entry 6 with 7). Increasing the distance between the Lewis basic site and the oxazaborolidine ring (ligand **6**) led to a decrease in selectivity



(2)

Table Reduction of Acetophenone using Oxazaborolidines Derived from Ligands 1-8

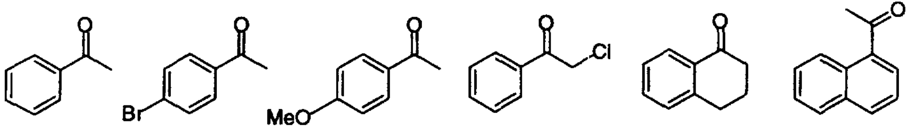
Entry	Ligand	Temp. °C	Yield, %[a]	% ee (Config)[b]
1	**1**	0	90	94 (R)
2	**1**	40	87	93 (R)
3	**2**	40	87	40 (R)
4	**3**	40	90	50 (R)
5	**4**	0	89	57 (R)
6	**4**	40	85	80 (R)
7	**5**	40	88	35 (R)
8	**6**	40	85	24 (R)
9	**7**	40	86	26 (R)
10	**8**	40	85	43 (R)

[a]Isolated yields after column purification. [b] ee's were determined by chiral HPLC. The absolute configuration was established by comparison to an authentic sample.

(compare entries 6 and 8; see entry 9 for a control experiment). Ligand **8**, a flexible analog of **4**, showed only moderate selectivity (entry 10). Having established that ligand **4** showed the best reaction profile, we examined the dependence of enantioselectivity on the catalyst stoichiometry. Increasing the catalyst loading showed only a modest improvement in selectivity (10 mol%, 80%ee; 20 mol%, 82% ee; 50 mol%, 87% ee; 100 mol%, 91%ee; average chemical yields of >85% for all experiments) and stoichiometric amounts of the ligand provided the best results.[9]

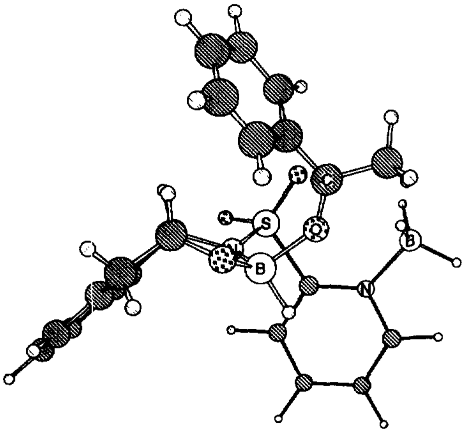
We have also investigated the efficacy of ligand **4** in the reduction of a variety of ketones and these results are shown in Figure 2. Thus reduction of a series of ketones using 10 mol% of ligand **4** under the established reaction conditions gave moderate to high selectivity and excellent chemical yields.

Figure 2



9	**10**	**11**	**12**	**13**	**14**
85 % Yield	91% Yield	90% Yield	92 % Yield	90 % Yield	83 % Yield
80 % ee	87% ee	77% ee	89 % ee	87 % ee	71 % ee
(R)	(R)	(R)	(S)	(R)	(R)

Results from control experiments using ligand **5** indicates that the pyridine nitrogen is important for selectivity. Additionally, reduction with ligand **6** also suggests that an optimal distance between the Lewis basic and acidic site is required for realizing high selectivity. It is conceivable that the borane could coordinate to oxazaborolidine oxygen or the sulfonyl oxygen. However, the low selectivity observed with ligands **5** and **7** suggests that is not likely. A tentative model accounting for the role of the additional Lewis basic site in **4** and the sense of stereoinduction is presented below.[10] In this model, the borane is bound to the pyridine nitrogen and the ketone is complexed to the Lewis acid using the lone pair *anti* to the large group. The carbonyl compound also orients itself anti to the indane portion of the chiral ligand for steric reasons. The attack of the hydride occurs through a nine-membered transition state on the *si* face of the complexed ketone. Experiments are underway to gain further insight into the role of the additional Lewis basic site and to use this strategy for other selective transformations.



Tentative Model for Selectivity

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5. Ligands **2-7** were prepared starting from **1**, and ligand **8** was synthesized from norephedrine by standard reaction sequences and they showed analytical characteristics consistent with their structure.
6. Ref. 3a,b, and c.
7. These reactions are unoptimized. We have tried a few other reaction conditions and solvents with all the modified ligands and the results in Table are the best at the present stage.
8. Several groups have noted the dependence of ee on temperature in oxazaborolidine reductions, see: Ref. 4b; Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255; Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465; Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625.

   Reduction of acetophenone at 50 °C using ligand **4** (10 mol%) and BH_3•DMS in THF gave the alcohol in 87% chemical yield and 58% ee.
9. Control experiments suggest that the non-catalyzed reductions at 40 °C may be responsible for lower selectivities. This is in accordance with the increase in selectivity with the amount of ligand used. i.,e. higher selectivity with 100 mol% catalyst.

   Typical Procedure: To a solution of **4** (0.1 mmol) in THF (10 mL) was added BH_3•DMS (2 M in THF; 0.4 mmol) slowly at 40 °C. The reaction mixture was stirred at this temperature for 2.5 h. Then BH_3•DMS (2M in THF, 1.0 mmol) was added. After stirring for an additional 1.5 h at 40 °C, a solution of acetophenone (1.0 mmol in 1 mL THF) was added over 2 h using a syringe pump. The reaction was monitored by TLC and after completion (~ 2 h), it was cooled to 0 °C and quenched carefully with methanol. Normal work up gave the product alcohol which after column chromatographic purification was analyzed by HPLC.
10. This is a very simplistic model based on the work of Corey (see ref. 2a) which explains the stereochemistry of the product. Refinement of our model by both experiment and computation are underway.