Stereocontrolled Catalytic Asymmetric Reduction of Ketones with Oxazaborolidines Derived from New Chiral Amino Alcohols

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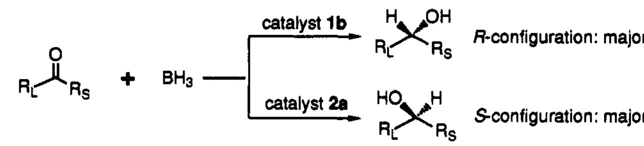
Received February 11, 1993

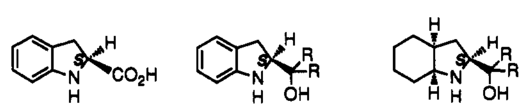
Summary: The highly stereocontrolled enantioselective reduction of ketones in the presence of catalytic amounts of new chiral (*S*)-β-amino alcohols **1** and **2** with borane in THF at −78 °C proceeds in high chemical and optical yields; secondary alcohols with the *R*-configuration are obtained in the presence of **1b**, but secondary alcohols with the *S*-configuration are obtained in the presence of **2a**.

In recent years, there have been many reports concerning asymmetric reductions of prochiral ketones with a variety of reagents prepared by mixing an aluminum or boron hydride and an enantioenriched diol or amino alcohol. Various types of chiral β-amino alcohols have been synthesized and tested as chiral ligands for the enantioselective reduction of ketones.[1-3] Although several efficient catalysts have been developed, most of the oxazaborolidines derived from L-amino acids[4-8] give access to only one enantiomer of the secondary alcohols; namely, (*S*)-amino alcohol–borane systems have been reported to give alcohols with the *R*-configuration. However, chiral auxiliaries that effect the highly sterecontrolled enantioselective reductions of ketones to alcohols of both the *R*- and *S*-configurations are desirable and important. Indeed, a few (*S*)- and (*R*)-chiral amino alcohols derived from L- and D-amino acids and from D-camphor have been reported to afford the corresponding *R*- and *S*-alcohols, respectively, in asymmetric reductions of ketones.[9,10] However, in contrast to L-amino acids which are readily available from natural sources, pure D-amino acids are often difficult to obtain.

In this paper, we describe a remarkable reversal of enantiofacial selectivity in the asymmetric reduction of ketones with borane when the new β-amino alcohol chiral auxiliaries **1** and **2** are used (see Scheme I). Amino alcohols **1** and **2** were readily prepared from (*S*)-indoline-2-carboxylic acid (**3**),[11] and their ability to effect enantioselective reductions of ketones was examined.

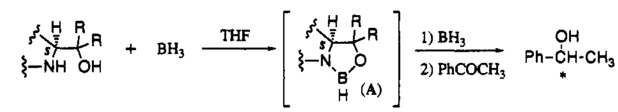
Scheme I





3 **1a**: R=R=H **1b**: R=R=Ph **2a**: R=R=H **2b**: R=R=Ph

Table I. Comparison of Asymmetric Reductions of Acetophenone with Borolidines of 1a, 1b, 2a, and 2b



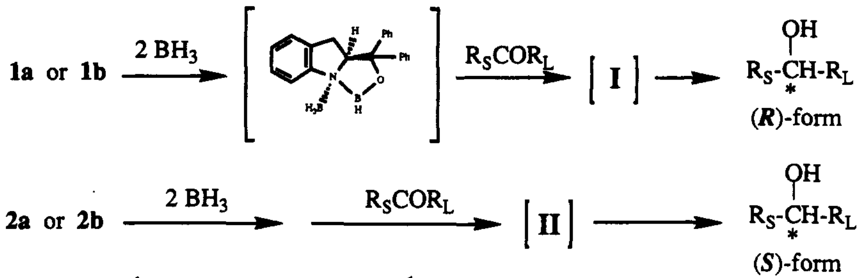
entry	amino alcohol	borolidine (A, equiv)	chemical yield[a] (%)	optical yield[b] (% ee)	config[c]
1	**1a**	0.1	96	82	*R*
2	**1b**	1.0	95	96	*R*
3	**1b**	0.1	94	96	*R*
4	**1b**	0.05	92	95	*R*
5	**1b**	0.025	90	82	*R*
6	**2a**	0.1	95	90	*S*
7	**2b**	0.1	96	49	*S*

[a] Isolated yield. [b] Determined by GC analysis of (−)-(menthyloxy)carbonyl derivatives on a capillary OV-17 column.[12] [c] Based on $[\alpha]_D$.[13]

When acetophenone was reduced with borane in the presence of a catalytic amount (0.1 equiv) of **1b**, (*R*)-1-phenylethanol was obtained in high optical yield (96% ee, Table I). In contrast, the same reduction in the presence of **2a** gave (*S*)-1-phenylethanol (90% ee, Table I). In a typical procedure, borane (3 mL of a 1 M solution in THF, 3 mmol) was added to the (*S*)-amino alcohol solution (1 mmol in THF, 4 mL) at −78 °C with stirring and the mixture then refluxed for 72 h. After solvent was removed, borane (10 mL of a 1 M solution in THF, 10 mmol) and ketone (10 mmol) were added. The reaction mixture was stirred at 25 °C for 10 min, and then 2 N HCl solution (5 mL) was added. The product was extracted with ether (10 mL × 3), washed with brine, dried over $MgSO_4$, and

(1) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469.
(2) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039.
(3) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 2615.
(4) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(5) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(6) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.
(7) Yoon, I. K.; Lee, S. W.; Park, C. S. *Tetrahedron Lett.* **1988**, *29*, 4453.
(8) Martens, J.; Dauelsberg, Ch.; Behnen, W.; Wallbaum, S. *Tetrahedron Asymmetry* **1992**, *3*, 347.
(9) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A.; Kaiwar, V. *Tetrahedron Lett.* **1990**, *31*, 2341.
(10) Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1311.
(11) Kim, Y. H.; Park, D. H.; Byun, I. S. *Heteroat. Chem.* **1992**, *3*, 51.
(12) Westly, J.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.
(13) Kanth, J. V. B.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1145.
(14) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(15) Davies, A. G.; White, A. M. *J. Chem. Soc.* **1952**, 3300.

0022-3263/93/1958-4511$04.00/0



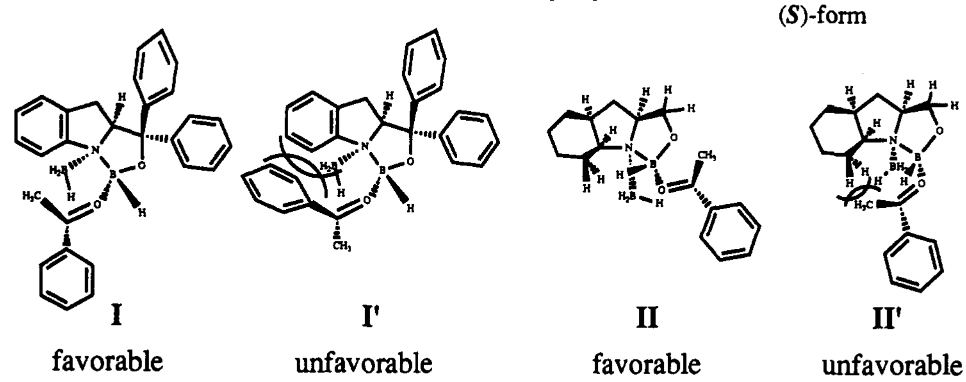


Figure 1. Possible models for oxazaborolidine reduction.

then concentrated to give the crude product. Further purification was accomplished by silica gel column chromatography or preparative silica gel TLC. All the products were identified by comparison of their ^{1}H-NMR and IR spectra with those of the known compounds. The absolute configurations of the secondary alcohols were assigned by comparison of their optical rotations with literature values. The optical purities of the alcohols were determined by GC analysis of the corresponding (menthyloxy)carbonyl esters or by their optical rotation values. The chiral β-amino alcohols **1b** and **2a** were recovered in over 90% yield after workup with dilute aqueous acid. The results of several stereocontrolled asymmetric reductions of acetophenone and the remarkable reversed enantiofacial selectivity are shown in Table I. It is interesting to note that the β-amino alcohol **1b** substituted with diphenyl groups at the α-position afforded the (*R*)-alcohol (96% ee), and the unsubstituted β-amino alcohol **2a** gave the (*S*)-alcohol (90% ee). The unsubstituted β-amino alcohol **1a** and disubstituted β-amino alcohol **2b** gave lower optical yields. In order to generalize the effects of the structures of the (*S*)-β-amino alcohols, various ketones were reduced to the corresponding secondary chiral alcohols with both **1b** and **2a**. The results obtained are summarized in Table II. In the presence of **1b**, all the ketones were reduced to the corresponding (*R*)-alcohols; in contrast, in the presence of **2a**, all the ketones were reduced to the (*S*)-alcohols. The optical and chemical yields were high for all the ketones except methyl propyl ketone (entries 9 and 10). Generally, asymmetric reductions of simple dialkyl ketones are well known to give reduced alcohols with low optical yields.[2] To our knowledge, **2a** is the first (*S*)-β-amino alcohol chiral auxiliary to give (*S*)-secondary alcohols with such high enantiomeric excesses.

Judging from the results in Table II, the structures of catalysts **1b** and **2a** must play an important role in controlling the asymmetric induction. Possible models and intermediates are illustrated in Figure 1. The steric effect of the diphenyl group in **1b** appears to be an important factor leading to the formation of favorable intermediate **I**, but in the case of **2a**, the steric effect of the cyclohexyl group appears to enforce the approach of the chiral auxiliary to the opposite face of the ketone for the formation of intermediate **II**. Intermediates **I** and **II** lead to the (*R*)- and (*S*)-phenylethyl alcohols, respectively. It has been well established by chemistry[4] and calculation[16] that coordination of the Lewis acid boron *anti* to the large group (R_L) of the ketone is favored. Transition state **II** may be more favorable than **II′** because of steric repulsion between the cyclohexane ring and the methyl group of the substrate.

Table II. Asymmetric Reduction of Ketones

entry	ketone	amino alcohol	alcohol: yield[a] (%)	alcohol: $[\alpha]_D$/deg (*c*, solvent)	alcohol: % ee (config[b])
1	$PhCOCH_3$	**1b**	93	+43.7 (2.5, $CHCl_3$)[13]	96 (*R*)[c]
2		**2a**	92	−40.9 (2.1, $CHCl_3$)[13]	90 (*S*)[c]
3	$PhCOC_2H_5$	**1b**	92	+42.3 (1.5, acetone)[13]	90 (*R*)
4		**2a**	94	−40.2 (1.5, acetone)[13]	85 (*S*)
5	$PhCH_2COCH_3$	**1b**	93	−38.4 (1.2, C_6H_6)[14]	92 (*R*)
6		**2a**	91	+36.0 (1.4, C_6H_6)[14]	86 (*S*)
7	α-tetralone	**1b**	91	−25.8 (2.2, $CHCl_3$)[14]	79 (*R*)
8		**2a**	92	+25.8 (3.1, $CHCl_3$)[14]	79 (*S*)
9	$C_3H_7COCH_3$	**1b**	92	−7.6 (neat)[15]	59 (*R*)
10		**2a**	90	+7.5 (neat)[15]	58 (*S*)

[a] Isolated yield. [b] Based on $[\alpha]_D$.[13] [c] Determined by GC analysis of (−)-(menthyloxy)carbonyl derivatives on a capillary OV-17 column.[12]

The structure of the β-amino alcohol chiral auxiliary plays an essential role in controlling the asymmetric reduction in carbonyl compounds, and either enantiomer of the secondary alcohol can be obtained by choosing the appropriate catalyst. Additional research will be required to better understand the operative stereochemical control element(s).

Acknowledgment. This work was supported by Center for Biofunctional Molecules and a grant from KOSEF.

(16) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 63.