Catalytic Asymmetric Borane Reduction of Prochiral Ketones by the Use of Chiral β-Diamines

Masatoshi Asami,* Shinsuke Sato, and Hiroyasu Watanabe
Department of Chemistry and Biotechnology, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501

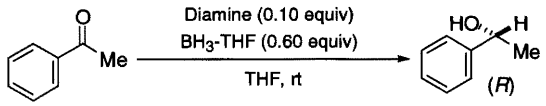
(Received June 7, 2000; CL-000552)

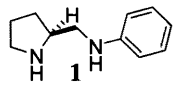
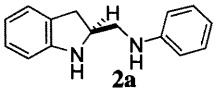
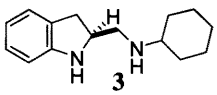
The catalytic asymmetric borane reduction of prochiral ketones was examined in the presence of chiral β-diamines. Chiral secondary alcohols were obtained with modest to high enantiomeric excesses (up to 92% ee) using (*S*)-2-[(*p*-trifluoromethyl)anilinomethyl]indoline.

The preparation of enantiomerically enriched secondary alcohols by catalytic enantioselective borane reduction of prochiral ketones has been studied extensively after the original studies of Itsuno *et al.*[1] and Corey *et al.*.[2] Usually the reaction is promoted effectively by the chiral catalyst generated by the reaction of borane and chiral amino alcohols,[3] sulfoximines,[4] phosphinamides,[5] or a mercapto alcohol.[6] There have been no reports using chiral β-diamines for the modification of borane to the best of our knowledge. Thus we examined the effectiveness of chiral β-diamines in the reaction as we have been studying asymmetric reactions by the use of chiral β-diamines derived from (*S*)-proline[7] or (*S*)-2-indolinecarboxylic acid.[8] Here we wish to report that the selectivity of the reaction largely depends on the structure of the diamine and high selectivity (up to 92% ee) was achieved in the case of aromatic ketones using (*S*)-2-[(*p*-trifluoromethyl)anilinomethyl]indoline.

In the first place, an enantioselective reduction of acetophenone was examined in the presence of a catalytic amount of (*S*)-2-(anilinomethyl)pyrrolidine (**1**), which was effective for the modification of lithium aluminum hydride in our previous work.[7a] The reaction was carried out in THF at room temperature using 0.10 equiv of **1** and 0.60 equiv of borane–THF complex. (*R*)-1-Phenylethanol was obtained after stirring for 16 h at room temperature in good yield (93%) with low ee (14% ee). When (*S*)-2-(anilinomethyl)indoline (**2a**)[9] was used instead of **1**, the reaction proceeded rapidly and the enantioselectivity was dramatically increased to 83% (*R*). However (*S*)-2-(cyclohexylaminomethyl)indoline (**3**)[9] required long reaction time and showed low selectivity (9% ee). Thus it is noteworthy that the aromatic rings on both nitrogen atoms of diamine are necessary to achieve both high catalytic activity and high selectivity (Table 1).

Table 1. Asymmetric reduction of acetophenone using chiral β-diamines

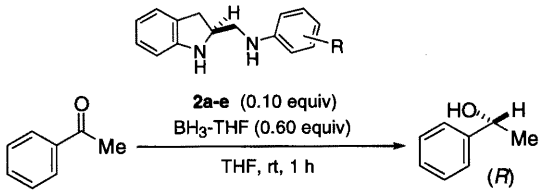


Diamine	Time / h	Yield / %[a]	ee / %[b]
 **1**	16	93	14
 **2a**	1	86	83
 **3**	16	87	9

[a]Isolated yield. [b]Determined by HPLC analysis.

Next, the substituent effect of the aromatic ring of the side chain of diamine **2**[9] was examined. The results are summarized in Table 2. The selectivity was decreased when sterically hindered diamine **2b** or **2c** was used (Entries 2,3). Diamine **2d** or **2e** having trifluoromethyl group(s) gave improved selectivity (Entries 4,5). The best result (88%, 92% ee) was obtained when the reaction was carried out at lower temperature (–15 °C) for 2 h using 0.15 equiv of **2d** and 1.0 equiv of borane–THF complex (Entry 6).

Table 2. Asymmetric reduction of acetophenone using **2a-e**

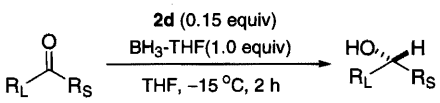


Entry	Diamine **2**	R	Yield / %[a]	ee / %[b]
1	**a**	-	86	83
2	**b**	2-Me	85	50
3	**c**	2,6-Me_2	84	27
4	**d**	4-CF_3	88	87
5	**e**	3,5-$(CF_3)_2$	90	84
6[c]	**d**	4-CF_3	88	92

[a]Isolated yield. [b]Determined by HPLC analysis. [c]The reaction was carried out at −15 °C for 2 h using 0.15 equiv of **2d** and 1.0 equiv of borane-THF complex.

Then asymmetric reduction of other prochiral ketones was carried out under the optimized reaction conditions. As shown in Table 3, relatively high enantioselectivities were achieved for aromatic ketones.

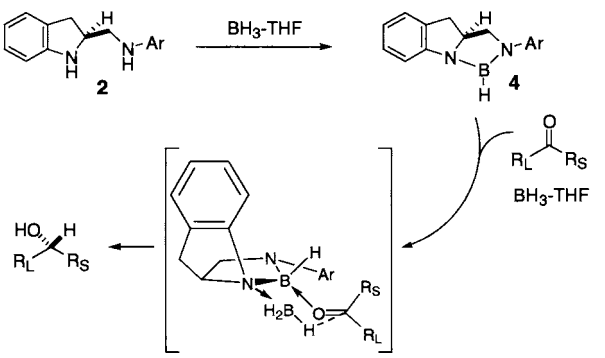
Table 3. Asymmetric reduction of prochiral ketones using **2d**



Ketone	Yield / %[a]	ee / % (Config.)[b]
Acetophenone	88	92(*R*)
o-Bromoacetophenone	96	91(*R*)
Phenacyl chloride	94	91(*S*)
Propiophenone	92	82(*R*)
α-Tetralone	92	81(*R*)
2-Octanone	93[c]	61[d](*R*)
Benzalacetone	80	59(*R*)

[a]Isolated yield. [b]Ee was determined by HPLC analysis and the absolute configuration was determined by specific rotation[5,7a,10] unless otherwise noted. [c]Isolated as benzoate. [d]Determined by HPLC of *p*-nitrobenzoate.

At present, we assume that diazaborolidine **4** generated by the reaction of diamine **2** and borane would be an actual catalyst of the reaction. After the coordination of BH_3 to the nitrogen atom of indoline ring of catalyst **4**, ketone approaches in a manner as shown in Scheme 1. Thus the alcohol having the configuration shown in Table 3 was obtained preferentially.



Scheme 1.

The catalytic activity of diamine **2** was increased and non-catalytic reaction was diminished, because Lewis aciditiy of boron atom in **4** was intensified by two aromatic rings on nitrogens. This effect was amplified by introducing trifluoromethyl group on the aromatic ring.

In summary, this study revealed that a novel chiral β-diamine derived from (*S*)-2-indolinecarboxylic acid, catalyzed asymmetric borane reduction of prochiral ketones effectively, and chiral secondary alcohols were obtained with high ee by the reduction of aromatic ketones.

References and Notes

1 S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc., Chem. Commun.*, **1983**, 469.

2 E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, **109**, 5551 (1987).

3 For reviews: L. Deloux and M. Srebnik, *Chem. Rev.*, **93**, 763 (1993); E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed. Engl.*, **37**, 1986 (1998); For recent examples: P. Pinho, D. Guijarro, and P. G. Andersson, *Tetrahedron*, **54**, 7897 (1998); M. Shimizu, K. Tsukamoto, T. Matsutani, and T. Fujisawa, *Tetrahedron*, **54**, 10265 (1998); T. Yanagi, K. Kikuchi, H. Takeuchi, T. Ishikawa, T. Nishimura, and T. Kamijo, *Chem. Lett.*, **1999**, 1203; C. Puigjaner, A. V. Ferran, A. Moyano, M. A. Pericàs, and A. Riera, *J. Org. Chem.*, **64**, 7902 (1999).

4 C. Bolm and M. Felder, *Tetrahedron Lett.*, **34**, 6041 (1993).

5 M. P. Gamble, A. R. C. Smith, and M. Wills, *J. Org. Chem.*, **63**, 6068 (1998).

6 T. K. Yang and D. S. Lee, *Tetrahedron: Asymmetry*, **10**, 405 (1999).

7 a) M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **51**, 1869 (1978). b) M. Asami, *Bull. Chem. Soc. Jpn.*, **63**, 721 (1990). c) M. Asami, K. Usui, S. Higuchi, and S. Inoue, *Chem. Lett.*, **1994**, 297. d) M. Asami, T. Ishizaki, and S. Inoue, *Tetrahedron: Asymmetry*, **5**, 793 (1994). e) M. Asami and S. Inoue, *Bull. Chem. Soc. Jpn.*, **70**, 1687 (1997). f) M. Asami, S. Sato, K. Honda, and S. Inoue, *Heterocycles*, **52**, 1029 (2000).

8 M. Asami, H. Watanabe, K. Honda, and S. Inoue, *Tetrahedron: Asymmetry*, **9**, 4165 (1998).

9 All new compounds are fully characterized by IR, 270 MHz ^{1}H-NMR, mass spectra and/or elemental analysis.

10 W. S. Huang, Q. S. Hu, and L. Pu, *J. Org. Chem.*, **64**, 7940 (1999).

11 Typical experimental procedure (Table 2, Entry 6) is as follows; Under an argon atmosphere borane–THF complex (1.0 M THF solution, 1.0 mL, 1.0 mmol) was added to a THF (0.5 mL) solution of **2d** (44 mg, 0.15 mmol) at 0 °C and stirring was continued for 0.5 h at the temperature. Then the reaction mixture was cooled to –15 °C and a THF (1.5 mL) solution of acetophenone (120 mg, 1.0 mmol) was added dropwise *via* syringe over two hours. The reaction mixture was stirred at the temperature for further two hours. After an addition of 1 M HCl at the temperature, the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was extracted twice with ether, and the combined organic layers were washed with 1 M HCl, water, and brine, successively. The organic layer was dried over anhyd $MgSO_4$ and the solvent was removed *in vacuo*. The resulting crude product was purified by silica-gel column chromatography (hexane:ether = 3:1), followed by bulb-to-bulb distillation (170 °C/15 mmHg) to give (*R*)-1-phenylethanol (108 mg, 88%, $[\alpha]_D^{20}$ +52.5 (*c* 1.00, $CHCl_3$)). The ee was determined by HPLC analysis using a Daicel Chiralcel OD-H column to be 92% ee.