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Catalytic Asymmetric Borane Reduction of Prochiral Ketones by Using (*S*)-2-(Anilinomethyl)pyrrolidine

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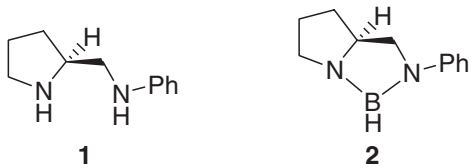
Catalytic asymmetric borane reduction of prochiral ketones was examined in the presence of (*S*)-2-(anilinomethyl)-pyrrolidine. Chiral secondary alcohols were obtained with moderate to high enantiomeric excesses (up to 96% ee).

Asymmetric synthesis of enantiomerically enriched secondary alcohols has been widely studied, because of their significance as intermediates in the syntheses of natural products and pharmaceuticals. Enantioselective borane reduction of prochiral ketones to chiral secondary alcohols using various chiral amino alcohols has been studied extensively,[1] since Itsuno et al. reported asymmetric reduction of aromatic ketones in the presence of 1.25 molar amount of a chiral amino alcohol derived from (*S*)-valine.[2] In 1987, Corey et al. reported a catalytic borane reduction of prochiral ketones with high enantioselectivity by using oxazaborolidine prepared from borane and (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine.[3] Other chiral catalysts, such as sulfoximines,[4] phosphinamides,[5,6] a mercapto alcohol,[7] sulfonamides,[8,9] and BINOL derivatives,[10] have also been employed for asymmetric borane reduction.

On the other hand, we have been working on asymmetric syntheses using chiral β-diamines prepared from (*S*)-proline[11,12] or (*S*)-indoline-2-carboxylic acid.[12,13] In 2000, we reported the asymmetric borane reduction of prochiral ketones using chiral β-diamine catalysts.[12] Although the reduction of acetophenone in the presence of a catalytic amount of (*S*)-2-(anilinomethyl)indoline gave (*R*)-1-phenylethanol with good enantioselectivity (83% ee), selectivity was low (14% ee) when (*S*)-2-(anilinomethyl)pyrrolidine (**1**) was employed. As **1** is commercially available and easily prepared from a natural amino acid, (*S*)-proline, it would be advantageous if high enantioselectivity could be achieved using **1**. We anticipated that the low selectivity was caused by incomplete formation of the actual catalyst, diazaborolidine **2**, from **1** and borane in situ (Scheme 1). Consequently, we examined the reaction conditions for each step, namely, the formation of **2** and the asymmetric reduction of ketones. As it turns out, we found that selectivity was dramatically increased by carrying out the preparation of **2** in refluxing THF, followed by reduction of the substrates at room temperature, and we have reported the preliminary results.[14,15] In this paper, we report the results of optimization of the reaction conditions in detail and the asymmetric reduction of various prochiral ketones.



Scheme 1. Structures of (*S*)-2-(anilinomethyl)pyrrolidine (**1**) and diazaborolidine **2**.

Results and Discussion

As mentioned in the introduction, the formation of diazaborolidine **2**, which acts as a chiral Lewis acid catalyst, is important to achieve high enantioselectivity in the reduction. In our previous work,[12b] we confirmed by ^{11}B NMR spectroscopy that diazaborolidine was formed from the reaction of (*S*)-2-(anilinomethyl)indoline and borane in THF at 0 °C, whereas diazaborolidine **2** was not observed when (*S*)-2-(anilinomethyl)pyrrolidine (**1**) was used under the same reaction conditions. Thus, the reaction conditions for the formation of **2** from **1** and borane were investigated first. Although Quirion et al. have prepared some diazaborolidines in dimethyl sulfide at 100 °C,[8] we examined the preparation of diazaborolidine **2** in situ in refluxing THF for 45 min after borane (6.0 molar amount) was added to a THF solution of **1** (1.0 molar amount) at 0 °C. ^{11}B NMR spectroscopy was performed after removal of the solvent and excess borane under reduced pressure. The spectrum of the resulting residue in benzene-d_6 showed a broad peak at +29.5 ppm from BF_3-OEt_2, which was assigned to diazaborolidine **2**. Thus, it became apparent that **2** could be formed under the forced reaction conditions using diamine **1**.

Next, the effects of reflux time of the reaction of diamine **1** and borane on the enantioselectivity were examined using acetophenone. After refluxing a mixture of **1** (0.1 molar amount) and borane (1.1 molar amount) in THF for 20 min, acetophenone (1.0 molar amount) was added to the resulting solution over 2 h at 0 °C, and stirring was continued for 2 h at room temperature. (*R*)-1-Phenylethanol was obtained in 95% yield with 69% ee (Table 1, Entry 1), which indicates that the formation of **2** as a chiral Lewis acid catalyst is essential to achieve high enantioselectivity. The selectivity was further improved to 75% ee by refluxing the mixture of **1** and borane for 45 min (Entries 2–4), which is higher than that obtained with a diazaborolidine prepared from borane and (*S*)-2-(*N*-

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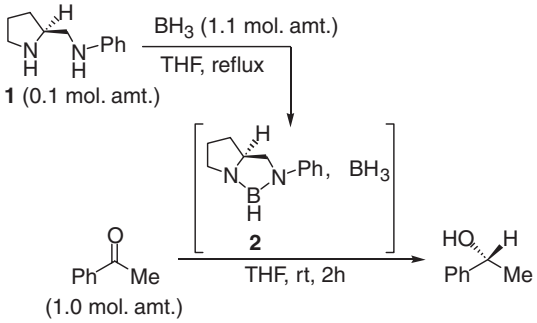
Table 1. Effect of Reflux Time of Diamine **1** and Borane on Enantioselectivity



Entry	Reflux time/min	Yield/%[a]	ee/%[b]
1	20	95	69
2	30	86	71
3	40	88	71
4	45	88	75
5	50	80	75
6	55	82	73

a) Isolated yield. b) ee was determined by HPLC analysis.

Table 2. Effect of Reduction Temperature of Acetophenone on Enantioselectivity

Entry	Temperature/°C	Yield/%[a]	ee/%[b]
1	40	87	69
2	30	85	72
3	rt	88	75
4	0	86	74
5	−15	86	69
6	−30	60	48

a) Isolated yield. b) ee was determined by HPLC analysis.

tosylaminomethyl)piperidine reported by Quirion et al. (72% ee).[8] However, yield and selectivity decreased when the reflux time was longer than 45 min (Entries 5 and 6). These results imply that **2** is formed efficiently by refluxing for 45 min.

Next, the effect of the reduction temperature of acetophenone was examined. Asymmetric reduction of acetophenone (1.0 molar amount) was carried out at various temperatures after a mixture of **1** (0.1 molar amount) and borane (1.1 molar amount) was refluxed in THF for 45 min and acetophenone was added to the solution over 2 h at 0 °C. The results are summarized in Table 2. The best selectivity and yield were obtained when the reduction was carried out at room temperature (Table 2, Entry 3). When the reduction was carried out at 40 or 30 °C, the enantiomeric excess decreased to 69 or 72% ee, respectively (Entries 1 and 2). Reduction at a temperature lower than room temperature resulted in the production of (*R*)-1-phenylethanol with lower ee (Entries 4–6).

Next, the effect of the amounts of **1** and borane was examined. Diamine **1** was added in the range of 0.10 to 0.30 molar amount and borane was added in the range of 1.10 to 1.30 molar amount based on acetophenone. The results are summarized in Table 3. The enantioselectivity improved by increasing the amounts of **1** and borane (Entries 2–5). The best result (95% yield, 85% ee) was obtained when 0.25 molar amount of **1** and 1.25 molar amount of borane were employed

Table 3. Effect of Amounts of Diamine **1** and Borane on Enantioselectivity

Entry	**1**/mol amt.	BH_3/mol amt.	Yield/%[a]	ee/%[b]
1	0.10	1.10	88	75
2	0.15	1.15	86	78
3	0.20	1.20	97	81
4	0.25	1.25	95	85
5	0.30	1.30	86	85
6	0.10	1.25	91	59

a) Isolated yield. b) ee was determined by HPLC analysis.

Table 4. Effect of Solvents on Enantioselectivity

Entry	Solvent	Yield/%[a]	ee/%[b]
1	THF	95	85
2	Benzene	87	73
3	Toluene	84	73
4	Cyclohexane	79	73
5	Dichloromethane	78	53
6[c]	THF	86	93

a) Isolated yield. b) ee was determined by HPLC analysis. c) Acetophenone was added at room temperature.

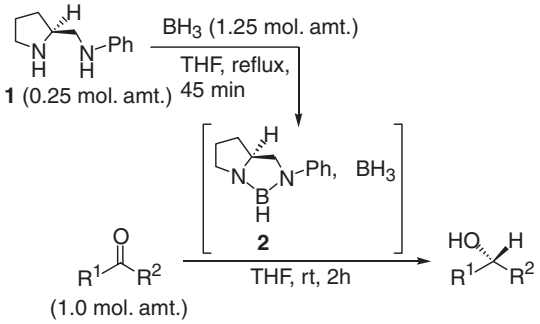
(Entry 4). The use of 0.10 molar amount of **1** and 1.25 molar amount of borane resulted in a lower ee (Entry 6).

The effect of solvent was also examined. The reduction was carried out in various solvents in the presence of 0.25 molar amount of **1** and 1.25 molar amount of borane. The results are summarized in Table 4. The best result (95% yield, 85% ee) was obtained when THF was used as the solvent (Entry 1). The selectivity of the reaction decreased to 73% ee in benzene, toluene, or cyclohexane (Entries 2–4), and 53% ee in dichloromethane (Entry 5). Furthermore, acetophenone was added to the THF solution at room temperature, instead of 0 °C, over 2 h, because the selectivity of the reduction at room temperature was greater than that at 0 °C (Table 2, Entries 3 and 4). As shown in Entry 6, the enantioselectivity improved to 93% ee.

Finally, the reaction was applied to other prochiral ketones using the optimized reaction conditions in order to examine the usefulness of **2** as a catalyst. As shown in Table 5, good to high enantioselectivities were achieved for aromatic ketones (74–96% ee, Entry 1–9). In particular, the reduction of phenacyl chloride showed excellent selectivity (96% ee, Entry 1). An aliphatic ketone, 3,3-dimethyl-2-butanone, was also reduced to a chiral secondary alcohol with high ee (95% ee, Entry 10). Moderate selectivities were obtained in the cases of other aliphatic ketones (51 and 47% ee, Entries 11 and 12, respectively) and an α,β-unsaturated ketone (67% ee, Entry 13).

Scheme 2 shows the stereochemical model that is proposed for the asymmetric borane reduction with catalyst **2**. At room temperature, the prochiral ketone is reduced via the six-membered transition state **TS-1**, in which the larger substituent of the ketone occupies the equatorial position to yield the major enantiomer with a high ee. However, the less preferred transition state **TS-2** can form at higher temperatures, which would cause a decrease in the enantioselectivity. On the other hand, at lower temperatures, a noncatalytic reaction probably occurs,

Table 5. Asymmetric Reduction of Prochiral Ketones Using Diamine **1**



Entry	Ketone	Yield/%[a)]	ee/% (Config.)[b)]
1	Phenacyl chloride	89	96(*S*)
2	3,4-Dihydro-1(2*H*)-naphthalenone	96	93(*R*)
3	Acetophenone	86	93(*R*)
4	Propiophenone	93	88(*R*)
5	2-Methoxyacetophenone	81	87(*S*)
6	1-Acetonaphthone	96	82(*R*)
7	1-Indanone	89	81(*R*)
8	2-Bromoacetophenone	90	78(*R*)
9	2-(Dimethylamino)-acetophenone	61	74(*S*)
10	3,3-Dimethyl-2-butanone	91[c)]	95[d)](*R*)
11	4-Phenyl-2-butanone	98	51(*R*)
12	2-Octanone	93[e)]	47[d)](*R*)
13	Benzalacetone	75	67(*R*)

a) Isolated yield. b) ee was determined by HPLC analysis, and the absolute configuration was determined by specific rotation.[5,16–19] c) Determined by GC analysis. d) Determined by HPLC analysis of *p*-nitrobenzoate. e) Isolated as *p*-nitrobenzoate.

because the regeneration of **2** is slower, which leads to a decrease in the rate of catalytic reaction to yield the major enantiomer with a low ee.

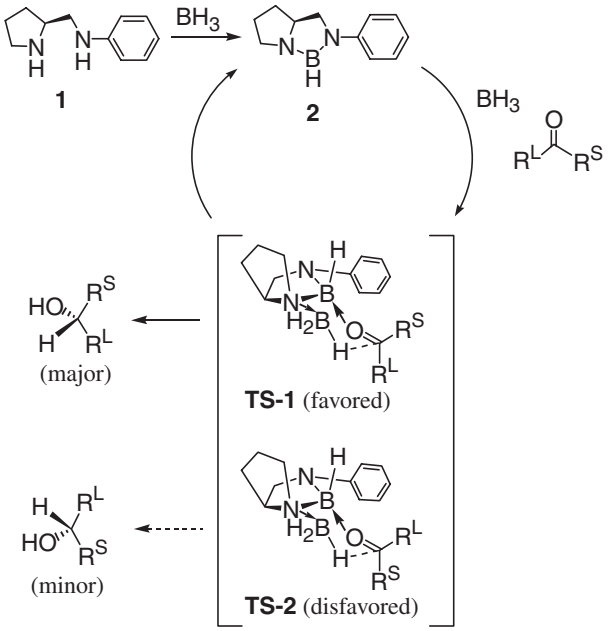
Conclusion

The catalytic asymmetric borane reduction of prochiral ketones using (*S*)-2-(anilinomethyl)pyrrolidine (**1**) was studied. It was found that diazaborolidine **2**, which acted as an efficient catalyst of the reduction, was prepared efficiently from **1** and borane by the examination of the reaction conditions. Using catalyst **2**, chiral secondary alcohols were obtained with moderate to high enantiomeric excesses from prochiral ketones under the optimized reaction conditions.

Experimental

General. Most manipulations were carried out under an atmosphere of argon. Solvents were dried and purified in the usual manner. (*S*)-2-(Anilinomethyl)pyrrolidine,[17] 2-(dimethylamino)-acetophenone,[18] and 2-methoxyacetophenone[19] were prepared in a manner reported previously.

^{1}H and ^{11}B NMR spectra were obtained on a JEOL JNM-EX-270 spectrometer using $CDCl_3$ and C_6D_6 as solvents, respectively. ^{1}H and ^{11}B NMR chemical shift values are given in ppm relative to Me_4Si and BF_3-OEt_2, respectively. Specific rotations were measured on a JASCO P-1010 polarimeter. High-performance liquid chromatography (HPLC) analyses were carried out with JASCO instruments (pump, PU-2080 Plus; detector, UV-2075 plus) and TOSOH instruments (pump, CCPS; detector, UV-8020). Gas chromatography (GC) analysis was carried out on a SHIMADZU GC-14B. Thin layer chromatography (TLC) analyses were carried out on silica-gel 60 F_{254}-coated plates (E. Merck). Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm × 20 cm). A syringe pump (Furue Science Co., Ltd., Micro Feeder JP-V) was used for the asymmetric borane reduction of prochiral ketones.



Scheme 2. Stereochemical model for asymmetric borane reduction with diazaborolidine catalyst **2**.

^{11}B NMR Measurement of Diazaborolidine 2. To a THF (0.5 mL) solution of (*S*)-2-(anilinomethyl)pyrrolidine (**1**) (35.6 mg, 0.2 mmol) was added borane–dimethyl sulfide complex (0.11 mL, 1.2 mmol) at 0 °C and stirring was continued for 45 min under reflux. The solvent and excess borane were removed under reduced pressure. ^{11}B NMR spectrum of the resulting residue was obtained in C_6D_6. A broad peak corresponding to diazaborolidine **2** was observed at +29.5 ppm from BF_3-OEt_2.

The Asymmetric Reduction of Acetophenone Catalyzed by (*S*)-2-(Anilinomethyl)pyrrolidine (1): Typical Procedure (Table 4, Entry 6). To a THF (1.25 mL) solution of (*S*)-2-(anilinomethyl)pyrrolidine (**1**) (88.8 mg, 0.5 mmol) was added borane–dimethyl sulfide complex (0.24 mL, 2.5 mmol) at 0 °C, and the mixture was refluxed for 45 min with stirring. After the mixture was cooled to room temperature, acetophenone (0.67 mol dm^{-3} THF solution, 3.0 mL, 2.0 mmol) was added dropwise via syringe pump over 2 h, and stirring at room temperature was continued for 2 h. Then, 1 mol dm^{-3} aqueous HCl was added at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. The aqueous layer was separated and extracted with ether, and the combined organic layer was washed with 1 mol dm^{-3} aqueous HCl, water, and brine successively. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting crude product was purified by preparative TLC (chloroform) to give

(*R*)-1-phenylethanol (210 mg, 86%). The ee was determined to be 93% by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 × 0.46 cm i.d.); eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 17.5 min for major peak, 21.0 min for minor peak. Asymmetric reduction of the other ketones was performed in a similar manner. The ee's were determined by HPLC using Daicel Chiralcel OD-H (25 × 0.46 cm i.d.) or Waters Optipak TA (30 × 0.39 cm i.d.) columns. 2-Chloro-1-phenylethanol: OD-H; eluent, 3% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 33.7 min for major peak, 38.8 min for minor peak. 1,2,3,4-Tetrahydro-1-naphthol: OD-H; eluent, 2% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 28.4 min for minor peak, 30.7 min for major peak. 1-Phenyl-1-propanol: OD-H; eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 15.5 min for major peak, 17.0 min for minor peak. 2-Methoxy-1-phenylethanol: OD-H; eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 26.8 min for major peak, 30.6 min for minor peak. 1-(1-Naphthyl)ethanol: OD-H; eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 31.5 min for minor peak, 57.0 min for major peak. 1-Indanol: OD-H; eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 18.9 min for minor peak, 21.0 min for major peak. 1-(*o*-Bromophenyl)ethanol: OD-H; eluent, 2% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 24.7 min for major peak, 27.7 min for minor peak. 2-Dimethylamino-1-phenylethanol: OD-H; eluent, 20% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 11.3 min for minor peak, 13.9 min for major peak. 3,3-Dimethyl-2-butanol (as *p*-nitrobenzoate): OD-H; eluent, 0.1% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 28.2 min for minor peak, 31.1 min for major peak. 4-Phenyl-2-butanol: OD-H; eluent, 5% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 21.2 min for major peak, 30.4 min for minor peak. 2-Octanol (as *p*-nitrobenzoate): TA; eluent, 0.1% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 21.5 min for minor peak, 29.9 min for major peak. 4-Phenyl-3-buten-2-ol: OD-H; eluent, 10% 2-propanol in hexane; flow rate, 0.5 mL min^{-1}; t_R, 16.5 min for major peak, 25.2 min for minor peak.

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