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Catalytic asymmetric borane reduction of prochiral ketones by the use of diazaborolidine catalysts prepared from chiral β-diamines

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Abstract

The catalytic asymmetric borane reduction of prochiral ketones was examined in the presence of chiral diazaborolidine catalysts prepared in situ from chiral β-diamines and borane. Chiral secondary alcohols were obtained with modest to high enantiomeric excesses (up to 92% ee) using (*S*)-2-[(4-trifluoromethyl)anilinomethyl]indoline **2f**.

1. Introduction

An asymmetric synthesis of enantiomerically enriched secondary alcohols has been extensively studied as chiral secondary alcohols are important synthetic intermediates for various other functionalities such as halide, amine, ester, and ether, and involved in many naturally occurring compounds. A catalytic enantioselective borane reduction of prochiral ketones using oxazaborolidine catalysts prepared by the reaction of borane or boronic acid and chiral amino alcohols is one of the most useful methods for the preparation of chiral secondary alcohols,[1] and a considerable number of studies have been reported over the decade after the original studies of Itsuno et al.[2] and Corey et al.[3] Other chiral borane catalysts prepared from chiral sulfoximines,[4] phosphinamides,[5] or a mercapto alcohol[6] were also reported to be effective for the reaction.

We have been working on asymmetric synthesis using chiral β-diamines prepared from (*S*)-proline[7] or (*S*)-indoline-2-carboxylic acid[8] and reported highly stereoselective asymmetric reactions using them. We then examined the effectiveness of chiral β-diamines for the modification of borane and reported that (*S*)-2-[(4-trifluoromethyl)anilinomethyl]indoline **2f** showed relatively high selectivity in asymmetric reduction of prochiral ketones.[9] Here we describe the results in detail.

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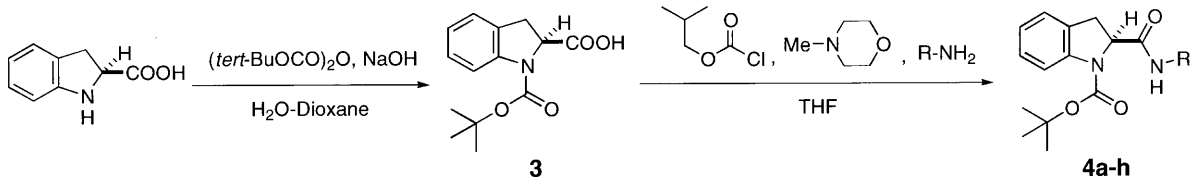
2. Results and discussion

Chiral β-diamines, (*S*)-2-(*N*-substituted aminomethyl)indoline **2a–h**, were prepared as shown in Scheme 1 starting from commercially available homochiral amino acid, (*S*)-indoline-2-carboxylic acid. After protection of the amino group with the *tert*-butoxycarbonyl group, (*S*)-*N*-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **3** was coupled with amines via mixed acid anhydride to afford corresponding amides **4a–h**. Homochiral β-diamines **2a–h** were obtained by removal of the *tert*-butoxycarbonyl group in **4a–h** by trifluoroacetic acid in dichloromethane, followed by reduction of *N*-substituted (*S*)-indoline-2-carboxamide **5a–h** with lithium aluminum hydride or borane–THF complex.

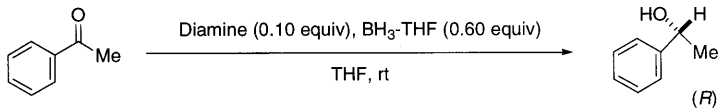


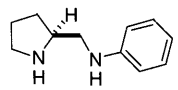
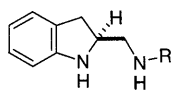
2, 4, 5	R
a	C_6H_5
b	*c*-C_6H_{11}
c	2-MeC_6H_4
d	2,6-$Me_2C_6H_3$
e	4-$MeOC_6H_4$
f	4-$CF_3C_6H_4$
g	3,5-$(CF_3)_2C_6H_3$
h	4-$NO_2C_6H_4$

Scheme 1.

In the first place, an enantioselective reduction of acetophenone was carried out using (*S*)-2-(anilinomethyl)pyrrolidine **1**, which was effective for the modification of lithium aluminum hydride in our previous work.[7a] A THF solution of acetophenone was added dropwise to the mixture of 0.60 equiv. of borane–THF complex in THF in the presence of 0.10 equiv. of **1** over 1 h period at room temperature, and stirring was continued for 16 h at the temperature. (*R*)-1-Phenylethanol was obtained in 93% yield with 14% ee (*R*) (Table 1, entry 1). The enantioselectivity was dramatically increased to 83% (*R*) when (*S*)-2-(anilinomethyl)indoline **2a** was used (Table 1, entry 2). However, (*S*)-2-(cyclohexylaminomethyl)indoline **2b** showed low selectivity (9% ee (*R*)) (Table 1, entry 3). Therefore, it turned out that aromatic rings on both nitrogen atoms of β-diamine **2** are necessary to achieve high selectivity. Next, the effect of the substituent on the aromatic ring of the side chain of **2a** upon the selectivity was examined using β-diamines **2c–h** derived from (*S*)-indoline-2-carboxylic acid and substituted anilines. In the first place, a steric effect was examined using sterically hindered β-diamine **2c** or **2d**. The enantioselectivity was decreased to 50 and 27% ee, respectively (Table 1, entries 4 and 5). Next, β-diamines **2e–h** were examined to evaluate electronic effects. The electron-withdrawing trifluoromethyl group was effective in increasing the selectivity, while the electron-donating methoxy group substantially decreased the selectivity (Table 1, entries 6–8). Another electron-withdrawing group, nitro, did not improve the selectivity (Table 1, entry 9).

Table 1
Asymmetric reduction of acetophenone using chiral β-diamine



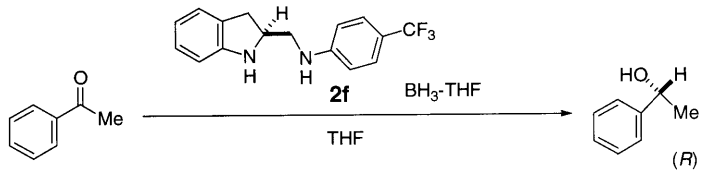
Entry	Diamine		R	Time (h)	Yield (%)[a]	Ee (%)[b]
1		**1**	-	16	93	14
2		**2a**	C_6H_5	1	86	83
3		**2b**	c-C_6H_{11}	16	87	9
4		**2c**	2-MeC_6H_4	1	85	50
5		**2d**	2,6-$Me_2C_6H_3$	1	84	27
6		**2e**	4-$MeOC_6H_4$	1	84	27
7		**2f**	4-$CF_3C_6H_4$	1	88	87
8		**2g**	3,5-$(CF_3)_2C_6H_3$	1	90	84
9		**2h**	4-$NO_2C_6H_4$	1	89	71

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

Next, the reaction was carried out under several reaction conditions to improve the selectivity using 0.1 equiv. of **2f**. The selectivity was improved when the reaction was conducted at a lower temperature (0°C), but the yield was decreased slightly (Table 2, entry 2). High selectivity and good yield were achieved by adding a THF solution of acetophenone during 2 h to a THF solution of **2f** and 1.0 equiv. of borane–THF complex (Table 2, entries 3 and 4). The selectivity was further improved to 92% ee by using 0.15 equiv. of **2f** at −15°C (Table 2, entry 6).

Then, the reaction was applied to other prochiral ketones to examine the generality of the new catalyst **2f**. The results, obtained under the optimized reaction conditions (Table 2, entry 6) are summarized in Table 3. High enantioselectivities were achieved for aromatic ketones (Table 3, entries 1–7) and modest selectivity was obtained in the cases of aliphatic ketones or α,β-unsaturated ketones (Table 3, entries 8 and 9).

Table 2
Examinations of reaction conditions

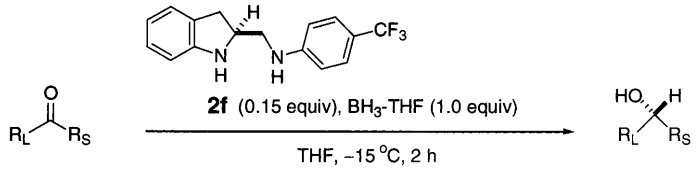


Entry	Temp. (°C)	**2f** (equiv.)	BH_3–THF (equiv.)	Time (h)	Yield (%)[a]	Ee (%)[b]
1	Rt	0.10	0.60	1[c]	88	87
2	0	0.10	0.60	1[c]	77	89
3	0	0.10	0.60	2[d]	82	90
4	0	0.10	1.0	2[d]	87	90
5	−15	0.10	1.0	2[d]	86	91
6	−15	0.15	1.0	2[d]	88	92
7	−30	0.10	1.0	2[d]	85	35

[a] Isolated yield.
[b] Determined by HPLC.
[c] Acetophenone was added to a THF solution of borane and **2f** during 1 h and then the reaction mixture was stirred for 1 h.
[d] Acetophenone was added to a THF solution of borane and **2f** during 2 h and then the reaction mixture was stirred for 2 h.

It is known that an oxazaborolidine, derived from chiral amino alcohol and borane, plays a crucial role as a chiral Lewis acid catalyst[1b] in the asymmetric borane reduction using a catalytic amount of chiral amino alcohol. In the present reaction, we anticipated that diazaborolidine **6** would also be formed in situ by the reaction of a β-diamine and borane and acts as a chiral Lewis acid catalyst. To confirm the formation of diazaborolidine **6**, a ^{11}B NMR study was carried out using β-diamine **1**, **2a**, **2b** and **2f**. To a THF solution of the β-diamine was added a THF solution of borane–THF complex (6 equiv.) and the solution was stirred for 30 min at 0°C. Then the solvent and excess borane were removed under reduced pressure. In the case of β-diamine **2a** or **2f**, a ^{11}B NMR spectrum of the resulting residue in benzene-d_6 showed the broad peak at +26 or +24 ppm from $BF_3{\cdot}OEt_2$ (external standard), respectively. The signal could be assigned to **6** based on the ^{11}B NMR spectrum of diazaborolidine in the literature.[11] On the other hand, the corresponding peak was not observed in the region in the case of **1** or **2b**. Therefore, the aromatic rings on both nitrogen atoms of β-diamine **2** were necessary to form the effective diazaborolidine catalyst **6** by the reaction of **2** and BH_3 at 0°C. The stereochemical cause of the reduction by **6** was rationalized on the basis of the configurations of the resulting alcohols as follows. Namely, after the coordination of BH_3 to the nitrogen atom of the indoline ring of catalyst **6**, ketone approaches the catalyst **6**–borane complex in a manner depicted in Scheme 2. The catalytic activity of diazaborolidine **6** was increased and noncatalytic borane reduction was diminished by introducing trifluoromethyl group (electron-withdrawing group) on the aromatic ring to afford the alcohol in higher ee (Table 1, entries 7 and 8). The catalytic

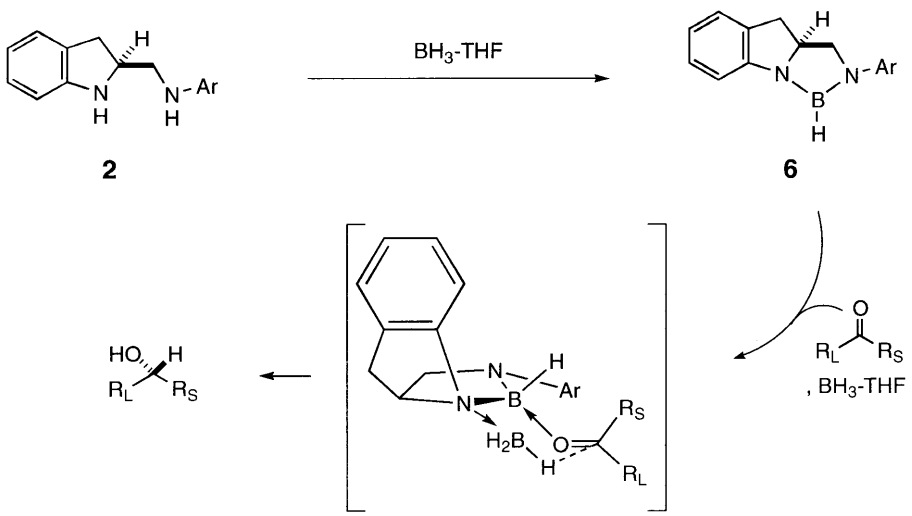
Table 3
Asymmetric reduction of prochiral ketones using **2f**



Entry	Ketone	Yield (%)[a]	Ee (%)[b]	$[\alpha]_D^{20}$	Config.[b]
1	Acetophenone	88	92	+52.5 (*c* 1.00, $CHCl_3$)	*R*
2	2′-Bromoacetophenone	96	91	+49.1 (*c* 0.99, $CHCl_3$)	*R*
3	Phenacyl chloride	94	91	+48.1 (*c* 1.00, cyclohexane)	*S*
4	1′-Acetonaphthone	94	88	+67.8 (*c* 1.00, MeOH)	*R*
5	Propiophenone	92	82	+39.4 (*c* 0.99, $CHCl_3$)	*R*
6	1-Tetralone	92	81	−27.0 (*c* 1.00, $CHCl_3$)	*R*
7	1-Indanone	90	80	−23.4 (*c* 0.99, $CHCl_3$)	*R*
8	2-Octanone	93[c]	61[d]	−6.3 (*c* 1.01, EtOH)	*R*
9	Benzalacetone	80	59	+18.3 (*c* 1.07, $CHCl_3$)	*R*

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

activity of **6** was decreased by introducing a methoxy group (electron-donating group) on the aromatic ring (Table 1, entry 6) or by the steric hindrance around the boron atom of **6** (Table 1, entries 4 and 5) to give a substantial amount of racemic alcohol via noncatalytic reaction.



Scheme 2.

3. Conclusion

In summary, we have studied catalytic asymmetric borane reductions of prochiral ketones using chiral β-diamines. It was found that diazaborolidines were generated in situ from chiral β-diamine and borane, which catalyzed the reaction effectively, and chiral secondary alcohols were obtained with good to high ee's. Furthermore, this study has shown that the reactivity and the selectivity of the reaction were affected significantly by steric and electronic effects of the substituent of the catalyst.

4. Experimental

4.1. General

Most manipulations were carried out under an atmosphere of argon. Solvents were dried and purified in the usual manner.

Melting points were obtained on a Büchi 535 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000. ^{1}H and ^{11}B NMR spectra were measured with a Jeol JNM-EX-270 spectrometer, using tetramethylsilane as the internal standard for ^{1}H and trifluoroborane-etherate as the external standard for ^{11}B. Mass spectra (MS) were obtained on a Jeol JMS SX102QQ mass spectrometer. Specific rotations were measured on a Horiba SEPA-200 polarimeter in the indicated solvent. HPLC analyses were carried out with Tosoh instruments (pump, CCPS; detector, UV-8020). TLC analyses were carried out on silica-gel 60 F_{254}-coated plates (E. Merck). Column chromatography was carried out with Wakogel C-200 gel unless otherwise described. Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20×20 cm).

4.2. Preparation of (S)-N-(tert-butoxycarbonyl)indoline-2-carboxylic acid **3**

To (*S*)-indoline-2-carboxylic acid (3.26 g, 20 mmol) in dioxane (20 ml) and 0.5 M NaOH (40 ml) was added slowly di-*tert*-butyl dicarbonate (4.80 g, 22 mmol) in dioxane (20 ml) at 0°C and stirring was continued for 16 h at room temperature. Hexane (20 ml) was added to the reaction mixture and the aqueous layer was separated. Then, the aqueous layer was acidified with saturated citric acid and extracted three times with ethyl acetate. The organic layer was washed with brine, and dried over anhyd. sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by recrystallization from ethyl acetate and hexane to give (*S*)-*N*-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **3** (4.59 g, 87%) (mp 124.1–124.8°C). $[\alpha]_D^{20}$ −77.3 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1708 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.43 (s, 9H, $OC(CH_3)_3$), 3.01 (d, $J=16.5$ Hz, 1H, 1×H-3), 3.52 (dd, $J=11.9$, 16.5 Hz, 1H, 1×H-3), 4.76 (dd, $J=4.0$, 11.6 Hz, 1H, H-2), 6.93 (dd, $J=7.4$, 7.4 Hz, 1H, Ar-H), 7.14–7.74 (m, 3H, Ar-H), 12.89 (s, 1H, COOH). Found: *m*/*z* 263.1153. Calcd for $C_{14}H_{17}NO_4$: M, 263.1157.

4.3. Preparation of N-phenyl-(S)-N$^{\alpha}$-(tert-butoxycarbonyl)indoline-2-carboxamide **4a**

To a THF solution (2 ml) of (*S*)-*N*-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **3** (263 mg, 1.0 mmol) was added a THF solution (1.5 ml) of *N*-methylmorpholine (101 mg, 1.0 mmol)

at −15°C. After stirring for 15 min, a THF solution (1.5 ml) of isobutyl chloroformate (155 mg, 1.1 mmol) was added slowly to the reaction mixture at −15°C and the reaction mixture was stirred for 15 min. Then a THF solution (1.5 ml) of aniline (93 mg, 1.0 mmol) was added at −15°C and the reaction temperature was then gradually warmed to room temperature. Stirring was continued for 14 h at this temperature. After addition of water and ethyl acetate to the reaction mixture, the separated organic layer was washed successively with 1 M HCl, saturated sodium hydrogencarbonate, and brine. The organic layer was dried over anhyd. sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (dichloromethane:hexane:ether = 16:16:1) to give *N*-phenyl-(*S*)-N^{α}-(*tert*-butoxycarbonyl)indoline-2-carboxamide **4a** (212 mg, 63%) (mp 178.3–178.8°C). $[\alpha]_D^{20}$ −67.6 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1701, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.56 (s, 9H, $OC(CH_3)_3$), 3.49 (brs, 2H, 2×H-3), 4.98–5.03 (m, 1H, H-2), 6.98–7.11 (m, 2H, Ar-H), 7.17–7.32 (m, 4H, Ar-H), 7.49 (d, J = 7.9 Hz, 2H, Ar-H), 7.63 (brs, 1H, Ar-H). Found: C, 70.97; H, 6.61; N, 8.28%. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28%. *N*-Substituted (*S*)-N^{α}-(*tert*-butoxycarbonyl)indoline-2-carboxamide **4b–f,h** were prepared in a similar manner.

4.3.1. N-*Cyclohexyl*-(S)-N$^{\alpha}$-*(*tert-*butoxycarbonyl)indoline-2-carboxamide* ***4b***

Yield: 66%; mp 164.9–165.4°C; $[\alpha]_D^{20}$ −87.8 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1710, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90–1.92 (m, 10H, 2×H-2′, 2×H-3′, 2×H-4′, 2×H-5′, 2×H-6′), 1.54 (s, 9H, $OC(CH_3)_3$), 3.23–3.28 (m, 1H, 1×H-3), 3.42–3.52 (m, 1H, 1×H-3), 3.68–3.82 (m, 1H, H-1′), 4.77–4.83 (m, 1H, H-2), 5.99 (brs, 1H, CONH), 6.98 (t, J = 7.4 Hz, 1H, Ar-H), 7.13–7.21 (m, 2H, Ar-H), 7.70 (brs, 1H, Ar-H). Found: C, 69.58; H, 8.04; N, 8.17%. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13%.

4.3.2. N-*(*o-*Tolyl)*-(S)-N$^{\alpha}$-*(*tert-*butoxycarbonyl)indoline-2-carboxamide* ***4c***

Yield: 56%; mp 154.4–155.1°C; $[\alpha]_D^{20}$ −76.5 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1712, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.59 (s, 9H, $OC(CH_3)_3$), 2.17 (s, 3H, Ar-CH_3), 3.53 (brs, 2H, 2×H-3), 5.04–5.09 (m, 1H, H-2), 6.99–7.06 (m, 2H, Ar-H), 7.13–7.25 (m, 4H, Ar-H), 7.64 (brs, 1H, Ar-H), 7.94 (d, J = 7.9 Hz, 1H, Ar-H). Found: *m*/*z* 352.1783. Calcd for $C_{21}H_{24}N_2O_3$: M, 352.1787.

4.3.3. N-*(2,6-Xylyl)*-(S)-N$^{\alpha}$-*(*tert-*butoxycarbonyl)indoline-2-carboxamide* ***4d***

Yield: 49%; mp 186.0–186.4°C; $[\alpha]_D^{20}$ −106.7 (*c* 0.99, $CHCl_3$); IR (KBr) *v*: 1708, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.61 (s, 9H, $OC(CH_3)_3$), 2.10 (s, 6H, Ar-CH_3), 3.39–3.62 (m, 2H, 2×H-3), 5.05–5.10 (m, 1H, H-2), 7.00–7.10 (m, 4H, Ar-H), 7.20–7.25 (m, 2H, Ar-H), 7.68 (brs, 1H, Ar-H). Found: *m*/*z* 366.1956. Calcd for $C_{22}H_{26}N_2O_3$: M, 366.1943.

4.3.4. N-*(4-Methoxyphenyl)*-(S)-N$^{\alpha}$-*(*tert-*butoxycarbonyl)indoline-2-carboxamide* ***4e***

Yield: 57%; mp 200.7–201.3°C; $[\alpha]_D^{20}$ −71.9 (*c* 1.01, $CHCl_3$); IR (KBr) *v*: 1714, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.57 (s, 9H, $OC(CH_3)_3$), 3.51 (brs, 2H, 2×H-3), 3.78 (s, 3H, Ar-OCH_3), 4.96–5.02 (m, 1H, H-2), 6.84 (dd, J = 2.0, 6.9 Hz, 2H, Ar-H), 7.01 (dd, J = 7.4, 7.4 Hz, 1H, Ar-H), 7.18–7.24 (m, 2H, Ar-H), 7.40 (d, J = 8.9 Hz, 2H, Ar-H), 7.67 (brs, 1H, Ar-H). Found: C, 68.21; H, 6.54; N, 7.60%. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60%.

4.3.5. N-*[(4-Trifluoromethyl)phenyl]-(*S*)-*N$^{\alpha}$*-(*tert*-*butoxycarbonyl)indoline-2-carboxamide* ***4f***

Yield: 60%; mp 143.0–143.5°C; $[\alpha]_D^{20}$ −37.3 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1710, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.58 (s, 9H, $OC(CH_3)_3$), 3.46–3.55 (m, 2H, 2×H-3), 5.03–5.08 (m, 1H, H-2), 7.03 (dd, *J*=7.4, 7.4 Hz, 1H, Ar-H), 7.19–7.24 (m, 2H, Ar-H), 7.54 (d, *J*=8.6 Hz, 2H, Ar-H), 7.63 (d, *J*=8.9 Hz, 2H, Ar-H), 7.53–7.65 (brs, 1H, Ar-H). Found: C, 62.11; H, 5.29; N, 6.90%. Calcd for $C_{21}H_{21}F_3N_2O_3$: C, 62.06; H, 5.21; N, 6.89%.

4.3.6. N-*(4-Nitrophenyl)-(*S*)-*N$^{\alpha}$*-(*tert*-*butoxycarbonyl)indoline-2-carboxamide* ***4h***

The reaction was carried out at 50°C for 20 h. Yield: 30% (yellow viscous oil); $[\alpha]_D^{20}$ −7.27 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1716, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.61 (s, 9H, $OC(CH_3)_3$), 3.44–3.60 (m, 2H, 2×H-3), 5.08–5.11 (m, 1H, H-2), 7.04 (dd, *J*=7.4, 7.4 Hz, 1H, Ar-H), 7.18–7.25 (m, 2H, Ar-H), 7.54 (brs, 1H, Ar-H), 7.68 (d, *J*=8.6 Hz, 2H, Ar-H), 8.17 (d, *J*=8.5 Hz, 2H, Ar-H). Found: *m*/*z* 383.1472. Calcd for $C_{20}H_{21}N_3O_5$: M, 383.1481.

4.4. Preparation of N-*[(3,5-bistrifluoromethyl)phenyl]-(*S*)-*N$^{\alpha}$*-(*tert*-*butoxycarbonyl)indoline-2-carboxamide* ***4g***

To a THF solution (4 ml) of (*S*)-*N*-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **3** (500 mg, 1.9 mmol) and triethylamine (192 mg, 1.9 mmol) was slowly added a THF solution (2 ml) of pivaloyl chloride (229 mg, 1.9 mmol) at −15°C. After stirring for 5 min at 0°C, a THF solution (2 ml) of 3,5-bis(trifluoromethyl)aniline (435 mg, 1.9 mmol) was added at −15°C. The reaction mixture was stirred at 0°C for 1 h. Then the reaction mixture was warmed to room temperature and stirring was continued for 27 h. After removal of the solvent under reduced pressure, water and ethyl acetate was added. The separated organic layer was washed successively with saturated sodium hydrogen carbonate, water, and brine. The organic layer was dried over anhyd. sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane:ethylacetate=5:1) to give *N*-[(3,5-bistrifluoromethyl)phenyl]-(*S*)-*N$^{\alpha}$*-(*tert*-butoxycarbonyl)indoline-2-carboxamide **4g** (392 mg, 44%) (mp 91.3–92.3°C). $[\alpha]_D^{20}$ −28.4 (*c* 0.99, $CHCl_3$); IR (KBr) *v*: 1718, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.63 (s, 9H, $OC(CH_3)_3$), 3.39–3.60 (m, 2H, 2×H-3), 5.10–5.15 (m, 1H, H-2), 7.03 (dd, *J*=7.4, 7.4 Hz, 1H, Ar-H), 7.19–7.24 (m, 2H, Ar-H), 7.52 (s, 2H, Ar-H), 7.98 (s, 2H, Ar-H). Found: C, 55.70; H, 4.34; N, 5.89%. Calcd for $C_{22}H_{20}F_6N_2O_3$: C, 55.70; H, 4.25; N, 5.91%.

4.5. Preparation of (S)-*2-(anilinomethyl)indoline* ***2a***

To a dichloromethane (10 ml) solution of *N*-phenyl-(*S*)-*N$^{\alpha}$*-(*tert*-butoxycarbonyl)indoline-2-carboxamide **4a** (167 mg, 0.50 mmol) was added trifluoroacetic acid (0.76 ml) at room temperature and stirring was continued for 3 h. After addition of trifluoroacetic acid (0.20 ml), the reaction mixture was stirred for 1 h at this temperature. The solvent and excess trifluoroacetic acid were removed under reduced pressure and dichloromethane was added to the residue. The organic layer was washed successively with saturated sodium hydrogencarbonate, water, and brine and dried over anhyd. sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (dichloromethane:hexane:ether=4:4:1) to give *N*-phenyl-(*S*)-indoline-2-carboxamide **5a** (112 mg, 94%) (mp 125.3–126.8°C). $[\alpha]_D^{20}$ −236.6 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.21 (dd, *J*=8.6, 16.5 Hz, 1H, 1×H-3), 3.67 (dd, *J*=10.9, 16.5 Hz, 1H, 1×H-3), 4.32

(brs, 1H, NH), 4.52 (dd, $J=8.6$, 10.9 Hz, 1H, H-2), 6.79–6.88 (m, 2H, Ar-H), 7.08–7.13 (m, 3H, Ar-H), 7.23–7.34 (m, 2H, Ar-H), 7.58 (d, $J=7.6$ Hz, 2H, Ar-H), 9.01 (s, 1H, CONH). Found: m/z 238.1089. Calcd for $C_{15}H_{14}N_2O$: M, 238.1106. Amide **5a** (1.90 g, 7.98 mmol) in THF (45 ml) was added slowly to lithium aluminum hydride (907 mg, 23.9 mmol) in THF (45 ml) at 0°C and the reaction mixture was stirred for 50 h at room temperature. Then saturated sodium sulfate was added to the reaction mixture at 0°C and the resulting inorganic material was removed by suction filtration. The organic layer was dried with anhyd. sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane:ether = 2:1) to afford (*S*)-2-(anilinomethyl)indoline **2a** (1.63 g, 91%) (mp 61.2–61.6°C). $[\alpha]_D^{20}$ +79.4 (*c* 0.99, $CHCl_3$); IR (KBr) ν: 3347, 3320 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.82 (dd, $J=7.6$, 15.8 Hz, 1H, 1×H-3), 3.11 (dd, $J=8.9$, 15.8 Hz, 1H, 1×H-3), 3.18 (d, $J=5.6$ Hz, 2H, C_2-CH_2N), 3.74 (brs, 2H, 2×NH), 4.01–4.11 (m, 1H, H-2), 6.57–6.61 (m, 3H, Ar-H), 6.70 (dt, $J=1.0$, 7.3 Hz, 2H, Ar-H), 7.01 (t, $J=7.6$ Hz, 1H, Ar-H), 7.07 (d, $J=7.3$ Hz, 1H, Ar-H), 7.13–7.18 (m, 2H, Ar-H). Found: C, 80.11; H, 7.01; N, 12.52%. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49%. (*S*)-2-(*N*-substituted aminomethyl)indoline **2b–d** were prepared in a similar manner.

4.5.1. (S)-2-(Cyclohexylaminomethyl)indoline **2b**

The reduction of amide **5b** was carried out under refluxing THF for 12 h and the crude product was purified by column chromatography (hexane:ether = 1:2) using Chromatorex DM1020 (Fuji Silysia Chemical). Yield: 42% (two steps from **4b**); mp 70.6–72.6°C; $[\alpha]_D^{20}$ +72.2 (*c* 0.99, $CHCl_3$); IR (KBr) ν: 3298 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.01–1.90 (m, 11H, NH, 2×H-2′, 2×H-3′, 2×H-4′, 2×H-5′, 2×H-6′), 2.41 (tt, $J=3.6$, 10.2 Hz, 1H, H-1′), 2.63–2.81 (m, 3H, 1×H-3, C_2-CH_2N), 3.15 (dd, $J=8.9$, 15.8 Hz, 1H, 1×H-3), 3.83–3.94 (m, 1H, H-2), 4.29 (brs, 1H, NH), 6.63 (d, $J=7.6$ Hz, 1H, Ar-H), 6.68 (dd, $J=7.4$, 7.4 Hz, 1H, Ar-H), 7.01 (t, $J=7.6$ Hz, 1H, Ar-H), 7.07 (d, $J=7.3$ Hz, 1H, Ar-H). Found: m/z 230.1758. Calcd for $C_{15}H_{22}N_2$: M, 230.1783.

4.5.2. (S)-2-(o-Toluidinomethyl)indoline **2c**

The reduction of amide **5c** was carried out under refluxing THF for 10 h. Yield: 59% (two steps from **4c**) (colorless viscous oil); bp 220°C (bath temperature)/0.2 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +80.0 (*c* 1.01, $CHCl_3$); IR (neat) ν: 3364 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (s, 3H, Ar-CH_3), 2.87 (dd, $J=7.1$, 15.7 Hz, 1H, 1×H-3), 3.17 (dd, $J=8.9$, 15.9 Hz, 1H, 1×H-3), 3.27 (d, $J=5.6$ Hz, 2H, C_2-CH_2N), 3.89 (brs, 2H, 2×NH), 4.08–4.18 (m, 1H, H-2), 6.60–6.74 (m, 4H, Ar-H), 6.99–7.16 (m, 4H, Ar-H). Found: m/z 238.1443. Calcd for $C_{16}H_{18}N_2$: M, 238.1470.

4.5.3. (S)-2-(2,6-Xylidinomethyl)indoline **2d**

The reduction of amide **5d** was carried out under refluxing THF for 18 h. Yield: 22% (two steps from **4d**) (colorless viscous oil); bp 220°C (bath temperature)/0.2 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ −27.2 (*c* 1.00, $CHCl_3$); IR (neat) ν: 3360 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.29 (s, 6H, Ar-CH_3), 2.88 (dd, $J=7.8$, 15.7 Hz, 1H, 1×H-3), 3.09 (d, $J=5.9$ Hz, 2H, C_2-CH_2N), 3.17 (dd, $J=7.8$, 15.7 Hz, 1H, 1×H-3), 3.66 (brs, 2H, 2×NH), 4.03–4.14 (m, 1H, H-2), 6.66 (d, $J=7.9$ Hz, 1H, Ar-H), 6.71 (dd, $J=7.4$, 7.4 Hz, 1H, Ar-H), 6.83 (dd, $J=7.4$, 7.4 Hz, 1H, Ar-H), 6.99 (d, $J=7.3$ Hz, 2H, Ar-H), 7.00–7.10 (m, 2H, Ar-H). Found: m/z 252.1646. Calcd for $C_{17}H_{20}N_2$: M, 252.1627.

4.6. Preparation of (S)-2-(p-anisidinomethyl)indoline **2e**

Amide **5e** was prepared in a similar manner as described for the preparation of **5a** from *N*-(4-methoxyphenyl)-(*S*)-N^{α}-(*tert*-butoxycarbonyl)indoline-2-carboxamide **4e**. To the THF (10 ml) solution of amide **5e** (279 mg, 1.04 mmol) was added slowly borane–THF complex (0.9 M THF solution, 3.5 ml, 3.1 mmol) at 0°C and the reaction mixture was stirred for 15 h at room temperature. Then 6 M HCl (2 ml) was added to the reaction mixture and stirring was continued for 30 min. After the solution was made basic with saturated sodium hydrogen carbonate, the aqueous layer was separated and extracted twice with ether. The combined organic layer was washed successively with water and brine, and dried over anhyd. sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by preparative TLC (hexane:ether = 1:1) to afforded (*S*)-2-(*p*-anisidinomethyl)indoline **2e** as colorless viscous oil (187 mg, 62% (two steps from **4e**)). Bp 220°C (bath temperature)/0.1 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +75.2 (*c* 1.00, $CHCl_3$); IR (neat) *v*: 3363 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.82 (dd, J = 7.4, 15.7 Hz, 1H, 1×H-3), 3.07–3.16 (m, 1H, 1×H-3), 3.14 (d, J = 5.6 Hz, 2H, C_2-CH_2N), 3.71 (s, 5H, 2×NH, Ar-OCH_3), 3.99–4.09 (m, 1H, H-2), 6.54–6.59 (m, 3H, Ar-H), 6.70 (dd, J = 7.8, 7.8 Hz, 1H, Ar-H), 6.76 (dd, J = 1.7, 8.9 Hz, 2H, Ar-H), 7.01 (dd, J = 7.6, 7.6 Hz, 1H, Ar-H), 7.07 (d, J = 7.3 Hz, 1H, Ar-H). Found: *m*/*z* 254.1403. Calcd for $C_{16}H_{18}N_2O$: M, 254.1419. (*S*)-2-(*N*-Substituted aminomethyl)indoline **2f–h** were prepared in a similar manner.

4.6.1. (S)-2-[(4-Trifluoromethyl)anilinomethyl]indoline **2f**

Yield: 86% (two steps from **4f**); mp 85.4–86.3°C; $[\alpha]_D^{20}$ +46.7 (*c* 1.00, $CHCl_3$); IR (KBr) *v*: 3434, 3351 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.88 (dd, J = 7.9, 15.8 Hz, 1H, 1×H-3), 3.18 (dd, J = 8.9, 15.8 Hz, 1H, 1×H-3), 3.30 (brs, 2H, C_2-CH_2N), 3.96 (brs, 1H, NH), 4.12–4.23 (m, 1H, H-2), 4.34 (brs, 1H, NH), 6.62 (d, J = 8.2 Hz, 2H, Ar-H), 6.64 (d, J = 7.3 Hz, 1H, Ar-H), 6.74 (dd, J = 7.4, 7.4 Hz, 1H, Ar-H), 7.04 (t, J = 7.6 Hz, 1H, Ar-H), 7.10 (d, J = 7.3 Hz, 1H, Ar-H), 7.40 (d, J = 8.2 Hz, 2H, Ar-H). Found: C, 65.94; H, 5.31; N, 9.70%. Calcd for $C_{16}H_{15}F_3N_2$: C, 65.75; H, 5.17; N, 9.58%.

4.6.2. (S)-2-[(3,5-Bistrifluoromethyl)anilinomethyl]indoline **2g**

Yield: 83% (two steps from **4g**) (colorless viscous oil); bp 200°C (bath temperature)/0.5 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +23.7 (*c* 1.00, $CHCl_3$); IR (neat) *v*: 3401 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.90 (dd, J = 7.9, 15.8 Hz, 1H, 1×H-3), 3.19 (dd, J = 8.9, 15.8 Hz, 1H, 1×H-3), 3.30 (t, J = 5.3 Hz, 2H, C_2-CH_2N), 3.90 (brs, 1H, NH), 4.14–4.24 (m, 1H, H-2), 4.48 (brs, 1H, NH), 6.65 (d, J = 7.9 Hz, 1H, Ar-H), 6.75 (dd, J = 7.4, 7.4 Hz, 1H, Ar-H), 6.95 (s, 2H, Ar-H), 7.03–7.09 (m, 2H, Ar-H), 7.15 (s, 1H, Ar-H). Found: *m*/*z* 360.1039. Calcd for $C_{17}H_{14}F_6N_2$: M, 360.1061.

4.6.3. (S)-2-(4-Nitroanilinomethyl)indoline **2h**

Yield: 77% (two steps from **4h**); mp 111.5–112.1°C; $[\alpha]_D^{20}$ +49.3 (*c* 0.99, $CHCl_3$); IR (KBr) *v*: 3364 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.90 (dd, J = 8.4, 15.7 Hz, 1H, 1×H-3), 3.21 (dd, J = 9.2, 15.8 Hz, 1H, 1×H-3), 3.40 (t, J = 5.3 Hz, 2H, C_2-CH_2N), 3.97 (brs, 1H, NH), 4.20–4.30 (m, 1H, H-2), 4.92 (brs, 1H, NH), 6.57 (d, 2H, J = 9.2 Hz, Ar-H), 6.67 (d, J = 7.6 Hz, 1H, Ar-H), 6.77 (dd, J = 7.4, 7.4 Hz, 1H, Ar-H), 7.03–7.12 (m, 2H, Ar-H), 8.09 (d, 2H, J = 9.2 Hz, Ar-H). Found: C, 66.79; H, 5.65; N, 15.51%. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60%.

4.7. The asymmetric reduction of acetophenone catalyzed by **2f**: typical procedure (Table 2, entry 6)

To a THF (0.5 ml) solution of **2f** (44 mg, 0.15 mmol) was added borane–THF complex (1.0 M THF solution, 1.0 ml, 1.0 mmol) at 0°C and stirring was continued for 30 min 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 during 2 h and the reaction mixture was stirred at the temperature for a further 2 h. After addition of 1 M HCl at the temperature, the reaction mixture was stirred at room temperature for 10 min. The aqueous layer was separated and extracted twice with ether, and the combined organic layer was washed with 1 M HCl, water, and brine successively. The organic layer was dried over anhyd. magnesium sulfate and the solvent was removed under reduced pressure. The resulting crude product was purified by 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 to be 92% 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; t_R, 16.7 min for major peak, 19.6 min for minor peak). The asymmetric reduction of the other ketones was performed by a similar manner. The ee's were determined by HPLC using Daicel Chiralcel OD-H (25×0.46 cm i.d.), Daicel Chiralcel OB (25×0.46 cm i.d.) or Waters Opti-pak TA (30×0.39 cm i.d.). 1-(2-Bromophenyl)ethanol: OB; eluent, 2% 2-propanol in hexane; t_R, 20.3 min for minor peak, 28.0 min for major peak. 1-Phenyl-2-chloroethanol: OD-H; eluent, 3% 2-propanol in hexane; t_R, 32.6 min for major peak, 40.4 min for minor peak. 1-(α-Naphthyl)ethanol: OD-H; eluent, 5% 2-propanol in hexane; t_R, 31.6 min for minor peak, 53.5 min for major peak. 1-Phenylpropanol: OD-H; eluent, 5% 2-propanol in hexane; t_R, 15.5 min for major peak, 17.0 min for minor peak. 1,2,3,4-Tetrahydro-1-naphthol: OD-H; eluent, 2% 2-propanol in hexane; t_R, 28.4 min for minor peak, 30.7 min for major peak. 1-Indanol: OD-H; eluent, 5% 2-propanol in hexane; t_R, 18.9 min for minor peak, 21.0 min for major peak. 2-Octanol (as *p*-nitrobenzoate): TA; eluent, 0.1% 2-propanol in hexane; t_R, 21.5 min for minor peak, 29.9 min for major peak. 1-Phenyl-1-buten-3-ol: OD-H; eluent, 10% 2-propanol in hexane; t_R, 16.5 min for major peak, 25.2 min for minor peak.

4.8. ^{11}B NMR measurement of diazaborolidine catalyst

Borane–THF complex (0.9 M THF solution, 1.33 ml, 1.2 mmol) was added to a THF (1 ml) solution of **2f** (58 mg, 0.2 mmol) at 0°C and stirring was continued for 30 min at the temperature. The solvent and excess borane were removed under reduced pressure. ^{11}B NMR of the resulting residue was measured in benzene-d_6. ^{11}B NMR peaks corresponding to diazaborolidine **6** (R = 4-CF_3Ph) were observed at +24 ppm using trifluoroborane-etherate as external standard. ^{11}B NMR experiments using **1**, **2a** and **2b** were carried out in a similar manner.

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