Synthesis of Chiral Secondary β-amino Alcohols and their Application in the Asymmetric Reduction of Prochiral Ketones

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Summary: Nine chiral secondary β-amino alcohols were synthesized from chiral primary amino alcohols and aromatic aldehydes, and their catalysis for the asymmetric reduction of prochiral ketone was studied with good yields up to 87% ee (enantiometric excess).

Introduction

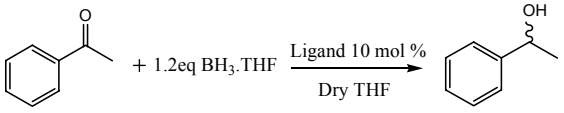
The asymmetric reduction of prochiral ketones is one of the most indispensable tools for approaching chiral secondary alcohols, which are obtained as versatile building blocks for biologically and pharmaceutically active compounds [1, 2]. Many asymmetric catalysts have been developed for this transformation, e.g., most useful oxazaborolidines [3, 4], which are prepared from chiral amino alcohols, give excellent ee values and often have wide substrate scope. Among most of these cases, oxygen and nitrogen are used as the coordinating atoms to boron. In recent years , Lee [5] and Velmathi [6] developed the O/N/O tridentate chiral ligands derived from salicylaldehyde, and the asymmetric reduction of ketones was performed with moderate to excellent enantioselectivities (Fig. 1)

In this paper we prepared a series of chiral secondary amino alcohols by reductive amination [7], and their catalytic activity was also tested for enantioselective ketone reduction.

Results and Discussion

Ligands were conveniently synthesized according to the literature method [6]. The condensation of various aldehydes with chiral primary amino alcohols gave corresponding imines, which were then reduced by $NaBH_4$ in THF/EtOH to obtain chiral secondary N-alkylated β-amino alcohols in satisfactory yields (Scheme-1). Initially the catalytic potential of all the ligands were evaluated in the borane reduction of acetophenone (Table-1).The ligands that were developed from salicylaldehyde (**L1**, **L2** and **L3**) gave better ee when compared with other ligands (entries 1-3). **L4**, which were developed from ferrocenecarboxaldehyde yielded the corresponding product with 34% ee. However, when the ferroceneyl-bearing amino alcohols developed from (S)-2-amino-2-phenyl ethanol (**L5**) was used, the enantioselectivity became very poor. The ligands (**L6**, **L7**, **L8** and **L9**), which were developed from 4-bromothiophene-2-carbaldehyde or furan-2-carbaldehyde or indole-3-carboxaldehyde failed to achieve good ee values.

Table-1: Asymmetric reduction of acetophenone with different Ligands [a].



Entry	Ligand	Yeild[b](%)	ee[c](%)	Config.[d]
1	L1	95	51	S
2	L2	95	15	S
3	L3	95	29	S
4	L4	87	34	S
5	L5	91	8	-
6	L6	81	<5	-
7	L7	90	<5	-
8	L8	91	<5	-
9	L9	83	13	S
10	L0	95	64	R

[a] All reactions were performed with 1.0 mmol of C_6H_5COMe and 1.2 mL(1M) BH_3·THF in 10 mL dry THF at room temperature.

[b] All yields were obtained by isolating of the products after purification.

[c] Determined by HPLC with chiral column (AD-H); HPLC analysis condition : hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_1 =11.6 min, t_2= 12.9 min.

[d] The absolute configuration was determined by comparing the HPLC elution order of the enantiomers with an authentic sample according to the literature [8].

Interestingly, the opposite alcohol enantiomer (R, 64%ee) was found to predominate when the borane reduction of acetophenone was catalyzed by primary amino alcohol **L0** [8]. In order to explain the conversion, two proposed favorite structures of transition state were developed based on the mechanism proposed previously [3, 5, 6]. The cyclic oxazaborolidine (left in red) and bicyclic oxazaborolidine in situ (right in red) might induced the opposite configuration respectively (Fig. 2)

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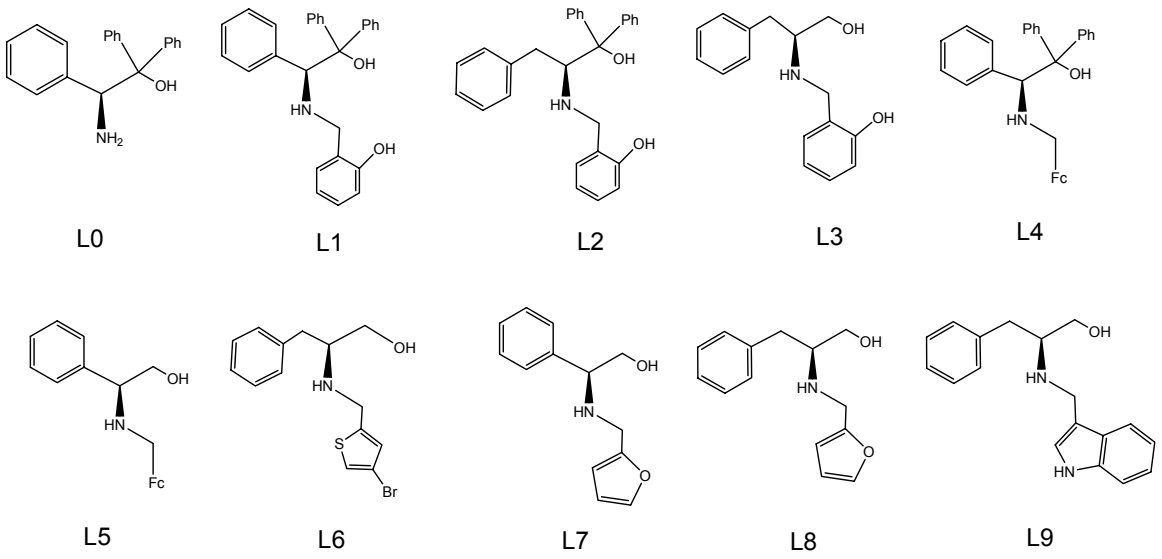


Fig. 1: The list of chiral ligands (**Fc** = Ferrocenyl).

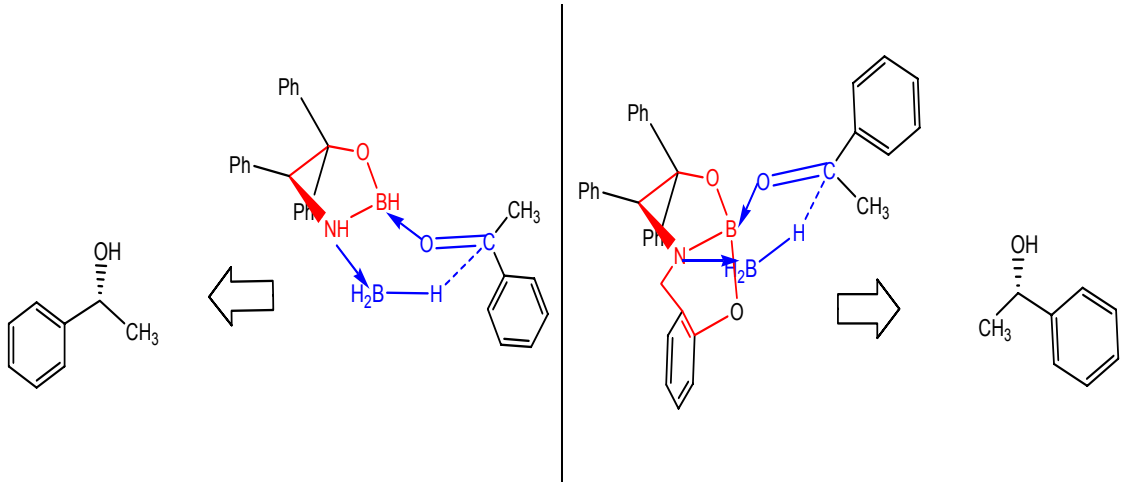
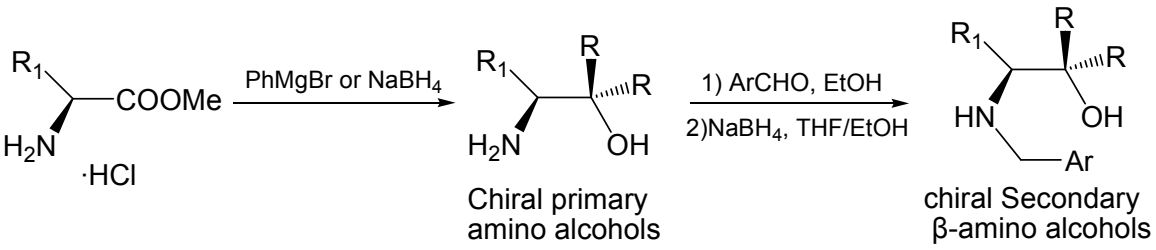


Fig. 2: Proposed favorite structures of transition state.



Scheme-1: The synthesis of chiral secondary β-amino alcohols.

L1 was chosen as a model ligand to asymmetric reduction of acetophenone in various conditions. When the catalyst loading was reduced to 5mol%, the corresponding product was obtained with 23% ee and good yield (Table-2, Entries 1, 2). When reduce the BH_3·THF (1M) from 1.2 ml to 0.5 ml (Table-2, Entries 1, 3, 4), the yield was decreased to 58% while the enantioselectivity nearly maintain the same. The reaction was also carried out in toluene, benzene and dichloromethane (Table-2, Entries 5, 6, 7), and the yields were not as good as those in THF.

Table-2: The asymmetric reduction of acetophenone with **L1** in various conditions [a]

Entry	Solvents	Ligand%	Yield (%)	ee (config. S, %)
1	THF	10 mol	95	51
2	THF	5 mol	95	23
3	THF	10 mol[b]	58	53
4	THF	10 mol[c]	80	54
5	Toluene	10 mol	95	45
6	Benzene	10 mol	95	42
7	CH_2Cl_2	10 mol	91	27

[a] All reactions were performed with 1.0 mmol of C_6H_5COMe and 1.2 mL BH_3·THF(1M)in 10 mL dry THF at room temperature unless otherwise noted.
[b] the reaction were performed with 0.5 mL BH_3·THF.
[c] the reaction were performed with 0.8 mL BH_3·THF.

The reduction of different prochiral ketones was carried out in dry THF with 1.2 mL of BH_3·THF (1M) and the catalyst loading was 10mol%. The results are presented in Table-3. It demonstrates that when the acetophenone had ortho-NO_2 substituted, **L1** was the catalyst with 10 mol% loading, the best result can be obtained with the corresponding product of 87% ee.

Table-3: Asymmetric borane reduction of prochiral ketones with10mol% **L1** [a]

Entry	Prochiral ketone	Yield (%)	ee(%)
1[b]	2'-Nitroacetophenone	95	87
2[c]	4'-Chloroacetophenone	91	19
3[d]	4'-fluoroacetophenone	95	8
4[e]	4'-Methoxyacetophenone	95	7
5[f]	Propiophenone	95	11
6[g]	2'-chloroacetophenone	95	15
7[h]	4'-Bromoacetophenones	95	29

[a] The reaction were performed with 1.0 mmol of prochiral ketone and 1.2mL BH_3·THF, with 10mol% **L1**, in 10 mL dry THF at room temperature.
[b] HPLC analysis condition for the corresponding alcohols: OJ-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_{minor} = 28.9 min, t_{major} = 30.7 min.
[c] HPLC analysis condition for the corresponding alcohols: OJ-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_{minor} =17.2min, t_{major} = 18.6 min.
[d] HPLC analysis condition for the corresponding alcohols: OJ-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_1 = 17.6min, t_2 =18.1min.
[e] HPLC analysis condition for the corresponding alcohols: AD-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_1 = 31.5 min, t_2 = 33.7 min.
[f] HPLC analysis condition for the corresponding alcohols: OJ-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_{major} = 14.5min, t_{minor} = 15.5 min.
[g] HPLC analysis condition for the corresponding alcohols: OJ-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_1 = 12.5 min, t_2=13.0 min.
[h] HPLC analysis condition for the corresponding alcohols: AD-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, t_{minor} = 22.1 min, t_{major} = 22.3 min.

Experimental

Standard method of drying was used for all solvents unless otherwise noted, commercially available reagents were used without further purification. All reactions were monitored by TLC. Column chromatography performed on 100–200 mesh silica gel with petrol ether/ethyl acetate as eluent. Melting points were obtained with an X-4 micro-melting point apparatus and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ on Bruker AVANCE III 500MHz and 125 MHz spectrometers respectively, using TMS as the internal reference. *J* values were given in Hz. Mass spectra were recorded by the EI method. Chiral HPLC analyses were performed by using a SHIMADZU LC-20AT instrument equipped with a SHIMADZU SPD-20A detector with chiral column (Daicel Co. Chiralcel AD-H, Daicel Co. Chiralcel OJ-H). Retention times are given in min.

Chiral primary amino alcohols were synthesized by known methods from L-Phenylglycine methyl ester hydrochloride or L-Phenylalanine methyl ester hydrochloride [9-11].

Ligands **L3** [12], **L5** [13], and **L7** [14] had been previously synthesized and characterization data was reported.

*Preparation of (S)-amino alcohol **L1***

The solution of (S)-2-amino-1,1,2-triphenylethanol (1.445 g, 5.0 mmol) and salicylaldehyde (0.53 ml, 5.0 mmol) in 30 mL EtOH was stirred at ambient temperature until the reaction was completed (monitored by TLC). The solvent was removed under reduced pressure. After the residue was dissolved in EtOH (20 mL) and THF (20 mL) again, the mixture was cooled to 0 ºC, and $NaBH_4$ was added (0.37 g 10.0 mmol) in portions, then the mixture was stirred at ambient temperature until the reaction was completed. After the removal of the solvent, aqueous hydrochloric acid (1M) was added carefully until pH = 8-9, the resulting mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried over with anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. Then the residue was decolorized with active charcoal and recrystallized from EtOH. 1.24g **of L1** was obtained as white crystal. Yield: 63%; mp 179–182 ºC. ^{1}H-NMR (500MHz, $CDCl_3$, ppm) δ: 2.78 (1H, br, OH), 3.74 (2H, q, *J* = 13.48 Hz, NCH_2), 4.71 (1H, s, C*H), 6.74-7.64 (19H, m, ArH). ^{13}C-NMR (ppm) δ: 157.55, 144.43, 144.34, 136.96, 129.31, 128.92, 128.67, 128.57, 128.08, 127.82, 127.71, 127.51, 126.80, 126.05, 125.81, 123.02, 119.20, 116.44, 80.82, 68.74, 50.53. IR (KBr, cm^{-1}): 3572 , 3305 ,

3026 , 2849 , 1583 , 1487 , 1450 , 1429 , 1384 , 1315 , 1282 , 1251 , 1198 , 1095 , 1057 , 1033 , 971 , 914 , 770 , 742 , 697 , 638 , 599 , 528 , 456. MS (EI): m/z = 396 $(M+1)^+$. Elem anal. Calcd (%) for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.95; H, 6.29; N, 3.49.

Preparation of (S)-amino alcohol **L2**

The title compound was prepared from (S)-2-amino-1,1,3-triphenylpropan-1-ol (1.5 g, 5.0 mmol) and salicylaldehyde (0.53 ml, 5.0 mmol), according to the former procedure. Recrystallization of the crude product from ethyl acetate gave 1.5g of **L2** as white solid. Yield: 70%, mp = 116 °C, IR (KBr): 3463, 3329, 3058, 3024, 2924, 2858, 1588, 1492, 1448, 1249, 1053, 1029, 752, 741, 702 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.28 (s, 1H, OH), 2.591 (dd, 1H, $PhCH_2$, *J* = 9.75 Hz, 4.5 Hz), 3.04 (dd, 1H, $PhCH_2$ *J* = 14.0 Hz,3.0Hz), 3.15-3.13 (d, 1H, CH_2N, *J* = 12.5 Hz) 3.39-3.37 (d, 1H, CH_2N, *J* = 12.5 Hz), 3.96-3.94 (dd, 1H, C*H, *J* = 9.5 Hz, 3.0 Hz), 7.65-6.48 (m, 19H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): δ: 157.13, 145.64, 144.64, 139.43, 129.11, 128.99, 128.80, 128.70, 128.54, 127.35, 127.11, 126.64, 125.68, 125.60, 123.44, 119.17, 116.21, 81.03, 66.16, 52.67, 37.74. MS (EI): m/z = 410 $[M+1]^+$. Elem anal. Calcd (%) for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 82.09; H, 6.67; N, 3.38.

Preparation of (S)-amino alcohol **L4**

The title compound was prepared from (S)-2-amino-1,1,2-triphenylethanol (1.445 g, 5.0 mmol) and ferrocenecarboxaldehyde (1.07 g, 5.0 mmol), according to the former procedure. Recrystallization the crude product directly from EtOH gave 1.7 g of **L4** as red crystal. Yield: 70%; mp 134-138 ºC. IR (KBr, cm^{-1}): 3440, 3087, 2803, 1641, 1492, 1449, 1383, 1265, 1174, 1105, 1048, 998, 961, 916, 814, 760, 734, 699, 672, 615, 484. ^{1}H-NMR (500MHz, $CDCl_3$, ppm) δ: 1.87 (1H, br, OH), 3.21 (1H, d, *J* = 13.53, $FcCH_2$), 3.43 (1H, d, *J* = 13.53, $FcCH_2$), 3.94 (5H, s, Fc), 4.03-4.14 (4H, m, Fc), 4.34 (1H, br, NH), 4.65 (1H, s, C*H), 7.02-7.68(15H, m, PhH). ^{13}C-NMR (125MHz, $CDCl_3$, ppm) δ: 145.79, 143.74, 137.28, 129.66, 128.57, 127.38, 127.30, 127.23, 126.66, 126.26, 126.11, 80.00, 68.28, 67.85, 67.83, 67.54 , 45.76 . MS (EI): m/z = 487$(M+1)^+$. Elem anal. Calcd (%) for $C_{31}H_{29}NOFe$: C, 76.39; H, 6.00; N, 2.87; Found: C, 76.35; H, 6.07; N, 2.83.

Preparation of (S)-amino alcohol **L6**

The title compound was prepared from (S)-2-amino-3-phenylpropan-1-ol (0.454 g, 3 mmol) and 4-bromothiophene-2-carbaldehyde (0.56 g, 3.0 mmol), according to the former procedure. The crude product was purified on silica gel column chromatography. 0.76 g of **L6** was obtained as light yellow solid. Yield: 78%; mp 68-69 ºC. IR (KBr, cm^{-1}): 3285, 3084, 2919, 2852, 1656, 1522, 1451, 1335, 1144, 854, 747, 613. ^{1}H-NMR (500 MHz, $CDCl_3$, ppm) δ: 1.98 (2H, br, NH and OH), 2.75 (1H, dd, *J* = 12.4, 5.7 Hz, CH_2Ph), 2.79 (1H, dd, *J* = 12.4, 5.7 Hz, CH_2Ph), 2.97 (1H, m, C*HN), 3.35 (1H, dd, *J* = 10.9, 5.7 Hz, CH_2O), 3.63 (1H, dd, *J* = 10.9, 3.9 Hz, CH_2O), 3.92 (2H, q, *J* = 14.5 Hz, CH_2N), 6.72 (1H, d, *J* = 1.12 Hz, thiophen-H), 7.08 (1H, d, *J* = 1.41 Hz, thiophen-H), 7.16 (1H, dd, *J* = 9.08, 2.18 Hz, Ph-H), 7.22-7.26 (1H, m, Ph-H), 7.31 (2H, dd, *J* = 10.07, 4.59 Hz, Ph-H). ^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ: 38.10, 45.62, 59.27, 62.82, 109.10, 121.72, 126.61, 127.22, 128.69, 129.19, 138.14, 145.59. MS (EI): m/z(%) = 294 (9.1), 236 (86.2), 234 (86.1), 178 (30.4), 177 (81.3), 176 (88.4), 175 (33.3), 124 (32.6), 96 (99.9), 91 (99.9), 77 (22.5). Elem anal. Calcd (%) for $C_{14}H_{16}NOSBr$: C, 51.54; H, 4.94; N, 4.29. Found: C, 51.35; H, 5.01; N, 4.23.

Preparation of (S)-amino alcohol **L8**

The title compound was prepared from (S)-2-amino-3-phenylpropan-1-ol (0.454 g, 3.0 mmol) and furan-2-carbaldehyde (0.302 g, 3.0 mmol), according to the former procedure. The crude product was purified on silica gel column chromatography give 0.54g of white crystal, Yield: 78%; mp. 77 ºC (Ref.[15] mp. 81ºC). IR (KBr, cm^{-1}): 3300, 3027, 2922, 1602, 1491, 1433, 1350, 1221, 1150, 824, 741, 700.^{1}H-NMR (500MHz, $CDCl_3$, ppm) δ: 2.06 (2H, br, NH and OH), 2.73 (1H, dd, *J* = 13.9, 7.4 Hz, $PhCH_2$), 2.77 (1H, dd, *J* = 14.0, 7.3 Hz, $PhCH_2$), 2.93 (1H, m, C*HN), 3.34 (1H, dd, *J* = 10.9, 5.2 Hz, CH_2O), 3.62 (1H, dd, *J* = 10.9, 3.8 Hz, CH_2O), 3.78 (2H, s, CH_2N), 6.10 (1H, d, *J* = 3.1 Hz, furan-H), 6.29 (1H, dd, *J* = 3.1, 1.9 Hz, furan-H), 7.14 (2H, d, *J* = 6.9 Hz, Ph-H), 7.22 (1H, dd, *J* = 8.42, 6.30 Hz, Ph-H), 7.26-7.30 (2H, m, Ph-H), 7.32 (1H, d, *J* = 1.07 Hz, furan-H). ^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ: 38.07, 43.67, 59.02, 62.49, 106.95, 110.18, 126.47, 128.60, 129.20, 138.36, 141.90, 153.59. MS (EI): m/z = 232 $[M+1]^+$. Elem anal. Calcd (%) for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.56; H, 7.58; N, 6.23.

Preparation of (S)-amino alcohol **L9**

The title compound was prepared from (S)-2-amino-3-phenylpropan-1-ol (0.454 g, 3 mmol) and

Indole-3-carboxaldehyde (0.435 g, 3.0 mmol), according to the former procedure. The crude product was purified on silica gel column chromatography. light yellow soild, Yield: 67.8%; mp.115 ºC. IR (KBr, cm^{-1}): 3345, 3058, 2919, 2855, 1878, 1596, 1495, 1375, 1161, 829, 740, 634. ^{1}H-NMR (500MHz, $CDCl_3$, ppm) δ: 2.20 (2H, br, NH and OH), 2.77 (1H, dd, *J* = 13.7, 6.8 Hz, $PhCH_2$), 2.83 (1H, dd, *J* = 13.6, 7.3 Hz, $PhCH_2$), 3.04 (1H, m, CHN), 3.37 (1H, dd, *J* = 10.7, 5.3 Hz, CH_2O), 3.69 (1H, dd, *J* = 10.7 and 3.9 Hz, CH_2O), 3.96 (2H, q, CH_2NH), 7.00 (1H, s, indole-H), 7.07 (1H, t, *J* = 7.5 Hz, indole-H), 7.15-7.29 (6H, m, Ph-H and indole-H), 7.32 (1H, d, *J* = 8.2 Hz, indole-H), 7. 43 (1H, d, *J* = 7.89 Hz, indole-H), 8.1 (1H, s, indole-NH). ^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ: 38.19, 42.48, 59.72, 62.60, 111.24, 114.67, 118.76, 119.66, 122.23, 122.40, 126.44, 126.86, 128.62, 129.23, 136.41, 138.56. MS (EI): m/z(%) = 249 (1.9), 201 (16.3), 189 (43.4), 131 (94.1), 130 (99.3), 129 (99.9), 128 (43.7), 120 (53.0), 118 (40.0), 117 (76.6), 116 (12.3), 103 (99.9), 102 (99.3), 91 (99.9), 77 (99.9), 72 (56.9). Elem anal. Calcd (%) for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.21; N, 9.94.

General Procedure of Asymmetric Reduction of Prochiral Ketones

BH_3·THF (1M) was added to a solution of ligand in dry THF (5 ml) under N_2. The mixture was stirred for 1h at room temperature. A solution of prochiral ketone (1 mmol) in dry solvents (5 ml) was injected in 30 min. After the addition, the reaction was completed (monitored by TLC). Then the reaction mixture was quenched with 2 N HCl (5mL) and extracted twice with AcOEt (10 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude mixture obtained was filtered on a thin pad of silica gel with AcOEt/petroleum ether and then submitted to HPLC analysis.

General Procedure of Preparation for the Racemic Products

BH_3·THF (1M) was injected slowly to a solution of dry THF (10 ml) and prochiral ketone (1 mmol) under N_2. The mixture was stirred at room temperature until the reaction was completed (monitored by TLC). Then the reaction mixture was quenched with 2 M HCl (5mL) and was extracted twice with ethyl acetate (10 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude racemic product was directly submitted to HPLC analysis. Retention time was determined using HPLC with Chiralpak AD-H or OJ-H chiral columns.

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References

1. K. Jennings and D. Diamod, *Analyst*, **126**, 1063 (2001).
2. A. K. Scott, *Drug Safety*, **8**, 149 (1993).
3. E. J. Corey and C. J. Helal, *Angewandte Chemie International Edition*, **37**, 1987 (1998).
4. C. Schunicht, A. Biffis and G. Wulff, *Tetrahedron*, **56**, 1693 (2000).
5. D. S. Lee, *Chirality*, **19**, 148 (2007).
6. U. Balakrishnan, N. Ananthi and S. Velmathi, *Tetrahedron: Asymmetry*, **20**, 1150 (2009).
7. R. F. Borch, M. D. Bernstein and H. D. Durst, *Journal of the American Chemical Society*, **93**, 2897 (1971).
8. K. R. K. Prasad and N. N. Joshi *Tetrahedron: Asymmetry*, **7**, 3147 (1996).
9. M. Poornachandran and R. Raghunathan, *Tetrahedron: Asymmetry,* **19**, 2177 (2008).
10. R. Fleischer, H. Wunderlich and M. Braun, *European Journal of Organic Chemistry*, 1063 (1998).
11. D. O'Hagan and M. Tavasli, *Tetrahedron: Asymmetry*, **10**, 1189 (1999).
12. V. Banphavichit, W. Bhanthumnavin and T. Vilaivan, *Tetrahedron*, **63**, 8727 (2007).
13. J. Blanchet, M. Bonin, L. Micouin and H. P. Husson, *The Journal of Organic Chemistry*, **65**, 6423 (2000).
14. J. C. J. Benningshof, R. H. Blaauw, A. E. Ginkel, J. H. Maarseveen, F. P. J. T. Rutjes and H. Hiemstra, *Journal of the Chemical Society, Perkin Transactions* 1, **14**, 1693 (2002).
15. M. Gacek and K. Undheim, *Acta chemica scandinavica*, **26**, 2655 (1972).