New Methods of Resolution and Purification of Racemic and Diastereomeric Amino Alcohol Derivatives Using Boric Acid and Chiral 1,1′-Bi-2-naphthol

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Received December 18, 2000

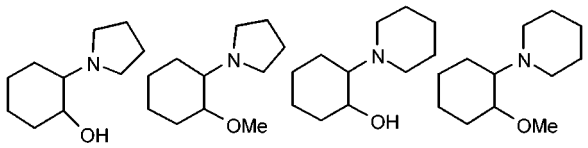
Resolution of the racemic amino alcohol derivatives **1**−**6** is readily achieved to obtain enantiomerically enriched compounds using chiral 1,1′-bi-2-naphthol and boric acid in solvents such as CH_3CN, THF, and MeOH. Purification of the diastereomeric mixture **7** has also been carried out following this method. The corresponding intermediate ammonium borate complexes were also characterized by X-ray diffraction methods.

Introduction

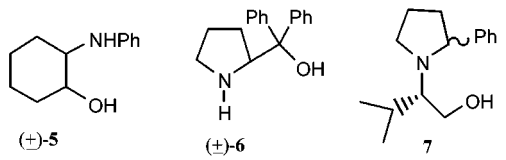
Amino alcohols are an important class of organic compounds. Several derivatives have found much use in medicinal chemistry as therapeutic agents for a wide variety of human diseases and disorders.[1] During the past few decades, the enantiomerically pure amino alcohols, especially β-amino alcohols, have also been employed as a chiral auxiliary resolving agents for acids and lactams and as chiral ligands in asymmetric catalysts for applications in catalytic asymmetric synthesis.[2] The chiral β-amino alcohols are generally prepared from the naturally occurring amino acids,[3] reduction of α-amino carbonyl compounds[4] or α-hydroxy carbonyl compounds,[5] from the stereo-, regio-, and enantioselective ring opening of epoxides,[6] amino hydroxylations of olefins,[7] and asymmetric hydroboration of enamines.[8] These amino alcohols can be also obtained in enantiomerically pure form via resolution of racemic amino alcohols that are easily prepared through a variety of procedures.[9] Several resolving agents have been utilized for the resolution of amine bases including amino alcohols.[10] The prominent resolving agents for amino alcohols are optically active tartaric acid,[11] *O*-acyl tartaric acid,[12] *O*-acyl mandelic acid,[13a] and chiral 1,1′-bi-2-naphthylphosphoric acid.[14]

Efforts have been undertaken in this laboratory to resolve racemic diols for applications in asymmetric organic transformations. For example, we have devised methods for the resolution of racemic diols such as 1,1′-bi-2-naphthol, 1,1,2-triphenylethane-1,2-diol, and 1,2-dicarboxylic acids through the preparation of diastereomeric inclusion complexes using (*S*)-proline.[15] Recently, we have employed inexpensive boric acid and (*R*)-(+)-1-phenylethylamine to resolve racemic 1,1′-bi-2-naphthol through the preparation of the diastereomeric borate complexes in solvents such as CH_3CN or THF (Scheme 1).[16a]

Accordingly, in principle, it should be possible to devise methods for the resolution of amine derivatives through preparation of such diastereomeric borate complexes using chiral 1,1′-bi-2-naphthol and boric acid. We describe here results of detailed studies undertaken to resolve the amine derivatives **1**−**7**.



(±)-**1** (±)-**2** (±)-**3** (±)-**4**



(±)-**5** (±)-**6** **7**

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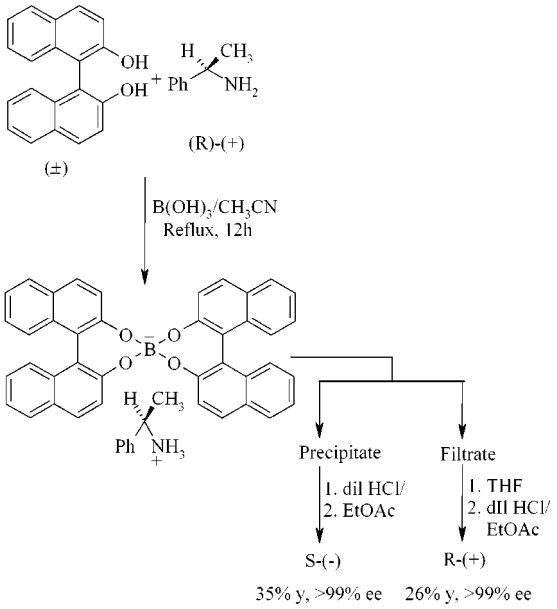
10.1021/jo0057755 CCC: $20.00
Published on Web 05/02/2001

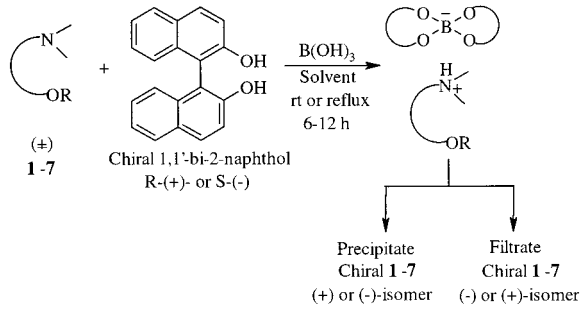
Scheme 1



Results and Discussion

Resolution of 1,2-*trans*-Amino Alcohol Derivatives 1−5 Prepared through Ring Opening of Cyclohexene Oxide with Amines. The racemic amino alcohols **1** and **3** were prepared through ring opening of cyclohexene oxide.[23a] The corresponding derivatives **2** and **4** were prepared by methylation using NaH/MeI.[23b] Also, the racemic amino alcohol **5** was prepared through ring opening of cyclohexene oxide with aniline using $CoCl_2$ as catalyst.[23c]

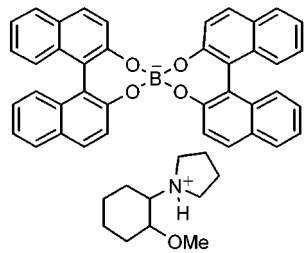
Scheme 2



Initially, it was observed that the reaction of racemic **1**, (*S*)-(−)-1,1′-bi-2-naphthol and boric acid in THF leads to the formation of the corresponding diastereomeric complexes (Scheme 2).[16b] The precipitate and filtrate fractions, after dilute HCl treatment, gave partially resolved **1**. Partially resolved **1** was obtained in 38% ee under these conditions. Further enrichment of this sample in two successive operations gave >99% ee (Table 1, entries 1−3).

We have observed that this method works better for the resolution of the corresponding racemic methyl ether **2**. Thus, optically pure (1*S*,2*S*)-(+)-**2** can be obtained through the reaction with (*R*)-(+)-1,1′-bi-2-naphthol and boric acid in CH_3CN under refluxing conditions. After workup, the precipitate fraction gave the amino ether (1*S*,2*S*)-(+)-**2** with >99% ee (Table 1, entry 4) (see the Experimental Section).

The structural analysis of the borate complex formed has been analyzed by X-ray diffraction method. The data revealed that complex formed is of the type **10a**.[16b]



10a

We have also examined the resolution of the amino alcohols **3** and **5** and the amino ether **4**. Experiments were carried out using boric acid and chiral 1,1′-bi-2-naphthol in solvents such as CH_3CN, THF, and MeOH. The results are summarized in Tables 2−4.

Like amino alcohol **1**, the resolution of the racemic **3** also has been carried out using (*R*)-(+)-1,1′-bi-2-naphthol and boric acid in CH_3CN under refluxing conditions to obtain the diastereomeric complexes. The precipitate and filtrate fractions, after dilute HCl treatment, gave partially resolved **3** (Scheme 2). For example, the partially resolved **3** was obtained with 28% ee (Table 2, entry 2) under these conditions. Unfortunately, further enrichment of the sample gave only 46% ee (Table 2, entry 3).

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(22) Shapiro, M. J.; Ardhinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826. The enantiomeric excess of the amino ether **4** with $[\alpha]^{25}_D = +36$ was analysed to be >99% ee by ^{1}H NMR (400 MHz) analysis in $CDCl_3$ using (*S*)-(+)-binaphthyl phosphoric acid. ^{1}H NMR for (±)-**4** with (*S*)-(+)-binaphthyl phosphoric acid in a 1:1 ratio was analyzed at 400 MHz and gave clear doublets at δ 3.27 and δ 3.28 indicating the 50:50 mixture of both enantiomers. Similarly, the optically active amino ether (1*S*,2*S*)-(+)-**4** with $[\alpha]^{25}_D = +36$ was analyzed and found to give only a single peak at δ 3.287. This shows that (1*S*,2*S*)-(+)-**4** was present in >99% optical purity. A typical experiment involves (3.94 mg, 0.02 mmol) of substrate (±)-**4** in 0.6 mL of $CDCl_3$ solvent. One equivalent of (*S*)-(+)-binaphthylphosphoric acid (8.4 mg, 0.024 mmol) was added to the NMR sample, and the NMR spectrum was recorded.

(23) (a) Compounds **1** and **3** were prepared following a reported procedure: Radesca, L.; Bowen, W. D.; Di Paolo, L.; De Costa, B. R. *J. Med. Chem.* **1991**, *34*, 3058. (b) Compounds **2** and **4** were prepared from **1** and **3** through reaction with NaH/CH_3I, and the structures were confirmed using IR, NMR, and mass spectral analysis. (c) Compound **5** was prepared following a reported procedure: Iqbal, J.; Pandey, A. *Tetrahedron Lett.* **1990**, *31*, 575.

Table 1. Resolution of 1 and 2 Using (*R*)-(+)- or (*S*)-(−)-1,1′-Bi-2-naphthol and Boric Acid

				chiral **1** or **2** obtained from			
				precipitate		filtrate	
S no.	substrate % ee	1,1′-bi-2-naphthol *R* or *S*	solvent	% ee[a]/config	yield[b] (%)	% ee[a]/config	yield[b] (%)
1[c]	**1**, 00	*S*	THF	38 (1*R*,2*R*)	40	36 (1*S*,2*S*)	45
2[d]	(1*R*,2*R*)-**1**, 38	*S*	THF	79 (1*R*,2*R*)	40	11 (1*S*,2*S*)	55
3[e]	(1*R*,2*R*)-**1**, 79	*S*	THF	99 (1*R*,2*R*)	35	08 (1*S*,2*S*)	50
4[f]	**2**, 00	*R*	CH_3CN	99 (1*S*,2*S*)	30	40 (1*R*,2*R*)	65

[a] Based on the maximum $[\alpha]^{25}_D$ value +41.4 observed for **2** (**1** was converted to **2** and the $[\alpha]^{25}_D$ was used to determine the ee). [b] Yields of isolated products. [c] (±)-**1** (125 mmol), $B(OH)_3$ (62.5 mmol), and (S)-(−)-1,1′-bi-2-naphthol (125 mmol) in THF (125 mL) were stirred for 6 h at room temperature. [d] (1*R*,2*R*)-**1** (49.4, 38% ee), $B(OH)_3$ (24.7 mmol), and (*S*)-(−)-1,1′-bi-2-naphthol (49.4 mmol) in THF (50 mL) were stirred for 6 h at room temperature. [e] (1*R*,2*R*)-**1** (17 mmol, 79% ee), $B(OH)_3$ (8.5 mmol), and (*S*)-(−)-1,1′-bi-2-naphthol (17 mmol) in THF (30 mL) were stirred for 6 h at room temperature. [f] (±)-**4** (60 mmol), $B(OH)_3$ (20 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (40 mmol) in CH_3CN (150 mL) were refluxed for 12 h.

Table 2. Resolution of 3 Using (*R*)-(+)- or (*S*)-(−)-1,1′-Bi-2-naphthol and Boric Acid

				chiral **3** obtained from			
				precipitate		filtrate	
S no.	substrate % ee	1,1′-bi-2-naphthol *R* or *S*	solvent	% ee[a]/config	yield[b] (%)	% ee[a]/config	yield[b] (%)
1[c]	**3**, 00	*R*	CH_3CN	33 (1*R*,2*R*)	40	20 (1*S*,2*S*)	50
2[d]	**3**, 00	*R*	CH_3CN	28 (1*R*,2*R*)	39	24 (1*S*,2*S*)	50
3[e]	(1*R*,2*R*)-**3**, 28	*R*	CH_3CN	46 (1*R*,2*R*)	41	23 (1*R*,2*R*)	52
4[f]	**3**, 00	*S*	CH_3CN	34 (1*S*,2*S*)	39	18 (1*R*,2*R*)	52

[a] Based on the $[\alpha]^{25}_D$ value +15.7 for 26% ee reported for **3**.[8] [b] Yields of isolated products. [c] (±)-**3** (10 mmol), $B(OH)_3$ (5 mmol) ,and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (20 mL) were refluxed for 12 h. [d] (±)-**3** (50 mmol), $B(OH)_3$ (25 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (50 mmol) in CH_3CN (100 mL) were refluxed for 12 h. [e] (1*R*,2*R*)-**3** (19.18 mmol, 27.7% ee), $B(OH)_3$ (9.59 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (19.18 mmol) in CH_3CN (50 mL) were refluxed for 12 h. [f] (±)-**3** (10 mmol), $B(OH)_3$ (5 mmol), and (*S*)-(−)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (20 mL) were refluxed for 12 h.

Table 3. Resolution of 4 Using (*R*)-(+)- or (*S*)-(−)-1,1′-Bi-2-naphthol and Boric Acid

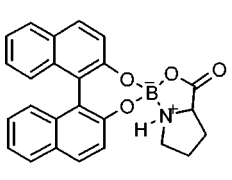
				chiral **4** obtained from			
				precipitate		filtrate	
S no.	substrate % ee	1,1′-bi-2-naphthol *R* or *S*	solvent	% ee[a]/config	yield[b] (%)	% ee[a]/config	yield[b] (%)
1[c]	**4**, 00	*R*	MeOH	40 (1*S*,2*S*)	44	45 (1*R*,2*R*)	32
2[d]	**4**, 00	*R*	MeOH	82 (1*S*,2*S*)	15	50 (1*R*,2*R*)	60
3[e]	**4**, 00	*R*	CH_3CN	40 (1*S*,2*S*)	45	61 (1*R*,2*R*)	35
4[f]	**4**, 00	*R*	CH_3CN	75 (1*S*,2*S*)	40	59 (1*R*,2*R*)	50
5[g]	**4**, 00	*R*	CH_3CN	91 (1*S*,2*S*)	30	72 (1*R*,2*R*)	50
6[h]	**4**, 00	*R*	CH_3CN	93 (1*S*,2*S*)	27	60 (1*S*,2*S*)	65
7[i]	**4**, 00	*R*	CH_3CN	92 (1*S*,2*S*)	25	59 (1*R*,2*R*)	60
8[j]	(1*S*,2*S*)-**4**, 92	*R*	CH_3CN	>99 (1*S*,2*S*)	40	74 (1*S*,2*S*)	50

[a] Based on the maximum $[\alpha]^{25}_D$ value +36 observed for **4**.[22] [b] Yields of isolated products. [c] (±)-**4** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3OH (20 mL) were stirred for 12 h at room temperature. [d] (±)-**4** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3OH (40 mL) were refluxed for 12 h. [e] (±)-**4** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (20 mL) were refluxed for 12 h. [f] (±)-**4** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (40 mL) were stirred for 12 h at room temperature. [g] (±)-**4** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (40 mL) were stirred for 12 h at room temperature. [h] (±)-**4** (15 mmol,), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (40 mL) were stirred for 12 h at room temperature. [i] (±)-**4** (80 mmol,), $B(OH)_3$ (26.6 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (53.2 mmol) in CH_3CN (300 mL) were stirred for 12 h at room temperature. [j] (1*S*,2*S*)-**4** (17.58 mmol, 91.6% ee), $B(OH)_3$ (8.79 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (17.58 mmol) in CH_3CN (80 mL) were stirred for 12 h at room temperature.

Efforts were undertaken to study the nature of the complex formed in the resolution. The precipitate obtained in the resolution of amino alcohol **3** was insoluble in organic solvents.

It was reported that the resolution of racemic 1,1′-bi-2-naphthol was effected by using (S)-proline and boric acid.[16c] The authors proposed the structure **8** on the basis of analytical and spectral data. Accordingly, there is a possibility of the formation of a Lewis acid complex of the type **9** under the present conditions. However, the IR spectrum of the diastereomeric complex obtained exhibited strong absorption at 3410 cm^{-1}, indicating the presence of free OH group. Unfortunately, we were not successful to obtain crystal suitable for X-ray analysis.

It was thought that the OH group of amino alcohol might pose difficulty in the clean formation of the borate complexes, and the possibility of the formation of small amounts of polymeric borate complexes cannot be ruled out. Hence, we have carried out the resolution study



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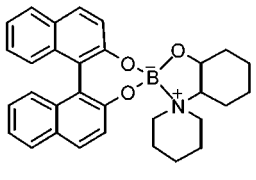


9

using amino ether **4**. Indeed, a significant improvement was observed. For example, when the resolution of amino ether **4** was tried with boric acid and chiral 1,1′-bi-2-naphthol, enantiomerically enriched amino ether **4** was obtained with an optical purity of 91% (Table 3, entry 5). When the amino ether **4** and boric acid were used in

Table 4. Resolution of 5 Using (*R*)-(+)- or (*S*)-(−)-1,1′-Bi-2-naphthol and Boric Acid

				chiral **5** obtained from			
				precipitate		filtrate	
S no.	substrate % ee	1,1′-bi-2-naphthol *R* or *S*	solvent	% ee[a]/config	yield[b] (%)	% ee[a]/config	yield[b] (%)
1[c]	**5**, 00	*R*	CH_3CN	65 (1*R*,2*R*)	25	17 (1*S*,2*S*)	60
2[d]	**5**, 00	*S*	CH_3CN	53 (1*S*,2*S*)	24	16 (1*R*,2*R*)	65
3[e]	(1*R*,2*R*)-**5**, 53	*S*	CH_3CN	84 (1*S*,2*S*)	21	28 (1*R*,2*R*)	67
4[f]	**5**, 00	*R*	THF	12 (1*R*,2*R*)	35	03 (1*S*,2*S*)	60

[a] The ee values reported here are based on reported maximum $[\alpha]^{25}_D = -98.0$ (*c* 0.5, CH_2Cl_2) for 98% ee.[6c] [b] Yields of isolated products. [c] (±)-**5** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (20 mL) were stirred for 6 h at room temperature. [d] (±)-**5** (75 mmol), $B(OH)_3$ (37.5 mmol), and (*S*)-(−)-1,1′-bi-2-naphthol (75 mmol) in CH_3CN (200 mL) were stirred for 6 h at room temperature. [e] (1*R*,2*R*)-**5** (10 mmol, 53 ee), $B(OH)_3$ (5 mmol), and (*S*)-(−)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (35 mL) were stirred for 12 h at room temperature. [f] (±)-**5** (10 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in THF (30 mL) were stirred for 6 h under refluxing conditions.

a 3:1 ratio, the enantiomerically enriched **4** was obtained in higher enantiomeric excess with lower chemical yield from the precipitate fraction (Table 3, entry 6). Enrichment of the partially resolved **4** can also be effected following the same procedure using **4** and boric acid in 2:1 ratio. From the precipitate fraction, the amino ether **4** was obtained in >99% ee (Scheme 2).[22a]

Also, the results were poor under refluxing conditions (Table 3, entry 3). In this case, after usual workup, the precipitate fraction gave the amino ether **4** with optical purity of 40% (45% yield). The filtrate fraction gave the opposite isomer with optical purity of 60% and 35% yield. Hence, we continued with the room-temperature operation. We have found that the THF and MeOH solvents were less effective in the resolution of **3** and **4.** The borate complex formed in the case of the amino ether **4** was analyzed using the X-ray diffraction method.

The crystal suitable for X-ray structure analysis was obtained as follows. The amino ether (±)-**4**, boric acid, and (*R*)-(+)-1,1′-bi-2-naphthol were stirred at room temperature for 12 h (Table 3, entry 7), and the reaction mixture was filtered. The filtrate on standing yielded crystals suitable for X-ray analysis. The data revealed that the borate complex formed in this case is of the type **10a**. The ORTEP diagram of the complex **10b** indicates that the borate complex crystallizes along with an acetonitrile molecule (see the Supporting Information).

We then turned our attention toward the amino alcohol (±)-**5** prepared using aniline to open the cyclohexene oxide. Although this was previously obtained in enantiomerically pure form through asymmetric ring opening of cyclohexene epoxide with aniline,[6C] we have decided to examine the efficacy of borate method for the resolution of **5** (Scheme 2).

It was found that (±)-**5** gave reasonable results in acetonitrile under ambient conditions. Samples with 84% ee have been obtained under these conditions (Table 4, entries 2−3). Previously, samples of **5** with >80% ee have been enriched to 98% ee after a single recrystallization from CH_2Cl_2/heptane.[6C] Unfortunately, the borate complex obtained in this case did not give crystals suitable for X-ray structure analysis.

Resolution of Racemic α,α-diphenyl-2-pyrrolidinemethanol (DPP). The (*S*)-(−)-DPP is required in the preparation of the important CBS oxazaborolidine catalyst, widely used in catalytic asymmetric reductions.[13a] It can be readily prepared from (*S*)-proline.[13b] The corresponding *R* isomer may be prepared from unnatural (*R*)-proline that is somewhat expensive. We have envisaged an economical synthetic route using racemic pyroglutamic acid by a slight modification of a reported procedure via $NaBH_4/I_2$ reduction of the corresponding amide in a crucial step (Scheme 3).[13a]

Scheme 3

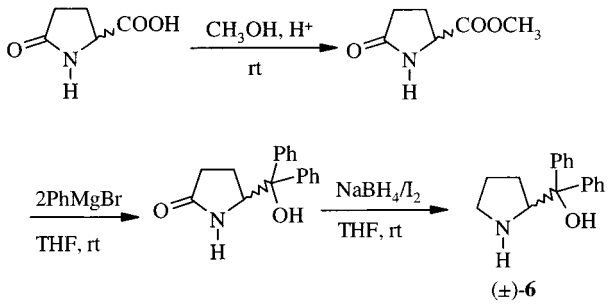


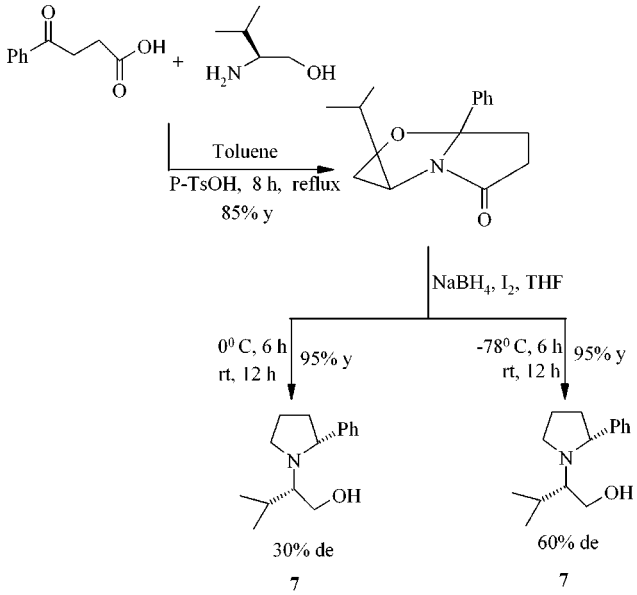
Table 5. Resolution of Racemic 6 Using (*R*)-(+)-1,1′-Bi-2-naphthol and Boric Acid

			chiral **6** obtained from			
			precipitate		filtrate	
S no.	substrate % ee	solvent	% ee[a]/ config	yield[b] (%)	% ee[a]/ config	yield[b] (%)
1[c]	**6**, 00	CH_3CN	90	18	20	80
2[d]	**6*R***, 42	CH_3CN	>99	28	25	69
3[e]	**6*R***, 90	CH_3CN	>99	78	30	20
4[f]	**6**, 00	CH_3OH	60	23	25	72

[a] The ee values reported here are based on reported maximum $[\alpha]^{25}_D = +69.0$ (*c* 3, $CHCl_3$) for the *R* isomer.[24] [b] Yields of isolated products. [c] (±)-**6** (5 mmol), $B(OH)_3$ (5 mmol),and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (10 mL) were stirred for 12 h under refluxing conditions. [d] **6*R*** (5 mmol, 42% ee), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (10 mL) were stirred for 12 h under refluxing conditions. [e] **6*R*** (5 mmol, 90% ee), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3CN (10 mL) were stirred for 12 h under refluxing conditions. [f] (±)-**6** (5 mmol), $B(OH)_3$ (5 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (10 mmol) in CH_3OH (15 mL) were stirred for 12 h at room temperature.

The (±)-DPP **6** was previously resolved using chiral methoxymandelic acid.[13] We have examined the resolution of DPP **6** through preparation of the corresponding diastereomeric borate complex using (*R*)-(+)- or (*S*)-(−)-1,1′-bi-2-naphthol and boric acid under various conditions in CH_3CN and CH_3OH at 25−67 °C. The (*R*)-(+)- and (*S*)-(−)-DPP **6** were obtained in 42−90% ee under these conditions. For example, when the (*R*)-(+)-1,1′-bi-2-naphthol, boric acid, and (±)-DPP **6** were refluxed in CH_3CN for 12 h, the (*R*)-(+)-DPP **6** was obtained after workup from the precipitate fraction with 90% ee (18% yield) (Scheme 2). The filtrate fraction gave (*S*)-(−)-DPP **6** in 20% ee (80% yield) (Table 5, entry 1). The enantiomeric purity of the sample with 90% ee was readily enriched to >99% ee in CH_3CN following the same procedure

Scheme 4



(Scheme 2) (Table 5, entry 3). The results are summarized in Table 5.

The borate complex formed using amino alcohol **6** was also analyzed using the X-ray diffraction method. For the crystal structure analysis, enanatiomerically pure (*R*)-(+)-DPP **6**, boric acid, and (*R*)-(+)-1,1′-bi-2-naphthol were refluxed in CH_3CN for 12 h. The reaction mixture was brought to room temperature and filtered. The filtrate on standing yielded crystals suitable for X-ray analysis. The data reveal that the borate complex is of the type **10a**. The ORTEP diagram of the borate complex **10c** indicates that it crystallizes along with three acetonitrile molecules (see the Supporting Information).

Synthesis and Purification of the Diastereomeric 2-Phenylpyrrolidine System. Asymmetric synthesis of 2-phenylpyrrolidines starting from chiral derivatives has been reported via the corresponding chiral bicyclic lactam prepared using 3-arylpropanoic acid and a chiral amino alcohol.[19] Reduction of this lactam with $LiAlH_4/AlCl_3$ in THF at −78 °C has been reported to give the corresponding pyrrolidine system in 95% de.[19] We have found that this transformation can be readily achieved using the inexpensive $I_2/NaBH_4$ reagent in THF at 0 °C or at −78 °C.[3c] Unfortunately, the amino alcohol **7** obtained at 0 °C was found to be only 30% de, and at −78 °C de of 60% was realized (Scheme 4).

Hence, efforts were undertaken to separate these diastereomers through preparation of the corresponding diastereomeric 1,1′-bi-2-naphthol borate complexes. Indeed, the separation can be readily carried out following this method. The reaction of the diastereomeric mixture **7** with boric acid and chiral 1,1′-bi-2-naphthol was carried out in refluxing CH_3CN for 12 h (Scheme 2).

It was found that the diastereomeric mixture of **7** with 30% de gave the sample with >99% de from precipitate fraction in 42% yield. Whereas the filtrate fraction gave a mixture with 10% de in 38% yield. Similarly, the mixture of 7 with 60% de could be purified to obtain a sample of >99% de in 43% yield (Table 6, entries 1−3).

The borate complex formed in this case was also analyzed using the X-ray diffraction method. The mixture of **7 (**60% de), boric acid and (*R*)-(+)-1,1′-bi-2-naphthol were refluxed in CH_3CN for 12 h. The reaction mixture was brought to room temperature and filtered. Recrystallization of the precipitate in CH_3CN yielded crystals suitable for X-ray crystal structural analysis.

The data revealed that the borate complex is of the type **10a**. The ORTEP diagram of this complex **10d** indicates that the borate complex crystallizes with one CH_3CN molecule (see the Supporting Information).

Table 6. Purification of Diastereomeric 7 Using (*R*)-(+)-1,1′-Bi-2-naphthol and Boric Acid

		chiral **7** obtained from			
		precipitate		filtrate	
S no.	substrate % de	% de[a]	yield[b] (%)	% de[a]	yield[b] (%)
1[c]	**7**, 30	99	42	10	38
2[d]	**7**, 60	99	43	20	39

[a] Based on the HPLC analysis. [b] Yields of isolated products. [c] A diastereomeric mixture of **7** (15 mmol, 30% de), $B(OH)_3$ (10 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (15 mmol) in CH_3CN (20 mL) were refluxed for 12 h. [d] A diastereomeric mixture of **7** (15, 60% de), $B(OH)_3$ (10 mmol), and (*R*)-(+)-1,1′-bi-2-naphthol (15 mmol) in CH_3CN (20 mL) were refluxed for 12 h.

Experimental Section

The chiral 1,1′-bi-2-naphthol was prepared following the resolution procedure developed in this laboratory using chiral 1-phenylethylamine, boric acid, and racemic 1,1′-bi-2-naphthol.[16] The resolving agent (*R*)-(+)-1-phenylethylamine (98−99% ee) was used. The amino alcohols and amino ethers were prepared following the reported procedures.[23] Cyclohexene oxide, pyrrolidine, piperidine, (*S*)-proline, and (*S*)-valine were used as received. Aniline was distilled before use.

Resolution of Racemic 1 Using (*S*)-(−)-1,1′-Bi-2-naphthol and Boric Acid (General Procedure). (*S*)-(−)-1,1′-Bi-2-naphthol (125 mmol, 35.75 g), $B(OH)_3$ (62.5 mmol, 3.86 g), and the racemic amino alcohol **1** (125 mmol, 21.1 g) were stirred in THF (125 mL) for 6 h. The reaction mixture was filtered. The precipitate was suspended in a mixture of ether (200 mL) and dilute HCl (1 N, 200 mL) and stirred until complete dissolution occurred. The (*S*)-(−)-1,1′-bi-2-naphthol (90%) was recovered from the ether layer. The aqueous layer was treated with NaOH/ether, and the free amino alcohol was extracted with ether (3 × 100 mL). The combined organic extracts were washed with saturated brine, dried over anhydrous magnesium sulfate, and evaporated to dryness to obtain (1*R*,2*R*)-(−)-**1**, 8.44 g, 38% ee (40% yield), $[\alpha]^{25}_D = -23.18$ (*c* 0.97, CH_2Cl_2).[16b] The filtrate was concentrated, and the residue was digested in a mixture of ether (200 mL) and dilute HCl (1 N, 200 mL). After workup as outlined above, the (1*S*,2*S*)-(+)-**1** was obtained: yield 9.50 g (45%); 36% ee; $[\alpha]^{25}_D = +21.91$ (*c* 1.02, CH_2Cl_2);[16b] bp 130 °C/12 mmHg, (lit.[23a] bp 76 °C/0.25 mmHg); ^{13}C NMR (200 MHz, $CDCl_3$) δ 70.73, 64.97, 47.18, 33.30, 25.36, 24.21, 23.62, 21.15.

The *trans*-(±)-1-methoxy-2-(1-pyrrolidinyl)cyclohexane **2** was resolved following the same procedure using (*R*)-(+)-1,1′-bi-2-naphthol (Table 1). After workup, (1*S*,2*S*)-(+)-**2** was obtained from the precipitate fraction: yield 3.14 g (30%); >99% ee; $[[\alpha]^{25}_D = +41.4$ (*c* 0.97, $CH_2Cl_2)]$.[16b] The filtrate fraction after workup gave the amino ether (1*R*,2*R*)-(−)-**2**: yield 6.28 g (60%); 40% ee; $[[\alpha]^{25}_D = +16.56$ (*c* 1.24, $CH_2Cl_2)]$;[16b] bp 120 °C/15 mmHg; IR (neat), ν_{max} (cm^{-1}) 2930, 2791, 1458, 1194, 1099; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10−1.45 (m, 4H), 1.52−2.09 (m, 8H), 2.25−2.40 (m, 1H), 2.50−2.70 (m, 1H), 3.15−3.29 (m, 1H), 3.32 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 80.70, 63.90, 56.01, 50.58, 28.05, 26.33, 23.44, 23.13, 22.79; MS *m*/*z* 183, 168, 110, 97, 84, 71, 41.

In a same way, the racemic **3** was also resolved using (*R*)-(+)-1,1′-bi-2-naphthol (Table 2). After workup, (1*R*,2*R*)-(−)-**3** was obtained from the precipitate fraction: yield 3.51 g (39%); 28% ee; $[\alpha]^{25}_D = -16.66$ (*c* 0.72, MeOH) [lit.[8] for 26% ee, $[\alpha]^{25}_D = +15.7$ (*c* 3, MeOH)] (Table 2, entry 2). The filtrate fraction after workup gave the amino alcohol (1*S*,2*S*)-(+)-**3**: yield 4.57

g (50%); 23.9% ee; $[\alpha]^{25}_D = +14.38$ (*c* 0.92, MeOH) [lit.[8] for 26% ee, $[\alpha]^{25}_D = +15.7$ (*c* 3, MeOH)]; bp 100 °C/1 mmHg [lit[8] bp 70−72 °C/0.2 mmHg]; ^{13}C NMR (200 MHz, $CDCl_3$) δ 71.00, 68.52, 49.72, 33.26, 26.73, 25.62, 24.85, 24.11, 22.13.

The racemic amino ether **4** was also resolved following the same procedure using (*R*)-(+)-1,1′-bi-2-naphthol (Table 3). After workup, (1*S*,2*S*)-(+)-**4** was obtained from the precipitate fraction: yield 3.9 g (25%); >92% ee [$[\alpha]^{25}_D = +33.2$ (*c* 0.97, CH_2Cl_2)][22] (Table 3, entry 7). The filtrate was concentrated, and the residue was digested in a mixture of ether (100 mL) and dilute HCl (1 N, 100 mL). After workup, the (1*R*,2*R*)-(−)-**4** was obtained: yield 9.45 g (60%); 59% ee [$[\alpha]^{25}_D = +21.24$ (*c* 1.02, CH_2Cl_2)];[22] bp 120 °C/2 mmHg; IR (neat), ν_{max} (cm^{-1}) 2928, 2854, 1452, 1190, 1103; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05−1.3 (m, 6H), 1.35−2.20 (m, 8H), 2.25−2.40 (m, 1H), 2.45−2.75 (m, 4H), 3.0−3.15 (m, 1H), 3.35 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 79.97, 68.57, 56.53, 50.44, 31.27, 26.82, 25.84, 25.28, 25.13, 24.53; MS *m*/*z* 197, 182, 168, 124, 110, 98, 84, 55, 41.

In a same way, the racemic **5** was also resolved using (*R*)-(+)-1,1′-bi-2-naphthol (Table 4). After workup, (1*S*,2*S*)-(+)-**5** was obtained from the precipitate fraction: yield 3.43 g (24%); 53% ee; $[\alpha]^{25}_D = +51.73$ (*c* 1.052, CH_2Cl_2) [lit.[6c] for 98% ee, $[\alpha]^{25}_D = -98.0$ (*c* 0.5, CH_2Cl_2)] (Table 4, entry 2). It was further enriched to obtain sample of 84% ee following the same procedure. The filtrate fraction after workup gave the amino alcohol (1*R*,2*R*)-(−)-**5**: yield 9.31 g (65%); 16% ee; $[\alpha]^{25}_D = -15.61$ (*c* 0.87, CH_2Cl_2);[6c] mp 79−81 °C (lit.[6d] mp 78−81 °C); ^{13}C NMR (200 MHz, $CDCl_3$) δ 147.91, 129.36, 118.34, 114.40, 74.54, 60.16, 33.23, 31.65, 25.04, 24.32

The same procedure was also followed for the resolution of (±)-DPP **6** using (*R*)-(+)-1,1′-bi-2-naphthol (Table 5). After workup, (*R*)-(+)-DPP **6** was obtained from the precipitate fraction: yield 0.22 g (18%); 90% ee; $[\alpha]^{25}_D = +62.1$ (*c* 3, $CHCl_3$) [lit.[24] for 100% ee, $[\alpha]^{25}_D = +69.0$ (*c* 3, $CHCl_3$)] (Table 5, entry 1). It was further enriched following the same procedure to obtain a sample of >99% ee (Table 5, entry 3). The filtrate fraction after workup gave the amino alcohol (*S*)-(−)-DPP **6**: yield 1 g (80%); 20% ee; $[\alpha]^{25}_D = -13.8$ (*c* 3, $CHCl_3$);[24] ^{13}C NMR (200 MHz, $CDCl_3$) δ 148.19, 145.48, 128.24, 127.97, 126.47, 126.38, 125.92, 125.58, 77.1, 64.55, 46.78, 26.33, 25.52.

In a same way, the diastereomeric mixture (+)-*N*-[2-(1-hydroxy-2(*S*)-isopropyl)ethyl]-5-phenyl-2-pyrrolidine **7** was purified using (*R*)-(+)-1,1′-bi-2-naphthol (Table 6). After workup, (2*R*,5*S*)-(+)-**7** was obtained from the precipitate fraction: yield 1.47 g (42%); >99% de; $[\alpha]^{25}_D = +81.89$ (C 0.81, $CHCl_3$); IR (neat), ν_{max} (cm^{-1}) 3443, 3061, 3028, 2960, 2873, 1602; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82−0.85 (d, *J* = 6.7 Hz, 3H), 0.9−1.0 (d, *J* = 6.78 Hz, 3H), 1.80−2.5 (m, 6H), 2.7−2.85 (q, 1H), 3.0−3.5 (m, 4H), 4.04 (t, *J* = 7.3 Hz, 1H), 7.26−7.32 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 143.94, 128.31, 127.40, 127.00, 65.76, 61.80, 59.60, 44.25, 34.30, 29.98, 23.31, 22.14, 19.50. HPLC analysis of this compound on chiralcel OD column using hexane/2-propanol (98:2) as eluent revealed that the diastereomer obtained was >99% de. The filtrate fraction after workup gave the amino alcohol (2*R*,5*S*)-(+)-**7**: yield 1.33 g (38%); 10% de; $[\alpha]^{25}_D = +8.2$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80−0.85 (m, 3H), 0.98−1.04 (m, 3H), 1.8−2.5 (m, 6H), 2.7−2.85 (q, 1H), 2.83−3.7 (m, 4H), 4.04 (t, *J* = 7.3 Hz, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 145.4, 144.07, 128.66, 128.17, 127.74, 127.37, 126.79, 66.13, 64.70, 64.45, 62.05, 59.83, 48.82, 44.51, 35.81, 34.56, 28.67, 27.26, 23.77, 23.59, 22.47, 21.29, 20.30, 19.80.

X-ray Crystal Structure Analysis. The X-ray structure data and ORTEP diagrams are given in the Supporting Information. Final atomic coordinates of the complexes **10b**−**d** along with lists of the anisotropic thermal parameters hydrogen coordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre. They can be obtained, on request, from the Director, Crystallographic Data Centre 12 Union Road, Cambridge CB2 1EZ, U.K.

Conclusions

Simple and convenient procedures for the resolutions of racemic amino alcohol derivatives **1**−**6** to obtain enantiomerically enriched compounds using chiral 1,1′-bi-2-naphthol and $B(OH)_3$ have been developed. Purification of the diastereomeric mixture **7** was also developed using the same method. The intermediate ammonium borate complexes were characterized by X-ray diffraction method. Besides being useful for the synthesis of these chiral amino alcohol derivatives, the method described here should also stimulate further work on the resolution of other related racemic amino alcohols, amines and polyols via such diastereomeric borate complexes.

Acknowledgment. We are thankful to the CSIR and UGC, New Delhi, for support under a Special Assistance Program. X-ray structure analysis was carried out using the National Single Crystal X-ray Facility, School of Chemistry, University of Hyderabad, funded by DST, New Delhi.

Supporting Information Available: ^{13}C NMR spectra of amino alcohol derivatives **1**−**7** and X-ray crystal structure analysis and ORTEP diagrams for the complexes **10b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0057755

(24) *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich: Milwaukee, 1998−1999; catalog no. 38, 233-7.