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Resolution of *trans*-(±)-2-(pyrrolidinyl)cyclohexanol and its methyl ether using boric acid and chiral 1,1′-bi-2-naphthol

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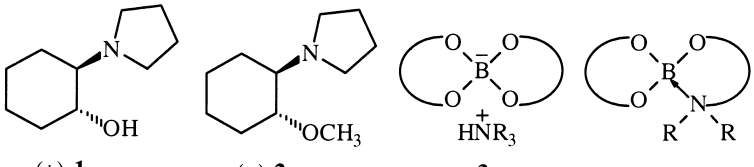
Abstract

The *trans*-(±)-2-(pyrrolidinyl)cyclohexanol **1**, and its methyl ether **2** were resolved using chiral 1,1′-bi-2-naphthol and boric acid in THF or CH_3CN. X-Ray structural analysis was carried out for the diastereomeric complex **3** obtained using **2**.

Chiral amino alcohols are important compounds used widely in asymmetric synthesis as chiral ligands or chiral auxiliaries[1] and in medicinal chemistry as therapeutic agents.[2] These compounds are generally prepared from the naturally occurring α-amino acids. However, they can also be readily prepared through opening of epoxides followed by resolution using tartaric acid[3] or binaphthyl phosphoric acid.[4]

During the course of our research efforts on the synthesis and application of chiral amino alcohols,[5] we attempted the resolution of the amino alcohol **1**, prepared through opening of cyclohexene oxide with pyrrolidine[6] and its methyl ether **2** using tartaric acid and binaphthyl phosphoric acid, but these experiments did not yield fruitful results.



(±)-**1** (±)-**2** **3** **4**

In recent years, we have developed resolution procedures for 1,1′-bi-2-naphthol, 1,2-diphenyl-1,2-ethanediol and 1,1,2-triphenyl-1,2-ethanediol using (*S*)-proline via preparation of diastereomeric inclusion complexes or borate complexes.[7] It has also been observed that racemic 1,1′-bi-2-naphthol can be readily resolved using chiral α-methylbenzylamine in the presence of $B(OH)_3$ in solvents such as CH_3CN and THF through formation of the corresponding Brønsted acid–ammonium salt **3**.[7] Accordingly, in principle, it should be possible to resolve the racemic amine derivatives through preparation of such diastereomeric salts using chiral 1,1′-bi-2-naphthol; indeed, this was observed. It was found that the

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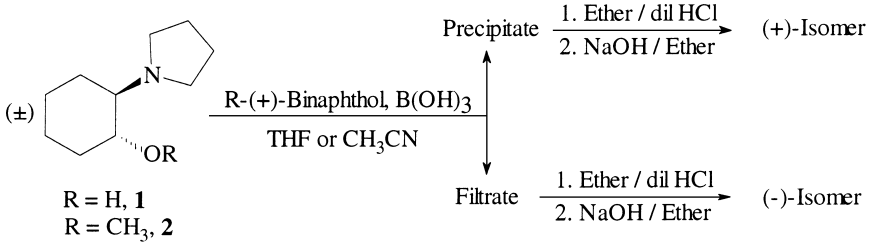
resolution of **1** and **2** can be readily achieved using chiral 1,1′-bi-2-naphthol and $B(OH)_3$ in various solvents (Scheme 1). The results are presented in Table 1.



Scheme 1.

When the amino ether **2** and $B(OH)_3$ were used in a 3:1 ratio (Table 1, entries 7 and 8), (1*S*,2*S*)-**2** was obtained in a higher ee with lower chemical yield from the precipitate fraction. Also the (1*R*,2*R*)-**2** was obtained in a lower ee from the filtrate fraction. Enrichment of the partially resolved amino ether **2** was also carried out following this procedure (Scheme 1). The maximum $[\alpha]_D^{25}$ value obtained was +41.4. No further enhancement of the $[\alpha]_D^{25}$ value was obtained when samples with $[\alpha]_D^{25}$=+41.4 were used.

Table 1
Resolution of **1** or **2** using (*R*)- or (*S*)-1,1′-bi-2-naphthol and boric acid

S No	Substrate % ee	1,1'-Bi-2-Naphthol R or S	Solvent	Chiral **1** or **2** obtained from: Precipitate % ee[a]/Conf.	Precipitate Yield (%)[b]	Filtrate % ee[a]/Conf.	Filtrate Yield (%)[b]
1[c]	**1**, 00	*S*	MeOH	67 (1*R*,2*R*)	20	22 (1*S*,2*S*)	60
2[d]	**1**, 00	*S*	THF	38 (1*R*,2*R*)	40	36 (1*S*,2*S*)	45
3[e]	(1*R*,2*R*)-**1**, 38	*S*	THF	79 (1*R*,2*R*)	40	11 (1*R*,2*R*)	55
4[f]	(1*R*,2*R*)-**1**, 79	*S*	THF	>99 (1*R*,2*R*)	35	08 (1*R*,2*R*)	50
5[g]	**1**, 00	*R*	THF	49 (1*S*,2*S*)	40	14 (1*R*,2*R*)	50
6[h]	**2**, 00	*R*	MeOH	74 (1*S*,2*S*)	20	18 (1*R*,2*R*)	65
7[i]	**2**, 00	*R*	CH_3CN	77 (1*S*,2*S*)	41	65 (1*R*,2*R*)	48
8[j]	**2**, 00	*R*	CH_3CN	83 (1*S*,2*S*)	30	44 (1*R*,2*R*)	63
9[k]	(1*S*,2*S*)-**2**, 83	*R*	CH_3CN	>99 (1*S*,2*S*)	42	66 (1*S*,2*S*)	42
10[l]	(1*R*,2*R*)-**2**, 67	*S*	CH_3CN	97 (1*R*,2*R*)	43	37 (1*R*,2*R*)	52

a. Based on the maximum $[\alpha]_D^{25}$ value +41.4 observed for **2** (**1** was converted to **2** and the $[\alpha]_D^{25}$ was used to determine the ee). b. Yields of isolated products. c. (±)-**1** (10 mmol), $B(OH)_3$, (5 mmol) and (*S*)-(-)-1,1'-bi-2-naphthol (10 mmol) in MeOH (20 ml) were stirred for 6 hr at rt. d. (±)-**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 hr at rt. e. (1*R*,2*R*)-**1** (49.4 mmol, 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 hr at rt. f. (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 hr at rt. g. (±)-**1** (10 mmol), $B(OH)_3$, (5 mmol) and (*R*)-(+)-1,1'-bi-2-naphthol (10 mmol) in THF (20 ml) were stirred for 6 hr at rt. h. (±)-**2** (10 mmol), $B(OH)_3$, (5 mmol) and (*R*)-(+)-1,1'-bi-2-naphthol (10 mmol) in MeOH (40 ml) were stirred for 12 hr at rt. i. (±)-**2** (19 mmol), $B(OH)_3$, (9.5 mmol) and (*R*)-(+)-1,1'-bi-2-naphthol (19 mmol) in CH_3CN (70 ml) were refluxed for 12 hr. j. (±)-**2** (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 hr. k. (1*S*,2*S*)-**2** (18.2 mmol, 83% ee), $B(OH)_3$, (9.1 mmol) and (*R*)-(+)-1,1'-bi-2-naphthol (18.2 mmol) in CH_3CN (80 ml) were refluxed for 12 hr. l. (1*R*,2*R*)-**2** (10 mmol, 67% ee), $B(OH)_3$, (5 mmol) and (*S*)-(-)-1,1'-bi-2-naphthol (10 mmol) in CH_3CN (40 ml) were refluxed for 12 hr.

The enantiomeric excess of the amino ether **2** with $[\alpha]_D^{25}$=+41.4 was analysed to be >99% by ^{1}H NMR (400 MHz) analysis in $CDCl_3$ using (*S*)-(+)-binaphthyl-2,2′-diyl phosphoric acid.[8]

X-Ray structural analysis[9] of the crystal of the complex obtained in the amino ether resolution experiment (Table 1, entry 8) was carried out. It revealed that the 1,1′-bi-2-naphthol forms a Brønsted acid with boric acid, which in turn gives diastereomeric salt **3** with the amino ether **2**. The complex **3** crystallised along with three CH_3CN molecules. The ORTEP diagram of the crystal structure is shown in Fig. 1.

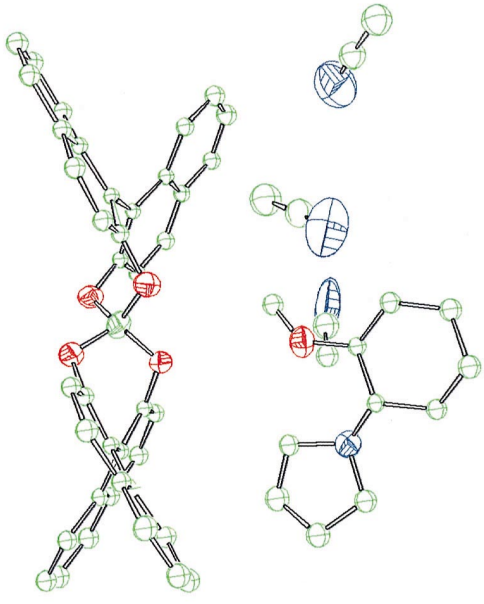


Figure 1. ORTEP diagram for complex **3**

Suitable crystals for X-ray analysis could not be obtained in the case of the diastereomeric complex prepared using amino alcohol **1**. In this case, there is a possibility of the formation of a Lewis acid complex of the type **4**.[10] However, the IR spectrum of the diastereomeric complex obtained from **1** exhibited an OH absorption at 3410 cm^{-1}, indicating that the complex formed here could also be the Brønsted acid complex **3**.

Experimental procedure for the resolution of **2**: (*R*)-(+)-1,1′-Bi-2-naphthol (40 mmol, 11.45 g), $B(OH)_3$ (20 mmol, 1.24 g) and the racemic amino ether **2** (60 mmol, 11 g) were refluxed in CH_3CN (150 ml) for 12 h. The reaction mixture was cooled to room temperature and filtered. The precipitate was suspended in a mixture of ether (80 ml) and dil. HCl (1N, 80 ml) and stirred until complete dissolution occured. The (*R*)-(+)-1,1′-bi-2-naphthol was recovered from the ether layer. The aqueous layer was treated with NaOH/ether and the free amino ether was extracted with ether (3×50 ml). The combined organic extracts were washed with saturated brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain (1*S*,2*S*)-**2**, 3.3 g, 83% ee (30% yield). The filtrate was concentrated and the residue was taken up in a mixture of ether (80 ml) and dil. HCl (1N, 80 ml) followed by workup as outlined above to obtain (1*R*,2*R*)-**2**, 6.9 g, 44% ee (63% yield). After further enrichment of the sample with 83% ee following the same procedure, (1*S*,2*S*)-**2** with >99% ee (42% yield) was obtained from the precipitate fraction (Table 1, entry 8). The filtrate fraction after workup gave the amino ether (1*S*,2*S*)-**2**, with 67% ee (42% yield).

Acknowledgements

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9. Crystal structure analysis: The X-ray diffraction measurements were carried out at 293 K on an automated Enraf–Nonius MACH 3 diffractometer using graphite monochromated Mo-Kα (λ=0.71073 Å) radiation. Intensity data were collected by the ω-scan mode. The data were reduced using the XTAL programme. No absorption correction was applied. The θ range for data collection is 1.54 to 24.97°. Crystal structure data: empirical formula $C_{57}H_{54}BN_4O_5$, colourless rectangular prism (0.3×0.3×0.4 mm), crystal system is orthorhombic, space group $P2_12_12_1$, unit cell dimensions: a=11.343(4) Å, b=16.169(6) Å, c=26.395(4) Å. Volume 4841(2) $Å^3$, Z=4, D_{calc}=1.216 Mg/m^3, absorption coefficient is 0.077 mm^{-1}, F(000)=1876, index ranges $0\leq h\leq 13$, $0\leq k\leq 19$, $0\leq l\leq 31$, total reflections collected were 4823 out of which 4736 were independent reflections with R(int)=0.0069 and R(sigma)=0.0941. The structure was solved by direct methods and refined by a full-matrix least-squares procedure using the SHELX 86 and SHELX 97 programme package, respectively. The refinement was carried out using 4736 observed [$F>4\sigma(F)$] reflections and converged to a final $R1$=0.0655, $wR2$=0.1268 and goodness of fit was 1.013 with the largest difference between peak and hole 0.231 and −0.196 e $Å^{-3}$, respectively. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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