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Synthesis and resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol and its application in the resolution of 2,2′-dihydroxy-1,1′-binaphthyl

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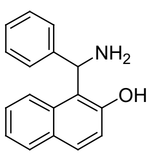
Abstract—1-(α-Pyrrolidinylbenzyl)-2-naphthol **2** is easily prepared in 95% yield using benzaldehyde, 2-naphthol and pyrrolidine in ethanol at 78 °C. It is resolved using inexpensive L-(+)-tartaric acid to obtain non-racemic samples that can be readily purified to enantiomeric purity through preparation of hydrogen bonded aggregates. The homochiral 1-(α-pyrrolidinylbenzyl)-2-naphthol **2** is useful in the resolution of racemic 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) **3** via preparation of the corresponding diastereomeric borate complexes using $B(OH)_3$.

1. Introduction

Resolution and asymmetric synthesis are the methodologies available to obtain homochiral compounds.[1] In recent years, there has been widespread interest in the development of new methodologies for asymmetric synthesis.[2–4] Though resolution methods are still widely used in large-scale preparations, especially if both the enantiomers are required, there has been much interest on the development of new resolution methods. As part of investigations into methods of resolutions via the preparation of diastereomeric borate complexes, we report the synthesis of enantiopure 1-(α-pyrrolidinylbenzyl)-2-naphthol **2** and its application in the resolution of (±)-2,2′-dihydroxy-1,1′-binaphthyl (BINOL) **3**.

2. Results and discussion

Aminonaphthol **1** is easily prepared by the condensation of 2-naphthol with ammonia and benzaldehyde.[5] Although, these derivatives have been known since the beginning of the 20th century, their applications in organic synthesis are of recent interest.[6,7] The original Betti base **1** is thermally unstable[5,8] and hence it is not suitable for the preparation of the corresponding *N*,*N*-dialkyl derivatives under drastic conditions.[9] Fortunately, the pyrrolidinyl derivative of aminonaphthol **2** can be readily prepared following the original Betti procedure,[10] starting from benzaldehyde, 2-naphthol and pyrrolidine at 78 °C. Racemic **2** can be readily resolved using the inexpensive L-(+)-tartaric acid (Scheme 1).



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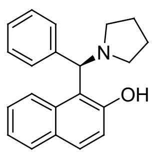

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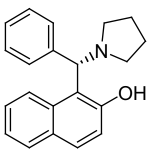

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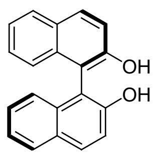

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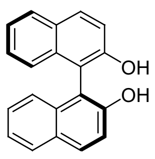

(*S*)-3

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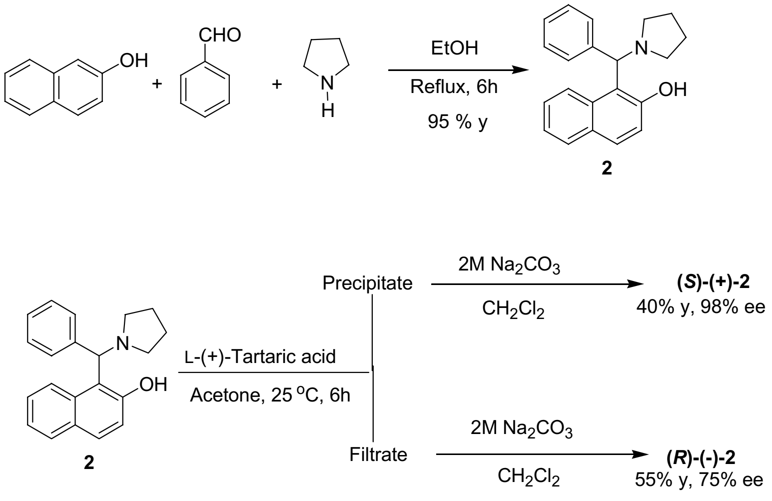


Scheme 1.

Recently, we have devised a simple method of purification of certain non-racemic samples of amino alcohols via preparation of the hydrogen bonded aggregates using achiral dicarboxylic acids.[11] We have found that this methodology is useful in the purification of the non-racemic samples of **2** using oxalic acid. Optimized results are obtained when the experiments were carried out using oxalic acid equivalent to the excess of the enantiomer of **2** present in the mixture. In these experiments, samples of **2** obtained from the precipitate fraction showed higher ees than those isolated from the filtrate fraction. The results are summarized in Table 1.

Most probably, this is due to the predominant formation of the homochiral aggregates through a hydrogen bonding network in the precipitate fraction. This was confirmed by single crystal X-ray analysis of the complex obtained using non-racemic sample **2** and oxalic acid (Figs. 1 and 2, Table 1, entry 4).[13] The packing diagram showed layers of intermolecularly hydrogen bonded mono-anions of the acid alternating with layers of intermolecularly hydrogen bonded aminonaphthol moieties through N–H···O and O–H···O interactions. The alternate layers of aminonaphthols are found to be homochiral to each other.

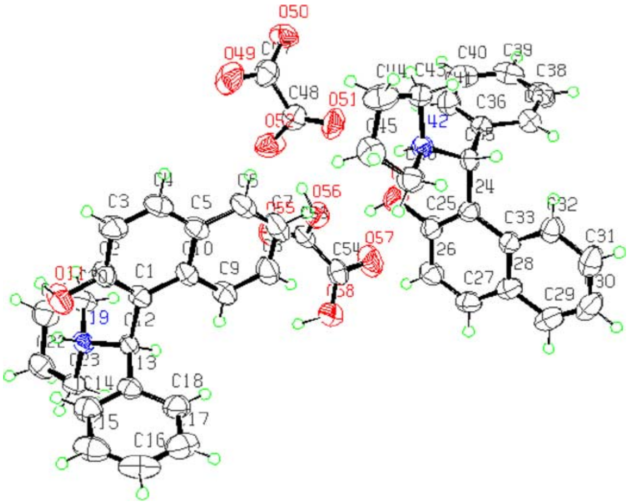


Figure 1. ORTEP diagram of the aminonaphthol (*R*)-**2** and oxalic acid complex (Table 1, entry 4).

Previously, it was observed in this laboratory that one of the most widely used chiral compounds BINOL **3** can be readily prepared in enantiomerically pure form by preparation of diastereomeric inclusion complexes with

Table 1. Purification of non-racemic aminonaphthol **2** using oxalic acid[a]

S. no	Substrate (%ee)	Oxalic acid (mmol)	Aminonaphthol obtained from			
			Precipitate		Filtrate	
			%Ee[b]/conf.	Yield (%)[c]	%Ee[b]/conf.	Yield (%)[c]
1	(*S*)-**2**, 40	2.00	73 (*S*)	40	20 (*S*)	38
2	(*R*)-**2**, 45	2.25	80 (*R*)	35	28 (*R*)	48
3	(*S*)-**2**, 50	2.50	96 (*S*)	58	05 (*S*)	34
4	(*R*)-**2**, 50	2.50	⩾99 (*R*)	42	09 (*R*)	46
5	(*S*)-**2**, 65	3.25	⩾99 (*S*)	60	10 (*S*)	30
6	(*R*)-**2**, 75	3.75	⩾99 (*R*)	67	15 (*R*)	25
7	(*S*)-**2**, 90	4.50	⩾99 (*S*)	87	56 (*S*)	09
8	(*R*)-**2**, 92	4.60	⩾99 (*R*)	85	60 (*R*)	05

[a] All the reactions were carried out using non-racemic aminonaphthol **2** (5 mmol) and oxalic acid in acetone (70 mL).

[b] All ee values reported here are based on maximum[12] $[\alpha]_D^{25} = +179.1$ (*c* 1.30, $CHCl_3$) for (*S*)-**2**. These maximum ees were further confirmed by using Eu(tfc)$_3$, as chiral shift reagent.

[c] The yields are of the isolated products, based on the total amount of the starting non-racemic mixture used.

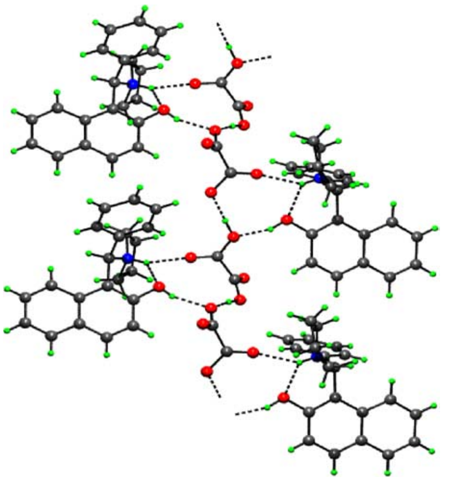
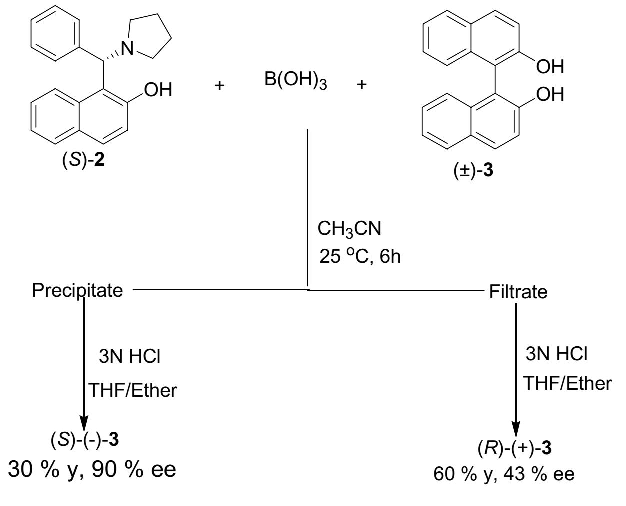


Figure 2. Packing diagram of the aminonaphthol (*R*)-**2** and oxalic acid complex (Table 1, entry 4).

(*S*)-proline or borate complexes using chiral α-methylbenzylamine and boric acid.[14,15] Also, the BINOL **3** forms diastereomeric borate complexes using certain amino alcohols.[16] Accordingly, we have examined the resolution of BINOL **3** using the readily accessible aminonaphthol **2**. We have observed that the racemic BINOL **3** reacts with aminonaphthol (*S*)-**2** and boric acid in CH_3CN solvent to give precipitate and filtrate fractions (Scheme 2). After digestion of the precipitate fraction BINOL **3** enriched in (*S*)-enantiomer (90% ee) was obtained. After workup, (*R*)-**3** isomer (43% ee) was obtained from the filtrate fraction. Comparable results were obtained in runs using aminonaphthol (*R*)-**2**. These partially resolved samples of 43–90% ee can be easily purified to obtain samples of >99% ee using $B(OH)_3$ and TMEDA.[17]



Scheme 2.

In conclusion, the readily accessible chiral aminonaphthol **2** is useful in the resolution of the widely used chiral 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) **3**. Since, it can be readily recovered and reused, it has good potential for further synthetic exploitations.

3. Experimental section

3.1. Synthesis of 1-(α-pyrrolidinylbenzyl)-2-naphthol *2*

Benzaldehyde (13.2 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this pyrrolidine (8.4 mL, 100 mmol) was added and the reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and washed with 90% ethanol to isolate 1-(α-pyrrolidinylbenzyl)-2-naphthol **2** as white solid. Yield: 28.8 g (95%); mp 176–177 °C. IR (KBr): 3120, 3057, 2970, 2845, 1620, 1452,1238,750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 13.9$ (br s, 1H), 7.91 (d, $J = 8.6$ Hz, 1H), 7.88–7.65 (m, 4H), 7.64–7.21 (m, 6H), 5.15 (s, 1H), 3.27 (br s, 1H), 2.44 (br s, 3H), 1.89 (br s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 155.6$, 141.3, 131.9, 129.4, 128.8, 128.6, 128.5, 127.8, 127.1, 126.3, 122.3, 121.1, 119.9, 116.7, 70.9, 53.5, 23.4.

3.2. Resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol 2

The L-(+)-tartaric acid (0.75 g, 5 mmol) and aminonaphthol **2** (1.5 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq Na_2CO_3 (2 M) and stirred until dissolution occurred. The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to obtain the (*S*)-(+)-**2** enantiomer (98% ee, 40% yield). The filtrate was concentrated and the residue was treated as outlined above to obtain **2** enriched in the (*R*)-(−)-enantiomer (75% ee, 55% yield).

3.3. Purification of non-racemic aminonaphthol 2

To a solution of non-racemic aminonaphthol (*R*)-**2** (75% ee, 5 mmol) in acetone (70 mL) anhydrous oxalic acid (0.34 g, 3.75 mmol) was added and the contents were stirred at room temperature for 6 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq Na_2CO_3 (2 M) and stirred until dissolution occurred. The organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to dryness to obtain the (*R*)-(−)-**2** isomer (99% ee, 67% yield). The filtrate was concentrated and the residue was treated as outlined above to obtain **2** enriched in the (*R*)-(−)-isomer (15% ee, 25% yield).

3.4. Resolution of 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) 3

(*S*)-(+)-Aminonaphthol **2** (1.5 g, 5 mmol), $B(OH)_3$ (0.31 g, 5 mmol) and racemic BINOL **3** (1.43 g, 5 mmol) were taken in CH_3CN (50 mL) and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of ether and dil HCl (2 N) and stirred until dissolution occurred. The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to obtain the (*S*)-(−)-**3** isomer (90% ee, 30% yield). The filtrate was concentrated and the residue was treated as outlined above to obtain **3** enriched in (*R*)-(+)-isomer (43% ee, 60% yield).

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