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Simple and convenient methods for synthesis, resolution and application of aminonaphthols

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Racemic aminonaphthols are obtained in 70-95% yield by simple and straightforward condensation of benzaldehyde, 2-naphthol and 1° or 2° amines in ethanol solvent under refluxing conditions. The racemic aminonaphthols 1-(α-aminobenzyl)-2-naphthol and 1-(α-pyrrolidinylbenzyl)-2-naphthol have been resolved using L-*(+)*-tartaric acid. The racemic 1-(α-*N*-butylaminobenzyl)-2-naphthol and 1-(α-piperidylbenzyl)-2-naphthol have been resolved using *R*-(+)-BINOL and boric acid. The racemic (2-methoxynaphth-1-yl)benzylamine is resolved using dibenzoyl-L-(-)-tartaric acid. The readiliy accessible chiral aminonaphthols are useful for resolution of important moieties like racemic BINOL, ibuprofen and mandelic acid.

Keywords: Betti reaction, diastereomeric complexes, L-(+)-tartaric acid, 1,1′-bi-2-naphthol, dibenzoyl-L-(-)-tartaric acid, ibuprofen, mandelic acid

Despite unprecedented advances in enantioselective transformations, large scale production of enantiopure substances is still heavily dependent upon the separation of diastereomers obtained from racemic mixtures using an optically active resolving agent[1]. In recent years, there has been widespread interest in the development of new methodologies for asymmetric synthesis[2-4]. Though established resolution methods are still widely used in large-scale preparations, especially if both the enantiomers are required, there has not been much interest on the development of new methods of resolution. Herein, it is wished to report the synthesis and resolution of aminonaphthols using chiral resolving agents such as L-(+)-tartaric acid **2**, *R*-(+)-BINOL **3** and dibenzoyl-L-(-)-tartaric acid **4** (**Figure 1**).

Results and Discussion

Aminonaphthol **1** is easily prepared by the condensation of 2-naphthol with ammonia and benzaldehyde[5]. Though these derivatives were known since the beginning of the 20th century, their application in organic synthesis is of recent origin[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]. Generally, the derivatives of aminonaphthols were prepared by condensation of benzaldehyde, 2-naphthol and amines in ethanol or DCM solvent for 6 days[10,11], in presence of acidic Al_2O_3 or $LiClO_4$ (Ref. 12). Condensation of β-naphthol and preformed iminium salts[13], and photo addition of nucleophiles to 1-alkenyl-2-naphthol also give the aminonaphthols[14].

Accordingly, a simple method has been developed for preparing various derivatives of aminonaphthols following the original Betti procedure[5], starting from benzaldehyde, 2-naphthol and various amines at 78°C in ethanol solvent (**Schemes I** and **II**). In the preparation of aminonaphthols **5-7** using 1° amines, the yields were moderate to good, as the aminonaphthols could react further with benzaldehyde to give the oxazine compounds. However, use of 2° amines gave the products in excellent yield.

Efforts were then undertaken on the resolution of some of these aminonaphthols through formation of diastereomeric complexes using readily available, inexpensive chiral resolving agents. It was observed that L-(+)-tartaric acid formed diastereomeric complexes with aminonaphthols **1** and **9** (**Scheme III**). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically.

To optimize the reaction conditions, the resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol **9** was initially examined using various solvents like acetone, THF,

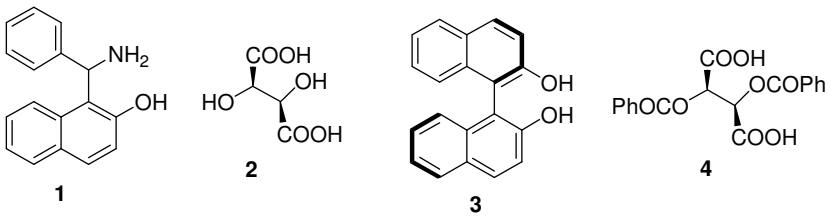
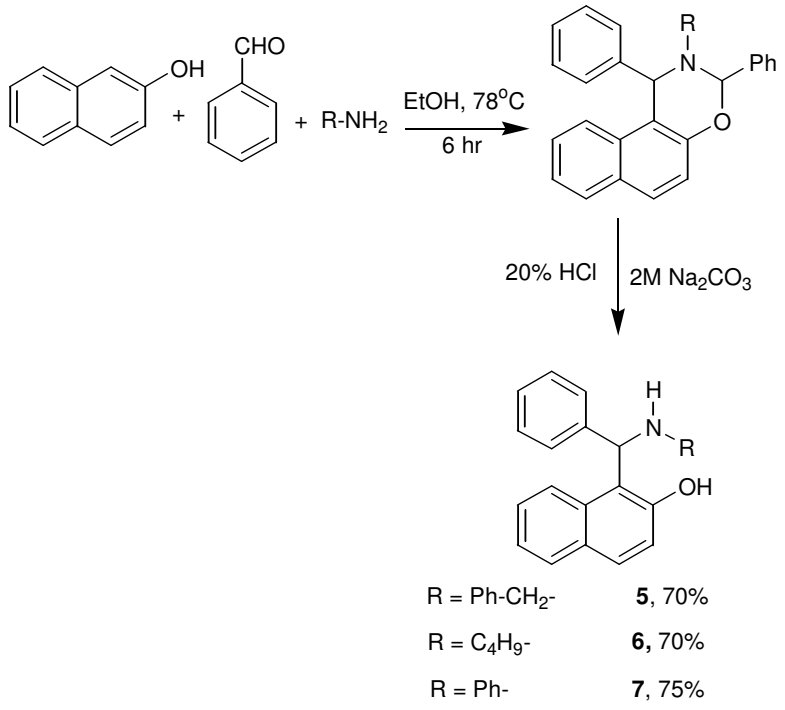
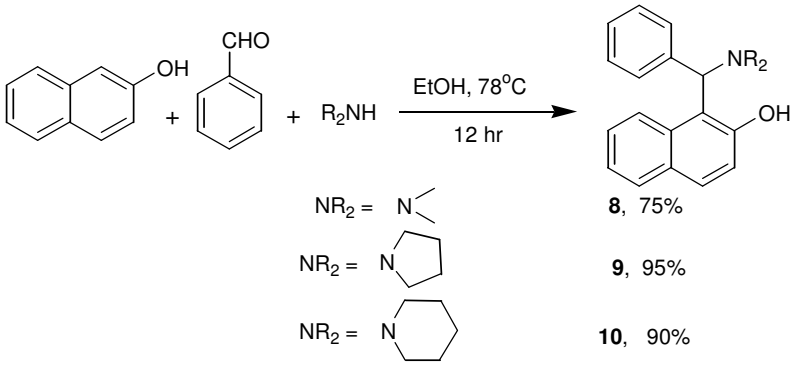


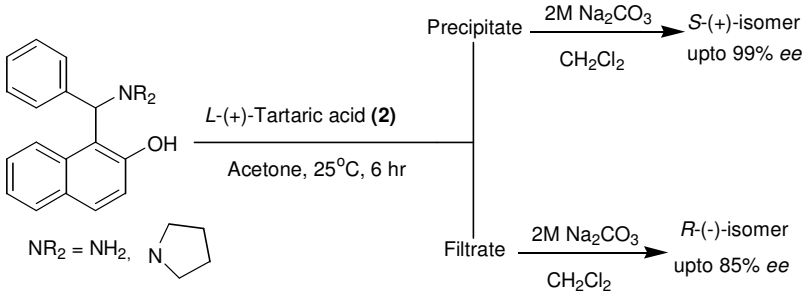
Figure 1 — Chiral resolving agents



Scheme I



Scheme II



Scheme III

Table I — Effect of various solvents on the resolution of aminonaphthol **9**[a]

S.No.	Time (hr)	Solvent	Chiral aminonaphthol **9** obtained from			
			Precipitate		Filtrate	
			% *ee*[b]/Conf.	Yield(%)[c]	% *ee*[b]/Conf.	Yield(%)[c]
1[a]	1	Acetone	35 (*S*)	45	30 (*R*)	50
2[a]	6	Acetone	98 (*S*)	40	75 (*R*)	55
3[a]	12	Acetone	95 (*S*)	40	68 (*R*)	50
4[a]	24	Acetone	94 (*S*)	38	60 (*R*)	53
5	6	DCM	20 (*S*)	35	18 (*R*)	54
6	6	CH_3CN	15 (*S*)	40	10 (*R*)	50
7	6	THF	35 (*S*)	25	15 (*R*)	65
8	6	Ethanol	60 (*S*)	30	30 (*R*)	60
9	6	MeOH	10 (*S*)	60	15 (*R*)	35

[a]Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol **9** (5 mmol) and L-(+)-tartaric acid **2** (5 mmol) in 70 mL of the solvent and stirred at 25°C, [b]All *ee* values reported here are based on reported maximum[15] $[\alpha]_D^{25}$ = +179.1° (*C* 1.30, $CHCl_3$) for (*S*)-**9** and $[\alpha]_D^{25}$ =-179.0° (*C* 1.30, $CHCl_3$) for (*R*)-**9**. These maximum *ee*'s were further confirmed by using $Eu(tfc)_3$ as chiral shift reagent and HPLC using chiralcel OD-H using 10% isopropanol in hexane, [c]The yields are of the isolated products, based on the total amount of starting racemic aminonaphthol **9** used.

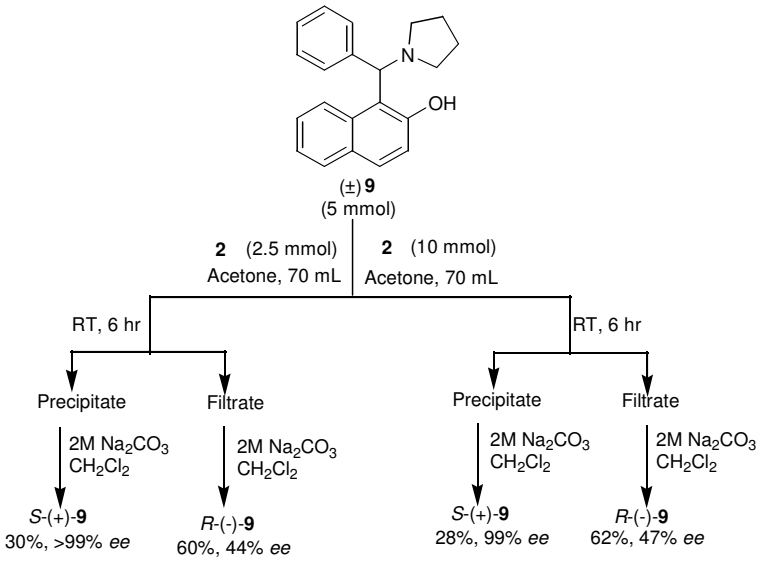
DCM, CH_3CN, ethanol and methanol. In all these solvents, aminonaphthol **9** gave a precipitate within 30 min leading to partial resolution. The results are summarized in **Table I**. Comparison of these results indicates that acetone is the best solvent for the resolution of the aminonaphthol **9**. Ethanol gave moderate *ee* and other solvents gave poor results. It was also observed that increasing the reaction time from 1.0 to 6.0 hr gave better results (**Table I**, entries 1-2) and there was no significant effect on the *ee*'s of the samples obtained when the reaction was carried out for more than 6 hr (**Table I**, entries 2-4).

To determine the optimum amount of the chiral resolving agent required for the resolution process, the effect of concentration of L-(+)-tartaric acid **2** (**Scheme IV**) has been studied.

It is clear that irrespective of the ratio of aminonaphthol **9** and L-(+)-tartaric acid **2** (1:2 or 2:1), enantiomerically pure sample of *S*-(+)-**9** is always obtained from precipitate fraction, and *R*-(-)-**9** obtained in 44-47% *ee* from the filtrate fraction.

The resolution of other aminonaphthols **1**, **6** and **10** was then studied. Recently, Cardellicchio *et al.*[16a] reported the resolution of aminonaphthol **1** using L-(+)-tartaric acid **2** using binary solvent and this procedure involves multiple steps and is somewhat tedious. It has been observed that this process can be readily carried out using only acetone as solvent. The use of aminonaphthol **1** (5 mmol) and L-(+)-tartaric acid **2** (5 mmol) in 60 mL of solvent gave optimum results (**Table II**). During the course of the investigations a similar paper appeared on the kinetic resolution of **1** based on enantioselective *N*,*O*-deketalisation[16b].

Cardellicchio *et al.*[10] also reported the resolution of aminonaphthol **6** using L-(+)-tartaric acid. This



Scheme IV

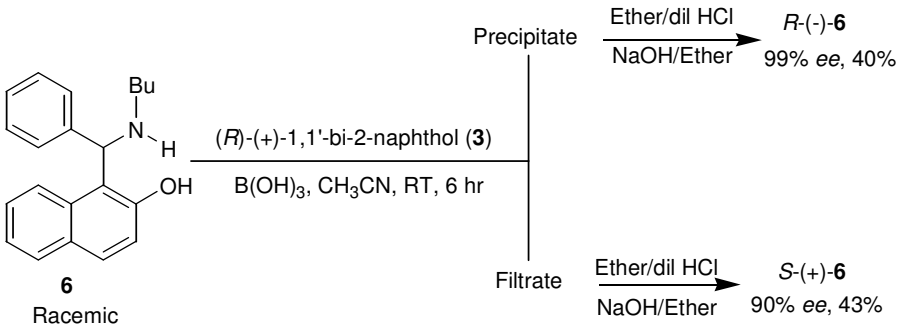
Table II — Resolution of Betti base **1** using L-(+)-tartaric acid[a]

S. No.	Ratio of 1:2	Acetone (mL)	Betti base 1 obtained from Precipitate % *ee*[b] /Conf.	Precipitate Yield (%)[c]	Filtrate % *ee*[b]/Conf.	Filtrate Yield (%)[c]
1[a]	1:1	10	15 (*S*)	50	10 (*R*)	38
2[a]	1:1	20	25 (*S*)	48	22 (*R*)	46
3[a]	1:1	40	50 (*S*)	46	45 (*R*)	44
4[a]	1:1	60	≥ 99 (*S*)	42	80 (*R*)	50
5[d]	1:2	60	≥ 99 (*S*)	25	38 (*R*)	67
6[e]	2:1	60	≥ 99 (*S*)	30	46 (*R*)	62

[a]Unless otherwise mentioned all the reactions were performed using racemic Betti base **1** (5 mmol) and L-(+)-tartaric acid **2** (5 mmol) in acetone and stirred at 25°C, [b]All *ee* values reported here are based on reported maximum[16] $[\alpha]_D^{25}$ = +58.8° (*C* 5, benzene) for (*S*)-**1** and $[\alpha]_D^{25}$ = -58.9° (*C* 5, benzene) for (*R*)-**1.** These maximum *ee*'s were further confirmed by HPLC using chiralcel OD-H using 5% isopropanol in hexane, [c]The yields are of the isolated products, based on the total amount of the starting racemic mixture **1** used, [d]Racemic Betti base **1** (5 mmol) and L-(+)-tartaric acid **2** (10 mmol) in 60 mL of the acetone and stirred at 25°C for 6 hr, [e]Racemic Betti base **1** (5 mmol) and L-(+)-tartaric acid **2** (2.5 mmol) in 60 mL of the acetone and stirred at 25°C for 6 hr.

procedure involves isolation of only *R*-(-)-isomer from precipitate fraction with good *ee*, whereas the *S*-(+)-isomer could not be obtained in optically pure from. In this laboratory, systematic investigations were carried out previously on the use of the chiral 1,1′-bi-2-naphthol (BINOL) for the resolution of several amino alcohols[17]. Accordingly, the resolution of aminonaphthol **6** has been examined through preparation of the corresponding diastereomeric borate complexes using chiral 1,1′-bi-2-naphthol **3** and boric acid in CH_3CN at RT (**Scheme V**). The (*R*)-(-) and (*S*)-(+)-aminonaphthol **6** were obtained in almost pure form under these conditions. When the (*R*)-(+)-1,1′-bi-2-naphthol **3**, boric acid and aminonaphthol **6** were stirred in CH_3CN for 6 hr at RT, the (*R*)-(-)-aminonaphthol **6** was obtained with 99% *ee* (40% yield) from the precipitate fraction. The filtrate fraction gave (*S*)-(+)-aminonaphthol in 90% *ee* (43% yield) after workup (**Table III**, entry 1).

The resolution of aminonaphthol **10** has been reported by using camphorsulfonic acid in ethyl acetate solvent[18]. However, the procedure involves 8



Scheme V

Table III — Resolution of racemic aminonaphthol **6** using (*R*)-(+)-1,1′-bi-2-naphthol and boric acid

S.No.	Substrate **6** (% *ee*)	Solvent (50 mL)	Aminonaphthol **6** obtained from			
			Precipitate		Filtrate	
			% *ee*[b]/Conf.	Yield(%)[c]	% *ee*[b]/Conf.	Yield(%)[c]
1[a]	**6**, 00	CH_3CN	99 (*R*)	40	90 (*S*)	43
2[d]	**6**, 00	CH_3CN	87 (*R*)	35	45 (*S*)	50
3[e]	(*S*)-**6**, 90	CH_3CN	99 (*S*)	75	10 (*S*)	08
4[e]	(*S*)-**6**, 45	CH_3CN	99 (*S*)	35	25 (*S*)	48

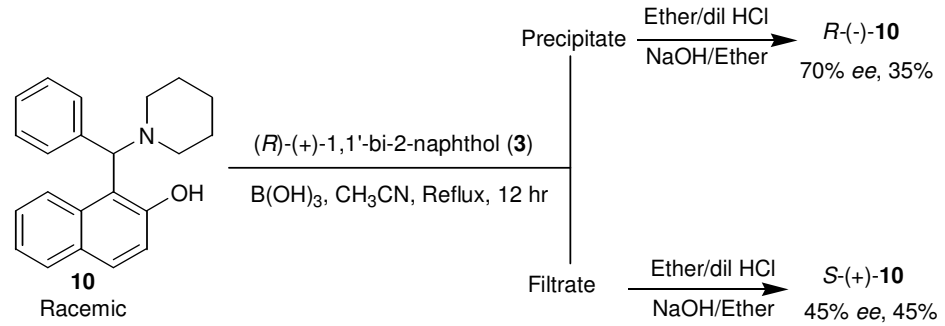
[a]Unless otherwise mentioned all the reactions were performed using *R*-(+)-BINOL **3** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **6** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25°C for 6 hr, [b]All *ee* values reported here are based on reported maximum[10] $[\alpha]_D^{25}$ = -212° (*C* 0.50, EtOH) for (*R*)-**6** and $[\alpha]_D^{25}$ = +210° (*C* 0.35, EtOH) for (*S*)-**6.** These maximum *ee*'s were further confirmed by HPLC using chiralcel OD-H using 10% isopropanol in hexane, [c]The yields are of the isolated products, based on the total amount of the starting racemic mixture **6** used, [d]*R*-(+)-BINOL **3** (10 mmol), boric acid (5 mmol) and racemic aminonaphthol **6** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25°C for 6 hr, [e]*R*-(+)-BINOL **3** (5 mmol), boric acid (5 mmol) and non-racemic aminonaphthol **6** (2.5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25°C for 6 hr.

to 10 crystallizations to obtain the pure enantiomers of aminonaphthol **10**. The resolution of aminonaphthol **10** has now been carried out through preparation of diastereomeric borate complexes using the (*R*)-(+)-1,1′-bi-2-naphthol **3** and boric acid in CH_3CN at RT as done for aminonaphthol **6**. After workup, the aminonaphthol **10** samples obtained from both precipitate and filtrate fractions were found to be racemic. This reaction was then carried out under refluxing conditions in the same solvent to obtain more fruitful results (**Scheme VI**).

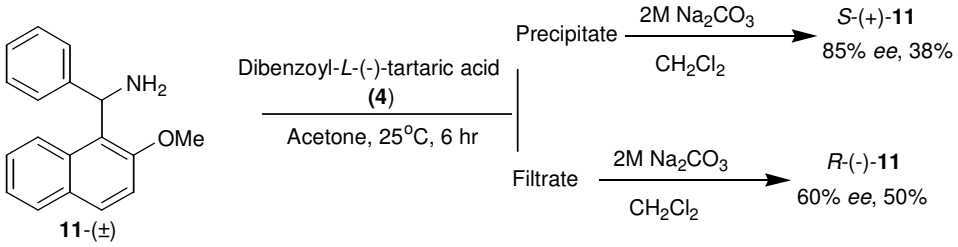
Optimum results were obtained when racemic aminonaphthol **10**, (*R*)-(+)-1,1′-bi-2-naphthol **3**, and boric acid were taken in the ratio 1:1:1 and stirred in CH_3CN under refluxing conditions. In this way, samples with moderate *ee* were obtained from both fractions. The results are summarized in **Table IV**.

Ray and coworkers reported the resolution of *O*-methyl Betti base **11** using chiral malic acid[19]. However, malic acid is relatively more expensive. A new and easy method has now been employed for the resolution of racemic *O*-methyl Betti base **11** using inexpensive dibenzoyl-L-tartaric acid **4** as resolving agent in acetone (**Scheme VII**). Enantiopure samples of *S*-(+)-**11** and *R*-(-)-**11** are readily obtained in this way (**Table V**). The racemic *O*-methyl Betti base **11** was prepared following a reported procedure[16a].

The use of chiral aminonaphthols has also been examined for the resolution of important chiral compounds. Previously, it was observed in this laboratory that 1,1′-bi-2-naphthol (BINOL) **3** can be readily prepared in enantiomerically pure form by preparation of diasteriomeric complexes using *S*-proline or borate complexes using chiral α-methylbenzylamine and boric acid[20-22]. In a previous communication, the resolution of racemic 1,1′-bi-2-naphthol (BINOL) **3** has been studied using the readily accessible chiral aminonaphthol **9** and boric



Scheme VI



Scheme VII

Table IV — Resolution of racemic aminonaphthol **10** using (*R*)-(+)-1,1′-bi-2-naphthol and boric acid[a]

S.No.	Substrate **10** (% *ee*)	Solvent	Aminonaphthol **10** obtained from			
			Precipitate		Filtrate	
	5 mmol	(50 mL)	% *ee*[b]/Conf.	Yield(%)[c]	% *ee*[b]/Conf.	Yield(%)[c]
1[d]	**10**, 00	CH_3CN	0	40	0	45
2[a]	**10**, 00	CH_3CN	70 (*R*)	35	45 (*S*)	45
3[e]	**10**, 00	CH_3CN	40 (*R*)	40	35 (*S*)	42
4[f]	(*R*)-**10**, 70	CH_3CN	99 (*R*)	60	20 (*R*)	25
5[f]	(*S*)-**10**, 45	CH_3CN	99 (*S*)	30	30 (*S*)	50

[a]Unless otherwise mentioned all the reactions were performed using *R*-(+)-BINOL **3** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **10** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 hr, [b]All *ee* values reported here are based on reported maximum[15] $[\alpha]_D^{25}$ = -193.5° (*C* 1.20, $CHCl_3$) for (*R*)-**10** and $[\alpha]_D^{25}$ = +193.8° (*C* 1.20, $CHCl_3$) for (*S*)-**10**. These maximum *ee*'s were further confirmed by HPLC using chiralcel OD-H using 5% isopropanol in hexane, [c]The yields are of the isolated products, based on the total amount of the starting racemic mixture **10** used, [d]*R*-(+)-BINOL **3** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **10** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25°C for 6 hr, [e]*R*-(+)-BINOL **3** (10 mmol), boric acid (5 mmol) and racemic aminonaphthol **10** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 hr, [f]*R*-(+)-BINOL **3** (5 mmol), boric acid (5 mmol) and non-racemic aminonaphthol **10** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 hr.

acid through formation of the corresponding diastereomeric borate complexes (**Scheme VIII**)[23].

One of the widely used chiral resolving agents in industry is chiral α-methylbenzylamine. However, this low molecular weight liquid amine poses problems during recovery. The corresponding chiral aminonaphthol **12** can be readily accessed using chiral α-methylbenzylamine (**Scheme IX**)[24].

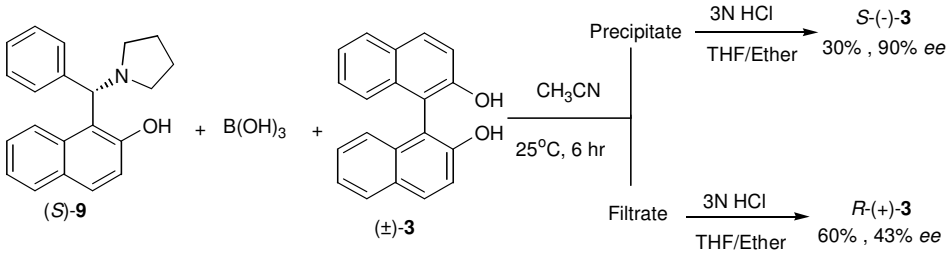
It has been observed that this readily accessible aminonaphthol **12** is useful for the resolution of ibuprofen **13** and mandelic acid **14**. The ibuprofen **13** forms a salt with aminonaphthol **12** in acetone to give precipitate and filtrate fractions which upon further work up give partially resolved enriched samples of **13** (**Scheme X** and **Table VI**).

Increasing the quantity of aminonaphthol did not lead to a significant change in the *ee* of sample obtained from the precipitate fraction (**Table VII**, entries 2-4). Fortunately, the partially resolved *R*-(-)-**13** sample can be further enriched to essentially pure

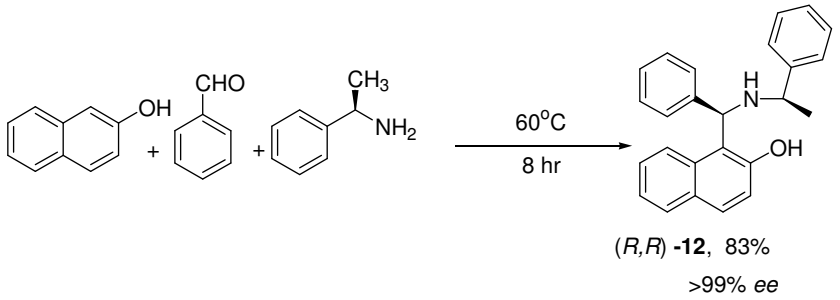
Table V — Resolution of racemic **11** using dibenzoyl-L-tartaric acid **4**[a]

S.No	Substrate **11** (% *ee*)	Acetone	Chiral **11** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mL)	% *ee*[b]/Conf.	Yield(%)[c]	% *ee*[b]/Conf.	Yield(%)[c]
1	**11**, 00	20	05 (*S*)	60	10 (*R*)	30
2	**11**, 00	40	22 (*S*)	45	25 (*R*)	43
3	**11**, 00	60	85 (*S*)	38	60 (*R*)	50
4[d]	(*S*)-**11**, 85	60	≥ 99 (*S*)	80	15 (*S*)	12
5[d]	(*R*)-**11**, 60	60	≥ 99 (*R*)	50	25 (*R*)	38

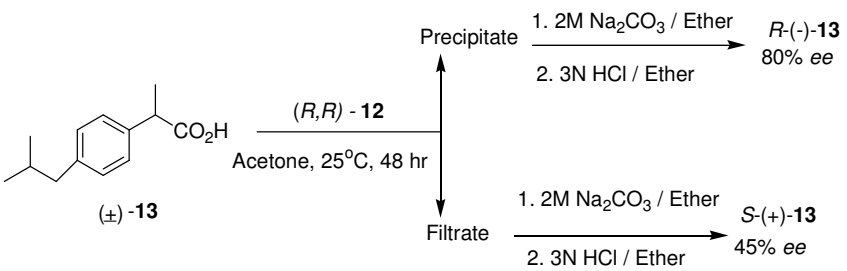
[a]Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol derivative **11** (5 mmol) and dibenzoyl-L-tartaric acid **4** (5 mmol) in acetone and stirred at 25°C for 6 hr, [b]All *ee* values reported here are based on reported maximum[19] $[\alpha]_D^{25}$ = +196° (*C* 1.6, $CHCl_3$) for (*S*)-**11** and $[\alpha]_D^{25}$ = -196° (*C* 1.6, $CHCl_3$) for (*R*)-**11**, [c]The yields are of the isolated products, based on the total amount of the starting racemic mixture **11** used, [d]Non-racemic aminonaphthol **11** (5 mmol) and dibenzoyl-L-tartaric acid **4** (5 mmol) in 60 mL of the acetone and stirred at 25°C for 6 hr.



Scheme VIII



Scheme IX



Scheme X

Table VI — Resolution of racemic ibuprofen **13** using aminonaphthol **12**[a]

Entry	Aminonaphthol **12** (equiv.)	Solvent (mL)	Precipitate			Filtrate		
			% *ee*[b]	Conf.[c]	Yield[d]	% *ee*[b]	Conf.[c]	Yield[d]
1	0.5	Acetone (2.5)	83	*R* (-)	19	24	*S* (+)	59
2	1	Acetone (2.5)	73	*R* (-)	31	38	*S* (+)	66
3	2	Acetone (6)	75	*R* (-)	28	31	*S* (+)	65
4	3	Acetone (10)	81	*R* (-)	24	33	*S* (+)	69
5[e]	1	Acetone (13)	80	*R* (-)	34	45	*S* (+)	60
6[f]	1	Acetone (5)	97	*R* (-)	44	57	*R* (-)	42
7[g]	1	Acetone (13)	78	*S* (+)	32	42	*R* (-)	67
8[h]	1	Acetone (5)	98	*S* (+)	35	64	*S* (+)	59
9	1	CH_3CN (5)	83	*R* (-)	12	14	*S* (+)	71
10[i]	(*R*)-α-PEA	Acetone (7)	42	*R* (-)	52	56	*S* (+)	35

[a]Unless otherwise mentioned all reactions were carried out using 2 mmol of (*R,R*) aminonaphthol **12**, 2 mmol of racemic ibuprofen **13** stirred at 25°C for 48 hr, [b]Determined by HPLC analysis using the chiral column, Chiralcel-OD-H, [c]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value, [d]The yields are of the isolated products. [e]Reaction carried out using 10 mmol of (*R,R*) aminonaphthol **12**, 10 mmol of ibuprofen **13** stirred at 25°C for 48 hr, [f]Non-racemic ibuprofen **13** (4 mmol) and aminonaphthol **12** (4 mmol) were stirred at 25°C for 48 hr, [g]Reaction carried out using 10 mmol of (*S,S*) aminonaphthol **12**, 10 mmol of ibuprofen **13** stirred at 25°C for 48 hr, [h]Non-racemic ibuprofen **13** (3 mmol) and (*S,S*) aminonaphthol **12** (3 mmol) were stirred at 25°C for 48 hr, [i]Reaction carried out using 2 mmol of (*R*)-α-phenylethylamine, 2 mmol of ibuprofen **13** stirred at 25°C for 48 hr.

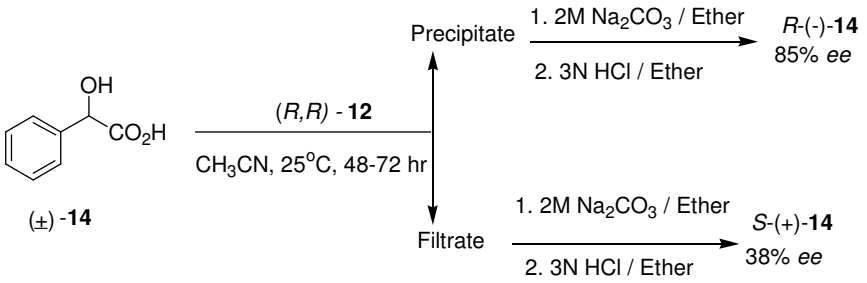
Table VII — Resolution of racemic mandelic acid **14** using aminonaphthol **12**[a]

Entry	Solvent (mL)	Precipitate			Filtrate		
		% *ee*[b]	Conf.[c]	Yield[d]	% *ee*[b]	Conf.[c]	Yield[d]
1[e]	CH_3CN (2)	82	*R* (-)	20	21	*S* (+)	76
2	CH_3CN (2)	85	*R* (-)	29	38	*S* (+)	64
3[f]	CH_3CN (5)	82	*R* (-)	24	20	*S* (+)	71
4[g]	CH_3CN (2)	97	*R* (-)	61	26	*R* (-)	27
5[h]	CH_3CN (5)	79	*S* (+)	24	23	*R* (-)	70
6[i]	CH_3CN (1)	97	*S* (+)	56	24	*S* (+)	41
7	THF(3)	81	*R* (-)	16	17	*S* (+)	66
8	Acetone (2.5)	46	*R* (-)	27	61	*S* (+)	62

[a]Unless otherwise mentioned all reactions were carried out using 2 mmol of (*R,R*) aminonaphthol **12**, 2 mmol of racemic mandelic acid **14** stirred at 25°C for 48 hr, [b]Determined by HPLC analysis using the chiral column, Chiralcel-OD-H, [c]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value, d. The yields are of the isolated products, [e]Racemic mandelic acid **14** (2 mmol) and (*R,R*) aminonaphthol **12** (2 mmol) stirred at 25°C for 24 hr, [f]Racemic mandelic acid **14** (5 mmol) and (*R,R*) aminonaphthol **12** (5 mmol) stirred at 25°C for 72 hr, [g]Non-racemic mandelic acid **14** (1 mmol) and (*R,R*) aminonaphthol **12** (1 mmol) stirred at 25°C for 24 hr, [h]Racemic mandelic acid **14** (5 mmol) and (*S,S*) aminonaphthol **12** (5 mmol) were stirred at 25°C for 72 hr, [i]Non-racemic mandelic acid **14** (1 mmol) and (*S, S*) aminonaphthol **12** (1 mmol) stirred at 25°C for 24 hr.

enantiomer by repeating the procedure (entries 6 and 8). Also, *S*-(+)-**13-**ibuprofen is obtained from the precipitate fraction by using (*S,S*) aminonaphthol **12** (entry 7). Use of other solvents like CH_3CN did not provide the desired yields (entry 9). The resolution has also been carried out using (*R*)-α-phenylethylamine *i.e.* (*R*)-α-PEA under similar reaction conditions and it was found that the results are an improvement upon using the aminonaphthol **12** (entry 10).

Acetonitrile proved to be a good solvent for resolution of mandelic acid. It was found that the racemic mandelic acid reacts with aminonaphthol **12** in acetonitrile solvent to give the precipitate and



Scheme XI

filtrate fractions (**Scheme XI** and **Table VII**). After digestion of the precipitate fraction with 2M Na_2CO_3/ether mixture, followed by acidification of the aq. layer with 3N HCl, mandelic acid **14** enriched in (*R)*-(-) enantiomer (85% *ee*) was obtained. After workup, (*S*)-(+)-**14** isomer (38% *ee*) was obtained from the filtrate fraction. Similarly, (*S*)-(+)-**14** mandelic acid can be obtained from the precipitate fraction by using readily accessible (*S,S*) aminonaphthol **12** as done earlier for ibuprofen (entry 5). These partially resolved samples were further enriched to enantiopure samples of upto 97% *ee* (entries 4 and 6).

Materials and Methods

Melting points reported in this paper are uncorrected and were determined using a Superfit capillary point apparatus. IR spectra were recorded on Perkin-Elmer IR spectrophotometer Model 1310. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-200 spectrometers with $CDCl_3$ as a solvent and TMS as reference. Optical rotations were measured in an AUTOPOL-II automatic polarimeter (readability ±0.01°) or Jasco DIP-370 digital polarimeter (readability ±0.001°). HPLC analyses were performed on an SCL-10ATVP Shimadzu instrument. The *ee* values were determined using CHIRALCEL OD-H normal phase chiral column (4.6 × 250 mm) using eluents: hexane, 2-propanol, trifluoroacetic acid with a flow rate 0.5-0.9 mL/min, and monitoring wavelength at 228 nm.

Experimental Section

General procedure for the synthesis of aminonaphthols by condensation of β-naphthol, benzaldehyde and 1° amines

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this mixture was added distilled amine (100 mmol). The reaction mixture was refluxed for 12 hr and brought to RT. The crystalline product was filtered and washed with 90% ethanol (2 × 20 mL), dried and suspended in 20% HCl (200 mL). The mixture was refluxed for 3 hr and brought to RT. The crystalline hydrochloride salt of the amine was filtered and washed with ethyl acetate (2 × 25 mL). The hydrochloride salt was suspended in H_2O (30 mL) and treated with 2M Na_2CO_3 until dissolution occurred and then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 to isolate the aminonaphthol as a white solid.

1-(α-*N*-phenylaminobenzyl)-2-naphthol, 7: Yield: 24.4 g (75%); m.p. 128-30°C (lit.[11] m.p. 131-32°C); IR (KBr): 3350, 1600, 1450, 1230, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 1H), 6.18 (s, 1H), 6.78 (d, *J* = 8 Hz, 2H), 6.94 (t, *J* = 8 Hz, 1H), 7.16 (m, 3H), 7.28-7.41 (m, 5H), 7.48 (d, *J* = 8 Hz, 2H), 7.78 (q, *J* = 8 Hz, 3H), 11.48 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 62.6, 116.1, 119.8, 121.2, 121.6, 122.6, 126.5, 127.7, 128.3, 128.8, 128.9, 129.1, 129.2, 129.7, 130.9, 131.4, 140.9, 146.6, 156.0.

1-(α-*N*-benzylaminobenzyl)-2-naphthol, 5: Yield: 23.6 g (70%); m.p. 140-42°C (lit.[16a] m.p. 143°C); IR (KBr): 3340, 3050, 1652, 1270, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (br s, 1H), 3.83 (dd, *J* = 8, 4 Hz, 1H), 4.05 (dd, *J* = 8, 4 Hz, 1H), 5.77 (s, 1H), 7.21-7.40 (m, 13H), 7.68-7.76 (m, 3H), 13.6 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.9, 62.9, 112.9, 120.1, 121.2, 122.5, 126.5, 127.7, 128.0, 128.5, 128.6,128.7, 128.8, 128.9, 129.7, 132.8, 138.1, 141.4, 156.9.

1-(α-*N*-butylaminobenzyl)-2-naphthol, 6: Yield: 21.3 g (70%); m.p. 130-32°C (lit.[10] m.p. 131-32°C); IR (KBr): 3314, 3058, 2958, 1621, 1601, 1456, 1241, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 8 Hz, 3H), 1.38-1.41 (m, 2H), 1.56-1.61 (m, 4H), 2.83 (t, *J* = 8 Hz, 2H), 5.67 (s, 1H), 7.18 (d, *J* = 12 Hz,

1H), 7.21-7.36 (m, 5H), 7.45-7.47 (m, 2H), 7.72-7.70 (m, 3H), 13.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 20.4, 31.7, 49.0, 64.5, 113.4, 120.2, 121.2, 122.4, 126.5, 127.8, 128.1, 128.7, 128.1, 128.9, 129.7, 132.8, 141.8, 157.0.

General procedure for the synthesis of aminonaphthols by condensation of β-naphthol, benzaldehyde and 2° amines

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this mixture was added 2° amine (100 mmol). The reaction mixture was refluxed for 12 hr and brought to RT. The precipitate was filtered and washed with 95% ethanol (2 × 20 mL) to isolate the aminonapthol as a white solid.

1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol, 8: Yield: 20.8 g (75%); m.p. 161-62°C (lit.[18] m.p. 164-64.5°C); IR (KBr): 3058, 2958, 1620, 1454, 1238, 1006 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (br s, 6H), 5.01 (s, 1H), 7.20-7.45 (m, 6H), 7.61-7.75 (m, 4H), 7.91 (d, *J* = 8 Hz, 1H), 13.69 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 44.2, 73.1, 116.3, 120.0, 121.1, 122.4, 126.4, 128.0, 128.8, 128.9, 129.5, 132.3, 140.5, 155.5.

1-(α-pyrrolidinylbenzyl)-2-naphthol, 9: Yield: 28.7 g (95%); m.p. 172-73°C (lit.[12c] m.p. 173°C); IR (KBr): 3120, 3057, 2970, 2845, 1620, 1452, 1238, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (br s, 4H), 2.63 (br s, 3H), 3.27 (br s, 1H), 5.14 (s, 1H), 7.15-7.28 (m, 5H), 7.38 (t, *J* = 8 Hz, 1H), 7.60-7.71 (m, 4H), 7.88 (d, *J* = 8 Hz, 1H), 13.88 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4, 53.5, 70.9, 116.7, 119.9, 121.1, 122.3, 126.3, 127.8, 128.5, 128.7, 128.9, 129.4, 132.0, 141.3, 155.6.

1-(α-piperidylbenzyl)-2-naphthol, 10: Yield: 28.4 g (90%); m.p. 195-96°C (lit.[18] m.p. 198-98.5°C); IR (KBr): 3214, 3058, 2958, 1621, 1601, 1456, 1241, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (br s, 1H), 1.78 (br s, 5H), 2.00 (br s, 1H), 2.18 (br s, 1H), 2.70 (br s, 1H), 3.30 (br s, 1H), 5.12 (s, 1H), 7.18-7.30 (m, 6H), 7.39 (t, *J* = 8 Hz, 1H), 7.57-772 (m, 3H), 7.85 (d, *J* = 8 Hz, 1H), 13.92 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.2, 26.1, 53.5, 72.4, 116.2, 120.0, 121.1, 122.4, 126.4, 127.9, 128.9, 129.1, 129.4, 132.5, 139.7, 155.6.

2.4.5.1 Synthesis of (2-methoxynaphth-1-yl)-benzylamine, 11 (Ref 16a): Freshly distilled benzaldehyde (6.1 mL, 60 mmol) was added to a solution of 2-naphthol (4.3 g, 30 mmol) in 50 mL of 95% ethanol. To this mixture was added 25% aqueous ammonia solution (4 mL) and the reaction mixture was left at RT for 12 hr, during which a crystalline product was formed. The crystalline product was filtered and washed with 95% ethanol (2 × 20 mL), dried and dissolved in THF (60 mL). To this was added powdered NaOH (1.8 g, 45 mmol). After 10 min, CH_3I was added using a syringe at 0°C and the reaction mixture was stirred at RT for 6 hr. The reaction mixture was quenched with water (10 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain the *O*-methylated imine product. It was suspended in 20% HCl (70 mL) and the mixture was refluxed for 1 hr and brought to RT. The crystalline hydrochloride amine salt was filtered and washed with ethyl acetate (2 × 10 mL). The hydrochloride salt was suspended in H_2O (10 mL) and the mixture was treated with 2M Na_2CO_3 until dissolution occurred and then extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and the solvent removed to obtain the (2-methoxynaphth-1-yl)benzylamine **11** as a light yellow solid. Yield: 4.7 g (60%); m.p. 98-100°C (lit.[16a] m.p. 102°C); IR (KBr): 3314, 3058, 2958, 1621, 1601,1456, 1241, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (br s, 2H), 3.72 (s, 3H), 6.14 (s, 1H), 7.13-7.16 (m, 1H), 7.22-7.31 (m, 4H), 7.35-7.41 (m, 3H), 7.75-7.78 (m, 2H), 8.03 (d-like, *J* = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.7, 56.2, 114.1, 123.2, 123.4, 125.6, 125.8, 126.3, 126.9, 127.7, 128.6, 129.0, 129.5, 131.9, 146.5, 154.6.

Synthesis of 1-((*R*)-phenyl{[(1′*R*)-1′-phenylethyl]amino}methyl)-2-naphthol, 12 (Ref 24): A mixture of benzaldehyde (17.80 g, 17.05 mL, 168 mmol), 2-naphthol (20.0 g, 140 mmol) and (*R*)-(+)-1-phenylethylamine (17.81 g, 18.71 mL, 147 mmol) were taken in a two neck RB flask. The contents were stirred at 60°C for 8 hr under N_2 atmosphere and brought to RT. The precipitate was filtered and washed with 95% ethanol (3 × 30 mL) to isolate the corresponding 1-((*R*)-phenyl{[(1′*R*)-1′-phenylethyl]amino}methyl)-2-naphthol as a white solid. It was purified by recrystallization from ethyl acetate/hexane mixture to obtain colourless crystals. Yield: 41.24 g (84%); m.p. 154-56°C (lit.[24] m.p. 155-56°C); $[\alpha]_D^{25}$ = -223.5° (*C* 1, $CHCl_3$) lit.[24] $[\alpha]_D^{25}$ = -220.7° (*C* 2.1, $CHCl_3$); IR (KBr): 3271, 1621, 1238, 1077, 743, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (d, 3H, *J* =

6.8 Hz), 2.35 (br s, 1H), 3.92 (q, 1H, *J* = 6.8 Hz), 5.47 (s, 1H), 7.20-7.76 (m, 16H), 13.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 56.7, 60.3, 113.1, 120.1, 121.1, 122.4, 126.4, 126.7, 127.7, 127.9, 128.0, 128.7, 128.8, 129.0, 129.1, 129.7, 132.6, 141.5, 143.1, 157.3.

General procedure for the resolution of aminonaphthols using L-(+)-tartaric acid: The L-(+)-tartaric acid **2** (0.75 g, 5 mmol) and the racemic aminonaphthol (5 mmol) were taken in acetone (70 mL) and the contents stirred at RT for 6 hr and then filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and the solvent evaporated completely to obtain the *S*-(+)-aminonaphthol. The filtrate was concentrated and the residue taken in CH_2Cl_2 (20 mL) and was digested using 1N KOH (10 mL) to obtain the *R*-(-)-sample.

Resolution of 1-(α-*N*-butylaminobenzyl)-2-naphthol, 6, using *R*-(+)-1,1′-bi-2-naphthol, 3 and B(OH)$_3$: A mixture of (*R*)-(+)-1,1′-bi-2-naphthol **3** (1.43 g, 5 mmol), $B(OH)_3$ (0.30 g, 5 mmol) and the racemic 1-(α-N-butylaminobenzyl)-2-naphthol **6** (1.5 g, 5 mmol) were taken in CH_3CN (50 mL). The contents were stirred at RT for 6 hr and filtered. The precipitate was suspended in a mixture of THF (50 mL) and dil. HCl (2N, 20 mL) and stirred until complete dissolution occured. The organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O (2 × 25 mL). *R*-(+)-1,1′-bi-2-naphthol was recovered from the combined organic layer. The aqueous layer was treated with 1N KOH/CH_2Cl_2 and the free aminonaphthol **6** was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain the *R*-(-)-**6** (0.61 g, 40% yield, 99% *ee*). $[\alpha]_D^{25}$ = -210° (*c* 1, C_2H_5OH) lit.[10] $[\alpha]_D^{25}$ =-212° (*c* 0.5, C_2H_5OH). The filtrate was concentrated and the residue was digested in a mixture of THF (50 mL) and dil. HCl (2N, 20 mL). After work up as outlined above, *S*-(+)-**6** (90% *ee*) was isolated. $[\alpha]_D^{25}$ = +191° (*c* 1, C_2H_5OH) lit.[10] $[\alpha]_D^{25}$ =+212° (*c* 0.5, C_2H_5OH). The samples were also analyzed using HPLC (CHIRALCEL OD-H, eluent: hexane: 2-propanol = 90:10; 0.9 mL/min).

Resolution of 1-(α-*N*-piperidylbenzyl)-2-naphthol, 10, using *R*-(+)-1,1′-bi-2-naphthol, 3 and B(OH)$_3$: A mixture of (*R*)-(+)-1,1′-bi-2-naphthol **3** (1.43 g, 5 mmol), $B(OH)_3$ (0.30 g, 5 mmol) and the racemic 1-(α-*N*-butylaminobenzyl)-2-naphthol **10** (1.5 g, 5 mmol) were taken in CH_3CN (50 mL) and the contents were refluxed for 12 hr. The reaction mixture was filtered while hot and washed with acetonitrile. After workup, the isomers *R*-(-)-**10** (0.55 g, 35% yield, 70% *ee*) was obtained from the precipitate fraction and *S*-(+)-**10** (0.71 g, 45% yield, 45% *ee*) was obtained from the filtrate fraction. Further enrichment of *R*-(-)-**10** with 70% *ee* following the repetitive resolution procedure gave *R*-(-)-**10** (0.95 g, 60% yield, 99% *ee*) from the precipitate. $[\alpha]_D^{25}$ = -193° (*c* 1, $CHCl_3$) lit.[15] $[\alpha]_D^{25}$ =-193.5° (*c* 1.2, $CHCl_3$). Similarly the *S*-(+)-**10** with 45% *ee* gave *S*-(+)-**10** (0.47 g, 30% yield, 99% *ee*) from the precipitate. $[\alpha]_D^{25}$ = +193° (*c* 1, $CHCl_3$) lit.[15] $[\alpha]_D^{25}$ =+193.8° (*c* 1.2, $CHCl_3$). The samples were also analyzed using HPLC (CHIRALCEL OD-H, eluent: hexane: 2-propanol = 95:5; 0.5 mL/min).

Resolution of (2-methoxynaphth-1-yl)benzylamine, 11, using dibenzoyl-L-(-)-tartaric acid, 4: The dibenzoyl-L-tartaric acid **4** (1.8 g, 5 mmol) and the (2-methoxynaphth-1-yl)benzylamine (1.32 g, 5 mmol) **11** were taken in acetone (60 mL) and the contents stirred at RT for 6 hr and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and the solvent evaporated completely to obtain the sample *S*-(+)-**11** (0.50 g, 38% yield, 85% *ee*). The filtrate was concentrated and the residue digested as outlined above to obtain the sample *R*-(-)-**11** (0.65 g, 50% yield, 60% *ee*). Further enrichment of *S*-(+)-**11** sample with 85% *ee* following the repetitive resolution procedure gave *S*-(+)-**11** (1.05 g, 80% yield, 99% *ee*) from the precipitate. $[\alpha]_D^{25}$ = +195° (*c* 1, $CHCl_3$) lit.[19] $[\alpha]_D^{25}$ = +193.5° (*c* 0.5, $CHCl_3$). Similarly, the *R*-(-)-**11** with 60% *ee* gave *R*-(-)-**11** (0.65 g, 50% yield, 99% *ee*) from the precipitate. $[\alpha]_D^{25}$ = -195° (*c* 1, $CHCl_3$) lit.[19] $[\alpha]_D^{25}$ = -196° (*c* 0.5, $CHCl_3$).

Resolution of ibuprofen, 13: The (*R,R*)-(-)-aminonaphthol **12** (3.53 g, 10 mmol) and racemic ibuprofen **13** (2.06 g, 10 mmol) were taken in acetone

(13 mL) and the contents were stirred at 25°C for 48 hr and filtered. The precipitate was suspended in a mixture of ether and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The aq. layer was treated with dil HCl (3N)/ether and the free acid was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain (*R*)-(-)-**13** enantiomer (0.70 g, 34% yield, 80% *ee*). The filtrate was concentrated and the residue was treated as outlined above to obtain (*S*)-(+)-**13** enantiomer (1.23 g, 60% yield, 45% *ee*). Further enrichment of (*R*)-(-)-**13** sample with 80% *ee* following the repetitive resolution procedure gave (*R*)-(-)-**13** enantiomer (0.30 g, 44% yield, 97% *ee*) from the precipitate fraction. $[\alpha]_D^{25}$ = -56° (*c* 1, C_2H_5OH) lit.[25] $[\alpha]_D^{25}$ =-58° (*c* 2, C_2H_5OH). The filtrate part after workup gave the (*R*)-(-)-**13** enantiomer (0.29 g, 42% yield, 57% *ee*). The samples were also analyzed using HPLC (CHIRALCEL OD-H, eluent: hexane: 2-propanol: trifluoroacetic acid=980:20:2.5 ;0.5 mL/min) (Ref 25).

Resolution of mandelic acid, 14: The (*R,R*)-(-)-aminonaphthol **12** (1.76 g, 5 mmol) and racemic mandelic acid **14** (0.76 g, 5 mmol) were taken in CH_3CN (5 mL) and the contents were stirred at 25°C for 72 hr and filtered. The precipitate was suspended in a mixture of ether and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The aq. layer was treated with dil HCl (3N)/ether and the acid was extracted with ether (3×25 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain (*R*)-(-)-**14** enantiomer (0.18 g, 24% yield, 82% *ee*). The filtrate part was concentrated and the residue was treated as outlined above to obtain (*S*)-(+)-**14** enantiomer (0.53 g, 71% yield, 20% *ee*). Further enrichment of (*R*)-(-)-**14** sample with 82% *ee* following the repetitive resolution procedure gave (*R*)-(-)-14 enantiomer (0.11 g, 61% yield, 97% *ee*) from the precipitate fraction. $[\alpha]_D^{25}$ = -151° (*c* 1, H_2O) lit.[26] $[\alpha]_D^{25}$ =-153° (*c* 2.5, H_2O). The filtrate part after workup gave the (*R*)-(-)-**14** enantiomer (49 mg, 27% yield, 26% *ee*). The samples were also analyzed using HPLC (CHIRALCEL OD-H, eluent: hexane: 2-propanol: trifluoroacetic acid = 875:125:2.5; 0.5 mL/min) (Ref 25).

Conclusion

In conclusion, a simple method to access aminonaphthols by condensation of benzaldehyde, 2-naphthols and 1° or 2° amines in ethanol solvent and resolution of these racemic samples using inexpensive chiral resolving agents such as L-(+)-tartaric acid, dibenzoyl-L-(-)-tartaric acid and *R*-(+)-BINOL to obtain both the enantiomers of these aminonaphthols has good potential for further exploitation as illustrated by the use of chiral aminonaphthols for the resolution of racemic bi-2-naphthol, ibuprofen and mandelic acid.

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