Synthesis, Resolution and Enhancement of Enantiomeric Purity of Amino Alcohols and Aminonaphthols and Their Synthetic Applications

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY

By

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Dedicated to

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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Professor M. Periasamy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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Certificate

Certified that the work embodied in this thesis entitled '**Synthesis, Resolution and Enhancement of Enantiomeric Purity of Amino Alcohols and Aminonaphthols and Their Synthetic Applications'** has been carried out by Mr. **M. Narsi Reddy** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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M. Narsi Reddy

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g. dm, are understood]
aq.	aqueous
Ar	aryl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*ter*-butoxycarbonyl
bp	boiling point
br	broad (spectral)
Bu	butyl
t-Bu	*ter*-butyl
^{o}C	degree celsius
cat.	catalytic
cm^{-1}	wavenumber(s)
δ	chemical shift in parts per million downfield from tetramethyl silane
DCM	dichloromethane
dr	diastereomeric ratio
DPPM	α,α-diphenyl-2-pyrrolidinemethanol
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol

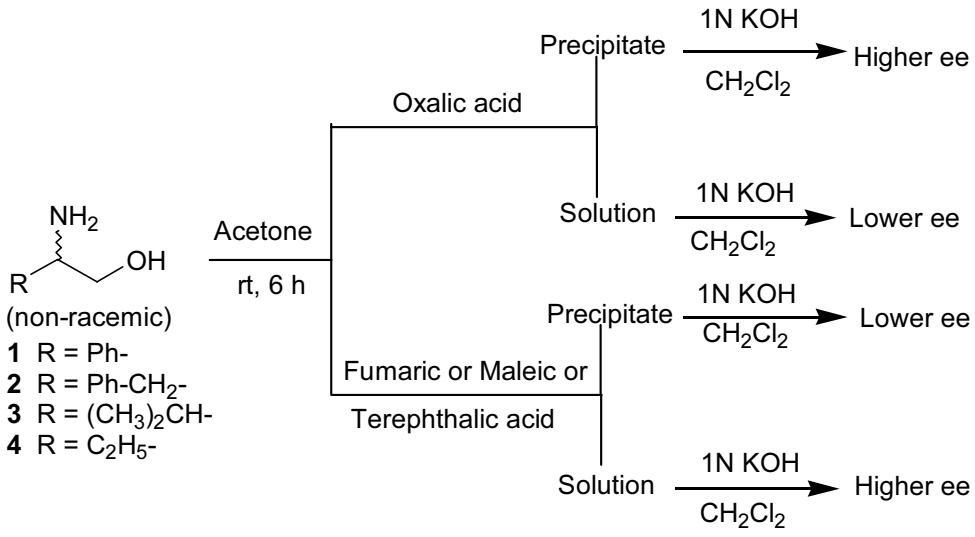
equiv.	equivalent
g	gram (s)
h	hour (s)
HPLC	high-performance liquid chromatography
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	Coupling constant (in NMR Spectrometry)
lit.	literature
m	multiplet (spectral)
Me	methyl
MHz	megahertz
min.	minute(s)
mmol	millimolar
mp	melting point
n-	primary
Nu	nucleophile
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
rt	room temperature
THF	tetrahydrofuran
TMS-Cl	trimethylsilyl chloride

Abstract

This thesis describes studies on the **"Synthesis, Resolution and Enhancement of Enantiomeric Purity of Amino Alcohols and Aminonaphthols and Their Synthetic Applications''.** It comprises of three chapters. Each chapter is subdivided into four parts namely, **Introduction, Results and Discussion, Conclusions** and **Experimental Section** along with **References.**

The first chapter describes studies on the enhancement of enantiomeric purity of non-racemic samples of 1,2-amino alcohols such as phenylglycinol, phenylalaninol, valinol, 2-amino butanol and 2-amino-1,1,2-triphenylethanol using achiral dicarboxylic acids. A conceptual method was developed for the enhancement of enantiomeric purity of non-racemic 1,2-amino alcohols (**1-4**) using achiral dicarboxylic acids such as oxalic, fumaric, maleic and terephthalic acids. In the case of oxalic acid, enhancement was observed in the precipitate fraction, whereas in the case of fumaric, maleic and terephthalic acids enhancement were observed in the solution fractions (Scheme 1).

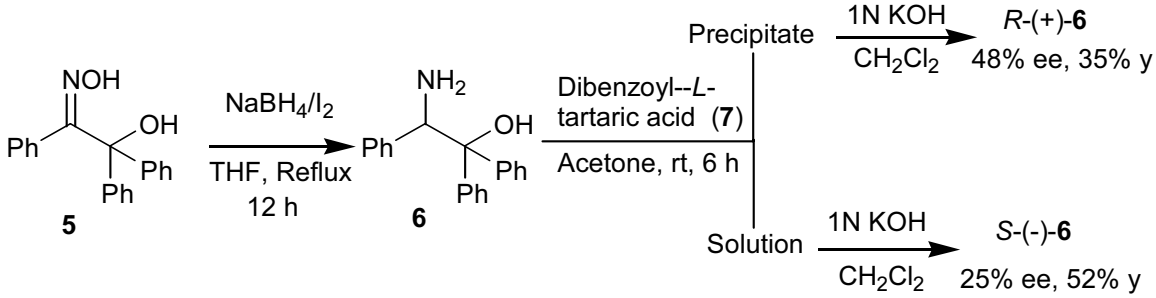
Scheme 1



X-ray crystal structure analyses were carried out for a few complexes and the results are discussed on the basis of predominant formation of hetero or homochiral aggregates.

A convenient method was developed for the preparation of 2-amino-1,1,2-triphenylethanol **6** by the reduction of α-keto alcohol oxime **5** using easily handle $NaBH_4/I_2$ reagent system in THF under refluxing conditions (Scheme 2) and it was partially resolved using dibenzoyl-*L*-tartaric acid **7** in acetone solvent.

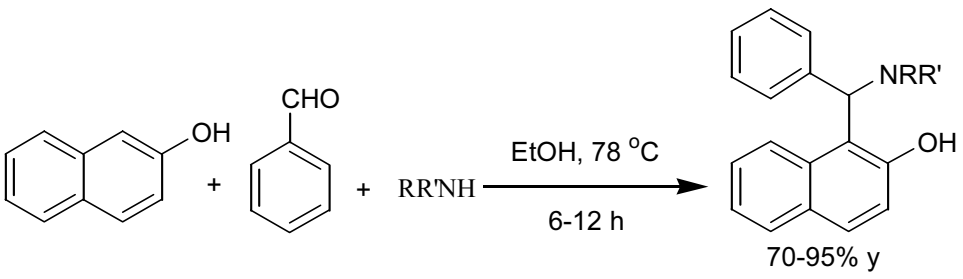
Scheme 2



These non-racemic samples were also purified using achiral dicarboxylic acids to obtain samples of >99% ee.

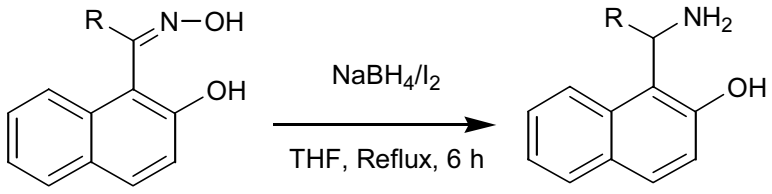
Chapter 2 describes the synthesis of chiral aminonaphthols and their applications in asymmetric synthesis. A convenient method was developed for the synthesis of aminonaphthols by straightforward condensation of β-naphthol, benzaldehyde and 1^o or 2^o amines in ethanol at 78 ^oC for 6-12 h (Scheme 3).

Scheme 3



A convenient and general method was developed for the synthesis of both aliphatic and aromatic aminonaphthols by the reduction of oximes of 1-acyl-2-naphthol using the $NaBH_4/I_2$ reagent system (Scheme 4).

Scheme 4

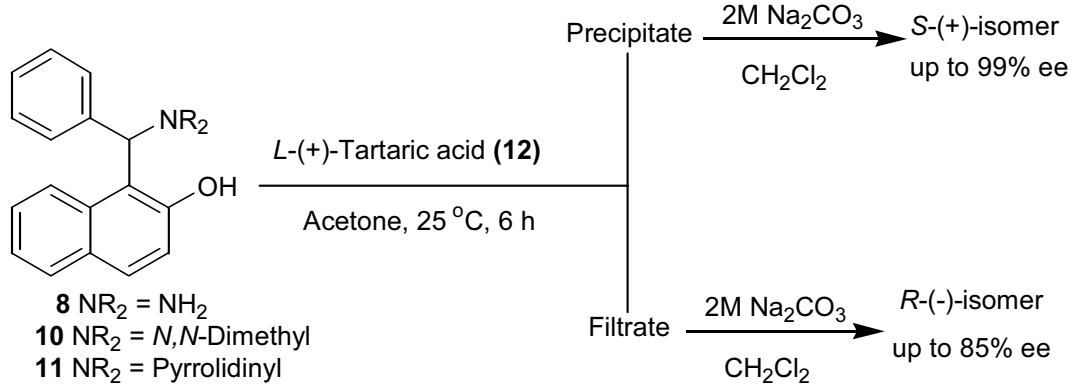


R = Ph **8**, 80% y

R = Me **9**, 70% y

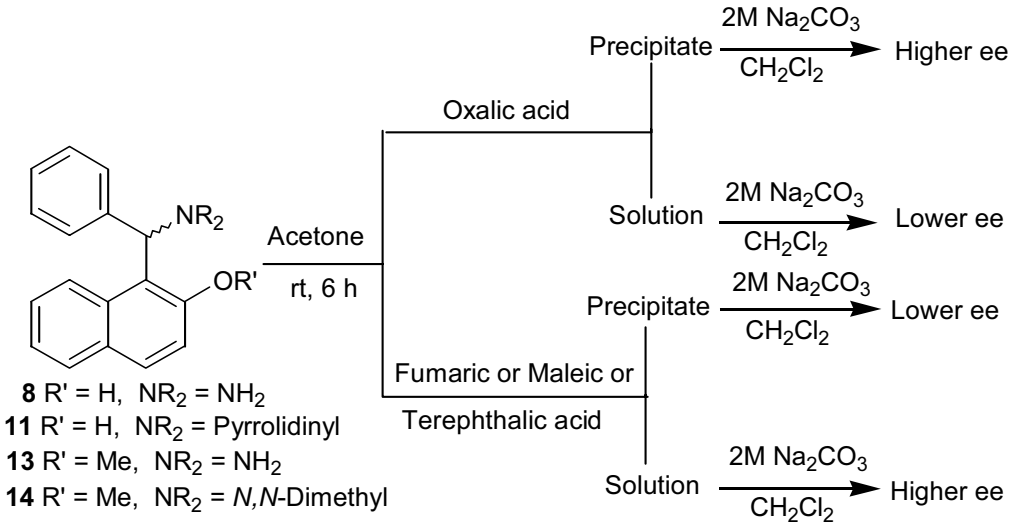
The aminonaphthols such as 1-(α-aminobenzyl)-2-naphthol **8**, 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol **10** and 1-(α-pyrrolidinylbenzyl)-2-naphthol **11** were resolved using inexpensive *L*-(+)-tartaric acid **12** in acetone through formation of diastereomeric complexes (Scheme 5).

Scheme 5



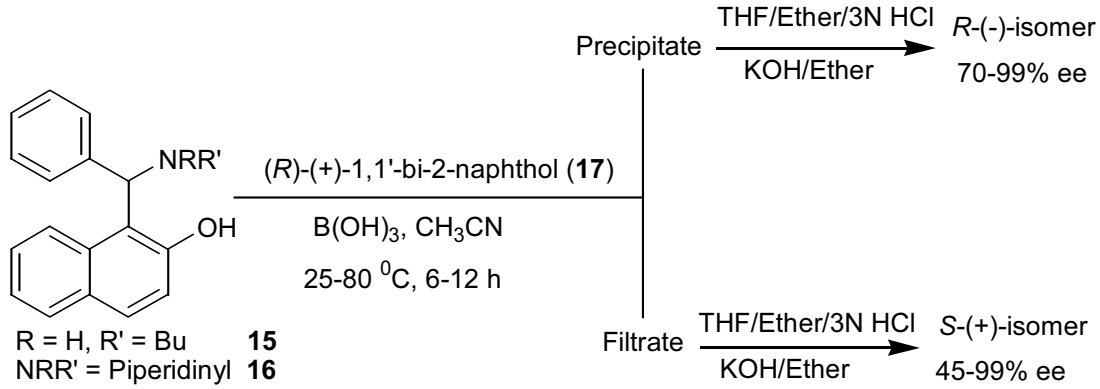
The non-racemic samples of aminonaphthols and their derivatives were also purified using achiral dicarboxylic acids, through formation of the corresponding homo or heterochiral aggregates (Scheme 6).

Scheme 6



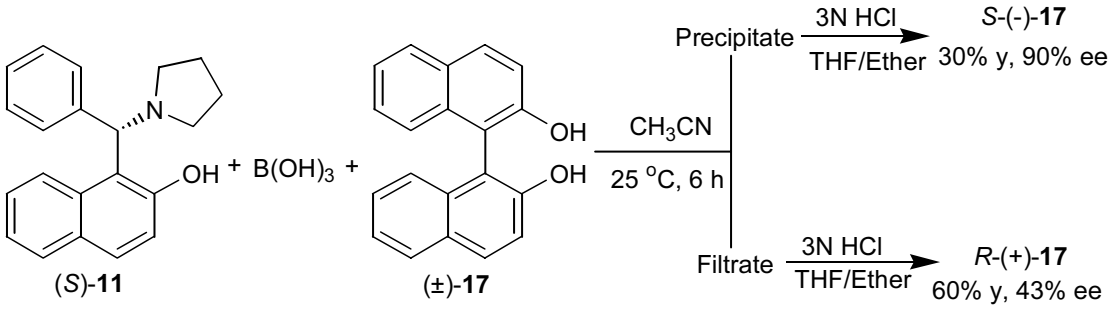
The aminonaphthols like 1-(α-*N*-butylaminobenzyl)-2-naphthol **15** and 1-(α-piperidylbenzyl)-2-naphthol **16** were also resolved using (*R*)-(+)-1,1'-bi-2-naphthol (BINOL) **17** and boric acid through formation of diastereomeric borate complexes in CH_3CN solvent (Scheme 7).

Scheme 7



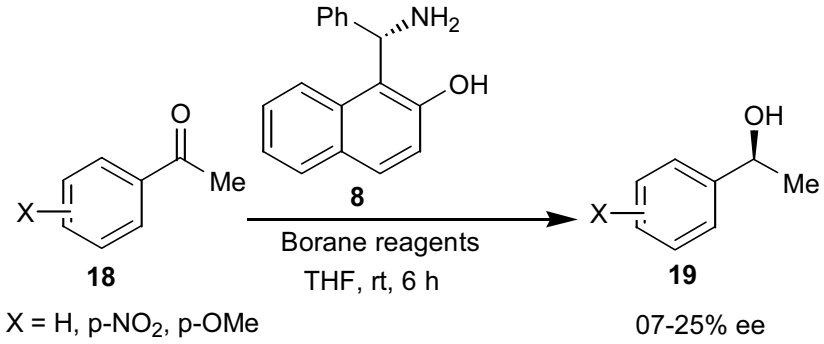
The racemic 1,1'-bi-2-naphthol **17** in turn could be resolved using the readily accessible aminonaphthol **11** and boric acid in CH_3CN solvent (Scheme 8).

Scheme 8



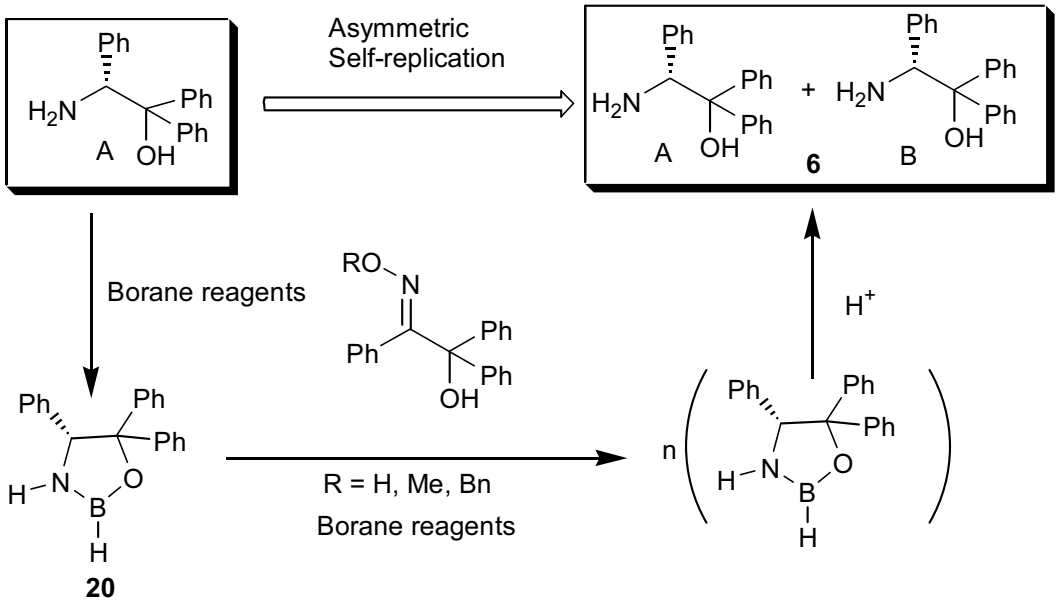
Efforts were undertaken for the asymmetric reduction of prochiral ketones **18** to obtain the secondary alcohols **19** using 20 mol% of aminonaphthol **8** and borane reagents through the anticipated oxazaborolidine intermediate (Scheme 9).

Scheme 9



In chapter 3, results of the studies undertaken to examine the duplication of chirality in the asymmetric borane reduction of the oxime derivatives of keto alcohols using the autocatalyst (*R*)-2-amino-1,1,2-triphenylethanol **6** are described. When the benzyl derivative of keto alcohol oxime was reduced using *N,N*-diethylaniline:BH_3 in the presence of (*R*)-2-amino-1,1,2-triphenylethanol, the product was obtained in 92% yield and 87% ee (Scheme 10).

Scheme 10



The results are discussed considering a reaction mechanism involving the corresponding oxazaborolidine intermediate.

Note: The compound numbers given here are different from the numbers given in the chapters.

Contents

Chapter 2

Synthesis and applications of chiral aminonaphthols

Chapter 3

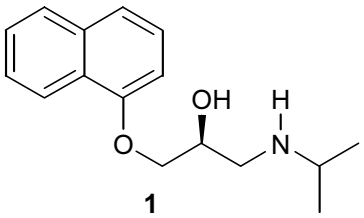
Efforts towards development of asymmetric autocatalytic borane reduction

Chapter 1

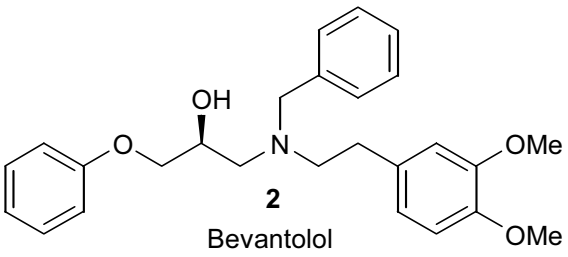
Enhancement of enantiomeric purity of non-racemic amino alcohols

1. 1 Introduction

Amino alcohols are important class of organic compounds. Among amino alcohols enantiomerically pure 1,2-amino alcohols have been found to be useful in medicinal chemistry as therapeutic agents for a wide variety of human diseases and disorders.[1] For example, enantiomerically pure 1,2-amino alcohols such as the β-adrenergic blockers propranolol **1** and bevantolol **2** are effective therapeutic agents in the treatment of heart diseases.[2-6]



1
Propranolol



2
Bevantolol

The enantiomeric purity in pharmaceuticals is important, as the enantiomers have different biological activities. For instance thalidomide is the most notorious example of this problem.[7] Besides pharmaceutical applications, several enantiomerically pure 1,2-amino alcohols are used as chiral auxiliaries and chiral catalysts in asymmetric organic transformations.[8-11] A large number of enantiomerically pure amino alcohols derived chiral auxiliaries and chiral catalysts have been synthesized and used for the past 20 years. It will be helpful for the discussion to briefly review the reports on the synthesis of chiral 1,2-amino alcohols.

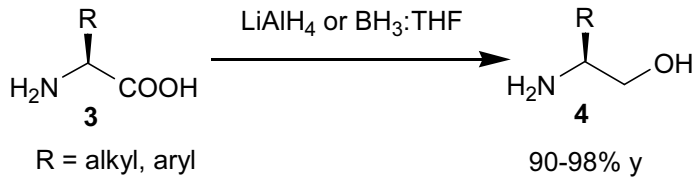
1. 1. 1 Synthesis of 1,2-amino alcohols

Currently, there are only a few methods available for the synthesis of racemic 1,2-amino alcohols.[12] Generally, enantiomerically pure 1,2-amino alcohols are prepared either from naturally occurring chiral amino acids or by synthesis and resolution of racemic mixtures.

1. 1. 1. 1 From amino acids and their derivatives

Amino acids **3** are reduced to the corresponding amino alcohols **4** using reducing agents such as $LiAlH_4$ and BH_3:THF. However, these reagents suffer from disadvantages of cost, inflammability and tedious isolation procedures (Scheme 1).[13-14]

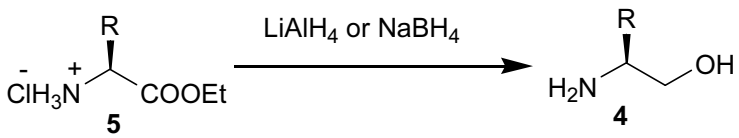
Scheme 1



Other reagents such as BH_3:SMe_2 in the presence of BF_3:OEt_2,[15] $NaBH_4/H_2SO_4$ system[16] and $LiBH_4$ in the presence of TMS-Cl[17] have also been used for the reduction of amino acids.

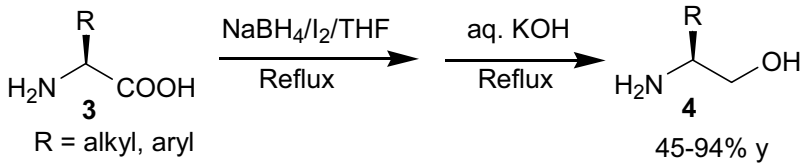
Amino ester salts **5** can be reduced to the corresponding amino alcohols **4** with $LiAlH_4$[18,19] or $NaBH_4$[20] (Scheme 2).

Scheme 2



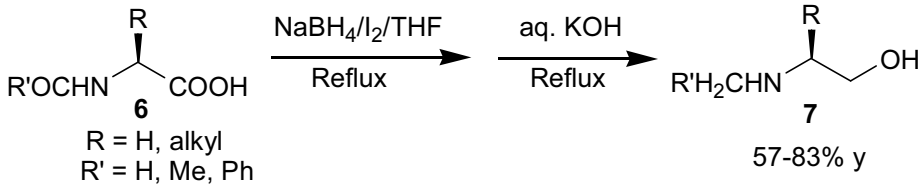
Meyers and coworkers[21] examined the reduction of amino acids using the $NaBH_4/I_2$ reagent system, previously developed in this laboratory for the reduction of organic compounds (Scheme 3).[22-23] It is of interest to note that no racemization occurs in the reduction of amino acids using the $NaBH_4/I_2$ reagent system. The results indicate that it is an excellent reagent system for the conversion of amino acids **3** to amino alcohols **4**. The $NaBH_4/I_2$ reagent system is safe, simple and inexpensive. Hence, it is useful, especially in the large-scale synthesis of chiral amino alcohols.

Scheme 3



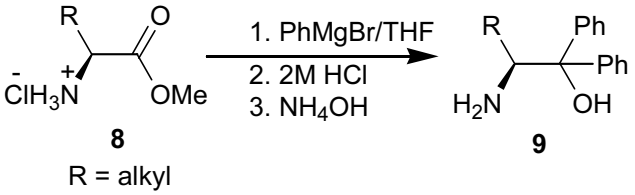
The *N*-acyl amino acids **6** are reduced to the corresponding *N*-alkyl amino alcohols **7** under these conditions (Scheme 4).[8]

Scheme 4



The diaryl carbinol derivatives have been found to be useful in asymmetric catalysis. For example, Itsuno and coworkers prepared the α,α-diphenyl 1,2-amino alcohols **9** from amino ester salts **8** using excess of the corresponding Grignard reagent (Scheme 5).[24]

Scheme 5



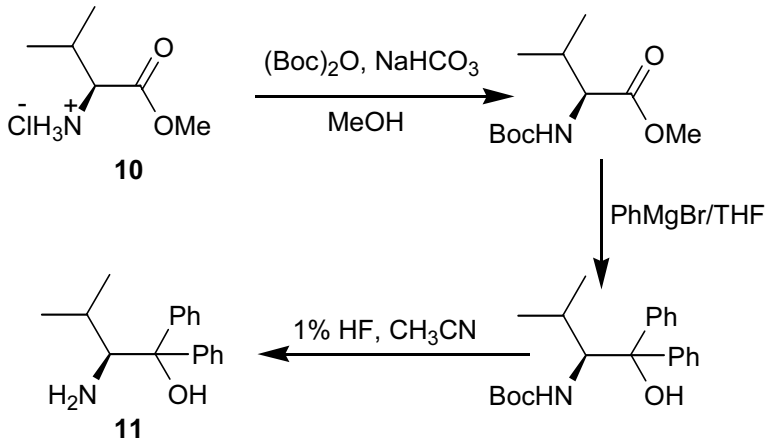
8

R = alkyl

9

Delair and coworkers[25] prepared the α,α-diphenylvalinol **11** via a method involving *N*-protection of valine ester salt **10** using base and $(Boc)_2O$ followed by the Grignard addition. No racemization was observed under these conditions. The deprotection of *N*-Boc amino alcohol was carried out using 1% hydrogen fluoride in acetonitrile (Scheme 6).[26]

Scheme 6

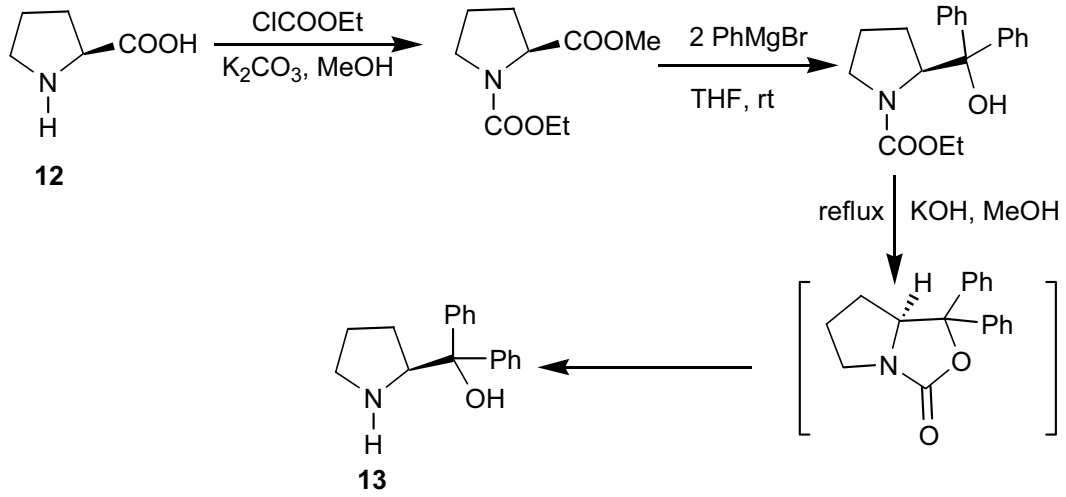


10

11

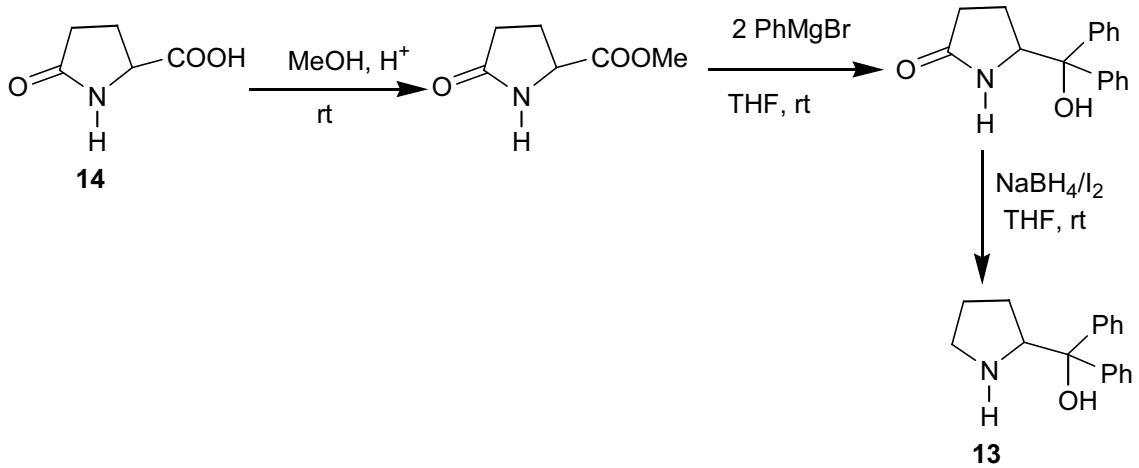
A convenient method of synthesis of chiral α,α-diphenyl-2-pyrrolidinemethanol (DPPM) **13** involving single step *N*- and *O*-protection of (*S*)-proline **12** using ethyl chloroformate followed by Grignard reaction and alkaline hydrolysis has been reported from this laboratory (Scheme 7).[27]

Scheme 7



The other isomer of the α,α-diphenyl-2-pyrrolidinemethanol (DPPM) **13** can also be prepared from unnatural (*R*)-proline, but it is expensive. So an alternate method for the synthesis of both enantiomers of DPPM, using racemic pyroglutamic acid **14** via $NaBH_4/I_2$ reduction of the corresponding amide in the crucial step has been developed in this laboratory (Scheme 8).[28]

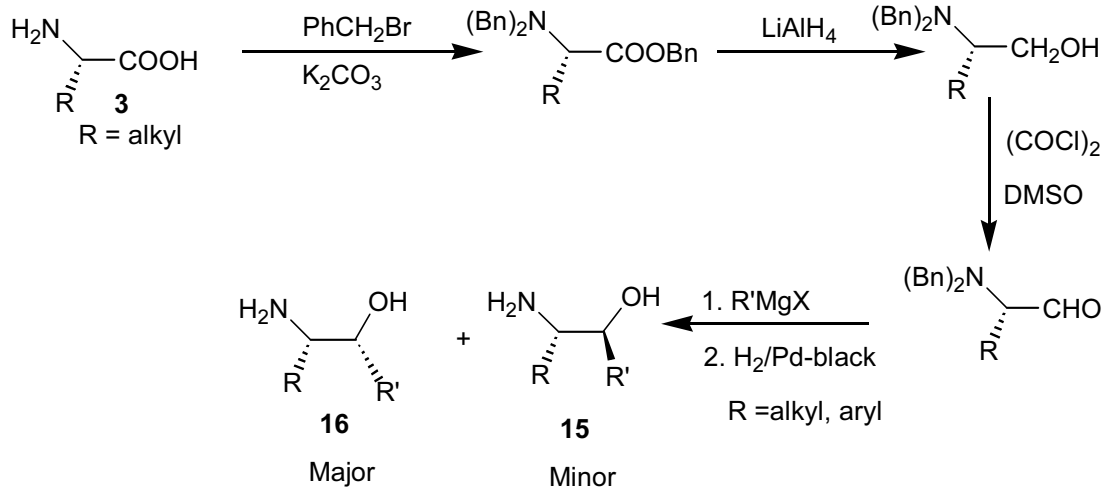
Scheme 8



Enantiomerically pure 1,2-amino alcohols with two stereo centers can be synthesized from natural α-amino acids. For example, Reetz and coworkers reported a

method of conversion of protected natural or unnatural α-amino acids into the α-amino aldehydes, which upon stereoselective Grignard or aldol addition and removal of the protecting group give the corresponding 1,2-amino alcohols **15** and **16** with high diastereoselectivity (Scheme 9).[29]

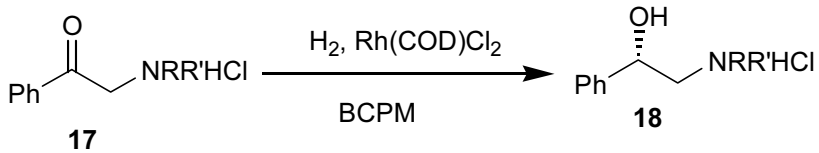
Scheme 9



1. 1. 1. 2 From α-amino carbonyl compounds

α-Amino carbonyl compounds **17** were reduced to obtain 1,2-amino alcohol derivatives **18** using $Rh(COD)Cl_2$ as catalyst (Scheme 10).[30]

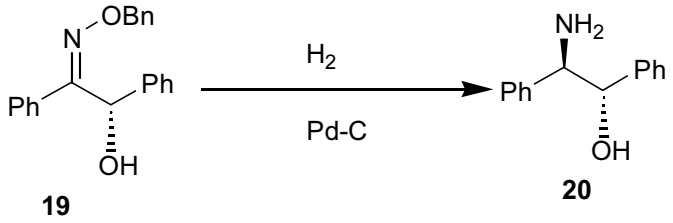
Scheme 10



1. 1. 1. 3 From alkoxy carbonyl compounds

α-Hydroxy carbonyl compounds were used to access 1,2-amino alcohols **20** through reduction of the corresponding oxime derivatives **19** (Scheme 11).[31]

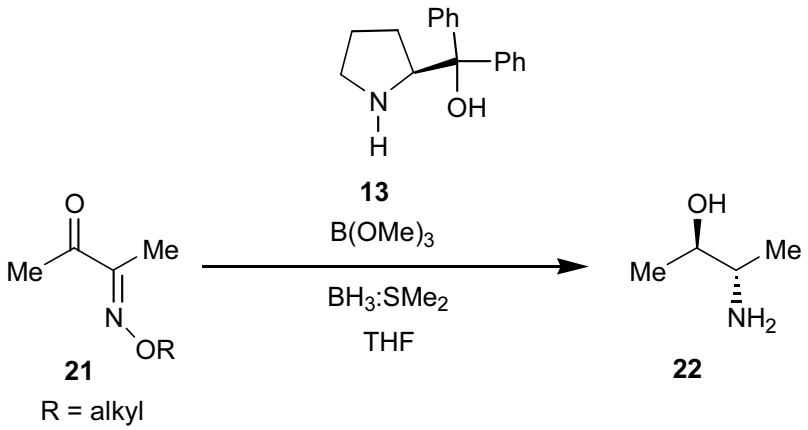
Scheme 11



1. 1. 1. 4 From α-oxoketoxime ethers

Mono oxime ethers of biacetyl **21** are converted to the 1,2-amino alcohols **22** by using chiral amino alcohol **13** and borane reagents (Scheme 12).[32]

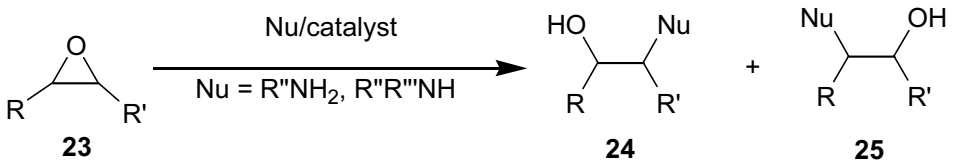
Scheme 12



1. 1. 1. 5 From epoxides

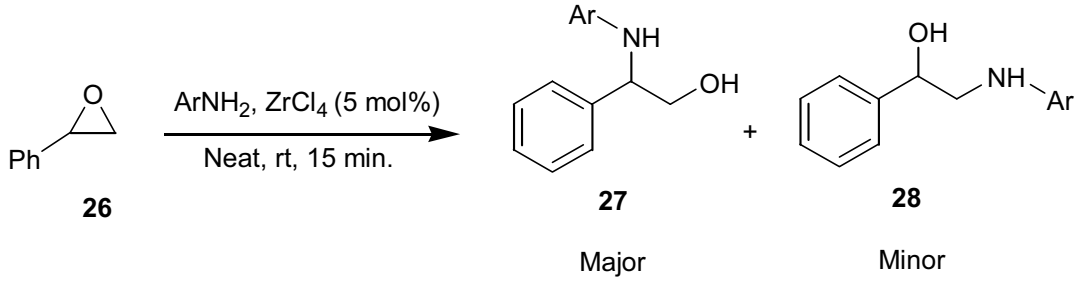
Several reports are available for the synthesis of 1,2-amino alcohols following this method. The classical approach involves heating of epoxides with amines in protic solvents.[33] Stereo, regio and enantioselective ring opening of the epoxides using nitrogen nucleophiles such as primary, secondary amines in presence of metal complexes as catalysts were reported (Scheme 13).[34-39]

Scheme 13



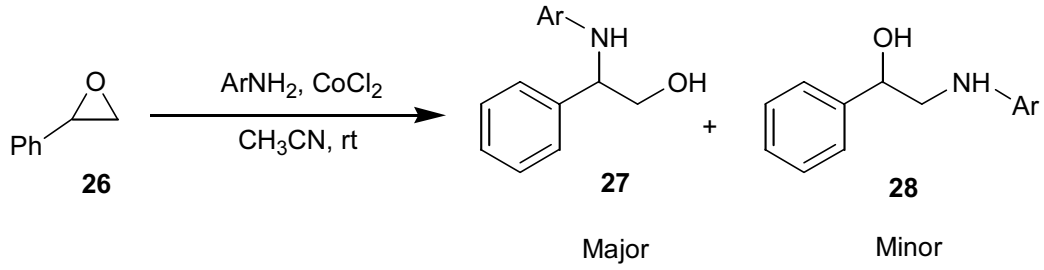
Chakraborti and coworkers prepared the 1,2-amino alcohol derivatives **27** and **28** by the regioselective ring opening of epoxides **26** with aniline derivatives using $ZrCl_4$ as catalyst (Scheme 14).[40]

Scheme 14



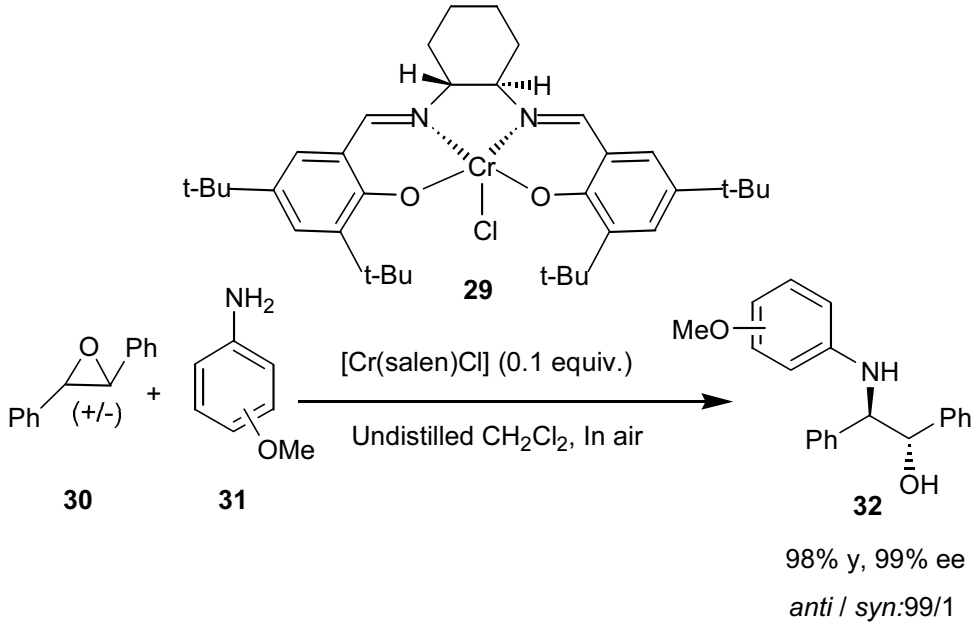
Recently, Sundararajan and coworkers reported that $CoCl_2$ catalyzed ring opening reaction of epoxides **26** by aniline derivatives affords the corresponding 1,2-amino alcohols **27** with high regioselectivity (Scheme 15).[41]

Scheme 15



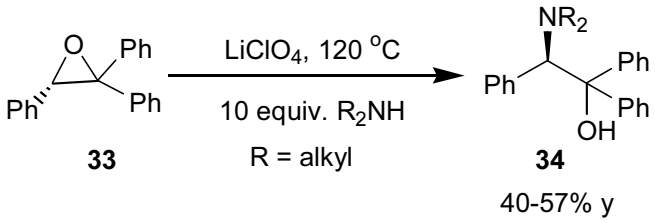
Bartoli and coworkers prepared the anti-1,2-amino alcohols **32** by the ring opening of *trans*-aromatic epoxides **30** with aniline derivatives **31** using commercially available [Cr(salen)Cl] **29** as a Lewis acid catalyst (Scheme 16).[42]

Scheme 16



α,α-Disubstituted 1,2-amino alcohols **34** are also synthesized by ring opening of the triphenyloxirane **33** with aliphatic secondary amines using $LiClO_4$ (Scheme 17).[43]

Scheme 17

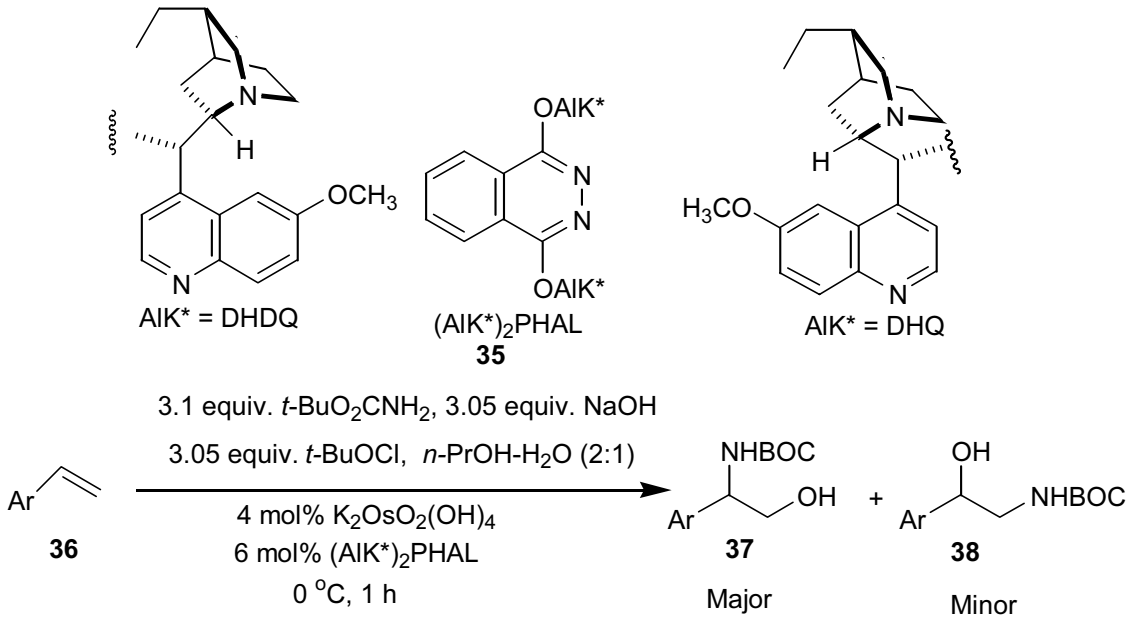


1. 1. 1. 6 From amino hydroxylation of olefins

Sharpless *et al.*[44-49] first reported the direct conversion of the olefins to amino alcohols by osmium-catalysed asymmetric amino hydroxylation reaction. This reaction was screened using chloramine-T, carbamates and amide derived oxidants as the nitrogen sources. Among these nitrogen sources, carbamates are especially useful because the resulting products are easily converted to free amino alcohols. Later,

O'Brien and coworkers[50] modified the Sharpless amino hydroxylation method using *ter*-butyl carbamate as nitrogen source (Scheme 18).

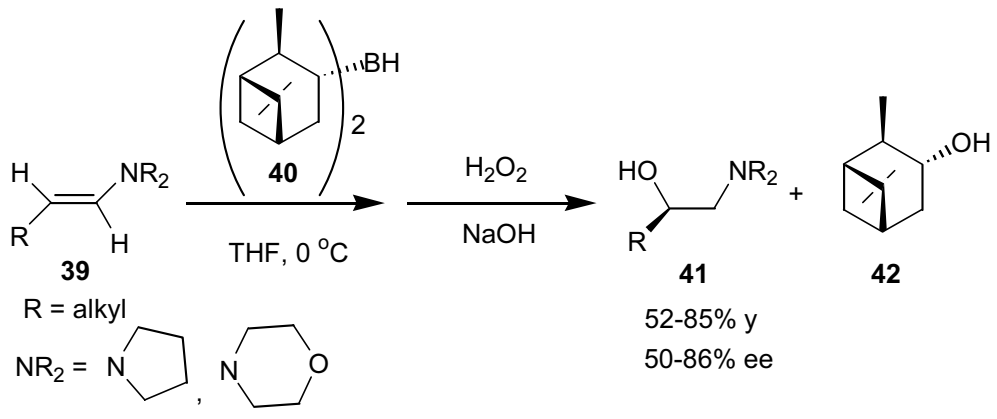
Scheme 18



1. 1. 1. 7 From hydroboration of enamines

Enantiomerically pure 1,2-amino alcohols **41** were also obtained by the asymmetric hydroboration of aldehyde enamines **39** followed by oxidation using H_2O_2/NaOH (Scheme 19).[51]

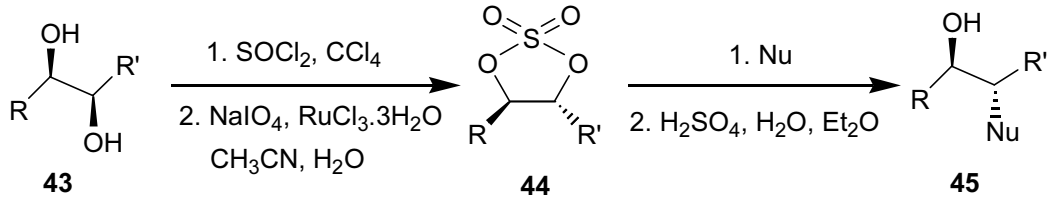
Scheme 19



1. 1. 1. 8 From cyclic sulfates

1,2-Cyclic sulfates are equivalent to epoxides. These are readily accessible via the Sharpless asymmetric dihydroxylation of the olefins. The 1,2-cyclic sulfates **44** react with nitrogen nucleophiles to give the corresponding 1,2-amino alcohol derivatives **45** (Scheme 20).[52]

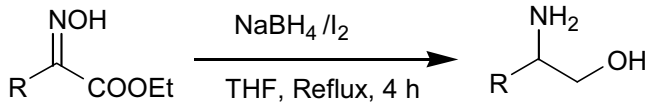
Scheme 20



1. 1. 2 Synthesis and resolution of 1,2-amino alcohols

The chiral amino alcohols are valuable synthetic intermediates. Accordingly, efforts have been made towards the synthesis and applications of these useful chiral compounds. Previously, a new, convenient and general methodology has been developed in this laboratory for the synthesis of racemic 1,2-amino alcohols by the reduction of oximes of the readily accessible α-keto esters using $NaBH_4$ in combination with I_2, CH_3COOH, $TiCl_4$, $ZrCl_4$, $CoCl_2$, H_2SO_4 and TMS-Cl. Comparison of the results indicated that the easy to handle $NaBH_4/I_2$ reagent system gives better yields. Accordingly, reduction of various oxime esters has been examined with this reagent system (Scheme 21).[53]

Scheme 21



46 R = Ph- 85%

47 R = Ph-CH_2- 80%

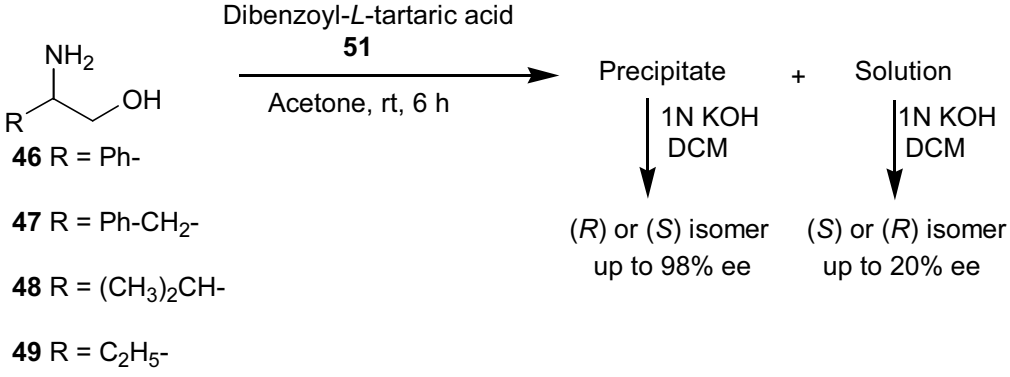
48 R = $(CH_3)_2CH$- 75%

49 R = C_2H_5- 60%

50 R = CH_3- 60%

The racemic 1,2-amino alcohols thus synthesized were readily resolved using dibenzoyl-*L*-tartaric acid through formation of diastereomeric salts in acetone solvent (Scheme 22). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically to get both the isomers.[53]

Scheme 22



46 R = Ph-

47 R = Ph-CH_2-

48 R = $(CH_3)_2CH$-

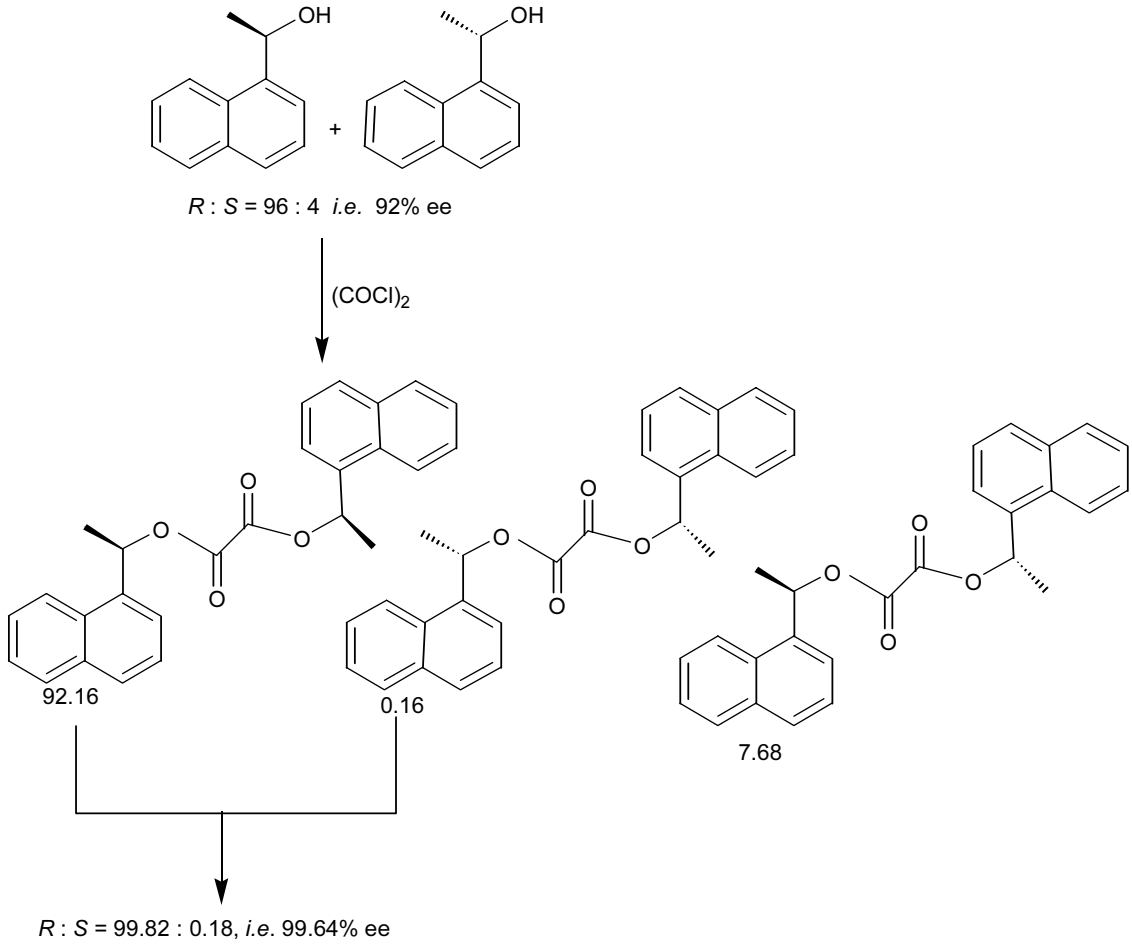
49 R = C_2H_5-

Although the dibenzoyl-*L*-tartaric acid **51** used in the resolution and enrichment of amino alcohols (Scheme 22) can be recovered easily, it would be advantageous if the partially resolved (scalemic, non-racemic) 1,2-amino alcohols could be further enriched

without using chiral source again. Enhancement of enantiomeric purity of samples with small enantiomeric excesses to obtain samples of high levels of enantiomeric purity has relevance not only to the evolution of chiral homogeneity in Nature[54-56] but also to the spectacular successes realized in recent years in Kagan's non-linear effects in asymmetric catalysis,[57] Mikami's asymmetric activation of racemic catalysts[58,59] and Soai's asymmetric autocatalysis in dialkylzinc additions.[60,61] Various processes developed so far for enhancement of enantiomeric purity of non-racemic (partially resolved) compounds include, amplification during: (i) evaporation and precipitation,[62,63] (ii) incomplete reaction,[64] (iii) stereoselective autocatalysis-crystallization [65,66] and (iv) polymerization.[67,68] Whereas the method of enhancement of purity by evaporation requires differential solubility of enantiomers and the racemate, most of the other methods involve enrichment by formation of diastereomers through covalent bonds.

In 1973, Horeau[64] reported the chemical duplication of non-racemic samples via preparation of corresponding carbonates, phthalates, malonates and oxalates. The enhancement of enantiomeric excess realized here are due to the formation of homochiral diester [(e.g. *R*,*R*)] derived from enantiomer (*R*) present in excess in the non-racemic sample compared to that of the homochiral diester (*S*,*S*) and the heterochiral (*R*,*S*) diester. The (*R*,*R*) and (*S*,*S*) enantiomers obtained in this way could be readily separated from the (*R*,*S*) diastereomer and upon decomposition yield the non-racemic alcohol sample in higher enantiomeric excess. Later, Fleming and Ghosh[69] applied this idea to enrich the enantiomeric excess of a scalemic alcohol (from 92% ee to 99.6% ee) using oxalyl chloride (Scheme 23).

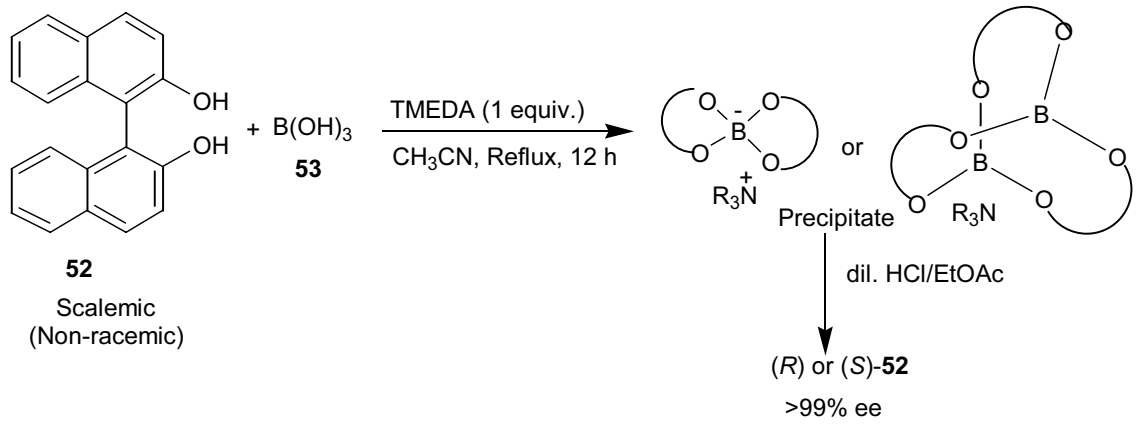
Scheme 23



Also, Fleming and Ghosh showed that if there were no stereo selection, the derivatives would be formed from the following the algebraic expression, X^2:Y^2:2XY. For example, if the starting enantiomeric excess is 80%, (i.e, X:Y= 90:10, X, Y are the concentration of the *R* and *S*, respectively) and since (X^2 + Y^2) and 2XY are diastereomers, separation of the *RR* and *SS* diastereomers (X^2 +Y^2) from the above mixture and regeneration of *R* and *S* enantiomers should give *R*:*S* in the ratio (X^2 + Y^2) 8100:100 = 98.8:1.2, corresponding to an ee of 97.6%.

Previously, it was discovered in this laboratory that the scalemic (non-racemic) 1,1'-bi-2-naphthol **52** could be enriched to obtain samples with 99% ee using inexpensive $B(OH)_3$ and TMEDA.[70] In this case, the precipitate fraction gave the enriched isomer, leaving behind the mixture with low ee in solution. When the $B(OH)_3$ was used in smaller amounts, mainly the complex of the enantiomer present in excess precipitates out (Scheme 24).

Scheme 24



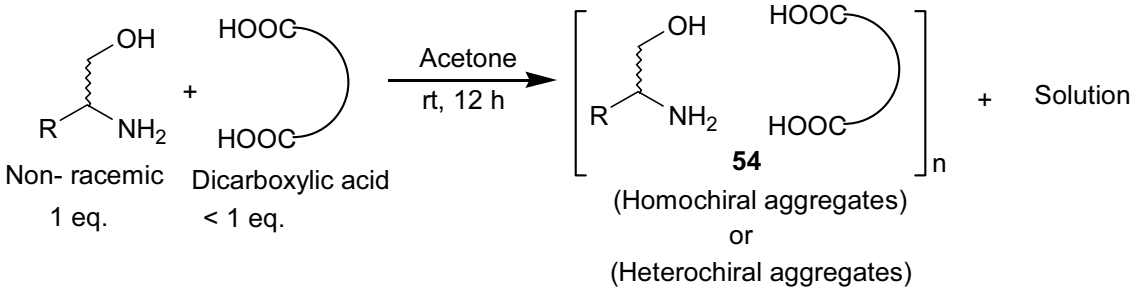
In all these studies, the diastereomeric complexes were prepared via transformations involving covalent bonds. It was of interest to examine whether the enantiomeric purity of partially resolved (non-racemic) 1,2-amino alcohols[53] could be enhanced using certain achiral dicarboxylic acids via preparation of the corresponding hydrogen bonded diastereomeric aggregates. The results are discussed in the next section.

1. 2 Results and Discussion

1. 2. 1 Enhancement of enantiomeric purity of non-racemic amino alcohols using oxalic acid

We have devised a conceptual method for the purification of partially resolved (non-racemic) 1,2-amino alcohols[53] using certain achiral dicarboxylic acids such as oxalic, fumaric, maleic and terephthalic acids through preparation of homochiral and heterochiral aggregates by inducing hydrogen-bonding network (Scheme 25).

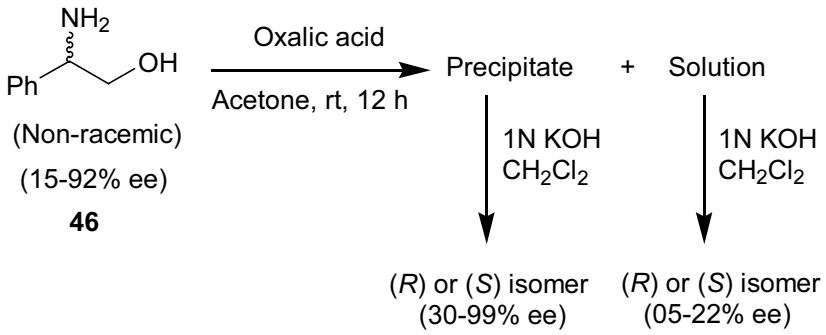
Scheme 25



We have envisaged that if the formation of diastereomeric aggregates **54** could be induced using achiral spacers through hydrogen bonds, it would result in the enhancement of enantiomeric excess, especially if the achiral spacers are used in lesser amounts than that required for interaction with all of the non-racemic material present in the mixture.

Initially, we have carried out the purification of non-racemic phenylglycinol **46** using oxalic acid in acetone solvent at room temperature for 12 h (Scheme 26). When, oxalic acid was added to a stirred solution of non-racemic sample of phenylglycinol in acetone, a precipitate was formed immediately. After separation of precipitate and filtrate fractions and workup, sample of higher enantiomeric excesses (ees) can be readily obtained in the precipitate fraction.[71] These results are summarized in Table 1.

Scheme 26



When non-racemic phenylglycinol **46** and oxalic acid were used in 1:1 ratio in acetone solvent. After workup, there was no enrichment observed from both precipitate and filtrate fractions (Table 1, entry 1). When oxalic acid was used in smaller amounts, enrichment is observed in the precipitate fraction and leaving the low ee in the solution. Optimum results were obtained when oxalic acid was used in 1:1 molar equivalent to the isomer present in excess in the non-racemic sample of phenylglycinol **46**. For example, when 5 mmol of 50% ee of phenylglycinol was treated with 2.5 mmol of oxalic acid in acetone at room temperature for 12 h, after workup of the precipitate fraction an enriched sample of 70% ee of phenylglycinol was obtained and from the solution fraction a sample with 5% ee was isolated (Table 1, entry 6).

Table 1. Enhancement of enantiomeric excess of non-racemic phenylglycinol 46 using oxalic acid[a]

S. No.	Substrate **46** (% ee)	Oxalic acid	Phenylglycinol **46** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 40	5.00	42 (*R*)	55	35 (*R*)	30
2	(*R*) 15	0.75	30 (*R*)	11	03 (*R*)	70
3	(*S*) 20	1.00	35 (*S*)	15	06 (*S*)	68
4	(*R*) 30	1.50	50 (*R*)	28	06 (*R*)	55
5	(*S*) 35	1.75	60 (*S*)	30	05 (*S*)	50
6	(*R*) 50	2.50	70 (*R*)	48	05 (*R*)	35
7	(*S*) 52	2.60	75 (*S*)	48	06 (*S*)	33
8	(*R*) 70	3.50	90 (*R*)	65	09 (*R*)	20
9	(*S*) 75	3.75	92 (*S*)	68	10 (*S*)	18
10	(*R*) 90	4.50	99 (*R*)	85	20 (*R*)	10
11	(*S*) 92	4.60	99 (*S*)	87	22 (*S*)	05

a. The reactions were carried out using non-racemic phenylglycinol **46** (5 mmol) and oxalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +33 (*C* 0.75, 1N HCl) for (*S*)-**46.** Studies to estimate the ee using chiral shift reagent and by chiral HPLC columns were not successful.

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

Then we have applied this idea for the purification of non-racemic samples of phenylalaninol **47** using oxalic acid in acetone solvent (Scheme 27). In this case also enhancement was observed in the precipitate fraction and the results are summarized in Table 2.

Scheme 27

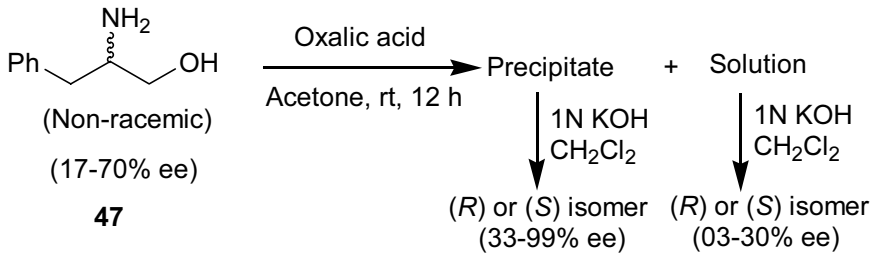


Table 2. Enhancement of enantiomeric excess of non-racemic phenylalaninol 47 using oxalic acid[a]

S. No.	Substrate **47** (% ee)	Oxalic acid	Phenylalaninol **47** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 17	0.85	33 (*R*)	20	03 (*R*)	65
2	(*R*) 33	1.75	70 (*R*)	40	09 (*R*)	50
3	(*R*) 70	3.50	99 (*R*)	65	30 (*R*)	22
4	(*R*) 50	2.50	98 (*R*)	52	20 (*R*)	30
5	(*S*) 20	1.00	35 (*S*)	25	06 (*S*)	60
6	(*S*) 35	1.75	75 (*S*)	40	10 (*S*)	50
7	(*S*) 50	2.50	98 (*S*)	48	15 (*S*)	35

a. The reactions were carried out using non-racemic phenylalaninol **47** (5 mmol) and oxalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +23 (*C* 1.2, 1N HCl) for (*R*)-**47.** Studies to estimate the ee using chiral shift reagent and by chiral HPLC columns were not successful.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **47** used.

The enrichment is more effective in the case of phenylalaninol **47** when compared to phenylglycinol **46** using oxalic acid. For example, when 50% ee of phenylalaninol was treated with oxalic acid, after workup samples with 98% ee was obtained from the precipitate fraction (Table 2, entries 4 and 7).

Similarly, we have carried out the purification of non-racemic samples of valinol **48** using oxalic acid (Scheme 28). In this case also enrichment was observed in the precipitate fraction and the enhancement effect was similar to that of phenylglycinol **46.** The results are summarized in Table 3.

Scheme 28

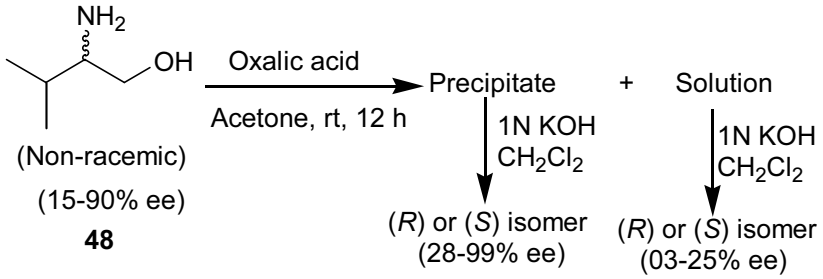


Table 3. Enhancement of enantiomeric excess of non-racemic valinol 48 using oxalic acid[a]

S. No.	Substrate **48** (% ee)	Oxalic acid	Valinol **48** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 20	1.00	35 (*R*)	20	03 (*R*)	75
2	(*R*) 35	1.75	55 (*R*)	40	06 (*R*)	58
3	(*R*) 75	3.75	99 (*R*)	65	20 (*R*)	25
4	(*S*) 15	0.75	28 (*S*)	12	03 (*S*)	75
5	(*S*) 28	1.40	50 (*S*)	30	05 (*S*)	55
6	(*S*) 50	2.50	70 (*S*)	48	15 (*S*)	40
7	(*S*) 70	3.50	90 (*S*)	65	15 (*S*)	20
8	(*S*) 90	4.50	99 (*S*)	87	25 (*S*)	08

a. The reactions were carried out using non-racemic valinol **48** (5 mmol) and oxalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +17 (*C* 10, EtOH) for (*S*)-**48**. Studies to estimate the ee using chiral shift reagent and by chiral HPLC columns were not successful.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **48** used.

We have also carried out the purification of non-racemic samples of 2-amino butanol **49** using oxalic acid (Scheme 29). In this also enrichment was observed in the precipitate fraction (Table 4). Sample of enantiomerically pure 2-amino butanol **49** could be obtained using oxalic acid even from sample of very low ee (18% ee), after three successive operations (Table 4, entries 4-6).

Scheme 29

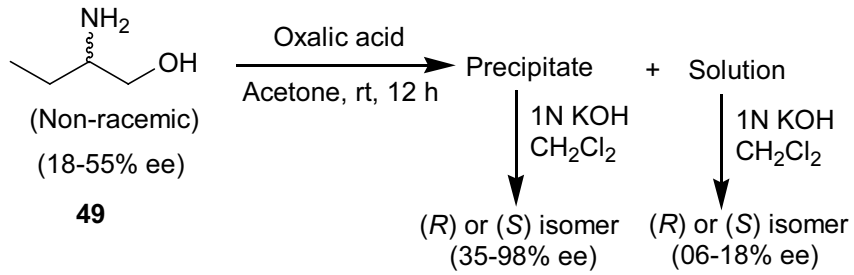


Table 4. Enhancement of enantiomeric excess of non-racemic 2-amino butanol 49 using oxalic acid[a]

S. No.	Substrate **49** (% ee)	Oxalic acid	2-Amino butanol **49** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 20	1.00	35 (*R*)	25	08 (*R*)	65
2	(*R*) 35	1.75	55 (*R*)	35	10 (*R*)	50
3	(*R*) 55	2.75	98 (*R*)	49	18 (*R*)	30
4	(*S*) 18	0.90	36 (*S*)	20	06 (*S*)	70
5	(*S*) 36	1.80	52 (*S*)	35	12 (*S*)	52
6	(*S*) 52	2.60	98 (*S*)	44	15 (*S*)	35

a. The reactions were carried out using non-racemic 2-amino butanol **49** (5 mmol) and oxalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH) for (*S*)-**49.** Studies to estimate the ee using chiral shift reagent and by chiral HPLC columns were not successful.

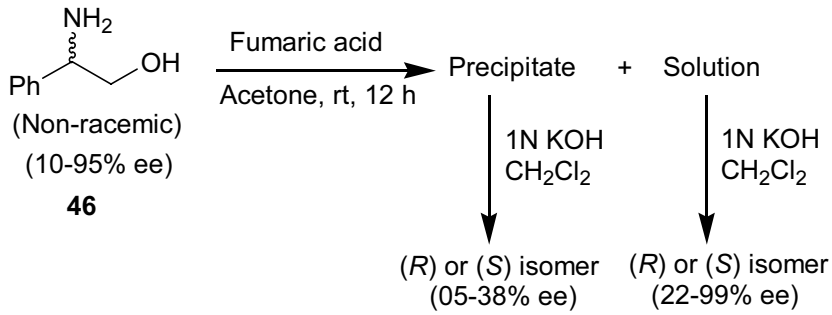
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **49** used.

These studies were also carried out using various solvents like acetone, CH_3CN, MeOH and THF. It was observed that acetone gave optimum results. Hence, we have carried out the purification of non-racemic amino alcohols using other achiral dicarboxylic acids in acetone solvent.

1. 2. 2 Enhancement of enantiomeric purity of non-racemic amino alcohols using fumaric acid

We have then examined the purification of non-racemic phenylglycinol **46** using fumaric acid in acetone solvent (Scheme 30).

Scheme 30



Surprisingly, it was observed that in this case, enriched samples of **46** were obtained in the solution fraction, whereas the precipitate fraction gave the samples with lower ee. This is exactly opposite to the results observed in the purification of non-racemic amino alcohols using oxalic acid, where enrichment was observed in the precipitate fraction. These results are summarized in Table 5.

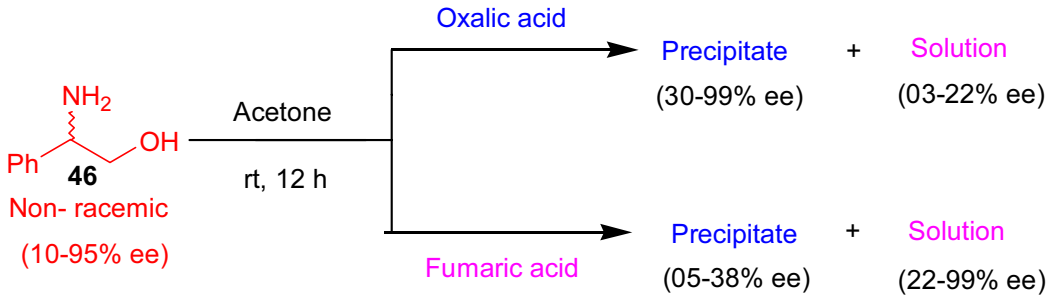
Table 5. Enhancement of enantiomeric excess of non-racemic phenylglycinol 46 using fumaric acid[a]

S. No.	Substrate **46** (% ee)	Fumaric acid	Phenylglycinol **46** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 10	0.50	05 (*R*)	70	22 (*R*)	20
2	(*S*) 15	0.75	05 (*S*)	58	29 (*S*)	30
3	(*R*) 20	1.00	06 (*R*)	55	40 (*R*)	31
4	(*S*) 30	1.50	12 (*S*)	50	70 (*S*)	38
5	(*R*) 40	2.00	17 (*R*)	43	85 (*R*)	45
6	(*S*) 50	2.50	26 (*S*)	40	96 (*S*)	48
7	(*R*) 70	3.50	30 (*R*)	28	99 (*R*)	50
8	(*S*) 85	4.25	32 (*S*)	18	99 (*S*)	75
9	(*R*) 90	4.50	36 (*R*)	10	99 (*R*)	84
10	(*S*) 95	4.75	38 (*S*)	08	99 (*S*)	87

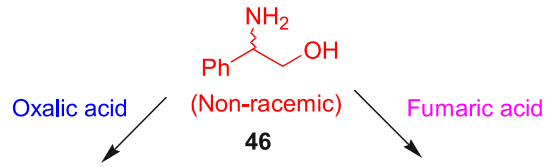
a. The reactions were carried out using non-racemic phenylglycinol **46** (5 mmol) and fumaric acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +33 (*C* 0.75, 1N HCl) for (*S*)-**46**.
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **46** used.

Presumably, in the case of oxalic acid, precipitation of predominantly homochiral aggregates (*R*,*R*… or *S*,*S*…) occurs and in the case of fumaric acid, heterochiral aggregates (*R,S,R,S*…) predominantly precipitates out (Scheme 31).

Scheme 31. Enhancement of enantiomeric purity of non-racemic phenylglycinol 46 using oxalic and fumaric acids



The difference in results can be readily illustrated graphically. The plots of the starting ees against the final ees in the case of oxalic acid (Table 1) and fumaric acid (Table 5) are shown in Figures 1 and 2 respectively.



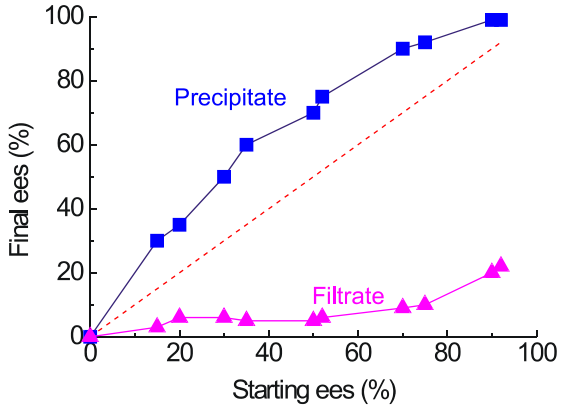


Figure 1. Purification of partially resolved 46 using oxalic acid
(■). Products obtained from precipitate fractions
(-). Data points expected assuming no selectivity
(▲). Products obtained from filtrate fractions

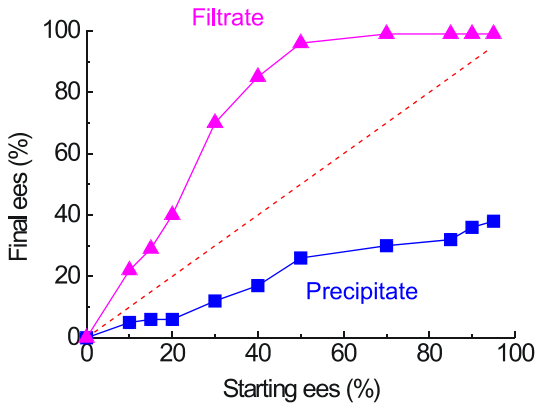


Figure 2. Purification of partially resolved 46 using fumaric acid
(▲). Products obtained from filtrate fractions
(-). Data points expected assuming no selectivity
(■). Products obtained from precipitate fractions

From these graphs, it is clear that in the case of oxalic acid, enrichment is observed in the precipitate fraction, whereas in the case of fumaric acid, enrichment occurs in the solution fraction.

These results may have relevance to the concept of chemical evolution of homogeneity of chirality in Nature through enrichment of small amounts of non-racemic materials that could be formed by chance.[1,73,74] Also, the formation of predominantly homo or heterochiral aggregates is relevant to the formation of such complexes *in situ* around central metals in systems that exhibit non-linear effects in asymmetric catalysis.[57-61]

This method is conceptually different from previously reported co-crystallization techniques for the purification of certain non-racemic carboxylic acids,[75,76] because in these cases, the enantiomer present in excess invariably crystallizes out. In contrast, in the method described here, enhancement is due to selective formation of predominantly homo or heterochiral aggregates in the precipitate fractions (Scheme 31, Tables 1 and 5, Figures 1 and 2). This method is also different from the Horeau duplication (see introductory section) in which enhancement of ees of the crystallized samples are due to the statistical distribution of dimers derived from the enantiomers present in the mixture without any selectivy.[64]

X-ray studies:

The fumaric acid-phenylglycinol complex gave single crystals suitable for X-ray analysis using MeOH as solvent. The ORTEP diagram consists of 1:1 complex of phenylglycinol with fumaric acid in which fumaric acid moiety exists as mono carboxylate anion and the phenylglycinol moiety exists as ammonium cation (Figure 3).

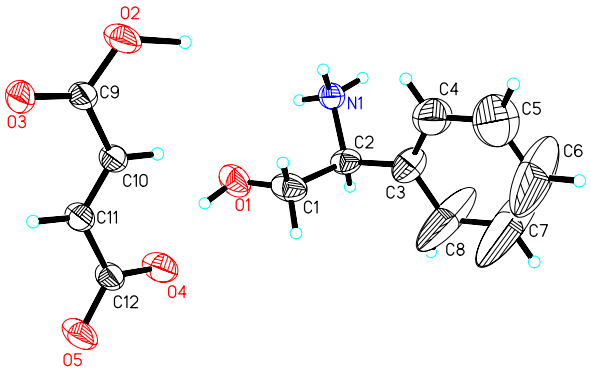


Figure 3. ORTEP diagram of racemic phenylglycinol 46 with fumaric acid

The packing diagram showed that layers of intermolecular hydrogen bonded mono carboxylate anion of the acid alternating with layers of intermolecular hydrogen bonded amino alcohol **46** through N-H···O and O-H···O interactions (Figure 4). The alternating layers of amino alcohol were found to be heterochiral with respect to each other.

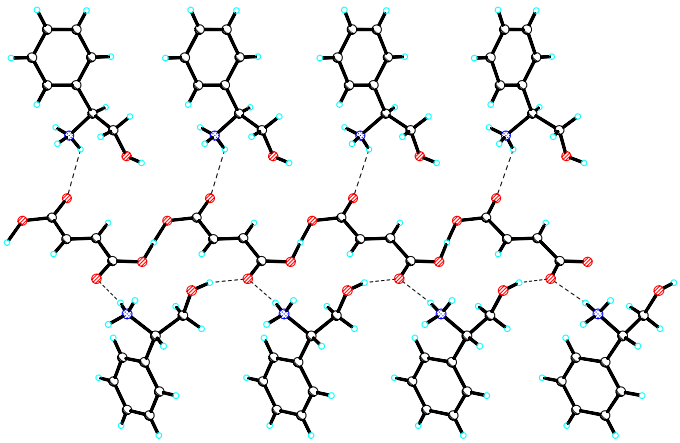


Figure 4. Packing diagram of racemic phenylglycinol 46 with fumaric acid

Unfortunately, crystals suitable for X-ray analysis could not be obtained by crystallization of oxalic acid-racemic phenylglycinol or chiral phenylglycinol complex.

Table 6. X-ray data collection and structure refinement for racemic phenylglycinol 46 with fumaric acid

Empirical formula	$C_{12}H_{15}NO_5$
Formula weight	253.25
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 12.816(3) Å, α = 90°
	b = 6.3361(13) Å, β = 105.78(3)°
	c = 16.490(3) Å, γ = 90°
Volume	1288.6(5) $Å^3$
Z	4
Calculated density	1.305 mg/m^3
Absorption coefficient	0.102 mm^{-1}
F(000)	536
θ Range for data collection	1.79 to 27.97°
Limiting indices	$0\leq h\leq 16$, $0\leq k\leq 8$, $-21\leq l\leq 21$
Reflections collected/unique	3097 / 2358 [R(int) = 0.0000]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	2358 / 0 / 184
Goodness-of-fit on F^2	1.055
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0559$, $wR_2 = 0.1670$
R indices (all data)	$R_1 = 0.0758$, $wR_2 = 0.1998$
Largest diff. peak and hole	0.404 and -0.327 $eÅ^{-3}$

We have then examined the purification of non-racemic phenylalaninol **47** using fumaric acid (Scheme 32). In this case also, enhancement in ee was observed for samples obtained from the filtrate fraction (Table 7). For example, the sample of **47**

with 50% ee of was treated with fumaric acid, after workup a sample of 90% ee was obtained in the solution fraction and a sample of 28% ee was obtained from the precipitate fraction (Table 7, entry 3).

Scheme 32

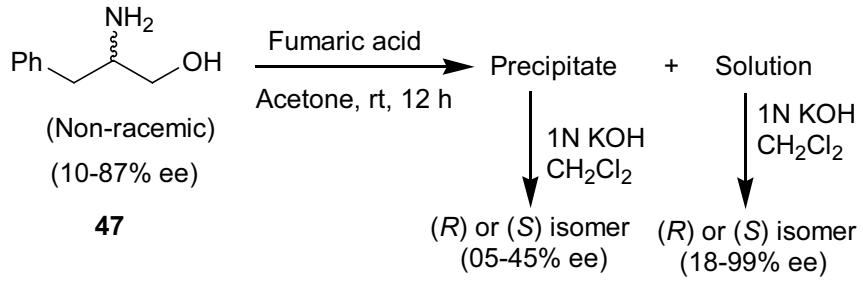


Table 7. Enhancement of enantiomeric excess of non-racemic phenylalaninol 47 using fumaric acid[a]

S. No.	Substrate **47** (% ee)	Fumaric acid	Phenylalaninol **47** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 20	1.00	05 (*R*)	60	35 (*R*)	30
2	(*R*) 35	1.75	12 (*R*)	50	65 (*R*)	38
3	(*R*) 50	2.50	28 (*R*)	40	90 (*R*)	45
4	(*R*) 65	3.25	40 (*R*)	35	99 (*R*)	55
5	(*S*) 10	0.50	05 (*S*)	65	18 (*S*)	20
6	(*S*) 18	0.90	06 (*S*)	58	36 (*S*)	32
7	(*S*) 36	1.80	15 (*S*)	45	70 (*S*)	43
8	(*S*) 50	2.50	30 (*S*)	38	87 (*S*)	45
9	(*S*) 70	3.50	40 (*S*)	30	99 (*S*)	60
10	(*S*) 87	4.35	45 (*S*)	10	99 (*S*)	80

a. The reactions were carried out using non-racemic phenylalaninol **47** (5 mmol) and fumaric acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +23 (*C* 1.2, 1N HCl) for (*R*)-**47.**

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

Similarly, we have carried out the enhancement of enantiomeric purity of partially resolved samples of valinol **48** using fumaric acid (Scheme 33). The results are again similar to that obtained in the case of phenylglycinol **46** and enrichment was observed in the solution fraction. The results are summarized in Table 8.

Scheme 33

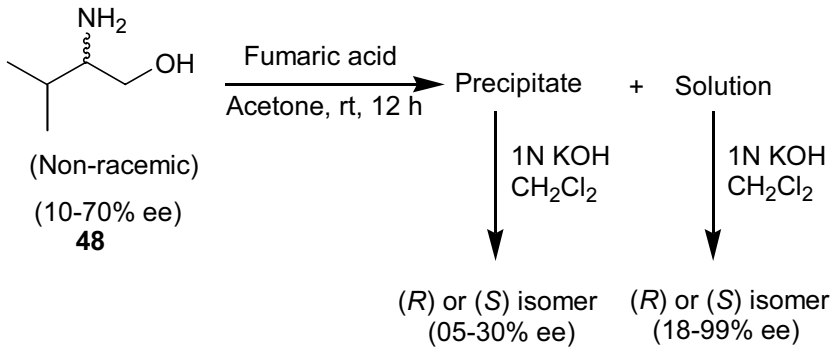


Table 8. Enhancement of enantiomeric excess of non-racemic valinol 48 using fumaric acid[a]

S. No.	Substrate **48** (% ee)	Fumaric acid	Valinol **48** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 25	1.25	10 (*R*)	50	50 (*R*)	38
2	(*R*) 50	2.50	18 (*R*)	45	95 (*R*)	42
3	(*R*) 70	3.50	25 (*R*)	30	99 (*R*)	60
4	(*S*) 10	0.50	05 (*S*)	65	18 (*S*)	20
5	(*S*) 15	0.75	08 (*S*)	60	30 (*S*)	28
6	(*S*) 30	1.50	12 (*S*)	50	50 (*S*)	40
7	(*S*) 50	2.50	20 (*S*)	40	94 (*S*)	45
8	(*S*) 65	3.25	30 (*S*)	28	99 (*S*)	60

a. The reactions were carried out using non-racemic valinol **48** (5 mmol) and fumaric acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +17 (*C* 10, EtOH) for (*S*)-**48**.

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

The non-racemic samples of 2-amino butanol were also purified using fumaric acid (Scheme 34) and the results are summarized in Table 9.

Scheme 34

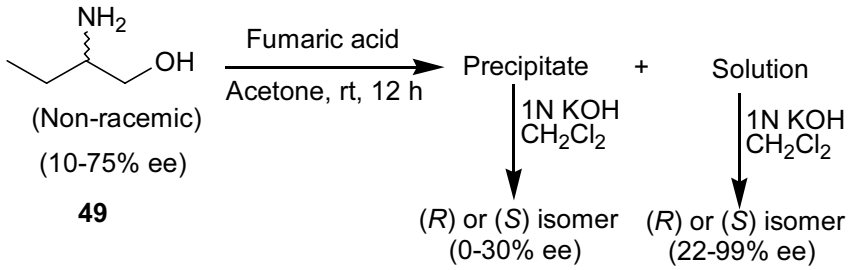


Table 9. Enhancement of enantiomeric excess of non-racemic 2-amino butanol 49 using fumaric acid[a]

S. No.	Substrate **49** (% ee)	Fumaric acid	2-Amino butanol **49** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 10	0.50	0	68	22 (*R*)	20
2	(*R*) 22	1.10	10 (*R*)	55	48 (*R*)	30
3	(*R*) 48	2.40	15 (*R*)	35	90 (*R*)	52
4	(*R*) 55	2.50	20 (*R*)	40	99 (*R*)	50
5	(*S*) 20	1.00	12 (*S*)	60	42 (*S*)	26
6	(*S*) 42	2.10	20 (*S*)	38	75 (*S*)	50
7	(*S*) 75	3.75	30 (*S*)	20	99 (*S*)	68

a. The reactions were carried out using non-racemic 2-amino butanol **49** (5 mmol) and fumaric acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH) for (*S*)-**49.**
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture used.

Again, a sample of 55% ee of 2-amino butanol **49** upon treatment with oxalic and fumaric acids in separate runs, after digestion, gave almost pure enantiomers from precipitate fraction in the case of oxalic acid (Table 4, entry 3) and filtrate fraction in the case of fumaric acid (Table 9, entry 4).

1. 2. 3 Enhancement of enantiomeric purity of non-racemic amino alcohols using maleic acid

We have then examined the use of maleic acid for the purification of non-racemic phenylglycinol **46** in acetone solvent (Scheme 35). Here also, the enhancement was observed in the solution fraction similar to that observed with fumaric acid (Table 10). However, the enhancement observed here is relatively low.

Scheme 35

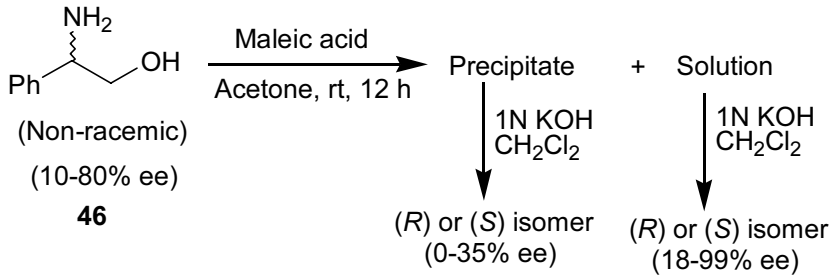


Table 10. Enhancement of enantiomeric excess of non-racemic phenylglycinol 46 using maleic acid[a]

S. No.	Substrate **46** (% ee)	Maleic acid	Phenylglycinol **46** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 30	1.50	15 (*R*)	45	50 (*R*)	40
2	(*R*) 50	2.50	24 (*R*)	38	75 (*R*)	52
3	(*R*) 75	3.75	35 (*R*)	26	99 (*R*)	65
4	(*S*) 10	0.50	0	70	18 (*S*)	15
5	(*S*) 18	0.90	05 (*S*)	62	35 (*S*)	25
6	(*S*) 35	1.75	18 (*S*)	50	58 (*S*)	40
7	(*S*) 58	2.90	25 (*S*)	32	80 (*S*)	60
8	(*S*) 80	4.00	30 (*S*)	16	99 (*S*)	72

a. The reactions were carried out using non-racemic phenylglycinol **46** (5 mmol) and maleic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +33 (*C* 0.75, 1N HCl) for (*S*)-**46.**

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

We have then examined the purification of non-racemic phenylalaninol **47** using maleic acid (Scheme 36). Again, enrichment was observed in the solution fraction and a sample of **47** with 50% ee can be purified to obtain a sample of 95% ee (Table 11, entry 6). The results are summarized in Table 11.

Scheme 36

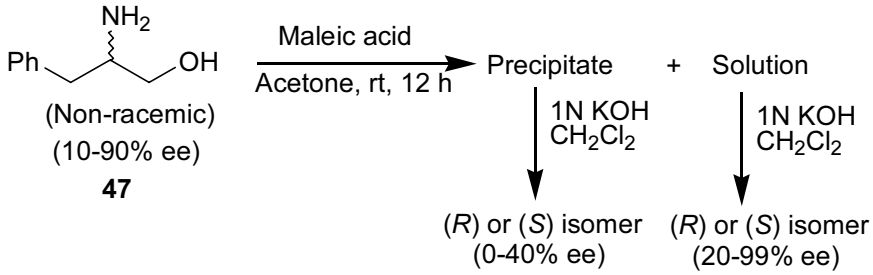


Table 11. Enhancement of enantiomeric excess of non-racemic phenylalaninol 47 using maleic acid[a]

S. No.	Substrate **47** (% ee)	Maleic acid	Phenylalaninol **47** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 25	1.00	08 (*R*)	50	48 (*R*)	35
2	(*R*) 48	2.40	20 (*R*)	38	90 (*R*)	50
3	(*R*) 90	4.50	40 (*R*)	10	99 (*R*)	78
4	(*S*) 10	0.50	0	65	20 (*S*)	22
5	(*S*) 22	1.00	10 (*S*)	55	50 (*S*)	30
6	(*S*) 50	2.50	25 (*S*)	42	95 (*S*)	45
7	(*S*) 70	3.50	30 (*S*)	26	99 (*S*)	65

a. The reactions were carried out using non-racemic phenylalaninol **47** (5 mmol) and maleic acid in acetone (60 mL) and the contents were stirred at 25 °C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +23 (*C* 1.2, 1N HCl) for (*R*)-**47**.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **47** used.

Similar results were obtained in the purification of non-racemic samples of valinol **48** using maleic acid. That is enhancement of purity was observed in the solution fraction (Scheme 37). The results are summarized in Table 12.

Scheme 37

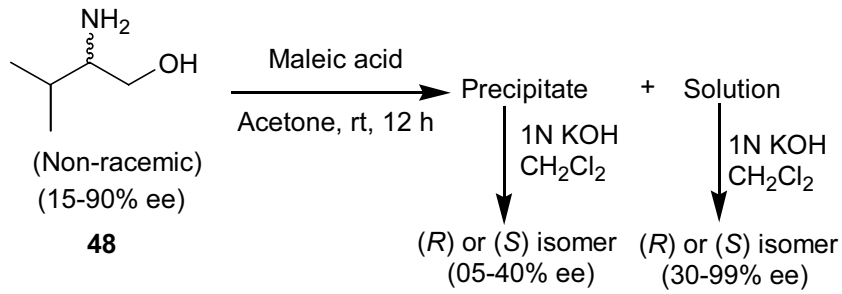


Table 12. Enhancement of enantiomeric excess of non-racemic valinol 48 using maleic acid[a]

S. No.	Substrate **48** (% ee)	Maleic acid	Valinol **48** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 15	0.75	05 (*R*)	60	30 (*R*)	30
2	(*R*) 30	1.50	10 (*R*)	50	58 (*R*)	38
3	(*R*) 58	2.90	20 (*R*)	35	99 (*R*)	52
4	(*R*) 90	4.50	40 (*R*)	10	99 (*R*)	80
5	(*S*) 25	1.25	10 (*S*)	48	50 (*S*)	40
6	(*S*) 50	2.50	20 (*S*)	40	99 (*S*)	45
7	(*S*) 35	1.75	18 (*S*)	50	70 (*S*)	40
8	(*S*) 70	3.50	30 (*S*)	25	99 (*S*)	60

a. The reactions were carried out using non-racemic valinol **48** (5 mmol) and maleic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +17 (*C* 10, EtOH) for (*S*)-**48.**
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **48** used.

The racemic valinol **48** and maleic acid formed a complex in acetone, which on crystallization from MeOH solvent gave single crystals suitable for X-ray analysis. The

ORTEP diagram showed that the complex is a salt in which valinol and maleic acid exists in 1:1 ratio (Figure 5).

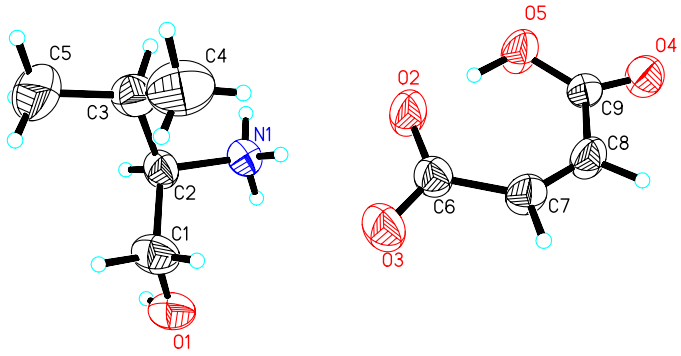


Figure 5. ORTEP diagram of racemic valinol 48 with maleic acid

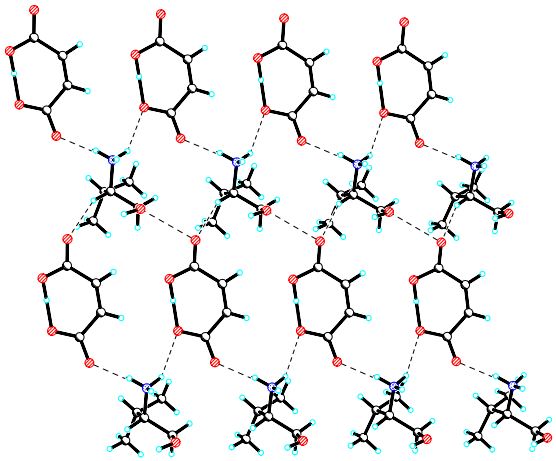


Figure 6. Packing diagram of racemic valinol 48 with maleic acid

The packing diagram showed that maleic acid forms a layer like structure through O-H···O intermolecular hydrogen bonding network. These layers are interlinked by ammonium cation of the valinol moieties through N-H···O and O-H···O intermolecular hydrogen bonding interactions. The alternative layers are found to be heterochiral to each other (Figure 6). Accordingly, it is not a surprise that the non-racemic amino alcohols readily forms heterochiral aggregates with maleic acid as indicated by the enrichment observed for the samples obtained from the filtrate fraction.

Table 13. X-ray data collection and structure refinement for racemic valinol 48 with maleic acid

Empirical formula	$C_9H_{17}NO_5$
Formula weight	219.4
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	a = 5.6110(8) Å, α = 62.529(2)˚
	b = 10.3072(15) Å, β = 80.451(3)˚
	c = 11.157(2) Å, γ = 81.088(2)˚
Volume	562.28(16) Å ^{3}
Z	2
Calculated density	1.295 mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	236
θ Range for data collection	2.07 to 27.00˚
Limiting indices	-7≤h≤7, -13≤k≤13, -14≤l14
Reflections collected/unique	6266 / 1496 [R(int) = 0.0418]
Data / restraints / params	1496 / 0 / 144
Goodness-of-fit on F^2	0.916
Final *R* indices [I> 2σ (I)]	R_1 = 0.0519, wR_2 = 0.1235
R indices (all data)	R_1 = 0.0862, wR_2 = 0.1377
Largest diff. peak and hole	0.47 and -0.30 eÅ^{-3}

Non-racemic samples of 2-amino butanol **49** can be also purified using maleic acid (Scheme 38). Again, enhancement of enantiomeric purity was observed for samples obtained from the solution fraction. The results are summarized in Table 14.

Scheme 38

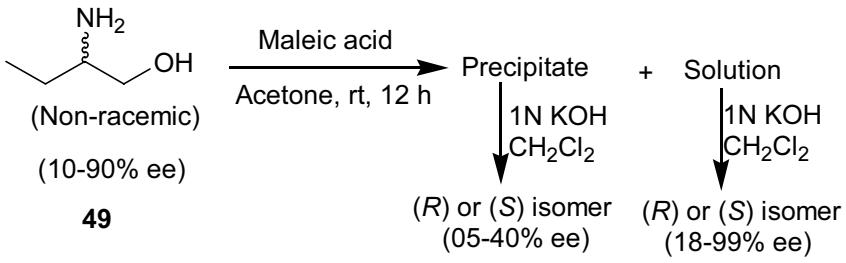


Table 14. Enhancement of enantiomeric excess of non-racemic 2-amino butanol 49 using maleic acid[a]

S. No.	Substrate **49** (% ee)	Maleic acid	2-Amino butanol **49** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*S*) 10	0.50	05 (*S*)	68	18 (*S*)	20
2	(*S*) 18	0.90	10 (*S*)	60	35 (*S*)	25
3	(*S*) 35	1.75	15 (*S*)	50	70 (*S*)	35
4	(*S*) 70	3.50	30 (*S*)	25	99 (*S*)	58
5	(*R*) 15	0.75	05 (*R*)	65	30 (*R*)	22
6	(*R*) 25	1.25	12 (*R*)	55	50 (*R*)	38
7	(*R*) 50	2.50	20 (*R*)	40	90 (*R*)	45
8	(*R*) 90	4.50	40 (*R*)	08	99 (*R*)	80

a. The reactions were carried out using non-racemic 2-aminobutanol **49** (5 mmol) and maleic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH) for (*S*)-**49**.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **49** used.

1. 2. 4 Enhancement of enantiomeric purity of non-racemic amino alcohols using terephthalic acid

We have also undertaken the efforts for the purification of non-racemic amino alcohols using dicarboxylic acids such as phthalic and terephthalic acids. In the case of phthalic acid, no precipitation occurs with amino alcohols in the solvents acetone, THF, DCM and CH_3CN. With the terephthalic acid, non-racemic phenylglycinol **46**,

phenylalaninol **47**, valinol **48** and 2-amino butanol **49** all formed precipitates using acetone as solvent (Schemes 39, 40, 41 and 42).

Scheme 39

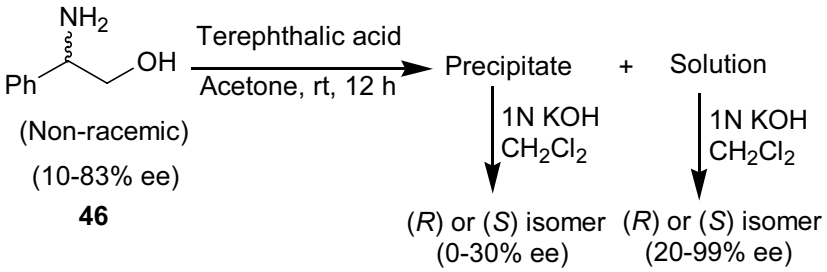


Table 15. Enhancement of enantiomeric excess of non-racemic phenylglycinol 46 using terephthalic acid[a]

S. No.	Substrate **46** (% ee)	Terephthalic acid	Phenylglycinol **46** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 15	0.75	05 (*R*)	70	30 (*R*)	20
2	(*R*) 20	1.00	06 (*R*)	60	38 (*R*)	30
3	(*R*) 30	1.50	10 (*R*)	55	73 (*R*)	38
4	(*R*) 73	3.65	25 (*R*)	25	99 (*R*)	65
5	(*S*) 10	0.50	0	75	20 (*S*)	10
6	(*S*) 20	1.00	05 (*S*)	62	40 (*S*)	30
7	(*S*) 40	2.00	15 (*S*)	48	78 (*S*)	45
8	(*S*) 50	2.50	20 (*S*)	30	83 (*S*)	52
9	(*S*) 83	4.15	30 (*S*)	10	99 (*S*)	78

a. The reactions were carried out using non-racemic phenylglycinol **46** (5 mmol) and terephthalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +33 (*C* 0.75, 1N HCl) for (*S*)-**46**.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **46** used.

Again, enrichment was observed in the solution fraction due to the predominant precipitation of heterochiral aggregates induced by hydrogen bonding network. These results are summarized in the Tables 15, 16, 17 and 18.

Scheme 40

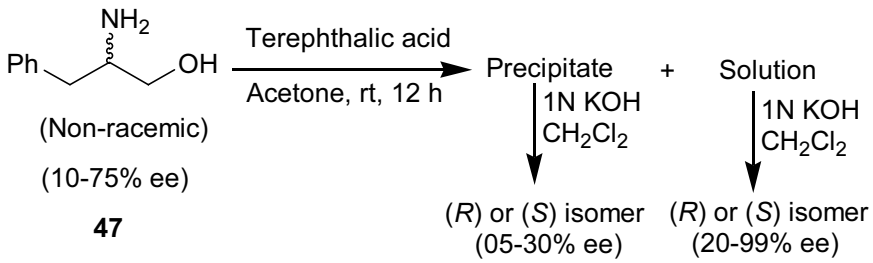


Table 16. Enhancement of enantiomeric excess of non-racemic phenylalaninol 47 using terephthalic acid[a]

S. No.	Substrate **47** (% ee)	Terephthalic acid	Phenylalaninol **47** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 15	0.75	05 (*R*)	60	30 (*R*)	22
2	(*R*) 30	1.50	12 (*R*)	50	62 (*R*)	36
3	(*R*) 62	3.10	20 (*R*)	30	99 (*R*)	58
4	(*S*) 10	0.50	05 (*S*)	65	20 (*S*)	18
5	(*S*) 20	1.00	08 (*S*)	60	40 (*S*)	25
6	(*S*) 40	2.00	15 (*S*)	52	75 (*S*)	35
7	(*S*) 50	2.50	20 (*S*)	50	99 (*S*)	40
8	(*S*) 75	3.75	30 (*S*)	22	99 (*S*)	65

a. The reactions were carried out using non-racemic phenylalaninol **47** (5 mmol) and terephthalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +23 (*C* 1.2, 1N HCl) for (*R*)-**47**.

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **47.**

Scheme 41

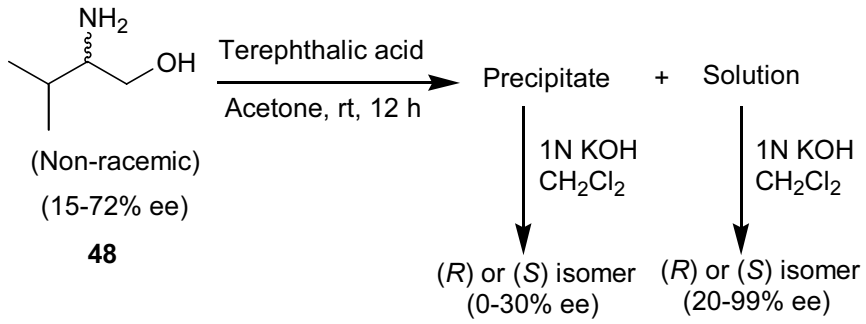


Table 17. Enhancement of enantiomeric excess of non-racemic valinol 48 using terephthalic acid[a]

S. No.	Substrate **48** (% ee)	Terephthalic acid	Valinol **48** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 15	0.75	05 (*R*)	65	35 (*R*)	20
2	(*R*) 35	1.75	15 (*R*)	48	72 (*R*)	35
3	(*R*) 72	3.60	30 (*R*)	25	99 (*R*)	65
4	(*S*) 10	0.50	0	70	20 (*S*)	18
5	(*S*) 20	1.00	08 (*S*)	65	50 (*S*)	20
6	(*S*) 30	1.50	10 (*S*)	50	70 (*S*)	40
7	(*S*) 50	2.50	20 (*S*)	38	99 (*S*)	48
8	(*S*) 70	3.50	30 (*S*)	25	99 (*S*)	62

a. The reactions were carried out using non-racemic valinol **48** (5 mmol) and terephthalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +17 (*C* 10, EtOH) for (*S*)-**48.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **48** used.

Scheme 42

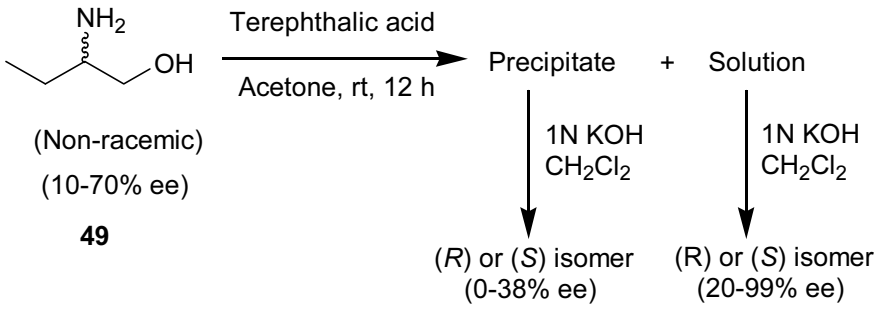


Table 18. Enhancement of enantiomeric excess of non-racemic 2-amino butanol 49 using terephthalic acid[a]

S. No.	Substrate **49** (% ee)	Terephthalic acid	2-Amino butanol **49** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 15	0.75	05 (*R*)	65	30 (*R*)	20
2	(*R*) 30	1.50	10 (*R*)	50	70 (*R*)	36
2	(*R*) 50	2.50	20 (*R*)	45	99 (*R*)	42
3	(*R*) 70	3.50	38 (*R*)	20	99 (*R*)	65
4	(*S*) 10	0.50	0	70	20 (*S*)	18
5	(*S*) 20	1.00	08 (*S*)	62	45 (*S*)	25
6	(*S*) 45	2.25	20 (*S*)	50	90 (*S*)	38

a. The reactions were carried out using non-racemic 2-aminobutanol **49** (5 mmol) and terephthalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

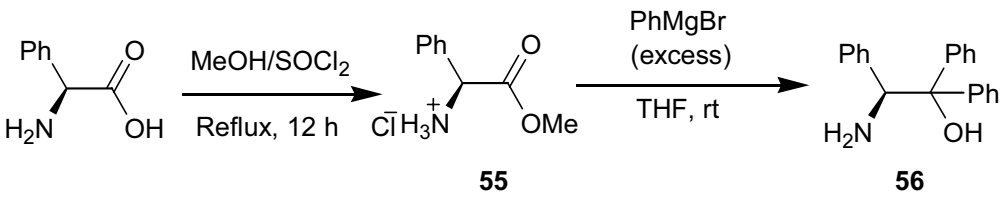
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH) for (*S*)-**49.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **49** used.

1. 2. 5 Synthesis, partial resolution and enhancement of enantiomeric purity of non-racemic 2-amino-1,1,2-triphenylethanol 56 using dicarboxylic acids

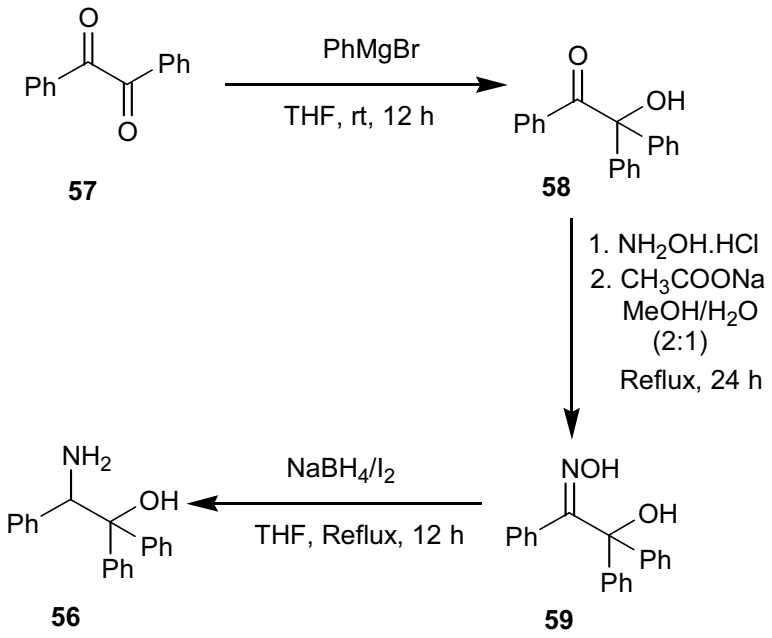
It has been reported that α,α-disubstituted 1,2-amino alcohols are more effective in asymmetric synthesis compared to the simple 1,2-amino alcohols.[77] So, we have undertaken efforts to synthesize the amino alcohol such as 2-amino-1,1,2-triphenylethanol **56**, which can be readily prepared by the addition of excess Grignard reagent to the ester of naturally occurring *L*-(+)-amino acid **55** (Scheme 43).[78]

Scheme 43



The corresponding *R* isomer can be prepared from the ester of unnatural (*R*)-phenylglycine, but it is expensive. Therefore, we have developed an alternative method for the synthesis of racemic amino alcohol **56** by the reduction of the oxime of the α-keto alcohol **59** using $NaBH_4/I_2$ reagent system in THF under refluxing conditions. The α-keto alcohol **58** was obtained by the addition of PhMgBr to benzil **57** following a reported procedure.[79] The corresponding oxime **59** was prepared by using hydroxylamine hydrochloride and sodium acetate (Scheme 44).[80]

Scheme 44



We have examined the resolution of this amino alcohol **56** using dibenzoyl-*L*-tartaric acid (Scheme 45) through formation of diastereomeric complexes in acetone solvent. The resolution mainly depends on the solubility of the complexes as the diastereomers have different solubilities. So, we have examined the effect of the volume of solvent in the resolution of amino alcohol **56** using acetone as solvent. As the volume of the solvent increased, the ee of the product increased, but the yield decreased as expected (Table 19, entries 1-4).

Optimum results were obtained when amino alcohol **56** and dibenzoyl-*L*-tartaric acid **51** were used in 1:1 ratio and stirred at rt for 6 h in acetone solvent. After digestion of the precipitate fraction with KOH, the amino alcohol **56** enriched in (*R*)-isomer (48% ee) was obtained. After workup, the (*S*)-isomer (25% ee) was obtained from the filtrate fraction. These partially resolved non-racemic samples were further purified using dibenzoyl-*L*-tartaric acid and the results are summarized in Table 19.

Scheme 45

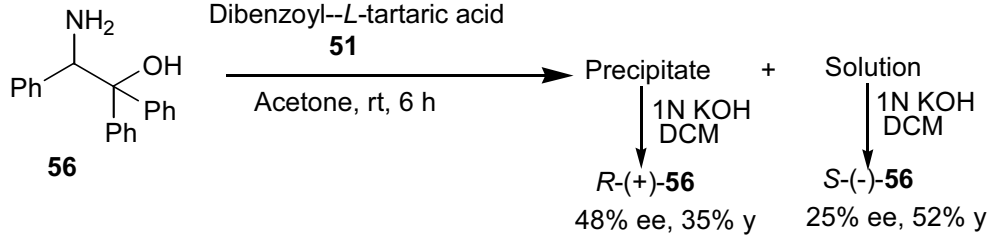


Table 19. Resolution of racemic amino alcohol 56 using dibenzoyl-*L*-tartaric acid[a]

S. No.	Substrate **56** (% ee)	Ratio of **56:51**	Acetone	Amino alcohol **56** obtained from			
				Precipitate		Filtrate	
	(5 mmol)		(mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	00	1:1	20	12 (*R*)	44	10 (*S*)	45
2[a]	00	1:1	40	20 (*R*)	43	15 (*S*)	45
3[a]	00	1:1	50	35 (*R*)	40	18 (*S*)	48
4[a]	00	1:1	70	48 (*R*)	35	25 (*S*)	52
5[d]	00	1:2	70	45 (*R*)	30	20 (*S*)	56
6[e]	00	2:1	70	30 (*R*)	40	20 (*S*)	50
7[f]	48 (*R*)	1:1	70	98 (R)	40	15 (*R*)	50
8[f]	25 (S)	1:1	70	60 (*S*)	35	10 (*S*)	52
9[f]	60 (*S*)	1:1	70	99 (S)	55	05 (S)	33

a. Unless otherwise mentioned all the reactions were performed using racemic amino alcohol **56** (5 mmol) and dibenzoly-*L*-tartaric acid **51** (5 mmol) in acetone and stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = +235 (*C* 1.0, $CHCl_3$) for (*R*)-**56** and $[\alpha]_D^{25}$ = -235 (*C* 1.0, $CHCl_3$) for (*S*)-**56**.
c. The yields are of the isolated products, based on the total amount of the starting racemic sample used.
d. Racemic amino alcohol **56** (5 mmol) and dibenzoly-*L*-tartaric acid **51** (10 mmol) in acetone and stirred at 25 °C for 6 h.
e. Racemic amino alcohol **56** (5 mmol) and dibenzoly-*L*-tartaric acid **51** (2.5 mmol) in acetone and stirred at 25 °C for 6 h.
f. Non-racemic amino alcohol **56** (5 mmol) and dibenzoly-*L*-tartaric acid **51** (5 mmol) in 70mL of the acetone and stirred at 25 °C for 6 h.

We have also studied the enhancement of enantiomeric purity of non-racemic samples of 2-amino-1,1,2-triphenylethanol **56** using oxalic, fumaric, maleic and

terephthalic acids (Schemes 46, 47, 48 and 49). In the case of oxalic acid, enhancement of ee was observed in the precipitate fraction, whereas the use of fumaric, maleic and terephthalic acids led to enrichment in the solution fraction. These results are summarized in the following Tables 20, 21, 22 and 23.

Scheme 46

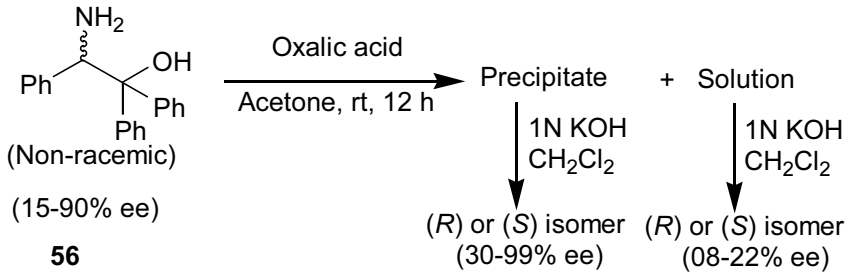


Table 20. Enhancement of enantiomeric excess of non-racemic 2-amino-1,1,2-triphenylethanol 56 using oxalic acid[a]

S. No.	Substrate **56** (% ee)	Oxalic acid	2-Amino-1,1,2-triphenylethanol **56** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 20	1.00	36 (*R*)	30	10 (*R*)	60
2	(*R*) 36	1.80	55 (*R*)	38	15 (*R*)	50
3	(*R*) 55	2.75	90 (*R*)	52	22 (*R*)	35
4	(*R*) 90	4.50	99 (*R*)	87	30 (*R*)	06
5	(*S*) 15	0.75	30 (*S*)	25	08 (*S*)	60
6	(*S*) 30	1.50	50 (*S*)	45	12 (*S*)	42
7	(*S*) 50	2.50	82 (*S*)	55	20 (*S*)	34
8	(*S*) 82	4.10	99 (*S*)	75	25 (*S*)	14

a. The reactions were carried out using non-racemic amino alcohol **56** (5 mmol) and oxalic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$) for (*R*)-**56.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **56** used.

Scheme 47

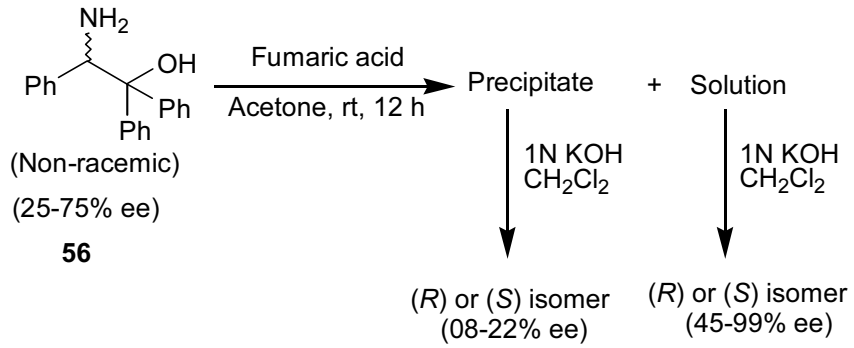


Table 21. Enhancement of enantiomeric excess of non-racemic 2-amino-1,1,2-triphenylethanol 56 using fumaric acid[a]

S. No.	Substrate **56** (% ee)	Fumaric acid	2-Amino-1,1,2-triphenylethanol **56** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*) 30	1.50	10 (*R*)	45	50 (*R*)	40
2	(*R*) 50	2.50	18 (*R*)	28	75 (*R*)	60
3	(*R*) 75	3.75	22 (*R*)	20	99 (*R*)	67
4	(*S*) 25	1.25	08 (*S*)	50	45 (*S*)	36
5	(*S*) 45	2.25	15 (*S*)	30	70 (*S*)	58
6	(*S*) 70	3.50	20 (*S*)	25	99 (*S*)	65

a. The reactions were carried out using non-racemic amino alcohol **56** (5 mmol) and fumaric acid in acetone (60 mL) and the contents were stirred at 25 °C for 12 h.

b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$) for (*R*)-**56.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **56** used

Scheme 48

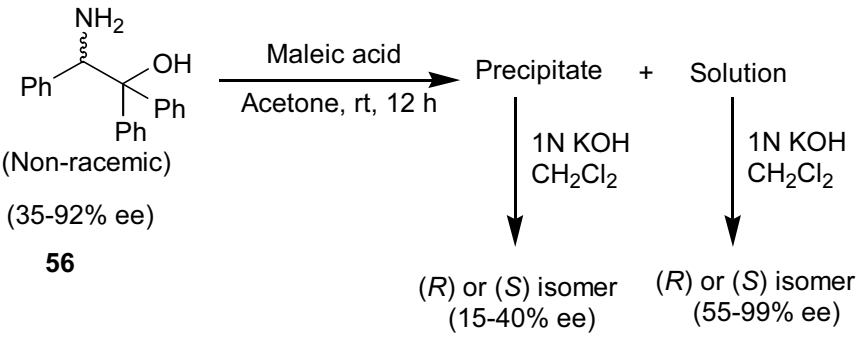


Table 22. Enhancement of enantiomeric excess of non-racemic 2-amino-1,1,2-triphenylethanol 56 using maleic acid[a]

S. No.	Substrate **56** (% ee)	Maleic acid	2-Amino-1,1,2-triphenylethanol **56** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf	Yield(%)[c]
1	(*R*) 35	1.75	15 (*R*)	50	55 (*R*)	40
2	(*R*) 55	2.75	20 (*R*)	30	75 (*R*)	56
3	(*R*) 75	3.75	25 (*R*)	20	99 (*R*)	65
4	(*S*) 40	2.00	18 (*S*)	35	65 (*S*)	52
5	(*S*) 65	3.25	25 (*S*)	28	92 (*S*)	65
6	(*S*) 92	4.60	40 (*S*)	07	99 (*S*)	85

a. The reactions were carried out using non-racemic amino alcohol **56** (5 mmol) and maleic acid in acetone (60 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$) for (*R*)-**56.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **56** used.

Scheme 49

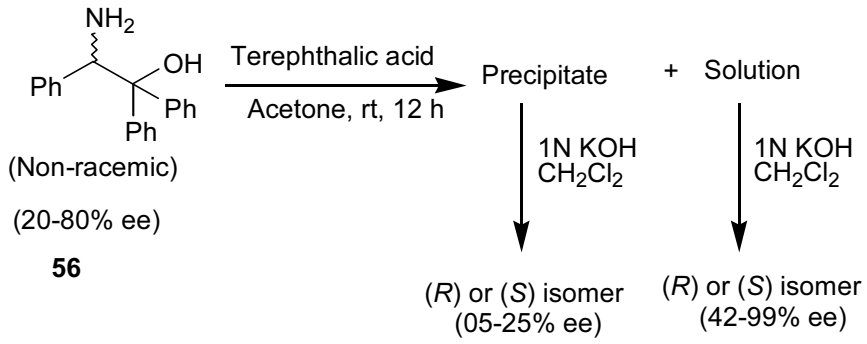


Table 23. Enhancement of enantiomeric excess of non-racemic 2-amino-1,1,2-triphenylethanol 56 using terephthalic acid[a]

S. No.	Substrate **56** (% ee)	Terephthlic acid	2-Amino-1,1,2-triphenylethanol **56** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield (%)[c]
1	(*R*) 20	1.00	05 (*R*)	50	42 (*R*)	35
2	(*R*) 42	2.10	12 (*R*)	35	80 (*R*)	50
3	(*R*) 80	4.00	20 (*R*)	12	99 (*R*)	75
4	(*S*) 50	2.50	15 (*S*)	32	75 (*S*)	52
5	(*S*) 75	3.75	25 (*S*)	18	99 (*S*)	70

a. The reactions were carried out using non-racemic amino alcohol **56** (5 mmol) and terephthalic acid in acetone (60 mL) and the contents were stirred at 25 °C for 12 h.

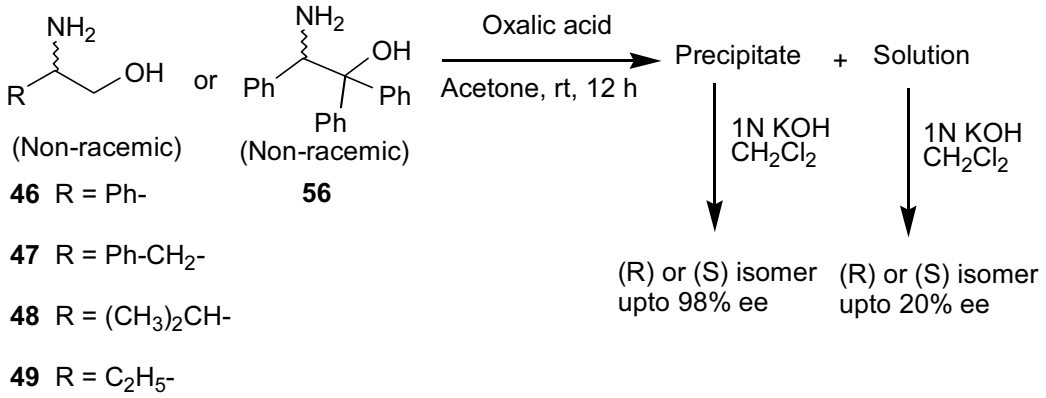
b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = +235 (C 1, $CHCl_3$) for (*R*)-**56.**

c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture **56** used.

From all these results, it is clear that the purification of non-racemic samples of 1,2-amino alcohols such as **46**, **47**, **48, 49** and 2-amino-1,1,2-triphenylethanol **56** could be achieved using oxalic, fumaric, maleic and terephthalic acids. Whereas use of oxalic acid led to enhancement of ees in the precipitate fractions (Scheme 50), the use of

fumaric, maleic and terephthalic acids gave enhancement in the solution fractions (Scheme 51).

Scheme 50



46 R = Ph-

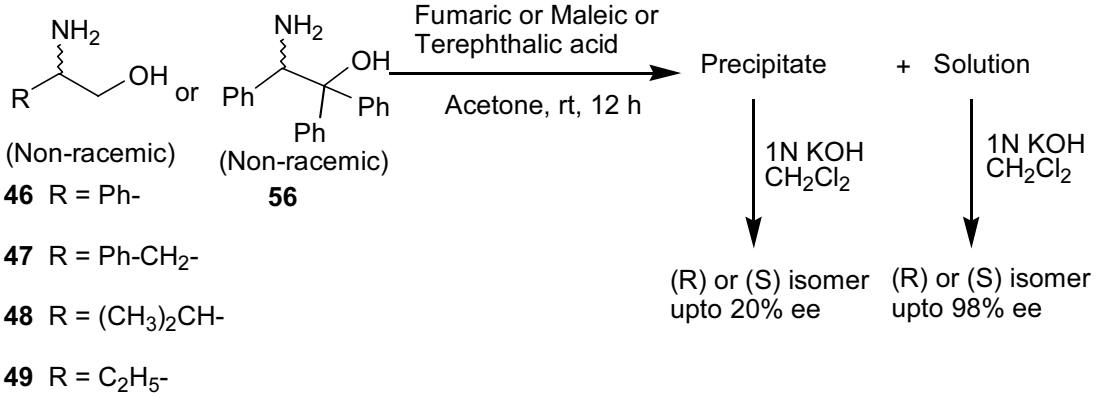
47 R = Ph-CH_2-

48 R = $(CH_3)_2$CH-

49 R = C_2H_5-

56

Scheme 51



46 R = Ph-

47 R = Ph-CH_2-

48 R = $(CH_3)_2$CH-

49 R = C_2H_5-

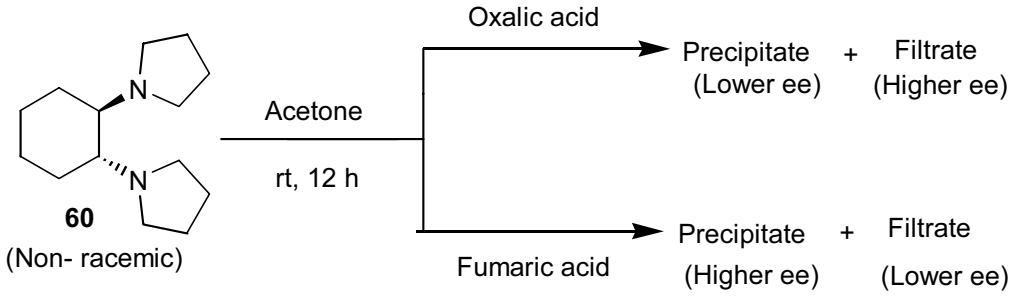
56

The only difference is that enrichment is less effective in the case of α,α-disubstituted 1,2-amino alcohol **56**. Among the simple amino alcohols enrichment is slightly more effective in the case of phenylalaninol **47** and 2-amino butanol **49** with oxalic acid compared to the amino alcohols **46** and **48.** With other dicarboxylic acids the enhancement is more effective in the case of amino alcohols **47**, **48** and **49** when compared to amino alcohol **46**. When samples of 75% ee or above of any amino alcohols were treated with a dicarboxylic acid, after workup, pure enantiomers were obtained with good yields in the precipitate or solution fraction. The enhancement is

due to precipitation of predominantly homochiral aggregates (*R*,*R*… or *S*,*S*…) in the case of oxalic acid with all amino alcohols, whereas it is due to precipitation of predominantly heterochiral aggregates (*R,S,R,S*…) in the case of fumaric, maleic and terephthalic acids.

This concept was also applied for the purification of diamine **60** using oxalic and fumaric acids in this laboratory.[71] Exactly opposite results were obtained in the case of this diamine compared to amino alcohols. That is in the case of oxalic acid, enrichment was observed in the filtrate fraction, whereas in the case of fumaric acid enrichment was observed in the precipitate fraction (Scheme 52).

Scheme 52



The selective precipitation of homo or heterochiral diamines should be further examined to understand whether the phenomena observed are due to thermodynamic stability of the complexes or just solubility factors. A systematic study using non-racemic samples of several diamines may throw light on the phenomena involved.

1. 3 Conclusions

A conceptual methodology was developed for the enhancement of enantiomeric purity of non-racemic 1,2-amino alcohols such as phenylglycinol **46**, phenylalaninol **47**, valinol **48** and 2-amino butanol **49** using achiral dicarboxylic acids such as oxalic, fumaric, maleic and terephthalic acids through formation of homochiral or heterochiral aggregates by inducing hydrogen-bonded network. Racemic amino alcohol **56** has been synthesized by the reduction of oxime of phenyl benzoin **59** using the $NaBH_4/I_2$ reagent system and was partially resolved using dibenzoyl-*L*-tartaric acid. Enhancement of enantiomeric purity of non-racemic samples of 2-amino-1,1,2-triphenylethanol **56** was also achieved using dicarboxylic acids.

1. 4 Experimental Section

1. 4. 1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and the neat IR spectra were recorded on SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (200 MHz), ^{13}C-NMR (50 MHz) and ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometer respectively with chloroform-d as a solvent and TMS as a reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the singnal of internal TMS. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240 C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Analytical thin layer chromatographic tests were carried out on glass plates (3x10 cm) coated with 250 mμ acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapour or UV light. Column chromatography was carried out using acme's silica gel (100-200 mesh).

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 6 h, assembled hot and cooled under a stream of dry nitrogen. Unless, otherwise mentioned, all the operations and transformations of reagents were carried out using standard syringe, septum technique recommended for handling air sensitive organometallic compounds.

Reagents prepared *in situ* in solvents were transformed using a double-ended stainless (Aldrich) needle under a stream of nitrogen whenever required.

In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler connected by a long tube to the atmosphere. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were concentrated on Heidolph-EL-rotary evaporator. All yields reported are isolated yields of materials judged homogeneous by TLC, IR and NMR spectroscopy. Optical rotations were measured in an AUTOPOL-II automatic polarimeter (readability $\pm 0.01^{o}$) or JASCO DIP-370 Digital polarimeter (readability $\pm 0.001^{o}$). The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of *R*-(+)-α-methylbenzylamine $[\alpha]_{D}^{25} = +30.2$ (*C* 10, EtOH).

Benzene and toluene were distilled over sodium benzophenone ketyl. THF supplied by E-Merck (India), was kept over sodium-benzophenone ketyl and freshly distilled before use. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves. $NaBH_4$ was purchased from Lancaster Synthesis Ltd., UK. Iodine supplied by E–Merck, India was used. Benzil, bromo benzene, hydroxylamine hydrochloride and sodium acetate were supplied by E–Merck, India. Dibenzoyl-*L*-tartaric acid was supplied by Fluka, Switzerland. Racemic 1,2-amino alcohols were synthesized and resolved using dibenzoyl-*L*-tartaric acid, following a procedure

reported in this laboratory.[53] Oxalic, fumaric, maleic, phthalic and terephthalic acids were supplied by E. Merck (India).

The X-ray diffraction measurements for the compounds **46** and **48** were carried out at 293 K on an automated Enraf-Nonius MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 A^o) radiation with CAD4 software. The single crystal was fixed to either a capillary head or capillary tube (in the case of solvent sensitive crystals) by an appropriate fixing material. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Stability of the crystal during the measurement was monitored by measuring the intensity of the three standard reflections after every one and half hour intervals. No appreciable variation of the crystal was detected. The data were reduced using XTAL programme.[81] No absorption correction was applied. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELXS-86[82] and SHELXL-93[83] program packages respectively.

1. 4. 2 Partial resolution of 1,2-amino alcohols using dibenzoyl-*L*-tartaric acid 51

1. 4. 2. 1 Resolution of phenylglycinol 46 using dibenzoyl-*L*-tartaric acid 51

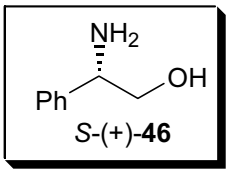
The dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) and the racemic phenylglycinol **46** (0.7 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of **46** enriched in (*S*) isomer. The filtrate was concentrated and the residue taken in DCM (20 mL) and was digested using 1N KOH (10 mL) to obtain the sample of **46** enriched in (*R*) isomer.

After decomposition:

From precipitate:

Yield 0.17 g (24%)

$[\alpha]_D^{25}$ +14.8 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +33.0 (*C* 0.76, 1N HCl)}

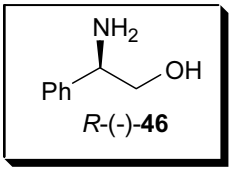


S-(+)-**46**

From filtrate:

Yield 0.42 g (60%)

$[\alpha]_D^{25}$ -1.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -31.7 (*C* 0.76, 1N HCl)}



R-(-)-**46**

1. 4. 2. 2 Resolution of valinol 48 using dibenzoyl-*L*-tartaric acid 51

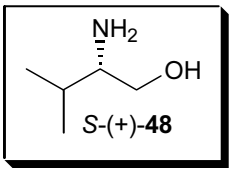
The partial resolution of the racemic valinol **48** (0.51 g, 5 mmol) was carried out using dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) using acetone (70 mL) following the above procedure.

After decomposition:

From precipitate:

Yield 0.10 g (20%)

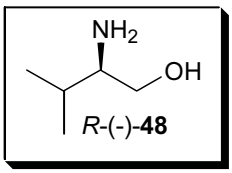
$[\alpha]_D^{25}$ +4.2 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +17.0 (*C* 10, EtOH)}



From filtrate:

Yield 0.35 g (70%)

$[\alpha]_D^{25}$ -1.6 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -16.0 (*C* 10, EtOH)}



1. 4. 2. 3 Resolution of phenylalaninol 47 using dibenzoyl-*L*-tartaric acid 51

The dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) was taken in actone (30 mL) and stirred for 5 min. To this stirred solution, the racemic phenylalaninol **47** (0.75 g, 5 mmol) dissolved in acetone (30 mL) was added and the contents were stirred at rt for 6h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of **47** enriched in (*S*) isomer. The filtrate was

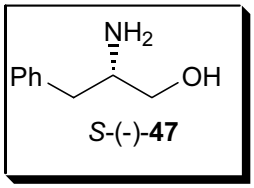
concentrated and the residue taken in DCM (20 mL) and was digested using 1N KOH (10 mL) to obtain the sample of **47** enriched in (*R*) isomer.

After decomposition:

From precipitate:

Yield 0.15 g (20%)

$[\alpha]_D^{25}$ -22.5 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}

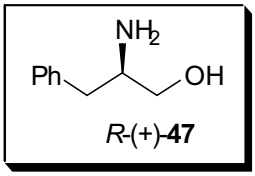


S-(-)-**47**

From filtrate:

Yield 0.45 g (60%)

$[\alpha]_D^{25}$ +4.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +23.0 (*C* 1.2, 1N HCl)}



R-(+)-**47**

1. 4. 2. 4 Resolution of 2-amino butanol 49 using dibenzoyl-*L*-tartaric acid 51

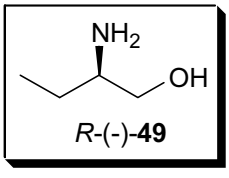
The dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) was taken in acetone (30 mL) and stirred for 5 min. To this stirred solution the racemic 2-amino butanol **49** (0.45 g, 5 mmol) dissolved in acetone (30 mL) was added. After KOH treatment and workup, the partially resolved 2-amino butanol was isolated

After decomposition:

From precipitate:

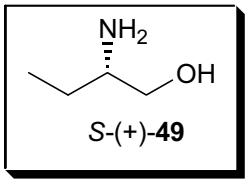
Yield 0.11 g (25%)

$[\alpha]_D^{25}$ -6.0 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -8.5 (*C* 2, EtOH)}



R-(-)-**49**

From filtrate:



S-(+)-**49**

Yield 0.27 g (60%)

$[\alpha]_D^{25}$ +2.5 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH)}

1. 4. 3 Enhancement of enantiomeric purity of non-racemic (partially resolved) 1,2-amino alcohols using achiral dicarboxylic acids

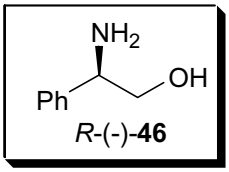
1. 4. 3. 1 Purification of non-racemic 1,2-amino alcohols using oxalic acid

1. 4. 3. 1. 1 Purification of non-racemic phenylglycinol 46 using oxalic acid

The partially resolved *R*-(-)-phenylglycinol (50% ee, 0.69 g, 5 mmol) was taken in acetone (60 mL), to this the oxalic acid (0.22 g, 2.5 mmol) was added and the contents were stirred at rt for 12 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of **46** enriched in *R*-(-)-isomer. The filtrate was concentrated and the residue taken in DCM (20 mL) and was digested using 1N KOH (10 mL) to obtain the sample of *R*-(-)-**46** with lower ee.

After decomposition:

From precipitate:

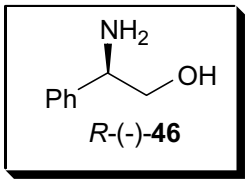


R-(-)-**46**

Yield 0.33 g (48%)

$[\alpha]_D^{25}$ -22.2 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -31.7 (*C* 0.76, 1N HCl)}

From filtrate:



Yield 0.24 g (35%)

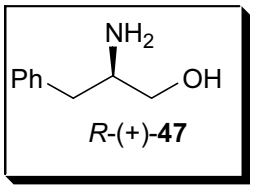
$[\alpha]_D^{25}$ -1.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -31.7 (*C* 0.76, 1N HCl)}

1. 4. 3. 1. 2 Purification of non-racemic phenylalaninol 47 using oxalic acid

The same procedure as mentioned above was followed for the purification of non-racemic phenylalaninol **47** using *R*-(+)-sample (50% ee, 0.75 g, 5 mmol) and oxalic acid (0.22 g, 2.5 mmol) in acetone (60 mL).

After decomposition:

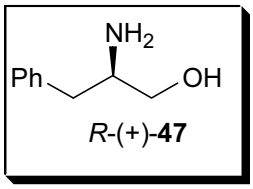
From precipitate:



Yield 0.39 g (52%)

$[\alpha]_D^{25}$ +22.5 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +23.0 (*C* 1.2, 1N HCl)}

From filtrate:



Yield 0.22 g (30%)

$[\alpha]_D^{25}$ +4.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +23.0 (*C* 1.2, 1N HCl)}

1. 4. 3. 1. 3 Purification of non-racemic valinol 48 using oxalic acid

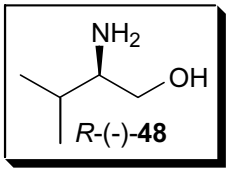
The partially resolved sample of *R*-(-)-valinol **48** (75% ee, 0.51 g, 5 mmol) was taken in acetone (60 mL) and oxalic acid (0.34 g, 3.75 mmol) was added. After further operation, following the same procedure as mentioned in the section 1.4.3.1.1, the sample of *R*-(-)-**48** was isolated in 99% ee from the precipitate fraction.

After decomposition:

From precipitate:

Yield 0.33 g (65%)

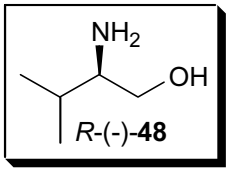
$[\alpha]_D^{25}$ -15.8 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -16.0 (*C* 10, EtOH)}



From filtrate:

Yield 0.13 g (25%)

$[\alpha]_D^{25}$ -3.2 (*C* 5, EtOH, {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -16.0 (*C* 10, EtOH)}



1. 4. 3. 1. 4 Purification of non-racemic 2-amino butanol 49 using oxalic acid

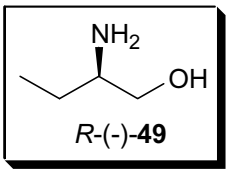
The partially resolved sample of *R*-(-)-2-amino butanol **49** (55% ee, 0.45 g, 5 mmol) was taken in acetone (60 mL) and oxalic acid (0.25 g, 2.75 mmol) was added. After further operation, following the same procedure as mentioned in the section 1.4.3.1.1, the sample of *R*-(-)-**49** was isolated in 99% ee from the precipitate fraction.

After decomposition:

From precipitate:

Yield 0.22 g (49%)

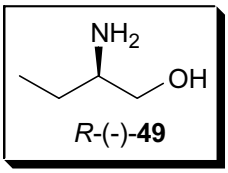
$[\alpha]_D^{25}$ -8.3 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -8.5 (*C* 2, EtOH)}



From filtrate:

Yield 0.13 g (30%)

$[\alpha]_D^{25}$ -1.5 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -8.5 (*C* 2, EtOH)}



1. 4. 3. 2 Purification of non-racemic 1,2-amino alcohols using fumaric acid

1. 4. 3. 2. 1 Purification of non-racemic phenylglycinol 46 using fumaric acid

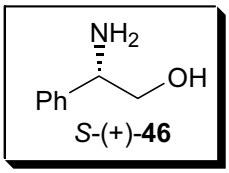
The partially resolved *S*-(+)-phenylglycinol **46** (50% ee, 0.69 g, 5 mmol) was taken in acetone (60 mL), to this the fumaric acid (0.29 g, 2.5 mmol) was added and the contents were stirred at rt for 12 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of *S*-(+)-**46**. The filtrate was concentrated and the residue was digested using DCM (20 mL) and 1N KOH (10 mL) to obtain the sample of **46** enriched in *S*-(+)-isomer.

After decomposition:

From precipitate:

Yield 0.28 g (40%)

$[\alpha]_D^{25}$ +8.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +33.0 (*C* 0.75, 1N HCl)}

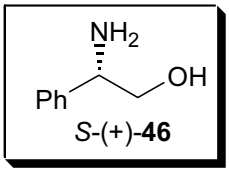


S-(+)-**46**

From filtrate:

Yield 0.33 g (48%)

$[\alpha]_D^{25}$ +31.7 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +33.0 (*C* 0.75, 1N HCl)}



S-(+)-**46**

1. 4. 3. 2. 2 Purification of non-racemic phenylalaninol 47 using fumaric acid

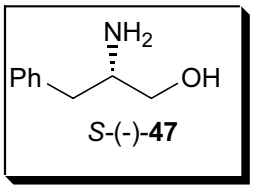
The same procedure as mentioned above was followed for the purification of non-racemic phenylalaninol **47** using *S*-(-)-sample (87% ee, 0.75 g, 5 mmol) and fumaric acid (0.50 g, 4.35 mmol) in acetone (60 mL).

After decomposition:

From precipitate:

Yield 0.07 g (10%)

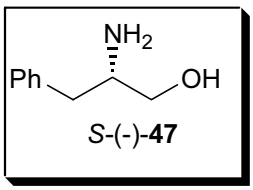
$[\alpha]_D^{25}$ -10.3 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}



From filtrate:

Yield 0.6 g (80%)

$[\alpha]_D^{25}$ -22.6 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}



1. 4. 3. 2. 3 Purification of non-racemic valinol 48 using fumaric acid

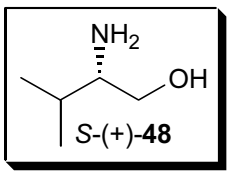
The partially resolved *S*-(+)-valinol **48** (50% ee, 0.51 g, 5 mmol) was taken in acetone (60 mL) and fumaric acid (0.29 g, 2.50 mmol) was added. The enriched sample of *S*-(+)-**48** was isolated from the filtrate fraction in 94% ee.

After decomposition:

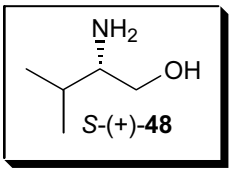
From precipitate:

Yield 0.20 g (40%)

$[\alpha]_D^{25}$ +3.4 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +17.0 (*C* 10, EtOH)}



From filtrate:



Yield 0.23 g (45%)

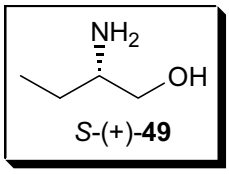
$[\alpha]_D^{25}$ +16.0 (*C* 5, C_2H_5OH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +17.0 (*C* 10, C_2H_5OH)}

1. 4. 3. 2. 4 Purification of non-racemic 2-amino butanol 49 using fumaric acid

The partially resolved *S*-(+)-2-amino butanol **49** (75% ee, 0.45 g, 5 mmol) was taken in acetone (60 mL) and fumaric acid (0.44 g, 3.75 mmol) was added. The enriched sample of *S*-(+)-**49** was isolated from the filtrate fraction in 99% ee.

After decomposition:

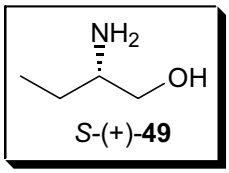
From precipitate:



Yield 0.09 g (20%)

$[\alpha]_D^{25}$ +3.7 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH)}

From filtrate:



Yield 0.31 g (68%)

$[\alpha]_D^{25}$ +12.4 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH)}

1. 4. 3. 3 Purification of non-racemic 1,2-amino alcohols using maleic acid

1. 4. 3. 3. 1 Purification of non-racemic phenylglycinol 46 using maleic acid

The partially resolved *S*-(+)-phenylglycinol (35% ee, 0.69 g, 5 mmol) was taken in acetone (60 mL), to this the maleic acid (0.20 g, 1.75 mmol) was added and the contents were stirred at rt for 12 h and filtered. The precipitate was suspended in a

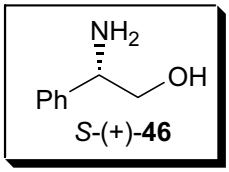
mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of *S*-(+)-**46**. The filtrate was concentrated and the residue taken in DCM (20 mL) and was digested using 1N KOH (10 mL) to obtain the enriched *S*-(+)-**46**.

After decomposition:

From precipitate:

Yield 0.34 g (50%)

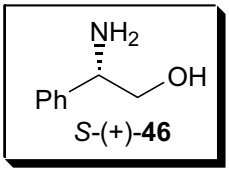
$[\alpha]_D^{25}$ +5.9 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +33.0 (*C* 0.75, 1N HCl)}



From filtrate:

Yield 0.28 g (40%)

$[\alpha]_D^{25}$ +19.1 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +33.0 (*C* 0.75, 1N HCl)}

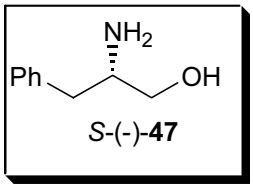


1. 4. 3. 3. 2 Purification of non-racemic phenylalaninol 47 using maleic acid

The same procedure as mentioned above was followed for the purification of non-racemic phenylalaninol **47** using *S*-(-)-sample (50% ee, 0.75 g, 5 mmol) and maleic acid (0.29 g, 2.50 mmol) in acetone (60 mL).

After decomposition:

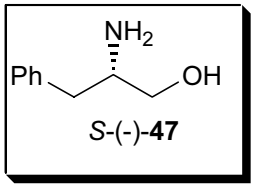
From precipitate:



Yield 0.31 g (42%)

$[\alpha]_D^{25}$ -5.7 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}

From filtrate:



Yield 0.34 g (45%)

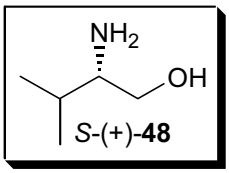
$[\alpha]_D^{25}$ -21.7 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}

1. 4. 3. 3. 3 Purification of non-racemic valinol 48 using maleic acid

The partially resolved *S*-(+)-valinol **48** (70% ee, 0.51 g, 5 mmol) was taken in acetone (60 mL) and maleic acid (0.40 g, 3.50 mmol) was added. The enriched sample of *S*-(+)-**48** was isolated from the filtrate fraction in 99% ee.

After decomposition:

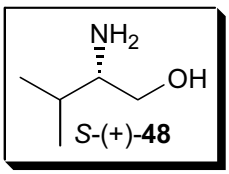
From precipitate:



Yield 0.13 g (25%)

$[\alpha]_D^{25}$ +5.1 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +17.0 (*C* 10, EtOH)}

From filtrate:



Yield 0.31 g (60%)

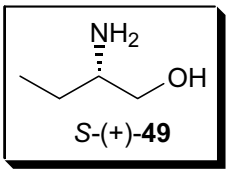
$[\alpha]_D^{25}$ +16.8 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +17.0 (*C* 10, EtOH)}

1. 4. 3. 3. 4 Purification of non-racemic 2-amino butanol 49 using maleic acid

The partially resolved *S*-(+)-2-amino butanol **49** (35% ee, 0.45 g, 5 mmol) was taken in acetone (60 mL) and maleic acid (0.20 g, 1.75 mmol) was added. The enriched sample of *S*-(+)-**49** was isolated from the filtrate fraction in 70% ee.

After decomposition:

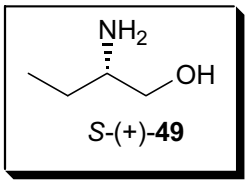
From precipitate:



Yield 0.22 g (50%)

$[\alpha]_D^{25}$ +1.9 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH)}

From filtrate:



Yield 0.16 g (35%)

$[\alpha]_D^{25}$ +8.7 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +12.5 (*C* 2, EtOH)}

1. 4. 3. 4 Purification of non-racemic 1,2-amino alcohols using terephthalic acid

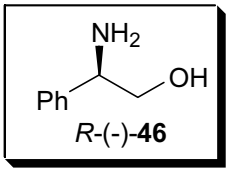
1. 4. 3. 4. 1 Purification of non-racemic phenylglycinol 46 using terephthalic acid

The partially resolved *R*-(-)-phenylglycinol (73% ee, 0.69 g, 5 mmol) was taken in acetone (60 mL), to this the terephthalic acid (0.61 g, 3.65 mmol) was added and the contents were stirred at rt for 12 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of *R*-(-)-46.

The filtrate was concentrated and the residue was digested using DCM (20 mL) and 1N KOH (10 mL) to obtain the enriched *R*-(-)-**46**.

After decomposition:

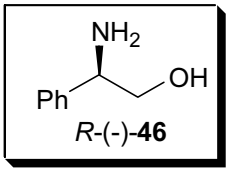
From precipitate:



Yield 0.17 g (25%)

$[\alpha]_D^{25}$ -7.9 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -31.7 (*C* 0.76, 1N HCl)}

From filtrate:



Yield 0.45 g (65%)

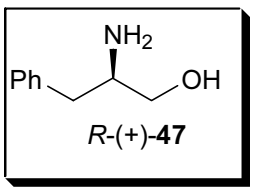
$[\alpha]_D^{25}$ -31.4 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -31.7 (*C* 0.76, 1N HCl)}

1. 4. 3. 4. 2 Purification of non-racemic phenylalaninol 47 using terephthalic acid

The same procedure as mentioned above was followed for the purification of non-racemic phenylalaninol **47** using *R*-(+)-sample (30% ee, 0.75 g, 5 mmol) and terephthalic acid (0.25 g, 1.50 mmol) in acetone (60 mL).

After decomposition:

From precipitate:



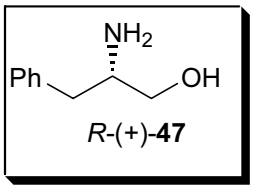
Yield 0.37 g (50%)

$[\alpha]_D^{25}$ -2.7 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}

From filtrate:

Yield 0.27 g (36%)

$[\alpha]_D^{25}$ -14.1 (*C* 1, 1N HCl), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -22.8 (*C* 1.2, 1N HCl)}



1. 4. 3. 4. 3 Purification of non-racemic valinol 48 using terephthalic acid

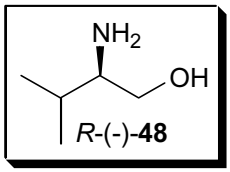
The partially resolved *R*-(-)-valinol **48** (35% ee, 0.51 g, 5 mmol) was taken in acetone (60 mL) and terephthalic acid (0.29 g, 1.75 mmol) was added. The enriched sample of *R*-(-)-**48** was isolated from the filtrate fraction in 72% ee.

After decomposition:

From precipitate:

Yield 0.24 g (48%)

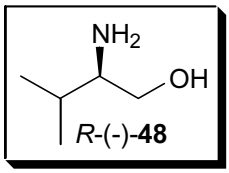
$[\alpha]_D^{25}$ -2.4 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -16.0 (*C* 10, EtOH)}



From filtrate:

Yield 0.18 g (35%)

$[\alpha]_D^{25}$ -11.5 (*C* 5, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -16.0 (*C* 10, EtOH)}

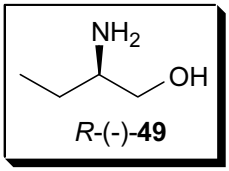


1. 4. 3. 4. 4 Purification of non-racemic 2-amino butanol 49 using terephthalic acid

The partially resolved *R*-(-)-2-amino butanol **49** (70% ee, 0.45 g, 5 mmol) was taken in acetone (60 mL) and terephthalic acid (0.58 g, 3.50 mmol) was added. The enriched sample of *R*-(-)-**49** was isolated from the filtrate fraction in 99% ee.

After decomposition:

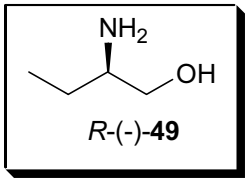
From precipitate:



Yield 0.09 g (20%)

$[\alpha]_D^{25}$ -3.2 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -8.5 (*C* 2, EtOH)}

From filtrate:



Yield 0.29 g (65%)

$[\alpha]_D^{25}$ -8.4 (*C* 2, EtOH), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -8.5 (*C* 2, EtOH)}

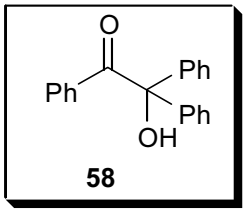
1. 4. 4 Synthesis and resolution of 2-amino-1,1,2-triphenylethanol 56

1. 4. 4. 1 Synthesis of phenyl benzoin 58[79]

Magnesium turnings (2.90 g, 120 mmol) in dry THF (30 mL) were taken in a two-necked RB flask. Freshly distilled bromobenzene (10.5 mL, 100 mmol) in dry THF (50 mL) was added drop wise through the pressure equalizer for 1 h at 0 ^oC. The contents were further stirred for 1 h at rt.

In another two necked RB flask, benzil **57** (21.0 g, 100 mmol) in dry THF (100 mL) was taken and cooled to 0 °C, under nitrogen atmosphere. Phenyl magnesium bromide prepared as above was added through a cannula. The contents were stirred for 13 h at 25 °C. The precipitated bromo magnesium salt was filtered by suction. The salt was decomposed with 2N HCl (30 mL) and extracted with Et_2O (2 X 50 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (2 X 20 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent gave crude product. It was

purified by column chromatography on silica gel using hexane:ethyl acetate (99:1) as eluent.



58

Yield 17.3 g (60%)

mp 82-84 °C (lit.[79] mp 84.5-85 °C)

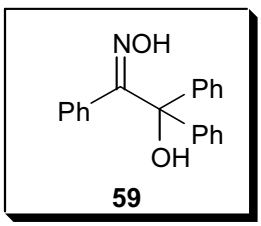
IR (KBr) (cm^{-1}) 3487, 3061, 1668, 1593, 1444, 1246, 1178

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 5.00 (s, 1H), 7.25-7.48 (m, 14H), 7.74 (d, *J* = 8 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 85.1, 128.1, 128.3, 128.7, 130.0, 130.8, 132.9, 135.2, 142.0, 200.8

1. 4. 4. 2 Synthesis of phenyl benzoin oxime 59

Hydroxylamine hydrochloride (1.40 g, 20 mmol) and sodium acetate (2.72 g, 20 mmol) were dissolved in water (10 mL) and added to a suspension of phenyl benzoin **58** (2.90 g, 10 mmol) in MeOH (20 mL). The resulting mixture was refluxed for 24 h. The solvent was removed in vacuo and to this residue, cold water (100 mL) was added and extracted with DCM (2 X 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain the crude product. It was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent.



59

Yield 2.3 g (75%)

mp 135 °C (lit.[80] mp 135-137 °C)

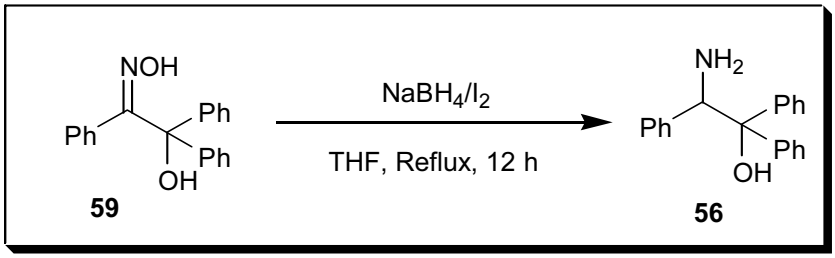
IR (KBr) (cm^{-1}) 3568, 3290, 1493, 1446, 962

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.57 (br s, 1H), 3.25 (s, 1H), 7.02 (d, *J* = 8 Hz, 1H) 7.28-7.40 (m, 12H), 7.47 (d, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 81.9, 127.5, 127.7, 128.1, 128.7, 128.9, 131.4, 143.3, 144.7, 162.5

1. 4. 4. 3 Reduction of phenyl benzoin oxime 59 to 2-amino-1,1,2-triphenylethanol 56

Iodine (0.64 g, 2.5 mmol) in dry THF (20 mL) was added through an addition funnel to the stirred suspension of $NaBH_4$ (0.19 g, 5 mmol) in dry THF (10 mL) under N_2 for 1h at 0 ^oC. Phenyl benzoin oxime **59** (1.51 g, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through addition funnel. After the addition was over, the contents were refluxed for 12 h. The reaction mixture was brought to 0 ^oC and then quenched carefully with dilute hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 2 h at room temperature, then made alkaline with NaOH, followed by extraction with Et_2O (2 X 20 mL). The organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent to obtain the product.



59 **56**

Yield 1.15 g (80%)

mp 145 ^oC (lit.[78] mp 146-148 ^oC)

IR (KBr) (cm^{-1}) 3450, 3400, 1650, 1450, 1170, 780

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.66 (br s, 3H), 5.04 (s, 1H), 7.03-7.09 (m, 3H), 7.14-7.17 (m, 6H), 7.28-7.33 (m, 2H), 7.43 (t, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H) **(Spectrum No. 1)**

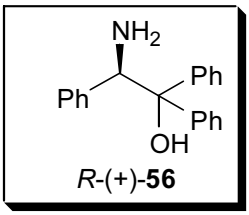
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 61.9, 79.6, 126.1, 126.3, 126.6, 127.0, 127.3, 127.4, 128.5, 128.7, 140.1, 144.0, 146.6 **(Spectrum No. 2)**

1. 4. 4. 4 Resolution of 2-amino-1,1,2-triphenylethanol 56 using dibenzoyl-*L*-tartaric acid 51

The dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) and the racemic 2-amino-1,1,2-triphenylethanol **56** (1.44 g, 5 mmol) were taken in acetone (60 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the enriched *R*-(+)-**56**. The filtrate was concentrated and the residue was digested using DCM (20 mL) and 1N KOH (10 mL) to obtain the enriched *S*-(-)-**56**.

<u>After decomposition:</u>

<u>From precipitate:</u>



R-(+)-**56**

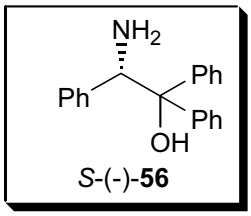
Yield 0.50 g (35%)

$[\alpha]_D^{25}$ +113 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

From filtrate:

Yield 0.75 g (52%)

$[\alpha]_D^{25}$ -58.7 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}



S-(-)-**56**

1. 4. 4. 5 Purification of partially resolved 2-amino-1,1,2-triphenylethanol 56 using dibenzoyl-*L*-tartaric acid 51

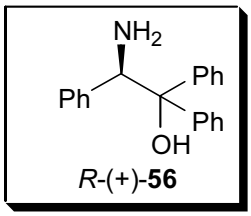
The dibenzoyl-*L*-tartaric acid **51** (1.8 g, 5 mmol) and the partially resolved *R*-(+)-2-amino-1,1,2-triphenylethanol **56** (48% ee, 1.44 g, 5 mmol) were taken in acetone (60 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 1N KOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the enriched *R*-(+)-56.

After decomposition:

From precipitate:

Yield 0.58 g (40%)

$[\alpha]_D^{25}$ +230 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

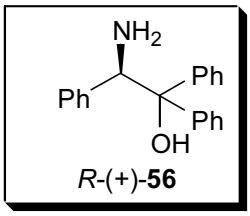


R-(+)-**56**

From filtrate:

Yield 0.72 g (50%)

$[\alpha]_D^{25}$ +35.2 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

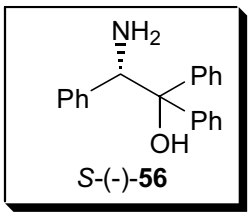


R-(+)-**56**

The partially resolved *S*-(-)-**56** (60% ee, 1.44 g, 5 mmol) was also enriched by following the same procedure as outlined above.

After decomposition:

From precipitate:

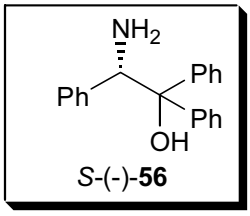


S-(-)-**56**

Yield 0.79 g (55%)

$[\alpha]_D^{25}$ -232 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}

From filtrate:



S-(-)-**56**

Yield 0.47 g (33%)

$[\alpha]_D^{25}$ -11.7 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}

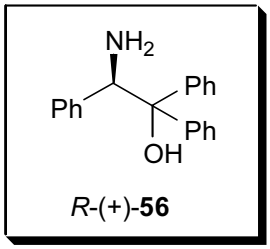
1. 4. 5 Enhancement of enantiomeric purity of non-racemic 2-amino-1,1,2-triphenylethanol 144 using dicarboxylic acids

1. 4. 5. 1 Purification of non-racemic 2-amino-1,1,2-triphenylethanol 56 using oxalic acid

The partially resolved *R*-(+)-2-amino-1,1,2-triphenylethanol **56** (90% ee, 1.44 g, 5 mmol) was taken in acetone (60 mL), to this oxalic acid (0.40 g, 4.50 mmol) was added. The enriched sample of *R*-(+)-**56** was isolated from the precipitate fraction in 99% ee.

After decomposition:

From precipitate:



R-(+)-**56**

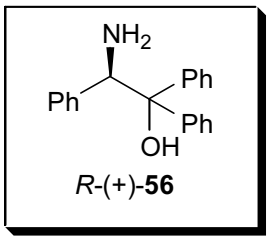
Yield 1.25 g (87%)

$[\alpha]_D^{25}$ +232 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

From filtrate:

Yield 0.09 g (06%)

$[\alpha]_D^{25}$ +70 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}



R-(+)-**56**

1. 4. 5. 2 Purification of non-racemic 2-amino-1,1,2-triphenylethanol 56 using fumaric acid

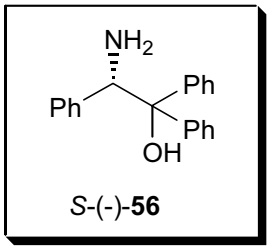
The partially resolved *S*-(-)-2-amino-1,1,2-triphenylethanol **56** (70% ee, 1.44 g, 5 mmol) was taken in acetone (70 mL) and fumaric acid (0.40 g, 3.50 mmol) was added. The enriched sample of *S*-(+)-**56** was isolated from the solution fraction in 99% ee.

After decomposition:

From precipitate:

Yield 0.36 g (25%)

$[\alpha]_D^{25}$ -47 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}

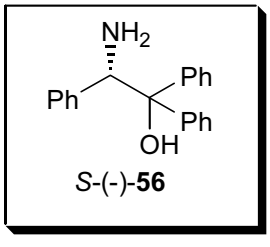


S-(-)-**56**

From filtrate:

Yield 0.94 g (65%)

$[\alpha]_D^{25}$ -233 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}



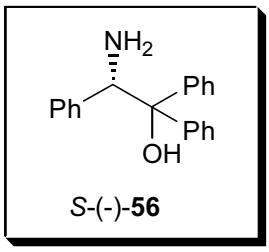
S-(-)-**56**

1. 4. 5. 3 Purification of non-racemic 2-amino-1,1,2-triphenylethanol 56 using maleic acid

The partially resolved *S*-(-)-2-amino-1,1,2-triphenylethanol **56** (40% ee, 1.44 g, 5 mmol) was taken in acetone (60 mL) and maleic acid (0.23 g, 2.00 mmol) was added. The enriched sample of *R*-(+)-**56** was isolated from the filtrate fraction in 65% ee.

After decomposition:

From precipitate:

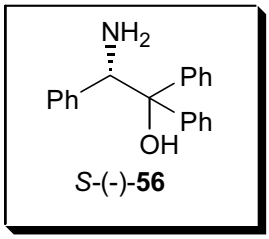


S-(-)-**56**

Yield 0.50 g (35%)

$[\alpha]_D^{25}$ -42.3 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}

From filtrate:



S-(-)-**56**

Yield 0.75 g (52%)

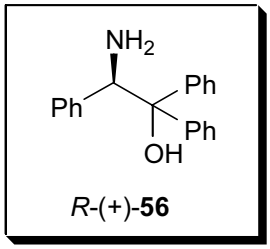
$[\alpha]_D^{25}$ -152.7 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -235 (*C* 1, $CHCl_3$)}

1. 4. 5. 4 Purification of non-racemic 2-amino-1,1,2-triphenylethanol 56 using terephthalic acid

The partially resolved *R*-(+)-2-amino-1,1,2-triphenylethanol **56** (80% ee, 1.44 g, 5 mmol) was taken in acetone (60 mL) and terephthalic acid (0.66 g, 4.00 mmol) was added. The enriched sample of *R*-(+)-**56** was isolated from the solution fraction in 99% ee.

After decomposition:

From precipitate:

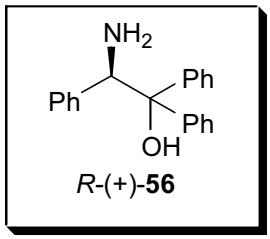


R-(+)-**56**

Yield 0.17 g (12%)

$[\alpha]_D^{25}$ +47.0 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

From filtrate:



R-(+)-**56**

Yield 1.10 g (75%)

$[\alpha]_D^{25}$ +233 (*C* 1, $CHCl_3$), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

1. 5 References

1. Grayson, M., Ed. *Kirk-Othmer Encycl. Chem. Technol*. **1982**, *17*, 311.
2. Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem*. **1983**, *48*, 3608.
3. Frishman, W. H. *New. Eng. J. Med.* **1981**, *305*, 1200.
4. Lefkowitz, R. *J. Ann. Rep. Med. Chem*. **1980**, *15*, 217.
5. Corey, E. J.; Link, J. O. *J. Org. Chem*. **1991**, *56*, 442.
6. Howe, R.; Shanks, R. G. *Nature* **1996**, *210*, 1336.
7. Enders, D. *Chemtech.* **1981**, *8*, 504.
8. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835.
9. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic compounds, John Wiley & Sons*, **1994**.
10. Tomioka, K. *Synthesis* **1990**, 541.
11. Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 49.
12. March, J. *Advanched Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, **1985**; pp 368, 738, 740.
13. Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc*. **1960**, *82*, 681.
14. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104,* 1737.
15. Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth*. **1990** *Coll. Vol*. *7*, 530.

16. Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1992**, *33*, 5517.

17. Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem*. **1993**, *58*, 766.

18. Karrer, P.; Naik, A. R. *Helv. Chim. Acta* **1948**, *31*, 1617.

19. Karrer, P.; Portmann, P.; Suter, M. *Helv. Chim. Acta* **1949**, *32*, 1156.

20. Seki, H.; Koga, K.; Matsuo, H.; Yamada, S. *Chem. Pharm. Bull*. **1965**, *13*, 995.

21. McKennon, M. J.; Meyers, A. I. *J. Org. Chem*. **1993**, *58*, 3568.

22. Periasamy, M.; Prasad, A. S. B.; Kanth, J. V. B. *Tetrahedron* **1992**, *48*, 4623.

23. Periasamy, M.; Kanth, J. V. B. *J. Org. Chem*. **1991**, *56*, 5964.

24. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2039.

25. Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem*. **1994**, *59*, 4680.

26. Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

27. Periasamy, M.; Kanth, J. V. B. *Tetrahedron Lett*. **1990**, *31*, 4985.

28. Sivakumar, S. Ph.D. Thesis, University of Hyderabad, Hyderabad.

29. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed. Eng*. **1987**, *26*, 1141.

30. Fujita, M.; Hiyama, T. *J. Am. Chem. Soc*. **1984**, *106*, 4629.

31. Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett*. **1997**, *38*, 5193.

32. Masui, M.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 5195.

33. Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683.

34. Smith, J. G. *Synthesis* **1984**, 629.

35. Nugent, W. A. *J. Am. Chem. Soc*. **1998**, *120*, 7139.

36. Sekar, G.; Singh, V. K. *J. Org. Chem*. **1999**, *64*, 287 and the references cited therein.

37. Harris, C. E.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem*. **1994**, *59*, 7746.

38. Fuziwara, M.; Imada, M.; Baba, A.; Matsuda, H. *Tetrahedron Lett*. **1989**, *30*, 739.

39. Pachon, L. D.; Gamez, P.; Brussel, J. J. M. V.; Reedijk. J. *Tetrahedron Lett*. **2003**, *44*, 6025.

40. Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett*. **2003**, *44*, 8315.

41. Sundararajan, G.; Vijayakrishna, K.; Varghese, B. *Tetrahedron Lett*. **2004**, *45*, 8253.

42. Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett*. **2004**, *6*, 2173.

43. Garcia-Delgado, N.; Fontes, M.; Pericas, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085.

44. Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng*. **1996**, *35*, 451.

45. Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng*. **1996**, *35*, 2810.

46. Rubin, A. E.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng*. **1997**, *36*, 2637.

47. Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng*. **1996**, *35*, 2637.

48. Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett*. **1998**, *39*, 3667.

49. Brucio, M.; Schlingloff, G. *Angew. Chem. Int. Ed. Eng*. **1997**, *36*, 1483.

50. O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1,* **1998**, 2519.

51. Fisher, G. B.; Goralski, T.; Nicholson, L. W.; Hasha, D. L.; Zakett, D.; Singaram, B. *J. Org. Chem*. **1995**, *60*, 2026.

52. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1988**, *110*, 7538.

53. Periasamy, M.; Sivakumar, S.; Reddy, M. N. *Synthesis* **2003**, 1965.

54. Bonner, W. A. Topics in Stereochemistry, Wiley, New York, **1988**, Vol. *18*, 1

55. Bada, J. L. *Nature* **1995**, *374*, 594.

56. Feringa, B. L.; van Delden, R. A. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3418.

57. Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed. Engl.* **1998***, 37*, 2923.

58. Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613.

59. Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Matsukawa, S. *Acc. Chem. Res*. **2000**, *33*, 391.

60. Soai, K.; Shibata, T.; Marioka, H.; Choji, K. *Nature* **1995**, *378*, 767.

61. Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res*. **2000**, *33*, 382.

62. Morowitz, H. J. *J. Theor. Biol*. **1969**, *25*, 491.

63. Thiemann, W. *J. Mol. Evol*. **1974**, *4*, 85.

64. Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

65. Kondepudi, D. K.; Nelson, G. W. *Physica* **1984**, *125A*, 465.

66. Kondepudi, D. K.; Kaufman, R. J.; Singh, N. S*cience* **1990**, *250*, 975.

67. van Mil, J.; Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc*. **1982**, *104*, 3429.

68. Tsuruta, T.; Matsuura, K.; Inoue, S. *Biopolymers* **1967**, *5*, 313.

69. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun*. **1994**, 99.

70. Venkatraman, L.; Periasamy, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2471.

71. Periasamy, M.; Sivakumar, S.; Reddy, M. N.; Padmaja, M. *Org. Lett*. **2004**, *6*, 265.

72. Aldrich Catalog Handbook of Fine Chemicals, *Aldrich*: Milwaukee, **2000-2001.**

73. Elias, W. E. *J. Chem. Edu.* **1972**, *49*, 448.

74. Brewster, J. H. *J. Chem. Edu.* **1986**, *63*, 667.

75. Gabard, A.; Collect, A. *New J. Chem*. **1986**, *10*, 685.

76. Potter, G. A.; Garcia, C.; McCauge, R.; Adger, B.; Collet, A. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1666.

77. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.

78. Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1994**, *5*, 165.

79. Greene, J. L.; Zook, H. D. *J. Am. Chem. Soc*. **1958**, *80*, 3629.

80. Blatt, A. H.; Barnes, R. P. *J. Am. Chem. Soc*. **1954**, *76*, 1148.

81. Hall, S. R.; King, G. S. D.; Stewart, J. M., Eds, *Xtal, 3.4 User's Manual,* Xtal System, University of Western Australia*,* **1995**.

82. Sheldrick, G. M., SHELXS-86, In Crystallographic computing 3, Sheldrick, G. M.; Kurger, G.; Goddard, R. Eds, *Oxford University Press*; Oxford, **1985**.

83. Sheldrick, G. M., SHELXL-93, *Crystal Structure Refinement Programme*, University of Gottingen, Gottingen, Germany, **1993**.

Chapter 2

Synthesis and applications of chiral aminonaphthols

2. 1 Introduction

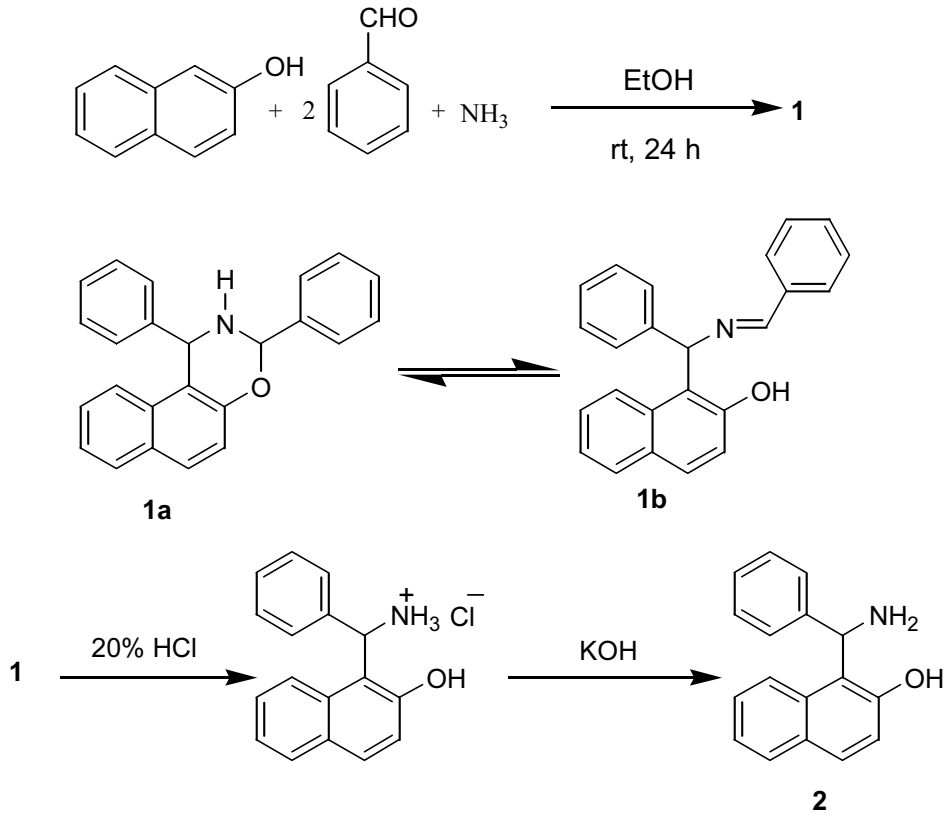
The search for new chiral ligands, which are useful in asymmetric transformations, is of great interest in modern organic chemistry research.[1-7] In this context, chiral 1,2- and 1,3-aminophenols and naphthols have proved to be useful ligands in a variety of asymmetric transformations catalyzed by metal complexes.[8-16] As discussed in Chapter 1, we have undertaken efforts to develop new methods of synthesis and resolution of chiral 1,2-amino alcohols. In continuation of these efforts, we have undertaken the studies on the synthesis and application of aminonaphthols. A brief review the reports on the synthesis and applications of aminonaphthols will be helpful for the discussion.

2. 1. 1 Synthesis of racemic aminonaphthols

In 1900, Betti, reported a simple straightforward condensation of β-naphthol, ammonia and 2 equivalents of benzaldehyde.[17-19] A mixture of products **1a** and **1b** was obtained, which on treatment with acid followed by the addition of KOH yielded the aminonaphthol **2** (Scheme 1). The aminonaphthol **2** is called Betti base.

The crystalline product **1** was first assigned as the 1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine structure **1a**[20-21] based on the reaction of **1** with nitrous acid in Et_2O which gives the *N*-nitroso-1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine derivative of **1a.**[22] Later, on the basis of its reaction with ethereal ferric chloride leading to an intense reddish-violet colour, the Schiff base structure, *N*-benzylidine-1-(α-aminobenzyl)-2-naphthol **1b** was proposed**.**[23]

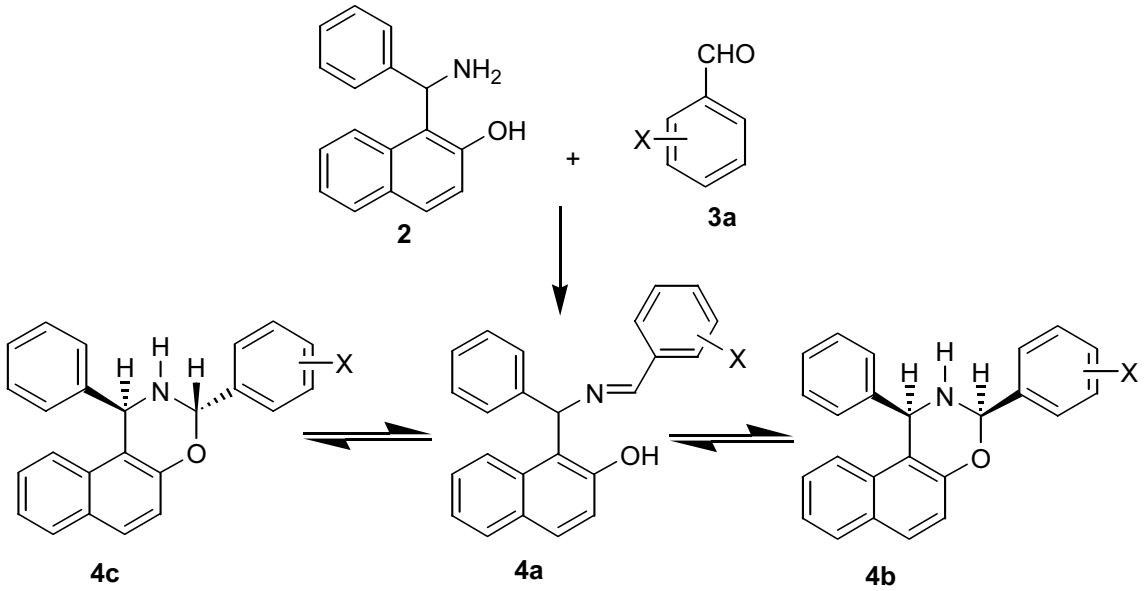
Scheme 1



Further, on the basis of IR data, it was confirmed that the structure **1a** is valid for the solid material, whereas a tautomeric equilibrium between **1a** and **1b** exists in solution.[24] The free Betti base **2** condenses with aliphatic aldehydes to give oxazines **1a,** whereas with aromatic aldehydes and aliphatic ketones Schiff bases **1b** are obtained.[25]

Later, Smith and Cooper[24] studied the reaction of Betti base **2** with benzaldehyde and substituted benzaldehydes **3a**. The IR spectra of these condensation products indicated that in the crystalline state the product has the oxazine structure, whereas in solution an equilibrium mixture of *cis*- and *trans*-naphthoxazine (ring) and the corresponding Schiff base (chain) exists through a ring chain tautomerism (Scheme 2).

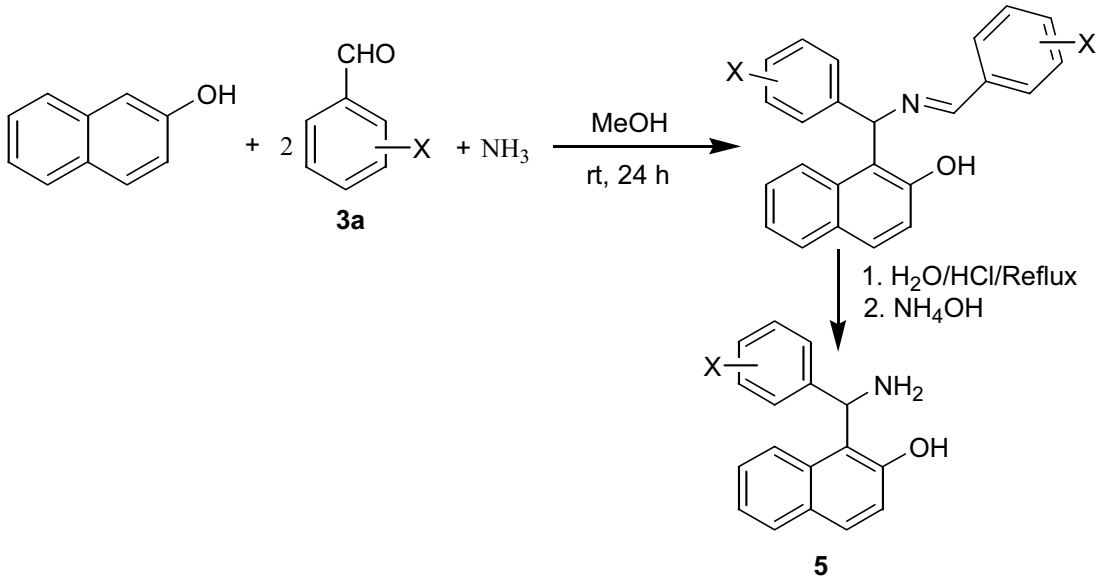
Scheme 2



The ratio of ring/chain tautomers depends on the substituent in the benzaldehyde moiety. The greater the electron-withdrawing power of the substituents, the larger is the ring/chain isomeric ratio.

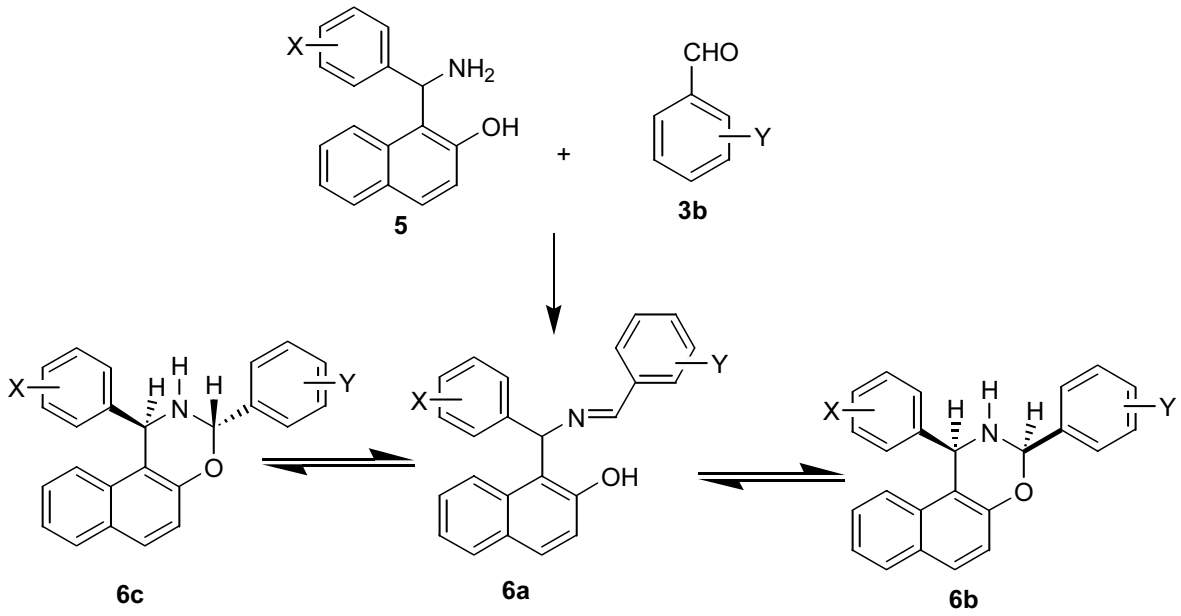
Very recently, Szatmari and coworkers[26] prepared the aminonaphthols **5** using β-naphthol, methanolic ammonia with 2 equivalents of substituted benzaldehydes **3a** (Scheme 3).

Scheme 3



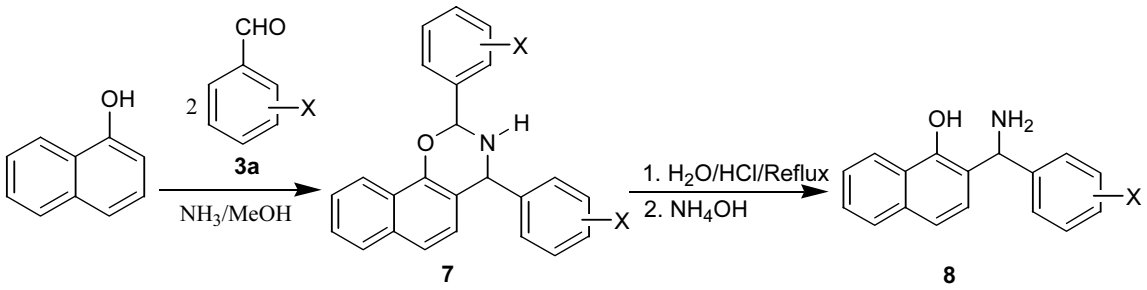
They also studied the effect of ring/chain isomers ratio of the condensation of substituted Betti bases **5** with substituted benzaldehydes **3b** (Scheme 4). It was reported that in the three-component equilibria **6b↔6a↔6c**, the chain↔*trans* (**6a↔6b**) equilibrium constants are significantly influenced by the inductive effect of substituent Y on the 1-phenyl ring. In contrast, no significant substituent dependence on Y was observed for the chain↔*cis* (**6a↔6c**) equilibrium.[27]

Scheme 4



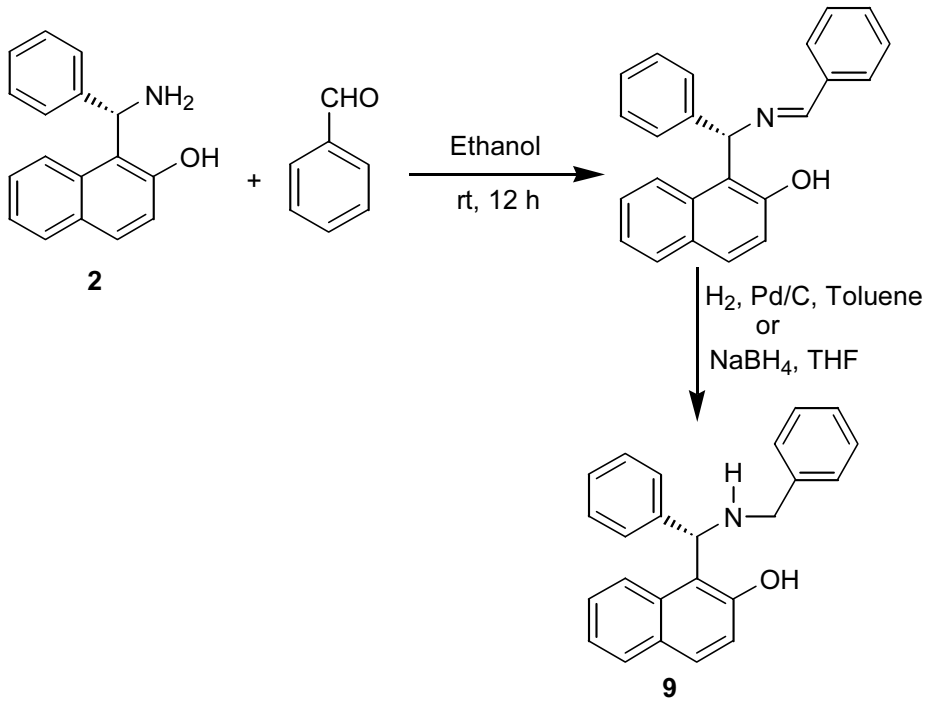
Very recently, the aminonaphthols **8** have been also prepared by the condensation of α-naphthol, ammonia and unsubstituted or substituted benzaldehydes **3a**. These are called reverse Betti bases. In these cases, yields are low compared to the reaction using β-naphthol (Scheme 5).[28]

Scheme 5



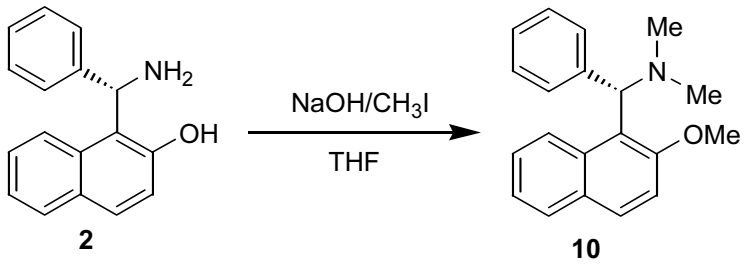
After a huge gap of 98 years after the discovery of Betti reaction, in 1998 Cardellicchio and coworkers[29] demonstrated the importance of aminonaphthols in asymmetric synthesis and prepared the derivatives of chiral aminonaphthols starting from Betti base **2**. For example, the *N*-benzyl derivative of the aminonaphthol **9** was prepared using Betti base **2** and benzaldehyde followed by reduction using H_2/Pd-C or $NaBH_4$ (Scheme 6).

Scheme 6



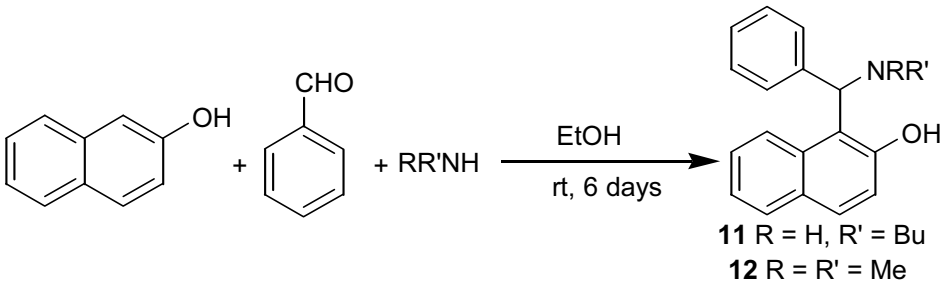
They also prepared the *N,N,O*-trimethyl derivative of the aminonaphthol **10** by methylation of the Betti base **2** (Scheme 7).

Scheme 7



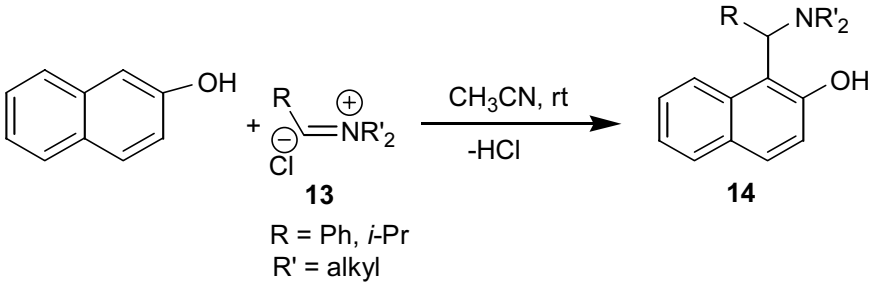
The *N*-alkyl and *N,N*-dialkyl derivatives of the aminonaphthols were also prepared by the straightforward condensation of the β-naphthol, benzaldehyde and alkyl amines in the place of ammonia (Scheme 8).[30] Similar reactions were also realized using other naphthols and quinoline derivatives.

Scheme 8



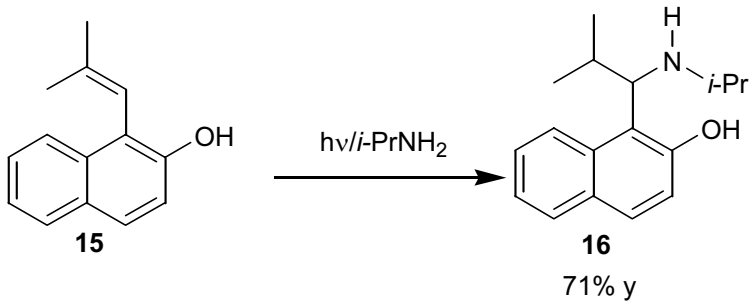
Risch and coworkers[31] prepared the *N,N*-dialkyl derivatives of aminonaphthols **14** using β-naphthol and preformed imminium salts (Scheme 9).

Scheme 9



The isopropyl derivative of aminonaphthol **16** has been prepared by photo-addition of nucleophiles such as isopropyl amine to 1-alkenyl-2-naphthol **15** (Scheme 10).[32]

Scheme 10

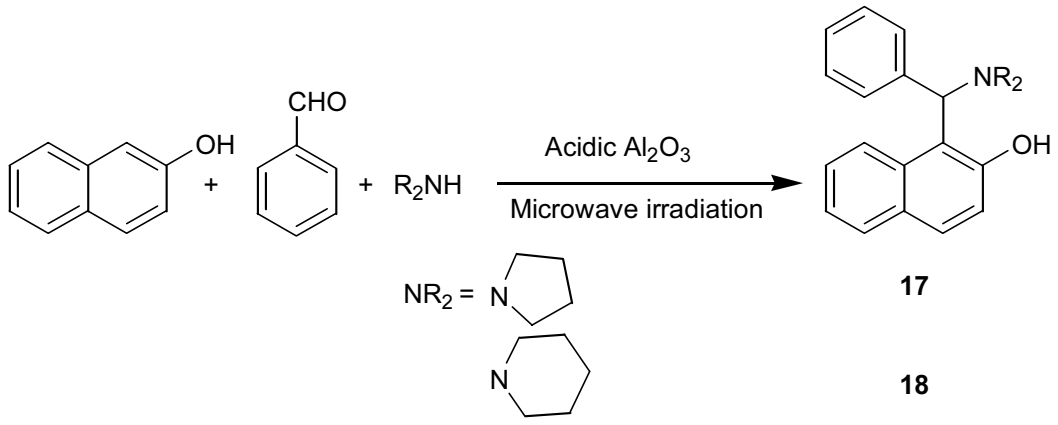


15 **16**

71% y

Pyrrolidine and piperidine moieties containing aminonaphthols **17** and **18** were prepared by the aminoalkylation of β-naphthol with heterocyclic amines and benzaldehyde under microwave irradiation (Scheme 11).[33]

Scheme 11

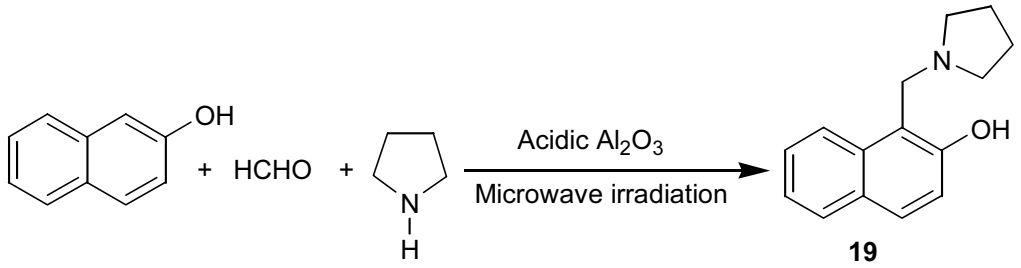


17

18

The unsubstituted aminonaphthol **19** was also prepared following this method using formaldehyde instead of benzaldehyde (Scheme 12).[34]

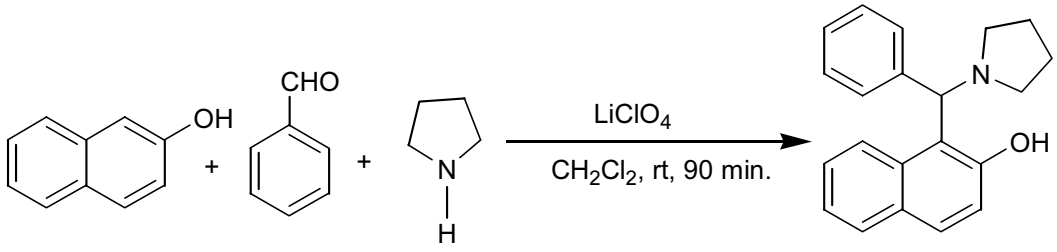
Scheme 12



19

Very recently, Saidi and coworkers[35] prepared the aminonaphthols by amino alkylation of aldehydes mediated by solid $LiClO_4$. For example, pyrrolidine based aminonaphthol **17** was prepared as shown in Scheme 13.

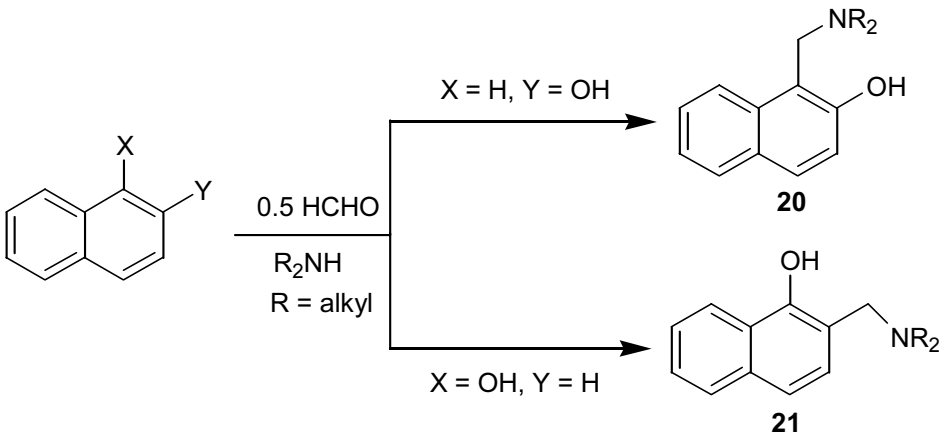
Scheme 13



17

The unsubstituted aminonaphthols **20** or **21** were also prepared by the condensation of α- or β-naphthol with formaldehyde and a variety of aliphatic secondary amines (Scheme 14).[36]

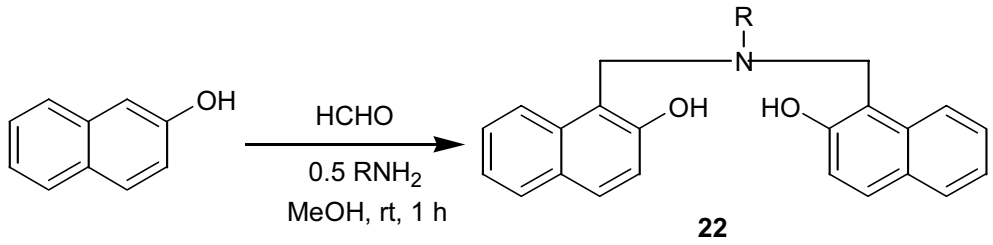
Scheme 14



20 **21**

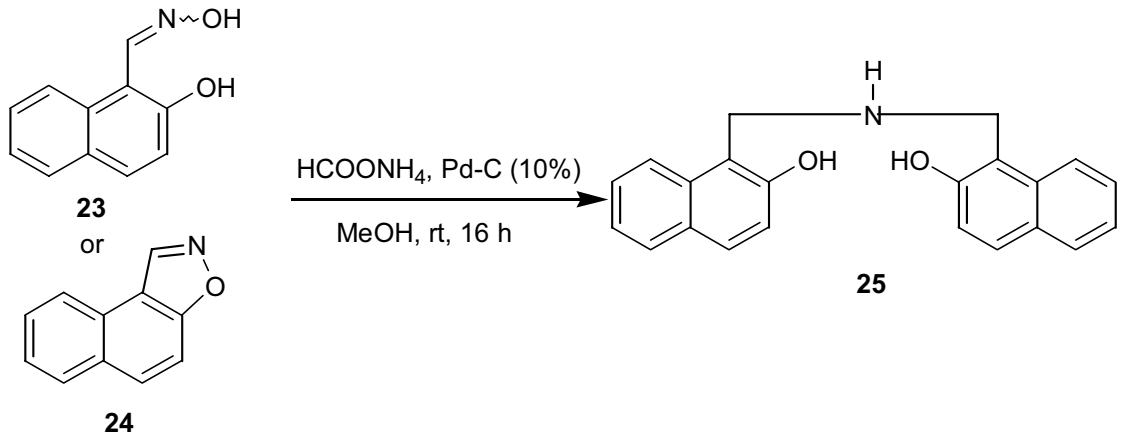
N,*N*-Bis(2-hydroxy-1-naphthyl-methyl)alkylamines **22** were also prepared by the condensation of β-naphthol with formaldehyde and primary amines in the ratio 2:2:1 (Scheme 15).

Scheme 15



Similarly, *N*,*N*-bis(2-hydroxy-1-naphthyl-methyl) amine **25** was prepared from oxime of β-naphthadehyde **23** or naphthisoxazole **24** using ammonium formate and Pd-C (Scheme 16). In this, ammonium formate acts as *N*-formylating agent as well as a source of hydrogen.[37]

Scheme 16



2. 1. 2 Synthesis of chiral aminonaphthols

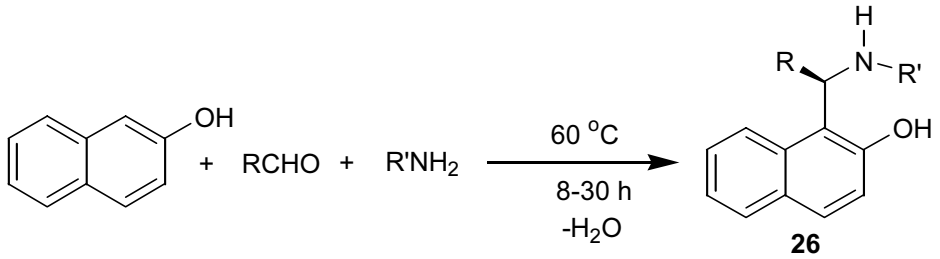
2. 1. 2. 1 Using chiral resolving agents

Chiral aminonaphthols are normally prepared by the resolution of racemic aminonaphthols using chiral resolving agents. For example, the Betti base **2** is easily resolved into pure enantiomers using inexpensive *L*-(+)-tartaric acid.[29]

2. 1. 2. 2 From asymmetric synthesis

Cimarelli and coworkers[38,39] synthesized the chiral aminonaphthols **26** by using β-naphthol, aldehydes and chiral amines under solvent free conditions (Scheme 17).

Scheme 17



26

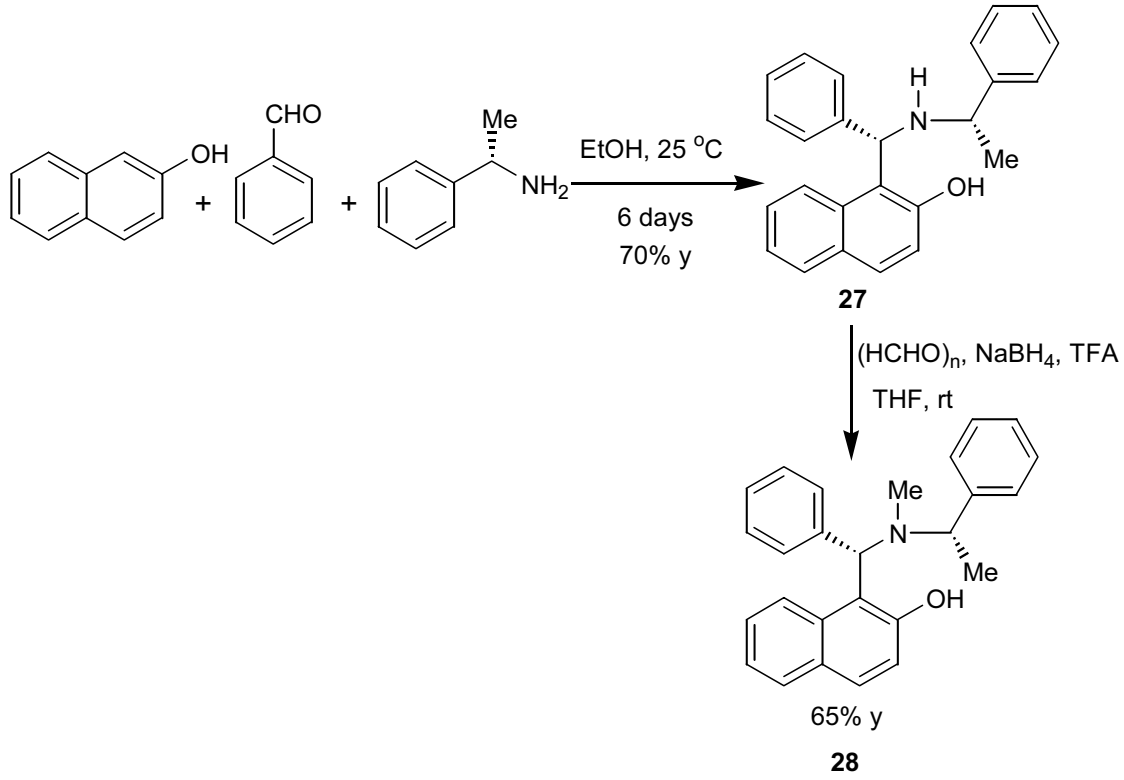
R = C_6H_5, C_6F_5, *i*-Pr, Cyclohexyl, 2-Pyridyl, 2-Furyl, 2-Thienyl

R' = (*R*)-PhCHMe, (*R*)-$PhCHCH_2OH$, (*R*)-(1-Naphthyl)CHMe

The yields and the diastereomeric ratios are very high with benzaldehyde, but only moderate using cyclohexylcarboxaldehyde. This method is also applicable to α-naphthol and 8-hydroxy quinoline. However, the yields of the products in these cases are moderate compared to yields obtained in the reaction with β-naphthol.

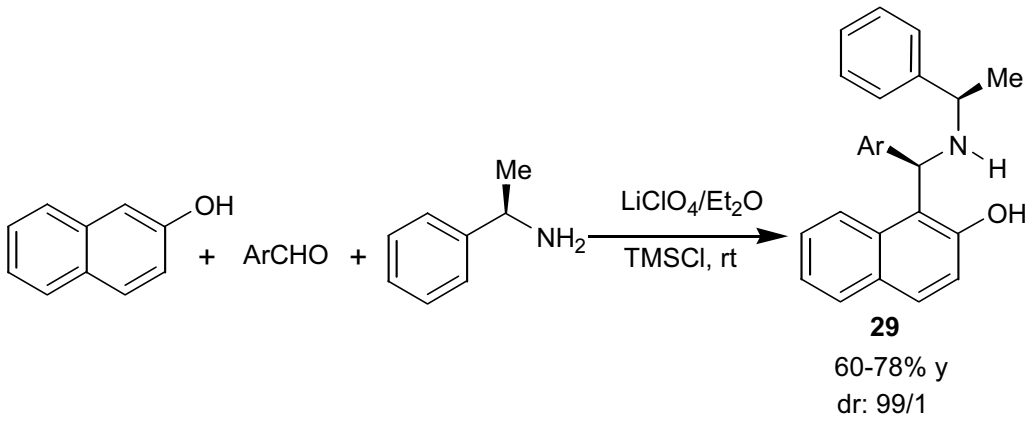
Optically active aminonaphthol **28** can be obtained by condensation of β-naphthol, benzaldehyde and (*S*)-α-methylbenzylamine followed by *N*-methylation (Scheme 18).[40]

Scheme 18



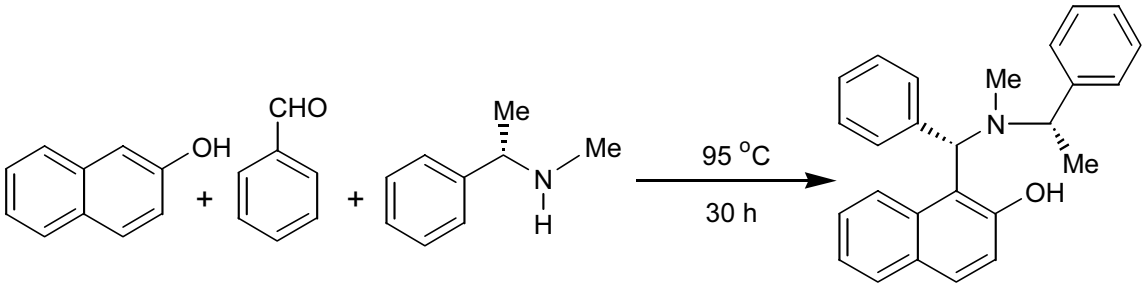
The aminonaphthols **29** were prepared in high diastereomeric ratio (dr) by direct condensation of β-naphthol, aromatic aldehydes with (*R*)-α-methylbenzylamine mediated by $LiClO_4$ solution in diethyl ether (Scheme 19).[41,42]

Scheme 19



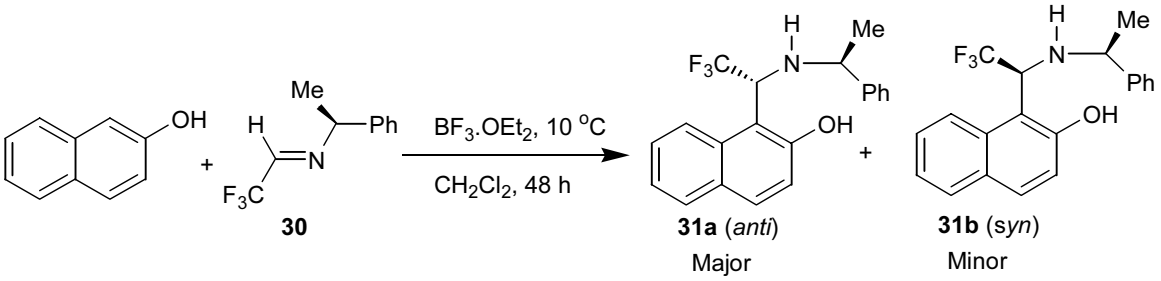
Recently, Chan and coworkers[43] prepared the tertiary aminonaphthol **28** by condensation of β-naphthol, benzaldehyde and (*S*)-*N*-α-dimethylbenzylamine under solvent free conditions (Scheme 20).

Scheme 20



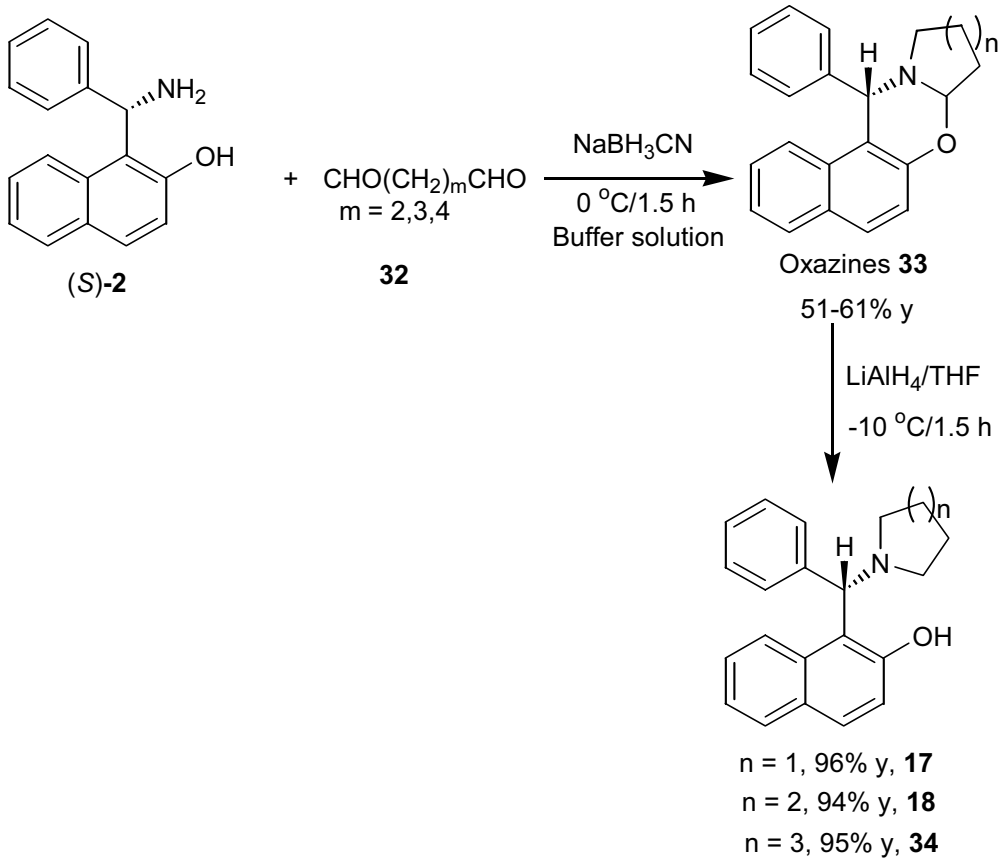
The chiral aminonaphthols **31** were also prepared by diastereoselective Friedel-Crafts reaction of α-trifluromethyl imines, prepared from chiral amines and electron rich aromatic compounds. The reaction takes places readily at room temperature in the presence of $BF_3.OEt_2$ (Scheme 21).[44]

Scheme 21



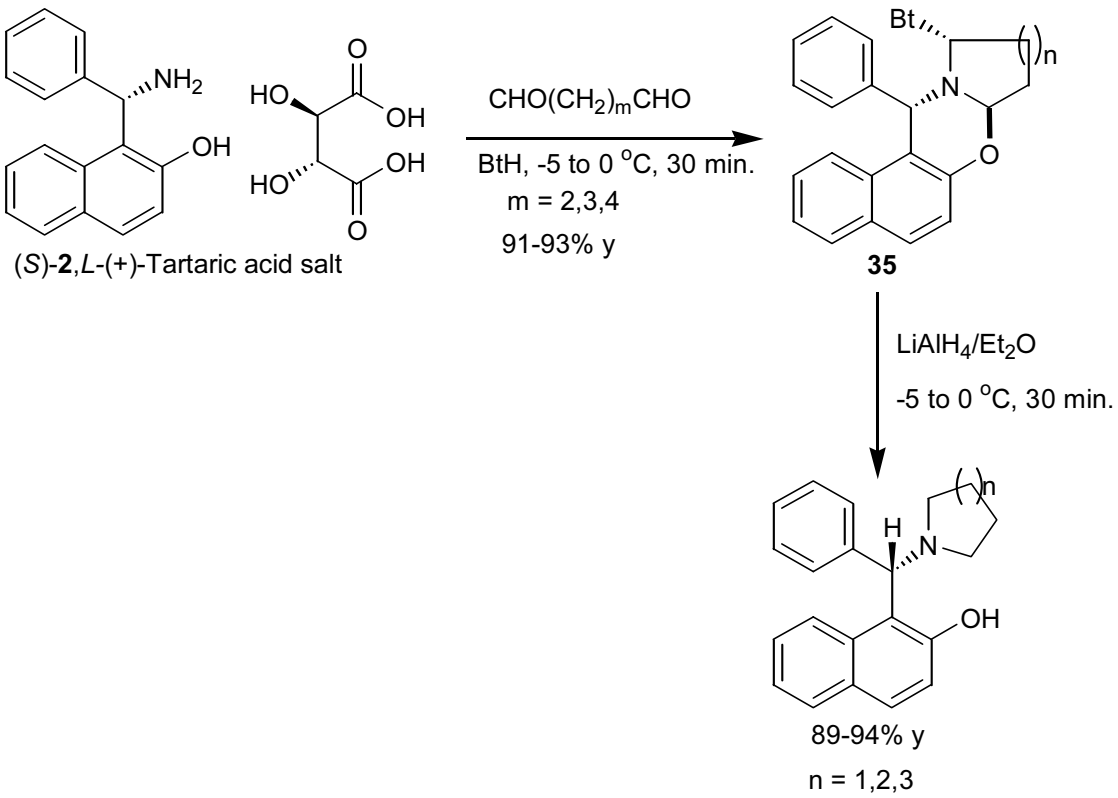
Lu and coworkers[45,46] synthesized the chiral *N*,*N*-dialkyl derivatives of aminonaphthols starting from optically active Betti base **2** (Scheme 22).

Scheme 22



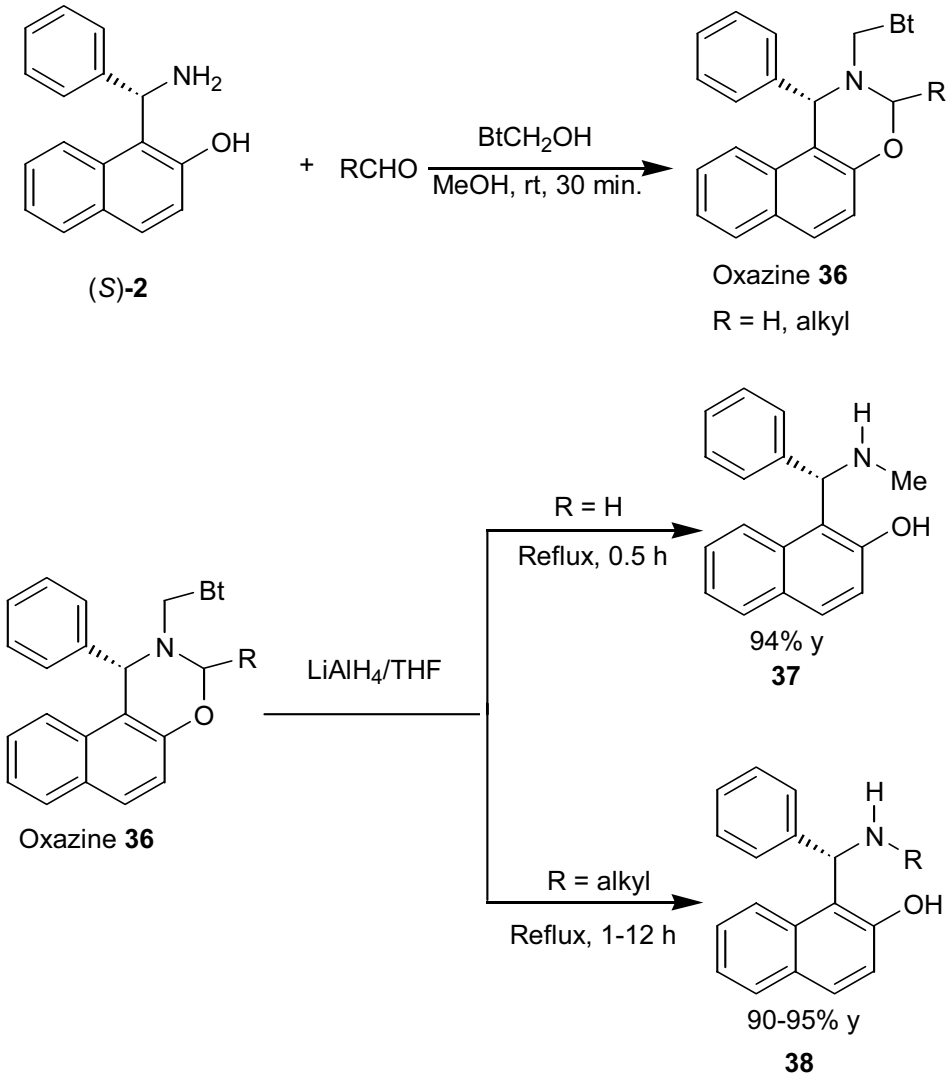
Since the Betti base **2** is thermally unstable, the yields of the oxazine products were somewhat low in this transformation. A modified procedure using the salt of *L*-(+)-tartaric acid and the Betti base **2** and benzotriazole (BtH) gave better yields (Scheme 23).[47,48]

Scheme 23



The NH_2 group in the Betti base **2** has a relatively lower nucleophilic reactivity compared to its hydroxyl groupl.. So, the *N*-alkylation of Betti base **2** is not regioselective. Dong *et al.*[49] reported the highly regioselective *N*-alkylation of aminonaphthols starting from the Betti base **2** (Scheme 24) through formation of benzotriazole based oxazine **36** intermediate followed by the reduction using $LiAlH_4$ under refluxing conditions.

Scheme 24



2. 1. 3 Applications of chiral aminonaphthols

2. 1. 3. 1 Enantioselective diethylzinc addition reactions to aldehydes

The major application of aminonaphthols, till now is the addition of diethylzinc to the aldehydes (Scheme 25). Various derivatives of aminonaphthols have been used for this reaction. These results are all summarized in Chart 1.

Scheme 25

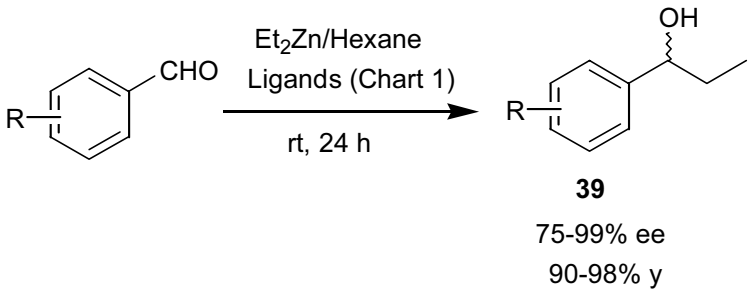
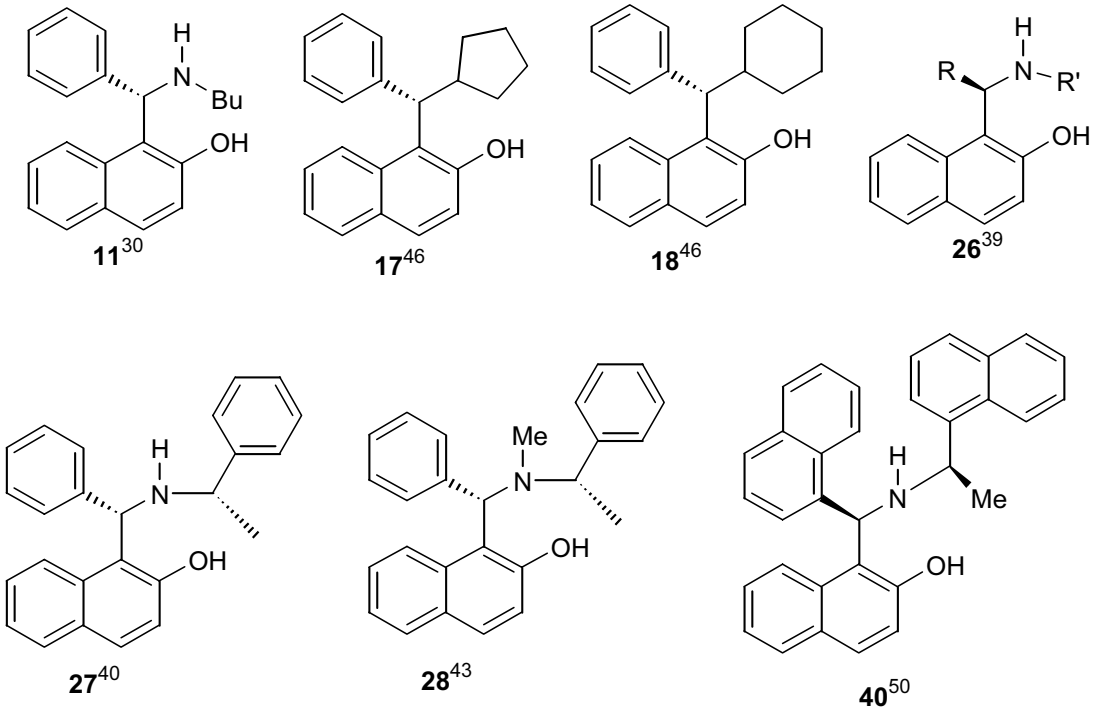


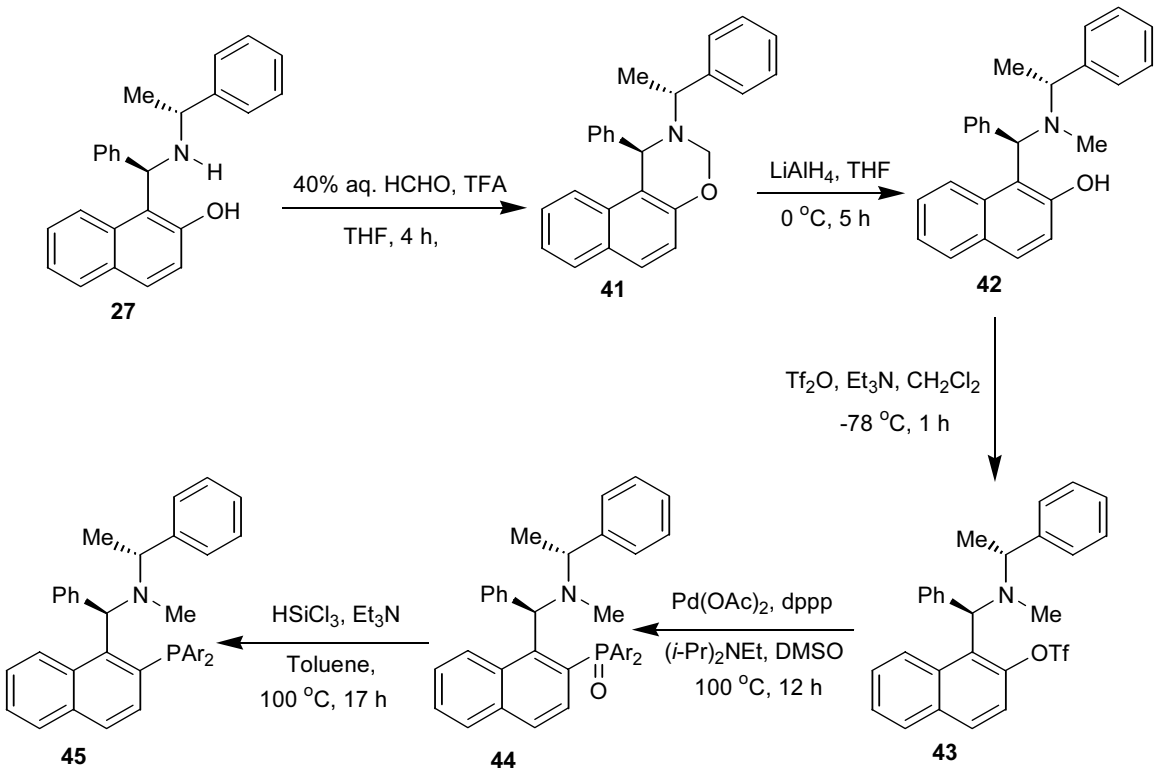
Chart 1



2. 1. 3. 2 Synthesis of chiral amino phosphine ligands

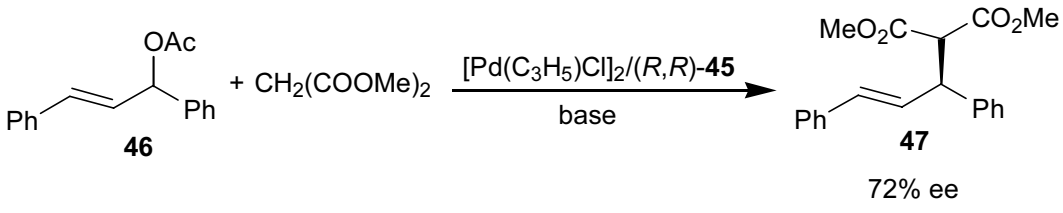
Chiral amino phosphine ligands have been prepared starting from chiral aminonaphthol **27** (Scheme 26).[51]

Scheme 26



This ligand has been used in the Pd-catalyzed asymmetric allylation of dimethyl malonate to obtain the product **47** in 72% ee and in quantitative yield (Scheme 27).

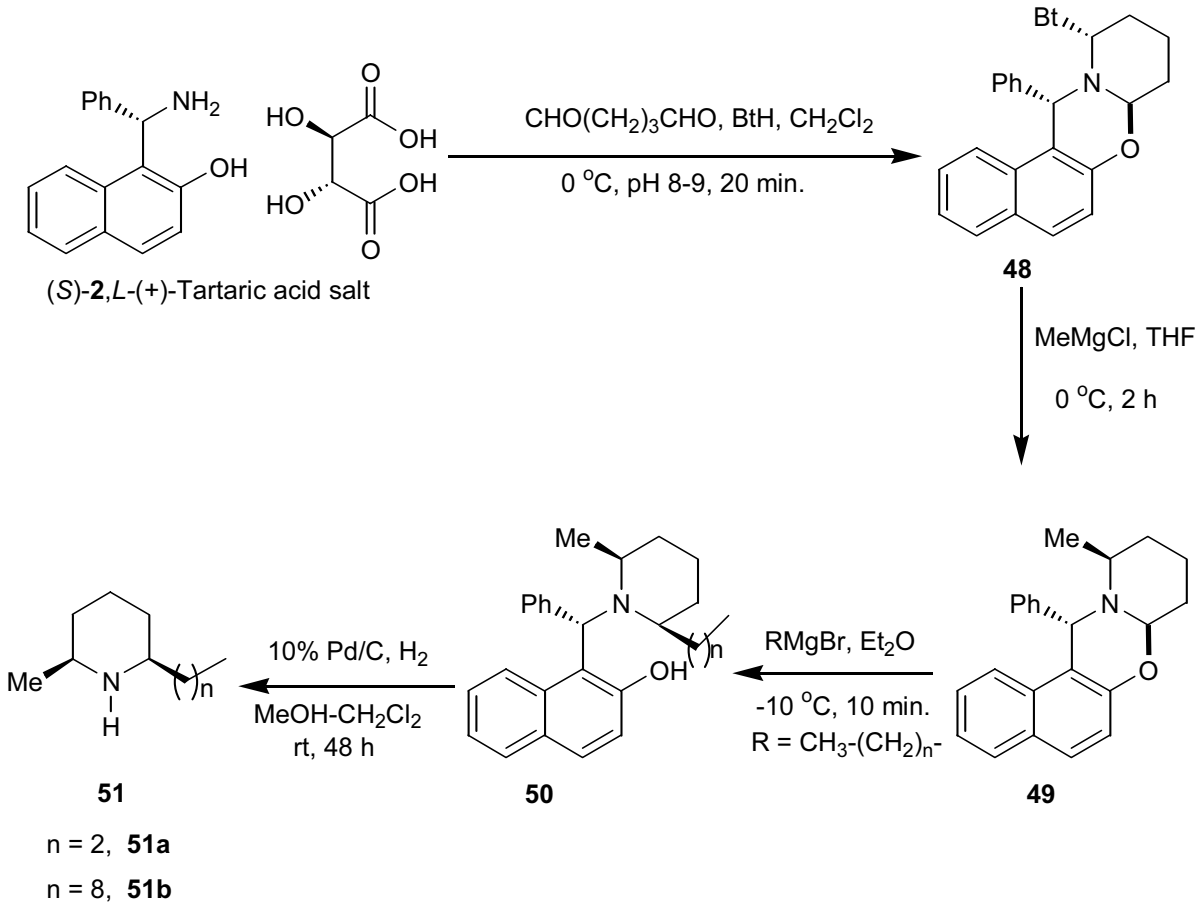
Scheme 27



2. 1. 3. 3 Total Synthesis of enantiopure (2*S*,6*R*)-dihydropinidine and (2*S*,6*R*)-isosolenopsins

Total syntheses of enantiopure alkaloid natural products (*2S*,6*R*)-dihydropinidine **51a** (as hydrochloride) and (2*S*,6*R*)-isosolenopsin **51b** (as hydrochloride) have been achieved in four steps and in 80-82% total yields by following a synthetic strategy of formation and cleavage of the corresponding 1,3-oxazine from *(S)*-Betti base **2,** followed by Pd/C catalyzed *N*-debenzylation in the presence of CH_2Cl_2 (Scheme 28).[52]

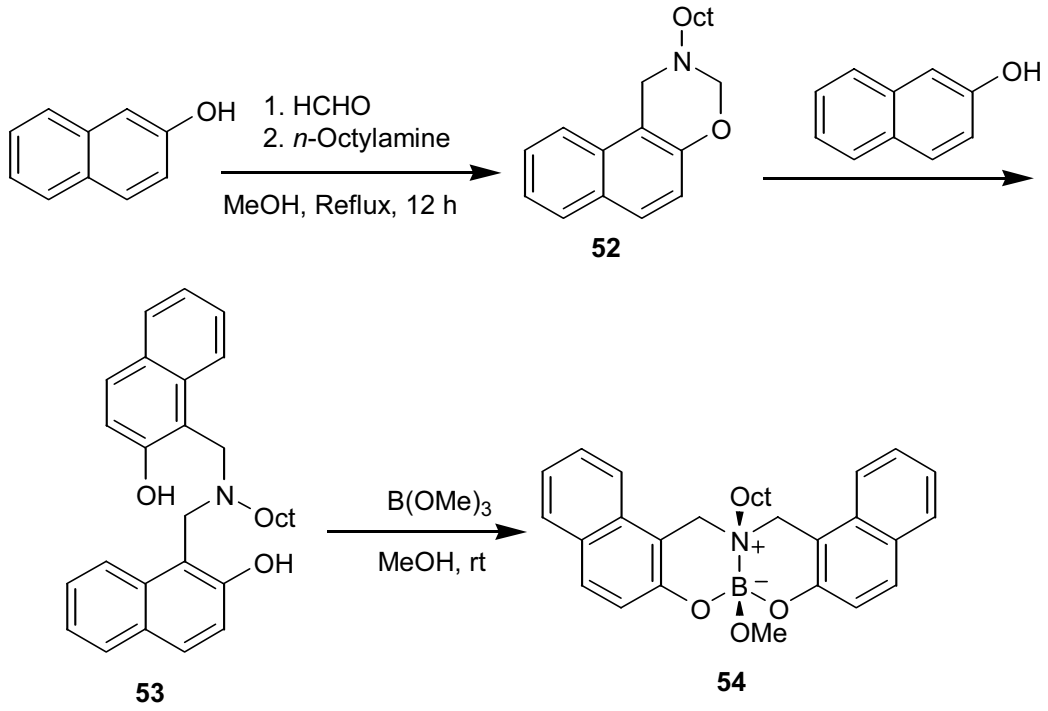
Scheme 28



2. 1. 3. 4 Synthesis of dioxazaborocines

Dioxazaborocines **54** can be prepared by the reaction of the unsubstituted 1,3-benzoxazines and β-naphthol followed by reaction with $B(OH)_3$ or $B(OR)_3$ (Scheme 29).[53] These compounds are capable of releasing borate ions and exhibit biological activities.

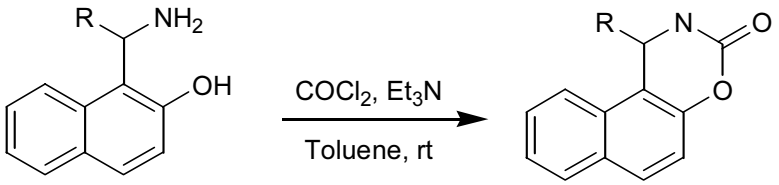
Scheme 29



2. 1. 3. 5 Synthesis of new heterocyclic compounds

Aminonaphthols are used in the preparation of a variety of heterocyclic compounds through the corresponding oxazine intermediates. For example, the Betti base **2** and 1-aminomethyl-2-naphthol **55** react with phosgene in the presence of Et_3N to give the corresponding 1,3-oxazine-2-ones (Scheme 30).[54]

Scheme 30



R = Ph, **2**

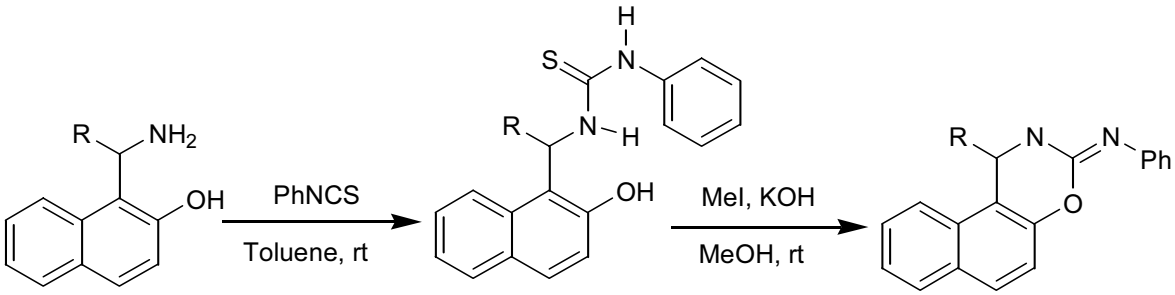
R = H, **55**

R = Ph, **56**

R = H, **57**

The aminonaphthols **2** and **55** react with phenyl isothiocyanate to give the corresponding thiourea derivatives **58** and **59**. These thiourea derivatives are easily converted to isothiourea derivatives using MeI. Further reaction with methanolic KOH gives the corresponding 2-arylimino-susbstituted 1,3-oxazines **60** and **61** via elimination of methyl mercaptan (Scheme 31).

Scheme 31



R = Ph, **2**

R =H, **55**

R = Ph, **58**

R = H, **59**

R = Ph, **60**

R = H, **61**

We have undertaken efforts towards the synthesis, resolution and applications of aminonaphthols. These results will be discussed in the next section.

2. 2 Results and Discussion

2. 2. 1 Synthesis of aminonaphthols

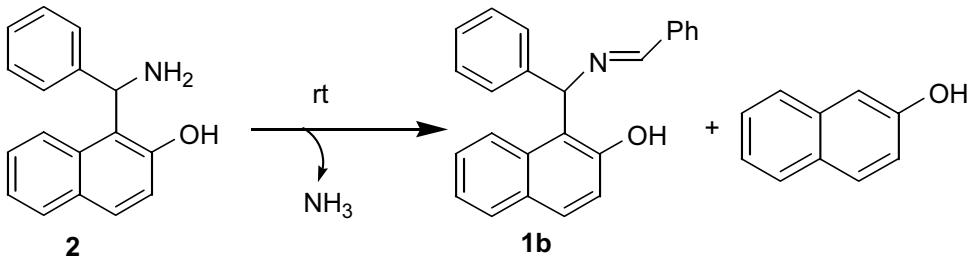
2. 2. 1. 1 Synthesis of 1-(α-aminobenzyl)-2-naphthol

Recently, the Betti reaction (Scheme 1) has received renewed interest, since the chiral aminonaphthol products are readily accessible through this reaction.[26,45-49] These aminonaphthols are useful as catalysts in asymmetric carbon-carbon bond forming reactions.[30,50] Thus, we have undertaken efforts towards the synthesis of aminonaphthols. The Betti aminonaphthol **2** was prepared by the condensation of 2-naphthol, benzaldehyde and ammonia in the ratio of 1:2:1 following a reported procedure.[19] The product **1** (Scheme 1) was obtained as intermediate, which on treatment with 20% hydrochloric acid followed by the addition of 2M Na_2CO_3 to the ammonium salt yielded the aminonaphthol **2** (Scheme 1).

2. 2. 1. 2 Synthesis of derivatives of aminonaphthol 2

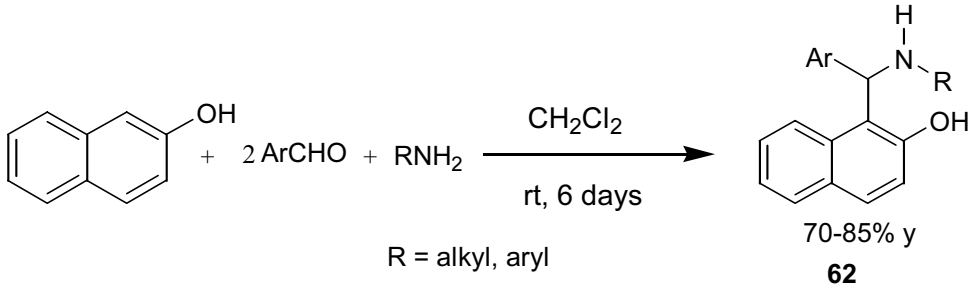
The Betti aminonaphthol **2** is thermally unstable[46,47] and decomposes easily to give **1b** and β-naphthol (Scheme 32).

Scheme 32



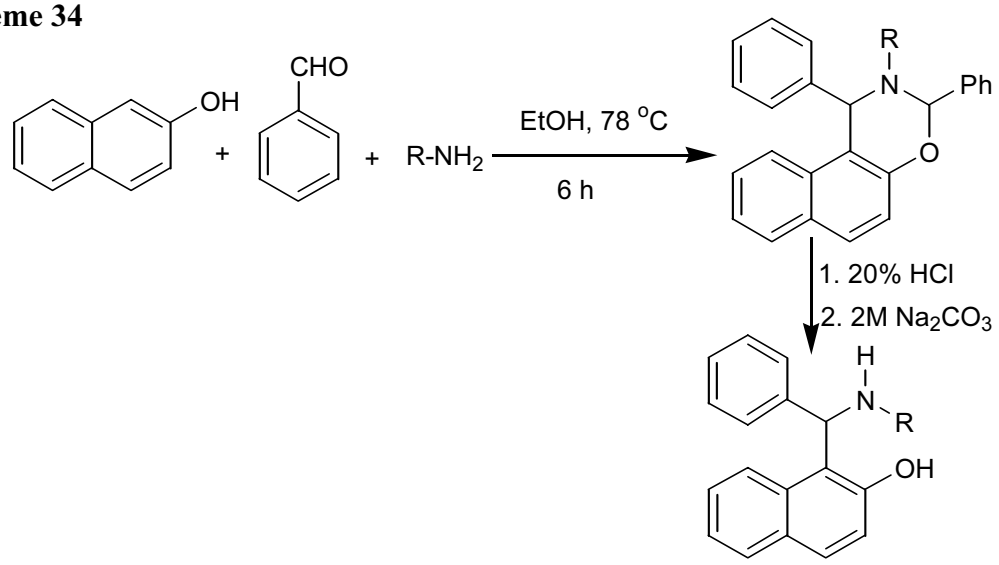
Generally, the derivatives of the Betti aminonaphthols are prepared by condensing the β-naphthol, benzaldehyde and amines in the ratio of 1:2:1 in ethanol or dichloromethane for 6 days (Scheme 33).[30,55]

Scheme 33

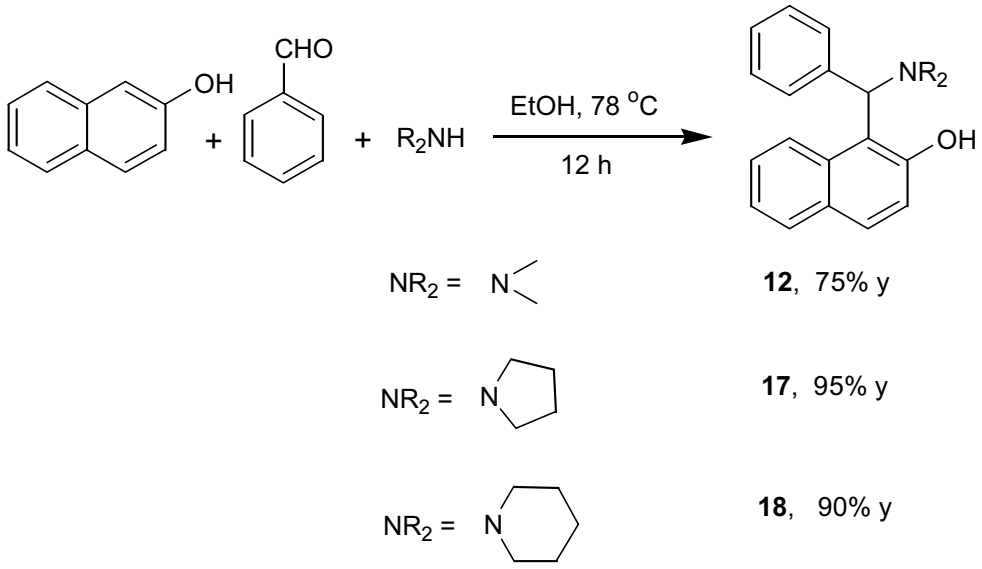


These reactions suffer from the requirement of a long reaction time. We have modified the procedure and carried out the reactions using ethanol as solvent under reflux conditions. The reaction is complete within 6-12 h under these conditions. Thus, the derivatives of the aminonaphthol **2** are readily prepared in good yields by condensation of β-naphthol, benzaldehyde and 1^{o} or 2^{o} amines in ethanol at 78 ^{o}C for 6-12 h (Schemes 34 and 35).

Scheme 34



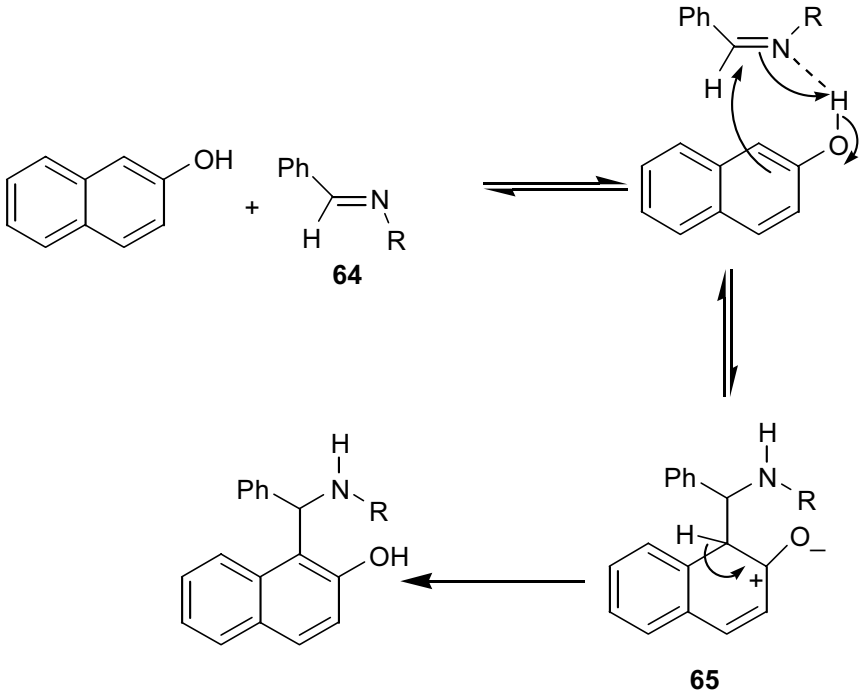
Scheme 35



In the preparation of aminonaphthols **9**, **11** and **63** using 1^{o} amines, the yields were moderate to good, as the aminonaphthols could react further with benzaldehyde to give the oxazine compounds as outlined in the introductory section (Scheme 1). However, use of 2^{o} amines gives the products in excellent yields. We have observed that the reaction did not take place using β-methoxynaphthalene, α-bromo β-naphthol and phenol.

This transformation is a Mannich type reaction and the mechanism involves the intermediacy of an imine, followed by the addition of β-naphthol. The OH group of naphthol protonates the C=N nitrogen, through a 'double' activation pathway. This activation consists of increasing of the elecrtophilicity of the imine and the enhancement of the electron density at the α-position of the naphthalene ring. The unreactivity of the β-methoxynaphthalene can be readily explained by this mechanism (Scheme 36).

Scheme 36. Possible mechanism for the synthesis of aminonaphthols

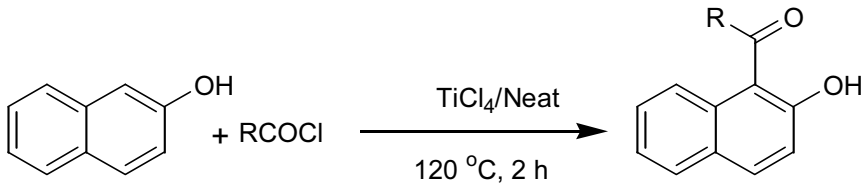


The 1-pyrrolidinylmethyl-2-naphthol **19** hydrochloride (TPY-β) which is an unsubstituted derivative of aminonaphthol **17,** reduces blood pressure (BP) and heart rate (HR) in anaesthetized rats.[56] Hence, the aminonaphthol derivatives are potential candidates to look for new biological activities

2. 2. 1. 3 Synthesis of aminonaphthols through an alternative method

The Betti reaction is applicable only to aromatic aldehydes and the use of aliphatic aldehydes did not give the corresponding aminonaphthols. Hence, we developed a simple and convenient methodology for the synthesis of aminonaphthols using 1-acyl 2-naphthol as precursor. This precursor was easily prepared by the Fries rearrangement of the intermediate prepared *in situ* from β-naphthol and the acid chloride using $TiCl_4$ as catalyst (Scheme 37).

Scheme 37

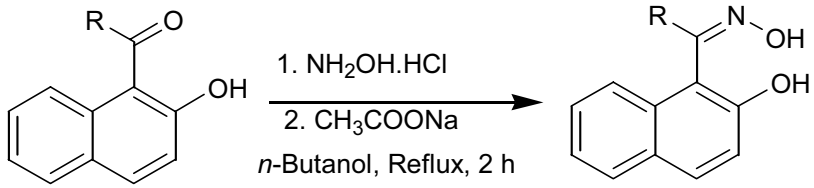


R = Ph **66**, 70% y

R = Me **67**, 65% y

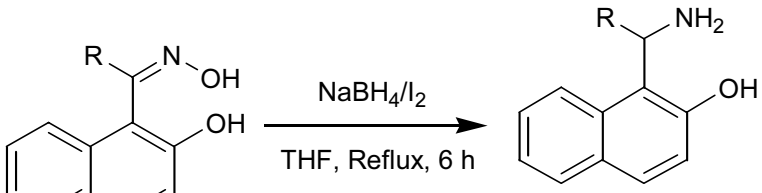
The corresponding oximes were prepared following a reported procedure.[57] The reduction of oximes to the corresponding aminonaphthols is readily carried out by using the simple and easy to handle $NaBH_4/I_2$ reagent system (Scheme 38).

Scheme 38



R = Ph **68**, 61% y

R = Me **69**, 45% y



R = Ph **2**, 80% y

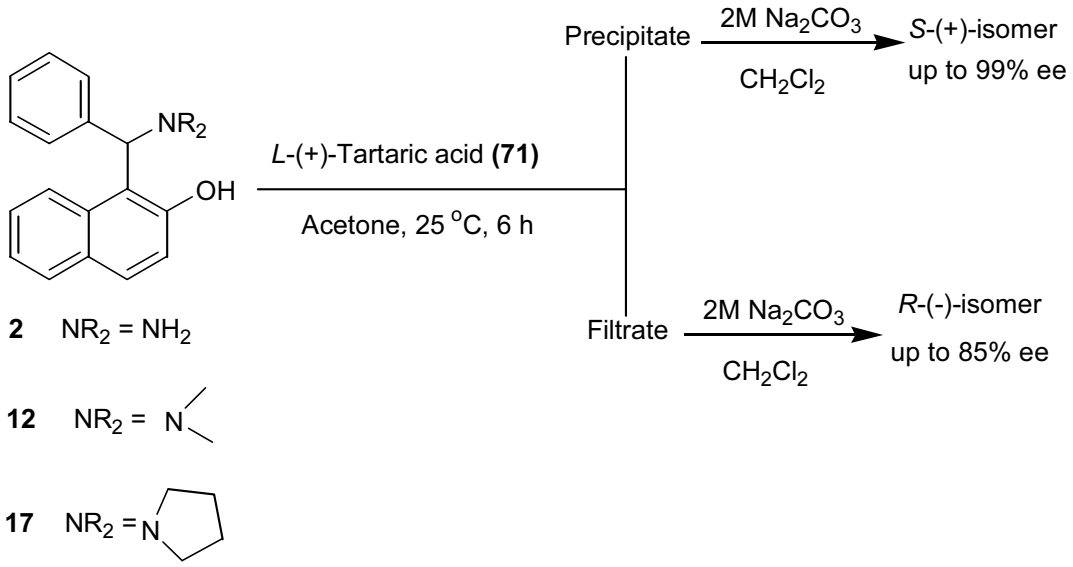
R = Me **70**, 70% y

The aminonaphthol **70** is highly unstable. It has to be stored as HCl salt, otherwise it is easily converted into oxazine with the elimination of ammonia.

2. 2. 2 Resolution of aminonaphthols

In recent years, there has been an immense research efforts in asymmetric synthesis to obtain enantiopure organic compounds compared to development of new methods of resolutions. However, still resolution methods are widely used in large-scale preparations, especially if both the enantiomers are required.[58] In continuation of development of new methods of resolution to obtain important chiral reagents,[59-66] we have undertaken the efforts for the resolution of aminonaphthols through formation of diastereomeric complexes using readily available, inexpensive chiral resolving agents, like *L*-(+)-tartaric acid. It was observed that *L*-(+)-tartaric acid formed diastereomeric complexes with aminonaphthols (Scheme 39). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically.

Scheme 39



To optimize the reaction conditions, we have initially examined the resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol **17** using various solvents like acetone, THF, DCM, CH_3CN ethanol and methanol. In all these solvents, aminonaphthol **17** gave precipitate

within 30 minutes leading to partial resolutions. The results are summarized in Table 1.[67]

Table 1. Effect of various solvents on the resolution of aminonaphthol 17[a]

S. No.	Time	Solvent	Chiral aminonaphthol **17** obtained from			
			Precipitate		Filtrate	
			% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	1 h	Acetone	35 (*S*)	45	30 (*R*)	50
2[a]	6 h	Acetone	98 (*S*)	40	75 (*R*)	55
3[a]	12 h	Acetone	95 (*S*)	40	68 (*R*)	50
4[a]	24 h	Acetone	94 (*S*)	38	60 (*R*)	53
5[d]	6 h	DCM	20 (*S*)	35	18 (*R*)	54
6[e]	6 h	CH_3CN	15 (*S*)	40	10 (*R*)	50
7[f]	6 h	THF	35 (*S*)	25	15 (*R*)	65
8[g]	6 h	Ethanol	60 (*S*)	30	30 (*R*)	60
9[h]	6 h	MeOH	10 (*S*)	60	15 (*R*)	35

a. Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol **17** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in 70 mL of the solvent and stirred at 25 °C.
b. All ee values reported here are based on reported maximum[46] $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)-**17** and $[\alpha]_D^{25}$ = -179.0 (*C* 1.30, $CHCl_3$) for (*R*)-**17.** These maximum ees were further confirmed by ^1H NMR using $Eu(tfc)_3$ as chiral shift reagent and HPLC using chiral column, chiralcel-OD.
c. The yields are of the isolated products, based on the total amount of the starting racemic aminonaphthol **17** used.
d. The substrates were taken in DCM (70 mL) and stirred at 25 °C for 6 h.
e. The substrates were taken in CH_3CN (70 mL) and stirred at 25 °C for 6 h
f. The substrates were taken in THF (70 mL) and stirred at 25 °C for 6 h.
g. The substrates were taken in ethanol (70 mL) and stirred at 25 °C for 6 h.
h. The substrates were taken in MeOH (70 mL) and stirred at 25 °C for 6 h.

Comparisons of these results indicate that acetone is best solvent for the resolution of the aminonaohthol **17**. Ethanol gave moderate ee and other solvents gave

poor results. It was also observed that increasing the reaction time from one to six hours gave better results (Table 1, entries 1-2) and there was no significant effect on the ees of the samples obtained when the reaction was carried out for more than 6 h (Table 1, entries 2-4).

The resolution mainly depends on the solubility of the complexes as the diastereomers have different solubilities. Therefore, we have examined the effect of the volume of solvent in the resolution of aminonnaphthol **17** using acetone as solvent (Table 2).

Table 2. Effect of amount of the solvent on the resolution of aminonaphthol 17[a]

S. No.	Acetone	Chiral aminonaphthol **17** obtained			
		Precipitate		Filtrate	
	(mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	10	15 (*S*)	55	12 (*R*)	36
2[a]	20	20 (*S*)	50	18 (*R*)	40
3[a]	30	35 (*S*)	48	32 (*R*)	45
4[a]	40	50 (*S*)	40	40 (*R*)	50
5[a]	50	75 (*S*)	42	55 (*R*)	52
6[a]	60	90 (*S*)	42	68 (*R*)	53
7[a]	70	98 (*S*)	40	75 (*R*)	55

a. Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol **17** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in acetone and stirred at 25 °C for 6 h.

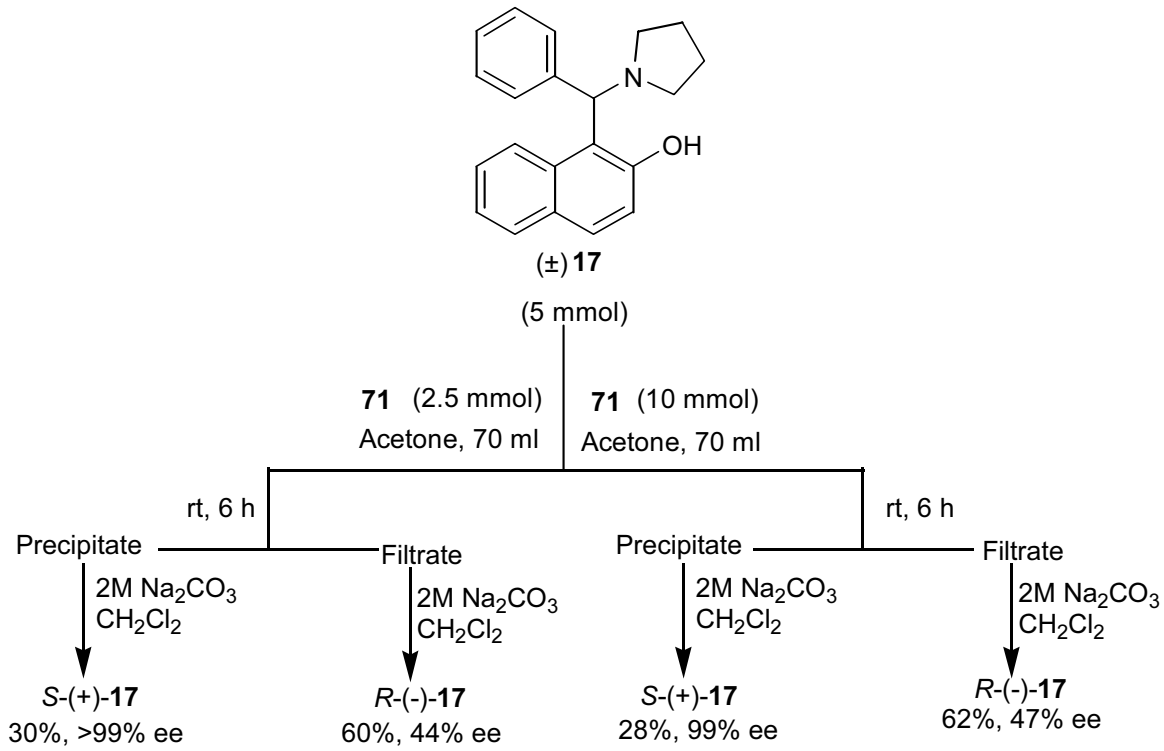
b. All ee values reported here are based on reported maximum[46] $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)-**17** and $[\alpha]_D^{25}$ = -179.0 (*C* 1.30, $CHCl_3$) for (*R*)-**17.**

c. The yields are of the isolated products, based on the total amount of the starting nracemic mixture **17** used.

As the volume of the solvent increased, the ee of the product increased, but the yield decreased as expected (Table 2 entries 1-7). Optimum results were obtained when aminonaphthol **17** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) were dissolved in 70 mL of acetone and stirred at rt for 6 h. From the precipitate fraction, almost pure enantiomeric sample of *S*-(+)-**17** was obtained and *R*-(-)-**17** was obtained in moderate ee (up to 75%) from the filtrate fraction.

To determine the optimum amount of the chiral resolving agent required for the resolution process, we have studied the effect of concentration of *L*-(+)-tartaric acid **71** (Scheme 40).

Scheme 40



It is clear that irrespective of the ratio of aminonaphthol **17** and *L*-(+)-tartaric acid **71** (1:2 or 2:1), always enantiomerically pure sample of *S*-(+)-**17** obtained from precipitate fraction and *R*-(-)-**17** obtained in 44-47% ee from the filtrate fraction.

We have then studied the resolution of other aminonaphthols **2**, **11**, **12** and **18**. Recently, Cardellicchio *et al*.[29] reported the resolution of aminonaphthol **2** using *L*-(+)-tartaric acid and ethanol as solvent. This procedure is somewhat tedious. We have observed that this reaction can be readily carried out using acetone. The use of aminonaphthol **2** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in 60 mL of solvent gave optimum results (Table 3).

Table 3. Resolution of Betti base 2 using *L*-(+)-tartaric acid[a]

S. No.	Ratio of **2:71**	Acetone	Betti base **2** obtained from			
			Precipitate		Filtrate	
		(mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	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 **2** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in acetone and stirred at 25 °C.
b. All ee values reported here are based on reported maximum[29] $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2** and $[\alpha]_D^{25}$ = -58.9 (*C* 5, benzene) for (*R*)-**2.** These maximum ees were further confirmed by HPLC using chiral column, chiralcel-OD.
c. The yields are of the isolated products, based on the total amount of the starting racemic mixture **2** used.
d. Racemic Betti base **2** (5 mmol) and *L*-(+)-tartaric acid **71** (10 mmol) in 60 mL of the acetone and stirred at 25 °C for 6 h.
e. Racemic Betti base **2** (5 mmol) and *L*-(+)-tartaric acid **71** (2.5 mmol) in 60 mL of the acetone and stirred at 25 °C for 6 h.

Similarly, we have also examined the resolution of aminonaphthol **12.** In this case also, the use of *L*-(+)-tartaric acid **71** (5 mmol), acetone (60 mL) for 5 mmol of aminonaphthol **12** gave optimum results (Table 4).

Table 4. Resolution of aminonaphthol 12 using *L*-(+)-tartaric acid[a]

S. No.	Ratio of **12:71**	Acetone (mL)	Aminonaphthol **12** obtained from			
			Precipitate		Filtrate	
			% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	1:1	10	18 (*S*)	52	15 (*R*)	40
2[a]	1:1	30	50 (*S*)	48	42 (*R*)	45
3[a]	1:1	50	85 (*S*)	46	75 (*R*)	47
4[a]	1:1	60	≥ 99 (*S*)	40	85 (*R*)	47
5[d]	1:2	60	≥ 99 (*S*)	28	45 (*R*)	60
6[e]	2:1	60	≥ 99 (*S*)	35	50 (*R*)	58

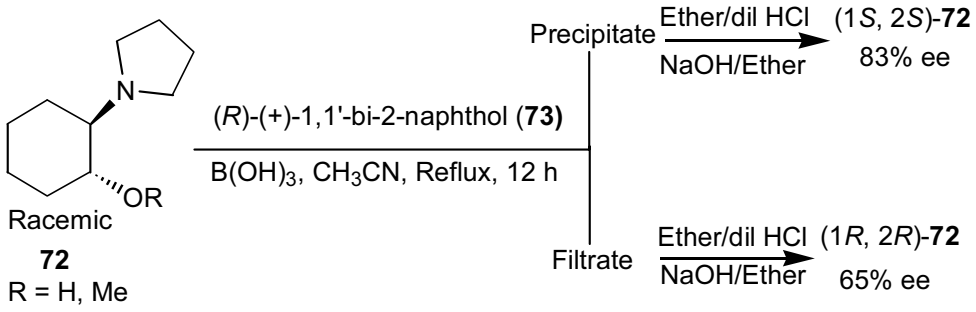
a. Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol **12** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in acetone and stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum[29] $[\alpha]_D^{25}$ = +238 (*C* 0.5, EtOH) for (*S*)**-2** and $[\alpha]_D^{25}$ = -238 (*C* 0.5, EtOH) for (*R*)-**2.** These maximum ees were further confirmed by HPLC using chiral column, chiralcel-OD.
c. The yields are of the isolated products, based on the total amount of the starting racemic mixture **12** used.
d. Racemic aminonaphthol **12** (5 mmol) and *L*-(+)-tartaric acid **71** (10 mmol) in 60 mL of the acetone and stirred at 25 °C for 6 h.
e. Racemic aminonaphthol **12** (5 mmol) and *L*-(+)-tartaric acid **71** (2.5 mmol) in 60 mL of the acetone and stirred at 25 °C for 6 h.

Cardellicchio *et al*.[30] reported the resolution of aminonaphthol **11** using *L*-(+)-tartaric acid in acetone solvent. Only the corresponding *R*-(-)-isomer from precipitate fraction was isolated with good ee and 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. For example, the *trans*-(±)-2-(pyrrolidinyl)cyclohexanol and its methyl ether

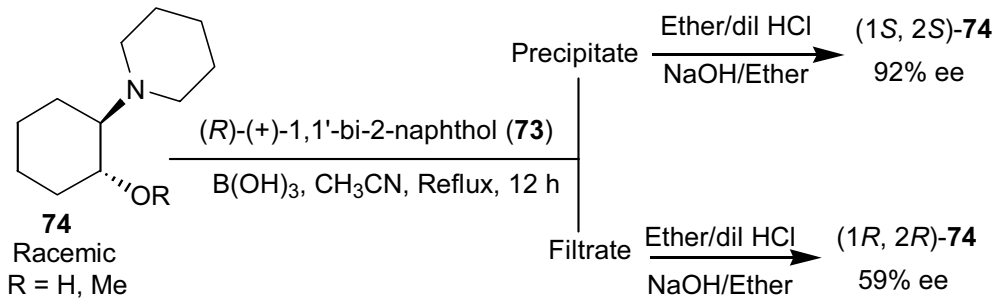
72 were resolved using chiral 1,1'-bi-2-naphthol and $B(OH)_3$ in THF or CH_3CN (Scheme 41).[68]

Scheme 41



The *trans*-(±)-2-(piperidinyl)cyclohexanol and its methyl ether **74** were also resolved using chiral 1,1'-bi-2-naphthol and $B(OH)_3$ in THF or CH_3CN (Scheme 42).

Scheme 42



Accordingly, we have examined the resolution of aminonaphthol **11** through preparation of the corresponding diastereomeric borate complexes using chiral 1,1'-bi-2-naphthol **73** and boric acid in CH_3CN at rt (Scheme 43). The (*R*)-(-)- and (*S*)-(+)-aminonaphthol **11** were obtained in almost pure forms under these conditions. For example, when the (*R*)-(+)-1,1'-bi-2-naphthol **73**, boric acid and aminonaphthol **11** were stirred in CH_3CN for 6 h at room temperature, the (*R*)-(-)-aminonaphthol **11** was obtained with 99% ee (40% yield) from the precipitate fraction (Scheme 43). The

filtrate fraction gave (*S*)-(+)-aminonaphthol in 90% ee (43% yield) after workup (Table 5, entry 1).

Scheme 43

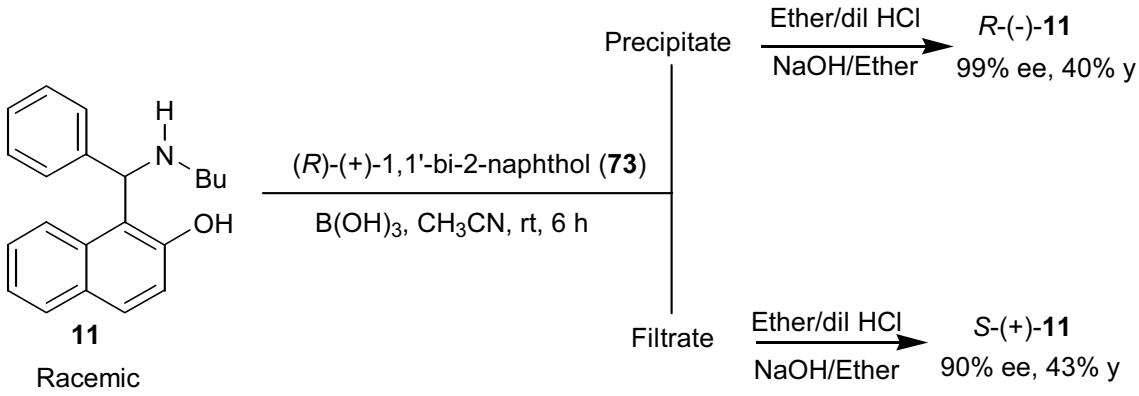


Table 5. Resolution of racemic aminonaphthol 11 using (*R*)-(+)-1,1'-bi-2-naphthol and boric acid

S. No.	Substrate **11** (% ee)	Solvent	Aminonaphthol **11** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(50 mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	**11**, 00	CH_3CN	99 (*R*)	40	90 (*S*)	43
2[d]	**11**, 00	CH_3CN	87 (*R*)	35	45 (*S*)	50
3[e]	(*S*)-**11**, 90	CH_3CN	99 (*S*)	75	10 (*S*)	08
4[e]	(*S*)-**11**, 45	CH_3CN	99 (*S*)	35	25 (*S*)	48

a. Unless otherwise mentioned all the reactions were performed using *R*-(+)-BINOL **73** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **11** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum[30] $[\alpha]_D^{25}$ = -212 (*C* 0.50, EtOH) for (*R*)-**11** and $[\alpha]_D^{25}$ = +210 (*C* 0.35, EtOH) for (*S*)-**11.** These maximum ees were further confirmed by HPLC using chiral column, chiralcel-OD.

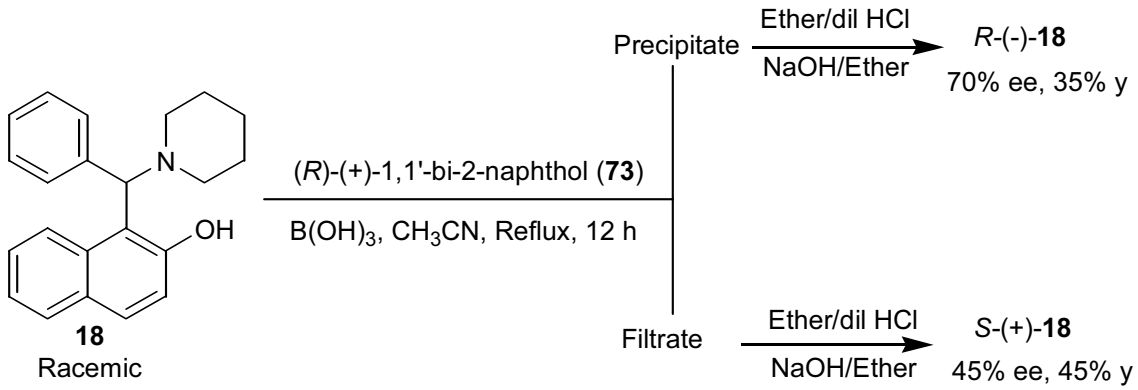
c. The yields are of the isolated products, based on the total amount of the starting racemic mixture **11** used.

d. *R*-(+)-BINOL **73** (10 mmol), boric acid (5 mmol) and racemic aminonaphthol **11** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.

e. *R*-(+)-BINOL **73** (5 mmol), boric acid (5 mmol) and non-racemic aminonaphthol **11** (2.5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.

The resolution of aminonaphthol **18** has been reported by using camphorsulfonic acid in ethyl acetate solvent.[69] However, the procedure involves 8-10 crystallizations to obtain the pure enantiomers of aminonaphthol **18**. Hence, we have carried out the resolution of aminonaphthol **18**, through preparation of diastereomeric borate complexes using the (*R*)-(+)-1,1'-bi-2-naphthol **73** and boric acid in CH_3CN at room temperature as aminonaphthol **11**. After workup, the aminonaphthol **18** samples obtained from both precipitate and filtrate fractions were found to be racemic. We have then carried out this reaction under refluxing conditions in the same solvent (Scheme 44). Optimum results were obtained when racemic aminonaphthol **18**, (*R*)-(+)-1,1'-bi-2-naphthol **73**, 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 6.

Scheme 44



The partially resolved samples of aminonaphthol **18** were readily enriched to >99% ee in CH_3CN following the same procedure (Table 6, entries 4 and 5)

Table 6. Resolution of racemic aminonaphthol 18 using (*R*)-(+)-1,1'-bi-2-naphthol and boric acid[a]

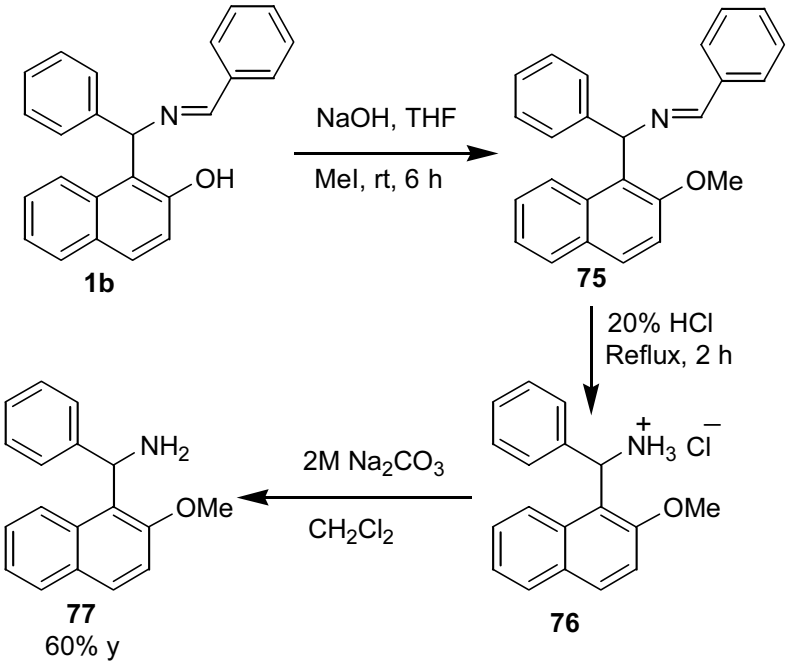
S. No.	Substrate **18** (% ee)	Solvent	Aminonaphthol **18** obtained from			
			Precipitate		Filtrate	
	5 mmol	(50 mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[d]	**18**, 00	CH_3CN	0	40	0	45
2[a]	**18**, 00	CH_3CN	70 (*R*)	35	45 (*S*)	45
3[e]	**18**, 00	CH_3CN	40 (*R*)	40	35 (*S*)	42
4[f]	(*R*)-**18**, 70	CH_3CN	99 (*R*)	60	20 (*R*)	25
5[f]	(*S*)-**18**, 45	CH_3CN	99 (*S*)	30	30 (*S*)	50

a. Unless otherwise mentioned all the reactions were performed using *R*-(+)-BINOL **73** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **18** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 h.
b. All ee values reported here are based on reported maximum[46] $[\alpha]_D^{25}$ = -193.5 (*C* 1.20, $CHCl_3$) for (*R*)-**18** and $[\alpha]_D^{25}$ = +193.8 (*C* 1.20, $CHCl_3$) for (*S*)-**18**. These maximum ees were further confirmed by HPLC using chiral column, chiralcel-OD.
c. The yields are of the isolated products, based on the total amount of the starting racemic mixture **18** used.
d. *R*-(+)-BINOL **73** (5 mmol), boric acid (5 mmol) and racemic aminonaphthol **18** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.
e. *R*-(+)-BINOL **73** (10 mmol), boric acid (5 mmol) and racemic aminonaphthol **18** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 h.
f. *R*-(+)-BINOL **73** (5 mmol), boric acid (5 mmol) and non-racemic aminonaphthol **18** (5 mmol) in 50 mL of the CH_3CN solvent and stirred under refluxing conditions for 12 h.

2. 2. 2. 1 Synthesis and resolution of *O*-methyl derivative of aminonaphthol 2

The seemingly simple *O*-alkylation of Betti base **2** is somewhat complicated and the reported procedure involves the methylation of *N*-benzylidine-1-(α-aminobenzyl)-2-naphthol **1b** using NaOH/MeI followed by hydrolysis of the intermediate **76** (Scheme 45).[29]

Scheme 45



Ray and coworkers[69] reported the resolution of *O*-methyl Betti base **77** using malic acid. However, malic acid is relatively more expensive. We have observed that *O*-methylated Betti base **77** can be readily resolved using inexpensive dibenzoyl-*L*-tartaric acid **78** as resolving agent in acetone (Scheme 46). After workup, a sample of *S*-(+)-**77** obtained from precipitate fraction and the *R*-(-)-**77** was obtained from the filtrate fraction in 10-60% ee (Table 7).

Scheme 46

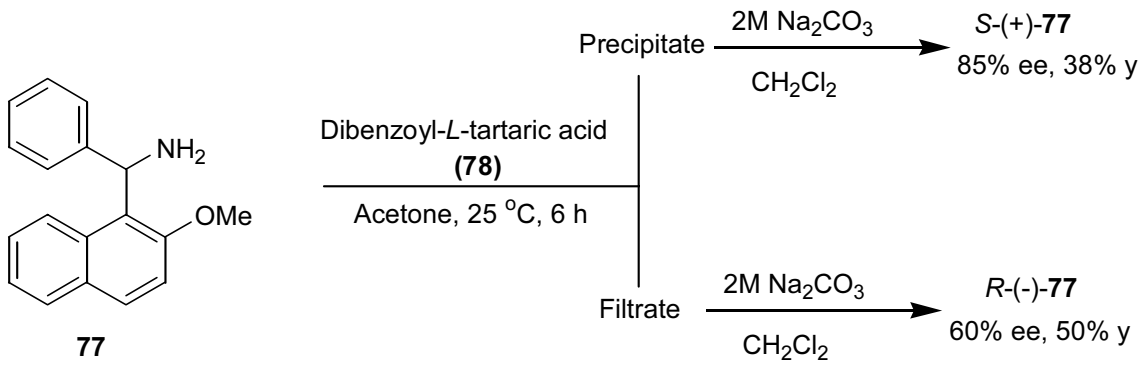


Table 7. Resolution of racemic *O*-methyl Betti base 77 using dibenzoyl-*L*-tartaric acid[a]

S. No.	Substrate **77** (% ee)	Acetone	Chiral **77** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mL)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	**77**, 00	20	05 (*S*)	60	10 (*R*)	30
2	**77**, 00	40	22 (*S*)	45	25 (*R*)	43
3	**77**, 00	60	85 (*S*)	38	60 (*R*)	50
4[d]	(*S*)-**77,** 85	60	≥ 99 (*S*)	80	15 (*S*)	12
5[d]	(*R*)-**77,** 60	60	≥ 99 (*R*)	50	25 (*R*)	38

a. Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol derivative **77** (5 mmol) and dibenzoyl-*L*-tartaric acid **78** (5 mmol) in acetone and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum[70] $[\alpha]_D^{25}$ = +196 (*C* 1.6, $CHCl_3$) for (*S*)-**77** and $[\alpha]_D^{25}$ = -196 (*C* 1.6, $CHCl_3$) for (*R*)-**77.**

c. The yields are of the isolated products, based on the total amount of the starting racemic mixture **77** used.

d. Non-racemic aminonaphthol **77** (5 mmol) and dibenzoyl-*L*-tartaric acid **77** (5 mmol) in 60 mL of the acetone and stirred at 25 °C for 6 h..

2. 2. 2. 2 Purification of the non-racemic aminonaphthols using *L*-(+)-tartaric acid

The non-racemic (partially resolved or scalemic) aminonaphthols, obtained by the partial resolution using *L*-(+)-tartaric acid (Tables 1, 3 and 4), can be further enriched using *L*-(+)-tartaric acid. A sample of ≥ 99% ee was obtained from the precipitate in a single step from non-racemic aminonaphthol **17** (75% ee) enriched in (*R*)-isomer. Similar results were obtained in the case of non-racemic aminonaphthols **2** and **12**. The results are summarized in Table 8.

Table 8. Enrichment of enantiomeric excess of the non-racemic aminonaphthols using *L*-(+)-tartaric acid[a]

S. No.	Substrates (% ee) (5 mmol)	Solvent	Aminonaphthols obtained from			
			Precipitate		Filtrate	
			% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*)-**17**, 75	Acetone	≥ 99 (*R*)	70	18 (*R*)	20
2	(*S*)-**17**, 60	Acetone	≥ 99 (*S*)	56	20 (*S*)	34
3	(*S*)-**2,** 50	Acetone	≥ 99 (*S*)	40	22 (*S*)	50
4	(*R*)-**2**, 80	Acetone	≥ 99 (*R*)	75	20 (*R*)	15
5	(*R*)-**12,** 85	Acetone	≥ 99 (*R*)	80	14 (*R*)	12
6	(*S*)-**12**, 75	Acetone	≥ 99 (*S*)	65	30 (*S*)	30

a. Unless otherwise mentioned all the reactions were performed using non-racemic aminonaphthols **17** or **2** or **12** (5 mmol) and *L*-(+)-tartaric acid **71** (5 mmol) in acetone and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)-**17,**[46] $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2**[29] and $[\alpha]_D^{25}$ = +238 (*C* 0.5, ethanol) for (*S*)-**12.**[29]

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

2. 2. 3 Enhancement of enantiomeric purity of non-racemic aminonaphthols and their derivatives using achiral dicarboxylic acids

Purification of non-racemic amino alcohols[71] can be easily achieved through preparation of hydrogen-bonded homochiral or heterochiral aggregates using achiral dicarboxylic acids as described in Chapter 1. We have undertaken efforts to examine the purification of non-racemic aminonaphthols using achiral dicarboxylic acids such as oxalic, fumaric, maleic and terephthalic acids. The results are discussed in this section.

2. 2. 3. 1 Enhancement of enantiomeric purity of non-racemic aminonaphthols using oxalic acid

Initially, we have carried out the purification of aminonaphthol **17** using oxalic acid in acetone solvent. The precipitate forms within 5-10 minutes. After workup, it was found that the precipitate fraction contained the enriched isomer, leaving behind the isomer with low ee in the solution (Scheme 47).[67] For example, when a sample of 50% ee was treated with oxalic acid, a sample of aminonaphthol **17** with 99% ee was isolated from the precipitate fraction leaving a sample with 9% ee in the filtrate fraction (Table 9, entry 6).

Scheme 47

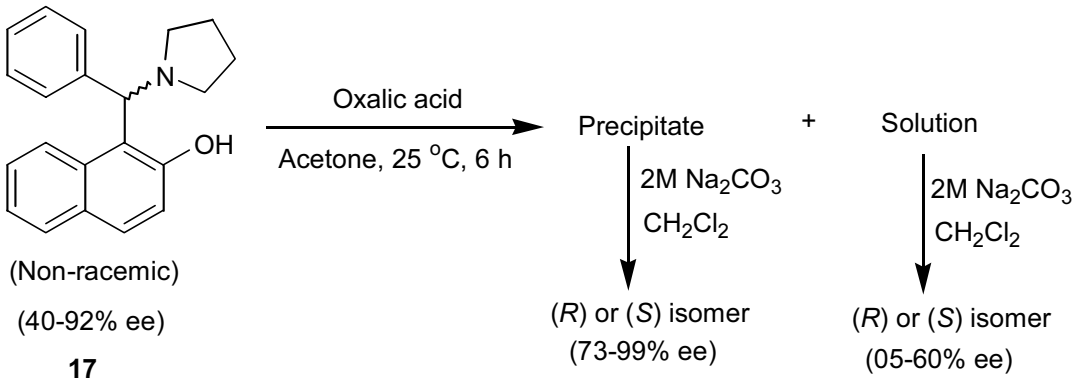


Table 9. Enhancement of enantiomeric purity of non-racemic aminonaphthol 17 using oxalic acid[a]

S. No.	Substrate (**17**) (% ee)	Oxalic acid	Aminonaphthol **17** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	40 (*S*)	2.00	73 (*S*)	40	20 (*S*)	50
2	50 (*S*)	2.50	96 (*S*)	52	05 (*S*)	40
3	65 (*S*)	3.25	≥99 (*S*)	60	10 (*S*)	30
4	90 (*S*)	4.50	≥99 (*S*)	87	56 (*S*)	09
5	45 (*R*)	2.25	80 (*R*)	35	28 (*R*)	48
6	50 (*R*)	2.50	≥99 (*R*)	42	09 (*R*)	46
7	75 (*R*)	3.75	≥99 (*R*)	67	15 (*R*)	25
8	92 (*R*)	4.60	≥99 (*R*)	85	60 (*R*)	05

a. All the reactions were carried out using non-racemic aminonaphthol **17** (5 mmol) and oxalic acid in acetone (60 mL) and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum[46] $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)**-17.** 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 **17** used.

The complex of non-racemic aminonaphthol **17** and oxalic acid (Table 9, entry 6) was crystallized in CH_3CN solvent (from precipitate fraction) to obtain the crystals suitable for single crystal X-ray analysis. The ORTEP diagram showed that it is a 2:2 complex of aminonaphthol and oxalic acid. It is a salt like structure in which one molecule of the acid exists as such and other molecule was fully deprotonated. To compensate this negative charge, both the aminonaphthols exists as ammonium cations (Figure 1).

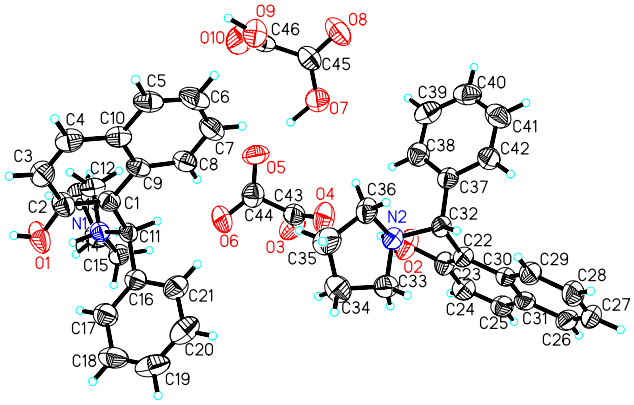


Figure 1. ORTEP diagram of the aminonaphthol (*R*)-17 and oxalic acid complex (Table 9, entry 6)

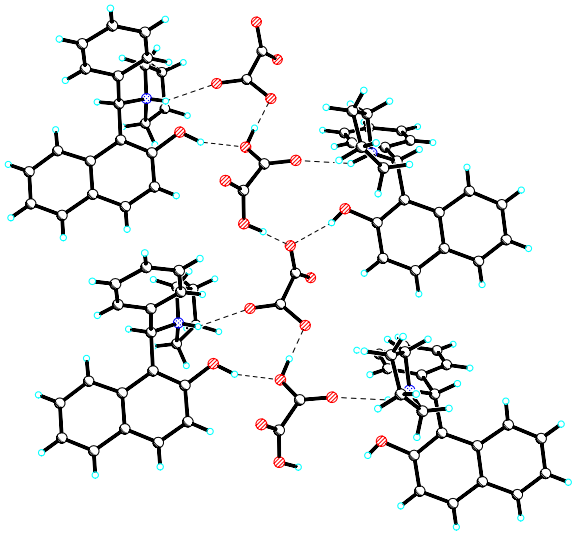


Figure 2. Packing diagram of the aminonaphthol (*R*)-2 and oxalic acid complex (Table 9, entry 6)

The packing diagram showed layers of intermolecularly hydrogen bonded mono-anion of the acid alternating with layers of intermolecularly hydrogen bonded ammonium cation of the aminonaphthol moieties through N–H···O and O–H···O interactions (Figure 2). The alternate layers of aminonaphthols were found to be

homochiral to each other. It is clear that the enrichment of aminonaphthol **17** is due to predominant precipitation of the homochiral aggregates with oxalic acid.

Table 10. X-ray data collection and structure refinement for non-racemic aminonaphthol 17 with oxalic acid

Empirical formula	$C_{46}H_{46}N_2O_{10}$
Formula weight	786.85
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.0792(18) Å, α = 90˚
	b = 12.572(3) Å, β = 93.60(3)˚
	c = 17.111(3) Å, γ = 90˚
Volume	1947.3(7) Å ^{3}
Z	2
Calculated density	1.341 mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	832.0
θ Range for data collection	1.19 to 26.97˚
Limiting indices	0≤h≤11, 0≤k≤16, -21≤l≤21
Reflections collected/unique	4433 / 3475 [R(int) = 0.0000]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	3475 / 1 / 547
Goodness-of-fit on F^2	1.035
Final *R* indices [I> 2σ (I)]	R_1 = 0.0493, wR_2 = 0.1133
R indices (all data)	R_1 = 0.0693, wR_2 = 0.1281
Largest diff. peak and hole	0.513 and -0.211 eÅ^{-3}

We have also carried out the single crystal X-ray analysis of the complex obtained using racemic aminonaphthol **17** and oxalic acid, which was crystallized in methanol solvent. The ORTEP (Figure 3) and packing diagrams (Figure 4) are similar to that of the non-racemic complex of aminonaphthol **17**. In this case, the alternative layers were found to be heterochiral to each other.

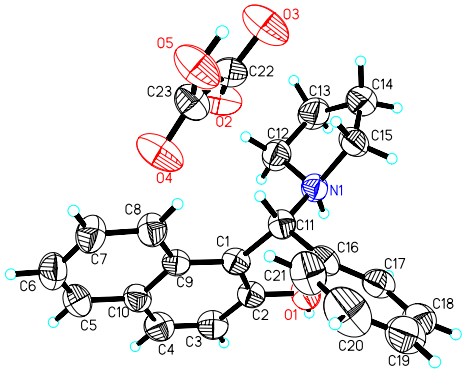


Figure 3. ORTEP diagram of the racemic aminonaphthol 17 with oxalic acid complex

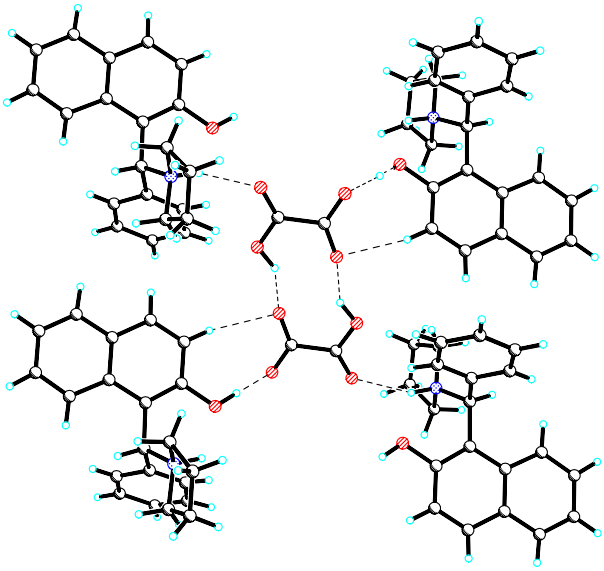


Figure 4. Packing diagram of the racemic aminonaphthol 17 with oxalic acid complex

Table 11. X-ray data collection and structure refinement for racemic amino-naphthol 17 with oxalic acid

Empirical formula	$C_{23}H_{23}NO_5$
Formula weight	393.44
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.3363(19) Å, α = 90˚
	b = 12.6(10) Å, β = 90.6(2)˚
	c = 16.750(5) Å, γ = 90˚
Volume	1972(156) Å ^{3}
Z	4
Calculated density	1.330 mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	832.0
θ Range for data collection	2.02 to 27.49 ˚
Limiting indices	0≤h≤12, 0≤k≤16, -21≤l≤21
Reflections collected/unique	4515 / 2142 [R(int) = 0.0000]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	2142 / 0 / 266
Goodness-of-fit on F^2	1.049
Final *R* indices [I> 2σ (I)]	R_1 = 0.0654, wR_2 = 0.1721
R indices (all data)	R_1 = 0.1614, wR_2 = 0.2587
Largest diff. peak and hole	0.31 and -0.29 eÅ^{-3}

Similarly, we have examined the purification of non-racemic samples of Betti base **2** using oxalic acid (Scheme 48). In this case also, enhancement of ee was observed in the precipitate fraction and the results are summarized in Table 12.

Scheme 48

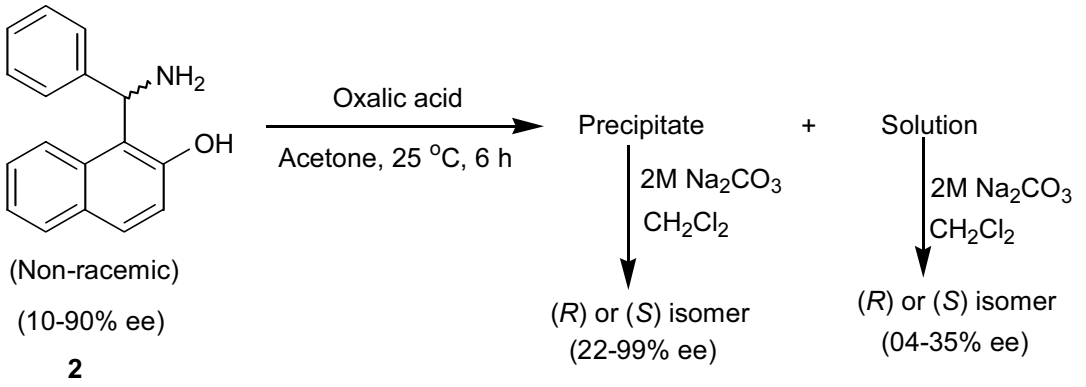


Table 12. Enhancement of enantiomeric excess of non-racemic Betti base 2 using oxalic acid[a]

S. No.	Substrate **2** (% ee)	Oxalic acid	Aminonaphthol **2** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[b]
1	10 (*S*)	0.50	22 (*S*)	15	04 (*S*)	60
2	22 (*S*)	1.10	46 (*S*)	25	08 (*S*)	48
3	46 (*S*)	2.30	85 (*S*)	35	15 (*S*)	40
4	50 (*S*)	2.50	90 (*S*)	40	18 (*S*)	34
5	85 (*S*)	4.25	≥99 (*S*)	65	30 (*S*)	08
6	90 (*S*)	4.50	≥99 (*S*)	70	35 (*S*)	06
7	45 (*R*)	2.25	80 (*R*)	36	12 (*R*)	40
8	80 (*R*)	4.00	≥99 (*R*)	60	25 (*R*)	12

a. All the reactions were carried out using non-racemic aminonaphthol **2** (5 mmol) and oxalic acid in acetone (60 mL) and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum[29] $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2**.

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

The complex obtained from non-racemic aminonaphthol **2** (Table 12, entry 8) with oxalic acid was crystallized in MeOH solvent. Single crystal X-ray analysis revealed that the complex consists of 1 equiv. of aminonaphthol as ammonium cation and half equiv. of oxalic acid as anion along with 1 equiv. of MeOH as solvent molecule in ORTEP diagram (Figure 5).

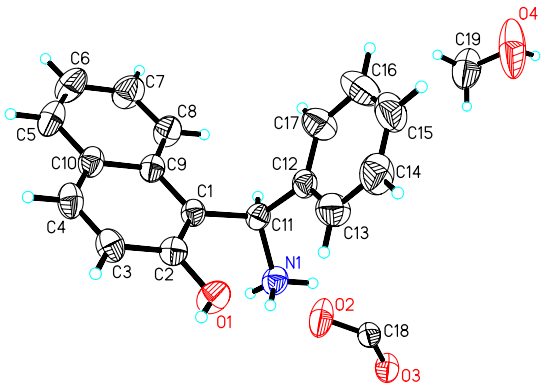


Figure 5. ORTEP diagram of the aminonaphthol (*R*)-2 and oxalic acid complex (Table 12, entry 8)

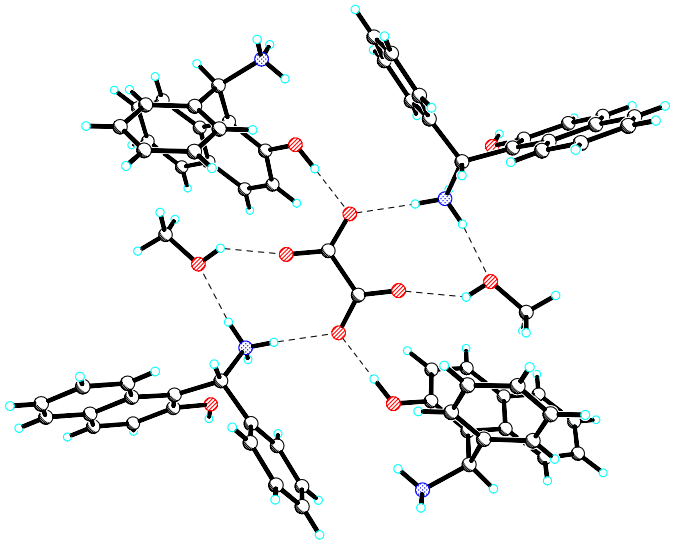


Figure 6. Packing diagram of the aminonaphthol (*R*)-2 and oxalic acid complex (Table 12, entry 8)

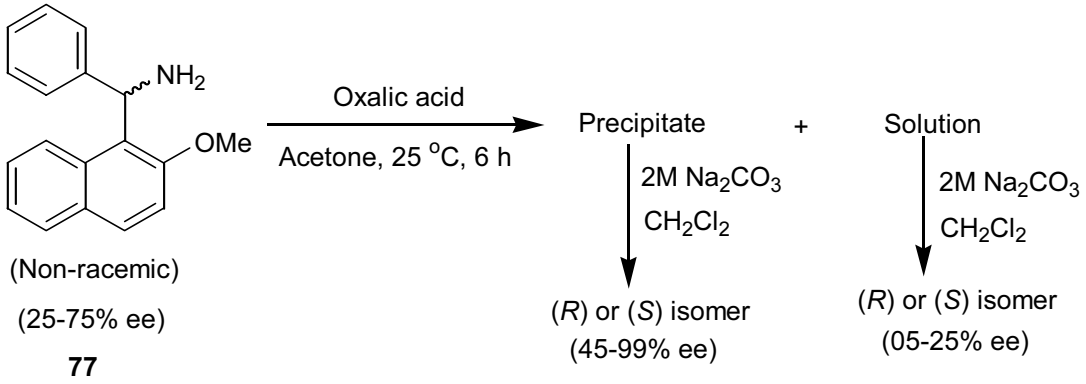
The packing diagram showed that the anion of the oxalic acid forms 3D network with the cation of the aminonaphthol **2** through N-H···O and O-H···O hydrogen bonding interactions. In this network, all the aminonaphthol moieties were found to be homochiral to each other (Figure 6).

Table 13. X-ray data collection and structure refinement for non-racemic amino-naphthol 2 with oxalic acid

Empirical formula	$C_{19}H_{20}NO_4$
Formula weight	326.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	$P4_32_12$
Unit cell dimensions	a = 10.1090(3) Å, α = 90°
	b = 10.1090(3) Å, β = 90°
	c = 32.3752(16) Å, γ = 90°
Volume	3308.5(2) $Å^3$
Z	8
Calculated density	1.310 mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	1384.0
θ Range for data collection	2.11 to 28.30°
Limiting indices	-12≤h≤7, -12≤k≤13, -42≤l≤43
Reflections collected/unique	21164 / 4013 [R(int) = 0.0225]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	4013 / 0 / 241
Goodness-of-fit on F^2	1.035
Final *R* indices [I> 2σ (I)]	R_1 = 0.0437, wR_2 = 0.1139
R indices (all data)	R_1 = 0.0490, wR_2 = 0.1181
Largest diff. peak and hole	0.25 and -0.24 $eÅ^{-3}$

However, the yields of the sample obtained from the precipitate and filtrate fractions were poor. To overcome this problem, we have converted the aminonaphthol **2** into *O*-methyl derivative of aminonaphthol **77** and carried out the purification of these non-racemic samples using oxalic acid (Scheme 49). In this case also sample obtained from precipitate fraction had higher ee compared to that obtained from the filtrate fraction. The results are summarized in Table 14.

Scheme 49



In the similar way, we have examined the purification of the non-racemic aminonaphthol **12**. It failed to form a precipitate in the solvents such as acetone, THF, CH_3CN, CH_2Cl_2 and MeOH. We have then converted this non-racemic aminonaphthol **12** into its *O*-methylated derivative **10** (Scheme 50).

Scheme 50

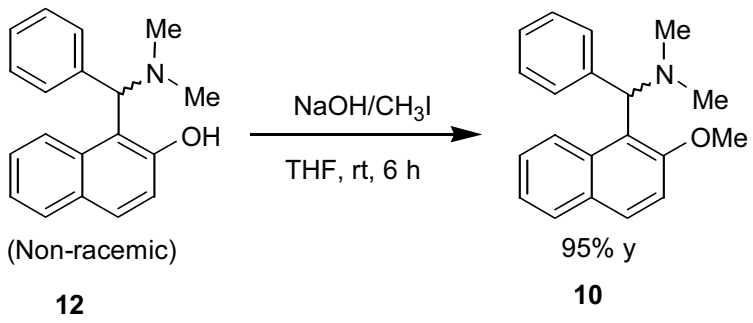


Table 14. Enhancement of enantiomeric excess of *O*-methylated non-racemic aminonaphthol 77 using oxalic acid[a]

S. No.	Substrate **77** (% ee)	Oxalic acid	Aminonaphthol **77** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	25 (*S*)	1.25	45 (*S*)	40	05 (*S*)	50
2	45 (*S*)	2.10	65 (*S*)	50	15 (*S*)	42
3	50 (*S*)	2.50	70 (*S*)	60	18 (*S*)	35
4	65 (*S*)	3.25	90 (*S*)	62	22 (*S*)	30
5	70 (*S*)	3.50	≥99 (*S*)	65	25 (*S*)	28
6	25 (*R*)	1.25	50 (*R*)	38	08 (*R*)	55
7	50 (*R*)	2.50	75 (*R*)	50	20 (*R*)	42
8	75 (*R*)	3.75	≥99 (*R*)	65	25 (*R*)	30

a. All the reactions were carried out using non-racemic aminonaphthol derivative **77** (5 mmol), oxalic acid in acetone (60 mL) and stirred at 25 ^{o}C for 6 h.

b. All ee values reported here are based on reported maximum[70] $[\alpha]_D^{25}$ = +196 (*C* 1.6, $CHCl_3$) for *(S)*-**77.**

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

Then, we have examined the purification of these non-racemic samples using oxalic acid (Scheme 51). Fortunately, enhancement of ee was observed in the precipitate fraction. The results are summarized in Table 15.

Scheme 51

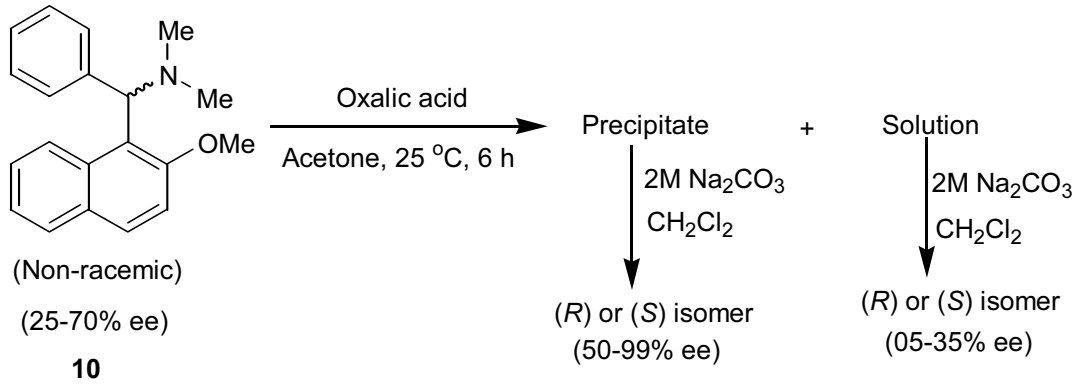


Table 15. Enhancement enantiomeric purity of *O*-methylated non-racemic aminonaphthol 10 using oxalic acid[a]

S. No.	Substrate **10** (% ee)	Oxalic acid	Aminonaphthol **10** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	25 (*S*)	1.25	50 (*S*)	40	08 (*S*)	55
2	50 (*S*)	2.50	90 (*S*)	45	20 (*S*)	48
3	90 (*S*)	4.50	≥99 (*S*)	82	35 (*S*)	10
4	20 (*R*)	1.00	38 (*R*)	32	05 (*R*)	60
5	38 (*R*)	1.90	70 (*R*)	44	15 (*R*)	50
6	70 (*R*)	3.50	≥99 (*R*)	64	25 (*R*)	30

a. All the reactions were carried out using non-racemic sample **10** (5 mmol) and oxalic acid in acetone (60 mL) and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum[29] $[\alpha]_D^{25}$ = -26.2 (*C* 1.1, $CHCl_3$) for (*S*)-**10.**

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

Crystals suitable for X-ray analysis were obtained by recrystallization of the complex of non-racemic aminonaphthol derivative **10** (Table 15, entry 3) with oxalic acid, from MeOH solvent. The ORTEP diagram consists of 1:1 ratio of sample of **10**

with oxalic acid in salt form (Figure 7). The packing diagram confirms that the homochiral aggregates are formed through N-H···O and O-H···O hydrogen bonding interactions of sample **10** with the acid (Figure 8).

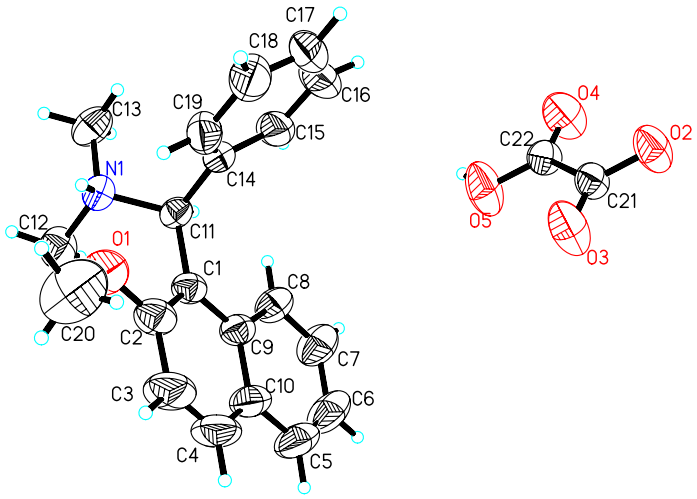


Figure 7. ORTEP diagram of the aminonaphthol derivative (*S*)-10 and oxalic acid complex (Table 15, entry 3)

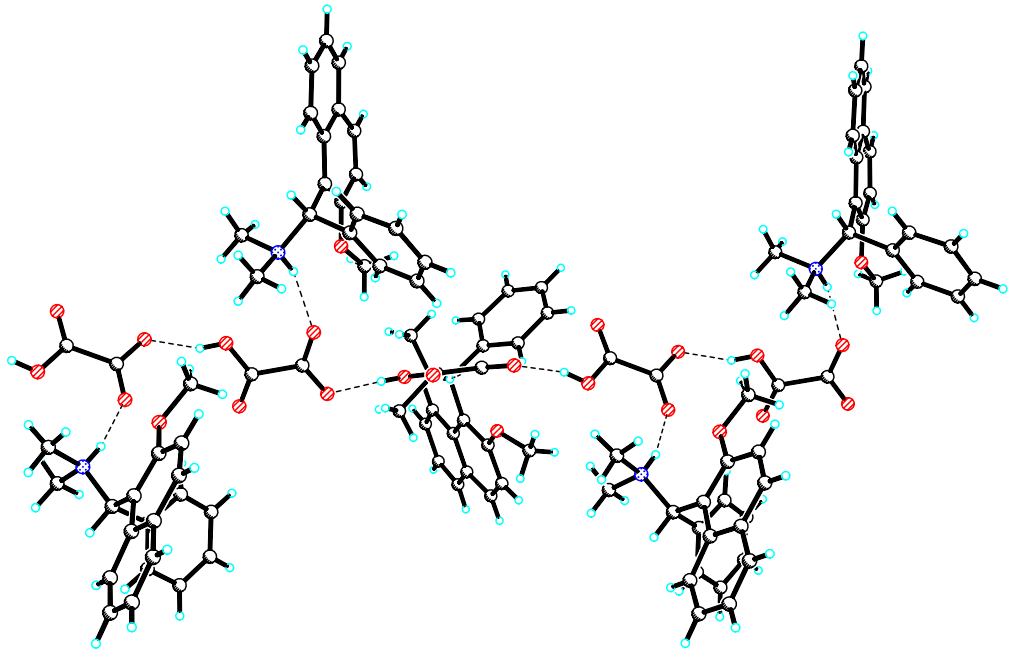


Figure 8. Packing diagram of the aminonaphthol derivative (*S*)-10 and oxalic acid complex (Table 15, entry 3)

Table 16. X-ray data collection and structure refinement for non-racemic amino-naphthol derivative 10 with oxalic acid

Empirical formula	$C_{22}H_{23}NO_5$
Formula weight	381.41
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Hexagonal
Space group	$P3_2$
Unit cell dimensions	a = 10.2239(3) Å, α = 90°
	b = 10.2239(3) Å, β = 90°
	c = 16.4790(11) Å, γ = 120°
Volume	1491.74(12) $Å^3$
Z	3
Calculated density	1.274 mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	606
θ Range for data collection	2.30 to 28.27°
Limiting indices	-13≤h≤13, -13≤k≤13, -21≤l≤21
Reflections collected/unique	11666 / 4505 [R(int) = 0.0312]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	4505 / 1 / 262
Goodness-of-fit on F^2	1.025
Final *R* indices [I> 2σ (I)]	R_1 = 0.0461, wR_2 = 0.1192
R indices (all data)	R_1 = 0.0517, wR_2 = 0.1239
Largest diff. peak and hole	0.17 and -0.23 $eÅ^{-3}$

2. 2. 3. 2 Enhancement of enantiomeric purity of non-racemic aminonaphthols and their derivatives using fumaric acid

We have also examined the use of fumaric acid for the purification of aminonaphthol **17** in acetone solvent. Interestingly, in this case, the sample obtained from the filtrate fraction had higher ees and the sample obtained from the precipitate fraction had lower ees (Scheme 52). Probably, this is due to precipitation of predominantly heterochiral aggregates in contrast to the results obtained using oxalic acid.

The non-racemic samples of Betti base **2** failed to give precipitation in acetone. Fortunately, precipitation was observed in dichloromethane solvent leading to enrichment of ee in the solution fraction. We have also observed that the non-racemic samples of derivatives of aminonaphthols such as **10** and **77** precipitate on reaction with fumaric acid in acetone solvent. In these cases also, enrichment was observed in the solution fraction. All these results are summarized in Table 17.

Scheme 52

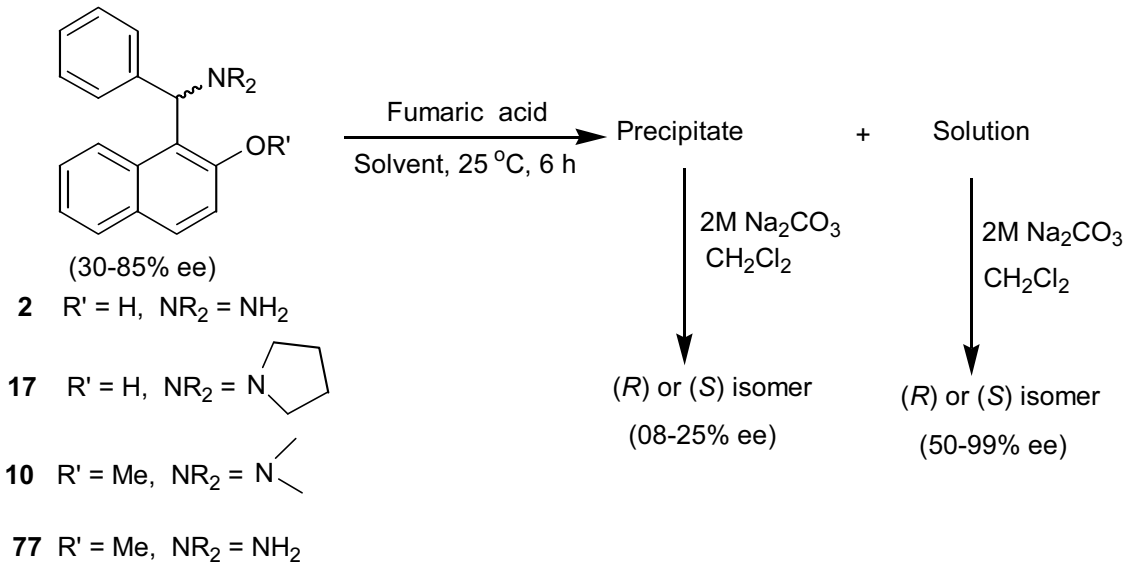


Table 17. Purification of non-racemic aminonaphthols and their derivatives using fumaric acid

S. No.	Substrates (% ee) (5 mmol)	Fumaric acid (mmol)	Aminonaphthols and its derivatives obtained from			
			Precipitate		Filtrate	
			% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*S*)-**2**, 45	2.25	15 (*S*)	40	78 (*S*)	35
2	(*S*)-**2**, 78	3.90	25 (*S*)	15	≥99 (*S*)	60
3	(*R*)-**2**, 30	1.50	10 (*R*)	50	50 (*R*)	25
4	(*S*)-**10**, 50	2.50	10 (*S*)	45	92 (*S*)	50
5	(*S*)-**10**, 75	3.75	20 (*S*)	25	≥99 (*S*)	70
6	(*R*)-**10**, 35	1.75	08 (*R*)	50	60 (*R*)	40
7	(*R*)-**17**, 30	1.50	12 (*R*)	40	50 (*R*)	52
8	(*R*)-**17**, 50	2.50	17 (*R*)	34	72 (*R*)	60
9	(*R*)-**17**, 72	3.60	20 (*R*)	25	≥99 (*R*)	65
10	(*R*)-**77**, 30	1.50	10 (*R*)	50	50 (*R*)	42
11	(*S*)-**77**, 60	3.00	20 (*S*)	32	85 (*S*)	61
12	(*S*)-**77**, 85	4.25	25 (*S*)	15	≥99 (*S*)	78

a. All the reactions were carried out using non-racemic aminonaphthols or derivatives (5 mmol) and fumaric acid in acetone (60 mL) and stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)-**17,**[46] $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2,**[29] $[\alpha]_D^{25}$ = -26.2 (*C* 1.1, $CHCl_3$) for (*S*)-**10**[29] and $[\alpha]_D^{25}$ = +196 (*C* 1.6, $CHCl_3$) for (*S*)-**77.**[70]

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

2. 2. 3. 3 Enhancement of enantiomeric purity of non-racemic aminonaphthols and their derivatives using maleic acid

We have also studied the purification of non-racemic samples of aminonaphthols **17** and **2** and the derivatives **10** and **77** using maleic acid (Scheme 53).

Scheme 53

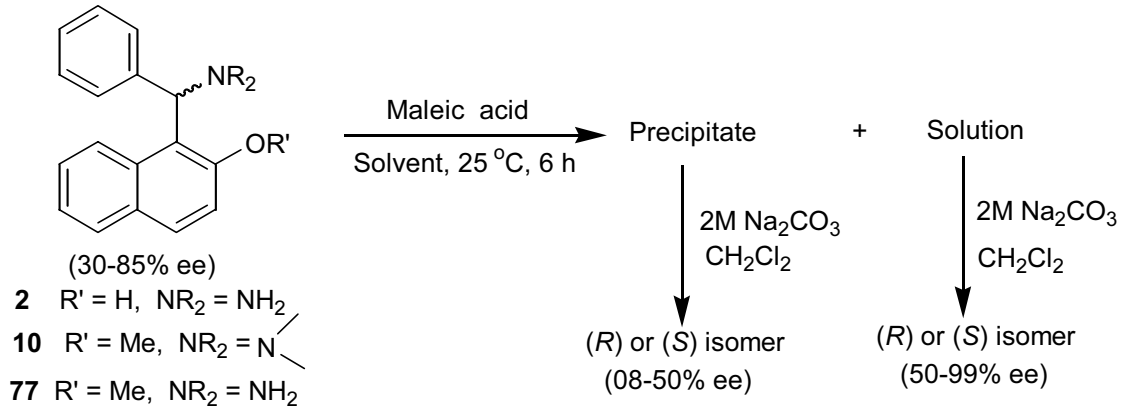


Table 18. Purification of non-racemic aminonaphthols and their derivatives using maleic acid[a]

S. No.	Substrates (% ee)	Maleic acid	Aminonaphthols and their derivatives obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	(*R*)-**2**, 30	1.50	08 (*R*)	47	50 (*R*)	24
2	(*R*)-**2**, 50	2.50	15 (*R*)	32	72 (*R*)	42
3	(*R*)-**2**, 72	3.60	22 (*R*)	15	≥99 (*R*)	60
4	(*S*)-**10**, 50	2.50	20 (*S*)	40	85 (*S*)	50
5	(*S*)-**10**, 85	4.25	50 (*S*)	15	≥99 (*S*)	78
6	(*R*)-**10**, 35	1.75	12 (*R*)	50	60 (*R*)	45
7	(*R*)-**10**, 60	3.00	25 (*R*)	32	99 (*R*)	55
8	(*R*)-**77**, 35	1.75	10 (*R*)	42	55 (*R*)	50
9	(*R*)-**77**, 55	2.75	15 (*R*)	35	80 (*R*)	60
10	(*R*)-**77**, 80	4.00	25 (*R*)	20	≥99 (*R*)	72

a. All the reactions were carried out using non-racemic aminonaphthols or derivatives (5 mmol) and maleic acid in acetone (60 mL) and stirred at 25 °C for 6 h

b. All ee values reported here are based on reported maximum $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2**,[29] $[\alpha]_D^{25}$ = -26.2 (*C* 1.1, $CHCl_3$) for (*S*)-**10**[29] and $[\alpha]_D^{25}$ = +196 (*C* 1.6, $CHCl_3$) for (*S*)-**77**.[70]

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

The samples **17** and **2** failed to give precipitate in acetone. Fortunately, the sample **2** gave enhancement in dichloromethane in the solution fraction. The samples **10** and **77** forms the precipitate in acetone and enrichment observed in the solution fraction. These results are summarized in Table 18.

2. 2. 3. 4 Enhancement of enantiomeric purity of non-racemic aminonaphthols and their derivatives using terephthalic acid

We have then examined the purification of non-racemic samples **2, 10, 17** and **77** using terephthalic acid (Scheme 54). In the case of sample **2,** enrichment was observed in the solution fraction using dichloromethane solvent and other samples gave enrichment in acetone solvent. The results are summarized in Table 19.

Scheme 54

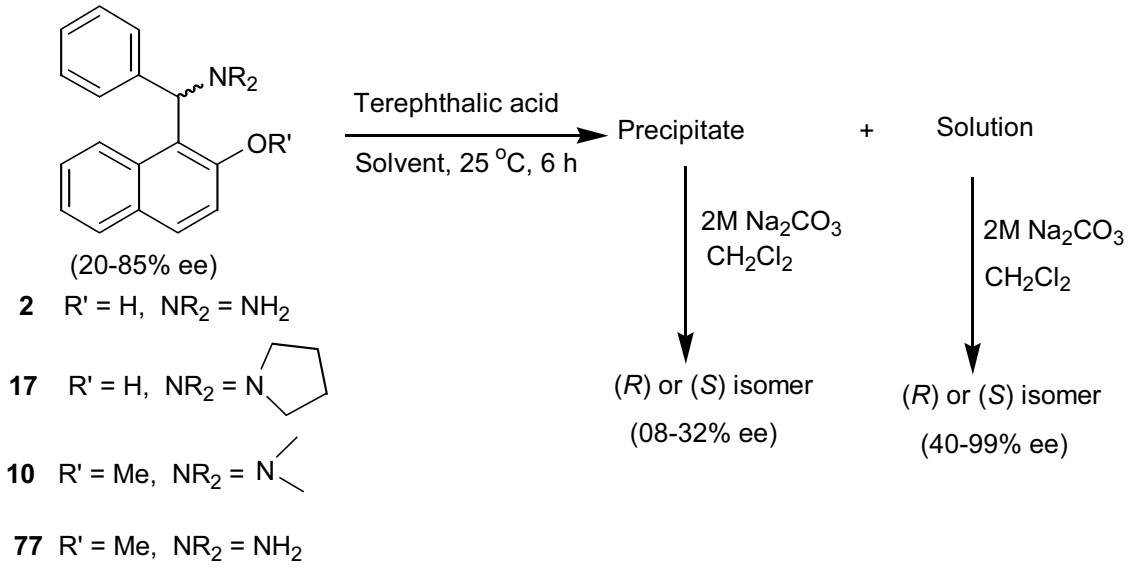


Table 19. Purification of non-racemic aminonaphthols and their derivatives using terephthalic acid

S. No.	Substrates (% ee) (5 mmol)	Terephthalic acid (mmol)	Aminonaphthols and their derivatives obtained from Precipitate % ee[b]/Conf.	Precipitate Yield(%)[c]	Filtrate % ee[b]/Conf.	Filtrate Yield(%)[c]
1	(*R*)-**2**, 30	1.50	10 (*R*)	43	58 (*R*)	32
2	(*R*)-**2**, 58	2.90	15 (*R*)	30	95 (*R*)	45
3	(*S*)-**2**, 25	1.25	08 (*S*)	50	50 (*S*)	24
4	(*S*)-**10**, 50	2.50	20 (*S*)	55	95 (*S*)	40
5	(*R*)-**10**, 40	1.50	15 (*R*)	60	80 (*R*)	30
6	(*R*)-**10**, 80	4.00	32 (*R*)	20	≥99 (*R*)	72
7	(*R*)-**17**, 50	2.50	12 (*R*)	30	70 (*R*)	60
8	(*R*)-**17**, 70	3.50	20 (*R*)	25	≥99 (*R*)	65
9	(*S*)-**17**, 20	1.00	08 (*S*)	60	40 (*S*)	30
10	(*R*)-**77**, 40	2.00	12 (*R*)	40	60 (*R*)	52
11	(*R*)-**77**, 60	3.00	20 (*R*)	32	85 (*R*)	60
12	(*R*)-**77**, 85	4.25	30 (*R*)	15	≥99 (*R*)	80

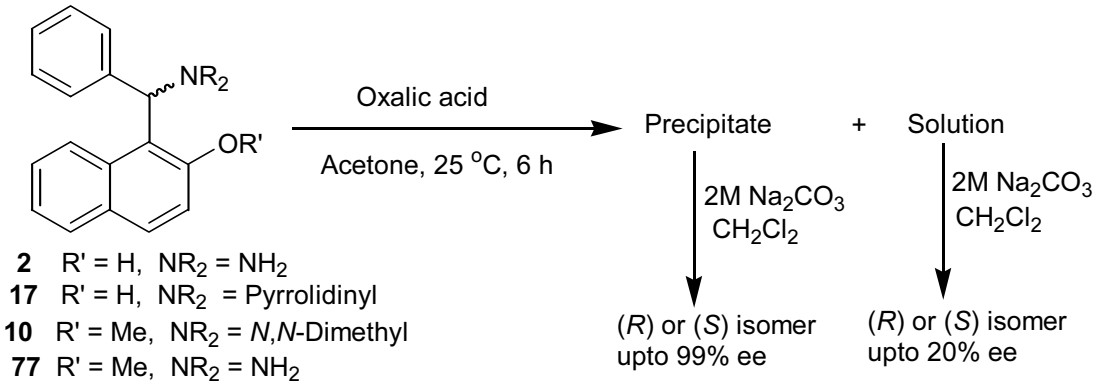
a. All the reactions were carried out using non-racemic aminonaphthols or derivatives (5 mmol) and terephthalic acid in acetone (60 mL) and stirred at 25 ^{o}C for 6 h

b. All ee values reported here are based on reported maximum $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$) for (*S*)-**17,**[46] $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene) for (*S*)-**2,**[29] $[\alpha]_D^{25}$ = -26.2 (*C* 1.1, $CHCl_3$) for (*S*)-**10**[29] and $[\alpha]_D^{25}$ = +196 (*C* 1.6, $CHCl_3$) for (*S*)-**77.**[70]

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

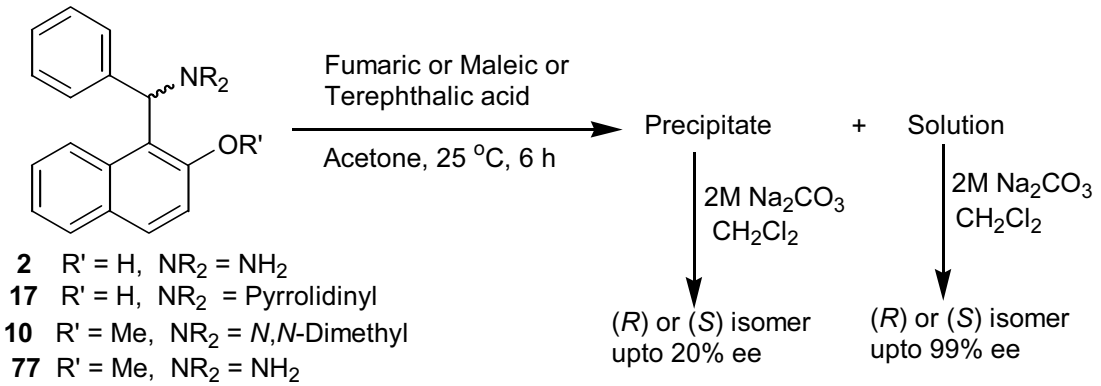
From all these results, it is evident that purification of non-racemic samples using achiral dicarboxylic acids such as oxalic, fumaric, maleic and terephthalic acids is general to aminonaphthols **2** and **17** and their derivatives **10** and **77**. In experiments using aminonaphthols and their derivatives with oxalic acid, the ees of the samples obtained from the precipitate fraction were higher (Scheme 55).

Scheme 55



The use of fumaric, maleic and terephthalic acids, led to higher ees in the solution fraction (Scheme 56).

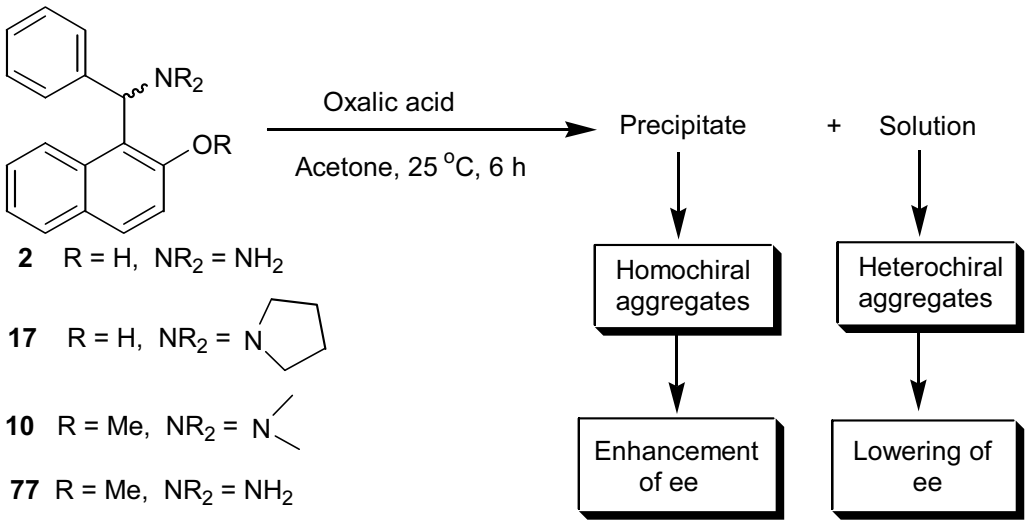
Scheme 56



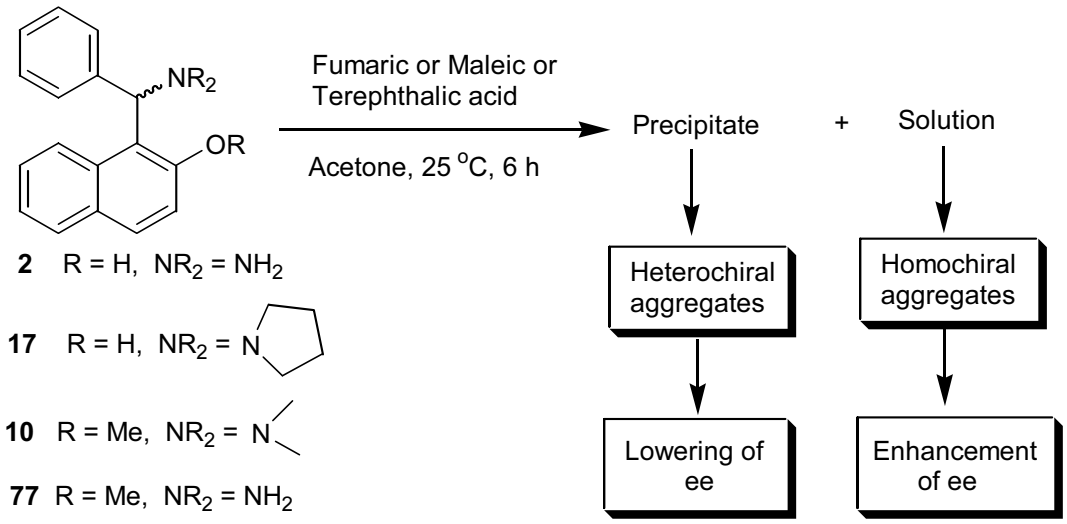
The precipitation of homochiral aggregates leads to enhancement of ees in the precipitate with oxalic acid, whereas precipitation of heterochiral aggregates leads to

lowering of ees in the precipitate fraction with other acids as outlined in Schemes 57 and 58.

Scheme 57



Scheme 58



2. 2. 3. 5 Enhancement of enantiomeric purity of non-racemic aminonaphthol 12 using trimesic acid

The aminonaphthol **12** did not give a precipitate in any of the above acids. Hence, we have examined the purification of this aminonaphthol **12** with trimesic acid

using acetone as solvent (Scheme 59). After workup, enrichment was observed in the precipitate fraction leaving behind the sample with low ee in the solution. The results are summarized in Table 20.

Scheme 59

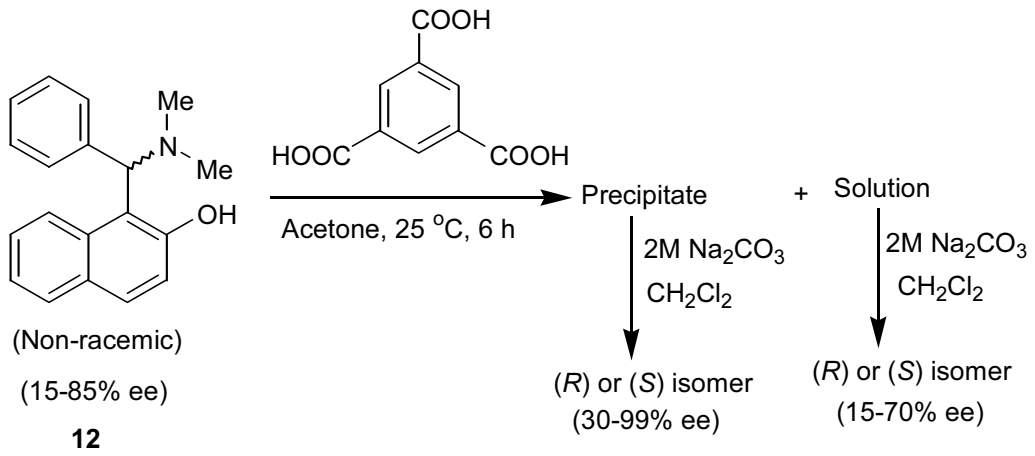


Table 20. Purification of non-racemic aminonaphthol 12 using trimesic acid

S. No.	Substrate **12** (% ee)	Trimesic acid	Aminonaphthol **12** obtained from			
			Precipitate		Filtrate	
	(5 mmol)	(mmol)	% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1	20 (*S*)	1.00	38 (*S*)	15	15 (*S*)	80
2	38 (*S*)	1.90	60 (*S*)	20	30 (*S*)	73
3	60 (*S*)	3.00	85 (*S*)	22	48 (*S*)	70
4	85 (*S*)	4.25	≥99 (*S*)	50	70 (*S*)	40
5	15 (*R*)	0.75	30 (*R*)	12	10 (*R*)	75
6	30 (*R*)	1.50	50 (*R*)	20	20 (*R*)	70
7	50 (*R*)	2.50	75 (*R*)	25	35 (*R*)	60
8	75 (*R*)	3.75	≥99 (*R*)	45	55 (*R*)	42

a. All the reactions were carried out using non-racemic aminonaphthol **12** (5 mmol) and trimesic acid in acetone (60 mL).

b. All ee values reported here are based on maximum[29] $[\alpha]_D^{25}$ = +238 (*C* 0.5, EtOH) for (*S*)-**12** and $[\alpha]_D^{25}$ = -238 (*C* 0.5, EtOH) for (*R*)-**12.**

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

Crystals suitable for X-ray analysis were obtained by crystallization from MeOH solvent. The ORTEP diagram showed that 1:1 ratio of racemic aminonaphthol **12** and trimesic acid in which aminonaphthol **12** exists as ammonium cation and trimesic acid as mono anion (Figure 9). The packing diagram showed that this complex also forms layer structure and all the layers are found to be heterochiral to each other and linked through intermolecular hydrogen bonding interactions (Figure 10).

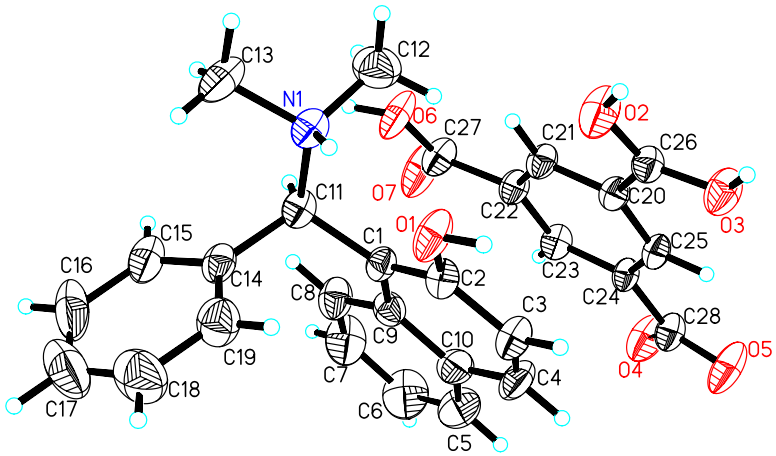


Figure 9. ORTEP diagram of the racemic aminonaphthol 12 with oxalic acid

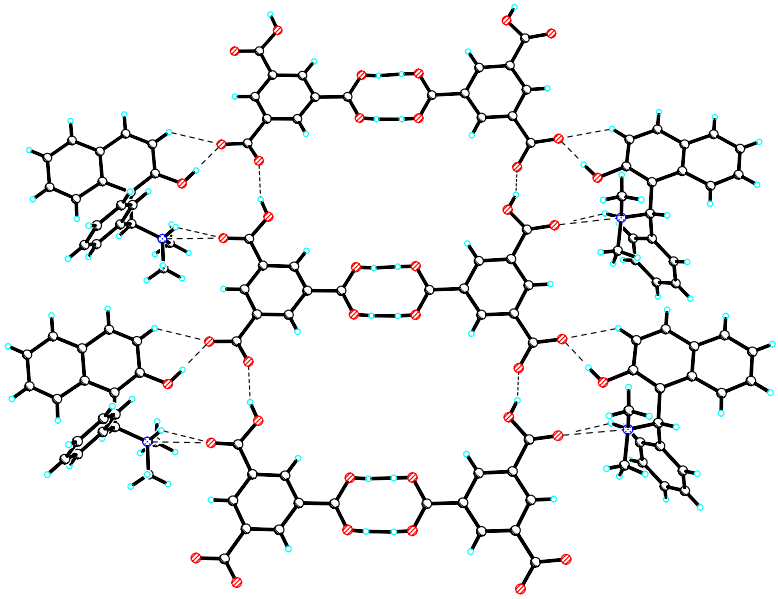


Figure 10. Packing diagram of the racemic aminonaphthol 12 with oxalic acid

Table 21. X-ray data collection and structure refinement for racemic aminonaphthol 12 with trimesic acid

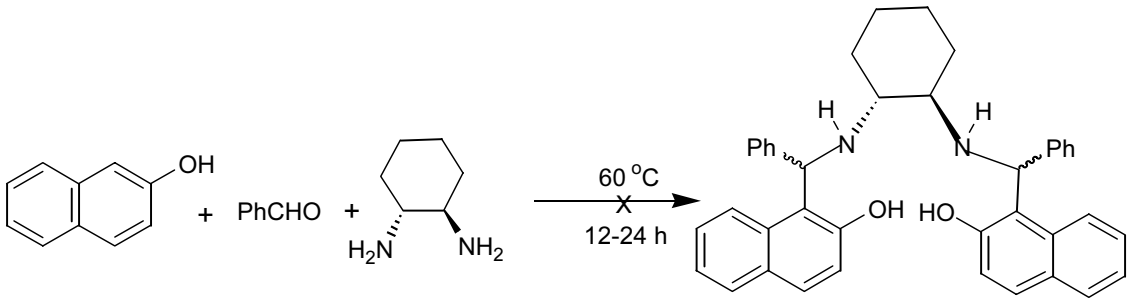
Empirical formula	$C_{28}H_{25}NO_7$
Formula weight	487.49
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C_2/c
Unit cell dimensions	a = 28.444(2) Å, α = 90˚
	b = 9.4157(8) Å, β = 94.007(3)˚
	c = 17.4985(14) Å, γ = 90˚
Volume	4675.0(7) $Å^3$
Z	8
Calculated density	1.385 mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	2048.0
θ Range for data collection	1.44 to 25.00˚
Limiting indices	-33≤h≤33, -11≤k≤11, -20≤l≤20
Reflections collected/unique	21860 / 4125 [R(int) = 0.0512]
Refinement method	full-matrix least-square on F^2
Data / restraints / params	4125 / 0 / 351
Goodness-of-fit on F^2	1.246
Final *R* indices [I> 2σ (I)]	R_1 = 0.0795, wR_2 = 0.1587
R indices (all data)	R_1 = 0.0986, wR_2 = 0.1666
Largest diff. peak and hole	0.26 and -0.24 $eÅ^{-3}$

2. 2. 4. Synthesis of chiral diaminonaphthols using chiral 1,2-diaminocyclohexane

As outlined in the introductory section, chiral aminonaphthols can be directly prepared by the condensation of β-naphthol, benzaldehyde and chiral amines like α-methylbenzylamine and (*S*)-*N*-α-dimethylbenzylamine.[38-43]

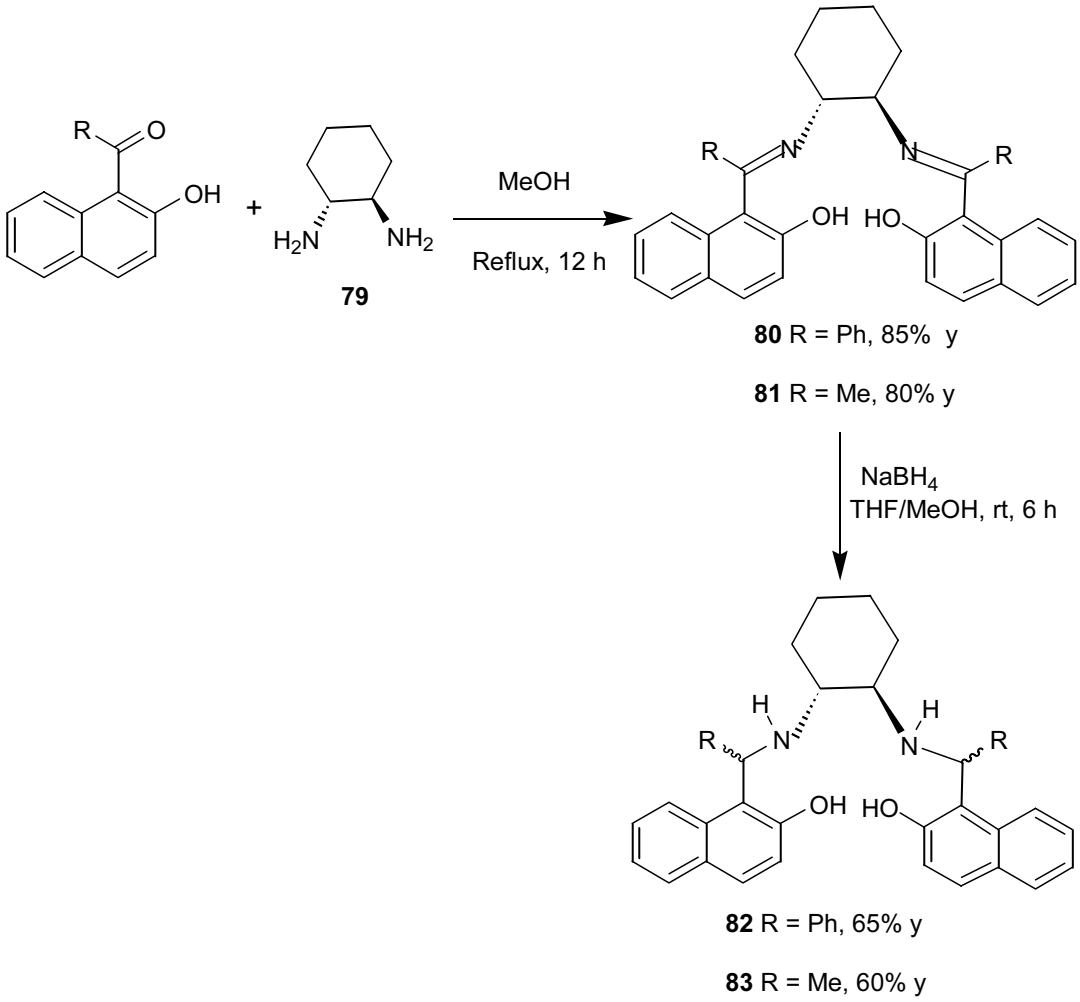
In a similar fashion, we have examined the reaction using chiral 1,2-diaminocyclohexane **79**. Unfortunately, the reaction did not take place in this case and only starting materials were recovered (Scheme 60)

Scheme 60



We have then devised an alternative method of synthesis of these chiral diaminonaphthols using 2 equiv. of 1-acyl-2-naphthol and 1 equiv. of (1*R*,2*R*)-1,2-diaminocyclohexane in methanol under refluxing conditions to obtain the C_2 symmetrical diimines **80** and **81** as white solid. The reduction of these imines using $NaBH_4$/THF gave a diastereomeric mixture of the corresponding diaminonaphthols (Scheme 61). The ^{13}C NMR spectra indicate that one of the three possible diastereomers in each case is formed as a major product. However, the configurations cannot assigned with the available data.

Scheme 61



2. 2. 5 Synthetic applications of chiral aminonaphthols

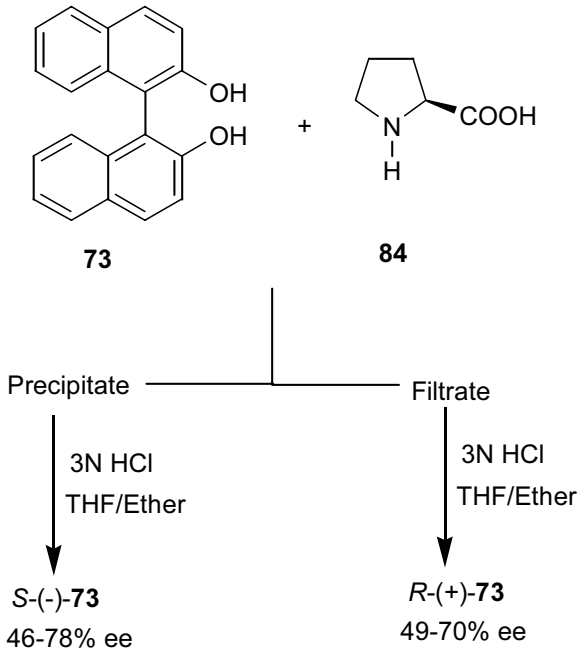
As outlined in the introductory section, there are only a very few reports on the applications of the readily accessible chiral aminonaphthols. So, we have undertaken to examine the synthetic applications of some of these readily accessible chiral aminonaphthols.

2. 2. 5. 1 Resolution of 1,1'-bi-2-naphthol using aminonaphthol and boric acid

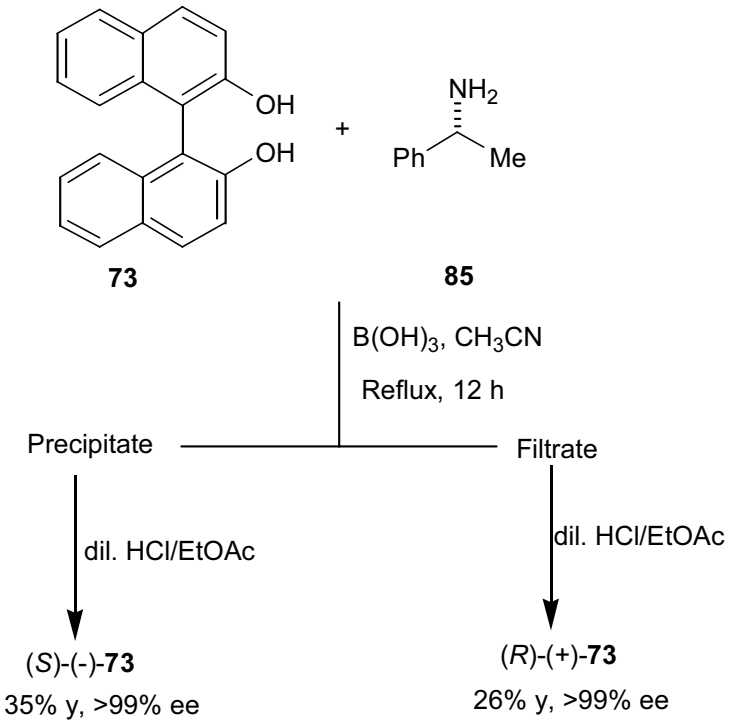
Previously, it was observed in this laboratory that 1,1'-bi-2-naphthol (BINOL) **73** can be readily prepared in enantiomerically pure form by preparation of

diasteriomeric complexes using *S*-proline (Scheme 62) or borate complexes using chiral α-methylbenzylamine and boric acid (Scheme 63).[59-65]

Scheme 62

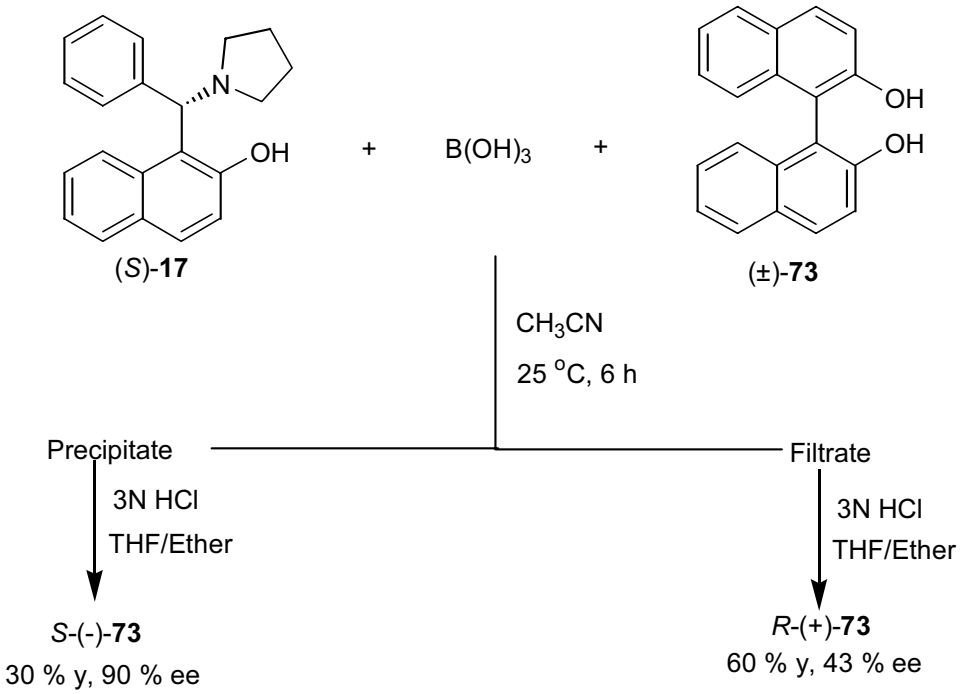


Scheme 63



Accordingly, we have examined the resolution of racemic 1,1'-bi-2-naphthol (BINOL) **73** using the readily accessible aminonaphthol **17** and boric acid through formation of the corresponding diastereomeric borate complexes (Scheme 64).[67]

Scheme 64



It was observed that optimum results were obtained, when aminonaphthol, boric acid and BINOL were taken in ratio of 1:1:1. For example, the racemic BINOL **73** reacts with aminonaphthol (*S*)-**17** and boric acid in CH_3CN solvent to give precipitate and filtrate fractions. After digestion of the precipitate fraction, BINOL **73** enriched in (*S*)-isomer (90 % ee) was obtained. After work up, (*R*)- isomer of **73** (43 % ee) was obtained from the filtrate fraction. These results are summarized in Table 22.

The non-racemic 1,1'-bi-2-naphthol **73** could be also enriched up to 99% ee using $B(OH)_3$ and TMEDA as Scheme 24 (Chapter 1).[61]

Table 22. Resolution of BINOL 73 using aminonaphthol 17 and boric acid [a]

S. No.	Substrate **73**	Aminona-phthol **17**	BINOL **73** obtained from			
			Precipitate		Filtrate	
	%ee	*S* or *R*	%ee[b]/Conf.	Yield(%)[c]	%ee[b]/Conf.	Yield(%)[c]
1[a]	0	(*S*)-**17**	90 (*S*)	30	43 (*R*)	60
2[d]	0	(*S*)-**17**	82 (*S*)	35	45 (*R*)	50
3[e]	0	(*S*)-**17**	30 (*S*)	30	20 (*R*)	62
4[f]	90 *S*	(*S*)-**17**	99 (*S*)	80	10 (*S*)	10
5[f]	43 *R*	(*R*)-**17**	75 (*R*)	45	20 (*R*)	38
6[f]	75 *R*	(*R*)-**17**	99 (*R*)	65	15 (*R*)	20
7[a]	0	(*R*)-**17**	88 (*R*)	32	45 (*S*)	57
8[d]	0	(*R*)-**17**	78 (*R*)	30	40 (*S*)	55
9[e]	0	(*R*)-**17**	32 (*R*)	29	18 (*S*)	60

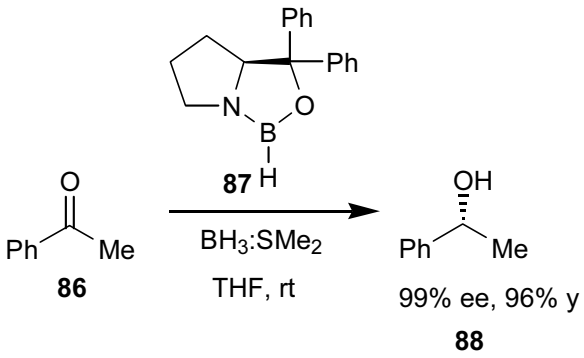
a. Unless otherwise mentioned all the reactions were performed using racemic **73** (5 mmol), boric acid (5 mmol) and aminonaphthol **17** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +35 (*C* 1, THF) for (R)-**73**.
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture used.
d. Racemic **73** (5 mmol), boric acid (2.5 mmol) and aminonaphthol **17** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.
e. Racemic **73** (10 mmol), boric acid (5 mmol) and aminonaphthol **17** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.
f. Non-racemic **73** (5 mmol), boric acid (5 mmol) and aminonaphthol **17** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.

2. 2. 5. 2 Asymmetric reduction of prochiral ketones using aminonaphthols as chiral ligands

The enantioselective reduction of the prochiral ketones using oxazaborolidine catalysts is one of the most widely used methods to obtain optically active secondary

alcohols in high enantiomeric purity.[73-75] The oxazaborolidines are generally prepared from amino alcohols and borane reagents. Corey et al.[76] discovered the oxazaborolidine intermediate in the reduction of prochiral ketones using α,α-diphenyl-2-pyrrolidinemethanol and borane reagents which gives better results than the corresponding α,α-diphenylvalinol initially developed by Itsuno *et al*.[77] (Scheme 65).

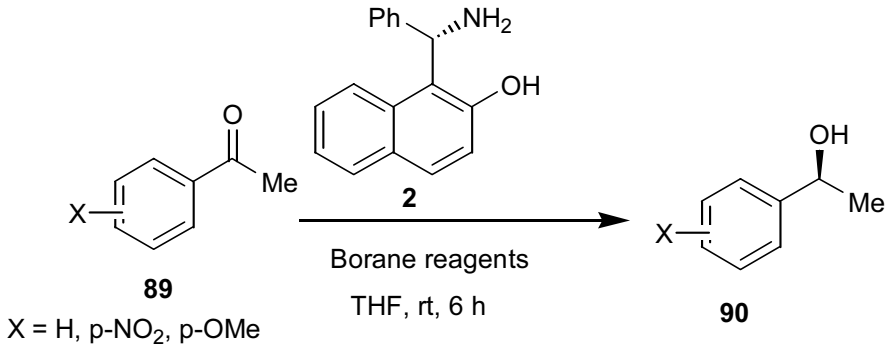
Scheme 65



Accordingly, efforts have been undertaken to examine the reduction of the prochiral ketones using aminonaphthol **2** (20 mol%) and borane reagents such as $NaBH_4/I_2$, $NaBH_4$/TMS-Cl, BH_3:SMe_2 and $Ph(C_2H_5)N$:BH_3 (Scheme 66).

Initially, we have made efforts to examine the preparation of the corresponding oxazaborolidine intermediate (Scheme 67) *in situ* from 20 mol% of aminonaphthol **2** and $NaBH_4/I_2$ reagent system and carried out the reduction of the acetophenone in THF at 25 ^oC. After 6 h reaction and workup, 1-phenyl ethanol was obtained in 95% yield with 17% ee. We have also examined the reduction using other borane reagents like $NaBH_4$/TMS-Cl, BH_3:SMe_2 and $Ph(C_2H_5)N$:BH_3. However, the ees of products were poor (07-25% ee).

Scheme 66



89

X = H, p-NO_2, p-OMe

90

Borane reagents

$NaBH_4/I_2$	88-95% y, 10-22% ee
$NaBH_4$/TMS-Cl	85-92% y, 13-25% ee
$Ph(C_2H_5)_2N:BH_3$	82-90% y, 07-18% ee
$BH_3:SMe_2$	90-95% y, 14-25% ee

Scheme 67

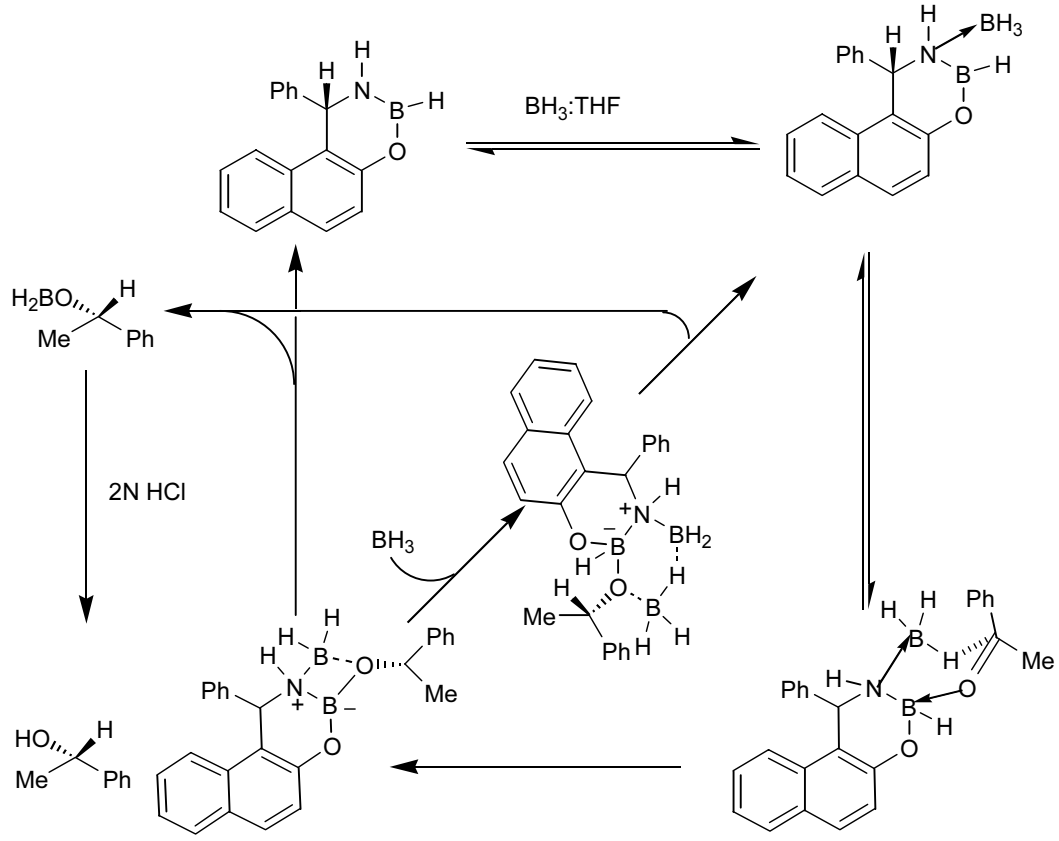


Table 23. Reduction of prochiral ketones using aminonaphthol (2) and borane reagents[a]

S. No.	Borane reagents	X	Yield(%)[c]	%ee./Conf.[b]
1	$NaBH_4/I_2$	H	95	17
2	$NaBH_4$/TMS-Cl	H	92	18
3	$Ph(C_2H_5)N:BH_3$	H	90	12
4	$BH_3:SMe_2$	H	95	18
5	$NaBH_4/I_2$	p-NO_2	92	22
6	$NaBH_4$/TMS-Cl	p-NO_2	90	25
7	$Ph(C_2H_5)N:BH_3$	p-NO_2	88	18
8	$BH_3:SMe_2$	p-NO_2	95	25
9	$NaBH_4/I_2$	p-OMe	88	10
10	$NaBH_4$/TMS-Cl	p-OMe	85	13
11	$Ph(C_2H_5)N:BH_3$	p-OMe	82	07
12	$BH_3:SMe_2$	p-OMe	90	14

a. All the reactions were carried out using 1 mmol of aminonaphthol **2**, 6 mmol of borane reagent and 5 mmol of prochiral ketone in THF solvent and stirred the reaction mixture at rt for 6 h.

b. All ee values reported here are based on reported maximum[78] $[\alpha]_D^{25}$ = -43 (*C* 1.0, MeOH) for (*S*)-**89a,** $[\alpha]_D^{25}$ = -31 (*C* 1.2, MeOH) for (*S*)-**89b** and $[\alpha]_D^{25}$ = -45.2 (*C* 1.0, EtOH) for (*S*)-**89c**.

c. The yields are of the isolated products.

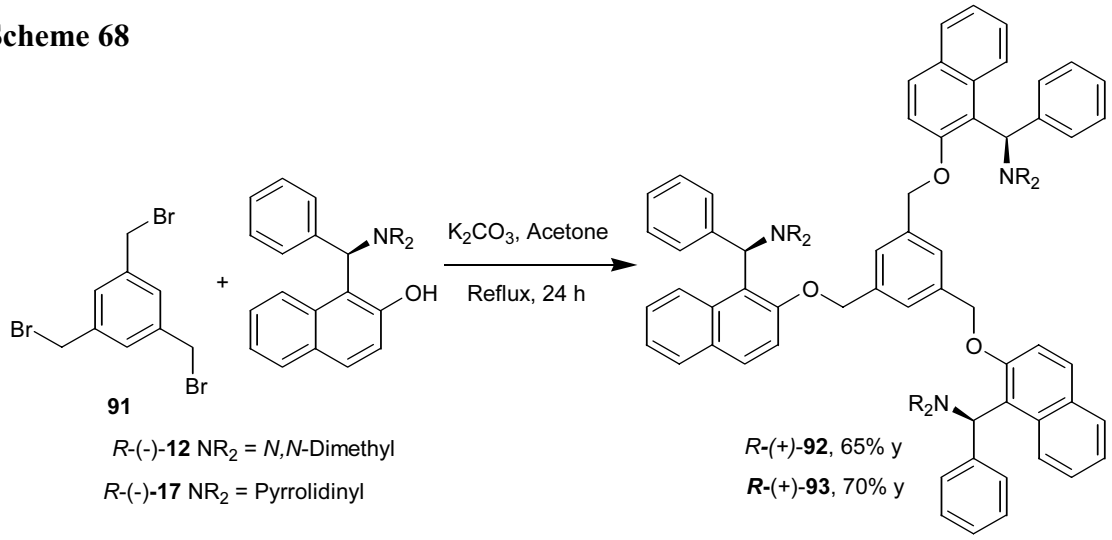
We have also examined the reduction of acetophenone using other aminonaphthols **17**, **18**, and **12.** After workup, only the racemic 1-phenyl ethanol was obtained in quantitative yield in these cases.

2. 2. 5. 3 Synthesis of tripodal amines and ammonium salts for molecular recognition studies

We have synthesized the chiral tripodal molecules staring from aminonaphthols **12** and **17**. These derivatives were prepared by the reaction of one equivalent of

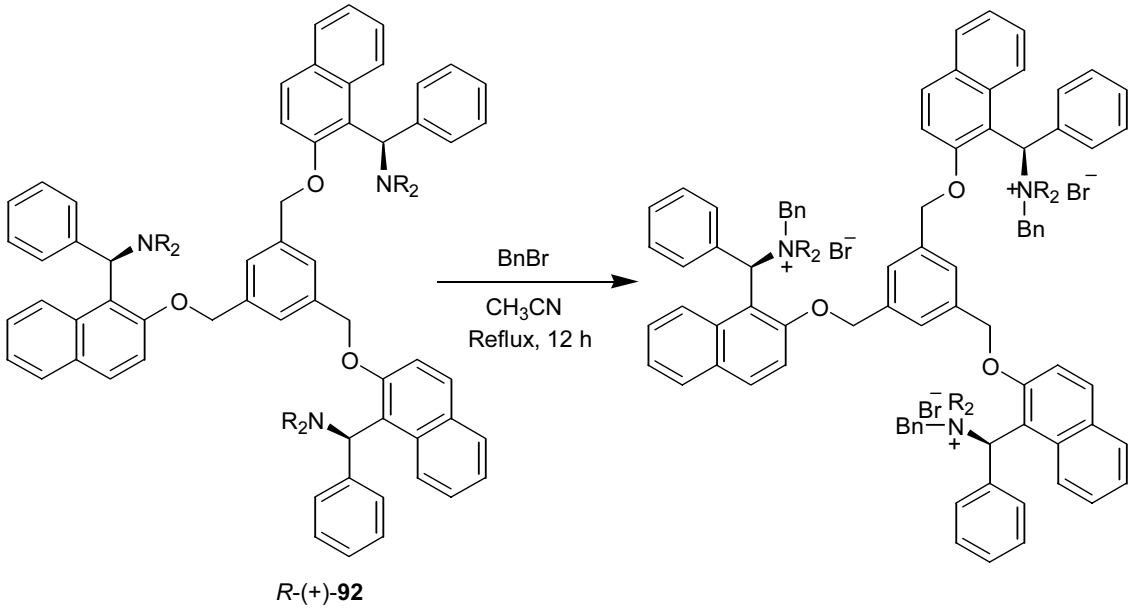
tribromide with three equivalents of aminonaphthol **12** or **17** under refluxing conditions in the presence of anhydrous K_2CO_3 (Scheme 68).

Scheme 68



The corresponding quaternary salts were also prepared using benzyl bromide in CH_3CN solvent (Scheme 69).

Scheme 69



Studies on the utility of these derivatives for molecular recognition and other synthetic applications would lead to fruitful results.

2. 3 Conclusions

Racemic aminonaphthols have been synthesized by condensation of β-naphthol, benzaldehyde with 1^{o} and 2^{o} amines using ethanol as solvent under refluxing conditions. A convenient and general method was developed for the synthesis of aminonaphthols by the reduction of oximes of 1-acyl-2-naphthols using the easily to handle $NaBH_4/I_2$ reagent system. The racemic aminonaphthols such as 1-(α-aminobenzyl)-2-naphthol, 1-(α-pyrrolidinylbenzyl)-2-naphthol, 1-(α-*N*,*N*-dimethyl-aminobenzyl)-2-naphthol, 1-(α-*N*-butylaminobenzyl)-2-naphthol, 1-(α-piperidylbenzyl)-2-naphthol and (2-methoxynaphth-1-yl)benzylamine were resolved using *L(+)*-tartaric acid, *R*-(+)-BINOL, boric acid and dibezoyl-*L*-tartaric acid respectively to obtain samples of >98% ee. Enhancement of enantiomeric excess of non-racemic aminonaphthols and their derivatives were studied using achiral dicarboxylic acid through formation of the corresponding diastereomeric homochiral or heterochiral hydrogen bonded aggregates. The racemic BINOL was resolved using the readily available aminonaphthol **17** and boric acid to obtain samples of >98% ee. Asymmetric reduction of prochiral ketones was studied using 20 mol% of aminonaphthol **2** in the presence of borane reagents to obtain the corresponding secondary alcohols in 07-25% ee.

2. 4 Experimental Section

2. 4. 1 General information

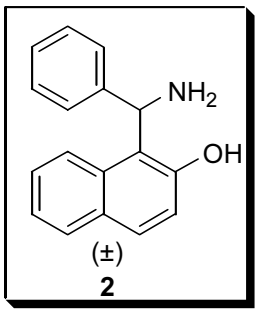
Most of the information given in the experimental section of Chapter 1 are also applicable to the experiments described here. β-Naphthol, *N*,*N*-dimethylamine, pyrrolidine, piperidine, acetyl chloride, benzyl chloride, acetophenone, p-metoxyacetophenone, p-nitroacetophenone and trimesic acid supplied by Loba chemie (P) Ltd, India were used as purchased. Benzaldehyde, ammonia solution, anline, benzylamine, *n*-butylamine were supplied by E. Merk (India). The mixture of *cis* and *trans*-1,2-diaminocyclohexane supplied by Acros, was resolved using *L*-(+)-tartaric acid following a reported procedure to obtain (1*R*,2*R*)-1,2-diaminocyclohexane.[79] X-ray diffraction measurements for the compounds **2, 10, 12, 17** using achiral acids were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system.

2. 4. 2 Synthesis of aminonaphthols by condensation of β-naphthol, benzaldehyde and amines

2. 4. 2. 1 Synthesis of 1-(α-aminobenzyl)-2-naphthol (2)[19]

Freshly distilled benzaldehyde (20.4 mL, 200 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 ml of 95% ethanol. To this 25% aqueous ammonia solution (10 mL) was added and the reaction mixture was left at room temperature for 12 h, during which a crystalline product was formed. The crystalline product was filtered and washed with 90% ethanol (2 X 20 mL), dried and suspended in 20% HCl (200 mL). The mixture was refluxed for 3 h and brought to room temperature. The crystalline hydrochloride salt of the amine was filtered and washed with ethyl acetate (2

X 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 X 100 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain 1-(α-aminobenzyl)-2-naphthol as a white solid.



Yield 17.4 g (70%)

mp 122-124 °C (lit.[19] mp 124-125 °C)

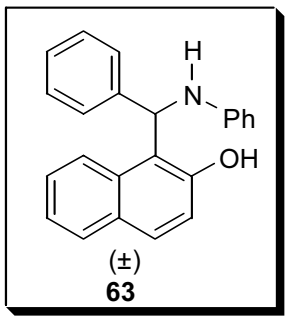
IR (KBr) (cm^{-1}) 3385, 3296, 1622, 1238, 770

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 6.11 (s, 1H), 7.18-7.50 (m, 8H), 7.71-7.77 (m, 3H) **(Spectrum No. 3)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 56.0, 115.2, 120.6, 121.3, 122.5, 126.5, 127.4, 127.9, 128.6, 128.8, 129.1, 129.8, 132.1, 142.5, 157.1 **(Spectrum No. 4)**

2. 4. 2. 2 Synthesis of 1-(α-*N*-phenylaminobenzyl)-2-naphthol (63)

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 distilled aniline (9.1 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl and 2M Na_2CO_3 as above to isolate the 1-(α-*N*-phenylaminobenzyl)-2-naphthol **35** as a white solid.



Yield 24.4 g (75%)

mp 128-130 °C (lit.[55] mp 131-132 °C)

IR (KBr) 3350, 1600, 1450, 1230, 770

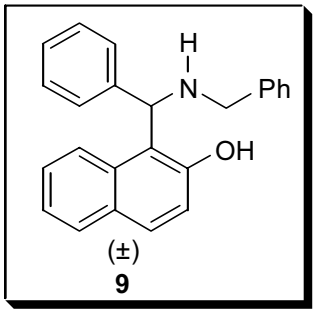
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 4.15 (s, 1H), 6.18 (s, 1H), 6.78 (d, J = 8 Hz, 2H), 6.94 (t, J = 8 Hz, 1H), 7.16 (m, 3H),

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) **(Spectrum No. 5)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 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 **(Spectrum No. 6)**

2. 4. 2. 3 Synthesis of 1-(α-*N*-benzylaminobenzyl)-2-naphthol (9)

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 distilled benzylamine (10.9 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl and 2M Na_2CO_3 as above to isolate the 1-(α-*N*-benzylaminobenzyl)-2-naphthol **9** as a white solid.



(±)
9

Yield 23.6 g (70%)

mp 140-142 °C (lit.[29] mp 143 °C)

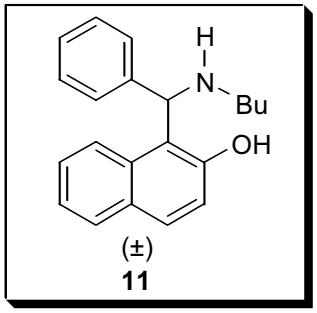
IR (KBr) 3340, 3050, 1652, 1270, 780

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 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), **(Spectrum No. 7)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 52.9, 62.9, 113.1, 120.2, 121.2, 122.5, 126.5, 127.8, 128.1, 128.6, 128.8, 129.1, 129.9, 132.8, 138.1, 141.4, 156.9 **(Spectrum No. 8)**

2. 4. 2. 4 Synthesis of 1-(α-*N*-butylaminobenzyl)-2-naphthol (11)

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 distilled *n*-butylamine (10.0 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl and 2M Na_2CO_3 as above to isolate the 1-(α-*N*-butylaminobenzyl)-2-naphthol **11** as a white solid.



(±)
11

Yield 21.3 g (70%)

mp 130-132 °C (lit.[30] mp 131-132 °C)

IR (KBr) (cm^{-1}) 3314, 3058, 2958, 1621, 1601, 1456, 1241, 1090

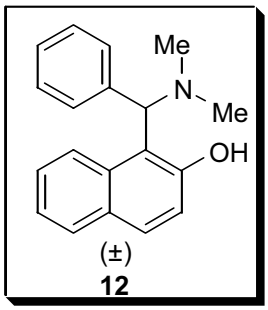
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.91 (t, *J* = 8 Hz, 3H), 1.38-141 (m, 2H), 1.56-1.61 (m, 2H), 2.83 (t, *J* = 8 Hz, 2H), 5.67 (s, 1H), 7.18 (d, *J* = 12 Hz, 1H), 7.21-7.36 (m, 5H), 7.46 (d, *J* = 8 Hz, 3H) 7.72 (t, *J* = 8 Hz, 2H) **(Spectrum No. 9)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 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 **(Spectrum No. 10)**

2. 4. 2. 5 Synthesis of 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol (12)

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 40% aqueous solution of N,N-dimethylamine (12.6 mL, 100 mmol) was added. The reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and

washed with 95% ethanol (2 X 20 mL) to isolate the 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol **12** as a white solid.



Yield 20.8 g (75%)

mp 161-162 °C (lit.[69] mp. 164-164.5 °C)

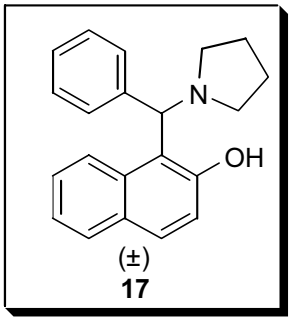
IR (KBr) (cm^{-1}) 3058, 2958, 1620, 1454, 1238, 1006

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm) 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) **(Spectrum No. 11).**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 44.2, 73.1, 116.3, 112.0, 121.1, 122.4, 126.4, 128.0, 128.8, 128.9, 129.5, 132.3, 140.5, 155.5 **(Spectrum No. 12)**

2. 4. 2. 6 Synthesis of 1-(α-pyrrolidinylbenzyl)-2-naphthol (17)

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 pyrrolidine (8.4 mL, 100 mmol) was added. The reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and washed with 95% ethanol (2 X 20 mL) to isolate the 1-(α-pyrrolidinylbenzyl)-2-naphthol **17** as a white solid.



Yield 28.7 g (95%)

mp 172-173 °C (lit.[33] mp 173 °C)

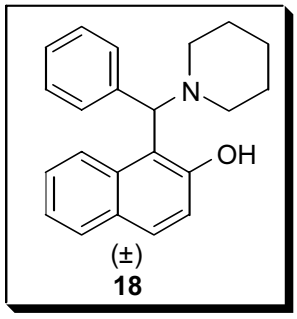
IR (KBr) (cm^{-1}) 3120, 3057, 2970, 2845, 1620, 1452,1238,750

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 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) **(Spectrum No. 13)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 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 **(Spectrum No. 14)**

2. 4. 2. 6 Synthesis of 1-(α-piperidylbenzyl)-2-naphthol (18)

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 piperidine (10.0 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 95% ethanol (2 X 20 mL) to isolate the 1-(α-piperidylbenzyl)-2-naphthol **18** as a white solid.



Yield 28.4 g (90%)

mp 195-196 °C (lit.[69] mp 198-198.5 °C)

IR (KBr) (cm^{-1}) 3214, 3058,2958, 1621, 1601, 1456, 1241, 109

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 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) **(Spectrum No. 15)**

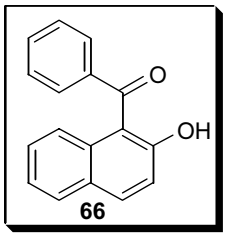
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 24.2, 26.1, 53.5, 72.4, 116.2, 120.0, 121.1, 122.4, 126.4, 127.9, 128.9, 129.1, 129.4, 132.5, 139.7, 155.6 **(Spectrum No. 16)**

2. 4. 3 Synthesis of aminonaphthols by using 1-acyl-2-naphthol

2. 4. 3. 1 Preparation of 1-acyl-2-naphthol by Fries rearrangement using $TiCl_4$

$TiCl_4$ (2.4 mL, 22 mmol) was added using a syringe to a mixture of β-naphthol (2.88 g, 20 mmol). The resulting dark cherrey-coloured mixture was stirred at rt until the evolution of HCl gas had ceased. Then acid chloride (30 mmol) was added to the reaction mixture and the resulting thick solution was stirred at rt for 15 min, then heated to 120 ^oC and stirring was continued at this temperature for 1 h. The reaction mixture was cooled to rt and quenched with water (30 mL) and extracted with DCM (2 X 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain the crude product as reddish brown solid. It was purified by silica gel column chromatography using hexane:ethyl acetate (99:1) as eluent.

Preparation of 1-benzoyl-2-naphthol (66)



66

Yield 3.5 g (70%)

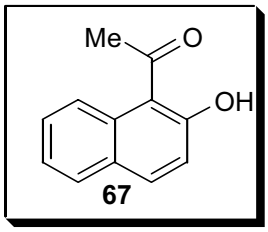
mp 92-94 ^oC (lit.[57] mp 95-96 ^oC)

IR (KBr) (cm^{-1}) 3267, 1655, 1575, 1431, 1234, 1176, 1022

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.18-7.20 (m, 2H), 7.26-7.34 (m, 4H), 7.44 (t, *J* = 8 Hz, 1H), 7.57 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 1H), 11.2 (br s, 1H) **(Spectrum No. 17)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 114.5, 119.1, 123.7, 126.3, 126.7, 128.6, 129.4, 130.2, 132.4, 132.7, 136.2, 140.3, 161.3, 200.3 **(Spectrum No. 18)**

Preparation of 1-acetyl-2-naphthol (67)



67

Yield 2.4 g (65%)

mp 116-118 ^{o}C (lit.[57] mp 120-121 ^{o}C)

IR (KBr) (cm^{-1}) 3352, 3055, 2927, 1624, 1575, 1465, 1245, 1024

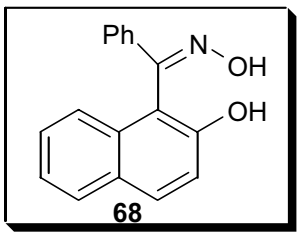
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 2.89 (s, 3H), 7.15 (d, *J* = 12 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.59 (t, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 8.11 (d, *J* = 8 Hz, 1H) 13.45 (br s, 1H) **(Spectrum No. 19)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 32.0, 114.4, 119.9, 123.0, 123.9, 127.5, 128.2, 128.7, 129.1, 131.8, 136.5, 164.0, 202.7 **(Spectrum No. 20)**

2. 4. 3. 2 Preparation of oximes of 1-acyl-2-naphthol[57]

Hydroxylamine hydrochloride (2.8 g, 40 mmol) and sodium acetate (5.44 g, 40 mmol) were dissolved in water (10 mL) and added to a suspension of 1-acyl-2-naphthol (10 mmol) in *n*-butanol. The resulting mixture was refluxed for 2 h. The solvent was removed in vacuo and to this residue cold water (100 mL) was added and extracted with DCM (2 X 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain the crude product. The product containing a mixture of *E* and *Z* isomers were purified by silica gel column chromatography using hexane and ethyl acetate as eluent.

(*Z*)-1-(2-Hydroxy-1-naphthyl)(phenyl)methanone oxime (68)



68

Yield 1.6 g (61%)

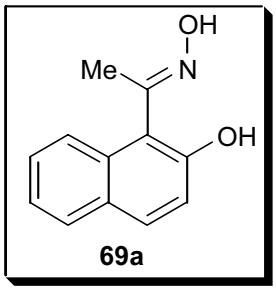
mp 203-204 ^{o}C (lit.[56] mp 205-206 ^{o}C)

IR (KBr) (cm^{-1}) 3410, 1620

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.24-7.44 (m, 9H) 7.82-7.86 (m, 2H), 9.97 (br s, 1H), 11.29 (br s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 114.1, 118.3, 122.6, 123.9, 125.9, 126.4, 127.6, 128.0, 128.3, 128.6, 129.6, 131.7, 136.3, 151.7, 152.2, 152.4

(*E*)-1-(2-Hydroxy-1-naphthyl)ethane-1-one oxime (69a)



69a

Yield 0.9 g (45%)

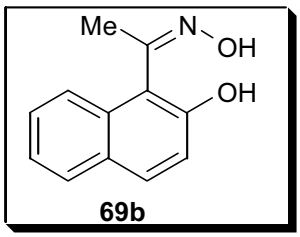
mp 131-133 °C (lit.[57] mp 130-132 °C)

IR (KBr) (cm^{-1}) 3400, 3300 1650

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.14 (s, 3H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.28 (td, *J* = 8.0, 1.2 Hz, 1H), 7.41 (td, *J* = 8.0, 1.2 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.76-7.70 (m, 2H), 9.79 (s, 1H), 11.00 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm), 20.7, 116.8, 118.1, 127.6, 127.8, 130.132.8, 150.7, 152.2, 152.6

(*Z*)-1-(2-Hydroxy-1-naphthyl)ethane-1-one oxime (69b)



69b

Yield 0.3 g (14%)

mp 140-142 °C (lit. mp[57] 140-141 °C)

IR (KBr) (cm^{-1}) 3315, 3300 1620

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.11 (s, 3H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.28 (td, *J* = 8.1, 1.5 Hz, 1H), 7.37-7.42 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 9.73 (br s, 1H), 10.27 (br s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 16.0, 20.5, 118.2, 122.6, 123.7, 124.1, 126.2, 126.3, 127.9, 129.0, 129.2

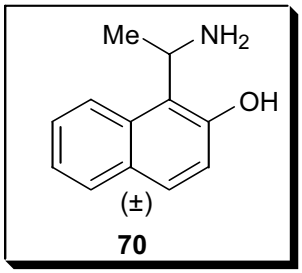
2. 4. 3. 3 Reduction of oximes of 1-acyl-2-naphthol to aminonaphthols using $NaBH_4/I_2$

Iodine (5.1 g, 2.5 mmol) in dry THF (20 mL) was added through an addition funnel to the stirred suspension of $NaBH_4$ (0.19 g, 5 mmol) in dry THF (15 mL) for 1h at 0 ^oC. The oxime (5 mmol) in dry THF (10 mL) was added drop wise and the reaction mixture were stirred at rt for 24 h. The reaction mixture was cooled to 0 °C, then quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 2 h at room temperature then, made alkaline with NaOH, followed by extraction with ether (2 X 20 mL). The organic extracts are washed with brine (10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography using hexane:ethyl acetate (97:3) as eluent to obtain the product.

1-(α-aminobenzyl)-2-naphthol (2)

Yield 1.0 g (80%)

1-(α-aminomethyl)-2-naphthol (70)



70

Yield 0.65 g (70%)

mp 74-75 (lit. mp[80] 74-76 ^oC

IR (KBr) (cm^{-1}) 3410, 1620, 1600, 1450, 1170, 950

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.65 (d, *J* = 8 Hz, 3H), 5.20 (q, 1H), 7.00 (d, *J* = 8 Hz, 1H), 7.31(t, *J* = 8 Hz, 1H), 7.47 (m, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.72-7.78 (m, 2H) **(Spectrum No. 21)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 21.8, 45.4, 119.1, 121.8, 122.8, 123.0, 126.0, 126.4, 128.3, 128.8, 129.0, 151.0 **(Spectrum No. 22)**

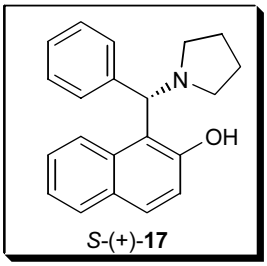
2. 4. 4 Resolution of aminonaphthols

2. 4. 4. 1 Resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol (17) using *L*-(+)-tartaric acid (71)

The *L*-(+)-tartaric acid **71** (0.75 g, 5 mmol) and the racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol **17** (1.5 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the *S*-(+)-**17**. The filtrate was concentrated and the residue taken in DCM (20 mL) and was digested using 1N KOH (10 mL) to obtain the *R*-(-)-**17**.

After decomposition:

From precipitate:



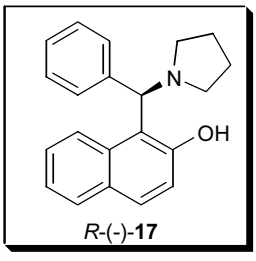
S-(+)-**17**

Yield 0.60 g (40%)

$[\alpha]_D^{25}$ +176 (*C* 1, $CHCl_3$), { lit.[46] for 100% ee, $[\alpha]_D^{25}$ = +179.1 (*C* 1.30, $CHCl_3$)}

Enantiomeric purity 99% ee (determined by HPLC using chiral column, chiralcel-OD)

From filtrate:



R-(-)-**17**

Yield 0.82 g (55%)

$[\alpha]_D^{25}$ -134 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}

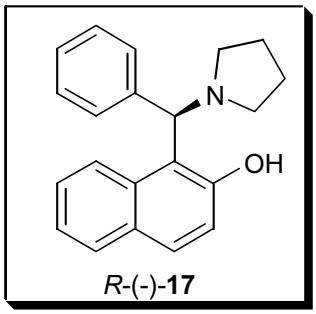
Enantiomeric purity 75% ee (determined by HPLC using chiral column, chiralcel-OD)

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes:IPA/90:10; flow rate 0.9 mL/min.) of racemic aminonaphthol **17** showed two peaks at 5.24 min. (*S*) and 5.69 min. (*R*) in 1:1 ratio on chiral column, chiralcel-OD. Similar HPLC analysis of the chiral aminonaphthol (*S*)-**17** showed single peak at 5.25 min. indicating that its enantiomeic purity is 99% ee (for precipitate fraction). In the similar way HPLC analysis of the chiral aminonaphthol (*R*)-**17** showed two peaks at 5.19 min. (*S*) and 5.63 (*R*) in the ratio of 13:87 indicating that its enatiomeric purity is 75% ee (for filtrate fraction).

2. 4. 4. 2 Purification of partially resolved 1-(α-pyrrolidinylbenzyl)-2-naphthol (17) using *L*-(+)-tartaric acid (71)

The partially resolved 1-(α-pyrrolidinylbenzyl)-2-naphthol *R*-(-)-**17** (75% ee,1.5 g, 5 mmol)) and the *L*-(+)-tartaric acid **71** (0.75 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the product enriched in *R*-(-)-**17** ((≥ 99% ee).



R-(-)-**17**

After decomposition:

From precipitate:

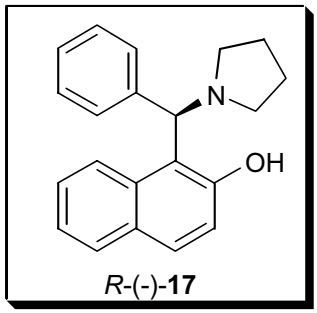
Yield 1.00 g (70%)

$[\alpha]_D^{25}$ -179 (*C* 1, $CHCl_3$), { lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}

From filtrate:

Yield 0.30 g (20%)

$[\alpha]_D^{25}$ -32 (*C* 1, $CHCl_3$), { lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}



R-(-)-**17**

2. 4. 4. 3 Resolution of 1-(α-aminobenzyl)-2-naphthol (2) using *L*-(+)-tartaric acid (71)

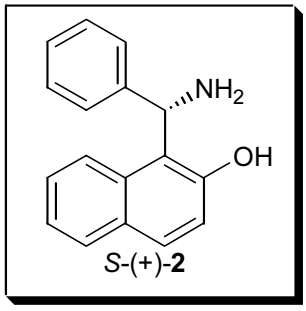
The same procedure as mentioned above was followed for the resolution of racemic 1-(α-aminobenzyl)-2-naphthol **2** (1.24 g, 5 mmol) using acetone (60 mL) as solvent.

After decomposition:

From precipitate:

Yield 0.52 g (42%)

$[\alpha]_D^{25}$ +58 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene)}



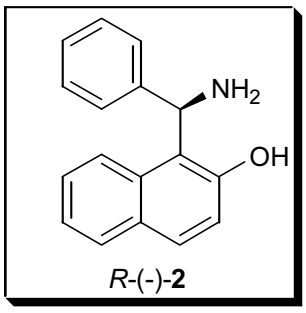
S-(+)-**2**

Enantiomeric purity 99% ee (determined by HPLC using chiral column, chiralcel-OD)

From filtrate:

Yield 0.62 g (50%)

$[\alpha]_D^{25}$ -47 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.9 (*C* 5, benzene)}



R-(-)-**2**

Enantiomeric purity 80% ee (determined by HPLC using chiral column, chiralcel-OD)

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes:IPA/95:05; flow rate 0.5 mL/min.) of racemic aminonaphthol **2** showed two peaks at 9.64 min. (*S*) and 10.23 min. (*R*) in 1:1 ratio on chiral column, chiralcel-OD. Similar HPLC analysis of the chiral aminonaphthol (*S*)-**2** showed single peak at 9.67 min. indicating that its enantiomeic purity is 99% ee (for precipitate fraction). In the similar way HPLC analysis of the chiral aminonaphthol (*R*)-**2** showed two peaks at 9.62 min. (*S*) and 10.25 (*R*) in the ratio of 10:90 indicating that its enatiomeric purity is 80% ee (for filtrate fraction).

2. 4. 4. 4 Purification of partially resolved 1-(α-aminobenzyl)-2-naphthol (2) using *L*-(+)-tartaric acid (71)

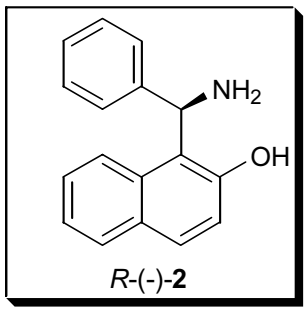
The procedure mentioned in 2.4.4.2 was followed for the purification of partially resolved 1-(α-aminobenzyl)-2-naphthol *R*-(-)-**2** (80% ee, 1.24 g, 5 mmol) using acetone (60 mL) as solvent.

After decomposition:

From precipitate:

Yield 0.93 g (75%)

$[\alpha]_D^{25}$ -58.2 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.8 (*C* 5, benzene)}

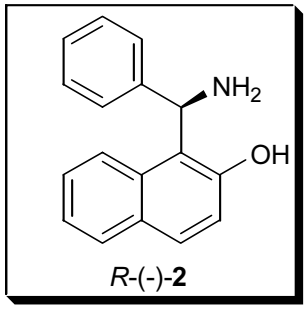


R-(-)-**2**

From filtrate:

Yield 0.19 g (15%)

$[\alpha]_D^{25}$ -11.8 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.9 (*C* 5, benzene)}

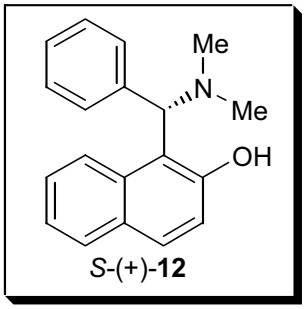


R-(-)-**2**

2. 4. 4. 5 Resolution of 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol (12) using *L*-(+)-tartaric acid (71)

The procedure mentioned in 2.4.4.1 was followed for the resolution of racemic 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol **12** (1.38 g, 5 mmol) using acetone (60 mL) as solvent.

After decomposition:



S-(+)-**12**

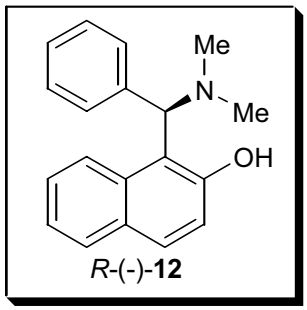
From precipitate:

Yield 0.55 g (40%)

$[\alpha]_D^{25}$ +236 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +238 (*C* 0.5, ethanol)}

Enantiomeric purity 99% ee (determined by HPLC using chiral column, chiralcel-OD)

From filtrate:



R-(-)-**12**

Yield 0.65 g (47%)

$[\alpha]_D^{25}$ -202 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -238 (*C* 0.5, ethanol)}

Enantiomeric purity 85% ee (determined by HPLC using chiral column, chiralcel-OD)

Determination of enantiomeric purity:

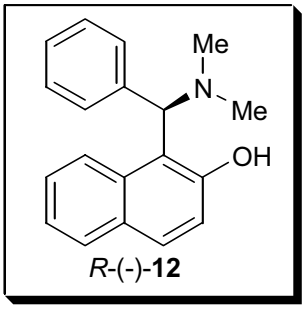
HPLC analysis (solvent system, hexanes:IPA/99.5:0.5; flow rate 1 mL/min.) of racemic aminonaphthol **2** showed two peaks at 7.57 min. (*S*) and 9.70 min. (*R*) in 1:1 ratio on chiral column, chiralcel-OD. Similar HPLC analysis of the chiral aminonaphthol (*S*)-**12** showed single peak at 7.60 min. indicating that its enantiomeic purity is 99% ee (for precipitate fraction). In the similar way HPLC analysis of the

chiral aminonaphthol (*R*)-1**2** showed two peaks at 7.54 min. (*S*) and 9.76 (*R*) in the ratio of 12.5:92.5 indicating that its enatiomeric purity is 85% ee (for filtrate fraction).

The partially resolved sample of non-racemic sample of *R*-(-)-**12** (85% ee, 1.38 g, 5 mmol) was purified using *L*-(+)-tartaric acid **71** following the same procedure as mentioned above in section 2.4.4.2.

After decomposition:

From precipitate:

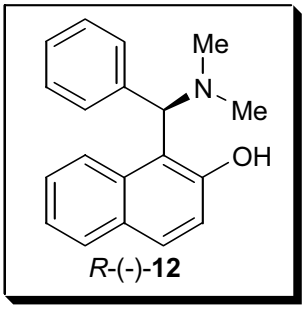


R-(-)-**12**

Yield 1.10 g (80%)

$[\alpha]_D^{25}$ +236 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +238 (*C* 0.5, ethanol)}

From filtrate:



R-(-)-**12**

Yield 0.17 g (12%)

$[\alpha]_D^{25}$ +33 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +238 (*C* 0.5, ethanol)}

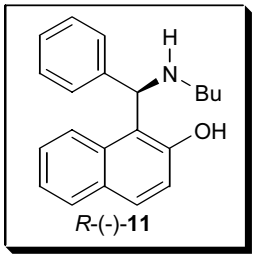
2. 4. 4. 6 Resolution of 1-(α-*N*-butylaminobenzyl)-2-naphthol (11) using *R*-(+)-1,1'-bi-2-naphthol (73) and $B(OH)_3$

A mixture of (*R*)-(+)-1,1'-bi-2-naphthol **73** (1.43 g, 5 mmol), $B(OH)_3$ (0.30 g, 5 mmol) and the racemic 1-(α-N-butylaminobenzyl)-2-naphthol **11** (1.5 g, 5 mmol) were taken in CH_3CN (50 mL). The contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of THF (50 mL) and dil. HCl (2N, 20 mL) and stirred until complete dissolution occurs. The organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O (2 X 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 **11** was extracted with CH_2Cl_2 (2 X 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*-(-)-**11** (99% ee). 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*-(+)-**11** (90% ee) was isolated.

After decomposition:

From precipitate:



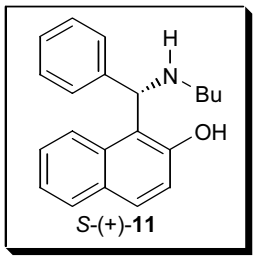
R-(-)-**11**

Yield 0.61 g (40%)

$[\alpha]_D^{25}$ -210 (*C* 1, ethanol), {lit.[30] for 100% ee, $[\alpha]_D^{25}$ = -212 (*C* 0.50, ethanol)}

Enantiomeric purity 99% ee (determined by HPLC using chiral column, chiralcel-OD)

From filtrate:



S-(+)-**11**

Yield 0.65 g (43%)

$[\alpha]_D^{25}$ +191 (*C* 1, ethanol), {lit.[30] for 100% ee, $[\alpha]_D^{25}$ = +212 (*C* 0.5, ethanol)}

Enantiomeric purity 90% ee (determined by HPLC using chiral column, chiralcel-OD)

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes:IPA/90:10; flow rate 0.9 mL/min.) of racemic aminonaphthol **11** showed two peaks at 5.58 min. (*S*) and 6.60 min. (*R*) in 1:1 ratio on chiral column, chiralcel-OD. Similar HPLC analysis of the chiral aminonaphthol (*R*)-**11** showed single peak at 6.57 min. indicating that its enantiomeic purity is 99% ee (for

precipitate fraction). In the similar way HPLC analysis of the chiral aminonaphthol (*R*)-**11** showed two peaks at 5.6 min. (*S*) and 6.54 (*R*) in the ratio of 95:5 indicating that its enatiomeric purity is 90% ee (for filtrate fraction).

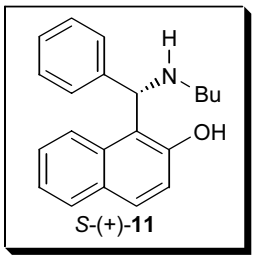
The partially resolved S-(+)-**11** (90% ee, 1.5 g, 5 mmol) was also enriched by following the same procedure as mentioned above.

After decomposition:

From precipitate:

Yield 1.14 g (75%)

$[\alpha]_D^{25}$ +210 (*C* 1, ethanol), {lit.[30] for 100% ee, $[\alpha]_D^{25}$ = +212 (*C* 0.50, ethanol)}

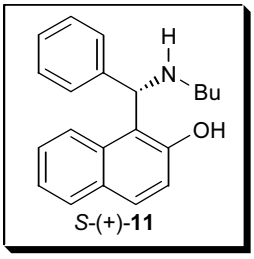


S-(+)-**11**

From filtrate:

Yield 0.12 g (08%)

$[\alpha]_D^{25}$ +21.2 (*C* 1, ethanol), {lit.[30] for 100% ee, $[\alpha]_D^{25}$ = +212 (*C* 0.5, ethanol)}



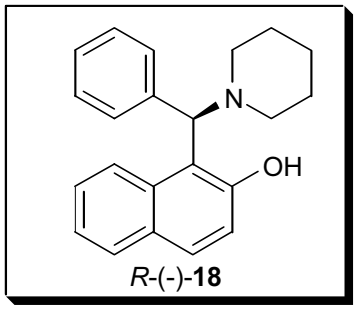
S-(+)-**11**

2. 4. 4. 7 Resolution of 1-(α-*N*-piperidylbenzyl)-2-naphthol (18) using *R*-(+)-1,1'-bi-2-naphthol (73) and $B(OH)_3$

A mixture of (*R*)-(+)-1,1'-bi-2-naphthol **73** (1.43 g, 5 mmol), $B(OH)_3$ (0.30 g, 5 mmol) and the racemic 1-(α-*N*-butylaminobenzyl)-2-naphthol **18** (1.5 g, 5 mmol) were taken in CH_3CN (50 mL) and the contents were refluxed for 12 h. The reaction mixture was filtered while hot and washed with acetonitrile. After workup, the isomers *R*-(-)-**18** and *S*-(+)-**18** were obtained.

After decomposition:

From precipitate:



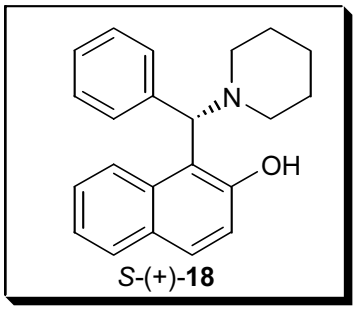
R-(-)-**18**

Yield 0.55 g (35%)

$[\alpha]_D^{25}$ -135 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -193.5 (*C* 1.20, $CHCl_3$)}

Enantiomeric purity 70% ee (determined by HPLC using chiral column, chiralcel-OD)

From filtrate:



S-(+)-**18**

Yield 0.71 g (45%)

$[\alpha]_D^{25}$ +87 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = +193.8 (*C* 1.20, $CHCl_3$)}

Enantiomeric purity 45% ee (determined by HPLC using chiral column, chiralcel-OD)

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes:IPA/95:05; flow rate 0.5 mL/min.) of racemic aminonaphthol **18** showed two peaks at 9.35 min. (*S*) and 10.00 min. (*R*) in 1:1 ratio on chiral column, chiralcel-OD. Similar HPLC analysis of the chiral aminonaphthol (*R*)-**18** showed two peaks at 9.38 min. (*S*) and 9.98 (*R*). in the ratio 15:85 indicating that its enantiomeic purity is 70% ee (for precipitate fraction). In the similar way HPLC analysis of the chiral aminonaphthol (*S*)-**18** showed two peaks at 9.32 min. (*S*) and 10.05 (*R*) in the ratio of 67.5:22.5 indicating that its enatiomeric purity is 40% ee (for filtrate fraction).

The samples of moderate ees were further purified upto 99% ee by following the same procedure.

2. 4. 5 Synthesis and resolution of (2-methoxynaphth-1-yl)benzylamine

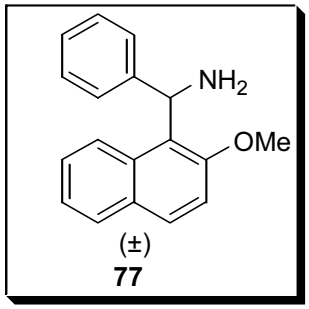
2. 4. 5. 1 Synthesis of (2-methoxynaphth-1-yl)benzylamine (77)[29]

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 25% aqueous ammonia solution (4 mL) was added and the reaction mixture was left at room temperature for 12 h, during which a crystalline product was formed. The crystalline product was filtered and washed with 90% ethanol (2 X 20 mL), dried and dissolved in THF (60 mL). To this powdered NaOH (1.8 g, 45 mmol) was added. After 10 minutes, CH_3I was added through syringe at 0 ^oC and the reaction mixture was stirred at rt for 6 h. The reaction mixture was quenched with water (10 mL) and extracted with ether (2 X 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 of the imine product. It was suspended in 20% HCl (70 mL) and the mixture was refluxed for 1 h and brought to rt. The crystalline hydrochloride of amine salt was filtered and washed with ethyl acetate (2 X 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 X 50 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain the (2-methoxynaphth-1-yl)benzylamine **77** as a light yellow solid.

Yield 4.7 g (60%)

mp 98-100 ^oC (lit.[29] mp 102 ^oC)

IR (KBr) (cm-[1]) 3314, 3058, 2958, 1621, 1601,1456, 1241, 1090



(±)
77

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 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 ppm) 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

2. 4. 5. 2 Resolution of (2-methoxynaphth-1-yl)benzylamine (77) using dibenzoyl *L*-tartaric acid (78)

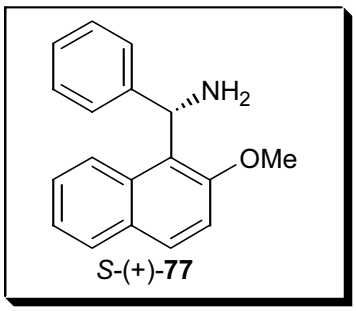
The dibenzoyl-*L*-tartaric acid **78** (1.8 g, 5 mmol) and the (2-methoxynaphth-1-yl)benzylamine (1.32 g, 5 mmol) **77** were taken in acetone (60 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample enriched in *S*-(+)-**77**. The filtrate was concentrated and the residue was digested as outlined above to obtain the sample enriched in *R*-(-)-**77**.

After decomposition:

From precipitate:

Yield 0.50 g (38%)

$[\alpha]_D^{25}$ +167 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = +196 (*C* 0.5, $CHCl_3$)}

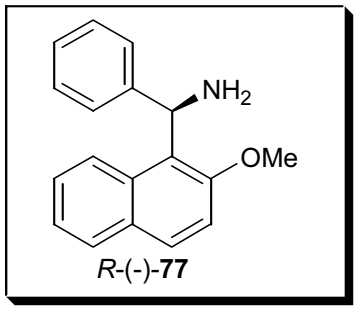


S-(+)-**77**

From filtrate:

Yield 0.65 g (50%)

$[\alpha]_D^{25}$ -118 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}



R-(-)-**77**

The partially resolved samples of *R*-(-)- or *S*-(+)-**77** were also purified to obtain the sample of 99% ee following the above procedure.

2. 4. 6 Enhancement of non-racemic aminonaphthols using achiral acids

2. 4. 6. 1 Enhancement of non-racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol (17) using oxalic acid

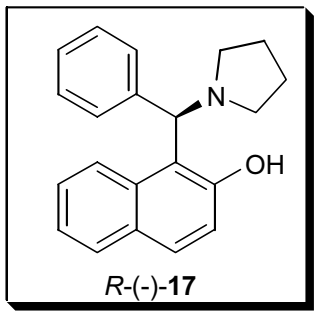
The partially resolved (*R*)-(-)-1-(α-pyrrolidinylbenzyl)-2-naphthol **2** (50% ee, 1.5 g, 5 mmol) was taken in acetone (70 mL), to this the oxalic acid (0.22 g, 2.5 mmol) was added and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample enriched in *R*-(-)-**17**.

After decomposition:

From precipitate:

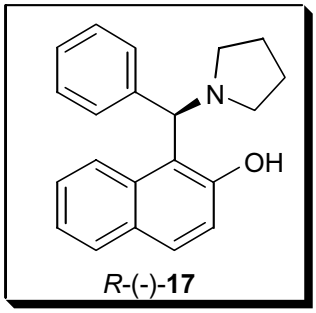
Yield 0.63 g (42%)

$[\alpha]_D^{25}$ -177 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}



R-(-)-**17**

From filtrate:



R-(-)-**17**

Yield 0.70 g (46%)

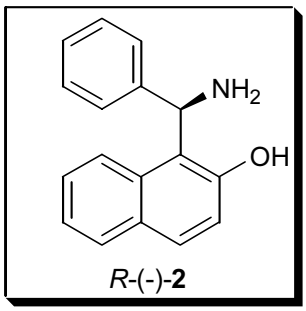
$[\alpha]_D^{25}$ -16 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}

2. 4. 6. 2 Enhancement of non-racemic 1-(α-aminobenzyl)-2-naphthol (2) using oxalic acid

The same procedure as mentioned above was followed for the purification of *R*-(-)-sample of 1-(α-aminobenzyl)-2-naphthol **2** (80% ee, 1.24 g, 5 mmol) using oxalic acid (0.36 g, 4 mmol) in acetone (60 mL).

After decomposition:

From precipitate:

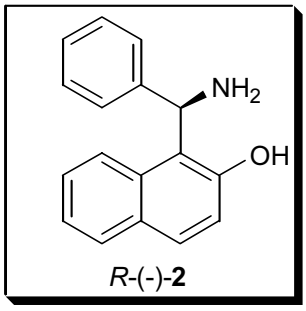


R-(-)-**2**

Yield 0.75 g (60%)

$[\alpha]_D^{25}$ -58.2 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.9 (*C* 5, benzene)}

From filtrate:



R-(-)-**2**

Yield 0.15 g (12%)

$[\alpha]_D^{25}$ -14.7 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.9 (*C* 5, benzene)}

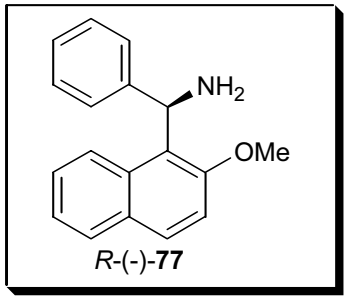
2. 4. 6. 3 Enrichment of non-racemic (2-methoxynaphth-1-yl)benzylamine (77) using oxalic acid

The partially resolved (*R*)-(-)-**77** of (2-methoxynaphth-1-yl)benzylamine **77** (75% ee, 1.32 g, 5 mmol) was taken in acetone (60 mL) and oxalic acid (0.34 g, 3.75

mmol) was added. The experimental procedure mentioned in the section 2.4.6.1 was followed and samples of R-(-)-**77** were obtained after workup.

After decomposition:

From precipitate:

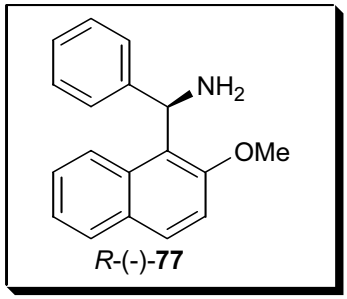


R-(-)-**77**

Yield 0.85 g (65%)

$[\alpha]_D^{25}$ -194 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}

From filtrate:



R-(-)-**77**

Yield 0.40 g (30%)

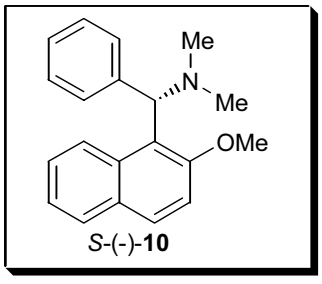
$[\alpha]_D^{25}$ -49 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}

2. 4. 6. 4 Purification of non-racemic [(2-methoxynaphth-1-yl)benzyl]dimethyl -amine (10) using oxalic acid

The non-racemic sample of *S*-(-)-[(2-methoxynaphth-1-yl)benzyl]dimethylamine **10** (50% ee, 1.45 g, 5 mmol) was taken in acetone (60 mL), to this the oxalic acid (0.22 g, 2.5 mmol) was added. The experimental procedure mentioned in the section 2.4.6.1 was followed to obtain the samples of *S*-(-)-**10.**

After decomposition:

From precipitate:

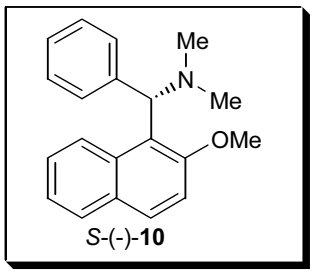


S-(-)-**10**

Yield 0.65 g (45%)

$[\alpha]_D^{25}$ -24.1 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

From filtrate:



S-(-)-**10**

Yield 0.7 g (48%)

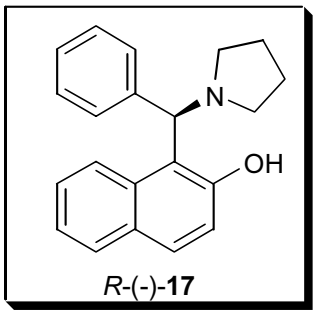
$[\alpha]_D^{25}$ -5.4 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

2. 4. 6. 5 Enhancement of non-racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol (17) using fumaric acid

The partially resolved (*R*)-(-)-1-(α-pyrrolidinylbenzyl)-2-naphthol **17** (72% ee, 1.5 g, 5 mmol) was taken in acetone (70 mL), to this fumaric acid (0.42 g, 3.6 mmol) was added and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the sample of *R*-(-)-**17**. The filtrate was concentrated and the residue was digested as outlined above to obtain the sample of *R*-(-)-**17** with higher ee.

After decomposition:

From precipitate:



R-(-)-**17**

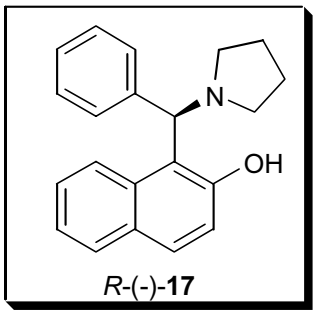
Yield 0.38 g (25%)

$[\alpha]_D^{25}$ -35.8 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}

From filtrate:

Yield 0.98 g (65%)

$[\alpha]_D^{25}$ -177 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}



R-(-)-**17**

2. 4. 6. 6 Enhancement of non-racemic 1-(α-aminobenzyl)-2-naphthol (2) using fumaric acid

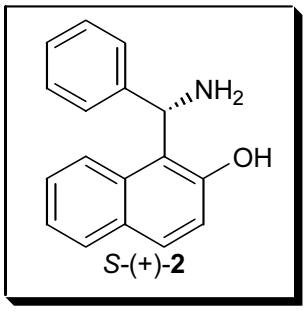
The same procedure as mentioned above was followed for the purification of non-racemic *S*-(+)-**2** of (1-(α-aminobenzyl)-2-naphthol (45% ee, 1.24 g, 5 mmol) using fumaric acid (0.26 g, 2.25 mmol) in DCM (60 mL).

After decomposition:

From precipitate:

Yield 0.5 g (40%)

$[\alpha]_D^{25}$ +8.8 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene)}

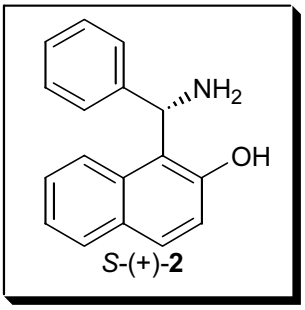


S-(+)-**2**

From filtrate:

Yield 0.43 g (35%)

$[\alpha]_D^{25}$ +45.9 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene)}



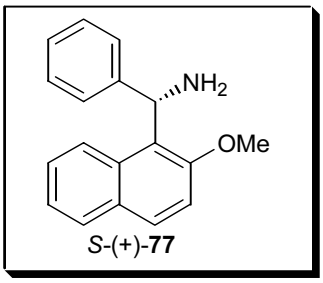
S-(+)-**2**

2. 4. 6. 7 Enrichment of non-racemic (2-methoxynaphth-1-yl)benzylamine (77) using fumaric acid

The partially resolved *S*-(+)-**77** of (2-methoxynaphth-1-yl)benzylamine (85% ee, 1.32 g, 5 mmol) was taken in acetone (60 mL), to this fumaric acid (0.49 g, 4.25 mmol) was added and following the experimental procedure as mentioned in the section 2.4.6.5, the *S*-(+)-**77** samples were isolated

After decomposition:

From precipitate:

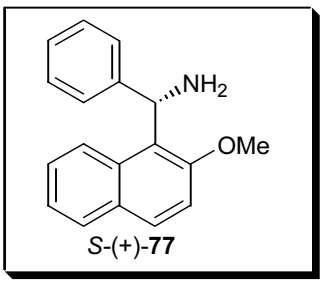


S-(+)-**77**

Yield 0.20 g (15%)

$[\alpha]_D^{25}$ +49 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = +196 (*C* 0.5, $CHCl_3$)}

From filtrate:



S-(+)-**77**

Yield 1.0 g (78%)

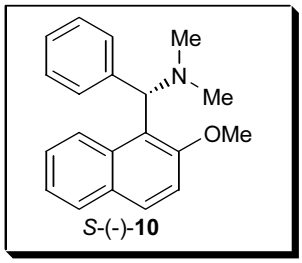
$[\alpha]_D^{25}$ +194 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = +196 (*C* 0.5, $CHCl_3$)}

2. 4. 6. 8 Purification of non-racemic [(2-methoxynaphth-1-yl)benzyl]dimethyl -amine 10 using fumaric acid

The non-racemic sample of (*S*)-(-)-[(2-methoxynaphth-1-yl)benzyl]dimethylamine **10** (50% ee, 1.45 g, 5 mmol) was taken in acetone (60 mL), to this fumaric acid (0.29 g, 2.5 mmol) was added and the experimental procedure as mentioned in the section 2.4.6.5 was followed.

After decomposition:

From precipitate:

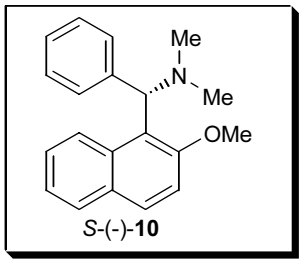


S-(-)-**10**

Yield 0.65 g (45%)

$[\alpha]_D^{25}$ -2.7 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

From filtrate:



S-(-)-**10**

Yield 0.72 g (50%)

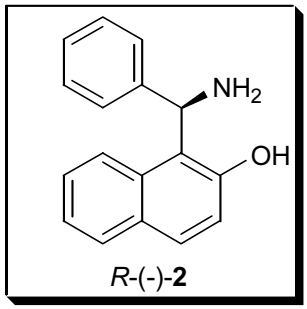
$[\alpha]_D^{25}$ -24.6 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

2. 4. 6. 9 Enhancement of non-racemic 1-(α-aminobenzyl)-2-naphthol (2) using maleic acid

The partially resolved (*R*)-(-)-1-(α-aminobenzyl)-2-naphthol **2** (72% ee, 1.24 g, 5 mmol was taken in DCM (60 mL), to this maleic acid (0.42 g, 3.6mmol)) was added and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the *R*-(-)-**2**. The filtrate was concentrated and the residue was digested as outlined above to obtain the samples of *R*-(-)-**2** with higher ee.

After decomposition:

From precipitate:



R-(-)-**2**

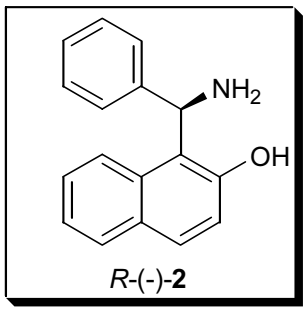
Yield 0.19 g (15%)

$[\alpha]_D^{25}$ -12.9 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.8 (*C* 5, benzene)}

From filtrate:

Yield 0.75 g (60%)

$[\alpha]_D^{25}$ -58.2 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -58.8 (*C* 5, benzene)}



R-(-)-**2**

2. 4. 6. 10 Enrichment of non-racemic (2-methoxynaphth-1-yl)benzylamine (77) using maleic acid

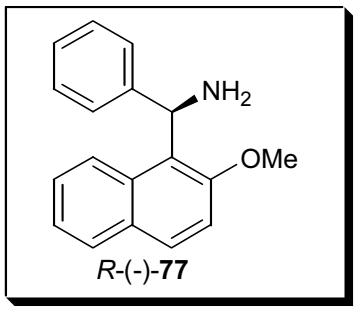
The same procedure as mentioned above was followed for the purification of the partially resolved *R*-(-)-(2-methoxynaphth-1-yl)benzylamine **77** (55% ee, 1.32 g, 5 mmol) using maleic acid (0.30 g, 2.60 mmol) in acetone (60 mL)

After decomposition:

From precipitate:

Yield 0.46 g (35%)

$[\alpha]_D^{25}$ -29.4 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}

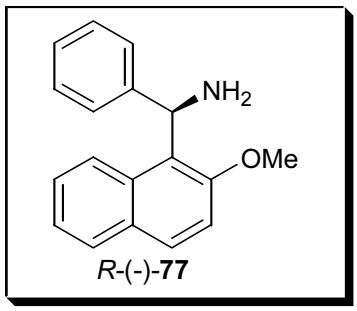


R-(-)-**77**

From filtrate:

Yield 0.8 g (60%)

$[\alpha]_D^{25}$ -157 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}



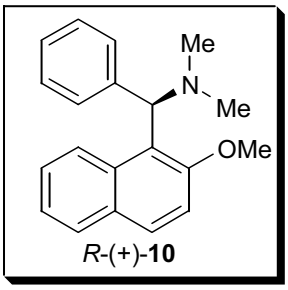
R-(-)-**77**

2. 4. 6 11 Purification of non-racemic [(2-methoxynaphth-1-yl)benzyl]dimethyl -amine 10 using maleic acid

The non-racemic sample of *R*-(+)-[(2-methoxynaphth-1-yl)benzyl]dimethylamine **10** (60% ee, 1.45 g, 5 mmol) was taken in acetone (60 mL), to this maleic acid (0.35 g, 3.0 mmol) was added and the experimental procedure outlined in the section 2.4.6.9 was followed to obtain samples of *R*-(+)-**10**.

After decomposition:

From precipitate:

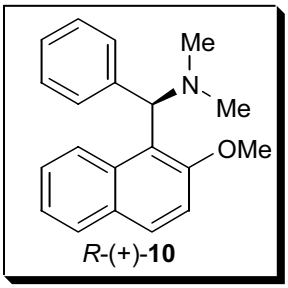


R-(+)-**10**

Yield 0.46 g (32%)

$[\alpha]_D^{25}$ +6.7 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +26.8 (*C* 1.1, $CHCl_3$)}

From filtrate:



R-(+)-**10**

Yield 0.80 g (55%)

$[\alpha]_D^{25}$ +26.5 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +26.8 (*C* 1.1, $CHCl_3$)}

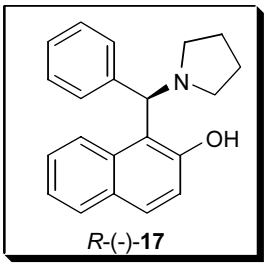
2. 4. 6. 12 Enhancement of non-racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol (17) using terephthalic acid

The partially resolved (*R*)-(-)-1-(α-pyrrolidinylbenzyl)-2-naphthol **17** (70% ee, 1.5 g, 5 mmol) was taken in acetone (70 mL), to this terephthalic acid (0.58 g, 3.5 mmol) was added and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with

brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the *R*-(-)-**17**. The filtrate was concentrated and the residue was digested as outlined above to obtain the sample of *R*-(-)-**17** with higher ee.

After decomposition:

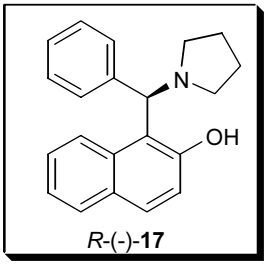
From precipitate:



Yield 0.38 g (25%)

$[\alpha]_D^{25}$ -35.8 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)}

From filtrate:



Yield 1.0 g (65%)

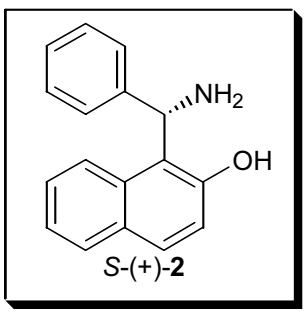
$[\alpha]_D^{25}$ -177 (*C* 1, $CHCl_3$), {lit.[46] for 100% ee, $[\alpha]_D^{25}$ = -179.1 (*C* 1.30, $CHCl_3$)

2. 4. 6. 13 Enhancement of non-racemic 1-(α-aminobenzyl)-2-naphthol (2) using terephthalic acid

The same procedure as mentioned above was followed for the purification of non-racemic *S*-(+)-1-(α-aminobenzyl)-2-naphthol **2** (25% ee, 1.24 g, 5 mmol) using terephthalic acid (0.21 g, 1.25 mmol) in DCM (60 mL).

After decomposition:

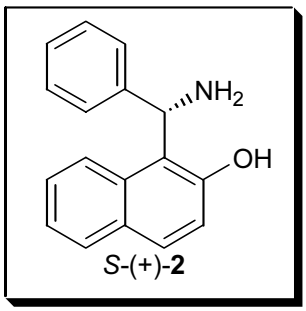
From precipitate:



Yield 0.62 g (50%)

$[\alpha]_D^{25}$ +4.7 (*C* 3, benzene), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene)}

From filtrate:



S-(+)-**2**

Yield 0.3 g (24%)

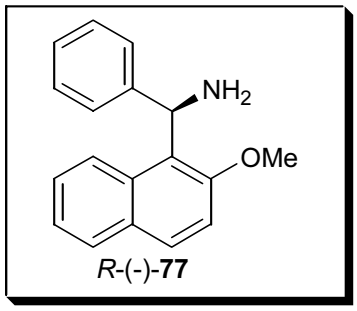
$[\alpha]_D^{25}$ +29.4 (*C* 3, benzene), {lit[29] for 100% ee, $[\alpha]_D^{25}$ = +58.8 (*C* 5, benzene)

2. 4. 6. 14 Enrichment of non-racemic (2-methoxynaphth-1-yl)benzylamine (77) using terephthalic acid

The partially resolved (*R*)-(-)-(2-methoxynaphth-1-yl)benzylamine **77** (85% ee, 1.32 g, 5 mmol) was taken in acetone (60 mL), to this terephthalic acid (0.7 g, 4.25 mmol) was added. The experimental procedure outlined in the section 2.4.6.12 was followed to obtain the samples of *R*-(-)-**77**.

After decomposition:

From precipitate:

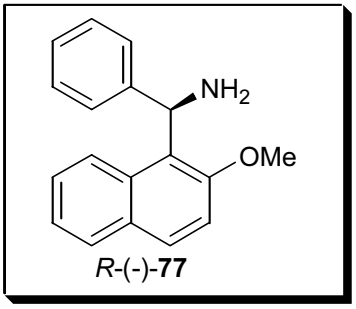


R-(-)-**77**

Yield 0.20 g (15%)

$[\alpha]_D^{25}$ -58.8 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}

From filtrate:



R-(-)-**77**

Yield 1.0 g (80%)

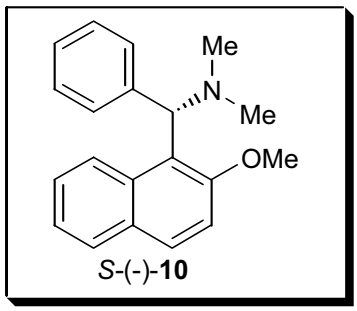
$[\alpha]_D^{25}$ -194 (*C* 1, $CHCl_3$), {lit.[70] for 100% ee, $[\alpha]_D^{25}$ = -196 (*C* 0.5, $CHCl_3$)}

2. 4. 6. 15 Purification of non-racemic [(2-methoxynaphth-1-yl)benzyl]dimethyl -amine using (10) terephthalic acid

The non-racemic sample of *S*-(-)-[(2-methoxynaphth-1-yl)benzyl]dimethylamine **10** (80% ee, 1.45 g, 5 mmol) was taken in acetone (60 mL), to this maleic acid (0.66 g, 4.0 mmol) was added and followed the same experimental procedure as mentioned in the section 2.4.6.12 was followed to obtain the samples of *S*-(-)-**10.**

After decomposition:

From precipitate:

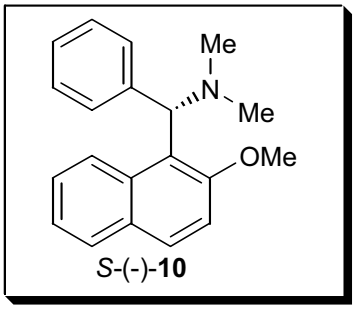


S-(-)-**10**

Yield 0.3 g (20%)

$[\alpha]_D^{25}$ -8.6 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

From filtrate:



S-(-)-**10**

Yield 1.0 g (72%)

$[\alpha]_D^{25}$ -26.5 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -26.8 (*C* 1.1, $CHCl_3$)}

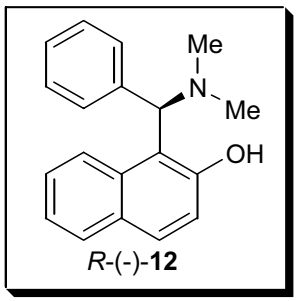
2. 4. 6. 16. Enhancement of non-racemic 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol (12) using trimesic acid

The partially resolved (*R*)-(-)-1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol **12** (75% ee, 1.38 g, 5 mmol) was taken in acetone (60 mL), to this trimesic acid (0.79 g, 3.75 mmol) was added and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were

washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the enriched samples of *R*-(-)-**12**. The filtrate was concentrated and the residue was digested as outlined above to obtain the *R*-(-)-**12**.

After decomposition:

From precipitate:

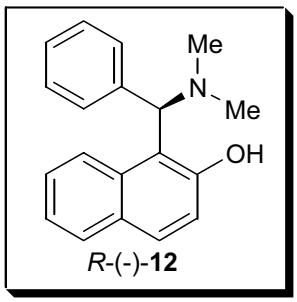


R-(-)-**12**

Yield 0.62 g (45%)

$[\alpha]_D^{25}$ -236 (*C* 1, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -238 (*C* 0.5, ethanol)}

From filtrate:



R-(-)-**12**

Yield 0.58 g (42%)

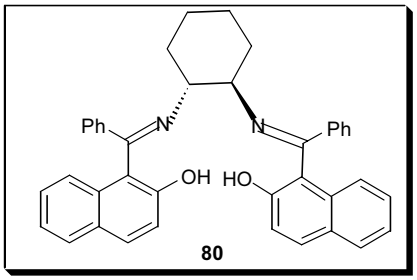
$[\alpha]_D^{25}$ -130 (*C* 0.5, $CHCl_3$), {lit.[29] for 100% ee, $[\alpha]_D^{25}$ = -238 (*C* 0.5, ethanol)}

2. 4. 7. Synthesis of chiral diaminonaphthols containing chiral 1,2-diamino-cyclohexane moiety

2. 4. 7. 1 Syntheis of chiral diiminonaphthols using chiral 1,2-diaminocyclohexane and 1-acyl-2-naphthol

(1*R*,2*R*)-1,2-Diaminocyclohexane (1.1 g, 10 mmol) was added to a stirred solution of 1-acyl-2-naphthol (20 mmol) in MeOH (30 mL). The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered and washed with MeOH (2 X 10 mL) to isolate the chiral diiminonaphthols.

1-[(1R,2R)-2-[(*E*)-1-(2-hydroxy-1-naphthyl)-1phenylmethylideneamino]cyclohexyl-imino(phenyl)methyl]-2-naphthol (80)



80

Yield 4.9 g (85%)

mp 263-265 ^{o}C,

IR (KBr) (cm^{-1}) 3236, 3059, 1620, 1512, 1435

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.04 (br s, 2H), 1.48-1.66 (m, 6H), 3.82 (br s, 2H), 7.24-7.33 (m, 12H), 7.42 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 4H), 7.80 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 8 Hz, 2H), 9.24 (br s, 2H) **(Spectrum No. 23)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 24.1, 31.6, 68.4, 117.0, 121.0, 123.5, 124.5, 126.1, 28.1, 128.3, 128.4, 129.1, 130.7, 132.0, 138.5, 151.0, 169.5 **(Spectrum No. 24)**

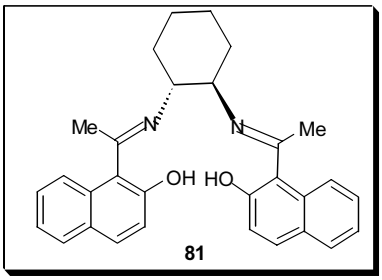
$[\alpha]_D^{25}$ +87 (*C* 1, THF)

Analysis Calculated for $C_{40}H_{34}N_2O_2$: C, 83.6%; H, 6.0%; N, 4.9%; O, 5.5%

Found : C, 83.5%; H, 6.0%; N, 4.8%; O, 5.6%

LCMS m/z 574 (M^+)

1-[(1*R*,2*R*)-2-[(*E*)-1-(2-hydroxy-1-naphthyl)-1phenylmethylideneamino]cyclohexyl-imino(phenyl)methyl]-2-naphthol (81)



81

Yield 3.6 g (80%)

mp 245-246 ^{o}C

IR (KBr) (cm^{-1}) 3250, 1639, 1593, 1224, 752

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.00 (br s, 2H), 1.49 (br s, 6H), 2H), 2.45 (s, 6H), 2.57 (s, 2H), 3.45 (br s, 2H), 7.30 (t, *J* = 8 Hz, 2H), 7.38-7.42 (m, 2H), 7.45-7.50 (m, 4H), 7.83-7.86 (m, 4H) **(Spectrum No. 25)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 20.5, 23.9, 24.5, 27.3, 31.1, 32.3, 61.4, 67.4, 112.8, 119.5, 121.4, 122.3, 123.3, 123.6, 124.6, 126.5, 126.9, 127.9, 128.4, 128.7, 129.1, 130.4, 130.8, 132.7, 134.5, 149.2, 168.5, 170.2, 171.4 **(Spectrum 26)**

$[\alpha]_D^{25}$ +84 (*C* 1, THF)

Analysis Calculated for $C_{30}H_{30}N_2O_2$: C, 80.0%; H, 6.7%; N, 6.2%; O, 7.1%

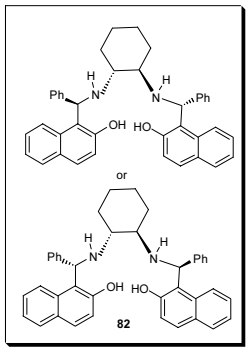
Found : C, 79.9%; H, 6.8%; N, 6.1%; O, 7.2%

LCMS m/z 450 (M^+)

2. 4. 7. 2 Reduction of the chiral diminonaphthols using $NaBH_4$

$NaBH_4$ (0.76 g, 20 mmol) was added through solid addition funnel to a solution of chiral diimine **80** or **81** (5 mmol) in THF (30 mL) at 0 ^oC. The resulting mixture was stirred at rt for 6 h. It was carefully quenched with water (5 mL) and extracted with ether (2 X 25 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography using hexane: ethyl acetate as eluent (95:5) to obtain the product.

1-[(1*R*,2*R*)-2-[2-hydroxy-1-naphthyl(phenyl)methylamino]cyclohexylamino-(phenyl)-methyl]-2-naphthol (82)



Yield 1.8 g (65%)

mp 112-114 ^oC

IR (KBr) (cm^{-1}) 3294, 1620, 1493, 1267, 814

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.87-0.94 (m, 2H), 1.30 (br s, 6H), 2.03 (d, *J* = 8 Hz, 3H), 2.45 (t, *J* = 8 Hz, 1H), 2.90 (s, 2H), 3.41 (t, *J* = 8 Hz, 1H), 5.82 (q, 1H), 7.11 (d, *J* = 12 Hz, 2H), 7.33 (t, *J* = 8 Hz, 2H), 7.45 (t, *J* = 8 Hz, 2H), 7.60 (d, *J* = 12 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H), 8.16 (d, *J* = 12 Hz, 2H) **(Spectrum No. 27)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 17.5, 29.7, 32.2, 49.8, 109.5, 118.1, 119.5, 121.9, 122.5, 122.8, 123.3, 126.3, 126.8, 128.6, 128.9, 129.6, 133.7, 152.5 **(Spectrum No. 28)**

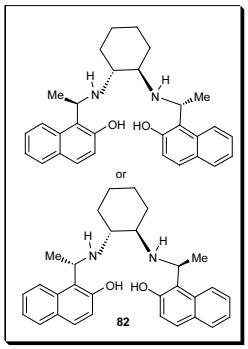
$[\alpha]_D^{25}$ -58 (*C* 1, THF)

Analysis Calculated for $C_{40}H_{38}N_2O_2$: C, 83.0%; H, 6.6%; N, 4.8%; O, 5.6%

Found : C, 83.0%; H, 6.5%; N, 4.9%; O, 5.6%

LCMS m/z 578 (M^+)

1-[(1*R*,2*R*)-2-[2-hydroxy-1-naphthyl)-1-phenylmethylideneamino]cyclohexyl-imino(phenyl)methyl]-2-naphthol (83)



Yield 1.4 g (60%)

mp 128-130 ^oC,

IR (KBr) (cm^{-1}) 3328, 1620, 1520, 1412, 1074

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.86-0.92 (m, 6H) 1.28 (br s, 12H), 2.03 (d, *J* = 8 Hz, 2H), 5.81 (q, 2H), 7.05 (d, *J* = 12 Hz, 2H), 7.35 (t, *J* = 8 Hz, 2H), 7.46 (t, *J* = 12 Hz, 2H), 7.63 (d, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H), 8.14 (d, *J* = 12 Hz, 2H) **(Spectrum No. 29)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 14.1, 20.0, 22.6, 29.7, 32.2, 119.2, 121.7, 122.5, 123.1, 127.0, 128.9, 129.8, 133.5, 142.0, 151.7 **(Spectrum No. 30)**

$[\alpha]_D^{25}$ -26 (*C* 1, THF)

Analysis Calculated for $C_{30}H_{34}N_2O_2$: C, 79.3%; H, 7.5%; N, 6.2%; O, 7.0%

Found : C, 79.1%; H, 7.6%; N, 6.3%; O, 7.0%

LCMS m/z 454 (M^+)

2. 4. 8 Synthetic applications of aminonaphthols

2. 4. 8. 1 Resolution of BINOL using aminonaphthol 17 and boric acid

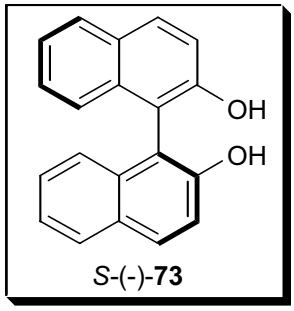
S-**(+)**-Aminonaphthol **17** (1.5 g, 5 mmol), $B(OH)_3$ (0.31 g, 5 mmol) and racemic BINOL **73** (1.46 g, 5 mmol) were taken in CH_3CN (50 ml) and the contents were stirred at 25 ^{0}C for 6 h and filtered. The precipitate was suspended in a mixture of THF (50 mL) and dil. HCl (2N, 20 mL) and stirred until complete dissolution occurs. The organic and aqueous layers were separated. The aqueous layer was extracted with ether (2 X 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to obtain the *S*-**(-)-73** (90% ee, 30% yield). The filtrate was concentrated and the residue was treated as outlined above to obtain **73** enriched in *R*-**(+)-73** (43% ee, 60% yield).

After decomposition:

From precipitate:

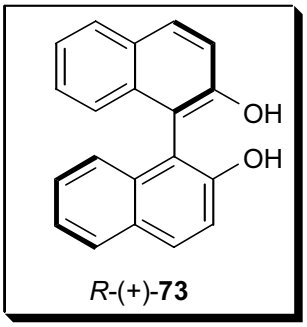
Yield 0.42 g (30%)

$[\alpha]_D^{25}$ -31.5 (*C* 1, THF), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = -35.0 (*C* 1, THF)}



S-(-)-**73**

From filtrate:



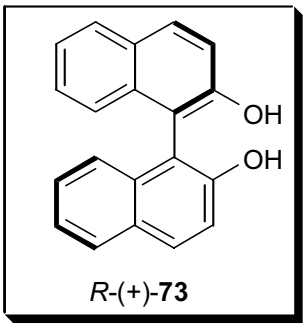
Yield 0.86 g (60%)

$[\alpha]_D^{25}$ +15.0 (*C* 1, THF), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +35 (*C* 1 THF)}

The partially resolved *R*-(+)-**73** (75% ee, 1.4 g, 5 mmol) was enriched by following the same procedure as mentioned above

After decomposition:

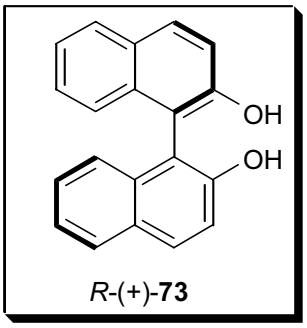
From precipitate:



Yield 0.93 g (65%)

$[\alpha]_D^{25}$ +34.6 (*C* 1, THF), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +35.0 (*C* 1, THF)}

From filtrate:



Yield 0.29 g (20%)

$[\alpha]_D^{25}$ +5.2 (*C* 1, THF), {lit.[72] for 100% ee, $[\alpha]_D^{25}$ = +35 (*C* 1 THF)}

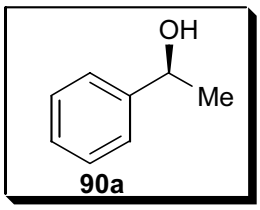
2. 4. 8. 2 Reduction of acetophenone (89a) to 1-phenyl ethanol using 20 mol% of aminonaphthol (2) and $NaBH_4/I_2$ reagent system

Iodine (0.77 g, 3 mmol) in dry THF (20 mL) was added through an addition funnel to the stirred suspension of $NaBH_4$ (0.23 g, 6 mmol) in dry THF (10 mL) under N_2 for 30 min at 0 ^oC. The (*S*)-(+)-aminonaphthol **2** (0.25 g, 1 mmol) in dry THF (10 mL) was added drop wise and the contents were stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and acetophenone **89a** (0.6 mL, 5 mmol) in dry THF (20

mL) was added drop wise for an hour through an addition funnel. After the addition was over, the contents were stirred at rt for 6 h. Then the reaction was quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL) at 0 ^{o}C. The mixture was stirred for 1 h at rt then, extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography using hexane:ethyl acetate (95:5) as eluent to obtain the product.

Yield 0.58 g (95%)

IR (neat) (cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900



90a

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.43 (d, *J* = 8 Hz, 3H), 2.65 (br s, 1H), 4.73 (q, *J* = 6.8 Hz, 1H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 25.1, 70.3, 125.5, 127.4, 128.5, 146.0

$[\alpha]_D^{25}$ -7.3 (*C* 1, MeOH), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -43 (*C* 1.0, MeOH)}

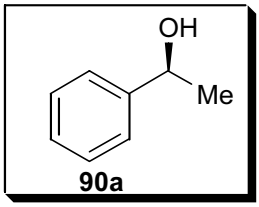
2. 4. 8. 3 Reduction of acetophenone (89a) to 1-phenyl ethanol using 20 mol% of aminonaphthol (2) and $NaBH_4$/TMSCl

TMS-Cl (1.9 g, 6 mmol) was added via syringe to the stirred suspension of $NaBH_4$ (0.23 g, 6 mmol) in dry THF (15 mL) under N_2 at rt. The contents were refluxed for 2 h. The reaction mixture was cooled to 0 °C and then the (*S*)-(+)-amino naphthol **2** (0.25 g, 1 mmol) in THF (10 mL) was added drop wise and the contents were stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and acetophenone **89a** (0.6 mL, 5 mmol) in dry

THF (20 mL) was added drop wise for an hour through an addition funnel. After further stirring for 6 h at 25 ^{o}C and workup the product was isolated.

Yield 0.56 g (92%)

$[\alpha]_D^{25}$ -7.7 (*C* 1, MeOH), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -43 (*C* 1.0, MeOH)}



90a

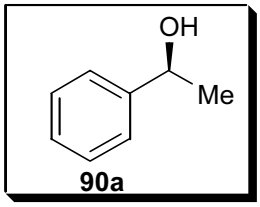
The spectral data were identical with that the sample obtained in the previous experiment.

2. 4. 8. 4 Reduction of acetophenone (89a) to 1-phenyl ethanol using 20 mol% of aminonaphthol (2) and *N, N*-diethylaniline:BH_3 system

A solution of *N,N*-diethylaniline:BH_3 (1M, 6 mL, 6 mmol) was added to the stirred solution of (*S*)-(+)-aminonaphthol **2** (0.25 g, 1 mmol) in dry THF (15 mL) under N_2 at rt. The contents were stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and acetophenone **89a** (0.6 mL, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through an additional funnel. After further stirring for 6 h at 25 ^{o}C and workup the product was isolated.

Yield 0.55 g (90%)

$[\alpha]_D^{25}$ -5.1 (*C* 1, MeOH), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -43 (*C* 1.0, MeOH)}



90a

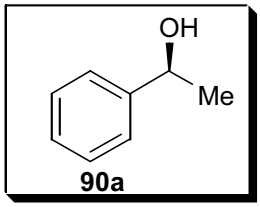
2. 4. 8. 5 Reduction of acetophenone (89a) to 1-phenyl ethanol using 20 mol% of aminonaphthol (2) and BH_3:SMe_2 system

BH_3:SMe_2 (1 mL, 6 mmol) was added to a stirred solution of *S*-(+)-aminonaphthol **2** (0.25 g, 1 mmol) in THF (15 mL) through syringe and the mixture was stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and acetophenone **89a** (0.6 mL, 5 mmol) in

dry THF (20 mL) was added drop wise for an hour through an addition funnel. After further stirring for 6 h at 25 ^{o}C and workup the product was isolated.

Yield 0.58 g (95%)

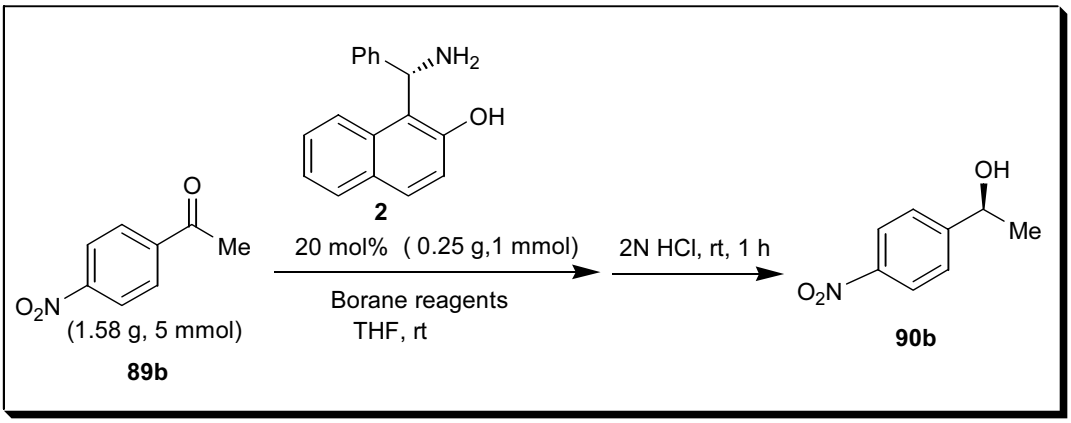
$[\alpha]_D^{25}$ -7.7 (*C* 1, MeOH), {lit.[78] for 100% ee, $[\alpha]_D^{25}$ = -43 (*C* 1.0, MeOH)}



90a

The p-nitroacetophenone **89b** and p-methoxyacetophenone **89c** were also reduced using borane reagents under various conditions. The yields and the $[\alpha]_D^{25}$ values are given below**.**

2. 4. 8. 6 Reduction of p-nitroacetophenone (89b) using 20 mol% of *S*-(+)-amino-naphthol (2) and borane reagents



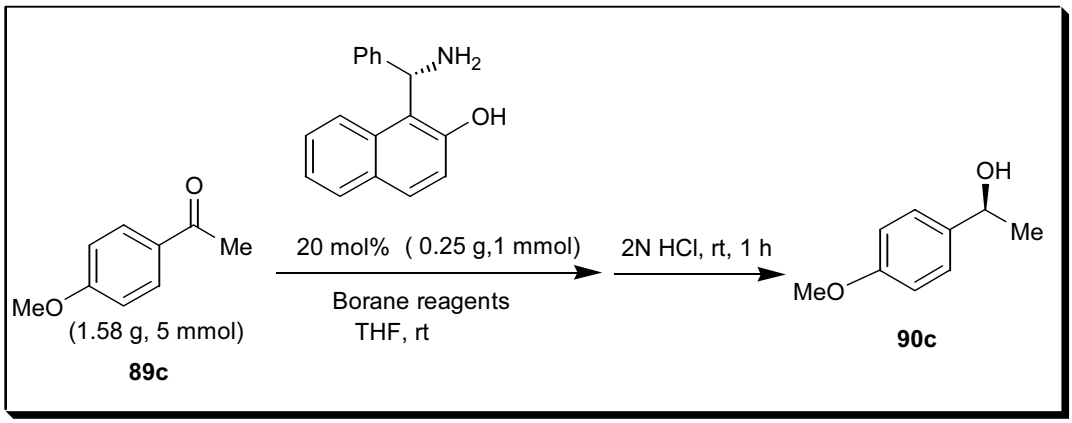
Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	0.76 g (92%)	-6.8 (*C* 1, MeOH)
$NaBH_4$/TMS-Cl	0.74 g (90%)	-7.7 (*C* 1, MeOH)
$Ph(C_2H_5)_2N{:}BH_3$	0.72 g (88%)	-5.6 (*C* 1, MeOH)
$BH_3{:}SMe_2$	0.78 g (95%)	-7.7 (*C* 1, MeOH)

IR (neat) (cm^{-1}) 3395, 3063, 2890, 1604, 1520, 1089, 752

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.53 (d, *J* = 8 Hz, 3H), 2.65 (br s, 1H), 5.02-5.04 (q, *J* = .8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 2H), 8.21 (d, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 25.1, 70.3, 122.5, 129.4, 145.8, 154.8

2. 4. 8. 7 Reduction of p-methoxyacetophenone (89c) using 20 mol% of *S*-(+)-aminonaphthol (2) and borane reagents



Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	0.67 g (88%)	-4.5 (*C* 1, EtOH)
$NaBH_4$/TMS-Cl	0.65g (85%)	-5.8 (*C* 1, EtOH)
$Ph(C_2H_5)_2N{:}BH_3$	0.62 g (82%)	-3.2 (*C* 1, EtOH)
$BH_3{:}SMe_2$	0.68 g (90%)	-6.3 (*C* 1, EtOH)

IR (neat) (cm^{-1}) 3363, 3063, 2972, 1602, 1458, 1076, 833

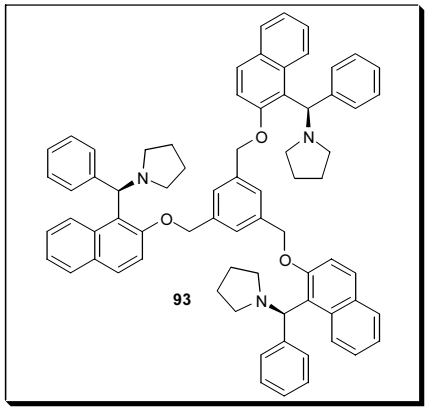
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.40 (d, *J* = 8 Hz, 3H), 1.75 (br s, 1H), 3.72 (s, 3H), 4.78 (q, *J* = 8 Hz, 1H), 6.79 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.0, 55.3, 70.0, 113.8, 126.9, 139.2, 158.0

2. 4. 9 Synthesis of tripodal compounds

2. 4. 9. 1 Synthesis of 1-[2-{3,5-di-[1-phenyl(tetrahydro-1H-1-pyrrolyl)methyl-2-naphthyloxymethyl]benzyloxy}-1-naphthyl(phenyl)methyl]pyrrolidine (93)

Anhydrous K_2CO_3 (1.38 g, 10 mmol) was added to a stirred solution of aminonaphthol *R*-(-)-**17** (2.7 g, 9 mmol) in acetone (30 mL) at rt. After 10 min tri bromide **91** (3 mmol) in acetone (15 mL) was added drop wise through an addition funnel. The resulting mixture was refluxed for 24 h. Then the solvent was evaporated under reduced pressure and the residue was washed with DCM (20 mL) and H_2O (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with DCM (2 X 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The evaporation of the solvent gave the product **93**. It was purified by silica gel column chromatography using hexane:ethyl acetate (90:10) as eluent



93

Yield 2.1 g (70%)

mp 165-166 ^{o}C

IR (KBr) (cm^{-1}) 2964, 1622, 1599, 1238, 951

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.75 (br s, 14H), 2.44 (br s, 5H), 2.65 (br s, 5H), 5.30 (s, 6H), 5.69 (s, 3H), 7.05-7.58 (m, 25H), 7.70 (d, *J* = 8 Hz, 8H), 9.46 (d-like, *J* = 8 Hz, 3H) **(Spectrum No. 31)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 23.7, 53.8, 66.7, 71.5, 115.3, 123.7, 125.9, 126.1, 126.7, 127.8, 128.2, 129.1, 130.0, 138.5, 144.0, 153.3 **(Spectrum No. 32)**

$[\alpha]_D^{25}$ +42 (*C* 1, THF)

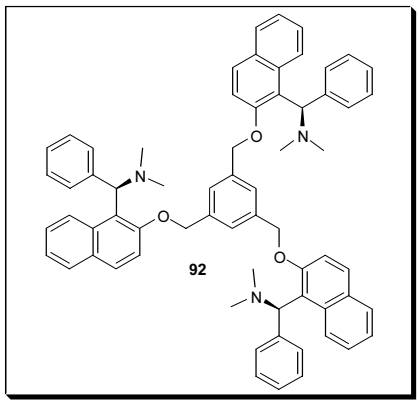
Analysis Calculated for $C_{72}H_{69}N_3O_3$: C, 84.4%; H, 6.8%; N, 4.1%; O, 4.7%

Found : C, 84.3%; H, 6.9%; N, 4.0%; O, 4.8%

GCMS m/z 1024 (M^+)

2. 4. 9. 2 Synthesis of *N,N*-dimethyl-2-{3,5-di[1-dimethylamino(phenyl)methyl-2-naphthyloxymethyl]benzyloxy}-1-naphthyl-phenylmethylamine (92)

Anhydrous K_2CO_3 (1.38 g, 10 mmol) was added to a stirred solution of aminonaphthol R-(-)-**12** (2.5 g, 9 mmol) in acetone (30 mL) at rt. After 10 min tri bromide (1.1 g, 3 mmol) in acetone (15 mL) was added drop wise through addition funnel and the same procedure as above was followed to obtain the crude product **92**. It was purified by columm chromatography on silica gel using hexane:ethyl acetate (92:8) as eluent.



Yield 1.8 g (65%)

mp 88-90 °C

IR (KBr) (cm^{-1}) 3057, 2984, 1622, 1595, 1215, 862

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.29 (br s, 18H), 5.29 (s, 6H), 5.49 (s, 3H), 7.08-7.51 (m, 25H), 7.64-7.71 (m, 8H), 9.42 (d-like, *J* = 8 Hz, 3H)

^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 45.3, 68.8, 70.8, 114.9, 123.8, 124.9, 126.1, 126.3, 126.5, 127.3, 128.0, 128.3, 129.4, 129.9, 132.9, 138.7, 142.8, 143.2, 153.4
$[\alpha]_D^{25}$	+32 (*C* 1, THF)
Analysis	Calculated for $C_{66}H_{63}N_3O_3$: C, 83.8%; H, 6.7%; N, 4.4%; O, 5.1%
	Found : C, 83.9%; H, 6.7%; N, 4.4%; O, 5.0%
GCMS	m/z 946 (M^+)

2. 5 References

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesi*s; Wiley: New York, **1994**.
2. Ojima, I. *Catalytic Asymmetric Synthesi*s; Ed.; VCH: New York, **1993**.
3. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysi*s; Eds.; Springer: Berlin, **1999**.
4. Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesi*s; Wiley: New York, **2001**.
5. Pu, L.; Yu, H. B. *Chem. Rev*. **2001**, *101*, 757.
6. Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833.
7. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835.
8. Vyskocil, S.; Jaracz, S.; Smrcina, M.; Sticha, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727.
9. Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schupfer, P.; Treptow, B.; Kundig, E. P. *Chirality* **2000**, *12*, 529.
10. Cimarelli, C.; Palmieri, G. *Tetrahedron* **1998**, *54*, 15711.
11. Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555.
12. Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361.
13. Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron* **2001**, *57*, 6089.
14. Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron* **2001**, *57*, 6809.
15. Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2011.

16. Cimarelli, C.; Palmieri, G.; Volpini, E. *J. Org. Chem*. **2003**, *68*, 1200.

17. Betti, M. *Gazz. Chim. Ital.* **1900**, *30 (II*), 301.

18. Betti, M. *Gazz. Chim. Ital*. **1900**, *30 (II*), 310.

19. Betti, M. *Organic Synthesis Collective* **1941**, *1*, 381.

20. Betti, M. *Gazz. Chim. Ital*. **1901**, *31 (I*), 377.

21. Betti, M. *J. Chem. Soc*. **1901**, *80* (*I*), 611.

22. Ahmed, N.; Hemphill, M. G.; Ray, F. E. *J. Am. Chem. Soc*. **1934**, *56*, 2403.

23. Betti, M. *J. Chem. Soc*. **1901**, *80* (*I*), 81.

24. Smith, H. E.; Cooper, N. E. *J. Org. Chem*. **1970**, *35*, 2212.

25. Betti, M. *Gazz. Chim. Ital*. **1903**, *33 (II*), 27.

26. Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. *Tetrahedron* **2003**, *59*, 2877.

27. Szatmari, I.; Martinek, T. A.; Lazar, L.; Koch, A.; Kleinpeter, E.; Neuvonen, K.; Fulop, F. *J. Org. Chem*. **2004**, *69*, 3645.

28. Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. *Eur. J. Org. Chem.* **2004**, 2231.

29. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667.

30. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685.

31. Grumbach, H-J.; Arend, M.; Risch, N. *Synthesis* **1996**, 883.

32. Yasuda, M.; Sone, T.; Tanabe, K.; Shima, K. *J. Chem. Soc., Perkin Trans.* I **1995**, 459.

33. Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *Monatsh. Chem*. **2001**, *132*, 875.

34. Mojtahedi, M. M.; Sharifi, A.; Mohsenzadeh, F.; Saidi, M. R. *Synth. Commun*. **2000,** *30*, 69.

35. Saidi, M. R.; Nazari, M. *Monatsh. Chem*. **2004**, *135*, 875.

36. Huang, M-H.; Wu, S-N.; Wang, J-P.; Lin, C-H.; Lu, S-I.; Liao, L-F.; Shen, A-Y. *Drug Dev. Res.* **2003**, *60*, 261.

37. Searcey, M.; Grewal, S. S.; Madeo, F.; Tsoungas, P. *Tetrahedron lett*. **2003**, *44*, 6745.

38. Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem*. **2001**, *66*, 4759.

39. Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2417.

40. Liu, D.-X.; Zhang, L.-C.; Wang, Q.; Da, C.-S.; Xin, Z.-Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett*. **200**1, *3*, 2733.

41. Saidi, M. R.; Azizi, N.; Naimi-Jamal, M. R. *Tetrahedron Lett*. **2001**, *42*, 8111.

42. Saidi, M. R.; Azizi, N. *Tetrahedron: Asymmetry* **2003**, *14*, 389.

43. Ji, J-X.; Qiu, L-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem*. **2003**, *68*, 1589.

44. Gong, Y.; Kato, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 2121.

45. Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. *Tetrahedron Lett*. **2002**, *43*, 8367.

46. Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans 1*, **2002**, 2900.

47. Xu, X.; Lu, J.; Li, R.; Ge, Z.; Dong, Y.; Hu, Y. *Synlett* **2004**, 122.

48. Xu, X.; Lu, J.; Dong, Y.; Li, R.; Ge, Z.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 475.

49. Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1667.

50. Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem*. **2005**, *70*, 1897.

51. Wang, Y.; Li, X.; Ding, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1291.

52. Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem*. **2005**, *70*, 575.

53. Woodgate, P. D.; Horner, G. M.; Maynard, N. P.; Rickard, C. E. F. *J. Organomet. Chem*. **1999**, *592*, 180.

54. Szatmari, I.; Hetenyi, A.; Lazar, L.; Fulop, F. *J. Heterocyclic Chem*. **2004,** *41,* 367.

55. Boga, C.; Martino, E. d.; Forlani, L.; Torri, F. *J. Chem. Research (s),* **2001**, 43.

56. Shen, A-Y.; Wu, S-N. *Drug Dev. Res.* **1998,** *44,* 87.

57. Supsana, P.; Tsoungas, P. G.; Aubry, A.; Skoulika, S.; Varvounis, G. *Tetrahedron* **2001**, *57*, 3445.

58. Sheldon, R. A. *Chirotechnology Industrial Synthesis of Enantiomerically Active Compounds*; Marcel Dekker: New York, **1993**.

59. Periasamy, M.; Prasad, A. S. B.; Kanth, J. V. B.; Reddy, Ch. K. *Tetrahedron: Asymmetry* **1995**, *6*, 341.

60. Periasamy, M. *Pure Appl. Chem.* **1996**, *68*, 663 (presented at the IUPAC International Conference in Organic Synthesis (ICOS 9), December 11-16, 1994, Abstract No. SL 36, Bangalore, India).

61. Venkatraman, L.; Periasamy, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2471.

62. Periasamy, M.; Venkatraman, L.; Thomas, K. R. J. *J. Org. Chem.* **1997**, *62*, 4302.

63. Periasamy, M.; Ramanathan, C. R.; Prasad, A. S. B.; Kanth, J. V. B. *Enantiomer* **1998**, *3*, 3.

64. Ramanathan, C. R.; Periasamy, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2651.

65. Periasamy, M.; Venkatraman, L.; Sivakumar, S.; kumar, N. S.; Ramanathan, C. R. *J. Org. Chem.* **1999**, *64*, 7643.

66. Periasamy, M.; kumar, N. S.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 7643.

67. Periasamy, M.; Reddy, M. N.; Anwar, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2307.

68. Periasamy, M.; Ramanathan, C. R.; Kumar, N. S. *Tetrahedron: Asymmetry* **1999**, *10*, 2307.

69. Brode, W. R.; Littman, J. B. *J. Am. Chem. Soc*. **1930**, *52*, 5056.

70. Ray F. E.; Roomaw, W. A. *J. Am. Chem. Soc*. **1933**, *55*, 3833.

71. Periasamy, M.; Sivakumar, S.; Narsireddy, M.; Padmaja, M. *Org. Lett*. **2004**, *6*, 265.

72. Brunel, J. M.; Buono, G. *J. Org. Chem*. **1993**, *58*, 7313.

73. Deloux, L.; Srebnik, M. *Chem. Rev*. **1993**, *93*, 763.

74. Singh, V. K. *Synthesis* **1991**, 605.

75. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.

76. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551.

77. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315.

78. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsten, K.; Carroll, J. D.; Corley, E. J.; Grabowski, E. J. J. *J. Org. Chem*. **1993**, *58*, 2880.

79. Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem*. **1994,** *59*, 1969.

80. Burke, W. J.; Reynolds, R. *J. Am. Chem. Soc*. **1954**, *76*, 1291.

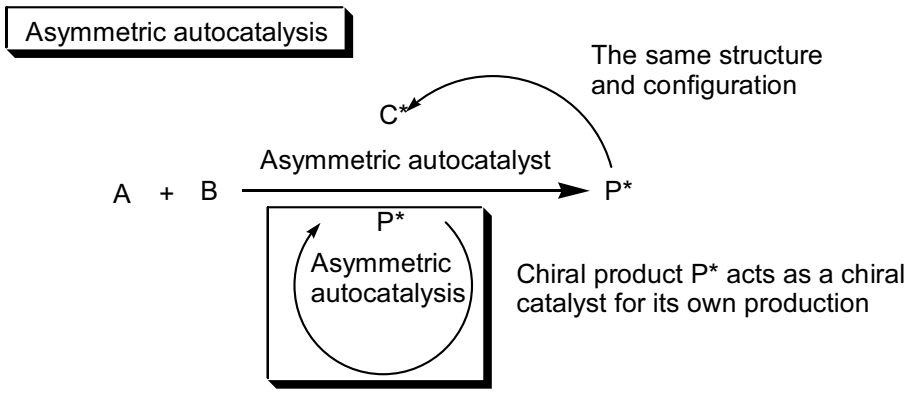
Chapter 3

Efforts towards development of asymmetric autocatalytic borane reduction

3. 1 Introduction

In recent years, there has been immense interest in the development of catalytic asymmetric processes because in this way a large amount of a chiral compound can be produced using only a small amount of a chiral catalyst.[1,2] In asymmetric catalysis, the structure of the chiral catalyst (C*) is generally quite different from that of the chiral product (P*). On the other hand, when a chiral product acts as a catalyst for its own production, the process is defined as asymmetric autocatalysis (Scheme 1).[3–10]

Scheme 1



Asymmetric autocatalysis has several advantages over ordinary asymmetric catalysis: (i) No chiral auxiliary other than the product is necessary and no separation of the product from the catalyst is required, (ii) asymmetric autocatalysis has high reaction efficiency. This is because the amount of chiral catalyst increases as the reaction proceeds; therefore, the reaction proceeds rapidly toward completion and (iii) there is no deterioration or loss of chiral catalyst.

We have examined the possibility of developing an asymmetric autocatalytic borane reduction involving oxazaborolidine intermediates. Accordingly, it may be of interest to review the asymmetric autocatalytic processes developed by various groups.

Although in 1953 Frank[11] has proposed kinetics of asymmetric autocatalysis, neither an actual compound nor an actual reaction was available at that time. In recent years, several autocatalytic processes were realized in the addition of dialkylzinc reagents to aromatic aldehydes.[12,13]

3. 1. 1 Discovery of asymmetric autocatalysis using organozinc reagents

Soai *et al*.[14] reported the catalytic enantioselective addition of dialkylzinc to aldehydes (Scheme 2) using *N*,*N*-dibutylnorephedrine (DBNE) **1,**[15] 1-phenyl-2-(1-pyrrolidinyl)-1-propanol (PPP) **2**[16] and diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) **3**[17] as catalysts (Chart 1).

Scheme 2

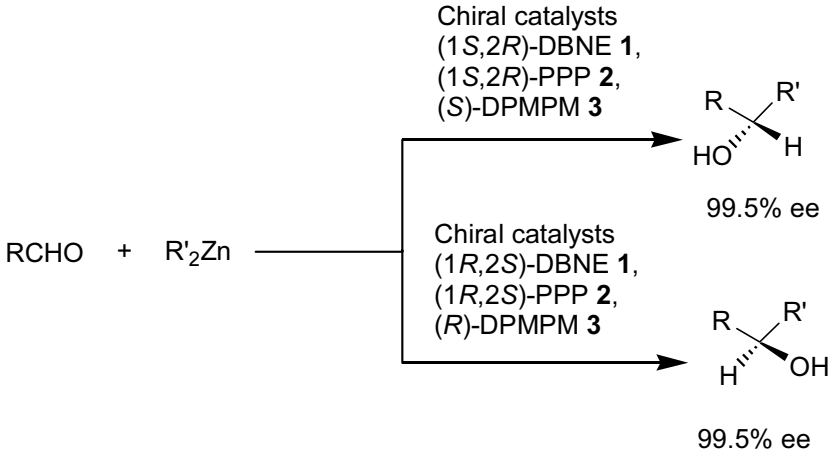
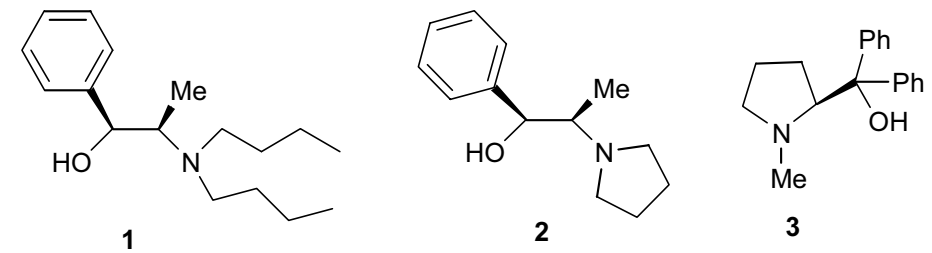


Chart 1



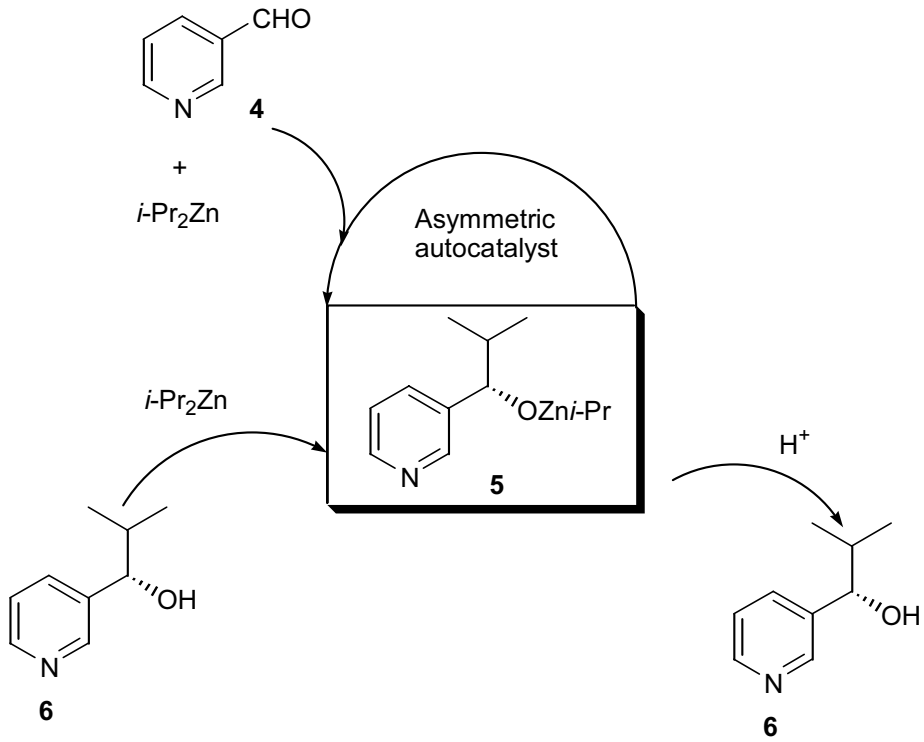
1 **2** **3**

They also examined the enantioselective addition of dialkylzinc to pyridine-3-carboxaldehyde and benzaldehyde using *N*,*N*-dibutylnorephedrine **1** as a chiral catalyst.[18] It was found that the reaction of pyridine-3-carboxaldehyde is faster than that of benzaldehyde, which indicated that the ethylzinc alkoxide of 3-pyridyl alkanol formed *in situ* may act as an asymmetric autocatalyst. These observations led to the discovery of autocatalysis.

3. 1. 1. 1 The first asymmetric autocatalysis of chiral pyridyl alcohol

In 1990, Soai *et al*.[19] discovered the first asymmetric autocatalysis in the enantioselective addition of diisopropylzinc to pyridine-3-carboxaldehyde **4** using catalytic amount of (*S*)-2-methyl-1-(3-pyridyl)-1-propanol **6**.

Scheme 3



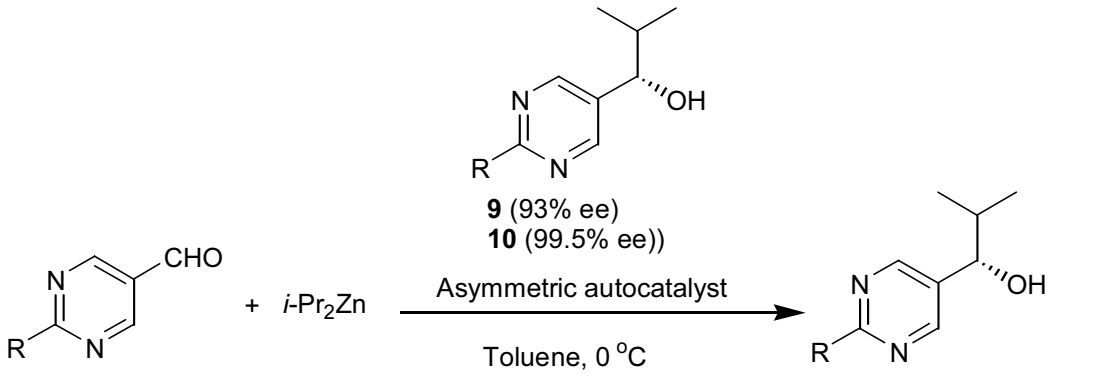
(*S*)-Pyridyl alkanol **6** automultiplied and the newly formed product possessed the same structure and configuration as the catalyst. Chiral alkoxide **5** formed *in situ* from

4 and *i*-Pr_2Zn is considered to be catalyzing the enantioselective addition of *i*-Pr_2Zn to aldehyde and to form itself. For example, when (*S*)-3-pyridyl alkanol **6** with 86% ee was used as an asymmetric autocatalyst in the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to pyridine-3-carboxaldehyde **4**, the newly formed (*S*)-3-pyridyl alkanol **6** had an ee of 35% (Scheme 3).

3. 1. 1. 2 Highly enantioselective asymmetric autocatalysis of chiral pyrimidyl alkanol

When enantiomerically enriched pyrimidyl alkanol **9** or **10** was used as an asymmetric autocatalyst in the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carboxaldehyde **7** or **8** the newly formed pyrimidyl alkanol **9** or **10** was found to be automultiplied without loss of enantiomeric purity (Scheme 4). This is the first example of the highly enantioselective asymmetric autocatalysis.[20]

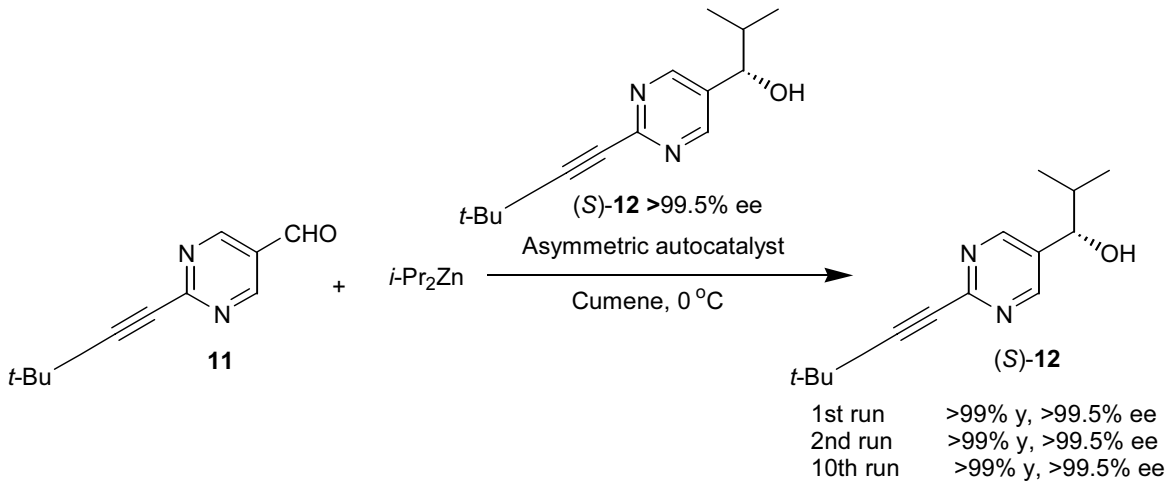
Scheme 4



After screening several substituted pyrimidines, Soai and coworkers found that the substituent on the 2-position of the pyrimidine ring is very important in achieving high enantioselectivity and that the alkynyl,[21] alkenyl[22] groups are the best for this

purpose. In the presence of (*S*)-5-pyrimidyl alkanol **12** (which has a *t*-butyl-ethynyl group on the second position of the pyrimidine ring), the enantioselective alkylation of 2-alkynyl-5-pyrimidine-carboxadehyde **11** was examined using 1.7 equivalents of diisopropylzinc in cumene solvent. In this case (*S*)-5-pyrimidyl alkanol **12** was obtained in a near quantitative yield (>99%) and in an almost enantiomerically pure form (>99.5% ee) (Scheme 5). In ten consecutive asymmetric autocatalytic reactions, in which the obtained product (*S*)-**12** was used as an asymmetric autocatalyst for the next run, a practically perfect asymmetric autocatalysis could be established. During the ten consecutive reactions, the initial (*S*)-5-pyrimidyl alkanol **12** was automultiplied by a factor of about 60,000,000.[21]

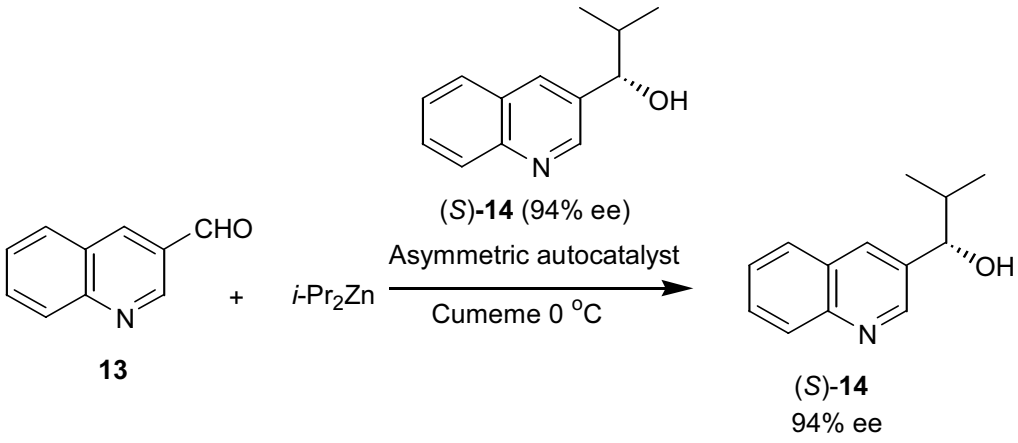
Scheme 5



3. 1. 1. 3 Asymmetric autocatalysis of chiral quinolyl alkanol

(*S*)-3-Quinolyl alkanol **14** was also found to act as an asymmetric autocatalyst. For example, (*S*)-3-quinolyl alkanol **14** with 94% ee catalyzes the enantioselective addition of *i*-Pr_2Zn to quinoline-3-carboxaldehyde **13** to afford (*S*)-**14** itself with 94% ee with the same configuration as the catalyst (Scheme 6).[23]

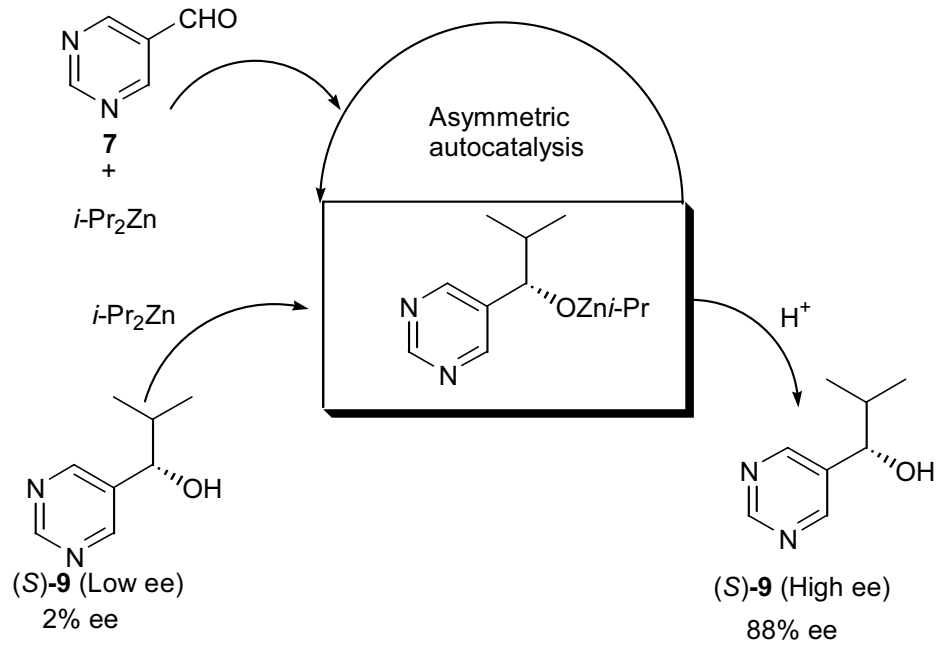
Scheme 6



3. 1. 1. 4 Asymmetric autocatalysis with amplification of enantiomeric excess

When pyrimidyl alkanol with low ee was used as an asymmetric autocatalyst, the ee of the product pyrimidyl alkanol was found to be higher than that of the initial asymmetric autocatalyst.[24]

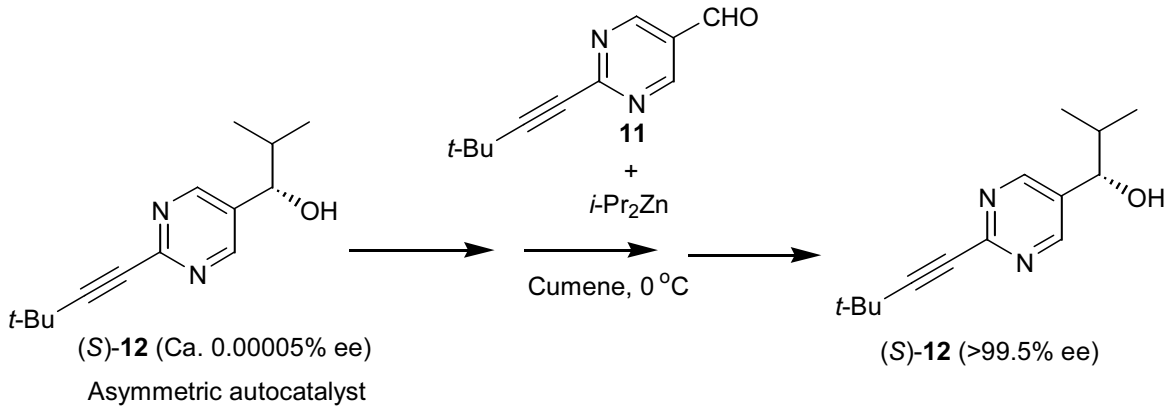
Scheme 7



For example, when (*S*)-5-pyrimidyl alkanol **9** with only 2% ee used as an asymmetric autocatalyst, after four successive asymmetric autocatalytic runs, in which each time the product was used as the asymmetric autocatalyst for the next round, the ee of the pyrimidyl alkanol **9** was raised to 88% (Scheme 7).[24]

This type of successive asymmetric autocatalysis is more effective in the case of 2-alkynyl substituted 5-pyrimidylalkanol. For example, when the slightly (*S*)-enriched 5-pyrimidyl alkanol **12** with ca. 0.00005% ee (*S*:*R* = 50.000025:49.999975) was used as an initial catalyst, an almost enantiomerically pure (>99.5% ee) pyrimidyl alkanol **12** was obtained after three consecutive autocatalytic enantioselective isopropylation of the aldehyde **11** (Scheme 8).[25]

Scheme 8

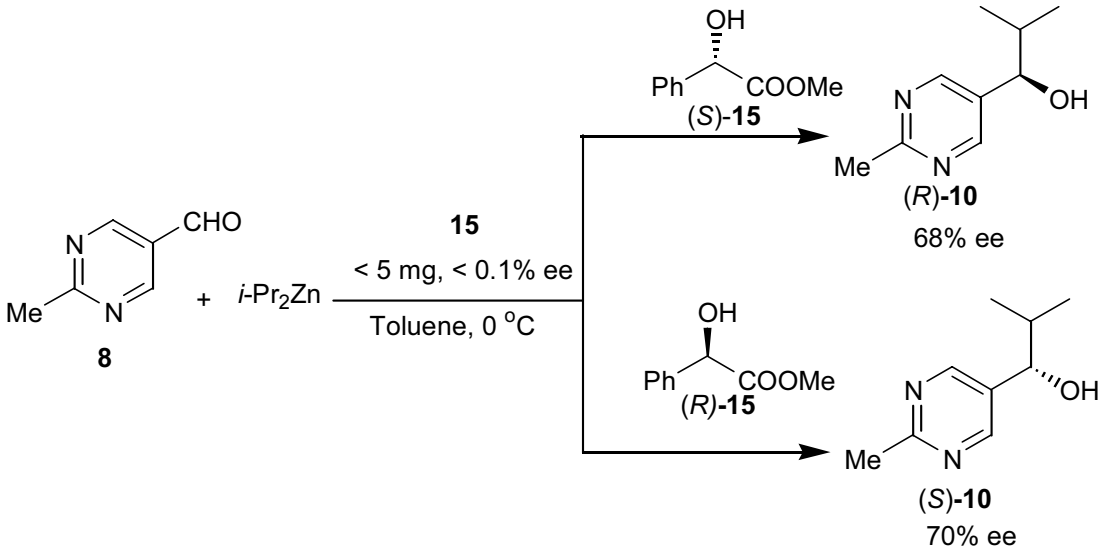


3. 1. 1. 5 Asymmetric autocatalysis using chiral initiators

If a chiral molecule with very low ee is used in the initial conditions, instead of an asymmetric autocatalyst, the chiral molecule may serve as a chiral initiator and the expected slight enantiomeric imbalance could be enhanced by the subsequent one pot asymmetric autocatalysis with an amplification of chirality. This had been realized, for example, in the asymmetric autocatalysis of pyrimidyl alkanol **10**, when (*S*)-methyl

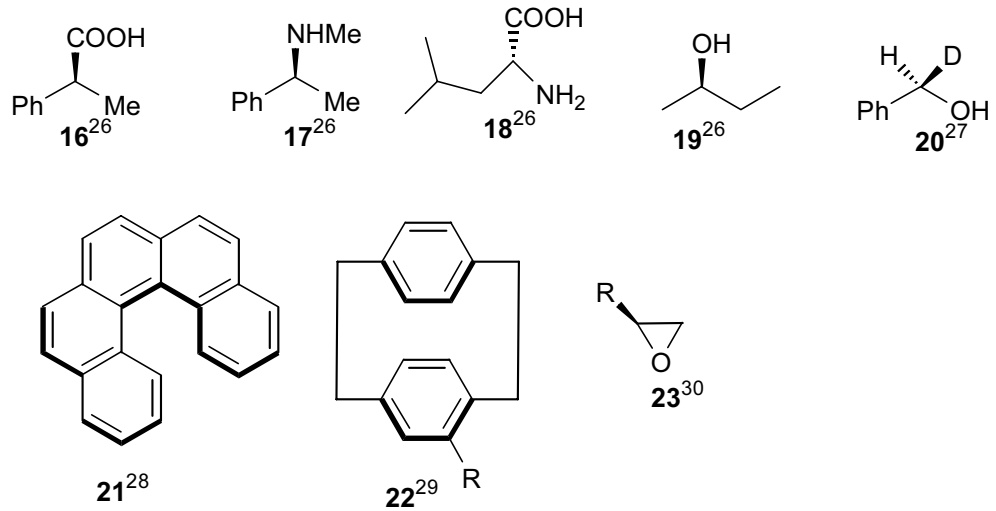
mandalate with a low ee (0.1% ee) as a chiral initiator and *i*-Pr_2Zn and pyrimidine-2-carboxaldehyde **8** were added in portions (Scheme 9).[26] In this run, the ee of the (*R*)-pyrimidyl alkanol was amplified up to 68% ee.

Scheme 9.



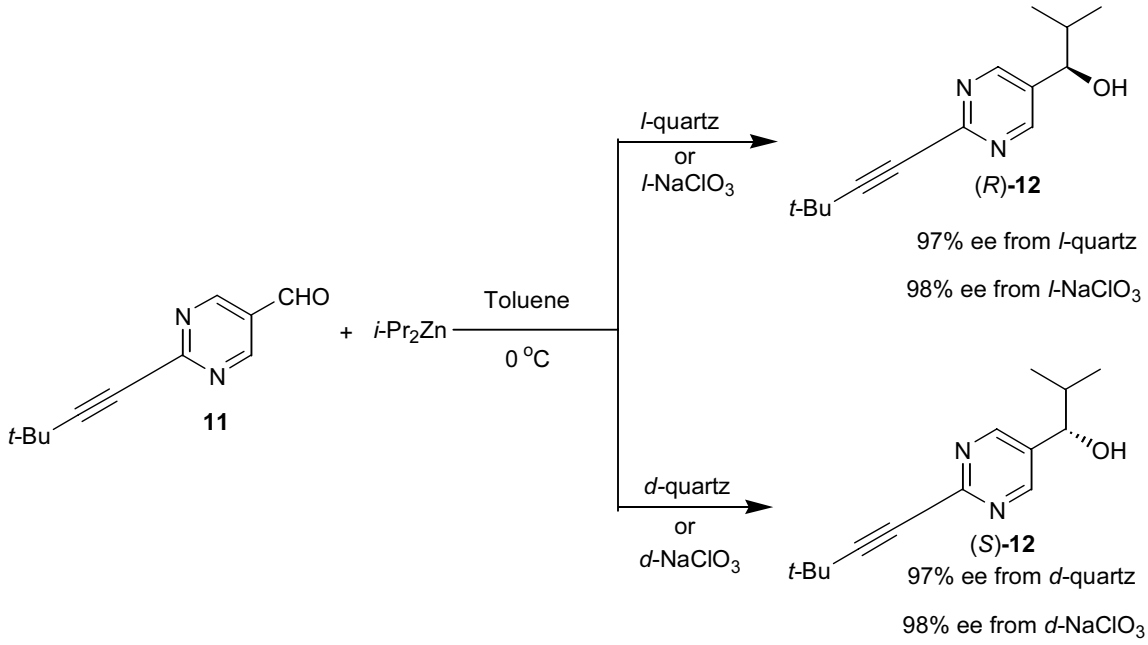
Similar results were obtained with other chiral initiators (Chart 2).[26-30]

Chart 2



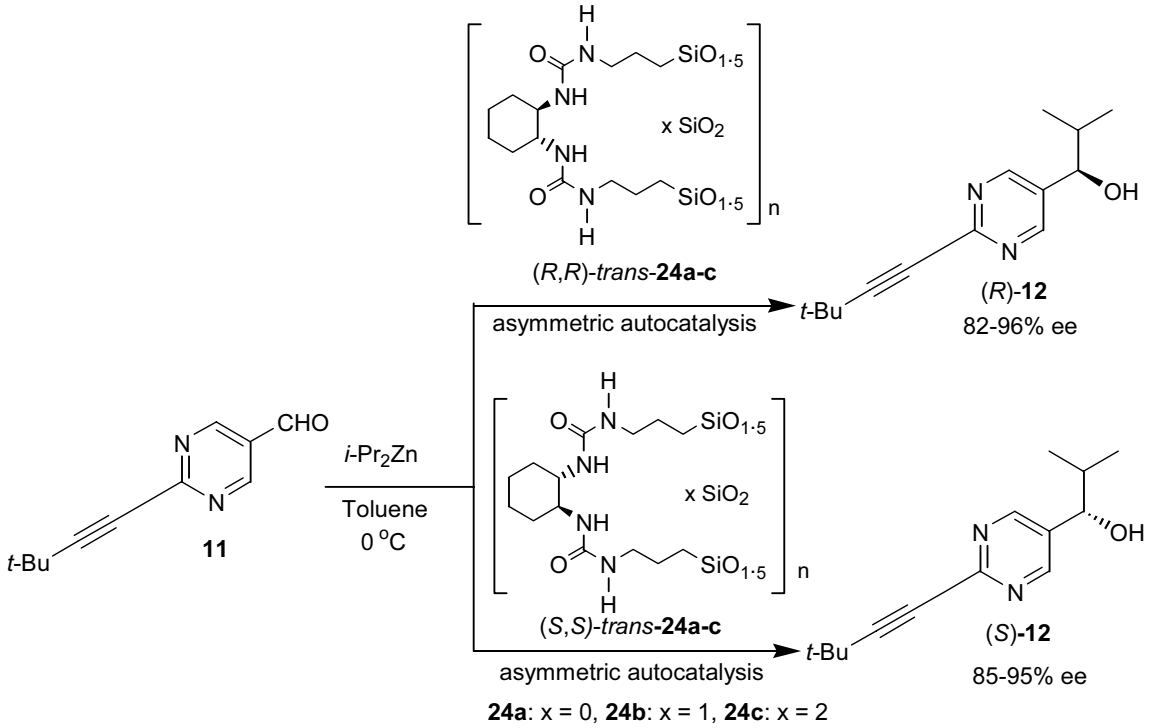
In the place of the chiral organic initiators, the chiral SiO_2 or $NaClO_3$ could be also used as chiral initiators. For example, the asymmetric isopropylation of 2-alkenyl-pyrimidine-5-carboxaldehyde **11** with *i*-Pr_2Zn in presence of *l*-quartz powder or *l*-$NaClO_3$ afforded (*R*)-pyrimidyl alkanol **12** with 97% ee (Scheme 10).[31-35]

Scheme 10



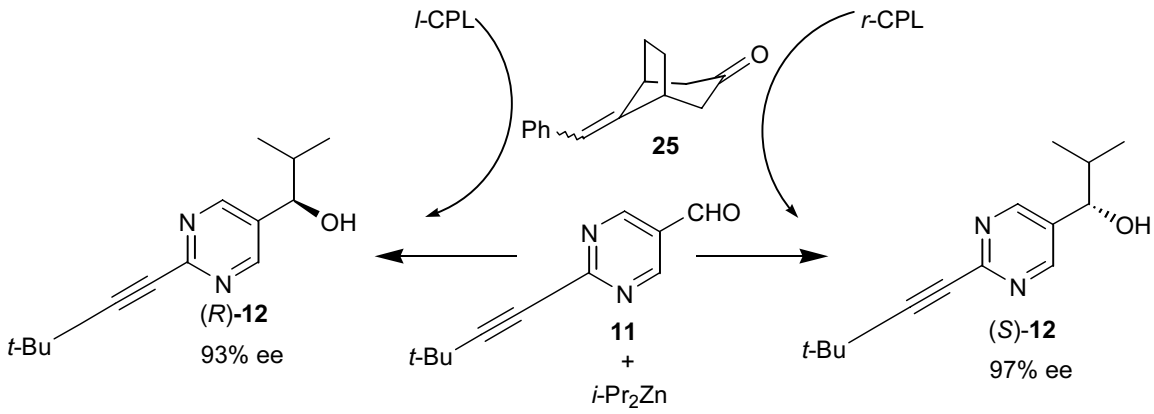
In a subsequent study, the same team has used chiral organic-inorganic hybrid silsesquioxanes prepared from silylated *trans*-(*R,R*)-1,2-diaminocyclohexane as initiator. Addition of this material to a solution of 2-alkynyl-pyrimidine-5-carbaldehyde **11** followed by addition of *i*-Pr_2Zn, resulted in the formation of pyrimidyl alkanol **12** with high yield and ee (Scheme 11).[36]

Scheme 11



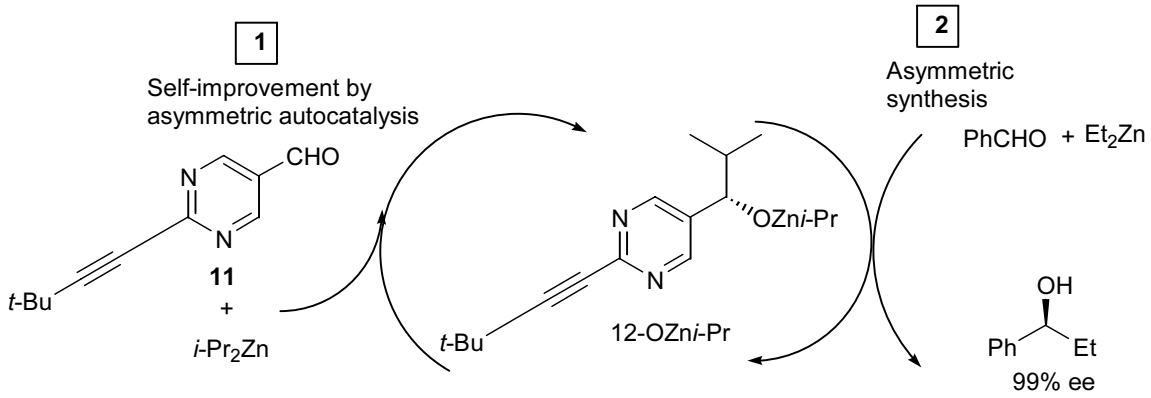
Racemic olefin **25** irradiated with *r*- or *l*-CPL (circularly polarized light) also induces enantioselective addition of *i*-Pr_2Zn, to 2-alkynyl-pyrimidine-5-carboxaldehyde **11**, afforded the pyrimidyl alkanol **12** with high enantiomeric excess (Scheme 12).[37]

Scheme 12



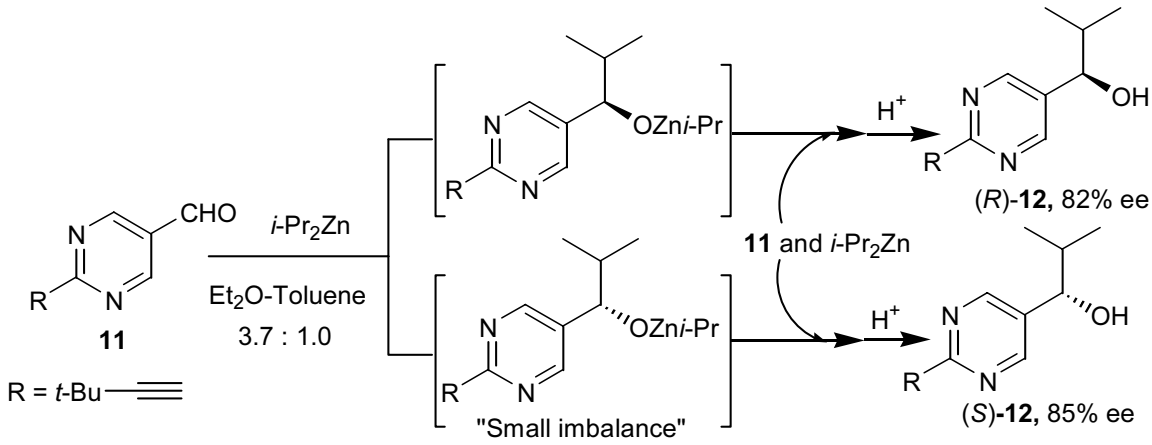
Recently Soai *et al.*[38] reported a new and efficient one-pot method of asymmetric catalysis in which a chiral catalyst for 5-pyrimidyl alkanol **12** self-improves its ee by asymmetric autocatalysis and then acts as a highly enantioselective chiral catalyst for other asymmetric synthesis such as addition of dialkylzinc to aldehydes to provide secondary alcohols with very high ee (Scheme 13).

Scheme 13



It has been also claimed that optically active pyrimidyl alkanol **12** is generated in the reaction between 2-alkynyl-pyrimidine-5-carbaldehyde **11** and *i*-Pr_2Zn in conjunction with subsequent asymmetric autocatalysis in a mixed solvent of ether and toluene without adding chiral substances (Scheme 14).[39]

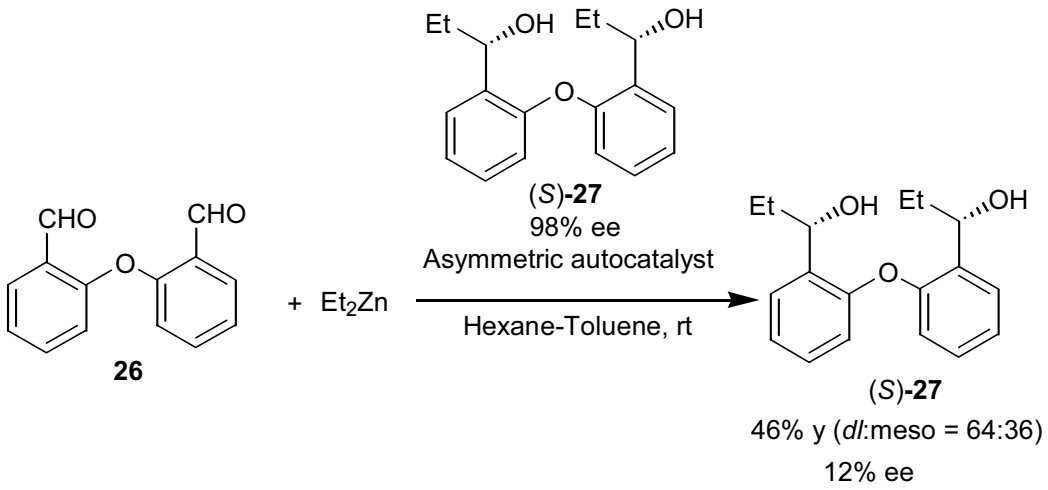
Scheme 14



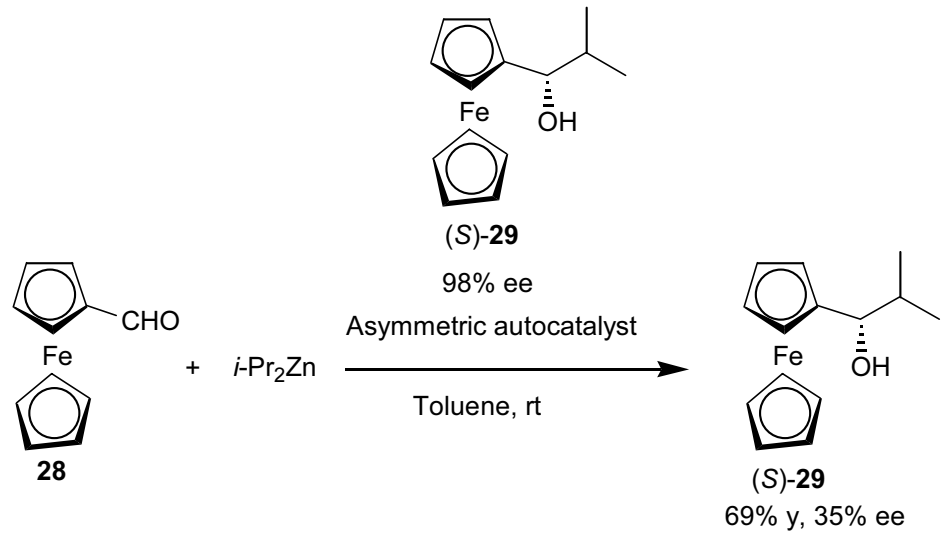
3. 1. 1. 6 Asymmetric autocatalysis of ferrocenyl alcohol and diol

Chiral diols having a diphenyl ether skeleton and a ferrocenyl alkanol were also found to serve as asymmetric autocatalysts. However, the ees of the products were lower than that of the asymmetric catalysts (Schemes 15 and 16).[40,41]

Scheme 15



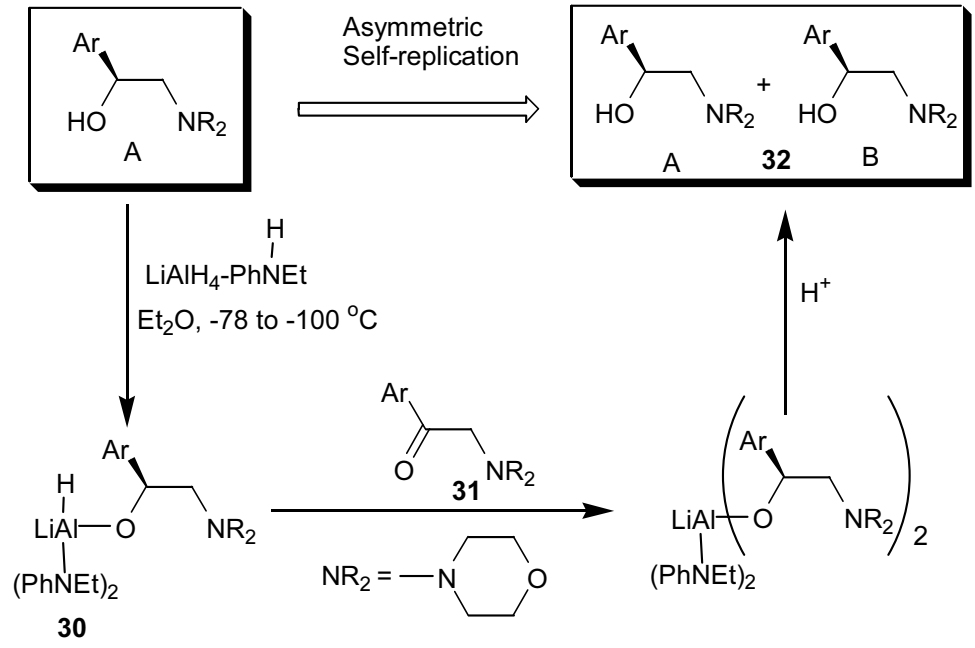
Scheme 16



3. 1. 1. 6 Autocatalytic reduction using $LiAlH_4$

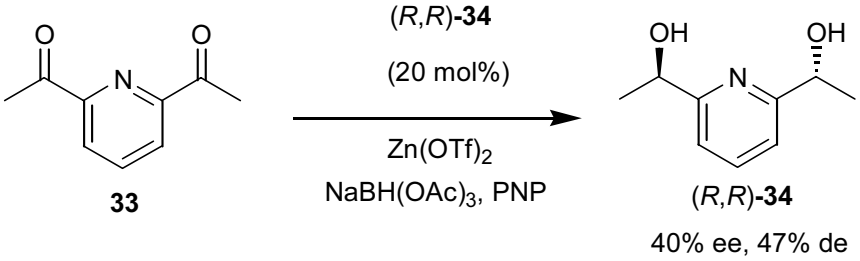
Recently, Soai *et al.*[42] reported the first highly enantioselective self-replication in an asymmetric autoinductive reduction in which the structures of the chiral ligand and product are expected to be identical. For example, 2-morpholinoacetophenone **31** was reduced with chirally modified $LiAlH_4$, which was prepared *in situ* from $LiAlH_4$, (*S*)-2-mophilino-1-phenylethanol A and *N*-ethyl-aniline in Et_2O at –78 °C. The 1,2-amino alcohol **32** (A+B) was obtained in 95.7% ee, which means that the newly formed product was obtained in 89.2% yield with 83.6% ee (Scheme 17). However, these authors used the starting chiral A in 2.5 times more than (1.27 mmol 254 mol%) the substrate **31** (0.5 mmol).

Scheme 17



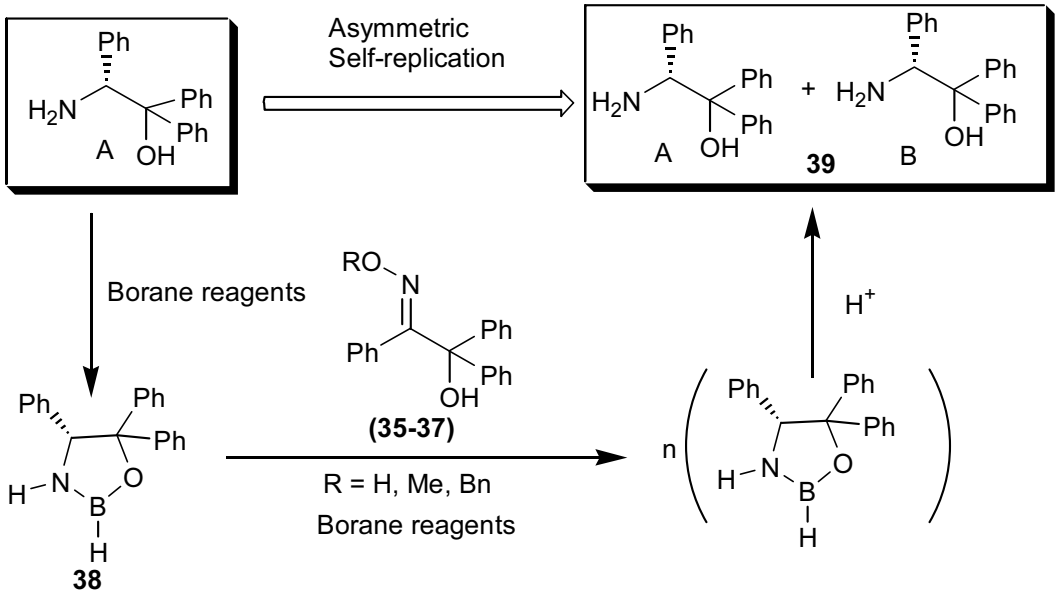
Very recently, Chin and coworkers[43] reported the autocatalytic asymmetric reduction of 2,6-diacetylpyridine **33** using 20 mol% of the pyridine based diol **34** ligand in presence of zinc trifluoromethanesulfonate (Scheme 18). But the results were poor.

Scheme 18



We have examined the possibility of asymmetric autocatalytic reduction of the oxime of the keto alcohol derivatives in presence of borane reagents. This transformation would involve the corresponding oxazaborolidine that is expected to catalyze its formation (Scheme 19). The results of these studies are described in this Chapter.

Scheme 19

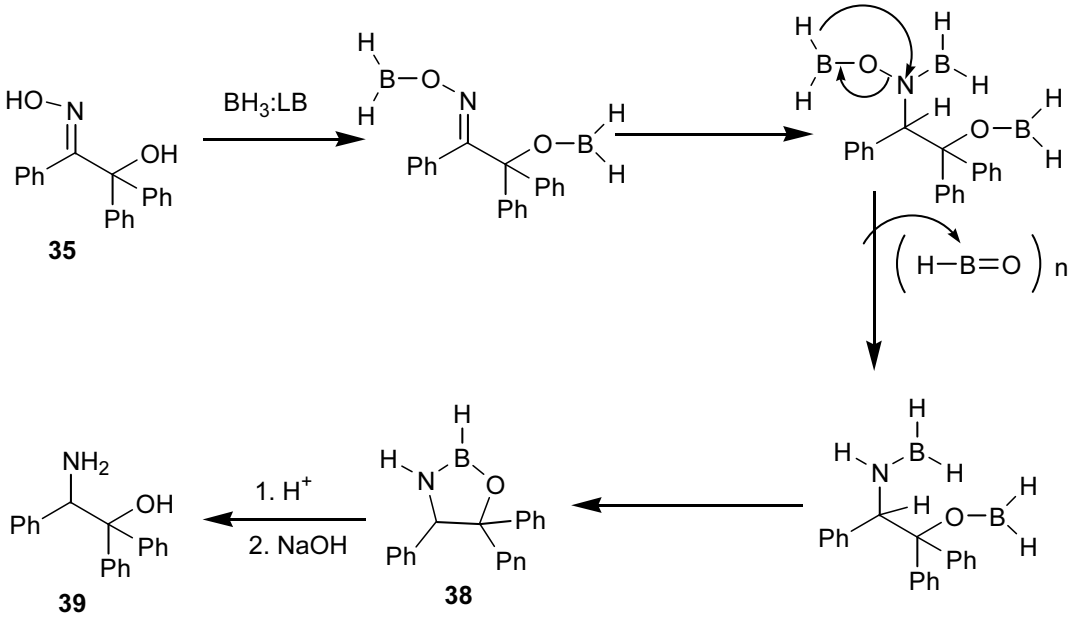


3. 2 Results and Discussion

3. 2. 1 Asymmetric autocatalytic reduction of α-keto alcohol oxime ethers using borane reagents in presence of 2-amino-1,1,2-triphenylethanol 39

As described in Chapter 1, reduction of α-keto alcohol oxime **35,** using borane reagents gives racemic 1,2-amino alcohol **39** (2-amino-1,1,2-triphenylethanol). In this reaction, the crucial step is the reduction of C=N in which an asymmetric center is created. It is likely that the oxazaborolidine **38** would be produced as an intermediate that upon workup could give the 1,2-amino alcohol (Scheme 20).

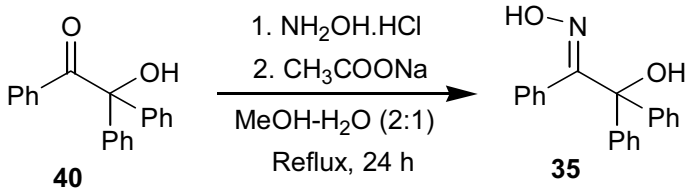
Scheme 20



We have decided to examine the preparation of oxazaborolidine *in situ* in this way using chiral amino alcohol **39** and borane reagents so as to examine the asymmetric reduction of the α-keto alcohol oxime **35**. The oxime **35** was prepared by refluxing the

α-keto alcohol **40** using hydroxylamine hydrochloride and sodium acetate in methanol-water for 24 h (Scheme 21).

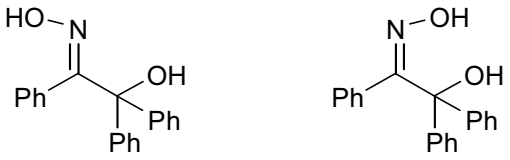
Scheme 21



40 **35**

90% y

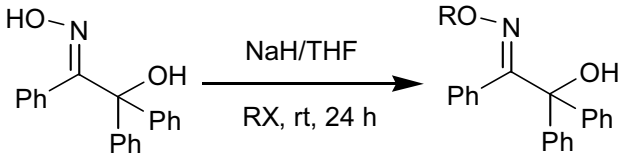
In this reaction, only (*E*)-isomer **35** is obtained and the corresponding (*Z*)-isomer **35** is not formed.



(*E*)-**35** (*Z*)-**35**

The corresponding oxime ether derivatives are readily prepared using alkyl halides in presence of NaH (Scheme 22).

Scheme 22



(*E*)-**35** (*E*)-**36-37**

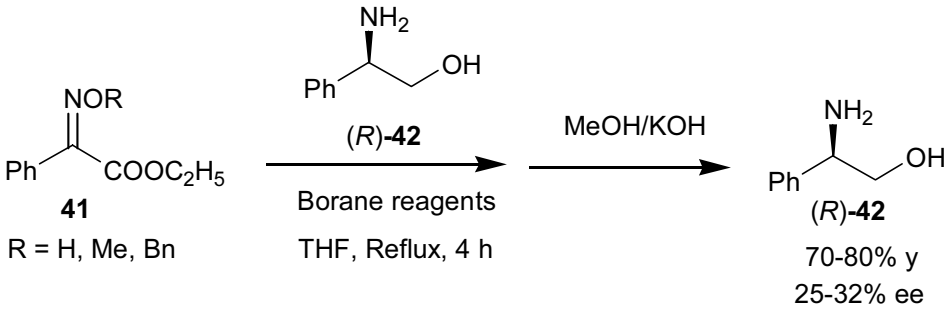
36 R = Me, 80% y

37 R = Bn, 85% y

The stereochemistry of these oxime ethers were confirmed by ^{1}H NMR spectroscopy and comparison with the reported data.[44]

In this laboratory, the reduction of oxime derivatives of ethyl phenyl glyoxalate **41** using (*R*)-phenylglycinol **42** and borane reagents was previously examined (Scheme 23).[45] The newly formed amino alcohol was obtained in 25-32% ee.

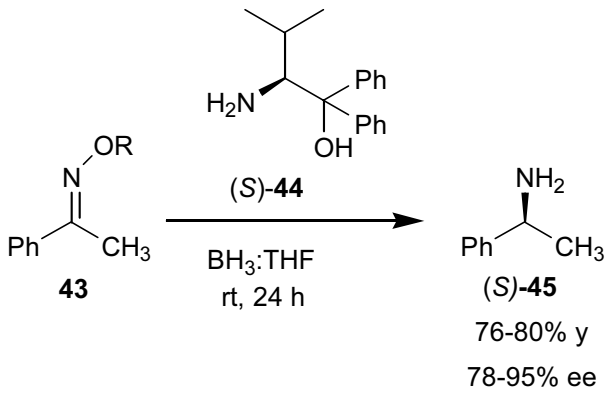
Scheme 23



It is well known that α,α-disubstituted 1,2-amino alcohols give better selectivity in oxazaborolidine reductions compared to the simple unsubstituted amino alcohols.[46] Accordingly, we have selected the amino alcohol **39** to examine the asymmetric autocatalytic reduction of α-keto alcohol oxime using borane reagents.

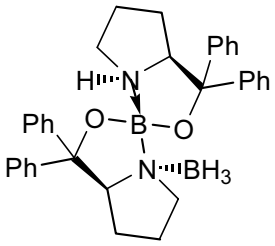
Previously, Itsuno *et al*.[47] reported the asymmetric reduction of acetophenone oxime ethers using stoichiometric quantity of chiral amino alcohol **44** and borane reagents (Scheme 24).

Scheme 24

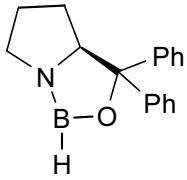


Initially, we have carried out the borane reduction of keto alcohol oxime **35** at 25 ^{o}C. The reaction was not clean and it was also incomplete under these conditions.

It has been reported that the inactive oxazaborolidine dimer **46A** is formed at 25 ^{o}C in the reaction of BH_3:SMe_2 with α,α-diphenyl-2-pyrrolidinemethanol in toluene.[48] Heating converts it to the corresponding reactive monomer **46B.**



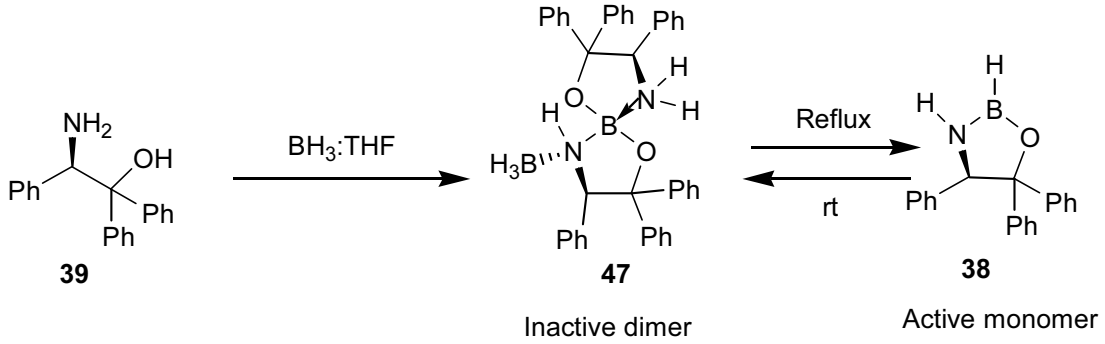
46A



46B

Presumably, in the reaction at 25 °C, the oxazaborolidine derived from amino alcohol **39** and borane reagents would also exist as inactive dimer **47** form and hence, the reaction would be slower when it is performed at lower temperature (Scheme 25).

Scheme 25

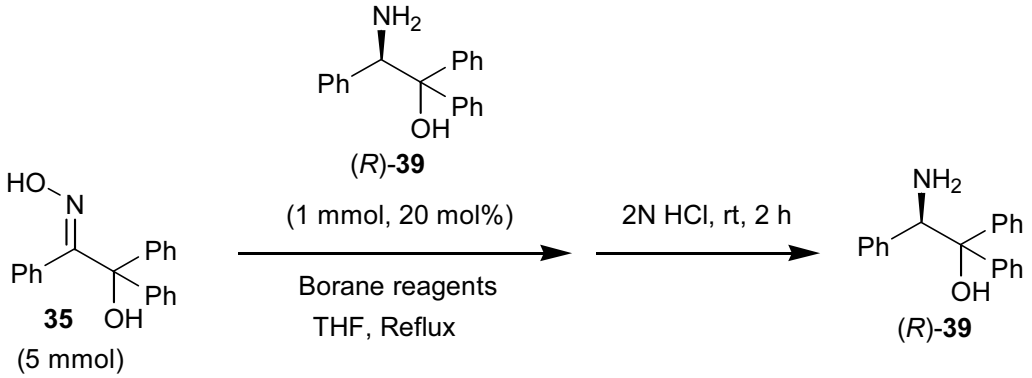


39 **47** **38**

Inactive dimer Active monomer

Therefore, we have carried out the reduction of α-keto alcohol oxime **35** using (*R*)-2-amino-1,1,2-triphenylethanol **39** under refluxing conditions in THF. The reaction proceeded smoothly using various borane reagents such as $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and $Ph(C_2H_5)N$:BH_3 (Scheme 26).

Scheme 26



Entry	Borane reagents	Total product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	79% (18% ee)	75% (`~0% ee)
2	$NaBH_4$/TMS-Cl	81% (18% ee)	77% (~0% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	82% (20% ee)	78% (~0% ee)

The (*R*)-(+)-2-amino-1,1,2-triphenylethanol **39** was obtained in 79-82% yields and 18-20% ee. The results indicate that the newly formed amino alcohol **39** would be almost racemic (based on the assumption that there is no loss in the yield of starting 1 mmol of (*R*)-**39** upon workup) as per the calculation outlined below for entry 3 in Scheme 26.

The product **39** is obtained in 82% yield and 20% ee.

Therefore the yield of product **39** = 6 x 0.82 = 4.92 mmol

The product is isolated in 20% ee of *R* = 60% *R* + 40% *S*

= (4.92 x 0.60) *R* + (4.92 x 0.40) *S*

= 2.952 mmol of *R* + 1.968 mmol of *S*

Amount of (*R*)-**39** taken initially = 1 mmol of 100% ee (*R*)

So, the newly formed **39** will contain = (2.95-1.00) mmol of *R* + 1.97 mmol of *S*

= 1.95 mmol of *R* + 1.97 mmol of *S*

Hence % ee of newly formed **39** = (*R*-*S*)÷(*R*+*S*) x 100 = (1.95-1.97)÷3.92 x 100

= ~0

Since the reduction of keto alcohol oxime **35** did not give fruitful results, we have decided to examine the asymmetric reduction of methyl and benzyl ethers of the α-keto alcohol oxime. The methyl ether of oxime **36** was reduced in the presence of amino alcohol **39** using borane reagent systems $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and *N,N*-diethylaniline:BH_3 in separate runs. After workup, the (*R*)-(+)-2-amino-1,1,2-triphenylethanol **39** was obtained with 25% ee, 26% ee and 30 % ee, respectively. These results indicate that the newly formed amino alcohol **39** would be a minimum of 05-13% ee (based on the assumption that there is no loss in the yield of starting 1 mmol of (*R*)-**39** upon workup) as per the calculation outlined below for entry 3 in Scheme 27.

The product **39** is obtained in 85% yield and 30% ee.

Therefore the yield of product **39** = 6 x 0.85 = 5.10 mmol

The product is isolated in 30% ee of R = 65% *R* + 35% *S*

= (5.10 x 0.65) *R* + (5.10 x 0.35) *S*

= 3.315 mmol of *R* + 1.785 mmol of *S*

Amount of (*R*)-**39** taken initially = 1 mmol of 100% ee (*R*)

So, the newly formed **39** will contain = (3.315-1.00) mmol of *R* + 1.785 mmol of *S*

= 2.315 mmol of *R* + 1.785 mmol of *S*

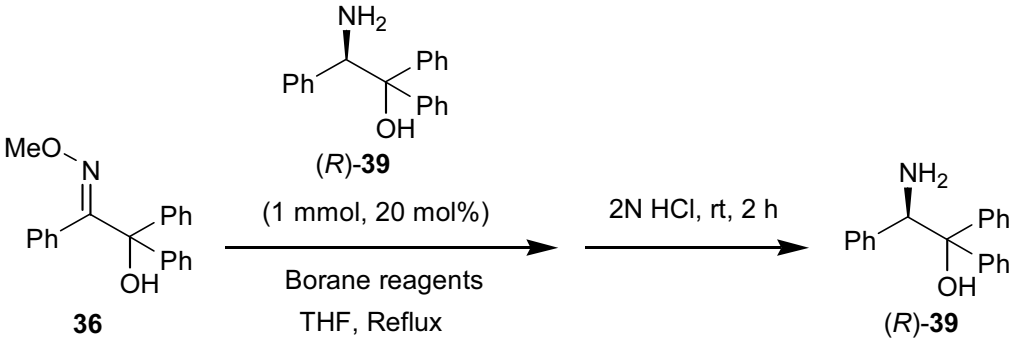
Hence % ee of newly formed **39** = (R-S÷R+S) x 100 = (2.315-1.785) ÷4.10 x 100

= 0.53÷4.10 x 100

= 0.129 x 100

= 13

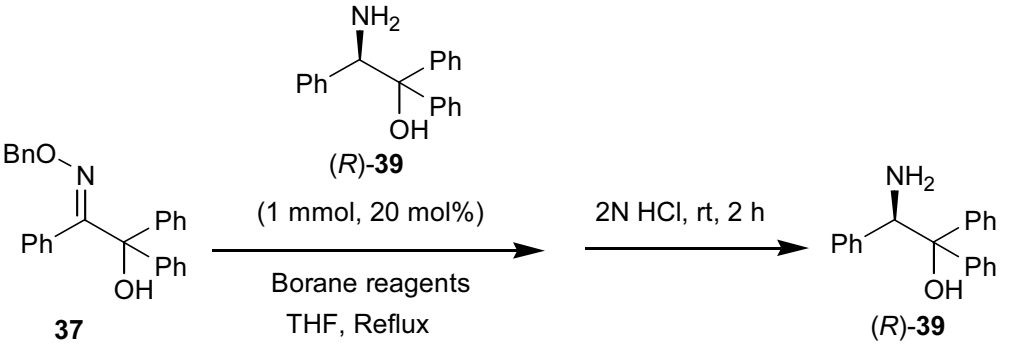
Scheme 27



Entry	Borane reagents	Total product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	80% (25% ee)	76% (05% ee)
2	$NaBH_4$/TMS-Cl	83% (26% ee)	80% (08% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	85% (30% ee)	82% (13% ee)

Similarly, we have carried out the reduction of the benzyl oxime ether **37** using different borane reagents to obtain the newly formed amino alcohol would be a minimum of about 18-25% ee (based on the assumption that there is no loss in the yield of starting 1 mmol of (*R*)-**39** upon workup) (Scheme 28).

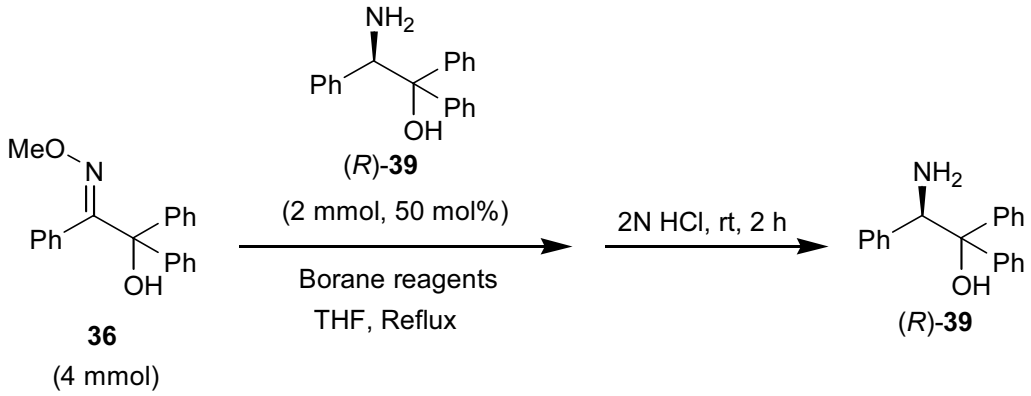
Scheme 28



Entry	Borane reagents	Total product 39 % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	82% (35% ee)	78% (18% ee)
2	$NaBH_4$/TMS-Cl	83% (37% ee)	80% (20% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	85% (40% ee)	82% (25% ee)

Presumably, the steric requirement about the double bond has an effect in the reaction. We have then studied the reaction of **36** using 50 mol% of amino alcohol **39** as catalyst. In these runs 1-3, after workup, the (*R*)-(+)-2-amino-1,1,2-triphenylethanol **39** was obtained in 55% ee, 56% ee and 58 % ee, respectively. The results indicate that the newly formed amino alcohol would be a minimum of 26-32% ee (based on the assumption that there is no loss in the yield of starting 2 mmol of (*R*)-**39** upon workup) (Scheme 29).

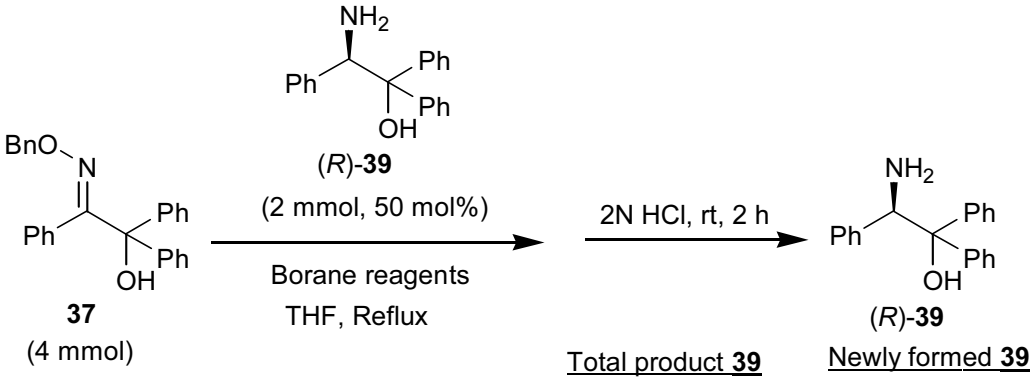
Scheme 29



Entry	Borane reagents	Total product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	85% (55% ee)	78% (26% ee)
2	$NaBH_4$/TMS-Cl	86% (56% ee)	79% (29% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	86% (58% ee)	79% (32% ee)

When the benzyl oxime ether **37** was reduced in the presence of 50 mol% of amino alcohol **39**, the product was obtained in 60-63% ee (85-88% y) (Scheme 30). The results indicate that the newly formed amino alcohol **39** would be a minimum of 34-40% ee (based on the assumption that there is no loss in the yield of starting 2 mmol of (*R*)-**39** upon workup) (Scheme 30).

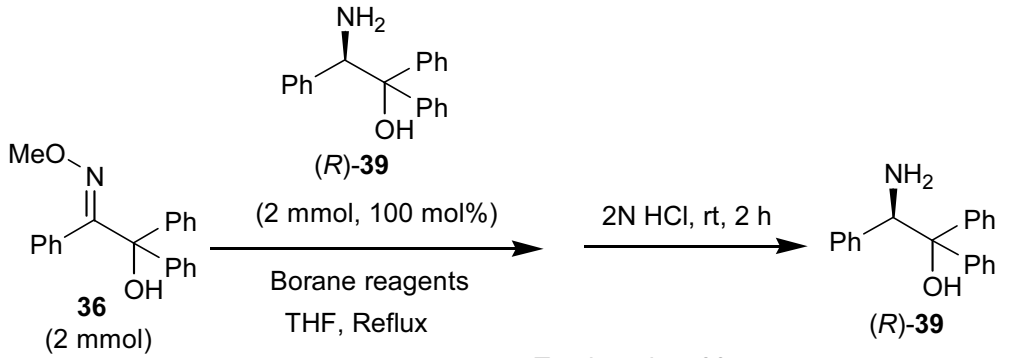
Scheme 30



Entry	Borane reagents	Total product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	85% (60% ee)	78% (34% ee)
2	$NaBH_4$/TMS-Cl	86% (61% ee)	79% (36% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	88% (63% ee)	82% (40% ee)

We have also examined the reduction of oxime derivatives using stoichiometric quantity of amino alcohol **39**. It was observed that the methyl oxime ether **36** was reduced in presence of (*R*)-(+)-2-amino-1,1,2-triphenylethanol **39** (100 mol%) to give the product in 75-79% ee (88-90% yield) (Scheme 31).

Scheme 31

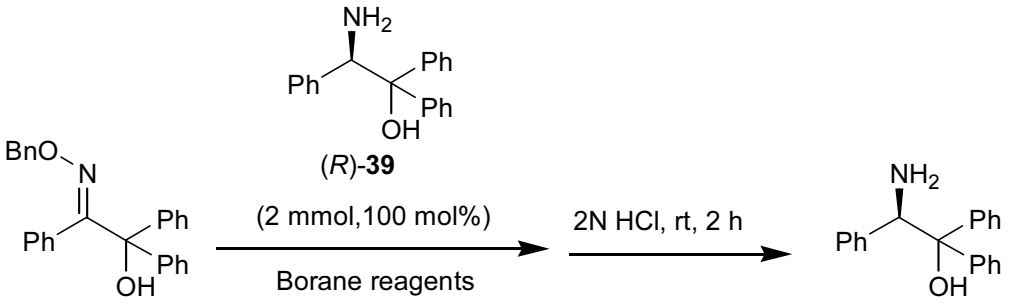


Entry	Borane reagents	Total product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	88% (75% ee)	76% (42% ee)
2	$NaBH_4$/TMS-Cl	87% (76% ee)	74% (43% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	90% (79% ee)	80% (53% ee)

In these cases the newly formed amino alcohol would be a minimum of 42-53% ee (based on the assumption that there is no loss in the yield of starting 2 mmol of (*R*)-**39** upon workup).

When the benzyl oxime ether **37** was reduced in the presence of (*R*)-(+)-amino alcohol in stoichiometric quantities, the product was obtained in 82-87% ee (88-92% yield) indicating that the newly formed amino alcohol would have a minimum enantiomeric purity of 58-72% ee (based on the assumption that there is no loss in the yield of starting 2 mmol of (*R*)-**39** upon workup) (Scheme 32).

Scheme 32

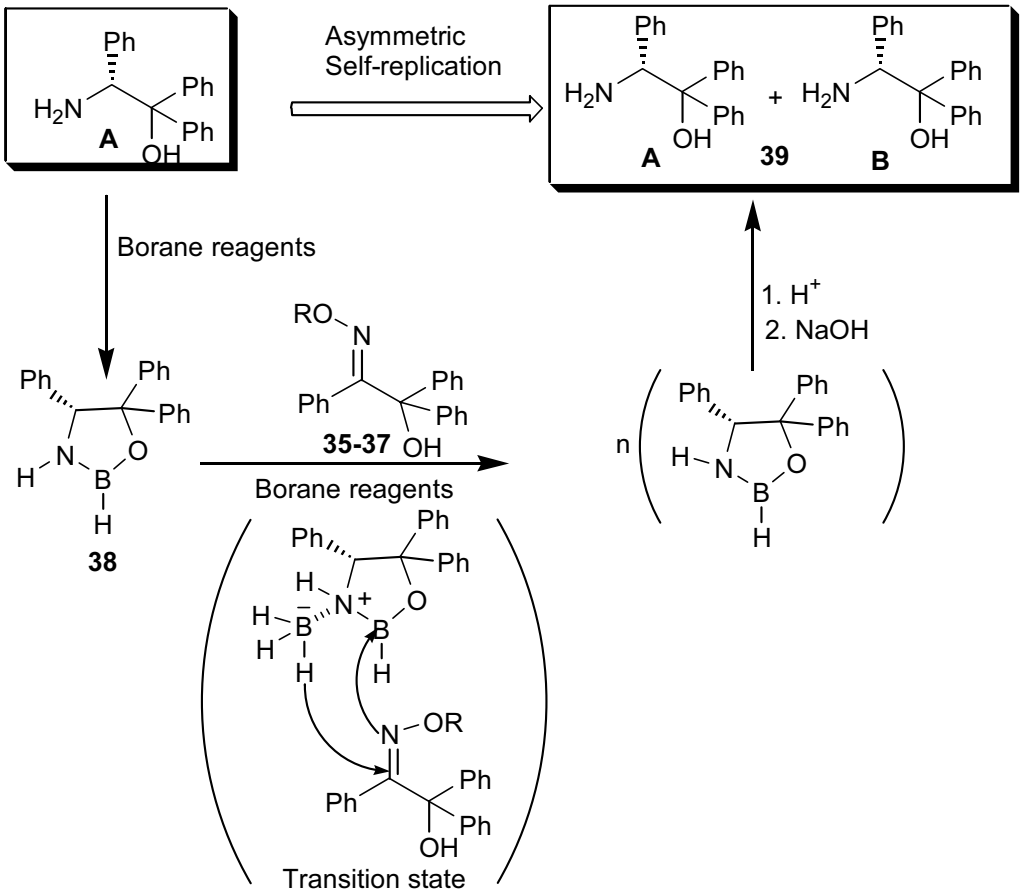


Entry	Borane reagents	Toatal product **39** % y (% ee)	Newly formed **39** % y (% ee)
1	$NaBH_4/I_2$	88% (82% ee)	76% (58% ee)
2	$NaBH_4$/TMS-Cl	90% (85% ee)	80% (66% ee)
3	$Ph(C_2H_5)_2N{:}BH_3$	92% (87% ee)	84% (72% ee)

Comparison of the results indicates that the results were better when the amino alcohol **39** was used in stochiometric quantities. Hence, the asymmetric duplication process seems to take place with modest enantioselectivity, instead of the anticipated autocatalytic process.

The mechanism of this reducion would probably involve the following steps in which the formation of the oxazaborolidine **38** is an important step (Scheme 19).

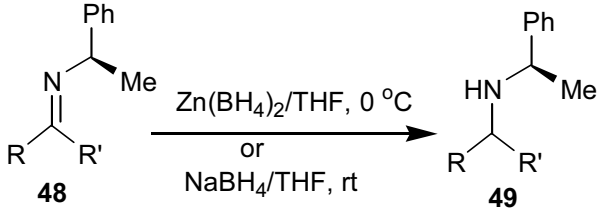
Scheme 19



3. 2. 2 Asymmetric reduction of imine of 1-acyl-2-naphthol using borane reagents

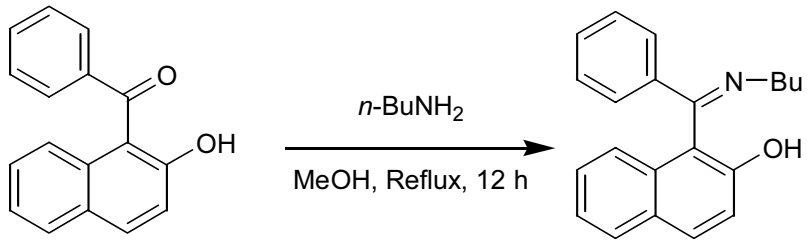
Generally, secondary amines are obtained by the reduction of Schiff bases using reducing agents. Recently, Palmieri and coworkers reported the reduction of chiral imines using $Zn(BH_4)_2$ or $NaBH_4$ (Scheme 33).[49]

Scheme 33



We have selected the readily accessible ketimine **51** for examining the asymmetric reduction. It was easily prepared from 1-benzoyl-2-naphthol **50** and *n*-butylamine in MeOH solvent under refluxing conditions (Scheme 34). We have selected the aminonaphthol **52** as ligand to examine the asymmetric reduction.

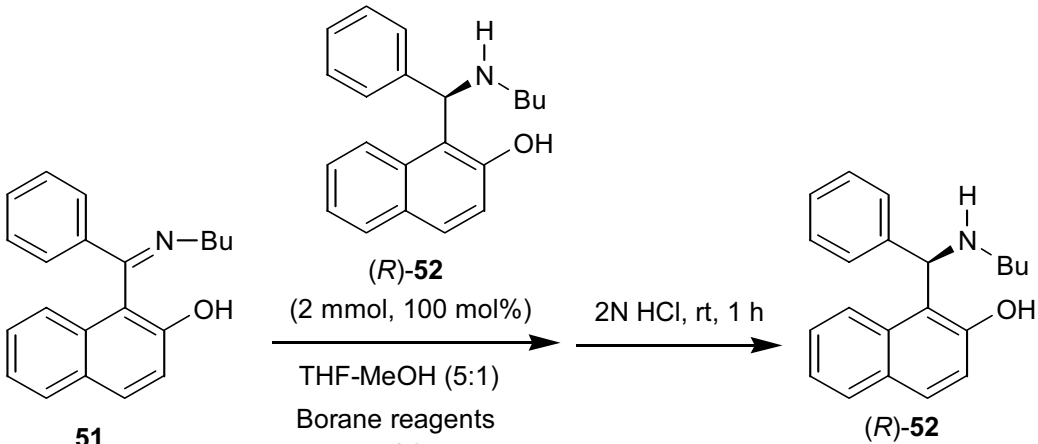
Scheme 34



50 **51**
80% y

We have carried out the reduction of ketimine **51** using $NaBH_4$ and $NaBH_4/I_2$ system in presence of aminonaphthol **52** in stoichoimetric quantity (Scheme 35).

Scheme 35

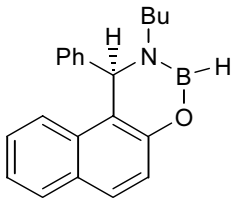


51
(2 mmol)

(*R*)-**52**

Entry	Borane reagents	Total product **52** % y (% ee)	Newly formed **52** % y (% ee)
1	$NaBH_4/I_2$	98% (65% ee)	96% (28% ee)
2	$NaBH_4$	99% (62% ee)	98% (23% ee)

After usual workup, the aminonaphthol was obtained in about 62-65% ee (98-99% yield). The newly formed aminonaphthol **52** would have a minimum of 23-28% ee (based on the assumption that there is no loss in the yield of starting 2 mmol of (*R*)-**52** upon workup). The chemical yields were excellent, but the optical yields were poor. Probably, the reaction would go through the corresponding oxazaborolidine intermediate **53**.



53

Further studies using different acyl imine derivatives may give fruitful results.

3. 3 Conclusions

Asymmetric borane reductions of oxime ethers **37** and **38** in the presence of (*R*)-amino alcohol **39** were studied using the reagents such as $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and *N,N*-diethylaniline:BH_3. The amino alcohol **39** was obtained in upto 87% ee under stoichiometric condition indicating that the newly formed (*R*)-amino alcohol **39** was obtained in up to 72% ee. Asymmetric reduction of the imine of 1-benzoyl-2-naphthol **51** was also examined using $NaBH_4/I_2$, $NaBH_4$ using aminonaphthol **52** and the newly formed aminonaphthol was obtained in 23-28% ee.

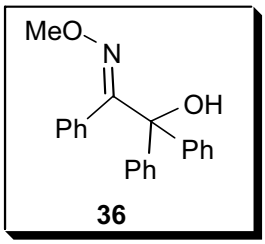
3. 4 Experimental Section

3. 4. 1 General Information

Several of the general experimental details given in Chapter 1 and Chapter 2 are also applicable here. Methyl iodide, benzyl bromide, hydroxylamine hydrochloride and sodium acetate were purchased from Loba Chemie, India.

3. 4. 2 Synthesis of methyl oxime ether 36

Sodium hydride (60% in mineral oil) (1.00 g, 40 mmol) was taken in dry THF (20 mL) and keto alcohol oxime (3.03 g, 10 mmol) in dry THF (20 mL) was added for an hour through addition funnel at 0 °C and the contents were stirred at 25 °C for 30 min. CH_3I (1.24 mL, 20 mmol) was added slowly using syringe and the contents were stirred for an additional 24 h at 25 °C. The reaction was quenched with water and extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (97:3) as eluent to obtain the product **36.**



36

Yield 2.59 g (82%)

mp 76-78 °C (lit.[44] mp 77-79 °C)

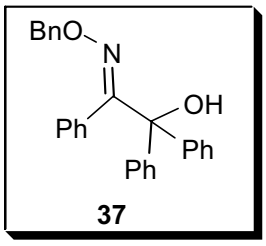
IR (KBr) (cm^{-1}) 3425, 3028,1674, 1446, 1234, 736

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 3.90 (s, 3H), 4.26 (s, 1H), 6.84-6.86 (m, 2H), 7.21-7.28 (m, 3H), 7.32-7.37 (m, 6H), 7.42-7.45 (m, 4H) **(Spectrum No. 33)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 62.6, 81.6, 127.7, 127.8, 128.4, 128.7, 132.2, 143.2, 160.4 **(Spectrum No. 34)**

3. 4. 3 Synthesis of benzyl oxime ether 37

Sodium hydride (60% in mineral oil) (1.00 g, 40 mmol) was taken in dry THF (20 mL) and keto alcohol oxime (3.03 g, 10 mmol) in dry THF (20 mL) was added for an hour through addition funnel at 0 °C and the contents were stirred at 25 °C for 30 min. Benzyl bromide (1.2 mL, 10 mmol) was added slowly via syringe and the contents were stirred for an additional 24 h at 25 °C. The reaction was quenched with water and extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (97:3) as eluent to obtain the product **37**.



37

Yield 3.34 g (85%)

mp 67-69 °C

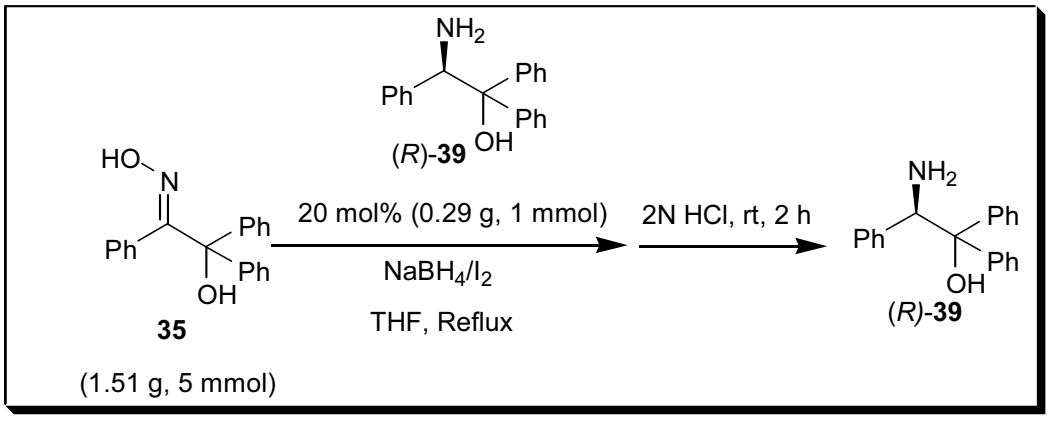
IR (KBr) (cm^{-1}) 3336, 3028,1660, 1446, 1278, 1068

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.82 (s, 1H), 5.10 (s, 2H), 6.83-6.85 (d, J = 8 Hz, 2H), 7.22-7.36 (m, 18H) **(Spectrum No. 35)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 76.4, 81.8, 127.6, 127.8, 127.9, 128.3, 128.5, 128.6, 130.1, 132.3, 138.1, 143.4, 161.5 **(Spectrum No. 36)**

3. 4. 4 Reduction of oxime 35 with *R*-(+)-2-amino-1,1,2-triphenylethanol 39 (20 mol%) using $NaBH_4/I_2$ system

Iodine (0.77 g, 3 mmol) in dry THF (20 mL) was added through an addition funnel to the stirred suspension of $NaBH_4$ (0.23 g, 6 mmol) in dry THF (10 mL) under N_2 for 1 h at 0 ^oC. *R*-(+)-Amino alcohol **39** (0.29 g, 1 mmol) in dry THF (10 mL) was added drop wise and the contents were refluxed for 2 h. The reaction mixture was cooled to 0 °C and the oxime **35** (1.51 g, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through an addition funnel. After the addition was over, the contents were refluxed for 12 h. The reaction mixture was brought to 0 ^oC and then quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 2 h at rt, made alkaline with NaOH and extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent to obtain the product *R*-(+)-39.



Yield 1.37 g (79%)

mp 131-132 ^oC (lit.[50] mp 131-133 ^oC)

IR (KBr) (cm^{-1}) 3450, 3400, 1650, 1450, 1170, 780

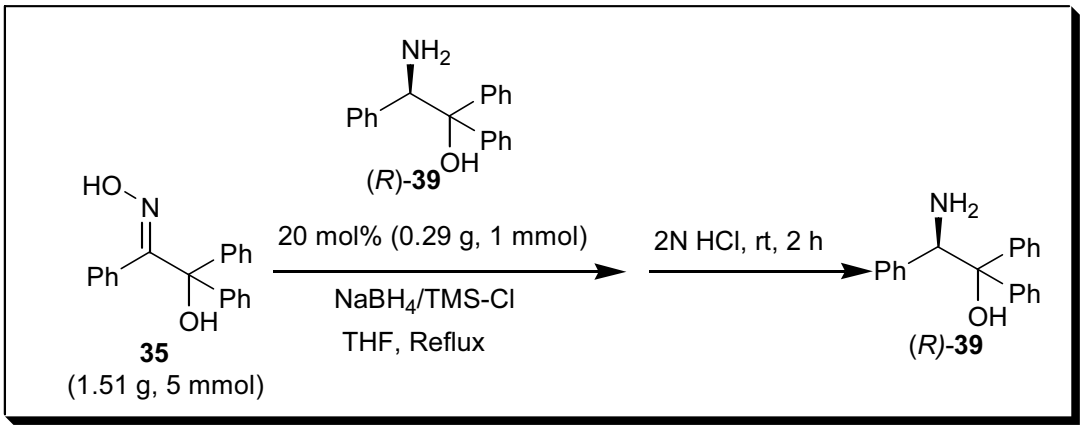
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.66 (br s, 3H), 5.04 (s, 1H), 7.03-7.09 (m, 3H), 7.14-7.17 (m, 6H), 7.28-7.33 (m, 2H), 7.43 (t, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 61.9, 79.6, 126.1, 126.3, 126.6, 127.0, 127.3, 127.4, 128.5, 128.7, 140.2, 144.0, 146.6

$[\alpha]_D^{25}$ +42.3 (*C* 1, $CHCl_3$), {lit[50] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

3. 4. 5 Reduction of oxime 35 with *R*-(+)-amino alcohol 39 (20 mol%) using $NaBH_4$/TMS-Cl system

$NaBH_4$ (0.23 g, 6 mmol) was taken in dry THF (15 mL) and TMS-Cl (1.9 g, 6 mmol) was added to this stirred suspension under N_2 at rt. The contents were refluxed for 2 h. The reaction mixture was cooled to 25 °C and then the *R*-(+)-amino alcohol **39** (0.29 g, 1 mmol) was added drop wise. The contents were again refluxed for 2 h. The reaction mixture was cooled to 0 °C and the oxime **35** (1.51 g, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through an addition funnel. After the addition was over, the contents were refluxed for 12 h. The reaction mixture was brought to 0 ^oC and then quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 2 h at room temperature, made alkaline with NaOH and extractd with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent to obtain the product *R*-(+)-**39.**

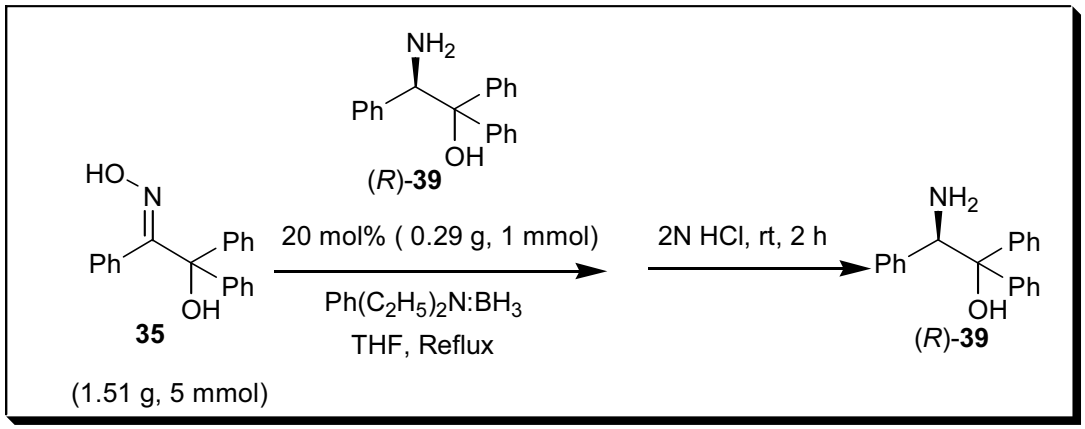


Yield 1.40 g (81%)

$[\alpha]_D^{25}$ +42.3 (*C* 1, $CHCl_3$), {lit[50] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

3. 4. 6 Reduction of oxime 35 with *R*-(+)-aminoalcohol 39 (20 mol%) using *N, N*-diethylaniline:BH_3 system

A solution of *N,N*-diethylaniline:BH_3 (1M, 6 mL, 6 mmol) was added to the stirred solution of *R*-(+)-amino alcohol **39** (0.29 g, 1 mmol) in dry THF (15 mL) under N_2 at 25 ^oC. The contents were refluxed for 2 h. It was cooled to 0 °C and oxime of keto alcohol **35** (1.51 g, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through an addition funnel. After the addition was over, the contents were refluxed for 12 h. The reaction mixture was brought to 0 ^oC and then quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 2 h at room temperature, made alkaline with NaOH and extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent to obtain the product *R*-(+)-**39.**

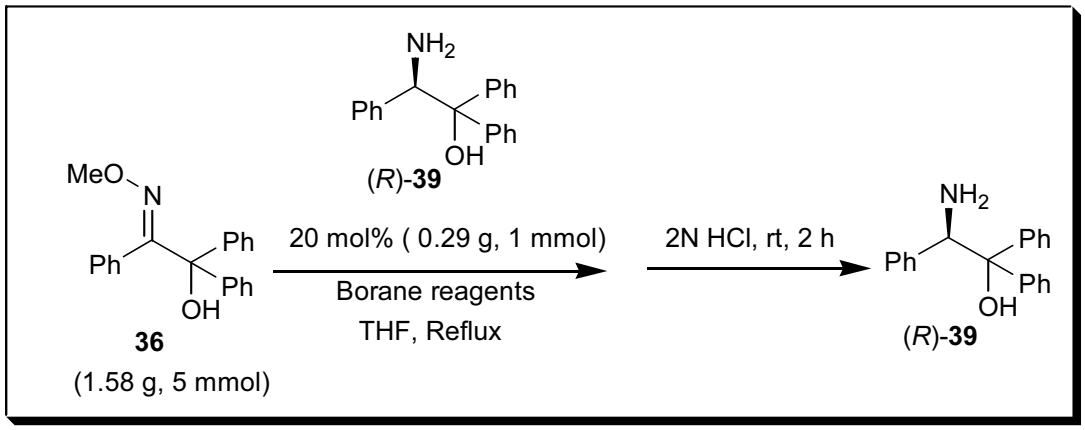


Yield 1.42 g (82%)

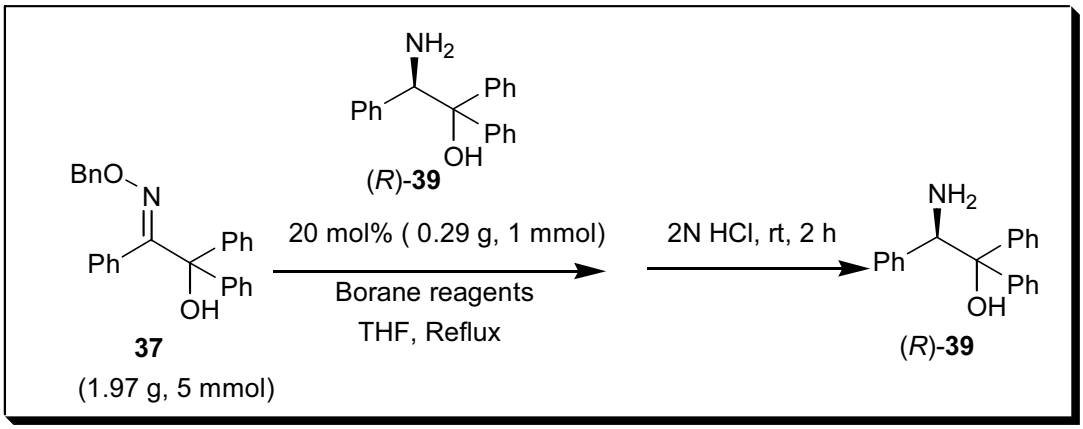
$[\alpha]_D^{25}$ +47.0 (*C* 1, $CHCl_3$), {lit[50] for 100% ee, $[\alpha]_D^{25}$ = +235 (*C* 1, $CHCl_3$)}

The oximes of methyl ether **36** and benzyl ether **37** were also reduced using borane reagents following the above mentioned procedure under different conditions. The yields and the $[\alpha]_D^{25}$ values are given below.

3. 4. 7 Reduction of oxime ethers 36 and 37 with *R*-(+)-amino alcohol 39 (20 mol%) using borane reagents

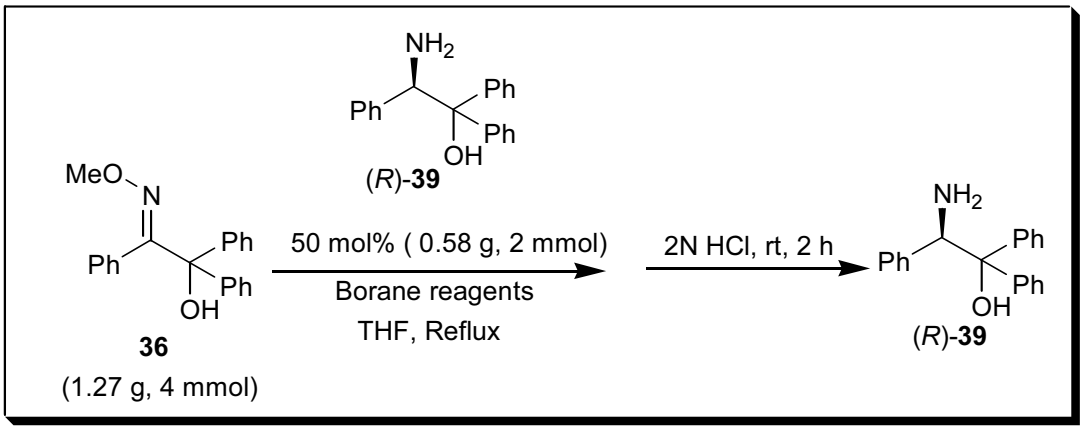


Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.39 g (80%)	+58.7 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.44 g (83%)	+61.1 (*C* 1, $CHCl_3$)
$Ph(C_2H_5)_2N:BH_3$	1.48 g (85%)	+70.5 (*C* 1, $CHCl_3$)

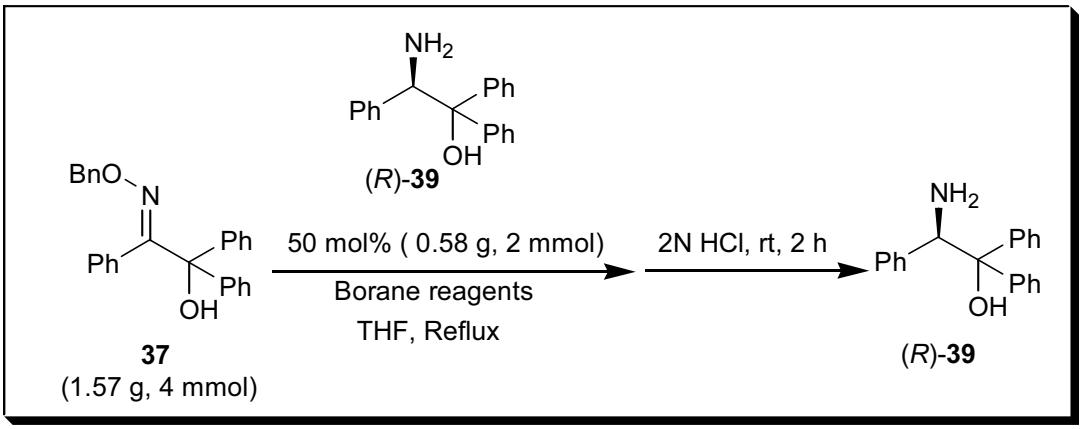


Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.42 g (82%)	+82.2 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.44 g (83%)	+87.0 (*C* 1, $CHCl_3$)
$Ph(C_2H_5)_2N{:}BH_3$	1.47 g (85%)	+94.0 (*C* 1, $CHCl_3$)

3. 4. 8 Reduction of oxime ethers 36 and 37 with *R*-(+)-amino alcohol 39 (50 mol%) using borane reagents

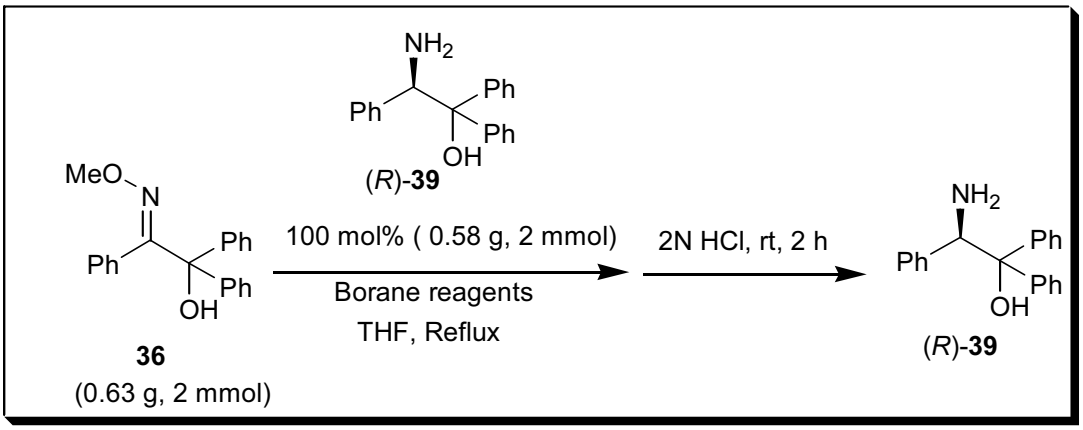


Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.47 g (85 %)	+129.2 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.50 g (86%)	+131.6 (*C* 1, $CHCl_3$)
$Ph(C_2H_5)_2N{:}BzH_3$	1.50 g (86%)	+136.3 (*C* 1, $CHCl_3$)

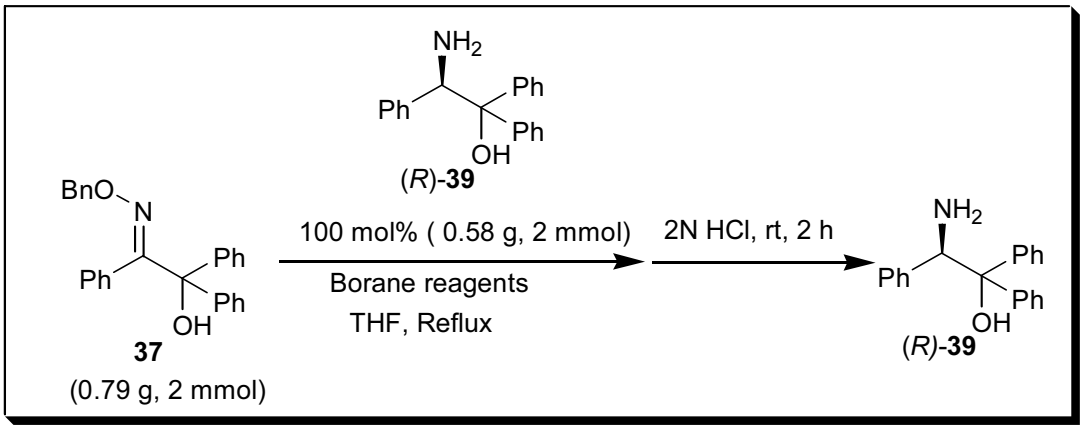


Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.47 g (85%)	+141.0 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.50 g (86%)	+143.3 (*C*1, $CHCl_3$)
$Ph(C_2H_5)_2N{:}BH_3$	1.53 g (88%)	+148.0 (*C* 1, $CHCl_3$)

3. 4. 9 Reduction of oxime ethers 36 and 37 with (*R*)-(+)-amino alcohol 39 (100 mol%) using borane reagents



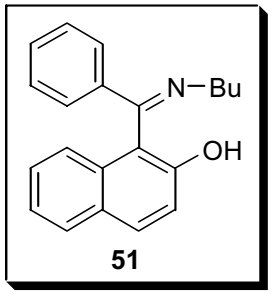
Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.00 g (88%)	+176.2 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.00 g (87%)	+178.6 (*C* 1, $CHCl_3$)
$Ph(C_2H_5)_2N{:}BH_3$	1.04 g (90%)	+185.6 (*C* 1, $CHCl_3$)



Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	1.00 g (88%)	+192.7 (*C* 1, $CHCl_3$)
$NaBH_4$/TMS-Cl	1.04 g (90%)	+200.0 (*C* 1, $CHCl_3$)
$Ph(C_2H_5)_2N{:}BH_3$	1.07 g (92%)	+204.4 (*C* 1, $CHCl_3$)

3. 4. 10 Synthesis of ketimine 51

n-Butylamine (1.0 mL, 10 mmol) was added through syringe to a stirred solution of 1-benzoyl-2-naphthol **50** (2.5 g, 10 mmol) in MeOH (20 mL). The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered and washed with MeOH (2 X 10 mL) to isolate the ketimine **51.**



Yield 2.4 g (80%)

mp 102-104 °C

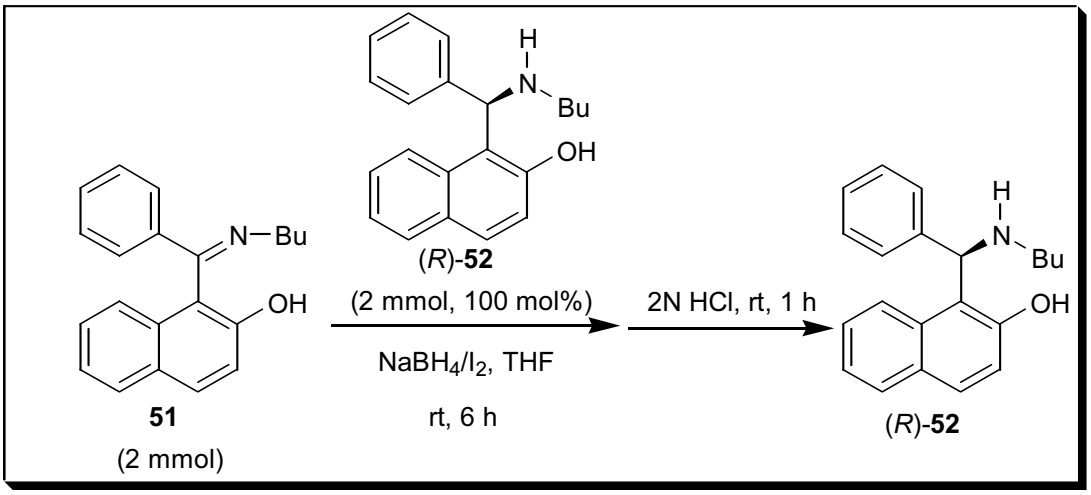
IR (KBr) (cm^{-1}) 3270, 3050, 1650, 1450, 1170, 980

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 1.01 (t, *J* = 8 Hz, 3H), 1.27-1.46 (m, 2H), 1.64-1.71 (m, 2H), 3.34 (t, *J* = 8 Hz, 2H), 6.60 (d, *J* = 8 Hz, 1H), 6.83 (t, *J* = 8 Hz, 1H), 7.01 (t, *J* = 8 Hz, 2H), 7.28-7.33 (m, 4H), 7.52-7.54 (m, 2H), 8.00 (d, *J* = 8 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 13.7, 20.8, 31.3, 55.3, 117.6, 121.6, 122.8, 123.3, 124.9, 127.5, 128.4, 129.1, 129.2, 130.7, 133.9, 136.1, 139.3, 161.2, 169.5

3. 4. 11 Reduction of ketimine 51 with *R*-(-)-aminonaphthol 52 (100 mol%) using $NaBH_4/I_2$ reagent system

Iodine (0.51 g, 2 mmol) in dry THF (15 mL) was added through an addition funnel to the stirred suspension of $NaBH_4$ (0.15 g, 4 mmol) in dry THF (10 mL) under N_2 for 1 h at 0 ^oC. The *R*-(-)-aminonaphthol **52** (0.61 g, 2 mmol) in dry THF (10 mL) was added drop wise and the contents were stirred at room temperature for 1 h. The ketimine **51** (0.6 g, 2 mmol) in dry THF (20 mL) was added drop wise for an hour through an addition funnel. After the addition was over, the contents were stirred at rt for 6 h. The reaction mixture was cooled to 0 ^oC and then quenched carefully with aqueous hydrochloric acid (2N HCl, 15 mL). The mixture was stirred for 1 h at room temperature, made alkaline using NaOH and extracted with ether (2 X 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate (98:2) as eluent to obtain the product *R*-(-)-**52.**



Yield 1.20 g (98%)

IR (KBr) (cm^{-1}) 3314, 3058, 2958, 1621, 1601, 1456, 1241, 1090

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.78 (t, *J* = 8 Hz, 3H), 1.22-1.25 (m, 2H), 1.38-1.50 (m, 2H), 2.68-2.71 (m, 2H), 5.55 (s, 1H), 7.06 (d, *J* = 8 Hz, 1H), 7.11-7.20 (m, 5H), 7.22-7.35 (m, 2H) 7.57-7.63 (m, 3H)

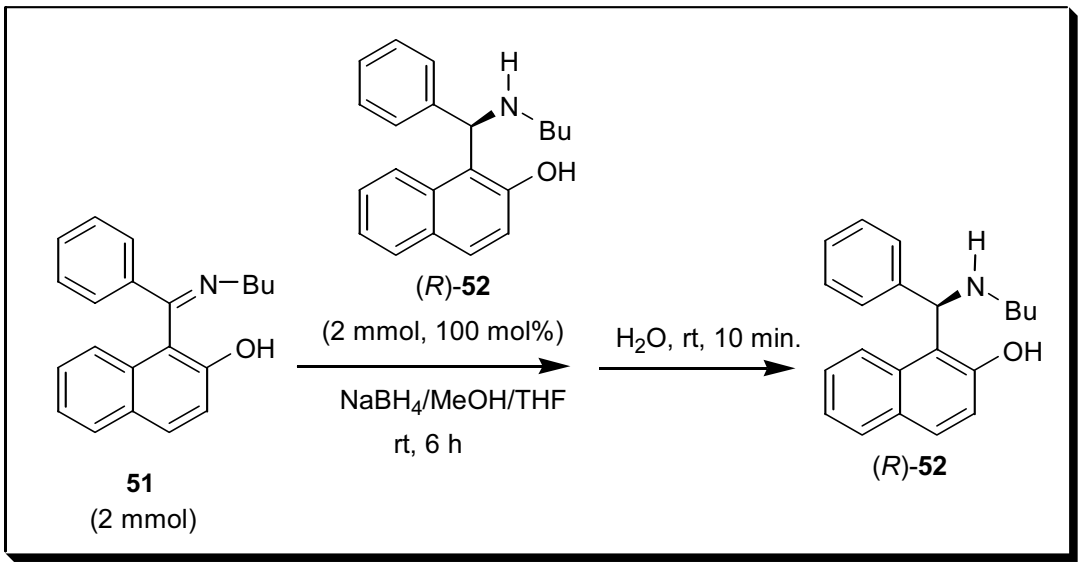
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 13.9, 20.4, 31.7, 49.0, 64.5, 113.4, 120.2, 121.2, 122.4, 126.5, 127.8, 128.1, 128.7, 128.1, 128.9, 129.7, 132.7, 141.8, 156.9

$[\alpha]_D^{25}$ -136.5 (*C* 0.5, EtOH), {lit.[51] for 100% ee, $[\alpha]_D^{25}$ = -212 (*C* 0.35, EtOH)}

3. 4. 12 Reduction of ketimine 51 with *R*-(-)-aminonaphthol 52 (100 mol%) using $NaBH_4$

Excess of $NaBH_4$ (0.60 g, 16 mmol) was added through a solid addition funnel to the stirred solution of (*R*)-(-)-aminonaphthol **52** (0.61 g, 2 mmol) in MeOH (15 mL) and THF (5 mL) under N_2 at rt. The contents were stirred at rt for 1 h. To this ketimine **51** (0.6 g, 2 mmol) in dry THF (10 mL) was added drop wise for 0.5 h through an

addition funnel. After the addition was over, the contents were stirred at rt for 6 h. The reaction mixture was cooled to 0 ^{o}C and then quenched carefully with H_2O (10 mL). The mixture was stirred for 10 min. at room temperature and organic solvents were evaporated the to obtain the residue. Water (10 mL) was added and extracted with CH_2Cl_2 (2 X 20 mL). The organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain the product *R*-(-)-**52** as a white solid.



Yield 1.21 g (99%)

$[\alpha]_D^{25}$ -131.4 (*C* 0.5, EtOH), {lit.[51] for 100% ee, $[\alpha]_D^{25}$ = -212 (*C* 0.35, EtOH)}

3. 5 References

1. Ozima, I. *Catalytic Asymmetric Synthesis, Second Edition; Ed.; Wiley: New York*, **2000**.
2. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis; Eds.; Springer: Berlin,* **1999.**
3. Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res*. **2000**, *33*, 382.
4. Soai, K. *Enantiomer* **1999**, *4*, 591.
5. Soai, K.; Sato, I.; Shibata, T. *Chem. Record* **2001**, *1*, 321.
6. Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1657.
7. Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Commun.* **2000**, 887.
8. Buschmann, H.; Thede, R.; Heller, D. *Angew. Chem. Int. Ed*. **2000**, *39*, 4033.
9. Todd, M. H. *Chem. Soc. Rev*. **2002**, *31*, 211.
10. Soai, K.; Shibata, T.; Sato, I. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1063.
11. Frank, F. C. *Biochem. Biophys. Acta* **1953**, *11*, 459.
12. Calvin, M. *Chemical Evolution; Oxford University Press: London*, **1969.**
13. Wynberg, H. *J. Macromol. Sci. Chem. A* 1**989**, *26*, 1033.
14. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
15. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem*. **1991**, *56*, 4264.
16. Sato, I.; Saito, T.; Omiya, D.; Takizawa, Y.; Soai, K. *Heterocycles* **1999**, *51*, 2753.

17. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc*. **1987**, *109*, 7111.

18. Soai, K.; Hori, H.; Niwa, S. *Heterocycles* **1989**, *29*, 2065.

19. Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun*. **1990**, 982.

20. Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5,* 789.

21. Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem. Int. Ed*. **1999**, *38*, 659.

22. Sato, I.; Yanagi, T.; Soai, K. *Chirality* **2002**, *14*, 166.

23. Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *Chem. Commun*. **1996**, 751.

24. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995,** *378*, 767.

25. Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 143.

26. Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. *J. Am. Chem. Soc.* **1998**, *120*, 12157.

27. Sato, I.; Omiya, D.; Saito, T.; Soai, K. *J. Am. Chem. Soc*. **2000**, *122*, 11739.

28. Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1096.

29. Sato, I.; Ohno, A.; Aoyama, Y.; Kasahara, T.; Soai, K. *Org. Biomol. Chem*. **2003**, *1*, 244.

30. Kawasaki, T.; Shimizu. M.; Suzuki, K.; Sato, I.; Soai, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3699.

31. Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235.

32. Sato, I.; Kadowaki, K.; Urabe, H.; Jung, J. H.; Ono, Y.; Shinkai, S.; Soai, K. *Tetrahedron Lett*. **2003**, *44,* 721.

33. Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem. Int. Ed*. **2000**, *39*, 1510.

34. Kondepudi, D. K.; Bullock, K. L.; Digits, J. A.; Hall, J. K.; Miller, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 10211.

35. Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* 1**990**, *250*, 975.

36. Kawasaki, T.; Ishikawa, K.; Sekibata, H.; Sato, I.; Soai, K. *Tetrahedron Lett.* **2004**, *45*, 7939.

37. Sato, I.; Sugie, R.; Matsueda, Y.; Furumura, Y.; Soai, K. *Angew. Chem. Int. Ed*. **2004,** *43,* 4490.

38. Sato, I.; Urabe, H.; Ishii, S.; Tanji, S.; Soai, K. *Org. Lett*. **2001**, *3*, 3851.

39. Soai, K.; Sato, I.; Shibata, T.; Komiya, S.; Hayashi, M.; Matsueda, Y.; Imamura, H.; Hayase, T.; Morioka, H.; Tabira, H.; Yamamoto, J.; Kowata, Y. *Tetrahedron: Asymmetry* 2**003**, *14,* 185.

40. Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637.

41. Soai, K.; Hayase, T.; Takai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637.

42. Shibata, T.; Takahashi, T.; Konishi, T.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2458.

43. Panosyan, F. B.; Chin, J. *Org. Lett*. **2003**, *5*, 3947.

44. Creary, X.; Burtch, E. A.; Jiang, Z. *J. Org. Chem*. **2003**, *68*, 1117.

45. Sivakumar, S. Ph.D. Thesis, University of Hyderabad, **2002**.

46. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.

47. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2039.

48. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsten, K.; Carroll, J. D.; Corey, E. J.; Grabowski, E. J. J. *J. Org. Chem*. **1993**, *58*, 2880.

49. Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555.

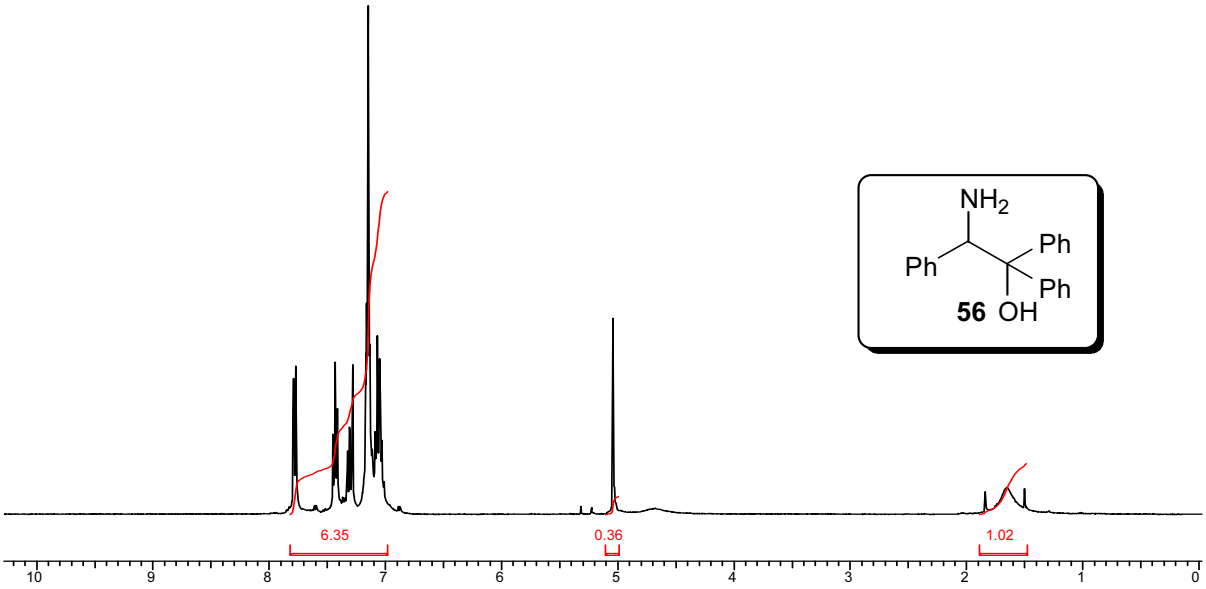
50. Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1994**, *5*, 165.

51. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685.

Appendix I

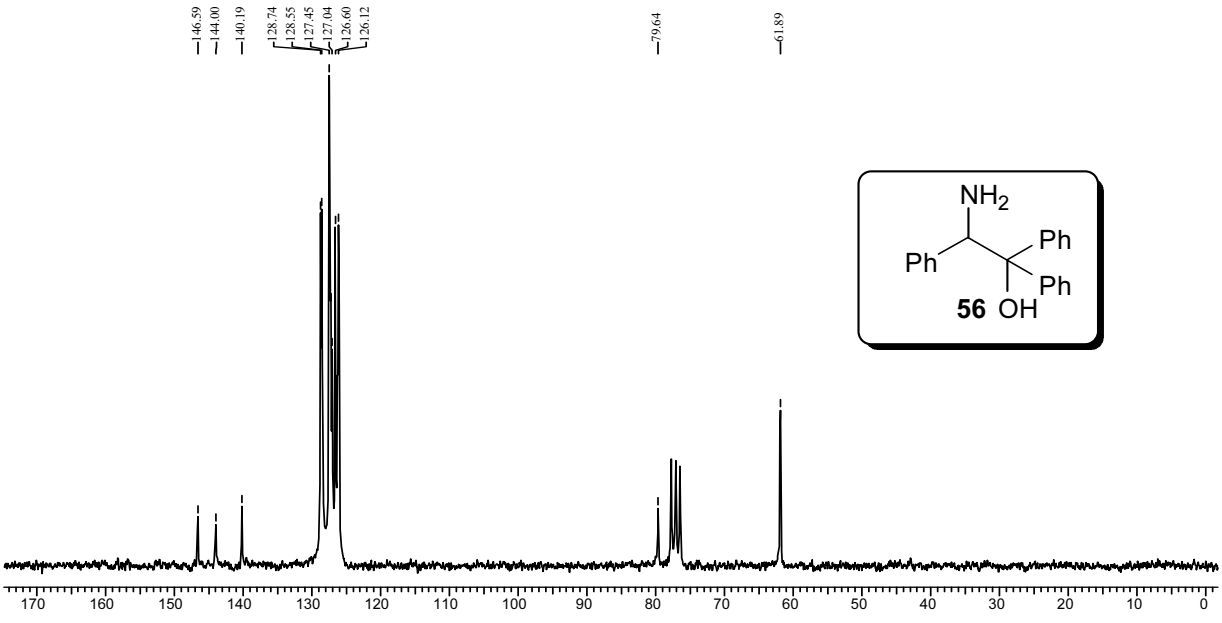
(Representative Spectra)

Spectrum No. 1 (Chapter 1, Section 1.4.4.3) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



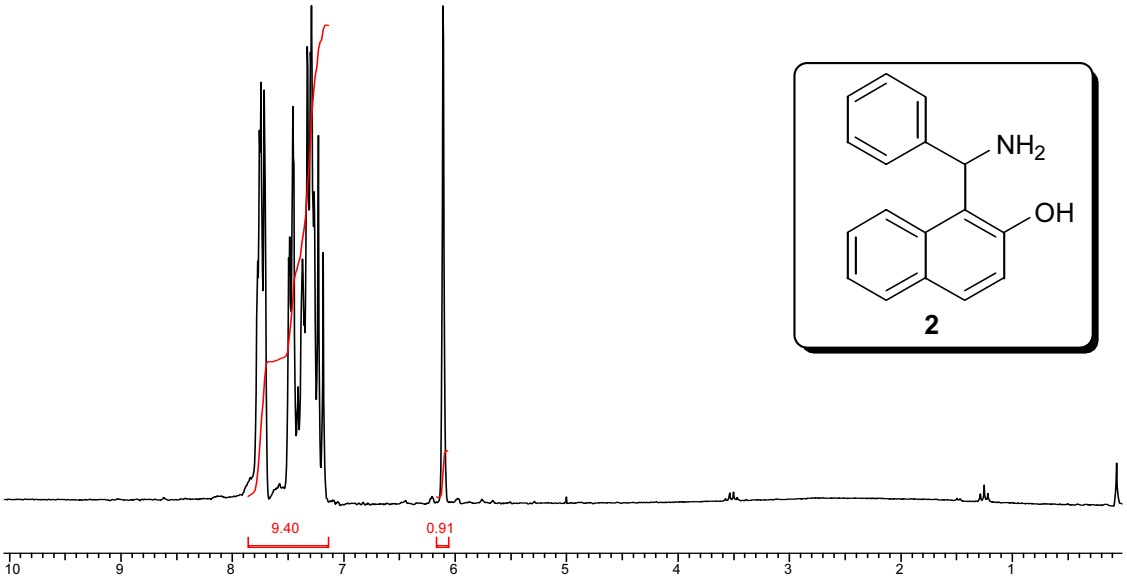
PPM

Spectrum No. 2 (Chapter 1, Section 1.4.4.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

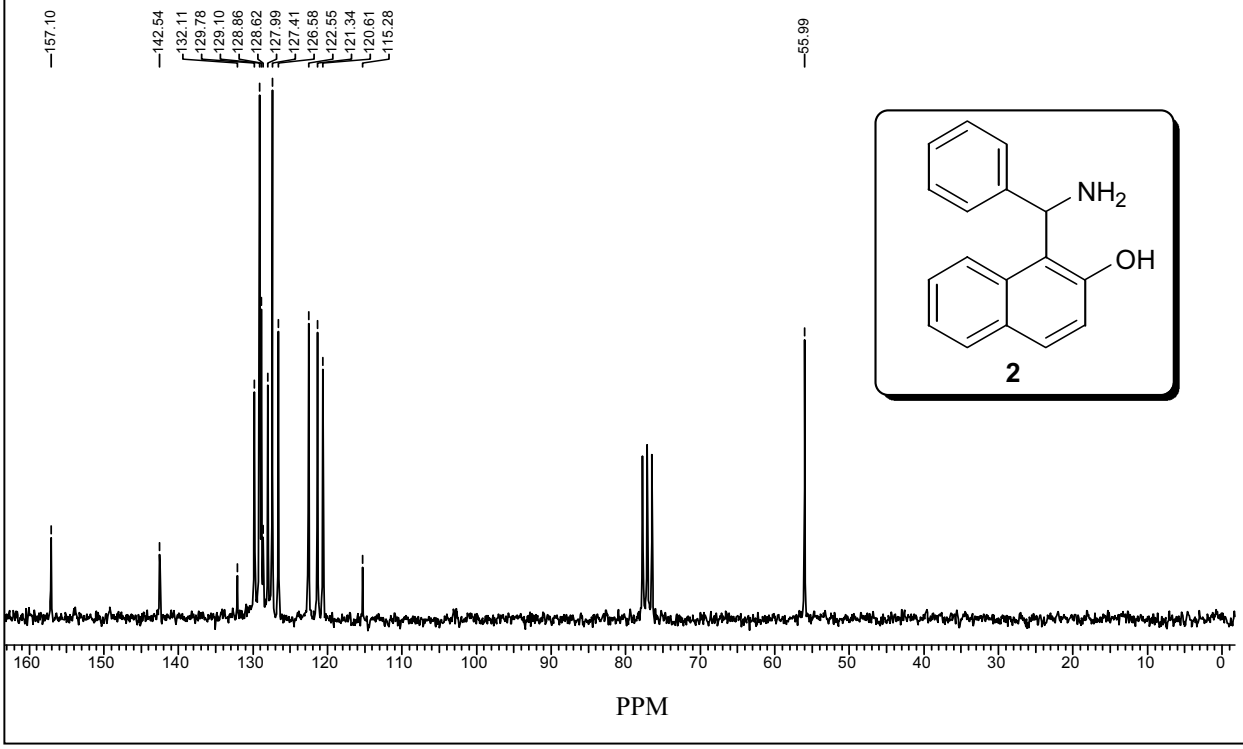


PPM

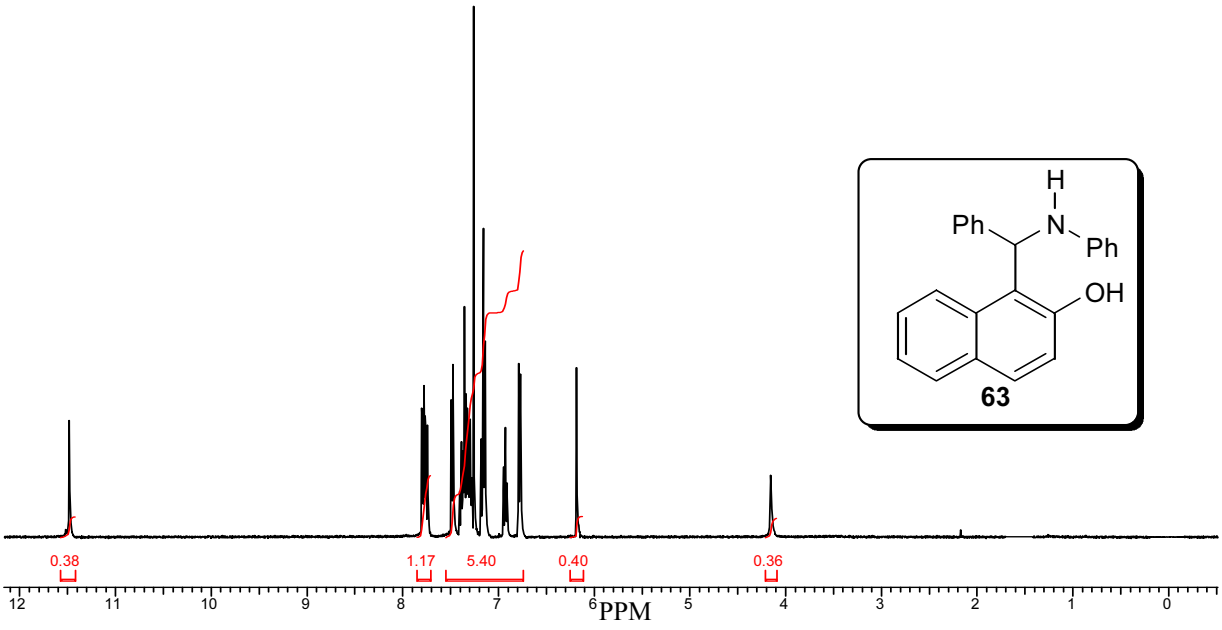
Spectrum No. 3 (Chapter 2, Section 2.4.2.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



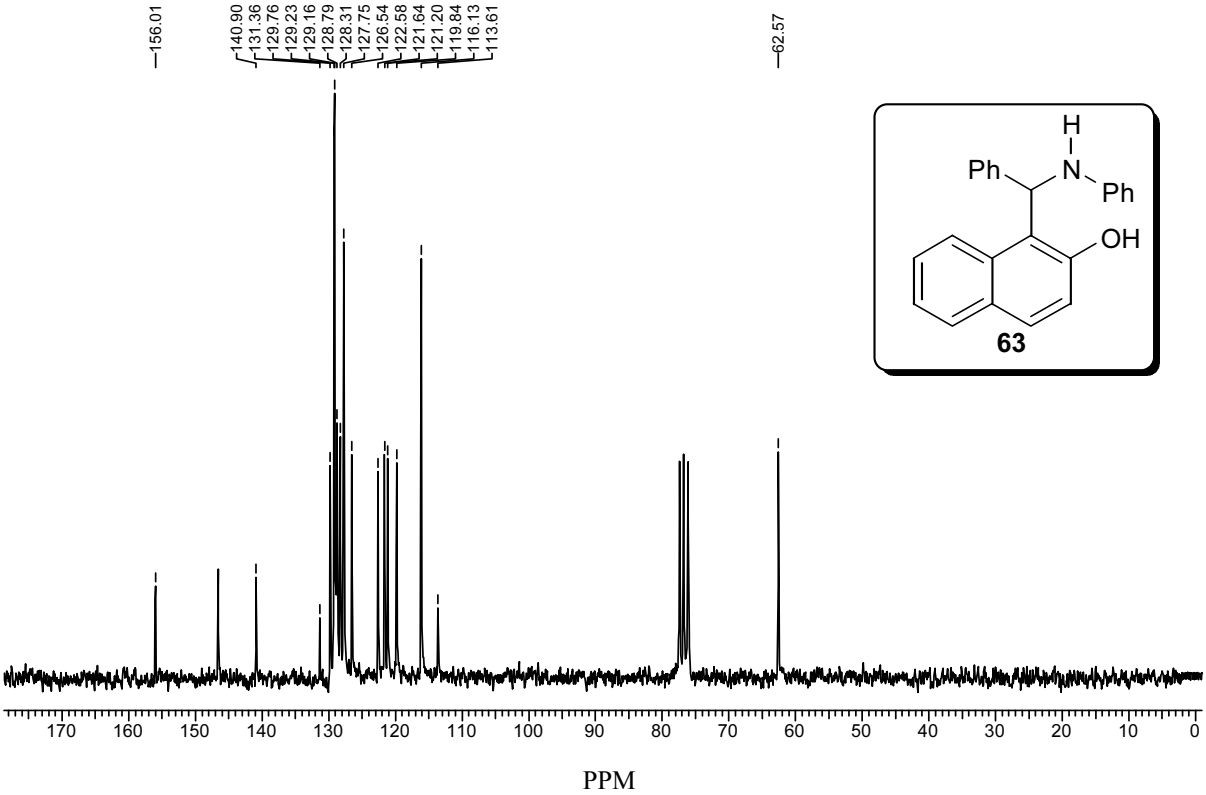
Spectrum No. 4 (Chapter 2, Section 2.4.2.1) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



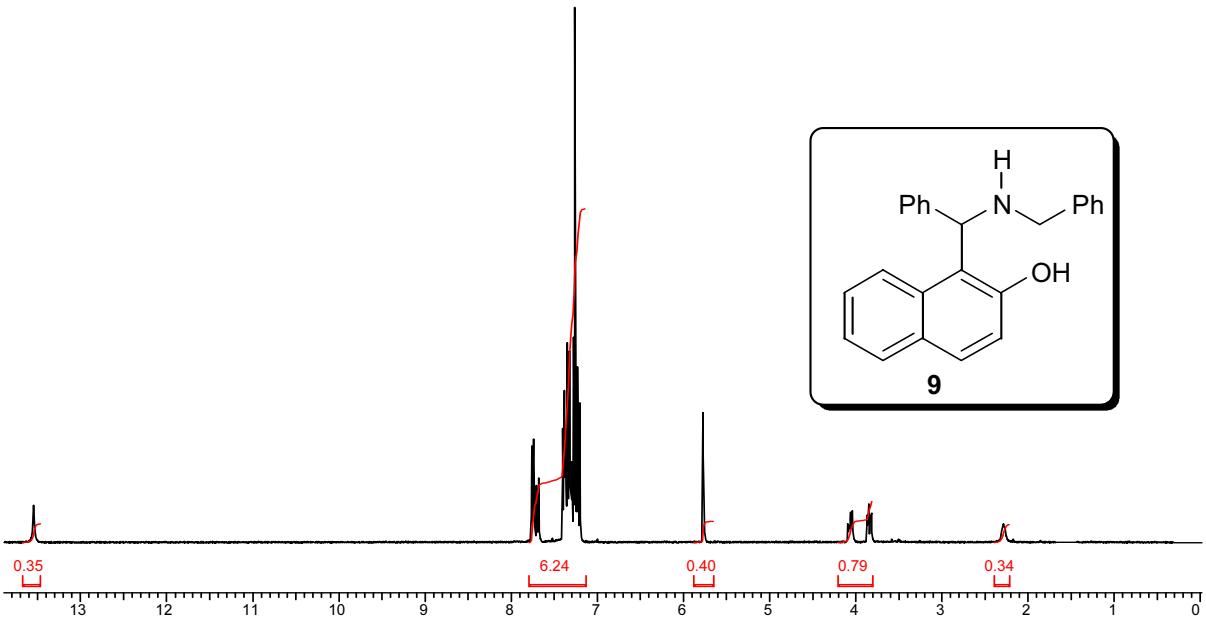
Spectrum No. 5 (Chapter 2, Section 2.4.2.2) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



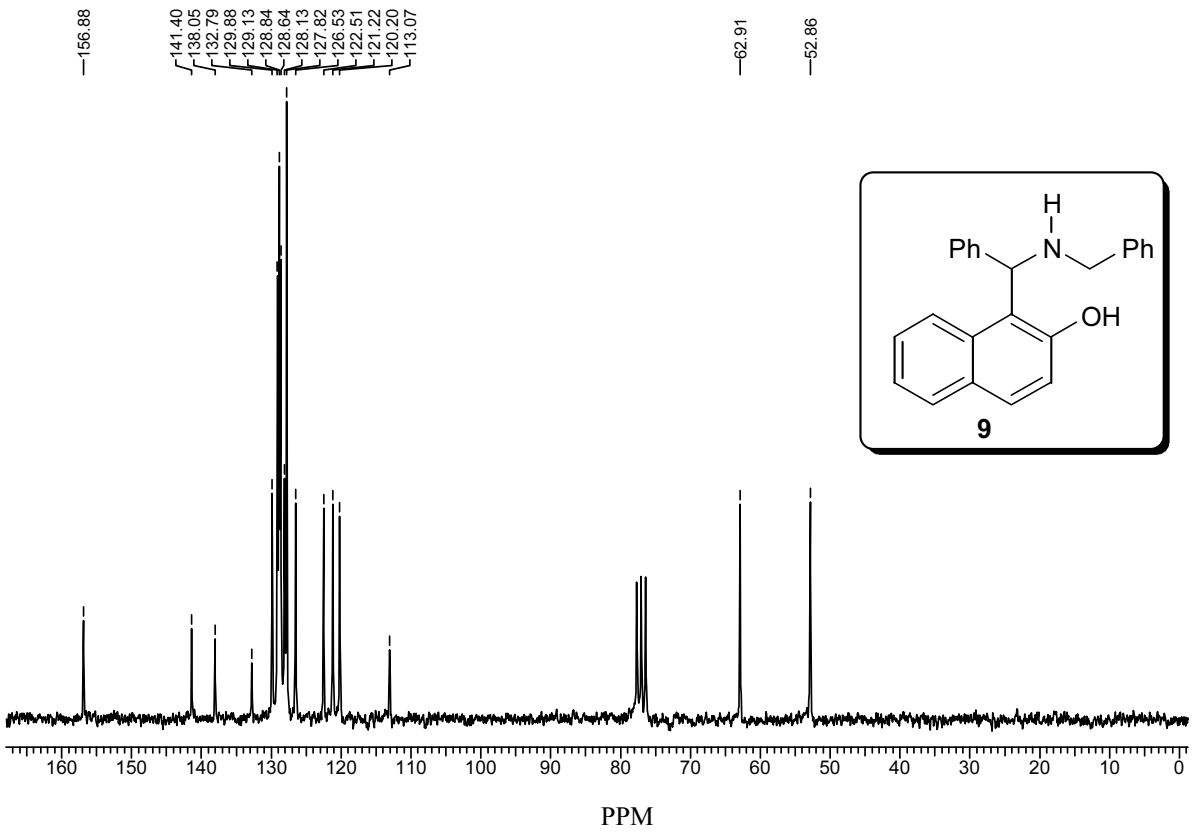
Spectrum No. 6 (Chapter 2, Section 2.4.2.2) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



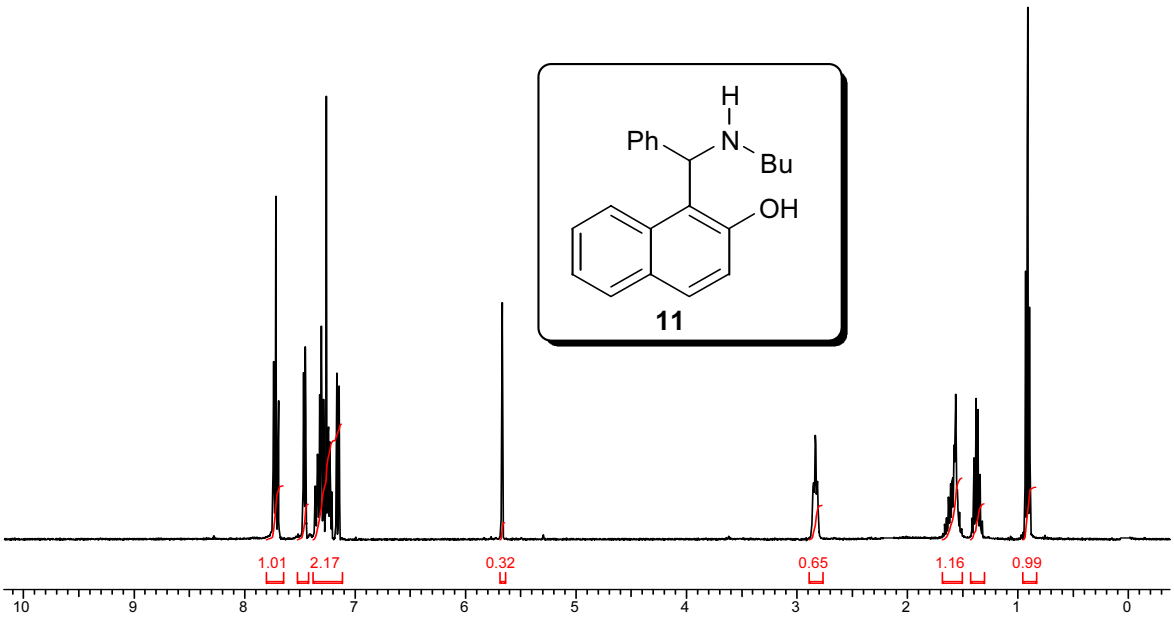
Spectrum No. 7 (Chapter 2, Section 2.4.2.3) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



Spectrum No. 8 (Chapter 2, Section 2.4.2.3) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



Spectrum No. 9 (Chapter 2, Section 2.4.2.4) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



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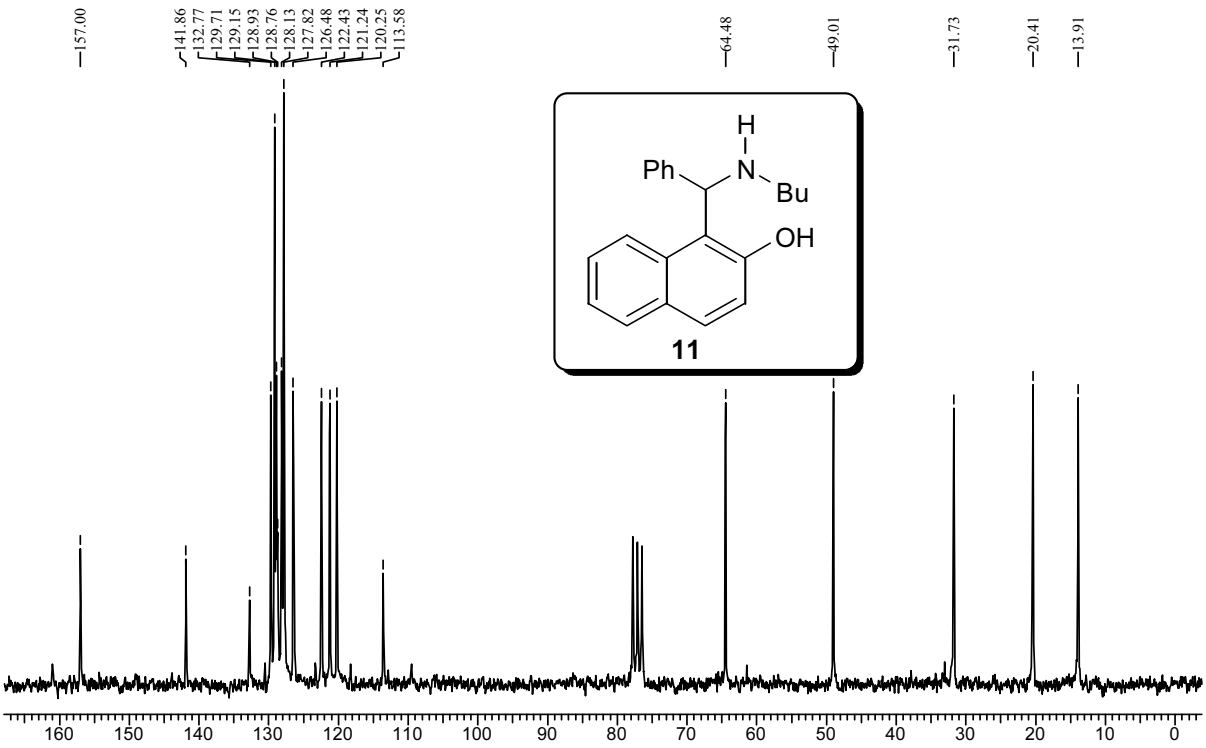
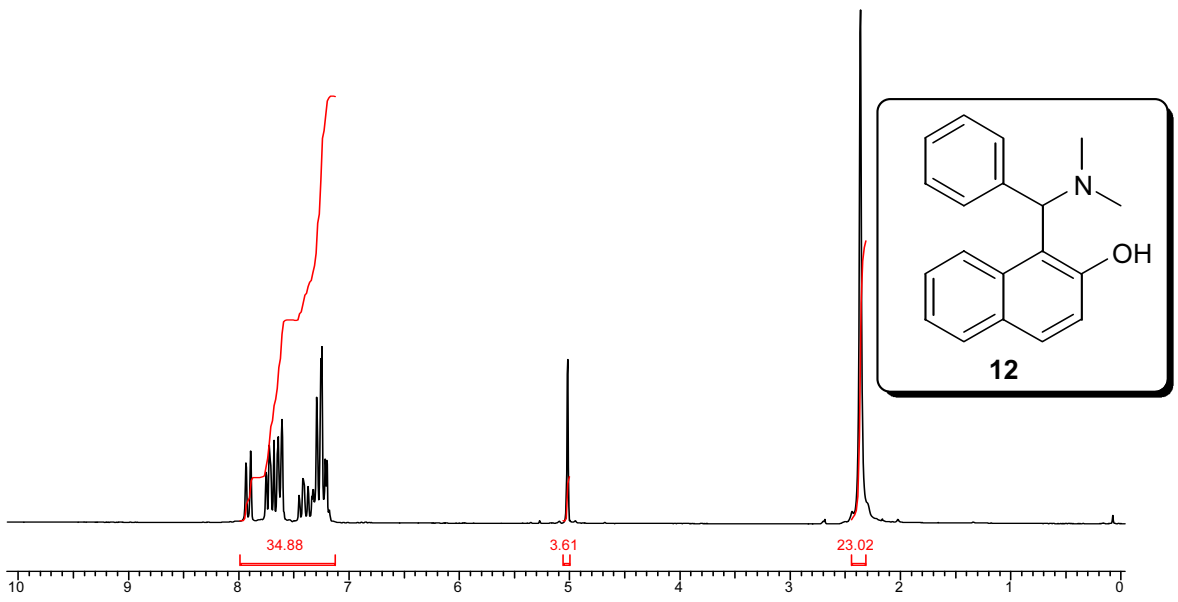
Spectrum No. 10 (Chapter 2, Section 2.4.2.4) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



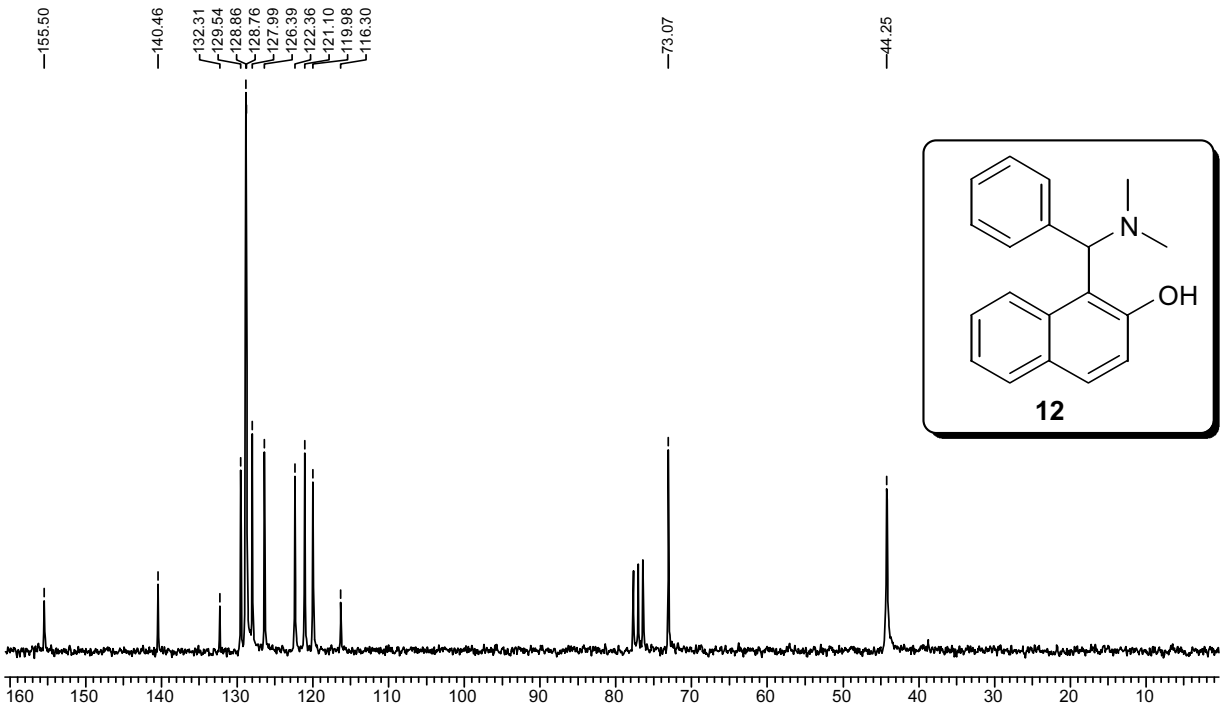
PPM

Spectrum No. 11 (Chapter 2, Section 2.4.2.5) ^{1}H NMR Spectrum (200 MHz,$CDCl_3$)



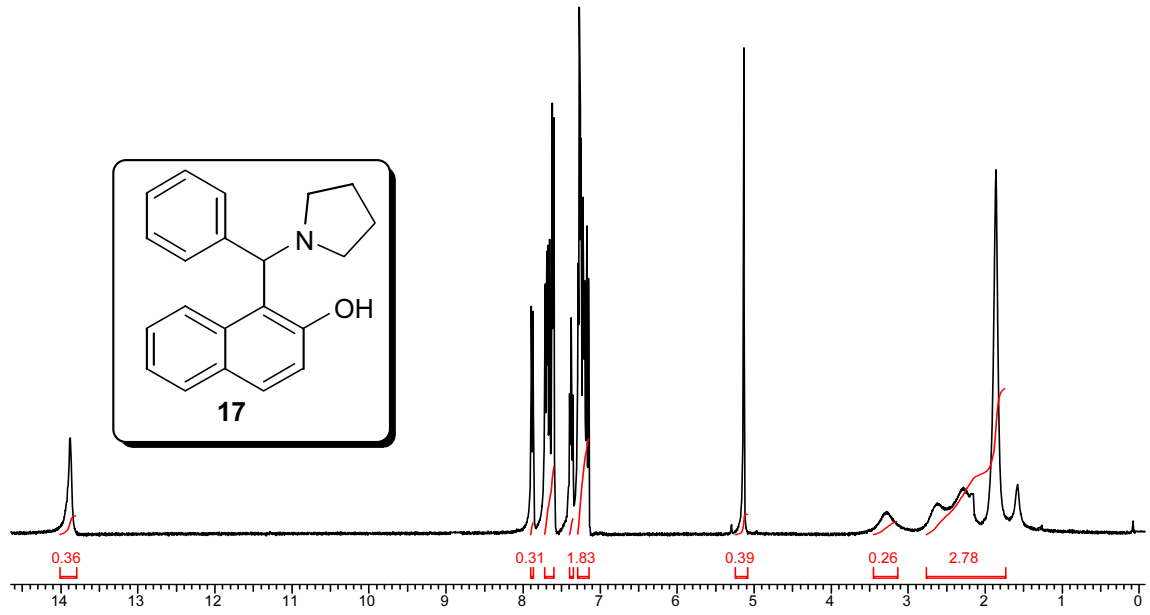
PPM

Spectrum No. 12 (Chapter 2, Section 2.4.2.5) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



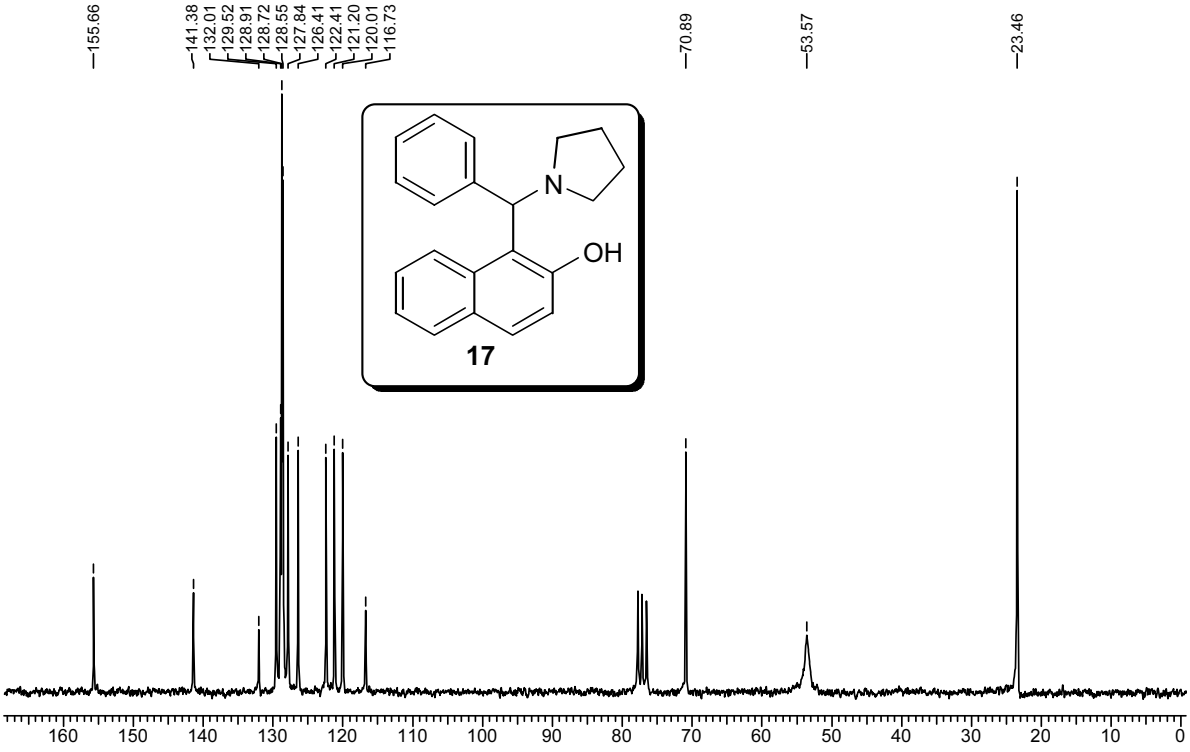
PPM

Spectrum No. 13 (Chapter 2, Section 2.4.2.6) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



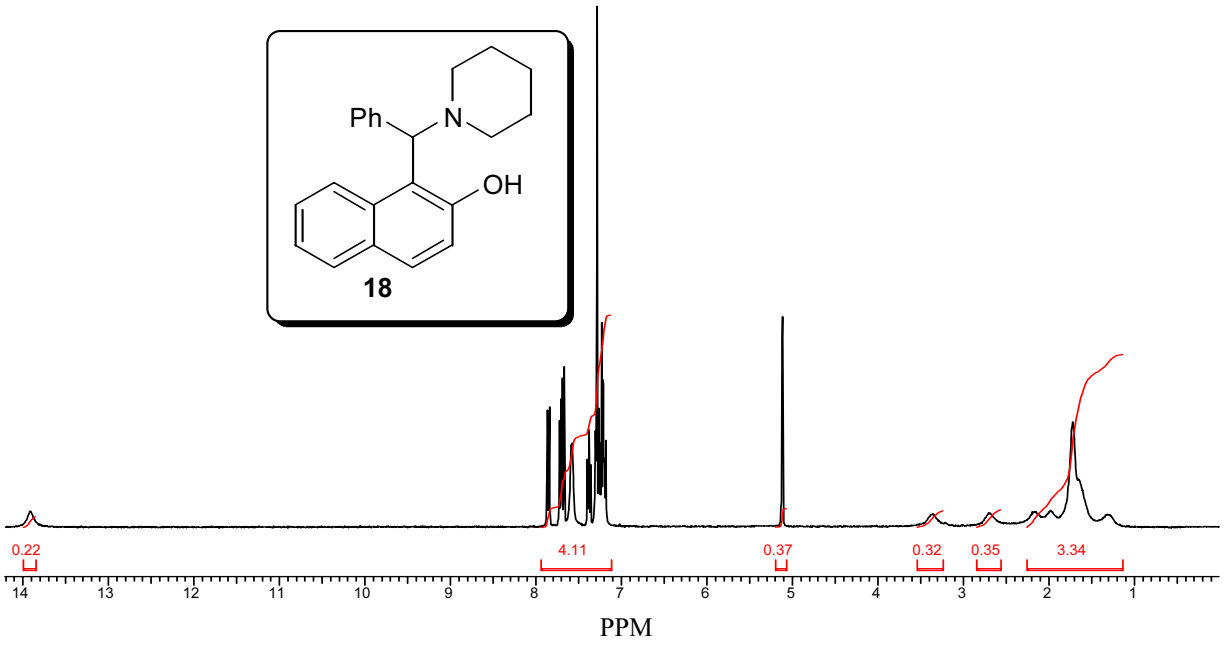
PPM

Spectrum No. 14 (Chapter 2, Section 2.4.2.6) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)

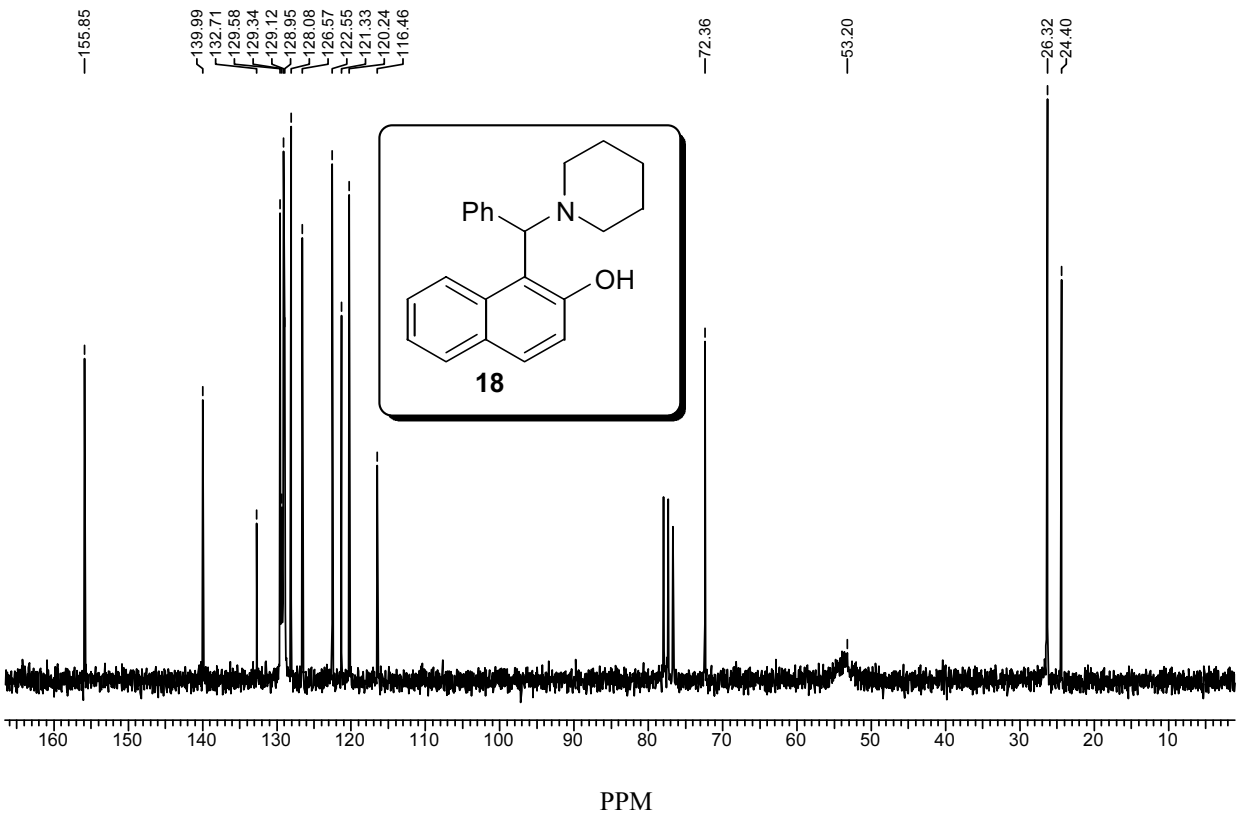


PPM

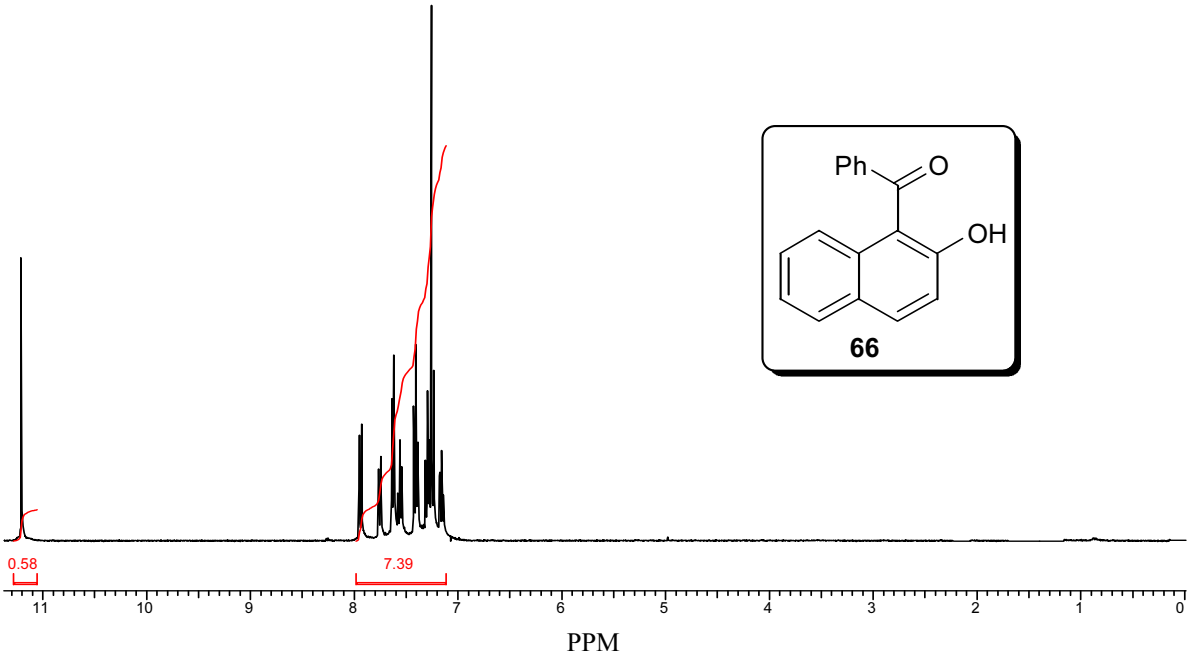
Spectrum No. 15 (Chapter 2, Section 2.4.2.7) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



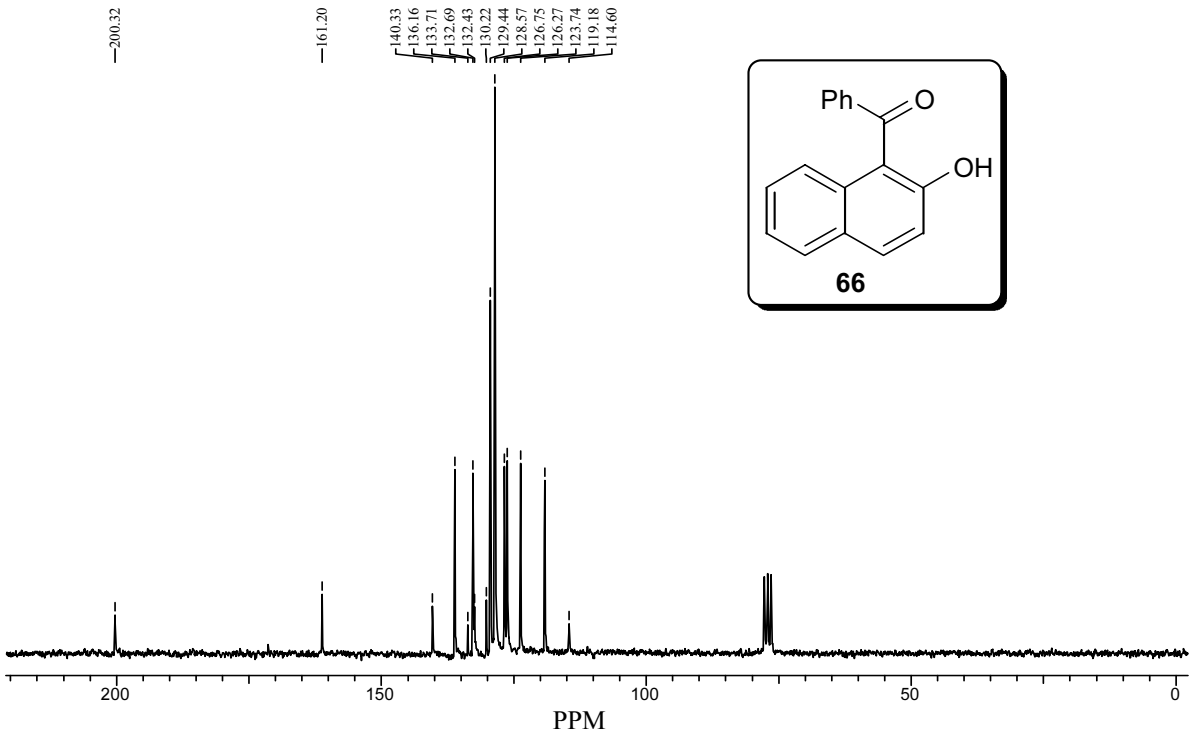
Spectrum No. 16 (Chapter 2, Section 2.4.2.7) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



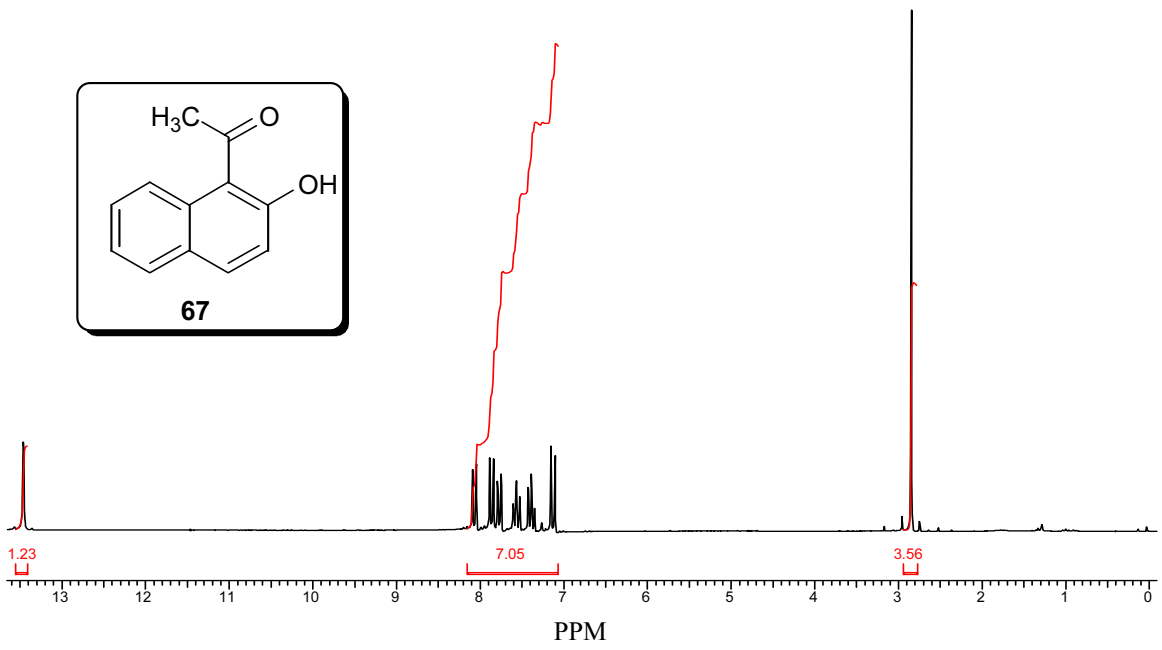
Spectrum No. 17 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



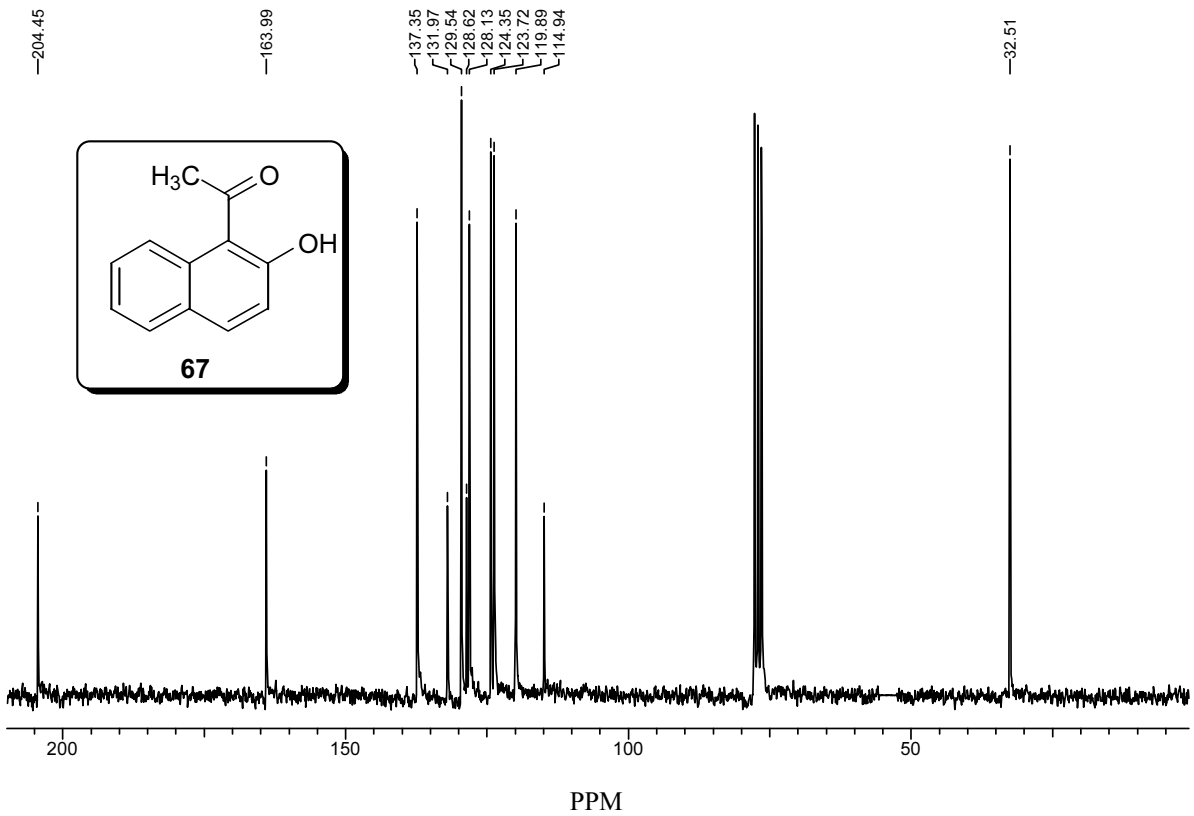
Spectrum No. 18 (Chapter 2, Section 2.4.3.1) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



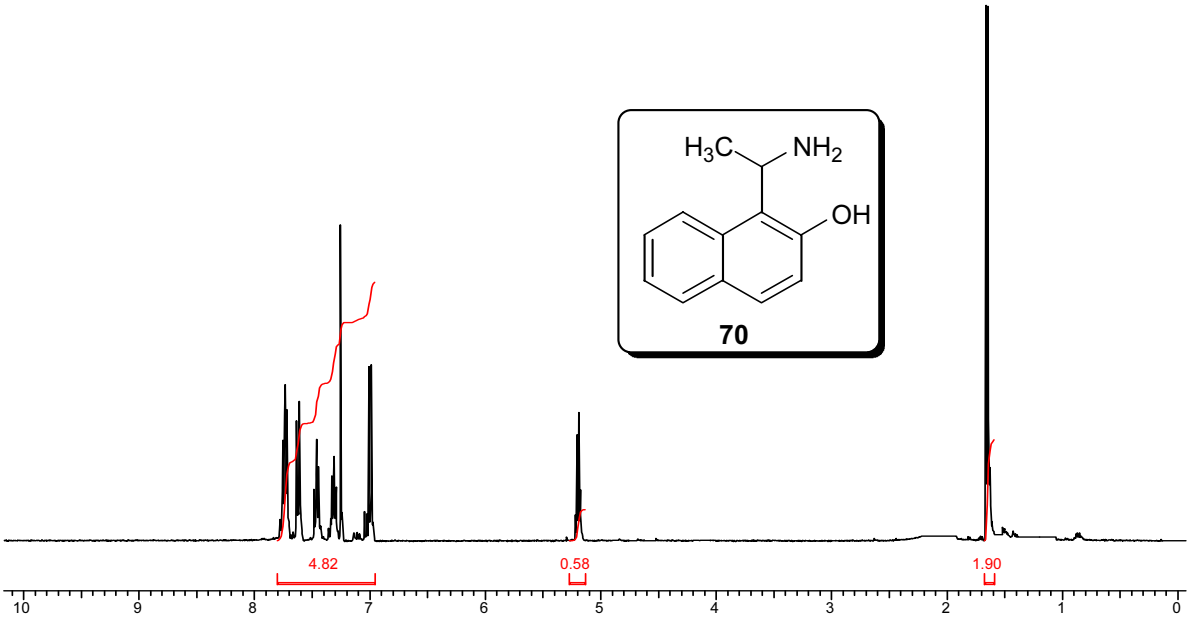
Spectrum No. 19 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



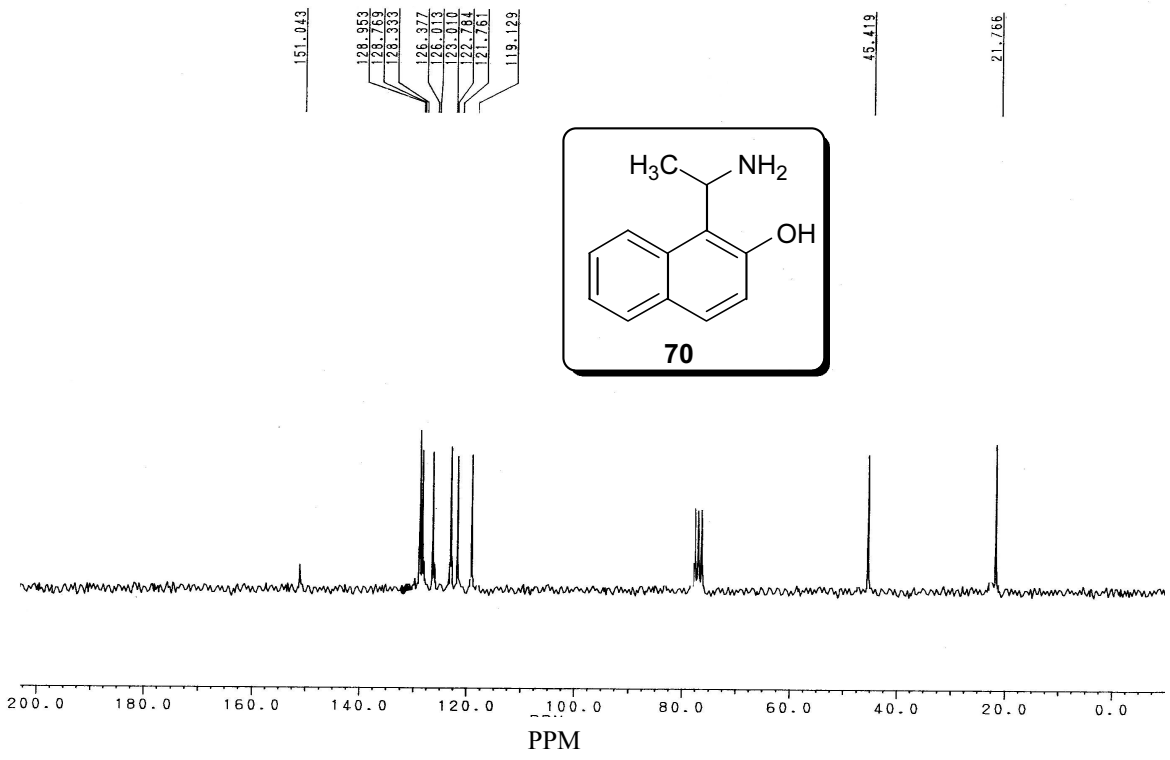
Spectrum No. 20 (Chapter 2, Section 2.4.3.1) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



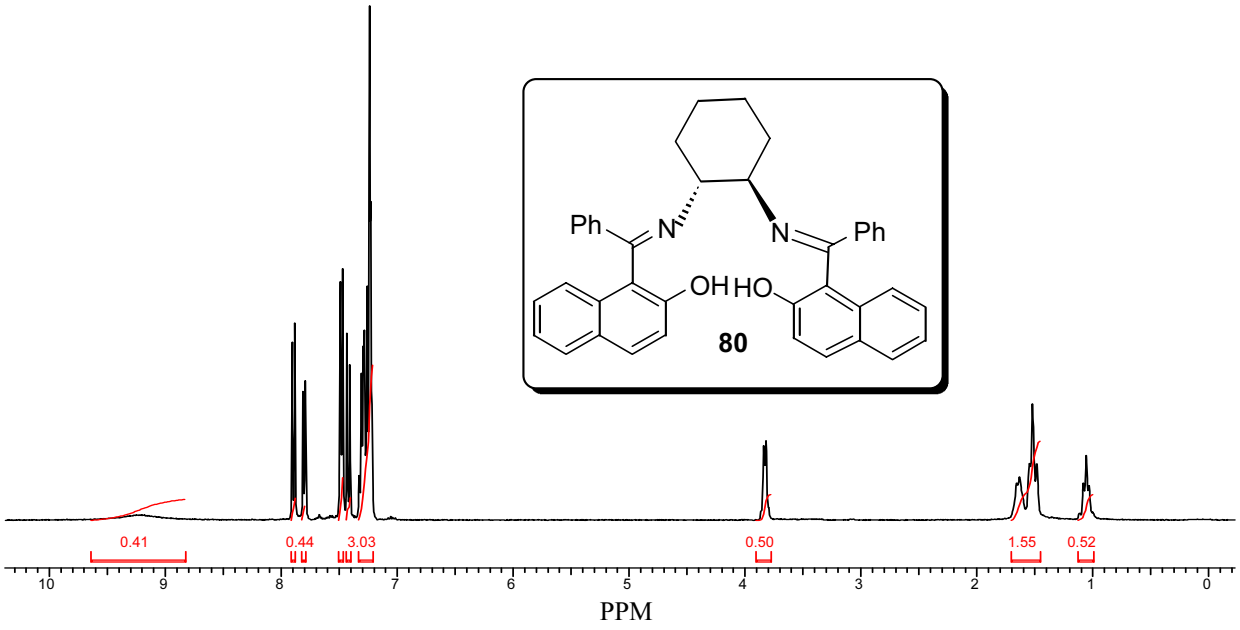
Spectrum No. 21 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



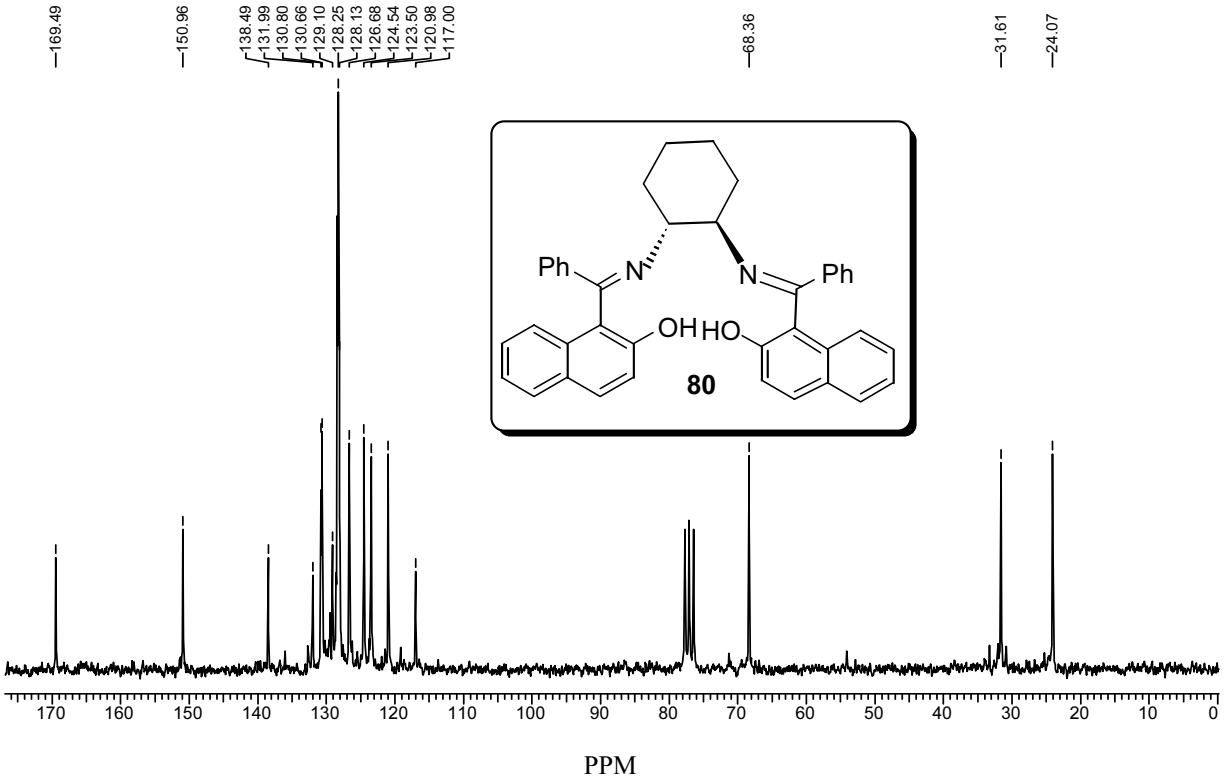
Spectrum No. 22 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (50 MHz,$CDCl_3$)



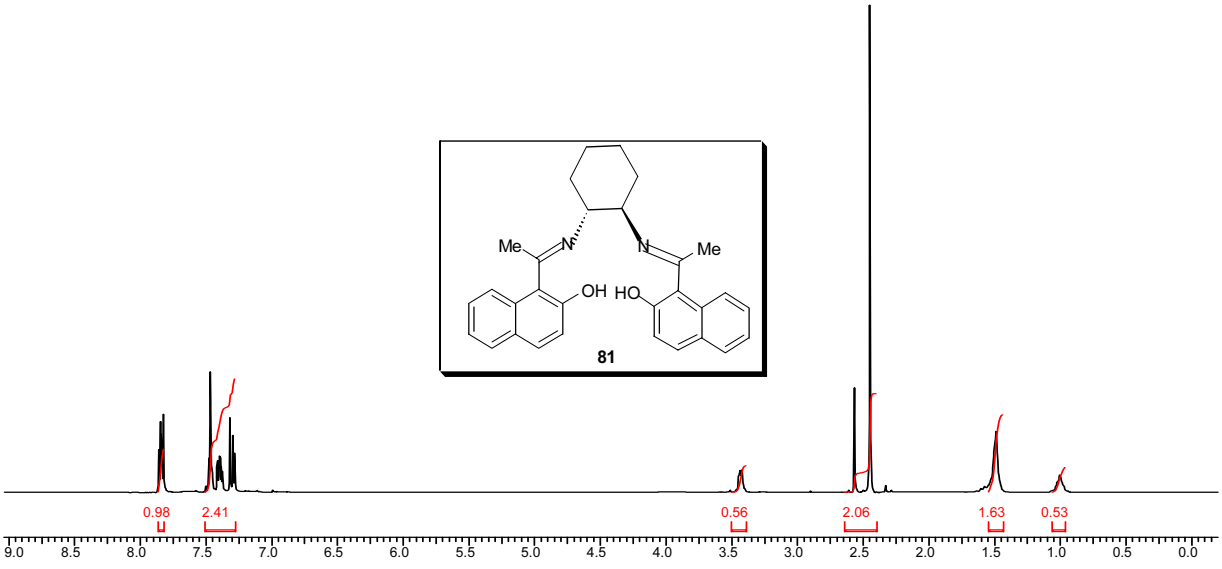
Spectrum No. 23 (Chapter 2, Section 2.4.7.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



Spectrum No. 24 (Chapter 2, Section 2.4.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Spectrum No. 25 (Chapter 2, Section 2.4.7.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



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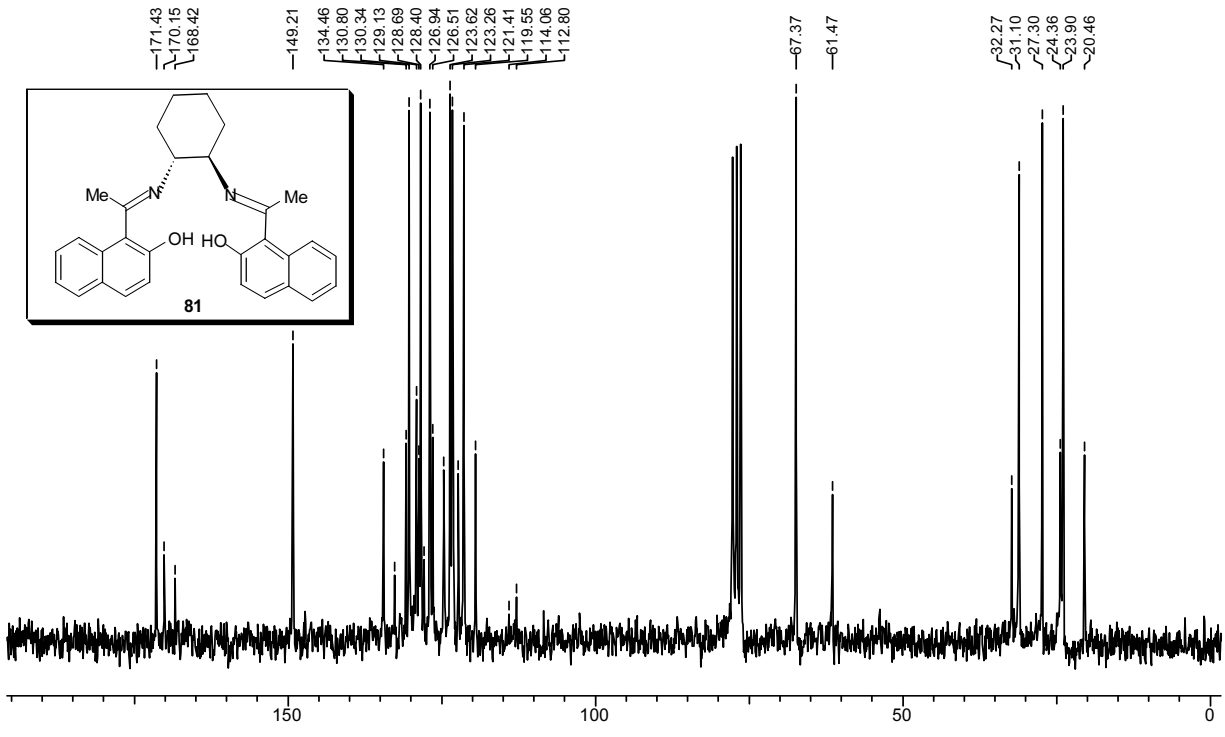
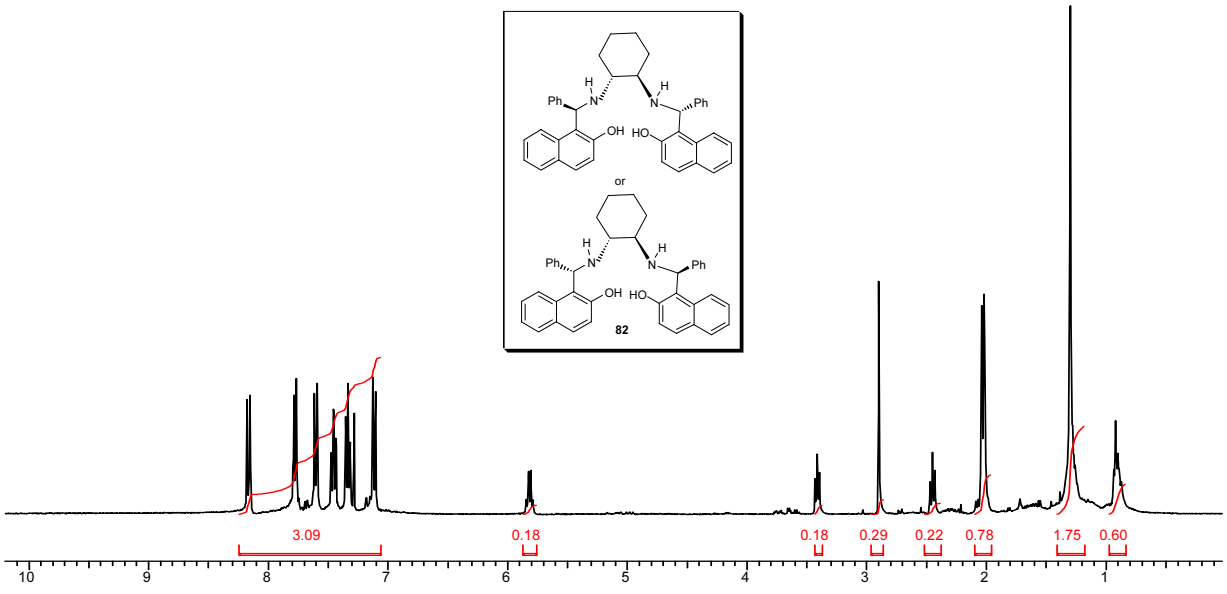
Spectrum No. 26 (Chapter 2, Section 2.4.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

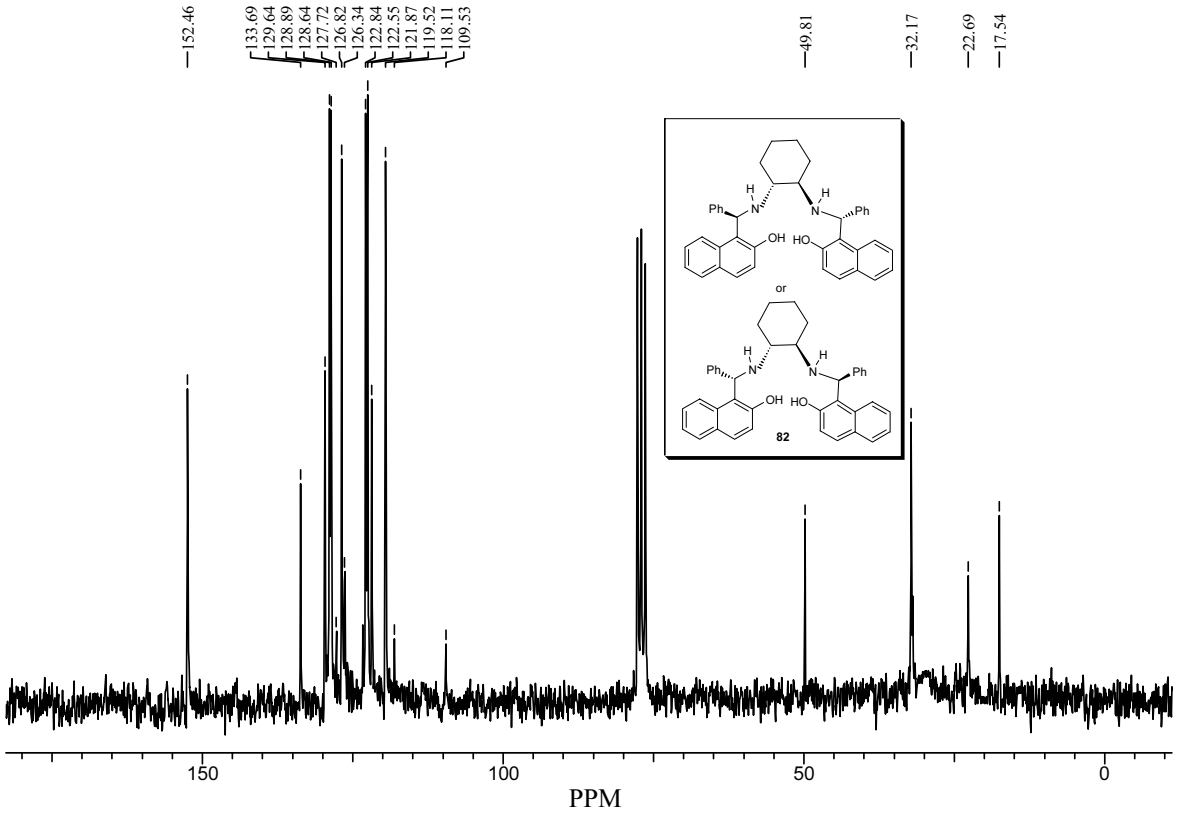


PPM

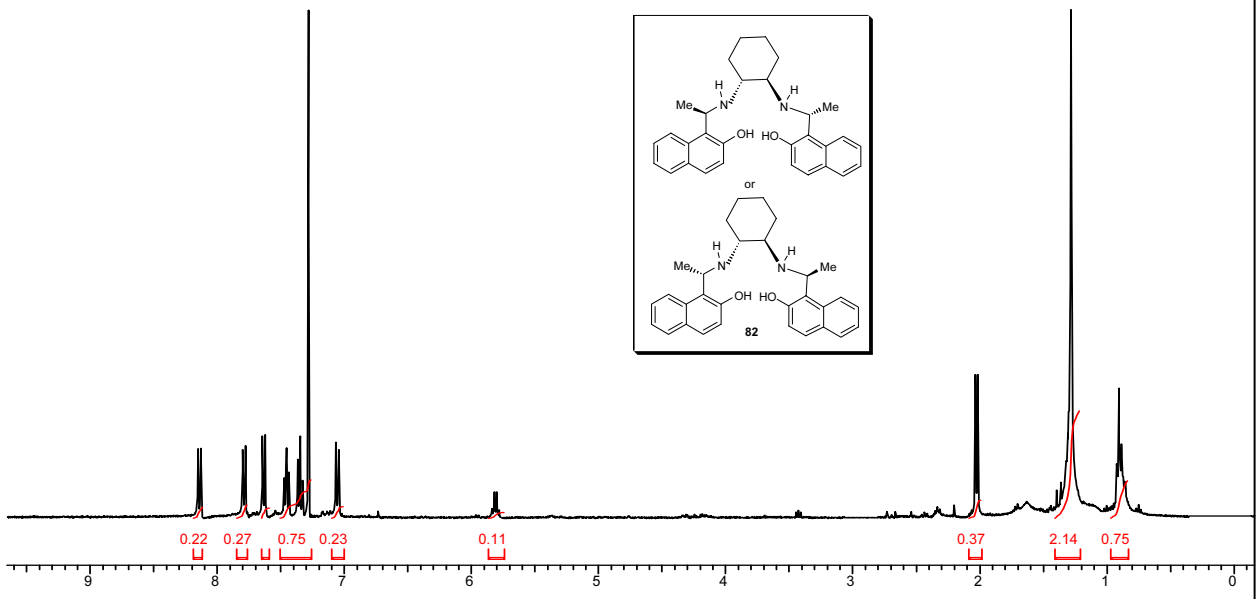
Spectrum No. 27 (Chapter 2, Section 2.4.7.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



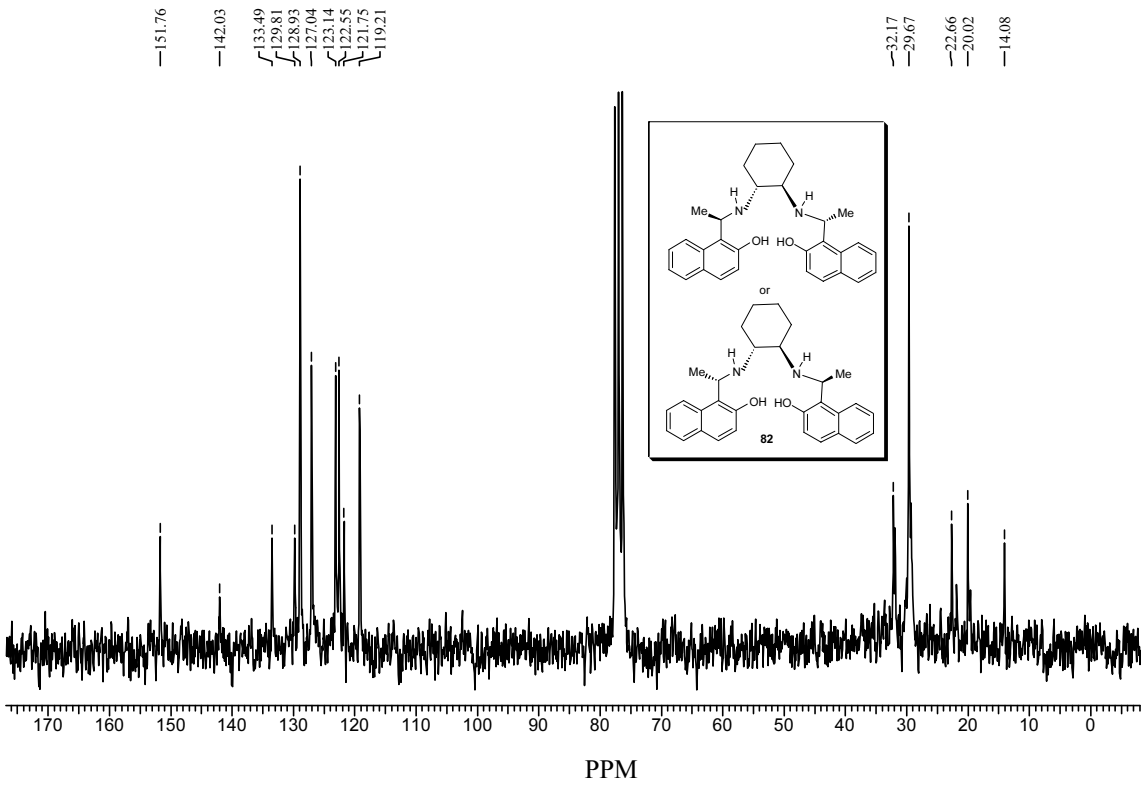
Spectrum No. 28 (Chapter 2, Section 2.4.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



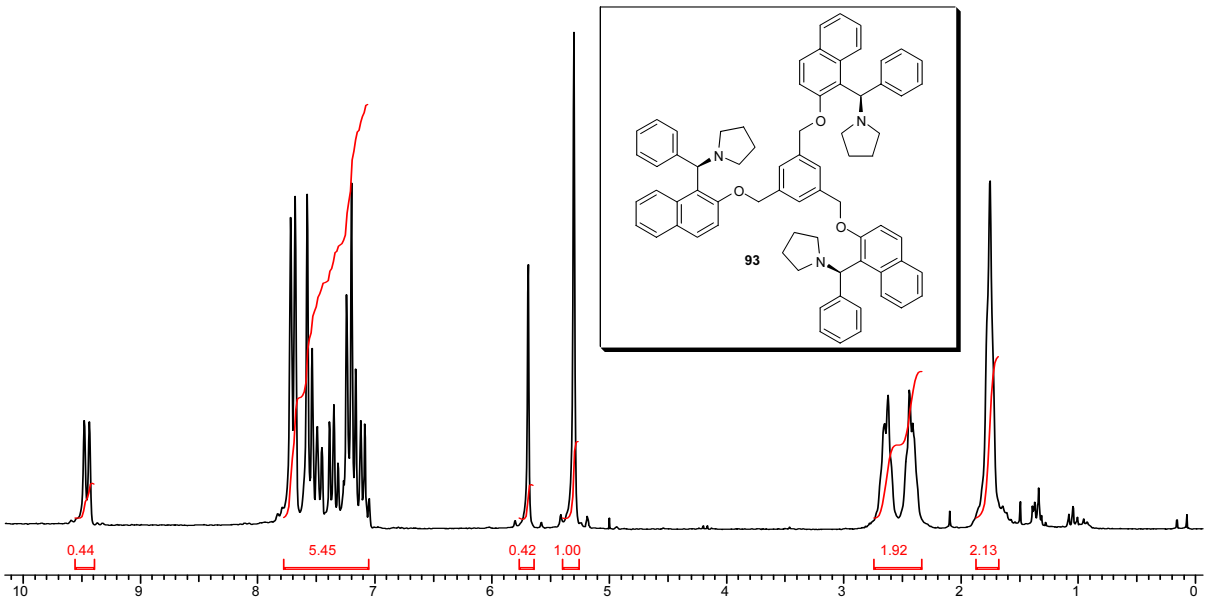
Spectrum No. 29 (Chapter 2, Section 2.4.7.1) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



Spectrum No. 30 (Chapter 2, Section 2.4.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

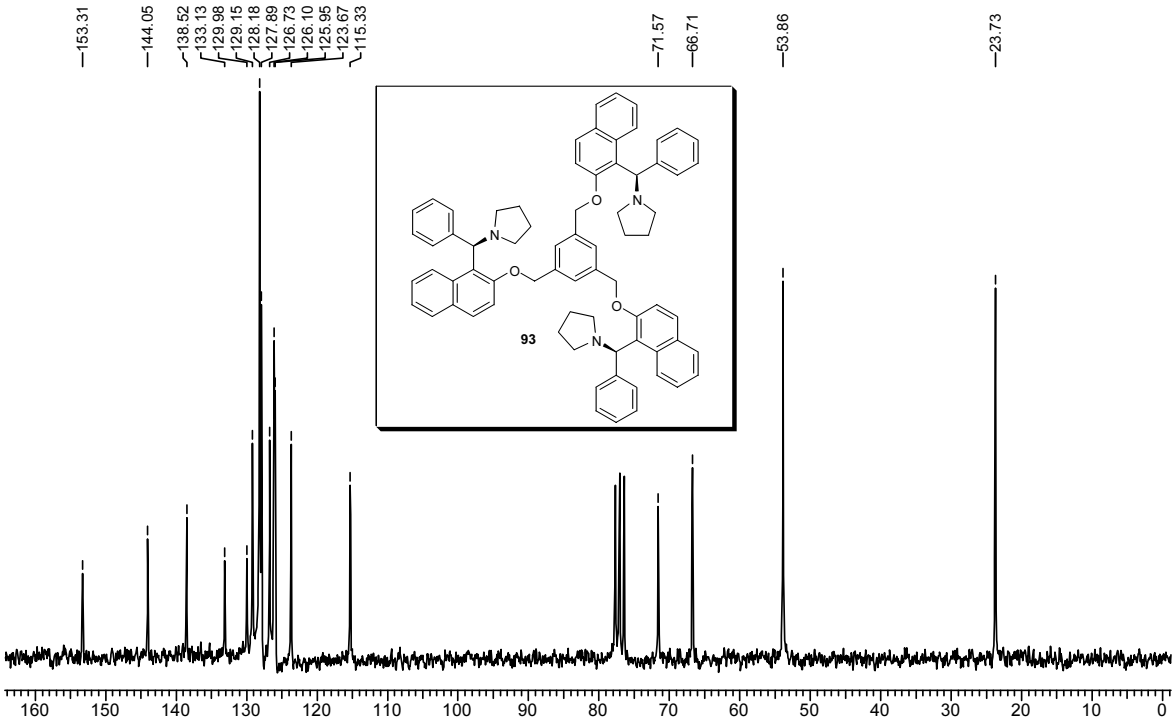


Spectrum No. 31 (Chapter 2, Section 2.4.9.1) ^{1}H NMR Spectrum (200 MHz,$CDCl_3$)



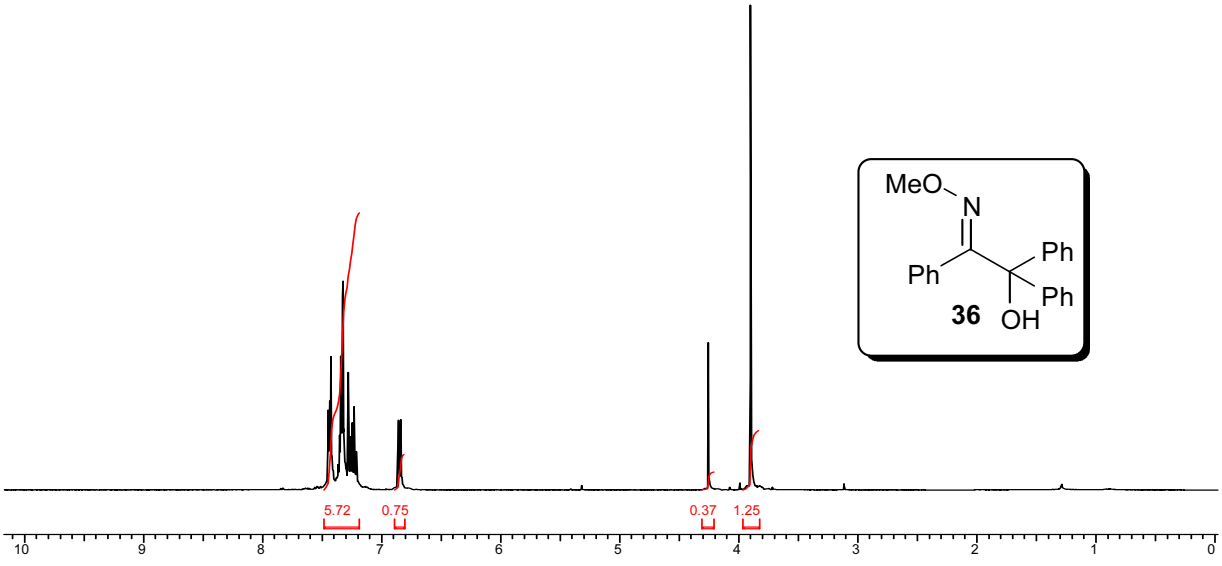
PPM

Spectrum No. 32 (Chapter 2, Section 2.4.9.1) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



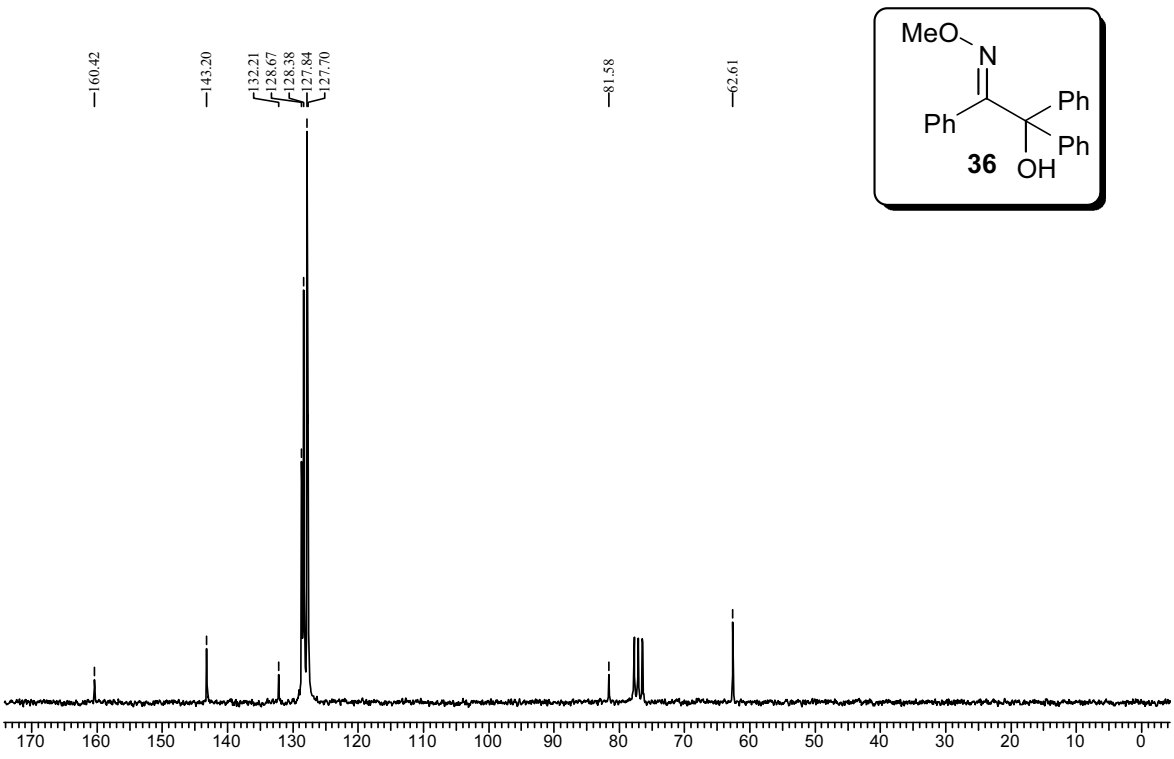
PPM

Spectrum No. 33 (Chapter 3, Section 3.4.2) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



PPM

Spectrum No. 32 (Chapter 3, Section 3.4.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



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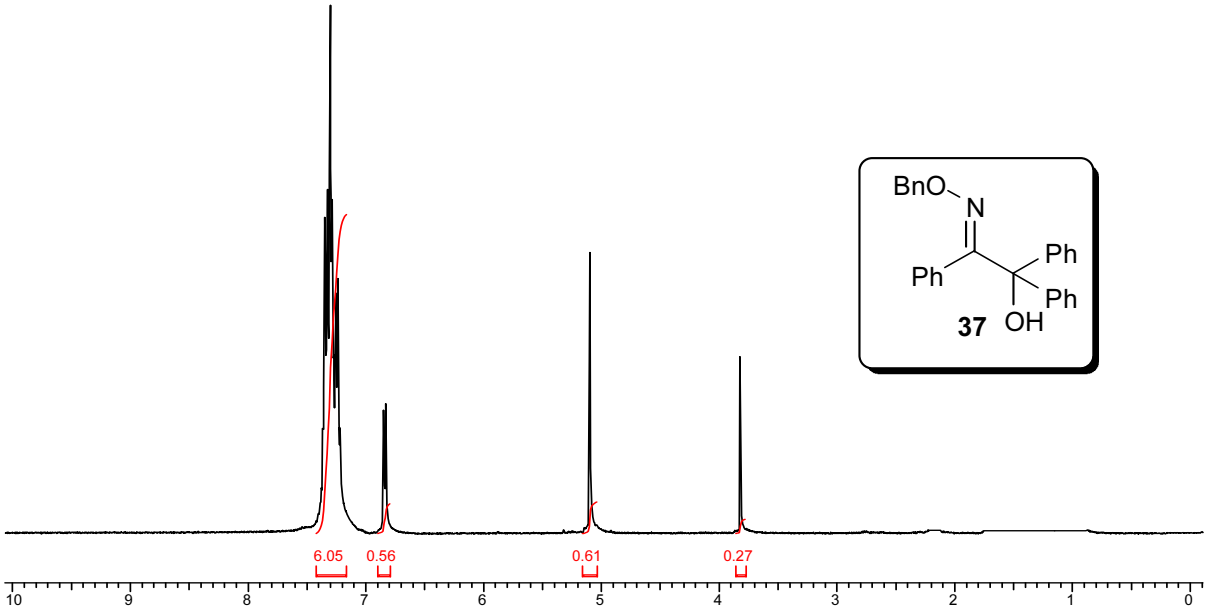
Spectrum No. 35 (Chapter 3, Section 3.4.3) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$)



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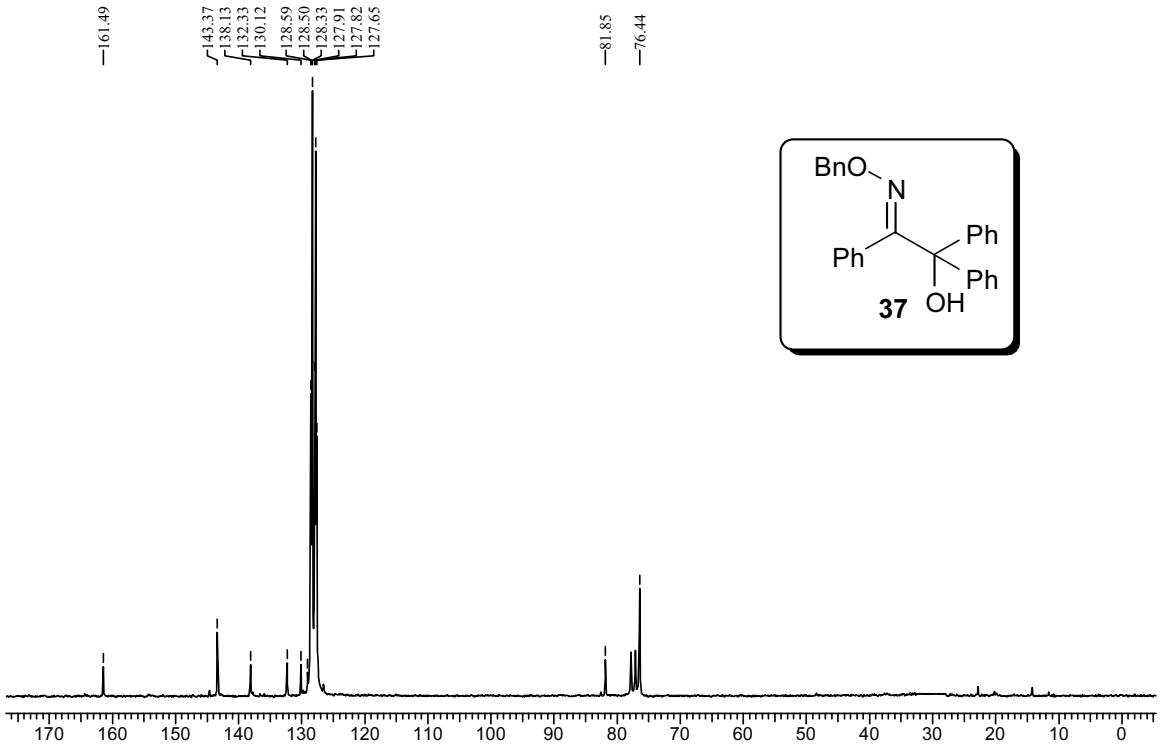
Spectrum No. 36 (Chapter 3, Section 3.4.3) ^{13} C NMR Spectrum (50 MHz, $CDCl_3$)



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Appendix II

(X-Ray Crystallographic Data)

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) **for racemic 46 with fumaric acid (Chapter 1, Section 1.2.2).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(1)	4811(1)	6063(2)	4014(1)	49(1)
O(2)	2478(2)	3705(2)	1051(1)	63(1)
O(3)	1661(1)	6549(2)	440(1)	43(1)
O(4)	4471(1)	9514(2)	2991(1)	54(1)
O(5)	3918(2)	12292(2)	2210(1)	60(1)
N(1)	565(1)	2021(3)	4421(1)	35(1)
C(1)	5687(2)	5361(3)	3716(1)	46(1)
C(2)	6321(2)	3736(3)	4330(1)	36(1)
C(3)	7266(2)	2870(4)	4061(1)	51(1)
C(4)	7185(2)	1204(4)	3516(2)	66(1)
C(5)	8070(3)	443(7)	3285(2)	96(1)
C(6)	9045(4)	1386(13)	3586(3)	172(3)
C(8)	8251(3)	3846(11)	4336(3)	160(3)
C(7)	9138(3)	3055(15)	4100(4)	236(5)
C(9)	2365(2)	5725(3)	1007(1)	37(1)
C(10)	3127(2)	6993(3)	1677(1)	38(1)
C(11)	3095(2)	9036(3)	1708(1)	39(1)
C(12)	3881(2)	10346(3)	2352(1)	37(1)

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **racemic 48 with maleic acid (Chapter 1, Section 1.2.3).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(1)	7731(3)	-517(2)	9333(2)	53(1)
O(2)	6400(3)	5031(2)	7739(2)	62(1)
O(3)	3800(3)	3591(2)	7835(2)	60(1)
O(4)	3775(3)	8215(2)	9219(2)	52(1)
O(5)	6388(2)	7019(2)	8316(2)	59(1)
N(1)	9488(3)	2266(2)	8293(2)	44(1)
C(1)	8081(4)	377(2)	7930(2)	52(1)
C(2)	10151(4)	1294(2)	7608(2)	40(1)
C(3)	10934(4)	2192(3)	6108(2)	55(1)
C(4)	8873(5)	3168(3)	5292(3)	85(1)
C(5)	12326(6)	1206(4)	5504(3)	86(1)
C(6)	4249(4)	4663(2)	7937(2)	43(1)
C(7)	208(4)	5542(2)	8326(2)	46(1)
C(8)	2191(3)	6629(2)	8653(2)	45(1)
C(9)	4225(3)	7333(2)	8743(2)	38(1)

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **non-racemic 17 with oxalic acid (Chapter 2, Section 2.2.3.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(1)	5409(3)	9777(3)	-905(2)	72(1)
O(2)	-787(3)	6232(3)	4190(2)	64(1)
O(3)	52(3)	5757(3)	1995(2)	65(1)

O(4)	1276(4)	6616(3)	3012(2)	70(1)
O(5)	3562(3)	5860(3)	2033(2)	63(1)
O(6)	2191(4)	7020(3)	1258(2)	74(1)
O(7)	4657(3)	5010(3)	3341(2)	61(1)
O(8)	6330(4)	3983(3)	3932(2)	79(1)
O(9)	7969(3)	5382(3)	2913(2)	55(1)
O(10)	6817(4)	4190(3)	2137(2)	69(1)
N(1)	3561(3)	8171(3)	-627(2)	38(1)
N(2)	1318(3)	7728(3)	4479(2)	39(1)
C(1)	5581(4)	8892(3)	277(2)	40(1)
C(2)	6274(4)	9460(4)	-275(2)	49(1)
C(3)	7799(4)	9679(4)	-190(3)	53(1)
C(4)	8598(4)	9362(4)	459(2)	50(1)
C(5)	8771(5)	8480(4)	746(2)	52(1)
C(6)	129(5)	7936(4)	2311(3)	60(1)
C(7)	6650(5)	7672(4)	2227(3)	55(1)
C(8)	807(4)	7956(3)	1578(2)	47(1)
C(9)	6410(4)	8548(3)	971(2)	39(1)
C(10)	7939(4)	8807(3)	1057(2)	42(1)
C(11)	3929(4)	8665(3)	162(2)	36(1)
C(12)	4475(4)	7206(4)	-774(3)	51(1)
C(13)	3632(5)	6632(4)	-1437(3)	59(1)
C(14)	2033(5)	6959(4)	-1394(3)	57(1)
C(15)	1991(4)	7770(4)	-745(2)	45(1)
C(16)	3025(4)	9656(3)	308(2)	40(1)
C(17)	2461(5)	10335(4)	-268(3)	55(1)
C(18)	1740(5)	11261(4)	-77(3)	64(1)
C(19)	1578(5)	11512(4)	688(4)	69(1)
C(20)	2095(5)	10827(4)	1272(3)	66(1)
C(21)	2814(4)	9902(4)	1086(3)	52(1)
C(22)	-557(4)	7118(3)	5389(2)	38(1)

C(23)	-1436(4)	6570(3)	4835(2)	45(1)
C(24)	-2953(4)	6383(4)	4934(2)	51(1)
C(25)	-3547(4)	6695(4)	5600(2)	50(1)
C(26)	-3342(5)	7551(4)	6891(3)	57(1)
C(27)	-2540(6)	8096(4)	7456(3)	62(1)
C(28)	-1084(6)	8352(4)	7350(3)	60(1)
C(29)	-418(5)	8048(3)	6687(2)	48(1)
C(30)	-1205(4)	7464(3)	6087(2)	38(1)
C(31)	-2707(4)	7221(3)	6193(2)	44(1)
C(32)	1073(4)	7271(3)	5273(2)	38(1)
C(33)	531(5)	8763(4)	4327(3)	54(1)
C(34)	1251(5)	9256(4)	3654(3)	61(1)
C(35)	2812(5)	8839(4)	3709(3)	69(1)
C(36)	2904(4)	7977(4)	4331(2)	50(1)
C(37)	1946(4)	6258(3)	5449(2)	41(1)
C(38)	2336(4)	5533(4)	4895(2)	51(1)
C(39)	3077(5)	4601(4)	5110(3)	59(1)
C(40)	3395(5)	4378(4)	5884(3)	60(1)
C(41)	3033(5)	5088(4)	6445(3)	62(1)
C(42)	2318(4)	6028(4)	6235(2)	52(1)
C(43)	1187(5)	6270(3)	2358(2)	50(1)
C(44)	2429(5)	6414(4)	1824(2)	54(1)
C(45)	5943(5)	4538(3)	3380(2)	49(1)
C(46)	6981(4)	4709(3)	2738(2)	43(1)

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **racemic 17 with oxalic acid (Chapter 2, Section 2.2.3.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(1)	-655(3)	5818(2)	1764(2)	55(1)
O(2)	1792(3)	9198(2)	3984(2)	59(1)
O(3)	3987(3)	9738(3)	4314(2)	68(1)
O(4)	1589(3)	8455(3)	5520(2)	66(1)
O(5)	639(3)	9188(3)	5826(2)	64(1)
N(1)	1209(3)	7457(3)	2115(2)	42(1)
C(1)	-820(4)	6788(3)	2946(2)	40(1)
C(2)	-1488(4)	6190(3)	2367(2)	41(1)
C(3)	-2964(4)	6001(3)	2368(2)	49(1)
C(4)	-3751(4)	6360(3)	2974(3)	52(1)
C(5)	-3967(4)	7285(4)	4265(3)	59(1)
C(6)\	-3380(5)	7823(4)	4882(3)	64(1)
C(7)	-1915(5)	8058(4)	4866(3)	60(1)
C(8)	-1070(4)	7748(3)	4250(2)	50(1)
C(9)	-1652(4)	7165(3)	3599(2)	39(1)
C(10)	-3147(4)	6927(3)	3614(2)	45(1)
C(11)	780(4)	7002(3)	2912(2)	40(1)
C(12)	339(5)	8400(3)	1866(3)	56(1)
C(13)	1201(5)	8907(4)	1228(3)	66(1)
C(14)	2746(5)	8616(4)	1396(3)	66(1)
C(15)	2713(4)	7857(3)	2095(2)	52(1)
C(16)	1697(4)	6050(3)	3139(2)	42(1)
C(17)	2212(4)	5333(3)	2599(3)	51(1)
C(18)	3033(4)	4468(4)	2850(3)	62(1)
C(19)	3312(5)	4323(4)	3642(4)	76(2)

C(20)	2790(6)	5027(6)	4192(4)	89(2)
C(21)	2009(5)	5897(4)	3942(3)	66(1)
C(22)	2821(4)	9340(3)	4448(2)	42(1)
C(23)	2602(4)	8943(3)	5317(2)	48(1

Table 5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **non-racemic 2 with oxalic acid (Chapter 2, Section 2.2.3.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(1)	3767(1)	-287(1)	3473(1)	47(1)
O(2)	4503(2)	2119(2)	5005(1)	66(1)
O(3)	3194(1)	2689(1)	5522(1)	43(1)
O(4)	6055(3)	10290(3)	4688(1)	141(1)
N(1)	4327(2)	1333(2)	4096(1)	38(1)
C(1)	5833(1)	790(1)	3514(1)	32(1)
C(2)	5057(2)	-226(2)	3362(1)	36(1)
C(3)	5601(2)	-1209(2)	3101(1)	41(1)
C(4)	6898(2)	-1173(2)	2995(1)	44(1)
C(5)	9091(2)	-136(2)	3032(1)	52(1)
C(6)	9904(2)	830(2)	3176(1)	61(1)
C(7)	9404(2)	1808(2)	3434(1)	58(1)
C(8)	8098(2)	1821(2)	3549(1)	46(1)
C(9)	7211(2)	834(2)	3408(1)	35(1)
C(10)	7739(2)	-166(2)	3142(1)	39(1)
C(11)	5209(1)	1896(1)	3768(1)	33(1)
C(12)	4485(2)	2892(1)	3498(1)	36(1)
C(13)	3218(2)	2700(2)	3352(1)	54(1)
C(14)	2638(2)	3611(2)	3086(1)	63(1)
C(15)	3305(3)	4711(2)	2968(1)	65(1)

C(16)	4564(3)	4916(2)	3111(1)	76(1)
C(17)	5152(2)	4020(2)	3377(1)	57(1)
C(18)	3551(2)	2701(2)	5149(1)	35(1)
C(19)	6834(3)	9361(4)	4852(1)	86(1)

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **non-racemic 10 with oxalic acid (Chapter 2, Section 2.2.3.1).** U(eq) is defined as one third of the trace of orthogonalized Uij tensor

atom	**x**	**y**	**z**	**U(eq)**
O(1)	701(2)	6140(2)	5522(1)	68(1)
O(2)	7014(2)	2683(2)	2367(1)	66(1)
O(3)	6541(3)	475(2)	2713(1)	77(1)
O(4)	6778(3)	1827(2)	3934(1)	78(1)
O(5)	6242(2)	3615(2)	4252(1)	77(1)
N(1)	695(2)	4396(2)	6780(1)	41(1)
C(1)	2954(2)	6289(2)	5943(1)	41(1)
C(2)	2233(2)	6951(2)	5552(1)	55(1)
C(3)	065(3)	8420(3)	5219(2)	77(1)
C(4)	4573(3)	9201(2)	5288(2)	76(1)
C(5)	6969(3)	9407(2)	5709(2)	73(1)
C(6)	7743(3)	8786(3)	6024(2)	82(1)
C(7)	6966(2)	7305(3)	6338(2)	71(1)
C(8)	5414(2)	6477(2)	6328(1)	54(1)
C(9)	4562(2)	7093(2)	6000(1)	45(1)
C(10)	5380(2)	8592(2)	5674(1)	59(1)
C(11)	2061(2)	4686(2)	6274(1)	38(1)
C(12)	1078(3)	5622(3)	7384(1)	62(1)
C(13)	62(2)	2911(2)	7201(1)	62(1)
C(14)	1640(2)	3486(2)	5625(1)	43(1)

C(15)	2429(2)	2712(2)	5608(2)	66(1)
C(16)	2137(3)	1655(3)	5010(3)	93(1)
C(17)	1037(3)	1327(3)	4457(2)	94(1)
C(18)	227(3)	2063(3)	4463(2)	78(1)
C(19)	534(2)	3161(2)	5046(1)	54(1)
C(20)	-102(4)	6587(5)	5002(3)	120(2)
C(21)	6723(2)	3414(2)	2863(1)	43(1)
C(22)	6589(2)	2861(2)	3756(1)	45(1)

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **non-racemic 12 with trimesic acid (Chapter 2, Section 2.2.3.5).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(1)	3804(1)	3505(2)	2473(1)	41(1)
O(2)	4841(1)	2135(2)	1786(2)	50(1)
O(3)	4810(1)	-221(2)	1788(1)	42(1)
O(4)	4029(1)	-1464(2)	-1621(1)	55(1)
O(5)	4088(1)	-2638(2)	-523(2)	59(1)
O(6)	4389(1)	4822(2)	-422(1)	53(1)
O(7)	4225(1)	3882(3)	-1571(1)	62(1)
N(1)	979(1)	5953(3)	1818(2)	31(1)
C(1)	3559(1)	3847(3)	1170(2)	27(1)
C(2)	3649(1)	2950(3)	1781(2)	31(1)
C(3)	3571(1)	1481(3)	1706(2)	38(1)
C(4)	3386(1)	936(3)	1037(2)	42(1)
C(5)	3072(1)	1243(4)	-299(2)	53(1)
C(6)	2969(2)	2082(5)	-918(2)	63(1)
C(7)	3071(1)	3524(4)	-868(2)	56(1)
C(8)	3262(1)	4112(4)	-210(2)	41(1)

C(9)	3370(1)	3281(3)	452(2)	30(1)
C(10)	3274(1)	1802(3)	393(2)	37(1)
C(11)	3592(1)	5457(3)	1235(2)	28(1)
C(12)	4452(1)	5549(4)	1590(2)	51(1)
C(13)	3961(1)	7520(3)	1940(2)	48(1)
C(14)	3123(1)	6103(3)	1391(2)	32(1)
C(15)	2935(1)	7173(4)	927(2)	45(1)
C(16)	2502(2)	7759(4)	1052(3)	66(1)
C(17)	2256(2)	7274(5)	1644(3)	75(2)
C(18)	2440(2)	6210(5)	2110(3)	66(1)
C(19)	2871(1)	5620(4)	1982(2)	48(1)
C(20)	4577(1)	1002(3)	641(2)	27(1)
C(21)	4548(1)	2281(3)	260(2)	30(1)
C(22)	4375(1)	2352(3)	-499(2)	30(1)
C(23)	4235(1)	1113(3)	-876(2)	32(1)
C(24)	4261(1)	-186(3)	-500(2)	28(1)
C(25)	4434(1)	-230(3)	258(2)	29(1)
C(26)	4755(1)	964(3)	1459(2)	30(1)
C(27)	4322(1)	3758(3)	-895(2)	37(1)
C(28)	4113(1)	-1546(3)	-912(2)	36(1)

LIST OF PUBLICATIONS

1. New, Convenient Methods of Synthesis and Resolution of 1,2-Amino- Alcohols, Periasamy, M.; Sivakumar, S; **Reddy, M. N**. *Synthesis,* **2003**,1965.
2. Toward Homogeneity of Chirality via Selective Formation of Homochiral or Heterochiral Aggregates, Periasamy, M.; Sivakumar, S; **Reddy, M. N**.; Padmaja, M. *Org. Lett*., **2004**, *6*, 265.
3. Synthesis and Resolution of 1-(α-Pyrrolidinylbenzyl)-2-naphthol and its Application in the Resolution of 2,2'-Dihydroxy-1,1'-Binaphthyl, Periasamy, M.; **Reddy, M. N**.; Anwar, S. *Tetrahedron: Asymmetry,* **2004**, *15*, 1809.
4. Acyloxyboranes: Preparations and Applications, Periasamy, M.; **Reddy, M. N**.; Kumar, N. S. *Science of Synthesis, Houben-weyl methods of molecular transformations*, Georg Thieme Verlag, Stuttgart, Volume 6, **2005**, 321.
5. Synthesis, and partial resolution of 2-amino-1,1,2-triphenylethanol and enhancement of its enantiomeric purity using achiral dicarboxylic acids, Periasamy, M.; **Reddy, M. N**. (*manuscript under preparation)*.
6. Enhancement of enantiomeric purity of non-racemic 1,2-amino alcohols using achiral dicarboxylic acids, Periasamy, M.; **Reddy, M. N**. (*manuscript under preparation)*.
7. Resolution of aminonaphthols and enhancement of their enantiomeric purity through homochiral or heterochiral hydrogen bonding aggregates, Periasamy, M.; **Reddy, M. N**. (*manuscript under preparation)*.
8. General and convenient method for the synthesis of aminonaphthols, Periasamy, M.; **Reddy, M. N**.; Anwar, S. (*manuscript under preparation).*

9. Asymmetric autoinductive reduction of oxime ether derivatives of phenyl benzoin using amino alcohol and borane reagents, Periasamy, M.; **Reddy, M. N**.; Sivakumar, S. (*manuscript under preparation).*

POSTERS/ PAPERS PRESENTED IN SYMPOSIA

1. A New, General Method of Synthesis and Resolution of 1,2-Amino-Alcohols, Sivakumar, S; **Reddy, M. N**.; Periasamy, M. presented a poster in the ***OMCOS-11*** International Symposium held at Taipei, Taiwan during July 22-26, **2001**.
2. Homogeneity of Chirality via Preparation of Hydrogen Bonded homochiral or Heterochiral Aggregates, **Reddy, M. N** and Periasamy, M. ***ChemFest*-2004**, University of Hyderabad, March 11, **2004**.
3. Amplification of Enantiomeric Purity of Non-racemic Aminonaphthols via Preparation of Hydrogen Bonded Homochiral or Heterochiral Aggregates, **Reddy, M. N** and Periasamy, M. **7th CRSI** NATIONAL SYMPOSIUM IN CHEMISTRY (NSC – 7) February 4-6, **2005** IACS, Kolkata.