Chapter 1

Studies on the methods of synthesis and resolution of 1,2-amino alcohols
1. 1 Introduction

Amino alcohols are important class of organic compounds. Several of these have been found to be useful in medicinal chemistry as therapeutic agents for a wide variety of human diseases and disorders. For example, enantiomerically pure propranol (1) and denopamine (2) are effective therapeutic agents in the treatment of heart diseases.\(^1\text{-}^5\)

In recent years, the importance of enantiomeric purity in pharmaceuticals has been amply demonstrated by the debilitating and sometimes tragic side-effects caused by the presence of non-therapeutic enantiomer of an otherwise beneficial drug. Difference in biological activity' has been also noted in certain amino acid derivatives. For instance, the chiral amino acid derivative, propoxyphene (3), is an analgesic agent, whereas, its antipode (4) has antitissive properties.
Besides pharmaceutical applications, enantiomerically pure amino alcohols, especially the 1,2-amino alcohols have also been used as chiral auxiliaries and chiral catalysts in asymmetric organic transformations.\textsuperscript{6-9} A large number of enantiomerically pure amino alcohol derived chiral auxiliaries and chiral catalysts have been synthesised and used for the past 20 years. It will be helpful for the discussion to briefly review the syntheses and applications of the 1,2-amino alcohols.

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

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

Several reagents are available (e.g. LiAlH\(_4\) and BH\(_3\)·THF) for the reduction of free as well as protected amino acids to the corresponding amino alcohols. However, these reagents suffer from disadvantages of cost, inflammability and tedious isolation procedures (Scheme 1).\textsuperscript{10-12}
Meyers and coworkers examined the reduction of amino acids using the NaBH₄/I₂ reagent system, previously developed in this laboratory for the reduction of organic compounds (Scheme 2). The results indicate that it is an excellent reagent system for the conversion of amino acids to amino alcohols. The NaBH₄/I₂ reagent system is safe, simple and inexpensive. Hence, it is useful, especially in the large scale synthesis of chiral amino alcohols.

The N-acy\-amino acids gave the corresponding N-alkyl amino alcohols under these conditions (Scheme 3).
Scheme 3

The reduction of pentachlorophenyl esters of the Boc protected amino acids and peptides gave the corresponding amino alcohols. (Scheme 4)\(^\text{16}\)

Scheme 4

Amino acids are also reduced using the inexpensive NaBH\(_4\)/H\(_2\)SO\(_4\) reagent system in THF. It is of interest to note that no racemisation occurs in the reduction of amino acids using NaBH\(_4\)/I\(_2\) or NaBH\(_4\)/H\(_2\)SO\(_4\) reagent systems (Scheme 5).\(^\text{17}\)

Scheme 5
α-Imino ester can be reduced to the corresponding amino ester, which upon reaction with Grignard reagent gives the corresponding amino alcohols as shown in the Scheme 6.\\(^\text{18}\)\\

**Scheme 6**

A convenient method of synthesis of chiral α,α-diphenyl-2-pyrrolidinemethanol 16 involving single step N and O- protection of (S)-proline using ethylchloroformate followed by Grignard reaction and alkaline hydrolysis, has been reported from this laboratory (Scheme 7).\\(^\text{19}\)\\

**Scheme 7**
Recently, the oxazolidinone intermediates of the type 15 have been readily prepared by the Grignard reaction of \( N \)-alkoxy-carbonyl-\( \alpha \)-amino esters, which on hydrolysis give the corresponding amino alcohols. It was observed that the success of the reaction is dependent on the nature of \( R' \) group. When \( R' = \text{Ph} \), no cyclisation occurs and when \( R' = \text{benzyl} \) or \( \text{H} \), yields of oxazolidinones are 30% and 60%, respectively (Scheme 8).\textsuperscript{20}

**Scheme 8**

The 1,2-amino alcohols 21 were also obtained by the reduction of \( N \)-protected \( N \)-carboxy anhydrides 20 using the \( \text{NaBH}_4/\text{H}_2\text{O} \) reagent system (Scheme 9).\textsuperscript{21-23}

**Scheme 9**
1.1.1.2 From α-amino carbonyl compounds

α-Amino carbonyl compounds are reduced using Rh(COD)Cl₂ catalyst to obtain the corresponding 1,2-amino alcohols (Scheme 10).²³

Scheme 10

1.1.1.3 From alkoxy carbonyl compounds

α-Hydroxy carbonyl compounds have been used to access 1,2-amino alcohols through reduction of oxime derivatives (Scheme 11).²⁴

Scheme 11

1.1.1.4 From epoxides

1,2-Amino alcohols are prepared by stereo, regio and enantioselective ring opening of epoxides using nitrogen nucleophiles such as primary, secondary amines or azides in the presence of metal complexes (Scheme 12).²⁵-³⁰
1.1.1.5 From cyclic sulfates

The 1,2-cyclic sulfates are synthetic equivalents of epoxides that are readily accessible through Sharpless asymmetric dihydroxylation reaction of olefins. 1,2-Cyclic sulfates react with nitrogen nucleophiles to give the corresponding 1,2-amino alcohol derivatives (Scheme 13).\(^{31}\)

**Scheme 13**

1.1.1.6 Other methods

1,2-Amino alcohols are also accessible from alkenes by oxyamination process\(^{32}\) as shown in the Scheme 14.
Asymmetric synthesis of 1,2-amino alcohols with moderate enantioselectivity (50-86% ee) has been achieved through hydroboration of aldehyde enamines (Scheme 15).  

Michael addition of an alkoxide to nitro olefins gave the Michael adduct, which upon hydrogenation in the presence of Pd-C afforded the 1,2-amino alcohol derivative (Scheme 16).
1. 1. 2 Synthetic applications of 1,2-amino alcohols

1. 1. 2. 1 Amino alcohols as chiral auxiliaries

1. 1. 2. 1. 1 Strecker synthesis

High level of diastereoselectivity was achieved in the Strecker synthesis using inexpensive phenylglycinol as a chiral auxiliary (Scheme 17). The product can be readily cleaved to obtain the corresponding optically active a-amino acids. A number of chiral amino acids are synthesized following this method.

Scheme 17

1. 1. 2. 1. 2 Alkylation

The chiral 1,2-amino alcohols or its ether derivatives react with carbonyl compounds to form the corresponding imines. These imines undergo reactions with Grignard or organolithium reagents and an alkyl halide to give the corresponding alkylated product (Scheme 18).
Scheme 18

1. 1. 2. 1. 3 Synthesis of lactams

Meyers et al.\textsuperscript{37-39} developed a general method for the synthesis of non-racemic bicyclic lactam 47 from chiral 1,2-amino alcohols 45 and keto carboxylic acids 46 (Scheme 19). The Meyers lactam 47 has proved to be an exceptional chiral template or vehicle for the construction of a wide variety of optically pure carbocycles and heterocycles.\textsuperscript{40}

Scheme 19
1. 1. 2. 1. 4 Oxazolidinones as chiral auxiliaries

Reactions of amino alcohols with trichloromethyl chloroformate provides a simple entry into oxazolidinones 48 (Scheme 20).\textsuperscript{41} Reaction between amino alcohols and diethyl carbonate is the most direct route to oxazolidinones 50.\textsuperscript{42}

Scheme 20

The oxazolidinones give excellent levels of asymmetric induction in alkylation reactions. For example, the $N$-acyloxazolidinone 51 moiety helps in realizing high degree of stereoselectivity during enolate formation (Scheme 21).\textsuperscript{3} Z-Enolates with high diastereoselectivity were obtained by the reaction of parent acyloxazolidinone with TiCl$_4$/R$_3$N reagent system (Scheme 21)
Scheme 21

The utility of the \(Z\)-enolates derived from \(N\)-acylimides of chiral oxazolidinones has been demonstrated in the \(\text{aldol}\) condensation reaction with aldehydes to obtain the corresponding \(\alpha\)-substituted-\(\beta\)-hydroxy imides 54 in high yields.\(^{44}\)

Scheme 22

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

1. 1. 2. 2. 1 Nucleophilic substitution

1,2-Amino alcohols can undergo nucleophilic substitution reaction under Mitsunobu conditions, with the stereochemistry controlled by the nitrogen protection (Scheme 23). Use of an amide to protect nitrogen leads to retention of configuration through formation of oxazoline intermediate. Whereas, the use of a
configuration through formation of oxazoline intermediate. Whereas, the use of a carbamate protection provides overall inversion at the reaction centre as no intramolecular reaction is involved.\textsuperscript{45}

Scheme 23

1.1. 2. 2 Preparation of chiral diamines

Chiral 1,2-amino alcohols are converted into chiral diamines in an efficient manner via mesylation followed by reaction with an amine. Over the past few years, many chiral diamine ligands were prepared through the aziridinium ion intermediates from chiral amino alcohols. For example, the chiral diamine 60 was prepared from (\textit{R})-phenylglycinol (Scheme 24) through an aziridinium ion intermediate.\textsuperscript{46}
1. 1. 2. 2. 3 Synthesis of 2-cyano azetidine

The enantiomerically pure form of 2-cyano azetidine (2R, 3R)-63 can be obtained in high yields starting from (R)-phenylglycinol (Scheme 25). This synthesis was shown to be general and is based on two important steps. First chlorination of a N-cyanomethylated 1,2-amino alcohol and then a 4-exo-ring closure via the alkylation of a lithiated amino nitrile. The former step is stereoselective, when ephedrine-derived 1,2-amino alcohols are used. In the case of a phenylglycinol derived system, this step also involves rearrangement.
1. 1. 2. 2. 4 Reactions with super acids

The reaction of amino alcohol has been studied in the superacidic media. These compounds have been found to ionize to give the corresponding dication intermediates. Several dicationic species have been directly observed by the low temperature $^{13}$C NMR spectroscopy.\textsuperscript{18} It was observed that amino alcohols undergo electrophilic substitution with benzene in triflic acid to give the corresponding amines (Scheme 26). The chiral a,a-diphenyl-2-pyrrolidinemethanol 16 gives the optically active trityl substituted amines 66 under these conditions (Scheme 26).\textsuperscript{48}
1.1.2.2.5 Synthesis of acynucleosides

Reaction of the 1,2-amino alcohol 67 with cyanogen bromide followed by condensation of the resulting heterocycle 68 with ethyl propiolate or ethyl butyrolate led to pyrimidinones 69 (Scheme 27).

Scheme 27
These pyrimidinones were chemoselectively reduced using metal catalysed hydrogenation and stereoselectively substituted by various nucleophiles to give the new pyrimidine acylnucleosides 70 that are potential antiviral agents (Scheme 27).

1.1.2.6 Synthesis of pyrroles

The valinol 71 reacts with 5-chloro-3-penten-2-one 72 in the presence of triethylamine to give the 2-methylpyrroles derivatives 73 in good yields without racemisation (Scheme 28).

Scheme 28

1.1.2.7 Synthesis of pyrrolidines

Asymmetric syntheses of 2-aryl and 2,5-bis(aryl) pyrrolidines 74 and 75 were described (Scheme 29) using chiral aromatic imines derived from (R)-phenylglycinol, in which the diastereoselective addition of Grignard reagents to the chiral imines and 1,3-oxazolidines are the key steps.
1. 1. 2. 2. 8 Oxazolidines

Oxazolidines derived from 1,2-amino alcohols are good substrates for nucleophilic additions as they act as acetal equivalents. They are very widely used as chiral auxiliaries and chiral catalysts in organic syntheses.\textsuperscript{22-25} For example, the oxazolidine 77 derived from (R)-phenylglycinol is useful for the alkylation reactions (Scheme 30).
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**Synthesis and resolution of 1,2-amino alcohols**

The oxazolidine 80a derived from L-valinol has been found to be a useful catalyst for the enantioselective addition of diethyl zinc to benzaldehyde. A dramatic change in the efficiency of the catalyst was realised when sterically more demanding (S)-α,α-diphenylvalinol 80b derivatives were used.\(^{54}\)

**Scheme 31**
1. 1. 2. 3 1,2-Amino alcohols as chiral ligands

1.1.2.3.1 Enantioselective reduction of ketones with oxazaborolidine catalysts

Asymmetric reductions were generally carried out using stoichiometric amounts of chiral auxiliaries before the oxazaborolidine catalysed borane reduction was discovered. Since then, asymmetric borane reduction of ketones using oxazaborolidine catalyst is one of the most widely used methods to obtain optically active alcohols in high enantiomeric purity. The catalytic behavior of the oxazaborolidine was first discovered when a simple amino alcohol, 2-aminoethanol was added to the borane and ketone. High levels of asymmetric induction were first realized by Itsuno et al in the reduction of acetophenone using (S)-diphenylvalinol in stoichiometric amounts (Scheme 32).

Scheme 32
Later, Corey et al.\textsuperscript{56-59} discovered that the intermediate involved in such asymmetric borane reduction is the corresponding oxazaborolidine. The oxazaborolidine derived from $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol 83 gives better results than the corresponding diphenylvalinol (Scheme 33).

Scheme 33

Several ketones were reduced using this oxazaborolidine system with high levels of asymmetric induction. Many other oxazaborolidine catalysts (84-105) have been prepared and used for the reduction of prochiral ketones (Chart 1)\textsuperscript{60}
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Chart 1
1. 1. 2. 3. 2  C2-Symmetric bis (oxazolines) derived from 1,2-amino alcohols as chiral ligands

The $C_2$-symmetric bis(oxazoline) ligands were prepared by condensing 1,2-amino alcohols and diethyl carboxylates, followed by treatment with $\text{SOCl}_2$ and exposure to base (Scheme 34).$^{83}$

**Scheme 34**

These ligands were applied for many catalytic asymmetric reactions (Chart 2).
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Chart 2

**Diels-Alder reaction**

\[
\text{Cyclopentadiene} + \text{R' conjugated diene} \xrightarrow{\text{Metal-ligand complex 110}} \text{Diene adduct} \xrightarrow{\text{KOH, HCl}} \text{Aldol product}
\]

91% ee, 82%

Ref. 84

**Hetero Diels-Alder reaction**

\[
\text{Cyclohexene} + \text{Acetylacetone (A)} \xrightarrow{\text{Cu(OTf)}_2, 110} \text{Aldol product}
\]

97% ee

Ref. 85

**1,3-Dipolar addition reaction**

\[
\text{Nitrile oxide} + \text{Homoallylamine} \xrightarrow{\text{Metal-ligand complex 110}} \text{Pyran product}
\]

endo 76% ee

Ref. 86

**Cyclopropanation**

\[
\text{Aromatic alkyne} + \text{Nitrene} \xrightarrow{\text{Cu(OTf)}_2, 110} \text{Cyclopropane}
\]

60% ee, 70%

Ref. 87

**Mukaiyama-aldol reaction**

\[
\text{Acetaldehyde} + \text{Chiral oxazaborolidine} \xrightarrow{0.5 \text{ mol% 110}} \text{Chiral aldol product}
\]

97% ee

Ref. 88

**Aziridination reaction**

\[
\text{Azoalkane} \xrightarrow{110, CuOTf} \text{Aziridine} \xrightarrow{\text{HCOOH, Pd(0)}} \text{Amino acid}
\]

94% ee (R= Me)

97% ee (R= Ph)

Ref. 93
In addition to the methods described above, enantiopure amino alcohols have been also prepared via resolution of the corresponding racemic mixtures. The prominent resolving agents for the resolution of amino alcohols are optically active tartaric acid, $O$-acyl tartaric acid, $O$-acyl mandelic acid, camphor-10-sulphonic acid.
and chiral 1,1'-bi-2-naphthyl phosphoric acid. We have undertaken efforts towards the synthesis and resolution of the racemic 1,2-amino alcohols. The results of these studies are described here.
1. 2 Results and Discussion

1. 2. 1 Synthesis and resolution of racemic a,a-diphenyl-2-pyrrolidinemethanol (DPPM):

The (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol 16 (DPPM) is a precursor in the preparation of the important CBS oxazaborolidine catalyst, widely used in catalytic asymmetric reductions (Scheme 33).

It can be readily prepared from (S)-proline through an optimized method developed in this laboratory (Scheme 7). The corresponding R isomer can be prepared from unnatural (R)-proline, but it is expensive.

Scheme 35

Therefore, we have envisaged an alternative synthetic route to access both the enantiomers of DPPM, using racemic pyroglutamic acid by a slight modification of
a reported procedure via NaBH₄/I₂ reduction of the corresponding amide in a crucial step (Scheme 35).

The (±)-DPPM 16 was earlier resolved using chiral (R)-(−)-O-acetylmandelic acid.⁵⁷ We have developed a new method for the resolution of racemic a,a-di-phenyl-2-pyrrolidinemethanol (DPPM) using chiral 1,1′-bi-2-naphthol 114. Previously, efforts were undertaken in this laboratory to resolve racemic diols.¹⁰⁴ For example, the racemic 1,1′-bi-2-naphthol 114 has been readily resolved in large scale via preparation of the corresponding diastereomeric borate complexes using α-methylbenzylamine and boric acid (Scheme 36).¹⁰⁴g

**Scheme 36**
Accordingly, in principle, it should be possible to devise a method for the resolution of amines and amino alcohols through borate complexes of the type 117 or 118 using chiral 1,1'-bi-2-naphthol 114. Hence, we have examined the resolution of racemic α,α-diphenyl-2-pyrrolidinemethanol 16 through preparation of the corresponding diastereomeric borate complexes using chiral 1,1'-bi-2-naphthol 114 and boric acid in CH$_3$CN and CH$_3$OH at 25-67 °C.

The (R)-(+) and (S)-(−)-DPPM 16 were obtained in 42-90% ee under these conditions. For example, when the (R)-(+)1,1'-bi-2-naphthol, boric acid and (±)-DPPM 16 were refluxed in CH$_3$CN for 12 h, the (R)-(+)DPPM 16 was obtained with 90% ee (18% yield) after workup from the precipitate fraction (Scheme 37). The filtrate fraction gave (S)-(−)-DPPM 16 in 20% ee (80% yield) after workup (Table 1, entry 1). The enantiomeric purity of the sample of 90% ee was readily enriched to >99% ee in CH$_3$CN following the same procedure (Table 1, entry 3). The results are summarized in Table 1.
Scheme 37

\[
\begin{array}{c}
\text{Chemistry and resolution of 1,2-amino alcohols} \\
\text{Chapter 1}
\end{array}
\]

Table 1: Resolution of racemic 16 using (R)-(+)-1,1′-bi-2-naphthol and boric acid

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Chiral 16 obtained from</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Precipitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% ee(^a)</td>
</tr>
<tr>
<td>1(^c)</td>
<td>16.00</td>
<td>CH(_3)CN</td>
<td>90 (R)</td>
</tr>
<tr>
<td>2(^d)</td>
<td>16/? 42</td>
<td>CH(_3)CN</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>3(^e)</td>
<td>16 R, 90</td>
<td>CH(_3)CN</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>4(^f)</td>
<td>16.00</td>
<td>CH(_3)OH</td>
<td>60 (R)</td>
</tr>
</tbody>
</table>

- **a.** The ee values reported here are based on reported maximum [\(\alpha\)]\(_D\) = 69.0 (c 3, CHCl\(_3\)) for both (R) and (S) isomer.\(^{19}\)
- **b.** (±) 16 (5 mmol), B(OH)\(_3\) (5 mmol) and (R)-(+)1,1′-bi-2-naphthol (10 mmol) were taken in CH\(_3\)CN (10 ml) and stirred for 12 h under refluxing conditions.
- **c.** 16 R (5 mmol, 42% ee), B(OH)\(_3\) (5 mmol) and (R)-(+)1,1′-bi-2-naphthol (10 mmol) were taken in CH\(_3\)CN (10 ml) and stirred for 12 h under refluxing conditions.
- **d.** 16 R (5 mmol, 90% ee), B(OH)\(_3\) (5 mmol) and (R)-(+)1,1′-bi-2-naphthol (10 mmol) were taken in CH\(_3\)CN (10 ml) and stirred for 12 h under refluxing conditions.
- **e.** (±) 16 (5 mmol), B(OH)\(_3\) (5 mmol) and (R)-(+)1,1′-bi-2-naphthol (10 mmol) were taken in CH\(_3\)OH (15 ml) and stirred for 12 h at 25 °C.
Efforts were also undertaken to examine the nature of the borate complex formed in this resolution method. It has been reported that the resolution of 1,1'-bi-2-naphthol was effected by using boric acid and (S)-proline through the complex of the type $117^{105}$. Hence, the complex of the type $119$ could be expected in the reaction of $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol 16, chiral 1,1'-bi-2-naphthol 114 and boric acid.

![Diagram of complex 119](image)

The IR spectrum of the precipitate complex obtained in the resolution of $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol 16 showed strong absorption at $3350 \text{ cm}^{-1}$, indicating the presence of the free OH group in the complex. The borate complex formed using $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol was also analyzed using the X-ray diffraction method. For obtaining the crystal required for X-ray structure analysis, enanatiomerically pure $(R)$-$(+)$-DPPM 16, boric acid and $(R)$-$(+)$-1,1'-bi-2-naphthol 114 were refluxed in CH$_3$CN for 12 h. The reaction mixture was brought to room temperature and then filtered. The filtrate on standing yielded single crystal
suitable for X-ray analysis. The data reveals that the borate complex is of the type \(120\). The ortep diagram of the borate complex indicates that it crystallizes along with three acetonitrile molecules.

Hence, 1,1'-bi-2-naphthol and boric acid tend to form \(\text{BL}_2\) complexes of the type \(120\) in refluxing acetonitrile in the presence of the \((R)-(+)-\alpha,\alpha\text{-diphenyl-2-pyrrolidinemethanol}\ 16\).
The X-ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-\(K\alpha\) (\(\lambda = 0.71073\) Å) radiation. Intensity data were collected by the \(\Theta\)-scan mode. The data were reduced using XTAL programme. No absorption correction was applied. The structure of the complex 120 was confirmed from the bond angles and bond lengths around the boron atom which showed the existence of boron in tetra coordinated form. The bond angles \(O_1\cdot B_1\cdot O_2 = 112.5^\circ\), \(O_1\cdot B_1\cdot O_3 = 104.6^\circ\), \(O_1\cdot B_1\cdot O_4 = 112.1^\circ\), \(O_2\cdot B_1\cdot O_3 = 114.5^\circ\), \(O_2\cdot B_1\cdot O_4 = 101.5^\circ\) and \(O_3\cdot B_1\cdot O_4 = 112.0^\circ\) showed the existence of boron in tetra coordinated form. The bond distances between \(B_1\) and four oxygen atoms of two chiral 1,1'-bi-2-naphthol units are \(B_1\cdot O_1 = 1.44\) Å, \(B_1\cdot O_2 = 1.46\) Å, \(B_1\cdot O_3 = 1.44\) Å, \(B_1\cdot O_4 = 1.49\) Å, supported "ate" complex nature of boron. The structure was solved by direct methods and refined by full-
matrix least-squares procedure using the SHELX 86 and SHELX 97 programme package respectively. The configuration of the DPPM 16 moiety present in the crystal structure was confirmed to be (R) by using platon 98 programme, A. L. Spak, version 2911.

<table>
<thead>
<tr>
<th>Table 2. Crystal data and structure refinement for compound120.</th>
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<tr>
<td><strong>Identification code</strong></td>
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<tr>
<td><strong>Empirical formula</strong></td>
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<tr>
<td><strong>Formula weight</strong></td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
</tr>
<tr>
<td><strong>Crystal system, space group</strong></td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td><strong>Z, Calculated density</strong></td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
</tr>
<tr>
<td><strong>Reflections collected / unique</strong></td>
</tr>
<tr>
<td><strong>Completeness 2θ = 29.94°</strong></td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
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<tr>
<td><strong>Data / restraints / parameters</strong></td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2σ(I)]</strong></td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Absolute structure parameter</strong></td>
</tr>
<tr>
<td><strong>Extinction coefficient</strong></td>
</tr>
</tbody>
</table>
In this laboratory, systematic investigations were carried out on the use of the chiral 1,1′-bi-2-naphthol for the resolution of several amino alcohols of interest. For example, the \(\text{trans}-(\pm)-2\)-(pyrrolidinyl)cyclohexanol and its methyl ether were resolved using chiral 1,1′-bi-2-naphthol and \(\text{B}(\text{OH})_{3}\) in THF or \(\text{CH}_{3}\text{CN}\) (Scheme 38).

Scheme 38

The \(\text{frw}\)\(.s-(\pm)-2\)-(pyrroldinyl)cyclohexanol and its methyl ether were resolved using chiral 1,1′-bi-2-naphthol and \(\text{B}(\text{OH})_{3}\) in THF or \(\text{CH}_{3}\text{CN}\) (Scheme 39).

Scheme 39
It was also discovered that the diastereomeric mixture of amino alcohols can be readily purified using the optically active 1,1’-bi-2-naphthol and B(OH)$_3$ through preparation of the corresponding diastereomeric complexes as outlined in Scheme 40.$^{107}$

**Scheme 40**

**1.2.2 Synthesis and resolution of 1,2-amino alcohols**

Enantiomerically pure 1,2-amino alcohols are generally prepared via reduction of chiral amino acids and through the methods outlined in the introductory section. Hence, there are only a few methods available for the synthesis of racemic mixture of 1,2-amino alcohols. A general synthetic methodology for the direct synthesis of amino alcohols in high yields is available via the amination of chiral epoxides and the asymmetric hydrogenation or reduction of prochiral β-amino ketones. The former method suffers from the limitation that chiral epoxides are not readily available and are very expensive. Also, mixtures of products are formed when mono-substituted and trans-symmetrically distributed epoxides are used. The
method involving asymmetric reduction of aminoketone requires highly expensive rhodium or ruthenium and BINAP catalysts and specialized high pressure equipment.

Therefore, we have undertaken efforts to develop a general method of synthesis of racemic 1,2-amino alcohols through borane reduction of oximes of the readily accessible α-keto esters. The α-keto esters are obtained by the addition of Grignard reagents to diethyl oxalate (Scheme 41). The corresponding oxime esters were prepared using hydroxylamine following a reported procedure.

Scheme 41
Table 3: Reduction of oxime ester to phenylglycinol using NaBH₄ in presence of additives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>4</td>
<td>67</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>CH₃COOH</td>
<td>48</td>
<td>25</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>ZrCl₄</td>
<td>4</td>
<td>67</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>ZrCl₄</td>
<td>24</td>
<td>25</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>CoCl₂</td>
<td>4</td>
<td>25</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>TiCl₄</td>
<td>4</td>
<td>25</td>
<td>65%</td>
</tr>
<tr>
<td>7</td>
<td>TMS-Cl</td>
<td>4</td>
<td>25</td>
<td>70%</td>
</tr>
<tr>
<td>8</td>
<td>H₂SO₄</td>
<td>4</td>
<td>25</td>
<td>60%</td>
</tr>
</tbody>
</table>

a. NaBH₄ was added to a stirred solution of oxime ester in THF. I₂ in THF was added dropwise for an hour at 0 °C. The contents were refluxed for 4 h.
b. The contents were stirred at 25 °C for 48 h.
c. NaBH₄ was added to a stirred solution of the oxime ester in THF. Then, CH₃COOH in THF was added dropwise for 1 h at 0 °C. The contents were refluxed for 4 h.
d. ZrCl₄ was added slowly to the NaBH₄ in THF and the contents were stirred for 24 h at 25 °C. Then, the oxime ester in THF was added dropwise and the contents were stirred at 25 °C for 12 h.
e. The contents were refluxed for 4 h.
f. NaBH₄ was added in portions to the stirred solution of CoCl₂ in THF. Oxime ester in THF was added dropwise and the contents were refluxed for 4 h.
g. TiCl₄ in DCM was added to stirred slurry of NaBH₄ in THF. The oxime ester was added dropwise and the contents were refluxed for 4 h.
h. TMS-Cl and NaBH₄ in THF were refluxed for 2 h. The oxime ester in THF was added dropwise and the contents were refluxed for 4 h.
i. H₂SO₄ in dry ether was added dropwise to a stirred suspension of NaBH₄ and the oxime ester in THF. Then the contents were refluxed for 4 h.
Chapter 1  Synthesis and resolution of 1,2-amino alcohols

The racemic 1,2-amino alcohols were then prepared by reduction of oximes of \(\alpha\)-keto esters by NaBH\(_4\) activated in the presence of additives. The results obtained are summarised in Table 3.

Scheme 42

![Scheme 42](image)

Comparison of the results (Table 3) indicates that the easy to handle NaBH\(_4\)/I\(_2\) reagent system\(^{109\text{-}110}\) gives better yields. Accordingly, reduction of various oxime esters has been examined with this reagent system. The results are summarised in Scheme 45.

Initially, we tried to resolve the racemic 1,2-amino alcohols by forming diastereomeric borate complexes using chiral 1,1'-bi-2-naphthol and B(OH)\(_3\) in CH\(_3\)CN. However, no precipitate was obtained. Subsequently, we have undertaken an exploratory research work for the resolution of 1,2-amino alcohols through
formation of diastereomeric complexes using readily available, inexpensive chiral resolving agents, such as diethyl tartrate and dibenzoyl-L-tartaric acid.

Scheme 43

It was observed that dibenzoyl-L-tartaric acid formed diastereomeric complexes with 1,2-amino alcohols. We have developed a general method for the resolution of 1,2-amino alcohols using dibenzoyl-L-tartaric acid (Scheme 43). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically.

To standardize the reaction conditions, we have examined the resolution of (±)-phenylglycinol using various solvents like acetone, DCM, acetonitrile, THF and methanol. No precipitation occurred when methanol was used as solvent.
Table 4: Effect of various solvents on the resolution of phenylglycinol $39^a$

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time</th>
<th>Solvent</th>
<th>Chiral 39 obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%ee$^b$</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1$^c$</td>
<td>24 h</td>
<td>Acetone</td>
<td>22(5)</td>
<td>40</td>
<td>20(R)</td>
</tr>
<tr>
<td>2$^c$</td>
<td>12 h</td>
<td>Acetone</td>
<td>30(5)</td>
<td>32</td>
<td>22(R)</td>
</tr>
<tr>
<td>3$^c$</td>
<td>6 h</td>
<td>Acetone</td>
<td>35(5)</td>
<td>30</td>
<td>10(R)</td>
</tr>
<tr>
<td>4$^c$</td>
<td>30 min</td>
<td>Acetone</td>
<td>22(5)</td>
<td>40</td>
<td>15(R)</td>
</tr>
<tr>
<td>5$^d$</td>
<td>6 h</td>
<td>DCM</td>
<td>20(5)</td>
<td>38</td>
<td>9(R)</td>
</tr>
<tr>
<td>6$^e$</td>
<td>6 h</td>
<td>CH$_3$CN</td>
<td>4(5)</td>
<td>60</td>
<td>0(R)</td>
</tr>
<tr>
<td>7$^f$</td>
<td>6 h</td>
<td>THF</td>
<td>30(5)</td>
<td>25</td>
<td>10(R)</td>
</tr>
</tbody>
</table>

a. Unless otherwise mentioned all the reactions were performed using racemic phenylglycinol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in 60 mL of the solvent and stirred at 25 °C.

b. All ee values reported here are based on reported maximum $\alpha_{D}^{25} = 33$ (c 0.75, 1N HCl) for both (S)-39 and (R)-39 isomers.

c. The substrates were taken in acetone (60 mL) and stirred at 25 °C for 6 h.

d. The substrates were taken in DCM (60 mL) and stirred at 25 °C for 6 h.

e. The substrates were taken in CH$_3$CN (60 mL) and stirred at 25 °C.

f. The substrates were taken in THF (60 mL) and stirred at 25 °C.

Other solvents gave moderate results (Table 4). It is evident that better results were obtained when acetone was used as a solvent.

It was observed that increasing the reaction time beyond 6 h led to decrease in ee. So, in most cases reactions were carried out for 6 h. Also, refluxing the mixture for 6 h in acetone gave poor results.
Table 5: Effect of amount of the solvent on the resolution of racemic phenylglycinol 39

<table>
<thead>
<tr>
<th>No.</th>
<th>Volume of acetone (mL)</th>
<th>Chiral 39 obtained from Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%ee&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
<td>5(5)</td>
<td>62</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20</td>
<td>10(5)</td>
<td>50</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>15(5)</td>
<td>48</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>20 (5)</td>
<td>38</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50</td>
<td>25 (5)</td>
<td>31</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60</td>
<td>32(5)</td>
<td>28</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70</td>
<td>45(5)</td>
<td>24</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40</td>
<td>22(5)</td>
<td>40</td>
</tr>
</tbody>
</table>

<sup>a</sup> All the reactions were performed using racemic phenylglycinol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in acetone and stirred at 25 °C for 6 h.
<sup>b</sup> Racemic phenylglycinol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetone (30 mL) and the contents were stirred at 25°C for 6 h.

The effect of amount of the acetone was examined in the resolution of (±)-phenylglycinol, since resolution mainly would depend on the solubility of the complex. As the amount of the solvent increased, the ee of the product increased, but the yield decreased as expected (entries 1-7, Table 5). Also, it was found that
when phenylglycinol dissolved in acetone was added to the solution of dibenzoyl-L-
tartaric acid in acetone, better results were obtained (entries 8-10, Table 5).

To determine the optimum amount of chiral resolving agent required for the resolution process, the effect of concentration of dibenzoyl-L-tartaric acid was studied. During this study, an interesting effect of the amount of the chiral resolving agent used, was observed.

**Scheme 44**

Whereas the phenylglycinol 39 enriched in (S) isomer precipitated when dibenzoyl-L-tartaric acid was used in 1:1 ratio, the 39 enriched in (R) isomer
precipitated out when (±)-39 and the resolving agent were used in 2:1 ratio (Scheme 44).

Efforts were also undertaken to examine the nature of the complex formed in this resolution method. It has been reported in this laboratory that the resolution of C$_2$-symmetric dicarboxylic acid was effected by using (S)-proline through the complex of the type 132. A similar complex 133 could be expected in the resolution of phenylglycinol using dibenzoyl-L-tartaric acid.

We have attempted crystal structure analysis of the complex prepared using 1:1 mixture of S-(+)-phenylglycinol 39 and dibenzoyl-L-tartaric acid 131. The complex was recrystallised from isopropanol to get crystal suitable for X-ray analysis. Although, the X-ray data were not satisfactory (“R” factor = 10), presence of dibenzoyl-L-tartaric acid 131 and S-(+)-phenylglycinol 39 in 2:1 ratio along with a molecule each of water and isopropanol in the unit cell could be readily discerned.

The results indicate that the concentration of chiral resolving agent determines whether the phenylglycinol is enriched in (R)-39 or (S)-39 in the
precipitate fraction (Scheme 44). Accordingly, we have carried out an experiment taking phenylglycinol in acetone and adding dibenzoyl-L-tartaric acid in portions successively to obtain the complex as precipitate. In this way, a sample of 39 enriched in \((R)\) isomer was obtained in 94\% ee and a sample enriched in \((S)\) isomer was obtained in 98\% ee (Scheme 45). The result clearly shows that whereas \((R)\) isomer precipitates when the concentration of phenylglycinol is more, the \((S)\) isomer precipitates when the concentration of dibenzoyl-L-tartaric acid is more.

The effect of sequential addition of racemic phenylglycinol 39 to the chiral resolving agent was also examined. Dibenzoyl-L-tartaric acid was taken in acetone and racemic phenylglycinol was added in portions successively to obtain the complex as precipitate (Scheme 46). In this way, a sample of 39 enriched in \((S)\) isomer was obtained in 45\% ee and the sample enriched in \((R)\) isomer (60\% ee) was finally obtained from the filtrate fraction. Again, the results indicate that the complex containing predominantly \((S)\)-isomer precipitates when the concentration of dibenzoyl-L-tartaric acid is more.
Scheme 45

\[
\text{Ph} \quad (\pm)\, 39 \quad (10 \text{ mmol}) + \quad \text{Dibenzoyl-}L\text{-tartaric acid} \quad 131 \quad (2.5 \text{ mmol})
\]

\[
\text{Acetone (15 mL)} \quad \text{rt, 6 h}
\]

\[
\text{Precipitate} \quad \text{Filtrate}
\]

\[
\begin{align*}
1\text{N KOH} & \quad \text{CH}_2\text{Cl}_2 \\
R\text{-}(\cdot)\text{-}39 & \quad 12\%, \ 94\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{Filtrate} & \quad \text{Precipitate}
\end{align*}
\]

\[
\begin{align*}
1\text{N KOH} & \quad \text{CH}_2\text{Cl}_2 \\
S\text{-}(\cdot)\text{-}39 & \quad 13\%, \ \geq 98\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{Filtrate} & \quad \text{Precipitate}
\end{align*}
\]

\[
\begin{align*}
1\text{N KOH} & \quad \text{CH}_2\text{Cl}_2 \\
S\text{-}(\cdot)\text{-}39 & \quad 10\%, \ 40\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{Filtrate} & \quad \text{Precipitate}
\end{align*}
\]

\[
\begin{align*}
1\text{N KOH} & \quad \text{CH}_2\text{Cl}_2 \\
R\text{-}(\cdot)\text{-}39 & \quad 10\%, \ 30\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{Residue} & \quad 1\text{N KOH} \quad \text{CH}_2\text{Cl}_2 \\
R\text{-}(\cdot)\text{-}39 & \quad 22\%, \ 58\% \text{ ee}
\end{align*}
\]
Scheme 46

\[
\text{Dibenzoyl-L-tartaric acid 131 (10 mmol)} + \text{(±) 39 (2.5 mmol)}
\]

Acetone (15 ml) rt, 6h

Precipitate

\[
\begin{align*}
1\text{N KOH} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

\text{S-}(+)\text{-39} 13\%, 45\% \text{ ee}

Filtrate

\[
\text{39 (2.5 mmol)} \\
\text{rt, 6 h}
\]

Precipitate

\[
\begin{align*}
1\text{N KOH} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

\text{S-}(+)\text{-39} 30\%, 10\% \text{ ee}

Filtrate

\[
\begin{align*}
\text{39 (2.5 mmol)} \\
\text{rt, 6 h}
\end{align*}
\]

Precipitate

\[
\begin{align*}
1\text{N KOH} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

\text{S-}(+)\text{-39} 40\%, 20\% \text{ ee}

Filtrate

\[
\text{residue}
\]

\[
\begin{align*}
1\text{N KOH} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

\text{R-}(+)\text{-39} 30\%, 60\% \text{ ee}

\[
\begin{align*}
1\text{N KOH} \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

\text{S-}(+)\text{-39} 10\%, 46\% \text{ ee}
We have then studied the resolution of other racemic amino alcohols such as (±)-phenylalaninol 49, (±)-valinol 73 and (±)-2-aminobutanol 129. We have also observed an interesting effect of addition of the racemic phenylalaninol to the chiral resolving agent. Whereas, non-racemic samples enriched in (S) and (R) isomers of 10-45% ee were obtained when the (±)-phenylalaninol mixed with dibenzoyl-L-tartaric acid were stirred in acetone for 6 h, when the (±)-phenylalaninol dissolved in 30 mL acetone was added to a stirred solution of dibenzoyl-L-tartaric acid in acetone (30 mL), a sample of (S)-49 was obtained in > 99% ee (Table 6). Presumably, randomization occurs when the amino alcohol and the dibenzoyl-L-tartaric acid were taken in acetone and stirred. When the acetone solution of racemic amino alcohol is added to the resolving agent dissolved in acetone, the initially formed complex may induce the formation of aggregates so as to form the homochiral complexes, leading to better results (see discussion under 1.2.4).
Chapter 1

Synthesis and Resolution of 1,2-Amino Alcohols

Table 6: Effect of Volume of Solvent on the Resolution of (±)-Phenylalaninol 49

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ratio</th>
<th>Acetone (mL)</th>
<th>Chiral 49 obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%eeb</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1a</td>
<td>1:1</td>
<td>40</td>
<td>40(6)</td>
<td>32</td>
<td>18 (R)</td>
</tr>
<tr>
<td>2a</td>
<td>1:1</td>
<td>50</td>
<td>42(6)</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>3a</td>
<td>1:1</td>
<td>60</td>
<td>45(6)</td>
<td>35</td>
<td>20 (R)</td>
</tr>
<tr>
<td>5c</td>
<td>2:1</td>
<td>25</td>
<td>20(6)</td>
<td>20</td>
<td>10 (R)</td>
</tr>
<tr>
<td>4d</td>
<td>1:1</td>
<td>50</td>
<td>&gt;99(5)</td>
<td>20</td>
<td>20 (R)</td>
</tr>
<tr>
<td>6e</td>
<td>2:1</td>
<td>50</td>
<td>&gt;99(6)</td>
<td>15</td>
<td>10 (R)</td>
</tr>
</tbody>
</table>

a. Unless otherwise mentioned all the reactions were performed using racemic phenylalaninol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in 60 mL of acetone and the contents were stirred at 25 °C for 6 h.

b. All ee values reported here are based on reported maximum13-14 [α]D = 23 (c 1.2, 1N HC1) for both (R)-49 and (S)-49 isomer.

c. Racemic phenylalaninol (5 mmol) and dibenzoyl-L-tartaric acid (2.5 mmol) were taken in 60 mL of the acetone and stirred at 25 °C for 6 h.

d. Racemic phenylalaninol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetone (30 mL) and the contents were stirred at 25 °C for 6 h.

e. Racemic phenylalaninol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (2.5 mmol) in acetone (30 mL) and the contents were stirred at 25 °C for 6 h.

It was observed that the racemic valinol was only partially resolved using dibenzoyl-L-tartaric acid (Table 7). Again, an interesting solvent effect was observed. Whereas the (S)-isomer precipitated when acetone was used as a solvent, the (R) isomer precipitated out when acetonitrile was used as a solvent (entry no. 5 and 6, Table 7).
Table 7: Solvent effect on the resolution of (±)-valinol 73

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Acetone (mL)</th>
<th>Chiral 73 obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%ee&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>13 (S)</td>
<td>18</td>
<td>5(7?)</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
<td>18 (S)</td>
<td>20</td>
<td>10 (R)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>23 (S)</td>
<td>20</td>
<td>12(7?)</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60</td>
<td>21(5)</td>
<td>20</td>
<td>10 (R)</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>60</td>
<td>18(5)</td>
<td>22</td>
<td>10 (R)</td>
</tr>
<tr>
<td>6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60</td>
<td>10 (R)</td>
<td>20</td>
<td>2(5)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>40 (R)</td>
<td>15</td>
<td>18(5)</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>25 (R)</td>
<td>12</td>
<td>9(5)</td>
</tr>
<tr>
<td>9&lt;sup&gt;h&lt;/sup&gt;</td>
<td>60</td>
<td>12 (7?)</td>
<td>15</td>
<td>8(5)</td>
</tr>
<tr>
<td>10&lt;sup&gt;i&lt;/sup&gt;</td>
<td>60</td>
<td>5 (R)</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

a. All the reactions were performed using racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in acetone and the contents were stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum absolute rotation<sup>13±14</sup> [\(\alpha\)]<sub>D</sub> = 17 (c 10, C<sub>2</sub>H<sub>5</sub>OH) for both (S)-73 and (R)-73 isomer.
c. Racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (2.5 mmol) were taken in acetone (30 mL) and stirred at 25 °C for 6 h.
d. Racemic valinol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetone (30 mL) and stirred at 25 °C for 6 h.
e. Racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) were taken in acetonitrile (60 mL) and stirred at 25 °C for 6 h.
f. Racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (2.5 mmol) were taken in acetonitrile (60 mL) and stirred at 25 °C for 6 h.
g. Racemic valinol (5 mmol) dissolved in acetonitrile (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetonitrile (30 mL) and stirred at 25 °C for 6 h.
h. Racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (2.5 mmol) were taken in THF (60 mL) and stirred at 25 °C for 6 h.
i. Racemic valinol (5 mmol) and dibenzoyl-L-tartaric acid (2.5 mmol) were taken in DCM (60 mL) and stirred at 25 °C for 6 h.
Table 8: Resolution of (±)-2-aminobutanol 129 using dibenzoyl-L-tartaric acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Condition</th>
<th>Chiral 129 obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%ee&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>rt, 6 h</td>
<td>30 (R)</td>
<td>20</td>
<td>10 (S)</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>rt, 12 h</td>
<td>25 (R)</td>
<td>22</td>
<td>12 (S)</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rt, 6 h</td>
<td>1 (R)</td>
<td>25</td>
<td>20 (S)</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>rt, 12 h</td>
<td>70 (R)</td>
<td>28</td>
<td>10 (S)</td>
</tr>
</tbody>
</table>

a. Unless otherwise mentioned all the reactions were performed using racemic 2-aminobutanol (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in 60 mL of the acetone and the contents were stirred at 25 °C for 6 h.
b. Ee values calculated on the basis of the reported value of [α]<sup>25</sup>°<sub>D</sub> = 12.5 (C 5, C2H5OH) for both (5)-129 and (*)-129 isomer.
c. Racemic 2-aminobutanol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetone (30 mL) and the contents were stirred at 25°C for 6 h.

We have also observed an interesting effect due to mode of addition of the chiral resolving agent during studies on the resolution of 2-aminobutanol. When the components were mixed in 60 ml of acetone and stirred, the non-racemic 2-aminobutanol enriched in (R)-isomer was obtained in 25-30% ee, but when the (±)-2-aminobutanol dissolved in 30 mL acetone was added to the stirred solution of dibenzoyl-L-tartaric acid in acetone (30 mL), the (R)-isomer sample of 71% ee was obtained from the precipitate fraction.
Table 9: Enrichment of enantiomeric excess of the 1,2-amino alcohols using dibenzoyl-L-tartaric acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate %ee</th>
<th>Solvent</th>
<th>Amino alcohols obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(S)-39, 45</td>
<td>Acetone</td>
<td>%ee&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>%ee&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>&gt;98(5)</td>
<td>52</td>
<td>27 (R)</td>
</tr>
<tr>
<td>2</td>
<td>(R)-39, 38</td>
<td>Acetone</td>
<td>94 (R)</td>
<td>53</td>
<td>30(5)</td>
</tr>
<tr>
<td>3</td>
<td>(R) 49 20</td>
<td>Acetone</td>
<td>61 (R)</td>
<td>25</td>
<td>9(5)</td>
</tr>
<tr>
<td>4</td>
<td>(R)-49, 61</td>
<td>Acetone</td>
<td>&gt;97 (R)</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>(R)-73, 25</td>
<td>Acetone</td>
<td>30 (S)</td>
<td>20</td>
<td>14 (R)</td>
</tr>
<tr>
<td>6</td>
<td>(R)-73, 40</td>
<td>CH₃CN</td>
<td><strong>47 (R)</strong></td>
<td>22</td>
<td>10(5)</td>
</tr>
<tr>
<td>7</td>
<td>(R)-129, 71</td>
<td>Acetone</td>
<td>9S(R)</td>
<td>42</td>
<td>20(5)</td>
</tr>
<tr>
<td>8</td>
<td>(S)-129, 20</td>
<td>Acetone</td>
<td>50(5)</td>
<td>25</td>
<td>7 (R)</td>
</tr>
<tr>
<td>9</td>
<td>(S)-129, 50</td>
<td>Acetone</td>
<td>&gt;98(5)</td>
<td>32</td>
<td>4 (R)</td>
</tr>
</tbody>
</table>

a. Unless otherwise mentioned all the reactions were performed using non-racemic aminoalcohols (5 mmol) and dibenzoyl-L-tartaric acid (5 mmol) in 60 mL of the acetone and the contents were stirred at 25 °C for 6 h.

1. 2. 3 Purification of the non-racemic 1,2-amino alcohols using dibenzoyl-L-tartaric acid

The non-racemic (partially resolved or scalemic) 1,2-amino alcohols can be further enriched using dibenzoyl-L-tartaric acid. A sample of > 98%ee was obtained from the precipitate in a single step from non-racemic phenylglycinol 39 (45% ee) enriched in (S)-isomer. The sample enriched in (R)-isomer with 35% ee was further
enriched to obtain the sample of > 97%ee (entry no.4 and 6, Table 8). Similar results were obtained in the case of non-racemic phenylalaninol 49, valinol 73 and 2-aminobutanol 129 as summarized in Table 9.

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

Although the dibenzoyl-L-tartaric acid used in the resolution and enrichment procedures 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 a chiral source again. In 1973, Horeau\textsuperscript{112} reported that the chemical duplication of a non-racemic substrate through formation of two diastereomeric carbonate diesters from a scalemic alcohol. Separation of the alcohol from the homochiral (RR, SS) dimer provided the non-racemic (scalemic, partially resolved) alcohol with increased enantiomeric excess.

Later, this idea was applied by Fleming and Ghosh\textsuperscript{113} to enrich the enantiomeric excess of a scalemic alcohol (R, S) (from 92% ee to 99.6% ee) using oxalylchloride (Scheme 47). Also, Fleming and Ghosh showed that since there is no stereoselection the derivatives are formed in the ratio $X^2:Y^2: 2XY$. 
Scheme 47

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 l,l'-bi-2-naphthol was enriched to obtain samples of 99% ee using inexpensive B(OH)$_3$ and TMEDA.$^{104c}$ 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 lesser amounts, the borate complex derived from the enantiomer present in excess precipitated out (Scheme 48).

Scheme 48

![Scheme 48 Image]

We were interested in adopting a similar method for the precipitation of the non-racemic 1,2-amino alcohols using achiral dicarboxylic acids such as oxalic, maleic, fumaric, phthalic and terephthalic acids through formation of hydrogen bonded aggregates as depicted in Fig 1.
We have carried out a series of experiments to examine this possibility. Good results were obtained when oxalic acid was used in quantities equivalent to the isomer present in excess in the non-racemic mixture. It is clear that the precipitate fraction contains the enriched isomer, leaving behind the isomer with low ee in solution (Scheme 49). The results obtained in the case of non-racemic phenylglycinol 39 and valinol 73 are summarized in Table 10 and Table 11, respectively.
Scheme 49

![Scheme 49](image)

Table 10: Enrichment of enantiomeric excess of non-racemic phenylglycinol using oxalic acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate (39) (5 mmol) % ee</th>
<th>Oxalic acid (mmol)</th>
<th>Phenylglycinol obtained from</th>
<th>Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%ee Yield (%)</td>
<td>%ee Yield(%)^b</td>
</tr>
<tr>
<td>1^a</td>
<td>15 (R)</td>
<td>0.75</td>
<td>30 (R)</td>
<td>11</td>
<td>03 (R) 78</td>
</tr>
<tr>
<td>2^b</td>
<td>30 (R)</td>
<td>1.5</td>
<td>50 (R)</td>
<td>28</td>
<td>06 (R) 60</td>
</tr>
<tr>
<td>3^c</td>
<td>50 (7?)</td>
<td>2.5</td>
<td>70 (R)</td>
<td>48</td>
<td>05 (R) 42</td>
</tr>
<tr>
<td>4^d</td>
<td>70 (R)</td>
<td>3.5</td>
<td>90 (R)</td>
<td>65</td>
<td>09 (R) 25</td>
</tr>
<tr>
<td>5^e</td>
<td>90 (R)</td>
<td>4.5</td>
<td>99 (R)</td>
<td>85</td>
<td>20 (R) 10</td>
</tr>
<tr>
<td>6</td>
<td>20 (S)</td>
<td>1.0</td>
<td>35 (S)</td>
<td>15</td>
<td>06 (S) 75</td>
</tr>
<tr>
<td>7</td>
<td>35 (S)</td>
<td>1.75</td>
<td>32 (S)</td>
<td>30</td>
<td>05 (S) 60</td>
</tr>
<tr>
<td>8</td>
<td>52 (S)</td>
<td>2.6</td>
<td>75 (S)</td>
<td>48</td>
<td>06 (S) 42</td>
</tr>
<tr>
<td>9</td>
<td>75 (S)</td>
<td>3.75</td>
<td>92 (S)</td>
<td>68</td>
<td>10 (S) 22</td>
</tr>
<tr>
<td>10</td>
<td>92 (S)</td>
<td>4.6</td>
<td>99 (S)</td>
<td>87</td>
<td>22 (S) 5</td>
</tr>
</tbody>
</table>

^a. The reaction was performed using non-racemic phenylglycinol (5 mmol) and oxalic acid in 60 mL of the acetone and the contents were stirred at 25 °C for 12 h.
### Table 11: Enrichment of enantiomeric excess of non-racemic valinol using oxalic acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate (73) (5 mmol) % ee</th>
<th>Oxalic acid (mmol)</th>
<th>Valinol obtained from Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% ee&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 (R)</td>
<td>LO</td>
<td>35 (R)</td>
<td>15</td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 (7?)</td>
<td>1.5</td>
<td>50(7?)</td>
<td>32</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 (7?)</td>
<td>2.5</td>
<td>70(7?)</td>
<td>45</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70 (7?)</td>
<td>3.5</td>
<td>87(7?)</td>
<td>64</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87 (R)</td>
<td>4.25</td>
<td>98(7?)</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>15(5)</td>
<td>0.75</td>
<td>35(5)</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>30 (S)</td>
<td>1.5</td>
<td>45(5)</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>45(5)</td>
<td>2.25</td>
<td>60(5)</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>60(5)</td>
<td>3.0</td>
<td>75(5)</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>75(5)</td>
<td>3.75</td>
<td>90(5)</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>90(5)</td>
<td>4.5</td>
<td>98(S)</td>
<td>87</td>
</tr>
</tbody>
</table>

<sup>a</sup> All the reactions were performed using non-racemic valinol (5 mmol) and oxalic acid in 60 mL of the acetone and the contents were stirred at 25 °C for 12 h.

Interestingly, similar experiments on the enrichment of enantiomeric excess of non-racemic phenylalaninol 49 (Table 12) and 2-aminobutanol 129 (Table 13) gave better results.
Table 12. Enrichment of enantiomeric excess of non racemic phenylalaninol using oxalic acid

<table>
<thead>
<tr>
<th>S. No</th>
<th>Substrate (49) (5 mmol) % ee</th>
<th>Oxalic acid (mmol)</th>
<th>Phenylalaninol obtained from</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Precipitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% ee&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>17 (R)</td>
<td>0.85</td>
<td>33 (R)</td>
</tr>
<tr>
<td>2</td>
<td>33 (R)</td>
<td>* 1.75</td>
<td>70 (R)</td>
</tr>
<tr>
<td>3</td>
<td>50(7?)</td>
<td>2.5</td>
<td>98 (R)</td>
</tr>
<tr>
<td>4</td>
<td>20(5)</td>
<td>1.0</td>
<td>35(5)</td>
</tr>
<tr>
<td>5</td>
<td>35 (5)</td>
<td>1.75</td>
<td>75(5)</td>
</tr>
<tr>
<td>6</td>
<td>50(5)</td>
<td>2.5</td>
<td>98(5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All the reactions were performed using non racemic phenylalaninol (5 mmol) and oxalic acid in 60 mL of the acetone and the contents were stirred at 25 °C for 12 h.

The results are in accordance with the predominant formation of homochiral, (R, R, R...) and (S, S, 5, ...) aggregates of oxalic acid-amino alcohol derived from the enantiomer present in excess over the racemic mixture. It may be of interest to note that these results have relevance to non-linear effects (i.e. ligand with lower ee giving higher ee of the products) encountered in asymmetric catalysis in recent years. 14
Table 13: Enrichment of enantiomeric excess of non-racemic 2-aminobutanol using oxalic acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate (129) (5 mmol) % ee</th>
<th>Oxalic acid (mmol)</th>
<th>2-Aminobutanol obtained from Precipitate</th>
<th>Filtrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%ee&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>20 (R)</td>
<td>1.0</td>
<td>35 (R)</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>37 (R)</td>
<td>1.85</td>
<td>50 (7?)</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>55 (R)</td>
<td>2.75</td>
<td>98 (R)</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>18 (S)</td>
<td>0.9</td>
<td>36 (S)</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>36 (S)</td>
<td>1.8</td>
<td>52 (S)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>52 (S)</td>
<td>2.6</td>
<td>98 (S)</td>
<td>60</td>
</tr>
</tbody>
</table>

a. All the reactions were performed using non-racemic 2-aminobutanol (5 mmol) and oxalic acid in 60 ml of the acetone and the contents were stirred at 25 °C for 12 h.

Such non-linear effects are observed due to greater reactivity of homochiral \((R, R\) or \(5, 5\)) complexes over the hetero chiral complexes \(R, 5\) in asymmetric catalysis. In the present case, initial statistical excess of one of the enantiomers, seems to control the formation of the homochiral aggregates. Unfortunately, the complexes formed in this way did not yield crystals suitable for single crystal X-ray analysis and hence the structure of the complexes formed reamins uncertain.

Very recently, it has been observed in this laboratory\textsuperscript{117} that these amino alcohols also form solid complexes with other dicarboxylic acids like maleic acid, fumaric acid, phthalic acid and terephthalic acids. Whereas, good results were
obtained by using fumaric and terephthalic acids, results were poor when maleic and phthalic acids were used. Detailed further studies would throw light on the nature of such complexes.

1.2.5 Determination of enantiomeric purity of 1,2-aminoalcohols

Since the simple 1,2-amino alcohols are generally prepared by reducing the optically active amino acids, only a very few methods were available in the literature to determine the enantiomeric purity of these derivatives. We have first examined the use of chiral shift reagents such as Eu(hfc)$_3$, Eu(fod)$_3$ and Eu(tfc)$_3$, but could not obtain fruitful results.

It was reported$^{115}$ that absolute configuration of certain amino alcohols could be determined by measuring their $^1$H NMR spectra in the presence of optically active 1,1'-bi-2-naphthol in higher magnetic fields. Hence, we have undertaken efforts to determine the enantiomeric excess of 1,2-amino alcohols using 1,1'-bi-2-naphthol by $^1$H NMR (200 MHz) analysis. Unfortunately, these studies did not give fruitful results.

The ($S$)-(+)-binaphthyl-2,2'-diyl phosphoric acid was previously used$^{116}$ for the determination of the optical purity of certain chiral amine derivatives. We have recorded the $^1$H NMR (200 MHz) spectra of (+)-phenylglycinol by adding ($S$)-(+)-binaphthyl-2,2'-diyl phosphoric acid in portions. However, there was no split in the
spectral signals and only line broadening was witnessed in the $^1$H NMR spectrum (200 MHz).

Since the values of ee estimated on the basis of optical rotation measurements could not be confirmed by $^1$H NMR analysis, we carried out HPLC analysis of the 1,2-amino alcohols on chirex (S)-valine column and chiralcell OD column using hexane/2-propanol (95:5) mixture as eluent. Unfortunately, these studies also did not yield fruitful results.

We have then decided to prepare and analyse certain derivatives of these amino alcohols. Recently, the diacetate derivative of 1,2-diphenylethane-1,2-diol was analysed in this laboratory using the chiral shift reagent Eu(fod)$^{118}$ Accordingly, we have prepared the derivatives 135 and 136 following closely related reported procedures.$^{54}$

However, the $^1$H NMR (200 MHz) studies of these derivatives using chiral shift reagents were not fruitful. Also, the chiral HPLC columns accessible to us could not separate these derivatives. Hence, the ee values could not be further
confirmed by the $^1$H NMR and HPLC analysis. Accordingly, we have proceeded with further conceptual studies reported in chapter 2.
1. 3 Conclusions

The (±)-α,α-diphenyl-2-pyrrolidinemethanol was synthesized and resolved using chiral 1,1’-bi-2-naphthol and B(OH)\textsubscript{3}. The NaBH\textsubscript{4}/I\textsubscript{2} reagent system is useful for the reduction of oximes of α-keto esters to obtain the corresponding racemic 1,2-amino alcohols in moderate to good yields. The racemic amino alcohols such as phenylglycinol, phenylalaninol, valinol and 2-aminobutanol are resolved using dibenzoyl-L-tartaric acid to obtain samples of >98% ee. Enrichment of enantiomeric excess of non-racemic amino alcohols using achiral dicarboxylic acids was also studied. The non-racemic amino alcohols obtained in the above resolution studies are further purified to obtain samples of > 98% ee using oxalic acid. In view of the applications of 1,2-amino alcohols in the preparation of the chiral oxazoline catalysts and in the syntheses of biologically active compounds, the methods of synthesis of chiral 1,2-amino alcohols reported here have good synthetic potential.
1. 4 Experimental Section

1.4. 1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Buchi-510 capillary point apparatus. Infrared spectra were recorded on Perkin-Elmer IR spectrophotometer Model 1310 and JASCO FT 5300 spectrophotometer with polystyrene as reference. $^1$H-NMR (200 MHz) and $^{13}$C-NMR (50 MHz) were recorded on Bruker-AC-200 spectrometer with chloroform-d as a solvent and TMS as a reference ($\delta = 0$ Ppm). Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240 C. Analytical thin layer chromatographic tests were earned out on glass plates (3x10 cm) coated with 250 $\mu$m acme's silica gel-G and GF$_{254}$ containing 13% calcium Sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's silica gel (100-200 mesh).

All the glassware were pre-dried at 140 °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 was 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 Buchi-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 ±0.01°) or JASCO DIP-370 Digital polarimeter (readability ±0.001°). The condition of the polarimeter was checked by measuring the optical rotation of a standard solution

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. NaBH₄ was purchased from Lancaster Synthesis Ltd., UK. Iodine supplied by E-Merck, India was used. Chiral 1,1'-bi-2-naphthol (> 99% ee)
supplied by Gerchem Lab (P) Ltd., India was used. The \( N,N \)-diethylaniline:BH\(_3\) was prepared following a procedure reported in this laboratory.

The X-ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonius MACH 3 diffractometer using graphite monochromated, Mo-K\(\alpha\) (\(\lambda = 0.71073\ \text{\AA}\)) 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 \(\omega\) 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.\(^{119}\) No absorption correction was applied. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELXS-86\(^{120}\) and SHELXL-93\(^{121}\) program packages respectively.
1. 4. 2 Synthesis and resolution of α,α-diphenyl-2-pyrrolidinemethanol

1. 4. 2. 1 Synthesis of racemic 2-pyrrolidone-5-carboxylic acid methyl ester

Racemic 2-pyrrolidone-5-carboxylic acid 112 (1.29 g, 10 mmol) was placed in dry methanol (20 mL). Thionyl chloride (1.77 g, 15 mmol) was added slowly during 10 min at 0 °C and stirred for 12 h at 25 °C. The solvent was evaporated under reduced pressure. The crude product was used for the Grignard reaction without further purification.

Yield 1.35 g (95%)
M.p. 120-123 °C
IR (neat) (cm\(^{-1}\)) 1732, 1681

1. 4. 2. 2 Grignard reaction of 2-pyrrolidone-5-carboxylic acid methyl ester

Magnesium turnings (1.92 g, 80 mmol) in dry THF (30 mL) were taken in a two-necked RB flask. Freshly distilled bromobenzene (3.9 g, 40 mmol) in dry THF (15 mL) was added dropwise through the pressure equalizer for 1 h. The contents were further stirred for 1 h.

In another two necked RB flask, 2-pyrrolidone-5-carboxylic acid methyl ester (1.43 g, 10 mmol) in dry THF (20 mL) was taken and cooled to 0 °C, under nitrogen atmosphere. Phenylmagnesium bromide prepared as above was added through a
cannula. The contents were stirred for 12 h at 25 °C. The reaction was quenched with saturated ammonium chloride solution and the supernatant liquid was decanted leaving the white precipitate. The precipitate was washed again with chloroform (2 X 10 mL) and the organic extract was washed with brine and dried over magnesium sulphate. Evaporation of the solvent gave the crude product. It was further purified by column chromatography on silica gel using hexane:ethylacetate (90:10)

Yield 2.0 g (78 %)
M.p. 180-182 °C
IR (neat) (cm⁻¹) 3357, 168

¹H NMR (δ ppm, CDCl₃) 2.0-2.5 (m, 4H), 4.75-4.78 (t, J = 7.1 Hz, 1H), 5.4 (s, 1H), 7.1-7.6 (m, 10H)

¹³C-NMR (δ ppm, CDCl₃) 21.6, 30.1, 60.6, 78.7, 125.6, 125.8, 126.9, 127.4, 128.2, 128.7, 143.3, 145.2, 179.2

1.4.2.3 Reduction of 113 using the NaBH₄/I₂ system

NaBH₄ (0.57 g, 15 mmol) was added to a stirred solution of 113 (1.33 g, 5 mmol) in THF. I₂ (1.9 g, 7.5 mmol) in THF was added through an addition funnel for 1 h at 0 °C. The contents were refluxed for 4 h or stirred at rt for 48 h. The reaction mixture was brought to 25 °C and then quenched with MeOH. The solvent
was removed under reduced pressure and the residue was refluxed with aqueous KOH solution for 3 h. The aqueous layer was extracted with (3 X 20 mL) DCM. The solvent was evaporated and the crude product was distilled to obtain the (±)- \(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol 16.

Yield 1.0 g (80%)
M. p. 77-80 °C, lit\(^{19}\) 80-82 °C
IR (neat) (cm\(^{-1}\)) 3350, 1600.

\(^{1}\)H-NMR (δ ppm, CDCl\(_3\)) 1.25-1.7 (m, 5H), 2.9 (m, 2H), 4.2 (t, \(J = 7.8\) Hz, 1H), 4.8 (s, 1H), 7.1-7.6 (m, 10H) (Spectrum No. 1).

\(^{13}\)C-NMR (5 ppm, CDCl\(_3\)) 25.4, 26.2, 46.7, 64.5, 77.1, 125.6, 126.0, 126.4, 126.5, 128.0, 128.7, 145.6, 148.3 (Spectrum No. 2),

1.4.2.4 Resolution of racemic DPPM 16 using (\(R\))-(+)\,-1,1’-bi-2-naphthol and boric acid

A mixture of (\(R\))-(+)\,-1,1’-bi-2-naphthol(2.86 g, 10 mmol), B(OH)\(_3\) (0.30 g, 5 mmol) and the (±)-\(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol (DPPM) 16 (2.53 g, 10 mmol) was refluxed under nitrogen atmosphere in CH\(_3\)CN (20 mL) for 12 h. The reaction mixture was filtered while hot and washed with acetonitrile. The precipitate was suspended in a mixture of ether (50 mL) and dil. HCl (5N, 25 mL)
and stirred until complete dissolution occurs. The \((R)-(+)\)-1,1′-bi-2-naphthol (92%) was recovered from the ether layer. The aqueous layer was treated with aqueous NaOH (1N, 20 ml)/ether (50 ml) and the free amino alcohol was extracted with ether (2 \times 25 \, \text{mL}). The combined organic extract was washed with brine (10 ml) and dried over anhydrous MgSO₄. The solvent was evaporated to obtain \((R)-(+)\)-\(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol (90% ee). The filtrate was concentrated and the residue was digested in a mixture of ether (50 mL) and dil. HCl (5N, 25 mL). After work up as outlined above, the amino alcohol (20% ee) was isolated.

**After decomposition:**

**From precipitate:**

Yield \(0.22 \, \text{g} \) (18%)

\([\alpha]_D^{25} \) (+) 62.1 \((c \, 3, \text{CHCl}_3)\), \{lit\} for 100% ee, \([\alpha]_D^{25} = (+) \, 69.0 \,(c \, 3, \text{CHCl}_3)\}\)

**From filtrate:**

Yield \(1.0 \, \text{g} \) (80%)

\([\alpha]_D^{25} \) (-) 13.5 \((c \, 3, \text{CHCl}_3)\), \{lit\} for 100% ee, \([\alpha]_D^{25} = (-) \, 69.0 \,(c \, 3, \text{CHCl}_3)\}\)
1.4.2.5 Enrichment of enantiomeric excess of partially resolved racemic DPPM 16 using \((R)-(+)\)-1,1’-bi-2-naphthol and boric acid

A mixture of \((R)-(+)\)-1,1’-bi-2-naphthol (2.86 g, 10 mmol), \(\text{B(OH)}_3\) (0.30 g, 5 mmol) and the partially enriched \(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol (90% ee, 10 mmol) was refluxed under nitrogen atmosphere in \(\text{CH}_3\text{CN}\) (20 mL) for 12 h. The reaction mixture was filtered while hot and washed with acetonitrile. The precipitate was suspended in a mixture of ether (50 mL) and dil. \(\text{HCl}\) (5 N, 25 mL) and stirred until complete dissolution occurs. The \((R)-(+)\)-1,1’-bi-2-naphthol (92% y) was recovered from the ether layer. The aqueous layer was treated with \(\text{NaOH/ether}\) and the free amino alcohol was extracted with ether (2 x 25 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous \(\text{MgSO}_4\). The solvent was evaporated to obtain \((R)-(+)\)-\(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol (>99% ee). The filtrate obtained was concentrated and the residue was digested in the mixture of ether (50 mL) and dil. \(\text{HCl}\) (5 N, 25 mL). After work up as outlined above, the amino alcohol (25% ee) was isolated.
After decomposition:

From precipitate:

Yield 1.20 g (48%)

\[\alpha\] \_D \quad (+) 69 (c 3, CHCl\textsubscript{3})

From filtrate:

Yield 1.0 g (42%)

\[\alpha\] \_D \quad (-) 16.9 (c 3, CHCl\textsubscript{3})

1. 4. 3 Synthesis and resolution of 1,2-amino alcohols

1. 4. 3. 1 Synthesis of \(a\)-keto esters from diethyl oxalate

Typical procedure: Magnesium turnings (2.42 g, 100 mmol) in dry THF (60 mL) were taken in a two-necked RB flask. Freshly distilled bromobenzene (10.53 g, 100 mmol) in dry THF (30 mL) was added drop wise through the pressure equalizer for 1 h. The contents were further stirred for 1 h.

In another two necked RB flask diethyl oxalate (42.8 g, 300 mmol) in dry THF (50 mL) was taken and cooled to -10 °C, under nitrogen atmosphere. Phenyl magnesium bromide prepared as above was transferred into a pressure equalizer through a cannula by flushing the nitrogen and added to the diethyl oxalate drop wise at -10 °C for 30 min. The contents were stirred for an additional 30 min. The reaction was quenched with dil. HCl solution and the supernatant liquid was
decanted leaving the white precipitate. The precipitate was washed again with ether (2 X 50 mL) and the organic extract was washed with brine and dried over magnesium sulphate. Evaporation of the solvent gave crude product, which was further purified by vacuum distillation.

Yield 7.12 g (40%)

B.p. 135-138 °C/18 mm; lit.\(^1\) 138-139 °C/18 mm

IR (neat) (cm\(^{-1}\)) 1740, 1695, 1600.

\(^1\)H NMR (5 ppm, CDCl\(_3\)) 1.4 (t, J = 8.33 Hz, 3H), 4.5 (q, J = 8.33 Hz, 2H), 7.4-8.0 (m, 5H)

\(^13\)C-NMR (5 ppm, CDCl\(_3\)) 14.0, 62.2, 128.8, 129.9, 132.5, 134.8, 163.8, 186.4

The other α-ketoesters 125, 126, 127 and 128 were also prepared by following the same procedure.

1. 4. 3. 2 Preparation of phenyl oxime ester 137 from ethyl phenylglyoxylate

Ethyl phenylglyoxalate (1.78 g, 10 mmol), hydroxylamine hydrochloride (1.4 g, 20 mmol) and sodium acetate (1.6 g, 20 mmol) were taken in ethanol (50 ml) and the contents were refluxed for 24 h. The solvent was evaporated and the residue was dissolved in ether (50 mL), washed with water and brine solution. The combined
ether extract were dried over magnesium sulphate. Evaporation of the solvent gave the oxime of ethyl phenylglyoxylate.

\[
\text{Yield} \quad 1.73 \text{ g (90\%)} \\
\text{M. p.} \quad 130 ^\circ \text{C} \\
\text{IR (neat)} \quad (\text{cm}^{-1}) 3307, 1724, 1602 \\
^{13}\text{C-NMR} \quad (5 \text{ ppm, CDCl}_3) 14.2, 59.9, 125.2, 127.1, 129.4, 129.5, 153.6, 162.3
\]

1.4.3 Reduction of oxime of ethyl phenylglyoxylate to (±)-phenylglycinol 39

\[
\text{NaBH}_4 (0.57 \text{ g, 15 mmol}) \text{ was added to a stirred solution of the oxime of ethyl phenylglyoxylate (0.97 g, 5 mmol) in THF. I}_2 (1.9 \text{ g, 7.5 mmol}) \text{ in THF was added through an addition funnel for 1 h at 0 \text{ oC. The contents were refluxed for 4 h or stirred at rt for 48 h. The reaction mixture was brought to 25 \text{ oC and then quenched with MeOH. The solvent was removed under reduced pressure. The residue was refluxed with KOH solution for 3 h. The aqueous layer was extracted with (3 X 20 mL) DCM. The solvent was evaporated and the crude product was distilled to obtain the racemic phenylglycinol 39.}
\]
Yield 0.6g (85 %)

M.p. 72-75 °C: lit. 75-78°C

IR (neat) (cm$^{-1}$) 3362, 1048

$^1$H-NMR (5 ppm, CDCl$_3$) 2.0(s, 3H), 3.5 (dd, J= 12Hz, 1H), 3.6(dd, J=8Hz, 1H), 4.0(dd, J=8Hz, 1H), 7.3(m, 5H) (Spectrum No. 3).

$^{13}$C-NMR (5 ppm, CDCl$_3$) 57.4, 67.8, 126.5, 127.1, 129.0, 142.4 (Spectrum No. 4).

The other 1,2-amino alcohols 49, 73, 129, 130 were also prepared by the same procedure by reducing the corresponding oximes of α-keto esters. The data are given below.
1. 4. 3. 4 Reduction of oxime of ethyl benzylglyoxylate to \((\pm)\)-phenylalaninol 49

\[
\begin{align*}
\text{Yield} & \quad 0.6 \text{g (80 \%)} \\
\text{M. p.} & \quad 92-94 \, ^\circ\text{C}; \text{lit.}\, 93-95\, ^\circ\text{C} \\
\text{IR (neat)} & \quad (\text{cm}^{-1}) \, 3350, 1053. \\
\text{\textsuperscript{1}H-NMR} & \quad (5 \, \text{ppm, CDCl}_3) \, 1.8 \, \text{(s, 3H)}, \, 2.5 \, \text{(dd, J=8Hz, 1H)}, \, 2.7 \, \text{(dd, J=5.6Hz, 1H)}, \, 3.1 \, \text{(m, 1H)}, \, 3.3 \, \text{(dd, J=6.6Hz, 1H)}, \, 3.62 \, \text{(dd, J=3.8Hz, 1H)}, \, 7.2 \, \text{(m, 5H)} \, (\text{Spectrum No. 5}). \\
\text{\textsuperscript{13}C-NMR} & \quad (5 \, \text{ppm, CDCl}_3) \, 40.6, \, 54.2, \, 66.0, \, 126.4, \, 128.5, \, 129.2, \, 138.6 \, \text{(Spectrum No. 6)}. 
\end{align*}
\]

1. 4. 3. 5 Reduction of oxime of ethyl isopropylglyoxylate to \((\pm)\)-valinol 73

\[
\begin{align*}
\text{Yield} & \quad 0.36 \, \text{g (70 \%)} 
\end{align*}
\]
B. p. 77 °C/8 mm; lit. 75-77 °C/8 mm

[R (neat)  (cm^{-1}). 3350, 1051

$^1$H-NMR (5 ppm, CDCl$_3$). 0.8 (d, J= 6.8Hz, 3H), 0.9 (d, J= 6.8Hz, 3H), 1.4-1.6 (m,lH), 1.7-2.1(b s, 3H), 2.4-2.6 (m,lH), 3.29 (dist. t, J=10Hz, 1H), 3.6(dd J=4Hz, 1H) (Spectrum No. 7).

$^{13}$C-NMR (5 ppm, CDCl$_3$) 18.3, 19.2, 31.2, 58.4, 64.6 (Spectrum No. 8).

1.4.3.6 Reduction of oxime of ethyl ethylglyoxylate to (±)-2-aminobutanol 129

\[
\begin{array}{c}
\text{NOH}
\end{array}
\begin{array}{c}
\text{NH}_2
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{C-CONH}_2
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{CH-CH}_2\text{OH}
\end{array}
\]

Yield 0.26g (60 %)

B.p. 176 °C; lit.$^{14}$ 176-178°C

IR (neat)  (cm$^{-1}$). 3350, 1050

$^1$H-NMR (6 ppm, CDCl$_3$) 0.9 (t, J=7.8Hz, 3H), 1.4 (m, 2H), 2.7 (m, 1H), 3.2 (dd, J=7.8Hz, 1H), 3.5 (dd, J=3.92Hz, 1H) (Spectrum No. 9).


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

\[ ^{13} \text{C-NMR} \quad (5 \text{ ppm, CDCl}_3) \ 10.4, 26.5, 54.3, 65.8 \text{ (Spectrum No. 10).} \]

1. 4. 3. 7 Reduction of oxime of ethyl methylglyoxylate to (±)-alaninol 130

![Diagram of reduction process]

Yield \quad 0.22 \text{ g (60\%)}

B.p. \quad 165-167^\circ \text{C; Lit.}^{14} 167-180^\circ \text{C}

IR (neat) \quad (\text{cm}^{-1}) 3352, 1051.

\[ ^{13} \text{C-NMR} \quad (5 \text{ ppm, CDCl}_3) \ 17.2, 45.5, 65.6 \text{ (Spectrum No. 11).} \]

1. 4. 3. 8 Resolution of (±)-phenylglycinol 39 using dibenzoyl-L-tartaric acid

The dibenzoyl-L-tartaric acid (1.8 g, 5 mmol) and the (±)-phenylglycinol 39 (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 and 1N KOH and stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain phenylglycinol enriched in (S) isomer. The filtrate was concentrated and the residue was digested as outlined above to obtain the product enriched in (R) isomer.
After decomposition:

From precipitate:

Yield 0.178 g (24 %)\(^d\)

\([\alpha]_{D}^{25}\) (+) 14.8 (\(c 1, 1\text{N HCl})\), \(\{\text{lit}\,^{13}\,\text{for 100\% ee,}\}\)

\([\alpha]_n^{25} = (+) 33.0 (c 0.75, 1\text{N HCl})\)

From filtrate:

Yield 0.42 g (60 %)

(-) 12.0 (\(c 1, 1\text{N HCl})\) \(\{}\text{lit}\,^{13}\,\text{for 100\% ee,}\\)

\([\alpha]_n^{25} = (-)33 (c 0.75, 1\text{N HCl})\)\}

1. 4. 3. 9 Purification of partially resolved phenylglycinol 39 using dibenzoyl-\(L\)-tartaric acid

The partially resolved \((S)-(+)\)-phenylglycinol 39 (45\% ee, 5 mmol) and the dibenzoyl-\(L\)-tartaric acid (1.8 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 and 1\text{N KOH} and stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain \((S)-(+)\)-phenylglycinol (> 98\% ee). The filtrate was
concentrated and the residue was digested as outlined above to obtain the product enriched in \((R)-(-)\)-phenylglycinol (25% ee).

**After decomposition:**

From precipitate:

Yield 0.36 g (52 %)

\([\alpha]_D^2\) (+) 32.3 (c 1, 1N HCl)

From filtrate:

Yield 0.26 g (38 %)

\([\alpha]_D^{25}\) (-) 8.6 (c 1, 1N HCl)

The partially resolved phenylglycinol 39 enriched in \((R)\) isomer (25% ee, 5 mmol) was also further enriched by following the same procedure as outlined above.

**After decomposition:**

From precipitate:

Yield 0.37 g (53 %)

\([\alpha]_D^*\) (-) 29.8 (c 1, 1N HCl)

From filtrate:

Yield 0.23 g (34 %)

\([\alpha]_D^{25}\) (+) 10 (c 1, 1N HCl).
1.4.3.10 Resolution of (±)-valinol 73 using dibenzoyl-L-tartaric acid

The same procedure as mentioned above was followed for the resolution of (±)-valinol 73 (5 mmol).

**After decomposition:**

**From precipitate:**

Yield 0.10 g (20%)

\[ r^{25} \]

(+) 4.25 (c 5, C\textsubscript{2}H\textsubscript{5}OH), \{lit\textsuperscript{13} for 100% ee, \[\alpha\]\textsubscript{n}\textsuperscript{25} = (+) 17.0 (c 10, C\textsubscript{2}H\textsubscript{5}OH)\} 

**From filtrate:**

Yield 0.35 g (70 %)

\[ [\alpha]_{D}^{25} \]

(-) 1.6 (c 5, C\textsubscript{2}H\textsubscript{5}OH) \{lit\textsuperscript{13} for 100% ee, \[\alpha\]\textsubscript{D}\textsuperscript{25} = (-) 17.0 (c 10, C\textsubscript{2}H\textsubscript{5}OH)\}

1.4.3.11 Resolution of (±)-phenylalaninol 49 using dibenzoyl-L-tartaric acid

The dibenzoyl-L-tartaric acid (1.8g, 5mmol) was taken in acetone (30 ml) and stirred for 5 min. To this stirred solution the (±)-phenylalaninol 49 (0.75g, 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 and 1N KOH and
stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain the phenylalaninol enriched in (S) isomer. The filtrate was concentrated and the residue was digested as outlined above to obtain the phenylalaninol enriched in (R) isomer.

**After decomposition:**

**From precipitate:**

<table>
<thead>
<tr>
<th>Yield</th>
<th>0.15 g (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ $^{25}$</td>
<td>(-) 22.5 (c 1, 1N HCl) {lit$^\text{13}$ for 100% ee, $[\alpha]_D^{25} = (-) 23.0$ (c 1.2, 1N HCl)}</td>
</tr>
</tbody>
</table>

**From filtrate:**

<table>
<thead>
<tr>
<th>Yield</th>
<th>1.0 g (60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$ $^{25}$</td>
<td>(+) 4.6 (c 1, 1N HCl) {lit$^\text{13}$ for 100% ee, $[\alpha]_D^{25} = (+) 23.0$ (c 1.2, 1N HCl)}</td>
</tr>
</tbody>
</table>

1. 4. 3. 12 Purification of partially resolved phenylalaninol 49 using dibenzoyl-L-tartaric acid

The partially resolved (R)-(+) phenylalaninol 49 (20% ee, 5 mmol) dissolved in acetone (30 ml) was added to the stirred solution of dibenzoyl-L-tartaric acid (1.8 g, 5 mmol) in acetone (30 mL) and the contents were stirred at rt for 6 h and
filtered. The precipitate was suspended in a mixture of DCM and 1N KOH and stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain the phenylalaninol enriched in (R) isomer. The filtrate was concentrated and the residue was digested as outlined above to obtain the product, which was found to be racemic.

**After decomposition:**

**From precipitate:**

Yield 0.39 g (52%)

\[ [\alpha]_D^{25} = (+) 21.6 \text{ (c 1, 1N HCl)} \] (lit\textsuperscript{13} for 100% ee, \[ [\alpha]_D^{25} = (+) 23.0 \text{ (c 1.2, 1N HCl)} \])

**From filtrate:**

Yield 0.26 g (35 %)

The phenylalaninol 49 sample obtained from the filtrate was found to be racemic.

1. 4. 3. 13 Resolution of (±)-2-aminobutanol 129 using dibenzoyl-L-tartaric acid

The procedure outlined as above was followed for the resolution and enrichment of the (±)-2-aminobutanol 129 (5 mmol).
After decomposition:

From precipitate:

Yield 0.11 g (25%)

\([\alpha]_{D}^{c} = (-) 9.0 \text{ (c 2, C}_2\text{H}_5\text{OH)}, \text{ [lit}^{15} \text{ for 100% ee, }}\]

\([\alpha]_{D}^{25} = (-) 12.5 \text{ (c 2, C}_2\text{H}_5\text{OH})\}

From filtrate:

Yield 0.29 g (70%)

\([\alpha]_{D}^{c} = (+) 2.5 \text{ (c 2, C}_2\text{H}_5\text{OH)}, \text{ [lit}^{15} \text{ for 100% ee, }}\]

\([\alpha]_{D}^{25} = (+) 12.5 \text{ (c 2, C}_2\text{H}_5\text{OH})\}

The partially resolved 2-aminobutanol 129 enriched in \((R)\) isomer (71% ee, 5 mmol) was also further purified by following the same procedure as outlined above.

After decomposition:

From precipitate:

Yield 0.18 g (42%)

\((-) 8.3 \text{ (c 5, C}_2\text{H}_5\text{OH).}\}

From filtrate:

Yield 0.21 g(48%)

\([\alpha]_{D}^{25} = (+) 2.5 \text{ (c 5, C}_2\text{H}_5\text{OH).}\}
1. 4. 3. 14 Purification of scalemic (non-racemic or partially resolved) phenylglycinol 39 using oxalic acid

**Typical procedure:** The partially resolved (R)-(−)-phenylglycinol 39 (90% ee, 5 mmol) was taken in acetone (60 mL). Oxalic acid (0.45 g, 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 and 1N KOH and stirred until the dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain the phenylglycinol 39 enriched in (R) isomer. The filtrate was concentrated and the residue was digested as outlined above to obtain the product enriched in (S) isomer.

**After decomposition:**

**From precipitate:**

Yield: 0.59 g (85 %)

\( [\alpha]_{D}^{25} \) (-) 31.3 (c 1, 1N HCl)

**From filtrate:**

Yield: 0.07 g (10%)

\( [\alpha]_{n}^{25} \) (+) 3.3 (c 0.75, 1N HCl)
1.4. 3.15 Purification of scalemic phenylalaninol 49 using oxalic acid

The same procedure as outlined above for the enrichment of non-racemic phenylglycinol 39 using oxalic acid was followed for the enrichment of non-racemic \((R)-(+)\)-phenylalaninol 49 (92% ee, 5 mmol).

After decomposition:

From precipitate:

Yield 0.60 g (87%)

\([\alpha]_{D}^{25}\) (+) 32.6 (c 0.75, 1N HCl)

From filtrate:

Yield 0.03 g (5%)

\([\gamma]_{D}^{25}\) (-) 6.8 (c 0.75, 1N HCl)

1.4. 3.16 Purification of scalemic valinol 73 using oxalic acid

The same procedure as mentioned above for the enrichment of phenylglycinol 39 using oxalic acid was followed for the enrichment of enantiomeric excess of non-racemic \((S)-(+)\)-valinol 73 (87% ee, 5 mmol).
After decomposition:

From precipitate:

Yield 0.40 g (80 %)

\([\alpha]_{D}^{25}\) (+) 16.6 (c 5, C\(_2\)H\(_5\)OH)

From filtrate:

Yield 1.0 g (60%)

\([\alpha]_{D}^{25}\) (-) 2.4 (c 5, C\(_2\)H\(_5\)OH)

1.4. 3. 17 Purification of scalemic 2-aminobutanol 129 using oxalic acid

The procedure as outlined above for the enrichment of phenylglycinol 39 using oxalic acid was followed for the enrichment of non-racemic \((S)\)-(+) 2-aminobutanol 129 (55% ee, 5 mmol).

After decomposition:

From precipitate:

Yield 0.28 g (62%)

\([\alpha]_{D}^{25}\) (+) 12.2 (c 2, C\(_2\)H\(_5\)OH)

From filtrate:

Yield 0.13 g (30%)

\([\alpha]_{D}^{25}\) (-) 1.5 (c 2, C\(_2\)H\(_5\)OH)
1. **5 References**


118. N. Sampathkumar and M. Periasamy, unpublished results.
