Synthesis, Resolution and Applications of 1,2 - Amino Alcohols

A Thesis

Submitted for the Degree of

DOC FOR OF PHILOSOPHY

By

SANGARAPPAN SIVAKUMAR

SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD 500 046
INDIA

September 2002

To

My Parents

Contents

Chapter 2

Asymmetric auto-inductive reduction of oxime derivatives of ethyl phenylglyoxylate using (R)-phenylglycinol

Chapter 3

Studies on the asymmetric Michael addition reaction

School of Chemistry
University of Hyderabad
Central University P. O.,
Hyderabad 500 046
India

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.

18/9/2002

S. SIVAKUMAR

School of Chemistry
University of Hyderabad
Central University P. O.,
Hyderabad 500 046
India

Certificate

Certified that the work embodied in this thesis entitled **'Synthesis, Resolution and Applications of 1,2-Amino Alcohols'** has been carried out by Mr. S. Sivakumar, under my supervision and the same has not been submitted elsewhere for a Degree.

M. Periasamy
18/9/2002

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

Dean
School of Chemistry

Acknowledgements

1 wish to express my deep sense of gratitude and indebtedness with profound respect to my mentor **Prof. M. Periasamy** for the keen interest, constant encouragement, helpful criticism, efficient guidance and untiring efforts throughout my tenure here. 1 shall always be indebted to him for this.

I extend my heartfelt thanks to Prof. P. S. Zacharias, Prof. M. Nagarajan and Prof. G. R. Desiraju, Deans, School of Chemistry, for providing all the facilities and encouragement to carry out my work. Further, I thank Prof. D. Basavaiah for his generous help in many ways. I would like to place on record my appreciation and gratitude to the faculty members of the School of Chemistry for helpful discussions and encouragement from time to time.

I would like to thank my colleague Mr. M. Narsireddy, for his timely help in carrying out some of the experiments. I am enormously thankful to my past and present labmates, Dr. P. Bharathi, Dr. L.V. Raman, Dr. C.R. Ramanathan, Dr. C. Ramesh Kumar, Dr. T. Rajesh, Mr. V. Dhanna Rao, Mr. G. Srinivas, Mr. N. Sampath Kumar, Mr. K.N. Jayakumar, Mr. G. V. Karunakar, Mr. A. Mukkanti, Mr. M. Seenivasaperumal, Mr. S. Suresh, Miss. M. Padmaja, Mr. Kishore Babu Neela, Mr. D. Shyam Raj and Mr. P. Vairaprakash for creating a pleasant work atmosphere.

I am equally thankful to all the research scholars of the school of chemistry for their needful help. I also thank all my friends from this campus who made my stay here a memorable one.

I thank Mr. Raghavaiah for his help in collecting the X-ray crystallographic data. All the non-teaching staff of the School have been extremely helpful, I thank them all. Mr. S. Satyanarayana, Mr. V. Bhaskar Rao, Mrs. Vijaya Lakshmi, Mr. K. R. B. V. Prasad, Mr. Sherry, Mr. Vijay, Mr. Vijaya Bhaskar, Mr. Ramana, Mr. Joseph, Mr. Santosh, Mr. Rangaiah, and Mrs. Asia Parwez are a few to mention.

I take this opportunity to gratefully acknowledge the flawless love, moral support and constant encouragement provided by my parents, my brothers and my sisters.

I also wish to extend my sincere thanks to the University authorities for providing all the necessary facilities for this work.

Finally, 1 would like to thank the CSIR for the financial support provided during my tenure.

Above all, I venerate the Lord to whom I cannot express my thankfulness in mere words, without His grace. I would not have reached to this extent despite others interest, encouragement, support and help.

Sangarappan Sivakumar

ABBREVIATIONS

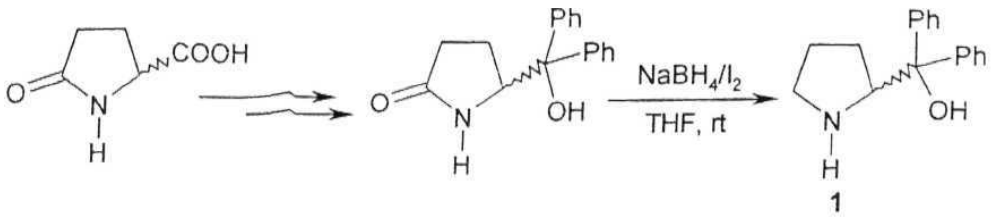
Ac	acetyl
aq.	Aqueous
Ar	aryl
Bu	butyl
Bn	benzyl
B.p.	boiling point
DCM	dichloromethane
DPPM	α,α-diphenyl-2-pyrrolidinemethanol
Et	ethyl
EtOAc	ethyl acetate
Eq.	equation
ee	enantiomeric excess
equiv.	equivalent
i	iso
i-Pr	isopropyl
liq.	Liquid
Me	methyl
M.P.	melting point
M	metal
n-	primary
OTf	triflouroacetate
Ph	phenyl
rt	room temperature
THF	tetrahydrofuran
TMS-C1	tetramethylsilyl chloride

ABSTRACT

This thesis describes studies on the **"Synthesis, Resolution and Applications of 1,2-Amino Alcohols".** It comprises of three chapters. Each chapter is subdivided into four parts namely, **Introduction. Results and Discussion, Conclusion** and **Experimental Section** along with **References.** The work described in this thesis is exploratory in nature.

The first chapter describes the synthesis and resolution of racemic a,oc-diphenyl-2-pyrrolidinemethanol and 1,2-amino alcohols such as phenylglycinol, phenylalaninol, valinol and 2-aminobutanol. A modified synthetic route was developed to access both enantiomers of the α,α-diphenyl-2-pyrrolidinemethanol, using racemic pyroglutamic acid via $NaBH_4/I_2$ reduction of the corresponding amide in a crucial step (Scheme 1).

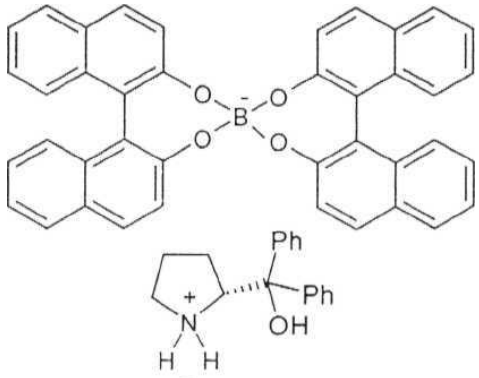
Scheme 1



1

The racemic α.α-diphenyl-2-pyrrolidinemethanol was easily resolved through preparation of the corresponding diastereomeric borate complexes using chiral 1,1'-bi-2-naphthol and boric acid to get samples of > 99% ee.

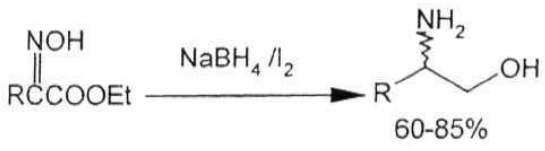
The nature of the diastereomeric complex formed in this method was elucidated using single crystal X-ray structure analysis. It was found to be the ammonium borate complex 2.



2

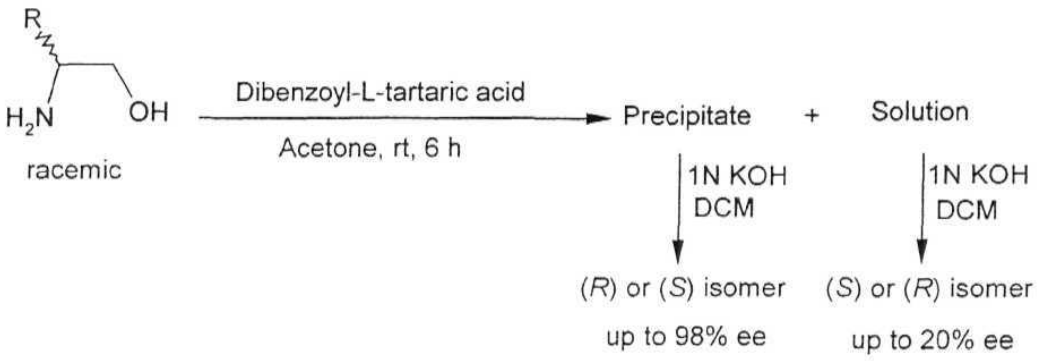
Efforts were undertaken to develop a general method of synthesis of racemic 1,2-amino alcohols through borane reduction of oximes of the readily accessible α-keto esters (Scheme 2).

Scheme 2



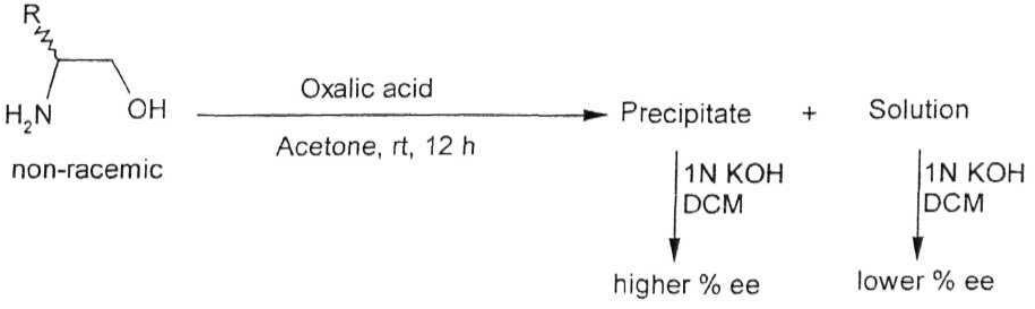
A general method for the resolution of the racemic 1,2-amino alcohols using dibenzoyl-*L*-tartaric acid was then developed (Scheme 3). These diastereomeric complexes prepared in this way are solid derivatives and are readily cleaved hydrolytically after resolution to obtain the amino alcohols.

Scheme 3



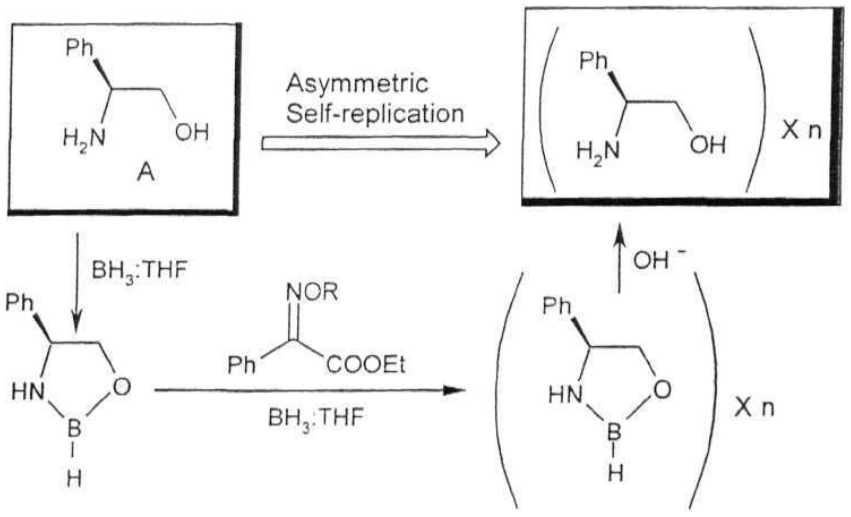
A conceptually novel method of purification of partially resolved non-racemic 1,2-amino alcohols was developed using achiral dicarboxylic acids through formation of diastereomeric aggregates (Scheme 4).

Scheme 4



In chapter 2, results of the studies undertaken to examine the replication of chirality in the asymmetric borane reduction of oxime ether of ethyl phenylglyoxylate using the autocatalyst (R)-phenylglycinol are described. When the benzyl derivative of oxime ether of ethyl phenylglyoxylate was reduced in the presence of (*R*)-(-)-phenylglycinol. the product was obtained in 78% yield with 82% ee (Scheme 5). This indicates that the newly formed product corresponds to duplication of chirality with modest enantioselectivity.

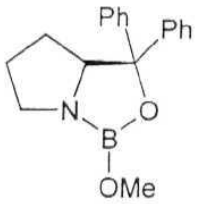
Scheme 5



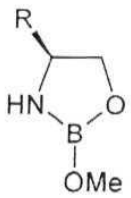
In chapter 3, results of the studies on the development of catalytic asymmetric Michael reaction using chiral ammonium borate complex, chiral amino alcohol derived oxazaborolidines and chiral amino alcohol derived lithium alkoxide

are described. Catalytic asymmetric Michael reaction of various malonate derivatives with different Michael acceptors using chiral ammonium borate complex 2 prepared using chiral l,l'-bi-2-naphthol, $B(OH)_3$, (*S*)-α,α-diphenyl-2-pyrrolidinemethanol was investigated.

Asymmetric Michael reaction using chiral oxazaborolidine 3 prepared from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol and $B(OMe)_3$ was also examined. The chiral oxazaborolidine complex catalyses the Michael reaction of diethyl malonate to cyclohexenone in the presence of $KOBu^t$, to give the corresponding adducts in < 62% ee.



3



4

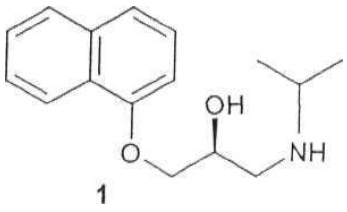
Studies on the Michael reaction using various oxazaborolidines 4 derived from amino alcohols like phenylglycinol, phenylalaninol, valinol and 2-aminobutanol are also examined. The results are discussed considering the coordination of the Michael donor with the oxazaborolidine prior to addition to the acceptors.

Chapter 1

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

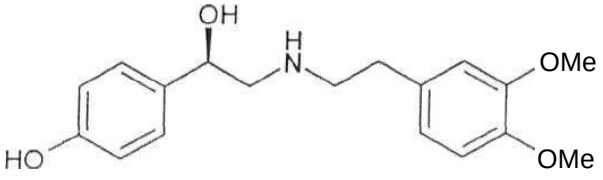
1. 1 Introduction

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.[1-5]



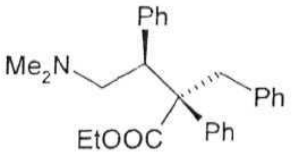
1

Propranol

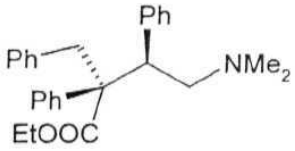


Denopamine

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.



3



4

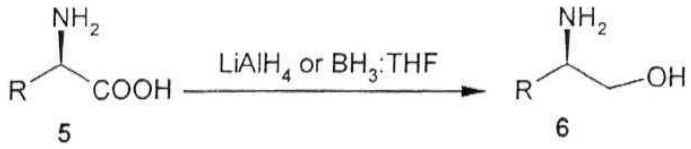
Besides pharmaceutical applications, enantiomerically pure amino alcohols, especially the 1,2-amino alcohols have also been used as chiral auxiliaries and chiral catalysts in asymmetric organic transformations.[6,9] A large number of enantiomerically pure amino alcohol derived chiral auxiliaries and 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. LiAIH4 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).[10-12]

Scheme 1

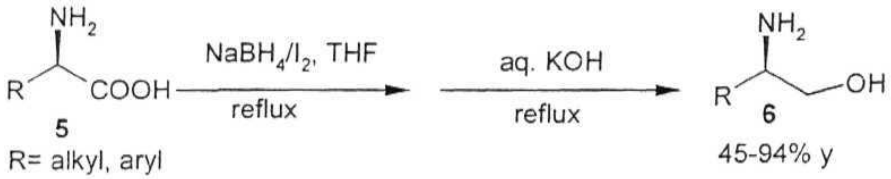


5 6

R= alkyl, aryl 90-98% y

Meyers and coworkers [12] 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 2).[109-110] The results indicate that it is an excellent reagent system for the conversion of amino acids to amino alcohols. 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 2

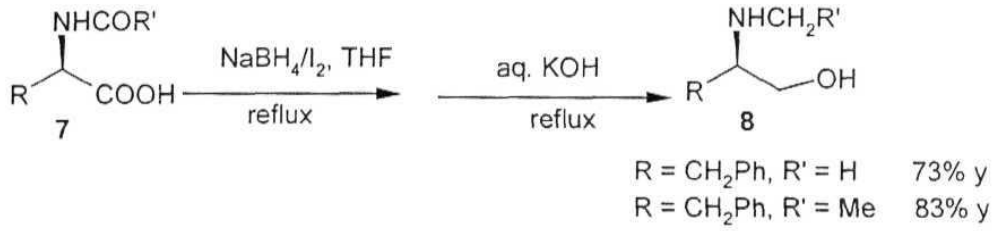


5 6

R= alkyl, aryl 45-94% y

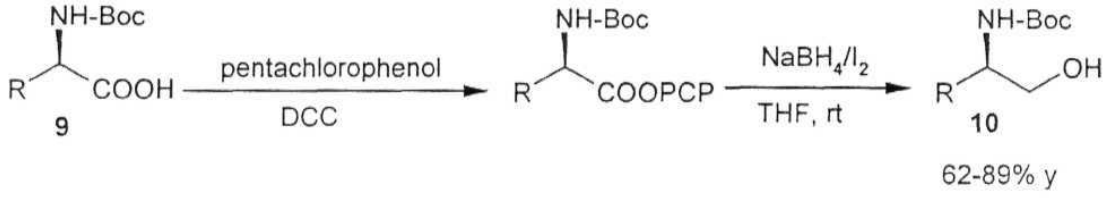
The *N-acyl* amino acids gave the corresponding *N*-alkyl amino alcohols under these conditions (Scheme 3)[6]

Scheme 3



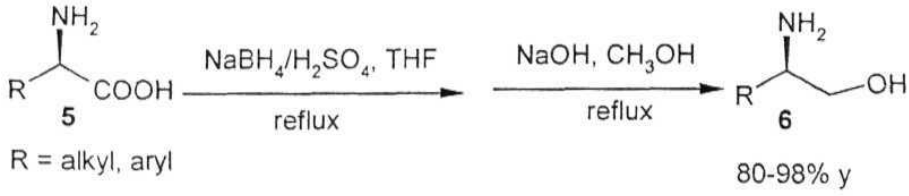
The reduction of pentachlorophenyl esters of the Boc protected amino acids and peptides gave the corresponding amino alcohols.(Scheme 4).[16]

Scheme 4



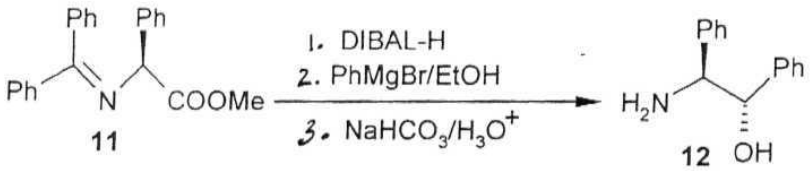
Amino acids are also reduced using the inexpensive $NaBH_4/H_2SO_4$ reagent system in THF. It is of interest to note that no racemisation occurs in the reduction of amino acids using $NaBH_4/I_2$ or $NaBH_4/H_2SO_4$ reagent systems(Scheme 5).[17]

Scheme 5



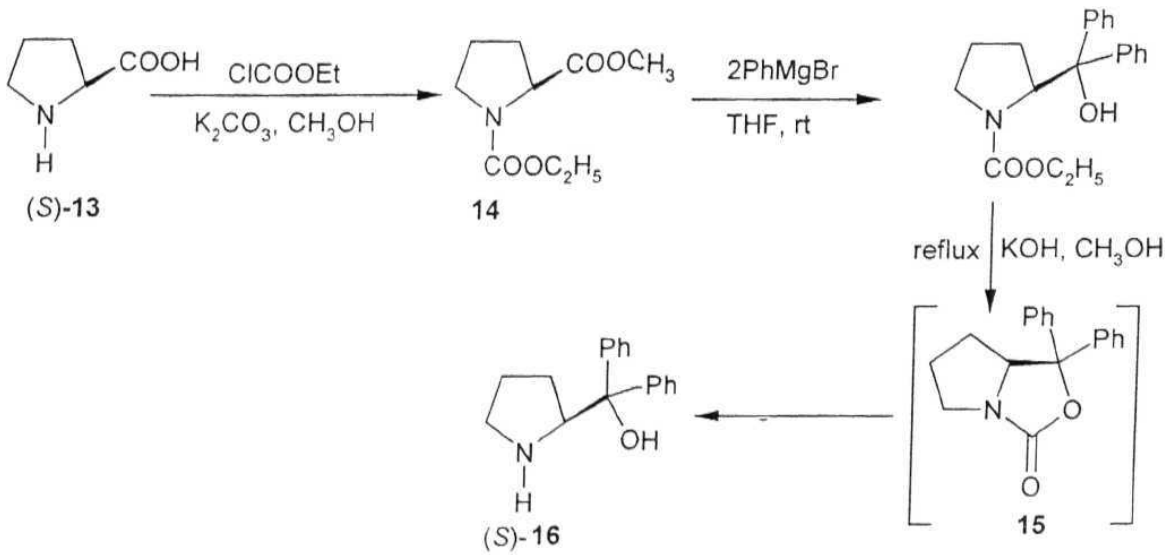
α-Imino ester can be reduced to the corresponding amino ester, which upon reaction with Grignard reagent gives the corresponding amino alcohols as shown in the Scheme 6.[18]

Scheme 6



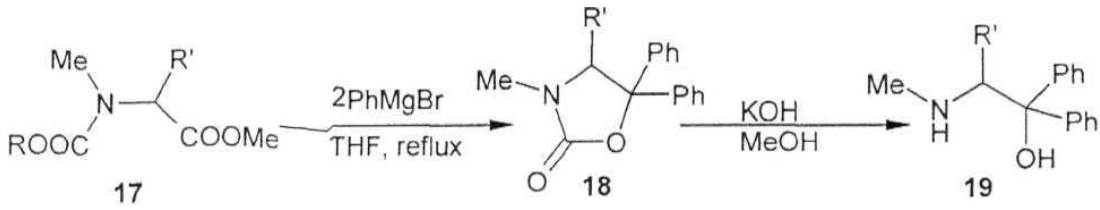
A convenient method of synthesis of chiral α,α-diphenyl-2-pyrrolidinemethanol 16 involving single step *N* and *O*- protection of (*S*)-proline using ethylchloroformate followed by Grignard reaction and alkaline hydrolysis, has been reported from this laboratory (Scheme 7).[19]

Scheme 7



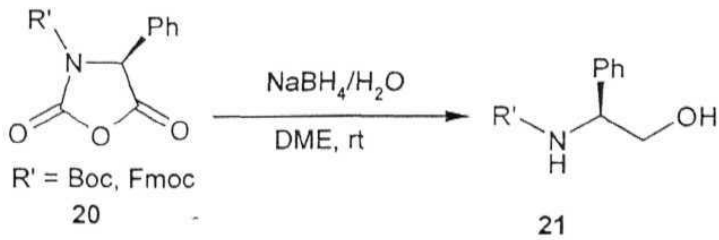
Recently, the oxazolidinone intermediates of the type 15 have been readily prepared by the Grignard reaction of *N*-alkoxy-carbonyl-α-amino esters, which on hydrolysis give the corresponding amino alcohols. It was observed that the success of the reaction is dependent on the nature of R' group. When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

Scheme 8



The 1,2-amino alcohols 21 were also obtained by the reduction of *N*-protected *N*-carboxy anhydrides 20 using the $NaBH_4/H_2O$ reagent system (Scheme 9).[21-23]

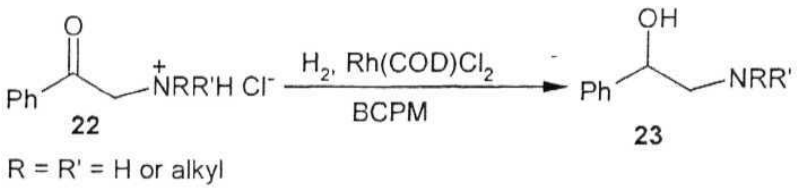
Scheme 9



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

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

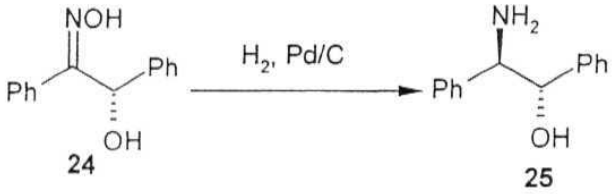
Scheme 10



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]

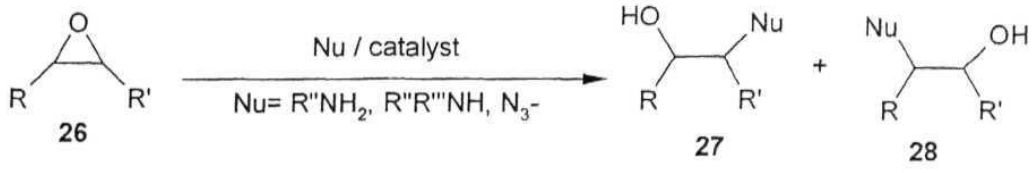
Scheme **11**



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]

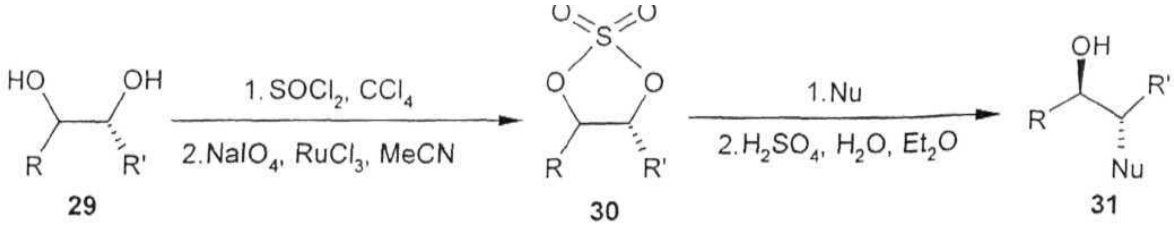
Scheme 12



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 30 react with nitrogen nucleophiles to give the corresponding 1,2-amino alcohol derivatives (Scheme 13).[31]

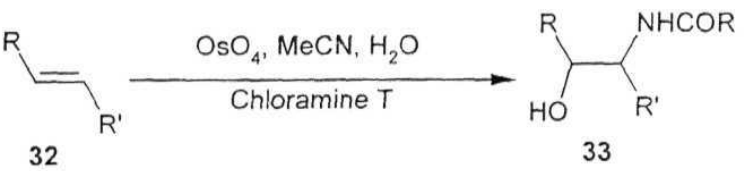
Scheme 13



1. 1. 1.6 Other methods

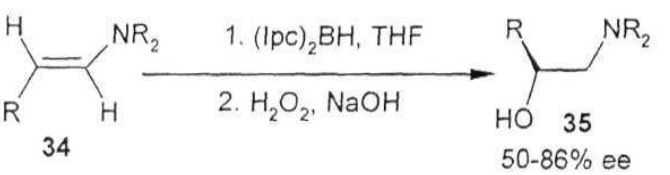
1,2-Amino alcohols are also accessible from alkenes by oxyamination process[32] as shown in the Scheme 14.

Scheme 14



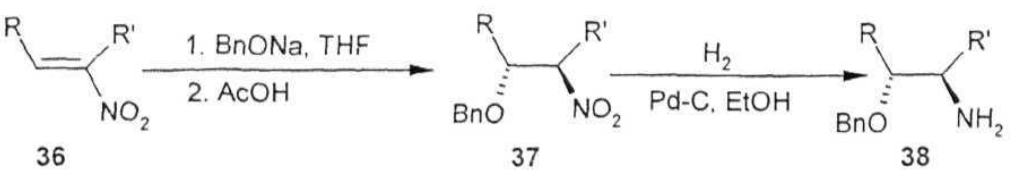
Asymmetric synthesis of 1,2-amino alcohols with moderate enantioselectivity (50-86% ee) has been achieved through hydroboration of aldehyde enamines (Scheme 15).[33]

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).[34]

Scheme 16



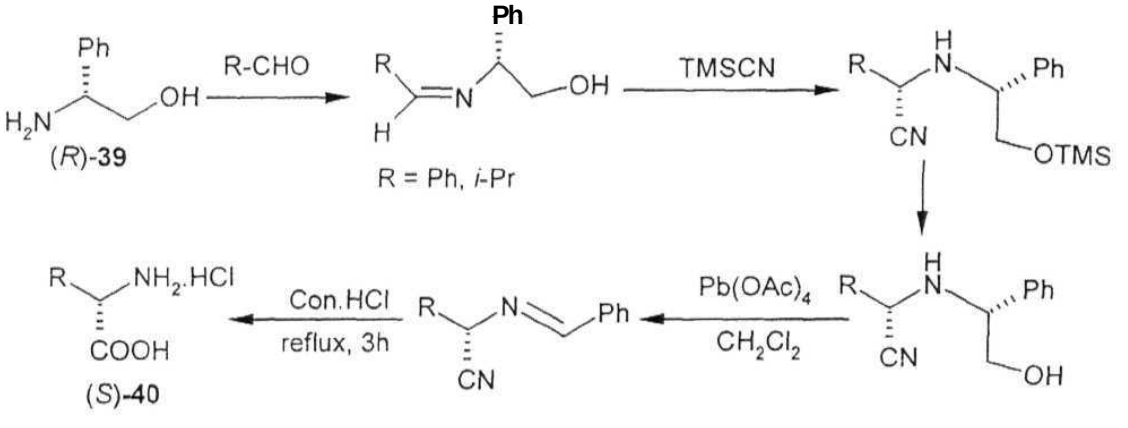
1. 1. 2 Synthetic applications of 1,2-amino alcohols

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.[35] A number of chiral amino acids are synthesized following this method.

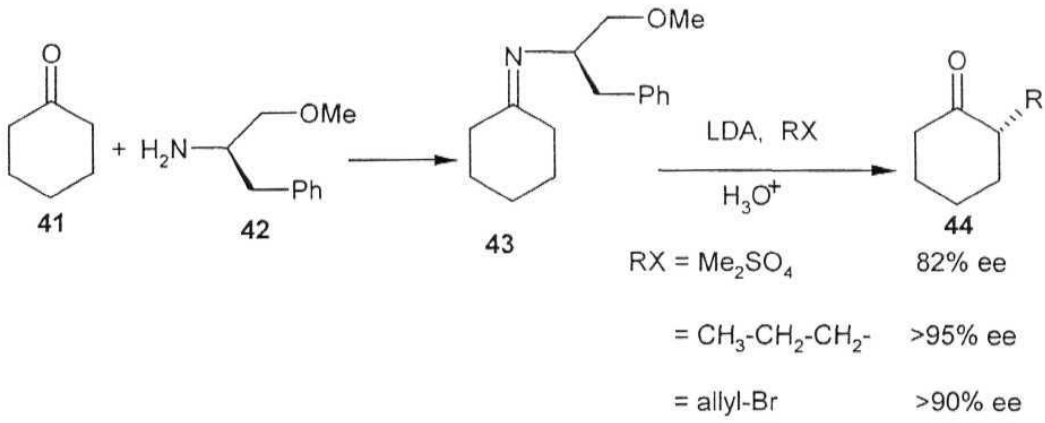
Scheme 17



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).[36-37]

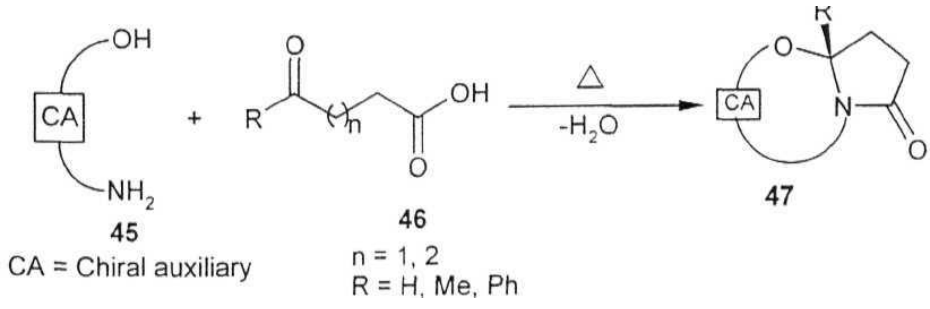
Scheme 18



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

Meyers *et al.*[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.[40]

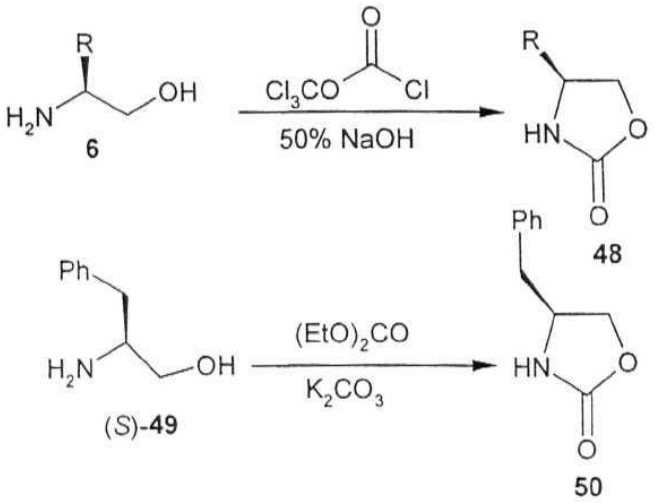
Scheme 19



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

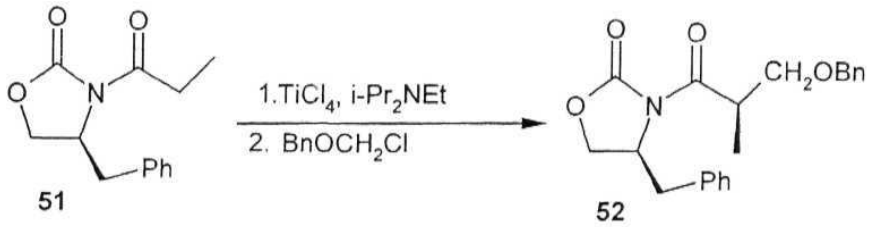
Reactions of amino alcohols with trichloromethyl chloroformate provides a simple entry into oxazolidinones 48 (Scheme 20).[41] Reaction between amino alcohols and diethyl carbonate is the most direct route to oxazolidinones **50.**[42]

Scheme 20



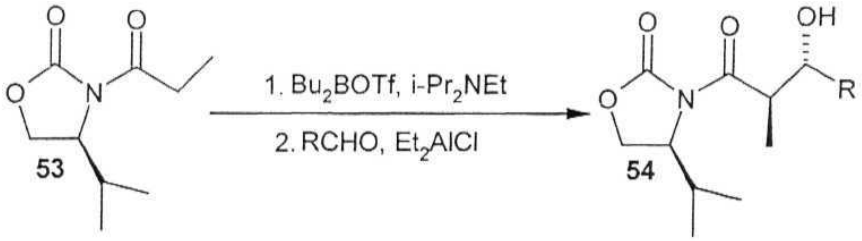
The oxazolidinones give excellent levels of asymmetric induction in alkylation reactions. For example, the *N*-acyloxazolidinone 51 moiety helps in realizing high degree of stereoselectivity during enolate formation (Scheme 21). *Z*-Enolates with high diastereoselectivity were obtained by the reaction of parent acyloxazolidinone with $TiCl_4/R_3N$ reagent system (Scheme 21)

Scheme 21



The utility of the *Z*-enolates derived from *N*-acylimides of chiral oxazolidinones has been demonstrated in the aldol condensation reaction with aldehydes to obtain the corresponding α-substituted-β-hydroxy imides 54 in high yields.[44]

Scheme 22



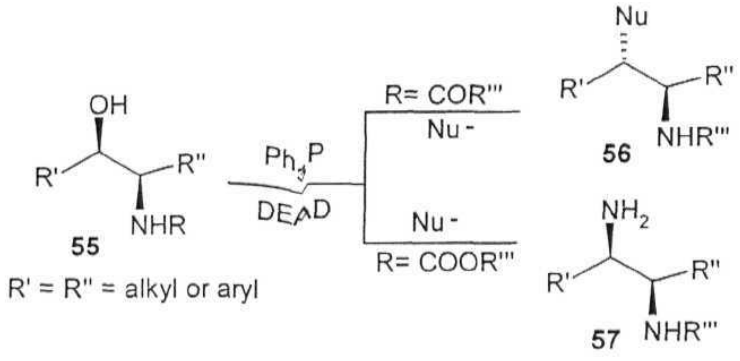
1. 1. 2. 2 Reactions of 1,2-amino alcohols

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.[45]

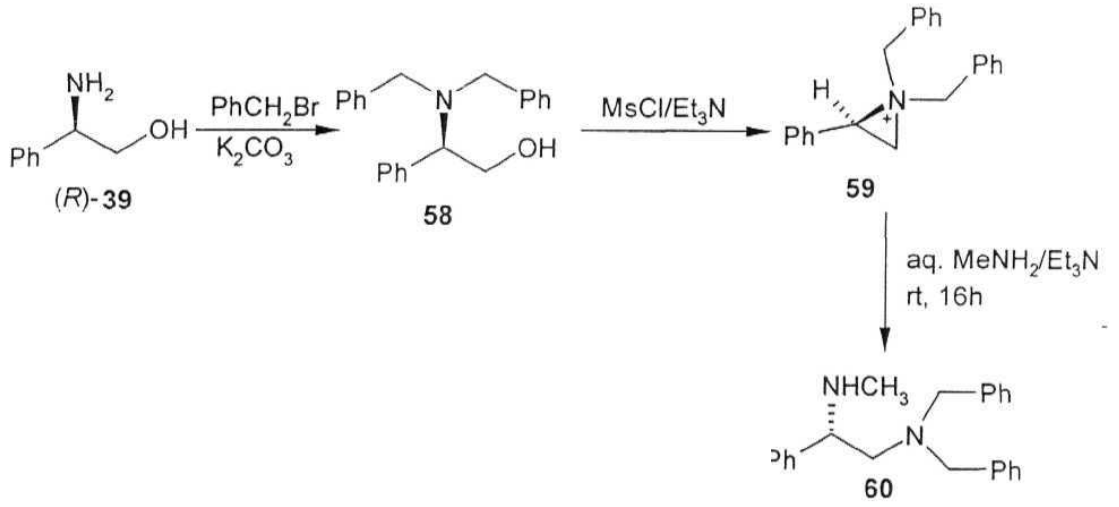
Scheme 23



1. 1. 2. 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 (*R*)-phenylglycinol (Scheme 24) through an aziridinium ion intermediate.[46]

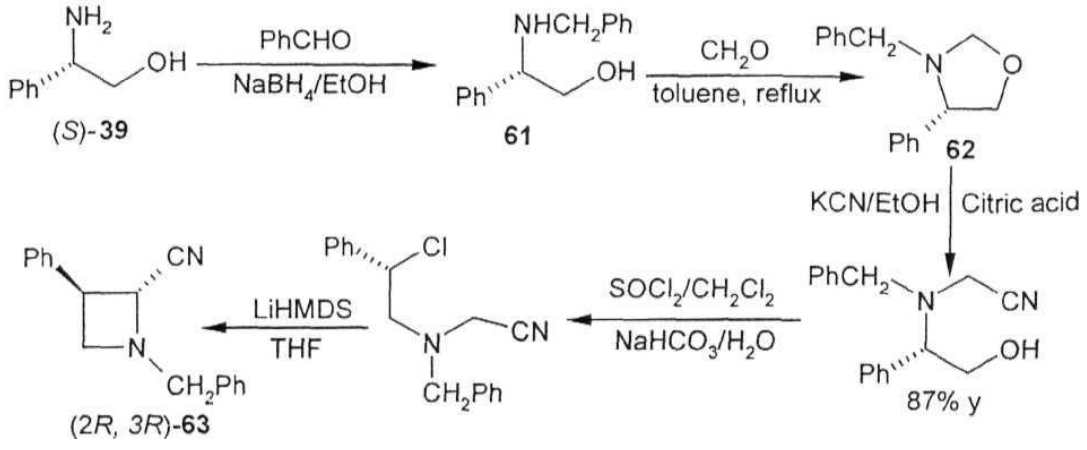
Scheme 24



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).[47] 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.

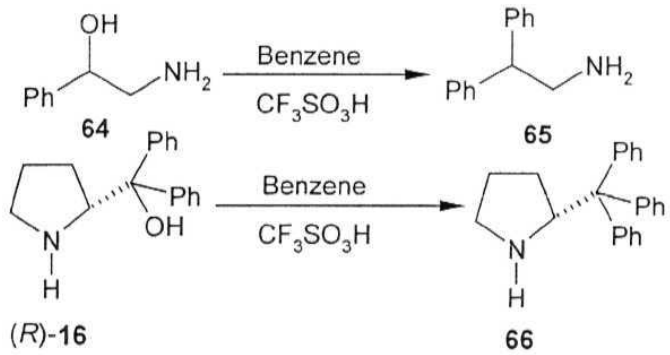
Scheme 25



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.[48] 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).[48]

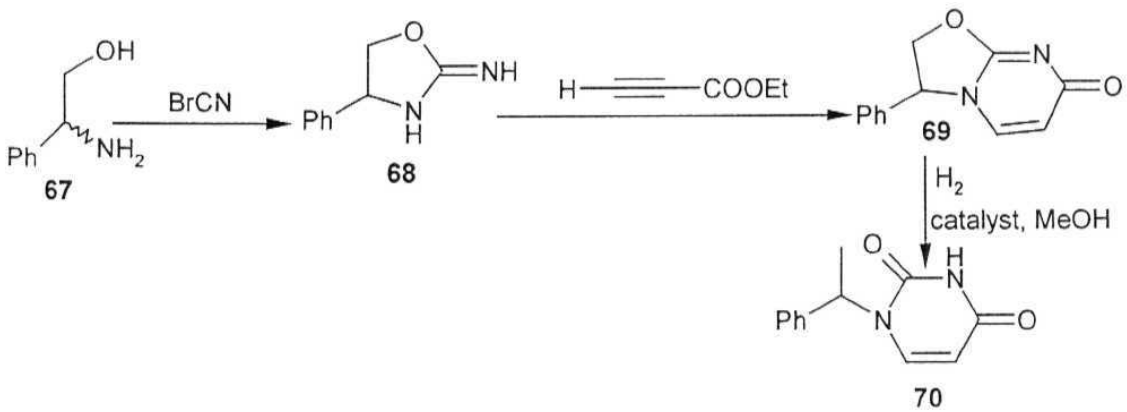
Scheme 26



1. 1. 2. 2. 5 Synthesis of acylnucleosides

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

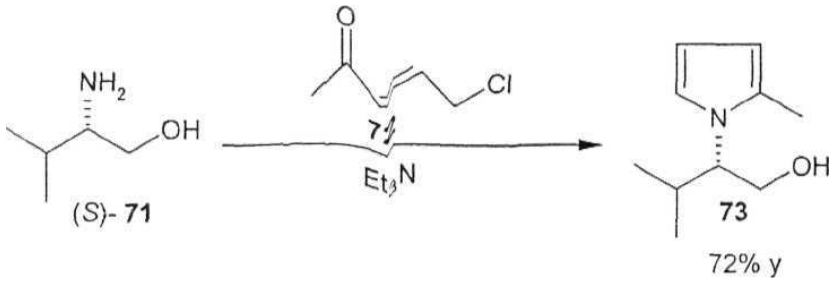


These pyrimidinones were chemoselectively reduced using metal catalysed hydrogenation and stereoselectively substituted by various nucleophiles to give the new pyrimidine acylnucleosides 70 that are potential antiviral agents (Scheme 27).[49]

1. 1. 2. 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).[50]

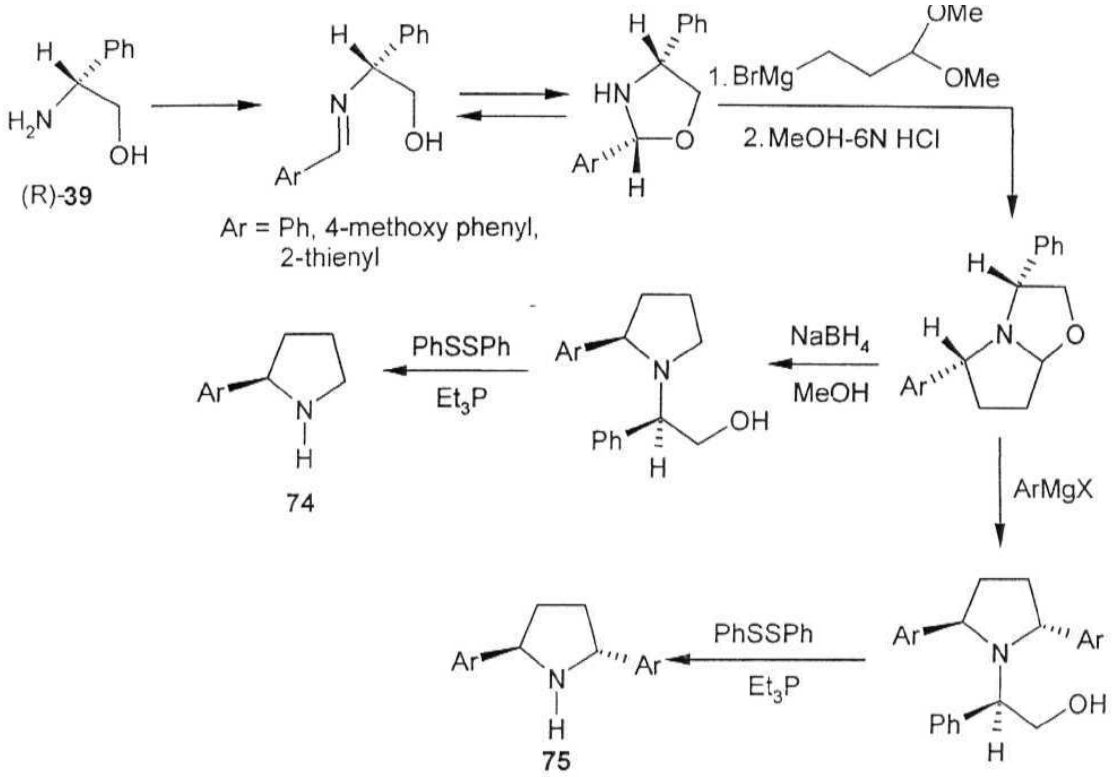
Scheme 28



1. 1. 2. 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.[51]

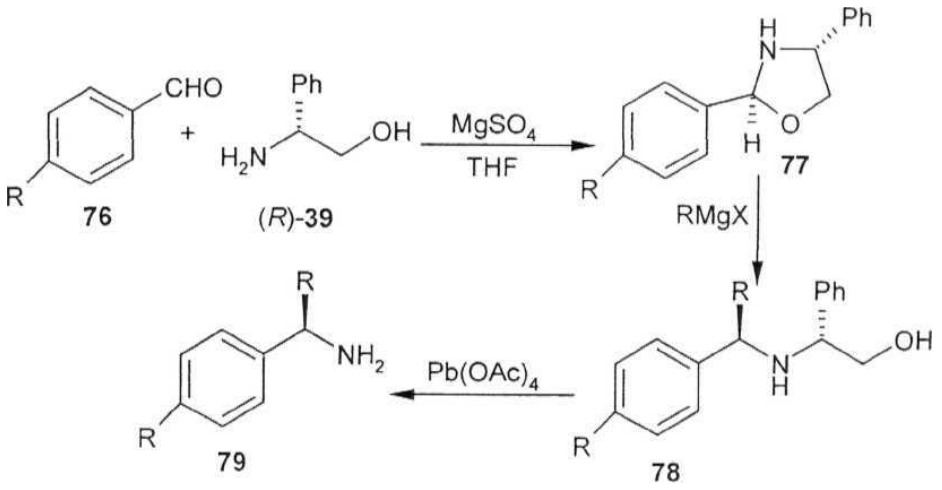
Scheme 29



1. 1. 2. 2. 8 Oxazolidines

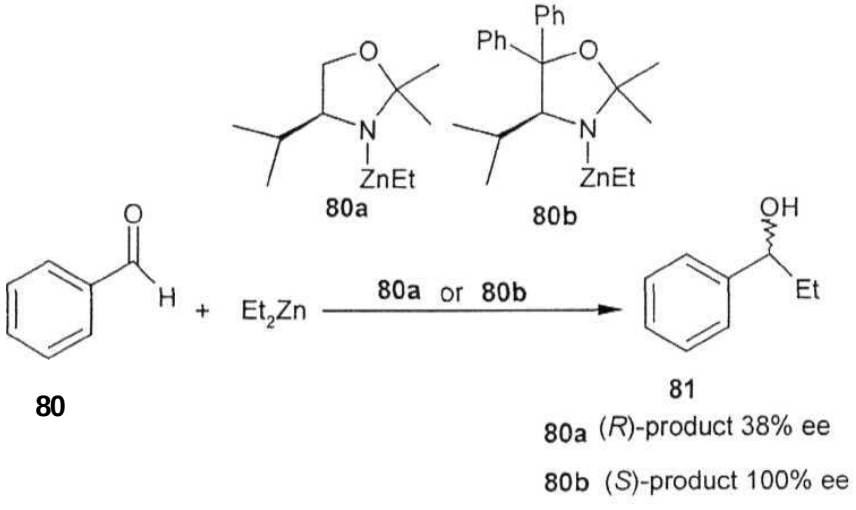
Oxazolidines derived from 1,2-amino alcohols are good substrates for nucleophilic additions as they act as acetal equivalents. They are very widely used as chiral auxiliaries and chiral catalysts in organic syntheses.[52-53] For example, the oxazolidine 77 derived from (*R*)-phenylglycinol is useful for the alkylation reactions (Scheme 30).

Scheme 30



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

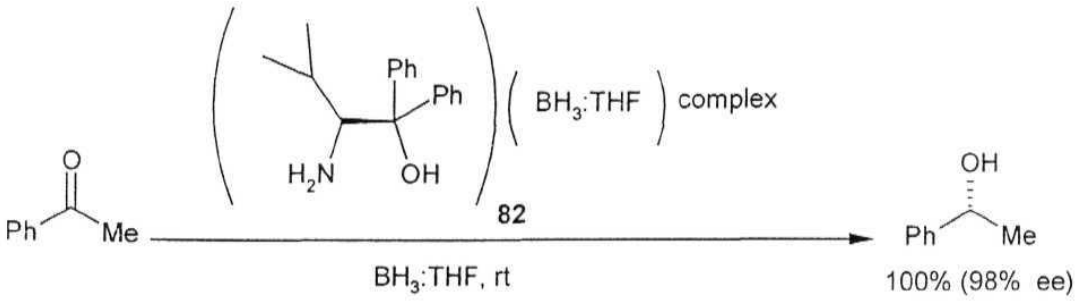


1. 1. 2. 3 1,2-Amino alcohols as chiral ligands

1. 1.2. 3. 1 Enantioselective reduction of ketones with oxazaborolidine catalysts

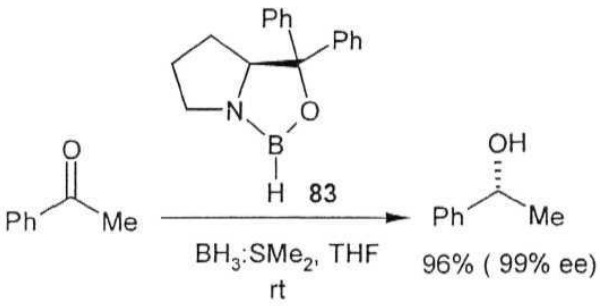
Asymmetric reductions were generally carried out using stoichiometric amounts of chiral auxiliaries before the oxazaborolidine catalysed borane reduction was discovered.[60] Since then, asymmetric borane reduction of ketones using oxazaborolidine catalyst is one of the most widely used methods to obtain 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.[60] 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



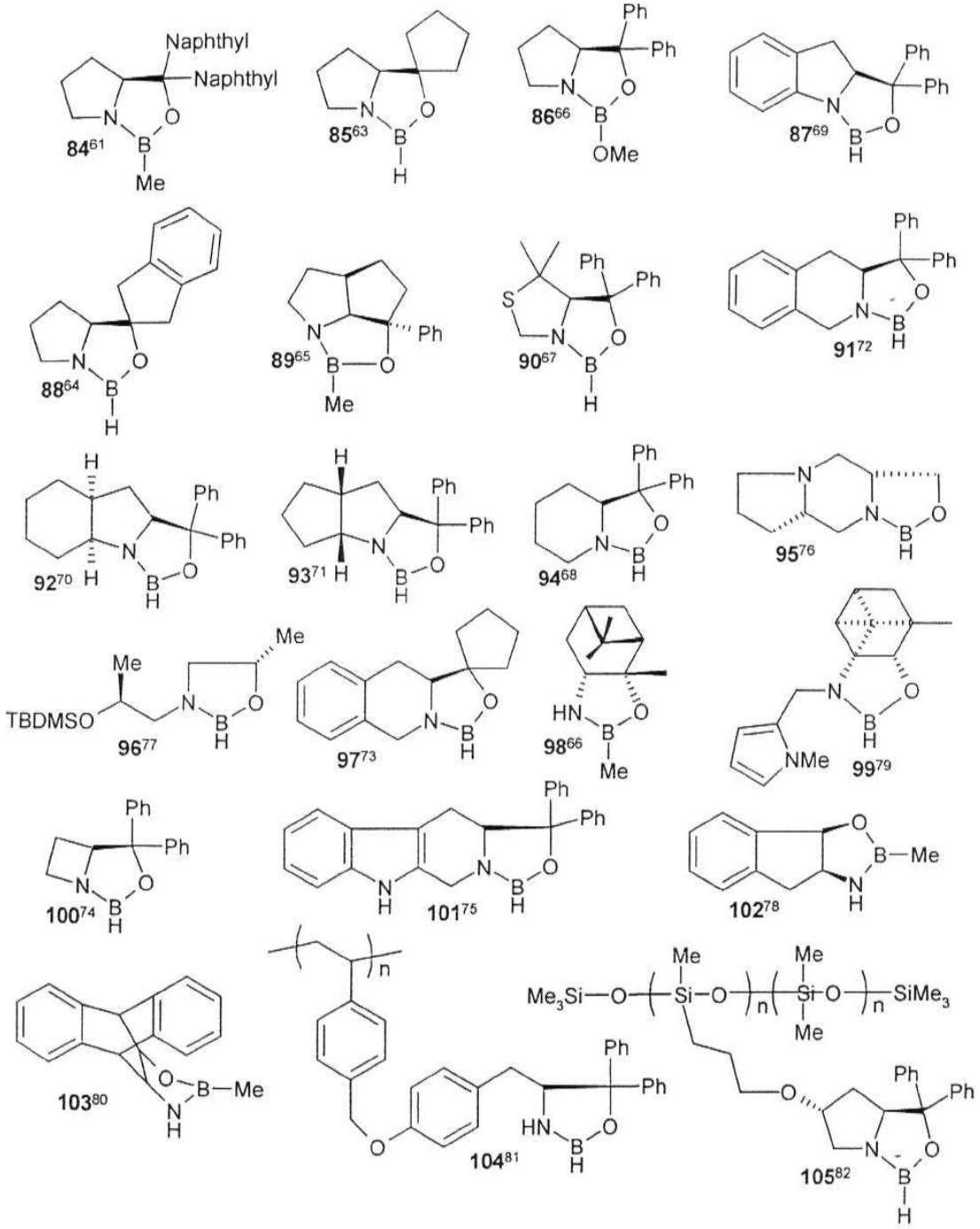
Later, Corey *et al.*[56-59] discovered that the intermediate involved in such asymmetric borane reduction is the corresponding oxazaborolidine. The oxazaborolidine derived from α,α-diphenyl-2-pyrrolidinemethanol 83 gives better results than the corresponding diphenylvalinol (Scheme 33).

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) [60]

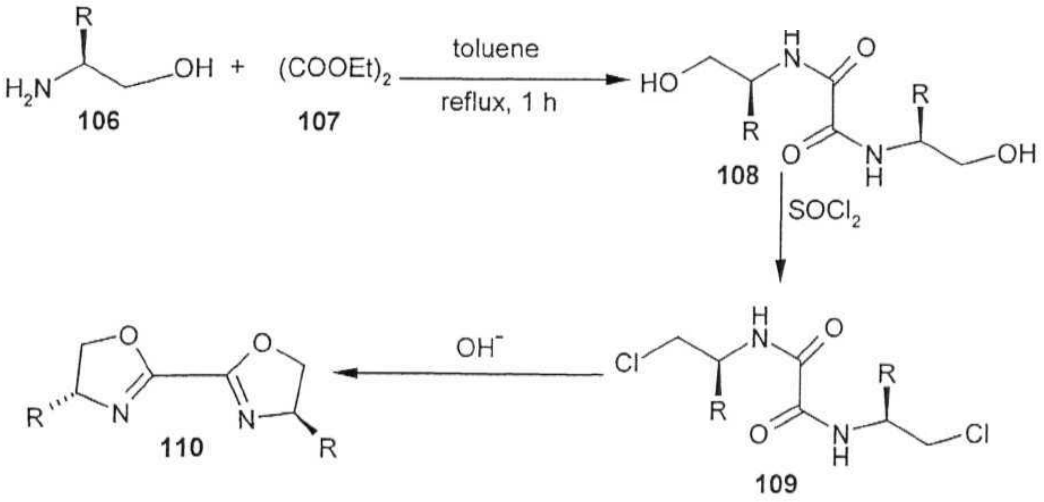
Chart 1


Naphthyl
Naphthyl
84[61]
85[63]
86[66]
87[69]
88[64]
89[65]
90[67]
91[72]
92[70]
93[71]
94[68]
95[76]
96[77]
97[73]
98[66]
99[79]
100[74]
101[75]
102[78]
103[80]
104[81]
105[82]

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 $SOCl_2$ and exposure to base (Scheme 34).[83]

Scheme 34



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

Chart 2

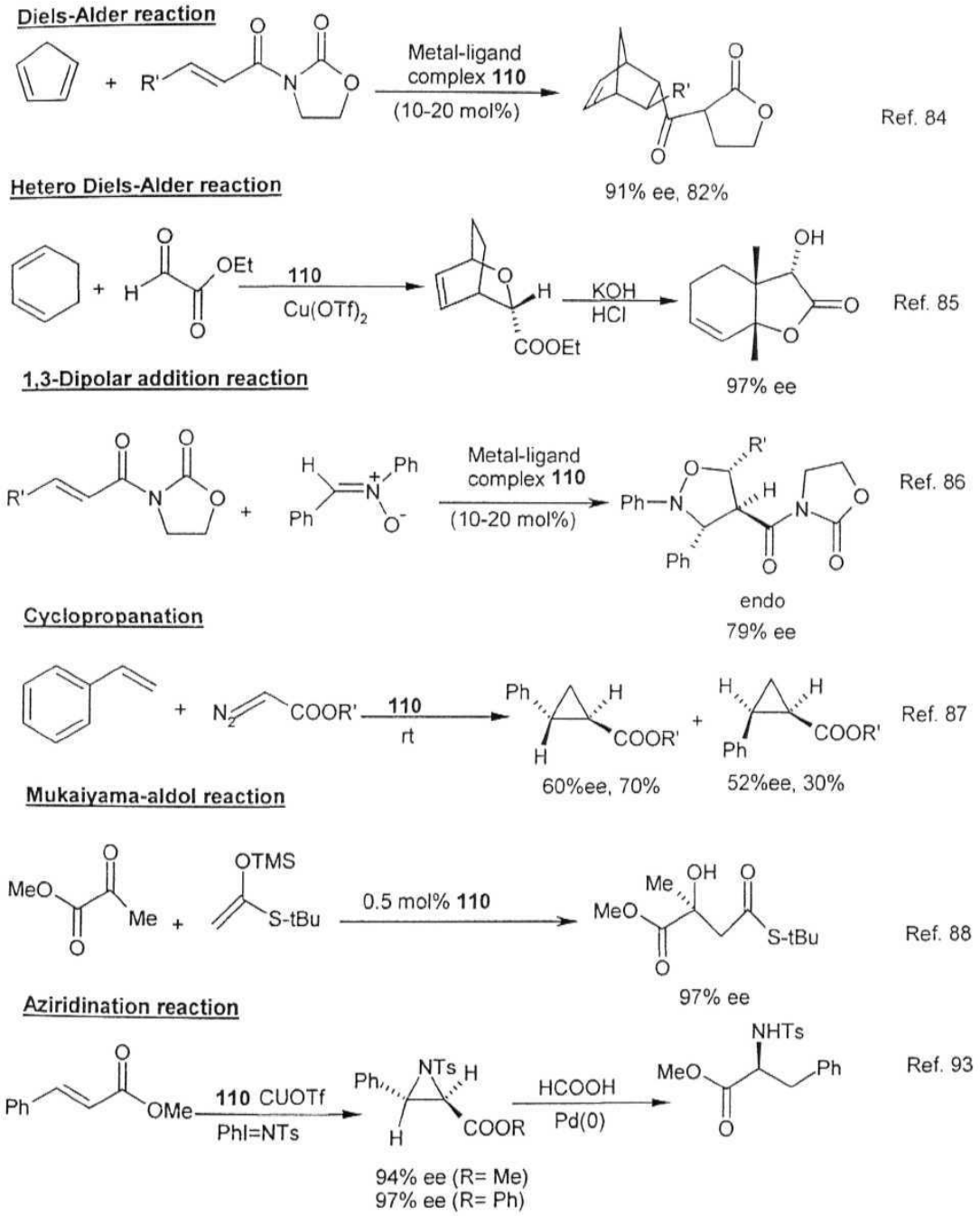
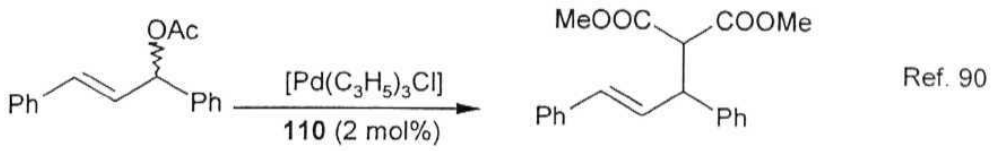

Diels-Alder reaction
Metal-ligand complex 110
(10-20 mol%)
91% ee, 82%
Ref. 84
Hetero Diels-Alder reaction
110
Cu(OTf)2
KOH
HCl
97% ee
Ref. 85
1,3-Dipolar addition reaction
Metal-ligand complex 110
(10-20 mol%)
endo
79% ee
Ref. 86
Cyclopropanation
110
rt
60%ee, 70%
52%ee, 30%
Ref. 87
Mukaiyama-aldol reaction
0.5 mol% 110
97% ee
Ref. 88
Aziridination reaction
110 CUOTf
PhI=NTs
HCOOH
Pd(0)
94% ee (R= Me)
97% ee (R= Ph)
Ref. 93

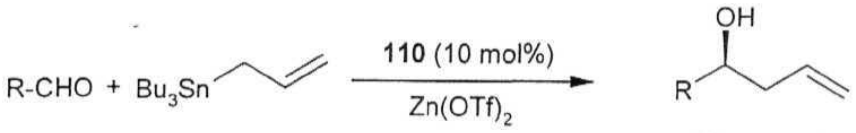
Chart 2 (continued).

Allylic substitution



Ref. 90

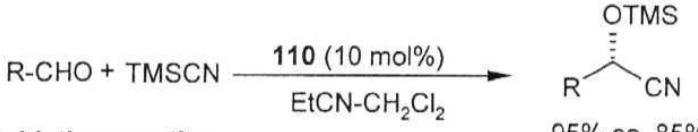
Allylation reaction



Ref. 91

46% ee, 45%

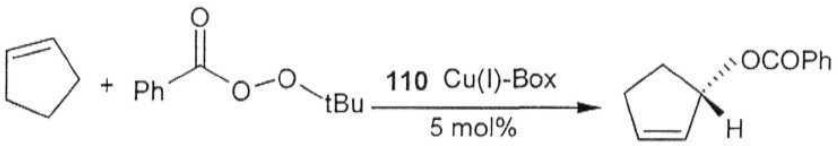
Cyanation reaction



Ref. 92

95% ee, 85%

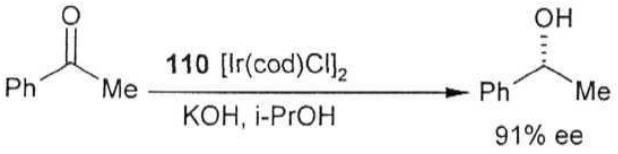
Oxidation reaction



Ref. 94

84% ee, 61%

Reduction



Ref. 95

91% ee

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

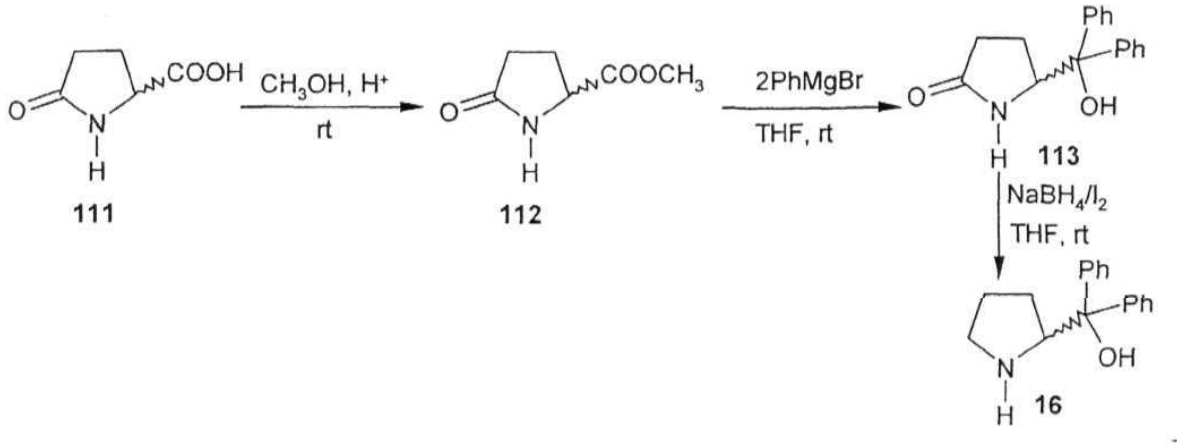
and chiral l,l'-bi-2-naphthyl phosphoric acid.[96-103] We have undertaken efforts towards the synthesis and resolution of the racemic 1,2-amino alcohols. The results of these studies are described here.

1. 2 Results and Discussion

I. 2. 1 Synthesis and resolution of racemic a,a-diphenyl-2-pyrrolidinemethanoI (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).[56-59] It can be readily prepared from (*S*)-proline through an optimized method developed in this laboratory (Scheme 7).[19] The corresponding *R* isomer can be prepared from unnatural (*R*)-proline, but it is expensive.

Scheme 35

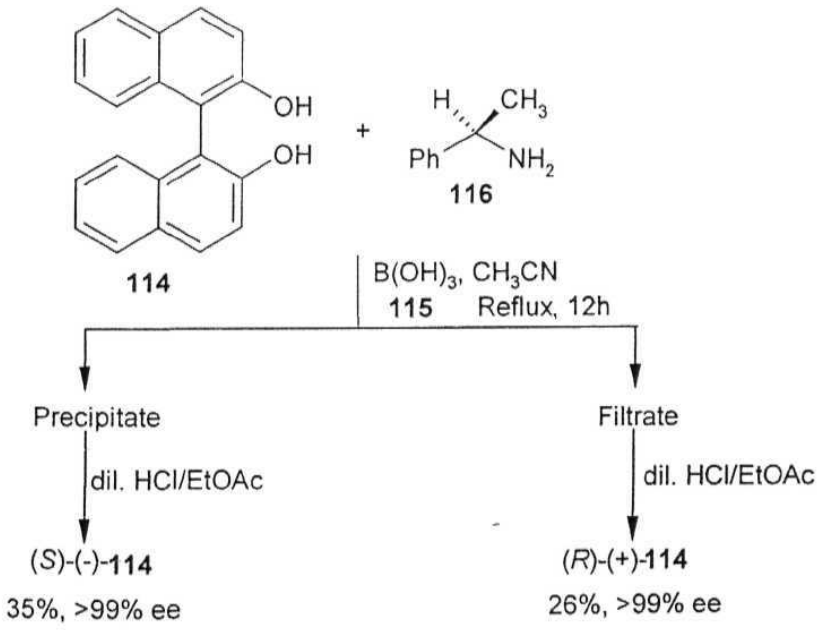


Therefore, we have envisaged an alternative synthetic route to access both the enantiomers of DPPM, using racemic pyroglutamic acid by a slight modification of

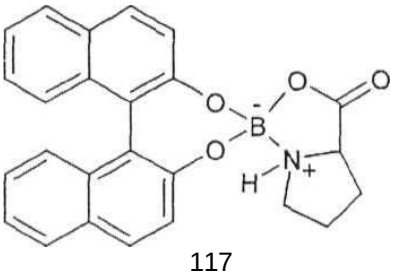
a reported procedure via $NaBH_4/I_2$ reduction of the corresponding amide in a crucial step (Scheme 35).

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-diphenyl-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 a-methylbenzylamine and boric acid (Scheme 36).[104g]

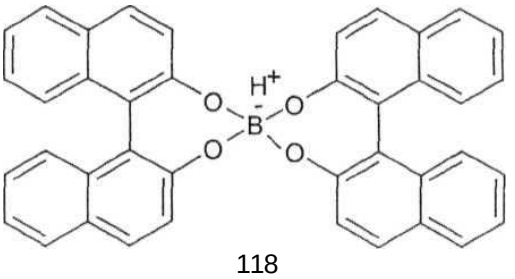
Scheme 36



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 l,l'-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 l,l'-bi-2-naphthol **114** and boric acid in CH_3CN and CH_3OH at 25-67 °C.



117



118

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_3CN 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 CH3CN following the same procedure (Table 1, entry 3). The results are summarized in Table 1.

Scheme 37

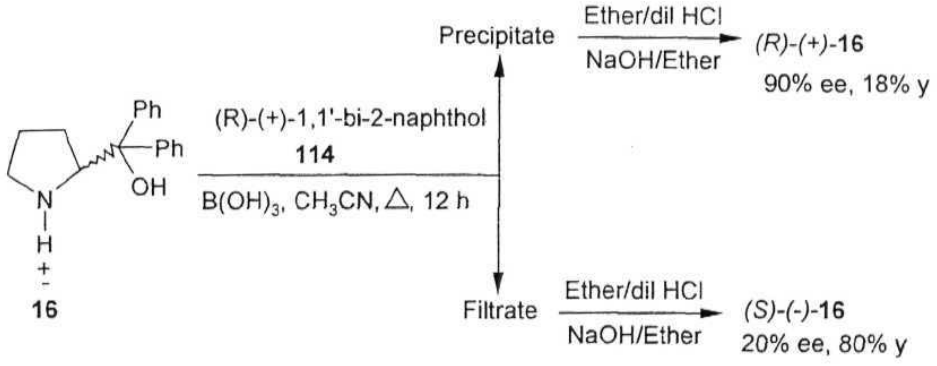


Table 1: Resolution of racemic 16 using (*R*)-(+)-1,1'-bi-2-naphthol and boric acid

S.No.	Substrate %ee	Solvent	Chiral 16 obtained from			
			Precipitate		Filtrate	
			% ee[a]	Yield (%)[b]	% ee[a]	Yield *(%f*
1[c]	16.00	CH_3CN	**90 *(R)***	18	20 (*S*)	80
2[d]	**16/?.** 42	CH_3CN	>99 *(R)*	28	25(5)	69
3[e]	**16 *R*, 90**	CH_3CN	>99 *(R)*	78	**30 *(S)***	20
4[f]	16,00	CH_3OH	**60 *(R)***	23	25 (*S*)	72

a. The ee values reported here are based on reported maximum $[\alpha]_D^{27}$ = 69.0 (*c* 3, $CHCl_3$) for both *(R)* and (5) isomer.[19]

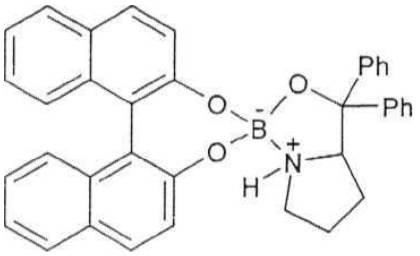
b. (±) 16 (5 mmol), $B(OH)_3$ (5 mmol) and (*R*)-(+)-1,1'-bi-2-naphthol (10 mmol) were taken in CH_3CN (10 ml) and stirred for 12 h under refluxing conditions.

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_3CN (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_3CN (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_3OH (15 mL) and stirred for 12 h at 25 °C.

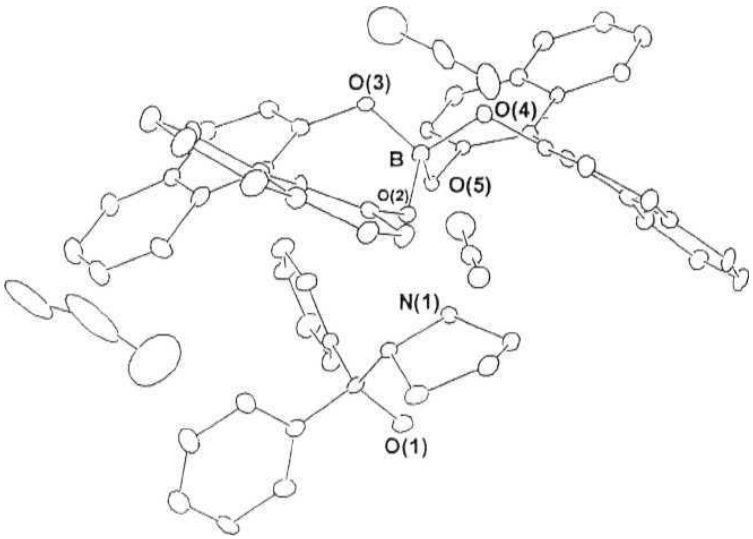
Efforts were also undertaken to examine the nature of the borate complex formed in this resolution method. It has been reported that the resolution of 1,1'-bi-2-naphthol was effected by using boric acid and (*S*)-proline through the complex of the type **117**[105]. Hence, the complex of the type **119** could be expected in the reaction of α,α-diphenyl-2-pyrrolidinemethanol 16, chiral 1,1'-bi-2-naphthol 114 and boric acid.



119

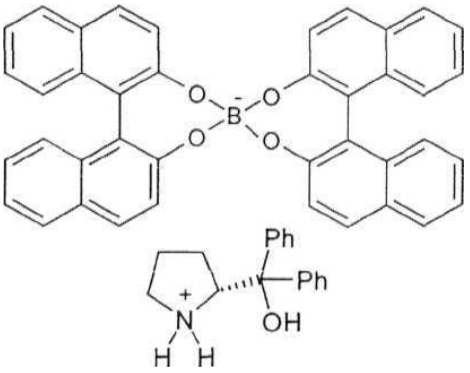
The IR spectrum of the precipitate complex obtained in the resolution of α,α-diphenyl-2-pyrrolidinemethanol 16 showed strong absorption at 3350 cm^{-1}, indicating the presence of the free OH group in the complex. The borate complex formed using α,α-diphenyl-2-pyrrolidinemethanol was also analyzed using 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 CH3CN 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.



ORTEP diagram for complex 120

Hence, l,l'-bi-2-naphthol and boric acid tend to form BL_2 complexes of the type **120** in refluxing acetonitrile in the presence of the (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol 16.



120

X-ray crystal structure analysis

The X-ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 A) radiation. Intensity data were collected by the ©-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-B_1-O_2 = 112.5^0, O_1-B_1-O_3 = 104.6°, O_1-B_1-O_4 = 112.1°, O_2-B_1-O_3 = 114.5°, O_2-B_1-O_4 = 101.5° and O_3-B_1-O_4 = 112.0° showed the existence of boron in tetra coordinated form. The bond distances between B_1 and four oxygen atoms of two chiral l,l'-bi-2-naphthol units are B_1-O_1 = 1.44A, B_1-O_2 = 1.46A, B_1-O_3 = 1.44A, B_1-O_4 = 1.49A, supported "ate" complex nature of boron. The structure **was** solved by direct methods and refined by full-

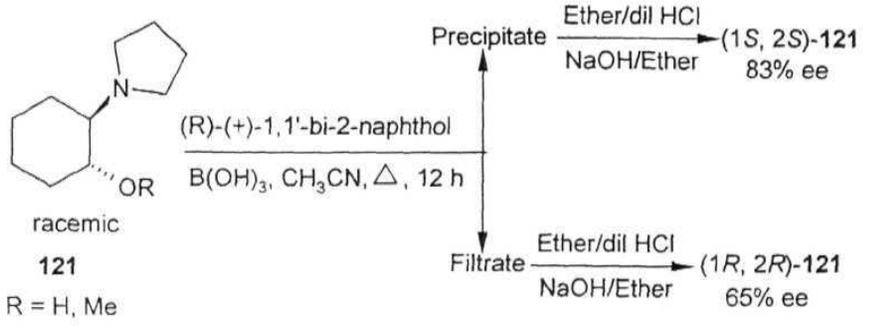
matrix least-squares procedure using the SHELX 86 and SHELX 97 programme package respectively. The configuration of the DPPM 16 moiety present in the crystal structure was confirmed to be (R) by using platon 98 programme, A. L. Spak, version 2911.

Table 2. Crystal data and structure refinement for compoundl20.

Identification code	120
Empirical formula	C_{57} H_{44} B N O_5
Formula weight	731.90
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a= 15.131(3) A α = 90° b= 16.594(3) A [3 = 90° c = 20.808(4) A Y = 90°.
Volume	5224.4(18) A^3
Z, Calculated density	5, 1.163 Mg/m^3
Absorption coefficient	0.072 mm^{-1}
F(000)	1932
Crystal size	0.28 x 0.28 x 0.32 mm
Theta range for data collection	1.57 to 29.94°.
Limiting indices	0<=h<=21,0<=k<=17,0<=l<=22
Reflections collected / unique	4553/4553 [R(int) = 0.0000]
Completeness 2θ =29.94	55.1%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4553/0/659
Goodness-of-fit on F^2	1.017
Final R indices [I>2σ(I)]	R1 = 0.0561, wR2 = 0.1218
R indices (all data)	R1 =0.1606, wR2 = 0.1807
Absolute structure parameter	-1(3)
Extinction coefficient	0.0016(4)
Largest diff. Peak and hole	0.203 and -0.163 $e.A^{-3}$

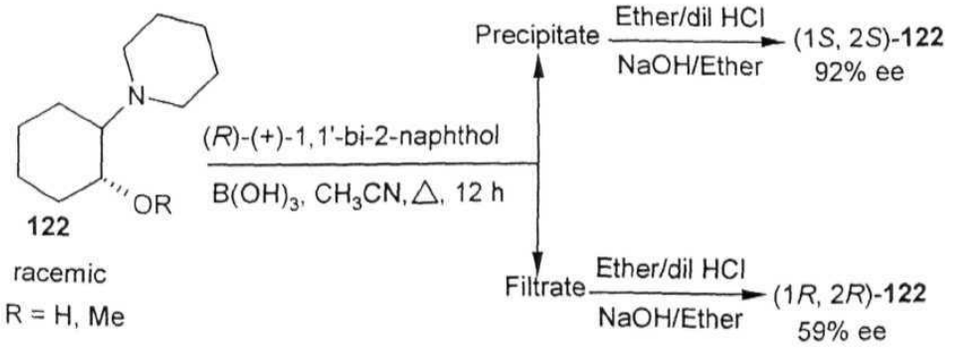
In this laboratory, systematic investigations were carried out on the use of the chiral 1,1'-bi-2-naphthol for the resolution of several amino alcohols of interest.[106] For example, the *trans*-(±)-2-(pyrrolidinyl)cyclohexanol and its methyl ether were resolved using chiral 1,1"-bi-2-naphthol and $B(OH)_3$ in THF or CH_3CN (Scheme 38).

Scheme 38



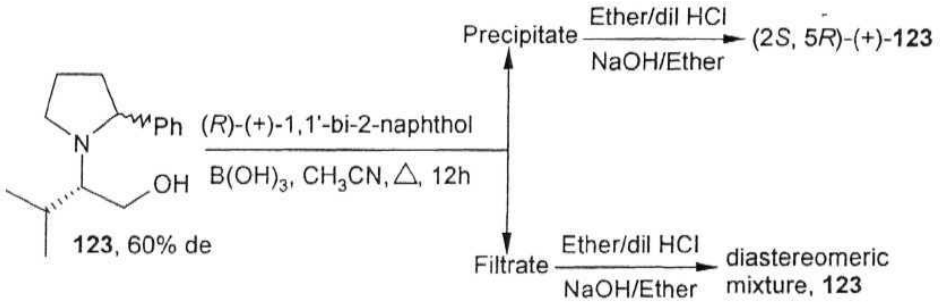
The frw?.s-(±)-2-(pyrridinyl)cyclohexanol and its methyl ether were resolved using chiral 1,1`-bi-2-naphthol and $B(OH)_3$ in THF or CH_3CN (Scheme 39).[107]

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



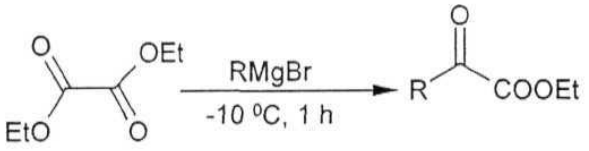
1. 2. 2 Synthesis and resolution of 1,2-amino alcohols

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 aminokctone 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 a-keto esters. The a-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



124 R=Ph- 40%

125 R=Ph-CH_2- 42%

126 R=$(CH_3)_2CH$- 38%

127 R= C_2H_5- 35%

128 R= CH_3- 30%

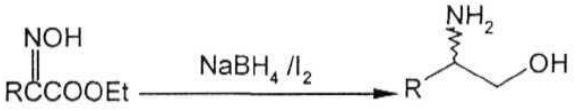
Table 3: Reduction of oxime ester to phenylglycinol using $NaBH_4$ in presence of additives

Entry	Additives	Time (h)	Temp (°C)	Yield (%)
1		4	67	85%
2	I_2[b]	48	25	70%
3	CH_3COOH[c]	4	67	70%
4	$ZrCl_4$[d]	24	25	60%
5	$ZrCl_4$[e]	4	25	65%
6	$CoCl_2$[f]	4	25	60%
7	$TiCl_4$[g]	4	25	65%
8	TMS-Cl[h]	4	25	70%
9	H_2SO_4[i]	4	25	60%

a. $NaBH_4$ was added to a stirred solution of oxime ester in THF. I_2 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. $NaBH_4$ 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. $ZrCl_4$ was added slowly to the $NaBH_4$ 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. $NaBH_4$ was added in portions to the stirred solution of $CoCl_2$ in THF. Oxime ester in THF was added dropwise and the contents were refluxed for 4 h.
g. $TiCl_4$ in DCM was added to stirred slurry of $NaBH_4$ in THF. The oxime ester was added dropwise and the contents were refluxed for 4 h.
h. TMS-C1 and $NaBH_4$ in THF were refluxed for 2 h. The oxime ester in THF was added dropwise and the contents were refluxed for 4 h.
i. H_2SO_4 in dry ether was added dropwise to a stirred suspension of $NaBH_4$ and the oxime ester in THF. Then the contents were refluxed for 4 h.

The racemic 1,2-amino alcohols were then prepared by reduction of oximes of α-keto esters by $NaBH_4$ activated in the presence of additives. The results obtained are summarised in Table 3.

Scheme 42



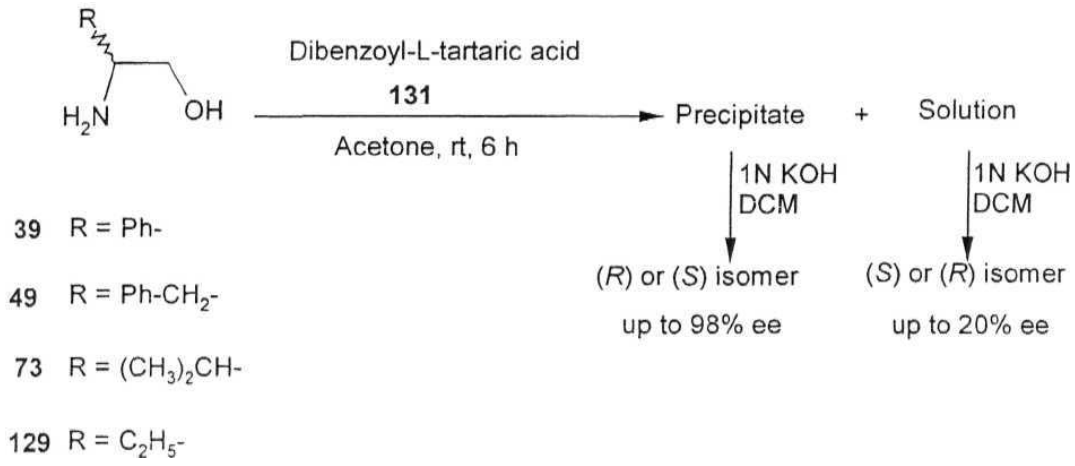
39	R=Ph-	85%
49	R=Ph-CH_2-	80%
73	R=$(CH_3)_2CH$-	75%
129	R= C_2H_5-	60%
130	R= CH_3-	60%

Comparison of the results (Table 3) indicates that the easy to handle $NaBH_4/I_2$ reagent system[109-110] gives better yields. Accordingly, reduction of various oxime esters has been examined with this reagent system. The results are summarised in Scheme 43

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_3CN. 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 tartarate 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]

S. No.	Time	Solvent	Chiral 39 obtained from			
			Precipitate		Filtrate	
			%ee[b]	Yield (%)	%ee[b]	Yiled (%)
1[c]	24 h	Acetone	22(5)	40	20 (R)	50
2[c]	12 h	Acetone	30 (5)	32	22 (R)	60
3[c]	6h	Acetone	35(5)	30	10 (R)	60
4[c]	30 min	Acetone	22(5)	40	15 (R)	52
5[d]	6h	DCM	20(5)	38	9(R)	52
6[e]	6 h	CH_3CN	4(5)	60	0(R)	32
7[f]	6h	THF	30(5)	25	10 (R)	65

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[13-14] $[\alpha]_D^{25} = 33$ (*c* 0.75, 1N HC1) 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 CH3CN (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

S. No.	Volume of acetone (mL)	Chiral 39 obtained from			
		Precipitate		Filtrate	
		%ee[a]	Yield(%)	%ee[a]	Yield (%)
1[a]	10	5(5)	62	0	27
2[a]	20	10(5)	50	0	40
3[a]	30	15(5)	48	5 (R)	43
4[a]	40	20 (5)	38	9(R)	52
5"	50	25 (5)	31	15 (R)	58
6[a]	60	32(*S*)	28	24 (R)	62
T	70	45(5)	24	38 (R)	65
8[b]	40	22(5)	40	10 (R)	52
9[b]	50	30(5)	30	25 (R)	62

a. 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.

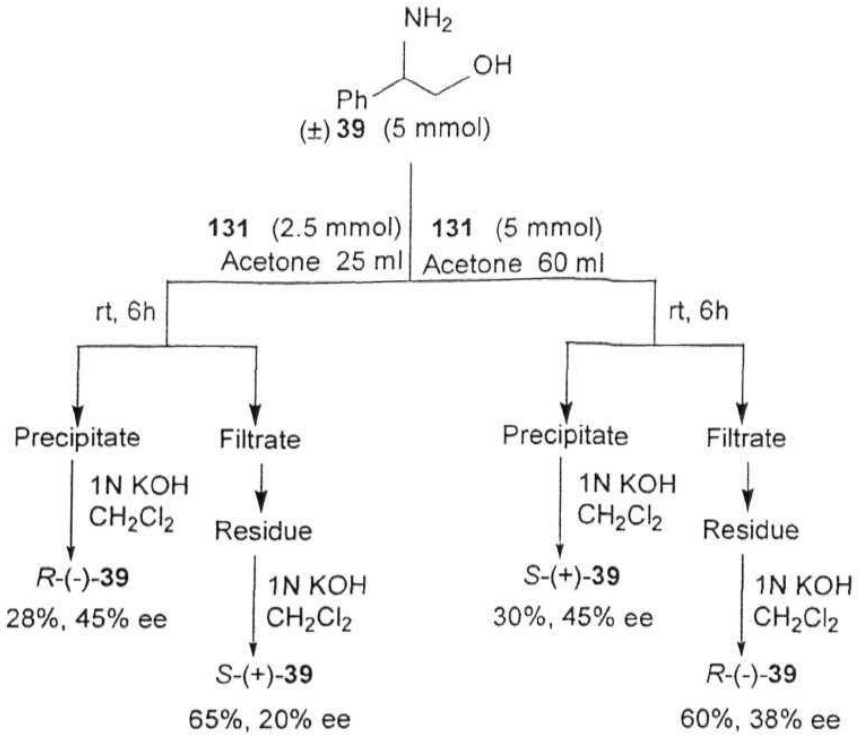
b. Racemic phenylglycinol (5 mmol) dissolved in acetone (30 mL) was added to the solution of dibenzoyl-L-tartaric acid (5 mmol) in acetone (30 mL) and the contents were stirred at 25°C for 6 h.

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.

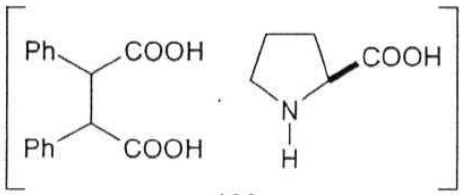
Scheme 44



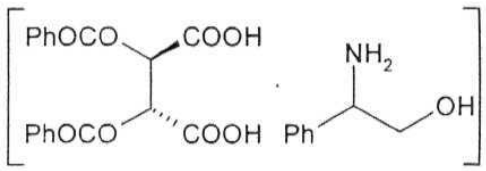
Whereas the phenylglycinol 39 enriched in (*S*) isomer precipitated when dibenzoyl-L-tartaric acid was used in 1:1 ratio, the 39 enriched in *(R)* isomer

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.[111] A similar complex 133 could be expected in the resolution of phenylglycinol using dibenzoyl-*L*-tartaric acid.



132



133

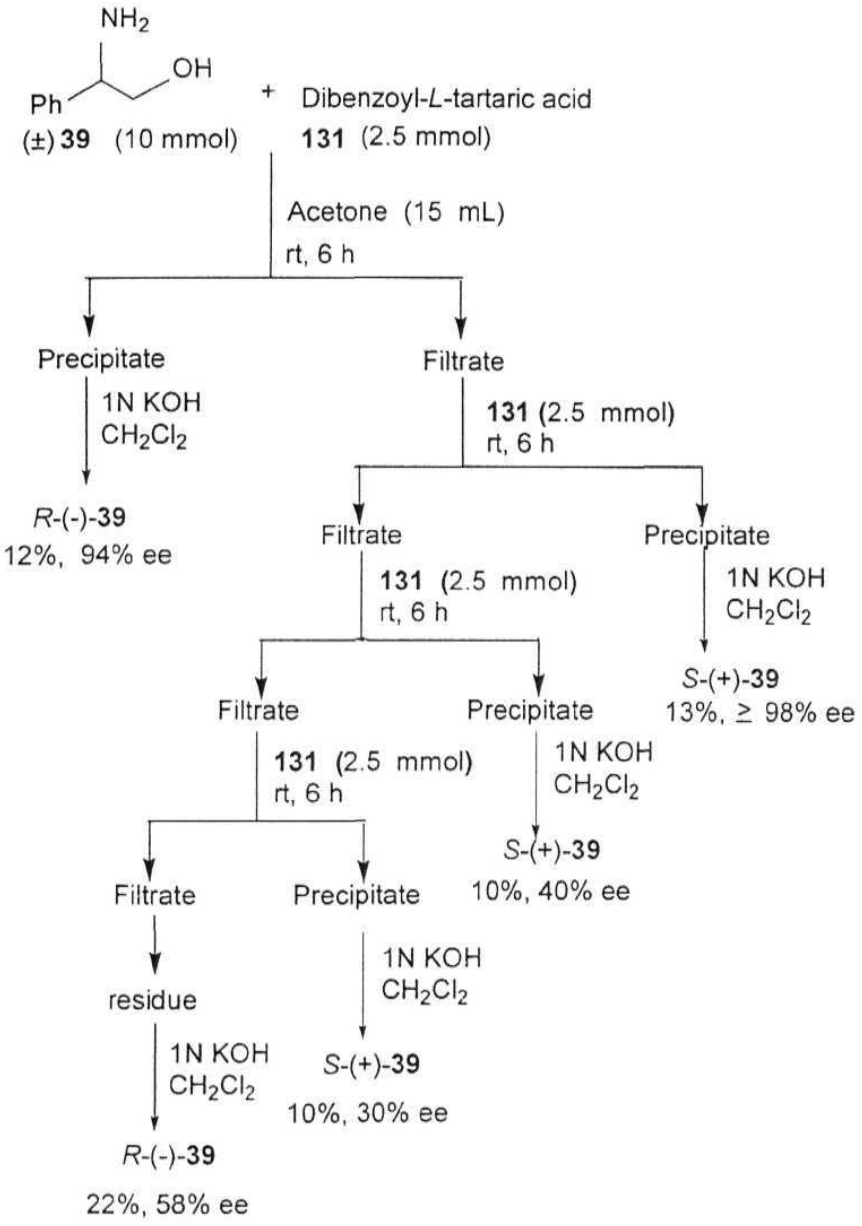
We have attempted crystal structure analysis of the complex prepared using 1:1 mixture of *S*-(+)-phenylglycinol 39 and dibenzoyl-*L*-tartaric acid 131. The complex was recrystallised from isopropanol to get crystal suitable for X-ray analysis. Although, the X-ray data were not satisfactory ("R" factor = 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

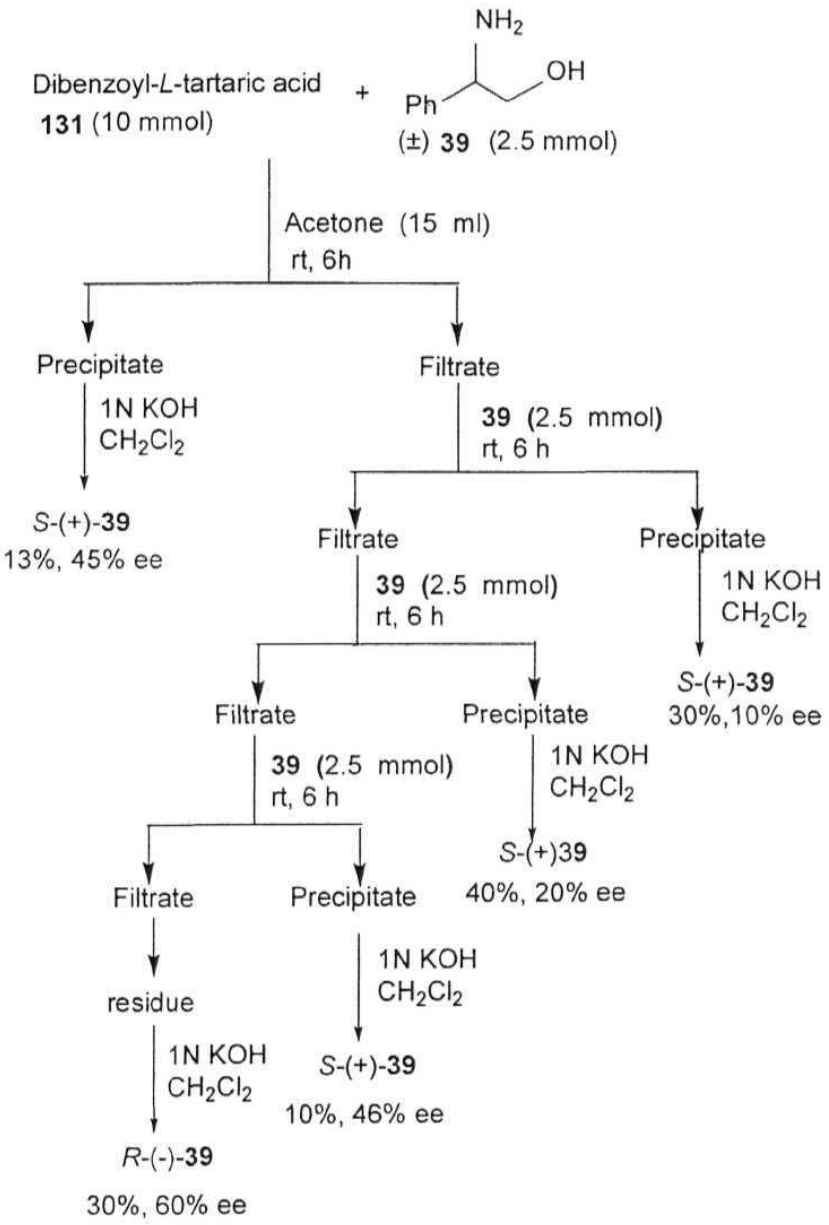
precipitate fraction (Scheme 44). Accordingly, we have carried out an experiment taking phenylglycinol in acetone and adding dibenzoyl-L-tartaric acid in portions successively to obtain the complex as precipitate. In this way, a sample of 39 enriched in *(R)* isomer was obtained in 94% ee and a sample 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


NH2
OH
Ph
(±) 39 (10 mmol)
+ Dibenzoyl-L-tartaric acid
131 (2.5 mmol)
Acetone (15 mL)
rt, 6 h
Precipitate
1N KOH
CH2Cl2
R-(-)-39
12%, 94% ee
Filtrate
131 (2.5 mmol)
rt, 6 h
Filtrate
Precipitate
131 (2.5 mmol)
rt, 6 h
1N KOH
CH2Cl2
S-(+)-39
13%, ≥ 98% ee
Filtrate
Precipitate
131 (2.5 mmol)
rt, 6 h
1N KOH
CH2Cl2
S-(+)-39
10%, 40% ee
Filtrate
Precipitate
residue
1N KOH
CH2Cl2
1N KOH
CH2Cl2
S-(+)-39
10%, 30% ee
R-(-)-39
22%, 58% ee

Scheme 46


Dibenzoyl-L-tartaric acid
131 (10 mmol)
+
NH2
OH
Ph
(±) 39 (2.5 mmol)
Acetone (15 ml)
rt, 6h
Precipitate
1N KOH
CH2Cl2
S-(+)-39
13%, 45% ee
Filtrate
39 (2.5 mmol)
rt, 6 h
Filtrate
Precipitate
1N KOH
CH2Cl2
S-(+)-39
30%,10% ee
39 (2.5 mmol)
rt, 6 h
Filtrate
Precipitate
1N KOH
CH2Cl2
S-(+)39
40%, 20% ee
39 (2.5 mmol)
rt, 6 h
Filtrate
Precipitate
residue
1N KOH
CH2Cl2
1N KOH
CH2Cl2
S-(+)-39
10%, 46% ee
R-(-)-39
30%, 60% 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**).

Table 6: Effect of volume of solvent on the resolution of (±)-phenylalaninol 49

S. No.	Ratio	Acetone (mL)	Chiral 49 obtained from			
			Precipitate		Filtrate	
			%ee[b]	Yield (%)•	%ee[b]	Yield(%)
1[a]	1:1	40	40(6)	32	18 (*R*)	62
2[a]	1:1	50	42(6)	30		60
3[a]	1:1	60	45(6)	35	**20** (*R*)	55
5[c]	2:1	25	20(6)	20	10 (*R*)	75
4[d]	1:1	50	>99(5)	20	20 ***(R)***	68
6[e]	2:1	50	>99(6)	15	10 ***(R)***	73

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 the acetone and the contents were stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum[13-14] $[\alpha]_D^{25}$ = 23 (*c* 1.2, 1N HC1) for both (*R*)-**49** and (5)-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

S. No.	Acetone (mL)	Chiral 73 obtained from			
		Precipitate		Filtrate	
		%ee[b]	Yield (%)	%ee[b]	Yield (%)
1[a]	40	13 (*S*)	18	5(7?)	70
2[a]	50	18 (*S*)	20	10 (*R*)	70
	60	23 (*S*)	20	12(7?)	70
4[c]	60	21(5)	20	10 (*R*)	70
5[d]	60	18(5)	22	10 (*R*)	69
6[e]	60	10 (*R*)	20	2(5)	72
7[f]	60	40 (*R*)	15	18(5)	75
8[g]	60	25 (*R*)	12	9(5)	77
9[h]	60	12 (7?)	15	8(5)	75
10[i]	60	5 (*R*)	22	0	68

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[13,14] $[\alpha]_D^{27}$ = 17 (*c* 10, C_2H_5OH) 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

S. No.	Condition	Chiral 129 obtained from			
		Precipitate		Filtrate	
		%ee[b]	Yield (%)	%ee[b]	rteld(%r
1[a]	rt, 6 h	30 *(R)*	20	10 (S)	**70**
2[b]	rt, 12 h	25 *(R)*	22	12 (S)	68
3[c]	rt, 6 h	*1\(R)*	25	20 (S)	67
4[d]	rt, 12 h	70 *(R)*	28	10 (S)	65

a. Unless otherwise mentioned all the reactions were performed using racemic 2-amino butanol (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 $[\alpha]_D^{25}$ = 12.5 (C 5, C2H5OH) for both (*S*)-**129** and (*R*)-**129** isomer.
c. Racemic 2-amino butanol (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

S. No.	Substrate %ee	Solvent	Amino alcohols obtained from			
			Precipitate		Filtrate	
			%ee[a]	Yield (%)[b]	%ee[a]	Yield(%)[b]
1	(*S*)-**39**, 45	Acetone	>98(5)	52	27 (*R*)	38
2	(*R*)-**39**, 38	Acetone	94 (*R*)	53	30(5)	34
3	*(R)* 49 20	Acetone	61 *(R)*	25	9(5)	60
4	(*R*)-**49**, 61	Acetone	> 97 *(R)*	52	0	35
5	(5)-73, 25	Acetone	30 (*S*)	20	14 (*R*)	55
6	(*R*)-**73**, 40	CH_3CN	**47 *(R)***	22	10(5)	52
7	(*R*)-**129,** 71	Acetone	*9S(R)*	42	20(5)	48
8	(*S*)-**129**, 20	Acetone	50(5)	25	7 (*R*)	60
9	(*S*)-**129,** 50	Acetone	>98(5)	32	4 (*R*)	58

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 (5)-isomer. The sample enriched in (*R*)-isomer with 35% ee was further

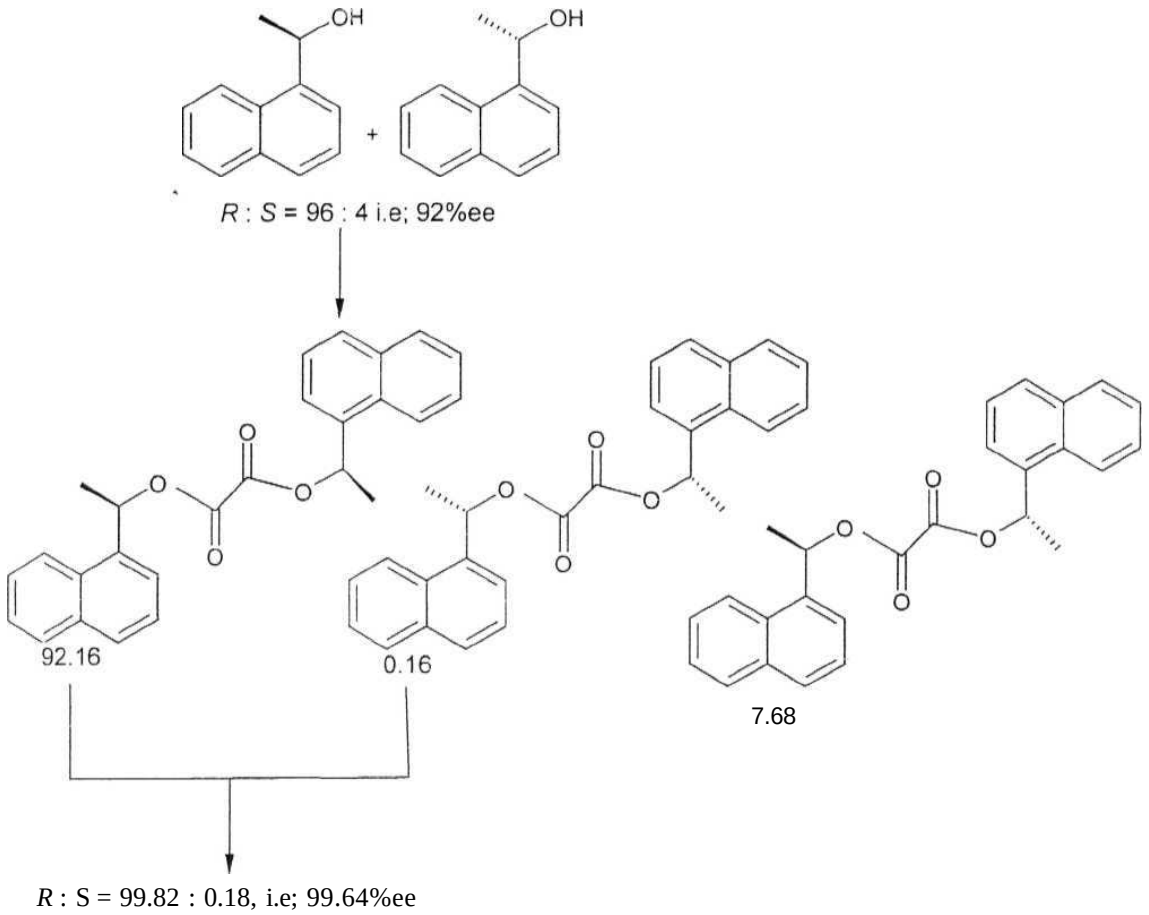
enriched to obtain the sample of > 97%ee (entry no.4 and 6, Table 8). Similar results were obtained in the case of non-racemic phenylalaninol 49, valinol 73 and 2-aminobutanol **129** as summarized in Table 9.

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[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[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.

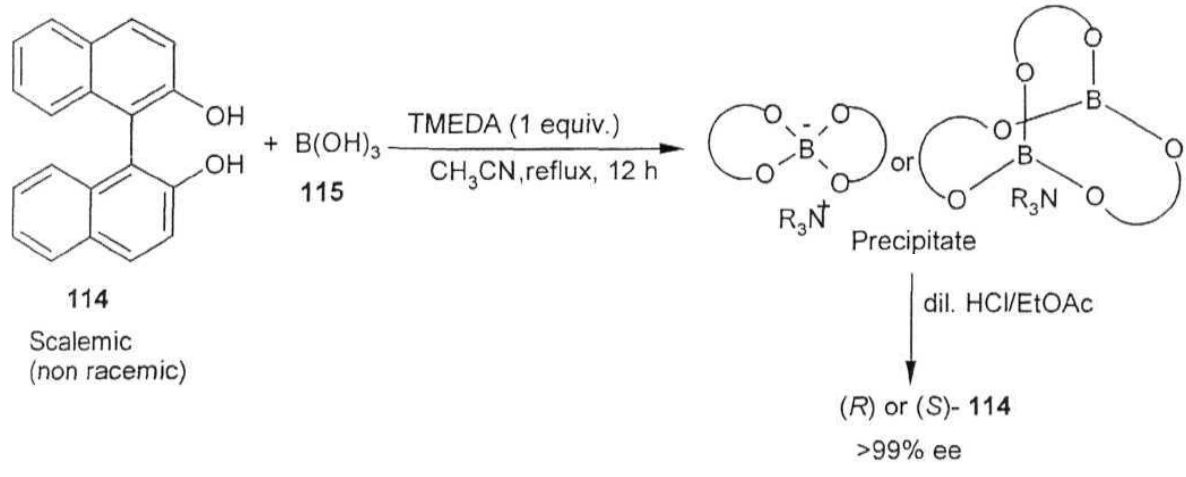
Scheme 47



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%.

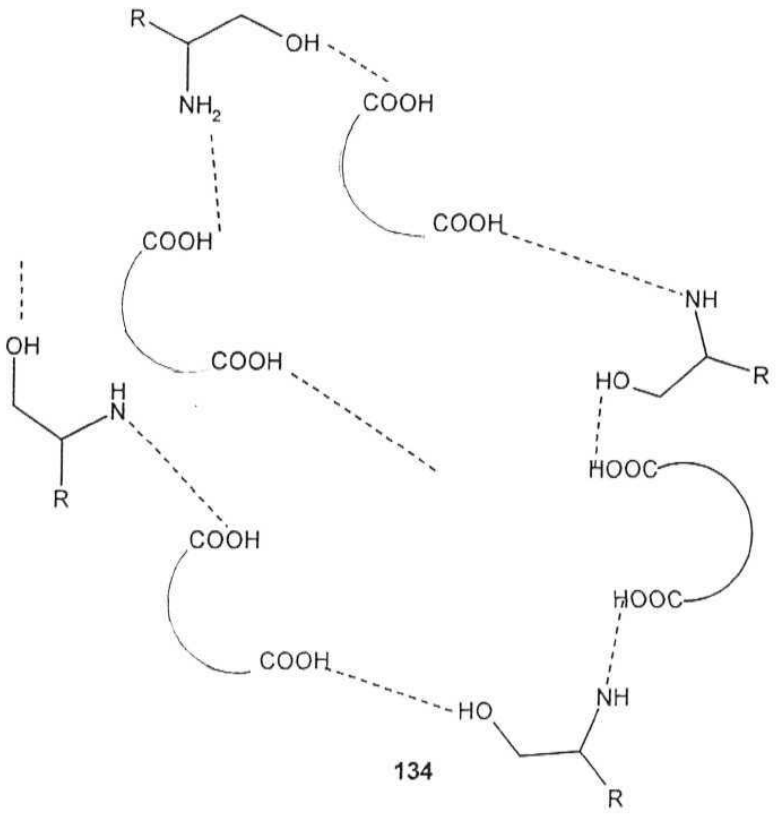
Previously, it was discovered in this laboratory that the scalemic 1,1'-bi-2-naphthol was enriched to obtain samples of 99% ee using inexpensive $B(OH)_3$ and TMEDA.[104c] In this case, the precipitate fraction gave the enriched isomer, leaving behind the mixture with low ee in solution. When the $B(OH)_3$ was used in lesser amounts, the borate complex derived from the enantiomer present in excess precipitated out (Scheme 48).

Scheme 48



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.

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

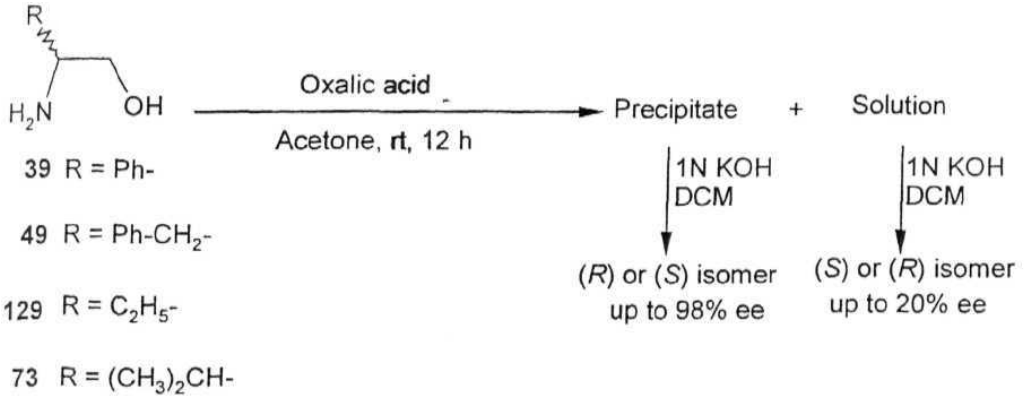


Table 10: Enrichment of enantiomeric excess of non-racemic phenylglycinol using oxalic acid

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

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

S. No.	Substrate (73) (5 mmol) % ee	Oxalic acid (mmol)	Valinol obtained from			
			Precipitate		Filtrate	
			%ee[a]	Yield (%)[b]	%ee[a]	Yield(%)[b]
1[a]	20 (*R*)	LO	35 (*R*)	15	03(7?)	75
	35 (7?)	1.5	50(7?)	32	06(7?)	58
3[a]	50 (7?)	2.5	70(7?)	45	05(7?)	43
4[a]	70 (7?)	3.5	87(7?)	64	09(7?)	25
5[a]	87 (*R*)	4.25	98(7?)	80	15(7?)	12
6	15(5)	0.75	35(5)	12	06(5)	78
7	30 (*S*)	1.5	45(5)	28	05(5)	60
8	45(5)	2.25	60(5)	42	06(5)	48
9	60(5)	3.0	75(5)	58	10(5)	30
10	75(5)	3.75	90(5)	70	22(5)	20
11	90(5)	4.5	98(*S*)	87	25(5)	8

a. 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

S. No-	Substrate (49) (5 mmol) % ee	Oxalic acid (mmol)	Phenylalaninol obtained from			
			Precipitate		Filtrate	
			%ee[a]	Yield (%)[b]	%ee[a]	Yield(%)[b]
1	17 (*R*)	0.85	33 *(R)*	20	03 (*R*)	72
2	33 *(R)*	1.75	70 *(R)*	40	09 *(R)*	50
3	50(7?)	2.5	98 *(R)*	60	20 (*R*)	30
4	20(5)	1.0	35(5)	25	06(5)	65
5	35 (5)	1.75	75(5)	40	09(5)	50
6	50(5)	2.5	98(5)	58	15(5)	35

a. 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

S. No.	Substrate **(129)** (5 mmol) % ee	Oxalic acid (mmol)	2-Aminobutanol obtained from			
			Precipitate		Filtrate	
			%ee[a]	Yield (%)[b]	%ee[a]	Yield (%)
1	20 (*R*)	1.0	35 *(R)*	25	03 (*R*)	65
2	37 *(R)*	1.85	50(7?)	40	09 Off)	50
3	55 *(R)*	2.75	98 *(R)*	62	18 (*R*)	30
4	18(5)	0.9	36 (5)	22	06(5)	70
5	36 (*S*)	1.8	52 (*S*)	40	09(5)	50
6	52(5)	2.6	98(5)	60	15(5)	30

a. All the reactions were performed using non-racemic 2-amino butanol (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[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.

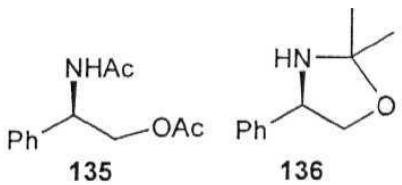
It was reported[115] that absolute configuration of certain amino alcohols could be determined by measuring their ^1H NMR spectra in the presence of optically active l,r-bi-2-naphthol in higher magnetic fields. Hence, we have undertaken efforts to determine the enantiomeric excess of 1,2-amino alcohols using 1,1'-bi-2-naphthol by ^1H 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 ^1H 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 l,2-diphenylethane-l,2-diol was analysed in this laboratory using the chiral shift reagent Eu(fod)$_3$.[118] Accordingly, we have prepared the derivatives **135** and **136** following closely related reported procedures.[54]



135 **136**

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 ^1H 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 l,l'-bi-2-naphthol and $B(OH)_3$. The $NaBH_4/I_2$ 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 (5 = 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 mμ 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. $NaBH_4$ was purchased from Lancaster Synthesis Ltd., UK. Iodine supplied by E–Merck, India was used. Chiral l,l'-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-Ka (λ = 0.71073 A^0) 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.[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

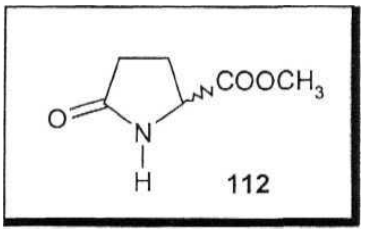
1. 4. 2. 1 Synthesis of racemic 2-pyrroIidone-5-carboxylic acid methyl ester

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



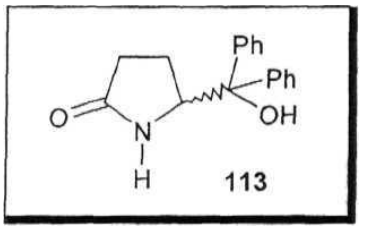
112

1. 4. 2. 2 Grignard reaction of 2-pyrroIidone-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)



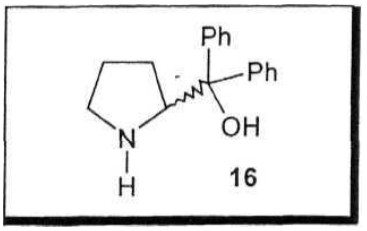
113

Yield	2.0 g (78 %)
M.p.	180-182 °C
IR (neat)	(cm^{-1}) .3357, 168
^{1}H NMR	(S ppm, $CDCl_3$) 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)
^{13}C-NMR	(δ ppm, $CDCl_3$) 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 $NaBH_4/I_2$ system

$NaBH_4$ (0.57 g, 15 mmol) was added to a stirred solution of **113** (1.33 g, 5 mmol) in THF. I? (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 (±)-α,α-diphenyl-2-pyrrolidinemethanol 16.



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 (±)-α,α-diphenyl-2-pyrrolidinemethanol (DPPM) 16 (2.53 g, 10 mmol) was refluxed under nitrogen atmosphere in CH3CN (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. HC1 (5N, 25 mL)

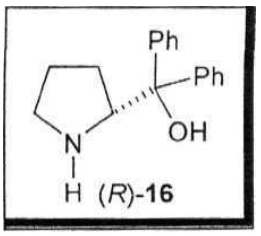
and stirred until complete dissolution occurs. The (*R*)-(+)-1,1'-bi-2-naphthol (92%) was recovered from the ether layer. The aqueous layer was treated with aqueous NaOH (1N, 20 ml)/ether (50 ml) and the free amino alcohol was extracted with ether (2 x 25 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (90% ee). The filtrate was concentrated and the residue was digested in a mixture of ether (50 mL) and dil. HC1 (5N, 25 mL). After work up as outlined above, the amino alcohol (20% ee) was isolated.

After **decomposition:**

From precipitate:

Yield 0.22 g (18%)

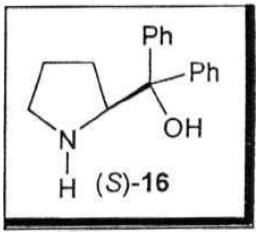
$[\alpha]_D^{25}$ (+) 62.1 (c 3, $CHCl_3$), {lit[24] for 100% ee, $[\alpha]_D^{25}$ = (+) 69.0 (*c* 3, $CHCl_3$)}



From filtrate:

Yield 1.0 g (80%)

$[\alpha]_D^{25}$ (-) 13.5 (*c* 3, $CHCl_3$), {lit[24] for 100% ee, $[\alpha]_D^{25}$ = (-) 69.0 (*c* 3, $CHCl_3$)}



1. 4. 2. 5 Enrichment of enantiomeric excess of partially resolved racemic DPPM 16 using (*R*)-(+)-1,1'-bi-2-naphthol and boric acid

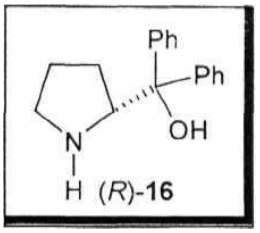
A mixture of (*R*)-(+)-1,1'-bi-2-naphthol (2.86 g, 10 mmol), $B(OH)_3$ (0.30 g, 5 mmol) and the partially enriched α,α-diphenyl-2-pyrrolidinemethanol (90% ee, 10 mmol) was refluxed under nitrogen atmosphere in CH3CN (20 mL) for 12 h. The reaction mixture was filtered while hot and washed with acetonitrile. The precipitate was suspended in a mixture of ether (50 mL) and dil. HC1 (5N, 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 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 $MgSO_4$. The solvent was evaporated to obtain (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (>99% ee). The filtrate obtained was concentrated and the residue was digested in the mixture of ether (50 mL) and dil. HC1 (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%)

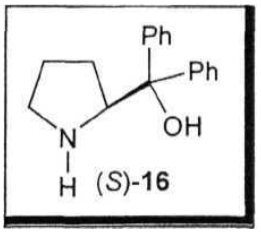
$[\alpha]_D^{25}$ (+) 69 (*c* 3, $CHCl_3$)



From **filtrate:**

Yield 1.0 g (42%)

[a]$_D^{25}$ (-) 16.9 (*c* 3, $CHCl_3$)



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

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

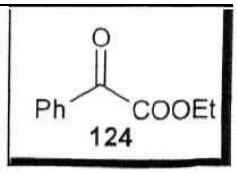
Typical procedure: Magnesium turnings (2.42 g, 100 mmol) in dry THF (60 mL) were taken in a two-necked RB flask. Freshly distilled bromobenzene (10.53 g, 100 mmol) in dry THF (30 mL) was added drop wise through the pressure equalizer for 1 h. The contents were further stirred for 1 h.

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. HC1 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 vaccum distillation.

Yield 7.12 g (40%)

B.p. 135-138 °C/18 mm; lit.[14] 138-139 °C/18 mm



124

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 (S 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.

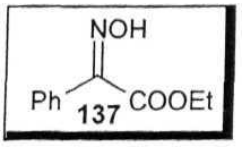
1. 4. 3. 2 Preparation of phenyl oxime ester 137 from ethyl phenylglyoxylate

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.

Yield 1.73 g (90%)

M.p. 130 °C



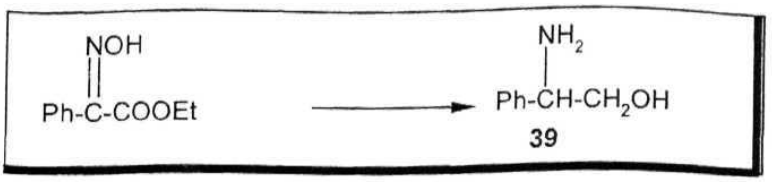
137

IR (neat) (cm^{-1}) 3307, 1724, 1602

^{13}C-NMR (5 ppm, $CDCl_3$) 14.2, 59.9, 125.2, 127.1, 129.4, 129.5, 153.6, 162.3

1. 4. 3. **3 Reduction of oxime of ethyl phenylglyoxylate to (±)-phenylglycinol 39**

$NaBH_4$ (0.57 g, 15 mmol) was added to a stirred solution of the oxime *of* ethyl phenylglyoxylate (0.97 g, 5 mmol) in THF. I_2 (1.9 g, 7.5 mmol) in THF was added through an addition funnel for 1h 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. 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.

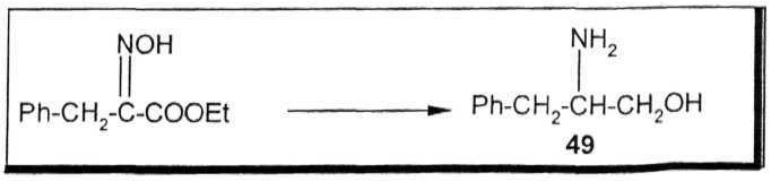


39

Yield	0.6g (85 %)
M.p.	72-75 °C: lit.[13] 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 a-keto esters. The data are given below.

1. 4. 3. 4 Reduction of oxime of ethyl benzylglyoxylate to (±)-phenylalaninol 49



Yield 0.6g (80 %)

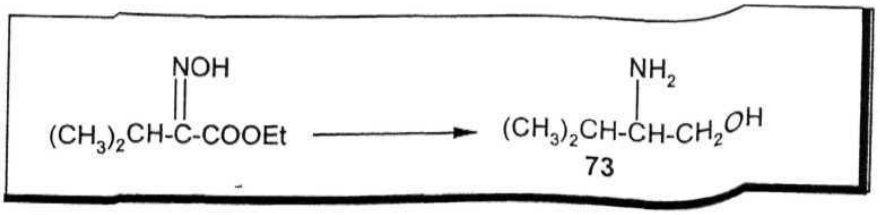
M. p. 92-94 °C; lit.[13] 93-95°C

IR (neat) (cm-[1]) 3350, 1053.

[1]H-NMR (5 ppm, $CDCl_3$) 1.8 (s, 3H), 2.5 (dd, J=8Hz, 1H), 2.7 (dd, J=5.6Hz, 1H), 3.1 (m, 1H), 3.3 (dd, J=6.6Hz, 1H), 3.62 (dd, J=3.8Hz, 1H), 7.2 (m, 5H) **(Spectrum** No. 5).

[13]C-NMR (S ppm, $CDCl_3$) 40.6, 54.2, 66.0, 126.4, 128.5, 129.2, 138.6 **(Spectrum No. 6).**

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



Yield 0.36 g (70 %)

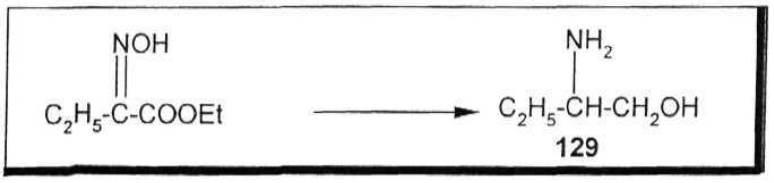
B. p. 77 °C/8 mm; lit. 75-77 °C/8 mm

[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



Yield 0.26g (60 %)

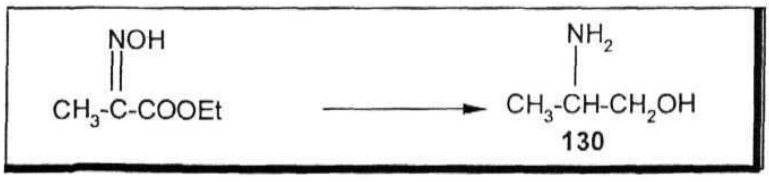
B.p. 176 °C; lit.[14] 176-178 °C

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).**

^{13}C-NMR (*5* ppm, $CDCl_3$) 10.4, 26.5, 54.3, 65.8 **(Spectrum No. 10).**

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



Yield 0.22 g (60%)

B.p. 165-167 °C; *Lit.*[14] 167-180 °C

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

^{13}C-NMR (5 ppm, $CDCl_3$) 17.2, 45.5, 65.6 **(Spectrum No. 11).**

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

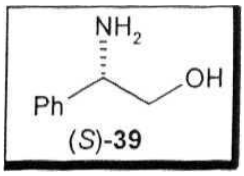
The dibenzoyl-*L*-tartaric acid (1.8 g, 5 mmol) and the (±)-phenylglycinol 39 (0.7 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at rt for 6 h and filtered. The precipitate was suspended in a mixture of DCM and 1N KOH and stirred until dissolution occurred. The organic extracts 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, 1N HC1), {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (+) 33.0 (*c* 0.75, 1N HC1}

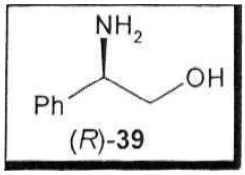


(*S*)-39

From filtrate:

Yield 0.42 g (60 %)

(-) 12.0 (c 1, 1N HC1) {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (-)33 (*c* 0.75, 1N HCl}}



(*R*)-39

1. 4. 3. **9 Purification of partially resolved phenylglycinol 39 using dibenzoy l-*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 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 (*S*)-(+)-phenylglycinol (> 98% ee). The filtrate was

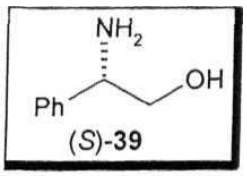
concentrated and the residue was digested as outlined above to obtain the product enriched in (*R*)-(-)-phenylglycinol (25% ee).

After decomposition:

From **precipitate:**

Yield 0.36 g (52 %)

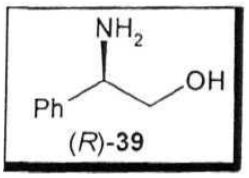
$[\alpha]_D^{25}$ (+) 32.3 (*c* 1, 1N HCl)



From **filtrate:**

Yield 0.26 g (38 %)

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



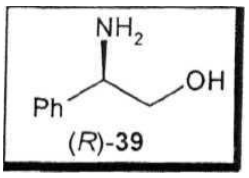
The partially resolved phenylglycinol 39 enriched in *(R)* isomer (25% ee, 5 mmol) was also further enriched by following the same procedure as outlined above.

After **decomposition:**

From precipitate:

Yield 0.37 g (53 %)

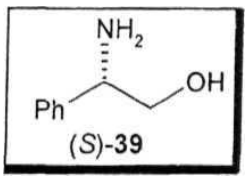
[a]* (-) 29.8 (*c* 1, 1N HCl)



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

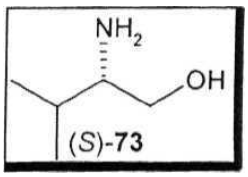
The same procedure as mentioned above was followed for the resolution of (±)-valinol 73 (5 mmol).

After decomposition:

From precipitate:

Yield 0.10 g (20%)

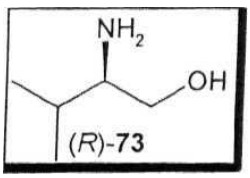
r]25 (+) 4.25 (*c* 5, C_2H_5OH), {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (+) 17.0 (*c* 10, C_2H_5OH)}



From filtrate:

Yield 0.35 **g (70 %)**

$[\alpha]_D^{25}$ (-) 1.6 (*c* 5, C_2H_5OH) {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (-) 17.0 (*c* 10, C_2H_5OH)}



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

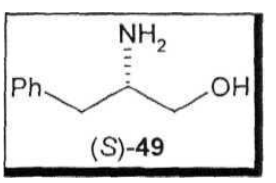
stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain the phenylalaninol enriched in (*S*) isomer. The filtrate was concentrated and the residue was digested as outlined above to obtain the phenylalaninol enriched in *(R)* isomer.

After decomposition:

From precipitate:

Yield 0.15 g (20%)

$[a]^{25}$ (-) 22.5 *(c* 1, 1N HC1) {lit[13] for 100% ee, $[\alpha]_D^{25}$= (-) 23.0 (*c* 1.2, 1N HCl}}

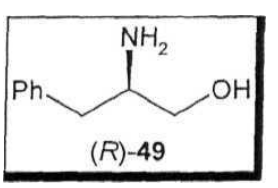


(*S*)-**49**

From **filtrate:**

Yield 1.0 g **(60%)**

r]25 (+) 4.6 (c 1, 1N HC1) {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (+) 23.0 *(c* 1.2, 1N HC1}}



(*R*)-**49**

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 (1.8g, 5mmol) in acetone (30 mL) and the contents were stirred at rt for 6 h and

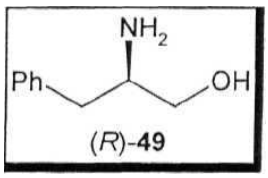
filtered. The precipitate was suspended in a mixture of DCM and 1N KOH and stirred until dissolution occurred. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and evaporated to dryness to obtain the phenylalaninol enriched in *(R)* isomer. The filtrate was concentrated 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 (*c* 1, 1N HC1) {lit[13] for 100% ee, $[\alpha]_D^{25}$ = (+) 23.0 (*c* 1.2, 1N HCl)}



(*R*)-**49**

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

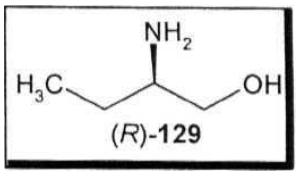
The procedure outlined as above was followed for the resolution and enrichment of the (±)-2-aminobutanol 129 (5 mmol).

After decomposition:

From precipitate:

Yield 0.11 g (25%)

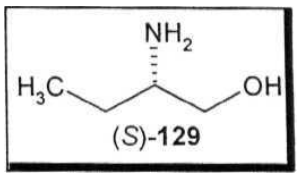
$[\alpha]_D^{25}$ (-) 9.0 (*c* 2, C_2H_5OH), {lit[15] for 100% ee, $[\alpha]_D^{25}$ = (-) 12.5 (*c* 2, C_2H_5OH)}



From filtrate:

Yield 0.29 **g (70 %)**

$[\alpha]_D^{25}$ (+) 2.5 (c 2, C_2H_5OH), {lit[15] for 100% ee, $[\alpha]_D^{25}$ = (+) 12.5 (*c* 2, C_2H_5OH)}



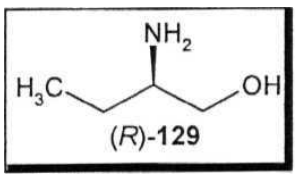
The partially resolved 2-aminobutanol **129** enriched in *(R)* isomer (71% ee, 5 mmol) was also further purified by following the same procedure as outlined above.

After decomposition:

From precipitate:

Yield 0.18 g (42%)

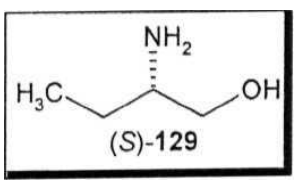
(-) 8.3 (*c* 5, C2H5OH).



From filtrate:

Yield 0 21 **g(48%)**

$[\alpha]_D^{25}$ (+) 2.5 (*c* 5, C_2H_5OH).



1. 4. 3. 14 Purification of scalemic (non-racemic or partially resolved) phenylglycinol 39 using oxalic acid

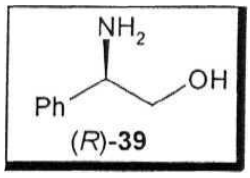
Typical procedure: The partially resolved (*R*)-(-)-phenylglycinol 39 (90% ee, 5 mmol) was taken in acetone (60 mL). Oxalic acid (0.45 g, 5 mmol) was added and the contents were stirred at rt for 12 h and filtered. The precipitate was suspended in a mixture of DCM and 1N KOH and stirred until the dissolution 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)

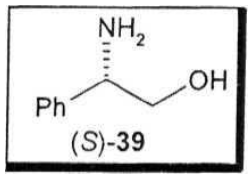


(*R*)-**39**

From filtrate:

Yield 0.07 g (10%)

$[\alpha]_D^{25}$ (+) 3.3 (c 0.75, 1N HCl)



(*S*)-**39**

1.4. 3. 15 Purification of scalemic phenylalaninol 49 using oxalic acid

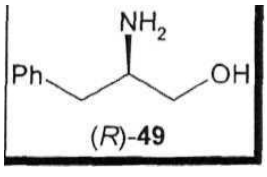
The same procedure as outlined above for the enrichment of non-racemic phenylglycinol 39 using oxalic acid was followed for the enrichment of non-racemic (*R*)-(+)-phenylalaninol 49 (92% ee, 5 mmol).

After decomposition:

From precipitate:

Yield 0.60 g (87%)

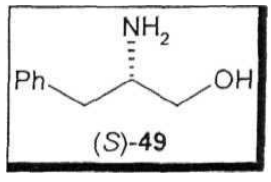
$[\alpha]_D^{25}$ (+) 32.6 (*c* 0.75, 1N HCl)



From filtrate:

Yield 0.03 g (5 %)

$[\alpha]^{25}$ (-) 6.8 (*c* 0.75, 1N HCl)



1.4. 3. 16 Purification of scalemic valinol 73 using oxalic acid

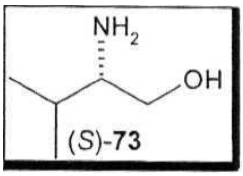
The same procedure as mentioned above for the enrichment of phenylglycinol 39 using oxalic acid was followed for the enrichment of enantiomeric excess of non-racemic (*S*)-(+)-valinol 73 (87% ee, 5 mmol).

After decomposition:

From precipitate:

Yield 0.40 g (80 %)

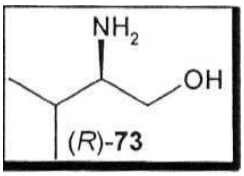
$[\alpha]_D^{25}$ (+) 16.6 (*c* 5, C_2H_5OH)



From filtrate:

Yield 1.0 g (60%)

$[\alpha]_D^{25}$ (-) 2.4 (*c* 5, C_2H_5OH)



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

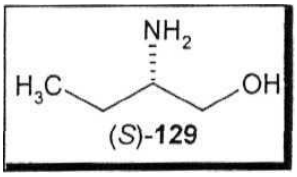
The procedure as outlined above for the enrichement of phenylglycinol 39 using oxalic acid was followed for the enrichment of non-racemic (*S*)-(+)-2-aminobutanol **129** (55% ee, 5 mmol).

After decomposition:

From precipitate:

Yield 0.28 g (62%)

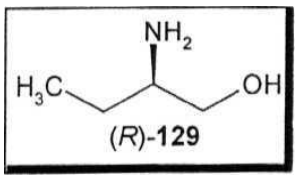
$[\alpha]_D^{25}$ (+) 12.2 (*c* 2, C_2H_5OH)



From filtrate:

Yield 0.13 g (30%)

$[\alpha]_D^{25}$ (-) 1.5 (*c* 2, C_2H_5OH)



1. 5 References

1. R. Howe and R. G. Shanks, *Nature*, **1966,** *210,* 1336.
2. A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.* **1953,** *75,* 4458.
3. A. Pohland, L. R. Peters and H. R. Sullivan, *J. Org. Chem.* **1963,** *28,* 2483.
4. E. J. Corey and J. O. Link, *J. Org. Chem.* **1991, *56,*** 442.
5. G. Protecter, *Asymmetric synthesis, Oxford University Press* Inc. New York, **1996,** Chapter 1.
6. D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.* **1996,** *96,* 835.
7. E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic compounds, John Wiley & Sons*, **1994.**
8. K. Tomioka, *Synthesis,* **1990,** 541.
9. R. Noyori and M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991,** *30,* 49.
10. H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.* **1960,** *82*, 681.
11. V. P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta.* **1948,** 31, 1617.

12. H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo and S. Yamada, *Chem. Pharm. Bull.* 1965, *13,* 995.

13. M. J. Mckennon and A. I. Meyers, *J. Org. Chem.* **1993**, *58,* 3568

14. Aldrich catalog handbook of fine chemicals, *Aldrich: Milwaukee,* **2001-2002.**

15. Fluka catalog of laboratory chemical and analytical Reagents, *Fluka*, **2001-2002.**

16. T. Naqvi, M. Bhattacharya and W. Haq, *J. Chem. Res. S.* **1999,** 424.

17. A. Abiko and S. Masamune, *Tetrahedron Lett.* **1992,** *33,* 5517..

18. R. Polt and M. A. Peterson, *Tetrahedron Lett.* **1990,** *31,* 4985.

19. J. V. B. Kanth and M. Periasamy, *Tetrahedron,1993, 49,* 5127.

20. D. Domimique and C. Maurice, *J. Chem. Soc. Perkin Trans* **1, 1994,** 3041.

21. J. A. Fehrentz, J. C. Califano, M. Amblard, A. Loffet and J. Martinez, *Tetrahedron Lett.* **1994,** 55, 569.

22. K. Ishizum, K. Koga and S. Yamada, *Chem. Pharm. Bull.* **1968,** *16,* 492

23. H. Takahashi, M. Hattori, M. Chiba, T. Morimoto and K. Achiwa, *Tetrahedron Lett.* **1986,** *27, 4411.*

24. F. A. Davis, M. S. Haque and R. M. Przeslawski, *J. Org. Chem.* **1989,** *54,* 2021.

25. L. E. Martinez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.* **1995,** 777,5897.

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

27. W. A. Nugent, *J. Am. Chem. Soc.* **1992,** *114,* 2768.

28. X. L. Hou, J. Wu, L. X. Dai and M. H. Tang, *Tetrahedron: Asymmetry,* 1998,9,1747.

29. H. Yamashita. *Chem. Lett.* **1987,** 525.

30. G. Sekar and V. K. Singh, *J. Org. Chem.* **1999,** *64,* 287 and reference cited therein.

31. Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538.

32. E. Herranz, K. B. Sharpless,, *J. Org. Chem.* **1980,** *45,* 2710.

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

34. A. Kamimura and N. Ono, *Tetrahedron Lett.* **1989**, *30,* 731.

35. T. K. Chakraborty, K. Azhar Hussain and G. Venkat Reddy, *Tetrahedron,* **1995**, *33*, 9179.

36. J. K. Whitesell, M. A. Whitesell, *J. Org. Chem.* **1977, 42,** 377.

37. A. I. Meyers, D. R. Williams, M. Druelinger, *J. Am. Chem. Soc.* **1976**, *98*, 3032.

38. D. Romo and A. I. Meyers, *Tetrahedron*. 1991, 47, 9503.

39. A. I. Meyers and G. P. Brengel, *J. Chem. Soc; Chem. Commun.* 1997, 1

40. A. I. Meyers and M. D. Groaning, *Tetrahedron*, 2000, 55, 9843.

41. L. N. Pridgen, J. Prol, B. Alexander and L. Gillyard, *J. Org. Chem;* 1989, 54,3231.

42. J. R. Gage and D. A. Evans, *Org. Synth.* 1990, 31, 1617.

43. D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.* 1982, *104*, 1737.

44. D. A. Evans, J. Bartroli and T. L. Shih. *J. Am. Chem. Soc.* 1981, *103*, 2127.

45. B. H. Lipshutz and T. A. Miller, *Tetrahedron Lett.* 1990, *31*, 5253.

46. P. O'Brien, S. E. De Sousa and P. Poumellec, *Tetrahedron: Asymmetry*, **1997**, *8*, 2613.

47. A. Claude, C. Francosis and E. Gwilherm, *Tetrahedron: Asymmetry*, **2002**, *13*, 297.

48. A. K. Douglas, L. A. Sharon, S. V. Gregorio and J. D. Sarah, *Org. Lett.* 2001,5,2781.

49. A. Claude, L. Dechoux and M. Melaimi, *Org. Lett.* **2000,** *2,* 633.

50. A. S. Demir, I. M. Akhmedov, Z. Gereck and R. A. Gadzhili, *Tetrahedron: Asymmetry,* **2002,** 73, 297.

51. K. Higashiyama, H. Inoue and H. Takahashi, *Tetrahedron,* **1994,** 50, 1083.

52. M. J. Wu and L. N. Pridgen, *Synlett.* **1990,** 636.

53. M. J. Wu and L. N. Pridgen, *J. Org. Chem.* **1991,** *56,* 1340.

54. K. R. K. Prasad and N. N. Joshi, *J. Org. Chem.* **1997,** *62,* 3770.

55. A. Hirao, S. Itsuno, S. Nakahama and N. Yamazaki, *J. Chem. Soc; Chem. Commun.* **1981**, 315.

56. E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.* **1987,** *109*, 5551.

57. E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen and V. K. singh, *J. Am. Chem. Soc.* **1987,** *109,* 7925.

58. E. J. Corey, R. K. Bakshi and S. Shibata, *J. Org Chem.* **1988,** 53, 2861.

59. E. J. Corey and J. O. Link, *Tetrahedron Lett.* **1989**, *30,* 6275.

60. E. N. Jacobsen, A. Pfaltz and H. Yammoto, *Comprehensive Asymmetric Catalysis I-III, Springer- Verlag Berlin,* **1999,** Chapter 6.4, 290.

61. D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsten, J. D. Carroll, E. G. Corley and E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58,* 2880.

62. T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. J. Jones, R. A. Reamer, F. E. Roberts and E. J. J. Grabowski, J. *Org. Chem.* **1991,** *56,* 763.

63. J. Wilken and J. Martens, *Liebigs. Ann. Rec.* **1997,** 563.

64. A. S. Demir, I. Mecitoglu, C. Tanyeli and V. Gulbeyaz, *Tetrahedron: Asymmetry,* **1997,** *8,* 335.

65. E. J. Corey, C. P. Chen and G. A. Reichard, *Tetrahedron Lett.* **1989,** *30,* 5547.

66. M. Masui and T. Shioiri, *Syn.Lett.* **1996,** 49.

67. G. J. Quallich and T. M. Woodall, *Tetrahedron Lett.* **1993,** *34,* 4145.

68. A. V. R. Rao, M. K. Gurjar, P. A. Sarma and V. Kaiwar, *Tetrahedron Lett.* **1990**, *31*, 2341.

69. I. K. Youn, S. W. Lee and C. S. Pak, *Tetrahedron Lett.* **1988,** *29*, 4453.

70. Y. H. Kim, D. H. Park and S. Byun II, *J. Org. Chem.* **1993,** *58,* 4511.

71. S. Wallbaum and J. Martens, *Tetrahedron: Asymmetry,* **1991,** *2,* 1093.

72. K. Stingel, J. Martens and S. Wallbaum, *Tetrahedron: Asymmetry,* **1992,** ***3,*** 223.

73. I. Reiners and J. Martens, *Tetrahedron: Asymmetry,* 1997, *8,* 227.

74. A. V. R. Rao, M. K. Gurjar and V. Kaiwar, *Tetrahedron:* Asymmetry, 1990,57,2341.

75. M. Nakagawa, T. Kawate, Tt. Kakikawa, H. Yamada, T. Matsui and T. Hino, *Tetrahedron*, 1993, *49,* 1739.

76. M. Falorni, C. Collu and G. Giacomelli, *Tetrahedron: Asymmetry,* 1996, 7, 2739.

77. L. Dubois, J. C. Fiaud and H. B. Kagan, *Tetrahedron: Asymmetry,* 1995, *6,* 1097.

78. Y. Hong, Y. Gao, X. Nie and C. M. Zepp, *Tetrahedron Lett.* 1994, *35,* 6631.

79. K. Tanaka, J. Matsui and H. Suzuki, *J. Chem. Soc; Chem. Commun.* 1991,1311.

80. T. Kunieda and T. Ishizuka, *J. Synth. Chem. Jpn.* 1997, *55,* 1018.

81. S. Itsuno, M. Naknao, K. Ito, A. Hirao, M. Ohwa, N. Kanada and S. Nakahama, *J. Chem, Soc;perkin Trans.* 1, **1983**,2615.

82. M. Felder, G. Giffels and C. Wandery, *Tetrahedron: Asymmetry,* 1997, 5, 975.'

83. A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron: Asymmetry,* **1998,** *9,* 1.

84. (a). E. J. Corey, N. Imai and H. Zhang, *J. Am. Chem. Soc.* **1991,** *113,* 728. (b). E. J. Corey and K. Ishihara, *Tetrahedron Lett.* **1992,** *33,* 6807.

85. (a). M. Johannsen and K. A. Jorgensen, *J. Org. Chem.* **1993,** *58,* 4511. (b) M. Johannsen and K. A. Jorgensen, *Tetrahedron,* **1996,** *52,* 7321.

86. K. V. Gothelf, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.* **1996,** *61,* 346.

87. K. Langer and J. Mattay, *J. Org. Chem.* **1995,** *60,* 7526.

88. (a). D. A. Evans, K. A. Woerpel, M. M. hinman and M. M. Faul, *J. Am. Chem. Soc.* **1991,** *113,* 726. (b). D. A. Evans, K. A. Woerpel and M. J. Scott, *Angew. Chem. Int. Ed. Engl.* **1992,** *31,* 430.

89. D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.* **1996,** 7/5,5814.

90. P. Von Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Ruegger, P. S. Pregosin, *Helv. Chim. Acta,* **1995,** 75,265.

91. M. Nakamura, M. Arai and E. Nakamura, *J. Am. Chem. Soc.* **1995,** *117,* 1179.

92. **I.** Iovel, Y. Popelis, M. Fleisher and E. Lukevics, *Tetrahedron: Asymmetry,* **1997,5,** 1279.

93. D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson and D. M. Barnes,./. *Am. Chem. Soc.* **1993,** *115*, 5328.

94. A. S. Gokhale, A. B. E. Mindis and A. Pfaltz, *Tetrahedron Lett.* **1995,** *36,* 1831.

95. H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo and K. Itoh, *Organometallic*,* **1989,** *8,* 846.

96. J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions, John Wiley & Sons, New York,* **1981.**

97. R. C. Kelly, I. Schletter, S. J. Stein and Wierenga, ./. *Am. Chem. Soc.* **1979,** 101, 1054.

98. M. H. A. Zarga and M. Shamma, *Tetrahedron Lett.* **1980,** *21,* 3739.

99. J. Jacques, C. Fouquey and R. Viterbo, *Tetrahedron Lett.* **1971,** 4617.

100. E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen and V. K. Singh, *J. Am. Chem. Soc;* **1987,** *109,* 7925.

101. M. M. Gharpure and A. S. Rao, *Synthesis,* **1988,** 410.

102. K. Faber, H. Honig and P. S. Wasserthal, *Tetrahedron Lett.* **1988,** *29,* 1903.

103. S. Miyano, L. D. L. Lu, S. M. Viti and K. B. Sharpless, *J. Org. Chem. Soc.* **1983,** *48,* 3608.

104. (a) M. Periasamy, *Pure & Appl. Chem.* **1996,** *68,* 663 (presented at the IUPAC International Conference in the Organic Synthesis (ICOS 9, December 11-16, **1994,** Abstract no. SL 36, Bangalore, India). (b) M. Periasmay, A. S. B. Prasad, J. V. B. Kanth and Ch. K. Reddy, *Tetrhedron: Asymmetry,* **1995,** 6, 341. (c) L. Venkatraman and M. Periasamy, *Tetrahedron: Asymmetry,* **1996,** 7, 2471. (d) M. Periasamy, L. Venkatraman and K. J. Thomas, *J. Org. Chem.* **1997,** 62, 4302. (e) M. Periasmay, C. R. Ramanathan, A. S. B. Prasad and J. V. B. Kanth, *Enantiomer,* **1998,** 5, 3. (f) C. R. Ramanathan and M. Periasamy, *Tetrahedron: Asymmetry,* **1998,** 9, 265. (g) M. Periasamy, L. Venkatraman, S. Sivakumar. N. S. Kumar and C. R. Ramanathan, *J. Org. Chem.* **1999,** *64,* 7643.

105. Z. Shan, Y. Xiong, W. Li and D. Zhao, *Tetrahedron: Asymmetry,* **1998,** *9,* 3985.

106. M. Periasmay, C. R. Ramanathan and N. S. Kumar, *Tetrahedron: Asymmetry,* **1999**, 10, 2307.

107. M. Periasamy, N. S. Kumar, S. Sivakumar, V. D. Rao, C. R. Ramanathan and L. Venkatraman, *J. Org. Chem.* **2001**, *66*, 3828.

108. K. Drauz, W. Jahn and M. Schwarm, *Chem. Eur. J.* **1995**, *1*, 538.

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

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

111. C. R. Ramanathan and M. Periasamy, *Tetrahedron: Asymmetry,* **1998,** *9*, 2651.

112. J. P. Vingneron, M. Dhaenens and A. Horeau, *Tetrahedron,* 1973, *29,* 1055.

113. I. Fleming and S. K. Ghosh, *J. Chem. Soc; Chem. Chem.* **1994,** 99.

114. C. Girard and H. B. Kagan, *Angew. Chem. Int. Ed. Engl.* **1998,** *37,* 2922.

115. F. Toda, K. Mori and A. Sato, *Bull, Chem. Soc. Jpn.* **1988,** *61*, 4167.

116. M. J. Shapiro, A. E. Archinal and M. A. Jarema, *J. Org. Chem.* **1989,** *54,* 5826.

117. M. Periasamy, S. Sivakumar and M. Narsireddy, unpublished results.

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

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

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

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

Chapter 2

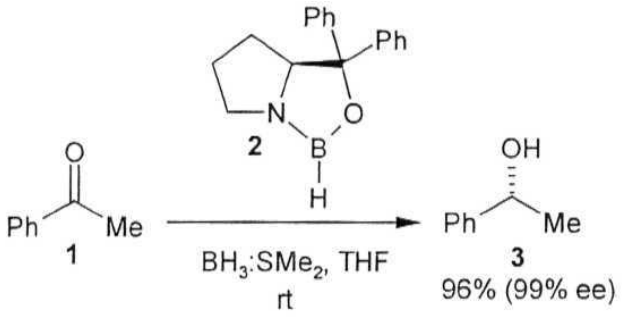
Asymmetric auto-inductive reduction of oxime derivatives of ethyl phenylglyoxylate using (R)-phenylglycinol

2. 1 Introduction

Chirality plays a central role in the fields of biological, chemical, pharmaceutical and material science. In recent years, spectacular progress has been achieved in the catalytic asymmetric processes. Indeed, catalytic asymmetric synthesis-2 has become the most desirable way of preparation of enantiomerically pure compounds.

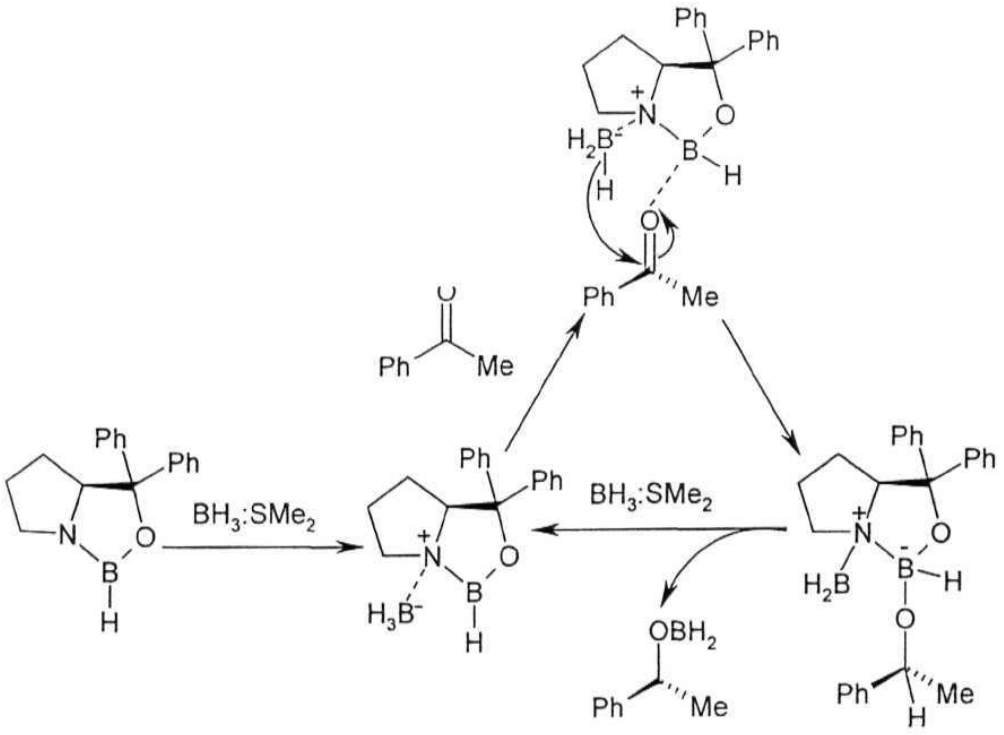
Production of asymmetric compounds in biological processes takes place through asymmetric catalysis. Such natural processes would go through the binding of the reactants to the active sites of the enzymes followed by chirality transfer. In most of the chemical systems, one of the reactants is bound to the chiral catalyst followed by the reaction with the other reactant present in the medium, to transfer chirality. In some cases, the asymmetric catalyst may bind with both the reactants followed by chirality transfer similar to enzymatic processes as observed in the Itsuno-Corey[3] oxazaborolidine catalysed asymmetric borane reduction (Scheme land 2).

Scheme 1



This reaction may occur by the following sequence: (a) complexation of borane to nitrogen (b) coordination of the ketone oxygen to the boron of oxazaborolidine (c) hydrogen transfer from the coordinated borane to the carbonyl via six-membered cyclic transition state (Scheme 2).

Scheme 2

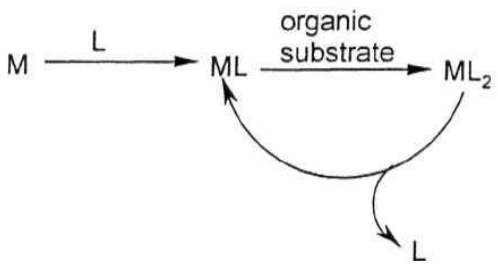


In this chapter, we have examined the possibility of developing an asymmetric autocatalytic process involving oxazaborolidine intermediates. Accordingly, it may be of interest to review the asymmetric autocatalytic processes developed so far by various research groups.

Asymmetric autocatalysis is an enantioselective synthesis, in which the chiral product acts as an asymmetric catalyst for it's own production. Asymmetric autocatalysis is expected to be an efficient method for the enantioselective auto-multiplication of a chiral molecule without the need for other chiral auxiliaries. Although, a mathematical model of asymmetric auto catalysis was suggested in 1953[4,5] and the implications of asymmetric autocatalysis have been discussed,[6-24] practical asymmetric autocatalytic processes have been discovered only very recently.

Duplication and replication of chirality through asymmetric autocatalytic process can be pictorially represented as shown in Scheme 3.

Scheme 3

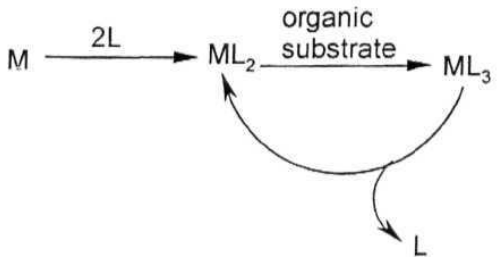


In an efficient autocatalytic process, the ML would preferentially form the homochiral ML_2 complex. If the product ML_2 does not decompose *in situ* to

produce ML and L after workup 2 moles of L would be isolated. Such a process would formally result in duplication of chirality.

If the starting complex is an ML_2 or ML_n or an aggregate containing several L, the process outlined in Scheme 4 may be realised.

Scheme 4



Since the ML_2 complex can be homo [i.e. *(R, R)* or *(S, S)*] or hetero [i.e. *(R, S)*], a non-linear effect could be expected (i.e. lower ee of starting L giving higher ec of product L) in addition to asymmetric autocatalysis, if the homochiral derivative is preferentially formed or it is more reactive. Although, such a model has been proposed[25] and suggested that this possibility may be realised in the reactions of transition metal complexes, such chemical processes have been widely realised in organozinc chemistry in recent years.

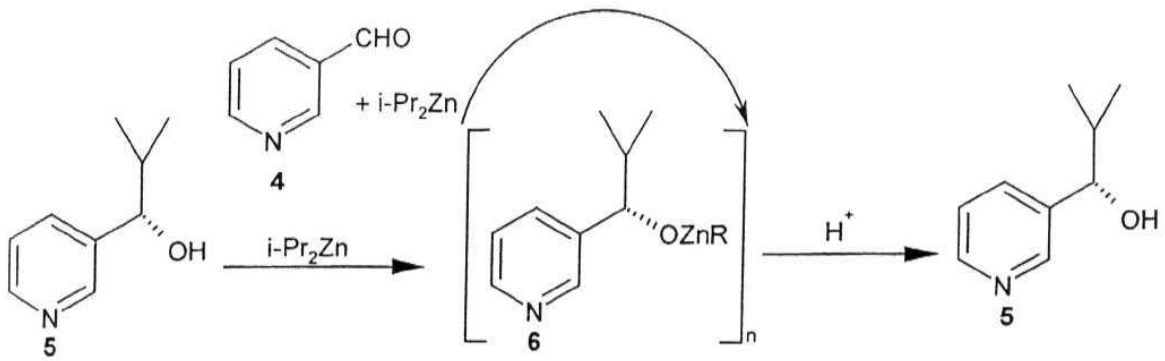
2. 1. 1 The asymmetric autocatalysis of organozinc addition

Soai *et al.*[26,33] reported the catalytic enantioselective addition of dialkylzinc to aldehydes using chiral 1,2-amino alcohols,[34] chiral piperazines[35] and chiral phosphoramidates.[36] They also examined the enantioselective addition of dialkylzinc to pyridine-3-carbaldehyde and benzaldehyde respectively, using

N, *N*-dibutyl-norephedrine as a chiral catalyst.[37] It was found that the reaction of pyridine-3-carbaldehyde is faster than that of benzaldehyde which suggests that the ethylzinc alkoxide of 3-pyridylalkanol formed *in situ*, may act as an asymmetric autocatalyst.

In 1990, Soai *et al.* reported the first asymmetric autocatalysis in the enantioselective addition of diisopropyl zinc to pyridine-3-carbaldehyde using catalytic amount of (*S*)-pyridylalkanol in which it was automultiplied, and the newly formed product possessed the same structure and configuration as the catalyst (Scheme 5). Chiral alkoxide 6 formed *in situ* from 4 and *i*-Pr_2Zn is considered to catalyze the enantioselective addition of *i*-Pr_2Zn to aldehyde to form itself.

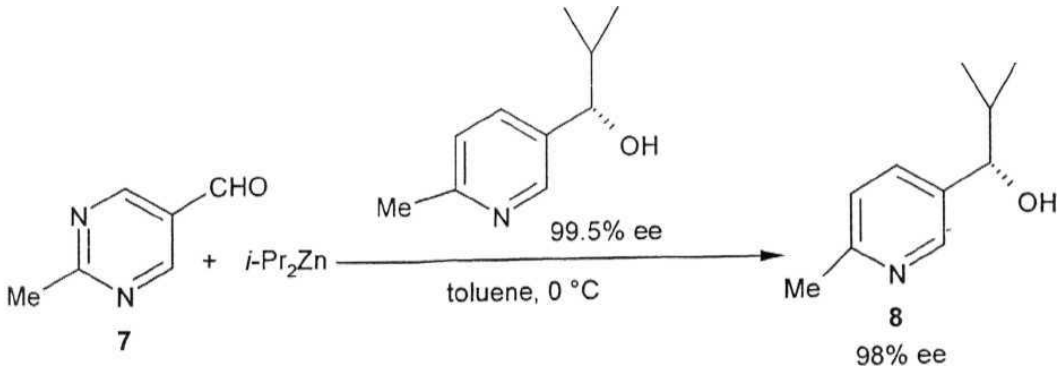
Scheme 5



When chiral (S)-pyrimidylalkanol 8 of 93% ee was used as an asymmetric autocatalyst, the newly formed (*S*)-product had an ee of 90%.[39] When chiral *(S)*-pyrimidylalkanol of 95%ee was used as an asymmetric autocatalyst, (*S*) automultiplied without any loss of enantiomeric purity. The ee of the newly

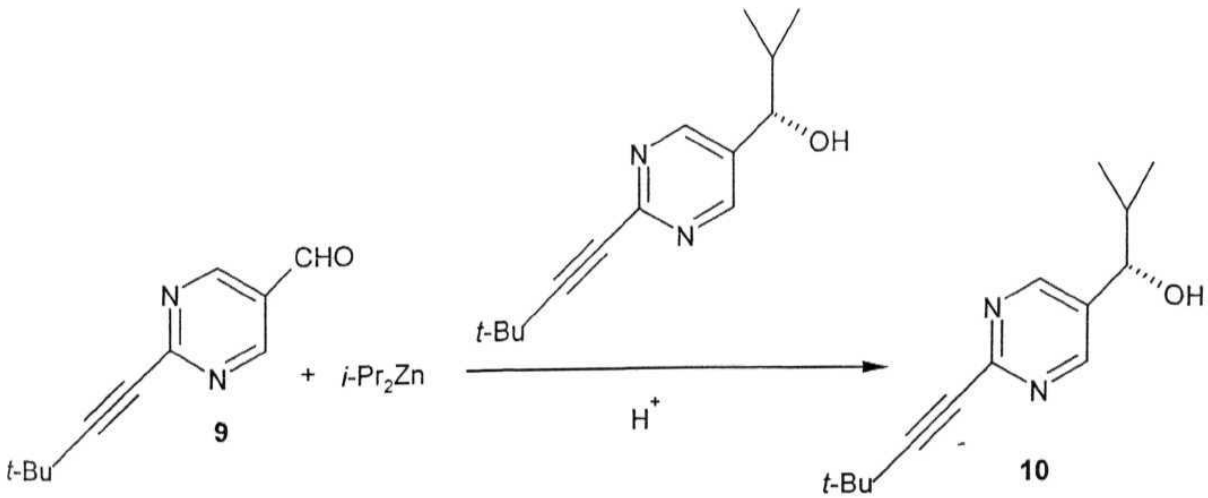
formed alkanol (*S*) reached 98%, when asymmetric autoctalyst (*S*) with >99.5% ee was used (Scheme 6).

Scheme 6



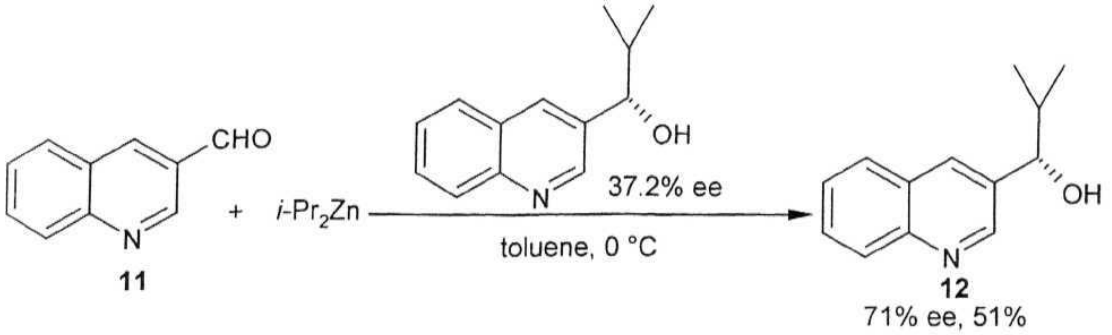
(*S*)-Pyrimidylalkanol 10 (>99.5% ee) automultiplied in >99% yield and >99 5%ee during the enantioselective addition of *i*-Pr_2Zn to 2-(tert-butylenyl)pyrimidine-5-carbaldehyde 9 in cumene at 0 °C (Scheme 7).

Scheme 7



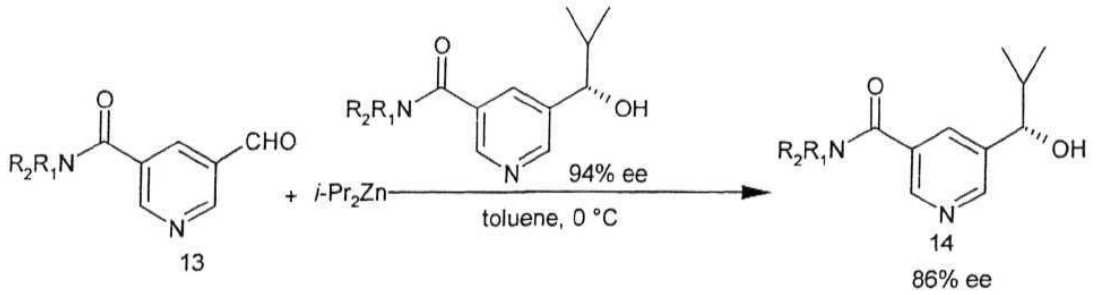
(*S*)-3-Quinoylalkanol 12 of 94% ee catalyses the enantioselective addition of *i*-Pr_2Zn to quinoline-3-carbaldehyde 11 to afford itself with 94% ee with the same configuration as the catalyst (Scheme 8).[41]

Scheme 8



Chiral (*S*)-(5-carbamoyl-3-pyridyl)alkanol catalyses the enantioselective addition of *i*-Pr_2Zn to 5-carbomyl-3-pyridine carbaldehyde to give itself in up to 86% ee with the same configuration as the catalyst (Scheme 9).[42]

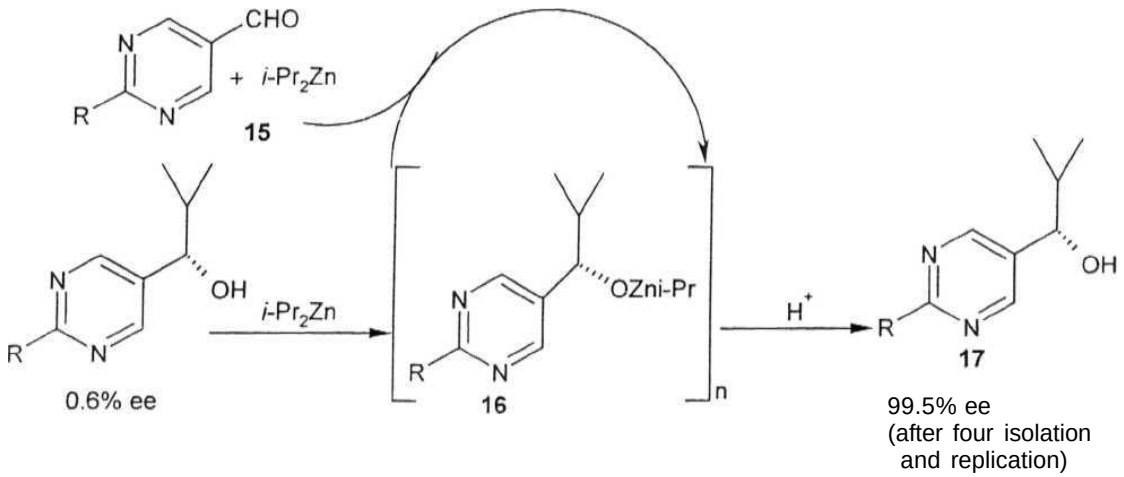
Scheme 9



It was observed that when chiral pyrimidylalkanol with a low ee *(0.6%)* was used as an asymmetric autocatalyst, the alkanol with the same configuration was obtained with higher ee (99%) in the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde.[43] Clearly, even when the initial ee of the asymmetric autocatalyst

is extremely low, there is considerable asymmetric amplification by consecutive asymmetric autocatalysis without using other chiral auxiliaries.[44-45]

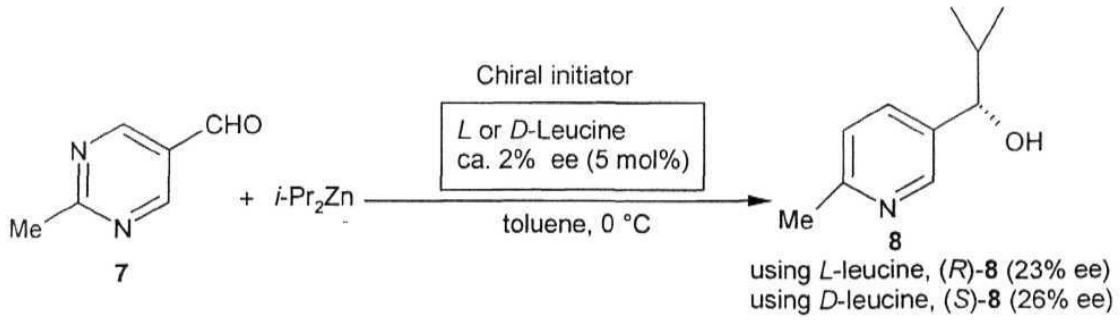
Scheme 10



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 slight enantiomeric imbalance will be expected to be enhanced by the subsequent one pot asymmetric autocatalysis of pyrimidylalkanol with an amplification of chirality.[46-50] This has been also realized, for example, in the asymmetric autocatalysis of pyrimidylalkanol 8, using leucine with a low ee as a chiral initiator. Leucine was chosen as chiral initiator because it is a biologically important α-amino acid. In the presence of *L*-leucine with *2%* ee, *i*-Pr_2Zn and 2-methylpyrimidine-5-carbaldehyde was added in portions (Scheme 11). The (*R*)-2-methyl-l(2-methyl-5-pyrimidyl)propan-l-ol with amplified ee of 23% was

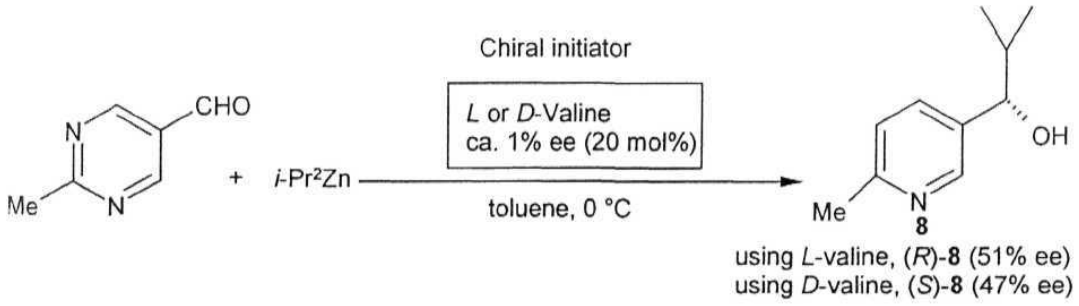
of D-leucine an amplified ee of 26% ee was realized in the formation of the corresponding (S)-isomer.[51]

Scheme 11



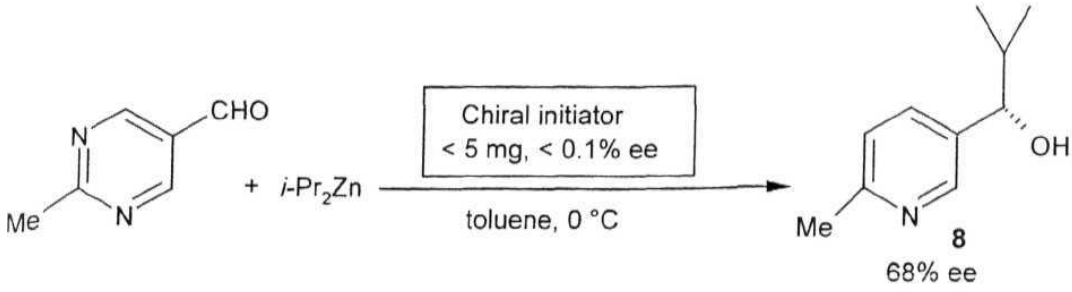
In presence of L and D-valine with ca. 1% ee (*R*) and (*S*)-pyrimidylalkanol with amplified ee of 51% and 47%, respectively were obtained (Scheme 12).[52]

Scheme 12



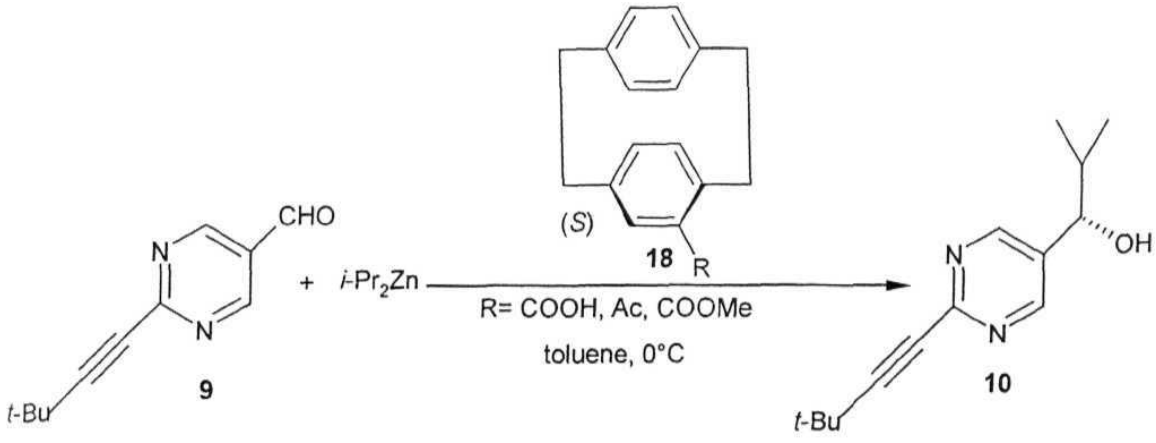
Apart from α-amino acids, several other chiral organic molecules of low ee (ca. 0.05-0.1%) were used to serve as chiral initiators in the asymmetric autocatalysis of pyrimidylalkanols. For example, (*S*)-methyl mandelate with 0.1% ee directed the formation of (*R*)-pyrimidylalkanol with 68% ee and the (S)-pyrimidylalkanol was obtained from (*R*)-methyl mandelate (Scheme 12).

Scheme 13



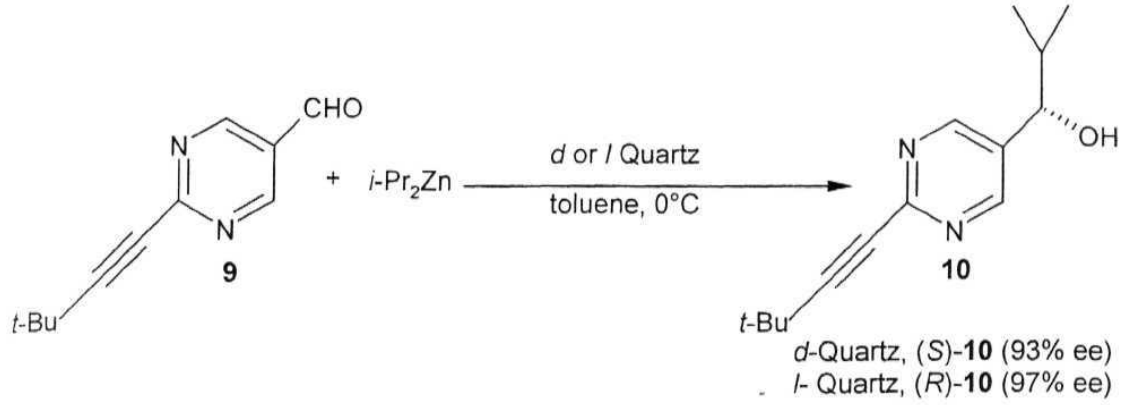
The planar chiral monosubstituted cyclophanes were found to act as chiral initiators in the enantioselective addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehyde to afford 2-alkynylpyrimidylalkanol 10 in up to 97% ee (Scheme 14).[54]

Scheme 14



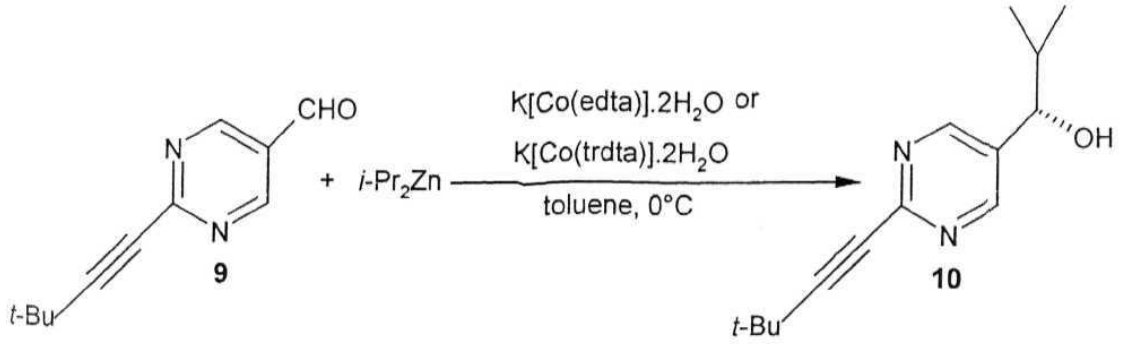
It is also remarkable that such enantioselective autocatalytic reactions have been conducted in the presence of (+)-quartz and (-)-quartz (Scheme 15). The former favoring the product possessing (S)-configuartion while the leavorotatory quartz produces (*R*)-isomer in high ee.[55]

Scheme 15



Chiral octahedral cobalt complexes, $K[Co(edta)].2H_2O$ and $K[Co(trdta)].2H_2O$, induce enantioselective addition of diisopropylzinc to pyrimidine carbaldehyde, affording the pyrimidylalkanol 10 with high (85-94%) enantiomeric excesses (Scheme 16).[56]

Scheme 16



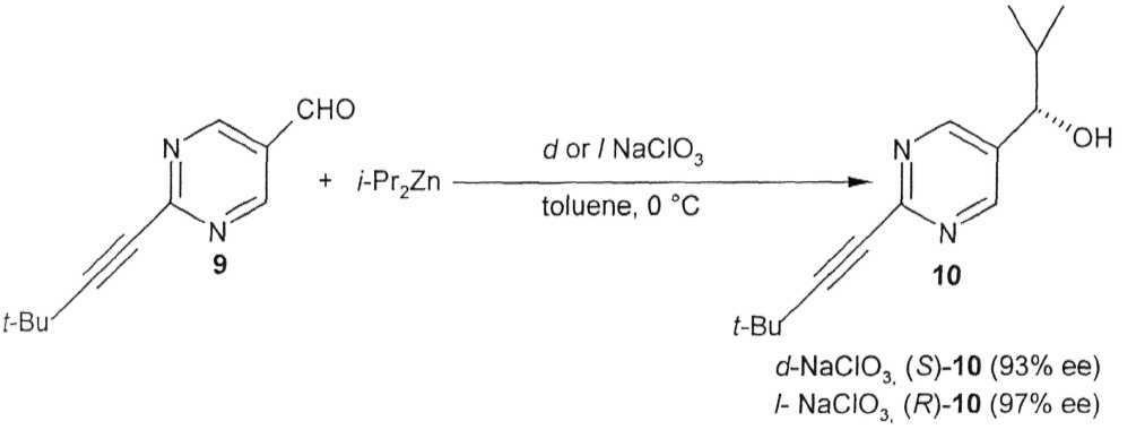
$K[Co(edta)].2H_2O$, (*S*)-**10** (91% ee)

$K[Co(trdta)].2H_2O$, (*R*)-**10** (88% ee)

In a subsequent study, the same team has used enantiomorphic crystal of sodium chlorate. Addition of crystals of dextrorotatory $NaClO_3$ to a solution of

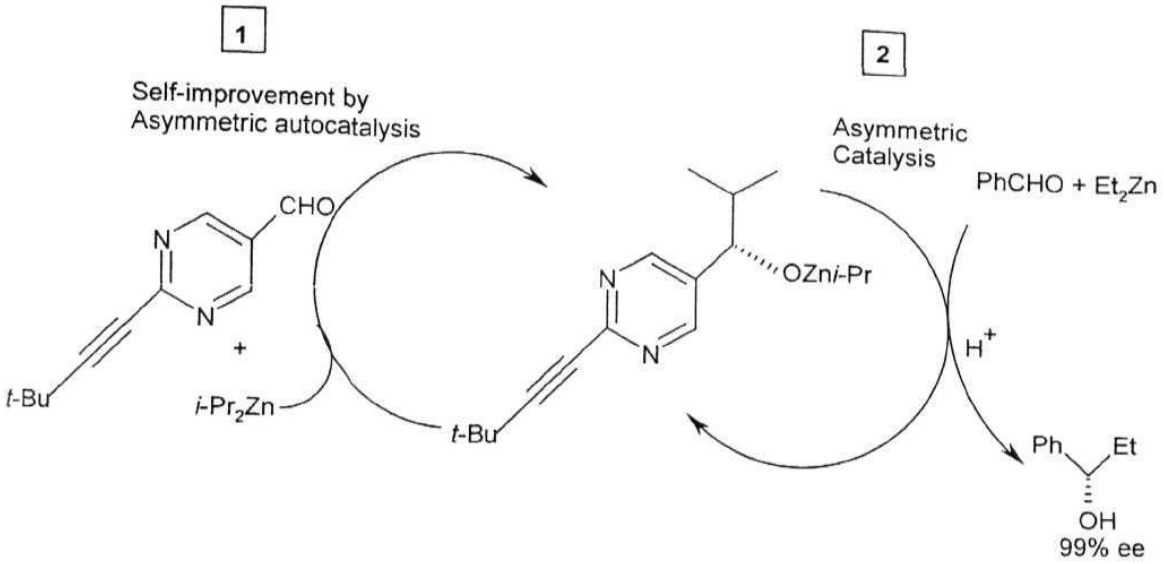
functionalised pyrimidine-5-carbaldehyde, followed by addition of diisoproplylzinc, resulted in the formation of the (*S*)-isopropyl-pyrimidinylalkanol 10 in 93% yield and 98% ee (Scheme 17). It has been suggested that the chiral crystal initiates the formation of the (*S*)-configurated alcohol, and as that isomer accumulates, it autocatalyses the production of more molecules with the same configuration.[57]

Scheme 17



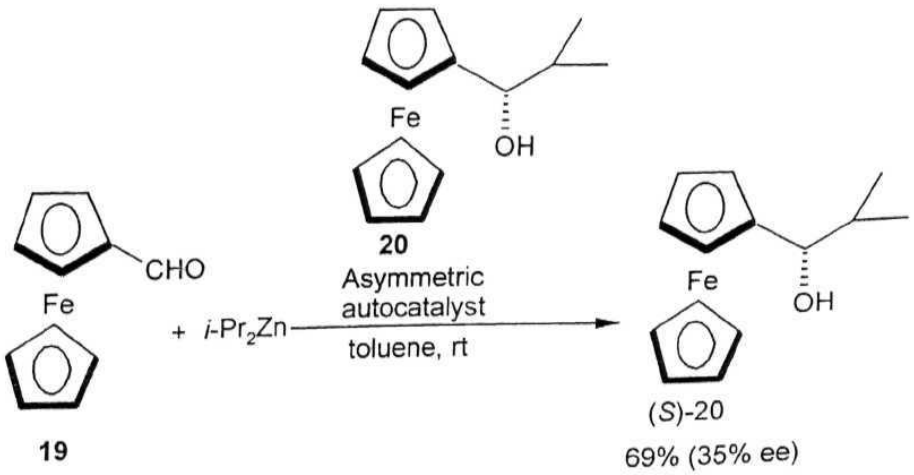
Recently, Soai *et al.*[58] reported a new and efficient one-pot method of asymmetric catalysis in which a chiral catalyst for 5-pyrimidylalkanol self-improves its ee by asymmetric autocatalysis and then acts as a highly enantioselective chiral catalyst for other asymmetric synthesis such as addition of dialkylzinc to aldehydes to provide secondary alcohols with very high ee (up to 99%) (Scheme 18).

Scheme 18



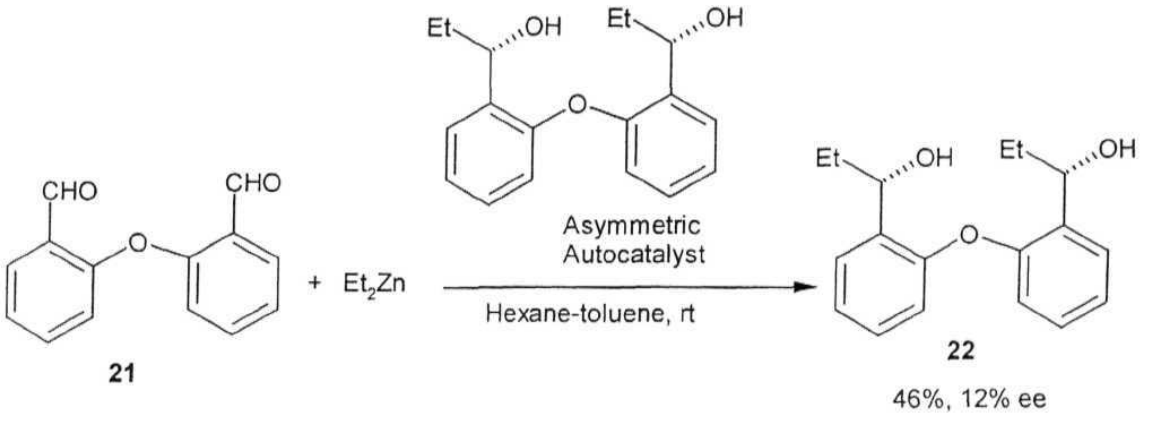
In addition to nitrogen containing alkanols, chiral ferrocenylalkanol have also been shown to serve as asymmetric autocatalyst. However, the ee of the products are poor. Chiral (*S*)-ferrocenylalkanol 20 with 96% ee automultiplies in the enantioselective addition of *i*-Pr_2Zn to ferrocenecarbaldehyde to give (*S*)- 20 in 69% yield and 35% ee (Schme 19).[59]

Scheme 19



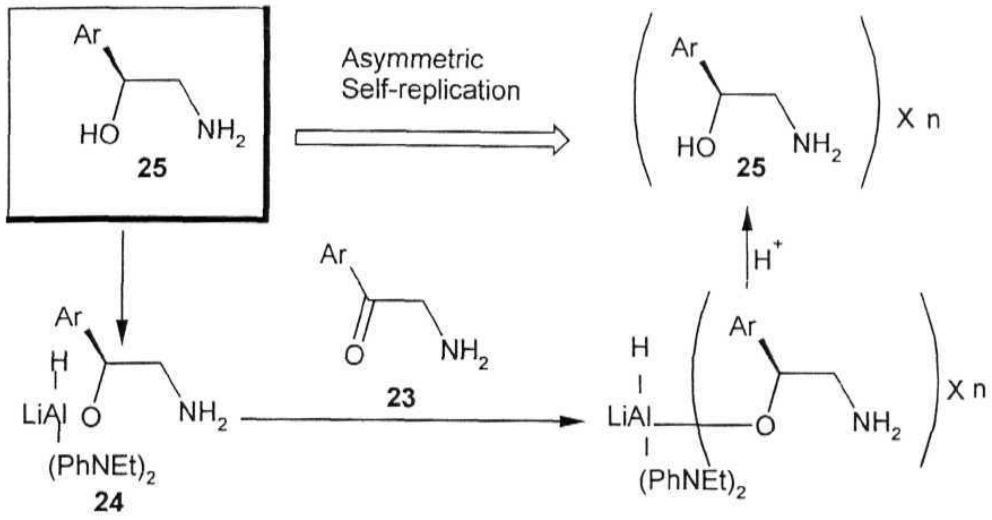
The chiral bis[2-(l-hydroxyalkyl)phenyl)]ether with very high ee's are synthesized by catalytic enantioselective alkylation of bis(2-formylphenyl)ether in the presence of autocatalysis (Scheme 20). Zinc alkoxide of this chiral diol was found to work as asymmetric autocatalyst in the reaction between bis-(2-formylphenyl)ether and dialkylzincs.[60] However, the results realized were poor.

Scheme 20



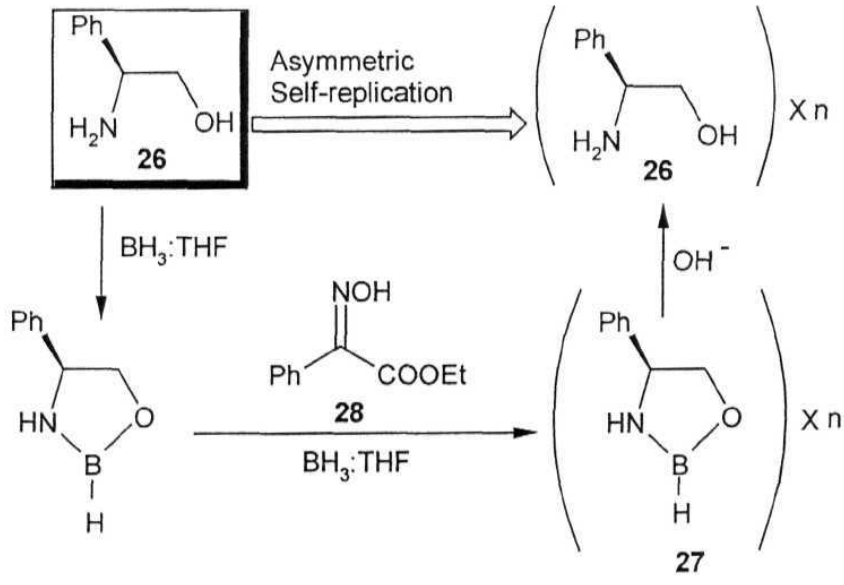
Recently, Soai *et al.*[61] reported the first highly enantioselective self-replication in an asymmetric autoinductive reduction in which the structure of the chiral ligand and product is expected to be identical. For example, morphilinoacetophenone was reduced with chirally modified $LiAlH_4$, which was prepared *in situ* from $LiAlH_4$, (*S*)-2-morphilino-1-phenylethanol and *N*-ethyl-aniline in Et_2O at -78 °C (Scheme 21). The 1,2-amino alcohol was obtained in 95.8% ee, which means that the newly formed product was obtained in 79% yield with 82.4% ee.

Scheme 21



We have examined the possibility of asymmetric borane reduction of the oxime ester of phenylglyoxylic acid derivatives that are expected to involve oxazaborolidine intermediates (Scheme 22).

Scheme 22



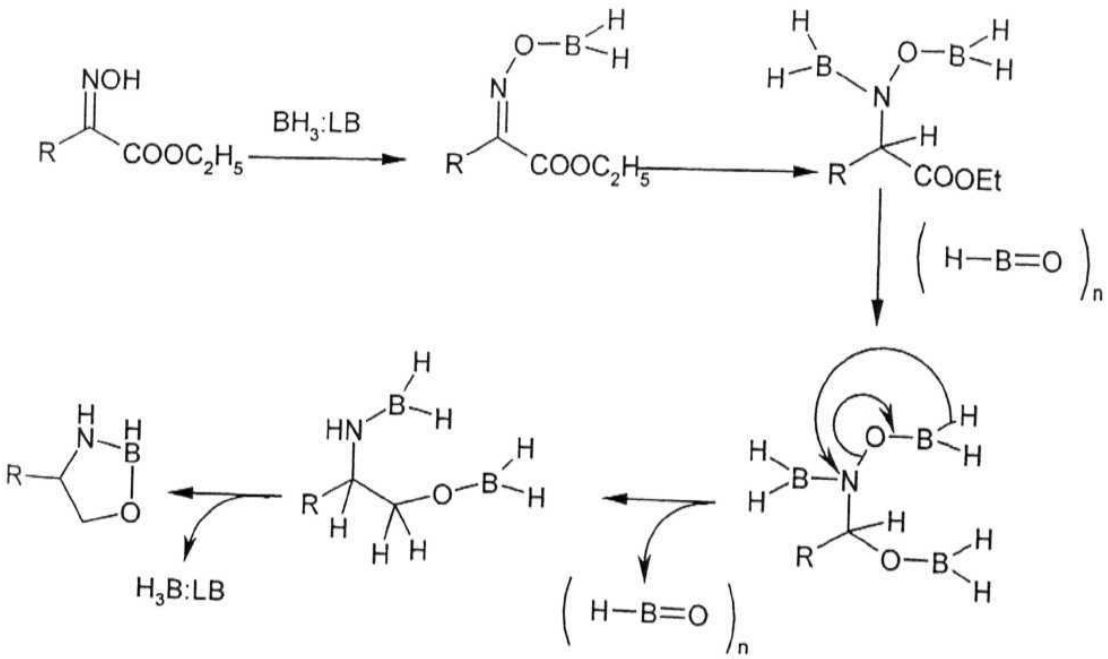
The results of these studies are described in this chapter.

2. 2 Results and Discussions

2. 2. 1 Asymmetric borane reduction of oxime of ethyl phenylglyoxylate 28 derivatives using (*R*)-phenylglycinol.

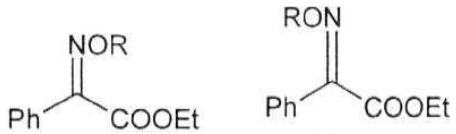
As described in chapter 1, reduction of the oxime of ethyl phenylglyoxylate 28 using various borane reagents gives racemic 1,2-amino alcohols. In these transformations, there are three reductions, i. e. reduction of (i) N=O to N-H, (ii) C=N to C-NH and (iii) COOEt to CH_2OH. The crucial reaction is the reduction of C=N during which the asymmetric centre is created. The steps and intermediates that may be involved are outlined in Scheme 23.

Scheme 23



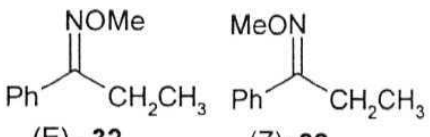
Though, the transformation is a complex one and there is ambiguity in the mechanism and intermediates, we decided to prepare the corresponding oxazaborolidine *in situ* for examining the asymmetric reduction of the corresponding oxime ester that could result in the formation of the oxazaborolidine moiety. We have chosen the oxime of ethyl phenylglyoxylate 28 for this study.

The oxime 28 was prepared by refluxing the ethyl phenylglyoxylate with hydroxyl amine hydrochloride in ethanol for 24 h. It could exist in both (E) and (Z) isomer forms, but only one isomer formed here.



(E)- **31** (Z)- **31**

To our knowledge, stereochemistry of these oxime derivatives has not been reported. However, the oxime derivatives 32 have been prepared and found to be a 85:15 mixture of (E) and (Z) isomers.[62] Accordingly, the isomer of 28 at hand could most probably be the (E)-isomer.

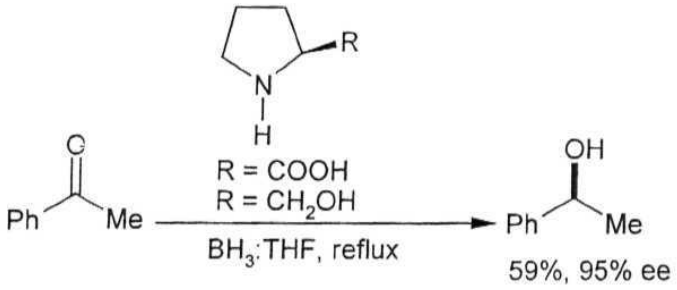


(E)- **32** (Z)- **32**

Initially, the borane reduction of oxime of ethyl phenylglyoxylate 28 was carried out at 25 °C. The reaction was not clean and was also incomplete under

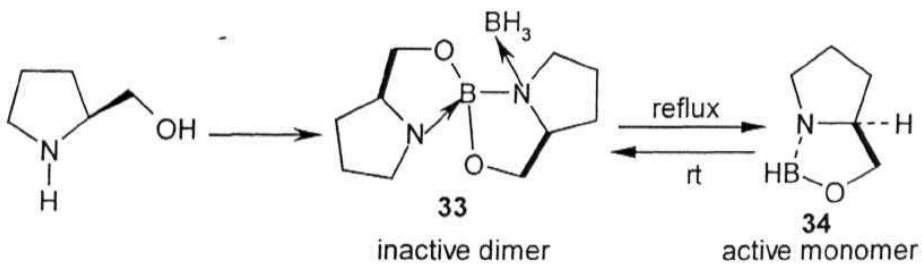
these conditions. Buono *et al.*[63] reported that the acetopheonone was reduced with BH_3:THF and (*S*)-proline at room temperature to yield (*R*)-1-phenylethanol in low enantiomeric excess.

Scheme 24

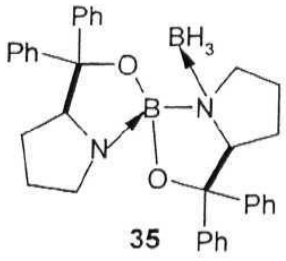


However, the enantioselectivity was reported to increase with the temperature and best results were obtained by running the reaction in refluxing toluene (Scheme 24). [63] It was suggested that there is a monomer 34 (catalytically active) and dimer 33 (inactive) equilibrium (Scheme 25) and in refluxing toluene, the equilibrium could shift towards the monomer 34 which would be responsible for the high ee encountered (Scheme 24). The increasing amount of dimer at lower temperature could explain the decrease in enantioselectivity, since the competing uncatalysed reduction could take place to a higher extent.

Scheme 25



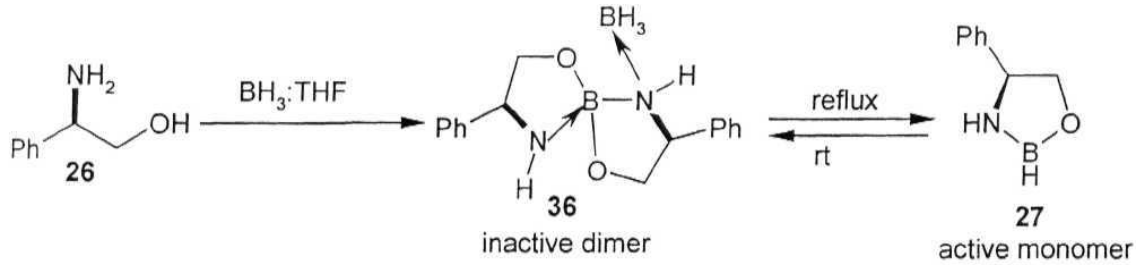
Recently, Mathre *et al.*[64] isolated the inactive dimer 35 by adding excess of BH_3:SMe_2 to a solution of α,α-diphenyl-2-pyrrolidinemethanol in toluene at room temperature.



35

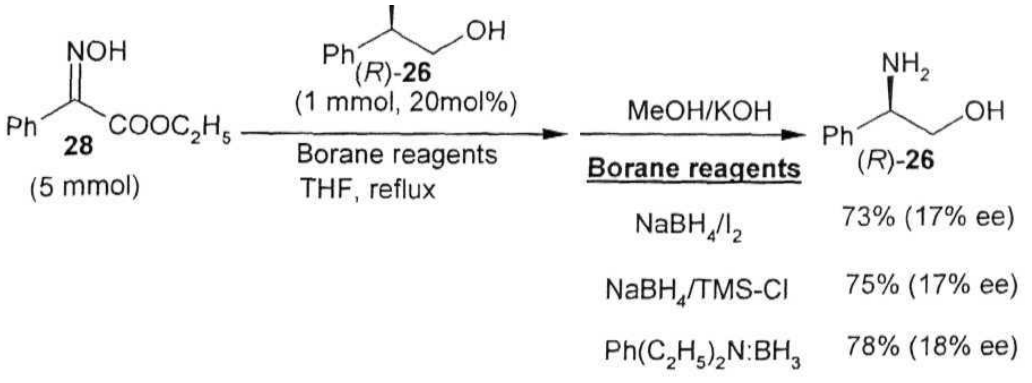
Accordingly, it was thought that the oxazaborolidine derived from (*R*)-phenylglycinol may exist as the inactive dimer form 36, which could be in equilibrium with the monomer 27 under refluxing conditions.

Scheme 26



Hence, we have carried out the reduction of the oxime of ethyl phenylglyoxylate 28 using (*R*)-phenylglycinol under refluxing conditions in toluene. The reaction proceeds smoothly under the refluxing conditions. The reduction was carried out using various borane reagents such as $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and $Ph(C_2H_5)_2N$:BH_3 (Scheme 27).

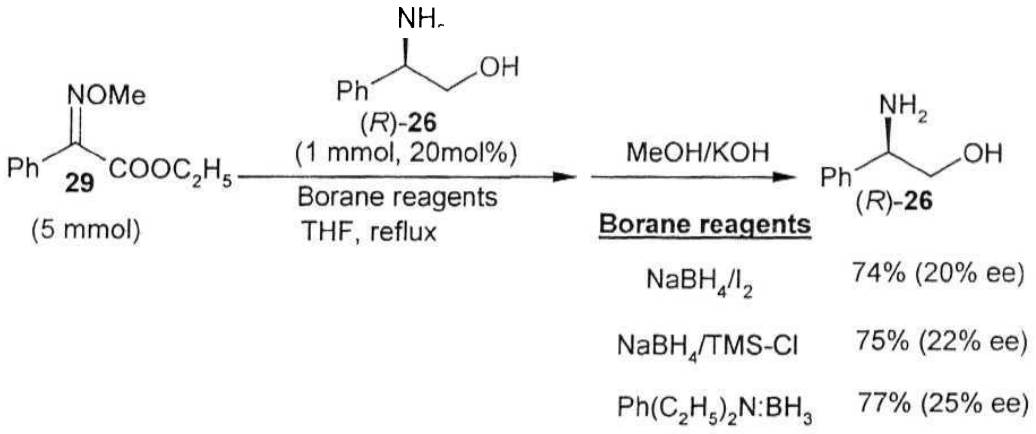
Scheme 27



The (*R*)-(-)-phenylglycinol was obtained in 73% yield (based on the formation of 6 mole equivalent of phenylglycinol as envisaged in Scheme 27) as a mixture of newly formed product and the chiral ligand in 17%ee. The results indicate that the newly formed phenylglycinol is only a racemic mixture.

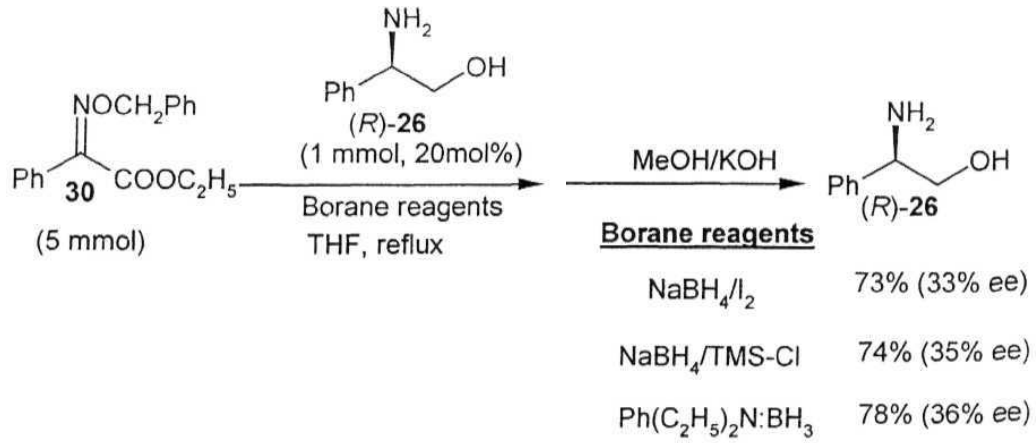
Since the reduction of the oxime ester 28 did not give fruitful results, we have decided to examine the asymmetric reductions using the methyl and benzyl oxime ethers of ethyl phenylglyoxalate 29 and 30 in further studies. The ether 29 was reduced in the presence of (*R*)-(-)-phenylglycinol using the reagent systems like $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and *N,N*-diethylaniline:BH_3 (Scheme 28). After workup, the (*R*)-phenylglycinol was obtained in 20% ee, 22% ee and 25% ee respectively. The results indicates that the newly formed phenylglycinol is produced only in very low ee (~ 3-8% ee) (based on the assumption that the ee would be 16.6% if the newly formed phenylglycinol is racemic) (Scheme 28).

Scheme 28



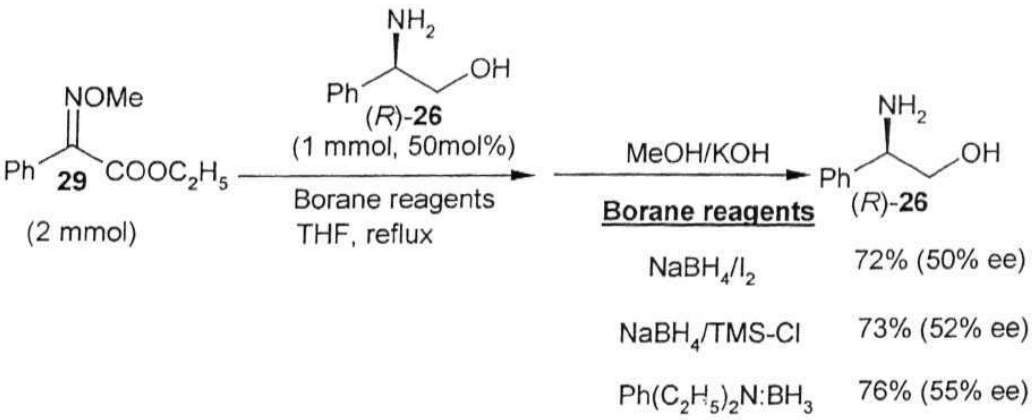
The reduction of the benzyl oxime ether derivative 30 gave better results (Scheme 29) and the newly formed phenylglycinol would be in about 17-20% ee (based on the assumption that the ee would be 16.6% if the newly formed phenylglycinol is racemic).

Scheme 29



We have then examined the reaction using 50 mol% of the catalyst. In these runs, the methyl oxime ether derivative 29 was reduced using $NaBH_4/I_2$ reagent system to give the (*R*)-(-)-phenylglycinol in 50% ee (Scheme 30).

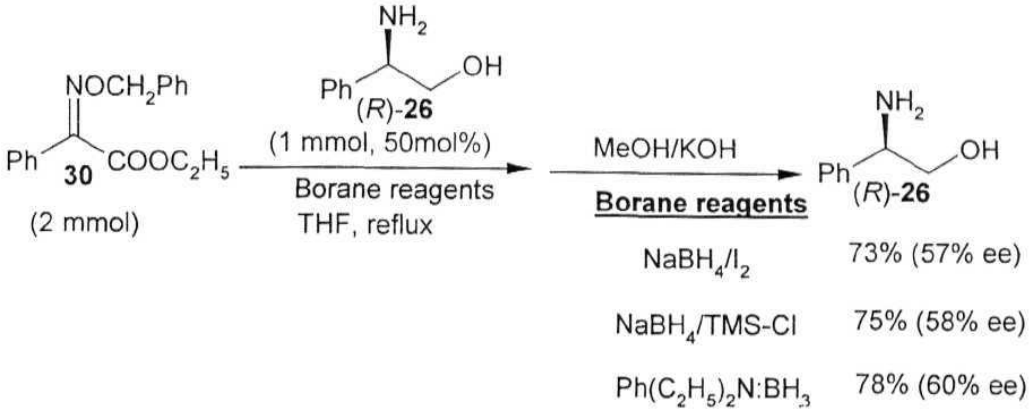
Scheme 30



When the same reaction was carried out using the $NaBH_4$/TMS-Cl and *N,N*-diethylaniline:BH_3 reagent systems, the (*R*)-(-)-phenylglycinol was obtained in 52% ee and 55% ee, respectively (Scheme 30). The results indicate that the newly formed phenylglycinol would be in about 17-22% ee (based on the assumption that the ee would be 33.3% if the newly formed phenylglycinol is racemic).

When the benzyl oxime ether derivative 30 was reduced using 50 mol% (*R*)-(-)-phenylglycinol, the (*R*)-(-)-phenylglycinol was obtained in 57-60% ee (73-78% yield) (Scheme 31).

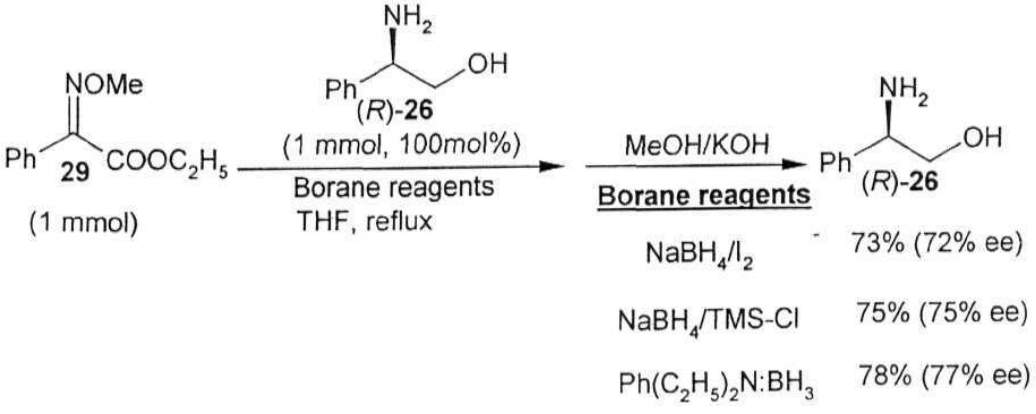
Scheme 31



The newly formed *(R)* enriched phenylglycinol would have an enantiomeric purity of about 23-27 % ee in these cases (based on the assumption that the ee would be 33.3% if the newly formed phenylglycinol is racemic).

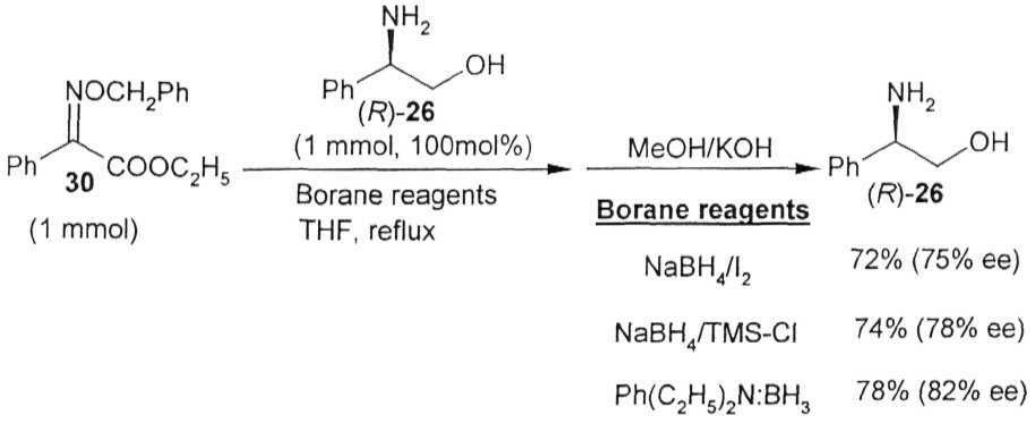
Later, we have examined the reduction using stoichiometric quantity of (*R*)-(-)-phenylglycinol. It was observed that the methyl oxime ether derivative 29 was reduced in the presence of (*R*)-(-)-phenylglycinol (100 mol%) to give (*R*)-(-)-phenylglycinol in 72-77% ee (73-78% yield) (Scheme 32).

Scheme 32



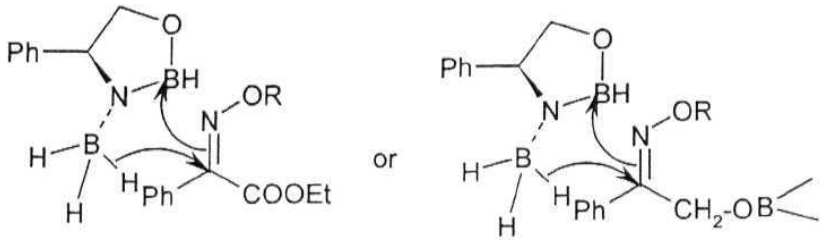
In these cases, the newly formed *(R)* enriched phenylglycinol would have an enantiomeric purity of 22-27% ee (based on the assumption that the ee would be 50% if the newly formed phenylglycinol is racemic).

In the case of reduction of benzyl oxime ether derivative 30 using (*R*)-(-)-phenylglycinol in stoichiometric quantities, the (*R*)-(-)-phenylglycinol was obtained in 75-82% ee (72-78% yield) indicating that the newly formed *(R)* enriched enantiomeric amino alcohol would have an enantiomeric purity of 25-32% ee (based on the assumption that the ee would be 50% if the newly formed phenylglycinol is racemic).



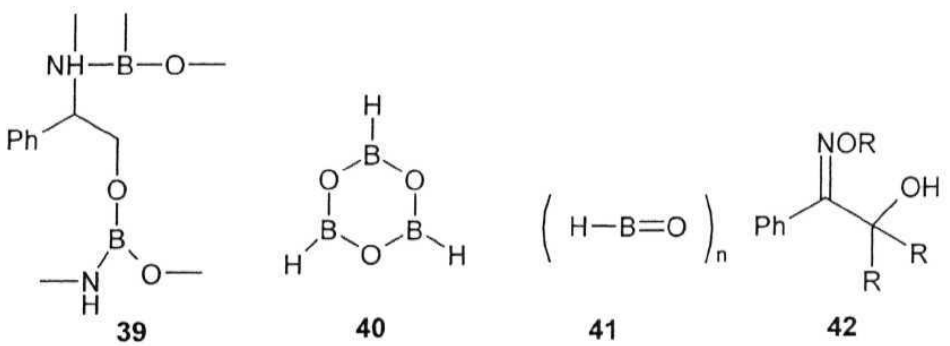
It is obvious from these studies that the results are better when stoichiometric quantities of the chiral amino alcohol was used. That is, the asymmetric duplication process seems to take place with modest enantioselectivity, instead of the anticipated autocatalytic process. As outlined in Scheme 23, this transformation would involve a complex mechanism involving several

intermediate steps. Also, it is not clear whether the reduction of ON bond would take place before or after the reduction of the ester group. Hence, there is uncertainity about the step involving the formation of the asymmetric centre and it is not clearly understood whether the reaction would go through the transition state 37 or 38.



37 38

The oxazaborolidine of the type 27 may be further transformed to give a complex mixture of borane species, which may not be efficient to catalyse the reaction. For instance, if the species formed are linear polymers of the type 39 instead of cyclic oxazaborolidines 37 or 38, then the catalysis would not be efficient. Also, the presence of several borane species such as 40 and/or 41 may also complicate, if they do not disproportionate to give BH_3 species for binding to the oxazaborolidine.



39 40 41 42

Although, this transformation involves a complex mixture of intermediates, further systematic studies on the synthesis of oxime derivatives of the type 42 for examining the duplication of chirality, may give more fruitful results. However, deferring these studies, we have proceeded to examine other aspects of applications of the chiral amino alcohols in asymmetric synthesis. The results of the studies undertaken on the asymmetric Michael reaction are discussed in the next chapter.

2. 3. Conclusions

Asymmetric reductions of various oxime ethers of ethyl phenylglyoxylate 28, 29 and 30 were studied in the presence of (*R*)-phenylglycinol using the $NaBH_4/I_2$, $NaBH_4$/TMS-Cl and *N*, *N*-diethylaniline:BH_3 reagent systems. The amino alcohols were obtained in up to 82% ee under stoichiometric conditions indicating that the newly formed (*R*)-amino alcohol would have an enantiomeric purity of 25-32% ee.

2. 4 Experimental Section

2. 4. 1 General Information

Several of the general experimental details given in Chapter 1 are also applicable here. Methyl iodide, benzyl bromide and hydroxylamine hydrochloride were purchased from Loba Chemie, India.

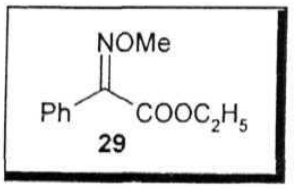
2. 4. 2 Synthesis of oxime methyl ether of phenylglyoxylate 29

Sodium hydride (60% in mineral oil) (1.75 g, 44 mmol) was taken in dry DMF and ethyl phenylglyoxylate oxime 28 (1.96 g, 10 mmol) in dry DMF was added for an hour through additional funnel at 0 °C and the contents were stirred for 30 min. CH_3I (1.24 g, 20 mmol) was added slowly via syringe and the contents were stirred for an additional 12 h at 25 °C. The solvent was evaporated under reduced pressure and the residue was extracted with ether (2 X 20 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography using hexane: ethyl acetate as eluent (97:3) to obtain the product.

Yield " 1.0 g (80%)

B.p. 150 °C/ 5 mm

IR (neat) (cm^{-1}) 1739, 1591



29

H NMR (5 ppm, $CDCl_3$) 1.4 (t, 8.3 Hz, 3H), 4.1 (S, 3H), 4.37 (q, 7.28 Hz, 2H), 7.4 (m, 5H) **(Spectrum** No. 12)

^{13}C-NMR (δ ppm, $CDCl_3$) 14.1, 62.0, 63.5, 127.9, 129.0, 129.5, 129.6, 149.4, 163.4 **(Spectrum No. 13)**

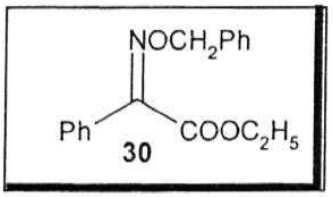
2. 4. 3 Synthesis of benzyl oxime ether of ethyl phenylglyoxylate 30

The compound was prepared by the following a reported procedure. Sodium hydride (60% in mineral oil) (1.75 g, 44 mmol) was taken in dry DMF and ethyl phenylglyoxylate oxime 28 (1.96 g, 10 mmol) was added for 1 h through additional funnel at 0 °C and the contents were stirred at 25 °C for 30 min. Then benzyl chloride (2.3 g, 10 mmol) was added slowly via syringe and the contents were stirred for 12 h at 25 °C. The solvent was evaporated under reduced pressure and the residue was extracted with ether (2 X 10 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography using hexane: ethylacetate as eluent (97:3) to obtain the product.

Yield 1.1 g (81%)

B.p. 170 °C/ 5 mm

JR (neat) (cm^{-1}) 1737, 1591



30

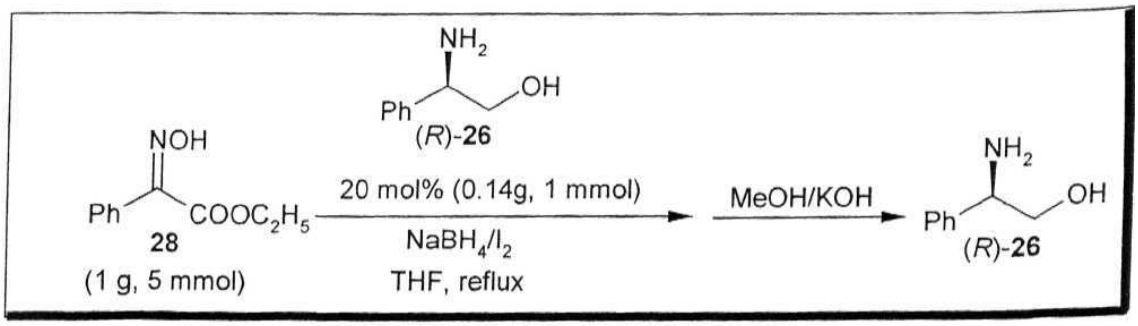
^{1}H NMR (δ ppm, $CDCl_3$) 1.4 (t, 10.5 Hz, 3H), 4.5 (q, J = 10.5 Hz, 2H), 5.4 (s, 2H), 7.5 (m, 10H) (Spectrum **No. 14**).

^{13}C-NMR (δ ppm, $CDCl_3$) 14.1, 60.0, 77.1, 125.8, 127.9, 128.9, 129.0, 129.2, 129.6, 137.4, 155.8, 161.3 **(Spectrum No. 15).**

2. 4. 4 Reduction of the ethyl phenylglyoxylate oxime 28 with (*R*)-(-) phenylglycinol (20 mol%) using the $NaBH_4/I_2$ reagent system

I_2 (2.3g, 9 mmol) in dry THF (20 mL) was added through an addition funnel to the stirred solution of $NaBH_4$ (0.68 g, 18 mmol) in dry THF (10 mL) for 1 h at 0 °C. The (*R*)-(-)-phenylglycinol (0.14 g, 1 mmol) in dry THF was added dropwise and the contents were refluxed for 30 min. The reaction mixture was cooled to 0 °C and the oxime of ethyl phenylglyoxylate (0.97 g, 5 mmol) in dry THF (20 mL) was added dropwise for an hour through additional funnel. After the addition was over, the contents were refluxed for 6 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 (1N, 20 ml) solution for 3 h. The aqueous layer was extracted with DCM (3 X 20 mL) and the combined extracts were dried over anhydrous magnesium sulphate. The solvent was evaporated and the product was separated by column

chromatography using $CHCl_3$:MeOH as eluent (92:8) to obtain the (*R*)-(-)-phenylglycinol.

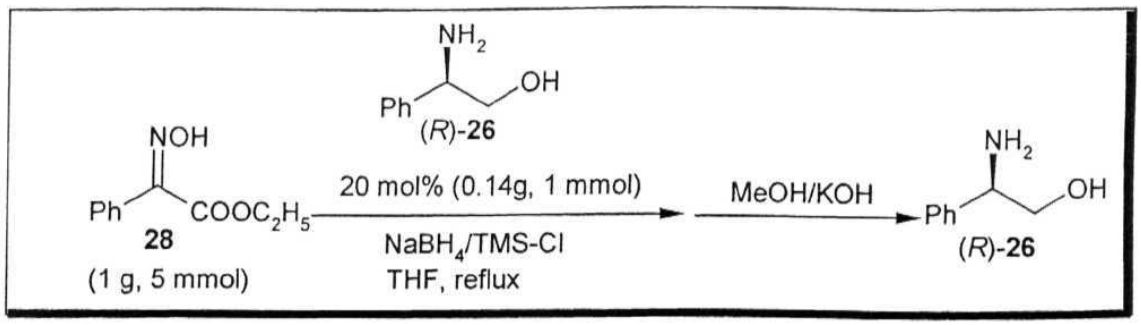


Yield	0.61g (73 %)
M. p.	72-75 °C; lit.[13] 75-78°C
IR (neat)	(cm^{-1}) .3362, 1048
^{1}H-NMR	(5 ppm, $CDCl_3$) 2.0(s, 3H), 3.5 (dd, J= 12Hz, 1H), 3.6(dd. J=8Hz, 1H), 4.0(dd, J=8Hz, 1H), 7.3(m, 5H).
^{13}C-NMR	(δ ppm, $CDCl_3$) 57.4, 67.8, 126.5, 127.1, 129.0, 142.4
$[\alpha]_D^{25}$	(-) 5.3 (*c* 1, 1N HC1), {lit[24] for 100%ee, $[\alpha]_D^{25}$ = (-) 31.7 (*c* 0.75, 1N HCl}

2. 4. 5 Reduction of ethyl phenylglyoxylate oxime 28 with (*R*)-phenylglycinol (20 mol%) using $NaBH_4$/TMS-Cl system

$NaBH_4$ (0.68 g, 18 mmol) was taken in dry THF (20 mL) and TMS-C1 (1.9 g, 18 mmol) was added to the stirred solution. The contents were refluxed for 2 h. The reaction mixture was cooled to 25 °C and then the (*R*)-(-)-

phenylglycinol (0.14 g, 1 mmol) was added dropwise and the contents were again refluxed for 30 min. The reaction mixture was cooled to 0 °C and the oxime of ethyl phenylglyoxylate (0.97 g, 5 mmol) in dry THF (20 mL) was added dropwise for 1 hour through additional funnel. After the addition was over the contents were refluxed for 6 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 (1N, 20 ml) solution for 3 h. The aqueous layer was extracted with DCM (3 X 20 mL) and the combined extracts were dried over anhydrous magnesium sulphate. The solvent was evaporated and the product was separated by column chromatography using $CHCl_3$:MeOH as eluent (92:8) to obtain the (*R*)-(-)-phenylglycinol

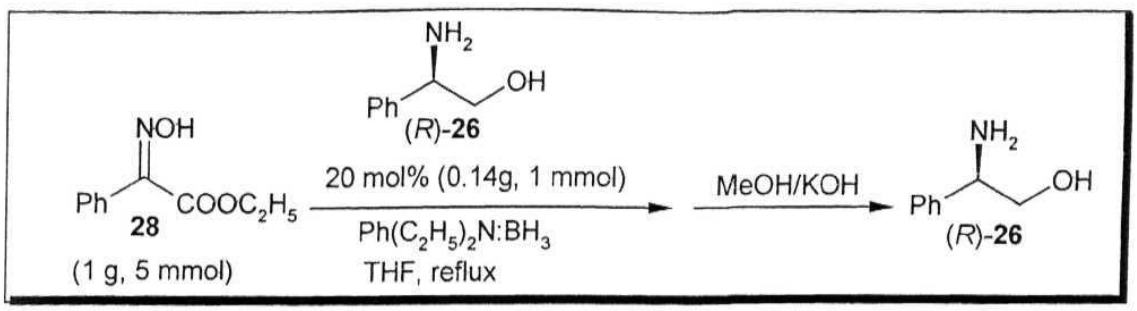


Yield 0.63 g (75 %)

[a]" (-) 5.3 (*c* 1, 1N HCl).

2. 4, 6 Reduction of ethyl phenylglyoxylate oxime 28 with (*R*)-(-)-phenylglycinol (20 mol%) using *N, N*-diethylaniline:BH_3 system

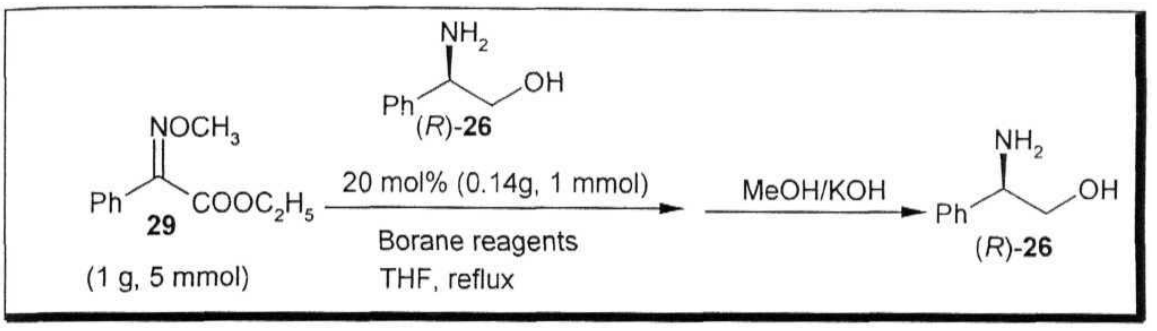
A solution of *N,N*-diethylaniline:BH_3 (1M 18 mL, 18 mmol) was added to the stirred solution of (*R*)-(-)-phenylglycinol (0.14 g, 1 mmol) in dry THF (20 ml). The contents were refluxed for 30 min. The reaction mixture was cooled to 0 °C and oxime of ethyl phenylglyoxylate (0.97 g, 5 mmol) in dry THF (20 mL) was added drop wise for an hour through additional funnel. After the addition was over the contents were refluxed for 6 h. The reaction mixture was brought to 25 ° C and then quenched with MeOH. The solvent was removed under reduced pressure. The residue was refluxed with aqueous KOFI solution for 3 h. The aqueous layer was extracted with DCM (3 X 20 mL) and the combined extracts were dried over anhydrous magnesium sulphate. The solvent was evaporated and the product was separated by column chromatography using $CHCl_3$:MeOH as eluent (92:8) to obtain the (*R*)-(-)-phenylglycinol.



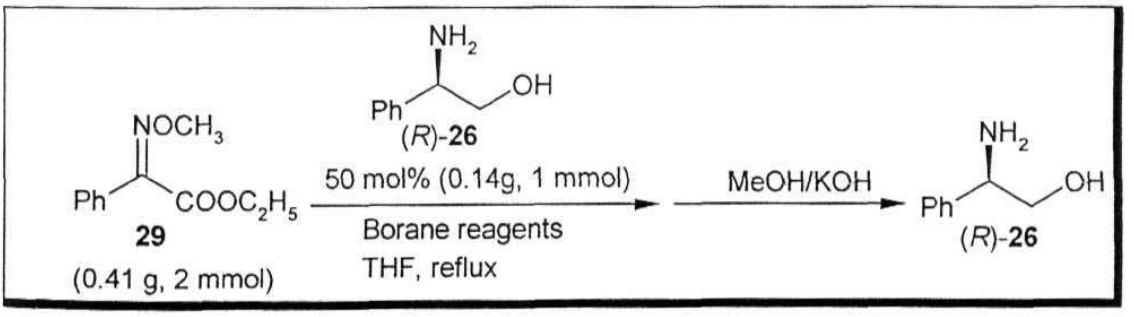
Yield 0.68 g (78 %)

$[\alpha]_D^{25}$ (-) 5.4 (*c* 1, 1N HCl).

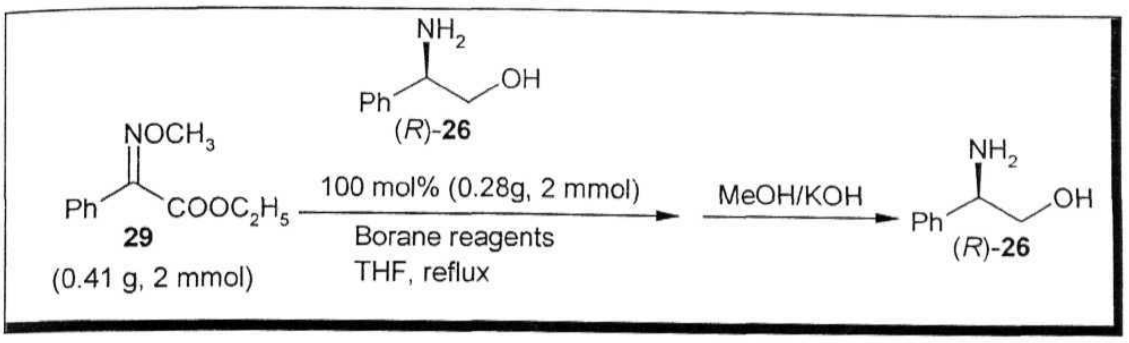
The methyl oxime ether derivative 29 and benzyl oxime ether derivative 30 were also reduced using borane reagents under various conditions. The yields and the $[\alpha]_D^{25}$ values are given below.



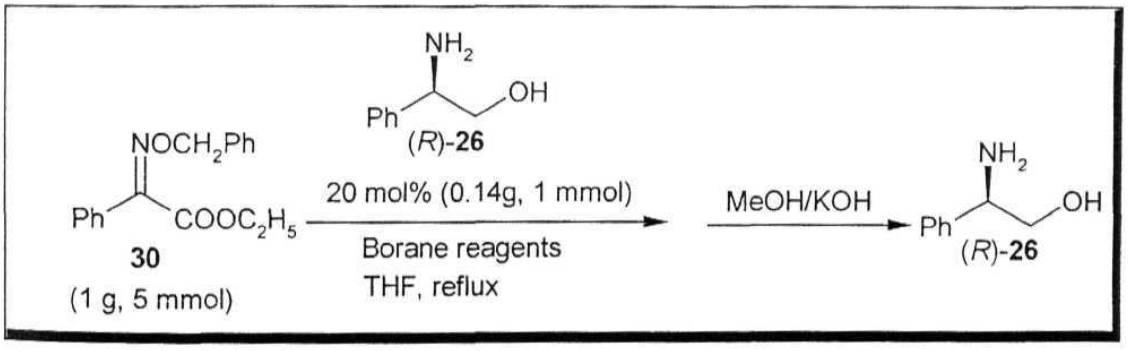
Borane reagents	Yield	r]25
$NaBH_4/I_2$	0.62 g (74%)	(-) 6.6 (*c* 1, 1N HCl)
$NaBH_4$/TMS-Cl	0.63 g (75%)	(-) 6.9 (*c* 1, 1N HC1)
$Ph(C_2H_5)_2N{:}BH_3$	0.64 g (77%)	(-) 8.0 (*c* 1, 1N HCl)



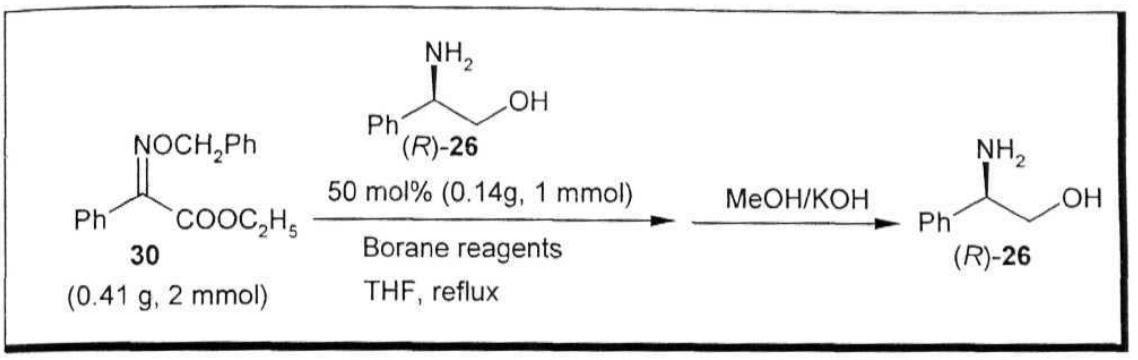
Borane reagents	Yield	r]25
$NaBH_4/I_2$	0.30 g (72%)	(-) 15.9 (*c* 1, 1N HCl)
$NaBH_4$/TMS-Cl	0.31 g (73%)	(-) 16.5 (*c* 1, 1N HCl)
$Ph(C_2H_5)_2N{:}BH_3$	0.32 g (76%)	(-) 17.4 (*c* 1, 1N HCl)



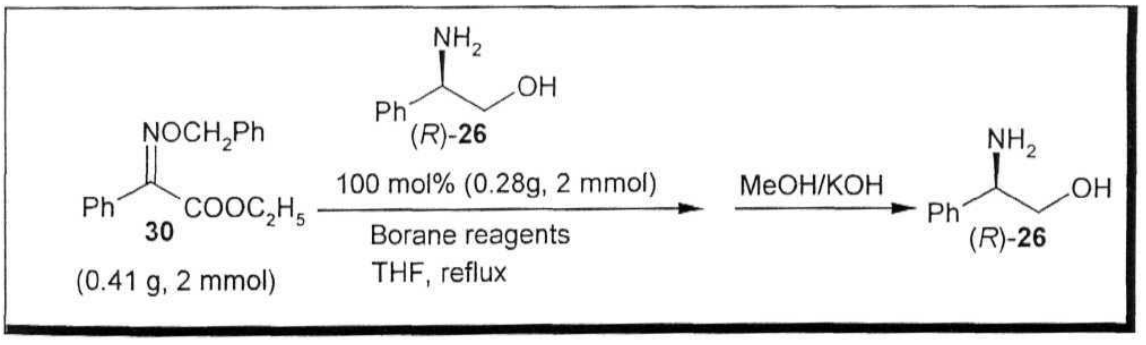
Borane reagents	Yield	$[\alpha]_D^{25}$
- $NaBH_4/I_2$	0.41 g (73%)	(-) 22.8 (*c* 1, 1N HC1)
$NaBH_4$/TMS-Cl	0.42 g (75%)	(-) 23.7 (c 1, 1N HC1)
$Ph(C_2H_5)_2N{:}BH_3$	0.44 g (78%)	(-) 24.4 (*c* 1, 1N HC1)



Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	0.61 g (73%)	(-) 10.4 (*c* 1, 1N HC1)
$NaBH_4$/TMS-Cl	0.62 g (74%)	(-) 11.0 (*c* 1, 1N HC1)
$Ph(C_2H_5)_2N{:}BH_3$	0.63 g (78%)	(-) 11.4 (*c* 1, 1N HC1)



Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	0.31 g (73%)	(-) 18.0 (*c* 1, 1N HC1)
$NaBH_4$/TMS-Cl	0.32 g (75%)	(-) 18.3 (*c* 1, 1N HC1)
$Ph(C_2H_5)_2N{:}BH_3$	0.33 g (78%)	(-) 19.0 (*c* 1, 1N HC1)



Borane reagents	Yield	$[\alpha]_D^{25}$
$NaBH_4/I_2$	0.40 g (72%)	(-) 23.7 (*c* 1, 1N HC1)
$NaBH_4$/TMS-Cl	0.41 g (74%)	(-) 24.7 (*c* 1, 1N HC1)
$Ph(C_2H_5)_2N{:}BH_3$	0.44 g (78%)	(-) 25.9 (*c* 1, 1N HC1)

2. 5 References

1. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer-verlag, Berlin, **1999.**
2. R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley: New York, **1994.**
3. E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen and V. K. Singh, *J. Am. Chem. Soc;* **1987,** 109, 7925.
4. F. C. Frank, *Biochim. Biophysics Acta.* 1953, 11, 459.
5. M. Calvin, *Molecular Evolution: Oxford University Press: Oxford.* **1969.**
6. K. Soai, Y. Inoue, T. Takahashi and T. Shibata, *Tetrahedron,* **1996,** *52,* 13355.
7. T. Shibata, T. Takahashi, T. Konishi and K. Soai, *Angew. Chem. Int. Ed. Engl.* 1997,56,2458.
8. W. RRr. Rough and X. Fatin, *J. Org. Chem.* **1991,** *56,* 5740.
9. G. E. Tranter, *Nature,* **1985,** 575, 172.
10. **D. K. Kondepudi and** G. W. Nelson, *Nature,* **1985,** *314,* **438.**
11. S. Mason, *Chem. Soc. Rev.* **1988,** *17,* 347.
12. A. Eschenmoser, *Science,* **1999,** *284,* 2118.

13. L. Keszthelyi, *Q. Rev. Biophysics*, **1995**. *28*, 473.

14. D. K. Kondepudi, J. Laudadio and K. Asakura, *J. Am. Chem. Soc.* 1999, 727, 1448.

15. N. P. M. Huck, W. F. Jager, B. De lange and B. L. Feringa, *Science, 1996,273,* 1686.

16. C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami and H. B. Kagan, *J. Am. Chem. Soc.* 1986, *108,* 2353.

17. N. Oguni, Y. Matsuda and T. Kaneko, *J. Am. Chem. Soc.* 1988, *110,* 7877.

18. M. Kitamura, S. Okada, S. Suga and R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028.

19. C. Girarad and H. B. Kagan, *Angew. Chem. Int. Ed. Engl.* 1998, *37,* 2922.

20. M. Avalos, R. Babinato, P. Cintas, J. Jimenez and J. C. Palacios, *Tetrahedron; Asymmetry,* 1997, *8*, 2997.

21. D. R. Fenwick and H. B. Kagan, *Topics in Sterochemistry, Denmark,* 1999,22,257.

22. C. Bolm, *In advanced Asymmetric synthesis,* 1996, 9.

23. T. Mukaiyama, K. Soai, T. Sato, H. Shimizu and K. Suzuki, *J. Am. Chem. Soc.* 1979, *101*, 1455.

24. D. G. Blackmond, C. R. Macmillan, S. Ramdeehul, A. Schorm and J. M. Brown, *J. Am. Chem. Soc.* **2001,** *123*, 10103.

25. P. D. Bailey, *J. Chem. Soc. Chem. Commun.* **1995,** 1797.

26. K. Soai and S. Niwa, *Chem. Rev.* 1992, *92,* 833.

27. K. Soai and T. Hayase, *J. Synth, Org Jpn.* **1995**, *53*, 138.

28. R. Noyori and M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991,** *30,* 49.

29. K. Soai, *Enantiomer,* **1999,** *4,* 591.

30. K. Soai and T. Shibata,./. *Synth. Org. Jpn.* 1997, 55, 994.

31. K. Soai, T. Shibata and P. Knochel, *Asymmetric Additions using Diorganozincs*, *Oxford University press, New York,* **1999,** 911.

32. K. Soai, A. Ookavva, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*1987, *109,* 7111.

33. K. Soai, S. Yokoyama and T. Hayasaka,./. *Org. Chem.* **1991,** *56,* 4264.

34. K. Soai, T. Hayae, K. Takai and T. Sugiyama, *J. Org. Chem.* **1994,** *59,* 7908.

35. S. Niwa and K. Soai, *J. Chem. Soc. Perkin Trans* 1, **1991,** 2717.

36. K. Soai, Y. Hirose and Y. ohno, *Tetrhedron: Asymmetry,* **1993,** *4,* 1473.

37. K. Soai, H. Mori and S. Niwa, *Heterocycles*, **1989,** *29,* 2065.

38. K. Soai, H. Hori and S. Niwa, *J. Chem. Soc. Chem. Commun.* **1990,** 982.

39. T. Shibata, H. Morioka, T. Hayase, K. Choji and K. Soai, *J. Am. Chem. Soc*. 1996,7/5,471.

40. T. Shibata, S. Yonekubo and K. Soai, *Angew. Chem. Int. Ed. Engl.* 1999, *38,* 659.

41. T. Shibata, K. Choji, H. Morioka, T. Hayase and K. Soai, *Chem. Commun*. 1996,751.

42. T. Shibata, H. Morioka, S. Tanji, T. Hayase and K. Soai, *Tetrahedron Lett.* 1996, *37,* 8783.

43. K. Soai, T. Shibata, H. Morioka and K.Choji, *Nature,* 1995, *378,* 767.

44. T. Shibata, K. Choji, T. Hayase, Y. Aizu and K. Soai, *Chem. Commun.* 1996, 1235.

45. T. Shibata, T. Hayase, J. Yamamoto and K. Soai, *Tetrahedron: Asymmetry*, 1997,5, 1717.

46. J. J. Flores, W. A. Bonner and G. A. Massey, *J. Am. Chem. Soc.* 1977, *99,* 3622.

47. S. A. Waratube, E. S. Johnson, M. G. Thorn, P. E. Fanwick and I. P. Rothwell, *Chem. Commun.* **1996**, 2617.

48. C. Bolm, F. Bienewald and A. Seger, *Angew. Chem. Int. Ed. Engl.* 1996,55, 1657.

49. K. Soai and T. Shibata, *Advances in Biochirality, Elsevier: Oxford,* 1999, chapter 1.

50. J. Bailey, A. Chrysostomou, J. H. Hough, T. M. Gledhill, A. Mgcall, S. Clark, F. Menard and M. Tamura, *Science*, **1998,** 281.

51. T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai and K. Soai, *J. Am. Chem. Soc*. **1998,** *120,* 12157.

52. K. Soai, S. Tanji, Y. Kodaka and T. Shibata, *Enantiomer*, **1998,** 5, 241.

53. S. Tanji, Y. Kodaka, T. Shibata, K. Soai, *Hetreocycles*, **2000,** *52,* 151.

54. S. Tanji, A. Ohno, I. Sato and K. Soai, *Org. Lett.* **2001,** *3,* 287.

55. K. Soai, S. Osanai, K. Kodawaki, S. Yonekubo, T. Shibata and I. Sato, *J. Am. Chem. Soc*.**1999**, *121,* 11235.

56. I. Sato, K. Kadowaki, Y. Ohgo, K. Soai and H. Ogino, *Chem, Commun.* **2001,** 1022.

57. I. Sato, K. Kadowaki and K. Soai, *Angew. Chem. Int. Ed. Engl.* **2000,** *39,* 1510.

58. I. Sato, H. Urabe, S. Ishii, S. Tanji and K. Soai, *Org. Lett.* **2001,** *3,* 3851.

59. K. Soai, T. Hayase and K. Takai, *Tetrhedron: Asymmetry,* **1995,** 6, 637.

60. K. Soai, T. Hayase and C. Shimada, *Tetrhedron: Asymmetry*, **1994,** 5, 789.

61. T. Shibata, T. Takahashi, T. Konishi and K. Soai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2458.

62. C. Bolm and M. Feider, *SynLett.* 1994, 655.

63. J. M. Brunei, M. Maffei and G. Buono, *Tetrhedron: Asymmetry*, 1993, 4,2255.

64. D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsten, J. D. Carroll, E. G. Corley and E. J. J. Grabowski, *J. Org. Chem.* 1993, *58*, 2880.

Chapter 3

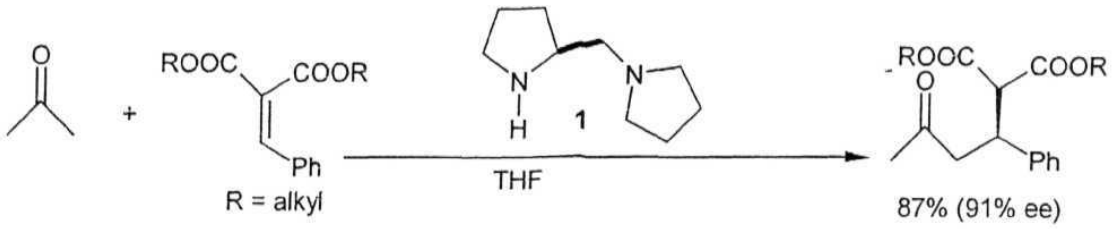
Studies on the asymmetric Michael addition reaction

3. 1 Introduction

Since it's discovery, in the mid 1880's, Michael reaction has been extensively explored and used in organic chemistry.[1-4] In the past two decades, much progress has been made in the development of asymmetric variants of this reaction, allowing the elaboration of Michael adducts of high enantiomeric purity. In recent years, catalysis of asymmetric Michael reaction by chiral metal complexes has been recognized as an efficient method for the enantioselective construction of carbon-carbon bonds.[5,6] We have undertaken studies on the use of chiral borate derivatives for such applications. Accordingly, it may be of interest to briefly review the recent advances in the asymmetric Michael reaction promoted by various chiral ligands.

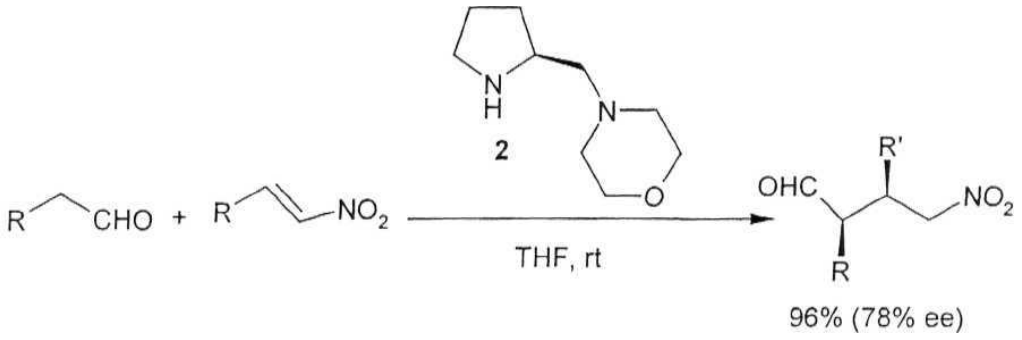
Barbas and coworkers[7] reported the catalytic enantioselective direct Michael additions of ketone enolates to alkylidine malonates. Michael adducts were obtained in up to 91% ee (Scheme 1).

Scheme 1



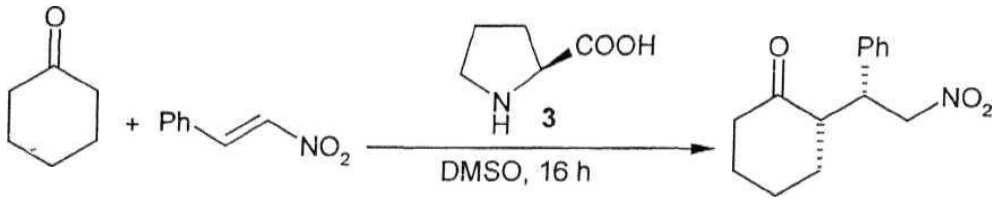
Recently, Barbas and Beatancort[8] reported the direct catalytic enantio and diastereoselective Michael additions of unmodified aldehydes using *(S)-2-*(morphonolinomethyl)pyrrolidine 2 as a catalyst (Scheme 2). The reaction proceeded in good yields in a highly *syn*-selective manner (up to 98:2) with enantioselectivity cipproaching 80%. The resulting γ-formyl nitro compounds are readily converted to chiral 3,4-disubstituted pyrrolidines.

Scheme 2



List *et al*[9] reported the chiral proline 3 catalysed Michael reaction of unmodified ketones with nitro olefins (Scheme 3). The y-nitro ketones are obtained with modest enantioselectivity and in excellent yields.

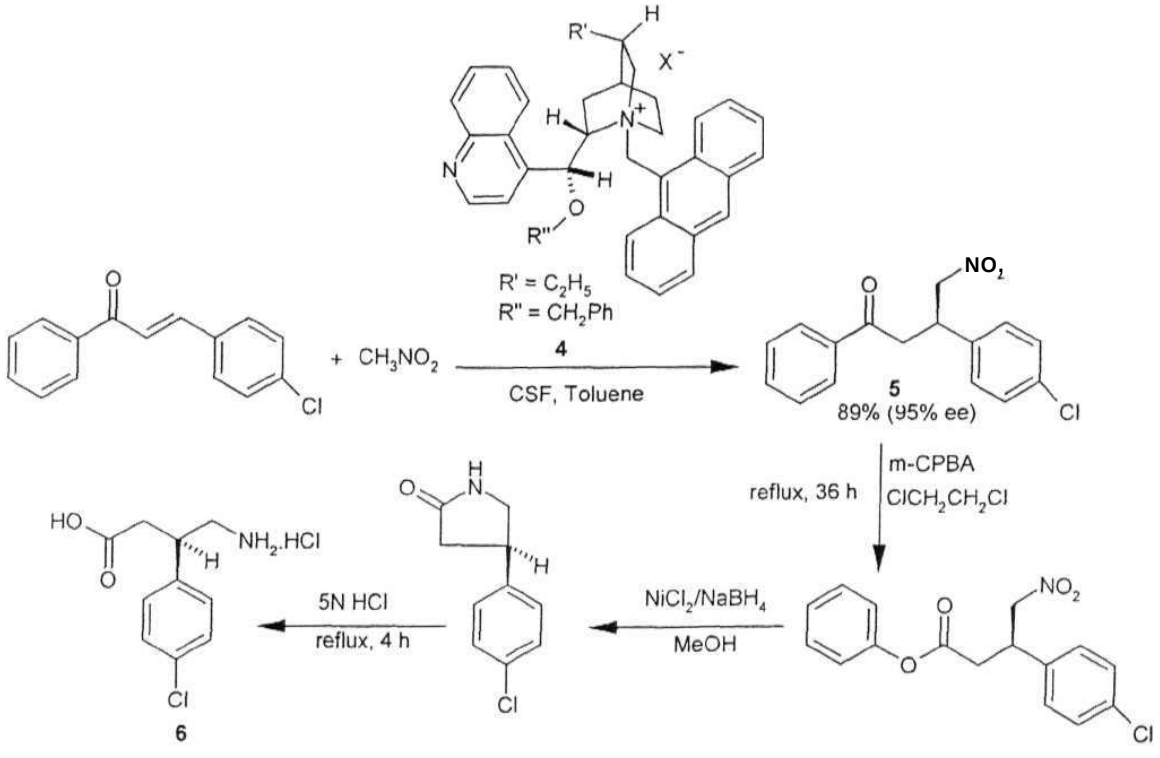
Scheme 3



94% (23% ee)

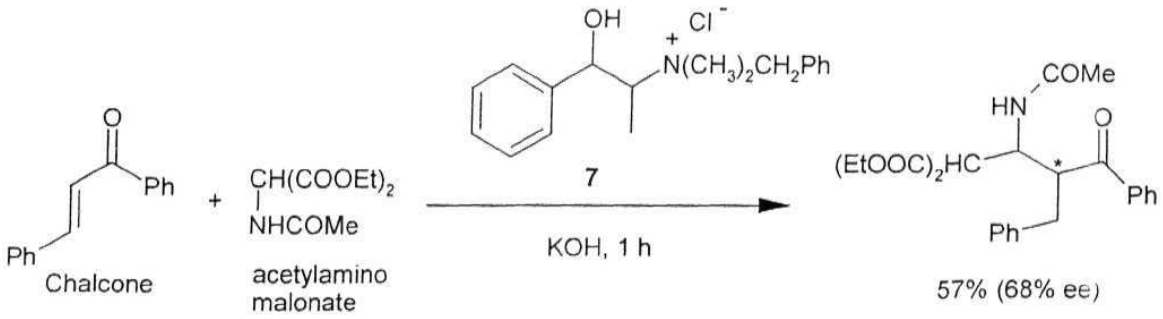
Recently, Corey *et al.*[11] reported the enantioselective Michael addition of nitromethane to an α,β-enone using chiral quarternary ammonium salt as chiral catalyst which is a key step in the synthesis of (*R*)-bacolfen **6** (Scheme 4).

Scheme 4



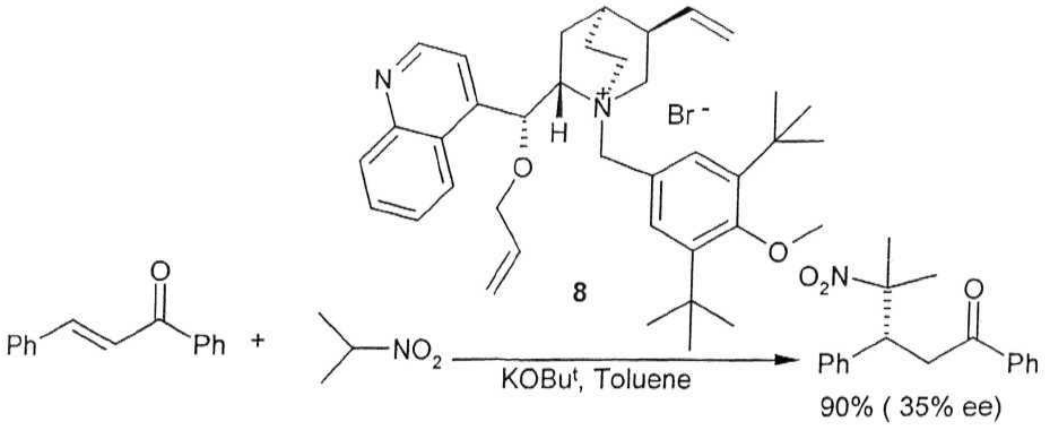
A solid-liquid phase transfer catalyst, efficiently promotes asymmetric Michael reaction without added solvent (Scheme 5). For example, in the reaction of chalcone with acetylamino malonate in the presence of quaternary salt derived from TV-methyl ephedrine, the corresponding adduct was obtained in 68% ee (Scheme 5).[10]

Scheme 5



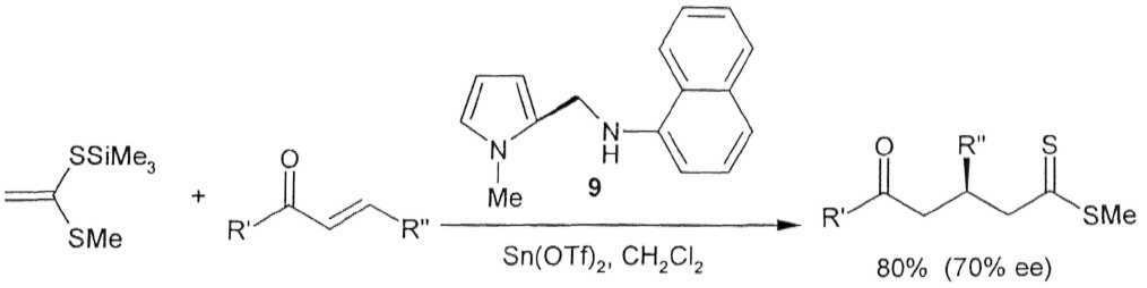
Kim *et al.* reported the catalytic asymmetric Michael addition, promoted by quarternary ammonium salt derived from cinconidine (Scheme 6). Treatment of nitroalkanes with chalcone derivatives under mild conditions afforded the corresponding Michael adducts in moderate to good enantiomeric excess (Scheme 6).[12]

Scheme 6



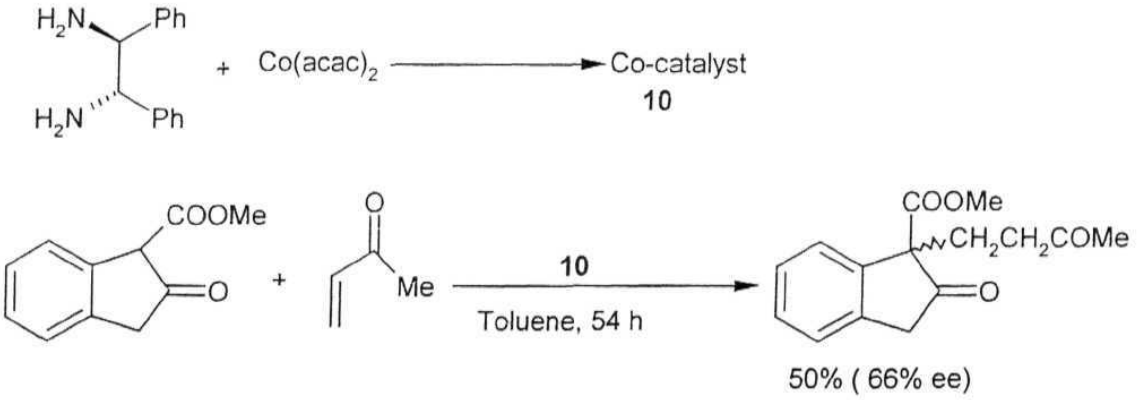
Mukaiyama and coworkers[13] reported the catalytic asymmetric Michael reaction of enethiolates, employing catalytic amount of stannous triflate and a chiral diamine (Scheme 7).

Scheme 7



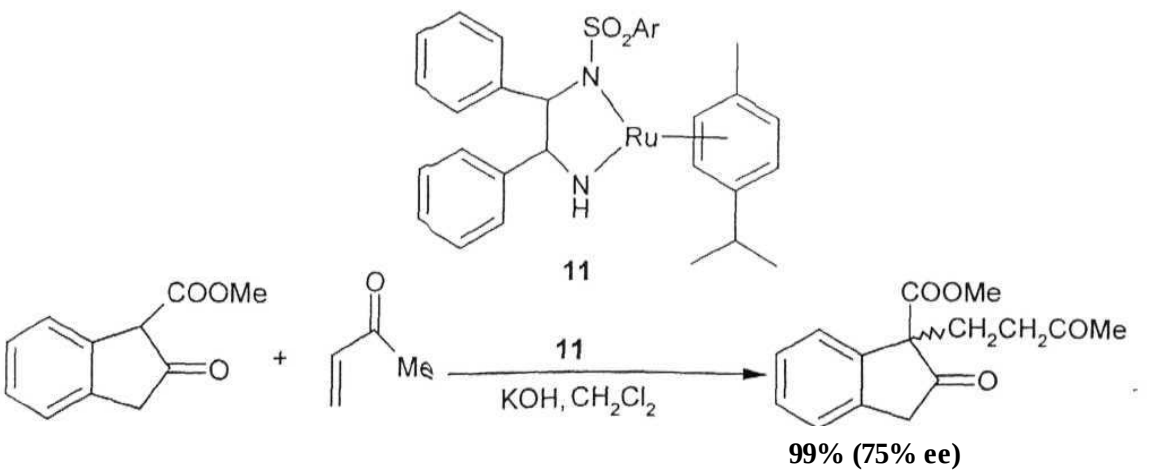
A cobalt catalyst, prepared from $Co(acac)_2$ and (+) or (-)-l,2-diphenylethane-l,2-diamine, is useful in the enantioselective Michael addition of β-keto ester to methyl vinyl ketone (Scheme 8). Asymmetric induction of 66% cc was realized in the reaction of methyl indane-1-one-2-carboxylate.[14]

Scheme 8



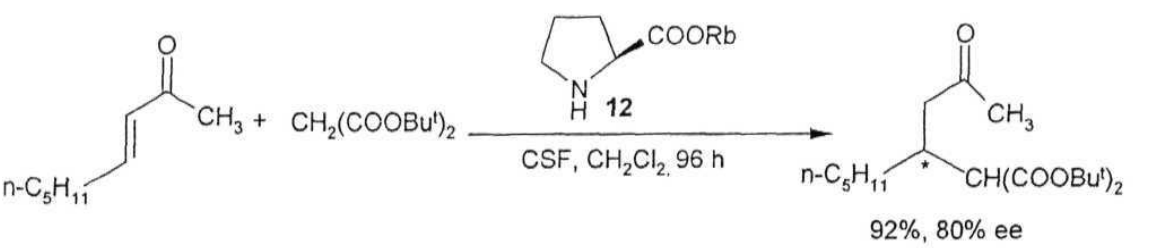
Catalytic asymmetric Michael reaction of (3-keto esters and methyl vinyl ketone was reported by Suzuki *et al.*[15] using a chiral diamine based Ru complex to obtain Michael adducts in up to 75% ee (Scheme 9).

Scheme 9



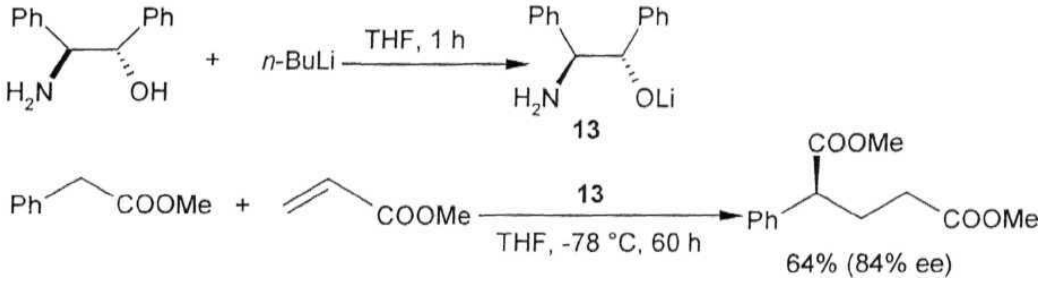
Yamaguchi *et al.*[16] found that the (*S*)-proline rubidium salt catalyses the asymmetric Michael reaction of malonate anions (Scheme 10). High enantiomeric excess was obtained when di(*t*-butyl)malonate was reacted with (*E*)-enones in the presence of CsF.

Scheme 10



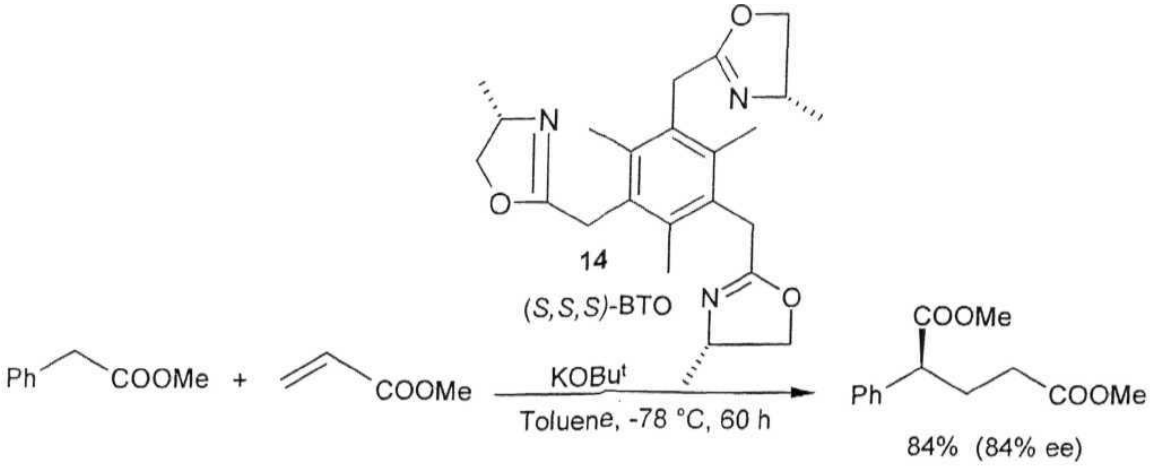
Koga *et al.*[17] prepared the chiral amino alcohol lithium alkoxides for use in the enantioselective Michael reaction of methyl phenylacetate and methyl acrylate. The corresponding adduct was obtained in 84% ee (Scheme 11).

Scheme 11



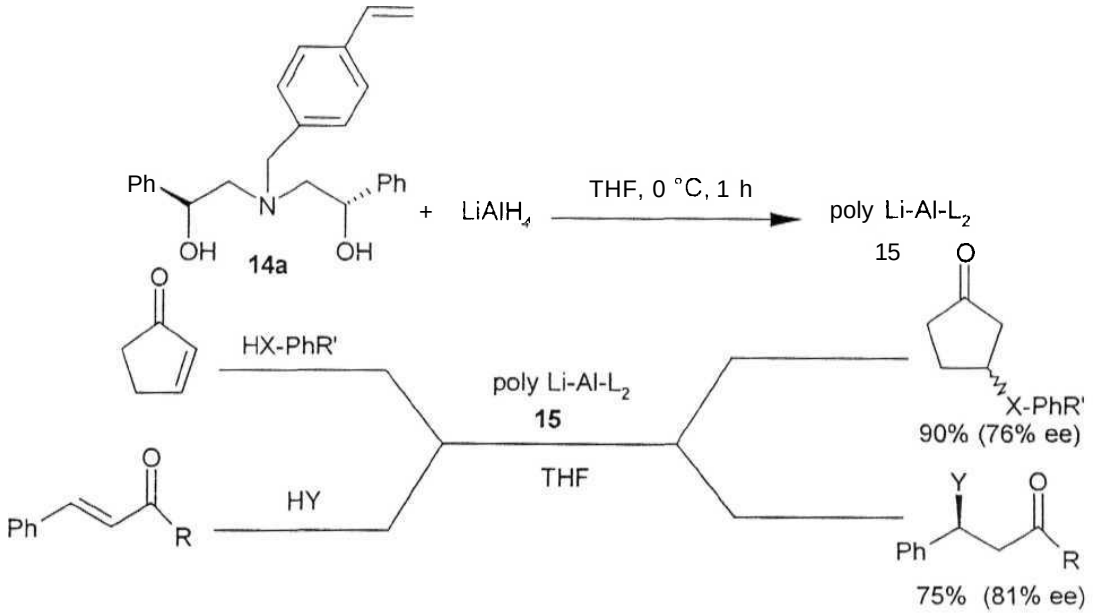
Benzene based tripodal oxazolines are found to be novel chiral ligands for the catalytic enantioselective Michael addition via potassium enolates (Scheme 12). Methyl phenylacetate undergoes 1,4-addition to methyl acrylate using a catalytic amount of a KOBu^t-oxazoline complex in toluene at -78 °C to give the corresponding adduct in 84% yield (82% ee).[18]

Scheme 12



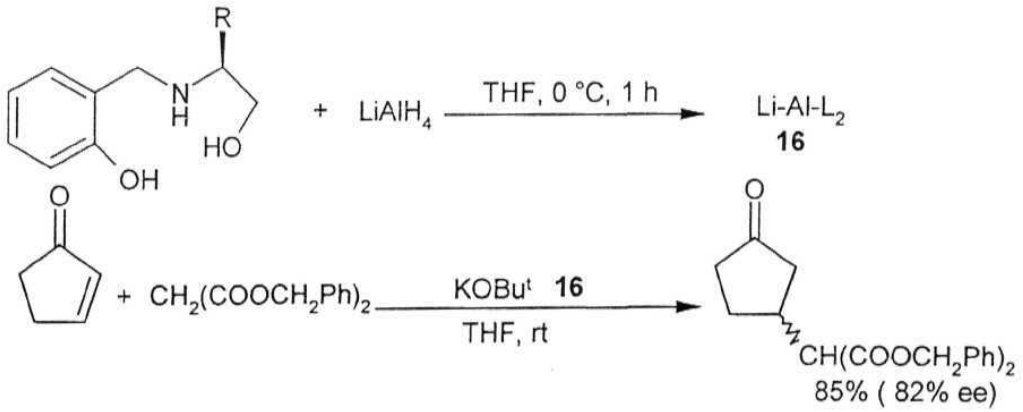
Sundararajan and Manickam[19-21] synthesised the C_2-symmetric chiral amino diol derived polymer anchored catalyst 15 for applications in asymmetric Michael addition reaction (Scheme 13).

Scheme 13



Narasimhan and coworkers[23] developed a chiral amino diol catalyst 16, which promotes certain asymmetric Michael additions (Scheme 14).

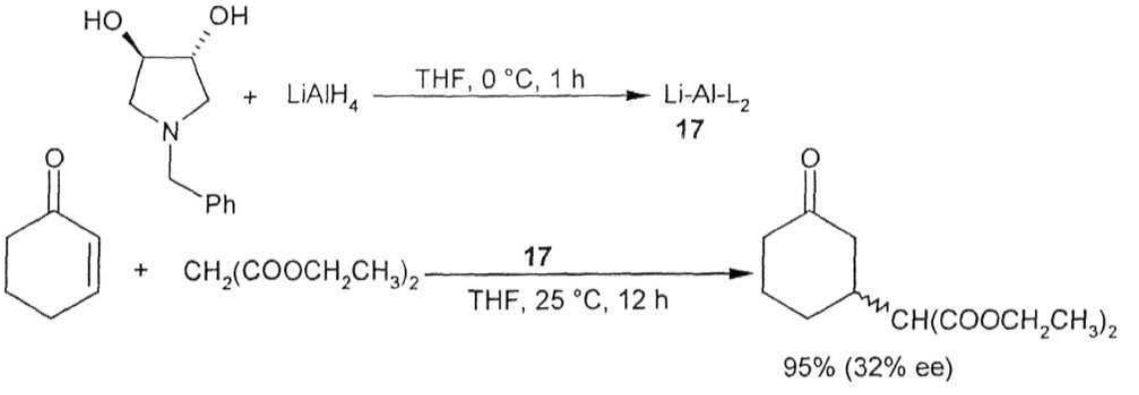
Scheme 14



Choudary and coworkers[24] prepared a heterobimetallic catalyst by the reaction of $LiAlH_4$ with an aminodiol derived from natural (+)-tartaric acid that promotes asymmetric Michael addition of malonic esters, thiophenols and nitro

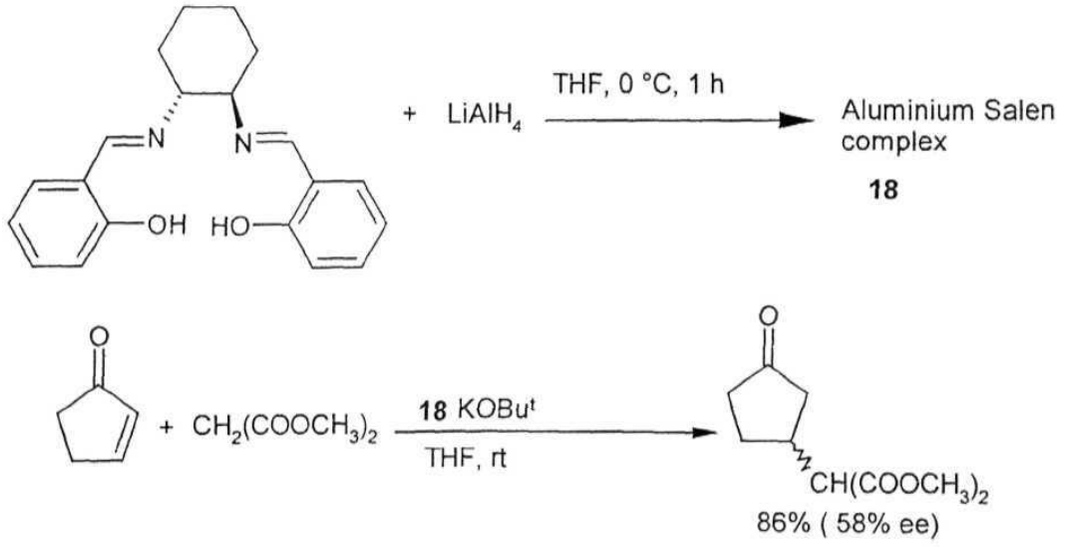
alkanes with acyclic enones in excellent yields, but with low enantiomeric excesses (Scheme 15).

Scheme 15



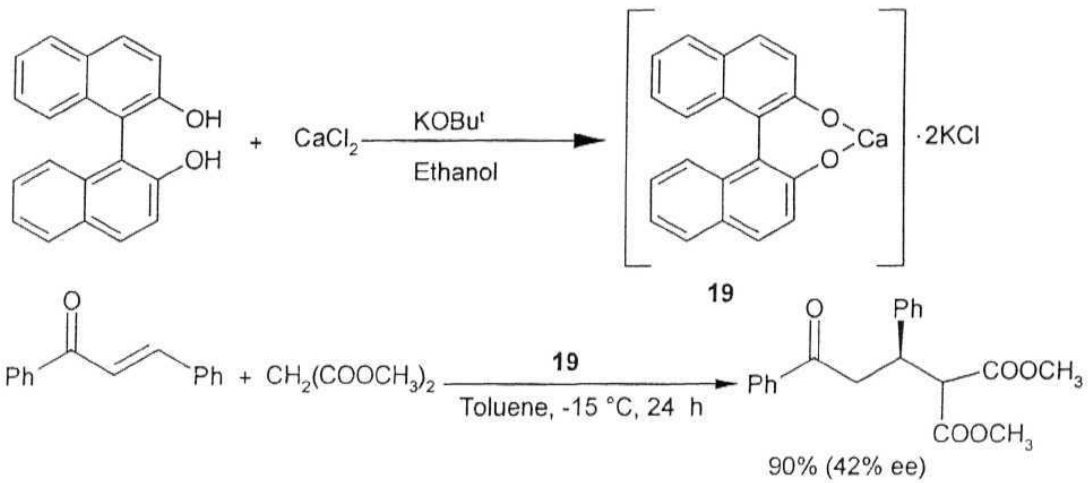
Joshi *et al.*[25] reported that the heterobimetallic complex **18,** prepared from a chiral SALEN ligand and RED-Al catalyses the Michael reaction between various dialkyl malonates and cycloalkenones to give adducts in high yields with up to 58% ee (Scheme 16).

Scheme 16



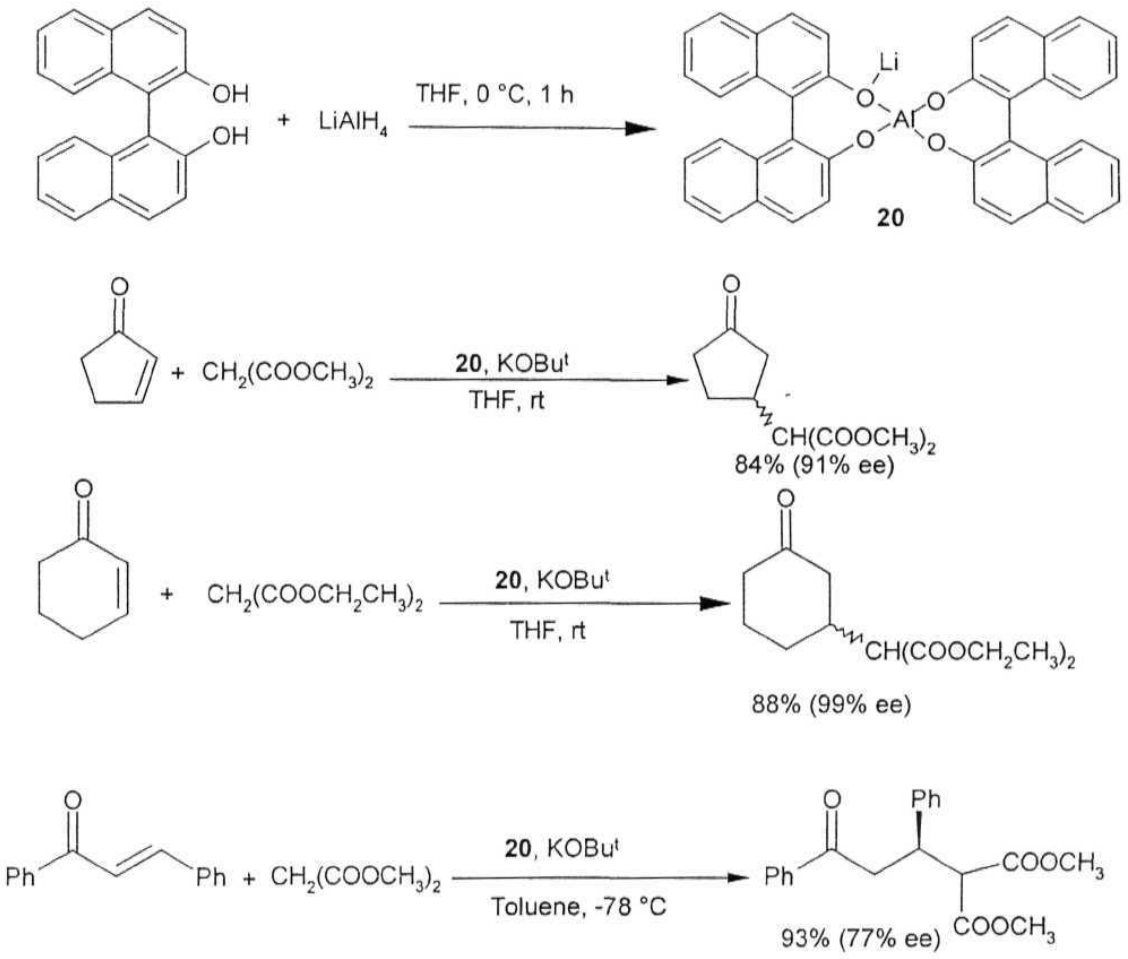
Recently, Kumarasamy *et al.*[26] reported a new calcium-binol catalyst 19 for asymmetric Michael addition of enones (Scheme 17). In the reaction between cyclopentenone and dimethyl malonte an asymmetric induction of 88% ee was realized (Scheme 17) using this catalyst.

Scheme 17



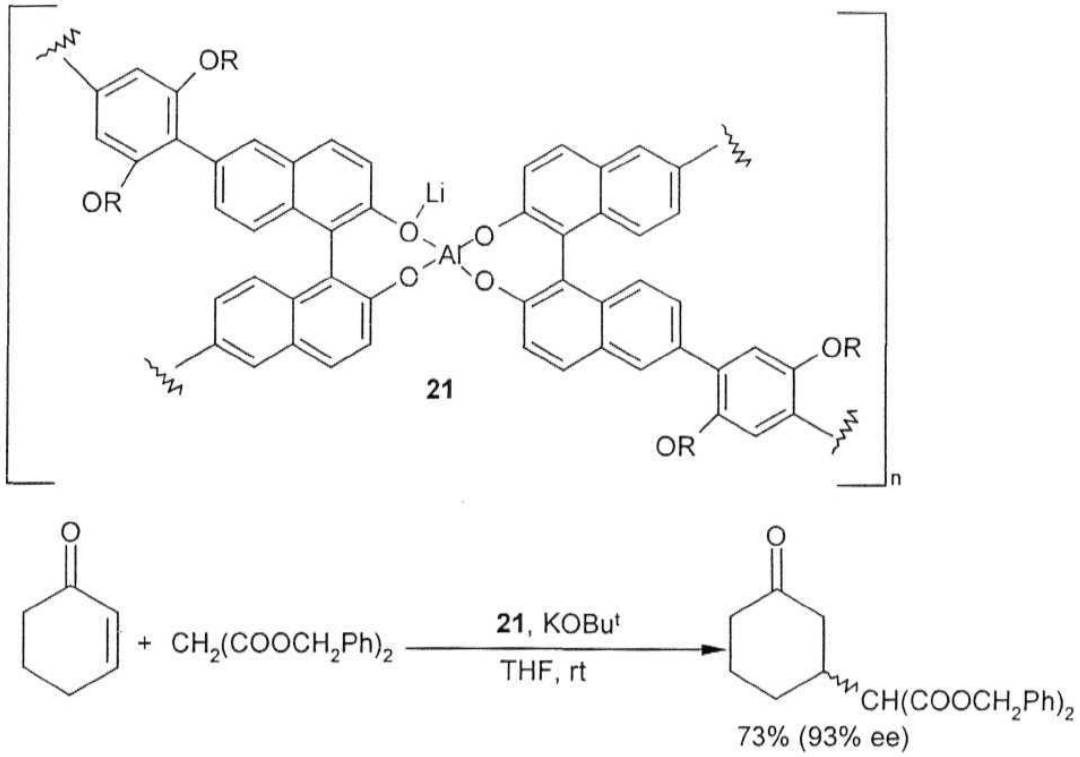
A spectacular achievement in the asymmetric Michael reaction is the discovery of heterobimetallic multifunctional asymmetric catalysis by Shibasaki and coworkers.[27-33] In a series of reports, these authors elaborated the ability of such heterobimetallic complexes of binol-aluminium 20 or binol-lanthanide alkali metal complexes to bring about highly enantioselective Michael addition reactions (Scheme 18).

Scheme 18



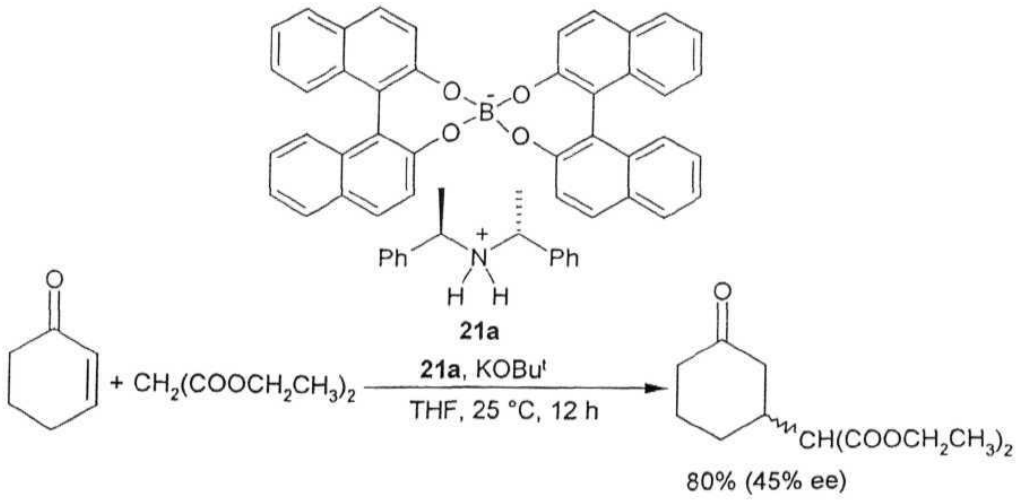
Recently, Sasai *et al.*[34] reported that the polymer anchored heterobimetallic binol-aluminium complex promote the asymmetric Michael addition reaction. The immoblised poly-ALBs 21 are readily prepared from polymeric BINOL derivatives and $LiAlH_4$ The combined use of 9 mol% of *n*-BuLi with 10 mol% of 6,6'-aryl-tethered poly-ALB gave the Michael adducts in up to 93% ee. After completion of the reaction, the insoluble catalyst was recovered and reused.

Scheme 19



Previously, it was found in this laboratory[35] that the ammonium borate complex, prepared using the chiral 1,1'-bi-2-naphthol, $B(OH)_3$ and (*R*,*R*)-α,α'-dimethyldibenzylamine, promotes the asymmetric Michael addition reaction of diethyl malonate to cyclohexenone in the presence of $KOBu^t$ to give the corresponding Michael adducts in up to 45% ee.

Scheme 20



In continuation of these efforts, we have examined the application of the borate complexes prepared using chiral 1,1'-bi-2-naphthol, α,α-diphenyl-2-pyrrolidine methanol and boric acid. We have also examined the application of oxazaborolidine derived from α,α-diphenyl-2-pyrrolidinemethanol for application in asymmetric Michael additions. The results are described in this chapter.

3. 2 Results and Discussion

3. 2. 1 Asymmetric Michael reaction promoted by chiral α,α-diphenyl-2-pyrrolidinemethanol derived ammonium borate complex 22

As discussed in chapter 1, the ammonium borate complex 22 can be readily prepared using chiral l,l'-bi-2-naphthol, α,α-diphenyl-2-pyrrolidinemethanol and boric acid. The reaction between diethyl malonate and cyclohexenone in THF solvent in the presence of the borate complex 22 (10 mol%) and $KOBu^t$ (20 mol%) gave the corresponding Michael adduct in 80% yield and 20% ee (Scheme 21). Since the complex is capable of catalyzing the Michael reactions, we undertook efforts to study the reaction under various conditions, so as to optimize the results.

Scheme 21

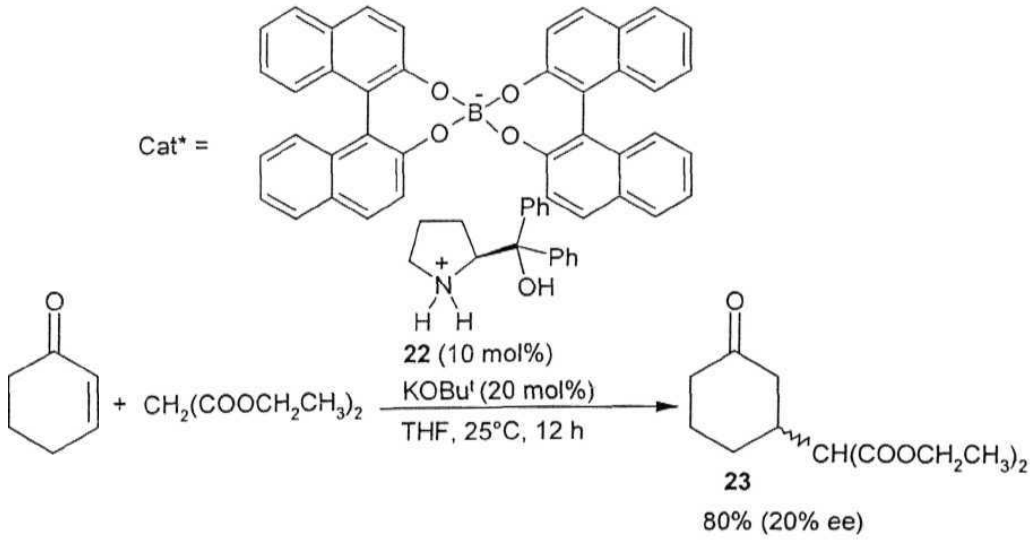


Table 1: Asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by chiral ammonium complex 22: Effect of various solvents[a]

Entry	Solvent	ee (%)[b]	Yield (%)
1.	THF	20	80
2.	Toluene	13	79
3.	DCM	10	75
4.	$CHCl_3$	6	72

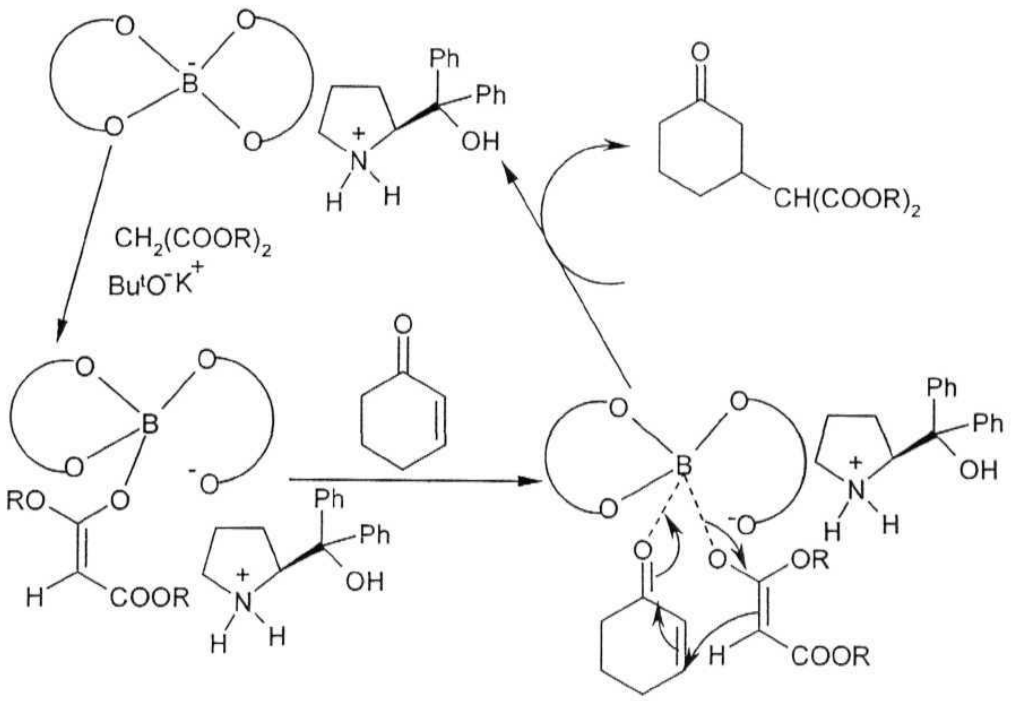
a. All the reactions were performed by dissolving ammonium borate complex 22 (0.5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in various solvents and the contents were stirred at rt for 12h.

b. The ee values are calculated on the basis of reported $[\alpha]_D^{27}$ values.[5]

Generally, lowering the temperature leads to improvement in the enantioselectivity. To examine this, we carried out the reactions at lower temperatures. Unfortunately, there was no significant increase in the ee of the product even when the reactions were carried out at -78 °C. Moreover, the chemical yields were very poor under these conditions. Reactions were also carried out in various solvents such as DCM, toluene and THF. The results were better in THF solvent (Table 1).

A tentative mechanism may be considered for the formation of the Michael adducts, where the donor is deprotonated and coordinated to the boron atom. The enone, would then accept the enolate as shown in the Scheme 22. After the 1,4-addition, the ketone is released abstracting a proton from the complex to afford the corresponding Michael adduct (Scheme 22).

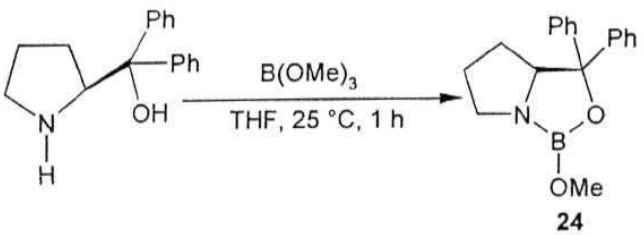
Scheme 22



3. 2. 2 Asymmetric Michael reaction promoted by the chiral oxazaborolidine derivatives

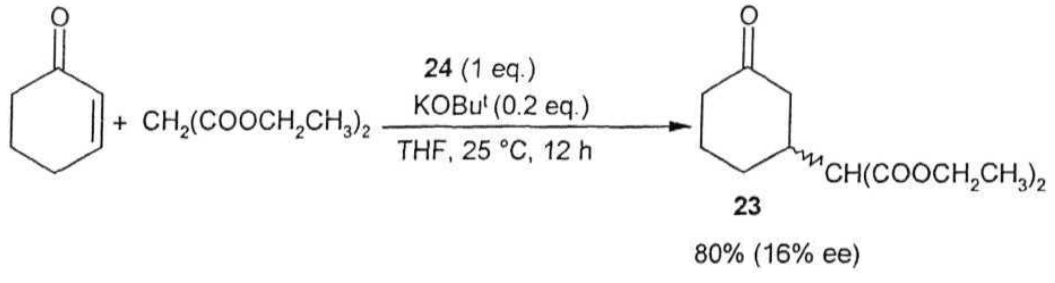
The chiral ammonium borate complex 22 (Scheme 21) provided only poor asymmetric induction. Accordingly, we have decided to examine the applications of the oxazaborolidine derivative 24 that can be readily prepared from (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol and trimethyl borate (Scheme 23).[37]

Scheme 23



We found that the Michael reaction of diethyl malonate anc cyclohexenone using this reagent, did not take place even after 7 days. Presumably, the complex is not basic enough to promote the Michael reaction. As discussed in the introductory section, sodium or potassium alkoxides (NaOR or KOR) are generally used for the preparation of bimetallic catalysts capable of catalyzing Michael reaction. Accordingly, we examined the use of oxazaborolidine catalyst 24 in the presence of $KOBu^t$. Indeed, it was observed that the use of $KOBu^t$ was effective in the catalysis of Michael reaction. For example, the reaction between diethyl malonate and cyclohexenone in the presence of the oxazaborolidine catalyst 24 and $KOBu^t$ in THF solvent gave the Michael adduct in 16% ee (80 % yield) (Scheme 24).

Scheme 24



Since, the complex 24 is capable of catalyzing the Michael reaction, we undertook efforts to study the reaction under various conditions. The reaction was carried out in different solvents like toluene and dicholoromethane (DCM). It was observed that the enantiomeric excess increased from 16% ee to 25% ee when toluene was used as solvent (Table 2)-

Table 2: Effect of solvents on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.[a]

Entry	Solvent	ee (%)	Yield (%)
1.	THF	16	80
2.	Toluene	25	78
3.	DCM	15	75
4.	$CHCl_3$	12	72

a. The oxazaborolidine complex 24 (5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in various solvents and stirred at rt for 12 h.

Table 3: Effect of temperature on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.[a]

Entry	Time (h)	Temp (^{0}C)	ee (%)	Yield (%)
1.	12 h	25	25	80
2.	20 h	0	***50***	
3.	24 h	-10	62	70

a. All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at various temperature.

The reactions were also carried out at lower temperatures. Fortunately, there was significant increase in the ee of product when the reactions were carried out at 0 °C. The ee increased from 25% to 50% in toluene at 0 °C (Table 3). Unfortunately, the chemical yields were very poor when the reactions were carried out below –10 °C.

Table 4: Effect of different bases on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.[a]

Entry	Additives	ee (%)	Yield (%)
1.	$NaOBu^t$	40	75
2.	*n*-BuLi	35	74
3.	NaH	0	77

a. All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), base (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0°C for 20 h.

Since carrying out reactions at lower temperature did not give fruitful results, we investigated the effect of the base used in the reaction. As outlined in the introductory section, Yamaguchi *et al*[6] reported that (*S*)-proline salts of ions such as Li, Na, K, Rb and Cs were effective catalyst for Michael addition. They noted that the sodium and potassium ions were more effective than the lithium ions. Hence, we have examined the reactions using various bases. However, there **was** no significant increase in the **ee** when compared to the use of $KOBu^t$ (Table 4).

It is known that the addition of molecular sieves to the reaction mixture facilitates the removal of traces of water present, leading to better results in certain reactions.[5] To examine this effect, reactions were carried out in the presence of molecular sieves (MS 4A°). Unfortunately, there was no significant difference in the ee under these conditions.

Table 5: Effect of concentration of the chiral oxazaborolidine catalyst 24 on the asymmetric Michael reaction between cyclohexenone and diethyl malonate.[a]

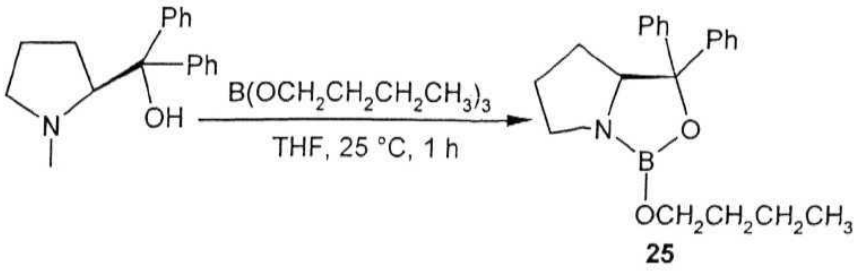
Entry	24 (eq.)	$KOBu^t$	ee (%)	Yield (%)
1.	0.1	0.2	11	72
2.	0.5	0.2	25	73
3.	1.0	0.2	50	75

a. All the reactions were performed by dissolving oxazaborolidine complex 24 (1-5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0 °C for 20 h.

As expected, increase in the concentration of the oxazaborolidine catalyst 24 led to increase in the enantioselectivity. The results are summarised in Table 5.

The effect of different R group in the (B-OR) moiety (R = *n*-Bu) was also studied (Scheme 25). It was observed that there is slight increase in the enantioselectivity under these conditions (Table 6).

Scheme 25



25

Table 6: Effect of different solvents and temperature on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 25.[a]

Entry	Additives	Time (h)	ee(%)	Yield (%)
1.[a]	THF	25 °C, 12 h	25	80
2.[a]	THF	0 °C, 20 h	50	75
3.[b]	Toluene	25 °C, 12 h	30	78
4.[b]	Toluene	0 °C, 20 h	58	74

a. The oxazaborolidine complex 25 (5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in THF and the contents were stirred at rt and 0 °C.

b. The oxazaborolidine complex 25 (5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in Toluene and the contents were stirred at rt and 0 °C.

Table.7: Effect of Lewis acids on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.[a]

Entry	Metalcomplex	ee(%)	Yield (%)
1.	$Ti(OPr^i)$	10	80
2.	$TiCl_4$	15	75
3.	$Al(OPr^i)_4$	30	78
4.	$LiAlH_4$	50	74

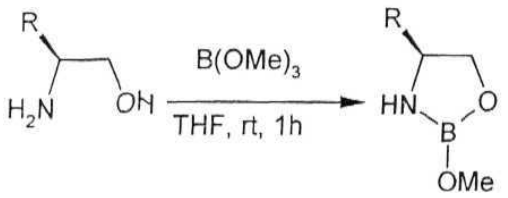
a. All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), $KOBu^t$ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0 °C for 20 h.

Since the boron centre is relatively less Lewis acidic, we have examined the use of more acidic aluminium and titanium derivatives. The metal complexes were prepared by reaction of the (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol

with $Ti(OPr^i)_4$, $TiCl_4$, $Al(OPr^i)_4$ and $LiAlH_4$. The results of Michael reactions are summarised in the Table 7.

As discussed in chapter 1 and chapter 2, we have developed convenient methods of preparation of enantiopure 1,2-amino alcohols like phenylglycinol, phenylalaninol, valinol and 2-amino butanol. Accordingly, we have also carried out studies on the Michael reaction using various oxazaborolidine derivatives 26-29 that can be readily prepared from the above mentioned amino alcohols and trimethyl borate (Scheme 26).

Scheme 26



26 R = Ph-

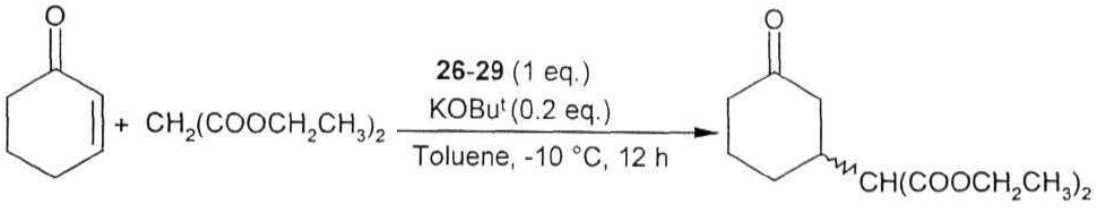
27 R = Ph-CH_2-

28 R = C_2H_5-

29 R = $(CH_3)_2$-CH-

For example, the reaction between diethyl malonate and cyclohexenone in the presence of the oxazaborolidine catalyst 26-29 and $KOBu^t$ in toluene solvent gave the Michael adduct in 25-32% ee (68-71% yield) (Scheme 27).

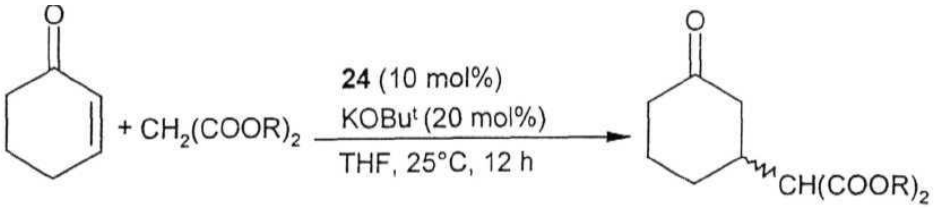
Scheme 27



26	R = Ph-	70% (30% ee)
27	R = Ph-CH_2-	71% (32% ee)
28	R = C_2H_5-	68% (25% ee)
29	R = $(CH_3)_2$-CH-	69% (25% ee)

It is evident from these studies that the (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol derived oxazaborolidines 24 and 25 in the presence of $KOBu^t$ gave better results. We have also examined the reactions using various malonate derivatives, such as dimethyl malonate, diethyl malonate, dibenzyl malonate and di-*t*-butyl malonate. The results are summarized in Scheme 28.

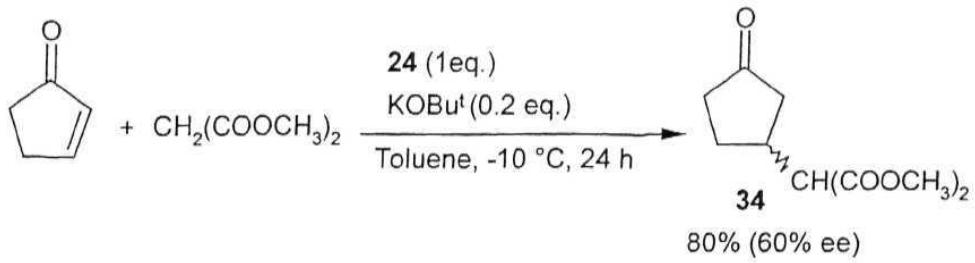
Scheme 28



30	R = CH_3	70% (60% ee)
31	R = Ph-CH_2	68% (60% ee)
32	R = Ph-$CH(CH_3)$	62% (20% ee)
33	R = Bu^t	65% (25% ee)

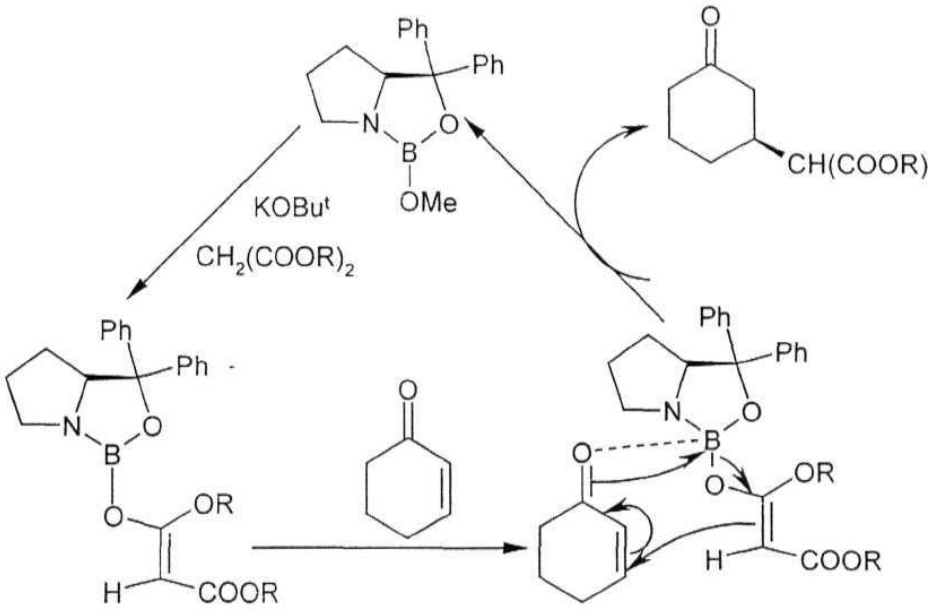
Studies using other enone derivatives like cyclopentenone were also carried out. It was found that the reaction between dimethyl malonate and cyclopentenone in toulene solvent at -10 °C in the presence of oxazaborolidine catalyst 24 and $KOBu^t$ gave the Michael adduct in 60% ee (80 % yield). It is of interest to note that the $[\alpha]_D^{25}$ value (lit[25] for 100 % ee, $[\alpha]_D^{25}$ = (+) 69.0 (C3.93, $CHCl_3$)) of the adduct obtained in this run is higher than that of the corresponding cyclohexyl derivatives (lit[29] for 75% ee, $[\alpha]_D^{25}$ = (+) 3.01 (C 2.1, $CHCl_3$)). The enantioselectivity realized is also high.

Scheme 29



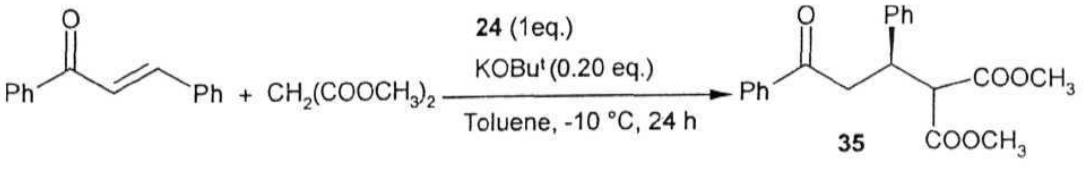
A tentative mechanism can be considered for the formation of the Michael adducts, where the dialkyl malonate is deprotonated and coordinated to the central boron atom via exchange of the alkoxy group (Scheme 30). The enone then accepts the enolate through coordination with the boron atom (Scheme 30).

Scheme 30



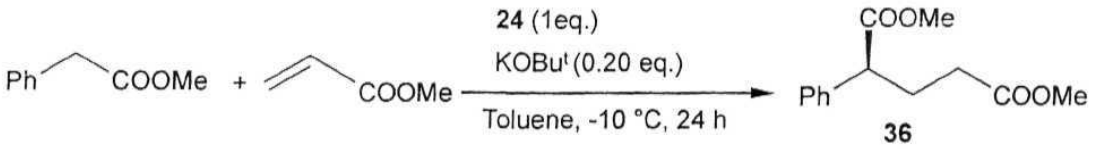
We have also briefly extended the studies to acyclic enones like *trans*-chalcone and enolate derived from methyl phenylacetate. In these cases, the Michael addition was smooth but the enantioselectivity realized was very poor. This may be due to the loss of rigidity in the acyclic system. For example, chalcone reacts with dimethyl malonate in the presence of oxazaborolidine catalyst 24 and KOBu^t to give the product in 64% yield with only 10% ee (Scheme 31).

Scheme 31



Methyl phenylacetate reacts with methacrylate in the presence of chiral oxazaborolidine 24 and $KOBu^t$ to give the product in 65% yield in only 5% ee (Scheme 32).

Scheme 32

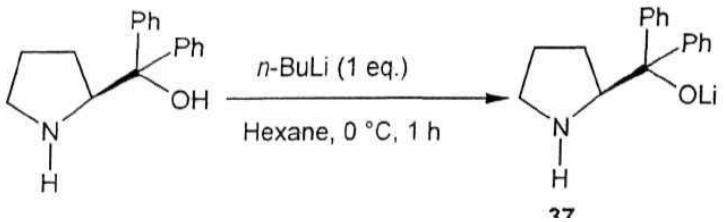


3. 2. 3 Asymmetric Michael reactions promoted by chiral α,α-diphenyl-2-pyrrolidinemethanol derived lithium alkoxide

As mentioned in the introductory section, Koga *et al.*[17] reported that the simple amino alcohol derived lithium alkoxide were effective catalyst for asymmetric Michael addition reaction. It was noted that the lithium alkoxide was more effective than the sodium and potassium alkoxides.

Therefore, we have examined the a,a-diphenyl-2-pyrrolidinemethanol derived lithium alkoxide prepared *in situ* as shown in the Scheme 33. It was found that this catalyst was also effective for promoting the Michael addition reactions.

Scheme 33



37

Table 8: Effect of temperatures on the asymmetric Michael reaction between cyclohexenone and dimethyl malonate using the chiral lithium alkoxide catalyst 37.[a]

Entry	Solvent	Condition	ee (%)	Yield (%)
1.	Hexane	25 °C, 12 h	21	90
2.	Hexane	0°C, 12 h	45	85
3.	Hexane	-78 °C, 12 h	70	80

a. All the reactions were performed by dissolving chiral lithium alkoxide catalyst 37 (5 mmol), *n*-BuLi (5 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in hexane.

The enantioselectivity realized was better when reactions were carried out at -78 °C as shown in the Table 8. It was found that only poor results were obtained (5-10% ee) in the reactions using α,α-diphenyl-2-pyrrolidinemethanol derived potassium and sodium alkoxides.

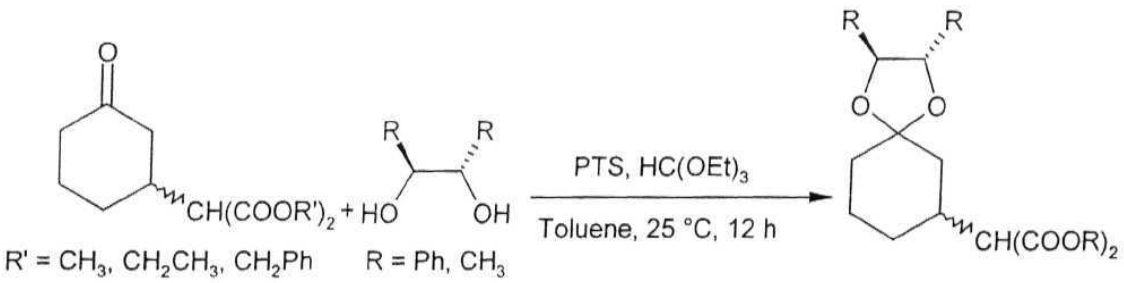
3. 2. 4 HPLC Analysis of the Michael adducts

The enantiomeric excesses of the adducts formed in the Michael reactions using the chiral ammonium borate complex 22 and oxazaborolidine 24 were calculated from the $[\alpha]_D^{25}$ values reported by Shibasaki and coworkers for these samples.[5] However, the $[\alpha]_D^{25}$ values exhibited by these derivatives are low and hence prone to have higher experimental errors. Therefore, we have carried out HPLC analysis of these samples. The adducts formed in the Michael reaction

could not be analysed using chiral columns accessible to us (chiral cell OD, chiral pak OP and chirex (S)-valine).

We have then made attempts to prepare the diastereomeric ketal derivatives for HPLC analysis. The ketal derivatives of (*S, S*)-(-)-1,2-diphenyl-1,2-ethane diol could be readily prepared (Scheme 34). The (±)-1,2-diphenyl-1,2-ethane diol has been resolved readily using (*S*)-proline to obtain (*S, S*)-(-)-1,2-diphenyl-1,2-ethane diol in > 99% ee following the procedure developed in this laboratory.[36]

Scheme 34



The H and ^{13}C NMR data of the diastereomeric ketals were not helpful to estimate the ee of these isomers. The HPLC analysis of the diastereomeric ketals of racemic adducts and the optically active adducts were carried out on chiralcell OD column (hexane/2-propanol (96:4) mixture as eluent). Unfortunately, accurate values of the ee could not be estimated as the column efficiency was poor and the values of ee could not be confirmed by ^{1}H NMR analysis or HPLC data.

It is of interest to note that the $[\alpha]_D^{25}$ values (lit[25] for 100 % ee, $[\alpha]_D^{25}$ = (+) 69.0 (C3.93, $CHCl_3$)) of the Michael adduct 34 obtained from cyclopentenone and dimethyl malonate are higher than that of the corresponding cyclohexyl adduct (lit[29] for 75% ee, $[\alpha]_D^{25}$ = (+) 3.01 (C 2.1, $CHCl_3$)). Although, the cyclopentenone is relatively expensive, it is desirable to use the cyclopentyl derivatives in further studies so as to minimize the error in ee values.

3. 3 Conclusions

Catalytic asymmetric Michael reaction of various malonate derivatives with different Michael acceptor using chiral ammonium borate complexes prepared from chiral l,l'-bi-2-naphthol, $B(OH)_3$, (*S*)-α,α-diphenylpyrrolidine methanol was investigated. The chiral ammonium borate complex catalyses the Michael addition of diethyl malonate to cyclohexenone in the presence of $KOBu^t$ to give the corresponding adducts in < 20% ee. Asymmetric Michael addition reaction using chiral oxazaborolidines derived from (*S*)-α,α-diphenylpyrrolidinemethanol and $B(OMe)_3$ catalyses the Michael reaction of diethyl malonate to cyclohexenone in the presence of $KOBu^t$ to give the corresponding adducts in < 62% ee. Plausible mechanism were considered. The asymmetric Michael addition reaction using chiral lithium alkoxide prepared from (*S*)-α,α-diphenylpyrrolidine methanol was also studied. The chiral lithium alkoxide complex in the presence of $KOBu^t$ catalyses the Michael reaction of diethyl malonate to cyclohexenone to give the corresponding adducts in < 70% ee.

3. 4 Experimental Section

3. 4. 1 General Information

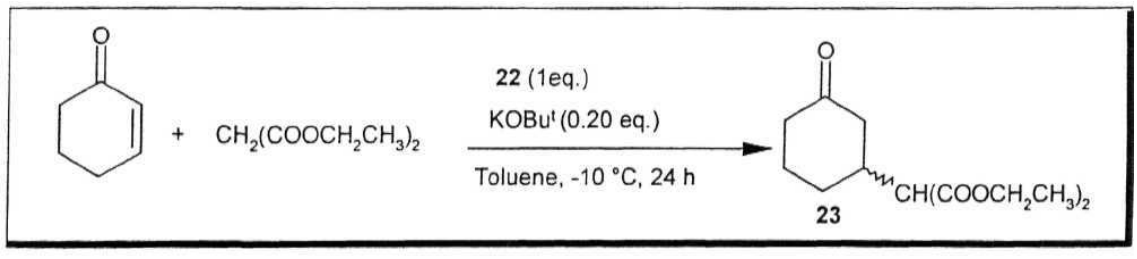
Several of the general experimental details given in Chapter 1 and Chapter 2 are also applicable here. Cyclohexenone, cyclopentenone, dibenzyl malonate, diethyl malonate, di(*t*-butyl)malonate were purchased from Lancaster, U.K. *(S)*-α,α-Diphenyl-2-pyrrolidinemethanol (DPPM) was synthesized as described in chapter 1.

3. 4. 2 Preparation of chiral l,l'-bi-2-naphthol ammonium borate complex 22

(*S*)-(-)-1,1'-Bi-2-naphthol (1.43 g, 5 mmol), $B(OH)_3$ (0.16 g, 2.5 mmol) and (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) were taken in CH3CN (20 mL). The contents were refluxed for 12 h. The reaction mixture was cooled to 25 °C and filtered. The precipitate was washed with CH3CN (2 X 5 mL) and dried under nitrogen atmosphere to get the corresponding ammonium borate complex **22.** It was stored under nitrogen atmosphere for further use.

3. 4. 2. 1 Typical procedure for the reaction between diethyl malonate and cyclohexenone using chiral l,l'-bi-2-naphthol ammonium borate complex 22.

To a stirred solution of the chiral l,l'-bi-2-naphthol ammonium borate complex **22** (0.1 g, 1 mmol) in dry THF (50 mL), $KOBu^t$ (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in THF (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HC1 (10 mL) and extracted with Et_2O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.



Yield 1.0g(80%)

IR (neat) (cm^{-1}) 1730,1230

^{1}H-NMR (5 ppm, $CDCl_3$) L20 (q, J = 6.8 Hz, 6H), 1.4-2.5 (m, 9H), 3.2

(d, **J = 7.9 Hz, 1H), 4.1 (t, J = 7.1 Hz, 4H) (Spectrum No. 16)**

^{13}C-NMR (δ ppm, $CDCl_3$) 13.9, 24.4, 28.6, 37.9, 40.9, 45.0, 56.8, 61.3, 167.7, 209.4 **(Spectrum** No. 17)

$[\alpha]_D^{25}$ $[\alpha]_D^{25}$ = (+) 0.7 (*c* 3, $CHCl_3$), {lit[29] for 78% ee, $[\alpha]_D^{25}$ = (+) 2.78 (*c* 2.56, $CHCl_3$)}

3. 4. 3 Preparation of chiral oxazaborolidine catalyst 24 using (*S*)-(-)-α, α-diphenyl-2-pyrrolidinemethanol and $B(OMe)_3$

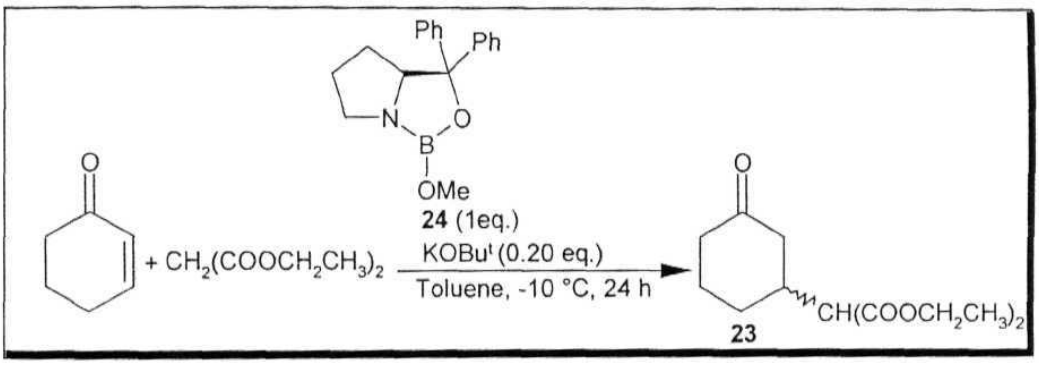
To a solution of (*S*)-(-)-α, α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) in dry THF (5 mL), was added trimethyl borate (0.6 g, 5.2 mmol)) and the mixture was stirred under nitrogen at 25 °C for 1 h. THF was removed under reduced pressure and dried under nitrogen to get oxazaborolidine complex **24.**

3. 4. 4 Michael addition reaction of cyclohexenone with various malonate derivatives

3. 4. 4. 1 Typical procedure for the Michael reaction between diethyl malonate and cyclohexenone:

To a stirred solution of the oxazaborolidine catalyst 24 (1.45 g, 5 mmol) in toluene (50 mL), $KOBu^t$ (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for

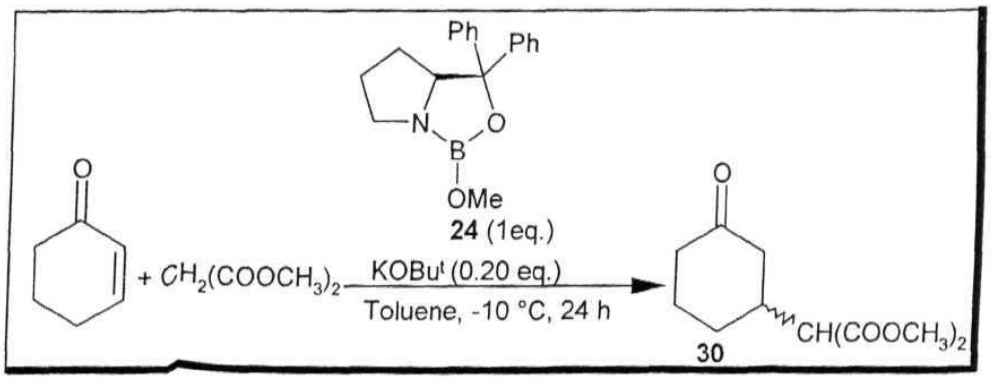
30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HC1 (10 mL) and extracted with Et_2O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.



Yield	0.9g (70 %)
IR (neat)	(cm^{-1}) 1730, 1230
^{1}H-NMR	(5 ppm, $CDCl_3$) L20 (q, J = 6.8 Hz, 6H), 1.4-2.5 (m, 9H), 3.2 (d, J = 7.9 Hz, 1H), 4.1 (t, J = 7.1 Hz, 4H)
^{13}C-NMR	(5 ppm, $CDCl_3$) 13.9, 24.4, 28.6, 37.9, 40.9, 45.0, 56.8, 61.3, 167.7,209.4
$[\alpha]_D^{25}$	$[\alpha]_D^{25}$ = (+) 2.2 (*c* 3, $CHCl_3$), {lit[29] for 78% ee, $[\alpha]_D^{25}$ = (+) 2.78 (*c* 2.56, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5] The above procedure is followed for the Michael reaction of various malonate esters with cyclohexenone, cyclopentenone, chalcone and methacrylate. The results are summarized in Scheme 26. The data are given below.

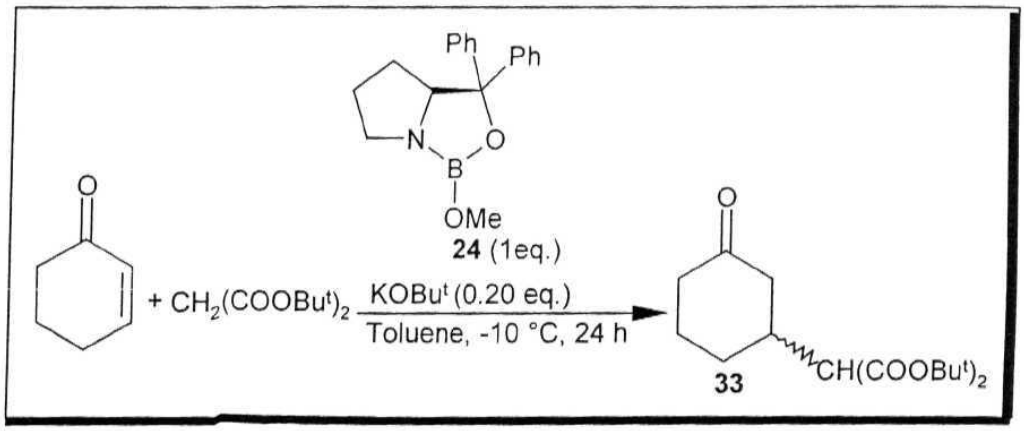
3. 4. 4. 2 Michael reaction of cyclohexenone with dimethyl malonate



Yield	0.80g (70 %)
IR (neat)	(cm^{-1}) 1736, 1259
^{1}H-NMR	(8 ppm, $CDCl_3$) .1.4-2.6 (m, **9H),** 3.30 (d, J = 7.9 Hz, 1H), 3.7 (s, 6H) **(Spectrum No. 18)**
^{13}C-NMR	**(S** ppm, $CDCl_3$) 24.4, 28.7, 38.0, 40.9, 45.0,52.4, 56.4, 168.1, 209.4 **(Spectrum No. 19)**
r ^{25}	$[\alpha]_D^{25}$ = (+) 2.4 (*c* 3, $CHCl_3$), {lit[29] for 75% ee, $[\alpha]_D^{25}$ = (+) 3.01 (*c* 2.1, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5]

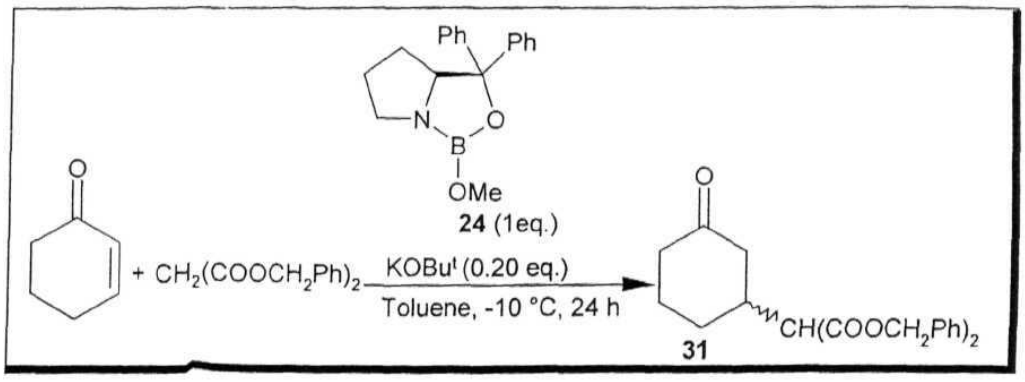
3. 4. 4. 3 Michael reaction of cyclohexenone with di-*t*-butyl malonate.



Yield	1.0g(65%)
IR (neat)	(cm^{-1}) 1734, 1209
^{1}H-NMR	(δ ppm, $CDCl_3$) 1.5 (s, 18H), 1.92-2.58 (m, 9H), 3.10 (d, J = 7.7 HZ, 1H), **(Spectrum** No. **20)**
^{13}C-NMR	(6 ppm, $CDCl_3$) 24.5, 27.8, 28.7, 37.7, 40.9, 45.0, 58.6, 81.6, 167.0, 209.5 **(Spectrum No. 21)**
$[\alpha]_D^{25}$	$[\alpha]_D^{25}$ = (+) 1.1 (*c* 3, $CHCl_3$), {lit[29] for 100% ee, $[\alpha]_D^{25}$ = (+) 4.2 (*c* 1.02, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.

3. 4. 4. 4 Michael reaction of cyclohexenone with dibenzyl malonate.



Yield 1.28g(68%)

M. p. 44-45 °C (Lit 43°C)

IR(neat) (cm^{-1}) 1739, 1261

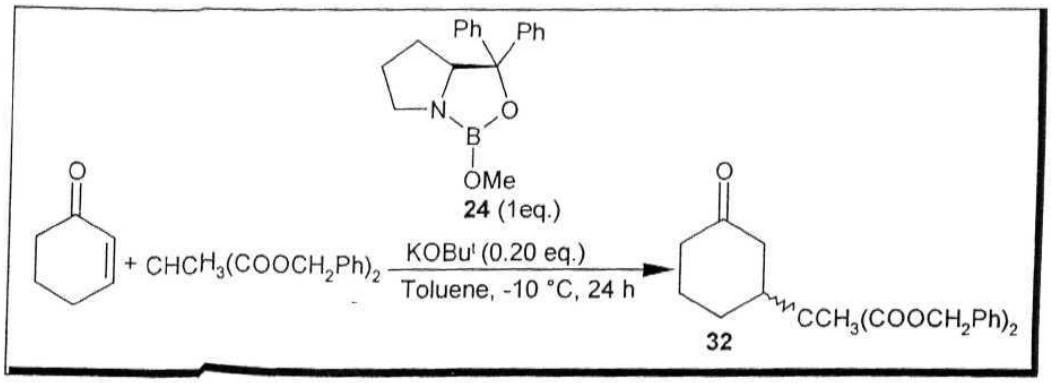
^{1}H-NMR (δ ppm, $CDCl_3$) 1.4-2.8 (m, 9H), 3.4 (d, J = 7.6 Hz, 1H), 5.2 (s, 4H) 7.2-7.4(m, **9H) (Spectrum No. 22)**

^{13}C-NMR (8 ppm, $CDCl_3$) 24.5, 28.6, 38.1, 41.0, 45.0, 56.8, 67.2, 128.3, 128.5, 128.6, 135.3, 167.5, 209.2 **(Spectrum No. 23)**

$[\alpha]_D^{25}$ $[\alpha]_D^{25}$ = (+) 0.75 (*c* 3, $CHCl_3$), {lit[29] for 92 %ee, $[\alpha]_D^{25}$ = (+) 1.15 (C 2.21, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5]

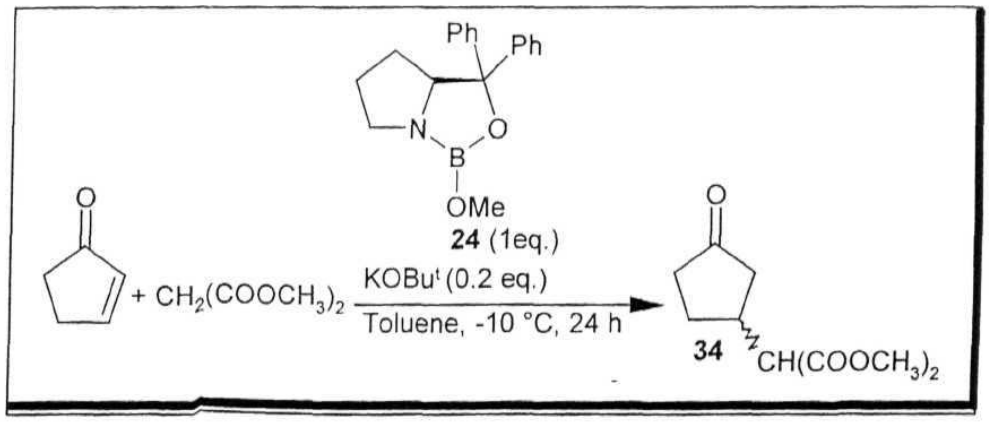
3. 4. 4. 5 Michael reaction of cyclohexenone with α-methyl dibenzyl malonate



Yield	1.0g (70 %)
IR (neat)	(cm^{-1}) 1732, 1231
^{1}H-NMR	ft ppm, $CDCl_3$) 1.20 (m, 1H), 1.4 (s, 3H), 1.5-2.7 (m, 8H), 5.1 (s, 4H), 7.3 (m, 10H)
^{13}C-NMR	(5 ppm, $CDCl_3$) 16.8, 24.7, 26.6, 41.0, 42.6, 43.3, 57.0, 67.1, 128.1, 128.4, 128.6, 135.4, 170.5, 170.6, 209.4
r $]^{25}$	$[\alpha]_D^{25}$ = 0.07(*c* 3, $CHCl_3$), {lit[29] for 87% ee, $[\alpha]_D^{25}$ = (+) 0.32 (*c* 3.93, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5]

3. 4. 4. 6 Michael reaction of cyclopentenone with diniethylmalonate.



Yield 0.79g (71 %)

IR (neat) (cm) 1732, 1231

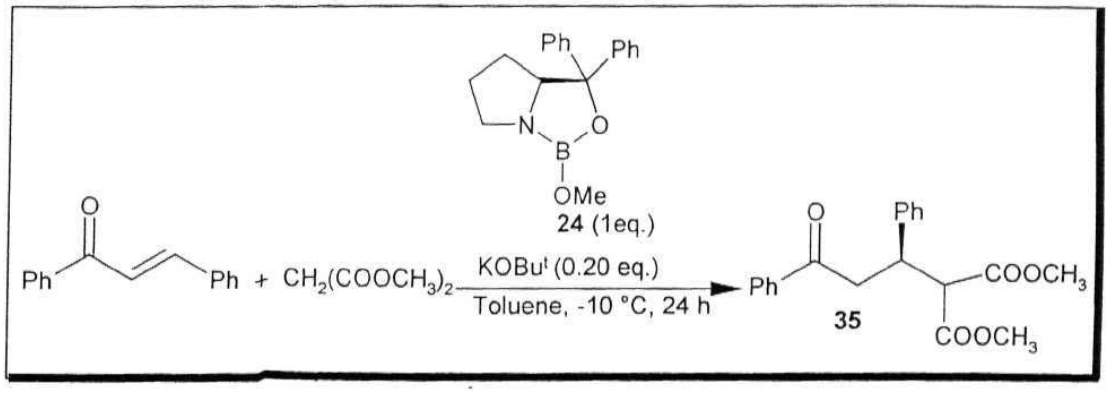
^{1}H-NMR (5 ppm, $CDCl_3$) 1.45-1.76 (m, 1H), 1.96 (dd, J=l 1.7, 1H), 2.05-2.35 (m, 3H), 2.46 (dd, J=6.8 Hz, 1H), 2.65-2.95 (m, 1H), 3.34 (d, J=9.3 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H) **(Spectrum No. 24)**

^{13}C-NMR (δ ppm, $CDCl_3$) 27.1, 36.1, 37.8, 42.5, 52.2, 55.8, 168.3, 216.4. **(Spectrum** No. **25)**

r *v*^{5} $[\alpha]_D^{25}$ = (+) 41.4 (*c* 3, $CHCl_3$), {lit^{25} for 100 % ee, $[\alpha]_D^{25}$ = (+) 69.0 (*c* 3.93, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5]

3. 4. 4. 7 Michael reaction of chalcone with dimethyl malonate



Yield 1.1 g(64%)

IR (neat) (cm^{-1}) 1739, 1680

^{1}H-NMR (5 ppm, $CDCl_3$) 3.5 (s, 3H), 3.6-3.7 (m, 2H), 3.8 (s, 3H), 3.9 (d, J = 8.3 Hz, 1H), 4.2 (m, 1H), 7.2-7.5 (m, 8H), 7.8-8.0 (m, 2H)

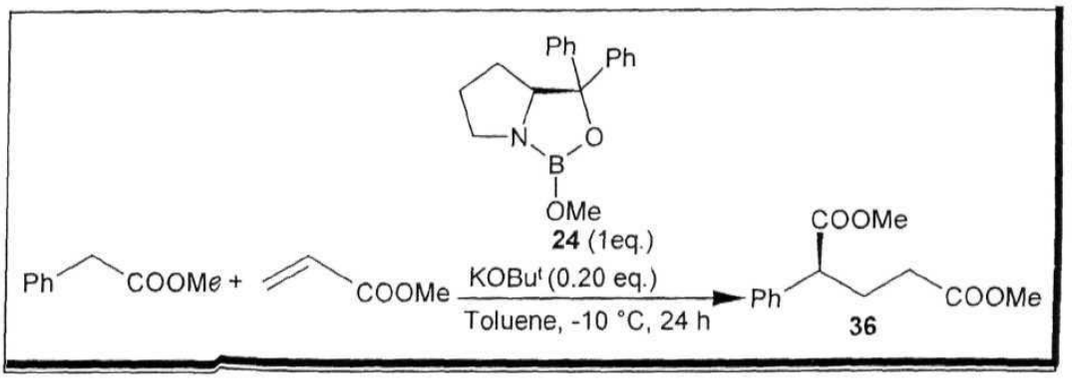
^{13}C-NMR (8 ppm, $CDCl_3$) 40.8, 42.3, 52.3, 52.6, 57.3, 127.2, 128.1, 128.4, 128.5, 128.6, 133.0, 136.9, 140.5, 168.1, 168.7, 197.5

(Spectrum No. **26)**

$[\alpha]_D^{25}$ $[\alpha]_D^{25}$ = (+) 3.3 (*c* 3, $CHCl_3$), {lit[29] for 77 %ee, $[\alpha]_D^{25}$ = (+) 25.64(*c* 2, $CHCl_3$)}

The spectral data showed 1:1 correspondence with the reported data.[5]

3. 4. 4. 8 Michael reaction of methylphenylacetate with methacrylate



Yield 0.76g (65 %)

IR (neat) (cm^{-1}) 1739, 1680

^{1}HNMR (5 ppm, $CDCl_3$) 2.1-2.6 (m, 5H), 3.65 (s, 1H), 3.66 (s, 1H), 7.2-7.3 (m, 5H)

^{13}C-NMR (5 ppm, $CDCl_3$) 28.3, 31.6, 50.4, 51.5, 51.9, 127.4, 127.9, 128.4, 138.2, 171.1, 173.2, 173.8. **(Spectrum No. 27)**

$[\alpha]_D^{25}$ $[\alpha]_D^{25}$ = (+) 4.4 (*c* 5, EtOH), {lit[18] for 100 %ee, $[\alpha]_D^{25}$ ≈(+) 89 (*c* 5, EtOH)}

The spectral data showed 1:1 correspondence with the reported data.

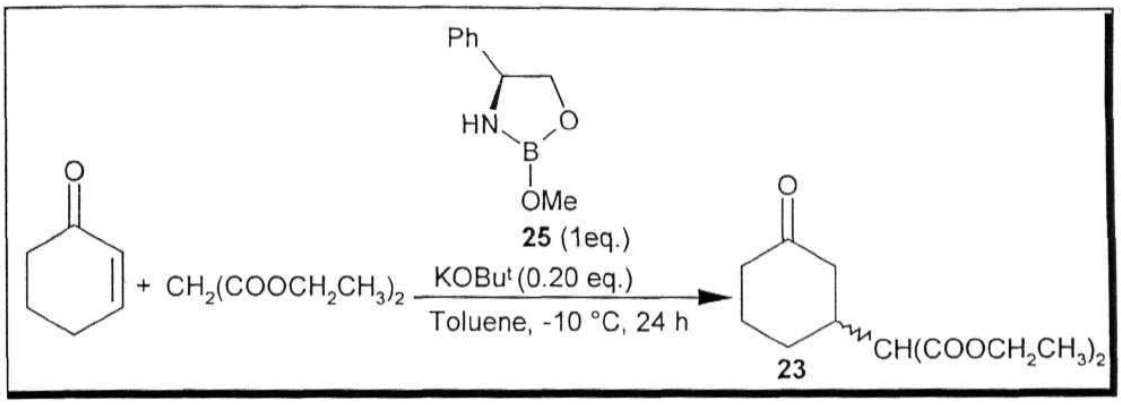
3. 4. 5 Preparation of chiral oxazaborolidine catalyst 25 using (*R*)-(-)-phenylglycinol and B(OMe)$_3$

To a solution of (*R*)-(-)-phenylglycinol (0.7 g, 5 mmol) in dry THF (5 mL), was added trimethyl borate or tributyl borate (0.6 g, 5.2 mmol)) and the

mixture was stirred under nitrogen at roorm temparature for 1 h. THF was removed under reduced pressure and dried under nitrogen to get the oxazaborolidine complex 25. The other oxazaborolidine complexes such as 26, 27 and 28 were also prepared by following the same procedure as mentioned above.

3. 4. 5. 1 Typical procedure for the reaction between diethyl malonate and cyclohexenone using oxazaborolidine complex 25.

To a stirred solution of the oxazaborolidine catalyst 25 (0.9 g, 5 mmol) in toluene (50 mL), $KOBu^t$ (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HC1 (10 mL) and extracted with Et_2O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.



Yield 0.87g(70%)

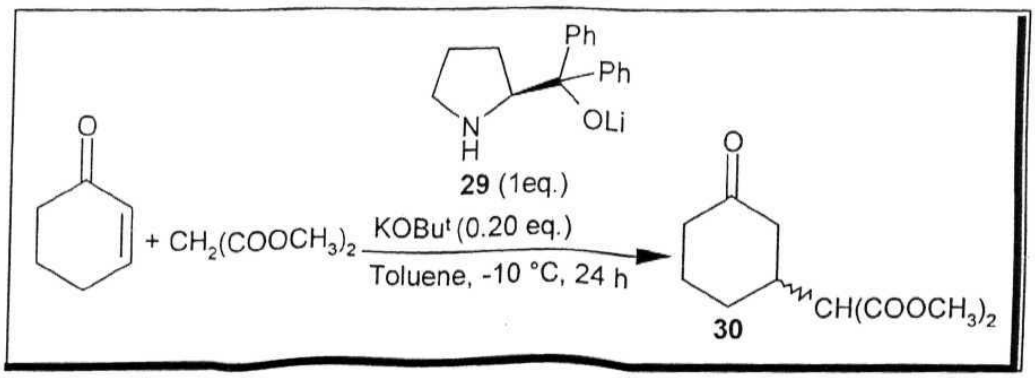
r]25 $[\alpha]_D^{25}$ = (+) 0.7 (*c* 3, $CHCl_3$), {lit[29] for 78% ee, $[\alpha]_D^{25}$ = (+) 2.78 (*c* 2.56, $CHCl_3$)}

3. 4. 6 Preparation of chiral lithium alkoxide catalyst 2 using (*S*)-(-)-α, *a*-diphenyl-2-pyrrolidinemethanol and *n*-BuLi

To a solution of (*S*)-(-)-α, α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) dry hexane (5 mL), was added *n*-BuLi (2.17 g, 5.2 mmol) and the mixture was stirred under nitrogen at roorm temparature for 1 h. The chiral lithium alkoxide 29 formed in hexane solution was directly used for the Michael addition reaction.

3. 4. 6. 1 Typical procedure for the reaction between dimethyl malonate and cyclohexenone using chiral lithium alkoxide catalyst 29.

The dimethyl malonate (0.8 g, 5 mmol) was added to a stirred solution of the chiral lithium alkoxide catalyst 29 (1.29 g, 5 mmol) under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HC1 (10 mL) and extracted with Et_2O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.



Yield 0.87g (70 %)

$[\alpha]_D^{25}$ $[\alpha]_D^{25}$= (+) 2. 8 (*c* 3, $CHCl_3$), {lit[29] for 75% ee, $[\alpha]_D^{25}$= (+) 3.01 (*c* 2.56, $CHCl_3$)}

3. 5 References

1. P. Berlmutter, *Conjugate Addition Reactions in Organic synthesis*, *Tetrahedron Organic chemistry Series, Pergamon Press: Oxford* **1992**.
2. D. A. Oare and C. H. Heathcock, *Top. Stereo Chem.* **1989,** *19,* 227.
3. B. E. Rossiter and N. M. Swingle, *Chem. Rev.* **1992,** *92,* 771.
4. N. Krause and A. Gerold, *Angew. Chem. Int. Ed Engl.* **1997,** *36,* 186.
5. M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997,** *36,* 1236.
6. M. Yamaguchi, T. Shiraishi and M. Hirama, *Angew. Chem. Int. Ed. Engl,* **1993**, *32*, 1176.
7. J. M. Betancort , K. Sakthivel, R. Thayumanavan, C. F. Barabas III, *Tetrahedron Lett.* **2001,** *42,* 4441.
8. J. M. Betancort and C. F. Barabas III, *Organic Lett.* **2001,** *23, 3731.*
9. B. List, P. Pojarliev and H. J. Martin, *Organic Lett.* **2001,** *16,* 2423.
10. A. Loupy, J. Sansoulet, A. Zaparucha and C. Merienne, *Tetrahedron Lett.* **1989,** *30,* 333.
11. E. J. Corey and F. Y. Zhang, *Organic Lett.* **2000,** 2, 4257.
12. D. Y. Kim, S. C. Huh and S. M. Kim, *Tetrahedron Lett;* **2001,** *42,* 6299.

13. T. Yura, N. Iwasawa, K. Narasaka and T. Mukaiyama, *Chem. Lett.* **1988**, 1025.

14. H. Brunner and B. Hammer, *Angew. Chem, Int. Ed. Engl.* **1984,** 23, 312.

15. T. Suzuki and T. Torii, *Tetrahedron: Asymmetry,* **2000,** *12,* 1077

16. M. Yamaguchi, T. Shiraishi and M. Hirama, *J. Org. Chem.* **1996,** *61,* 3520.

17. T. Kumamoto, S. Aoki, M. Nakajima and K. Koga, *Tetrahedron: Assymmetry*, **1994,** 5, 1431.

18. S. G. Kim and K. Y. Ahn, *Tetrahedron Lett.* **2001,** *42,* 4175.

19. G. Manickam and G. Sundararajan, *Ind. J. Chem.* **1997,** *36* A & B, 516.

20. G. Manickam and G. Sundarrajan, *Tetrahedron: Asyemmtry*, **1997,** *8,* 2771.

21. N. Prabagaran and G. Sundarrajan, *Tetrahedron: Asyemmtry,* **2002,** *13*, 1053.

22. G. Sundararajan and N. Prabagaran, *Organic Lett.* **2001,** 3, 389.

23. S. Narasimhan, S. Velmathi, R. Balakumar and V. Ravikrishnan. *Tetrahedron Lett.* **2001,** *42,* 719.

24. B. M. Choudary, N. S. Choudary and M. L. Kantam, *J. Mol. Cat.* **1999,** 142,389.

25. S. C. Jha and N. N. Joshi, *Tetrahedron: Asymmetry*, **2001.** *12*, 2463.

26. G. Kumaraswamy, M. V. Sastry and N. Jena, *Tetrahedron. Lett.* **2001,** *42*, 8515.

27. H. Sasai, T. Arai, Y. Satow, K. N. Houk and M. Shibasaki, *J. Am. Chem. Soc.* **1995,** *117*, 6194.

28. H. Sasai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.* **1994,** 116, 1571.

29. T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date and M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1996,** 35. 106.

30. M. Shibasaki and H. Sasai, *Pure & Appl. Chem.* **1996,** *68,* 523.

31. H. Sasai, E. Emori, T. Arai and M. Shibasaki, *Tetrahedron Lett.* **1996,** 57,5561.

32. T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai and M. Shibasaki, *Chem. Eur. J.*1996,2, 1368.

33. Y. S. Kim, S. Matsunga, J. Das, A. Sekine. T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.* **2000,** *122,* 6506.

34. T. Arai, Q. Hu. X. Zheng, L. Pu and H. Sasai, *Org. Lett.* **2000,** 2, 4261.

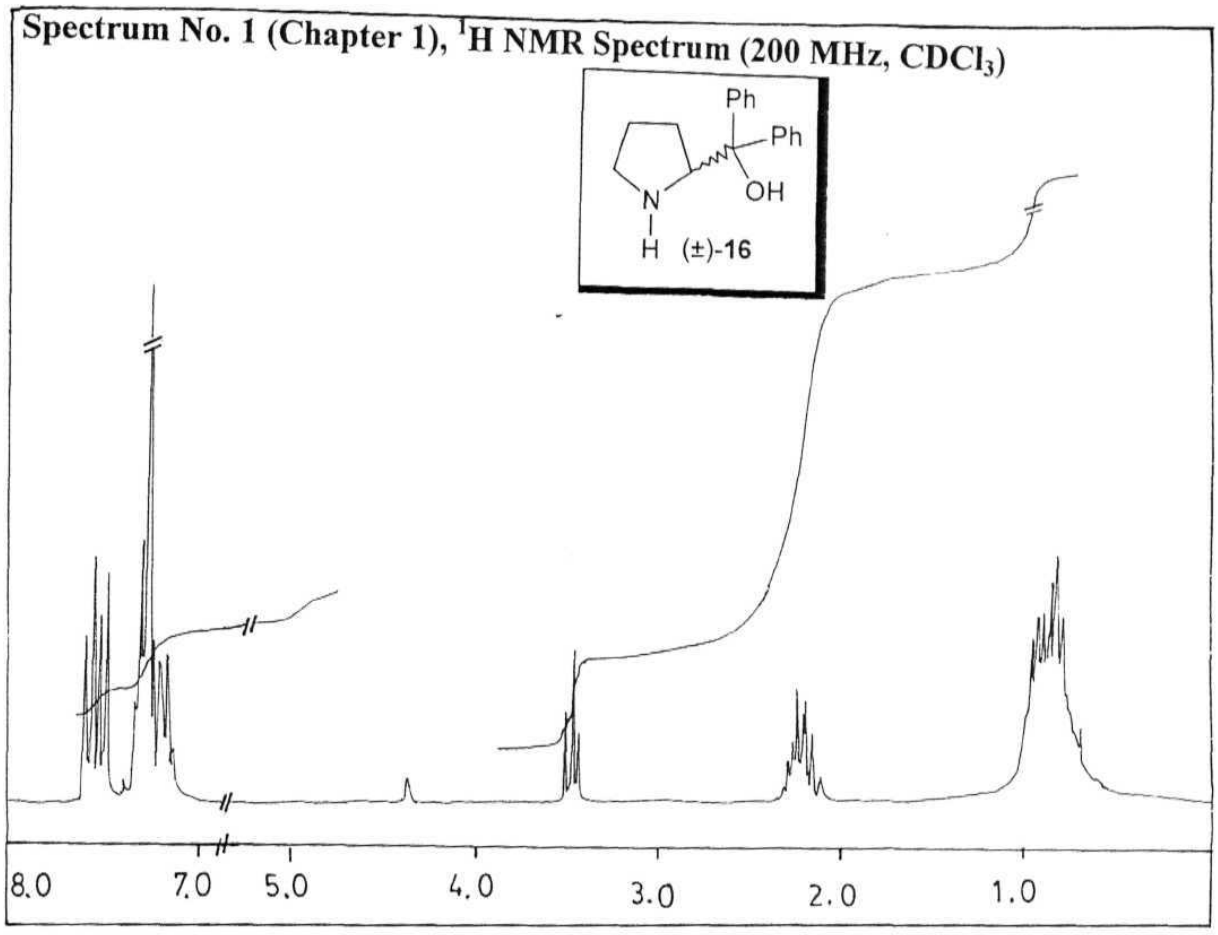
35. L. Venkatraman, Ph.D. Thesis, University of Hyderabad, **2000.**

36. M. Periasamy. C. R. Ramanathan, A. S. B. Prasad and J. V. B. Kanth, *Enantiomer,* **1998**, *3,* 3.

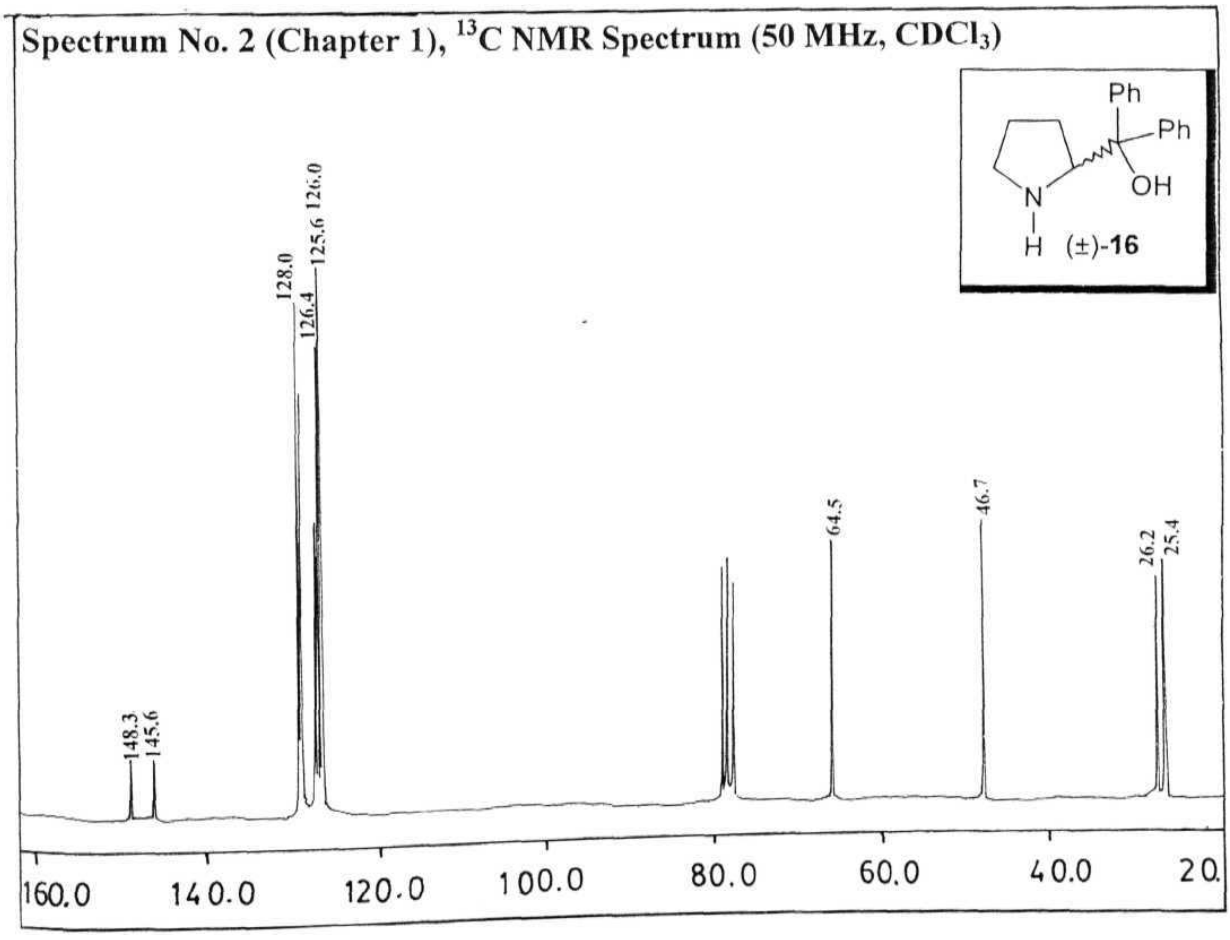
37. M. Masui, T. Shiori, *Syn. Lett.* **1997,** 273.

Representative Spectra

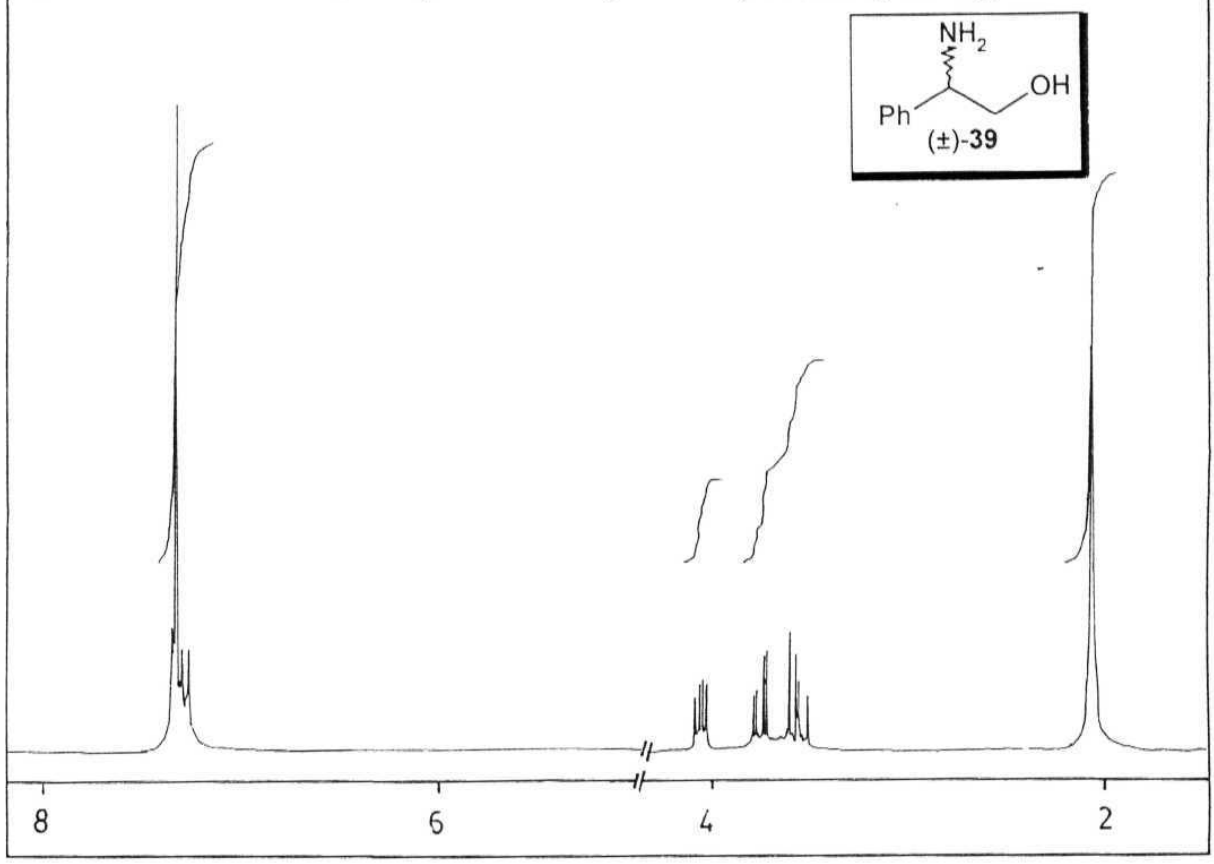
Spectrum No. 1 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



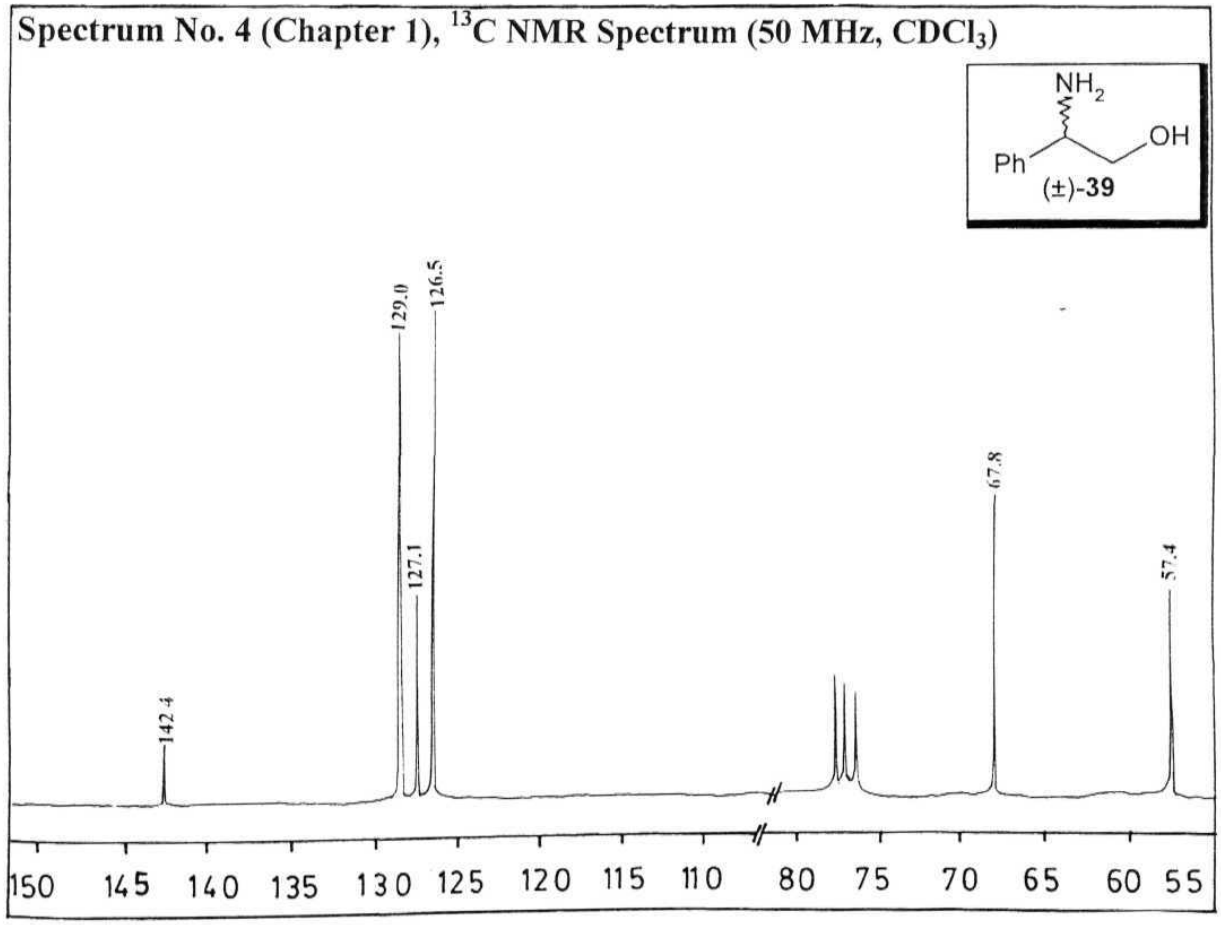
Spectrum No. 2 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



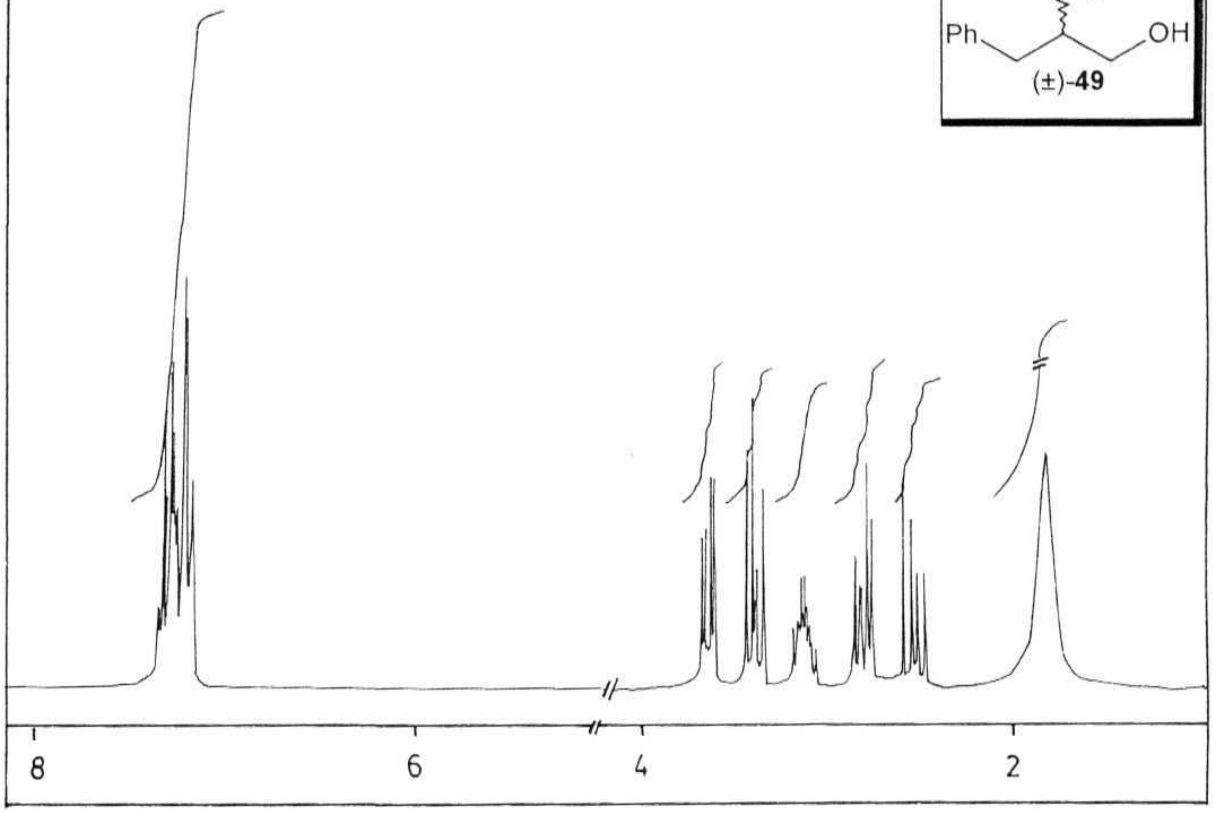
Spectrum No. 3 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



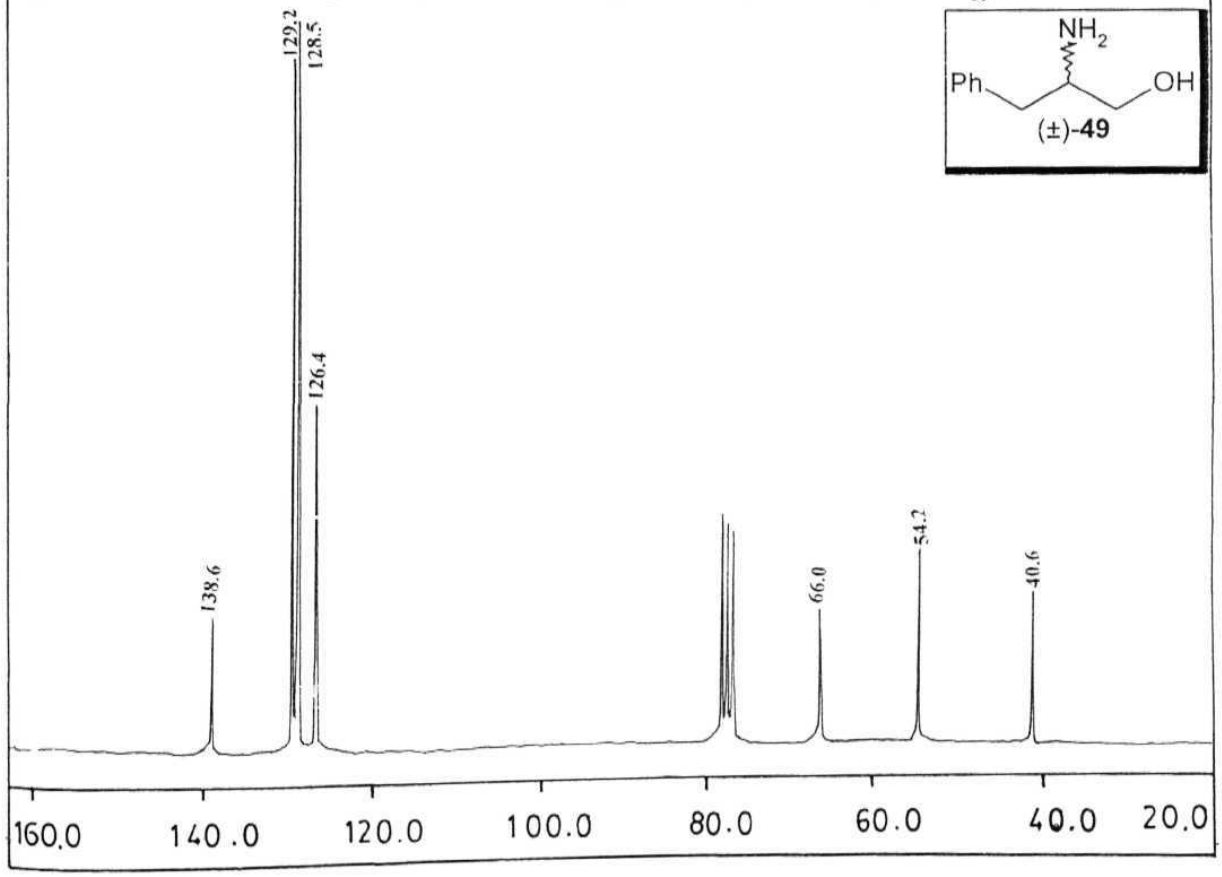
Spectrum No. 4 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



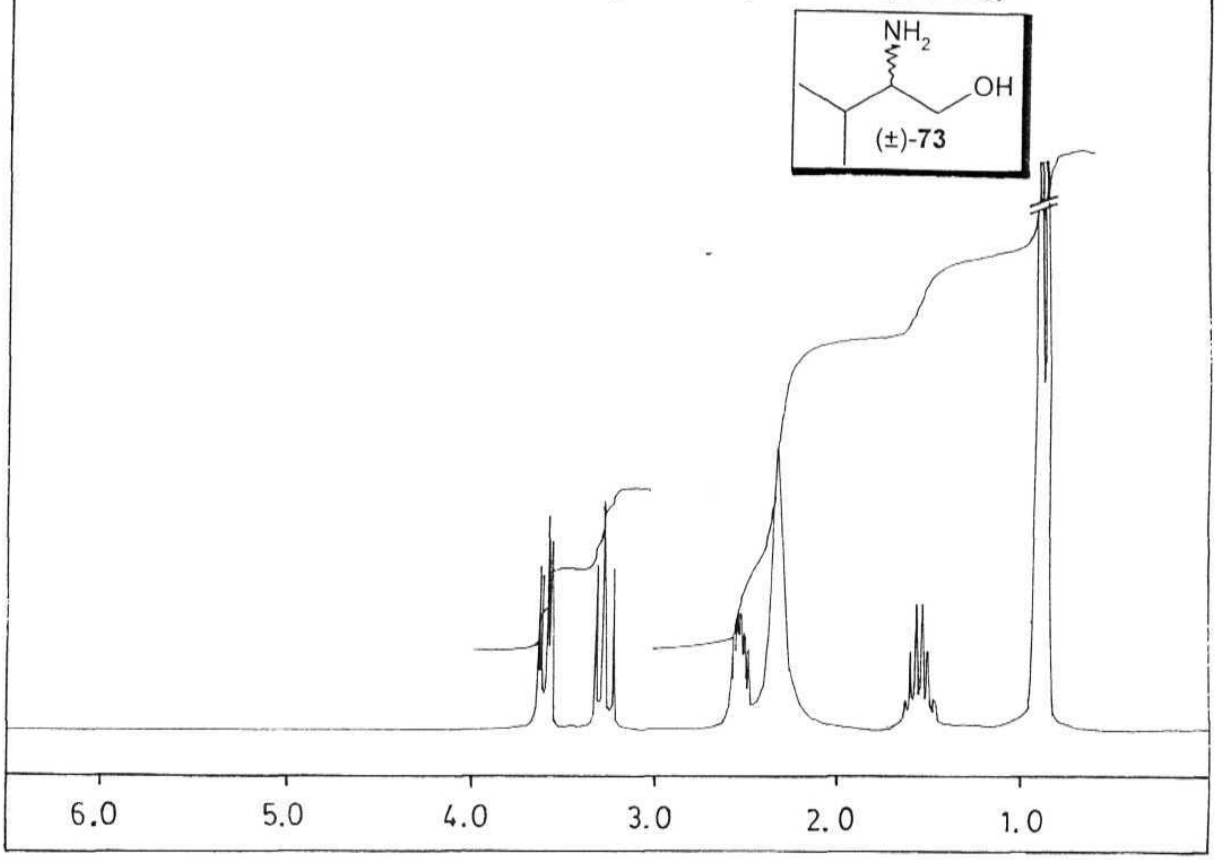
Spectrum No. 5 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



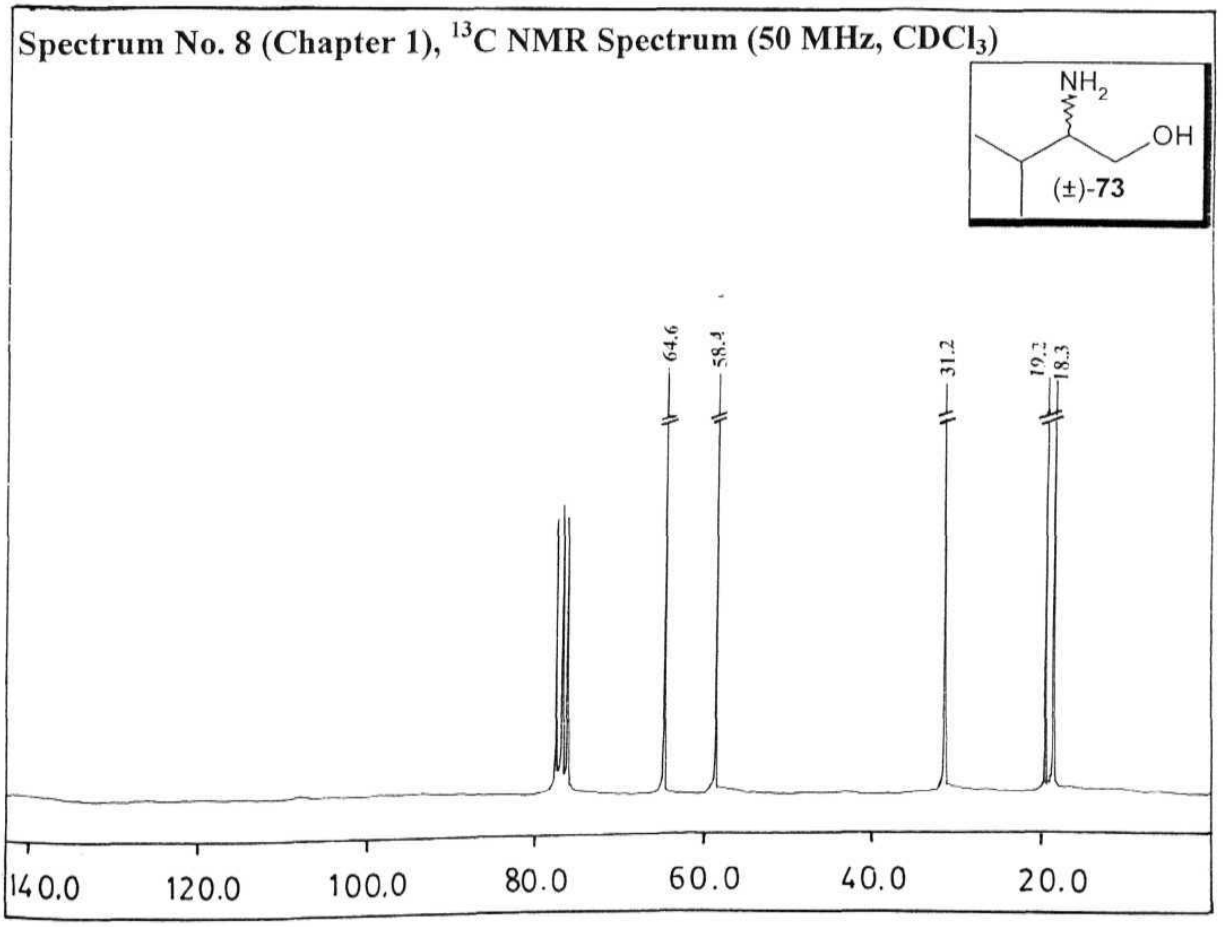
Spectrum No. 6 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



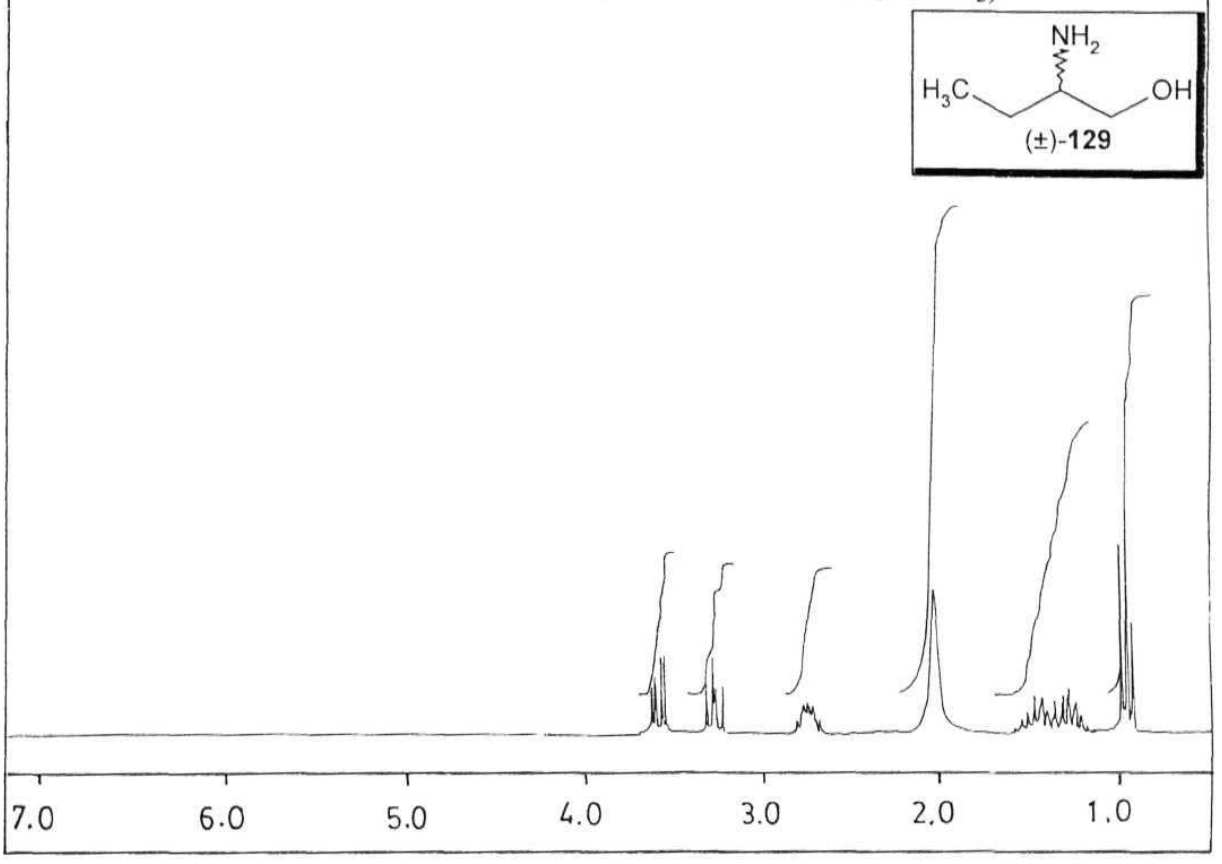
Spectrum No. 7 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



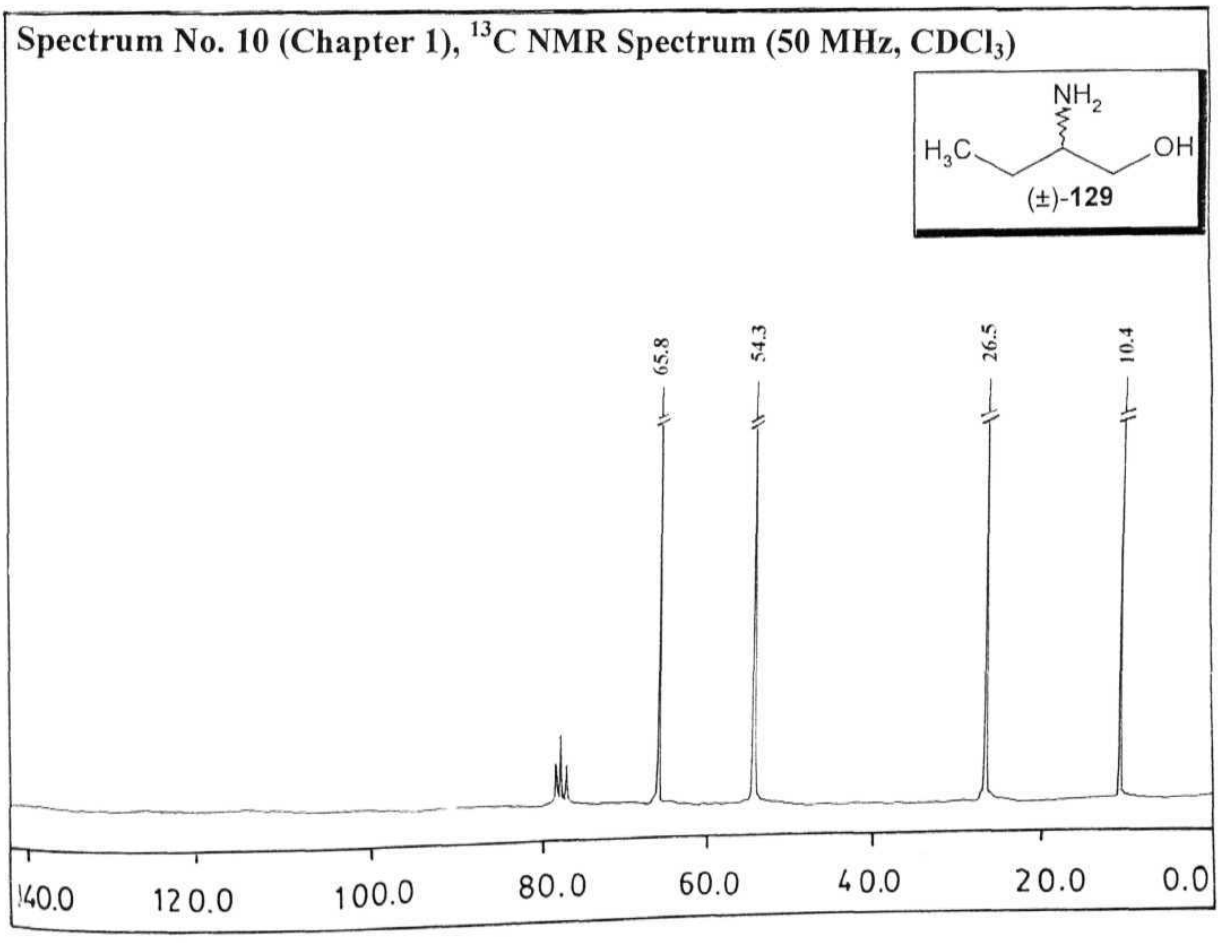
Spectrum No. 8 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

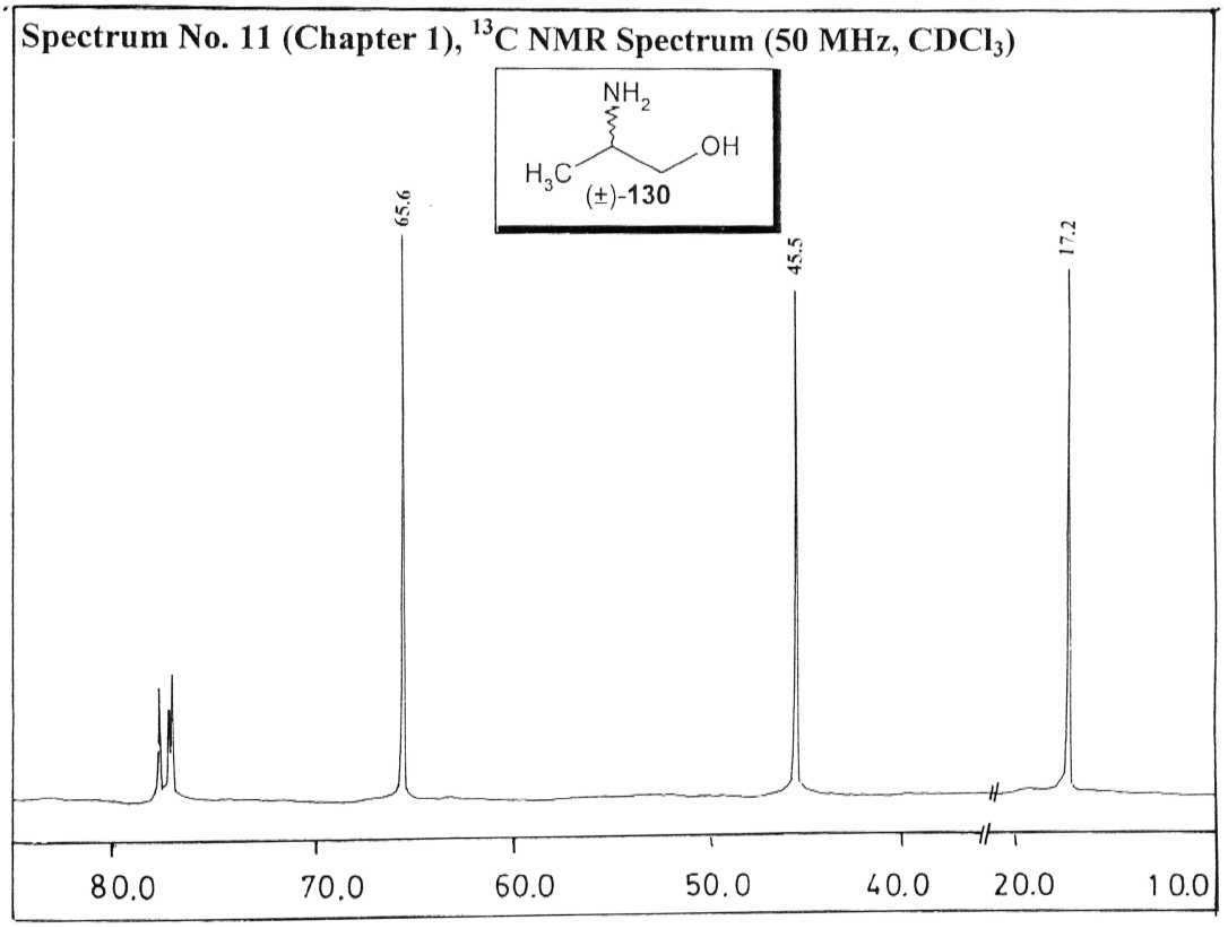


Spectrum No. 9 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

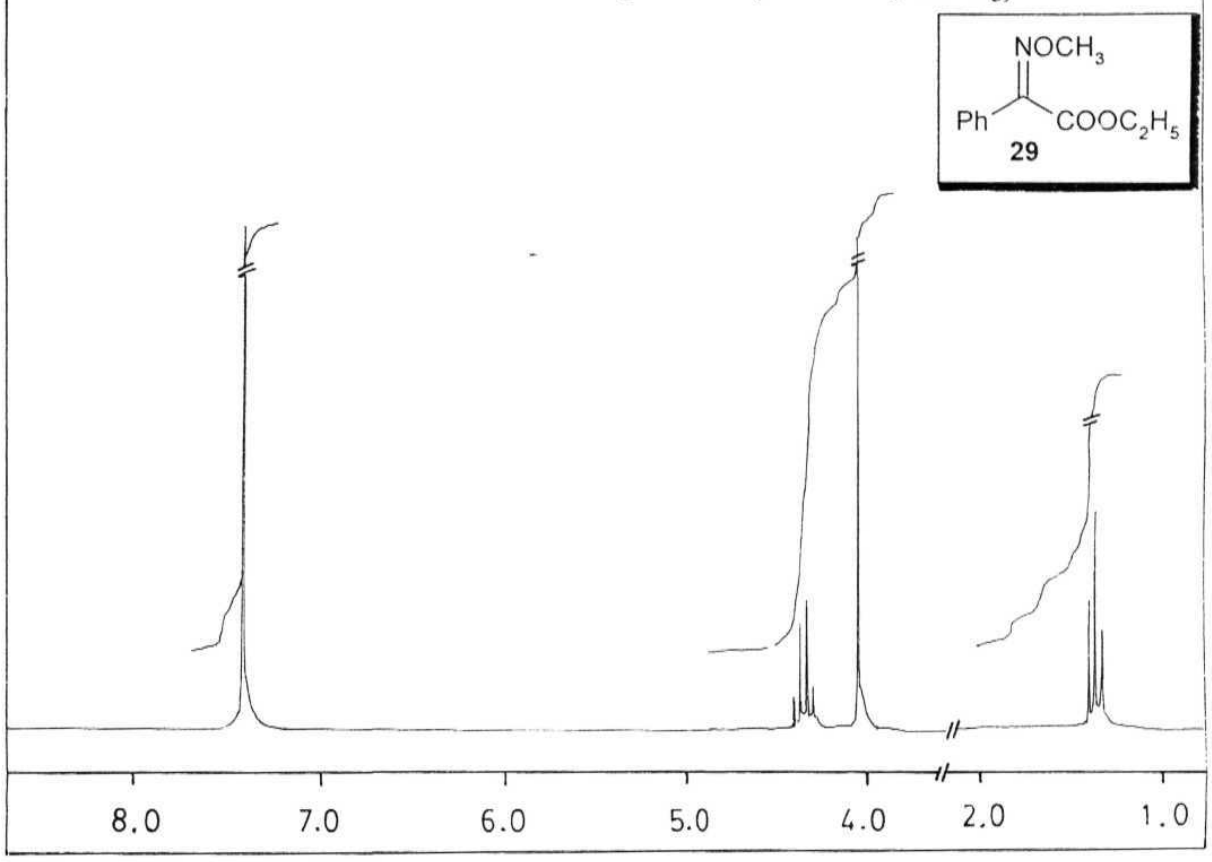


Spectrum No. 10 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

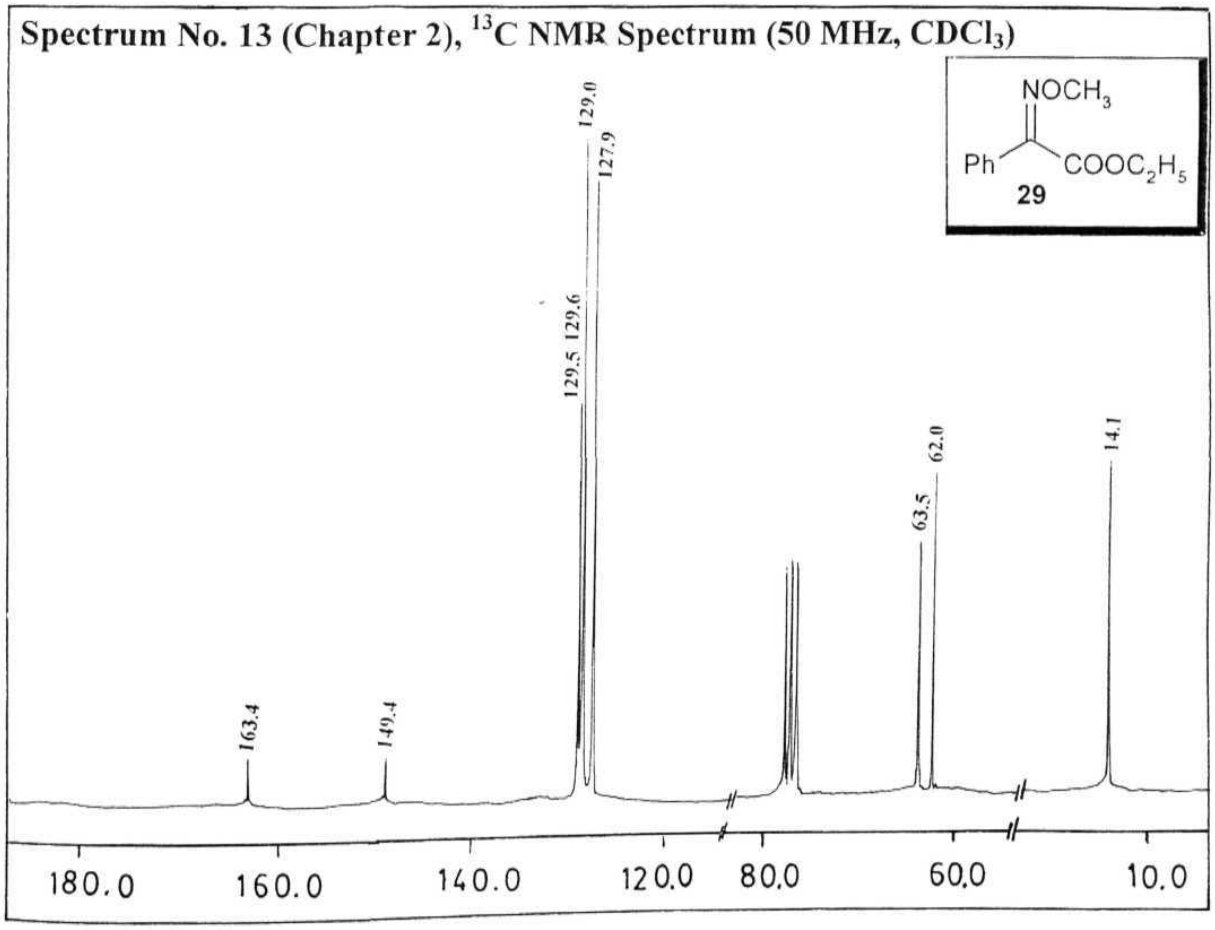



Spectrum No. 11 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)
NH_2
OH
H_3C
(±)-130
65.6
45.5
17.2
80.0
70.0
60.0
50.0
40.0
20.0
10.0

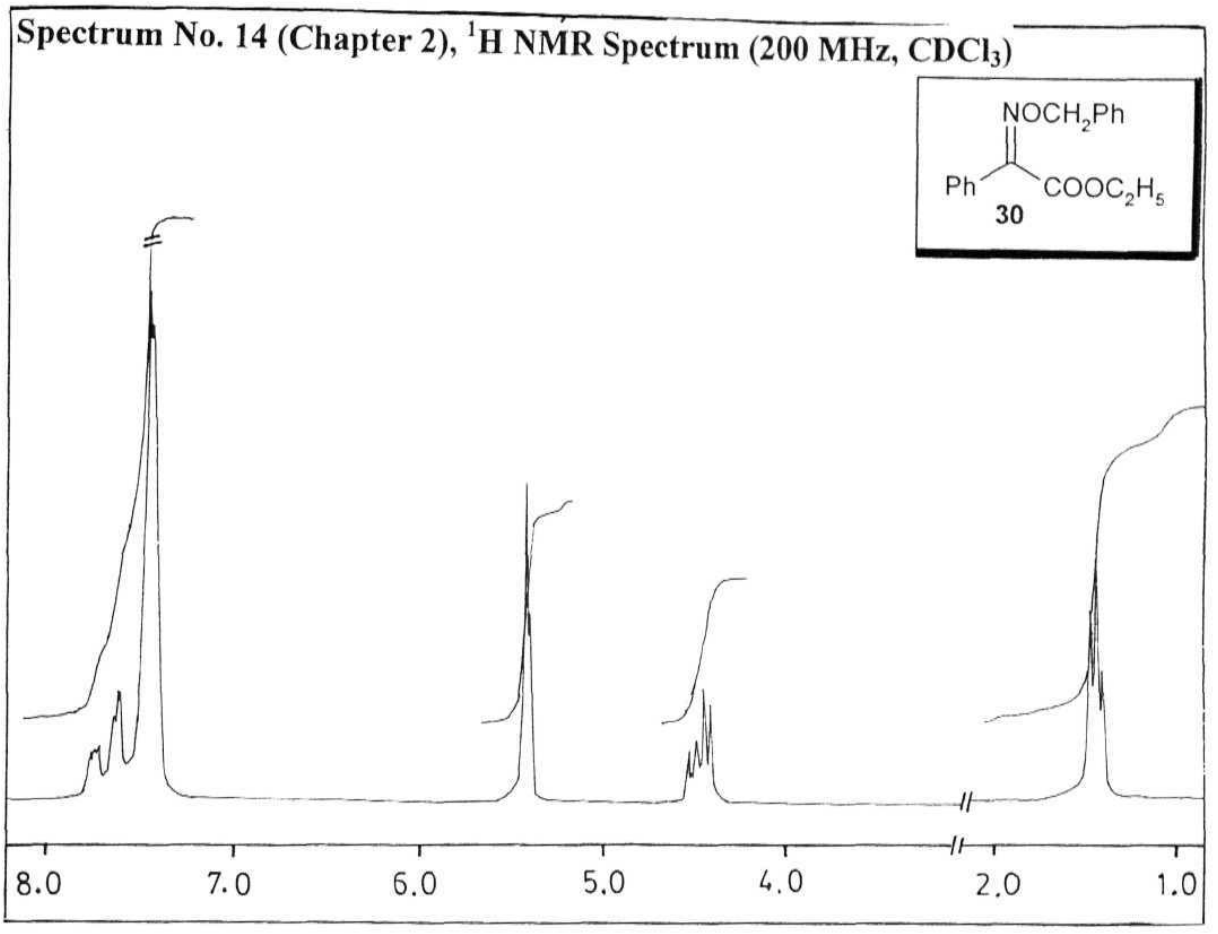
Spectrum No. 12 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



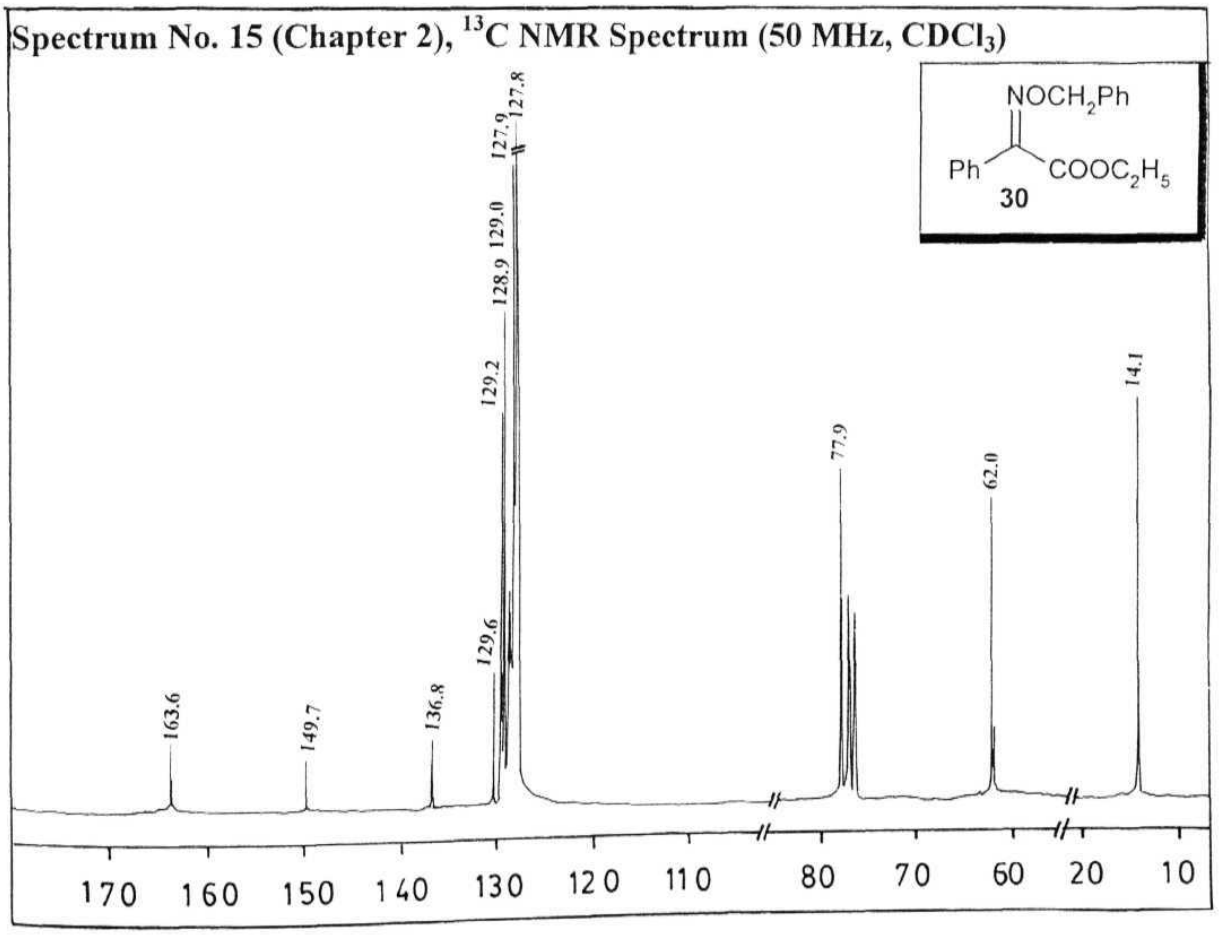
Spectrum No. 13 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



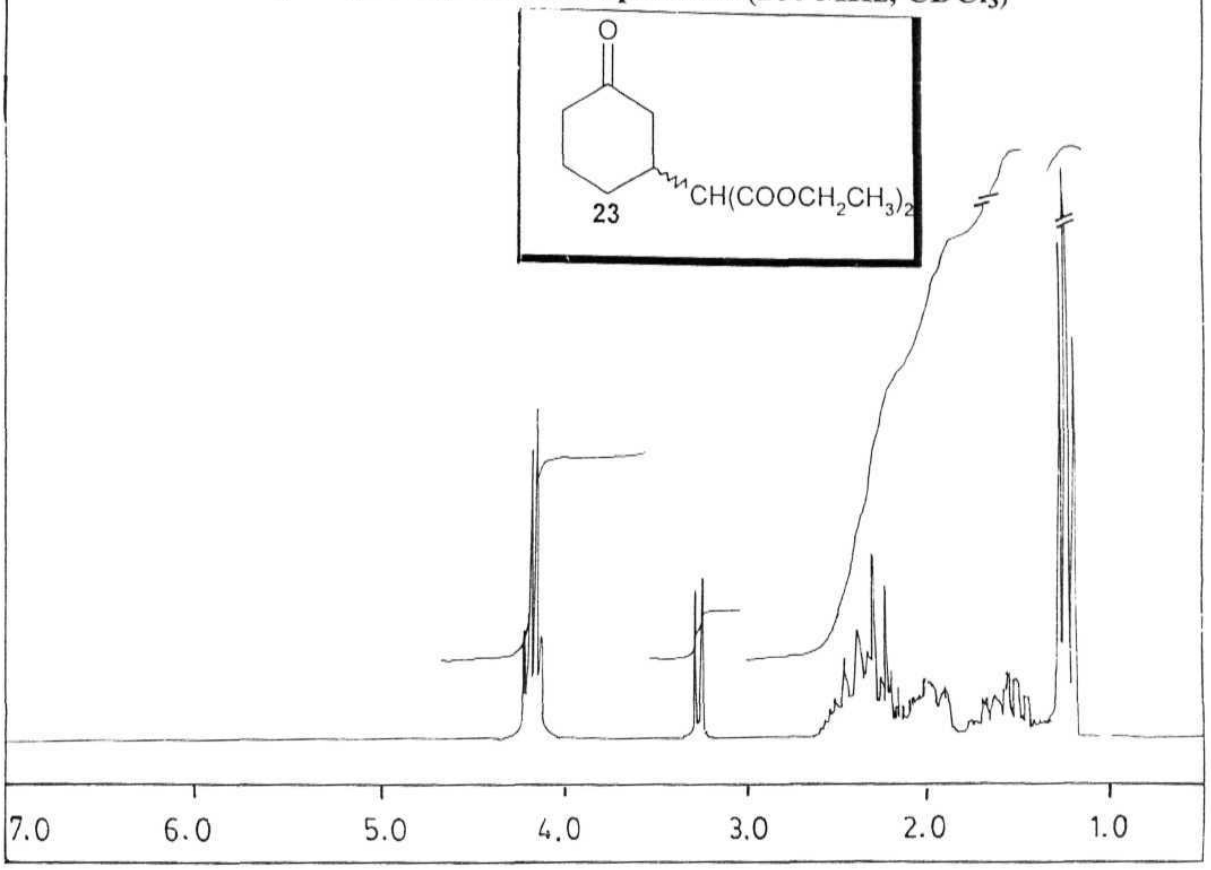
Spectrum No. 14 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



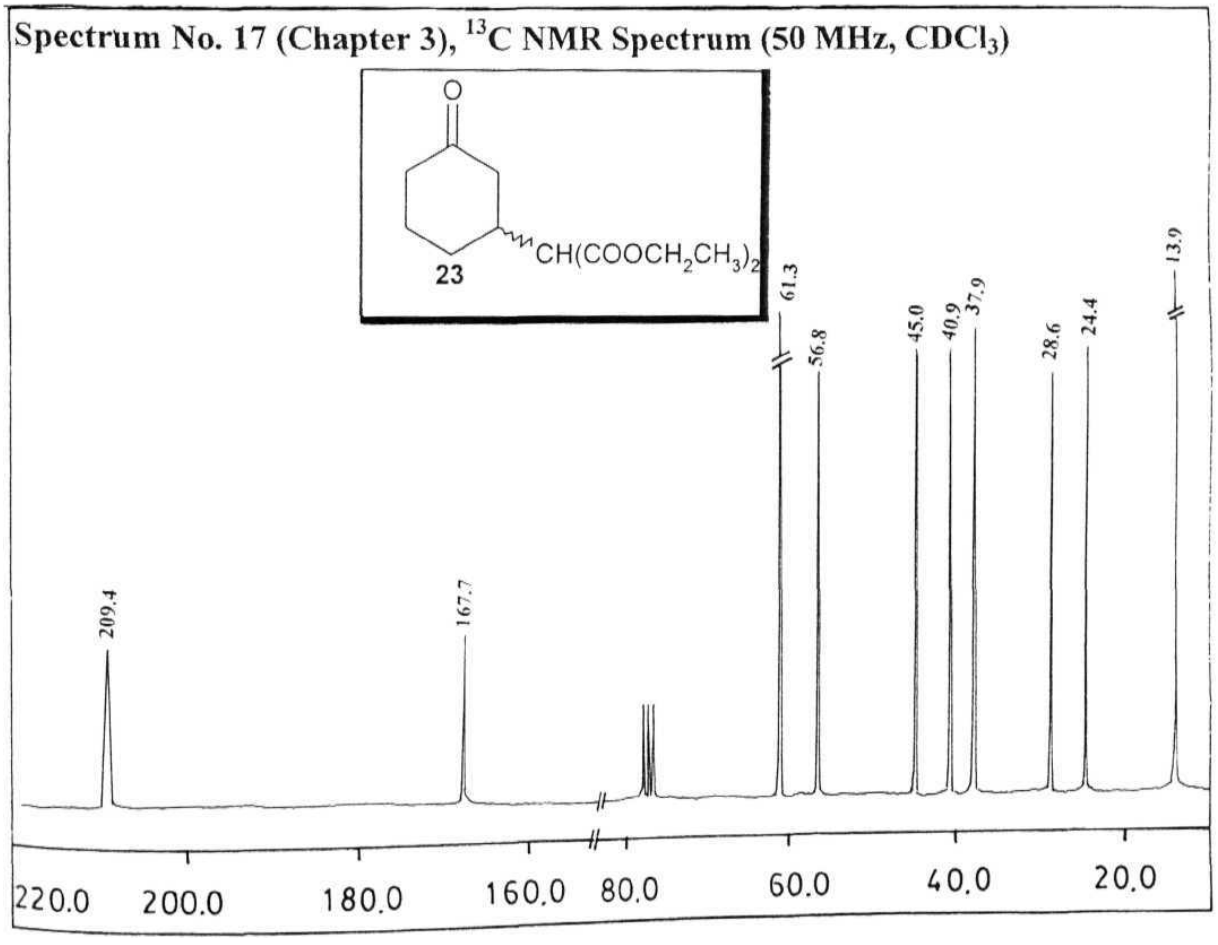
Spectrum No. 15 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



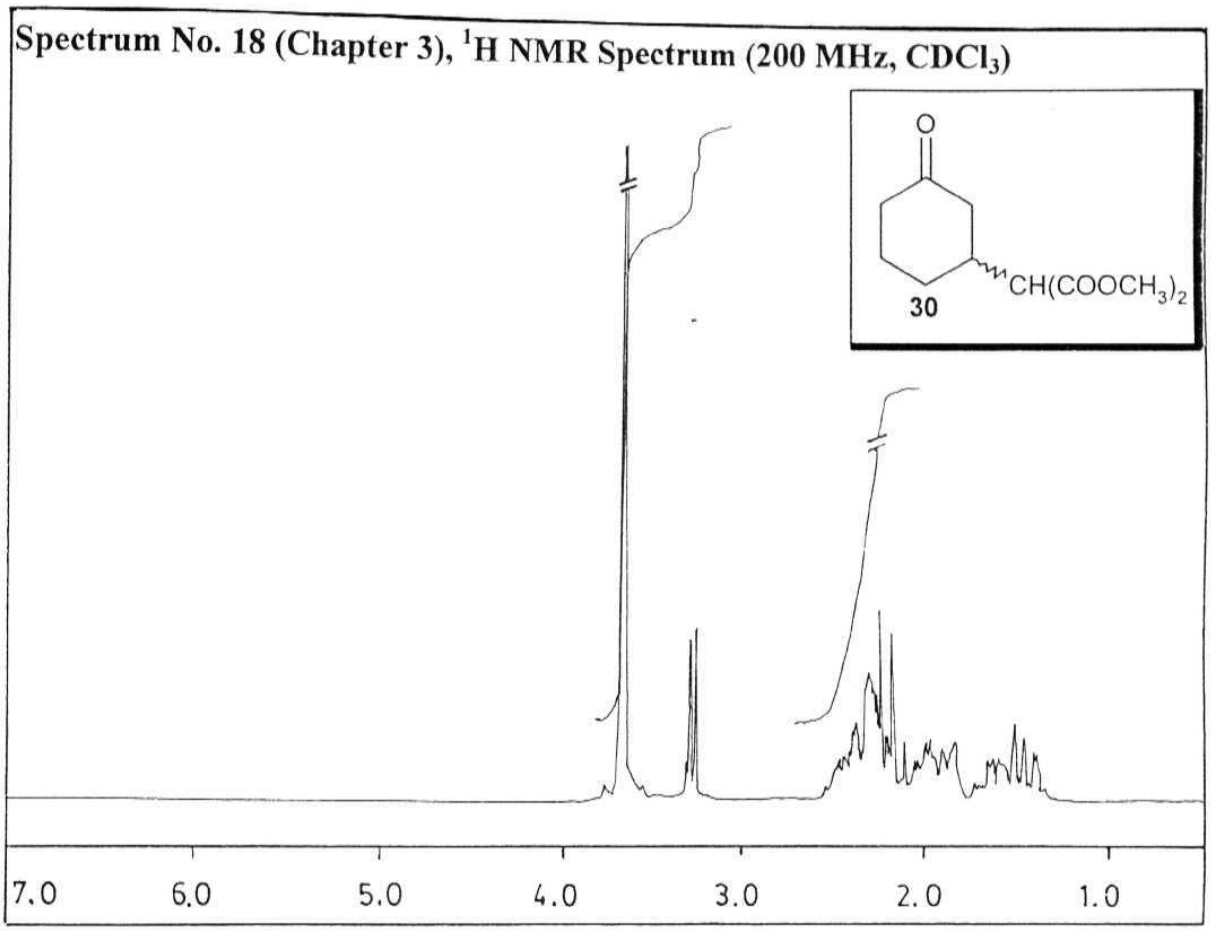
Spectrum No. 16 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



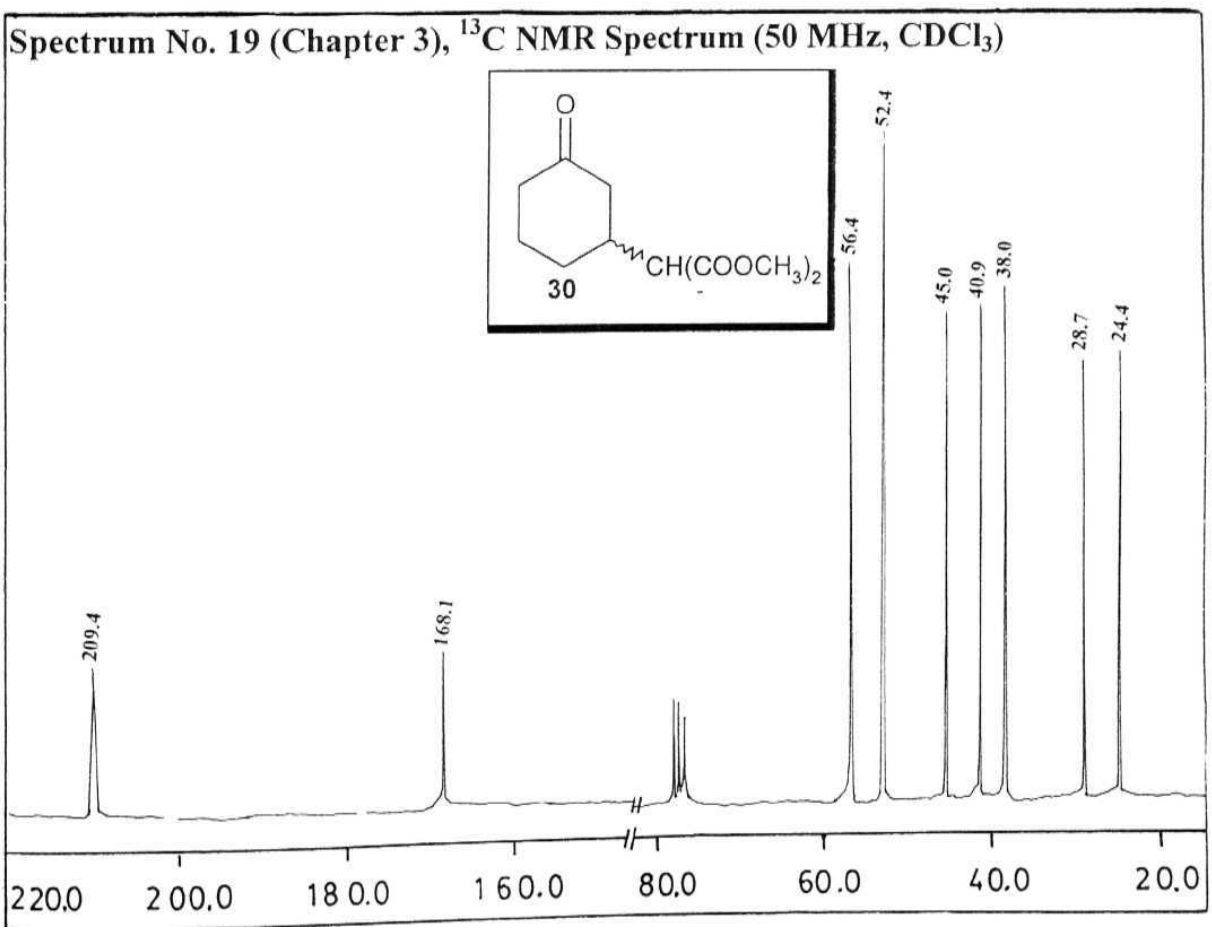
Spectrum No. 17 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



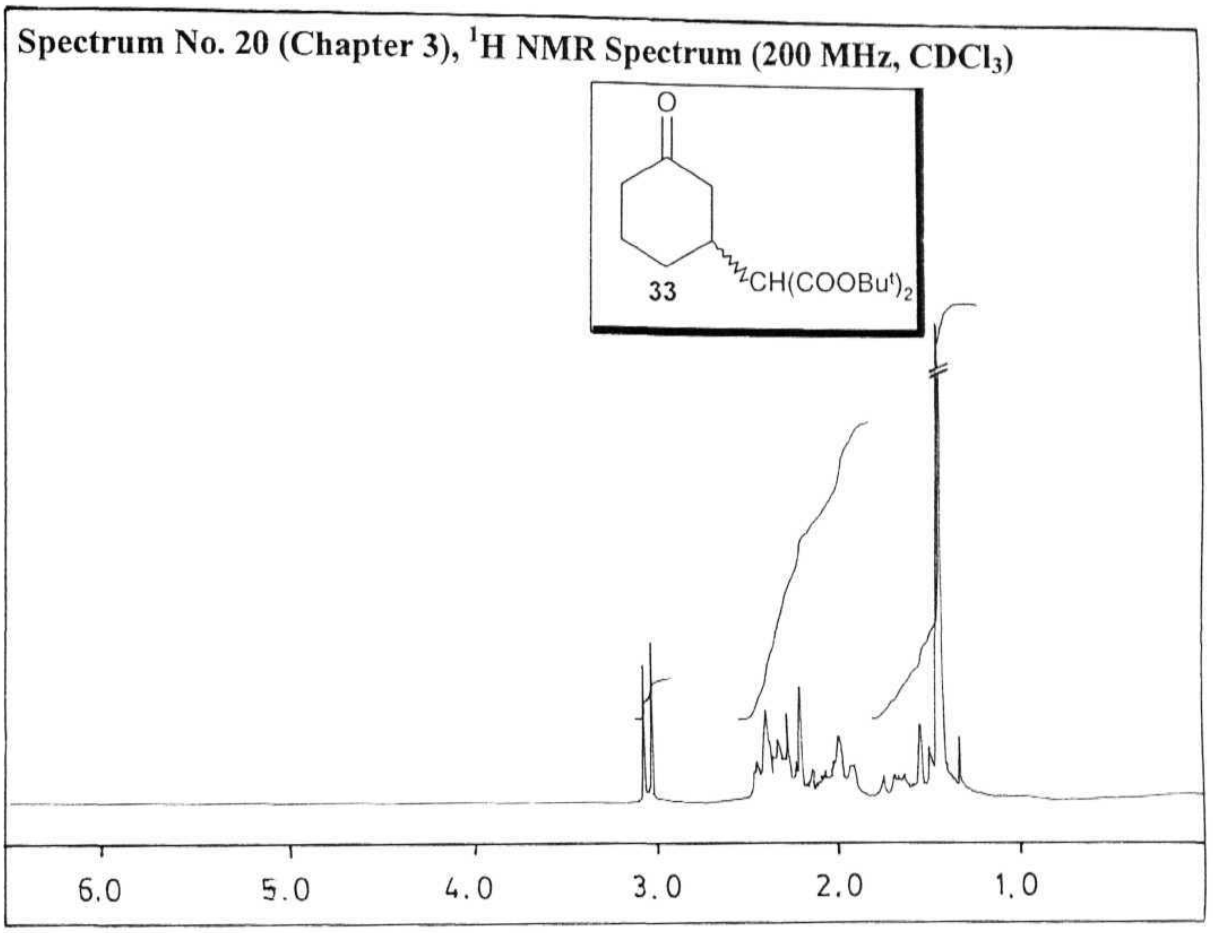
Spectrum No. 18 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



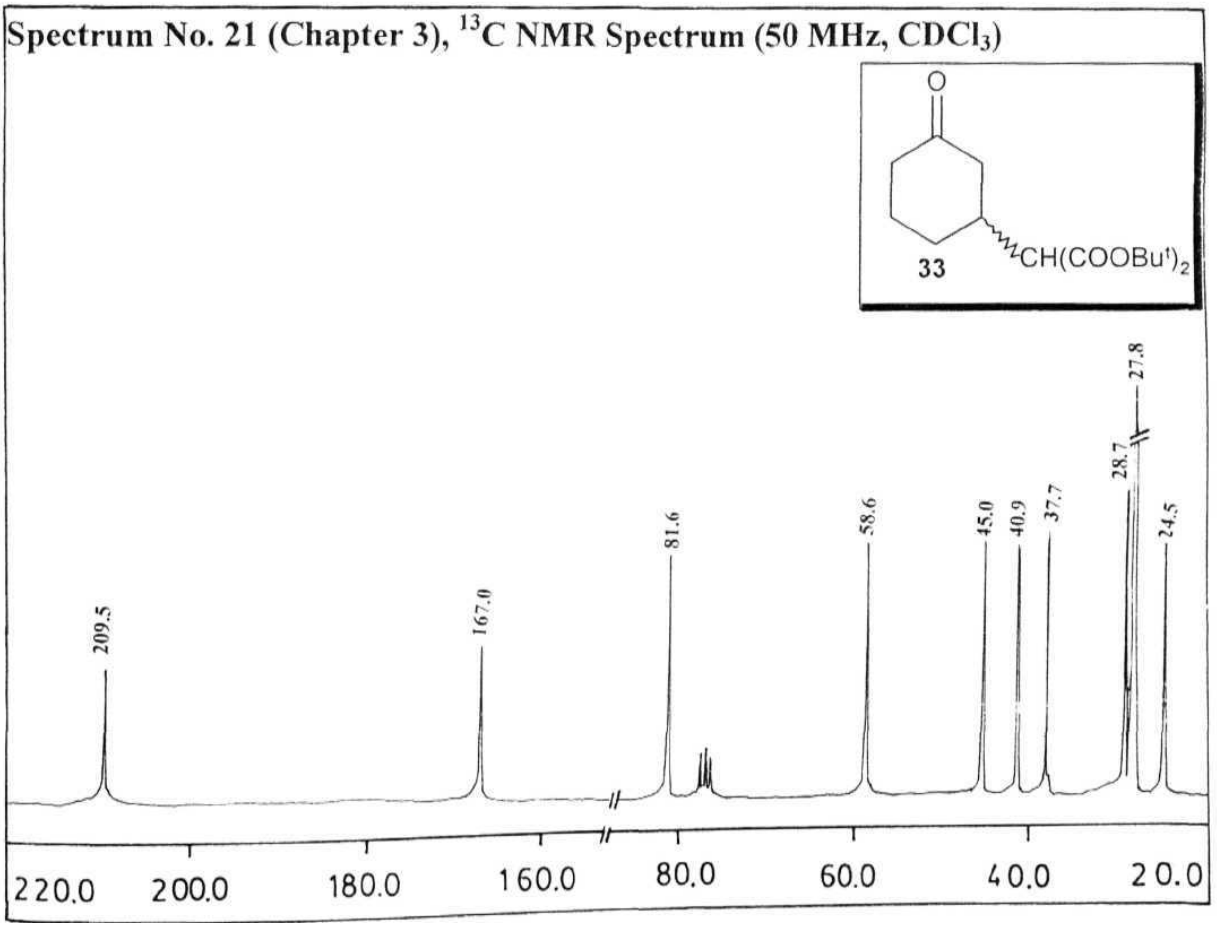
Spectrum No. 19 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



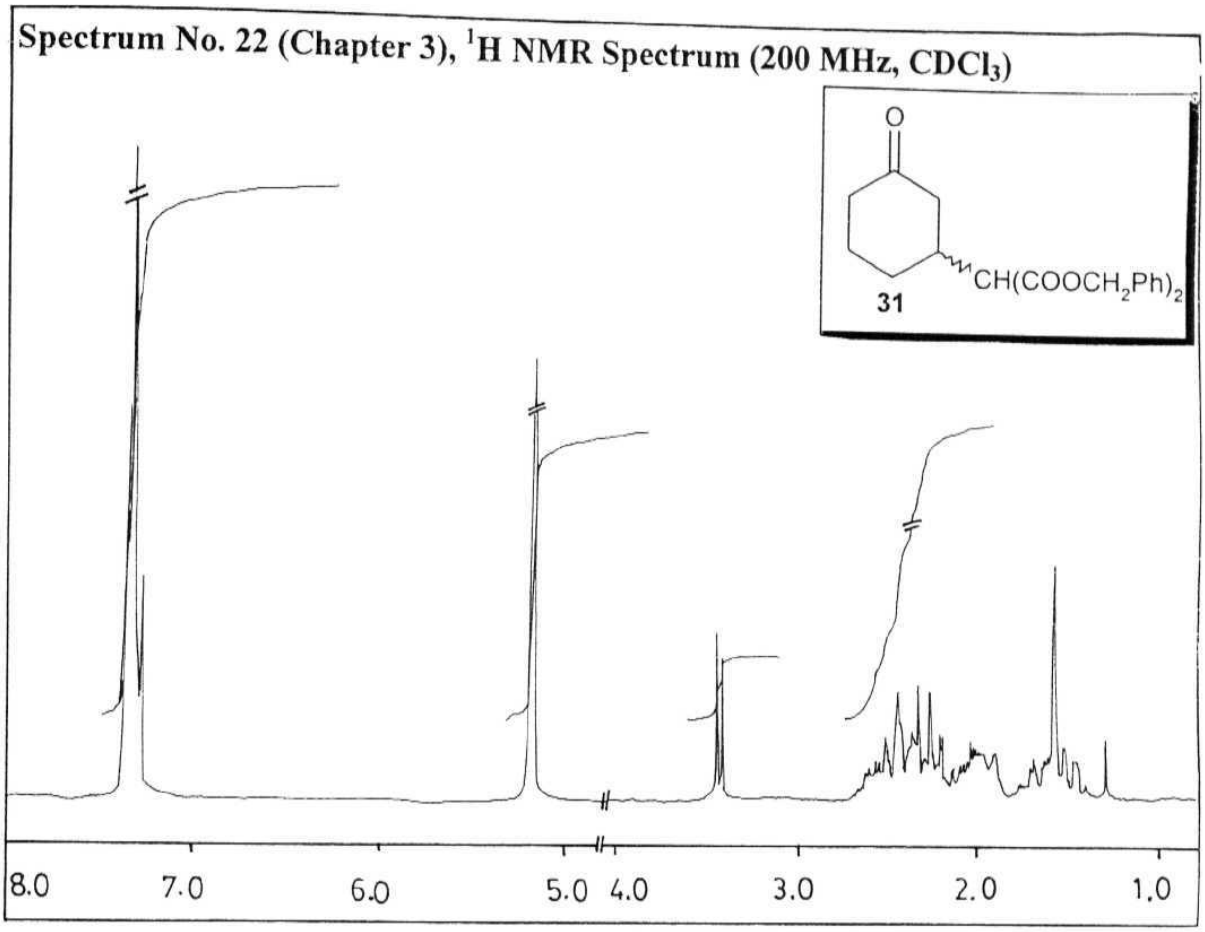
Spectrum No. 20 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



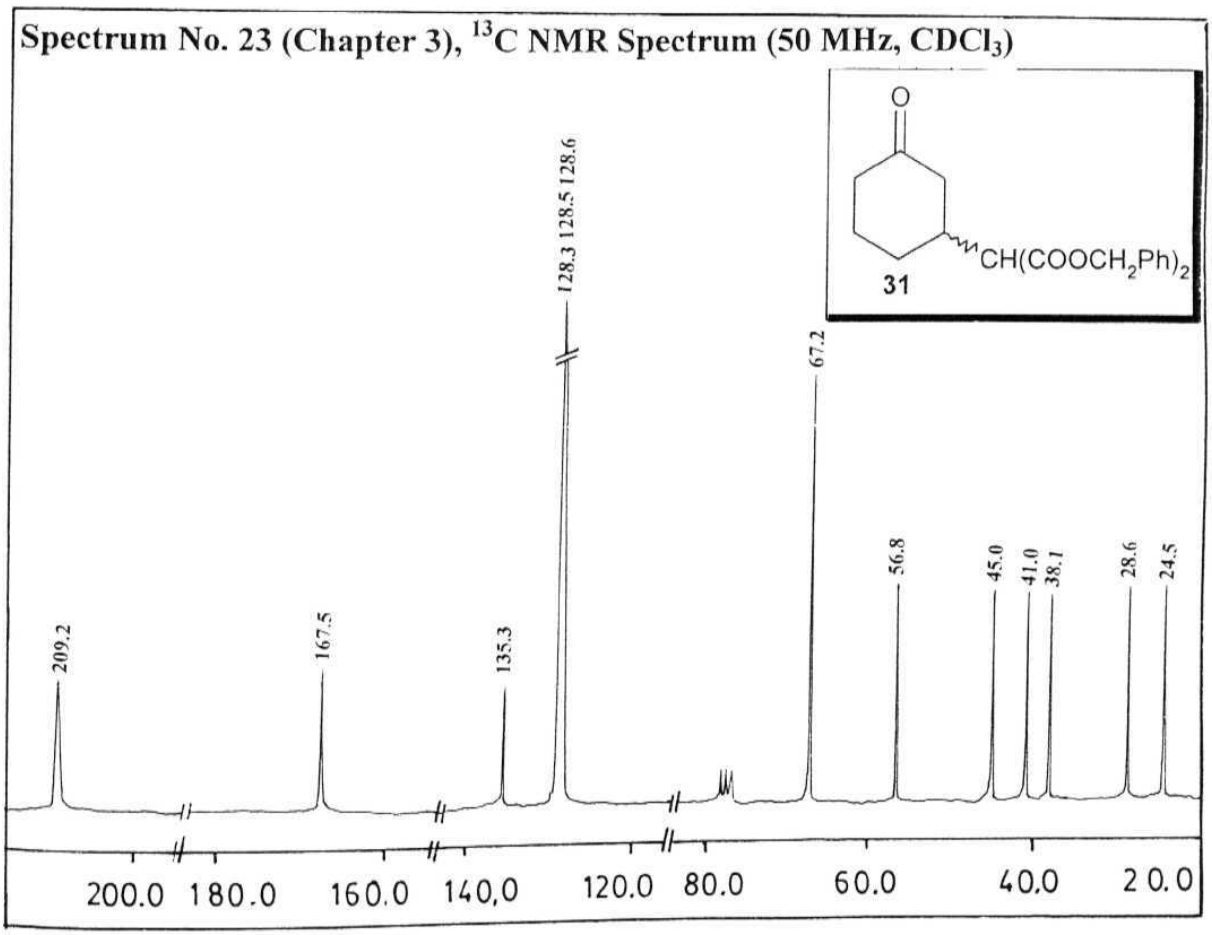
Spectrum No. 21 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



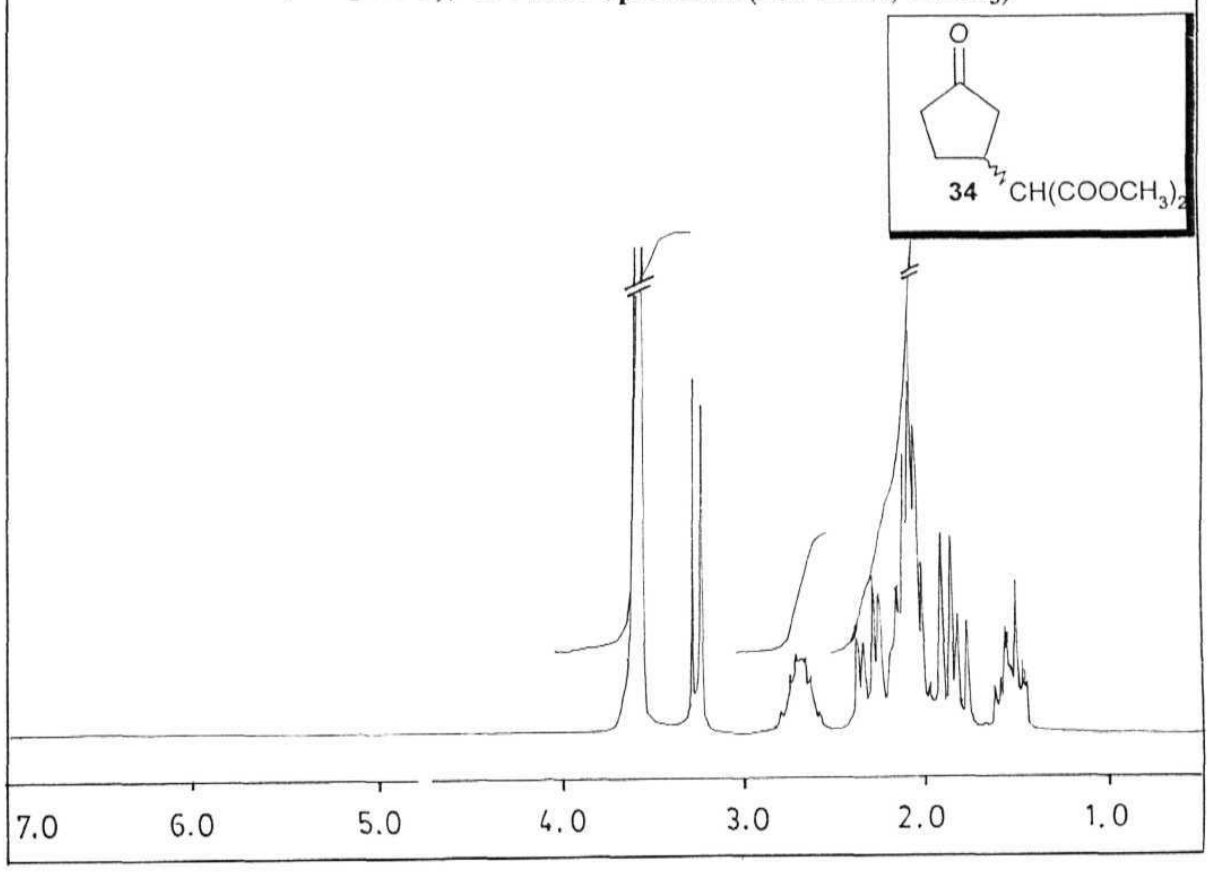
Spectrum No. 22 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



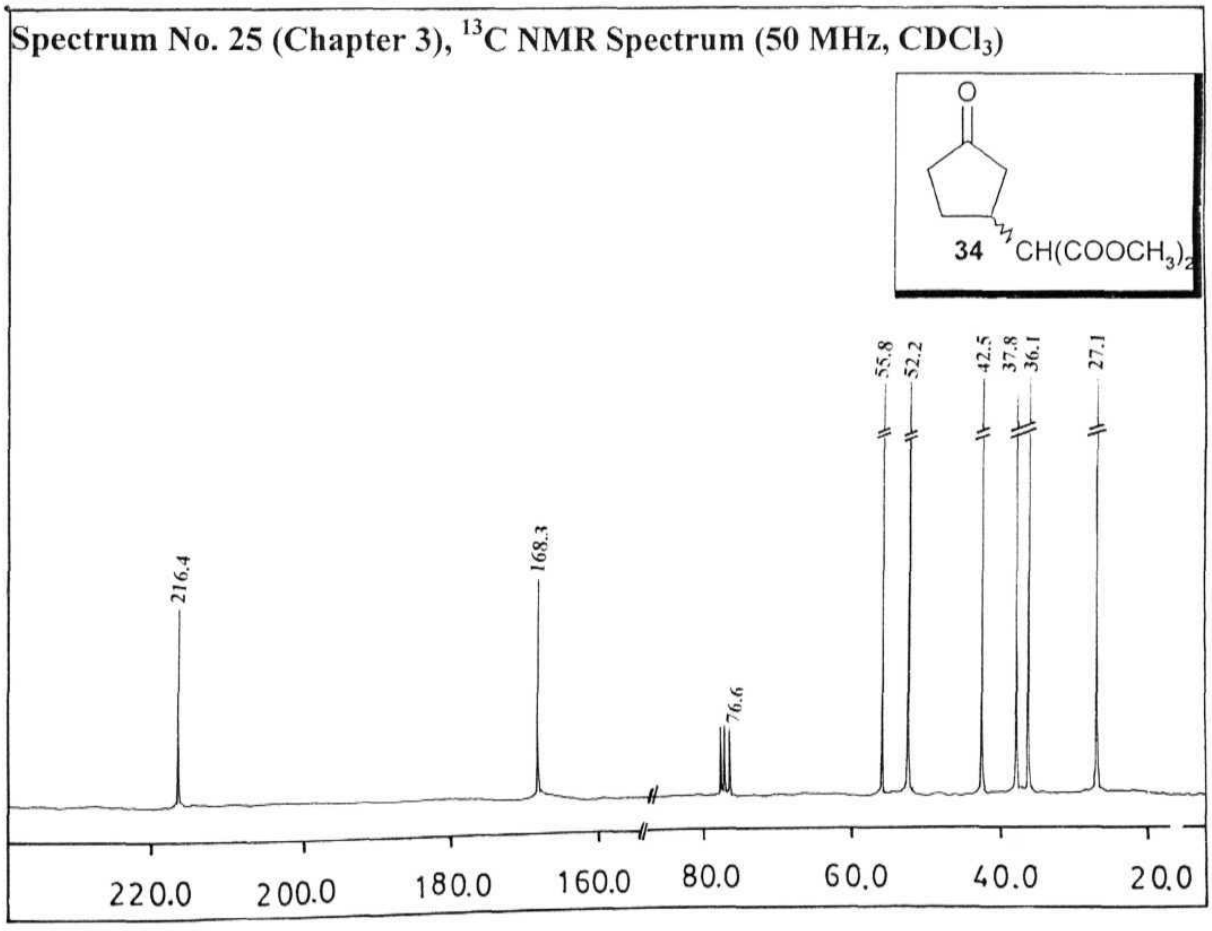
Spectrum No. 23 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



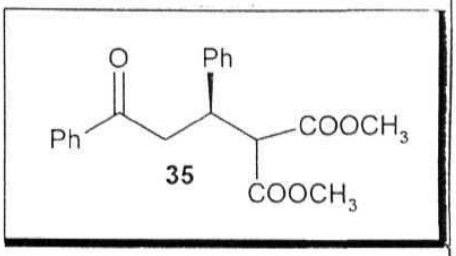
Spectrum No. 24 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



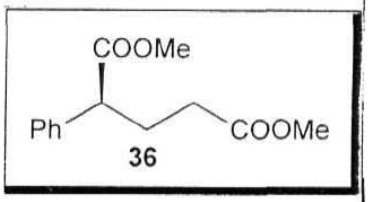
Spectrum No. 25 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

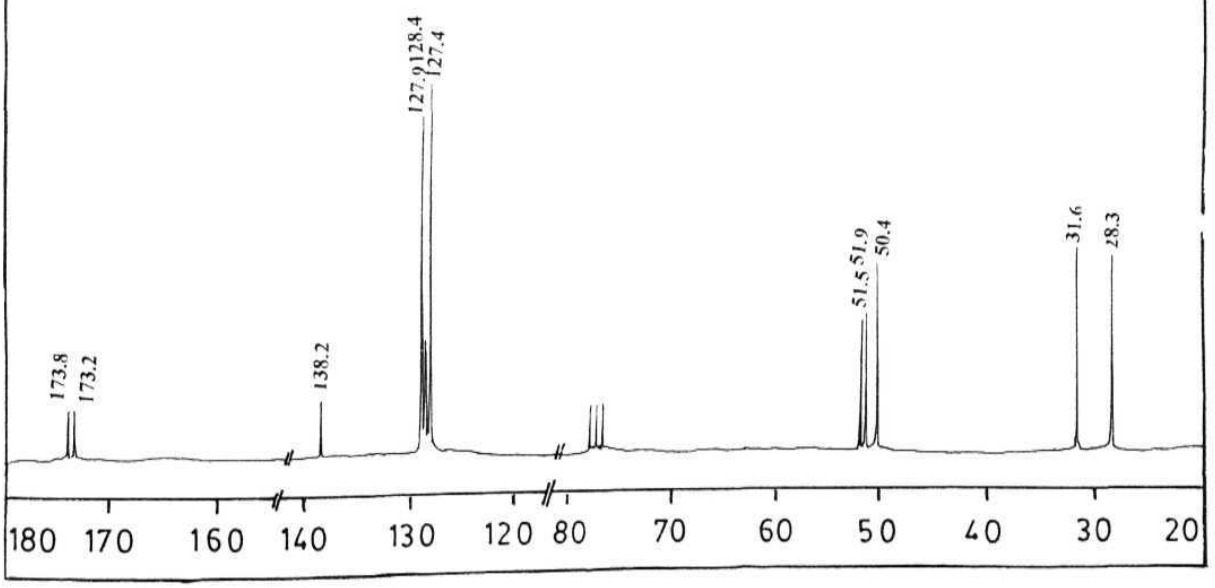


Spectrum No. 26 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Spectrum No. 27 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)





Appendix

(X-Ray Crystallographic Data)

Table A1. Atomic coordinates (x 10) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **120** (Chapter 1). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor:

	X	Y	Z	U(eq)
0(5)	9813(3)	8627(3)	2030(3)	45(1)
0(4)	10359(3)	9296(3)	2996(3)	50(1)
0(3)	9009(4)	9691(3)	2593(3)	52(2)
0(2)	9152(3)	8305(3)	2976(3)	50(1)
0(1)	8988(4)	5687(3)	1326(3)	66(2)
C(57)	10444(5)	8993(5)	1660(4)	43(2)
C(56)	11947(5)	9443(5)	1488(4)	43(2)
C(55)	12438(6)	7654(5)	3138(5)	55(2)
C(54)	11535(5)	8601(5)	2482(4)	47(2)
C(53)	10182(5)	9319(5)	1075(4)	48(2)
C(52)	11327(5)	9004(5)	1866(4)	50(2)
C(51)	7947(6)	9890(5)	1765(4)	60(3)
N(l)	9726(4)	6984(4)	1962(3)	56(2)
C(49)	12222(5)	7996(5)	2528(4)	49(2)
C(48)	7818(5)	8865(5)	3379(4)	48(2)
C(60)	8399(6)	6311(5)	1520(4)	57(2)
C(47)	11054(5)	8772(5)	3026(4)	48(2)
C(46)	7574(4)	9133(5)	2723(4)	43(2)
C(45)	11289(6)	8471(5)	3628(4)	61(3)
B	9567(6)	8981(6)	2653(5)	49(3)

C(44)	12631(5)	7658(5)	1990(4)	57(2)
C(43)	8573(5)	8435(5)	3462(4)	48(2)
C(42)	6738(6)	8965(5)	2440(4)	61(3)
C(41)	6572(5)	9612(6)	3892(5)	73(3)
C(40)	11672(6)	9795(5)	903(4)	57(2)
C(39)	7499(6)	8714(6)	4514(5)	61(2)
C(38)	7271(5)	9066(5)	3920(4)	51(2)
C(37)	7471(6)	5971(5)	1684(4)	59(2)
C(36)	6519(6)	9277(5)	1825(5)	59(3)
C(35)	13375(6)	10017(6)	1320(5)	79(3)
C(34)	8772(6)	8086(5)	4045(4)	62(3)
C(33)	13232(6)	7047(6)	2042(5)	75(3)
C(32)	11978(6)	7948(6)	3689(4)	64(3)
C(31)	9793(7)	6371(6)	2970(5)	74(3)
C(30)	6100(6)	8446(6)	2745(5)	71(3)
C(29)	8175(5)	9565(5)	2364(4)	54(2)
C(28)	12822(6)	9569(5)	1677(4)	61(3)
C(27)	8309(5)	6882(5)	949(4)	53(2)
C(50)	8875(7)	6180(5)	2717(4)	67(3)
C(25)	7216(7)	5228(6)	1450(5)	77(3)
C(24)	8138(6)	7690(6)	1003(4)	68(3)
C(23)	13462(6)	6747(6)	2644(6)	80(3)
C(22)	7120(7)	9777(6)	1507(5)	71(3)
C(21)	6972(7)	8932(6)	5060(5)	82(3)
C(20)	8229(6)	8209(6)	4558(5)	68(3)

C(19)	8397(6)	6566(6)	332(4)	75(3)
C(18)	13079(5)	7051(6)	3181(5)	73(3)
C(17)	8792(5)	6717(5)	2125(4)	50(2)
C(16)	10342(6)	6542(6)	2398(5)	75(3)
C(15)	10770(6)	9715(6)	697(4)	66(3)
C(14)	8104(8)	7863(7)	-121(6)	90(4)
C(13)	5094(7)	8608(7)	1846(6)	94(4)
C(12)	5315(7)	8300(7)	2450(6)	88(3)
C(11)	6299(7)	9468(6)	5013(5)	83(3)
C(10)	8283(8)	7062(8)	-206(5)	98(4)
C(9)	5691(6)	9102(6)	1548(5)	81(3)
C(8)	12274(7)	10244(6)	531(5)	76(3)
C(7)	13120(7)	10336(6)	740(5)	83(3)
C(6)	6073(7)	9808(6)	4428(6)	82(3)
C(5)	6854(6)	6426(6)	2023(5)	79(3)
C(4)	8013(7)	8160(6)	479(5)	86(3)
C(3)	5760(8)	5394(9)	1912(7)	115(5)
C(2)	6030(7)	6125(8)	2111(6)	106(4)
C(l)	6368(8)	4939(7)	1571(6)	104(4)
C(63)	10725(7)	7577(7)	244(6)	85(4)
C(62)	10636(8)	7293(7)	700(5)	83(4)
C(67)	9430(8)	9863(10)	4848(10)	136(8)
C(61)	9710(10)	9468(12)	5278(10)	170(9)
N(2)	10856(8)	7987(8)	-412(6)	166(5)
C(65)	5010(20)	7870(30)	4410(20)	310(40)

N(3)	5583(19)	7299(18)	4350(20)	390(20)
N(4)	9007(12)	10322(10)	4358(8)	201(7)
C(64)	4366(13)	8180(20)	4441(14)	200(14)

List of Publications

1 A new convenient method of resolution of racemic 1,1'-bi-2-naphthol using boric acid and *R*-(+)-α-methylbenzylamine, M. Periasamy, L. Venkatraman, S. Sivakumar, N. S. Kumar and C. R. Ramanathan, *J. Org. Chem*; **1999**, *64*, 7643.

2 New methods of resolution and purification of racemic and diastereomcric amino alcohol derivatives using boric acid and chiral 1,1'-bi-2-naphthol; M. Periasamy, N.S. Kumar, S. Sivakumar, V. D. Rao. C. R. Ramanathan and L. Venkatraman;./. *Org. Chem,* 2001, *66,* 3828.

3 A new general method of synthesis and resolution of 1,2- amino alcohols. S. Sivakumar, M. Narsireddy and M. Periasamy, presented a poster in the *OMCOS-11* International Symposium held at Taipei, Taiwan during July 22-26,2001.

4 A new synthesis of chiral 1,2-amino alcohols via borane reduction of oximes of α-kcto esters: Duplication of chirality via borane reduction of oxime derivatives of ethyl phenylglyoxylate using (*R*)-phenylglycinol, M. Periasamy, S. Sivakumar and M. Narsireddy, Communicated.

5 Boraxanes : preparation and applications, M. Periasamy, S. Sivakumar, N. S. Kumar and M. Thirumalaikumar; *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Georg Thieme Verlag, Stuttgart.* **2003.**

6 Acyloxyboranes : preparation and applications, M. Periasamy, N.S. kumar. S. **Sivakumar** and M. Thirumalaikumar; *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Georg Thieme Verlag, Stuttgart,* **2003.**

7 Enrichment of enantiomeric excess of non-racemic 1,2-amino alcohols using achiral dicarboxylic acids, M. Periasamy, S. **Sivakumar** and M. Narsireddy, Manuscript under preparation.

8 Asymmetric Michael addition reactions using the oxazaborolidines derived from 1,2-amino alcohols, S. **Sivakumar** and M. Periasamy, Manuscript under preparation.