# ASYMMETRIC CATALYSIS USING CHIRAL OXAZABOROLIDINES

THESIS SUBMITTED TO THE UNIVERSITY OF KERALA
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IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

BY

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SEPTEMBER, 1999

*To*
*My Teachers*

## Declaration

I hereby declare that the matter embodied in the thesis entitled *"ASYMMETRIC CATALYSIS USING CHIRAL OXAZABOROLIDINES"* is the result of investigations carried out by me at the Organic Chemistry Division of Regional Research Laboratory [CSIR], Trivandrum under the supervision of **Dr. J. Madhusudana Rao** and the same has not been submitted elsewhere for a degree.

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# Certificate

This is to certify that the work contained in the thesis entitled "ASYMMETRIC CATALYSIS USING CHIRAL OXAZABOROLIDINES" has been carried out by Santhi, V. under my supervision at the Organic Chemistry Division of Regional Research Laboratory [CSIR], Trivandrum and the same has not been submitted elsewhere for any other degree.

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Santhi V.

Thiruvananthapuram

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# PREFACE

The importance and utility of asymmetric synthesis to obtain enantiopure molecules have been widely acknowledged by chemists. Among the types of asymmetric reactions, the most desirable and the most challenging is the catalytic asymmetric synthesis since one chiral catalyst molecule can create a number of chiral product molecules. As compared to the enzyme activity in biological systems catalytic asymmetric synthesis has an important impact in industrial scale production of chiral molecules. Because of this the efforts to find new efficient catalysts for asymmetric synthesis are in progress. The 1,3,2-oxazaborolidines developed by Itsuno *et al.* are versatile catalysts in the area of asymmetric synthesis. This thesis entitled "***ASYMMETRIC CATALYSIS USING CHIRAL OXAZABOROLIDINES***" deals with the asymmetric reduction of prochiral ketones using oxazaborolidines derived from 1,2-amino alcohols of (1R)-(+)-camphor. The thesis is divided into four chapters and relevant references are given towards the end of each chapter.

In the first chapter a brief overview on the development, synthesis and applications of oxazaborolidine catalysts in the area of asymmetric synthesis is presented.

The second chapter deals with the synthesis of amino alcohols and amino alcohol derivatives from (1R)-(+)-camphor.

The third chapter deals with the catalytic asymmetric borane reduction of various ketones using the oxazaborolidine catalysts derived from

(1R)-(+)-camphor. It consists of three parts. In the first part an overview of important methods available in literature for the enantioselective reduction of ketones is given. Part II deals with the synthesis of oxazaborolidine catalysts from amino alcohol derivatives of (1R)-(+)-camphor and the asymmetric borane reduction of ketones using these. oxazaborolidines as catalysts. The same reductions carried out with oxazaborolidines derived from 1,2-amino alcohols of (1R)-(+)-camphor as catalysts forms the subject matter of the third part.

The final chapter describes an indepth study of the effect of various parameters such as temperature, reaction medium, the substrate - catalyst ratio and reducing agents on the enantioselectivity of asymmetric reduction of ketones. A summary of the thesis is presented towards the end.

## List of Abbreviations

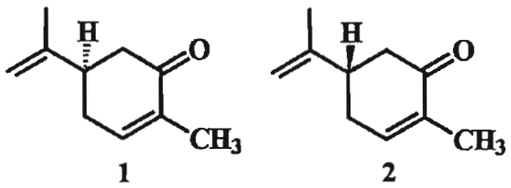
| | |
|---|---|
| Ac | : acetyl |
| BBN | : borabiclo[3.3.1]nonane |
| BINALH | : 2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminium hydride |
| BINAP | : 2.2'-bis(diphenylphosphino)-1.1'-binaphthyl |
| Bn | : benzyl |
| brs | : broad singlet |
| bu | : butyl |
| CBS process | : Corey-Bakshi-Shibata process |
| cod | : cyclooctadiene |
| d | : doublet |
| DEPT | : Distortionless enhancement by polarisation transfer |
| DHQD | : dihydroquinidine |
| DIBALH | : diisobutyl aluminium hydride |
| DIPT | : diisopropyl tartrate |
| DME | : Dimethoxyethane |
| *ee* | : enantiomeric excess |
| Et | : ethyl |
| h | : hour |
| $(IPC)BH_2$ | : Monoisopinocampheylborane |
| $(IPC)_2BH$ | : Diisopinocampheylborane |
| IR | : Infra red |
| *J* | : Coupling constant |
| LAH | : Lithium aluminium hydride. |
| LDA | : Lithium diisopropylamide |
| LTA | : Lead tetraacetate |
| m | : multiplet |
| Me | : methyl |
| MOM | : Methoxymethyl |
| m. p. | : melting point |
| MS | : Mass spectrum |
| MTPA | : $\alpha$–methoxy-$\alpha$-(trifluoromethyl) phenylacetic acid |
| Np | : Naphthyl |
| NMO | : N-methylmorpholine N-oxide |
| NMR | : nucler magnetic resonance |
| Ph | : phenyl |
| Pr | : propyl |
| R. T. | : room temperature |
| s | : singlet |
| salen | : bis(salicylidene)ethylenediamine |
| t | : triplet |
| TBHP | : t-Butyl hydroperoxide |
| TEA | : triethylamine |
| THF | : Tetrahydrofuran |
| TLC | : Thin layer chromatography |
| TMS | : tetramethylsilane |
| Ts | : tosyl |

# CHAPTER I

# ASYMMETRIC SYNTHESIS USING CHIRAL OXAZABOROLIDINES - A REVIEW

## 1.1 INTRODUCTION

Fundamental phenomena and laws of nature result from chirality. In this regard, two enantiomeric biologically active compounds often behave differently in chiral surroundings. The optical activity of the compounds in nature results from the chirality of the enzymes responsible for their production. Although the apparent physical differences between the two forms of optically active molecule may seem small, the spatial orientation of a single functional group drastically affects the property of the compound. Our olfactory response to the two enantiomeric forms of carvone, a terpene is a well known example. The (R)-form **1** has the odour of the spearmint whereas, (S)-carvone **2** smells like caraway (Figure 1.1).[1-3]




1 2

**Figure 1.1**

The enantiomers of certain $\alpha$–amino acids like leucine, phenylalanine, tyrosine, tryptophan etc. exhibit taste differences. The *l*-form is bitter in taste while the *d*-form is sweet.[4] It is well known that the *l*-enantiomer is used by nature for protein synthesis.

The advantages of using enantiomeric compounds for pharmaceuticals, agrochemicals, vitamins, etc. have been recognized for many years.[5] These are now used as components of new materials such as liquid crystals and as biodegradable polymers.[6] Although more than 50% of the commercial drugs are chiral, less than half of these are marketed in an enantiomerically pure form. The different pharmacological response of the two enantiomers is well known.

(S)-Warfarin **3** is six times more active as an anticoagulant than the (R)-enantiomer. (S)-propranolol **4** is an antihypertensive and antiarhythmic used in the treatment of heart diseases, while the (R)-enantiomer acts as a contraceptive. The alkaloid (-)-levorphanol **5** is a potent narcotic analgesic, while the (+) form is marketed as a cough suppressant in the form of its methyl ether (Figure 1.2).[7]

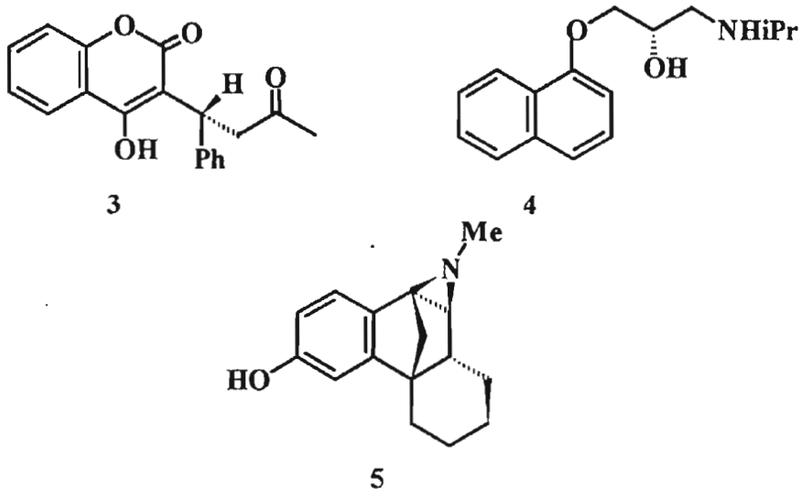



**Figure 1.2**

The drastic differences in the pharmacological properties of the enantiomer of the thalidomide, a conteragen which was commercialized in the 60's is most demonstrative.[8] Its R enantiomer **6** shows a weak sedative activity, while the S enantiomer **7** taken together with the racemate caused expectant mothers a teratogenic effect (malformation in the foetal stage) (Figure 1.3).

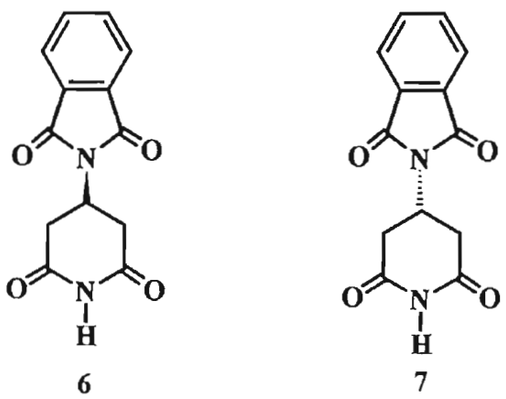



**Figure 1.3**

These are several examples which show the differences in the biological activity of the enantiomers, that are used as drugs. The new single

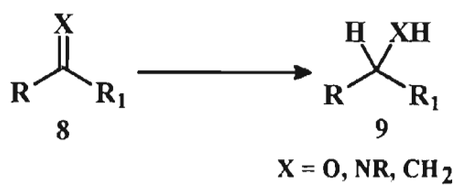
isomer products in the chiral market create demand for novel enantiomeric intermediates and enantioselective methods to get pure isomers.

In the laboratory, synthesis of a chiral molecule always results in racemic modification, since the free energy of formation of both enantiomers are identical. One method to obtain enantiopure molecule involves the resolution of the racemate into optically active form by mechanical, enzymatic or by diastereomer formation. But all the above mentioned methods are tedious and are not economically favorable, since in many cases half of the material will be wasted. Another method to get optically pure material is by carrying out functional group transformations on an optically pure starting material, without affecting the chiral centre. But this also requires resolution in order to get the optically pure starting materials, except for some which are found in an optically pure form in nature.

The solution to the aforementioned problems is the asymmetric synthesis. Asymmetric synthesis involves the synthesis of chiral products starting from prochiral or achiral substrates by exploiting the use of chiral auxiliaries or catalysts. In asymmetric synthesis the chiral catalysts are used as external reagents in substoichiometric amounts, whereas auxiliaries are used as parts of substrate in stoichiometric amounts.

Important areas of current interest in asymmetric catalysis are :-

(i) The reduction of functionalised C=O, C=C and C=N groups (Scheme 1.1).

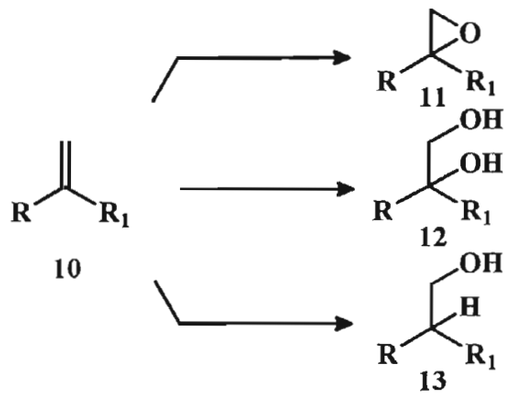



8 9

X = O, NR, $CH_2$

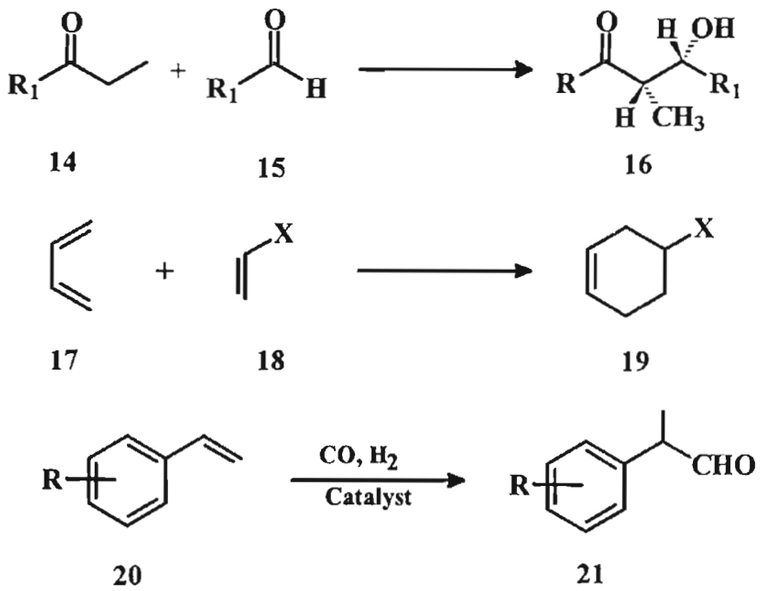
**Scheme 1.1**

(ii) The oxidation (epoxidation, dihydroxylation, & hydroboration) of the C=C systems (Scheme 1.2).




**Scheme 1.2**

(iii) Various C-C bond formations (aldol condensation, Diels-Alder reaction, hydroformylation etc.) which can create new asymmetric centres (Scheme 1.3).[9]

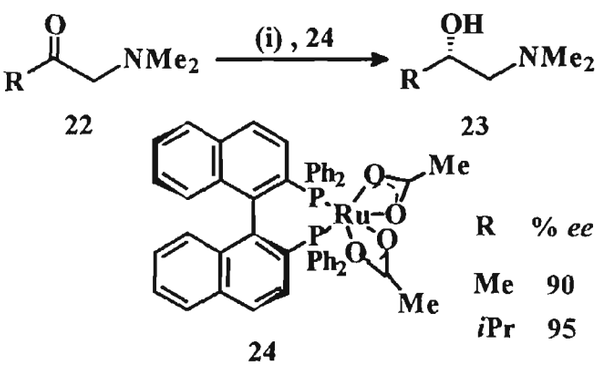



**Scheme 1.3**

Early attempts for the asymmetric synthesis made use of naturally occurring optically active materials as catalysts. In 1972, Erlinmeyer

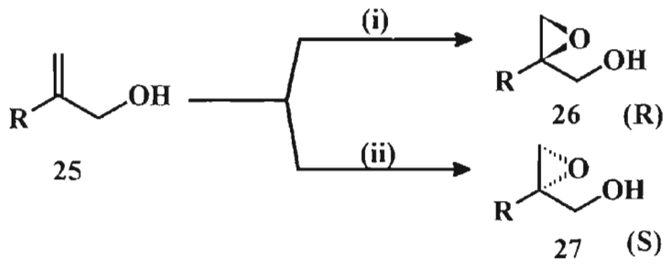
presented ZnO/Fructose catalyst that promoted the addition of bromine to cinnamic acid with an *ee* of 50%.[10] Later polypeptides were used as catalysts in asymmetric synthesis. In 1979, Ovito *et al.* used the cinchona alkaloid modified Pt catalyst for the reduction of α- keto esters.[11] Because of the potential advantage of asymmetric catalysis chemists are in search of novel chiral catalysts.

Diphosphine complexes of Rh and Ru have been used as the catalysts for the asymmetric reduction of ketones.[12] Complexes of Rh can catalyse the reduction of aminoketones to amino alcohols with high *ee* (Scheme 1.4).




**Scheme 1.4**

Various chiral dialkyl tartrates and titanium alkoxides were developed by Sharpless for the synthesis of asymmetric epoxides from primary allylic alcohols (Scheme 1.5).[13]

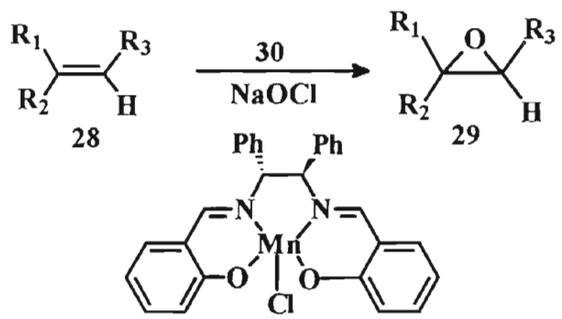



**(i)** (-) **DIPT, Ti(O-iPr)$_4$, TBHP**

**(ii)** (+) **DIPT, Ti(O-iPr)$_4$, TBHP**

**Scheme 1.5**

The chiral salen complexes developed by Jacobsen *et al.* were used as asymmetric catalysts for the epoxidation reactions (Scheme 1.6).[14]

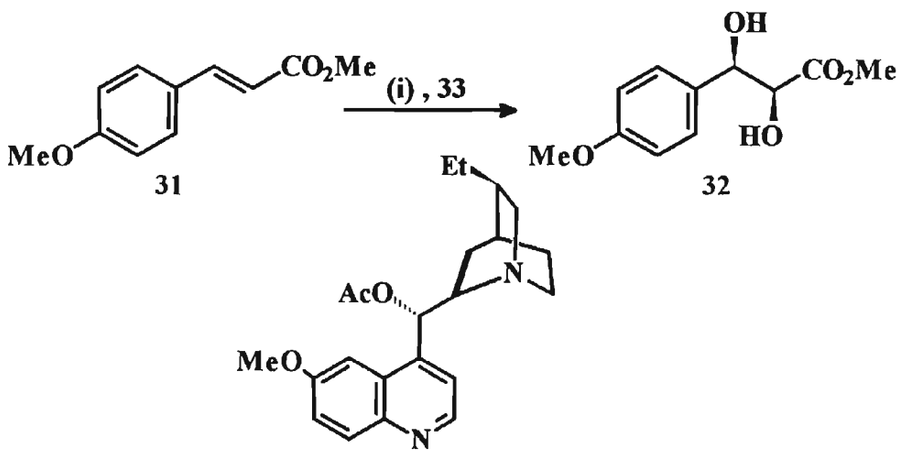



**Mn Salen Complex**

**30**

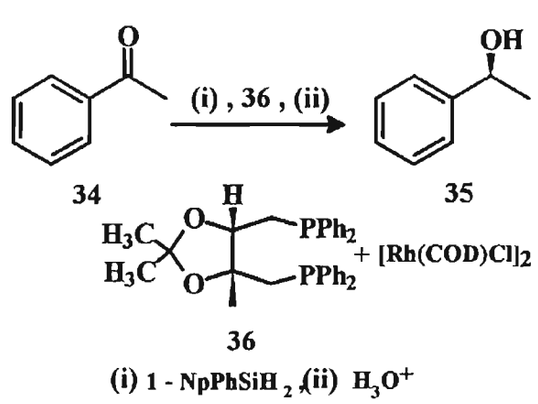
**Scheme 1.6**

Asymmetric dihydroxylation of olefins can be achieved by using $OsO_4$ in the presence of chiral amine complexes (Scheme 1.7).[15]




**Scheme 1.7**

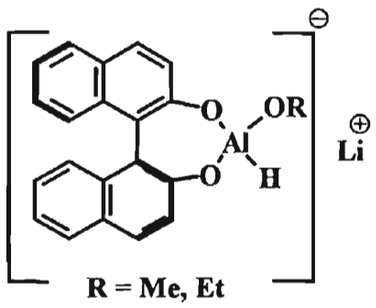
The chiral phosphine ligands have been used for the asymmetric hydrosilylation reaction of prochiral ketones (Scheme 1.8).[16]




**Scheme 1.8**

The above examples illustrate the importance of some catalysts in the area of asymmetric synthesis. Inspite of excellent results obtained, in many cases the practical difficulties associated with these catalysts limit their

application in many transformations. Besides, useful catalysts are not available for a number of reactions. For the reduction of prochiral carbonyl group, chirally modified aluminium hydrides are in use.[17] BINAL-H **37**, complex formed from an equimolar mixture of lithium aluminium hydride and 2,2'-dihydroxy-1,1'-binaphthyl and ethanol is found to be a good catalyst. BINAL-H is available in both enantiomeric forms and due to the C2 symmetry of the molecule the number of possible isomers in the reaction medium is reduced. Products with *ee* ranging from 95-100% were obtained on reduction of prochiral ketones using these catalysts.




**R = Me, Et**

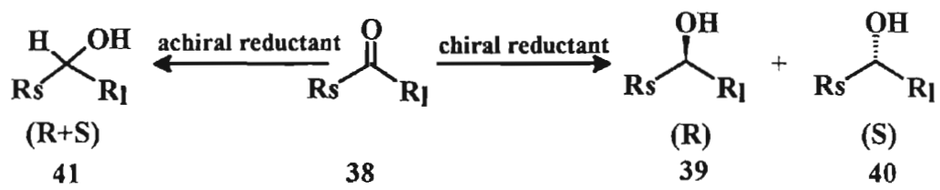
**37**

**Figure 1.4**

The second generation of homochiral reduction catalysts is the 1,3,2-oxazaborolidines.[18] In the following sections, a brief review on the use of oxazaborolidines in the area of asymmetric synthesis is described.

## 1.2 OXAZABOROLIDINES IN ASYMMETRIC SYNTHESIS – AN INTRODUCTION

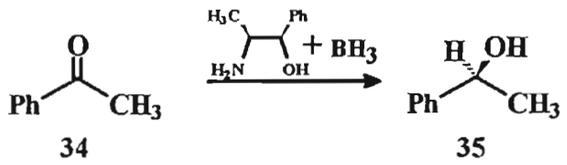
The reduction of a prochiral ketone with an achiral reductant will always lead to racemic alcohols since the hydride ion can attack from both sides of the carbonyl moiety. In the presence of a chiral catalyst, the catalyst favours the attack of the hydride ion from one side preferentially leading to the formation of one enantiomer (Scheme 1.9).




**Scheme 1.9**

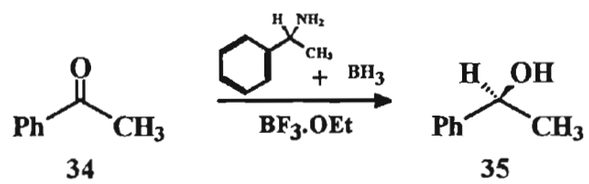
Microbial processes,[19] heterogeneous metal catalysts,[20] the enantioselective homogeneous catalytic reduction using chirally modified hydride reagents[21]etc. are the usual methods to introduce chirality.

In 1969, Fiand and Kagen tested ephedrine boranes as reducing agents for the reduction of prochiral ketones, but the optical yield of alcohol was low (Scheme 1.10).[22]



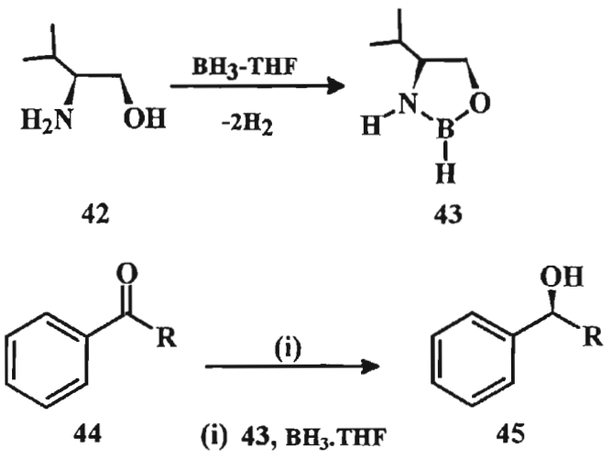

**Scheme 1.10**

The amine borane in the presence of $BF_3$.etherate was used for the reduction of ketones and the alcohols were obtained with *ee* up to 20% (Scheme 1.11).[23]



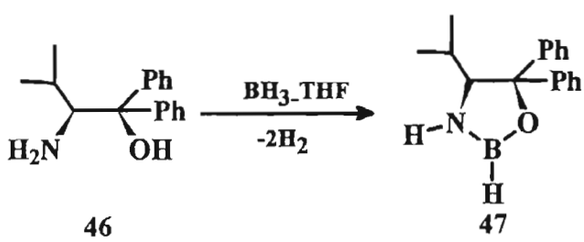

**Scheme 1.11**

In 1981, Itsuno *et al.* reported the first effective enantioselective ketone reduction using a stoichiometric amount of an amino alcohol borane complex.[24] The complex is a 5-membered 1,3,2-oxazaborolidine derived from $\beta$-amino alcohol of (S)-valine (Scheme 1.12).



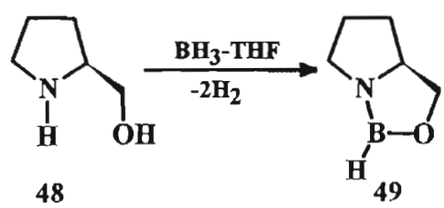

**Scheme 1.12**

Later asymmetric reduction of both aliphatic and alkyl phenyl ketones were reported using a bulky derivative of (S)-valine derived oxazaborolidine (Scheme 1.13).[25]




**Scheme 1.13**

Itsuno's group also developed structurally more rigid (S)-proline derived $\beta$-amino alcohols as the precursors of oxazaborolidine. But these were found to be less effective in asymmetric induction (Scheme 1.14).[26]

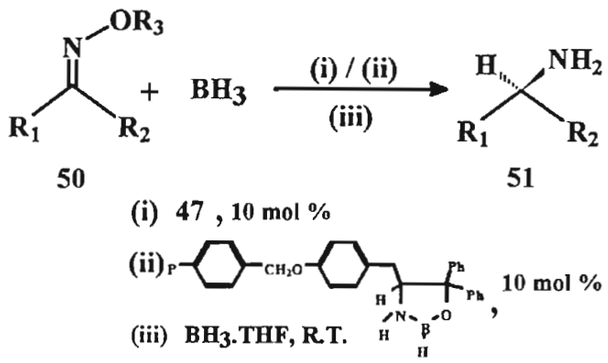



**Scheme 1.14**

Since the initial reports, a number of groups have investigated the reduction of prochiral ketones with stoichiometric amount of amine borane complex or the oxazaborolidine as reductant.[27]

## 1.3 OXAZABOROLIDINES AS ASYMMETRIC CATALYSTS

In 1987, Itsuno *et al.* reported the first enantioselective reduction of ketoxime ethers using (S)-valine derived oxazaborolidine as catalyst and borane as the stoichiometric reductant (Scheme 1.15).[28] The results are summarized in table 1.1.

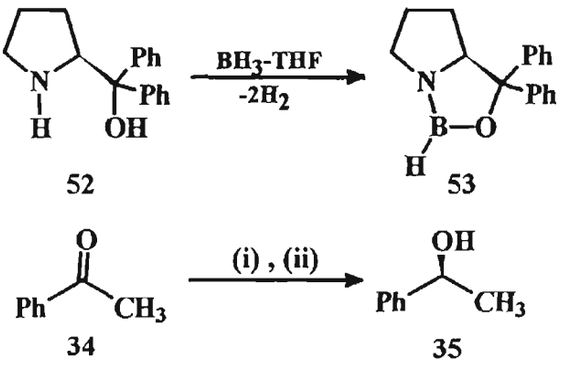



**Scheme 1.15**

**Table 1.1** Results obtained in the ketoxime reduction.

| Ketoxime | Catalyst | *ee* (%) | Yield (%) |
|---|---|---|---|
| $R_1$=Ph, $R_2$=Me, $R_3$=Me | 1 | 99 | 100 |
| | 2 | 18 | 100 |
| $R_1$=Ph, $R_2$=Me $R_3$=$CH_2$Ph | 1 | 91 | 100 |
| | 2 | 26 | 100 |

The process pioneered by Itsuno was then developed by Corey *et al.* as the CBS (Corey-Bakshi-Shibata) process.[29] The CBS process is the enantioselective reduction with borane or catecholborane as stoichiometric reductant and oxazaborolidine as the catalyst.. On the basis of the studies by Itsuno, oxazaborolidines such as **53** has been introduced and identified by Corey's group (Scheme 1.16).




52 53

34 35

(i) 53 , 0.5 mol %

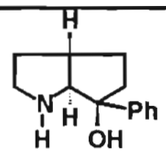
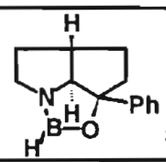
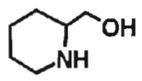
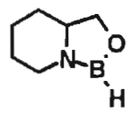
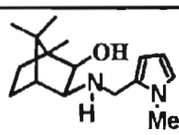
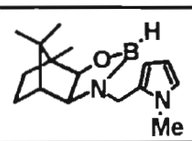
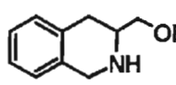
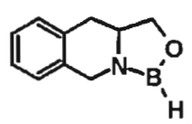
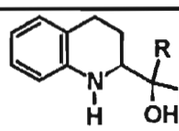
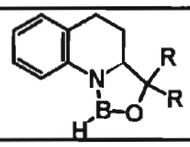
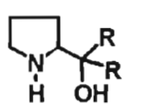
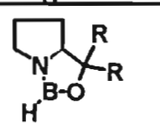
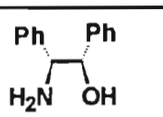
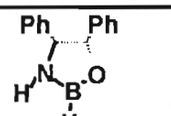
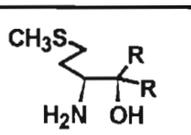
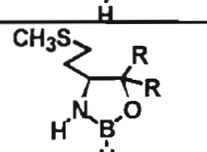
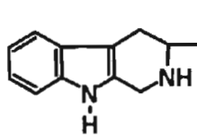
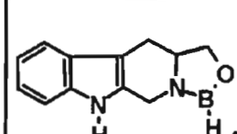
(ii) $BH_3$.THF, 120 mol %, R. T.

100 % , 97 % *ee*

**Scheme 1.16**

It is known that neither borane nor the oxazaborolidine reduce the ketone asymmetrically, but in combination, the asymmetric reduction occurs. Since then a number of groups have investigated the asymmetric reduction using oxazaborolidine. Many of the oxazaborolidines are generated *in situ* and are derived from the corresponding amino alcohols. A summary of the oxazaborolidines used in the asymmetric reduction of ketones is given in the table 1.2.

**Table 1.2** Oxazaborolidine catalysts used for the asymmetric reduction of ketones.

| Entry | Catalyst Precursor | Catalyst | Reference |
|---|---|---|---|
| 1 |  54 |  55 | 30 |
| 2 |  56 |  57 | 31 |
| 3 |  58 |  59 | 32 |
| 4 |  60 |  61 | 33 |
| 5 |  62 |  63 | 34 |
| 6 |  64 |  65 | 35 |
| 7 |  66 |  67 | 36 |
| 8 |  68 |  69 | 37 |
| 9 |  70 |  71 | 38 |

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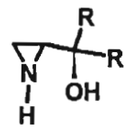
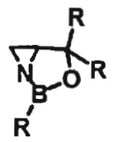
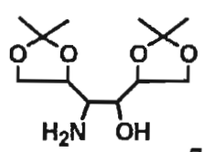
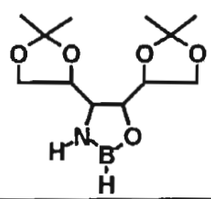
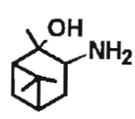
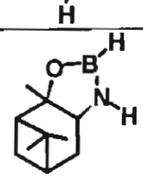
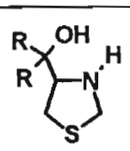
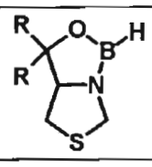
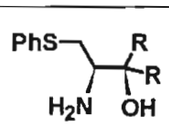
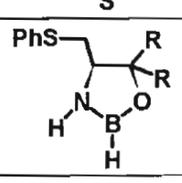
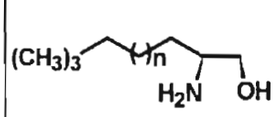
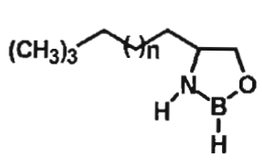
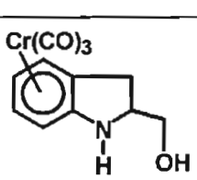
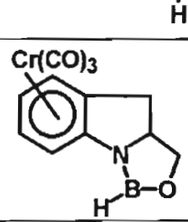
| 10 |  72 |  73 | 39 |
| 11 |  74 |  75 | 40 |
| 12 |  76 |  77 | 41 |
| 13 |  78 |  79 | 42 |
| 14 |  80 |  81 | 43 |
| 15 |  82 |  83 | 44 |
| 16 |  84 |  85 | 45 |

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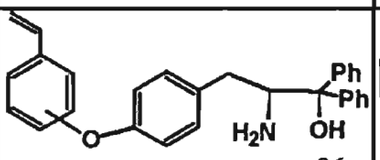
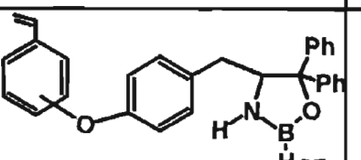
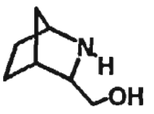
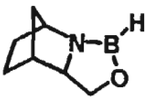
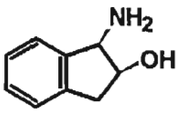
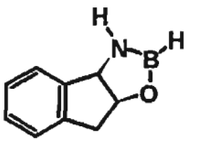
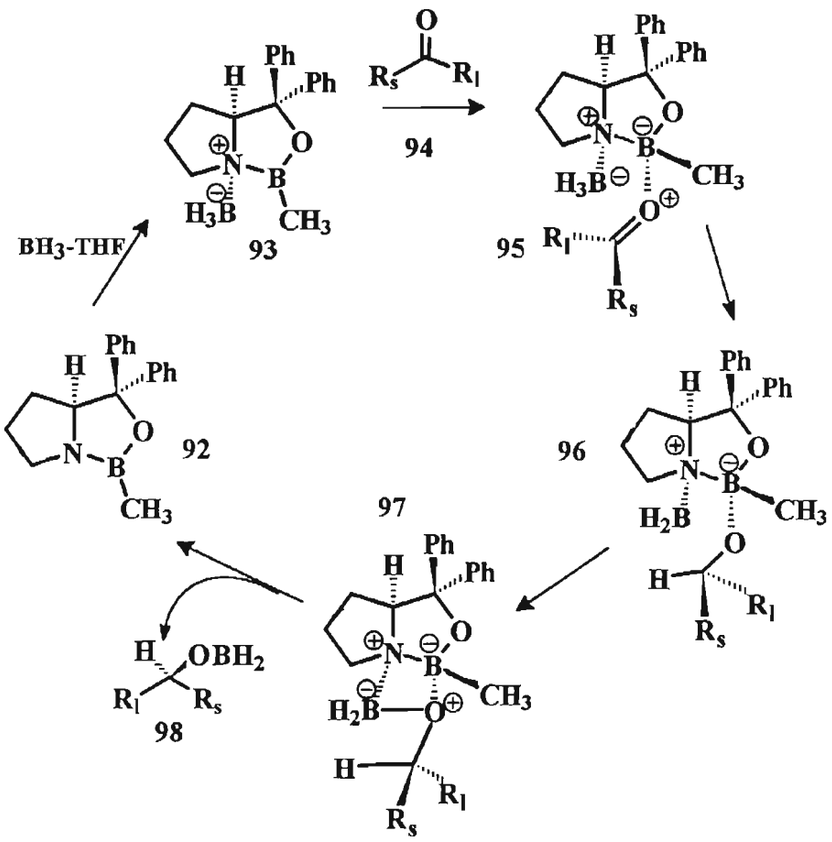
| 17 |  86 |  87 | 46 |
| 18 |  88 |  89 | 47 |
| 19 |  90 |  91 | 48 |

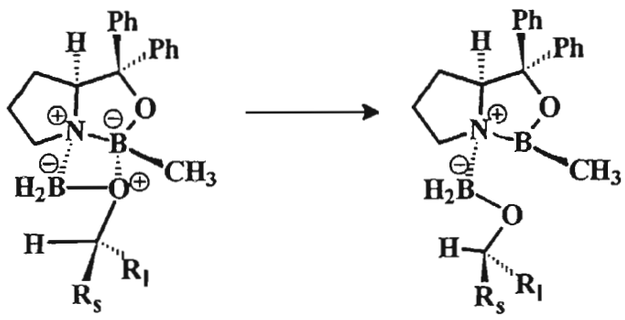
## 1.4 MECHANISTIC CONSIDERATIONS

Oxazaborolidines are classified as non-transition metal catalysts. They are called as chemzymes or molecular robots, as they can recognize two different enantiomers, bind them in a specific and predictable manner, and after activation can release the enantiomer of the selective reaction.[29] This is an example of two centred catalysis.[49] The mechanism suggested by Corey *et al.* is given in scheme 1.17.[50]




**Scheme 1.17**

The *ab initio* MO method studies also favours the above mechanistic pathway.[51] It also suggests a reactive 1,3-oxazaboretane intermediate which generates the oxazaborolidine. The 1,3-oxazaboretane system **97** which is formed after the intramolecular hydride transfer, can react by eliminating the alkoxy moiety to give the oxazaborolidine, or could rearrange to a alkoxy borane adduct **99** (Scheme 1.18).




97 99

**Scheme 1.18**

The alkoxy borane adduct can act as the reducing species and after elimination co-ordinate back to the oxazaborolidine and serve as a hydrogen donor. The relative energy of formation of the borane adduct and alkoxy borane were studied and it was concluded that the alkoxy borane adduct can act as good reducing agent as the borane adduct.

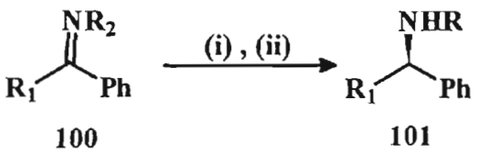
## 1.5 OXAZABOROLIDINES IN ASYMMETRIC SYNTHESIS

The oxazaborolidines were used as catalysts for asymmetric reduction of imines and asymmetric reduction of enol ethers, asymmetric addition of dialkylzinc to aldehydes, asymmetric Diels-Alder reaction, asymmetric hydroboration of alkenes and for the asymmetric synthesis of a large number of biologically active molecules. These are illustrated in the following sections.

### 1.5.1 Asymmetric reduction of C=N bonds

Optically active amines are important starting materials for the synthesis of biologically active molecules. The first oxazaborolidine catalyzed asymmetric synthesis of chiral amines was reported by Itsuno *et al.*[28] They have used (S)-valine derived oxazaborolidine as the catalyst for the reduction of ketoxime ethers.

The first asymmetric reduction of ketimines using oxazaborolidines as catalyst was reported by Cho and Chun.[52] A stoichiometric amount of (S)-valine derived oxazaborolidine was used as the catalyst for this reduction (Scheme 1.19).




100 101

(i) **53** (Scheme 1.16), 110 mol

(ii) $BH_3$.THF, 110 mol %

$R_1$=Et, $R_2$=Ph *ee* = 78%

$R_1$=Me, $R_2$= n-$C_7H_{13}$ *ee* = 52%

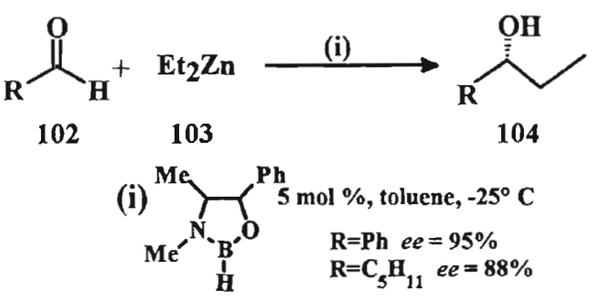
$R_1$=n-$C_3H_7$, $R_2$=Ph *ee* = 88%

**Scheme 1.19**

There are some other reports in literature on the oxazaborolidine catalyzed reduction of C=N bonds.[53]

### 1.5.2 Asymmetric addition of diethylzinc to aldehydes

The addition of diethylzinc to aldehydes catalyzed by oxazaborolidines was reported by Brown *et al.*[54] They used ephedrine and pseudoephedrine derived oxazaborolidines as the catalyst (Scheme 1.20).




102 103 104

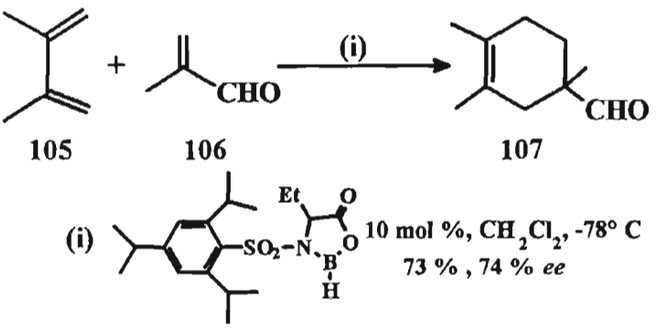
**Scheme 1.20**

### 1.5.3 Asymmetric Diels-Alder reaction

The oxazaborolidine catalyzed asymmetric Diels-Alder reactions were reported by Helmchen *et al.*[55] and Yamamoto *et al.*[56] They synthesized

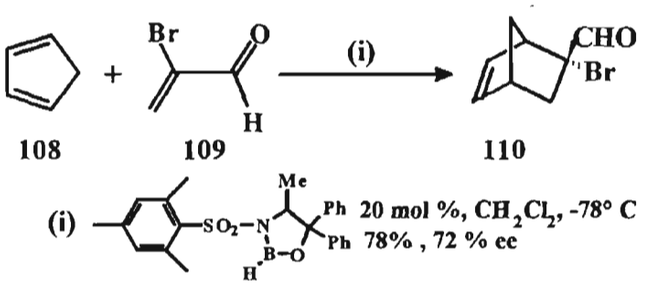
oxazaborolidines from N-sulfonamides of amino acids and borane. Yamamoto *et al.* synthesized oxazaborolidine from 2,4,6-triisopropylbenzene sulphonamide of (S)-ethyl glycine.

The cycloaddition of methacrolein with 2,3-dimethyl-1,3-butadiene in presence of the 10 mol % of the catalyst yielded the cycloadduct with 74% *ee* (Scheme 1.21).



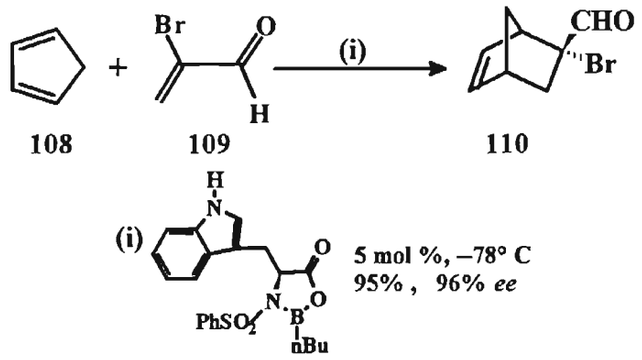

**Scheme 1.21**

Helmchen used mesityl sulfonanamide of (S)-valine as the catalyst precursor and studied the Diels-Alder reaction between cyclopentadiene and various dienophiles (Scheme 1.22).



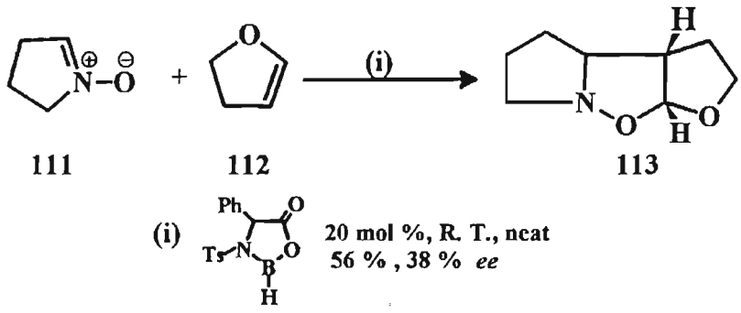

**Scheme 1.22**

Later Corey *et al.* developed (S)-tryptophan derived oxazaborolidine as catalyst for the asymmetric Diels-Alder reaction between cyclopentadiene and 2-bromoacrolein (Scheme 1.23).[57]




**Scheme 1.23**

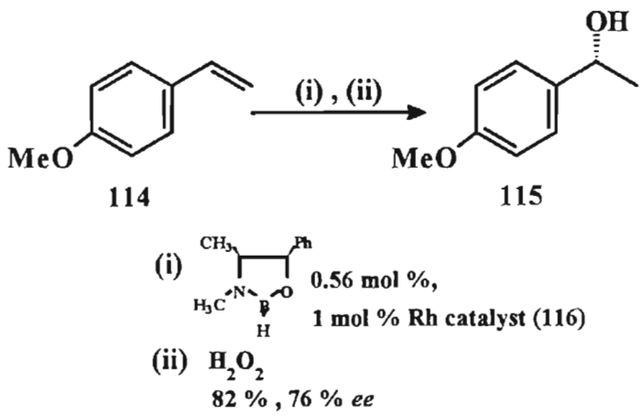
The cycloaddition of pyrroline-N-oxide with 2,3-dihydrofuran catalyzed by oxazaborolidine yielded the product with moderate enantioselectivity (Scheme 1.24).[58]




**Scheme 1.24**

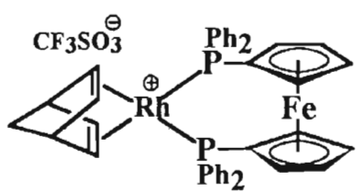
### 1.5.4 Catalytic asymmetric hydroboration

The first catalytic asymmetric hydroboration reaction of styrenes using ephedrine and pseudoephedrine derived oxazaborolidines and Rh complex as catalyst was reported by Brown *et al.* (Scheme 1.25).[59]




**Scheme 1.25**

In this transformation, oxazaborolidine functioned as the borane equivalent in stoichiometric amounts and the Rh compound **116** acts as the catalyst.



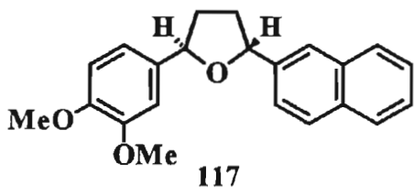

**116**

**Figure 1.5**

## 1.6 SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

The oxazaborolidine catalyzed reduction of ketone functionality has been used as a key step in the synthesis of a wide variety of biologically active chiral natural products. Syntheses of some of these biologically active compounds are illustrated below.

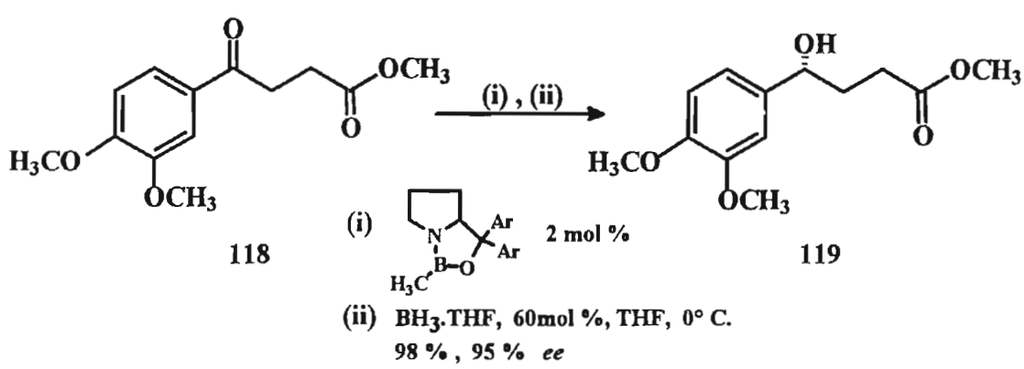
Racemic trans-2,5-diarylfurans **117** have been found to be potent antagonists of platelet activating factor.




117

**Figure 1.6**

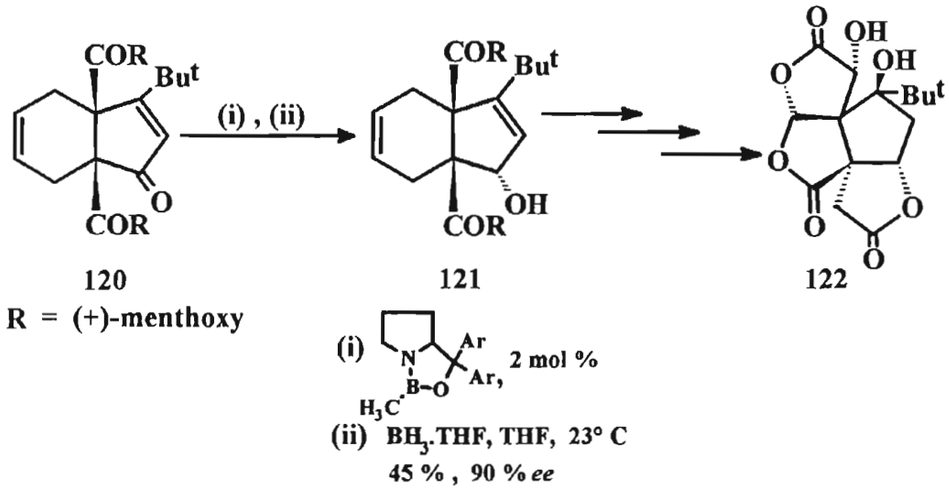
Corey *et al.* reported the first asymmetric route to these compounds in which the key step is the reduction of a γ–ketoester with an oxazaborolidine catalyst (Scheme 1.26).[60]




118 119

**Scheme 1.26**

The total synthesis of (-)-bilobalide **122,** a $C_{15}$ ginkgolide involves a CBS reduction as the key step (Scheme 1.27).[61]

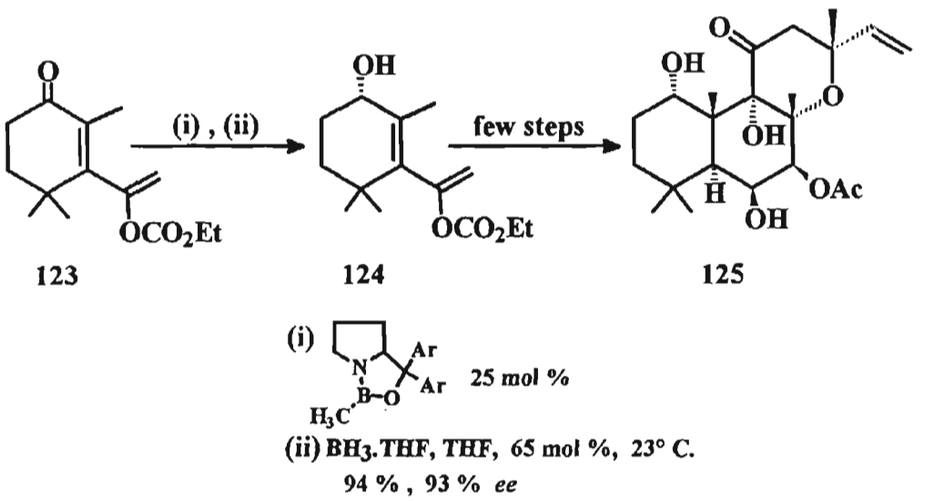



120 121 122

R = (+)-menthoxy

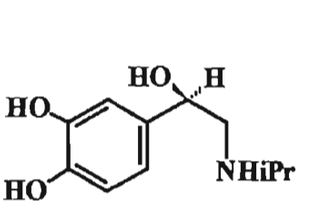
**Scheme 1.27**

The total synthesis of (-)-forskolin **125** an activator of ATP-AMP cyclase involves an oxazaborolidine catalyzed reduction as illustrated in Scheme 1.28.[62]

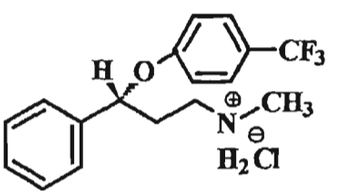



**Scheme 1.28**

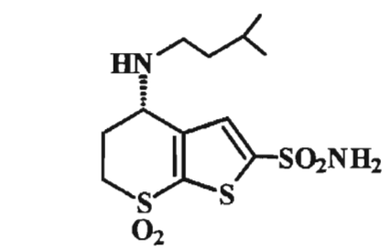
The total syntheses of isoproternol **126**, a $\beta$-adrene receptor agonist,[63] fluoxetine **127** an antidepressant,[64] the water soluble carbonic anhydrase inhibitor MK-0417 **128** used for the treatment of glucoma[65] the plant growth regulator triapenthenol **129**[66] the potent dopamine D1 agonist A77636 **130**[67] and salmeterol a long acting $\beta$-agonist **131**,[68] involve the oxazaborolidine catalyzed reduction as the key step (Figure 1.7).



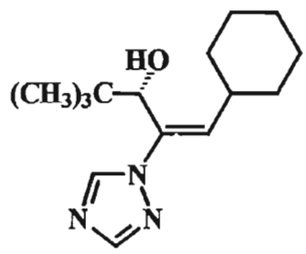

126



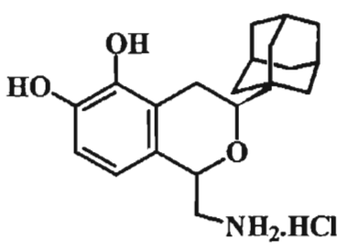

127



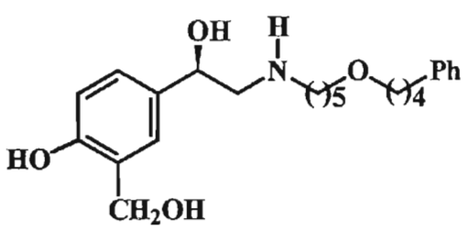
128



129



130

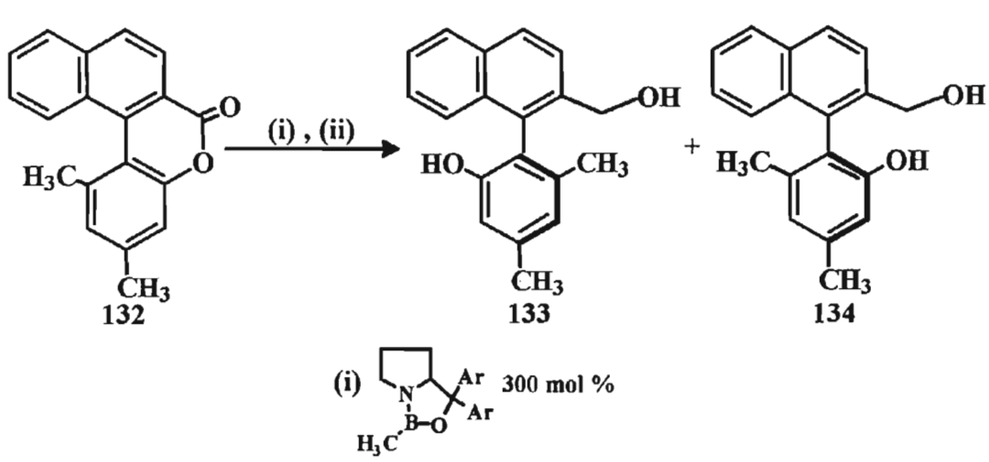


131

**Figure 1.7**

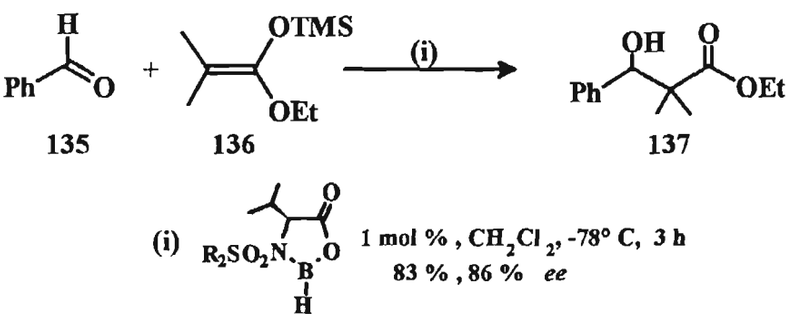
## 1.7 MISCELLANEOUS REACTIONS

Bringmann *et al.* reported the atrop enantioselective ring opening of axial prochiral lactone bridged biaryl compounds using an oxazaborolidine catalyzed reaction (Scheme 1.29).[69]



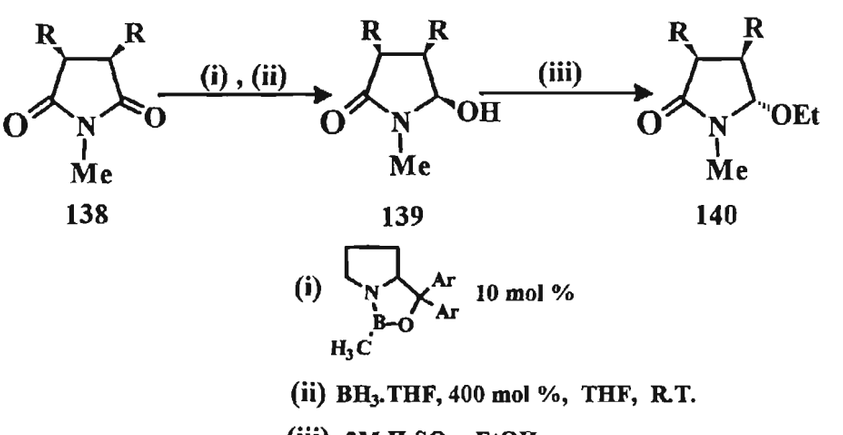
**Scheme 1.29**

Kiyooka *et al.* have reported the catalytic asymmetric aldol reactions of silyl ketene acetals with aldehydes in presence of oxazaborolidine derived from *p*-nitrobenzene sulfonamide of (S)-valine.[70] *β*-hydroxy alcohols were obtained with good enantioselectivity and in good yield (Scheme 1.30).




**Scheme 1.30**

The asymmetric reduction of cyclic meso imides catalyzed by oxazaborolidine derived from (S)-*α,α*-diphenylprolinol yielded Trans-ethoxylactams with 68 – 94 % *ee* (Scheme 1.31).[71]




**Scheme 1.31**

## 1.8 CONCLUSION

The literature survey of the oxazaborolidines reveals their importance in the area of asymmetric synthesis. The use of oxazaborolidines as asymmetric catalysts is becoming widespread. The catalyst precursors can be easily prepared and the reduction procedures are relatively simple. However, as evident from the above literature survey the oxazaborolidines derived from amino alcohols of naturally occurring and readily available (1R)-(+)-camphor have not been used extensively in the asymmetric reduction of ketones. In the light of these observations, a systematic study has been carried out on the asymmetric reduction of ketones using oxazaborolidines derived from camphor amino alcohols as catalysts. The results of these studies are presented in the following chapters.

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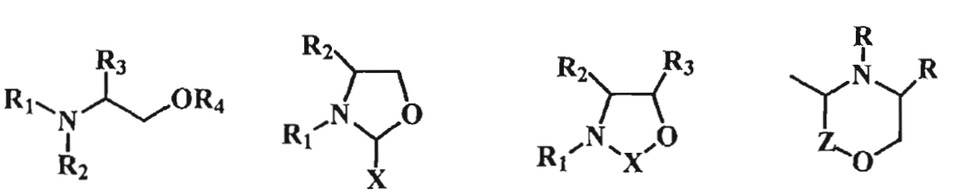
# CHAPTER 2

# SYNTHESIS OF AMINO ALCOHOLS AND AMINO ALCOHOL DERIVATIVES FROM (1R)-(+)-CAMPHOR

## 2.1 INTRODUCTION

The plethora of methods available for the preparation of 1,2-amino alcohols allows the chemistry of these compounds to be exploited for their use in asymmetric synthesis. The five membered rings formed by amino alcohols constitute a class of important chiral auxiliaries and chiral catalysts (Figure 2.1).[1]




1 2 3 4

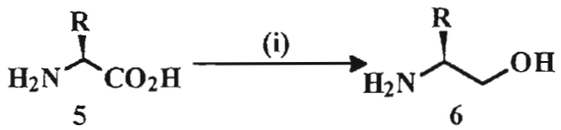
**Figure 2.1**

Both the cyclic and acyclic derivatives of 1,2-amino alcohols can act as ligands and catalysts. In both cases, the heteroatoms of amino alcohol will form complexes with the reaction centre.

A large number of natural products contain the 1,2-amino alcohol functionality. *e.g.* aminosugars, nucleosides, nucleotides etc. Many of these amino alcohol derivatives have chemotherapeutic properties.

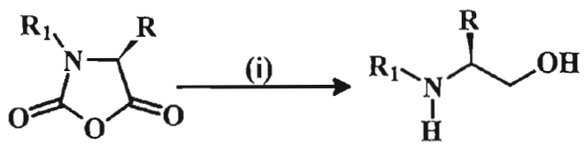
## 2.2 GENERAL METHODS OF PREPARATION OF 1,2-AMINO ALCOHOLS

1,2-amino alcohols can be prepared by the reduction of amino acids **5**, amino acid ester hydrochlorides, N-protected N-carboxy anhydrides **7**, iminoesters **9**, $\alpha$-amino carbonyl compounds **13** and oximes **15** with reducing agents such as lithium aluminium hydride[2] (LAH), sodium borohydride[3] ($NaBH_4$), sodium and alcohol[4] or diisobutyl aluminium hydride (DIBALH) (Scheme 2.1).[5]



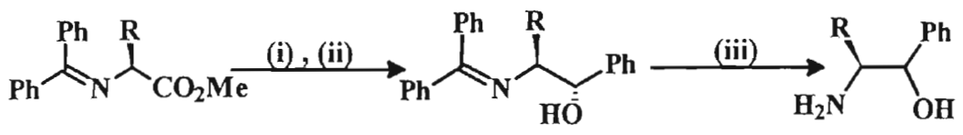

5 6

(i) $NaBH_4$, $H_2SO_4$, THF




7 8

(i) $NaBH_4$, $H_2O$, DME, R. T.

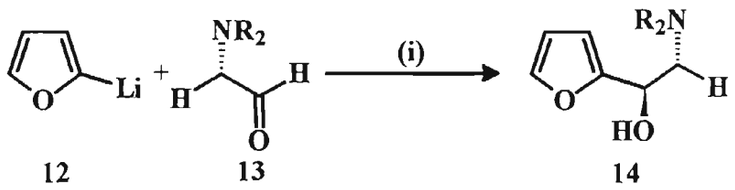



9 10 11

(i) DIBALH, PhMgBr, Ether

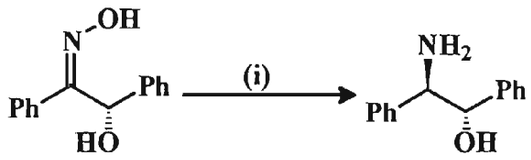
(ii) $NaHCO_3$, Ether

(iii) $H^+$, $H_2O$




12 13 14

(i) Ether, -78 °C R= Bn *ds* = 91: 9

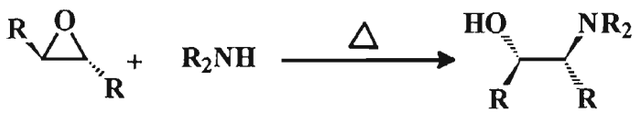



15 16

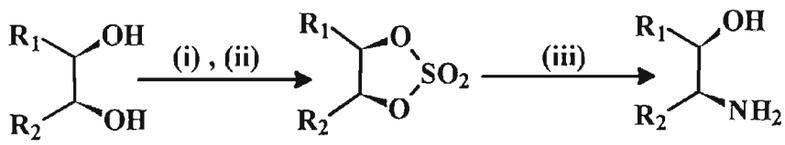
(i) $H_2$, Pd/C, MeOH

**Scheme 2.1**

Epoxides **17** and 1,2-cyclic sulphates **21** can be converted to 1,2-amino alcohols (Scheme 2.2).[6,7]




17 18 19




20 21 22

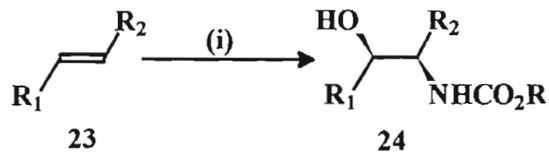
(i) $SOCl_2$, $CCl_4$

(ii) $NaIO_4$, $RuCl_3$, $H_2O$

(iii) $NaNH_2$, $H_3O^+$, Ether

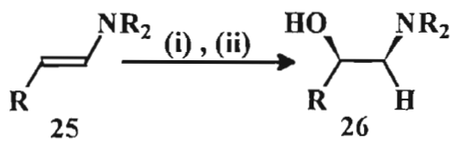
**Scheme 2.2**

They can also be prepared from alkenes by oxyamination or by the hydroboration of aldehyde enamines (Scheme 2.3).[8, 9]




23 24

(i) Cat. $OsO_4$, MeCN, $H_2O$




25 26

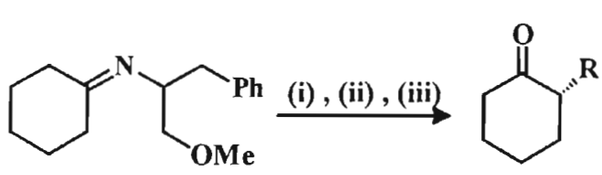
(i) $(IPC)_2BH$, THF, 0° C

(ii) $H_2O_2$, NaOH

**Scheme 2.3**

## 2.3 THE ROLE OF 1,2-AMINO ALCOHOLS IN ASYMMETRIC SYNTHESIS

Alkylation of cyclohexanone derivatives with very good selectivity has been achieved by the use of imine derivatives. The stereoselectivity achieved here can be attributed to chelation of the heteroatom with the lithium ion (Scheme 2.4).[10]




27 28

(i) LDA, Ether

(ii) RX, Ether, -78° C

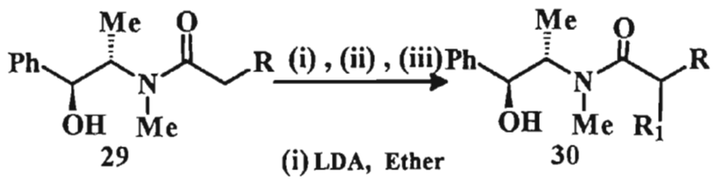
(iii) $H_3O^+$

R = nPr, *ee* = >95 %

R = Allyl, *ee* = >90 %

**Scheme 2.4**

Amide derivatives from pseudoephedrin **29** on alkylation followed by hydrolysis yielded carboxylic acids with very high selectivity (Scheme 2.5).[11]



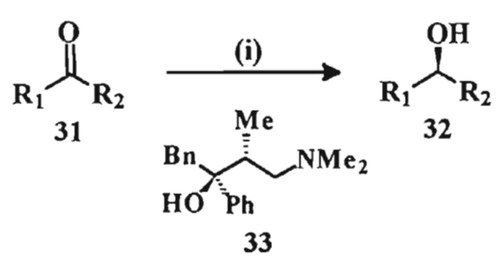

(i) LDA, Ether

(ii) $R_1X$, Ether, -78° C

(iii) $H_3O^+$

**Scheme 2.5**

Lithium aluminium hydride modified with amino alcohols was found to reduce aralkyl and propargylic ketones with good selectivity. *e.g.* Darvon alcohol **33** in combination with LAH was found to induce high level of stereospecificity (Scheme 2.6).[12]



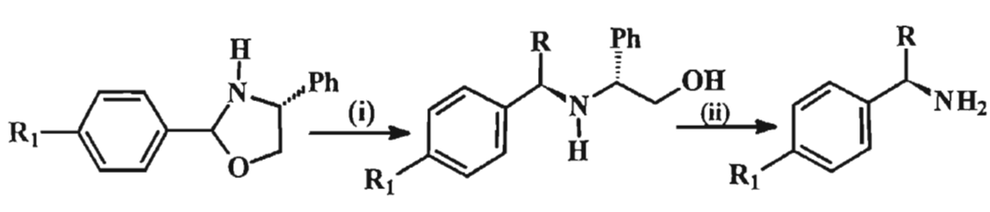

(i) 33, LAH, Ether, -78° C

$R_1$=Ph, $R_2$ =Me 75 % *ee*

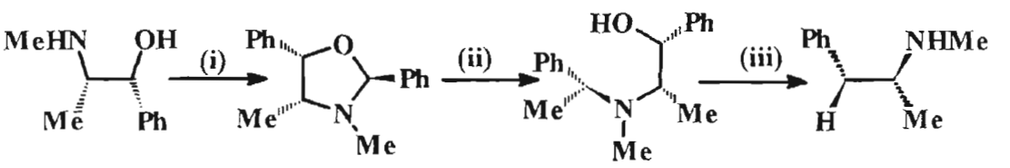
$R_1$ = Me, $R_2$ =Bu 91 % *ee*

**Scheme 2.6**

Oxazolidines **34**, a class of 1,2-amino alcohol derivatives have been used as reagents for nucleophilic addition, as acetal and imine equivalents (Scheme 2.7).[13]




(i) RMgX, Ether (ii) LTA, Ether *ds* = 96:4




37 38 39 40

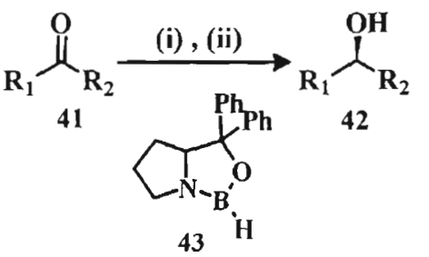
(i) PhCHO, Ether

(ii) MeMgI, Ether, R. T.

(iii) LTA, Ether

**Scheme 2.7**

Oxazaborolidines **43**, synthesized from 1,2-amino alcohols were employed as chiral catalysts for the asymmetric reduction of ketones, imines etc.(Scheme 2.8).[14]



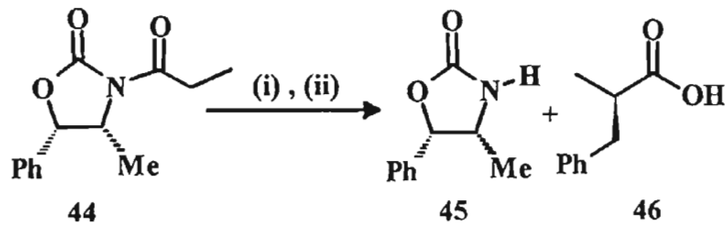

41 42 43

(i) 43, 10 mol %

(ii) $BH_3$. $Me_2S$ , THF $R_1 = Ph, R_2 = Me$; 94% *ee*
$R_1 = Et, R_2 = iPr$; 94% *ee*

**Scheme 2.8**

Oxazolidin-2-ones **44** and oxazolines **47** derived from 1,2-amino alcohols were reported as chiral auxiliaries for asymmetric alkylation aldol condensation and pericyclic reactions as illustrated in schemes 2.9 and 2.10.[15]



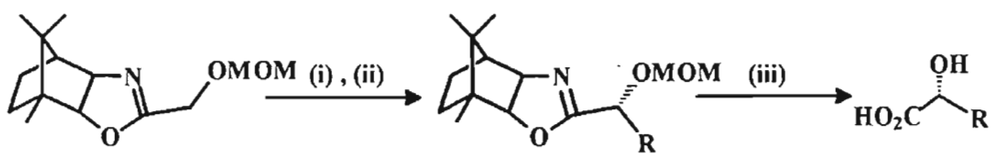

44 45 46

*de*≃ 100 %

(i) LDA, Ether, -78° C, $PhCH_2Br$

(ii) LiOOH, $Na_2SO_3$

**Scheme 2.9**



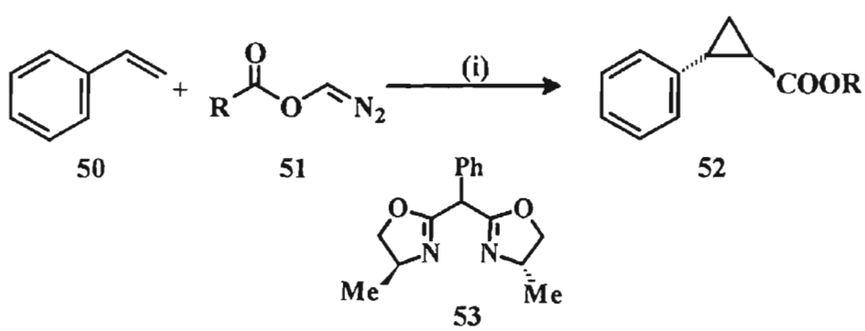

47 48 49

(i) BuLi, Ether, -78° C

(ii) RX, Ether, R. T(iii) $H_3O^{\oplus}$ 26-70 %, 77-92 % *ee*

**Scheme 2.10**

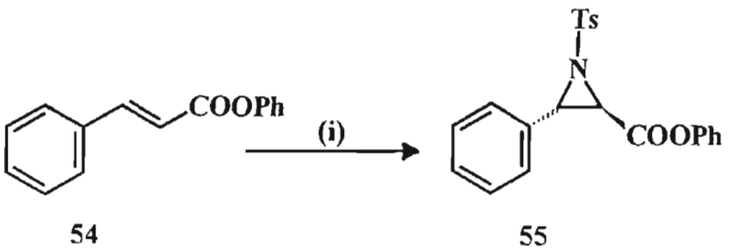
Bis(oxazolines) **53,** a class of compounds derived from 1,2-amino alcohols, were used as ligands for asymmetric cyclopropanation[16] and asymmetric aziridination[17] of olefins (Schemes 2.11 and 2.12).




50 51 52 53

(i) 53, CuX

**Scheme 2.11**

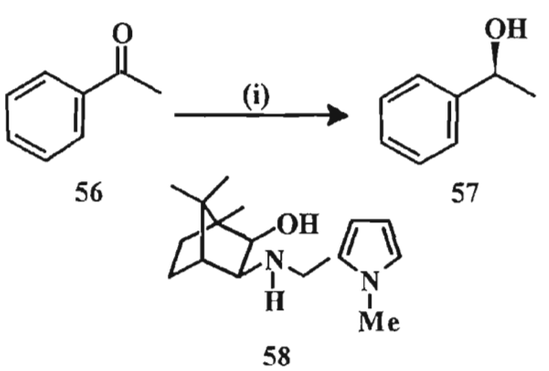



54 55

(i) 53, PhI=NTs, CuOTf

**Scheme 2.12**

The $\beta$-amino alcohols of camphor have been used extensively for the asymmetric addition of diethylzinc to aldehydes,[18, 20] asymmetric Diels-Alder reaction etc.[19] There was a report in the literature where 1,2-amino alcohols of (1R)-(+)-camphor were used as chiral auxiliaries in the asymmetric reduction of prochiral ketones.[21] In 1991, Tanaka reported the asymmetric borane reduction of ketones using heterocyclic derivatives of camphor derived amino alcohols like **58** as catalysts (Scheme 2.13).[22]




56 57

58

(i) 58, 0.25 mmol, $BH_3$.THF, 68 %, 73 % *ee*

**Scheme 2.13**

## 2.4 DEFINITION OF THE PROBLEM

Although various amino alcohols were used for the oxazaborolidine synthesis, the amino alcohols derived from (1R)-(+)-camphor have not been exploited well in this area. The study of natural products as chiral catalysts shows that the configuration of -OH bearing

carbon atom plays a crucial role in asymmetric induction. The different isomers of camphor amino alcohols such as *exo-exo, endo-endo* and *exo-endo* provide us the opportunity to study the effect of relative configuration of the amino group and hydroxyl group on the enantioselectivity of reactions. Also the structure of camphor, which is a rigid bicyclic system with a methylene bridge, influences the direction of approach of reactant molecules.

This chapter deals with the synthesis of various amino alcohols of (1R)-(+)-camphor and the derivatives of these amino alcohols.

## 2.5 RESULTS AND DISCUSSION

The eight possible amino alcohols of (1R)-(+)-camphor are shown in figure 2. 2.

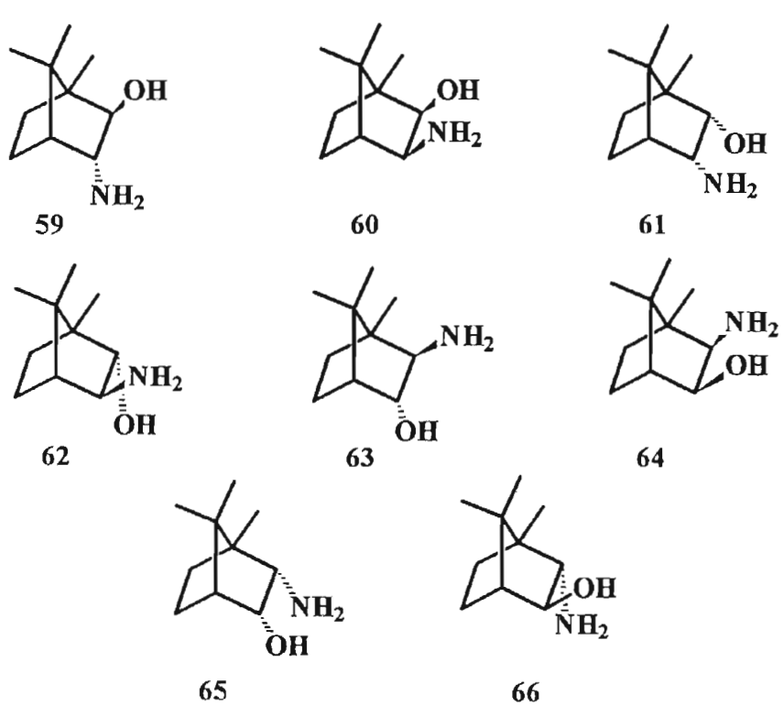



**Figure 2.2**

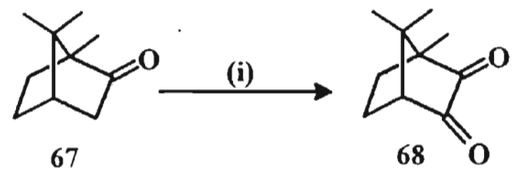
In the *exo-endo* isomer **59**, the -OH group is trans to the amino group, which is away from the methylene bridge. In **60** and **61** both

groups are of cis configuration. In **60,** both -$NH_2$ and -OH groups are on the same side of the bridge whereas, in **61** both groups are away from the bridge. In **62** which is a trans isomer, the amino group is cis to the methylene bridge. **63** is also a trans isomer here -$NH_2$ occupies the $2^{nd}$ position and is cis to the bridge. **64** and **65** are cis isomers. **66** is a trans isomer in which the $NH_2$ group is away from the bridge. The stereochemical outcome of reductions catalyzed by oxazaborolidines derived from these amino alcohols will give us an idea of the effect of orientation of the amino and hydroxyl groups in asymmetric induction.

Of the eight possible isomers shown in figure 2.2, the synthesis of **59** and **61** were known from 1900.[23] Later Daniel *et al.* [24] and Chittenden *et al.*[25] independently synthesized seven of them. The isomer **66** could not be synthesized. In the present study we have synthesized five amino alcohols **59, 60, 61, 62, 65** and their derivatives. Subsequently, oxazaborolidines were prepared from these isomers and asymmetric reduction of ketones were carried out using these as catalysts.

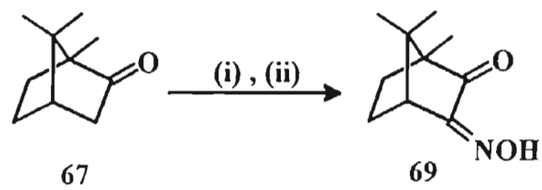
## 2.6 SYNTHESIS OF AMINO ALCOHOLS FROM (1R)-(+)-CAMPHOR

(1R)-(+)-Camphor **67** was first converted to camphor quinone (bornan-2,3-dione) **68** by $SeO_2$ oxidation.[26] Camphor **67** was converted to 3-hydroximinocamphor **69** by treating with sodium amide and isoamyl nitrite (Scheme 2.14).[27]




67 68

(i) $SeO_2$, AcOH, 120° C, 6h, 96 %




67 69

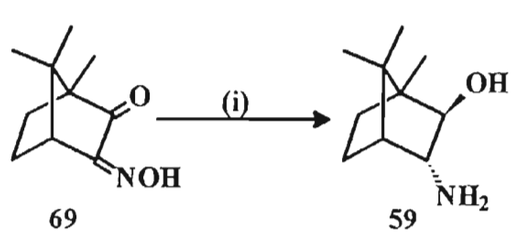
(i) $NaNH_2$, Ether, R. T., 4h

(ii) Isoamyl nitrite, 0° - 5° C, 74 %

**Scheme 2.14**

These two compounds were the intermediates and the reduction of the oxime and ketone functionalities is the key step in the synthesis of various amino alcohols of camphor.

The reduction of 3-hydroximinocamphor **69** with sodium and ethanol yielded the 3-*endo*-amino-2-*exo*-hydroxybornane **59** (Scheme 2.15).

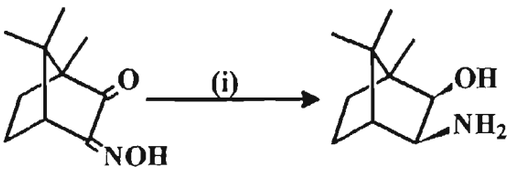



69 59

(i) Na / EtOH , R. T. & 78° C, 1.5 h, 66 %

**Scheme 2.15**

3-hydroximinocamphor **69** on reduction with LAH gave 3-*exo*-amino-2-*exo*-hydroxybornane **60** (Scheme 2.16).

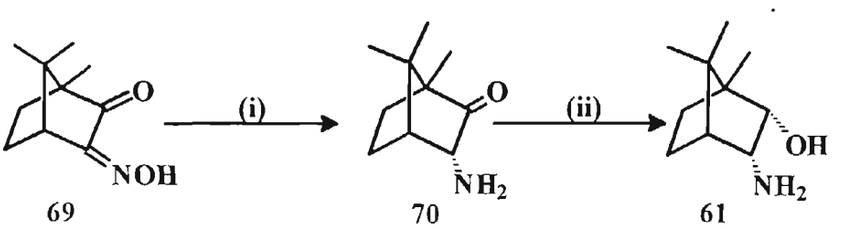



69 60

(i) LAH, Ether, R. T., 24 h, 55 %

**Scheme 2.16**

The 3-hydroximinocamphor **69** on reduction with zinc and sodium hydroxide yielded 3-*endo*-aminocamphor **70.** Reduction of this compound with LAH in ether afforded 3-*endo*-amino-2-*endo*-hydroxybornane **61** (Scheme 2.17).[28]

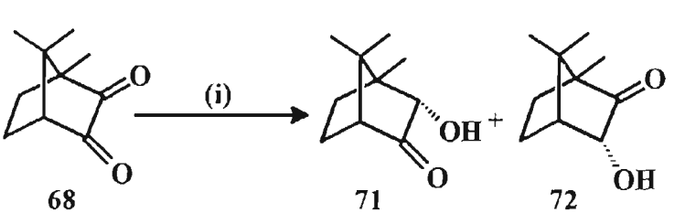



69 70 61

(i) Zn / NaOH, $H_2O$, R. T., 1. 5 h, 86 %
(ii) LAH, Ether, R. T., 12 h, 58 %

**Scheme 2.17**

The camphor quinone **68** on reduction with Zn / AcOH gave a mixture of hydroxybornanones **71** and **72** (Scheme 2.18).

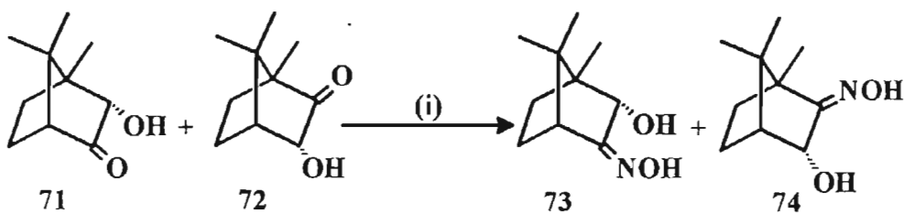



68 71 72

(i) Zn / AcOH, R. T., 1h, 81 %

**Scheme 2.18**

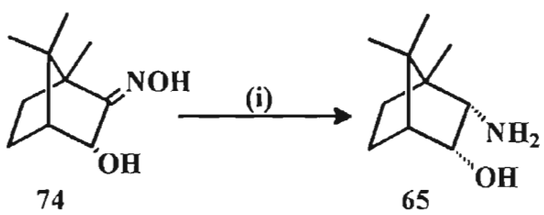
These were converted to hydroximino bornanols **73** and **74** (Scheme 2.19).




**(i) $NH_2OH.HCl$, $CH_3COONa$, MeOH, $H_2O$, 60° C, 2 h, 83 %**

**Scheme 2.19**

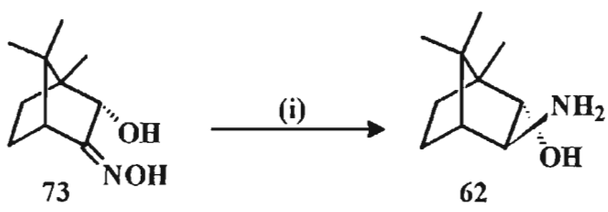
The hydroximinobornanol **74** on LAH reduction yielded 2-*endo*-amino-3-*endo*-hydroxybornane **65** (Scheme 2.20).




**(i) LAH, THF, 65° C, 12 h, 55 %**

**Scheme 2.20**

**73** on reduction with sodium and alcohol gave 3-*exo*-amino-2-*endo*- hydroxybornane **62** (Scheme 2.21).

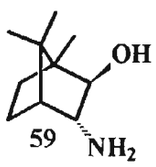
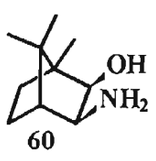
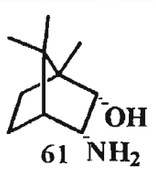
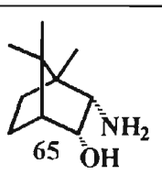
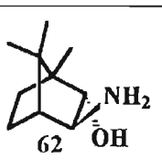



**(i) Na / EtOH, R. T. & 78 °C, 4 h, 45 %**

**Scheme 2.21**

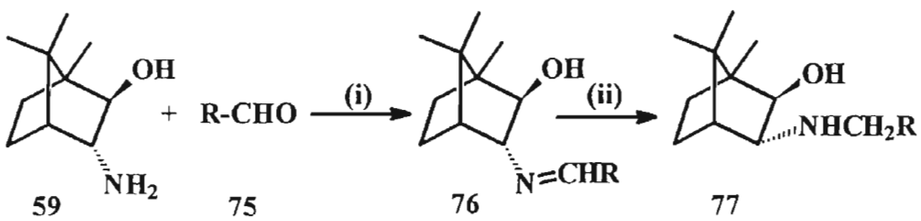
All the amino alcohols **59**, **60**, **61**, **65** and **62** are further purified by repeated crystallization so as to obtain constant specific rotation. The purity and specific rotation values of these compounds are presented in table 2.1.

**Table 2.1** Percentage purity and specific rotation values of amino alcohols

| Entry | Amino alcohol | Purity (%) | Purity after further crystallization ($^1$H NMR) (%) | $[\alpha]_D^\circ$ |
|---|---|---|---|---|
| 1 |  59 | **90** | **94** | **+32.017** |
| 2 |  60 | **95** | **97** | **+26.074** |
| 3 |  61 | **96** | **97** | **+36.915** |
| 4 |  65 | **95** | **97** | **+20.152** |
| 5 |  62 | **94** | **94** | **+27.448** |

## 2.7 SYNTHESIS OF DERIVATIVES OF AMINO ALCOHOLS

The *exo-endo* amino alcohol obtained was converted to benzylamino and naphthylmethylamino derivatives by treating with benzaldehyde and 1-naphthaldehyde in absolute ethanol respectively, followed by the *in situ* reduction of the imine formed (Scheme 2.22).




59 75 76 77

75a R = Ph
75b R = 1-Naphthyl

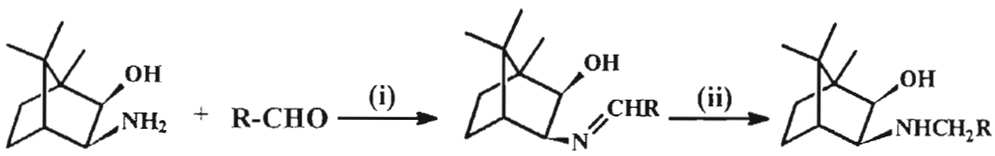
77a (63 %)
77b (65 %)

(i) Ethanol, R. T., 4 h

(ii) $NaBH_4$, Ethanol, 12 h

**Scheme 2.22**

The cis *exo-exo* amino alcohol was converted to the benzylamino and naphthylmethylamino derivatives by refluxing with benzaldehyde and 1-naphthaldehyde in benzene followed by the reduction of the imine with sodium borohydride in methanol (Scheme 2.23).




60 75 78 79

75a R = Ph
75b R = 1-Naphthyl

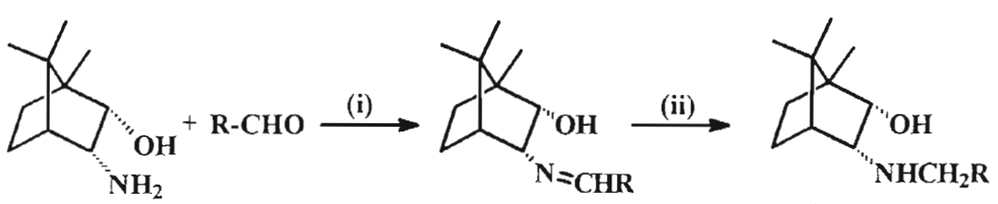
79a (60 %)
79b (56 %)

(i) Benzene, 80° C, 5 h

(ii) $NaBH_4$, Methanol, R. T., 12 h

**Scheme 2.23**

The cis *endo-endo* amino alcohol was also converted to the derivatives as shown in scheme 2.24.




61 75 80 81

75a R = Ph
75b R = 1-Naphthyl

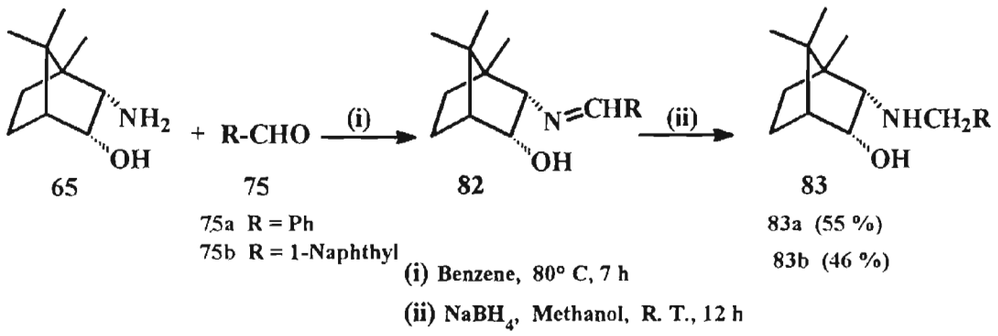
(i) Ethanol, R. T., 4 h

(ii) $NaBH_4$, Ethanol, 12 h

81a (65 %)
81b (60 %)

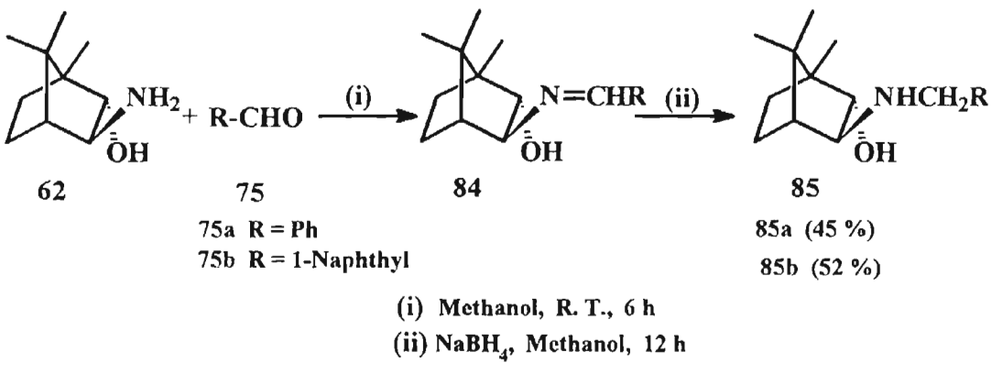
**Scheme 2.24**

The 2-*endo*-amino-3-*endo*-hydroxybornane was converted to the derivatives by refluxing benzaldehyde or 1-naphthaldehyde in benzene followed by sodium borohydride reduction in methanol (Scheme 2.25).




**Scheme 2.25**

The 3-*exo*-amino-2-*endo*-hydroxybornane was converted to the benzylamino and naphthylmethylamino derivatives by treating with benzaldehyde or 1-naphthaldehyde in methanol at room temperature followed by the *in situ* reduction of the imine **84** (Scheme 2.26).




**Scheme 2.26**

The spectroscopic and analytical data obtained for these amino alcohols were in good agreement with the literature data.[24, 25] The structures of the derivatives were confirmed on the basis of IR, $^{1}H$ and $^{13}C$ NMR data. For example, the spectral identification of the two derivatives, 3-*exo*-benzylamino-2-*exo*-hydroxybornane (79a) and 3-*exo*-naphthylmethylamino-2-*exo*-hydroxybornane (79b) is discussed below in detail.

**3-*exo*-benzylamino-2-*exo*-hydroxybornane (79a)**

The IR spectrum of *exo-exo* benzylamino derivative showed a broad peak around 3339 $cm^{-1}$ for the -NH and -OH stretching vibrations. There was a band around 1610 $cm^{-1}$ corresponding to the -NH bending vibration. The -CH stretching vibration band at 3029 $cm^{-1}$ shows the presence of aromatic group in the molecule. There was an absorption at 1398 - 1390 $cm^{-1}$ corresponds to -CH bending vibration of the gem dimethyl groups in bornane skelton confirming the proposed structure.

In the $^{1}H$ NMR spectrum, the aromatic protons resonated at δ 7.3 as a multiplet. The benzylic protons appeared as a singlet at δ 3.7. The proton adjacent to the -OH group and the proton adjacent to the amino group appeared as doublets at δ 3.41 and at δ 2.8 with a J value of 7.2 respectively. The methyl groups of camphor resonated at δ 1.0, 0.94, 0.77 in the $^{1}H$ NMR (Figure 2.3).

In the $^{13}C$ NMR spectrum, the aromatic carbons appeared at δ 139.94 - 127.23. The carbon bearing hydroxyl group resonated at δ 78.75 and the carbon attached to the amino group was visible at δ 65.70. The benzylic carbon appeared at δ 54.80. The alicyclic carbons of camphor were seen within δ 51.57 - 11.35 range (Figure 2.4).

The mass spectrum of **79a** showed a peak at m/z 259 corresponding to the molecular ($M^{+}$) ion further confirming the assigned structure. The structure was supported by satisfactory elemental data. The other benzylamino derivatives were identified similarly.

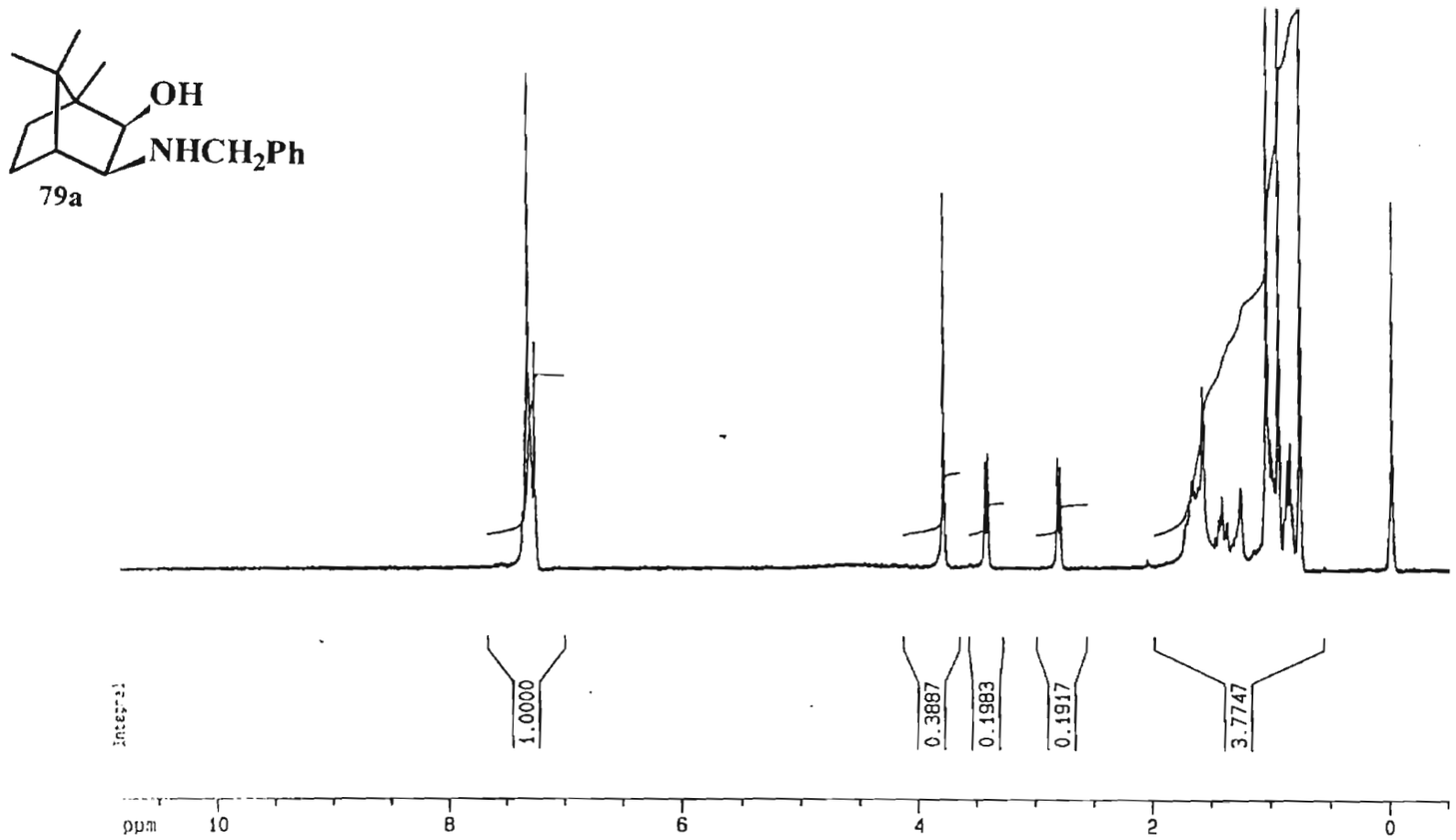



Figure 2.3 300 MHz $^{1}$H NMR spectrum of 3-*exo*-benzylamino-2-*exo*-hydroxybornane

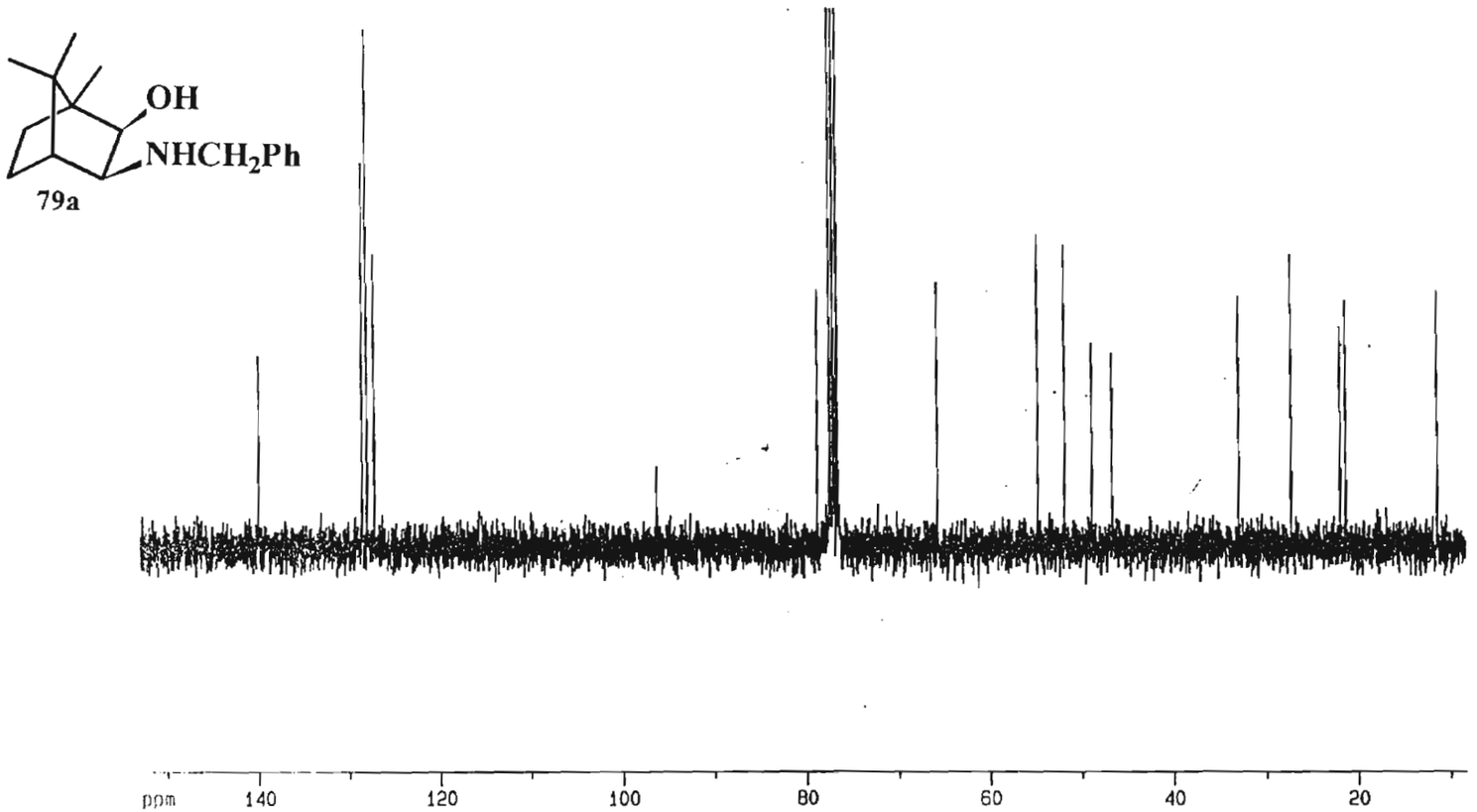



Figure 2.4 75 MHz $^{13}C$ NMR spectrum of 3-*exo*-benzylamino-2-*exo*-hydroxybornane

**3-*exo*-naphthylmethylamino-2-*exo*-hydroxybornane (79b)**

The IR spectrum of the *exo-exo* naphthylmethylamino compound showed a broad peak around 3333 $cm^{-1}$ for the -OH and -NH stretching vibrations. The band due to the aromatic group was observed at 3030 $cm^{-1}$. The -NH bending vibration appeared as a sharp band at 1607 $cm^{-1}$.

In the $^{1}H$ NMR spectrum, the aromatic protons resonated at δ 7.49 - 7.39. The $-CH_2$ of the naphthylmethyl group was appeared as singlet at δ 4.23. The protons adjacent to the hydroxyl and amino groups appeared as doublets at δ 3.47 and δ 2.93 with a J value of 7.2 respectively. The methyl groups of camphor appeared within δ 1.0 - 0.75 (Figure 2.5).

In the $^{13}C$ NMR, the aromatic carbons were observed at δ 134.95 - 123.14. The carbon atoms attached to the hydroxyl and amino groups resonated at δ 78.81 and 66.17 respectively. The carbon of the naphthylmethyl group appeared at δ 52.35. The alicyclic carbons of camphor moiety appeared within δ 51.56 - 11.29 range (Figure 2.6). The DEPT-135 showed three $-CH_2$ groups, which further confirmed the structure.

The structure was further confirmed by the mass spectrum, which showed the [M+1] peak at 310, and also by the satisfactory elemental analysis data. The other naphthylmethylamino derivatives were also identified similarly.

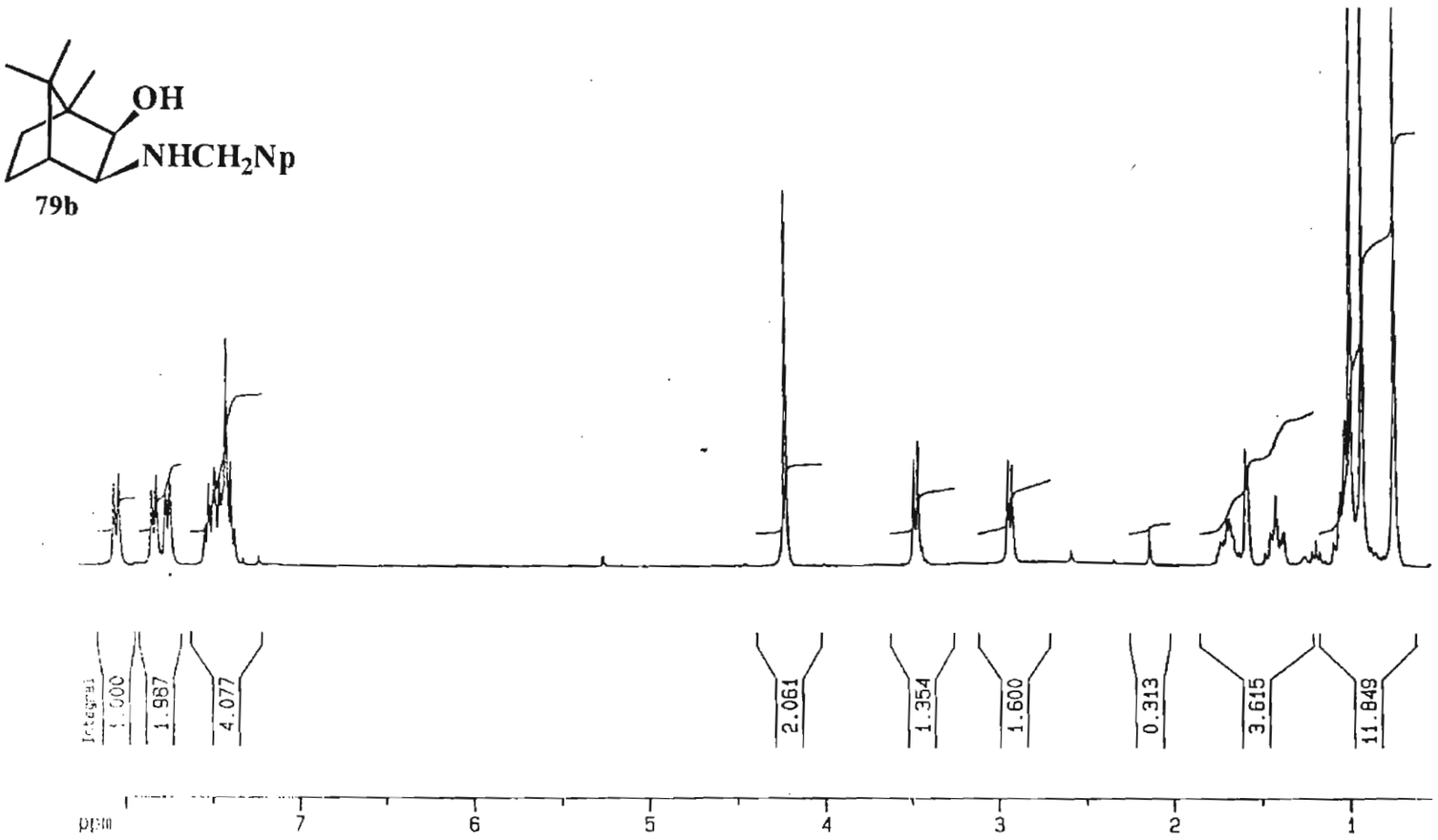



Figure 2.5 300 MHz $^{1}$H NMR spectrum of 3-*exo*-naphthylmethylamino-2-*exo*-hydroxybornane

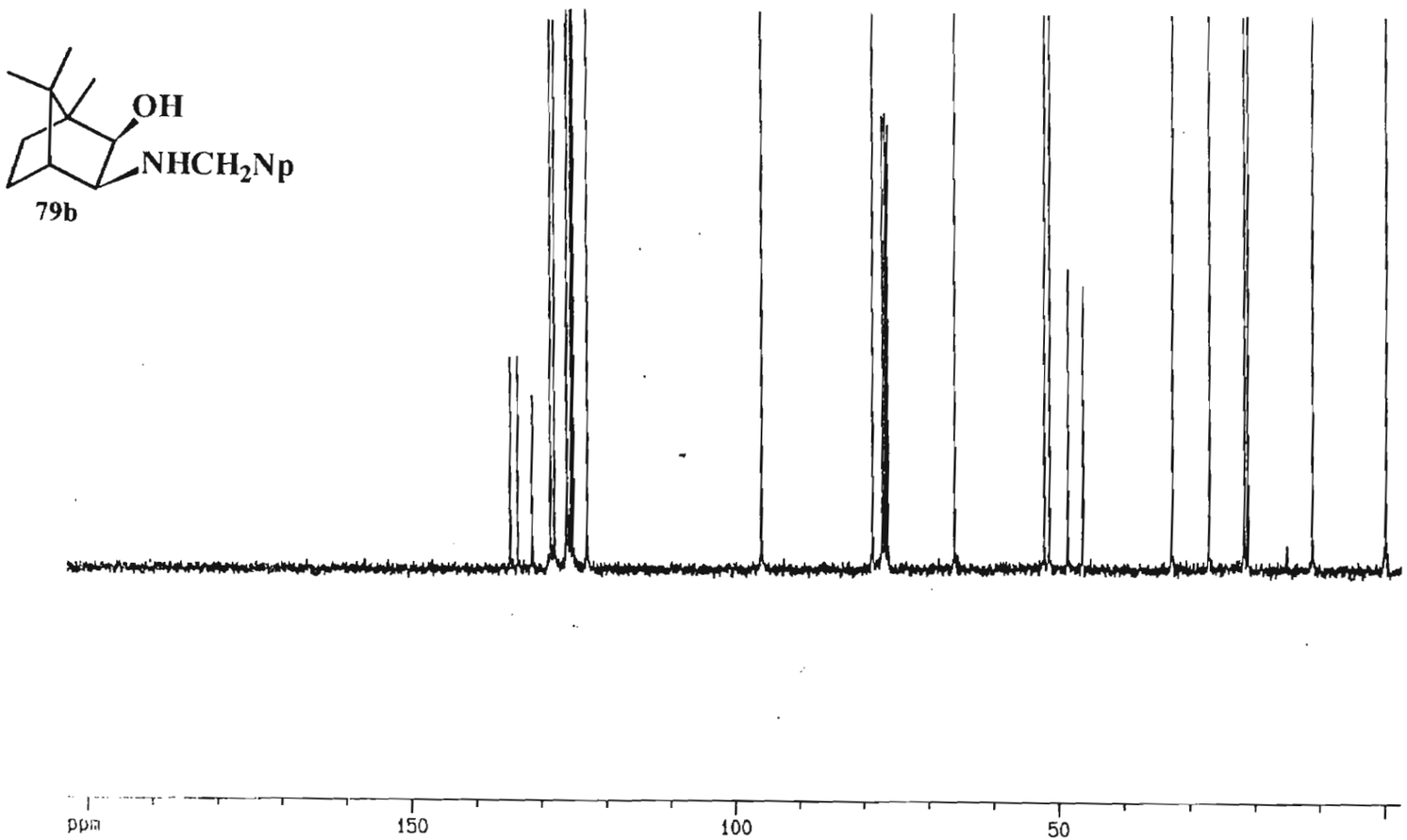
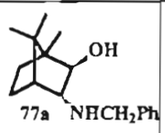
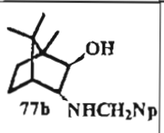
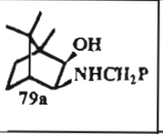
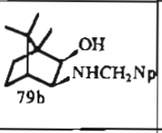
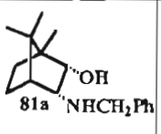
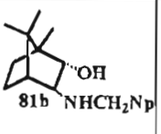
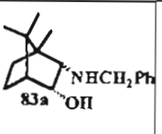
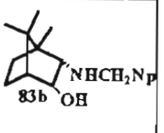
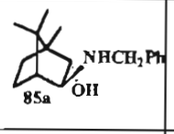
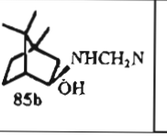



Figure 2.6 75 MHz $^{13}C$ NMR spectrum of 3-*exo*- naphthylmethylamino - 2-*exo*-hydroxybornane

**Table 2.2** Percentage purity and specific rotation values of the amino alcohol derivatives.

| Entry | Structure | Purity(%) | Purity (%) after crystallisation ($^1$HNMR) | $[\alpha]_D°$ |
|---|---|---|---|---|
| 1 |  77a | 97 | 97 | +30.613 |
| 2 |  77b | 95 | 98 | +36.994 |
| 3 |  79a | 98 | >99 | +26.220 |
| 4 |  79b | 97 | >99 | +25.814 |
| 5 |  81a | 97 | >99 | +28.741 |
| 6 |  81b | 95 | >99 | +22.749 |
| 7 |  83a | 95 | 95 | -14.292 |
| 8 |  83b | 93 | 93 | +13.250 |
| 9 |  85a | 94 | 95 | -19.858 |
| 10 |  85b | 95 | 95 | +28.995 |

All the solid amino alcohol derivatives were further purified by *repeated crystallization* so as to obtain constant specific rotation. The purity and $[\alpha]_D$ values of all derivatives are given above in table 2.2

## 2.8 EXPERIMENTAL DETAILS

Melting points were recorded on Toshniwal and Büchi melting point apparatus and are uncorrected. The infrared spectra were recorded on Nicolet Impact 400D and Bomem MB Series FT-IR spectrophotometers. The NMR spectra were recorded on Jeol EX-90, Bruker 300 MHz spectrometers. The NMR spectra were recorded at 300 ($^1$H) and 75 ($^{13}$C) MHz with $CDCl_3$ as the solvent unless otherwise mentioned. Chemical shifts are reported (δ) relative to TMS ($^1$H) and $CDCl_3$ ($^{13}$C) as the internal standards. For NMR spectra unless otherwise mentioned measurements were made at 300 MHz ($^1$H NMR) and 75 MHz ($^{13}$C NMR) spectra. The mass spectra were recorded on a HewLett Packard Series II mass spectrometer. Elemental analysis was carried out using Perkin-Elmer elemental analyser. Optical rotations were measured using Jasco DIP-370 digital polarimeter at ambient temperature (24 – 27 °C) using chloroform as the solvent. Solvents were removed under vacuum using Büchi rotary evaporator.

Analytical thin layer chromatography was performed on glass plates coated with silica gel containing 13 % calcium sulphate as binder. The spots were developed in an iodine chamber. Gravity column chromatography was performed using silica gel (100 - 200 mesh) and neutral $Al_2O_3$. All reactions were monitored by TLC employing appropriate solvent systems for development. Moisture sensitive reactions were carried out by syringe and septum technique and were conducted under argon atmosphere. Solvents were distilled and dried prior to use

according to the literature procedure.[29] (1R)-(+)-camphor with specific rotation $[\alpha]_D$ 43.5° (c=10, EtOH) was purchased from Fluka.

**3-Hydroximinocamphor (69)**[27]

(1R)-(+)-Camphor **67** (10 g, 65.7 mmol) was dissolved in dry ether (50 mL), sodium amide (4 g, 98.5 mmol) was added and stirred for two hours at room temperature. Then the reaction mixture was cooled to 0° C and cold isoamyl nitrite[30] (9 mL, 78 mmol) was added dropwise. The temperature was maintained 0 - 5° C during the addition. The reaction mixture was allowed to attain room temperature and was stirred overnight. Excess $NaNH_2$ present in the reaction mixture was destroyed by adding cold water. The ether layer was washed with water and the aqueous layers were pooled together. The aqueous layer was acidified to pH 4 with acetic acid, extracted with dichloromethane (3 x 20 mL), organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and solvent was removed to get the crude product. This was then chromatographed on a silica gel column with a mixture of ethylacetate and hexane (5 %) as eluent to afford 3-hydroximinocamphor **69** as a pale yellow solid (8.8 g, 74 %). It was then recrystallized from dichloromethane - hexane mixture as white crystals.

m. p. : 152 - 154° C

IR (KBr) $\nu_{max}$ : 3140, 2969, 2928, 2881, 1748, 1640, 1398, 1378, 1007, 939, 730 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 9.2 (brs, 1H), 3.21 (m, 1H), 1.79 (m, 4H) 1.02 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H).

**3-*endo*-amino-2-*exo*-hydroxybornane (59)**[25]

Sodium was added to 3-hydroximinocamphor **69** (1 g, 5.52 mmol) dissolved in super dry ethanol, till the solution becomes saturated. The reaction mixture was then refluxed for 1 h. The excess ethanol was removed, diluted with water and extracted with dichloromethane (3 x 20 mL). The organic layers were pooled together, washed with water till the washings were neutral to litmus. The organic extracts were washed with brine, dried over $Na_2SO_4$ and solvent was removed to get the crude product. This was then purified on a column of neutral alumina using a mixture of methanol - chloroform (10 %) as eluent to get the amino alcohol **59** as a white solid (0.62 g, 66 %). This was then recrystallized from pentane.

m. p. : 192 - 194°C

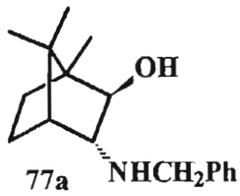
IR (KBr) $\nu_{max}$ : 3353, 2928, 2861, 1647, 1458, 1384, 1081, 1007, 890 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 3.4 (brs, 1H), 3.05 (d, 1H, $J$ = 9 Hz), 2.45 (brs, 2H), 1.65 (m, 6H), 1.1 (s, 3H) 0.8 (s, 6H).

**3-*endo*-benzylamino-2-*exo*-hydroxybornane (77a)**

3-*endo*-amino-2-*exo*-hydroxybornane **59** (0.5 g, 2.95 mmol) was dissolved in 10 mL absolute ethanol. Benzaldehyde **75a** (0.344 g, 3.25 mmol) was then added to this and the reaction mixture was stirred for 4 h. Molecular sieves (4 Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.235 g, 6.22 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the

crude product. This was purified on a column of silica using ethylacetate - hexane (5 %) as eluent to give a viscous liquid (0.482 g, 63 %).




**77a**

$[\alpha]_D^{25}$ : (c=0.668, $CHCl_3$) = +30.613°

IR ($CCl_4$) $\nu_{max}$ : 3417, 3311, 3013, 2956, 2868, 1657, 1451, 1364, 1076, 739, 689 $cm^{-1}$.

$^1H$ NMR (δ) : 7.155 (m, 5H), 3.975 (brs, 2H), 3.54 (q, 2H, *J* = 12.78 Hz), 3.16 (s, 1H), 3.00 (s, 1H), 1.255 (m, 5H), 0.96 (s, 3H), 0.75 (s, 3H) 0.72 (s, 3H).

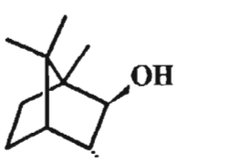
$^{13}C$ NMR (δ) : 139.26, 128.26, 128.12, 126.85, 85.13, 67.67, 60.01, 51.80, 49.03, 47.02, 34.46, 20.89, 19.50, 18.35, 11.35.

MS (m/z) (%) : 260 $(M+1)^+$ (2), 259 (2), 244 (4), 230 (6), 174 (25), 146 (4), 120 (8), 106 (12), 95 (12), 91 (100), 77 (5), 65 (15), 43 (10), 41 (12), 30 (8), 18 (3).

**3-*endo*-naphthylmethylamino-2-*exo*-hydroxybornane (77b)**

3-*endo*-amino-2-*exo*-hydroxybornane **59** (0.300 g, 1.78 mmol) was dissolved in 8 mL absolute ethanol. 1-Naphthaldehyde **75b** (0.306 g, 1.96 mmol) was added to this and the reaction mixture was stirred for 4 h. Molecular sieves (4 Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.148 g, 3.9 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h. and then the excess $NaBH_4$ was quenched by adding cold water. This was then

dichloromethane (3 x 10mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica using ethylacetate - hexane (8 %) as eluent to give a pale yellow solid (0.356 g, 65 %). This was recrystallized from dichloromethane - hexane solvent system as pale yellow crystals.




**77b**

$[\alpha]_D^{25}$ : (c=0.790, $CHCl_3$) = +36.994°

m.p. : 215 - 217 °C

IR (KBr) $\nu_{max}$ : 3442, 3321, 3046, 2932, 2885, 1602 1467, 1373, 1071 1004, 776 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 7.6 (m, 7H). 4.25 (q, 2H, J = 13.89 Hz), 3.7 (s, 1H), 3.5 (s, 1H), 1.385 (m, 7H), 0.90 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H).

$^{13}C$ NMR ($\delta$) : 133.7, 131.2, 130.4, 129.7, 128.9, 127.4, 126.4, 126.0, 125.3, 123.1, 116.8, 80.4, 69.6, 49.2, 48.1, 46.5, 46.0, 34.4, 20.4, 19.7, 19.6, 11.2.

MS (m/z) : 310 $(M+1)^+$ (3), 309 (6), 294 (4), 281 (7), 280 (7), 239 (25), 238 (25), 225 (8), 224 (5), 168 (50), 142 (12), 141(100), 109 (2), 95 (2), 91(2), 53 (10), 43 (10), 41(20).

**3-exo-amino-2-exo-hydroxybornane (60)**[24]

3-hydroximinocamphor **69** (1 g, 5.52 mmol) in 30 mL dry diethyl ether was added dropwise to a suspension of LAH (0.3 g, 8.28 mmol) in 30 mL dry ether, and stirred for 12 h. Then the unreacted LAH was

destroyed by the dropwise addition of 10 % NaOH solution (5 mL), followed by few drops of cold water. The ether layer was decanted and the residue was washed several times with ether. The organic layers were combined, washed with water, brine, dried over $Na_2SO_4$ and concentrated. The crude product obtained was recrystallized from dichloromethane - hexane solvent system (0.512 g, 55 %)

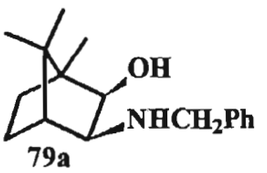
m. p. : 195 - 197 °C

IR (KBr) $\nu_{max}$ : 3361, 3308, 2952, 2865, 1636, 1566, 1455, 1374, 1334, 1066, 1025, 951, 830, 730, 642 $cm^{-1}$.

$^1H$ NMR (90 MHz) ($\delta$) : 5.35 (brs, 3H), 4.2 (s, 1H), 2 (m, 6H), 1.4 (s, 3H), 0.98 (s, 3H), 1.2 (s, 3H).

**3-*exo*-benzylamino-2-*exo*-hydroxybornane (79a)**

3-*exo*-amino-2-*exo*-hydroxybornane **60** (0.338 g, 2 mmol) was dissolved in 10 mL dry benzene. Benzaldehyde (0.233 g, 2.2 mmol) was added to this and the reaction mixture was refluxed for 5 h using a Dean-Stark apparatus. The imine formed was reduced with sodium borohydride (0.220 g, 5.84 mmol) after removing benzene and adding methanol. The temperature of the reaction mixture was kept at 0° C during the $NaBH_4$ addition. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica gel using ethylacetate - hexane (10 %) as eluent to give a white solid (0.310 g, 60 %). This was recrystallized from dichloromethane - hexane solvent system.



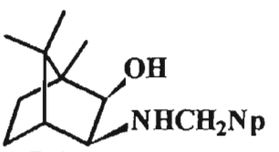

**79a**

| | |
|---|---|
| $[\alpha]_D^{25}$ | : (c=0.856, $CHCl_3$) = +26.220° |
| m. p. | : 77 - 79 °C |
| IR (KBr) $\nu_{max}$ | : 3339, 3029, 2962, 2888, 1637, 1485, 1458, 1398, 1378, 1290, 1101, 751, 710 $cm^{-1}$. |
| $^1H$ NMR (δ) | : 7.3 (m, 5H). 3.79 (s, 2H), 3.415 (d, 1H, *J* = 7.2 Hz), 2.85 (d, 1H, *J* = 7.2 Hz), 1.465 (m, 7H), 0.9 (s, 3H), 1.04 (s, 3H), 0.76 (s, 3H). |
| $^{13}C$ NMR (δ) | : 139.9, 128.5, 128.0, 127.2, 78.7, 65.7, 54.8, 51.8, 48.8, 46.6, 32.9, 27.2, 21.9, 21.3, 11.3. |
| MS (m/z) (%) | : 259 $(M+)^+$ (5), 256 (5), 244 (15), 243 (12), 231 (15), 230 (8), 214 (8), 188 (8), 175 (3), 174 (10), 168 (5), 161 (5), 146 (8), 144 (8), 133 (8), 120 (5), 108 (8), 106 (10), 104 (2), 95 (16), 91 (100), 79 (6), 77 (10), 71 (4), 67 (9), 65 (20), 56 (5), 55 (10), 53 (5), 43 (15). |
| Analysis | : $C_{17}H_{25}NO$ |
| Calcd (%) | : C, 78.53; H, 9.71; N, 5.38. |
| Found (%) | : C, 78.53; H, 9.61; N, 5.38. |

**3-*exo*-naphthylmethylamino-2-*exo*-hydroxybornane (79b)**

3-*exo*-amino-2-*exo*-hydroxybornane **59** (0.338 g, 2 mmol) was dissolved in 10 mL dry benzene. 1-Naphthaldehyde (0.343 g, 2.2 mmol) was added to this and the reaction mixture was refluxed for 5 h using a Dean-Stark apparatus. The imine formed was reduced with sodium borohydride (0.246 g 6.5 mmol) after removing benzene, adding

methanol and cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 hours and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica gel using ethylacetate - hexane (10 %) as eluent to give a light yellow solid (0.345 g, 56 %). This was recrystallized from dichloromethane - hexane solvent system as pale yellow crystals.




**79b**

| | |
|---|---|
| $[\alpha]_D^{25}$ | : (c=1.008, $CHCl_3$) = +25.814° |
| m. p. | : 63 - 65 ° C |
| IR (KBr) $\nu_{max}$ | : 3333, 3043, 2962, 2921, 2888, 1607, 1452, 1411, 1297, 1115, 791$cm^{-1}$. |
| $^1$H NMR (δ) | : 7.44 (m, 7H), 4.2 (s, 2H), 3.475 (d, 1H, *J* = 7.23 Hz), 2.93 (d, 1H, *J* = 7.26 Hz) 1.5 (m, 7H), 1.00 (s, 3H), 0.9 (s, 3H), 0.75 (s, 3H). |
| $^{13}$C NMR. (δ) | : 134.9, 128.7, 126.1, 125.6, 125.6, 125.2, 123.1, 78.8, 66.1, 52.3, 51.5, 48.8, 46.5, 32.8, 27.1, 21.8, 21.3, 11.2. |
| Analysis | : $C_{21}H_{27}NO$ |
| Calcd (%) | : C, 81.51; H, 8.79; N, 4.53. |
| Found (%) | : C, 81.44; H, 8.79; N, 4.53. |

**3-*endo*-aminocamphor (70)**[28]

3-hydroximinocamphor **69** (1 g, 5.52 mmol) was dissolved in 30 % NaOH solution (10 mL). Zinc dust (0.72 g, 11.04 mmol) was added slowly to the reaction mixture. The reaction mixture was allowed to stir for 30 min. When the reaction was completed as noted by TLC, the reaction mixture was extracted with dichloromethane (3 x 10 mL). The organic layers were pooled together, washed with water, brine dried over $Na_2SO_4$ and concentrated to get a pale yellow oil (0.89 g, 86 %). This being unstable, was used immediately for the synthesis of **61**

**3-*endo* -amino-2-*endo*-hydroxybornane (61)**

A solution 3-*endo*-aminocamphor **70** (0.85 g, 5.09 mmol) in 20 mL dry ether was added dropwise to a suspension of LAH (0.39 g, 10.2 mmol) in 20 mL ether and stirred for 12 h at room temperature. The excess LAH was destroyed by the dropwise addition of 10 % NaOH solution (5 mL). The ether layer was decanted and the residue was washed several times with ether. The organic layers were collected, washed with water, brine, dried over $Na_2SO_4$ and concentrated. The crude product obtained was purified on a neutral alumina column using methanol - chloroform (5 %) as eluent. This was then recrystallized from dichloromethane - hexane (0.50 g, 58 %)

m. p. : 193 - 194 °C

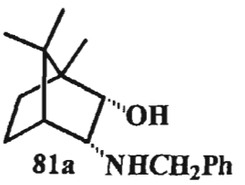
IR (KBr) $\nu_{max}$ : 3373, 3151, 2955, 1580, 1472, 1398, 1378, 1067, 1020, 933, 838 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 3.55 (m, 2H), 2.2 (brs, 3H), 1.01 (m, 5H), 0.94 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H).

**3-*endo*-benzylamino-2-*endo*-hydroxybornane (81a)**[31]

3-*endo*-amino-2-*endo*-hydroxybornane **61** (0.507 g, 3 mmol) was dissolved in 15 mL dry ethanol. Benzaldehyde (0.35 g, 3.3 mmol) was

added to this and the reaction mixture was stirred for 4 h at room temperature. Molecular sieves (4Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.388 g, 4.47 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a silica column using ethylacetate - hexane (5 %) as eluent to give a white solid (0.508 g, 65 %). This was recrystallized from dichloromethane - hexane solvent system.

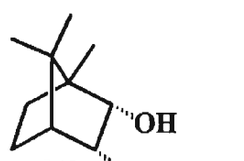



**81a**

| | |
|---|---|
| $[\alpha]_D^{25}$ | : (c=0.44, $CHCl_3$) = +28.741° |
| m. p. | : 58 - 60 °C |
| IR (KBr) $\nu_{max}$ | : 3333, 3023, 2948, 1609, 1458, 1398, 1391, 1101, 1067, 757, 751 $cm^{-1}$. |
| $^1H$ NMR ($\delta$) | : 7.3 (m, 5H), 3.715 (d, 2H, $J$ = 3.4 Hz), 3.665 (m, 1H), 3.195 (m, 1H), 1.77 (brs, 2H), 1.5 (m, 5H), 0.89 (s, 6H), 0.86 (s, 3H). |
| $^{13}C$ NMR ($\delta$) | : 139.7, 128.5, 128.1, 127.2, 126.9, 72.7, 65.1, 56.5, 53.3, 49.6, 45.3, 25.4, 20.0, 18.9, 18.3, 14.4. |
| MS (m/z) | : 259 $(M+)^+$ (10), 244 (6), 230 (25), 174 (40), 146 (10), 120 (10), 106 (9), 95 (9), 91 (100), 77 (6), 65 (20), 43 (12), 41 (25). |

**3-*endo*-naphthylmethylamino-2-*endo*-hydroxybornane (81b)**

3-*endo*-amino-2-*endo*-hydroxybornane **61** (0.338 g, 2 mmol) was dissolved in 10 mL absolute ethanol. 1-Naphthaldehyde (0.343 g, 2.2 mmol) was added to this and the reaction mixture was stirred for 4 h. Molecular sieves (4Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.246 g, 6.5 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica using ethylacetate - hexane (10 %) as eluent to give a pale yellow solid (0.37 g, 60 %). This was recrystallized from dichloromethane - hexane solvent system.




**81b**

$[\alpha]_D^{25}$ : (c=0.963, $CHCl_3$) = +22.749°

m. p. : 88 - 90 ° C

IR (KBr) $\nu_{max}$ : 3330, 3057, 2942, 2920, 2877, 1602, 1516, 1478, 1408, 1084, 1005 $cm^{-1}$.

$^1H$ NMR (δ) : 7.61 (m, 7H), 4.1 (s, 2H), 3.7 (d, 1H, $J$ = 8.9 Hz), 3.2 (m, 1H), 1.7 (brs, 1H), 1.45 (m, 6H), 0.89 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H).

$^{13}C$ NMR (δ) : 136.3, 133.7, 128.6, 125.8, 125.3, 123.6, 72.8, 63.4, 57.2, 50.3, 49.6, 45.4, 25.4, 19.9, 19.0, 18.3, 14.3.

Analysis : $C_{21}H_{27}NO$

Calcd (%) : C, 81.51; H, 8.79; N, 4.53.

Found (%) : C, 81.30; H, 8.75; N, 4.54.

**Camphor quinone (68)**[26]

(1R)-(+)-Camphor **67** (10 g, 65.8 mmol) was dissolved in 40 mL glacial AcOH. To this $SeO_2$ (10.9 g, 98.7 mmol) was added and refluxed for 6 h, monitoring the reaction by TLC. When the reaction was over, the reaction mixture was cooled to room temperature and was made alkaline with sodium bicarbonate solution. This was then filtered and the residue was washed several times with dichloromethane (6 x 20 mL). The organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get camphor quinone as an yellow solid (9.8 g, 96 %). This was then recrystallized from dichloromethane - hexane solvent system.

m. p. : 198 - 200 °C

IR (KBr) $\nu_{max}$ : 2975, 2935, 2888, 1782, 1748, 1492, 1458, 1404, 1378, 1207, 1202, 1169, 1108, 1054, 1000, 973, 906, 826, 744, 690, 629 $cm^{-1}$.

**Hydroxybornanones (71 & 72)**[24]

Camphor quinone **68** (10 g, 60.24 mmol) was dissolved in 50 mL acetic acid and 30 mL water was added. This is stirred well and zinc dust (7.8 g, 120.48 mmol) was added to this in small portions. The reaction was monitored by TLC and was complete within 1h. Then the unreacted Zinc was filtered and washed with ether. The filtrate was extracted with ether (3 x 20 mL). The organic layers were pooled together, washed with saturated sodium bicarbonate, water, brine respectively, dried over $Na_2SO_4$ and solvent was removed to get a mixture of hydroxybornanones (8.2 g, 81 %).

IR ($CCl_4$) $\nu_{max}$ : 3461, 3306, 2948, 2874, 1647, 1465, 1276, 1169, 1101, 926, 804 $cm^{-1}$.

**Hydroximinobornanols (73 & 74)**[24]

The mixture of **71** and **72** (10 g, 59.52 mmol) was dissolved in 40 mL methanol. To this hydroxylamine hydrochloride (8.7 g, 125 mmol) and sodium acetate (18.6 g, 149 mmol) dissolved in 30 mL water was added and refluxed for 2 h. This was then cooled to room temperature and extracted with ether (4 x 20 mL). The organic layer was then washed with sat. $NaHCO_3$ solution, water, brine, dried over $Na_2SO_4$ and concentrated to get a viscous liquid containing the mixture of hydroximinobornanols (9 g, 83 %).

The reaction mixture on chromatographic separation on a neutral alumina column using ethylacetate - hexane (20 %) as eluent afforded the compound **74** as a viscous liquid (4 g, 37 %).

IR ($CCl_4$) $\nu_{max}$ : 3218, 3130, 2962, 2888, 1694, 1485, 1391, 1344, 1290, 1256, 1209, 1196, 1020, 926, 852, 825, 757, 690 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 9.55 (brs, 1H), 4.845 (d, 1H, $J$ = 4.51 Hz), 3.565 (brs, 1H), 1.61 (m, 5H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82 (s, 3H).

$^{13}C$ NMR ($\delta$) : 170.28, 168.11, 74.03, 69.56, 52.27, 51.19, 50.11, 48.88, 45.82, 45.66, 33.84, 26.04, 25.54, 19.49, 19.00, 18.61, 18.47, 18.18, 12.84, 11.19.

Further elution with 50 % ethylacetate - hexane yielded other isomer **73** as a white solid (4.2 g, 39 %). It was then recrystallized from dichloromethane – hexane solvent system.

m. p. : 163 - 165°C

IR (KBr) $\nu_{max}$ : 3258, 3144, 2962, 2921, 2874, 1703, 1465, 1398, 1378, 1310, 1249, 1196, 1081, 980, 946 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 9.5 (brs, 1H), 4.82 (brs, 1H), 4.2, (s, 1H), 2.955 (d, 1H, $J$ = 4.99 Hz), 1.935 (m, 2H), 1.39 (m, 2H), 0.96 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H).

$^{13}C$ NMR ($\delta$) : 168.82, 75.36, 50.08, 48.61, 45.08, 25.76, 24.37, 19.39, 18.45, 12.99.

**2-*endo*-amino-3-*endo*-hydroxybornane (65)**[24]

The compound **74** (2 g, 10.92 mmol) dissolved in 30 mL dry THF was added dropwise to a suspension of LAH (0.82 g, 21.84 mmol) in 30 mL THF and this is then refluxed for 24 h. When the reaction was complete, the reaction mixture was cooled to room temperature and the excess LAH was destroyed by the dropwise addition of 10 % NaOH solution (5 mL) followed by the dropwise addition of cold water. Then the reaction mixture was filtered and the precipitate was washed a number of times with ether. All the organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. (1.01 g, 55 %). This was then crystallized from dichloromethane - hexane solvent system.

m. p. : 192 - 194 °C

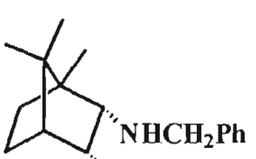
IR (KBr) $\nu_{max}$ : 3461, 3306, 2948, 2874, 1647, 1465, 1276, 1169, 1101, 926 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 4.3 (s, 2H), 3.92 (brs, 1H), 3.185 (d, 1H, $J$ = 13.03 Hz), 2.9 (d, 1H, $J$ = 11.89 Hz), 1.695 (m, 5H), 1.04 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H).

$^{13}$C NMR (δ) : 53.20, 47.02, 45.44, 42.30, 41.27, 34.48, 25.62, 24.22, 18.29, 17.47.

**2-*endo*-benzylamino-3-*endo*-hydroxybornane (83a)**

2-*endo*-amino-3-*endo*-hydroxybornane **65** (0.507 g, 3 mmol) was dissolved in 10 mL dry benzene. Benzaldehyde (0.350 g, 3.3 mmol) was added to this and the reaction mixture was refluxed for 5 h using a Dean-Stark apparatus. When the reaction was complete the reaction mixture was cooled to room temperature, solvent was removed. The imine thus formed was dissolved in methanol and reduced with sodium borohydride (0.235 g, 6.22 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 20 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a silica column using ethylacetate - hexane (5 %) as eluent to give a viscous liquid (0.426 g, 55 %).




**83a**

$[\alpha]_D^{25}$ : (c=0.72, $CHCl_3$) = -14.292°

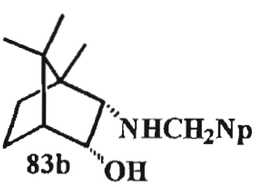
IR ($CCl_4$) $\nu_{max}$ : 3341, 3031, 2949, 2880, 1654, 1456, 1389, 1373, 1325, 1287, 1259, 1083, 1063, 921, 825, 809 $cm^{-1}$.

$^1$H NMR (δ) : 7.26 (m, 5H), 3.7 (s, 2H), 3.685 (m, 1H), 3.485 (d, 1H, *J* = 8.27 Hz), 1.55 (m, 7H), 0.97 (s, 3H), 0.98 (s, 3H), 0.70 (s, 3H).

$^{13}$C NMR (δ) : 140, 128.43, 128.19, 127.01, 65.17, 56.54, 54.99, 50.45, 47.97, 44.67, 35.76, 25.68, 24.08, 21.38, 18.67.

**2-*endo*-naphthylmethylamino-3-*endo*-hydroxybornane (83b)**

2-*endo*-amino-3-*endo*-hydroxybornane **65** (0.507 g, 3 mmol) was dissolved in 10 mL dry benzene. 1-Naphthaldehyde (0.515 g, 3.3 mmol) was added to this and the reaction mixture was refluxed at 80° C for 4 h using a Dean - Stark apparatus. When the reaction was complete, the reaction mixture was cooled to room temperature and the solvent was removed. The imine formed was dissolved in methanol and reduced with sodium borohydride (0.225 g, 5.86 mmol) after cooling the reaction mixture to 0 °C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica gel using ethylacetate - hexane (10 %) as eluent to give a viscous liquid (0.425 g, 46 %).




**83b**

$[\alpha]_D^{25}$ : (c=0.98, $CHCl_3$) = +13.250°

IR ($CCl_4$) $\nu_{max}$ : 3311, 3055, 2956, 2881, 1655, 1588, 1507, 1468,1451, 1389, 1370, 1095, 1058, 920 $cm^{-1}$.

$^1$H NMR (δ) : 7.735 (m, 7H), 4.215 (q, 2H, $J$ = 12.63 Hz), 3.82 (s, 1H), 2.565 (d, 1H, $J$ = 3.42 Hz), 1.88 (m, 7H), 0.87 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H).

$^{13}$C NMR (δ) : 135.04, 133.79, 131.68, 128.68, 128.33, 126.5, 126.01, 125.91, 225.33, 123.56, 83.84, 73.01, 69.64, 50.48, 45.58, 33.18, 27.83, 25.34, 21.40, 18.72, 11.20.

MS (m/z) (%) : 309 $(M+)^+$ (10), 294 (5), 280 (10), 238 (10), 224 (30), 211 (5), 196 (4), 168 (10), 156 (5), 141 (100), 115 (10).

**3-*exo*-amino-2-*endo*-hydroxybornane (62)**[24]

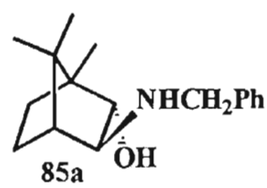
3-hydroximino-2-*endo*-hydroxybornane **73** (2 g, 10.91 mmol) was dissolved in 30 mL super dry ethanol and stirred well. Sodium metal was added to this till the reaction mixture becomes saturated. The reaction mixture is allowed to reflux for another 1h. The reaction mixture was cooled to room temperature and cold water was added to destroy the sodium ethoxide formed and the solvent was evaporated. The residue was then extracted with dichloromethane. All the organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product (0.83 g, 45 %).

IR ($CCl_4$) $\nu_{max}$ : 3299, 3118, 2962, 2864, 1651, 1551, 1451, 1376, 1384, 1245, 1089, 1058, 1002, 914, 802 $cm^{-1}$.

**3-*exo*-benzylamino-2-*endo*-hydroxybornane (85a)**

3-*exo*-amino-2-*endo*-hydroxybornane **62** (0.338 g, 2 mmol) was dissolved in 10 mL absolute ethanol. Benzaldehyde (0.235 g, 2.2 mmol) was added to this and the reaction mixture was stirred for 4 h. Molecular sieves (4Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.220 g, 5.84 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was quenched by adding cold water. This was then extracted with dichloromethane (3 x 10

mL). The organic extracts were pooled together, washed with water, brine, dried over anhydrous sodium sulphate and concentrated to get the crude product. This was purified on a silica column using ethylacetate and hexane (5 %) as eluent to give a white solid (0.233 g, 45 %). This was recrystallized from dichloromethane - hexane solvent system.




**85a**

$[\alpha]_D^{25}$ : (c=0.2, $CHCl_3$) = -19.858°

m. p. : 157 - 160°C

IR (KBr) $\nu_{max}$ : 3349, 3193, 3068, 2956, 2874, 1676, 1496, 1479, 1448, 1387, 1368, 1319, 1276, 1113, 1070, 1035, 992, 837, 813, 751, 724, 707 $cm^{-1}$

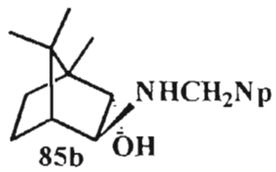
$^1H$ NMR (δ) : 8.2 (s, 1H), 7.365 (m, 5H), 4.1 (s, 1H), 3.79 (s, 2H), 3.08 (s, 1H), 1.5 (m, 6H), 0.89 (s, 3H), 0.82 (s, 3H), 0.85 (s, 3H).

$^{13}C$ NMR (δ) : 142.59, 129.09, 128.53, 127.20, 70.80, 56.04, 53.18, 47.20, 45.93, 35.59, 27.03, 26.50, 21.07, 16.94, 13.22

**3-*exo*-naphthylmethylamino -2-*endo*-hydroxybornane (85b)**

3-*exo*-amino-2-*endo*-hydroxybornane **62** (0.507 g, 3 mmol) was dissolved in 10 mL absolute ethanol. 1-Naphthaldehyde (0.516 g, 3.3 mmol) was added to this and the reaction mixture was stirred for 4 h. Molecular sieves (4Å) were added to remove the water formed during the reaction. The imine formed was reduced *in situ* with sodium borohydride (0.209 g, 5.54 mmol) after cooling the reaction mixture to 0° C. The reaction mixture was stirred for 12 h and then the excess $NaBH_4$ was

quenched by adding cold water. This was then extracted with dichloromethane (3 x 20 mL). The organic extracts were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was purified on a column of silica using ethylacetate - hexane (10 %) as eluent to give a yellow viscous liquid (0.48 g, 52 %).




$[\alpha]_D^{25}$ : (c=0.8, $CHCl_3$) = +28.995°

IR ($CCl_4$) $\nu_{max}$ : 3305, 3055, 2956, 2874, 1651, 1545, 1513, 1457, 1395, 1376, 1257, 1064, 1026, 808, 777 $cm^{-1}$.

$^1H$ NMR (δ) : 7.52 (m, 7H), 3.90 (s, 2H), 2.62 (d, 1H, *J* = 10.44 Hz), 2.15 (d, 1H, *J* = 10.31 Hz), 1.87 (m, 7H), 0.96 (s, 3H), 0.83 (s, 3H), 0.73 (s, 3H).

$^{13}C$ NMR (δ) : 132.69, 128.14, 128.08, 125.95, 124.95, 121.76, 72.33, 64.57, 56.48, 53.68, 48.69, 45.34, 28.64, 24.66, 18.51, 17.86, 12.90.

MS (m/z) (%) : 309 $(M^+)^+$ (10), 280 (12), 238 (10), 224 (30), 168 (15), 156 (5), 141 (100), 115 (10).

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# CHAPTER 3

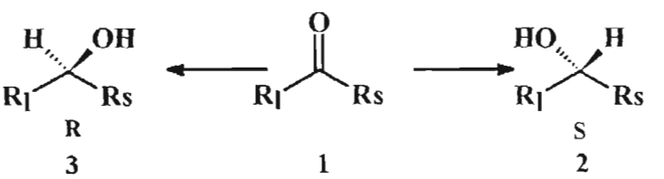
# ASYMMETRIC BORANE REDUCTION OF PROCHIRAL KETONES USING OXAZABOROLIDINES DERIVED FROM (1R)-(+)-CAMPHOR AS CATALYSTS

This chapter consists of three parts. In Part I of this chapter, a brief review on various methods available in literature for the enantioselective reduction of ketones is presented. Part II deals with the asymmetric reduction of ketones catalyzed by the oxazaborolidines derived from amino alcohol derivatives of (1R)-(+)-camphor. Part III contains the same reductions catalyzed by oxazaborolidines derived from amino alcohols of (1R)-(+)-camphor.

# PART I

## 3.1 INTRODUCTION

Enantioselective reduction of prochiral ketones is an important reaction in synthetic organic chemistry. During the reduction, the hydride ion can approach from both faces of the carbonyl moiety with an angle close to 109° which will result in enantiomers (Scheme 3.1).[1]




**Scheme 3.1**

Optically active alcohols thus produced serve as the starting materials for the synthesis of a number of enantiopure compounds including biologically active natural products. The known methods for the reduction of prochiral ketones are the use of stoichiometric amount of modified chiral hydride reagents both lithium aluminium hydride and sodium borohydride, using enantiopure alkylboranes, transition metal catalyzed hydrogenation and hydrosilylation of ketones, catalytic asymmetric borane reduction and asymmetric reduction with the enzymes.[2]

An overview of the important methods for the reduction of prochiral ketones is given in the following sections.

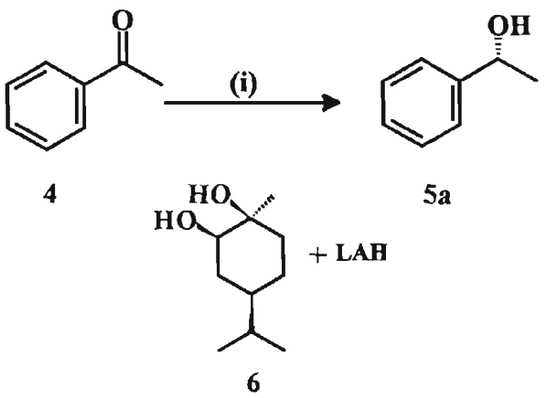
### 3.1.1 Chirally modified lithium aluminium hydride reagents

The first enantioselective reduction of ketones with the reagent prepared from LAH and D-camphor was reported in 1951.[3] Since then a number of chirally modified reagents have been developed. Chiral reagents are prepared from LAH by replacing the active hydrogen atoms of LAH by chiral alcohols, biphenols, amino acids, amines diamines etc.

### 3.1.1A Chiral alcohols as modifiers

Preliminary studies of alcohol modification of LAH was with (+)-borneol, but the optical purity of the product was low.[4] This may be due to the rapid disproportion of the alkoxy aluminium hydride to free LAH.

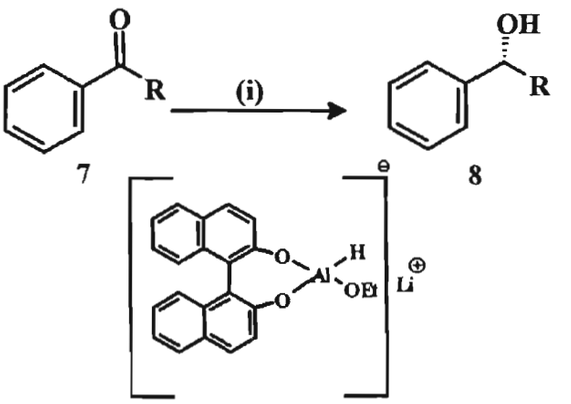
Inorder to overcome this, chiral diols were used as modifiers as depicted in scheme 3.2.[5]




**(i) 6, EtOH, Ether, 99 %, 30 %*ee***

**Scheme 3.2**

BINAL-H prepared from binaphthol and LAH was found to be a good reducing agent for the asymmetric reduction of aromatic, $\alpha, \beta$–unsaturated and acetylinic ketones. But this was found to be a poor reagent for aliphatic ketones.[6]

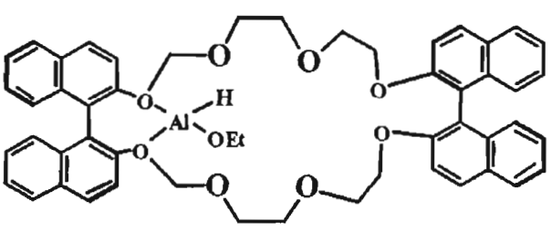



9

**(i) 9, Ether, -78° C, 61-92 % , 44-100 %ee**

**Scheme 3.3**

The chiral aluminium hydride reagent **10** (Fig 3.1) has been found to be a good reducing agent for all types of ketones.[7]




10

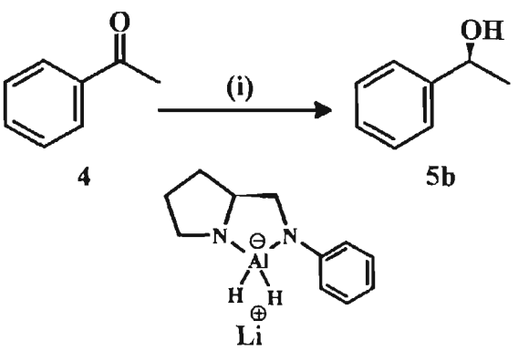
**Figure 3.1**

### 3.1.1B Chiral amino alcohols

Darvon alcohol[8] and amino alcohols derived from ephedrine, (S)-aspartic acid, (1R)-(-)-myrtenol were used as chiral modifiers for LAH. The reactions yielded products with moderate enantioselectivity.[9]

### 3.1.1C Chiral diamines

The asymmetric reduction of aromatic ketones with the reagent prepared from LAH and (S)-2-anilinomethylpyridine yielded alcohol with high enantioselectivity (Scheme 3.4).[10]




11

**(i) 11, 1 mol %, Xylene, 80 %, 95 % *ee***

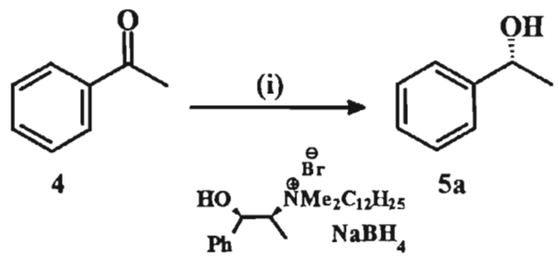
**Scheme 3.4**

### 3.1.2 Chirally modified borohydride reagents

Sodium borohydride can also be modified by a number of ways.

(i) The borohydride anion $[BH_4]^-$ can be modified by the use of chiral counter ions. (ii) The hydrides can be replaced by chiral modifiers including chiral alcohol, carboxylic acid, hydroxy acid, amino alcohol etc.

An example to the first approach is the replacement of sodium ion with a chiral quartenary ammonium ion, but the optical purity of the product was low (Scheme 3.5).[11]

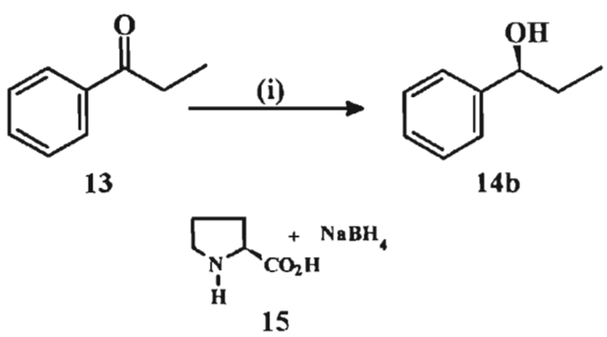



12

(i) 12, $CH_2Cl_2$ / $H_2O$, 79 %, 39 % *ee*

**Scheme 3.5**

An example to the second category is given in scheme 3.6. Here the chiral reagent prepared from (S)-proline and $NaBH_4$ is used as the reducing agent.




15

(i) 15, THF, R. T., 92 %, 50 %*ee*

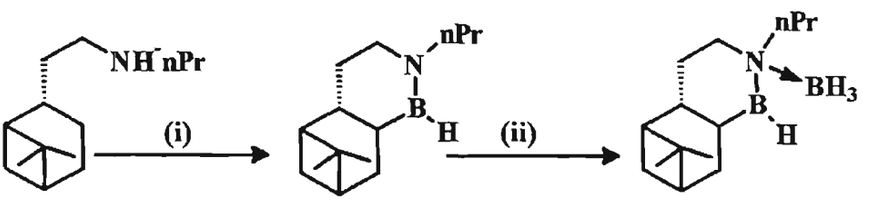
**Scheme 3.6**

There are reports in literature using modified form of borohydride for the asymmetric reduction of ketones but the enantioselectivity of the product in most cases were found to be low.[12]

### 3.1.3 Chirally modified boranes

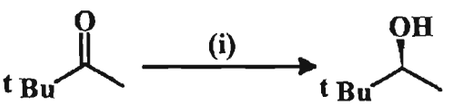
Lewis acidic boranes can be modified with chiral bases and the resultant complex can be used for the enantioselective reduction of ketones. Midland reagents derived from terpenic azaboracyclohexanes complexed

with $BH_3$ act as good reducing agents for all kinds of ketones (Scheme 3.7).[13]




16 17 18

(i) TEA, $BH_3$, PhMe, 110° C (ii) $BH_3$.THF

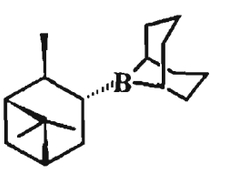



19 20

(i) 18, THF, R. T., 61 %, 82 %*ee*

**Scheme 3.7**

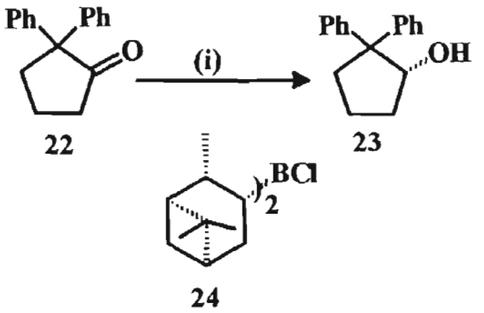
Alpine-borane ® **21,** prepared by the hydroboration of α-pinene with 9-BBN was found to be a good reducing agent for acetylinic ketones but a poor reagent for other types of ketones.[14]




21

**Figure 3.2**

Diisopinocampheylchloroborane $Ipc_2BCl$, (DIP-Cl) **24,** developed by Brown is found to be a good reagent for a variety of ketones (Scheme 3.8).[15]

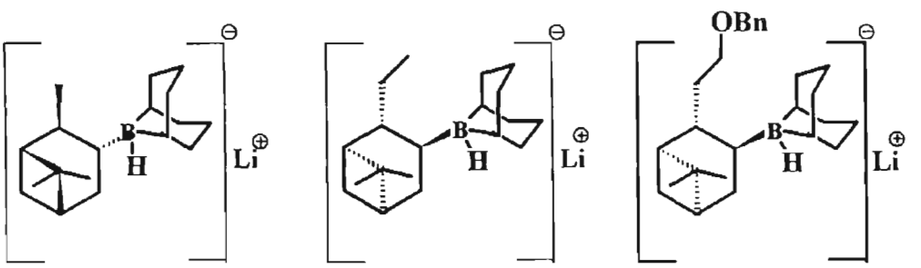



22 23 24

(i) 24, THF, R. T., 5d. 71%, 98 % *ee*

**Scheme 3.8**

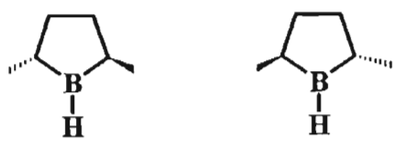
The reaction of Li, Na, or K hydrides with enantiopure alkylboranes will afford the corresponding alkylborohydrides. Lithium *β*-3-pinanyl-9-borabicyclo[3.3.1]nonyl hydride (alpine hydride) ® **25**,[16] Lithium *β*-3- (iso-2-ethyl apopinocampheyl)-9-borabicyclo[3.3.1]nonyl hydride (Eapine hydride ® **26**[17] and lithium hydrido(9-BBN-nopol benzyl ether adduct) (NB-Enantride) ® **27**[18] are examples of these class of reagents. Alpine hydride when used as a reducing agent yielded secondary alcohols with moderate enantioselectivity. Eapine hydride and NB-enantride are found to be good reducing agents for aliphatic ketones.




25 26 27

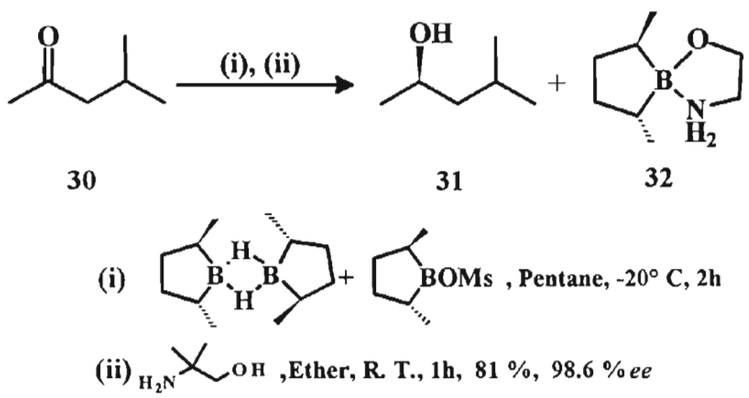
**Figure 3.3**

Masamune developed (R, R) or (S, S) dimethyl borolane **28** and **29** which are good reducing agents for aliphatic ketones. Pure **28** reduces 2-butanone with only 4 % *ee*. But high enantioselectivity was observed with the reagent which is a mixture of 2,5-dimethylborolanyl mesylate (0.2 equiv) and **28** (1 equiv.) as shown in scheme 3.9.[19]



**28** **29**

**Figure 3.4**




**Scheme 3.9**

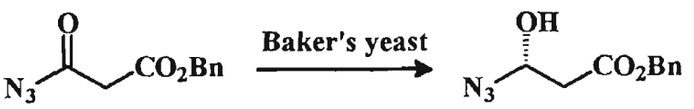
### 3.1.4 Transition metal catalyzed reductions

Rhodium, ruthenium and iridium complexes of enantiopure diphosphine ligands have been used as catalysts for the asymmetric hydrogenation of prochiral ketones. BINAP-Ru complexes developed by Noyori were found to be good reducing agents for the asymmetric reduction of a variety of ketones.[20] Rhodium complexes bearing chiral phosphine

ligands have used for the asymmetric hydrosilylation of a wide variety of ketones.[21]

### 3.1.5 Enzymatic reductions

Various alcohol dehydrogenases have been used as chiral catalysts for the asymmetric reduction of prochiral ketones. The reduction of acetophenone by Bakers yeast in presence of 2.5 % glucose yielded alcohol with 95 % *ee*. The advantage of enzymatic reduction is that ketones can be reduced with chemoselectivity and in high enantioselectivity (Scheme 3.10).[22]



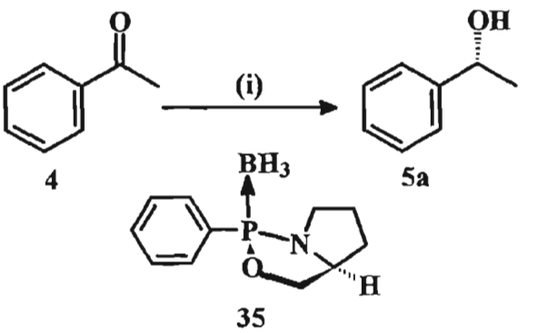

33 90 %, 95 % *ee* 34

**Scheme 3.10**

### 3.1.6 Catalytic borane reductions

Oxazaborolidine developed by Itsuno is an important chiral catalyst for the asymmetric reduction of prochiral ketones. A review of this has been presented in the first chapter.

In addition to this chiral oxazaphospholidines derived from 1,2-amino alcohols were reported as catalysts for the asymmetric borane reductions (Scheme 3.11).[23]

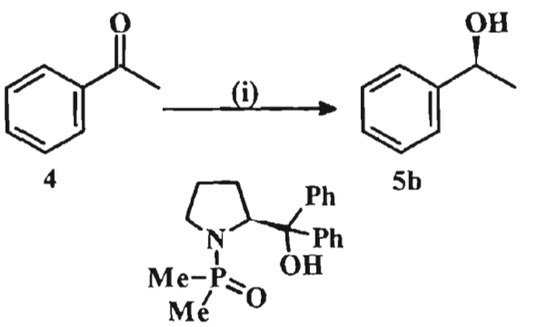



35

**(i) 35, 1equiv., PhMe, 110° C, 77 %, 99 %*ee***

**Scheme 3.11**

Chiral phosphinamides are another class of chiral catalysts used for the asymmetric borane reduction of ketones.[24] The example given in scheme 3.12 shows the enantioselective reduction of acetophenone using phosphinamide **36** as catalyst.

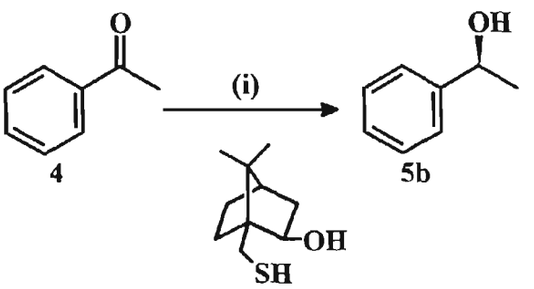



36

**(i) 36, 10 mmol, PhMe, 110° C, 1h., 90 %, 62 %*ee***

**Scheme 3.12**

Recently, chiral hydroxythiols were reported as asymmetric catalysts for the borane reduction of prochiral ketones. In this study D-camphor derived hydroxy thiol **37** is used as the catalyst (Scheme 3.13).[25]




37

**(i) 37, 10 mol %, $BH_3$.THF, 1 mol %, THF, 35° C, 95 %, 64 % *ee***

**Scheme 3.13**

## 3.2 RESULTS AND DISCUSSION

Eventhough a number of chiral reducing agents and chiral catalysts are known, chiral catalysts of general nature that can reduce all types of ketones with high enantioselectivity are yet to be discovered. So chemists are in search of new methods and reagents for the asymmetric reduction of ketones. Hence we have carried out an indepth study concerning the use oxazaborolidines from (R)-camphor. In this chapter results of our investigations in the area of oxazaborolidine catalyzed reductions is given in next two parts.

# PART II

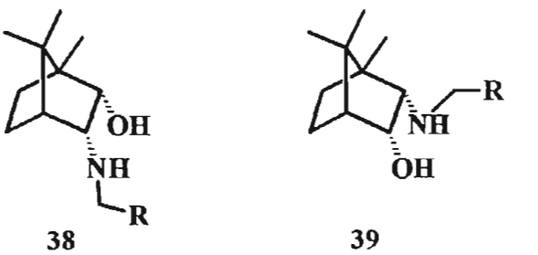
### 3.2.1 Asymmetric borane reduction using oxazaborolidines derived from 1,2-amino alcohol derivatives of (1R)-(+)-camphor as catalysts

From the survey of literature, it is found that the oxazaborolidine catalysts prepared from amino alcohols containing a secondary amino group act as good catalysts for the asymmetric reduction than the amino alcohols containing a primary amino group.[26] With this in mind, we prepared the amino derivatives, the benzyl and naphthylmethylamino derivatives of amino alcohols of camphor. These were then used for the oxazaborolidine synthesis.

The preparation of these derivatives is described in chapter 2. (Section 2.7).

### 3.2.2 Catalysts derived from cis *endo-endo* amino alcohol derivatives

The amino alcohol derivatives selected for the oxazaborolidine synthesis are given in figure 3.5.




**38** **39**

**38a R = Ph** **39a R = Ph**
**38b R = 1-Naphthyl** **39b R = 1-Naphthyl**

**Figure 3.5**

The following ketones were selected for study (Figure 3.6).

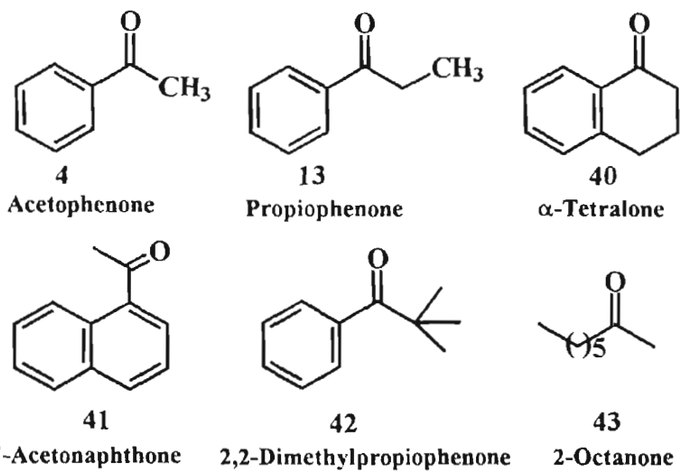
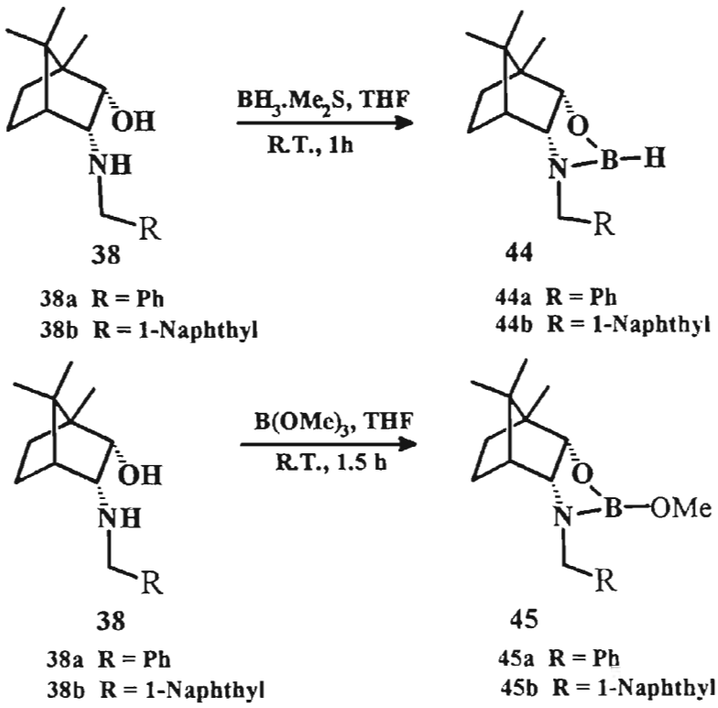



**Figure 3.6**

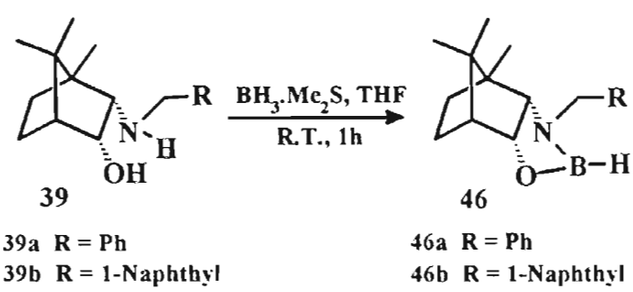
The oxazaborolidines were generated *in situ* by the treatment of borane, or the trimethyl borate with the amino alcohol derivatives under anhydrous conditions. Attempts were made to isolate the catalyst, but failed due to its high decomposing nature. While carrying out the reaction there was a well defined spot on TLC and the spot of starting material was absent. The formation of the oxazaborolidine catalyst was speculated because when the reduction was carried out with the amino alcohol alone in catalytic amount and using borane as the reducing agent no appreciable enantioselectivity was observed. This was further confirmed by carrying out the reaction in an NMR tube. The catalyst formation was evident by the absence of -OH and -NH peaks in the resultant spectrum.

The catalysts were generated *in situ* from the *endo-endo* benzylamino and naphthylmethylamino derivatives by the reaction with borane and trimethyl borate respectively as shown below. The probable structures of the catalysts are given in scheme 3.14.



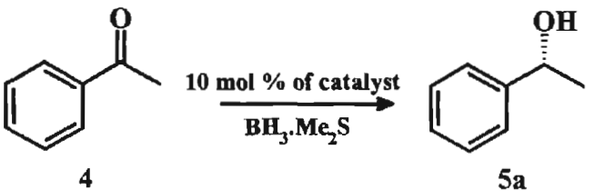

**Scheme 3.14**

The catalysts were prepared from cis 2-*endo*-amino-3-*endo*-hydroxybornane derivatives in a similar manner as depicted in scheme 3.15.




**Scheme 3.15**

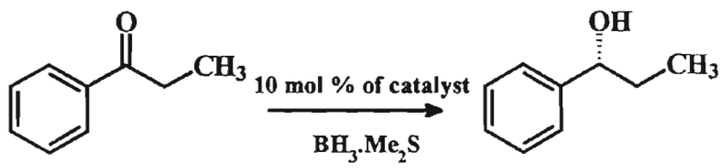
The results obtained for the asymmetric reduction of ketones are given in tables 3.1-3.5.




**Scheme 3.16**

**Table 3.1** Asymmetric reduction of acetophenone using oxazaborolidines derived from *endo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **44a** | 16.804° | 39 | R | 90 |
| 2 | **45a** | 11.774° | 27 | R | 80 |
| 3 | **44b** | 29.734° | 70 | R | 88 |
| 4 | **45b** | 11.050° | 25 | R | 76 |
| 5 | **46a** | 2.7945° | 6.5 | R | 68 |
| 6 | **46b** | 1.6323° | 3.8 | R | 64 |

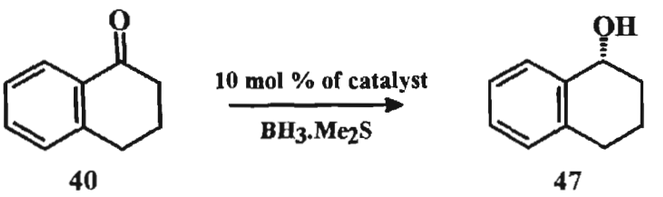



**13** **14a**

**Scheme 3.17**

**Table 3.2** Asymmetric reduction of propiophenone using oxazaborolidines derived from *endo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **44a** | 9.4121° | 29 | R | 92 |
| 2 | **45a** | 6.7412° | 20 | R | 84 |
| 3 | **44b** | 17.014° | 52 | R | 85 |
| 4 | **45b** | 10.514° | 32 | R | 80 |
| 5 | **46a** | 3.5177° | 11 | R | 76 |
| 6 | **46b** | 3.4111° | 10 | R | 95 |

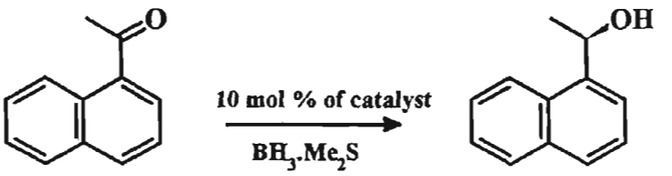



40 47

**Scheme 3.18**

**Table 3.3** Asymmetric reduction of $\alpha$-tetralone using oxazaborolidines derived from *endo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **44a** | -14.082° | 44 | R | 69 |
| 2 | **45a** | -7.9812° | 25 | R | 67 |
| 3 | **44b** | -24.208° | 76 | R | 78 |
| 4 | **45b** | -15.548° | 49 | R | 75 |
| 5 | **46a** | -2.7761° | 8 | R | 65 |
| 6 | **46b** | -1.7922° | 5 | R | 51 |

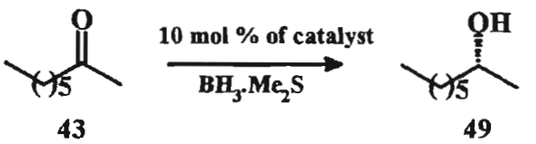



**41** **48**

**Scheme 3.19**

**Table 3.4** Asymmetric reduction of 1'-acetonaphthone using oxaza-borolidines derived from *endo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **44a** | 21.023° | 27 | R | 70 |
| 2 | **45a** | 3.5833° | 5 | R | 65 |
| 3 | **44b** | 20.2881° | 26 | R | 72 |
| 4 | **45b** | 0.01933° | 0 | R | 75 |
| 5 | **46a** | 4.0619° | 5.2 | R | 72 |
| 6 | **46b** | 1.6412° | 3.8 | R | 92 |




**Scheme 3.20**

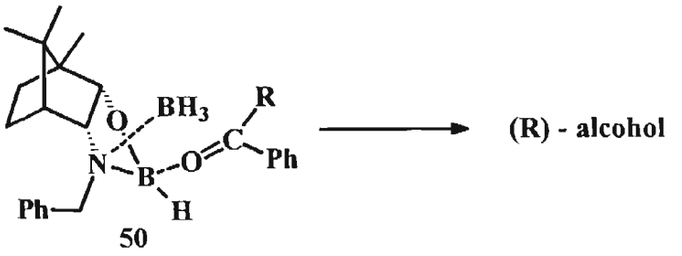
**Table 3.5** Asymmetric reduction of 2-octanone using oxazaborolidines derived from *endo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **44a** | -4.5126° | 47 | R | 80 |
| 2 | **45a** | -1.1981° | 12 | R | 67 |
| 3 | **44b** | -5.9121° | 62 | R | 65 |
| 4 | **45b** | -3.3514° | 35 | R | 58 |
| 5 | **46a** | -0.8386° | 8 | R | 50 |
| 6 | **46b** | -0.9254° | 9 | R | 64 |

When *endo-endo* naphthylmethylamino alcohol and borane derived oxazaborolidine was used as the chiral catalyst, moderate enantioselectivity

of the product alcohol was obtained compared to the catalyst derived from *endo-endo* benzylamino alcohol and borane. The catalyst derived from amino alcohols and trimethyl borate were found be poor catalysts in all cases. The catalytic activity of **44a** and **44b** over **45a** and **45b** can be explained as per Corey's mechanism (Scheme 1.17 of chapter 1).[27] The electron donating nature of the -OMe group on the oxazaborolidine moiety increases the electron density on the boron atom leading to weak interactions between the free borane and the nitrogen atom. This reduces the interactions between carbonyl oxygen and the boron atom of the oxazaborolidine moiety favoring the attack of free borane on the ketone leading to the low enantioselectivity of the product.

In all cases the configuration of the product obtained was R. This can be explained by the transition state diagram. The transition state in which the ketone attached on its *si* face leading to R alcohol is sterically favored over the other side attack which suffers the repulsion between the phenyl group on the ketone and the camphor part of the molecule.

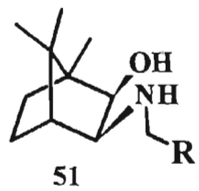



50

**Scheme 3.21**

### 3.2.3 Catalysts derived from cis *exo-exo* amino alcohol derivatives

The following amino alcohol derivatives are selected as precursors for the oxazaborolidine synthesis (Figure 3.7).

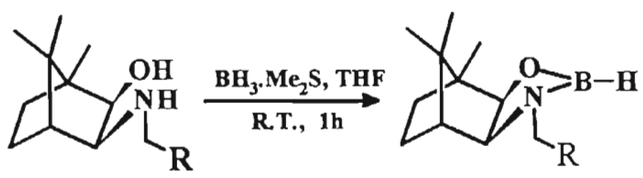



51

**51a R = Ph**
**51b R = 1-Naphthyl**

**Figure 3.7**

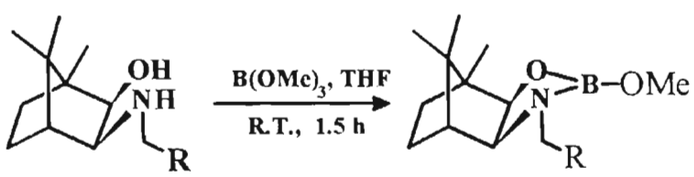
The method of preparation and the probable structures of the catalysts used in the study are given in schemes 3.22 and 3.23.




**51** **52**

**51a R = Ph** **52a R= Ph**
**51b R = 1-Naphthyl** **52b R= 1-Naphthyl**

**Scheme 3.22**

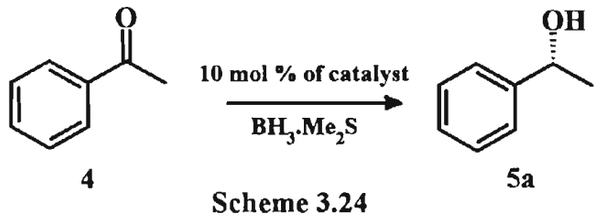



**51** **53**

**51a R = Ph** **53a R= Ph**
**51b R = 1-Naphthyl** **53b R= 1-Naphthyl**

**Scheme 3.23**

The results obtained for the asymmetric reduction of ketones are given in tables 3.6 - 3.10.

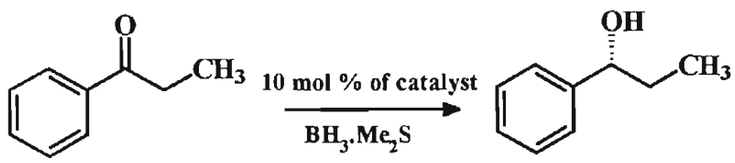



4 5a

**Scheme 3.24**

**Table 3.6** Asymmetric reduction of acetophenone using oxazaborolidines derived from *exo-exo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **52a** | 15.765° | 37 | R | 79 |
| 2 | **53a** | 9.0812° | 21 | R | 78 |
| 3 | **52b** | 22.301° | 52 | R | 82 |
| 4 | **53b** | 11.583° | 27 | R | 76 |

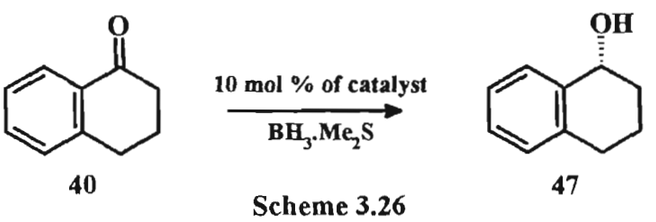



13 14a

**Scheme 3.25**

**Table 3.7** Asymmetric reduction of propiophenone using oxazaborolidines derived from *exo-exo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee*(%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **52a** | 22.252° | 52 | R | 85 |
| 2 | **53a** | 7.0841° | 27 | R | 77 |
| 3 | **52b** | 17.117° | 52 | R | 83 |
| 4 | **53b** | 13.403° | 41 | R | 75 |

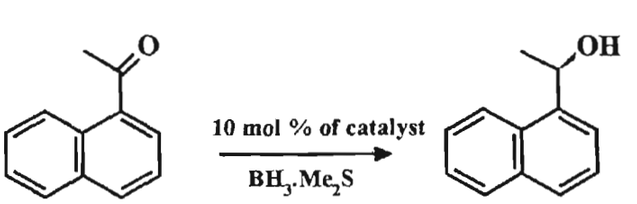



**40** **47**

**Scheme 3.26**

**Table 3.8** Asymmetric reduction of $\alpha$-tetralone using oxazaborolidines derived from *exo-exo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **52a** | -9.0791° | 28 | R | 76 |
| 2 | **53a** | -7.7762° | 24 | R | 85 |
| 3 | **52b** | -15.193° | 47 | R | 74 |
| 4 | **53b** | -13.660° | 43 | R | 75 |

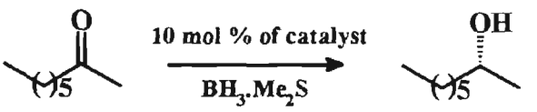



**41** **48**

**Scheme 3.27**

**Table 3.9** Asymmetric reduction of 1'-acetonaphthone using oxaza-borolidines derived from *exo-exo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **52a** | 11.309° | 14 | R | 78 |
| 2 | **53a** | 11.162° | 14 | R | 61 |
| 3 | **52b** | 6.5804° | 8 | R | 75 |
| 4 | **53b** | 6.8875° | 9 | R | 70 |



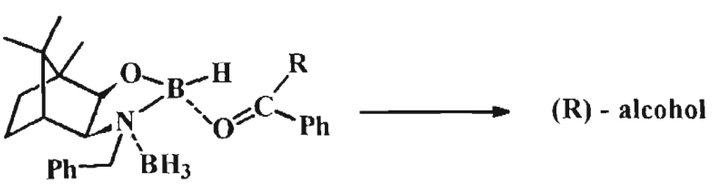

43 49

**Scheme 3.28**

**Table 3.10** Asymmetric reduction of 2-octanone using oxazaborolidines derived from *exo-exo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **52a** | -4.8012° | 50 | R | 59 |
| 2 | **53a** | -2.2881° | 24 | R | 65 |
| 3 | **52b** | -5.7102° | 60 | R | 60 |
| 4 | **53b** | -2.0872° | 22 | R | 64 |

When *exo-exo* amino alcohol derivatives derived oxazaborolidines were used for catalytic reduction similar pattern of reactivity as that of *endo-endo* amino alcohol derivatives derived catalyst were observed. The configurations of the product molecules were found to be R. This suggests that the reaction is occurring through a transition state in which the ketone is attached on the *re* face of the molecule just reverse of the transition state discussed in the scheme 3.21

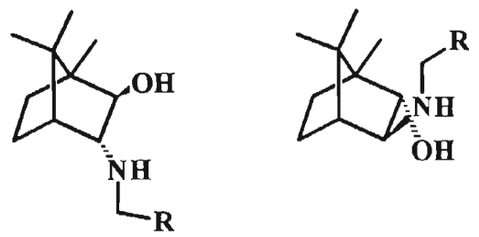



54

**Scheme 3.29**

### 3.2.4 Catalysts derived from trans *exo-endo* amino alcohol derivatives

Having obtained moderate *ee* with the cis *exo-exo* and cis *endo-endo* amino alcohol derivatives, we turned our attention to the trans *endo-exo* amino alcohol derived oxazaborolidines as catalysts.

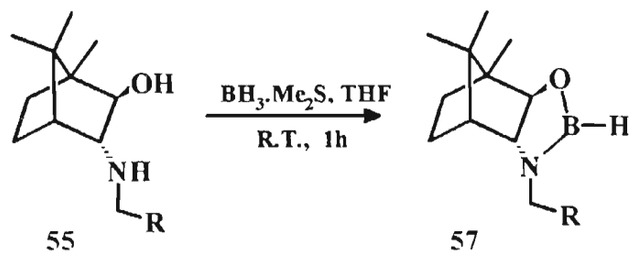



55 56

55a R = Ph 56a R = Ph
55a R - 1-Naphthyl 56 b R = 1-Naphthyl

**Figure 3.8**

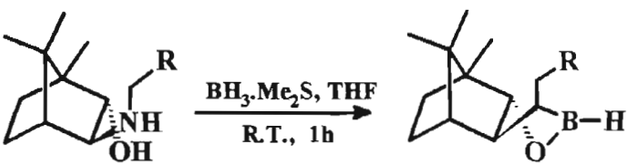
The method of preparation and the probable structures of the catalysts used in the study are given in schemes 3.30 and 3.31.




55 57

55a R = Ph 57a R = Ph
55b R = 1-Naphthyl 57b R = 1-Naphthyl

**Scheme 3.30**

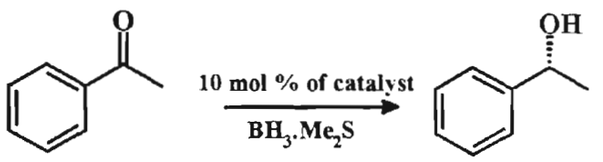



**56**
**56a R = Ph**
**56b R = 1-Naphthyl**

**58**
**58a R = Ph**
**58b R = 1-Naphthyl**

**Scheme 3.31**

The results obtained for the asymmetric reduction of ketones are given in tables 3.11 - 3.15

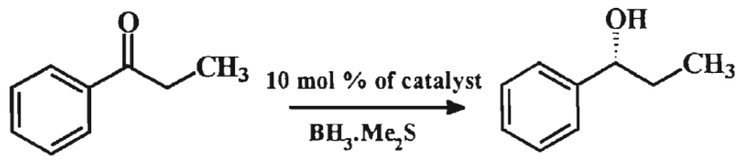



**4** **5a**

**Scheme 3.32**

**Table 3.11** Asymmetric reduction of acetophenone using oxazaborolidines derived from *exo-endo* amino alcohol derivatives as catalysts.

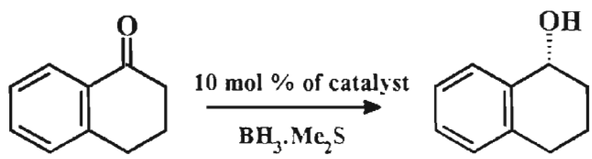
| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **57a** | 8.0959° | 19 | R | 73 |
| 2 | **57b** | 9.0879° | 21 | R | 80 |
| 3 | **58a** | 16.491° | 38 | R | 80 |
| 4 | **58b** | 15.089° | 35 | R | 85 |




13 **Scheme 3.33** 14a

**Table 3.12** Asymmetric reduction of propiophenone using oxaza-borolidines derived from *exo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **57a** | 10.158° | 30 | R | 82 |
| 2 | **57b** | 8.2786° | 25 | R | 77 |
| 3 | **58a** | 11.609° | 35 | R | 65 |
| 4 | **58b** | 13.008° | 39 | R | 60 |

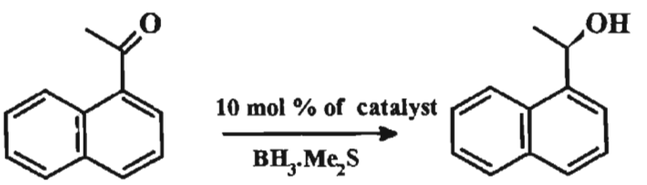



40 47

**Scheme 3.34**

**Table 3.13** Asymmetric reduction of $\alpha$-tetralone using oxazaborolidines derived from *exo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **57a** | -9.2491° | 29 | R | 82 |
| 2 | **57b** | -7.7726° | 24 | R | 77 |
| 3 | **58a** | -10.085° | 31 | R | 69 |
| 4 | **58b** | 11.850° | 37 | R | 80 |

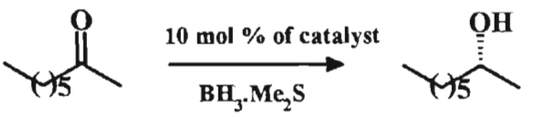



41 48

**Scheme 3.35**

**Table 3.14** Asymmetric reduction of 1'-acetonaphthone using oxaza-borolidines derived from *exo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **57a** | 2.8786° | 4 | R | 86 |
| 2 | **57b** | 3.8966° | 5 | R | 88 |
| 3 | **58a** | 4.0812° | 5 | R | 79 |
| 4 | **58b** | 6.0018° | 7 | R | 85 |




43 49

**Scheme 3.36**

**Table 3.15** Asymmetric reduction of 2-octanone using oxazaborolidines derived from *exo-endo* amino alcohol derivatives as catalysts.

| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **57a** | -3.4833° | 36 | R | 75 |
| 2 | **57b** | -4.3018° | 45 | R | 77 |
| 3 | **58a** | -4.3091° | 45 | R | 70 |
| 4 | **58b** | -4.7216° | 49 | R | 69 |

It can be seen that very low enantioselectivity was observed with all ketone reductions. This can be explained as follows. In this trans isomer, the -OH and -NHR groups are away compared to that in a cis isomer, so the complex formed may not be very stable. This will decompose rapidly facilitating free borane reduction, thus lowering the enantioselectivity of the reaction.

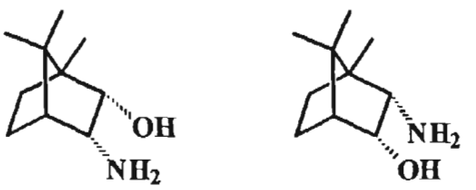
# PART III

## 3.3 ASYMMETRIC BORANE REDUCTION USING OXAZABOROLIDINES DERIVED FROM 1,2-AMINO ALCOHOLS OF (1R)-(+)-CAMPHOR AS CATALYSTS

When we carried out the asymmetric reduction using oxazaborolidines derived from amino alcohol derivatives of (1R)-(+)-Camphor we obtained products with low enantioselectivity than expected. With this results in hand we synthesized oxazaborolidines from 1,2-amino alcohols of (1R)-(+)-Camphor. These were prepared *in situ* by the reaction of amino alcohol with borane or trimethyl borate and used as catalysts for the asymmetric borane reductions

### 3.3.1 Catalysts derived from cis *endo-endo* amino alcohols

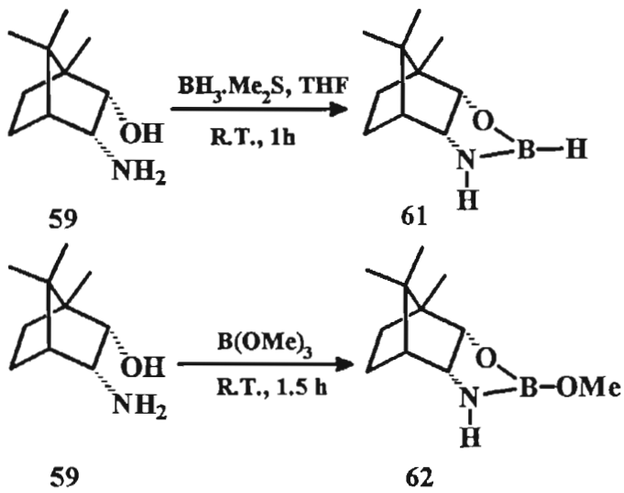
The catalyst precursors selected for the study are given in figure 3.9.




59 60

**Figure 3.9**

The method of preparation and the probable structures of the catalysts used in the study are given in scheme 3.37.

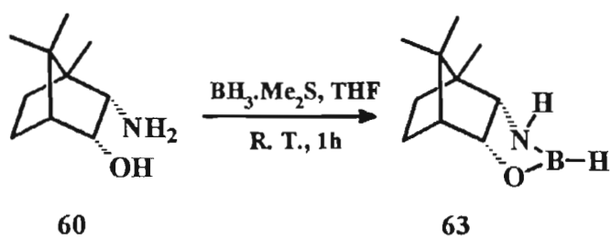



59 61

59 62

**Scheme 3.37**

Similarly catalyst was also prepared from the 2-*endo*-amino-3-*endo*-hydroxybornanol (Scheme 3.38).

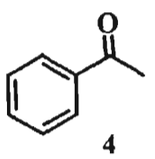
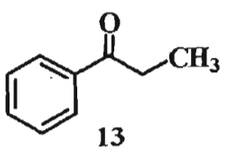
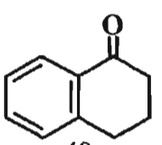
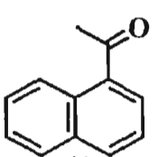
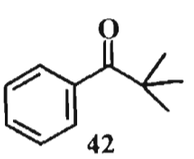
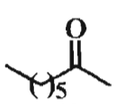



60 63

**Scheme 3.38**

The results obtained for the asymmetric reduction of ketones are summarized in tables 3.16 and 3.17.

**Table 3.16** Asymmetric reduction of ketones using oxazaborolidines derived from cis *endo*-amino-*endo* hydroxybornanols as catalysts.

| Entry | Ketone | Catalyst | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **4** | **61** | 93 | R | 84 |
| 2 | | **62** | 78 | R | 86 |
| 3 | | **63** | 2 | S | 71 |
| 4 |  **13** | **61** | 86 | R | 93 |
| 5 | | **62** | 43 | R | 90 |
| 6 | | **63** | 0.7 | S | 88 |
| 7 |  **40** | **61** | 74 | R | 95 |
| 8 | | **62** | 71 | R | 97 |
| 9 | | **63** | 8 | S | 81 |
| 10 |  **41** | **61** | 90 | R | 78 |
| 11 | | **62** | 68 | R | 74 |
| 12 | | **63** | 0.9 | S | 81 |
| 13 |  **42** | **61** | 59 | R | 84 |
| 14 | | **62** | 49 | R | 80 |
| 15 |  **43** | **61** | 85 | R | 73 |
| 16 | | **62** | 58 | R | 70 |
| 17 | | **63** | 9 | S | 69 |

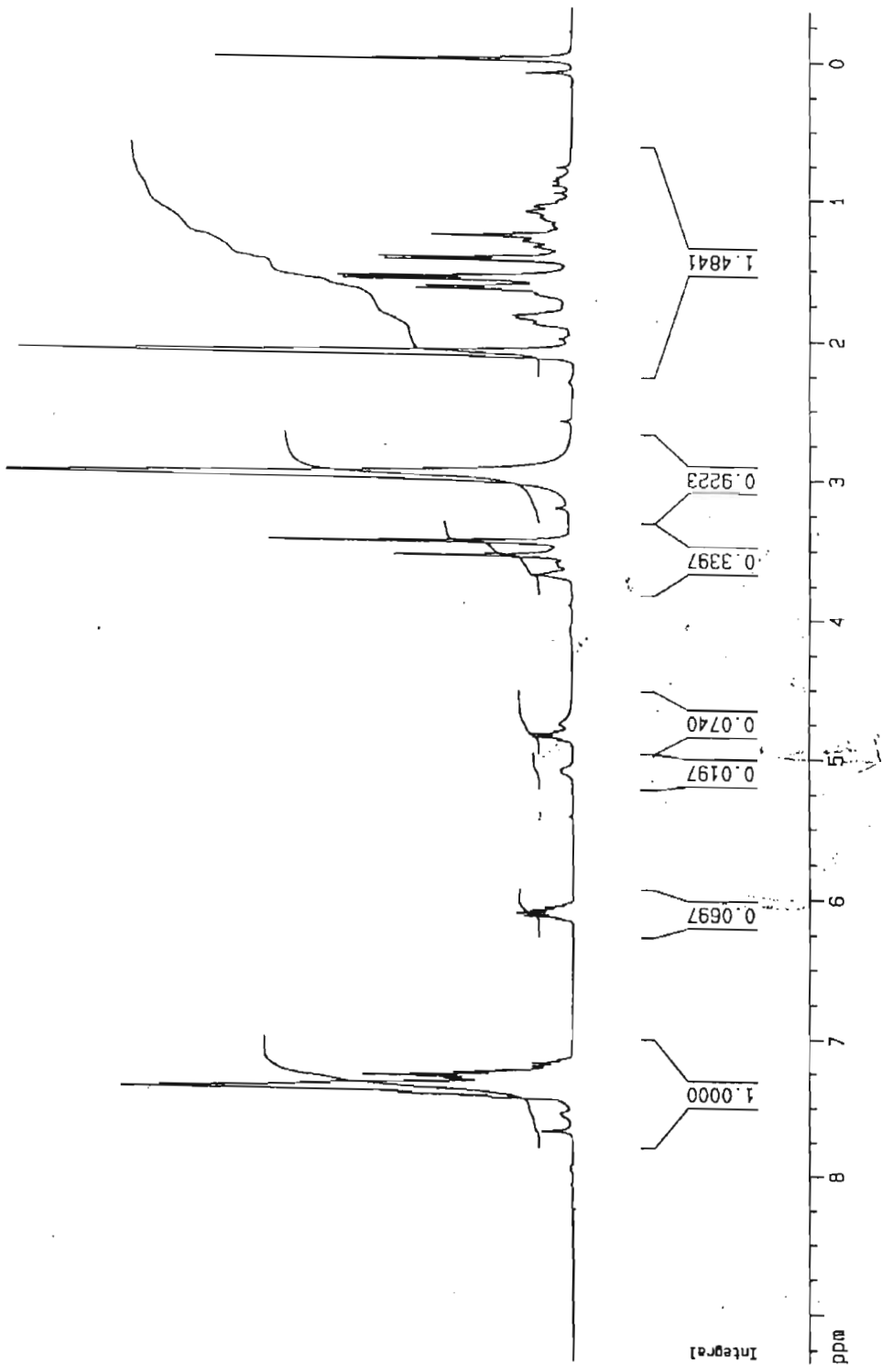



Figure 3.10 300 MHz $^{1}$H NMR spectrum of MTPA ester of racemic 1-phenylethanol.

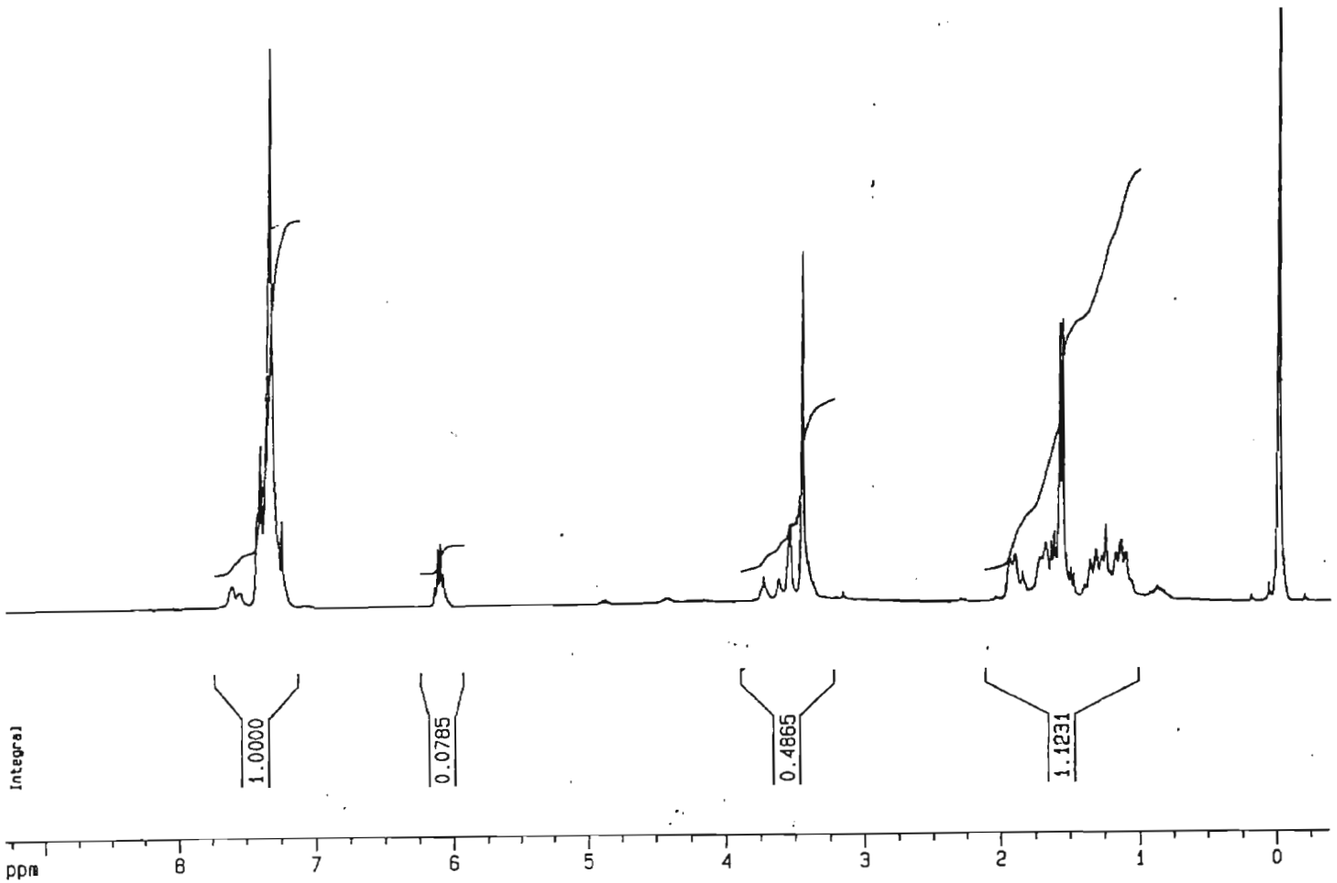
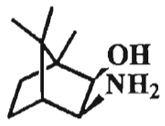



Figure 3.11 300 MHz $^{1}H$ NMR spectrum of MTPA ester of 1-phenylethanol (obtained from the cis-3-*endo*-amino-*2-endo* hydroxybornanol and borane derived oxazaborolidine catalyzed reduction)

It is evident from the above table that the cis *endo-endo* amino alcohol and borane derived oxazaborolidine is found to be an efficient catalyst for the asymmetric reduction of ketones. The configuration of the products in all cases were found to be R. The very low value of enantioselectivity observed with cis 2-*endo*-amino-3-*endo*-hydroxybornane can be explained on the basis of the steric factors. The free borane cannot coordinate with the nitrogen atom of the oxazaborolidine moiety because of the steric repulsion of the methyl group on the camphor skeleton thus facilitating free borane reduction.

### 3.3.2 Catalysts derived from cis *exo-exo* amino alcohol

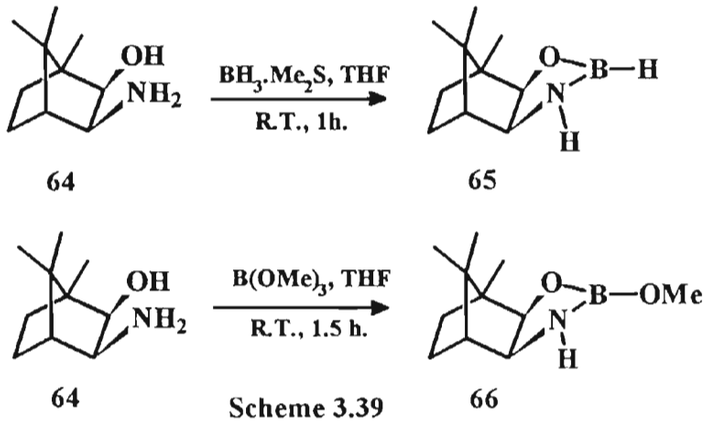
The amino alcohol selected for the oxazaborolidine synthesis is given in fig.3.12.




64

**Figure 3.12**

The method of preparation and the probable structures of the catalysts used in the study are given in scheme 3.39.



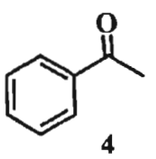
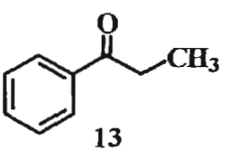
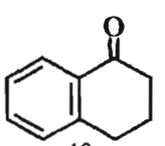
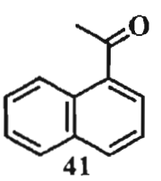
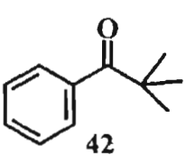
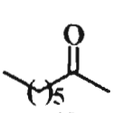

64 65

64 66

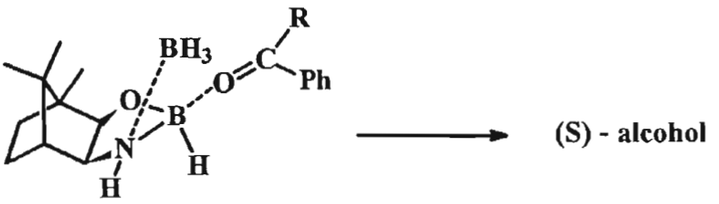
**Scheme 3.39**

The results obtained for the asymmetric reduction of ketones are given in table 3.17

**Table 3.17** Asymmetric reduction of ketones using oxazaborolidines derived from cis *exo*-amino-*exo*-hydroxybornanol as catalysts.

| Entry | Ketone | Catalyst | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **4** | **65** | 79 | S | 94 |
| 2 | | **66** | 56 | S | 70 |
| 3 |  **13** | **65** | 68 | S | 70 |
| 4 | | **66** | 41 | S | 83 |
| 5 |  **40** | **65** | 63 | S | 98 |
| 6 | | **66** | 47 | S | 91 |
| 7 |  **41** | **65** | 78 | S | 85 |
| 8 | | **66** | 50 | S | 63 |
| 9 |  **42** | **65** | 74 | S | 79 |
| 10 | | **66** | 59 | S | 70 |
| 11 |  **43** | **65** | 69 | S | 88 |
| 12 | | **66** | 62 | S | 79 |

In the case of cis *exo-exo* amino alcohol derived oxazaborolidine catalyzed reductions, the configuration of the products were found to be S. This can be explained by a transition state **67** in which the oxygen atom of the ketone interacts with the boron atom inorder to minimise the steric repulsion between the phenyl group and the camphor skeleton so that the addition of the borane on the *re* face of the ketone takes place leading to the S alcohol.




67

**Scheme 3.40**

It is noteworthy that higher *ee* values were obtained when amino alcohols with unsubstituted amino group was used for the oxazaborolidine synthesis. In the case of amino alcohols with substituted amino group, the *ee* values were found to be lower. This may be attributed to the non-availability of lone pair on nitrogen and the effect of steric hindrance at the nitrogen part of the oxazaborolidine moiety. The trans *exo-endo* amino alcohols were not used for the oxazaborolidine synthesis as the alcohols prepared were not so pure. The amino alcohols were directly converted to the derivatives and used for the oxazaborolidine synthesis.

The synthesis of amino alcohols and the amino alcohol derivatives were carried out as described in the previous chapter. The secondary alcohols obtained after reduction were identified by IR and NMR spectral studies. The enantiomeric excess of the products were determined by using polarimeter and confirmed by NMR studies of (R)-MTPA ester of the

alcohols.[28] The enantiomeric excess was determined by comparing the optical rotation value with the literature value.[29, 31, 32]

## 3.4 EXPERIMENTAL

A general description of experimental procedure is given in chapter 2 (Section 2.8). Borane $BH_3.Me_2S$ (10M) purchased from Aldrich Chemical Co., USA was made upto 2M using anhydrous THF, and used for the reactions. THF was collected over Na-benzophenone ketyl complex. All reactions were carried out in perfectly dry conditions under inert atmosphere using syringe and septum technique. All ketones were distilled before use.[30] All reactions were carried out at room temperature 25°-30°C unless otherwise mentioned. TLC spots were visualised by iodine vapors.

A typical procedure for the asymmetric reduction using oxazaborolidines is described with 3-*endo*-amino-2-*endo*-hydroxybornane **59** as the starting material.

The amino alcohol (0.033 g, 0.2mmol) was dissolved in 3 mL of dry THF in a three necked R.B. flask fitted with a septum, an argon source and a pressure equalizing funnel. To this 1.5 equiv. of 2M $BH_3.Me_2S$ in THF was added and stirred for 1 h at room temperature. Reaction was monitored by TLC. When the amino alcohol was fully consumed, another 0.7 equiv. of 2 M $BH_3.Me_2S$ was added and the reaction mixture was stirred for another 10 minutes. To this, acetophenone (0.240 g, 2 mmol) in 4 mL THF was added dropwise. The reaction was complete within 2 h as observed by TLC. The excess borane was destroyed by dropwise addition of cold water (2 mL). The reaction mixture was extracted with ether (4 x 5 mL). The organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated. The crude product was then purified on silica gel using

ethylacetate - hexane mixture (2 %) as the eluent to afford the alcohol in 85% yield $[\alpha]_D^{25} = 39.895°$. Literature value 42.9°. This was again confirmed by taking the NMR spectra of the MTPA ester of the alcohol [28] (Figure 2.10 and 2.11).

**1-Phenylethanol (5)**

| | |
|---|---|
| Standard $[\alpha]_D$ for R isomer | : 42.9° (neat) |
| Standard $[\alpha]_D$ for S isomer | : -42.9° (neat) |
| IR ($CCl_4$) $\nu_{max}$ | : 3360, 2967, 1494, 1459, 1207, 1087, 1010, 898, 709 $cm^{-1}$. |
| $^1H$ NMR ($\delta$) | : 7.3 (m, 5H), 4.87 (q, 1H, $J$ = 6 Hz), 1.97 (brs, 1H), 1.48 (d, 3H, $J$ = 6 Hz). |
| MS (m/z) (%) | : 122 (15), 107 (85), 103 (15), 81 (10), 77 (100), 68 (8), 52 (17), 51 (17). |

**1-Phenyl–1-propanol (14)[31]**

| | |
|---|---|
| Standard $[\alpha]_D$ for R isomer | : 33° (C=5, EtOH) |
| Standard $[\alpha]_D$ for S isomer | : -33° (C=5, EtOH) |
| IR ($CCl_4$) $\nu_{max}$ | : 3387, 3043, 2982, 2935, 2881, 1458, 1108, 1027, 973, 919, 764, 724 $cm^{-1}$. |
| $^1H$ NMR ($\delta$) | : 7.28 (m, 5H), 4.55 (t, 1H, $J$ = 6.5 Hz), 2.12 (brs, 1H), 1.7 (m, 2H), 0.895 (t, 3H, $J$ = 7.4 Hz). |
| MS (m/z) (%) | : 137 (2), 136 (20), 119 (15), 118 (15), 117 (35), 115 (30), 107 (70), 105 (3), 91 (12), 79 (100), 77 (65), 65 (5), 53 (5), 43 (10). |

**1,2,3,4-Tetrahydro-1-naphthol (47)**

Standard $[\alpha]_D$ for R isomer : -32° (c=2.5, $CHCl_3$)

Standard $[\alpha]_D$ for S isomer : 32° (c=2.5, $CHCl_3$)

IR ($CCl_4$) $\nu_{max}$ : 3346, 3070, 3029, 2935, 2861, 1593, 1452, 1276, 1074, 1040, 960, 744 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 7.1 (m, 4H), 4.60 (s, 1H), 2.6 (m, 2H), 2.21 (brs, 1H), 1.72 (m, 4H).

**α–Methyl-1-naphthalenemethanol (48)**

Standard $[\alpha]_D$ for R isomer : 78° (c=1, $CH_3OH$)

Standard $[\alpha]_D$ for S isomer : -78° (c=1, $CH_3OH$)

IR ($CCl_4$) $\nu_{max}$ : 3360, 3056, 2982, 2928, 1593, 1378, 1270, 1121, 1074, 1020, 906, 798, 791 $cm^1$.

$^1H$ NMR ($\delta$) : 7.58 (m, 7H), 5.57 (q, 1H, $J$ = 6.33 Hz), 1.9 (brs, 1H), 1.58 (d, 3H, $J$ = 6.4 Hz).

**2-Octanol (49)**

Standard $[\alpha]_D$ for R isomer : -9.5° (neat)

Standard $[\alpha]_D$ for S isomer : 9.5° (neat)

IR ($CCl_4$) $\nu_{max}$ : 3339, 2962, 2928, 2861, 1472, 1384, 1128, 1074 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 3.76 (m, 1H), 1.73 (s, 1H), 1.34 (m, 10H), 1.16 (m, 3H), 0.88 (m, 3H).

**2, 2-Dimethyl -1-phenyl -1-propanol (64)**[32]

Standard $[\alpha]_D$ for R isomer : -22.9° (c=2, $CHCl_3$)

Standard $[\alpha]_D$ for S isomer : 22.9° (c=2, $CHCl_3$)

IR ($CCl_4$) $\nu_{max}$ : 3447, 2969, 2881, 1492, 1465, 1378, 1061, 1018, 751, 724, 548 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 7.26 (m, 5H), 4.38 (s, 1H), 1.85 (brs, 1H), 0.92 (s, 9H).

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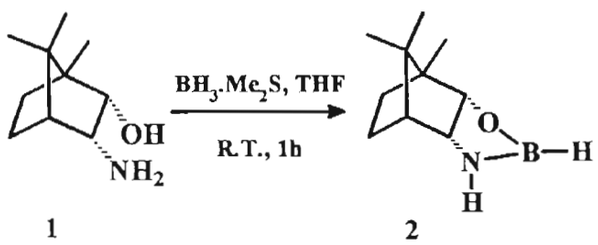
# CHAPTER 4

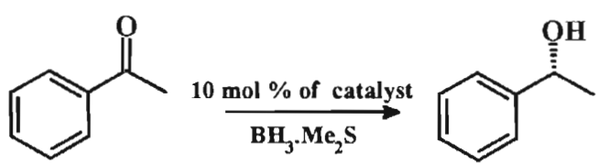
# EFFECT OF VARIOUS PARAMETERS ON ASYMMETRIC KETONE REDUCTION

## 4.1 INTRODUCTION

The results presented in the third chapter demonstrated the relation between the structure of the catalyst and the enantioselectivity of the product. The structure of the catalyst thus plays an important role in determining the stereoselectivity of the reaction. Besides this, other factors such as solvent, temperature of the reaction, and the catalyst substrate ratio also influence the enantioselectivity of the reduction. Herein we report, the effect of these parameters on the asymmetric reduction of acetophenone and the results of this systematic and indepth investigations are presented in the following sections. Among the various catalysts used, the catalyst **2** synthesized from the *endo-endo* amino alcohol and borane was found to give high enatioselectivities. So this catalyst was taken as a model catalyst to study the effect of various parameters on the asymmetric reduction of acetophenone (Scheme 4.1).




1 2




3 4

**Scheme 4.1**

## 4.2 EFFECT OF SOLVENT

The dielectric constant is a measure of both the dipole moment and the polarizability. It is a good indicator of the ability of the solvent to accommodate the separation of charges.

Two types of ion pairs are found in organic reactions. They are the loose external or solvent separated ion pairs and the tight internal or intimate ion pairs. In solvents, the solvated free ions can approach its counter ion without difficulty when the two solvation shells touch forming the loose ion pair. When the two ion shells can come even closer a contact ion pair is formed. The tight or contact ion pair usually shows high stereospecificity.[1] The solvents with low dielectric constant which do not solvate the ions much, tend to increase the stereoselectivities by allowing the formation of tight ion pairs. In order to study the solvent effect, the asymmetric reduction

of acetophenone was carried out in different solvents of varying dielectric constants. The results are shown in table 4.1.

**Table 4.1** Effect of solvent on asymmetric ketone reduction.

| Entry | Solvent | Dielectric constant | *ee* (%) | Yield (%) |
|---|---|---|---|---|
| 1 | Dichloromethane | 9.1 | 31 | 75 |
| 2 | Tetrahydrofuran | 7.6 | 85 | 93 |
| 3 | Chloroform | 4.8 | 11 | 86 |
| 4 | Diethyl ether | 4.3 | 23 | 98 |
| 5 | Toluene | 2.38 | 11 | 84 |
| 6 | Benzene | 2.32 | 18 | 73 |
| 7 | Carbon tetrachloride | 2.24 | 39 | 75 |
| 8 | Hexane | 1.9 | 25 | 78 |

We expected the enantioselectivity to decrease with increasing solvent polarity. But no specific relationship between the enantioselectivity of the product and dielectric constant was observed. When the reaction was carried out in solvents other than THF low enantioselectivity of the product was obtained confirming the need of a donor type solvent like THF for the reduction. Eventhough many oxazaborolidine reductions in literature used toluene as the solvent[2], very low *ee* of the product was obtained with toluene in this reduction. In the chlorinated solvents $CH_2Cl_2$ and $CCl_4$ moderate *ee* of the product was obtained. These experiments clearly indicate that the solvent plays an important role in determining the enantioselectivity of the product in the oxazaborolidine catalyzed asymmetric reduction of ketones.

## 4.3 EFFECT OF TEMPERATURE

The early reports on the effect of temperature on oxazaborolidine catalyzed reductions show a decrease in the enantioselectivity of the product with the decrease of temperature.[3] We carried out the oxazaborolidine reduction of acetophenone at various temperatures in order to study the effect of temperature on the enantioselectivity of the ketone reduction. The results are summarized in table 4.2.

**Table 4.2** Effect of temperature on asymmetric ketone reduction.

| Entry | Temperature (°C) | *ee* (%) | Yield (%) |
|---|---|---|---|
| 1 | -78 | 50 | 45 |
| 2 | 0 - 10 | 65 | 76 |
| 3 | R.T. (25) | 85 | 93 |
| 4 | 65 | 6 | 80 |

It is evident from the study that good enantioselectivity is obtained only at room temperature. At -78°C and at 65°C reaction leads to low *ee* of the product. The catalyst may not be stable at 65°C and at -78°C the catalyst formation may be slow. In such cases, free borane reduction may occur at a faster rate leading to low enantioselectivity of the product. At low temperature like -78° the rate of reaction may be slow leading to low yield and low enantioselectivity of the product.

## 4.4 EFFECT OF CATALYST - SUBSTRATE RATIO

Increasing the concentration of the catalyst to substrate is known to increase the asymmetric induction in some cases. The effect of catalyst concentration on the enantioselectivity of the acetophenone reduction was

studied by employing 1, 5, 10 and 20 mol % of the catalyst for the reduction in THF. The results are tabulated in table 4.3.

**Table 4.3** Effect of catalyst concentration on asymmetric ketone reduction.

| Entry | Catalyst mol (%) | *ee* (%) | Yield (%) |
|---|---|---|---|
| 1 | 0 | 0 | 99 |
| 2 | 1 | 79 | 78 |
| 3 | 5 | 80 | 69 |
| 4 | 10 | 85 | 93 |
| 5 | 20 | 76 | 86 |

It can be concluded from the study that good *ee* is obtained using 10 mol % of the catalyst.

## 4.5 EFFECT OF REDUCING AGENTS

In all the above mentioned oxazaborolidine catalysed reductions, borane was used as the stoichiometric reductant. In order to study the effect of reducing agents on enantioselectivity of reduction, other boranes such as 9-BBN, (+)-$(IPC)_2BH$, (+)-$(IPC)BH_2$ were used as the stoichiometric reductant and the results are summarized in table 4.4.

**Table 4.4** Effect of reducing agents on asymmetric ketone reduction

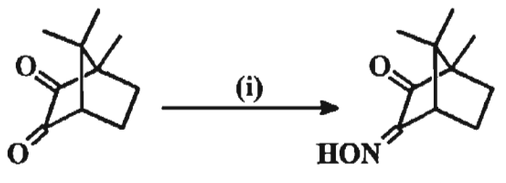
| Entry | Reducing agent | Reaction time (h) | *ee* (%)[a] | *ee* (%)[b] | Yield (%) |
|---|---|---|---|---|---|
| 1 | 9-BBN | 6 | 66 | - | 91 |
| 2 | $(IPC)_2BH$ | 12 | 31.8 | 9 | 80 |
| 3 | $(IPC)BH_2$ | 12 | 57 | 15 | 86 |

a *ee* obtained when used as reducing agent along with oxazaborolidine catalyst b *ee* obtained when used as reducing agent without the catalyst.

(+)-$(IPC)_2BH$, (+)-$(IPC)BH_2$ developed by H. C. Brown from (1S)-(-)-($\alpha$)-Pinene were found to be effective reagents for asymmetric hydroboration.[6] But they were found to be less effective for asymmetric reduction of ketones. [5, 6] From the table 4.4, it is evident that better enantioselectivities of the product is obtained when these boranes are used along with oxazaborolidine catalyst. The $(IPC)_2BH$, $(IPC)BH_2$ were prepared by reported procedures[7, 8] and stoichiometric amounts were used for the reduction. 9-BBN being a sterically crowded borane is found to enhance the enantioselectivity of reduction.

## 4.6 ASYMMETRIC BORANE REDUCTION USING OXAZABOROLIDINES DERIVED FROM (1S)-(-)-CAMPHOR AMINO ALCOHOLS AS CATALYSTS

To study the effect of configuration of the catalyst on the enantioselectivity of reduction, we carried out experiments with oxazaborolidines derived from (-)-aminohydroxybornanes. The (1S)- (+)-camphor quinone **5** was converted to 3-hydroximinobornanone **6** (Scheme 4. 2).[4]

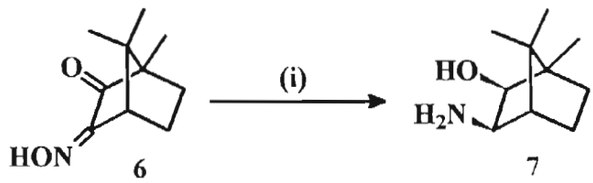



**5** **6**

**(i) $NH_2OH.HCl$, $CH_3COONa$, MeOH, 65° C, 2**

**Scheme 4.2**

LAH reduction of **6** afforded (-)-cis-3-*exo*- amino-2-*exo*-hydroxybornane **7** (Scheme 4.3).

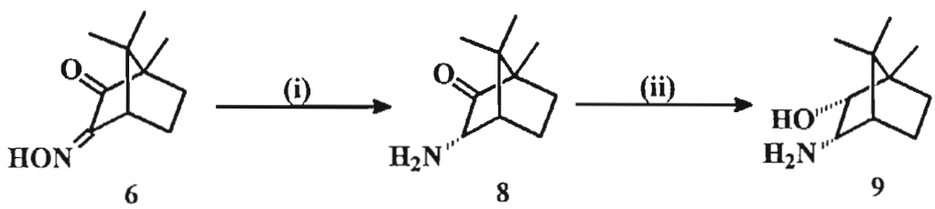



6 7

**(i) LAH, Ether, R. T., 24 h**

**Scheme 4.3**

(-)-3-hydroximinobornanone **6** was transformed to (-) cis 3-*endo*-amino-2-*endo*-hydroxybornane **9** by Zn / NaOH reduction followed by LAH reduction. (Scheme 4.4).

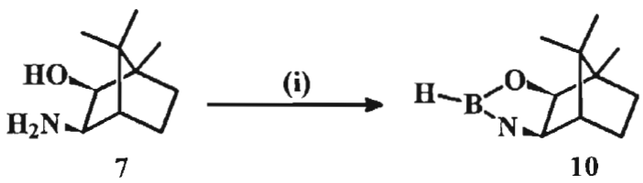



6 8 9

**(i) Zn / NaOH, R. T., 1 h**
**(ii) LAH, Ether, R. T., 24 h**

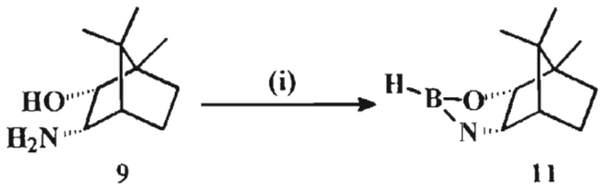
**Scheme 4.4**

The oxazaborolidines were generated *in situ* from these amino alcohols by treatment with borane and reduction of acetophenone was carried out (Scheme 4.5).




7 10

**(i) $BH_3$.THF, THF, R. T., 2 h**




9 11

(i) $BH_3$.THF, THF, R. T., 2 h

**Scheme 4.5**

The results are summarized in the table 4.5.

**Table 4.5** Effect of configuration of the catalyst on asymmetric ketone reduction

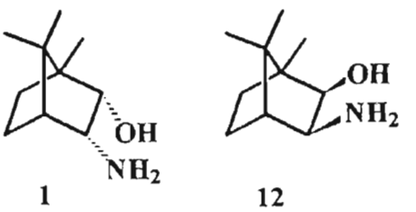
| Entry | Catalyst | Observed $[\alpha]_D$ | *ee* (%) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | **10** | 18.087° | 42 | R | 78 |
| 2 | **11** | -20.008° | 46 | S | 76 |

It can be seen from the results that we are getting products with opposite configuration as to that obtained with (1R)-(+)-camphor derived oxazaborolidine catalyzed reductions.

## 4.7 ASYMMETRIC REDUCTION OF ACETOPHENONE USING HYDRIDE REAGENTS MODIFIED WITH AMINO ALCOHOLS DERIVED FROM (1R)-(+)-CAMPHOR

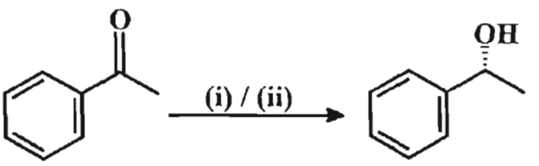
As mentioned earlier in chapter 3 (Part 1), prochiral ketones can be reduced with hydride reagents modified with chiral alcohols, amines, amino alcohols, diamines etc.[9] Though a number of amino alcohols were used, the 1,2-amino alcohols derived from (1R)-(+)-camphor have not been used as chiral modifier for hydride reagents. In this section the results of a study on

the asymmetric reduction of acetophenone using LAH and $NaBH_4$ modified with cis 3-*endo*-amino-3-*endo*-hydroxybornane **1** and cis 3-*exo*-amino-3-*exo*-hydroxybornane **12** are presented in table 4.6.




**1** **12**

**Figure 4.1**




**3** **4**

**(i) 1 / 12, LAH, 1.1 equiv., THF, R. T., 4 h**

**(i) 1 / 12, $NaBH_4$, 1.1 equiv., THF, R. T., 6 h**

**Scheme 4.6**

**Table 4.6** Asymmetric reduction of ketone using chirally modified hydride reagents

| Entry | Amino alcohol | Hydride reagent | $[\alpha]_D$ observed | *ee* (%) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **1** | LAH | 23.253 | 54 | 76 |
| 2 | **12** | LAH | 20.628 | 48 | 83 |
| 3 | **1** | $NaBH_4$ | 25.139 | 58 | 86 |
| 4 | **12** | $NaBH_4$ | 18.283 | 42 | 82 |

In all these reductions, products with R configuration were obtained. Earlier in the oxazaborolidine catalyzed reductions, the *endo-endo* amino alcohol derived catalysts afforded products with R configuration while *exo-exo* amino alcohol derived catalysts afforded products with S configuration. In the present case no such difference was observed.

## 4.8 EXPERIMENTAL

A general description of experimental procedure is given in chapter 2 (Section 2.8) and in chapter 3 (Section 3.10). (1S)-(+)-Camphor quinone, 9-BBN dimer, (1S)-(-)-α-pinene (99 %), observed $(\alpha)_D^{27}$ = -51.902 (c, 1.242, $CHCl_3$), reported $(\alpha)_D^{20}$ = -50.7° (neat) were purchased from Aldrich Chemical Co., USA. All reactions were carried out under argon atmosphere with oven-dried glassware.

### (1S)-(-)-3-Hydroximinocamphor (6)

(1S)-(+)-Camphor quinone (0.1g, 0.602 mmol) was dissolved in 4 mL methanol. To this, hydroxylamine hydrochloride (0.05 g, 0.72 mmol) and sodium acetate (0.123 g, 0.903 mmol) dissolved in 5 mL water was added and refluxed for 2 h. The reaction mixture was then cooled to room temperature and extracted with ether (4 x 5 mL). The organic layer was then washed with saturated $NaHCO_3$ solution, water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was then purifed by passing through a silica gel column using 5% ethylacetate - hexane mixture to get a white solid (0.09 g, 82 %). The solid obtained was then recrystallized from hexane - dichloromethane solvent system.

m. p. : 149 - 151 °C

IR (KBr) $\nu_{max}$ : 3420, 2962, 2928, 2881, 1742, 1654, 1458, 1404, 1378, 1303, 1189, 1081, 1013, 933, 906, 865, 724 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 9.44 (brs, 1H), 2.05 (m, 1H), 1.8 (m, 2H), 1.57 (m, 2H), 1.00 (s, 3H), 1.92 (s, 3H), 0.89 (s, 3H).

$^{13}C$ NMR ($\delta$) : 204.67, 204.03, 159.62, 58.61, 49.67, 46.75, 45.05, 30.83, 30.09, 25.17, 23.93, 20.85, 20.74, 18.18, 17.83, 9.12, 8.60.

MS (m/z) : 181 (60), 164 (10), 136 (100), 120 (45), 109 (40), 95 (15), 91 (15), 82 (20), 67 (25), 55 (30). There were two peaks in GC with area 50.34 % and 49.66 %.

**3-*exo*-amino-2-*exo*-hydroxybornane (7)**

3-Hydroximinocamphor (0.1 g, 0.55 mmol) dissolved in 5 mL dry THF was added dropwise to a suspension of LAH (0.049 g, 1.38 mmol) in 5 mL THF and refluxed for 24h. The reaction on completion, was cooled to room temperature and the excess LAH was destroyed by the addition of 10 % NaOH solution (1 mL) followed by addition of cold water. It was then filtered and the precipitate was washed several times with ether. The organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the product (0.065 g, 71 %) as a viscous solid.

$[\alpha]_D^{27}$ : (c=0.76, $CHCl_3$) -35.847°

IR ($CCl_4$) $\nu_{max}$ : 3265, 2962, 2928, 2874, 1655, 1431, 1344, 1373, 1366, 1081, 1007, 960, 804 $cm^{-1}$.

$^1H$ NMR ($\delta$) : 3.9 (s, 1H), 3.03 (s, 1H), 1.72 (m, 5H), 1.24 (m, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H).

$^{13}$C NMR (δ) : 77.76, 62.9, 57.3, 49.1, 46.86, 32.74, 29.64, 21.56, 18.39, 11.27.

**3-*endo*-amino-2-*endo*-hydroxybornane (9)**

3-hydroximinocamphor (0.1 g, 0.55 mmol) was dissolved in 30 % NaOH solution (2 mL). To this zinc dust (0.072 g, 1.1mmol) was added slowly and was stirred for 30 minutes. The reaction on completion, as noted by TLC, was extracted with dichloromethane (3 x 5 mL). The organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get a pale yellow oil (0.065 g, 60 %). This was used for the next step without further purification.

A solution 3-*endo*-amino camphor (0.060 g, 0.36 mmol) in 2 mL dry ether was added dropwise to a suspension of LAH (0.0259 g, 0.72 mmol) in 5 mL ether and stirred for 12 h. at room temperature. The excess LAH was then destroyed by the addition of 10 % NaOH solution
(1 mL). The ether layer was decanted and the residue was washed several times with ether. The organic layers were collected, washed with water, brine, dried over $Na_2SO_4$ and concentrated. The crude product was purified on a neutral alumina column using methanol - chloroform (5 %) as eluent to get the pure product. (0.035 g, 57 %)

$[\alpha]_D^{27}$ : (c=0.4, $CHCl_3$) -31.138°

IR ($CCl_4$) $\nu_{max}$ : 3366, 2949, 2924, 2874, 1645, 1507, 1445, 1389, 1365, 1089, 1034, 789 $cm^{-1}$.

$^1$H NMR (δ) : 3.4 (m, 3H), 3.1 (s, 1H), 1.52 (m, 6H), 1.01 (s, 3H), 0.91 (s, 3H), 0.75 (s, 3H).

$^{13}$C NMR (δ) : 77.5, 62.64, 57.49, 49.39, 48.94, 34.04, 29.96, 21.65, 18.60, 11.45.

**Procedure for asymmetric ketone reduction using 9-BBN as reducing agent**

The cis-3-*endo*-amino-2-*endo*-hydroxybornane (0.017 g, 0.1mmol) was dissolved in 3 mL of dry THF in a three necked R.B. flask fitted with a septum, an argon source and a pressure equalizing funnel. To this 1.5 equiv. of 2M $BH_3.Me_2S$ in THF was added and stirred for one hour at room temperature. Reaction was monitored by TLC. When the amino alcohol fully consumed, to the *in situ* generated oxazaborolidine, 9-BBN dimer (0.268 g, 1.1 mmol) dissolved in 3 mL dry THF was added and stirred for 10 min. To this, acetophenone (0.120 g, 1 mmol) in 4 mL THF was added dropwise. The reaction was stirred for 6 h and the excess 9-BBN was destroyed by the addition of cold water (2 mL). The reaction mixture was extracted with ether (4 x 5 mL). The organic layers were pooled together, washed with water, brine, dried over $Na_2SO_4$ and concentrated. The crude product was then purified on silica gel using ethylacetate - hexane mixture (2 %) as the eluent to get the alcohol (0.122 g, 91 %) $[\alpha]_D$= 28.212°. Literature value for optically pure (R)-1-phenylethanol = 42.9°.

**Procedure for asymmetric ketone reduction using $(IPC)_2BH$ as reducing agent**

The oxazaborolidine was generated *in situ* as reported in the above procedure. (+)-$(IPC)_2BH$ was prepared using the reported procedure from (1S)-(-)-(α)-pinene.[7] To the oxazaborolidine generated, $(IPC)_2BH$ ( 0.625 g,

2.2 mmol) is added and stirred well for 10 min. To this acetophenone (0.120 g, 1 mmol) in 3 mL THF was added, and stirred overnight. The excess $(IPC)_2BH$ was destroyed by the addition of cold water, reaction mixture was extracted with ether. The organic layers were collected together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was then purified as in the above experiment (0.097 g, 80 %), $[\alpha]_D = 13.662°$.

**Procedure for asymmetric ketone reduction using (+)-(IPC)$BH_2$ as reducing agent**

The oxazaborolidine was generated *in situ* as reported in the above procedure. (+)-(IPC)$BH_2$ was prepared using the reported procedure from (1S)-(-)-(α)-pinene.[8] To the oxazaborolidine generated, (IPC)$BH_2$ (0.178 g, 1.2 mL of 1M solution in THF, 1.2 mmol) is added and stirred well for 10 min. To this, acetophenone (0.120 g, 1 mmol) in 3 mL THF was added, and stirred overnight. The excess (IPC)$BH_2$ was destroyed by the addition of cold water, and the reaction mixture was extracted with ether. The organic layers were collected together, washed with water, brine, dried over $Na_2SO_4$ and concentrated to get the crude product. This was then purified as in the above experiment (0.104 g, 86 %), $[\alpha]_D = 24.991°$.

**General procedure for hydride reductions**

Cis-3-*endo*-amino-2-*endo*-hydroxybornane (0.169 g, 1mmol) dissolved in 2 mL dry THF was added to a suspension of LAH (0.04 g, 1.1 mmol) in 3 mL dry THF under inert conditions. This was allowed to stir for 10 minutes. To this, acetophenone (0.120 g, 1 mmol) dissolved in 2 ml dry

THF was added dropwise and stirred. When the reaction was complete, the excess LAH was destroyed by adding cold water. This was then extracted with ether and usual work up yielded the crude alcohol, which was then purified on a silica gel column using ethylacetate – hexane (2 %) as eluent to get the pure alcohol (0.092 g, 76 %).

## 4.9 REFERENCES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# SUMMARY

This thesis entitled as *"ASYMMETRIC CATALYSIS USING CHIRAL OXAZABOROLIDINES"* embodies the results of our investigation undertaken to study the reactivities of oxazaborolidine catalysts derived from (1R)-(+)-camphor in the enantioselective reduction of prochiral ketones.

A general introduction to the asymmetric synthesis and a brief overview of history, synthesis and application in the area of asymmetric synthesis and mechanism of action of oxazaborolidines are given in the first chapter.

The synthesis of 1,2-amino alcohols and amino alcohol derivatives from (1R)-(+)-camphor is dealt in chapter 2. Of the possible eight isomers of amino alcohols derived from (1R)-(+)-camphor five amino alcohols were synthesized. The literature procedures were modified wherever it is necessary to improve the yields. The cis *endo-endo*, cis *exo-exo*, trans *exo endo* amino alcohols were prepared. These were transformed to benzylamino and naphthylmethylamino derivatives by treating with the corresponding aldehyde and reducing the imine formed. The derivatives were obtained in moderate yields and all the derivatives have been characterized by spectral data. The purities of the amino alcohols and amino alcohol derivatives were checked by NMR spectra of recrystallized samples in the case of solids. The purities were further confirmed by taking the optical rotation of the samples repeatedly to a constant value.

The third chapter deals with the synthesis of oxazaborolidines from 1,2-amino alcohols of camphor. The chapter consists of three parts. In the first part a brief review on the methods available in literature for the enantioselective reduction of ketones is given. Part II deals with the asymmetric reduction of prochiral ketones catalyzed by the *in situ* generated oxazaborolidines derived from amino alcohol derivatives of (1R)-(+)-camphor. The oxazaborolidines were generated by the reaction of the amino alcohol derivatives with borane or trimethyl borate respectively. Moderate to low enantioselectivities of the products were observed in all cases. The catalysts generated from the naphthylmethylamino alcohols and borane **[44b, 45b, 52b, 53b, 57b** and **58b]** catalyzed the reduction of acetophenone and yielded alcohols with % *ee* 70, 25, 52, 27, 21, 35 respectively. Thus these were found to be better catalysts than corresponding benzylamino alcohol analogues **[(44a, 45a, 52a, 53a**, **57a** and **58a]** which yielded alcohols with 39, 27, 37, 21, 19, 38 % *ee* for the same reduction. Among the naphthylmethylamino hydroxybornanes the compound with *endo-endo* stereochemistry **44b** is found be a good catalyst giving an *ee* of the products in the range 50-80 %. The enantiomeric excess of the products were determined by using polarimetry. The enantiomeric excesses obtained were further confirmed by taking the NMR spectra of the corresponding MTPA esters. All catalysts yielded products with R configuration. The formation of this was explained by transition state diagrams. Catalysts **[46a and 46b]** were found to be poor catalysts than others.

Part 3 of chapter III deals with the above mentioned reductions catalyzed by the *in situ* generated oxazaborolidines from cis *endo-endo*, cis *exo-exo* amino alcohols of (1R)-(+)-camphor. The oxazaborolidines were

generated by the reaction of amino alcohols with borane or trimethyl borate. It was found that the *endo-endo* amino alcohol and borane derived catalyst **61** which catalyzed the acetophenone reduction to yield alcohol with 93 % *ee* is a good catalyst for the reduction followed by corresponding *exo-exo* analogue **65** which yielded alcohol with 79 % *ee*. The -B(OMe) substituted oxazaborolidines **62** (78 % *ee*) and **66** (56 % *ee*) showed somewhat lower catalytic activity than the BH oxazaborolidines. The configuration of the products are R when cis *endo-endo* amino alcohol derived catalysts were used, and as of S configuration when cis *exo-exo* amino alcohol derived catalysts were used. Attempts to isolate the catalysts were unsuccessful due to its highly decomposing nature.

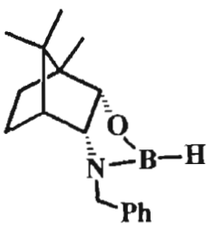
The fourth chapter deals with the effect of parameters such as temperature, medium of reaction, catalyst substrate ratio and nature of reducing agents on the enantioselectivity of asymmetric ketone reduction. The catalyst **61** synthesized *in situ* from cis *endo-endo* amino alcohol and borane was taken as the model catalyst and acetophenone was taken as model ketone for these studies. Solvent was found to play an important role in the enantioselectivity of reduction products, but no specific relationship between the enantioselectivity and dielectric constant of the solvent was observed. Moderate enantioselectivity was observed in THF, confirming the need of a donor type solvent for the reduction. When the reduction was carried out at different temperatures maximum enantioselectivity of the product was obtained at room temperature (25° C). At –78° C and at 65° C, low enantioselectivity was observed. The catalyst concentration also found to affect the enantioselectivity of the product, but not much variation was observed. The effect of reducing agents on enantioselectivity of reduction

was also studied by carrying out the reduction with different reducing agents such as 9-BBN, (+)-$(IPC)_2BH$, (+)-$(IPC)BH_2$. $(IPC)_2BH$, $(IPC)BH_2$ were found to reduce ketones with low enantioselectivity (9 % and 15 % *ee* respectively, but in combination with the oxazaborolidine catalyst better enantioselectivity of the product was observed (31 % and 57 % *ee* respectively). The enantioselectivity of the product 1-phenylethanol has enhanced by 3-4 times in the oxazaborolidine catalyzed reductions. In order to study the effect of configuration of the catalyst on the enantioselectivity of reduction, cis amino alcohols from (1S)-(-)-camphor were prepared and used for the oxazaborolidine synthesis. Asymmetric reduction of acetophenone was performed with the *in situ* generated oxazaborolidines. As expected alcohols with reverse configuration as that obtained from (1R)-(+)-camphor cis amino alcohols were obtained. Asymmetric reduction of acetophenone by hydride reagents modified with chiral 1,2-amino alcohols derived from (1R)-(+)-camphor was also carried out. Products with moderate enantioselectivity and with R configuration were obtained in all cases.

In conclusion the work embodied in the thesis has unraveled a method to synthesize both (R) and (S) secondary alcohols with predictable stereochemistry from prochiral ketones by using chiral catalysts prepared from the readily available and naturally occuring (1R)-(+)-camphor. It is also anticipated that these catalysts developed here may find use in other catalytic asymmetric reactions also.

# APPENDIX

## NEW CHIRAL OXAZABOROLIDINE CATALYSTS PREPARED FROM (1R)-(+)-CAMPHOR

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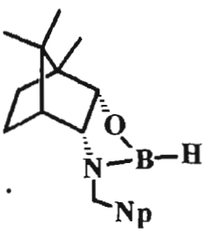


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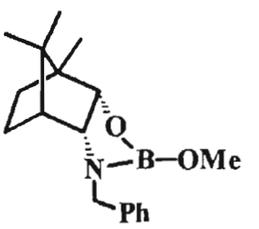


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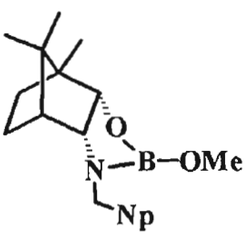


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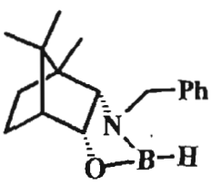


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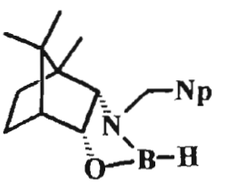


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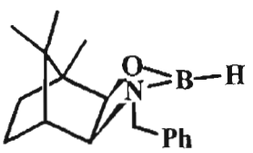


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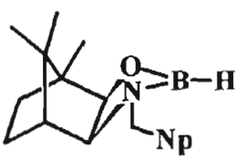


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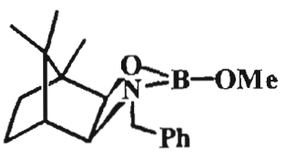


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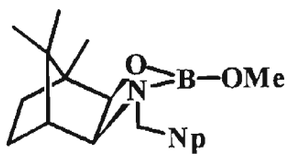


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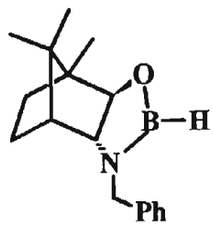


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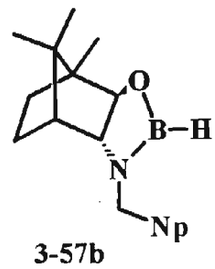


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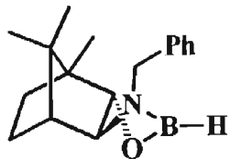


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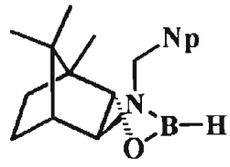


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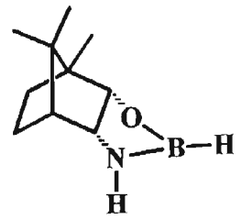


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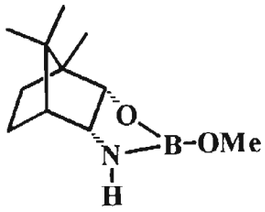


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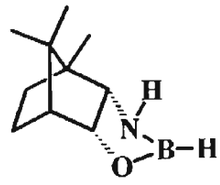


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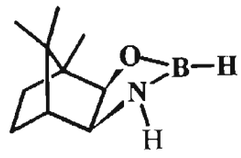


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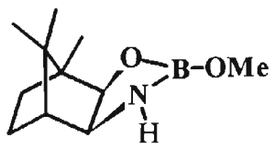


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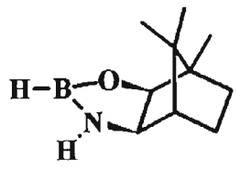
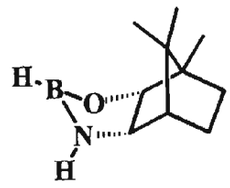



4-10




4-11

## LIST OF PUBLICATIONS AND POSTERS PRESENTED AT VARIOUS SYMPOSIA

1. **V. Santhi** and J. Madhusudana Rao. "*Asymmetric reduction of ketones using in situ generated oxazaborolidines from (1R)-(+)-camphor as catalysts*". **Tetrahedron Asymmetry** (Communicated).
2. **V. Santhi** and J. Madhusudana Rao. "*Asymmetric reduction of prochiral ketones using oxazaborolidines derived from (1R)-(+)-camphor as catalysts*". **Tetrahedron Asymmetry** (To be communicated).
3. **V. Santhi** and J. Madhusudana Rao "*Asymmetric reduction of ketones using oxazaborolidines derived from D-camphor*". UGC–DRC National Symposium on Newer Vistas in Synthetic Protocols and Structural Elucidation in Chemistry held at Madurai, April 22-24, 1998, Poster # P.12.
4. **V. Santhi** and J. Madhusudana Rao. "*Asymmetric reduction of ketones using oxazaborolidines derived from amino alcohol deivatives of D-camphor*". National Symposium in Chemistry held at Bangalore, Jan. 27-30, 1999, Poster # PS 1-58.