DEVELOPMENT OF NEW ORGANIC SYNTHETIC METHODS BASED ON BORANE, CATECHOLBORANE REAGENTS AND RESOLUTION OF RACEMIC DIOLS

A THESIS
SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

APPANA S. BHANU PRASAD

SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD - 500 046
INDIA

Dedicated to

my father

CONTENTS

STATEMENT

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

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

A.S. BHANU PRASAD

CERTIFICATE

Certified that the work contained in this thesis entitled **'Development of New Organic Synthetic Methods Based on Borane, Catecholborane Reagents and Resolution of Racemic Diols'** has been carried out by Mr. A.S. Bhanu Prasad, under my supervision and the same has not been submitted elsewhere for a Degree.

M. Periasamy 10/3/95

PROFESSOR M. PERIASAMY

(THESIS SUPERVISOR)

P. S. Iyer

DEAN

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ACKNOWLEDGEMENTS

It is with great pleasure that I acknowledge my profound gratitude to my research supervisor, **PROFESSOR M. PERIASAMY**, for suggesting this research problem and for constantly guiding and encouraging me throughout the course of this work.

I am grateful to Prof. G. Mehta, Prof. R. Jagannathan, Prof. K.D. Sen and Prof. P.S. Zacharias, Deans, School of Chemistry during my stay here, for providing all facilities to carry out my work. I take this opportunity to thank all the other faculty members for their inspiring lectures which prompted me to take this profession.

I would like to thank Dr. D. Basavaiah for extending the HPLC and LASER facilities.

I appreciate the help rendered by my colleagues past and present, Dr. A. Devasagayaraj, Dr. Y. Suseela, Dr. Ch. Kishan Reddy, Dr. J.V. Bhaskar Kanth, Messers. M. Rama Reddy, M.L.N. Rao, U. Radhakrishnan, L. Venkatraman, C.R. Ramanathan and P. Bharathi during the course of my work.

It is a pleasure to thank my friends , Dr. Ch. Veera Mohan, Dr. Ch. Rama Kishan Rao, , Dr. C.V.K.M. Sharma, , Messers B. Satish Goud, D. Shekar Reddy, P. Bheema Rao, M. Sirish, R. Murali, P.K. Vasudeva, Dr. R.K. Subramanium , Dr. S. Hari Krishna Reddy, Dr. G.N. Sastry, Dr. Rajender Reddy, Dr. M.S. Reddy, and Dr. K. Narkunan all other friends, who made my stay here an enjoyable and memorable one.

I would like to thank my friends Dr. P. Rama Krishna, Dr. S. Bhaskar

Raju and Mr. S. Pandiaraju for helping in recording the HPLC spectra.

All the non-teaching staff of the School have been extremely helpful, I thank them all. Messers S. Satyanarayana, V. Bhaskar Rao, K.R.B.V. Prasad, Sathya Bhaskar, Shetty, Vijaya Bhaskar, Ramana and Mrs. Vijaya Lakshmi, are a few to mention. I am thankful to Mr. P.O. Koshy for typing this thesis and Mr. A. Anantha Rao for drawings.

I wish to express my profound gratitude to my parents, brother, sisters, in-laws and my friends in Khammam for their affection and co-operation during the crucial phase of my life.

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

Financial assistance from DAE, CSIR and DST is gratefully acknowledged.

March, 1995

A.S. Bhanu Prasad

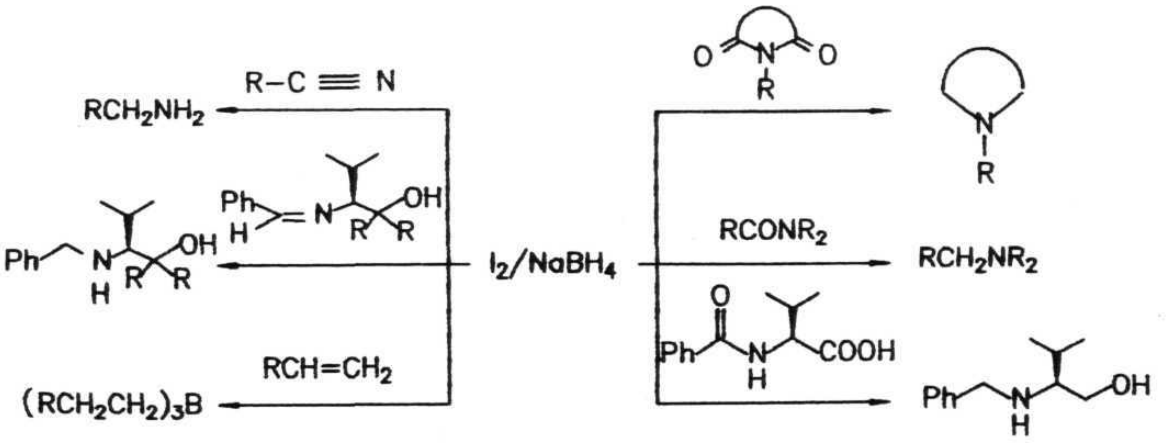
ABBREVIATIONS

AcOH	acetic acid
9-BBN	9-bora bicyclo[3.3.1]nonane
BMS	borane dimethylsulfide complex
Cy_2BH	dicyclohexylborane
DCM	dichloromethane
DG	diglyme
DMS	dimethyl sulfide
EtOH	ethanol
ee	enantiomeric excess
Ipc	isopinocampheyl borane
Pyr.	pyridine
$Pd(OAc)_2$	Palladium(II)acetate
r.t.	room temperature
Sia_2BH	disiamylborane
THF	tetrahydrofuran
Thexyl	2,3-dimethyl-2-butyl
TMS	tetramethylsilane

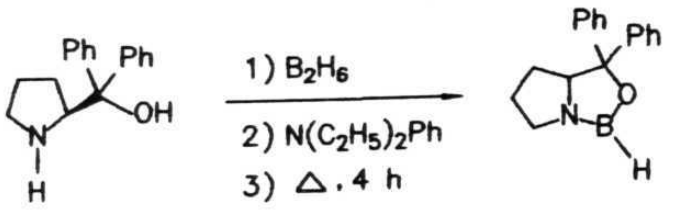
SYNOPSIS

This thesis describes studies on the, 'Development of New Organic Synthetic Methods Based on Borane, Catecholborane Reagents and Resolution of Racemic Diols.' It comprises three chapters. Each chapter is subdivided into three parts, namely, "Background and Objectives", "Results and Discussions" and "Experimental Sections". The work described in this thesis is exploratory in nature and the chapters are arranged in the order the investigations were executed.

The first chapter describes the synthetic methods developed for reductions and hydroborations. An operationally simple procedure has been developed for the generation of diborane in THF using the $I_2/NaBH_4$ combination. The H_3B:THF complex obtained in this way was used for the reduction of an imide, primary, secondary and tertiary amides and nitriles. This reagent system was also utilized for the synthesis of N-alkylamino alcohols through the reduction of the corresponding Schiff bases or N-acylamino acids. The $I_2/NaBH_4$ combination was also employed for the hydroboration of olefins.

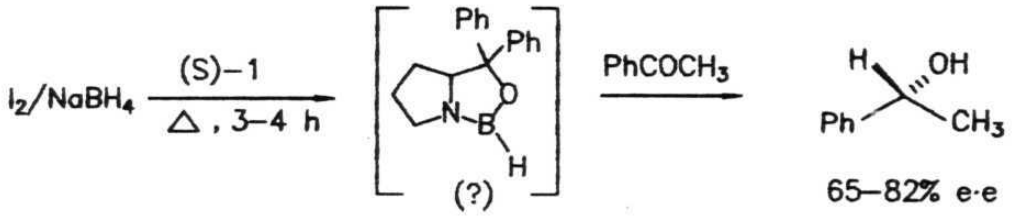


It was found in this laboratory that the Itsuno–Corey oxazaborolidine system can be readily prepared *in situ* using the H_3B:$N(C_2H_5)_2Ph$ complex.

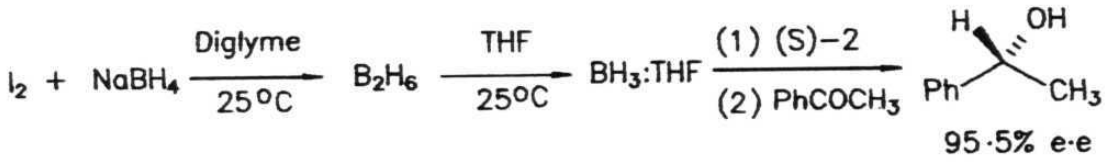


(S)−1 (S)−2

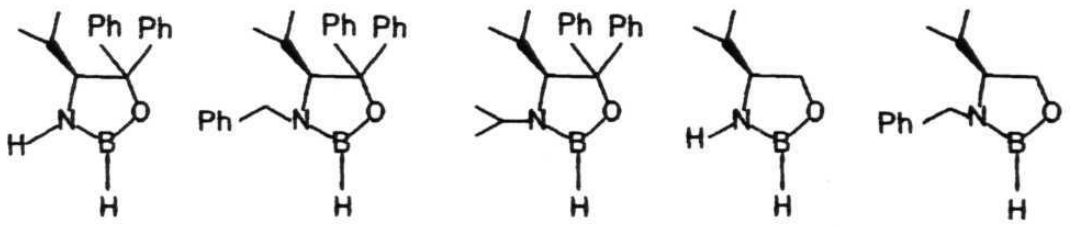
We have examined the synthesis of this reagent using the easily accessible $I_2/NaBH_4$ reagent system.



Several experiments were carried out using this combination of reagents for the enantioselective reduction of acetophenone. The corresponding 1-phenylethanol was obtained in 65–82% e.e. When the CBS catalyst, synthesized using diborane and N,N-diethylaniline, was used in combination with H_3B:THF (prepared separately by bubbling diborane into THF) better enantioselectivies were realized (95.5% e.e).

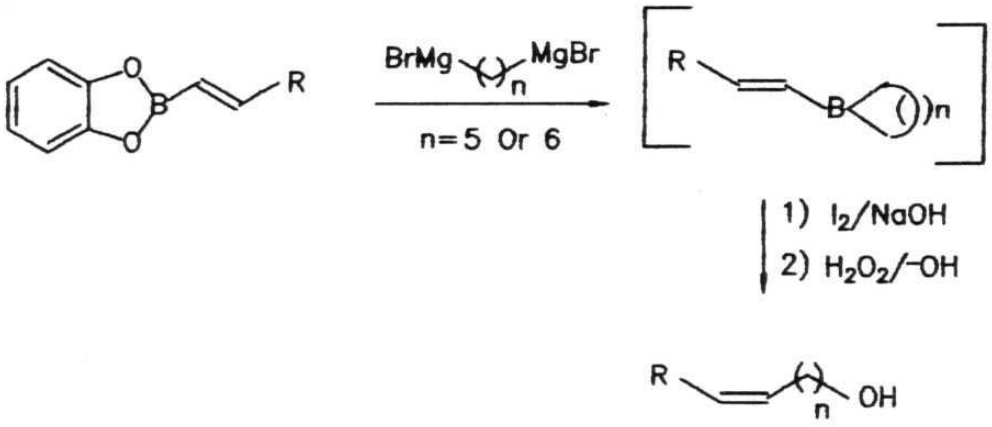


We have also synthesized various (S)-valine derived amino alcohols and the corresponding borane:oxazaborolidine derivatives in order to examine the utility of these reagents in the reduction and hydroboration of acetophenone and the isoelectronic α-methylstyrene. These results are discussed.



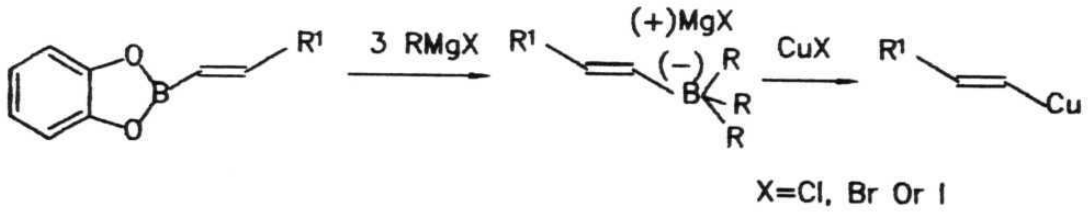
(S)−3 (S)−4 (S)−5 (S)−6 (S)−7

Chapter 2 describes studies on the carbon-carbon bond formation reactions using 1-alkenylcatecholborane derivatives. It was found in this laboratory that (Z)-1-phenyl-1-decene can be prepared using 1-decenylcatecholborane and phenylmagnesium bromide followed by I_2/NaOH treatment. We have optimized conditions for the synthesis of (Z)-1-cyclohexyl-1-heptene and (Z)-2-methyl-7-octadecene, using the corresponding alkenylcatecholborane and the Grignard reagents. The use of diorganomagnesium derivatives followed by iodine treatment and oxidation provided the corresponding (Z)-olefinic alcohols in 30-47% yields.



These methodologies were employed for the synthesis of precursors of some naturally occurring insect pheromones.

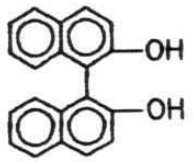
We have also investigated the alkenyl transfer reactions from 1-alkenylcatecholborane using Grignard reagents and CuX treatment.



Unfortunately, only a mixture of (E)-1-phenyl-1-decene and (E,E)-9,11-eicosadiene were obtained in low yields (23-29%).

Chapter 3 describes exploratory studies on the development of convenient methods for the resolution of racemic diols using readily accessible reagents. The C_2-symmetric chiral diols such as 2,2'-dihydroxy-

1,1'-binaphthyl and 1,2-diphenylethanediol are useful in several stoichiometric and catalytic asymmetric transformations. We have selected these representative diols for our studies.



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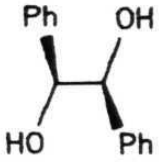

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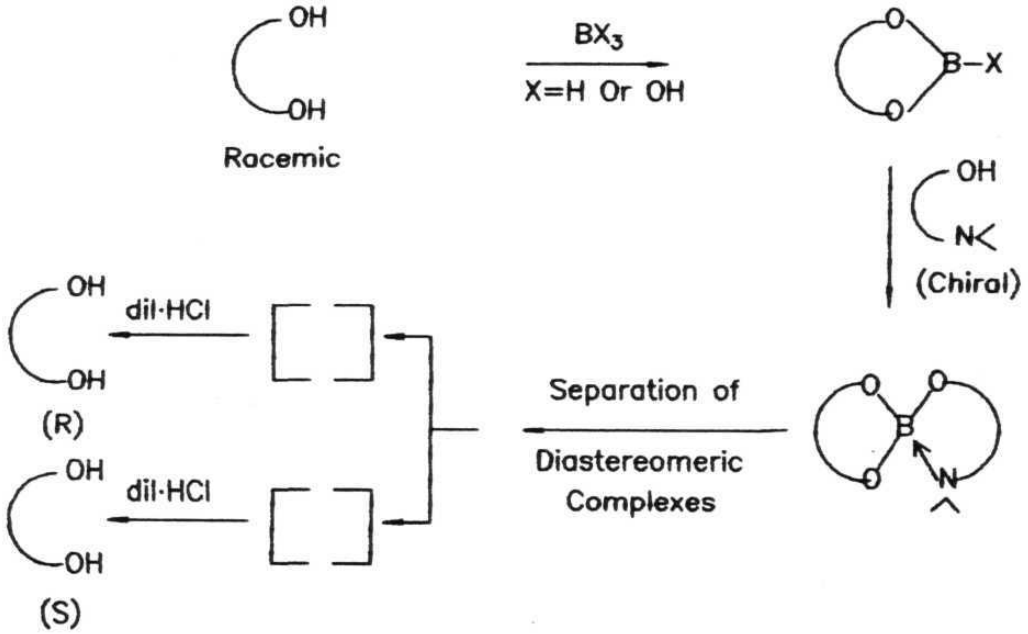
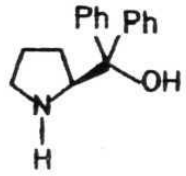
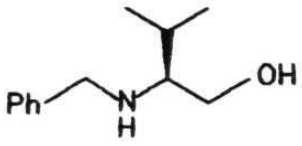
Efforts were undertaken towards the development of a boron-based methodology for the resolution of racemic diols via synthesis and separation of the corresponding diastereomeric complexes.



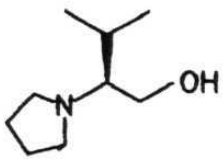
The following chiral amino alcohols were used for the resolution of the racemic 2,2'-dihydroxy-1,1'-binaphthyl.



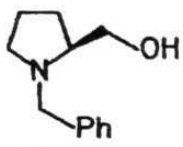
(S)-1



(S)-10

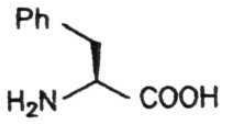


(S)-11

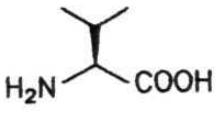


(S)-12

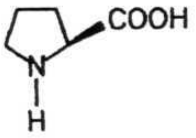
However, the racemic mixture 8 was only partially resolved using these derivatives. We have also utilized the following readily available amino acids for the resolution studies. Again, the racemic mixture 8 was only partially resolved.



(S)–13



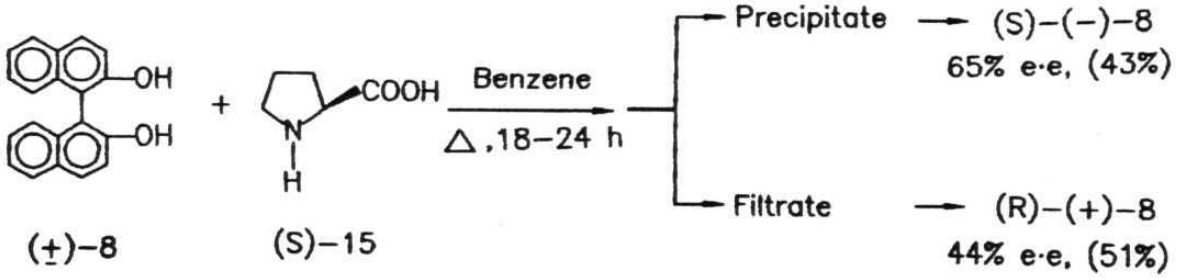
(S)–14



(S)–15

The resolution studies of racemic 1,2-diphenylethanediol gave more fruitful results when (S)-proline and boric acid were used. Highly enriched (S,S)-(–)-1,2-diphenylethanediol (83.4–91.4% e.e) can be prepared in this way. The other isomer (R,R)-(+)-9 was obtained in 22–39% e.e. Efforts were also made to examine the structure of the complexes involved.

Similar efforts on the resolution of enantiomers of 8 using $B(OH)_3$ and chiral amino acids were not successful. Fortunately, however, it was found that the racemic 8 can be readily resolved using (S)-proline alone by refluxing in benzene.



(±)–8 (S)–15

Using this procedure, the enantiomerically pure (S)-(–) and (R)-(+) isomers of 2,2′-dihydroxy-1,1′-binaphthyl were obtained in three successive operations. Efforts were also made to delineate the structures of species involved in this process of resolution/enrichment.

Chapter 1

Studies on the Development of New Organic Synthetic Methods using $I_2/NaBH_4$ Combination for Reductions and Hydroborations

1.1. BACKGROUND AND OBJECTIVES

The sodium borohydride reagent is one of the most widely used reagents in synthetic organic chemistry. This relatively inexpensive, widely available reagent readily reduces the functional groups such as aldehydes,[1] ketones,[2] acid chlorides, [3] oximes,[4] lactones,[5] and imines.[6] However, it does not reduce functional groups such as carboxylic acids, carboxylic acid salts, esters, amides, imides, nitriles, halides, nitro compounds and olefins under ambient conditions. The efforts to increase the reactivity of $NaBH_4$ towards esters using $AlCl_3$ lead to the discovery of hydroboration of olefins in ether solvents.[7]

Although various Lewis acid additives were employed for this purpose, efforts are still continuing for developing more convenient methods. In this laboratory, there have been efforts to develop new convenient methods for reductions and hydroborations.

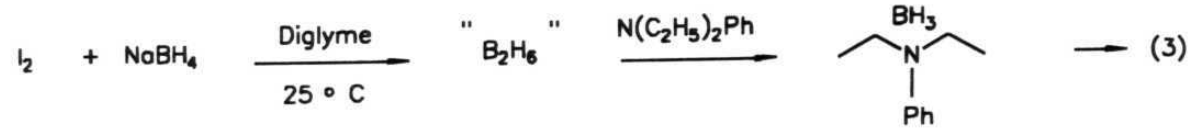
The $RCOOH/NaBH_4$ reagent combination has been shown to be useful in selective hydroboration (eqns. 1 and 2).[8-10]

$$NaBH_4 + CH_3COOH \xrightarrow[2)\ H_2O_2/\ NaOH]{1)\ RCH=CH_2} RCH_2CH_2OH \qquad (1)$$

$$NaBH_4 + \text{(CH}_2\text{)}_n\text{COOH} \xrightarrow[2)\ HCl]{1)\ H_2O_2/NaOH} HO\text{(CH}_2\text{)}_n\text{COOH} \qquad (2)$$

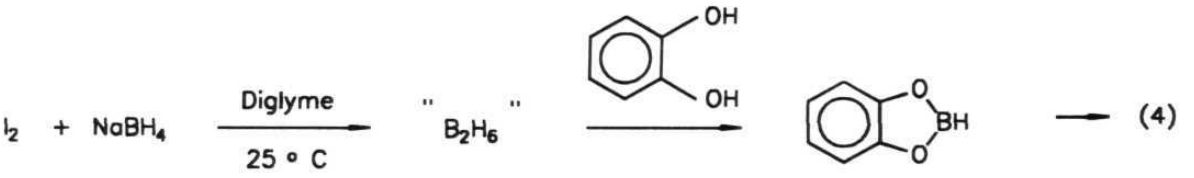
Diborane has been generated using the $I_2/NaBH_4$ combination in diglyme through a slight modification of a reported method.[11] Stable hydroborating agents such as amine boranes have been prepared for synthetic utilization

using diborane generated in this way (eqn. 3).[12]



(3)

Catecholborane can be readily prepared in benzene for synthetic applications (eqns. 4-7).[13,14]



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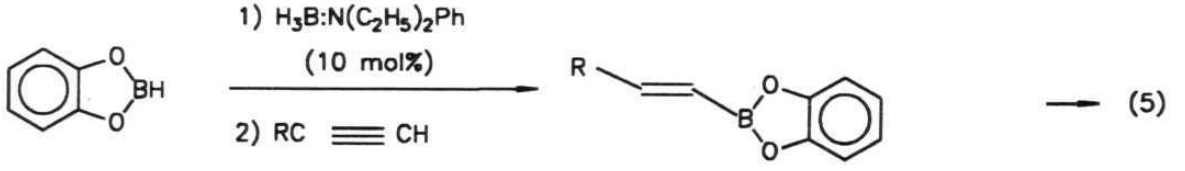

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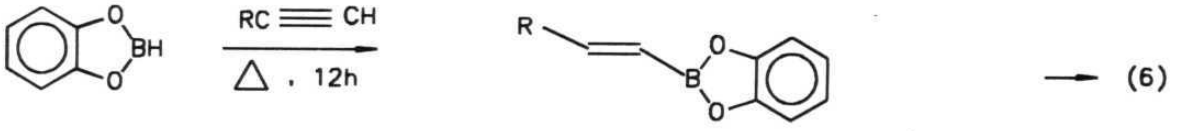
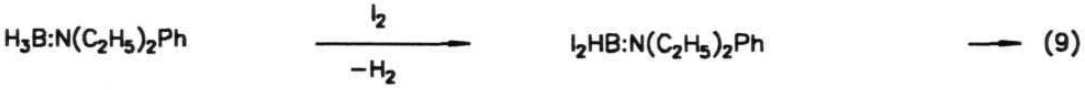


(6)

(7)

Various iodoborane complexes have been prepared for applications in some useful transformations (eqns. 8-10).[15-17]

(8)



(9)

$$H_3B{:}N(C_2H_5)_2Ph \xrightarrow[-3/2\ H_2]{3/2\ I_2} I_3B{:}N(C_2H_5)_2Ph \longrightarrow \quad (10)$$

It appeared desirable to further examine the development of new reduction procedures using the $I_2/NaBH_4$ combination.

1.2. RESULTS AND DISCUSSION

1.2.1. Reduction of organic functional groups using $I_2/NaBH_4$ combination in THF:

Recently, Yamakawa et al reported that the carboxylic acid esters and amides are reduced to alcohols and amines using $NaBH_4/ZnCl_2$ in THF in the presence of a tertiary amine under refluxing conditions.[18] Akabori et al used a novel $NaBH_4/R_2SeBr_2$ system for the reduction of tertiary amides and nitriles and the corresponding amines are obtained in moderate to good yields.[19] It was reported that the reagent generated in this way has reactivity characteristic of H_3B:THF.[19]

As outlined earlier, the diborane can be generated by dropwise addition of I_2 in diglyme to $NaBH_4$ in diglyme.[12] The above report describing the $R_2SeBr_2/NaBH_4$ system prompted us to examine the more readily accessible, safer to handle $I_2/NaBH_4$ combination in THF. So, we have decided to investigate the synthetic utility of the reagent prepared using this combination (eqn. 11).

$$2\ NaBH_4\ (\text{in THF}) \xrightarrow[(\text{in THF})]{I_2} 2\ H_3B{:}THF + 2\ NaI + H_2 \qquad (11)$$

The side product of this reaction is sodium iodide which should not interfere in several transformations utilizing this reagent. In order to examine this, we have carried out an experiment by adding I_2 (1 eq.)/THF slowly (2.5h) into $NaBH_4$ (2.4 eq.) in dry THF at $0^{\circ}C$. Addition of PPh_3 to this mixture afforded >95% of $Ph_3P{:}BH_3$. This clearly indicates that the

diborane generated *in situ* is present as the H_3B:THF complex in the reaction mixture. Later, we have also found that the iodine addition to $NaBH_4$ for 0.5h, also give similar results. However, sodium borohydride was used in small excess (20%) over the stoichiometric amount because further reaction of borane with iodine would produce iodoboranes which are known to cleave ethers.[20]

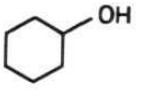
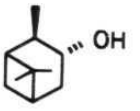
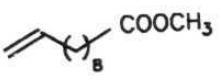
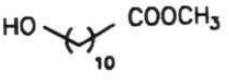
Applications of this $I_2/NaBH_4$ combination for hydroborations and reductions were then examined. The reagent prepared in THF readily hydroborates olefins (eqn. 12).

$$I_2 + 2\ NaBH_4 \longrightarrow \text{"}B_2H_6\text{"} \xrightarrow{THF} 2\ H_3B{:}THF \xrightarrow{3\ RCH=CH_2} (RCH_2CH_2)_3B \qquad (12)$$

The borane reagent prepared using sodium borohydride (2.4 eq.) and iodine (1 eq.) in dry THF, hydroborates 1-decene (3 eq.) during 2h at room temperature to give the organoborane species which was oxidized using alkaline hydrogen peroxide to obtain 1-decanol in 92% yield. Reaction with several other olefins was examined. These results are summarized in Table 1.

It is interesting to note that the olefin moiety was selectively hydroborated in the presence of an ester group (entry 5, Table 1). This reactivity pattern is similar to that observed with H_3B:THF.[21]

Table 1: Hydroboration of alkenes using $I_2/NaBH_4$ in THF[a]

S.No.	Substrate	Conditions Temp. (Time)	Product[e]	Yield (%)
1.	$PhCH=CH_2$	25°C (2h)[b]	$PhCH_2CH_2OH$[f]	90
2.	$C_8H_{17}CH=CH_2$	25°C (2h)[b]	$C_9H_{19}CH_2OH$	92
3.		25°C (4h)[c]		85
4.		25°C (4h)[c]		81
5.		25°C (2h)[d]		78

a) The experiments were carried out using $NaBH_4$ (7 mM) and I_2 (2.8 mM). Products were purified by column chromatography.

b) 15 mM alkene was utilized and the organoborane was oxidized using H_2O_2/ NaOH.

c) 10 mM alkene was used and the organoborane was oxidized using H_2O_2/ NaOH.

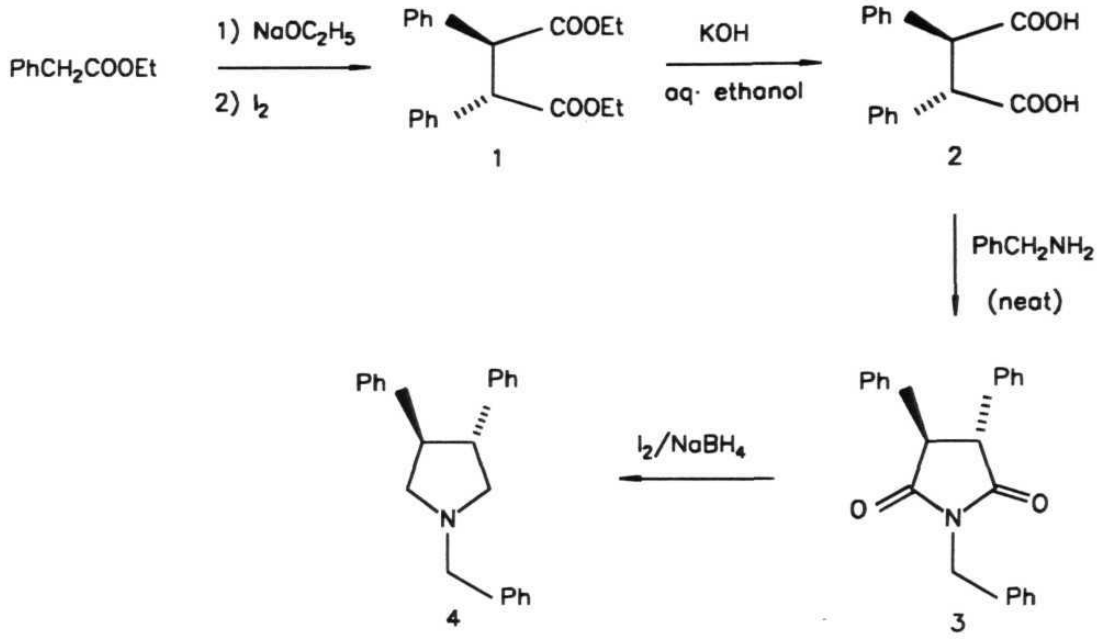
d) The olefinic ester was utilized in 15 mM and the organoborane species was oxidized using H_2O_2/NaOAc.

e) The products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR) and also by comparison with the data reported in the literature.

f) Contains the isomeric 1-phenylethanol up to 20% (^1H NMR analysis).

The $I_2/NaBH_4$ reagent combination has been also useful in the reduction of amides. The corresponding amines are obtained in 70–74% yields. These results are summarized in Table 2. The d,l-imide 3 prepared through the sequence of reactions shown in Scheme 1 following closely related reported procedures,[22] on reduction with $I_2/NaBH_4$ gave the corresponding N-benzyl-3,4-diphenylpyrrolidine 4 in 76% yield (entry 1, Table 2).

Scheme 1:



Reduction of N-benzoylvaline using the $I_2/NaBH_4$ combination gave N-benzylvalinol in 57% yield (entry 5, Table 2) (Scheme 2).

Scheme 2:

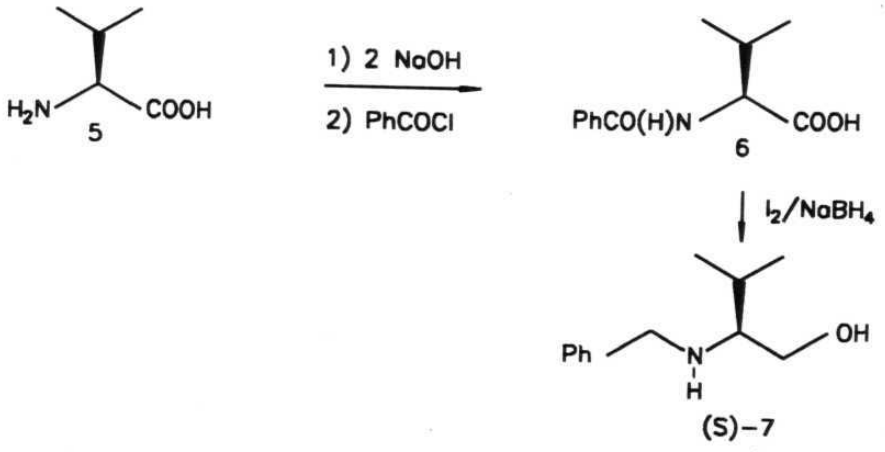
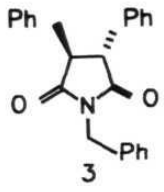
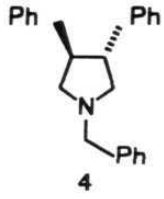
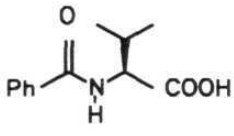
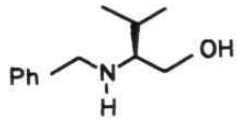


Table 2. Reduction of amides using $I_2/NaBH_4$ in THF[a]

S.NO.	Substrate	Conditions Temp. (Time)	Product[e]	Yield (%)[f]
1.	 3	70°C (6h)[b]	 4	76
2.	$PhN(CH_3)COCH_3$	70°C (3h)[c]	$PhN(CH_3)C_2H_5$	74
3.	$PhN(H)COCH_3$	70°C (3h)[c]	$PhN(H)C_2H_5$	75
4.	$PhCONH_2$	70°C (3h)[c]	$PhCH_2NH_2$	70
5.		25°C (36h)[d]		57

a) All the experiments were carried out by the addition of I_2 into a mixture containing $NaBH_4$ and the substrate in THF at 0°C for 2.5h followed by stirring at the temperature given in Table 2.

b $NaBH_4$ (27 mM), I_2 (12 mM) and imide (5 mM) were used.

c) $NaBH_4$ (23 mM), I_2 (10 mM) and amide (10 mM) were utilized.

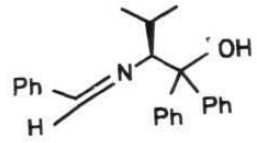
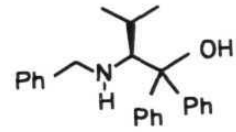
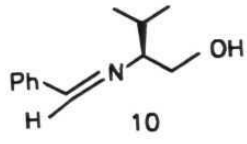
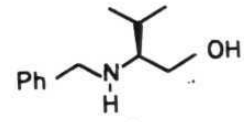
d) $NaBH_4$ (55 mM), I_2 (25 mM) and N-benzoylvaline (20 mM) were used.

e) The products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR).

f) Yields are of products isolated by either column chromatography or distillation under reduced pressure.

The $I_2/NaBH_4$ reagent is also useful for the reduction of nitriles and the corresponding amines were obtained in 70–75% yields. These results are summarized in Table 3.

Table 3. Reduction of nitriles and imines using $I_2/NaBH_4$ in THF

S.NO.	Substrate	Conditions Temp. (Time)	Product[c]	Yield (%)[d]
1.	PhCN	70°C (3h)[a]	$PhCH_2NH_2$	70
2.	$CH_3(CH_2)_7CN$	70°C (3h)[a]	$CH_3(CH_2)_8NH_2$	75
3.	 8	25°C (6h)[b]	 (S)-9	85
4.	 10	25°C (6h)[b]	 (S)-7	83

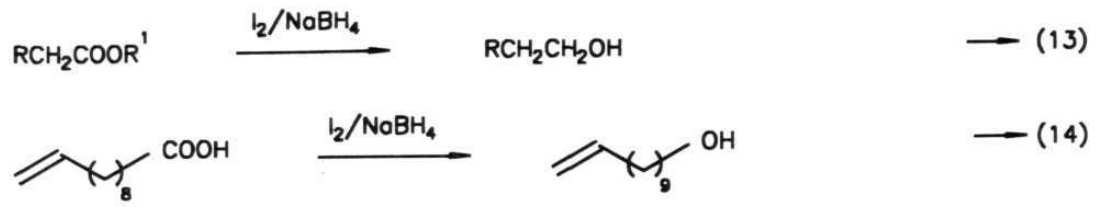
a) All the experiments were carried out by adding I_2 (10 mM) to a mixture of the substrate (10 mM) and $NaBH_4$ (25 mM) in THF (25 mL) for 2.5h at 0°C followed by heating at the temperature mentioned in Table 3.

b) Borane reagent was prepared using $NaBH_4$ (15 mM) and I_2 (6 mM) in THF (45 mL). The imine (10 mM) was taken in THF (15 mL) and added to the reagent at 0°C.

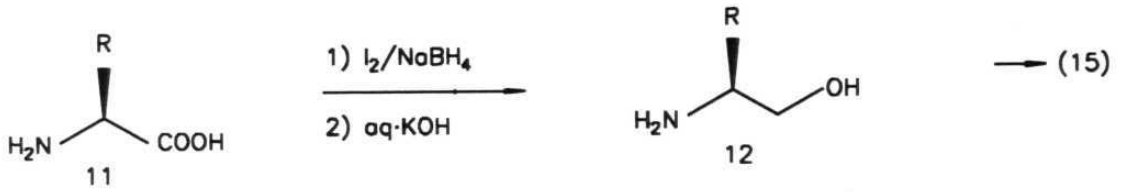
c) The products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR).

d) Yields are of products isolated either by column chromatography or distillation under reduced pressure.

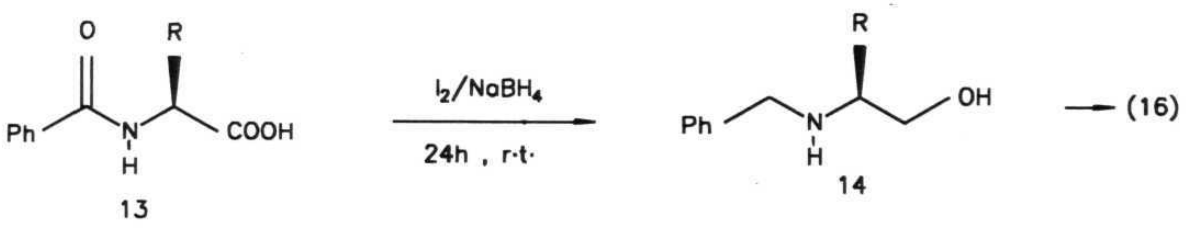
This reagent system was also successfully utilized for the reduction of esters and selective reduction of acids (eqns.13 and 14).[23,24]



Subsequent to initial reports on the $I_2/NaBH_4$ system from this laboratory, Meyers et al have found that this reagent combination is excellent for the reduction of amino acids to amino alcohols (eqn. 15).[25]



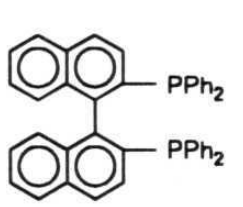
Meyers et al have also reduced various N-benzoyl amino acids to obtain the corresponding N-benzyl amino alcohols (eqn. 16).[25]



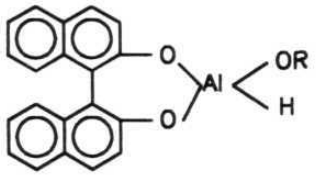
1.2.2. Enantioselective synthesis of chiral alcohols from prochiral substrates:

There have been several reports describing asymmetric synthesis of chiral alcohols from prochiral substrates using stoichiometric amounts of chiral auxiliaries/hydride reagent combinations (Scheme 3).

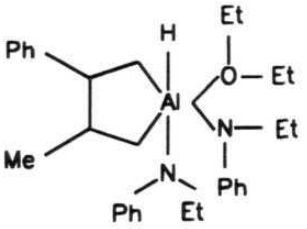
Scheme 3:



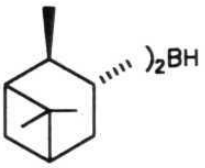
(BINAP) 15[26]



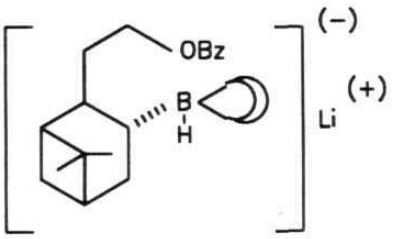
(BINAL–H) 16[27]



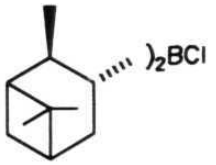
17[28]



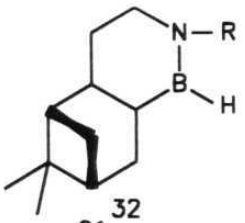
(Ipc_2BH) 18[29]



(NB–Enantride) 19[30]

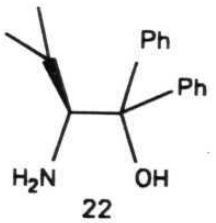


(Ipc_2BCl) 20[31]



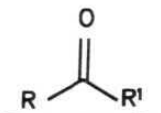
21[32]

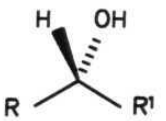
Itsuno and co–workers utilized an amino alcohol modified reagent for the stoichiometric asymmetric reduction of prochiral ketones (eqn. 17).[33]



22

\+ 2 H_3B:THF





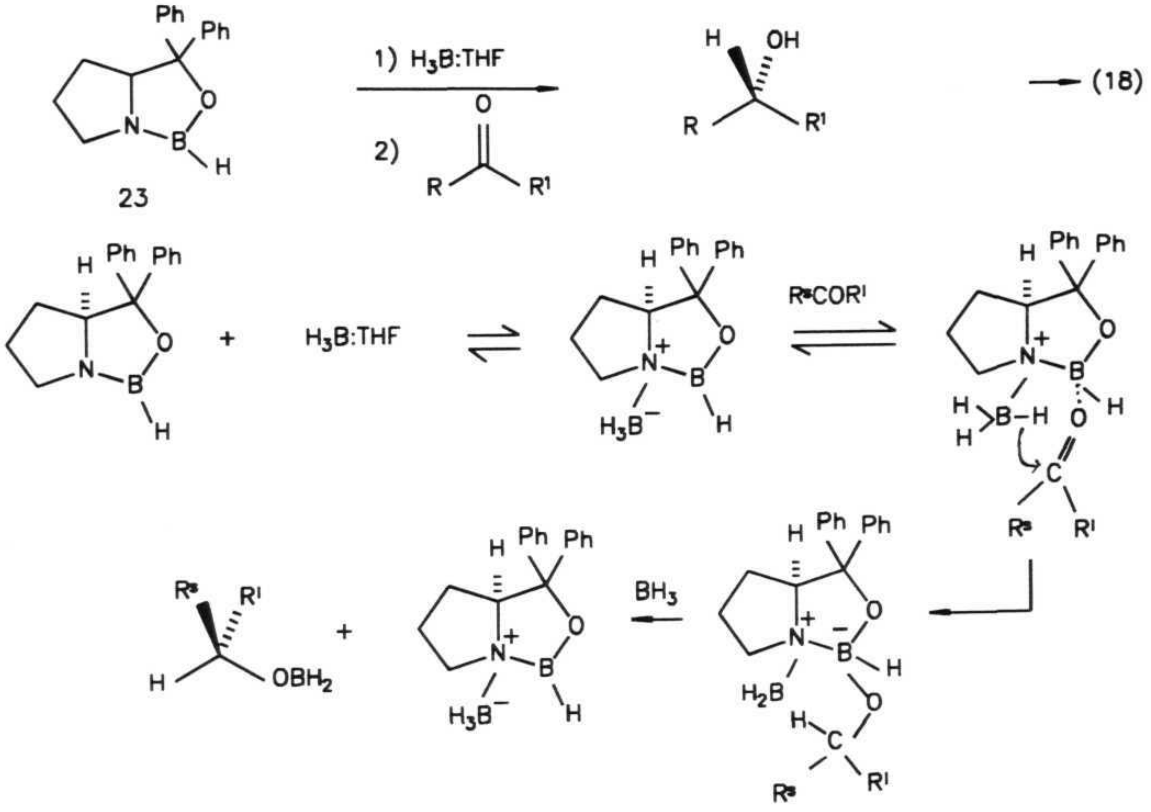
(17)

Using this reagent system, aryl alkyl ketones were reduced to the corresponding alcohols in 94–100% ee. However, less selectivities were observed in the case of dialkyl ketones (55–78% ee).[34]

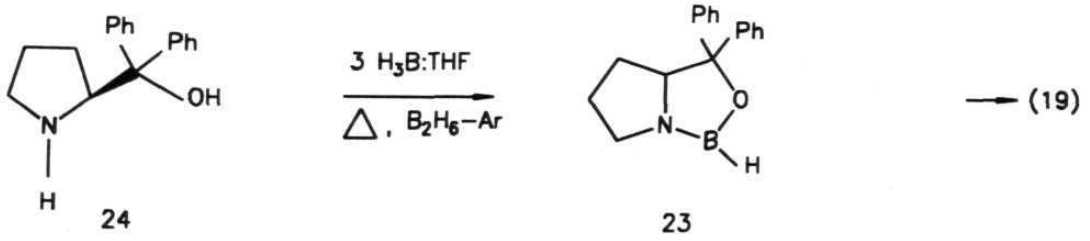
Later, Corey and co–workers prepared the proline analogue of the above reagent for the enantioselective reduction of prochiral ketones. Moreover,

they have established that the reaction is catalytic with the chiral reagent (Scheme 4). Also, better selectivities were obtained in the reduction of several aryl alkyl and dialkyl ketones.[35-37]

Scheme 4:

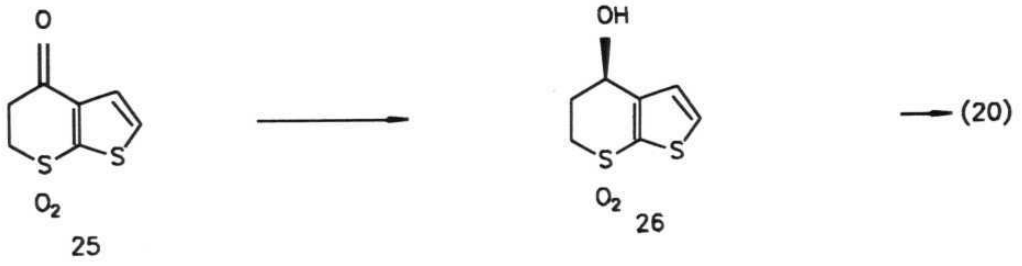


Corey et al prepared this catalyst by heating 3 equivalents of H_3B:THF and (S)-α,α-diphenylpyrrolidinemethanol in THF at reflux under argon-diborane atmosphere (total pressure 1.7 bar). Removal of solvent, sublimation at 150°C-160°C (0.1 torr) and resublimation at 145°C-160°C (0.05 torr) gave the catalyst (eqn. 19).



Even though this catalyst gives excellent results in asymmetric

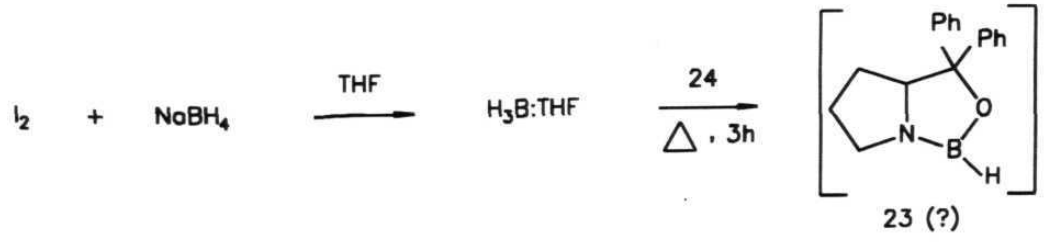
reduction of several ketones, the corresponding B-methylated oxazaborolidine is generally employed for the reductions since the unsubstituted reagent is air and moisture sensitive. Recently, Mathre and co-workers reported that they have obtained erratic results when the B-alkyl oxazaborolidine derivatives prepared using alkylboronic acids were used for the catalytic reduction of a ketone-intermediate in the synthesis of MK-0417 (eqn. 20).[38]



It was reported that 1 mg of water present in 1 g of ketone reduction lowers the enantiomeric excess from 95% to 50%.[38]

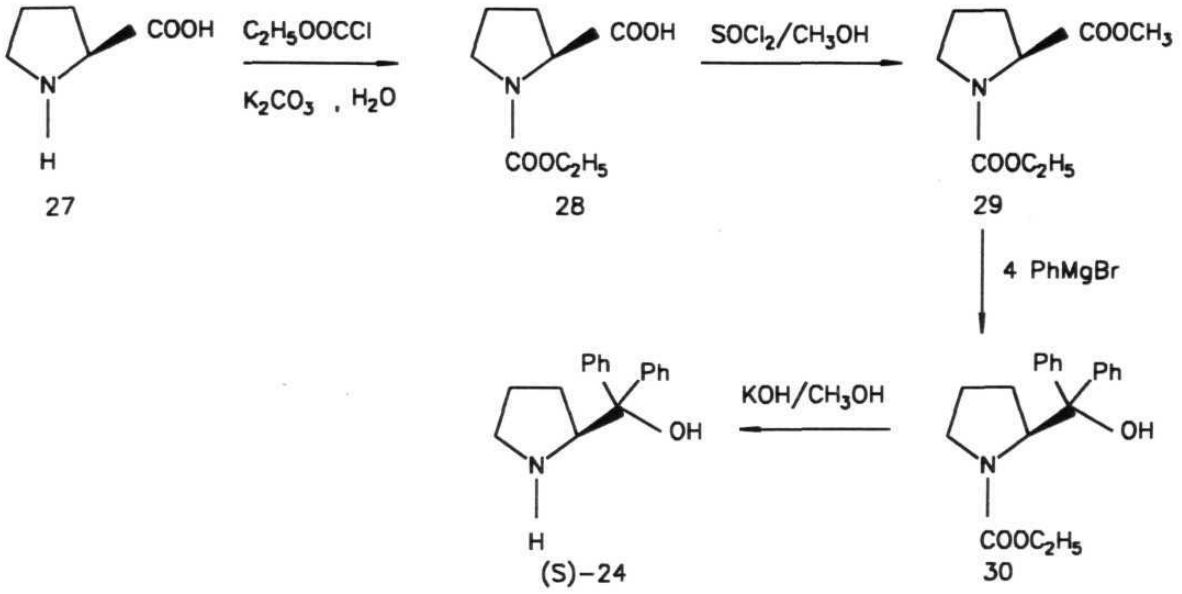
The preparation of oxazaborolidine **23** using (S)-**24** and borane does not involve the water formation. It appeared that this reagent was not extensively utilized because of the air and moisture sensitivity of the reagent and also complicated method of preparation. We have decided to explore the synthesis of this reagent *in situ* for synthetic applications, using the readily accessible $I_2/NaBH_4$ combination as envisioned in scheme 5.

Scheme 5:



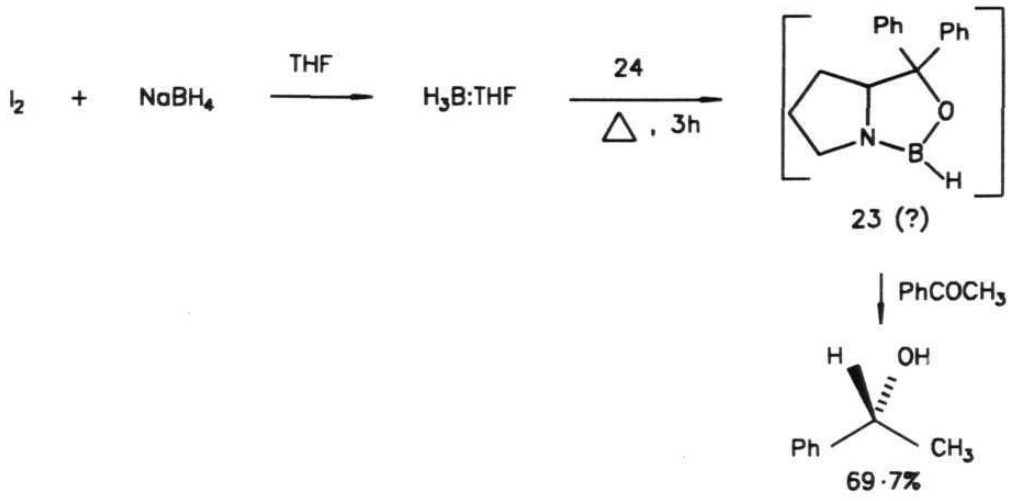
The required chiral synthon α,α-diphenylpyrrolidinemethanol (S)-24 was prepared from (S)-proline following a modified procedure developed in this laboratory (Scheme 6).[39]

Scheme 6:



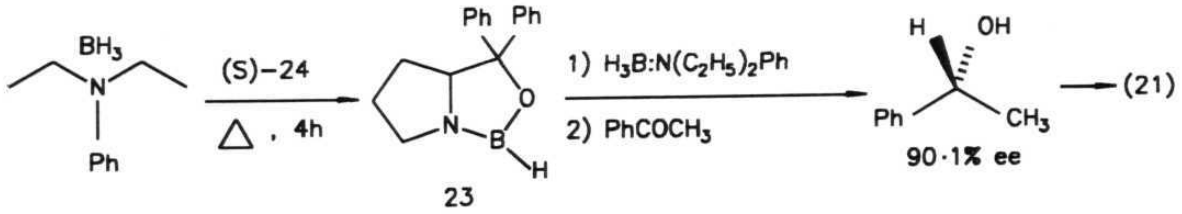
In order to examine the synthesis of the oxazaborolidine **23**, we have carried out the following experiment. H_3B:THF (2 eq.) was prepared in THF using $NaBH_4$ (20 mM) and I_2 (10 mM). (S)-24 (1 eq.) in dry THF was added and the contents were refluxed for 3h. Acetophenone (1 eq.) was added and the contents were stirred for 10 min. at room temperature. 1-Phenylethanol was obtained in 69.7% ee (entry 1, Table 4) (Scheme 7).

Scheme 7:



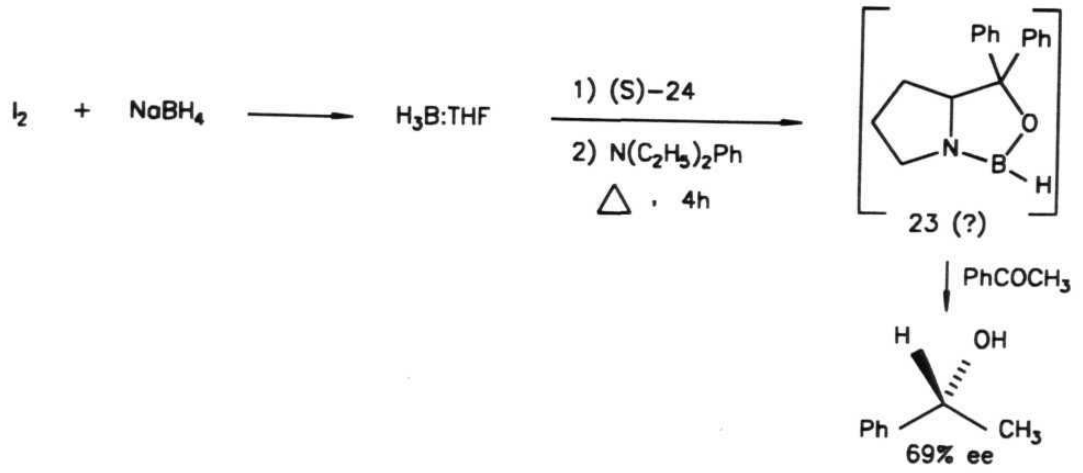
In a separate experiment, H_3B:THF (1.2 eq.) generated using $NaBH_4$ (12 mM)/I_2 (6 mM) and (S)-24 (0.2 eq.) were used. Reduction of acetophenone (1 eq.) using this combination gave 1-phenylethanol in 65% ee (entry 2, Table 4). It was thought that the enantioselectivities obtained were somewhat low in these cases due to the incomplete formation of the catalyst.

Recently, it was found in this laboratory that the use of a tertiary amine such as N,N-diethylaniline in the oxazaborolidine formation gives better results (eqn. 21).[40]



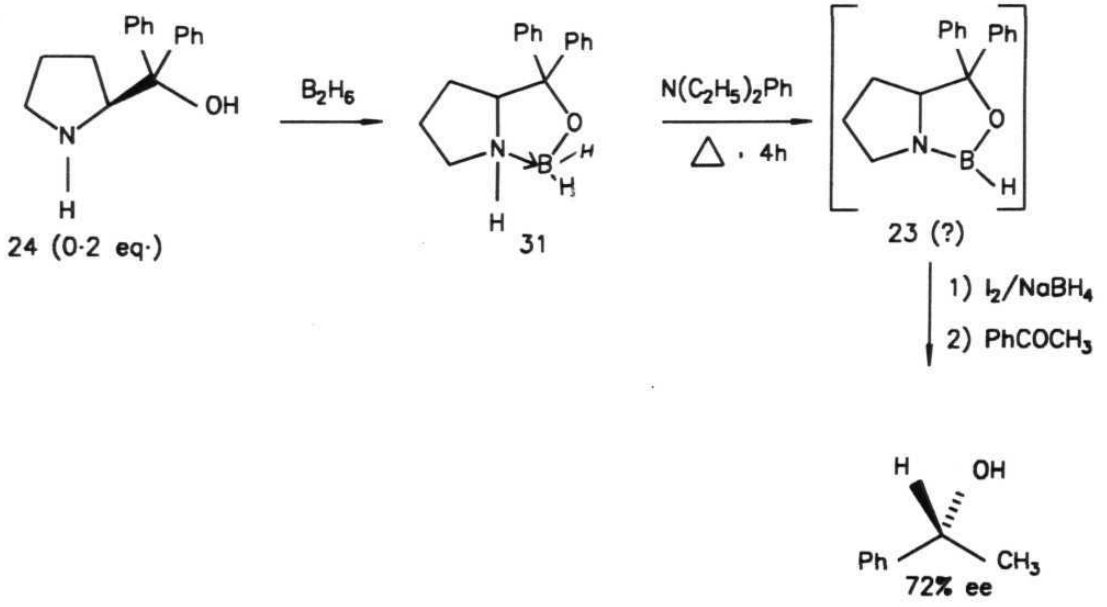
Accordingly, we have carried out an experiment using N,N-diethylaniline to facilitate the catalyst formation (Scheme 8).

Scheme 8:



However, the 1-phenylethanol was obtained only in 69% ee (entry 3, Table 4). In order to further examine this problem, the catalyst prepared in benzene solvent was used in combination with $I_2/NaBH_4$ combination (entry 4, Table 4) (Scheme 9).

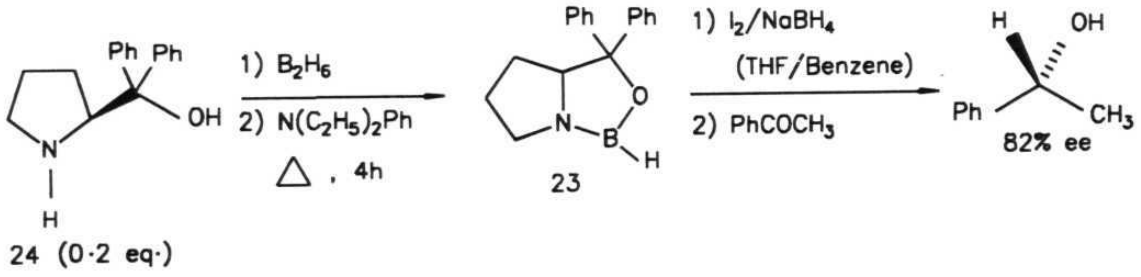
Scheme 9:



As reported above, the reagent prepared in benzene solvent (0.25 eq.) in combination with borane:N,N-diethylaniline (1 eq.) reduces acetophenone upto 90.1% ee in contrast to lower selectivities (72% ee) obtained using the $I_2/NaBH_4$ system (entry 4, Table 4). It was thought that the 'NaI' present along with the reducing agent may be responsible for the complications.

In order to avoid such a problem, we have carried the following experiment. To the borane solution prepared using $I_2/NaBH_4$ system, dry benzene (10 mL) was added and the contents were refluxed for 0.5h. The supernatent borane solution in THF/benzene mixture was used for the reduction (entry 5, Table 4) (Scheme 10). However, there is only slight improvement.

Scheme 10:



In order to further improve the results, we have prepared pure H_3B:THF by bubbling diborane, generated using $I_2/NaBH_4$ in diglyme, into the THF solvent. When this reducing system was used for the reduction of acetophenone along with the oxazaborolidine (20 mol%) prepared in benzene

Table 4: Reduction of acetophenone using oxazaborolidine 23 prepared along with various borane systems[a]

S.No.	Catalyst	Catalyst quantity (in molar eq.)	Reducing agent	Yield[b] (%)	$[\alpha]_D^{25}$	ee (%)[c]
1.	(S)-24 + ($NaBH_4/I_2$)[d]	1.0	$NaBH_4/I_2$	90	+ 31.0	69.7
2.	(S)-24 + ($NaBH_4/I_2$)[e]	0.2	$NaBH_4/I_2$	85	+ 29.6	65.0
3.	(S)-24 + ($NaBH_4/I_2$)[f]	0.2	$NaBH_4/I_2$	80	+ 31.4	69.0
4.	(S)-24 + B_2H_6[g]	0.2	$NaBH_4/I_2$	82	+ 32.3	72.0
5.	(S)-24 + B_2H_6	0.2	$NaBH_4/I_2$[h]	80	+ 37.3	82.0
6.	(S)-24 + B_2H_6	0.2	H_3B:THF[i]	91	+ 42.1	95.5[j]
7.	(S)-24 + B_2H_6	0.1	H_3B:THF[i]	90	+ 42.0	94.7[j]

a) To the catalyst prepared, reducing agent (10 mM) was added followed by acetophenone (10 mM) and the contents were stirred for 10 min. at 30°C.

b) Yields are of isolated, purified and distilled products. Products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR).

c) Based on the maximum $[\alpha]_D^{25}$ = -45.5 (C3, CH_3OH).

d) To the H_3B:THF prepared *in situ* using $NaBH_4$ (20 mM) and I_2 (10 mM), amino alcohol (10 mM) was added and the contents were heated for 3h.

e) To the H_3B:THF prepared *in situ* using $NaBH_4$ (12 mM) and I_2 (6 mM), amino alcohol (2 mM) was added and the contents were refluxed for 3h.

f) To the H_3B:THF (12 mM) prepared amino alcohol (2 mM), N,N-diethylaniline (2 mM) were added and refluxed for 4h.

g) To the benzene solution (15 mL) of amino alcohol (2 mM) excess diborane was bubbled, N,N-diethylaniline (2 mM) was added and heated for 4h.

h) To the H_3B:THF prepared using $NaBH_4$ (10 mM) and I_2 (5 mM), dry benzene (10 mL) was added and refluxed for 0.5h. The supernatent solution was transferred into the reaction flask under nitrogen atmosphere.

i) Diborane prepared using $NaBH_4$ (10 mM) and I_2 (5 mM) was bubbled into THF (15 mL) at 0^oC for 3h.

j) Enantiomeric excess was determined using chiral HPLC on chiralcel OD column using 95:5/hexane:isopropanol solvent.

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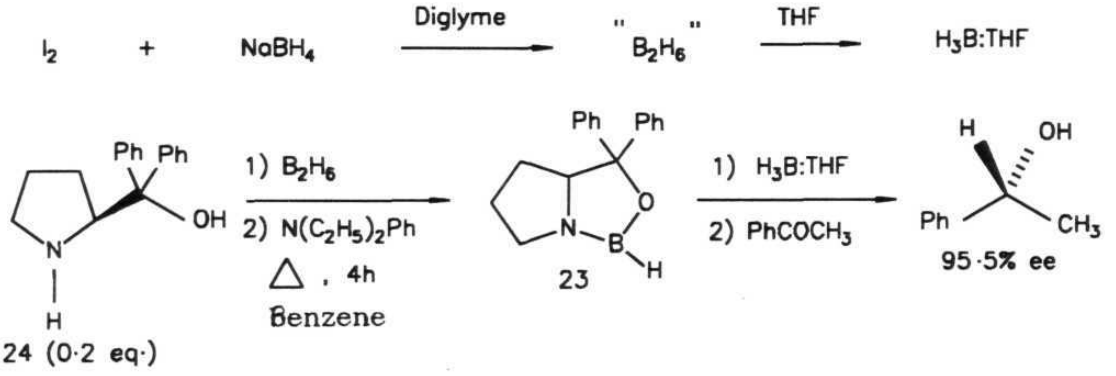
using **24**, 1-phenylethanol was obtained in 95.5% ee (entry 6, Table 4) (Scheme 11).

Scheme 11:



When 10 mol% of the oxazaborolidine catalyst was used, the 1-phenylethanol was obtained in 94.7% ee (entry 7, Table 4). This modified procedure compares well with the *in situ* procedure reported recently by Quallich et al.[41]

1.2.3. Synthesis and utilization of various amino alcohols derived from (S)-valine:

1.2.3.1. Hydroboration of olefins using borane-amino alcohol complexes:

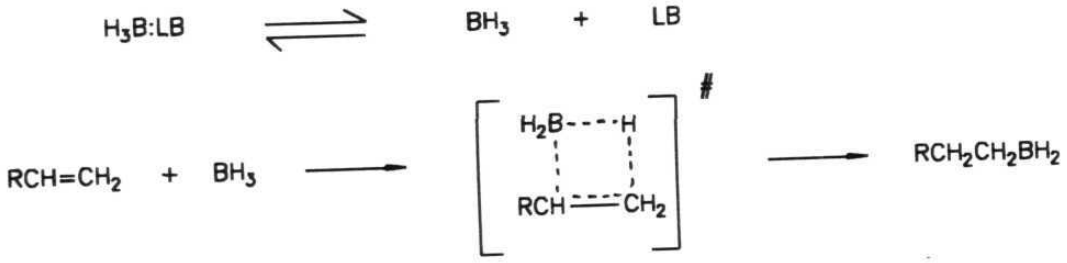
The hydroboration of olefins with H_3B-Lewis base complexes is a very

useful reaction in synthetic organic chemistry. However, the mechanism of this important reaction is not clearly understood. This problem has been debated by various groups of people and several mechanistic pathways were proposed.[42-57] Three mechanistic pictures can be deduced for the hydroboration of olefins using borane–Lewis base complexes from various reports.

i) S_N1-like mechanism:

The H_3B-Lewis base dissociates prior to the borane addition to olefins. Kinetic data were presented in support of this mechanism (Scheme 12).[47]

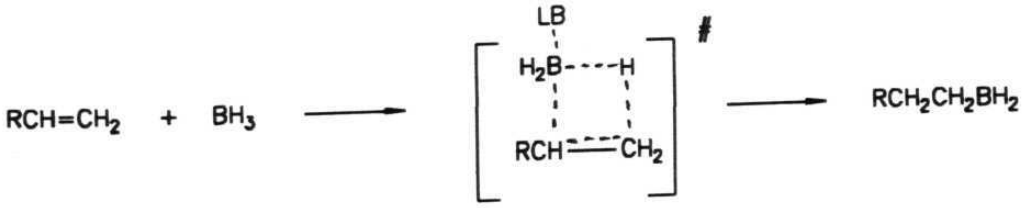
Scheme 12:



ii) S_N2-like mechanism:

This mechanism involves the presence of Lewis base in the transition state during the >B-H addition to olefins (Scheme 13).

Scheme 13:



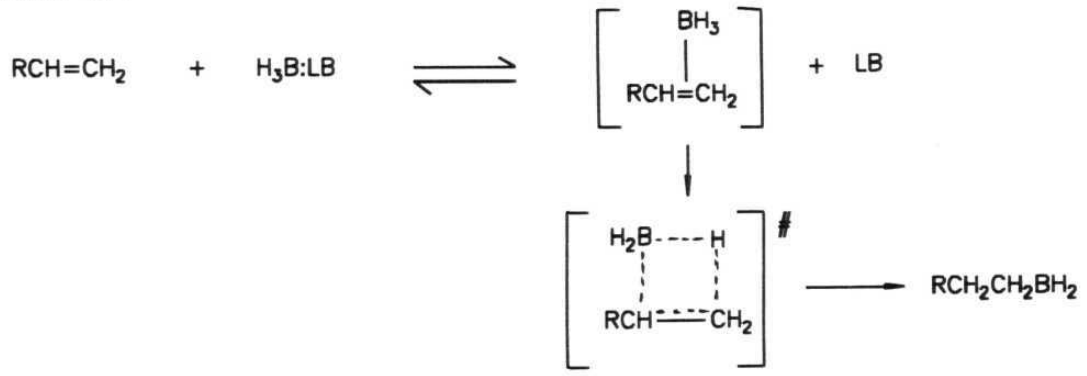
Kinetic data and theoretical calculations have been presented in support of this mechanism.[48-52]

iii) Formation of Π-complex intermediate:

Lewis base may or may not be present in the transition state during the >B-H addition to olefins (Scheme 14). This mechanism was considered to explain the dehydroboration (i.e. the reverse) reaction in certain cases.[57]

The Π-complex intermediates were also considered for the gas phase reaction of 'BH_3' with olefins[53] and also for explaining the asymmetric hydroboration results using Ipc_2BH.[55] This mechanistic picture was not considered for explaining the kinetic data although the available data

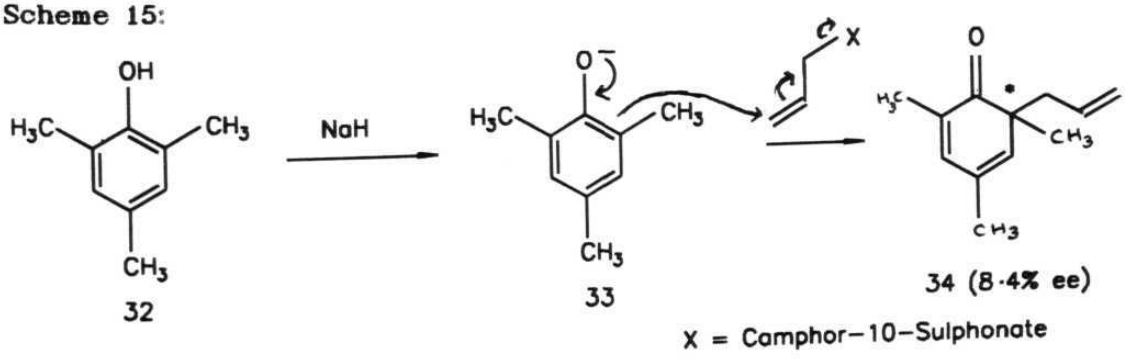
Scheme 14:



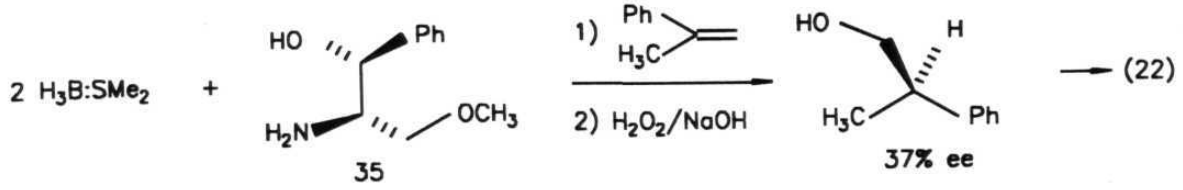
cannot distinguish this mechanism from the S_N1 like mechanism.[47]

In an S_N2-displacement reaction, a chiral leaving group has been reported to give asymmetric induction up to 8.4% ee as shown in Scheme 15.[58]

Scheme 15:

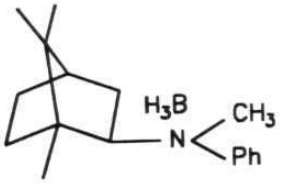


Mandal and co-workers used an amino alcohol modified borane reagent for the asymmetric hydroboration of prochiral olefins (eqn. 22).[59]

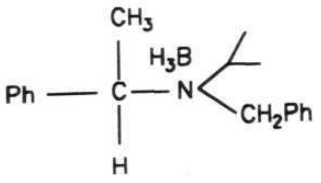


Using this reagent, α-methylstyrene was hydroborated and the corresponding alcohol was obtained in 37% ee after oxidation. However, the authors did not specify the structure of the hydroborating agent. The intermediate species involved may be similar to the oxazaborolidine reported by Corey et al..[35]

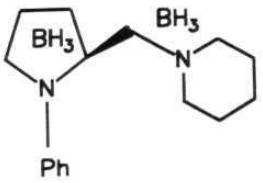
From this laboratory, the following chiral amine borane complexes 36-40 were synthesized and used for the hydroboration of prochiral olefins. The corresponding alcohols were obtained in 3-19.2% ee after oxidation (Scheme 16).[60,61]



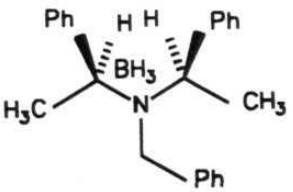
36



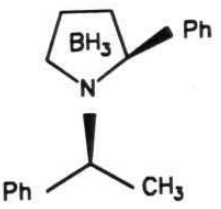
37



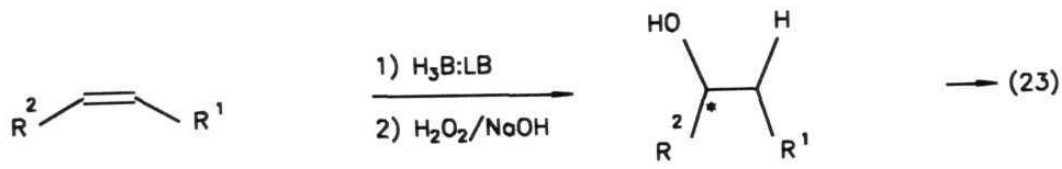
38



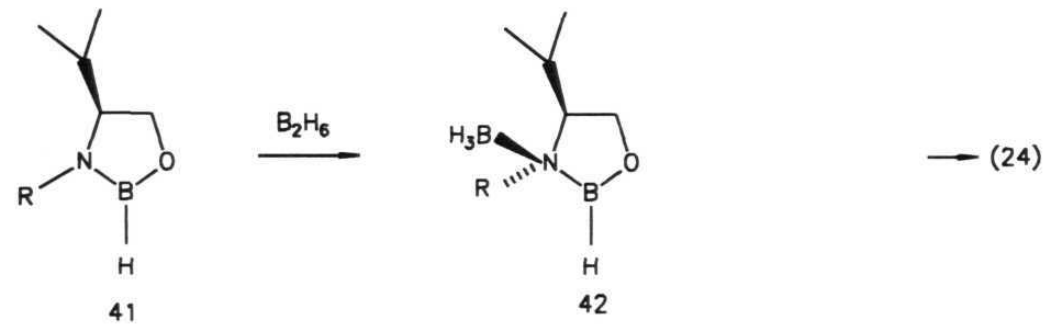
39



40

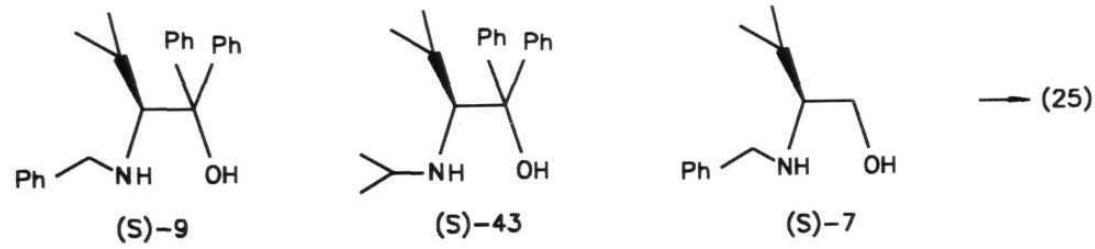


The obtention of relatively higher ee using the Mandal's amino alcohol prompted us to synthesize various (S)-valine derived amino alcohols for the hydroboration studies. It was thought that in an N-substituted borane-oxazaborolidine the borane moiety will be cis to the isopropyl group and hence better enantioselectivities can be realized (eqn. 24).



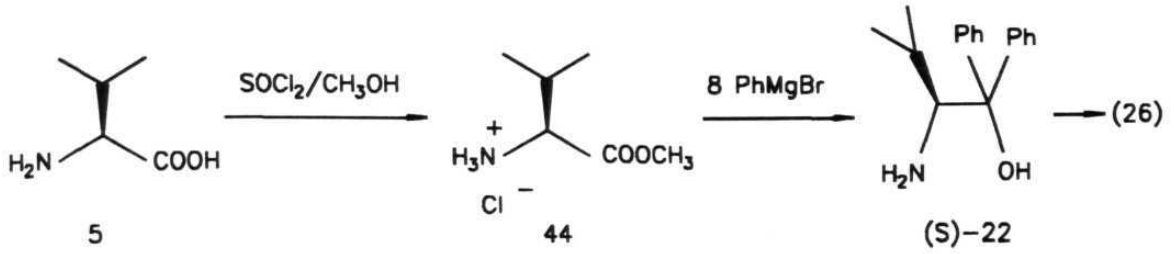
41 42

With this idea in mind, we have decided to prepare the following amino alcohols (eqn. 25).



(S)-9 (S)-43 (S)-7

The syntheses of amino alcohols (S)-9 and (S)-43 were carried out using (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol (i.e. diphenylvalinol) (S)-22, which in turn was prepared following a reported procedure (eqn. 26).[34]

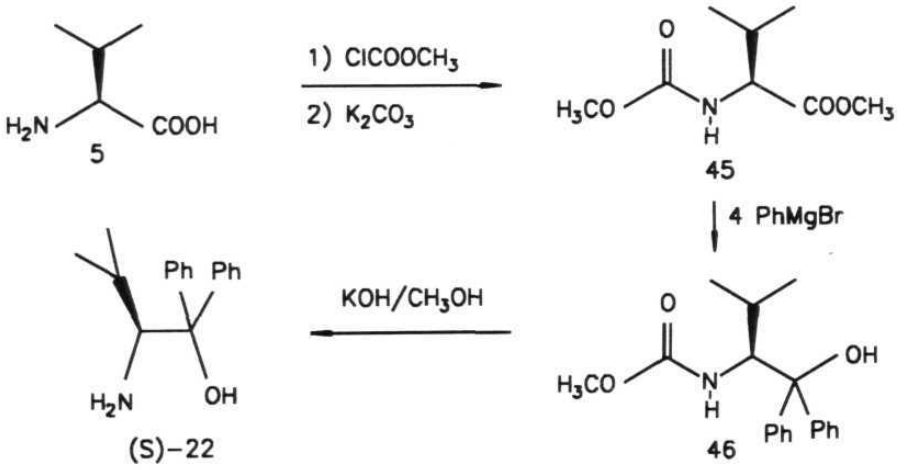


5 44 (S)–22

However, this sequence (eqn. 26) gave the product (S)–22 only in 28% overall yield.

We have developed an alternate procedure for the synthesis of diphenylvalinol (S)–22 in the lines of the method reported for the synthesis of α,α– diphenylpyrrolidinemethanol 24 (Scheme 17).[39]

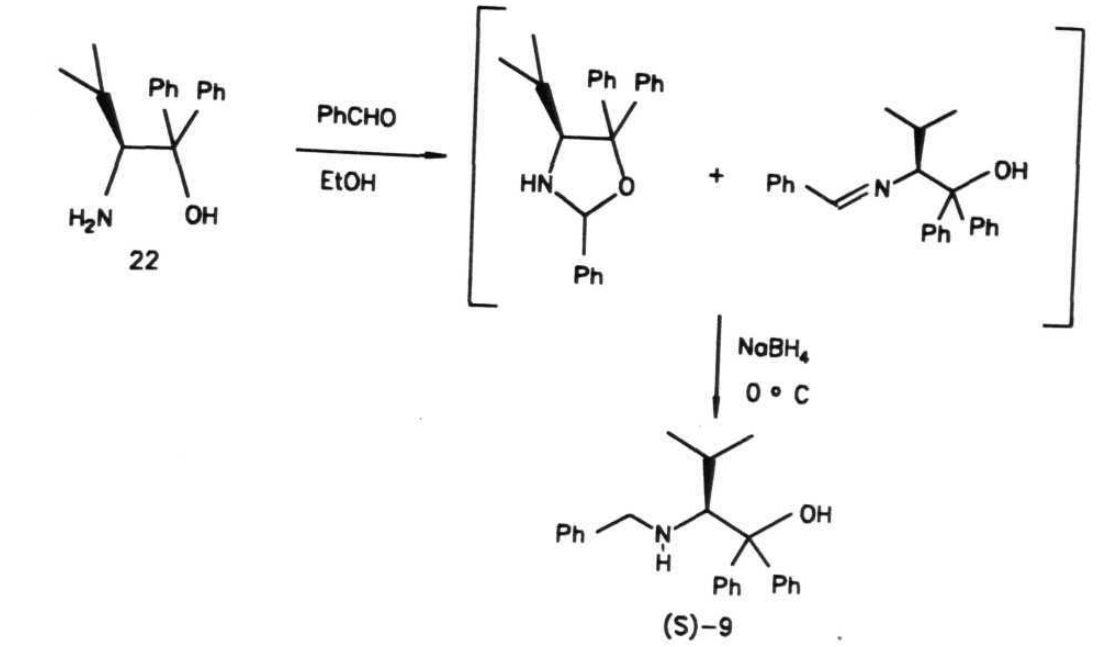
Scheme 17:

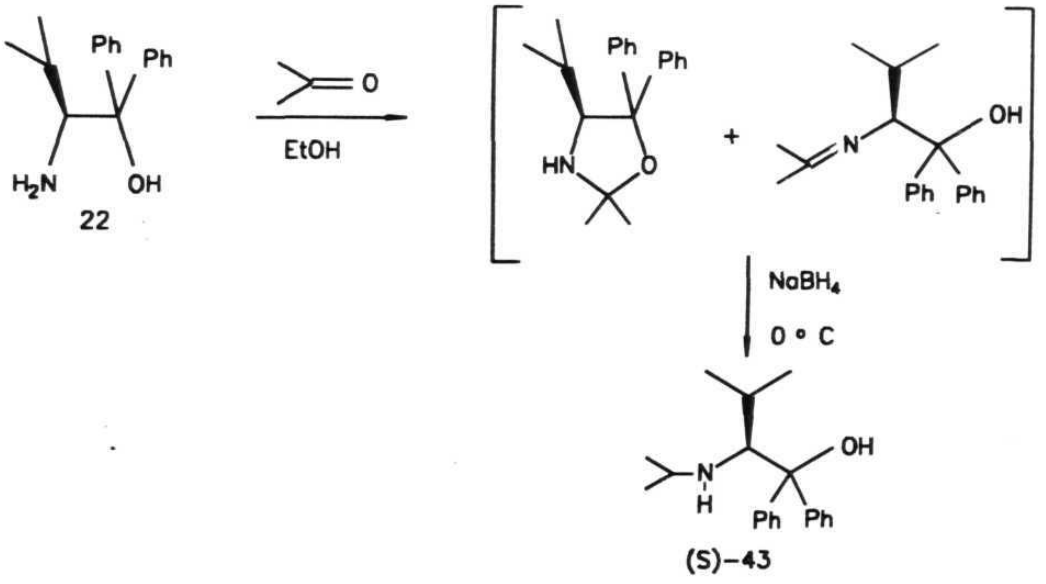


Following this method, the diphenylvalinol (S)–22 was obtained in 46% overall yield.

The diphenylvalinol (S)–22 was converted to (S)–2–(N–benzylamino)–3–methyl–1,1′–diphenylbutan–1–ol, (S)–9 and (S)–2–(N–isopropylamino)–3–methyl–1,1′–diphenylbutan–1–ol, (S)–43 using benzaldehyde and acetone following a closely reported procedure (Scheme 18).[61]

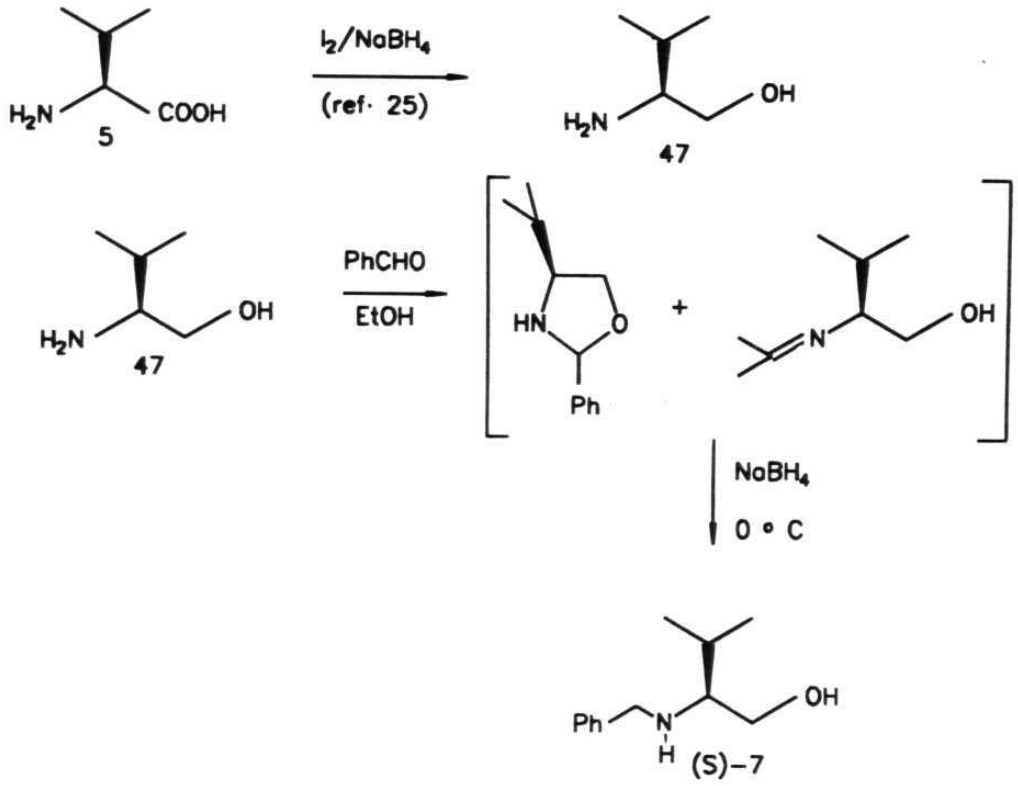
Scheme 18:



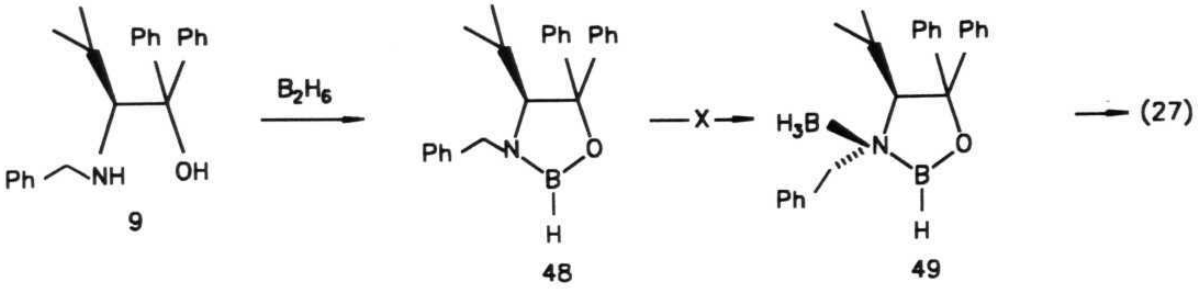


The amino alcohol (S)-7 was prepared from (S)-valine as outlined in Scheme 19.

Scheme 19:

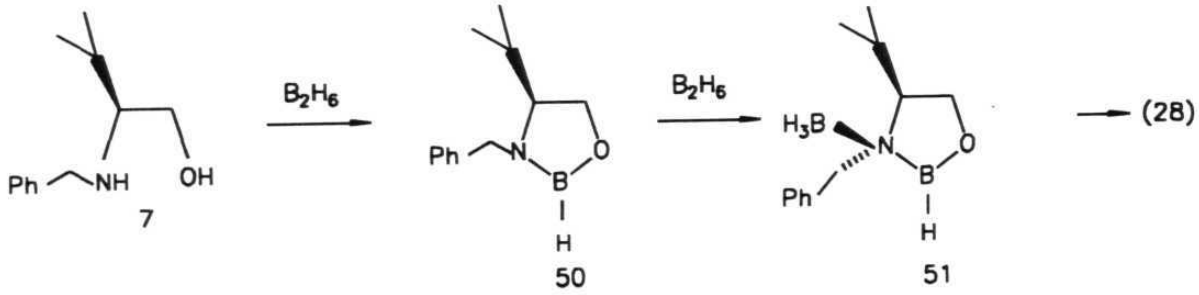


The synthesis of borane–oxazaborolidine complexes was then examined. The amino alcohol (S)–9 was taken in dry benzene and excess diborane generated by dropwise addition of I_2 in diglyme to $NaBH_4$ in diglyme was bubbled for 3–4h. The reaction mixture was refluxed for 6h and the solution IR spectra was recorded. A sharp absorption at 2550 cm^{-1} corresponding to >B–H stretching was noted, indicating the formation of the oxazaborolidine. Diborane (1 eq.) was again bubbled through this reagent and the IR spectra of this mixture was recorded. It was found that there was no change in the spectrum and the 'BH' absorptions characteristic of 'BH_3' moiety (2200–2400 cm^{-1}) were absent. Presumably, this Lewis base is too sterically hindered to form the corresponding borane complex.

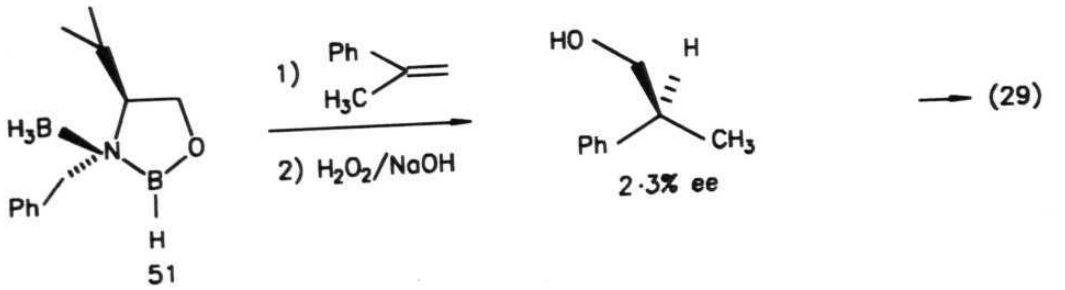


The absence of "BH_3" complex was further confirmed by the reaction with α-methylstyrene (1 eq.) which was quantitatively recovered.

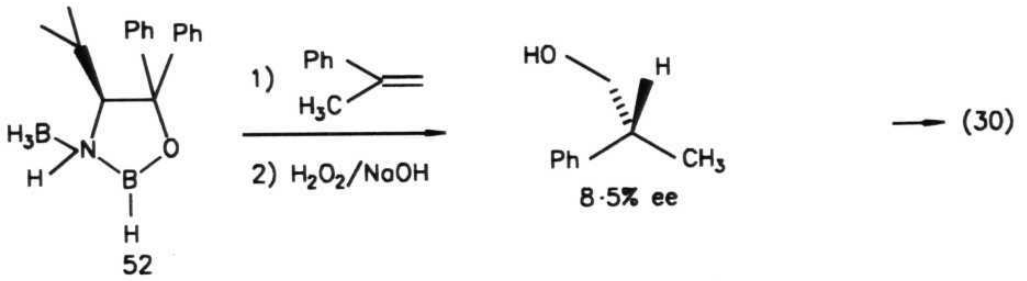
A similar reaction using amino alcohol (S)-43 also did not give the 'BH_3' complex. However, the reaction using (S)-N-benzylvalinol 7 gave the borane complex. The solution IR spectrum in this case showed strong absorptions corresponding to 'BH_3' moiety at 2260, 2300 and 2450 cm^{-1}, indicating the formation of the required borane complex (eqn. 28).



This borane-Lewis base complex was used for the hydroboration of α-methylstyrene. Unfortunately, the product 2-phenyl-1-propanol was obtained only in 2.3% ee after oxidation (eqn. 29).



The borane–oxazaborolidine complexes prepared from the amino alcohols (S)–22 and (S)–valinol were also used for the hydroboration of α–methyl–styrene (eqns. 30 and 31).



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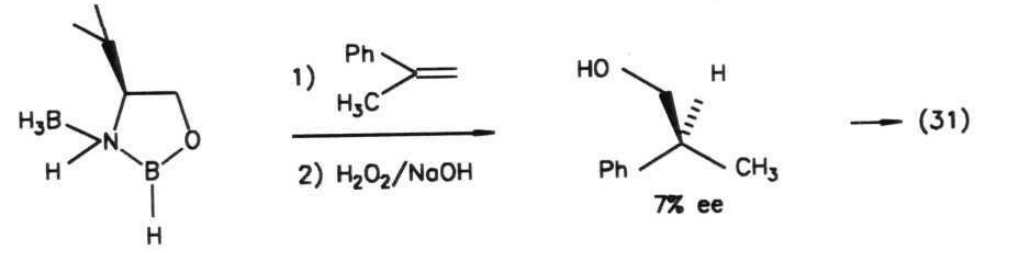
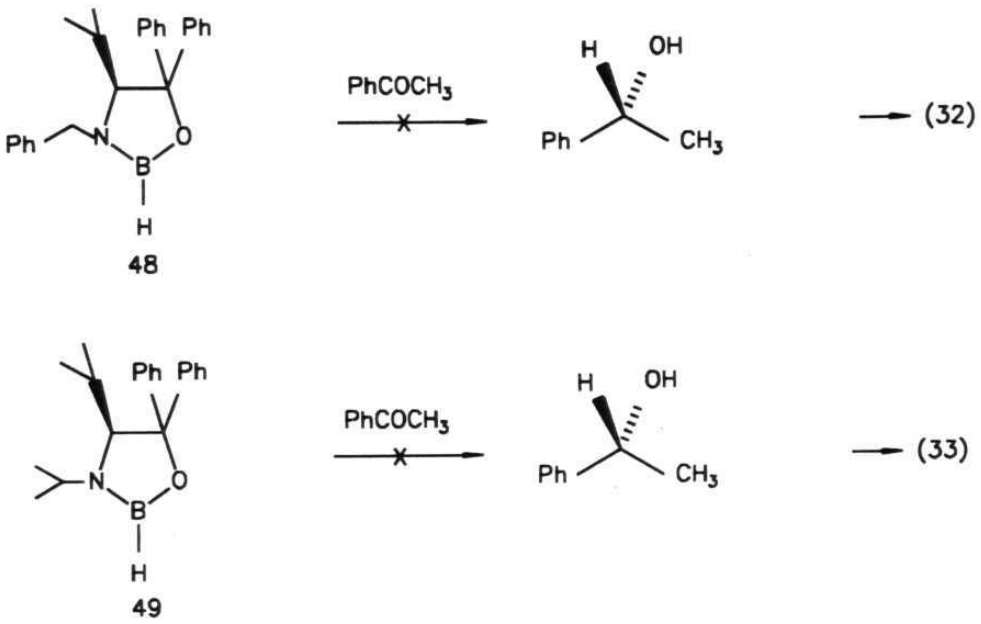


53

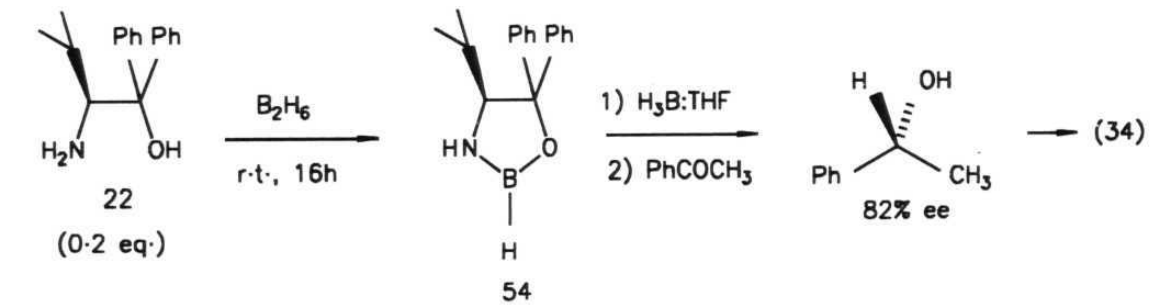
Again, the asymmetric inductions are only poor. However, it should be noted that even if the S_N2 type mechanism (Scheme 13) operates, the inductions may not be very high as the Lewis base partially gets detached in the transition state even in this mechanism. Also, operation of more than one mechanistic pathways cannot be ruled out. Hence, the mechanistic question is not completely settled.

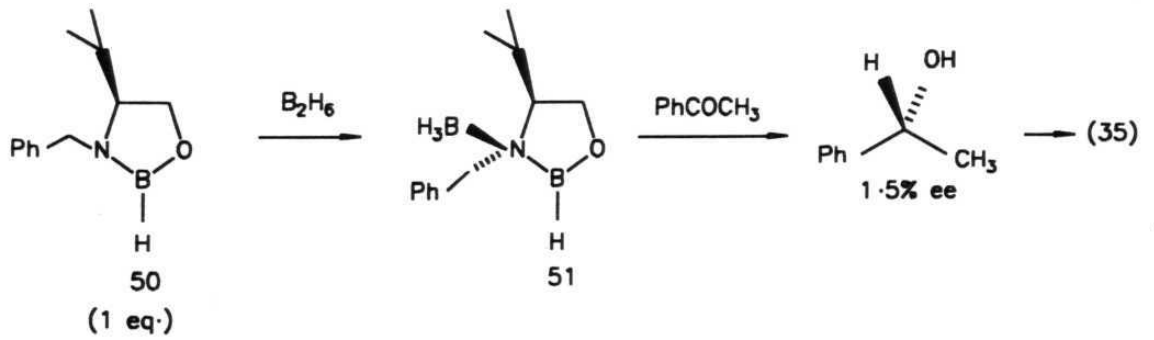
1.2.3.2. Reduction of acetophenone using borane–amino alcohol complexes:

Asymmetric reduction of acetophenone using the borane complexes prepared using (S)–valine derived amino alcohols was also examined. The complexes prepared using the amino alcohols (S)–9 and (S)–43 did not reduce acetophenone. It is not surprising since, as discussed above, these complexes failed to form 'BH_3' adducts.



The reduction of acetophenone was also examined using the amino alcohols (S)-22 and (S)-7. The results outlined in equations 34 and 35 were obtained.

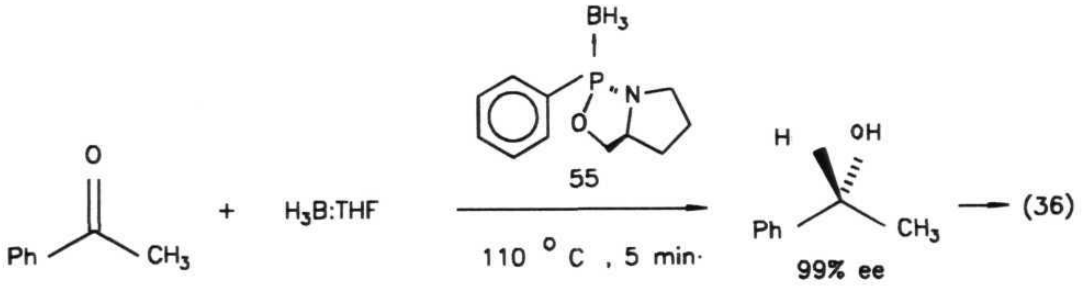




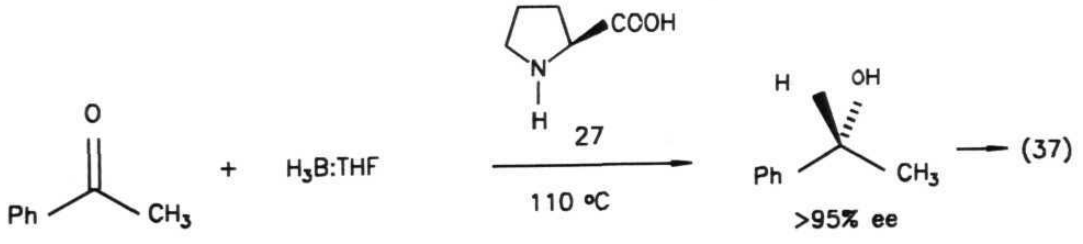
The results obtained using N-benzylvalinol derivative is somewhat unexpected since the oxazaborolidine derived from (S)-valinol itself was

reported to reduce acetophenone to 1-phenylethanol in 49% ee.[33] However, this poor result is close to that obtained in reductions using chiral amine borane complexes without $F_3B{:}OEt_2$ catalysis.[63,64] Presumably, presence of N-benzyl group prevents coordination of ketone with the boron of the oxazaborolidine ring.

Very recently, Buono and co-workers reported that the phosphine-borane complex (55) reduces acetophenone at refluxing conditions to give 1-phenylethanol in 99% ee (eqn. 36).[65]



They have also found that (S)-proline itself gives good results in the asymmetric reduction of acetophenone at refluxing conditions (eqn. 37).[66]



Since, these more readily accessible reagents also give good results, we did not pursue studies on the structural modification of the amino alcohols for use in asymmetric reductions further.

1.3. CONCLUSIONS

An operationally simple procedure has been developed for the *in situ* generation of diborane in THF using $I_2/NaBH_4$ system. This reagent system has been used for the hydroboration of olefins (78-92%), reduction of amides (57-76%), nitriles (70-75%) and imines (83-85%). Alternate routes have been developed for the synthesis of (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol, and its derivatives (S)-2-(N-benzylamino)-3-methyl-1,1'-diphenylbutan-1-ol, (S)-2-(N-isopropylamino)-3-methyl-1,1'-diphenylbutan-1-ol and (S)-2-(N-benzylamino)-3-methylbutan-1-ol. Various borane reagents prepared using the $I_2/NaBH_4$ system in combination with α,α-diphenylpyrrolidinemethanol and other amino alcohols were utilized for the asymmetric reduction and hydroboration studies.

General Information:

Melting points reported in this thesis are uncorrected and were determined using a Buchi 510 capillary point apparatus. Infrared spectra were recorded on Perkin-Elmer Model 1310 and Jasco FT-IR Model 5300 spectrophotometers with polystyrene as reference. ^{1}H NMR and ^{13}C NMR were recorded on JEOL-FX-100 and BRUCKER-AC-200 spectrometers. Spectra for all the samples were measured in deuterated chloroform using tetramethylsilane as internal standard. The chemical shifts (δ) are expressed in δ down field from the signal for internal Me_4Si.

Optical rotations were measured on a AUTOPOL-II automatic polarimeter (accuracy $\pm$ 0.01^{o}). The condition of the polarimeter was checked by measuring optical rotation of a standard solution of (+)-α-methylbenzyl-amine, $[\alpha]_D^{25}$ = + 30.2^{o} (C10, EtOH) supplied by Fluka. The polarimeter was set to zero reading using the solvent used. Elemental analyses were performed on Perkin-Elmer elemental analyzer model 240C. Analytical thin layer chromatographic tests were carried out on glass plates (3X10 cm) coated with (250 mμ) Acme's silica gel G or GF 254 containing 13% calcium sulphate as binder. The spots were visualized by short exposure to iodine vapor or UV light.

Column chromatography was carried out using Acme's silica gel (100-200 mesh).

All the glassware were predried at 140^{o}C for atleast 4h, assembled hot

and cooled under a stream of purified dry nitrogen. Unless otherwise mentioned, all the operations/transformations were carried out using standard syringe, septum techniques as recommended for handling organoboranes.[21] In general, all the reactions were carried out in a RB flask with a side arm and a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler. All dry solvents were distilled from appropriate drying agents just before use. Hexane refers to the fraction boiling between 60-80°C. As a routine, all the organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ and concentrated on a Buchi-EL rotary evaporator (at reduced pressure). All yields reported are yields of isolated materials, judged homogeneous by TLC, IR, and NMR spectroscopy.

Benzene, toluene, THF, ether and diglyme were distilled over benzophenone-sodium ketyl. $NaBH_4$ (97%) and I_2 supplied by SD fine chemicals, (S)-proline and (S)-valine supplied by Sisco-Chem, India and ethyl chloroformate and methyl chloroformate supplied by Spectrochem, India were used. Acetophenone, α-methylstyrene, benzaldehyde and N,N-diethylaniline supplied by SD fine chemicals were distilled prior to utilization. Diglyme supplied by Aldrich, USA was used.

Generation of diborane in THF solvent using $I_2/NaBH_4$ system and preparation of H_3B:THF complex:

$NaBH_4$ (0.45 g, 12 mM) was taken in dry THF (25 mL) under nitrogen atmosphere. The flask was cooled to 0°C and iodine (1.25 g, 5 mM) dissolved in dry THF (15 mL) was added dropwise for 2.5h at 0°C using a pressure equalizer. The diborane generated *in situ* was quantitatively trapped as

H_3B:THF complex. The H_3B:THF complex thus prepared was used for further reactions.

Estimation of H_3B:THF prepared using triphenylphosphine:

Diborane was generated in THF using $NaBH_4$ (0.45 g, 12 mM) and I_2 (1.25 g, 5 mM) as mentioned above. PPh_3 (2.62 g, 10 mM) dissolved in dry THF (10 mL) was added through cannula under nitrogen atmosphere. The contents were stirred for 2h at room temperature. On evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (95:5), Ph_3P:BH_3 was isolated.

Yield : 2.62 g (95%)

M.P. : 187°C; Lit.[67] 189°C

IR (KBr) ν_{max} : 2350 (b), 750, 700 cm^{-1}

Hydroboration of styrene using $I_2/NaBH_4$ system in THF solvent:

Diborane was generated using $NaBH_4$ (0.27 g, 7 mM) and I_2 (0.71 g, 2.8 mM) in dry THF (40 mL) as mentioned above. Styrene (1.56 g, 15 mM) was added and the reaction mixture was stirred for 2h at room temperature. It was quenched with water (2 mL) and oxidized using 3N NaOH (30 mL) and H_2O_2 (30%, 30 mL). The contents were further stirred for 3h at room temperature. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extract was washed with water, brine and dried over anhydrous $MgSO_4$. On evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (90:10), a mixture of 2-phenylethanol and 1-phenylethanol was isolated.

Yield	:	1.65 g (90%)
B.P.	:	96°C/10 mm; Lit.[68] 219°C/760 mm
IR (neat) ν_{max}	:	3300, 1600, 1050 cm^{-1}
^1H NMR (100 MHz, $CDCl_3$) δ ppm:		1.44 (d, 3H), 2.44 (bs, 1H), 2.78 (t, 2H), 3.70 (t, 2H), 4.72 (q, 1H), 7.01-7.32 (m, 5H)

The signals at δ 1.44 ppm and 4.72 ppm corresponding to the presence of 1-phenylethanol to the extent of 20%.

This procedure was followed for the hydroboration of a few other olefins.

$$3\ H_3C(CH_2)_7CH{=}CH_2 \longrightarrow 3\ H_3C(CH_2)_8CH_2OH$$

Yield	:	2.18 g (92%)
B.P.	:	110°C/10 mm; Lit.[68] 231°C/760 mm
IR (neat) ν_{max}	:	3350, 1060 cm^{-1}
^1H NMR (100 MHz, $CDCl_3$) δ ppm:		0.90 (t, 3H), 1.20 (m, 16H), 2.41 (bs, 1H), 3.60 (t, 2H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		14.23, 22.25, 25.95, 29.47, 29.77, 32.35, 32.83, 62.83

In the case of internal olefins, 10 mM of olefin was used instead of 15 mM and the hydroboration was carried out for 4h at room temperature.

Yield : 0.85 g (85%)

B.P. : 56-58°C/25 mm; Lit.[68] 160-161°C/760 mm

IR (neat) ν_{max} : 3350, 1060 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 1.20-1.40 (m, 10H), 2.80 (bs, 1H), 3.21 (m, 1H)

^{13}C NMR (25 MHz, $CDCl_3$) δppm: 24.25, 25.49, 35.39, 69.96

Yield : 1.25 g (81%)

B.P. : 94-96°C/10 mm; Lit.[69] 217°C/760 mm

IR (neat) ν_{max} : 3350, 1120 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δppm: 0.87-1.90 (m, 16H), 2.35 (bs, 1H), 3.90 (m, 1H)

^{13}C NMR (25 MHz, $CDCl_3$) δppm: 20.91, 23.84, 27.83, 34.51, 38.32, 39.14 41.85, 47.75, 47.92, 71.50

Yield : 2.53 g (78%)

IR (neat) ν_{max} : 3250, 1720 1040 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 1.28-1.64 (m, 18H), 2.2-2.38 (m, 3H), 3.52-3.64 (m, 5H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 24.40, 25.30, 28.60, 28.70, 28.90, 32.11, 33.40, 50.82, 61.71, 173.90

Preparation of N-benzyl-3,4-diphenylsuccinimide 3:

Ethyl diphenylsuccinate was prepared using ethyl phenylacetate (35 g, 210 mM) sodium ethoxide (obtained from sodium (5.7 g)) and iodine (27.3 g, 210 mM).[22] It was hydrolyzed to the α-diphenylsuccinic acid following a reported procedure.[22] A mixture of α-diphenylsuccinic acid (5.4 g, 20 mM) and N-benzylamine (2.14 g, 20 mM) was heated at 220°C for 0.5h. The contents were cooled to room temperature and extracted with chloroform. The chloroform layer was washed with brine, and dried over anhydrous $MgSO_4$. On evaporation of the solvent and purification by column chromatography on silica gel (hexane:ethyl acetate/90:10), the imide 3 was isolated.

Yield : 6.2 g (91%)

IR (KBr) υ_{max} : 1680, 1600 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 2.04–2.08 (d, 2H), 4.40–4.44 (d, 2H), 7.20–7.40 (m, 15H)

Reduction of imide 3 using $I_2/NaBH_4$ system:

Diborane was generated using $NaBH_4$ (1 g, 27 mM) and I_2 (3 g, 12 mM) in dry THF (45 mL) as described earlier. Imide 3 (1.7 g, 5 mM) dissolved in dry THF (15 mL) was added through cannula and the reaction mixture was refluxed for 6h. The contents were cooled to 0°C and the excess hydride was carefully destroyed using water (2 mL) and 3N HCl (5 mL). After the gas evolution ceased, the mixture was neutralized using 3N NaOH (8 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extract was washed with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was treated with $F_3B{:}OEt_2$ followed by aq. NaOH (3N, 5 mL) to

obtain the amine. The product was purified by column chromatography on silica gel using hexane:ethyl acetate (85:15).

Yield : 1.2 g, (76%)

IR (neat) ν_{max} : 3050, 3025, 2900, 2850, 1600, 1450, 730, 690 cm^{1}

^{1}H NMR (100 MHz, $CDCl_3$) δ ppm: 3.08-3.60 (m, 6H), 3.96 (s, 2H), 7.16-7.68 (m, 15H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 53.80, 60.81, 63.10, 126.10, 127.60, 128.00, 129.00, 129.80, 139.80, 144.90

Reduction of N-methylacetanilide using $I_2/NaBH_4$ system:

N-methylacetanilide (1.49 g, 10 mM) and $NaBH_4$ (0.88 g, 23 mM) were taken in dry THF (25 mL) under a static nitrogen atmosphere. Iodine (2.54 g, 10 mM) in dry THF (25 mL) was added dropwise at 0°C and the reaction mixture was refluxed for 3h. The contents were brought to 0°C and excess hydride was destroyed carefully using HCl (3N, 6 mL). After the gas evolution was ceased, it was neutralized using NaOH (3N, 8 mL). After work up as described above, the solvent was removed and the product N-ethyl-N-methylaniline was isolated by column chromatography on silica gel (hexane:ethyl acetate/95:5).

Yield : 1.0 g (74%)

B.P. : 84°C/10 mm; Lit.[68] 203-205°C/760 mm

IR (neat) ν_{max} : 3020 , 2950, 2800, 1600, 740, 690 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) δ ppm: 1.12 (t, 3H), 2.84 (s, 3H), 3.24-3.44 (q, 2H), 6.62-7.24 (m, 5H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 11.00, 37.20, 46.61, 112.40, 116.00, 129.12, 149.10

The spectral data of this product exhibited 1:1 correspondence with the data of the product reported.[19]

$PhNHCOCH_3$ ⟶ $PhNHCH_2CH_3$

Yield	:	0.90 g (75%)
B.P.	:	100°C/25 mm; Lit.[68] 205°C/760 mm
IR (neat) ν_{max}	:	3350 (s), 2950, 2800, 1600, 740, 690 cm^{-1}
^1H NMR (100 MHz, $CDCl_3$) δ ppm:		1.23 (t, 3H), 3.01-4.19 (q, 2H), 3.55 (bs, 1H), 6.51-7.22 (m, 5H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		15.00, 38.60, 113.00, 117.00, 129.50, 148.80

$PhCONH_2$ ⟶ $PhCH_2NH_2$

Yield	:	0.75 g (70%)
B.P.	:	72-74°C/25 mm; Lit.[68] 184-185°C/760 mm
IR (neat) ν_{max}	:	3300 (b), 1600, 740, 690 cm^{-1}
^1H NMR (100 MHz, $CDCl_3$) δ ppm:		1.54 (bs, 2H), 3.80 (s, 2H), 7.24 (s, 5H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		46.10, 126.50, 126.80, 127.90, 128.30

Reduction of benzonitrile using $I_2/NaBH_4$ system:

Benzonitrile (1.00 g, 10 mM) and $NaBH_4$ (0.88 g, 23 mM) were taken in dry THF (30 mL) under nitrogen atmosphere. The reaction flask was cooled to 0°C and iodine (2.54 g, 10 mM) dissolved in dry THF (20 mL) was added dropwise for 2.5h. The contents were refluxed for 3h. The reaction mixture was brought to 0°C and 6N HCl (8 mL) was added carefully and the

contents were further refluxed for 0.5h. The reaction flask was brought to 0°C and neutralized using solid NaOH (3 g). After usual work up, evaporation of solvent and distillation under reduced pressure, N-benzylamine was isolated.

Yield : 0.75 g (70%)

B.P. : 72-74°C/25 mm; Lit.[68] 184-185°C/760 mm

The spectral data of the product is in 1:1 correspondence with the data reported in the earlier experiment.

$CH_3(CH_2)_7CN \longrightarrow H_3C(CH_2)_7CH_2NH_2$

Yield : 1.10 g (77%)

B.P. : 76°C/10 mm; Lit.[68] 201°C/760 mm

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H), 1.26 (m, 14H), 2.80 (dist. t, 2H), 5.41 (bs, 2H)

Preparation of imine 8 using (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol 22 and benzaldehyde:

(S)-2-Amino-3-methyl-1,1'-diphenylbutan-1-ol 22 (2.55 g, 10 mM), benzaldehyde (1.27 g, 12 mM) and anhydrous Na_2SO_4 (2.2 g, 15 mM) were taken in dry methanol (20 mL) and refluxed for 6h. The reaction mixture was cooled to room temperature and filtered. Methanol was evaporated and the crude imine 8 was used further.

IR (KBr) ν_{max} : 3350, 1645, 1600, 1030 cm^{-1}

Preparation of imine 10 using (S)-valinol and benzaldehyde:

(S)-Valinol (1.03 g, 10 mM), benzaldehyde (1.27 g, 12 mM) and Na_2SO_4 (2.2 g, 15 mM) were taken in dry methanol (20 mL) and refluxed for 6h. The crude imine 10 obtained was used further.

IR (neat) ν_{max} : 3373, 1645, 1599, 1026 cm^{-1}

Reduction of imine 8 using $I_2/NaBH_4$ system:

Diborane in dry THF (45 mL) was generated using $NaBH_4$ (0.46 g, 12 mM) and I_2 (1.5 g, 6 mM) as above. The imine 8 (3.43 g, 10 mM) in dry THF (15 mL) was added to the above reagent at 0°C. The contents were stirred for 6h at room temperature, excess hydride was quenched with 3N HCl (5 mL) and neutralized using 3N NaOH (8 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extract was washed with water, brine and dried over $MgSO_4$. After evaporation of solvent and purification by column chromatography on silica gel (hexane:ethyl acetate/95:5), (S)-2-(N-benzylamino-1,1'-diphenyl-3-methyl-1-butanol 9 was isolated.

Yield : 2.95 g (85%)

M.P. : 103°C

IR (KBr) ν_{max} : 3450 (b), 3341 (s), 2957, 1600, 1074, 754, 636 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.66-0.98 (dd, 6H), 1.50 (bs, OH), 1.90-2.10 (m, 1H), 3.20-3.50 (dd, 2H), 3.65 (d, 1H), 5.10 (bs, -NH), 7.11-7.80 (m, 15H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 16.02, 22.72, 28.82, 55.09, 68.60, 78.73, 125.89, 126.17, 126.51, 127.24, 127.94,

128.09, 128.33, 128.44, 140.24, 145.41, 148.00

$[\alpha]_D^{25}$ = -39.0 (C1, $CHCl_3$)

Analysis: Calculated: C: 83.443; H: 7.873; N: 4.050

Found: C: 83.580; H: 7.930; N: 3.858

Reduction of imine 10 using $I_2/NaBH_4$ system:

Diborane in dry THF (45 mL) was generated using $NaBH_4$ (0.46 g, 12 mM) and I_2 (1.5 g, 6 mM) as mentioned earlier. The imine 10 (1.9 g, 10 mM) dissolved in dry THF (15 mL) was added at 0°C and stirred for 6h at 25°C. After work up as described in the previous experiment, N-benzylvalinol 7 was isolated by distillation under reduced pressure.

Yield : 1.60 g (83%)

B.P. : 203°C/25 mm; Lit.[70] 105-110°C/0.3 mm

IR (neat) ν_{max} : 3300, 1600, 1050, 750, 690 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.91-1.00 (dd, 6H), 1.86-1.94 (m, 1H), 2.20 (bs, 1H), 2.42-2.58 (m, 1H), 3.36-3.48 (m, 2H), 3.65-3.74 (dd, 2H), 3.80 (d, 1H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 18.35, 19.41, 28.71, 51.36, 60.42, 63.83, 127.19, 128.25, 128.54, 140.48

$[\alpha]_D^{25}$ = +15 (C1, $CHCl_3$) : Lit.[70] $[\alpha]_D^{25}$ = +1.6 (C1, MeOH)

The spectral data of this compound showed 1:1 correspondence with the data reported earlier.[70]

Preparation of (S)-N-benzoylvaline 6 using (S)-valine and benzoyl chloride:

(S)-Valine (2.34 g, 20 mM) was taken in water (20 mL) and NaOH (1.6 g, 40 mM) was added at 0°C. Benzoyl chloride (2.8 g, 20 mM) was added dropwise for 15 min. The reaction mixture was further stirred for 1h at 0°C. It was acidified with 3N HCl and neutralized to pH 7. The reaction mixture was extracted with ether (2 x 20 mL). The ether layer was washed with water, brine and dried over anhydrous $MgSO_4$. The crude (S)-N-benzoylvaline 6 was used without further purification.

Yield : 4.0 g (90%)

IR (KBr) ν_{max} : 3350, 1699, 1641, 1600 cm^{-1}

Reduction of (S)-N-benzoylvaline 6 using $I_2/NaBH_4$ system:

$NaBH_4$ (1.9 g, 55 mM) was taken in dry THF (25 mL) and N-benzoylvaline 6 (4.42 g, 20 mM) dissolved in dry THF (30 mL) was added at 0°C. The contents were stirred for 0.5h and I_2 (6.4 g, 25 mM) dissolved in dry THF (50 mL) was added to the reaction mixture at 0°C. The mixture was further stirred for 36h at room temperature. Excess hydride was carefully destroyed using water (2 mL) and 3N HCl (5 mL) and neutralized using 3N NaOH (8 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extract after usual work up gave a residue which was purified by column chromatography on silica gel (hexane:ethyl acetate/70:30) to obtain N-benzylvalinol 7. It was further purified by distillation under reduced pressure.

Yield : 2.2 g (57%)

B.P. : 203°C/25 mm; Lit.[70] 105-110°C/0.3 mm

IR (neat) ν_{max} : 3350, 1600, 1020 cm^{1}

$[\alpha]_D^{25}$ = +15.0 (C1, $CHCl_3$) Lit.[70] $[\alpha]_D^{25}$ = +1.6 (C1, MeOH)

The spectral data of this product is in 1:1 correspondence with the data reported in the earlier experiment.

Preparation of α,α-diphenylpyrrolidinemethanol 24:[39]

a) Preparation of (S)-proline-N-ethylcarbamate 28:

(S)-Proline-N-ethylcarbamate **28** was prepared using (S)-proline (1.15 g, 10 mM), anhydrous K_2CO_3 (1.32 g, 10 mM) and ethyl chloroformate (1.1 g, 10 mM) following a reported procedure.[39]

Yield : 1.76 g (96%)

IR (neat) ν_{max} : 1720, 1670 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 1.20 (t, 3H), 2.11 (m, 4H), 3.50 (m, 2H), 4.11 (m, 2H), 4.41 (t, 1H), 9.00 (bs, 1H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.01, 20.20, 23.00, 23.70, 29.30, 30.30, 46.11, 46.30, 58.00, 61.31, 154.90, 155.50, 175.80, 176.21 (more number of signals are due to the slower inversion of nitrogen lone pair)

b) Preparation of (S)-proline-N-ethylcarbamate methyl ester 29:

The methyl ester of (S)-proline-N-ethylcarbamate was prepared using (S)-proline-N-ethylcarbamate **28** (1.87 g, 10 mM) and thionyl chloride (1.77 g, 15 mM) following a reported procedure.[39] After work up, the required product was purified by column chromatography on silica gel column (hexane:

ethyl acetate/90:10).

Yield : 1.9 (95%)

IR (neat) ν_{max} : 1740, 1700 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) δ ppm: 1.20 (t, 3H), 2.01 (m, 4H), 3.50 (m, 2H), 3.71 (s, 3H), 4.10 (bs, 3H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.10, 22.91, 23.70, 29.30, 30.31, 45.51, 46.20, 51.50, 58.50, 60.60, 150.21, 153.50, 172.40, 172.90

c) Preparation of N-ethylcarbamato-α,α-diphenylpyrrolidinemethanol 30:

N-Ethylcarbamato-α,α-diphenylpyrrolidinemethanol 30 was prepared using (S)-proline-N-ethylcarbamate methyl ester 29 (2.01 g, 10 mM) and phenyl-magnesium bromide (prepared using magnesium turnings (1.94 g, 80 mM), bromobenzene (6.28 g, 40 mM)) following a reported procedure.[39] After work up, it was purified by column chromatography on silica gel (hexane:ethyl acetate/90:10).

Yield : 2.53 g (78%)

IR (KBr) ν_{max} : 3375, 1680 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 1.20 (t, 3H), 1.61 (s, 1H), 2.01 (m, 2H), 3.00 (m, 2H), 3.40 (m, 2H), 4.10 (m, 2H), 5.01 (m, 1H), 7.20-7.60 (m, 10H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.41, 22.70, 29.40, 47.60, 61.70, 65.80, 81.40, 127.10, 127.40, 127.60, 127.80, 128.01, 143.70, 146.30, 158.20

d) N-Deprotection of N-ethylcarbamato-α,α-diphenylpyrrolidinemethanol 30:

N-Deprotection was carried out using N-ethylcarbamato-α,α-diphenyl-pyrrolidinemethanol **30** (3.26 g, 10 mM) and KOH (5.6 g). The α,α-diphenyl-pyrrolidinemethanol **24** was obtained as a gummy liquid which upon standing crystallized.

Yield	:	2.3 g (90%)
M.P.	:	73°C; Lit.[37] 74.0–74.8°C
IR (neat) ν_{max}	:	3350, 1600 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) δ ppm:		1.25–1.70 (m, 5H), 2.90 (m, 2H), 4.21 (t, 1H), 4.81 (s, 1H), 7.10–7.60 (m, 10H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		25.41, 26.20, 46.70, 64.50, 77.10, 125.60, 126.01, 126.40, 126.50, 128.00, 128.72, 145.60, 148.30
$[\alpha]_D^{20}$ = −68° (C3, CH_3OH)	:	Lit.[37] $[\alpha]_D^{20}$ = −68.1 (C3.17, CH_3OH)

Preparation of (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol 22:

a) Preparation of (S)-valine methyl ester hydrochloride 44:[71]

(S)-Valine methyl ester hydrochloride **44** was prepared using (S)-valine (10.54 g, 90 mM), double distilled thionyl chloride (12 mL, 165 mM) following a reported procedure.[71] The crude (S)-valine methyl ester hydrochloride **44** obtained was recrystallized from dry methanol/ether (1:10) at 0°C.

Yield	:	13.5 g (90%)
M.P.	:	166°C; Lit.[71] 167–168°C
IR (KBr) ν_{max}	:	3300–2900 (b), 1960, 1720, 1680
$[\alpha]_D^{25}$ = +23° (C2, CH_3OH)	:	Lit.[34] $[\alpha]_D^{25}$ = +23.5° (C2, CH_3OH)

b) Preparation of (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol 22:[34]

(S)-2-Amino-3-methyl-1,1'-diphenylbutan-1-ol **22** was prepared using (S)-valine methyl ester hydrochloride **44** (4.2 g, 25 mM) and phenylmagnesium bromide (prepared from bromobenzene (34.6 g, 220 mM) and magnesium (6.0 g, 250 mM)) following a reported procedure.[34] It was purified by column chromatography on silica gel column using hexane:ethyl acetate (85:15) as eluent.

Yield	:	2.0 g (31%)
M.P.	:	94°C; Lit.[34] 94-95°C
IR (KBr) ν_{max}	:	3125, 1630 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) δ ppm:		0.90 (dd, 6H), 1.61 (bs, 3H, -NH, OH), 1.80 (m, 1H), 3.85 (d, 1H), 7.20-7.70 (m, 10H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		14.06, 22.94, 27.83, 60.18, 75.89, 125.56, 126.01, 126.36, 128.13, 128.22, 128.48, 145.07, 148.19
$[\alpha]_D^{25}$ = -125° (C1, $CHCl_3$)		Lit.[34] $[\alpha]_D^{25}$ = -127.7° (C 0.639, $CHCl_3$)

An alternate procedure was developed for the synthesis of **22** following a closely reported procedure.[39]

a) Preparation of (S)-valine-N-methylcarbamate methyl ester 45:

(S)-Valine (1.15 g, 10 mM) and dry K_2CO_3 (1.32 g, 10 mM) were taken in dry methanol (20 mL) and methyl chloroformate (2.1 g, 22 mM) was slowly added at 25°C. The reaction mixture was stirred for 12h and methanol was evaporated. Distilled water (10 mL) was added and the product was extract-

ed with chloroform (3 x 15 mL). After work up and purification by chromatography on silica gel (hexane:ethyl acetate/95:5), (S)-valine-N-methylcarbamate methyl ester 45 was isolated.

Yield : 1.6 g (84%)

IR (neat) ν_{max} : 3350 (b), 1720, 1680 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.86-0.97 (dd, 6H), 1.67 (d, 1H), 2.13-2.15 (m, 1H), 3.68 (s, 3H), 3.73 (s, 3H), 4.23-4.30 (m, 1H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 17.47, 18.88, 31.80, 58.12, 58.40, 59.06, 157.06, 172.83

b) Preparation of (S)-(N-methylcarbamato)-1,1'-diphenylbutan-1-ol 46:

Phenylmagnesium bromide was prepared using bromobenzene (6.28 g, 40 mM) and magnesium turnings (1.2 g, 50 mM) in THF (50 mL). In the reaction flask (S)-valine-N-methylcarbamate methyl ester 45 (1.89 g, 10 mM) was taken in dry THF (20 mL) and cooled to 0°C. Phenylmagnesium bromide prepared as above was added through a cannula under nitrogen atmosphere. The reaction mixture was further stirred for 3h at 0°C and quenched with saturated ammonium chloride solution (2 mL). The organic layer was decanted from the magnesium salts and it was extracted with chloroform (2 x 10 mL). The combined organic extract was washed with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (90:10), the diphenyl carbinol 46 was isolated.

Yield : 2.3 g (74%)

IR (KBr) ν_{max} : 3350, 1660, 1600, 1060 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.78-0.88 (dd, 6H), 1.50 (s, 1H), 1.68-

1.86 (m, 1H), 2.50 (bs, 1H), 3.50 (s, 3H), 4.56 (d, 1H), 7.10-7.50 (m, 10H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 17.30, 22.70, 28.82, 52.11, 59.80, 82.20, 125.50, 125.70, 126.90, 129.41, 145.51, 146.50, 157.80

c) **N-Deprotection of (S)-(N-methylcarbamato)-1,1'-diphenylbutan-1-ol 46:**

In an round-bottom flask, (S)-(N-methylcarbamato)-1,1'-diphenylbutan-1-ol **46** (3.15 g, 10 mM) was taken in dry methanol (20 mL). KOH (5.6 g, 100 mM) was added and the contents were refluxed for 4h. Methanol was evaporated and water (15 mL) was added. The reaction mixture was extracted with chloroform (3 x 20 mL). After work up, the product (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol **22** obtained was purified on silica gel column using hexane:ethyl acetate (85:15).

Yield : 1.90 g (74%)

The spectral data of this product showed 1:1 correspondence with the data of the product obtained in the earlier experiment.

Preparation of (S)-2-(N-benzylamino)-3-methyl-1,1'-diphenylbutan-1-ol 9:

(S)-2-Amino-3-methyl-1,1'-diphenylbutan-1-ol **22** (2.55 g, 10 mM) was taken in dry ethanol (20 mL) and the reaction flask was flushed with nitrogen gas. Benzaldehyde (1.6 g, 15 mM) was added and the mixture was stirred for 12h. The contents were cooled to 0°C and sodium borohydride (0.8 g, 20 mM) was added and the reaction mixture was further stirred for 6h. Excess hydride was destroyed using 3N HCl (5 mL) and neutralized using

3N NaOH (7 mL). The reaction mixture was extracted with ethyl acetate (3 x 15 mL). After usual work up, (S)-2-(N-benzylamino)-3-methyl-1,1'-diphenyl-butan-1-ol 9 obtained was purified on silica gel column using hexane:ethyl acetate (98:2) as eluent.

Yield : 2.6 g (75%)

M.P. : 102°C

$[\alpha]_D^{25}$: -39.0^{o} (C1, $CHCl_3$)

The spectral data of this product showed 1:1 correspondence with the data of the product obtained in an earlier experiment.

Preparation of (S)-2-(N-isopropylamino)-3-methyl-1,1'-diphenylbutan-1-ol 43:

The experimental procedure described above was followed except that acetone was used instead of benzaldehyde. The required product (S)-2-(N-isopropylamino)-3-methyl-1,1'-diphenylbutan-1-ol 43 was purified on silica gel column using hexane:ethyl acetate (98:2).

Yield : 2.1 g (70%)

M.P. : 121°C

IR (KBr) ν_{max} : 3341, 3175, 2964, 1597, 1055, 758, 632 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.65 (d, 3H), 0.85 (d, 3H), 0.96-1.06 (dd, 6H), 1.40 (bs, OH), 1.90-2.30 (m, 2H), 3.65 (d, 1H), 5.21 (bs, -NH), 7.10-7.80 (m, 10H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 15.85, 22.97, 23.07, 23.93, 28.54, 47.26, 65.14, 78.07, 126.18, 126.38, 127.77,

127.93, 145.80, 149.09

$[\alpha]_D^{25}$: -51.0^{o} (C1, $CHCl_3$)

Analysis: Calculated: C: 83.443; H: 7.873; N: 4.05

Found: C: 83.580; H: 7.90; N: 3.858

Reduction of (S)-valine using the $I_2/NaBH_4$ system:[25]

(S)-Valine (8.8 g, 75 mM) and sodium borohydride (6.8 g, 170 mM) were taken in dry THF (200 mL). I_2 (18.8 g, 75 mM) dissolved in dry THF (50 mL) was added dropwise to the above slurry at 0°C for 1h. The reaction mixture was refluxed for 20h. The contents were cooled to 10°C and excess hydride was quenched carefully by dropwise addition of methanol until the solution becomes clear. The reaction mixture was concentrated and to the paste obtained, 10N KOH solution (100 mL) was added and the contents were refluxed for 4h. The reaction flask was brought to room temperature and extracted with ether (3 x 50 mL). The ether layer was washed with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and distillation of the residue, (S)-valinol was obtained.

Yield : 5.4 g (70%)

B.P. : 80°C/7 mm; Lit.[25] 75°C/ 6 mm

IR (neat) ν_{max} : 3350, 1050 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.82-1.02 (dd, 6H), 1.42-1.68 (m, 1H), 2.43 (bs, 1H), 3.30 (dist. t, 2H), 3.52-3.76 (m, 1H), 5.05 (bs, $-NH_2$)

$[\alpha]_D^{25}$ = $+17^{o}$ (C10, EtOH) : Lit.[25] $[\alpha]_D^{25}$ = $+17^{o}$ (C10, EtOH)

Preparation of (S)-2-(N-benzylamino)-3-methylbutan-1-ol 7 using (S)-valinol and benzaldehyde:[62]

(S)-2-(N-benzylamino)-3-methylbutan-1-ol 7 was prepared using (S)-valinol (1.03 g, 10 mM) , benzaldehyde (1.6 g, 1.5 mM) and sodium borohydride (0.8 g, 20 mM) following a reported procedure.[62] After work up, the required product was purified by distillation under reduced pressure.

Yield : 1.35 g (70%)

B.P. : 203°C/25 mm; Lit.[70] 105-110°C/0.3 mm

$[\alpha]_D^{25}$ = +15° (C1, $CHCl_3$) : Lit.[69] $[\alpha]_D^{25}$ = +1.6° (C1, MeOH)

The spectral data of this product showed 1:1 correspondence with the data obtained in the earlier experiment.

Reduction of acetophenone (1 eq.) using $NaBH_4$ (2 eq.)/I_2 (1 eq.) system in the presence of α,α-diphenylpyrrolidinemethanol 24 (1 eq.):

In a two-necked side-arm flask, $NaBH_4$ (0.76 g, 20 mM) was taken in dry THF (30 mL). Iodine (2.54 g, 10 mM) dissolved in dry THF (20 mL) was added dropwise for 0.5h at 0°C. α,α-Diphenylpyrrolidinemethanol **24** (2.54 g, 10 mM) dissolved in dry THF (20 mL) was added through cannula at 0°C. The contents were refluxed for 3h. The reaction flask was brought to room temperature and acetophenone (1.2 g, 10 mM) was added and the contents were further stirred for 10 min. at room temperature. Excess hydride was destroyed carefully using water (2 mL) and α,α-diphenylpyrrolidinemethanol **24** was removed as hydrochloride salt using 3N HCl (3 x 15 mL). The organic layer was washed with water, saturated sodium thiosulphate solution, brine and dried over anhydrous $MgSO_4$. After evaporation of solvent and distil-

lation under reduced pressure, 1-phenylethanol was isolated.

Yield : 1.1 g (90%)

B.P. : 108°C/25 mm, Lit.[72] 203°C/760 mm

IR (neat) ν_{max} : 3350, 3026, 1600 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 1.40 (d, 3H), 2.90 (bs, 1H), 4.80 (q, 1H), 7.30 (m, 5H)

$[\alpha]_D^{25}$ = +31° (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Reduction of acetophenone (1 eq.) using $NaBH_4$ (1.2 eq.)/I_2 (0.6 eq.) system in the presence of α,α-diphenylpyrrolidinemethanol 24 (0.2 eq.):

In a two-necked round-bottom flask, $NaBH_4$ (0.46 g, 12 mM) was taken in dry THF (20 mL). Iodine (1.5 g, 6 mM) dissolved in dry THF (15 mL) was added dropwise at 0°C for 0.5h. α,α-Diphenylpyrrolidinemethanol **24** (0.51 g, 2 mM) dissolved in dry THF (10 mL) was added through cannula at 0°C. The contents were refluxed for 3h. The reaction mixture was brought to room temperature and acetophenone (1.2 g, 10 mM) was added and the contents were further stirred for 10 min. Excess hydride was destroyed using water (2 mL) and α,α-diphenylpyrrolidinemethanol **24** was removed as hydrochloride salt using 3N HCl (2 x 10 mL). The organic layer was washed with water, sodium thiosulphate solution, brine and dried over anhydrous $MgSO_4$. On evaporation of solvent and distillation under reduced pressure, 1-phenylethanol was isolated.

Yield : 1.04 g (85%)

$[\alpha]_D^{25}$ = +29.6° (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Reduction of acetophenone (1 eq.) using $NaBH_4$ (1.2 eq.)/I_2 (0.6 eq.) system in the presence of α,α-diphenylpyrrolidinemethanol 24 (0.2 eq.) and N,N-diethylaniline (0.2 eq.):

In a two-necked round-bottom flask, $NaBH_4$ (0.46 g, 12 mM) was taken in dry THF (20 mL). Iodine (1.5 g, 6 mM) dissolved in dry THF (15 mL) was added dropwise at 0°C for 0.5h. α,α-Diphenylpyrrolidinemethanol **24** (0.51 g, 2 mM) dissolved in dry THF (10 mL) was added followed by N,N-diethylaniline (0.31 g, 2 mM). The contents were refluxed for 4h and then cooled to room temperature. Acetophenone (1.2 g, 10 mM) was added . The reaction mixture was stirred for 10 min. at room temperature. Excess hydride was carefully quenched with water (2 mL) and both the amines were removed as hydrochloride salts using 3N HCl (3 x 10 mL). The organic layer was further washed with water, sodium thiosulphate, brine and dried over anhydrous $MgSO_4$. After evaporation of solvent and distillation under reduced pressure, 1-phenylethanol was obtained.

Yield : 0.98 g (80%)

$[\alpha]_D^{25}$ = +31.4° (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Reduction of acetophenone (1 eq.) using $NaBH_4$ (1 eq.)/I_2 (0.5 eq.) and oxazaborolidine catalyst 23 (0.2 eq.) prepared in benzene:

In a two-necked round-bottom flask, H_3B:THF complex (10 mM) was prepared using $NaBH_4$ (0.38 g, 10 mM) and I_2 (1.27 g, 5 mM) as described above. In another two-necked round-bottom flask, α,α-diphenylpyrrolidinemethanol **24** (0.51 g, 2 mM) was taken in dry benzene (30 mL). Diborane (2.5 mM) generated, using iodine (0.65 g, 2.5 mM) and $NaBH_4$ (0.2 g, 5 mM) in diglyme, was bubbled through the above solution for 2h at 10°C. N,N-di-

ethylaniline (0.31 g, 2mM) was added and the contents were refluxed for 4h. The reaction mixture was brought to room temperature H_3B:THF complex prepared above was transferred through cannula. Acetophenone (1.2 g, 10 mM) was added and the contents were further stirred for 10 min. The excess hydride was destroyed carefully with water (2 mL) and the amines were removed as hydrochloride salts using 3N HCl (3 x 10 mL). The organic layer was washed with water, sodium thiosulphate, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and distillation under reduced pressure, 1-phenylethanol was isolated.

Yield : 1.0 g (82%)

$[\alpha]_D^{25} = +32.3^o$ (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

This experiment was repeated except that dry benzene (10 mL) was added to borane solution prepared in THF. The contents were refluxed for 0.5h and the supernatant borane solution in THF/benzene mixture was utilized. After work up, the product was purified by distillation under reduced pressure and the optical rotation was measured.

Yield : 0.98 g (80%)

$[\alpha]_D^{25} = +37.30^o$ (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

Preparation of H_3B:THF complex by bubbling diborane generated using $NaBH_4/I_2$ system in diglyme into THF solvent:

In a two-necked generation flask, $NaBH_4$ (0.38 g, 10 mM) was placed in diglyme (10 mL) and iodine (1.27 g, 5 mM) dissolved in diglyme (10 mL) was added dropwise for 3h. Thus generated diborane and hydrogen gas was bubbled through a side tube into reaction flask containing dry THF (15 mL) at 0°C. H_3B:THF complex (~80%, reaction with Ph_3P) thus prepared was used

for reduction in the next experiments.

Reduction of acetophenone (1 eq.) using H_3B:THF complex (0.8 eq.) in the presence of oxazaborolidine 23 (0.2 eq.) prepared in benzene:

The H_3B:THF complex (~8 mM) was prepared as mentioned above. In another two-necked round-bottom flask, oxazaborolidine **23** catalyst (0.2 eq.) was prepared by bubbling diborane (2.5 mM) through benzene solution of α,α-diphenylpyrrolidinemethanol **24** (0.51 g, 2 mM) as outlined earlier. The H_3B:THF complex prepared as above was transferred into this reaction flask through cannula under nitrogen atmosphere. Acetophenone (1.2 g, 10 mM) was added and the contents were stirred for 10 min. at 30°C. Excess hydride was carefully destroyed using water (2 mL) and the amines were removed as hydrochloride salts using 3N HCl (3 x 15 mL). The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. After evaporation of solvent and distillation under reduced pressure, 1-phenylethanol was isolated.

Yield : 1.12 g (91%)

$[\alpha]_D^{25} = +42.1^o$ (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

Enantiomeric excess was found to be 95.5% (HPLC chart No. 2) using HPLC on chiral column, chiralcel OD using hexane:isopropanol (95:5) solvent.

Reduction of acetophenone (2 eq.) using H_3B:THF complex (1.6 eq.) in the presence of oxazaborolidine 23 (0.2 eq.) prepared in benzene:

The reduction was carried out in the same way as described in the

previous experiment. After work up and distillation under reduced pressure, 1-phenylethanol was obtained.

Yield : 2.2 g (90%)

$[\alpha]_D^{25} = +42^o$ (C3,CH_3OH) : Lit [72] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

Enantiomeric excess was also determined using chiral HPLC on chiral column, chiralcel OD using hexane:isopropanol (95:5) solvent and was found to be 94.7% (R) (HPLC chart No. 3).

Reduction of acetophenone (1 eq.) using H_3B:THF complex (0.8 eq.) in the presence of diphenylvalinol 22 derived oxazaborolidine 54 (0.2 eq.) prepared in benzene:

The H_3B:THF complex was prepared using $NaBH_4$ (0.4 g, 10 mM) and I_2 (1.27 g, 5 mM) in THF (10 mL) as described earlier.

In another reaction flask, oxazaborolidine catalyst 54 (0.2 eq.) was prepared by bubbling diborane (2.5 mM) through benzene solution of (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol 22 (0.51 g, 2mM) at 10°C. The contents were stirred for 16h at room temperature. The H_3B:THF complex prepared was transferred into the reaction flask through cannula. Acetophenone (1.2 g, 10 mM) was added and the contents were further stirred for 0.5h at room temperature. Rest of the procedure mentioned as above was followed and the product 1-phenylethanol was purified by distillation under reduced pressure.

Yield : 1.05 g (86%)

$[\alpha]_D^{25} = +37.67^o$ (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

The spectral data of the product showed 1:1 correspondence with the authentic sample.

Reduction of acetophenone (1 eq.) using borane:oxazaborolidine complex prepared from (S)-N-benzylvalinol 7 (1 eq.):

Diborane gas (20 mM) was bubbled through the benzene solution of (S)-N-benzylvalinol 7 (1.93 g, 10 mM) for 4h at 10°C. The bubbler was replaced by a glass stopper and the contents were refluxed for 6h. The reaction mixture was brought to 10°C and again diborane (20 mM) was bubbled. The reaction flask was flushed with nitrogen gas. Acetophenone (1.2 g, 10 mM) was added at room temperature and stirred for 2h. The mixture was quenched with water (2 mL). After usual work up, the product 1-phenylethanol, was isolated by distillation under reduced pressure.

Yield : 1.04 g (85%)

$[\alpha]_D^{25}$ = +0.67° (C3, CH_3OH) : Lit.[72] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Attempted reduction of acetophenone (1 eq.) using oxazaborolidine prepared from (S)-2-(N-benzylamino)-1,1'-diphenylbutan-1-ol 9:

Diborane gas (20 mM) was bubbled through the benzene solution of (S)-2-(N-benzylamino)-1,1'-diphenylbutan-1-ol 9 (3.45 g, 10 mM) for 4h at 0°C. The contents were refluxed for 6h. The reaction mixture was brought to 10°C. Diborane (20 mM) was bubbled again. Acetophenone (1.2 g, 10 mM) was added and the mixture was stirred for 24h at room temperature. The reaction mixture was quenched with water (2 mL) and the amino alcohol was removed as hydrochloride salt using 3N HCl (3 x 10 mL). After work up, acetophenone was recovered.

Yield : 1.1 g (91%)

IR (neat) ν_{max} : 1680, 1600 cm^{-1}

In the reduction of acetophenone (1 eq.) using oxazaborolidine prepared from (S)-2-(N-isopropylamino)-1,1'-diphenylbutan-1-ol **43**, the acetophenone was quantitatively recovered.

Hydroboration of α-methylstyrene (1 eq.) using borane:oxazaborolidine complex 53 prepared using (S)-valinol (1 eq.):

Diborane gas (20 mM) was bubbled through the benzene solution of (S)-valinol (1.0 g, 10 mM) for 4h at 10°C. The contents were further stirred for 16h at room temperature. The reaction mixture was brought to 10°C and again diborane (20 mM) was bubbled. The reaction flask was flushed with nitrogen gas and α-methylstyrene (1.2 g, 10 mM) was added at 10°C and the mixture was further stirred for 12h at room temperature. The mixture was quenched with water (2 mL), THF (10 mL) was added and oxidized using 3N NaOH (15 mL)/H_2O_2 (30%, 15 mL) at 10°C. The contents were stirred for 4h. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic extract was treated with 3N HCl (2 x 10 mL) to remove valinol and washed with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (85:15) as eluent , 2-phenylpropan-1-ol was isolated. It was further purified by distillation under reduced pressure.

Yield : 1.12 g (82%)

B.P. : 136°C/25 mm; Lit.[68] 110-111°C/10 mm

IR (neat) ν_{max} : 3375, 3050, 2900, 1600, 1080 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 1.28 (d, 3H), 1.55 (s, -OH), 2.90-3.10 (m, 1H), 3.72 (d, 2H), 7.20-7.60 (m, 5H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 25.20, 70.35, 125.27, 127.29, 128.31, 145.66

$[\alpha]_D^{25}$ = +0.33° (C3, CH_3OH) Lit.[72] $[\alpha]_D^{25}$ = -12.0° (C3.76, CH_3OH), 85% ee

Hydroboration of α-methylstyrene (1 eq.) using borane-oxazaborolidine complex prepared using (S)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol 22 (1 eq.):

The above mentioned experimental procedure was followed except that the (S)-diphenylvalinol 22 was used instead of (S)-valinol. After work up, the product was purified by distillation under reduced pressure.

Yield : 1.0 g (73%)

$[\alpha]_D^{25}$ = -1.2° (C3, CH_3OH); Lit.[72] $[\alpha]_D^{25}$ = -12.0° (3.76, CH_3OH) for 85% ee

Hydroboration of α-methylstyrene (1 eq.) using borane:oxazaborolidine complex prepared using (S)-2-(N-benzylamino)-3-methylbutan-1-ol 7 (1 eq.) was carried out following the procedure outlined for reduction of acetophenone. After work up, the product 2-phenylpropan-1-ol was purified by distillation under reduced pressure.

Yield : 1.05 g (77%)

$[\alpha]_D^{25}$ = +1.0° (C3, CH_3OH) Lit.[72] $[\alpha]_D^{25}$ = -12.0° (C3.76, CH_3OH) for 85% ee

Attempted hydroboration of α-methylstyrene (1 eq.) using borane:oxazaborolidine complex prepared using (S)-2-(N-benzylamino)-3-methyl-1,1'-diphenylbutan-1-ol 9 (1 eq.):

The above mentioned experimental procedure was followed except that (S)-N-benzyldiphenylvalinol 9 was used instead of N-benzylvalinol 7. α-Methylstyrene (1.2 g, 10 mM) was added and the contents were stirred for 24h at room temperature. After H_2O_2/NaOH oxidation and work up, only unreacted α-methylstyrene (90%) was recovered.

In a similar hydroboration experiment, using (S)-N-isopropyldiphenylvalinol 43 in the place of (S)-N-benzyldiphenylvalinol 7 also only α-methylstyrene (80%) was recovered.

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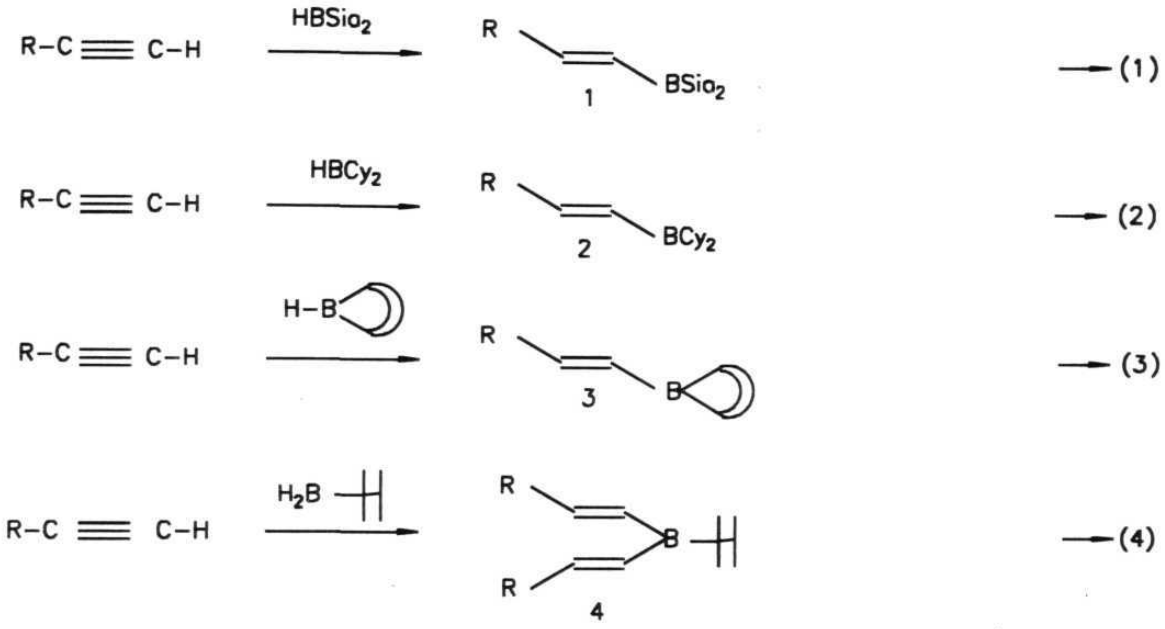
Chapter 2

Studies on the Development of Carbon-Carbon Bond Formation Reactions Using Alkenylcatecholborane Derivatives

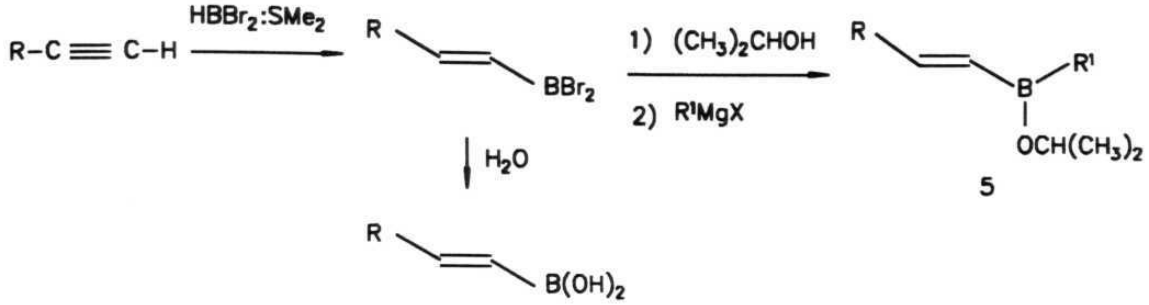
2.1. BACKGROUND AND OBJECTIVES

Alkenylboranes can be synthesized using several monohydroborating agents. For example, the dialkylboranes such as disiamylborane,[1] dicyclohexylborane,[2] 9-BBN[3] and monoalkylborane such as thexylborane[3] were used for the preparation of alkenylborane intermediates (eqns 1-4).



However, there are disadvantages in the use of these alkyl substituted alkylboranes as the alkyl group also participate in the transfer reactions. The dihaloboranes are more useful since the halo groups can be replaced by other alkyl groups later. Also, they can be readily converted to the corresponding boronic acid derivatives (Scheme 1).[4]

Scheme 1:



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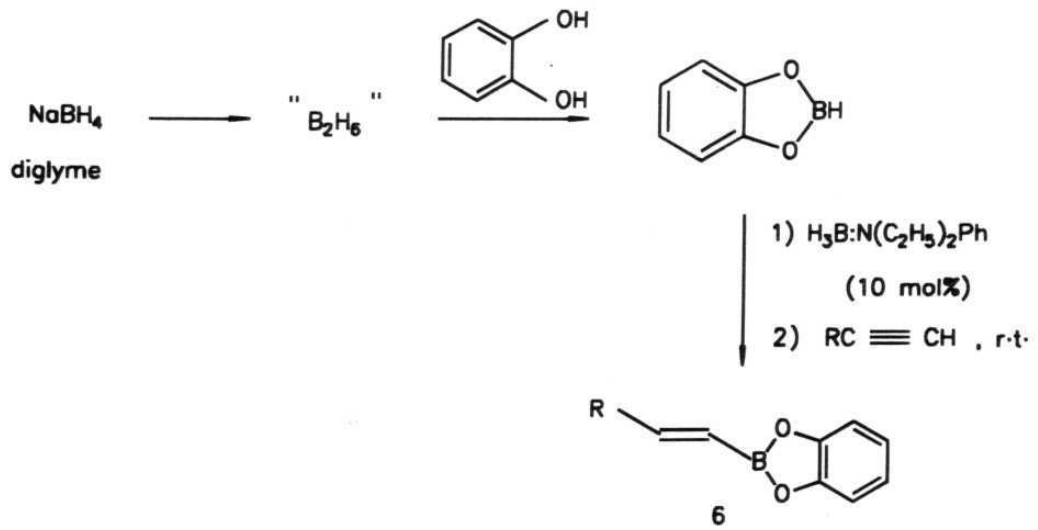
The alkenyl boronic ester derivatives can be also readily prepared by hydroboration of alkynes using catecholborane. Generally, catecholborane is prepared in THF solvent by the reaction of catechol with H_3B:THF[5] Catecholborane prepared in this manner needs prior distillation before usage as excess of H_3B:THF is generally used for preparation of the reagent. From this laboratory, it was reported that catecholborane can be readily prepared by bubbling B_2H_6 generated by dropwise addition of I_2 in diglyme to $NaBH_4$, through a suspension of catechol in benzene.[6] It was found that this reagent can be used for the hydroboration of alkynes and alkenes at refluxing conditions.[7] It was also observed that H_3B:N,N-diethylaniline complex (10 mol%) catalyzes the formation of 1-alkenylborane derivatives at ambient temperature (Scheme 2).[6]

Scheme 2:



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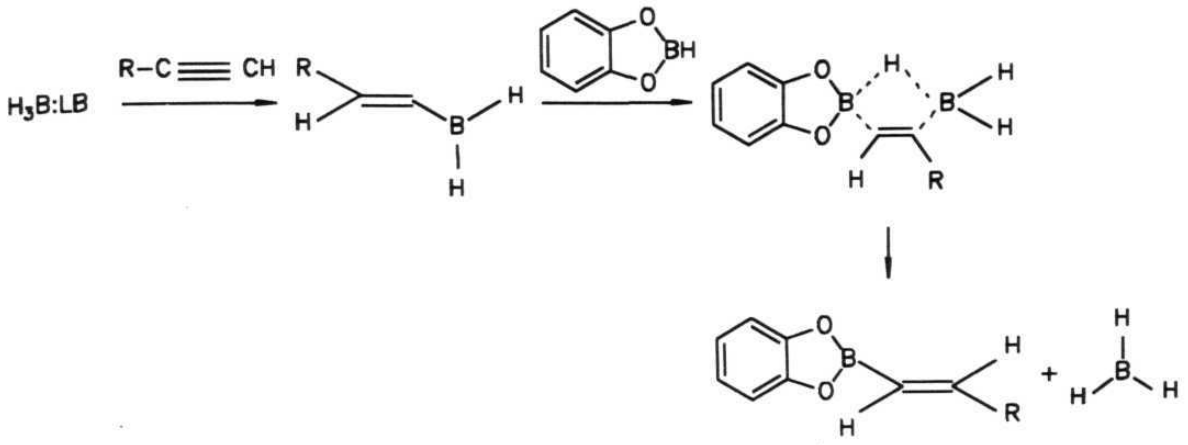
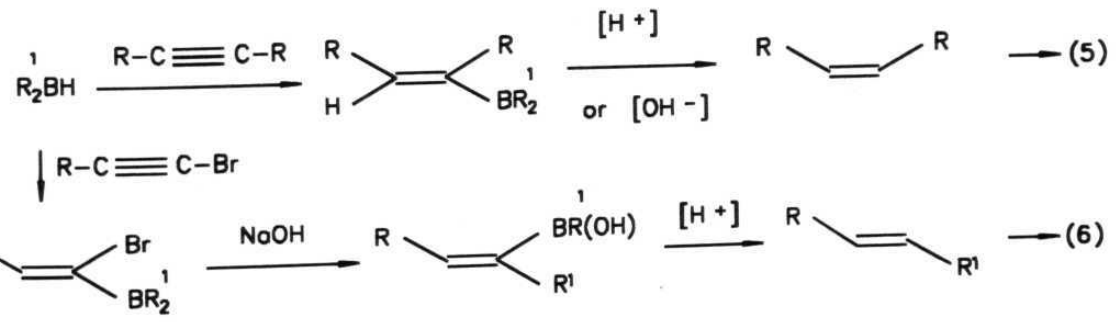


In continuation of this study, we became interested in developing C-C bond formation reactions using alkenyl catecholborane. We have decided to investigate both inter- and intramolecular alkyl transfer reactions using 1-alkenylcatecholborane and various Grignard reagents in order to synthesize (Z)- and (E)-olefins.

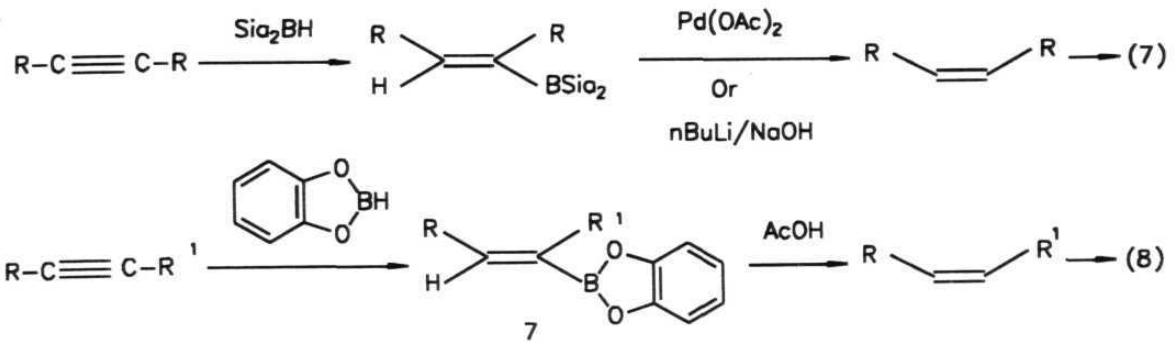
Highly stereospecific syntheses of (Z)- and (E)-disubsituted alkenes via organoboranes are well documented in the literature.[4,8-17] It may be helpful to briefly review the reports on the synthesis of (Z)- and (E)-alkenes from alkenylboranes.

The (E)-(1-alkenyldialkyl)borane derivatives on protonolysis gives (Z)-alkenes (eqns. 5 and 6).[8,9]



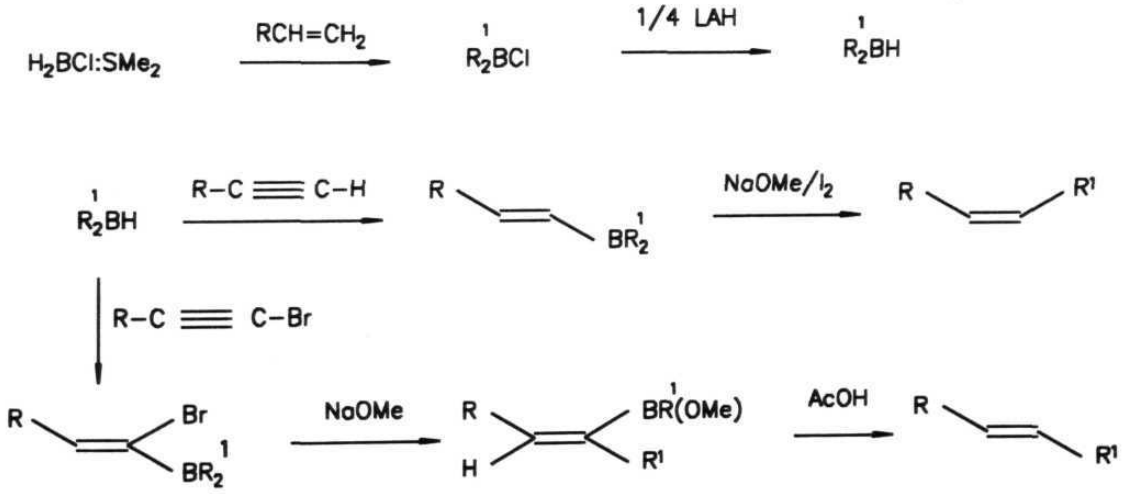
However, the limitation of this method is the requirement of hindered alkenes for the preparation of the hydroborating agent.

Brown and co-workers developed several methods for the synthesis of both (Z)- and (E)-alkenes. Some of these important methods are outlined here. It was reported that disubstituted alkynes on hydroboration and protonolysis sequence afforded the corresponding (Z)-alkenes (eqns. 7 & 8).[11-13]



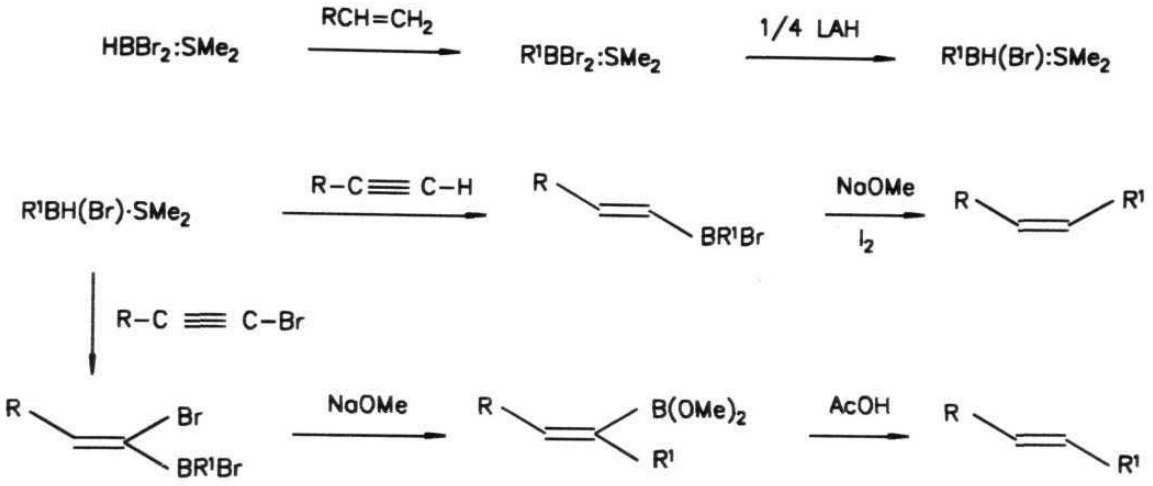
Various haloborane reagents were also utilized to prepare the desired (Z)-alkenes through a stepwise process (Scheme 3).[4,14]

Scheme 3:



The drawback of this method is requirement of two equivalents of 1-alkene, especially when the 1-alkene is precious or difficult to synthesize. This problem was surmounted by using dibromoborane:dimethylsulfide complex (Scheme 4).[4,15]

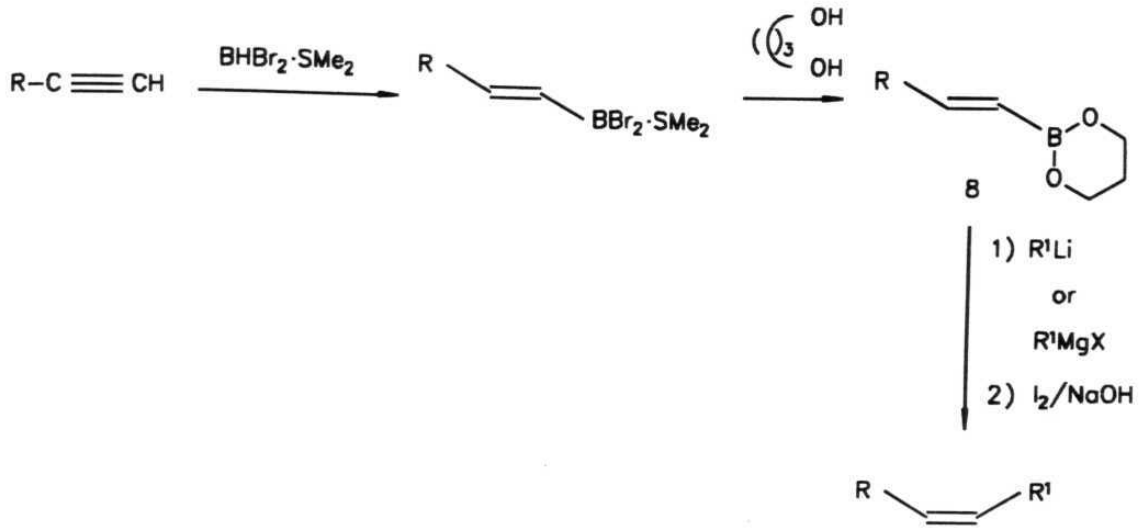
Scheme 4:



The method outlined above (Scheme 4) provides a convenient procedure for the synthesis of stereochemically pure olefins. The only disadvantage is that the alkyl groups which are not available through hydroboration cannot be synthesized following this method.

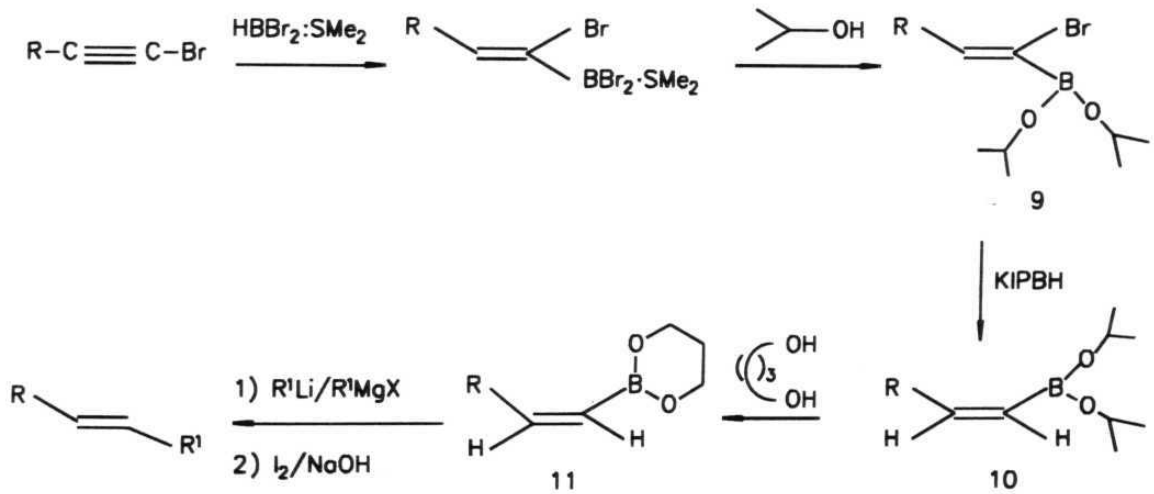
Brown and co-workers also employed various Grignard and lithium reagents for this purpose (Schemes 5 and 6).[4]

Scheme 5:



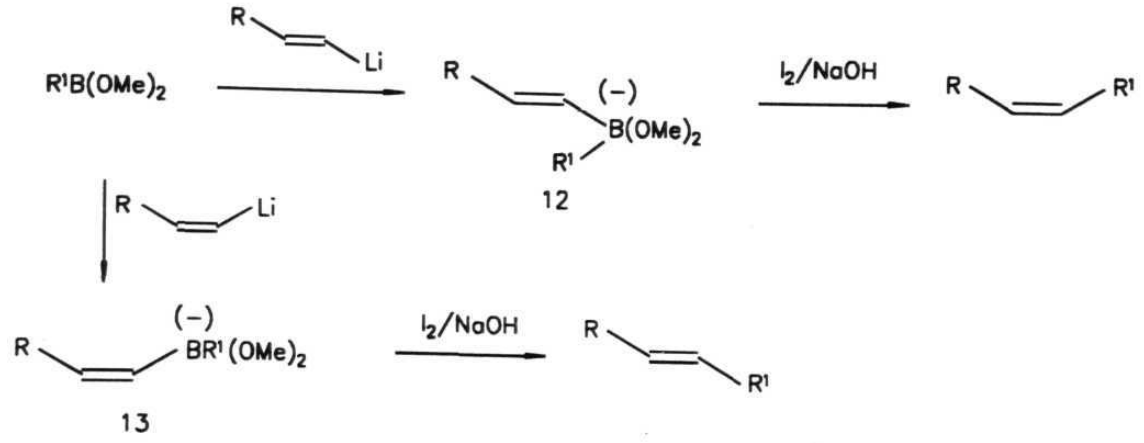
An interesting (E)–olefin synthesis was developed using 1–bromoalkynes for hydroboration (Scheme 6).

Scheme 6:



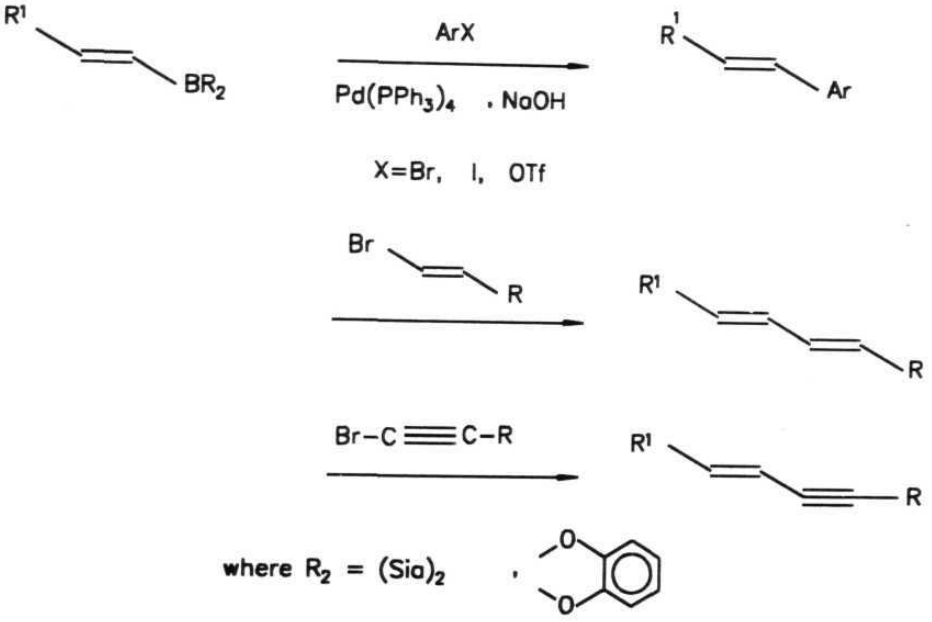
Evans et al have reported the synthesis of (Z)– and (E)–olefins as outlined in Scheme 7.[16]

Scheme 7:



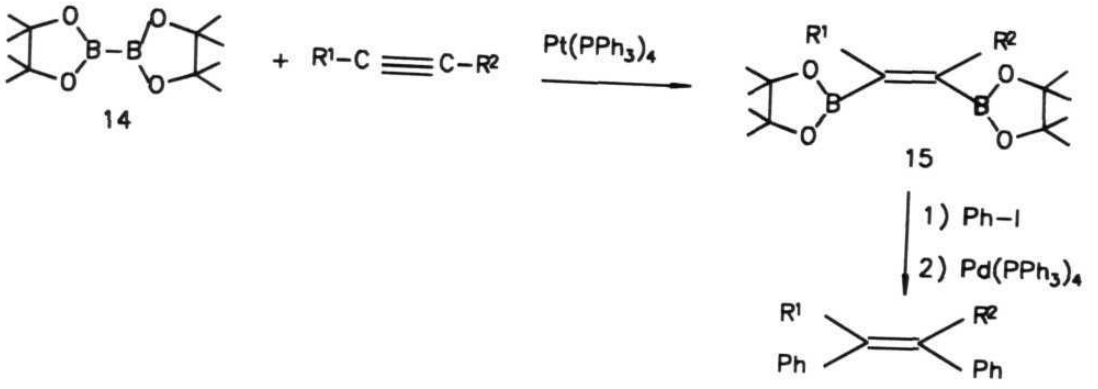
Suzuki et al have reported the cross-coupling of 1-alkenylborane derivatives with aryl halides, alkenyl halides and alkynyl halides in the presence of palladium complexes.[17-23]

Scheme 8:



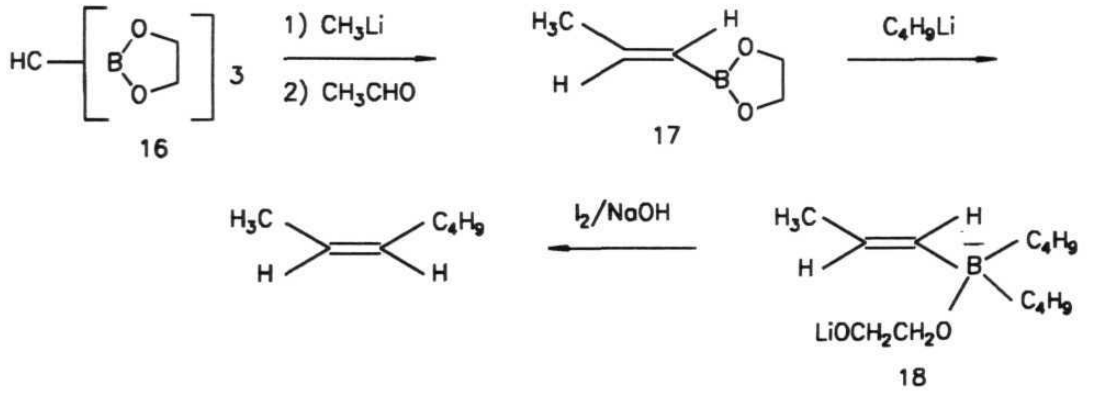
Very recently, they have developed a cis-diboration and cross-coupling sequence using transition metal catalysts for the synthesis of tri and tetra substituted olefins (Scheme 9).[24]

Scheme 9:



Sometime back, Matteson and co-workers briefly reported the synthesis of (Z)-alkenes using tris[ethylenedioxyboryl]methane 16 as synthon (Scheme 10).[10]

Scheme 10:



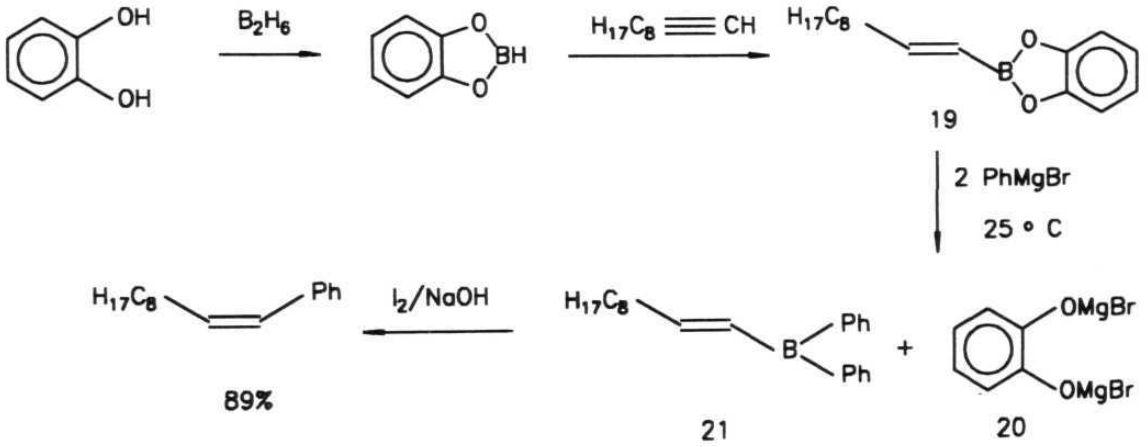
In this laboratory, utilization of alkenylcatecholboranes obtained through hydroboration was briefly explored for the synthesis of alkenes through reaction with RMgX followed by I_2 induced rearrangement.[25] We have decided to further examine this process and also investigate the application of this methodology for certain naturally occurring (Z)-olefins and (Z)-olefinic alcohols.

2.2. RESULTS AND DISCUSSION

2.2.1. Synthesis of (Z)-olefins and (Z)-olefinic alcohols:

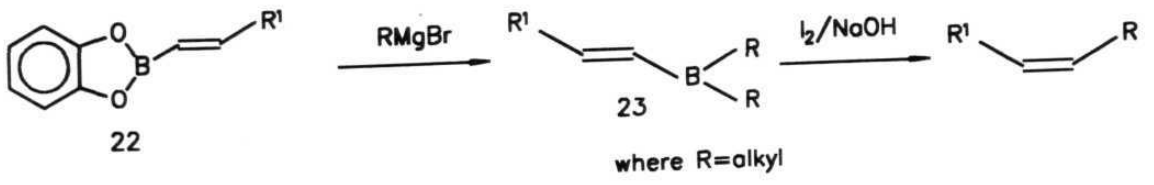
As outlined earlier, a convenient procedure has been developed for the preparation of catecholborane in this laboratory which can be used for the synthesis of alkylcatecholborane and 1-alkenylcatecholborane. It was briefly reported that (Z)-1-phenyl-1-decene can be prepared using 1-decenylcatecholborane and phenylmagnesium bromide followed by iodine-induced rearrangement (Scheme 11).[24]

Scheme 11:

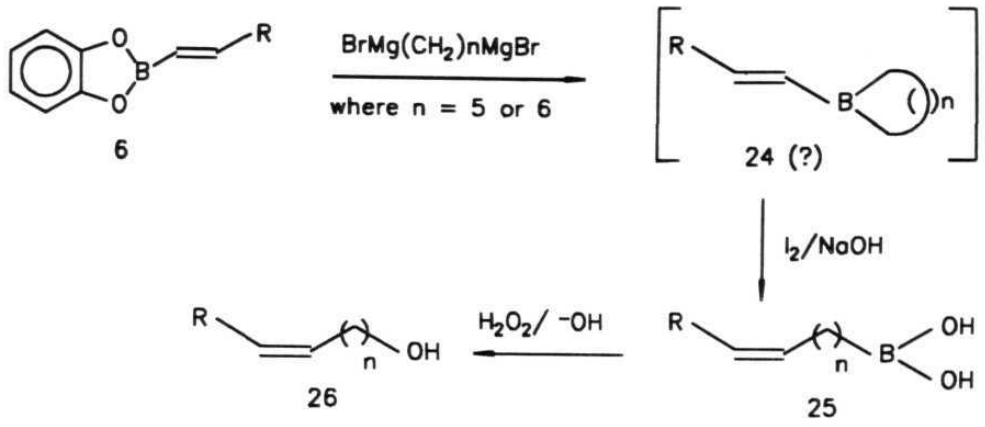


However, in the case of alkylmagnesium bromides, the corresponding (Z)-olefins were obtained in low yields (30%). We have further explored the synthesis of (Z)-olefins using various mono and di-Grignard reagents as envisaged in Schemes 12 and 13.

Scheme 12:



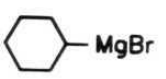
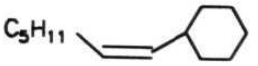
Scheme 13:



It was found that the reaction of 1-heptenylcatecholborane with cyclohexylmagnesium bromide under refluxing conditions followed by I_2/NaOH treatment at $-10^{o}C$, gave the corresponding (Z)-1-cyclohexyl-1-heptene in 62% yield (entry 1, Table 1). Following this methodology, the natural product *disparlure* precursor olefin, (Z)-2-methyl-7-octadecene, was obtained in 59% yield, starting from 1-dodecenylcatecholborane and 5-methylhexylmagnesium bromide (entry 2, Table 1). Small amount (~ 10%) of the aldehyde produced by the oxidation of the 1-dodecenylboronic acid was also obtained in this reaction. Fortunately, the desired hydrocarbon product could be readily separated.

We have also used various di-Grignard reagents, prepared from the corresponding dibromides for the synthesis of the corresponding (Z)-olefinic alcohols. As outlined in Scheme 13, the formation of 1-alkenylborinane and 1-alkenylborepane intermediates **24** were envisaged in the reaction of the 1,5- and 1,6-di-Grignard reagents with 1-alkenylcatecholboranes. These intermediates on NaOH/I_2 treatment followed by $H_2O_2/^{-}OH$ oxidation produced the corresponding unsaturated olefinic alcohols **26**.

Table 1. Synthesis of (Z)-olefins and (Z)-olefinic alcohols using various Grignard reagents

Entry No.	Alkyne[a]	Grignard reagent[b]	Product[c]	Yield (%)[e]
1	$C_5H_{11}C\equiv CH$			62[d]
2	$C_{10}H_{21}C\equiv CH$	$(CH_3)_2CH(CH_2)_4MgBr$	$C_{10}H_{21}CH=CH(CH_2)_4CH(CH_3)_2$	59
3	$C_{10}H_{21}C\equiv CH$	$BrMg(CH_2)_5MgBr$	$C_{10}H_{21}CH=CH(CH_2)_5-OH$	47[d]
4	$C_8H_{17}C\equiv CH$	$BrMg(CH_2)_5MgBr$	$C_8H_{17}CH=CH(CH_2)_5-OH$	44
5	$C_4H_9C\equiv CH$	$BrMg(CH_2)_5MgBr$	$C_4H_9CH=CH(CH_2)_5-OH$	40
6	$C_8H_{17}C\equiv CH$	$BrMg(CH_2)_6MgBr$	$C_8H_{17}CH=CH(CH_2)_6-OH$	40
7	$C_6H_{13}C\equiv CH$	$BrMg(CH_2)_6MgBr$	$C_6H_{13}CH=CH(CH_2)_6-OH$	35
8	$C_4H_9C\equiv CH$	$BrMg(CH_2)_6MgBr$	$C_4H_9CH=CH(CH_2)_6-OH$	30

a) All the reactions were carried out using 5.2 mM of catecholborane and 5 mM of 1-alkyne.

b) RMgBr prepared using RBr (10 mM) and Mg (15 mM) and $BrMg(CH_2)_nMgBr$ prepared using $Br(CH_2)_nBr$ (7.5 mM) and Mg (20 mM) were utilized.

c) All the products were identified by IR, ^1H NMR and ^{13}C NMR data.

d) Analytical data were also obtained.

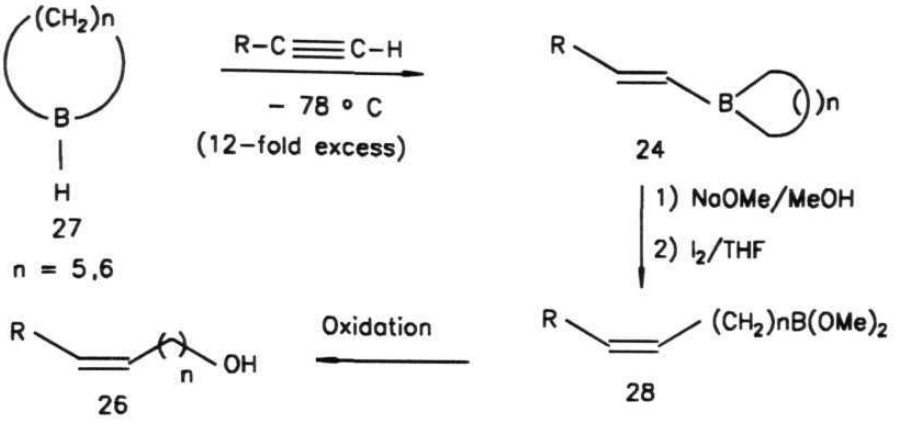
e) Yields are of isolated and purified products.

A series of (Z)-olefinic alcohols were prepared in moderate yields (30-47%) and these results are summarized in Table 1. A major side product identified in these reactions is the aldehyde (13-19%) derived from the oxidation of the starting 1-alkenylboron compound 6. A mixture of (Z)-olefin and vinyl iodide formed by the protonolysis of the intermediate (25) and iodinolysis of vinylboronic acid was isolated in low yields. We have also carried out several experiments using sodium methoxide and sodium methoxide in methanol instead of 3N aqueous sodium hydroxide to avoid the formation of these side products. However, these attempts to get the required (Z)-olefinic alcoholic products in higher yields were unsuccessful. However, this required products can be readily separated from the side products.

Some of these unsaturated olefinic alcohols synthesized as described above have been reported to be biologically active and are insect pheromones.[26-32] The product (Z)-7-hexadecenol (entry 6, Table 1) is the precursor of the aldehydic insect pheromone *Iridomyrex humilis*.[33] The acetate of the product (Z)-7-tetradecenol (entry 7, Table 1) is pheromone *Amathes C-nigum*.[34] The product (Z)-7-dodecenol (entry 8, Table 1) is the insect pheromone *Raphia frater Grt*.[31] Although the yields are somewhat poor, this method of preparation may compare well with the procedures available for such transformations.

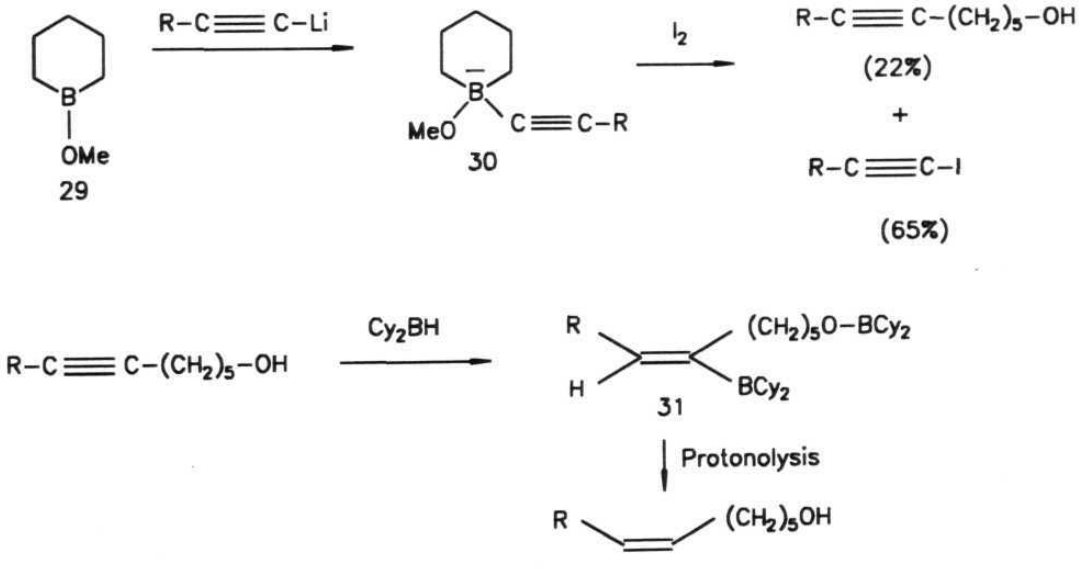
For example, Brown and co-workers reported various methods for the synthesis of these pheromones.[35,36] Some of these methods are outlined in the Schemes 14 and 15.

Scheme 14:



It should be noted that this procedure requires the use of the 1-alkyne in large excess in addition to requiring the cyclic borane **27** for hydroboration.

Scheme 15:

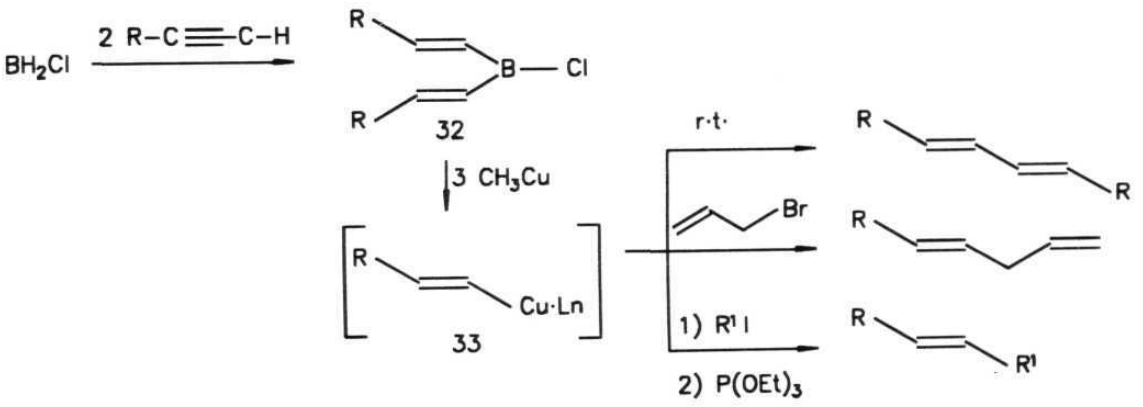


Again, the method outlined in Scheme 15 starts from more complex starting materials.[36]

2.2.2. Attempted alkenyl transfer reactions using alkenylcatecholboranes:

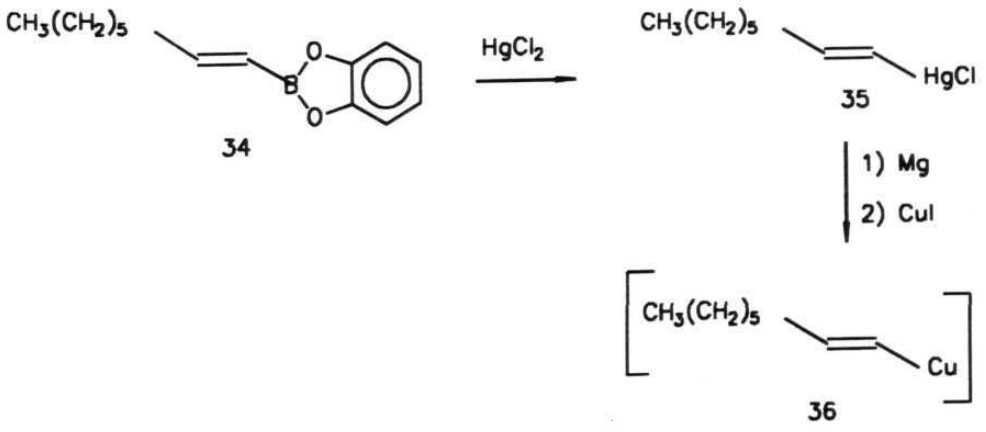
It was of interest to us to investigate the transmetallation of the alkenyl group from 1-alkenylborane to copper in order to obtain alkenyl copper since such derivatives have been found to be valuable synthetic intermediates. There have been some efforts by several workers to achieve this transformation. Organoborane derivatives, normally, do not undergo transmetallation reactions with other metal salts. The actual reactive species in all these reactions is most probably the corresponding tetraborate complexes. Various borane reagents were used for this purpose (Schemes 16 and 17).[38-43]

Scheme 16:



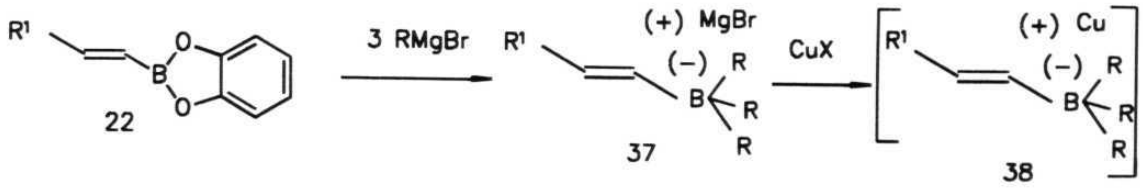
Alkenylcatecholborane derivatives were also used for this purpose through initial preparation of a mercury derivative.[44]

Scheme 17:



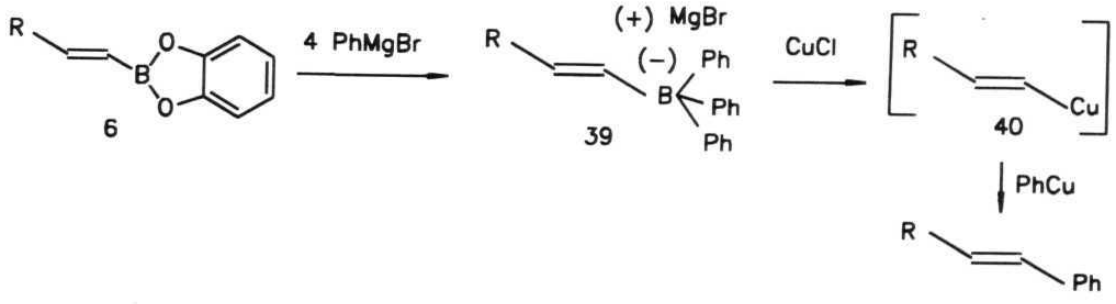
It was of interest to examine the synthesis of trialkylalkenylborate derivatives using 3 eq. of Grignard reagents in the reaction with alkenylcatecholboranes so as to explore the transmetallation reactions of such species (Scheme 18).

Scheme 18:



Generally, boron likes to get its valency satisfied by like groups. We have anticipated the extrusion of alkenylcopper derivatives **40** from such tetraborate derivatives (Scheme 19) and hence carried out experiments to utilize them for the synthesis. It was decided to explore this problem using various Grignard reagents and copper halides. The (E)-olefin synthesis as envisaged in the scheme 19 was first attempted.

Scheme 19:

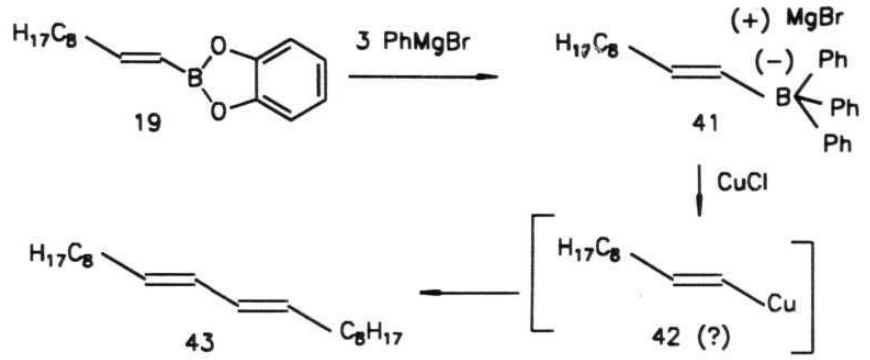


We have used 1-decenylcatecholborane for this purpose and freshly prepared phenylmagnesium bromide was added followed by CuCl. The expected (E)-1-phenyl-1-decene was obtained only in 23% yield besides (E,E)-9,11-eicosadiene, **43** the dimerized product, in 14% yield. We have also isolated

1-decanal (29%) after oxidation of the reaction mixture.

A similar experiment using three equivalents of phenylmagnesium bromide was also carried out (Scheme 20).

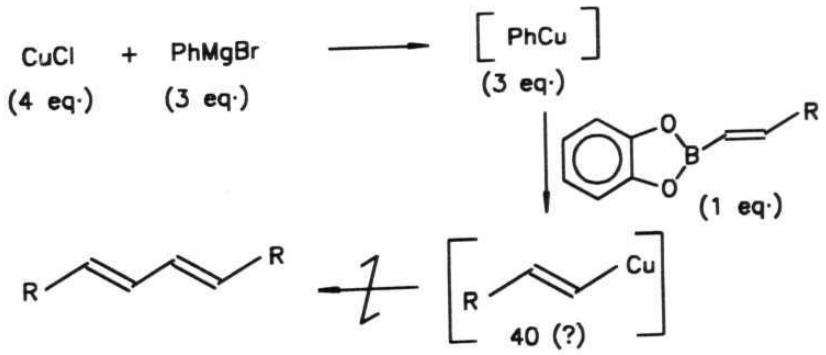
Scheme 20:



It was anticipated that the (E,E)-diene would be the sole product in this reaction. Unfortunately, however, (E,E)-9,11-eicosadiene **43** was again formed in low yields (29%) besides (E)-1-phenyl-1-decene (14%) and 1-decanal (26%).

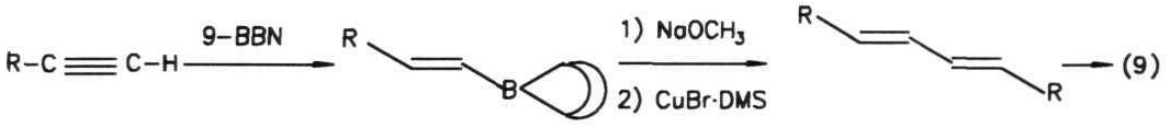
As outlined in Scheme 16, methylcopper was used to synthesize the (E,E)-dienes. We have carried out an experiment using phenylcopper.[45] However, there was no improvement in the formation of (E,E)-diene (Scheme 21).

Scheme 21:

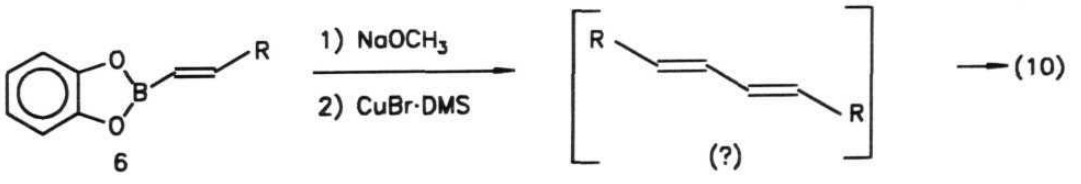


In order to further examine the reactivity of the supposed alkenylcopper intermediates in the above mentioned transformations, we have used various Michael acceptors such as methyl acrylate, acrylonitrile and electrophiles such as benzoyl chloride before work up in the experiments using various Grignard reagents, such as phenylmagnesium bromide, ethylmagnesium bromide, isopropylmagnesium bromide and also in the presence of different copper salts, such as CuCl, CuBr or CuBr.DMS. However, in all cases, only small amounts of unidentified, polymeric carbonyl products were obtained.

It has been reported that the tetraborate complexes prepared from 1-alkenyldialkylborane derivatives and sodium methoxide decompose in the presence of CuBr (eqn. 9).[42]



In order to examine this possibility, we have carried out an experiment using 1-decenylcatecholborane, finely powdered sodium methoxide and CuBr.DMS (eqn. 10).



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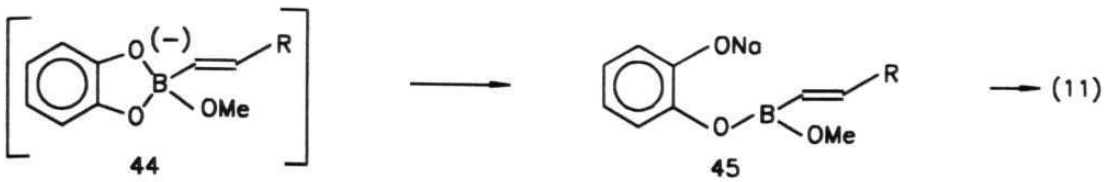
However, in this case the corresponding (E,E)-diene was formed only in trace amount and 1-decanal was isolated as the major product. Presumably, the tetraborate complex **44** is unstable and it decomposes to give the



tricoordinated boron derivative **45** (eqn. 11), which on oxidation gives the aldehyde.

Hence, our research efforts on the development of synthetic method based on C-C bond formation using catecholboranes are only partly successful. Fortunately, this experience led us to investigate the use of cyclic borate complexes for optical resolution of racemic diols which gave more fruitful results (Chapter 3).

2.3. CONCLUSIONS

(Z)-Olefins and (Z)-olefinic alcohols were prepared in moderate to good yields using 1-alkenylcatecholborane, mono-Grignard and di-Grignard reagents. Using this methodology, some naturally occurring insect pheromones or their precursors were synthesized. Transmetallation of 1-alkenyl group from boron to copper were attempted using 1-alkenylcatecholborane and various Grignard reagents in the presence of different copper(I) salts. The supposed alkenylcopper intermediates gave the (E)-olefins and (E,E)-dienes only in low yields (23-29%) under various conditions.

2.4. EXPERIMENTAL SECTION

General Details:

Several items given in the experimental section of Chapter 1 are also applicable for the experiments outlined here.

Sodium borohydride, and iodine supplied by SD fine chemicals, India were utilized. Catechol supplied by SD fine chemicals, India was twice sublimed and stored under nitrogen atmosphere was used. All the bromides supplied by Sisco-Chem, India and Aldrich, USA were distilled prior to utilization. Methyl acrylate and benzoyl chloride were supplied by E-Merck, India. The copper halides supplied by Aldrich, USA were purified and utilized. Sodium methoxide was prepared from sodium and methanol. 1-Alkynes were prepared from 1-alkenes following a reported procedure.[46] 1-Heptyne and 1-hexyne were supplied by Fluka, Switzerland.

Generation of diborane utilizing the $I_2/NaBH_4$ system and preparation of catecholborane:[6]

Iodine (3.2 g, 12.5 mM) dissolved in diglyme (15 mL) was added dropwise for 3h into a generation flask (two-neck RB flask) containing $NaBH_4$ (1.0 g, 25 mM) in diglyme (5 mL) at room temperature under a static nitrogen atmosphere. The generated diborane was carried off through a side tube and bubbled into reaction flask containing catechol (0.55 g, 5 mM) in benzene (30 mL). When the bubbling of diborane is ceased, the bubbler was removed under nitrogen atmosphere and replaced by a glass stopper. The excess diborane above the benzene solution was flushed out with a stream of

nitrogen. The catecholborane solution thus prepared was utilized for further reactions.

Preparation of (Z)-1-cyclohexyl-1-heptene:

Catecholborane (5.2 mM) was prepared as described previously. 1-Heptyne (0.48 g, 5 mM) was added and the contents were refluxed for 12h.[25] The reaction mixture was brought to 0°C and cyclohexylmagnesium bromide prepared using cyclohexyl bromide (1.65 g, 10 mM) and magnesium (0.36 g, 15 mM) in THF (25 mL) was added through cannula under nitrogen atmosphere. The contents were further stirred for 3h at 10°C and refluxed for 12h. The reaction mixture was brought to -10°C and 3N NaOH (5 mL) was added followed by dropwise addition of I_2 (1.25 g, 5 mM) dissolved in THF (15 mL). The contents were further stirred for 4h at -10°C. The reaction was quenched with sodium thiosulphate solution and filtered over celite pad. The filtrate was oxidized using 3N NaOAc (5 mL) and H_2O_2 (30%, 5 mL). The organic extract was washed with 3N NaOH (3 x 20 mL), water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification on silica gel column using hexane as eluent, (Z)-1-cyclohexyl-1-heptene was isolated.

Yield	:	0.56 g (62%)
B.P.	:	88-90°C/5 mm
IR (KBr) ν_{max}	:	1650, 725 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) δ ppm:		0.85-1.73 (m, 19H), 2.01 (m, 3H), 5.23 (m, 2H)
^{13}C NMR (25 MHz, $CDCl_3$) δ ppm:		14.06, 22.65, 26.12, 27.00, 29.47, 29.86, 30.30, 31.53, 31.65, 36.41, 43.60, 128.25, 136.13

Analysis: Calculated C: 86.57, H: 13.41;

Found C: 86.75, H: 13.48.

This product has been reported in the literature.[47]

The product eluted with hexane:ethyl acetate/98:2 was identified as 1-heptanal.

Yield : 0.10 g (17%)

IR (KBr) ν_{max} : 2700, 1726 cm^{-1}

Preparation of (Z)-2-methyl-7-octadecene:

1-Dodecenylcatecholborane was prepared from 1-dodecyne (0.83 g, 5 mM) and catecholborane as mentioned earlier. 5-methylhexylmagnesium bromide prepared using 5-methylhexyl bromide (1.79 g, 10 mM) and magnesium (0.36 g, 15 mM) was added to the alkenylcatecholborane solution at 0°C. The contents were stirred for 3h at 10°C and refluxed for 12h. The reaction mixture was brought to -10°C and 3N NaOH (5 mL) was added followed by dropwise addition of I_2 (1.25 g, 5 mM) dissolved in THF (15 mL). The contents were further stirred for 4h at -10°C. The reaction mixture was quenched with sodium thiosulphate solution and filtered over celite pad. The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extract was oxidized using 3N NaOAc (5 mL) and H_2O_2 (30%, 5 mL). After usual work up and purification by silica gel column using hexane as eluent solvent, (Z)-2-methyl-7-octadecene was isolated.

Yield : 0.79 g (59%)

B.P. : 162-164°C/2 mm; Lit.[48] 125-129°C/0.2 mm

IR (neat) ν_{max} : 1650, 725 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.76–0.94 (m, 9H), 1.21–1.38 (m, 23H) 1.80–1.96 (m, 4H), 5.40 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 14.21, 22.49, 22.85, 27.46, 28.85, 29.35, 29.53, 29.76, 29.86, 32.10, 36.53, 128.59, 130.74

This product has been reported in the literature.[48]

The product eluted with hexane:ethyl acetate (98:2) was identified as 1-dodecanal.

Yield : 0.12 g (13%)

IR (neat) ν_{max} : 2700, 1726 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.80 (t, 3H), 1.20–1.51 (m, 18H), 2.30 (m, 2H), 9.20 (bs, 1H)

Preparation of diorganomagnesium derivatives:[49]

In a two-necked RB flask, magnesium (0.48 g, 20 mM) was taken in dry THF (15 mL). The dibromide (7.5 mM) in dry THF (15 mL) was added dropwise for 1h. The contents were further stirred for 6h at room temperature. The diorganomagnesium derivatives thus prepared were used for further reactions.

Preparation of (Z)-6-pentadecene-1-ol:

1-Decenylcatecholborane was prepared using 1-decyne (0.69 g, 5 mM) and catecholborane (5.2 mM) as mentioned earlier. The $BrMg(CH_2)_5MgBr$ deriva-

tive prepared using $Br(CH_2)_5Br$ (1.73 g, 7.5 mM) and magnesium (0.48 g, 20 mM) in dry THF (30 mL) was added at 0°C, stirred for 3h at this temperature and refluxed for 12h. The reaction mixture was cooled to -10°C and 3N NaOH (5 mL) was added. Iodine (1.5 g, 6 mM) dissolved in THF (10 mL) was added over 0.5h. The contents were further stirred for 4h at this temperature. Saturated sodium thiosulphate solution (5 mL) was added and the reaction mixture was filtered over celite pad. The filtrate was oxidized using 3N NaOH (10 mL) and H_2O_2 (30%, 10 mL). The organic extract was washed with 3N NaOH solution (2 x 10 mL), water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column, the product which eluted first with hexane as solvent was identified as a mixture of (E)-1-decenyl iodide and (Z)-6-pentadecene, the fraction eluted with hexane:ethyl acetate (98:2) was identified as 1-decanal and the fraction eluted with hexane:ethyl acetate (90:10) was identified as (Z)-6-pentadecene-1-ol.

Fraction 1: [(E)-1-iodo-1-decene + (Z)-6-pentadecene]

Yield : 0.10 g

IR (neat) ν_{max} : 1650, 1610, 720 cm^{-1}

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.06, 22.71, 29.00, 29.36, 29.53, 31.99, 32.65, 74.38, 129.90, 130.50, 146.77

Fraction 2: (1-decanal)

Yield : 0.11 g (14%)

IR (neat) ν_{max} : 2700, 1726 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) δ ppm: 0.80 (t, 3H), 1.20-1.50 (m, 14H), 2.31 (m, 2H), 9.20 (bs, 1H)

Fraction 3: ((Z)-6-pentadecene-1-ol)

Yield : 0.50 g (44%)

B.P. : 163-165°C/1 mm

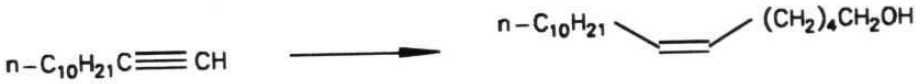
IR (neat) ν_{max} : 3300, 1650, 1050, 725 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.90 (t, 3H), 1.10–1.60 (m, 18H), 2.02 (m, 4H), 2.95 (br, exchanges with D_2O), 3.6 (t, 2H), 5.31 (m, 2H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 13.90, 22.59, 25.41, 25.83, 27.12, 29.29, 29.59, 31.88, 32.59, 62.29, 129.54, 130.00

The olefinic alcohol product has been reported.[35]

The above procedure using $Br(CH_2)_5Br$ was followed for the conversion of a few other 1–alkynes into the corresponding (Z)–olefinic alcohol.



Yield : 0.60 g (47%)

B.P. : 184–185°C/1 mm

IR (neat) ν_{max} : 3300 (b), 1650, 1050, 725 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.90 (t, 3H), 1.20–1.70 (m, 22H), 2.05 (m, 4H), 3.64 (t, 3H, 1H exchanges with D_2O), 5.35 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 14.17, 22.76, 25.48, 25.83, 27.23, 27.31, 29.42, 29.72, 31.40, 32.79, 63.08, 129.58, 130.28

Analysis: Calculated: C: 80.39, H: 13.49;

Found: C: 80.15, H: 13.50

This product has been reported.[35]

Yield	:	0.34 g (40%)
B.P.	:	160–162°C/4 mm; Lit.[36] 78–80°C/0.01 mm
IR (neat) ν_{max}	:	3300, 1650, 1050, 725 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) δ ppm:		0.88 (dist. t, 3H), 1.20–1.70 (m, 10H), 2.0 (m, 4H), 3.60 (t, 3H, 1H exchanges with D_2O), 5.35 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$) δ ppm:		13.77, 22.24, 25.41, 26.86, 27.16, 29.53, 31.88, 32.59, 62.59, 129.60, 130.12

This product has been reported.[36]

Preparation of (Z)-7-hexadecene-1-ol:

1-Decenylcatecholborane was prepared from 1-decyne (0.69 g, 5 mM) and catecholborane (5.2 mM) as mentioned earlier. The $BrMg(CH_2)_6MgBr$ derivative prepared using $Br(CH_2)_6Br$ (1.85 g, 7.5 mM) and magnesium (0.48 g, 20 mM) in THF (30 mL) was added at 0°C, stirred for 3h and refluxed for 12h. The reaction mixture was cooled to -10°C and 3N NaOH (5 mL) was added. Iodine (1.5 g, 6 mM) in THF (10 mL) was added over 0.5h. The contents were further stirred for 4h at that temperature. Saturated sodium thiosulphate solution (5 mL) was added and the reaction mixture was filtered over celite pad. The filtrate was oxidized using 3N NaOH (10 mL) and H_2O_2 (30%, 10 mL). The organic layer was separated and the aqueous layer was extracted

with ether (2 x 15 mL). The combined organic extract was washed with 3N NaOH solution (2 x 10 mL), water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column, the product which eluted first with hexane as solvent was identified as a mixture of trans-1-decenyl iodide and cis-7-hexadecene, the fraction eluted with hexane:ethyl acetate (98:2) was identified as 1-decanal and the product eluted with hexane:ethyl acetate (90:10) was identified as (Z)-7-hexadecene-1-ol.

Fraction 1: [(E)-1-iodo-1-decene + (Z)-7-hexadecene]

Yield : 0.08 g

IR (neat) ν_{max} : 1650, 1610, 720 cm^{1}

Fraction 2: (1-decanal)

Yield : 0.15 g (19%)

IR (neat) ν_{max} : 2700, 1726 cm^{-1}

Fraction 3: ((Z)-7-hexadecene-1-ol)

Yield : 0.48 g (40%)

B.P. : 180-82°C/1 mm; Lit.[35] 135-36°C/0.01 mm

IR (neat) ν_{max} : 3300, 1650, 1050, 725 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 0.88 (dist. t, 3H), 1.20-1.70 (m, 20H), 2.01 (m, 4H), 3.65 (t, 3H, 1H exchanges with D_2O), 5.35 (m, 2H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 13.88, 22.53, 25.65, 27.06. 29.24, 29.41, 31.83, 32.53, 62.34, 129.66, 129.95

This product was converted into the natural product aldehyde using PCC following a reported procedure.[51]

Preparation of (Z)-7-hexadecene-1-al:

Pyridinium chlorochromate (0.86g, 4 mM) and sodium acetate (0.07 g, 0.8 mM) were taken in DCM (5 mL) and (Z)-hexadecene-ol (0.48g, 2 mM) in DCM (5 mL) was added in one portion to the above reagent. After 2h dry ether (25 mL) was added and the supernatent solution was decanted. It was purified by column chromatography on silica gel using hexane:ethyl acetate (98:2) as eluent solvent.

Yield : 0.38 g (80%)

IR (neat) ν_{max} : 2700, 1726, 1650, 723 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H), 1.10-1.70 (m, 18H), 1.81-2.52 (m, 6H), 5.30 (m, 2H), 9.80 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 14.13, 22.10, 22.78, 27.04, 27.31, 28.86, 29.40, 29.57, 29.82, 31.96, 43.95, 129.40, 130.37, 202.75

This product has been reported.[35]

The above procedure using $Br(CH_2)_6Br$ was followed for the conversion of few other 1-alkynes into the corresponding (Z)-olefinic alcohols.

Yield : 0.37 g (35%)

B.P. : 168-70°C/1 mm; Lit.[36] 94-96°C/0.01 mm

IR (neat) ν_{max} : 3300, 1650, 1050, 725 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.88 (dist. t, 3H), 1.21-1.60 (m, 16H), 2.01 (m, 4H), 3.65 (t, 3H), 5.30 (m, 2H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.00, 22.60, 25.81, 29.40, 29.70, 31.50, 31.90, 32.91, 63.12, 127.70, 128.80

This product has reported.[36]

Yield	:	0.28 g (30%)
B.P.	:	175-76°C/4 mm; Lit.[36] 74-76°C/0.01 mm
IR (neat) υ_{max}	:	3329, 1650, 1050, 725 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) δ ppm:		0.90 (dist. t, 3H), 1.21-1.70 (m, 12H), 2.01 (m, 4H), 3.65 (t, 3H, 1H exchanges with D_2O), 5.35 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$) δ ppm:		13.94, 22.35, 25.70, 27.01, 27.20, 29.12, 29.77, 32.06, 32.88, 63.06, 129.7, 130.30

The spectral data of the product showed 1:1 correspondence with the spectral data of the product reported.[36]

Attempted (E)-olefin synthesis using 1-decenylcatecholborane (1 eq.), phenylmagnesium bromide (5 eq.) and CuCl (3 eq.):

1-Decenylcatecholborane was prepared from 1-decyne (0.69 g, 5 mM) and catecholborane (5.2 mM) as described earlier. Phenylmagnesium bromide prepared using bromobenzene (4.7 g, 30 mM) and magnesium (0.84 g, 35 mM) in THF (40 mL) was added through cannula to the reaction mixture at 0°C under nitrogen atmosphere and the contents were stirred for 12h at 25°C. The reaction mixture was cooled to -10°C and CuCl (1.5 g, 15 mM) was added

through solid addition flask. The contents were further stirred for 3h at -22°C and then 12h at room temperature. The reaction mixture was quenched with water (2 mL) and oxidized using 3N NaOAc (10 mL) and H_2O_2 (30%, 10 mL). The reaction mixture was filtered through celite pad. The organic layer was separated and the aqueous layer was extracted with ether (2 X 15 mL). The combined organic extract was washed with 3N NaOH (3 x 20 mL), water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by silica gel column, the products isolated with hexane as eluent were identified as (E,E)-9,11-eicosadiene and (E)-1-phenyl-1-decene and the product isolated using hexane:ethyl acetate (98:2) was identified as 1-decanal.

Fraction 1: (E,E)-9,11-eicosadiene

Yield : 0.10 g (14%)

IR (neat) ν_{max} : 2910, 2840, 950 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.99 (t, 6H), 1.31 (m, 24H), 2.01 (m, 4H), 5.30–6.21 (m, 4H)

^{13}C NMR (25 MHz, $CDCl_3$) δ ppm: 14.20, 22.81, 29.30, 29.52, 29.70, 32.10, 32.80, 130.60, 132.20

This product has been reported in the literature.[52]

Fraction 2: (E)-1-phenyl-1-decene

Yield : 0.25 g (23%)

IR (neat) ν_{max} : 3020, 1610, 1600, 960 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) δ ppm: 0.90 (t, 3H), 1.30 (m, 12H), 2.31 (m, 2H), 6.4 (m, 2H), 7.4 (m, 5H)

This product has been reported in the literature.[52]

Fraction 3: 1-decanal

Yield : 0.23 g (29%)

IR (neat) ν_{max} : 2700, 1720 cm^{-1}

The ^{1}H NMR spectra data of this product showed 1:1 correspondence with the data obtained for the sample in earlier experiments.

Attempted (E,E)-diene synthesis using 1-decenylcatecholborane phenylmagnesium bromide (3 eq.) and CuCl (3 eq.):

1-Decenylcatecholborane was prepared from 1-decyne (0.69 g, 5 mM) and catecholborane (5.2 mM) as described earlier. Phenylmagnesium bromide prepared using bromobenzene (2.80 g, 18 mM) and magnesium (0.60 g, 25 mM) in THF (30 mL) was added and rest of the procedure mentioned in the previous experiment was followed. The products eluted with hexane as solvent were identified as (E,E)-eicosadiene and (E)-1-phenyl-1-decene and the product isolated using hexane:ethyl acetate (98:2) was identified as 1-decanal.

Fraction 1: (E,E)-eicosadiene

Yield : 0.2 g (29%)

The spectral data of this compound showed 1:1 correspondence with the data obtained in the earlier experiment.

Fraction 2: (E)-1-phenyl-1-decene

Yield : 0.15 g (14%)

The spectral data of this compound showed 1:1 accordance with the data

of the product obtained earlier.

Fraction 3: 1-decanal

Yield : 0.20 g (26%)

Attempted (E,E)-diene synthesis by the reaction of phenylcopper with 1-decenylcatecholborane:

1-Decenylcatecholborane was prepared from 1-decyne and catecholborane as described earlier. In a two-necked flask CuCl (2.0 g, 20 mM) in THF (15 mL) was taken and phenylmagnesium bromide (18 mM) prepared as above was added dropwise for 1h at 0°C. At the same temperature 1-decenylcatecholborane prepared earlier was added and further stirred for 2h. The reaction mixture was quenched with water and oxidized with 3N NaOAc (10 mL) and H_2O_2 (30%, 10 mL). The reaction mixture was worked up as described earlier and the product obtained was purified by column chromatography using hexane as eluent solvent. The expected (E,E)-diene was obtained in low yields (20%) besides 1-decanal as the major product (26%).

Attempted 1,4-addition of methyl acrylate with 1-decenylcatecholborane in the presence of methylmagnesium iodide (3 eq.) and CuCl (3 eq.):

1-Decenylcatecholborane (5 mM) was prepared as described previously. Methylmagnesium iodide was prepared using methyl iodide (2.6 g, 18 mM) and magnesium (0.6 g, 25 mM) in ether (30 mL). The Grignard reagent was added to 1-decenylcatecholborane at 0°C and stirred for 12h at 25°C. The reaction mixture was brought to -22°C and CuCl (1.5 g, 15 mM) was added followed by the addition of methyl acrylate (0.86 g, 10 mM). It was further stirred

for 3h at -22°C and 12h at 25°C. The reaction mixture was worked up as described previously. A small amount of unidentified polymeric carbonyl compound was isolated.

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Chapter 3

Studies on the Optical Resolution of Racemic Diols

3.1. BACKGROUND AND OBJECTIVES

It has been recognized that biological activities of enantiomeric compounds could be very much different. Thus one may act as a therapeutic drug, whereas the other may be toxic in some cases. Hence, there is immense interest in the development of methods to obtain enantiomerically pure chiral compounds.

There are several methods to obtain enantiomerically pure materials which include optical resolution via formation of diastereomers, chromatographic separation of enantiomers, enzymatic resolutions, kinetic resolutions and asymmetric synthesis.

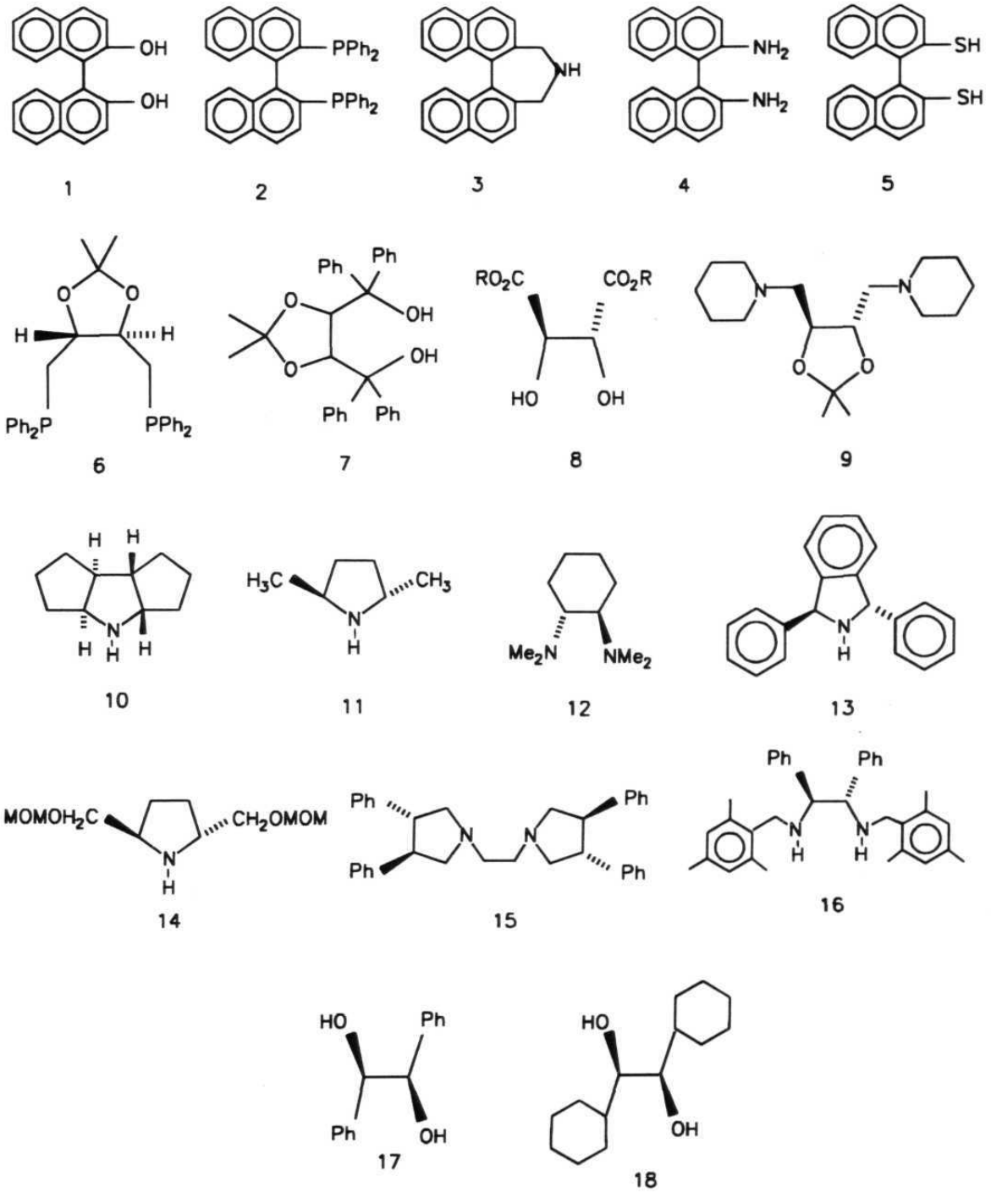
The importance of asymmetric synthesis to obtain pure molecules has been acknowledged by synthetic organic chemists. In the last two decades, several important developments of newer and more efficient methods were made. With these developments, the enantiomerically pure precursors required for the synthesis of natural products, pharmaceuticals and agricultural agents could be synthesized very efficiently.

Among the various types of asymmetric reactions, the most challenging one is catalytic asymmetric synthesis since one chiral catalyst molecule can produce multiple of products just as enzymes do in biological systems. As discussed in chapter 1, the Itsuno–Corey oxazaborolidine systems and other related reagent systems have been found to be very useful for asymmetric synthesis.[1]

Among various reagents developed as chiral auxiliaries, the systems

possessing C_2 symmetry were found to be better in obtaining high levels of asymmetric induction.[2-9] The following C_2 symmetric chiral auxiliaries were utilized for various chemical transformations (Scheme 1).

Scheme 1:



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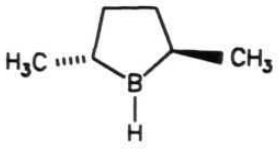

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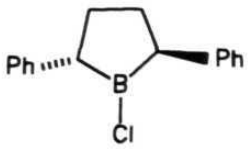

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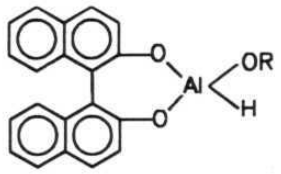
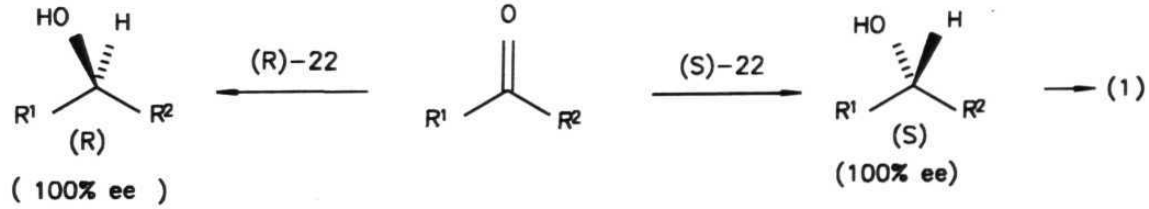
The synthetic methods developed using such derivatives have been reviewed.[10–15] A very rich chemistry has been uncovered, especially using chiral auxiliary 1.[15,16] Since our objective is to develop new methods of resolution of racemic diols, a brief review on the utilization of 1 and 17 in various transformations will be helpful.

Noyori et al reported the chiral aluminum reagent 22 for asymmetric reductions.[2]

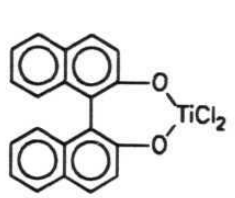


22

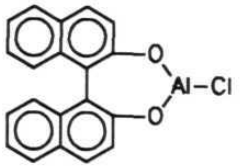


The Lewis acids 23–27 derived from chiral binaphthol 1 were used for asymmetric Diels–Alder reactions.

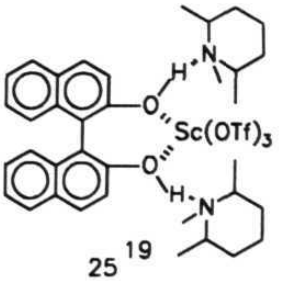
Scheme 2:



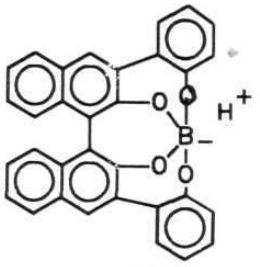
23 [17]



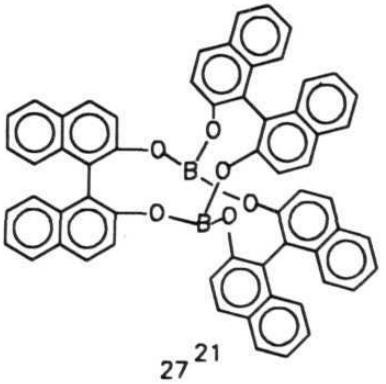
24 [18]



25 [19]

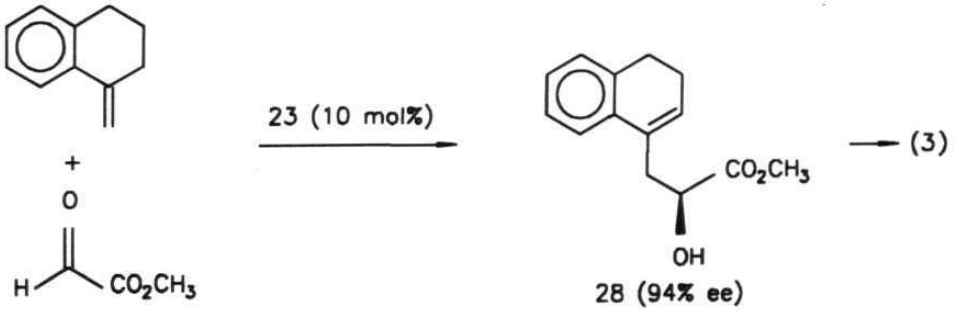


26 [20]



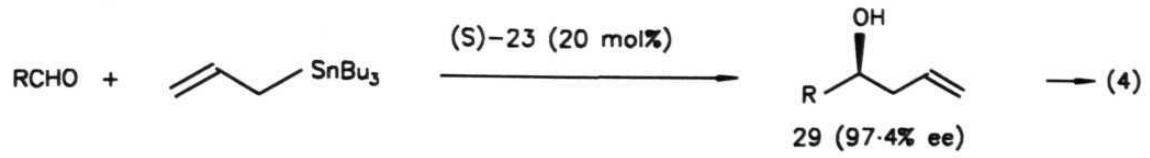
27 [21]

Van der Meer et al used the catalyst **23** for the enantioselective glyoxylate ene reactions (eq. 3).[22]

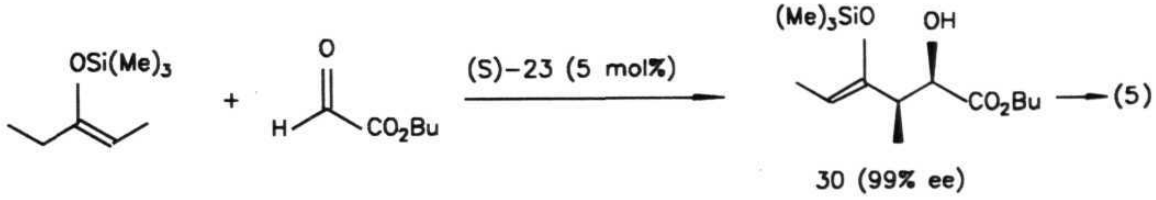


28 (94% ee)

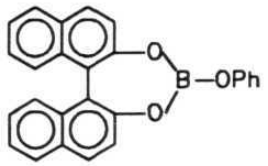
Costa et al prepared the essentially pure allylic alcohols using the catalyst **23** (eqn. 4).[23]



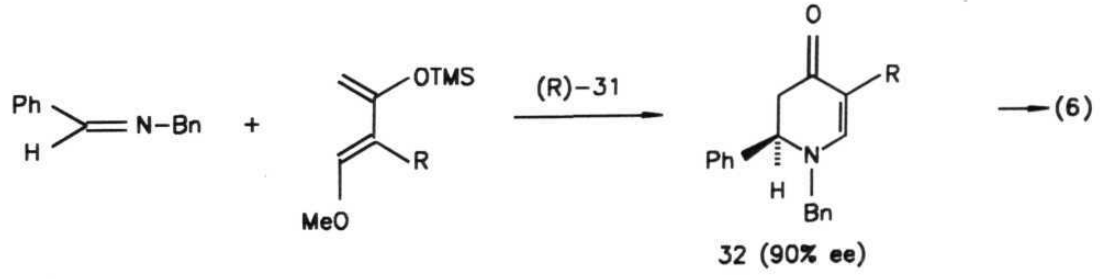
Mikami et al used the same catalyst for enantioselective and diastereoselective Mukaiyama aldol-ene reaction (eqn. 5).[24]



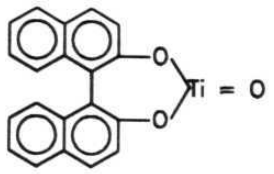
Yamamoto et al used the catalyst 31 for aza-Diels-Alder reaction (eqn. 6).[25]



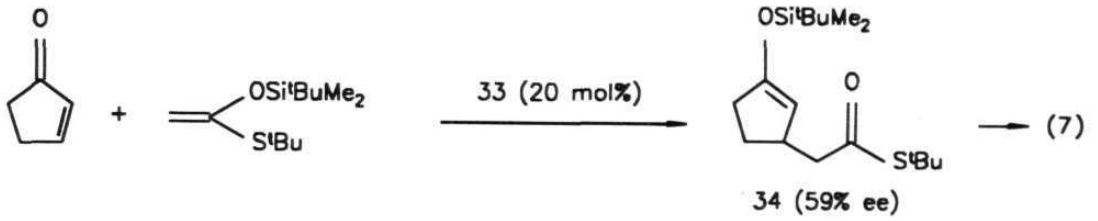
31



Kobayashi and co-workers used the catalyst 33 for asymmetric Michael reaction (eqn. 7).[26]

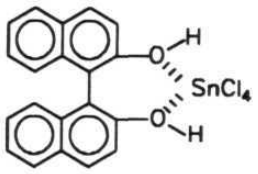


33

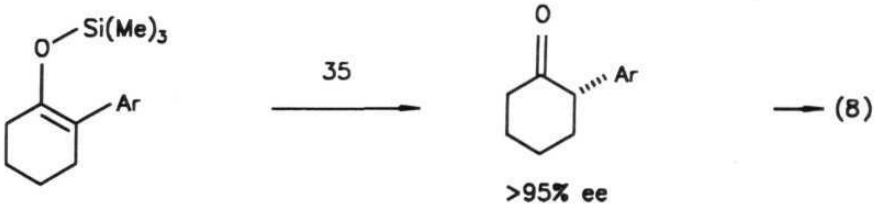


34 (59% ee)

Very recently, Yamamoto and co-workers prepared a chiral tin derivative 35 for use in the enantioselective protonation of enol ethers (eqn. 8).[27]

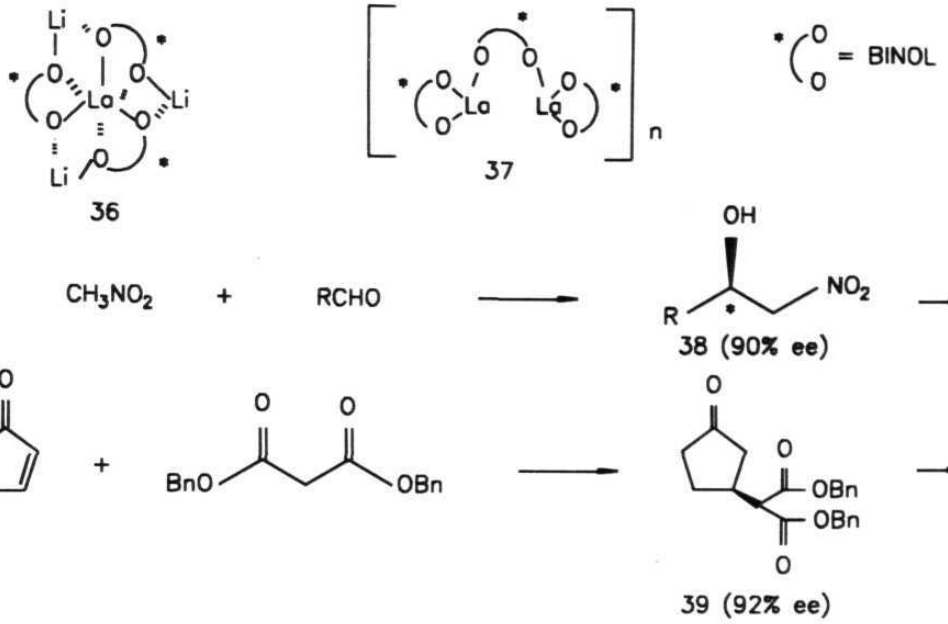


35



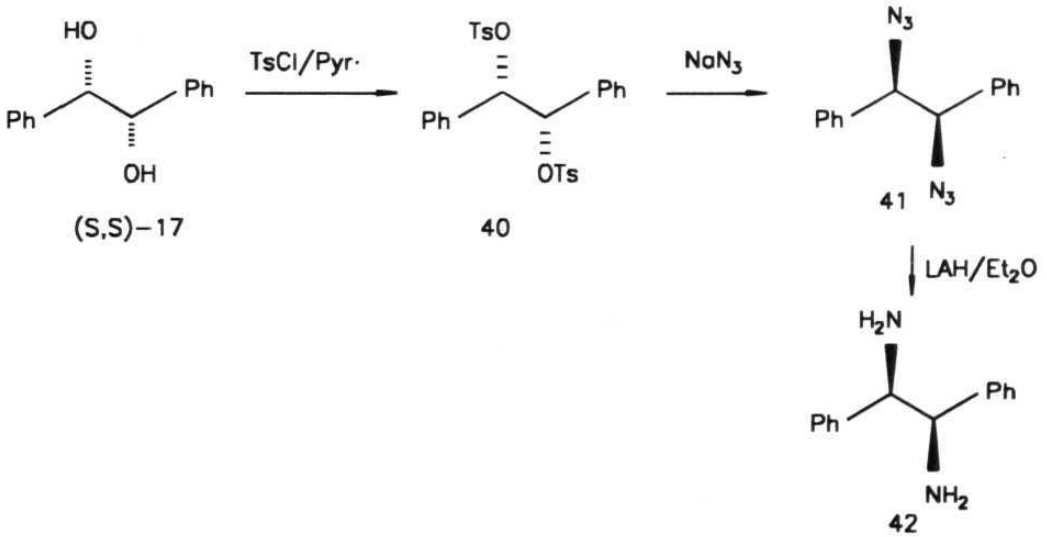
>95% ee

Shibasaki et al prepared various rare earth binaphthol catalysts 36 and 37 which act as chiral bases in the enantioselective nitroaldol and Michael reactions (eqns. 9 and 10).[28-30]

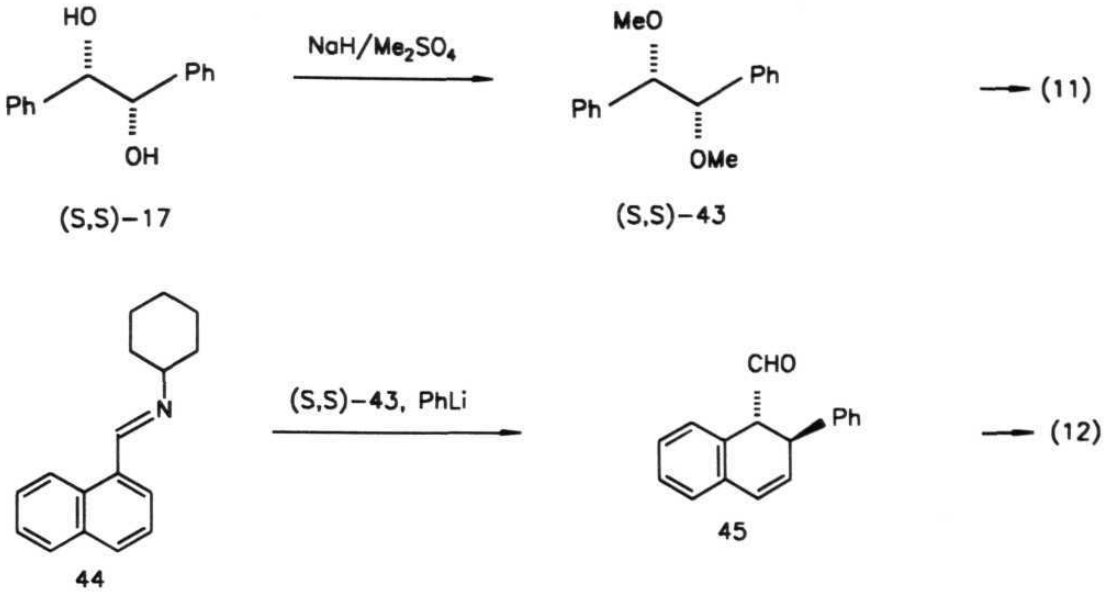


The other chiral diol 17, which is of interest to us, has been also used in several transformations. For example, the trans-(R,R)-stilbene diamine 42 (Scheme 3) can be readily prepared from this chiral diol 17.[31]

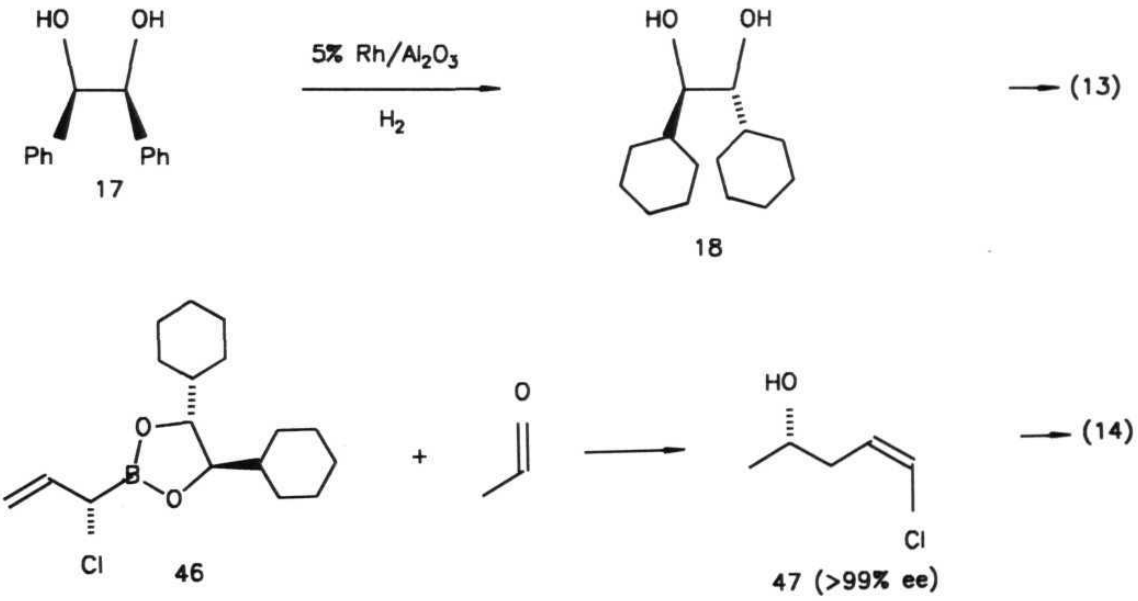
Scheme 3:



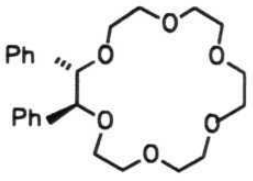
Tomioka et al used the dimethyl ether of 17 for the enantioselective conjugate addition of organolithium reagents to α,β-unsaturated aldimines (eqn. 11).[32]



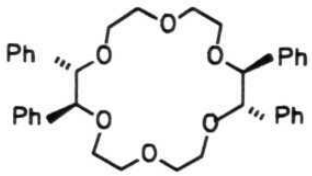
Hoffmann and co-workers utilized the (R,R)- and (S,S)-dicyclohexylethanediol 18 derived compound 46 for allylboration (eqn. 14). This diol 18 has been prepared by the hydrogenation of 17 (eqn. 13).[33]



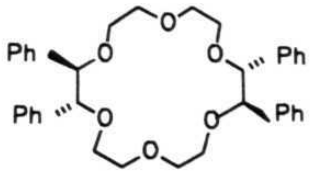
Stoddart et al used the crown ethers 48-50 derived from the diol 17 for asymmetric Michael reaction, acylcyanation of benzaldehyde and also for the reduction of prochiral ketones (eqns. 15-17).[34-36]



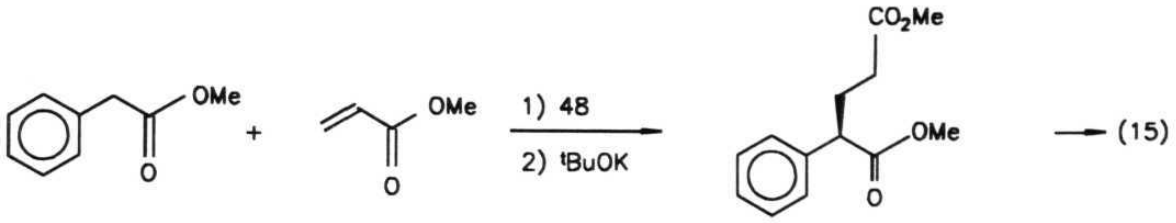
48
(S,S)-DP18C6



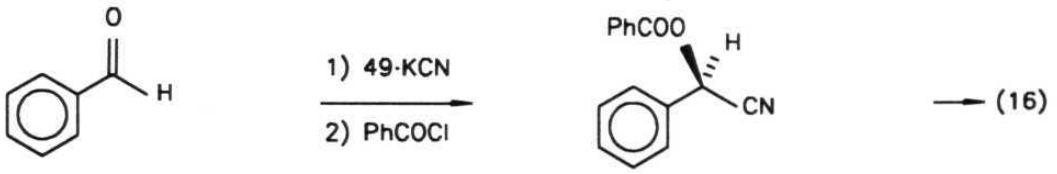
49
(S,S,S,S)-TP18C6



50
(R,R,R,R)-TP18C6



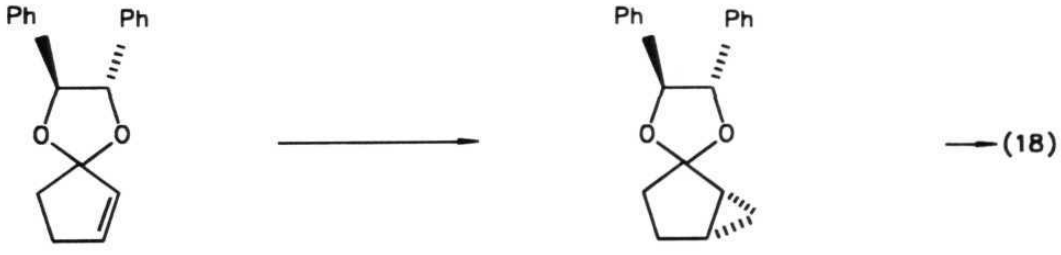
51 (79% ee)



52 (46% ee)

67% ee

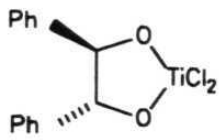
Mash et al reported Simmon-Smith cyclopropanation reaction on hydrobenzoin modified ene-ketals (eqn. 18).[37]



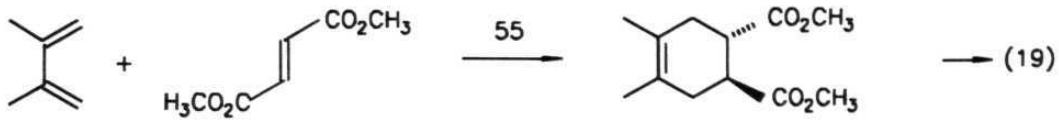
53

54 (13:1)

Devine and co-workers prepared the titanium reagent 55 for asymmetric Diels-Alder reactions (eqn. 19).[3]



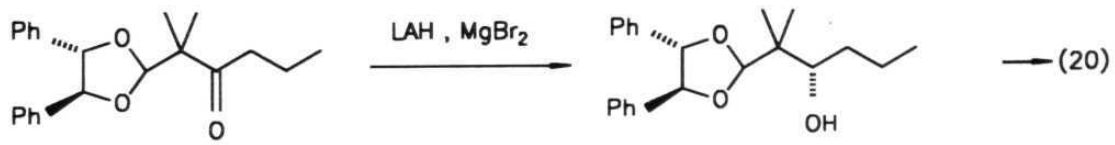
55



56 (92% ee)

(19)

Hasegawa and co-workers prepared a diol modified precursor 57 and subjected it towards diastereomeric reduction (eqn. 20).[38]

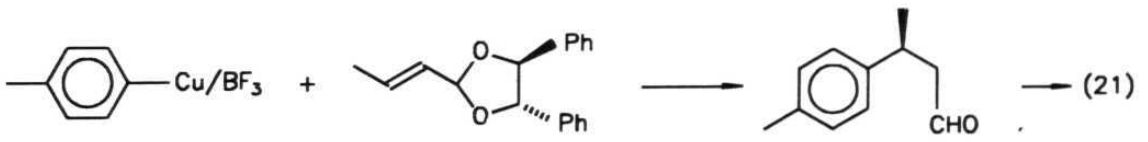


57

58 (82% de)

(20)

Alexakis and co-workers reported the asymmetric alkylcopper and Grignard addition on diol 17 modified synthons (eqn. 21).[39]



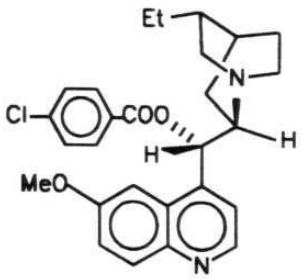
59

60

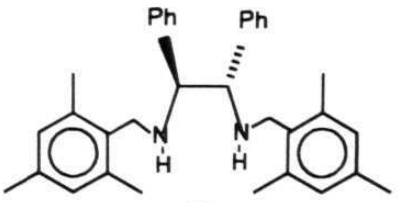
(21)

Obviously, there has been immense interest to prepare the enantiomers of this important chiral auxiliaries. The chiral diol 17 can be readily prepared through Sharpless catalytic asymmetric dihydroxylation of trans-stilbene (Scheme 4).

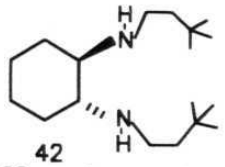
Scheme 4:



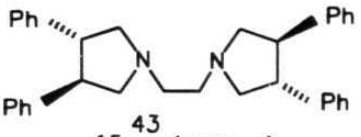
61[40] (> 99% ee)



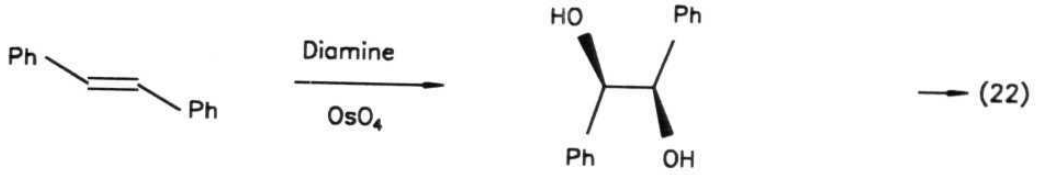
16[41] (98% ee)



62[42] (99% ee)



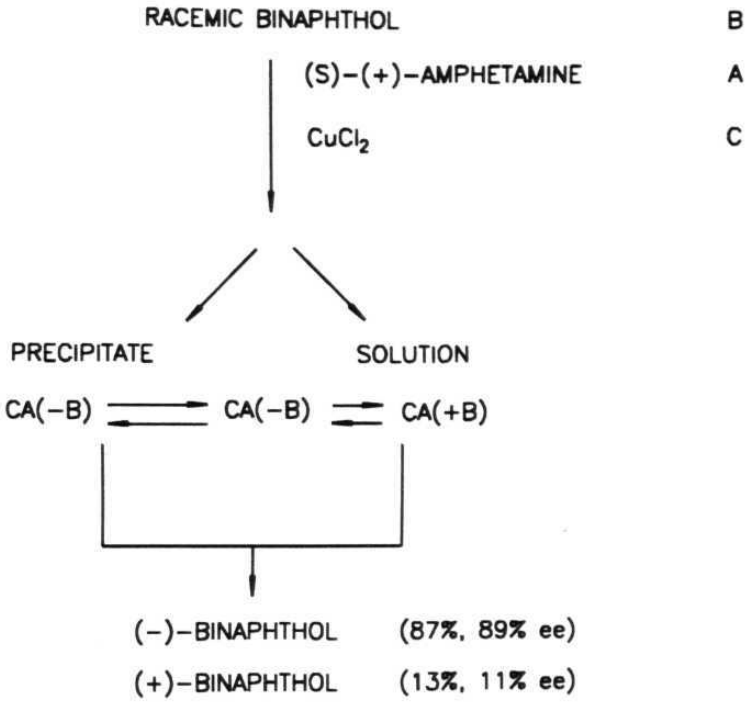
15[43] (95% ee)



A brief review on the synthesis of chiral 1 will be helpful for the discussion.

Several reports on the asymmetric synthesis of 1 starting from 2-naphthol have appeared. Brusee and co-workers utilized various copper(II) amines and amino alcohol complexes for the asymmetric coupling of 2-naphthol.[44,45] Using (S)-(+)-amphetamine complex, they have obtained (S)-(-)-binaphthol in 89% ee. They also found that in these reactions racemic binaphthol formed initially was 'deracemized' to the optically active binaphthol (Scheme 5).

Scheme 5:



Using $CuCl_2$-(-)-sparteine complex, (S)-(-)-binaphthol was obtained in enantiomerically pure form in 36% yield.[46]

An electrochemical coupling of 2-naphthol and 2-naphthol methyl ether 63 in the presence of (-)-sparteine gave the corresponding coupling products in high ee (eqns. 23 and 24).[47]

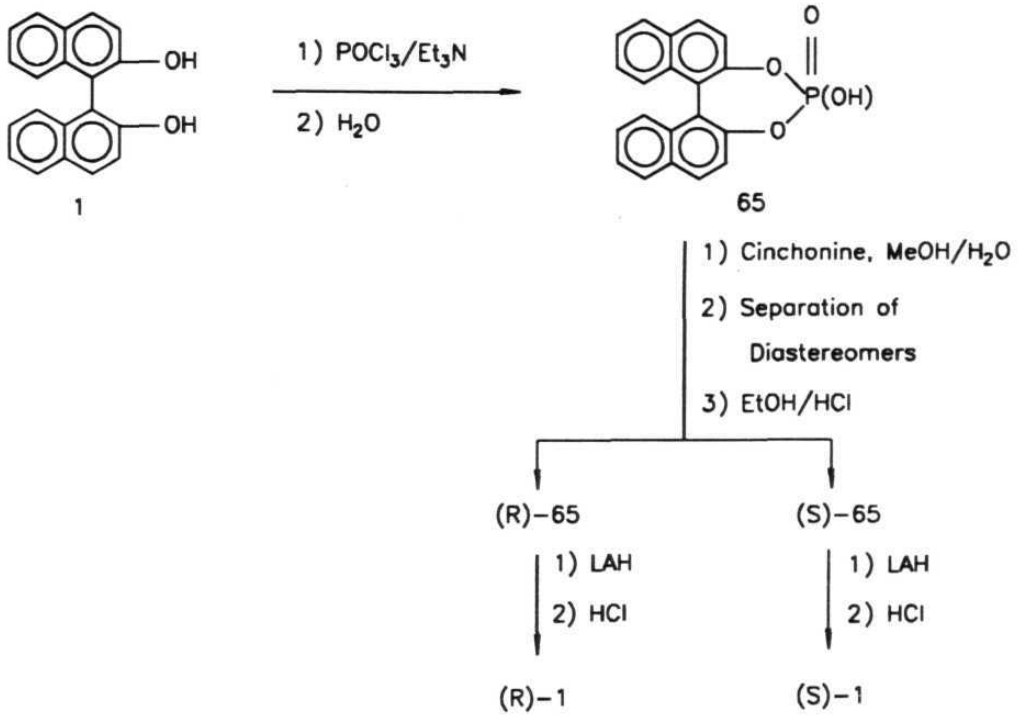
1 (99·7% ee) — (23)

63

64 (93·6% ee) — (24)

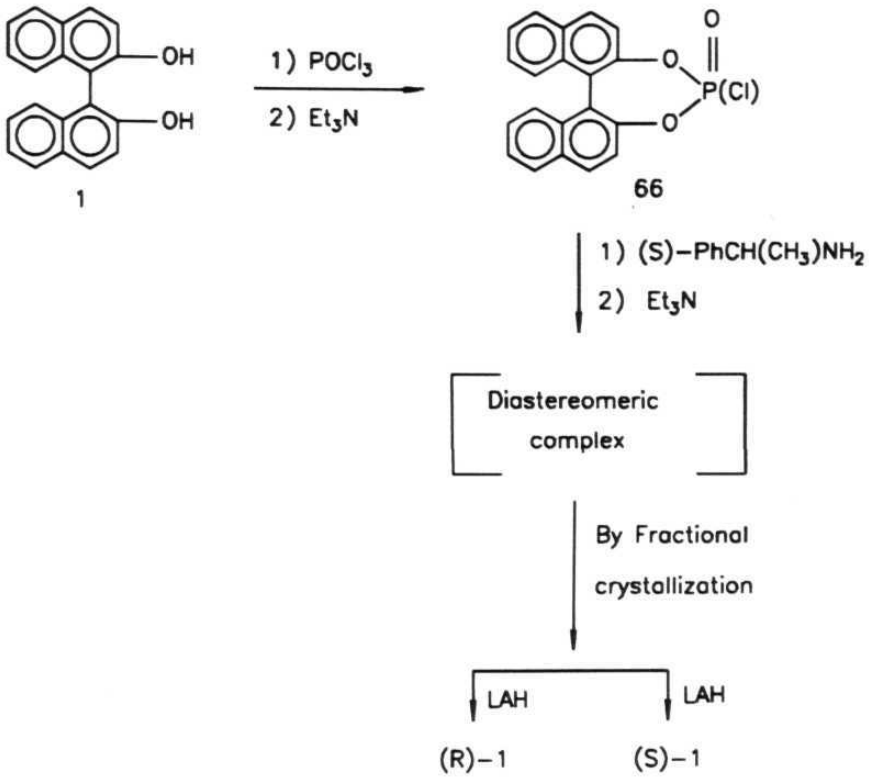
For the large scale preparation of optically active binaphthols, generally, the resolution methods developed using the phosphoric acid based derivatives were utilized. Cinchonine was used to resolve the racemic phosphoric acid derivative 65 (Scheme 6).[48-51]

Scheme 6:



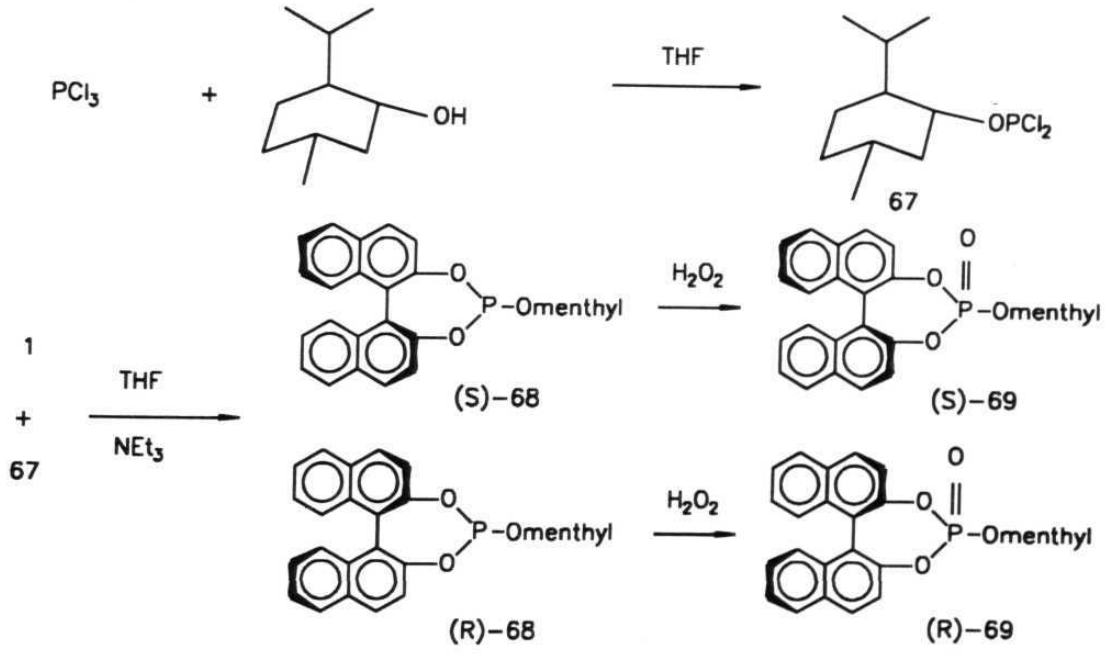
Very recently, Hu et al utilized α-methylbenzylamine and the diastereomeric phosphoramides obtained were separated by fractional crystallization (Scheme 7).[52]

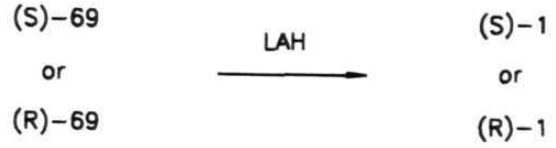
Scheme 7:



Buono et al utilized l-menthol and the diastereomeric phosphites were separated by recrystallization from diethyl ether (Scheme 8).[53]

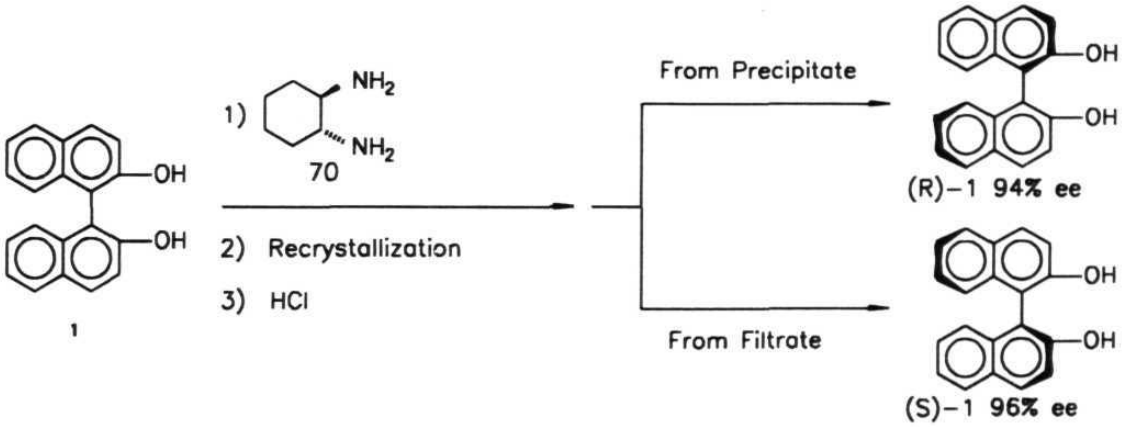
Scheme 8:





Kawashima and co-workers utilized chiral amines such as (1R, 2R)-1,2-diaminocyclohexane 70 and threo-1,2-diamino-1,2-diphenylethane for the direct resolution of racemic binaphthol. The diastereomeric inclusion complexes obtained were separated by repeated crystallizations (Scheme 9).[54]

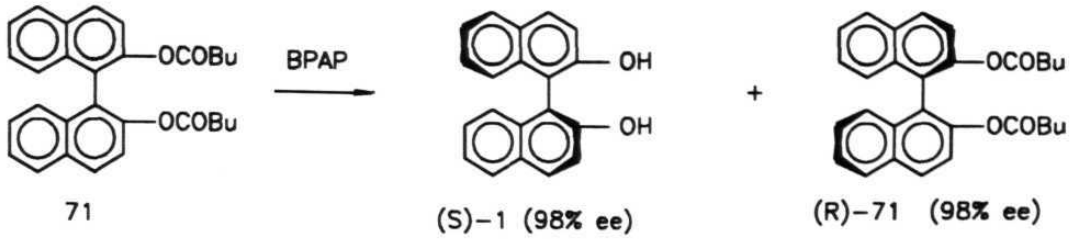
Scheme 9:



They have also developed an epimerization-recrystallization procedure using the above diamines and the racemic binaphthol (1:1). The required enantiomerically pure 2,2'-binaphthols were obtained in 154-160% chemical yields.[55]

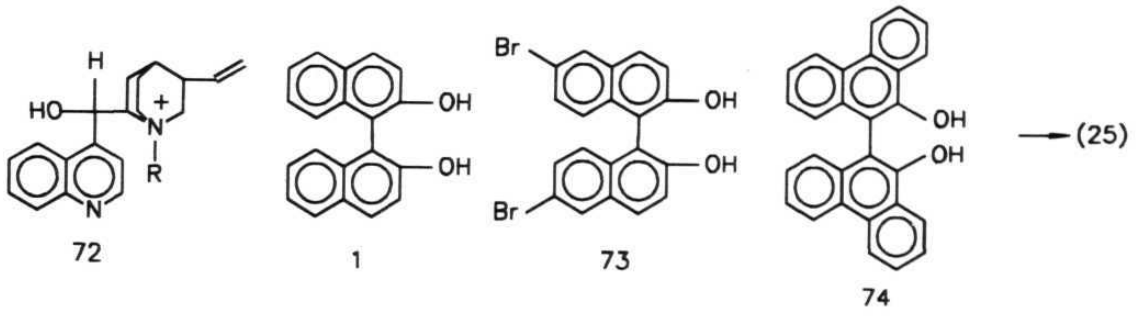
Kazlauskas used bovine pancreas acetone powder (BPAP) for the enzymatic hydrolysis of the corresponding binaphthol esters on a 100 Kg scale (Scheme 10).[56]

Scheme 10:



71 (S)-1 (98% ee) (R)-71 (98% ee)

Very recently, Toda and co-workers employed commercially available N-alkylcinchonidium halide **72** for the resolution of various binaphthol and biphenanthryldiol derivatives (eqn. 25).[57]



72 1 73 74

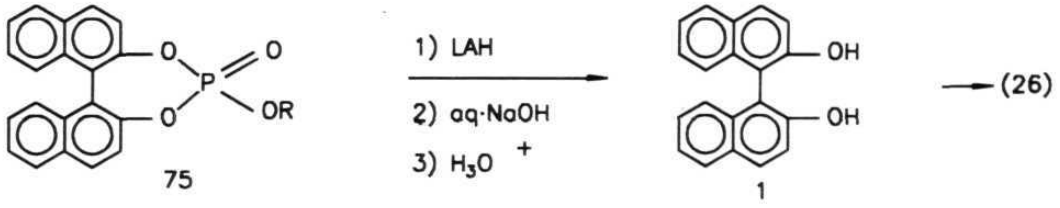
Following this method, the (R)-(+)-1 was obtained in 95% ee with 72% chemical yield.

Our interest in the synthesis and utilization of catecholborane derivatives (Chapter 2) led us to investigate the development of methods based on aryloxyborate complexes for the development of new, more convenient resolution procedures using readily accessible reagents.

3.2. RESULTS AND DISCUSSION

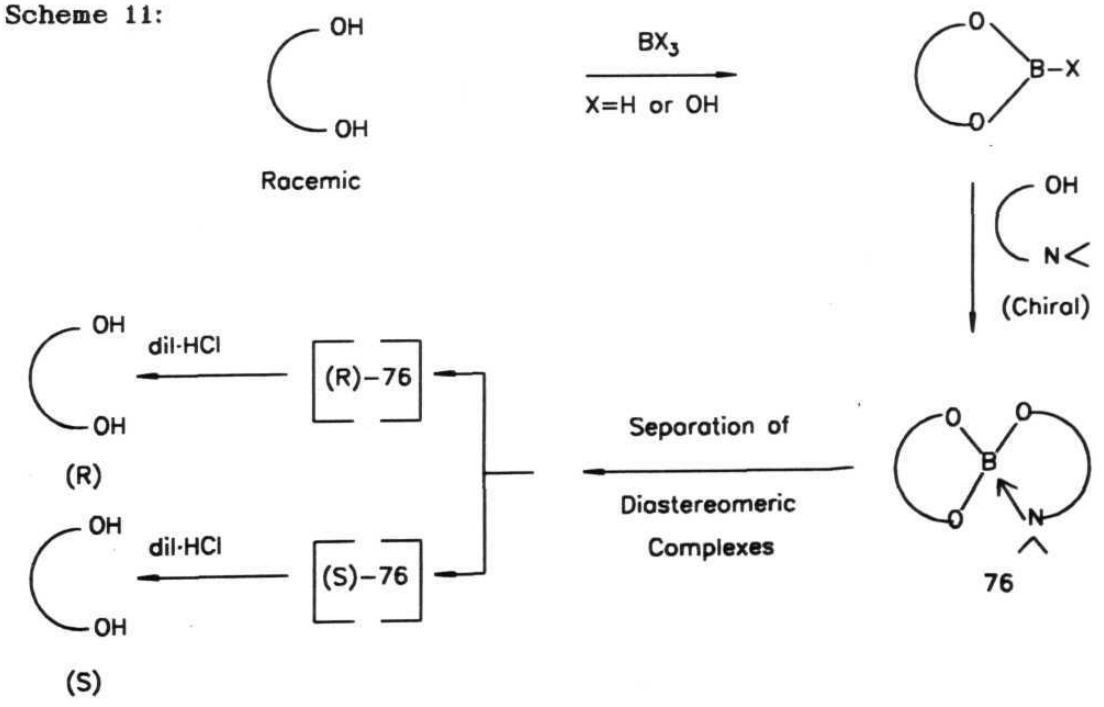
3.2.1. Resolution of racemic diols through cyclic borates:

As outlined earlier, the cyclic phosphate method is more widely utilized for the resolution of racemic binaphthol. However, in addition to requiring several steps, this procedure is severely handicapped by the use of $LiAlH_4$ for the cleavage of the cyclic phosphate derivative 75 (eqn. 26).

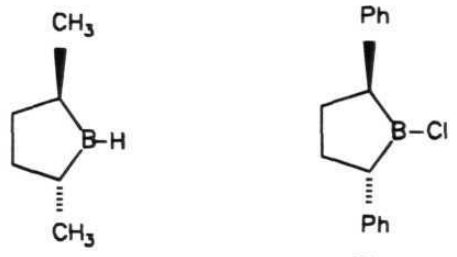


We envisaged the synthesis of the diastereomeric cyclic borates for the separation of the enantiomers of diols using various amino acid derivatives (Scheme 11).

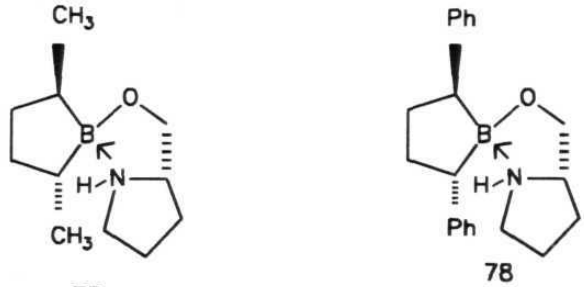
Scheme 11:



Although, the synthesis of diastereomeric borate complexes of this type has not been reported (to our knowledge), resolution of racemic dialkylboranes through such complexes using amino alcohols are known. For example, Masamune et al resolved the trans-2,5-dimethylborolane 20 using (S)-prolinol (eqn. 27).[58] Also, Reetz et al resolved the diphenyl derivative 21 using (S)-prolinol (eqn. 28).[59]

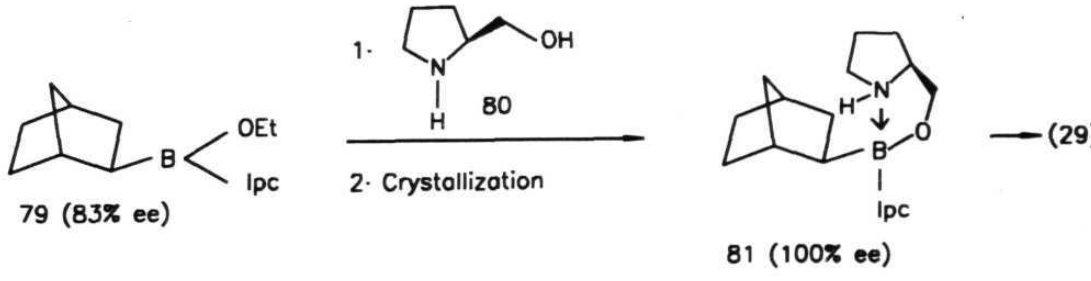


20 21 —(27)



77 78 —(28)

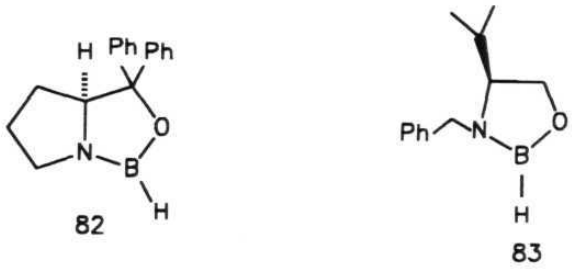
It is also of interest to note that Brown and co-workers used (S)-prolinol for the upgradation of the optical purity of exo-norbornyl boron derivative 79 obtained through asymmetric hydroboration of norbornene with Ipc_2BH (eqn. 29).[60]



79 (83% ee) 81 (100% ee) —(29)

We have decided to investigate the resolution of the racemic diols as envisaged in Scheme 11. We have selected a representative phenolic diol (i.e., binaphthol 1) and an alkoxy diol (i.e., 1,2-diphenylethanediol 17) for this investigation.

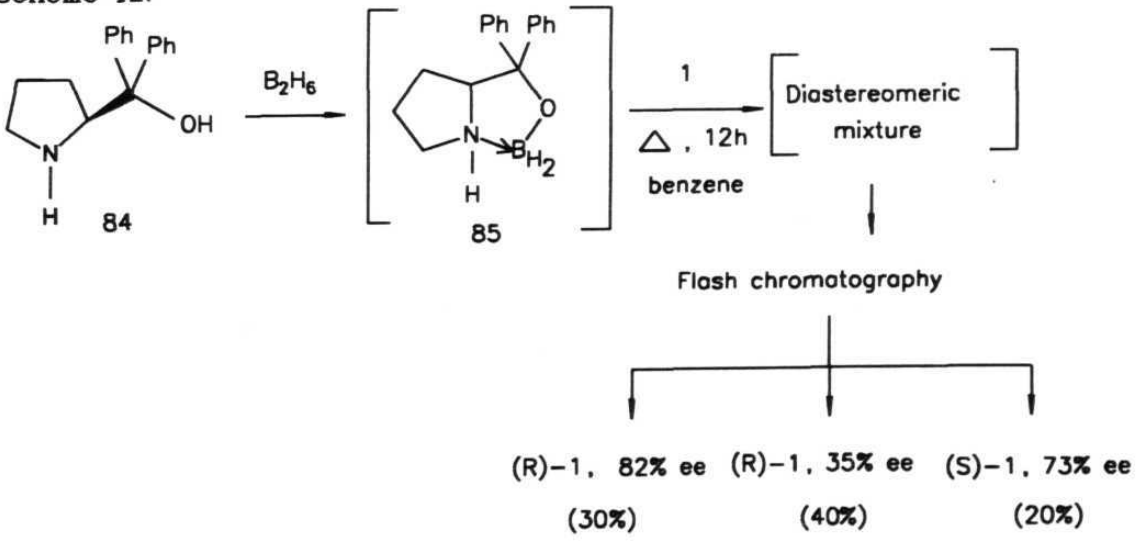
As discussed in Chapter 1, we have prepared various oxazaborolidines derived from (S)-proline and (S)-valine for asymmetric reductions and hydroborations (eqn.30).



(30)

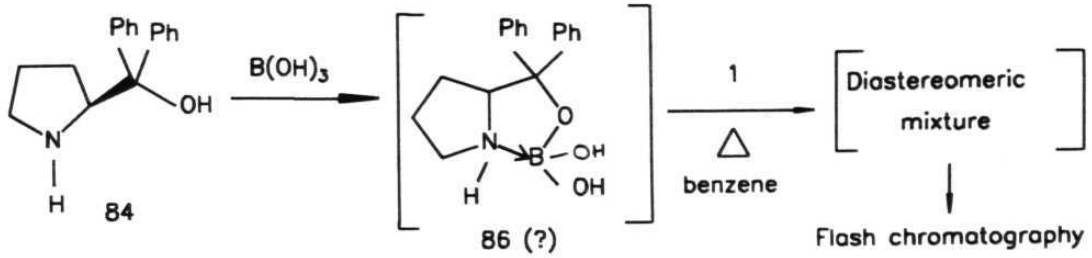
We have carried out the synthesis of diastereomeric borate complexes for the resolution of binaphthol 1 using these reagents 82 and 83 (Scheme 12 and 14). Initially, we tried to isolate and characterize such complexes. However, it was found that in no case the complex obtained was pure (see discussion later). So, we have proceeded with the optical resolution studies.

Scheme 12:



This experiment was also carried out using inexpensive boric acid in the place of diborane (Scheme 13).

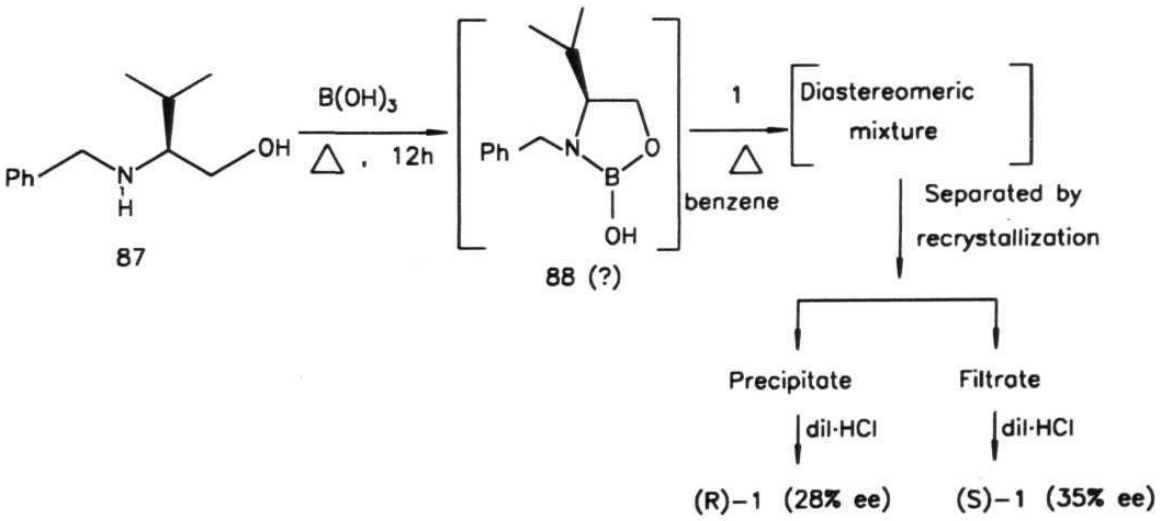
Scheme 13:



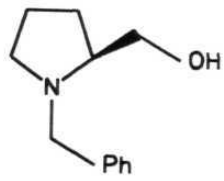
The results obtained were found to be comparable.

The use of N-benzylvalinol **87** and boric acid combination also gave similar results (Scheme 14). However, in this case the contents could be separated by crystallization.

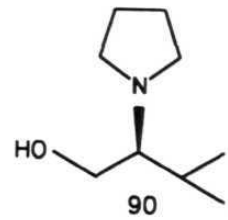
Scheme 14:



It was of interest to examine the use of amino alcohols which contain tertiary amine moiety. In order to examine this, the following tertiary amino alcohols have been prepared (eqn. 31).



89

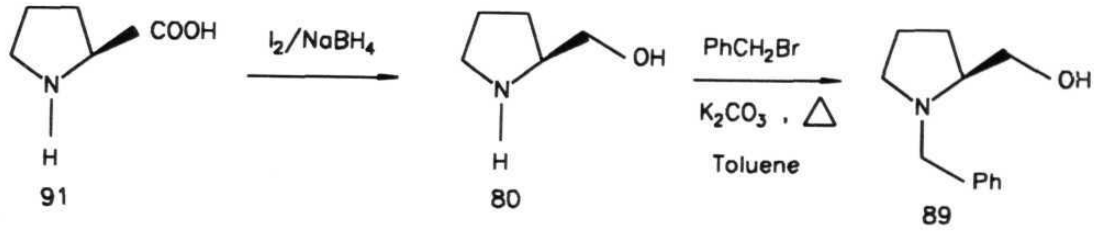


90

(31)

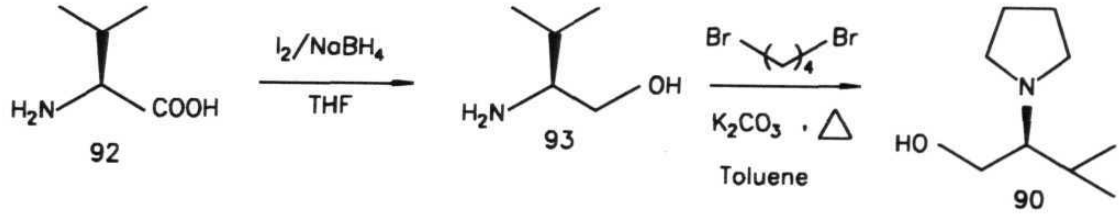
The amino alcohol 89 was prepared from (S)-proline (Scheme 15).

Scheme 15:



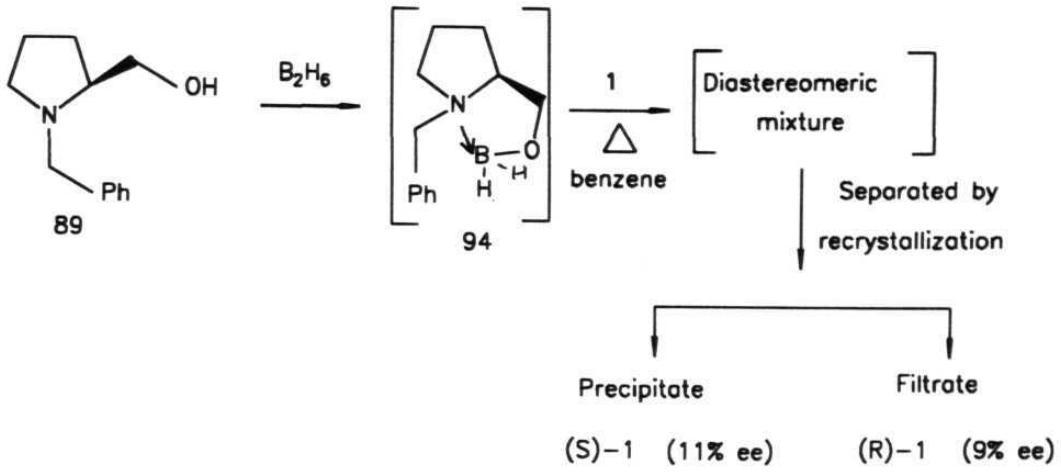
The amino alcohol 90 was synthesized following the sequence of transformations outlined in Scheme 16.

Scheme 16:



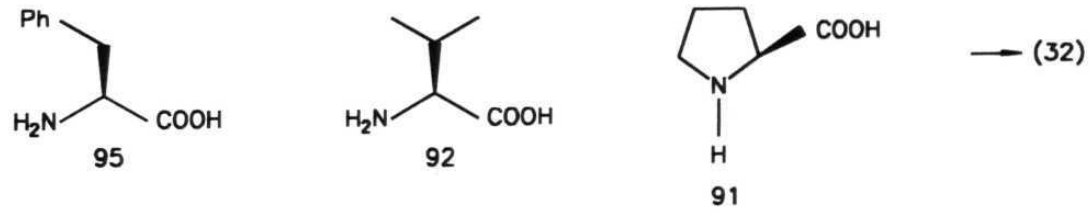
Resolution of racemic binaphthol 1 was examined using the amino alcohol 89 (Scheme 17).

Scheme 17:



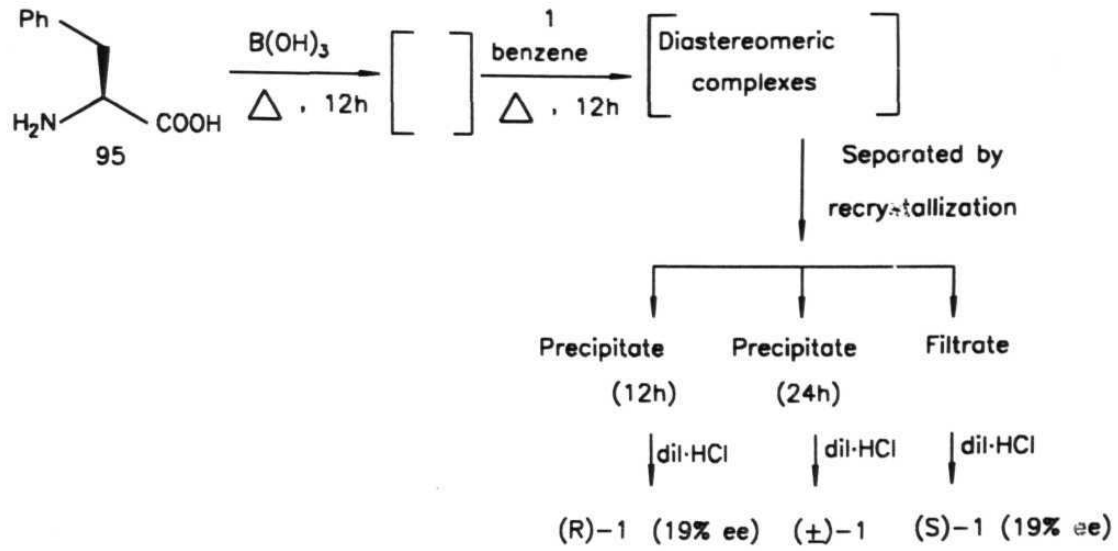
When boric acid was used in the place of diborane, (S)-(−)-1 was obtained in 6% ee from the precipitate. From the filtrate, (R)-(+)-1 was obtained in 9% ee. Repetition of this experiment using amino alcohol 90 gave (R)-(+)-1 (10% ee) from precipitate and (S)-(−)-1 (15% ee) from the filtrate.

We have also examined the synthesis of diastereomeric borate complexes for the resolution using chiral amino acids themselves. Surprisingly, as will be discussed later, the (S)-proline itself gave more fruitful results. We have selected the following readily accessible amino acids for this purpose (eqn. 32).



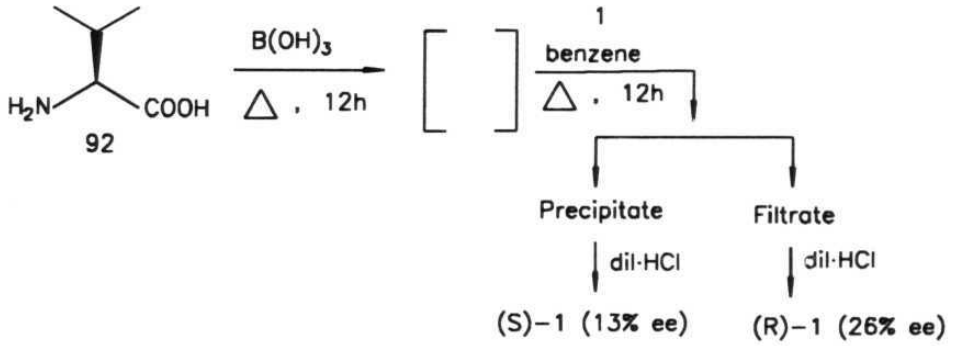
The following experiment was performed to resolve racemic 1 (Scheme 18).

Scheme 18:



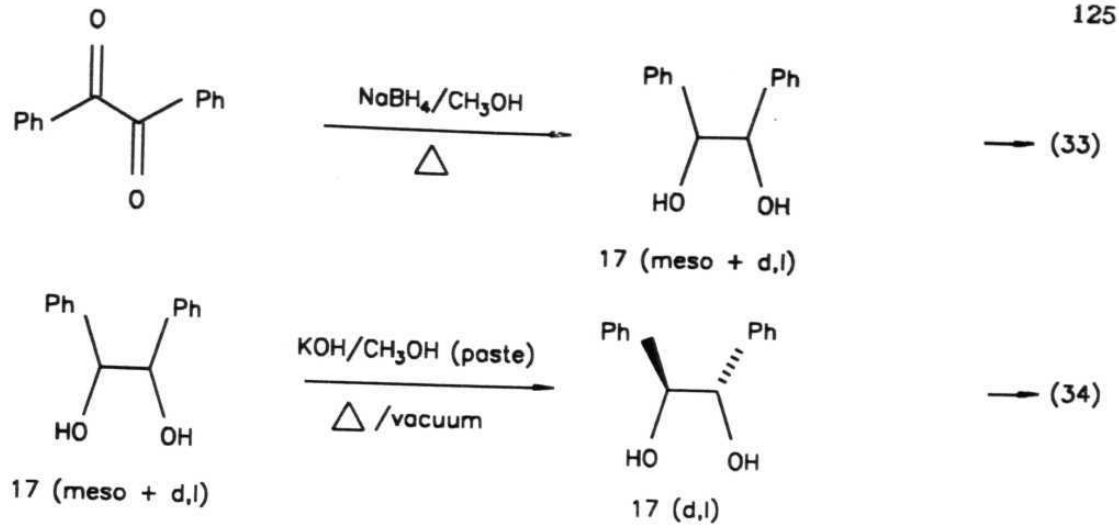
This experiment was also carried out using (S)-valine instead of (S)-phenylalanine (Scheme 19) and comparable results were obtained.

Scheme 19:



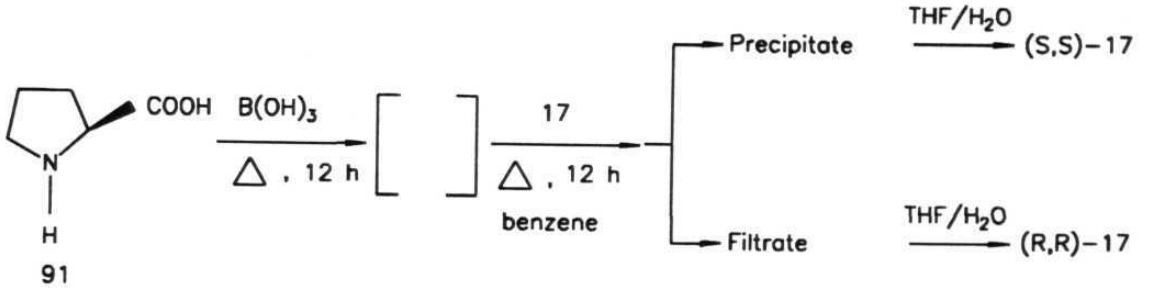
When (S)-proline was used in these reactions, (S)-(-)-1 (13% ee) was obtained from precipitate and (R)-(+)-1 (26% ee) from filtrate.

We have then turned our attention towards the resolution of racemic 1,2-diphenylethanediol 17. The d,l-mixture 17 was prepared following a reported procedure (eqns. 33 and 34).[61]



Synthesis of the diastereomeric complexes for the resolution of **17** was carried out as envisaged in Scheme 20.

Scheme 20:



To examine this, we have carried out the following experiment. A mixture of (S)-proline (1.1 eq.) and boric acid (1.1 eq.) was taken in dry benzene and refluxed. The diol **17** (1 eq.) in hot benzene was added and refluxed. The precipitate obtained was decomposed and (S,S)-**17** was isolated in 91.4% ee (25% yield). From the benzene solution (R,R)-**17** was isolated in 37.4% ee (54% yield) (entry 1, Table 1).

Several experiments were carried out in order to optimize the conditions and the results are summarized in Table 1.

Table 1: Optical resolution of Racemic 1,2-Diphenylethanediol (Scheme 20)

S.No.	Procedure	1,2-Diphenylethanediol isolated[h]			
		From Precipitate		From Filtrate	
		(% ee)[g]	(Yield)	(% ee)[g]	(Yield)
1.	(S)-Proline + $B(OH)_3$[a]	(-) 91.4	(25%)	(+) 37.4	(54%)
2.	(S)-Proline + $B(OH)_3$[b]	(-) 83.8	(24%)	(+) 30.8	(56%)
3.	Diol 17 + $B(OH)_3$[c]	(-) 90.6	(27%)	(+) 39.6	(45%)
4.	Diol 17 + $B(OH)_3$[d]	(-) 83.4	(23%)	(+) 22.4	(50%)
5.	(S)-Proline + $B(OH)_3$[e]	(-) 99.0	(71%)	(+) 26.5	(10%)
6.	(S)-Proline + $B(OH)_3$[f]	(-) 6.8	(32%)	(+) 63.9	(54%)

a) A mixture of (S)-proline (5.5 mM) and boric acid (5.5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. Racemic 1,2-diphenylethanediol (5 mM) dissolved in hot benzene (40 mL) was added and refluxed for 12h in a Dean-Stark set up.

b) (S)-Proline (5 mM), boric acid (5 mM) and racemic 1,2-diol (5 mM) were taken in dry benzene (80 mL) and refluxed for 24h in a Dean-Stark set up.

c) 1,2-Diol (5 mM) and boric acid (5 mM) were taken in dry benzene (40 mL) and refluxed for 12h in a Dean-Stark set up. (S)-Proline (5 mM) and dry benzene (40 mL) were added and refluxed again for 12h.

d) 1,2-Diol (10 mM) and boric acid (5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. (S)-Proline (5 mM) and dry benzene (40 mL) were added and refluxed for 12h in a Dean-Stark set up.

e) (S)-Proline (5.5 mM) and boric acid (5.5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. (-)-1,2-Diol (5 mM, 73% ee) dissolved in

hot benzene (40 mL) was added and refluxed again for 12h in a Dean-Stark set up.

f) (S)-Proline (5.5 mM), boric acid (5.5 mM) and (+)-1,2-diol (5 mM, 30% ee) were used.

g) Optical rotations were determined on an Autopol-II polarimeter using ethanol as solvent. All %ee reported here are based on reported maximum $[\alpha]_D^{25}$ = -94 (C2.5, EtOH)[60] for (-)-17 and +93 (C2.5, EtOH) for (+)-17.

h) Yields are of diols isolated by column chromatography on silica gel using hexane/ethyl acetate (70:30) as eluent.

In an experiment, (S)-proline (1.1 eq.), boric acid (1.1 eq.) and 1,2-diol (1 eq.), were taken in dry benzene and refluxed. From the precipitate, (S,S)-(-)-isomer (83.8% ee, 24%) was obtained. From the filtrate, (R,R)-(+)-isomer (30.8% ee, 56%) was obtained (entry 2, Table 1).

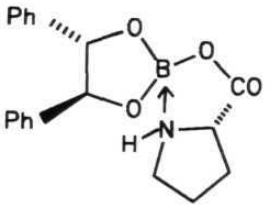
In a different experiment, 1,2-diol (1 eq.) and boric acid (1 eq.) were taken in dry benzene and refluxed for 12h. (S)-Proline (1 eq.) was added and refluxed again for 12h. From the precipitate, (S,S)-(-)-isomer (90.6% ee, 27%) was obtained. From the filtrate, (R,R)-(+)-isomer (39.6% ee, 45%) was obtained (entry 3, Table 1).

In another experiment, 1,2-diol (2 eq.), boric acid (1 eq.) and (S)-proline (1 eq.) were utilized. From the precipitate, (S,S)-(-)-isomer (83.4% ee, 23%) was isolated. From the filtrate, (R,R)-(+)-isomer (22.4% ee, 50%) was isolated (entry 4, Table 1).

This method of resolution was also found to be useful in enriching a mixture of partially resolved 1,2-diols 17. The chiral reagent prepared using (S)-proline (1.1 eq.) and boric acid (1.1 eq.) was used to enrich the

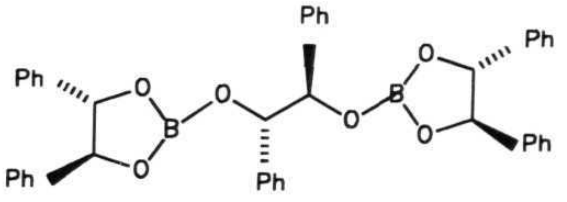
(S,S)-(-)-diol (73% ee). From the precipitate, enantiomerically pure (S,S)-(-)-1,2-diphenylethanediol (71%) was obtained (entry 5, Table 1). We have also attempted to enrich (R,R)-(+)-diol (30% ee) using the same reagent. In this case, from the precipitate, (S,S)-(-)-isomer (6.8% ee, 32%) was obtained and from the filtrate, (R,R)-(+)-isomer (63.9% ee, 54%) was isolated.

Efforts were also undertaken to characterize the precipitate obtained in the experiment using pure (S,S)-(-)-17 in order to determine the nature of the complexes involved. The following cyclic borate complex 96 was anticipated.



96

The complex has been prepared according to the procedure reported for the entry 1 in Table 1. It was found to be sparingly soluble in chloroform. It was crystallized from chloroform for analyses. However, the ^{1}H NMR (200 MHz) spectrum indicated the presence of unidentified impurities. Combustion analysis data also did not correspond to this structural formula. Presumably, the precipitate may also contain small amounts



97

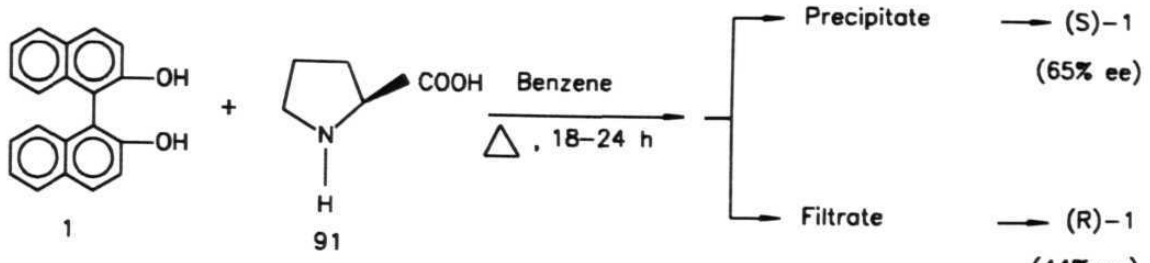
of borate complexes (eg. of the type 97) which are not separable from the complex 96. Further efforts to characterize these complexes are underway in this laboratory.

3.2.2. Resolution of racemic diols 1 and 17 using (S)-proline:

As outlined earlier, there has been some recent reports describing resolution of 1 using diamines[54] and some quartenary salts.[57] So, we have carried out an experiment to examine whether boric acid is necessary in these reactions. It was found that refluxing of a mixture of (S)-proline and racemic 1,2-diphenylethanediol 17, led to small amount of precipitate which was found to be (S)-proline. The racemic diol was isolated from the filtrate quantitatively, indicating that the boric acid is necessary for the resolution of the diol 17.

As discussed earlier, the borate complex method did not give fruitful results in the case of racemic binaphthol 1. Fortunately, however, it was found that the racemic binaphthol 1 could be readily resolved into enantiomers using (S)-proline alone. Refluxing of a 1:1 mixture of racemic binaphthol and (S)-proline in dry benzene led to a precipitate and a solution. The precipitate obtained was filtered off from the solution. The binaphthol was isolated from the precipitate by extracting with anhydrous ether. The binaphthol thus obtained was found to be enriched in (S)-(-)-isomer (65% ee, 43%). The insoluble portion of precipitate contains essentially (S)-proline. From the filtrate, (R)-(+)-isomer (44% ee, 51%) was obtained. Only a small portion of (S)-proline (2-3%) was found in the filtrate.

Scheme 21:



Similar results were obtained when 1:1 proportion of (5–20 mM) of (S)–proline and binaphthol (5–20 mM) were refluxed in benzene for 18–24h. This method of resolution of binaphthol using (S)–proline was found to be useful for enriching a mixture of partially resolved binaphthols. We have carried out several experiments using various mixtures partially resolved binaphthols with (S)–proline and the results are summarized in Table 2.

To study this phenomenon of resolution, we have used a binaphthol enriched in (S)–(–)–isomer (10% ee). A 1:1 mixture with (S)–proline was taken in dry benzene and refluxed. From the precipitate, (S)–(–)–isomer enriched in up to 64% ee (65%) was obtained. From the filtrate, (R)–(+)–isomer enriched in up to 70% ee (25%) was obtained (entry 2, Table 2). We have also carried out a similar experiment using binaphthol enriched in (R)–(+)–isomer (10% ee) and found that this phenomenon is not as effective as was found with (S)–(–)–isomer. From the precipitate, (R)–(–)–isomer (6% ee, 56%) and from filtrate, (S)–(–)–isomer (18% ee, 30%) were obtained (entry 3, Table 2).

Table 2: Separation of enantiomers of binaphthol using (S)-proline

S.No.	Substrate 1[a] config., ee %	Binaphthols obtained from					
		Precipitate			Solution		
		Conf.	% ee	% Yield	Conf.	% ee	% Yield
1.	(R,S)-(±), 0[b]	S	65	43	R	44	51
2.	(S)-(-), 10[c]	S	64	65	R	70	25
3.	(R)-(+), 10[d]	R	06	56	S	18	31
4.	(S)-(-), 65[e]	S	87	66	S	06	22
5.	(R)-(+), 44[f]	R	90	45	R	06	41
6.	(S)-(-), 87[g]	S	100[i]	77	S	35	11
7.	(R)-(+), 90[h]	R	98[j]	70	R	28	18

a) Experiments were carried out using 1:1 mixtures of binaphthol and (S)-proline in dry benzene and refluxed for 24h.

b) (R,S)-(±)-1 (5.72 g, 20 mM), (S)-(-)-91 (2.3 g, 20 mM) and 240 ml of benzene were used.

c) (S)-(-)-1 (1.0 g), (S)-(-)-91 (0.4 g) and 50 ml of benzene were utilized.

d) (R)-(+)-1 (1.0 g), (S)-(-)-91 (0.4 g) and 50 ml of benzene were used.

e) (S)-(-)-1 (2.5 g), (S)-(-)-91 (1.0 g) and 105 ml of benzene were utilized.

f) (R)-(+)-1 (2.9 g), (S)-(-)-91 (1.2 g) and 120 ml of benzene were used.

g) (S)-(-)-1 (0.9 g), (S)-(-)-91 (0.37 g) and 50 ml of benzene were used.

h) (R)-(+)-1 (0.96 g), (S)-(-)-91 (0.39 g) and 45 ml of benzene were utilized.

i) Enantiomeric excess was determined by HPLC analysis on chiralcel OP

column using methanol as solvent. All other % ee values reported here are based on $[\alpha]_D^{25}$ values, maximum $[\alpha]_D^{25} = 34^o$ (C1, THF).

j) 100% ee based on $[\alpha]_D^{25}$ value. However, presence of 1-2% of the (S)-(-) enantiomer was determined in the HPLC analysis (Chart 6).

However, the results are better when binaphthol with 44%-90% ee were utilized. When a mixture of (S)-(-)-binaphthol (65% ee) and (S)-proline were refluxed in benzene, the (S)-(-)-isomer (87% ee, 66%) was obtained from the precipitate (entry 4, Table 2). When a mixture of (R)-(+)-binaphthol (44% ee) and (S)-proline were refluxed in benzene, significantly enriched (R)-(+)-isomer (90% ee, 45%) was obtained from precipitate (entry 5, Table 2). The later result indicates that when the (R)-(+)-isomer is present in larger quantity, it has comes out in the precipitate fraction.

The binaphthols obtained in ~ 90% ee through different methods can be made essentially pure by recrystallization from methanol.[57] However, we have decided to employ our method of resolution for the enrichment of such binaphthols. Essentially pure binaphthols were isolated in this way. As may be seen in Table 2, the third repetition of the above process using (S)-proline gives essentially pure binaphthols (entries 6 and 7, Table 2). The enantiomeric purities in these cases were determined using chiral HPLC analysis on chiral column using methanol as solvent (Table 2).

It should be pointed out that although this method of resolution/ enrichment requires three cycles to get enantiomerically pure binaphthols from a racemic mixture, essentially all of the binaphthol can be resolved into its antipodes. The solvent used can be recycled and the reagent (S)-proline can be readily recovered (> 70%) and reused after recrystalli-

zation from ethanol.

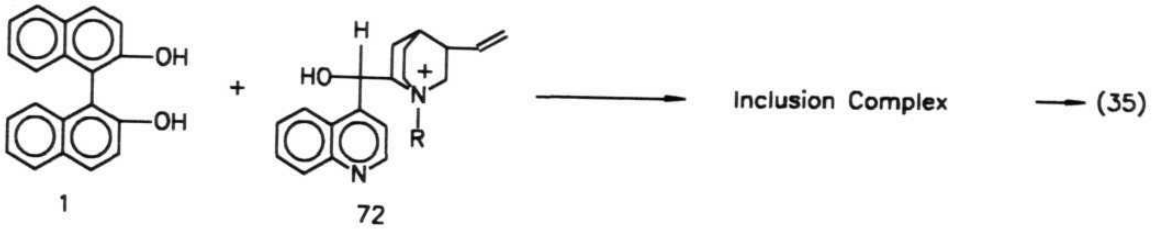
When this method of resolution was performed in toluene solvent at 80-90°C using racemic binaphthol and (S)-proline, low enantioselectivities were obtained. From the precipitate, (S)-(-)-binaphthol was obtained in 38% ee and from filtrate, (R)-(+)-binaphthol was obtained in 11% ee.

It is also of interest to understand this resolution process and the nature of the complexes involved. Efforts were made to delineate the structures involved in these complexes. IR spectral analysis of the precipitate indicated the presence of a complex of binaphthol and (S)-proline and some free (S)-proline. This complex was found to be insoluble in chloroform and dichloromethane and dissociates when stirred with anhydrous ether or THF. The precipitate obtained on evaporation the benzene solution (Scheme 21) is essentially pure binaphthol containing small amount of a complex. Unfortunately, our efforts to obtain the complex free of 'free' binaphthol or 'free' proline were not successful. However, the method should be attractive for synthetic applications.

As mentioned in the earlier section, resolution of binaphthol was reported using diamines such as cyclohexyldiamine 70 and 1,2-diphenyl-ethanediamine.[54] The crystalline derivatives obtained were found to be products containing both the diamine and diol. However, the authors have not specified anything about the structure of the complexes.[54]

Recently, Toda et al have used N-alkylcinchonidium halides for the resolution of racemic binaphthol.[57] They have also performed X-ray studies and found that these complexes are the *inclusion complexes formed through*

weak hydrogen bonding.[57]



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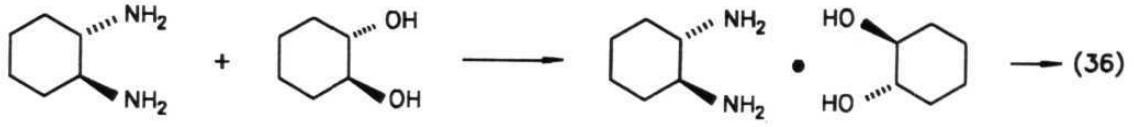
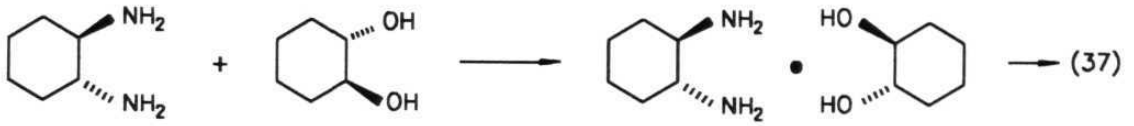
It is of interest to note the report by Hanessian that the trans-1,2-diaminocyclohexane and the diol, (S,S)-trans-1,2-cyclohexanediol form a supramolecular helicate structures through *hydrogen bonding.*[63]



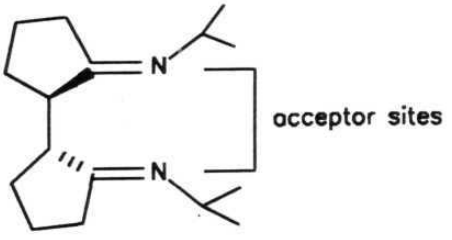
(S,S)-70 (S,S)-98 (S,S/S,S)-99



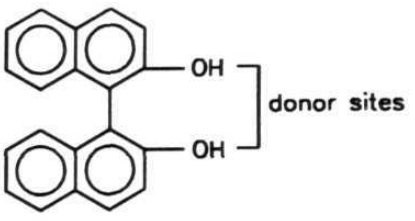
(R,R)-70 (S,S)-98 (R,R/S,S)-99

X-ray crystallographic analysis of these adducts showed a 1:1 complex between one molecule of diol and one of diamine linked by a pair of interactions well within the distance of a definite hydrogen bond.[63]

Recently, Dobashi et al have reported a complex formation between (R,R)-4,4′-bis[5-(2)-N-isopropylimino)]-1,3-dioxolane 100 and (S)-2,2′-bi-naphthol, through *N- -H- -O bonding.*[64]



100

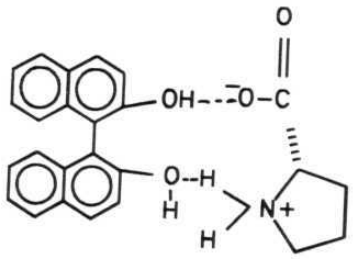


1

Crystallographic data of this complex is in accordance with a *dual N-H- - -O bonding* between the diamine and (S)-binaphthol.[64]

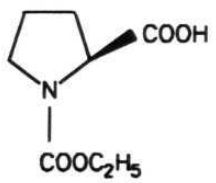
Apparently, as remarked by Lehn in a different context,[65,66] *the diamine/diol motif consists of mutually complementary partners possessing encoded stereochemical and functional information that is read by the recognition process.*

Presumably, in the present case in our hands, the complex might have formed between (S)-proline and binaphthol through ion-dipole hydrogen bonding as envisaged in structure 101.

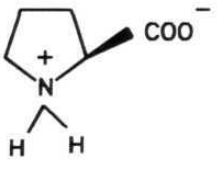


101

Recently, it was found in this laboratory that the resolution does not work in slightly acidic (i.e. addition of p-toluene sulphonic acid) or basic medium (i.e. addition of a tertiary amine). Also, the N-carbamate of (S)-proline 102 failed to give the resolution.



102



103

— (38)

These results may further indicate the necessity of the zwitter ionic form of the proline 103 for complexation and resolution.

3.3. CONCLUSIONS

A boron-based methodology was developed for the resolution of racemic diols. Various amino alcohols and natural amino acids were used for this purpose. Racemic 2,2'-binaphthol was partially resolved using the amino alcohol/amino acid and diborane/boric acid combinations. However, enantiomerically pure (S,S)-1,2-diphenylethanediol was obtained when (S)-proline and boric acid combination was used. (S)-Proline itself was found to be useful for the direct resolution of 2,2'-binaphthol by refluxing in benzene. Essentially pure (R)- and (S)-isomers were obtained in three successive operations in this way.

3.4. EXPERIMENTAL SECTION

General details:

Several items given in the experimental section of Chapter 1 are also applicable for the experiments outlined here. The resolution procedures reported here were carried out at least twice in each case. In each case, the optical rotations were measured at two concentrations. (S)-Proline and (S)-valine supplied by Aldrich (USA), (S)-phenylalanine supplied by LOBA-chem., India were utilized. Boric acid, β-naphthol, and benzil were supplied by Sisco-chem, India.

Preparation of 2,2′-binaphthol 1 using β-naphthol and ferric chloride:

A reported procedure was followed.[67] β-Naphthol (14.4 g, 100 mM) was taken in water (600 mL) and the contents were refluxed. To the oily suspension obtained, ferric chloride (28 g, 100 mM) dissolved in water (60 mL) was added dropwise. The reaction mixture was refluxed for 0.5h and filtered at hot. The precipitate obtained was washed with hot water (50 mL). The crude binaphthol obtained was recrystallized from benzene.

Yield : 6.5 g (45%)

M.P. : 217°C; Lit.[67] 218°C

IR (KBr) ν_{max} : 3487, 3404, 1618, 1595, 1174 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.1 (bs, 2H), 7.1-8.0 (m, 12H)

Preparation of d,l-1,2-diphenylethanediol 17:[61]

a) Reduction of benzil using sodium borohydride in methanol:

Benzil (21 g, 100 mM) was taken in methanol (150 mL) and cooled to 0°C. Sodium borohydride (4.6 g, 120 mM) was added portion-wise to the reaction mixture. The contents were refluxed for 12h. Methanol was evaporated and it was extracted with ethyl acetate (3 x 30 mL). The organic extracts were washed with 3N HCl (5 mL), water, brine and dried over $MgSO_4$. On evaporation of the solvent, a mixture of meso and d,l-1,2-diphenylethanediol, 17 was obtained.

M.P : 138°C

IR(KBr) ν_{max} : 3381, 3030, 3020, 2899, 1600, 1033, 754, 698 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 2.93 (s, 2H), 4.71-4.83 (d, 2H) 7.25-7.30 (m, 10H).

b) Conversion of the meso-d,l mixture to d,l-diol 17:

Finely powdered mixture of 1,2-diphenylethanediol 17 (16.6 g, 30 mM) and potassium hydroxide (60 g) were taken in a round bottom flask. Methanol (15 mL) was added to make a paste. The flask was connected to a vacuum pump through a Claisen condenser. The reaction mixture was rapidly heated to 100-110°C. The pressure was gradually reduced to 15-20 mm of Hg. These conditions (110-115°C/15-20 mm Hg) were maintained for 0.5h. The temperature was then raised to 170-180°C and heating was continued for another 1h. The reaction mixture was cooled under vacuum to room temperature and water (30 mL) was added. It was extracted with ether (3 x 20 mL)

and the combined ether extract was washed successively with 3N HCl (5 mL), water, brine and dried over $MgSO_4$. On evaporation of the solvent and recrystallization from water/methanol mixture (4:1), pure d,l-1,2-diphenylethanediol 17 was isolated.

Yield	:	5.3 g (80%)
M.P.	:	121^0C; Lit.[61] 121°C
IR (KBr) ν_{max}	:	3381, 3030, 3020, 2899, 1600, 1033, 754, 698 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$) δ ppm:		2.93 (s, 2H), 4.71 (s, 2H), 7.25-7.30 (m, 10H)
^{13}C NMR (50 MHz, $CDCl_3$) δ ppm:		77.86, 79.25, 127.16, 128.03, 128.30, 140.14

Resolution of racemic 2,2'-binaphthol 1 (1 eq.) using (S)-N-benzylvalinol 7 (1.1 eq.) and boric acid (1.1 eq.):

(S)-N-benzylvalinol 7 (0.97 g, 5 mM) and boric acid (0.31 g, 5 mM) were taken in dry benzene (40 mL) and the contents were refluxed for 6h. Water produced was removed using a Dean-Stark apparatus. Racemic binaphthol (1.43 g, 5 mM) was dissolved in hot benzene (40 mL) and was added at once to the reaction mixture under nitrogen atmosphere. The contents were further refluxed for 12h. The reaction mixture was cooled to room temperature and hexane (20 mL) was added and the contents were kept for crystallization. After 24h, the precipitate 'A' formed was filtered and the benzene, hexane mixture was concentrated. The solid obtained was taken in ether and decomposed using 3N HCl (10 mL). The ether layer was washed successively with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on

silica gel column using hexane:ethyl acetate (80:20), (S)-(-)-binaphthol was isolated. The precipitate 'A' after work up as above gave (R)-(+)-binaphthol.

From precipitate:

After decomplexation:

(R)-(+)-2,2'-binaphthol : 0.69 g (42%)

M.P. : 214°C

IR (KBr) ν_{max} : 3051, 1589, 1068 cm^{-1}

$[\alpha]_D^{25}$ = +9.5° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

From filtrate:

After decomplexation:

(S)-(-)-2,2'-binaphthol : 0.5 g (35%)

M.P. : 214°C

IR (KBr) ν_{max} : 3034, 1616, 1070 cm^{-1}

$[\alpha]_D^{25}$ = -12.0° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1, THF)

Spectral data of the product obtained was in accordance with the data reported in the earlier experiment.

Resolution of racemic 2,2'-binaphthol 1 (1 eq.) using phenylalanine (1.1 eq.) and boric acid (1.1 eq.):

(S)-Phenylalanine (0.9 g, 5.5 mM) and boric acid (0.34 g, 5.5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. Water produced was removed using Dean-Stark apparatus. Racemic binaphthol 1 (1.43 g, 5 mM) dissolved in hot benzene (40 mL) was added to the reaction mixture under nitrogen atmosphere. The contents were further refluxed for 12h. The homogeneous solution obtained was kept for crystallization. The precipi-

tate obtained after 12h and 24h were collected, taken in ether and decomposed individually using 3N HCl. The ether solution was washed with water, brine and dried over anhydrous $MgSO_4$. On evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (80:20), binaphthol was isolated. The benzene mother liquor was concentrated. After work up as above, the third fraction of binaphthol was obtained.

From first precipitate:

After decomplexation:

(R)-(+)-2,2'-binaphthol : 0.26 g (18%)

M.P. : 214°C

$[\alpha]_D^{25}$ = +6.0° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

From second precipitate:

After decomplexation:

(R)-(+)-2,2'-binaphthol : 0.65 g (45%)

M.P. : 216°C

$[\alpha]_D^{25}$ = +0.2° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

From filtrate:

After decomplexation:

(S)-(-)-2,2'-binaphthol : 0.29 g (20%)

M.P. : 214°C

$[\alpha]_D^{25}$ = -6.0° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1, THF)

Resolution of racemic 2,2'-binaphthol 1 using (S)-proline (1 eq.) and boric acid (1.1 eq.):

(S)-Proline (0.64 g, 5.5 mM) and boric acid (0.34 g, 5.5. mM) were taken in dry benzene (40 mL) and the contents were refluxed for 12h. Water

produced was removed with Dean-Stark apparatus. Racemic binaphthol (1.43 g, 5 mM) dissolved in hot benzene (40 mL) was added to the reaction mixture under nitrogen atmosphere and refluxed. The slurry becomes homogeneous after 1h and precipitation starts after 4h. The refluxing was continued for 24h and the contents were brought to room temperature. The precipitate was filtered off and decomposed using 1:1 mixture of THF and ethylene glycol (15 mL). Water was added and it was extracted with ether (2 x 25 mL), washed with 3N HCl (2 x 5 mL), water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (80:20) as solvent, (S)-binaphthol was isolated. The benzene solution was concentrated, worked up as above to obtain (R)-binaphthol.

From precipitate:

After decomplexation:

(S)-(-)-2,2'-binaphthol : 0.45 g (31%)

M.P. : 214°C

$[\alpha]_D^{25} = -6^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = -34^o$ (C1, THF)

From filtrate:

After decomplexation:

(R)-(+)-2,2'-binaphthol : 0.65 g (45%)

M.P. : 215°C

$[\alpha]_D^{25} = +3^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = +34^o$ (C1, THF)

Resolution of racemic 1,2-diphenylethanediol 17 (1 eq.) using (S)-proline (1.1 eq.) and boric acid (1.1 eq.):

(S)-Proline (0.64 g, 5.5 mM) and boric acid (0.34 g, 5.5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. Water produced was

removed using Dean-Stark apparatus. 1,2-Diphenylethanediol (1.1 g, 5 mM) dissolved in hot benzene (40 mL) was added to the reaction mixture under nitrogen atmosphere. The slurry becomes homogeneous and precipitation starts after 6h. The contents were further refluxed for 6h and cooled to room temperature and the precipitate 'A' was filtered off. The organic solution was concentrated and the residue obtained was decomposed using a 1:1 mixture of THF and water (10 mL). It was extracted with ethyl acetate (2 x 25 mL) and the organic extract was washed successively with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by chromatography on silica gel column using hexane:ethyl acetate (70:30) solvent, (R,R)-(+)-1,2-diphenylethanediol 17 was isolated. The precipitate 'A' was decomposed with 1:1 mixture of THF and water (15 mL). After work up and purification by column chromatography (S,S)-(-)-1,2-diphenylethanediol 17 was obtained.

From precipitate 'A':

Wt. : 0.7 g

M.P. : >225°C

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.28 g (25%)

M.P. : 145°C

$[\alpha]_D^{25}$ = -85.88° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH)

From filtrate: (Complex obtained after evaporation of benzene solution)

Wt. : 1.2 g

M.P. : 176°C

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 1.7-2.5 (m, 5H), 3.24-4.6 (m, 2H), 3.96-4.14 (m, 1H), 4.78 (s, 1H), 7.08-7.36 (m, 10H) (Septrum No.13) (more signals due to impurities)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 25.65, 28.98, 47.36, 62.54, 85.85, 125.95, 126.31, 126.96, 127.94, 128.43, 128.73, 128.94, 139.91, 172.77 (Septrum No.14)
(more signals due to impurities)

After decomplexation:

(R,R)-1,2-diphenylethanediol : 0.6 g (54%)

M.P. : 130°C

$[\alpha]_D^{25}$ = +34.80° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = +93.0° (C2.5, EtOH)

Resolution of racemic 1,2-diphenylethanediol 17 (1 eq.) using (S)-proline (1.1 eq.) and boric acid (1.1 eq.): Single step procedure:

(S)-Proline (0.64 g, 5 mM), boric acid (0.34 g, 5 mM) and racemic 1,2-diphenylethanediol 17 (1.1 g, 5 mM) were taken in dry benzene (80 mL) and the contents were refluxed for 24h. Water produced was removed using Dean-Stark apparatus. After work up as described in earlier experiments, (R,R)-(+) and (S,S)-(-)-diphenylethanediols were isolated.

From precipitate:

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.27 g (24%)

M.P. : 144°C

$[\alpha]_D^{25}$ = -78.8° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH)

From filtrate:

After decomplexation:

(R,R)-1,2-diphenylethanediol : 0.62 g (56%)

M.P. : 126°C

$[\alpha]_D^{25}$ = +28.63° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = +93.0° (C2.5, EtOH)

Resolution of racemic 1,2-diphenylethanediol 17 (1 eq.) using (S)-proline (1 eq.) and boric acid (1 eq.):

(±)-1,2-Diphenylethanediol 17 (1.1 g, 5 mM) and boric acid (0.30 g, 5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. Water produced was removed using Dean-Stark apparatus. The contents were cooled to room temperature and (S)-proline (0.58 g, 5 mM) and benzene (40 mL) were added and the contents were further refluxed for 12h. After work up as described in earlier experiments, from precipitate and filtrate 1,2-diphenylethanediols 17 were obtained.

From precipitate:

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.30 g (27%)

M.P. : 145°C

$[\alpha]_D^{25} = -85.20^o$ (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25} = -94.0^o$ (C2.5, EtOH)

From filtrate:

After decomplexation:

(R,R)-1,2-diphenylethanediol : 0.5 g (45%)

M.P. : 131°C

$[\alpha]_D^{25} = +36.86^o$ (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25} = +93.0^o$ (C2.5, EtOH)

Resolution of racemic 1,2-diphenylethanediol 17 (2 eq.) using (S)-proline (1 eq.) and boric acid (1 eq.):

(±)-1,2-Diphenylethanediol (2.2 g, 10 mM) and boric acid (0.30 g, 5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. The slurry becomes homogeneous in 2h and water was removed using Dean-Stark apparatus. After 12h, the reaction mixture was brought to room temperature and

(S)-proline (0.58 g, 5 mM) and dry benzene (40 mM) were added. The contents were refluxed for 12h. After work up as described in earlier experiments, diphenylethanediols were isolated from the precipitate and benzene solution.

From precipitate:

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.5 g

M.P. : 144°C

$[\alpha]_D^{25}$ = -78.4° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH)

From filtrate:

After decomplexation:

(R,R)-1,2-diphenylethanediol : 1.1 g

M.P. : 125°C

$[\alpha]_D^{25}$ = +20.8° (2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = +93.0° (C2.5, EtOH)

Enrichment of (S,S)-(-)-1,2-diphenylethanediol 17 (1 eq.) using (S)-proline (1.1 eq.) and boric acid (1.1 eq.):

(S)-Proline (0.64 g, 5.5 mM) and boric acid (0.34 g, 5.5 mM) were taken in dry benzene (30 mL) and refluxed for 12h. (S,S)-1,2-diphenylethanediol 17 (1.1 g, 5 mM, 73% ee) dissolved in hot benzene (30 mL) was added under nitrogen atmosphere. The contents were refluxed for 12h. After work up as described in earlier experiments, the diol 17 was obtained from the precipitate and benzene solution.

Precipitate:

M.P. : 165°C (crystallized from $CHCl_3$)

IR (KBr) ν_{max} : 3050 (b), 1624, 1590, 700 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) δ ppm: 1.70-2.51 (m, 5H), 3.24-4.61 (m, 2H),

3.96-4.14 (m, 1H), 4.78 (s, 2H), 7.08-7.36 (m, 10H)

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.78 g (71%)

M.P. : 148°C

$[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH)

Filtrate:

After decomplexation:

(R,R)-1,2-diphenylethanediol : 0.10 g (10%)

M.P. : 126°C

$[\alpha]_D^{25}$ = +24.62° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = +93.0° (C2.5, EtOH)

Enrichment of (R,R)-(+)-1,2-diphenylethanediol 17 using (S)-proline (1.1 eq.) and boric acid (1.1 eq.):

(S)-Proline (0.64 g, 5.5 mM) and boric acid (0.34 g, 5.5 mM) were taken in dry benzene (40 mL) and refluxed for 12h. (R,R)-(+)-1,2-diphenylethanediol (1.1 g, 5 mM, 32% ee) dissolved in hot benzene (40 mL) was added under nitrogen atmosphere. The contents were refluxed for 12h. The slurry becomes homogeneous solution as reaction goes on. The reaction mixture was cooled to room temperature and kept for recrystallization for 48h. The precipitate obtained was filtered off. After usual work up, diol 17 was obtained from the precipitate and the benzene solution.

From precipitate:

After decomplexation:

(S,S)-1,2-diphenylethanediol : 0.35 g (32%)

M.P. : 124°C

$[\alpha]_D^{25}$ = -6.4° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = -94.0° (C2.5, EtOH)

From filtrate:

After decomplexation:

(R,R)-1,2-diphenylethanediol : 0.6 g (54%)

M.P. : 140°C

$[\alpha]_D^{25}$ = +59.4° (C2.5, EtOH) Lit.[62] $[\alpha]_D^{25}$ = +93.0° (C2.5, EtOH)

Control experiment to examine the necessity of boric acid:

A mixture of (S)-proline (0.58 g, 5 mM) and (±)-1,2-diphenylethanediol 17 (1.1 g, 5 mM) were taken in dry benzene (80 mL) and refluxed for 24h. The contents were cooled to room temperature and the precipitate obtained was filtered off. The precipitate and filtrate were separated and subjected to the usual work up procedure. From precipitate no, 1,2-diphenylethanediol was isolated. The 1,2-diol was quantitatively recovered from the filtrate (1.0 g, 90%).

Resolution of Racemic 2,2′-binaphthol 1 (1 eq.) using (S)-proline:

Racemic binaphthol (5.72 g, 20 mM) and (S)-proline (2.3 g, 20 mM) were taken in dry benzene (240 mL) and the contents were refluxed. The slurry becomes homogeneous in 1h and precipitation starts in 3h. After 24h, the reaction mixture was brought to room temperature and the precipitate 'A' was filtered off. It was washed with dry benzene (20 mL) and the combined benzene solution was concentrated. The residue obtained was extracted with anhydrous ether (2 X 40 mL), leaving behind small amount of (S)-proline (0.2 g). The ether extracts were concentrated and the residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (80:20) as eluent to obtain (R)-(+)-binaphthol. The precipitate 'A'

obtained was extracted with ether (4 x 50 mL), leaving behind insoluble (S)-proline (1.78 g). The ether extracts were concentrated and the residue obtained was purified by column chromatography on silica gel column using hexane:ethyl acetate (80:20) as eluent to obtain (S)-(-)-binaphthol.

Precipitate:

Wt. : 5.0 g

M.P. : 202°C

IR (KBr) ν_{max} : 3450 (b), 3063, 1622, 1450, 1084, 750, 665 cm^{-1}

After work up:

(S)-(-)-2,2'-binaphthol : 2.50 g (43%)

M.P. : 207°C

$[\alpha]_D^{25} = -22^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = -34^o$ (C1, THF)

The spectral data of this product is in 1:1 correspondence with the data reported in the earlier experiment.

From filtrate: (Residue obtained after evaporation of benzene solution)

Weight of the residue : 3.1 g

M.P. : 203°C

$[\alpha]_D^{25}$ = $+13^o$ (C1, THF)

IR (KBr) ν_{max} : 3487 (s), 3404 (s), 1618, 1595, 1462, 750, 665 cm^{-1}

After work up:

(R)-(+)-2,2'-binaphthol : 2.9 g (50%)

M.P. : 209°C

$[\alpha]_D^{25} = +15^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = +34^o$ (C1, THF)

The spectral data of this product showed 1:1 correspondence with the data of an authentic sample.

Enrichment of (S)-(-)-2,2'-binaphthol 1 using (S)-proline (1 eq.):

(S)-(-)-2,2'-Binaphthol 1 (1.0 g, 3.5 mM, 11% ee) and (S)-proline (0.4 g, 3.5 mM) were taken in dry benzene (50 mL) and refluxed for 24h. The precipitate obtained was separated and both precipitate and filtrate after work up as described above gave 2,2'-binaphthol 1.

From precipitate:

After work up:

(S)-(-)-2,2'-binaphthol : 0.65 g (65%)

M.P. : 207°C

$[\alpha]_D^{25} = -21^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = +34^o$ (C1, THF)

From filtrate:

After work up:

(R)-(+)-2,2'-binaphthol : 0.25 g (25%)

M.P. : 207°C

$[\alpha]_D^{25} = +24^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = +34^o$ (C1, THF)

Attempted enrichment of R-(+)-2,2'-binaphthol 1 (1 eq.) using (S)-proline (1 eq.):

(R)-(+)-2,2'-Binaphthol 1 (1.43 g, 5 mM, 11% ee) and (S)-proline (0.575 g, 5 mM) were taken in dry benzene (45 mL) and the contents were refluxed for 24h. After work up as described earlier, binaphthol was obtained.

From precipitate:

After work up:

(R)-(+)-2,2'-binaphthol : 0.8 g (56%)

M.P. : 214°C

$[\alpha]_D^{25}$ = +2° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

From filtrate:

After work up:

(S)-(-)-2,2'-binaphthol : 0.45 g (31%)

M.P. : 213°C

$[\alpha]_D^{25}$ = -6° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1, THF)

Enrichment of (S)-(-)-2,2'-binaphthol 1 (1 eq.) using (S)-proline (1 eq.):

(S)-(-)-2,2'-Binaphthol (2.5 g, 9.2 mM, 65% ee) and (S)-proline (1.0 g, 9.2 mM) were taken in dry benzene (105 mL) and refluxed for 24h. After usual work up, (R)-(+) and (S)-(-)-binaphthols were isolated.

From precipitate:

After work up:

(S)-(-)-2,2'-binaphthol : 1.65 g (65%)

M.P. : 208°C

$[\alpha]_D^{25}$ = -29.7° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1, THF)

From filtrate:

After work up:

(R)-(+)-2,2'-binaphthol : 0.55 g (22%)

M.P. : 214°C

$[\alpha]_D^{25}$ = -2° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1, THF)

Enrichment of (R)-(+)-2,2'-binaphthol 1 (1 eq.) using (S)-proline (1 eq.):

(R)-(+)-2,2'-Binaphthol 1 (2.9 g, 10 mM, 44% ee) and (S)-proline (1.17 g, 10 mM) were taken in dry benzene (120 mL) and refluxed for 24h. After usual work up, enriched binaphthols were isolated.

From precipitate:

After work up:

(R)-(+)-2,2'-binaphthol : 1.30 g (45%)

M.P. : 208°C

$[\alpha]_D^{25}$ = +30.6° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

From filtrate:

After work up:

(R)-(+)-2,2'-binaphthol : 1.20 g (41%)

M.P. : 215°C

$[\alpha]_D^{25}$ = +2° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

Enrichment of (S)-(-)-2,2'-binaphthol 1 (1 eq.) using (S)-proline (1 eq.):

(S)-(-)-2,2'-Binaphthol (0.9 g, 3.2 mM, 87% ee) and (S)-proline (0.37 g, 3.2 mM) were taken in dry benzene (50 mL) and the contents were refluxed for 24h. After usual work up, the enriched binaphthols were isolated.

From precipitate:

After work up:

(S)-(-)-2,2'-binaphthol : 0.7 g (77%)

M.P. : 209°C

$[\alpha]_D^{25}$ = -34° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1,THF)

The enantiomeric excess was also determined on chiral HPLC on chiral

cel OP column using methanol as solvent and was found to be 100% (see Chart Nos. 4 and 5).

From filtrate:

(S)-(-)-2,2'-binaphthol : 0.1 g (11%)

M.P. : 207°C

$[\alpha]_D^{25}$ = -12° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = -34° (C1,THF)

Enrichment of (R)-(+)-2,2'-binaphthol 1 (1 eq.) using (S)-proline (1 eq.):

(R)-(+)-2,2'-Binaphthol 1 (0.96 g, 3.4 mM, 90% ee) and (S)-proline (0.39 g, 3.4 mM) were taken in dry benzene (45 mL) and refluxed for 24h. After usual work up, enriched binaphthols were isolated.

From precipitate:

After work up:

(R)-(+)-2,2'-binaphthol : 0.67 g (70%)

M.P. : 209°C

$[\alpha]_D^{25}$ = +34° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

The enantiomeric excess also determined on chiral HPLC using chiralcel OP column with methanol as solvent and was found to be 98-99% (see Chart No. 4 and 6).

From filtrate:

After work up:

(R)-(+)-2,2'-binaphthol : 0.17 g (18%)

M.P. : 207°C

$[\alpha]_D^{25}$ = +9.5° (C1, THF) Lit.[62] $[\alpha]_D^{25}$ = +34° (C1, THF)

Resolution of Racemic 2,2′-binaphthol 1 (1 eq.) using (S)-proline (1 eq.) in toluene solvent:

Racemic binaphthol (1.43 g, 5 mM) and (S)-proline (0.575 g, 5 mM) were taken in dry toluene (60 mL) and the contents were heated for 24h at 80–90°C. After usual work up, enriched binaphthols were isolated.

From precipitate:

After work up:

(S)-(-)-2,2′-binaphthol : 0.26 g (18%)

M.P. : 207°C

$[\alpha]_D^{25} = -13^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = -34^o$ (C1, THF)

From filtrate:

After work up:

(R)-(+)-2,2′-binaphthol : 1.3 g (66%)

M.P. : 213°C

$[\alpha]_D^{25} = +4^o$ (C1, THF) Lit.[62] $[\alpha]_D^{25} = +34^o$ (C1, THF)

3.5. REFERENCES

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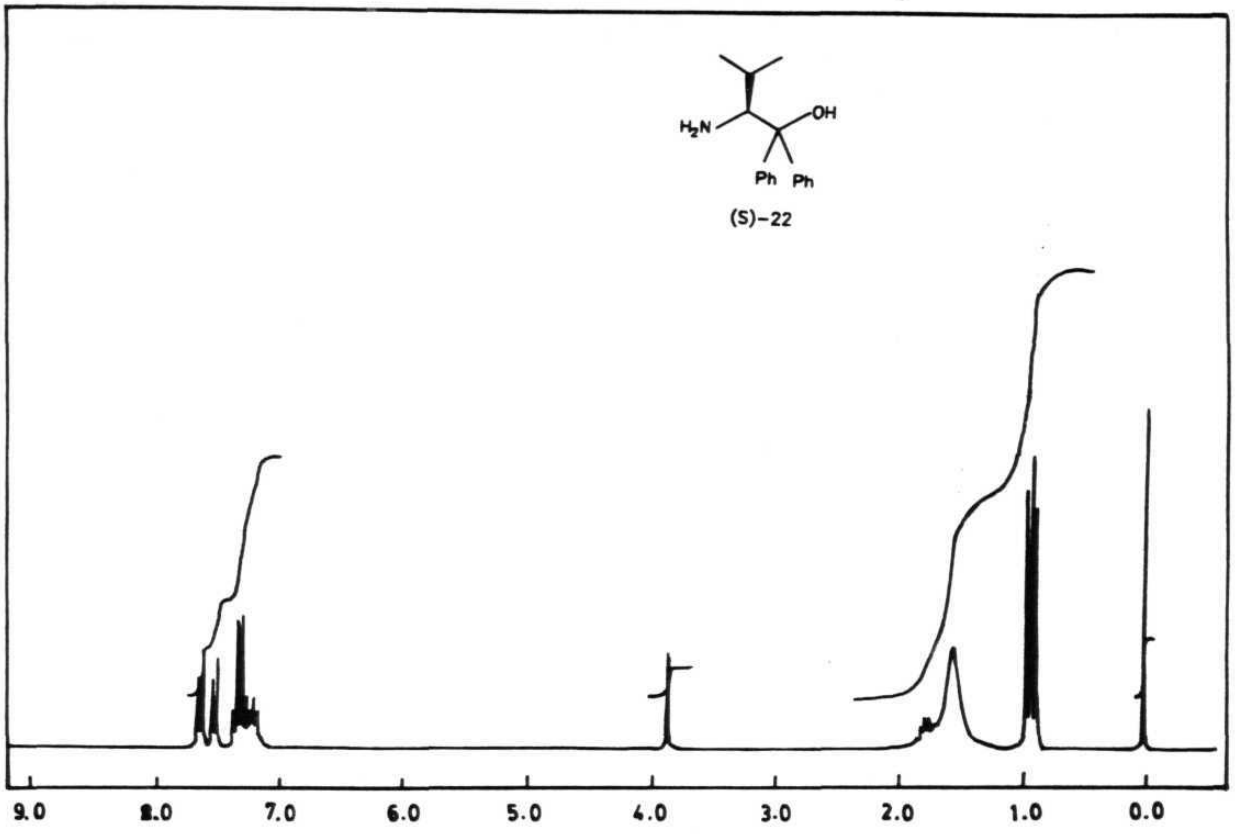
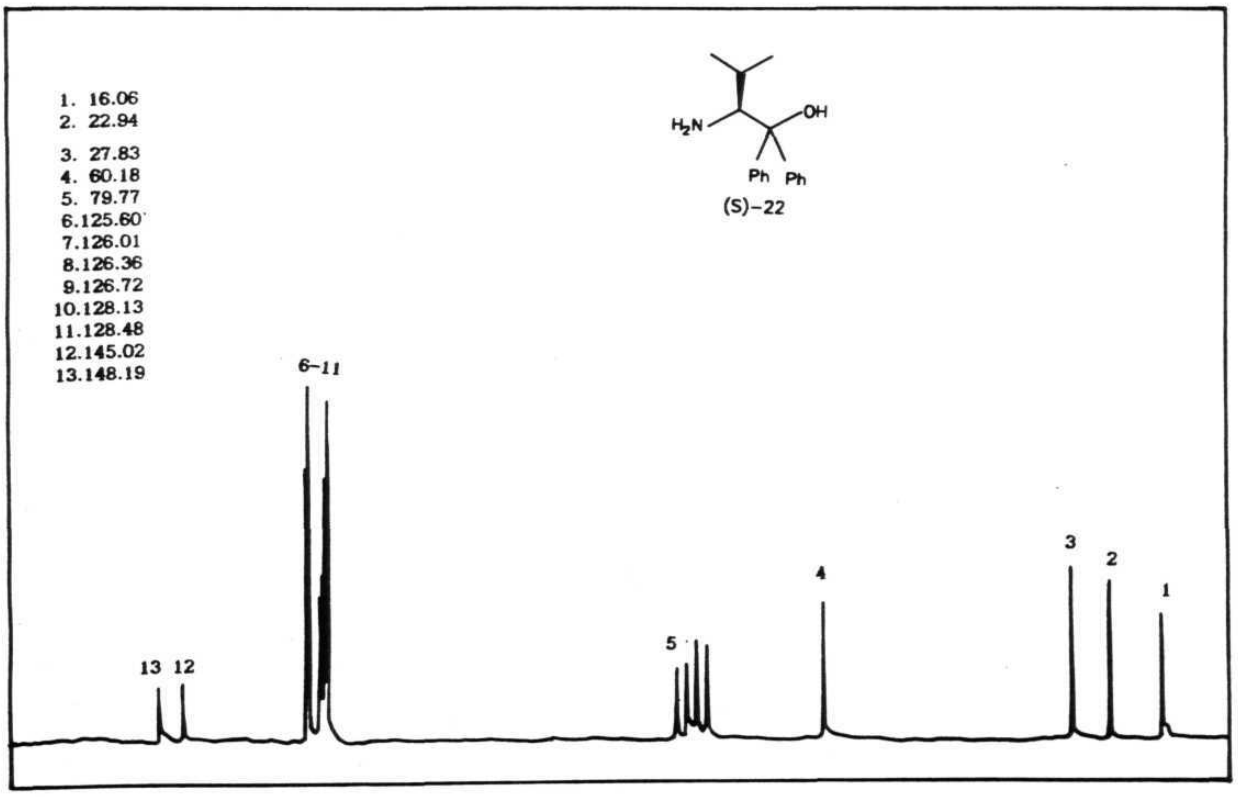
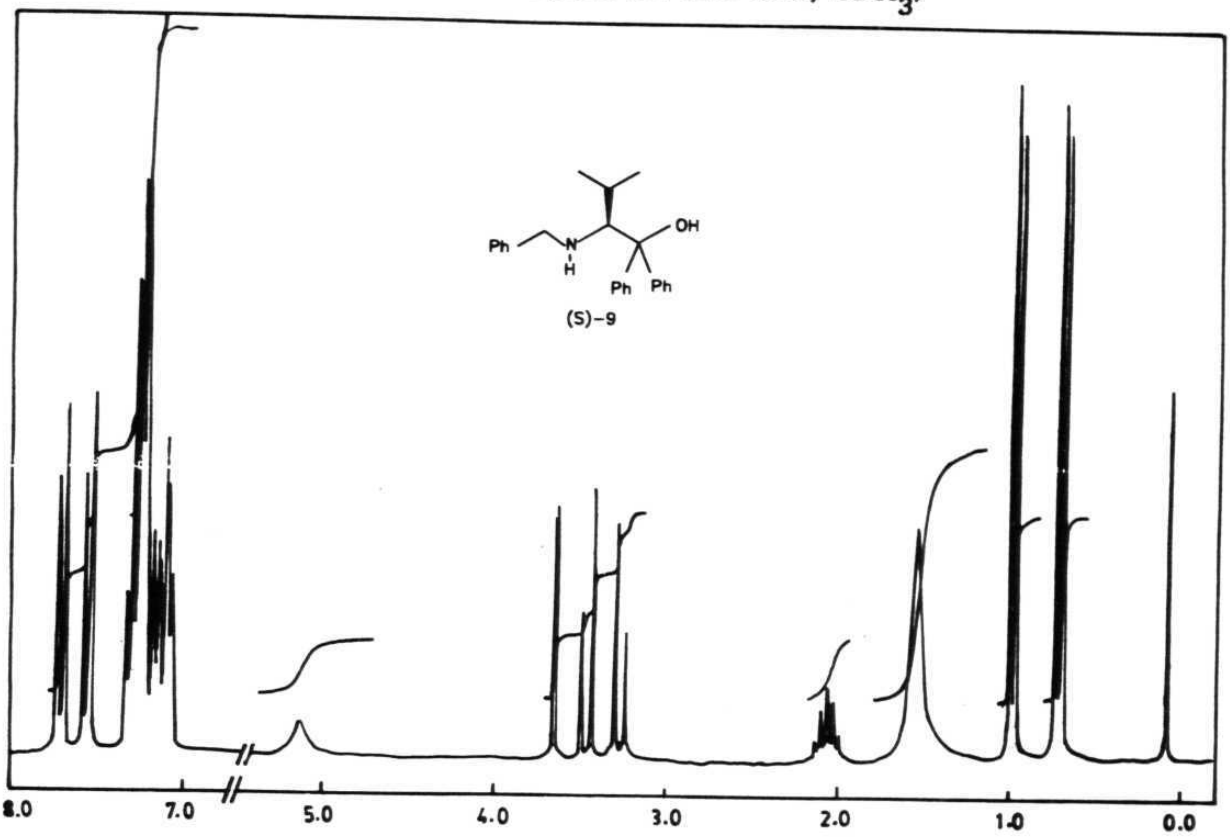
Spectrum Number 1 ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



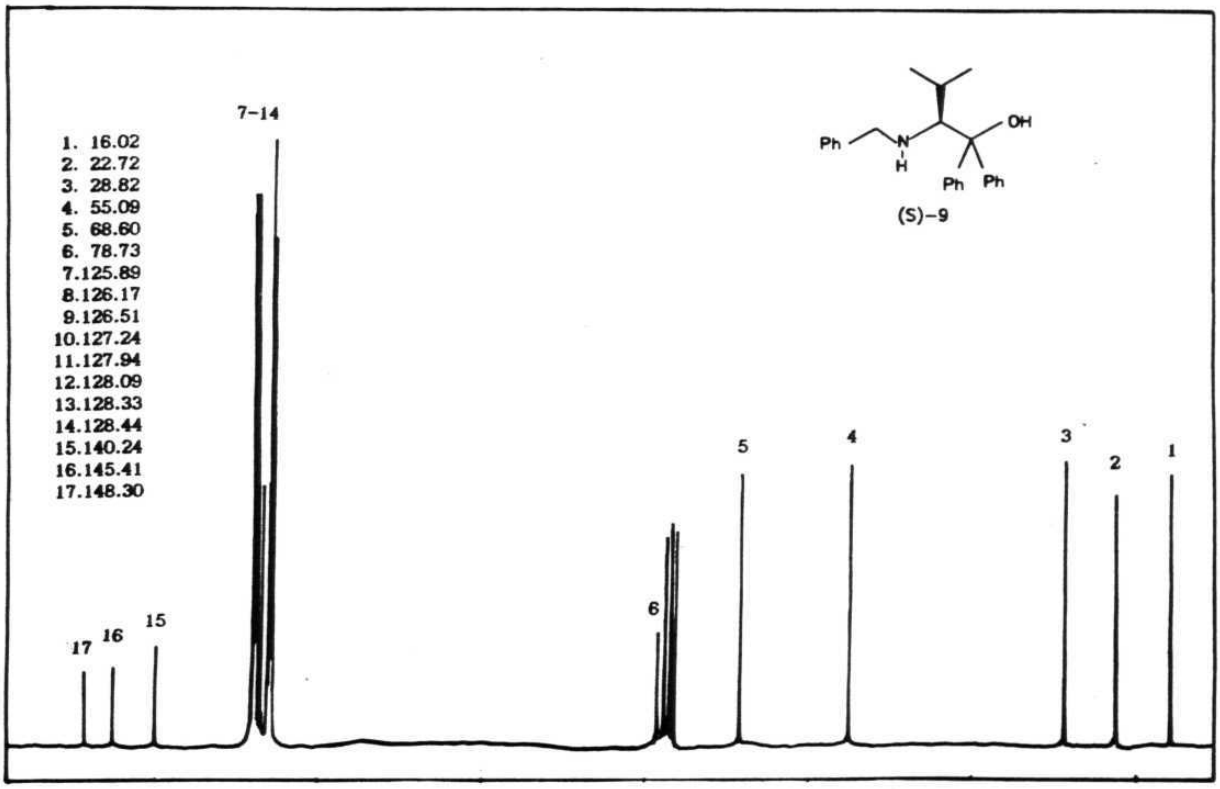
Spectrum Number 2 ^{13}C NMR Spectrum decoupled (25 MHz, $CDCl_3$)



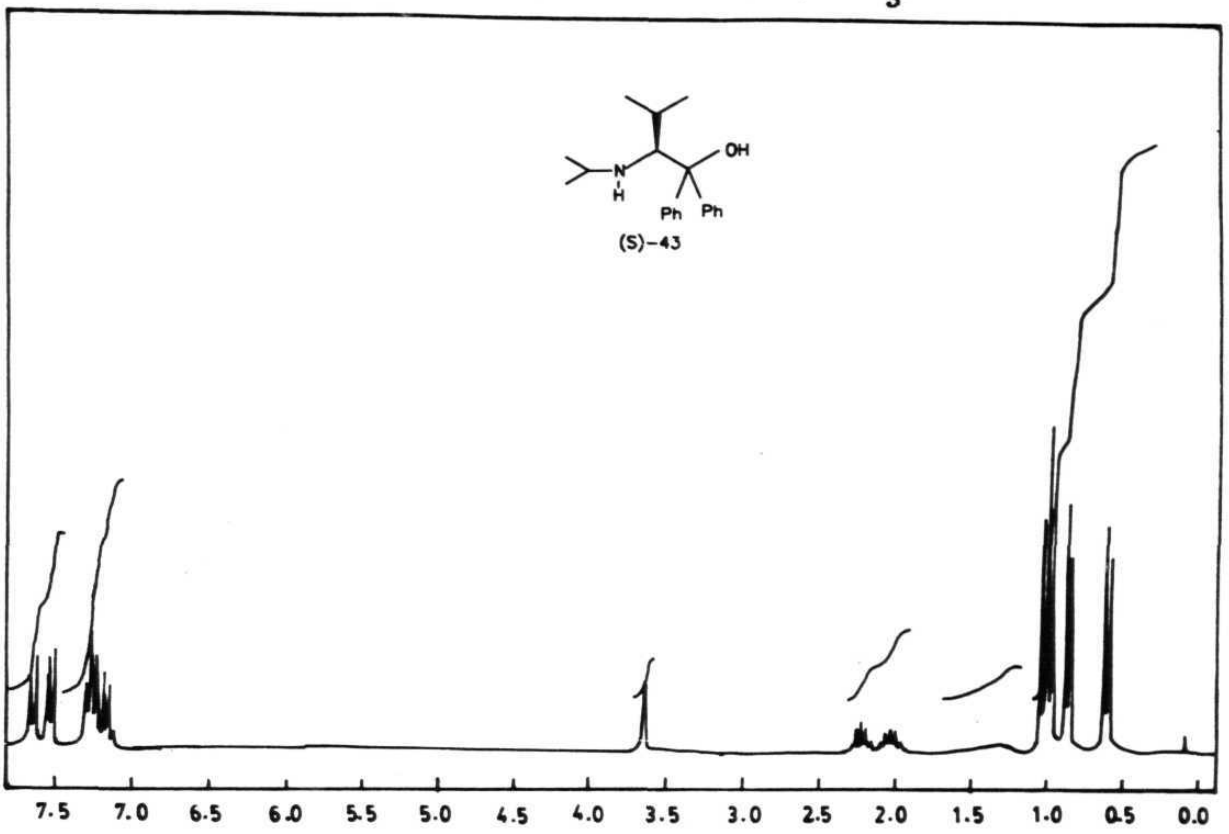
Spectrum Number 3 ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



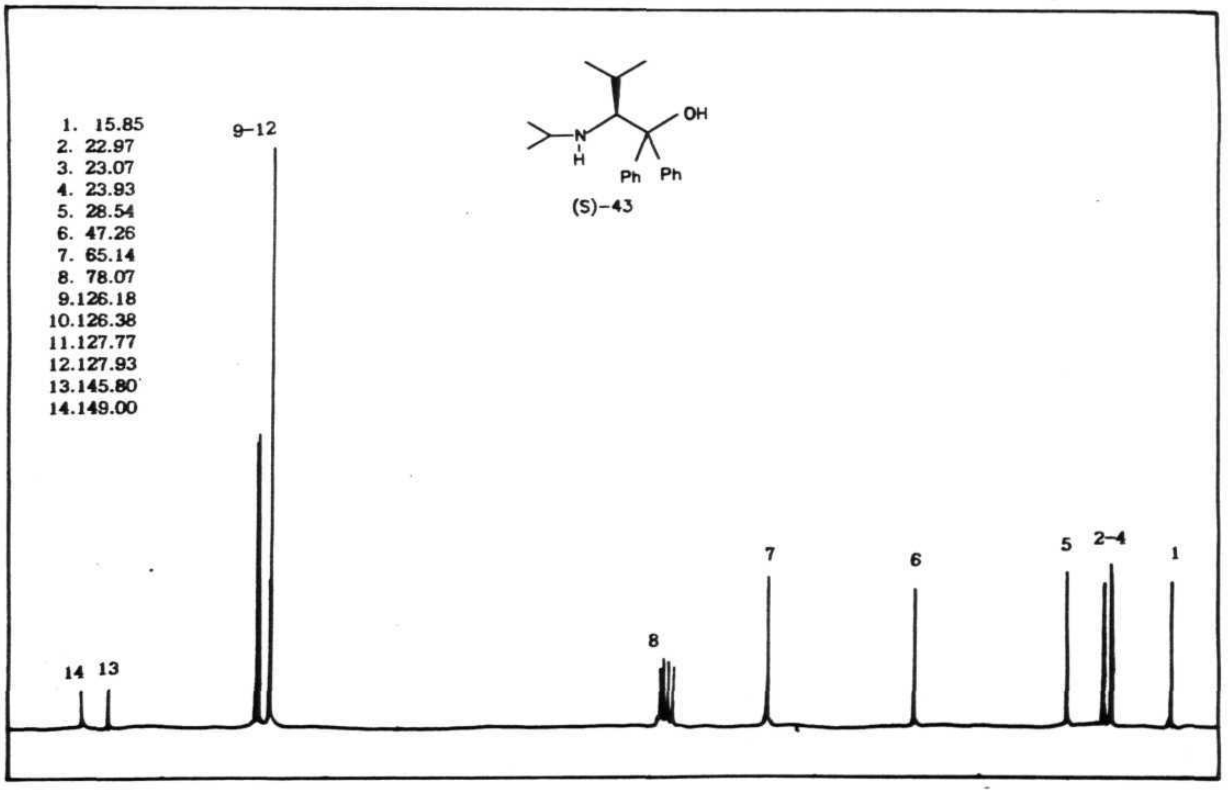
Spectrum Number 4 ^{13}C NMR Spectrum decoupled (50 MHz, $CDCl_3$)



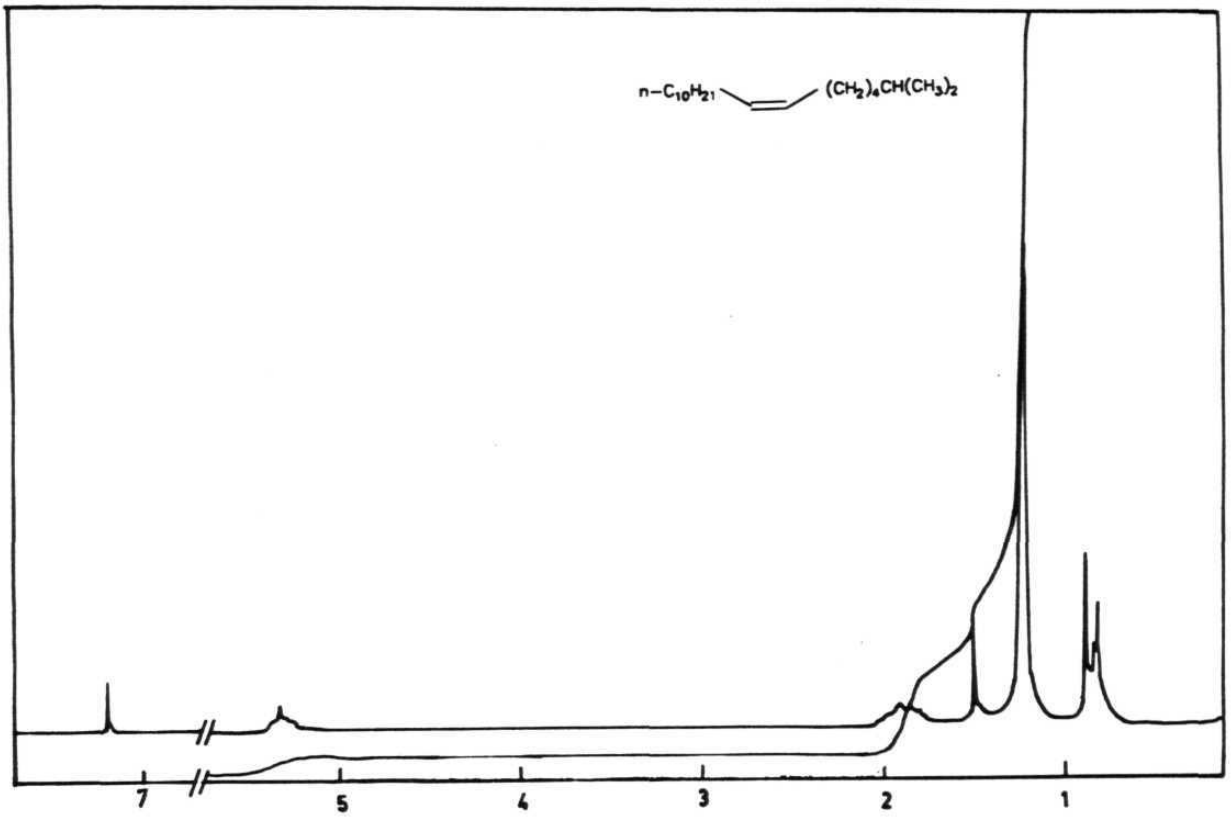
Spectrum Number 5 ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



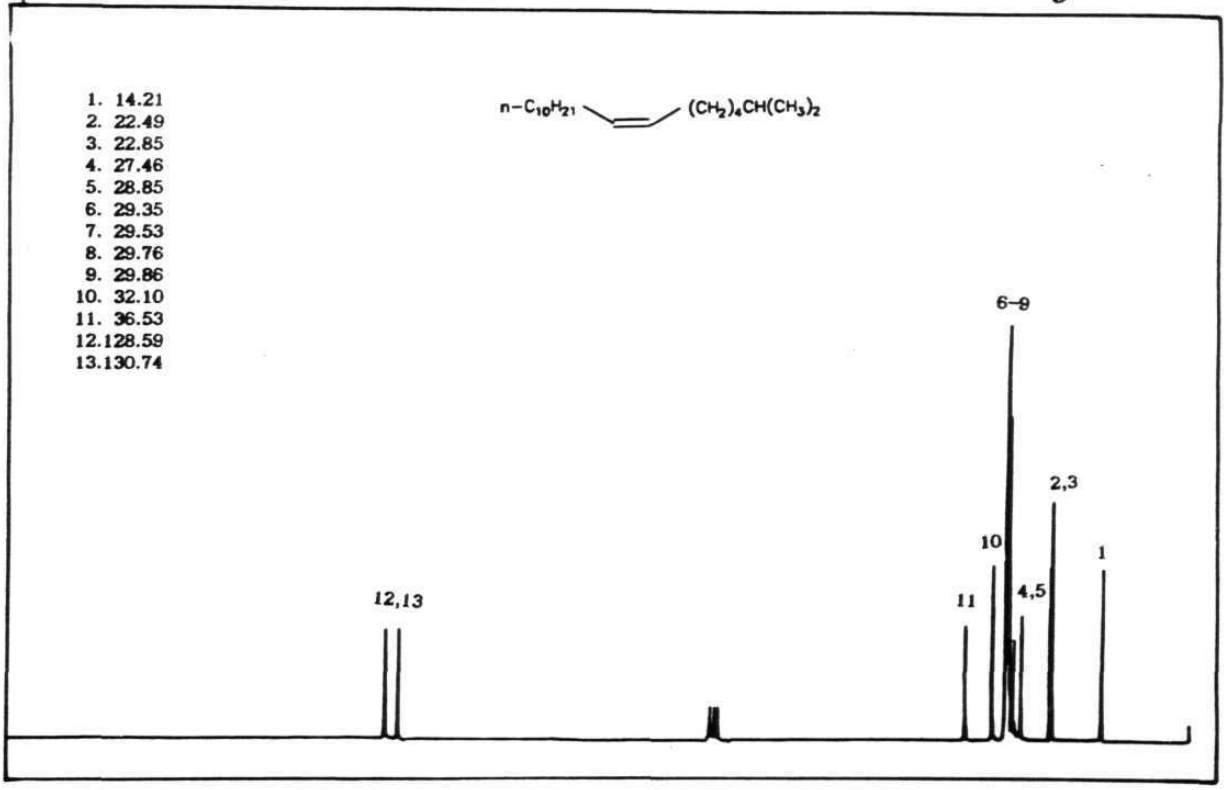
Spectrum Number 6 ^{13}C NMR Spectrum decoupled (25 MHz, $CDCl_3$)



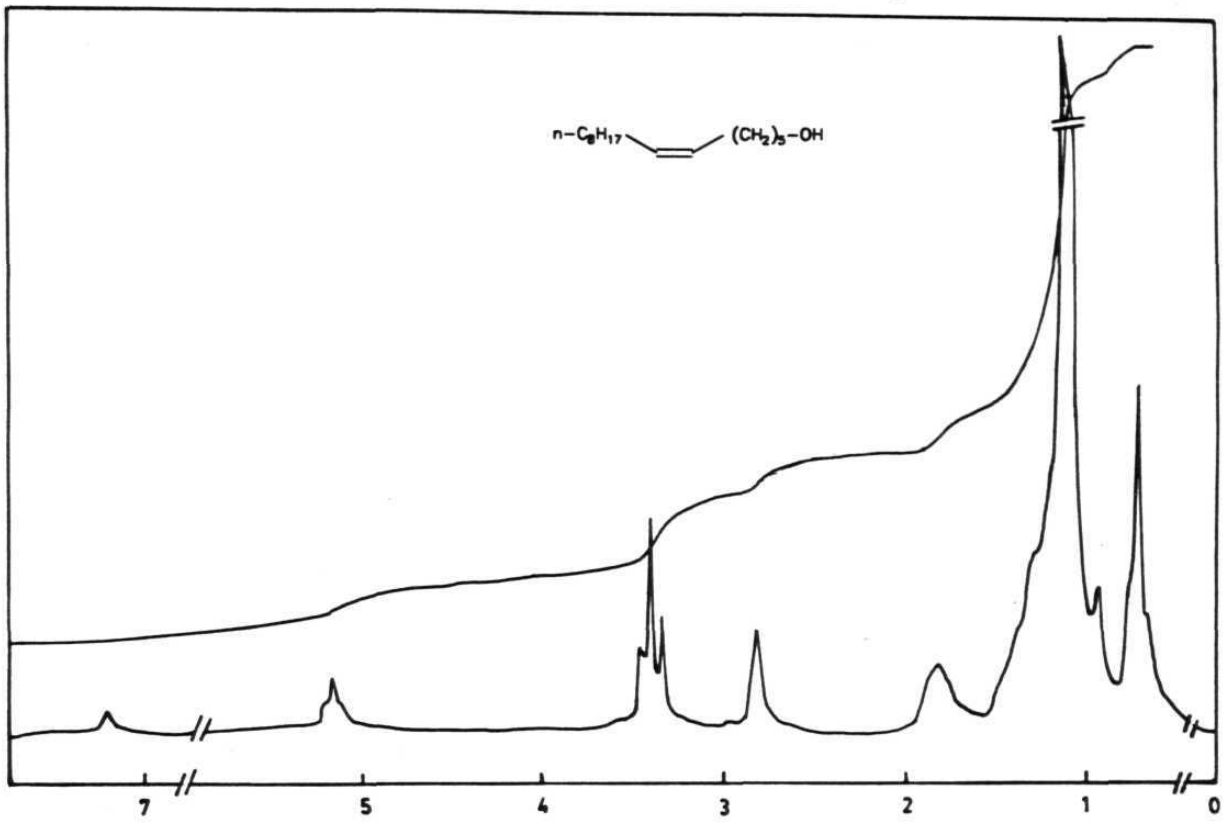
Spectrum Number 7 ^{1}H NMR Spectrum (100 MHz, $CDCl_3$)



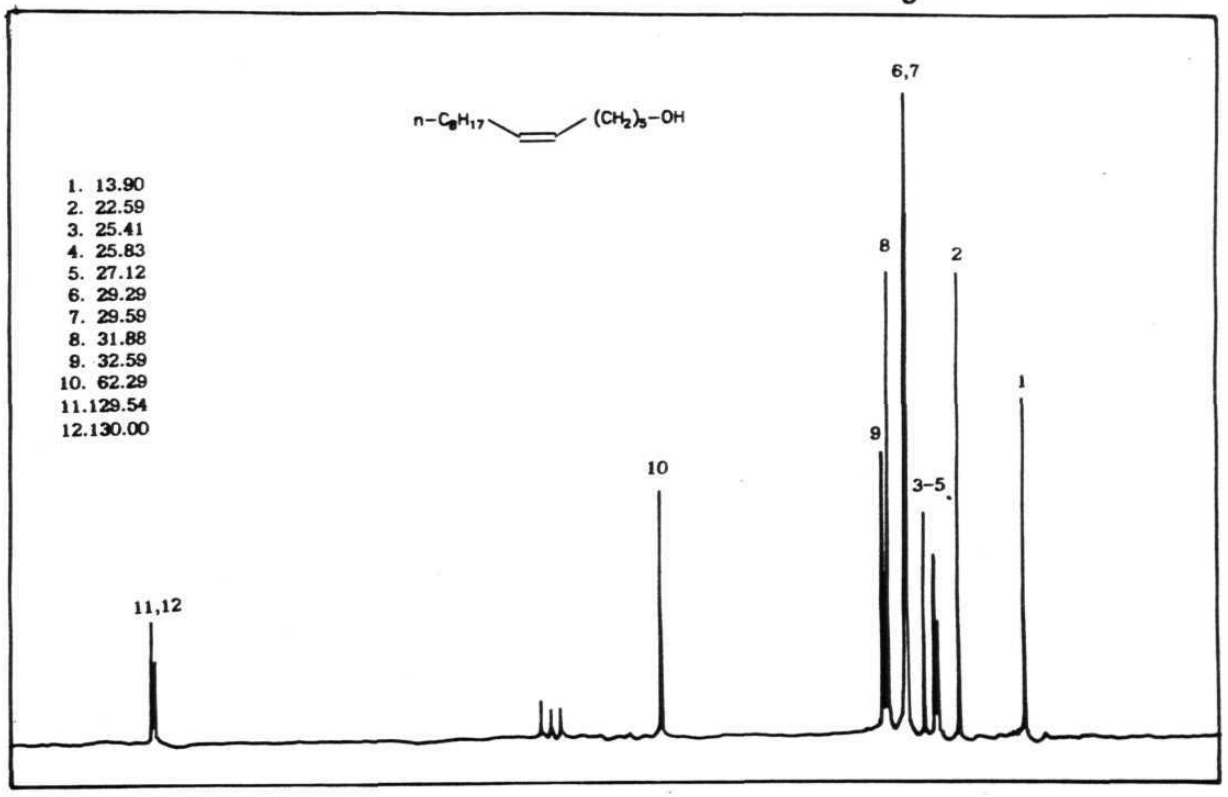
Spectrum Number 8 ^{13}C NMR Spectrum decoupled (50 MHz, $CDCl_3$)



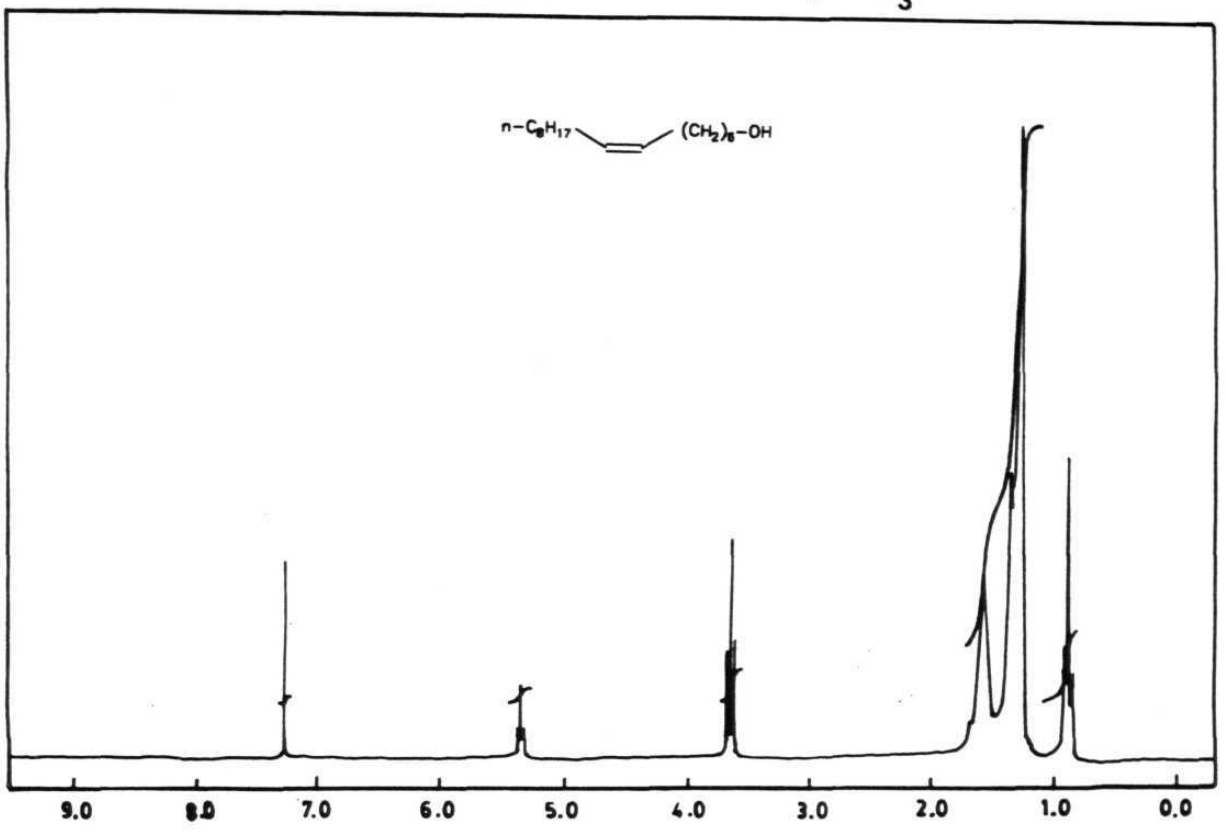
Spectrum Number 9 ^{1}H NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum Number 10 ^{13}C NMR Spectrum (25 MHz, $CDCl_3$)



Spectrum Number 11 ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



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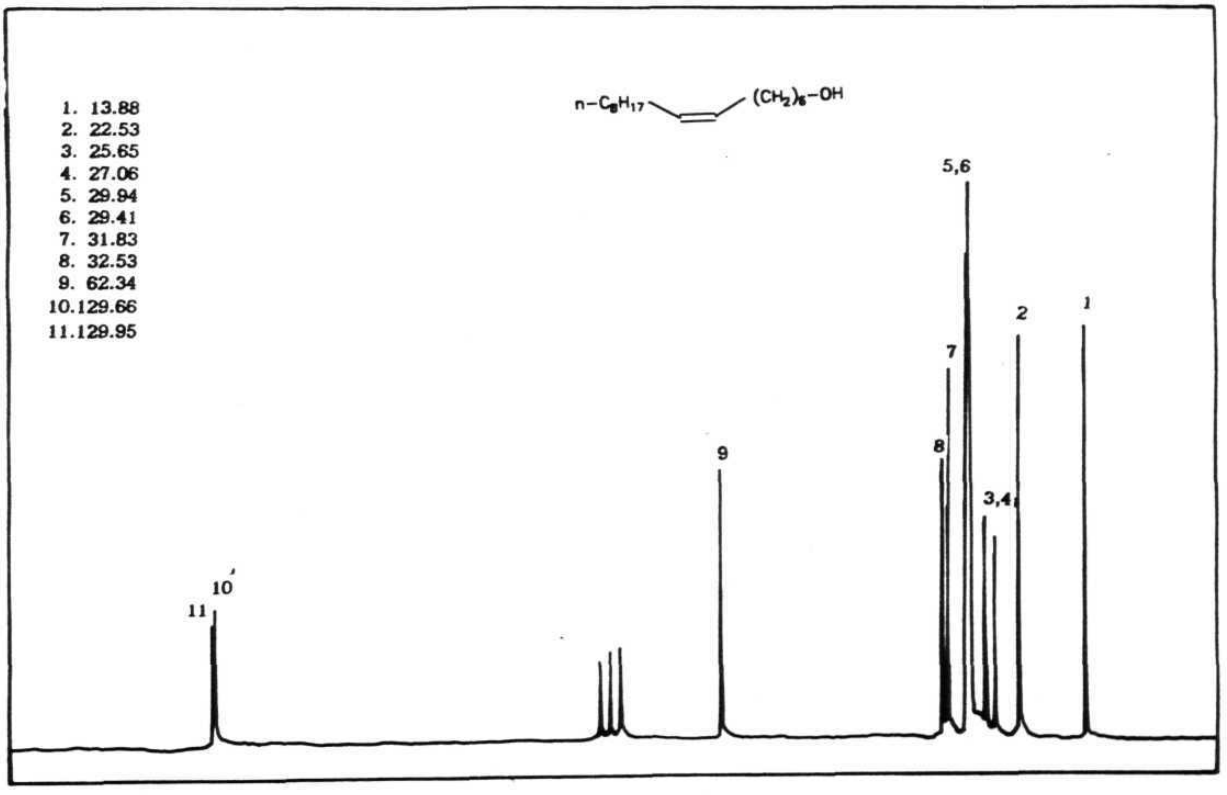
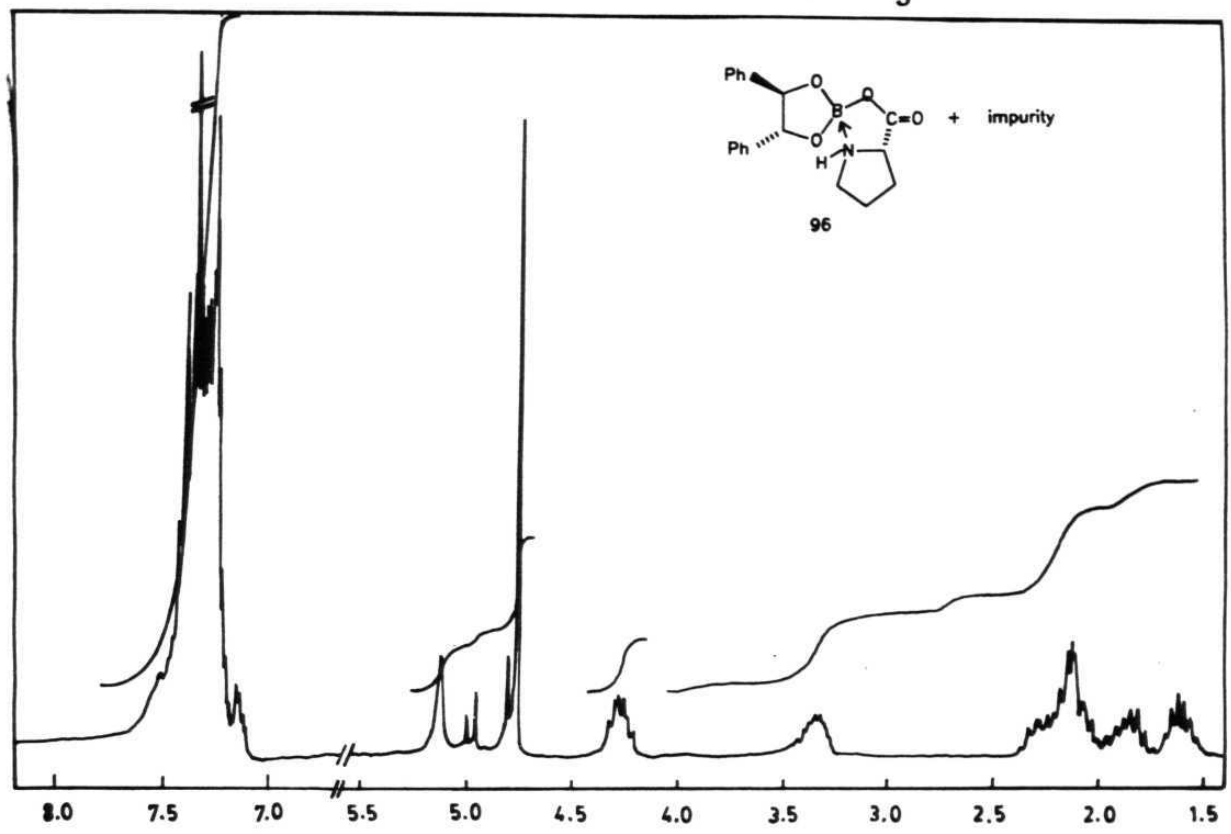
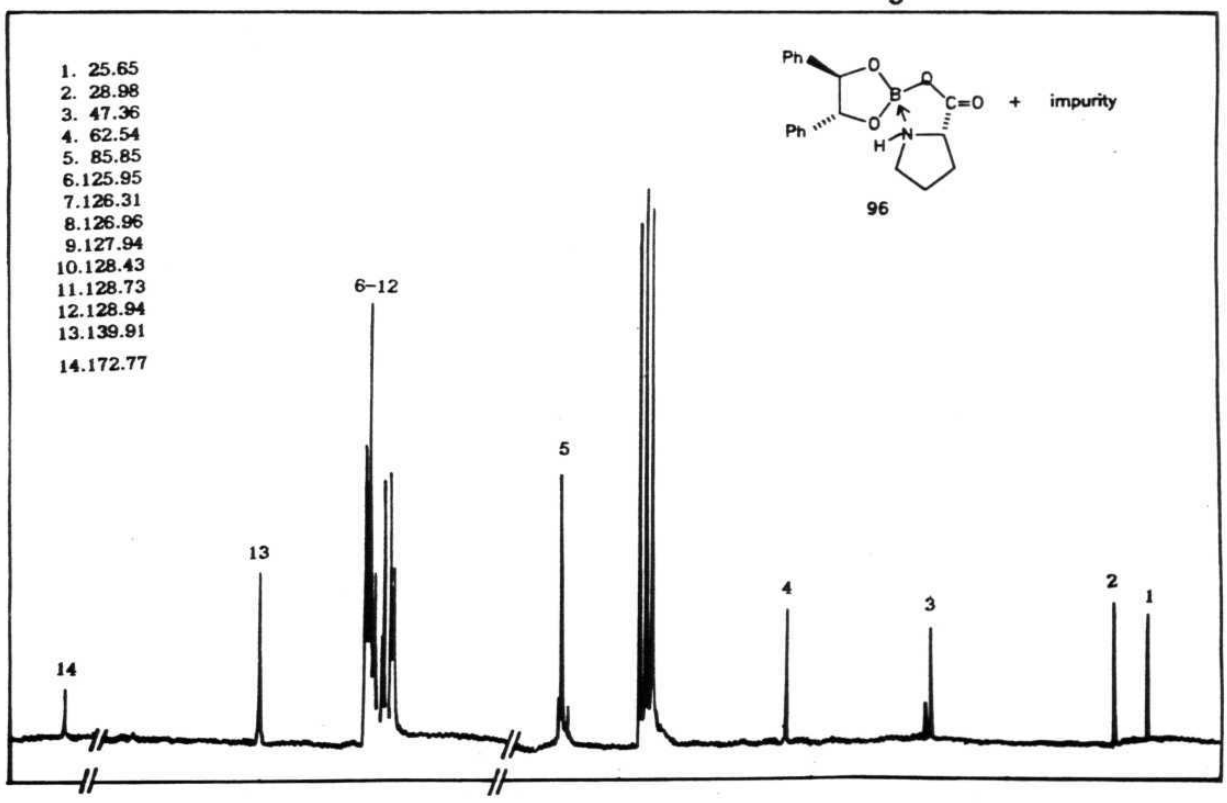


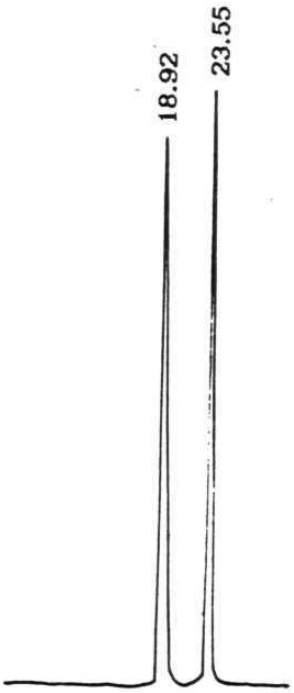
Spectrum Number 13 ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

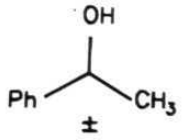


Spectrum Number 14 ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

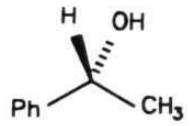


HPLC Chart No. 1



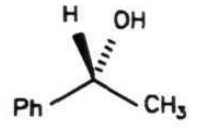


HPLC Chart No. 2



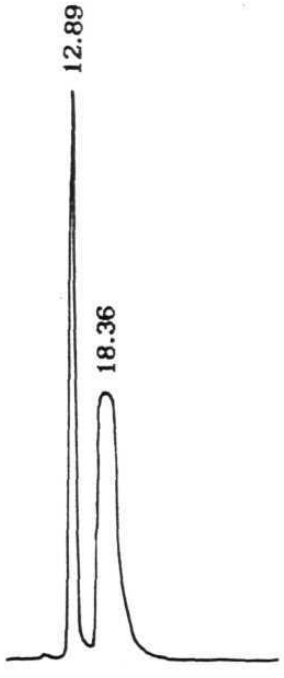
(R)-(+)
95.4% ee

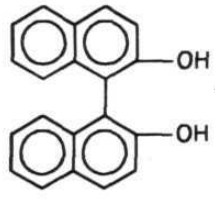
HPLC Chart No. 3



(R)-(+)
94.7% ee

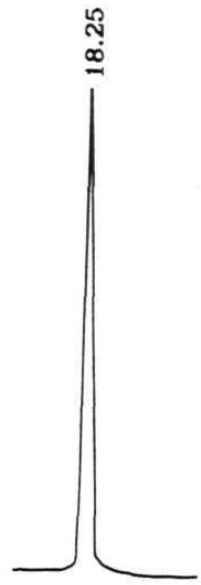
HPLC Chart No. 4

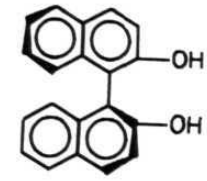




(R,S)-1

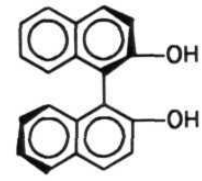
HPLC Chart No. 5





(S)-1
100% ee

HPLC Chart No. 6



(R)-1
98-99% ee

LIST OF PUBLICATIONS:

(i) Catalytic Effect of a BH_3:N,N-Diethylaniline Complex in the Formation of Alkenyl Catecholboranes from Alk-1-ynes and Catecholborane.
Y. Suseela, A.S. Bhanu Prasad and M. Periasamy
J.Chem.Soc., Chem.Commun., 1990, 446.

(ii) Convenient methods for the reduction of amides, nitriles, carboxylic esters, acids and hydroboration of alkenes using $NaBH_4/I_2$ system.
A.S. Bhanu Prasad, J.V. Bhaskar Kanth and M. Periasamy
Tetrahedron, 1992, 48, 4623.

(iii) Convenient procedures for the asymmetric reductions utilizing α,α-diphenylpyrrolidinemethanol and borane complexes generated using the $I_2/NaBH_4$ system.
M. Periasamy, J.V. Bhaskar Kanth and A.S. Bhanu Prasad
Tetrahedron, 1994, 50, 6411.

(iv) Synthesis of Z-Alkenes from Alkenylcatecholboranes Through Reaction with RMgX and I_2 Induced Rearrangement.
M. Periasamy, A.S. Bhanu Prasad and Y. Suseela
Tetrahedron, 1995, 0000.

(v) A Simple Convenient Method for the Resolution of Racemic 2,2′-dihydroxy-1,1′-binaphthyl using (S)-Proline.
M. Periasamy, A.S. Bhanu Prasad, J.V. Bhaskar Kanth and Ch.K. Reddy
Tetrahedron:Asymmetry, 1995, 0000.

(vi) A Novel Method of Resolution of Racemic 1,2-Diols
M. Periasamy and A.S. Bhanu Prasad
To be submitted for publication.

(vii) A Simple and Convenient method for the Synthesis of (S)-2-Amino-3-methyl-1,1'-diphenylbutan-1-ol
M. Periasamy and A.S. Bhanu Prasad
To be submitted for publication

(viii) Hydroboration of Prochiral Olefins with Borane Chiral Lewis base Complexes: Evidence for a Spectrum of Mechanism for the Hydroboration reaction.
M. Periasamy and A.S. Bhanu Prasad
To be submitted for publication

Poster Presentations :

i) A.S.Bhanu Prasad, J.V.Bhaskar Kanth and M.Periasamy (1993):Organic Synthetic Methods Through $I_2/NaBH_4$ Reagent System. National Symposium on ORGANIC SYNTHESIS AND CATALYSIS VIA METALLORGANICS held at NCL, Pune, India.

ii) A.S.Bhanu Prasad and M.Periasamy (1994):Synthesis of (Z)-Olefins And (Z)-Olefinic Alcohols Through 1-Alkenylcatecholborane. International Conference on ORGANIC SYNTHESIS-10, held at Bangalore, India.