SYNTHESIS OF CHIRAL AMINES AND AMINE BORANES FOR ASYMMETRIC TRANSFORMATIONS AND DEVELOPMENT OF NEW ORGANIC SYNTHETIC METHODS

A THESIS
SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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To

My Teachers and Parents

Corrected Version

The typographical and other minor errors have been corrected as required by one of the examiners. It has been found that the experiment and data describing the reaction of L-valine with ethyl chloroformate and t-butyl alcohol have not been presented correctly in the original. This has been clarified in this corrected version in pages 78, 78a and 180. The corrected version has been arranged without changes in page numbers so that it can be readily compared with the original. The corrections have been made in consultation with the supervisor.

J. V. Bhaskar Kanth

M. Periasamy
Supervisor

19/2/94

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STATEMENT

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

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

J. V. B. Kanth 13/9/93

J. V. BHASKAR KANTH

CERTIFICATE

Certified that the work contained in this thesis entitled 'Synthesis of Chiral Amines and Amine Boranes for Asymmetric Transformations and Development of New Organic Synthetic Methods' has been carried out by Mr. J. V. Bhaskar Kanth, under my supervision and the same has not been submitted elsewhere for a Degree.

M. Periasamy
13/9/93

PROFESSOR M.PERIASAMY

(THESIS SUPERVISOR)

DEAN

SCHOOL OF CHEMISTRY

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Praveen, K. Vinoda Kumari, B. Shyamala, S. Geetha, and all my other friends, who made my stay here an enjoyable and memorable one.

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 and Mrs. Vijaya Lakshmi are a few to mention.

I wish to express my profound gratitude to my parents, brother, sister and other relatives for their constant encouragement and support throughout my academic career.

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

Financial assistance from the CSIR is gratefully acknowledged.

J. V. BHASKAR KANTH

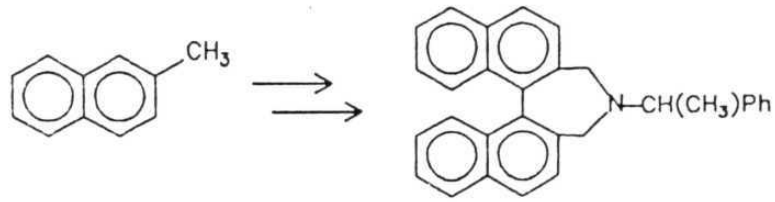
ABBREVIATIONS

AcOH	acetic acid
Ar	argon
9-BBN	9-borabicyclo[3.3.1]nonane
BMS	borane-dimethyl sulphide complex
Bn	benzyl
n-Bu	n-butyl
n-BuLi	n-butyllithium
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DG	diglyme
DME	dimethoxyethane
DMF	dimethylformamide
ee	enantiomeric excess
Et	ethyl
IPC_2BH	isopinocampheylborane
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
NBS	N-bromosuccinimide
α-naph	α-naphthyl
Ph	phenyl
Pr	propyl
THF	tetrahydrofuran
Tf	triflate
TMS	tetramethylsilane
Ts	tosyl

ABSTRACT

This thesis deals with the synthesis of chiral amines and amine boranes for asymmetric transformations and development of new organic synthetic methods. It comprises of three chapters. Each chapter is subdivided into three parts, Introduction, Results and Discussion and Experimental Sections.

Chapter 1 describes the synthesis of certain chiral amines and development of some new organic synthetic methods. Synthesis and utilization of various chiral amines have been briefly reviewed in the introduction. Convenient procedures for the synthesis of certain chiral amine systems have been developed following closely related reported procedures. The chiral amine (1) diastereomers were prepared in several steps starting from 2-methylnaphthalene.

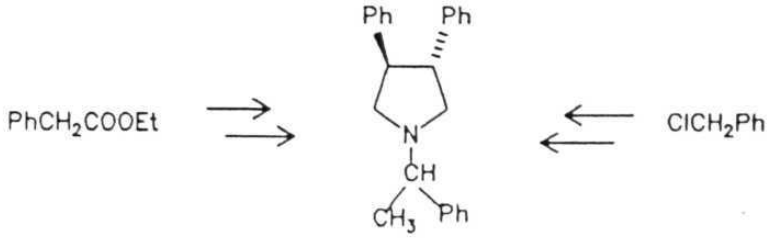


1

In the final step, the corresponding dibromide precursor was condensed with optically active (+)-α-methylbenzylamine. The resulting two diastereomers were separated by column chromatography. One of the diastereomers was obtained in crystalline form, $[\alpha]_D^{25} = -173^o$(C1, $CHCl_3$) and the other diastereomer was obtained as a gum, $[\alpha]_D^{25} = +253^o$(C1, $CHCl_3$).

The chiral amine system (2) was prepared starting from ethyl

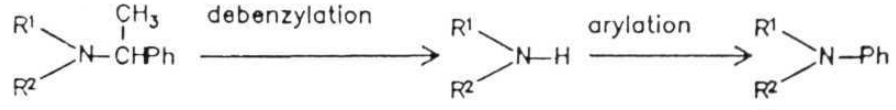
phenylacetate or benzyl chloride in several steps through (±)-2,3-diphenylsuccinic acid.



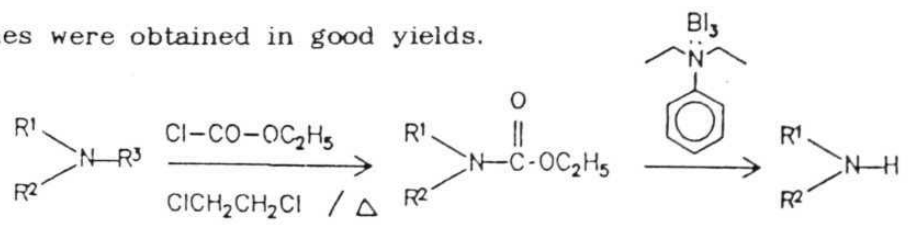
2

The diphenylsuccinic acid was condensed with (-)-α-methylbenzylamine. After reduction, the diastereomeric amines were separated by column chromatography. The diastereomer eluted first was obtained in optically pure form.

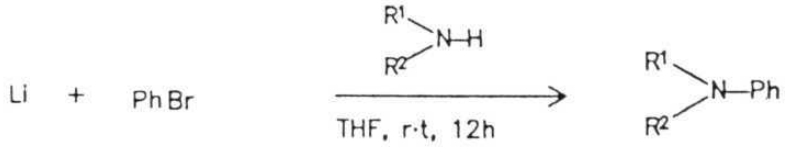
Efforts were made to synthesize chiral N-phenyl tertiary amines from the corresponding N-benzylamines. It was found that the reported methods of conversion of N-benzyl tertiary amines to N-phenyl amines are not suitable for our requirements. A more convenient debenzylation, N-phenylation sequence has been developed.



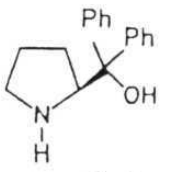
The debenzylations have been carried out using readily accessible, convenient reagent systems. The corresponding secondary amines were obtained in good yields.



The N-phenyl compounds were obtained by treating the secondary amines with bromobenzene and lithium powder in THF. Several secondary and tertiary amines were prepared. Following this procedure, N-phenyl derivatives of a few optically active amines were also prepared.



In recent years, the amines and amino alcohols derived from L-proline have been found to be useful in several chiral transformations. We have undertaken the synthesis of the L-proline derived chiral auxiliaries 3 and 4 for reduction and hydroboration studies.



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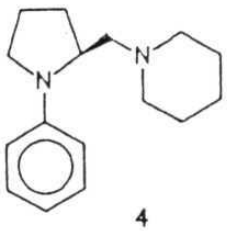

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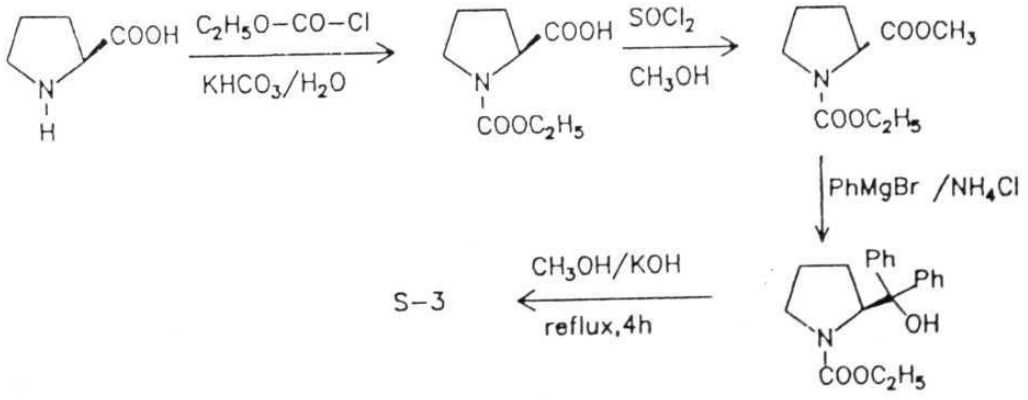
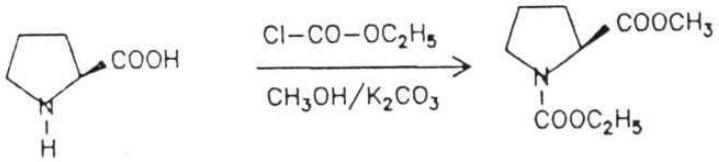
A more convenient route for the synthesis of α,α-diphenyl-2-pyrrolidinemethanol, a precursor for the CBS reduction catalyst has been developed.



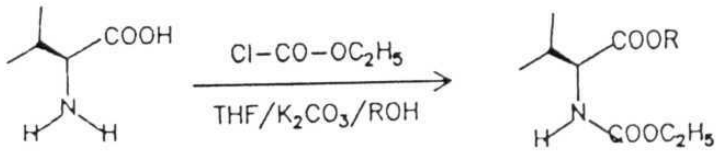
In this procedure, a relatively less expensive ethyl chloroformate

was used for N-protection. The resulting N-carbamate was cleaved by refluxing in CH_3OH/KOH, to obtain the α,α-diphenyl-2-pyrrolidine-methanol.

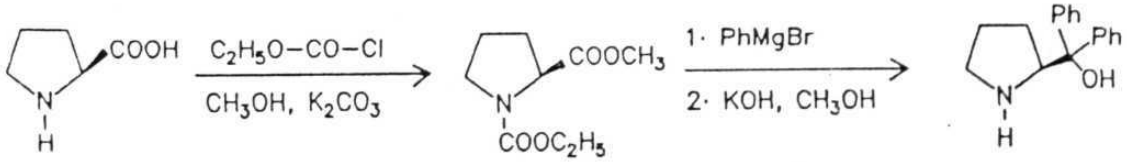
Later, it was found that both N- and O-protections could be performed in a single pot operation using two equivalents of ethyl chloroformate in methanol in the presence of K_2CO_3.



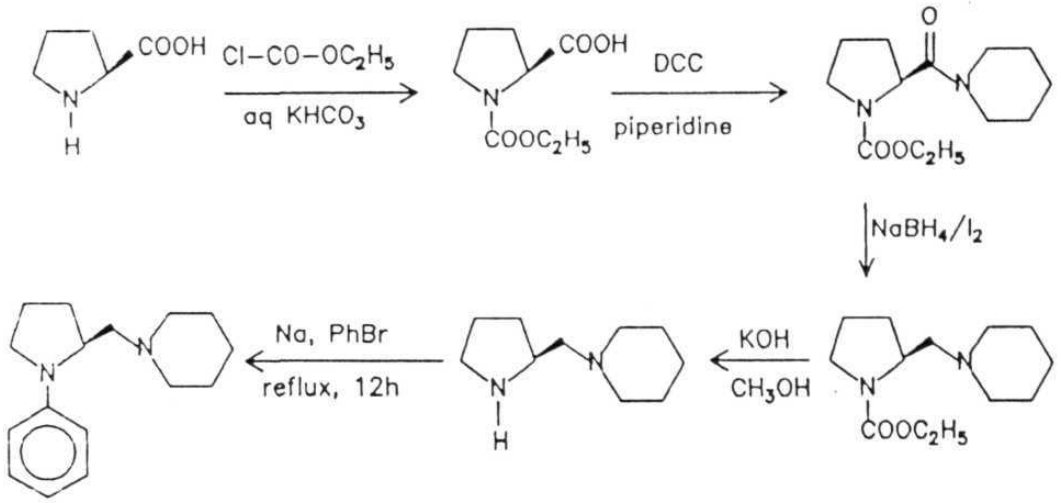
When the reaction was carried out in THF solvent and benzyl alcohol was added in molar ratio, the N-protected benzyl ester of L-proline was obtained. Methyl, benzyl and t-butyl esters of N-carbamates of L-valine have been also prepared in this way.



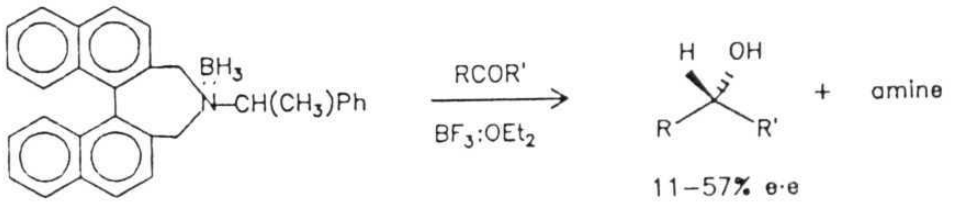
The synthesis of α,α-diphenyl-2-pyrrolidinemethanol has been further simplified, incorporating this one pot N- and O- protections sequence.



The diamine (4) has been prepared following the sequence of reactions outlined below.



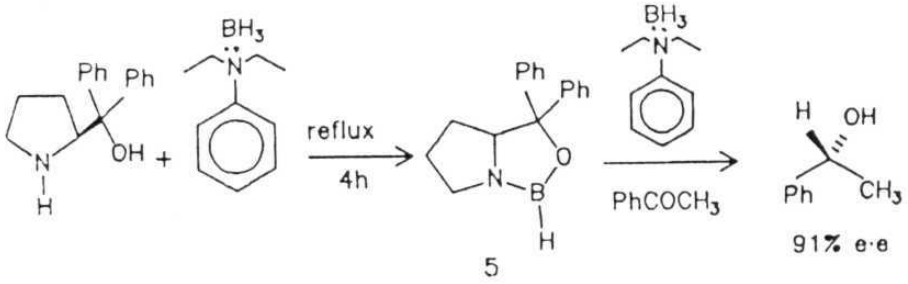
In chapter 2, results obtained in the reductions and hydroborations using chiral amine borane complexes are discussed. The (-)-N-α-methylbenzyl-3,5-dihydrodinaphthazepine forms a strong complex with borane. This amine borane failed to reduce acetophenone under ambient conditions. However, when one equivalent of BF_3:OEt_2 was added, the reduction is complete in 2h at 0^oC and 1-phenylethanol was obtained in 51% e.e. Several other prochiral ketones were also reduced following this procedure in 11-57% e.e.



The role of BF_3:OEt_2 in these reductions is not clearly understood. Several experiments were carried out in order to examine this. It was found that a combination of chiral amine-BF_3 and an achiral amine-BH_3 also gives similar results. Also, the reagent prepared using a chiral amine:BF_3 and diborane reduced acetophenone in 48.9% e.e. A transition state comprising the amine-BF_3, BH_3 and ketone was proposed to explain the results.

The diastereomerically pure N-α-methylbenzyl-3,4-diphenylpyrrolidine was also found to complex strongly with BH_3. Here also, addition of BF_3:OEt_2 facilitated the reduction of acetophenone. However, enantioselectivity realized was poor (17.6% e.e).

A simple procedure for the preparation of the CBS oxazaborolidine reagent *in situ* has been developed. The oxazaborolidine catalyzes the asymmetric reduction of acetophenone with H_3B:$N(C_2H_5)_2Ph$. Similar results were also obtained with propiophenone.



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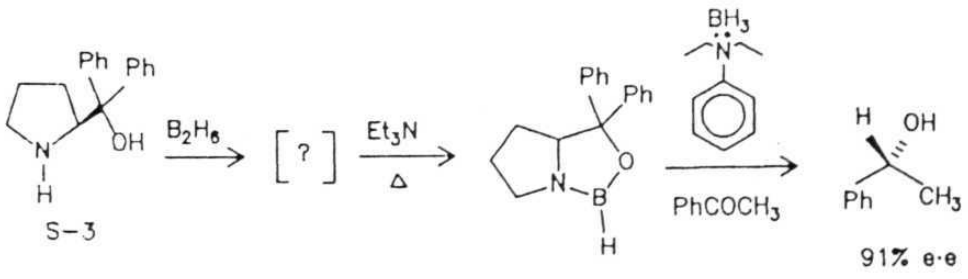
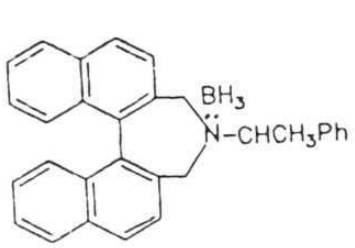
The reported procedure for the preparation of this oxazaborolidine catalyst utilizing S-3, H_3B:THF under B_2H_6-Argon atmosphere, is somewhat complicated. Presumably, presence of amine facilitates the formation of oxazaborolidine under the present reaction conditions. In order to examine this, excess of B_2H_6 was bubbled into a benzene solution of S-(3) and the reaction mixture was refluxed after adding 0.2 eq. of triethylamine. The resulting reagent was found to catalyze the reduction of acetophenone with $Ph(C_2H_5)_2N$:BH_3.



S-3

We have also carried out hydroboration studies using the chiral amine-BH_3 complexes 6-9.



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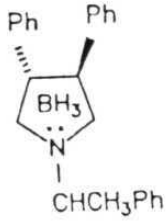

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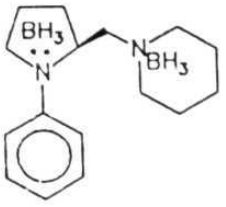

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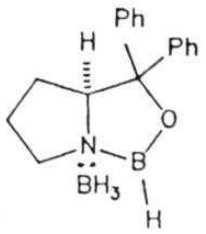

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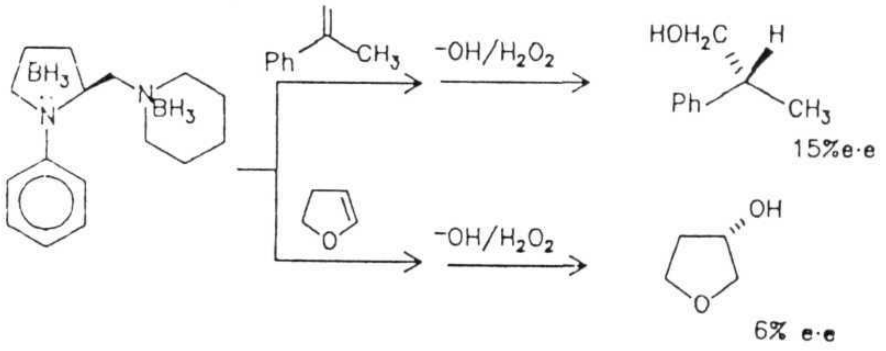
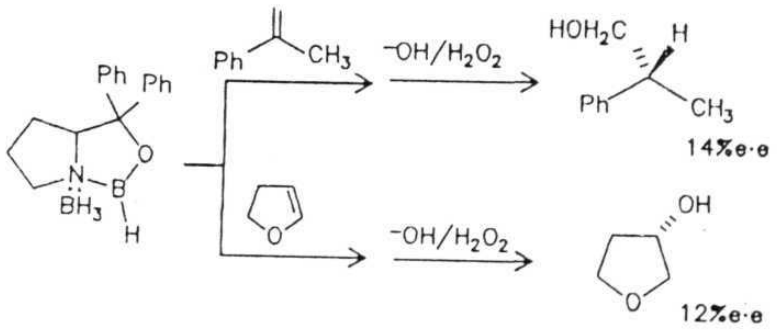
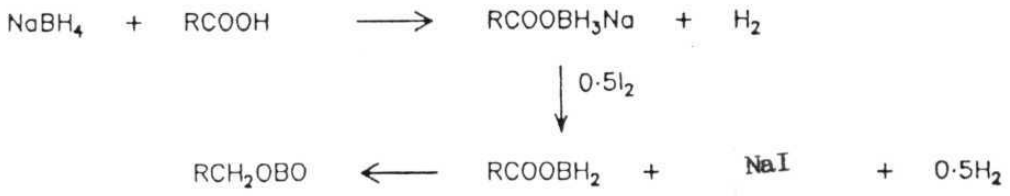
Amine boranes 6 and 7 failed to hydroborate olefins even after 48h at room temperature. The borane complexes 8 and 9 hydroborated α-methylstyrene and 2,3-dihydrofuran at room temperature. However, the enantioselectivities observed are somewhat poor.



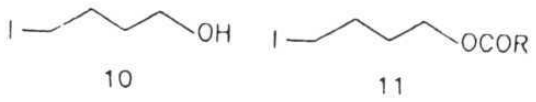


Mechanistic implications of these results are discussed.

In chapter 3, results obtained in the reduction of carboxylic acids and esters using the $NaBH_4/I_2$ system are discussed. It was found that addition of carboxylic acids to $NaBH_4$ suspension in THF followed by slow addition of iodine in THF gives the corresponding alcohols. Also, it was found that selective reduction of the carboxylic acid group can be achieved when it is present along with olefins and esters.



However, when this reagent was used in larger scale (50 mmol) reactions, substantial amounts of products (10 and/or 11) derived from THF cleavage were also obtained.



10 11

This problem was obviated by adding I_2 to $NaBH_4$ in THF at 0^oC followed by the addition of carboxylic acid. However, some of the selectivities obtained earlier were lost here. Whereas the previous procedure leads to the reduction of 10-undecenoic acid to 10-undecenol in 89% yield, in the later case, a mixture of 1,11-undecanediol and 11-hydroxyundecanoic acid was obtained.

This reagent system has been found to be useful for the reduction of several functional groups in this laboratory and also by others. For example, **Meyers *et al*[30*]** found that the $I_2/NaBH_4$ combination is an excellent system for the reduction of amino acids *(Ref. 30 in Chapter 3).

Chapter 1

Synthesis of Chiral Amines and Development of New Organic Synthetic Methods.

INTRODUCTION

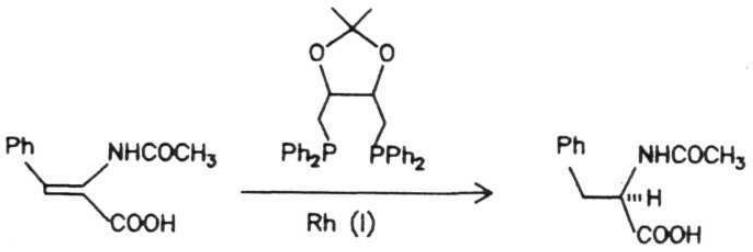
Asymmetric synthesis is one of the front line areas of research in organic chemistry. A wide range of significant chemical, biological processes are governed through precise molecular recognition which requires strict matching of chirality. For a long time, access to highly enantiomerically pure compounds has been accomplished by biological or biochemical transformations. Efficient creation of optically active organic molecules from prochiral molecules by chemical means has remained difficult. Generally, this has been achieved through optical resolutions and structural modification of naturally occurring chiral substances.

In recent years, synthesis of enantiomerically pure compounds from prochiral compounds using chiral reagents has become a topic of immense interest. Persistent efforts by synthetic organic chemists in the last two decades converted this difficult task practically possible. Many chiral molecules have been synthesized in excellent optical purities through chemical processes which rival natural processes.

In order to achieve maximum synthetic efficiency, stereoselective production of a large quantity of a chiral target compound utilizing catalytic amount of chiral source is obviously desirable. Several catalytic asymmetric processes utilizing chiral auxiliaries having a C_2-symmetry axis (or even pseudo-C_2 symmetry) have been developed. [1,2]

Kagan's DiOP is historically the first C_2-chiral auxiliary and the transformation outlined in Scheme 1 represents the first general, high level catalytic asymmetric induction process.[3,4]

Scheme 1



70%e·e

In recent years, many chiral phosphine ligands, derived from chiral diols have been prepared and utilized in several transformations such as hydrogenations, reductions and coupling reactions. The results have been extensively reviewed.[5]

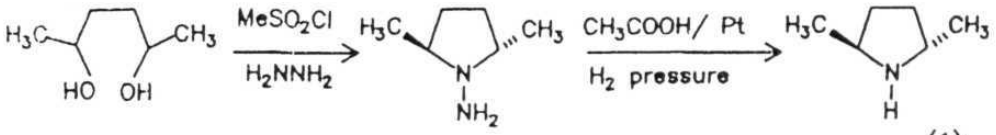
Optically active amines and alkaloids, with a wide range of molecular structures, are used as chiral ligands. Many of these can be also readily resolved. Amines are hard ligands than phosphines and are good complexing agents of hard ions such as Li^+. However, various classes of amines, mono or bidentate ligands, also form complexes with transition metals which can be used for enantioselective transformations. Results in this area are less abundant than with chiral phosphines.

In recent years , there is increased interest in the synthesis and utilization of chiral amines. A brief review of recent reports in this field would facilitate further discussion.

Synthesis and utilization of chiral pyrrolidine systems

As mentioned earlier, presence of C_2 symmetry axis in molecules reduce the number of possible competing diastereomeric transition states in reactions. Efforts were directed towards the synthesis of C_2-symmetric chiral amines. Whitesell *et al* prepared 2,5-dimethylpyrrolidine, starting from (d,l)-2,5-hexanediol as shown in Scheme 2.[6]

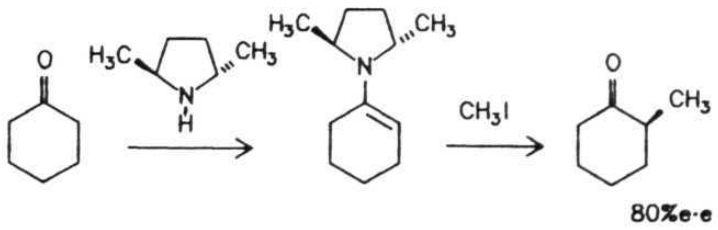
Scheme 2



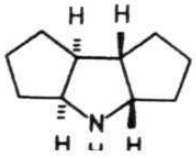
(1)

This stands as the first example of a monodentate C_2-chiral auxiliary. When this was used as the amine component in enamine alkylations, the corresponding alkylated product was obtained in 80% e.e. Whereas the use of optically pure 2-methylpyrrolidine as amine component gave only 50% e.e.[7-9]

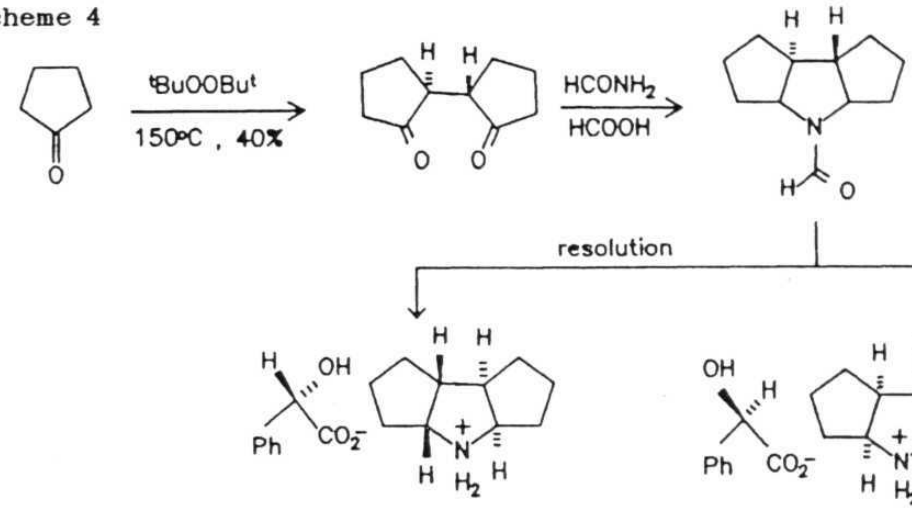
Scheme 3



Recently, Whitesell *et al* prepared a new C_2-chiral amine (2) starting from cyclopentanone, following the transformations outlined in Scheme 4. The racemic amine was readily resolved using chiral mandelic acid.[10]

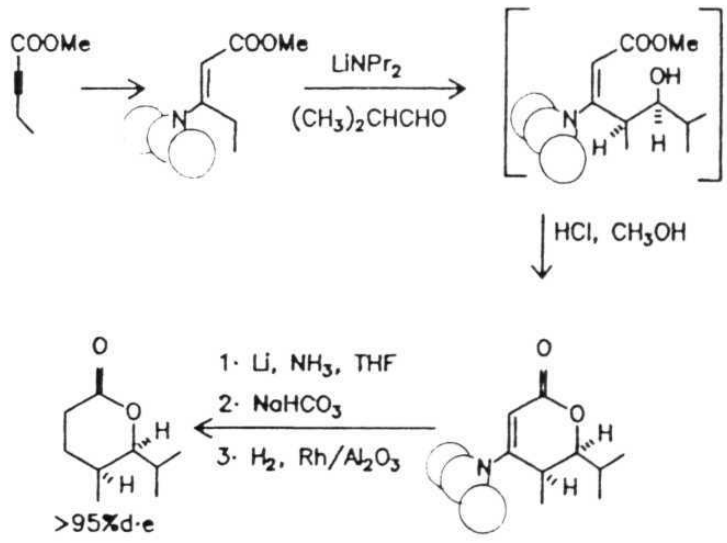


Scheme 4



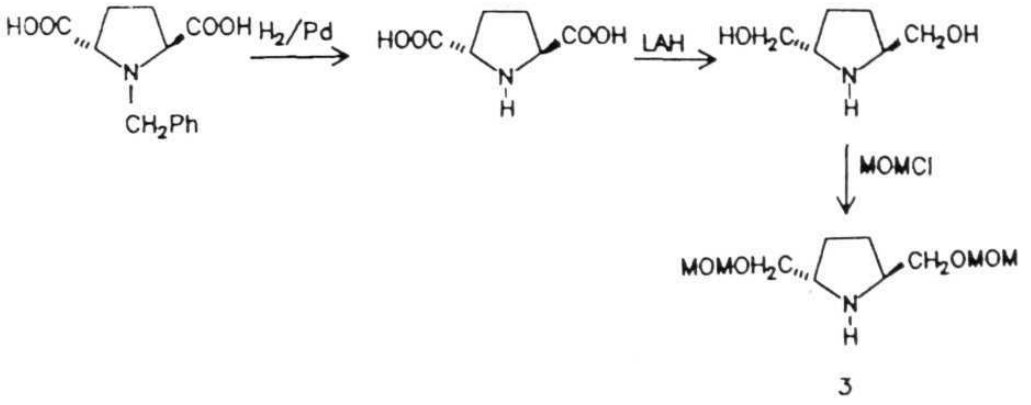
The utility of this amine has been demonstrated in the synthesis of a six membered ring lactone with diastereomeric purity of > 95%.[10]

Scheme 5

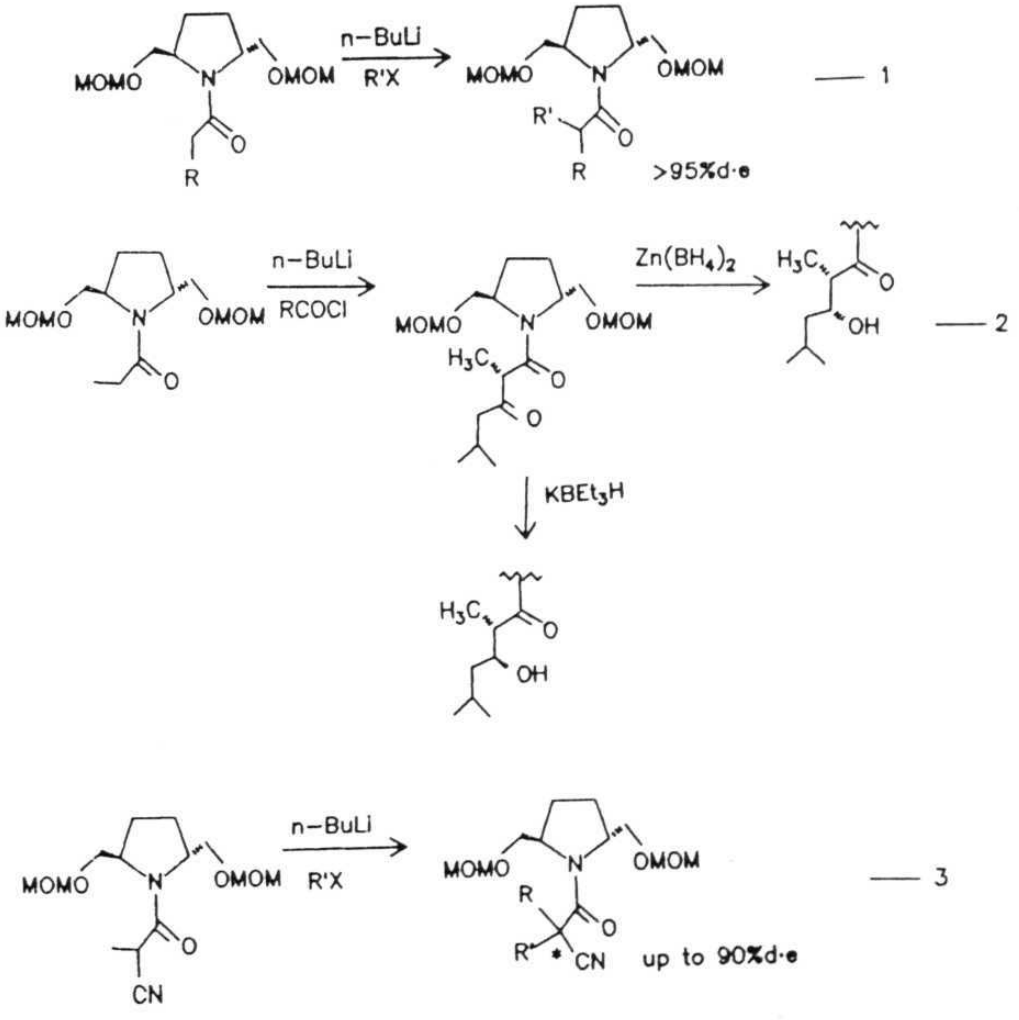


Trans-2,5-bis(methoxymethylene)-pyrrolidine (3) was found to be an effective chiral auxiliary. It gives high level of asymmetric induction in a number of reactions. This has been conveniently prepared from (d,l)-N-benzyl-2,5-pyrrolidine dicarboxylic acid. The d,l acid could be readily resolved using D-(-)-threo-(p-nitrophenyl)-2-amino-1,3-propanediol.[11]

Scheme 6

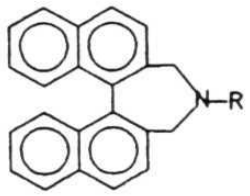


This chiral amine was used in asymmetric alkylations, acylations and diastereoselectivity up to 95% was achieved (eq. 1-3).[12-17]



Synthesis and applications of binaphthyl-based systems

Applications of C_2-chiral amines described above for asymmetric synthesis have been seriously hampered by the difficulty with which they have to be prepared. One of the problems is the formation of a meso compound. This difficulty is obviated in the dissymmetric C_2-chiral binaphthyl system (4).



(a) R= H

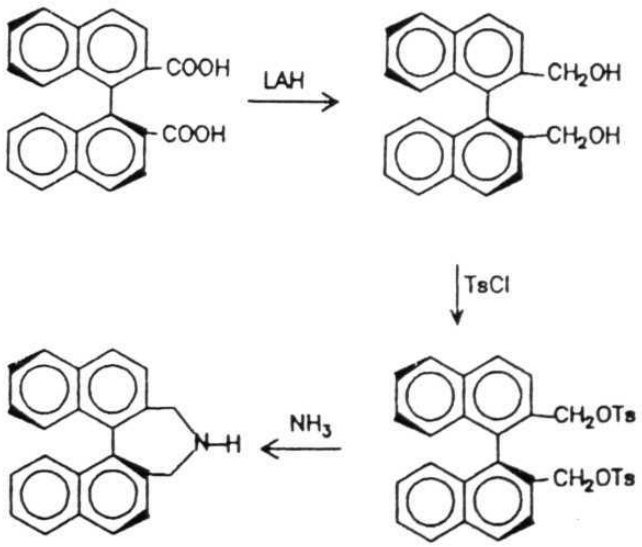
(b) R= CH_2Ph

(c) R= $CH(CH_3)Ph$

4

The chiral amines **4** can be prepared from chiral 1,1'-binaphthyl-2,2'-dicarboxylic acids the maximum rotations and absolute configurations of which have been established.[18]

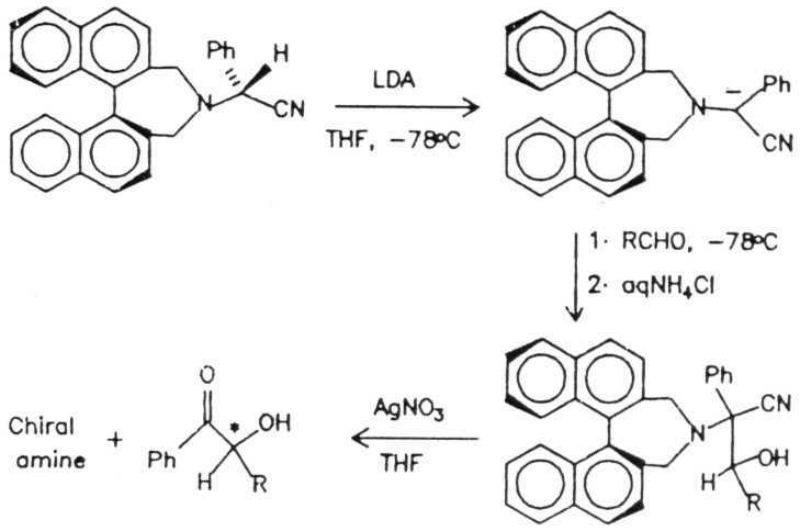
Scheme 7



Mazaleyrat *et al* synthesized α-amino nitriles from this secondary amine and used them as chiral acyl anion equivalents in nucleophilic

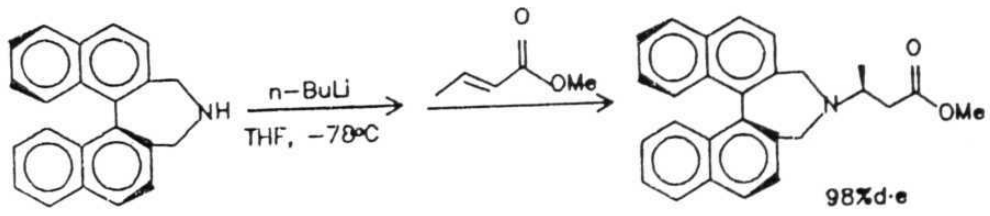
addition to aldehydes. This is the first example of asymmetric induction by axially dissymmetric compounds in nucleophilic acylation reactions. α-Hydroxy ketones were obtained in 56% e.e.[19]

Scheme 8



Hawkins *et al* used lithium amide of this amine (4a) in conjugate addition reaction with methyl crotonate. Diastereomeric excess up to 98% was achieved.[20]

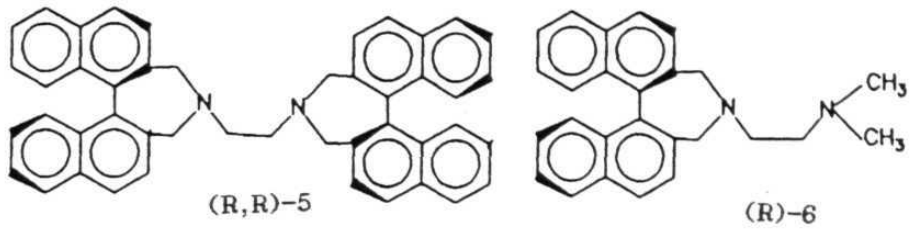
Scheme 9



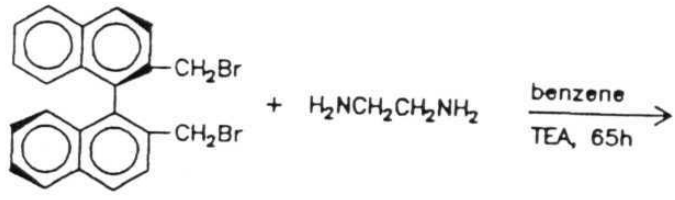
Synthesis and utilization of chiral diamines

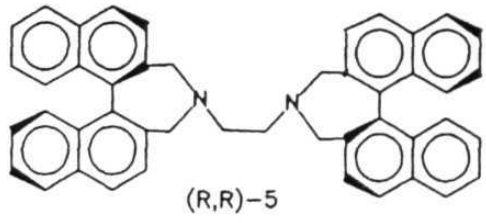
Cram and Mazaleyrat prepared the diamines (R,R)-5 and (R)-6 from

2,2'-bis(bromomethyl)-1,1'-binaphthyl following the scheme outlined in Scheme 10.[21]



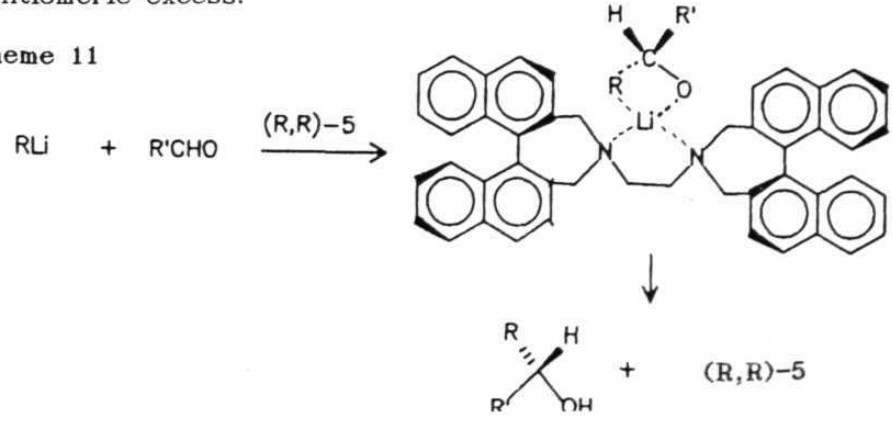
Scheme 10



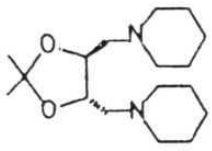


These diamines are useful in the alkyllithium additions to aldehydes. The corresponding alcohols are obtained in high enantiomeric excess.[21]

Scheme 11



Oxidation of carbon–carbon double bonds with osmium tetroxide–tertiary amine is one of the versatile methods for the preparation of cis-glycols from olefins. Sharpless et al. found that use of alkaloid derivatives such as quinine acetate and quinidine acetate in place of tertiary amine gives optical inductions up to 83.7% e.e.[22] The following C_2-chiral diamines were also found to be useful for this purpose.[23–26] Tomioka's diamine (9), prepared from 3,4-diphenylpyrrolidine was found to be the most efficient and cis-glycols with enantioselectivities up to 95% were obtained (eq. 4–6).



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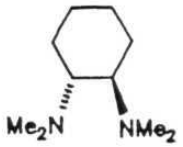

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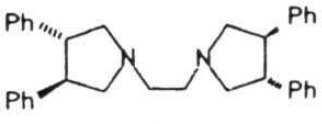
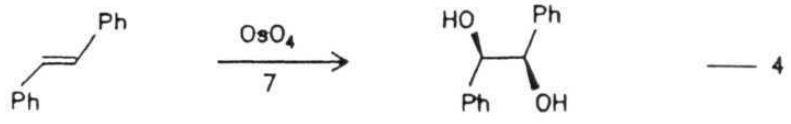
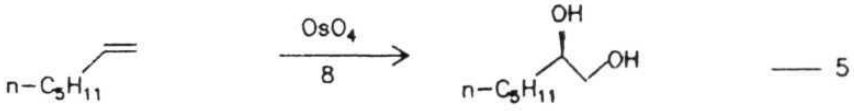


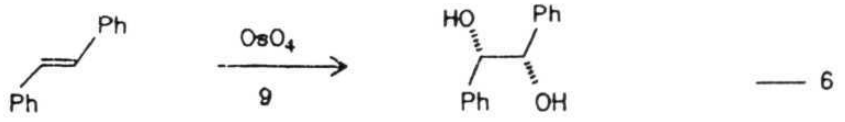
9



— 4

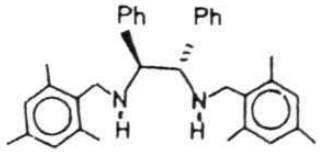


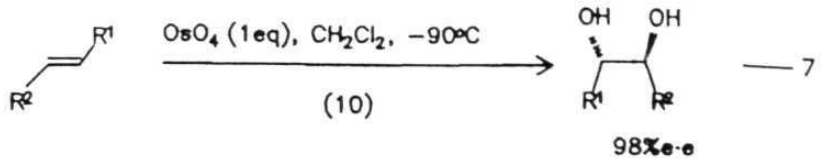
— 5



— 6

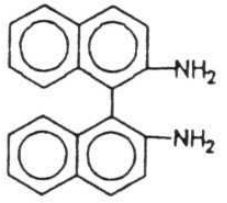
Very recently, Corey *et al* prepared S,S-1,2-diphenyl-1,2-bis (2,4,6-trimethylbenzylamino)ethane, a C_2 chiral amine. It was found that this reagent accelerates the reaction of olefins with osmium tetroxide even at $-90^{\circ}C$. Diols with enantiomeric excess up to 98% were isolated in goodyields (eq. 7).[27]





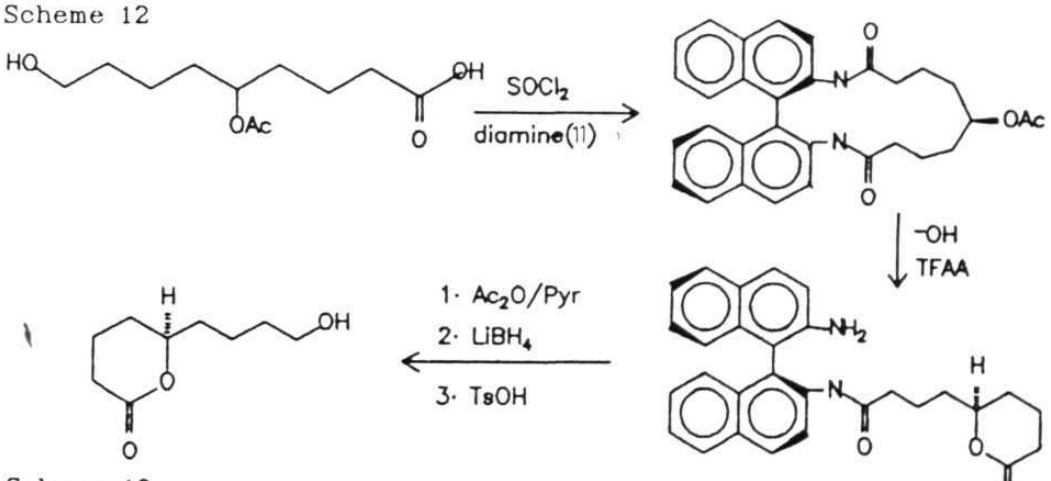
— 7

Chiral 2,2'-diamino-1,1'-binaphthyl (11), which can be prepared from R- or S-2,2'-dihydroxy-1,1'-binaphthyl, was found to be effective in several chiral transformations. Yamamoto *et al* used this as chiral base in the synthesis of six membered lactones with excellent asymmetric inductions. However, this chiral auxiliary gives somewhat poor inductions in the five membered lactone synthesis.[28,29]

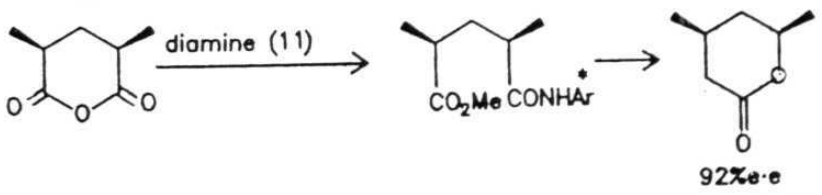


11

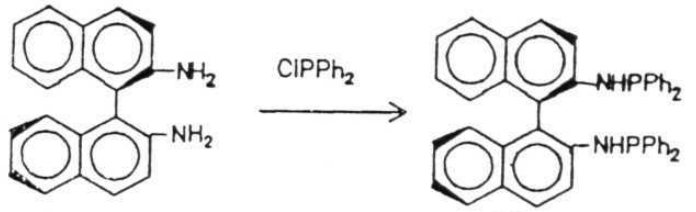
Scheme 12



Scheme 13

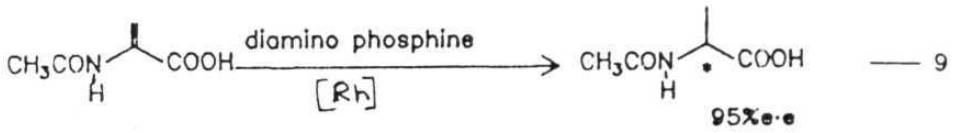


Efforts to use these binaphthyl diamines in rhodium-catalyzed hydrogenations were unsuccessful. The diamine (11) has been converted into the corresponding phosphinamide (also referred as amino phosphine). These ligands have been found to be effective chiral ligands in rhodium-catalyzed hydrogenations (eq. 8).[30]



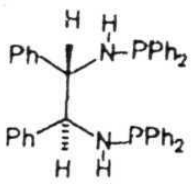
12 — 8

For example, in rhodium catalyzed asymmetric hydrogenation of α-acylaminoacrylic acids, the corresponding amino acids can be obtained in 95% e.e (eq. 9).[30]

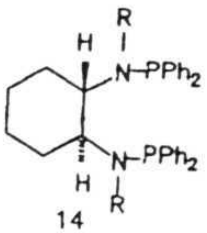


— 9

The following diaminophosphines (13, 14) have been also found to be useful in similar transformations.[31-33]



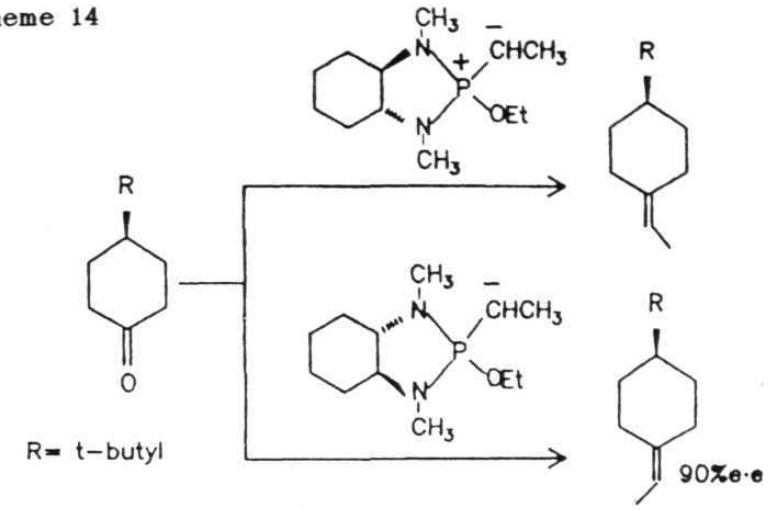
13



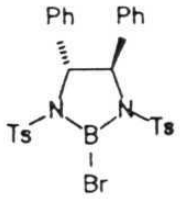
14

Hanessian *et al* developed a chiral phosphinamide ylide from C_2-cyclohexyldiamine for certain olefination reactions. This ylide gives a good control of stereochemistry at a remote center.[34]

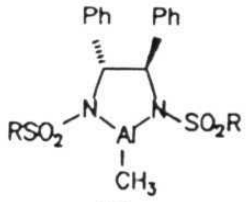
Scheme 14



Recently, Corey *et al* prepared a number of chiral Lewis acid catalysts from 1,2-diphenylethylenediamine and BBr_3 or $AlCl_3$. These chiral Lewis acids have been used as catalysts in aldol, Diels-Alder, and allyl boration reactions.[35]



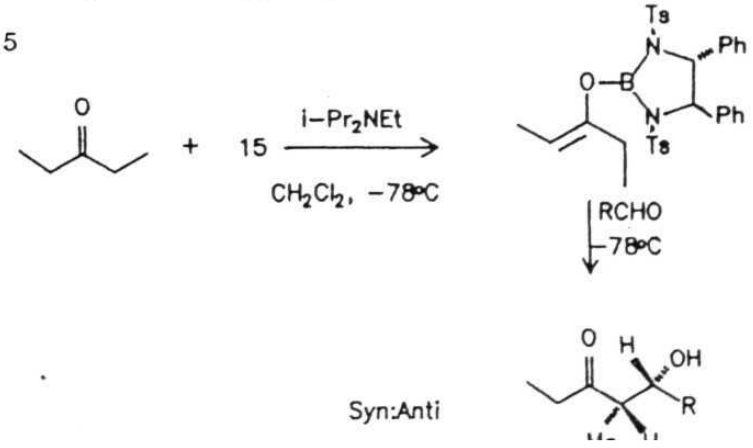
15



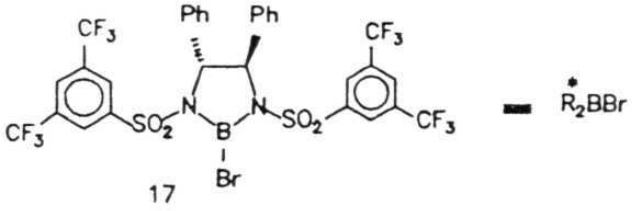
16

Reaction of (R,R)-15 with 1eq. of 3-pentanone and 2eq. of di-isopropyl N-ethylamine in CH_2Cl_2 at -78^oC generates the Z-boron enolate which reacts with propionaldehyde to give the corn weevil pheromone sitophilure in good yield with 98% e.e[35]

Scheme 15

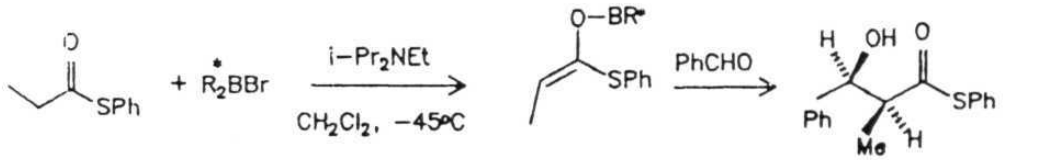


A slight modification of above Lewis acid catalyst was found to be even more effective for aldol reactions.[36]

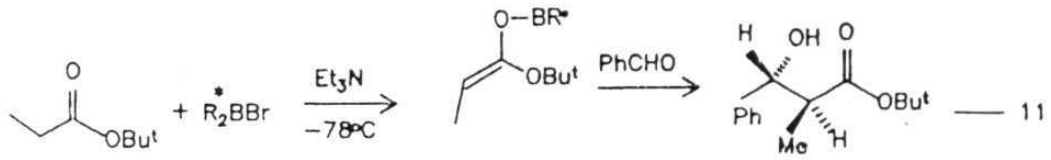


17

Using this chiral Lewis acid (17), both syn and anti aldol products were obtained selectively by changing α-substitution on the carbonyl compound (eq. 10,11).[36]

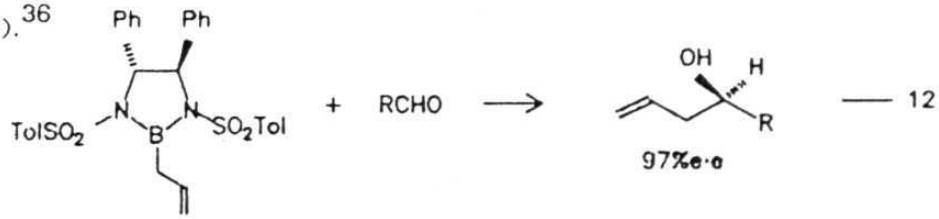


Syn:Anti/99:1 —— 10

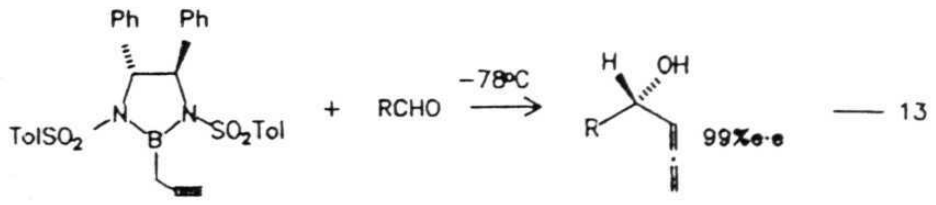


Anti:Syn/98:2

This Lewis acid reagent was also found to be highly selective in allyl boron addition to aldehydes and allenylation of aldehydes (eq. 12,13).[36]

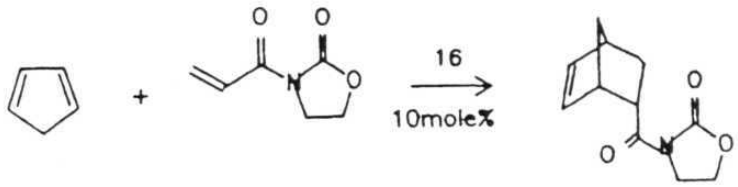


—— 12



—— 13

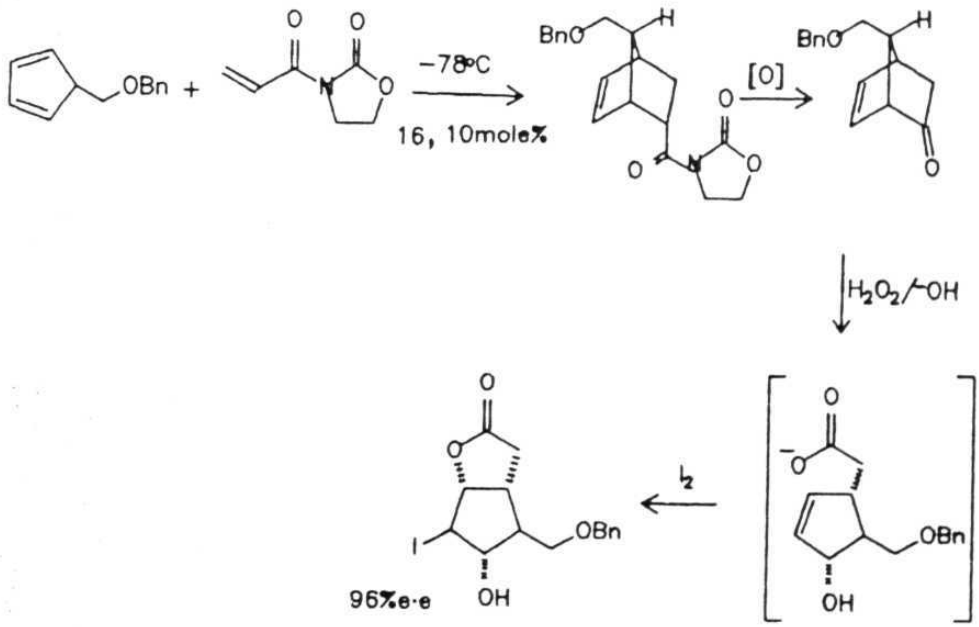
Corey *et al* found another application of (R,R) or (S,S)-1,2-chiral derivative 16 in catalytic enantioselective Diels-Alder reaction between cyclopentadiene and 3-acryloxalidin-2-one. Endo Diels-Alder adduct was obtained in 95% e.e (eq. 14).[37]



— 14

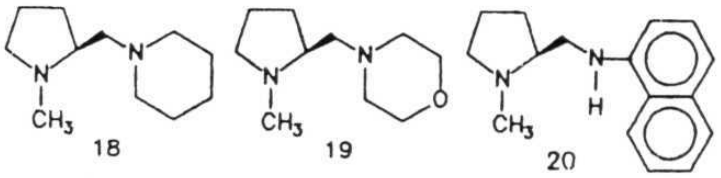
Reaction of 5-benzyloxymethyl-1,3-cyclopentadiene and acryloxazolidinone provides a valuable intermediate for prostaglandin synthesis with 96% e.e[38]

Scheme 16



As mentioned earlier, synthesis of these C_2 chiral amines, by and large, are somewhat tedious. For example, 2,2'-bis(bromomethyl) 1,1'-binaphthalene was prepared from the corresponding 1,1'-binaphthyl-2,2'-dicarboxylic acid. This acid in turn has to be

prepared from 2-methylnaphthalene in 7 steps. So, there has been efforts to develop more simple, economical chiral auxiliaries. Several naturally occurring amino acids and their derivatives are useful as chiral handles. Especially, S-proline derived chiral ligands have been found to be useful in several applications. Mukaiyama et al postulated that chiral diamines derived from S-proline forms rigid cis-fused five membered bicyclic structures by chelation to metal centers and so are effective ligands for highly enantioselective reactions.[39]



18

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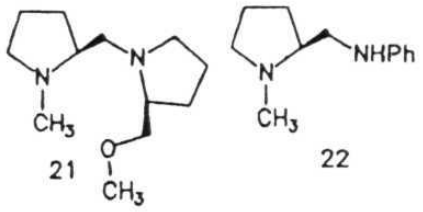
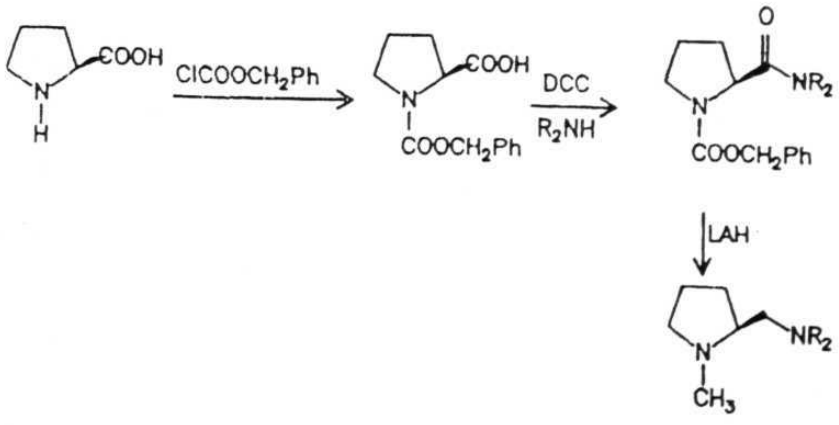


21

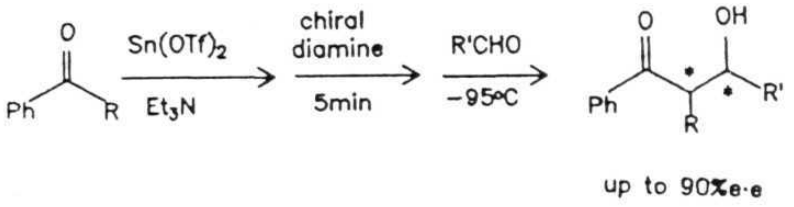
22

They prepared several chiral diamines (18 to 22) from S-proline following the general procedure outlined in Scheme 17.[40]

Scheme 17

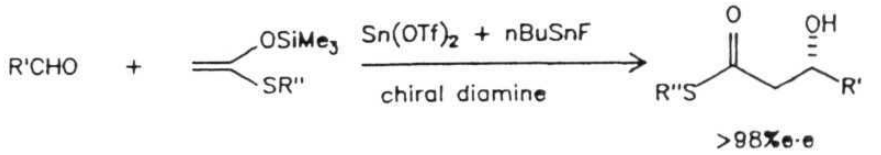


The combination of these chiral diamines and tin triflates is useful in enantioselective aldol reactions (eq.15).[40]



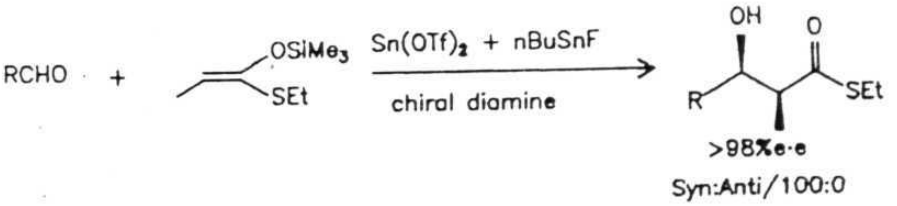
— 15

Kobayashi and Mukaiyama used these diamines in asymmetric aldol reaction of silyl ethers of S-ethyl or S-tert.- butyl ethanethioate with aldehydes. Enantioselectivity >98% was achieved (eq. 16).[41]



— 16

Following this method, α-methyl-β-hydroxythioesters have been prepared in 100% syn selectivity with enantiomeric excess > 98% (eq. 17).[41]

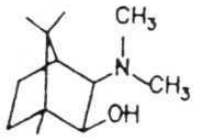


— 17

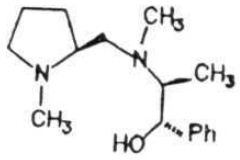
Synthesis and utilization of chiral Amino Alcohols:

The addition of dialkylzinc reagents to aldehydes is relatively

slow. It has been found that amino alcohols catalyze alkylzinc addition to aldehydes. An asymmetric version of this reaction has been developed using chiral amino alcohols. For example, the following chiral amino alcohols (23, 24) catalyze diethylzinc additions to aromatic aldehydes in high e.e[42,43]

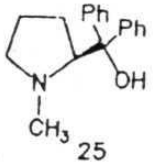


23



24

Even though several chiral amino alcohols have been developed for dialkylzinc additions,[44–47] studies describing the use of amino alcohols derived from S-proline are more prevalent for such applications.[48–50]



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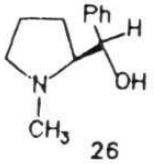

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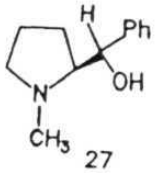

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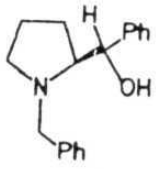

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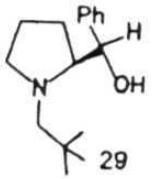
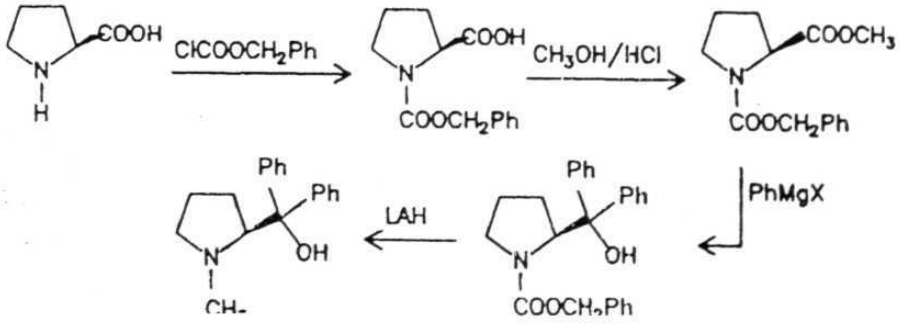


29

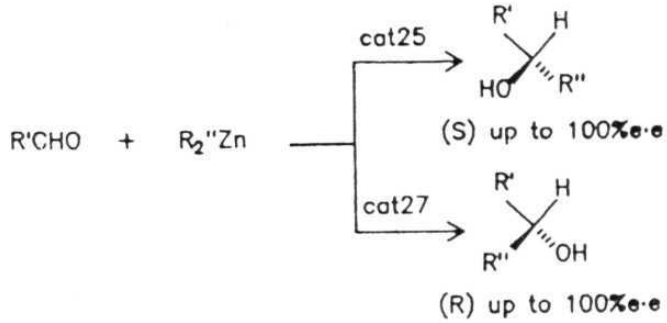
Soai *et al* prepared a number of S-proline derived amino alcohols following the general procedure outlined in Scheme 18.[48]

Scheme 18

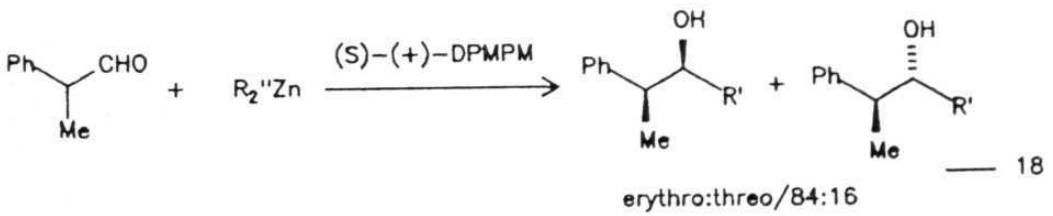


These amino alcohols have been successfully used as chiral catalysts in dialkylzinc additions to aldehydes. Excellent yields of secondary alcohols were obtained with selectivities reaching 100%. Also, both R and S alcohols can be obtained depending on the structure of the amino alcohol. Whereas the tertiary amino alcohol (25) gives exclusively S-alcohol in 100% e.e, the secondary alcohol (27) yields R-alcohol in 100% e.e.[48]

Scheme 19



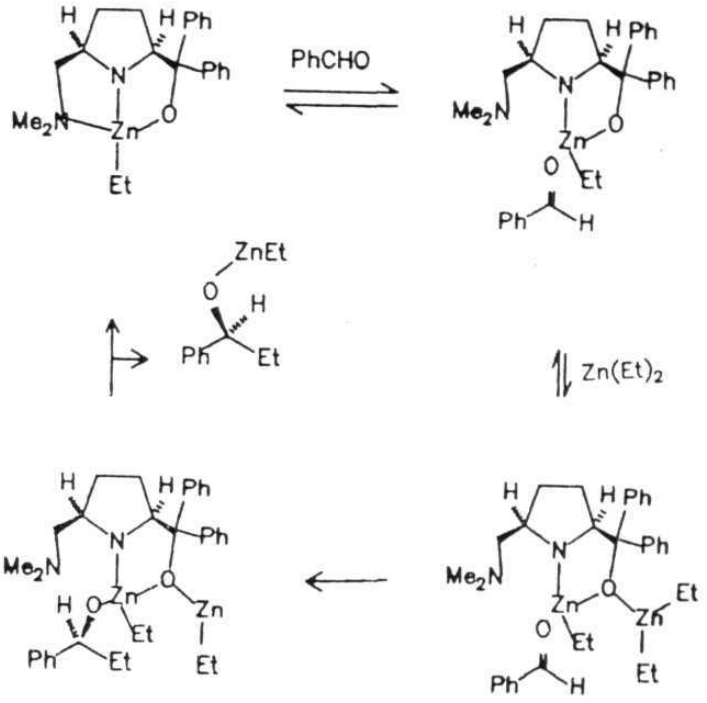
The (S)-(+)-diphenyl-1-methylpyrrolidine-2-yl-methanol (DPMPM) catalyzes diastereo- and enantioselective addition of dialkylzinc reagents to 2-phenylpropanal. Optically active alcohols with two chiral centers have been obtained in good enantiomeric excess (eq.18).[50]



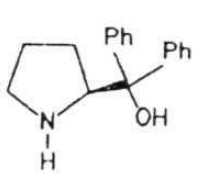
Corey *et al* prepared a diamino alcohol, which on treatment with equimolar amount of diethylzinc gives a complex (Scheme 19). This complex catalyzes diethylzinc additions to aldehydes even in 10 mol%

ratio. The S-alcohols were obtained in good yields with high e.e (94%).[51]

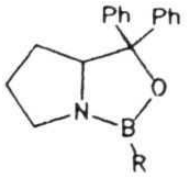
Scheme 19



The major application of these chiral aminols is in the synthesis of Corey's oxazaborolidine (31) (CBS reagent) which can be prepared from α,α-diphenylpyrrolidinemethanol (30).[52]



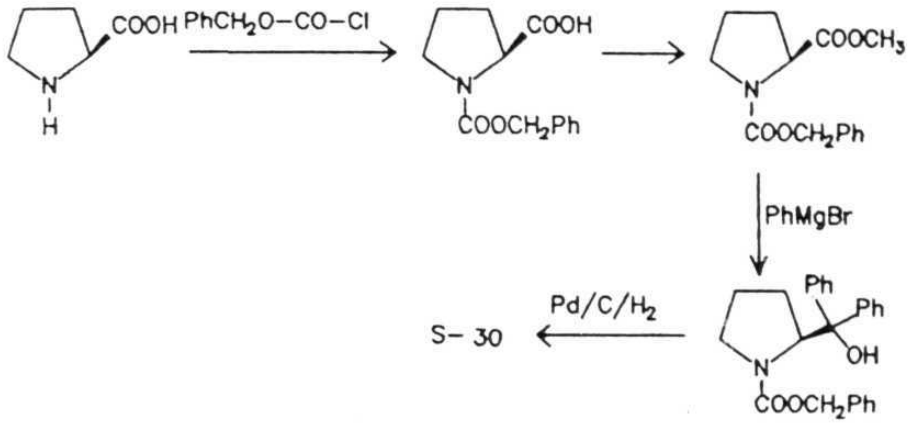
S- 30



31

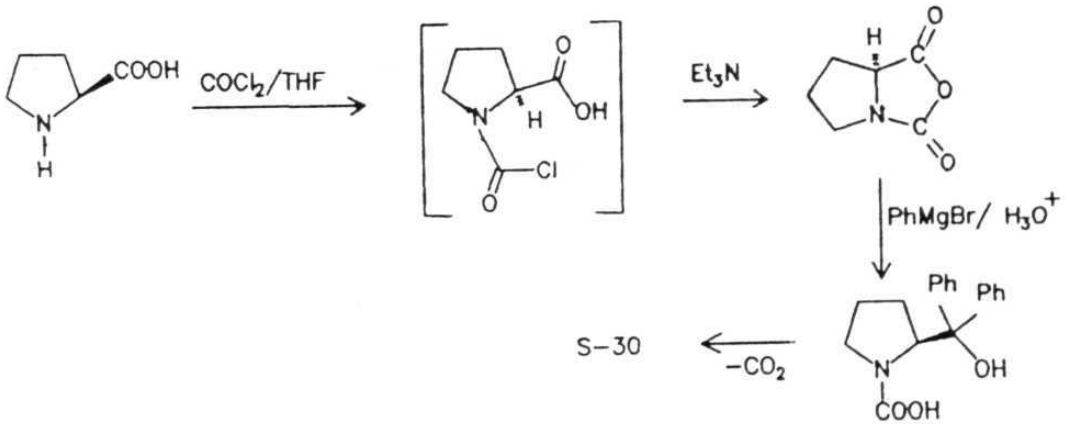
The S-(-)α,α-diphenylpyrrolidinemethanol has been conveniently prepared starting from S-proline following the operations outlined in Scheme 20.[53]

Scheme 20

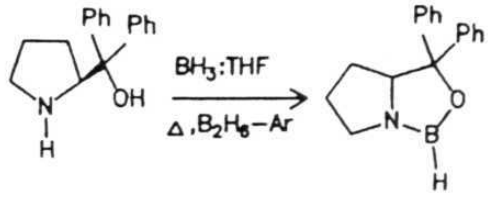


There have been efforts to prepare this useful compound in more convenient ways. Recently, Mathre *et al* reported a new method for the synthesis of this compound.[54]

Scheme 21



The pyrrolidinemethanol on heating with an excess of BH_3:THF, in an Argon–B_2H_6 atmosphere gives the corresponding oxazaborolidine (eq. 19).[51,55]



— 19

Methods have been also developed for the synthesis of the

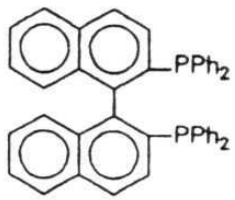
corresponding $B-CH_3$ derivative. This reagent system is popularly known as CBS reagent. It is useful for catalytic asymmetric reductions of prochiral ketones. These aspects will be discussed in Chapter-2 in detail. Chiral amino alcohols are also useful for the synthesis of oxazolines. Meyers *et al*[33*] pioneered the synthetic applications of these reagents (Ref. 33 in Chapter 3).

We undertook to prepare different types of chiral amines and amine-borane complexes which can be used for asymmetric reductions and hydroborations. The results of these synthetic efforts are described in the next section.

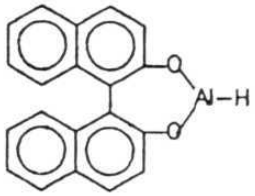
RESULTS AND DISCUSSION

Synthesis of Chiral Binaphthyl Amines

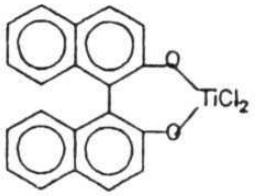
The dissymmetric 1,1'-binaphthyl moiety has found extensive use as chiral auxiliary in asymmetric synthesis. For example the binaphthyl chiral systems such as BINAP (32), BINAL-H (33), $TiCl_2$ complex of binaphthol (34) were found to give high levels of asymmetric induction in certain transformations.[56-60]



32

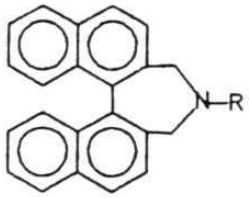


33



34

These observations prompted us to undertake the synthesis of chiral amines, the borane complexes of which can be used in asymmetric reductions and hydroborations.



4

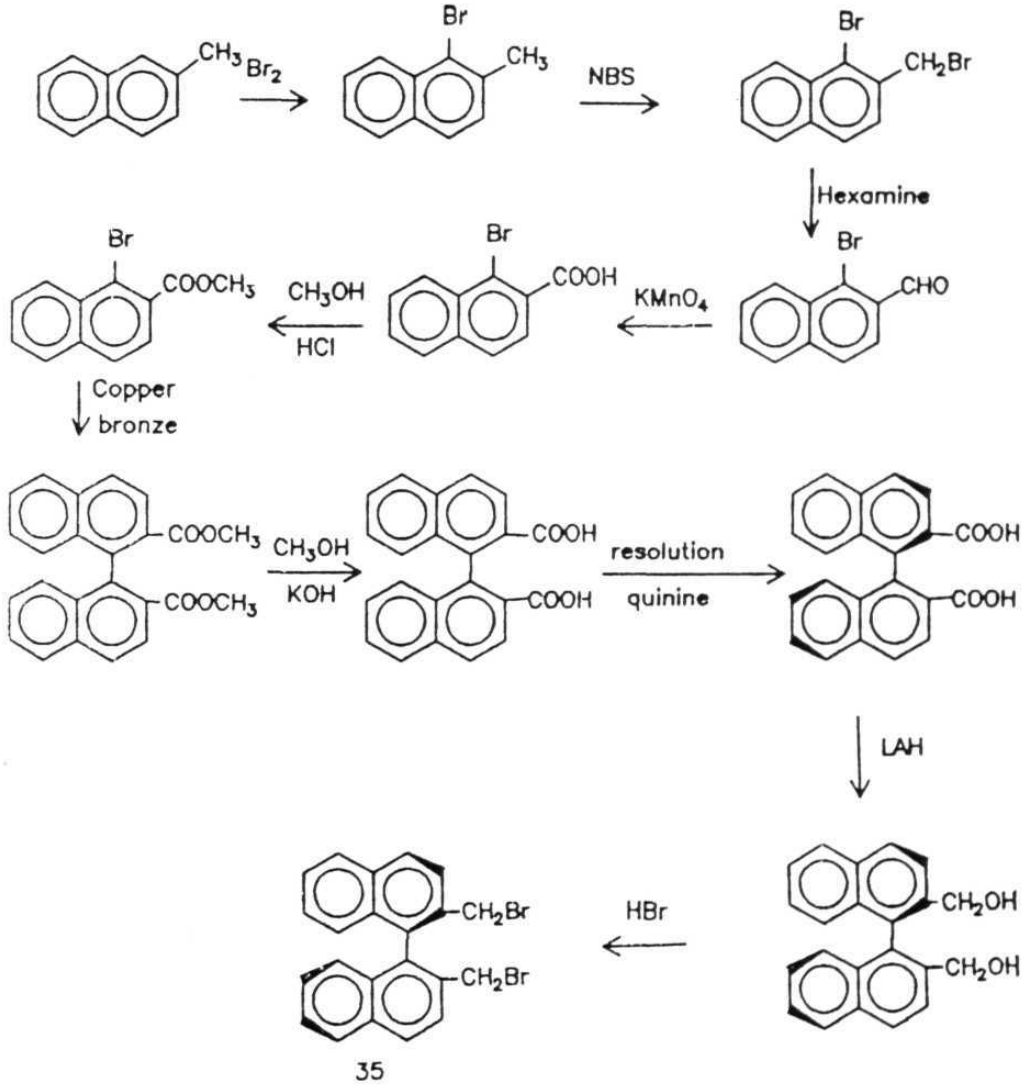
a. R=H
b. R=CH_2Ph
c. R=$CHCH_3Ph$

Two strategies can be envisaged for the synthesis of this amine. (i) Synthesis and separation of diastereomers. (ii) Synthesis and resolution of the racemic amine. The crucial intermediate was identified as 2,2'-bis(bromomethyl)-1,1'-binaphthyl, which can be

prepared from 1,1'-binaphthyl-2,2'-dicarboxylic acid.

The synthesis of 1,1'-binaphthyl-2,2'-dicarboxylic acid has been reported starting from 2-methylnaphthalene. The racemic mixture of dicarboxylic acids has been resolved using quinine.[12]

Scheme 22

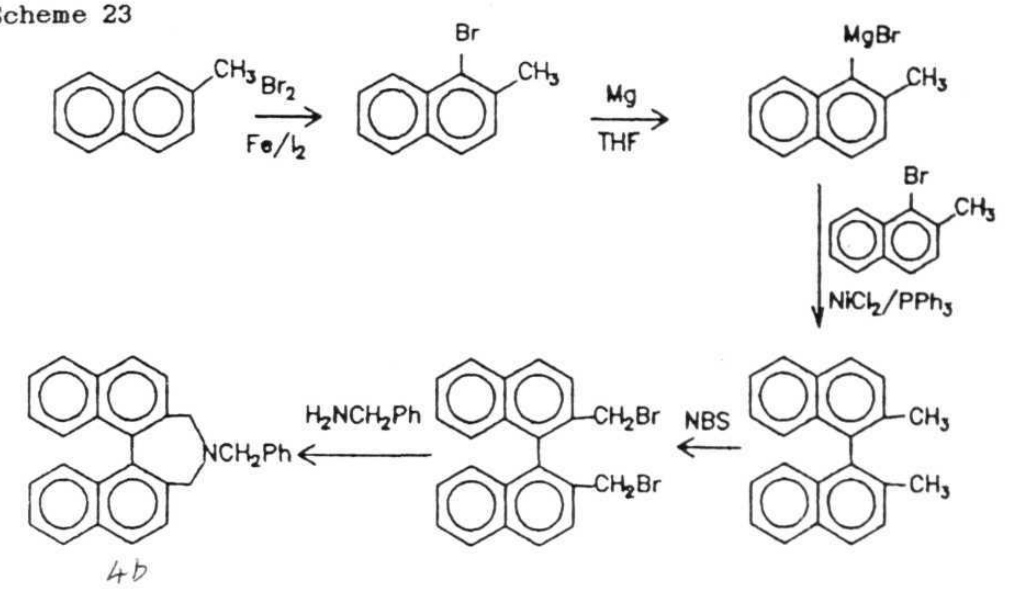


35

This method involves several steps and the resolution of the diacid requires quinine. We decided to examine the synthesis of the racemic amines via the dibromide 35.

The following scheme of operations was adopted for the synthesis of the racemic amine, following closely related reported procedures.[61]

Scheme 23

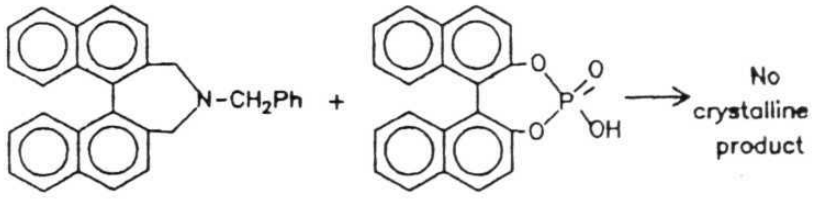


4b

The racemic mixture of amines (4b) was obtained and the optical resolution was attempted using chiral tartaric acid and camphor-10-sulphonic acid. But these attempts were not successful.

Resolution of this racemic mixture was also attempted using binaphthyloxyphosphoric acid, an effective reagent for resolution of certain racemic amines.[62] However, no crystalline derivative could be isolated from a mixture of these two compounds in several solvent systems under different conditions.

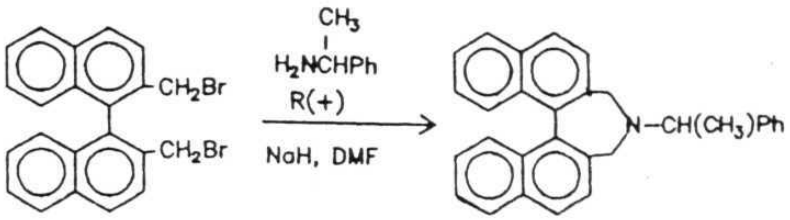
Scheme 24



4b

We then turned our attention towards the synthesis of diastereomeric amines and separation of the diastereomers. The relatively less expensive α-methylbenzylamine was selected for this purpose.

Scheme 25



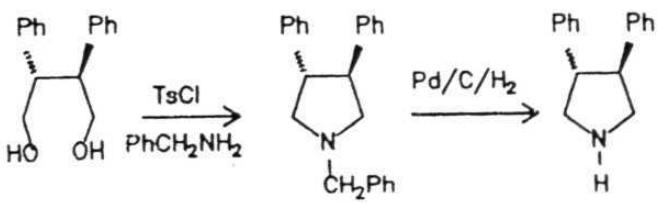
35

It has been found that the reaction of dibromide 35 with (+)-α-methylbenzylamine in the presence of NaH in DMF at 70°C for 2h gives a mixture of diastereomers in 85% yield. The two diastereomers were separated by column chromatography on silica gel column with hexane:ethyl acetate/95:5 as eluent. The (-) isomer $[\alpha]_D^{25}$= -173°(C1, $CHCl_3$) was obtained in 40% yield as a crystalline compound. The (+)-isomer was obtained as a gum $[\alpha]_D^{25}$= +253°(C1, $CHCl_3$). Synthetic utilities of this chiral amine will be discussed in Chapter 2.

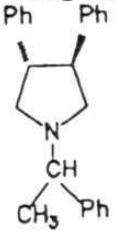
Synthesis of N-α-methylbenzyl-3,4-diphenylpyrrolidine

The synthesis of 3,4-diphenylpyrrolidine has been reported starting from optically pure 2,3-diphenyl-1,4-butanediol.[63]

Scheme 26



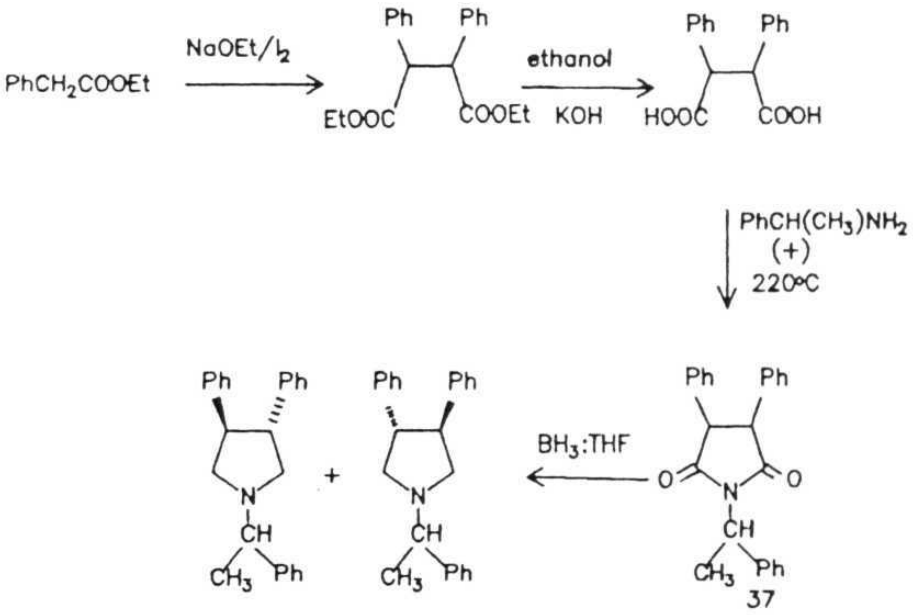
It was decided to synthesize the diastereomeric amines 36 for the preparation of corresponding amine-boranes.



36

The synthesis of this amine was carried out starting from ethyl phenylacetate following closely related reported procedures.[64]

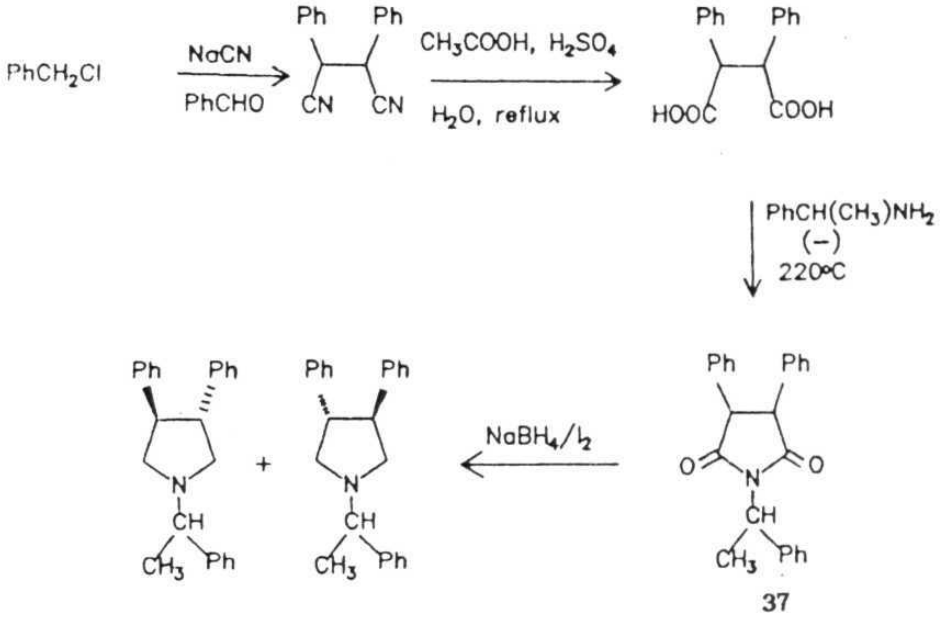
Scheme 27



The diastereomeric mixture of amine (36) was obtained in 17% yield starting from ethyl phenylacetate. In this sequence, the first step is the condensation of ethyl phenylacetate with $NaOEt/I_2$. The condensed product was obtained in low yields. We attempted a number of alterations such as performing the reaction at different temperatures, varying the reaction time and carrying out the reaction

in THF rather than ether. In spite of all these efforts, there was not much improvement. So, we have followed another method involving condensation of benzylchloride with NaCN and benzaldehyde for the synthesis.[65]

Scheme 28



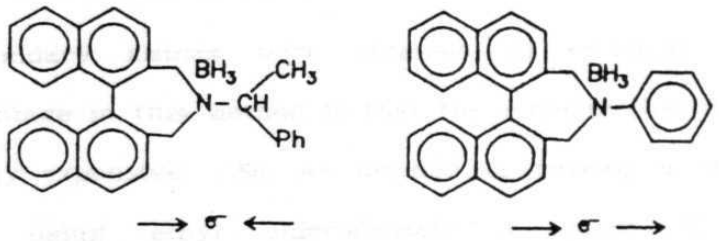
37

Following this scheme, the diphenylsuccinic acid was obtained in good yield. The condensation of the diacid was carried out using (-)-α-methylbenzylamine to obtain the cyclic imide 37. The separation of the diastereomeric mixture at this stage was not successful.

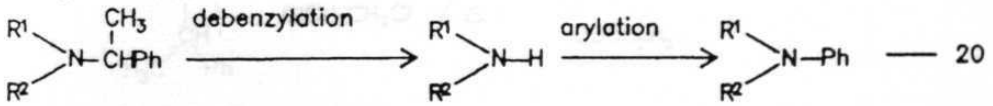
The cyclic imide (37) was reduced following a simple, convenient $I_2/NaBH_4$ reagent system developed in this laboratory.[66] The diastereomeric amine mixture was separated by column chromatography on alumina . The isomer eluted first was obtained in diastereomerically pure form with $[\alpha]_D^{25} = -80^{O}(C1,CHCl_3)$ in adequate quantities for utilization.

Synthesis of chiral secondary amines through cleavage of tertiary amines.

The tertiary N-alkyl amines described here have been found to complex strongly with borane (Chapter 2). These chiral amine borane complexes failed to hydroborate prochiral olefins at room temperature (Chapter 2). However, tertiary N-phenylamine-BH_3 complexes hydroborate olefins under ambient conditions.



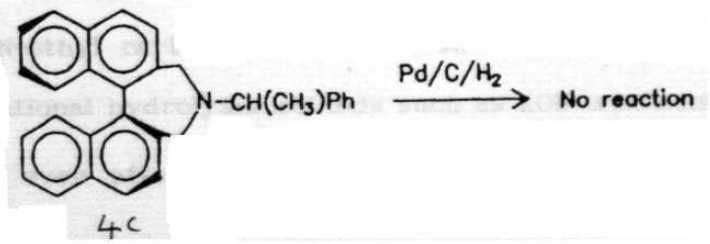
This increase in reactivity is due to the relatively weak B-N bond in the corresponding borane complex. The N-phenyl compounds can be prepared through N-debenzylation and N-phenylation sequence (eq. 20).



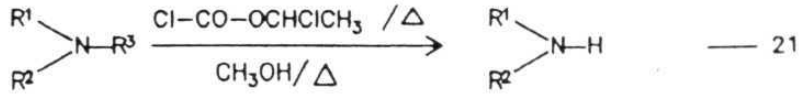
— 20

Attempts towards N-debenzylation of the amine 4c using conventional debenzylation procedures such as $Pd/C/H_2$ in several solvents were not successful.

Scheme 29

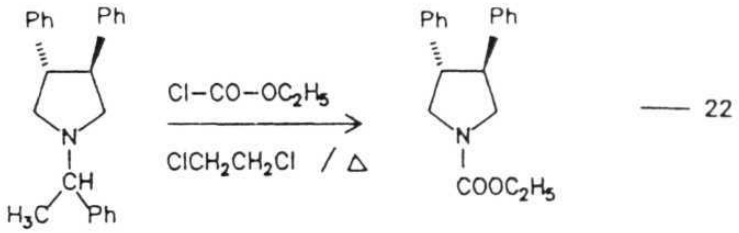


Olofson *et al* developed a new process for debenzylation of tertiary amines using chloroformate derivatives such as phenyloxy chloroformate, vinyloxychloroformate and α-chloroethyl chloroformate. The last reagent was found to be useful (eq. 21).[67-70]



— 21

Secondary amines were obtained in excellent yields. The disadvantage in this method is that the α-chloroethyl chloroformate is relatively expensive. So, we decided to develop a more convenient method using ethyl chloroformate in place of α-chloroethyl chloroformate for debenzylation (eq. 22).

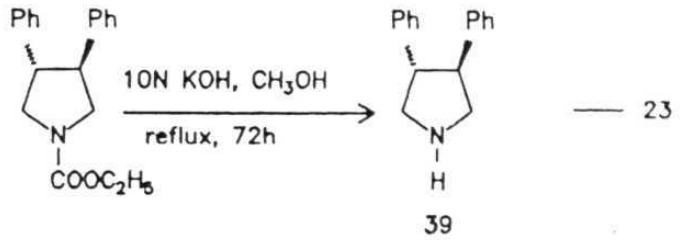


— 22

38

When α-methylbenzyl-3,4-diphenylpyrrolidine was heated with ethyl chloroformate in dichloroethane, the corresponding N-ethyl carbamate derivative of 3,4-diphenylprrolidine was obtained in quantitative yields. The N-ethyl carbamate 38 has been found to be unreactive towards conventional hydrolysis methods such as KOH treatment. It was observed that even after refluxing for 72h in a 10N KOH solution of

methanol, the secondary amine was obtained only in 30% yield besides unreacted starting material (eq. 23).

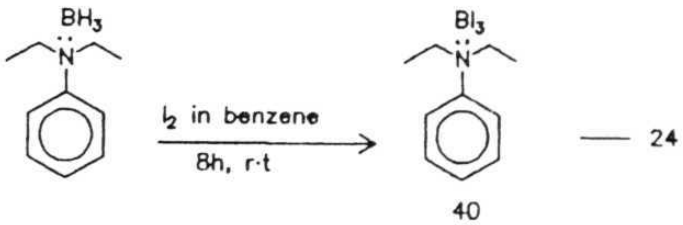


39 — 23

Several other reagent systems such as Me_3SiI, HBr and $BF_3{:}OEt_2$ have also failed to cleave this carbamate derivative.

The Lewis acids BCl_3 and BBr_3 have been reported to cleave ethers.[71] However, they are not widely used since they are highly corrosive and handling these reagents is also somewhat difficult. Moreover, these reagents are not readily accessible.

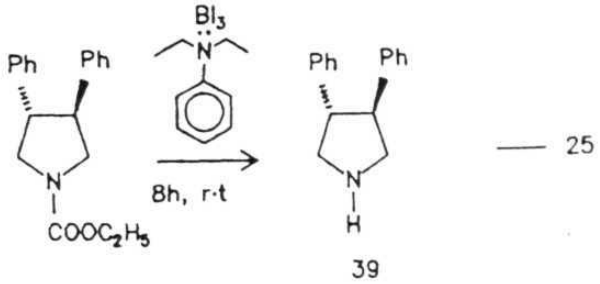
Recently, a simple convenient method of preparation of the BI_3 complex of N,N-diethylaniline *in situ* through the reaction of I_2 with N,N-diethylaniline–borane complex has been developed in this laboratory (eq. 24).[72]



40 — 24

The cleavage of N-ethyl carbamate was readily effected by the N,N-diethylaniline–BI_3 complex by stirring the N-ethyl carbamate

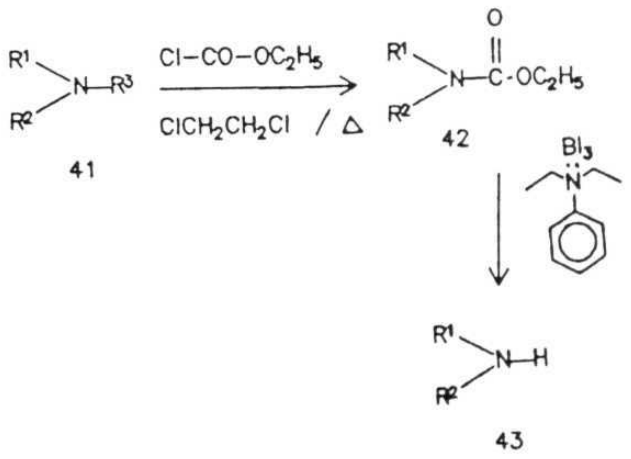
derivative with the BI_3 complex (40) at room temperature for 8h (eq.25).



39 — 25

It was found that this ethyl chloroformate/N,N-diethylaniline–BI_3 reagent system is also useful in the conversion of a few other N-benzyl tertiary amines to the corresponding secondary amines.[73] The results are summarized in Table I.

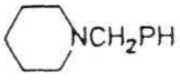
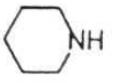
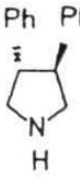
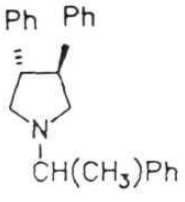
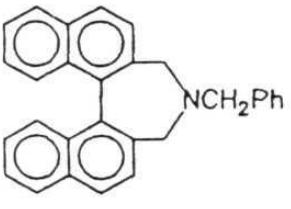
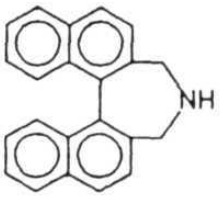
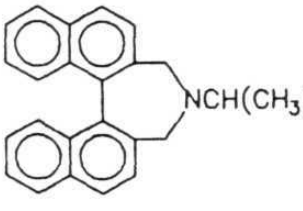
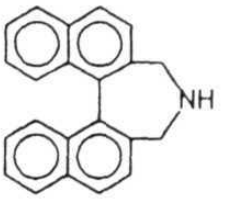
Scheme 30



Following this method, optically pure 3,4-diphenylpyrrolidine was obtained from the corresponding diastereomerically pure N-α-methyl benzyl derivative.

Unfortunately, when the diastereomerically pure amine 4c was treated with ethyl chloroformate, the corresponding racemic mixture of N-carbamates was isolated. Presumably, the racemization takes place

Table I: N-Debenzylation of tertiary amines.[a]

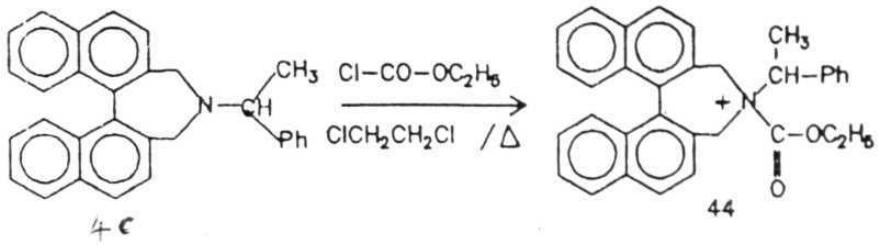
S.No.	Substrate	Reaction time[b] (h)		Product	Yield[c] %
1		12	8		80
2		4	8		89
3		4	8		88
4	$(PhCH_2)_2NCH(CH_3)Ph$	20	8	$(PhCH_2)_2NH$	87
5		8	8		85
6		8	8		87

(a) All reactions were carried out in 5 mmol scale.

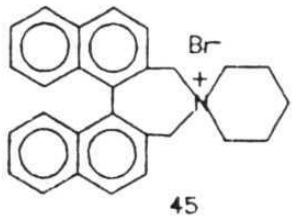
(b) The transformation (41-42) (scheme 30) was carried out in refluxing dichloroethane. The conversion of (42-43) was carried out at 25°C.

(c) Yields are of isolated and purified products.

because of the intermediacy of quaternary nitrogen (44) during the transformation. It is of interest to note that the (+)-2,7-dihydro-dinaphtho(2',1-3,4)(1",2"-5,6)azepinium-1-spiro-1-piperidinium bromide 45 racemizes in hot ethylene glycol solution.[12]



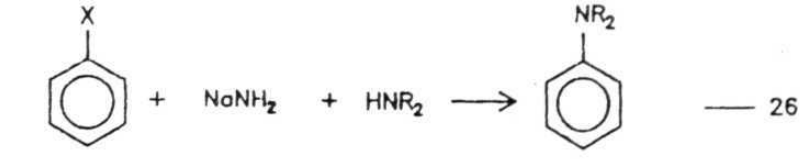
4c 44



45

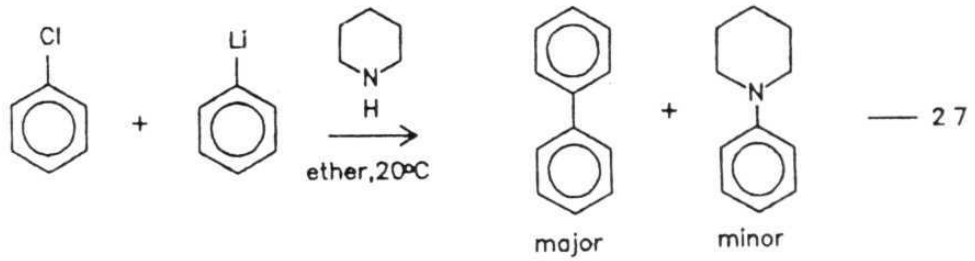
N-Phenylation of amines.

Even though the racemization of the amine 4c hampered our protocol to prepare N-phenyl-3,5-dihydrodinaphthazepine, we have undertaken a project to synthesize optically active N-phenyl tertiary amines required in the preparation of the borane complexes. Although several methods have been reported for N-phenylation of amines in recent years,[74-76] the earlier method utilizing alkali metal (Li or Na), halobenzene and the amine is simplest for synthetic applications (eq. 26).[77-81]



— 26

Unfortunately, these methods require amine as solvent and hence are not good for use in cases where amines are precious. It has been reported that piperidine catalyzes the reaction of chlorobenzene and phenyllithium to give biphenyl. In this reaction, the N-phenyl-piperidine was obtained as a minor side product (eq. 27).[82]



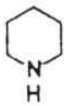
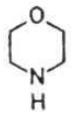
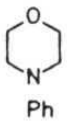
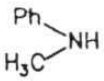
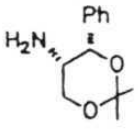
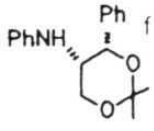
— 27

It occurred to us that a convenient method for N-phenylation of amines can be developed based on this observation, using excess halobenzene and lithium in relation to amine.

A mixture of lithium powder suspension in THF and diethylamine was treated with bromobenzene at room temperature to obtain N,N-diethyl aniline in 82% yield. This transformation was found to be general and N-phenylation of several secondary and primary amines have been carried out following this procedure.[84] The results are summarized in Table II.

Following this procedure, the secondary amines can be converted to N-phenyl tertiary amines. The primary amines are converted to the corresponding N-phenyl secondary amines. The secondary phenyl amines are not affected. This method is successfully adopted for the

Table II: N-Phenylation of amines.[a]

S.No.	Substrate	Product[b]	Yield[c] %
1	$(C_2H_5)_2NH$	$(C_2H_5)_2NPh$	82
2	$(i\text{-}C_3H_7)_2NH$	$(i\text{-}C_3H_7)_2NPh$	78
3			80
4			86
5			81
6	$C_6H_5NH_2$	$(C_6H_5)_2NH$	65
7	$(C_6H_5)_2NH$	No reaction	
8		No reaction	
9	$t\text{-}C_4H_9NH_2$	$t\text{-}C_4H_9NHPh$	80
10	$C_6H_5CH(CH_3)NH_2$ (±)	$C_6H_5CH(CH_3)NHPh$ (±)	71
11	$C_6H_5CH(CH_3)NH_2$ (−)	$C_6H_5CH(CH_3)NHPh$[d] (+)	70
12	$C_6H_5CH(CH_3)NH_2$ (+)	$C_6H_5CH(CH_3)NHPh$[e] (−)	70
13			72

(a) All reactions were carried out using 30 mmol of lithium dispersion in mineral oil (30%), 30 mmol of bromobenzene and 10 mmol of amine in dry THF at room temperature.

(b) All products were identified by IR, ^{1}H NMR, ^{13}C NMR and physical constant data and comparison with the data reported in literature.

(c) Yields are of isolated and purified products.

(d) $[\alpha]_D^{25} = +17^{o}$(C1, CH_3OH) Lit[83] $[\alpha]_{578}^{24} = +18.5^{o}$(C1, CH_3OH)

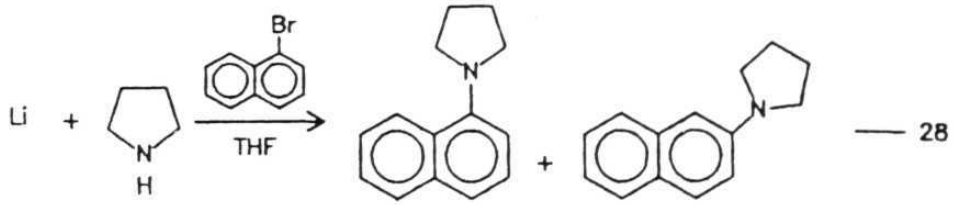
(e) $[\alpha]_D^{25} = -16^{o}$(C1, CH_3OH) Lit[83] $[\alpha]_{578}^{24} = -17.7^{o}$(C1, CH_3OH)

(f) $[\alpha]_D^{25} = -86.5^{o}$(C1.26, $CHCl_3$)

---

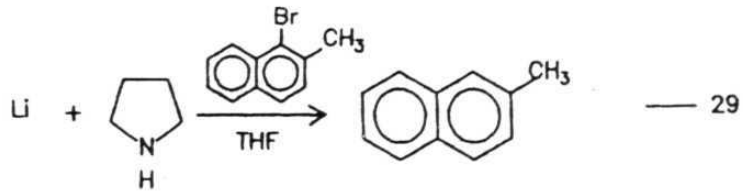
preparation of optically active N-phenyl amines starting from a few optically active amines (entries 11-13, Table II).

Such N-phenylations are known to go through a benzyne intermediate. This was confirmed by the following observations. Reaction of 1-bromo naphthalene with pyrrolidine and lithium in dry THF leads to a mixture of 1- and 2-naphthylpyrrolidines (eq. 28).[79]



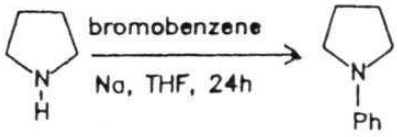
— 28

Also, the reaction of 1-bromo-2-methylnaphthalene with pyrrolidine and lithium in THF gives 2-methylnaphthalene as expected (eq. 29).[79]



— 29

When sodium was used in place of lithium, N-phenyl amines have been obtained in comparable yields. However, the reactions using Na metal have been found to take more time than the corresponding lithium reactions (eq. 30).



— 30

Table III: N-Phenylations of amines[a]

S.No.	Substrate	Product[b]	Yield[c] %
1	$(C_2H_5)_2NH$	$(C_2H_5)_2NPh$	72
2	$(i\text{-}C_3H_7)_2NH$	$(i\text{-}C_3H_7)_2NPh$	73
3			73
4			80

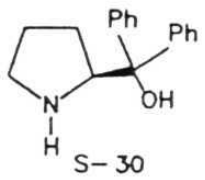
(a) All reactions were carried out using 30 mmol of sodium, 30 mmol of bromobenzene and 10 mmol of amine in dry THF at room temperature.

(b) All products were identified by IR, ^1H NMR, ^{13}C NMR and physical constant data and comparison with the data reported in literature.

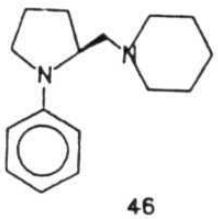
(c) Yields are of isolated and purified products.

Synthesis of L-Proline derived chiral amines.

As discussed in the introductory section, amino alcohols and diamines derived from L-proline give high levels of asymmetric induction in several transformations. We have undertaken the synthesis of the following L-proline derived chiral systems, the borane complexes of which can be used for asymmetric reductions and hydroborations.



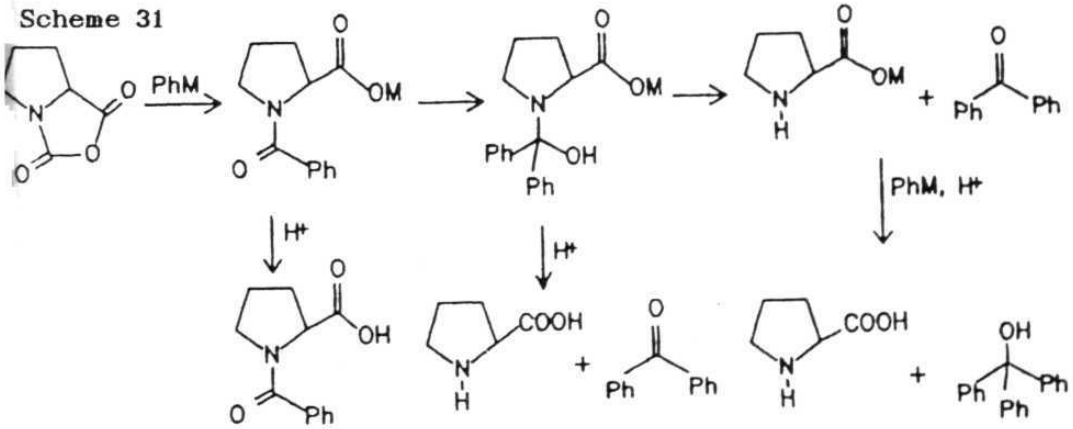
S-30



46

Several methods are available for the synthesis of α,α-diphenyl-pyrrolidinemethanol, the precursor for the CBS asymmetric reduction catalysts. Recently, Mathre et al reported a new procedure which they found suitable for their needs (see p-20 for details).[55] Unfortunately, this method requires utilization of highly toxic phosgene and the intermediate proline-N-carboxanhydride is not stable. Even at $0^{o}C$, it polymerizes rapidly on standing, releasing CO_2. Also, in this method a number of side products are possible.

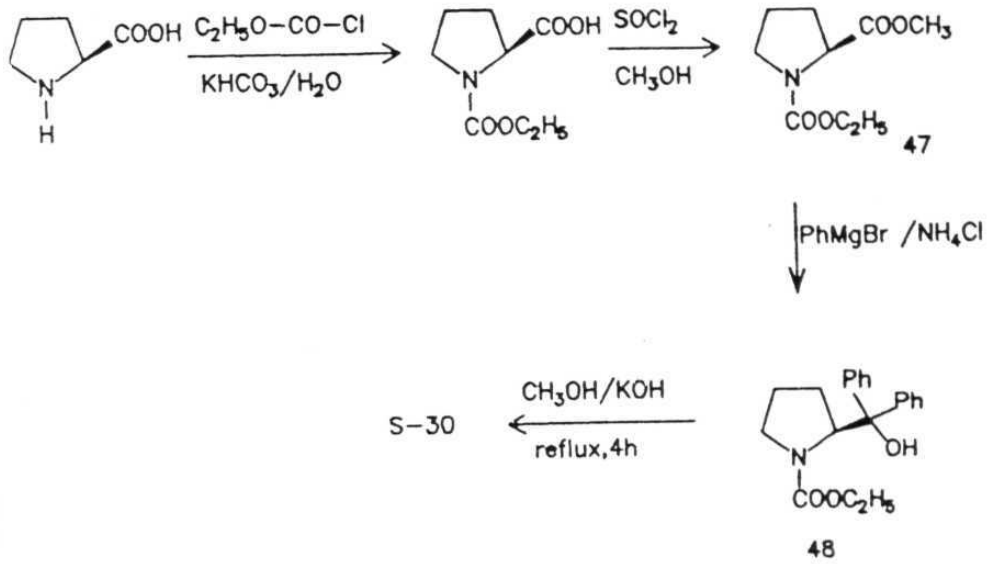
Scheme 31



It appeared desirable to develop more convenient methods for the

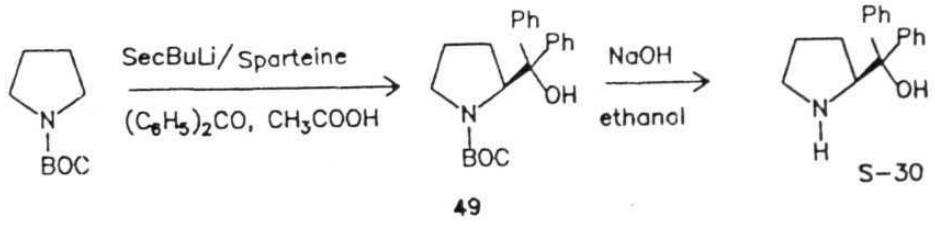
synthesis of this important chiral auxiliary.

Scheme 32



Following the sequence of reactions outlined in Scheme 32, the α,α-diphenylpyrrolidinemethanol S-(30) was obtained in 4 steps. In the first step, N-protection was carried out using ethyl chloroformate, a relatively less expensive reagent.[84] Recently, it has been reported that the N-t-butylcarbamate (49), prepared from pyrrolidine-N-butylcarbamate through asymmetric deprotonation using *sec*.BuLi/(-)sparteine followed by the addition of benzophenone can be readily deprotected by refluxing in $NaOH/C_2H_5OH$.[85]

Scheme 33

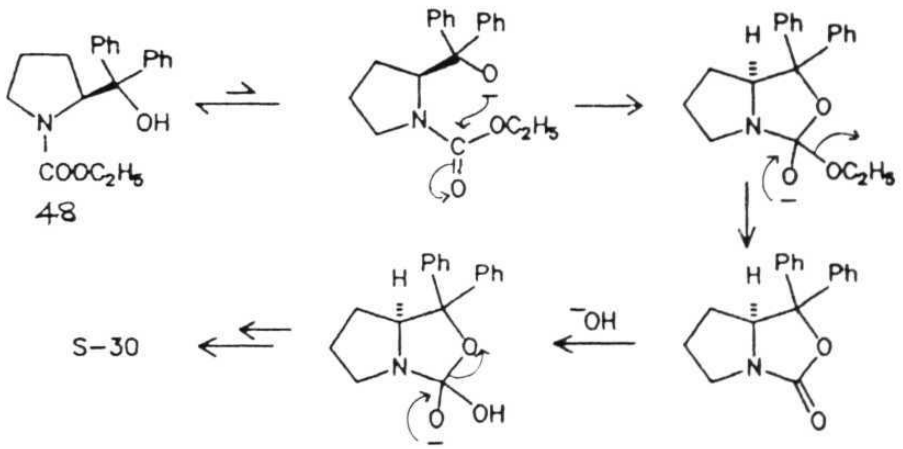


Since the alkaline hydrolysis of the carbamate would go through

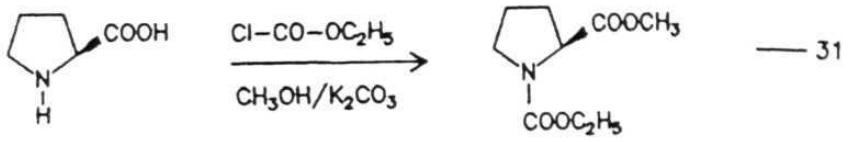
the corresponding tetrahedral intermediate, it should work equally well with the corresponding ethyl carbamate. Indeed, we have observed this in the case of 48. The ease of deprotection of the N-carbamate through alkaline hydrolysis may also have some interesting mechanistic implications. For example, it was found that attempted deprotection of the N-ethyl carbamate derivative of 3,4-diphenylpyrrolidine even under relatively harsh conditions, using 10M KOH in methanol and refluxing for 72h, gives only 30% of the secondary amine (39) besides unreacted carbamate (eq. 23, p-30).

Presumably, presence of the 2-substituent facilitates the hydrolysis which may be tentatively explained as outlined in Scheme 34.

Scheme 34



It was thought that the procedure could be further simplified if both N- and O-protections can be performed in a single pot operation. This objective has been attained by performing the reaction using two equivalents of ethyl chloroformate to one equivalent of L-proline in methanol using K_2CO_3 as base (eq. 31).

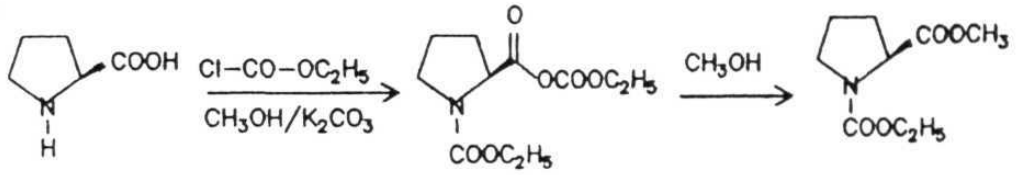


— 31

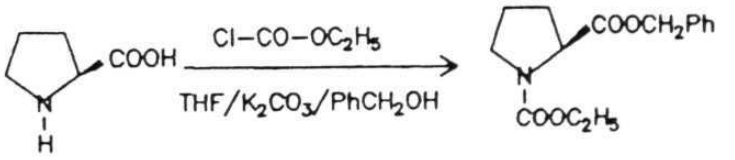
47

This single pot N- and O-protections would most probably go through the intermediacy of the anhydride shown in Scheme 35.

Scheme 35



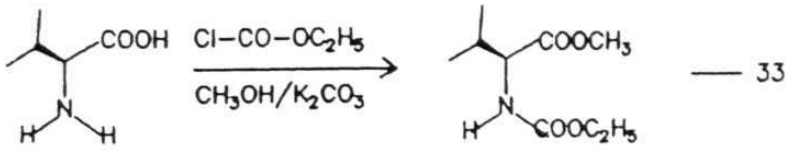
If this is the case, it should be possible to prepare different carboxylic esters using other alcohols. Indeed, it was observed that N-protected benzyl ester of L-proline can be prepared by adding two equivalents of ethyl chloroformate to L-proline, K_2CO_3 mixture in dry THF followed by benzyl alcohol at room temperature. After usual work-up, the N- and O-protected L-proline was isolated in 85% yield(eq. 32).



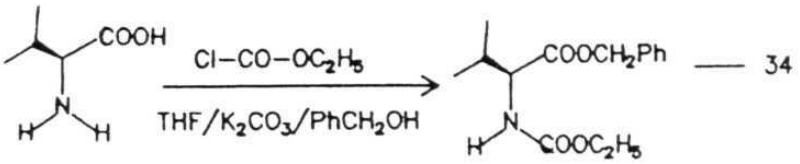
— 32

85%

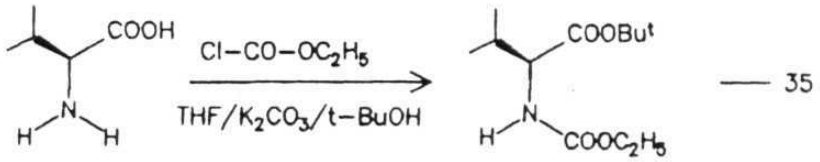
Methyl, benzyl, t-butyl esters of N-protected L-valine have been also prepared following this procedure (eq. 33-35) (see experimental section for details).



— 33

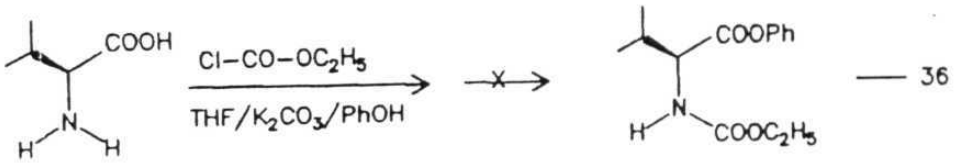


— 34



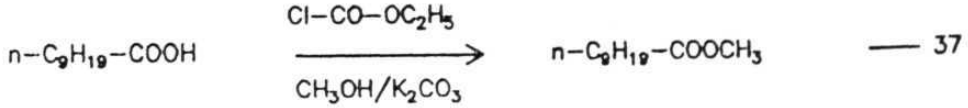
— 35

Attempted preparation of the phenolic ester using phenol in the place of alcohol, did not give the corresponding N- and O-protected amino acid (eq. 36).

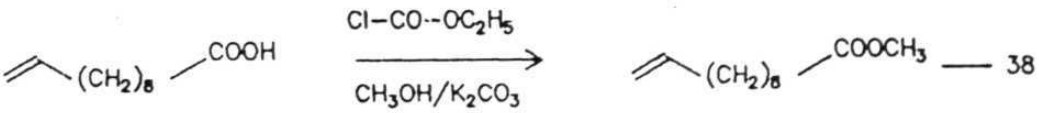


— 36

We have also found that the chloroformate/methanol combination can be also used for esterification of simple carboxylic acids. When capric acid and undecylenic acid were treated with ethyl chloroformate in the presence of K_2CO_3 in methanol, the corresponding methyl esters were obtained in good yields (eq. 37,38).



— 37

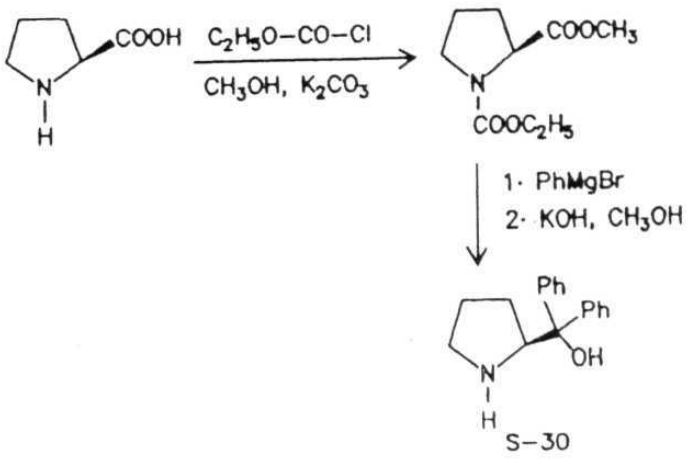


— 38

Incorporating this one pot preparation of N- and O-protections of

L-proline, the α,α-diphenyl-2-pyrrolidinemethanol was prepared by a procedure involving only two isolations (Scheme 36).

Scheme 36

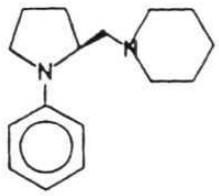


In the second step, the Grignard addition product (48 in Scheme 32) was directly hydrolysed without purification and the amino alcohol was purified by crystallization. This procedure is the simplest and convenient method for the preparation of S-(30).

Synthesis of diamine (46)

As mentioned in the introduction, Mukaiyama *et al* prepared a number of L-proline derived chiral diamines (18-22), which are useful as chiral catalysts in certain transformations.[39]

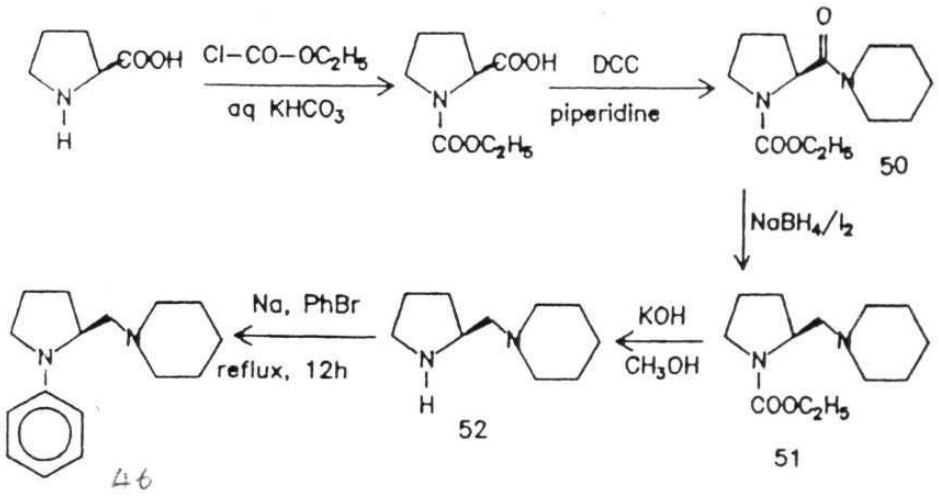
However, these chiral diamines would form strong complexes with BH_3 and hence are not useful for hydroboration studies. The corresponding N-phenyl compounds are expected to form relatively weak complexes with BH_3 due to the delocalization of nitrogen lone pair into the phenyl ring. Accordingly, we have decided to synthesize the diamine (46).



46

The synthesis of the diamine 46 was envisaged starting from L-proline (Scheme 37).

Scheme 37



The N-protected amide (50) was prepared following the procedure reported by Tomioka et al. The amide group in the N-carbamate amide (50) was selectively reduced by adding I_2 in THF to a mixture of (50) and $NaBH_4$ in dry THF at $10^{o}C$ and stirring for 24h at room temperature (for details of synthetic utility and selectivities of this reagent system see Chapter 3). The N-deprotection of (51) was achieved by refluxing it in KOH/CH_3OH for 12h. The secondary amine thus obtained (52) was subjected to N-phenylation to get 46. However, the general procedure (Table II) developed for N-phenylation of other secondary amines was found to give low yields in this case. The N-phenyl diamine was obtained in moderate yields under refluxing conditions

using sodium and bromobenzene in dry THF for 24h.

Conclusions

Convenient syntheses of optically active N-α-methylbenzyl-2,3-dihydrodinaphthazepine (4c), N-α-methylbenzyl-3,4-diphenylpyrrolidine (36) were developed. A new sequence of reactions was developed to convert these tertiary amines to secondary amines. However, the N-H-2,3-dihydrodinaphthazepine (4a) was obtained only in racemic form starting from the corresponding diastereomerically pure tertiary amine (4c). Following this method, diastereomerically pure N-α-methylbenzyl-3,4-diphenylpyrrolidine (36) was converted to the optically pure 3,4-diphenylpyrrolidine (39). A simple and convenient method for N-phenylation of primary and secondary amines utilizing stoichiometric amounts of amine was developed. This method should be advantageous over other methods in which the amine is used as solvent, especially when secondary amine is a solid or it is precious (eg. chiral).

Convenient methods have been also developed for the preparation of α,α-diphenyl-2-pyrrolidinemethanol and N-(2-methylpyrrolidyl)-N-phenylpiperidine through simplified esterification and hydrolysis procedures. These simplified procedures of preparation of α,α-diphenyl-2- pyrrolidinemethanol should make this important chiral auxiliary more attractive for synthetic applications. A one pot method for the N- and O-protections of amino acids has been developed. This method is also useful for esterification of carboxylic acids.

EXPERIMENTAL SECTION

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 spectrophotometer with polystyrene as reference. ^{1}H NMR were recorded on JEOL-FX-100 and BRUKER-AC-200 spectrometers and ^{13}C NMR were run on JEOL-FX-100 spectrometer. Spectra for all the samples were measured in deuterated chloroform using tetramethylsilane as internal standard. The chemical shifts (δ) are expressed in δ ppm down field from the signal for internal Me_2Si. Mass spectra were recorded on Finnigon MAT instrument (70 ev, 100 A, 180^{o}C).

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-methylbenzylamine, $[\alpha]_D^{25}$= +30.2^{o} (C10, EtOH) supplied by Fluka. The polarimeter was set to zero reading using the solvent used. Elemental analysis were performed on Perkin-Elmer elemental analyzer Model 240C. Catalytic hydrogenations were carried out on Parr hydrogenation apparatus in 250ml pressure bottle. Gas chromatography analysis was carried out on Chemito 2800 Model instrument equipped with a flame ionization detector on SE-30 or Carbowax column using nitrogen as carrier gas. Analytical thin layer chromatographic tests were carried out on glass plates (3x10 cm) coated with (250 mμ) Acmes' 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 Acmes' silica gel (100–200 mesh).

All the glassware were predried at 140°C for at least 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. In general, all the reactions were carried out in a 250 ml 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 isolated yields of material judged homogeneous by TLC and IR, NMR spectroscopy.

Benzene, toluene, THF, ether and diglyme were distilled over benzophenone–sodium. 2-Methylnaphthalene (98%), (+), (–)–α–methyl–benzylamine (99.8%) and ethyl phenylacetate (98%) supplied by Fluka, Switzerland were utilized. S-Proline (99%) supplied by SD fine chemicals India, ethylchloroformate (98%) supplied by Spectrochem (India) and lithium powder suspended in mineral oil (30%) supplied by Alpha (Danvers) were utilized. All amines were distilled over KOH prior to use. $NaBH_4$ (97%) supplied by Loba-Chemie (India) was used and was kept under N_2 in a desicator after opening the bottle.

Preparation of 1-bromo-2-methylnaphthalene:

1-Bromo-2-methylnaphthalene was prepared following a literature procedure[18]. In a flask containing 2-methylnaphthalene (14.2 g, 100 mmol) in CCl_4 (50 ml), a pinch of iron powder and a spec of iodine were added. The flask was cooled to $-10^{o}C$ using ice-salt mixture. To this bromine (24 g, 150 mmol) in CCl_4 (30 ml) was added slowly during 30 min. The reaction mixture was further stirred for 1h. 3N NaOH solution was added till the organic layer becomes colorless. The organic layer was separated and aqueous layer was further extracted with CCl_4 (2 x 15 ml). The combined organic extract was washed with brime and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was distilled under reduced pressure to obtain 1-bromo-2-methylnaphthalene.

Yield : 20.5 g (93%)

B.P. : $120^{o}C$ (5 mm) Lit.[86] $157^{o}C$ (15 tor)

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

^{1}H NMR (100 MHz,$CDCl_3$) : 2.4 (s, 3H), 7.2-7.9 (m, 6H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 21.2, 123.0, 125.8, 126.5, 127.0, 127.4, 127.8, 128.2, 130.2, 131.1, 136.0.

Coupling reaction of 1-bromo-2-methylnaphthalene:

In a oven dried two necked, septum RB flask fitted with a reflux condenser, magnesium turnings (1.25 g, 50 mmol) were taken and the flask was cooled to room temperature under nitrogen. Dry THF (30 ml) was added. 1-Bromo-2-methylnaphthalene (5.52 g, 25 mmol) in dry THF (20 ml) was added dropwise during 1h. The reaction was initiated by

adding 0.2 ml of 1,2-dibromoethane. The mixture was stirred further for 2h under nitrogen atmosphere.

In a separate two neck RB flask anhydrous $NiCl_2$ (26 mg, 0.32 mmol), PPh_3 (110 mg, 0.4 mmol) were taken and the Grignard reagent prepared above was added. 1-Bromo-2-methylnaphthalene (5.52, 25 mmol) in dry THF (20 ml) was added and the contents were stirred for 40h at room temperature. The reaction was quenched with water (10 ml) and 3N HCl (20 ml) was added. The mixture was extracted into ether (3 x 30 ml) and the combined organic extract was washed with water, brine and dried over anhydrous $MgSO_4$. The organic layer was concentrated and distilled under reduced pressure to separate 1-bromo-2-methyl-naphthalene and 2-methylnaphthalene. The residue from the distillation was subjected to column chromatographic separation over silica gel. The 2,2'-dimethyl-1-1'-binapthyl was eluted with hexane.

Yield : 5.07 g (72%)

IR (neat)ν_{max} : 3150, 3100, 2950, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 2.1 (s, 6H), 7.1-8.0 (m, 12H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 19.9, 125.1, 125.7, 126.3, 127.6, 128.7, 128.8, 132.4, 132.9, 134.2, 135.3.

Preparation of 2,2'-bis(bromomethyl)-1,1'-binaphthalene:

2,2'-Dimethyl-1,1'-binaphthalene (5.62 g, 20 mmol) was taken in dry CCl_4 (70 ml). N-Bromosuccinamide (3.9 g, 22 mmol) was added followed by benzoyl peroxide(100 mg). The mixture was refluxed for 4h. The reaction mixture was filtered in hot condition. The white precipitate was washed with hot CCl_4 (2 x 10 ml). The organic layer

was evaporated under reduced pressure. The residue was recrystallised form benzene/hexane (1:3) to obtain 2,2'-bis(bromomethyl)-1,1'-binaphthalene in pure form.

Yield : 6.6 g (75%)

M.P. : 146°C Lit.[87] 148-149°C

^{1}H NMR (100 MHz,$CDCl_3$) : 4.2 (s, 2H), 7.1-8.0 (m, 12H).

Cyclisation of 2,2'-bis(bromomethyl)-1,1'-binaphthalene with benzylamine:

2,2'-Bis(bromomethyl)-1,1'-binaphthalene (4.47 g, 10 mmol), was placed in dry toluene (80 ml). Freshly distilled benzylamine (1.07 g, 10 mmol) was added followed by K_2CO_3 (1.64 g, 20 mmol). The mixture was refluxed for 36h. Toluene was distilled out and the residue was column chromatographed on silica gel using hexane:ethyl acetate/95:5 as eluent, to obtain the cyclised amine.

Yield : 2.96 g (77%)

IR (neat)ν_{max} : 3100, 3050, 2850, 1600 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 1.9 (s, 2H), 3.2 (d, 2H), 3.8 (d, 2H), 7.7-7.9 (m, 17H) Spectrum Number 1

^{13}C NMR (25.0 MHz,$CDCl_3$): 55.1, 59.2, 125.6, 125.9, 127.4, 127.6, 128.0, 128.4, 128.6, 129.5, 131.6, 133.4, 133.5, 135.3, 135.9.

Mass m/e : 385 (M^+, 12%), 266 (base) Spectrum Number 2

Cyclisation of 2,2'-bis(bromomethyl)1,2'-binaphthalene with benzyl amine using NaH/DMF.

To a mixture of benzylamine (1.07 g, 10 mmol) in dry DMF and 60%

sodium hydride in mineral oil (1.75 g, 44 mmol), 2,2'-bis(bromomethyl)-1,1'-binaphthalene (4.4 g, 10 mmol) was added and the mixture was heated at 70°C for 3h. The reaction mixture was treated with aqueous sodium bicarbonate and extracted with ether (3 x 30 ml). The ether extracts were washed with water, brine and dried over anhydrous magnesium sulphate. It was concentrated and the residue was subjected to column chromatography using hexane:ethyl acetate/95:5 as eluent to obtain the cyclised tertiary amine.

Yield : 3.11 g (81%)

Spectral data showed 1:1 correspondence with that obtained earlier.

Cyclisation of 2,2'-bis(bromomethyl)-1-1'-binaphthalene with (+)-α-methylbenzylamine:

Sodium hydride (60% in mineral oil) (1.75 g, 44 mmol) was taken in dry DMF and (+)-α-methylbenzylamine (1.21 g, 10 mmol) was added and the mixture was heated at 70°C for 30 min. To this, 2,2'-bis (bromomethyl)-1,1'-binaphthalene (4.4 g, 10 mmol) in dry DMF (20 ml) was added and the mixture was further heated at 70°C for 2h. The reaction mixture was treated with aqueous sodium bicarbonate and extracted with ether (3 x 30 ml). Combined organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. It was concentrated and the residue was subjected to column chromatography on silica gel using hexane:ethyl acetate/95:5 as eluent to obtain diastereomeric mixture of cyclised amine (3.39g, 85%). The diastereomers were

separated by column chromatography using hexane:ethyl acetate/95:5 as eluent.

Fraction -1

Yield : 1.59 g (40%)

M.P. : 177°C (crystallised from hexane:ethyl acetate/85:15).

IR (KBr)ν_{max} : 3100, 3050, 2950, 1600 cm^{-1}

$[\alpha]_D^{25}$: -173°C (C1, $CHCl_3$)

^1H NMR (100 MHz,$CDCl_3$) : 1.3 (d, 3H), 3.1 (d, 2H), 3.5 (q, 1H), 3.8 (d, 2H), 7.1-8.0 (m, 17H) Spectrum Number 3

^{13}C NMR (25.0 MHz,$CDCl_3$): 22.7, 53.2, 62.6, 124.5, 125.8, 127.2, 127.4, 128.1, 128.3, 128.4, 128.8, 131.5, 133.2, 134.2, 135.3, 146.6. Spectrum Number 5

Mass (m/e) : 399 (21% M^+), 265 (100%) Spectrum Number 6

Analysis data :

	C	H	N
Calcd	90.18	6.31	3.50
Found	89.75	6.34	3.51

Fraction - 2:

Yield : 1.51 g (38%)

$[\alpha]_D^{25}$: +253° (C1, $CHCl_3$)

^1H NMR (100 MHz,$CDCl_3$) : 1.6 (d, 3H), 3.1 (d, 2H), 3.4 (q, 1H), 3.8 (d, 2H), 7.1-8.0 (m, 17H) Spectrum Number 4

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.4, 52,4, 57.4, 123.6, 125.4, 126.5, 126.9, 127.1, 127.3, 127.6, 127.9, 128.3, 132.2, 133.3, 127.5, 145.1.

Mass m/e : 399 (M^+, 22%), 264 (100%)

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Preparation of ethyl diphenylsuccinate.

Ethyl phenylacetate (35 g, 210 mmol) in dry ether (70 ml) and finely powdered sodium ethoxide obtained from (5.7 g) of sodium were taken in a two necked RB flask. A solution of iodine (27.3 g, 210 mmol) in dry ether (140 ml) was slowly added at $0^{o}C$ during 2h. The color of iodine disappeared instantly and a white precipitate formed. The contents were kept for 24h at room temperature. The precipitate was treated with water and sodium thiosulphate solution. Ether layer was separated and an yellowish precipitate left out was filtered off. The aqueous layer was extracted with ether (2 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous Na_2SO_4. Solvent was evaporated to get a mixture of ethyl-α-diphenylsuccinate and unreacted ethyl phenylacetate which was separated by distillation under reduced pressure. The ethyl-α-diphenylsuccinate was recrystallised from hexane.

Yield : 9 g (25%)

M.P. : $79^{o}C$ Lit.[64] $82-83.5^{o}C$

IR (KBr) ν_{max} : 1720, 1600 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 0.9 (t, 6H), 3.9 (m, 4H), 4.4 (s, 2H), 7.2-7.6 (m, 10H).

Hydrolysis of ethyl-α-diphenylsuccinate:

Ethyl-α-diphenylsuccinate (6.5 g, 20 mmol) was taken in aqueous ethanol (water:ethanol/1:1) and excess KOH (5.6 g) was added. The reaction mixture was refluxed for 6h. The contents were cooled and was acidified with 3N HCl. The α-diphenylsuccinic acid was separated

by filtration and dried.

Yield : 5 g (92%)

M.P. : 220°C Lit[64] 220–221°C

IR (neat)ν_{max} : 1700, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 4.4 (s, 2H), 7.2–7.6 (m, 10H), 10.2 (bs, 2H).

Cyclisation of α–diphenylsuccinic acid with (+)–α–methylbenzylamine:

A mixture of α–diphenylsuccinic acid (5.4 g, 20 mmol) and (+)–α–methylbenzylamine (4.4 g, 20 mmol) was heated under neat condition to 220°C for 30 min. It was cooled and the yellow cake formed was dissolved in chloroform. The chloroform layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent gave yellow solid which was purified by column chromatography over silica gel using hexane:ethyl acetate/90:10 as eluent.

Yield : 6.3 g (89%)

IR (KBr) ν_{max} : 1680, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.9 (2d, 3H), 4 (d, 2H), 5.5 (m, 1H), 7.0–7.6 (m, 15H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 15.0, 15.5, 49.4, 49.7, 53.8, 126.4, 126.7, 127.3, 128.0, 135.6, 138.2, 138.4, 175.2. (more signals due to the presence of diastereomers).

Reduction of the cyclic imide(37).

The cyclic imide (7.1 g, 20 mmol) was placed in dry THF (40 ml)

in a two necked R.B. flask. B_2H_6 (80 mmol) generated using the procedure mentioned earlier was passed through the solution during 6h at 10^oC. The gas inlet was replaced with a glass stopper and the reaction mixture was refluxed for 12h. The reaction mixture was cooled and BF_3:OEt_2 was added to liberate complexed borane. The contents were treated with 3N NaOH solution, organic layer separated and aqueous layer was extracted with ether (2 x 20 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent gave a diastereomeric mixture of amines which were separated by column chromatography on silica gel using hexane as eluent.

Yield : 4.9 g (75%)

The diastereomer eluted first was obtained in pure form after repeated column chromatography separation using hexane as eluent.

Yield : 0.9 g

$[\alpha]_D^{20}$: $+72^o$ (Cl, $CHCl_3$)

IR (neat)ν_{max} : 3050, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.7 (d, 3H), 3.0-3.7 (m, 7H), 7.3-7.7 (m, 15H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 23.4, 53.1, 61.6, 66.1, 126.6, 127.3, 127.4, 127.8, 128.7, 144.1, 145.6.

Spectrum Number 7

Preparation of 2,3-diphenylsuccinonitrile:

Sodium cyanide (1.11 g, 2.25 ml) was taken in 600 ml methanol and water mixture (5:1). The mixture was heated to gentle reflux and benzyl chloride (4.0 g, 0.35 ml) was added dropwise during 15 min.

with vigorous stirring. A mixture of benzyl chloride (90 g, 0.79 ml) and benzaldehyde (53 g, 10.5 ml) was added during 35 min. at gentle reflux with vigorous stirring. The reaction mixture was further refluxed for one hour, allowed to cool and was filtered. The solid was washed with 70% methanol, water; 70% methanol, ether and then air dried. It was recrystallised from acetic acid to obtain 2,3-diphenyl-succinonitrile.

Yield : 95 g (82%)

M.P. : 235°C Lit[65] 235-236°C

IR (KBr)ν_{max} : 3100, 2250, 1600 cm^{-1}

Hydrolysis of 2,3-diphenylsuccinonitrile:

A reported procedure for the hydrolysis of benzyl cyanide was adopted here.[88] In a RB flask fitted with reflux condenser, water (100 ml) was taken and concentrated sulfuric acid (100 ml) was added slowly and carefully followed by glacial acetic acid (100 ml). To this 2,3-diphenylsuccinonitrile (50 g) was added and the mixture was refluxed for 24h. The reaction mixture was poured into 500 ml of water and the crude 2,3-diphenylsuccinic acid was filtered. It was recrystallised from acetic acid.

Yield : 48.8 g (84%)

M.P. : 222°C Lit.[64] 220-221°C

Condensation of α-diphenylsuccinic acid with (-)-α-methylbenzylamine:

Diphenylsuccinic acid (5.29 g, 20 mmol) and (-)-α-methylbenzyl-amine (2.42 g, 20 mmol) were heated to 220°C under neat conditions for

one hour. The mixture was cooled to room temperature to get an yellow cake. It was dissolved in chloroform. This solution was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent gave crude cyclic imide (37) which was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent.

Yield : 3.26 g (92%)

IR (KBr) ν_{max} : 3100, 3000, 1680, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.8 (2d, 3H), 4.1 (d, 2H), 5.5 (m, 1H), 7.0-7.6 (m, 15H).

Reduction of cyclic imide (37).

The cyclic imide (7.1 g, 20 mmol) was taken in dry THF in a two-necked RB flask. $NaBH_4$ (108 mmol, 4 g) was added. I_2 (12 g, 48 mmol) in THF was added slowly during 2h. under nitrogen atmosphere. The mixture was refluxed for 6h. The reaction was quenched with water. Organic layer was separated and washed with 3N NaOH (2 x 10 ml), brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was taken in dry ether, BF_3:OEt_2 was added to liberate the complexed borane. 3N NaOH solution was added to this and the amine was extracted in to ether. The combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude amine which was purified by column chromatography on silica gel using hexane as eluent.

Yield : 5.1 (78%)

This diastereomeric mixture was separated by repeated column chromatography using hexane eluent. The amine eluted first was

obtained in pure form. The other diastereomer contained some amount of first diastereomer.

Yield : 1.0 g

$[\alpha]_D^{25}$: -80^{o} (Cl, $CHCl)_3$

Selective debenzylation of 3^{o} amines to 2^{o} amines

Preparation of N,N-diethylaniline $-BI_3$ complex:

N,N-Diethylaniline-BI_3 complex was prepared following the procedure reported earlier from this laboratory.[72] N,N-Diethylaniline-BH_3 complex (5 mmol) in dry benzene (20 ml) was prepared following the literature procedure.[89] I_2 (7.5 mmol) in dry benzene (20 ml) was added through a pressure equalizer during 15 min at room temperature under nitrogen atmosphere. The reaction mixture was further stirred for 8h at room temperature.

N-Debenzylation of (+)-α-methylbenzyl-3,4-diphenylpyrrolidine:

Diastereomerically pure (+)-N-α-methylbenzyl-3,4-diphenylpyrrolidine (1.63 g, 5 mmol) in dry dichloroethane (20 ml) was taken in a two-necked RB flask. Ethyl chloroformate (0.66 g, 5 mmol) was added under nitrogen atmosphere and the mixture was refluxed for 4h. Solvent was removed under reduced pressure to yield essentially pure N-ethyl carbamate derivative of 3,4-diphenylpyrrolidine.

Yield : 1.4 g (95%)

IR (neat)ν_{max} : 1680, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.2 (t, 3H), 3.4-4.2 (m, 8H), 7.1 (m, 10H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.6, 50.4, 51.3, 53.1, 60.9, 126.9, 127.4, 128.5, 139.2, 154.9.

N,N-Diethylaniline–BI_3 complex (5 mmol) in benzene was prepared as outlined earlier. N-Ethyl carbamate derivative of 3,4-diphenylpyrrolidine (1.44 g, 5 mmol) in dry benzene (20 ml) was added using a pressure equalizer during 15 min. under nitrogen atmosphere. The contents were further stirred for 8h at room temperature. The reaction was quenched with water and neutralized with 3N NaOH solution. The organic layer was separated and washed with 3N NaOH solution (3 x 10 ml), brine and dried over anhydrous $MgSO_4$. Solvent was evaporated to yield crude secondary amine which was separated from N,N-diethylaniline using column chromatography on alumina (neutral). Hexane eluted N,N-diethylaniline and hexane:ethyl acetate/80:20 eluted 3,4-diphenylpyrrolidine.

Yield : 0.95 g (89%)

IR (neat)ν_{max} : 3345, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 2.3(s, 1H), 2.8-3.4(m, 6H), 6.9-7.1(m, 10H)

$[\alpha]_D^{20}$= -222^o (C1, $CHCl_3$) Lit.[90] $[\alpha]_D^{20}$ = -226^o ($CHCl_3$)

N-Debenzylation of N-benzylpiperidine:

N-Benzylpiperidine (0.87 g, 5 mmol) in dichloroethane (20 ml) was taken in two-necked RB flask. Ethyl chloroformate (0.60 g, 6 mmol) was added and the mixture was refluxed for 12h. The solvent was removed under reduced pressure to yield essentially pure N-ethyl carbamate derivative of piperidine.

Yield : 0.75 g (95%)

IR (neat)ν_{max} : 2900, 2800, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.3 (t, 3H), 1.6 (m, 6H), 3.5 (m, 4H), 4.2 (m, 2H).

N,N-Diethylaniline-BI_3 complex (5 mmol) in benzene was prepared as mentioned earlier. Piperidine-N-ethyl carbamate (0.78 g, 5 mmol) in benzene (20 ml) was added slowly during 15 min under nitrogen atmosphere. The contents were further stirred for 8h at room temperature. The reaction was quenched with water and neutralized using 3N NaOH solution. The organic layer was separated and washed with 3N NaOH solution (3 x 10 ml), brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded crude secondary amine which was purified by distillation.

Yield : 80% (0.34 g)

B.P. : 105°C (760 mm) Lit.[91] 106°C (760 mn)

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

Following this procedure N-benzyl-3,4-diphenyl pyrrolidine was converted to 3,4-diphenylpyrrolidine.

Yield : 89% (0.99 g)

IR (neat)ν_{max} : 3350, 3030, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 2.2 (s, 1H), 2.9-3.5 (m, 6H), 7.0-7.2 (m, 10H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 53.4, 54.5, 126.8, 127.6, 129.7, 141.0.

N-Debenzylation of N-α-methylbenzyl-3,5-dihydrodinaphthazepine:

Diastereomerically pure N-α-methylbenzyl-3,5-dihydrodinaphthazepine (1.99 g, 5 mmol) in dry dichloroethane was taken in a two necked R.B. flask. Ethyl chloroformate (0.66 g, 6 mmol) was added at room temperature and refluxed for 8h. The solvent was removed under reduced pressure to yield essentially pure N-ethyl carbamate derivative.

Yield : 96% (1.76 g)

IR (neat)ν_{max} : 3100, 3050, 2900, 1640, 1610 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 1.2 (t, 3H), 3.6 (d, 2H), 4.1 (m, 2H), 4.9 (m, 2H), 7.0–7.9 (m, 12H). Spectrum Number 8

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.4, 47.5, 61.2, 125.6, 125.8, 127.2, 128.1, 129.0, 131.2, 132.2, 1331, 134.8, 154.8. Spectrum Number 9

Mass (m/e) : 367 (M^+, 70%), 266 (100%) Spectrum Number 10

N,N-Diethylaniline–BI_3 complex (5 mmol) in benzene was prepared as outlined earlier. N-Ethyl carbamate derivative of 3,5-dihydrodinaphthazepine (1.83 g, 5 mmol) in benzene (20 ml) was added slowly during 15 min under nitrogen atmosphere at room temperature. The contents were further stirred for 8h at the same temperature. The reaction was quenched with water and neutralized using 3N NaOH solution. The organic layer was separated and washed with 3N NaOH (3 x 10 ml), brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude secondary amine which was separated from N,N-diethylaniline using column chromatography on alumina (neutral). Hexane eluted N,N-diethylaniline, hexane:ethyl acetate /80:20 eluted

3,4-dihydrodinaphthazepine.

Yield : 84% (1.23 g)

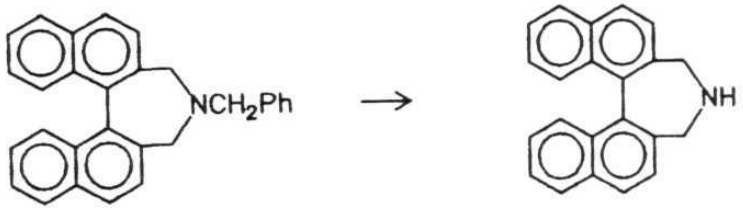
M.P. : 146-147.5^{O}C Lit.[14] 147-149^{O}C

IR (neat)ν_{max} : 3350, 3100, 3050, 1610 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 2.1 (bs, 1H), 3.1-3.8 (m, 4H), 7.2-8.1 (m, 12H). Spectrum Number 11

This compound showed no optical rotation.

Following the above procedure, the racemic N-benzyl-3,5-dihydrodinaphthazepene was converted to 3,5-dihydrodinapthazepene.



Yield : 85% (1.25 g)

M.P. : 146^{O}C Lit.[14] 147-149^{O}C

Spectral data obtained showed 1:1 correspondence with that of sample obtained earlier.

$(PhCH_2)_2NCH(CH_3)Ph \longrightarrow (PhCH_2)_2NH$

The procedure followed was similar to above experiments except for the change that 20h refluxing time was required for the formation N-ethyl carbamate derivative.

Yield : 0.81 g (87%).

IR (neat)ν_{max} : 3350, 3100, 1600 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 3.8 (s, 4H), 4.8 (bs, 1H), 7.3 (m, 10H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 46.2, 126.7, 127.5, 128.5, 147.4.

N-Phenylation of Amines:

N-Phenylation of pyrrolidine:

To a suspension lithium powder (0.3 g, 30 mmol) in hexane (20 ml), pyrrolidine (0.71 g, 10 mmol) was injected under dry nitrogen atmosphere. Bromobenzene (4.71 g, 30 mmol) was added slowly through a pressure equalizer during 15 min at room temperature. The contents were further stirred at room temperature for 12h. The reaction was carefully quenched with methanol (5 ml). The mixture was acidified with 20% HCl (10 ml) and the aqueous layer was separated. The amine was regenerated by the addition of aqueous KOH and extracted into ether (3 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded crude N-phenylpyrrolidine which was further purified on silica gel column using hexane as eluent.

Yield : 1.2 g (82%)

IR (neat)ν_{max} : 3100, 2800, 1600 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 2.0 (m, 4H), 3.3 (m, 4H), 6.6-7.3 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.2, 47.3, 111.6, 115.3, 129.0, 147.9.

The above procedure was adopted for several other amines.

$(i\text{-}C_2H_5)_2NH \longrightarrow (i\text{-}C_3H_7)_2NPh$

Yield : 1.3 g (73%)

B.P. : 93°C (10 mm) Lit.[81] 95-96°C

IR (neat)ν_{max} : 3100, 2900, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.2 (d, 12H), 3.7 (m, 2H), 6.8-7.3 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 21.3, 47.4, 118.4, 119.7, 128.5, 148.2.

Yield : 1.28 g (79%)

IR (neat)ν_{max} : 3100, 2800, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 3.2 (t, 4H), 3.9 (5, 4H), 6.9-7.4 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 49.0, 66.7, 115.5, 119.9, 129.1, 151.2.

Spectrum Number 12

N-Phenylation of N,N-diisopropylamine:

Lithium powder suspension (0.3 g, 30 mmol) in dry THF was taken in a two-necked RB flask. Diisopropylamine (1.01 g, 10 mmol) was added slowly during 5 min under nitrogen atmosphere. Bromobenzene (4.7 g, 30 mmol) in dry THF was added slowly through a pressure equalizer during 15 min under nitrogen atmosphere. A vigorous reaction was observed. The contents were further stirred for 6h at room temperature. The reaction was quenched carefully with methanol (5 ml). The reaction mixture was acidified with 20% HCl (10 ml) and the aqueous layer was separated. The amine was regenerated by the

addition of aqueous KOH (3N, 20 ml) and extracted into ether (3 x 20 ml). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solution afforded crude N,N-diisopropylaniline which was further purified by column chromatography over silica gel using hexane as eluent.

Yield : 1.48 g (78%)

B.P. : 93°C (10 mm) Lit.[81] 95-96° (11 mm)

^1H NMR (100 MHz,$CDCl_3$) : 1.2 (d, 12H), 3.7 (m, 2H), 6.8-7.3 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 21.3, 47.4, 118.4, 119.7, 128.5, 148.2.

This procedure was found to be generally applicable. Several other N-phenylamines were also prepared following this procedure.

$(C_6H_5)_2NH \longrightarrow (C_6H_5)_2NPh$

Yield : 1.22 g (82%)

B.P. : 75°C (5 mm) Lit.[79] 70°C (3 mm)

IR (neat)ν_{max} : 3050, 1605 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.1 (t, 6H), 3.3 (m, 4H), 6.6 (m, 2H), 7.2 (m, 3H).

Yield : 1.25 g (86%)

IR (neat)ν_{max} : 3050, 2800, 1600 cm^{-1}

Spectral data showed 1:1 correspondence with that of the compound obtained earlier.

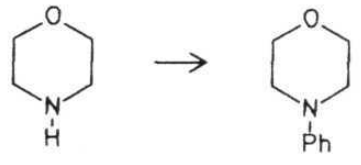
Yield : 1.28 g (80%)

B.P. : 96°C (5 mm) Lit.[79] 95-98° (5 mm)

IR (neat)ν_{max} : 3050, 2850, 1600 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.6 (m, 6H), 3.1 (m, 4H), 6.7-7.3 (m, 5H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 24.4, 25.9, 50.8, 116.7, 119.3, 129.2, 152.5.

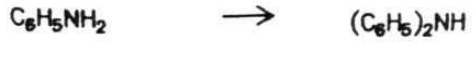


Yield : 1.32 g (81%)

IR (neat)ν_{max} : 3100, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 3.2 (t, 4H), 3.9 (t, 4H), 6.9-7.4 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 49.0, 66.7, 115.5, 119.9, 129.1, 151.2.



Yield : 1.1 g (65%).

M.P. : 50°C (5 mm) Lit.[82] 51°C

IR (neat)ν_{max} : 3350, 3100, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 3.6 (bs, 1H), 6.7-7.3 (m, 10H).

$t\text{-}C_4H_9NH_2 \longrightarrow t\text{-}C_4H_9NHPh$

Yield : 1.2 g (80%)

B.P. : 90°C (10 mm) Lit.[91] 208-211°C (760 mm)

IR (neat)ν_{max} : 3350, 3050, 1605 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.4 (s, 9H), 5.6 (bs, 1H), 6.7-7.3 (m, 5H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 29.9, 51.2, 117.4, 119.3, 128.8, 146.5.

$C_6H_5CH(CH_3)NH_2$ (±) $\longrightarrow$ $C_6H_5CH(CH_3)NHPh$ (±)

Yield : 1.4 g (71%)

IR (neat)ν_{max} : 3350, 3100, 3050, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.5 (d, 3H), 4.01 (s, 1H), 4.5 (q, 1H), 6.5-7.5 (m, 10H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 24.6, 53.1, 113.3, 117.1, 125.8, 126.7, 128.5, 129.0, 145.1, 147.3. Spectrum Number 13

Analysis data : Calcd C : 85.24; H 7.66; N 7.10

Found 85.39 7.7 7.15

$C_6H_5CH(CH_3)NH_2$ S(−) $\longrightarrow$ $C_6H_5CH(CH_3)NHPh$ S(+)

Yield : 1.38 g (70%)

$[\alpha]_D^{24}$ = +17° (1, CH_3OH) Lit.[77] $[\alpha]_{578}^{24}$ = +18.5° (CH_3OH)

$C_6H_5CH(CH_3)NH_2$ R(+) $\longrightarrow$ $C_6H_5CH(CH_3)NHPh$ R(−)

Yield : 1.38 g (70%)

$[\alpha]_D^{24} = -16^o$ (C1, CH_3OH); Lit.[77] $[\alpha]_{578}^{24} = -17.7^o$ (C1, CH_3OH)

N-Phenylation of (4S, 5S)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane

Lithium powder suspension (0.3 g, 30 mmol) in dry THF (20 ml) was taken in a two necked RB flask. Amine (2.07g, 10 mmol) in dry THF (10 ml) was added slowly through a cannula under nitrogen pressure and bromobenzene (4.7 g, 30 mmol) in THF (10 ml) was added slowly during 15 min using a pressure equalizer under nitrogen atmosphere. The reaction mixture was further stirred for 6h at room temperature. The reaction was carefully quenched with methanol (5 ml) followed by water (10 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 x 20 ml). Combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded crude N-phenyl secondary amine which was further purified by column chromatography on silica gel using hexane:ethyl acetate/95:5 as eluent.

Yield : 2 g (72%)

^1H NMR (100 MHz,$CDCl_3$) : 1.6 (s, 6H), 3.5 (br s, 1H), 3.9-4.2 (m, 3H), 5.2 (d, 1H), 6.4-7.4 (m, 10H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 18.1, 29.2, 50.4, 63.1, 72.5, 99.0, 112.9, 116.7, 125.4, 127.7, 128.3, 128.6, 138.6, 146.7. Spectrum Number 14

Analysis data : Calcd. C : 76.29; H 7.47; N 4.94

: Found C : 75.83; H 7.40; N 5.07

N-Arylation of pyrrolidine with 1-bromonaphthalene:

Lithium powder suspension (0.3 g, 30 mmol), in dry THF (20 ml) was taken in a two-necked RB flask. Pyrrolidine (0.71 g, 10 mmol) in THF (10 ml) was added using cannula under nitrogen atmosphere. 1-Bromonaphthalene (6.24 g, 30 mmol) in THF (10 ml) was added slowly during 15 min using pressure equalizer. The reaction mixture was further stirred for 6h at room temperature. The reaction was quenched carefully with methanol (5 ml) followed by the addition of water (10 ml). The reaction mixture was acidified with 3N HCl (15 ml). The aqueous layer was separated and amine was regenerated by adding 3N KOH solution (20 ml). The amine was extracted into ether (3 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded N-arylpyrrolidine which was further purified by passing through silica gel column using hexane as eluent.

Yield : 1.69 g (86%)

IR (neat)ν_{max} : 3050, 1620, 1590 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.4 (m, 12H), 3.4 (m, 2H), 6.9-7.8 (m, 6H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 24.9, 25.6, 47.9, 52.9, 113.2, 122.1, 122.7, 125.9, 126.0, 127.0, 127.5, 127.8, 135.2, 145.8.

N-Phenylation of pyrrolidine:

Fine pieces of sodium (0.90 mg, 30 mmol) in dry THF (20 ml) were taken in a two necked RB flask. Pyrrolidine (0.71 g, 10 mmol) in dry THF (10 ml) was added using a cannula under nitrogen atmosphere at room temperature. Bromobenzene (4.7 g, 30 mmol) in dry THF was added using pressure equalizer during 15 min under nitrogen atmosphere. The reaction mixture was further stirred for 24h at room temperature. The reaction mixture was quenched with methanol (5 ml) followed by water (10 ml). The reaction mixture was acidified with 3N HCl (15 ml). The aqueous layer was separated and the amine was regenerated by the addition of 3N KOH (20 ml). It was extracted with ether (3 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded crude N-phenyl-pyrrolidine which was further purified by column chromatography on silica gel using hexane as eluent.

Yield : 1.18 g(80%)

Spectral data of this compound showed 1:1 correspondence with the data of the compound obtained earlier.

The above procedure was followed for the N-phenylation of a few other amines.

Yield : 1.17 g (73%)

$Et_2NH \longrightarrow Et_2NPh$

Yield : 1.1 g (74%)

$(i\text{-}C_3H_7)_2NH \longrightarrow (i\text{-}C_3H_7)_2NPh$

Yield : 1.28 g (72%)

Spectral data of all these compounds showed 1:1 correspondence with the data of samples obtained earlier.

Attempted N-arylation of pyrrolidine using 2-methyl-1-bromo-naphthalene.

Lithium powder suspension (0.3 g, 30 mmol) in dry THF (20 ml) was taken in a two necked RB flask. Pyrrolidine (0.71 g, 10 mmol) in THF (10 ml) was added using a cannula under nitrogen atmosphere. 1-Bromo-2-methylnaphthalene (6.66 g, 30 mmol) in THF (10 ml) was added slowly during 15 min using pressure equalizer. The reaction mixture was further stirred at room temperature for 6h. The reaction was quenched with methanol (5 ml) followed by water (10 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 ml). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded 2-methylnaphthalene as major product besides 2-methyl-1-bromo-naphthalene. No N-arylation product was formed.

Yield : 80% (3.3 g)

IR (neat)ν_{max} : 3100,3050, 2900, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.4 (s, 3H), 7.1-7.7 (m, 7H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 21.2, 124.6, 125.9, 126.9, 127.4, 127.8, 131.5, 133.5, 135.1.

Preparation of α,α–diphenylpyrrolidinemethanol:

(a) Preparation of S–proline–N–ethyl carbamate:

S–Proline (1.15 g, 10 mmol) in water (20 ml) was taken in a RB flask. $NaHCO_3$ (0.84 g, 10 mmol) was added followed by ethyl chloroformate (1.1 g, 10 mmol) and the reaction mixture was stirred for 12h at room temperature. It was extracted with ethyl acetate (3 x 15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded essentially pure proline–N–ethyl carbamate.

Yield : 1.76 g (96%)

IR (neat)ν_{max} : 1720, 1670 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.2 (t, 3H), 2.1 (m, 4H), 3.5 (m, 2H), 4.1 (m, 2H), 4.4 (t, 1H), 9.0 (bs, 1H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.0, 20.2, 23.0, 23.7, 29.3, 30.3, 46.1, 46.3, 58.0, 61.3, 154.9, 155.5, 175.8, 176.2 (more number of signals due to the slower inversion of the nitrogen).

Preparation of S–proline–N–ethyl carbamate methyl ester (47).

S–Proline–N–ethyl carbamate (1.87 g, 10 mmol) in dry methanol (20 ml) was taken in a two–necked RB flask. Thionyl chloride (17.7 g, 15 mmol) was added slowly during 10 min at 0^oC. The reaction mixture was

further stirred for 8h at room temperature. Evaporation of the solvent under reduced pressure gave S-proline-N-ethyl carbamate methyl ester.

Yield : 1.9 g (95%)

IR (neat)ν_{max} : 1740, 1700 cm^{-1}

^{1}H NMR (100 MHz,$CDCl_3$) : 1.2 (t, 3H), 2.0 (m, 4H), 3.5 (m, 2H), 3.7 (s, 3H), 4.1 (br, 3H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.1, 22.9, 23.7, 29.3, 30.3, 45.5, 46.2, 51.5, 58.5, 58.3, 60.6, 154.2 153.5 172.4 172.9

Spectrum Number 15

Grignard reaction of proline-n-ethyl carbamate methyl ester:

Magnesium turnings (1.94 g, 80 mmol) in dry THF (30 ml) were taken in a two-necked RB flask. Freshly distilled bromobenzene (6.28 g, 40 mmol) in dry THF (15 ml) was added drop wise through a pressure equalizer during 15 min. The contents were further stirred for 30 min.

In another two-necked RB flask proline-N-ethyl carbamate methyl ester (2.01 g, 10 mmol) in dry THF (20 ml) was taken and cooled to $0^{o}C$, under nitrogen atmosphere. Phenyl magnesium bromide prepared as above was added through a cannula under nitrogen atmosphere. The contents were further stirred for 3h at $0^{o}C$. The reaction was quenched with saturated ammonium chloride solution (20 ml). The supernatant liquid was decanted leaving behind white precipitate. The precipitate was stirred with chloroform (2 x 10 ml) and the organic extract was collected. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave

crude product which was further purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent.

Yield : 2.53 g (78%)

IR (neat)ν_{max} : 3375, 1680 cm^{-1}

^{1}H NMR (200 MHz,$CDCl_3$) : 1.2 (t, 3H), 1.6 (s, 1H), 2.0 (m, 2H), 3.0 (m, 2H), 3.4 (m, 2H), 4.1 (m, 2H), 5.0 (m, 1H), 7.2-7.6 (m, 10H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.4, 22.7, 29.4, 47.6, 61.7, 65.8, 81.4, 127.1, 127.4, 127.6, 127.8, 128.0, 143.7, 146.3, 158.2. Spectrum Number 16

Analytical data : Calcd. C : 73.82, H : 7.12; N : 4.30

Found 73.58, 6.99; 4.35.

N-Deprotection of N-ethylcarbamate of α,α-diphenylpyrrolinemethanol (48).

N-Ethylcarbamato-α,α-diphenylpyrrolidinemethanol in dry methanol (20 ml) was taken in a RB flask. To this KOH (5.6 g) was added and the reaction mixture was refluxed for 4h. Methanol was distilled off and water (15 ml) was added. The contents were extracted with chloroform (3 x 20 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded α,α-diphenylpyrrolidinemethanol as a gummy liquid which upon standing crystallises.

Yield : 2.3 g (2%)

M.P. : 74°C Lit.[54] 74-74.8°C

$[\alpha]_D^{20} = -68^{\circ}$ (3, CH_3OH) Lit.[54] $[\alpha]_D^{20} = -68.1^{\circ}$ (C3.17, CH_3OH)

IR (neat)ν_{max} : 3350, 1600 cm^{-1}

^{1}H NMR (200 MHz,$CDCl_3$) : 1.25–1.7 (m, 5H), 2.9 (m, 2H), 4.2 (t, 1H), 4.8 (s, 1H), 7.1–7.6 (m, 10H). Spectrum Number 17

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.4, 26.2, 46.7, 64.5, 77.1, 125.6, 126.0, 126.4, 126.5, 128.0, 128.7, 145.6, 148.3.

Spectrum Number 18

Preparation of S-proline–N-ethyl carbamate methyl ester (47). Single pot reaction.

S-Proline (1.15 g, 10 mmol) in dry methanol (20 ml) was taken in a two necked RB flask. Anhydrous K_2CO_3 (1.32 g, 10 mmol) was added followed by the addition of ethyl chloroformate (2.5 g, 22 mmol) during 5 min at 25°C. The reaction mixture was further stirred for 12h at 25°C. Methanol was evaporated and distilled water (10 ml) was added. The contents were extracted with chloroform (3 x 15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded essentially pure N,O–protected S-proline.

Yield : 1.90 (95%)

Data of this compound showed 1:1 correspondence with that of earlier which was obtained via two step process.

Preparation of α,α–diphenyl-2-pyrrolidinemethanol S-(30).

S-Proline–N-ethyl carbamate methyl ester (2.01 g, 10 mmol) in dry THF (20 ml) was taken in a two-necked RB flask. The flask was cooled to 0°C under nitrogen atmosphere. Phenylmagnesium bromide (40 mmol), prepared as outlined earlier was added through a cannula under nitrogen atmosphere. The reaction mixture was further stirred for 3h

at $0^{o}C$. The reaction was quenched with saturated ammonium chloride solution (20 ml). The supernatant liquid was collected leaving behind a white precipitate. The white precipitate was stirred with chloroform (2 x 15 ml) and the organic extracts were collected. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was taken in dry methanol (20 ml) and KOH (5.6 g) was added. The mixture was refluxed for 4h. Methanol was distilled off and water (10 ml) was added. The contents were extracted with chloroform (3 x 15 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to yield a gummy product which crystallised on standing. This is further purified by recrystallising from hexane.

Yield : 1.83 g (72.5%)

Physical constants and spectral data showed 1:1 correspondence with that of a sample obtained earlier.

Preparation of S-valine N-ethyl carbamate methyl ester:

S-Valine (1.17 g, 10 mmol) in dry methanol (20 ml) was taken in two-necked RB flask. Anhydrous K_2CO_3 (1.32 g, 10 mmol) was added followed by ethyl chloroformate (2.5 g, 22 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 12h at room temperature. Methanol was evaporated and distilled water (10 ml) was added. The contents were extracted with chloroform (3 x 15 ml). The combined organic extract was washed with brine and dried over

anhydrous $MgSO_4$. Evaporation of solvent afforded essentially pure N- and O-protected S-valine.

Yield : 1.84 g (91%)

IR (neat)ν_{max} : 3350, 2910, 2850, 1720, 1680 cm^{-1}

^1H NMR (200 MHz,$CDCl_3$) : 0.9 (m, 6H), 1.2 (t, 3H), 2.15 (m, 1H), 3.75 (s, 3H), 4.1-4.35 (m, 3H), 5.25 (bs, 1H). Spectrum Number 19

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.2, 17.3, 18.7, 30.9, 51.8, 58.8, 60.8, 156.5, 172.7. Spectrum Number 20

Preparation of S-proline-N-ethyl carbamate benzyl ester:

S-Proline (1.15 g, 10 mmol) in dry THF (30 ml) was taken in a two-necked RB flask. Anhydrous K_2CO_3 (1.32 g, 10 mmol) and benzyl alcohol (1.1 g, 10 mmol) were added under nitrogen at room temperature. Ethyl chloroformate (2.5 g, 22 mmol) was added during 5 min. The contents were further stirred for 12h at 25°C. Water (10 ml) was added and the organic layer was separated. The aqueous layer was extracted with chloroform (2 x 10 ml). The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude product which was further purified using column chromatography on silica gel using hexane:ethyl acetate / 90:10 as eluent.

Yield : 2.35 g (85%)

IR (neat)ν_{max} : 2900, 2850, 1740, 1700 cm^{-1}

^1H NMR (200 MHz,$CDCl_3$) : 1.1 (t, 3H), 2.0 (m, 4H), 3.5 (m, 2H), 4.1 (m, 3H), 4.5 (s, 2H), 7.3 (m, 5H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 13.9, 22.7, 23.6, 29.2, 30.1, 45.2, 46.1, 58.3, 58.6, 60.4, 60.7, 66.0, 126.3, 127.5, 127.7, 141.6, 154.3, 154.8, 172.2.

Preparation of S-valine-N-ethyl carbamate benzyl ester:

Procedure followed was the same as in previous experiment.

Yield : 2.34 g (84%)

IR (neat)ν_{max} : 3350, 3100, 2900, 2850, 1700, 1680, 1600 cm^{-1}

^{1}H NMR (200 MHz,$CDCl_3$) : 0.9 (m, 6H), 1.2 (t, 3H), 2.1 (m, 1H), 4.2 (m, 3H), 4.7 (s, 2H), 5.2 (s, 1H), 7.3 (m, 5H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.0, 17.1, 18.6, 36.7, 58.7, 60.8, 66.6, 126.7, 128.1, 128.3, 141.0, 156.5, 172.0.

Preparation of S-valine-N-ethyl carbamate t-butyl ester:

Procedure followed was the same as in earlier experiment except for the change that t-butyl alcohol (0.74 g, 10 mmol) was taken in place of benzyl alcohol. The crude product (2.1 g) exhibited the following spectral characteristics.

IR (neat)ν_{max} : 3340, 2970, 2850, 1730-1640 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.6, 17.1, 18.7, 30.6, 30.9, 58.5, 61.0, 69.4, 156.8, 174.6. (The spectrum also exhibits signals corresponding to minor amounts of the N-ethyl carbamate of S-valine)

This product was found to decompose on silica gel. The product isolated after column chromatography (silica gel, hexane/ethyl acetate) exhibited the spectral characteristics expected for the N-ethyl carbamate of S-valine.

IR (neat)ν_{max} : 3350, 2910, 2850, 1720, 1680 cm^{-1}

^{1}H NMR (200 MHz,$CDCl_3$) : 0.9 (m, 12H), 1.25 (m, 6H), 2.15 (m, 1H), 4.1 (m, 2H), 4.25 (m, 1H), 5.4 (bs, 1H), 9.27 (bs, 1H). Spectrum Number 21.

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.3, 17.2, 18.8, 30.9, 58.7, 60.5, 61.3, 156.9, 176.6.

Preparation of chiral diamine (46)

Dicyclohexylcarbodiimide (4.12 g, 20 mmol) was taken in dry dichloroethane (20 ml). To this proline-N-ethyl carbamate (3.74 g, 20 mmol) in dichloroethane (0 ml) was added at $0^{o}C$ and the mixture was stirred for 15 min. Piperidine (1.7 g, 20 mmol) was added slowly during 15 min. at $0^{o}C$. The reaction mixture was slowly warmed to room temperature and further stirred for 12 h. The solvent was evaporated in vacuum and ethyl acetate (100 ml) was added. The precipitate was removed by filtration. The organic layer was washed with 10% citric acid solution, 5% $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the crude product was purified by silica gel column chromatography using hexane: ethyl acetate/90:10 as eluent, to afford the corresponding amide.

Yield : 3.8 g (75%)

IR (neat)ν_{max} : 1690, 1650 cm^{-1}

^{1}H NMR (200 MHz,$CDCl_3$) : 1.2 (t, 3H), 2.0 (m, 10H), 3.6 (m, 6H), 4.1 (m, 2H), 4.5 (3, 1H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 13.4, 22.4, 22.8, 23.1, 25.0, 28.2, 29.1, 44.7, 44.9, 45.7, 45.8, 56.4, 56.8, 59.6, 153.3, 153.8, 169.7, 169.8.

Reduction of (50) using $NaBH_4$ and I_2:

The amide (5.08, 20 mmol) was taken in dry THF (30 ml), $NaBH_4$ (1.6 g, 40 ml) was added following slow addition of I_2 (5.04 g, 20 mmol) in THF (20 ml) during 2h at $0^{o}C$, under static nitrogen

temperature and further stirred for 24h. The reaction was quenched with water, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated, the residue was taken in ether and treated with BF_3:OEt_2. 3N NaOH solution was added to this and organic layer was separated. The aqueous layer was further extracted with ether (3 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude N-ethyl carbamate derivative of the diamine which was purified by silica gel column chromatography using hexane:ethyl acetate/ 95:5 as eluent.

Yield : 3.74 g (78%)

IR (neat)ν_{max} : 2900, 2850, 1640 cm^{-1}

^1H NMR (200 MHz,$CDCl_3$) : 1.3 (t, 3H), 1.5-2.6 (m, 14H), 3.4 (t, 2H), 3.9 (m, 1H), 4.2 (m, 2H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 14.3, 22.6, 24.0, 25.7, 29.1, 45.9, 55.0, 60.2, 61.3, 154.9.

N-Deprotection of (51)

N-Ethyl carbamate derivative of diamine (4.8 g, 20 mmol) was taken in dry methanol (40 ml) and KOH (5.6 g) was added and the mixture was refluxed for 24h. Methanol was distilled out and water was added. The organic compound was extracted with $CHCl_3$ (3 x 20 ml). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the diamine in essentially pure form.

Yield : 2.92 g (87%)

IR (neat)ν_{max} : 3300 (w), 2900, 1420 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.1-2.0 (m, 10H), 2.1-2.6 (m, 8H), 3.5 (m, 1H).

N-Phenylation of diamine (52)

The diamine (3.36 g, 20 mmol) was taken in dry THF (20 ml) and fine pieces of sodium (1.1 g) were added. Bromobenzene (9.4 g, 60 mmol) was added and the mixture was refluxed for 30h. The reaction was quenched with methanol and 3N HCl (30 ml) was added. Aqueous layer was separated and amine was regenerated by adding 3N NaOH (20 ml). The amine was extracted with $CHCl_3$ (3 x 20 ml) combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded N-phenyl diamine which was purified by column chromatography on alumina using hexane:ethyl acetate / 95:5 as eluent.

Yield : 2.19 g (45%)

IR (neat)ν_{max} : 3100, 2850, 1610 cm^{-1}

^1H NMR (100 MHz,$CDCl_3$) : 1.4-1.8 (m, 10H), 2.0-2.6 (m, 6H), 3.3 (m, 2H), 3.8 (m, 1H), 6.7 (m, 2H), 7.3 (m, 3H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 23.1, 24.2, 25.9, 29.9, 48.2, 55.4, 56.8, 60.9, 111.7, 115.4, 129.1, 147.5.

$[\alpha]_D^{25}$ -126^oC (1, $CHCl_3$) Spectrum Number 22

Analaysis data : Calcd. C:78.63 H:9.89 N:11.46

Found 78.05 9.70 10.94

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CHAPTER 2

Studies on the Asymmetric Reductions aand Hydroborations Utilizing Chiral Amine-Boranes.

INTRODUCTION

Asymmetric synthesis has become an important area of research activity in organic chemistry. Stereochemistry often plays a major role in the biological activity of molecules. Hence, development of synthetic methods for achieving high enantiomeric purity is an important area of research. Synthesis of optically active molecules can be divided into three categories. (i). Stereo selective transformation of optically active starting materials, (ii) resolution of racemic mixtures and (iii) asymmetric synthesis from prochiral substrates.

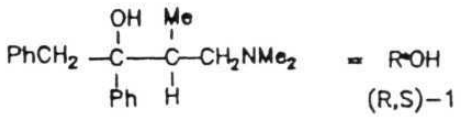
Synthesis of chiral alcohols from prochiral compounds is one of the well studied process in asymmetric transformations. The alcohols produced in such a process could be the desired end product or can serve as chiral building blocks for further conversions. The chiral alcohols can be obtained through asymmetric reduction of prochiral ketones, asymmetric synthesis via hydroboration and asymmetric ring opening of epoxides.[1-3]

Selection of asymmetric reagent for a particular transformation often poses problems. In choosing the reagent, one often seeks to use reagents that are catalytic, selective, economical and readily accessible. Clearly, no one reagent can be expected to provide all these requirements. Thus, there is sustained interest in developing new reagents in this area. We have initiated research activities utilizing amine boranes for reductions and hydroborations. It may be of interest to briefly review the results reported in this area.

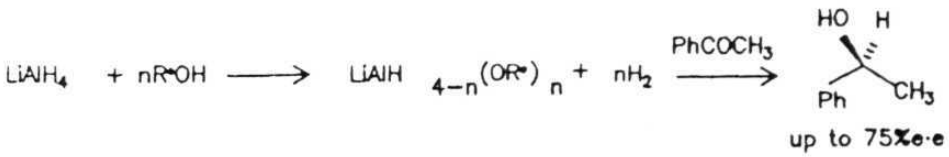
Reduction of prochiral ketones with chirally modified reducing agents.

Reduction of prochiral ketones by a chiral reducing agent has received a lot of attention. Initial research efforts in asymmetric reduction via asymmetric Meerwein-Ponndorf-Verley reductions and asymmetric Grignard reactions were not successful.[4] Later, modifications of lithium aluminum hydride with chiral alcohols and amines or amino alcohols have been explored by several research groups. Mosher's darvon alcohol-LAH complex, Noyori's BINAL-H and Terashima's N-methylephedrine-LAH complex have been found to be highly selective and useful.

Mosher *et al* prepared a derivative of LAH using (+)-(2S,3R)-4-dimethyl-amino-3-methyl-1,2-diphenyl-2-butanol and used it for reduction of prochiral ketones to achieve enantiomeric excess up to 75%.[5]

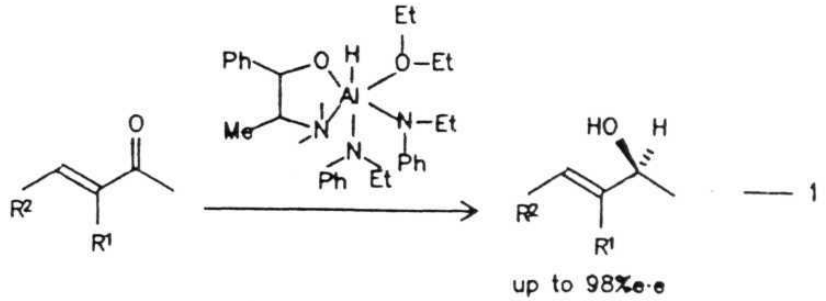


Scheme 1



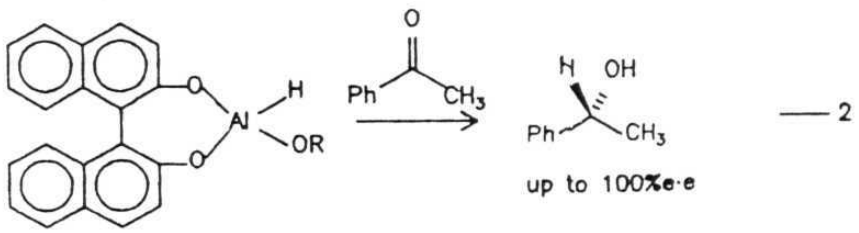
Terashima's LAH/N-ethylaniline/(-)-N-methylephidrin system has been found to convert open chain enones into the corresponding

Optically active allylic alcohols in high e.e (78–98%) and good chemical yields (90–100%) (eq. 1).[6]



— 1

A notable invention has been made by Noyori *et al.* It was found that BINAL-H, prepared from (R)- or (S)- 2,2'-binaphthol and $LiAlH_4$ gives excellent asymmetric inductions (eq. 2).[7]



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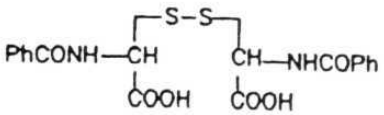
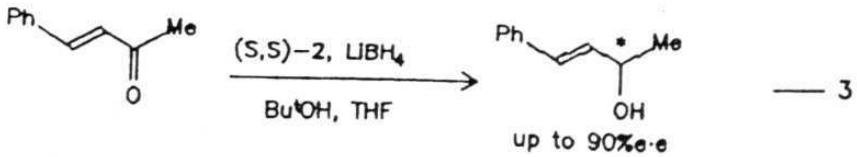
Soai's $LiBH_4$/N-benzoylcystine combination was found to be effective in reducing β-keto esters. However, this reagent is not very effective in reducing more simple ketones (eq. 3).[8]



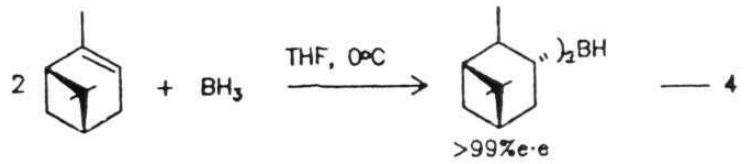
(S,S)–2



— 3

Attempts were also made to modify $NaBH_4$. However, only limited success was obtained.[9] The failure of these borohydride modified reagents may be due to the formation of a mixture of reactive species.

In recent years, a number of chiral organoborane reagents and chiral amino alcohol-borane reagents have been developed. Among these reagents, α-pinene based asymmetric reducing agents could be expected to give better selectivities, since these reagents give high level of asymmetric inductions in hydroboration reactions.[9] However, the reagent prepared using chiral α-pinene and H_3B:THF gives poor results, 37% e.e (eq. 4 and 5).[10,11]



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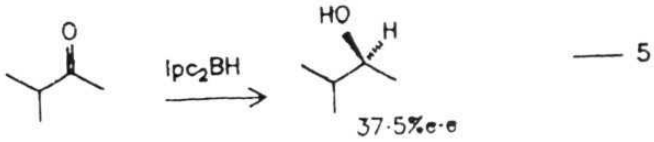
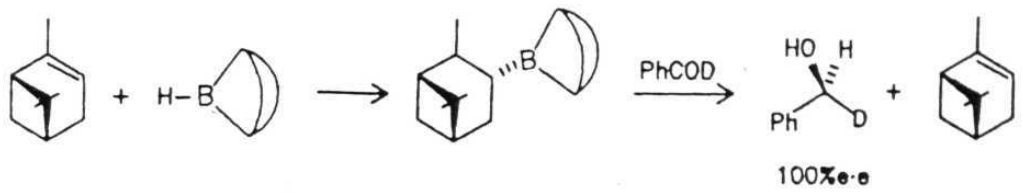


— 5

Another chiral reducing agent derived from α-pinene is lithium-3-pinanyl-9-borabicyclo[3,3,1]nonyl hydride (Alpine-hydride). This is also ineffective in transferring chirality to the product alcohols.[12] Midland *et al* synthesized the first successful chiral organoborane reducing agent, β-isopinocamphey-9-borabicyclo[3,3,1] nonane. Using this reagent, deuterated alcohols were obtained from aldehydes in

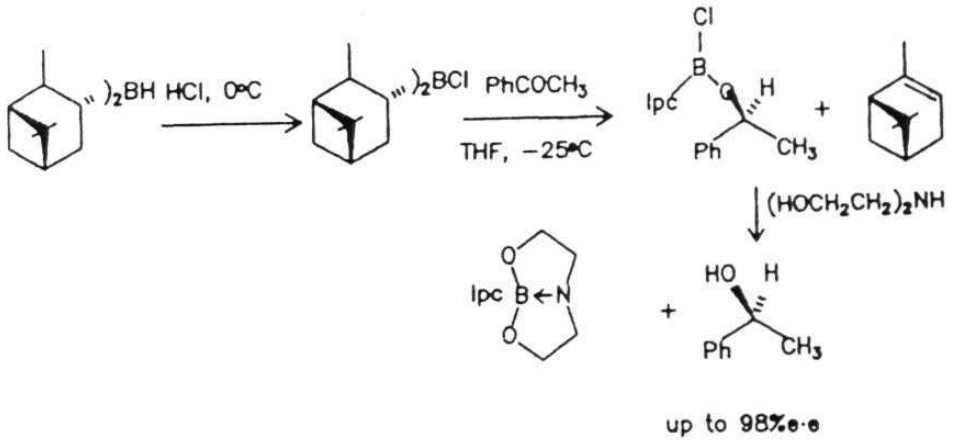
essentially optically pure form. These reductions involve a Meerwein-Ponndorf-Verley type of process. The chiral auxiliary, α-pinene can be readily recovered.[13]

Scheme 2



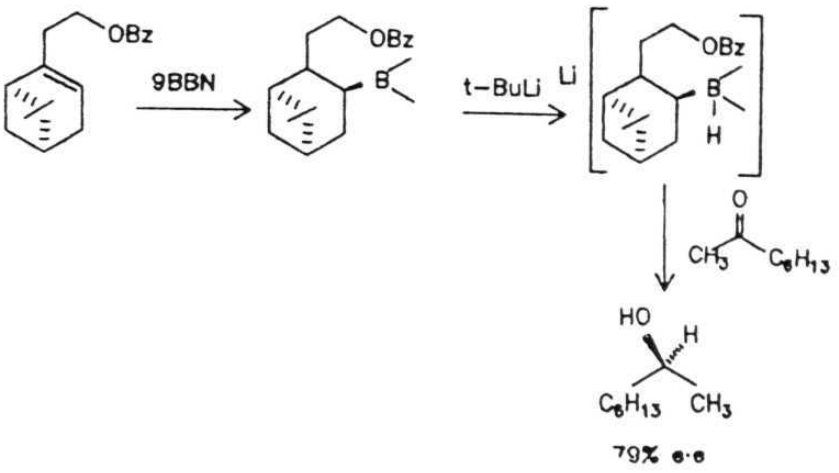
The reducing agent, B-chlorodiisopinocampheylborane has been proved to be efficient for the reduction of aryl alkyl ketones.[14,15]

Scheme 3



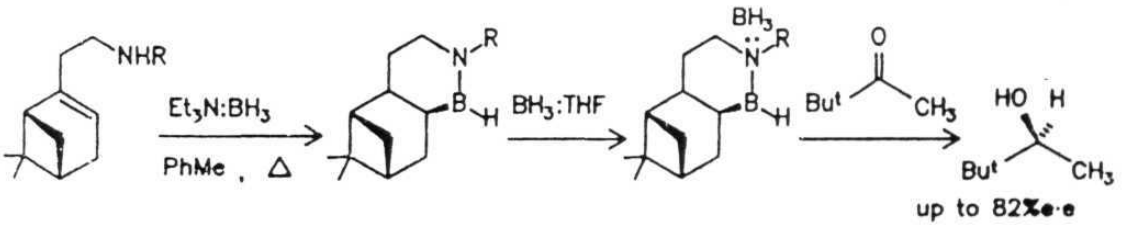
Midland *et al* have also developed chiral reducing agents starting from nopol. The NB-enantride was prepared by hydroboration of nopol benzyl ether with 9-BBN followed by treatment with t-BuLi. This reagent system reduces prochiral aliphatic ketones in good selectivities.[16]

Scheme 4



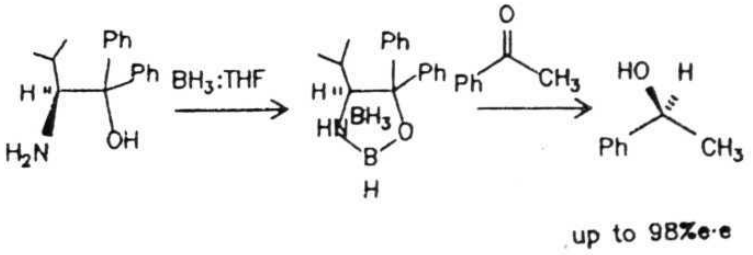
More recently, an interesting chiral reducing system has been prepared staring from nopylamine. The borane complex of this amine reduces prochiral ketones with up to 82% e.e.[17]

Scheme 5



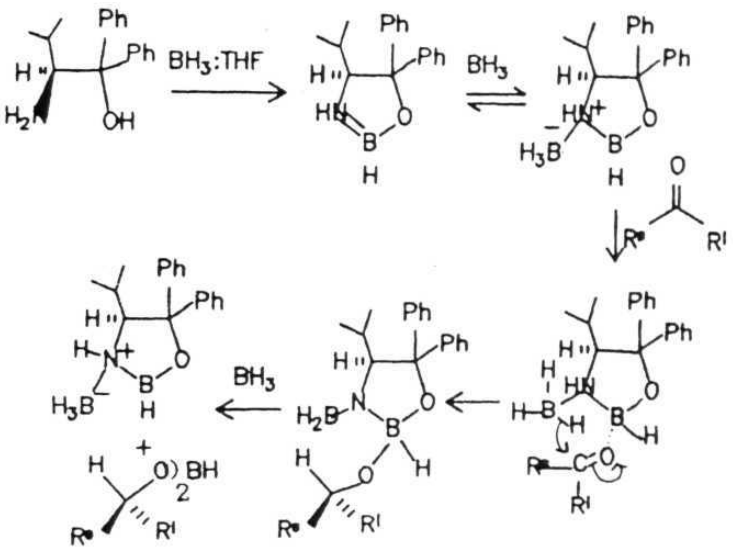
Itsuno *et al* developed a reducing system from chiral diphenylvalinol and borane. This reagent reduces aromatic ketones in very high selectivities (up to 100% e.e). However, aliphatic ketones are reduced with lesser e.e.[18-20]

Scheme 6



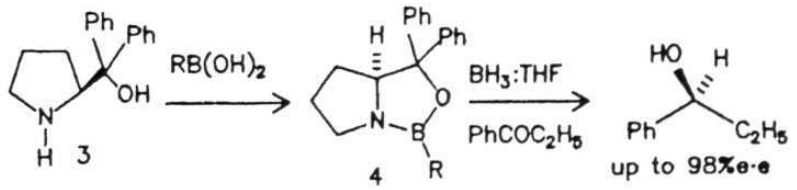
Later, Corey *et al* discovered that the valinol/BH_3 system can be made catalytic. They showed that the reaction goes through the catalytic process shown in Scheme 7.[21]

Scheme 7



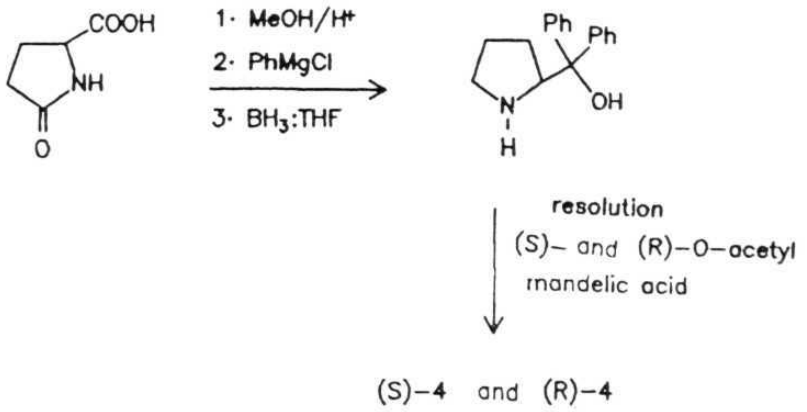
They also found that the corresponding prolinol gives better results. Several ketones were reduced using this oxazaborolidine catalyst with high levels of asymmetric inductions.[22,23] Many other oxazaborolidine catalysts have been prepared and used in a variety of syntheses. The results have been recently reviewed.[24]

Scheme 8



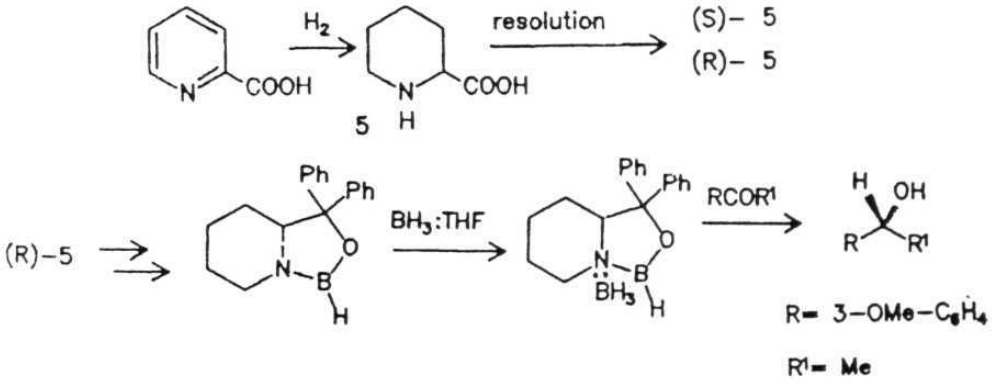
A problem is that only the L-derivative of proline is readily available. Corey *et al* devised a synthetic route for the preparation of the R-derivative starting from pyroglutamic acid in several steps as shown in Scheme 9.[22]

Scheme 9



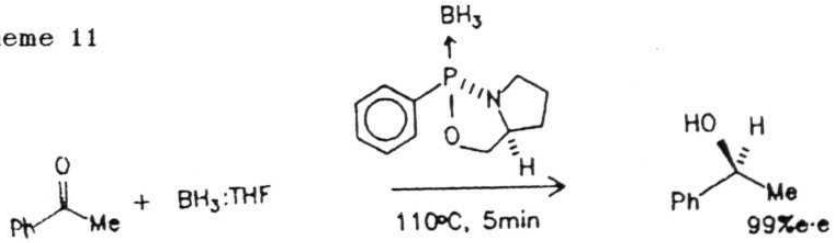
Rao *et al* synthesized a 2-piperidine amino alcohol in both R and S forms through resolution. It has been found that asymmetric reductions of prochiral ketones utilizing these auxiliaries give good selectivities (up to 92% e.e). However, relatively higher amounts of the auxiliaries are required.[25]

Scheme 10



Very recently, Buono *et al* observed that a phosphine–BH_3 complex derived from prolinol reduces prochiral ketones in 99% e.e.[26]

Scheme 11



We have initiated our efforts in this area with a view of studying the asymmetric reduction characteristics of amine boranes. We have also undertaken efforts towards studying the hydroboration characteristics of some of these amine boranes.

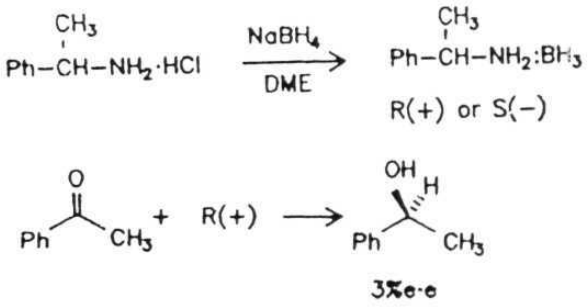
RESULTS AND DISCUSSION

Reduction of prochiral ketones using chiral amine–borane complexes.

Amine–borane complexes have practical advantages as reducing agents in organic synthesis owing to their stability and solubility in a wide variety of solvents. The applications of chiral amine–borane complexes in asymmetric reductions of ketones have not been extensively investigated.[27–29]

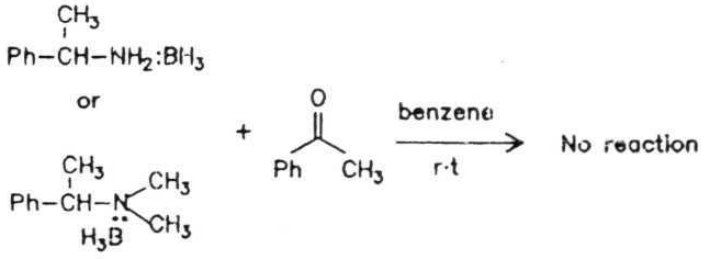
Borch *et al* used R(+) and S(−)–α–methylbenzylamine–borane complexes *in situ* for the reduction of prochiral ketones.[30]

Scheme 12

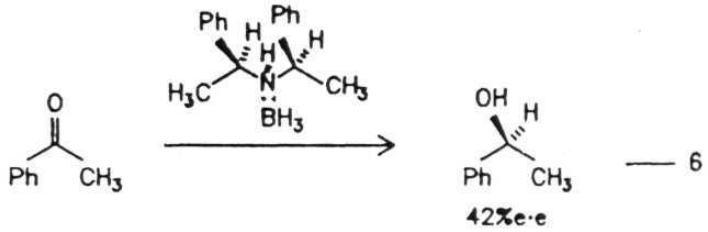


These amine–boranes reduce prochiral ketones at reflux temperatures. The enantiomeric excess of alcohols thus obtained was found to be very low (1–3% e.e). Also, it has been reported that borane complexes of α–methylbenzylamine and N,N–dimethyl–α–methylbenzylamine do not reduce ketones at room temperature in benzene solvent.[31]

Scheme 13



However, when one equivalent of BF_3:OEt_2 was added, the reaction goes to completion in 0.5h at 0^oC. But alcohols were obtained only in 13% e.e. More recently, it has been reported that N,N-di-α-methyl-benzylamine-borane complex reduces acetophenone in the presence of BF_3:OEt_2 to corresponding alcohol in 42% e.e (eq. 6).[32]



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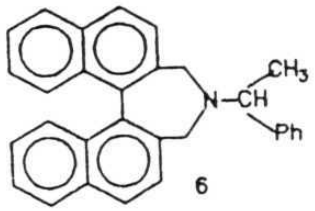
It appeared that higher level of enantioselectivity can be achieved by selection of a suitable chiral amine. As discussed in chapter 1, chiral ligands containing binaphthyl moiety such as BINAP, BINAL-H have been found to be very effective in chiral recognition. Hence, it was thought that an amine containing binaphthyl system would serve as a good chiral handle. The (-)-N-α-methylbenzyl-3,5-dihydrodinaphthazepine (6) was prepared in diastereomerically pure form as described in Chapter 1.



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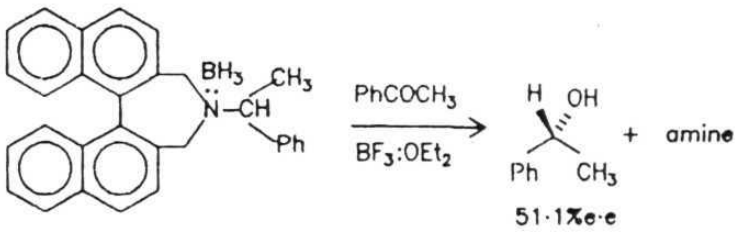
Borane complex of the chiral amine 6 was prepared by bubbling excess of diborane gas through a benzene solution of 6. Infra-red spectrum of this solution showed a strong BH absorption at 2400 cm^{-1}.

When the reduction of acetophenone was attempted using this borane

complex in benzene unreacted acetophenone was recovered even after stirring for 24h at room temperature. When the reaction was carried out in the presence of BF_3:OEt_2, 1-phenylethanol was obtained in 51% e.e.

Scheme 14



Reduction of a few other ketones were also carried out using this amine borane in the presence of BF_3:OEt_2 and the results are summarized in Table I

The configurations of the products are consistently R. The optical induction decreases with increasing chain length of the alkyl moiety. Similar features have been reported with the Itsuno and Corey oxazaborolidine reagents.[18–22]

The role of BF_3:OEt_2 in these reductions is not well understood. Grundon *et al* suggested a mechanism involving a hydrogen transfer reaction followed by a fluorine transfer process.[31]

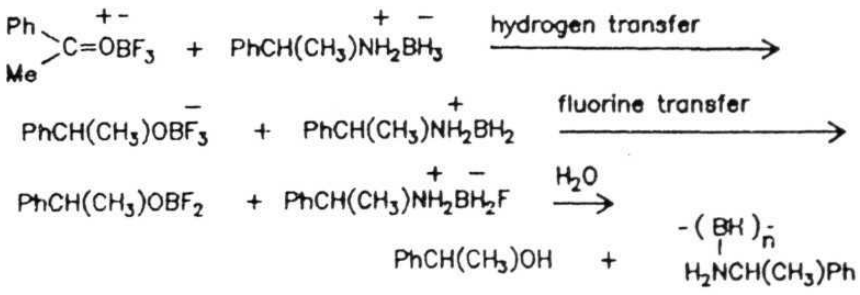
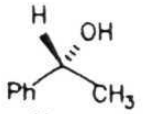
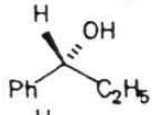
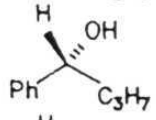
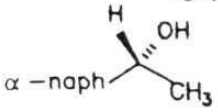


Table I: Reduction of prochiral ketones using amine-borane complex.[a]

Substrate	Product[b]	yield[c]	$[\alpha]_D^{25}$(C, solvent)[d]	e.e%
$PhCOCH_3$		82	+23°(C3, CH_3OH)[e]	51·1
$PhCOC_2H_5$		81	+20°(C1, Me_2CO)[f]	41·1
$PhCOC_3H_7$		80	+5°(C2, benzene)[g]	11·0
α-naphCOCH$_3$		78	+45°(C_2, CH_3OH)[h]	57·0

(a). All reactions were carried out at 0^oC with 10mmol of amine-BH_3 10mmol of ketone and 10mmol of BF_3:OEt_2 in benzene. The experiments were run at least twice in each case.

(b). Products were identified by analysis of spectral data (IR, ^1H NMR) and comparison with the reported data.

(c). Yields are of isolated, chromatographed and distilled products.

(d). Optical rotations were measured with an Autopol-II automatic polarimeter (observed rotation accuracy 0.01^o)

(e). Based on the maximum [33] $[\alpha]_D^{25} = -45.5^o$(C3, MeOH)

(f). Based on the maximum [34] $[\alpha]_D^{25} = -47.03^o$(C1, Me_2CO)

(g). Based on the maximum [34] $[\alpha]_D^{25} = +45.2^o$(C3, benzene)

(h). Based on the maximum [35] $[\alpha]_D^{25} = -78.9^o$(C3, MeOH)

We have carried out further investigations in order to understand the role of BF_3:OEt_2 in this reaction. It is known that BF_3:OEt_2 liberates diborane from amine-BH_3.[35] Also, diborane does not displace BF_3 from amine-BF_3 adducts (eq. 7 & 8).[35]

$$NR_3{:}BH_3 + BF_3{:}OEt_2 \longrightarrow NR_3{:}BF_3 + B_2H_6 \qquad \text{— 7}$$

$$NR_3{:}BF_3 + B_2H_6 \text{ or } BH_3{:}LB \not\longrightarrow \text{No reaction} \qquad \text{— 8}$$

Accordingly, the formation of an amine-BF_3 complex as an intermediate cannot be ruled out. In any case , it was of interest to prepare the amine-BF_3 complex and examine whether it would catalyze the asymmetric reduction of acetophenone by achiral Lewis base borane complexes such as N,N-diethylaniline-borane.

The chiral amine-BF_3 complex was prepared by the addition of stiochiometric amount of BF_3:OEt_2 to chiral amine 6 in dry ether under nitrogen. The ether solvent was pumped off under dry nitrogen to obtain the amine-BF_3 complex. To this N,N-diethylaniline-borane complex (1eq) in dry benzene was added followed by acetophenone (1eq). After usual workup, the alcohol product was obtained in 51% e.e. The result is same as that obtained following the earlier procedure. In order to examine whether the reaction can be made catalytic on the chiral amine-BF_3, we have carried out experiments using various amounts of chiral amine-BF_3 complex in the reduction of acetophenone by N,N-diethylaniline-BH_3 or triethylamine-BH_3 and the results are summarized in Table II.[36]

These results (Table II) indicate that the asymmetric inductions

Table II: Catalytic reduction of acetophenone in the presence of chiral amine–BF_3 complex.[a]

Ketone:Amine–BF_3 mol.equiv.	Reaction time(h)	External reducing agent	Yield[b] (%)	$[\alpha]_D^{25}$ (C3, CH_3OH)	e.e%[c]
1:1	3	$PhEt_2N{:}BH_3$	81	+23	51.1
1:1	15	$Et_3N{:}BH_3$	80	+22	48.9
1:0.75	3	$PhEt_2N{:}BH_3$	82	+23	51.1
1:0.5	3	$PhEt_2N{:}BH_3$	80	+22	48.9
1:0.5	15	$Et_3N{:}BH_3$	80	+22	48.9
1:0.4	3	$PhEt_2N{:}BH_3$	80	+19	42.2
1:0.25	3	$PhEt_2N{:}BH_3$	75	+9	20.0

(a). Reactions were carried out with ketone (10 mmol) and amine–BH_3 (10 mmol) at 0^oC. The experiments were run at least twice in each case.

(b). Yields are of isolated, chromatographed and distilled products.

(c). Enantiomeric excess based on the maximum [33] $[\alpha]_D^{25} = -45.5^o$(C3, CH_3OH)

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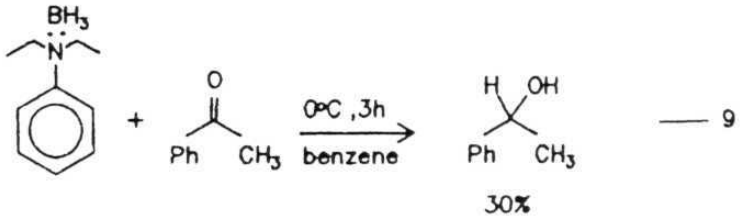
are decreased only to a small extent by reducing the concentration of chiral amine–BF_3 complex by 50%. However, further reduction of concentration of the chiral amine–BF_3 leads to a significant decrease in asymmetric inductions. This may be due to the competitive uncatalyzed reduction of the ketone by the N,N-diethylaniline–BH_3 complex. We have also observed that in the absence of amine–BF_3

acetophenone reacts with the N,N-diethylaniline–BH_3 complex at 0°C in 3h to give the corresponding alcohol in 30% yield (eq. 9).



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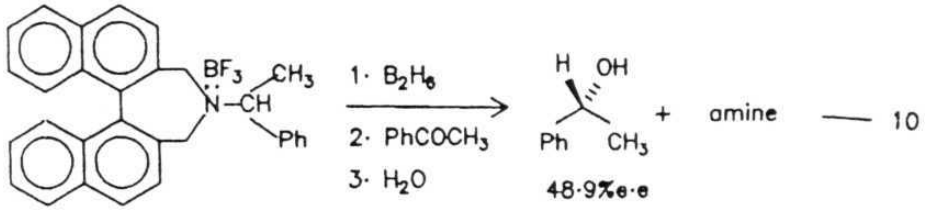
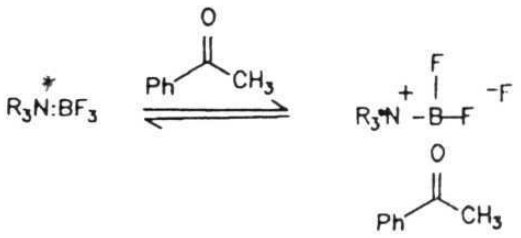
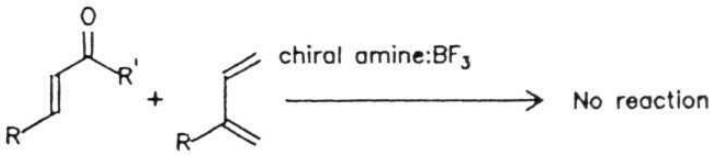
The catalysis of the reduction by amine–BF_3 is interesting as there is no free coordination site available on the boron for further complexation with the ketone. The nature of the actual reactive species may be deduced from the results summarized in Table I and II. The reaction of $R_3N{:}BH_3$ with $BF_3{:}OEt_2$ is expected to give $R_3N{:}BF_3$ and borane. Since the diborane is not liberated, the >B–H unit must present in an associated form along with the $R_3N{:}BF_3$ to provide the reactive intermediate. Also, the same reactive intermediate would have been formed in the reaction of chiral $R_3N{:}BF_3$ with $PhEt_2N{:}BH_3$ or $Et_3N{:}BH_3$. In order to get further information about the reactive species, we have prepared chiral amine–BF_3 as described above. This was taken in dry benzene and diborane gas was bubbled through the solution. The IR spectrum of the solution exhibits strong >B–H at 2450 cm^{-1}. Since diborane cannot displace BF_3 from the $R_3^*N{:}BF_3$ complex, the >B–H must be present in an associated form with $R_3^*N{:}BF_3$. When triphenylphosphine was added to this, after workup a solid product was isolated along with the chiral amine. This solid melted at 183°C which is 5°C less than triphenylphosphine–borane. ^{11}B NMR spectrum of this compound was found to be same as that of PPh_3–BH_3. The associated complex prepared in this way reduced acetophenone to the corresponding alcohol in 48.9% e.e (eq. 10)

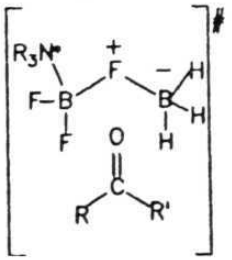


Initially, it was thought that this catalysis may be explained by considering displacement of one of the fluorides by the ketone oxygen to give the reactive intermediate. If this is true the amine–BF_3 should also catalyze other types of reactions of ketones. For example, if this can activate an α,β-unsaturated carbonyl moiety, it should be possible to catalyze certain Diels-Alder reactions using this amine–BF_3 species. We have attempted Diels-Alder additions using certain dienes and dienophiles which do not react without Lewis acid catalysis. It was found that the adducts were not formed in these cases.



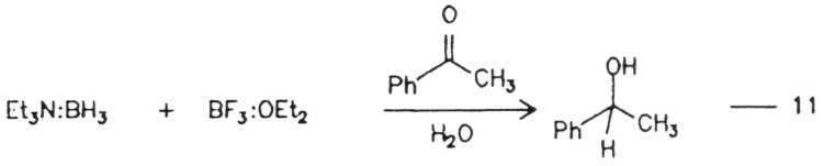


The asymmetric reduction results can be best explained by considering the transition state outlined in the following figure.[37]



In order to further examine the species involved in this reaction, we carried out similar experiments using strongly complexing achiral tertiary amine with borane.

Triethylamine forms a strong complex with borane which does not reduce acetophenone at 0°C. However, we have found that addition of one equivalent of BF_3:OEt_2 facilitates the rate of reduction and the reaction is completed in 8h at 0°C. After usual workup and purification 1-phenylethanol was obtained in 85% yield (eq. 11).



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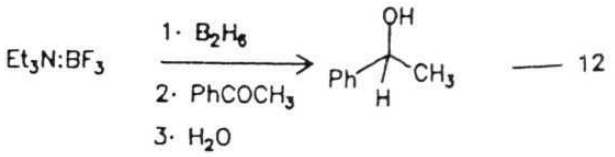
We have also tried the reduction of acetophenone using the associated complex of triethylamine-BF_3 and diborane. Triethylamine-BF_3 complex was prepared as mentioned earlier. This was taken in dry benzene. Diborane gas was bubbled through the solution at 10°C and the reduction of acetophenone was carried out. After usual workup, 1-phenylethanol was obtained in 84% yield (eq. 12).



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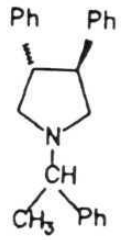
Reduction of acetophenone and propiophenone using N-α-methylbenzyl-3,4-diphenylpyrrolidine.

As discussed in Chapter 1, substituted chiral pyrrolidines were

proved to be excellent chiral recognizing systems in certain enantioselective transformations. We decided to prepare and examine the reactivities of the chiral 3,4-diphenylpyrrolidine system.

The diasteriomerically pure N-α-methylbenzyl-3,4-diphenyl-pyrrolidine 7 $[\alpha]_D^{25}$= +80°(C1, $CHCl_3$) was prepared following the sequence of reactions outlined in Chapter 1.



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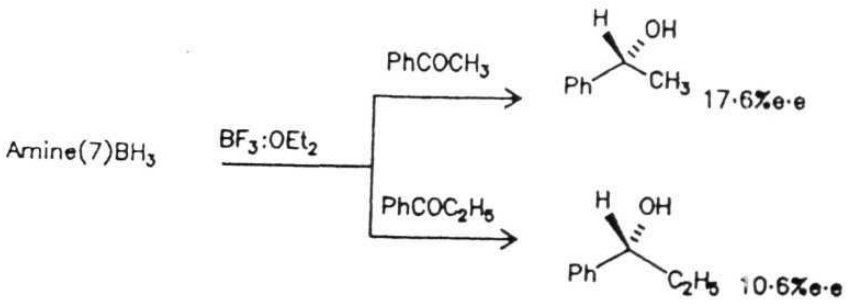
It was found that this amine also forms a strong complex with borane which does not reduce acetophenone at room temperature. Addition of BF_3:OEt_2 facilitates the reduction and the reaction is complete in 4h at 0°C. After usual workup, the alcohol was obtained in only 17.6% e.e (Scheme 14).

Scheme 14

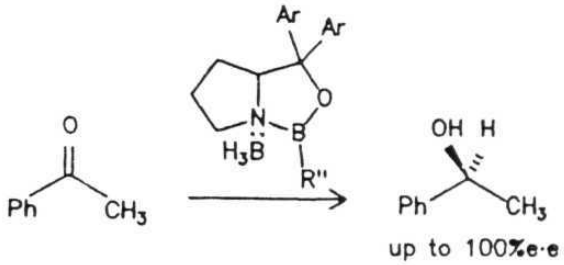


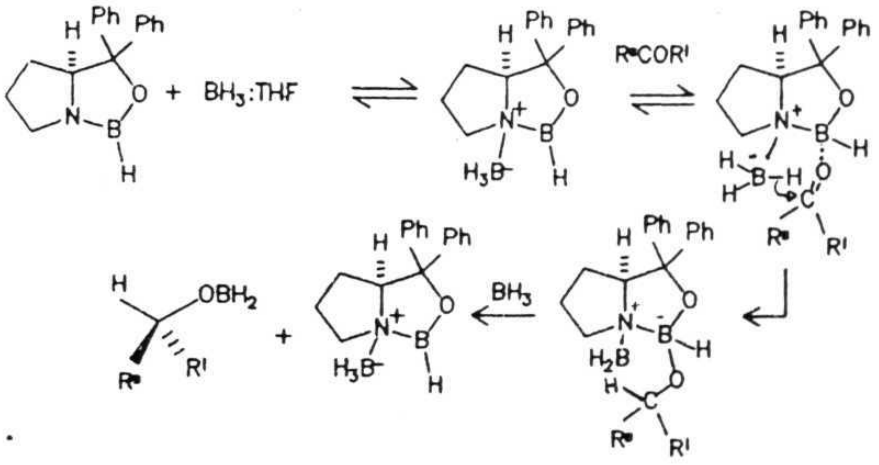
Reduction of propiophenone was also carried out following this procedure. Here also, the selectivity was found to be poor. Therefore we did not pursue research on this topic further.

Enantioselective reductions using chiral oxazaborolidine reagent derived from (S)-α,α-diphenyl-2-pyrrolidinemethanol.

Enantioselective reductions of prochiral ketones with oxazaborolidine-BH_3 complexes to chiral secondary alcohols is a topic of immense interest. Studies by Corey *et al* demonstrated that the reductions are catalyzed by the oxazaborolidine as outlined in Scheme 15.[24]

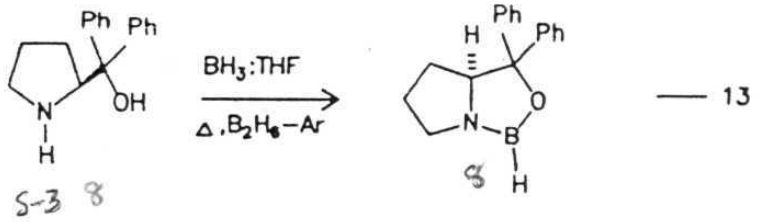
Scheme 15





The oxazaborolidine catalysts give high levels of enantioselectivities in the reduction of carbonyl compounds.[24] The oxazaborolidines are referred as chemzymes as they act by binding the ketone and borane to have close encounter leading to high level of asymmetric inductions.

Corey *et al* prepared this catalyst by heating 3 equiv. of BH_3:THF and (S)-α,α-diphenyl-2-pyrrolidinemethanol in THF at reflux under a closed argon-BH_3 atmosphere (total pressure 1.7 bar). Removal of solvent, sublimation at 150–160°C (0.1 torr) and resublimation at 145–160°C (0.05 torr) gave the catalyst. The crystals so obtained had m.p 107–124°C.[21]



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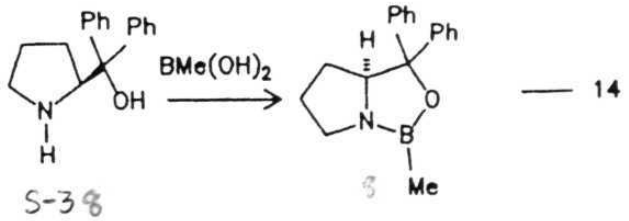
Even though this catalyst gives excellent results in asymmetric reduction of several prochiral ketones, the corresponding B-methylated oxazaborolidine is preferred since the unsubstituted reagent is more sensitive to air and moisture. The B-methyl oxazaborolidine can be stored in closed containers and can be also transferred in air.[22] This reagent has been prepared by the reaction of (S)-α,α-diphenyl-2-pyrrolidinemethanol and methyl boronic acid either in toluene at 23°C in the presence of 4 A° molecular sieves for 1.5h or in toluene at reflux for 3h using a Dean-Stark trap for water removal.



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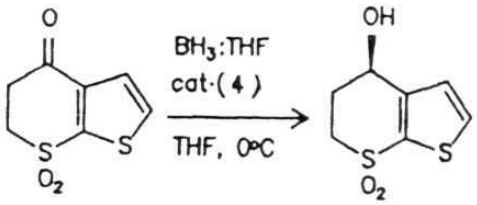
Recently, Mathre *et al* have reported that they have obtained erratic results in the oxazaborolidine catalyzed reductions of a ketone intermediate in the synthesis of MK-0417.[38]

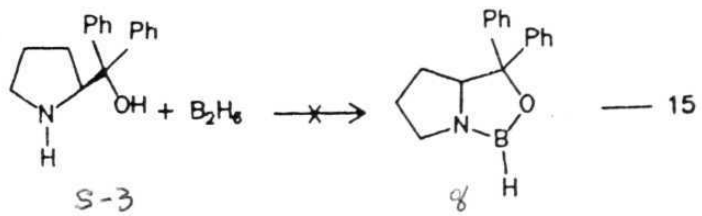
Scheme 16



They attributed this to the presence of some water in the oxazaborolidine. It was found that 1mg of water present in 1g of ketone reduction lowers the enantiomeric excess from 95% to 50%.

The preparation of oxazaborolidine (8) using (S)-3 and borane does not involve water formation. It appeared that this catalyst has not been extensively used due to the reported air and moisture sensitivities. Also, the reported procedure for the preparation of oxazaborolidine (heating under diborane-argon atmosphere) is also somewhat complicated. We have decided to explore the synthesis of this reagent *in situ* for synthetic applications.

Initially, we attempted the preparation of oxazaborolidine by passing excess of diborane gas through benzene solution of (S)-3 at 10^{o}C. The reagent prepared in this way failed to reduce acetophenone at room temperature (eq. 15) (see experimental section for details).

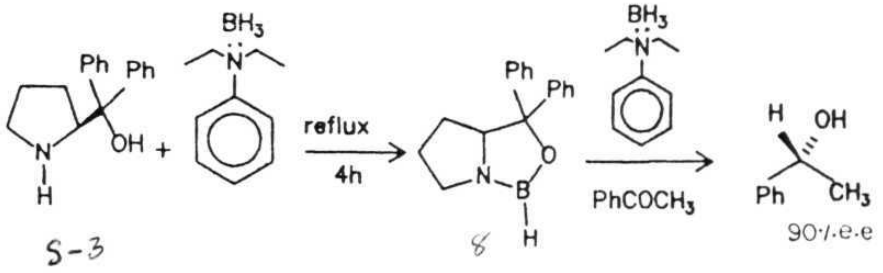


Clearly, the BH_3 complex of the oxazaborolidine or any other

species capable of reducing acetophenone is not formed here. In another experiment, diborane gas was passed through the benzene solution of (S)-3 at $10^{o}C$ and the resulting mixture was heated under reflux for 3h. The mixture was cooled to $10^{o}C$ and again diborane gas was passed through this mixture. Acetophenone (1eq) was added and the reduction was carried out for 1h at room temperature. After usual workup, 1-phenylethanol was obtained in 86% yield with 57%e.e.

In order to further examine this system, N,N-diethylaniline-BH_3 (1 eq) in dry benzene and (S)-3 (1 eq) in THF were mixed at $0^{o}C$ and the contents were refluxed for 4h. The reaction mixture was cooled to $10^{o}C$ and N,N-diethylaniline-borane (1 eq) was added followed by acetophenone (1 eq) at $0^{o}C$. After usual workup, 1-phenylethanol was obtained in 90% e.e.

Scheme 17



Reduction of acetophenone was carried out using different amounts of oxazaborolidine catalyst utilizing N,N-diethylaniline-borane complex and the results are summarized in Table III. Reduction of propiophenone also gives comparable results.

The optical inductions realized are somewhat low compared to that originally reported by Corey *et al.* However, the present method

Table III: Reduction of prochiral ketones with N,N-diethylaniline–borane complex in the presence of chiral oxazaborolidine (8).

Achiral amine borane: chiral oxazaborolidine molar equiv	Ketone used	Yield %	$[\alpha]_D^{25}$ = (C3, CH_3OH)	e.e%
1:1	$PhCOCH_3$	90	$+41^o$	90.1
1:0.75	$PhCOCH_3$	86	$+41.5^o$	91.2
1:0.5	$PhCOCH_3$	87	$+41^o$	90.1
1:0.25	$PhCOCH_3$	83	$+41^o$	90.1
1:0.25	$PhCOC_2H_5$	84	$+43^o$	91.4
1:0.1	$PhCOCH_3$	85	$+37^o$	82.0

(a). All reductions were carried out using 10 mmol of N,N-diethyl aniline–borane, 10 mmol of ketone and oxazaborolidine as mentioned above (see experimental section for details).

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

(c). Based on the maximum [33] $[\alpha]_D^{25} = -45.5^o$(C3, CH_3OH).

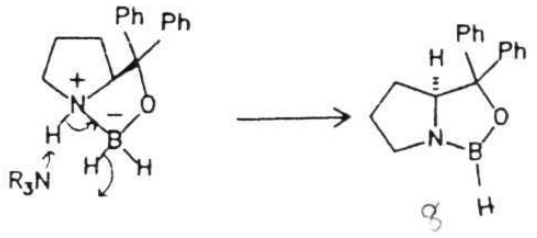
(d). Based on the maximum [34] $[\alpha]_D^{25} = -47.03^o$(C1, CH_3COCH_3)

(e). Enantiomeric excess was also confirmed by HPLC analysis using Chirosel-OD column with 5% isopropanol in hexane as solvent.

avoids the isolation and purification of the oxazaborolidine catalyst. Moreover, stiochiometric amount of N,N-diethylaniline-borane is used for the preparation of chiral catalyst in the present method. In the original procedure three equivalents of borane-THF were utilized and also the preparation requires heating under B_2H_6 argon atmosphere.

It appeared that the presence of amine facilitates the 5,5-ring fusion.

Scheme 18



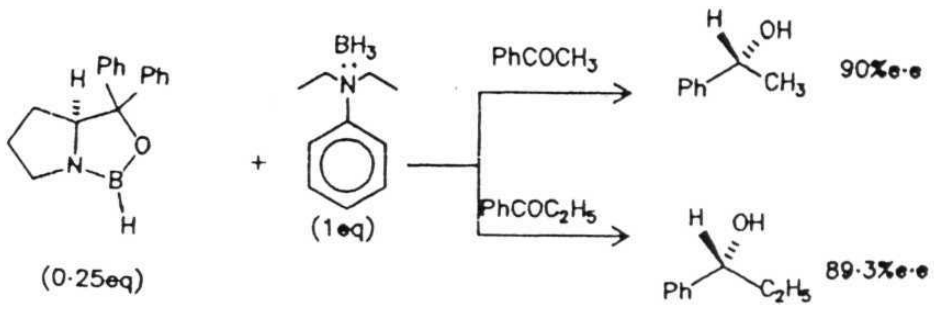
In order to further examine this, we carried out the following experiment. Excess of diborane gas was bubbled through the benzene solution of (S)-4 (1 eq) during 4h at 10^{o}C. To this triethylamine (0.2 eq) was added and the mixture was refluxed for 4h. Again, diborane gas was bubbled through this mixture. Acetophenone (1 eq) was added and the reaction was carried out at 10^{o}C. After usual workup the reduced product was obtained in 90.7% e.e.

It is to be noted that when a similar experiment was carried out without using triethylamine, the reduction product was obtained only in 57% e.e. This enhancement in enantiomeric excess indicates that the catalyst formation is facilitated by the amine as suggested above in the case of reaction with N,N-diethylaniline.

The oxazaborolidine was also separately prepared and used in the

catalytic asymmetric reduction of acetophenone (1 eq) and propiophenone (1eq) using N,N-diethylaniline-borane (1eq). The corresponding reduced products were obtained in 90% and 89.3% e.e respectively.

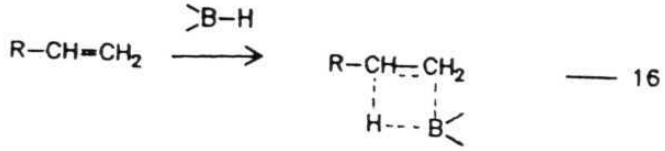
Scheme 19



Recently, during the preparation of this dissertation, a report appeared on the enhancement of sterioselectivity in the reduction of prochiral ketones using stiochiometric amounts of oxazaborolidine-borane complex in the presence of triethylamine.[38] It was suggested that presence of triethylamine suppresses the uncatalyzed reaction.

Mechanistic studies on the hydroboration of olefins utilizing chiral amine-borane complexes.

The hydroboration reaction is one of the most useful reactions in synthetic organic chemistry.

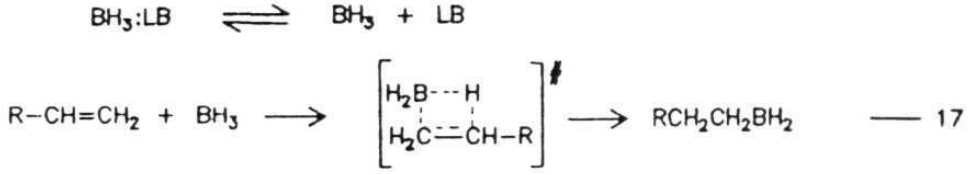


— 16

However, the mechanism of this important reaction is not clearly understood. Several mechanistic proposals have been reported for hydroboration but no mechanism can explain all the traits satisfactorily.[39–56] Three mechanistic pictures can be deduced for the hydroboration of alkenes with BH_3:Lewis base complexes based on various published data and reports.

(i) S_N1-like mechanism

This involves a prior dissociation of Lewis-base to give a free 'BH_3' moiety which then hydroborates olefins. Kinetic data have been presented in support of this mechanism (eq. 17).[46]



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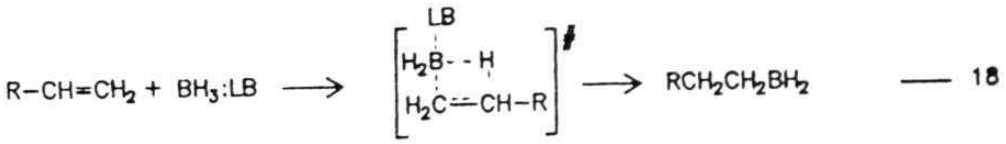
(ii) S_N2-Like mechanism

This mechanistic picture suggests that the reaction takes place without complete detachment of the Lewis-base during the reaction (eq. 18).



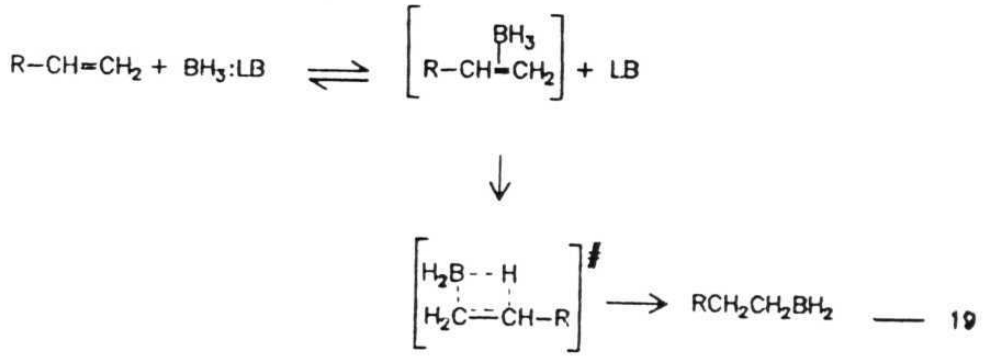
— 18

Kinetic data and theoretical calculations have been presented in

support of this mechanism.[47,51] Also, the Lewis-base (eg. aldehyde and ketone) must be present in the transition state of certain dehydroboration-reduction processes (Scheme 2 and 3) although the transition state is six membered in these cases.[13-15]

(iii) **Mechanism involving π - complex intermediate**

This mechanistic proposal has been considered for the reverse (i.e dehydroboration) reaction (eq. 19).[54,56]



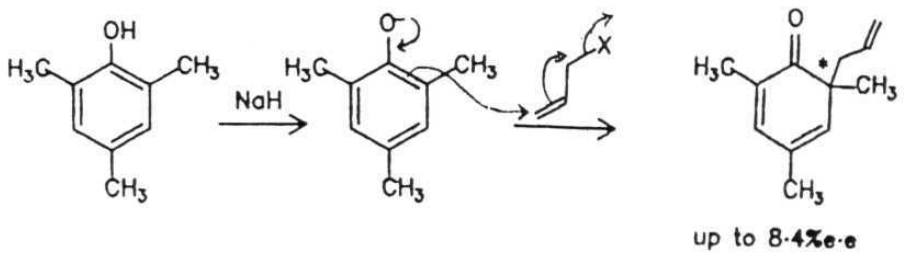
The π-complex intermediates were also considered for the reaction of BH_3 with olefins in the gas phase[52] and also for explaining the asymmetric hydroboration results using Ipc_2BH. Curiously, this mechanistic picture was not considered for explaining the kinetic data although the available data cannot distinguish this mechanism from the S_N1 like mechanism.

In the case of S_N1 like mechanism, the Lewis base gets detached from boron before hydroboration. The S_N2 like mechanism implies that the Lewis base is still attached to boron in the transition state. In the third mechanism involving π-complex intermediate, it is not understood whether the Lewis base will be present or absent during the >B-H addition, since the possibility of Lewis base interaction with boron while the hydrogen is delivered from boron to carbon in the

π-complex cannot be ruled out.

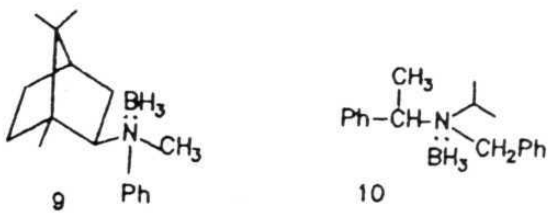
In an S_N2 displacement reaction, a chiral leaving group has been reported to give asymmetric inductions up to 8.4% e.e as shown in Scheme 20.[57]

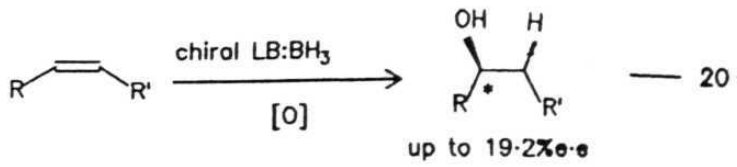
Scheme 20



This indicates that the presence of a chiral leaving group in the transition state leads to asymmetric induction. It appeared that this tool could be applied to the hydroboration reaction.

Recently, it has been reported from this laboratory that chiral amine–borane complexes hydroborate prochiral olefins, giving alcohols up to 19.2% e.e after oxidation (eq. 20).[58]

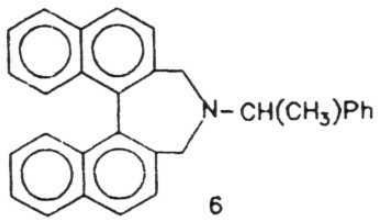




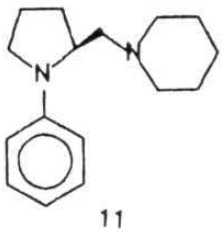
— 20

We have carried out some experiments utilizing the chiral amines prepared in the course of the present investigation in order to further examine the various mechanistic proposals.

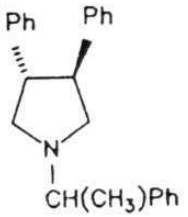
It was thought that chiral amines containing the nitrogen as part of ring system in skeletons with proven abilities in discriminating chiral faces will be helpful. The chiral tertiary amines **6–8** and **11** have been prepared following the procedures described in Chapter 1.



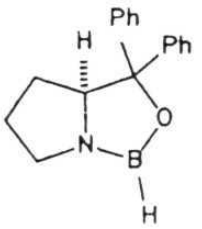
6



11

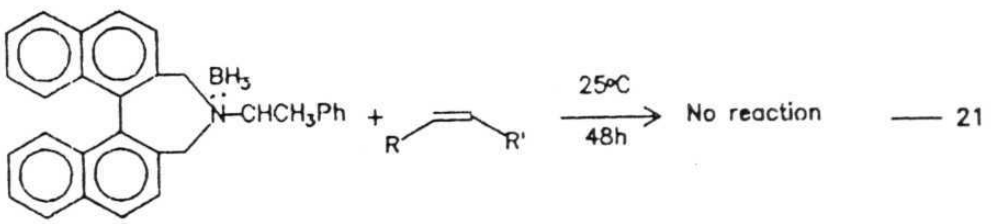


7

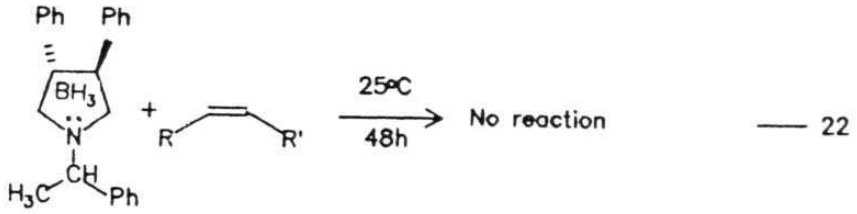


8

The N-α-methylbenzyl derivatives of 3,5-dihydrodinaphthazepine and 3,4-diphenylpyrrolidine were found to form very strong complexes with borane. Attempts to hydroborate prochiral olefins at $0^{o}C$ or room temperature using these complexes were not successful (eq. 21 & 22).

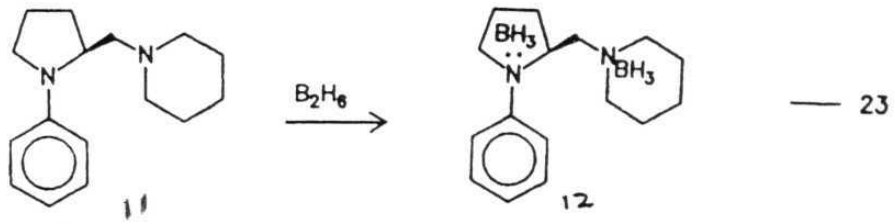


— 21



— 22

The corresponding N-phenyl compounds are expected to form comparatively weak complexes and hence would hydroborate olefins under ambient conditions. We were successful in the preparation of the N-phenyl derivative of the chiral diamine (12)- borane complex in benzene solution (eq. 23).

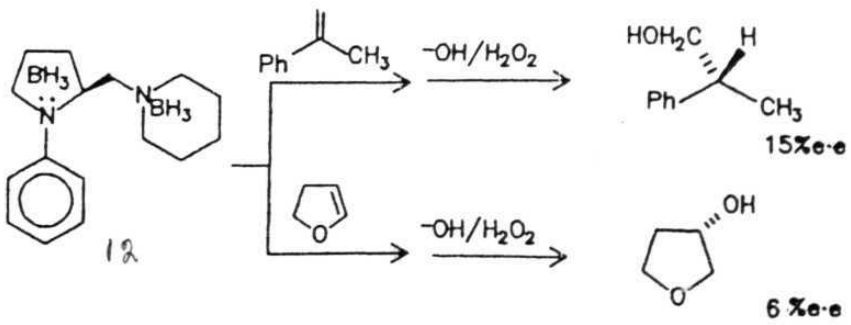


— 23

This amine has two tertiary nitrogen centers which can complex with borane. However, the reactivity should differ since one of the nitrogens is attached to phenyl group. The N-phenyl nitrogen is expected to form weak complex with BH_3 which should hydroborate olefins under ambient conditions.

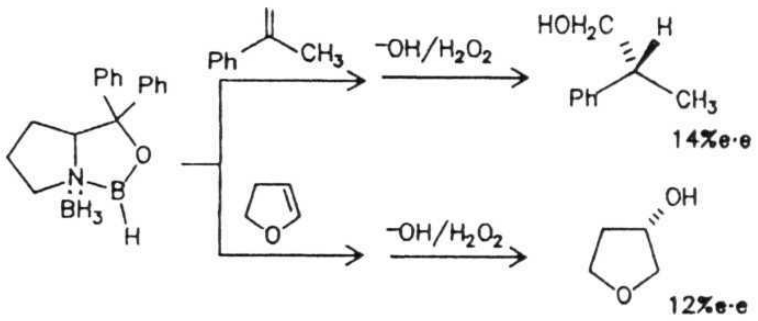
Accordingly, the hydroboration studies of α-methylstyrene and 2,3-dihydrofuran were carried out using this amine-BH_3 in separate runs.

Scheme 21



Similar hydroboration studies were carried out using borane complex of another important chiral ligand, the S(-)-α,α-diphenyl-2-pyrrolidinemethanol. Borane complex of this was prepared as described previously (see experimental section for details) in the presence of triethylamine. The amine-BH_3 prepared in this way will contain some amount of $Et_3N{:}BH_3$. However, this complex does not hydroborate alkenes under ambient conditions and hence it is not expected to interfere in this reaction.

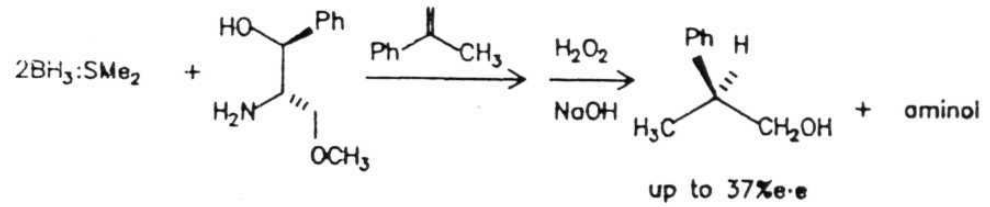
Scheme 22



As discussed previously, the oxazaborolidine system gives very high level of asymmetric inductions in the case of reductions of prochiral ketones. But in the hydroborations, the optical inductions are very poor. In the olefin hydroborations, there will not be catalytic effect due to the presence of N-BH-O group and hence the low asymmetric inductions are not entirely unexpected.

It has been reported by Mandal *et al* that the (1S, 2S)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol/$BH_3{:}SMe_2$ combination hydroborates α-methylstyrene in 37% e.e.[59]

Scheme 23



up to 37%e.e

Unfortunately, the authors did not attempt to clarify the nature of the reactive species.

The asymmetric inductions obtained in the hydroboration of alkenes with different amine-boranes studied so far are somewhat poor. This is not completely unexpected since in all mechanisms the Lewis base gets detached from the BH_3 moiety to some extent in the course of reaction. Another problem is the formation of dialkylborane species R_2BH, involving the intermediacy of RBH_2 species. The mechanism of hydroboration by the RBH_2 species could be different from that of the BH_3-Lewis base complexes. Although a safe conclusion cannot be drawn based on the results obtained, it appears that the Lewis base does play a role in the transition state of the hydroboration of olefins by BH_3-Lewis base complexes. However, operation of more than one mechanistic pathway cannot be also ruled out.

Conclusions

The (-)-N-α-methylbenzyl-3,5-dihydrodinaphthazepine-BH_3 complex was prepared and utilized along with BF_3:OEt_2 in the asymmetric reduction of prochiral ketones to obtain the corresponding alcohols in 11-57% e.e. Catalytic reduction of acetophenone was also achieved

using achiral amine–borane complexes in the presence of a chiral amine–BF_3 complex. A transition state comprising of $R_3^*N{:}BF_3{-}BH_3$ and ketone was considered. Similar studies have been also carried out using optically active N-α-methylbenzyl-3,4-diphenylpyrrolidine–BH_3 complex.

A convenient method for the preparation of Corey's oxazaborolidine (CBS catalyst) *in situ* was developed. Prochiral ketones have been reduced using N,N-diethylaniline–borane complex in the presence of this catalyst in 90% e.e. It has been also observed that tertiary amines such as triethylamine and N,N-diethylaniline facilitate the formation of oxazaborolidine.

Chiral diamine–borane and oxazaborolidine–borane complexes were prepared and utilized in the hydroboration of prochiral olefins and alcohols were obtained after oxidation in up to 15% e.e. The results indicate that the Lewis base does play a role in the transition state of the hydroboration reaction. However, operation of more than one mechanistic pathway cannot be also ruled out.

EXPERIMENTAL SECTION

General details

Several items given in the experimental section of chapter 1 are also applicable for the experiments outlined here. The N,N-diethyl-aniline was distilled over anhydrous KOH in small (20 ml) quantities and kept under nitrogen for utilization. The reduction and hydroboration reactions were carried out at least twice in each case. In each case the optical rotations were measured at two concentrations.

Acetophenone (98%), propiophenone (98%), butyrophenone (98%), α-napthyl methyl ketone (98%) and BF_3:OEt_2 (98%) supplied by Fluka (Switzerland) were distilled prior to utilization. α-Methylstyrene (98%), supplied by SD Fine chemicals (India) and 2,3-dihydrofuran (98%) supplied by Fluka (Switzerland) were further purified by distillation and were utilized in hydroborations.

Attempted reduction of acetophenone using chiral amine-borane complex:

Diborane gas (20 mmol) generated through the slow addition of I_2 (5.2 g, 20 mmol) in diglyme to $NaBH_4$ (1.6 g, 40 mmol) in diglyme at room temperature, was bubbled into the benzene solution of (-)-N-α-methylbenzyl-3,4-dihydrodinaphthazepine (3.99 g, 10 mmol) slowly during 2h. To this acetophenone (1.2 g, 10 mmol) was added at room temperature and the reaction mixture was stirred for 24h. Reaction was quenched with water and HCl (3N, 10 ml) was added.

Organic layer was separated and washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent and column separation using hexane:ethyl acetate/98:2 gave unreacted acetophenone along with the amine borane complex.

Reduction of acetophenone using chiral amine (6)-borane complex in the presence of $BF_3.OEt_2$.

Chiral amine (6)-borane complex (10 mmol) was prepared in benzene (40 ml) as mentioned in the previous experiment. This was cooled to 0^oC under nitrogen atmosphere and $BF_2.OEt_2$ (1.42 g, 10 mmol) was slowly added during 5 min. Acetophenone (1.2 g, 10 mmol) was added at 0^oC and the reaction mixture was stirred for 2h at the same temperature. The reaction was quenched with water and organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated under reduced pressure. Amine present in the mixture was precipitated as BF_3 salt using BF_3:OEt_2 in ether solvent. Ether layer was decanted and concentrated to give crude alcohol product. This was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent. It was further purified by distillation under reduced pressure.

Yield : 1.0 g (82%)

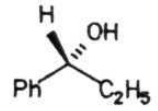
B.P. : 80^oC (6mm) Lit.[62] 203^oC (760 mm)

$[\alpha]_D^{25}$ = + 23^o (C3, MeOH) Lit.[33] $[\alpha]_D^{15}$ = -45.5^o(C3, MeOH)

IR (neat) ν_{max} : 3350, 3050, 1600 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 1.4 (d, 3H), 2.9 (bs, H), 4.8 (q, 1H), 7.3 (m, 5H).

Several other prochiral ketones were also reduced following the above procedure.

$PhCOC_2H_5$ → 

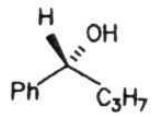
Yield : 1.1 g (81%)

B.P. : 87°C (10 mm) Lit.[62] 213-215°C (760 mm)

$[\alpha]_D^{25}$ = + 20° (C1, Me_2CO) Lit.[34] $[\alpha]_D^{25}$ = -47.03°(C1, Me_2CO)

IR (neat) ν_{max} : 3400, 1600, 1100 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 0.9 (t, 3H), 1.7 (m, 2H), 2.0 (s, 1H), 4.5 (t, 1H), 7.3 (m, 5H).

$PhCOC_3H_7$ → 

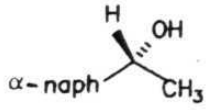
Yield : 1.2 g (80%)

B.P. : 100°C (6 mm) Lit.[62] 232°C (760 mm)

$[\alpha]_D^{25}$ = + 5° (C2, benzene) Lit.[34] $[\alpha]_D^{25}$ = +45.2° (C3, benzene)

IR (neat) ν_{max} : 3400, 1600, 1060 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 0.9 (t, 3H), 1.3 (m, 2H), 1.7 (m, 2H), 2.0 (bs, 1H), 4.6 (t, 1H), 7.3 (m, 5H).

α-naphCOCH$_3$ → 

Yield : 1.17 g (78%)

M.P. : 34°C

$[\alpha]_D^{25}$= + 45° (C3, MeOH) Lit.[35] $[\alpha]_D^{25}$ = -78.9° (C3, CH_3OH)

IR (neat) ν_{max} : 3400, 1600, 1070 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 1.7 (d, 3H), 2.0 (bs, 1H), 5.5 (q, 1H), 7.3-8.2 (m, 7H).

Examination of the formation of chiral amine-borane complex through the formation of PPh_3:BH_3

Diborane gas (20 mmol) generated by the addition I_2 (5.3 g, 20 mmol) in diglyme to $NaBH_4$ (1.6 g, 40 mmol) in diglyme at room temperature was passed through the benzene solution of chiral amine (6), (3.99 g, 10 mmol) slowly during 3h. To this triphenylphosphene (2.62 g, 10 mmol) in benzene (20 ml) was added and reaction mixture was stirred for 12h at room temperature. Solvent was evaporated and the residue was subjected to column chromatography using silica gel. Hexane eluted triphenylphosphene borane and hexane:ethyl acetate/ 95:5 eluted amine.

Yield of PPh_3:BH_3 : 2.6 g (86%)

M.P. : 186.5°C Lit.[61] 188°C

IR (neat) ν_{max} : 2350 (b), 740, 710 cm^{-1}

Reduction of acetophenone using N,N-diethylaniline-borane complex in the presence of chiral amine (6)-BF_3 complex as Lewis acid catalyst:

Chiral amine (6)(3.99 g, 10 mmol) was taken in dry ether (20 ml) and BF_3:OEt_2 (1.42 g, 10 mmol) was added at 0°C. Chiral amine BF_3 complex was precipitated and solvent ether was pumped off under

nitrogen atmosphere.

Into a separate two-necked septum flask N,N-diethylaniline (1.49 g, 10 mmol) in benzene (40 ml) was taken and diborane gas (20 mmol) was bubbled through this at $10^{o}C$ during 3h. The N,N-diethylaniline-borane thus prepared was transferred to the flask containing chiral amine-BF_3 complex under nitrogen atmosphere. To this, acetophenone (1.2 g, 10 mmol) was added at $0^{o}C$ and stirred for 3h at the same temperature. Reaction was quenched with water (5 ml). The organic layer was separated and washed with 3N HCl (3 x 10 ml) to remove N,N-diethylaniline. The chiral amine was removed as BF_3 complex to obtain amine free reduced product. The alcohol was purified by column chromatography over silica gel using hexane:ethyl acetate/90:10 as eluent. This was further purified by distillation under reduced pressure.

Yield : 1.0 g (82%)

$[\alpha]_D^{25}$= + 23^{o} (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5^{o} (C3, CH_3OH).

Reduction of acetophenone (1 eq) using triethylamine-borane complex (1 eq) in the presence of chiral amine (6)-BF_3 complex(1 eq.):

Chiral amine (6)-BF_3 complex (10 mmol) was prepared as outlined earlier.

Triethylamine-borane complex (10 mmol) was prepared by passing diborane (20 mmol) through a benzene (40 ml) solution of triethyl-amine (0.71 g, 10 mmol) at $10^{o}C$ during 3h. The chiral amine-BF_3 complex (10 mmol) was added to this followed by acetophenone (1,2 g,

10 mmol) at 0°C. The mixture was stirred for 15h at room temperature. Reaction was quenched with water (5 ml), organic layer was separated washed with 3N HCl (3 x 10 ml) then with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and chiral amine was removed as amine BF_3 complex. The alcohol thus obtained was purified by column chromatography on silica gel using hexane ethyl acetate/90:10 as eluent. This was further purified by distillation under reduced pressure.

Yield : 0.98 g (80%)

$[\alpha]_D^{25}$= + 22° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH).

Reduction of acetophenone (1 eq.) using N,N-diethylaniline-borane complex (1 eq.) in the presence of chiral amine-BF_3 complex (0.75 eq.)

N,N-Diethylaniline-borane (10 mmol) was prepared in benzene (30 ml) as mentioned earlier. To this was added chiral amine (6) BF_3 complex (7.5 mmol) followed by acetophenone (1.2 g, 10 mmol) at 0°C. The contents were further stirred 3h at this temperature. The reaction was quenched with water (5 ml) and HCl (3N, 10 ml) was added. Organic layer was separated, washed with 3N HCl (2 x 10 ml) and dried over anhydrous $MgSO_4$. Solvent was evaporated and chiral amine was precipitated as BF_3 complex. The alcohol was separated and subjected to column separation on silica gel using hexane:ethyl acetate/90:10 as eluent. This was further purified by distillation under reduced pressure.

Yield : 1.0 g (82%)

$[\alpha]_D^{25}$= + 23° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH).

Reduction of acetophenone (1 eq.) using N,N-diethylaniline-borane complex (1 eq.) in the presence of chiral amine-BF_3 complex (0.5 eq.):

The procedure followed was same as mentioned in the earlier experiment except for the change that 5 mmol of chiral amine (6)-BF_3 was used instead of 7.5 mmol. The product alcohol was purified as mentioned in earlier experiments and optical rotation was measured.

Yield : 0.97 g (80%)

$[\alpha]_D^{25}$= + 22° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH).

Reduction of acetophenone (1 eq.) using N,N-diethylaniline-borane complex (1 eq.) in the presence of chiral amine (6)-BF_3 complex (0.4 eq.):

The procedure followed was same as mentioned in earlier experiment except for the change that chiral amine-BF_3 complex (4 mmol) was employed. The product alcohol was purified and optical rotation was measured.

Yield : 1.0 g (80%)

$[\alpha]_D^{25}$= + 23° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Reduction of acetophenone (1 eq.) using N,N-diethylaniline-borane complex (1 eq.) in the presence of chiral amine (6)-BF_3 complex (0.25 eq.):

The procedure followed was same as mentioned earlier but for the change that chiral amine-BF_3 complex (2.5 mmol) was utilized. The alcohol was purified as mentioned earlier and optical rotation was

measured.

Yield : 0.97 g (80%)

$[\alpha]_D^{25}$= + 9° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH).

Reduction of acetophenone (1 eq.) using triethylamine-borane complex (1 eq.) in the presence of chiral amine (6)-BF_3 complex (0.5 eq.):

Triethylamine-borane complex (10 mmol) in benzene (30 ml) was prepared as mentioned earlier. To this chiral amine (6)-BF_3 complex prepared as outlined earlier was added (5 mmol) followed by acetophenone (1.2 g, 10 mmol) at 0°C and stirred for 15h at the same temperature. The reaction was quenched with water (5 ml) and alcohol was separated as mentioned earlier. Optical rotation of the pure alcohol was measured.

Yield : 0.97 g (80%)

$[\alpha]_D^{25}$= + 22° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH).

Reduction of acetophenone by the chiral amine:BF_3/B_2H_6 system:

N-α-Methylbenzyl dihydrodinaphthazepine (3.97 g, 10 mmol) was taken in dry ether and $BF_3.OEt_2$ (1.4 g, 10 mmol) was added at 0°C. Solvent ether was evaporated with a stream of dry nitrogen. Dry benzene (50 ml) was added to this and diborane (20 mmol) generated as described earlier was passed through this solution at 10°C. Acetophenone (1.2 g, 10 mmol) was added and stirred for 2h at 10°C. Reaction was quenched with water and HCl (3N, 10 ml) was added organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated on rotavapour. The product was taken in ether

and BF_3:OEt_2 (12 mmol) was added to precipitate the amine as BF_3 complex. Ether layer was decanted and evaporated to isolate the alcohol. This was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent. It was further purified by distillation under reduced pressure.

Yield : 1.0 g (82%)

B.P. : 97^{o} (5 mm) Lit.[62] 203^{o}C (760 mm)

$[\alpha]_D^{25}$= + 23^{o} (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5^{o} (C3, CH_3OH).

Reduction of acetophenone using chiral amine (7)-borane complex in the presence of BF_3:OEt_2:

Chiral amine (7)-borane complex (10 mmol) in benzene was prepared as mentioned in earlier experiment. To this BF_3:OEt_2 (1.42 g, 10 mmol) was added at 0^{o}C followed by the addition of acetophenone (1.2 g, 10 mmol) under static nitrogen atmosphere. The contents were further stirred for 4h at 0°C. The reaction was quenched with water and dil.HCl (3N, 10 ml) was added. Organic layer was separated and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic extract was washed with 3N NaOH (3 x 10 ml), brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chromatography on silica gel. Hexane:ethyl acetate 95:5 eluted chiral amine and hexane:ethyl acetate 90:10 eluted 1-phenylethanol. The alcohol was further purified by distillation under reduced pressure.

Yield : 1.05 g (86%)

$[\alpha]_D^{25}$= + 8^{o} (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5^{o} (C3, CH_3OH)

Reduction of propiophenone using chiral amine (7)-borane complex in the presence of BF_3:OEt_2:

Procedure followed was similar to earlier experiments.

Yield : 1.14 g (84%)

$[\alpha]_D^{25}$= + 5° (C1, Me_2CO) Lit.[34] $[\alpha]_D^{25}$ = -47.03° (C1, Me_2CO)

Spectral data showed 1:1 correspondence with that of same compound obtained earlier.

Reduction of acetophenone using triethylamine-borane in the presence of BF_3:OEt_2:

Triethylamine-borane (10 mmol) was prepared by passing B_2H_6 (20 mmol), through a benzene (30 ml) solution of triethylamine (1.1 g, 10 mmol) at 10°C. To this BF_3.OEt_2 (1.42 g, 10 mmol) was added at 0°C followed by acetophenone (1.2 g, 10 mmol). The reaction mixture was stirred for 8h at the same temperature. The reaction was quenched with water (5 ml) and HCl (3N, 10 ml) was added. Organic layer was separated, washed with 3N HCl (3 x 10 ml) brine solution and dried over anhydrous $MgSO_4$. Solvent was evaporated to yield crude alcohol product which was purified by column chromatography on silica gel using hexane.ethyl acetate/90:10 as eluent followed by distillation under reduced pressure.

.Yield : 1.04 g (85%)

Spectral data showed 1:1 correspondence with 1-phenylethanol.

Reduction of acetophenone using the associated complex of triethylamine–BF_3 with B_2H_6:

Triethylamine (1.1 g, 10 mmol) was taken in dry ether (20 ml) and BF_3:OEt_2 (1.42 g, 10 mmol) was added under nitrogen atmosphere. Ether was evaporated by passing a stream of dry nitrogen. To this dry benzene (30 ml) was added. Diborane gas (20 mmol) generated as mentioned earlier was bubbled through this during 4h at 10^{o}C. The bubbler was replaced with a glass stopper and acetophenone (1.2 g, 10 mmol) was added and the mixture was stirred for 8h. at 0^{o}C. The reaction was quenched with water. Organic layer was separated and washed with 3N HCl (3 x 10 ml), brine solution successively and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude alcohol product which was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent. This was further purified by distillation under reduced pressure.

Yield : 1.0 g (84%)

Spectral data showed 1:1 correspondence with 1-phenylethanol obtained earlier.

Reduction of acetophenone using α,α–diphenylpyrrolidinemethanol–borane complex:

Diborane gas (20 mmol) was bubbled through the benzene (30 ml) solution of α,α–diphenylpyrrolidinemethanol (2.52 g, 10 mmol) during 4h at 10^{o}C. The bubbler was replaced by a glass stopper and the mixture was refluxed for 3h. The contents were brought to 10^{o}C and

again diborane gas (20 mmol) was bubbled through the reaction mixture during 4h at $10^{o}C$. Acetophenone (1.2 g, 10 mmol) was added and the contents were further stirred for 1h $10^{o}C$. The reaction was quenched with water and the organic layer was washed with 3N HCl (3 x 10 ml) to remove the amino alcohol (3) as hydrochloride salt. The organic layer was further washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chromatography using hexane:ethyl acetate/85:15 as eluent. The alcohol thus obtained was further purified by distillation under reduced pressure.

Yield : 1.05g (86%)

B.P. : 85^{o} (9 mm) Lit. $203^{o}C$ (760 mm)

$[\alpha]_D^{25}$= + 26^{o} (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5^{o} (C3, CH_3OH)

Reduction of prochiral ketones using the reagent prepared from α,α-diphenyl-2-pyrrolidinemethanol and $H_3B{:}N(C_2H_5)_2Ph$.

N,N-Diethylaniline borane was prepared (10 mmol) in benzene as mentioned earlier. To this α,α-diphenyl-2-pyrrolidinemethanol (2.53 g, 10 mmol) in dry THF (20 ml) was added through a cannula under nitrogen atmosphere at 0°C. The contents were slowly brought to room temperature and then refluxed for 4h. The reaction mixture was cooled to $0^{o}C$ under nitrogen atmosphere and N,N-diethylaniline-borane (10 mmol) in benzene (30 ml) was added under nitrogen atmosphere. Acetophenone (1.2 g, 10 mmol) was added at $10^{o}C$ and the contents were stirred for another 30 min. The reaction was quenched with water (5 ml) N,N-diethylaniline and α,α-diphenyl-2-pyrrolidinemethanol were removed as hydrochloride salts by stirring with 3N HCl (3 x 15 ml). The organic layer was separated and washed with brine and dried over

anhydrous $MgSO_4$. Evaporation of solvent afforded crude alcohol which was purified by column chromatography on silica gel using hexane:ethyl acetate/90:10 as eluent, followed by distillation under reduced pressure.

Yield : 1.1 g (90%)

Physical and spectral data showed 1:1 correspondence with the compound reported earlier.

$[\alpha]_D^{20} = +41^o$ (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25} = -45.5^o$ (C3, CH_3OH)

The reduction of acetophenone (10mmol) was carried at various concentrations of the oxazaborolidine complex following the above procedure and the results are summarized in Table III.

Experiment for examining whether the presence amine facilitates the formation of oxazaborolidine:

Diborane gas (20 mmol) generated as mentioned earlier was bubbled through the benzene (30 ml) solution of α,α-diphenylpyrrolidine-methanol (2.5 g, 10 mmol) during 4h at 10^oC. The bubbler was replaced with a glass stopper and triethylamine (0.2 g, 2 mmol) was added. The reaction mixture was refluxed for 4h and then cooled to 10^oC under nitrogen atmosphere. Again diborane gas (20 mmol) was bubbled through the solution during 4h at 10^oC and bubbler was replaced with a glass stopper. Acetophenone (1.2 g, 10 mmol) was added and the contents were further stirred for 1h at 10^oC. The reaction was quenched with water. The organic layer was separated and the pyrrolidinemethanol was removed as hydrochloride salt by washing with 3N HCl (3 x 10 ml).

Organic layer was further washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was column separated on silica gel. Hexane eluted triethylamine-borane complex and hexane:ethyl acetate/85:15 eluted 1-phenylethanol which was further purified by distillation under reduced pressure.

Yield : 1.05 g (86%)

$[\alpha]_D^{25}$= +41.3° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

Reduction of acetophenone (1 eq.) with N,N-diethylaniline-borane complex (1 eq.) in the presence of chiral oxazaborolidine catalyst (8) (0.25 eq.):

Diborane gas (5 mmol) was bubbled through the benzene (30 ml) solution of α,α-diphenylpyrrolidinemethanol (0.65 g, 2.1 mmol) during 4h at 10°C. The bubbler was replaced with a glass stopper and triethylamine (0.1 g, 1 mmol) was added. The reaction mixture was refluxed for 4h and then cooled to 10°C nitrogen atmosphere. To this was added N,N-diethylaniline-borane complex (10 mmol) followed by acetophenone (1.2 g, 10 mmol). The contents were further stirred for 1h at 10°C. The reaction was quenched with water. Amines were removed as hydrochloride salts by washing the organic layer with 3N HCl (3 x 10 ml). The organic layer was further washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chromatography on silica gel. Hexane eluted triethylamine-borane (1 mmol) and hexane:ethyl acetate/85:15 eluted 1-phenylethanol which was further purified by distillation under reduced pressure.

Yield : 1.1 g (90%)

$[\alpha]_D^{25}$= + 41° (C3, CH_3OH) Lit.[33] $[\alpha]_D^{25}$ = -45.5° (C3, CH_3OH)

This procedure was also used for the reduction of propiophenone.

Yield : 1.2 g (88.2%)

$[\alpha]_D^{25}$= + 42° (C1, Me_2CO) Lit.[34] $[\alpha]_D^{25}$ = -47.03°(C1, Me_2CO)

Hydroboration of α-methylstyrene using chiral oxazaborolidine-borane complex:

Diborane gas (20 mmol) was slowly bubbled through benzene (40 ml) solution of α,α-diphenylpyrrolidinemethanol (2.53 g, 10 mmol) during 4h at 10°C. The bubbler was replaced by a glass stopper. Free borane gas present in the flask was flushed out with a stream of nitrogen gas. Triethylamine (0.2 g, 2 mmol) was added and the mixture was refluxed for 5h. The contents were cooled to 10°C under nitrogen and again diborane gas (20 mmol) was bubbled through the reaction mixture during 4h. The bubbler was replaced with a stopper and the flask was flushed with stream of nitrogen gas to remove uncomplexed borane gas. α-Methylstyrene (1.2 g, 10 mmol) was added and the reaction mixture was further stirred for 10h at room temperature. Reaction was quenched with water and THF (20 ml) was added. The organoborane was oxidized using 3N NaOH (15 ml), H_2O_2 (16%, 10 ml) and stirring for 4h at room temperature. Organic layer was separated and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic extract was washed with 3N HCl (3 x 10 ml) to remove aminol, brine and

dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chromatography on silica gel. Hexane:ethyl acetate/ 85:15 eluted 2-phenylpropanol which was further purified by distillation under reduced pressure.

Yield : 1.15 g (84%)

$[\alpha]_D^{25}$= +3° (C3, CH_3OH) Lit.[62] $[\alpha]_D^{25}$ = -12.0° (3.76, CH_3OH) for 85% e.e

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

^1H NMR (200 MHz, $CDCl_3$) : 1.24, (t, 3H), 1.8 (bs, 1H), 2.9 (m, 1H), 3.65 (d, 2H), 7.24 (m, 5H).

Hydroboration of 2,3-dihydrofuran using chiral oxazaborolidine-borane complex:

Oxzazaborolidine (8) borane complex (10 mmol) in dry benzene (30 ml) was prepared as mentioned in the previous experiment. To this 2,3-dihydrofuran (0.7 g, 10 mmol) was added at 10°C and the reaction mixture was stirred for 10h at room temperature. The reaction was quenched with water and THF (20 ml) was added and the organoborane was oxidized using 3N NaOH (1.5 ml) H_2O_2 (16%, 12 ml) and stirring for 4h at room temperature. Organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. Aqueous layer was saturated with excess of K_2CO_3 (~ 40 g) and extracted with ether (3 x 20 ml). Combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was subjected to column chromatography on silica gel. Hexane:ethyl acetate/85:15 eluted 3-hydroxytetrahydrofuran which was further purified by distillation under reduced pressure.

Yield : 0.62 g (71%)

B.P. : 74°C (10 mn) Lit.[65] 80°C (15 mn)

$[\alpha]_D^{25}$ = + 2.08° (C2.4, CH_3OH) Lit.[65] $[\alpha]_D^{25}$ = −17.3° (C2.4, CH_3OH).

IR (neat) ν_{max} : 3450, 2950, 2870, 1120, 1060 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 34.9, 66.3, 70.9, 74.9.

Hydroboration of α-methylstyrene with chiral diamine-borane (12) complex:

Chiral diamine borane complex (12) (10 mmol) was prepared by bubbling diborane gas (40 mmol) through the benzene (40 ml) solution of diamine (25.2 g, 10 mmol) during 4h at 10°C. Bubbler was replaced by a glass stopper and the flask was flushed with dry nitrogen gas to remove any uncomplexed borane. α-Methylstyrene (1.2 g, 10 mmol) was added at 10°C and the contents were further stirred for 10h at room temperature. The reaction was quenched with water and THF (20 ml) was added. The organoborane was oxidized using 3N NaOH (15 ml) and 16% H_2O_2 (15 ml) and the reaction mixture was stirred for 4h at room temperature. The organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). Combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was treated with BF_3:OEt_2 to liberate complexed borane. To this 3N NaOH (15 ml) was added and extracted with ether (3 x 20 ml).The combined ether extract was washed with 3N HCl (3 x 10 ml) to remove amine as hydrochloride salt, then with brine solution and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded crude alcohol which was purified by column chromatography on silica gel using hexane:ethyl acetate/85:15 as eluent.It was further purified by distillation under reduced pressure

Yield : 0.98 g (72%)

$[\alpha]_D^{25}$= +2.12°(C3.3, CH_3OH) Lit. $[\alpha]_D^{25}$= -12.0°(3.76, CH_3OH) for 85% e.e

Spectral data showed 1:1 correspondence with that of the authentic sample obtained earlier.

Hydroboration of 2,3-dihydrofuran with chiral diamine-borane complex (12)

Chiral diamine-borane complex (12) (10 mmol) in benzene (30 ml) was prepared as described in earlier experiment. To this 2,3-dihydrofuran (0.7 g, 10 mmol) was added and 10°C and the mixture was stirred for 10h at room temperature. The reaction was quenched with water (5 ml) and THF (20 ml) was added. The organoborane was oxidized using 3N NaOH (15 ml) H_2O_2 (16%, 12 ml) and stirring at room temperature for 4h. The organic layer was separated and washed with 3N NaOH (2 x 5 ml), brine and dried over anhydrous $MgSO_4$. The aqueous layer was separated, excess of K_2CO_3 (40 g) was added and extracted ether (3 x 20 ml). The combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Organic solvent was evaporated and the residue was subjected to column separation on silica gel. Hexane: ethyl acetate/85:15 eluted 3-hydroxytetrahydrofuran. The product was further purified by distillation under reduced pressure.

Yield : 70% (0.61 g)

B.P. : 73°C (10 mm) Lit.[65] 80°C (15 mm)

$[\alpha]_D^{25}$= + 1° (C2, CH_3OH) Lit.[65] $[\alpha]_D^{25}$ = -17.05° (2.4, CH_3OH).

Spectral data showed 1:1 correspondence with that of the authentic sample obtained earlier.

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Chapter 3

Selective Reductions Using $NaBH_4$ and I_2

INTRODUCTION

Sodium borohydride is one of the most useful reducing agents available to organic chemists. It is widely available and it is easy to handle this reagent. Unlike several other metal hydride reagents, sodium borohydride is not very much sensitive to moisture and atmospheric oxygen under ambient conditions. In fact, most of the sodium borohydride reductions can be carried out in solvents such as alcohol and water. Functional groups such as aldehydes,[1] ketones,[2] acid chlorides,[3] oximes,[4] lactones[5] and imines[6] are readily reduced by sodium borohydride. However, it does not reduce functional groups such as carboxylic acids, carboxylic 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 generation of diborane and discovery of hydroboration of olefins in ether solvents (eq. 1-5).[7-9]

$$NaBH_4 + AlCl_3 \longrightarrow Al(BH_3)_3 + NaCl \qquad \text{— 1}$$

$$3NaBH_4 + BCl_3 \xrightarrow{\text{diglyme}} 3NaCl + 2B_2H_6 \qquad \text{— 2}$$

$$3NaBH_4 + 4BF_3{:}OEt_2 \xrightarrow{\text{diglyme}} 3NaBF_4 + 2B_2H_6 \qquad \text{— 3}$$

$$2NaBH_4 + Hg_2Cl_2 \xrightarrow{\text{diglyme}} 2Hg + 2NaCl + H_2 + B_2H_6 \qquad \text{— 4}$$

$$2NaBH_4 + I_2 \xrightarrow{\text{diglyme}} 2NaI + H_2 + B_2H_6 \qquad \text{— 5}$$

The diborane generated in this way can be complexed with Lewis

bases such as ethers and amines. Several of these borane complexes are commercially available and they have a very rich chemistry.[10]

However, efforts are still continuing for developing convenient methods for the reduction of functional groups using $NaBH_4$ along with other additives. For example, it has been recently reported that carboxylic acids, esters and amides are reduced to the corresponding alcohols and amines using $NaBH_4/ZnCl_2$ in THF in the presence of certain amines under reflux conditions.[11] It has also been reported that a mixture of R_2SeBr_2 (where R= CH_2CH_2Br or C_2H_5) and $NaBH_4$ reduces amides and nitriles to the corresponding amines.[12] It has been shown that the later combination gives borane in THF.

Carboxylic acids are not normally reduced by $NaBH_4$ in protolytic solvents. However, a number of aromatic and aliphatic carboxylic acids are reduced to alcohols using $NaBH_4$ at 300°C. Treatment of $NaBH_4$ with carboxylic acids gives hydrogen and acyloxyborohydride species (eq. 6). Even in neat carboxylic acids, the triacyloxy borohydride $Na(RCOO)_3BH$ is relatively stable and the last hydride is lost only upon heating or prolonged exposure to RCOOH.[13] The mono and diacyloxyborohydrides have been reported to form, utilizing requisite amounts of RCOOH.[13]

$$NaBH_4 + xRCOOH \longrightarrow Na\,BH_{4-x}(OCOR)_x + xH_2 \quad \text{—— 6}$$

$$x = 1-3$$

The reagents obtained in this way have been found useful in several applications. For example, acyloxyborohydride reagent obtained in the reaction of acetic acid and $NaBH_4$ was used for the hydroboration of 1-hexene.[14]

$$n\text{-}C_4H_9CH{=}CH_2 \xrightarrow[2\cdot\ NaOH,\ H_2O_2]{1\cdot\ NaBH_4/AcOH} n\text{-}C_4H_9\text{-}CH_2\text{-}CH_2OH \qquad \text{---- 7}$$

Originally, it was observed that upon reaction of $NaBH_4$ with CH_3COOH in equimolar amounts, a material analyzed for '$NaBH_3OAc$' crystallized out of THF.[14] The reaction of this material with water liberates three moles of hydrogen. The material gives $(RO)_3P{:}BH_3$ in good yields on treatment with trialkylphosphites.

It has been observed that the reaction of isobutyric acid (1 eq.) and $NaBH_4$ (1 eq.) in THF actually gives a suspension in which $NaBH_4$ is in equilibrium with the mono-, di-, tri-, and tetra-acyloxy-borohydride species.[15]

$$NaBH_4 \rightleftharpoons NaBH_3OAc \rightleftharpoons NaBH_2(OAc)_2 \rightleftharpoons$$

$$NaBH(OAc)_3 \rightleftharpoons NaB(OAc)_4$$

Among the above acyloxyborohydride species, the following hydride delivering ability order was observed.[16]

$$\text{-}BH_3OCOR > \text{-}B(OCOR)_2 > \text{-}BH(OCOR)_3$$

The $RCOOH/NaBH_4$ combinations in neat carboxylic acids or in solvents such as benzene, THF, dioxane, DMF or DCM have been utilized for several useful synthetic transformations. An excellent review has appeared.[13] We have undertaken this work in order to examine the possibility of reducing carboxylic acids under ambient conditions.

RESULTS AND DISCUSSION

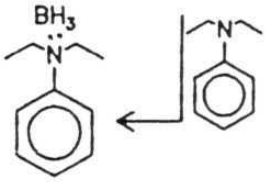
Although it has been known for a long time that pure diborane can be obtained by the reaction of I_2 with $NaBH_4$ in diglyme, this readily accessible reagent system did not receive much attention in synthetic applications(eq.8).[7]

$$2NaBH_4 + I_2 \xrightarrow{\text{diglyme}} 2NaI + B_2H_6 + H_2 \qquad \text{— 8}$$

A convenient procedure has been developed in this laboratory to trap the diborane generated in this way to form borane Lewis base complexes for utilization in organic transformations (Scheme 1).[17]

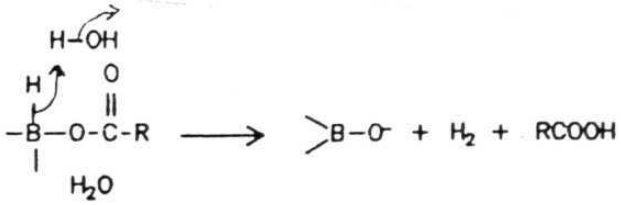
Scheme 1

$$2NaBH_4 + I_2 \xrightarrow{\text{diglyme}} 2NaI + B_2H_6 + H_2$$



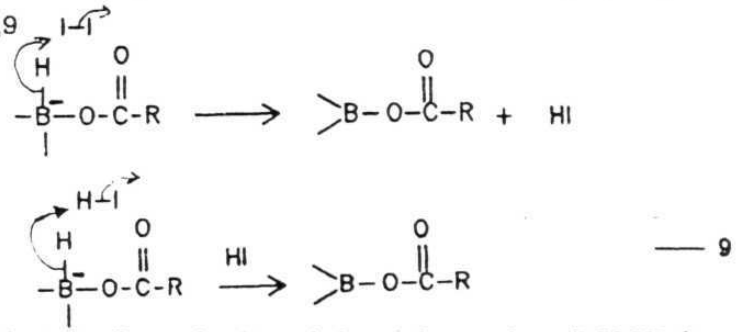
Reaction of $NaBH_4$ (1 eq) with carboxylic acid (1 eq) gives acyloxy borohydride species. The resulting material reacts with H_2O to liberate three moles of hydrogen. The acid was recovered after workup.[14]

Scheme 2



It was thought that addition of a reagent such as iodine to this

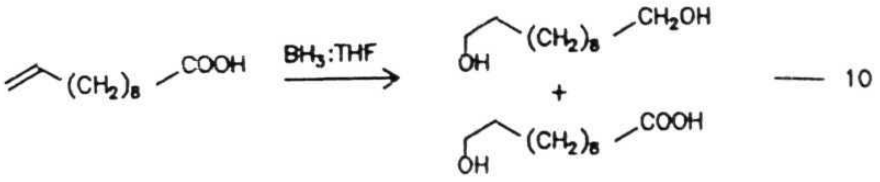
acyloxyborohydride species would facilitate the reduction of the carboxylic acids since the boron in the resulting acyloxyborane will be tricoordinated. Such species are known to undergo very fast reductions (eq. 9).[8,9]



— 9

We have found that facile reduction takes place when RCOOH (1 eq) in THF is added slowly to a suspension of $NaBH_4$ in THF followed by iodine (0.5 eq) in THF (see experimental section for details). After usual workup the corresponding alcohols were isolated in good yields. This procedure was found to be a general one and several carboxylic acids were converted into the corresponding alcohols in good yields.[18] The results are summarized in the Table I.

Following this procedure, aliphatic and aromatic carboxylic acids (entries 1-7 in Table I) are reduced to the corresponding alcohols in very good yields. Reduction of cinnamic acid gives the corresponding α,β-unsaturated alcohol. It is interesting to note that reduction of this substrate using $LiAlH_4$ leads to 1-phenylpropanol.[19] Moreover, the olefinic group is not affected when it is away from carboxylic group. For example, 10-undecenoic acid on reduction with this reagent system gives 10-undecenol. However, the same substrate when treated with even insufficient amount of BH_3:THF gives 1,11-undecanediol (after oxidation with $H_2O_2/^-OH$) as the major product along with minor amounts of 11-hydroxyundecenoic acid (eq. 10).[20]



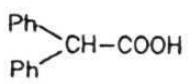
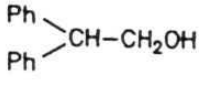
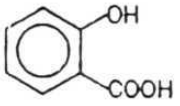
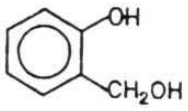
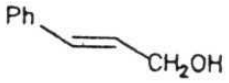
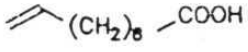
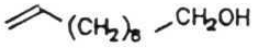
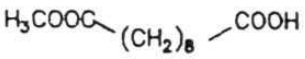
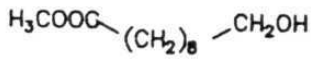
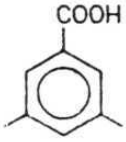
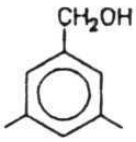
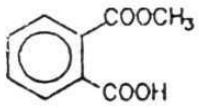
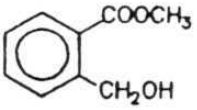
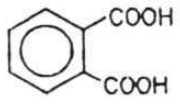
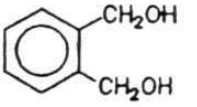
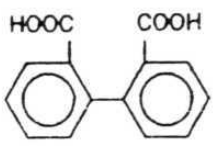
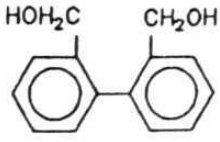
— 10

The present reagent system is also effective in reducing an acid group, leaving behind an ester group unaffected when both the groups are present in the compound. This is so even when the ester group is near the acid group (entries 10 and 11, Table I).

Dicarboxylic and hydroxycarboxylic acids react with borane reagents to give insoluble, polymeric intermediates. Once these insoluble polymers form, the inevitable result is an incomplete reduction.[20] Sometimes the corresponding lactone is obtained as the major product.[21] The $NaBH_4/I_2$ system completely reduces dicarboxylic acids such as phthalic acid and diphenic acid to the corresponding diols in very good yields (entries 12 & 13, Table I).

The selectivities realized with the $NaBH_4/I_2$ combination over the borane reagents such as BH_3:THF deserve an explanation. Hydroboration of olefins with $RCOOH/NaBH_4$ system is relatively slow compared to hydroborations using BH_3:THF.[22,23] Also, the rates of reaction of cyclohexene and caproic acid with diborane are comparable.[24] Presumably, the present reagent system is more selective because the reactive $RCOOBH_2$ (or similar acyloxyborane) species is produced in the absence of more reactive borane species such as BH_3:THF (Scheme 3).[25-27]

Table I: Selective reduction of carboxylic acids to alcohols.[a]

S.No.	Substrate	Product[c]	Temp.°C	Yield %[b]
1	C_6H_5-COOH	$C_6H_5CH_2OH$	r·t	93
2	$C_6H_5CH_2-COOH$	$C_6H_5CH_2-CH_2OH$	r·t	98
3	$p-ClC_6H_5-COOH$	$p-ClC_6H_5-CH_2OH$	r·t	98
4	$CH_3-(CH_2)_8-COOH$	$CH_3-(CH_2)_8-CH_2OH$	r·t	92
5			r·t	96
6			r·t	92
7			0	97
8			0	89
9			0	89
10			r·t	92
11			0	82
12			r·t	86
13			r·t	87

(a). All experiments were carried out by using $NaBH_4$ (12 mmol), I_2(0.5 mmol) and carboxylic acid (10 mmol).

(b). Yields are of isolated and purified products.

(c). Products were identified by physical constants data, IR, ^1H NMR and ^{13}C NMR and comparison with the data reported.

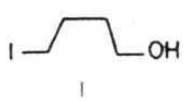
Scheme 3

$$NaBH_4 + RCOOH \longrightarrow RCOOBH_3Na + H_2$$

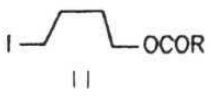
$$\downarrow 0.5I_2$$

$$RCH_2OBO \longleftarrow RCOOBH_2 + 0.5NaI + 0.5H_2$$

The $RCOOH/NaBH_4/I_2$ reagent system gives good results in 10 mmol scale. However, when the reactions were carried out in more than 50 mmol scale, substantial amounts of products (I and/or II) derived from THF cleavage were also obtained.



I



II

Similar THF cleaved products were also obtained when $NaBH_4$ was added in portions to THF solution of carboxylic acid followed by I_2 in THF. This complication may be due to the formation of insoluble acyloxyborohydride species, leading to the formation of >B-I species by the reaction of I_2 with BH_3:THF, which is known to cleave ethers. The I_2 will react with $NaBH_4$ to give BH_3:THF if the acyloxyborohydride is not present in sufficient quantities in solution. However, this

problem has been circumvented by the addition of I_2 into $NaBH_4$ at 0^oC followed by the addition of carboxylic acid. The corresponding alcohols were obtained in good yields after workup (Table II).

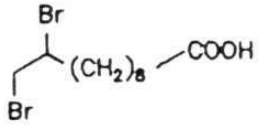
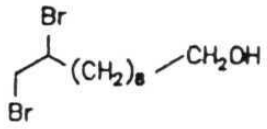
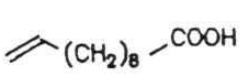
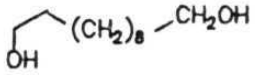
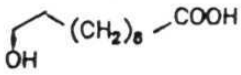
It was observed that addition of I_2 (5 mmol) to $NaBH_4$ (12 mmol) in THF (30 ml) at 0^oC for 2.5h and treatment of the contents with PPh_3(10 mmol)in THF (20 ml) give $PPh_3:BH_3$ in 94% yield, indicating the formation of BH_3:THF in the reaction of $NaBH_4$ with I_2 (eq. 11).

$$2NaBH_4 + I_2 \xrightarrow{THF} 2NaI + 2BH_3{:}THF \xrightarrow{PPh_3} PPh_3{:}BH_3 \qquad \text{—— 11}$$

It was found that esters can also be reduced by the I_2-$NaBH_4$ combination at THF reflux temperature during 0.5h. Some esters and acids were reduced using this reagent system and the results are summarized in Table II.[29]

However, by performing the reaction in this way, the chemoselectivity achieved in the reduction of olefinic acids is lost. For example, the reduction of 10-undecenoic acid gives 10-undecenol in 89% yield by the addition of acid to $NaBH_4$ at room temperature followed by I_2 in THF at 0^oC.[18] However, addition of I_2 to $NaBH_4$ at 0^oC followed by the olefinic acid, leads to hydroboration of the double bond and a mixture of 1,11-undecanediol (59%) and 11-hydroxy-undecanoic acid (20%) is obtained (entry 5, Table II) after oxidation with $H_2O_2/^-OH$ and protonolysis.[29]

Table II: Reduction of carboxylic acids and esters using $NaBH_4$ and I_2 in THF.[a]

S. No.	Substrate	Conditions temp/time[b]	Product(s)[d]	Yield %
1	$PhCH_2COOC_2H_5$	70°C (0·5h)[b]	$PhCH_2CH_2OH$	85
2	$CH_3(CH_2)_8COOCH_3$	70°C (0·5h)[b]	$CH_3(CH_2)_8CH_2OH$	89
3	$CH_3(CH_2)_8COOH$	25°C (1h)[c]	$CH_3(CH_3)_8CH_2OH$	90
4		25°C (1h)[c]		86
5		25°C (1h)[c]	 + 	59 + 20

(a). The experiment was carried out by adding I_2 (5 mmol) in THF (30 ml) in portions to $NaBH_4$ (12 mmol) at 0^oC for 2.5h.

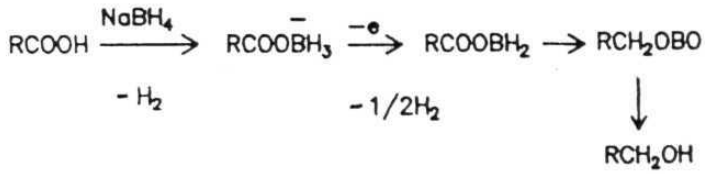
(b). After the addition of ester, the reaction mixture was refluxed for 0.5h.

(c). The acids were added at 25^oC to $I_2/NaBH_4$ reagent.

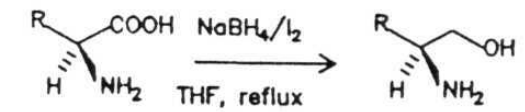
(d). The products were isolated by chromatography on silica gel column (hexane/ethyl acetate eluent) and identified by spectral data (IR, ^1H NMR, ^{13}C NMR).

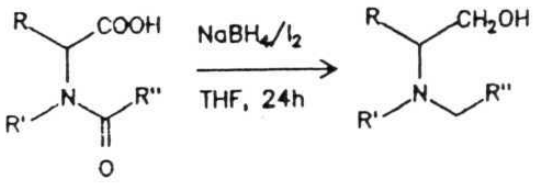
The I_2-$NaBH_4$ reducing system has been also found to be useful in the reduction of amides, nitriles, carboxylic esters, imides and hydroboration of olefins.[29]

It is of interest to note that Matsurbara *et al* recently developed similar oxidation induced transformation of $RCOOBH_3Na$ to RCH_2OH by electrochemical means.[28]

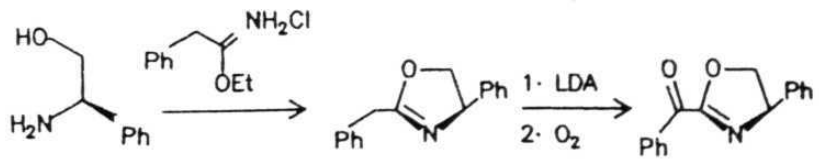


Meyers *et al* found that the $I_2/NaBH_4$ combination is an excellent reagent for the reduction of amino acids to the corresponding amino alcohols. It was found that the reduction of N-acylamino acid gives N-alkylamino alcohols.[30]





Some of these amino alcohols have been used in the synthesis of chiral oxazolines. Meyers *et al* discovered many applications of these oxazolines.[39]



Conclusions

A convenient reducing reagent system has been developed for the selective reduction of carboxylic acid group when it is present along with other functionalities such as olefins and esters. Several carboxylic acids and dicarboxylic acids have been reduced to the corresponding alcohols in very good yields using $NaBH_4/I_2$. This reagent system also gives borane–THF (BH_3:THF) in the absence of RCOOH which has been used to reduce carboxylic acids and esters.

EXPERIMENTAL SECTION

General Details:

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

All carboxylic acids utilized are commercial materials. Half-ester acid of sebacic acid and phthalic acid were prepared from the corresponding dicarboxylic acids following a literature procedure.[37] Cobalt naphthenate supplied by Fluka, Switzerland was utilized for the oxidation of mesitylene to 3,5-dimethylbenzoic acid. 10-Undecylenic acid supplied by Spectrochem (India) was utilized.

For selective reductions sodium borohydride was purified by dissolving it in dry DME and collecting the precipitate at $0^{o}C$ by the addition of dry ether. The precipitate was dried under nitrogen atmosphere and used immediately.

Reduction of carboxylic acids into alcohols using $NaBH_4$ and I_2:

Several carboxylic acids were reduced to the corresponding alcohols using $NaBH_4$ and I_2 in THF. Procedure followed for phenylacetic acid is representative.

$NaBH_4$ (0.45 g, 12 mmol) was taken in a two-necked RB flask and dry THF (20ml) was added. A solution of phenylacetic acid (1.50 g, 10 mmol) in THF (20 ml) was slowly added during 15 min under nitrogen

atmosphere at room temperature. The mixture was stirred until evolution of gas ceases. Iodine (1.2 g, 5 mmol) in THF (20 ml) was added slowly during 10 min. under nitrogen atmosphere at room temperature. Additional evolution of hydrogen gas was observed. The reaction was further stirred for 1h at r.t. The reaction was carefully quenched with HCl (5 ml, 3N) organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic layer was washed with 3N NaOH (3 x 10 ml), brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The product 2-phenylethanol was found to be essentially pure.

Yield : 1.12g (93%)

B.P. : $96^{o}C$ (10 mm) Lit.[31] $120^{o}C$ (12 mm)

IR (neat) ν_{max} : 3400, 3050, 1600, 1050 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) : 1.8 (bs, H), 2.8 (t, 2H), 3.8 (t, 2H), 7.2 (m, 5H).

$p\text{-}ClC_6H_5\text{-}COOH \longrightarrow p\text{-}ClC_6H_5\text{-}CH_2OH$

Yield : 1.41g (98%)

M.P. : $73^{o}C$ Lit.[33] $75^{o}C$

IR (KBr) ν_{max} : 3400, 1600, 1050 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 64.1, 128.2, 128.5, 133.2, 139.2.

$CH_3\text{-}(CH_2)_8\text{-}COOH \longrightarrow CH_3\text{-}(CH_2)_8\text{-}CH_2OH$

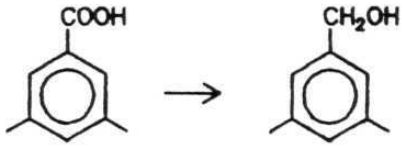
Yield : 1.5g (95%)

B.P. : $102^{o}C$ (5 mm) Lit.[34] $120^{o}C$ (12 mm)

IR (neat) ν_{max} : 3400, 900, 2850 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 0.8 (t, 3H), 1.2 (m, 14H), 1.4 (m, 2H), 1.9 (s, 1H), 3.5 (t, 2H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 13.6, 22.3, 25.6, 29.1, 29.3, 31.6, 32.3, 62.0.



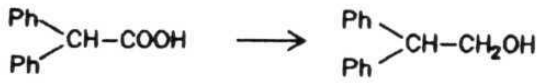
Yield : 1.25g (92%)

B.P. : 101°C (5 mm) Lit.[35] 220°C (760 mm)

IR (neat) ν_{max} : 3400, 2900, 1600, 1050 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 2.5 (s, 6H), 4.7 (s, 2H), 7.1 (s, 3H)

^{13}C NMR (25.0 MHz,$CdCl_3$): 21.2, 65.1, 125.0, 129.2, 138.2, 141.2.



Yield : 1.9g (96%)

M.P. : 50°C Lit.[38] 52°C

IR (KBr) ν_{max} : 3400, 3050, 2800,1600, 1050 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 53.5, 66.3, 126.8, 127.2, 128.4, 128.8, 139.0, 141.5.

Reduction of salicylic acid using $NaBH_4$ and I_2:

The procedure followed was similar to that described above except for the workup procedure. After quenching the reaction carefully with

3N HCl (5 ml), the organic layer was separated and aqueous layer was washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude alcohol was purified by column chromatography on silica gel using hexane ethyl acetate/80:20 as eluent.

Yield : 1.14g (92%)

M.P. : 80^oC Lit.[38] 83-85^oC

IR (KBr) ν_{max} : 3400, 3050, 1600, 1050 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 62.5, 126.5, 127.7, 128.5, 128.6, 131.1, 150.9.

Reduction of benzoic acid using $NaBH_4/I_2$:

$NaBH_4$ (0.45 g, 12 mmol) in THF (20 ml) was taken in a two-necked RB flask. A solution of benzoic acid (1.22 g, 10 mmol) in THF (20 ml) was slowly added during 15 min under nitrogen atmosphere at room temperature. The mixture was stirred until gas evolution ceases . Iodine (1.25 g, 5 mmol) in THF (20 ml) was added slowly during 10 min under nitrogen atmosphere at room temperature. Additional evolution of gas was observed. The contents were further stirred for 1h. The reaction was carefully quenched with HCl (5 ml, 3N). Organic layer was separated and aqueous layer was extracted with ether combined organic extract was dried over anhydrous $MgSO_4$. Solvent was evaporated and the residue was distilled under reduced pressure to obtain bezylalcohol.

Yield : 0.93 g (93%)

B.P. : 91^oC (10 mm) Lit.[32] 205^oC (760 mm)

IR spectrum of product showed 1:1 correspondence with that of an authentic sample.

Selective reduction of carboxylic acids using $NaBH_4$ and I_2:

Several carboxylic acids containing another reactive functional groups have been selectively reduced. Procedure followed for cinnamic acid is representative.

$NaBH_4$ (0.45 g, 12 mmol) in THF (20 ml) was taken in a two necked RB flask. A solution of cinnamic acid (1.48g, 10 mmol) in THF (20 ml) was slowly added during 15 min under nitrogen atmosphere at room temperature. The mixture was stirred until the gas evolution ceases . The reaction mixture was cooled to $0^{o}C$ under nitrogen. Iodine (1.21 g, 5 mmol) in THF (20 ml) was added slowly during 10 min at $0^{o}C$. Additional evolution of hydrogen gas was observed. The contents were further stirred for 1h at 0°C. The reaction was carefully quenched with 3N HCl (5 ml). The organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic layer was washed with 3N NaOH (3 x 10 ml), brine solution, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The product cinnamyl alcohol was found to be essentially pure which was further purified on a silica gel column using hexane:ethyl acetate/90:10 as eluent.

Yield : 1.3g (97%)

IR (neat) ν_{max} : 3400, 3100, 3050, 1610, 1100 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) : 2.0 (bs, 1H), 4.3 (d, 2H), 6.2-6.8 (m, 2H), 7.3 (m, 5H).

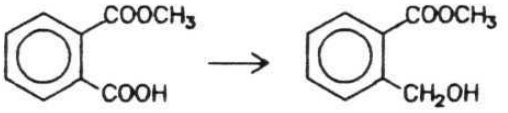
^{13}C NMR (25.0 MHz,$CDCl_3$): 62.9, 125.5, 126.2, 127.3, 128.4, 130.2, 136.6, 141.8.

Yield : 1.51g (89%)

IR (neat) ν_{max} : 3400, 3020, 1620, 1100 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) : 1.3 (m, 14H), 1.7 (s, 1H), 2.0 (m, 2H), 3.6 (m, 2H), 4.8-5.9 (m, 3H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.7, 28.8, 29.0, 29.3, 29.4, 32.5, 33.6, 62.4, 114.0, 139.0.



Yield : 1.28g (82%)

IR (neat) ν_{max} : 3400, 3050, 1720, 1600 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 52.5, 63.1, 128.1, 128.5, 129.1, 129.9, 131.1, 138.9, 168.1.

Yield : 1.78g (89%)

IR (neat) ν_{max} : 3400, 1720, 1070 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) : 1.4 (m, 12H), 1.6 (m, 2H), 3.0 (s, 1H), 2.3 (m, 2H), 3.75 (s, 3H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 24.4, 25.3, 28.7, 28.8, 32.1, 33.5, 33.7, 50.9, 61.9, 173.6.

Reduction of phthalic acid using $NaBH_4$ and I_2:

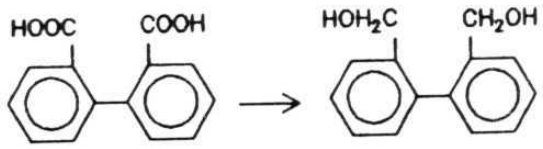
$NaBH_4$ (0.9 g, 24 mmol) in THF (30 ml) was taken in a two necked RB flask. A solution of phthalic acid (1.66g, 10 mmol) in THF (20 ml) was slowly added during 15 min under nitrogen atmosphere at room temperature. The mixture was stirred until the gas evolution ceases . Iodine (2.5 g, 10 mmol) in THF (30 ml) was added slowly during 15 min. Additional evolution of hydrogen gas was observed. The reaction mixture was further stirred for 1h at room temperature. The reaction was carefully quenched with 3N HCl (10 ml). The organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic layer was washed with bicarbonate. brine solutions, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude diol was purified on a silica gel column using hexane:ethyl acetate/85:15.

Yield : 1.18g (86%)

M.P. : $62^{o}C$ Lit.[38] $63-65^{o}C$

IR (KBr) ν_{max} : 3400, 3100, 1600, 1100 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 63.6, 128.5, 129.6, 139.4.



Yield : 1.84g (87%)

IR (neat) ν_{max} : 3400, 3100, 1600 cm^{-1}

^{13}C NMR (25.0 MHz,$CDCl_3$): 62.6, 127.7, 128.2, 129.5, 129.7, 138.8, 140.1.

Examination of the reactive species formed in the reaction of I_2 and $NaBH_4$ in THF: Trapping of the 'BH_3' as $Ph_3P:BH_3$:

$NaBH_4$ (0.45 g, 12 mmol) was taken in dry THF (30 ml) and I_2 (1.26 g, 5 mmol) in dry THF (20 ml) was added dropwise during 2h under static nitrogen pressure at 10^oC. To this was added PPh_3 (2.62 g, 10 mmol) in THF (20 ml) and the reaction mixture stirred for 2h at room temperature. Reaction was quenched with water. The organic layer was separated, washed with dil.HCl (3N, 5 ml), brine and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded triphenylphosphine borane complex in essentially pure form. This was further purified by passing through silica gel column using hexane as eluent.

Yield : 2.62 g (95%)

M.P. : 187^oC Lit.[36] 188^oC

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

Reduction of ethyl phenylacetate using $NaBH_4$ and I_2:

$NaBH_4$ (0.45 g, 12 mmol), ethyl phenylacetate (1.64 g, 10 mmol) in dry THF (30 ml) were taken in a two necked RB flask I_2 (1.22 g, 5 mmol) was added slowly during 2.5 h at 0^oC under nitrogen atmosphere. The reaction mixture was refluxed for 0.5h and then cooled to 0^oC. 3N HCl (5 ml) was added carefully. Organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The product 2-phenylethanol was found to be pure which was further purified by distillation under reduced pressure.

Yield : 1.0g (85%)

B.P. : $96^{O}C$ (10mm) Lit[31] $120^{O}C$ (12 mm)

IR (neat) ν_{max} : 3400, 3050, 1600 1100 cm^{-1}

^{1}H NMR (100 MHz, $CDCl_3$) : 2.0 (bs, 1H), 2.9 (t, 2H), 3.9 (t, 2H), 7.3 (m, 5H).

$$CH_3-(CH_2)_8-COOCH_3 \longrightarrow CH_3-(CH_2)_8-CH_2OH$$

The procedure followed was same as in earlier experiment.

Yield : 1.4g (89%)

B.P. : $102^{O}C$ (5 mm) Lit.[35] $120^{O}C$ (12 mm)

Spectral data showed 1:1 correspondence with 1-decanol obtained in an earlier experiment.

Reduction of caproic acid using $NaBH_4$ and I_2:

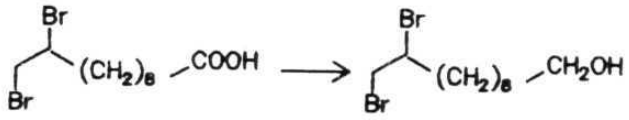
$NaBH_4$ (0.45 g, 12 mmol) in dry THF (20 ml) was taken in a two necked RB flask. I_2 (1.26 g, 5 mmol) in THF (20 ml) was added slowly during 2.5h through a pressure equalizer at $0^{O}C$ under nitrogen atmosphere. Caproic acid (1.72 g, 10 mmol) in dry THF (10 ml) was added slowly during 15 min using double ended needle and the contents were stirred for 1h at room temperature. The reaction was quenched carefully with 3N HCl (5 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 ml). Combined organic extract was washed with 3N NaOH (3 x 5 ml), brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The product 1-decanol was found to be essentially pure which was further purified by

distillation under reduced pressure.

Yield : 1.42g (90%)

B.P. : 103°C (5 mm) Lit.[34] 120°C (12 mm)

The product showed 1:1 correspondence with an authentic sample of 1-decanol. This procedure was also followed for the reduction of few other acids:



Yield : 2.83g (86%)

IR (neat) ν_{max} : 3325, 2900, 2850, 1450, 1050 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 1.3 (m, 10H), 1.6 (s, 1H), 2.0 (m, 2H), 3.4-4.1 (m, 5H).

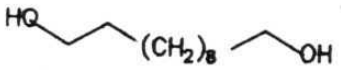
^{13}C NMR (25.0 MHz,$CDCl_3$): 25.4, 26.4, 28.5, 29.1, 32.2, 35.7, 36.1, 52.8, 62.1.

Reduction of 10-undecenoic acid using $NaBH_4$ and I_2:

The procedure followed was similar to earlier experiment except for workup procedure. After quenching the reaction with water (5 ml) the reaction mixture was oxidized using NaOH (3N, 15ml) and H_2O_2 (16%, 15ml). Stirring was continued for 4h. Organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was subjected to column chromatography on a silica gel column to obtain 1,10-undecanediol in

pure form. The aqueous layer was neutralized with 3N HCl and extracted with ether (3x15 ml). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of organic layer afforded hydroxy acid which was further purified using column chromatography on silica gel using hexane:ethyl acetate/80:20 as eluent.

FRACTION I



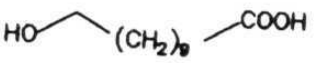
Yield : 1.1g (59%)

IR (neat) ν_{max} : 3400, 2900, 1050 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 1.3 (m, 8H), 1.6 (bs, 1H), 3.6 (t, 2H)

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.6, 29.3, 29.5, 32.6, 62.8.

FRACTION II:



Yield : 0.4g (20%)

IR (neat) ν_{max} : 3400, 1700, 1100 cm^{-1}

^1H NMR (100 MHz, $CDCl_3$) : 1.3 (m, 16H), 2.1 (s, 1H), 3.6 (m, 2H), 4.1 (m, 2H), 10.2 (s, 1H).

^{13}C NMR (25.0 MHz,$CDCl_3$): 25.7, 25.9, 28.6, 29.4, 34.3, 64.4, 174.3.

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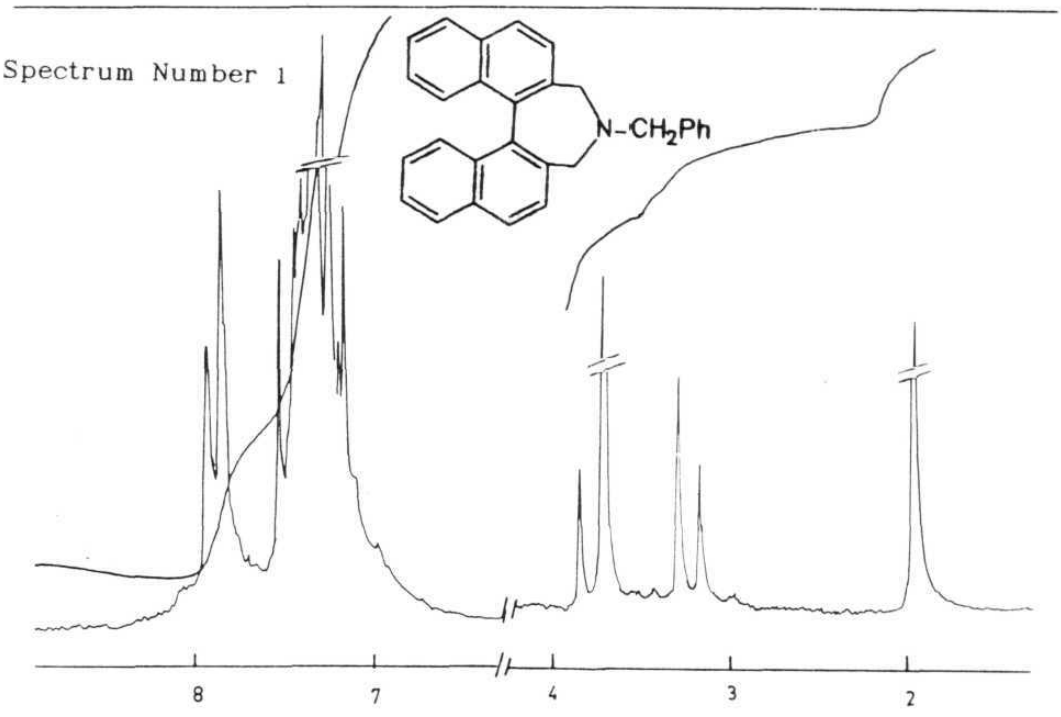
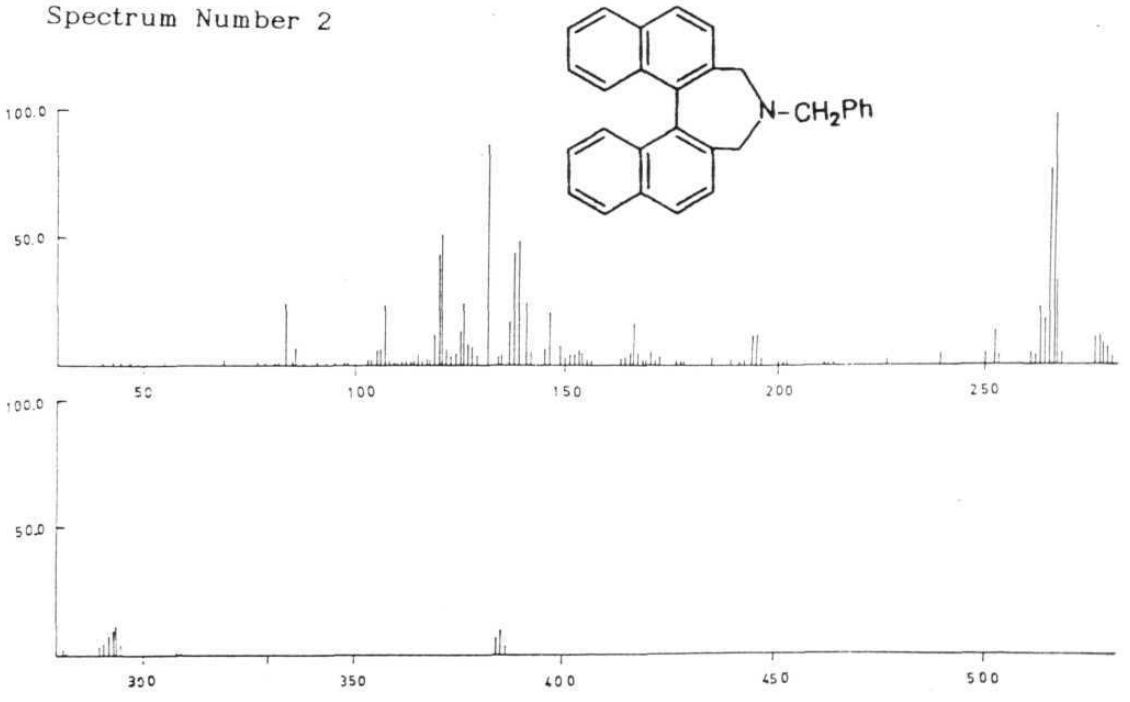
Spectrum Number 1



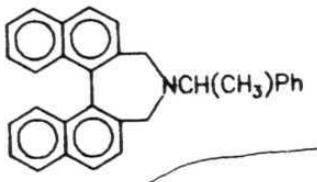
^{1}H NMR Spectrum (100 MHz, $CDCl_3$)

Spectrum Number 2



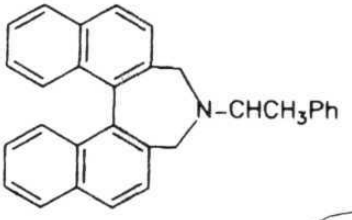
Mass Spectrum (M/e)

Spectrum Number 3



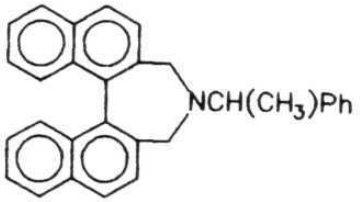
^{1}H NMR Spectrum (100 MHz, $CDCl_3$)

Spectrum Number 4



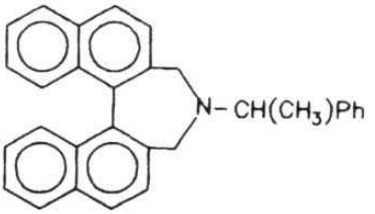
^{1}H NMR Spectrum (100 MHz, $CDCl_3$)

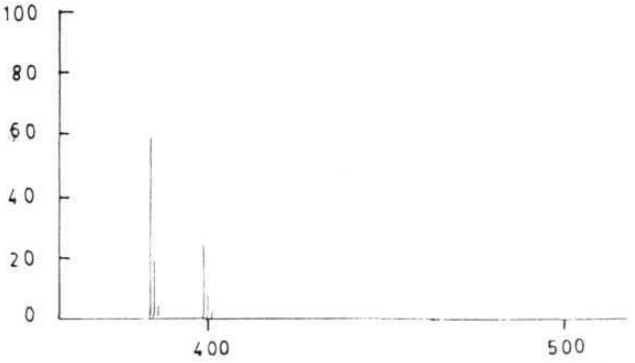
Spectrum Number 5



^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

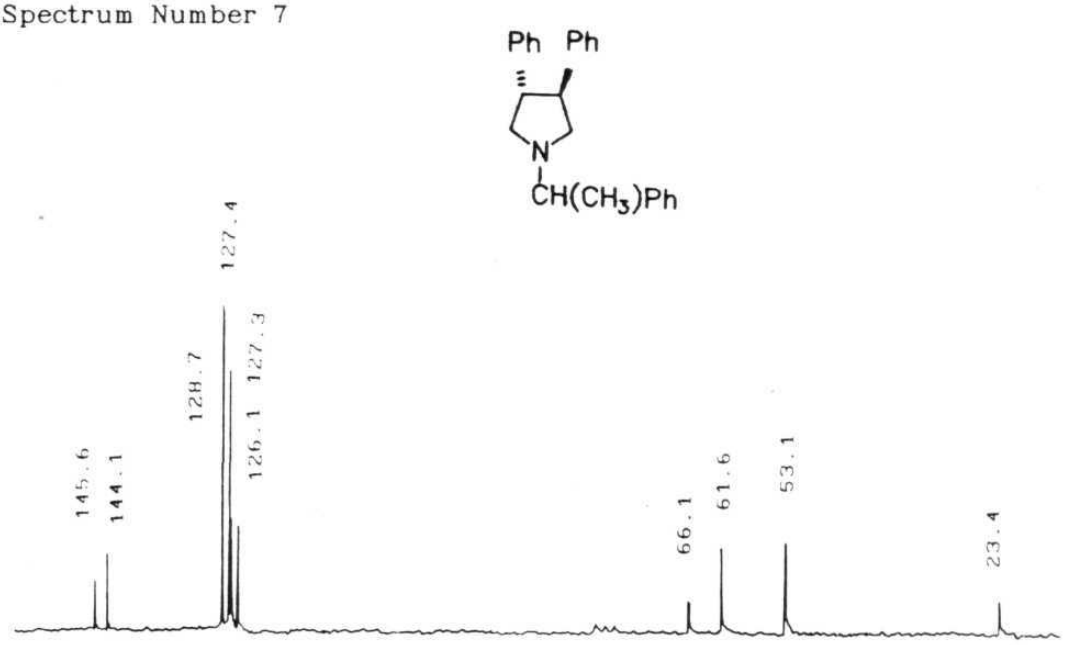
Spectrum Number 6





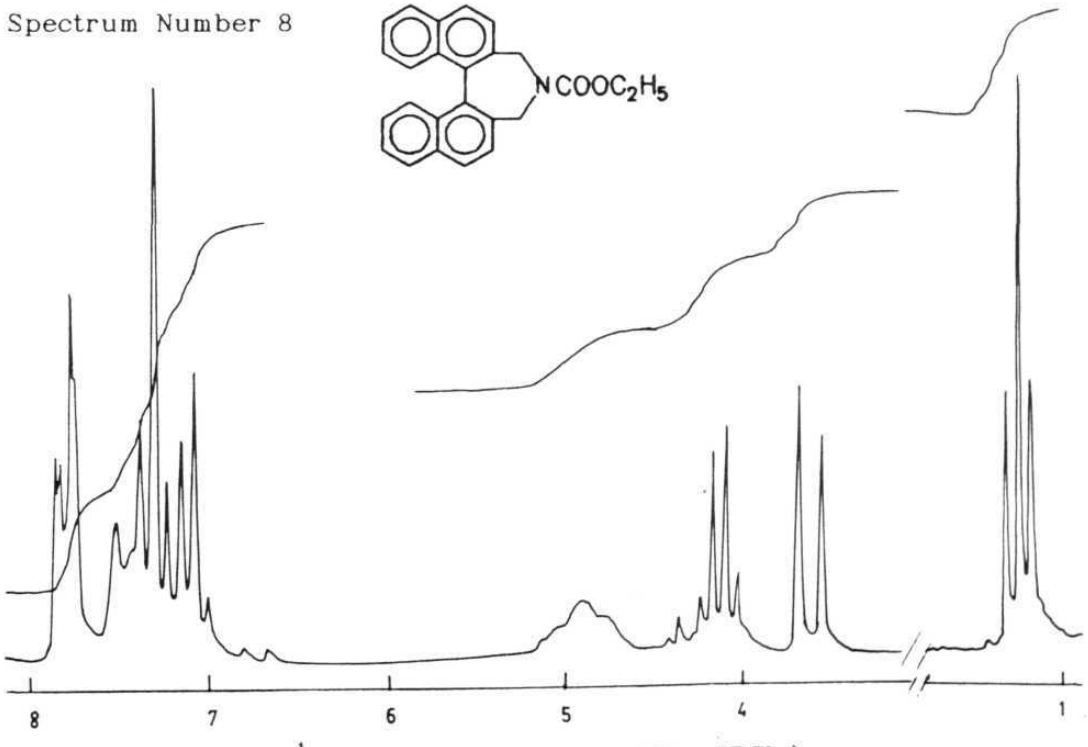
Mass Spectrum (M/e)

Spectrum Number 7



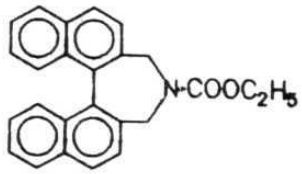
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 8



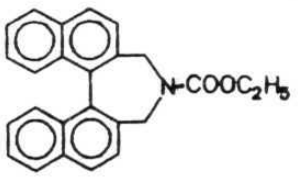
^{1}H NMR Spectrum (100 MHz, $CDCl_3$)

Spectrum Number 9



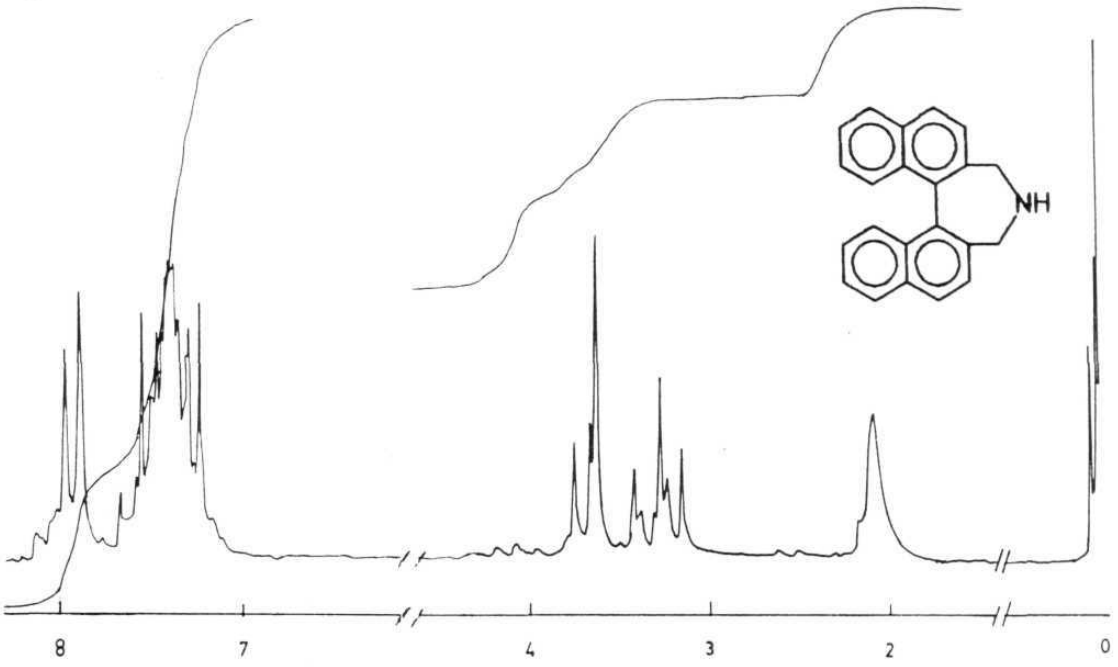
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 10



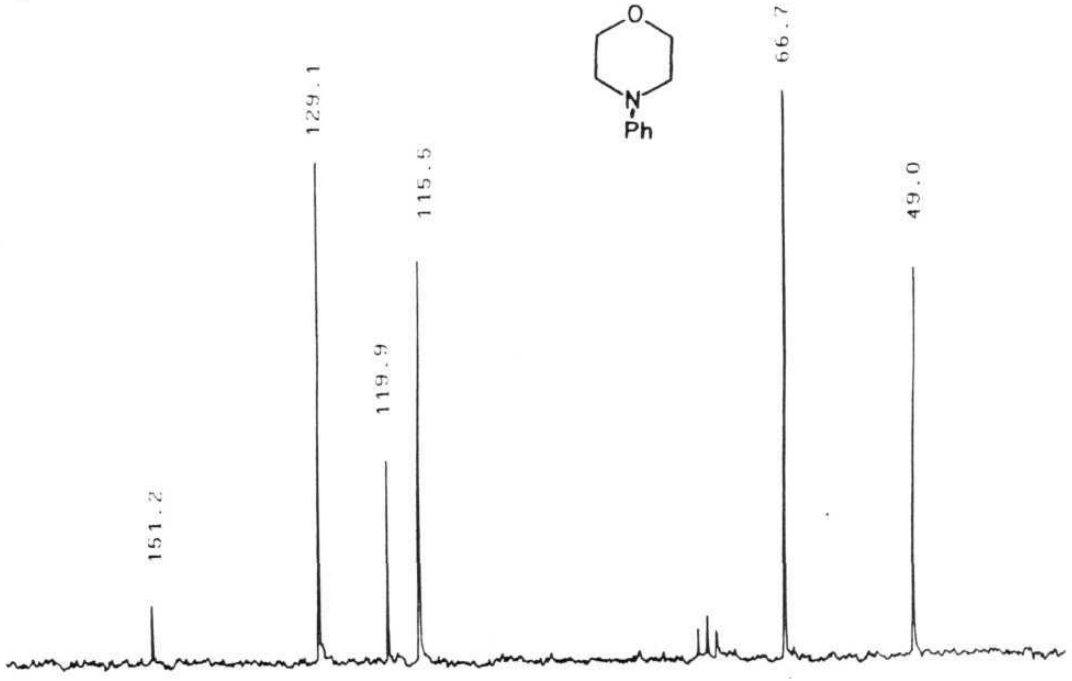
Mass Spectrum (M/e)

Spectrum Number 11



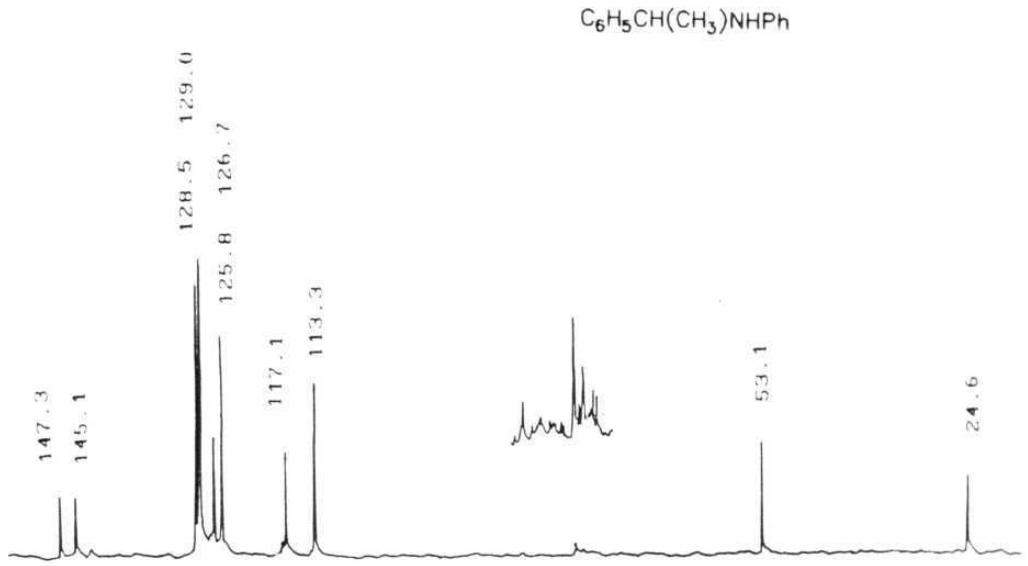
^{1}H NMR Spectrum (100 MHz, $CDCl_3$)

Spectrum Number 12



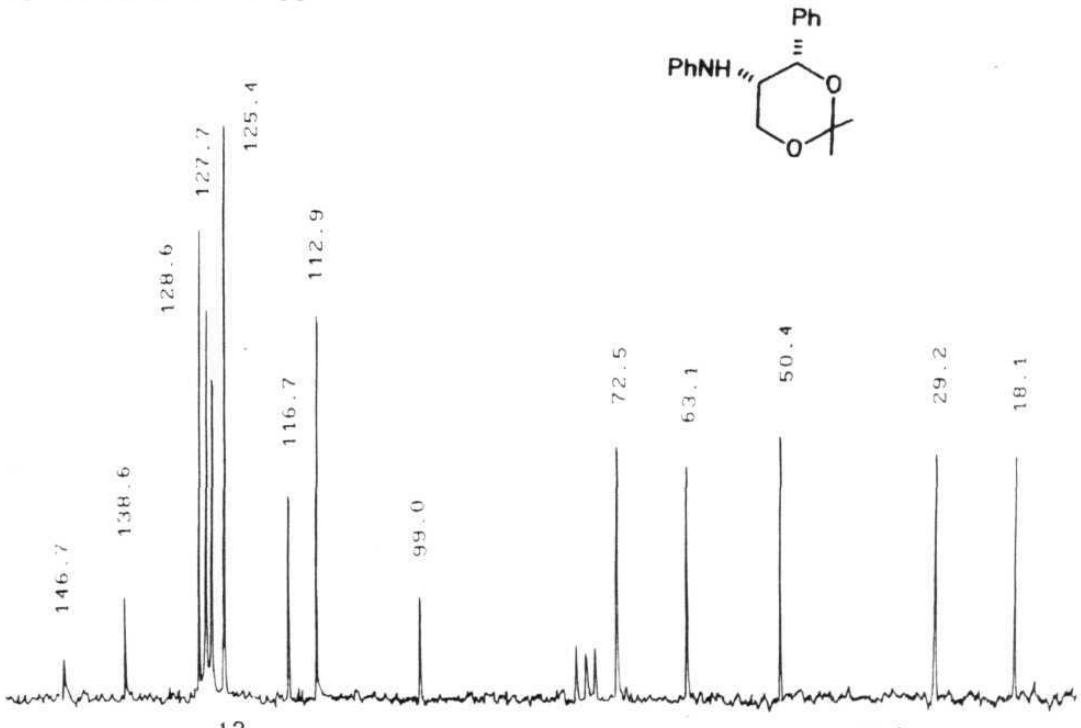
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 13



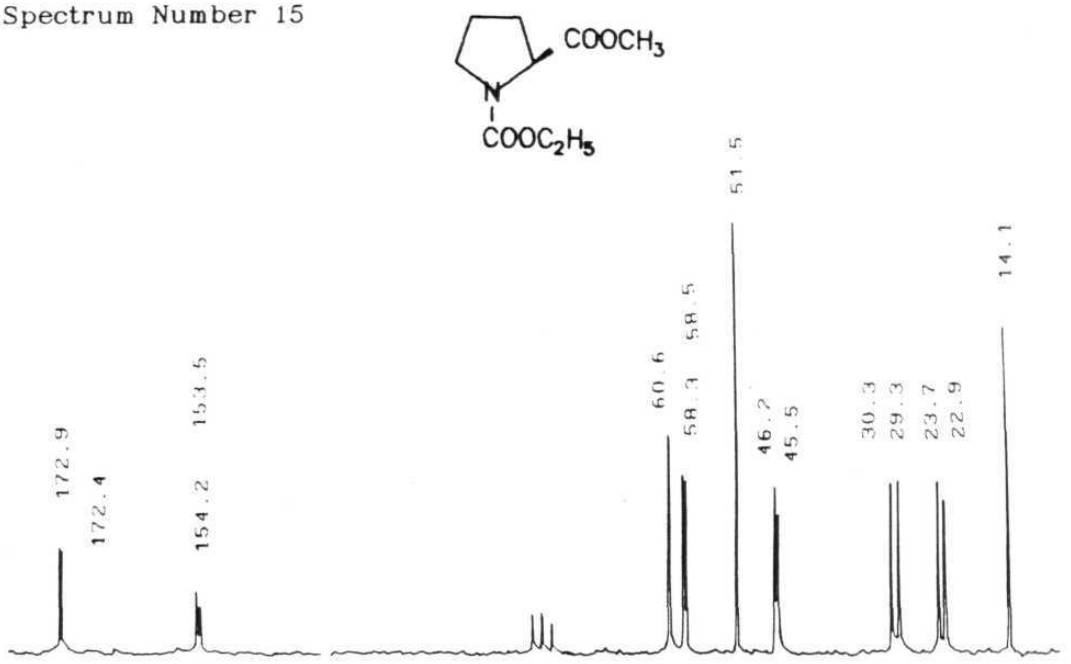
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 14



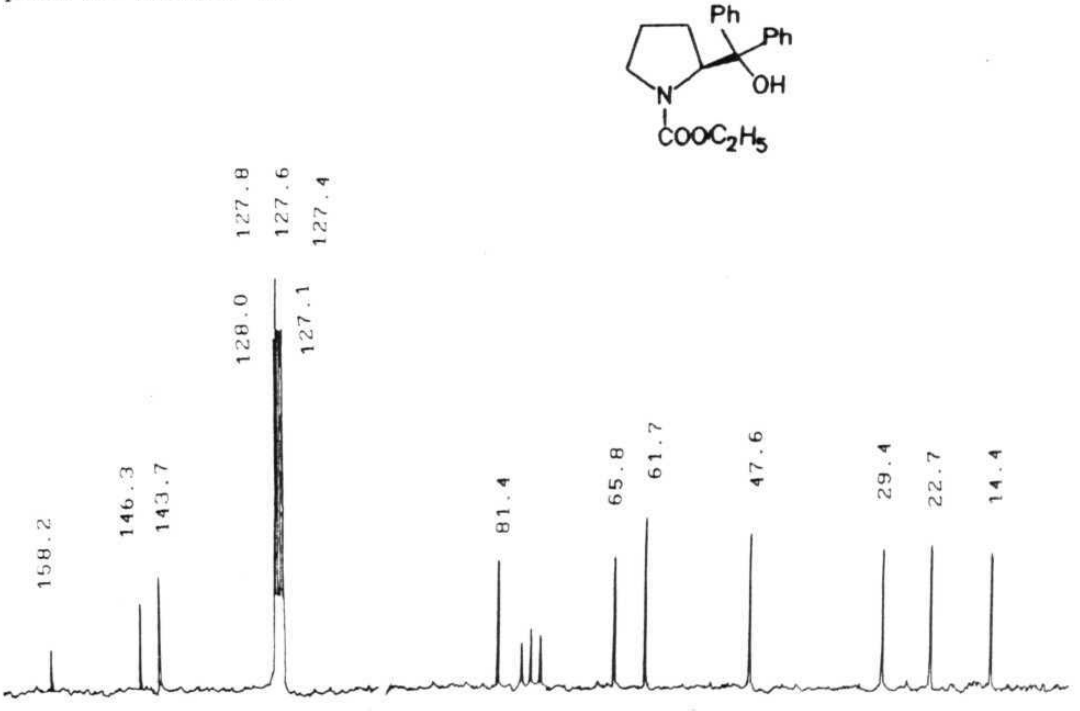
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 15



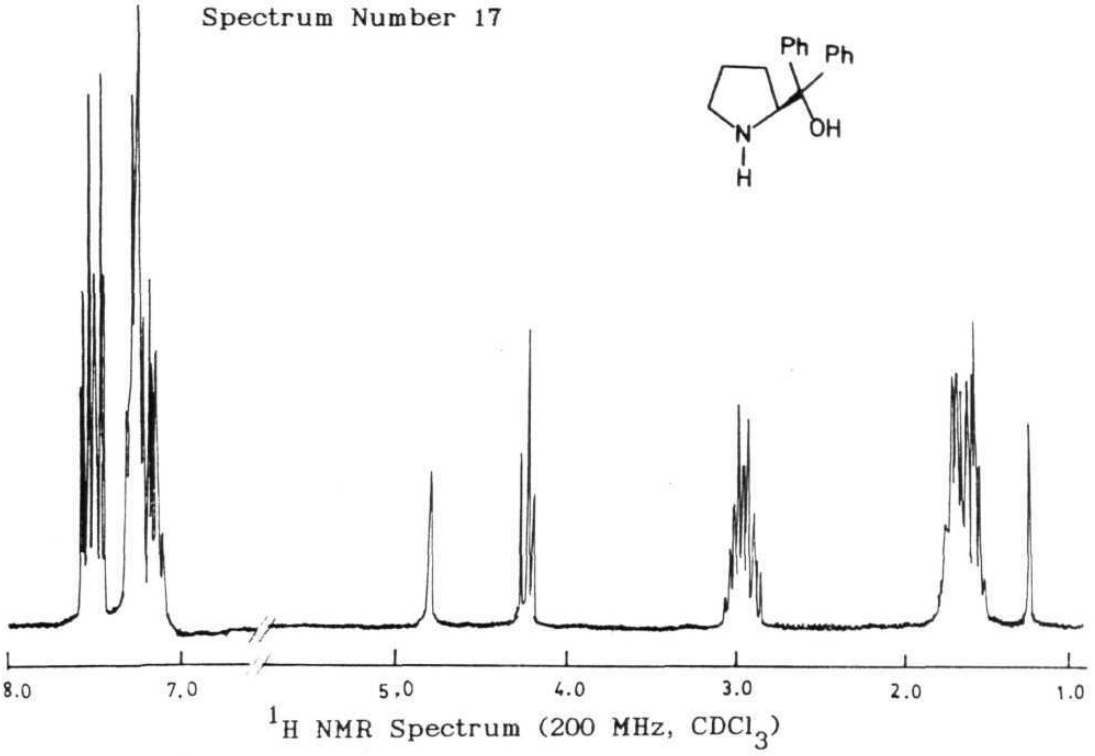
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 16



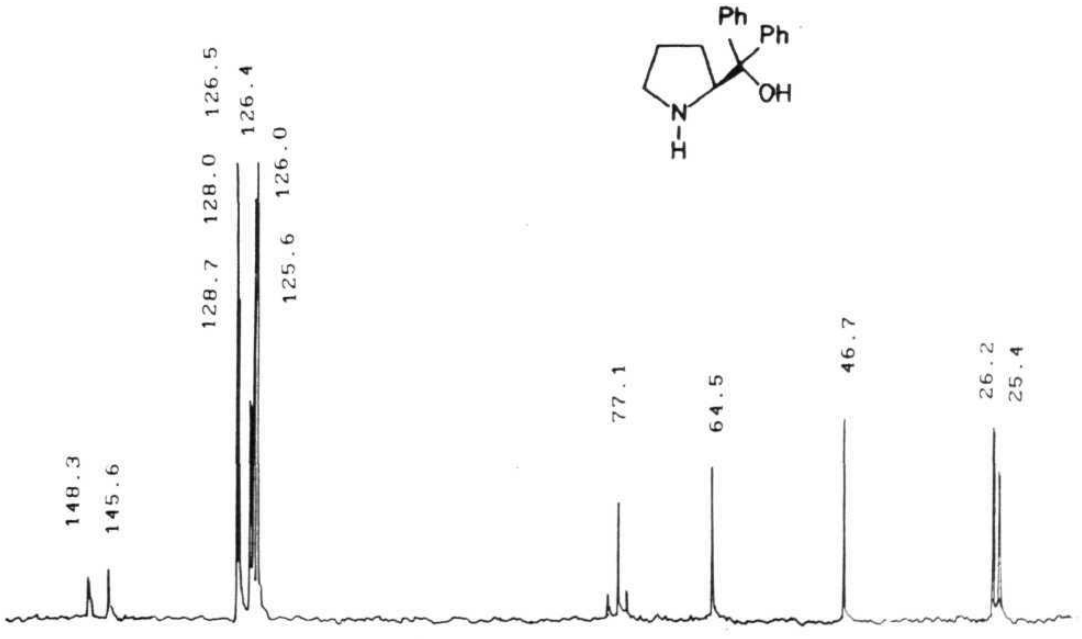
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 17



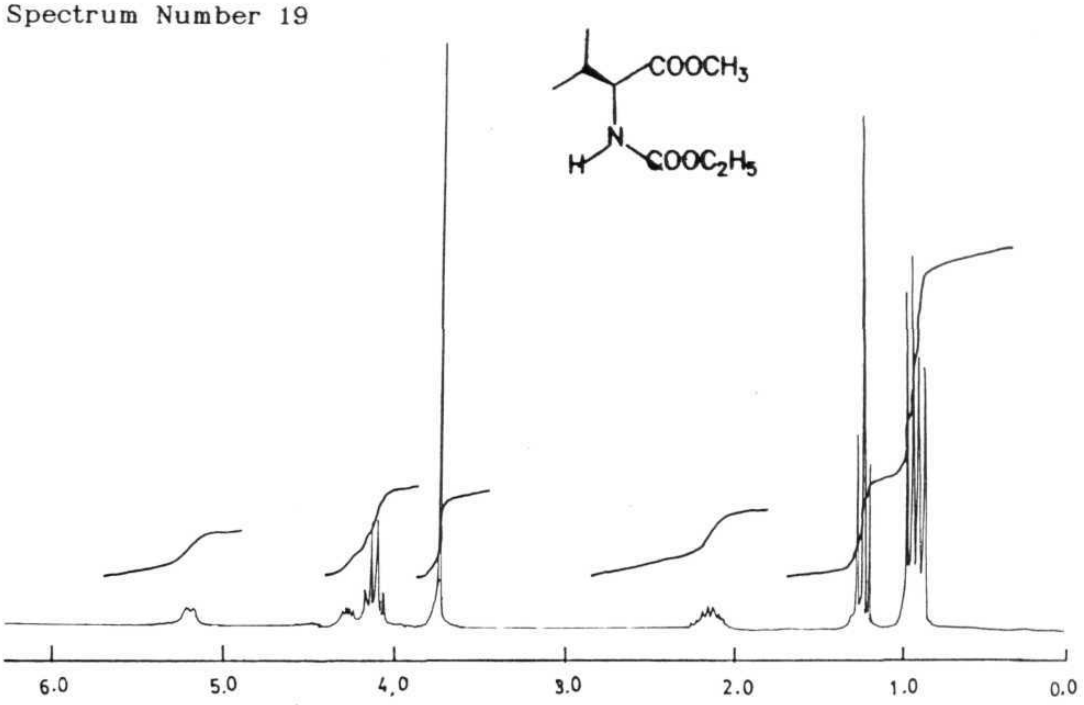
^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

Spectrum Number 18



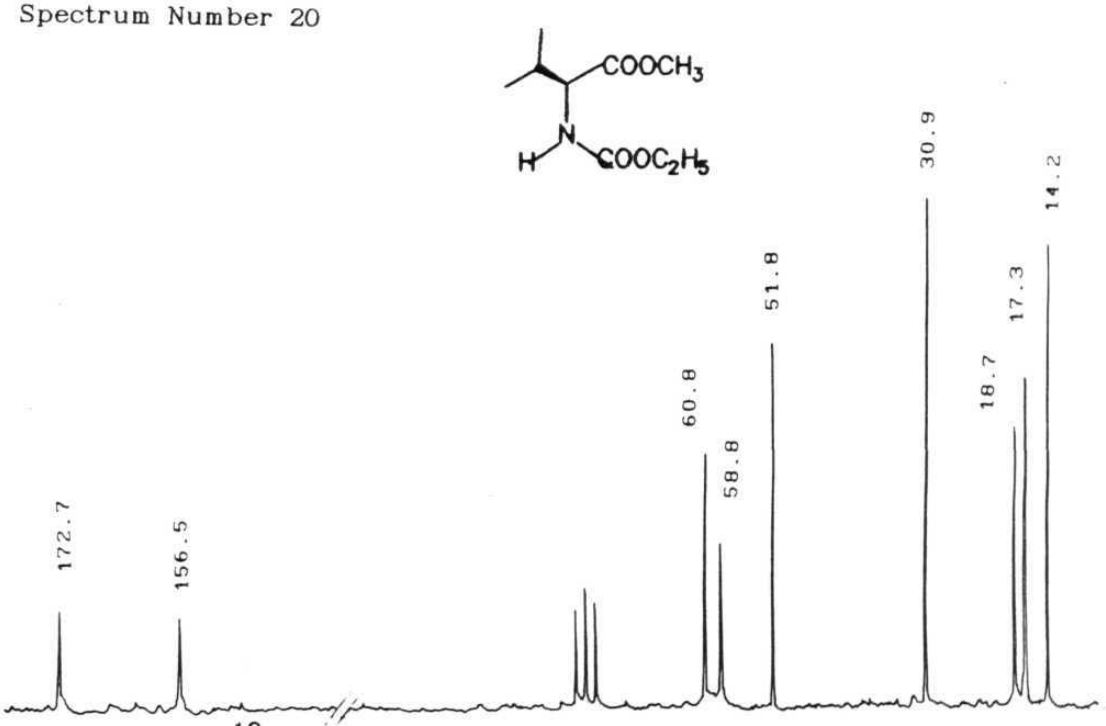
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 19



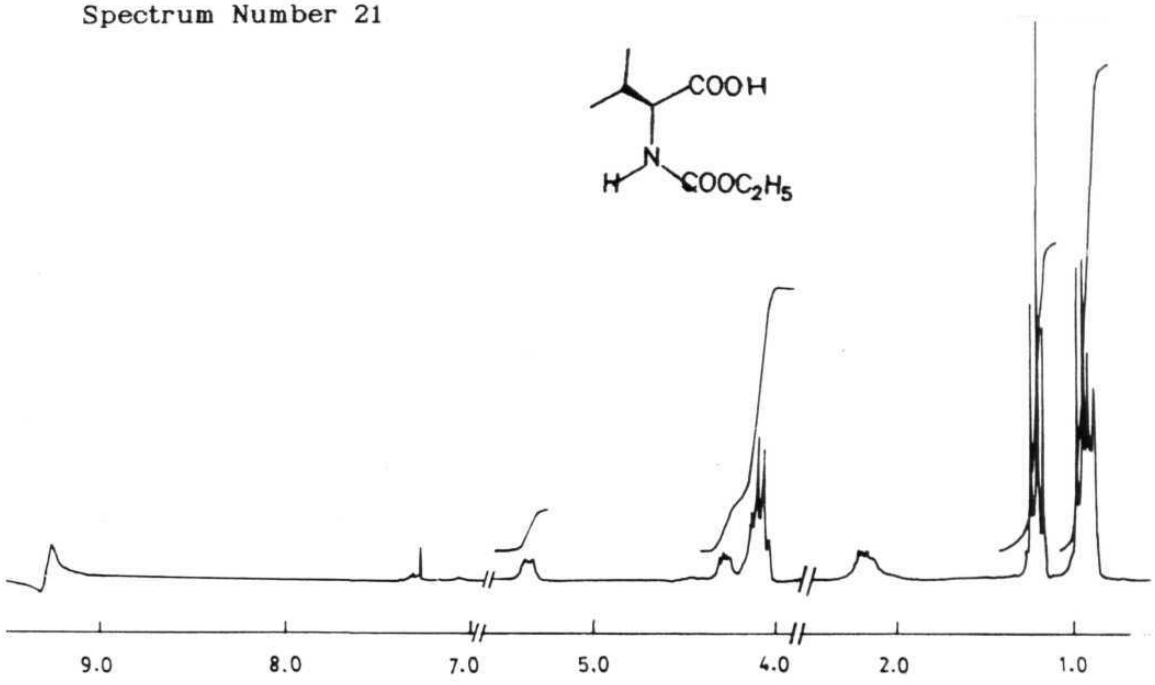
^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

Spectrum Number 20



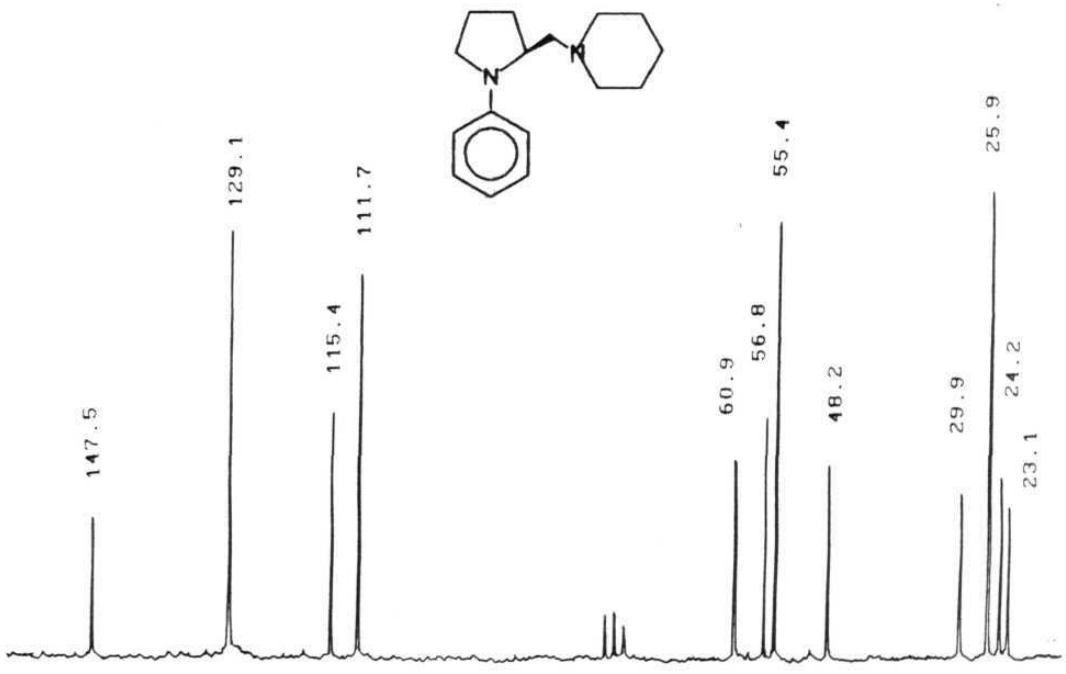
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 21



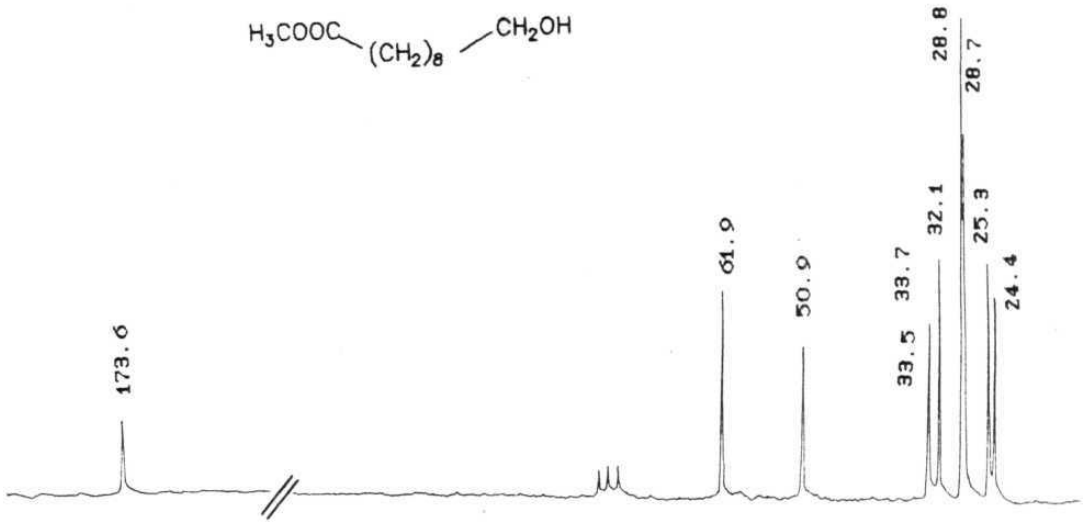
^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

Spectrum Number 22



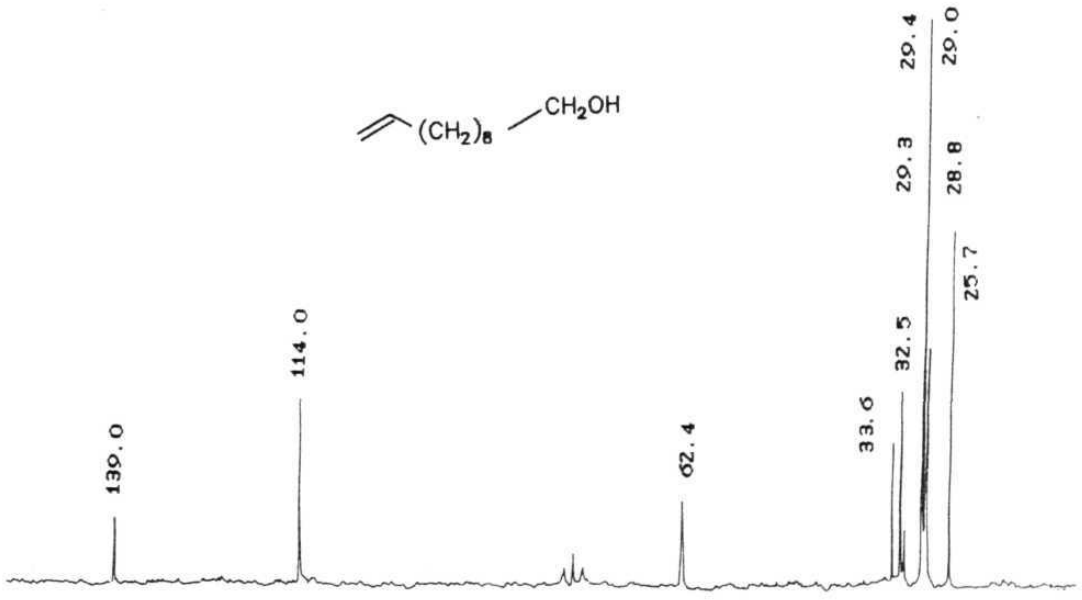
^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 23



^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

Spectrum Number 24



^{13}C NMR Spectrum decoupled (25.0 MHz, $CDCl_3$)

VITAE

J. V. Bhaskar Kanth was born on 9th October 1966 at Sanapally-lanka near Amalapuram, Andhra Pradesh. Following his early education at The Hindu High School, Machilipatnam, he joined The Hindu College, Machilipatnam and obtained a B.Sc., degree from Andhra/Nagarjuna University in 1986. He received his M.Sc. degree from from the School of Chemistry, University of Hyderabad in 1988 and subsequently joined the Ph.D. programme in the same School and he presently continuing as a Senior Research Fellow. During the course of his education, he was awarded a number of prizes and scholarships besides best student award for three consecutive years during B.Sc. and the Junior and Senior Research Fellowships by the CSIR on the basis of CSIR-UGC National level test.

List of Publications:

1. Asymmetric reduction of prochiral aromatic ketones by borane-amine complexes in the presence of a chiral amine-BF_3 catalyst
   J. V. Bhaskar Kanth and M. Periasamy, *J. Chem. Soc., Chem. Commun.,* 1990, 1145.

2. Selective reduction of carboxylic acids into alcohols using $NaBH_4$ and I_2.
   J. V. Bhaskar Kanth and M. Periasamy, *J. Org. Chem.,* 1991, **56**, 5964.

3. 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.

4. Convenient procedure for N-phenylation of amines.
J. V. Bhaskar Kanth and M. Periasamy, *J. Org. Chem.*, 1993, 58, 3156.

5. Convenient method for the synthesis of chiral α,α-diphenyl-2-pyrrolidine methanol.
J. V. Bhaskar Kanth and M. Periasamy, *Tetrahedron*, 1993, 49, 5127.

6. Convenient method for N-debenzylation of tertiary amines.
J. V. Bhaskar Kanth, Ch. Kishan Reddy and M. Periasamy, *Synth. Commun.*, 1993, 0000.

7. A simple onepot method for simultaneous N- and O-protection of amino acids.
J. V. Bhaskar Kanth and M. Periasamy, manuscript in preparation.

8. Amine assisted formation of chiral oxazaborolidine (CBS reagent) catalyst and *in situ* asymmetric reduction of prochiral ketones using Lewis base borane complexes.
J. V. Bhaskar Kanth and M. Periasamy, to be submitted for publication.

9. Asymmetric reduction of prochiral aromatic ketones by borane-amine complexes in the presence of chiral amine-BF_3 catalysts.
J. V. Bhaskar Kanth and M. Periasamy, to be submitted for publication.

10. Hydroboration of prochiral olefins with borane chiral Lewis base complexes: Evidence for a spectrum of mechanism for hydroboration reaction.
J. V. Bhaskar Kanth, and M. Periasamy, to be submitted for publication.