STUDIES IN THE BORANE-MEDIATED ASYMMETRIC REDUCTION OF PROCHIRAL KETONES CATALYZED BY CHIRAL PHOSPHORAMIDES, DIAMINES AND AMIDES

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ABBREVIATIONS

Ac	acetyl
Alpine-Borane	*B*-3-pinanyl-9-borabicyclo[3.3.1]nonane
Aq.	aqueous
ATH	asymmetric transfer hydrogenation
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl lithium aluminium hydride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Bp	boiling point
Bu	*n*-butyl
cat.	catalyst
DIP-Chloride	diisopinocampheylchloroborane
DMSO	dimethyl sulfoxide
Eapine-Borane	*B*-(*Iso*-2-ethylapopinocampheyl)-9-borabicyclo-[3.3.1]nonane
ee	enantiomeric excess
Et	ethyl
equiv	equivalents
HMB	hexamethylbenzene
Ipc_2BH	diisopinocampheylborane
Ipc_2BCl	diisopinocampheylchloroborane
IpcB-*t*-BuCl	isopinocampheyl-*tert*-butylchloroborane
KRED	ketoreductase enzymes
LAH	lithium aluminium hydride
Me	methyl
min	minutes
Mp	melting point

NADH	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
Ph	phenyl
Pr	propyl
Prapine-Borane	*B*-(*Iso*-2-*n*-propylapopinocampheyl)-9-borabicyclo-[3.3.1]-nonane
i-Pr or Pr^i	*iso* propyl
rt	room temperature
TBA Br_3	tetrabutylammonium tribromide
tert-	*tertiary*
THF	tetrahydrofuran
TFA	trifluroacetic acid
K-Xylide	potassium 9-*O*-(1,2-isopropylidene-5-deoxy-α-D-xylofuranosyl)-9-boratabicyclo[3.3.1]nonane

ABSTRACT

Enantiomerically pure (or enriched) secondary alcohols occupy an important place in chiral chemistry because several chiral secondary alcohols are medicinally useful compounds. Due to the remarkable applications of chiral secondary alcohols as medicinally relevant molecules and also as synthon for obtaining various biologically active compounds there has been an increasing interest in developing simple and practical methodologies for synthesis of different chiral secondary alcohols. Among various available and known methods, asymmetric reduction of prochiral ketones has become one of the most important methods for obtaining enantiopure (or enriched) secondary alcohols.

This thesis deals with the synthesis and application of chiral catalytic sources containing N-P=O structural framework, diamines and amides for the borane-mediated asymmetric reduction of prochiral ketones and it contains three chapters: 1) Introduction, 2) Objectives, Results & Discussion and 3) Experimental. The first chapter presents brief/relevant and also recent literature on the application of chiral borane based reagent and borane-mediated asymmetric reduction of prochiral ketones under the influence of various catalysts.

The second chapter deals with the synthesis and application of chiral catalysts including phosphoramides, diamines and amides in case of borane-mediated asymmetric reduction of representative prochiral ketones with the following objectives.

1. a) To prepare (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine and study its application as a chiral source for the borane-mediated asymmetric reduction of prochiral ketones.

   b) To prepare (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonyl-pyrrolidine, (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)carbonylpyrr-olidine, (2*S*)-1-(diphenylphosphory)-2-(4-fluoroanilino)carbonylpyrrolidine, (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine and study towards understanding the influence of nature of substituent on amide ar-omatic ring on the enantioselectivity in the borane-mediated asymmetric reduct-ion process.

2. To synthesize (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline and (2*R*)-2-anilinomethylpiperidine and examine their catalytic potentials for borane-med-iated asymmetric reduction of prochiral ketones with a view to understand the influence of the nature of ring size/bicyclic diamine framework in directing the stereochemical course of the reduction process.

3. To prepare a representative class of amides based on the [(2S)-2-(arylamino)-carbonylpyrrolidines] framework and study their potential in the borane-medi-ated asymmetric reduction of ketones in order to understand the influence of different aromatic groups on carboxamide moiety, on the stereochemical direct-ion of the reduction process.

4. To examine the potential of (*R, R*)-1,2-diaminocyclohexane as possible catalyst in the borane-mediated asymmetric reduction of ketones.

(2*S*)-1-(Diphenylphosphoryl)-2-anilinocarbonylpyrrolidine as a catalyst for borane-mediated asymmetric reduction of ketones

We have synthesized chiral catalytic source containing N-P=O structural framework, (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) starting from (*S*)-proline according to the Scheme 14 (Page no. 48). This chiral catalytic source was then applied for the borane-mediated asymmetric reduction of prochiral ketones to provide the resulting secondary alcohols in good enantiomeric purities (eq. 85, Table 2 & 3). Four more catalytic source containing N-P=O structural framework eg., (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine (**227**), (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)carbonylpyrrolidine (**228**), (2*S*)-1-(diphenyl-phosphoryl)-2-(4-fluoroanilino)carbonylpyrrolidine (**229**) and (*S*)-1-(diphenyl-phosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine (**230**) were also synthesized (eq. 96, Page no. 60) with a view to understand the substituent effect of the amide aromatic ring in these reduction procedures. The results (Table 4, 5, 6) indicate that substituent have very little or no effect in controlling the enantioselectivity of the reduction procedure.

Towards chiral diamines as chiral catalytic precursors for borane-mediated enantioselective reduction of prochiral ketones

Two chiral diamines (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) and (2*R*)-2-anilinomethylpiperidine (**232**) were synthesized starting from (*S*)-phenylalanine (**233**) and (*R*)-pipecolinic acid (**238**) {which was obtained after resolution of racemic pipecolinic acid using (*R, R*) tartaric acid} according to the Scheme 15 and 16. Both the

catalysts were employed for the borane-mediated asymmetric reduction of prochiral ketones and the resulting secondary alcohols were obtained in upto 81% *ee*. These studies certainly throw some light on the understanding of the structural framework of diamine catalysts which actually play a key role to provide high enantioselectivities.

Chiral amides as possible catalytic sources for the borane-mediated asymmetric reduction of prochiral α-halo ketones:

Six amides [(**242-247**), Fig. 44] based on (2*S*)-2-arylcarbonylpyrrolidine frameworks were synthesized (Scheme. 18-21, 23, 24) starting from (2*S*)-N-*tert*-butoxycarbonylproline (**248**). We have also examined the possibility of enantioselective reduction of prochiral ketones by borane at refluxing toluene/THF using these six chiral amides (Table 12 & 14, eq. 100-106) and the resulting alcohols were obtained in 22-77% enantiomeric purities.

Towards (*R*,*R*)-1,2-diaminocyclohexane as a chiral catalytic precursor for borane-mediated enantioselective reduction of prochiral ketones

We have examined the application of (*R*,*R*)-1,2-diaminocyclohexane (**255**) as a catalyst for the borane-mediated asymmetric reduction of prochiral ketones and noticed that enantioselectivities are not high.

The third chapter deals with detailed experimental procedures, physical constants like Mp & Bp, optical rotations, IR, ^{1}H & ^{13}C NMR, mass spectral & elemental analyses, and the details of HPLC analysis.

INTRODUCTION

Enantiomerically pure (or enriched) secondary alcohols occupy an important place in chiral chemistry because several chiral secondary alcohols are medicinally useful compounds.[1] For example (*S*)-isoproterenol[2] (**1**) is a drug for asthma and (*R*)-denopamine[3] (**2**) is a drug for congestive heart failure (Fig.1). (*R*)-2-Fluoroepinephrine[4] (**3**) is a well known β-andregenic agonist. Isocoumarin compound[5] (**4**) is known to possess root promoting activity and antibiotic activity against plant cells bacteria and plant-pathogenic fungi. Acetylenic allylic secondary alcohol[6] (**5**) exhibits remarkable immunosuppressive and antitumor activities. (*R*)-3-Octanol[7] (**6**) is the sex pheromone of *Myrmica scabrinodis* and (*R*)-2-methyl-4-heptanol[7](**7**) is identified as male-produced aggregation pheromone of the West Indian sugarcane weevils *Metamasius hemipterus*. Also certain chiral secondary alcohols are well known synthons for obtaining various biologically active or natural compounds. For example, sphinganine[8] (**8**) is an intermediate in the biosynthesis of sphingolipids and also found to be an inhibitor of protein kinase *C*. Statine[9] (**9**) is one of the key components of peptidomimetic protease inhibitors (Fig. 1).

Due to these remarkable applications[1-9] of chiral secondary alcohols as medicinally relevant molecules and also as synthon for obtaining various biologically active compounds there has been an increasing interest in developing simple and practical methodologies for synthesis of different chiral secondary alcohols. Among various available and known methods, asymmetric reduction of prochiral ketones has become one of the most important methods for obtaining enantiopure (or enriched) secondary alcohols.

During the last three decades several interesting strategies have been developed for synthesis of enantiopure secondary alcohols *via* the reduction of prochiral ketones.

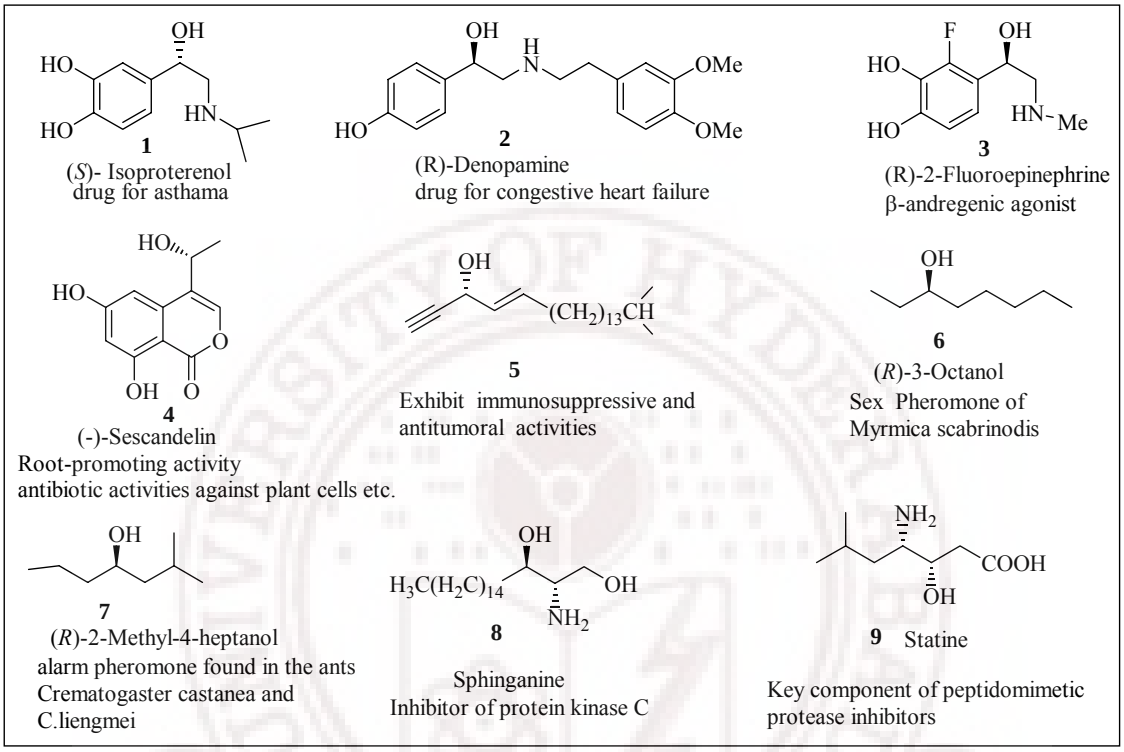


Fig. 1

These can be broadly classified into the following six categories, (i) chirally modified metal hydride reagents (specially, LAH and chiral boron based reagents),[10-12] (ii) asymmetric hydrogenation[13,14] (iii) hydrogen transfer reactions[15-17] (iv) biotransformations, (v) reduction by enzyme models[18-20] and (vi) reductions using chiral catalysts.[21-26] In recent years, development of simple and facile strategies for asymmetric reduction of prochiral ketones providing secondary alcohols in high enantiomeric purities, based on the concept of chiral catalysts has become one of the challenging and attractive tasks in chiral chemistry.

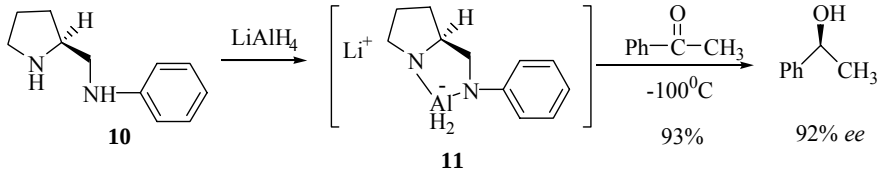
Since this thesis deals with the development of appropriate chiral catalysts for borane-mediated asymmetric reduction of prochiral ketones, this section will present briefly the relevant literature dealing with the boron based chiral reducing reagents and also on the borane-mediated reduction of prochiral ketones under the influence of various chiral catalysts. Before presenting the relevant literature methods in this direction, we feel that it would be appropriate to present first briefly the literature examples from other methods (non-boron based methods).

Chirally modified metal hydride reagents

Lithium aluminium hydride (LAH) is one of the most-powerful and commonly used reagent for reduction of ketones and other carbonyl groups. Various chiral diamines and diols have been systematically used for chiral modification of LAH with a view to develop appropriate reagent for reduction of prochiral ketones to obtain chiral secondary alcohols in high enantiomeric purities. Some selected examples from literature are given in this section.

Mukiyama and coworkers[27] in the year 1977 developed the complex (**11**), obtained *via* the treatment of one equivalent of lithium aluminium hydride with diamine (2*S*)-2-anilinomethylpyrrolidine (**10**), as a reagent for reduction of prochiral ketones to provide the resulting secondary alcohols in high enantiomeric purities. Thus asymmetric reduction of acetophenone with chiral hydride reagent (**11**), provided (*S*)-1-phenylethanol in 92 % *ee* (Scheme 1).

Scheme 1



Subsequently Noyori and co-workers[28-30] developed the chiral binaphthol-modified lithium aluminium hydride reagents (**12**, **13** BINAL-H, Fig. 2) for the reduction of prochiral ketones to provide the resulting secondary alcohols in high enantiomeric purities. In this methodology both the enantiomers of the secondary alcohol can be obtained by choosing either *R* or *S* 1,1'-bi(2-naphthol) (**12** & **13**) for the chiral modification of LAH. Selected examples are given in Scheme 2 and equation 1.

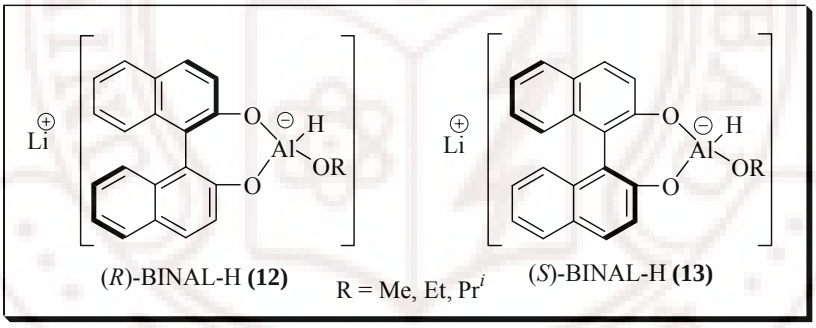
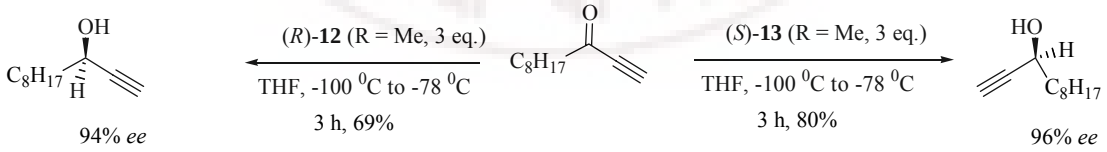
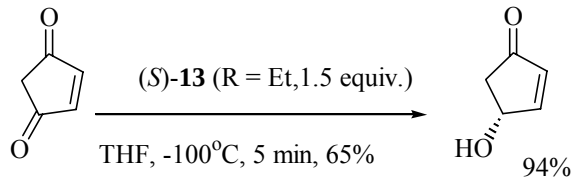


Fig. 2

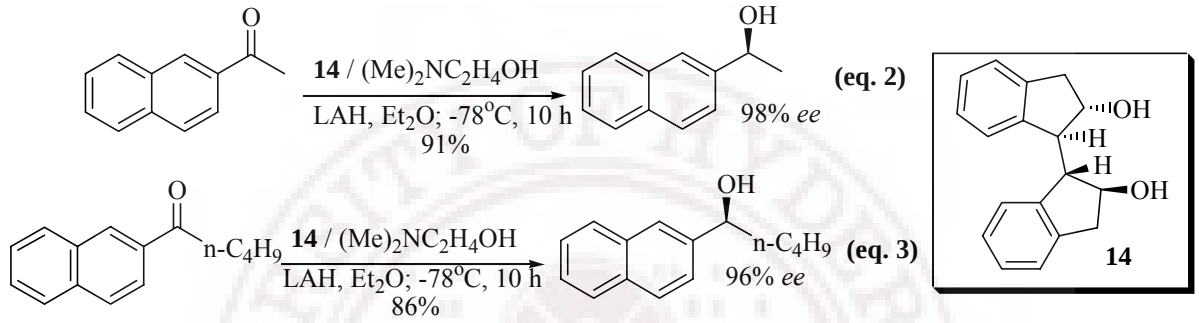
Scheme 2





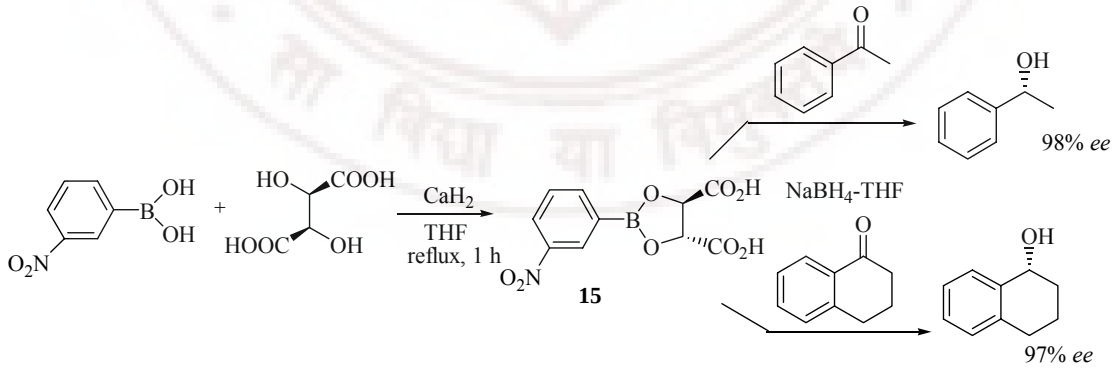
(eq 1)

Xu and co-workers[31] have reported an interesting enantioselective reduction of prochiral ketones using 1:1 complex of LAH and chiral diol (**14**) in the presence of N,N-dimethylethanolamine (1 equiv.) to provide the resulting secondary alcohol in high enantioselectivity. Two examples are presented in equations 2 and 3.



Recently Singaram and coworkers[32] reported an interesting C_2-symmetrical cyclic borane compound **15,** obtained from phenylboronic acid and (*R*, *R*)-tartaric acid, for reduction of prochiral ketones in the presence of $NaBH_4$ to provide the secondary alcohols in high enantiomeric purities. Representative examples are presented in Scheme 3.

Scheme 3



Asymmetric hydrogenation of prochiral ketones mediated by transition metal complexes

Asymmetric hydrogenation of prochiral ketones is another important method for obtaining secondary alcohols in high enantiomeric purities. Several Ru-based BINAP catalysts **16-20** (Fig. 3) were developed by Noyori and co-workers[14,33,34] for this purpose. All these catalysts were found to offer encouraging results. Selected examples are presented in equations 4 & 5. Thus β-keto ester, methyl acetoacetate, on hydrogenation in the presence of [$RuCl_2$(*R*)binap] (**16**) provided the resulting β-keto alcohol in 99% enantiomeric purity. Similarly asymmetric hydrogenation of *tert*-butyl methyl ketone in the presence of the chiral catalyst **18** provided the resulting secondary alcohol in 97% enantiomeric purity.

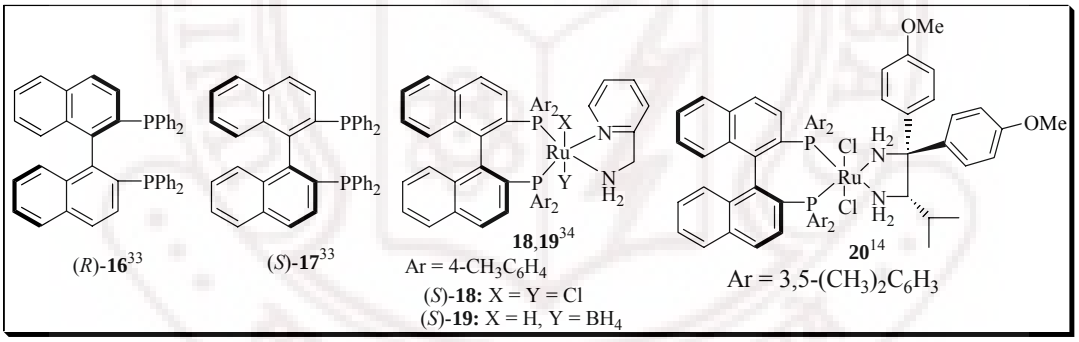
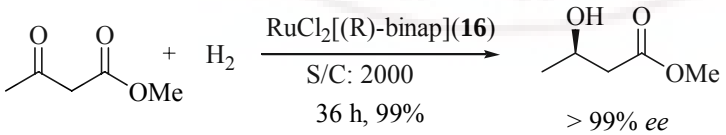
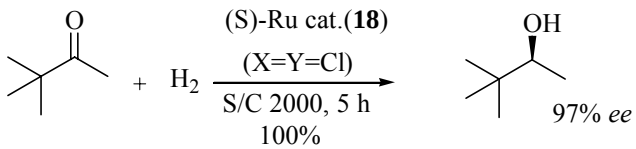


Fig. 3



(eq. 4)[33]



(eq. 5)[34]

Zhang and co-workers[35] in the year 2004 reported an efficient protocol for asymmetric hydrogenation of α-phthalimide ketones using ruthenium complxes of chiral phosphine **21** (Fig. 4) as a catalyst. About the same time Lin and co-workers[36] have also developed useful catayst ligands **22** (as ruthenium complexes) and ruthenium complex **23** for asymmetric hydrogenation of α-phthalimide ketones to provide the resulting secondary alcohols in high enantioselectivity (Scheme 4).

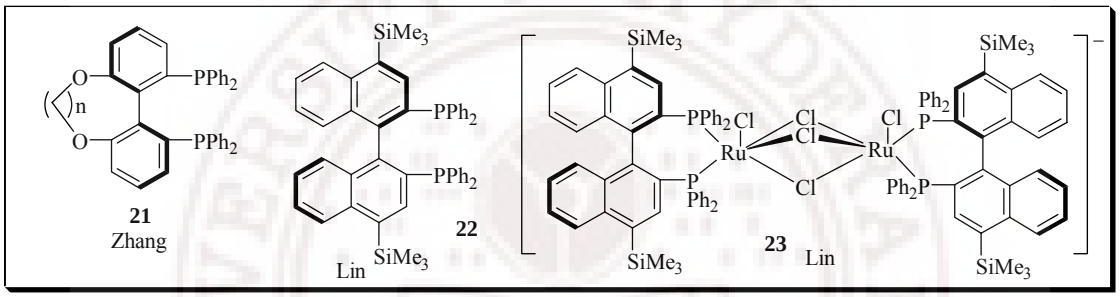
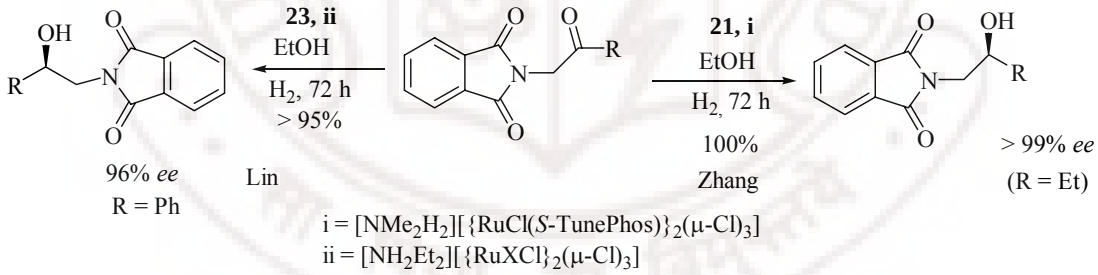
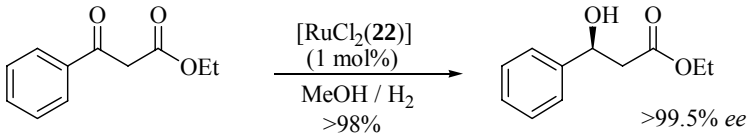


Fig. 4

Scheme 4



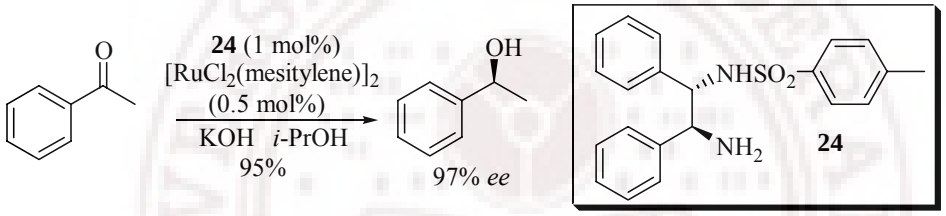
Lin and co-workers[37] also used Ru-complex of the ligand **22** as catalyst for asymmetric hydrogenation of ethyl 3-phenyl-3-oxopropanoate to provide the resulting alcohol, ethyl 3-phenyl-3-hydroxypropanoate in high enantioselectivity (eq. 6).



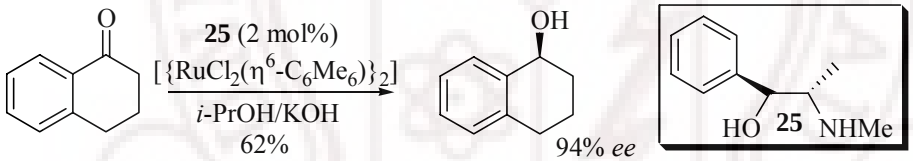
(eq. 6)[37]

Asymmetric transfer Hydrogenation (ATH)

Asymmetric transfer hydrogenation (ATH) is yet another important process for asymmetric reduction of prochiral ketones providing the secondary alcohols in high enantiomeric purities. Various chiral catalysts have been developed for this purpose. Noyori and co-workers[38,39] used ruthenium complexes of chiral compound **24, 25** for ATH reaction for synthesis of secondary alcohols in high enantiomeric purities. Representative examples are given in equation 7 & 8.

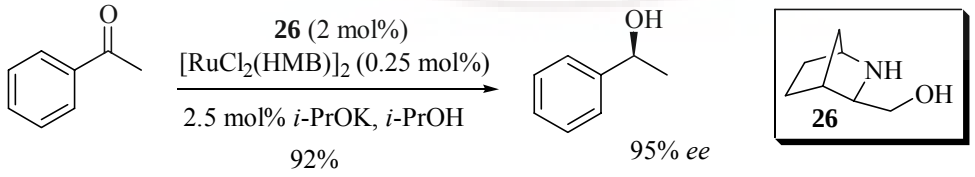


(eq. 7)[38]



(eq. 8)[39]

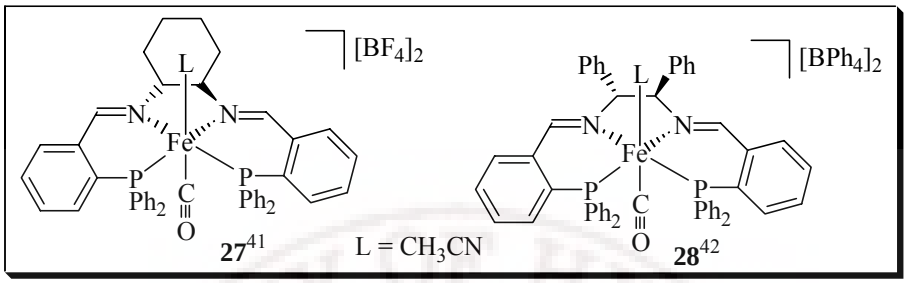
Subsequently, Andersson and co-workers[40] have successfully employed Ru-bicyclic amino alcohol (**26**)-complex as a catalyst for the ATH reaction. Representative example is given in equation 9.



(eq. 9)[40]

Very recently, Morris and co-workers[41,42] reported, for the first time, an interesting ATH procedure for reduction of prochiral ketones with chiral iron catalysts **27, 28** (Fig. 5**)** to

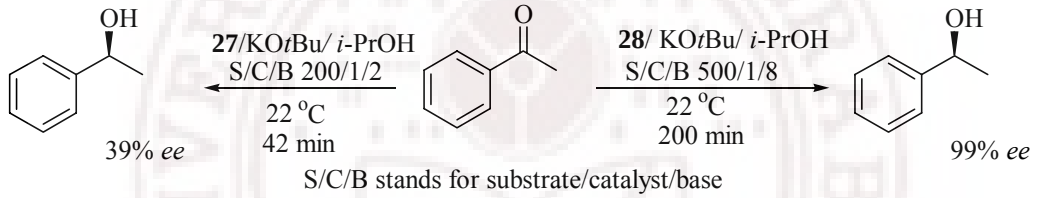
provide the resulting secondary alcohols in very high enantiomeric purities (Scheme 5).



27[41] **28**[42]

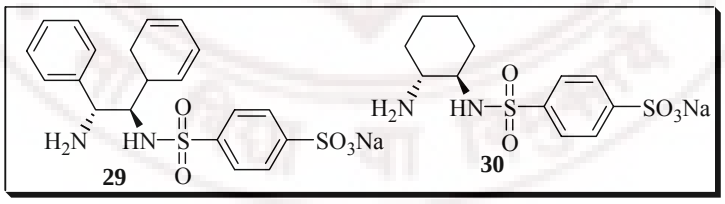
Fig. 5

Scheme 5



S/C/B stands for substrate/catalyst/base

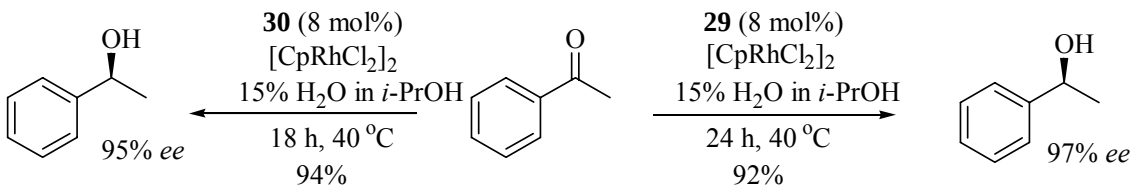
Willams and co-workers[43] reported, for the first time, an useful Ru-catalysed ATH reaction methodology for reduction of prochiral ketones in aqueous media using water soluble ligands **29, 30** (Fig. 6). Representative examples are given in Scheme 6.



29 **30**

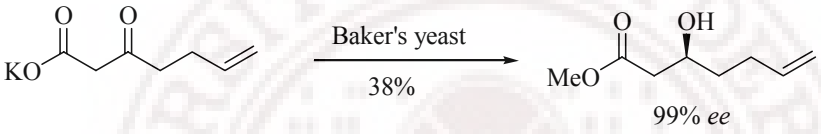
Fig. 6

Scheme 6

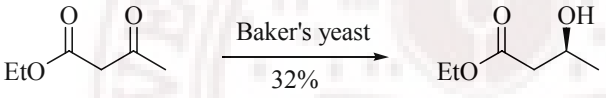


Reduction prochiral ketones *via* biotransformations and by enzymatic models

Enzymes have been used extesively for obtaining enantiomerically pure secondary alcohols *via* the reduction of prochiral ketones. Baker's yeast[44] mediated asymmetric reduction is one of the very useful methodologies for reduction of β-keto ester to provide the secondary alcohol in high enantiomeric purities. Representative examples are presented in equations 10, 11.

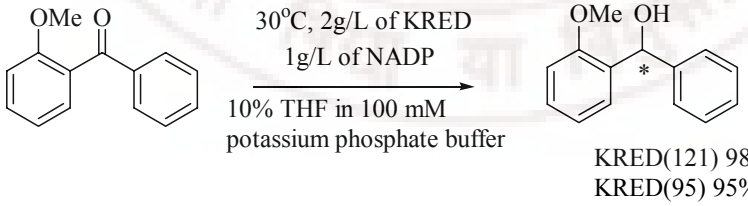


(eq. 10)[44]



(eq. 11)[44]

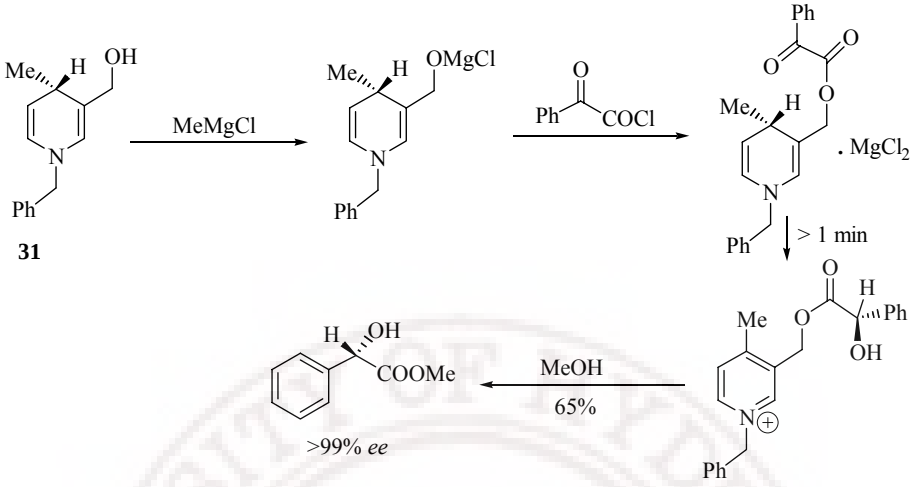
Recently Truppo and co-workers[45] reported an interesting methodology for the enantioselective reduction of diaryl ketones by using isolated enzymes KRED, (ketoreductase enzymes) to provide the resulting secondary alcohols in high enantiomeric purities. One such example is presented in equation 12.



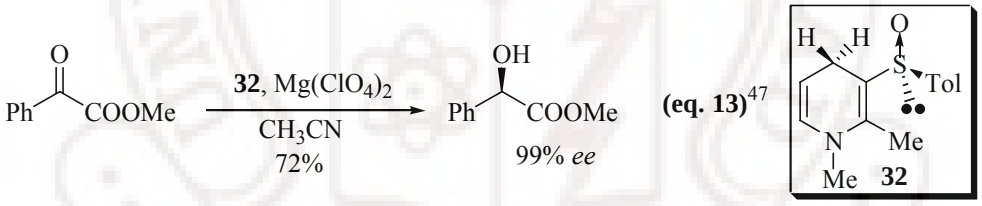
(eq. 12)[45]

Meyers and Brown[46] used compound **31** as NADH model for obtaining methyl mandelate in 99% *ee via* an elegant intramolecular reduction protocol as indicated in Scheme 7.

Scheme 7

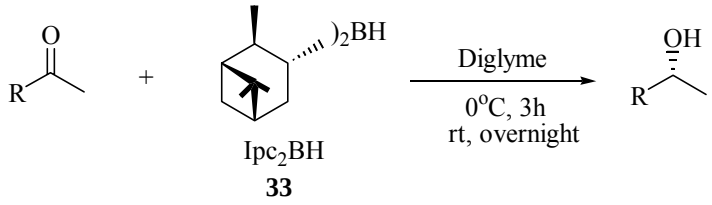


Compound **32** has been successfully used by Imanishi and co-workers,[47] as NADH model for the reduction of methyl benzoylformate to provide the resulting methyl mandelate in 99% enantiopurity (eq. 13).



Chiral organoboron compounds:

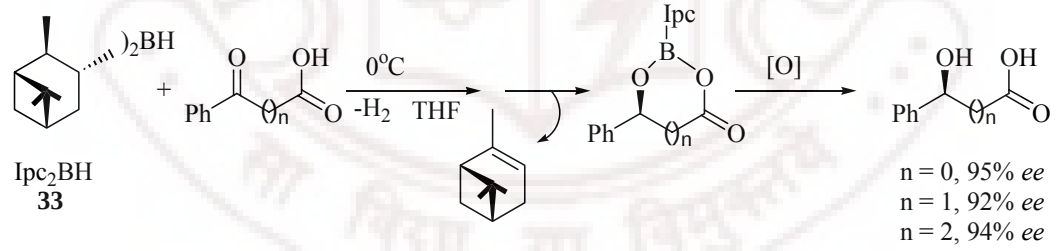
In 1961 Brown and Bigley[48] for the first time reported the use of diisopinocamphenylborane (**33**) for the asymmetric reduction of prochiral ketones (eq. 14). Although the enantioselectivities are not encouraging, this methodology provided the basic guidance to the chiral chemists to develop better reagents for asymmetric reduction of prochiral ketones.



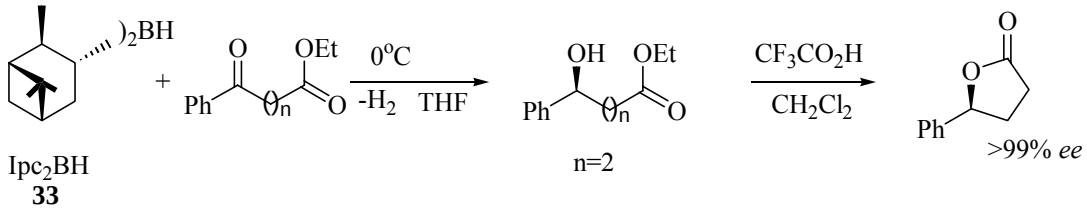
(eq.14)[48]

Recently Ramachandran and co-workers[49] have found that the same reagent, Ipc_2BH (**33**), provided an excellent enantioselectivity for the reductions of α, β, and γ-keto acids and also the corresponding esters in much better enantiosectivities than simple ketones. Selected examples are given in Scheme 8 & 9. These two interesting results (Schemes 8 & 9) using diisopinocamphenylborane (**33**) certainly demonstrate that selection of substrates (ketone) plays an important role in understanding the efficiency of the reagent thus clearly indicating that the reagent that is not suitable for certain substrates may be more suitable for different substrates.

Scheme 8



Scheme 9



Based on the Browns elegant initial original observations, several chiral borane reagents based on isopinocampheylborane framework were synthesized and examined for various chiral reduction processes by various research groups **34-37** (Fig. **7**). A significant development in these investigations was made by Midland and co-workers[50] who introduced *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane, **34**) as a chiral reducing agent. This is an efficient reducing agent for reduction of deuterio aldehydes and α,β-acetylenic ketones,[51] to provide the corresponding alcohols in high enantiomeric purities. Two representative examples are given in equations 15 & 16

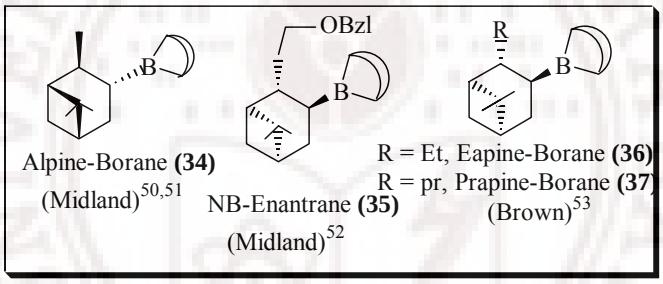
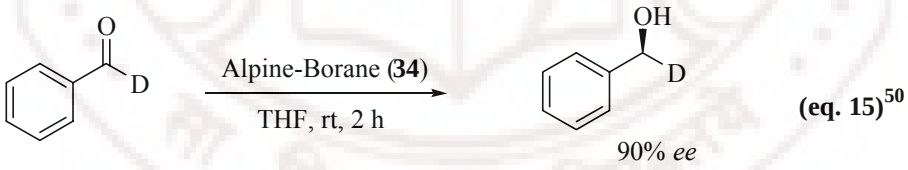
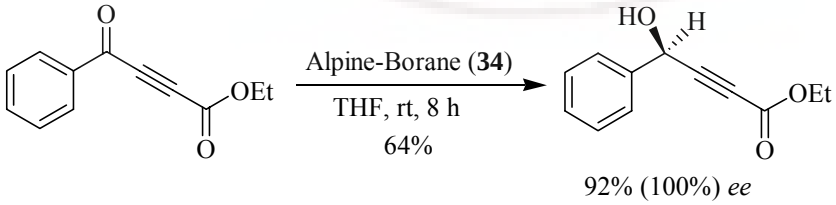


Fig 7



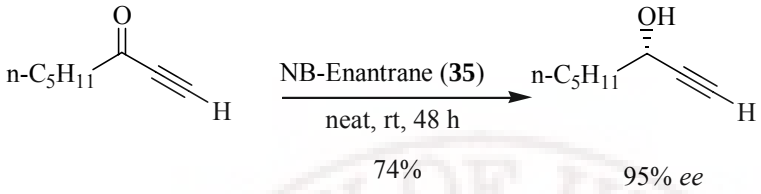
(eq. 15)[50]



(eq. 16)[51]

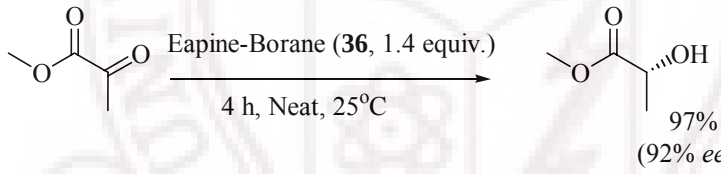
(The number in parentheses are corrected for 92% *ee* α-pinene)

Midland and co-workers[52] also reported NB-Enantrane (**35**), another interesting reagent for asymmetric reduction of α,β-acetylenic ketones to provide the resulting secondary alcohol in high enantiomeric purity (eq. 17).

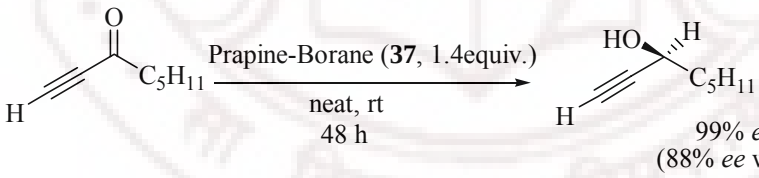


(eq. 17)[52]

Subsequently, Brown and co-workers[53] examined the application of Eapine-Borane (**36**) and Prapine-borane (**37**), for the reduction of α-keto esters and α,β-acetylenic ketones and found that these reagents offer better enantioselectivity than Alpine-borane (**34**). Representative examples are given in equation 18 and 19.

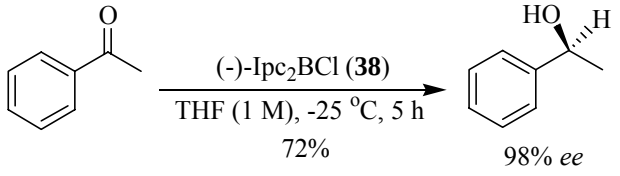


(eq. 18)[53]

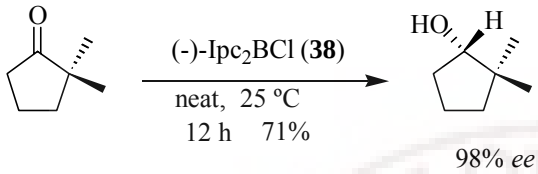


(eq. 19)[53]

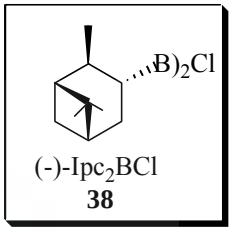
The most interesting discovery came from Brown and co-workers[54,55] in the year 1988 who reported (-)-diisopinocampheylchloroborane [(-)-Ipc_2BCl, **38**] as a highly efficient reducing agent for reduction of prochiral ketones to provide the resulting secondary alcohols in high enantiomeric purity. Representative examples are presented in equations 20-22.

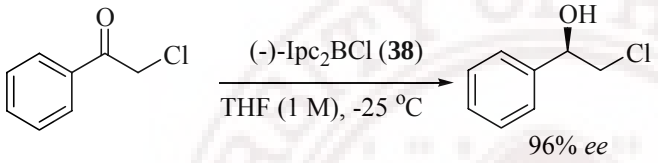


(eq. 20)[54]



(eq. 21)[54]

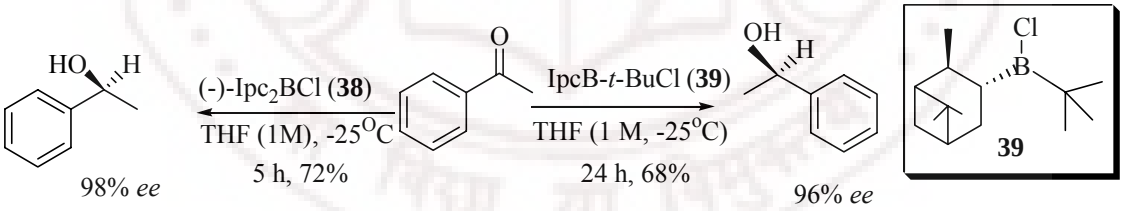




(eq. 22)[55]

Subsequently Brown and co-workers[56] also reported application of yet another important reducing reagent IpcB-*t*-BuCl (isopinocampheyl-*tert*-butylchloroborane, **39**). It must be mentioned here that this reagent provides the resulting secondary alcohols with opposite configuration to that of Ipc_2BCl in the reduction of aryl alkyl ketones (Scheme 10).

Scheme 10



Chiral borohydride reagents:

In addition to the above mentioned chiral borane reagents, various chiral borohydrides **(40-43)** have also been developed (Fig. 8) and their application has been well studied for the asymmetric reduction of a number of prochiral ketones by several research groups.[57-60] Among these reagents, Midland's reagent **(42)**[59] is particularly important because of its

high efficiency in the asymmetric reduction of dialkyl ketones to provide the resulting secondary alcohols in high enantioselectivity. Representative example is given in equation 23.

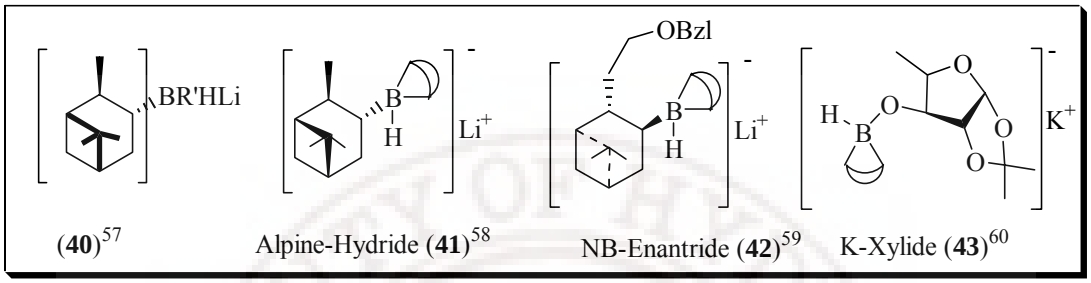
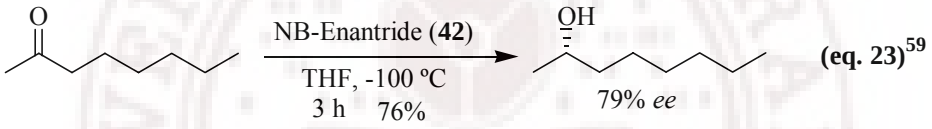
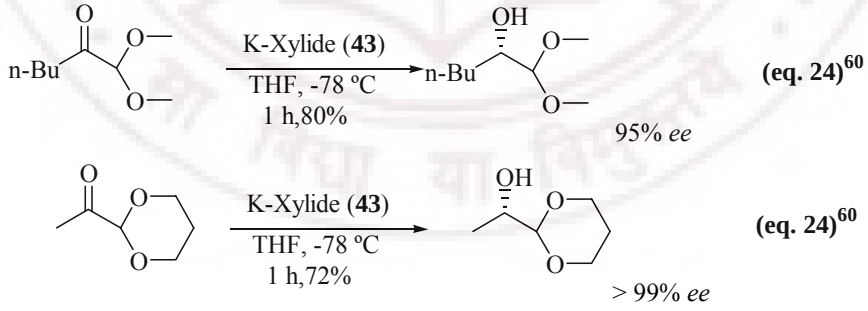


Fig 8



Cho and co-worker,[60] for the first time, reported K-Xylide **(43)** as an efficient reagent for asymmetric reduction of α-keto acetals to provide the resulting secondary alcohols in high enantiomeric purities. Two representative examples are given in equations 24 & 25.



Chiral amino alcohol based borane reagents:

Fiaud and Kagan[61] reported for the first time the potential of amino alcohol-BH_3 complexes for reduction of prochiral ketones and observed that the resulting secondary

alcohols were obtained in low enantioselectivities. The best result obtained in this study was in the case of ephedrine-borane complex which provided the resulting alcohols in 3-5 % *ee* in the reduction of acetophenone. Later on Itsuno and co-workers[62] systematically studied the application of borane-complexes of several chiral amino-alcohols **(44-48)**, derived from various α-amino acids, for the asymmetric reduction of prochiral ketones and obtained the corresponding secondary alcohols upto 60% enantiomeric purity (Fig. 9, eq. 26).

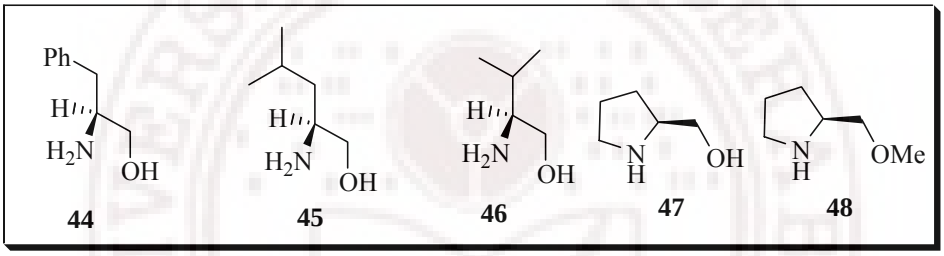
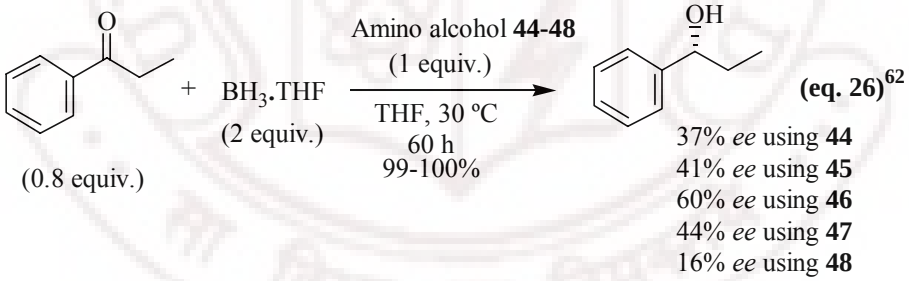
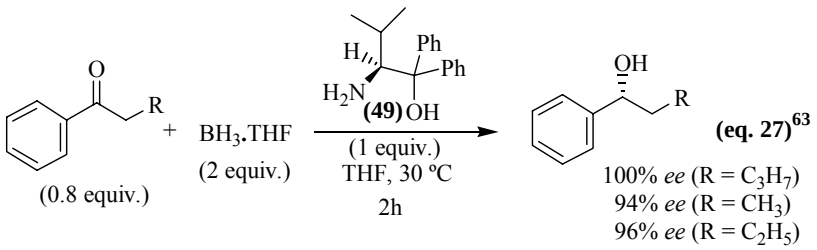


Fig. 9

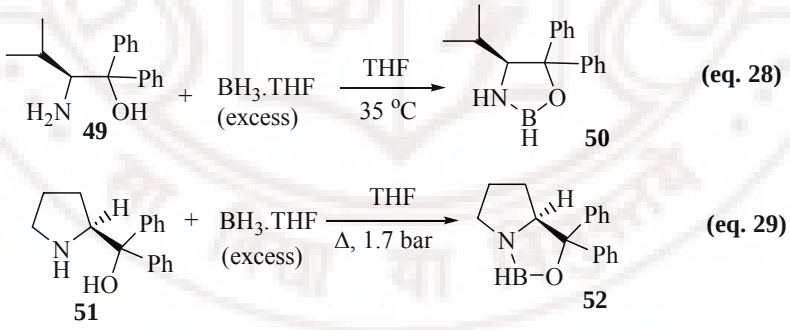


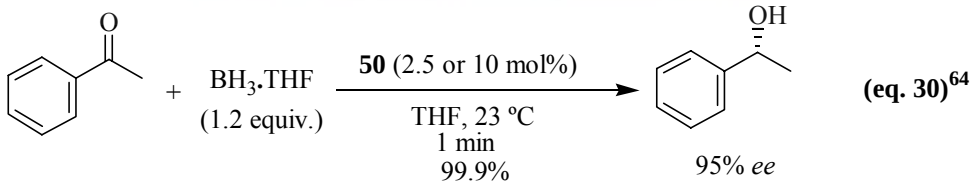
Subsequently they found that α,α-diphenylvalinol (**49**)-borane complex provided high enantioselectivity in the reduction of aryl alkyl ketones (eq. 27) [63].

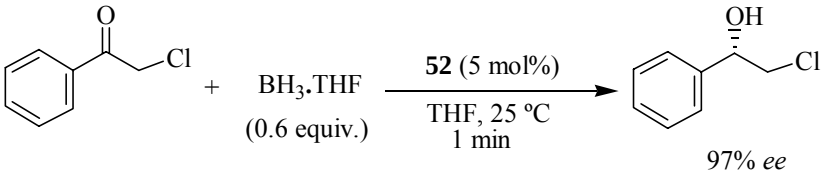


Chiral catalytic approach

In recent years asymmetric organic synthesis, particularly synthesis of medicinally relevant compounds, demands the development of catalytic processes as the stoichiometric processes involve the use of large amount of chiral reagent which makes the process expensive. Also most of the time the recovery of the chiral reagents become difficult. Based on the elegant observations of Itsuno using amino alcohol-borane complex as useful reducing agents, Corey and co-workers[64] developed an interesting catalytic process for the first time in the year 1987, recognizing the importance of oxazaborolidines as chiral catalysts for the reduction of prochiral ketones using BH_3 as hydride source. Corey first prepared oxazaborolidines **50** and **52** (equation 28, 29) and found that oxazaborolidine **52** derived from (*S*)-α,α-diphenylmethylprolinol (**51**) to be more efficient catalyst for reduction of prochiral ketones (eq. 30 & 31).







(eq. 31)[64]

Subsequently Corey and co-workers[65-67] also prepared a number of oxazaborolidines **53a-56** (Fig. 10) and successfully used them as catalysts for the reduction of prochiral ketones (eq. 32-34). Due to efficiency of these catalysts in inducing chirality, Corey coined the word *chemzymes* as these catalysts match the catalytic efficiency of enzymes in enantioselective processes, although they are chemicals.

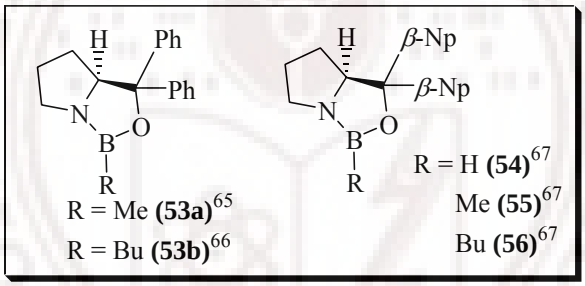
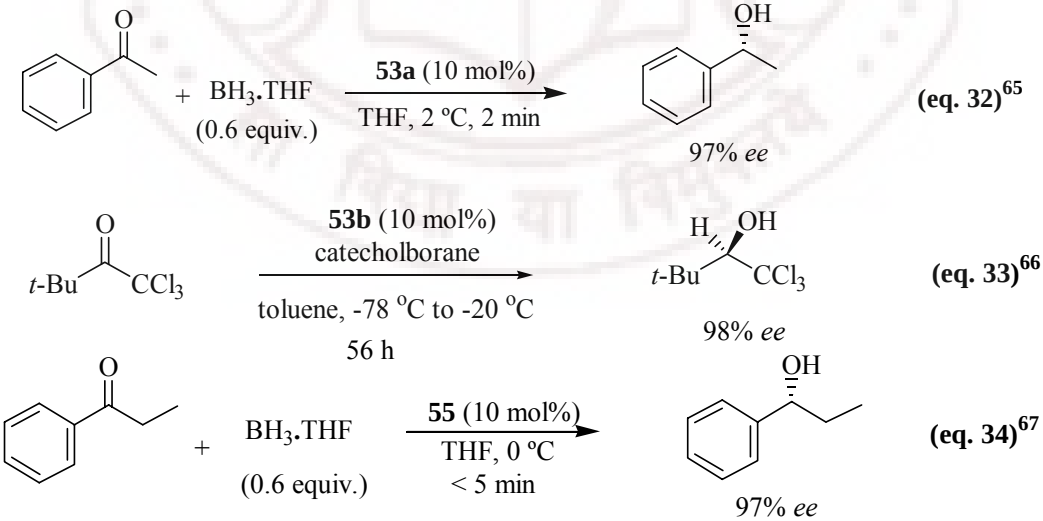


Fig. 10



(eq. 32)[65]

(eq. 33)[66]

(eq. 34)[67]

After the brilliant demonstration of oxazaborolidines, as catalysts by Corey, a large number of oxazaborolidines **57-82** (Fig. 11) were prepared over the past two decades by various research groups and their application has been well studied for asymmetric reduction of several prochiral ketones. Selected applications are presented in equations 35-39.

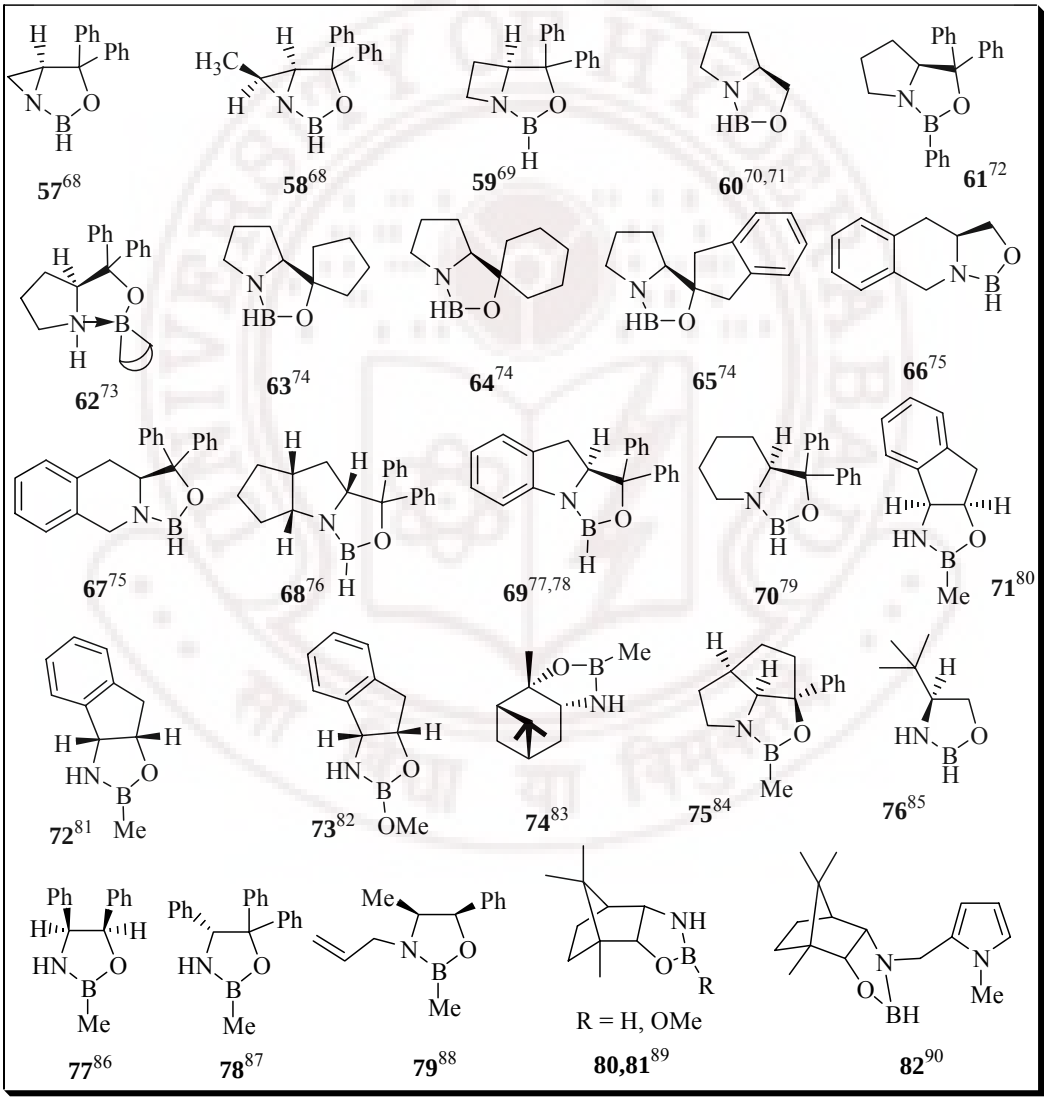
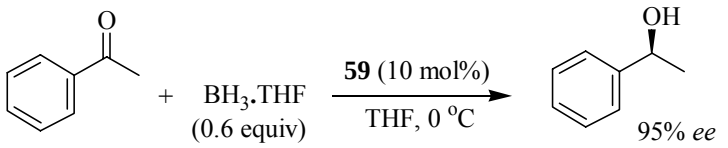
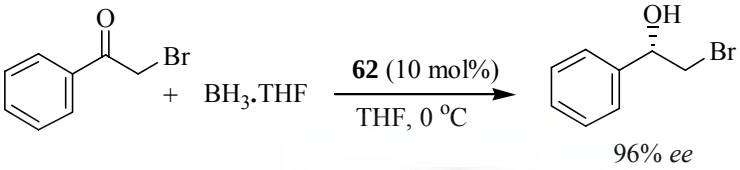


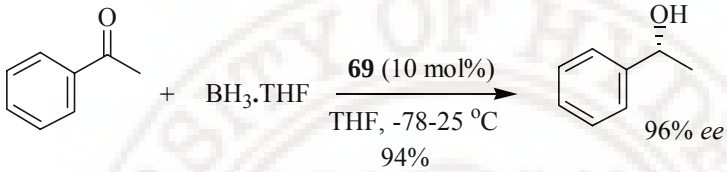
Fig. 11



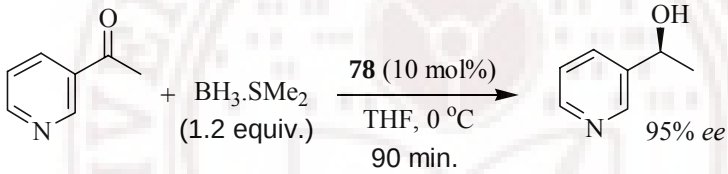
(eq. 35)[69]



(eq. 36)[73]

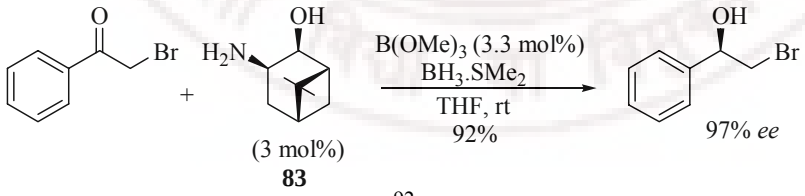


(eq. 37)[78]



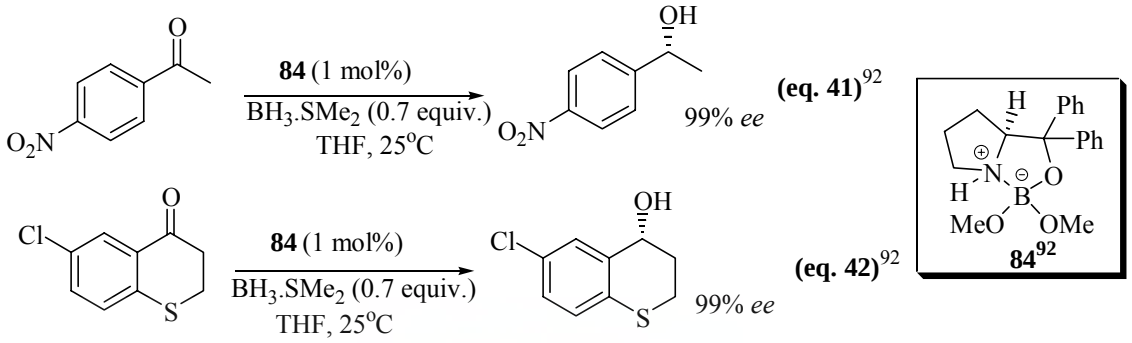
(eq. 39)[87]

Recently amino alcohol (**83**) has been used for the *in situ* generation of *B*-methoxy-oxazaborolidine catalyst, for the borane-mediated asymmetric reduction of alkyl-aryl ketones. One example is given in equation 40.[91]



(eq. 40)[91]

More recently Garcia and co-workers[92] have reported a borate complex (**84**) derived from (*S*)-α,α-diphenylmethylprolinol, as an useful catalyst for the borane-mediated asymmetric reduction of prochiral ketones. Representative examples are given in equation 41, 42.



Spiroborate complexes[93] **85-87** (Fig. 12) have also been used as effective catalysts for the borane-mediated asymmetric reduction of ketones. Representative examples are given in equations 43.

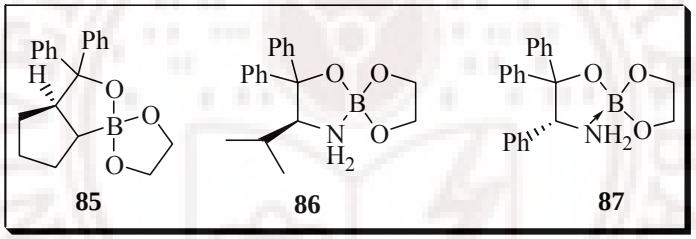
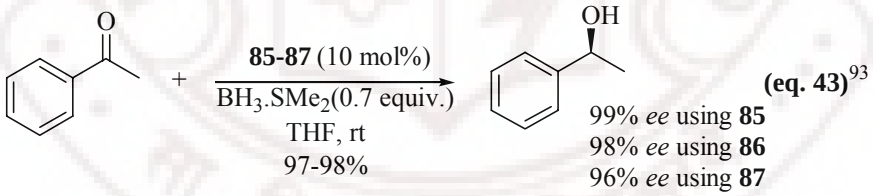


Fig. 12



Braun and co-workers[94] have used phenyl-glycine derived amino alcohols **88-91** (Fig. 13) as catalytic precursors for borane-mediated reductions of ketones to provide the resulting alcohols in high enantiomeric excess (eq. 44).

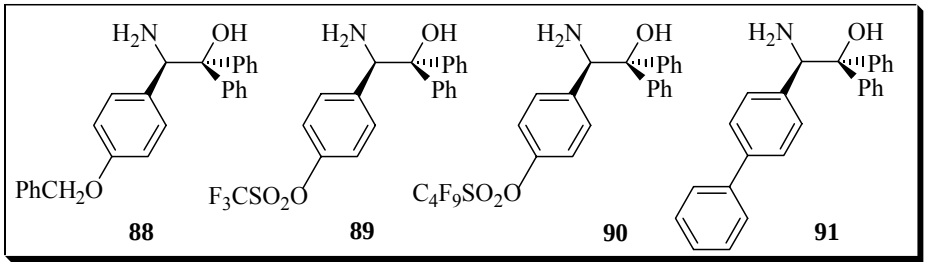
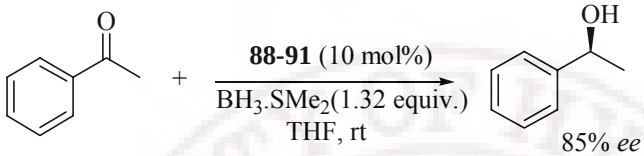


Fig. 13



85% *ee* using **88**
95% *ee* using **89**
96% *ee* using **90**
97% *ee* using **91**

(eq. 44)[94]

Periasamy and co-workers[95,96] developed an interesting procedure for reduction of prochiral ketones in the presence of (*S*)-α,α-diphenylmethylprolinol (**51**) as catalyst using *in situ* generated borane, obtained *via* the treatment of tetrabutylammonium borohydride with methyl iodide (Fig. 14). The resulting secondary alcohols were obtained in high enantiomeric purities (one example is presented in eq. 45).

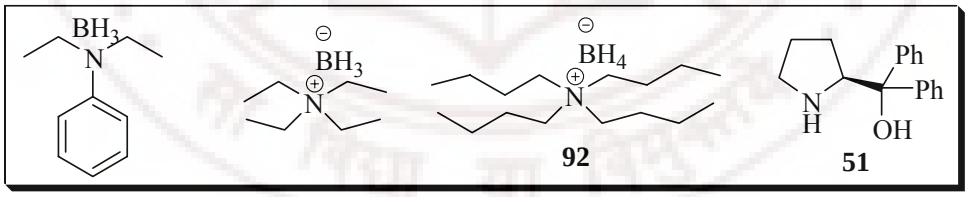
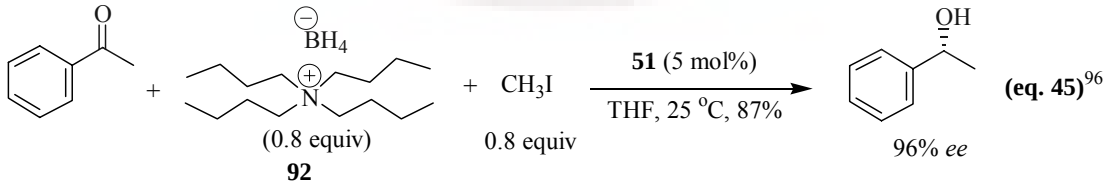


Fig. 14



(eq. 45)[96]

Cho and co-workers [97] have described a simple and convenient procedure for obtaining terminal 1,2-diols with high enantiomeric excess using the oxazaborolidine catalyst **50**,

52, **71** (Fig. 15) *via* the borane-mediated reduction of aryl trialkylsilyloxymethyl ketones. Representative examples are given in Scheme 11.

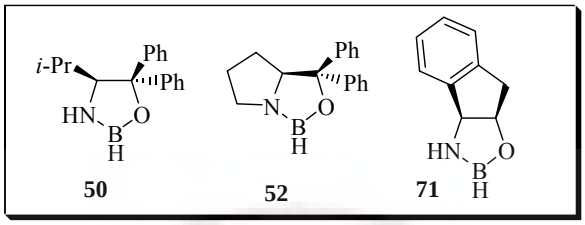
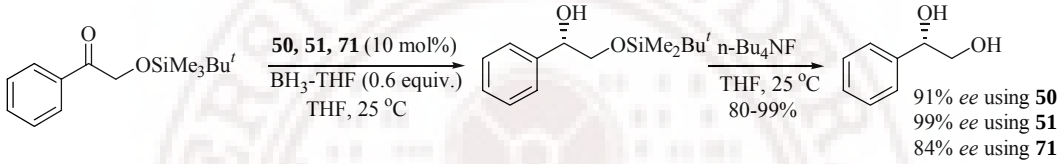
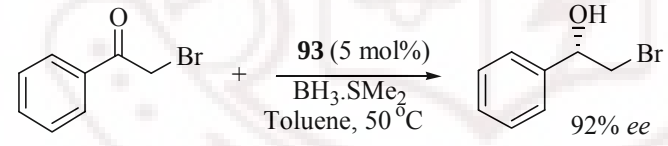


Fig. 15

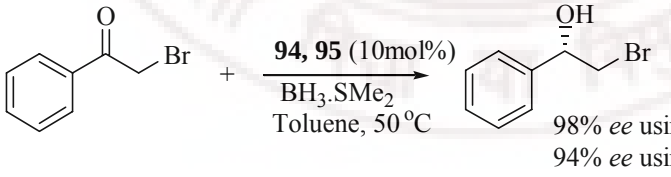
Scheme 11



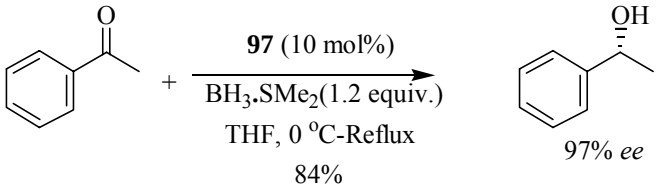
Various squaric acid, ferrocine, and pyridine based amino alcohols have also been used as possible catalytic precursors in borane mediated asymmetric reduction of prochiral ketones **93-100** (Fig. 16). Selected examples are presented in equations 46-49.



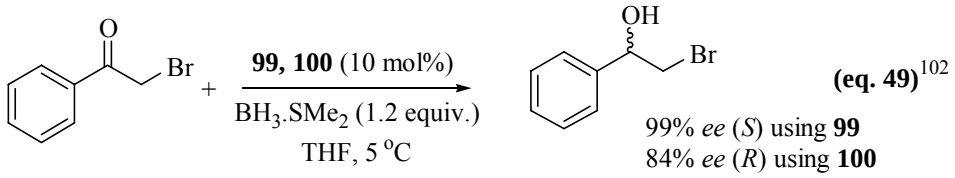
(eq. 46)[98]



(eq. 47)[98,99]



(eq. 48)[101]



(eq. 49)[102]

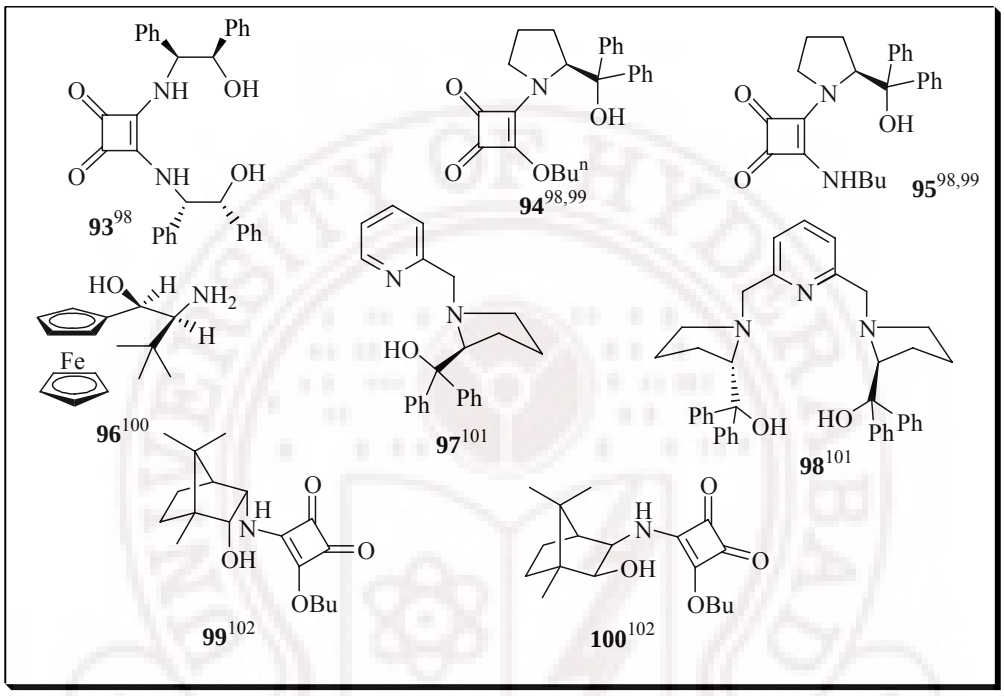
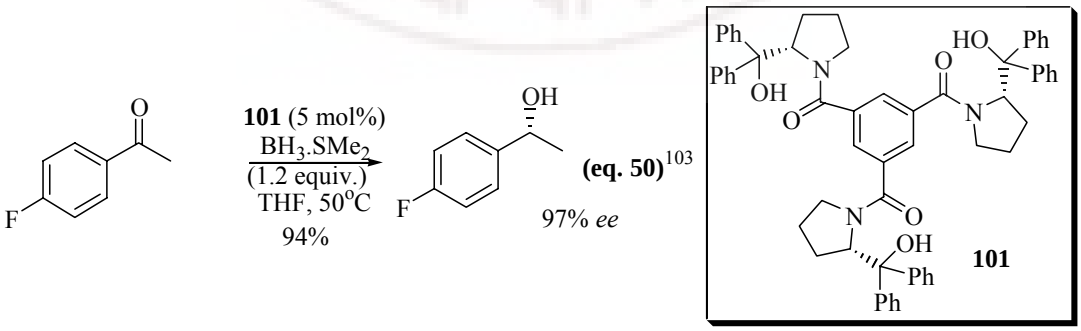


Fig. 16

Du and co-workers[103] reported a C_3-symmetric tripodal tris (β-hydroxyamide) ligand **(101)** as a catalyst in the borane-mediated asymmetric reduction of prochiral ketones (eq.50).



(eq. 50)[103]

Polymer supported chiral catalysts:

Polymer supported catalysts are in demand because of easy work-up procedures and easy recoverability of the catalysts, for borane-mediated asymmetric reduction of prochiral ketones. Itsuno and co-workers[104,105] have prepared several years ago some interesting polymer supported chiral reagents **102-104** (Fig. 17) and examined in borane-mediated asymmetric reduction of prochiral ketones. Although these polymers are used in stoichiometric amount and enantioselectivities are not that high, these studies provided the basic guidance / idea for the preparation of better polymer supported catalysts (eq. 51).

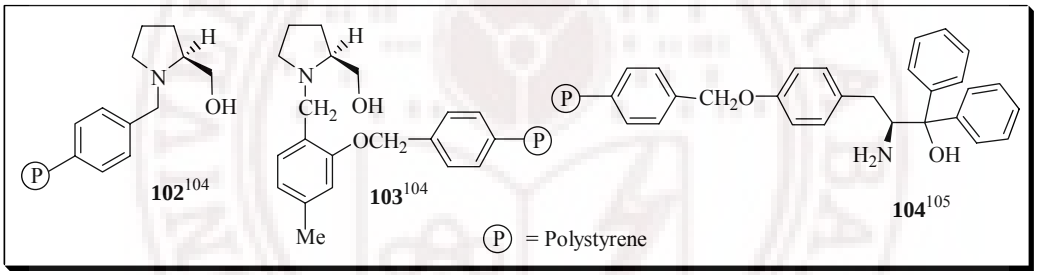
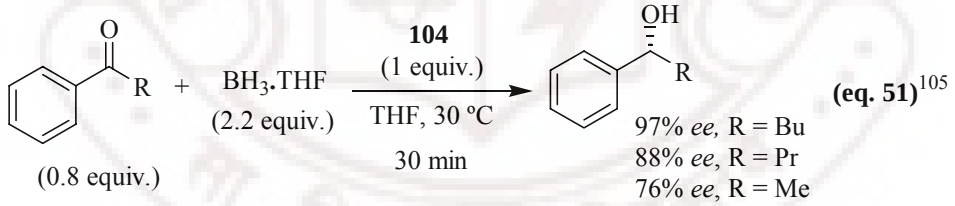
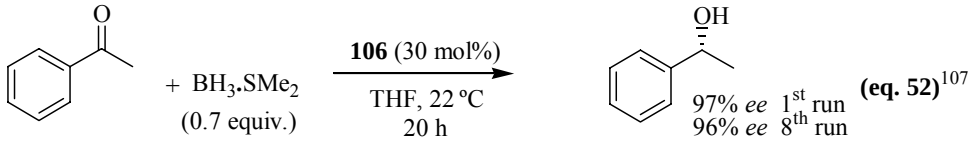


Fig. 17

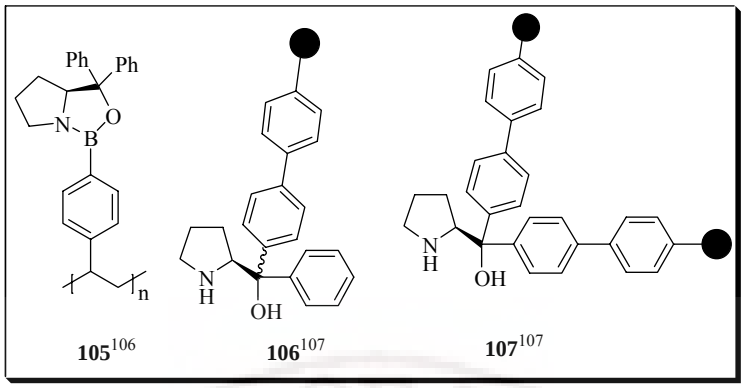


(eq. 51)[105]

Based on the elegant initial studies by Itsuno, various polymer supported catalysts **105-107** (Fig. 18) have been synthesized by various research groups and applied systematically for the borane-mediated asymmetric reduction of ketones. One example is given in equation 52.[106,107]



(eq. 52)[107]

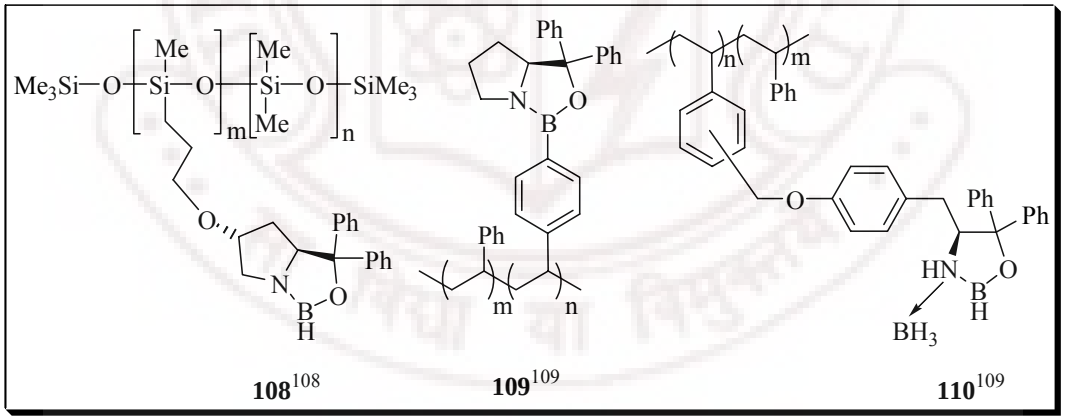


105[106] **106**[107] **107**[107]

Fig. 18

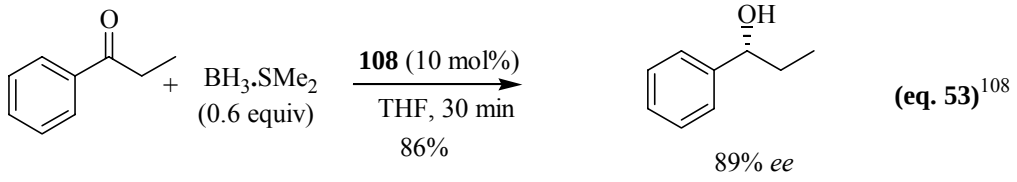
Homogeneous soluble polymers:

Soluble polymer oxazaborolidine catalysts **108-110** (Fig. 19) were reported by Wandrey[108] and Kragl[109] for enantioselective borane reduction of ketones. The catalyst **108** can be retained by a nonfiltration membrane and thus can be recovered after reaction or used in a continuously operated membrane reactor. One selected example is shown in equation 53.



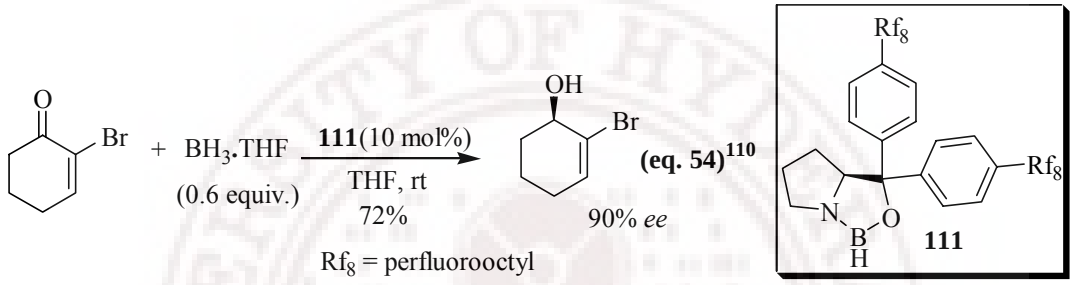
108[108] **109**[109] **110**[109]

Fig. 19



(eq. 53)[108]

In the year 2005 Soos and co-workers[110] have described an operationally simple and recoverable fluorous diphenylprolinol derivative (**111**) as catalyst (for *in situ* generation of oxazaborolidine) for borane mediated reduction of ketones. The precatalyst can be easily separated from the reaction mixture using fluorous solid phase extraction and can be recycled. Representative example is given in equation 54.



Bolm and co-workers[111] used optically active dendritic amino alcohols **112-115** (Fig. 20) as catalysts for the borane mediated asymmetric reduction of prochiral ketones (eq. 55).

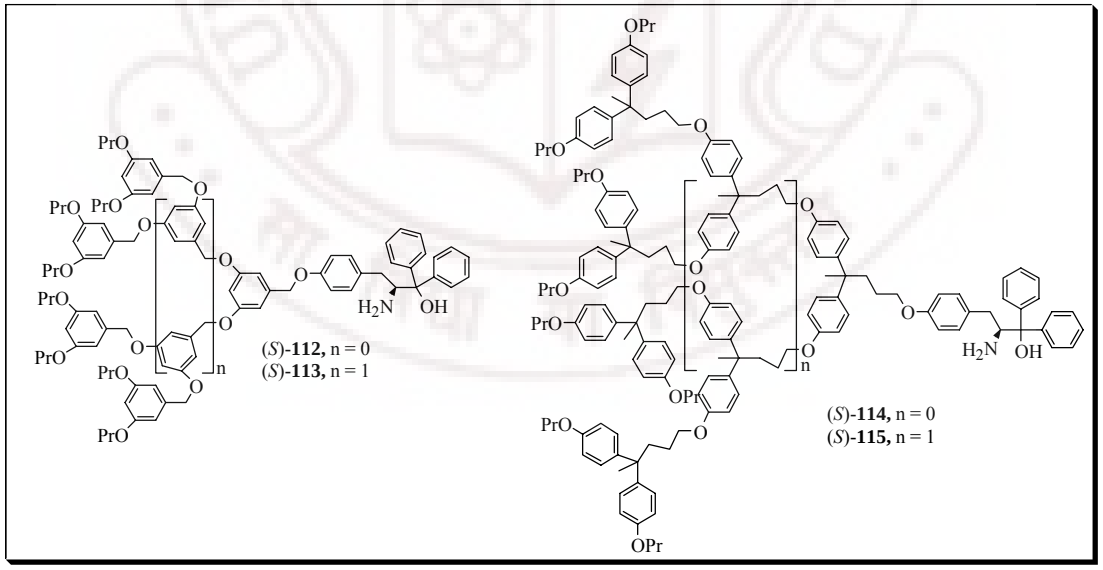
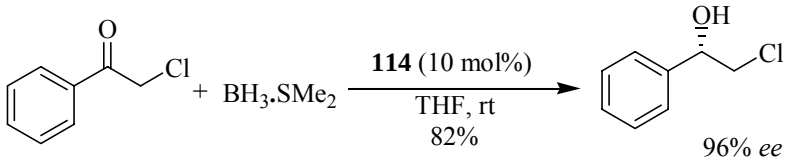


Fig. 20



(eq. 55)[111]

Later on research group of Zhao[112] and Liang[113] have employed dendritic amino alcohols based catalysts **116-124** (Fig. 21) for this borane-mediated asymmetric reduction of ketones. Representative examples are given in equation 56 and 57.

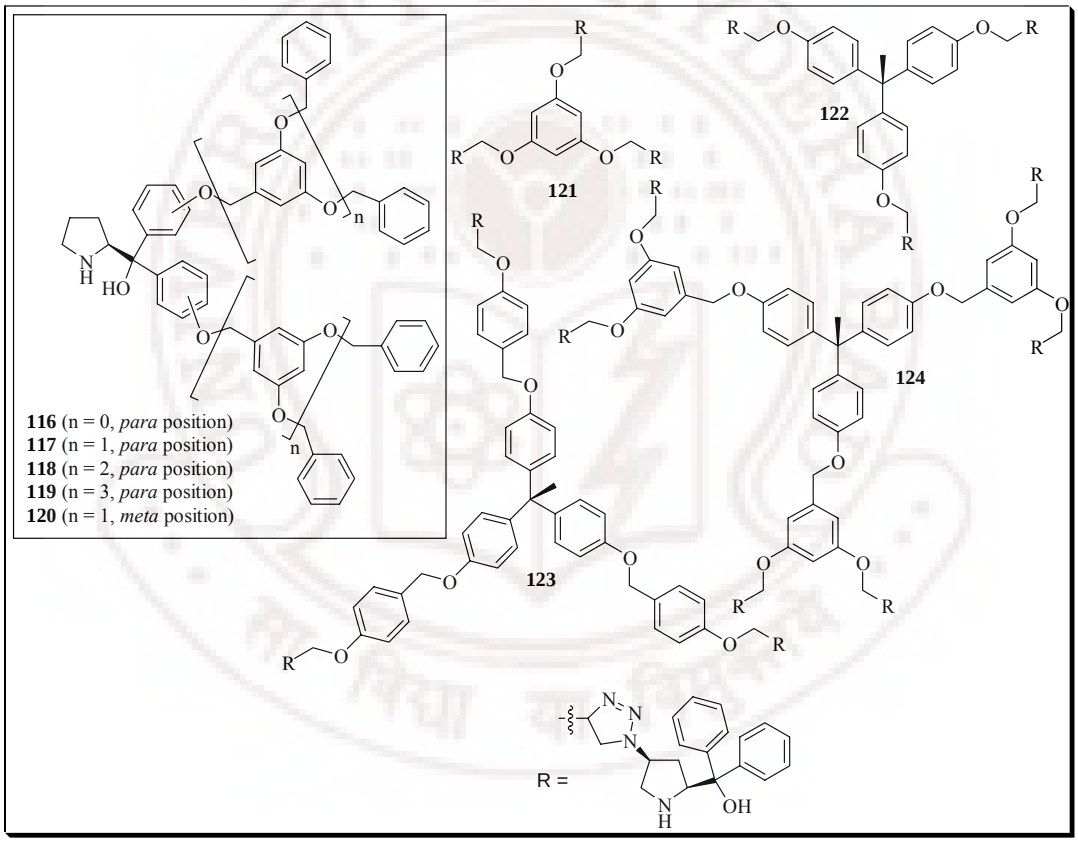
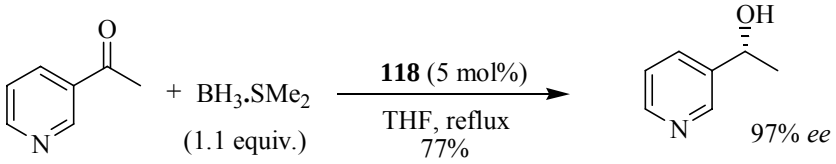
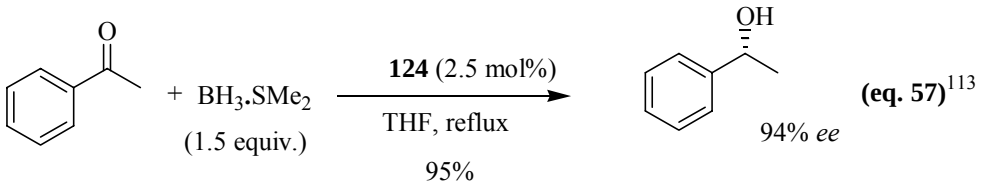


Fig. 21



(eq. 56)[112]



(eq. 57)[113]

Phosphorus Based Chiral Catalysts:

Phosphorus (III) Based Chiral Catalysts:

Since oxazaborolidines (Framework A) were found to be exceptionally good catalyst for the borane-mediated asymmetric reduction of prochiral ketones, structurally similar oxazaphospholidine Framework B, [(Fig. 22)] was also systematically examined as possible catalyst by several research groups. The first report was due to Buono[114] in the year 1992 who used the phosphorus compound **125** for reduction of acetophenone using BH_3 as a reducing agent. The best result in this study was obtained when the compound **125** was used in stoichiometric amount, thus providing the resulting alcohol in more than 99% enantioselectivity in the reduction of acetophenone (eq. 58).

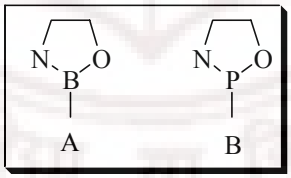
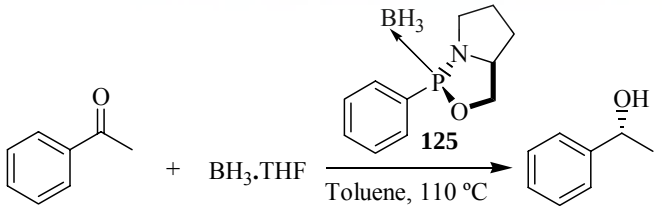


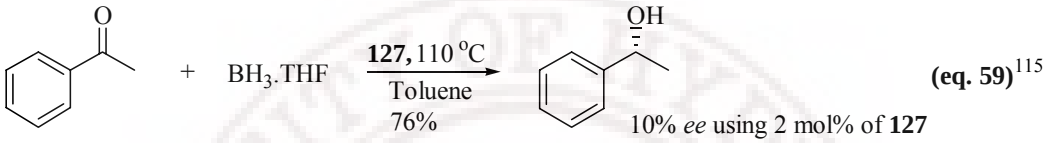
Fig. 22



(eq. 58)[114]

33% *ee* using 2 mol%
55% *ee* using 8 mol%
>99% *ee* using 100 mol%.

Subsequently, Buono[115] prepared a number of oxazaphospholidine catalysts **126a-131** (Fig. 23) and examined systematically as a reducing agents. Among these catalysts, compound **127** provided 99% enantioselectivity when used in 100 mol% in the reduction of acetophenone. However, enantioselectivity was very low when this compound was used in catalytic amount. One representative example is given in equation 59.



(eq. 59)[115]

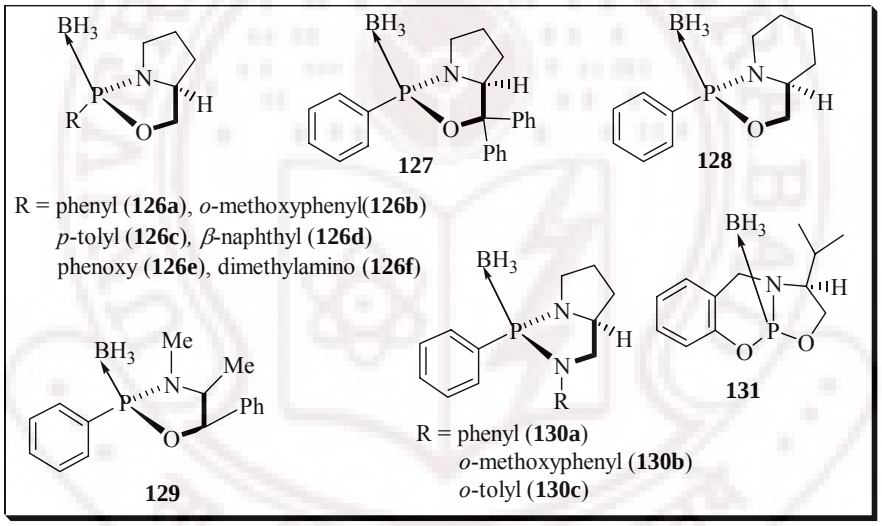
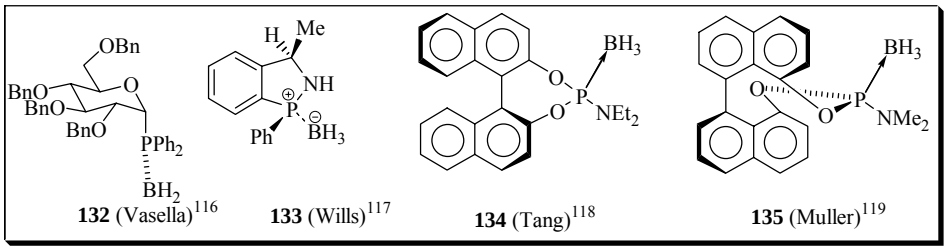


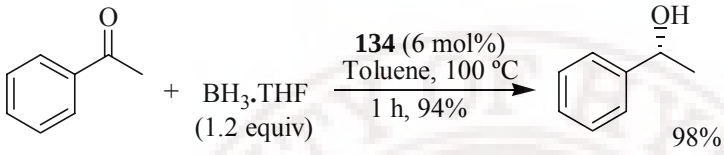
Fig. 23

Based on Buono's successful observations, other research group[116-119] prepared a number of phosphorous based compounds **132-135** (Fig. 24) and examined their application as reagents / catalysts in reduction of prochiral ketones. The catalytic precursor **134**, offered the best result, thus providing the resulting secondary alcohol in the reduction of acetophenone upto 98% enantioselectivity (eq. 60).



132 (Vasella)[116] **133** (Wills)[117] **134** (Tang)[118] **135** (Muller)[119]

Fig. 24



(eq. 60)[118]

Phosphorus (V) Based Chiral Catalysts:

Based on these results, Wills in 1993[120] described, for the first time, a new class of catalysts **136-138** containing a N-P=O structural framework (Fig. 25) for borane-mediated asymmetric reduction of prochiral ketones. Among these, catalyst precursor **137** was found to be the best and provided upto 35% enentioselectivity in the reduction of acetophenone (eq. 61).

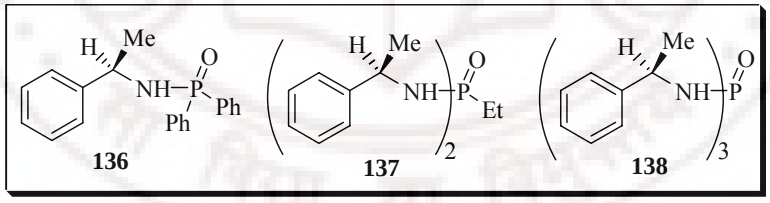
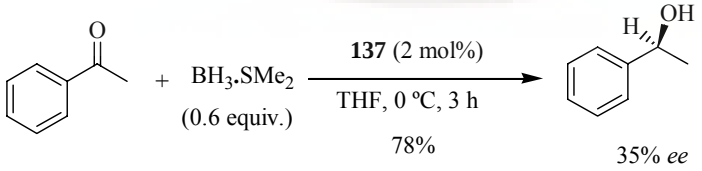


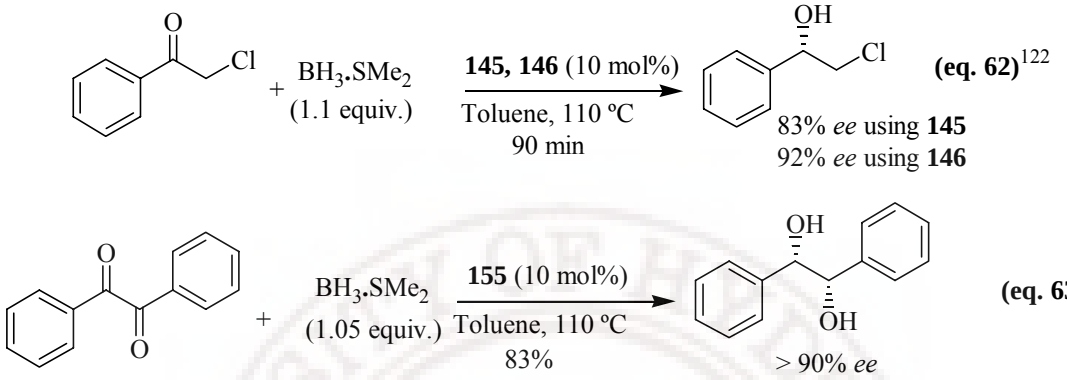
Fig. 25



(eq. 61)[120]

Subsequently the same research group[121-125] prepared a large number of catalysts **139-155** containing N-P=O framework (Fig. 26) and studied their potential as a catalysts for

borane-mediated reduction of prochiral ketones. Representative examples are given in equations 62 & 63.



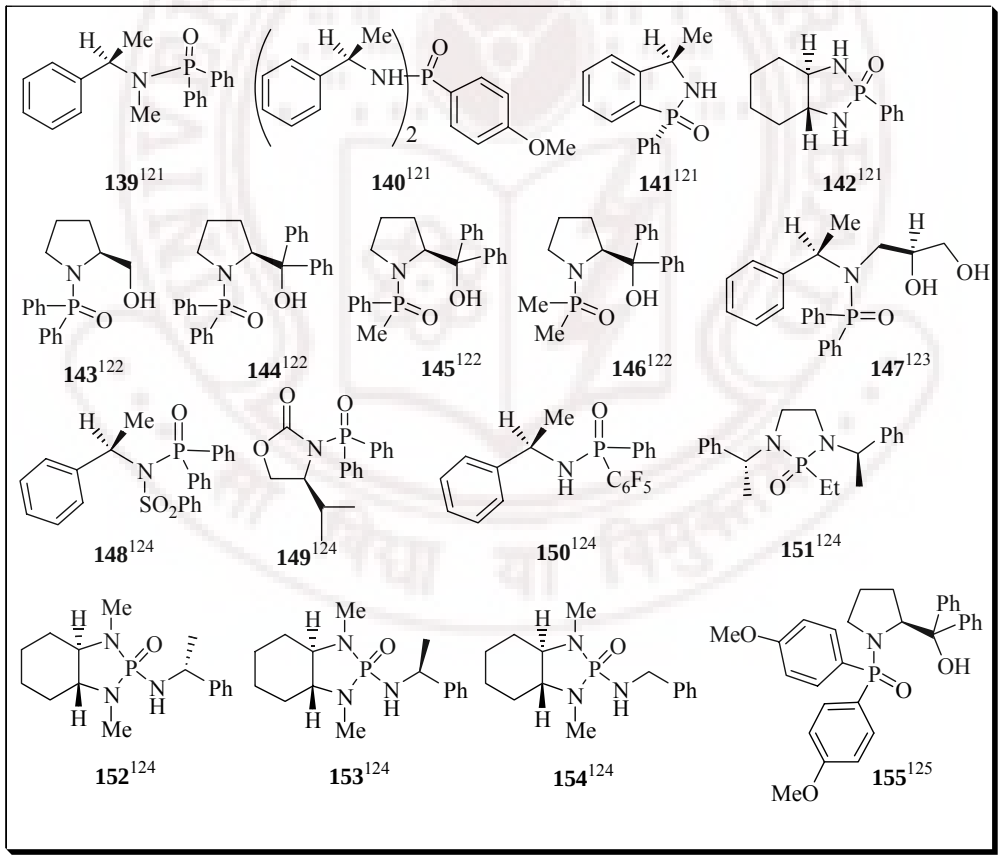


Fig. 26

With a view to understand the role of phosphorous chirality in this reduction processes, Wills and co-workers[125] prepared a diasteromer pair of catalysts **156** and **157** (Fig. 27), having different stereochemistry at the phosphorous centre and used them as catalysts for the borane mediated reduction of acetophenone (eq. 64). They observed that both these catalysts provided the resulting alcohol in same stereochemistry. However the catalyst **156** provided slightly higher enantioselectivity than catalyst **157**. This study to some extent demonstrates that phosphorous chirality has not much significant role to play in the reduction process.

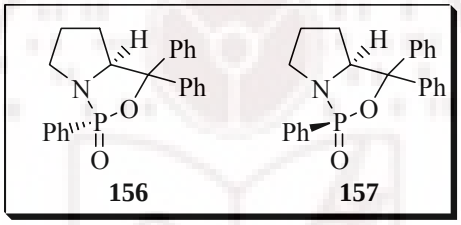
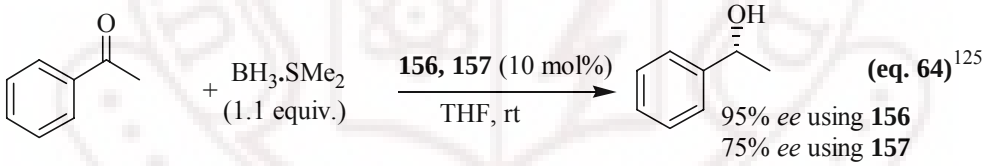
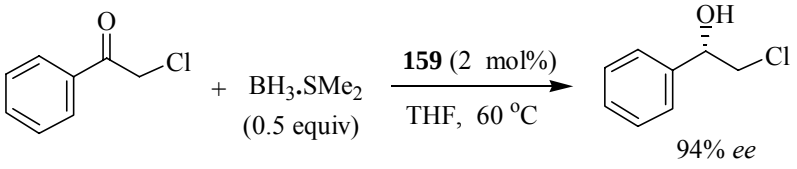


Fig. 27

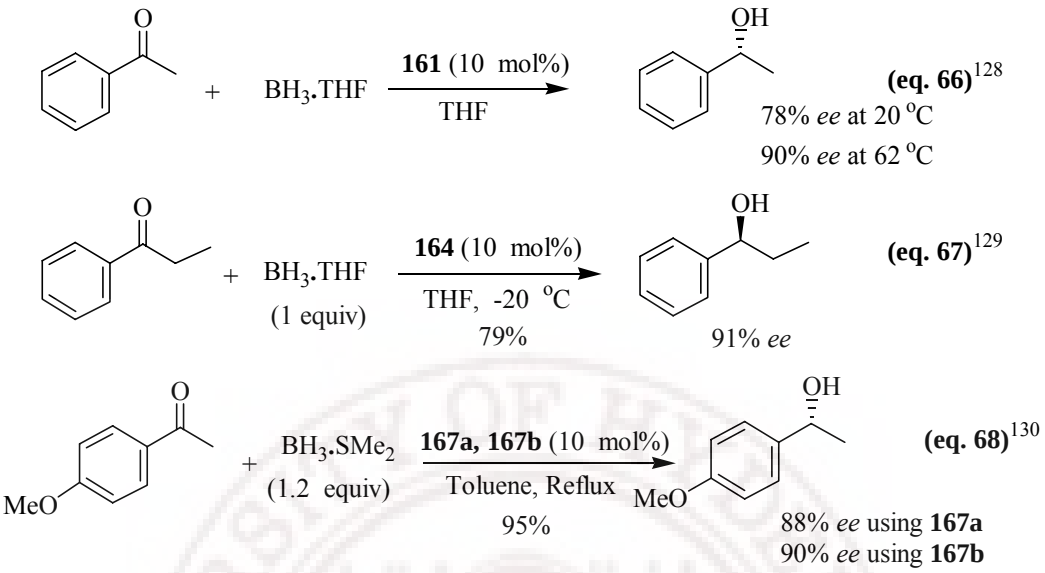


(eq. 64)[125]

Subsequently various new chiral organophosphorous catalysts **158-168** (Fig. 28)[126-131] were synthesized and used as catalysts for reduction of representative ketones. Some of their application for borane-mediated asymmetric reduction are presented in equations 65-68.



(eq. 65)[126]



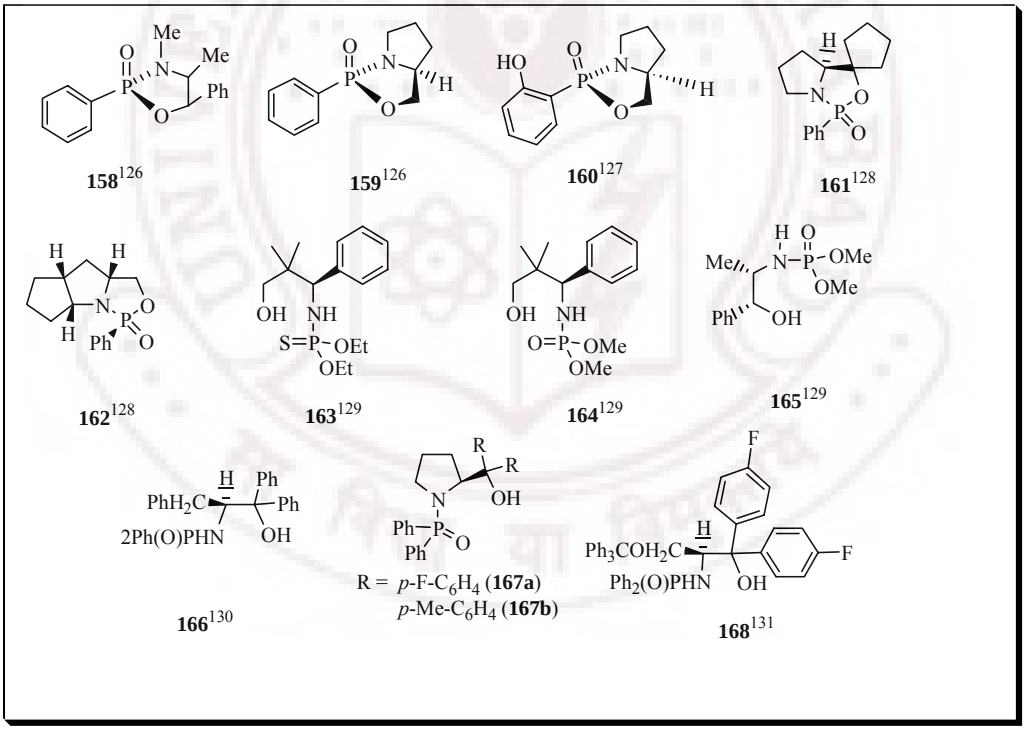
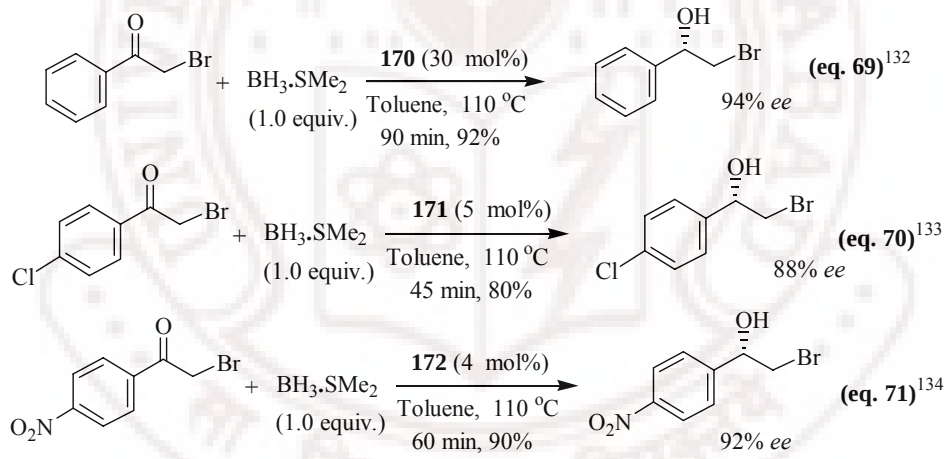


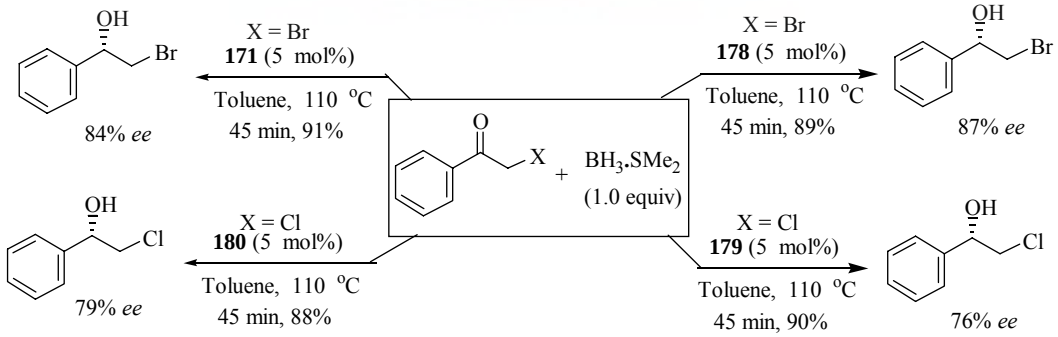
Fig. 28

Based on elegant observations of Wills and co-workers our research group[132-136] has synthesized a number of chiral catalysts **169-182** containing N-P=O structural framework

mainly built on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* framework (**I**, Fig. 29), for the borane mediated asymmetric reduction of prochiral ketones (eq. 69-71). With view to understand the role of phosphorus chirality in directing the streochemical pathway of the reaction, we have synthesized three diastereomeric pairs of catalysts[136] (**171, 178-182**) having different stereochemistry at phosphorous and examined them as catalysts in chiral reductions. Based on the similar enantioselectivities provided by these diastereomeric pair catalysts it can be to some extent concluded that phosphorus chirality has a very little role in directing the stereochemical course of the reduction process. Representative examples are given in scheme 12.



Scheme 12



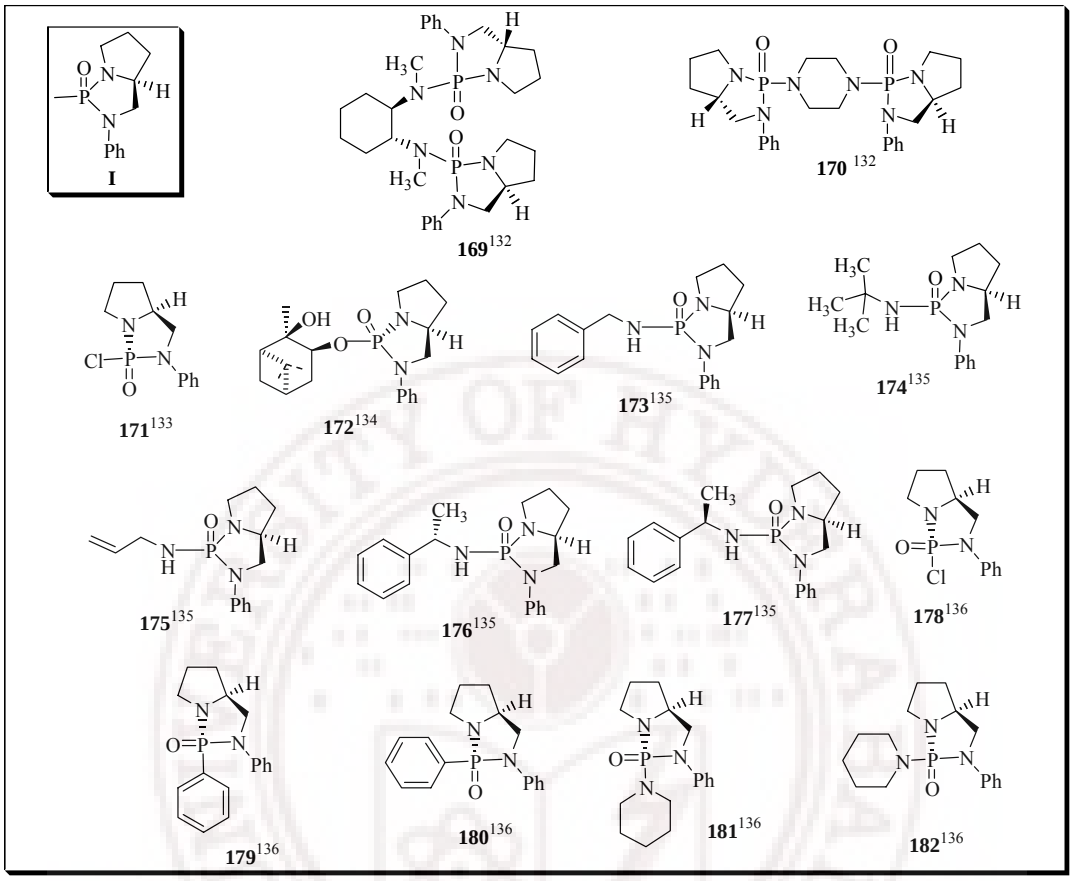
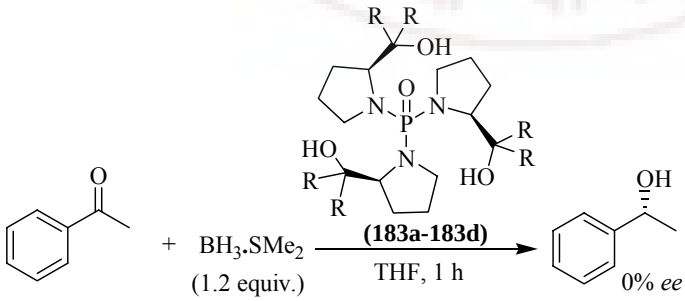


Fig. 29

Du and coworkers[137] have recently reported a recoverable C_3-symmetric triphosphoramide catalysts **183a-183d** for enantioselective borane-mediated reduction of prochiral ketones (eq. 72).

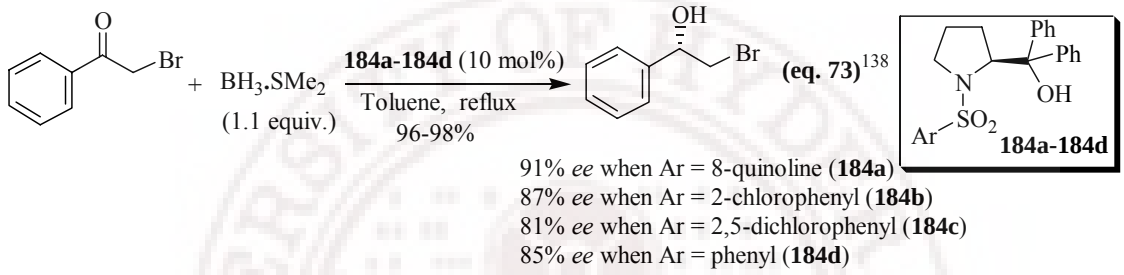


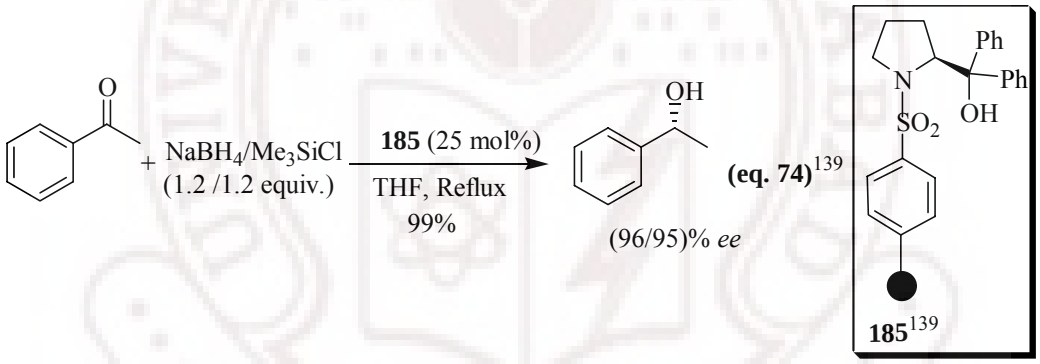
(eq. 72)[137]

0% *ee* when R = H (**183a**, 10 mol%, rt)
23% *ee* when R = Me (**183b**, 10 mol%, rt)
76% *ee* when R = Et (**183c**, 10 mol%, rt)
95% *ee* when R = Ph (**183d**, 5 mol%, 70 ºC)

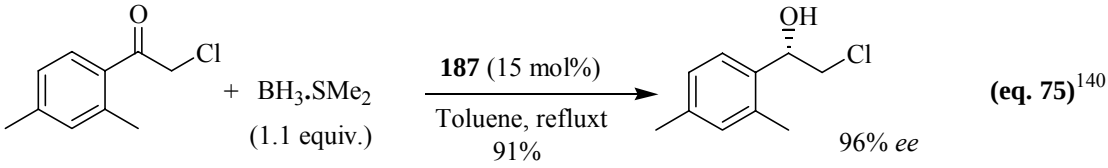
Sulphonamide Based Chiral Catalysts:

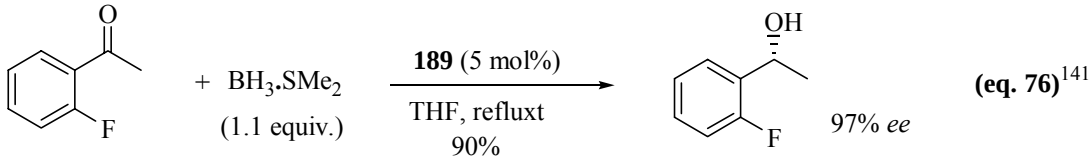
Zhao and co-workers[138, 139] have used sulphonamide derivatives **(184a-184d, 185)** of (*S*)-α,α-diphenylmethylprolinol (**51**) as catalysts for borane-mediated enantioselective reduction of ketones and the resulting secondary alcohols were obtained in high enantioselectivities. Representative examples are given in equations 73 and 74.





Subsequently Liang *et al.*[140,141] have used various sulphonamide catalysts **186-189** (Fig. 30) built on framework **51** for reduction of prochiral ketones. Representative examples are given in equation 75 and 76.





(eq. 76)[141]

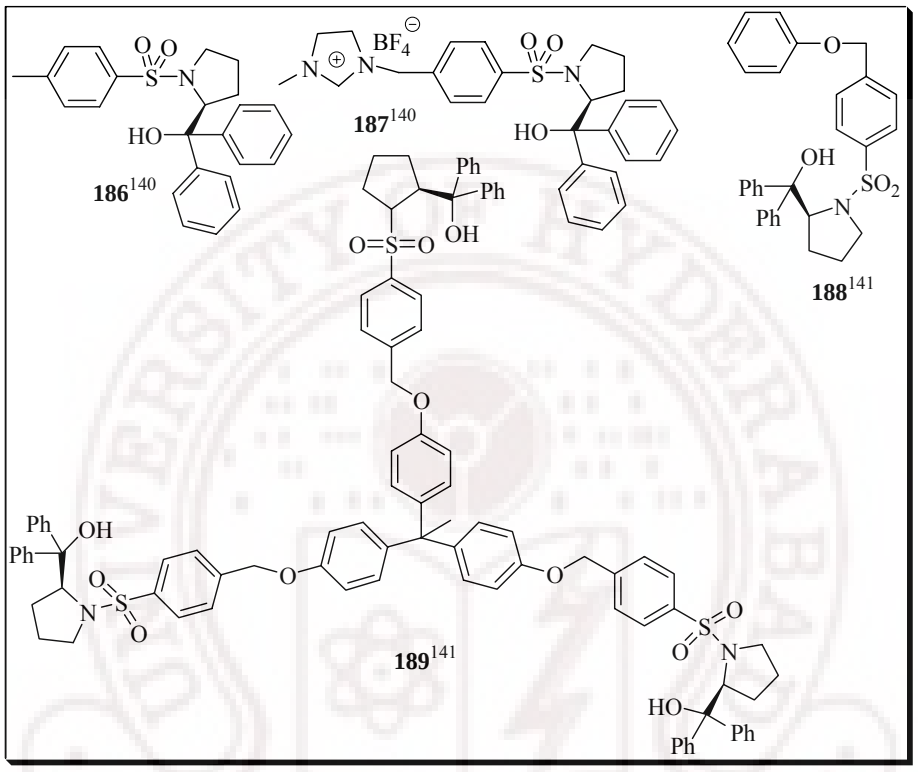
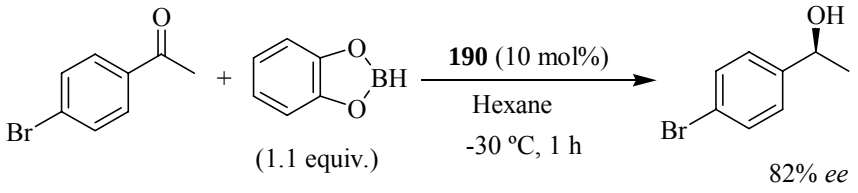


Fig. 30

Chiral titanium Catalysts:

Wandrey and co-workers[142] have reported that chiral diol based titanium catalysts **190-195** for the borane-mediated enantioselective reduction of ketones (Fig. 31). One representative example is shown in equation 77.



(eq. 77)[142]

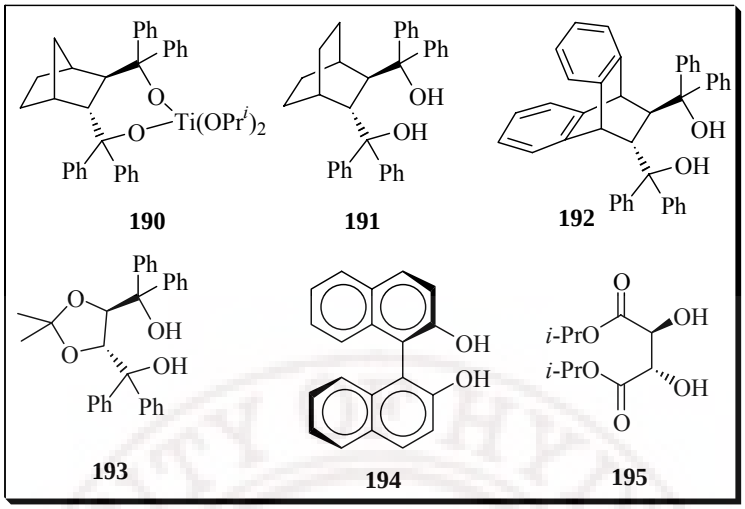
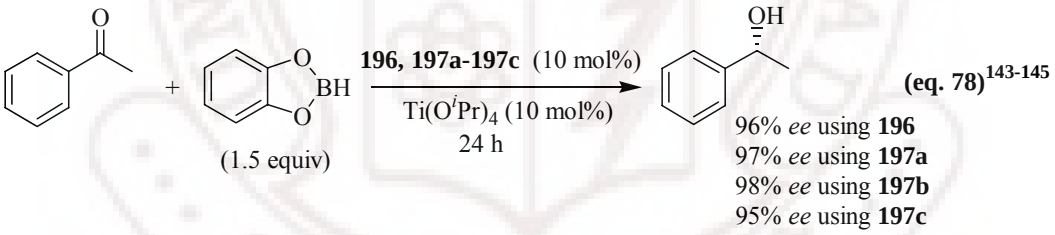


Fig. 31

Later on, Frejd *et al.*[143-145] have used diols **196-203** built on the bicycle[2.2.2]octane framework as ligands **196-203** (Fig. 32) for titanium based catalytic reduction of representative ketones with catecholborane as the reducing agent (eq. 78).



(eq. 78)[143-145]

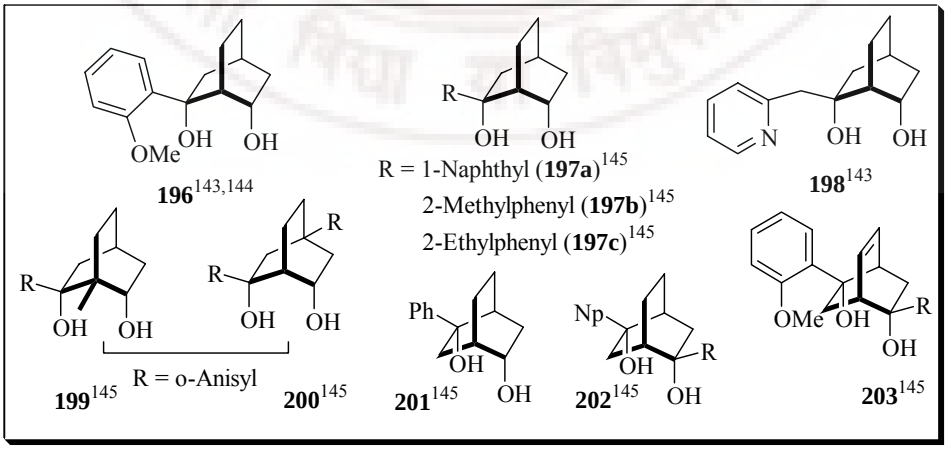


Fig. 32

Chiral N-(C=N)-N and N-(C=N)-O based catalysts:

Our research group[146,147] have for the first time reported new chiral catalysts **204** [containing N-(C=N)-N framework] and **205** [containing N-(C=N)-O] (Fig. 33) for the borane-mediated asymmetric reduction of ketones. One representative example is given in equation 79.

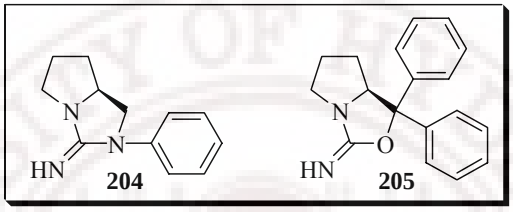
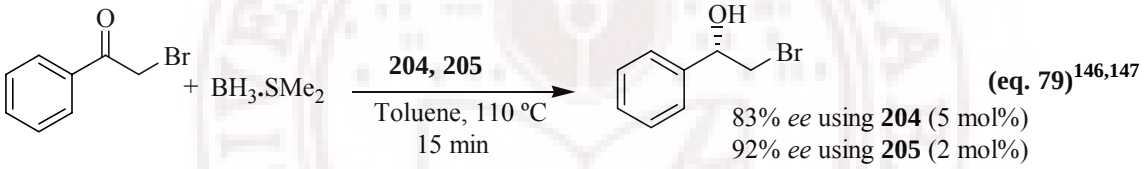


Fig. 33



(eq. 79)[146,147]

Chiral diamines as a catalyst: Asami and co-workers[148,149] for the first time reported in the year 2000, catalytic asymmetric borane reduction of prochiral ketones in the presence of chiral *β*-diamines **(10, 206a-e, 207)**. They obtained modest to high enantiomeric purity in case of diamines **(206, 207)** derived from (*S*)-2-indolinecarboxylic acid [(Fig. 34), eq. 80]. The compound **206d** provided the highest enantioselectivity of 92% *ee* when used as a catalyst at -15°C in the reduction of acetophenone.

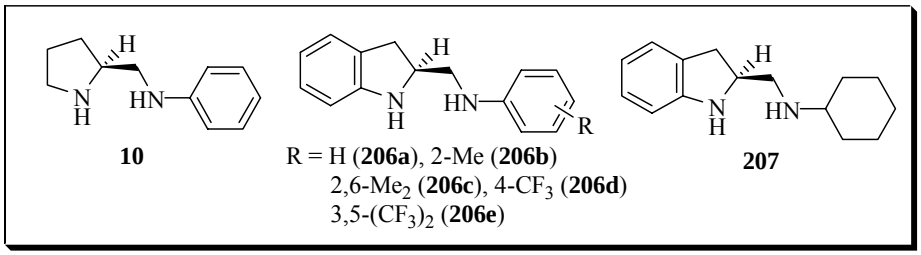
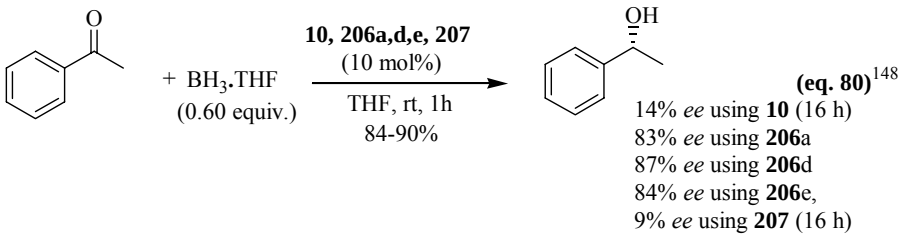


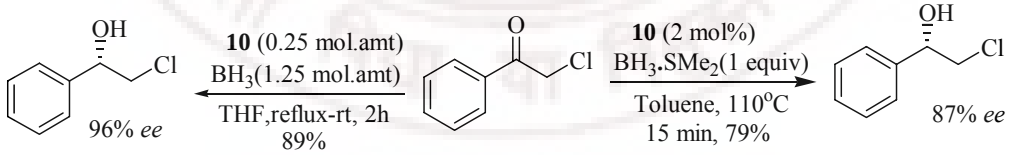
Fig. 34



(eq. 80)[148]

Our research group[150] studied systematically the application of chiral diamine (**10**) as catalyst at high temperature in the borane-mediated asymmetric reduction of prochiral ketones and found 'refluxing in toluene' is the best condition. One such example is given in Scheme 13. These results demonstrated the effect of high temperature on the enantioselectivity in the reduction of prochiral ketones. These results clearly demonstrate that high temperature is necessary for the formation of diazaborolidine catalytic species, while at room temperature formation of such catalytic species is not possible. Since the diazaborolidine is formed only at high temperature (110 ^{o}C), the reduction at this temperature furnished high enantioselectivity. Very recently Asami and co-workers[151] reported similar result.

Scheme 13



Recently Juaristi and co-workers[152] have used a number of chiral diamines **10, 208-214** (Fig. 35) mediated asymmetric reduction of prochiral ketones under microwave irradiation with simultaneous external cooling. The resulting secondary alcohols were obtained in

moderate to good enantioselectivities. However these diamines provided high selectivity when used in stoichiometric amounts (eq. 81).

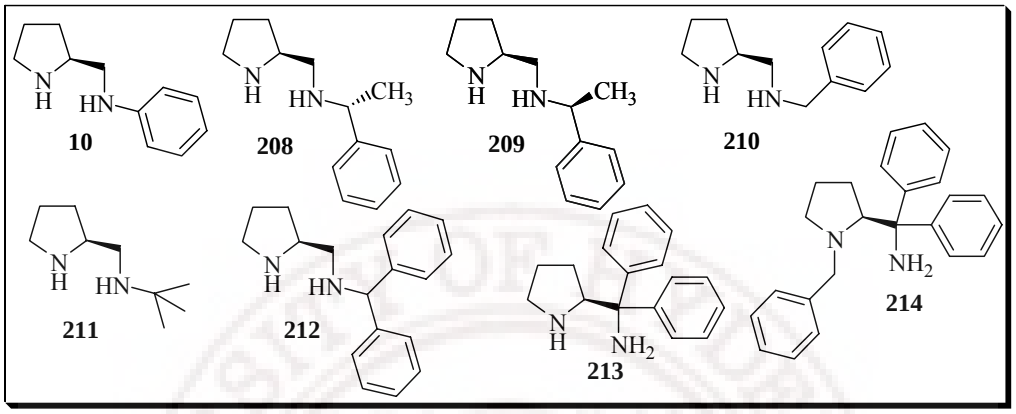
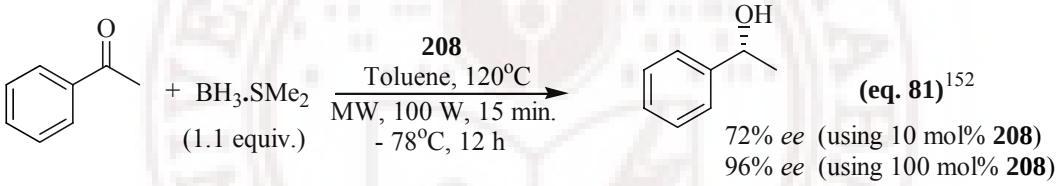


Fig. 35

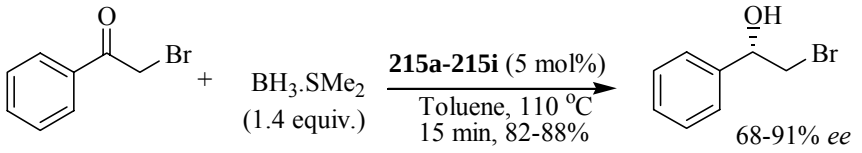


(eq. 81)[152]

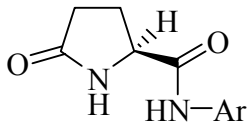
72% *ee* (using 10 mol% **208**)
96% *ee* (using 100 mol% **208**)

Chiral diamides as a catalysts:

Our research group[153] has also successfully utilized chiral diamides **(205a-i)** as a effective chiral catalytic precursors in the borane-mediated asymmetric reduction of prochiral ketones (Fig. 36, eq. 82) to provide the resulting secondary alcohols in high enantiomeric purities. The reductions are believed to proceed through first formation of diamines and then diazaborolidines which act as catalysts.



(eq. 82)[153]



215a-215i

Ar = Phenyl (**215a**), 4-Bromophenyl (**215b**),
4-Chlorophenyl (**215c**), 4-Fluorophenyl (**215d**),
4-Nitrophenyl (**215e**), 2,4-Difluorophenyl (**215f**),
3,5-Difluorophenyl (**215g**),
3,5-Bis(trifluoromethyl)phenyl (**215h**), 1-Naphthyl (**215i**)

Fig. 36

OBJECTIVES, RESULTS AND DISCUSSION

From the preceding section it is quite clear that boron-based catalysts play an important role in providing the secondary alcohols in high enantiomeric purities *via* the borane-mediated asymmetric reduction of prochiral ketones. Therefore the development of appropriate chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones providing the desired secondary alcohols in high enantiomeric purities or in homochiral form has been and continues to be attractive and challenging endeavors in chiral chemistry.

Our research group has been working on the design and synthesis of chiral catalyst built on the *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* framework (**I**, Fig. 29) for the borane-mediated asymmetric reduction of prochiral ketones and infact, made significant contributions in this direction. In continuation of our efforts in developing new chiral catalysts, we have undertaken this thesis work with the following objects:

Objectives

1. To prepare (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine, (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine, (2*S*)-1-(diphenylphophosphoryl)-2-(4-bromoanilino)carbonylpyrrolidine, (2*S*)-1-(diphenylphosphoryl)-2-(4-fluroanilino)carbonylpyrrolidine, (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine and study their applications as chiral catalysts in

borane-mediated asymmetric reduction of representative prochiral ketones.

2. To synthesize (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline and (2*R*)-2-anilinomethylpiperidine and examine their catalytic potentials for borane-mediated asymmetric reduction of prochiral ketones with a view to understand the influence of ring size/bicyclic diamine framework in directing the stereochemical course of the reduction process.
3. To prepare a representative class of amides based on the [(2*S*)-2-(arylamino)carbonylpyrrolidines] framework and study their potentials in the borane-mediated asymmetric reduction of ketones in order to understand the influence of different aromatic groups on carboxamide moiety, on the stereochemical direction of the reduction process.
4. To examine the potential of (*R*,*R*)-1,2-diaminocyclohexane as possible catalyst in the borane-mediated asymmetric reduction of prochiral ketones.

RESULTS AND DISCUSSION

(2*S*)-1-(Diphenylphosphoryl)-2-anilinocarbonylpyrrolidine as a catalyst for borane-mediated asymmetric reduction of prochiral ketones

Over the past few years, we have been actively involved in the synthesis and application of various chiral catalysts based on the N-P=O structural framework[132-136] built mainly on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* framework (**I,** Fig. 37). In continuation of our efforts in designing new catalysts based on N-P=O structural framework for the borane-mediated reduction of prochiral ketones, we planned to synthesize (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) and study its potential as a catalyst (Fig. 37) with a view to compare the potential of the acyclic phosphorous moiety (**216**) with that of cyclic phosphorous moiety (**I**) having N-P=O structural framework in directing the stereochemical course of the reduction process.

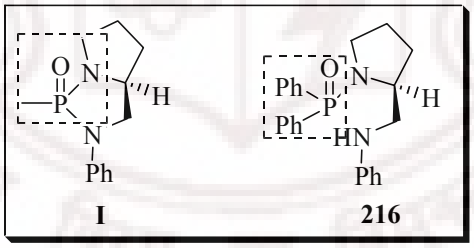
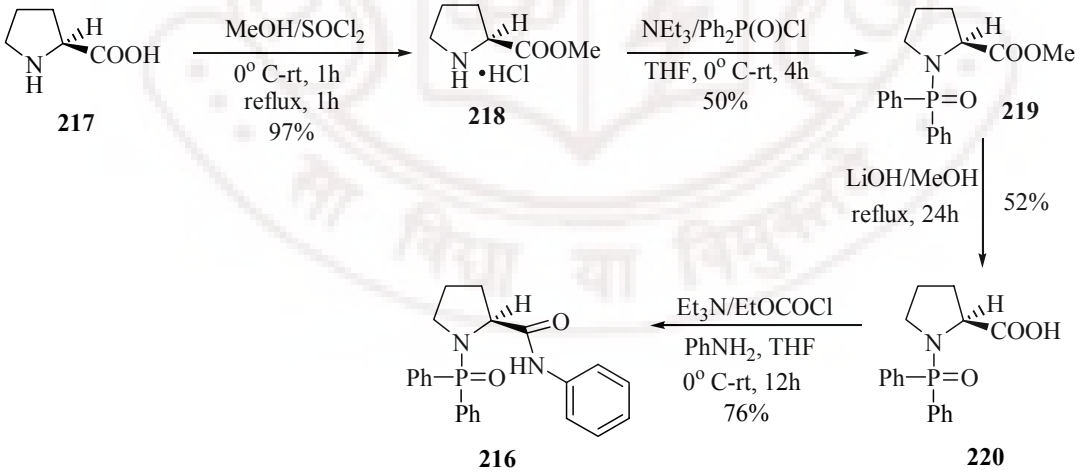


Fig. 37

Accordingly we have prepared (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) starting from commercially available (*S*)-proline (**217**) following the reaction sequence as shown in Scheme 14. (*S*)-Proline (**217**) was converted to its methyl ester hydrochloride (**218**) following the literature procedure.[154] Treatment of this ester with diphenylphosphinyl chloride provided (2*S*)-1-(diphenylphosphoryl)-2-

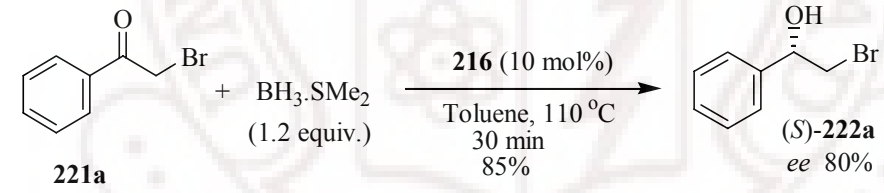
methoxycarbonylpyrrolidine (**219**)[155] in 50% yield. The structure of this compound was confirmed by IR, ^{1}H, ^{13}C, & ^{31}P NMR spectral data. This ester was hydrolysed with LiOH[155] to provide the corresponding acid, (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid (**220**) in 52% yield. This compound (**220**) was treated successively with ethyl chloroformate and aniline to provide the desired compound (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) in 76% yield as a colorless crystalline solid. The structure of this compound was established by IR, ^{1}H, ^{13}C, & ^{31}P (Spectrum 1, 2 and 3 respectively) NMR spectral data, LC MS and elemental analysis. The structure of this compound was further confirmed by single crystal X-ray data analysis [The structure refinement of this molecule is presented in Table **I** and the ORTEP diagram is shown in Fig. 38].

Scheme 14

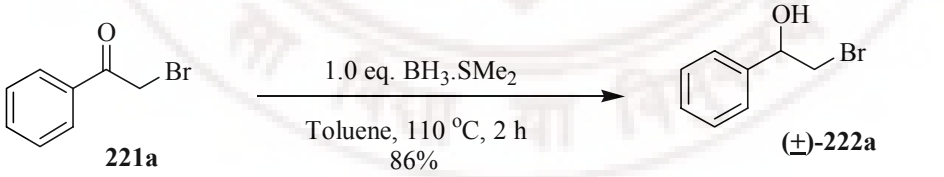


We have then examined the catalytic potential of this molecule **216** for the borane-mediated asymmetric reduction of prochiral ketones. We have first selected phenacyl

bromide (**221a**) as a substrate. On the basis of our earlier work in this direction we have carried out the reduction of phenacyl bromide (**221a**) with borane-dimethyl sulphide (1.2 equiv.) in the presence of 10 mol% **216** in toluene at reflux temperature to provide the resulting (*S*)-2-bromo-1-phenylethanol as a colorless liquid [**(*S*)-222a**] in 80% *ee* (eq. 83). Structure of this alcohol was confirmed by spectral data (IR, ^{1}H, & ^{13}C NMR). Enantiomeric purity of **(*S*)-222a** was determined by HPLC analysis using chiral column, Chiralcel-OD H with reference to the racemic 2-bromo-1-phenylethanol [**(±)-222a**] and absolute stereochemistry was assigned in comparision with the sign of optical rotation with that of known compound.[156] Racemic 2-bromo-1-phenylethanol [**(±)-222a**] was obtained by the treatment of phenacyl bromide with $BH_3.SMe_2$ in refluxing toluene as shown in eq. 84.



221a (*S*)-**222a** *ee* 80% **(eq. 83)**



221a **(±)-222a** **(eq. 84)**

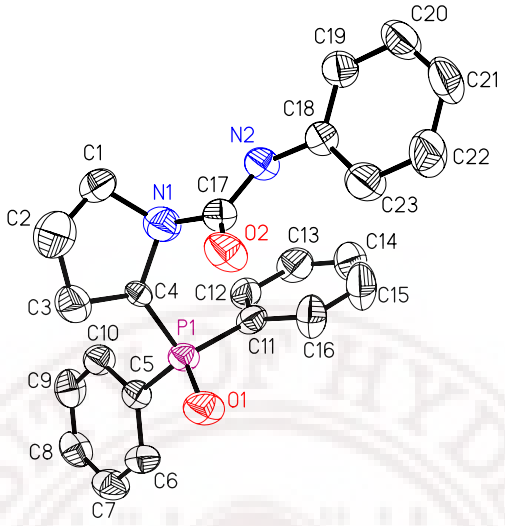


Figure 38: ORTEP diagram of 216

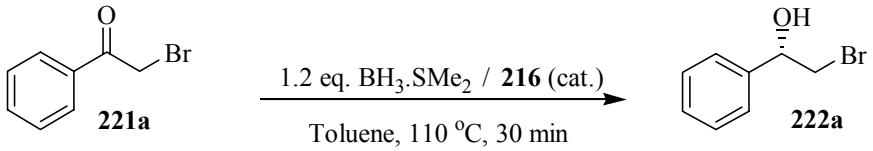
(*Hydrogen atoms were omitted for clarity*)

With a view to understand the optimum requirement of catalyst for obtaining maximum enantioselectivity, we have examined systematically the reduction of phenacyl bromide (**221a**) with different catalytic quantities of **216**, under the influence of $BH_3.SMe_2$. The best results were obtained when phenacyl bromide (**221a**) was treated with $BH_3.SMe_2$ (1.2 equiv.) under the influence of (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) (15 mol%) in refluxing toluene for 30 min to provide the corresponding alcohol in 89% *ee*.(Chromatogram **1A**). The results are summarized in Table 1.

Table I: Crystal data and structure refinement for the compound 216

Identification	: **216**
Empirical formula	: C_{23} H_{23} N_2 O_2 P
Formula weight	: 390.40
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: *P* 2_1 2_1 2_1
Unit cell dimensions	: *a* = 6.6195(12) Å α = 90.00
	: *b* = 17.123(3) Å β = 90.00
	: *c* = 17.767(3) Å γ = 90.00
Volume	: 2013.7(6) $Å^3$
Z	: 4
Density (calculated)	: 1.288 g/cm^3
Absorption coefficient	: 0.158 mm^{-1}
F (000)	: 824
Crystal size	: 0.38 X 0.24 X 0.24 mm^3
Theta range for data collection	: 1.65 to 24.99 deg.
Index ranges	: $-7 \leq h \leq 7$, $-20 \leq k \leq 20$, $-21 \leq l \leq 21$
Reflections collected	: 19408
Independent reflections	: 3553
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3553 / 0 / 257
Goodness-of-fit on F^2	: 1.108
Final R indices [I> 2 sigma (I)]	: R1 = 0.0529; wR^2 = 0.1447
R indices (all data)	: R1 = 0.0548; wR^2 = 0.1464
Absolute structure parameters	: 0.08(15)
Largest diff. Peak and hole	: 0.425 and -0.343 e. A^{-3}

Table 1: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **216:** Standardization of reaction conditions[a]



Entry	Catalyst (mol%)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	5	85	76	*S*
2	10	85	80	*S*
3	**15**	**84**	**89**	***S***
4	20	84	76	*S*

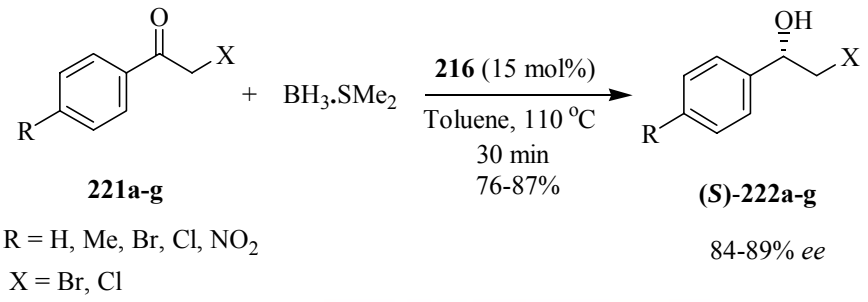
[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**221a**) with 1.2 equivalent of $BH_3.SMe_2$ in the presence **216** in toluene for 30 min at 110 °C.

[b]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c]Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[d]Absolute configuration was assigned by comparison of the sign of the optical rotation with that of reported molecule.[156]

This is indeed an encouraging result. In order to understand the generality of this methodology, we have performed the reduction of representative prochiral α-haloketones **221b-g** with 15 mol% catalyst **216** in refluxing toluene. The resulting secondary alcohols [**(*S*)-222b-g**] were obtained in 84-89% enantioselectivities (eq. 85, Table 2). The structures of these compounds [**(*S*)-222b-g**] were confirmed by IR, ^1H and ^{13}C NMR spectral data.



221a-g

R = H, Me, Br, Cl, NO_2

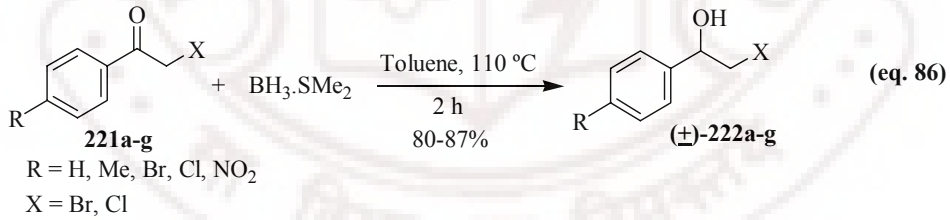
X = Br, Cl

(*S*)-222a-g

84-89% *ee*

(eq. 85)

The required racemic alcohols **(±)-222b-g** were prepared *via* the treatment of corresponding α-halo ketones **221b-g** with $BH_3.SMe_2$ (eq. 86). The required α-bromo ketones **(221c,e,f)** were in turn prepared by bromination with the corresponding aryl methyl ketones according to the literature procedure.[157] Thus 4-methylphenacyl bromide (**221c**), 4-bromophenacyl bromide (**221e**) and 4-chlorophenacyl bromide (**221f**) were prepared by treatment of the corresponding aryl methyl ketones with TBA Br_3 as shown in eq. 87.



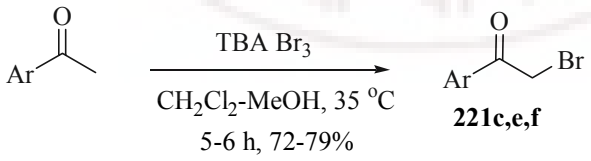
221a-g

R = H, Me, Br, Cl, NO_2

X = Br, Cl

(±)-222a-g

(eq. 86)



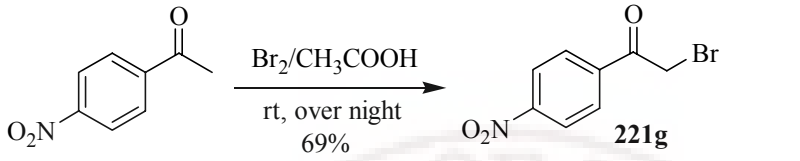
221c,e,f

(eq. 87)

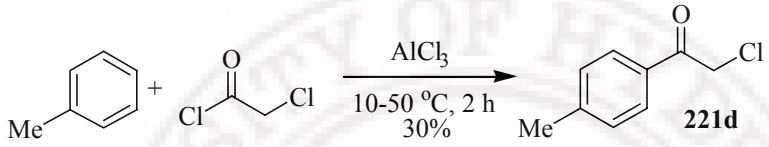
Ar = 4-Methylphenyl, 4-Bromophenyl, 4-Chlorophenyl

4-Nitrophenacyl bromide (**221g**) was prepared by α-bromination of 4-nitroacetophenone[α] using bromine and acetic acid according to the literature procedure (eq. 88).[158] 4-

Methylphenacyl chloride (**221d**)[β] was prepared *via* the Friedel-Crafts reaction of toluene with chloroacetyl chloride in the presence of $AlCl_3$ (eq. 89). The structures of these α-halo ketones were established by spectral data (IR, ^1H and ^{13}C NMR) analysis.



(eq. 88)



(eq. 89)

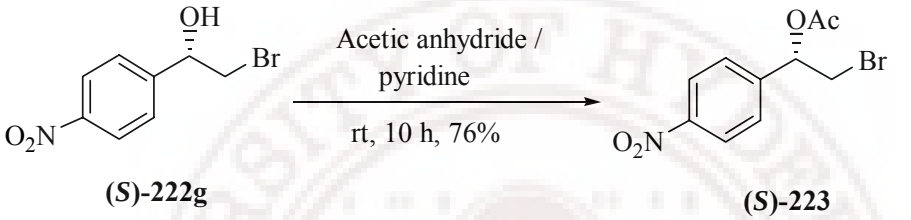
Determination of Enantiomeric Purities of Alcohols:

Enantiomeric purities of the chiral alcohols [**(*S*)-222b-d**] were determined by HPLC analyses using the chiral column, Chiralcel-OD H with reference to the corresponding racemic alcohols [**(±)-222b-d**], (Chromatogram **1B** for compound **222b**) while the enantiomeric purities of the alcohols [**(*S*)-222e, f**] have been determined by similar HPLC analyses using the chiral column, Chiralcel-OJ H with reference to the corresponding racemic alcohols [**(±)-222e, f**]. Our attempts to determine the enantiomeric purity of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [**(*S*)-222g**] using the above mentioned chiral columns were not successful as the enantiomers could not be separated using these columns. However, we were able to determine the enantiomeric purity of this alcohol **222g** (*ee* 84%) by converting into the corresponding acetate, (*S*)-1-acetoxy-2-bromo-1-(4-nitrophe-

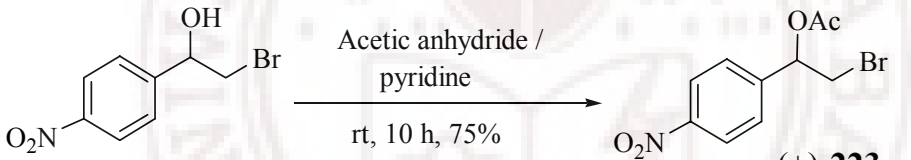
---

[α] *Starting materials were not given numbering for continuity and easy understanding.*
[β] *4-Methyl phenacyl chloride is given number* **221d** *for continuity and easy understanding.*

nyl)ethane [(*S*)-**223**], on HPLC analysis using chiral column, Chiralcel-OD H with reference to (±)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(±)-223**]. The chiral acetate, (*S*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(*S*)-223**] and racemic acetate [**(±)-223**] were prepared *via* the reaction of the corresponding chiral [**(*S*)-222g**] alcohol and racemic alcohol [**(±)-222g**] respectively with acetic anhydride as presented in eq. 90 & 91.[γ]



(*S*)-222g **(*S*)-223** **(eq. 90)**

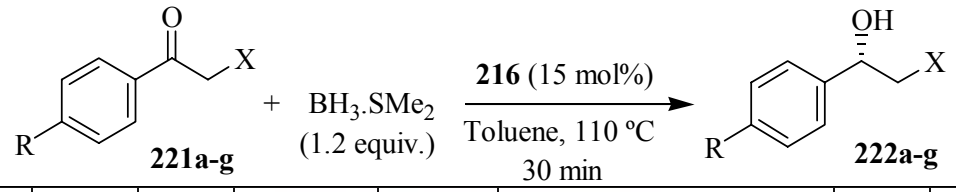


(±)-222g **(±)-223** **(eq. 91)**

Encouraged by these results, we have directed our attention towards the reduction of simple aryl alkyl ketones using this catalyst (**216**). We have first selected acetophenone (**224a**) as a substrate for our study. Reduction of acetophenone (**224a**) was carried out with borane-dimethyl sulfide in the presence of 15 mol% catalyst **216** following the same procedure, as in the case of *α*-haloalkyl ketones, to provide the resulting (*R*)-1-phenylethanol [**(*R*)-225a**] in 74% *ee* (eq. 92).

[γ]*For continuity and easy understanding acetates derived from* ***(±)-222g*** *&* ***(S)-222g*** *are numbered as* ***(±)-223*** *&* ***(S)-223*** *respectively.*

Table 2: Enantioselective reduction of α-halo ketones with $BH_3.SMe_2$ using 15 mol% **216**[a]



221a-g **222a-g**

Substrate	R	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*Ee* (%)[d]
221a	H	Br	**222a**	84	+39.51 (*c* 0.83, $CHCl_3$)	*S*[156]	89
221b	H	Cl	**222b**	83	+33.24 (*c* 0.74, C_6H_{12})	*S*[156]	88
221c	CH_3	Br	**222c**	87	+31.97 (*c* 0.91, $CHCl_3$)	*S*[132]	87
221d	CH_3	Cl	**222d**	85	+40.06 (*c* 1.61, $CHCl_3$)	*S*[132]	85
221e	Br	Br	**222e**	82	+28.82 (*c* 1.02, $CHCl_3$)	*S*[159]	88[e]
221f	Cl	Br	**222f**	86	+33.54 (*c* 0.96, $CHCl_3$)	*S*[132]	86[e]
221g	NO_2	Br	**222g**	80	+23.37 (*c* 0.89, $CHCl_3$)	*S*[133]	84[f]

[a] All reactions were carried out on 1 mM scale of α-halo ketones **221a-g** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 30 min at 110 °C using 15 mol% **216** .

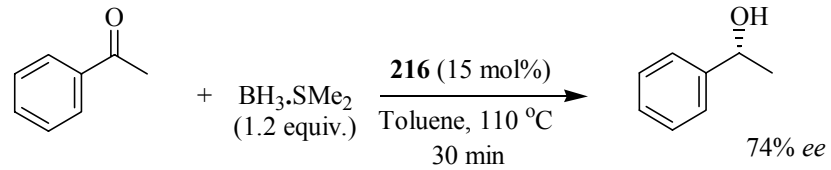
[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

[d] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

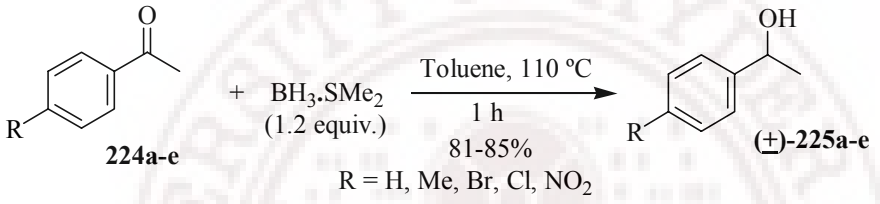
[e] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OJ H.

[f] Enantiomeric purity was determined by HPLC analysis of its acetate using chiral column, Chiralcel-OD H.



224a 80% **225a** **(eq. 92)**

With a view to understand the generality of this methodology various aryl alkyl ketones **224b-e**, having different substitutions on aromatic ring, were subjected to borane-mediated asymmetric reduction under the influence of 15 mol% catalyst **216**. Enantiomeric purities of the resulting secondary alcohols **(*R*)-225b-e** were in the range of 70-75% (Table 3). The required racemic alcohols **(±)-225a-e** were prepared *via* the treatment of corresponding ketones **224a-e** with $BH_3.SMe_2$ (eq. 93).



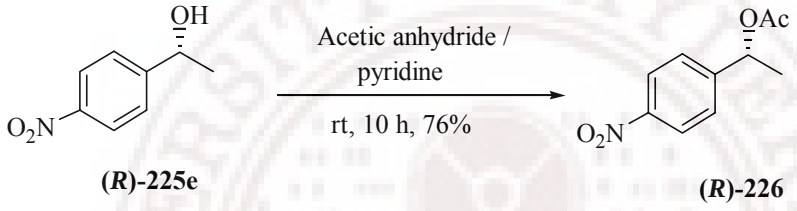
(eq. 93)

Determination of the Enantiomeric Purity:

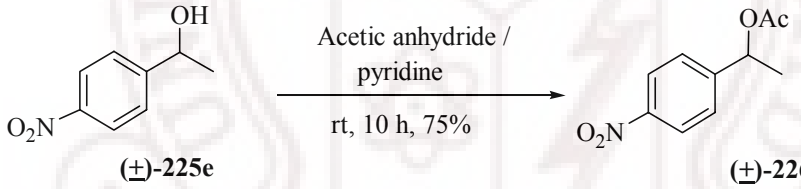
The enantiomeric purities of all the secondary alcohols were determined by HPLC analysis using appropriate chiral columns. In case of (*R*)-1-phenylethanol [**(*R*)-225a**] enantiomeric purity was determined by using the chiral column, Chiralcel-OD H with reference to (±)-1-phenylethanol [**(±)-225a**]. Enantiomeric purities of the chiral alcohols {(*R*)-1-(4-methylphenyl)ethanol [**(*R*)-225b**], (*R*)-1-(4-chlorophenyl)ethanol [**(*R*)-225c**], (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-225d**], (Chromatogram **1C**) } were determined by HPLC analyses using chiral column, Chiralcel OJ-H with reference to the corresponding racemic alcohols {(±)-1-(4-methylphenyl)ethanol [**(±)-225b**], (±)-1-(4-chlorophenyl)-ethanol [**(±)-225c**], (±)-1-(4-bromophenyl)ethanol [**(±)-225d**] respectively}.

Determination of enantiomeric purity of (*R*)-1-(4-nitrophenyl)ethanol [**(*R*)-225e**] was not successful by using above mentioned two chiral columns. However enantiomeric purity of

this compound was determined by HPLC analysis of its acetate, (*R*)-1-acetoxy (4-nitrophenyl)ethane [**(*R*)-226**] using the chiral column, Chiralcel-OD H with reference to the corresponding racemic acetate [**(±)-226**] and found to be 70% enantioselective. (*R*)-1-Acetoxy (4-nitrophenyl)ethane [**(*R*)-226**] and racemic acetate [**(±)-226**] were prepared by the reaction of the corresponding chiral [**(*R*)-225e**] alcohol and racemic alcohol [**(±)-225e]** respectively with acetic anhydride according to the eq. 94 & 95.[δ]



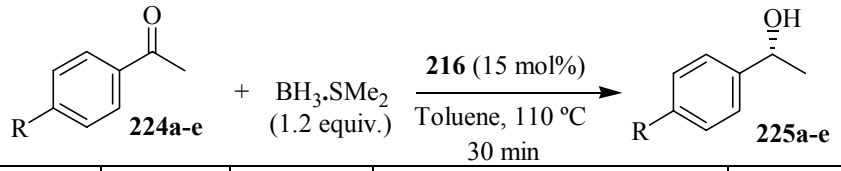
(*R*)-225e **(*R*)-226** **(eq. 94)**



(±)-225e **(±)-226** **(eq. 95)**

[δ]*For continuity and easy understanding acetates derived from* ***(±)-225e*** *&* ***(R)- 225e*** *are numbered as* ***(±)-226*** *&* ***(R)- 226*** *respectively.*

Table 3: Enantioselective reduction of aryl alkyl ketones with $BH_3.SMe_2$ using 15 mol% **216**[a]



Substrate	R	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*Ee* (%)
224a	H	**225a**	80	+32.80 (*c* 0.87, MeOH)	*R*[160]	74[d]
224b	CH_3	**225b**	84	+29.51 (*c* 0.72, MeOH)	*R*[161]	75[e]
224c	Cl	**225c**	83	+27.45 (c 0.85, Et_2O)	*R*[161]	73[e]
224d	Br	**225d**	84	+30.99 (*c* 0.95, $CHCl_3$)	*R*[161]	74[e]
224e	NO_2	**225e**	81	+24.32 (*c* 0.92, EtOH)	*R*[162]	70[f]

[a] All reactions were carried out on 1 mM scale of ketones **224a-e** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 30 min at 110 °C using 15 mol% **216**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

[d] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[e] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OJ H.

[f] Enantiomeric purity was determined by HPLC analysis of its acetate using chiral column, Chiralcel-OD H.

Next, we have turned our attention towards understanding the influence of nature of substituents on amide aromatic ring on the enantioselectivity in the borane-mediated asymmetric reduction process. Accordingly we selected four representative chiral phosphoramides **227-230** (Fig. 39) for our study having different substitution on the amide aromatic ring. These compounds **227-230** were synthesized *via* the successive treatment of

compound (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid (**220**) with ethyl chloroformate and then with appropriate aniline as presented in eq. 96. All the compounds were characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR spectra, LC MS and elemental analysis (Spectrum 4-15). The structure of the compound **228** was further confirmed by single crystal X-ray data analysis (Fig. 40, Table II).

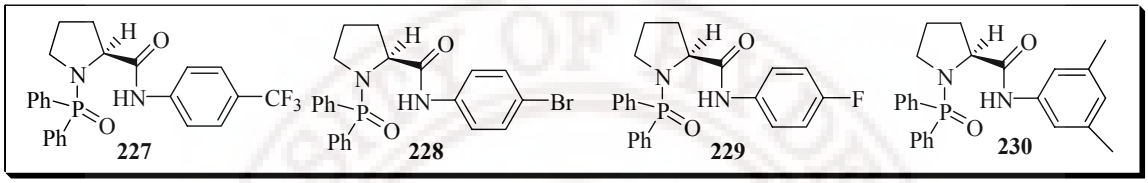
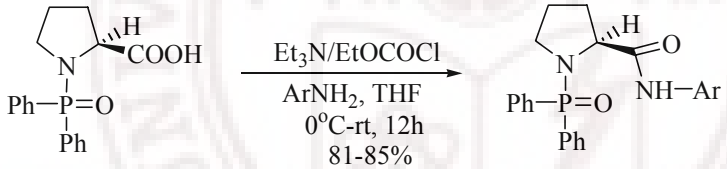


Fig. 39



220 **227-230** **(eq. 96)**

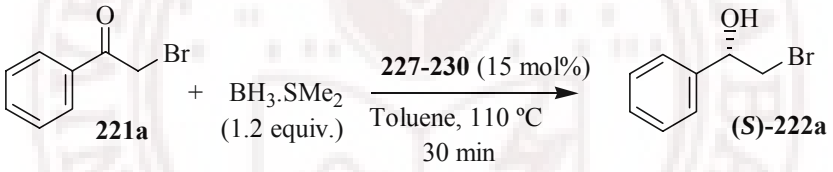
Ar = 4-Trifluoromethylphenyl (**227**); 4-Bromophenyl (**228**)
4-Fluorophenyl (**229**); 3,5-Dimethylphenyl (**230**)

Phenacyl bromide (**221a**), phenacyl chloride (**221b**) and 4-bromoacetophenone (**224d**) were selected as prochiral ketones as substrates for our study with a view to understand the potential of the chiral catalysts **227-230**. First we have examined the asymmetric reduction of phenacyl bromide with $BH_3.SMe_2$ in the presence of the catalyst **227-230** in separate experiments to provide the resulting secondary alcohols in 84%, 86%, 84%, and 85% enantiomeric purity respectively. In all the cases the reductions were carried out

under the optimized reaction conditions (using 15 mol% catalyst) as in the case of catalyst **216** and the results are presented in Table 4.

In similar way borane-mediated asymmetric reductions of phenacyl chloride (**221b**) and 4-bromoacetophenone (**224d**) were carried out using 15 mol% catalysts (**227-230**) under the influence of $BH_3.SMe_2$. The resulting alcohol **222b** was obtained in 81, 84, 86, 85% enantiomeric purity and **225d** was obtained in 74, 77, 72, 73% enatiomeric purities respectively and these results are presented in Table 5-6 (Chromatogram **2-5**)

Table 4: Enantioselective reduction of phenacyl bromide (**221a**) with $BH_3.SMe_2$ using 15 mol% **227-230**[a]



Entry	Catalyst	Yield (%)[b]	$[\alpha]_D^{25}$	*ee*[c]
1	**227**	87	+35.18 (*c* 1.20, $CHCl_3$)	84
2	**228**	84	+35.04 (*c* 1.09, $CHCl_3$)	86
3	**229**	86	+35.38 (*c* 1.30, $CHCl_3$)	84
4	**230**	85	+36.36 (*c* 1.10, $CHCl_3$)	85

[a] All reactions were carried out on 1 mM scale of phenacyl bromide **221a** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 30 min at 110 °C by using 15 mol% **227-230**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

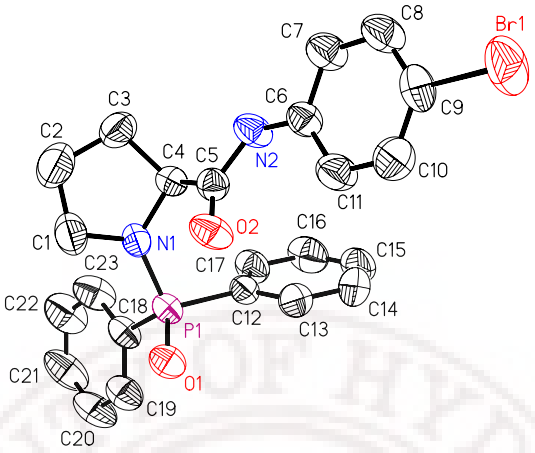
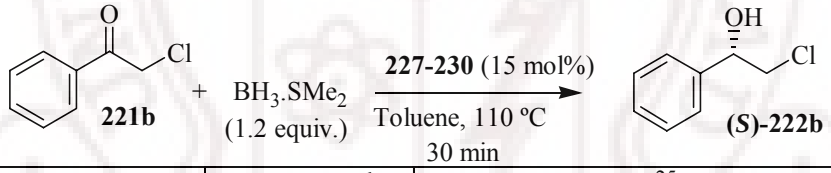


Figure 40: ORTEP diagram of 228

(Hydrogen atoms were omitted for clarity)

Table 5: Enantioselective reduction of phenacyl chloride (**221b**) with $BH_3.SMe_2$ using 15 mol% **227-230**[a]



Entry	Catalyst	Yield (%)[b]	$[\alpha]_D^{25}$	*ee*[c]
1	**227**	85	+37.94 (*c* 1.02, C_6H_{12})	81
2	**228**	86	+39.33 (*c* 0.90, C_6H_{12})	84
3	**229**	87	+38.66 (*c* 1.05, C_6H_{12})	86
4	**230**	84	+38.25 (*c* 1.20, C_6H_{12})	85

[a] All reactions were carried out on 1 mM scale of phenacyl chloride **221b** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 30 min at 110 °C by using 15 mol% **227-230**.

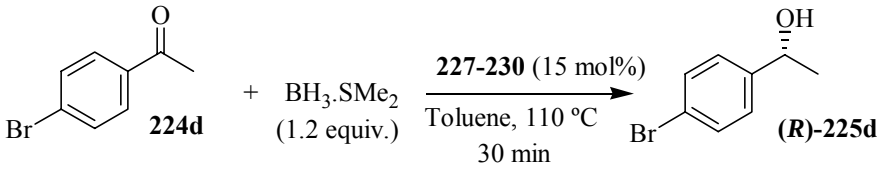
[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

Table II: Crystal data and structure refinement for the compound 228

Identification	: **228**
Empirical formula	: C_{23} H_{22} Br N_2 O_2 P
Formula weight	: 469.31
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: *P* 2_1 2_1 2_1
Unit cell dimensions	: a = 8.9091(16) Å α = 90.00
	: b = 10.4810(19) Å β = 90.00
	: c = 23.211(4) Å γ = 90.00
Volume	: 2167.4(7) $Å^3$
Z	: 4
Density (calculated)	: 1.438 g/cm^3
Absorption coefficient	: 1.992 mm^{-1}
F (000)	: 960
Crystal size	: 0.28 X 0.25 X 0.24 mm^3
Theta range for data collection	: 1.75 to 25.00 deg.
Index ranges	: $-10 \leq h \leq 10$, $-12 \leq k \leq 12$, $-27 \leq l \leq 27$
Reflections collected	: 20818
Independent reflections	: 2199
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2199 / 0 / 262
Goodness-of-fit on F^2	: 0.968
Final R indices [I> 2 sigma (I)]	: R1 = 0.0334, wR2 = 0.0829
R indices (all data)	: R1 = 0.0413, wR2 = 0.0858
Absolute structure parameters	: 0.0 (10)
Largest diff. Peak and hole	: 0.404 and -0.284 e. A^{-3}

Table 6: Enantioselective reduction of 4-bromoacetophenone (**224d**) with $BH_3.SMe_2$ using 15 mol% **227-230**[a]



Entry	Catalyst	Yield (%)[b]	$[\alpha]_D^{25}$	*ee*[c]
1	**227**	85	+26.94 (*c* 1.33, $CHCl_3$)	74
2	**228**	85	+27.24 (*c* 1.09, $CHCl_3$)	77
3	**229**	84	+27.72 (*c* 1.32, $CHCl_3$)	72
4	**230**	83	+27.04 (*c* 1.15, $CHCl_3$)	73

[a] All reactions were carried out on 1 mM scale of 4-bromo acetophenone **224d** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 30 min at 110 °C by using 15 mol% **227-230**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OJ H.

In conclusion, we have demonstrated the application of five novel chiral catalysts (**216, 227-230**) containing N-P=O structural framework for the borane-mediated asymmetric reduction of prochiral ketones providing the resulting secondary alcohols in upto 89% enantiomeric purities. From Tables 2-6 it is quite clear that all the catalysts (**216, 227-230**) provided almost same enantioselectivities thus indicating that substitution on amide aromatic ring has no significant role to play in directing the stereochemical course of the reduction process.

Towards chiral diamines as chiral catalytic precursors for borane-mediated enantioselective reduction of prochiral ketones

Next we have directed our attention towards the development of diamine based catalysts for the borane-mediated asymmetric reduction of prochiral ketones. Asami and co-workers[148,149] examined the application of chiral diamines **10**, **206a-e, 207** (Fig. 34) for the borane-mediated asymmetric reduction of prochiral ketones and obtained 92% enantiomeric purity in case of catalyst **206d** (eq. 80, Page no. 41 & 42) when the reduction was performed at -15 ^{o}C. However the catalyst **10** provided inferior selectivity. Based on these observations, our research group[150] have used catalyst (2*S*)-2-anilinomethylpyrrolidine (**10**) for reduction of prochiral ketones at reflux temperature and obtained resulting alcohols in high enantiomeric purities (Scheme 13, page no. 42).

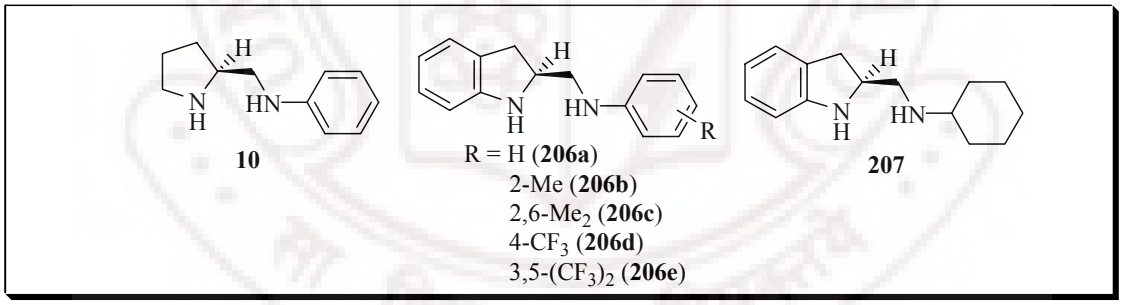
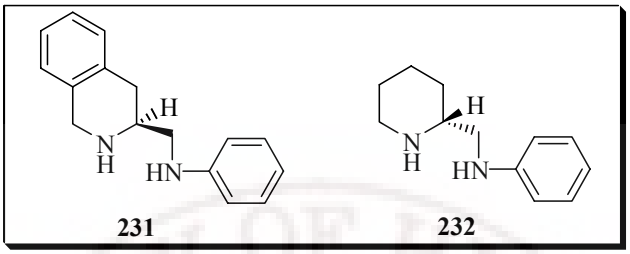


Fig. 34

With a view to understand the potential of (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) having six membered benzofused nitrogen heterocyclic ring and also the potential of (2*R*)-2-anilinomethylpiperidine (**232**) as chiral catalysts in the borane-mediated asymmetric reduction of prochiral ketones, we have directed our studies for the synthesis of these two chiral diamines **231, 232** (Fig. 41). The major difference

between the chiral catalyst **10** and **232** is that the first one has five membered nitrogen heterocyclic ring and the later has six membered nitrogen heterocyclic ring.

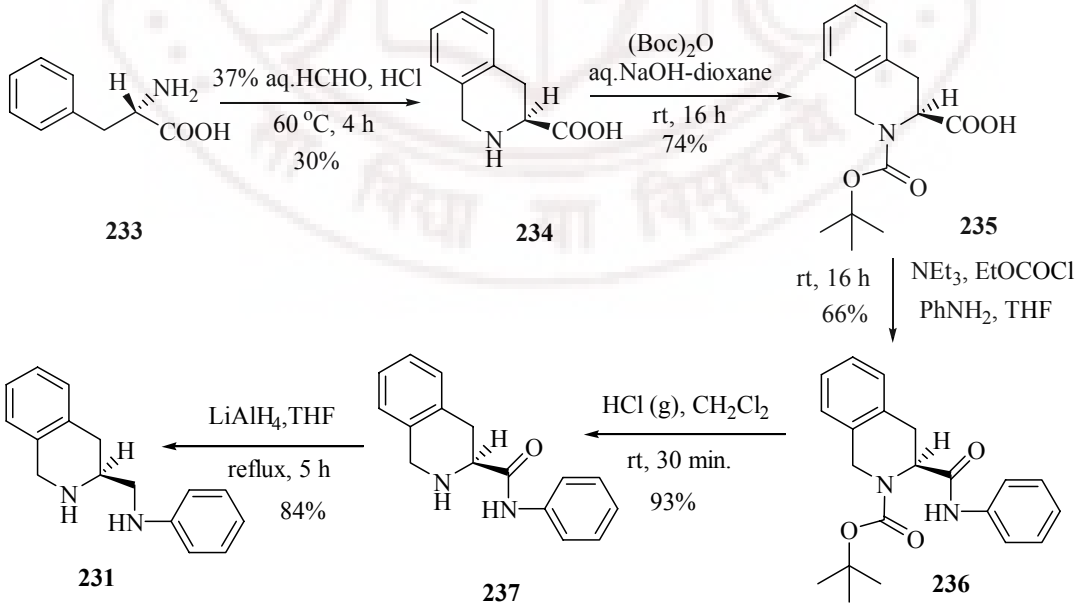


231 **232**

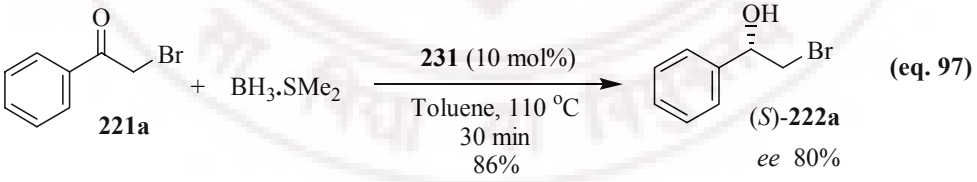
Fig.41

Catalytic source **231** was prepared according to the reaction sequence as shown in Scheme 15 starting from commercially available (*S*)-phenylalanine (**233**). Pictet-Spengler condensation[163] of (*S*)-phenylalanine (**233**) with 37% aq. formaldehyde provided (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**234**) in 30% isolated yield. The amino group of this compound (**234**) was then protected with a *tert*-butoxycarbonyl group under

Scheme 15



standard conditions[164] to give (*S*)-N-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**235**). Subsequent treatment of this acid with ethyl chloroformate and then with aniline provided (3*S*)-2-(*tert*-butoxycarbonyl)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (**236**) as colorless solid in 66% yield. Removal of the Boc group under acidic conditions afforded (3*S*)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (**237**)[165] as colorless solid in 93% yield. The compound was characterized by IR, ^{1}H &^{13}C NMR spectral data. The structure of the compound **237** was further confirmed by single crystal X-ray data [The structure refinement of this compound is presented in Table III and the ORTEP diagram is shown in Figure 42]. This amide (**237**) was reduced with lithium aluminium hydride in refluxing THF to give the (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) in 84% isolated yield. This compound was initially obtained as viscous liquid but solidified upon standing at room temperature. This compound was characterized by IR, ^{1}H &^{13}C NMR spectral data, LC MS and elemental analysis (Spectrum 16 & 17).

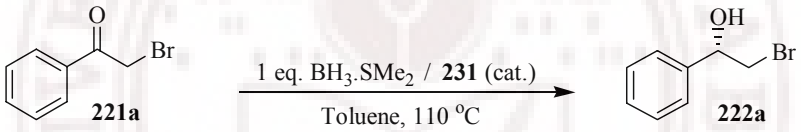


(eq. 97)

We have first selected phenacyl bromide (**221a**) as a substrate for our study using **231** as chiral catalyst. We performed the borane-mediated asymmetric reduction of phenacyl bromide (**221a**) with varying catalytic amounts of (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) with a view to understand the requirement of minimum amount of the catalyst for obtaining highest selectivity (Table 7). The best result was

obtained when phenacyl bromide (**221a,** 1mM) was treated with $BH_3.SMe_2$ (1 mM) in the presence of 10 mol% **231** in refluxing toluene for 30 min, thus providing the resulting secondary alcohol (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] in 86% yield with 80% enantiomeric excess (eq. 97, Table 7). The enantiomeric excess of (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-222a,** Chromatogram **6A**]. The results are summarized in Table 7.

Table 7: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **231:** Standardization of reaction conditions[a]



Entry	Catalyst (mol%)	Time (min.)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	5	45	78	68	*S*
2	7.5	45	85	73	*S*
3	10	45	84	78	*S*
4	15	45	81	75	*S*
5	20	45	82	76	*S*
6	**10**	**30**	**86**	**80**	***S***
7	10	15	83	72	*S*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**221a**) with 1 equivalent of $BH_3.SMe_2$ in the presence of **231** in toluene at 110 °C.

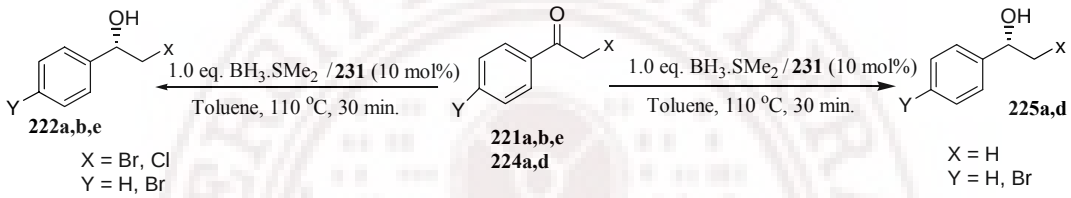
[b]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c]Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[d]Absolute configuration was assigned by comparison of the specific rotation with that of reported molecule.[156]

Encouraged by this result and with a view to examine the generality of this methodology, we have subjected representative class of prochiral α-halo ketones **221b,e** [Chromatogram **7B** for compound **222b**] and aryl alkyl ketones **224a,d** [Chromatogram **8B** for compound **225a**] to the borane-mediated asymmetric reduction using this catalytic source (**231**). The resulting secondary alcohols were obtained in 57-80% enantiomeric purity (Table 8).

Table 8. Asymmetric reduction of representative ketones by catalytic source **231**[a]



Substrate	X	Y	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*ee* (%)[d]
221a	Br	H	**222a**	86	+32.6 (*c* 0.9, $CHCl_3$)	*S*[156]	80
221b	Cl	H	**222b**	83	+37.2 (*c* 0.8, C_6H_{12})	*S*[156]	72
221e	Br	Br	**222e**	81	+27.5 (*c* 0.9, $CHCl_3$)	*S*[159]	79[e]
224a	H	H	**225a**	84	+23.5 (*c* 0.8, MeOH)	*R*[160]	57
224d	H	Br	**225d**	83	+21.5 (*c* 0.5, $CHCl_3$)	*R*[161]	59[e]

[a]All reactions were carried out on 1 mM scale of ketone with $BH_3.SMe_2$ (1 mM) in the presence of the catalyst **231** (10 mol%) in toluene for 30 min at 110 °C.

[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes)

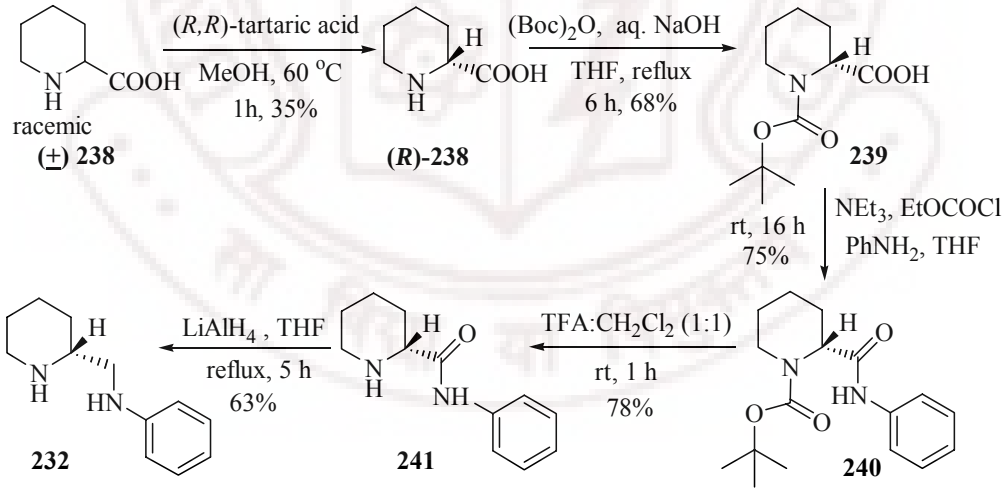
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.

[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.

We have next turned our attention towards the application of (2*R*)-2-anilinomethylpiperidine (**232**) as a catalyst in the borane-mediated reduction processes. This diamine (**232**) was prepared following the reaction sequence as described in Scheme 16 starting from the (*R*)-pipecolinic acid (**238**) which was obtained *via* the resolution of racemic pipecolinic acid using (*R*,*R*)-(+)-tartaric acid according to the known procedure.[166] Amino group of (*R*)-pipecolinic acid was protected by Boc group following the literature procedure[166] to give (*R*)-N-(*tert*-butoxycarbonyl)pipecolinic acid (**239)** as colorless solid in 68% yield. Successive treatment of this acid with ethyl chloroformate and aniline provided (*R*)-N-(*tert*-butoxycarbonyl)-2-anilinocarbonylpiperidine (**240**) in 75% yield. Deprotection of Boc group was achieved by using TFA-CH_2Cl_2 (1:1) mixture at room tem

Scheme 16



-perature to give (2*R*)-2-anilinocarbonylpiperidine (**241**)[167] in 78% yield. This compound (**241**) was characterized by IR, ^1H &^{13}C NMR spectral data and was further confirmed by

single crystal X-ray data analysis [The structure refinement of this compound is presented in Table IV and the ORTEP diagram is shown in Figure 43] as TFA salt. The desired diamine (2*R*)-2-anilinomethylpiperidine (**232**)[168] was obtained *via* the reduction of the amide with LAH in refluxing THF, as colorless viscous liquid. This diamine (**232**) was characterized by IR, ^{1}H &^{13}C NMR, LC MS data and elemental analysis (Spectrum 18 & 19).

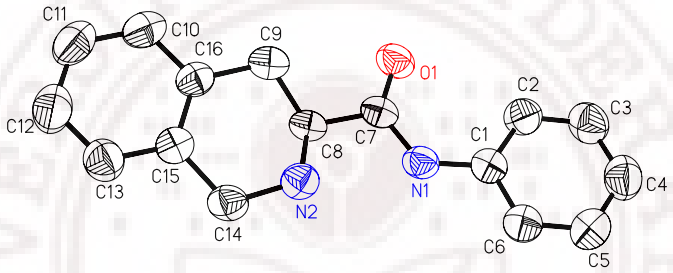


Figure 42: ORTEP diagram of 237
(*Hydrogen atoms were omitted for clarity*)

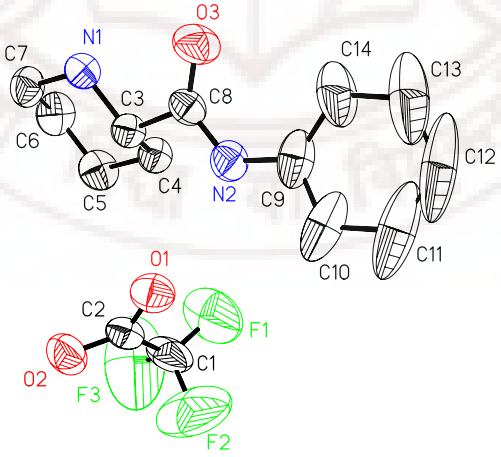


Figure 43: ORTEP diagram of 241.TFA
(*Hydrogen atoms were omitted for clarity*)

Table III: Crystal data and structure refinement for the compound 237

Identification	: **237**
Empirical formula	: $C_{16}\ H_{16}\ N_2\ O$
Formula weight	: 252.31
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: $P\ 2_1\ 2_1\ 2_1$
Unit cell dimensions	: a = 5.8274(6) Å α = 90.00
	: b = 8.2330(8) Å β = 90.00
	: c = 27.680(3) Å γ = 90.00
Volume	: 1328.0(2) $Å^3$
Z	: 4
Density (calculated)	: 1.262 g/cm^3
Absorption coefficient	: 0.080 mm^{-1}
F (000)	: 536
Crystal size	: 0.46 X 0.37 X 0.25 mm^3
Theta range for data collection	: 1.47 to 24.99 deg.
Index ranges	: $-4 \leq h \leq 6, -9 \leq k \leq 9, -32 \leq l \leq 29$
Reflections collected	: 6639
Independent reflections	: 2306
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2306 / 0 / 181
Goodness-of-fit on F^2	: 0.954
Final R indices [I> 2 sigma (I)]	: R1 = 0.0399, wR2 = 0.0717
R indices (all data)	: R1 = 0.0577, wR2 = 0.0764
Absolute structure parameters	: -0.4(18)
Largest diff. Peak and hole	: 0.108 and -0.127 e. A^{-3}

Table IV: Crystal data and structure refinement for the compound 241.TFA

Identification	: **241.TFA**
Empirical formula	: $C_{14}\ H_{17}\ F_3\ N_2\ O_3$
Formula weight	: 318.30
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: *C2*
Unit cell dimensions	: a = 23.409(3) Å α = 90.00
	: b = 8.0598(10) Å β = 107.005(2)
	: c = 8.7079(10) Å γ = 90.00
Volume	: 1571.1(3) $Å^3$
Z	: 4
Density (calculated)	: 1.346 g/cm^3
Absorption coefficient	: 0.118 mm^{-1}
F (000)	: 664
Crystal size	: 0.45 X 0.37 X 0.25 mm^3
Theta range for data collection	: 1.82 to 25.00 deg.
Index ranges	: $-27 \leq h \leq 26$, $-9 \leq k \leq 6$, $-9 \leq l \leq 10$
Reflections collected	: 4019
Independent reflections	: 1497
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1497 / 1 / 211
Goodness-of-fit on F^2	: 1.090
Final R indices [I> 2 sigma (I)]	: R1 = 0.0717, wR2 = 0.2040
R indices (all data)	: R1 = 0.0803, wR2 = 0.2126
Absolute structure parameters	: 0.(10)
Largest diff. Peak and hole	: 0.475 and -0.389 e. A^{-3}

We have then examined the catalytic potential of this diamine (**232**) in the borane-mediated asymmetric reduction of prochiral ketones. Phenacyl bromide (**221a**) was selected as a substrate and the best result was obtained when phenacyl bromide was treated with 10 mol% (2*R*)-2-anilinomethylpiperidine (**232**) in refluxing toluene for 30 min to provide the desired alcohol in 81% enantiomeric purity (eq. 98). The enantiomeric excess of (*R*)-2-bromo-1-phenylethanol [**(*R*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H (Chromatogram **6B**) with reference to the racemic alcohol [**(±)-222a**]. The results are presented in Table 9.

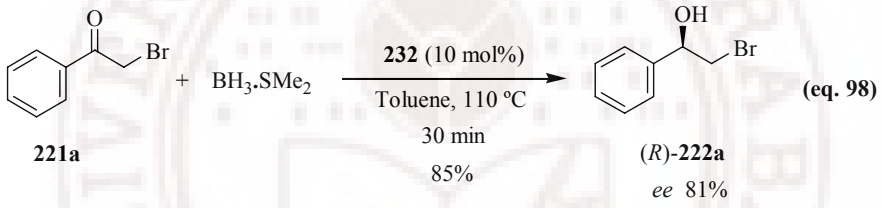
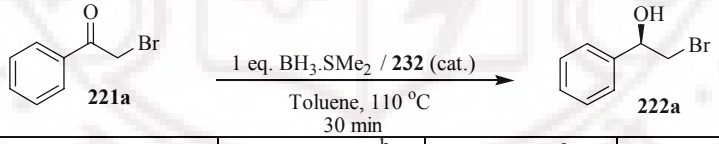


Table 9: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **232:** Standardisation of reaction conditions[a]



Entry	Catalyst (mol%)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	3	85	60	*R*
2	5	83	68	*R*
3	7.5	84	73	*R*
4	**10**	**85**	**81**	***R***
5	15	72	72	*R*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**221a**) with 1 equivalent of $BH_3.SMe_2$ in the presence of **232** in toluene at 110 °C for 30 min.

[b]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

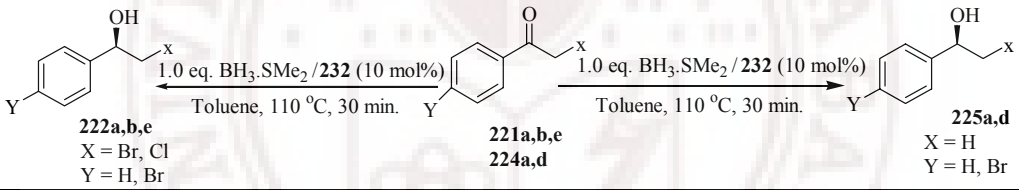
[c]Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.

With a view to understand the generality of the methodology, representative prochiral α-halo ketones **221a,b,e** [Chromatogram **7A** for compound **222b**] and aryl alkyl ketones **224a,d** [Chromatogram **8A** for compound **225a**] were subjected to the borane-mediated asymmetric reduction using this catalytic source (**232**). The resulting secondary alcohols were obtained in 62-81% enantiomeric purity (Table 10).

As expected the diamine **232** with *R*-configuration provided the resulting secondary alcohols with opposite configuration as that of the chiral diamine **231** with *S*-configuration.

Table 10. Asymmetric reduction of representative ketones by catalytic source **232**[a]



Substrate	X	Y	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*ee* (%)[d]
221a	Br	H	**222a**	85	-33.2 (*c* 0.5, $CHCl_3$)	*R*[156]	81
221b	Cl	H	**222b**	83	-36.1 (*c* 0.3, C_6H_{12})	*R*[156]	77
221e	Br	Br	**222e**	83	-24.3 (*c* 0.7, $CHCl_3$)	*R*[159]	76[e]
224a	H	H	**225a**	86	-25.3 (*c* 0.7, MeOH)	*S*[160]	62
224d	H	Br	**225d**	85	-24.6 (*c* 1.2, $CHCl_3$)	*S*[161]	70[e]

[a]All reactions were carried out on 1 mM scale of ketone with $BH_3.SMe_2$ (1 mM) in the presence of the catalyst **232** (10 mol%) in toluene for 30 min at 110 °C.

[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).

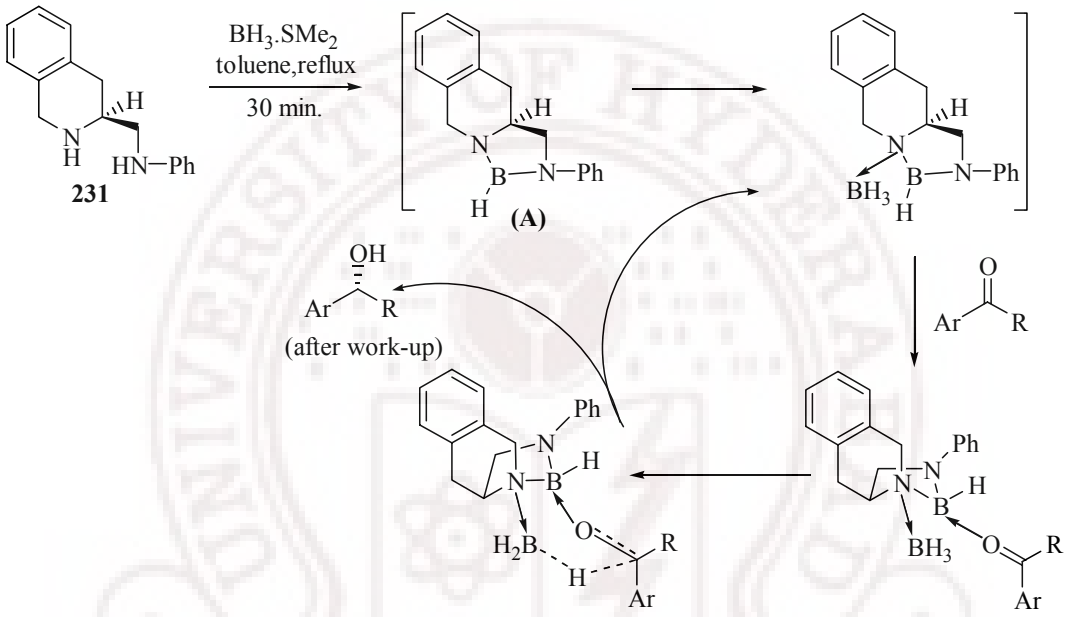
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.

[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.

A possible mechanism of the reduction process with the diamine **231** as catalytic source is presented in the Scheme **17**. The reaction is belived to proceed *via* the formation of diazaborolidine (**A**) based on our earlier report.[153]

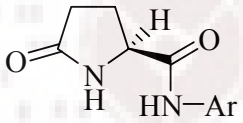
Scheme 17



In conclusion, two new chiral diamines have been prepared from (*S*)-phenylalanine and (*R*)-pipecolinic acid respectively and their catalytic potential for the enantioselective reduction of prochiral ketones by borane has been examined. On the basis these results we can not generalize that all six membered ring catalysts provide inferior selectivities than the corresponding five membered ring catalysts. Although enantioselectivities are low in comparision to chiral source (2*S*)-2-anilinomethylpyrrolidine (**10**) these studies certainly throw some light on the understanding of the structural framework of diamine catalysts which actually play a key role to provide high enantioselectivities.

Chiral amides as possible catalytic sources for the borane-mediated asymmetric reduction of prochiral α-halo ketones: Influence of the nature of aryl group of the 2-carbonyl amino group

Our research group has recently demonstrated[153] the catalytic potential of representative chiral diamides **215a-215i** (Fig. 36, Page 44) based on (2*S*)-5-oxo-2-arylcarbonylpyrrolidine as catalyst in the borane-mediated asymmetric reduction of prochiral ketones to provide the resulting secondary alcohols in upto 91% enantiomeric purities.



215a-215i

Ar = Phenyl (**215a**), 4-Bromophenyl (**215b**),
4-Chlorophenyl (**215c**), 4-Fluorophenyl (**215d**),
4-Nitrophenyl (**215e**), 2,4-Difluorophenyl (**215f**),
3,5-Difluorophenyl (**215g**),
3,5-Bis(trifluoromethyl)phenyl (**215h**), 1-Naphthyl (**215i**)

Fig. 36

Encouraged by these results and with a view to understand the influence of the nature of aryl group of the 2-carbonyl amino group, we have selected six representative amides **242-247** (Fig. 44) for our study as catalysts in the borane-mediated reduction of prochiral ketones.

Compound **242** was prepared starting from (2*S*)-N-*tert*-butoxycarbonylproline (**248**) according to the literature procedure[169] as shown in Scheme 18. Then (2*S*)-N-*tert*-butoxycarbonylproline (**248**) upon successive treatment with ethyl chloroformate and 4-aminopyridine provided (2*S*)-N-*tert*-butoxycarbonyl-2-(pyrid-4-ylamino)carbonylpyrroli-

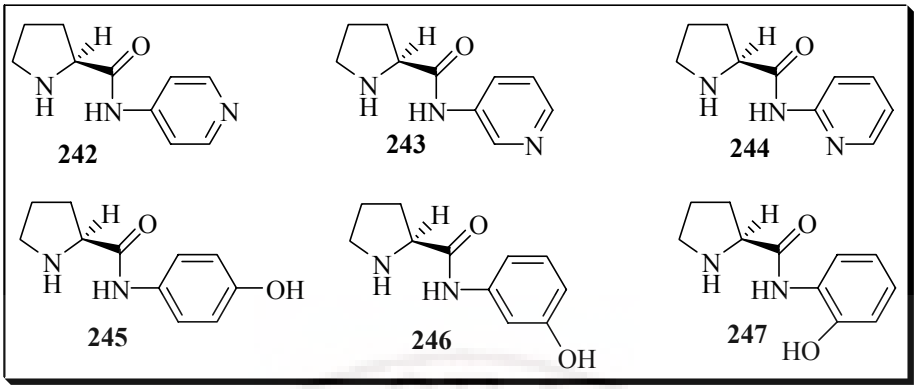
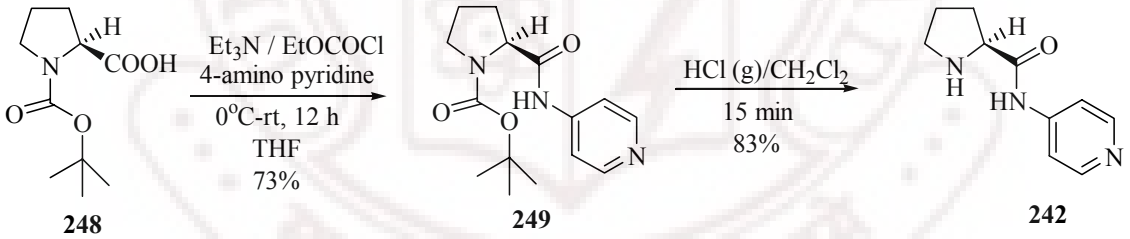


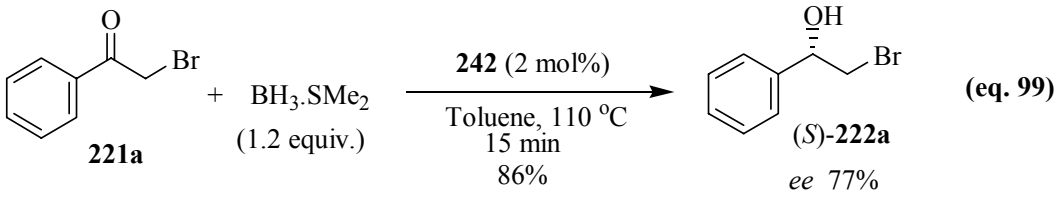
Fig. 44

dine (**249**) as colorless solid in 73% yield. Deprotection of *tert*-butoxycarbonyl group under acidic condition gave the desired compound (2*S*)-2-(pyrid-4-ylamino)-carbonylpyrrolidine (**242**) as pale brown viscous liquid. This compound was characterized by IR, ^{1}H and ^{13}C NMR, LC MS data (Spectrum 20 & 21) and elemental analysis.

Scheme 18



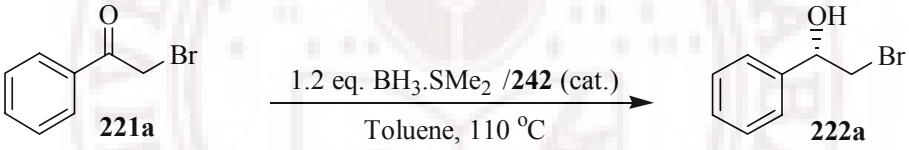
We have then directed our studies to examine the potential of this catalyst in borane-mediated asymmetric reduction of prochiral ketones. In this case also we have selected phenacyl bromide as the substrate. With a view to understand the minimum amount of catalyst required for obtaining high enantioselectivity, we have carried out number of experiments with varying amount of catalyst. We noticed that 2 mol% (2*S*)-2-(pyrid-4-yla mino)carbonylpyrrolidine (**242**) in refluxing toluene for 15 min gave the best result, thus



(eq. 99)

providing the resulting secondary alcohol in 77% enantiomeric purity (eq. 99) [Chromatogram **9**]. The enantiomeric purity of the resulting (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-222a**]. The results are presented in Table 11.

Table 11: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **242:** Standardisation of reaction conditions[a]



Entry	Catalyst **242** (mol%)	Time (min.)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	10	30	88	44	*S*
2	5	30	87	69	*S*
3	4	30	86	73	*S*
4	**2**	**15**	**86**	**77**	***S***
5	1	15	88	65	*S*

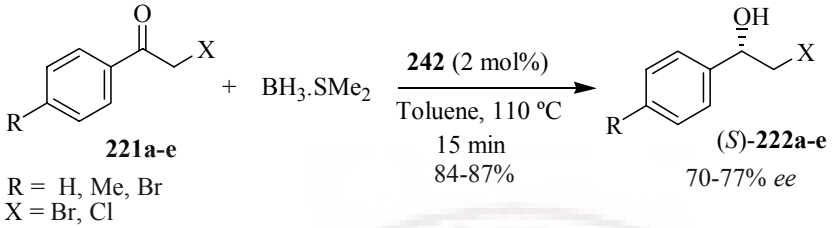
[a]All reactions were carried out on 1 mM scale (2 mM for entry 4 & 5) of phenacyl bromide (**221a**) with 1.2 equivalent of $BH_3.SMe_2$ in the presence of **242** in toluene at 110 °C.

[b]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c]Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[156]

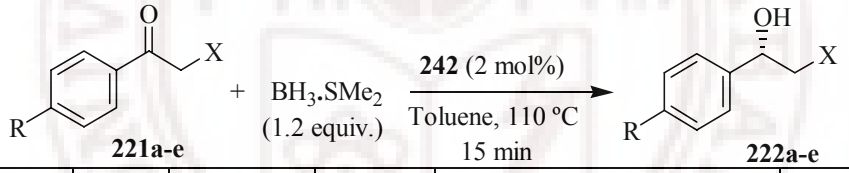
With a view to understand the generality of this catalyst, we have subjected representative α-halo ketones **221a-e** (eq. 100) to the borane-mediated asymmetric reduction of prochiral



(eq. 100)

ketones under the influence of 2 mol% the catalyst. The resulting alcohols **(222a-e)** were obtained in 70-77% enantioselectivities. The results are summarized in Table 12.

Table 12: Enantioselective reduction of *α*-halo ketones with $BH_3.SMe_2$ using 2 mol% **242**[a]



Entry	R	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*ee* (%)[d]
1	H	Br	**222a**	86	+31.53 (*c* 1.24, $CHCl_3$)	*S*[156]	77
2	H	Cl	**222b**	84	+28.37 (*c* 0.86, C_6H_{12})	*S*[156]	70
3	CH_3	Br	**222c**	86	+30.52 (*c* 0.96, $CHCl_3$)	*S*[132]	70
4	CH_3	Cl	**222d**	86	+32.35 (*c* 0.95, $CHCl_3$)	*S*[132]	72
5	Br	Br	**222e**	87	+24.88 (*c* 1.25, $CHCl_3$)	*S*[159]	75[e]

[a] All reactions were carried out on 2 mM scale of *α*-halo ketones **221a-e** with 1.2 equivalent of $BH_3.SMe_2$ in toluene for 15 min at 110 °C using 2 mol% **242**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

[d] Determined by HPLC analysis using chiral column, Chiralcel OD-H.

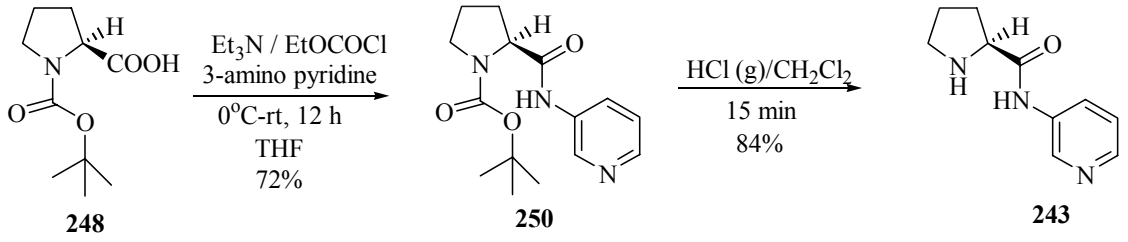
[e] Determined by HPLC analysis using chiral column, Chiralcel OJ-H.

Determination of Enantiomeric Purities of Alcohols:

The enantiomeric purities of the alcohols [**(*S*)-222b-d**] were determined by HPLC analyses using the chiral column, Chiralcel-OD H with reference to the corresponding racemic alcohols [**(±)-222b-d**], whereas the enantiomeric purity of the alcohols [**(*S*)- 222e**] have been determined by HPLC analyses using the chiral column, Chiralcel-OJ H with reference to the corresponding racemic alcohol [**(±)-222e**].

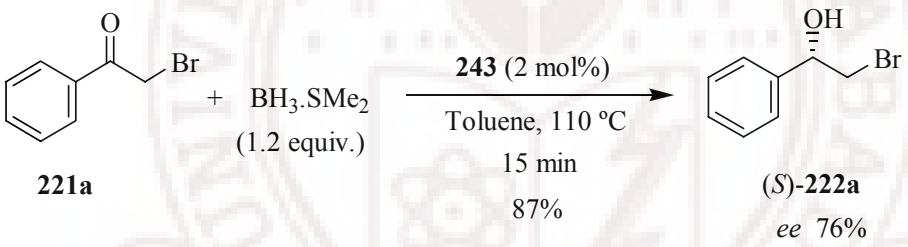
With a view to understand the effect of pyrid-3-ylamino group on the carbonyl amine group, we have prepared (2*S*)-2-(pyrid-3-ylamino)carbonylpyrrolidine (**243**) according to the literature procedure[169] starting from (2*S*)-N-*tert*-butoxycarbonylproline (**248**) as presented in Scheme 19. The compound **248** upon successive treatment with ethyl chloroformate and then with 3-aminopyridine provided (2*S*)-1-*tert*-butoxycarbonyl-2-(pyrid-3-ylamino)carbonylpyrrolidine (**250**) as colorless solid in 72% yield. The desired compound (2*S*)-2-(pyrid-3-ylamino)carbonylpyrrolidine (**243**) was obtained in 84% yield after removal of Boc group under acidic condition as pale yellow viscous liquid. This compound was characterized by IR, ^{1}H and ^{13}C NMR, LC MS data and elemental analysis (Spectrum 22 & 23).

Scheme 19



248 **250** **243**

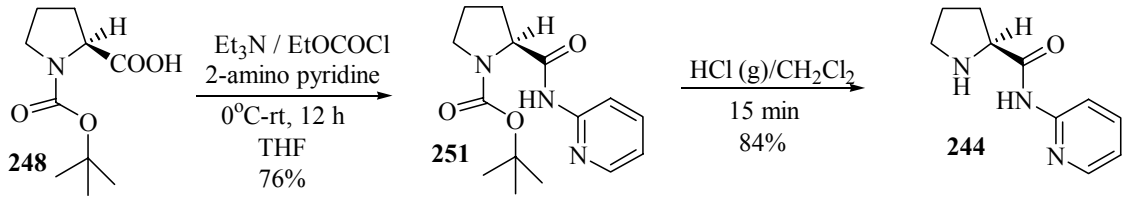
We then examined its potential as a catalyst in borane-mediated asymmetric reduction of phenacyl bromide. Thus, when phenacyl bromide was treated, as in the case of amide **242,** with 2 mol% (2*S*)-2-(pyrid-3-ylamino)carbonylpyrrolidine (**243**) in the presence of $BH_3.SMe_2$ in refluxing toluene for 15 min, provided the desired alcohol in 76% enantiomeric purity (eq. 101). The enantiomeric purity of (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-222a,** (Chromatogram **10**)]. Since the enantiomeric purity obtained by the amide **243** is almost same as in the case of amide **242**, we did not further examine the potential of this catalyst (**243**).



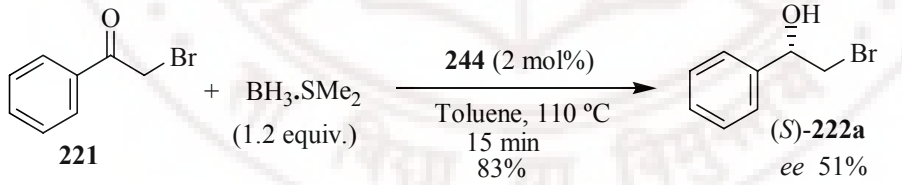
221a (*S*)-**222a** *ee* 76% **(eq. 101)**

Then we have directed our focus towards the application of (2*S*)-2-(pyrid-2-ylamino)carbonylpyrrolidine (**244**) with a view to examine the influence of the 2-aminopyridyl group on the enantioselectivity of reduction process. This catalyst **244** was prepared according to the literature procedure[169] starting from (2*S*)-N-*tert*-butoxycarbonylproline (**248**) following the similar way as mentioned for the compound **242**, as pale yellow viscous liquid (Scheme 20). This compound was characterized by IR, ^1H and ^{13}C NMR, LC MS data and elemental analysis (Spectrum 24 & 25).

Scheme 20



We have then examined the potential of this amide **244** as a catalyst in borane-mediated asymmetric reduction of phenacyl bromide. Thus reduction of phenacyl bromide as in the case of amide **242** with 2 mol% (2*S*)-2-(pyrid-2-ylamino)carbonylpyrrolidine (**244**) using $BH_3.SMe_2$ as reducing agent in refluxing toluene for 15 min, provided the desired alcohol in 51% enantiomeric purity (eq. 102). The enantiomeric excess of (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-222a,** (Chromatogram **11**)]. Since the enantioselectivity is inferior in the case of the catalyst **244** we did not proceed further to examine the utility of this catalyst.



(eq. 102)

The low enantioselectivity in the case of (2*S*)-2-(pyrid-2-ylamino)carbonylpyrrolidine (**244**) compared to (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (**242**) might be attributed to the coordination of diazaborolidine boron with the pyridine nitrogen (Fig 45), which might not allow the carbonyl oxygen of the ketone to coordinate with boron of the diazaborolidine, thereby reducing the possibility of chiral catalytic pathway of the

reduction process and probably allowing the normal reduction with $BH_3.SMe_2$ thus leading to low enantioselectivities.

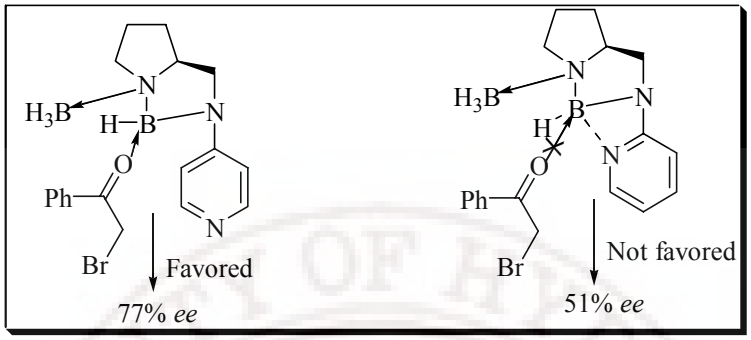


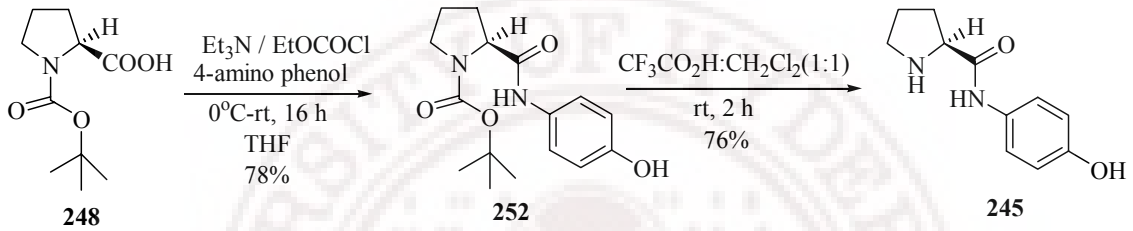
Fig. 45

After examining the effect of aminopyridines as groups of amide portions of the pyrrolidine-2-carboxamide framework in the borane-mediated asymmetric reduction of prochiral ketones, we have turned our attention towards the catalysts, (2*S*)-N-(4-hydroxyphenylamino)carbonylpyrrolidine (**245),** (2*S*)-N-(3-hydroxyphenylamino)-carbonylpyrrolidine (**246)** and (2*S*)-N-(2-hydroxyphenylamino)carbonylpyrrolidine (**247)** having 4-hydroxyanilino, 3-hydroxyanilino and 2-hydroxyanilino groups respectively on amide portions of pyrrolidine-2-carboxamide framework. (2*S*)-N-(4-Hydroxyphenylamino)carbonylpyrrolidine (**245**) was obtained as shown in Scheme 21. Compound (2S)-N-*tert*-butoxycarbonyl-2-(4-hydroxyphenylamino)carbonylpyrrolidine (**252**) was obtained as a colorless solid by successive treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248**) with ethyl chloroformate and 4-amino phenol following the similar method described for the compound **242**. (2*S*)-N-(4-Hydroxyphenylamino)-carbonylpyrrolidine (**245**) was obtained after removal of Boc group by CF_3CO_2H as brick

colour solid. This compound was characterized by IR, ^{1}H and ^{13}C NMR, LC MS data and elemental analysis (Spectrum 26 & 27).

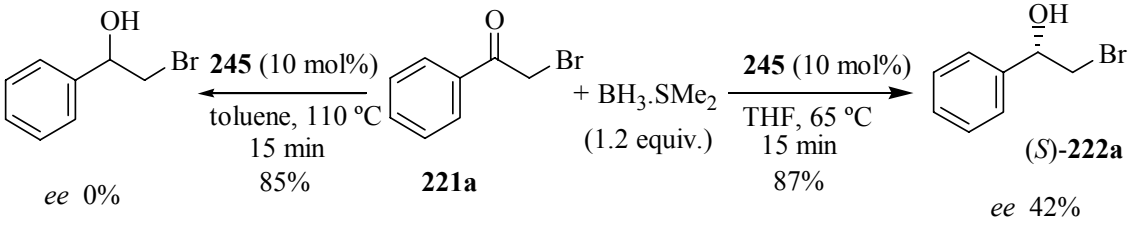
With a view to understand the potential of this catalyst **245** for the borane-mediated asymmetric reduction of prochiral ketones we have carried out the reduction of phenacyl

Scheme 21

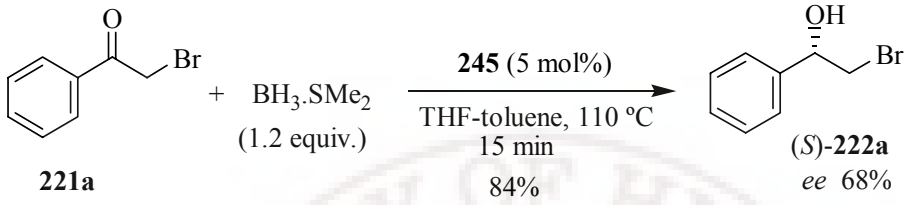


bromide (**221a**) with catalyst **245** (10 mol%) in the presence of borane-dimethyl sulfide at 110 ^{o}C in toluene. The resulting secondary alcohol (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was obtained almost in racemic form. This might be due to the low solubility nature of the catalyst in toluene even at reflux temperature or even after addition of $BH_3.SMe_2$. Accordingly we changed the solvent from toluene to THF in which the catalyst is soluble and performed the reduction at 65 ^{o}C (reflux temperature). The desired alcohol was obtained in 42% enantiomeric purities (Scheme 22) as determined using chiral column, chiralcel OD-H with respect to racemic alcohol.

Scheme 22



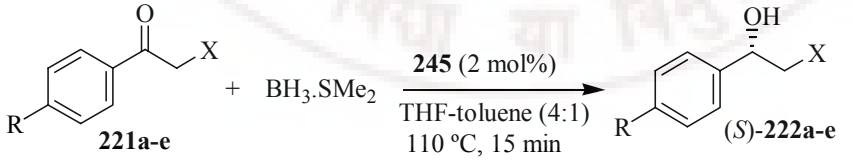
Surprisingly the same reaction (eq. 103) provided 68% *ee* when performed at 110 ^{o}C in THF and toluene mixture (4:1) with 5 mol% **245**. This observation clearly indicates that *in situ* formation of diazaborolidine complex is much favourable at higher temperature.



221a (*S*)-**222a** *ee* 68% **(eq. 103)**

With a view to understand the minimum requirement of catalyst for obtaining maximum enantioselectivity, we have carried out the reduction of phenacyl bromide (**221a**) with different catalytic quantities of **245**, under the same reaction conditions. Enantioselectivities of the resulting (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] are given in Table 13. It is clear from the Table 13 that 2 mol% catalyst provided the best result (Chromatogram **12**).

In order to understand the generality of the reaction we have employed representative α-halo ketones (**221a-e**) as substrate for borane-mediated asymmetric reduction. The desired secondary alcohols were obtained in 72-77% enantiomeric purities (eq. 104, Table-14).

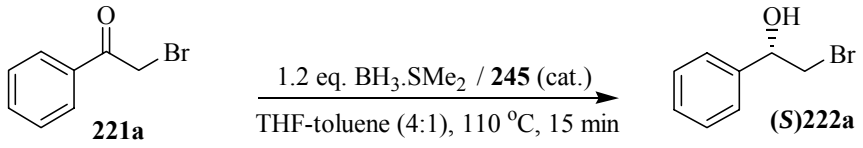


221a-e (*S*)-**222a-e** **(eq. 104)**

R = H, Me, Br
X = Br, Cl

72-77% *ee*

Table 13: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **245:** Standardisation of reaction conditions[a]



Entry	Catalyst (mol%)	Yield (%)[d]	*ee* (%)[e]	Configuration[f]
1	10	88	58	*S*
2	5	84	68	*S*
3[b]	5	89	67	*S*
4[c]	**2**	**86**	**72**	***S***

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**221a**) with 1.2 equivalent of $BH_3.SMe_2$ in the presence of **245** in THF-toluene (4:1) at 110 °C for 15 min.

[b]reactions was carried out at 150 °C.

[c]reaction was carried out on 2 mM scale of phenacyl bromide.

[d]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

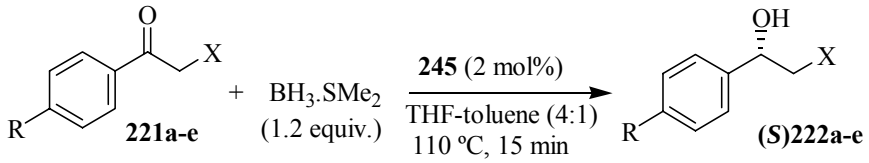
[e]Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD H.

[f]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[156]

Determination of Enantiomeric Purities of Alcohols:

The enantiomeric purities of the alcohols [**(*S*)-222b-d**] were determined by HPLC analyses using the chiral column, Chiralcel-OD H with reference to the corresponding racemic alcohols [**(±)-222b-d**], whereas the enantiomeric excesses of the alcohols [**(*S*)-222e**] have been determined by HPLC analyses using the chiral column, Chiralcel-OJ H with reference to the corresponding racemic alcohol [**(±)-222e**].

Table 14: Enantioselective reduction of α-halo ketones with $BH_3.SMe_2$ using 2 mol% **245**[a]



Entry	R	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*ee* (%)[d]
1	H	Br	**222a**	86	+30.54 (*c* 0.91, $CHCl_3$)	*S*[156]	72
2	H	Cl	**222b**	86	+31.53 (*c* 0.91, C_6H_{12})	*S*[156]	73
3	CH_3	Br	**222c**	85	+33.73 (*c* 0.91, $CHCl_3$)	*S*[132]	74
4	CH_3	Cl	**222d**	84	+39.20 (*c* 0.98, $CHCl_3$)	*S*[132]	73
5	Br	Br	**222e**	85	+23.40 (*c* 0.93, $CHCl_3$)	*S*[159]	77[e]

[a] All reactions were carried out on 2 mM scale of α-halo ketones **221a-e** with 1.2 equivalent of $BH_3.SMe_2$ in THF-toluene (4:1) for 15 min at 110 °C using 2 mol% **245**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

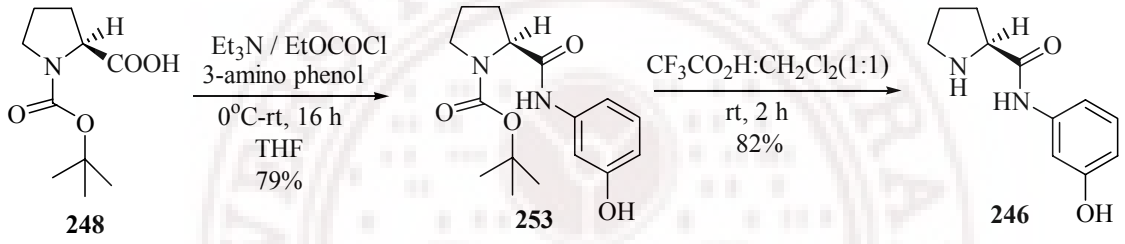
[d] Determined by HPLC analysis using chiral column, Chiralcel-OD H.

[e] Determined by HPLC analysis using chiral column, Chiralcel-OJ H.

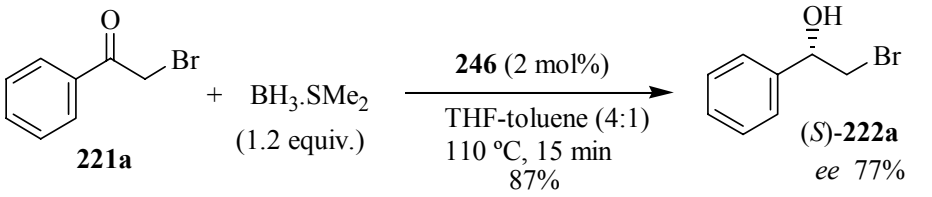
We have next prepared (2*S*)-2-(3-hydroxyphenylamino)carbonylpyrrolidine (**246**) according to the literature procedure as presented in Scheme 23. Compound (2*S*)-N-*tert*-butoxycarbonyl-2-(3-hydroxyphenyl)carbonylpyrrolidine (**253**) was prepared as a colorless solid by successive treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248**) with ethyl chloroformate and 3-aminophenol following the similar method described for the

compound **245** as colorless solid (Scheme 23) in 79% yield. Subsequent removal of Boc group by CF_3CO_2H at room temperature provided (2*S*)-2-(3-hydroxyphenylamino)carbonylpyrrolidine (**246**) as pale yellow viscous liquid. This compound was characterized by IR, ^1H and ^{13}C NMR, LC MS data and elemental analysis (Spectrum 28 & 29).

Scheme 23



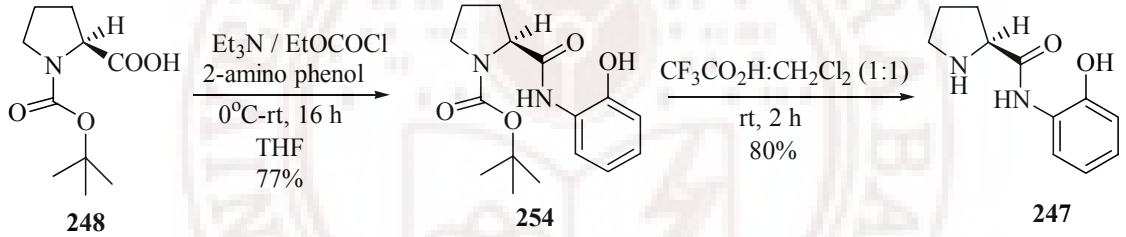
The amide (**246**) was then examined as a catalyst in borane-mediated asymmetric reduction of phenacyl bromide as in the case of amide **245** with 2 mol% in refluxing THF-toluene (4:1) for 15 min, to provide the desired alcohol in 77% enantiomeric purity (eq. 105). The enantiomeric purity of (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H (Chromatogram **13**) with reference to the racemic alcohol [**(±)-222a**]. Since the enantiomeric purity provided by the catalyst **246** is similar as in the case of catalyst **245**, we did not proceed further with this catalyst.



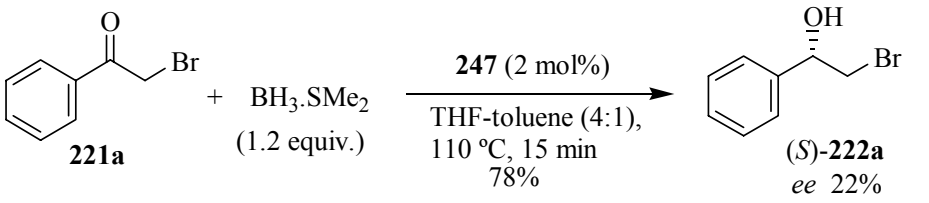
(eq. 105)

Then we have directed our attention towards catalyst **247** which was prepared following the similar procedure as in the case of **245** and obtained as brick red solid (Scheme 24). The structure of this compound was established by IR, ^{1}H and ^{13}C NMR, LC MS data and elemental analysis (Spectrum 30 & 31).

Scheme 24



We have next examined the reduction of phenacyl bromide (**221a**) using 2 mol% catalyst **247** in refluxing THF-toluene for 15 min in the presence of borane-dimethyl sulfide to provide the desired alcohol in 22% enantiomeric purity (eq. 106). The enantiomeric purity of (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H (Chromatogram **14**) with reference to the racemic alcohol [**(±)-222a**]. Since the enantioselectivity is is not good we did not further examine the utility of this catalyst.



(eq. 106)

Low enantioselectivity provided by (2*S*)-2-(2-hydroxyphenylamino)carbonylpyrrolidine (**247**) as compared to (2*S*)-2-(4-hydroxyphenylamino)carbonylpyrrolidine (**245**) can be attributed to the competitive coordination of boron of diazaborolidine species with phenolic-OH, (or to the formation of O-B bond *via* the reaction of phenolic OH group with oxazaborolidine B-H group) which might not favour the carbonyl oxygen of the ketone to coordinate with boron of the diazaborolidine. Thus this transition state might disfavour the chiral catalytic pathway for reduction process and mostly favour the non-catalytic pathway (reduction of ketone with $BH_3.SMe_2$) leading to low enantioselectivities as presented in Fig. 46.

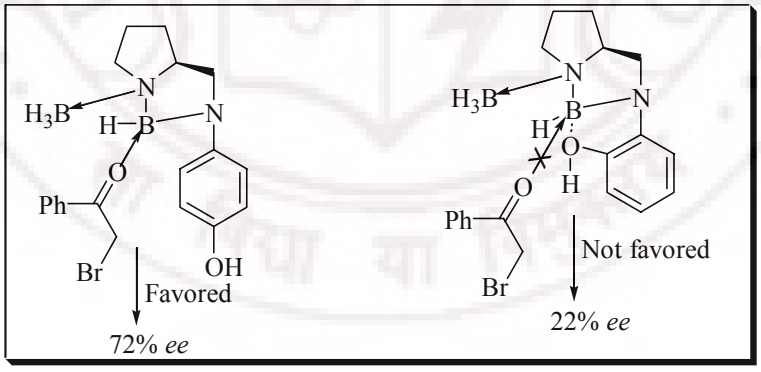


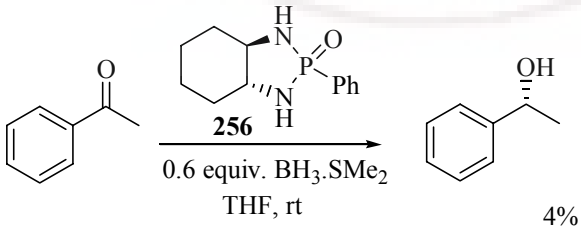
Fig. 46

In conclusion, six chiral amides **(242-247)** have been prepared from commercially available (2S)-N-*tert*-butoxycarbonylproline. We have also explored the possibility of enantioselective reduction of prochiral ketones by borane at refluxing toluene / THF using

these six chiral amides. From these results it is quite clear that 2-aminopyridyl and 2-hydroxyamino group provide low enantioselectivities as they may not favour the catalytic pathway as explained in Fig. 45 and 46. It is also quite clear that the other groups studied, have no significant role to play in the stereochemical course of the reduction process.

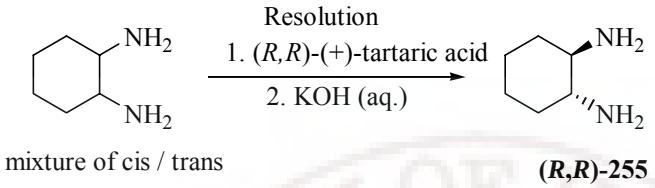
Towards (*R*,*R*)-1,2-diaminocyclohexane as a chiral catalytic precursor for borane-mediated enantioselective reduction of prochiral ketones

In continuation of our interest in finding appropriate diamine as catalyst for borane-mediated asymmetric reduction of prochiral ketones we thought of exploring the possibility of (*R*,*R*)-1,2-diaminocyclohexane (**255**) as catalyst in borane-mediated asymmetric reduction of prochiral ketones. Wills and co-workers[121] have used phosphorous-based (*R*,*R*)-1,2-diaminocyclohexane derivative **256** for the reduction of ketone with borane-dimethyl sulfide complex. They obtained low enantiomeric purity (4%) using 10 mol% **256** in the case of acetophenone (eq. 107). Surprisingly literature survey reveals that (*R*,*R*)-1,2-diaminocyclohexane (**255**) was not used as a catalyst in the borane-mediated asymmetric reductions of prochiral ketones.



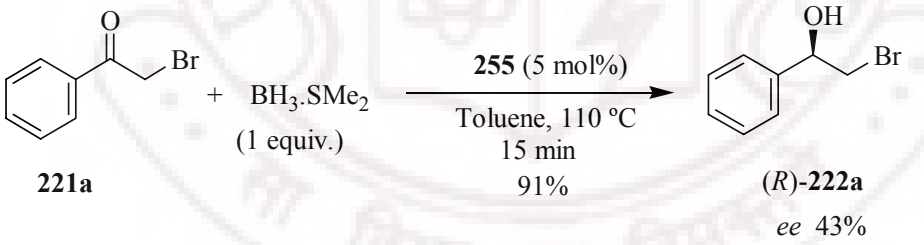
(eq. 107)

(*R*,*R*)-1,2-diaminocyclohexane (**255**) was obtained *via* the resolution of cis / trans-1,2-diaminocyclohexane according to the literature[170] procedure by using (*R*,*R*)-(+)-tartaric acid (eq. 108) to provide the desired (*R,R*)-isomer.



(eq. 108)

Accordingly, we have treated phenacyl bromide (**221a**) with $BH_3.SMe_2$ under the catalytic influence of (*R*,*R*)-1,2-diaminocyclohexane (5 mol%) in refluxing toluene. The desired alcohol (*R*)-2-bromo-1-phenylethanol [**(*R*)-222a**] was obtained in 43% *ee* (eq. 109). The enantiomeric purity of (*R*)-2-bromo-1-phenylethanol [**(*R*)-222a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-222a**].

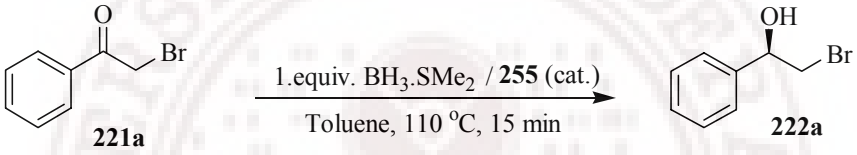


(eq. 109)

With a view to understand the minimum requirement of catalyst for obtaining maximum enantioselectivity, we have carried out the reduction of phenacyl bromide (**221a**) with different catalytic quantities of **(*R,R*)-255**, under the same reaction conditions. Enantioselectivities of the resulting (*R*)-2-bromo-1-phenylethanol [(*R*)-**222a**] are given in Table 15. It is clear from the Table 15 that 5 mol% catalyst provides the best result (43%).

The generality of this methodology was tested by using two more prochiral ketones **221b** and **224a**. The resulting secondary alcohols were obtained in 45 and 23% enantiomeric purities respectively. {HPLC analysis using the chiral column, Chiralcel OD-H with reference to the corresponding racemic alcohol [**(±)-222b, 225a**]}. The results are presented in Table 16.

Table 15: Enantioselective reduction of phenacyl bromide with $BH_3.SMe_2$ using **255:** Standardisation of reaction conditions[a]



221a **222a**

Entry	Catalyst (mol%)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	15	81	18	*R*
2	10	85	43	*R*
3	**5**	**91**	**43**	***R***
4[c]	3	83	18	*R*

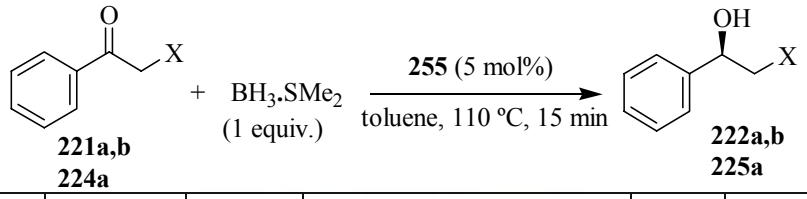
[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**221a**) with 1 equivalent of $BH_3.SMe_2$ in the presence of **255** in toluene at 110 °C for 15 min.

[b]Isolated yields of alcohol **222a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c] Determined by HPLC analysis using chiral column, Chiralcel-OD H.

[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[156]

Table 16: Enantioselective reduction of representative ketones with $BH_3.SMe_2$ using 5 mol% **255**[a]



221a,b
224a

222a,b
225a

Entry	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	*ee* (%)[d]
1	Br	**222a**	91	-20.0 (*c* 1.22, $CHCl_3$)	*R*[156]	43
2	Cl	**222b**	88	-20.47 (*c*1.05, C_6H_{12})	*R*[156]	45
3	H	**225a**	90	-10.0 (*c* 1.11, $CHCl_3$)	*S*[160]	23

[a] All reactions were carried out on 1 mM scale of ketones **221a,b** and **224a** with 1 equivalent of $BH_3.SMe_2$ in toluene for 15 min at 110 °C using 5 mol% **255**.

[b] Isolated yields of alcohols after chromatographic purification on silica gel column.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

[d] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-OD H.

In conclusion, (*R*,*R*)-1,2-diaminocyclohexane has been examined as possible chiral catalyst in the borane-mediated enantioselective reduction of prochiral ketones and found to provide low enantioselectivity.

CONCLUSION

We have made reasonable success in achieving our objectives of this thesis mentioned in the beginning of this chapter. We have synthesized novel chiral catalysts (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**), (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine (**227**), (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)carbonylpyrrolidine (**228**), (*S*)-1-(diphenylphosphoryl)-2-(4-fluoroanilino)-carbonylpyrrolidine (**229**) and (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino) carbonylpyrrolidine (**230**), containing N-P=O structural framework, and examined their applications as catalysts in the borane-mediated asymmetric reduction of prochiral ketones which provided the resulting secondary alcohols in 70-89% enantiomeric purities. We have demonstrated the application of two new chiral diamines (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) and (2*R*)-2-anilinomethylpiperidine (**232**) as chiral catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones. We have also examined the application of chiral amides, (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (**242**), (2*S*)-2-(pyrid-3-ylamino)carbonylpyrrolidine (**243**), (2*S*)-2-(pyrid-2-ylamino)carbonylpyrrolidine (**244**), (2*S*)-N-(4-hydroxyphenylamino)-carbonylpyrrolidine (**245**), (2*S*)-N-(3-hydroxyphenylamino)carbonylpyrrolidine (**246**) and (2*S*)-N-(2-hydroxyphenylamino)carbonylpyrrolidine (**247**) as catalysts for borane-mediated asymmetric reduction of prochiral α-halo ketones. We have also noticed that (*R*,*R*)-1,2-diaminocyclohexane (**255**) provided low enantioselectivity as a catalyst in the borane-mediated asymmetric reduction of prochiral ketones.

EXPERIMENTAL

Melting Points: All melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected.

Elemental Analyses: Elemental analyses were performed on a Thermo Finnigan Flash 1112 analyzer.

Infrared Spectra: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates, peaks are reported in cm^{-1}.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on Bruker-Avance-400 spectrometer. ^{1}H NMR (400 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned, with TMS (δ = 0 ppm) as internal standard. ^{13}C NMR (100 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned, with its middle peak of the triplet (δ = 77.1 ppm) as internal reference. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

Mass Spectral Analysis: Mass spectra were recorded on Shimadzu LCMS 2010A mass spectrometer.

Optical Rotations: Optical rotations were measured on Jasco DIP-370 digital polarimeter at the wavelength of the sodium D-line (589 nm) at ambient temperature, and are reported as follows $[\alpha]_D^T$, concentration (c = g/100 mL), and solvent.

Chromatography: Analytical Thin Layer Chromatography (TLC) was performed on glass plates (7×2 cm) coated with Acme's silica gel GF 254 (254 mμ) containing 13% calcium sulfate as a binder. The spots were visualized by short exposure to UV light or iodine vapor. Column chromatography was carried out using Acme's silica gel (60-120 mesh or 100-200 mesh).

HPLC: High performance liquid chromatography (HPLC) analysis was carried out on Shimadzu LC-10AD Chromatopac equipped with SPD-10A or SPD-10A *VP* UV-VIS detector. The standard UV light of λ-254 nm and the solvents of HPLC grade were used, for determination of enantiomeric purity utilizing chiral columns, Chiralcel-OD H (0.46 x 25 cm) and Chiralcel-OJ H (0.46 x 25 cm) supplied by Daicel, Japan.

X-Ray Crystallography:

Single crystal X-ray data for the respective compounds were collected on a Bruker SMART APEX CCD area detector system [Mo-Kα (λ = 0.71073 Å)] at 298 ^oK, graphite monochromator with a ω scan width 0.3^o, crystal detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the data extraction. In each case, absorption

correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F^2 was carried out using SHELXS-97 (or SHELXTL).

General: All the solvents were dried and distilled using suitable drying agents before use. All the glassware was pre-dried for overnight at 130 ^{o}C in an oven unless otherwise mentioned. All the operations and transfer of reagents were carried out using standard syringe-septum technique under nitrogen atmosphere recommended for handling air sensitive reagents. All reactions were monitored using thin layer chromatography (TLC) unless otherwise mentioned.

(2*S*)-1-(Diphenylphosphoryl)-2-methoxycarbonylpyrrolidine (219):

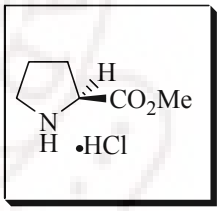
This compound was prepared according to the literature procedure with some modification.[155]

To a stirred solution of (*S*)-proline [**217** (2.3 g, 20 mM)] in MeOH (30 mL) was slowly added thionyl chloride (24 mM, 1.74 mL) dropwise at 0°C and stirred at this temperature for 30 min. The reaction mixture was allowed to warm to room temperature and stirring continued for 30 min at room temperature. Reaction mixture was then heated under reflux for 1 h and then allowed to cool to room temperature. Solvent was removed under reduced pressure to afford the corresponding methyl ester-HCl salt [**218** (3.2 g)] in 97% yield as a colorless solid.

This compound was used as such in the next step without any further purification.

$[\alpha]_D^{25}$: - 31.6 (*c* 1, H_2O)

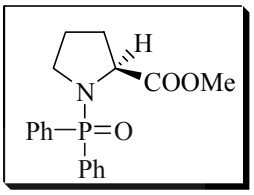
[Lit.[171] $[\alpha]_D^{20}$: -31.0 (*c* 0.5, H_2O)]



IR: ν 3439, 1745 cm^{-1}

To the stirred solution of the crude (*S*)-proline methyl ester hydrochloride (**218**) obtained as above (1.65 g, 10 mM) in THF (20 mL) was added triethylamine (2.02 g, 20 mM) at room temperature. The reaction mixture was cooled to 0 °C and a solution of diphenylphosphinyl chloride (2.36 g, 10 mM) in THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred further 4 h. Salts were removed by filtration and washed with EtOAc (3 × 10 mL). The filtrate and washings were combined and was dried over anhydrous Na_2SO_4 and then concentrated.

The residue thus obtained was purified by column chromatography (silica gel, 60% ethyl acetate in hexanes) to provide the desired compound (**219**) as a colorless solid in 50% (1.65 g) yield.



Mp: 82-84 ^{o}C

$[\alpha]_D^{25}$: + 2.78 (*c* 1.15, $CHCl_3$)

IR: ν 3053, 2949, 1738, 1481 1439, 1213 cm^{-1}

^{31}P NMR: δ 26.34

^{1}H NMR: δ 1.87-2.07 (m, 3H), 2.17-2.33 (m, 1H), 3.19-3.30 (m, 1H), 3.31-3.42 (m, 1H), 3.51 (s, 3H), 4.07-4.20 (m,1H), 7.35-7.59 (m, 6H), 7.73-7.91 (m, 2H), 8.01-8.14 (m, 2H).

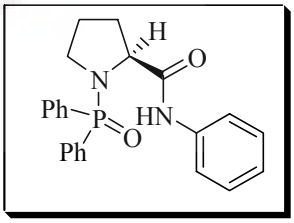
^{13}C NMR: δ 25.77 (d, *J* = 4.9 Hz), 32.20 (d, *J* = 4.2 Hz), 47.55 (d, *J* = 2.3 Hz), 51.86, 59.77 (d, *J* = 3.9 Hz), 128.38 (d, *J* = 12.6 Hz), 128.70 (d, *J* = 12.6 Hz), 131.23 (d, *J* = 22.1 Hz), 131.89 (d, *J* = 2.4 Hz), 131.99 (d, *J* = 2.6 Hz), 132.24 (d, *J* = 9.7 Hz), 132.52 (d, *J* = 27.4 Hz), 132.87 (d, *J* = 9.4 Hz), 174.86 (d, *J* = 4.1 Hz).

(2*S*)-1-(Diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (216):

To a stirred solution of (2*S*)-1-(diphenylphosphoryl)-2-methoxycarbonylpyrrolidine (**219**, 1.65 g, 5 mM) in MeOH (15 mL) was added $LiOH.H_2O$ (0.46 g, 11 mM) at room temperature. The reaction mixture was heated under reflux for 24 h. Then the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue thus obtained was diluted with water (3 mL) and dil. HCl

was added until *p*H became 2 and was extracted by EtOAc (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated to give the desired compound (**220**) as colorless solid. The resulting crude compound was used as such without any further purification for the next step.

To a stirred solution of (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid (**220** 0.946 g, 3 mM) in THF (20 mL) was added triethylamine (0.303 g) at room temperature and cooled to 0 ^oC. Ethyl chloroformate (0.325 g, 3 mM) was added at this temperature dropwise and stirring was continued for 30 min at 0 ^oC. Aniline (0.279 g, 3mM) was then added (in 2 mL of THF) dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued for further 12 h. Solvent was removed under reduced pressure and the residue thus obtained was dissolved in EtOAc (30 mL) and washed successively with 10% aq. HCl (5 mL) and with saturated aq. $NaHCO_3$ (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated. The residue, thus obtained, was purified by column chromatography (silica gel, 70% ethyl acetate in hexanes) to provide the desired compound (**216**) as a colorless solid in 76% (0.89 g) yield.



Mp : 190-192 ^oC

$[\alpha]_D^{25}$: - 107.65 (*c* 1.15, $CHCl_3$)

IR : ν 3300-3000 (multiple bands), 1684, 1601, 1498, 1300 cm^{-1}

^{31}P NMR: δ 28.37

^{1}H NMR: δ 1.90-1.98 (m, 2H), 1.99-2.12 (m, 1H), 2.51-2.62 (m, 1H), 3.13-3.28 (m, 2H), 4.15-4.23 (m, 1H), 7.06-7.13 (m, 1H), 7.28-7.36 (m, 2H), 7.43-7.59 (m, 6H), 7.67 (d, 2H, J = 7.6 Hz), 7.77-7.90 (m, 4H), 10.20 (bs, 1H).

^{13}C NMR: δ 25.12 (d, J = 6.7 Hz), 30.43 (d, J = 6.4 Hz), 48.28 (d, J = 3.6 Hz), 62.76 (d, J = 2.6 Hz), 119.70, 124.01, 128.83, 128.89, 128.96, 129.09, 129.84 (d, J = 36.7 Hz), 131.10 (d, J = 40.4 Hz), 132.05 (d, J = 2.5 Hz), 132.15 (d, J = 2.0 Hz), 132.49 (d, J = 2.4 Hz), 132.54 (d, J = 3.0 Hz), 138.55, 170.96.

LCMS (m/z): 391 $(M+H)^+$

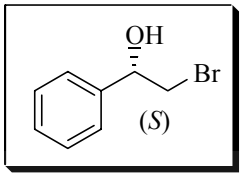
Anal. calcd. for $C_{23}H_{23}N_2O_2P$: C, 70.76; H, 5.94; N, 7.18.

Found: C, 70.77; H, 5.99; N, 7.49.

Asymmetric reduction of phenacyl bromide (221a) using 10 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (216): Synthesis of (*S*)-2-bromo-1-phenylethanol [(*S*)-222a]: Representative procedure:

To a stirred solution of (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**, 0.058 g, 0.15 mM) in toluene (2 mL) was added $BH_3.SMe_2$ (1 mM, 1 mL, 1 M solution in toluene) at room temperature and the reaction mixture was heated under reflux for 15 min. Then a solution of phenacyl bromide (**221a**) (1 mM, 0.199 g), in toluene (2 mL), was added dropwise and heated under reflux for further 30 minutes. The reaction mixture was cooled to room temperature and quenched with MeOH. Solvent was removed under

reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] as colorless oil.



Yield: 84% (0.168 g)

$[\alpha]_D^{25}$: + 39.51 (*c* 0.83, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 89% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±) 222a**]

IR (neat): ν 3431 cm^{-1}

^{1}H NMR: δ 2.72 (s, 1H), 3.48-3.66 (m, 2H), 4.82-4.95 (m, 1H), 7.26-7.42 (m, 5H).

^{13}C NMR: δ 40.22, 73.87, 126.04, 128.53, 128.75, 140.38.

Determination of enantiomeric purity:

Racemic alcohol (±)-**222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.16 min and 9.81 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 94.5:5.5 [retention times: 8.15 min (*S*) and 9.82 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 89%.

(±)-2-Bromo-1-phenylethanol [(±)-222a]:

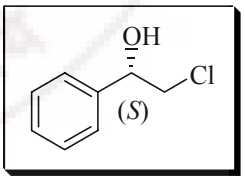
To a stirred solution of phenacyl bromide (**221a**) (0.398 g, 2 mM) in toluene (10 mL) was

added BH_3**.**SMe_2 (0.152 g, 2 mM) and heated under reflux for 2 h. The reaction mixture was allowed to come to room temperature and methanol (4 ml) was added carefully. The solvent was removed under reduced pressure and the residue, thus obtained, was subjected to column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the title compound as colorless oil in 90% (0.18 g) isolated yield. The spectral data (IR, ^{1}H & ^{13}C NMR) of this compound are in full agreement with that of the chiral compound **(*S*)-222a**

All the required racemic alcohols* (222a-g) *were prepared following the above-mentioned procedure. The spectral data (IR, ^{1}H & ^{13}C NMR) of these alcohols are in full agreement with that of chiral alcohols.

(*S*)-2-Chloro-1-phenylethanol [**(S)-222b**]**:**

This compound was obtained *via* asymmetric reduction of phenacyl chloride (**221b**) with BH_3.SMe_2 in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilino carbonylpyrrolidine (**216**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a**.



Yield: 83%

$[\alpha]_D^{25}$: + 33.24 (*c* 0.74, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 88% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

IR (neat): ν 3393 cm^{-1}

^{1}H NMR: δ 2.68 (s, 1H), 3.45-3.71 (m, 2H), 4.70-4.85 (m, 1H), 7.18-7.35, (m, 5H).

^{13}C NMR: δ 50.91, 74.13, 126.12, 128.51, 128.72, 140.01.

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min;] of racemic alcohol **(±)-222b** showed two peaks at retention times: 7.82 min and 8.50 min in 1:1 ratio arising from *S* and *R* enantiomers. Chiral alcohol **(*S*)-222b** showed two peaks in 94:6 ratio [retention times: 7.81 min (*S*) and 8.49 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 88%.

Tetrabutylammonium tribromide (TBA Br_3):

This compound was prepared according to the known procedure.[157]

Tetrabutylammonium bromide (32.24 g, 100 mM) and sodium bromate (5.13 g, 34 mM) were dissolved in 200 mL water. Hydrobromic acid (48%, 24 mL) was added dropwise to this solution with stirring at room temperature. After 10 minutes, the orange precipitate formed, was filtered and recrystallized from ether-dichloromethane (1:1) to provide TBA Br_3 as orange crystals.

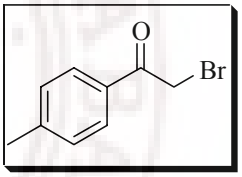
Yield: 90% (43.49 g)

Mp: 73-74 ^oC (Lit.[157] 74-75 ^oC)

4-Methylphenacyl bromide (221c):

This compound was prepared following the literature method.[157]

To a stirred solution of 4-methylacetophenone (0.54 g, 4 mM) in dichloromethane (50 mL)-methanol (20 mL) was added TBA Br_3 (2.12 g, 4.4 mM) at room temperature. The reaction mixture was stirred for 5 h at 35 ^oC (until decoloration of the orange solution). The solvent was evaporated. The residue, thus obtained, was extracted with ether (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained was recrystallized from ethanol to provide the 4-methylphenacyl bromide (**221c**) as a colorless solid.



Yield: 0.61 g (72%)

Mp: 49-51 ^oC[Lit.[157] 45-48 ^oC]

IR (KBr): ν 1697 cm^{-1}

^1H NMR: δ 2.42 (s, 3H), 4.44 (s, 2H), 7.28 (d, 2H, J = 8.0 Hz), 7.87 (d, 2H, J = 8.4 Hz).

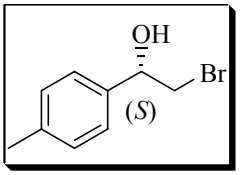
^{13}C NMR: δ 21.79, 31.00, 129.10, 129.60, 131.54, 145.06, 191.00.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-222c]:

Asymmetric reduction of 4-methylphenacyl bromide (**221c**) using $BH_3.SMe_2$ under the influence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**), provided the title compound as a colorless liquid, following the similar procedure described for the compound **(*S*)-222a**.

Yield: 87%

$[\alpha]_D^{25}$: + 31.97 (*c* 0.91, $CHCl_3$)



[Lit.[132] $[\alpha]_D^{25}$: + 41.8 (*c* 1.00, $CHCl_3$), (*S*)-configuration, 95% *ee*]

Enantiomeric purity: 87% (determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222c**)

IR (neat): ν 3348 cm^{-1}

^{1}H NMR: δ 2.34 (s, 3H), 2.60 (s, 1H), 3.47-3.66 (m, 2H), 4.81-4.94 (m, 1H), 7.18 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR: δ 21.24, 40.33, 73.77, 125.97, 129.44, 137.44, 138.37.

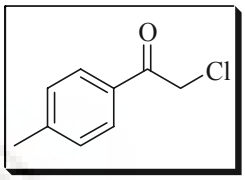
Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min] of the racemic compound **(±)-222c** with retention times 15.69 min (*S*) and 17.77 min (*R*). The chiral alcohol **(*S*)-222c** showed two peaks at 15.89 min (*S*) and 18.02 min (*R*) in the ratio of 93.5:6.5 on similar HPLC analysis indicating that the reaction is 87% enantioselective.

4-Methylphenacyl chloride (221d):

Chloroacetyl chloride (5.64 g, 50 mM) was added carefully to a stirred suspension of aluminium chloride (1.33 g, 10 mM) in toluene (30 mL) at 10 ^oC over a period of 15 min. and the reaction mixture was heated at 50 ^oC for 2 h. Then the reaction mixture was

cooled to 0 ^{o}C. Ice-cold water (16 mL) was added carefully and then extracted with ether (3 X 100 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was recrystallized from ether-hexanes mixture (1:5) to provide the title compound (**221d**) as a colorless solid.



Yield: 30% (2.52 g)

Mp: 50-52 ^{o}C

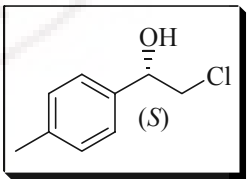
IR (KBr): ν 1699 cm^{-1}

^{1}H NMR: δ 2.42(s, 3H); 4.67(s, 2H); 7.28 (d, 2H, J = 8.0Hz); 7.84 (d, 2H, J = 8.0Hz).

^{13}C NMR: δ 21.77; 45.98; 128.67; 129.61; 131.81; 145.08; 190.74.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-222d]:

This secondary alcohol was obtained as a colorless liquid by $BH_3.SMe_2$ mediated reduction of 4-methylphenacyl chloride (**221d**) in the presence of 15 mol% chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) following the similar procedure described for the compound **(*S*)-222a**.



Yield: 85%

$[\alpha]_D^{25}$: + 40.06 (*c* 1.61, $CHCl_3$)

{Lit.[132] $[\alpha]_D^{25}$: + 47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*}

Enantiomeric purity: 85% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222d**]

IR (Neat) : ν 3481 cm^{-1}

^{1}H NMR: δ 2.34 (s, 3H), 2.70 (s, 1H), 3.58-3.75 (m, 2H), 4.81-4.90 (m, 1H), 7.17 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz).

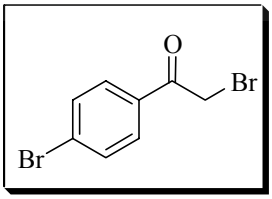
^{13}C NMR: δ 21.21, 50.92, 74.04, 126.05, 129.39, 137.11, 138.35.

Determination of enantiomeric purity:

Racemic alcohol **(±)-222d** and chiral alcohol [**(*S*)-222d**] were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (97.5:2.5); flow rate: 0.9 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 15.54 min and 17.26 min due to *S* and *R* enantiomers. The chiral alcohol [**(*S*)-222d**] showed two peaks in the ratio of 92.5:7.5 [retention times: 15.43 min (*S*) and 17.19 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 85%.

4-Bromophenacyl bromide (221e):

Bromination of 4-bromoacetophenone with TBA Br_3 following the similar procedure described for the compound **221c** (Page no. 107) provided the title compound as colorless crystals.



Time: 6 h

Yield: 76%

Mp: 106-108 ^{o}C (Lit.[157] 107.5-108 ^{o}C)

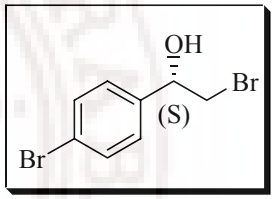
IR (KBr): ν 1699 cm^{-1}

^{1}H NMR: δ 4.39 (s, 2H), 7.67(d, 2H, *J* = 8.4 Hz) 7.85 (d, 2H, *J* = 8.4 Hz).

^{13}C NMR: δ 30.39, 129.37, 130.49, 132.30, 132.74, 190.48.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-222e]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-bromophenacyl bromide (**221e**) in the presence of (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine, (**216**, 15 mol%) furnished the chiral alcohol [**(*S*)-222e**] as a colorless liquid following the method described for the compound [**(*S*)-222a**].



Yield: 82%

Mp: 68-70 °C (Lit.[159] 70-72 °C)

$[\alpha]_D^{25}$: + 28.82 (*c* 1.02, $CHCl_3$)

{Lit.[159] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

Enantiomeric purity: 88% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-222e**]

IR (Neat) : ν 3302 cm^{-1}

^{1}H NMR: δ 2.76 (bs, 1H), 3.45-3.54 (m, 1H), 3.57-3.63 (m, 1H), 4.83-4.93 (m, 1H), 7.26 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR: δ 39.86, 73.16, 122.41, 127.74, 131.86, 139.32.

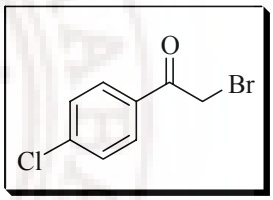
Determination of enantiomeric purity:

Racemic alcohol **(±)-222e** showed two peaks in equal intensity on HPLC analysis [chiral

column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 20.86 min and 23.06 min] due to *R* and *S* enantiomers. Chiral alcohol [**(*S*)-222e**] showed two peaks in 6:94 ratio [retention times: 21.49 min (*R*) and 23.75 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 88%.

4-Chlorophenacyl bromide (221f):

This compound was obtained as colorless crystals *via* the treatment of 4-chloroacetophenone with TBA Br_3 following the similar procedure described for the compound **221c** (Page no. 107).



Time: 6 h

Yield: 79%

Mp: 92-94 ^{o}C (Lit.[157] 97-97.5 ^{o}C)

IR (KBr): ν 1697 cm^{-1}

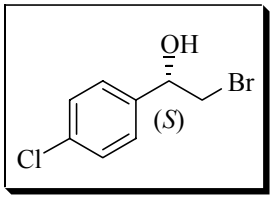
^{1}H NMR: δ 4.40 (s, 2H), 7.46 (d, 2H, J = 8.4 Hz), 7.95 (d, 2H, J = 8.4 Hz).

^{13}C NMR: δ 30.40, 129.32, 130.45, 132.36, 140.63, 190.30.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-222f]:

This compound was obtained *via* asymmetric reduction of 4-chlorophenacyl bromide (**221f**) with $BH_3.SMe_2$ in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a**.

Yield: 86%



Mp: 46-48 ^{o}C

$[\alpha]_D^{25}$: + 33.54 (*c* 0.96, $CHCl_3$)

[Lit.[132] $[\alpha]_D^{25}$: + 38.60 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91%*ee*]

Enantiomeric purity: 86% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-222f**]

IR (neat): ν 3244 cm^{-1}

^{1}H NMR: δ 2.67 (d, 1H, *J* = 3.2 Hz), 3.45-3.67 (m, 2H), 4.86-4.96 (m, 1H), 7.29-7.41 (m, 4H).

^{13}C NMR: δ 40.02, 73.17, 127.45, 128.95, 134.33, 138.82.

Determination of enantiomeric purity:

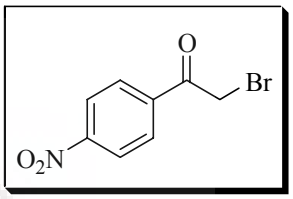
HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.75 mL/min] of the racemic compound **(±)-222f** showed two peaks at 24.94 min (*R*) and 27.18 min (*S*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-222f** showed two peaks at 25.37 min (*R*) and 27.50 min (*S*) in the ratio of 7:93 indicating that the reaction is 86% enantioselective.

4-Nitrophenacyl bromide (221g):

This compound was prepared following the literature procedure.[158]

4-Nitroacetophenone (1.65 g, 10 mM) was dissolved in glacial acetic acid (8 mL). Bromine (0.5 mL, 10 mM) was added slowly with stirring at the same temperature. After

stirring for 12 h, the reaction mixture was diluted with ice-cold water (10 mL), and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography to obtain light yellow solid of **221g**.



Yield: 69% (1.68 g)

Mp: 90-92 °C [lit.[157] 96-96.5 °C]

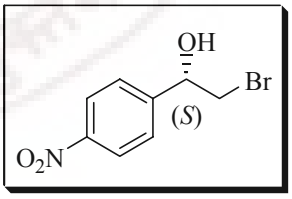
IR (KBr): ν 1703 cm^{-1}

^{1}H NMR: δ 4.47 (s, 2H), 8.16 (d, 2H, J = 8.8Hz), 8.35 (d, 2H, J = 8.8Hz).

^{13}C NMR: δ 30.20, 124.10, 130.14, 138.46, 150.78, 189.97.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-222g]:

Asymmetric reduction of 4-nitrophenacyl bromide (**221g**) using $BH_3.SMe_2$ under the influence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a**.



Yield: 80%

Mp: 80-82 °C [Lit.[134] 78-80 °C]

$[\alpha]_D^{25}$: + 23.37 (*c* 0.89, $CHCl_3$)

[Lit.[133] $[\alpha]_D^{25}$: + 32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*]

Enantiomeric purity: 84% [determined by HPLC analysis of acetate (*S*)-**223** using chiral column, Chiralcel-OD H, with reference to racemic acetate **(±)-223**]

IR (KBr): ν 3547 cm^{-1}

^{1}H NMR: δ 2.87 (d, 1H, J = 3.2 Hz), 3.48-3.58 (m, 1H), 3.65-3.74 (m, 1H) 5.04-5.10 (m, 1H), 7.59 (d, 2H, J = 8.8 Hz), 8.24 (d, 2H, J = 8.6 Hz).

^{13}C NMR: δ 39.42, 72.74, 123.93, 127.02, 147.37, 147.91.

Determination of enantiomeric purity:

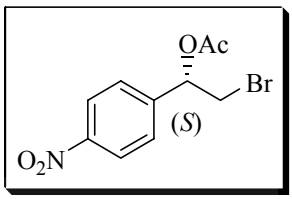
Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 10.86 min and 12.14 min] due to *R* and *S* enantiomers for racemic acetate **(±) 223**. The chiral acetate **(*S*)-223** showed two peaks in the ratio of 8:92 [retention times: 10.83 min (*R*) and 12.08 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 84%.

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-223]:

This compound was prepared according to the known procedure[156]

To a stirred solution of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [**(*S*)-222g**] (0.123 g, 0.5 mM) and acetic anhydride (29 mL) was added pyridine (5.85 mL) and stirred for 10 h at room temperature. The reaction mixture was diluted with water (80 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively with 5% HCl and 10% sodium bicarbonate solution and was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Residue thus obtained was purified by column

chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the title compound as colorless solid.



Mp: 100-102 °C [Lit.[134] 102-105 °C]

Yield: 76% (0.109 g)

$[\alpha]_D^{25}$: + 32.28 (*c* 1.18, $CHCl_3$)

[Lit.[134] $[\alpha]_D^{25}$: + 46.6 (*c* 0.9, $CHCl_3$), (*S*)-configuration, 92% *ee*]

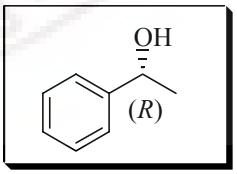
IR (KBr): ν 1747 cm^{-1}

^1H NMR: δ 2.17 (s, 3H), 3.58-3.70 (m, 2H), 6.01-6.06 (m, 1H), 7.55 (d, 2H, *J* = 8.8 Hz), 8.24 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR: δ 20.91, 33.43, 73.66, 123.98, 127.70, 144.58, 148.13, 169.63.

(*R*)-1-Phenylethanol [(*R*)-225a]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of acetophenone (**224a**) in the presence of chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) (15 mol%), following the similar procedure described for the compound **(*S*)-222a**.



Yield: 80%

$[\alpha]_D^{25}$: + 32.80 (*c* 0.87, MeOH)

[Lit.[160] $[\alpha]_D^{25}$: + 44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 74% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-225a**]

IR (neat): ν 3371 cm^{-1}

^{1}H NMR: δ 1.50 (d, 3H, J = 6.8 Hz), 1.92 (br, 1H), 4.90 (q, 1H, J = 6.4 Hz), 7.24-7.42 (m, 5H).

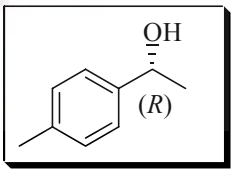
^{13}C NMR: δ 25.21, 70.49, 125.45, 127.55, 128.57, 145.87.

Determination of enantiomeric purity:

Racemic alcohol **(±)-225a** and chiral alcohol **(*R*)-225a** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.30 min and 9.85 min due to (*R*) and (*S*) enantiomers. The chiral alcohol **(*R*)-225a** showed two peaks in the ratio of 87:13 [retention times: 8.29 min (*R*) and 9.83 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 74%.

(*R*)-1-(4-Methylphenyl)ethanol [(*R*)-225b]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-methylacetophenone (**224b**) in the presence of (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine, (15 mol%) furnished the chiral alcohol [**(*R*)-225b**] as a colorless liquid following the method described for the compound [**(*S*)-222a**].



Yield: 84%

$[\alpha]_D^{25}$: + 29.51 (*c* 0.72, MeOH)

[Lit.[161] $[\alpha]_D^{26}$: -43.5 (*c* 0.99, MeOH), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 75% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol [**(±)-225b**]

IR (neat): ν 3385 cm^{-1}

^1H NMR: δ 1.45 (d, 3H, J = 6.4 Hz), 2.09 (bs, 1H), 2.33 (s, 3H), 4.82 (q, 1H, J = 6.4 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz).

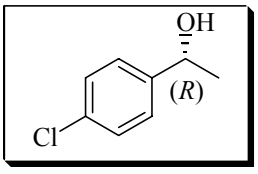
^{13}C NMR: δ 21.12, 25.09, 70.23, 125.40, 129.17, 137.13, 142.93.

Determination of enantiomeric purity:

Racemic alcohol **(±)-225b** and chiral alcohol **(*R*)-225b** were analysed on HPLC using chiral column, Chiralcel-OJ H [solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min]; The racemic alcohol showed two peaks of equal intensities at retention times: 14.13 min and 16.00 min due to *S* and *R* enantiomers. The chiral alcohol **(*R*)-225b** showed two peaks in the ratio of 12.5:87.5 [retention times: 14.74 min (*S*) and 16.79 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 75%.

(*R*)-1-(4-Chlorophenyl)ethanol [(*R*)-225c]:

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of 4-chloroacetophenone (**224c**) with $BH_3.SMe_2$ in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**) [following the similar procedure described for the compound **(*S*)-222a**].



Yield: 83%

$[\alpha]_D^{25}$: + 27.45 (*c* 0.85, Et_2O)

[Lit.[161] $[\alpha]_D^{25}$: - 49.0 (*c* 1.84, Et_2O), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 73% [determined by HPLC analysis of its alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225c**].

IR (neat): ν 3420 cm^{-1}

^{1}H NMR: δ 1.45 (d, 3H, *J* = 6.8 Hz), 2.14 (br, 1H), 4.83(q, 1H, *J* = 6.4 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz).

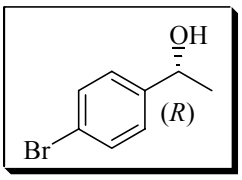
^{13}C NMR: δ 25.31, 69.78, 126.85, 128.65, 133.10, 144.30.

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min] of the racemic compound **(±)-225c** showed two peaks at 13.92 min (*S*) and 14.85 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-225c** showed two peaks at 13.98 min (*S*) and 14.92 min (*R*) in the ratio of 13.5:86.5 indicating that the reaction is 73% enantioselective.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

This compound was obtained *via* asymmetric reduction of 4-bromoacetophenone (**224d**) with $BH_3.SMe_2$ in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (**216**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a**.



Yield: 84%

$[\alpha]_D^{25}$: + 30.99 (*c* 0.95, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 74% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

IR (neat): ν 3360 cm^{-1}

^{1}H NMR: δ 1.45 (d, 3H, *J* = 6.8 Hz), 2.23 (br, 1H), 4.82 (q, 1H, *J* = 6.4 Hz), 7.22 (d, 2H, *J* = 7.2 Hz), 7.45 (d, 2H, *J* = 7.2 Hz).

^{13}C NMR: δ 25.25, 69.76, 121.16, 127.20, 131.57, 144.80.

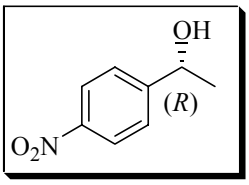
Determination of enantiomeric purity:

Racemic alcohol **(±)-225d** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min; retention times: 15.34 min and 16.48 min] due to *S* and *R* enantiomers. The chiral alcohol **(*R*)-225d** showed two peaks in the ratio of 13:87 [retention times: 15.34 min (*S*) and 16.44 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 74%.

(*R*)-1-(4-Nitrophenyl)ethanol [(*R*)-225e]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-nitroacetophenone (**224e**) in the presence of (2*S*)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine, (15 mol%) furnished the chiral alcohol **(*R*)-225e** as a colorless liquid following the method described for the compound **(*S*)-222a**.

Yield: 81%



$[\alpha]_D^{25}$: + 24.32 (*c* 0.92, EtOH)

[Lit.[162] $[\alpha]_D^{24.5}$: - 29.7 (*c* 1.0, EtOH)

(*S*)-configuration, >99% *ee*]

Enantiomeric purity: 70% [determined by HPLC analysis of corresponding acetate **(*R*)-226** using chiral column, Chiralcel-OD H, with reference to its racemic acetate **(±)-226**]

IR (neat): ν 3406 cm^{-1}

^{1}H NMR: δ 1.51 (d, 3H, *J* = 6.4 Hz), 2.42 (br, 1H), 4.95-5.07 (m, 1H), 7.53 (d, 2H, *J* = 8.8 Hz), 8.18 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR: δ 25.49, 69.49, 123.77, 126.17, 147.17, 153.21.

Determination of enantiomeric purity:

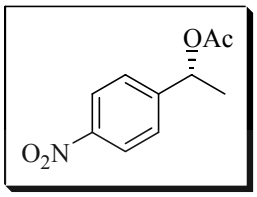
Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (98:2); flow rate: 0.5 mL/min; retention times: 20.05 min and 21.17 min] due to *S* and *R* enantiomers for racemic acetate **(±)-226**. The chiral acetate **(*R*)-226** showed two peaks in the ratio of 15:85 [retention times: 20.27 min (*S*) and 21.47 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 70%.

(*R*)-1-Acetoxy-1-(4-nitrophenyl)ethane [(*R*)-226]:

This compound was prepared as a colorless liquid *via* the reaction of (*R*)-1-(4-nitrophenyl)

ethanol [**(*R*)-225e**] with acetic anhydride in presence of pyridine following the similar procedure as described for the compound **(*S*)-223** (Page no 115).

Yield: 83 %



$[\alpha]_D^{25}$: + 70.23 (*c* 0.84, $CHCl_3$)

{Lit.[172] $[\alpha]_D^{25}$: +99.2 (c 1.4, $CHCl_3$), (*R*)-configuration, >99% *ee*}

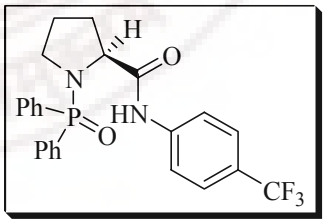
IR (KBr): ν 1743 cm^{-1}

^{1}H NMR: δ 1.55 (d, 3H, *J* = 6.4 Hz), 2.11 (s, 3H), 5.92(q, 1H, *J* = 6.4 Hz), 7.51 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR: δ 21.18, 22.29, 71.30, 123.89, 126.81, 147.52, 149.05, 170.10.

(2*S*)-1-(Diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine (227):

This compound was obtained from (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid (**220)** following the similar procedure described for the compound **216** (Page no 101).



Yield : 85.2%

Mp : 146-148 ^oC

$[\alpha]_D^{25}$: - 107.17(*c* 1.11, $CHCl_3$)

IR : ν 3250-2800 (multiple bands), 1699, 1610, 1552 cm^{-1}

^{31}P NMR: δ 29.51

^{1}H NMR: δ 1.86-2.12 (m, 3H), 2.54-2.68 (m, 1H), 3.09-3.28 (m, 2H), 4.21-4.34 (m, 1H), 7.44-7.64 (m, 8H), 7.74-7.93 (m, 6H), 10.87 (bs, 1H).

^{13}C NMR: δ 25.14 (d, J = 6.8 Hz), 30.12 (d, J = 6.3 Hz), 48.68 (d, J = 3.7 Hz), 62.45, 119.26, 124.31 (q, J = 268.8), 125.49 (q, J = 32.7), 126.05 (d, J = 3.6 Hz), 128.87*, 129.01*, 129.15*, 129.58 (d, J = 46.1 Hz), 130.84 (d, J = 50.6 Hz), 131.97 (d, J = 2.7 Hz), 132.07 (d, J = 1.9 Hz), 132.66, 141.85, 171.52.

LCMS (m/z): 459 $(M+H)^+$

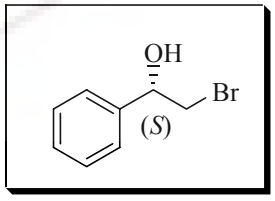
Anal. calcd. for $C_{24}H_{22}F_3N_2O_2P$: C, 62.88; H, 4.84; N, 6.11.

Found: C, 62.81; H, 4.88; N, 6.18.

** Some of these peaks may be due to fluorine coupling.*

(*S*)-2-Bromo-1-phenylethanol [(*S*)-222a]:

This compound was obtained *via* asymmetric reduction of phenacyl bromide (**221**) with $BH_3.SMe_2$ in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoro-methylanilino)carbonylpyrrolidine (**227**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a** (Page no. 103).



Yield: 87%

$[\alpha]_D^{25}$: + 35.18 (*c* 1.20, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

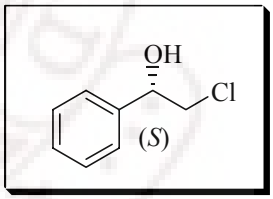
Enantiomeric purity: 84% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±) 222a**]

Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.85 min and 9.93 min] due to *S* and *R* enantiomers for racemic alcohol **(±) 222a**. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 92:8 [retention times: 8.87 min (*S*) and 9.96 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 84%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

Asymmetric reduction of phenacyl chloride (**221b**) using $BH_3.SMe_2$ under the influence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine (**227**) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page no 103).



Yield: 85%

$[\alpha]_D^{25}$: + 37.94 (*c* 1.02, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 81% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

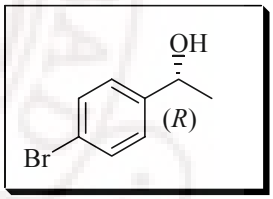
Racemic alcohol **(±)-222b** and chiral alcohol **(*S*)-222b** were analysed on HPLC using

chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.64 min and 9.19 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222b** showed two peaks in the ratio of 90.5:9.5 [retention times: 8.68 min (*S*) and 9.25 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 81%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of 4-bromoacetophenone (**224d**) in the presence of chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-(4-trifluoromethylanilino)carbonylpyrrolidine (**227**) (15 mol%), following the similar procedure described for the compound **(*S*)-222a** (Page no 103).

Yield: 85%



$[\alpha]_D^{25}$: + 26.96 (*c* 1.33, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 74% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

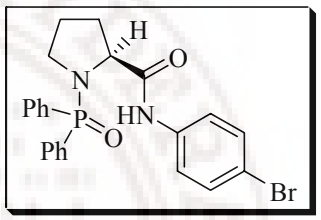
Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min] of the racemic compound **(±)-225d** showed two peaks at 16.18 min (*S*) and 17.68 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-225d**

showed two peaks at 16.17 min (*S*) and 17.66 min (*R*) in the ratio of 13:87 indicating that the reaction is 74% enantioselective.

(2*S*)-1-(Diphenylphosphoryl)-2-(4-bromoanilino)carbonylpyrrolidine (228):

This compound was prepared from (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid **(220)** following the similar procedure mentioned for the compound **216** (Page no 101).



Yield : 83%

Mp : 74-76 ^{o}C

$[\alpha]_D^{25}$: - 120.45 (*c* 1.10, $CHCl_3$)

IR : ν 3250-2870 (multiple bands), 1693, 1543, 1487, 1182 cm^{-1}

^{31}P NMR: δ 29.02

^{1}H NMR: δ 1.86-2.12 (m, 3H), 2.53-2.65 (m, 1H), 3.10-3.29 (m, 2H), 4.16-4.26 (m, 1H), 7.38-7.66 (m, 10H), 7.75-7.88 (m, 4H), 10.53 (bs, 1H).

^{13}C NMR: δ 25.11 (d, *J* = 6.9 Hz), 30.18 (d, *J* = 6.6 Hz), 48.47 (d, *J* = 3.7 Hz), 62.67, 116.45, 121.23, 128.88, 129.01, 129.14, 129.62 (d, *J* = 45.3 Hz), 130.88 (d, *J* = 49.9 Hz), 131.80, 132.00 (d, *J* = 3.2 Hz), 132.10 (d, *J* = 2.4 Hz), 132.63, 137.81, 171.05.

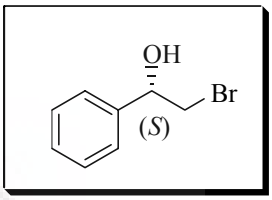
LCMS (m/z): 470 $(M+H)^+$

Anal. calcd. for $C_{23}H_{22}BrN_2O_2P$: C, 58.86; H, 4.72; N, 5.97.

Found: C, 58.81; H, 4.78; N, 5.93.

(*S*)-2-Bromo-1-phenylethanol [(*S*)-222a]:

Borane-dimethylsulfide mediated asymmetric reduction of phenacyl bromide (**221a**) in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)carbonyl-pyrrolidine **(228)** furnished the chiral alcohol as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a** (Page no 103).



Yield: 84%

$[\alpha]_D^{25}$: + 35.04 (*c* 1.09, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 86% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±) 222a**]

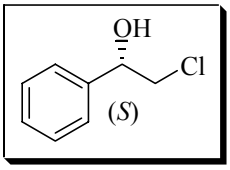
Determination of enantiomeric purity:

Racemic alcohol **(±) 222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 9.21 min and 9.81 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 93:7 [retention times: 9.13 min (*S*) and 9.72 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 86%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

This compound was obtained *via* asymmetric reduction of phenacyl chloride (**221b**) with $BH_3.SMe_2$ in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)carbonylpyrrolidine (**228**), as a colorless liquid following the procedure

described for the compound **(*S*)-222a** (Page no 103).



Yield: 86%

$[\alpha]_D^{25}$: + 39.33 (*c* 0.90, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 84% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

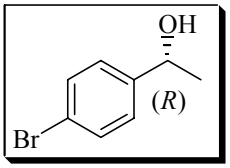
Racemic alcohol **(±)-222b** and chiral alcohol **(*S*)-222b** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.24 min and 8.72 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222b** showed two peaks in the ratio of 92:8 [retention times: 8.72 min (*S*) and 9.28 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 84%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

Asymmetric reduction of 4-bromoacetophenone (**224d**) using $BH_3.SMe_2$ under the influence of chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-(4-bromoanilino)-carbonylpyrrolidine (**228**) (15 mol%), provided the title compound as a colorless liquid, following the similar procedure described for the compound **(*S*)-222a** (Page no 103).

Yield: 85%

$[\alpha]_D^{25}$: + 27.24 (*c* 1.09, $CHCl_3$)



[Lit.[161] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 77% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

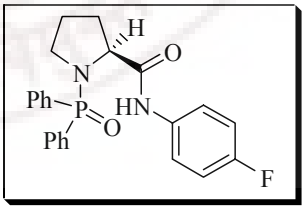
Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min] of the racemic compound **(±)-225d** showed two peaks at 16.19 min (*S*) and 17.05 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-225d** showed two peaks at 16.35 min (*S*) and 17.09 min (*R*) in the ratio of 11.5:88.5 indicating that the reaction is 77% enantioselective.

(*S*)-1-(Diphenylphosphoryl)-2-(4-fluoroanilino)carbonylpyrrolidine (229):

This compound was obtained from (2*S*)-1-(diphenylphosphoryl)pyrrolidine-2-carboxylic acid **(220)** following the similar method described for the compound **216** (page no 101)

Yield : 84%



Mp : 184-186 ^oC

$[\alpha]_D^{25}$: - 114.87 (*c* 1.21, $CHCl_3$)

IR : ν 3252-2870 (multiple bands), 1687, 1618, 1558, 1209 cm^{-1}

^{31}P NMR: δ 28.69

^{1}H NMR: δ 1.87-2.13 (m, 3H), 2.51-2.67 (m, 1H), 3.12-3.31 (m, 2H), 4.18-4.28 (m, 1H), 6.95-7.09 (m, 2H), 7.42-7.61 (m, 6H), 7.62-7.73 (m, 2H), 7.78-7.94 (m, 4H), 10.40 (bs, 1H).

^{13}C NMR δ 25.10 (d, J = 6.8 Hz), 30.36 (d, J = 6.7 Hz), 48.38 (d, J = 3.6 Hz), 62.62, 115.41 (d, J = 22.2 Hz), 121.26 (d, J = 7.3 Hz), 128.83, 128.97, 129.10, 129.70 (d, J = 40.9 Hz), 130.97 (d, J = 45.1 Hz), 132.02, 132.11, 132.57 (unresolved multiplet), 134.71 (d, J = 2.6 Hz), 159.21(d, J = 241.2 Hz), 170.90.

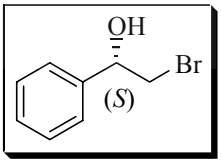
LCMS (m/z): 409 $(M+H)^+$

Anal. calcd. for $C_{23}H_{22}FN_2O_2P$: C, 67.64; H, 5.43; N, 6.86

Found: C, 67.61; H, 5.48; N, 6.90.

(*S*)-2-Bromo-1-phenylethanol [(*S*)-222a]:

This secondary alcohol was obtained as a colorless liquid by $BH_3.SMe_2$ mediated reduction of phenacyl bromide (**221a**) in the presence of chiral catalyst of (2*S*)-1-(diphenylphosphoryl)-2-(4-fluoroanilino)carbonylpyrrolidine (**229**, 15 mol%), following the procedure mentioned for the compound **(*S*)-222a** (Page no 103).



Yield: 86%

$[\alpha]_D^{25}$: + 35.38 (*c* 1.30, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: -39.0

(*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

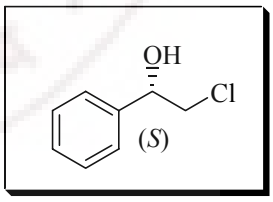
Enantiomeric purity: 84% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol (±)-**222a**]

Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 9.17 min and 9.76 min] due to *S* and *R* enantiomers for racemic alcohol **(±)-222a**. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 92:8 [retention times: 9.12 min (*S*) and 9.73 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 84%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

$BH_3.SMe_2$ mediated asymmetric reduction of phenacyl chloride (**221b**) in the presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-fluoroanilino)carbonylpyrrolidine (**229**), furnished the chiral alcohol **[(*S*)-222b]** as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page no 103).



Yield: 87%

$[\alpha]_D^{25}$: + 38.66 (*c* 1.05, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

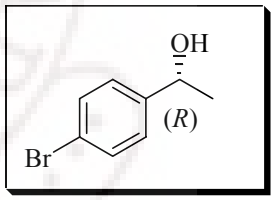
Enantiomeric purity: 86% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222b** and chiral alcohol **[(*S*)-222b]** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.70 min and 9.27 min due to *S* and *R* enantiomers. The chiral alcohol **[(*S*)-222b]** showed two peaks in the ratio of 93:7 [retention times: 8.69 min (*S*) and 9.27 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 86%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

This compound was obtained *via* asymmetric reduction of 4-bromoacetophenone (**224d**) with $BH_3.SMe_2$ in presence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(4-fluoro-anilino)carbonylpyrrolidine (**229**) as a colorless liquid, following the similar procedure described for the compound **(*S*)-222a** (Page no 103).



Yield: 84%

$[\alpha]_D^{25}$: + 27.72 (*c* 1.32, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 72% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

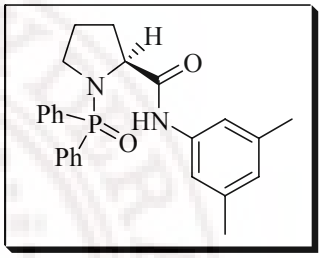
Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min] of the racemic compound **(±)-225d** showed two peaks at 15.87 min (*S*) and 17.31 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-225d**

showed two peaks at 15.95 min (*S*) and 17.34 min (*R*) in the ratio of 14:86 indicating that the reaction is 72% enantioselective.

(2*S*)-1-(Diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine (230):

The above mentioned compound was prepared from (2*S*)-1-(diphenylphosphoryl)-pyrrolidine-2-carboxylic acid **(220)** according to the procedure described for the compound **216** (Page no 101).



Yield : 81%

Mp : 70-72 ^{o}C

$[\alpha]_D^{25}$: - 120.62 (*c* 1.11, $CHCl_3$)

IR : ν 3277-2868 (multiple bands), 1693,1616, 1568,1122 cm^{-1}

^{31}P NMR: δ 28.61

^{1}H NMR: δ 1.86-2.12 (m, 3H), 2.31(s, 6H), 2.51-2.62 (m, 1H), 3.14-3.32 (m, 2H), 4.14-4.25 (m, 1H), 6.75 (s, 1H), 7.35 (s, 2H), 7.43-7.60 (m, 6H), 7.79-7.94 (m, 4H), 10.10 (bs, 1H).

^{13}C NMR: 21.35, 25.03 (d, *J* = 6.6 Hz), 30.51 (d, *J* = 6.1 Hz), 48.17 (d, *J* = 3.4 Hz), 62.60, 117.30, 125.72, 128.74, 128.86, 128.98, 129.75 (d, *J* = 29.2 Hz), 131.01 (d, *J* = 33.1 Hz), 131.98, 132.07, 132.40, 138.28, 138.46, 170.88.

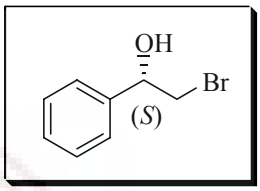
LCMS (m/z): 419 $(M+H)^+$

Anal. calcd. for $C_{25}H_{27}N_2O_2P$: C, 71.75; H, 6.50; N, 6.69.

Found: C, 71.69; H, 6.54; N, 6.73.

(*S*)-2-Bromo-1-phenylethanol [(*S*)-222a]:

Asymmetric reduction of phenacyl bromide (**221a**) using $BH_3.SMe_2$ under the influence of 15 mol% (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine (**230**) provided the title compound as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a** (Page no 103).



Yield: 85%

$[\alpha]_D^{25}$: + 36.36 (*c* 1.10, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 85% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

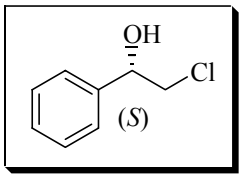
Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 9.74 min and 10.36 min] due to *S* and *R* enantiomers for racemic alcohol **(±)-222a**. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 93:8 [retention times: 9.57 min (*S*) and 10.27 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 85%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

This secondary alcohol was obtained as a colorless liquid by $BH_3.SMe_2$ mediated asymmetric reduction of phenacyl chloride (**221b**) in the presence of chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine (**230**, 15 mol%),

following the procedure described for the compound **(S)-222a** (Page no 103).



Yield: 84%

$[\alpha]_D^{25}$: + 38.25 (*c* 1.20, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 85% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222b** and chiral alcohol **(*S*)-222b** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.69 min and 9.26 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222b** showed two peaks in the ratio of 92.5:7.5 [retention times: 8.70 min (*S*) and 9.30 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 85%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

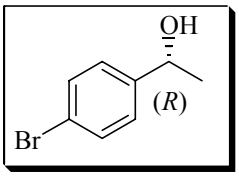
This compound was obtained by borane-mediated reduction of 4-bromoacetophenone (**224d**) in the presence of 15 mol% chiral catalyst (2*S*)-1-(diphenylphosphoryl)-2-(3,5-dimethylanilino)carbonylpyrrolidine (**230**) as a colorless liquid, following the similar procedure described for the compound **(*S*)-222a** (Page no 103).

Yield: 83%

$[\alpha]_D^{25}$: + 27.04 (*c* 1.15, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$),

(*S*)-configuration, >99% *ee*]



Enantiomeric purity: 73% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

Determination of enantiomeric purity:

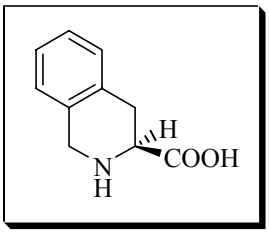
HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min] of the racemic compound **(±)-225d** showed two peaks at 16.08 min (*S*) and 17.57 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-225d** showed two peaks at 16.06 min (*S*) and 17.50 min (*R*) in the ratio of 13.5:86.5 indicating that the reaction is 73% enantioselective.

(*S*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (234)

This compound was prepared according to the literature procedure.[163]

To a stirred suspension of (*S*)-phenylalanine (**233**, 9.91g, 60 mM) in formalin (24.2 mL) was added conc. HCl (72.8 mL) at room temperature and the reaction mixture was heated at 60 ^oC for 1 h. Additional formalin (9.8 mL) and conc. HCl (19.4 mL) were added at the same temperature and stirring was continued for another 3 h. The reaction mixture was allowed to cool to room temperature and then cooled to 0 ^oC. Solid thus obtained was collected by filtration under vacuum and then dissolved in hot water (15 mL) and hot methanol (125 mL) was added. While hot, conc. NH_4OH was added to adjust *p*H 6-7. The resulting precipitate was collected by filtration under vacuum and dried in vacuo at room

temperature to afford (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid as a colorless solid.



Yield: 30% (3.2 g)

Mp: ›300 ^{o}C

$[\alpha]_D^{25}$: - 164.3 (*c* 0.49,NaOH) {Lit. [163] $[\alpha]_D^{25}$: - 26.4 (*c* 1.00, H_2O)}

IR (KBr): ν 3200-2400, 1633 cm^{-1}

^{1}H NMR: (D_2O + KOH) δ 2.63-2.82 (m, 1H), 2.88-3.02 (m, 1H), 3.27-3.41 (m,1H), 3.75-4.00 (m, 2H), 7.00-7.20 (m, 4H).

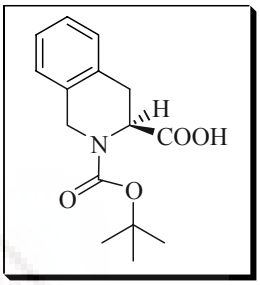
^{13}C NMR: (D_2O + KOH) δ 34.17, 48.88, 60.11, 128.63, 128.78, 128.94, 131.70, 136.78, 137.18, 183.22.

(*S*)-N-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (235)

This compound was prepared according to the literature procedure.[164]

To a stirred mixture of the (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**234**, 3.89 g, 22 mM) in dioxane (30 mL) and aqueous. NaOH (60 mL, 0.5 M) was added slowly di-*tert*-butyl dicarbonate (5.67 g, 26 mM) in dioxane (20 mL) at 0 ^{o}C. The reaction mixture was allowed to come to room temperature and stirring continued for 16 h. The reaction mixture was diluted with 5 mL of hexanes with stirring and organic layer was separated to remove unreacted di-*tert*-butyl dicarbonate if any. Aqueous layer was acidified with saturated citric acid and extracted with ethyl acetate (3 × 25mL). The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed

under reduced pressure and the crude product, thus obtained was purified by crystallization (1:1 mixture of ethyl acetate and hexanes) to provide the desired (*S*)-N-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**235**) as a colorless solid.



Yield: 74% (4.51 g)

Mp: 104-106 ^{o}C

$[\alpha]_D^{25}$: + 17.5 (*c* 0.96, MeOH)

IR (KBr): ν 3300-2400 (multiple bands), 1749, 1637 cm^{-1}

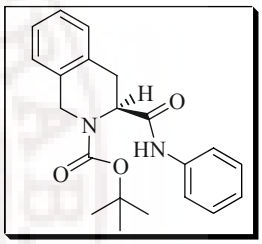
^{1}H NMR: δ 1.53 (s, 9H), 3.01-3.30 (m) and 4.40-5.15 (m) [5H], 7.05-7.22 (m, 4H).

^{13}C NMR: δ 28.23, 28.41, 30.86, 31.34, 43.91, 44.52, 52.35, 54.18, 81.03, 81.08, 126.22, 126.38, 126.74, 126.80, 126.98, 127.79, 128.54, 131.63, 131.94, 132.69, 133.82, 154.87, 155.72, 176.82, 177.52. (mixture of isomers).

(3*S*)-2-(*tert*-Butoxycarbonyl)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (236)

To a stirred solution of (*S*)-N-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**235**, 2.77 g, 10 mM) in anhydrous THF (30 mL) was added triethylamine (1.01 g, 10 mM) at room temperature and the mixture was cooled to 0 ^{o}C. Ethyl chloformate (1.08 g, 10 mM) was added to this mixture dropwise slowly and stirring continued at 0 ^{o}C for further 30 min. Then a solution of aniline (0.93 g, 10 mM) in THF (5

mL) was added slowly at 0 ^{o}C and the reaction mixture was allowed to warm to room temperature and stirred further for 16 h. Aftter completion of the reaction (monitored by TLC), solvent was removed under reduced pressure and the residue thus obtained was diluted with ethyl acetate (25 ml) and washed successively with 1(N) HCl (5 mL), saturated solution of sodium bicarbonate (10 mL) and brine (10 mL).The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue thus obtained was purified by column chromatography (silica gel, 15% ethyl acetate in hexanes) to provide the desired compound (**236**) as colorless solid.



Yield: 66% (2.32 g)

Mp: 149-150 ^{o}C

$[\alpha]_D^{25}$: - 61.69 (*c* 1, MeOH)

IR (KBr): ν 3400-3000 (multiple bands), 1699, 1666, 1602 cm^{-1}

^{1}H NMR: δ 1.50 (s, 9H), 2.90-3.60 (m, 2H), 4.20-5.20 (m, 3H), 6.90-7.70 (m, 9H), 8.52 (br, 1H).

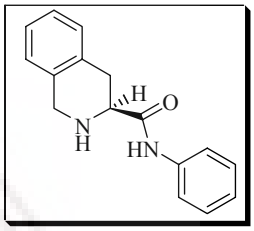
^{13}C.NMR: δ 28.42, 44.85, 81.68, 119.92, 124.40, 126.04, 126.91, 127.75, 128.10, 128.95, 133.87.

(3*S*)-3-Anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (237)

This compound was prepared following the literature procedure.

To a stirred solution of (3*S*)-2-(*tert*-butoxycarbonyl)anilinocarbonyl-1,2,3,4-tetrahydro-3-isoquinoline (**236**, 1.76 g, 5 mM) in CH_2Cl_2 was bubbled HCl gas for a period of 30 min at room temperature. Solvent was evaporated. The residue was dissolved in EtOAc (50 mL)

and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was then re-extracted with EtOAc (25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated to provide the desired compound as colorless solid.



Yield: 93% (1.17 g)

$[\alpha]_D^{25}$: $[\alpha]_D^{25}$: - 81.16 (*c* 0.6, MeOH)

Mp: 160-162 ^oC [lit.[165] 150-152 ^oC for **237**-TFA salt]

IR (KBr): ν 3300-2900 (multiple bands), 1678, 1601 cm^{-1}

^1H NMR: δ 2.92 (dd, 1H, *J* =10.8 Hz. and 16.2 Hz.), 3.35 (dd, 1H, *J* =5.6 Hz. and 16.4 Hz.), 3.69 (dd, 1H, *J* =5.2 Hz. and 10.8 Hz.), 4.03 and 4.08 (ABq, 2H, 16.0 Hz.), 7.06-7.38 (m, 8H), 7.61 (d, 2H, *J*=8.0Hz.), 9.34 (br, 1H).

^{13}C NMR δ 30.57, 47.55, 56.87, 119.48, 124.17, 125.57, 126.38, 126.82, 129.04, 129.22, 134.42, 136.11, 137.76, 171.31.

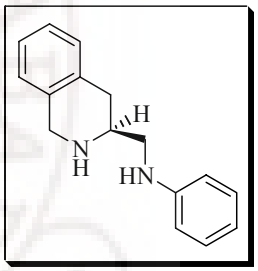
It is worth mentioning here that $[\alpha]_D^{25}$ of this salt changes to -58.63 on standing this solution (12 h) which might be attributed to the possible decomposition of this salt] [lit.[165] 237-TFA salt $[\alpha]_D^{20}$: - 33.1, *c* 1, MeOH]

(3*S*)-3-Anilinomethyl-1,2,3,4-tetrahydroisoquinoline (231):

This compound was prepared from **237** following the literature procedure.[149]

To a stirred suspension of lithium aluminium hydride (0.228 g, 6 mM) in THF (20 mL), (3*S*)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (**237**, 0.504 g, 2 mM) was added

portion wise at room temperature. After the addition was complete, the reaction mixture was heated under reflux for 5 h. The reaction mixture was cooled to 5 ^{o}C and water (1 mL) was added carefully, followed by the addition of NaOH solution (2.5 N, 5 mL). The reaction mixture was diluted with dichloromethane (10 mL) and stirred for 10 min. The organic layer was separated and the solid aluminium salts were washed with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was distilled [Bp: 180-182 ^{o}C (oil bath) / 0.2 mm] under reduced pressure to furnish the compound as a viscous liquid which solidified upon standing at room temperature.



Yield: 84% (0.40 g)

Mp: 80-82 ^{o}C

$[\alpha]_D^{25}$: - 64.79 (*c* 0.98, $CHCl_3$)

IR (KBr): ν 3300, 3213, 1602 cm^{-1}

^{1}H NMR: δ 1.61-1.82 (br, 1H), 2.60-2.72 (m, 1H), 2.80-2-90 (m, 1H), 3.04-3.14 (m, 1H), 3.15-3.25 (m, 1H), 3.31-3.41 (m,1H), 4.06 (s, 2H), 4.25 (br, 1H), 6.62-6.76 (m, 3H), 7.01-7.06 (m, 1H), 7.07-7.22 (m, 5H).

^{13}C NMR: δ 33.17, 48.16, 49.31, 53.10, 113.03, 117.57, 125.98, 126.10, 126.26, 129.33, 129.36, 134.11, 135.80, 148.49.

LCMS (m/z): 239 $(M+H)^+$

Anal. calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75.

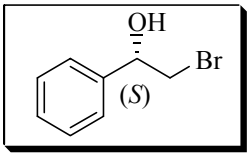
Found: C, 80.83; H, 7.67; N, 11.68.

Spectral data (IR, ^{1}H, ^{13}C NMR) of the chiral alcohols (S)-222a,b,e and (R)-225a,d obtained via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 221a,b,e and 224a,d under the influence of chiral source (3S)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (231) and of the secondary alcohols (R)-222a,b,e and (S)-225a,d obtained via borane-mediated asymmetric reduction of corresponding ketones 221a,b,e and 224a,d in the presence of chiral source (2R)-2-anilinomethylpiperidine (232) are in full agreement with the spectral data of the above mentioned chiral alcohols in case of chiral source (2S)-1-(diphenylphosphoryl)-2-anilinocarbonylpyrrolidine (216). Therefore we have not mentioned the spectral data again in the following experiments.

Asymmetric reduction of phenacyl bromide (**221a**) **using the catalyst 231**: **Synthesis of (*S*)-2-bromo-1-phenylethanol** [**(*S*)-222a**]: **Representative procedure**:

To a stirred solution of (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**, 0.1 mM, 1 mL, 0.1 M solution in toluene) in toluene (2 mL) was added $BH_3.SMe_2$ (1 mM, 1 mL, 1 M solution in toluene) at room temperature and the reaction mixture was heated under reflux for 15 min. Then a solution of phenacyl bromide (**221a**) (1 mM, 0.199 g), in toluene (2 mL), was added dropwise and heated under reflux for further 30 minutes. The reaction mixture was cooled to room temperature and quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column

chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] in 86% (0.172 g) yield as a colorless oil.



Yield: 86% (0.172 g)

$[\alpha]_D^{25}$: + 32.62 (*c* 0.9, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

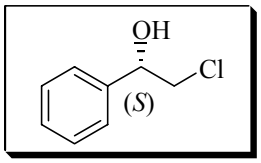
Enantiomeric purity: 80% [determined by HPLC analysis using chiral column,Chiralcel-OD H, with reference to racemic alcohol (±)-**222a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.18 min and 8.81 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 90:10 [retention times: 8.18 min (*S*) and 8.82 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 80%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

This compound was obtained by asymmetric reduction of phenacyl chloride (**221b**) with $BH_3.SMe_2$ in the presence of 10 mol% (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydro-isoquinoline (**231**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a** (Page no 142).



Yield: 83%

$[\alpha]_D^{25}$: + 37.23 (*c* 0.8, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: - 48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

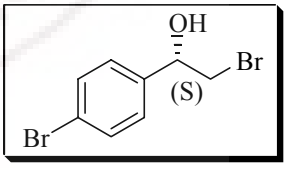
Enantiomeric purity: 72% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222b** showed two peaks in equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 7.87 min and 8.53 min] arising from *S* and *R* enantiomers. Chiral alcohol **(*S*)-222b** showed two peaks in 86:14 ratio [retention times: 7.86 min (*S*) and 8.53 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 72%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-222e]:

Asymmetric reduction of 4-bromophenacyl bromide (**221e**) using $BH_3.SMe_2$ under the influence of 10 mol% (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page no 142).



Yield: 81%

Mp: 68-70 °C (Lit. [159] 70-72 °C)

$[\alpha]_D^{25}$: + 27.51 (*c* .09, $CHCl_3$) {Lit.[159] $[\alpha]_D^{25}$: - 31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

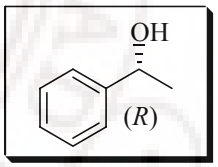
Enantiomeric purity: 79% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-222e**]

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min] of the racemic compound **(±)-222e** showed two peaks at 19.48 min (*R*) and 20.86 min (*S*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-222e** showed two peaks at 19.87 min (*R*) and 21.03 min (*S*) in the ratio of 89:10 indicating that the reaction is 79% enantioselective.

(*R*)-1-Phenylethanol [(*R*)-225a]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of acetophenone (**224a**) in the presence of chiral catalyst (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**231**, 10 mol%), following the similar procedure described for the compound (*S*)-**222a** (Page no 142).



Yield: 84%

$[\alpha]_D^{25}$: + 23.50 (*c* 0.87, MeOH)

[Lit.[160] $[\alpha]_D^{25}$: + 44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 57% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-225a**]

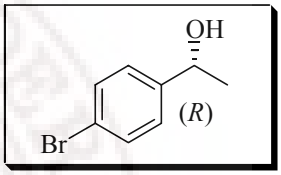
Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 8.33 min and 9.72 min] due to *R* and *S* enantiomers for racemic alcohol **(±)-225a**. The chiral alcohol **(*R*)-225a** showed two peaks in the ratio of 78.5:21.5 [retention times: 8.30 min (*R*)

and 9.67 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 57%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-225d]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-bromoacetophenone (**224d**) in the presence of (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline, (**231**, 10 mol%) furnished the chiral alcohol [**(*R*)-225d]** as a colorless liquid following the method described for the compound **(*S*)-222a** (Page no 142).



Yield: 83%

$[\alpha]_D^{25}$: + 21.5 (*c* 0.5, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$:-37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*].

Enantiomeric purity: 59% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

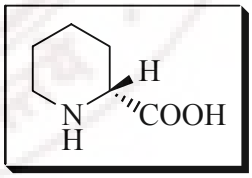
Determination of enantiomeric purity:

Racemic alcohol **(±)-225d** and chiral alcohol **(*R*)-225d** were analysed on HPLC using chiral column, Chiralcel-OJ H [solvent system, hexanes:IPA (95:5); flow rate: 0.8 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 15.21 min and 16.01 min due to *S* and *R* enantiomers. The chiral alcohol **(*R*)-225d** showed two peaks in the ratio of 20.5:79.5 [retention times: 15.06 min (*S*) and 15.78 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 59%.

(*R*)-Pipecolinic acid [(*R*)-238]:

Resolution of (±) pipecolinic acid was carried out following the literature procedure.[166]

To stirred solution of (±) pipecolinic acid (9.68 g, 75 mM) in MeOH (45 mL) at 60 ^{o}C was added (*R,R*)-tartaric acid (11.25 g, 75 mM). The resulting slurry was heated under reflux for 1 h and then cooled to room temperature. The precipitate [containing (*R*)-pipecolinic acid/ (*R,R*)-tartaric acid salt] was collected by filtration and the filtrate containing the other isomer was collected separately. This salt (9.59 g) was taken in 2:1 water–acetone (10 mL & 5 mL) and was heated under reflux till all solids dissolved. Additional acetone (33.2 mL) was added slowly while maintaining reflux and was further heated under reflux for 2 h.The reaction mixture was cooled to 15-20 ^{o}C. Solid precipitated was collected by filtration and washed with 4:1 water–acetone (2 mL & 8 mL) and dried under vacuum (to remove acetone). The resulting acetone free salt (6.98 g) was taken in MeOH (65 mL) and added 28% NH_4OH (3.0 mL, 1 equiv.) slowly. The ammonium tartarate precipitate was removed by filtration and washed with MeOH (6 mL). The filtrate and methanol washings were combined. Evaporation of the solvents provided (*R*) pipecolinic acid **[(*R*)-238]** as a colorless solid.



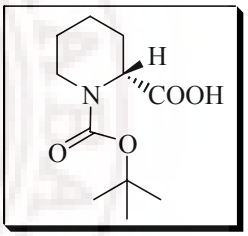
Yield:	35% (3.4 g)
Mp:	270-272 ^{o}C
$[\alpha]_D^{25}$:	+ 24.45 (*c* 0.96, H_2O)
	{Lit.[173] $[\alpha]_D^{25}$: + 27 (*c* 1.00, H_2O)}
IR (KBr) :	ν 3300-2500 (multiple bands), 1633 cm^{-1}
^{1}H NMR : (D_2O)	δ 1.40-1.65 (m, 3H), 1.71-1.82 (m, 2H), 2.05-2.18 (m, 1H), 2.85-2.96 (m, 1H), 3.27-3.36 (m, 1H), 3.42-3.54 (m, 1H).

^{13}C NMR : δ 21.52, 21.78, 26.48, 43.63, 59.01, 174.52.
(D_2O)

(*R*)-N-(*tert*-Butoxycarbonyl)pipecolinic acid (239)

This compound was prepared according to the literature procedure.[166]

To a stirred solution of (*R*)-pipecolinic acid (**238**, 1.80 g, 14 mM) and di-*tert*-butyl dicarbonate (3.71 g, 17 mM) in 1:1 THF-water (10ml) was added 50% aq. NaOH and heated under reflux for 5 h.The reaction mixture was cooled to room temperature and THF was removed under reduced pressure and then similar work-up procedure was followed as for the compound **235**, to furnish the title compound as colorless solid.



Yield: 68% (2.18 g)

$[\alpha]_D^{25}$: + 61.96 (*c* 0.91,CH_3CO_2H)

[lit.[174]. $[\alpha]_D^{25}$: + 68 (*c* 1, CH_3CO_2H)

Mp: 114-116 ^oC [lit.[174] 116-119 ^oC]

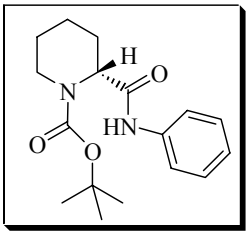
IR (Neat) : ν 3500-2600 (multiple bands), 1631 cm^{-1}

^{1}H NMR: δ 1.23-1.76 (m,14H), 2.23 (bs, 1H), 2.82-3.10 (m, 1H), 3.86-4.10, (m, 1H), 4.70-5.04 (m, 1H), 7.50 (br, 1H).

^{13}C NMR : δ 20.80, 24.54, 24.77, 26.63, 28.34, 41.07, 42.12, 53.60, 54.72, 80.38, 155.70, 156.21, 177.53 (mixture of isomers).

(*R*)-N-(*tert*-Butoxycarbonyl)-2-anilinocarbonylpiperidine (240):

This compound was prepared from (*R*)-N-(*tert*-butoxycarbonyl)pipecolinic acid (**239**) according to the literature procedure[149] described as for the compound **236**.



Yield: 75%

Mp: 170-172 ^{o}C

$[\alpha]_D^{25}$: + 58.20 (*c* 1, MeOH)

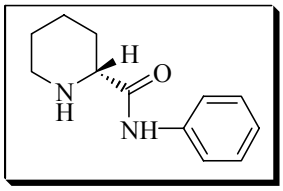
IR (Neat) : ν 3350-2900 (multiple bands), 1670, 1602 cm^{-1}

^{1}H NMR : δ 1.40-1.75 (s, 13H), 2.29-4.86 (m, 5H), 7.04-7.60 (m, 5H), 8.15 (br, 1H).

^{13}C NMR : δ 14.57, 20.35, 24.85, 25.24, 28.39, 42.37, 81.02, 119.68, 123.25, 124.18, 128.97, 137.88, 169.72.

(2*R*)-2-Anilinocarbonylpiperidine (241):

This compound was prepared following the literature procedure[167] with some modification. To a stirred solution of (*R*)-N-(*tert*-butoxycarbonyl)-2-anilinocarbonylpiperidine (**240**, 1.52 g, 5 mM) in dichloromethane (20 mL) was added 20 mL of TFA at room temperature. After 1 h solvent was evaporated and the residue was dissolved in EtOAc (50 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous phase was again extracted with EtOAc (25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue thus obtained was purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to provide the desired compound as colorless solid.



Yield: 78% (0.79 g)

Mp: 190-192 ^{o}C

$[\alpha]_D^{25}$: + 18.82 (*c* 1.02, MeOH)

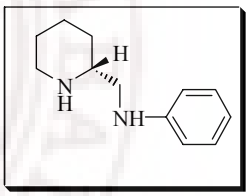
IR (Neat): ν 3300-2849 (multiple bands), 1685, 1601 cm^{-1}

^1H NMR: δ 1.38-1.70 (m, 4H), 1.74-1.91 (m, 1H), 1.98-2.20 (m, 2H), 2.65-2.85 (m, 1H), 2.97-3.16 (m, 1H), 3.28-3.45 (m, 1H), 7.05-7.16 (m, 1H), 7.25-7.44 (m, 2H), 7.57 (d, 2H, *J* = 7.6 Hz), 8.88 (bs, 1H).

^{13}C NMR: δ 23.84, 25.92, 29.67, 45.62, 60.51, 119.53, 124.07, 129.00, 137.90, 172.18.

(2*R*)-2-Anilinomethylpiperidine (232)[168]:

This compound was prepared as a viscous liquid from the amide **241** according to the literature procedure[149] described for the compound **231**.



Yield: 63%

Bp: 145-147 ^oC (oil bath) / 0.5 mm Hg

$[\alpha]_D^{25}$: - 29.02 (*c* 1.45, EtOH)

IR (Neat) : ν 3381, 3300, 2928, 1602 cm^{-1}

^1H NMR: δ 1.14-1.28 (m, 1H), 1.31-1.50 (m, 2H), 1.54-1.74 (m, 2H), 1.78-2.05 (m, 2H), 2.57-2.68 (m, 1H), 2.72-2.83 (m, 1H), 2.94-3.20 (m, 3H), 4.03 (br, 1H), 6.58-6.73 (m, 3H), 7.12-7.22 (m, 2H).

^{13}C NMR: δ 24.51, 26.60, 30.75, 46.77, 50.09, 55.88, 112.73, 117.15, 129.18, 148.47.

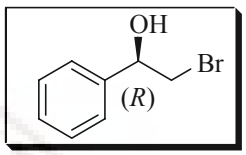
LCMS (m/z): 191 $(M+H)^+$

Anal. calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72.

Found: C, 75.76; H, 9.50; N, 14.74.

(*R*)-2-Bromo-1-phenylethanol [**(*R*)-222a**]:

This compound was obtained *via* asymmetric reduction of phenacyl bromide (**221a**) with $BH_3.SMe_2$ in the presence of 10 mol% (2*R*)-2-anilinomethylpiperidine (**232**), as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page no 142).



Yield: 85%

$[\alpha]_D^{25}$: - 33.27 (*c* 0.52, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 81% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

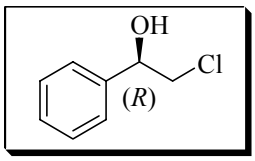
Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.23 min and 8.98 min] due to *S* and *R* enantiomers. The chiral alcohol **(*R*)-222a** showed two peaks in the ratio of 9.5:90.5 [retention times: 8.24 min (*S*) and 8.97 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 81%.

(*R*)-2-Chloro-1-phenylethanol [(*R*)-222b]:

Asymmetric reduction of phenacyl chloride (**221b**) using $BH_3.SMe_2$ under the influence of 10 mol% (2*R*)-2-anilinomethylpiperidine (**232**) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page no 142).

Yield: 83%

$[\alpha]_D^{25}$: - 36.1 (*c* 0.31, cyclohexane) [Lit.[156] $[\alpha]_D^{25}$: - 48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]



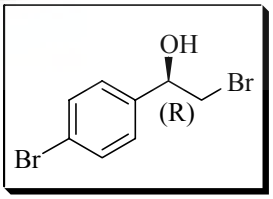
Enantiomeric purity: 77% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min] of the racemic compound **(±)-222b** showed two peaks at 7.49 min (*S*) and 8.40 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-222b** showed two peaks at 7.56 min (*S*) and 8.50 min (*R*) in the ratio of 11.5:88.5 indicating that the reaction is 77% enantioselective.

(*R*)-2-Bromo-1-(4-bromophenyl)ethanol [(*R*)-222e]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of 4-bromophenacyl bromide (**221e**) in the presence of chiral catalyst (2*R*)-2-anilinomethylpiperidine (**232**) (10 mol%), following the similar procedure described for the compound **(*S*)-222a (**Page no 142**)**.



Yield: 83%

Mp: 68-70 ^oC (Lit[159] 70-72 ^oC)

$[\alpha]_D^{25}$: - 24.35 (*c* 0.78, $CHCl_3$)

{Lit.[159] $[\alpha]_D^{25}$: - 31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

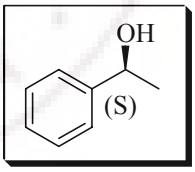
Enantiomeric purity: 76% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol [**(±)-222e**]

Determination of enantiomeric purity:

Two peaks of equal intensity were obtained on HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 21.02 min and 22.45 min] due to *R* and *S* enantiomers for racemic alcohol **(±)-222e**. The chiral alcohol **(*R*)-222e** showed two peaks in the ratio of 88:12 [retention times: 21.82 min (*R*) and 23.40 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 76%.

(*S*)-1-Phenylethanol [(*S*)-225a]:

Borane-dimethylsulfide mediated asymmetric reduction of acetophenone (**224a**) in the presence of (2*R*)-2-anilinomethylpiperidine, (**232**, 10 mol%) furnished the chiral alcohol **(*S*)-225a** as a colorless liquid following the method described for the compound **(*S*)-222a** (Page no 142).



Yield: 86%

$[\alpha]_D^{25}$: - 25.33 (*c* 0.75, MeOH)

[Lit.[160] $[\alpha]_D^{25}$: + 44.1

(*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

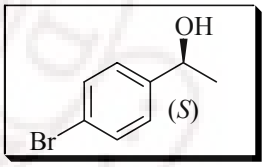
Enantiomeric purity: 62% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-225a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-225a** and chiral alcohol **(*S*)-225a** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.11 min and 9.67 min due to *R* and *S* enantiomers. The chiral alcohol (***S***)-**225a** showed two peaks in the ratio of 19:81 [retention times: 8.20 min (*R*) and 9.83 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 62%.

(*S*)-1-(4-Bromophenyl)ethanol [(*S*)-225d]:

This compound was obtained *via* asymmetric reduction of 4-bromoacetophenone (**224d**) with $BH_3.SMe_2$ in the presence of 10 mol% (2*R*)-2-anilinomethylpiperidine (**232**), as a colorless liquid following the procedure mentioned for the compound **(*S*)-222a** (Page no 142).



Yield: 85%

$[\alpha]_D^{25}$: - 24.6 (*c* 1.27, $CHCl_3$)

[Lit.[161] $[\alpha]_D^{23}$: - 37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*].

Enantiomeric purity: 70% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-225d**]

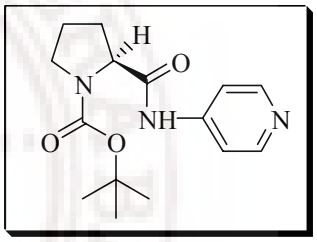
Determination of enantiomeric purity:

The racemic alcohol (±)-**225d** showed two peaks in 1:1 ratio at 15.96 min (*S*) and 16.86 min (*R*) on HPLC analysis using chiral column, Chiralcel-OJ H [solvent system, hexanes:IPA (95:05); flow rate: 0.8 mL/min]. The chiral alcohol **(*S*)-225d** showed two

peaks at 15.80 min (*S*) and 16.72 min (*R*) in the ratio of 85:15 on similar HPLC analysis, indicating that its enantiomeric purity is 70%.

(2*S*)-N-*tert*-Butoxycarbonyl-2-(pyrid-4-ylamino)carbonylpyrrolidine (249):

This compound was obtained as a colorless solid by treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248,** 2.15 g, 10 mM) with ethyl chloroformate (1.08 g, 10 mM) and 4-aminopyridine (0.941 g, 10 mM) in the in presence of triethylamine (1.01 g, 10 mM) in THF (30 mL) following the similar method described for the compound **236.**



Time: 12 h

Yield: 73% (2.12 g)

Mp: 198-200 ^{o}C

$[\alpha]_D^{25}$: - 123.90 (*c* 1.05, $CHCl_3$)

IR (KBr): ν 3240-2795 (multiple bands), 1714, 1597 cm^{-1}

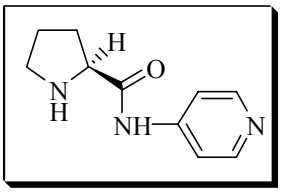
^{1}H NMR: *δ* 1.51 (s, 9H), 1.94 (bs, 3H), 2.41 (bs, 1H), 3.20-3.65 (br, 2H), 4.50 (bs, 1H), 7.38 (bs, 2H), 8.38 (bs, 2H), 10.00 (bs, 1H).

^{13}C NMR: *δ* 24.53, 28.02, 28.41, 47.30, 60.59, 81.10, 113.57, 145.42, 150.25, 156.25, 171.36.

(2*S*)-2-(Pyrid-4-ylamino)carbonylpyrrolidine (242):

This compound was obtained following the procedure described for the preparation of compound **237**, *via* the treatment of (2*S*)-N-*tert*-butoxycarbonyl-2-(pyrid-4-ylamino)-

carbonylpyrrolidine (**249**, 0.874 g, 3 mM) with HCl (g) in dichloromethane (10 mL) as viscous liquid.



Time: 15-20 min

Yield: 83% (0.476 g)

$[\alpha]_D^{25}$: - 57.67 (*c* 0.86, MeOH)

[Lit.[169] $[\alpha]_D^{25}$: - 69.7 (*c* 1, MeOH)].

IR (KBr): ν 3312, 1695, 1597 cm^{-1}

^1H NMR: δ 1.70-1.85 (m, 2H), 1.97-2.09 (m, 1H), 2.15-2.29 (m, 1H), 2.36 (bs, 1H), 2.92-3.17 (m, 2H), 3.81-3.91 (m, 1H), 7.53 (d, 2H, *J* = 6.0 Hz), 8.48 (d, 2H, *J* = 6.0 Hz), 9.98 (bs, 1H).

^{13}C NMR: δ 26.34, 30.71, 47.38, 61.07, 113.32, 144.56, 150.66, 174.57.

LCMS (m/z): 192 $(M+H)^+$

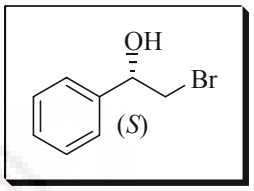
Anal. calcd. for $C_{12}H_{18}N_2$: C, 62.81; H, 6.85; N, 21.97.

Found: C, 62.76; H, 6.88; N, 22.11.

Asymmetric reduction of prochiral α-halo ketones in the presence of 2 mol% (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine [(242)], Prepartion of (*S*)-2-bromo-1-phenylethanol [(*S*)-222a]: Representative procedure:

To a stirred solution of (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (**242**, 0.04 mM, 0.008 g) in toluene (2 mL) was added $BH_3.SMe_2$ (2.4 mM, 2.4 mL, 1 M solution in toluene) at room temperature and the reaction mixture was heated under reflux for 15 min. Then a solution of phenacyl bromide (**221a**) (2 mM, 0.398 g), in toluene (3 mL), was

added dropwise and heated under reflux for further 15 minutes. The reaction mixture was cooled to room temperature and quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-222a**] as colorless liquid.



Yield: 86% (0.344 g)

$[\alpha]_D^{25}$: + 31.53 (*c* 1.24, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 77% [determined by HPLC analysis using chiral column,Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

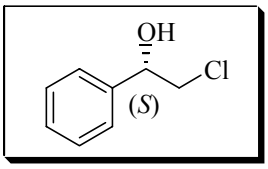
Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.67 min and 9.23 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 88.5:11.5 [retention times: 8.63 min (*S*) and 9.18 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 77%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

Asymmetric reduction of phenacyl chloride (**221b**) using $BH_3.SMe_2$ under the influence of 2 mol% (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (**242**) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page

no 156).



Yield: 84%

$[\alpha]_D^{25}$: + 28.37 (*c* 0.86, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: - 48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

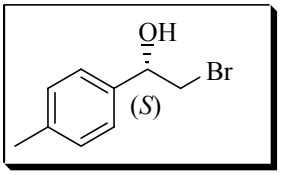
Enantiomeric purity: 70% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min] of the racemic compound **(±)-222b** showed two peaks at 8.33 min (*S*) and 8.91 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-222b** showed two peaks at 8.37 min (*S*) and 8.95 min (*R*) in the ratio of 85:15 indicating that the reaction is 70% enantioselective.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-222c]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of 4-methylphenacyl bromide (**221c**) in the presence of chiral catalyst (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (**242**, 2 mol%), following the similar procedure described for the compound **(*S*)-222a** (Page no 156).



Yield: 86%

$[\alpha]_D^{25}$: + 30.52 (*c* 0.96, $CHCl_3$)

[Lit.[132] $[\alpha]_D^{25}$: + 41.8 (*c* 1.00, $CHCl_3$), (*S*)-configuration, 95% *ee*]

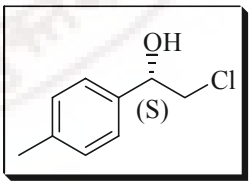
Enantiomeric purity: 70% (determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222c**

Determination of enantiomeric purity:

HPLC analysis of racemic alcohol **(±)-222c** [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min; retention times: 15.28 min and 16.78 min] showed two peaks of equal intensity due to *S* and *R* enantiomers The chiral alcohol **(*S*)-222c** showed two peaks in the ratio of 85:15 [retention times: 15.31 min (*S*) and 16.84 min (*R*) respectively] on similar HPLC analysis, indicating that the reaction is 70% enantioselective.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-222d]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-methylphenacyl chloride (**221d**) in the presence of (2*S*)-2-(pyrid-4-ylamino)carbonylpyrrolidine (2 mol%) furnished the chiral alcohol **(*S*)-222d** as a colorless liquid following the method described for the compound **222a**.



Yield: 86%

$[\alpha]_D^{25}$: + 32.35 (*c* 0.95, $CHCl_3$)

{Lit.[132] $[\alpha]_D^{25}$: + 47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*}

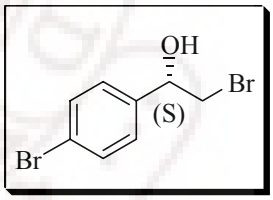
Enantiomeric purity: 72% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol [**(±)-222d**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222d** and chiral alcohol **(*S*)-222d** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (97.5:2.5); flow rate: 0.9 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 14.59 min and 16.78 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222d** showed two peaks in the ratio of 86:14 [retention times: 14.57 min (*S*) and 16.77 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 72%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-222e]:

This compound was obtained *via* the borane-mediated reduction of 4-bromophenacyl bromide (**221e**) under the catalytic influence of (2*S*)-2-(pyrid-4-ylamino)carbonyl-pyrrolidine (**242**) (2 mol%) as a colorless solid, following the similar procedure described for the compound **(*S*)-222a** (Page no. 156).



Yield: 87%

Mp: 68-70 ^{o}C (Lit. [159] 70-72 ^{o}C)

$[\alpha]_D^{25}$: + 24.88 (*c* 1.25, $CHCl_3$) {Lit.[159] $[\alpha]_D^{25}$: - 31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

Enantiomeric purity: 75% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-222e**].

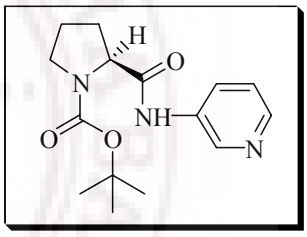
Determination of enantiomeric purity:

Racemic alcohol (±)-**222e** showed two peaks in 1:1 ratio on HPLC analysis [chiral column

Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 20.37 min and 22.24 min] arising from *R* and *S* enantiomers. In case of chiral alcohol **(*S*)-222e** showed two peaks in 12.5:87.5 ratios [retention times: 20.56 min (*R*) and 22.33 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 75%.

(2*S*)-1-*tert*-Butoxycarbonyl-2-(pyrid-3-ylamino)carbonylpyrrolidine (250):

This compound was prepared *via* the successive treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248**) with ethyl chloroformate and 3-aminopyridine in the presence of triethylamine following the similar procedure described for compound **236**.



Time: 12 h

Yield: 72%

Mp: 152-154 ^{o}C

$[\alpha]_D^{25}$: - 134.09 (*c* 1.05, $CHCl_3$)

IR (KBr): ν 3308-2878 (multiple bands), 1701, 1666, 1604 cm^{-1}

^{1}H NMR: δ 1.50 (s, 9H), 1.81-2.15 (m, 3H), 2.43 (br, 1H), 3.40-3.61 (m, 2H), 4.52 (br, 1H), 7.17 (br, 1H), 8.02 (br, 1H), 8.26 (br, 1H), 8.60 (d, 1H, J = 2.4 Hz), 9.83 (br, 1H)

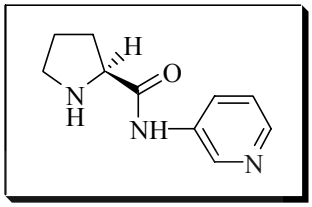
[broad peaks are due to free rotation of *tert*-butoxycarbonyl group].

^{13}C NMR: δ 24.59, 27.69, 28.42, 47.30, 60.44, 81.08, 123.53, 126.56, 135.36, 141.10, 144.65, 156.50, 170.75.

(2*S*)-2-(Pyrid-3-ylamino)carbonylpyrrolidine (243):

This compound was prepared following the procedure described for the preparation of

compound **242** *via* the treatment of (2*S*)-1-*tert*-butoxycarbonyl-2-(pyrid-3-ylamino) carbonylpyrrolidine (**250**) with HCl (g) in dichloromethane (10 mL) as a viscous liquid.



Time: 15-20 min

Yield: 84%

$[\alpha]_D^{25}$: - 51.90 (*c* 1.02, $CHCl_3$)

[Lit.[169] $[\alpha]_D^{20}$: - 53.1 (*c* 1.0, $CHCl_3$)].

IR (KBr): ν 3260, 1689, cm^{-1}

^1H NMR: δ 1.70-1.85 (m, 2H), 1.94-2.15 (m, 2H), 2.16–2.25 (m, 1H) 2.96-3.04 (m, 1H), 3.06-3.15 (m, 1H), 3.86-3.92 (m, 1H), 7.21-7.32 (m, 1H), 8.24-8.29 (m, 1H), 8.33 (dd, 1H, *J* = 1.6, 4.8 Hz), 8.61 (d, 1H, *J* = 2.4 Hz), 9.88 (br, 1H).

^{13}C NMR: δ 26.42, 30.80, 47.46, 61.04, 123.70, 126.39, 134.66, 140.97, 145.05, 174.21.

LCMS (m/z): 192 $(M+H)^+$

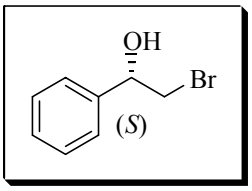
Anal. calcd. for $C_{12}H_{18}N_2$: C, 62.81; H, 6.85; N, 21.97.

Found: C, 62.85; H, 6.82; N, 21.91.

(*S*)-2-Bromo-1-phenylethanol [**(*S*)-222a**]:

This compound was prepared *via* asymmetric reduction of phenacyl bromide (**221a**) with $BH_3.SMe_2$ in the presence of 2 mol% (2*S*)-2-(pyrid-3-ylamino)carbonylpyrrolidine (**243**), as a colorless liquid following the procedure described for the compound **(*S*)-222a** (Page

no 156).



Yield: 87%

$[\alpha]_D^{25}$: + 34.74 (*c* 0.99, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

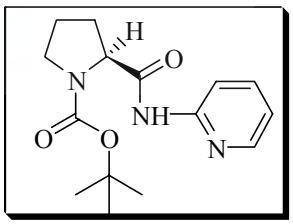
Enantiomeric purity: 76% [determined by HPLC analysis using chiral column,Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min] of the racemic compound **(±)-222a** showed two peaks at 8.55 min (*S*) and 9.95 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-222a** showed two peaks at 8.49 min (*S*) and 9.85 min (*R*) in the ratio of 88:12 indicating that the reaction is 76% enantioselective.

(2*S*)-1-*tert*-Butoxycarbonyl-2-(pyrid-2-ylamino)carbonylpyrrolidine (251):

This compound was prepared *via* the successive treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248**) with ethyl chloroformate and 2-aminopyridine in the presence of triethylamine following the similar procedure described for compound **236**.



Time: 12 h

Yield: 76%

Mp: 156-158 ^oC

$[\alpha]_D^{25}$: - 109.0 (*c* 1, $CHCl_3$)

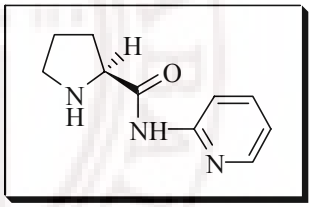
IR (KBr): ν 3219-2885 (multiple bands), 1707, 1695 cm^{-1}

^{1}H NMR: δ 1.45 (s, 9H), 1.85-2.50 (m, 4H), 3.25-3.74 (m, 2H), 4.20-4.62 (m, 1H), 7.03 (bs, 1H), 7.69 (br, 1H), 8.21 (d, 1H, J = 8.0 Hz), 8.28 (d, 1H, J = 4 Hz), 8.51 & 9.30 (2 br,1H).

^{13}C NMR: δ 23.96, 24.61, 28.36, 31.03, 47.27, 61.23, 62.05, 80.95, 113.85, 119.82, 138.26, 148.01, 151.21, 171.46 (mixture of isomers).

(2*S*)-2-(Pyrid-2-ylamino)carbonylpyrrolidine (244):

This compound was prepared following the procedure described for the preparation of compound **242** *via* the reaction between (2*S*)-1-*tert*-butoxycarbonyl-2-(pyrid-2-ylamino)carbonylpyrrolidine (**251**) and HCl (g) in dichloromethane (10 mL).



Time: 20 min

Yield: 84%

$[\alpha]_D^{25}$: - 60.25 (*c* 2, MeOH)

[Lit. [169] $[\alpha]_D^{20}$: -56.0 (*c* 1.0, MeOH)].

IR (Neat): ν 3275, 1693, 1300 cm^{-1}

^{1}H NMR: δ 1.64-1.86 (m, 2H), 1.97-2.11 (m, 1H), 2.15-2.29 (m, 1H), 2.39 (br, 1H), 2.97-3.14 (m, 2H), 3.83-3.95 (m, 1H), 6.97-7.07 (m, 1H), 7.64-7.75 (m, 1H), 8.25 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, J = 4.8 Hz), 10.22 (br, 1H).

^{13}C NMR: δ 26.18, 30.82, 47.26, 60.94, 113.51, 119.55, 138.17, 147.88, 151.09, 174.43.

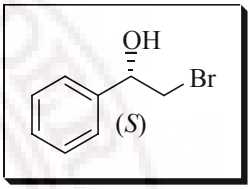
LCMS (m/z): 192 $(M+H)^+$

Anal. calcd. for $C_{12}H_{18}N_2$: C, 62.81; H, 6.85; N, 21.97.

Found: C, 62.88; H, 6.86; N, 22.05.

(*S*)-2-Bromo-1-phenylethanol [**(*S*)-222a**]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of phenacyl bromide (**221a**) in the presence of chiral catalyst (2*S*)-2-(pyrid-2-ylaminocarbonyl)pyrrolidine (**244**, 2 mol%), following the similar procedure described for the compound **(*S*)-222a** (Page no 156).



Yield: 83%

$[\alpha]_D^{25}$: + 24.24 (*c* 1.13, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

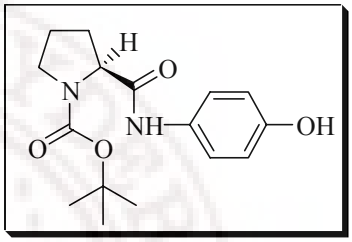
Enantiomeric purity: 51% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.48 min and 9.85 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 75.5:24.5 [retention times: 8.53 min (*S*) and 9.89 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 51%.

(2S)-N-*tert*-Butoxycarbonyl-2-(4-hydroxyphenylamino)carbonylpyrrolidine (252):

This compound was obtained as a colorless solid by treatment of (2*S*)-N-*tert*-butoxycarbonylproline (**248**, 2.15 g, 10 mM) with ethyl chloroformate (1.08 g, 10 mM) and then with 4-aminophenol (1.09 g, 10 mM) in the presence of triethylamine (1.01 g, 10 mM) in THF (30 mL) following the similar method described for the compound **236**.



Time: 16 h

Yield: 78% (2.38 g)

Mp: 218-220 ^{o}C

$[\alpha]_D^{25}$: - 74.37 (*c* 0.96, MeOH)

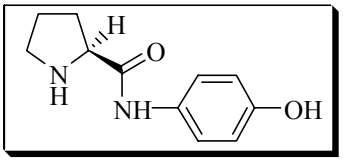
IR (KBr): ν 3296, 1691, 1682, 1516 cm^{-1}

^{1}H NMR (10%DMSO-d_6 in $CDCl_3$): δ 1.30-1.57 (m, 9H), 1.75-2.32 (m, 4H), 3.01-3.62 (m, 2H), 4.22 & 4.35 (2 br,1H), 6.74 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 8.83 (bs, 1H), 9.04 & 9.27 (2 br, 1H).

^{13}C NMR (20%DMSO-d_6 in $CDCl_3$): δ 22.61, 22.94, 23.60, 27.50, 28.22, 30.52, 46.08, 59.57, 60.23, 78.74, 114.47, 120.60, 121.06, 129.52, 152.92, 169.47 (mixture of isomers).

(2*S*)-N-(4-Hydroxyphenylamino)carbonylpyrrolidine (245):

This compound was prepared by the reaction of (2S)-N-*tert*-butoxycarbonyl-2-(4-hydroxyphenylamino)carbonylpyrrolidine (**252**, 0.306 g, 1 mM) and TFA in dichloromethane (4 mL) as described earlier for compound **241**.



Yield: 76% (0.157 g)

Mp: 150-152 ^{o}C

$[\alpha]_D^{25}$: - 22.45 (*c* 0.85, MeOH)

IR (KBr): ν 3350-2924 (multiple bands), 1682, 1518, 1257 cm^{-1}

^1H NMR: δ 1.67-1.84 (m, 2H), 1.85-1.99 (m, 1H), 2.08-2.24 (m, 1H), 2.91-3.11 (m, 2H), 3.31 (br, 1H), 3.72-3.86 (m, 1H), 6.74 (d, 2H, *J* = 8.8 Hz), 7.36 (d, 2H, *J* = 8.8 Hz), 9.08 (br, 1H), 9.65 (bs, 1H).

^{13}C NMR: ($20\%DMSO\text{-}d_6$ in $CDCl_3$) δ 24.94, 29.53, 45.90, 59.61, 114.18, 119.82, 128.80, 152.60, 171.57.

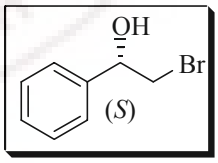
LCMS (m/z): 207 $(M+H)^+$

Anal. calcd. for $C_{12}H_{18}N_2$: C, 64.06; H, 6.84; N, 13.58.

Found: C, 64.12; H, 6.81; N, 13.62.

(*S*)-2-Bromo-1-phenylethanol [**(*S*)-222a**]:

This compound was obtained *via* asymmetric reduction of phenacyl bromide (**221a**) with $BH_3.SMe_2$ using 2 mol% (2*S*)-N-(4-hydroxyphenylamino)carbonylpyrrolidine (**245**) in THF-toluene (4:1), as a colorless liquid following the procedure described for the compound **(*S*)-222a** in case of catalyst **242** (Page no 156).



Yield: 86%

$[\alpha]_D^{25}$: + 30.54 (*c* 0.91, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$) (*R*)-configuration, 93% *ee*]

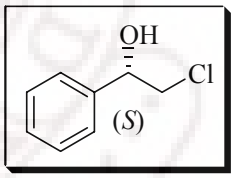
Enantiomeric purity: 72% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.04 min and 9.52 min] due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 86:14 [retention times: 8.22 min (*S*) and 9.86 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 72%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-222b]:

Asymmetric reduction of phenacyl chloride (**221b**) using $BH_3.SMe_2$ under the influence of 2 mol% (2*S*)-N-(4-hydroxyphenylamino)carbonylpyrrolidine (**245**) in THF-toluene (4:1) provided the title compound as a colorless liquid following the procedure described for the compound **(*S*)-222a** in case of catalyst **242** (Page no 156).



Yield: 86%

$[\alpha]_D^{25}$: + 31.53 (*c* 0.91, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: - 48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 73% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

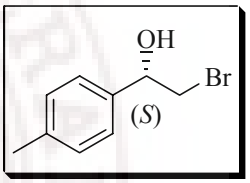
Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min] of the racemic compound **(±)-222b** showed two peaks at 8.02 min

(*S*) and 9.62 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-222b** showed two peaks at 8.04 min (*S*) and 9.65 min (*R*) in the ratio of 86.5:13.5 indicating that the reaction is 73% enantioselective.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-222c]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of 4-methylphenacyl bromide (**221c**) using chiral catalyst (2*S*)-N-(4-hydroxyphenylamino)-carbonylpyrrolidine (**245**, 2 mol%) in THF-toluene (4:1), following the similar procedure described for the compound **(*S*)-222a**.



Yield: 86%

$[\alpha]_D^{25}$: + 33.73 (*c* 0.91, $CHCl_3$)

[Lit.[132] $[\alpha]_D^{25}$: + 41.8 (*c* 1.00, $CHCl_3$), (*S*)-configuration, 95% *ee*]

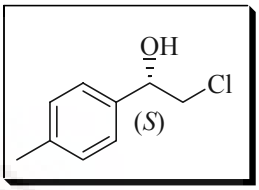
Enantiomeric purity: 74% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222c**.]

Determination of enantiomeric purity:

HPLC analysis of racemic alcohol **(±) 222c** [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min; retention times: 13.85 min and 17.03 min] showed two peaks of equal intensity due to *S* and *R* enantiomers The chiral alcohol **(*S*)-222c** showed two peaks in the ratio of 87:13 [retention times: 14.59 min (*S*) and 18.26 min (*R*) respectively] on similar HPLC analysis, indicating that the reaction is 74% enantioselective.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-222d]:

Borane-dimethylsulfide mediated asymmetric reduction of 4-methylphenacyl chloride (**221d**) in the presence of (2*S*)-N-(4-hydroxyphenylamino)carbonylpyrrolidine (**245**, 2 mol%) in THF-toluene (4:1) furnished the chiral alcohol **(*S*)-222d** as a colorless liquid following the method described for the compound **(*S*)-222a** (Page no 156).



Yield: 84%

$[\alpha]_D^{25}$: + 39.2 (*c* 0.98, $CHCl_3$)

{Lit.[132] $[\alpha]_D^{25}$: + 47.2 (*c* 1.1, $CHCl_3$) (*S*)-configuration, 92% *ee*}

Enantiomeric purity: 73% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222d**]

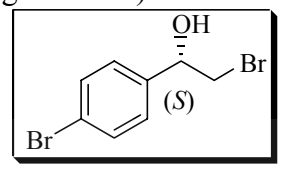
Determination of enantiomeric purity:

Racemic alcohol **(±)-222d** and chiral alcohol **(*S*)-222d** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (97.5:2.5); flow rate: 0.9 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 15.28 min and 18.09 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222d** showed two peaks in the ratio of 86.5:13.5 [retention times: 15.37 min (*S*) and 18.36 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 73%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-222e]:

This compound was obtained *via* the borane-mediated reduction of 4-bromophenacyl

bromide (**221e**) under the catalytic influence of (2*S*)-N-(4-hydroxyphenylamino)-carbonylpyrrolidine (**245**, 2 mol%) in THF-toluene (4:1) as a white solid, following the similar procedure described for the compound **(*S*)-222a** (Page no. 156).



Yield: 85%

Mp: 69-71 ^{o}C (Lit [159] 70-72 ^{o}C)

$[\alpha]_D^{25}$: + 23.4 (*c* 0.93, $CHCl_3$) {Lit.[159] $[\alpha]_D^{25}$: - 31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

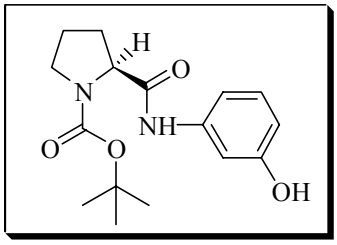
Enantiomeric purity: 77% [determined by HPLC analysis using chiral column, Chiralcel-OJ H, with reference to racemic alcohol **(±)-222e**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222e** showed two peaks in 1:1 ratio on HPLC analysis [chiral column, Chiralcel-OJ H, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 23.70 min and 27.11 min] arising from *R* and *S* enantiomers. Chiral alcohol **(*S*)-222e** showed two peaks in 11.5:88.5 ratio [retention times: 21.63 min (*R*) and 24.42 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 77%.

(2*S*)-N-*tert*-Butoxycarbonyl-2-(3-hydroxyphenylamino)carbonylpyrrolidine (253):

This compound was obtained as a colorless solid by successive treatment of (2*S*)-N-*tert*-butoxycarbonylproline, **(248)** with ethyl chloroformate and 3-aminophenol in the presence of triethylamine in THF following the similar method described for the compound **236**.



Time: 16 h

Yield: 79%

Mp: 200-202 ^{o}C

$[\alpha]_D^{25}$: - 80.10 (*c* 1, MeOH)

IR (KBr): ν 3306-2874 (multiple bands), 1682, 1618, 1558 cm^{-1}

^{1}H NMR: (δ 1.24 & 1.39 (2S, 9H), 1.76-2.35 (m, 4H), 3.30-3.91 (m, 2H)
(10%DMSO-d_6 in $CDCl_3$)

4.24 & 4.38 (2 br, 1H), 6.48-6.62 (m, 1H), 6.88-7.15 (m, 2H),

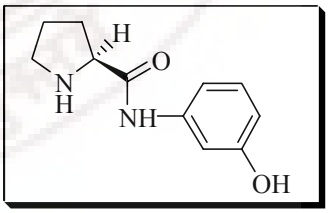
7.21 (s, 1H), 8.96 (s, 1H), 9.03 & 9,37 (2 br, 1H).

^{13}C NMR: (δ 23.18, 23.76, 27.68, 28.02, 30.63, 46.27, 59.90, 60.64, 79.24,
(10%DMSO-d_6 in $CDCl_3$)

106.62, 110.14, 110.46, 128.73, 138.85, 157.05, 169.81, 170.84.
(mixture of isomers)

(2*S*)-2-(3-Hydroxyphenylamino)carbonylpyrrolidine (246):

This compound was prepared by the reaction of (2*S*)-N-*tert*-butoxycarbonyl-2-(3-hydroxyphenylamino)carbonylpyrrolidine (**253**) and TFA in dichloromethane as described earlier for compound **241**, as viscous liquid.



Yield: 82%

$[\alpha]_D^{25}$: - 38.26 (*c* 0.80, MeOH)

IR (KBr): ν 3500-2876 (multiple bands), 1682, 1606 cm^{-1}

^{1}H NMR: (δ 1.67-1.84 (m, 2H), 1.96-2.07 (m, 1H), 2.23-2.37 (m, 1H),

2.93-3.03 (m, 1H), 3.04-3.13 (m, 1H), 3.86-3.96 (m, 1H), 6.47-

6.53 (m, 1H), 6.63-6.68 (m, 1H), 7.11-7.18 (m, 1H), 8.25-8.31 (m, 1H), 9.83 (bs, 1H).

^{13}C NMR: δ 26.55, 30.88, 47.42, 60.91, 106.95, 110.08, 111.82, 129.62, 138.33, 158.27, 174.76.

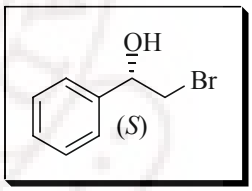
LCMS (m/z): 207 $(M+H)^+$

Anal. calcd. for $C_{12}H_{18}N_2$: C, 64.06; H, 6.84; N, 13.58;

Found: C, 63.98; H, 6.87; N, 13.55.

(*S*)-2-Bromo-1-phenylethanol [**(*S*)-222a**]**:**

This compound was obtained *via* asymmetric reduction of phenacyl bromide (**221a**) with $BH_3.SMe_2$ using 2 mol% (2*S*)-2-(3-hydroxyphenylamino)carbonylpyrrolidine (**246**) in THF-toluene (4:1), as a colorless liquid following the procedure described for the compound **(*S*)-222a** in case of catalyst **242** (Page no 156).



Yield: 87%

$[\alpha]_D^{25}$: + 33.23 (*c* 1.76, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 77% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.99 min and 9.53 min] due to *S* and *R* enantiomers. The chiral alcohol

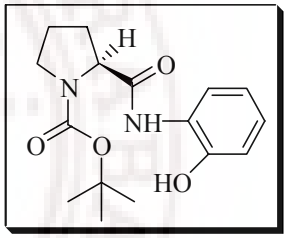
(*S*)-222a showed two peaks in the ratio of 88.5:11.5 [retention times: 9.14 min (*S*) and 9.73 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 77%.

(2*S*)-N-*tert*-Butoxycarbonyl-(2-hydroxyphenylamino)carbonylpyrrolidine (254):

This compound was obtained as a colorless solid by the successive treatment of (*S*)-N-*tert*-butoxycarbonylproline, (**248**) with ethyl chloroformate and 2-aminophenol in the presence of triethylamine in THF following the similar method described for the compound **236.**

Time: 16 h

Yield: 77%



Mp: 132-134 ^{o}C

$[\alpha]_D^{25}$: - 98.62 (*c* 1.02, MeOH)

IR (KBr): ν 3271, 2976, 1676, 1541 cm^{-1}

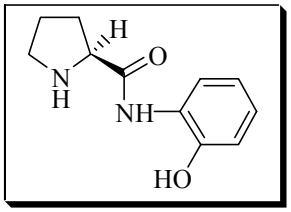
^{1}H NMR: δ 1.49 (s, 9H), 1.95 (bs, 3H), 1.80-2.50 (m, 1H), 3.29-3.70 (m, 2H), 4.54 (br, 1H), 6.77-6.88 (m,1H), 6.92-7.17 (m, 2H), 9.04 (br, 1H), 8.34 & 9.65 (2br, 1H).

^{13}C NMR: δ 24.51, 28.40, 47.30, 60.20, 60.48, 81.41, 119.20, 120.30, 122.43, 125.63, 126.71, 148.48, 171.79.

(2*S*)-2-(2-Hydroxyphenylamino)carbonylpyrrolidine (247):

This compound was prepared by the reaction of (2*S*)-N-*tert*-butoxycarbonyl-(2-hydroxyp-

henylamino)carbonylpyrrolidine (**254**) and TFA in dichloromethane as described earlier for compound **241**.



Yield: 80%

Mp: 164-166 ^{o}C [lit.[175] 170 ^{o}C]

$[\alpha]_D^{25}$: - 46.1 (*c* 1, CH_2Cl_2)

[Lit.[175] $[\alpha]_D^{20}$: - 45.6 (*c* 1.0, CH_2Cl_2)]

IR (KBr): ν 3354-2872 (multiple bands), 1643, 1454 cm^{-1}

^{1}H NMR: *δ*.1.70-1.85 (m, 2H), 1.97-2.11 (m, 1H), 2.15-2.32 (m, 1H), 2.95-3.17 (m, 2H), 3.85-4.02 (m, 1H), 6.79-6.88 (m, 1H), 6.91-7.04 (m, 2H), 7.06-7.15 (m,1H), 9.98 (br, 1H).

^{13}C NMR: *δ* 26.38, 30.95, 47.42, 60.31, 119.91, 120.01, 122.00, 125.18, 127.05, 149.09, 175.45.

LCMS (m/z): 207 $(M+H)^+$

Anal. calcd. for $C_{12}H_{18}N_2$: C, 64.06; H, 6.84; N, 13.58;

Found: C, 64.15; H, 6.78; N, 13.62.

(*S*)-2-Bromo-1-phenylethanol [**(*S*)-222a**]**:**

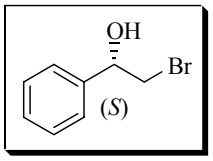
Borane-dimethylsulfide mediated asymmetric reduction of phenacyl bromide (**222a**) in the presence of (2*S*)-2-(2-hydroxyphenylamino)carbonylpyrrolidine, (**247**, 2 mol%) in THF-toluene (4:1) furnished the chiral alcohol **(*S*)-222a** as a colorless liquid following the method described for the compound **(*S*)-222a** for the catalyst **242** (Page no 156).

Yield: 78%

$[\alpha]_D^{25}$: + 11.89 (*c* 1.37, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0

(*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]



Enantiomeric purity: 22% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** and chiral alcohol **(*S*)-222a** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 8.01 min and 9.58 min due to *S* and *R* enantiomers. The chiral alcohol **(*S*)-222a** showed two peaks in the ratio of 61:39 [retention times: 8.05 min (*S*) and 9.66 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 22%.

Resolution of *cis* / *trans*-1,2-diaminocyclohexane [(*R*,*R*)-255]:

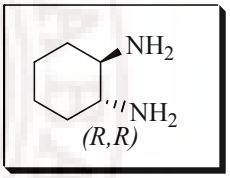
This compound was resoloved following the literature method.[170]

A mixture of *cis* / *trans*-1,2-diaminocyclohexane (59 mL, 490 mM) was added to a stirred solution of L-(+)-tartaric acid (37.5 g, 250 mM) in distilled water (100 mL) at such a rate that the reaction temperature just reached 70 ^oC. Glacial acetic acid (25 mL, 436 mM) was added to the resulting mixture in such a way that the reaction temperature just reached 90 ^oC. The white slurry formed immediately upon addition of the acid and was vigorously stirred for 2 h. Then the reaction mixture was cooled to 5 ^oC and stirred for 2 h. The

precipitate was collected by filtration under vacuum and thus obtained solid was washed with cold water (3 x 50 mL) followed by methanol (5 x 50 mL). The solid, thus obtained, was air dried to yield (*R*,*R*)-1,2-diammonium cyclohexane mono-(+)tartarate salt (30.2 g) as a white solid. Saturated KOH solution (100 mL) was added to this (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartarate salt, and stirred for 5 min at room temperature and extracted with dichloromethane (5 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the oil, thus obtained, was distilled to furnish the enantiomerically pure (*R*,*R*)-1,2-diaminocyclohexane [**(*R*,*R*)-255**] as a low melting solid (8.75 g) in 65% yield (from tartaric acid salt).

$[\alpha]_D^{25}$: - 22.13 (*c* 1.55, 1(N) HCl

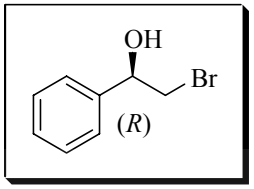
[Lit.[170] $[\alpha]_D^{25}$: - 25.0 (*c* 5, 1N HCl)].



Asymmetric reduction of phenacyl bromide (221a) by employing (*R*,*R*)-255 as a catalytic source: Synthesis of (*R*)-2-bromo-1-phenylethanol [(*R*)-222a]: Representative procedure.

To a stirred solution of (*R*,*R*)-1,2-diammoniumcyclohexane (5 mol%, 0.5 mL, 0.1 M solution in toluene) in toluene (2 mL) was added $BH_3.SMe_2$ (1 mM, 1 mL, 1 M solution in toluene) at room temperature and the reaction mixture was heated under reflux for 15 min at this temperature. A solution of phenacyl bromide [**221a**, 1 mM, 0.199 g] was added dropwise at this reflux temperature and the reaction was continued for further 15 min. The reaction mixture was cooled to room temperature and then solvent was removed under

reduced pressure. The residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*R*)-2-bromo-1-phenylethanol **(*R*)-222a** as colorless liquid.



Yield: 91% (0.182 g)

$[\alpha]_D^{25}$: - 20.0 (*c* 1.22, $CHCl_3$)

[Lit.[156] $[\alpha]_D^{25}$: - 39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 43% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222a**]

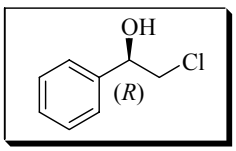
Determination of enantiomeric purity:

Racemic alcohol **(±)-222a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 9.01 min and 9.62 min] due to *S* and *R* enantiomers. The chiral alcohol **(*R*)-222a** showed two peaks in the ratio of 28.5:71.5 [retention times: 8.84 min (*S*) and 9.37 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 43%.

(*R*)-2-Chloro-1-phenylethanol [(*R*)-222b]:

Asymmetric reduction of phenacyl chloride (**221b**) using $BH_3.SMe_2$ under the influence of 5 mol% (*R*,*R*)-1,2-diaminocyclohexane (**255**) provided the title compound as a colorless liquid following the procedure described for the compound **(*R*)-222a** (Page no 177).

Yield: 88%



$[\alpha]_D^{25}$: - 20.47 (*c* 1.05, cyclohexane)

[Lit.[156] $[\alpha]_D^{25}$: - 48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

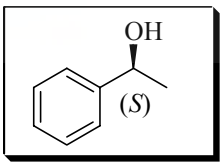
Enantiomeric purity: 45% [determined by HPLC analysis using chiral column, Chiralcel-OD H, with reference to racemic alcohol **(±)-222b**]

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OD H, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min] of the racemic compound **(±)-222b** showed two peaks at 8.45 min (*S*) and 9.02 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*R*)-222b** showed two peaks at 8.58 min (*S*) and 9.15 min (*R*) in the ratio of 27.5:72.5 indicating that the reaction is 45% enantioselective.

(*S*)-1-Phenylethanol [(*S*)-225a]:

This secondary alcohol was obtained as a colorless liquid by borane-mediated reduction of acetophenone (**224a**) in the presence of chiral catalyst (*R*,*R*)-1,2-diaminocyclohexane (**255,** 5 mol%), following the similar procedure described for the compound (*R*)-**222a** (Page no 177).



Yield: 90%

$[\alpha]_D^{25}$: - 10.0 (*c* 1.11, MeOH)

[Lit.[160] $[\alpha]_D^{25}$: + 44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

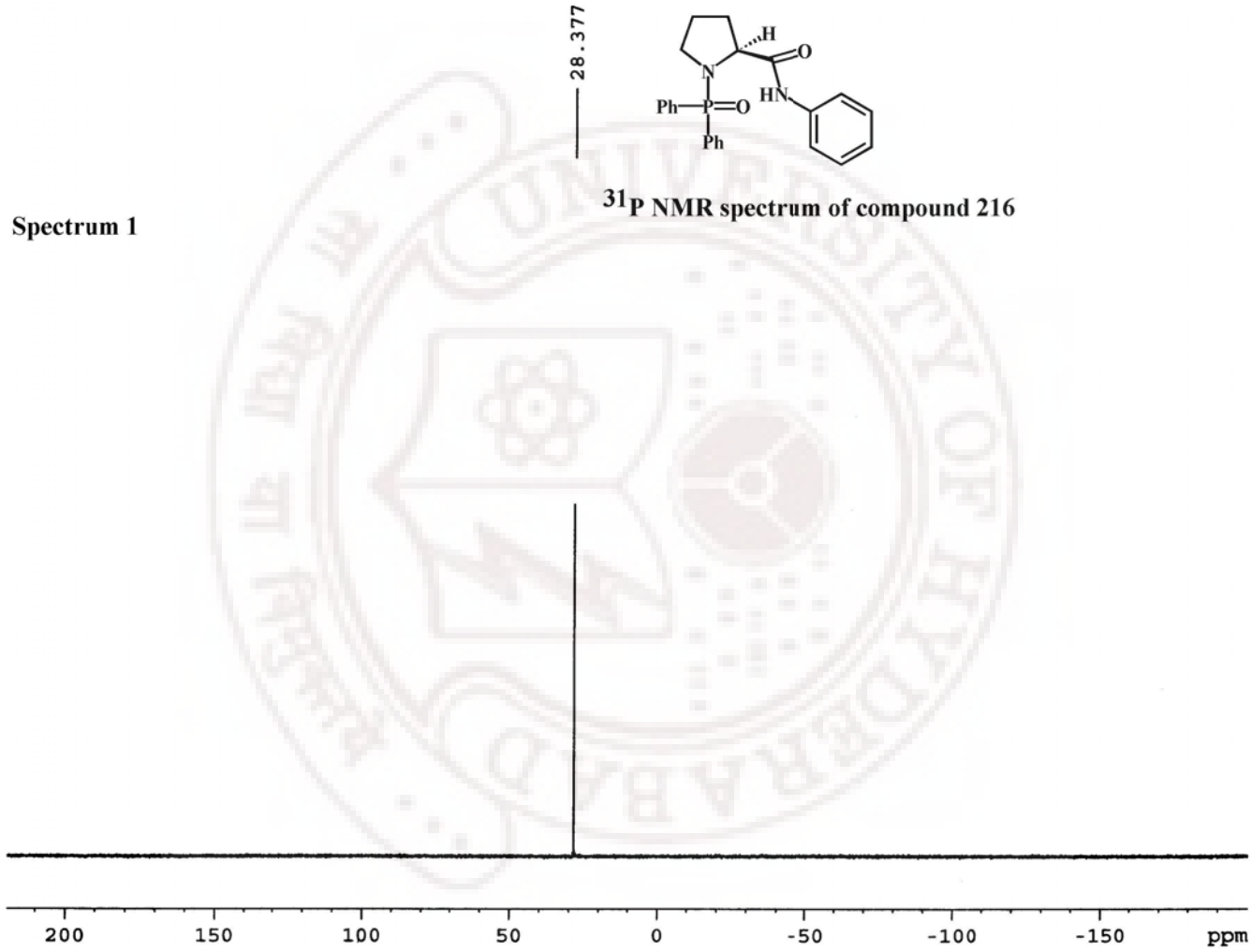
Enantiomeric purity: 23% [determined by HPLC analysis using chiral column, Chiralcel-

OD H, with reference to racemic alcohol **(±)-225a**]

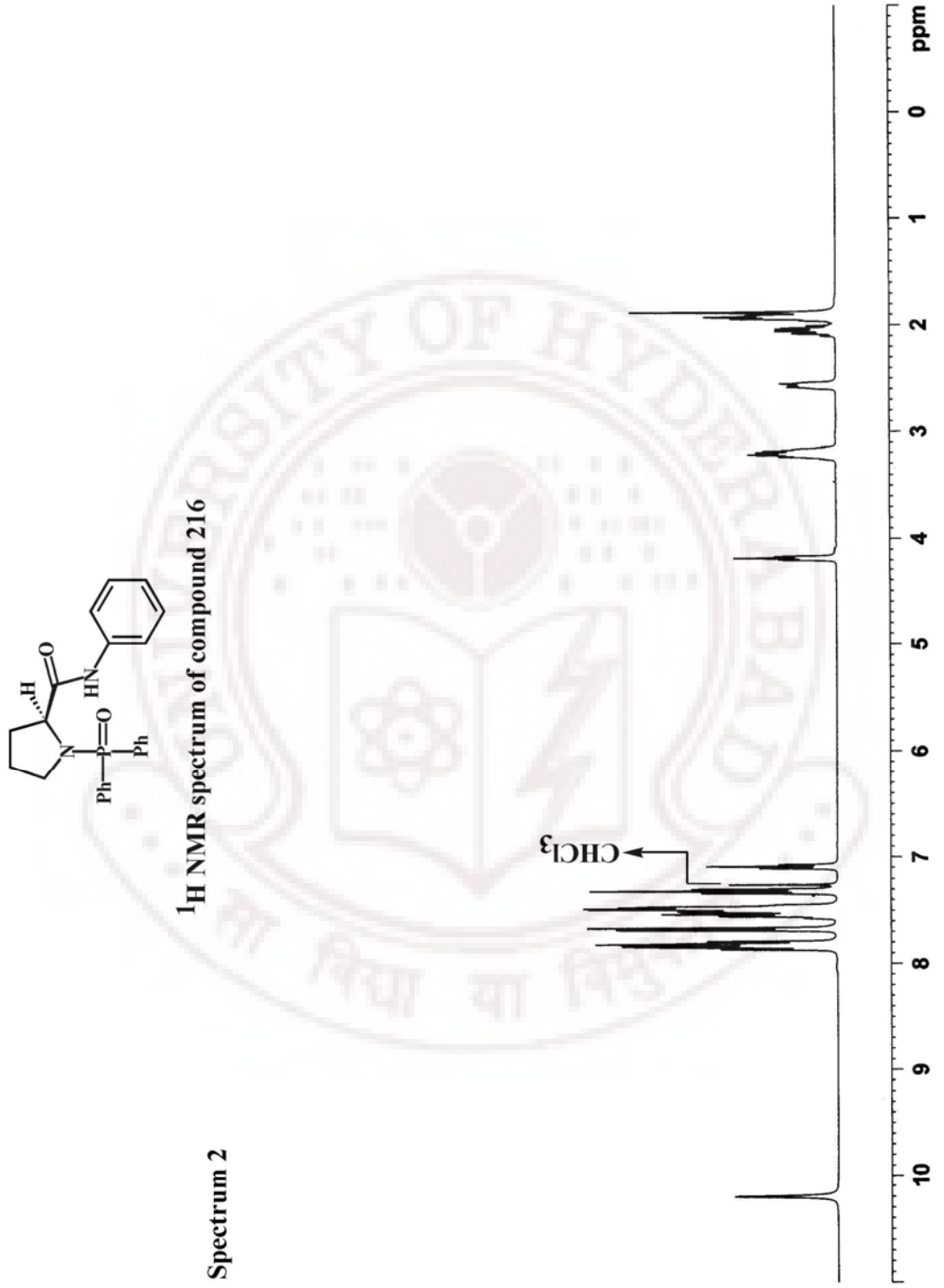
Determination of enantiomeric purity:

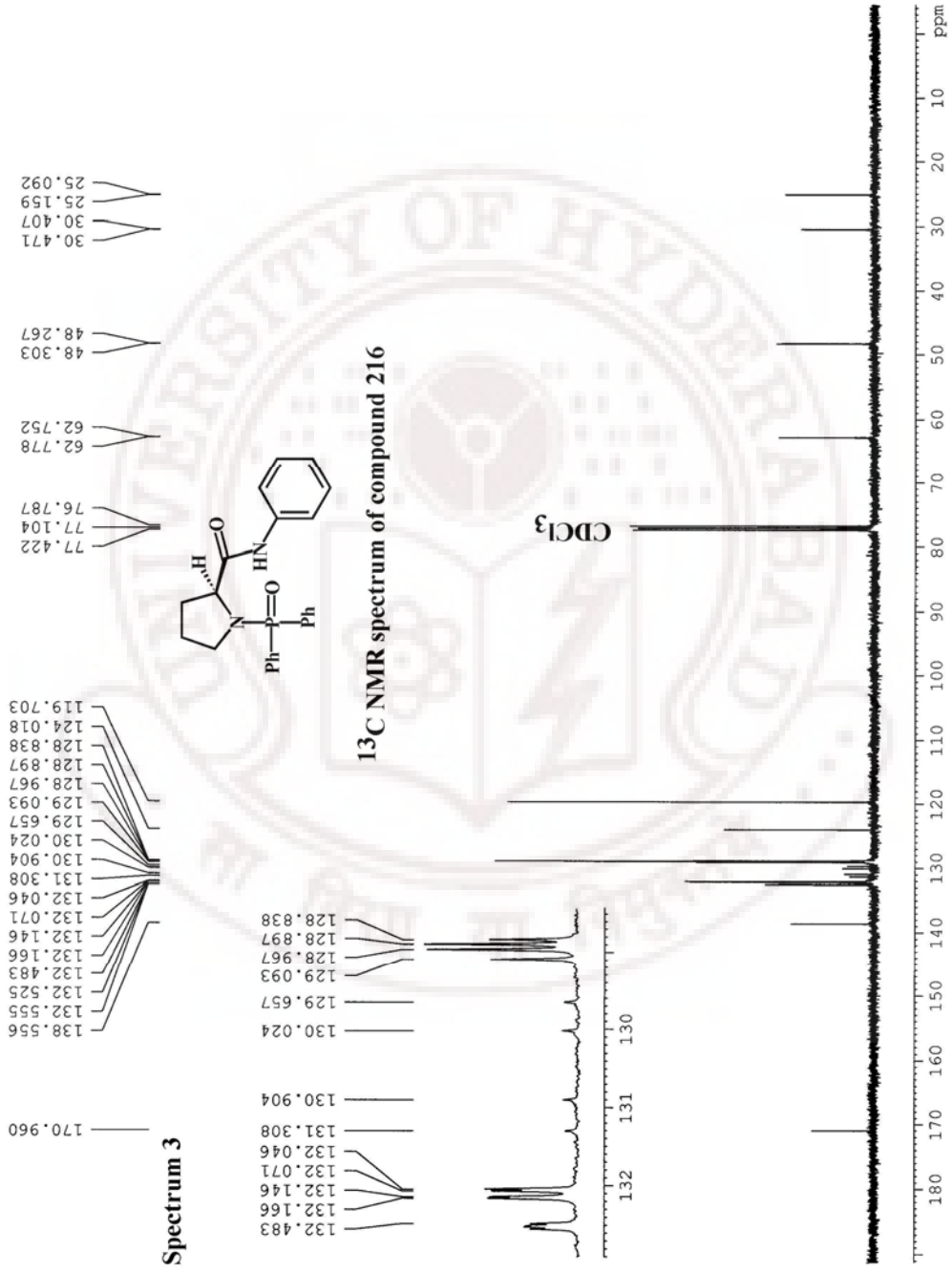
Racemic alcohol **(±)-225a** and chiral alcohol **(*S*)-225a** were analysed on HPLC using chiral column, Chiralcel-OD H [solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min]; the racemic alcohol showed two peaks of equal intensities at retention times: 9.48 min and 11.06 min due to *R* and *S* enantiomers. The chiral alcohol **(*S*)-225a** showed two peaks in the ratio of 38.5:61.5 [retention times: 9.50 min (*R*) and 11.12 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 23%.

Spectrum 1

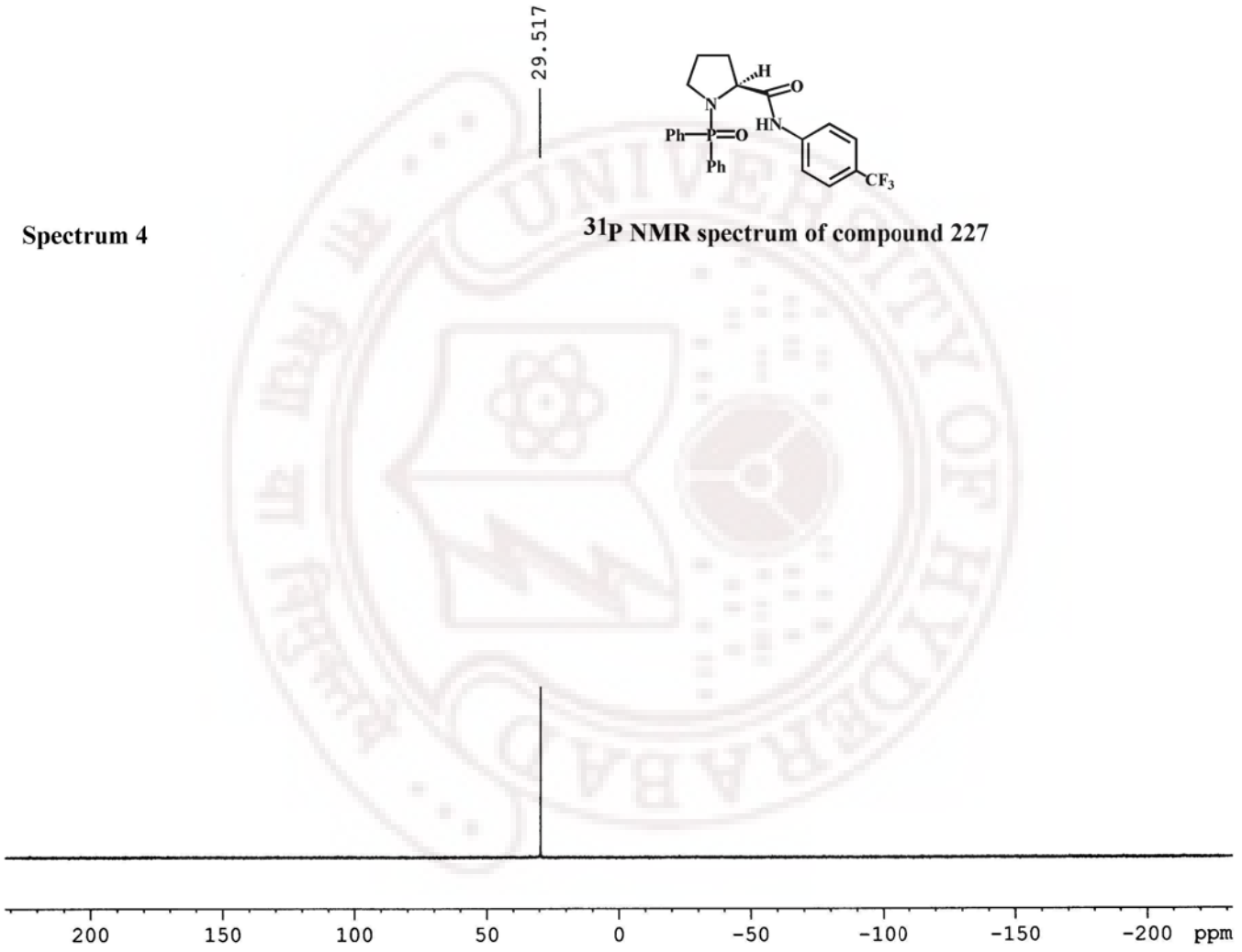


^{31}P NMR spectrum of compound 216

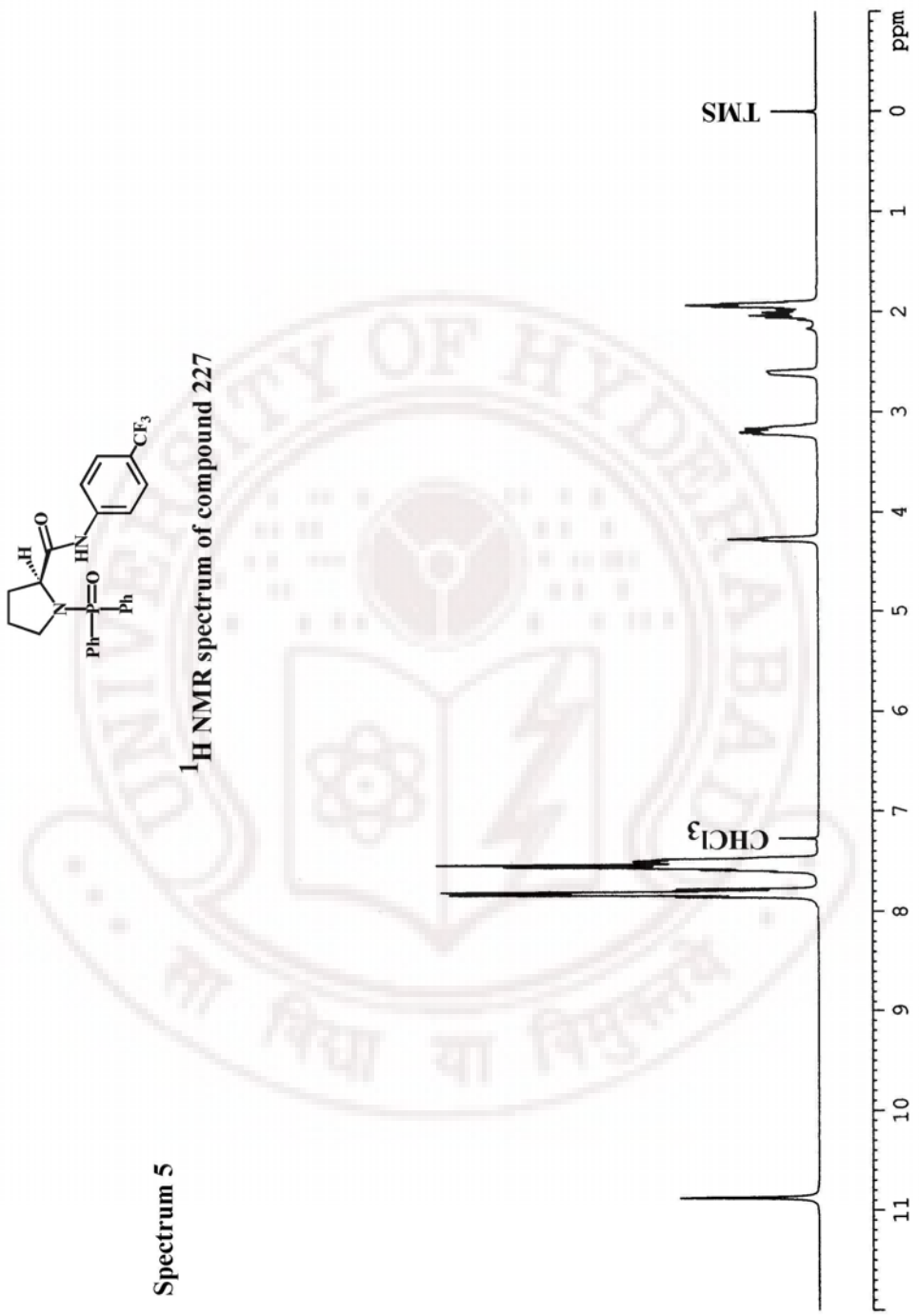

Spectrum 2
^{1}H NMR spectrum of compound 216
CHCl$_3$
ppm

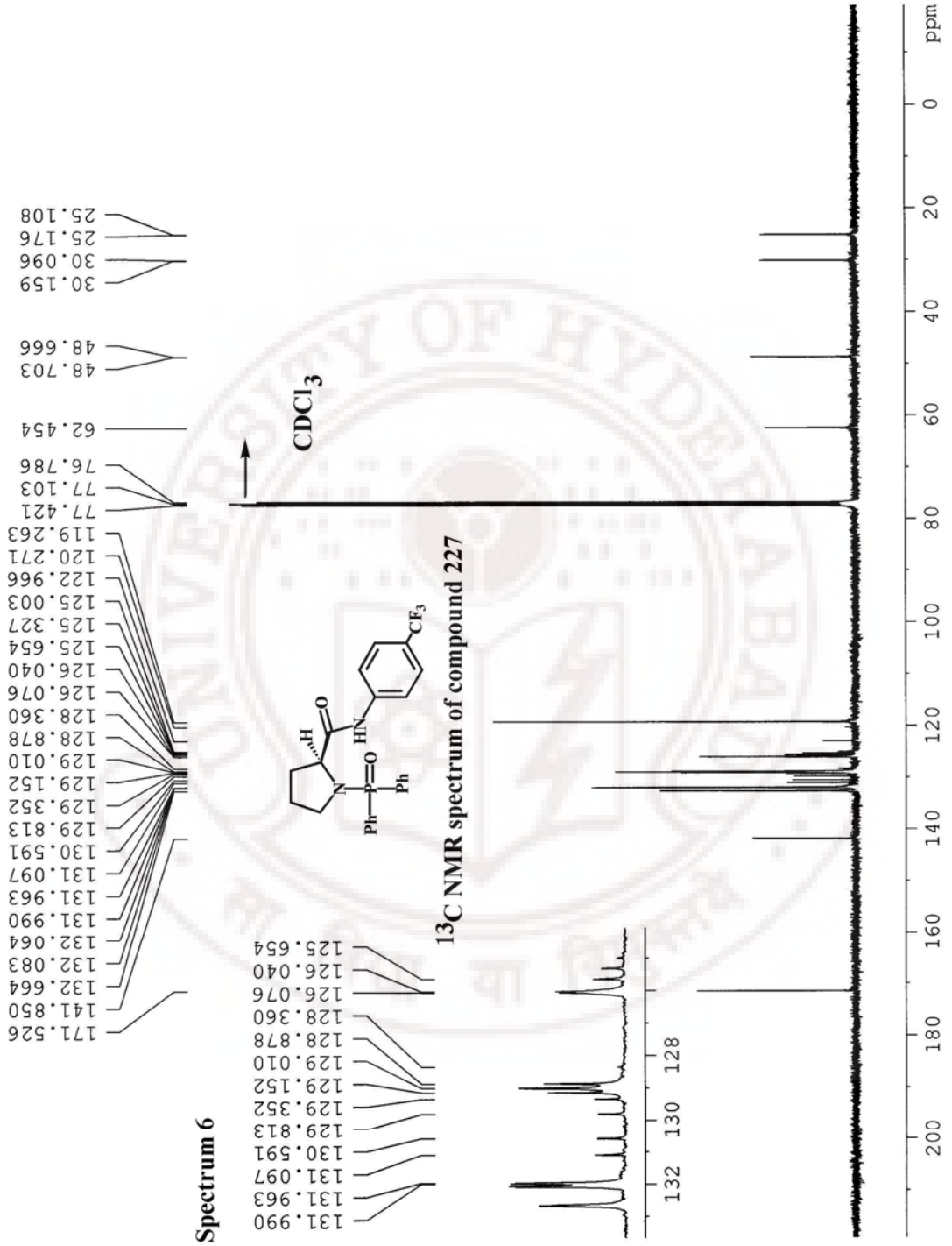

Spectrum 3
^{13}C NMR spectrum of compound 216
CDCl$_3$
ppm

Spectrum 4

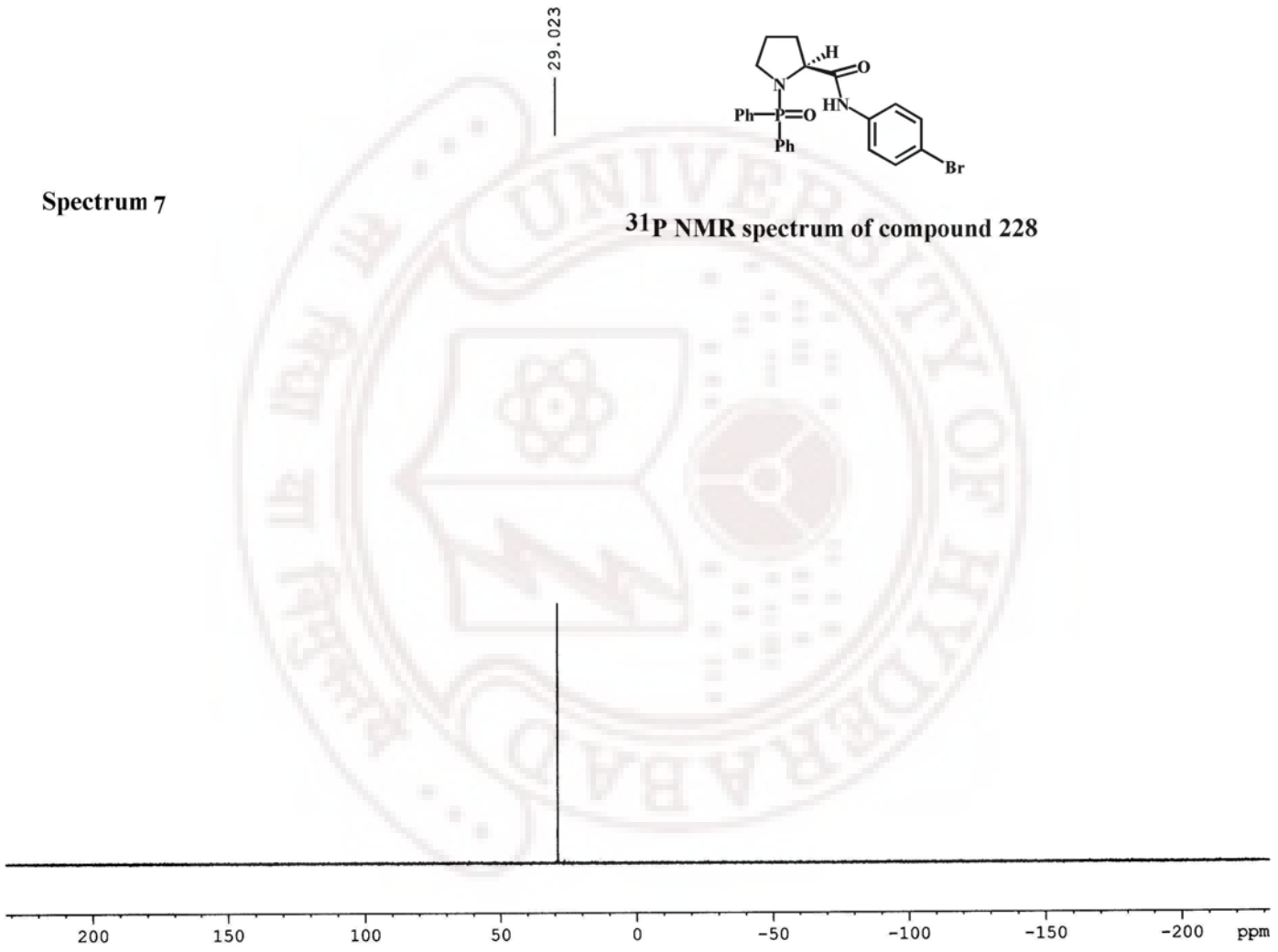


^{31}P NMR spectrum of compound 227

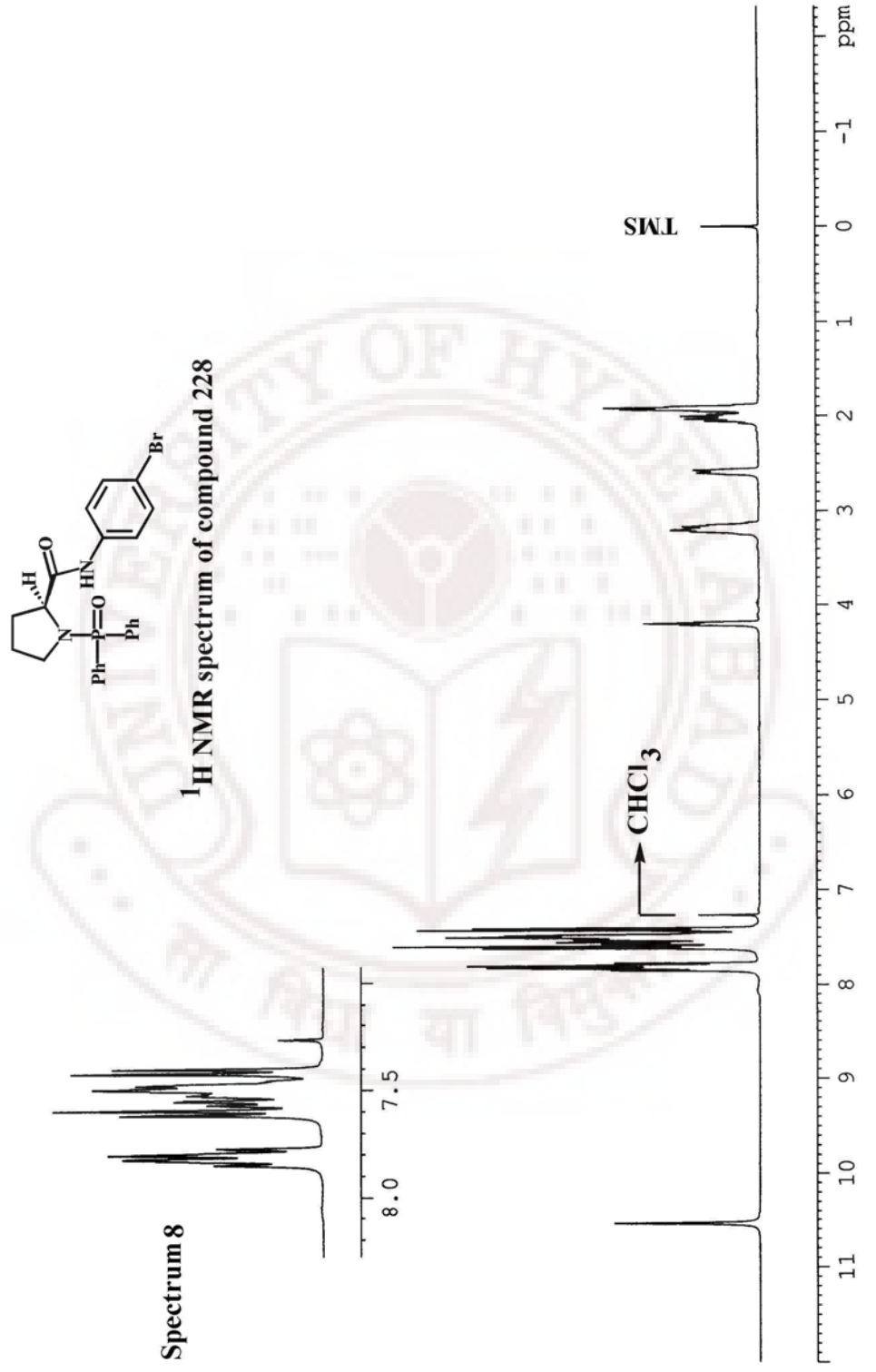

Spectrum 5
^{1}H NMR spectrum of compound 227
CHCl3
TMS
ppm

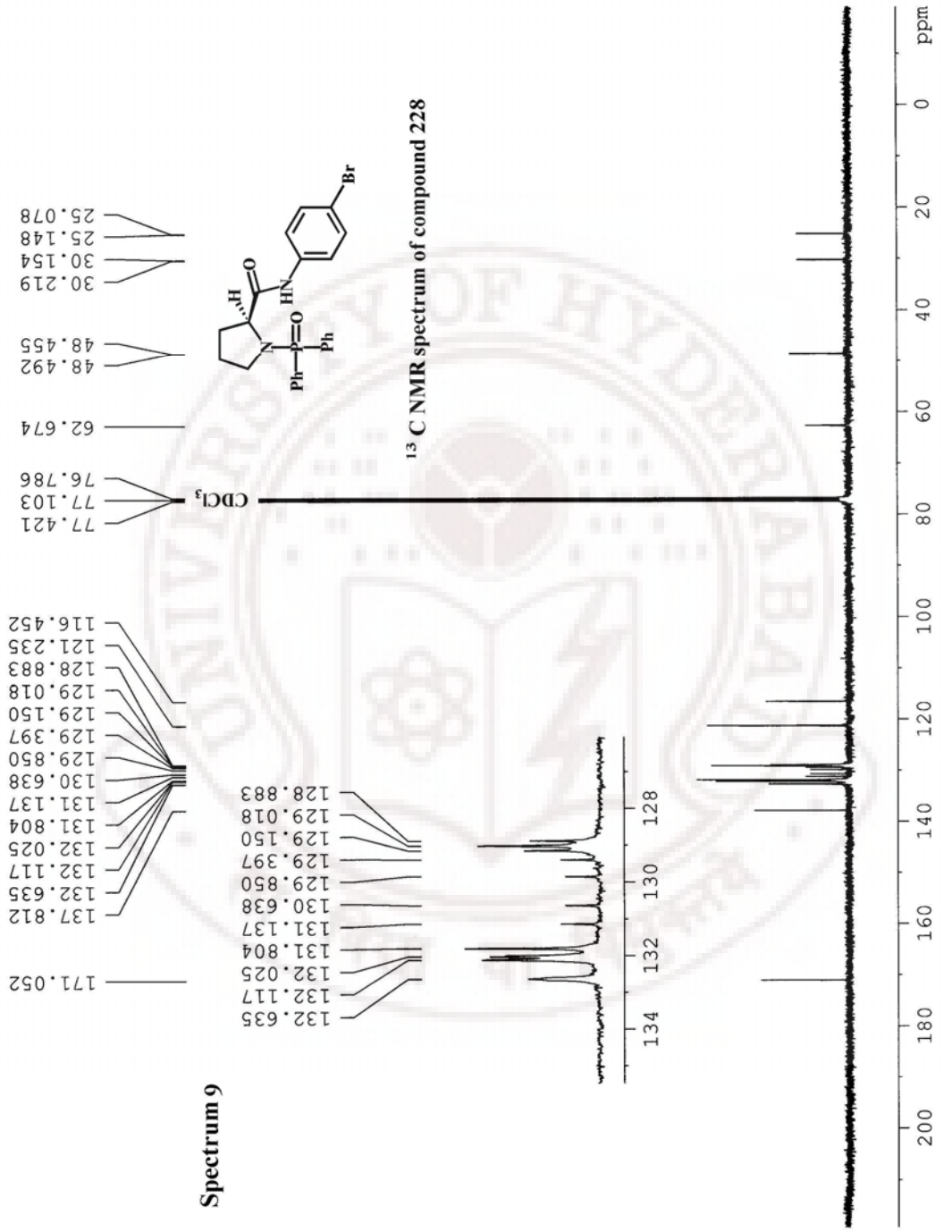

^{13}C NMR spectrum of compound 227
Spectrum 6
$CDCl_3$
171.526
141.850
132.664
132.083
132.064
131.990
131.963
131.097
130.591
129.813
129.352
129.152
129.010
128.878
128.360
126.076
126.040
125.654
77.421
77.103
76.786
62.454
48.703
48.666
30.159
30.096
25.176
25.108
ppm

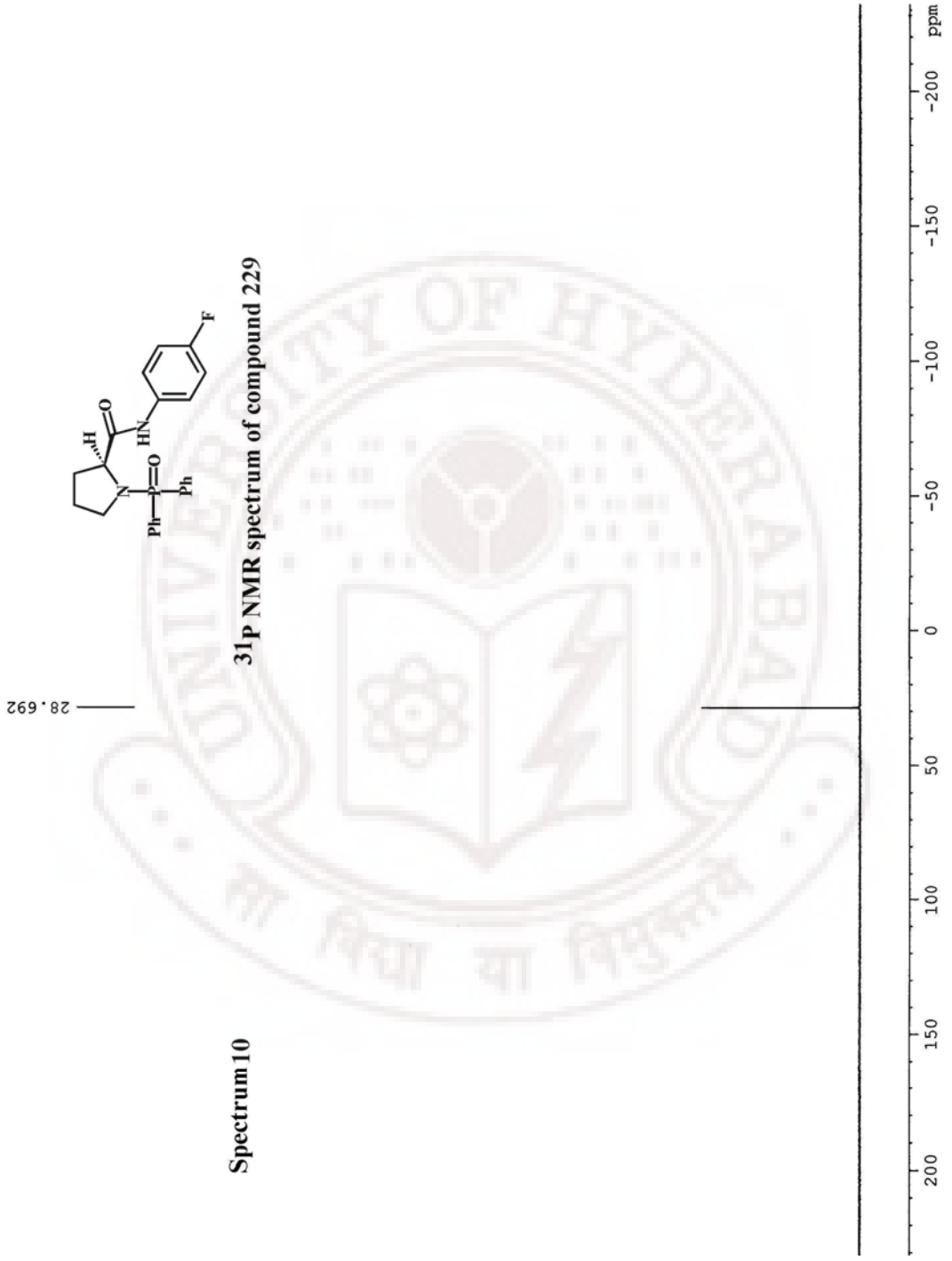
Spectrum 7



^{31}P NMR spectrum of compound 228

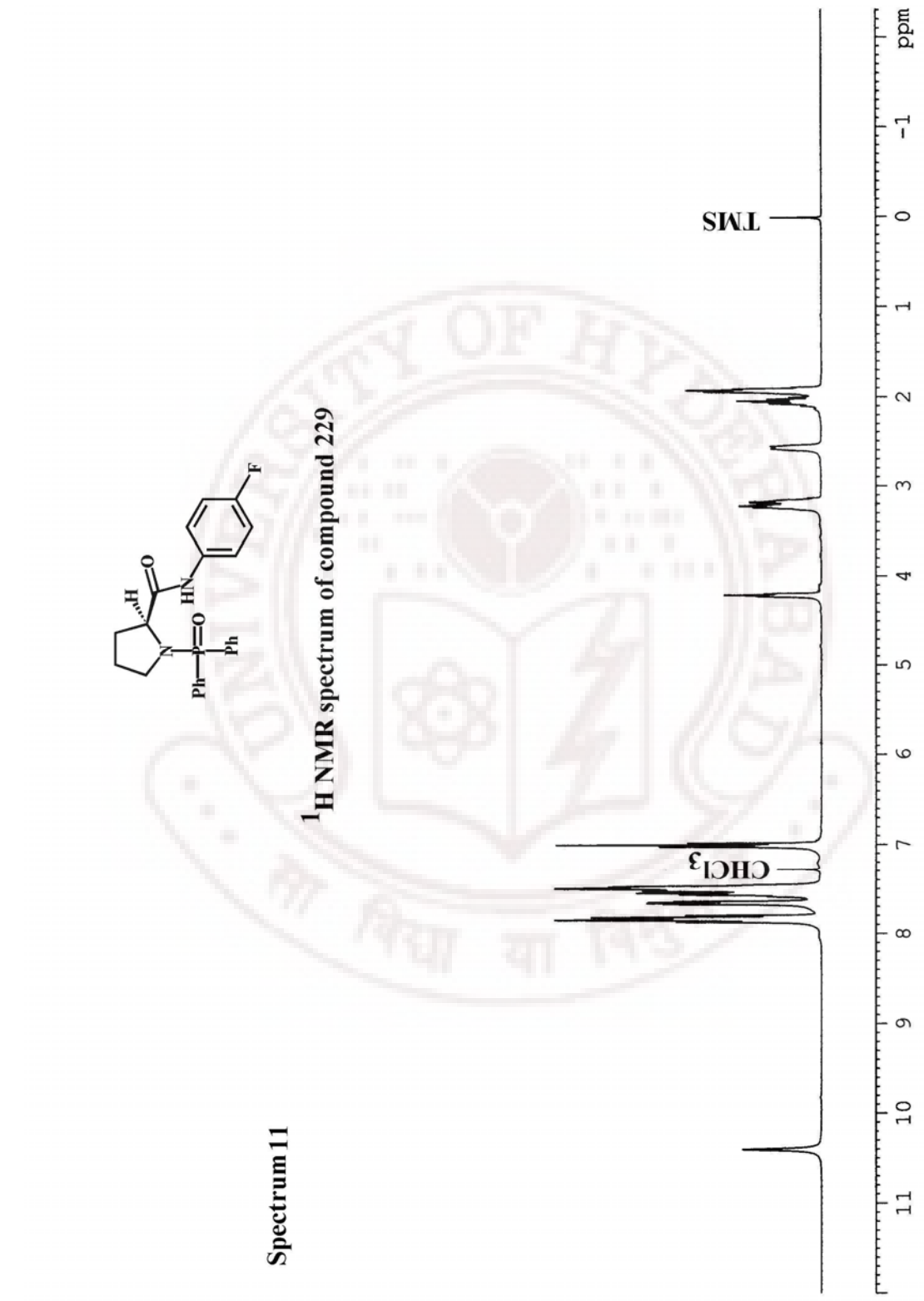

Spectrum 8
^{1}H NMR spectrum of compound 228
Br
HN
O
H
N
P
O
Ph
Ph
Ph
8.0
7.5
CHCl$_3$
TMS
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm

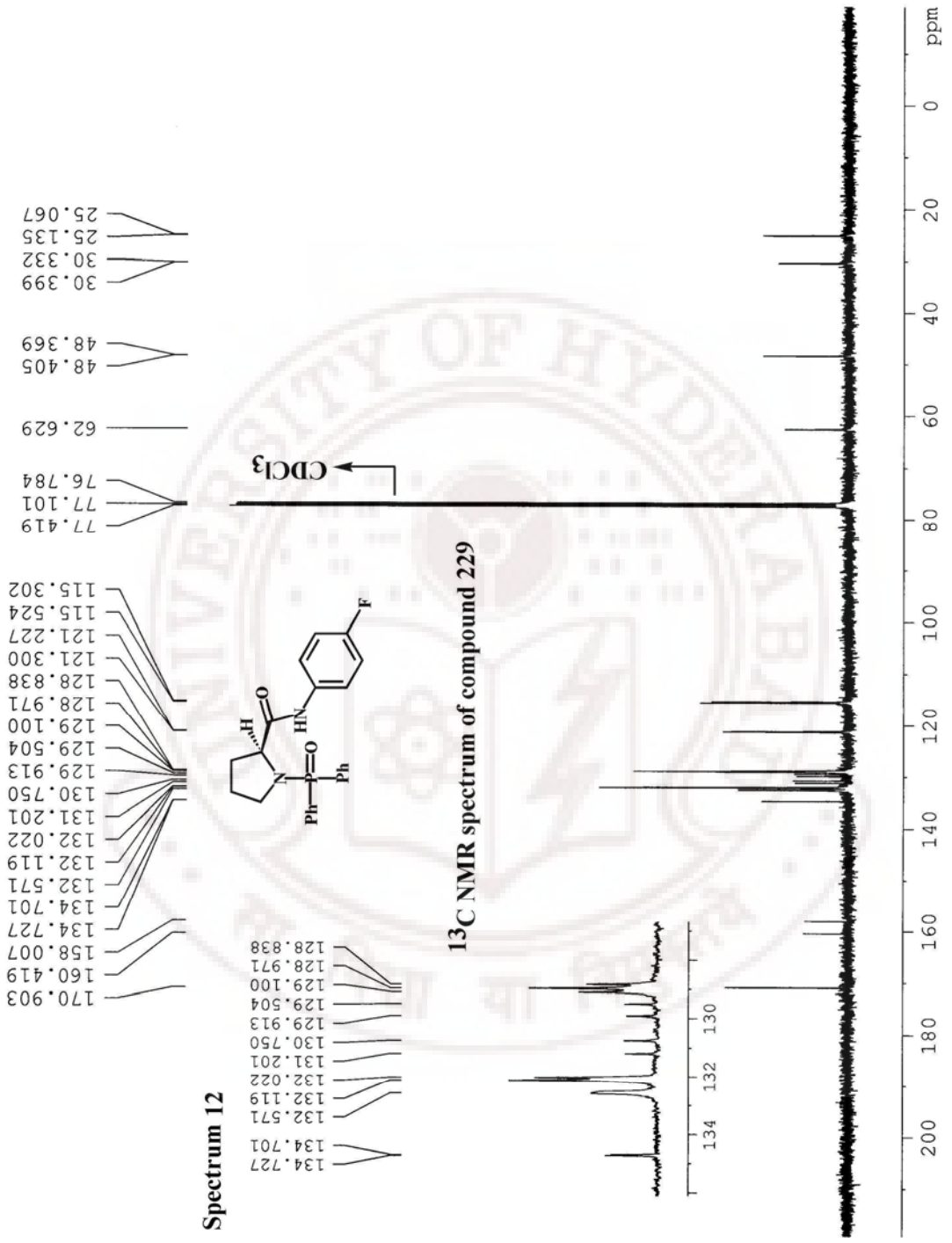

Spectrum 9
^{13}C NMR spectrum of compound 228
CDCl$_3$
77.421
77.103
76.786
62.674
48.492
48.455
30.219
30.154
25.148
25.078
171.052
137.812
132.635
132.117
132.025
131.804
131.137
130.638
129.850
129.397
129.150
129.018
128.883
121.235
116.452
Br
Ph
Ph
ppm

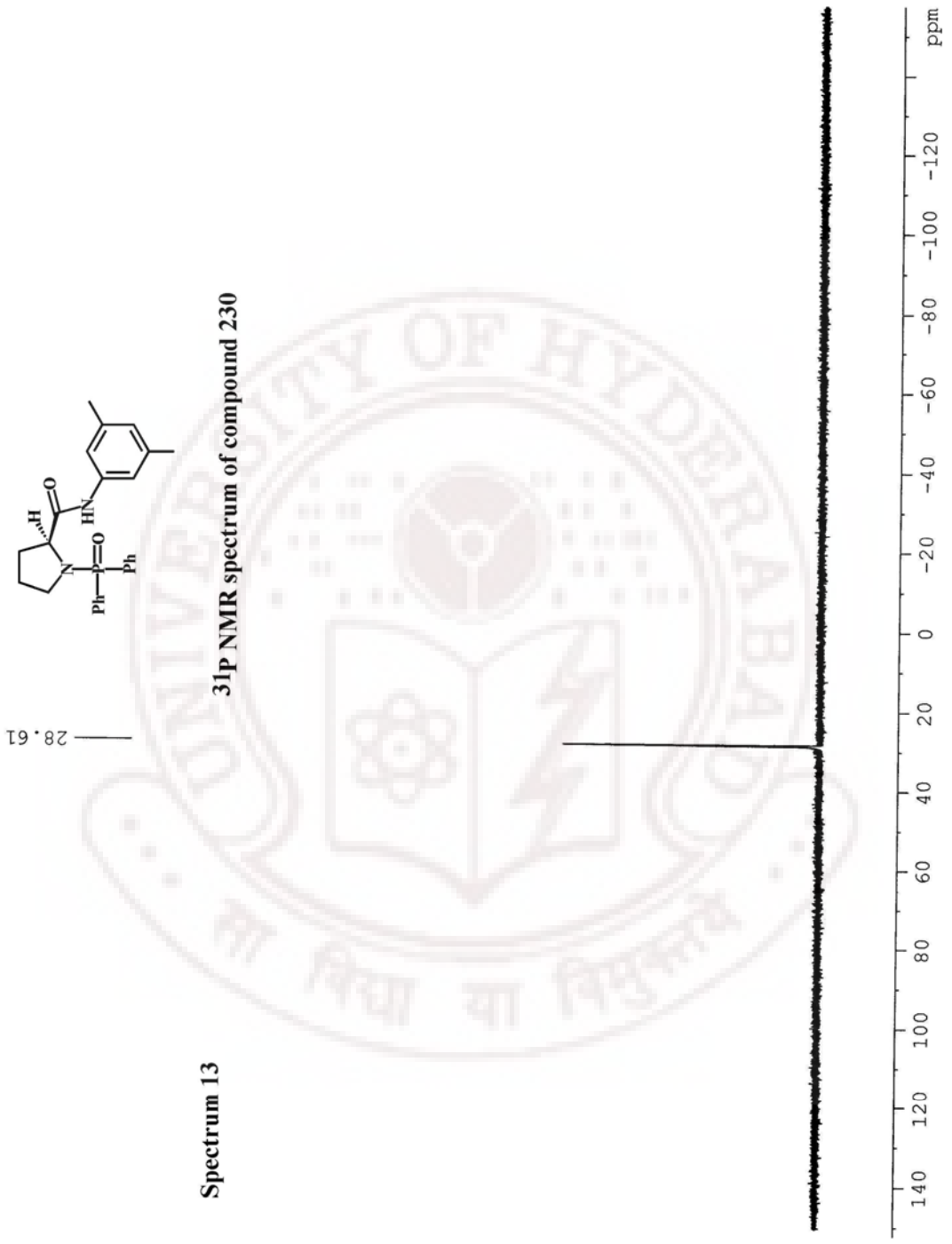


Spectrum 10

^{31}P NMR spectrum of compound 229

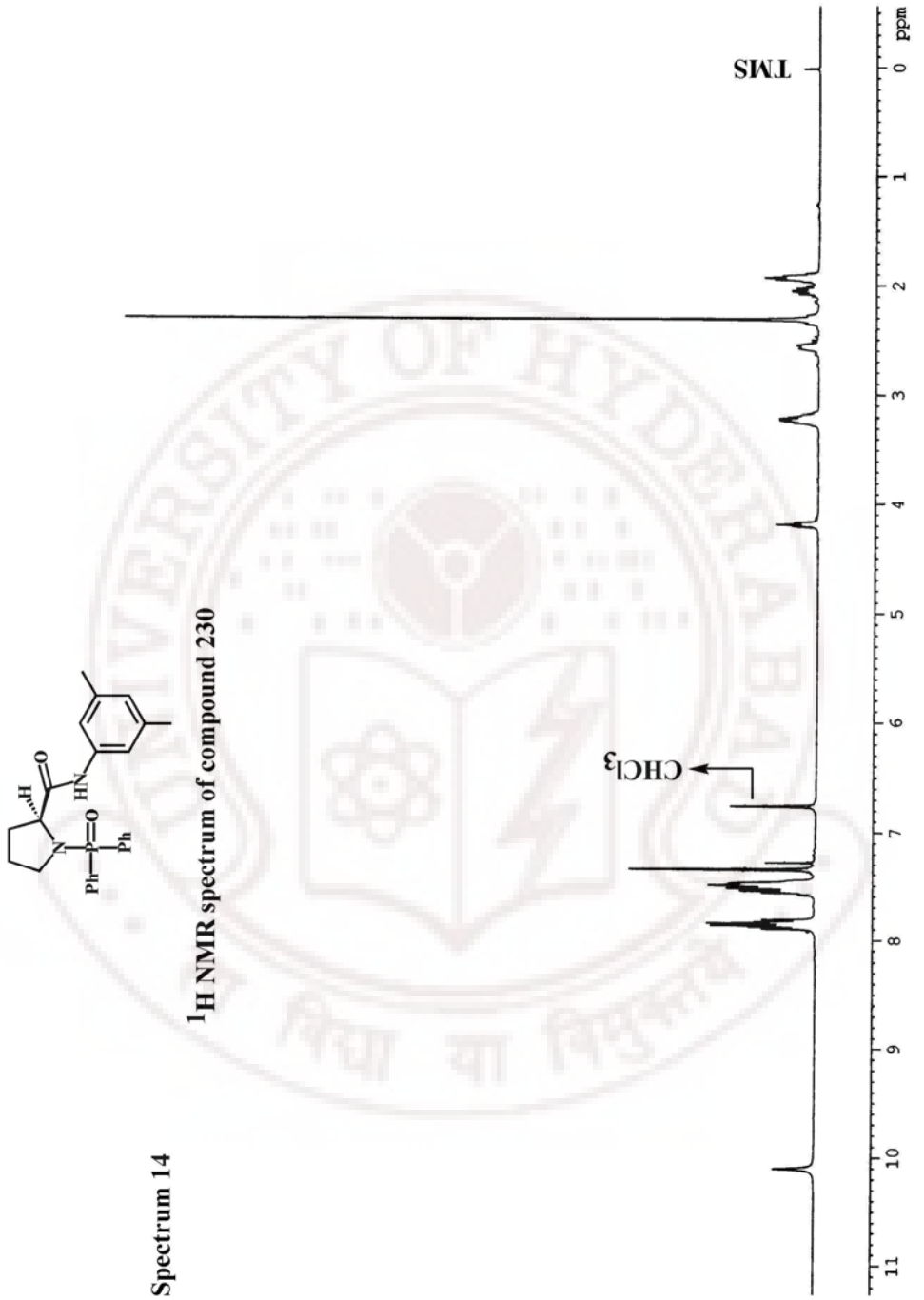

Spectrum 11
^{1}H NMR spectrum of compound 229
CHCl3
TMS
ppm

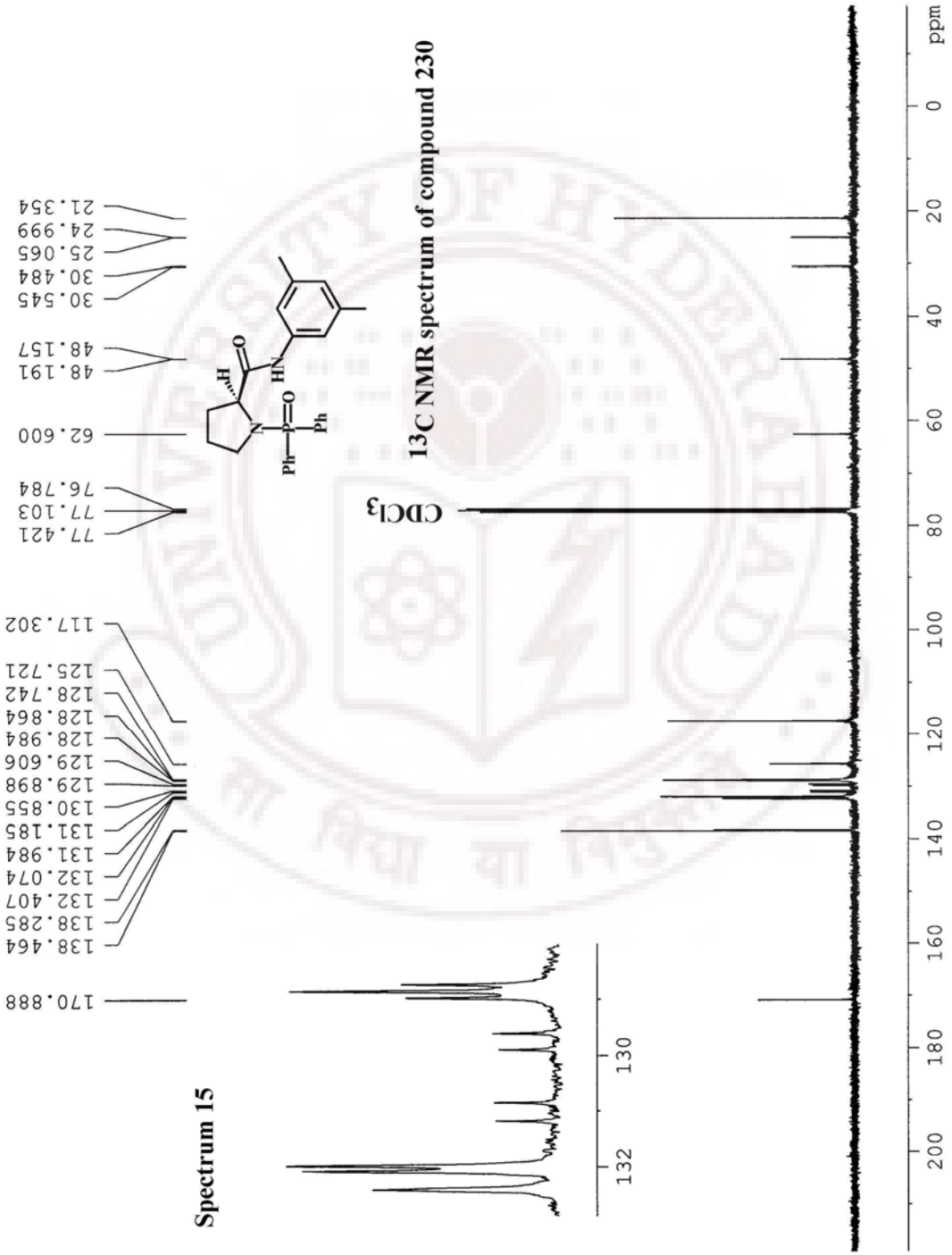

13C NMR spectrum of compound 229
Spectrum 12
CDCl3
ppm
0
20
40
60
80
100
120
140
160
180
200
130
132
134
170.903
160.419
158.007
134.727
134.701
132.571
132.119
132.022
131.201
130.750
129.913
129.504
129.100
128.971
128.838
121.227
121.300
115.524
115.302
77.419
77.101
76.784
62.629
48.405
48.369
30.399
30.332
25.135
25.067
O
H
HN
F
N
P
O
Ph
Ph

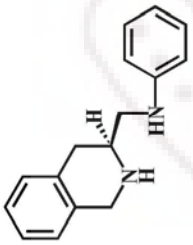


Spectrum 13

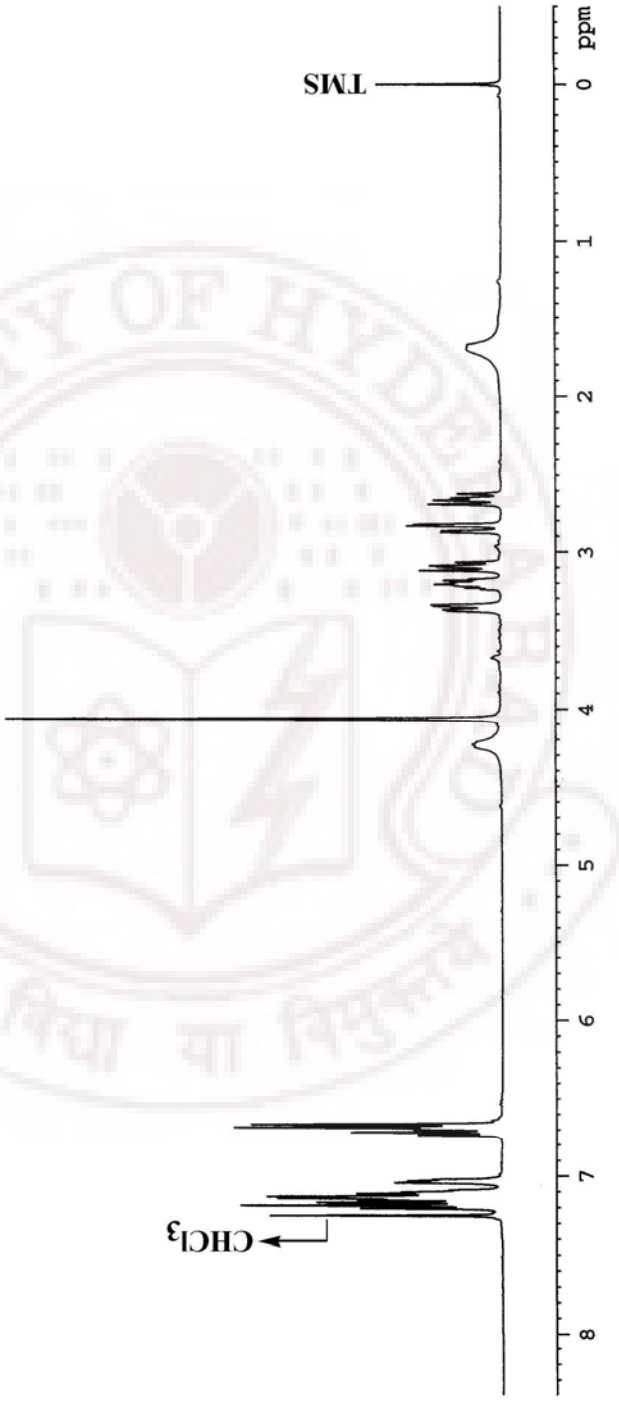
^{31}P NMR spectrum of compound 230

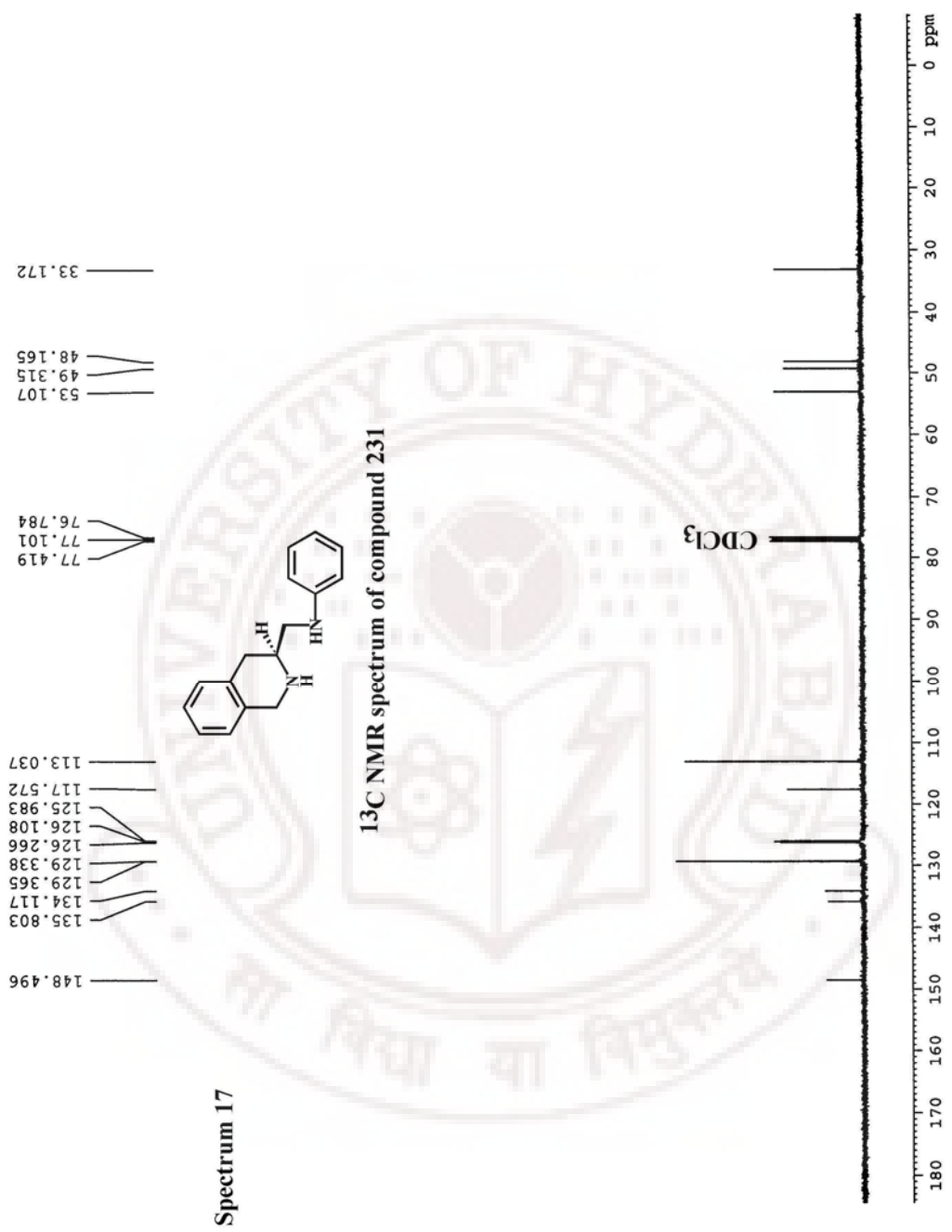

Spectrum 14
^{1}H NMR spectrum of compound 230
CHCl$_3$
TMS
ppm


Spectrum 15
13C NMR spectrum of compound 230
CDCl3
170.888
138.464
138.285
132.407
132.074
131.984
131.185
130.855
129.898
129.606
128.984
128.864
128.742
125.721
117.302
77.421
77.103
76.784
62.600
48.191
48.157
30.545
30.484
25.065
24.999
21.354
ppm



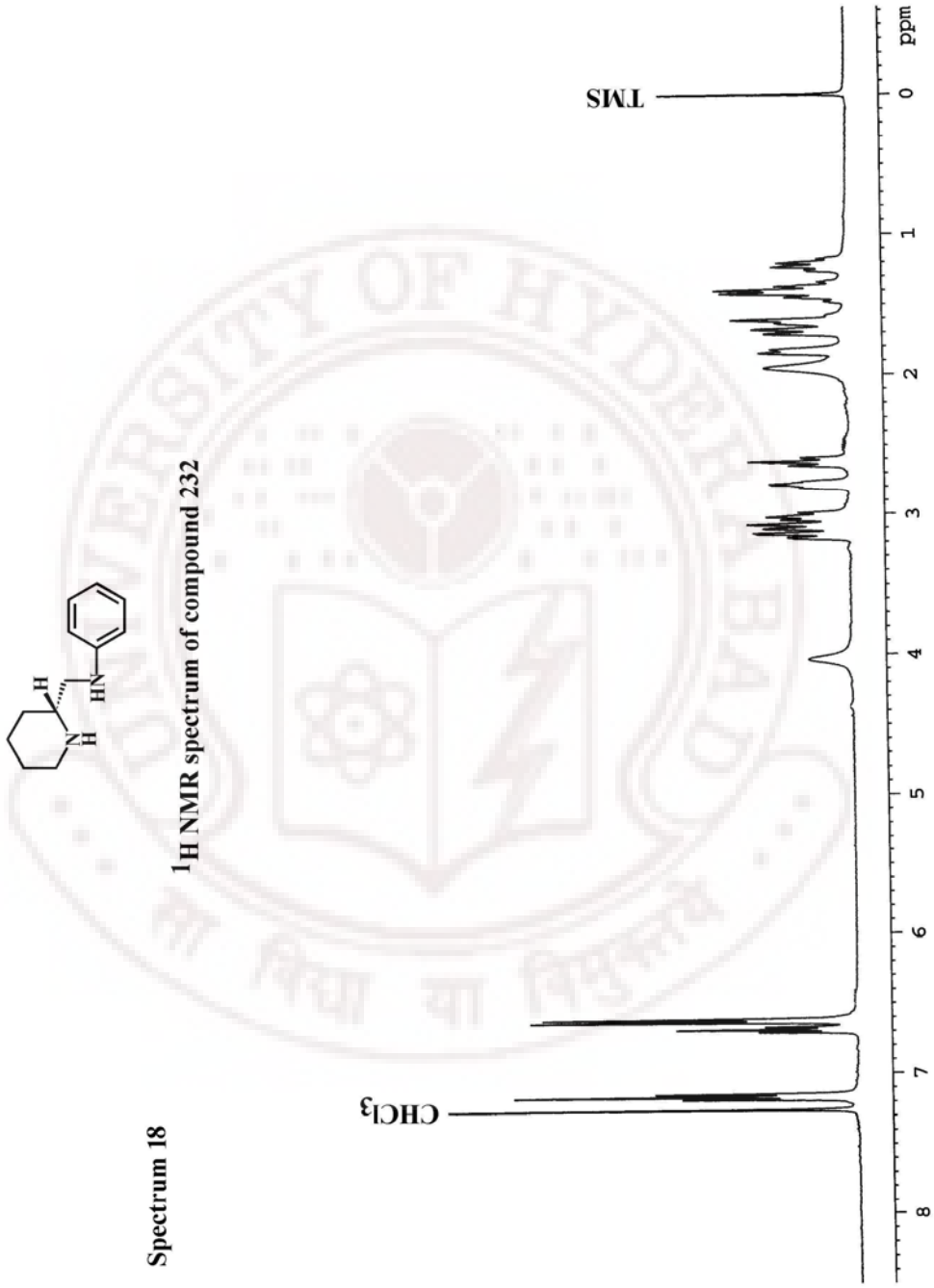
Spectrum 16 ^{1}H NMR spectrum of compound 231

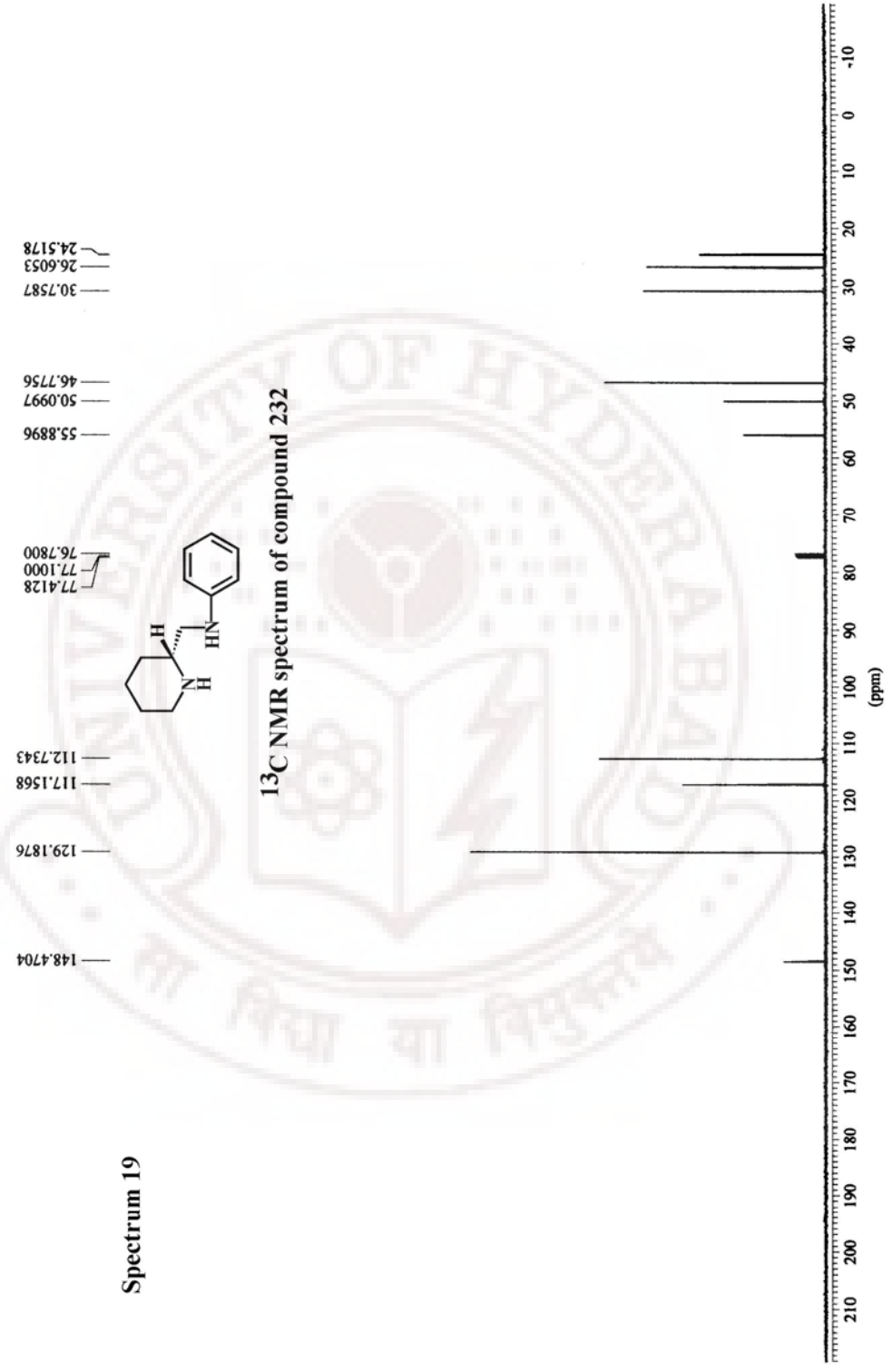


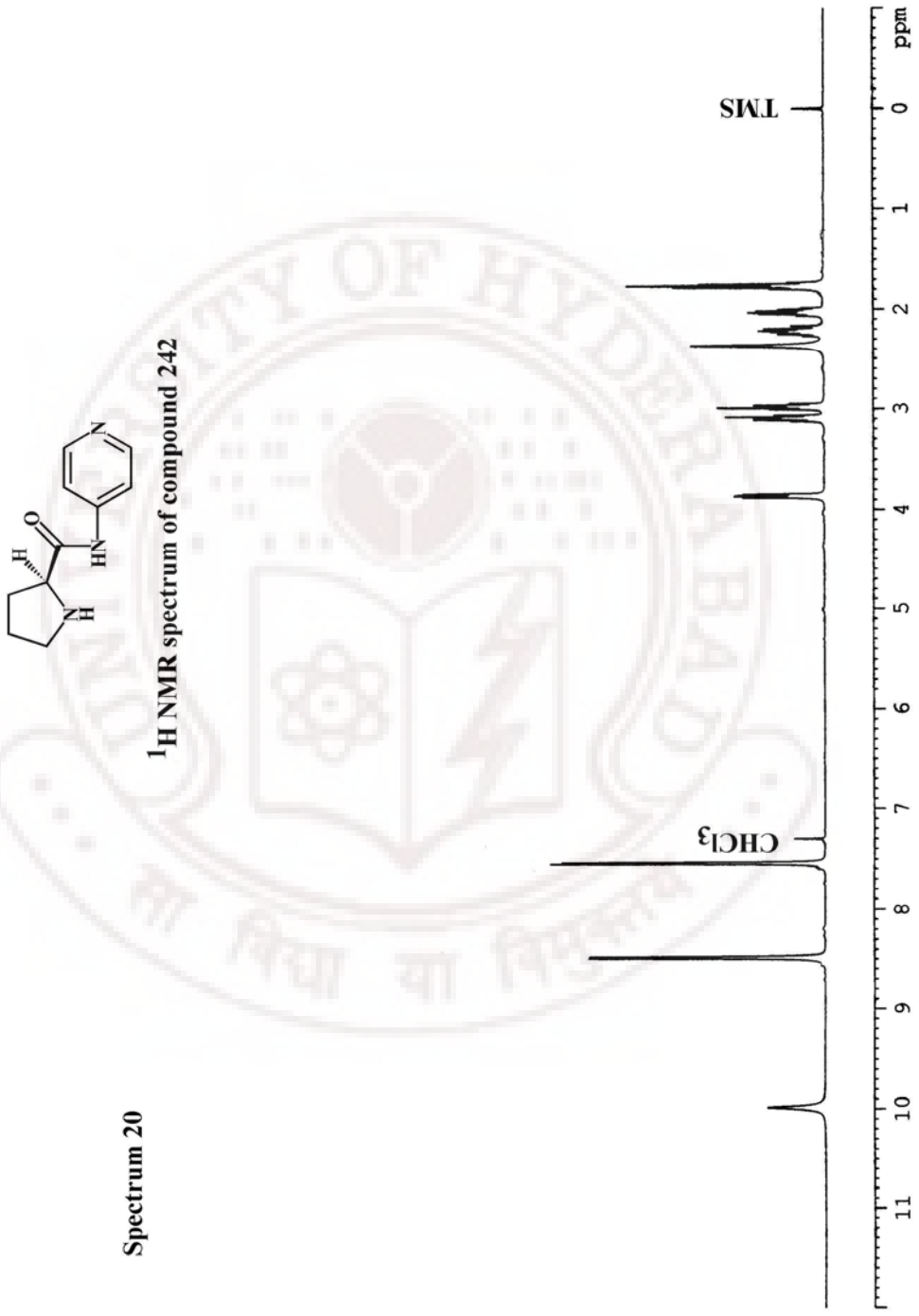


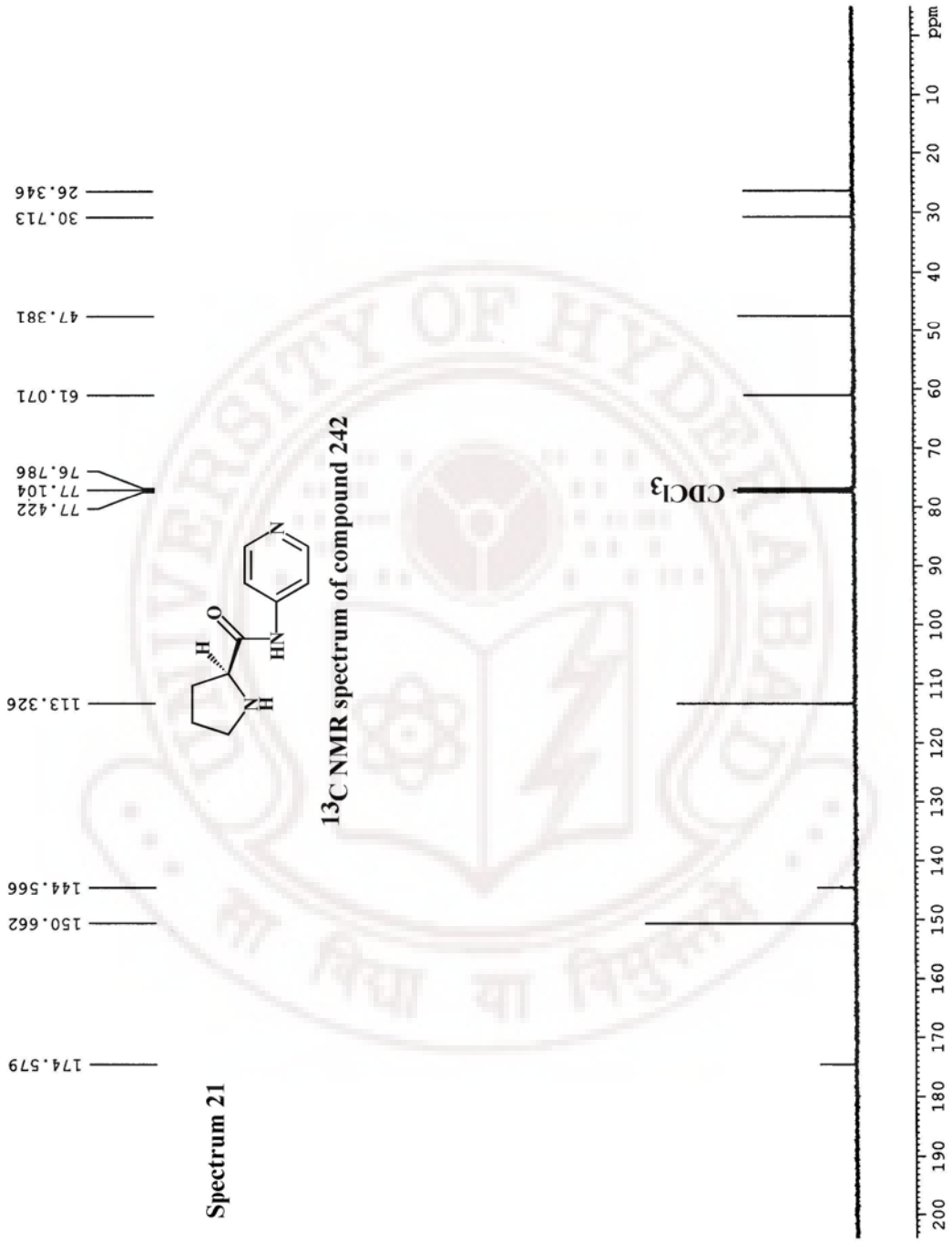
Spectrum 17

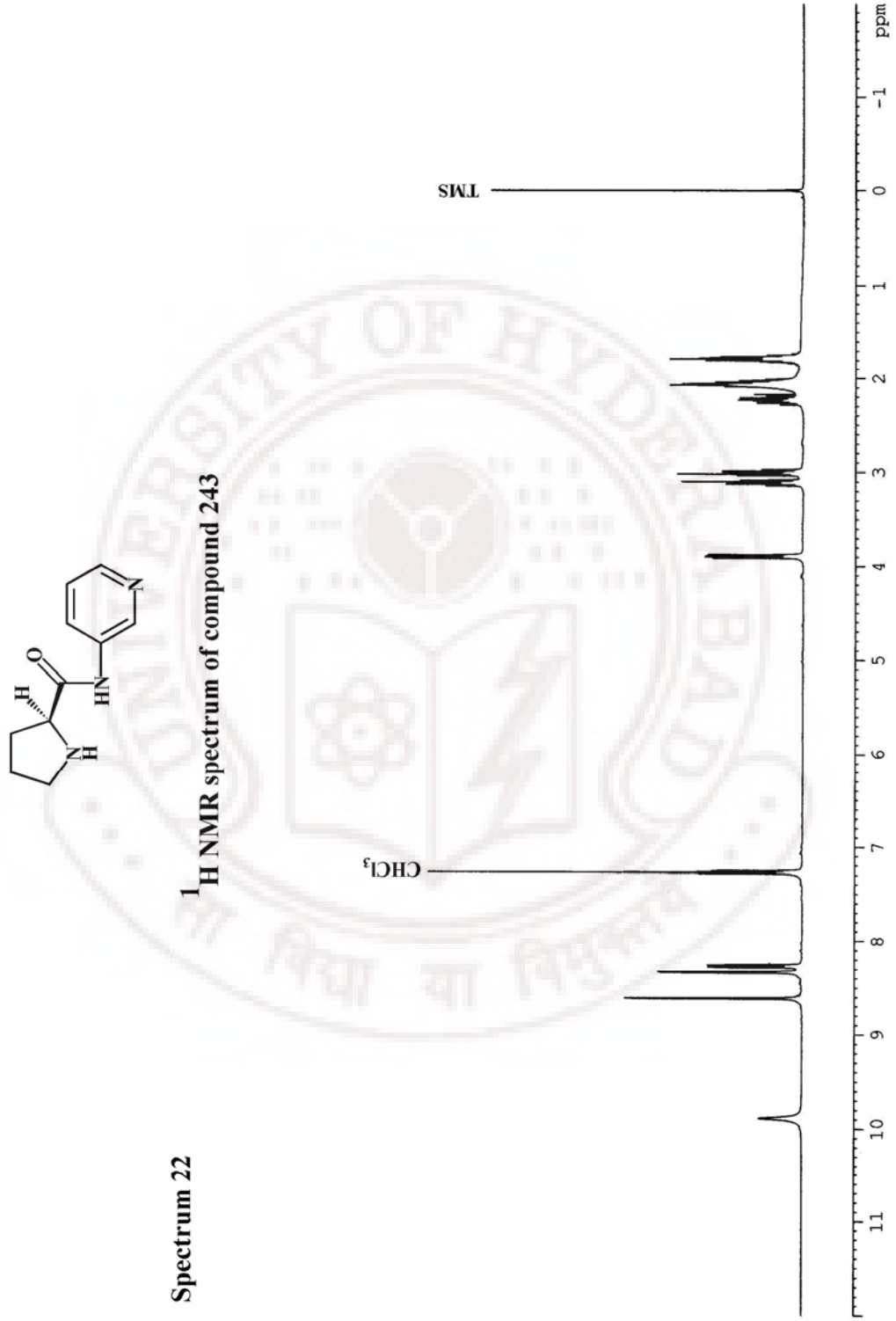
^{13}C NMR spectrum of compound 231

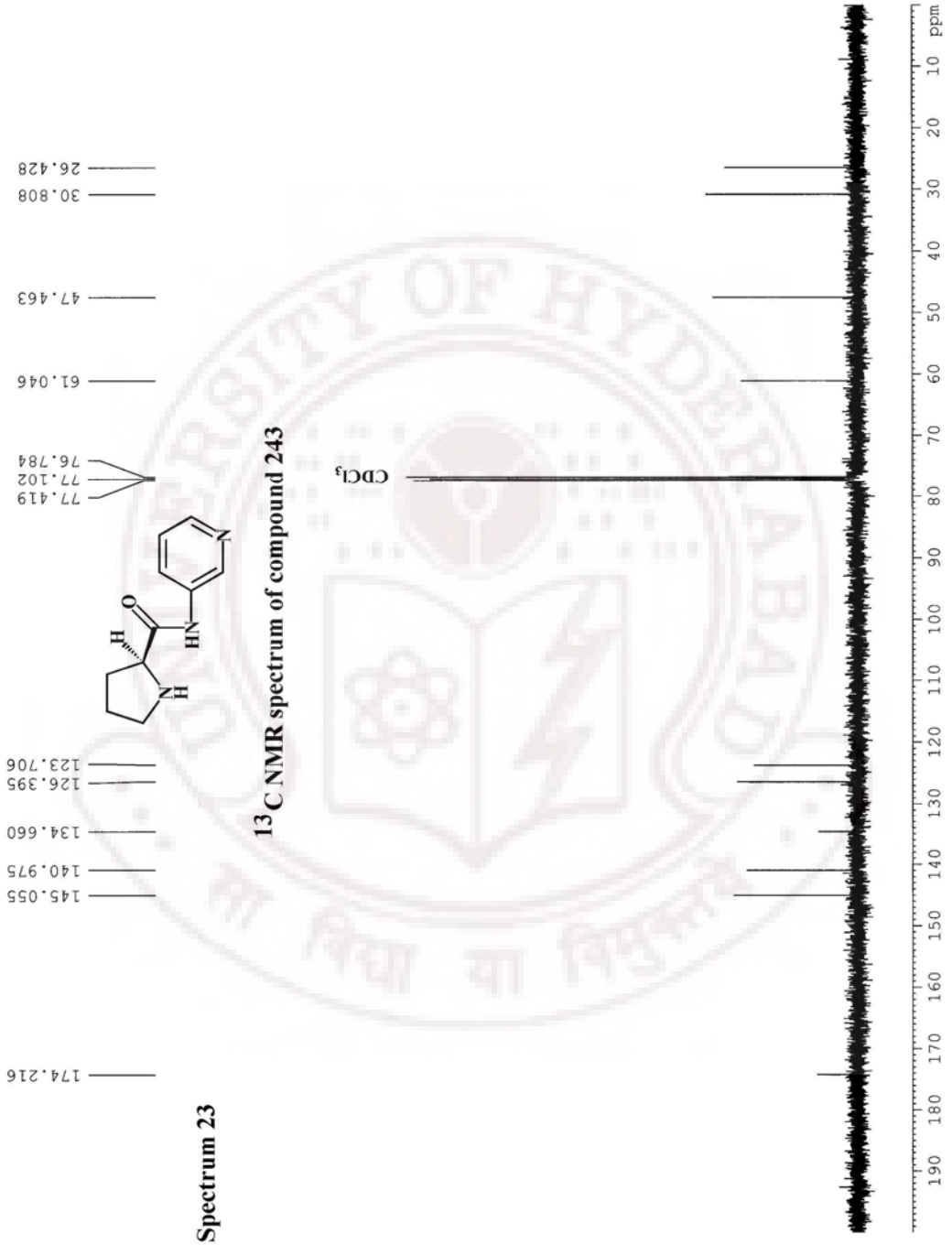

Spectrum 18
^{1}H NMR spectrum of compound 232
CHCl$_3$
TMS
ppm
0
1
2
3
4
5
6
7
8


Spectrum 19
^{13}C NMR spectrum of compound 232
148.4704
129.1876
117.1568
112.7343
77.4128
77.1000
76.7800
55.8896
50.0997
46.7756
30.7587
26.6053
24.5178
(ppm)


Spectrum 20
^{1}H NMR spectrum of compound 242
CHCl3
TMS
ppm
0
1
2
3
4
5
6
7
8
9
10
11

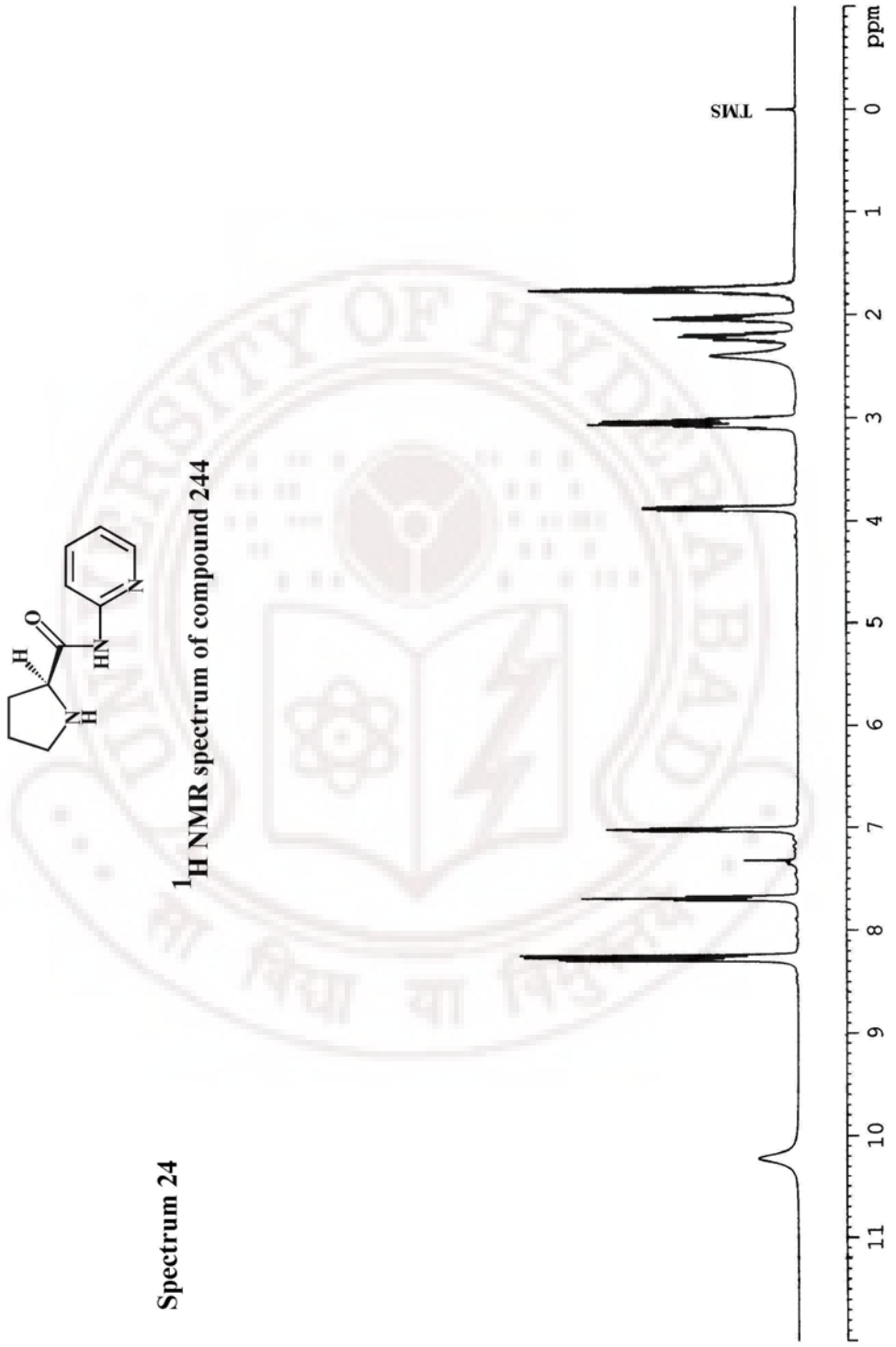

Spectrum 21
^{13}C NMR spectrum of compound 242
174.579
150.662
144.566
113.326
77.422
77.104
76.786
61.071
47.381
30.713
26.346
CDCl3
ppm

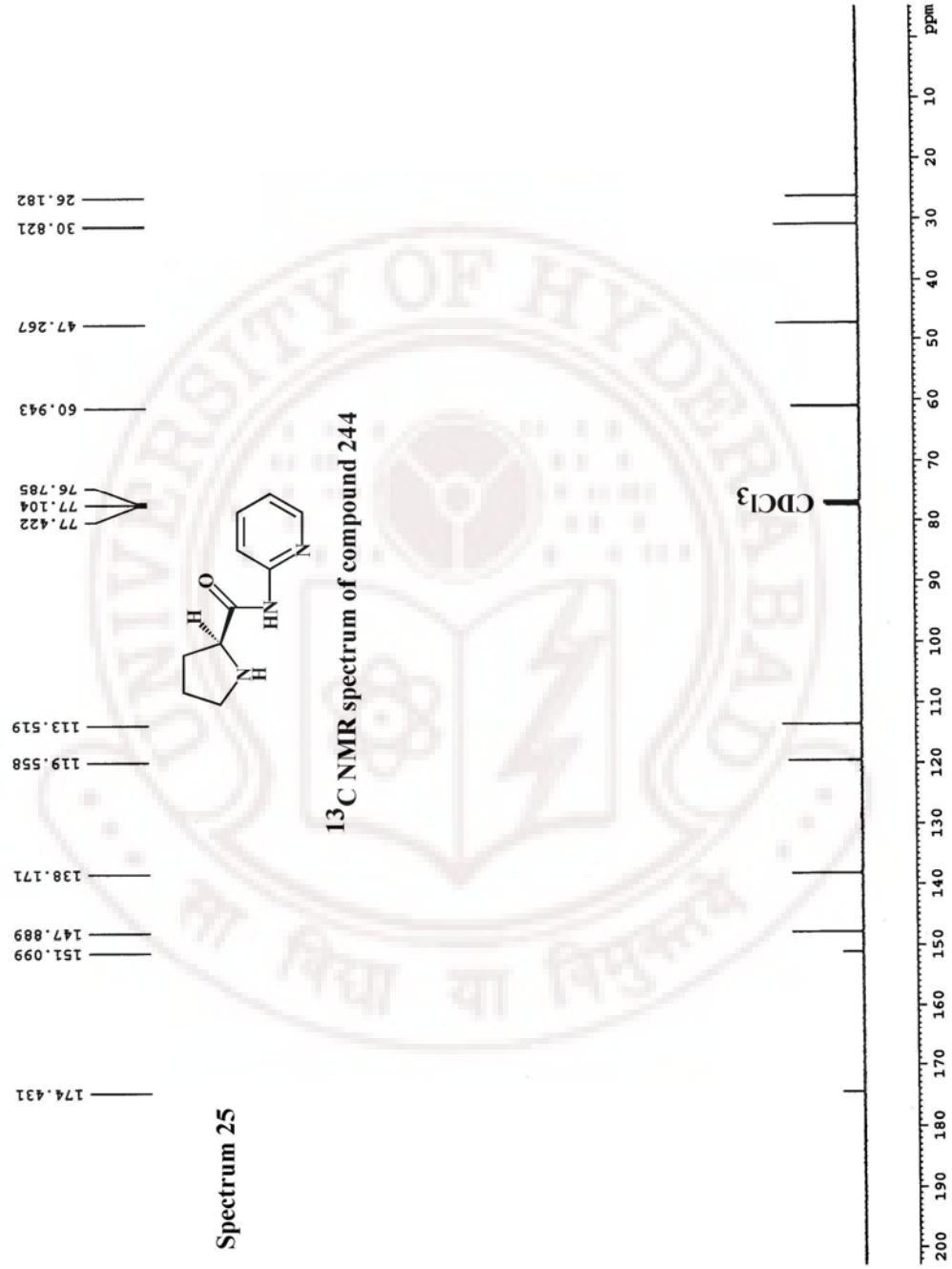

Spectrum 22
^{1}H NMR spectrum of compound 243
CHCl$_3$
TMS
ppm


Spectrum 23
^{13}C NMR spectrum of compound 243
CDCl$_3$
174.216
145.055
140.975
134.660
126.395
123.706
77.419
77.102
76.784
61.046
47.463
30.808
26.428
ppm

Spectrum 24

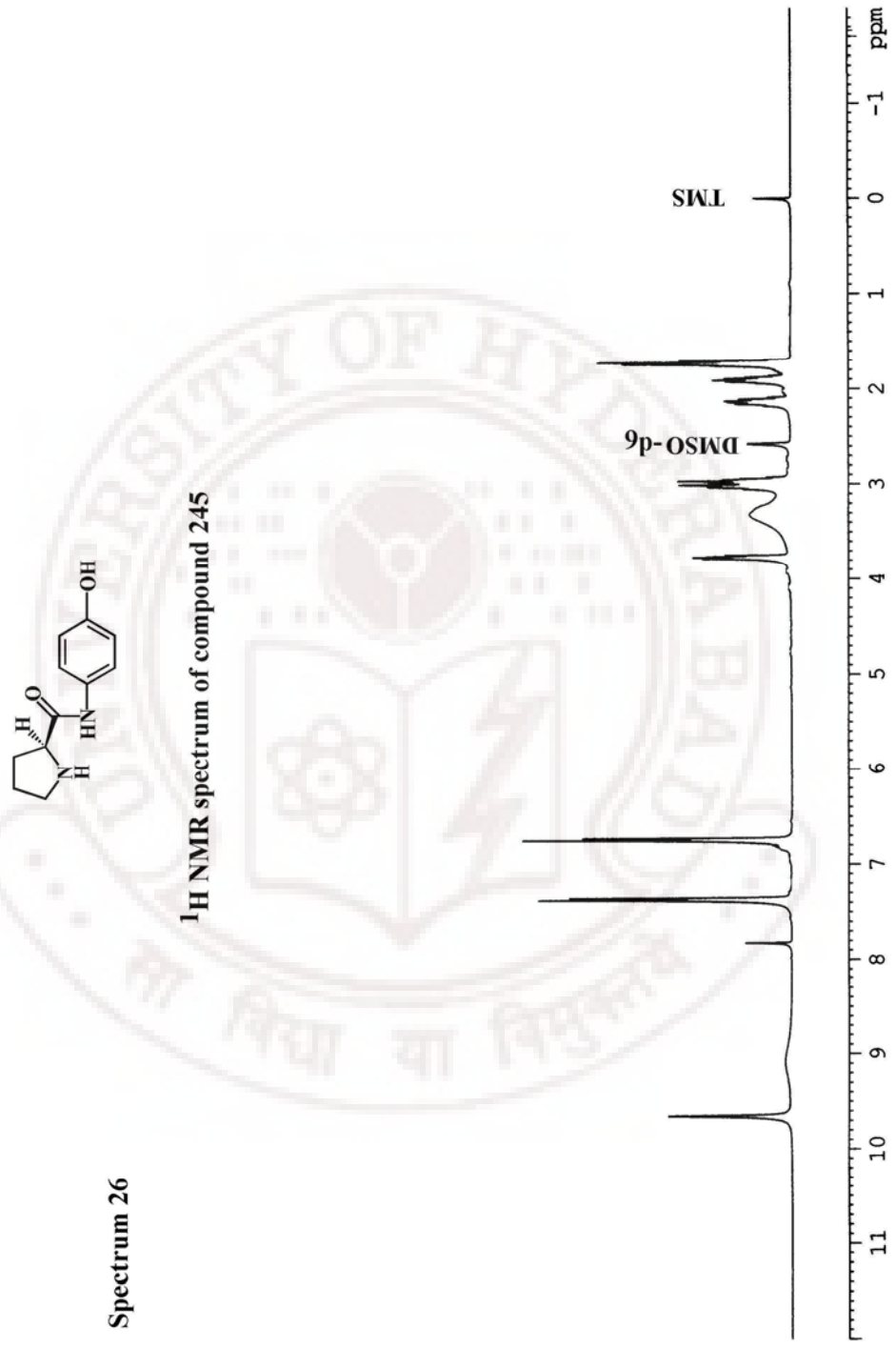
^{1}H NMR spectrum of compound 244

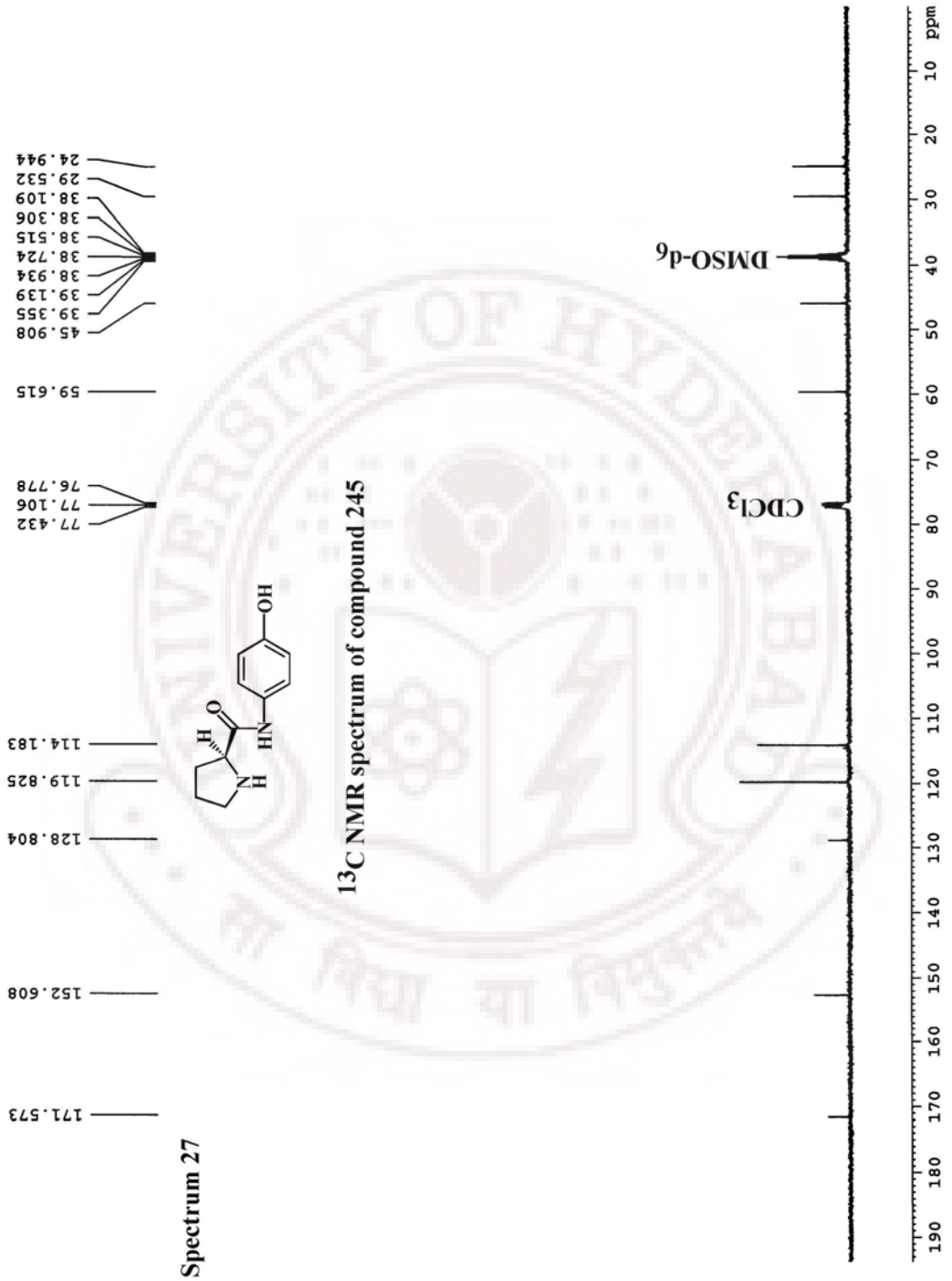




Spectrum 25

^{13}C NMR spectrum of compound 244

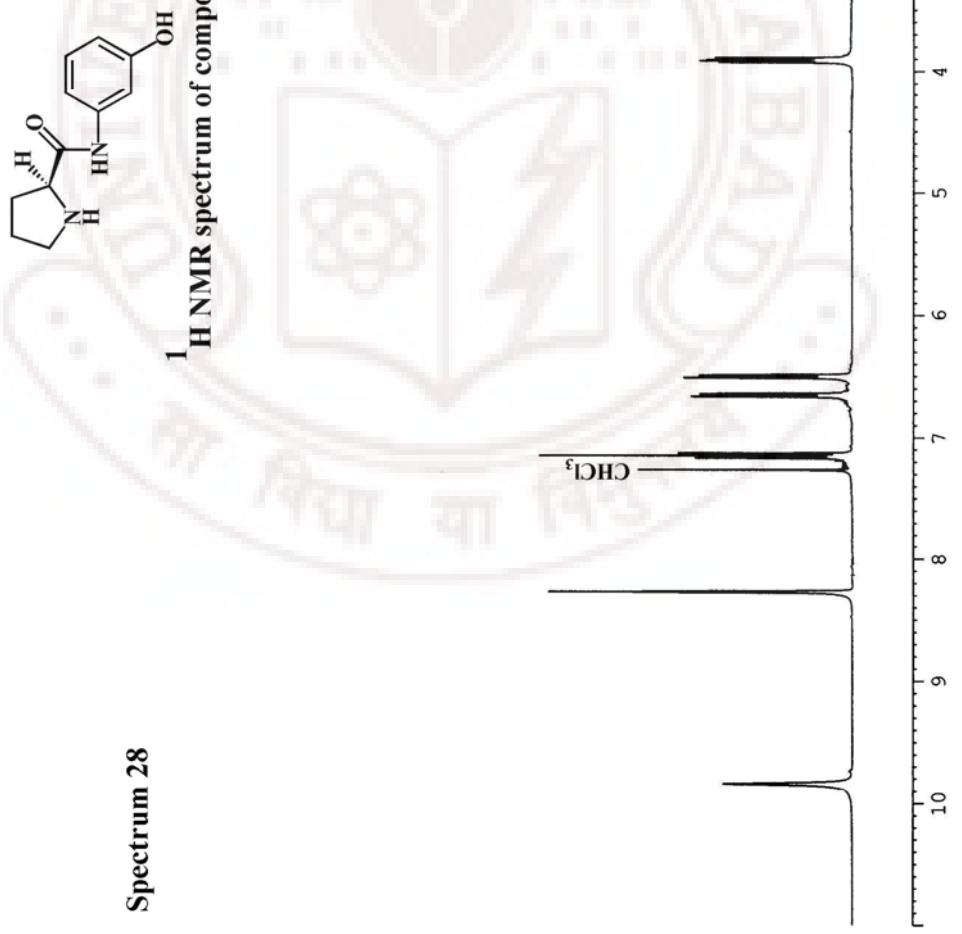

Spectrum 26
^{1}H NMR spectrum of compound 245
DMSO-d6
TMS
ppm

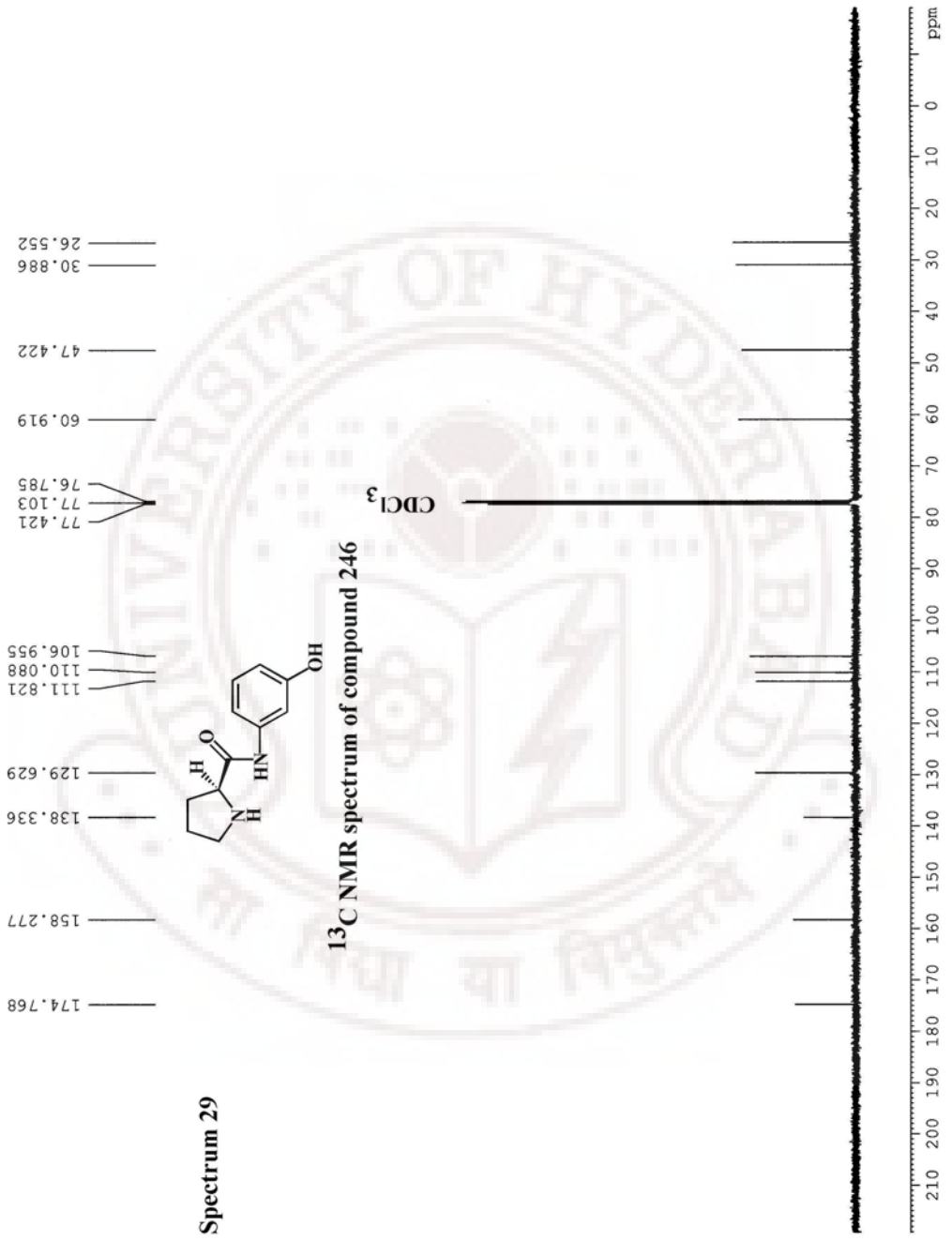


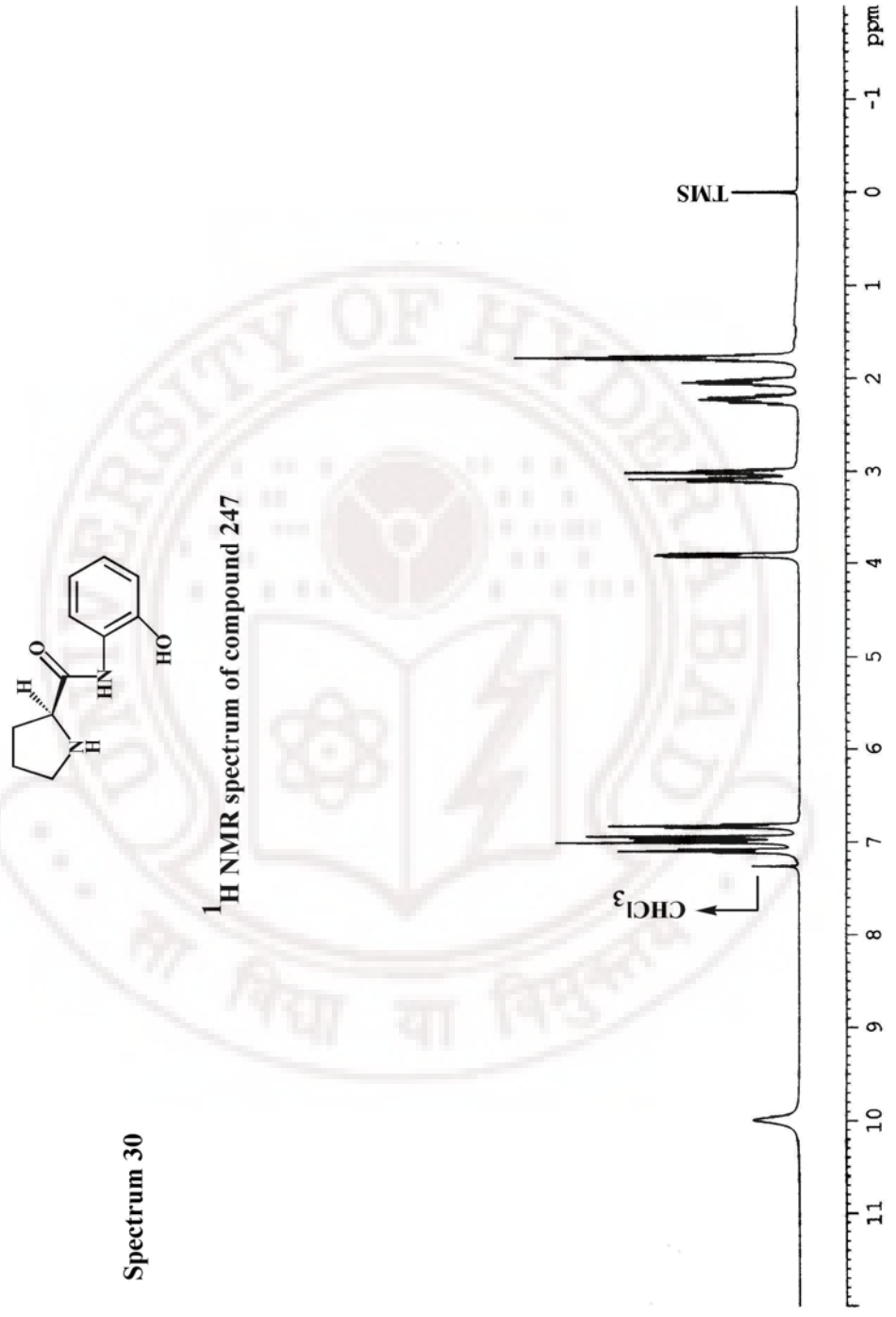
^{13}C NMR spectrum of compound 245

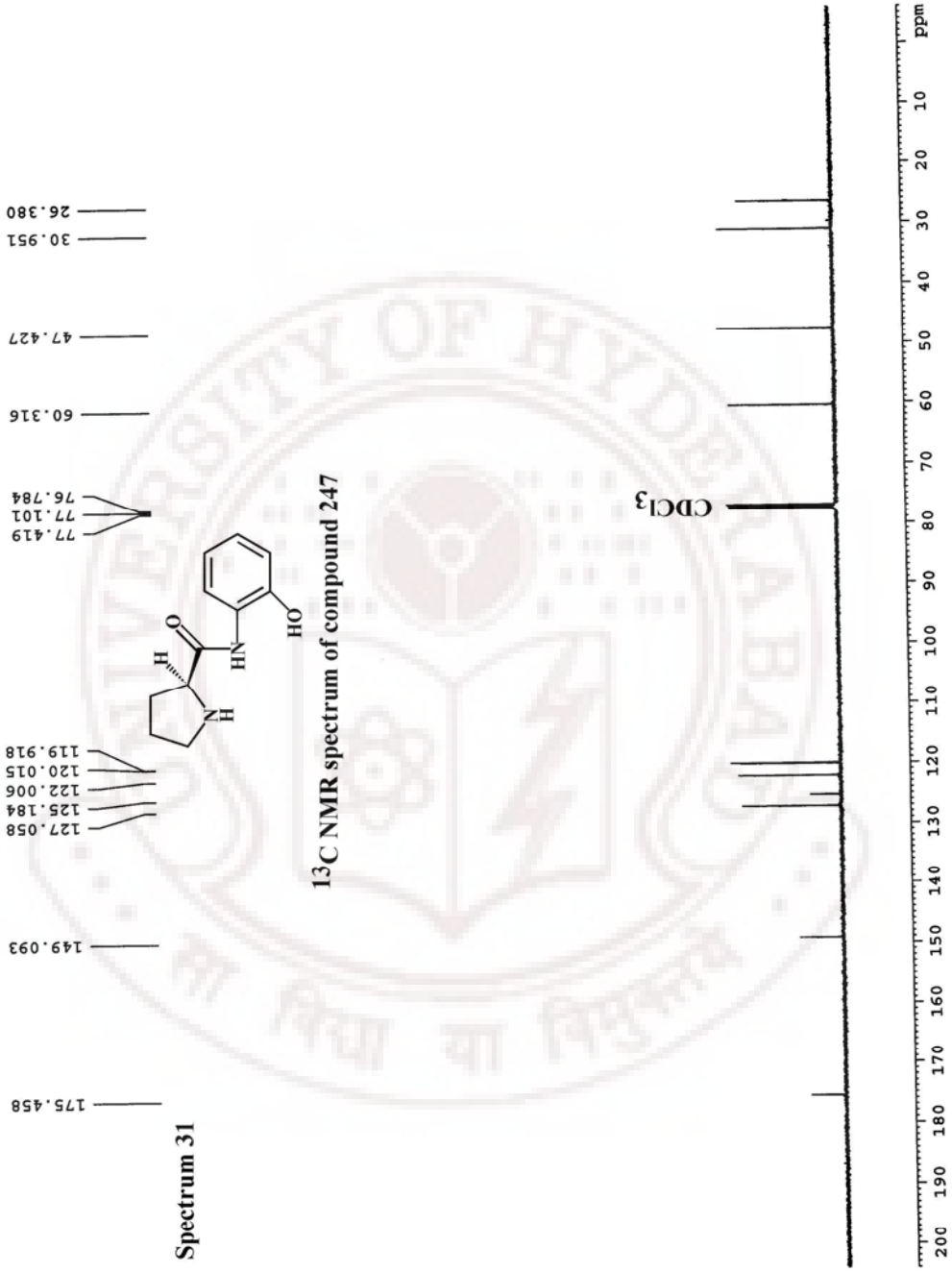
Spectrum 28

^{1}H NMR spectrum of compound 246



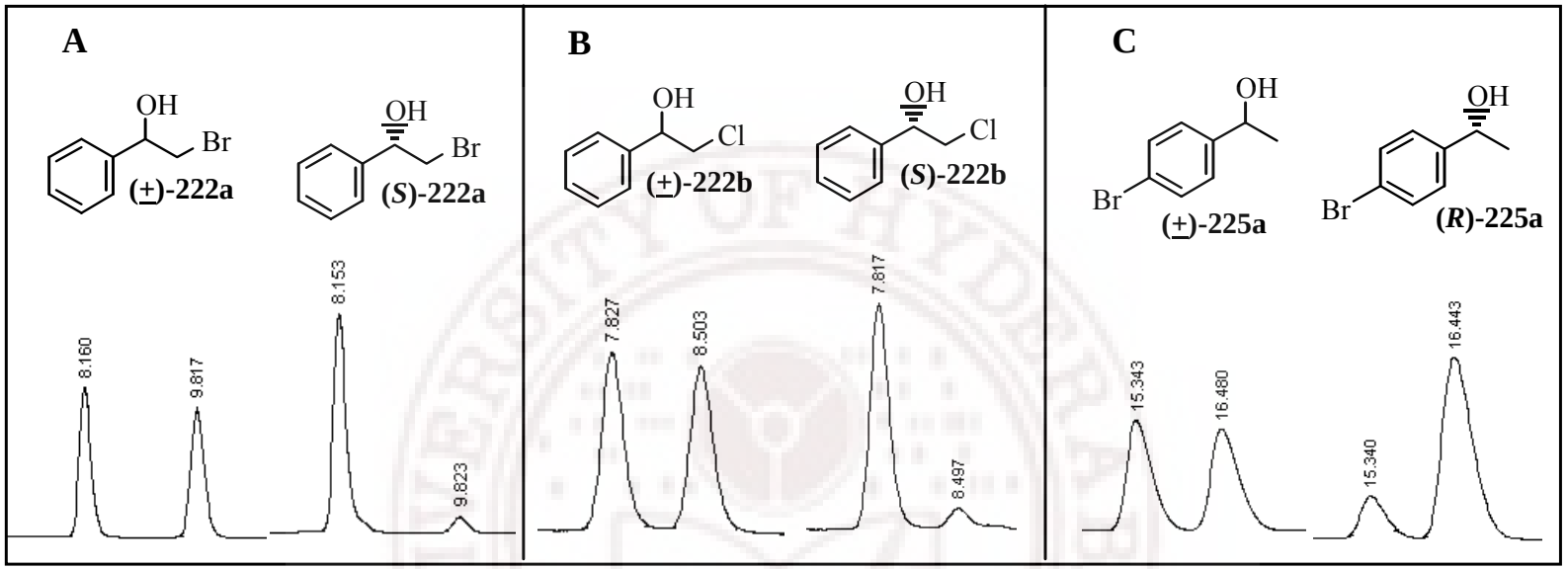

Spectrum 29
^{13}C NMR spectrum of compound 246
CDCl$_3$
174.768
158.277
138.336
129.629
111.821
110.088
106.955
77.421
77.103
76.785
60.919
47.422
30.886
26.552
ppm


Spectrum 30
^{1}H NMR spectrum of compound 247
CHCl$_3$
TMS
ppm



Spectrum 31

^{13}C NMR spectrum of compound 247

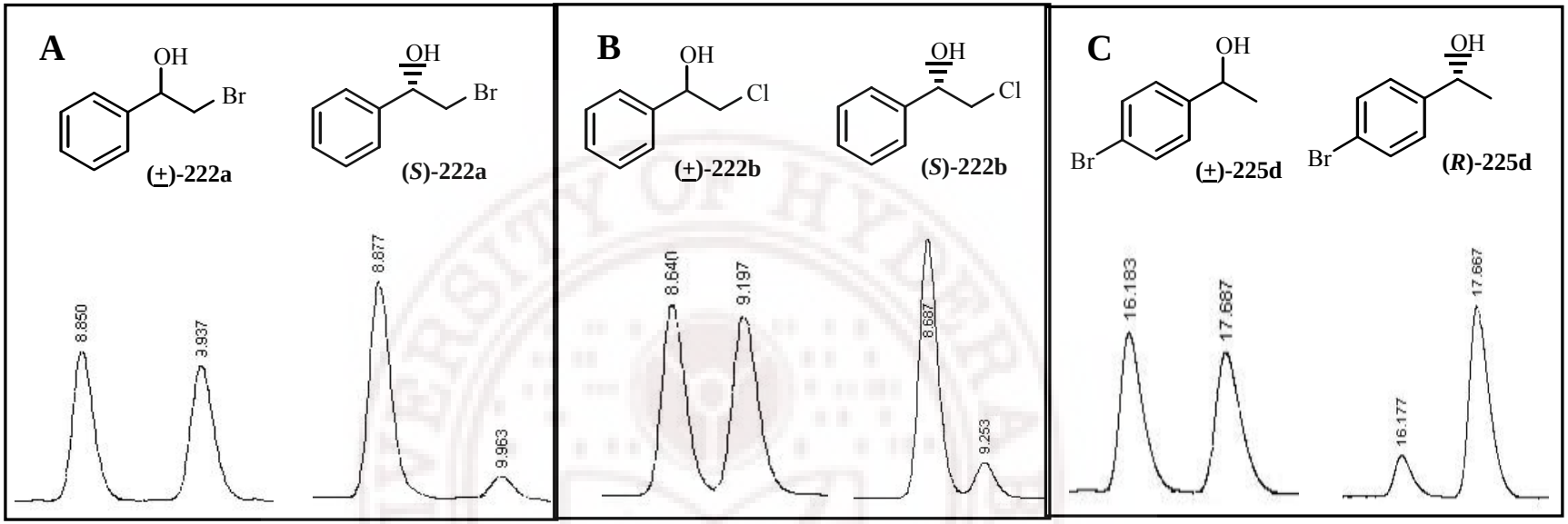


A. **(*S*)-222a** (89% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 15 mol% **216**.

B. **(*S*)-222b** (88% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 15 mol% **216** .

C **(*R*)-225d** (74% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**224d**) using 15 mol% **216**.

HPLC analysis: Chromatogram 1

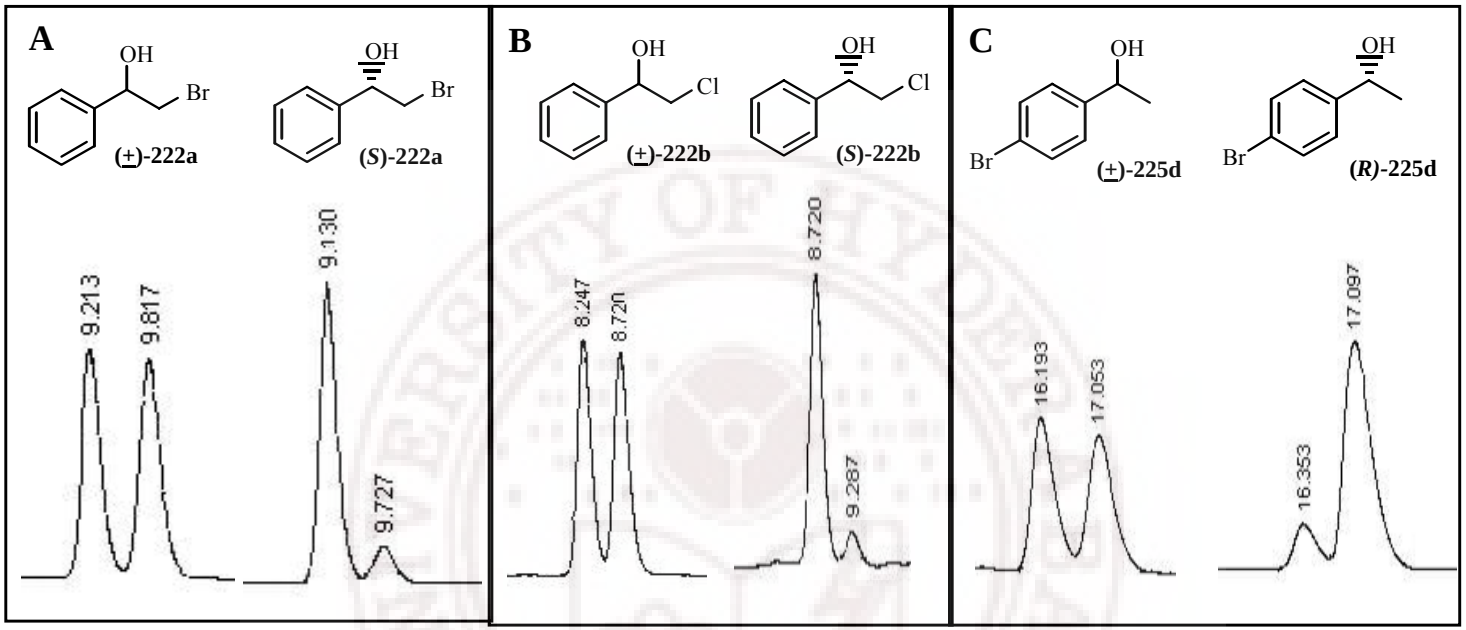


A. **(*S*)-222a** (84% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 15 mol% **227**.

B. **(*S*)-222b** (81% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 15 mol% **227**.

C. **(*R*)-225d** (74% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**224d**) using 15 mol% **227**.

HPLC analysis: Chromatogram 2

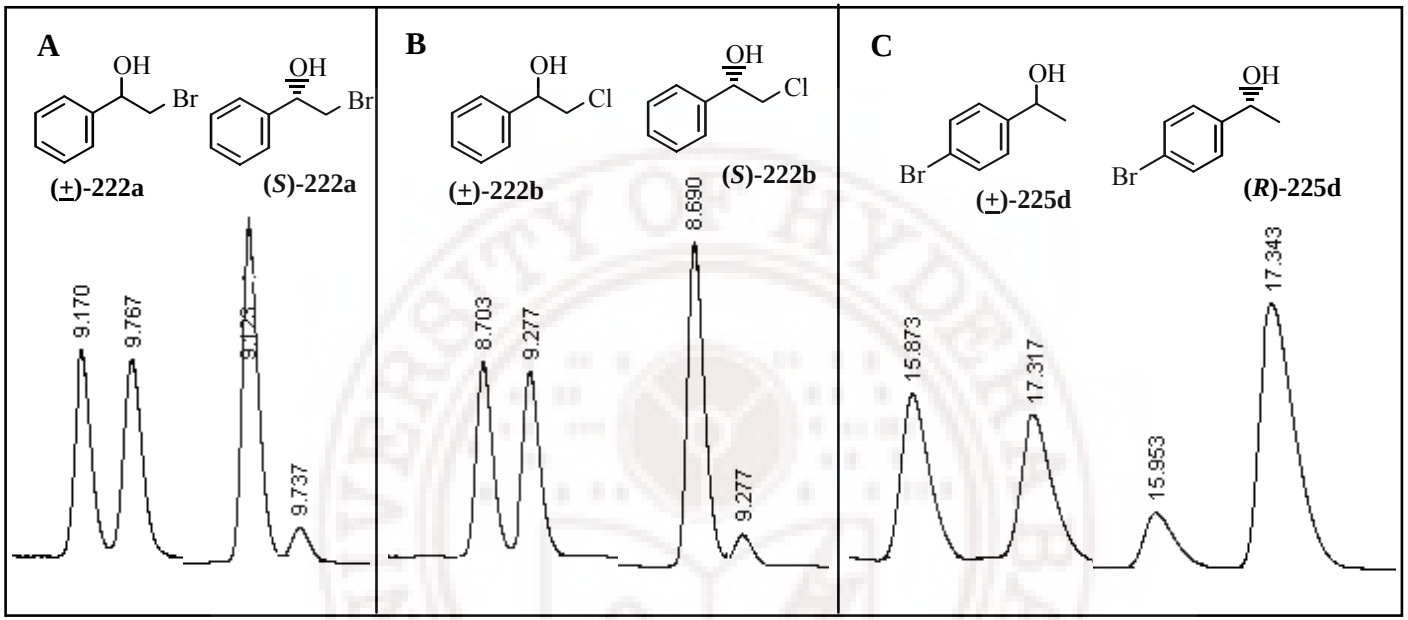


A. **(*S*)-222a** (86% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 15 mol% **228**.

B. **(*S*)-222b** (84% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 15 mol% **228**..

C. **(*R*)-225d** (77% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**224d**) using 15 mol% **228**.

HPLC analysis: Chromatogram 3

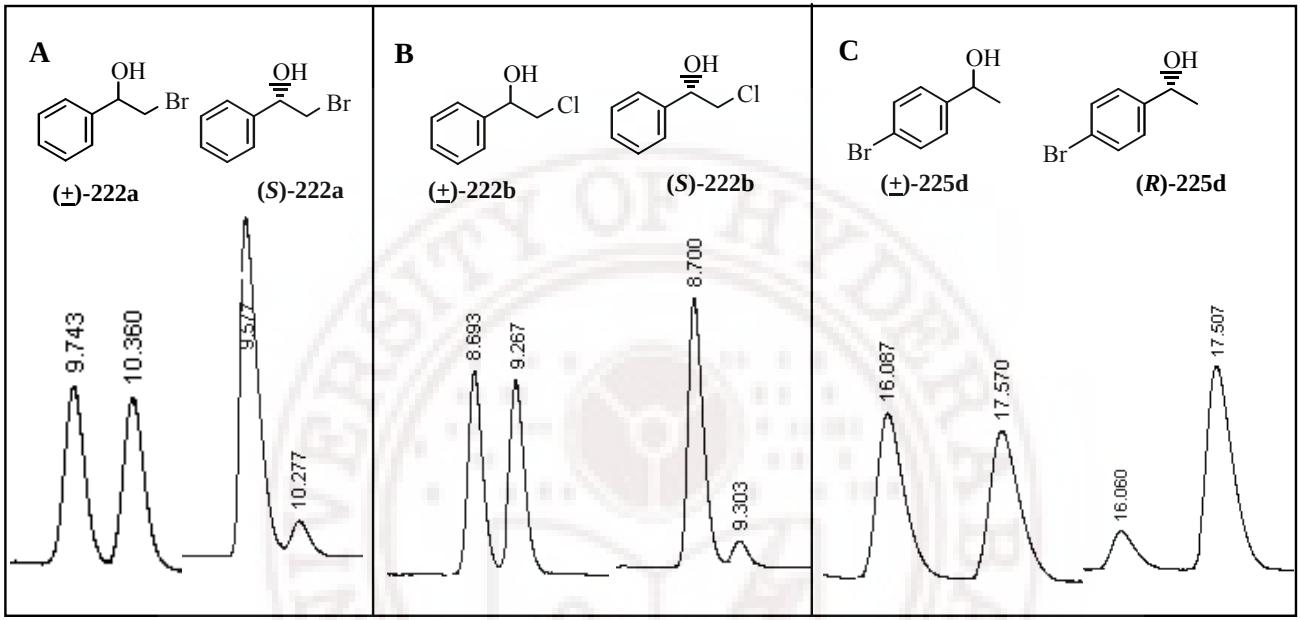


A. **(*S*)-222a** (84% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 15 mol% **229**.

B. **(*S*)-222b** (86% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 15 mol% **229**.

C. **(*R*)-225d** (72% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**224d**) using 15 mol% **229**.

HPLC analysis: Chromatogram 4

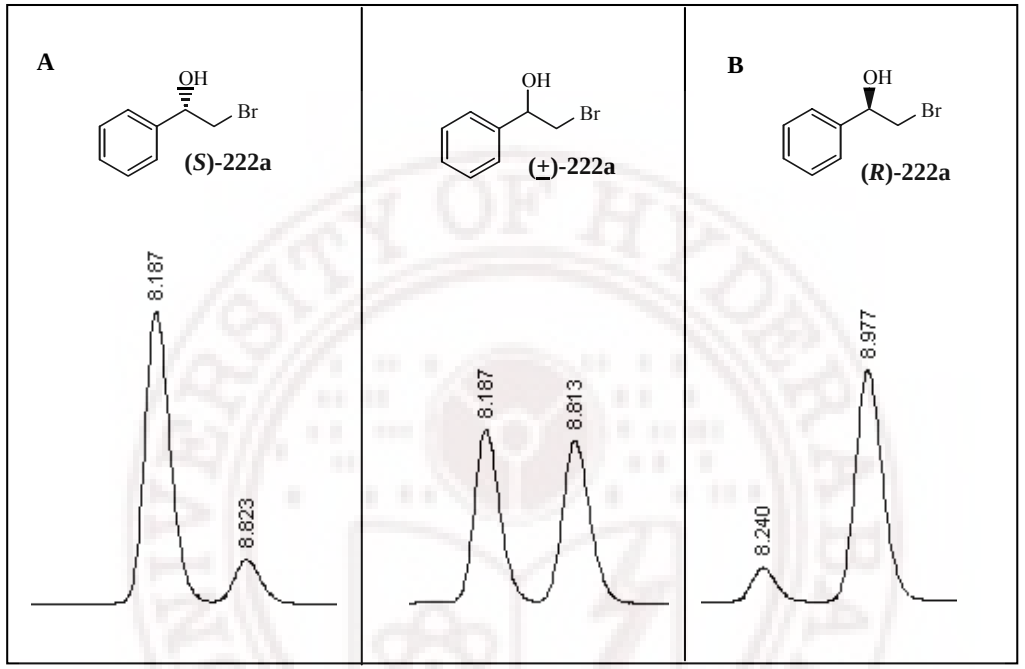


A. **(*S*)-222a** (85% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 15 mol% **230**.

B. **(*S*)-222b** (85% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 15 mol% **230**.

C. **(*R*)-225d** (73% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**224d**) using 15 mol% **230**.

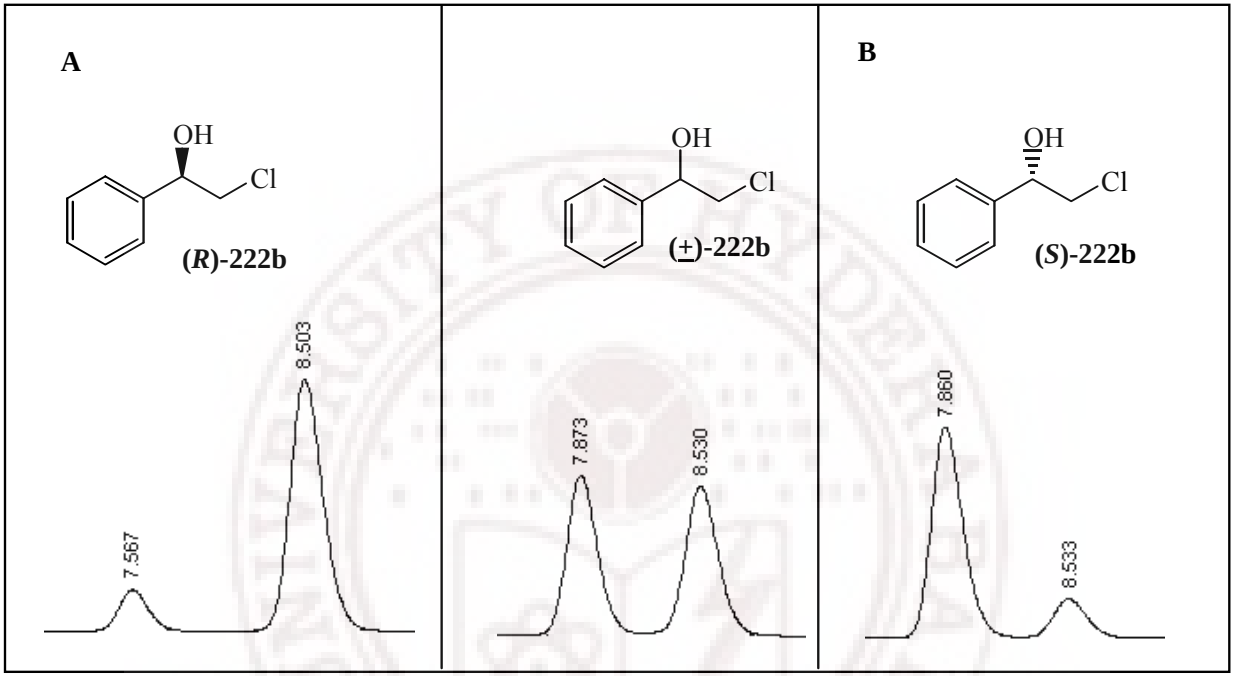
HPLC analysis: Chromatogram 5



A. **(*S*)-222a** (80% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 10 mol% **231**.

B. **(*R*)-222a** (81% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 10 mol% **232**.

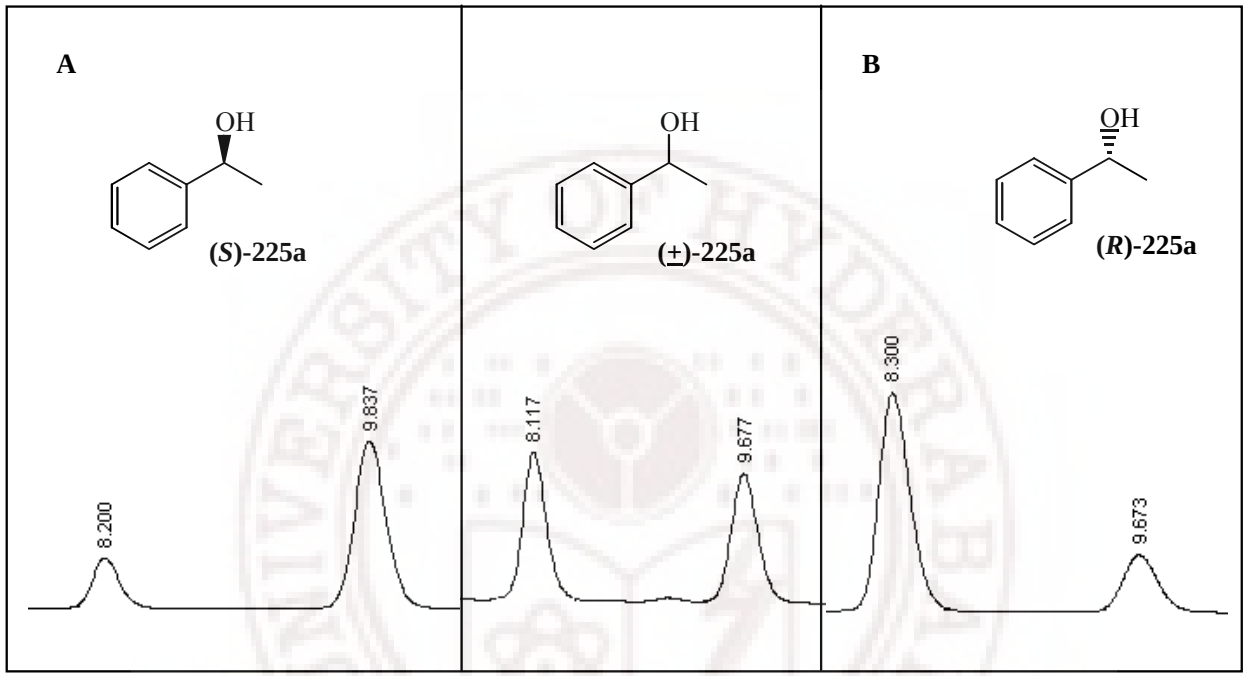
HPLC analysis: Chromatogram 6



A. **(*R*)-222b** (77% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 10 mol% **232**.

B. **(*S*)-222b** (72% *ee*) was obtained *via* the reduction of phenacyl chloride (**221b**) using 10 mol% **231**.

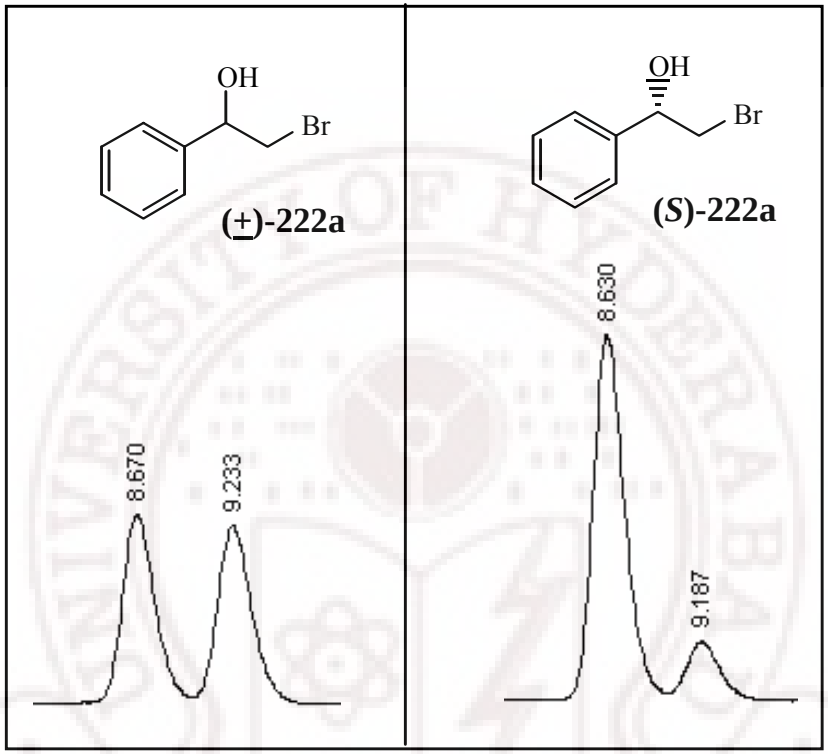
HPLC analysis: Chromatogram 7



A. **(*S*)-225a** (62% *ee*) was obtained *via* the reduction of acetophenone (**224a**) using 10 mol% **232.**

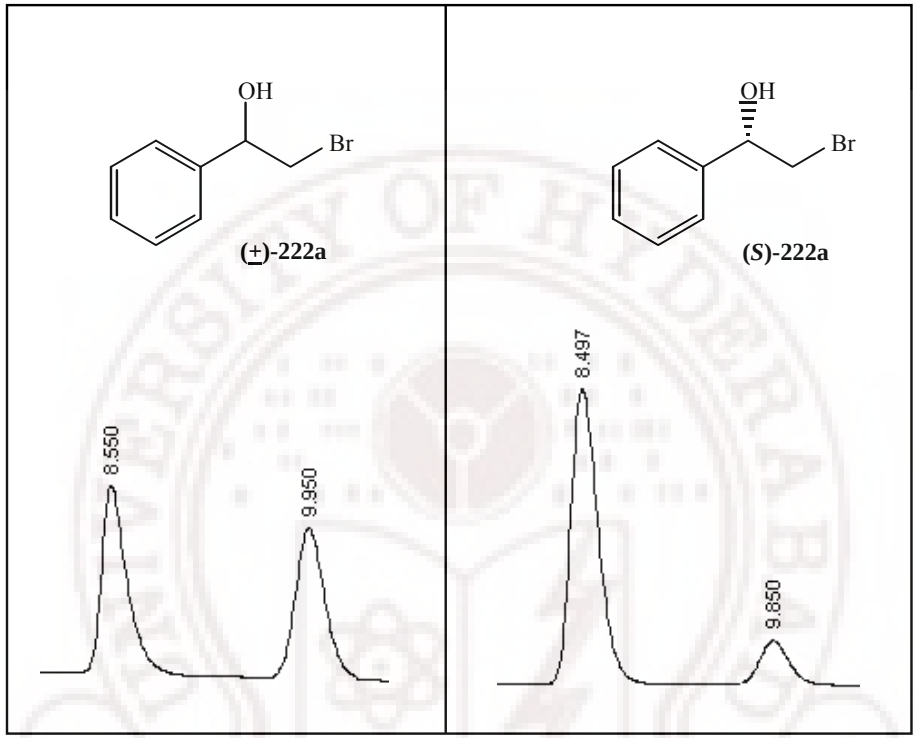
B. **(*R*)-225a** (57% *ee*) was obtained *via* the reduction of acetophenone (**224a**) using 10 mol% **231.**

HPLC analysis: Chromatogram 8



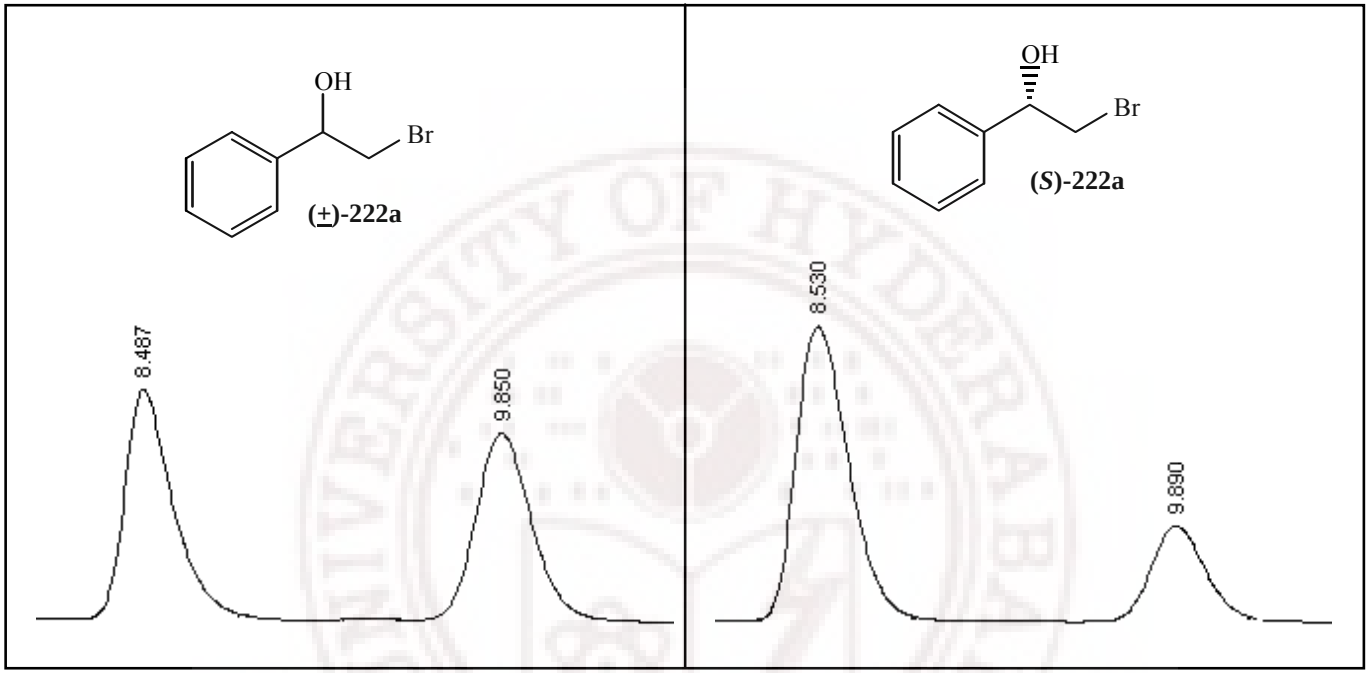
(*S*)-**222a** (77% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **242**.

HPLC analysis: Chromatogram 9



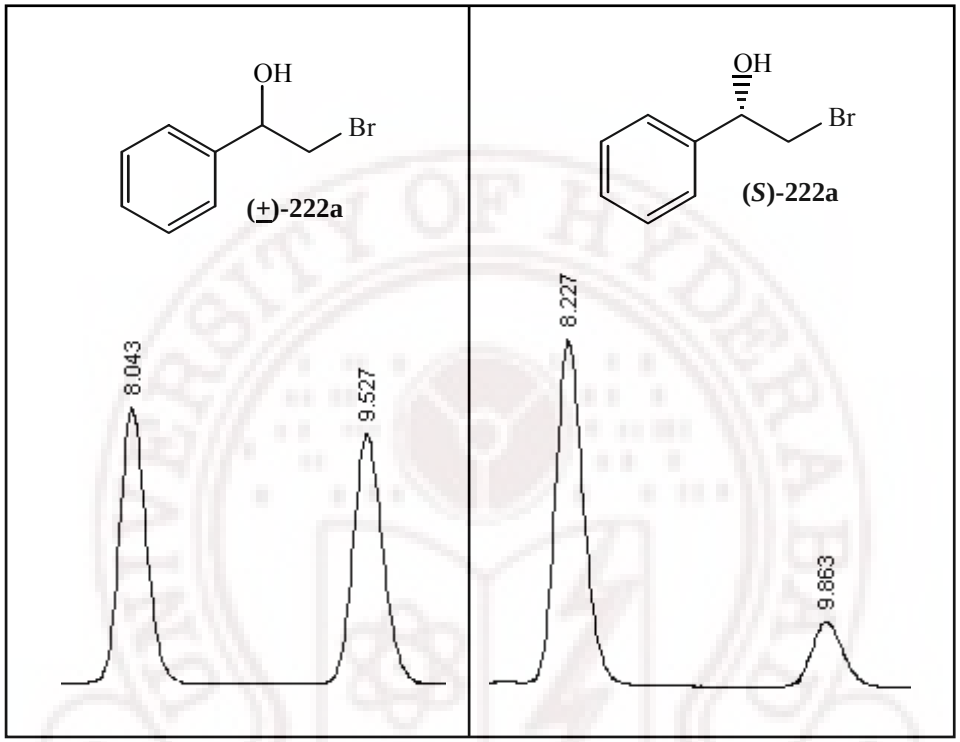
(*S*)-**222a** (76% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **243**.

HPLC analysis: Chromatogram 10



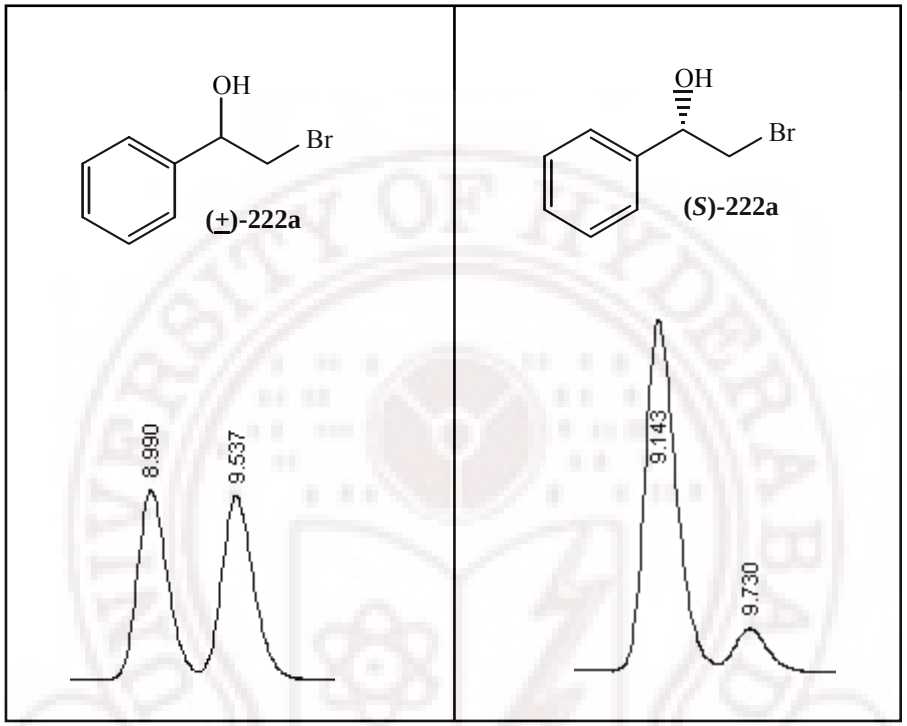
(*S*)-**222a** (51% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **244**.

HPLC analysis: Chromatogram 11



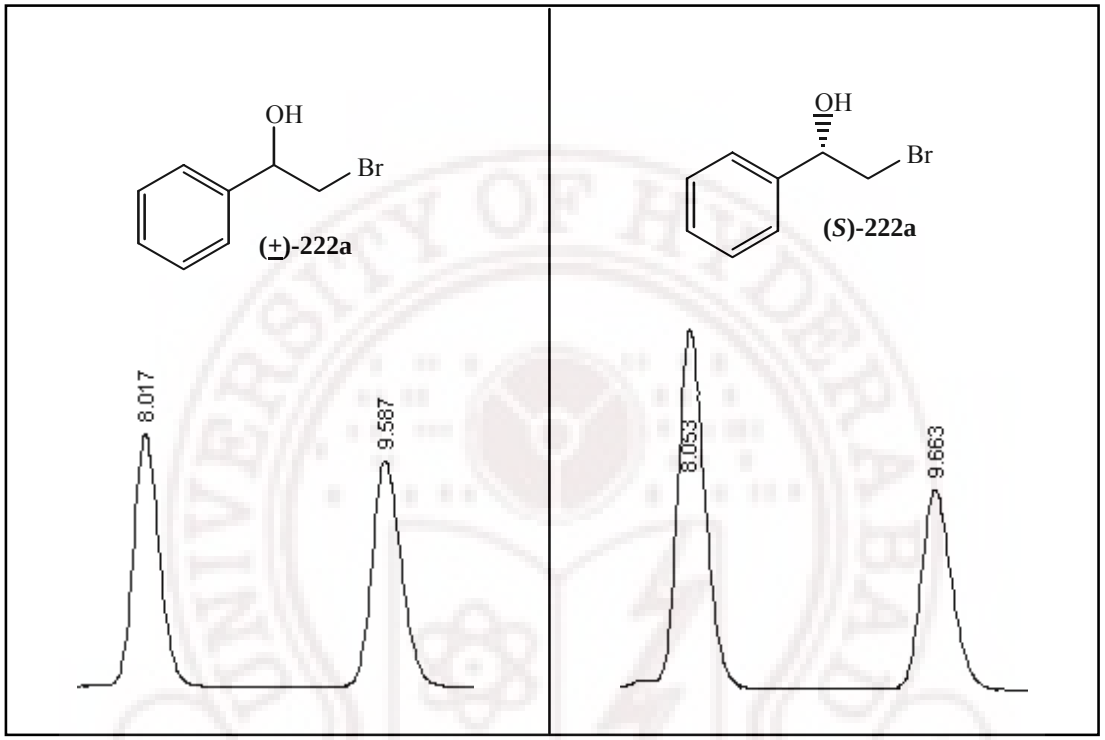
(*S*)-**222a** (72% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **245**.

HPLC analysis: Chromatogram 12



(*S*)-**222a** (77% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **246**.

HPLC analysis: Chromatogram 13



(*S*)-**222a** (22% *ee*) was obtained *via* the reduction of phenacyl bromide (**221a**) using 2 mol% **247**.

HPLC analysis: Chromatogram 14

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I: Atomic coordinates and equivalent isotropic displacement parameters for compound **216**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	6036(6)	-293(2)	7509(3)	64(1)
C(2)	7856(8)	-738(3)	7728(3)	87(2)
C(3)	9506(7)	-482(2)	7214(2)	61(1)
C(4)	8818(4)	270(2)	6909(2)	28(1)
C(5)	11166(5)	369(2)	5641(2)	39(1)
C(6)	13088(5)	500(2)	5357(2)	49(1)
C(7)	13662(6)	147(2)	4692(2)	58(1)
C(8)	12356(6)	-322(2)	4303(2)	56(1)
C(9)	10449(7)	-449(2)	4580(2)	58(1)
C(10)	9848(5)	-110(2)	5247(2)	47(1)
C(11)	8893(5)	1696(2)	6239(2)	42(1)
C(12)	7562(5)	1679(2)	5636(2)	49(1)
C(13)	6346(6)	2323(3)	5488(3)	64(1)
C(14)	6462(8)	2966(3)	5926(3)	74(1)
C(15)	7765(9)	2996(2)	6513(3)	80(1)
C(16)	8996(7)	2363(2)	6680(2)	61(1)
C(17)	6993(5)	1099(2)	7835(2)	40(1)
C(18)	4979(5)	2154(2)	8411(2)	40(1)
C(19)	3001(5)	2313(2)	8610(2)	51(1)
C(20)	2601(7)	2887(2)	9138(3)	64(1)
C(21)	4123(7)	3309(2)	9454(2)	67(1)
C(22)	6083(7)	3165(3)	9238(3)	71(1)
C(23)	6520(6)	2594(3)	8722(2)	64(1)
N(1)	6816(5)	488(2)	7201(2)	58(1)
N(2)	5344(5)	1554(2)	7885(2)	42(1)
O(1)	12231(4)	1093(2)	6930(1)	57(1)
O(2)	8466(4)	1144(2)	8243(1)	59(1)
P(1)	10420(1)	866(1)	6496(1)	38(1)

Table II: Atomic coordinates and equivalent isotropic displacement parameters for compound **228**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Br(1)	10600(1)	6855(1)	10808(1)	93(1)
C(1)	11239(5)	6988(5)	6478(2)	71(1)
C(2)	12539(6)	6146(5)	6540(2)	90(2)
C(3)	12261(5)	5325(5)	7050(2)	70(1)
C(4)	10625(4)	5571(3)	7238(1)	45(1)
C(5)	10520(4)	6292(3)	7805(2)	45(1)
C(6)	10868(4)	5961(3)	8852(1)	48(1)
C(7)	11754(5)	5304(4)	9238(2)	61(1)
C(8)	11698(6)	5559(4)	9817(2)	64(1)
C(9)	10746(5)	6506(4)	10006(2)	62(1)
C(10)	9869(5)	7175(4)	9629(2)	66(1)
C(11)	9940(5)	6904(4)	9053(2)	63(1)
C(12)	7222(4)	5678(3)	7131(2)	46(1)
C(13)	6737(4)	6114(4)	7658(2)	60(1)
C(14)	5916(5)	5308(5)	8013(2)	76(1)
C(15)	5577(5)	4086(5)	7832(2)	81(2)
C(16)	6096(5)	3654(4)	7317(2)	77(1)
C(17)	6918(5)	4446(4)	6962(2)	61(1)
C(18)	7830(5)	6371(3)	5935(2)	51(1)
C(19)	6631(5)	6999(4)	5676(2)	64(1)
C(20)	6256(6)	6730(5)	5115(2)	81(1)
C(21)	7064(7)	5859(4)	4802(2)	88(2)
C(22)	8236(8)	5236(5)	5053(2)	90(2)
C(23)	8623(6)	5484(4)	5619(2)	71(1)
N(1)	10011(3)	6314(3)	6756(1)	46(1)
N(2)	10937(4)	5587(3)	8267(1)	55(1)
O(1)	7866(3)	8106(2)	6791(1)	53(1)
O(2)	10101(3)	7388(2)	7836(1)	61(1)
P(1)	8264(1)	6754(1)	6678(1)	43(1)

Table III. Atomic coordinates and equivalent isotropic displacement parameters for compound **237**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	3999(3)	3871(2)	1426(1)	51(1)
C(2)	5993(4)	3066(2)	1306(1)	65(1)
C(3)	6540(4)	2826(3)	827(1)	75(1)
C(4)	5166(5)	3389(3)	466(1)	80(1)
C(5)	3207(4)	4220(3)	585(1)	80(1)
C(6)	2624(4)	4463(2)	1061(1)	66(1)
C(7)	4148(3)	3546(2)	2319(1)	47(1)
C(8)	2775(3)	3988(2)	2766(1)	46(1)
C(9)	2989(3)	2745(2)	3168(1)	57(1)
C(10)	1980(4)	2588(2)	4052(1)	68(1)
C(11)	639(5)	2981(3)	4443(1)	80(1)
C(12)	-1188(5)	4015(3)	4386(1)	80(1)
C(13)	-1634(4)	4663(2)	3938(1)	67(1)
C(14)	-739(3)	5103(2)	3063(1)	57(1)
C(15)	-287(3)	4286(2)	3543(1)	51(1)
C(16)	1525(3)	3216(2)	3595(1)	51(1)
N(1)	3257(3)	4111(2)	1904(1)	54(1)
N(2)	394(3)	4381(2)	2649(1)	53(1)
O(1)	5920(2)	2760(2)	2348(1)	63(1)

Table IV. Atomic coordinates and equivalent isotropic displacement parameters for compound **241-TFA** salt. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	1016(3)	9144(8)	6473(10)	86(2)
C(2)	1595(2)	8914(6)	7813(6)	52(1)
C(3)	1999(2)	4132(6)	8470(5)	45(1)
C(4)	1544(2)	4299(7)	6806(5)	51(1)
C(5)	1864(3)	4797(9)	5581(6)	65(2)
C(6)	2343(3)	3582(9)	5539(6)	69(2)
C(7)	2781(2)	3364(8)	7175(6)	60(1)
C(8)	1713(2)	3506(7)	9721(6)	48(1)
C(9)	966(2)	4402(11)	11048(5)	70(2)
C(10)	707(3)	5831(15)	11430(8)	98(3)
C(11)	317(4)	5720(20)	12394(10)	148(6)
C(12)	192(4)	4260(30)	12936(9)	169(8)
C(13)	447(4)	2830(20)	12560(11)	149(6)
C(14)	837(3)	2863(14)	11600(8)	98(3)
F(1)	668(2)	7932(9)	6128(9)	152(3)
F(2)	729(3)	10425(10)	6633(14)	215(5)
F(3)	1128(4)	9500(20)	5102(8)	233(6)
N(1)	2470(2)	2927(6)	8398(5)	48(1)
N(2)	1338(2)	4601(8)	10056(5)	58(1)
O(1)	1570(2)	7894(5)	8871(4)	66(1)
O(2)	2016(2)	9699(6)	7677(5)	74(1)
O(3)	1819(2)	2129(6)	10299(5)	73(1)