SYNTHESIS AND APPLICATIONS OF NOVEL CHIRAL CATALYSTS CONTAININC *N-P=O* STRUCTURAL FRAMEWORK FOR THE BORANE-MEDIATED ASYMMETRIC REDUCTION OF PROCHIRAL KETONES

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

GONE JAYAPAL REDDY

SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

HYDERABAD - 500 046

INDIA

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To My
Beloved Parents

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STATEMENT

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

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

HYDERABAD

NOVEMBER, 2003

G. JAYAPAL REDDY

CERTIFICATE

Certified that the work embodied in this thesis entitled **"Synthesis and Applications of Novel Chiral Catalysts Containing *N-P=O* Structural Framework for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones"** has **been** carried out **by Mr. G. JAYAPAL REDDY,** under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH

(THESIS SUPERVISOR)

DEAN

SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

DEAN
of Chemistry
niversity ofHyd.
Hyderabad-46.

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I am extremely thankful to the my seniors and colleagues Dr. P. Rama Krishna, Dr. K. Muthukumaran, Dr. K. Padmaja, Dr. M. Krishnamacharyulu, Dr. M. Bakthadoss, Dr. N. Kumaragurubaran, Dr. R. Mallikarjuna Reddy, Dr. B Sreenivasulu, Dr. A. Jagan Mohan Rao, Ms. D. S. Sharada, Mr. J. Srivardhana Rao, Mr. T. Satyanarayana. Mr. V. Chandrashekar, Mr. D. Lenin Babu, Mr. B. Devendar, Ms. P. Anupama, Mr. K. Venkateswara Rao, Mr. J. Raju, Mr. A. Veerendhar, Mr. K. Ramesh Reddy, Mr. U. das for their timely help and pleasant association.

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. Jayapal Reddy

ABBREVIATIONS

Ac	acetyl
aq.	aqueous
BINAP	2,2′-bis(diphenylphosphino)-1,1'-binaphthyl
Bp	boiling point
Bu	*n*-butyl
/-Bu or Bu'	/-butyl
t-Bu or Bu'	/-butyl
9-BBN	9-borabicyclo(3.3.1)nonane = HB
BINOL	1,1'-bi-2-naphthol
cat.	catalyst
cod	1,5-cyclooctadiene
DCC	1,3-dicyclohexylcarbodiimide
DCU	1,3-dicyclohexylurea
DIP-Chloride	B-chlorodiisopinocampheylborane
DMSO	dimethyl sulfoxide
DMF	N,N-dimethylformamide
Eap_2BCl	B-chlorobis(iso-2-ethylapopinocampheyl)borane
ee	enantiomeric excess
Et	ethyl
eq.	equivalents
$Eu(hfc)_3$	Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
IPA	*iso*-propyl alcohol
Ipc_2BH	diisopinocampheylborane
$IpcBH_2$	monoisopinocampheylborane

K-9-*O*-DIPGF-9-BBNH	potassium 9-*O*-(1,2 : 5,6-di-*O*-isopropylidene-α-D-gluco-furanosyl)-9-boratabicyclo[3.3.1jnonane.
LAH	lithium aluminum hydride
Me	methyl
Mp	melting point
NADH	nicotinamide adenine dinucleotide
Ph	phenyl
Pr	propyl
/-Pr	/-propyl
rt	room temperature
TBA Br_3	tetrabutylammonium tribromide
TBDPS	*tert*-butyldiisopropylsilyl
TBSC1	*tert*-butyldimethylsilyl chloride
TESC1	triethylsilyl chloride
THF	tetrahydrofuran
TMSC1	trimethylsilyl chloride

ABSTRACT

Development of simple and convenient methodologies for an efficient asymmetric transformation of prochiral ketones into the corresponding enantiomerically pure secondary alcohols represents one of the fascinating and challenging endeavors in the present day synthetic organic chemistry. This thesis deals with the synthesis and applications of novel chiral catalysts containing N-P=O structural framework for the borane-mediated asymmetric reduction of prochiral ketones and consists of three chapters, that is, 1. Introduction 2. Objectives, Results & Discussion and 3. Experimental. The first chapter, that is, Introduction presents a brief literature survey on the important and recent developments in the asymmetric reduction of prochiral ketones.

The second chapter deals with the objectives, results and discussion. With a view to develop novel class of chiral catalysts / sources containing *N-P=O* structural framework and study their applications in the borane-mediated asymmetric reduction of prochiral ketones, particularly α-halo ketones, we have undertaken a long range research program with the following objectives.

1). To synthesize chiral molecules containing *N-P=O* structural framework having *(S)*-2-anilinomethylpyrrolidine moiety and to study their applications as catalysts in the borane-mediated asymmetric reduction of prochiral a-halo ketones.

2). To study the applications of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyl-bicyclo(3.3.0)octane as a catalytic source for the borane-mediated asymmetric reduction of prochiral ketones. Our objective also includes to synthesize the analogues of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)-octane and to study their applications as possible catalysts with a view to develop recoverable, reusable and air stable catalysts for the borane-mediated asymmetric reduction of prochiral ketones.

3). To study the applications of (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethyl-bicyclo(3.1.1)heptan-3-yloxy]-l,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octane, obtained *via* the treatment of (25, 5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane with (1*R*,2*R*,3*S*,5*R*)-2,6,6-trimethylbicyclo(3.1.1)hep-tane-2,3-diol, with a view to examine the effect of proximal hydroxyl group (in the catalyst) on enantioselectivities in the borane-mediated asymmetric reduction of prochiral ketones.

4). To synthesize and study the applications of various molecules containing *N-P=O* structural framework obtained *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane with representative amines of varying steric requirements, as catalysts for the borane-mediated asymmetric reduction of prochiral ketones, with a view to understand the effect of substituents on phosphorous in the (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety.

Novel and effective chiral phosphoramide catalysts for the borane-mediated asymmetric reduction of prochiral a-halo ketones

We have designed and synthesized two novel chiral phosphoramides *i. e.* (1*R*,2*R*)-1,2-cyclohexane **(158)** and 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octan-2-yl]piperazine **(159)** (Scheme 16 & eq. 78) and successfully employed as catalysts (30 mol%) for the borane-mediated asymmetric reduction of prochiral a-halo ketones **(166a-g),** to provide the corresponding 2-halo-1-arylethanols [(*S*)-**167a-g**] in 82-95% enantiomeric purities (eqs. 74, 76, 79-81, Table 1).

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane: a novel chiral source for borane-mediated catalytic chiral reductions

Above methodology requires 30 mol% catalyst for reduction of prochiral a-halo ketones **(166a-g)** to provide the resulting 2-halo-l-arylethanols (167a-g) in high enantiomeric purities with (*S*)-configuration. We felt that 30 mol% catalyst is too large an amount, thus rendering the methodology expensive and it is therefore, necessary to develop new frameworks / molecules that can catalyze the reaction when used in very small amounts. We also felt that it would be highly useful if such molecules can be easily accessible in large amounts. Accordingly, we have used easily available and

hither to unexplored (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane **[(2*S*,5*S*)-165]** as a catalytic chiral source (5 mol%) for the borane-mediated asymmetric reduction of prochiral a-halo ketones **(166a-f, 166h)** to provide the desired (*S*)-secondary alcohols **[(*S*)-167a-f**, (S)-167h] in 81-91% enantiomeric purities (eq. 88-90, Table 2). Though we do not understand the structure of the actual catalyst / catalytic spices, we have for the first time, demonstrated the potential of *N-**P(=O)Cl*** framework as a chiral catalytic source to generate a recoverable, reusable and air stable catalyst (165A or 165B) for the borane-mediated enantioselective reduction processes.

We have also synthesized the molecule (2*S*,5*S*)-**177** & (2*R*,5*S*)-**178** having ***N-P(=O)Cl*** structural framework and examined their potential as catalysts for the borane-mediated asymmetric reduction of prochiral ketones (**166b** and 175a) (Scheme 20, 21 eqs. 102-105, Table 3-5). However, these catalysts provided inferior enantioselectivities (up to 65%).

A new chiral catalytic source with an N-P=O structural framework containing a proximal hydroxyl group for the borane-mediated asymmetric reduction of prochiral ketones

With a view to examine the effect of proximal hydroxyl group (in the catalyst) on enantioselectivities in the borane-mediated asymmetric reduction of prochiral ketones,

we have synthesized chiral source (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethyl-bicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(188),** containing proximal hydroxyl group (eq. 106) and successfully employed as a chiral catalytic source (4 mol%) for the borane-mediated asymmetric reduction of prochiral ketones **(166a-f, 166h, 175a-e),** thus providing the resulting secondary alcohols [(*S*)-**167a-f**, (*S*)-**167h**, (*R*)-**176a-e**] upto 96% enantiomeric purities (eq. 107-112, Table 6-8).

Towards novel chiral catalysts containing N-P=O structural framework for the borane-mediated asymmetric reduction of prochiral ketones

With a view to understand the influence of various amino groups of varying steric requirements on phosphorous in the (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenyl-bicyclo(3.3.0)octane moiety, we have prepared five representative chiral catalysts *i. e.*, (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(190),** *(SS)*-\ ,3-diaza-2-(/-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**191**), (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(192),** (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A)** and (5S)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**193B**) (eqs. 115-117, 125, 128) and studied their applications

in the borane-mediated asymmetric reduction of prochiral ketones **(166a, 166b, 175a)** (eqs. 118-121, 123, 124, 126, 127, 129-132, 134, Table 9, 10, 12). The best results were obtained with the chiral phosphoramide **193A** as a catalyst, thus providing the resulting secondary alcohols up to 94% enantiomeric purities (eqs. 133, 135, 136, Table 11, 13).

The third chapter deals with the detailed experimental procedures, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, microanalyses, physical constants (bp, mp), X-ray crystallographic data, optical rotations and HPLC analysis using chiral columns Chiralcel OD, Chiralcel OD-H, and Chiralcel OJ-H.

INTRODUCTION

Development of simple and convenient methodologies for an efficient asymmetric transformation of prochiral ketones into the corresponding enantiomerically pure secondary alcohols represents one of the fascinating and challenging endeavors in the present day synthetic organic chemistry.[1-20] During the last two decades several efforts have been made in this direction by the organic / bioorganic chemists and in fact remarkable success has been achieved (i) using several chiral reagents such as chirally modified metal hydride reagents (most commonly modified lithium aluminum hydride and borane hydride reagents),[4-8] (ii) *via* catalytic asymmetric hydrogenation / hydrogen transfer reactions using transition metal based chiral catalysts,[9-15] (iii) *via* biotransformation (using enzymes)[16-18] and also (iv) *via* reduction through enzyme models.[19,20]

Since this thesis deals with the studies in the design, synthesis and applications of novel chiral catalysts / sources for the borane-mediated asymmetric reduction of prochiral ketones, this chapter presents the literature dealing with the applications of chiral reagents, chiral catalysts and strategies in asymmetric reduction of prochiral ketones. Since there are large number of publications in this area it will not be possible to present all the literature here. However, attempts were made to present the most relevant, recent and important representative literature examples of chiral reagents.

chiral catalysts and strategies mediated asymmetric reduction of prochiral ketones in this section.

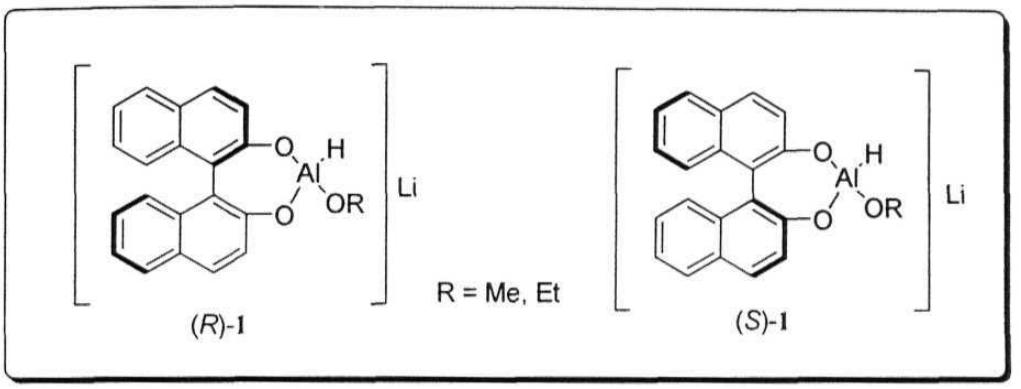
Chirally modified lithium aluminum hydride reagents

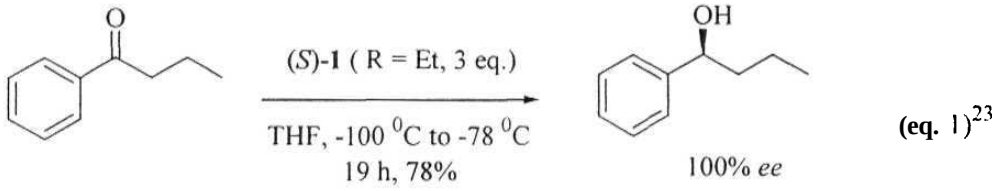
Lithium aluminum hydride, which is one of the most useful reducing agents for various reduction processes in organic synthesis, has been conveniently modified with various chiral molecules such as diols, diamines and amino alcohols and successfully employed for reduction of various prochiral ketones to provide the corresponding secondary alcohols in high enantiomeric purities.

The first report in this direction was due to Bothner-By, who, in 1951 first time examined the asymmetric reduction of methyl ethyl ketone and methyl *tert*-butyl ketone with modified lithium aluminum hydride reagent derived from lithium aluminum hydride (LAH) and (+)-camphor.[21] Subsequently, organic chemists directed their studies towards the development of appropriate chirally modified lithium aluminum hydride reagents to achieve high enantioselectivities in reduction of various prochiral ketones.

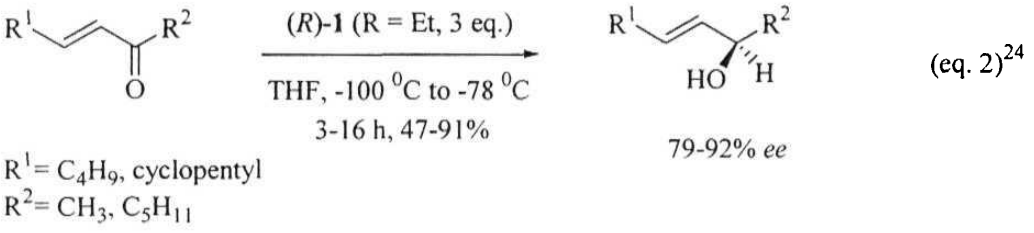
In this direction, in 1979, Noyori developed elegant chiral reducing agents *(R)-l* and (*S*)-**1** [(*R*) and (*S*)-BINAL-H] (Fig. 1), *via* the modification of lithium aluminum hydride with enantiomerically pure (*S*) or (*R*)-BINOL, which were successfully employed for the reduction of various prochiral ketones to provide the corresponding secondary alcohols with high enantiomeric purities. Some representative examples are given in equations (1-3).[22-24]

Figure 1:

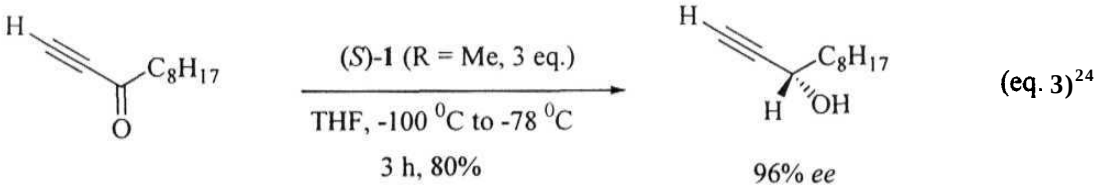




(eq. 1)[23]

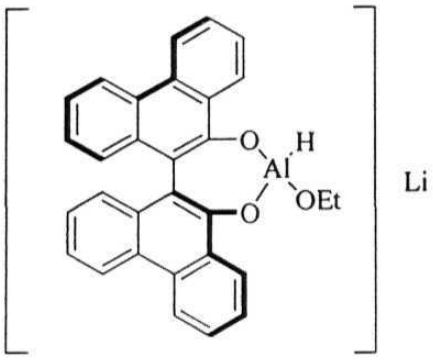


(eq. 2)[24]

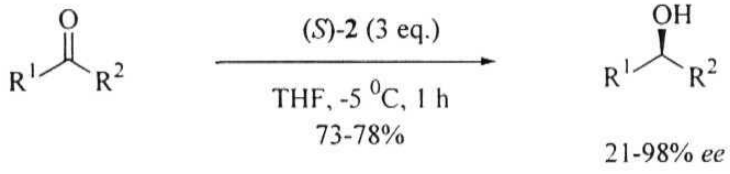


(eq. 3)[24]

Subsequently Yamamoto and co-workers[25] reported an important chirally modified lithium aluminum hydride reagent (*S*)-**2** for the reduction of prochiral ketones to provide the secondary alcohols in high optical purities (eq.4).



(*S*)-2

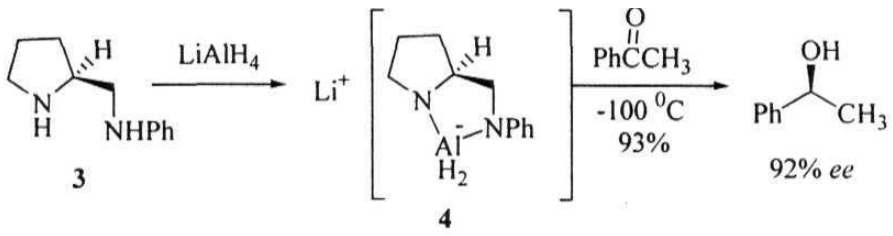


(eq. 4)

R^1 = Ph, CH_2Ph, Bu^t
R^2 = D, Me, Et, CH_2Ph

The hydride reagent (4) obtained *via* the reaction of bicyclic diamine (3) with lithium aluminum hydride (LAH), has been successfully utilized by Mukaiyama *et al.* [1] for the asymmetric reduction of prochiral ketones to provide the chiral secondary alcohols in high enantioselectivities. Representative example is given in Scheme 1.

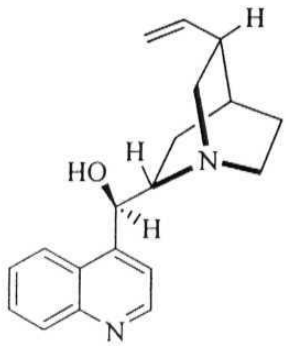
Scheme 1:



In addition to above mentioned reagents (1, 2, 4), organic chemists have used number of chiral amines, alcohols and amino alcohols (5-20, Fig. 2) for modification of lithium

aluminum hydride and successfully employed the resulting hydride reagents in reduction of various prochiral ketones to provide the desired secondary alcohols in enantiomerically enriched form.

Figure 2:



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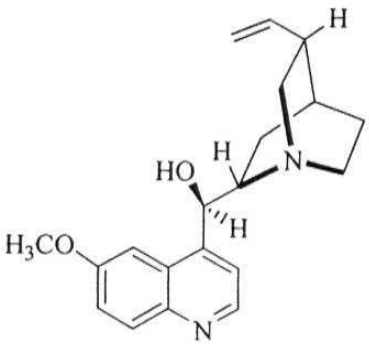

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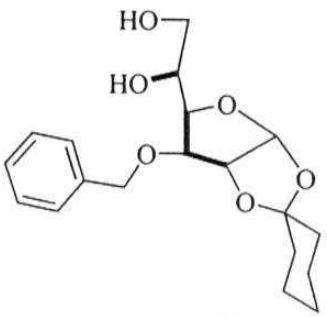

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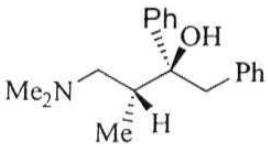

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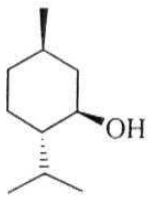
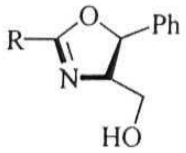
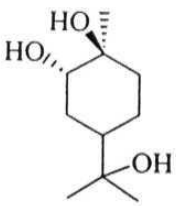


9[32]



R= Me, Et, *i*-Pr, $PhCH_2$

10[33]



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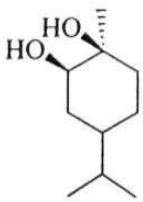

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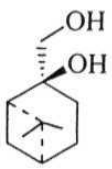

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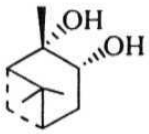

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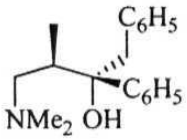

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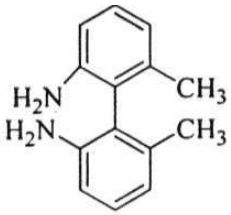
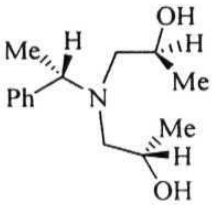
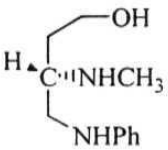


(*R*) and (*S*)

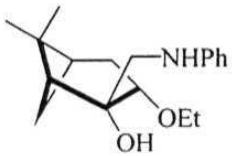
16[36]



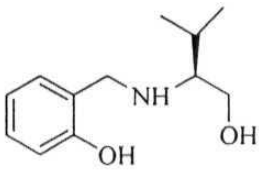
17[37]



18[38]



19[39]



20[40]

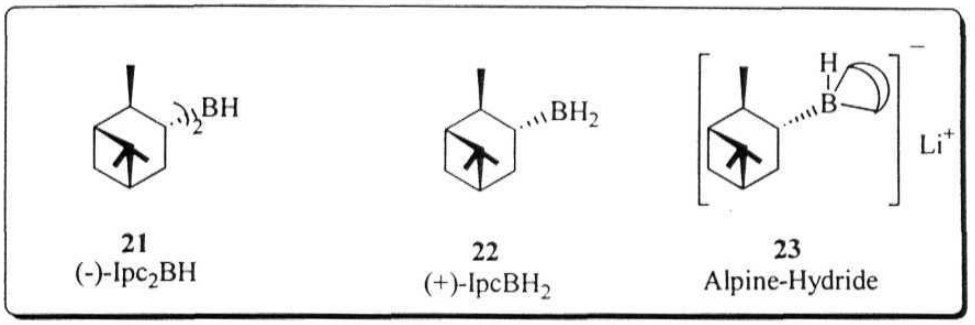
Boron reagents

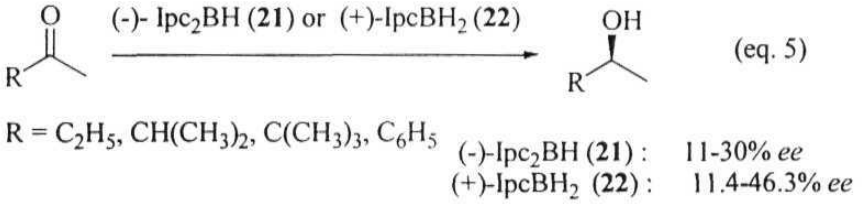
Chiral boron reagents represent another family of reagents which have been widely used for the asymmetric reduction of various prochiral ketones to provide the corresponding secondary alcohols in high optical purities.[4-8, 41-43] The first report in the application of borane reagents in the asymmetric reduction was due to Brown and Bigley who, in 1961, described the reduction of prochiral ketones with diisopino-campheylborane (Ipc_2BH) (21) (Fig. 3) to provide the resulting secondary alcohols in 11-30% enantiomeric purities (eq. 5).[44]

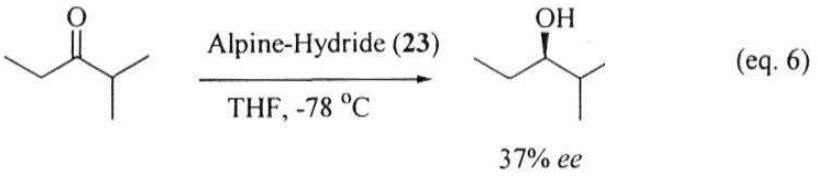
Later on, monoisopinocampheylborane ($IpcBH_2$) (22)[45] and Alpine-Hydride (23)[46] (Fig. 3) were examined for chiral reduction of prochiral ketones by Brown and co-workers (eq. 5 & 6). Although the enantioselectivities were low in these cases, these preliminary

studies provided direction and new-outlook towards the designing better reagents for achieving high enantioselectivities.

Figure 3:

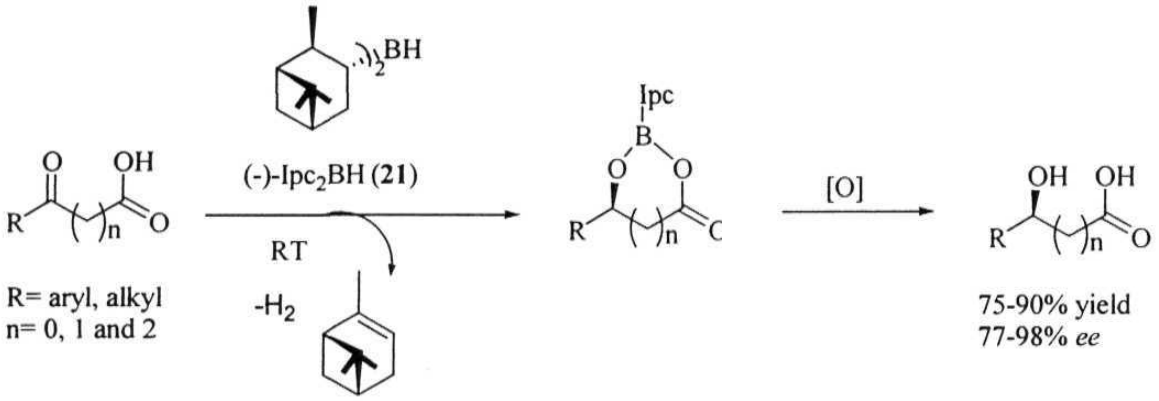






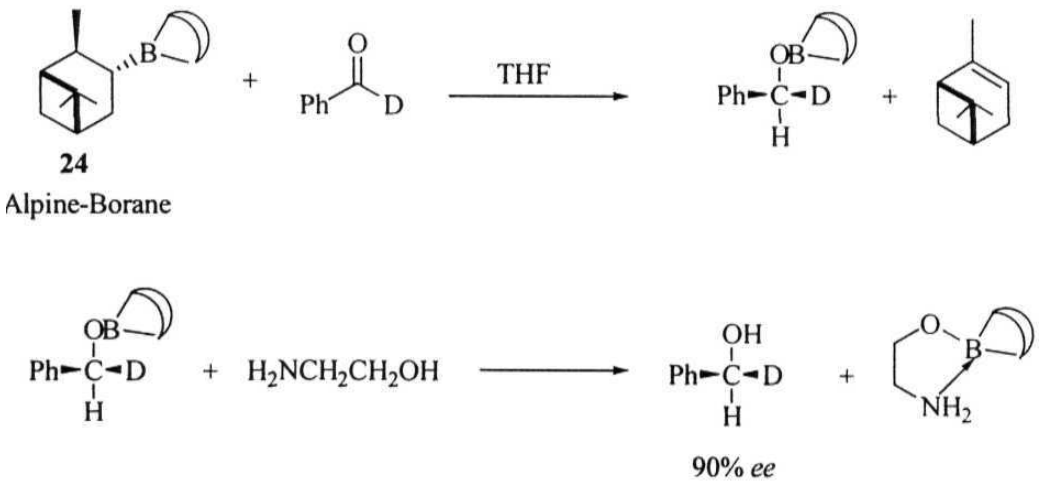
Recently, Ramachandran *et al.*[47] proved that diisopinocampheylborane (21) is an efficient and effective chiral reagent for intramolecular asymmetric reduction of a, β and y-keto acids to provide the corresponding hydroxy acids in 77-98% enantio-selectivities with predictable stereochemistry (Scheme 2).

Scheme 2:

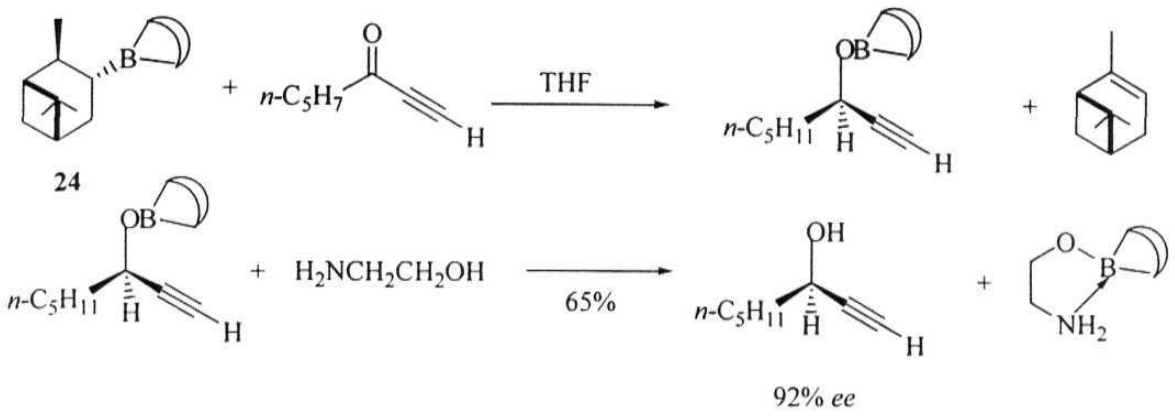


In 1979, Midland[48,49] has reported the application of *B*-3-pinanyl-9-bora-bicyclo[3.3.1]nonane (Alpine-Borane) (24) as an important chiral reagent for asymmetric reduction of various prochiral ketones. Some representative examples are given in Scheme 3 & 4.

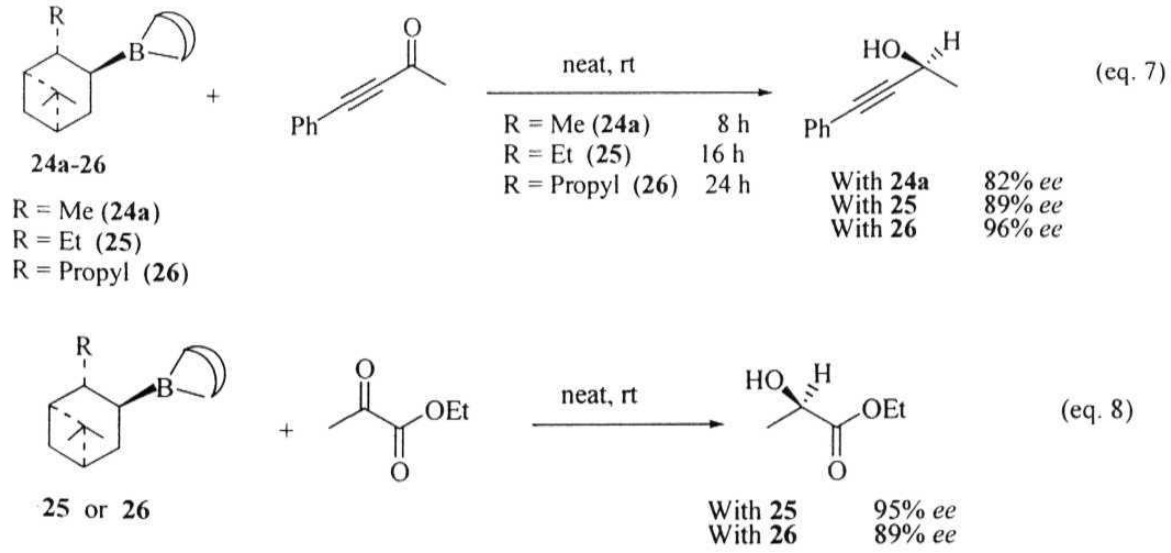
Scheme 3:



Scheme 4:



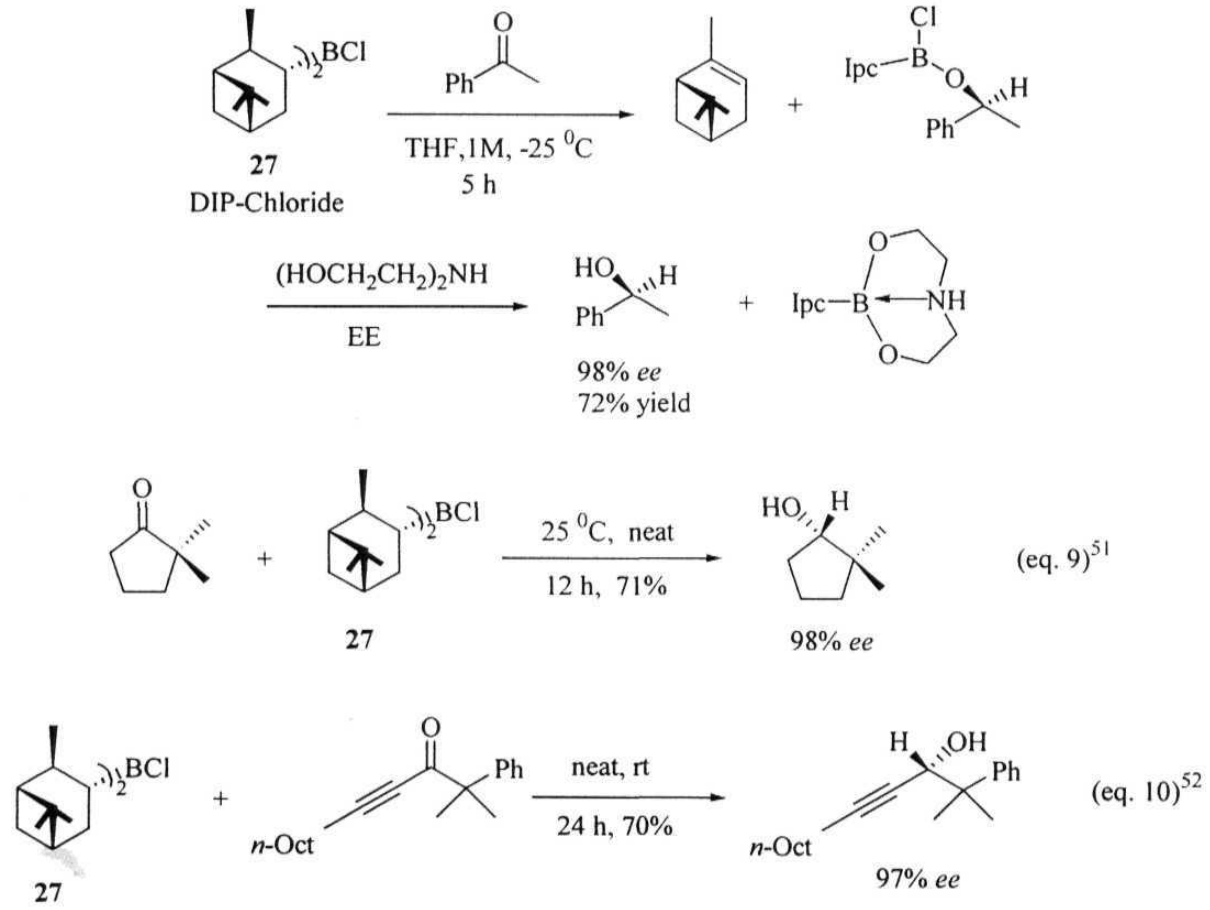
Later on, Brown and co-workers[5] prepared Eapine-borane (25) and Papine-borane (26) and examined their applications in asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols in high enantioselectivities. They also noticed that these reagents offer better enantioselectivities than Alpine-Borane reagent. Some representative examples are presented in equations 7 & 8.



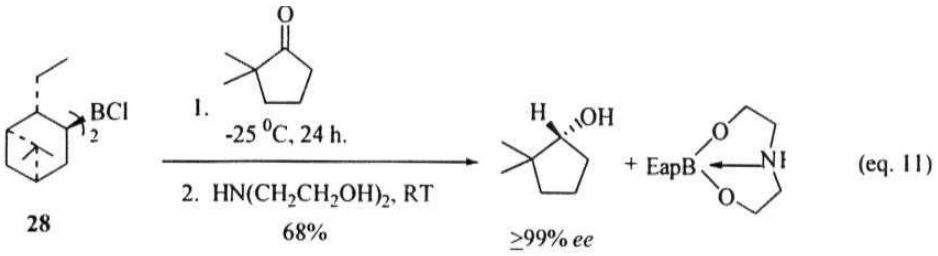
Subsequently, Brown and co-workers[51,52] developed an extremely efficient reagent B-chlorodiisopinocampheylborane (DIP-Chloride) (27) for the asymmetric reduction of

various prochiral ketones to provide the resulting secondary alcohols in high optical purities. DIP-Chloride shows extraordinary consistency in the reduction of various prochiral ketones with predictable stereochemistry. Representative examples are described in Scheme 5, equations 9 & 10.

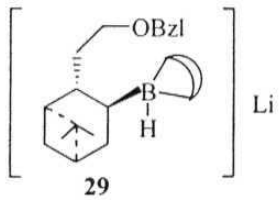
Scheme 5:

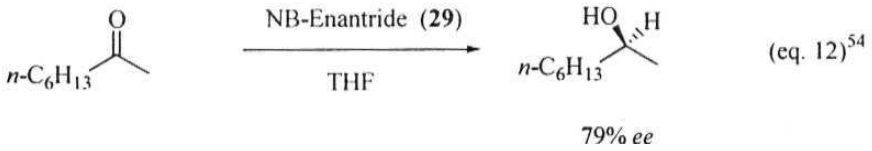


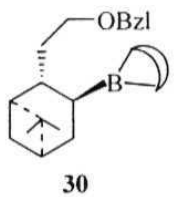
Later, Brown *et al.*[53] have found that Eap$_2$BCl (28) provides better enantioselectivities than DIP-Chloride. Representative example is shown in equation 11.

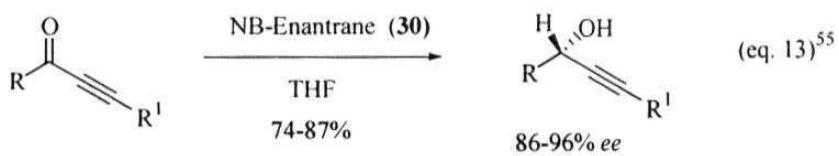


Midland and co-workers designed and synthesized three interesting chiral reagents NB-Enantride (**29**),[54] NB-Enantrane (**30**)[55] and *cis*-myrtanylborane (**31**)[56] and examined their applications in asymmetric reduction (eq. 12-14). They have noticed that NB-Enantrane (30) reduces a,p-acetylenic ketones to provide the optically active secondary propargyl alcohols in 86-96% enantiomeric purities (eq. 13).

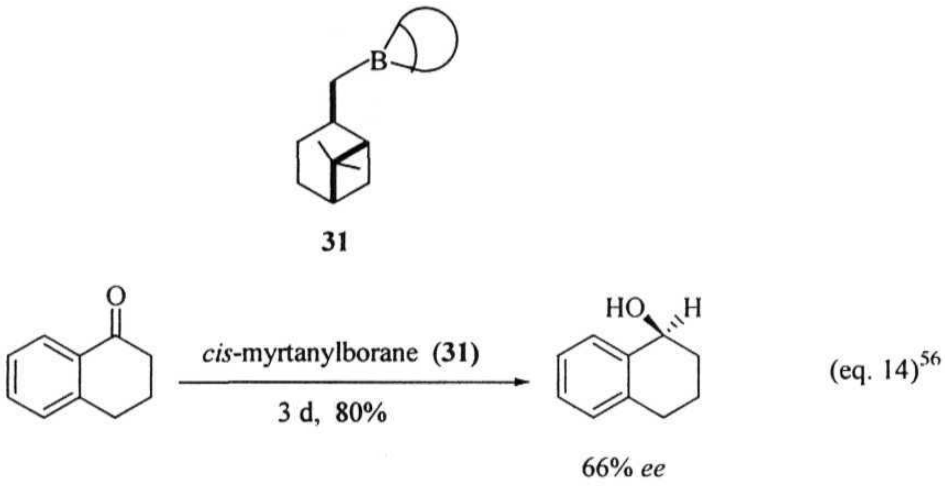




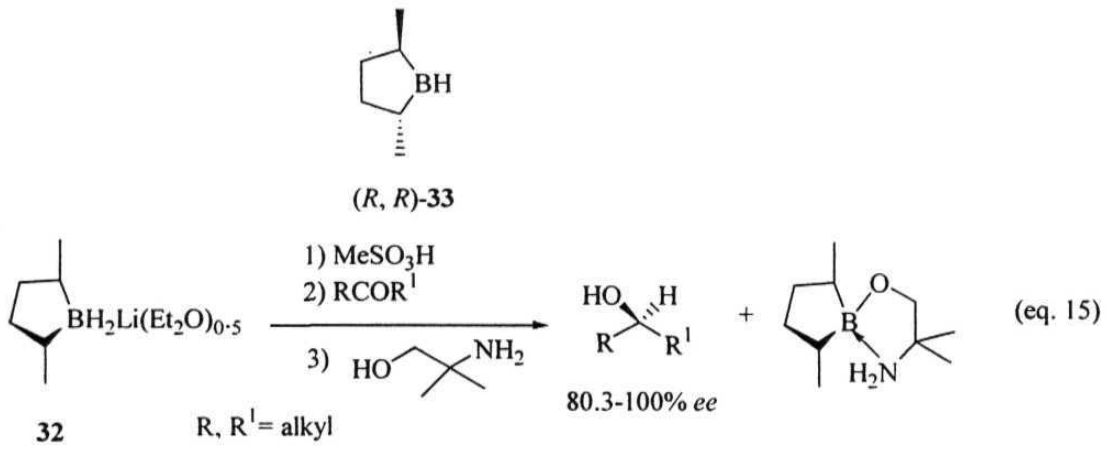




R = CH_3, C_2H_5, C_5H_{11}, cyclohexyl
R^1 = H, CH_3, C_2H_5, C_5H_{11}, C_6H_5, $CO_2C_2H_5$, $Si(CH_3)_3$

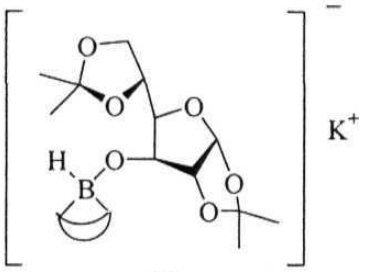


Masamune *et al.* [57,58] have employed the chiral lithium dihydridoborate (32) derived from (*R,R*) or (*S,S*)-2,5-dimethylborolane (33) for asymmetric reduction of prochiral dialkyl ketones to afford the secondary alcohols in 80.3-100% enantiomeric purities (eq. 15).

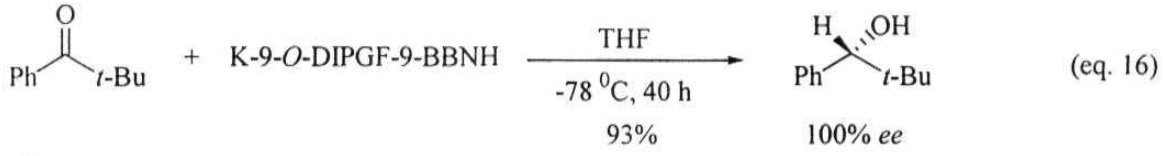


The chiral borohydride, K-9-*O*-DIPGF-9-BBNH (34), derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was successfully used as a chiral reducing agent by

Brown and co-workers[59] for the preparation of secondary alcohols in high enantiomeric purities. Representative example is given in equation 16.

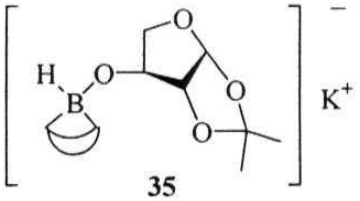


34
K-9-*O*-DIPGF-9-BBNH

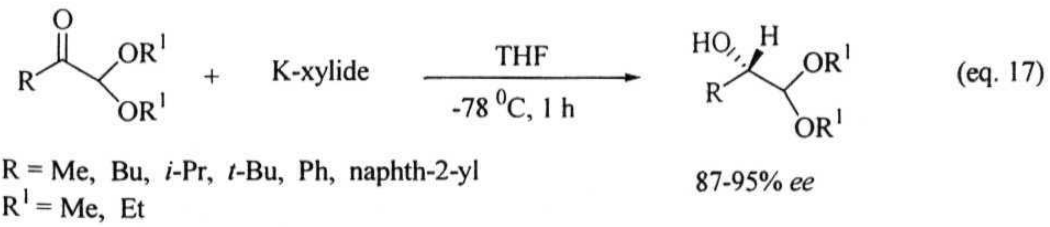


(eq. 16)

Subsequently, application of chiral reducing agent, K-xylide (35) derived from 1,2-isopropylidene-5-deoxy-α-D-xylofuranose, was reported by Cho and Chum for the reduction of a-keto acetals to provide the corresponding α-hydroxy acetals in 87->99% enantiomeric purities (eq. 17, 18).[60]



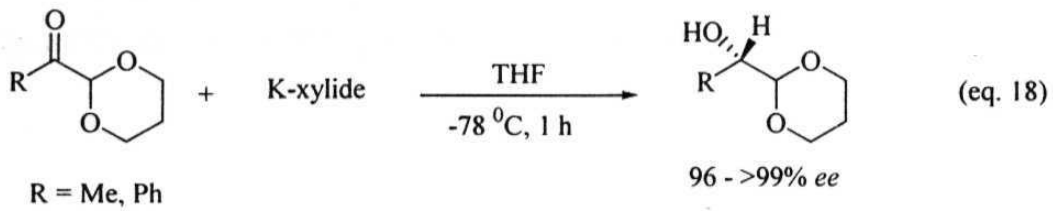
35
K-xylide



(eq. 17)

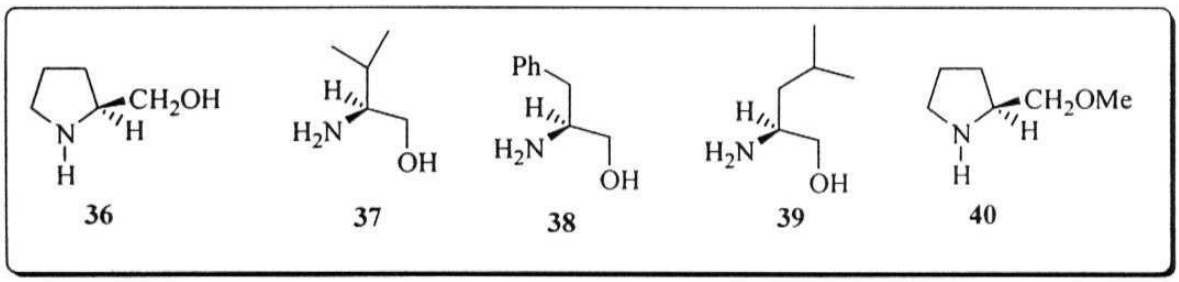
R = Me, Bu, *i*-Pr, *t*-Bu, Ph, naphth-2-yl
R^1 = Me, Et

87-95% *ee*

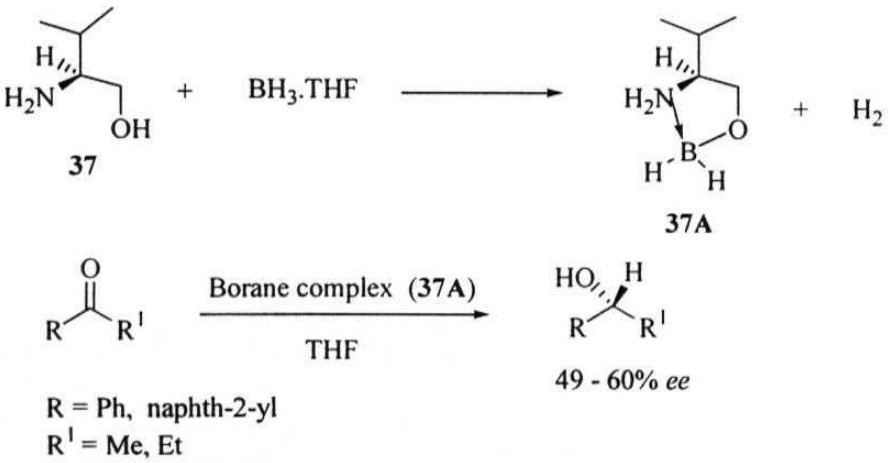


Hirao and coworkers[61] have reported an interesting asymmetric reduction of prochiral aromatic ketones utilizing the borane complexes of chiral amino alcohols 36-40 (Fig. 4), derived from α-amino acids. The resulting secondary alcohols were obtained in moderate enantioselectivities (Scheme 6).

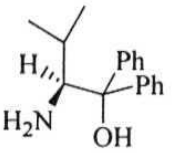
Figure 4:



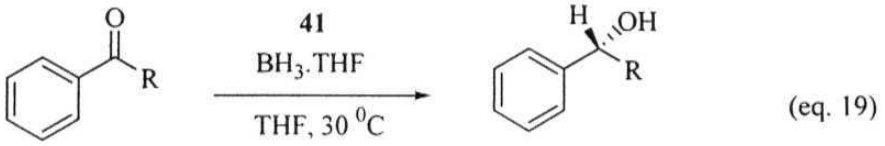
Scheme 6:



Later, Itsuno and co-workers[62] discovered that borane-mediated asymmetric reduction of prochiral ketones, in the presence of β-amino alcohol (41), provides the resulting secondary alcohols in 94-100% enantiomeric purities (eq. 19).



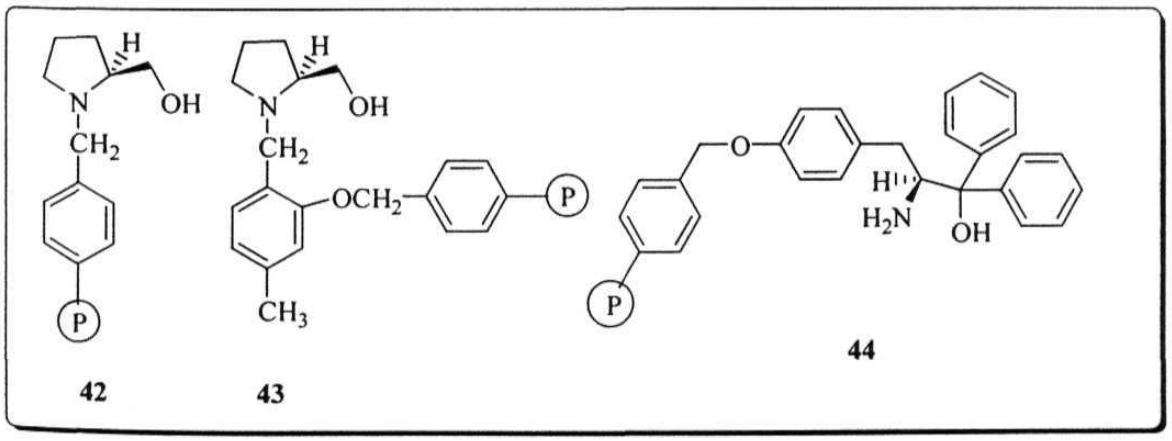
41

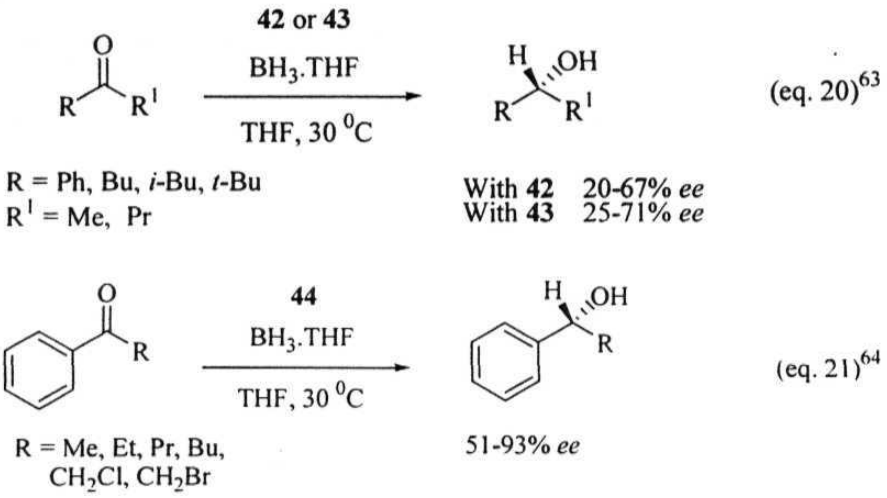


(eq. 19)

Subsequently, Itsuno and co-workers also prepared an interesting recoverable and reusable chiral polymeric reagents (42-44) (Fig. 5) from (*S*)-prolinol and (*S*)-tyrosine and successfully employed for the borane-mediated asymmetric reduction of prochiral ketones (eq. 20, 21).[63,64]

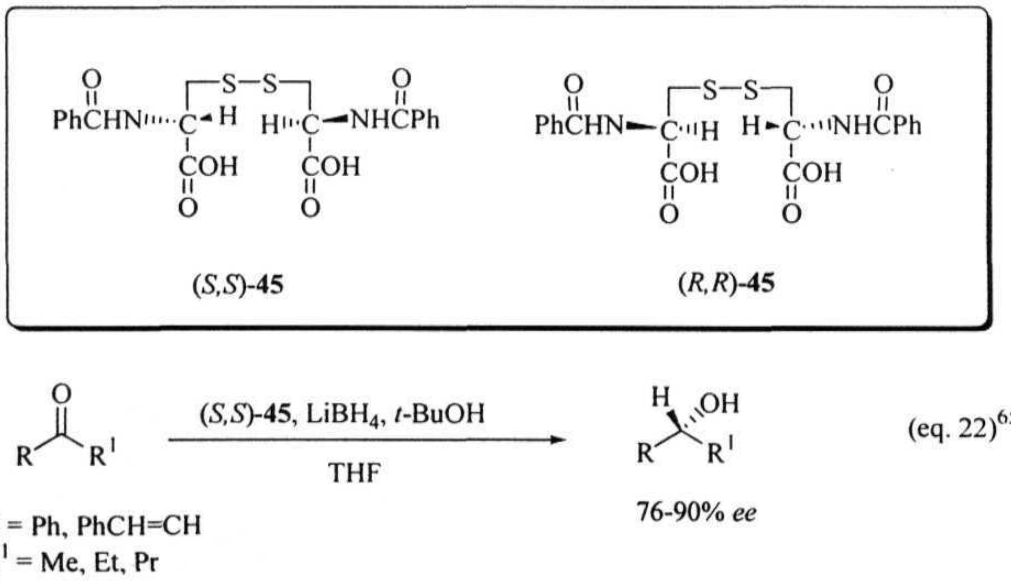
Figure 5:

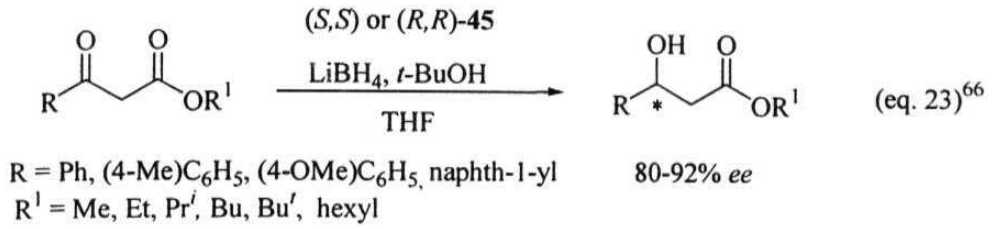




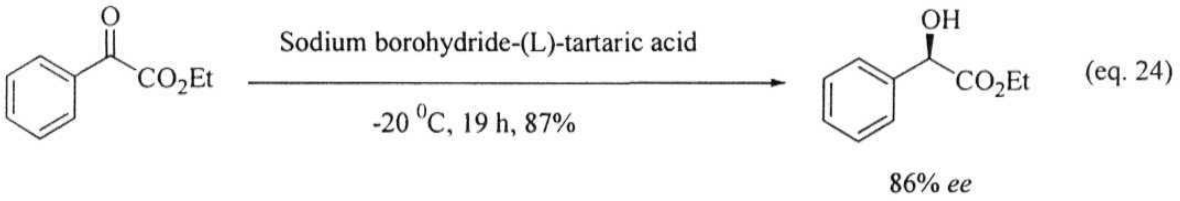
Soai and co-workers [65,66] have examined the applications of *N, N'*-dibenzoylcystine (45) (Fig. 6) as an efficient chiral auxiliary for $LiBH_4$ mediated asymmetric reduction of prochiral ketones and 3-aryl-3-oxoesters to afford the corresponding secondary alcohols in 76-90% and 3-aryl-3-hydroxyesters in 80-92% enantiomeric purities (eq. 22, 23).

Figure 6:



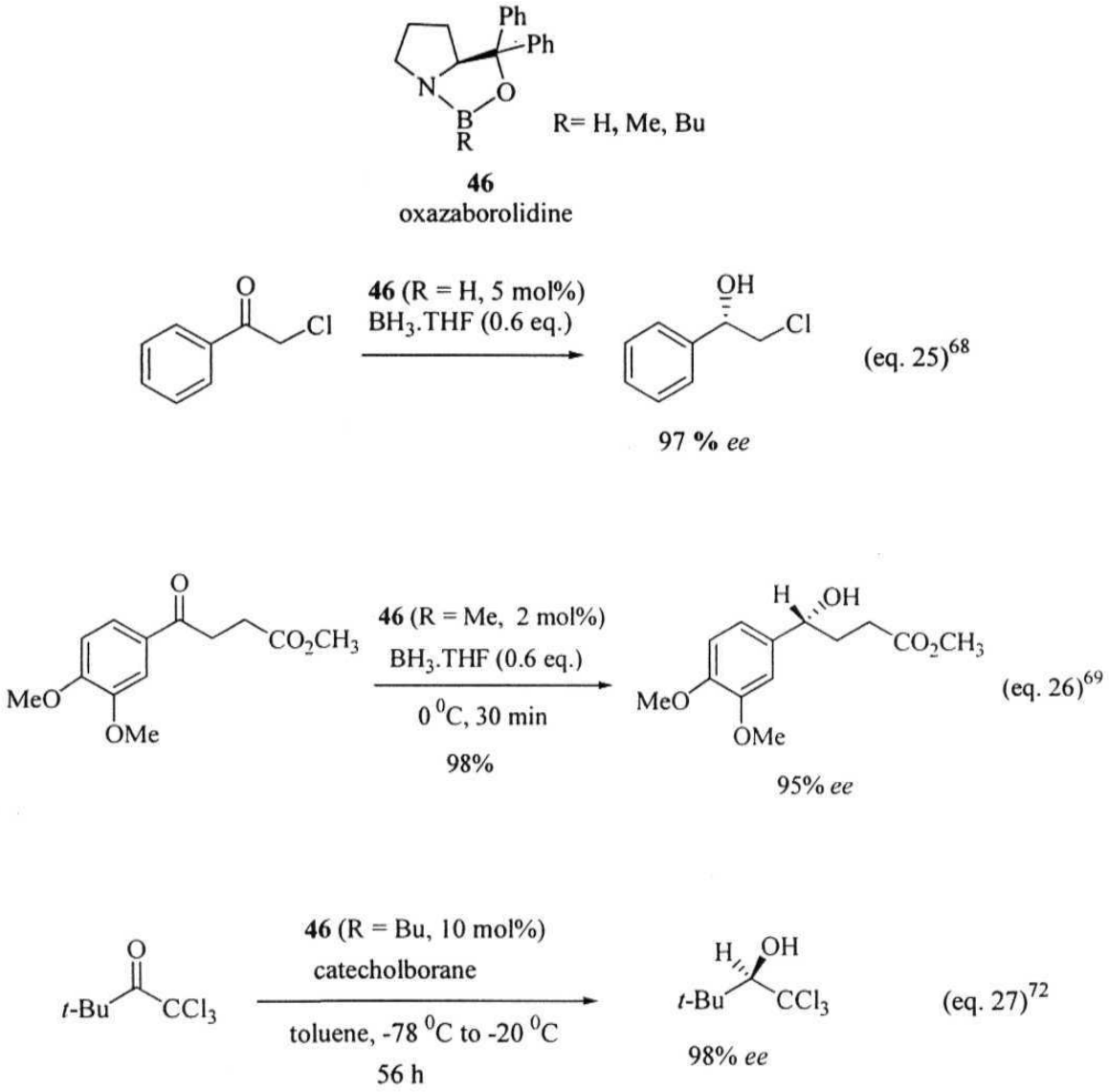


Yatagai and Ohnuki have successfully employed chiral reagent, obtained *via* the treatment of sodium borohydride with (L)-tartaric acid, for the asymmetric reduction of various prochiral ketones to provide the corresponding secondary alcohols in high enantioselectivities. Representative example is given in equation 24.[67]



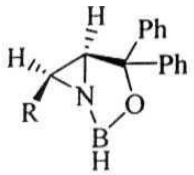
Catalytic Reagents:

In 1987, Corey and co-workers[7,68-74] for the first time demonstrated oxazaborolidines (46), derived from (*S*)-proline as catalysts for the borane-mediated asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols in high enantioselectivities. Some important and relevant examples are presented in the equations 25-27. Corey has named these molecules as *chemzymes* due to the high efficiency of these molecules as catalysts in inducing chirality almost matching the efficiency of enzymes.



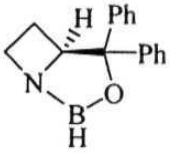
Subsequently, organic chemists have designed and synthesized a large number of chiral amino alcohols for the preparation of oxazaborolidines (47-68) and examined their applications as catalysts in asymmetric reduction of representative prochiral ketones. Some important and relevant examples are listed in Figure 7. Representative applications of these catalysts are described in the following equations (eq. 28-31).

Figure 7:

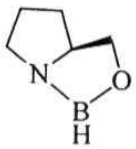


47[75]

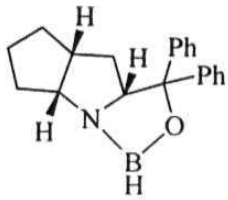
R = H, Me



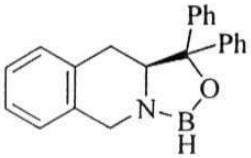
48[76, 77]



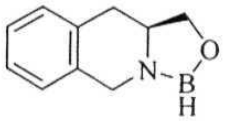
49[78]



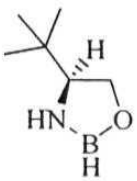
50[79]



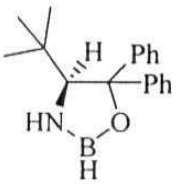
51[80]



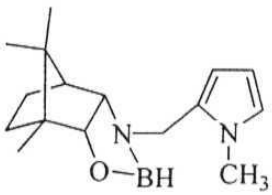
52[80]



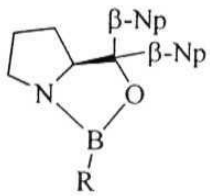
53[76]



54[76]

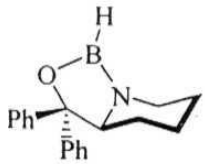


55[81]

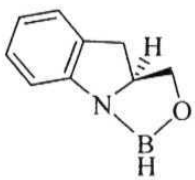


R = H, Me, Bu

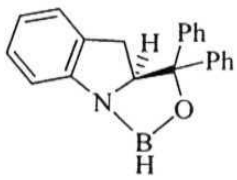
56[82]



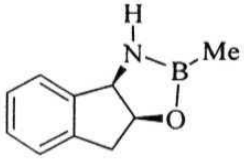
57[83]



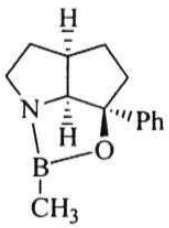
58[84,85]



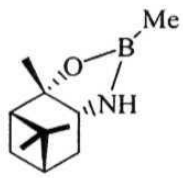
59 [85]



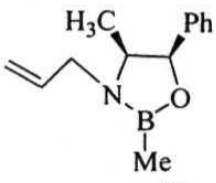
60[86]



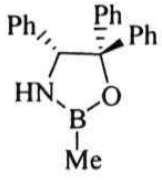
61[87]



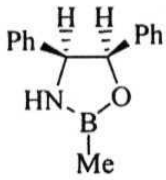
62 [88]



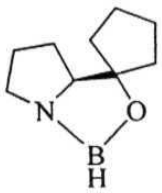
63[89]



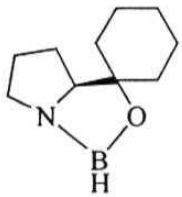
64[90]



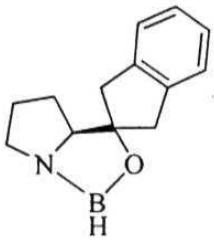
65[91]



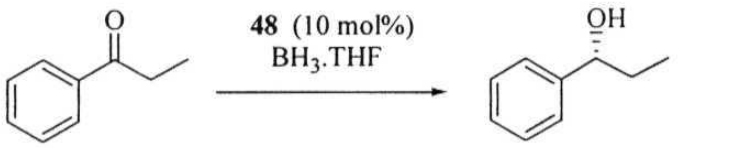
66[92]



67[92]

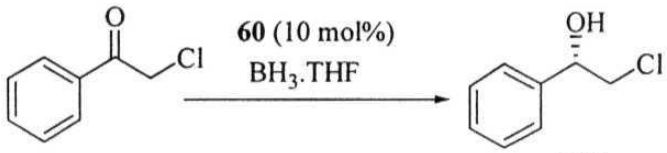


68[92]



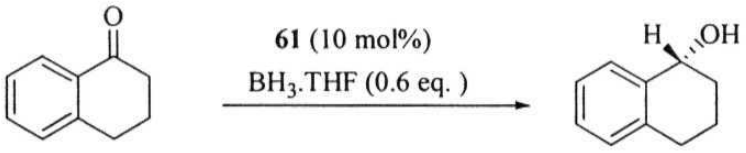
(eq. 28)[76]

99% *ee*



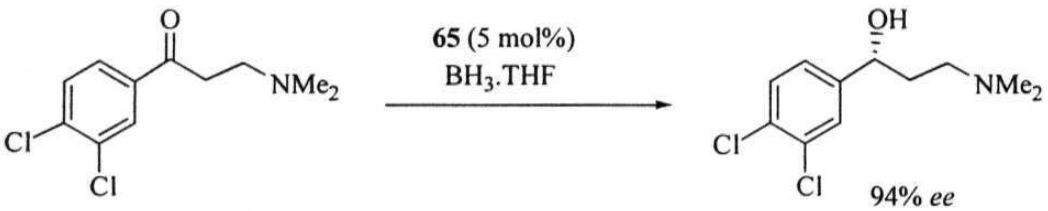
(eq.29)[86]

96% *ee*



(eq. 30)[87]

95.3% *ee*



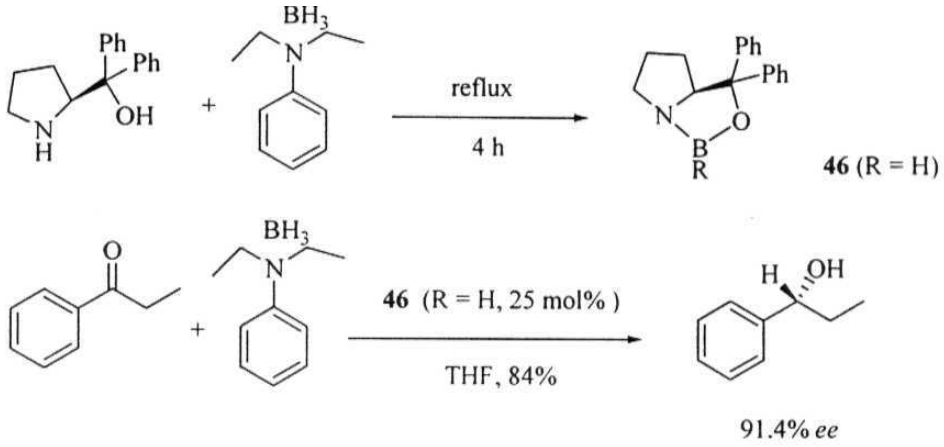
(eq. 31)[91]

94% *ee*

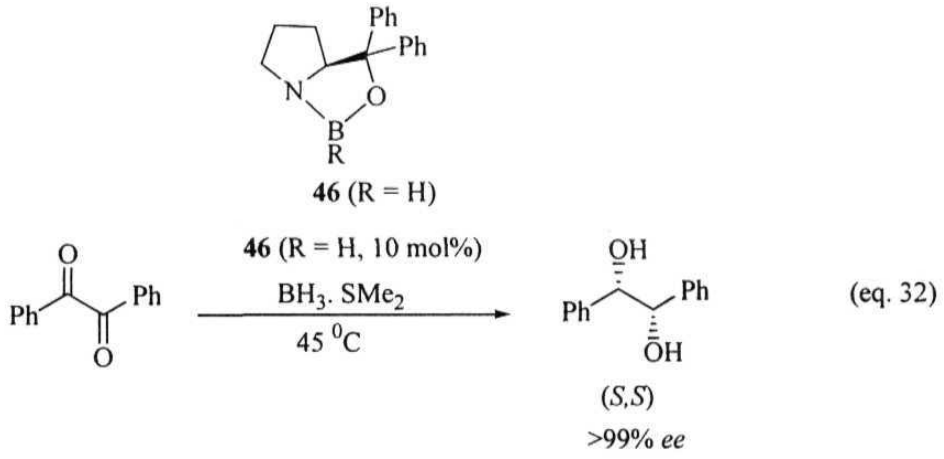
Periasamy *et al.*[93] have developed a convenient procedure for the α,α-diphenylpyrrolidinemethanol catalyzed asymmetric reduction of prochiral ketones in the presence of

N, N-diethylaniline-BH_3 (generated from I_2 / $NaBH_4$ and N, N-diethylaniline). Representative example is given in Scheme 7.

Scheme 7:

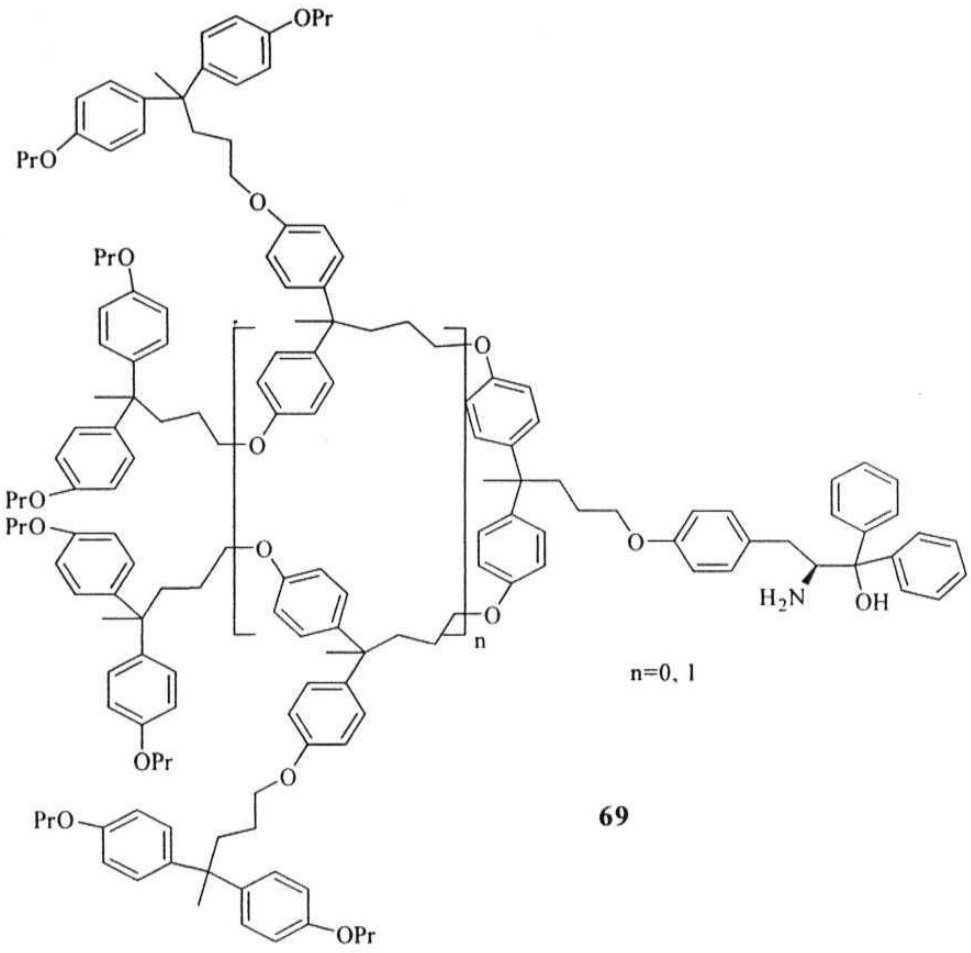


Joshi and Prasad have utilized the oxazaborolidine catalyst 46 (prepared *in situ)* for the borane-mediated asymmetric reduction of various 1,2-diones to provide the corresponding diols in high enantioselectivities. Representative example is given in equation 32.

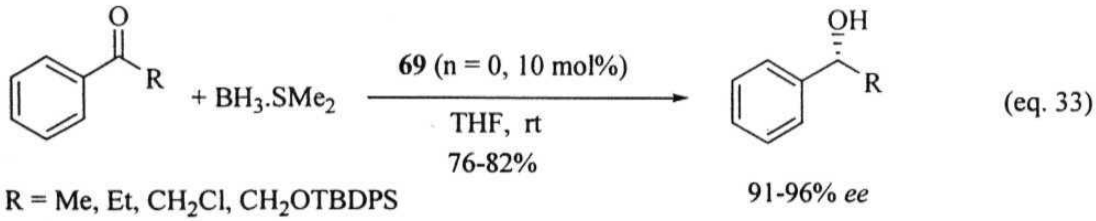


Bolm and co-workers [95] have reported the application of chiral dendrimer based amino alcohols (69) as catalysts for the enantioselective borane-mediated reduction of

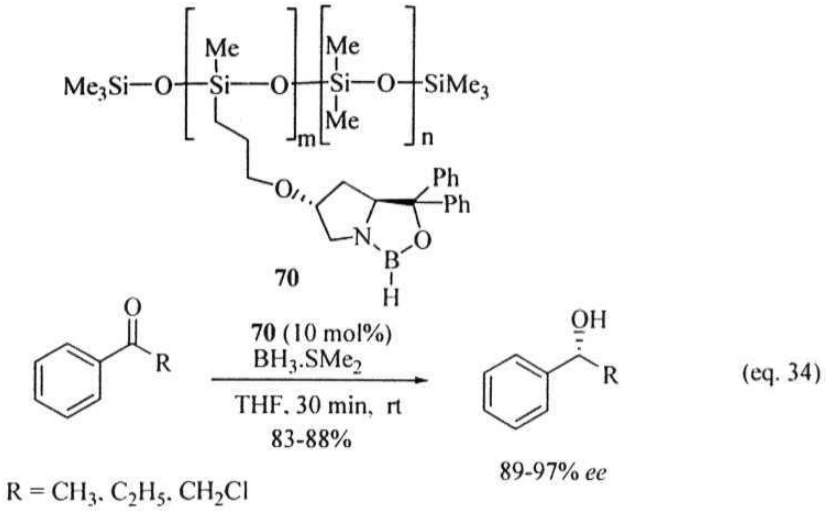
prochiral ketones. The resulting secondary alcohols are obtained in 91-96% enantioselectivities (eq. 33).



69

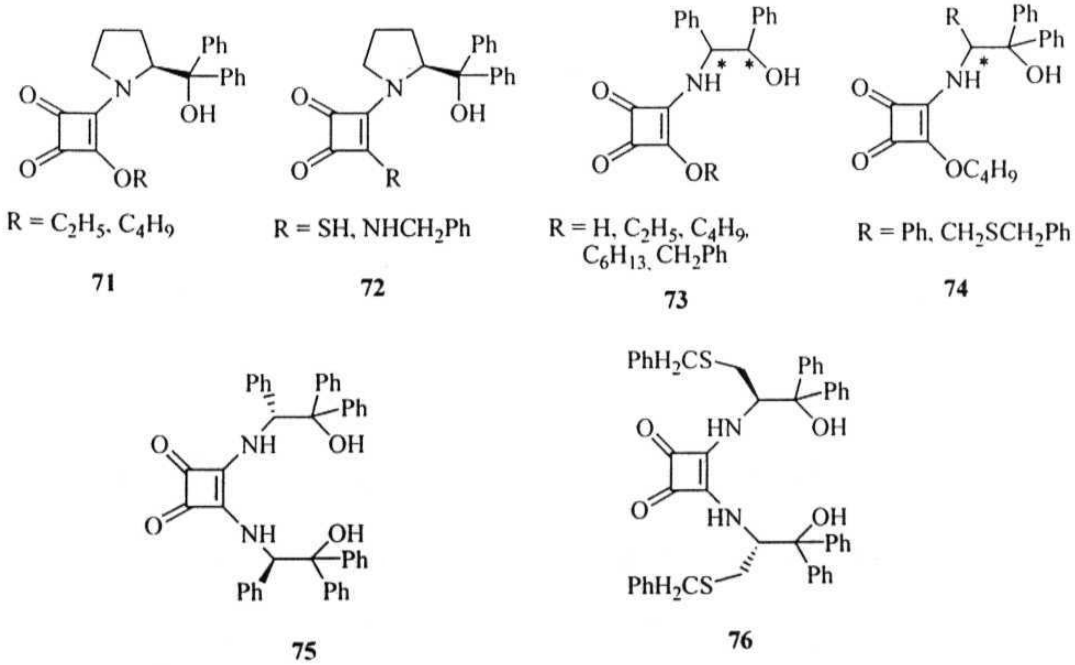


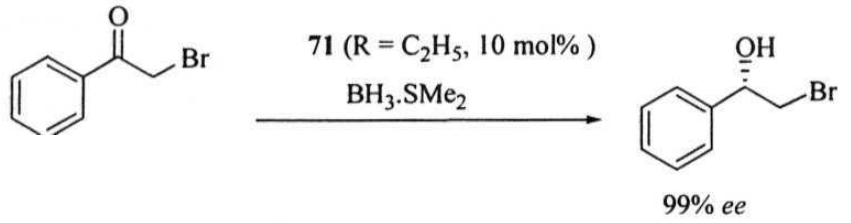
Recoverable polymer-enlarged homogeneously soluble oxazaborolidine (70) catalyst has been employed by Wandrey *et al.* for the borane-mediated asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols in 89-97% enantioselectivities (eq. 34).[96]



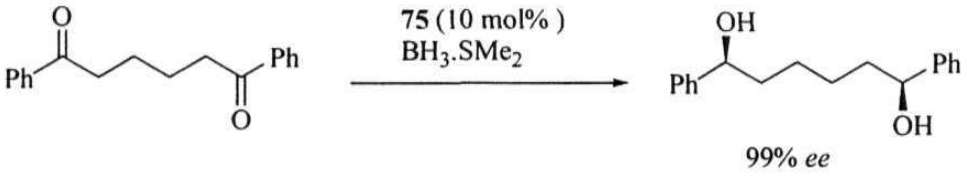
Xie and co-workers [97,98] have synthesized a series of chiral amino alcohols **(71-76)** (Fig. 8) having squaric acid moiety, and used these ligands for *in situ* synthesis of oxazaborolidines, which were subsequently used as catalysts for the borane-mediated asymmetric reduction of prochiral ketones. Some representative examples are given in equations 35 & 36.

Figure 8:



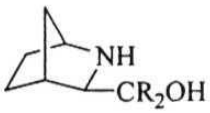


(eq. 35)



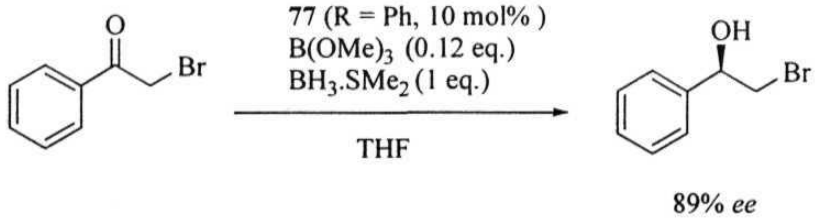
(eq. 36)

Andersson and co-workers" have examined the applications of bicylic β-amino alcohols (77) as catalysts in the borane-mediated asymmetric reduction of prochiral ketones to obtain the secondary alcohols in high enantioselectivities. Representative example is given in equation 37.



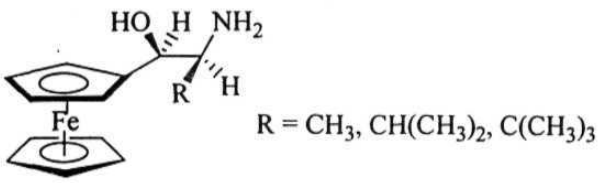
R = H, Me, C_6H_5, (4-Cl)C_6H_4, (4-OMe)C_6H_4, (4-Me)C_6H_4, (4-CF_3)C_6H_4, (4-C_6H_5)C_6H_5, naphth-2-yl

77

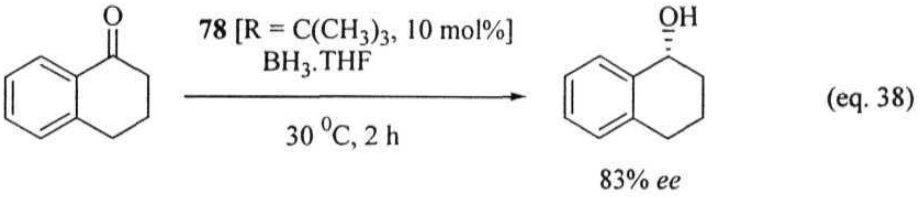


(eq. 37)

Pelinski and co-workers[100] have reported an interesting catalytic application of ferrocenyl amino alcohols (78) in the borane-mediated asymmetric reduction of prochiral ketones. Representative example is given in equation 38.



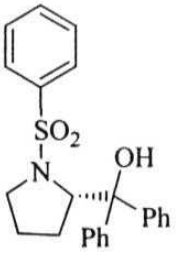
78



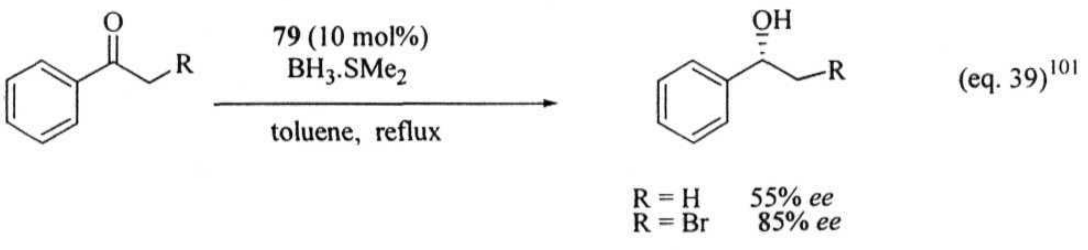
(eq. 38)

Sulfonamide based chiral catalysts

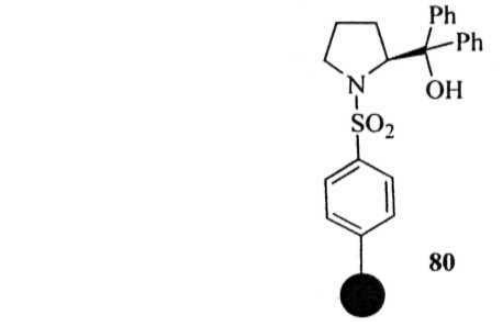
Zhao and co-workers[101,102] have reported chiral sulfonamide (79) and polymer supported sulfonamide (80) derived from (*S*)-proline as catalysts for the borane-mediated asymmetric reduction of prochiral ketones to provide the secondary alcohols in high enantioselectivities. Some representative examples are given in equations 39-41.



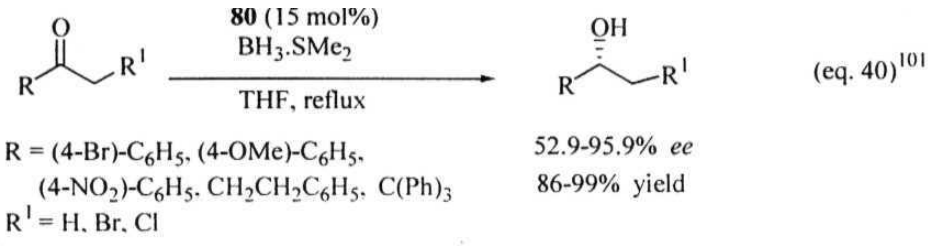
79

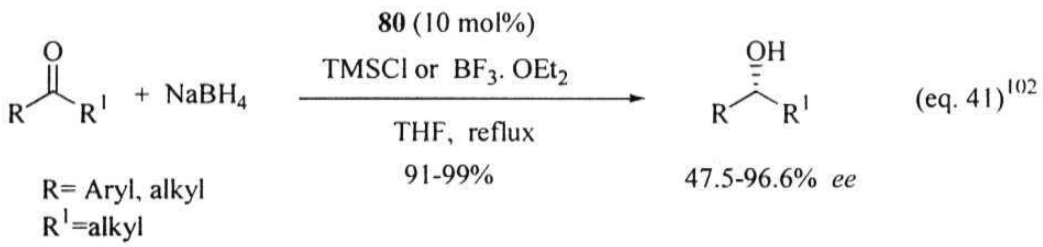


(eq. 39)[101]



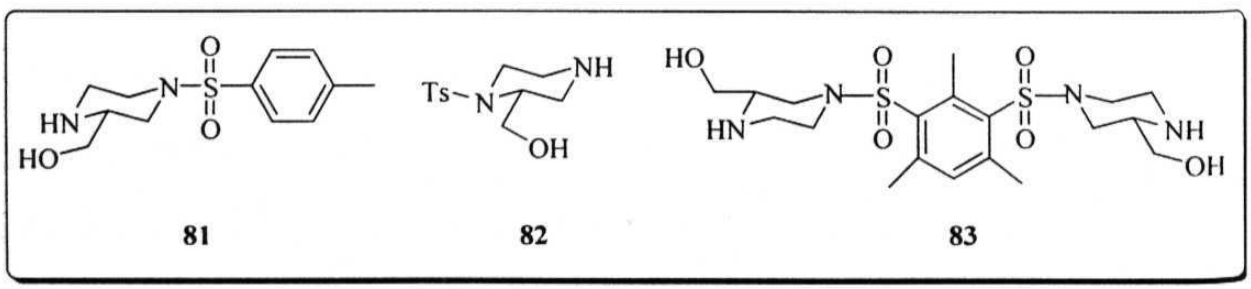
80



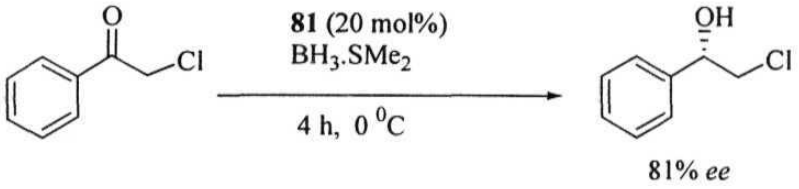


New amino alcohols **81-83** (Fig. 9) containing piperazine ring and sulfonamide moieties have been utilized as catalysts for the borane-mediated asymmetric reduction of prochiral ketones by Itsuno *et al.*[103] to provide the enantiomerically enriched alcohols (eq. 42).

Figure 9:

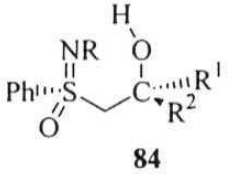


81 **82** **83**



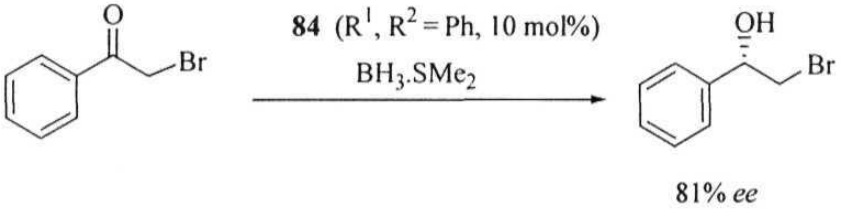
(eq. 42)

Bolm and Felder have successfully employed optically active β-hydroxysulfoximines (84) as catalysts for the borane-mediated asymmetric reduction of prochiral ketones (eq. 43).



84

R = H, Me
R^1, R^2 = Me, *i*-Pr, Ph, adamantyl

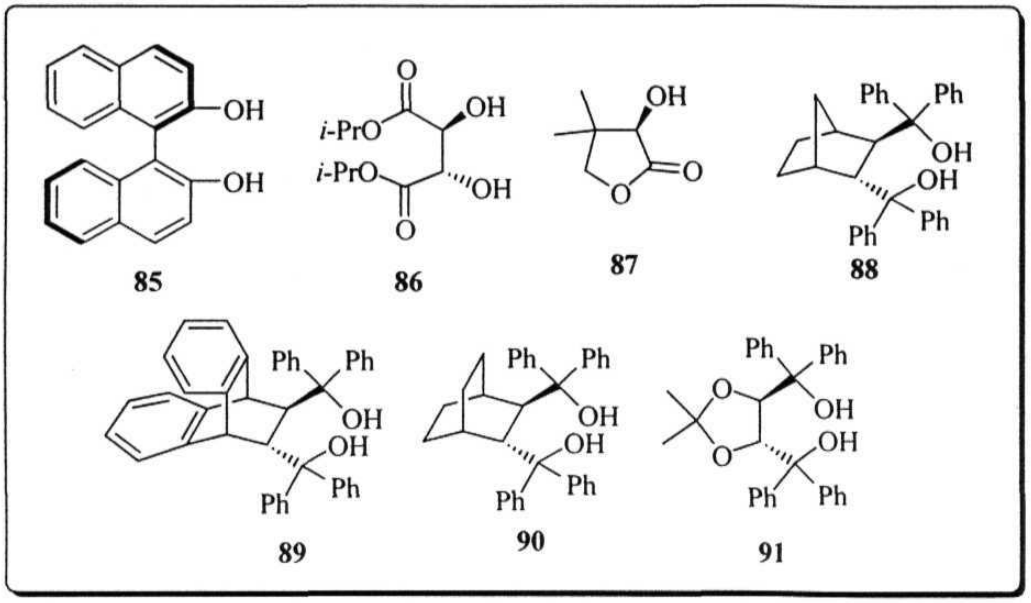


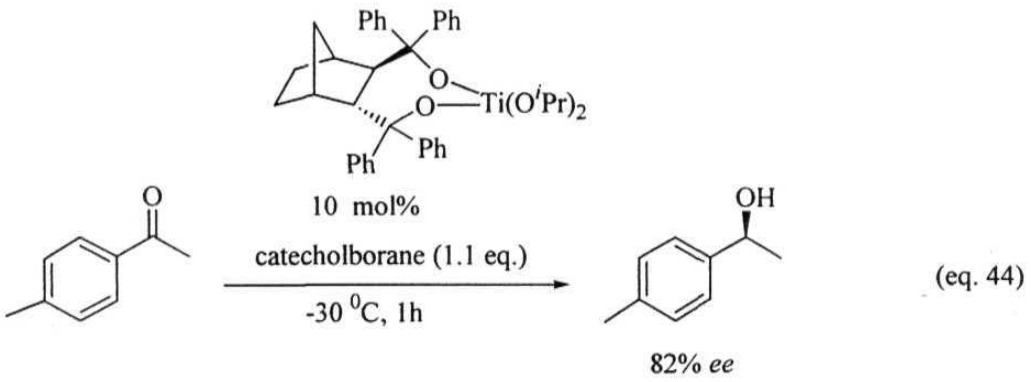
(eq. 43)

Titanium based chiral catalysts

Wandrey and co-workers[105] have developed an interesting chiral titanium alkoxides, prepared from various chiral diols (85-91), as catalysts (Fig. 10) for the borane-mediated enantioselective reduction of ketones to furnish the secondary alcohols in high enantioselectivities. One representative example is described in equation 44.

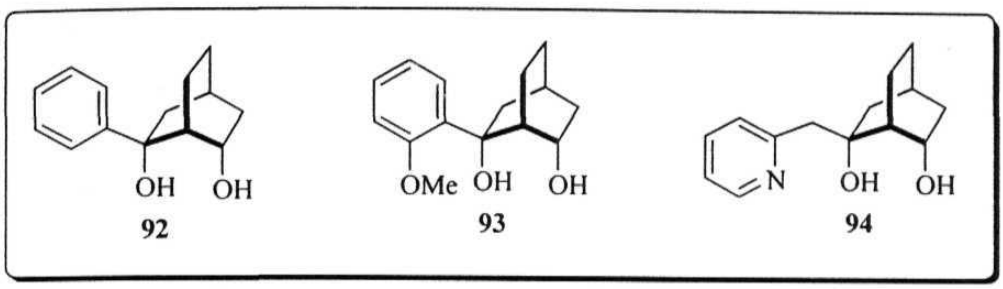
Figure 10:

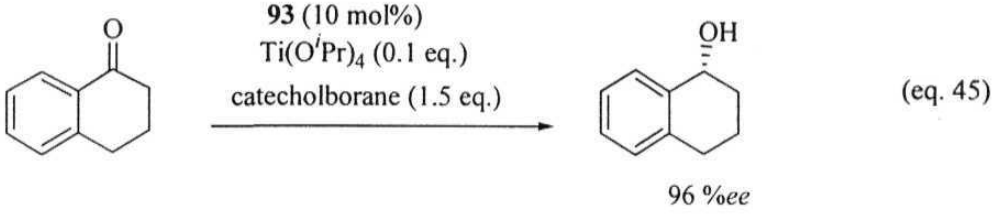




Subsequently, Frejd and co-workers[106] examined the application of titanium complexes of chiral bicyclic diols **(92-94)** (Fig. 11) as catalysts for the borane-mediated enantioselective reduction of ketones to provide the secondary alcohols in high enantioselectivities (eq. 45).

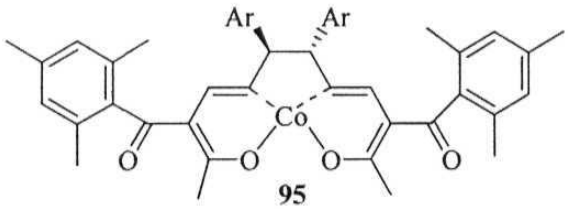
Figure 11:



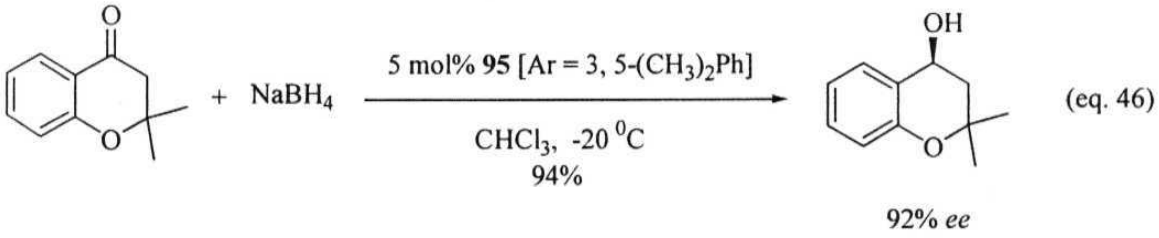


(eq. 45)

Mukaiyama and co-workers[107] have reported the highly efficient enantioselective reduction of prochiral ketones using 5 mol% chiral cobalt (II) complex (95), under the influence of $NaBH_4$ (eq. 46).



Ar = Ph, 3, 5-$(CH_3)_2$Ph



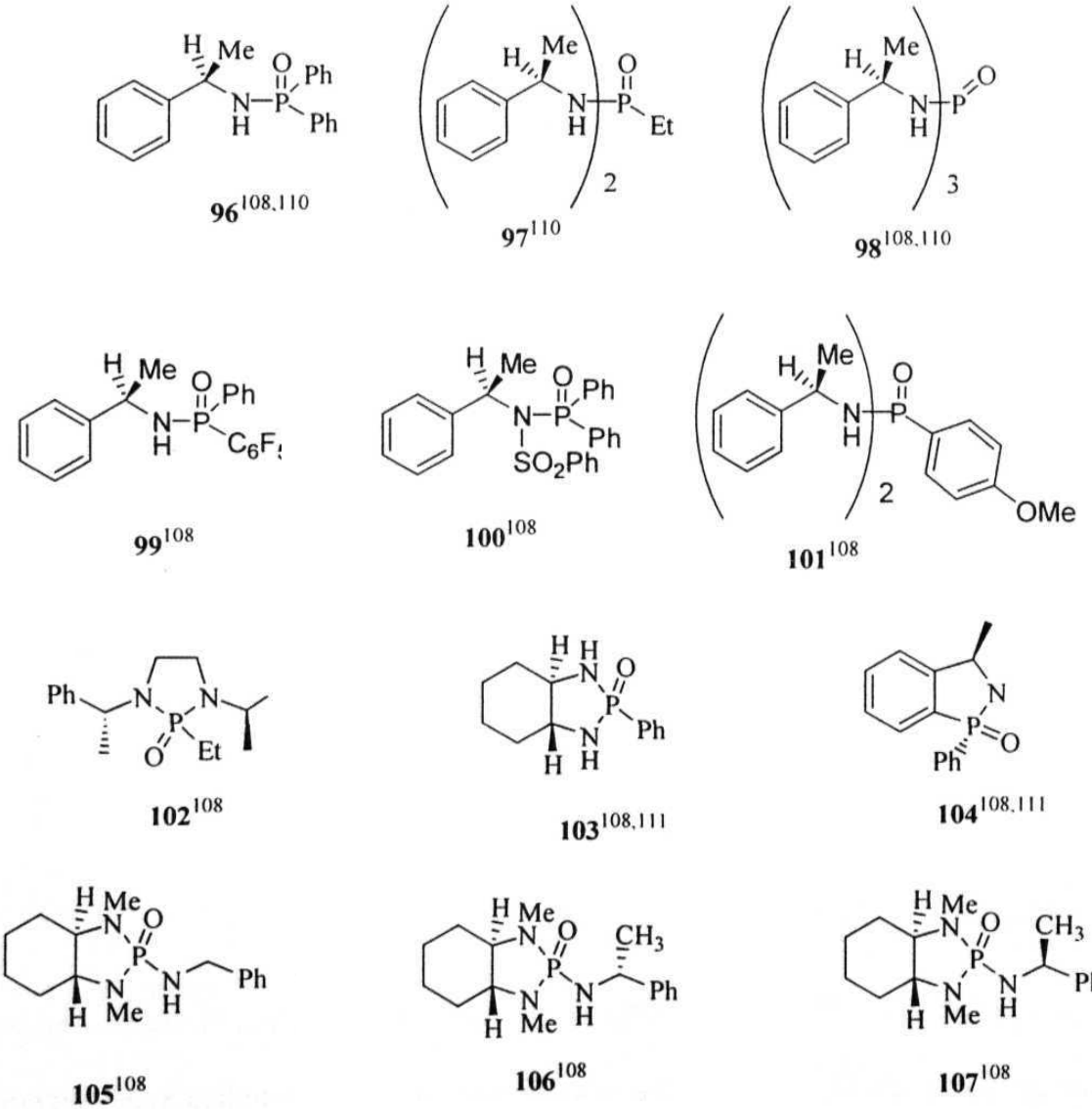
(eq. 46)

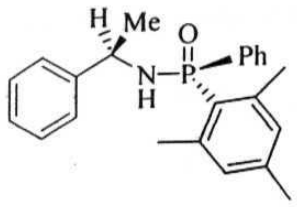
Phosphorous based chiral catalysts

Wills and co-workers[108-112] have introduced a novel ingenious class of chiral catalysts containing the ***N-P=O*** structural framework for the borane-mediated asymmetric

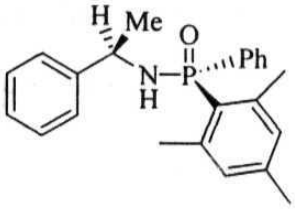
reduction of prochiral ketones. They have prepared a series of chiral catalysts (**96-111**) (Fig. 12) (containing the *N-P=O* structural framework) and examined their potential as chiral catalysts for the borane-mediated asymmetric reduction of acetophenone. The resulting secondary alcohol 1-phenylethanol was obtained in low to moderate enantioselectivities (0-46%).

Figure 12:

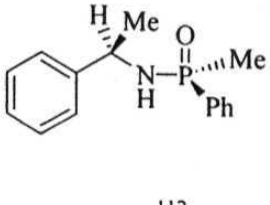




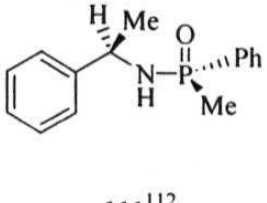
108[112]



109[112]



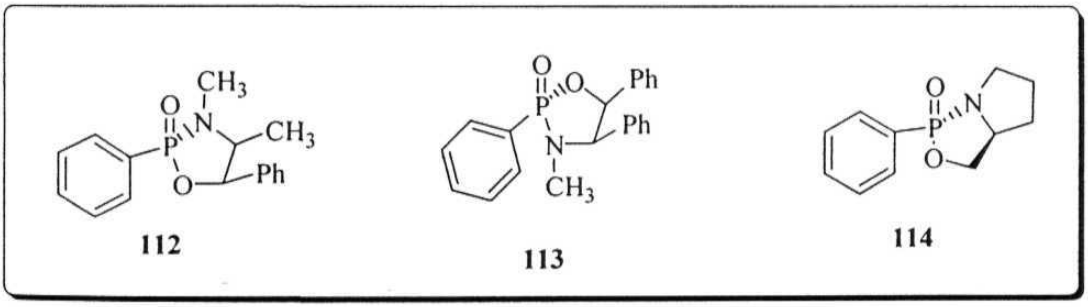
110[112]



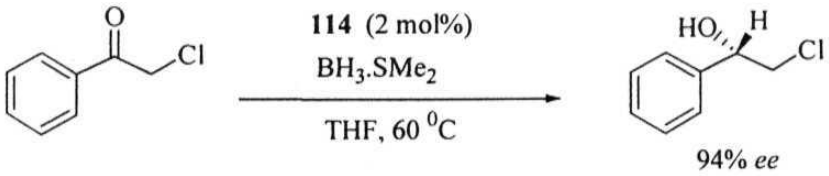
111[112]

Subsequently, Buono and co-workers[113] have employed oxazaphospholidine oxides (112-114) (Fig. 13) as catalysts for the borane-mediated asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols in high enantioselectivities. Two representative examples are described in equations 47 & 48.

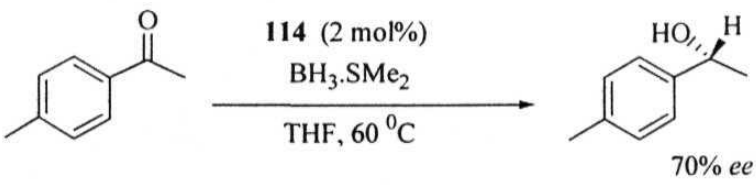
Figure 13:



112 **113** **114**



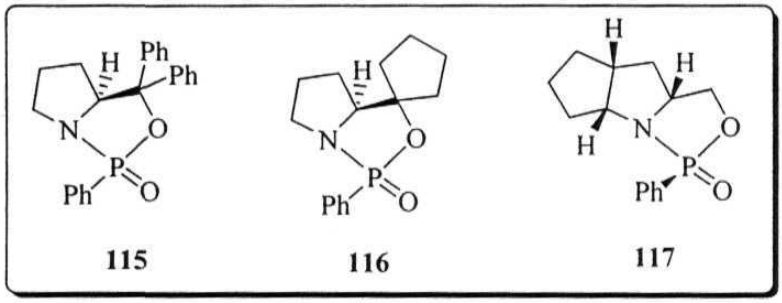
(eq. 47)

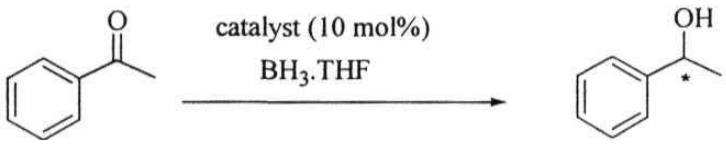


(eq. 48)

Chiral oxazaphospholidine oxides **(115-117)** (Fig. 14) derived from corresponding β-amino alcohols, were found to be efficient chiral catalysts by Martens and Peper [114] for the borane-mediated asymmetric reduction of prochiral ketones to provide the secondary alcohols in high enantioselectivities (eq. 49).

Figure 14:



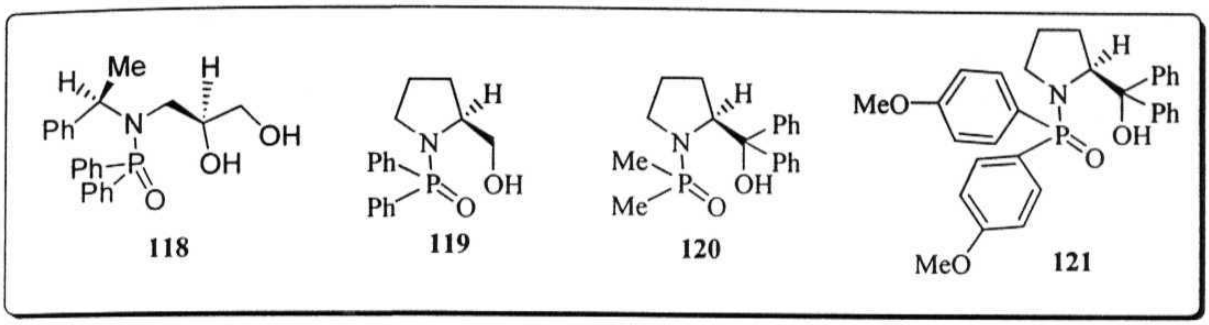


(eq. 49)

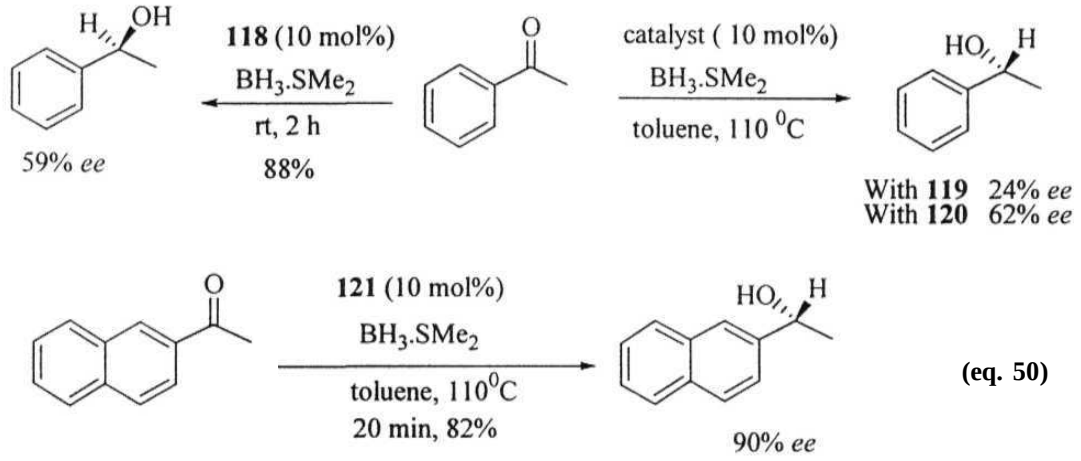
catalyst (temp.)	*ee*%
115 (19 ^{0}C)	97 (*R*)
116 (62 ^{0}C)	90 (*R*)
117 (rt)	39 (*S*)

Wills and co-workers[115-117] found that incorporation of proximal hydroxyl group in the catalyst will enhance the enantioselectivities. They have designed and synthesized representative chiral phosphinamide catalysts **(118-121)** (Fig. 15) containing proximal hydroxyl group, and used as catalysts for the borane-mediated asymmetric reduction of prochiral ketones. Some important examples are given in Scheme 8 and equation 50.

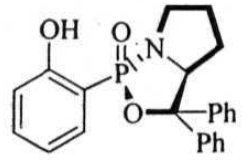
Figure 15:



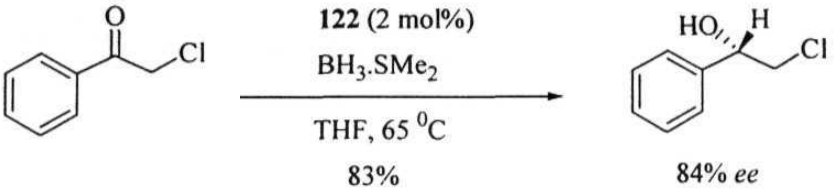
Scheme 8:



Later on, Buono and co-workers[118] have designed and synthesized chiral bifunctional catalyst **(122)** and examined its catalytic potential for asymmetric reduction of phenacyl chloride. The resulting secondary alcohol was obtained in 84% enantiomeric purity (eq. 51).



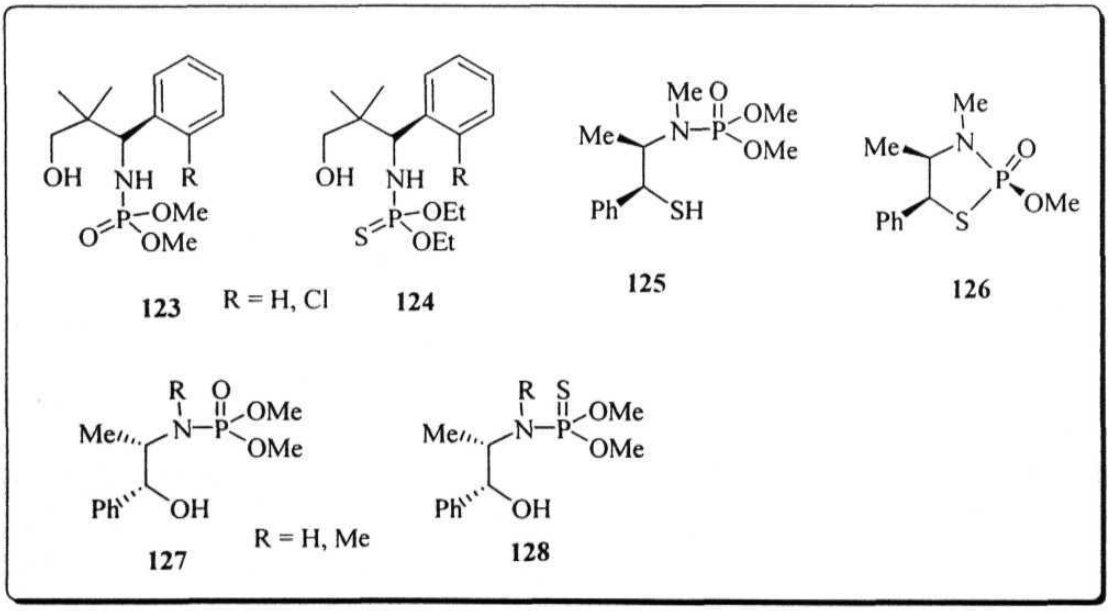
122

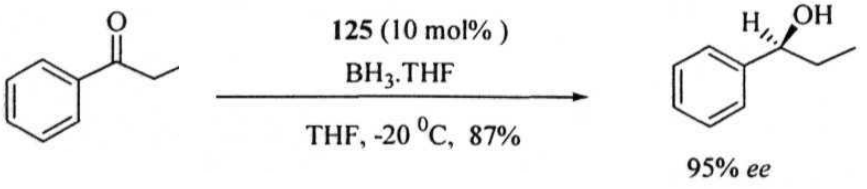


(eq. 51)

Kellogg and co-workers[119] have prepared chiral catalysts **(123-128)** (Fig. 16) containing the ***N-P=O*** and ***N-P=S*** structural frameworks derived from the corresponding chiral β-amino alcohols and studied their application in asymmetric reduction of propiophenone. One representative example is presented in equation 52.

Figure 16:

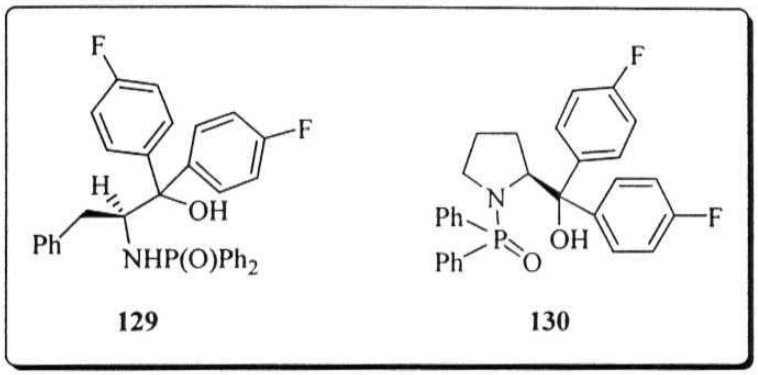




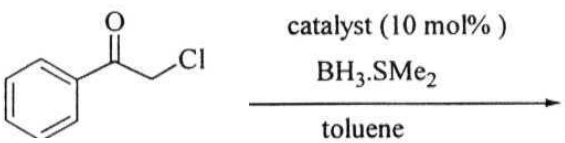
(eq.52)

Very recently, Tang and co-workers[120] have prepared an interesting chiral phosphinamides **(129, 130)** (Fig. 17) derived from L-amino acids and studied their applications in the asymmetric borane reduction of prochiral ketones to provide chiral secondary alcohols in high optical purities. Representative example is given in equation 53.

Figure 17:



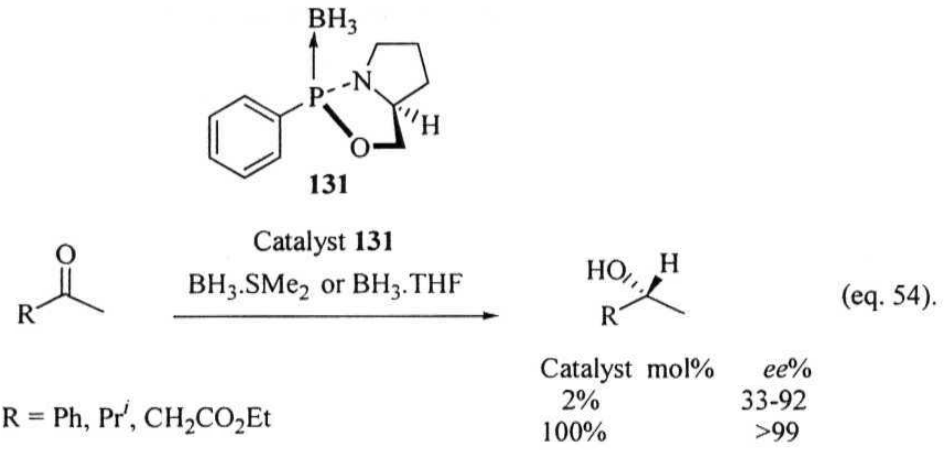
129 **130**



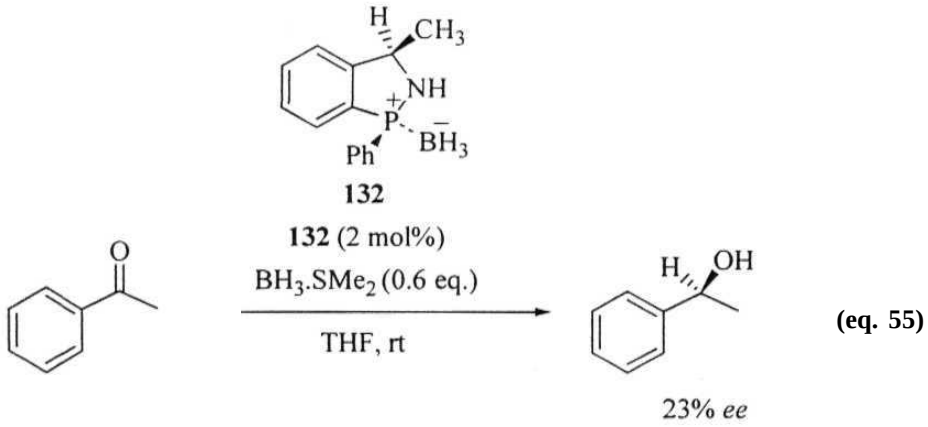
(eq. 53)

catalyst (Temp.)	*ee %*
129 (30-40 ^{0}C)	82
130 (Reflux)	92

Buono and co-workers[121] have examined the applications of oxazaphospholidine-borane complex **(131)** in the borane-mediated asymmetric reduction of prochiral ketones. The resulting secondary alcohols were obtained in 33-92% enantiomeric purities in the presence of 2 mol% catalyst and in >99% optical purities when catalyst used in stoichiometric amount (eq. 54).



Subsequently, Wills *et al.*[122] have employed chiral catalyst 132 for the borane-mediated asymmetric reduction of acetophenone. The resulting 1-phenylethanol was obtained in 23% enantiomeric excess (eq.55).

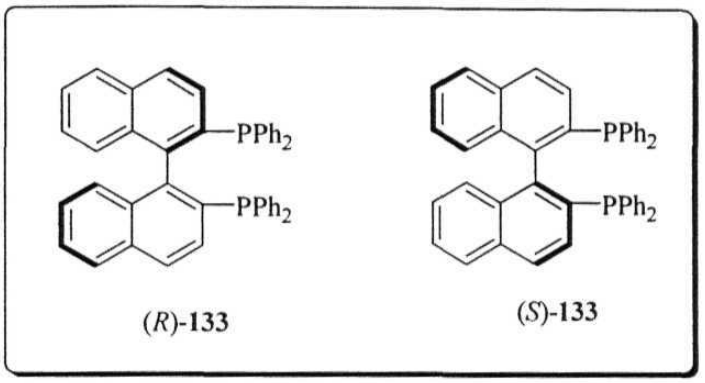


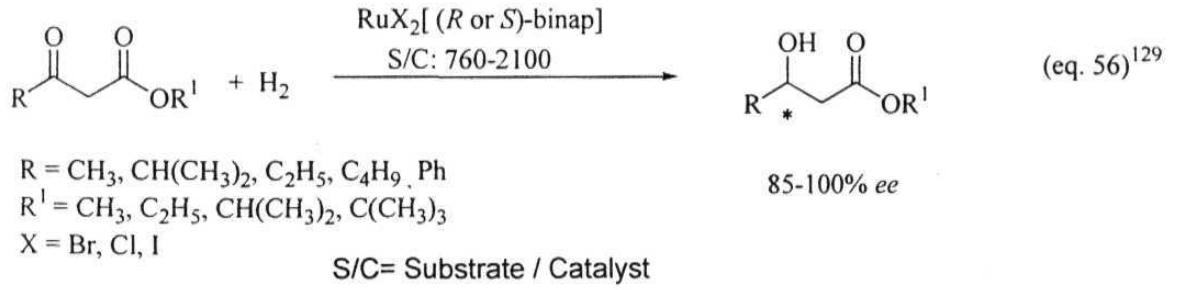
Transition metal-complex catalyzed hydrogenation of carbonyl compounds

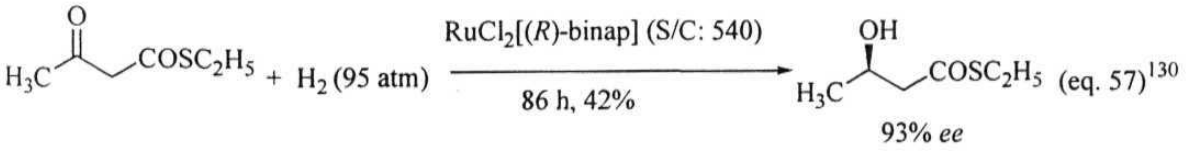
Asymmetric catalytic hydrogenation of prochiral ketones is one of the most efficient and convenient methods for preparation of a wide range of enantiomerically pure secondary alcohols.[9-11,123-128] Noyori *et al.* developed highly effective transition metal chiral catalysts $RuCl_2$[(*R* or *S*)-binap 133][129,130] (Fig. 18) and *trans*-[$RuCl_2$(phosphane)$_2$(1,2-

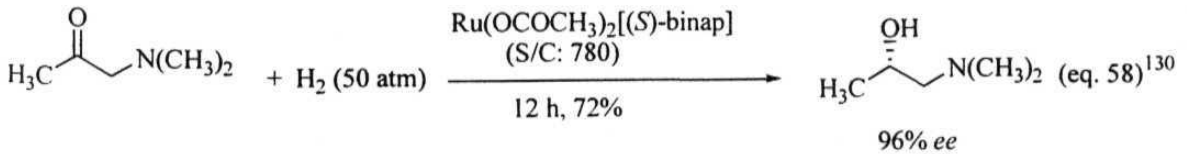
diamine)] **(134)**[131,132] for asymmetric hydrogenation of various functionalized prochiral carbonyl compounds to provide the corresponding chiral secondary alcohols in high optical purities (eq. 56-61).

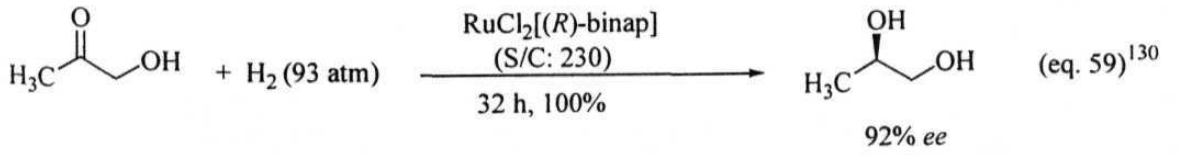
Figure 18:

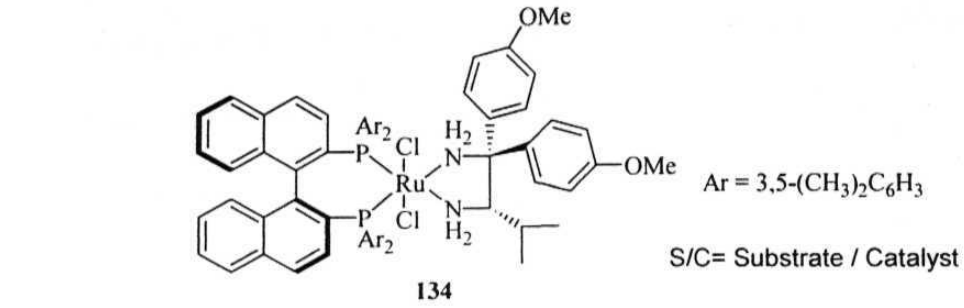




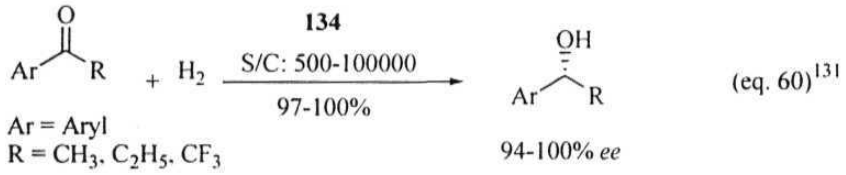


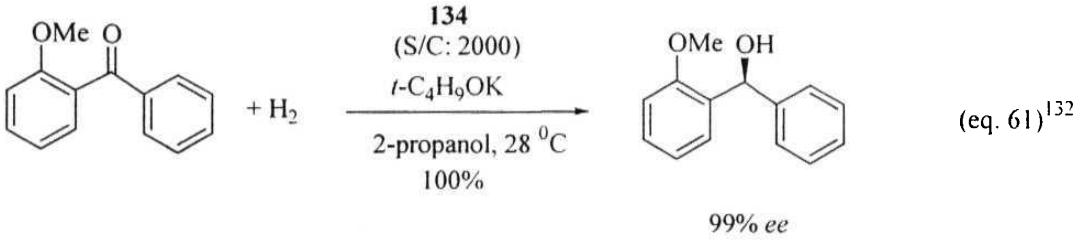




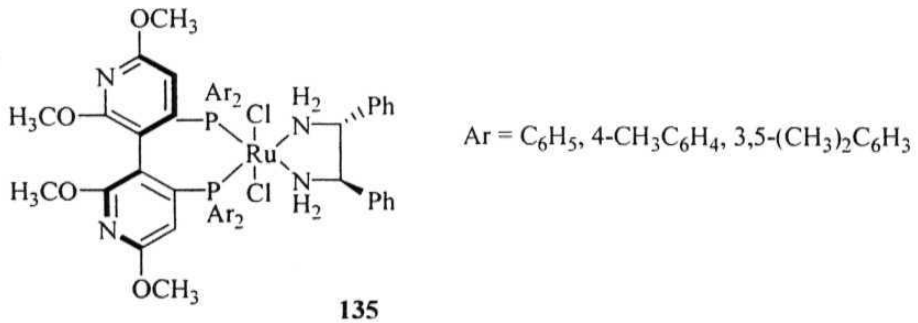


134

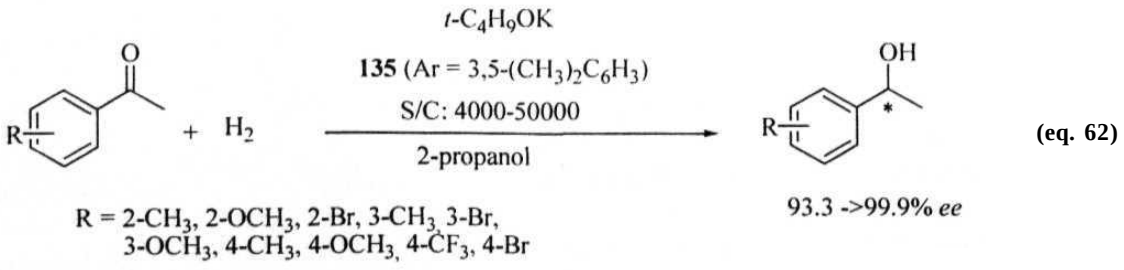




Very recently Chan and co-workers[133] have achieved high asymmetric induction in the hydrogenation of aryl alkyl ketones in the presence of catalytic amount of transition metal complex, *trans*-[$RuCl_2$(dipyridylphosphine)(1,2-diamine)] (135) (eq. 62).



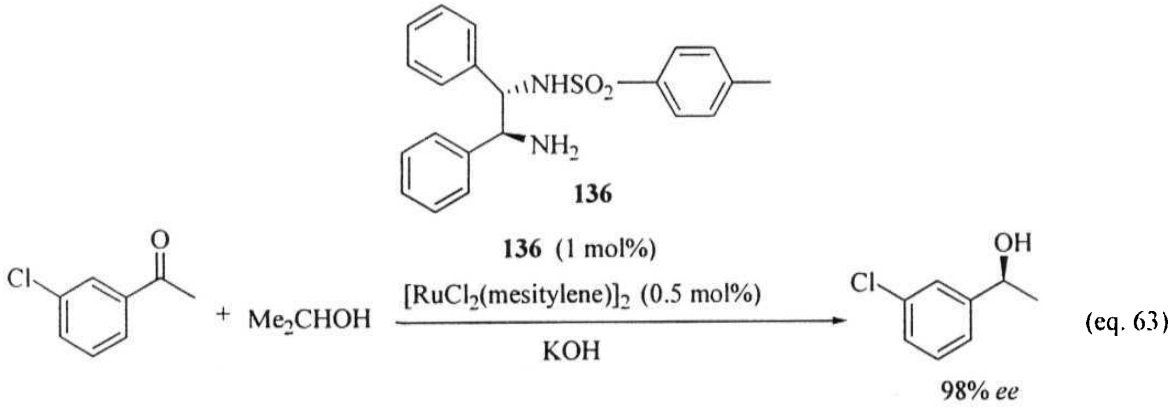
135



(eq. 62)

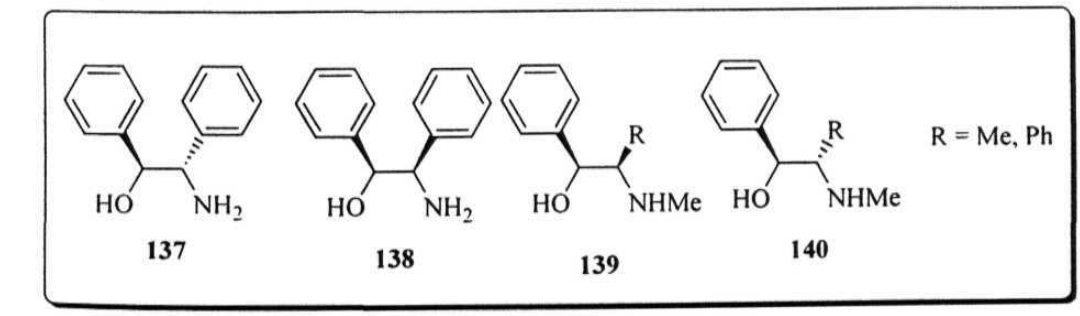
Asymmetric transfer hydrogenation

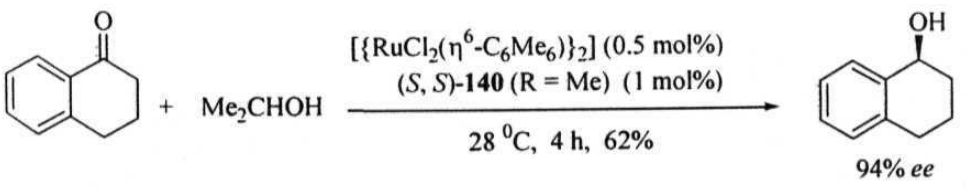
Asymmetric transfer hydrogenation is yet another interesting, effective and efficient method to obtain the enantiomerically pure secondary alcohols.[134-137] Noyori and co-workers have extensively utilized chiral ruthenium complexes of chiral sulfonamides (**136**)[138] and amino alcohols (137-140)[139] (Fig. 19) as catalysts and 2-propanol as hydrogen donor for asymmetric transfer hydrogenation of prochiral ketones to provide the secondary alcohols in high optical purities. Representative examples are given in equations 63 & 64.



(eq. 63)

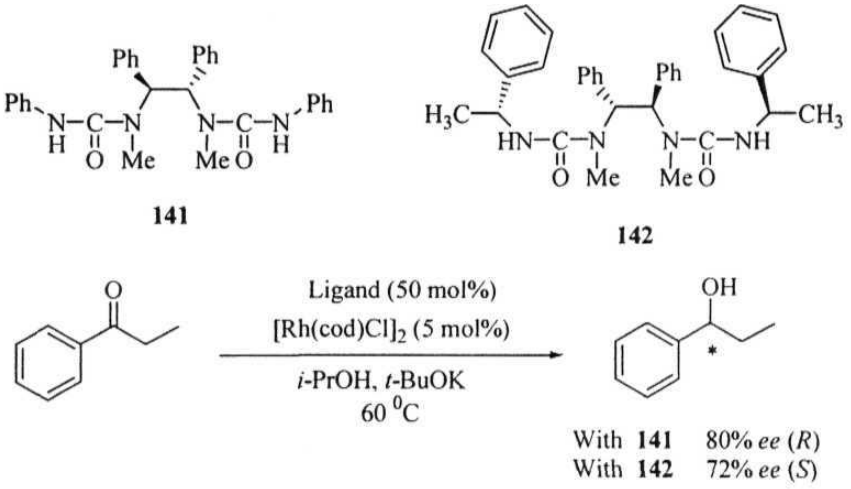
Figure 19:





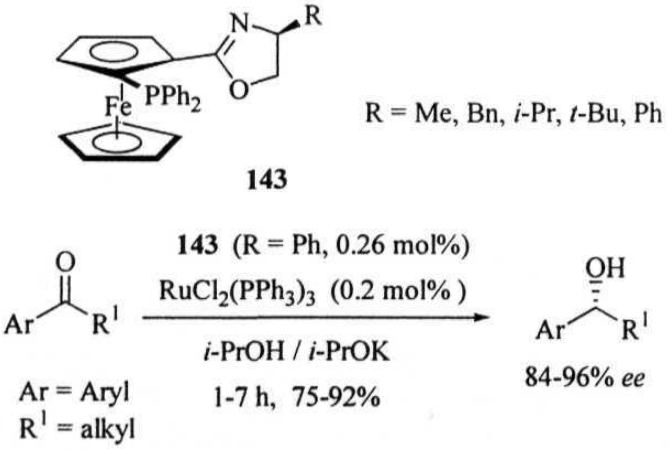
(eq. 64)

Lemaire and co-workers[140] have successfully utilized rhodium complexes of chiral diureas **(141, 142)** as catalysts for asymmetric transfer hydrogenation of prochiral ketones in the presence of 2-propanol. One representative example is given in equation 65.



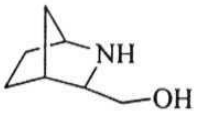
141 **142** **(eq. 65)**

Subsequently, Sammakia and Stangeland reported ruthenium complexes of (phosphinoferrocenyl)oxazolines **(143)** as catalysts for asymmetric transfer hydrogenation of prochiral ketones leading to the formation of the secondary alcohols in 84-96 % enantioselectivities (eq. 66).[141]

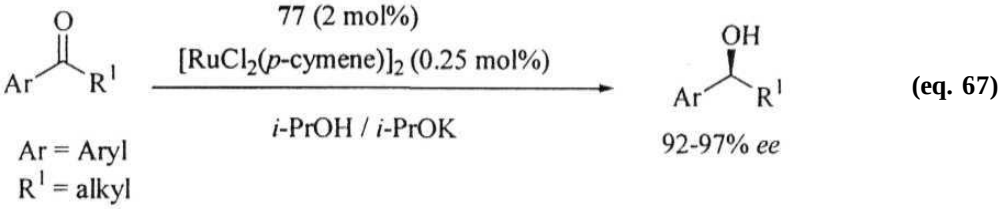


143 **(eq. 66)**

Recently, Andersson and co-workers[142] have described bicyclic chiral p-amino alcohol (77) as an efficient ligand for ruthenium catalyzed asymmetric transfer hydrogenation of prochiral ketones to afford the corresponding secondary alcohols in 92-97% optical yields (eq. 67).



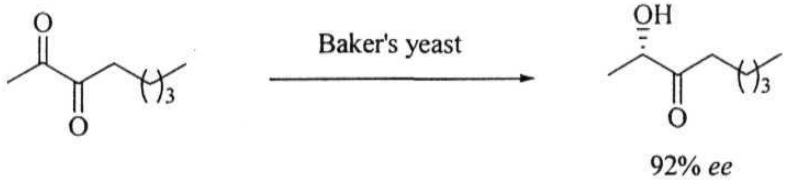
77



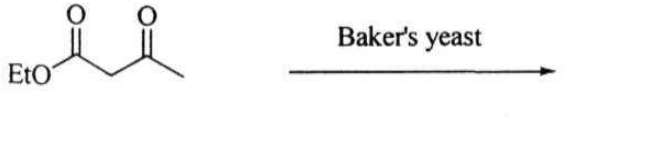
(eq. 67)

Asymmetric reduction of ketones using enzymes

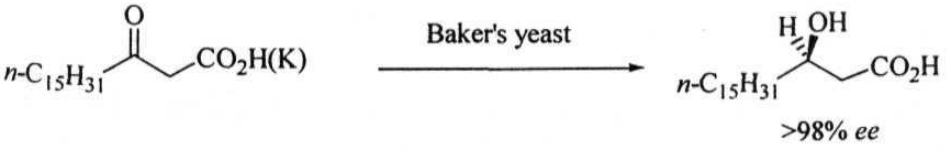
Baker's yeast[16,143-145] has been extensively utilized for the synthesis of a wide range of enantiomerically pure secondary alcohols *via* the reduction of various prochiral ketones (eq. 68-70).



(eq. 68)[143]



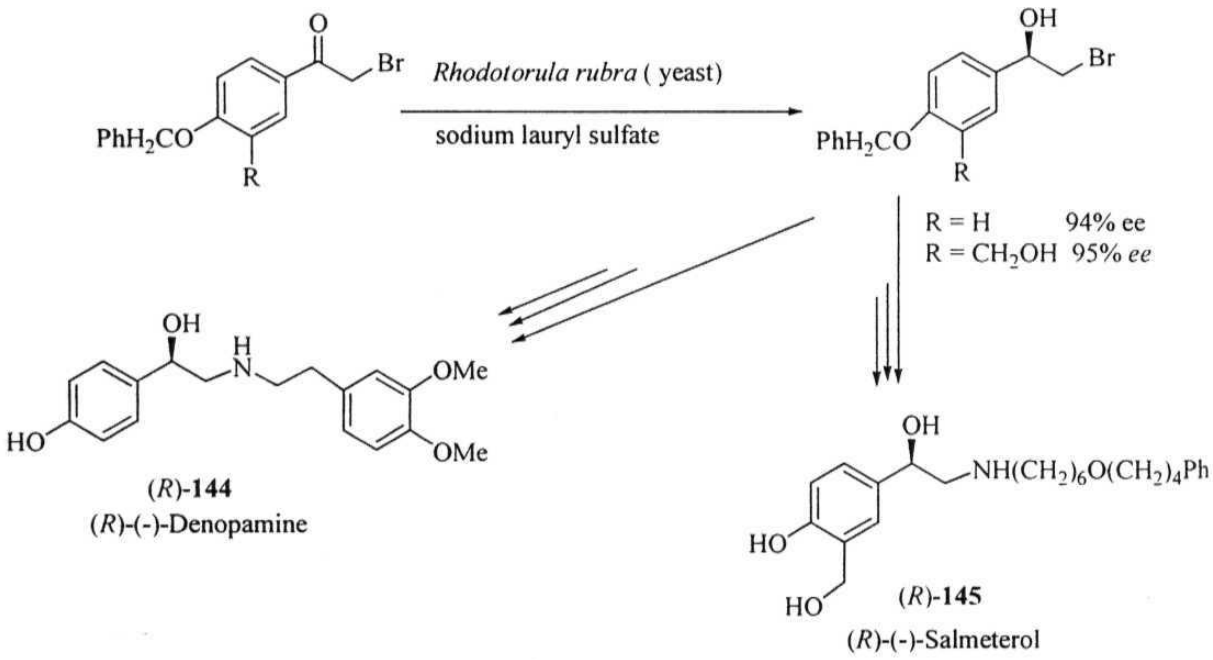
(eq. 69)[144]



(eq. 70)[145]

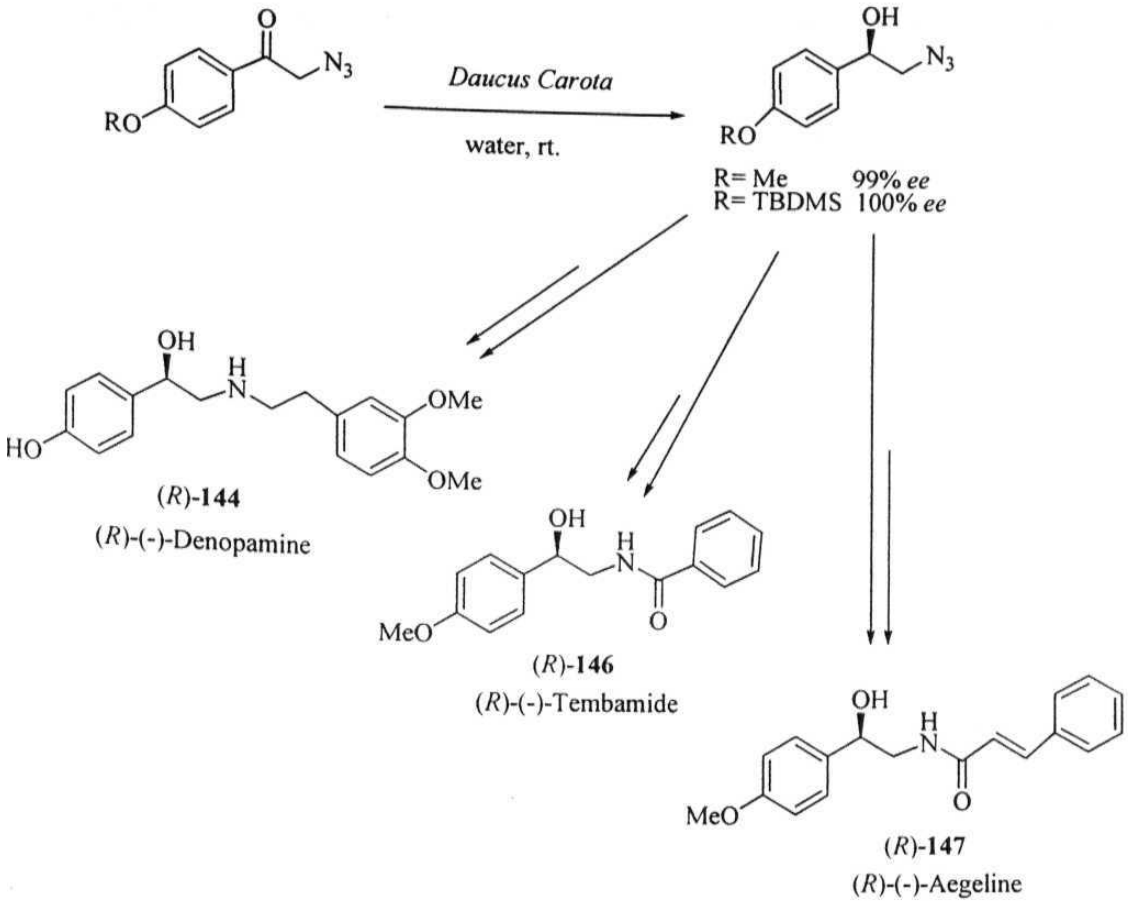
Recently, Goswami and co-workers[146] have synthesized (*R*)-(-)-denopamine [(*R*)-**144**] and (i?)-(-)-salmeterol [(*R*)-**145**] according to the reaction sequence as described in Scheme 9, which involves the microbial reduction of substituted phenacyl bromide using *Rhodotorula rubra* (a yeast microbe isolated from local brewery waste) in the presence of sodium lauryl sulfate, as the key step.

Scheme 9:



Very recently, asymmetric bio-reduction of azidoketones by *Daucus carota* in aqueous medium has been reported by Yadav and co-workers to provide the (*R*)-2-azido-1-arylethanols in 99-100% enantioselectivities.[147] (*R*)-2-Azido-1-arylethanols are important synthons in the synthesis of many drugs and biological active molecules [(*R*)-**144**, (*R*)-**146**, (*R*)-**147**](Scheme 10).

Scheme 10:

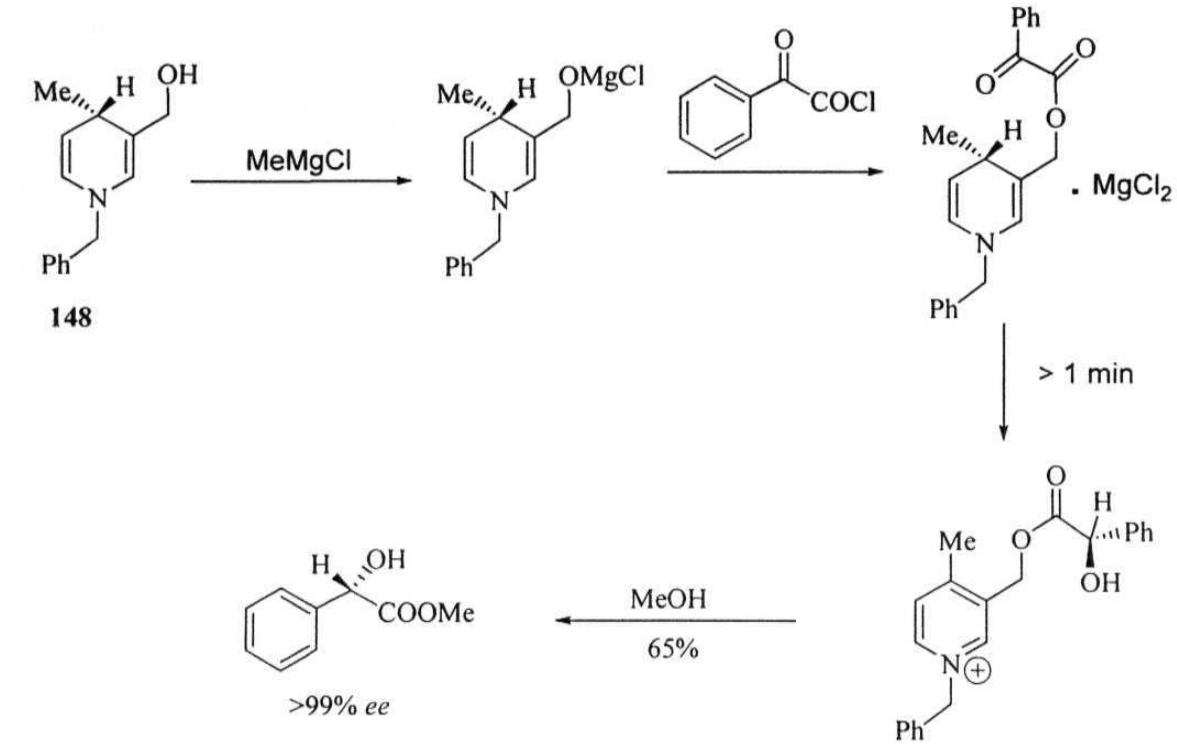


Asymmetric reduction of ketones using enzyme models

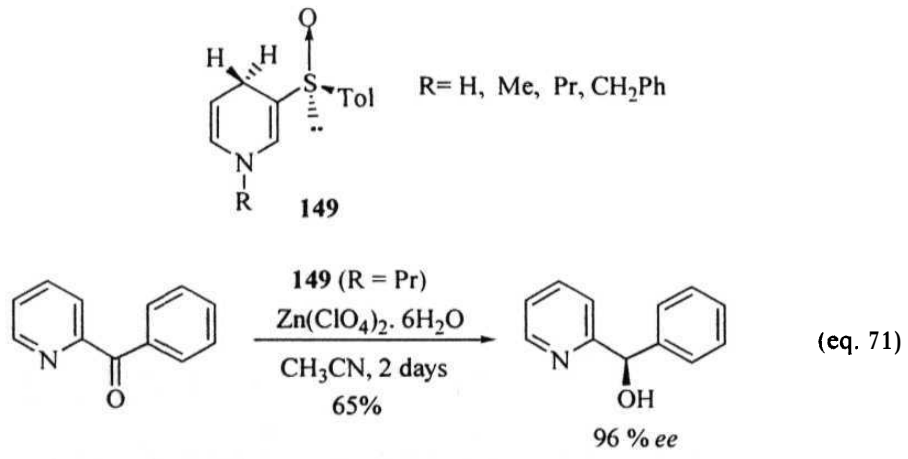
Oragnic chemists have also developed an interesting enzyme models for asymmetric reduction of various prochiral ketones to provide the corresponding secondary alcohols in high optical yields.[19,20,148-153] Some important and recent enzyme models and their applications are described below.

Meyers and Brown[151] have developed an efficient NADH model **(148)** for synthesis of chiral methyl mandelate in high enantiomeric purity according to Scheme 11.

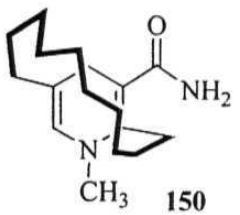
Scheme 11:



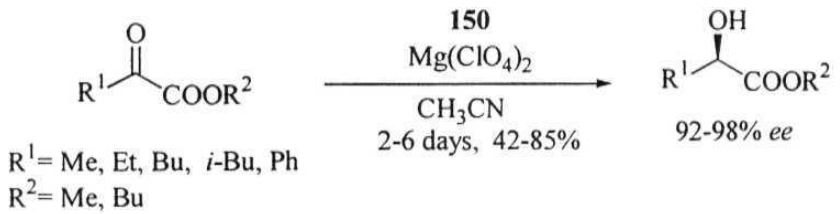
Imanishi and co-workers [152] have designed and synthesized NADH model compounds **(149)** for asymmetric reduction of various prochiral ketones to provide the corresponding secondary alcohols in high optical yields. Representative example is given in equation 71.



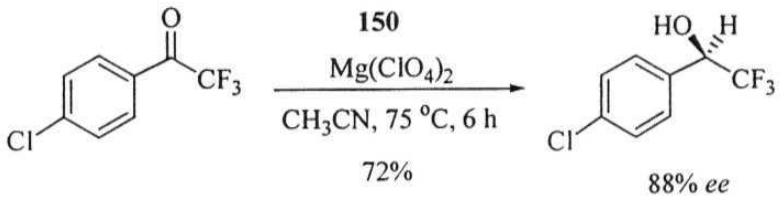
Very recently, Nakata *et al.*[153] elegantly used an efficient bridged NADH models (150) as chiral reducing agents, in the presence of $Mg(ClO_4)_2$ for enantioselective reduction of prochiral ketones. Representative examples are given in equations 72 & 73.



150



(eq. 72)



(eq. 73)

OBJECTIVES, RESULTS AND DISCUSSION

From the preceding chapter it is clear that asymmetric reduction of prochiral ketones, providing secondary alcohols in high enantiomeric purities, is one of the fundamental reactions in chiral chemistry and applications of various borane based chiral reducing agents for this purpose have been well documented.[1-20] The recent work of Wills and co-workers on the application of chiral catalysts containing *N-P=O* structural framework has created a new out look in the chiral catalytic reduction chemistry.[108-117] This thesis deals with our endeavors towards the design and synthesis of novel class of chiral catalysts / sources containing *N-P=O* structural framework and study their applications in the borane-mediated asymmetric reduction of prochiral ketones particularly α-halo ketones with the following objectives.

Objectives

1). To synthesize the chiral molecules containing *N-P=O* structural framework having (*S*)-2-anilinomethylpyrrolidine moiety and to study their applications as catalysts in the borane-mediated asymmetric reduction of prochiral a-halo ketones.

2). To study the applications of (2*S*,5*S*)- 1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyl-bicyclo(3.3.0)octane as a catalytic source for the borane-mediated asymmetric reduction of prochiral ketones. Our objective also includes to synthesize the

analogues of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)-octane and to study their applications as possible catalysts with a view to develop recoverable, reusable and air stable catalysts for the borane-mediated asymmetric reduction of prochiral ketones.

3). To study the applications of (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethyl-bicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octane, obtained *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane with (1*R*,2*R*,3*S*,5*R*)-2,6,6-trimethylbicyclo(3.1.1)heptane-2,3-diol, with a view to examine the effect of proximal hydroxyl group (in the catalyst) on enantioselectivities in the borane-mediated asymmetric reduction of prochiral ketones.

4). To synthesize and study the application of various molecules containing *N-P=O* structural framework obtained *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane with representative amines of varying steric requirements, as catalysts for the borane-mediated asymmetric reduction of prochiral ketones, with a view to understand the effect of substituents on phosphorous in the (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety.

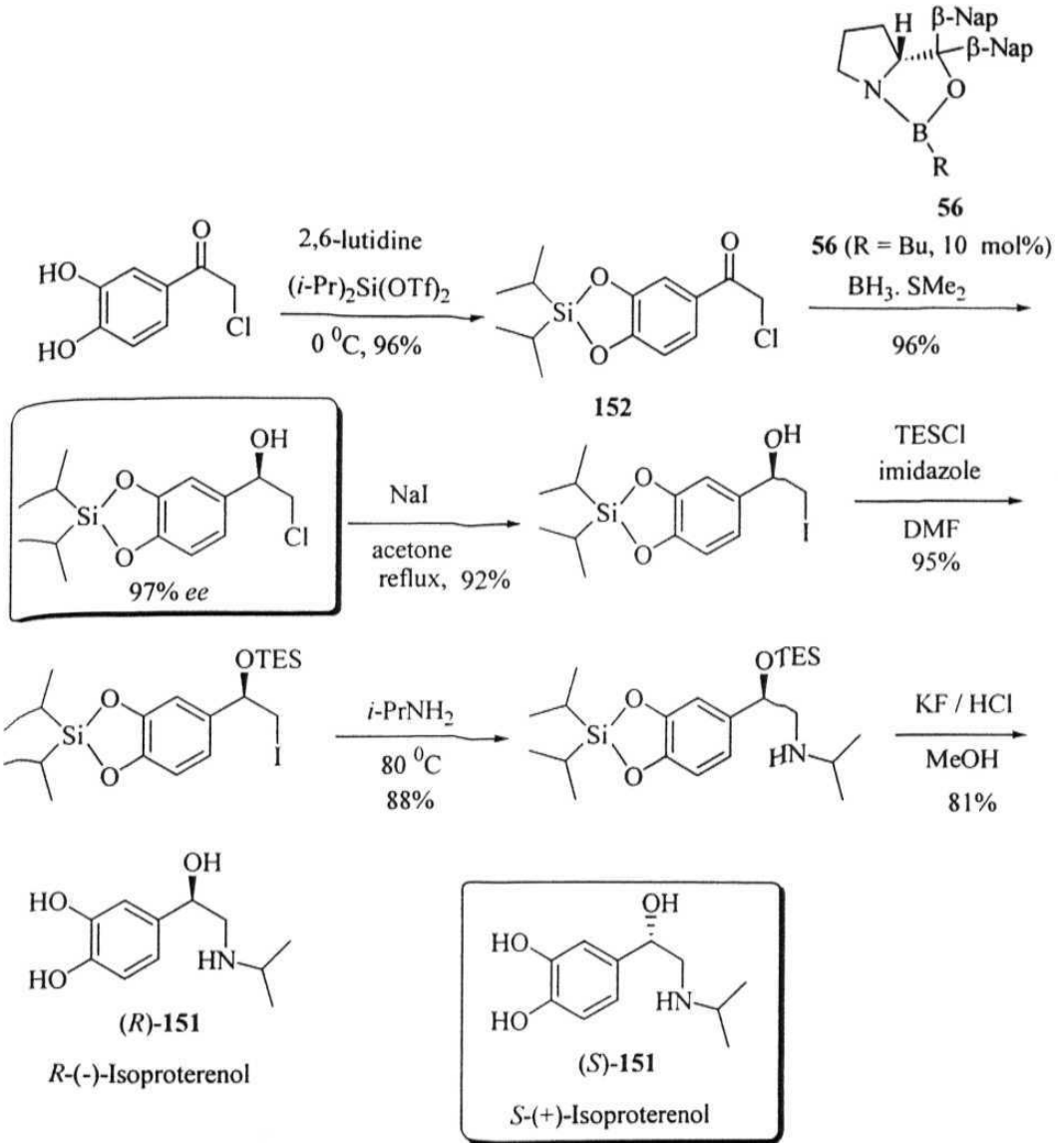
RESULTS AND DISCUSSION

Novel and effective chiral phosphoramide catalysts for the borane-mediated asymmetric reduction of prochiral α-halo ketones

Enantiomerically pure secondary alcohols represent an important class of molecules in organic chemistry because of their extensive use as starting materials, intermediates and chiral auxiliaries in the synthesis of biologically active compounds.[4-8] In fact optically pure 2-halo-1-arylethanols occupy a special place in synthetic organic chemistry due to their applications as synthons in synthesis of many drugs and biological active molecules.[7,8,154-157] Representative and relevant examples are described in the following.

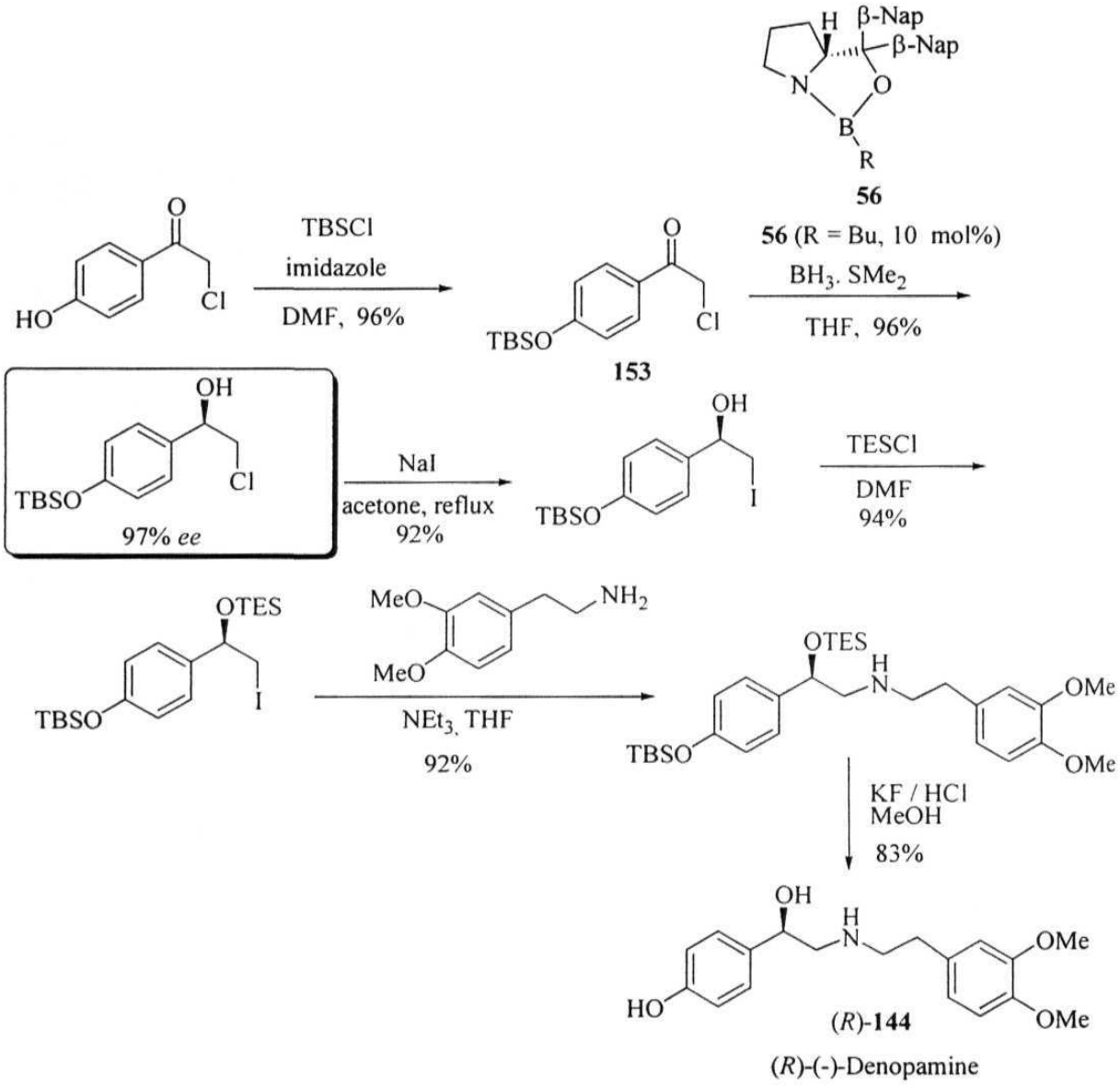
Corey and Link reported[154] first enantioselective synthesis of therapeutic agent *R*-(-)-isoproterenol [(*R*)-**151**] according to the reaction sequence as described in Scheme 12 which involves the borane-mediated enantioselective reduction of substituted phenacyl chloride (152) using oxazaborolidine catalyst (56), as the key step. They also synthesized *S*-(+)-isoproterenol [(*S*)-**151**] using the other enantiomer of oxazaborolidine catalyst (56).

Scheme12:



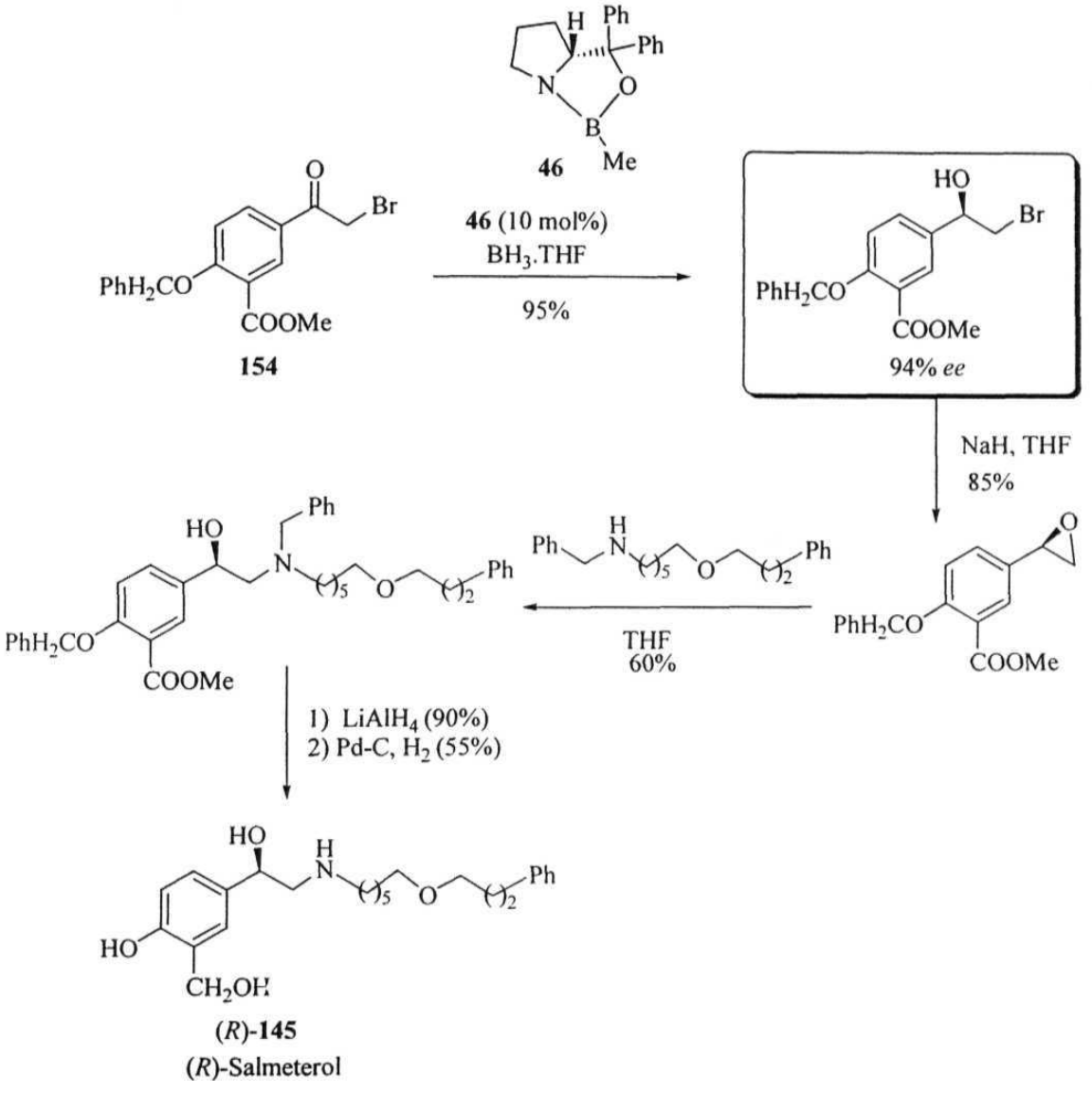
Subsequently, they have also synthesized optically pure (*R*)-(-)-denopamine [(*R*)-**144**], β-adrenoreceptor active drug, *via* the borane-mediated enantioselective reduction of 1-[4-(*tert*-butyldimethylsiloxy)phenyl]-2-chloroethanone (153) with oxazaborolidine catalyst (**56**), as the key step, according to thereaction sequence as described in Scheme 13.[155]

Scheme 13:



Helquist and co-workers[156] reported enantioselective synthesis of (*R*)-salmeterol *[(R)-***145],** (potent β-agonist and used in the therapy of asthma and chronic bronchitis) which involves the borane-mediated asymmetric reduction of substituted phenacyl bromide **(154)** in the presence of oxazaborolidine (46), as a key step (Scheme 14).

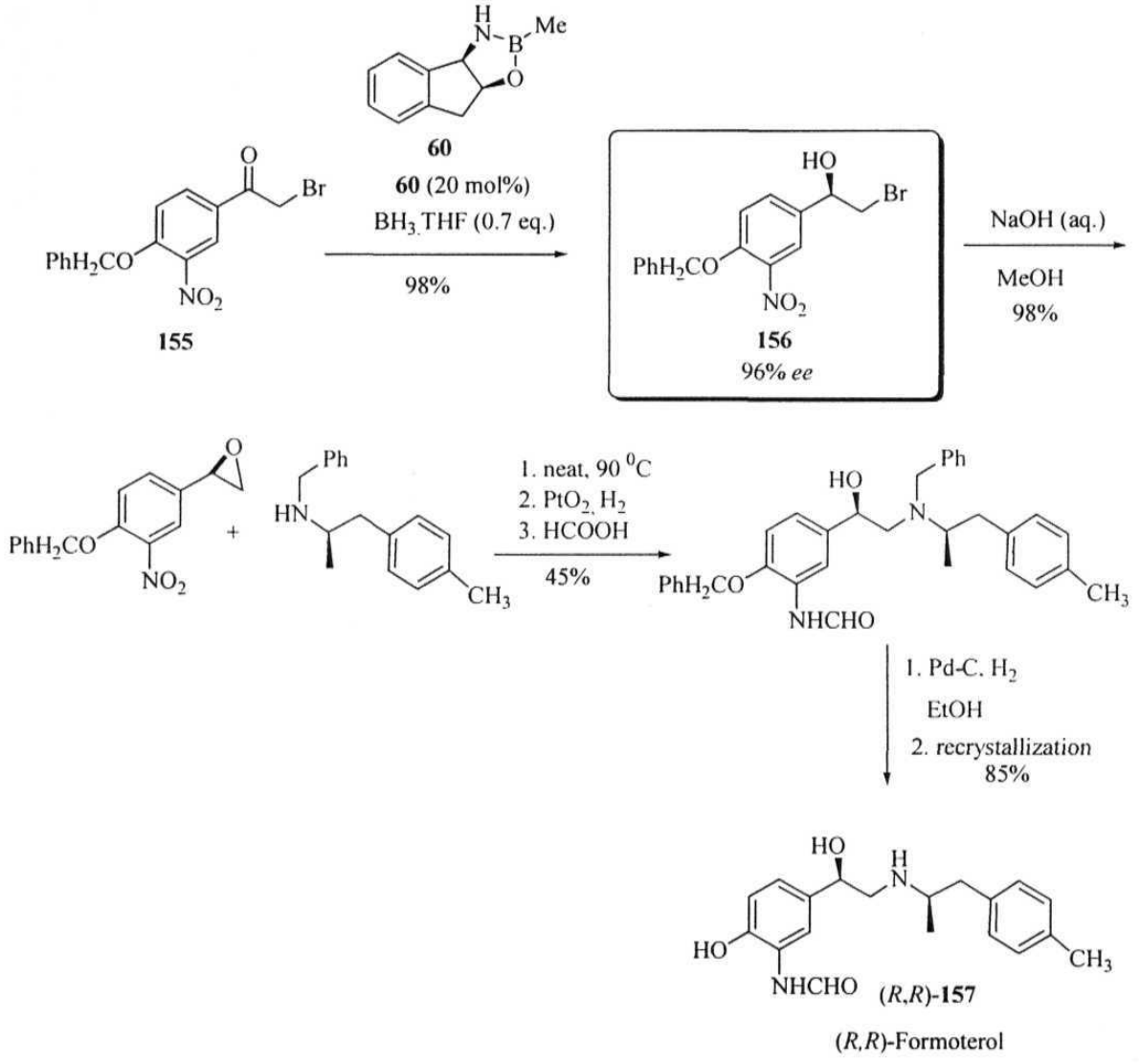
Scheme 14:



Hett and co-workers[157] have elegantly employed the oxazaborolidine catalyst (60) for the asymmetric reduction of substituted phenacyl bromide **(155)** to provide the desired secondary alcohol **156** with 96% enantiomeric purity. The optically active alcohol was subsequently transformed into optically pure (*R*,*R*)-formoterol (157) potent p-agonist,

which is used as a bronchodilator in the therapy of asthma and chronic bronchitis (Scheme 15).

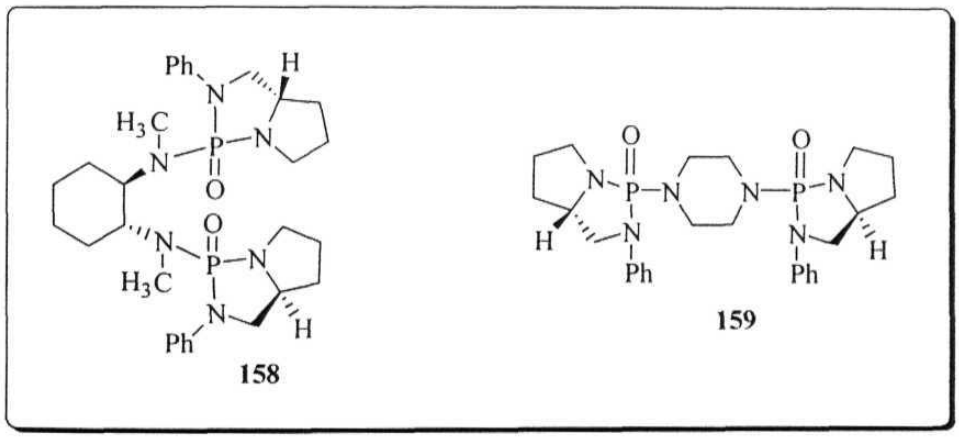
Scheme 15:



The importance of enantiomerically pure 2-halo-1-arylethanols as synthons in various biologically active molecules has directed us to develop the novel and effective chiral catalysts for the borane-mediated asymmetric reduction of prochiral α-halo ketones with a view to provide convenient and simple methodology for the synthesis of 2-halo-

1-arylethanols with high enantiomeric purities. Fascinated by the catalysts containing *N-P=O* structural framework introduced by Wills, we planed to synthesize (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]-cyclohexane **(158)** and 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octan-2-yl]piperazine **(159)** (Fig. 20) and study their applications as possible catalysts for the borane-mediated asymmetric reduction of prochiral α-halo ketones.

Figure 20:

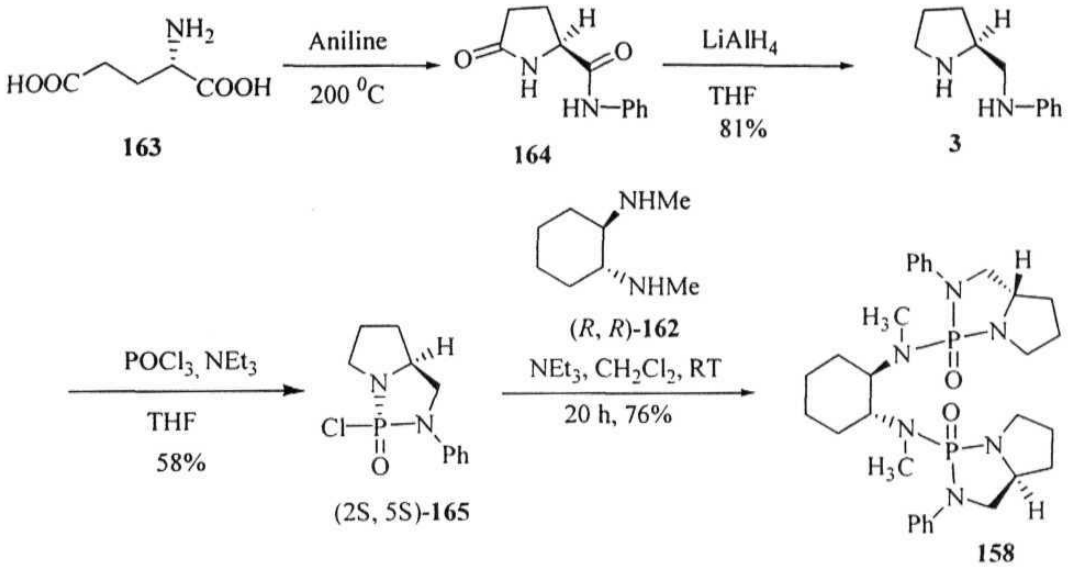


The chiral phosphoramide *i. e.*, (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]cyclohexane **(158)** was prepared according to the Scheme 16. Easily accessible, inexpensive, and commercially available (*S*)-glutamic acid **(163)** was transformed into the (*S*)-5-oxopyrrolidine-2-carboxanilide **(164),** $[\alpha]_D^{25}$: +18.52 (*c* 0.98, MeOH) [Lit.[158] $[\alpha]_D^{25}$: +18.60 (*c* 1.0, MeOH)], *via* the treatment with aniline according to the literature procedure.[158] This molecule was reduced with lithium aluminum hydride, following the known

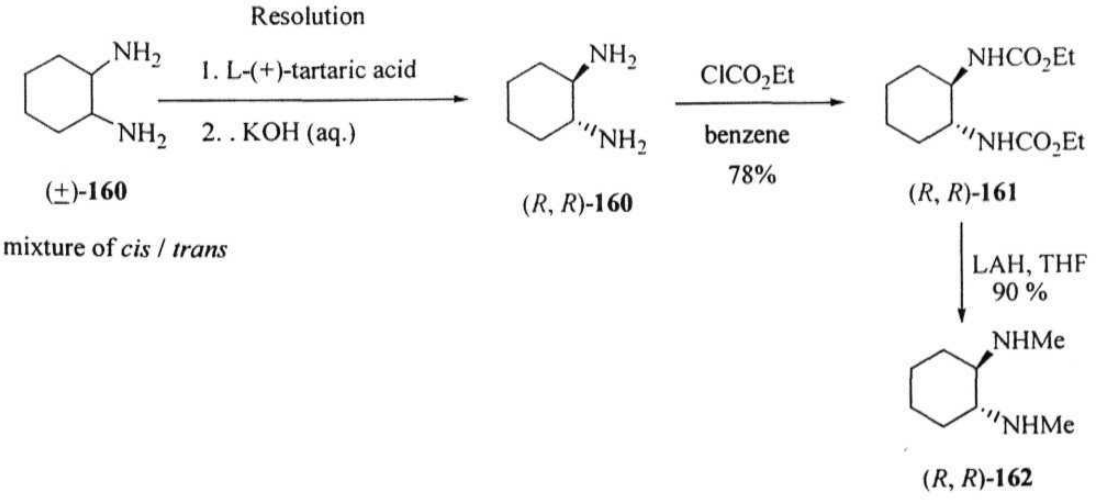
procedure,[158] to afford (5)-2-anilinomethylpyrrolidine (3) in 81% yield, $[\alpha]_D^{25}$: +18.06 (c 1.5, EtOH) [Lit.[158] $[\alpha]_D^{25}$: +18.50 (c 1.087, EtOH)]. The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data. Treatment of (5)-2-anilinomethylpyrrolidine (3) with $POCl_3$ in the presence of triethylamine, following the known procedure,[159] provided two diastereomers of 165 in the ratio of 90:10. The major diastereomer (more polar) (25,55)-l,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(25,55)-165] was isolated in 58% yield after column chromatography (silica gel, 20% ethyl acetate in hexanes). The structure of this compound was confirmed by IR, ^1H NMR (Spectrum 7), ^{13}C NMR (Spectrum 8), ^{31}P NMR (Spectrum 16), mass spectral data and elemental analysis. The absolute (*S*)-configuration at the phosphorous atom was further confirmed by single crystal X-ray data. The X-ray crystal data and structure refinement for this molecule is presented in the Table I and the ORTEP diagram for the molecule is shown in Fig. X1. Treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with (*1R,2R*)-1,2-di(methylamino)cyclohexane [(*R*,*R*)-**162**] provided the desired phosphoramide (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]cyclohexane (158) in 76% isolated yield after usual work-up followed by column chromatography (silica gel, 35% ethyl acetate in hexanes), $[\alpha]_D^{25}$: +35.0 (*c* 1.40, $CHCl_3$) (Scheme 16). The structure of the compound was confirmed by IR, ^1H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), ^{31}P NMR (Spectrum 5), mass spectral data and elemental analysis. The desired (*1R,2R*)-1,2-di(methylamino)cyclohexane [(*R*,*R*)-

162] was prepared according to known procedure following the reaction sequence as described in Scheme 17.[160,161]

Scheme 16:



Scheme 17:



We have then directed our studies towards the possible applications of (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]

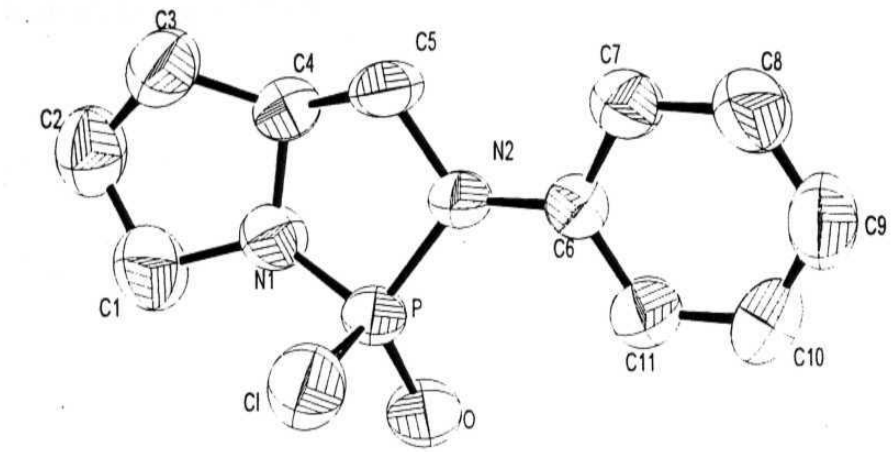


Fig. X1

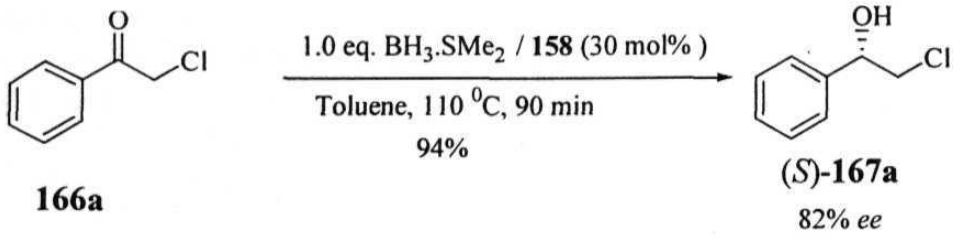
ORTEP diagram of the compound (2*S*, 5*S*)-165

{Hydrogen atoms were omitted for clarity)

cyclohexane **(158)** as a catalyst in the borane-mediated asymmetric reduction of prochiral α-halo ketones. In this direction, we have first examined the reduction of phenacyl chloride **(166a)** under the catalytic influence of the molecule **158** in the presence of borane-dimethyl sulphide under various conditions. The best results were obtained when phenacyl chloride **(166a)** (0.5 mM) was treated with $BH_3.SMe_2$ (0.5 mM) in the presence of 30 mol% catalyst **158** in refluxing toluene, thus providing the desired 2-chloro-1 -phenylethanol **(167a)** in 82% *ee*, $[\alpha]_D^{25}$: +39.70 *(c* 2.25, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 *(c* 1.73, cyclohexane), *R*-configuration, 100% *ee]* with (*S*)-configuration (eq. 74). The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data. The enantiomeric purity was determined by HPLC analysis (Chromatogram 1) using chiral column, Chiralcel-OD with reference to racemic alcohol **(±)-167a**.

Table 1: Crystal data and structure refinement for compound (2*S*,5*S*)-165

Identification	: (2*S*,5*S*)-**165**
Empirical formula	: $C_{11}H_{14}ClN_2OP$
Formula weight	: 256.66
Temperature	:293(2)° K
Wavelength	: 0.71073 A
Crystal system	: Orthorhombic
Space group	: P 2_1 2_1 2_1
Unit cell dimensions	: a = 6.844(3) Å α = 90°
	: b = 12.325(4) Å β = 90°
	: c = 14.4861(19) A y = 90°
Volume	: 1221.9(6) A^3
Z	:4
Density (calculated)	: 1.395 g / cm^3
Absorption coefficient	: 0.424 mm^{-1}
F (000)	: 536
Crystal size	: 0.68 x 0.60 x 0.56 mm
Theta range for data collection	:2.17<0<27.44
Index ranges	: 0<h<8, 0<k< 15, 0<l< 18
Reflections collected	: 1619
Independent reflections	: 1442
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1619/0/146
Goodness-of-fit on F^2	: 1.104
Final R indices [I> 2 sigma (I)]	: R1 = 0.0294, wR2 = 0.0796
R indices (all data)	: R1=0.0356, wR2 = 0.0860
Absolute structure parameters	: 0.33(12)
Largest diff. Peak and hole	: 0.217 and -0.186 e. A^{-3}

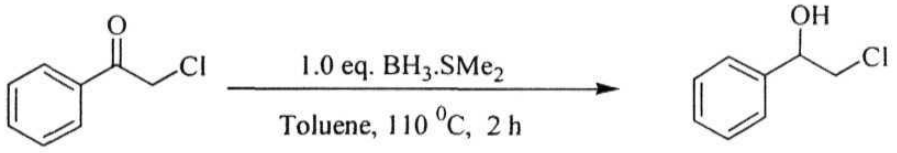


166a

(*S*)-167a
82% *ee*

(eq. 74)

The required racemic alcohol (±)-**167a** was prepared by treating phenacyl chloride **(166a)** (2 mM) with $BH_3.SMe_2$ in toluene as solvent (eq. 75). The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**167a.**

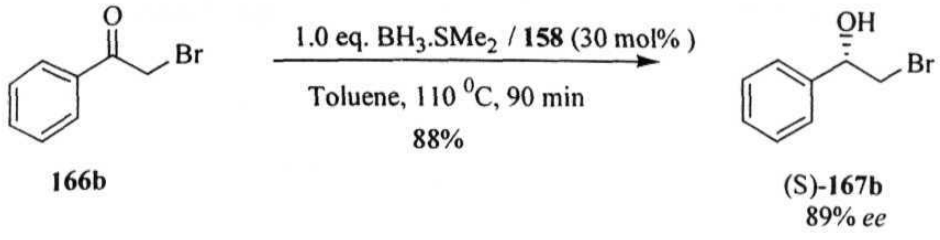


166a

(±)-167a

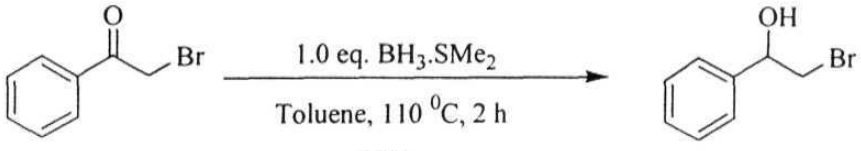
(eq. 75)

We have also performed the reduction of phenacyl bromide **(166b)** under the catalytic influence of the molecule **158** in the presence of borane-dimethyl sulphide under various conditions. The best results were obtained when phenacyl bromide **(166b)** (0.5 mM) was treated with $BH_3.SMe_2$ (0.5 mM) in the presence of 30 mol% catalyst **158** in refluxing toluene, thus providing the desired 2-bromo-1-phenylethanol **(167b)** in 89% *ee*, $[\alpha]_D^{25}$: +39.40 (c 2.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]* with (*S*)-configuration (eq. 76). The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data. The enantiomeric purity of this chiral alcohol (*S*)-**167b** was determined by HPLC analysis (Chromatogram 2) using chiral column, Chiralcel-OD with reference to racemic alcohol **(+)-167b.**



166b (S)-167b 89% *ee* **(eq. 76)**

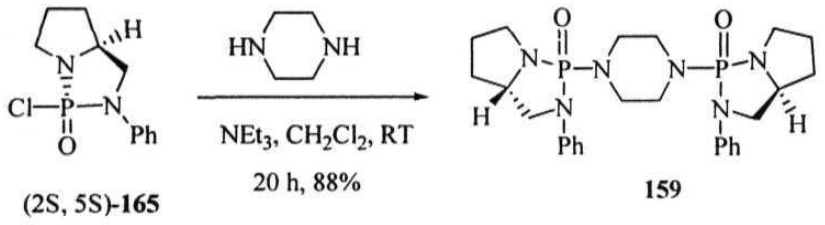
The required racemic alcohol (±)-**167b** was prepared by treating phenacyl bromide (166b) (2 mM) with $BH_3.SMe_2$ in toluene at 110 ^{0}C (eq. 77). This molecule has identical IR, ^{1}H & ^{13}C NMR spectral data as that of the chiral molecule (5)-167b.



166b (±)-167b **(eq. 77)**

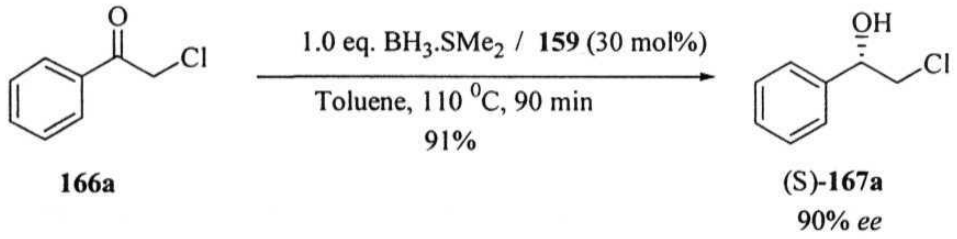
Though the enantioselectivities are encouraging, with a view to compare the effect of piperazine moiety with that of (1*R*,2*R*)-1,2-di(methylamino)cyclohexane moiety on phosphorous in (55)-l,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety, we planed to prepare phosphoramide, l,4-bis[(55)-l,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (**159**), and study its potential as a catalyst for the borane-mediated asymmetric reduction of prochiral α-halo ketones. The desired catalyst 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159)** was prepared by the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with piperazine in presence of triethylamine, in 88% isolated yield after usual work-up followed by column chromatography (silica gel, 1% methanol in ethyl acetate), $[\alpha]_D^{25}$: -59.40 (*c* 1.40, $CHCl_3$) (eq. 78). The structure of the compound was confirmed by IR, H NMR

(Spectrum 3), ^{13}C NMR (Spectrum 4), ^{31}P NMR (Spectrum 5), mass spectral data and elemental analysis.



(eq. 78)

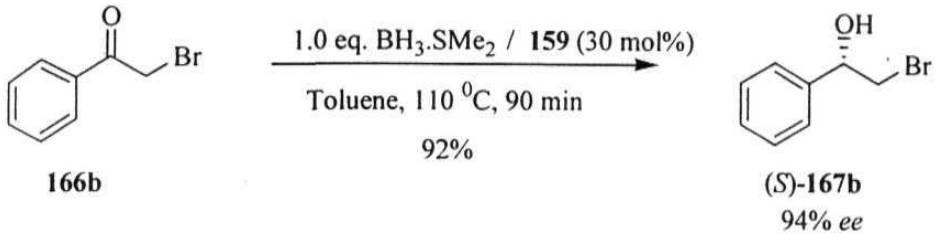
We have then first performed the reduction of phenacyl chloride **(166a)** under the catalytic influence of the molecule **159** in the presence of borane-dimethyl sulphide under various conditions. The best results were obtained when phenacyl chloride **(166a)** (0.5 mM) was treated with $BH_3.SMe_2$ (0.5 mM) in the presence of 30 mol% catalyst **159** in refluxing toluene, thus providing the desired (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] with 90% *ee*, in 91% yield (eq. 79). The enantiomeric purity of this chiral alcohol (*S*)-**167a** was determined by HPLC analysis (Chromatogram 1) using chiral column, Chiralcel-OD with reference to racemic alcohol (+)-167a.



(eq. 79)

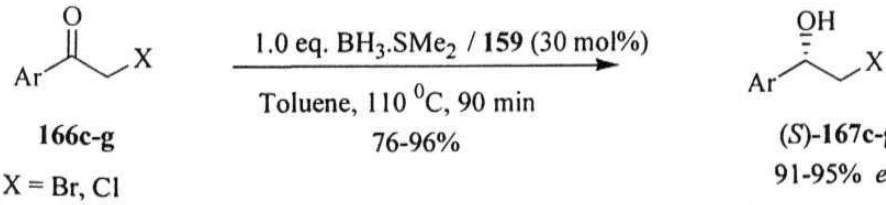
Next, we have performed the reduction of phenacyl bromide **(166b)** under the catalytic influence of the molecule **159** in the presence of borane-dimethyl sulphide under various conditions. The best results were obtained when phenacyl bromide **(166b)** (0.5 mM) was treated with $BH_3.SMe_2$ (0.5 mM) in the presence of 30 mol% catalyst **159** in refluxing toluene, thus providing the desired (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**)]

with 94% enantiomeric purity in 92% yield (eq. 80). The enantiomeric purity of this chiral alcohol (*S*)-**167b** was determined by HPLC analysis (Chromatogram 3) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.



166b (*S*)-**167b** 94% *ee* (eq. 80)

Since the phosphoramide **159** offered slightly better selectivities than phosphoramide **158** as a chiral catalyst in these reductions, we have successfully extended the application of phosphoramide **159** for the reduction of various prochiral α-halo ketones (166c-g) (eq. 81, Table. 1). The resulting secondary alcohols (*S*)-**167c-g** were obtained in 91-95% enantiomeric purities. The structures of these molecules were established by IR, ^{1}H and ^{13}C NMR spectral data.

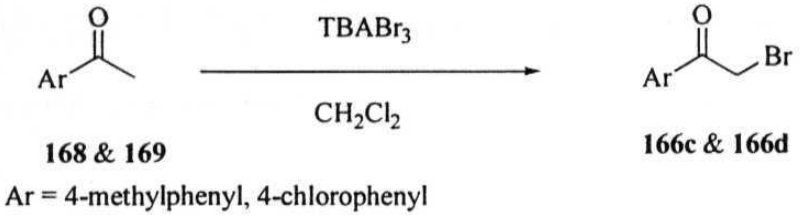


166c-g (*S*)-**167c-g** 91-95% *ee* (eq. 81)

X = Br, Cl

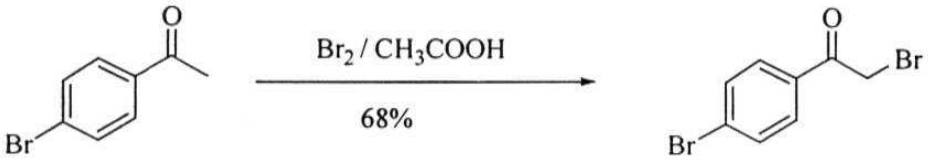
Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-ethylphenyl

The required α-bromo ketones were prepared according to the known procedures (eq. 82 & 83) [163-164] The desired α-chloro ketones were prepared *via* the reaction of aryl



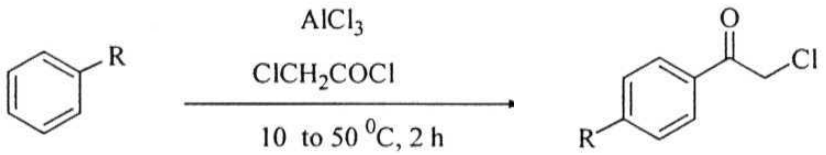
168 & 169 **166c & 166d** **(eq. 82)**

Ar = 4-methylphenyl, 4-chlorophenyl

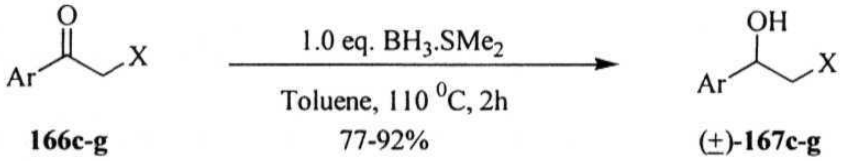


170 **166e** **(eq. 83)**

alkanes with chloroacetyl chloride, in presence of $AlCl_3$ (eq. 84). The racemic alcohols (±)-**167c-g** were prepared *via* the treatment of corresponding α-halo ketones with $BH_3.SMe_2$ (eq. 85). The structures of these molecules (α-halo ketones and corresponding racemic alcohols) were established by IR, ^1H and ^{13}C NMR spectral data.



R = Me, Et **166f, g** **(eq. 84)**



166c-g (±)-**167c-g** **(eq. 85)**

X = Br, Cl

Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-ethylphenyl

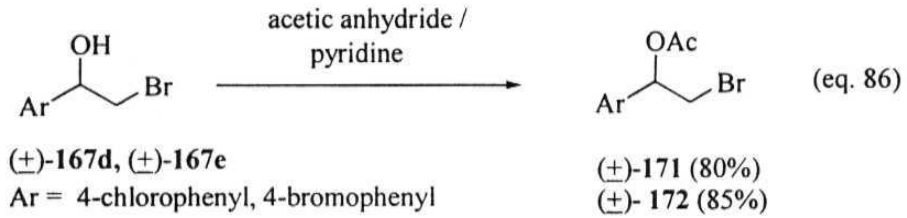
Determination of enantiomeric purities of alcohols:

Enantiomeric purities of the chiral alcohols (*S*)-**167c** (95%), (*S*)-**167f** (92%) and *(S)* 167g (92%) were determined by HPLC analyses using chiral column, Chiralcel-OD with reference to corresponding racemic alcohols (±)-**167c**, (±)-167f, (±)-167g. Our efforts to determine the enantiomeric purities of alcohols (*S*)-**167d** and (*S*)-**167e** using HPLC analysis with chiral column, Chiralcel-OD, were not successful. However, we were able to determine the enantiomeric purities of these alcohols by ^{1}H NMR (200 MHz) spectral studies of the corresponding acetates in the presence of chiral shift reagent, Eu(hfc)3, with reference to their corresponding racemic acetates. In the ^{1}H NMR (200 MHz) spectrum of racemic acetate (±)-**171**, the original singlet at 5 2.13 due to methyl protons of OCOCH3 splits into two singlets of equal integration in the presence of Eu(hfc)3, clearly indicating that these two singlets arise due to *(R)* and (*S*) enantiomers. The ^{1}H NMR (200 MHz) spectrum of chiral acetate (*S*)-**171**, in presence of Eu(hfc)$_3$, showed two distinct singlets for methyl protons of OCOCH3 in the ratio of 95.5:4.5 revealing that the enantiomeric purity of the alcohol (*S*)-**167d** is 91%.

Similarly, the enantiomeric purity of the alcohol (S)-167e was determined by ^{1}H NMR spectral analysis (Spectrum 6) of its acetate (*S*)-**172**, in the presence of chiral shift reagent, Eu(hfc)$_3$, with reference to racemic acetate (±)-172. The ^{1}H NMR (200 MHz) spectrum of acetate (*S*)-**172**, in presence of Eu(hfc)$_3$, showed two distinct singlets for methyl protons of OCO$\underline{CH_3}$ in the ratio of 96.5:3.5 indicating that the enantiomeric purity of alcohol (*S*)-**167e** is 93% [while ^{1}H NMR (200 MHz) spectrum of racemic acetate (±)-**172**, in presence of Eu(hfc)$_3$, showed two distinct singlets in the ratio of 1:1

for methyl protons of OCOCH3 due to *(R)* and (5) **enantiomers]**.

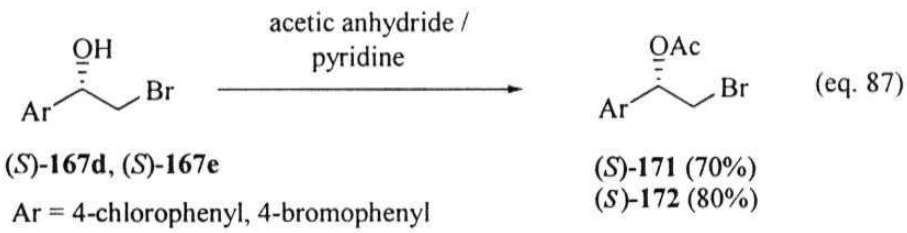
The required **racemic** acetates **(±)-171, (±)-172** and chiral acetates **(S)-171, (S)-172** were prepared by the treatment of corresponding racemic and chiral alcohols **167d** and **167e** with acetic anhydride in the presence of pyridine (eq. 86 & 87). The structures of these molecules were established by IR, ^{1}H and ^{13}C NMR spectral data.



(±)-167d, (±)-167e
Ar = 4-chlorophenyl, 4-bromophenyl

(±)-171 (80%)
(±)- 172 (85%)

(eq. 86)



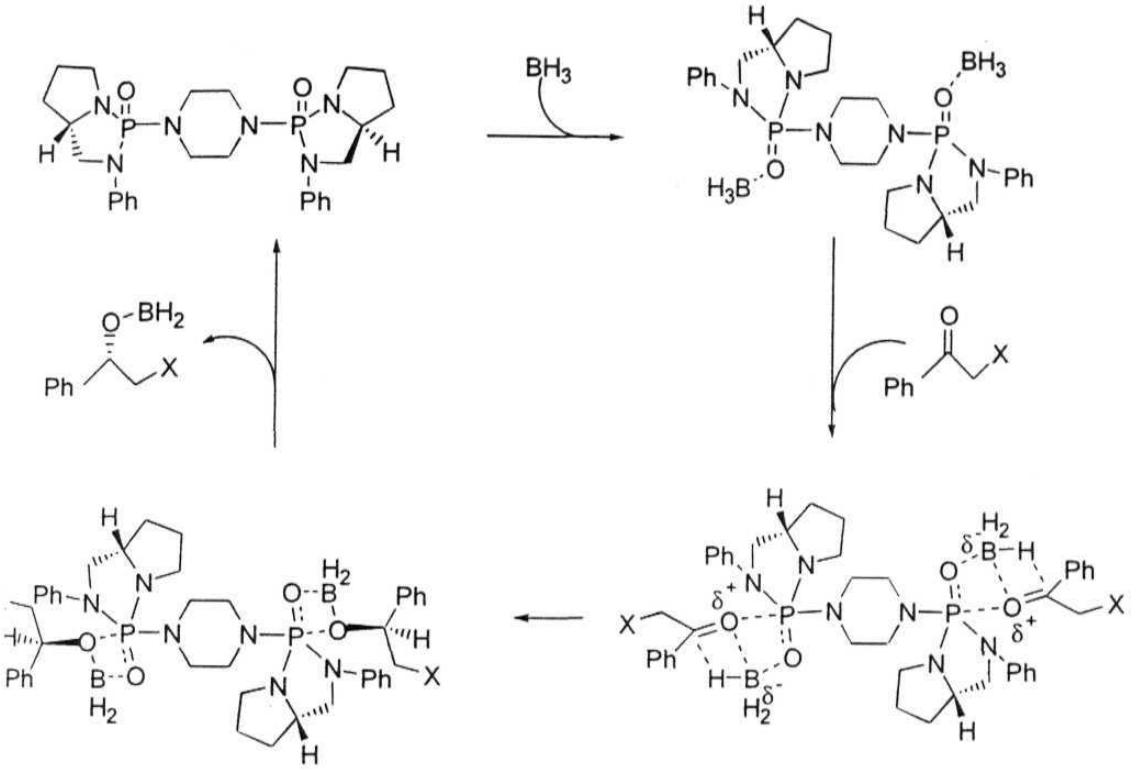
(*S*)-167d, (*S*)-167e
Ar = 4-chlorophenyl, 4-bromophenyl

(*S*)-171 (70%)
(*S*)-172 (80%)

(eq. 87)

A possible mechanism of the asymmetric reduction process is presented in Scheme 18. The first step of the catalytic cycle might involve the coordination of the phosphoramide oxygen to the electron deficient boron, there by generating a partial negative charge on the boron atom, thus rendering the phosphoramide electron deficient so that it can act as a Lewis acid for possible coordination with ketone. Subsequent hydride transfer from borane to ketone leads to the formation of alkoxyborane which then dissociates and releases the chiral phosphoramide for another catalytic cycle.

Scheme 18:



In conclusion, we have developed two novel chiral catalysts (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]cyclohexane (158) and 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (159) for the borane-mediated reduction of prochiral α-halo ketones, thus providing a simple methodology for synthesis of a-halo alcohols with high enantiomeric purities.

Table. 1: Asymmetric reduction of a- halo ketones using the catalysts 158 and 159[a]

Substrate	Ar	X	Catalyst (30 mol %)	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf[c]	E.e (%)[d]
166a	Phenyl	Cl	**158**	**(S)-167a**	94	+39.7 (c 2.25)[e]	***S***	82
166b	Phenyl	Br	**158**	**(*S*)-167b**	88	+39.4 (c 2.0/	***S***	89
166a	Phenyl	Cl	**159**	**(*S*)-167a**	91	+43.5 (*c* 2.4)[e]	***S***	90
166b	Phenyl	Br	**159**	**(5)-167b**	92	+42.45 (c 2.0/	***S***	94
166c	4-methylphenyl	Br	**159**	**(*S*)-167c**	83	+41.8 (c 1.0/		95
166d	4-chlorophenyl	Br	**159**	**(*S*)-167d**	90	+38.6 (c 1.15/		91[h]
166e	4-bromophenyl	Br	**159**	**(*S*)-167e**	76	+32.75 (c 1.3/	***S***	93[h]
166f	4-methylphenyl	Cl	**159**	**(*S*)-167f**	96	+47.2 (*c* 1.1/		92
166g	4-ethylphenyl	Cl	**159**	**(5)-167g**	84	+41.0 (c 1.0/		92

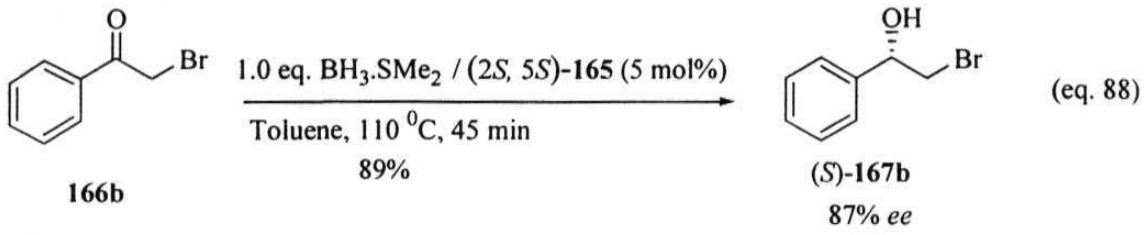
a) All reactions were carried out on 0.5 mM scale of a-halo ketone with 0.5 mM of $BH_3.SMe_2$ in the presence of 30 mol% catalyst in toluene for 90 min at 110 °C. b) Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes). c) Absolute configuration was assigned by comparison of sign of the optical rotation with that of reported molecules.[162.165] d) Determined by HPLC analysis using chiral column, Chiralcel-OD. e) Optical rotations were recorded in cyclohexane. f) Optical rotations were recorded in chloroform. g) Absolute configuration was tentatively assigned in analogy with **167a, 167b** and **167e.** h) Enantiomeric purity was determined by ^1H NMR (200 MHz) analysis of corresponding acetates **(*S*)-171** & **(*S*)-172** in the presence of chiral shift reagent, $Eu(hfc)_3$, with reference to the corresponding racemic acetates **(±)-171 & (±)-172.**

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane: a novel chiral source for the borane-mediated catalytic chiral reductions

Above methodology requires 30 mol% catalyst **(158** or **159)** for the reduction of prochiral α-halo ketones to provide the resulting 2-halo-1-arylethanols in high enantiomeric purities with (*S*)-configuration. We felt that 30 mol% catalyst is too large an amount, thus rendering the methodology expensive and it is therefore necessary to develop new frameworks / molecules that can catalyze the reaction when used in very small amounts. We also felt that it would be highly useful if such molecules can be easily accessible in large amounts. Literature survey reveals that potential of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane[(2*S*,5*S*)-**165**] which also is easily available in large quantites[159] has not been examined for catalytic chiral reduction processes. We envisioned that this molecule, (2*S*,5*S*)-**165**, containing *N*-*P(=O)Cl* framework might offer promise as a catalytic chiral source for the borane mediated catalytic chiral reductions.

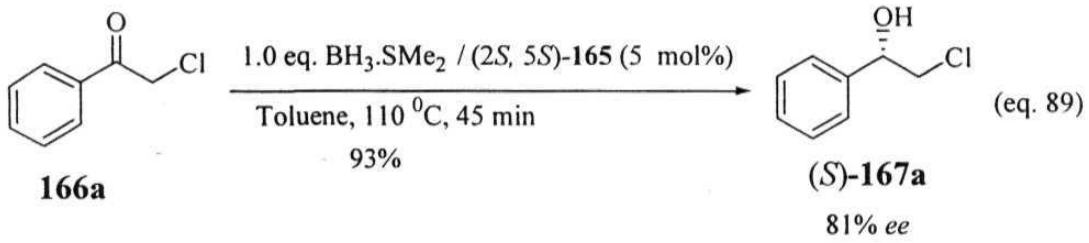
Accordingly, we have first examined the borane-mediated asymmetric reduction of phenacyl bromide using different catalytic amounts of the molecule (2*S*,5*S*)-**165**. The best results were obtained when phenacyl bromide (**166b**) (1 mM) was treated with borane-dimethyl sulfide (1 mM) under the influence of (2*S*,5*S*)-**165** (5 mol%) in refluxing toluene for 45 minutes thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol **[(*S*)-167b]** with 87% enantiomeric purity in 89% yield (eq. 88). The enantiomeric purity of this alcohol (5)-167b was determined by HPLC analysis

(Chromatogram 4) using chiral column, Chiralcel-OD with reference to racemic alcohol **(±)-167b.**



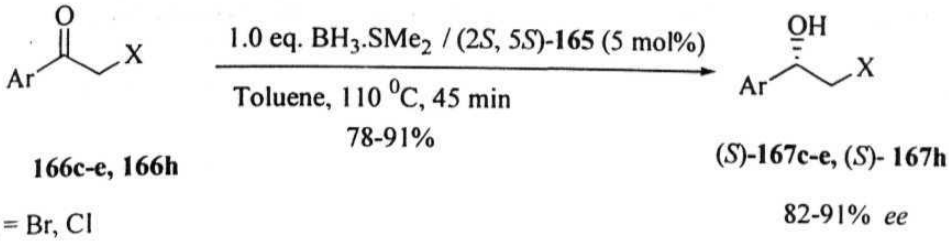
(eq. 88)

We have also performed the reduction of phenacyl chloride **(166a)** (1 mM) with borane-dimethyl sulfide (1 mM) under the influence of (2*S*,5*S*)-**165** (5 mol%) in refluxing toluene for 45 min to provide the desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] with 81% enantiomeric purity in 93% yield (eq. 89). The enantiomeric purity of the resulting secondary alcohol was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



(eq. 89)

These results are indeed encouraging. We have then extended the same reaction to a representative class of prochiral α-halo ketones (aryl halomethyl ketones) **166c-e** and **166h.** The resulting secondary alcohols (*S*)-**167c-e** and (*S*)-**167h** were obtained in 82-91% enantiomeric purities (eq. 90, Table 2).



166c-e, 166h

X = Br, Cl

(*S*)-167c-e, (*S*)- 167h

82-91% *ee*

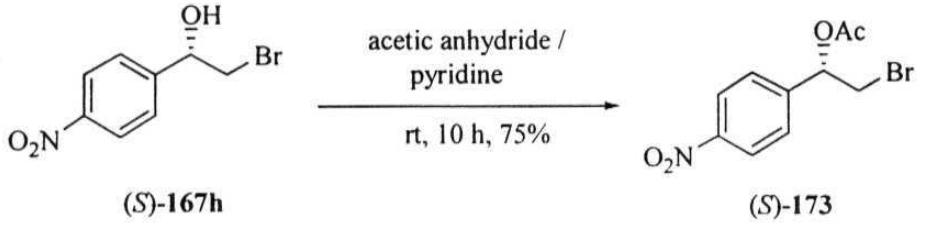
Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl

Determination of enantiomeric purity:

Enantiomeric purities of the chiral alcohols (*S*)-**167c** (83%), (*S*)-**167f** (82%) were determined by HPLC analyses using the chiral column, Chiralcel-OD with reference to the corresponding racemic alcohols. The enantiomeric purities of alcohols **(S)-167d** (88%), (*S*)-**167e** (86%) were determined by ^{1}H NMR (200 MHz) spectral analyses of the corresponding acetates (*S*)-**171** and (*S*)-**172** in the presence of chiral shift reagent, Eu(hfc)$_3$, with reference to their racemic acetates (±)-171 and (±)-**172**. The enantiomeric purity of the chiral alcohol (*S*)-**167h** (91%) was determined by ^{1}H NMR (200 MHz) spectral analysis (Spectrum 9) of the corresponding acetate (*S*)-**173** in the presence of chiral shift reagent, Eu(hfc)$_3$, with reference to its racemic acetate (±)-**173**.[$]

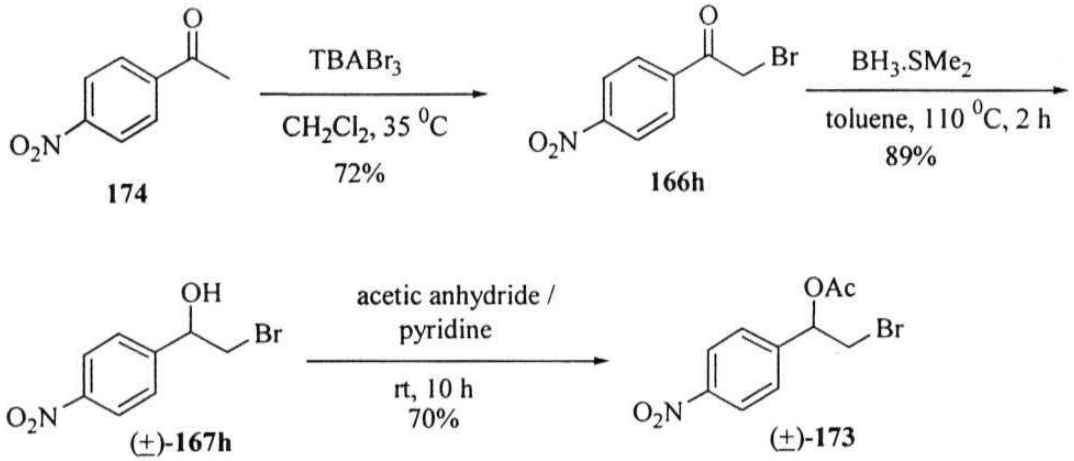
In the ^{1}H NMR (200 MHz) spectrum of racemic acetate (±)-**173** the original singlet at δ 2.13 due to acetoxy methyl protons (OCOCH3) splits into two singlets of equal integration in presence of Eu(hfc)$_3$, clearly indicating that these two singlets arise due to *(R)* and (*S*) enantiomers. The ^{1}H NMR (200 MHz) spectrum of chiral acetate (*S*)-**173** in presence of Eu(hfc)$_3$, showed two distinct singlets for methyl protons of OCO$\underline{CH_3}$ in the ratio 95.5:4.5 indicating that the enantiomeric purity of the alcohol (*S*)-**167h** is **91%.**

The required chiral acetate (*S*)-**173** and racemic acetate (±)-l 73 were prepared from the chiral alcohol (*S*)-**167h** and racemic alcohol (±)-**167h** respectively (eq. 91, Scheme 19). The required racemic alcohol was obtained from 4-nitroacetophenone **(174)** according to Scheme 19.[163] The structures of these molecules were established by IR, ^{1}H and ^{13}C NMR spectral data.



(*S*)-**167h** (*S*)-**173** (eq. 91)

Scheme 19:



With a view to recover and reuse the chiral source and also understand the mechanism, we have carried out the reduction of phenacyl bromide **(166b)** on 4 mM scale with borane-dimethyl sulfide (4 mM) under the influence of (2*S*,5*S*)-**165** (5 mol%, 51.4 mg) in refluxing toluene for 45 minutes thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 85% enantiomeric purity in 87% yield. We have also

Table 2: Asymmetric reduction of α-halo ketones using the chiral source (2*S*,5*S*)-165[a]

	Ar	X	Product	Yield(%)[b]	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)[d]
166a	Phenyl	Cl	(*S*)-**167a**	93	+40.0 (*c* 1.0, C_6H_{12})	*S*[162]	81
166b	Phenyl	Br	(*S*)-**167b**	89	+39.0 (*c* 1.0, $CHCl_3$)	*S*[162]	87
166c	4-Methylphenyl	Br	(*S*)-**167c**	87	+37.5 (*c* 1.0, $CHCl_3$)	*S*	83
166d	4-Chlorophenyl	Br	(*S*)-**167d**	80	+37.9 (*c* 1.2, $CHCl_3$)	*S*	88[e]
166e	4-Bromophenyl	Br	(*S*)-**167e**	88	+30.7 (*c* 2.4, $CHCl_3$)	*S*[165]	86[e]
166f	4-Methylphenyl	Cl	(*S*)-**167f**	91	+42.0 (*c* 1.0, $CHCl_3$)	*S*	82
166h	4-Nitrophenyl	Br	(*S*)-**167h**	78	+32 (*c* 1.0, $CHCl_3$)	*S*[f]	91[e]

[a] All reactions were carried out on 1 mM scale of α-halo ketone with 1mM of $BH_3.SMe_2$ in the presence of (2*S*,5*S*)-**165** (5 mol%) in toluene for 45 min at 110 ^{0}C.

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

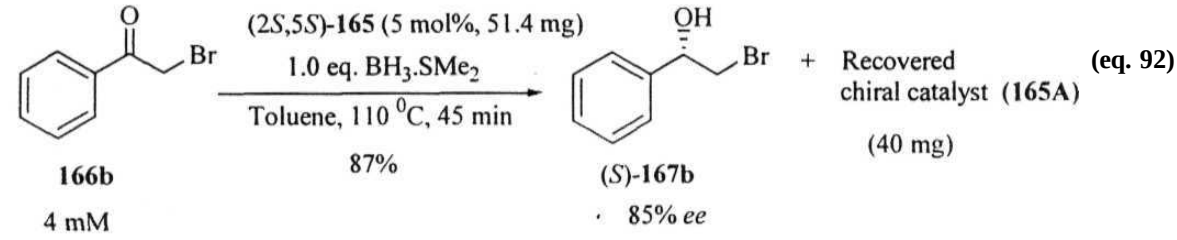
[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.[162,165]

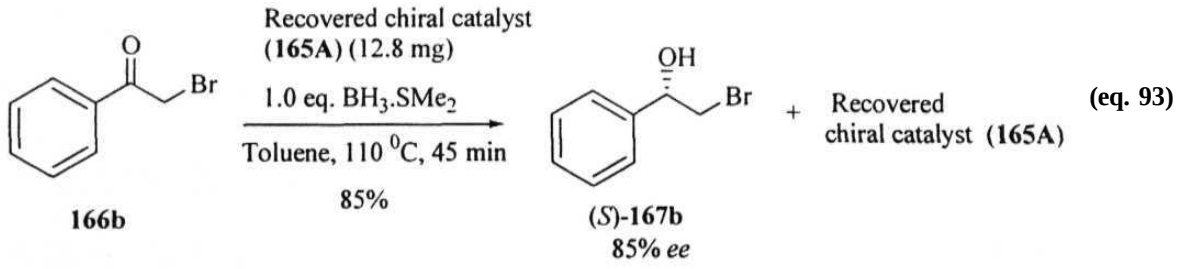
[d] Determined by HPLC analysis using the chiral column, Chiralcel-OD.

[e] Enantiomeric purities were determined by ^{1}H NMR (200 MHz) spectral analyses of the acetates in the presence of the chiral shift reagent, $Eu(hfc)_3$, with reference to the corresponding racemic acetates.

[f] Absolute configuration was tentatively assigned in analogy with **167a-f**

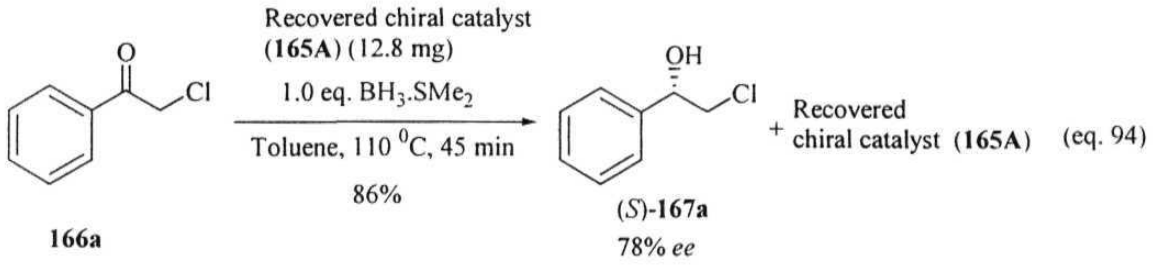
recovered the chiral catalyst as a light yellow solid **165A** (40 mg) (eq. 92). The enantiomeric purity of alcohol (*S*)-**167b** was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-167b. With a view to understand the reusability of the recovered chiral catalyst **165A**, we have performed the reduction of phenacyl bromide (166b) (1 mM) with borane-dimethyl sulfide in the presence of catalytic amount of the recovered chiral catalyst 165A (12.8 mg)$^{\phi}$ in refluxing toluene for 45 minutes thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 85% enantiomeric purity in 85% yield (eq.93). The enantiomeric purity of this alcohol was determined by HPLC analysis (Chromatogram 5) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.





$^{\phi}$ We have taken 12.8 mg of recovered chiral catalyst 165A on the basis of the molecular weight of the chiral source (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2S,5S)-165] (Mwt: 256.6).

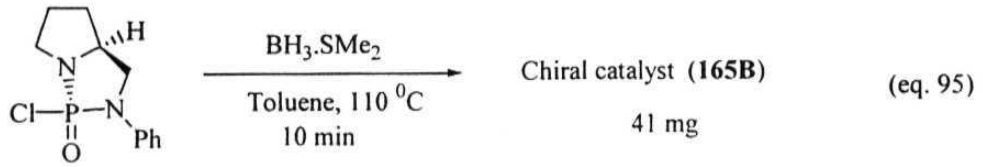
We have also performed the reduction of phenacyl chloride **(166a)** (1 mM) with borane-dimethyl sulfide in the presence of catalytic amounts of the recovered chiral catalyst **165A** (12.8 mg) in refluxing toluene for 45 minutes thus providing the desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] with 78% enantiomeric purity in 86% yield (eq. 94). The enantiomeric purity of the resulting secondary alcohol was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.

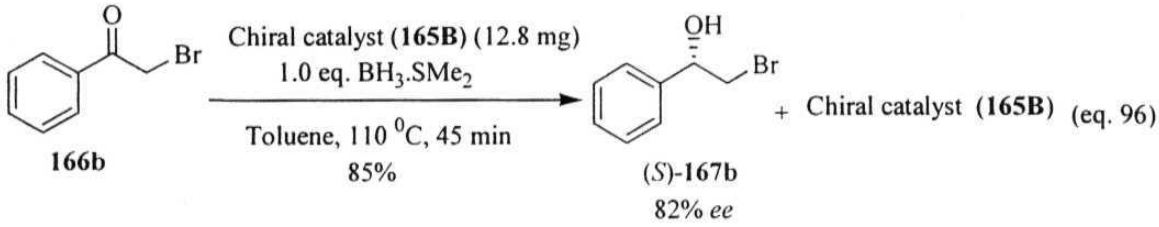


In order to understand the nature of the catalyst we have treated the molecule (2*S*,5*S*)-165 (0.2 mM, 51.4 mg) with $BH_3.SMe_2$ (0.3 mM, 22.8 mg) in toluene for 10 minutes at reflux temperature (eq. 95). The excess borane was destroyed by the addition of methanol. The resulting solid was filtered, washed with ether and dried under reduced pressure to provide a light yellow solid **165B** (41 mg). Next we have carried out the reduction of phenacyl bromide **(166b)** (1 mM) with borane-dimethyl sulfide (1 mM) in the presence of catalytic amount of this solid **165B** (12.8 mg)[#] in refluxing toluene for

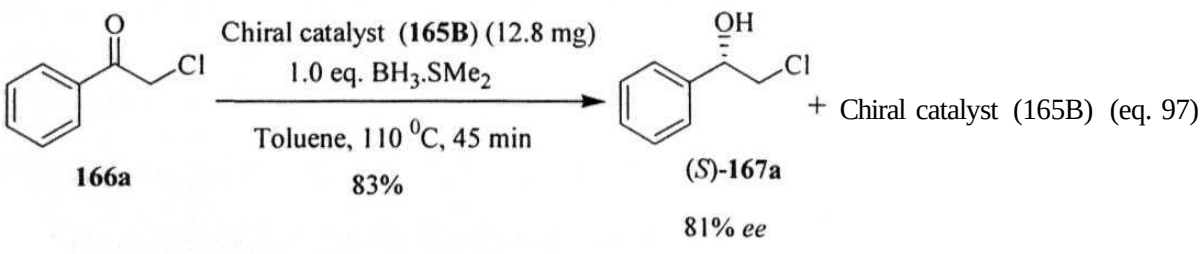
We have taken 12.8 mg of chiral source **165B** on the basis of the molecular weight of the chiral source (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)-octane [(25,55)-165] (Mwt: 256.6).

45 minutes thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 82% enantiomeric purity in 85% yield (eq. 96). The enantiomeric purity of the resulting secondary alcohol (*S*)-**167b** was determined by HPLC analysis (Chromatogram 5) using chiral column, Chiralcel-OD with reference to racemic alcohol **(±)-167b.**

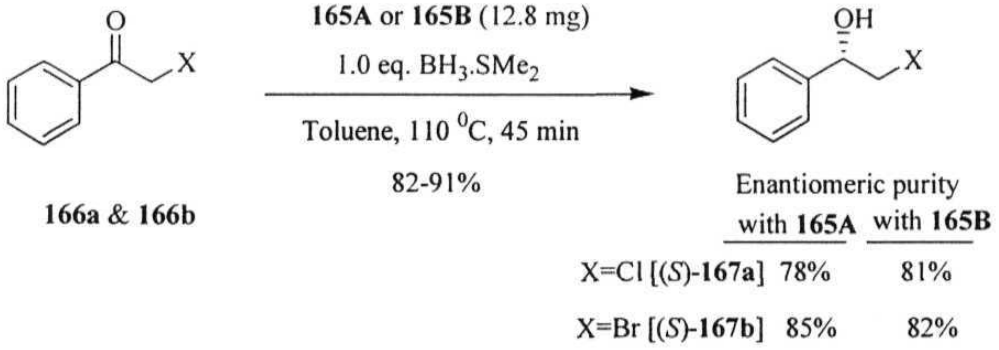




We have also performed the reduction of phenacyl chloride **(166a)** (1 mM) with borane-dimethyl sulfide in the presence of catalytic amount of the chiral catalyst **165B** (12.8 mg) in refluxing toluene for 45 minutes thus providing the desired alcohol (*S*)-2-chlcro-1-phenylethanol [(*S*)-**167a**] with 81% enantiomeric purity in 83% yield (eq. 97). The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (+)-167a.



These results clearly indicate that the solids **165A** and **165B** have almost the same chiral directing efficiency as the original chiral source *i.e.* the molecule (2*S*,5*S*)-**165** (eq. 98). Both the recovered 165A and prepared 165B catalysts are air stable, recoverable and reusable. A comparison of ^{1}H and ^{13}C NMR spectral studies of original chiral source (2*S*,5*S*)-**165** with that of 165A (Spectrum 10) and 165B (Spectrum 11) clearly indicates that they may have similar structural organization (the chiral diamine moiety is intact). The IR, ^{1}H, ^{13}C and ^{31}PNMR spectral studies of solids **165A** and 165B indicate that these solids (while determining the melting points we found that both these solids decompose at 126-129 °C) may have the same structure.

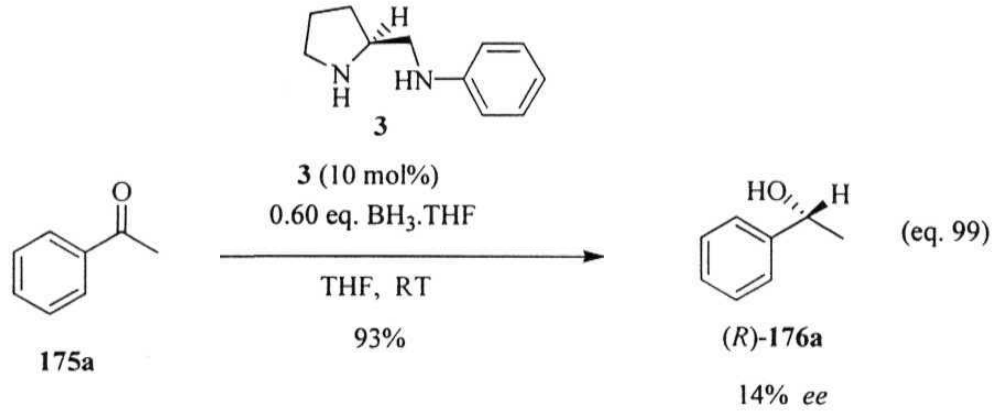


(eq. 98)

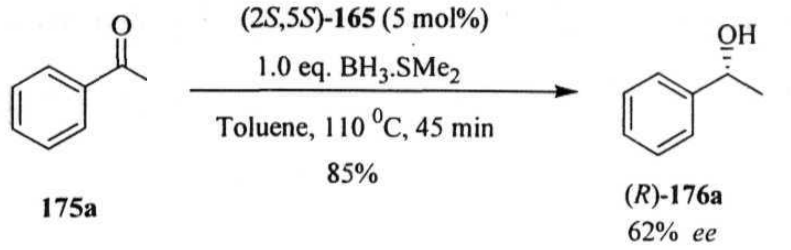
The major striking difference between the chiral source (2*S*,5*S*)-**165** and the solids 165A & 165B is their solubility profile (The solids both 165A and 165B are insoluble in most of the organic solvents such as hexanes, ether, chloroform, dichloromethane, ethyl acetate, THF, methanol and water, while the original chiral source (2*S*,5*S*)-**165** is soluble in ether, chloroform and dichloromethane *etc.).* In both the cases (solid 165A & 165B), the ^{11}B NMR spectrum shows a very weak broad signal at 6 2.80 indicating that the actual catalyst (solids 165A or 165B), may not contain any boron species. This

weak signal may be attributed to the presence of minor amounts of some boron species in the actual catalysts **(165A** or **165B).** On the basis of these preliminary studies, we assume that the catalyst **165A** or **165B** may not be monomeric in nature.

It is worth mentioning here the interesting work of Asami and co-workers[166] who reported chiral p-diamines as catalysts for the borane-mediated chiral reduction of prochiral ketones. During this study they reported that the reduction of acetophenone **(175a)** with BH3.THF in the presence of (*S*)-2-anilinomethylpyrrolidine 3 (10 mol %) provided the desired secondary alcohol *(R)-l* 76a in 14 % enantiomeric purity (eq. 99).

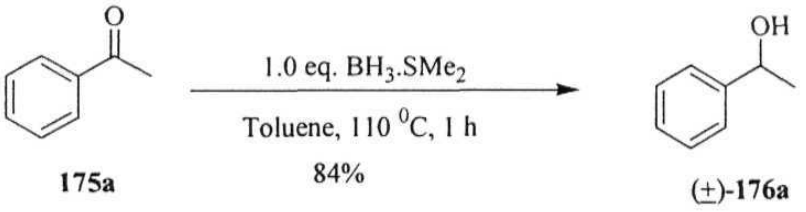


With a view to understand the mechanism and to examine the applications of *NP(=O)Cl* framework we have performed the borane mediated reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] (5 mol %) in refluxing toluene. The resulting secondary alcohol **176a** was obtained in 62% enantiomeric purity with (*R*)-configuration, $[\alpha]_D^{25}$: +27.5 (*c* 0.4, MeOH) [Lit.[167] $[\alpha]_D^{25}$: + 37.7 (*c* 3.81, MeOH) *R*-configuration, 84% *ee.]* (eq. 100).



(eq. 100)

The structure of the compound was confirmed by IR, ^{1}H and ^{13}C NMR spectral data. The enantiomeric purity of the resulting secondary alcohol (*R*)-**176a** was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**176a**. The required racemic alcohol (±)-**176a** was prepared by treating the acetophenone (175a) with $BH_3.SMe_2$ in toluene at 110 °C (eq. 101).



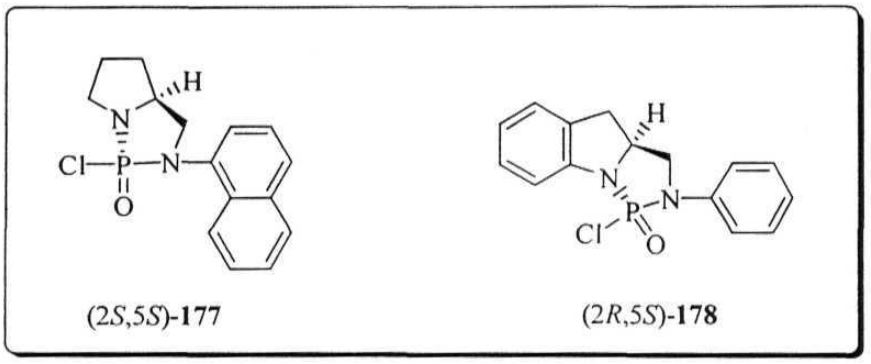
(eq. 101)

This experiment (eq. 100) demonstrates that the diazaborolidine is not generated in our reaction and also indicates that ***NP(=O)N*** framework has considerable role on the stereodirection in comparison with that of chiral diamine 3.

Though we have developed air stable, recoverable and reusable catalyst for the borane mediated asymmetric reduction of prochiral ketones, the enantioselectivities are not that high. It occurred to us that sterically more demanding groups on (*S*)-2-anilinomethylpyrrolidine moiety might provide better enantioselectivities in the borane mediated asymmetric reduction of prochiral ketones. Accordingly, we have selected (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-1-yl)bicyclo(3.3.0)octane [(2*S*, 5S)-177] and (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.$0^{1,5}$)-

dodeca-7(12),8,10-triene [(2*R*,5*S*)-**178**] (Fig. 21) with a view to that these molecules might offer better enantioselectivities in the borane-mediated asymmetric reduction of prochiral ketones.

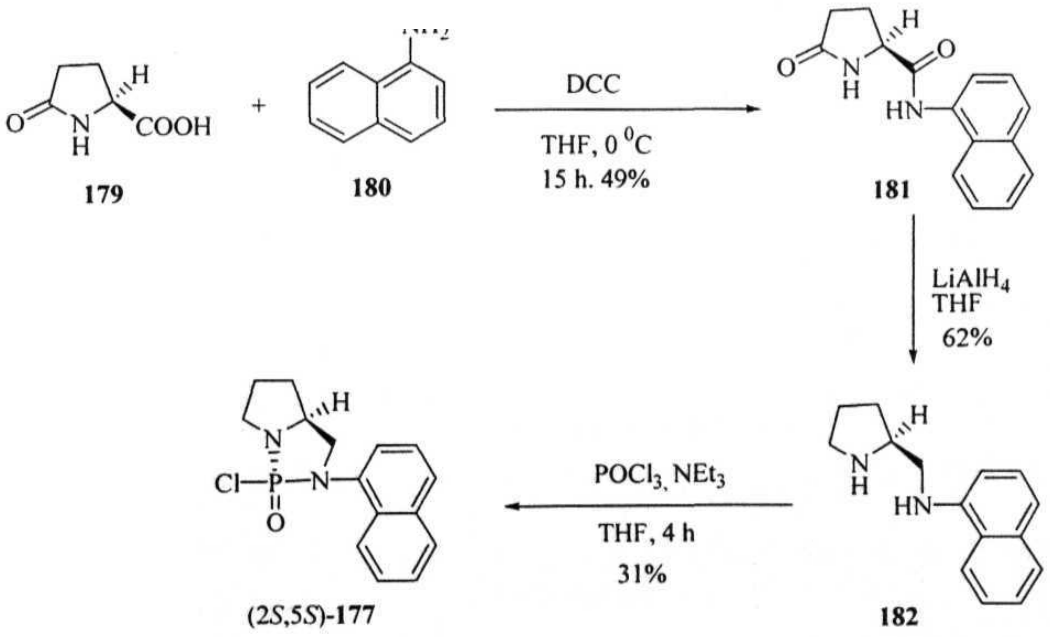
Figure 21:



We have first prepared the desired (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yl)bicyclo(3.3.0)octane [(2*S*,5*S*)-**177**] according to the Scheme 20. Treatment of (*S*)-pyroglutamic acid (179) with α-naphthylamine (180) in the presence of DCC provided the required N′-(naphth-1-yl)-5-oxo-(2*S*)-2-pyrrolidine-2-carboxamide (181) as a white solid in 49% isolated yield after usual work-up followed by column chromatography (silica gel, 2.5% methanol in ethyl acetate), $[\alpha]_D^{25}$:-7.53 (*c* 1.09, methanol). The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data. Subsequent reduction with lithium aluminum hydride afforded the desired (25)-2-(1-naphthylaminomethyl)pyrrolidine (182) as a viscous liquid in 62% yield, $[\alpha]_D^{25}$: +29.46 (*c* 1.02, ethanol) [Lit.[27] $[\alpha]_D^{25}$: +29.50 (*c* 1.03, ethanol)]. The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data.

Treatment of (2*S*)-2-(1-naphthylaminomethyl)pyrrolidine **(182)** with $POCl_3$ in the presence of triethylamine provided two diateromeres of **177** in the ratio of 4:1. The major diastereomer (more polar) (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yl)bicyclo(3.3.0)octane [(2*S*,5*S*)-**177**] was separated by column chromatography (silica gel, 10% ethyl acetate in hexanes) in 31% isolated yield, $[\alpha]_D^{25}$: +5.0 (*c* 1.0, $CHCl_3$). The structure of the compound was confirmed by IR, ^1H NMR (Spectrum 12), ^{13}C NMR (Spectrum 13), ^{31}P NMR (Spectrum 16) spectral data and elemental analysis. The absolute (*S*)-configuration at the phosphorous atom was determined by single crystal X-ray data. The X-ray crystal data and structure refinement for this molecule is presented in the Table II and the ORTEP diagram for the molecule is shown in Fig. X2.

Scheme 20:



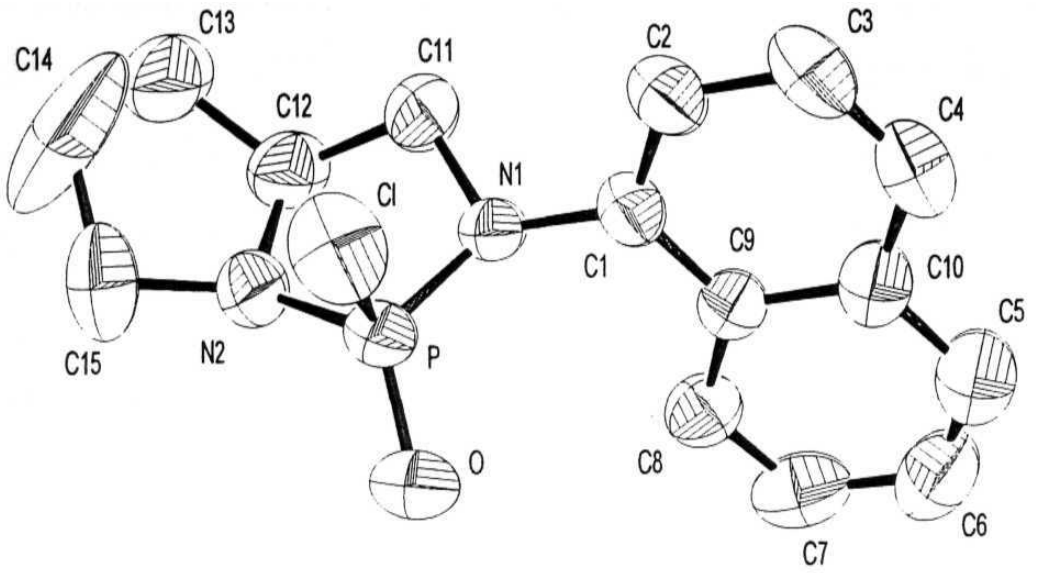


Fig. X2

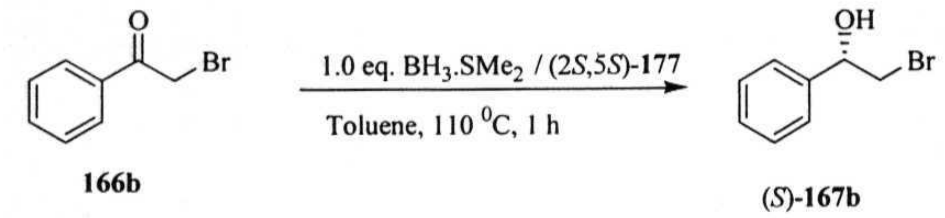
ORTEP diagram of the compound *(2S,5S)-177*

(Hydrogen atoms were omitted for clarity)

Next we have directed our studies towards the borane-mediated asymmetric reduction of phenacyl bromide (166b) under the catalytic influence of the chiral molecule (2*S*,5*S*)-**177** with varied amounts. The best results were obtained when phenacyl bromide (166b) (0.5 mM) was treated with borane-dimethyl sulfide (0.5 mM) under the influence of 20 mol% (2*S*,5*S*)-**177** in refluxing toluene for 1 h thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 55% enantiomeric purity in 89% yield (eq. 102, Table 3). The enantiomeric purity of this alcohol was determined by HPLC analysis (Chromatogram 6) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.

Table II: Crystal data and structure refinement for compound (2*S*,5*S*)-177

Identification	: (2*S*,5*S*)-**177**
Empirical formula	: $C_{15}H_{16}ClN_2OP$
Formula weight	: 306.72
Temperature	:293(2)° K
Wavelength	: 0.71073 A
Crystal system	: Orthorhombic
Space group	: P 2_1 2_1 2_1
Unit cell dimensions	:a = 6.441(8) Å α = 90°
	: b = 9.970(8) A β = 90°
	:c = 22.921(16) Å γ = 90°
Volume	: 1472(2) A^3
Z	:4
Density (calculated)	: 1.384 g/ cm^3
Absorption coefficient	: 0.365 mm^{-1}
F (000)	:640
Crystal size	: 0.32 x 0.32 x 0.24 mm
Theta range for data collection	: 1.78<0<27.45
Index ranges	:0<h<8, 0<k< 12, 0<l<29
Reflections collected	: 1967
Independent reflections	: **1130**
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1967/0/181
Goodness-of-fit on F^2	: 0.696
Final R indices [I> 2 sigma (I)]	:R1 =0.0540, wR2 = 0.1241
R indices (all data)	: R1 = 0.1146, wR2 = 0.1746
Absolute structure parameters	: 0.3(3)
Largest diff. Peak and hole	: 0.181 and -0.201 e. A^{-3}



166b (*S*)-167b (eq. 102)

Table 3: Asymmetric reduction of phenacyl bromide (166b) using varying catalytic amounts of molecule (2*S*,5*S*)-177 [a]

Catalyst (2*S*,5*S*)-177 Mol %	Yield (%)[b] (*S*)-167b	Enantiomeric purity (%)[c] (5)-167b	Configuration[d]
5	82	25	*S*
10	80	40	*S*
20	89	55	***S***
30	81	43	***S***
50	82	20	***S***

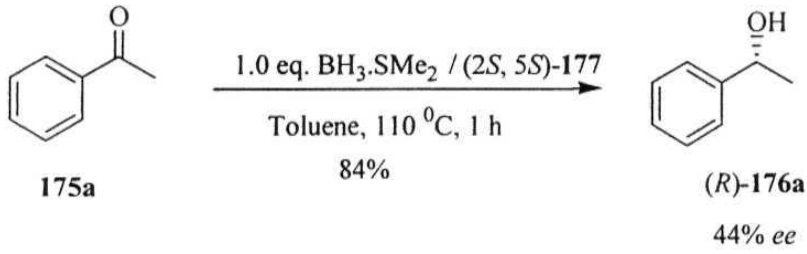
[a] All reactions were carried out on 0.5 mM scale of phenacyl bromide **(166b)** with 0.5 mM of $BH_3.SMe_2$ in the presence of (2*S*,5*S*)-177 in toluene for 1 h at 110 °C.

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

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

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[162]

These results are discouraging. However, with a view to examine the potential of chiral catalyst (2*S*,5*S*)-**177** in the reduction of acetophenone (175a) under the influence of borane, we have performed the reduction of acetophenone (175a) with various catalytic amounts of chiral molecule (2*S*,5*S*)-**177**. The best results were obtained when acetophenone (175a) (0.5 mM) was treated with borane-dimethyl sulfide (0.5 mM) under the influence of (2*S*,5*S*)-**177** (20 mol%) in refluxing toluene for 1 h thus providing the desired alcohol (*R*)-1-phenylethanol [(*R*)-**176a**] with 44% *ee* in 84% yield (eq. 103. Table 4). The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**176a**.



175a (*R*)-**176a** 44% *ee* (eq. 103)

Since the chiral molecule *(2S, 5S)*-**177** provided inferior selectivities as a catalyst in the borane-mediated asymmetric reduction of phenacyl bromide (166b) and acetophenone (175a), we have focused our studies towards the chiral molecule (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.0^{1,5})dodeca-7(12),8,10-triene [(2*R*,5*S*)-178]. We have synthesized this molecule (2*R*,5*S*)-**178**, from commercially available amino acid (*S*)-indoline-2-carboxylic acid (183) according to Scheme 21.[168] The amino group was protected with the terf-butoxycarbonyl group in the presence of NaOH to provide (*S*)-N-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid (184) in 85% yield,

Table 4: Asymmetric reduction of acetophenone (175a) using varying catalytic amounts of the molecule (2*S*, 5*S*)-177[a]

Catalyst (2*S*,5*S*)-**177** Mol %	Yield (%)[b] (*R*)-**176a**	Enantiomeric purity (%)[c] (*R*)-**176a**	Configuration [d]
1	85	Racemic	Racemic
5	84	27	***R***
20	84	44	***R***

[a] All reactions were carried out on 0.5 mM scale of acetophenone (175a) with 0.5 mM of $BH_3.SMe_2$ in the presence of (2*S*,5*S*)-**177** in toluene for 1 h at 110 °C.

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

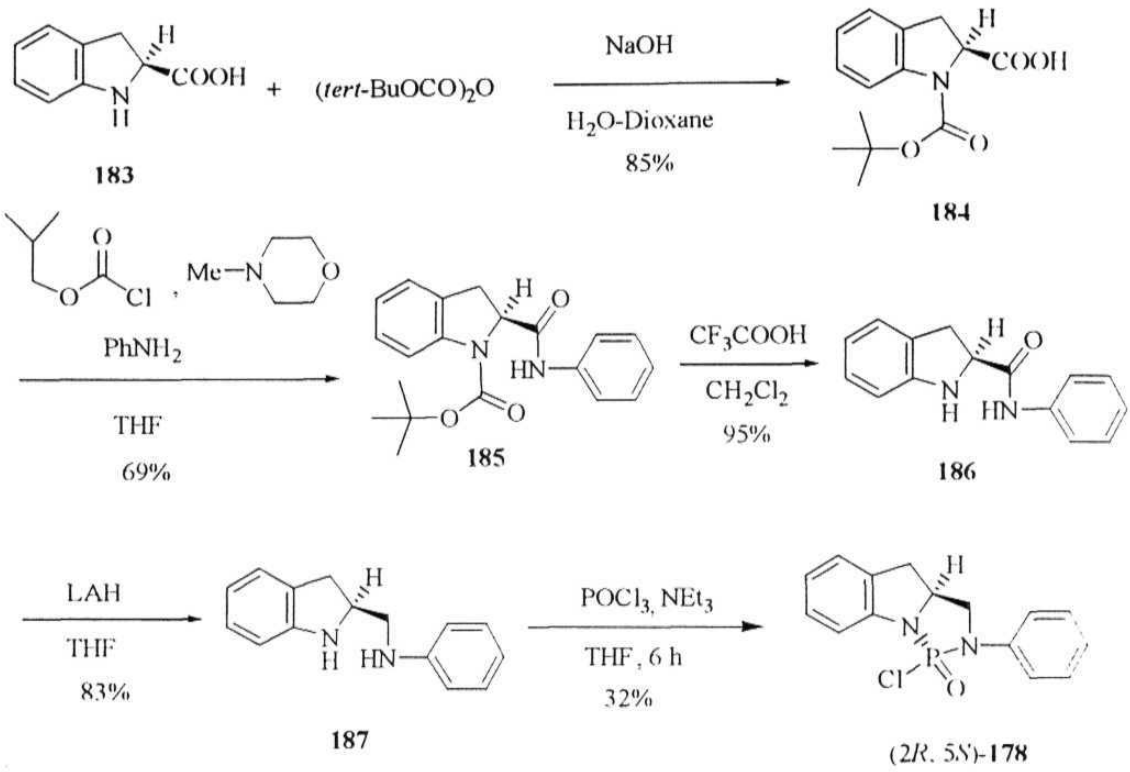
[c] Determined by HPLC analysis using the chiral column, Chiralcel-OD.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[167]

$[\alpha]_D^{25}$: -75.30 (*c* LO, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: -77.3 (*c* LO, $CHCl_3$)]. Treatment of (*S*)-N-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **(184)** with aniline in the presence of isobutyl chloroformate provided the N-phenyl-(*S*)-N^{α}-(*tert*-butoxycarbonyl)indoline-2-carboxamide **(185)** in 69% isolated yield after usual work-up followed by column chromatography (silica gel, 30% ethyl acetate in hexanes), $[\alpha]_D^{25}$: -71.6 (*c* 2.5, $CHCl_3$)

[Lit.[168] $[\alpha]_D^{25}$: -67.6 (*c* 1.0, $CHCl_3$)]. tert-Butoxycarbonyl group was removed by the treatment of trifluoroacetic acid in dichloromethane to provide the N-phenyl-(*S*)-indoline-2-carboxamide **(186)** in 95% isolated yield after usual work-up followed by column chromatography (silica gel, 35% ethyl acetate in hexanes), $[\alpha]_D^{25}$: -238 (*c* 0.95, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: -236 (*c* 1.0, $CHCl_3$)]. Subsequent reduction with lithium aluminum hydride provided (*S*)-2-(anilinomethyl)indoline **(187)** as a white solid, in 83% isolated yield after usual work-up followed by column chromatography (silica gel, 40% ethyl acetate in hexanes), $[\alpha]_D^{25}$: +85.2 (*c* 0.75, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: +79.4 (*c* 0.99, $CHCl_3$]. The structure of the compound was confirmed by IR, ^1H and ^{13}C NMR spectral data. Treatment of (*S*)-2-(anilinomethyl)indoline **(187)** with $POCl_3$ in the presence of triethylamine provided two diastereomers of **178** in the ratio of 4:1. The major diastereomer (more polar) (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.$0^{1,5}$)dodeca-7(12),8,10-triene [(2*R*,5*S*)-**178**] was separated by column chromatography (silica gel, 10% ethyl acetate in hexanes) in 32% isolated yield, $[\alpha]_D^{25}$: +55.62 (*c* 0.8, $CHCl_3$). The structure of the compound was confirmed by IR, ^1H NMR (Spectrum 14), ^{13}C NMR (Spectrum 15), ^{31}P NMR (Spectrum 16), spectral data and elemental analysis. The absolute (*R*)-configuration at the phosphorous atom was determined by single crystal X-ray data. The X-ray crystal data and structure refinement for this molecule is presented in the Table III and the ORTEP diagram for the molecule is shown in Fig. X3.

Scheme 21:



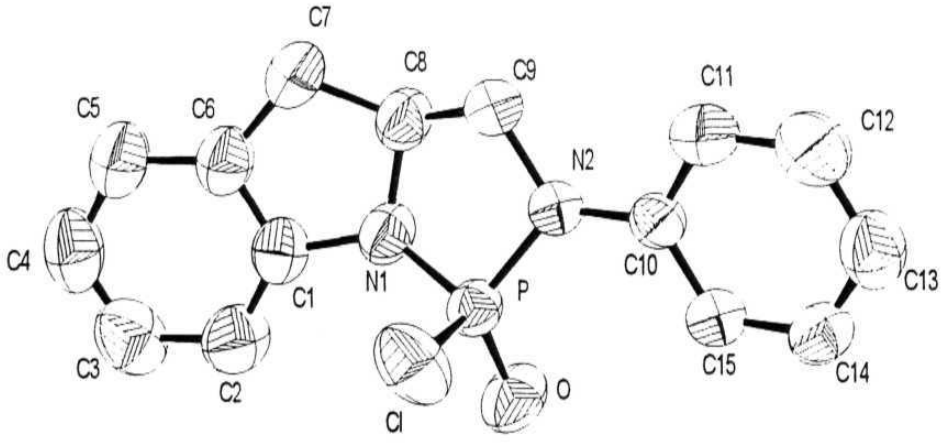


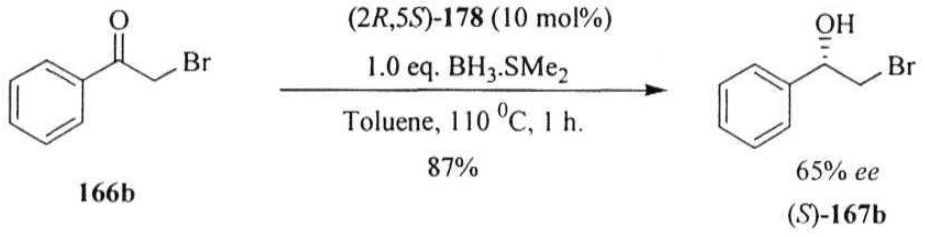
Fig. X3

ORTEP diagram of the compound (2*R*,5*S*)-178
(Hydrogen atoms were omitted for clarify)

Table III: Crystal data and structure refinement for the molecule (2*R*,5*S*)-178

Identification	: (2*R*,5*S*)-**178**
Empirical formula	: $C_{15}H_{14}ClN_2OP$
Formula weight	: 304.70
Temperature	: 293 (2) °K
Wavelength	: 0.71073 A
Crystal system	: Orthorhombic
Space group	: P 2 1 1
Unit cell dimensions	:a = 6.034 Å α = 90°
	: b = 7.990 A β = 90°
	:c = 29.124 Å γ = 90^0
Volume	: 1404.1 A^3
Z	:4
Density (calculated)	: 1.441 g/cm^3
Absorption coefficient	: 0.38 mm^{-1}
F (000)	: 632
Crystal size	: 0.64 x 0.44 x 0.36 mm
Theta range for data collection	: 1.40 ≤ ∅ ≤ 29.96
Index ranges	: 0 ≤ h ≤ 8, 0 ≤ k ≤ 11, 0 ≤ l ≤ 40
Reflections collected	:2456
Independent reflections	:2382
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2382 / 0 / 182
Goodness-of-fit on F^2	: 1.14
Final R indices [I> 2 sigma (I)]	: R1 = 0.0384, wR2 = 0.0852
R indices (all data)	:R1 = 0.0553, wR2 = 0.0981
Absolute structure parameters	: 0.0166(16)
Largest diff. Peak and hole	: 0.303 and -0.239 e. A^{-3}

We have then examined the borane-mediated asymmetric reduction of phenacyl bromide (166b) under the catalytic influence of the chiral molecule (2*R*,5*S*)-**178** with varying amounts. The best results were obtained when phenacyl bromide (166b) (0.5 mM) was treated with borane-dimethyl sulfide (0.5 mM) under the influence of (2*R*,5*S*)-**178** (10 mol%) in refluxing toluene for 1 h thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 65% *ee* in 87% yield (eq. 104, Table 5). The enantiomeric purity of this alcohol (*S*)-**167b** was determined by HPLC analysis (Chromatogram 7) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.



(eq. 104)

With a view to examine the potential of chiral catalyst (2*R*,5*S*)-**178** in the reduction of acetophenone (**175a**) under the influence of borane, we have performed the reduction of acetophenone (175a) with different catalytic amounts of (2*R*,5*S*)-**178**. The best results were obtained when acetophenone (175a, 0.5 mM) was treated with borane-dimethyl sulfide (0.5 mM) under the influence of (2*R*,5*S*)-**178** (10 mol %) in refluxing toluene for 1 h thus providing the desired alcohol (*R*)-1-phenylethanol [(*R*)-**1** 76a] with

35% enantiomeric purity in 85% yield (eq. 105). The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**176a**.

Table 5: Asymmetric reduction of phenacyl bromide (166b) using varying catalytic amounts of the molecule (2*R*,5*S*)-178 [a]

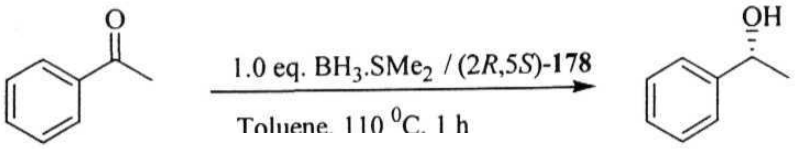
Catalyst (2*R*,5*S*)-**178** Mol %	Yield (%)[b] (*S*)-**167b**	Enantiomeric purity (%)[c] (*S*)-**167b**	Configuration [d]
5	82	**55**	*S*
10	87	**65**	***S***
20	81	**64**	***S***
30	82	**57**	***S***
50	85	**48**	***S***

[a] All reactions were carried out on 0.5 mM scale of phenacyl bromide **(166b)** with 0.5 mM of $BH_3.SMe_2$ in the presence of (2*R*,5*S*)-**178** in toluene for 1 h at 110 °C.

Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).

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

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



175a (*R*)-176a (eq. 105)

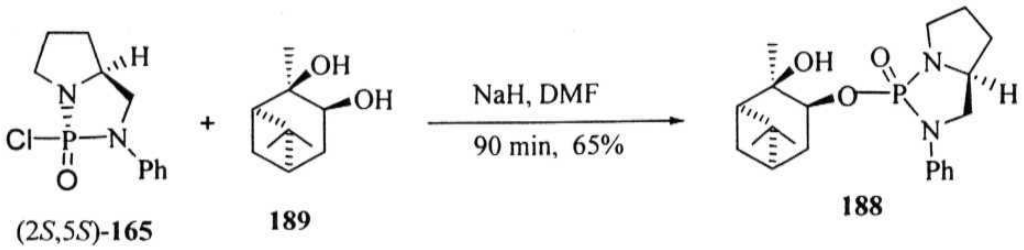
Catalyst mol%	Yield%	ee%
5	73	31
10	85	35

Since the enantioselectivities are inferior in the borane-mediated asymmetric reduction of phenacyl bromide (166b) and acetophenone (175a) using catalysts (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yl)bicyclo(3.3.0)octane [(2*S*, 5*S*)-**177**] and (2*R*, 5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.0^{1,5})dodeca-7(12),8,10-triene [(2*R*,5*S*)-**178**], no attempts were made to recover and reuse the catalysts in these cases. Though, we do not understand the structure of the actual catalyst / catalytic species, obtained from chiral source (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], we have for the first time, demonstrated the potential of *N-P(=O)Cl* framework as a chiral catalytic source to generate a recoverable, reusable and air stable catalyst for the borane-mediated enantioselective reduction processes.

A new chiral catalytic source with an *N-P=O* structural framework containing a proximal hydroxyl group for the borane-mediated asymmetric reduction of prochiral ketones

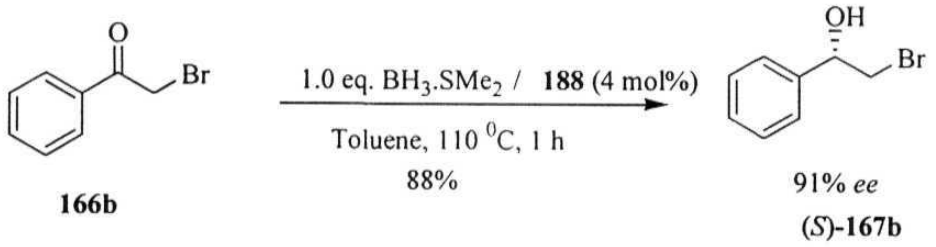
Though the chiral source (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane [(2*S*,5*S*)-165] is recoverable, reusable & air stable, and the enantioselectivities are reasonably high in the case of a-halo ketones, the enantioselectivity in the case of acetophenone (175a) is not that high. The interesting work of Wills[115,117] and Buono[113,118] on the role of proximal hydroxyl group in the catalysts for the asymmetric reduction of prochiral ketones, has led us to design the catalyst having such a proximal hydroxyl group. Accordingly, we have planned to prepare the catalyst (5*S*)-2-[(1*R*,2*R*,-3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (188) and study its catalytic applications in the reduction of prochiral ketones.

The desired catalyst 188 was prepared *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-165] with (1*R*,2*R*,-3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol (189) in the presence of NaH, in 65% isolated yield after usual work-up followed by column chromatography (silica gel, 40% ethyl acetate in hexanes) (eq. 106). The structure of the compound was confirmed by IR, ^{1}H NMR (Spectrum 17), ^{13}C NMR (Spectrum 18), ^{31}P NMR (Spectrum 19), mass spectral data and elemental analysis.



(2*S*,5*S*)-**165** **189** **188** (eq. 106)

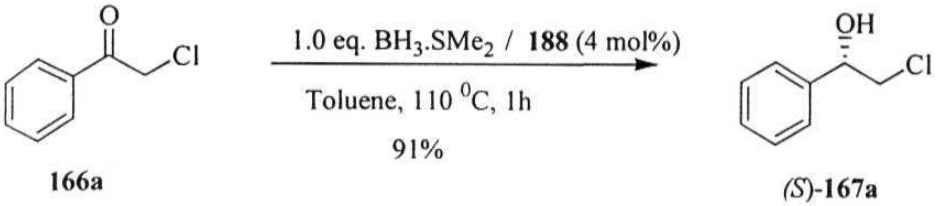
We have first examined the borane-mediated asymmetric reduction of phenacyl bromide **(166b)** under the influence of the chiral molecule **188** with different catalytic amounts (Table 1). The best results were obtained when phenacyl bromide **(166b)** was treated with borane-di methyl sulfide under the influence of **188** (4 mol%) in re fluxing toluene for 1 h, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b]** with 91% enantiomeric purity in 88% yield (eq. 107, Table 6). The enantiomeric purity of resulting alcohol was determined by HPLC analysis (Chromatogram 8) using the chiral column Chiralcel-OD with reference to the corresponding racemic alcohol (±)-**167b**. This reaction is indeed very encouraging.



166b (*S*)-**167b** (eq. 107)

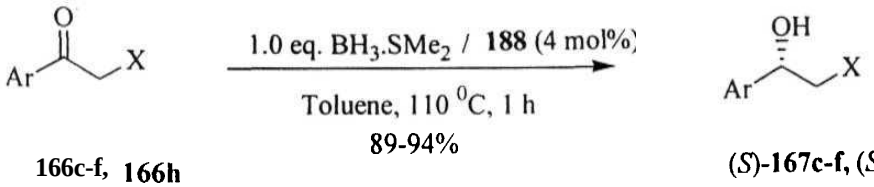
We have also performed the reduction of phenacyl chloride **(166a,** 1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 4 mol% chiral source **188** in refluxing toluene for 1 h to provide the desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] in 86% enantiomeric purity (eq. 108). The enantiomeric purity of the resulting

secondary alcohol was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



166a (*S*)-**167a** 86% *ee* (eq. 108)

With a view to understand the generality of the reaction, we have then employed a representative class of prochiral α-halo ketones **166c-f, 166h** for the borane-mediated asymmetric reduction under the catalytic influence of the molecule **188** (4 mol %). The resulting secondary alcohols (*S*)-**167c-f** and (*S*)-**167h** were obtained in 88-96% enantiomeric purities (eq. 109, Table 7). The enantiomeric purities of the chiral alcohols (*S*)-**167c (91%)** and (*S*)-**167f (88%)** were determined by HPLC analysis using the chiral column, Chiralcel-OD with reference to the corresponding racemic alcohols. The enantiomeric purities of alcohols (*S*)-**167d (89%),** (*S*)-**167e (96%)** and (*S*)-**167h** (92%) were determined by ^{1}H NMR (200 MHz) analysis of the corresponding chiral acetates in presence of chiral shift reagent, Eu(hfc)$_3$, with reference to corresponding racemic acetates.



166c-f, 166h (*S*)-**167c-f, (*S*)-167h** 88-96% *ee* (eq. 109)

X = Br, Cl
Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl

Table 6. Asymmetric reduction of phenacyl bromide (166b) with varying catalytic amounts of 188[a]

Entry	Catalyst 188 (mol %)	Yield (%)[b] (*S*)-**167b**	Enantiomeric purity (%)[c] (*S*)-**167b**	Configuration[d]
1	2	81	71	***S***
2	3	80	87	***S***
3	4	**88**	91	***S***
4	5	80	89	***S***
5	7	84	87	***S***
6	10	86	83	***S***

[a] All reactions were carried out on 0.5 mM scale of phenacyl bromide (166b) with 0.5 mM of $BH_3.SMe_2$ in the presence of **188** in toluene for 1 h at 110 °C.

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

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

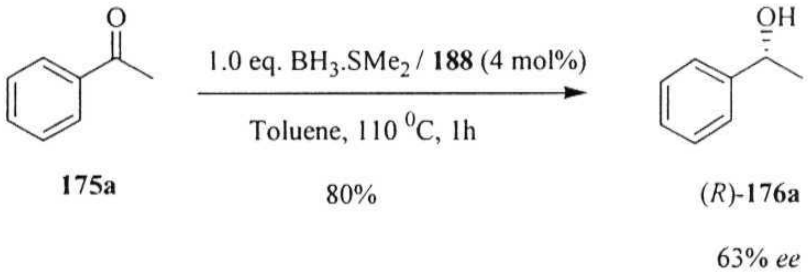
[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[162]

Table 7. Asymmetric reduction of α-halo ketones using the catalyst 188[a]

Substrate	Ar	X	Product	Yield(%)[b]	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)[d]
166a	Phenyl	Cl	(*S*)-**167a**	91	+42.1 (*c* 1.0, C_6H_{12})	*S*	86
166b	Phenyl	Br	(*S*)-**167b**	88	+41.5 (*c* 1.2, $CHCl_3$)	*S*	91
166c	4-Methylphenyl	Br	(*S*)-**167c**	94	+39.9 (*c* 1.1, $CHCl_3$)	*S*	91
166d	4-Chlorophenyl	Br	(*S*)-**167d**	92	+39.0 (*c* 1.0, $CHCl_3$)	*S*	89[e]
166e	4-Bromophenyl	Br	(*S*)-**167e**	89	+33.8 (*c* 2.4, $CHCl_3$)	*S*	96[e]
166f	4-Methylphenyl	Cl	(*S*)-**167f**	92	+44.0 (*c* 1.0, $CHCl_3$)	*S*	88
166h	4-Nitrophenyl	Br	(*S*)-**167h**	90	+33.2 (*c* 1.0, $CHCl_3$)	*S*	92[e]

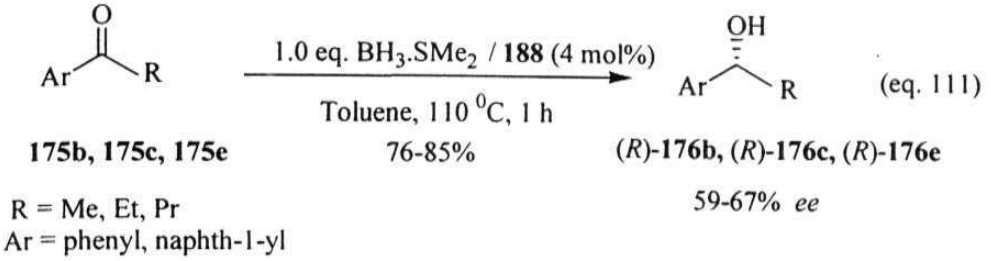
[a] All reactions were carried out on 1 mM scale of α-halo ketone (**166a-f, 166h**) with 1 mM of $BH_3.SMe_2$ in the presence of **188** (4 mol%) in toluene for 1 h at 110 ^{0}C. [b] Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes). [c] Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.[162,165] [d] Determined by HPLC analysis using the chiral column, Chiralcel-OD. [e] Enantiomeric purities were determined by ^{1}H NMR (200 MHz) spectral analyses of the acetates in the presence of the chiral shift reagent, $Eu(hfc)_3$, with reference to the corresponding racemic acetates.

With a view to examine the catalytic efficiency of (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(188),** we have also performed the reduction of acetophenone **(175a)** under the influence of the molecule **188** (4 mol%) with $BH_3.SMe_2$. The resulting 1-phenylethanol **(176a)** was obtained in 63% enantiomeric purity with *R*-configuration (eq. 110). The enantiomeric purity was determined by HPLC analysis using the chiral column, Chiralcel-OD with reference to the corresponding racemic alcohol (±)-**176a**.



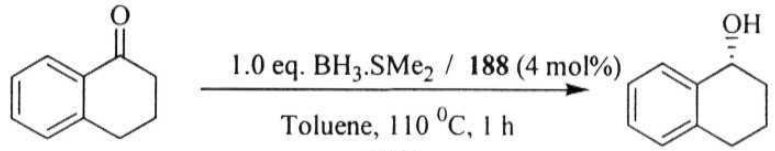
175a (*R*)-176a 63% *ee* (eq. 110)

To understand the applicability of this catalyst 188. we have subjected the representative prochiral ketones (175b-e) to the borane-mediated reduction under the influence of 4 mol% catalyst 188. The resulting secondary alcohols [(*R*)-**176b-e**] were obtained in 59-70% enantiomeric purities (eq. 111 & 112, Table 8). The structure of these molecules were established by IR, ^1H and ^{13}C NMR spectral data. The enantiomeric purities of the chiral alcohols (*R*)-**176b,** (*R*)-**176d** and (*R*)-**176e** were determined by HPLC analyses using chiral column, Chiralcel-OD with reference to their racemic alcohols. The enantiomeric purity of the chiral alcohol (*R*)-**176c** was determined by HPLC analysis using chiral column, Chiralcel-OD-H with reference to racemic alcohol (±)-**176c**.



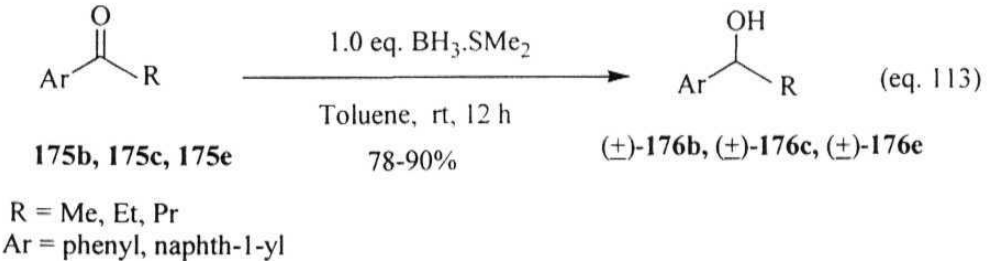
175b, 175c, 175e 76-85% **(*R*)-176b, (*R*)-176c, (*R*)-176e** 59-67% *ee* (eq. 111)

R = Me, Et, Pr
Ar = phenyl, naphth-1-yl



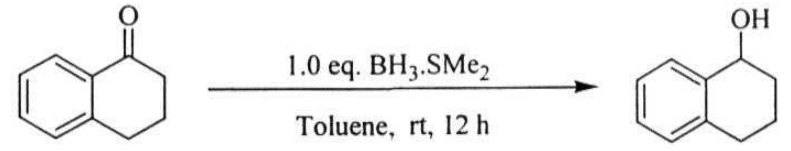
175d 71% **(*R*)-176d** 70% *ee* (eq. 112)

The required racemic alcohols (±)-**176b-e** were obtained by the reduction of the corresponding ketones **175b-c** with $BH_3.SMe_2$ in toluene solvent (eq. 113, 114).



175b, 175c, 175e 78-90% **(±)-176b, (±)-176c, (±)-176e** (eq. 113)

R = Me, Et, Pr
Ar = phenyl, naphth-1-yl



175d 81% **(±)-176d** (eq. 114)

With a view to understand the mechanistic pathway of reduction process, we have attempted to recover the catalyst by carrying out the reaction of acetophenone **(176a)**

(2 mM) with $BH_3.SMe_2$ (2 mM) in the presence of the catalyst 188 (0.08 mM). However, we found that the catalyst is not recoverable as the catalyst is not intact in the reaction as evidenced by the ^{31}P NMR spectrum of the reaction mixture, which showed broad signals at 8 80-115 where as the ^{31}P NMR spectrum of the original catalyst showed a single peak at 8 19.88. To understand the nature of the catalyst, we have also treated the molecule 188 (0.1 mM) with $BH_3.SMe_2$ (0.2 mM) in toluene (0.5 mL) for 10 minutes at reflux temperature and recorded ^{31}P NMR spectrum of the reaction mixture, which showed broad signals at 8 85-125. Since the enantioselectivities are also reasonably high in the case of acetophenone (175a) and other ketones 175b-e, it probably indicates that diazaborolidine is not generated during the reaction process.[166] From these studies, it is clear that the catalyst is not intact, probably decomposing during the course of reaction. Though the nature of the catalyst and the reaction pathway are not clearly understood, we have developed a novel chiral catalytic source for the borane-mediated asymmetric reduction of prochiral ketones, particularly α-halo ketones, to provide the resulting secondary alcohols up to 96% enantiomeric purities.

In conclusion, we have demonstrated the potential of (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (188) containing proximal hydroxyl group for the borane-mediated asymmetric reduction of prochiral ketones providing the resulting secondary alcohols in moderate to high enantioselectivities.

Table 8: Enantioselective reduction of prochiral ketones using the catalyst 188[a]

Ketone	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)[d]
Acetophenone (**175a**)	(*R*)-**176a**	80	+29.0 (*c* 1.0, MeOH)	*R*	63
Propiophenone (**175b**)	(*R*)-**176b**	85	+30.7 (*c* 1.9, $CHCl_3$)	*R*	67
Butyrophenone (**175c**)	(*R*)-**176c**	83	+28.0 (*c* 0.7, benzene)	*R*	59[e]
α-Tetralone (**175d**)	(*R*)-**176d**	71	-16.4 (*c* 0.75, MeOH)	*R*	70
1-Acenaphthone (**175e**)	(*R*)-**176e**	76	+50.3 (*c* 1.08, ether)	*R*	63

[a] All reactions were carried out on 1 mM scale of prochiral ketone with 1 mM of $BH_3.SMe_2$ in the presence of **188** (4 mol%) in toluene for 1 h at 110 ^{0}C.

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

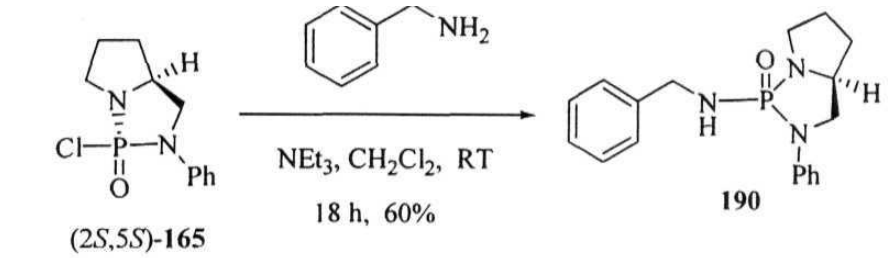
[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.[23,167,169,170]

[d] Enantiomeric purities were determined by the HPLC analyses using the chiral column, Chiralcel-OD.

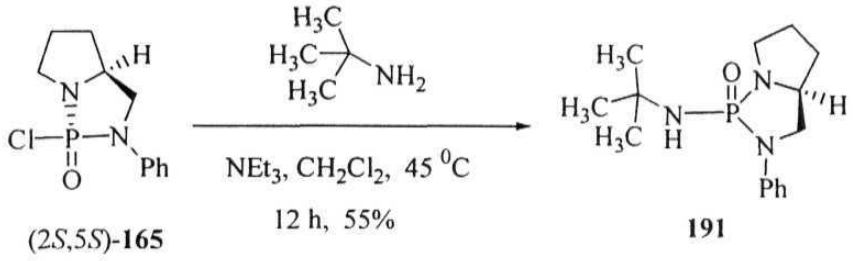
[e] Enantiomeric purity was determined by the HPLC analysis using the chiral column, Chiralcel-OD-H.

Towards novel chiral catalysts containing N-P=O structural frame work for the borane-mediated asymmetric reduction of prochiral ketones

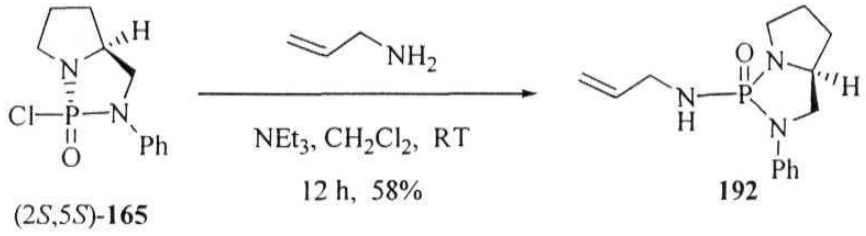
With a view to understand the influence of various amino groups of varying steric requirements on phosphorous in the (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane moiety, we have planned to prepare representative catalysts containing different amino groups of varying steric requirements on phosphorous for the borane-mediated asymmetric reduction of prochiral ketones. In this direction, we have first selected three representative molecules 190-192 containing (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety for our study. The required chiral catalysts (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (190), (5*S*)-1,3-diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (191) and (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (192) were prepared *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with corresponding amine as shown in equations 115-117. The structures of all these compounds were established by IR, ^{1}H NMR (Spectrum 20, 22, 24), ^{13}C NMR (Spectrum 21, 23, 25), ^{31}P NMR (Spectrum 26), mass spectral data and elemental analyses.



(eq. 115)

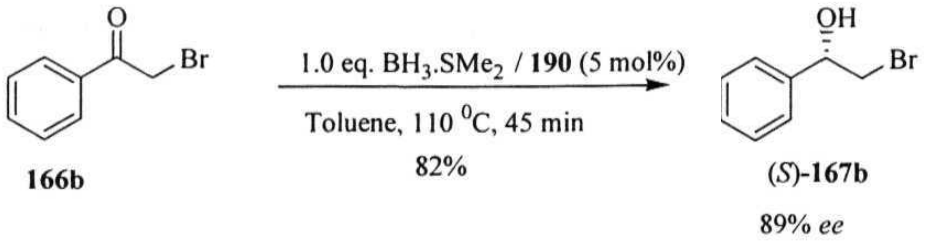


(eq. 116)



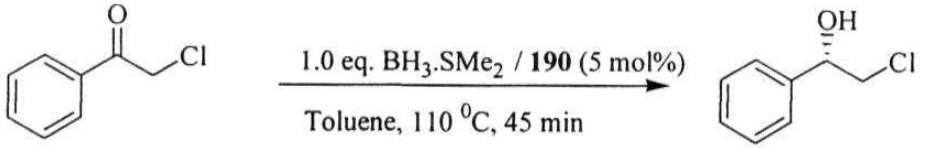
(eq. 117)

We have first examined the borane-mediated asymmetric reduction of phenacyl bromide (166b) under the influence of the chiral molecule 190 with different catalytic amounts. The best results were obtained when phenacyl bromide (166b) (1mM) was treated with borane-dimethyl sulfide (1 mM) under the influence of 190 (5 mol%) in refluxing toluene for 45 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] with 89% enantiomeric purity in 82% yield (eq. 118, Table 9). The enantiomeric purity of the alcohol (*S*)-**167b** was determined by HPLC analysis (Chromatogram 11) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.



166b **(*S*)-167b** 89% *ee* (eq. 118)

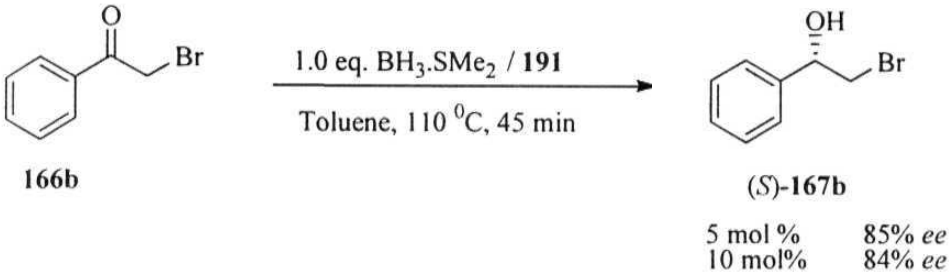
We have also examined the reduction of phenacyl chloride **(166a)** with phosphoramide **190** in the presence of borane, with a view to understand the selectivity when 'Cl' is present in the substrate instead of 'Br'. Thus, we have performed the reduction of phenacyl chloride **(166a)** (1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 5 mol% chiral phosphoramide **190** in refluxing toluene for 45 min. The desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] was obtained in 84% enantiomeric purity (eq. 119). The enantiomeric purity of the resulting secondary alcohol (*S*)-**167a** was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



166a **(*S*)-167a** 84% *ee* (eq. 119)

Similarly, we have also examined the potential of chiral molecule **191** as a catalytic source for the borane-mediated asymmetric reduction of phenacyl bromide (**166b**) Thus, we have performed the reduction of phenacyl bromide **(166b)** in the presence of chiral phosphoramide **191** (5 mol% and also 10 mol%) in refluxing toluene for 45 min to provide the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] in 85% (with 5

mol%) and 84% (with 10 mol%) enantiomeric purities (eq. 120). The enantiomeric purities of resulting secondary alcohols were determined by HPLC analyses (Chromatogram 12) using chiral column, Chiralcel-OD with reference to racemic alcohol **(±)-167b.**

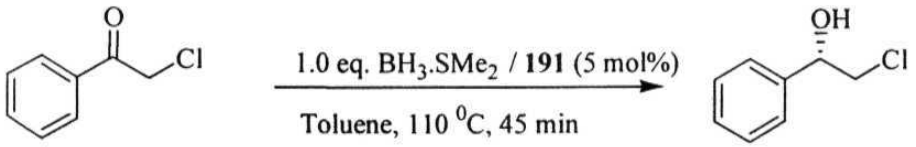


166b

(*S*)-167b

5 mol % 85% *ee*
10 mol% 84% *ee*

We have also examined the reduction of phenacyl chloride **(166a)** with catalyst **191.** Thus, the reduction of phenacyl chloride **(166a)** (1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 5 mol% chiral phosphoramide **191** in refluxing toluene for 45 min provided the desired alcohol (*S*)-2-chloro-1 -phenylethanol [(*S*)-**167a**)] in 65% enantiomeric purity (eq. 121). The enantiomeric purity of the resulting secondary alcohol (*S*)-**167a** was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



166a

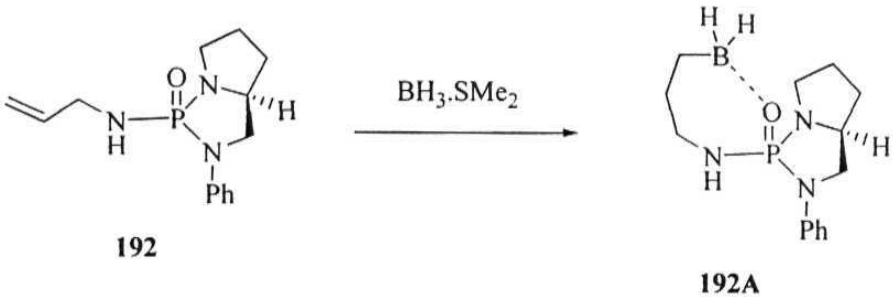
(*S*)-167a

65% *ee*

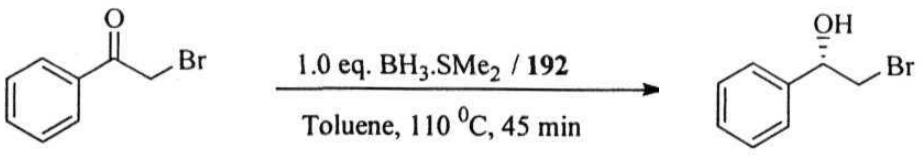
(eq. 121)

We have next selected (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(192)** containing the allylamine group on phosphorous in the (5*S*)-1,3-

diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety with a view to examine the influence of borane moiety **(192A)** which might have formed due to the hydroboration of the olefin in (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane **(192)** (eq. 122). Thus, we have carried out the reduction of phenacyl bromide **(166b)** in the presence of chiral phosphoramide **192** (5 mol% and 10 mol%) in refluxing toluene for 45 min to provide the desired alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] in 81% (with 5 mol%) and 83% (with 10 mol%) enantiomeric purities (eq. 123). The enantiomeric purities of resulting secondary alcohols were determined by HPLC analyses (Chromatogram 12) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.



192 **192A** (eq. 122)

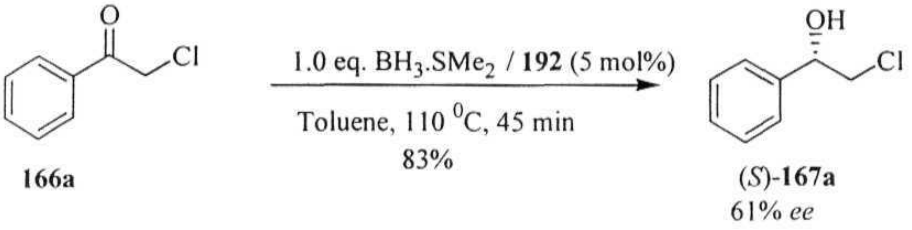


166b (*S*)-**167b** (eq. 123)

5 mol % 81% *ee*
10 mol% 83% *ee*

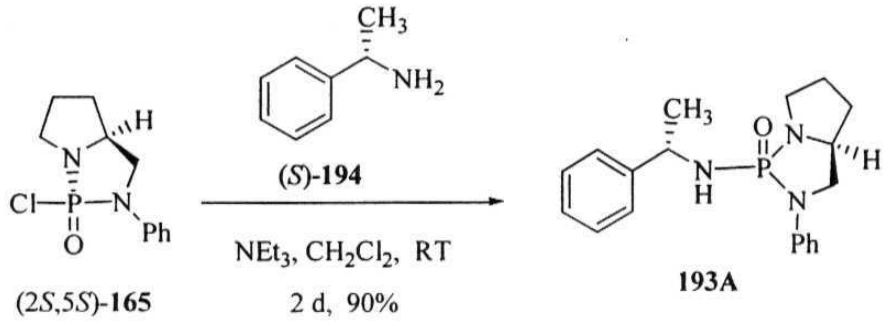
We have also examined the reduction of phenacyl chloride **(166a)** with phosphoramide **192** in the presence of borane. The reduction of phenacyl chloride **(166a) (1** mM) with

borane-dimethyl sulfide (1 mM) in the presence of 5 mol% chiral phosphoramide 192 in refluxing toluene for 45 min afforded the desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] in 61% enantiomeric purity (eq. 124). The enantiomeric purity of the resulting secondary alcohol was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



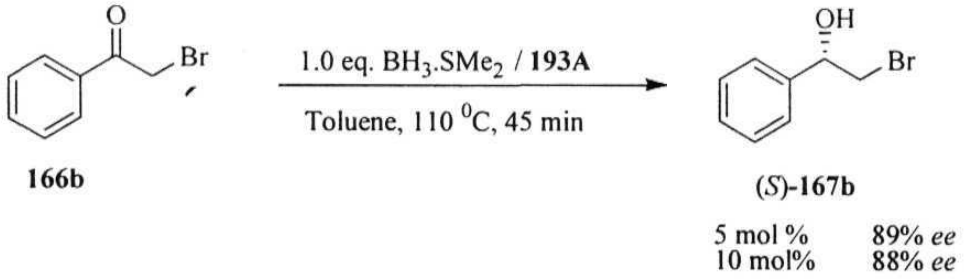
166a (*S*)-**167a** 61% *ee* (eq. 124)

Next we have directed our studies to investigate the role of chiral amine group on phosphorous in the bicyclic moiety [(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane moiety]. In this direction, we have first selected (*S*)-1-phenylethylamine [(*S*)-**194**]. Thus, we have prepared required (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193A) in 90% isolated yield *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with (*S*)-1-phenylethylamine [(*S*)-**194**] in the presence of triethylamine, after usual work-up followed by column chromatography (silica gel, 60% ethyl acetate in hexanes) (eq. 125). The structure of this compound was confirmed by IR, ^{1}H NMR (Spectrum 27), ^{13}C NMR (Spectrum 28), ^{31}P NMR (Spectrum 30), mass spectral data and elemental analysis.



(eq. 125)

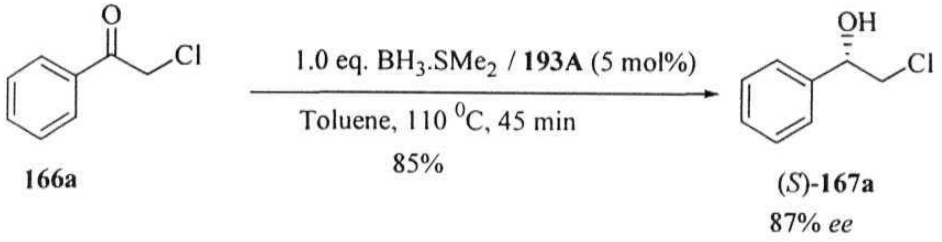
Then we have first carried out the reduction of phenacyl bromide **(166b)** in the presence of chiral phosphoramide **193A** (5 mol% as well as 10 mol%) in refluxing toluene for 45 min under the influence of borane. In both cases the resulting secondary alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] was obtained in similar enantioselectivities [89% (with 5 mol%) and 88% (with 10 mol%) enantiomeric purities] (eq. 126). The enantiomeric purities of resulting secondary alcohols were determined by HPLC analyses (Chromatogram 13) using chiral column, Chiralcel-OD with reference to racemic alcohol (+)-167b.



(eq. 126)

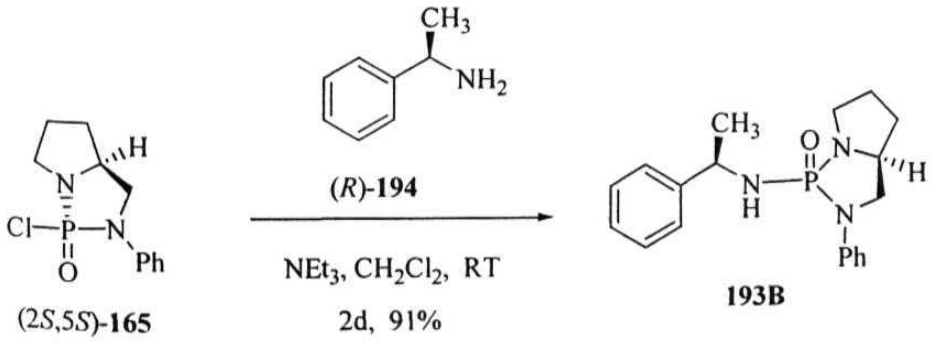
Similar reduction of phenacyl chloride **(166a,** 1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 5 mol% chiral phosphoramide **193A** in refluxing toluene for 45 min gave the desired alcohol (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] in 87% enantiomeric purity (eq. 127). The enantiomeric purity of the resulting secondary

alcohol (*S*)-**167a** was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



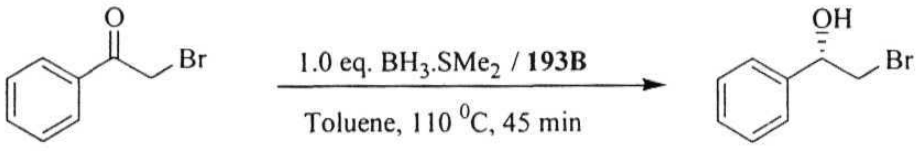
(eq. 127)

With a view to see the effect of (*R*)-1-phenylethylamine [(*R*)-**194**] group on phosphorous in the bicyclic moiety [(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane moiety] and to compare the results with that of (5)-l-phenylethylamine group, we have prepared the (5*S*)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**193B**) *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with (i?)-l-phenylethylamine [(*R*)-**194**] in the presence of triethylamine, in 91% isolated yield after usual work-up followed by column chromatography (silica gel, 60% ethyl acetate in hexanes) (eq. 128). The structure of this compound was confirmed by IR, ^{1}H NMR, ^{13}C NMR (Spectrum 29), ^{31}P NMR (Spectrum 30), mass spectral data and elemental analysis.



(eq. 128)

We have conducted the reduction of phenacyl bromide **(166b)** using 5 mol% also 10 mol% chiral phosphoramide **193B** in refluxing toluene for 45 min under the influence of borane. In both cases the resulting secondary alcohol (*S*)-2-bromo-1-phenylethanol **[(*S*)- 167b)]** was obtained with similar enantioselectivities (88% *ee* with 5 mol% and 89% *ee* with 10 mol%) (eq. 129). The enantiomeric purities of resulting secondary alcohols were determined by HPLC analyses (Chromatogram 13) using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**.

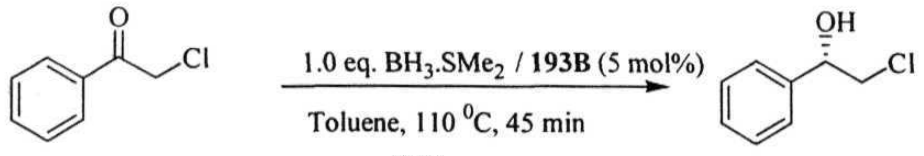


166b (*S*)-**167b**

5 mol% 88% *ee*
10 mol% 89% *ee*

(eq. 129)

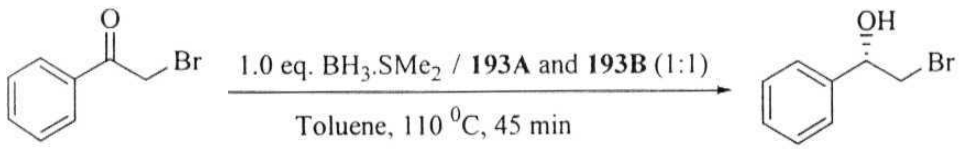
We have also performed the reduction of phenacyl chloride **(166a)** with chiral phosphoramide **193B** in the presence of borane. Thus, the reduction of phenacyl chloride **(166a,** 1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 5 mol% chiral phosphoramide **193B** in refluxing toluene for 45 min gave the desired alcohol (*S*)-2-chloro-1-phenylethanol **[(*S*)-167a]** in 84% enantiomeric purity (eq. 130). The enantiomeric purity of this alcohol was determined by HPLC analysis using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**.



166a (*S*)-**167a**
84% *ee*

(eq. 130)

With a view to examine the effect of combination of both the catalysts (55)-l,3-diaza-2-[(*S*)-1 -phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**193A**) and (5*S*)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193B), we have carried out the reduction of phenacyl bromide (166b) in the presence of 1:1 mixture of chiral phosphoramides 193A & 193B (with 5 mol% also with 10 mol%) in refluxing toluene for 45 min under the influence of borane. In both cases the resulting secondary alcohol (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] was obtained in similar enantioselectivities *i. e.*, 85% (with 5 mol%) and 86% (with 10 mol%) enantiomeric purities (eq. 131). The enantiomeric purities of resulting secondary alcohols were determined by HPLC analyses (Chromatogram 13) using chiral column, chiralcel-OD with reference to racemic alcohol (±)-**167b**.



166b (*S*)-**167b** (eq. 131)

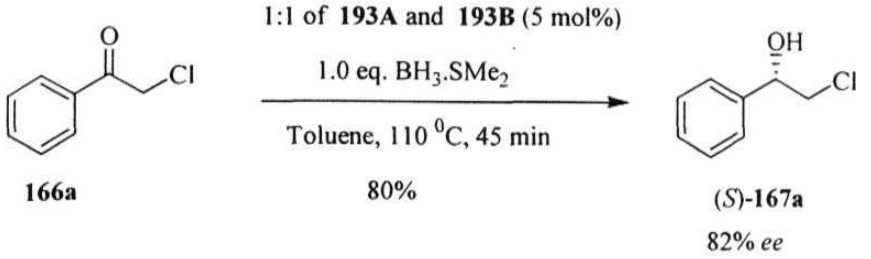
5 mol% (2.5 mol% 193A and 2.5 mol% 193B) 85% *ee*
10 mol% (5 mol% **193A** and 5 mol% **193B**) 86% *ee*

Then we have performed the reduction of phenacyl chloride (166a, 1 mM) with borane-dimethyl sulfide (1 mM) in the presence of 2.5 mol% 193A and 2.5 mol% 193B in refluxing toluene for 45 min. The desired alcohol (*S*)-2-chloro-1-phenylethanol [(5)-**167a**] was obtained in 82% enantiomeric purity (eq. 132). The enantiomeric purity of this alcohol (5)-167a was determined by HPLC analysis using chiral column, chiralcel-OD with reference to racemic alcohol (±)-**167a**.

Table 9: Asymmetric reduction of phenacyl bromide (166b)[a]: A comparison of catalytic efficiency of catalysts 190-192, 193A, 193B and 1:1 mixture of 193A & 193B

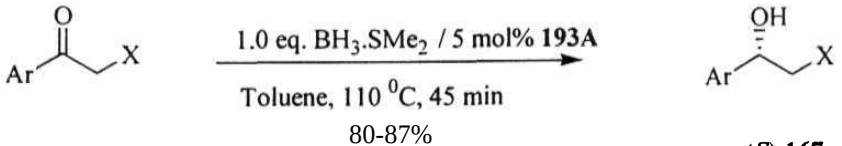
Catalyst	Mol %	Yield (%)[b] (*S*)-**167b**	Enantiomeric purity (%)[c] (*S*)-**167b**	Configuration[d]
190	5	82	89	*S*
	10	87	86	*S*
	20	85	81	*S*
191	5	86	85	*S*
	10	83	84	*S*
192	5	84	81	*S*
	10	82	83	*S*
193A	5	80	89	*S*
	10	85	88	*S*
193B	5	81	88	*S*
	10	82	89	*S*
193A & 193A (1:1)	5	80	85	*S*
	10	82	86	*S*

[a] All reactions were carried out on 1 mM scale of phenacyl bromide (**166b**) with 1 mM of $BH_3.SMe_2$ in the presence of catalyst in toluene for 45 min at 110 ^{0}C. [b] Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes). [c] Determined by HPLC analysis using the chiral column, Chiralcel-OD. [d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[162]



(eq. 132)

Since the chiral phosphoramide (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193A) provided better enantioslectivities in the borane-mediated asymmetric reduction of phenacyl chloride (166a) and phenacyl bromide (166b) than the other phosphoramides 190-192, 193B (Table 9, 10) we have employed this catalyst 193A to reduction of representative class of prochiral α-halo ketones 166c-f, 166h to provide the chiral secondary alcohols (*S*)-**167c-f,** (*S*)-**167h** in high enantiomeric purities (89-94%) (eq. 133, Table 11). Enantiomeric purities of the chiral alcohols (*S*)-**167c,** (*S*)-**167f** were determined by HPLC analyses using the chiral column, Chiralcel-OD with reference to the corresponding racemic alcohols. Enantiomeric purities of alcohols (*S*)-**167d,** (*S*)-**167e** and (*S*)-**167h** were determined by ^{1}H NMR spectral analyses of their acetates in the presence of chiral shift reagent, Eu(hfc)$_3$, with reference to their corresponding racemic acetates.



(eq. 133)

X = Br, Cl
Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl

Table 10: Asymmetric reduction of phenacyl chloride (166a) *: A comparison of catalytic potential of catalysts 190-192, 193A, 193B and 1:1 mixture of 193A & 193B

Catalyst	Mol %	Yield (%)[b] (*S*)-**167a**	Enantiomeric purity (%)[c] (*S*)-167a	Configuration[d]
190	5	82	84	***S***
191	5	81	65	***S***
192	5	83	61	***S***
193A	**5**	85	87	***S***
193B	5	83	84	***S***
193A&193B(1:1)	5	80	82	***S***

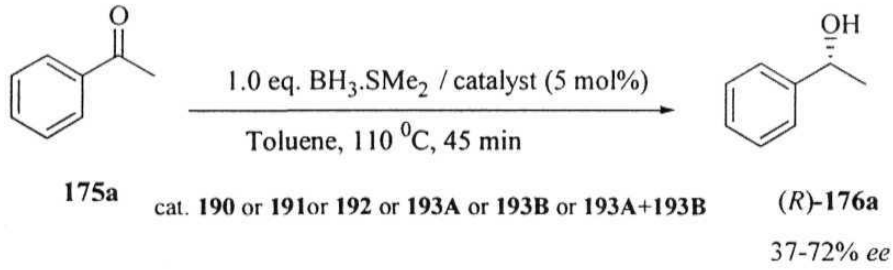
[a] All reactions were carried out on 1 mM scale of phenacyl chloride (166a) with 1 mM of $BH_3.SMe_2$ in the presence of catalyst in toluene for 45 min at 110 °C. [b] Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes). [c] Determined by HPLC analysis using the chiral column, Chiralcel-OD. [d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[162]

Table **11:** Asymmetric reduction of prochiral a-halo ketones using the catalyst **193A**[a]

Substrate Ar	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)[d]
4-Methylphenyl (**166c**)	Br	(*S*)-**167c**	84	+37.87 (*c* 1.08, $CHCl_3$)	***S***	91
4-Chlorophenyl **(166d**)	Br	(*S*)-**167d**	87	+39.0 (*c* 1.0 $CHCl_3$)	***S***	89[e]
4-Bromopheny! **(166e)**	Br	(*S*)-**167e**	80	+32.23 (*c* 0.9, $CHCl_3$)	***S***	94[e]
4-Methylphenyl **(166f)**	Cl	(*S*)-**167f**	82	+44.88 (c 1.0 $CHCl_3$)	***S***	89
4-Nitrophenyl **(166h)**	Br	(*S*)-**167h**	82	+32.1 (*c* 1.0 $CHCl_3$)	***S***	91[e]

[a] All reactions were carried out on 1 mM scale of a-halo ketone with 1 mM of $BH_3.SMe_2$ in the presence of catalyst 193A (5 mol%) in toluene for 45 min at 110 °C. [b] 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 the specific rotation with that of reported molecules.[162.165] [d]Determined by HPLC analyses using the chiral column, Chiralcel-OD. [e] Enantiomeric purities were determined by ^1H NMR (200 MHz) spectral analyses of the acetates in the presence of the chiral shift reagent, $Eu(hfc)_3$, with reference to the corresponding racemic acetates.

With a view to have proper understanding of the chiral directing potential of the catalysts **190-192, 193A, 193B** and combination of **193A** and **193B,** we have reduced acetophenone **(175a)** under the influence of these catalysts **190-192, 193A**, **193B** and combination of **193A** and **193B** in the presence of $BH_3.SMe_2$ (eq. 134, Table 12). The resulting alcohols (*R*)-**176a** were obtained in 37-72% enantiomeric purities. The enantiomeric purities of alcohols were determined by HPLC analyses using chiral column, Chiralcel-OD with reference to corresponding racemic alcohol (±)-**176a**. The results are summarized in Table 12.



(eq. 134)

Since the chiral phosphoramide (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A)** provided better enantioselectivity than the other catalysts in the case of acetophenone **(175a)** (72% *ee),* we have used this chiral phosphoramide **193A** for the reduction of representative class of aryl alkyl ketones **175b-d, 168-170** with a view to understand the generality of the catalyst **193A** . The resulting secondary alcohols (*R*)-**176b-d**, (*R*)-**195a-c** were obtained in 43-76% enantiomeric purities (eq. 135, 136, Table 13). The enantiomeric purities of alcohols (*R*)-**176b-d** were determined by HPLC analyses using chiral column, Chiralcel-OD

with reference to corresponding racemic alcohols. The required racemic alcohols (±)-196a-c were prepared *via* the treatment of corresponding prochiral ketones with $BH_3.SMe_2$ in toluene (Scheme 22).

Table **12: Borane-mediated asymmetric reduction of acetophenone (175a)[a]: A comparison of catalytic potential of molecules 190-192, 193A, 193B and 1:1 mixture of 193A& 193B**

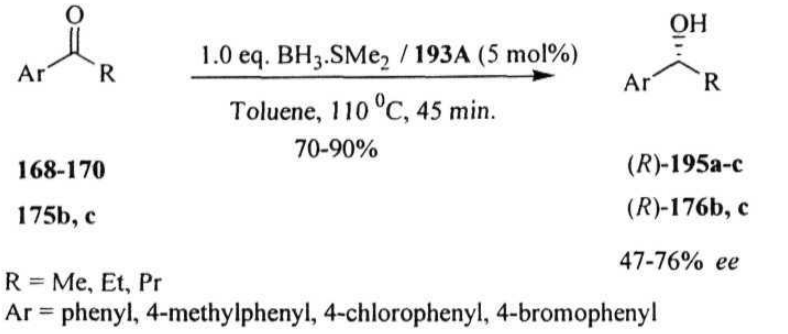
Catalyst	Yield (%)[b] (*R*)-**176a**	Enantiomeric purity (%)[c] (*R*)-**176a**	Configuration[d]
190	74	62	***R***
191	84	44	***R***
192	82	37	***R***
193A	87	72	***R***
193B	82	70	***R***
193A & **193B** (1:1)	**72**	60	***R***

[a] All reactions were carried out on 1 mM scale of acetophenone **(175a)** with 1 mM of $BH_3.SMe_2$ in the presence of catalyst in toluene for 45 min at 110 C.

Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).

Determined by HPLC analysis using the chiral column, Chiralcel-OD.

Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[167]



168-170

175b, c

(*R*)-**195a-c**

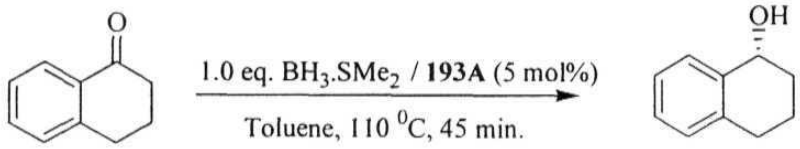
(*R*)-**176b, c**

47-76% *ee*

(eq. 135)

R = Me, Et, Pr

Ar = phenyl, 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl



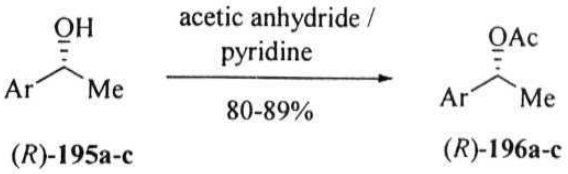
175d

(*R*)-**176d**

43% *ee*

(eq. 136)

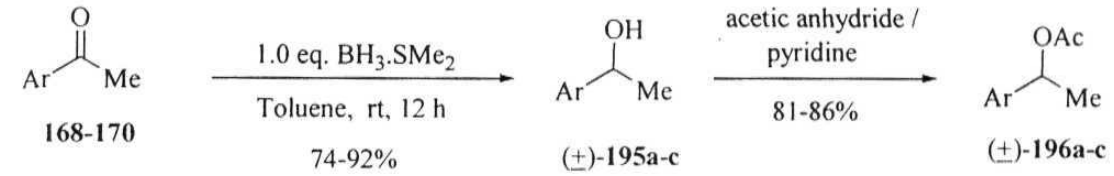
Our efforts to determine the enantiomeric purities of alcohols (*R*)-**195a-c** using HPLC analyses (chiral columns, chiralcel-OD and Chiralcel-OD-H) were not successful. However, the enantiomeric purities of these alcohols (*R*)-**195a-c** were determined by HPLC analyses (Chromatogram 15, 16) of their acetates (*R*)-**196a-c** using chiral column, Chiralcel-OJ-H with reference to corresponding racemic acetates (±)-196a-c. The desired chiral acetates (*R*)-**196a-c** were prepared *via* the treatment of corresponding chiral alcohols (*R*)-**195a-c** with acetic anhydride in presence of pyridine (eq. 137). The required racemic acetates (±)-**196a-c** were prepared according to Scheme. 22.



(*R*)-**195a-c** (*R*)-**196a-c** (eq. 137)

Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl

Scheme 22



168-170 (±)-**195a-c** (±)-**196a-c**

Ar = 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl

From these studies, it is quit clear that (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenyl-bicyclo(3.3.0)octane moiety (bicyclic phosphorous moiety) directs the reaction face and other groups on phosphorous has no significant role on the facial selectivity. These studies also clearly emphasized that the actual chiral directing group is (*S*)-2-anilinomethylpyrrolidine moiety.

Table 13: Enantioselective reduction of aryl alkyl ketones using the catalyst 193A[a]

Ketone	Product	Yield (%)[b]	$[\alpha]_D^{25}$	E.e (%)[c]	Conf.[e]
Acetophenone (175a)	(*R*)-176a	87	+32.6 (c 1.60, MeOH)	72	***R***
Propiophenone **(175b)**	(*R*)-**176b**	81	+27.84 (*c* 0.79, $CHCl_3$)	61	***R***
Butyrophenone **(175c)**	(*R*)-**176c**	80	+21.95 (c 1.5, benzene)	47	***R***
α-tetralone (175d)	(*R*)-**176d**	72	-11.56 (*c* 0.9 MeOH)	43	***R***
4-Methylacetophenone(168)	(*R*)-**195a**	77	+22.87 (*c* 0.6, MeOH)	51[d]	***R***
4-Chloroacetophenone(169)	(*R*)-**195b**	70	+38.4 (*c* 1.25, Et_2O)	76[d]	***R***
4-Bromoacetophenone (170)	(*R*)-**195c**	90	+30.0 (c 1.0, $CHCl_3$)	74[d]	***R***

[a] All reactions were carried out on 1 mM scale of prochiral ketone with 1mM of $BH_3.SMe_2$ in the presence of **193A** (5 mol%) in toluene for 45 min at 110 °C.

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

[c] Enantiomenc purities were determined by HPLC analyses using the chiral column, Chiralcel-OD.

[d]. Enantiomeric purities were determined by HPLC analyses of the corresponding acetates using the chiral column, Chiralcel-OJ-H.

[e] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[23,167,169,171]

CONCLUSIONS

We have made a considerable success in achieving our objectives mentioned in the beginning of this chapter. We have designed and synthesized novel chiral catalysts (1*R*, 2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl} -methylamino]cyclohexane (158) and 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (159) containing *N-P=O* structural framework having (*S*)-2-anilinomethylpyrrolidine moiety, for the borane-mediated reduction of prochiral α-halo ketones, thus providing a simple methodology for synthesis of 2-halo-1 -arylethanols with high enantiomeric purities. We have successfully employed (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (2*S*,5*S*)-**165** as a catalytic chiral source for the borane-mediated asymmetric reduction of prochiral a-halo ketones to provide the desired (*S*)-secondary alcohols in 81-91% enantiomeric purities. Though, we do not understand the structure of the actual catalyst / catalytic species responsible for enantioselectivity, we have for the first time, demonstrated the potential of ***N-P(=O)Cl*** framework as a chiral catalytic source to generate a recoverable, reusable and air stable catalyst for the borane-mediated enantioselective reduction processes. We have also developed a chiral catalyst (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-Phenylbicyclo(3.3.0)octane (188) containing a proximal hydroxyl group for the borane-mediated asymmetric reduction of prochiral ketones, thus providing the resulting secondary alcohols upto 96% enantiomeric purities. We have studied the applications

of various chiral catalysts **(190-192, 193A, 193B** and combination **of 193A** & **193B**) containing *N-P=O* structural framework obtained *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane with representative amines of varying steric requirements, to understand the effect of substituents on phosphorous in the (5*S*)-1,3-diaza-2-phos-pha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety for the borane-mediated asymmetric reduction of prochiral ketones. The resulting secondary alcohols were obtained in moderate to high enantiomeric purities.

EXPERIMENTAL

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

Boiling Points: Boiling points refer to the temperature measured using short path distillation units and are uncorrected.

Elemental Analysis: Elemental analyses were performed on a Perkin–Elmer 240C-CHN 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 or solution spectra in CH_2Cl_2.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 spectrometer. ^1H NMR (200 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with TMS (8 = 0 ppm) as internal standard. C NMR (50 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with its middle peak of the triplet (δ = 77.10 ppm) as internal standard. ^{31}P NMR (81 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, using 85% H3PO4 (δ = 0 ppm) **as** external standard.

Spectral assignments are as follows: (1) chemical shifts on the 6 scale, (2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, b = broad, d of ABq = doublet of AB quartet, (3) number of hydrogens integrated for the signal, (4) coupling constant J in Hertz.

Mass Spectral Analysis: Mass spectra were recorded either on VG7070H mass spectrometer using EI technique or on Auto spec mass spectrometer using LSIMS technique (EI & FAB) and HP 5989 A (LC) (CI-method) 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.

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 iodine vapor or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh). High pressure liquid chromatography (HPLC) analysis was carried out on Shimadzu LC-10AD Chromatopac equipped with SPD-10A UV-VIS detector using HPLC grade solvents. Enantiomeric purities were determined using chiral column. Chiralcel-OD (24 cm), Chiralcel-OD-H (24 cm) and Chiralcel-OJ-H (24 cm) supplied by Daicel, Japan.

X-ray Crystallography:

The X- ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (X = 0.71073 A^0) radiation with CAD4 software. The single crystal was fixed to a capillary head by an appropriate fixing material. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Stability of the crystal during the measurements was monitored measuring the intensity of the standard reflections after every one and half hour intervals. No appreciable variation of the crystal was detected. The data were reduced using XTAL program. No absorption correction was applied. The structure was resolved by direct methods and refined by full-matrix least-squares using the SHELXS-86 and SHELXL-93 program packages respectively.

General: All the solvents were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All reactions were monitored using Thin Layer Chromatography (TLC).

Resolution of *cis* / *trans*-1,2-diaminocyclohexane [(±)-160]:

Resolution was carried out following the literature procedure.[160]

To a stirred solution of L-(+)-tartaric acid (37.5 g, 250 mM) in distilled water (100 mL) was added a mixture of *cis* / *trans*-1,2-diaminocyclohexane [(±)-**160**] (60.1 mL, 490 mM) at a rate such that the reaction temperature just reached 70 ^{0}C. To the resulting solution was added glacial acetic acid (25 mL, 436 mM) at a rate such that the reaction temperature just reached 90 ^{0}C. A white precipitate formed immediately upon addition of the acid, and the slurry was vigorously stirred for 2 h. Then the reaction mixture was cooled to 5 ^{0}C and stirred for 2 h. The precipitate was collected by vacuum filtration and thus obtained, wet cake 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-(+) tartrate salt (31 g) as a white solid.

To this (*R*,*R*)- 1,2-diammoniumcyclohexane mono-(+)-tartratc salt, saturated KOH solution (100 mL) was added 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*)-**160**] as a low melting solid (9.16 g) in 68% yield (from tartaric acid salt).

Bp: 70-75 °C / 10 mm

$[\alpha]_D^{25}$: -23.13 (*c* 1.5, 1N HC1) [Lit.[172] $[\alpha]_D^{25}$: -25.0 (*c* 5, 1N HC1)].

IR (neat): v 3323 cm^{-1}

^{1}H NMR: 8 0.79-1.45 (m, 8H), 1.46-1.89 (m, 4H), 2.01-2.37 (m, 2H).

^{13}C NMR: δ 25.33,35.45,57.62.

(*R*,*R*)-1,2-Diaminocyclohexane-*N*,*N*′-diethyl dicarbamate [(*R*,*R*)-161]:

This compound was prepared according to the known procedure.[161]

To a stirred solution of NaOH (9.4 g, 235 mM) in water (45 mL), was added (*R*, *R*)-1,2-diaminocyclohexane (5.70 g, 50 mM) and the resulting mixture was stirred vigorously at 0 ^{0}C for 10 min. A solution of ethyl chloroformate (10.2 mL, 107 mM) in benzene (45 mL) was added over a period of 30 min at 0 °C. The mixture was then stirred vigorously at room temperature for 2 h. The resulting white precipitate was filtered and dried under vacuum (phosphorus pentoxide) for 3 h and recrystallized from absolute ethanol to provide 10.06 g (78%) of the desired dicarbamate (*R*,*R*)-**161** as a white solid.

Mp: 167-169 °C (Lit.[161] 166.5-168.5 °C)

$[\alpha]_D^{25}$: +43.25 (*c* 1.60, $CHCl_3$) [Lit.[161] $[\alpha]_D^{25}$: + 45.50 (*c* 1.0, $CHCl_3$)].

IR (KBr): ν 3412, 1680 cm^{-1}

^{1}H NMR: δ 1.22 (t, 6H, J=6.8 Hz), 1.59-1.89 (m, 4H), 1.95-2.20 (m, 4H), 3.32-3.48 (m, 2H), 4.09 (q, 4H, J=6.8 Hz), 4.95 (b, 2H).

^{13}C NMR: 5 14.49, 24.75, 32.73, 55.09, 60.58, 156.95.

(*R*,*R*)-*N*,*N*′-Dimethyl-1,2-diaminocyclohexane [(*R*,*R*)-162]:

This molecule was prepared according to the literature procedure.[161]

To a stirred suspension of LAH (5.5 g, 144.9 mM) in THF (200 mL) was added (*R*,*R*)-1,2-diaminocyclohexane-*N*,*N*′-diethyl dicarbamate [(*R*,*R*)-**161**] (4.9 g, 18.97 mM) portion wise at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was heated under reflux for 14 h. The resulting gray suspension was cooled to 0 ^{0}C. Water (6 mL), 15% NaOH (6 mL) and water (20 mL) were successively added, and stirring continued for 1 h at room temperature. The resulting white precipitate (lithium salts) was filtered off and rinsed with warm THF (2 x 50 mL). The filtrates were combined and the solvent was evaporated under reduced pressure. The residue was acidified (10% HC1) (pH=2) and extracted with dichloromethane (3 x 50 mL). The aqueous layer was treated with NaOH (10%) until basic pH, and then extracted with dichloromethane (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated to give a yellowish residue which solidified (low melting solid) to furnish 2.43 g (90% yield) of the desired amine (*R*,*R*)-**162**.

$[\alpha]_D^{25}$: -143.46 (*c* 1.50, $CHCl_3$) [Lit.[161] $[\alpha]_D^{25}$: -144.2 (c 1.15, $CHCl_3$)].

IR (neat): v 3300, 2930, 1448, 1145 cm^{-1}

^{1}H NMR: 8 0.8-1.45 (m, 4H), 1.60-3.33 (m, 8H), 2.46 (s, 6H).

^{13}C NMR: δ 24.66, 30.46, 33.12, 62.83.

(*S*)-5-Oxopyrrolidine-2-carboxanilide (164):

This molecule was prepared according to the known procedure.[158]

A mixture of L-glutamic acid **(163)** (10 g, 68 mM) and aniline (75 mL) was stirred for

1 h at 195-200 C. After 1 h, the reaction mixture becomes clear solution and stirring was continued for further 30 min. Aniline was distilled off under reduced pressure. The hot oily residue was dissolved in acetone (60 mL) and cooled. The solid was separated by filtration and crystallized from methanol, to provide (*S*)-5-oxopyrrolidine-2-carboxanilide **(164)** as a crystalline solid.

Mp: 185 °C (Lit.[158] 189-191 °C)

Yield: 3.72 g (27%)

$[\alpha]_D^{25}$: +18.52 (*c* 0.98, MeOH) [Lit.[158] $[\alpha]_D^{25}$: +18.6 (*c* 1, MeOH)].

IR (KBr): v 3327, 1666 cm^{-1}

^1H NMR (20% DMSO-d_6 in $CDCl_3$): δ 2.09-2.51 (m, 4H), 4.12-4.32 (m, 2H), 4.60 (b, 1H), 6.91-7.10 (m, 1H), 7.11-7.32 (m, 2H), 7.33-7.68 (m, 2H), 9.15 (bs, 1H).

^{13}C NMR (20% DMSO-d_6 in $CDCl_3$): 5 25.42, 29.47, 57.47, 120.17, 124.27, 128.76, 137.98, 170.72, 178.90.

(*S*)-2-Anilinomethylpyrrolidine (3):

This compound was prepared according to the literature procedure.

To a stirred suspension of lithium aluminum hydride (2.99 g, 78.78 mM) in THF (90 mL), (*S*)-5-oxopyrrolidine-2-carboxanilide (164) (6.02 g, 29.5 mM) was added portion wise at 0 °C. After the addition was complete, the reaction mixture was refluxed for 4 h with stirring. The reaction mixture was cooled to 5 °C and water (4 mL) was added

carefully by dropwise, followed by addition of 2.5 N sodium hydroxide solution. Then the reaction mixture was diluted with dichloromethane and stirred for 5 min. The organic layer was decanted and the residue was extracted with dichloromethane (3 X 100 mL). The combined organic layer was dried over Na_2SO_4. The Solvent was evaporated and the residue was distilled under reduced pressure to afford the (*S*)-2-anilinomethylpyrrolidine (3) as a viscous liquid (4.19 g) in 81% yield.

Bp: 118-121 ^{0}C / 0.4 mm (Lit.[158] 117-120 °C / 0.4 mm)

$[\alpha]_D^{25}$: +18.06 (*c* 1.5, EtOH) [Lit.[158] $[\alpha]_D^{25}$: +18.5 (*c* 1.087, EtOH)].

IR(neat): ν 3331 cm^{-1}

^{1}H NMR: 5 1.32-1.59 (m, 1H), 1.61-2.02 (m, 3H), 2.82-3.03 (m, 3H), 3.10-3.22 (m, 1H), 3.28-3.43 (m, 1H), 4.10 (b, 2H), 6.60-6.79 (m, 3H), 7.11-7.23 (m,2H).

^{12}C NMR: 5 25.81, 29.60, 46.56, 48.71, 57.76, 113.01, 117.24, 129.20. 148.40.

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane[(2*S*,5*S*)-165]:

This molecule was prepared according to the literature procedure.[159]

To a stirred solution of (*S*)-2-anilinomethylpyrrolidine (3) (4.4 g, 25 mM) and triethyl amine (6.96 mL, 50 mM) in THF (160 mL) was added $POCl_3$ (2.33 mL, 25 mM) in THF (20 mL) dropwise over 30 min at 0 °C. Then the reaction mixture was stirred for

2 h at room temperature. The salts formed, were filtered off and the THF solution was evaporated under reduced pressure. The residue, thus obtained, was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes). The solid, thus obtained, was crystallized from 1:1 mixture of ethyl acetate, hexanes to provide the desired (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-165] as white needles (3.7 g) in 58% yield.

Mp: 138-140 °C [Lit.[159] 135 ^{0}C]

$[\alpha]_D^{25}$: +127.2 (*c* 2.1, $CHCl_3$)

IR(KBr): v 1601, 1269 1172 cm^{-1}

^{1}H NMR: 5 1.51-1.79 (m, 1H), 1.92-2.25 (m, 3H), 3.08-4.28 (m, 5H), 7.01-7.42 (m, 5H).

^{13}C NMR: 5 27.03 (d, J=4.15 Hz), 30.98, 44.73, 50.75 (d, J=18.6 Hz), 58.58 (d, J=9.45 Hz), 117.85 (d, J=3.95 Hz), 123.22, 129.16, 140.01 (d, J=4.95 Hz).

^{31}P NMR: 5 18.47 ($CDCl_3$); 20.88 (DMSO-d_6).

MS (m/z): 257 (M^+)

Analysis calcd. for $C_{11}H_{14}ClN_2OP$: C, 51.47; H, 5.50; N, 10.91.

Found: C, 51.70; H, 5.47; N, 10.85.

(1*R*,2*R*)-1,2-Bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]cyclohexane (158):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane [(2*S*,5*S*)-**165**] (1.0 g, 3.92 mM) in CH_2Cl_2 (20 mL) were added triethylamine (0.793 g, 7.84 mM) and (1*R*,2*R*)-1,2-di(methylamino)cyclohexane [(*R*,*R*)-162] (0.278 g, 1.96 mM) at room temperature. After 20 h (monitored by TLC) the reaction mixture was diluted with water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed successively with water and brine and was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue, thus obtained, was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to afford the desired (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2yl}methylamino]cyclohexane (158) as a crystalline solid (0.863 g) in 76% yield.

Mp:	260-262 °C
$[\alpha]_D^{25}$:	+35.00 (*c* 1.40, $CHCl_3$)
IR (KBr):	v 2934, 1601, 1502, 1305, 1215 cm^{-1}
^1H NMR:	6 1.12-2.19 (m, 16H), 2.30 (s, 3H), 2.35 (s, 3H), 2.75-3.03 (m, 2H), 3.30-3.51 (m,2H), 3.54-4.04 (m,8H), 6.92-7.39 (m,10H).
^{13}C NMR:	5 25.52, 26.06, 30.62, 32.47, 45.43, 48.88 (d, J=16.3 Hz), 55.66, 58.07 (d, J=8.0 Hz), 117.47 (d, J=3.4 Hz), 121.27, 128.68.

141.64 (d, J=5.7 Hz).

^{31}P NMR: 5 23.37.

MS (FAB) (*m/z*): 583 $(M+H)^+$

Analysis calcd. for $C_{30}H_{44}N_6O_2P_2$: C, 61.84; H, 7.61; N, 14.42

Found: C, 61.75; H, 7.64; N, 14.52.

Asymmetric reduction of phenacyl chloride (166a) using 30 mol% (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]cyclohexane (158):

(1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}-methyllamino]cyclohexane **(158)** (87.39 mg, 0.15 mM) was first dried by azeotropic drying with anhydrous toluene (2 × 3 mL) under nitrogen. The phosphoramide **158** was then diluted with toluene (5 mL) and to this stirred solution, borane-dimethyl sulphide (38 mg, 0.5 mM) was added and the reaction mixture was heated to 110 ^{0}C. Once the temperature has stabilized at 110 °C, phenacyl chloride **(166a)** (77 mg, 0.5 mM) in toluene (1 mL) was added dropwise. After completion of the addition, the reaction mixture was stirred for a further 90 min (monitored by TLC) at 110 °C. Then the reaction mixture was allowed to cool to room temperature and quenched with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by

column chromatography (silica gel, 5% ethyl acetate in hexanes) to obtain the desired (*S*)-2-chloro-1-phenylethanol [(*S*)-**167a**] in 94% yield (73.6 mg), as a colorless oil.

$[\alpha]_D^{25}$: +39.7 (c 2.25, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee*].

Enantiomeric purity: 82% (determined by HPLC using chiral column, Chiralcel-OD).

IR (neat): v 3408 cm^{-1}

^1H NMR: 5 2.63 (d, 1H, J = 3.0 Hz), 3.59-3.82 (m, 2H), 4.88-4.96 (m, 1H). 7.28-7.49 (m, 5H).

^{13}C NMR: 8 50.77,74.11, 126.11, 128.45, 128.67, 140.10.

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min) of the racemic alcohol **(+)-167a** showed two peaks at 20.91 min *(S)* and 23.65 min *(R)* in 1:1 ratio on chiral column, Chiralcel-OD. Similar HPLC analysis of the chiral alcohol (*S*)-**167a** showed two peaks at 20.55 min (*S*) and 23.50 min *(R)* in the ratio of 91:9 indicating that its enantiomeric purity is 82%.

(±)-2-Chloro-1-phenylethanol [(±)-167a]:

To a stirred solution of phenacyl chloride **(166a)** (154.6 mg, 1 mM) in toluene (5 mL) was added $BH_3.SMe_2$ **(76** mg, 1mM) and refluxed for 2 h. Then the reaction mixture was allowed to cool to room temperature and quenched with methanol. The 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 (±)-2-chloro-1-phenylethanol [(+)-167a] as a colorless oil.

Yield: 91% (142 mg).

This molecule has identical IR, ^{1}H & ^{13}C NMR spectral data as that of the chiral molecule (*S*)-**167a**.

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of phenacyl bromide (**166b**) with $BH_3.SMe_2$ in the presence of 30 mol% (1*R*,2*R*)-1,2-bis[{(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl}methylamino]-cyclohexane **(158),** following the similar procedure described for the molecule (*S*)-167a.

Yield: 88%

$[\alpha]_D^{25}$: +39.4 (*c* 2.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*

Enantiomeric purity: 89% (determined by HPLC using chiral column, Chiralcel-OD).

IR(neat): ν 3387 cm^{-1}

^{1}H NMR: 5 2.62 (d, 1H, J = 3.8 Hz), 3.50-3.71 (m, 2H), 4.87-5.03 (m, 1H), 7.32-7.51 (m, 5H).

^{13}C NMR: 8 40.08, 73.84, 126.03, 128.47, 128.70, 140.43.

Determination of enantiomeric purity:

Racemic alcohol (±)-**167b** showed two peaks in equal intensity on HPLC analysis (chiral column, Chiralcel-OD, solvent system, hexanes: IPA / 90:10; flow rate: 0.5 mL / min; retention times: 17.11 min and 20.82 min) arising from *S* and *R* enantiomers. The chiral alcohol (*S*)-**167b** showed two peaks in 94.5:5.5 ratio [retention times: 17.09 min (*S*) and 20.80 min *(R)* respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 89%.

(±)-2-Bromo-1-phenylethanol [(±)-167b]:

This compound was obtained *via* the reaction of phenacyl bromide **(166b)** with $BH_3.SMe_2$ in toluene following the similar procedure described for the molecule (±)-**167a,** as colorless liquid.

Yield: 87%

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**167b**.

1,4-Bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (159):

This product was prepared *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] (1 g, 3.92 mM) with piperazine (0.169 g, 1.96 mM) at room temperature for 20 h following the similar procedure

mentioned for molecule **158,** as a crystalline solid (0.91 g), in 88% yield (after purification by column chromatography, silica gel , 1% methanol in ethyl acetate).

Mp: 260 °C (dec.)

$[\alpha]_D^{25}$: -59.40 (*c* 1.40, $CHCl_3$)

IR (KBr): ν 2957, 1602, 1500, 1300, 1224 cm^{-}

^1H NMR: 5 1.51-2.12 (m, 8H), 2.73-3.85 (m, 18H), 6.83-7.29 (m, 10H).

^{13}C NMR: 8 26.06, 32.07, 44.37, 44.97, 48.86 (d, J = 16.6 Hz), 57.88 (d, J = 8.0 Hz), 116.23 (d, J = 3.7 Hz), 121.04, 128.93, 141.57 (d, J = 5.4 Hz).

^{31}P NMR: δ 20.51

MS (ES) (*m/z*): 527 $(M+H)^+$

Analysis calcd. for $C_{26}H_{36}N_6O_2P_2$: C, 59.30; H, 6.89; N, 15.96.

Found: C, 59.42; H, 6.91; N, 15.85.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of phenacyl chloride (166a) with $BH_3.SMe_2$ in the presence of 30 mol % 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159),** following the similar procedure described for the molecule **(*S*)-167a** using the catalyst **158.**

Yield: **91%**

$[\alpha]_D^{25}$: +43.5 (*c* 2.4, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee*].

Enantiomeric purity: 90 % [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol **(+)-167a].**

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min) of the alcohol **(*S*)-167a** (for similar HPLC analysis of racemic alcohol see page no. 132) on chiral column, Chiralcel-OD showed two peaks at 20.90 min (*S*) and 23.63 min *(R)* in the ratio of 95:5 indicating that its enantiomeric purity is 90%.

This molecule has identical IR, ^1H & ^{13}C NMR data as that of the chiral molecule (*S*)-**167a,** prepared from the asymmetric reduction of phenacyl chloride **(166a)** using the catalyst **158** (page no. 132).

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was obtained *via* the asymmetric reduction of phenacyl bromide **(166b)** with $BH_3.SMe_2$ in the presence of 30 mol % 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (159), following the similar procedure described for the molecule **(*S*)-167a** using the catalyst **158,** as a colorless liquid.

Yield: 92%

$[\alpha]_D^{25}$: +42.45 (*c* 2.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), *R*-configuration, 93% *ee].*

Enantiomeric purity: 94 % (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

Racemic alcohol (±)-**167b** showed two peaks in equal intensity on HPLC analysis (Chiralcel-OD, solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min) retention times 20.45 min *(S)* and 23.96 min (*R*) arising from *S* and *R* enantiomers. The chiral alcohol (*S*)-**167b** showed two peaks at (retention times) 20.48 min (*S*) and 23.91 min *(R)* in the ratio of 97:3 on similar HPLC analysis, indicating that the reaction is 94 % enantioselective.

The spectral data (1R, ^{1}H & ^{13}C NMR) of this molecule are in the full agreement with that of the chiral molecule (*S*)-**167b**, prepared from the asymmetric reduction of phenacyl bromide **(166b)** using the catalyst **158** (page no. 133).

Tetrabutylammonium tribromide (TBA Br_3):

This compound was prepared following the literature procedure. [163]

To a stirred solution of tetrabutylammonium bromide (9.67 g, 30 mM) and potassium bromide (1.19 g, 10 mM) in water (60 mL) was added dropwise hydrobromic acid (48%, 7 mL) 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: 95% (13.73 g).

Mp: 74 °C (Lit.[163] 74-75 °C).

4-Methylphenacyl bromide (166c):

This molecule was prepared according to the known procedure.

To a stirred solution of 4-methylacetophenone (168) (4 mM, 0.54 g) in dichloromethane (50 mL)-methanol (20 mL) was added TBA Br_3 (4.4 mM, 2.12 g) at room temperature. After stirring for 5 h at 35 °C (until a decoloration of the orange solution), the solvent was removed and the residue, thus obtained, was extracted with ether (4 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was recrystallized from ethanol-water (1:2) to provide the 4-methylphenacyl bromide (166c) as a colorless solid.

Yield: 80% (0.68 g)

Mp: 49-51 °C (Lit.[163] 45-48 °C).

IR (KBr): v 1689 cm^{-1}

^1H NMR: 5 2.43 (s, 3H), 4.43 (s, 2H), 7.29 (d, 2H, J=8.0 Hz) 7.88(d, 2H, J=8.0 Hz).

^{13}C NMR: 5 21.7, 30.95, 129.03, 129.54, 131.54, 144.96, 190.88.

4-Chlorophenacyl bromide (166d):

This product was obtained as colorless needles *via* the treatment of *p*-chloroacetophenone (169) with TBA Br_3 following the similar procedure described for the molecule 166c.

Time: 6 h.

Yield:	84%
Mp:	94-96 °C (Lit.[163] 97-97.5 °C)
IR (KBr):	ν 1695 cm^{-1}
^{1}H NMR:	δ 4.40 (s, 2H), 7.47 (d, 2H, J=8.8 Hz), 7.93 (d, 2H, J=8.8 Hz).
^{13}C NMR:	δ 30.51, 129.18, 130.32, 132.23, 140.44, 190.0.

4-Bromophenacyl bromide (166e):

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

To a stirred solution of 4-bromoacetophenone **(170)** (0.995 g, 5 mM) in glacial acetic acid (2 mL), was added bromine (0.25 mL, 5 mM) at 15 °C. After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C. Thus obtained, crude solid was filtered, washed with ethanol till it become colorless and recrystallized from ethanol to furnish the pure 4-bromophenacyl bromide **(166e)** as colorless needles.

Yield:	68% (0.95 g)
Mp:	109-111 ^{0}C (Lit.[164] 109 ^{0}C)
IR (KBr):	v 1699 cm^{-1}
^{1}H NMR:	δ 4.40 (s, 2H), 7.63 (d, 2H, J=8.6 Hz), 7.85 (d, 2H, J=8.6 Hz).
^{13}C NMR:	δ 30.51, 129.22, 130.36, 132.16, 132.61, 190.33.

4-Methylphenacyl chloride (166f):

To a stirred suspension of $AlCl_3$ (1.48 g, 1.11 mM) in toluene (3 mL) at 10 °C was added, chloroacetyl chloride (0.564 g, 5 mM) dropwise over a period of 15 min. The reaction mixture was heated at 50 °C for 2 h. Then the reaction mixture was cooled to 0 °C and quenched with ice cooled water (8 mL) and extracted with ether (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product, thus obtained, was recrystallized from ether-hexane mixture (1:5) to provide the 4-methylphenacyl chloride (166f) as a white solid.

Yield:	30% (0.252 g)
Mp:	50-52 ^{0}C
IR (KBr):	v 1699 cm^{-1}
^{1}H NMR:	5 2.42 (s, 3H), 4.68 (s, 2H), 7.29 (d, 2H, J=8.2 Hz) 7.85(d, 2H, J=8.2 Hz).
^{13}C NMR:	6 21.45,45.95, 128.33, 129.33, 131.51, 144.80, 190.40.

4-Ethylphenacyl chloride (166g):

This compound was prepared by treatment of ethylbenzene with chloroacetyl chloride following the similar procedure described for the molecule **166f,** as a colorless solid.

Time: 2 h

Yield:	25%
Mp:	52-55 °C.
IR (KBr):	v 1690 cm^{-1}
^{1}H NMR:	δ 1.26 (t, 3H, J=7.0 Hz), 2.72 (q, 2H, J=7.0 Hz), 4.68 (s, 2H), 7.31 (d, 2H, J=8.0 Hz), 7.88 (d, 2H, J=8.0 Hz)
^{13}C NMR:	5 14.93,28.89,45.93, 128.29, 128.67, 131.90, 151.04, 190.59.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-167c]:

This molecule was prepared *via* the asymmetric reduction of 4-methylphenacyl bromide **(166c)** with $BH_3.SMe_2$ in the presence of 30 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159),** as a viscous liquid, following the similar procedure described for the molecule **(S)-167a** using the catalyst **158**

Yield:	83%
$[\alpha]_D^{25}$:	+41.80 (*c* 1.0, $CHCl_3$)
Enantiomeric purity:	95% (determined by HPLC using chiral column, Chiralcel-OD).
IR (neat):	ν 3375 cm^{-1}
^{1}H NMR:	6 2.35 (s, 3H), 2.54 (b, 1H), 3.49-3.68 (m, 2H), 4.90 (1H, dd, J=8.6, 3.8 Hz), 7.18 (d, 2H, J=8.0 Hz), 7.27 (d, 2H, J=8.0 Hz).
^{13}C NMR:	8 21.19,40.14, 73.70, 125.93, 129.36, 137.46, 138.25.

Determination of enantiomeric purity:

HPLC analysis (chiral column, chiralcel-OD, solvent system, hexanes : IP A / 95:05; flow rate: 0.5 mL / min) of the racemic compound (±)-**167c** showed two peaks at 26.01 min (*S*) and 28.53 min *(R)* in 1:1 ratio. Similar HPLC analysis of the chiral alcohol *(S)*-**167c** showed two peaks at 26.05 min (*S*) and 28.58 min *(R)* in the ratio of 97.5:2.5 indicating that the reaction is 95% enantioselective.

(±)-2-Bromo-1-(4-methylphenyl)ethanol |(±)-167c]:

This compound was prepared by treatment of 4-methylphenacyl bromide **(166c)** with $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**167a**, as a colorless liquid.

Yield: 89%

The spectral data (IR, ^1H & ^{13}CNMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**167c**.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-167d]:

This product was obtained as a colorless liquid *via* the asymmetric reduction of 4-chlorophenacyl bromide **(166d)** with $BH_3.SMe_2$ in the presence of 30 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159),** following the similar procedure described for the molecule (*S*)-**167a** using the catalyst **158.**

Yield: 90%

$[\alpha]_D^{25}$: +38.60 (*c* 1.15, $CHCl_3$).

Enantiomeric purity: 91% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**171** in the presence of chiral shift reagent, Eu(hfc)3].

IR (neat): v 3242 cm^{-1}

^1H NMR: 5 2.64 (bs, 1H), 3.43-3.68 (m, 2H), 4.91 (1H, dd, J = 8.6, 3.6 Hz), 7.22-7*Al* (m, 4H).

^{13}C NMR: δ 39.64, 73.05, 127.39, 128.81, 134.15, 138.86.

Determination of enantiomeric purity:

The ^1H NMR spectrum of racemic acetate (±)-**171** (5 mg) was recorded in the presence of Eu(hfc)3 (20 mg). The original singlet at 5 2.13 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets of equal integration arising due to *S* and *R* enantiomers. Acetate (*S*)-**171** of chiral alcohol of (*S*)-**167d** was subjected to similar ^1H NMR analysis in which the original singlet of acetoxy methyl (OCOMe) protons showed two singlets in the ratio of 95.5:4.5 indicating the enantiomeric purity of alcohol (*S*)-**167d** is **91%.**

(*S*)-1-Acetoxy-2-bromo-1-(4-chlorophenyl)ethane [(*S*)-171]:

This molecule was prepared according to the literature procedure described for the synthesis of (*R*)-1-acetoxy-2-bromo-1-phenylethane.[162]

A solution of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [(*S*)-**167d**] **(80 mg,** 0.34 **mM)** and

pyridine (4 mL) in acetic anhydride (20 mL) was stirred at room temperature for 10 h. The reaction mixture was diluted with water (80 mL) and the reaction mixture was extracted with ether (3 x 20 mL). The combined organic layer was washed successively with aqueous 5 % HCl and 10 % sodium bicarbonate solution and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue, thus obtained was purified by column chromatography (5% ethyl acetate in hexanes) to provide the desired (*S*)-1-acetoxy-2-bromo-1-(4-chlorophenyl)ethane *[(S)*-171] as a colorless oil.

Yield:	80% (75.4 mg)
$[\alpha]_D^{25}$:	+54.1 (*c* 1.35, $CHCl_3$)
IR(neat):	ν 1745 cm^{-1}
^1H NMR:	5 2.13 (s, 3H), 3.53-3.69 (m, 2H), 5.90-5.99 (m, 1H), 7.23-7.40 (m, 4H).
^{13}C NMR	6 20.89, 33.88, 74.10, 128.06, 128.93, 134.73, 136.22, 169.69.

(+)-2-Bromo-l-(4-chlorophenyl)ethanoI [(±)-167d]:

This compound was obtained as a colorless oil *via* the reaction between 4-chlorophenacyl bromide **(166d)** and $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**167a**.

Yield: 87%

This molecule has identical IR, ^{1}H & ^{13}C NMR data as that of the chiral molecule (*S*)-**167d**.

(±)-1-Acetoxy-2-bromo-1-(4-chlorophenyl)ethane [(±)-171]:

This product was prepared as a colorless liquid *via* the treatment of (±)-2-bromo-1-(4-chlorophenyl)ethanol [(±)-167d] with acetic anhydride in presence of pyridine, following the procedure described for the compound (*S*)-**171**.

Yield: 80%

The spectral data (IR, ^{1}H & ^{13}C NMR) of this molecule is in full agreement with that of the chiral molecule (*S*)-**171**.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-167e]:

This molecule was obtained *via* the asymmetric reduction of 4-bromophenacyl bromide (**166e**) with $BH_3.SMe_2$, in the presence of 30 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159),** as a white solid, following the similar procedure described for the molecule (*S*)-**167a** using the catalyst **158.**

Yield: 76%

Mp: 70-72 °C

(a $]_D^{25}$: +32.75 (*c* 1.3, $CHCl_3$) [Lit.[165] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), *R*-configuration, 94% *ee*].

Enantiomeric purity: 93% [determined by ^{1}H NMR spectral analysis of the corresponding acetate (*S*)-**172** in the presence of chiral shift

reagent, $Eu(hfc)_3$].

IR(KBr): ν 3242 cm^{-1}

^1H NMR: 8 2.65 (d, 1H, J = 3.0 Hz), 3.42-3.69 (m, 2H), 4.86-4.96 (m, 1H), 7.27 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz).

^{13}C NMR: δ 39.65,73.10, 122.34, 127.71, 131.79, 139.35.

Determination of enantiomeric purity:

The ^1H NMR spectrum of racemic acetate (±)-172 (5 mg) was recorded in the presence of Eu(hfc)3 (15 mg). It was observed that the original singlet at 5 2.13 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets of equal integration indicating that the two singlets arise from *S* and *R* enantiomers. The acetate *(S)-172* of chiral alcohol (S)-167e was subjected to ^1H NMR analysis under identical conditions. The original singlet of acetoxy methyl protons (OCOMe) showed two distinct singlets in the ratio of 96.5:3.5, indicating that the enantiomeric purity of alcohol (*S*)-**167e** is 93%.

(*S*)-1-Acetoxy-2-bromo-1-(4-bromophenyl)ethane[(*S*)-172]:

This compound was prepared by treating (*S*)-2-bromo-1-(4-bromophenyl)ethanol [(*S*)-**166e]** with acetic anhydride in presence of pyridine following the similar procedure described for the molecule (*S*)-**171**, as a colorless liquid.

Yield: 70%

$[\alpha]_D^{25}$: +42.2 (*c* 2.50, $CHCl_3$)

IR(neat): ν 1743 cm^{-1}

^1H NMR: 8 2.13 (s, 3H), 3.50-3.69 (m, 2H), 5.86-5.98 (m, 1H), 7.23 (d, 2H, J= 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz).

^{13}C NMR: δ 20.95,33.83,74.18, 122.93, 128.38, 131.93, 136.74, 169.68.

(±)-2-Bromo-1-(4-bromophenyl)ethanol

This compound was prepared by treatment of 4-bromophenacyl bromide **(166e)** with $BH_3.SMe_2$ following the similar procedure described for the molecule **(±)-167a**, as a white solid.

Yield: 77%

Mp: 70-72 °C

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**167e**.

(±)-1-Acetoxy-2-bromo-1-(4-bromophenyl)ethane [(±)-172]:

This compound was prepared as a colorless liquid *via* the treatment of (+)-2-bromo-l-(4-bromophenyl)ethanol [(+)-167e] with acetic anhydride in presence of pyridine, according to the procedure described for the compound (*S*)-**171**.

Yield: 85%

This molecule has identical IR, ^{1}H & ^{13}C NMR data as that of the chiral molecule (*S*)-**172.**

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-167f]:

This molecule was prepared by the asymmetric reduction of 4-methylphenacyl chloride **(166f)** with $BH_3.SMe_2$ in the presence of 30 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine (159), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167a** using the catalyst **158.**

Yield: 96%

$[\alpha]_D^{25}$: +47.2 (*c* 1.10, $CHCl_3$)

Enantiomeric purity: 92% (determined by HPLC using chiral column, Chiralcel-OD).

IR(neat): v 3414 cm^{-1}

^{1}H NMR: 5 2.36 (s, 3H), 2.62 (b, 1H), 3.58-3.80 (m, 2H), 4.87 (1H, dd, J = 8.2, 3.8 Hz), 7.19 (d, 2H, J = 7.8 Hz), 7.28 (d, 2H, J = 7.8 Hz).

^{13}C NMR: 5 21.14, 50.74, 73.94, 126.02, 129.32, 137.11, 138.20.

Determination of enantiomeric purity:

The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OD. The racemic alcohol (+)-167f showed two peaks at 21.41 min (*S*) and 23.50 min (*R*) in 1:1 ratio (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min). Similar HPLC analysis of the chiral alcohol (*S*)-**167f** showed two peaks at 21.49

min (S) and 23.54 min (*R*) in the ratio of 96:4 indicating that its enantiomeric purity is **92%.**

(±)-2-Chloro-1-(4-methylphenyl)ethanol [(±)-167fJ:

This compound was prepared by the treatment of 4-methylphenacyl chloride (**166f**) with $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**167a**, as a colorless liquid.

Yield: 92%

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**167f**.

(*S*)-2-Chloro-1-(4-ethylphenyl)ethanol [(*S*)-167g]:

This product was obtained *via* the asymmetric reduction of 4-ethylphenacyl chloride (166g) with $BH_3.SMe_2$ in the presence of 30 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-yl]piperazine **(159),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167a** using the catalyst **158.**

Yield: 84%

$[\alpha]_D^{25}$: +41.0 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 92% (determined by HPLC using chiral column Chiralcel-OD)

IR (neat): v 3408 cm^{-1}

^1H NMR: 8 1.23 (t, 3H, J = 7.8 Hz), 2.58-2.70 (m, 3H), 3.59-3.80 (m, 2H),

4.84-4.93(m, 1H), 7.20 (d, 2H, J= 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz).

^{13}C NMR: 6 15.48, 28.58, 50.76, 74.00, 126.11, 128.14, 137.35, 144.58.

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-167g showed two peaks at 19.08 min and 20.92 min due to *S* & *R* enantiomers in 1:1 ratio (Chiralcel-OD, solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min). The chiral alcohol (*S*)-**167g** showed two peaks at 19.00 min *(S)* and 20.88 min *(R)* in 96:4 ratio on similar HPLC analysis, indicating that its enantiomeric purity is 92%.

(±)-2-Chloro-1-(4-ethylphenyl)ethanol [(±)-167g]:

This product was prepared as a colorless oil by the treatment of 4-ethylphenacyl chloride **(166g)** with $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**167a**.

Yield: 88%

This molecule has identical IR, ^{1}H & ^{13}C NMR data as that of the chiral molecule (*S*)-**167g.**

Asymmetric reduction of prochiral ketones using 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-165]:

Spectral data (IR, ^{1}H & ^{13}C NMR) of the chiral alcohols **(5)-167a,** (*S*)-**167b**, (*S*)-**167c**,

(*S*)-**167d**, (*S*)-**167e** and (5)-167f prepared using (25,55)-165 as a catalyst, are in full agreement with that of the chiral alcohols (5)-167a, (*S*)-**167b**, (5)-167c, (5)-167d, (5)-**167e** and (5)-167f prepared *via* the asymmetric reduction of corresponding prochiral ketones (166a-f) using the catalysts 158 or 159. Therefore, we have not presented this data again in this section.[Ψ]

Similarly, spectral data (IR, ^{1}H & ^{13}C NMR) of the acetates (*S*)-**171** & (*S*)-**172** of chiral alcohols (5)-167d & (S)-167e [obtained *via* the asymmetric reduction of corresponding prochiral ketones (166d & 166e) using the catalyst (2*S*,5*S*)-**165**] are in full agreement with that of the acetates (*S*)-**171** & (*S*)-**172** of chiral alcohols (5)-167d & (*S*)-**167e** | obtained *via* the asymmetric reduction of corresponding prochiral ketones (166d & 166e) using the catalyst 159]. Therefore, these spectral data are also not presented again in this section.[Ω]

General procedure: Borane-mediated asymmetric reduction of phenacyl bromide (166b) using 5 mol% **(2*S*,5*S*)-165: (*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:**

Borane-dimethyl sulphide (1.0 mM, 76 mg) was added to a stirred solution of (25,55)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] (0.05 mM, 12.8 mg) in toluene (5 mL) and the reaction mixture was heated to 110 °C. A solution of phenacyl bromide (166b) (1.0 mM, 199 mg) in toluene (2 mL) was added

[Ψ]Though it looks repetitive, with a view to have better understanding and perspective the details of the determination of enantiomeric purities of the chiral alcohols [HPLC analysis and ^{1}H NMR spectral analysis using chiral shift reagent, $Eu(hfc)_3$] have been Presented in each case.

dropwise over 10 min and the reaction mixture was stirred for a further 45 min (monitored by TLC) at 110 °C. Then the reaction mixture was allowed to cool to room temperature and quenched with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the 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 pure (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] as a colorless oil.

Yield: 89 % (179 mg)

$[\alpha]_D^{25}$: +39.0 (*c* 1.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*

Enantiomeric purity: 87% [determined by HPLC using chiral column, Chiralcel-OD].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the racemic alcohol (+)-167b showed two peaks at 8.62 min (*S*) and 10.63 min *(R)* in 1:1 ratio on chiral column, Chiralcel-OD. The chiral alcohol (*S*)-**167b** showed two peaks at 8.63 min (*S*) and 10.63 min (*R*) in the ratio of 93.5:6.5 on similar HPLC analysis, indicating that its enantiomeric purity is 87%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of phenacyl chloride **(166a)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 93%

$[\alpha]_D^{25}$: +40.0 (*c* 1.0, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee*].

Enantiomeric purity: 81% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the racemic alcohol (+)-167a showed two peaks at 7.94 min (5) and 9.22 min (*R*) in 1:1 ratio. Similar HPLC analysis of the alcohol (5)-**167a** showed two peaks at 8.18 min (5) and 9.65 min *(R)* in the ratio of 90.5:9.5 indicating that the reduction is 81% enantioselective.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-167c]:

This molecule was prepared *via* the asymmetric reduction of 4-methylphenacyl bromide **(166c)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(25,55)-165], as a viscous liquid, following the similar procedure described for the molecule (5)-167b.

Yield: 87%

$[\alpha]_D^{25}$: +37.5 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 83% [determined by HPLC using chiral column Chiralcel-OD with reference to racemic alcohol (±)-**167c**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min) of the chiral alcohol (*S*)-**167c** (for similar HPLC analysis of racemic alcohol see page no. 142) showed two peaks at 26.05 min (*S*) and 28.56 min *(R)* on chiral column Chiralcel-OD in the ratio of 91.5:8.5 indicating that its enantiomeric purity is 83%.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-167d]:

This compound was obtained *via* the asymmetric reduction of 4-chlorophenacyl bromide **(166d)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 80 %

$[\alpha]_D^{25}$: +37.9 (*c* 1.2, $CHCl_3$).

Enantiomeric purity: 88% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**171** in the presence of chiral shift reagent, $Eu(hfc)_3$, with reference to racemic acetate (±)-**171**].

(*S*)-1-Acetoxy-2-bromo-1-(4-chlorophenyl)ethane [(*S*)-

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [(*S*)-**167d**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 80 %

$[\alpha]_D^{25}$: +56.10 (*c* 1.05, $CHCl_3$).

Determination of enantiomeric purity:

The ^1H NMR spectrum of chiral acetate (*S*)-**171** (5 mg) (for similar ^1H NMR spectral analysis of racemic acetate, see page no. 143) was recorded in the presence of Eu(hfc)3 (20 mg). The original singlet at 6 2.13 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets in the ratio of 94:6 indicating that the enantiomeric purity of alcohol (*S*)-**167d**is 88%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-167e]:

This molecule was obtained as a white solid *via* the asymmetric reduction of 4-bromophenacyl bromide **(166e)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 88%

Mp: 70-72 °C

$[\alpha]_D^{25}$: +30.7 (*c* 2.4, $CHCl_3$) [Lit.[165] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), *R*-configuration, 94% *ee]*.

Enantiomeric purity: 86% [determined by ^1H NMR spectral analysis of the corresponding acetate *(S)-172* in the presence of chiral shift reagent, Eu(hfc)3].

(*S*)-1-Acetoxy-2-bromo-1-(4-bromophenyl)ethane [(*S*)-172]:

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-bromophenyl)ethanol (*S*)-**167e** with acetic anhydride in presence of pyridine following the similar procedure described for the molecule (*S*)-**171** (page no. 143).

Yield: 70 %

$[\alpha]_D^{25}$: +42.55 (*c* 0.94, $CHCl_3$).

Determination of enantiomeric purity:

The ^1H NMR spectrum of racemic acetate (±)-**172** (5 mg) was recorded in the presence of Eu(hfc)3 (20 mg). It was observed that the original singlet at 8 2.13 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets of equal integration indicating that the two singlets arise from *S* and *R* enantiomers. The acetate (*S*)-**172** of chiral alcohol **(S)-167e** was subjected to ^1H NMR analysis under identical conditions. The original singlet at δ 2.13 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets in the ratio of 93:7 indicating that the enantiomeric purity of alcohol (*S*)-**167e** is 86%.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-167f]:

This molecule was prepared by the asymmetric reduction of 4-methylphenacyl chloride **(166f)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 91%

$[\alpha]_D^{25}$: +42.0 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 82% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol **(±)-167f** on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 97.5:2.5; flow rate: 0.8 mL / min) showed two peaks at 16.32 min (5) and 18.36 min *(R)* in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(5)-167f** showed two peaks at 16.29 min (5) and 18.36 min *(R)* in the ratio of 91:9 indicating that its enantiomeric purity is 32%.

4-Nitrophenacyl bromide (166h):

This compound was obtained as a light yellow solid *via* the treatment of 4-nitro acetophenone **(174)** with TBA Br_3 following the similar procedure described for the molecule **166c.**

Time: 6 h

Yield: **72%**

Mp: 94-96 ^{0}C (Lit.[163] 96-96.5 °C)

IR (KBr): v 1703 cm^{-1}

^{1}H NMR: 8 4.45 (s, 2H), 8.15 (d, 2H, J=8.8 Hz), 8.34 (d, 2H, J=8.8 Hz)

^{13}C NMR: 8 30.11,124.13, 130.15, 138.54, 150.86, 189.96.

(*S*)- 2-Bromo-l-(4-nitrophenyl)ethanoI **[(*S*)-167h]:**

This compound was obtained *via* the asymmetric reduction of 4-nitrophenacyl bromide (166h) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], as a white solid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 78%

Mp: 78-80 °C

$[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 91% [determined by ^{1}H NMR spectral analysis of the corresponding acetate (*S*)-**173** in the presence of chiral shift reagent, Eu(hfc)3].

IR (KBr): v 3543 cm^{-1}

^{1}H NMR: 5 2.77 (d, 1H J=3.6 Hz), 3.45-3.73 (m, 2H), 4.98-5.10 (m, 1H), 7.58 (d, 2H, J=8.6 Hz), 8.23 (d, 2H, J=8.6 Hz).

^{13}C NMR: 5 39.13, 72.68, 123.80, 127.01, 147.54, 147.83.

Determination of enantiomeric purity:

The ^1H NMR spectrum of racemic acetate (±)-**173** (5 mg) was recorded in the presence of Eu(hfc)$_3$ (20 mg). The original singlet at 8 2.18 due to acetoxy methyl (OCOMe) protons splits into two distinct singlets of equal integration arising due to *S* and *R* enantiomers. Acetate (*S*)-**173** of chiral alcohol (*S*)-**167h** was subjected to similar ^1H NMR analysis. The original singlet of acetoxy methyl (OCOMe) protons showed two singlets in the ratio of 95.5:4.5 indicating that the enantiomeric purity of the alcohol (*S*)-**167h** is 91%.

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-173]:

This compound was prepared by the reaction of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [(*S*)-**167h**] with acetic anhydride in presence of pyridine following the similar procedure described for the molecule (*S*)-**171** (page no. 143), as a colorless liquid.

Yield: 75%

$[\alpha]_D^{25}$: +47.33 (c 0.9, $CHCl_3$)

IR (KBr): v 1751 cm^{-1}

^1H NMR: δ 2.18 (s, 3H), 3.58-3.74 (m, 2H), 5.99-6.08 (m, 1H), 7.55 (d, 2H, J=8.6 Hz), 8.25 (d, 2H, J=8.6 Hz)

^{13}C NMR: δ 20.87,33.38,73.70, 124.00, 127.73, 144.61, 148.26, 169.56.

(±)-2-Bromo-1-(4-nitrophenyl)ethanol [(±)-167hJ:

This compound was prepared by the treatment of 4-nitrophenacyl bromide **(166h)** with $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**167a**, as a colorless liquid.

Yield: 89%

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (5)-167h

(±)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(±)-173]:

This molecule was obtained, as a colorless liquid *via* the reaction of (±)-2-bromo-1-(4-nitrophenyl)ethanol [(±)-167h] with acetic anhydride in presence of pyridine following the similar procedure described for the molecule (*S*)-**171** (page no. 143).

Yield: 70%

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**173**.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This product was obtained as a colorless liquid by the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**], following the similar procedure described for the molecule (5)-167b.

Yield: 85%

$[\alpha]_D^{25}$: +27.5 (*c* 0.4, MeOH) [Lit.[167] $[\alpha]_D^{25}$:+37.7 (c 3.81, MeOH), *R*-configuration, 84% *ee]*

Enantiomeric purity: 62% (determined by HPLC using chiral column, Chiralcel-OD).

IR(neat): v 3362 cm^{-1}

^1H NMR: o 1.46 (d, 3H, J=6.8 Hz), 2.10 (bs, 1H), 4.84 (q, 1H, J=6.8 Hz), 7.18-7.41 (m, 5H).

^{13}C NMR: 8 25.11, 70.43, 125.45, 127.49, 128.54, 145.94.

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-**176a** showed two peaks at 13.83 min *(R)* and 15.91 min (*S*) in 1:1 ratio on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min). The chiral alcohol (*R*)-**176a** showed two peaks at 13.89 min *(R)* and 15.99 min (5) in the ratio of 81:19 on similar HPLC analysis, indicating that its enantiomeric purity is 62%.

(±)-l-Phenylethanol [(±)-176a]:

This compound was obtained as a colorless oil *via* the reaction between acetophenone **(175a)** and $BH_3.SMe_2$ following the similar procedure described for the molecule (+)-167a.

Yield: 84%

This molecule has identical IR, ^1H & ^{13}C NMR spectral data as that of the chiral molecule (*R*)-**176a**.

Chiral catalyst 165A (recovered catalyst):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane [(2*S*,5*S*)-**165**] (0.2 mM, 51.4 mg) in toluene (5 mL) was added borane-dimethyl sulphide (4.0 mM, 304 mg) and the reaction mixture was heated to 110 ^{0}C. Once the temperature has stabilized at 110 °C, phenacyl bromide **(166b)** (4.0 mM, 796 mg) in toluene (3 mL) was added dropwise over 10 min. After the completion of the addition, the mixture was stirred for further 45 min (monitored by TLC) at 110 °C. The reaction mixture was cooled to room temperature and quenched with methanol (to destroy the excess borane). Solvent was evaporated and the residue was diluted with ether. The solid, thus obtained was filtered, washed with ether and dried under reduced pressure to provide the chiral catalyst **165A** (40 mg) as a light yellow solid.

IR (KBr): ν 3219, 1194 cm^{-1}

Mp: 126-129 ^{0}C (dec.)

^{1}H NMR (DMSO-d_6): 5 1.48-2.23[m, (4 x *n)* H], 2.69-4.21 [m, (5 x *n*) H], 6.50-6.73 [m, (3 x *n*) H], 7.00-7.42 [m, (2 × *n*)H] [(*n* can be 1 or any integer more than 1) the proton count has been written as (x *ri)* as the exact structure is not known].

^{13}C NMR (DMSO-d_6): 5 23.17, 27.82, 44.21, 44.78, 58.64, 112.73, 116.91. 129.26, 148.18.

^{31}P NMR (DMSO-d_6): 8 0.01,2.48.

^{11}B NMR (DMSO-d_6): 6 2.85 (weak broad signal).

The solvent (filtrate) from the above reaction was evaporated and the residue (alcohol) thus obtained, was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to obtain the desired (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**], as a colorless oil.

Yield: 87% (0.70 g)

$[\alpha]_D^{25}$: +38.89 (*c* 0.54, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 85% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the racemic alcohol (+)-167b showed two peaks at 13.95 min *(S)* and 15.62 min (*R*) in 1:1 ratio on chiral column, Chiralcel-OD. Similar HPLC analysis of the chiral alcohol (*S*)-167b showed two peaks at 13.49 min (*S*) and 15.34 min *(R)* in the ratio of 92.5:7.5 indicating that the reduction is 85% enantioselective.

Asymmetric reduction of phenacyl bromide (166b) using the catalyst 165A:

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide **(166b)** (1mM) with $BH_3.SMe_2$ (1mM) in the presence of catalyst **165A** (12.8 mg), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b** using the chiral source (2*S*,5*S*)-**165**.

Yield: 85%

$[\alpha]_D^{25}$: +37.12 (*c* 0.62, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 85% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

HPLC analysis (chiral column, Chiralcel-OD, solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 163) showed two peaks at 13.49 min (*S*) and 15.34 min *(R)* in the ratio of 92.50:7.50 indicating that its enantiomeric purity is 85%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of phenacyl chloride **(166a)** (1mM) with $BH_3.SMe_2$ (1mM) in the presence of 12.8 mg of catalyst **165A** following the similar procedure described for the molecule (*S*)-**167b** using the chiral source (2*S*,5*S*)-**165**.

Yield: 86%

$[\alpha]_D^{25}$: +39.78 (c 1.0, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee]*.

Enantiomeric purity: 78% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

Racemic alcohol (±)-**167a** showed two peaks in equal intensity on HPLC analysis (chiral column, Chiralcel-OD, solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min; retention times: 12.94 and 14.63 min) arising from *S* and *R* enantiomers. The chiral alcohol (*S*)-**167a** showed two peaks in 89:11 ratio [retention times: 12.86 min *(S)* and 14.61 min *(R)* respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 78%.

Preparation of chiral catalyst 165B:

To a stirred solution of (2S,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane [(2*S*,5*S*)-**165**] (0.2 mM, 51.4 mg) in toluene, was added $BH_3.SMe_2$ (22.8 mg, 0.3 mM) and refluxed for 10 minutes. The reaction mixture was cooled to room temperature and the excess borane was destroyed by the addition of methanol. The resulting solid was filtered, washed with ether and dried under reduced pressure to provide a light yellow solid **165B** (41 mg).

Mp: 126-129 ^{0}C (dec.)

IR (KBr): v 3219, 1194 cm^{-1}

^{1}H NMR (DMSO-d_6): 8 1.52-2.22[m, (4 x *ri)* H], 3.01-3.94[m, $(5 \times n)$H], 6.52-6.73[m, (3 x *ri)* H], 7.07-7.23[m, (2 x n)H] [(*n* can be 1 or any integer more than 1) the proton count has been written as (x *ri)* as the exact structure is not known].

^{13}C NMR (DMSO-d_6): 5 23.02, 27.66, 43.99, 44.52, 58.41, 112.56, 116.71, 129.10, 148.03.

^{31}P NMR (DMSO-d_6): 8 0.01, 2.37.

^{11}B NMR (DMSO-d_6): δ 2.80 (weak broad signal).

Asymmetric reduction of phenacyl bromide (166b) using catalyst 165B:

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was prepared as a colorless liquid *via* the asymmetric reduction of phenacyl bromide **(166b)** (1mM) with $BH_3.SMe_2$ (1mM) in the presence of 12.8 mg of catalyst **165B,** following the similar procedure described for the molecule (*S*)-**167b** using the chiral source (2*S*,5*S*)-**165**.

Yield: 85%

$[\alpha]_D^{25}$: +36.06 (c 0.66, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 82% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

The alcohol ***(S)-161b*** (for similar HPLC analysis of racemic alcohol see page no. 163) showed two peaks at (retention times) 13.52 min *(S)* and 15.30 min (*R*) in the ratio of 91:9 on HPLC analysis using chiral column (Chiralcel-OD, solvent system, hexanes:

IPA / 95:05; flow rate: 1.0 mL / min) indicating that the reaction is 82% enantio-selective.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of phenacyl chloride (166a) (1mM) with $BH_3.SMe_2$ (1mM) in the presence of 12.8 mg of catalyst **165B** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 83%

$[\alpha]_D^{25}$: +38.40 (*c* 0.5, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee]*.

Enantiomeric purity: 81% [determined by HPLC using chiral column. Chiralcel-OD with reference to racemic alcohol (±)-**167a**].

Determination of enantiomeric purity:

HPLC analysis using chiral column, Chiralcel-OD of the chiral (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 165) showed two peaks at 12.93 min (*S*) and 14.65 min (*R*) in the ratio of 90.5:9.5 (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) indicating that its enantiomeric purity is 81%.

N'-(Naphth-1-yl)-5-oxo-(2*S*)-pyrrolidine-2-carboxamide (181):

To a stirred solution of (L)-pyroglutamic acid **(179)** (3.09 g, 24 mM) in THF (100 mL), DCC (4.95 g, 240 mM) and 1-naphthylamine **(180)** (3.44 g, 24 mM) were added at 0°C.

After stirring for 15 h at 0 °C, precipitate formed (DCU) was removed through filtration. Solvent was evaporated under reduced pressure. The residue, thus obtained was purified by column chromatography (silica gel, 2.5% methanol in ethyl acetate) followed by crystallization (ethyl acetate) to provide the desired N'-(naphth-l-yl)-5-oxo-(2*S*)-pyrrolidine-2-carboxamide (181) as a white solid.

Yield: 49% (2.98 g)

Mp: 189-191 °C

$[\alpha]_D^{25}$: -7.53 (*c* 1.09, methanol)

IR (KBr): ν 3250, 1722, 1669 cm^{-1}

^1H NMR: 6 2.09-2.88 (m, 4H), 4.23-4.37 (m, 1H), 7.19-7.91 (m, 7H), 9.18 (bs, 1H).

^{13}C NMR: 5 24.74, 28.77, 56.17, 121.07, 121.48, 124.58, 125.03, 127.21, 127.38, 131.86, 133.13, 170.90, 177.43.

(2*S*)-2-(1-Naphthylaminomethyl)pyrrolidine (182):

This compound was obtained as a viscous liquid *via* the treatment of N'-(naphth-l-yl)-5-oxo-(2*S*)-pyrrolidine-2-carboxamide (181) with lithium aluminum hydride in THF, following the similar procedure described for the molecule 3.

Time: 6 h

Yield: 62%

Bp: 160-163 °C / 0.3 mm (Lit.[27] 159-161 °C / 0.3 mm)

$[\alpha]_D$: +29.46 (*c* 1.02, ethanol) [Lit.[27] $[\alpha]_D^{25}$: +29.50 (c 1.03, ethanol)]

IR (neat): v 3344 cm^{-1}

^1H NMR: 5 1.41-2.10 (m, 5H), 2.91-3.69 (m, 5H), 4.96 (bs, 1H), 6.60 (d, 1H, J=7.2 Hz), 7.18-7.51 (m, 4H), 7.71-7.98 (m, 2H).

^{13}C NMR: 5 25.97, 29.82, 46.65, 48.71, 57.54, 104.44, 117.19, 120.24, 123.76, 124.58, 125.68, 126.64, 128.56, 134.42, 143.97.

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-(naphth-1-yl)bicyclo(3.3.0)octane [(2*S*,5*S*)-177]:

This product was obtained as a white solid *via* the treatment of *(2S)-2-(*\-naphthylaminomethyl)pyrrolidine **(182)** with $POCl_3$ in the presence of triethylamine following the similar procedure described for the molecule (2*S*,5*S*)-**165**.

Time: 4h

Yield: 31%

Mp: 97-99 ^0C

No^{25}: +5.0 (*c* 1.0, $CHCl_3$)

IR (KBr): v 1275 cm^{-1}

^1H NMR: 5 1.52-1.85 (m, 1H), 1.93-2.29 (m, 3H), 3.09-3.33 (m, 1H), 3.43-3.88 (m, 3H), 4.21-4.46 (m, 1H), 7.37-7.68 (m, 4H), 7.73-7.93 (m, 2H), 8.20-8.34 (m, 1H).

^{13}C NMR: 5 27.47 (d, J=4.7 Hz), 30.83, 45.07, 56.05 (d, J=20.5 Hz), 60.42

(d, J=8.7 Hz), 123.44, 124.38, 125.53, 126.53, 126.77, 128.16, 128.30, 131.35 (J=3.2 Hz), 134.85, 134.97.

^{31}P NMR: 6 19.28

Analysis calcd. for $C_{15}H_{16}N_2OPCl$: C, 58.74; H, 5.26; N, 9.13.

Found: C, 58.60; H, 5.20; N, 9.08.

Asymmetric reduction of phenacyl bromide (166b) using (25,55)-l,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yI)bicyclo(3.3.0)octane [(2*S*,5*S*)-177] as a catalyst:

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (166b) with $BH_3.SMe_2$ in the presence of 20 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yl)bicyclo(3.3.0)octane [(2*S*,5*S*)-**177**], as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b** using chiral source (2*S*,5*S*)-**165**.

Yield: 89 %

$[\alpha]_D^{25}$: +25.1 (*c* 1.39, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*].

Enantiomeric purity: 55% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

HPLC analysis of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) using chiral column (Chiralcel-OD, solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) showed two peaks at 8.51 min (*S*) and 10.50 min *(R).* The peaks are in the ratio of 77.5:22.5 indicating that its enantiomeric purity is 55%.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This compound was obtained as a colorless liquid by the borane-mediated asymmetric reduction of acetophenone (175a) in the presence of 20 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-(naphth-l-yl)bicyclo(3.3.0)octane [(2*S*,5*S*)-**177**), following the similar procedure described for the molecule (*S*)-**167b** using chiral source (2*S*,5*S*)-165.

Yield: 84%

$[\alpha]_D^{25}$: +19.9 *(c* 5.0, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 *(c* 3.81, MeOH), *R*-configuration, 84% *ee*].

Enantiomeric purity: 44% [determined by HPLC using chiral column, Chiralcel-OD]

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-**176a** showed two peaks at 8.60 min (*R*) and 10.28 min (*S*) in 1:1 ratio on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min). Similar HPLC analysis of the chiral alcohol *(R)*-

176a showed two peaks at 8.43 *(R)* min and 9.95 *(S)* min in the ratio of 72:28 indicating that its enantiomeric purity is 44%.

(*S*)-N-(*tert*-Butoxycarbonyl)indoline-2-carboxylic acid (184):

This compound was prepared according to the known procedure.

To a stirred solution of (*S*)-indoline-2-carboxylic acid (183) (1.3 g, 8 mM) in dioxane (8 mL) and 0.5 M NaOH (16 mL) was added slowly di-*tert*-butyl dicarbonate (2.09 g, 9.6 mM) in dioxane (8 mL) at 0 ^{0}C. The reaction mixture was stirred for 16 h at room temperature. Then the reaction mixture was diluted with hexanes (10 mL) and organic layer was removed. Aqueous layer was acidified with saturated citric acid and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine, and dried over anhydrous sodium Sulfate. The solvent was removed under reduced pressure and the crude product, thus obtained was purified by recrystallization (1:1 mixture of ethyl acetate and hexanes) to provide the desired (*S*)-N-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid (184) as a white solid.

Yield:	85% (1.79 g)
Mp:	125-126 °C (Lit.[168] 124.1-124.8 °C)
$[\alpha]_D^{25}$:	-75.30 (*c* 1.0, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: -77.3 (*c* 1.0, $CHCl_3$)]
IR (KBr):	v 3300-2500, 1707, 1602 cm^{-1}
^{1}H NMR:	5 1.52 (s, 9H), 3.12-3.34 (m, 1H), 3.42-3.67 (m, 1H), 4.91 (m, 1H), 6.91-7.06 (m, 1H), 7.07-7.31 (m, 3H), 10.15 (b, 1H).

^{13}C NMR: 5 28.29, 33.39, 60.06, 81.65, 114.74, 122.79, 124.54, 127.98, 141.80, 178.10,218.22.

N-Phenyl-(*S*)-N$^{\alpha}$-(*tert*-butoxycarbonyl)indoline-2-carboxamide (185):

This molecule was prepared according to the literature procedure.[168]

To a stirred solution of (*S*)-N-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid **(184)** (1.316g, 5 mM) in THF (10 mL), was added a THF solution (7.5 mL) of N-methylmorpholine (0.55 mL, 5 mM) at -15 ^{0}C. After stirring for 15 min, isobutyl chloroformate (0.71 mL, 5.5 mM) in THF (7.5 mL) was added slowly to the reaction mixture at -15 °C and the stirring was continued for 15 min. Then a THF solution (7.5 mL) of aniline (0.46 mL, 5 mM) was added at -15 ^{0}C and the reaction mixture was stirred at room temperature for 14 h. To this reaction mixture, water (25 mL) and ethyl acetate (50 mL) were added and stirred for 5 min. The organic layer was separated and washed successively with 1 M HC1, saturated sodium hydrogencarbonate solution, and brine. The organic layer was dried over anhydrous sodium Sulfate and the solvent was removed under reduced pressure. The crude product, thus obtained was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to provide the N-phenyl-(*S*)-N$^{\alpha}$-(*tert*-butoxycarbonyl)indoline-2-carboxamide **(185)** as white solid.

Yield: 69% (1.167 g)

Mp: 178-180 ^{0}C (Lit.[168] 178.3-178.8 °C)

$[\alpha]_D^{25}$: -71.6 (*c* 2.5, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: -67.6 (*c* 1.0, $CHCl_3$)

IR (KBr): ν 3314, 1701, 1672, 1601 cm^{-1}

^1H NMR: 6 1.57 (s, 9H), 3.40-3.71 (m, 2H), 4.94-5.09 (m, 1H), 6.98-7.55 (m, 9H), 7.70 (bs, 1H).

^{13}C NMR: 6 28.34, 31.54, 62.55, 82.77, 115.59, 119.94, 123.51, 124.41, 124.94, 127.66, 129.00, 129.74, 137.70, **141.37,** 153.28, 169.38.

N-Phenyl-(*S*)-indoline-2-carboxamide (186):

This product was prepared according to the known procedure.

To a stirred solution of N-phenyl-(*S*)-N^{α}-(*tert*-butoxycarbonyl)indoline-2-carboxamide **(185)** (1.0 g, 2.95 mM) in dichloromethane (60 mL) was added trifluoroacetic acid (4.55 mL) at room temperature and stirring continued for 3 h. Then additional 1.2 mL of trifluoroacetic acid was added and the reaction mixture was stirred for further 1 h. The solvent and excess trifluoroacetic acid were removed under reduced pressure. Then the residue was diluted with dichloromethane (40 mL) and washed successively with saturated $NaHCO_3$ solution, water and brine. The organic layer was dried over anhydrous sodium Sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to furnish N-phenyl-(*S*)-indoline-2-carboxamide **(186)** as white solid.

Yield: 95% (0.67 g)

Mp: 126-128 ^{0}C (Lit.[168] 125.3-126.8 °C)

$[\alpha]_D^{25}$: -238 (*c* 0.95, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: -236.6 (*c* 1.0, $CHCl_3$)

IR(KBr): v 3423, 3341, 1645 cm^{-1}

^{1}H NMR: 5 3.19 (dd, 1H, J=8.6, 16.4 Hz), 3.64 (dd, 1H, J=11.2, 16.4 Hz), 4.32 (bs, 1H), 4.41-4.59 (m,1H), 6.70-7.42 (m,7H), 7.57 (d, 2H, J=7.8Hz), 8.98 (bs, 1H).

^{13}C NMR: δ 35.76, 61.79, 111.51, 119.72, 121.23, 124.47, 124.98, 127.81, 128.30, 129.09, 137.51, 149.17, 172.04.

(*S*)-2-(Anilinomethyl)indoline (187):

This compound was prepared following the literature procedure.[168]

To a stirred suspension of lithium aluminum hydride (0.26 g, 6.83 mM) in THF (13 mL), N-phenyl-(*S*)-indoline-2-carboxamide (186) (0.54 g, 2.27 mM) in THF (13 mL) was added at 0 °C. After the addition was complete, the reaction mixture was stirred for 50 h at room temperature. Then saturated aqueous sodium Sulfate solution was added to the reaction mixture at 0 °C and the resulting precipitate was removed by filtration. The organic layer (filtrate) was dried over anhydrous sodium Sulfate and the solvent was removed under reduced pressure. The crude product, thus obtained, was purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to furnish (*S*)-2-(anilinomethyl)indoline **(187)** as white solid.

Yield: 83% (0.422 g)

Mp: 62-63 °C (Lit. [168] 61.2-61.6 °C)

$[\alpha]_D^{25}$: +85.2 (c 0.75, $CHCl_3$) [Lit.[168] $[\alpha]_D^{25}$: +79.4 (c 0.99, $CHCl_3$)

IR (KBr): v 3373, 1602 cm^{1}

^1H NMR: 8 2.85 (dd, 1H, J=7.4, 15.6 Hz), 3.15 (dd, 1H, J=9.0, 15.6 Hz), 3.22 (d, 1H, J=5.8 Hz), 3.98 (bs, 2H), 4.05-4.20 (m, 1H), 6.57-6.82 (m, 5H), 6.92-7.26 (m, 4H).

^{13}C NMR: 8 33.62, 48.59, 58.50, 109.69, 113.02, 117.72, 118.99, 124.91, 127.48, 128.44, 129.35, 148.25, 150.58.

(2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.0^{1,5})dodeca-7(12),8,10-triene [(2*R*,5*S*)-178]:

This product was obtained as a white solid *via* the treatment of *(S)-2*-(anilinomethyl)indoline (187) with $POCl_3$ in the presence of triethylamine, following the similar procedure described for the molecule (2*S*,5*S*)-**165**.

Time: 6 h

Yield: 32%

$[\alpha]_D^{25}$: +55.62 *(c* 0.80, $CHCl_3$).

Mp: 198 °C

IR(KBr): v 1601, 1278 cm^{-1}

^1H NMR: 8 3.09 (dd, 1H, J=9.2, 15.8 Hz), 3.27-3.48 (m, 1H), 3.61-3.78 (m,

1H), 4.05 (ddd, 1H, J=7.0, 9.0, 28.6 Hz), 4.80-4.98 (m, 1H), 7.01-7.48 (m,9H).

^{13}C NMR: 6 35.67, 52.43 (d, J=16.7 Hz), 59.43 (d, J=10.0 Hz), 114.52, 118.82 (d, J=3.8 Hz), 123.81, 124.25, 125.50, 128.18, 129.58, 132.35 (d, **J=9.3** Hz), 139.72, 141.45.

^{31}PNMR: 5 10.07.

Analysis calcd. for $C_{15}H_{16}N_2OPCl$: C, 59.13; H, 4.63; N, 9.19.

Found: C, 59.25; 11, 4.60; N, 9.22.

Asymmetric reduction of phenacyl bromide (166b) in the presence of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.0^{1,5})dodeca-7(12),8,10-triene [(2*R*,5*S*)-178]as a catalyst:

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide **(166b)** with $BH_3.SMe_2$ in the presence of 10 mol% (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.0^{1,5})dodeca-7(12),8,10-triene [(2*R*,5*S*)-**178**], as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b** using the chiral source (2*S*,5*S*)-**165**.

Yield: 87%

$[\alpha]_D^{25}$: +28.8 (*c* 1.25, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*].

Enantiomeric purity: 65% [determined by HPLC using chiral column Chiralcel-OD with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:5; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 163) showed two peaks at 13.89 min (*S*) and 15.53 min *(R)* in the ratio of 82.5:17.5 indicating that its enantiomeric purity is 65%.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 10 mol% (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenyltricyclo(4.6.0.$0^{1,5}$)dodeca-7(12),8,10-triene [(2*R*,5*S*)-**178],** following the similar procedure described for the molecule *(S)*- **167b** using the chiral source (2*S*,5*S*)-**165**.

Yield: 85%

$[\alpha]_D^{25}$: +15.6 *(c* 2.25, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 *(c* 3.81, MeOH), *R*-configuration, 84% *ee].*

Enantiomeric purity: 35% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

HPLC analysis on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at 8.59 min (*R*) and 10.34 min (5) in the ratio of 72.5:37.5 indicating that its enantiomeric purity is 35 %.

(5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane(188):

To a stirred suspension of oil free NaH (2.0 mM, 48 mg) in DMF, was added slowly (1*R*,2*R*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol **(189)** (1.0 mM, 170 mg) at room temperature. After 5 min the reaction mixture was cooled to 0 °C and (25,55)-1, 3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] (1.10 mM, 282.7 mg) was added slowly . Then the reaction mixture was stirred for 90 min at room temperature and quenched with water and diluted with ether (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 X 20 mL). The combined organic layer was dried over anhydrous sodium Sulfate and the solvent was removed under reduced pressure. The crude product, thus obtained was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) followed ty crystallization (40% ethyl acetate in hexanes) to afford the desired (55)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-Phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(188)** as white needles.

Yield: 65% (254 mg)

Mp: 138-140°C

$[\alpha]_D^{25}$: -22.28 (*c* 1.05, $CHCl_3$).

IR (KBr): v 3335, 1602, 1523, 1325, 1242 cm^{-1}

^1H NMR: 5 0.89 (s, 3H), 1.31 (s, 3H), 1.41-2.57 (m, 13H), 2.95-3.12 (m, 1H), 3.16-3.48 (m, 3H), 4.02-4.21 (m, 1H), 4.53-4.78 (m, 2H), 6.58-6.72 (m, 3H), 7.08-7.23 (m, 2H).

^{13}C NMR: 5 24.17, 24.77 (d, J=9.1 Hz), 26.01. 27.03, 28.72, 30.06 (d, J=8.9 Hz), 34.89 (d, J=5.8 Hz), 38.95, 39.64, 47.11 (d, J=3.5 Hz), 48.88, 51.69 (d, J=8.2 Hz), 58.81 (d, J=6.6 Hz), 76.73, 86.22, 112.45, 116.67, 129.04, 148.35.

MS (LC-CI) (*m/z*): 390 $(M)^+$, 391 $(M+H)^+$

^{31}P NMR: 5 19.88.

Analysis calcd. for $C_{21}H_{31}N_2O_3P$: C, 64.59; H, 8.00; N, 7.17.

Found: C, 64.48; H, 8.05; N, 7.12.

Asymmetric reduction of prochiral ketones using 4 mol% (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane(188):

Spectral data (IR, ^1H & ^{13}C NMR) of the chiral alcohols (*S*)-**167a**, **(5)-167b,** (*S*)-**167c**, (*S*)-**167d**, (*S*)-**167e**, (*S*)-**167f**, (*S*)-**167h** and (*R*)-**1 76a** (prepared in this section using the

catalyst 188) are in full agreement with that of the chiral alcohols (*S*)-**167a**, (S)-167b, (S)-167c, (S)-167d, (*S*)-**167e**, (*S*)-**167f**, (*S*)-**167h**, and (*R*)-**176a** prepared *via* the asymmetric reduction of corresponding prochiral ketones 166a-f, 166h, 175a using the catalysts 159 or (2*S*,5*S*)-**165**. Therefore, we have not presented their spectral data again in this section. [Ψ]

Similarly, spectral data (IR, ^{1}H & ^{13}C NMR) of the acetates (*S*)-**171**, (*S*)-**172** and (*S*)-173 of alcohols (*S*)-**167d**, (*S*)-**167e** and (*S*)-**167h** are in complete agreement with that of the acetates (*S*)-**171**, (*S*)-**172** and (*S*)-**173** of alcohols (*S*)-**167d**, (*S*)-**167e** and (*S*)-**167h** [obtained *via* the asymmetric reduction of corresponding prochiral ketones 166d, 166c and 166h using the catalyst 159 or (2*S*,5*S*)-**165**]. Therefore, we have not presented their spectral data in this section. [Ψ]

General procedure for asymmetric reduction of prochiral ketones using 4 **mol%** **(5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)heptan-3-yl-oxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (188):**

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

To a stirred solution of (5*S*)-2-[(1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo(3.1.1)-heptan-3-yloxy]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**188**) (0.04

[Ψ] Though it looks repetitive, with a view to have better understanding and perspective the details of the determination of enantiomeric purities of the chiral alcohols [HPLC analysis and ^{1}H NMR spectral analysis using chiral shift reagent, Eu(hfc)$_3$] have been Presented in each case.

mM, 15.6 mg) in toluene (5 mL) was added borane-dimethyl sulphide (1.0 mM, 76 mg) at room temperature and the reaction mixture was heated to 110 C. Once the temperature has stabilized at 110 °C, phenacyl bromide **(166b)** (1.0 mM, 199 mg) in toluene (2 mL) was added dropwise over 10 min and stirring was continued for further 1 h (monitored by TLC). Then the reaction mixture was allowed to cool to room temperature and quenched with methanol. The 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*)-**167b**] in 88% yield (177 mg) as a colorless oil.

$[\alpha]_D^{25}$: +41.5 (*c* 1.2, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 91% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (+)-167b].

Determination of enantiomeric purity:

HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IP A / 90:10; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) showed two peaks at 8.12 min (*S*) and 9.60 min *(R)* in the ratio of 95.5:4.5 indicating that its enantiomeric purity is 91%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This molecule was prepared as a colorless liquid by the asymmetric reduction of phenacyl chloride **(166a)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 91%

$[\alpha]_D^{25}$: +42.1 (*c* 1.0, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee]*.

Enantiomeric purity: 86% [determined by HPLC using chiral column, Chiralcel-OD with reference to racemic alcohol (±)-**167a**].

Determination of **enantiomeric** purity:

The alcohol (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at (retention times) 7.89 min (*S*) and 9.09 min (*R*) in the ratio of 93.0:7.0 on HPLC analysis using chiral column (Chiralcel-OD, solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that the reaction is 86% enantioselective.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-167c]:

This compound was prepared *via* the asymmetric reduction of 4-methylphenacyl bromide **(166c)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** as a viscous liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 94%

fa],,[25]: +39.9 (*c* 1.1, $CHCl_3$).

Enantiomeric purity: 91% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis (chiral column, Chiralcel-OD, solvent system, hexanes: IPA / 97.5:2.5; flow rate: 1.0 mL / min) of the racemic alcohol (+)-167c showed two peaks at 15.76 min *(S)* and 18.86 min *(R)* in 1:1 ratio. Similar HPLC analysis of the chiral alcohol (*S*)-**167c** showed two peaks at 16.15 min (*S*) and 19.36 min *(R)* in the ratio of 95.5:4.5 indicating that its enantiomeric purity is 91%.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-167d]:

This product was obtained as a colorless liquid *via* the asymmetric reduction of 4-chlorophenacyl bromide **(166d)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 92%

la],)[25]: +39.0 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 89% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**171** in the presence of chiral shift reagent, Eu(hfc)3, with reference to racemic acetate (±)-**171**].

(*S*)-1-Acetoxy-2-bromo-1-(4-chlorophenyl)ethane [(*S*)-171]:

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol **[(*S*)-167d]** with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 67%

$[\alpha]_D^{25}$: +53.0 (*c* 1.0, $CHCl_3$).

Determination of enantiomeric purity:

The ^1H NMR spectrum of chiral acetate (*S*)-**171** (5 mg) (for similar ^1H NMR spectral analysis of racemic acetate see page no. 143) was recorded in the presence of $Eu(hfc)_3$ (20 mg). The original singlet (at 5 2.13) of acetoxy methyl (OCOMe) protons splits into two distinct singlets in 94.5:5.5 ratio indicating that the enantiomeric purity of the alcohol (*S*)-**167d** is 89%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-167e]:

This product was obtained *via* the borane-mediated asymmetric reduction of 4-bromophenacyl bromide **(166e)** in the presence of 4 mol% chiral source **188,** following the similar procedure described for the molecule (*S*)-**167b**, as white solid.

Yield: 89%

Mp: 71-72 °C

fa],)[25]: +33.8 (c 2.4, $CHCl_3$) [Lit.[165] $[\alpha]_D^{25}$: -31.0 *(c* 2.9, $CHCl_3$), *R*-configuration, 94% *ee].*

Enantiomeric purity: 96% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**172** in the presence of chiral shift reagent, Eu(hfc)3, with reference to racemic alcohol (±)-**172**].

(*S*)-1-Acetoxy-2-bromo-1-(4-bromophenyl)ethane *[(S)-172]:*

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-bromophenyl)ethanol [(*S*)-**167e**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule *(S)*-\7\ (page no. 143).

Yield: 87%

$[\alpha]_D^{25}$: +48.27 (*c* 1.16, $CHCl_3$).

Determination of enantiomeric purity:

The ^1H NMR spectrum of chiral acetate (*S*)-**172** (5 mg) (for similar ^1H NMR spectral analysis of racemic acetate see page no. 156) was recorded in the presence of Eu(hfc)$_3$ (20 mg). The original singlet (at 5 2.13) of acetoxy methyl protons (OCOMe) splits into two distinct singlets in the ratio of 98:2 indicating the enantiomeric purity of alcohol is 96%.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-167f]:

This molecule was prepared *via* the asymmetric reduction of 4-methylphenacyl chloride

(**166f**) with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 92%

$[\alpha]_D^{25}$: +44.0 (*c* 1.0, $CHCl_3$).

Enantiomeric purity: 88% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 97.50:2.50; flow rate: 1.0 mL / min) of the racemic alcohol (±)-**167f** showed two peaks at 14.60 min *(S)* and 17.05 min (*R*) in 1:1 ratio on chiral column, Chiralcel-OD. The chiral alcohol (*S*)-**167f** showed two peaks at 14.64 min *(S)* and 16.80 min (*R*) in the ratio of 94:6 on similar HPLC analysis, indicating that its enantiomeric purity is 88%.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-167h]:

This compound was obtained *via* the asymmetric reduction of 4-nitrophenacyl bromide **(166h)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** as a white solid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 90%

Mp: 78-80 °C

$[\alpha]_D^{25}$: +33.2 (*c* 1.0, $CHCl_3$)

Enantiomeric purity: 92% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**173** in the presence of chiral shift reagent, Eu(hfc)3, with reference to racemic acetate (±)-**173**].

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-173]:

This compound was prepared as a colorless liquid by the reaction of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [(*S*)-**167h**] with acetic anhydride in presence of pyridine following the similar procedure described for the molecule (*S*)-**171** (page no. 143).

Yield: 75 %

Mp: 102-105 ^{0}C

$[\alpha]_D^{25}$: +46.60 (*c* 0.9, $CHCl_3$)

Determination of enantiomeric purity:

The ^1H NMR spectrum of chiral acetate (*S*)-**173** (5 mg) (for similar ^1H NMR spectral analysis of racemic acetate see page no. 159) was recorded in the presence of Eu(hfc)3 (20 mg). The original singlet (at 8 2.18) of acetoxy methyl (OCOMe) protons splits into two distinct singlets in 96:4 ratio indicating that the enantiomeric purity of the alcohol is 92%.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This compound was obtained by the asymmetric reduction of acetophenone (**175a**) with $BH_3.SMe_2$ in the presence of 4 mol% catalyst **188** following the similar procedure described for the molecule (*S*)-167b, as a colorless liquid.

Yield: 80%

$[\alpha]_D^{25}$: +29.0 (c 1.0, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 *(c* 3.81, MeOH), *R*-configuration, 84% *ee].*

Enantiomeric purity: 63% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

HPLC analysis using chiral column, Chiralcel OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at 8.76 min *(R)* and 10.72 min (*S*) in the ratio of 81.5:18.5 indicating that its enantiomeric purity is 63 %.

(*R*)-1-Phenylpropan-1-ol [(*R*)-176b]:

This compound was obtained as a colorless liquid *via* the asymmetric reduction of propiophenone **(175b)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: **85%**

$[\alpha]_D^{25}$: +30.7 *(c* 1.9, $CHCl_3$) [Lit.[169] $[\alpha]_D^{25}$: +43.03 *(c* 5.1, $CHCl_3$), *R*-configuration, 96% *ee].*

Enantiomeric purity: 67% (determined by HPLC using chiral column, Chiralcel-OD).

IR (neat): v 3373 cm^{-1}

^{1}H NMR: 6 0.93 (t, 3H, J=7.0 Hz), 1.68-1.93 (m, 3H), 4.61 (t, 1H, J=6.8 Hz), 7.22-7.44 (m, 5H).

^{13}C NMR: 8 10.12, 31.85, 75.93, 126.02, 127.41, 128.35, 144.66.

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-**176b** showed two peaks at 8.10 min *(R)* and 9.84 min (*S*) in 1:1 ratio on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min). The chiral alcohol (*R*)-**176b** showed two peaks al 8.32 min *(R)* and 10.05 min (*S*) in the ratio of 83.5:16.5 on similar HPLC analysis, indicating that its enantiomeric purity is 67%.

(±)-1-Phenylpropan-1-ol [(±)-176b]:

To a solution of propiophenone **(175b)** (2 mM, 268 mg) in toluene (5 mL) was added $BH_3.SMe_2$ (152 mg, 2 mM) and stirred for 12 h. Then the reaction mixture was allowed to cool to 0 ^{0}C and quenched with methanol. The 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 (±)-1-phenylpropan-1-ol [(+)-**176b**] as a colorless oil.

Yield: 90% (245 mg)

This molecule has identical IR, ^{1}H & ^{13}C NMR spectral data as that of the chiral molecule (*S*)-**176b**.

(*R*)-1-Phenylbutan-1-ol [(*R*)-176c]:

This compound was obtained as a colorless liquid by the asymmetric reduction of butyrophenone **(175c)** with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188,** following the similar procedure described for the molecule (*S*)-**167b**.

Yield:	83%
$[\alpha]_D^{25}$:	+28.0 (*c* 0.7, benzene) [Lit.[23] $[\alpha]_D^{25}$: -45.2 (*c* 4.81, benzene), *V*-configuration, 100% *ee*].
Enantiomeric purity:	59% (determined by HPLC using chiral column, Chiralcel-OD-H).
IR (neat):	v 3300 cm^{-1}
^1H NMR:	5 0.93 (t, 3H, J=7.0 Hz), 1.21-1.91 (m, 5H), 4.68 (t, 1H, J=6.6 Hz), 7.19-7.40 (m,5H).
^{13}C NMR:	δ 13.93, 19.00,41.23,74.33, 125.93, 127.38, 128.36, 145.02.

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-**176c** showed two peaks at 12.39 min *(R)* and 12.98 min (*S*) in 1:1 ratio on chiral column, Chiralcel-OD-H (solvent system, hexanes: IPA / 95:05; flow rate: 0.7 mL / min). The chiral alcohol (*R*)-**176c** showed two peaks at 12.30 min (*R*) and 13.10 min (*S*) in the ratio of 79.5:20.5 on similar HPLC analysis, indicating that the reaction is 59% enantioselective.

(±)-1-Phenylbutan-1-ol [(±)-176c]:

This compound was obtained as a viscous liquid *via* the reduction of butyrophenone (175c) with $BH_3.SMe_2$, following the similar procedure described for the molecule (±)-**176b.**

Yield: 83%

This compound has identical IR, ^1H & ^{13}C NMR data as that of the chiral molecule (*R*)-**176c.**

(*R*)-1,2,3,4-Tetrahydronaphth-1-ol [(*R*)-176d]:

This product was obtained as a colorless liquid *via* the asymmetric reduction of α-tetralone (175d) with $BH_3.SMe_2$ in the presence of 4 mol% chiral source **188** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 71%

$[\alpha]_D^{25}$: -16.4 (*c* 0.75, MeOH) [Lit.[169] $[\alpha]_D^{25}$: -23.14 (*c* 1.3, MeOH), *R*-configuration, 94% *ee*].

Enantiomeric purity: 70% (determined by HPLC using chiral column, Chiralcel-OD)

IR (neat): v 3356 cm^{-1}

^1H NMR: 5 1.45-2.14 (m, 5H), 2.61-2.92 (m, 2H), 4.70-4.92 (m, 1H), 7.04-7.33 (m, 3H), 7.38-7.56 (m, 1H).

^{13}C NMR: 5 18.84, 29.19, 32.21, 67.96, 126.02, 127.38, 128.60, 128.84, 137.00, 138.86.

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 97.5:2.5; flow rate: 0.4 mL / min) of the racemic alcohol **(±)-176d** showed two peaks at 35.42 min (*S*) and 39.44 min *(R)* in 1:1 ratio. Similar HPLC analysis of the chiral alcohol (*S*)-**176d** showed two peaks at 35.50 min (*S*) and 39.52 min (*R*) in the ratio of 15:85 indicating that its enantiomeric purity is 70 %.

(±)-1,2,3,4-Tetrahydronaphth-1-ol [(±)-176d]:

This product was obtained as a colorless liquid *via* the reduction of α-tetralone **(175d)** with $BH_3.SMe_2$, following the similar procedure described for the molecule (±)-**176b**.

Yield: 81%

The spectral data (IR, ^1H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*R*)-**176d**.

(*R*)-1-(Naphth-1-yl)ethanol [(*R*)-176e]:

This compound was prepared by the asymmetric reduction of 1-acetonaphthone (175e) with $BH_3.SMe_2$ in the presence of 4 mol% catalyst **188,** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 76%

$[\alpha]_D^{25}$: +50.3 (*c* 1.08, ether) [Lit.[170] $[\alpha]_D^{25}$: +82.1 (*c* 1.0, ether). *R*-

configuration, >99% *ee]*.

Enantiomeric purity: 63% (determined by HPLC using chiral column, Chiralcel-OD).

IR (neat): v 3368 cm^{-1}

^1H NMR: 6 1.64 (d, 3H, J=6.0 Hz), 2.65 (bs, 1H), 5.59 (q, 1H, J=6.0 Hz), 7.36-8.20 (m, 7H).

^{13}C NMR: 6 24.41, 67.04, 122.11, 123.28, 125.57, 126.04, 127.89, 128.94. 130.36, 133.89, 144.51.

Determination of enantiomeric purity:

HPLC analysis of the racemic alcohol (±)-176e showed two peaks at 24.68 min *(R)* and 37.82 min *(S)* in 1:1 ratio on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min). Similar HPLC analysis of the chiral alcohol *(R)*-**176e** showed two peaks at 24.44 min *(R)* and 37.72 min (*S*) in the ratio of 81.5:18.5 indicating that its enantiomeric purity is 63 %.

(±)-1-(Naphth-1-yl)ethanol [(±)-176e]:

This compound was obtained as a viscous liquid *via* the reduction of 1-acetonaphthone **(175e)** with $BH_3.SMe_2$, following the similar procedure described for the molecule (±)-**176b.**

Yield: 78%

This compound has identical IR, ^1H & ^{13}C NMR spectral data as that of the chiral molecule (*R*)-**176e**.

(5*S*)-1,3-Diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (190):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane [(2*S*,5*S*)-**165**] (0.5 mM, 128 mg) in CH_2Cl_2 (5 mL) were successively added triethylamine (1 mM, 0.14 mL) and benzylamine (0.5 mM, 53.5 mg) at room temperature. After 18 h (monitored by TLC) the reaction mixture was diluted with water (5 mL). Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed successively with water and brine and was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue, thus obtained was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to provide the desired (5,V)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (190) as a crystalline solid (98 mg) in 60% yield.

Mp: 117-120 °C

$[\alpha]_D^{25}$: -42.28 (*c* 1.05, $CHCl_3$)

IR (KBr): ν 3190, 1599, 1207 cm^{-1}

^1H NMR: 5 1.57-2.17 (m, 4H), 2.83-3.25 (m, 2H), 3.30-3.51 (m, 1H), 3.65-4.16 (m, 5H), 6.92-7.06 (m, 1H), 7.09-7.46 (m, 9H).

^{13}C NMR: 6 26.27, 32.23, 44.95 (d, J=10.4 Hz), 48.95 (d, J=16.6 Hz), 57.86 (d, J=8.5 Hz), 116.41 (d, J=4.2 Hz), 121.00, 126.94. 127.24, 128.26, 129.04, 139.81 (d, J=6.2 Hz), 141.88 (d, J=5.8 Hz).

^{31}P NMR: 521.16

Mass (m/z): **327** (M^+)

Analysis cald. for $C_{18}H_{22}N_3OP$: C, 66.04; H, 6.77; N, 12.84.

Found: C, 66.29; H, 6.75; N, 12.75.

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (190):

Spectral data (IR, ^1H & ^{13}C NMR) of the chiral alcohols (*S*)-**167a**, (*S*)-**167b** and ***(R)*-176a** (prepared using chiral catalysts **190-192** or **193A** or **193B** or mixture of **193A** and **193B)** are in full agreement with that of the chiral alcohols (*S*)-**167a**, (*S*)-**167b** and *(R)*-**176a** prepared *via* the asymmetric reduction of corresponding prochiral ketones **166a, 166b** and **175a** using the catalysts 159 or (2*S*,5*S*)-**165**. Therefore, we have not presented their spectral data again in this section.[Ψ]

General procedure for the asymmetric reduction of prochiral ketones using 5 mol% (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (190):

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

To a stirred solution of (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(190)** (0.05 mM, 16.3 mg) in toluene (5 mL) was added

[Ψ]Though it looks repetitive, with a view to have better understanding and perspective the details of the determination of enantiomeric purities of the chiral alcohols (HPLC analysis) have been presented in each case.

borane-dimethyl sulphide (1.0 mM, 76 mg) at room temperature and the reaction mixture was heated to 110 °C. Once the temperature has stabilized at 110 ^{0}C, phenacyl bromide **(166b)** (1.0 mM, 199 mg) in toluene (2 mL) was added dropwise over 10 min and stirring was continued for further 45 min (monitored by TLC) at the same temperature (110 ^{0}C). Then the reaction mixture was allowed to cool to room temperature and quenched with methanol. The 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*)-**167b**] as a colorless oil.

Yield: 82% (165 mg)

$[\alpha]_D^{25}$: +39.66 (*c* 0.9, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), *R*-configuration, 93% *ee*].

Enantiomeric purity: 89% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) using chiral column, Chiralcel-OD showed two peaks at 8.38 min *(S)* and 10.14 min *(R)* in the ratio of 94.5:5.5 indicating that its enantiomeric purity is 89%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This alcohol was prepared by the borane-mediated asymmetric reduction of phenacyl chloride **(166a)** in the presence of 5 mol% (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(190),** following the similar procedure described for the molecule **(*S*)-167b**, as a colorless liquid.

Yield: 82 %

$[\alpha]_D^{25}$: +39.52 (*c* 2.75, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee].*

Enantiomeric purity: 84% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167a**].

Determination of **enantiomeric purity:**

HPLC analysis of the chiral alcohol **(*S*)-167a** (for similar HPLC analysis of racemic alcohol see page no. 153) using chiral column, Chiralcel-OD, (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) showed two peaks at 7.69 min (*S*) and 9.47 min *(R).* The peaks are in the ratio of 92:08 indicating that its enantiomeric purity is 84%.

(*R*)-1-Phenylethanol[(*R*)-176a]:

This compound was prepared *via* the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-(benzylamino)-2-phospha-

2-oxo-3-phenylbicyclo(3.3.0)octane **(190),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 74%

$[\alpha]_D^{25}$: +29.82 (*c* 0.86, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 (*c* 3.81, MeOH), *R*-configuration, 84% *ee*].

Enantiomeric purity: 62% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at 8.87 min *(R)* and 10.96 min (*S*) in the ratio of 81:19 indicating that the reduction is 62% enantioselective.

(5*S*)-1,3-Diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (191):

This product was obtained as a white solid *via* the treatment of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with *t*-butylamine in the presence of triethylamine at 45 °C, following the similar procedure described for **190.**

Time: 12 h

Yield: 55%

Mp: 129-132 °C

$[\alpha]_D^{25}$: -36.84 (*c* 1.05, $CHCl_3$)

IR(KBr): ν 3171, 1601, 1224 cm^{-1}

^1H NMR: 6 1.13 (s, 9H), 1.57-2.19 (m, 4H), 2.66 (d, 1H, J= 8.8 Hz), 2.83-3.07 (m, 1H), 3.30-3.46 (m, 1H), 3.61-3.89 (m, 3H), 6.88-6.98 (m, 1H), 7.12-7.38 (m,4H).

^{13}C NMR: 5 26.15, 31.00 (d, J=4.9 Hz), 32.70, 44.44, 47.96 (d, J=17.0 Hz), 50.75, 57.13 (d, J=7.3 Hz), 116.29, 120.61, 128.86, 142.05.

^{31}P NMR: 8 17.17

Mass (m/z): 293 (M^+)

Analysis cald. for $C_{15}H_{24}N_3OP$: C, 61.42; H, 8.25; N, 14.32.

Found: C, 61.26; H, 8.30; N, 14.35.

Asymmetric reduction of prochiral ketones with **(5*S*)-1,3-diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (191)**

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was obtained as a colorless liquid *via* the borane-mediated asymmetric reduction of phenacyl bromide **(166b)** in the presence of 5 mol% (5*S*)-1,3-diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(191),** following the similar procedure described for the molecule (*S*)-**167b** using chiral catalyst **190.**

Yield: 86 %

fa].)^{25}: +37.12 (*c* 1.84, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*].

Enantiomeric purity: 85% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

The chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) showed two peaks at (retention times) 8.12 min (*S*) and 9.77 min (*R*) in the ratio of 92.50:7.50 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that the reaction is 85% enantioselective.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was prepared by the asymmetric reduction of phenacyl chloride **(166a)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(191),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b** using chiral catalyst **190.**

Yield: 81%

$[\alpha]_D^{25}$: +31.93 (*c* 0.88, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee*].

Enantiomeric purity: 65% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167a**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at 7.95 min (*S*) and 9.23 min (*R*) on chiral column, Chiralcel-OD, in the ratio of 82.5:17.5 indicating that the reaction is 65% enantioselective.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This molecule was obtained as a colorless liquid by the asymmetric reduction of acetophenone (175a) with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-(*t*-butylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(191),** following the similar procedure described for the molecule (*S*)-**167b** using chiral catalyst **190.**

Yield: 84%

$[\alpha]_D^{25}$: +20.58 (*c* 0.51, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 (*c* 3.81, MeOH), *R*-configuration, 84% *ee].*

Enantiomeric purity: 44% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

HPLC analysis of the chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) showed two peaks at 8.92 min (*R*) and 10.85 min (*S*). The peaks are in the ratio of 72:28 indicating that its enantiomeric purity is 44%.

(5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (192):

This compound was prepared *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-ehloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with allylamine in the presence of triethylamine, as a white solid, following the similar procedure described for the molecule **190.**

Time:	12 h
Yield:	58%
Mp:	70-72 °C
$[\alpha]_D^{25}$:	-33.18 (*c* 1.1, $CHCl_3$)
IR (KBr):	ν 3190, 1599, 1201 cm^{-1}
^1H NMR:	5 1.59-2.18 (m, 4H), 2.72-3.09 (m, 2H), 3.22-3.51 (m, 311). 3.63-3.94 (m, 3H), 4.92-5.15 (m, 2H), 5.60-5.82 (m, 1H), 6.90-7.01 (m, 1H), 7.14-7.37 **(m,4H).**

^{13}C NMR: 8 26.17, 32.14, 43.53, 44.85, 48.95 (d, J=16.8 Hz), 57.73 (d, J=8.4 Hz), 114.82, 116.28 (d, J=4.1 Hz), 120.81, 128.91, 136.48 (d, J=5.9 Hz), 141.88 (d, J=5.9 Hz).

^{31}P NMR: δ 21.38

Mass (m/z): 277 (M^+)

Analysis cald. for $C_{14}H_{20}N_3OP$: C, 60.64; H, 7.27; N, 15.15.

Found: C, 60.84; H, 7.30; N, 15.18.

Asymmetric reduction of prochiral ketones with (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (192)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of phenacyl bromide **(166b)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(192),** following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst **190.**

Yield: 84 %

$[\alpha]_D^{25}$: +34.91 (*c* 1.10 $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*].

Enantiomeric purity: 81% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

HPLC analysis of the chiral alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) showed two peaks at 8.12 min (*S*) and 9.76 min *(R)* in the ratio of 90.5:9.5 on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that its enantiomeric purity is 81%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was prepared by the borane-mediated asymmetric reduction of phenacyl chloride (166a) in the presence of 5 mol% (5*S*)-1,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(192),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst 190.

Yield: 83%

$[\alpha]_D^{25}$: +29.82 *(c* 0.93, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee].*

Enantiomeric purity: 61% [determined by HPLC using chiral column Chiralcel-OD, with reference to racemic alcohol (±)-**167a**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at 8.12 min (*S*) and 9.67 min *(R)* on chiral column, Chiralcel-OD, in the ratio of 80.5:19.5 indicating that the reduction is 61% enantioselective.

(*R*)-1-Phenylethanol

This molecule was obtained as a colorless liquid by the asymmetric reduction of acetophenone (175a) with $BH_3.SMe_2$ in the presence of 5 mol% (55)-l,3-diaza-2-(allylamino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(192),** following the similar procedure described for the molecule (5)-167b using the chiral catalyst **190.**

Yield: 82%

$[\alpha]_D^{25}$: +17.2 *(c* 2.75, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 *(c* 3.81, MeOH), *R*-configuration, 84% *ee].*

Enantiomeric purity: 37% (determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**).

Determination of enantiomeric purity:

The alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at (retention times) 8.78 min *(R)* and 10.77 min (5) in the ratio of 68.50:31.50 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) indicating that the reaction is 37% enantioselective.

(5*S*)-1,3-Diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane (193A):

This molecule was prepared **as** a white solid *via* the reaction between (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] and (5)-l-meth-

ylbenzylamine [(*S*)-**194**] in the presence of triethylamine, following the similar procedure described for the molecule **190.**

Time: 2 days

Yield: 90%

Mp: 148-150 °C

$[\alpha]_D^{25}$: -26.0 (*c* 1.0, $CHCl_3$)

IR (KBr): ν 3211, 1601, 1205 cm^{-1}

^1H NMR: 5 1.22 (d, 3H, J=6.6 Hz), 1.46-2.06 (m, 4H), 2.48-2.69 (m, 1H), 3.24-3.83 (m, 4H), 3.97-4.18 (m, 1H), 6.91-7.02 (m, 1H), 7.15-7.39 (m, 9H).

^{13}C NMR: 6 25.06 (d, J=7.9 Hz), 26.50, 32.25, 43.98, 49.33 (d, J=l 6.0 Hz), 51.19, 57.37 (d, J=9.5 Hz), 116.29 (d, J=4.0 Hz), 120.83, 125.86, 126.64, 128.13, 129.07, 142.22 (d, J=5.6 Hz), 146.00.

^{31}P NMR: 6 17.88

Mass(m/z): 342 (M^++1)

Analysis cald. for $C_{19}H_{24}N_3OP$: C, 66.85; H, 7.09; N, 12.31.

Found: C, 66.70; H, 7.12; N, 12.25.

Asymmetric reduction of prochiral ketones with 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane(193A):

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

Borane-dimethyl sulphide (1.0 mM, 76 mg) was added, to a stirred solution of (55)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A)** (0.05 mM, 17.19 mg) in toluene (5 mL) at room temperature and the reaction mixture was heated to 110 °C. A solution of phenacyl bromide **(166b)** (1.0 mM, 199 mg) in toluene (2 mL) was added dropwise over 10 min and stirring was continued for further 45 min (monitored by TLC) at 110 C. Then the reaction mixture was allowed to cool to room temperature and quenched with methanol. The 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 pure (*S*)-2-bromo-1-phenylethanol [(*S*)-**167b**] as a colorless oil.

Yield: 80 % (161 mg)

$[\alpha]_D^{25}$: +39.41 (*c* 1.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 89% [determined by HPLC using chiral column, Chiralcel-OD, **with** reference to racemic alcohol (±)- **167b].**

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: **1.0** mL / min) of the chiral alcohol ***(S)-\67b*** (for similar HPLC analysis of racemic alcohol see page no.

152) showed two peaks at 9.08 min (*S*) and 11.29 min *(R)* on chiral column, Chiralcel-OD, in the ratio of 94.5:5.5 indicating that its enantiomeric purity is 89%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This compound was obtained *via* the asymmetric reduction of phenacyl chloride **(166a)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 85%

$[\alpha]_D^{25}$: +42.3 (*c* 1.5, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), *R*-configuration, 100% *ee*].

Enantiomeric purity: 87% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167a**].

Determination of **enantiomeric purity:**

The chiral alcohol (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at 8.08 min (5) and 9.58 min *(R)* in the ratio of 93.5:6.5 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min), indicating that its enantiomeric purity is 87%.

(*R*)-1-Phenylethanol [(*R*)-176a]

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-

1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**193A**), following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 87%

$[\alpha]_D^{25}$: +32.60 (*c* 1.60, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 (*c* 3.81, MeOH), *R*-configuration, 84% *ee]*.

Enantiomeric purity: 72% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

The chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at (retention times) 9.08 min *(R)* and 10.50 min (*S*) in the ratio of 86:14 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) indicating that the reaction is 72% enantioselective.

(5*S*)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane (193B):

This compound was prepared *via* the reaction of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane [(2*S*,5*S*)-**165**] with (*R*)-1-methylbenzylamine [(*R*)-**194]** in the presence of triethylamine, as a viscous liquid, following the similar procedure described for the molecule **190.**

Time: 2 days

Yield: 91%

$[\alpha]_D^{25}$: -22.90 (*c* 1, $CHCl_3$)

IR(neat): ν 3211, 2966, 1601, 1201 cm^{-1}

^1H NMR: 5 1.40 (d, 3H, J=6.6 Hz), 1.51-2.18 (m, 4H). 2.83-3.42 (m, 4H), 3.56-3.88 (m, 2H), 4.16-4.38 (m, 1H), 6.80-7.45 (m, 10H).

^{13}C NMR: 5 25.04 (d, J=8.1Hz), 26.06, 32.33, 44.76, 47.76 (d, J=16.9 Hz), 51.70, 57.72 (d, J=8.2 Hz), 116.28 (d, J=3.7 Hz), 120.50, 125.78, 126.51, 127.91, 128.57, 141.66 (d,J=6.0 Hz), 144.53.

^{31}P NMR: 5 20.14

Mass(m/z): 341 (M^+)

Analysis cald. for $C_{19}H_{24}N_3OP$: C, 66.85; H, 7.09; N, 12.31.

Found: C, 66.66; H, 7.15; N, 12.35.

Asymmetric reduction of prochiral ketones with **(5*S*)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane** (193B)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This compound was obtained as a colorless liquid *via* the borane-mediated asymmetric reduction of phenacyl bromide **(166b)** in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*R*)-l-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193B)** following the similar procedure described for the molecule (*S*)-**167b** using chiral catalyst **193A.**

Yield: 81%

[a],)^{25}: +39.2 *(c* 1.25, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 *(c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee]*.

Enantiomeric purity: 88% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167b**].

Determination of enantiomeric purity:

The alcohol (*S*)-**167b** (for similar HPLC analysis of racemic alcohol see page no. 152) showed two peaks at (retention times) 9.13 min (*S*) and 11.41 min *(R)* in the ratio of 94:6.0 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that the reaction is 88% enantioselective.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This molecule was prepared as a colorless liquid by the asymmetric reduction of phenacyl chloride (166a) with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*R*)-1 -phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193B) following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst **193**A.

Yield: 83%

$[\alpha]_D^{25}$: +39.59 *(c* 2.0, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 (c 1.73, cyclohexane), *R*-configuration, 100% *ee].*

Enantiomeric purity: 84% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**167a**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) of the chiral alcohol (*S*)-**167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at 7.99 min (*S*) and 9.27 min *(R)* in the ratio of 92:8.0 indicating that its enantiomeric purity is 84%.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This compound was prepared as a colorless liquid *via* the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*R*)-l-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193B)** following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst **193A.**

Yield: 82%

$[\alpha]_D^{25}$: +31.6 *(c* 1.70, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 *(c* 3.81, MeOH), *R*-configuration, 84% *ee].*

Enantiomeric purity: 70% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol **(±)-176a].**

Determination of enantiomeric purity:

HPLC analysis of the chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) showed two peaks at 9.09 min *(R)* and 10.55 min (*S*). The peaks are in the ratio of 85:15 indicating that its enantiomeric purity is 70%.

Asymmetric reduction of prochiral ketones using 2.5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193 A) and 2.5 mol% (5*S*)-1,3-diaza-2-[(*R*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenyl-bicyclo(3.3.0)octane (193B):

(*S*)-2-Bromo-1-phenylethanol [(*S*)-167b]:

This molecule was obtained as a colorless liquid by the borane-mediated asymmetric reduction of phenacyl bromide **(167b)** using 2.5 mol% **193A** and 2.5 mol% 193B, following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst **193A.**

Yield: 80%

$[\alpha]_D^{25}$: +37.8 *(c* 1.0, $CHCl_3$) [Lit.[162] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), *R*-configuration, 93% *ee].*

Enantiomeric purity: 85% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol **(+)-167b].**

Determination of enantiomeric purity:

HPLC analysis of the chiral alcohol **(*S*)-167b** (for similar HPLC analysis of racemic alcohol see page no. 152) showed two peaks at 9.01 min (*S*) and 11.22 min *(R)* in the ratio of 92.5:7.5 on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that its enantiomeric purity is 85 %.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-167a]:

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride **(166a)** with $BH_3.SMe_2$ in the presence of 2.5 mol% **193A** and 2.5 mol% **193B,** following the similar procedure described for the molecule (*S*)-**167b**using the chiral catalyst 193A.

Yield: 80%

$[\alpha]_D^{25}$: +40.36 *(c* 1.1, cyclohexane) [Lit.[162] $[\alpha]_D^{25}$: -48.10 *(c* 1.73, cyclohexane), *R*-configuration, 100% *ee].*

Enantiomeric purity: 82% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-167a].

Determination of enantiomeric purity:

The alcohol **(*S*)-167a** (for similar HPLC analysis of racemic alcohol see page no. 153) showed two peaks at (retention times) 7.98 min (*S*) and 9.26 min *(R)* in the ratio of 91:9 on HPLC analysis using chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min) indicating that the reaction is 82% enantioselective.

(*R*)-1-Phenylethanol [(*R*)-176a]:

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone **(175a)** with $BH_3.SMe_2$ in the presence of 2.5 mol% **193A** and **2.5** mol% **193B**, following the similar procedure described for the molecule (*S*)-**167b** using the chiral catalyst **193A**.

Yield: 72%

$[\alpha]_D^{25}$: +28.58 (*c* 0.88, MeOH) [Lit.[167] $[\alpha]_D^{25}$: +37.7 (*c* 3.81, MeOH), *R*-configuration, 84% *ee*].

Enantiomeric purity: 60% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176a**].

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the chiral alcohol (*R*)-**176a** (for similar HPLC analysis of racemic alcohol see page no. 171) showed two peaks at 8.89 min *(R)* and 11.00 min (*S*) in the ratio of 80:20 indicating that its enantiomeric purity is 60%.

Asymmetric reduction of prochiral ketones using 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylcthylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane(193A)

Spectral data (IR, ^1H & ^{13}C NMR) of the chiral alcohols (*S*)-**167c**, (*S*)-**167d**, (*S*)-**167e**, (*S*)-**167f**, (*S*)-**167h** (*R*)-**176b**, (*R*)-**176c** and (*R*)-**176d** (prepared using the chiral catalyst

193A) are in full agreement with that of the chiral alcohols **(5)-167c,** (*S*)-**167d**, (*S*)-**167e,** (*S*)-**167f**, (*S*)-**167h** (*R*)-**176b**, (*R*)-**176c** and (*R*)-**176d** prepared via the asymmetric reduction of corresponding prochiral ketones **166c-f, 166h, 175b-d** using the catalysts 159 or **188** or (2*S*,5*S*)-**165**. Therefore, we have not presented their spectral data again in this section.[Ψ]

Similarly, spectral data (IR, ^{1}H & ^{13}C NMR) of the acetates (*S*)-**171**, (*S*)-**172** and *(S)*-173 of chiral alcohols (5)-167d, (*S*)-**167e** and (*S*)-**167h** (prepared using the chiral catalyst **193** A) are in complete agreement with that of the acetates (*S*)-**171**, (*S*)-**172** and (*S*)-**173** of chiral alcohols **(S)-167d,** (*S*)-**167e** and (*S*)-**167h** [obtained *via* the asymmetric reduction of corresponding prochiral ketones **166d, 166e** and **166h** using the catalyst **159** or (2*S*, 5*S*)-**165**]. Therefore, we have not presented their spectral data again in this section.[Ψ]

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-167c]:

This molecule was obtained *via* the borane-mediated asymmetric reduction of 4-methylphenacyl bromide **(166c)** in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** following the similar procedure described for the molecule (*S*)-**167b**, as a viscous liquid.

[Ψ]Though it looks repetitive, with a view to have better understanding and perspective the details of the determination of enantiomeric purities of the chiral alcohols [HPLC analysis and ^{1}H NMR spectral analysis using chiral shift reagent, $Eu(hfc)_3$] have been presented in each case.

Yield: 84%

$[\alpha]_D^{25}$: +37.87 (*c* 1.08, $CHCl_3$)

Enantiomeric purity: 91% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol **(+)-167c].**

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min) of the chiral alcohol (*S*)-**167c** (for similar HPLC analysis of racemic alcohol see page no. 142) showed two peaks at 26.02 min (*S*) and 28.51 min *(R)* on chiral column, Chiralcel-OD, in the ratio of 95.5:4.5 indicating that the reaction is 91% enantioselective.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-167d]:

This compound was obtained as a colorless liquid *via* the asymmetric reduction of 4-chlorophenacyl bromide **(166d)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193A), following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 87%

$[\alpha]_D^{25}$: +39.0 (*c* 1 $CHCl_3$)

Enantiomeric purity: 89% [determined by ^1H NMR spectral analysis of the corresponding acetate (*S*)-**171** in the presence of chiral shift reagent, $Eu(hfc)_3$, with reference to racemic acetate (±)-**171**].

(*S*)-1-Acetoxy-2-bromo-1-(4-chlorophenyl)ethane [(*S*)-171]:

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [(*S*)-**167d**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 80 %

[a],)^{25}: +53.10 (*c* 1.05, $CHCl_3$)

Determination of enantiomeric purity:

The ^{1}H NMR spectrum of chiral acetate (*S*)-**171** (5 mg) (for similar ^{1}H NMR spectral analysis of racemic acetate see page no. 143) was recorded in the presence of Eu(hfc)3 (20 mg). The original singlet (at 8 2.13) of acetoxy methyl (OCOMe) protons splits into two distinct singlets in the ratio of 94.5:5.5 indicating that the enantiomeric purity of the alcohol is 89%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-167e]:

This chiral alcohol was obtained *via* the asymmetric reduction of 4-bromophenacyl bromide (**166e**) with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** as a white solid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 80%

M.P: 70-72 °C

[a],)^{25}: +32.23 (*c* 0.9, $CHCl_3$) [Lit.[165] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), *R*-configuration, 94% *ee]*.

Enantiomeric purity: 94% [determined by ^1H NMR spectral analysis of the corresponding acetate in the presence of chiral shift reagent, Eu(hfc)3, with reference to racemic alcohol (±)-**172**].

(*S*)-1-Acetoxy-2-bromo-1-(4-bromophenyl)ethane [(*S*)-172]:

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-2-bromo-1-(4-bromophenyl)ethanol [(*S*)-**167e**] with acetic anhydride in presence of pyridine following the similar procedure described for the molecule ***(S)-lll*** (page no. 143).

Yield: 70 %

$[\alpha]_D^{25}$: +42.55 (*c* 0.94, $CHCl_3$)

Determination of enantiomeric purity:

The ^1H NMR spectrum of chiral acetate (*S*)-**172** (5 mg) (for similar ^1H NMR spectral analysis of racemic acetate see page no. 156) was recorded in the presence of chiral shift reagent, $Eu(hfc)_3$ (20 mg). The original singlet (at 5 2.13) of acetoxy methyl (OCOMe) splits into two distinct singlets in the ratio of 97:03 indicating that the enantiomeric purity of the alcohol is 94%.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-167f]:

This molecule was prepared by the borane-mediated asymmetric reduction of 4-

methylphenacyl chloride **(166f)** in the presence of 5 mol % (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** following the similar procedure described for the molecule (*S*)-**167b** as a colorless liquid.

Yield: 82 %

$[\alpha]_D^{25}$: +44.88 (*c* 1.0, $CHCl_3$)

Enantiomeric purity: 89%[determined by HPLC using chiral column Chiralcel-OD, with reference to racemic alcohol (±)-**167f**].

Determination of enantiomeric purity:

HPLC analysis (Chiralcel-OD, solvent system, hexanes: IPA / 97.5:2.5; How rate: 0.8 mL / min) of the chiral alcohol (*S*)-**167f** (for similar HPLC analysis of racemic alcohol see page no. 157) showed two peaks at 16.38 min (*S*) and 18.42 min *(R)* in the ratio of 94.5:5.5 on similar HPLC analysis, indicating that its enantiomeric purity is 89%.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-167h]:

This compound was obtained *via* the asymmetric reduction of 4-nitrophenacyl bromide **(166h)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethyl-amino)-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** as a white solid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 82%

$la],)^{25}$: +32.1 (*c* 1.0, $CHCl_3$)

Enantiomeric purity: 91% [^{1}H NMR spectral analysis of the corresponding acetate *(S)*-**173** in the presence of chiral shift reagent, $Eu(hfc)_3$, with reference to racemic alcohol (±)-**173**].

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-173]

This product was prepared as a colorless liquid by the reaction of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [(*S*)-**167h**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 75 %

Mp: 102-105 °C

$[\alpha]_D^{25}$: +47.35 (*c* 1.1, $CHCl_3$)

Determination of enantiomeric purity:

The ^{1}H NMR spectrum of chiral acetate (*S*)-**173** (5 mg) (for similar ^{1}H NMR spectral analysis of racemic acetate see page no. 159) was recorded in the presence of chiral shift reagent, $Eu(hfc)_3$ (20 mg). The original singlet (at 5 2.18) of acetoxy methyl (OCOMe) protons splits into two distinct singlets in 95.5:4.5 ratio indicating the enantiomeric purity of the alcohol is 91%.

(*R*)-1-Phenylpropan-1-ol [(*R*)-176b]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of propiophenone **(175b)** with $BH_3.SMe_2$ in the presence of 5 mol % (5*S*)-1,3-diaza-2-

[(*S*)- 1 -phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 81%

lab^{25}: +27.84 (*c* 0.79, $CHCl_3$) [Lit.[169] $[\alpha]_D^{25}$: +43.03 (c 5.1, $CHCl_3$), *R*-configuration, 96% *ee]*.

Enantiomeric purity: 61% [determined by HPLC using chiral column, Chiralcel-OD, with reference to racemic alcohol (±)-**176b**].

Determination of **enantiomeric purity:**

HPLC analysis of the chiral alcohol (*R*)-**176b** (for similar HPLC analysis of racemic alcohol see page no. 190) showed two peaks at 8.11 min *(R)* and 9.86 min *(S)* in the ratio of 80.5:19.5 on chiral column, Chiralcel-OD (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) indicating that its enantiomeric purity is 61%.

(*R*)-1-Phenylbutan-1-ol [(*R*)-176c]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of butyrophenone **(175c)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1 -phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 80%

[a],)^{25}: +21.95 (*c* 1.5, benzene) [Lit.[23] $[\alpha]_D^{25}$: -45.2 (c 4.81, benzene), *S*-

configuration, 100% *ee*].

Enantiomeric purity: 47% (determined by HPLC using chiral column, Chiralcel-OD).

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 0.7 mL / min) of the racemic alcohol [(±)-176c] showed two peaks at 11.21 min *(R)* and 12.74 min (*S*) in 1:1 ratio on chiral column, Chiralcel-OD. Similar HPLC analysis of the chiral alcohol [(*R*)-**176c]** showed two peaks at 11.27 min *(R)* and 12.78 min (*S*) in the ratio of 73.5:26.5 indicating that its enantiomeric purity is 47%.

(*R*)-1,2,3,4-Tetrahydronaphth-1-ol *[(R)-l* 76d]:

This product was prepared as a colorless liquid by the asymmetric reduction of α tetralone (**175d**) with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A)** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 72%

$[\alpha]_D^{25}$: -11.56 (*c* 0.9, MeOH)) [Lit.[169] $[\alpha]_D^{25}$: -23.14 (*c* 1.3, MeOH), *R*-configuration, 94% *ee]*.

Enantiomeric purity: 43% [determined by HPLC using chiral column Chiralcel-OD, with reference to racemic alcohol (±)-**176d]**.

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 97.5:2.5; flow rate: 0.4 mL / min) of chiral alcohol (*R*)-**176d** (for similar HPLC analysis of racemic alcohol see page no. 193) showed two peaks at 35.44 min (*S*) and 39.47 min (*R*) in the ratio of 28.5:71.5 on chiral column, Chiralcel-OD, indicating that its enantiomeric purity is 43 %.

(*R*)-1-(4-Methylphenyl)ethanol [(*R*)-195a]:

This molecule was obtained by the asymmetric reduction of 4-methylacetophenone (168) with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethyl-amino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (193A), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 77%

$[\alpha]_D^{25}$: +22.87 *(c* 0.6, MeOH) [Lit.[171] $[\alpha]_D^{25}$: -43.5 (c 0.994, MeOH), *S*-configuration, >99% *ee]*.

Enantiomeric purity: 51% [determined by HPLC analysis of corresponding acetate using chiral column, Chiralcel-OJ-H, with reference to racemic acetate **(±)-196a].**

IR(neat): v 3352 cm^{-1}

^1H NMR: 6 1.48 (d, 3H, J=6.6 Hz), 2.25 (bs, 1H), 2.37 (s, 3H), 4.84 (q, 1H, J=6.6 Hz), 7.17 (d, 2H, J=8.0 Hz), 7.27 (d, 2H, J=8.0 Hz).

^{13}C NMR: 6 21.10,25.08,70.17, 125.40, 129.15, 137.06, 142.97.

Determination of enantiomeric purity:

The racemic acetate (±)-**196a** showed two peaks at 7.70 min *(R)* and 10.87 min *(S)* in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJ-H (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) . The chiral acetate (*R*)-**196a** showed two peaks at 7.66 min *(R)* and 10.82 min (*S*) in the ratio of 75.5:24.5 on similar HPLC analysis, indicating that its enantiomeric purity is 51 %.

(*R*)-1-Acetoxy-1-(4-methylphenyl)ethane [(*R*)-196a]:

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-1-(4-methylphenyl)ethanol [(*R*)-**195a**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 83 %

$[\alpha]_D^{25}$: +61.49 (*c* 1.0, $CHCl_3$)

IR(neat): v 1739 cm^{-1}

^1H NMR: 6 1.53 (d, 3H, J=6.8 Hz), 2.06 (s, 3H), 2.35 (s, 3H), 5.87 (q, 1H, J=6.8 Hz), 7.16 (d, 2H, J=8.2 Hz), 7.26 (d, 2H, J=8.2 Hz).

^{13}C NMR: 8 21.10, 21.32, 22.07, 72.22, 126.14, 129.16, 137.60, 138.77, 170.27.

(±)-1-(4-Methylphenyl)ethanol [(±)-195a]:

This compound was obtained as colorless liquid *via* the reaction of 4-methylacetophenone **(168)** with $BH_3.SMe_2$ in toluene following the similar procedure described for the molecule (±)-**176b**.

Yield: 74%

This compound has identical IR, ^1H & ^{13}C NMR spectral data as that of the chiral molecule (*R*)-**195a**

(±)-1-Acetoxy-1-(4-methylphenyl)ethane [(±)-196a]:

This compound was prepared as a colorless liquid *via* the treatment of (±)-l-(4-methylphenyl)ethanol [(±)-195a] with acetic anhydride in presence of pyridine, according to the procedure described for the compound (*S*)-**171** (page no. 143).

Yield: 83%

The spectral data (IR, ^1H & ^{13}CNMR) of this molecule are in full agreement with that of the chiral molecule (*R*)-**196a**

(*R*)-1-(4-Chlorophenyl)ethanol [(*R*)-195b]:

This molecule was obtained as a colorless liquid by the asymmetric reduction of 4-chloroacetophenone **(169)** with $BH_3.SMe_2$ in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenylethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 70%

[a],,^{25}: +38.4 (c 1.25, Et_2O) [Lit.[171] $[\alpha]_D^{25}$: -49.0 *(c* 1.84, Et_2O), *S*-configuration, >99% *ee]*.

Enantiomeric purity: 76% [determined by HPLC analysis of corresponding acetate using chiral column, Chiralcel-OJ-H, with reference to racemic acetate (+)-196b].

IR (neat): v 3352 cm^{-1}

^{1}H NMR: 5 1.41 (d, 3H, J=6.4 Hz), 2.81 (bs, 1H), 4.77 (q, 1H, J=6.4 Hz), 7.13-7.33 (m,4H).

^{13}C NMR: 5 25.13, 69.54, 126.78, 128.49, 132.92, 144.25.

Determination of enantiomeric purity:

HPLC analysis of the racemic acetate **(+)-196b** showed two peaks at 6.90 min *(R)* and 8.13 min *(S)* in 1:1 ratio on chiral column, Chiralcel-OJ-H (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min). Similar HPLC analysis of the chiral acetate (*R*)-**196b** showed two peaks at 6.83 min (*R*) and 8.06 min (*S*) in the ratio of 88:12 indicating that its enantiomeric purity is 76%.

(*R*)-1-Acetoxy-1-(4-chlorophenyl)ethane *[(R)-196b]:*

This molecule was prepared as a colorless liquid *via* the treatment of (*S*)-1-(4-chlorophenyl)ethanol [(*R*)-**195b**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 89 %

[a],)^{25}: +74.68 (c 0.39, $CHCl_3$)

IR(neat): v 1738 cm^{-1}

^{1}H NMR: o 1.52 (d, 3H, J=6.8 Hz), 2.07 (s, 3H), 5.85 (q, 1H, J=6.8 Hz), 7.25-7.38 (m,4H).

^{13}C NMR: 5 21.31,22.18,71.64, 127.59, 128.74, 133.71, 140.32, 170.21.

(±)-1-(4-Chlorophenyl)ethanol [(±)-195b]:

This product was prepared by treatment of 4-chloroacetophenone **(169)** with $BH_3.SMe_2$ following the similar procedure described for the molecule (+)-176b, as a colorless liquid.

Yield: 84%

The spectral data (IR, ^{1}H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*R*)-**195b**

(±)-1-Acetoxy-1-(4-chlorophenyl)ethane [(±)-196b]:

This molecule was prepared as a colorless liquid *via* the treatment of **(±)-l-(4-chlorophenyl)ethanol [(±)-195b] with** acetic anhydride in presence **of pyridine, according to the procedure described for the compound** (*S*)-**171** (page no. **143).**

Yield: 86%

This alcohol has identical IR, ^{1}H & ^{13}CNMR spectral data as that of the chiral molecule (*R*)-**196b**.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-195c]:

This compound was prepared *via* the borane-mediated asymmetric reduction of 4-bromoacetophenone **(170)** in the presence of 5 mol% (5*S*)-1,3-diaza-2-[(*S*)-1-phenyl-ethylamino]-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane **(193A),** as a colorless liquid, following the similar procedure described for the molecule (*S*)-**167b**.

Yield: 90%

$[\alpha]_D^{25}$: +30 (*c* 1.0, $CHCl_3$)[Lit.[171] $[\alpha]_D^{25}$: -37.90 (*c* 1.13, $CHCl_3$), *S*-configuration, >99% *ee]*.

Enantiomeric purity: 74% [determined by HPLC analysis of corresponding acetate using chiral column, Chiralcel-OJ-H, with reference to racemic acetate (±)-**196c**].

IR (neat): v 3358 cm^{-1}

^{1}H NMR: 5 1.47 (d, 3H, J=6.8 Hz), 1.79 (d, 1H, J= 4.0 Hz), 4.80-4.95 (m, 1H), 7.25 (d, 2H, J=8.8 Hz), 7.47 (d, 2H, J=8.8 Hz).

^{13}C NMR: 6 25.09,69.51, **121.00, 127.13, 131.43, 144.75.**

Determination of enantiomeric purity:

HPLC analysis (solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min) of the racemic acetate (±)-196c showed two peaks at 7.13 min *(R)* and 8.38 min *(S)* in 1:1 ratio. Similar HPLC analysis of the chiral acetate (*R*)-**196c** showed two peaks at 7.13 (*R*) min and 8.39 min (*S*) in the ratio of 87:13 indicating that its enantiomeric purity is 74%.

(*R*)-1-Acetoxy-1-(4-bromophenyl)ethane [(*R*)-196c]:

This molecule was prepared as a colorless liquid *via* the treatment of (*R*)-1-(4-bromophcnyl)ethanol [(*R*)-**195c**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**171** (page no. 143).

Yield: 80%

$[\alpha]_D^{25}$: +60.24 (*c* 1.23, $CHCl_3$)

IR (neat): v 1736 cm^{-1}

^1H NMR: o 1.50 (d, 3H, J=6.6 Hz), 2.06 (s, 3H), 5.80 (q, 1H, .1=6.6 Hz), 7.21 (d, 2H, J=8.3 Hz), 7.46 (d, 2H, J=8.3 Hz).

^{13}C NMR: 6 21.15,22.03,71.54, 121.71, 127.83, 131.62, 140.82, 169.95.

(+)-l-(4-BromophenyI)ethanoI[(+)-195c]:

This compound was prepared by the treatment of 4-bromoacetophenone **(170)** with $BH_3.SMe_2$ following the similar procedure described for the molecule (±)-**176b**, as a

colorless **liquid.**

Yield: 92%

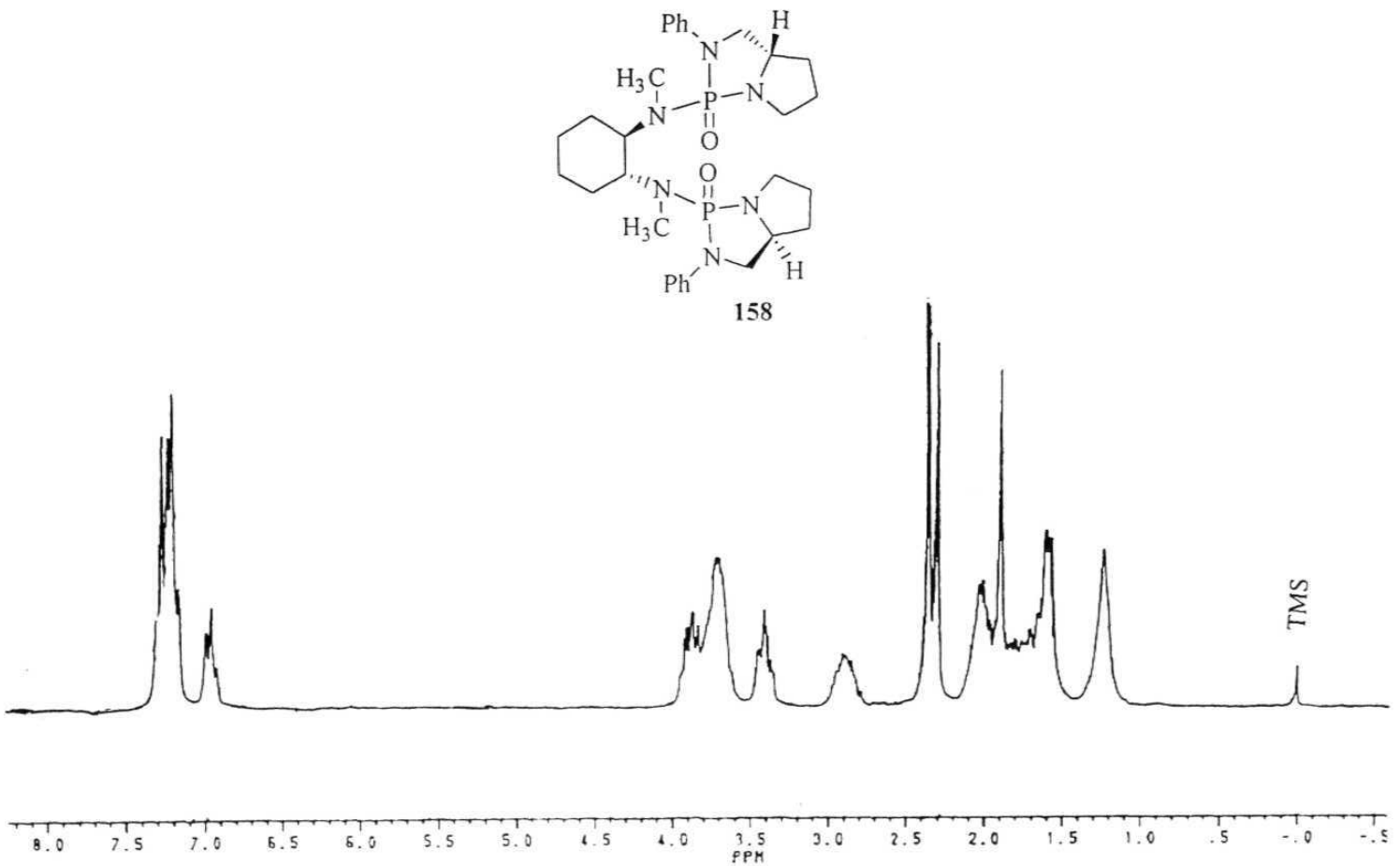
This alcohol has identical IR, ^{1}H & ^{13}C NMR spectral data as that of the **chiral** molecule (*R*)-**195c**.

(±)-1-Acetoxy-1-(4-bromophenyl)ethane [(±)-196c]:

This compound was prepared as a colorless liquid *via* the treatment of (±)-l-(4-bromophenyl)ethanol [(±)-**195c**] with acetic anhydride in presence of pyridine, according to the procedure described for the compound (*S*)-**171** (page no. 143).

Yield: 80%

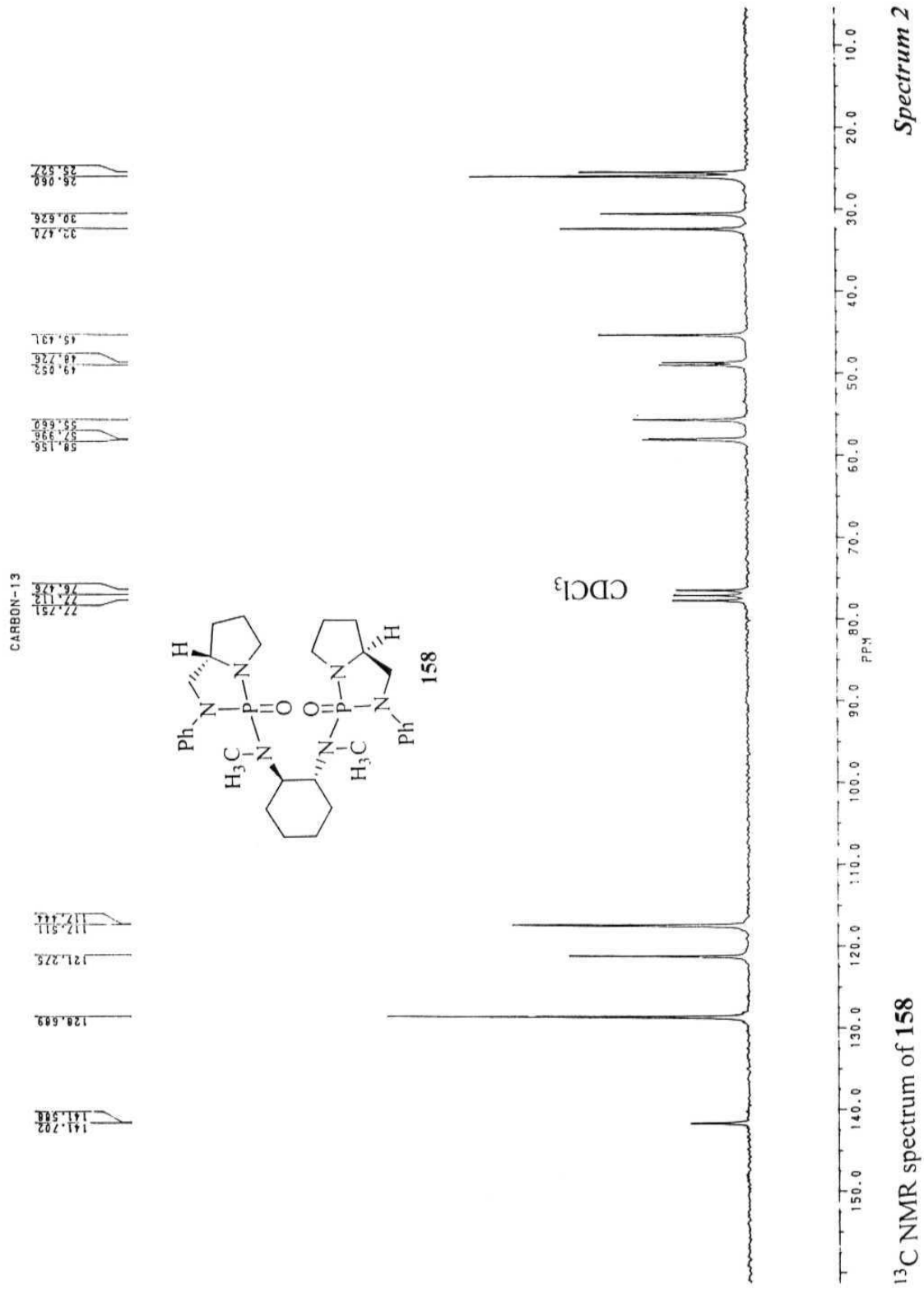
The spectral data (1R, ^{1}H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*R*)-**196c**.



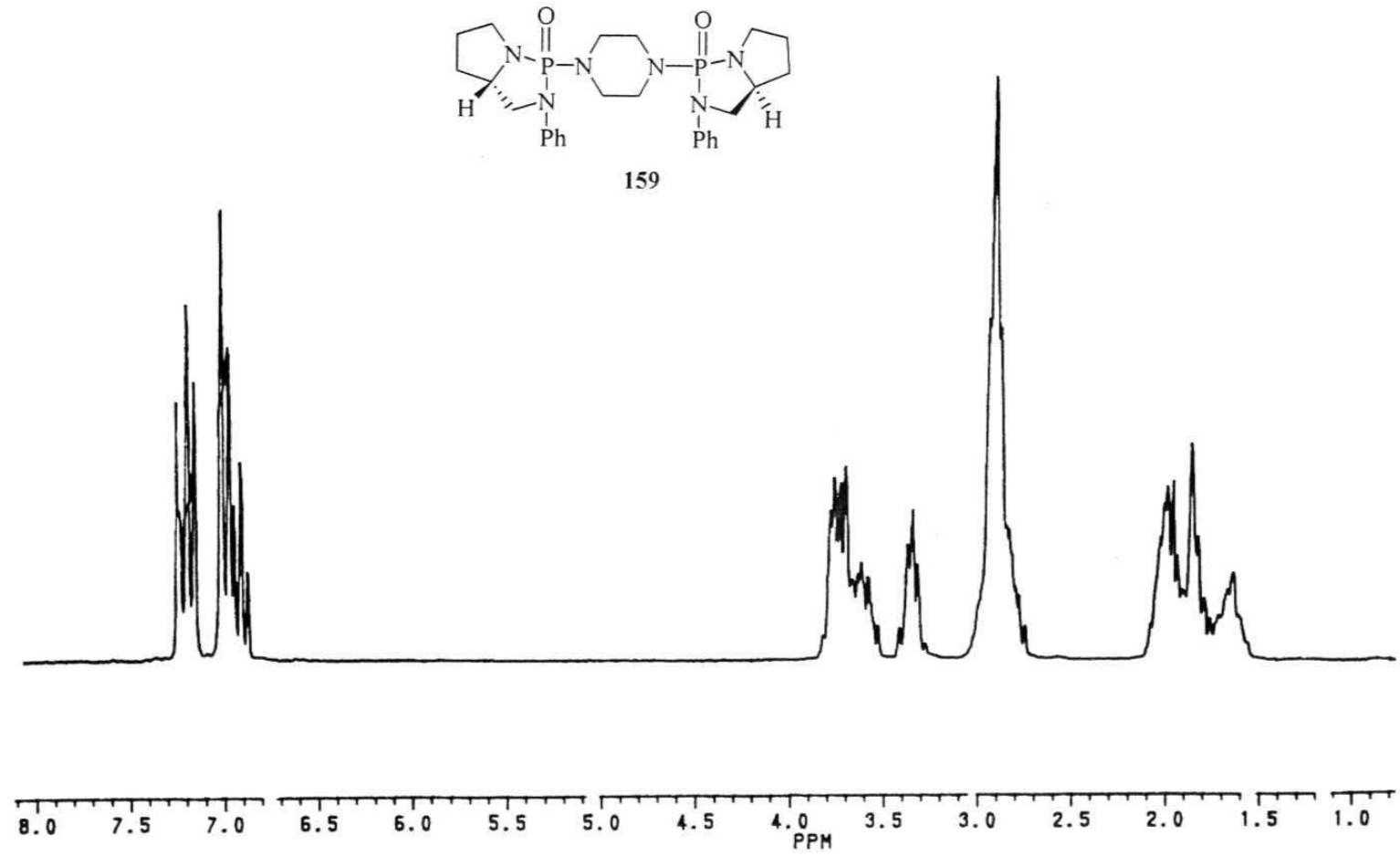
158

Spectrum 1

^{1}H NMR spectrum of **158**



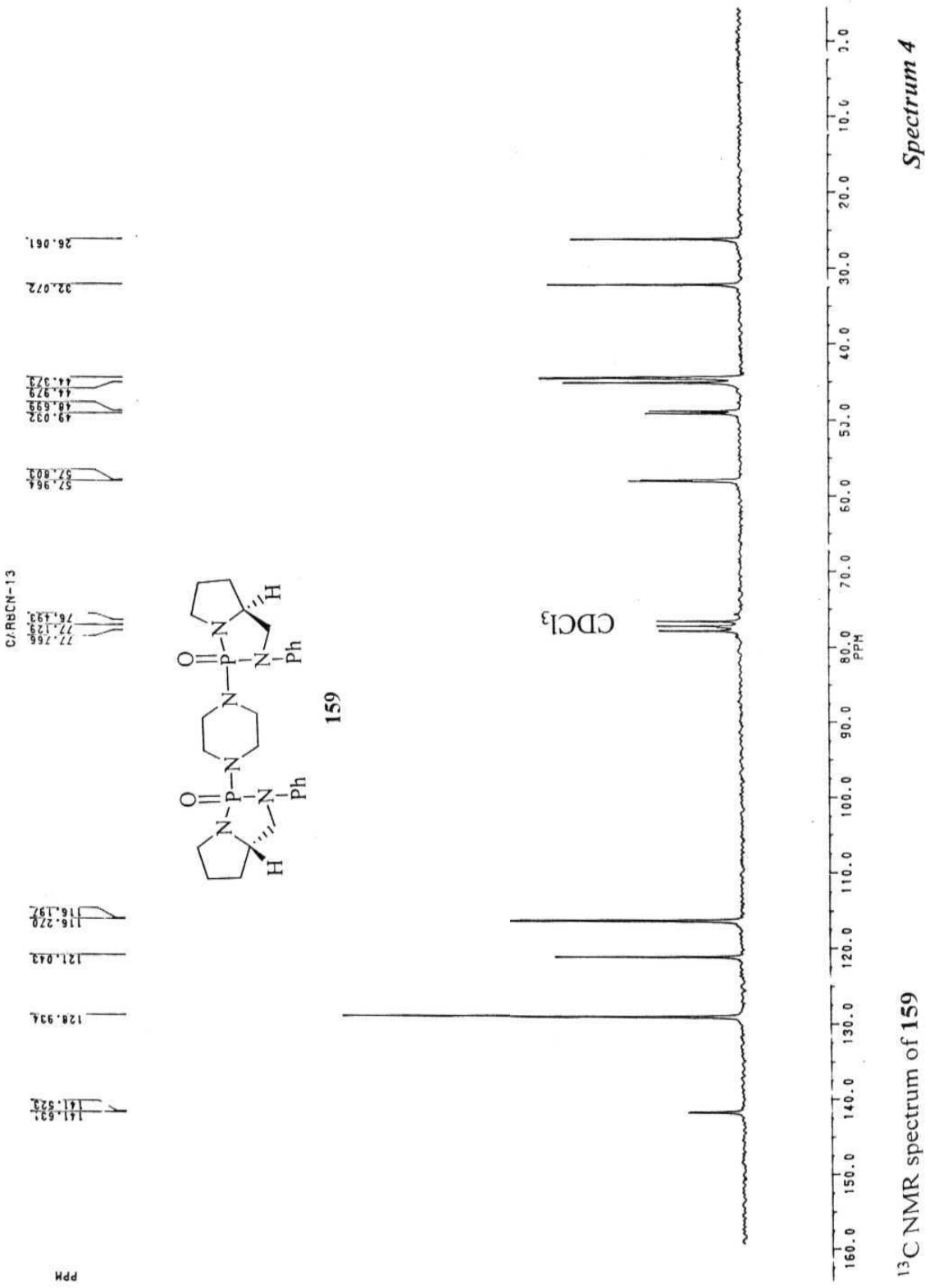
^{13}C NMR spectrum of **158**



159

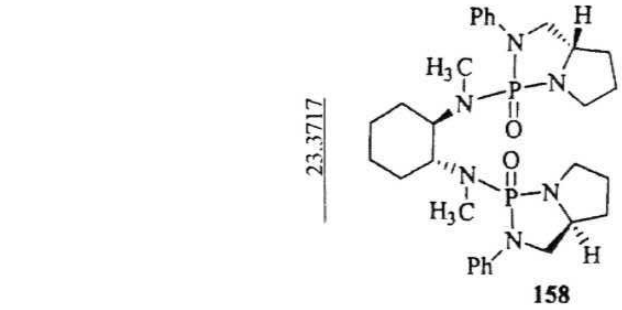
^{1}H NMR spectrum of **159**

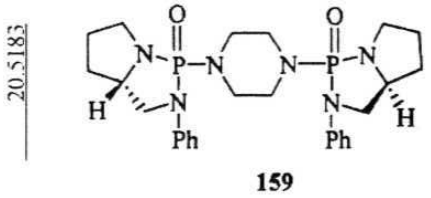
Spectrum 3

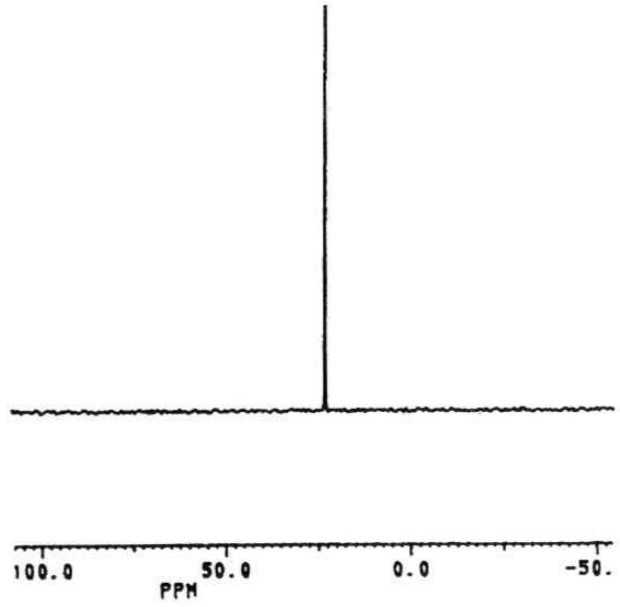


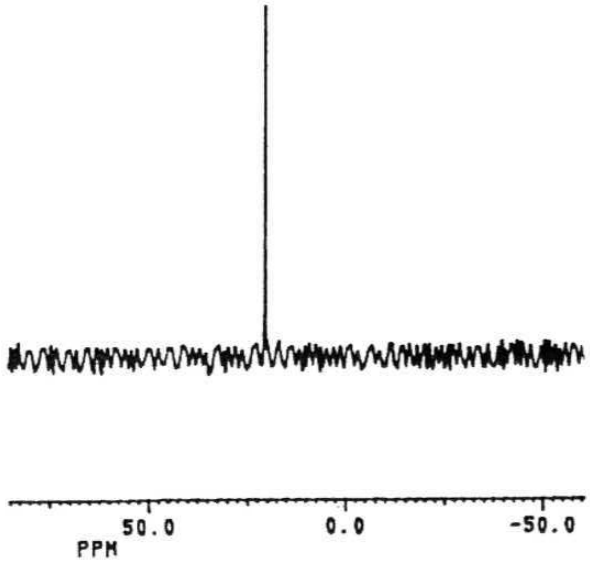
^{13}C NMR spectrum of **159**

Spectrum 4



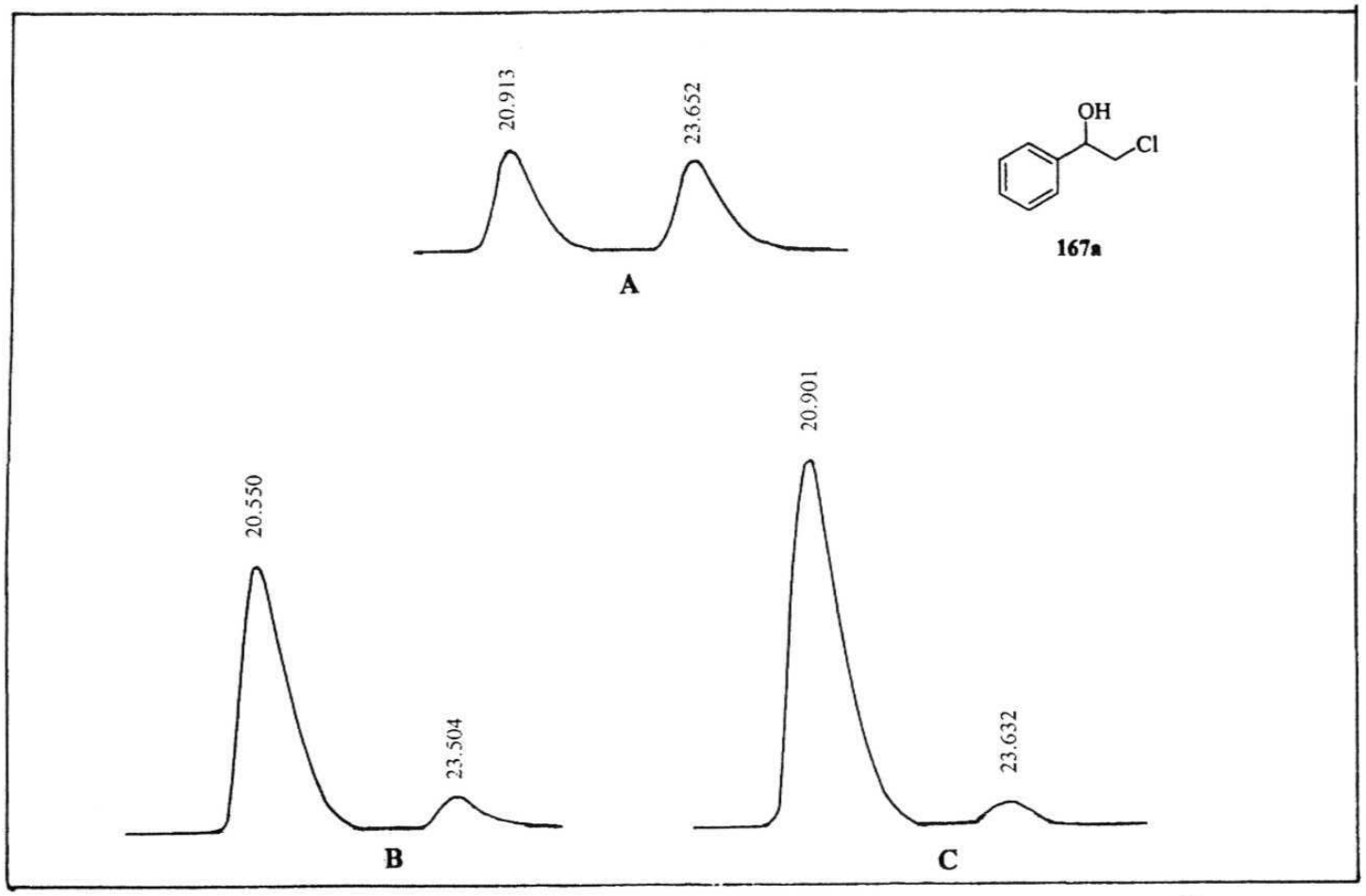




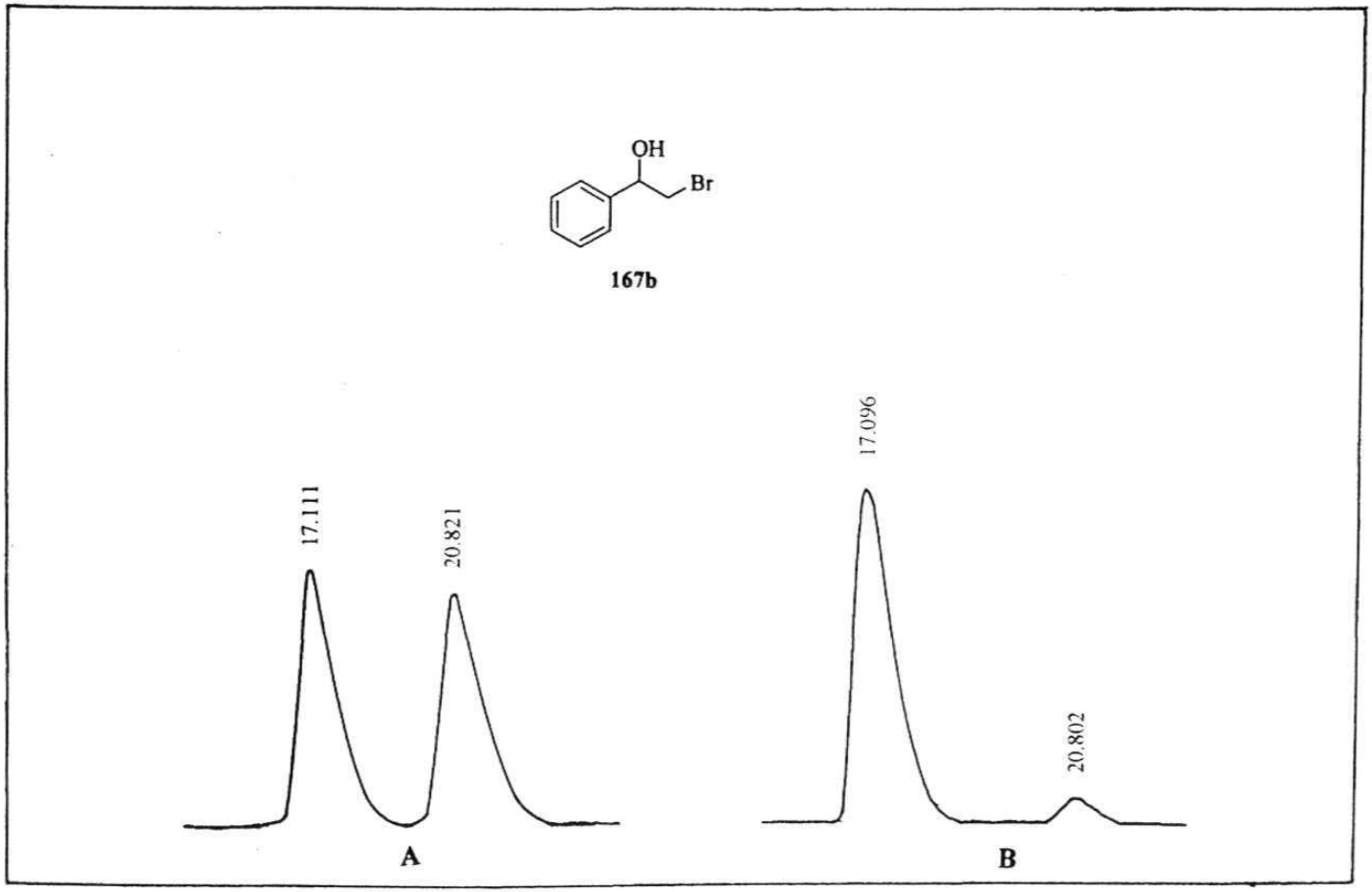


Spectrum 5

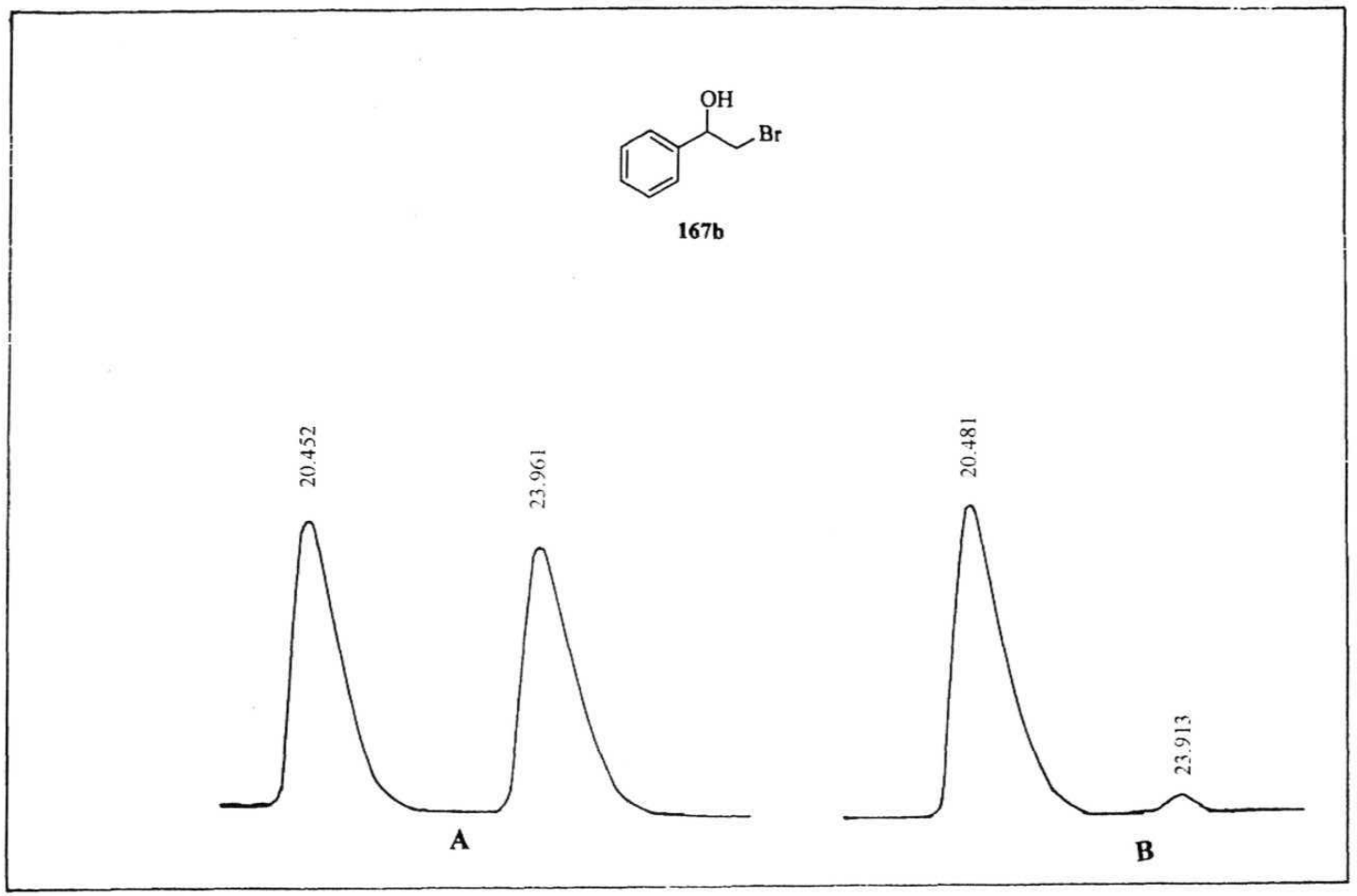
(A) ^{31}P NMR spectrum of **158** (B) ^{31}P NMR spectrum of **159**



HPLC analysis of **167a** (A) Chromatogram of (±)-**167a**, (B) Chromatogram of (*S*)-**167a**, 82% ee (obtained *via* the asymmetric reduction of **166a** using 30 mol% catalyst **158**), (C) Chromatogram of (*S*)-**167a**, 90% ee (obtained *via* the asymmetric reduction of **166a** using 30 mol% catalyst **159**). ***Chromatogram 1***

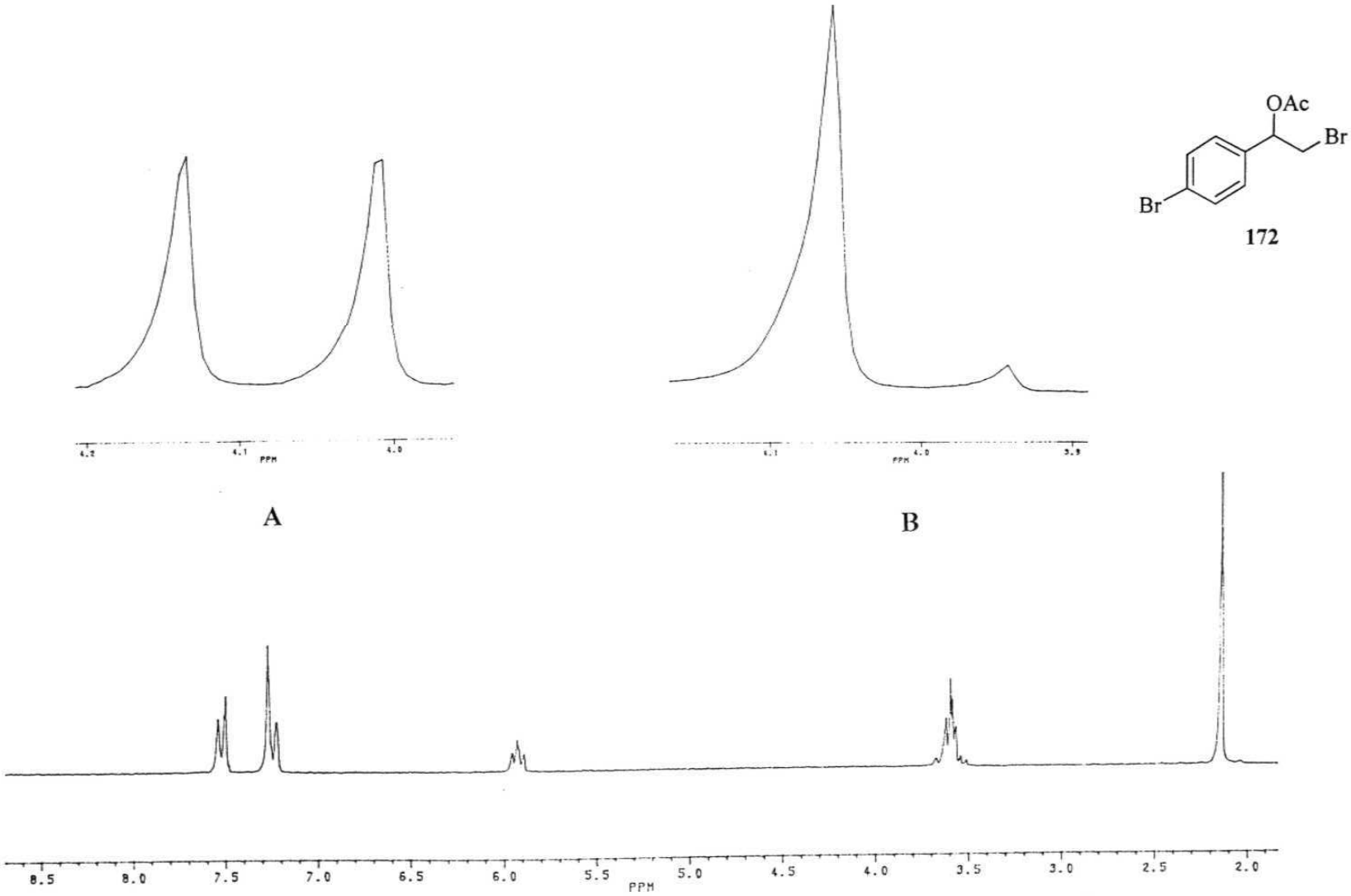


HPLC analysis of 167b (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 89% ee ***Chromatogram 2***
(obtained *via* the asymmetric reduction of 166b using 30 mol% catalyst **158)**
Solvent system, hexanes: IPA / 90:10; flow rate: 0.5 mL / min.



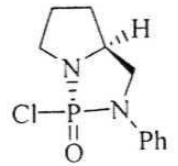
HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 94% ee (obtained *via* the asymmetric reduction of **166b** using 30 mol% catalyst **159**). ***Chromatogram 3***

Solvent system, hexanes: IPA / 95:05; flow rate: 0.5 mL / min.

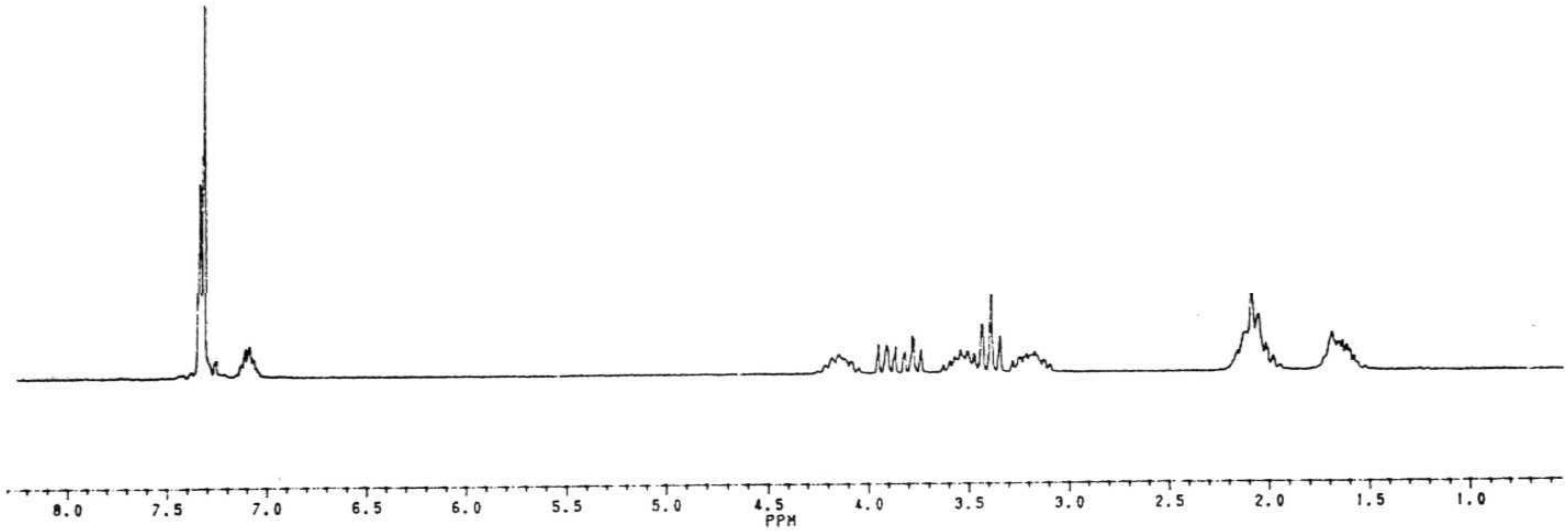


Spectrum 6

^{1}H NMR spectrum of **172** (A) splitting of acetoxy methyl protons ($OCO\underline{CH_3}$) of the molecule (±)-**172** in the presence of $Eu(hfc)_3$ (B) splitting of acetoxy methyl protons ($OCO\underline{CH_3}$) of the molecule (*S*)-**172** [acetate of alcohol (*S*)-**167e**, obtained *via* the asymmetric reduction of **166e** using 30 mol% catalyst **159**] in the presence of $Eu(hfc)_3$, 93% ee.

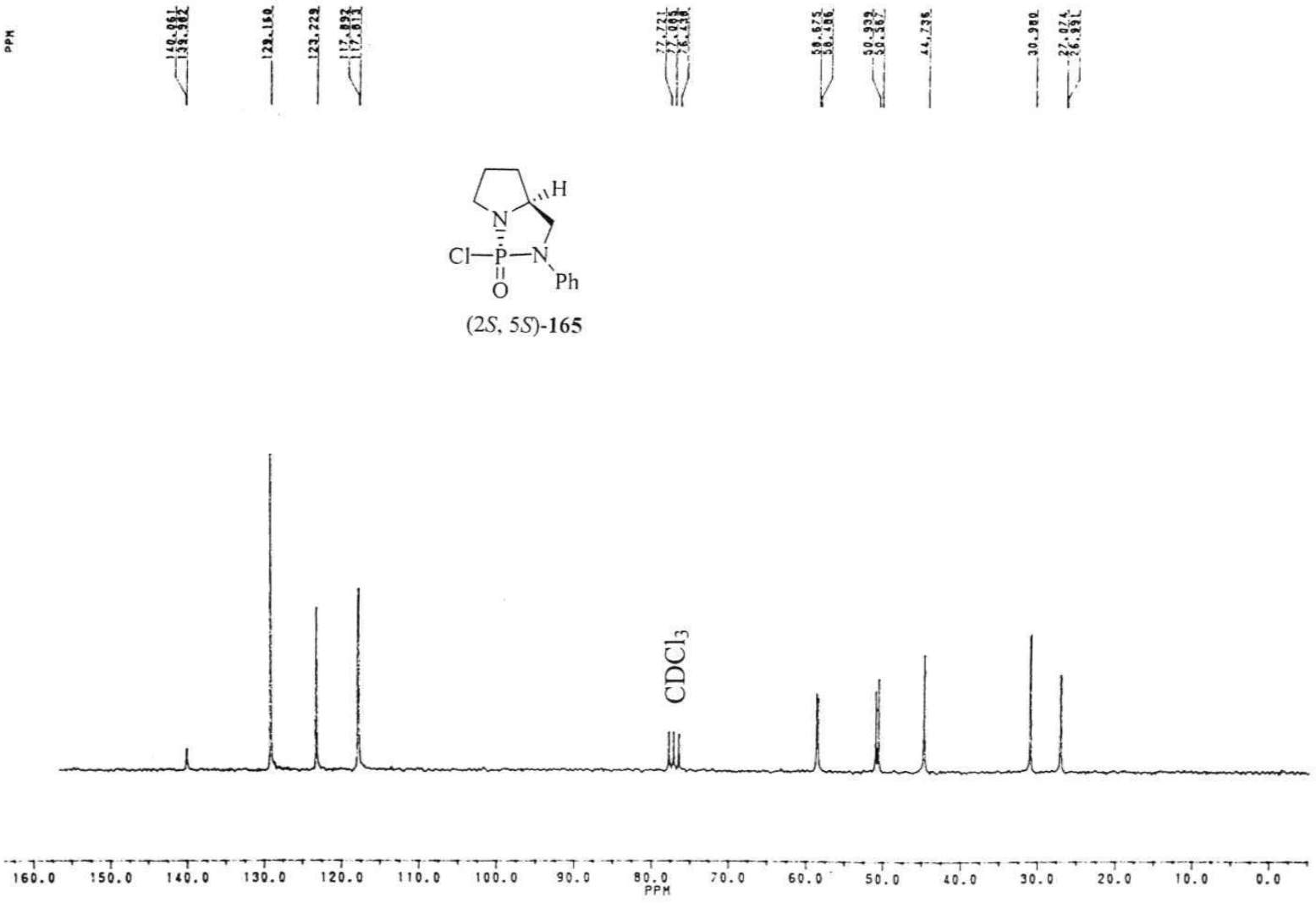


(2*S*, 5*S*)-**165**



^{1}H NMR spectrum of (2*S*, 5*S*)-**165**

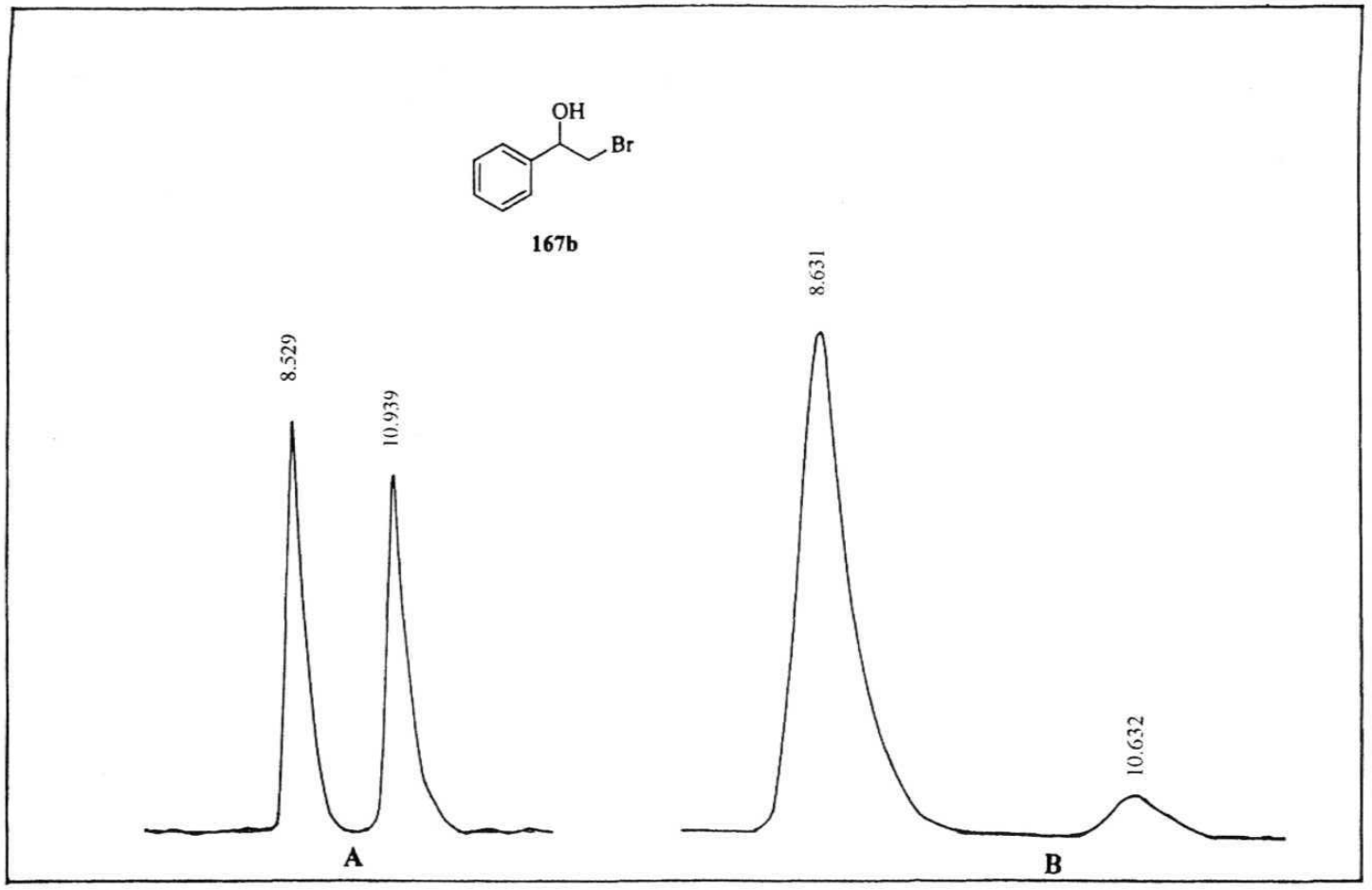
Spectrum 7



(2*S*, 5*S*)-**165**

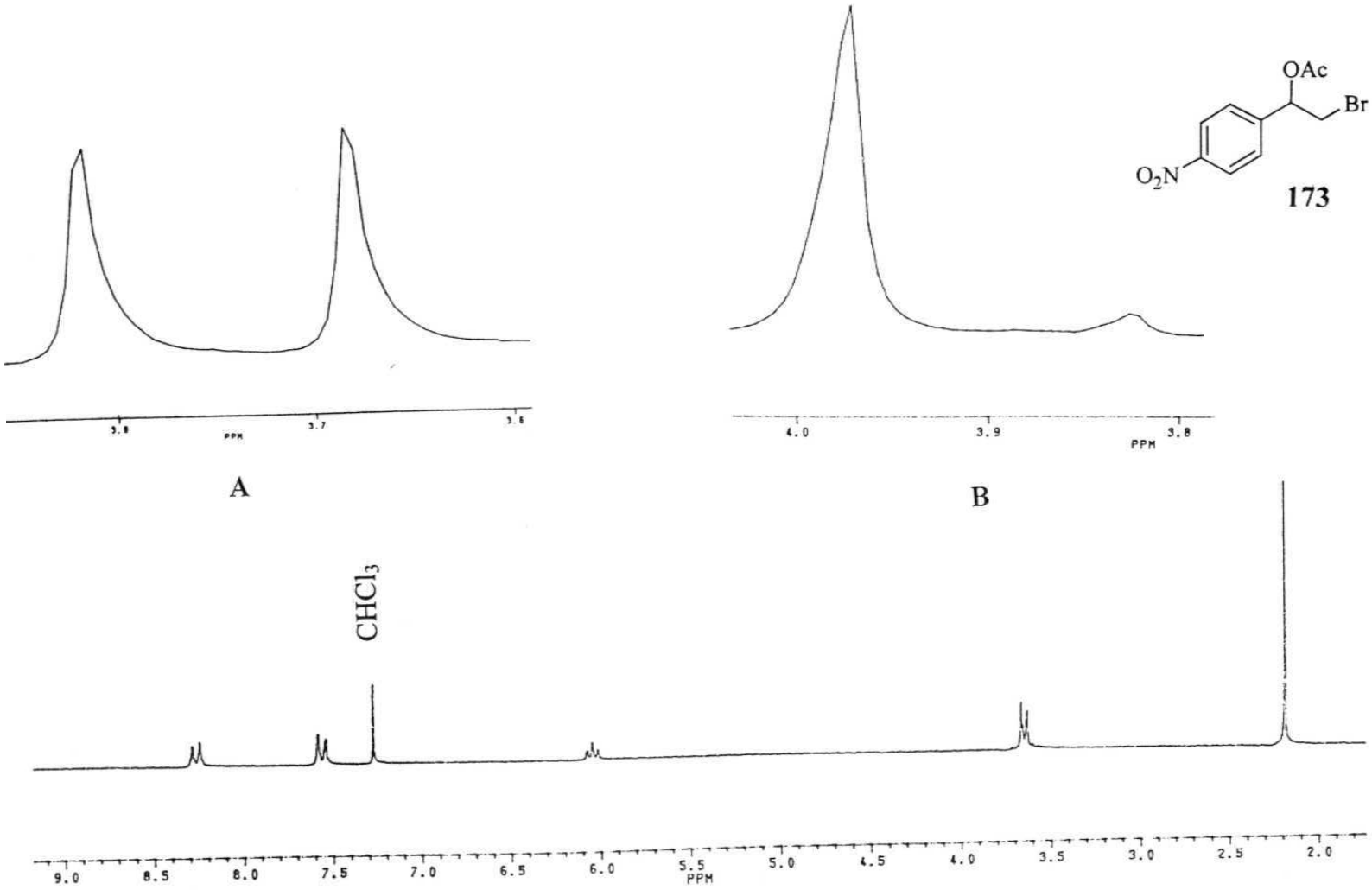
^{13}C NMR spectrum of (2*S*, 5*S*)-**165**

Spectrum 8



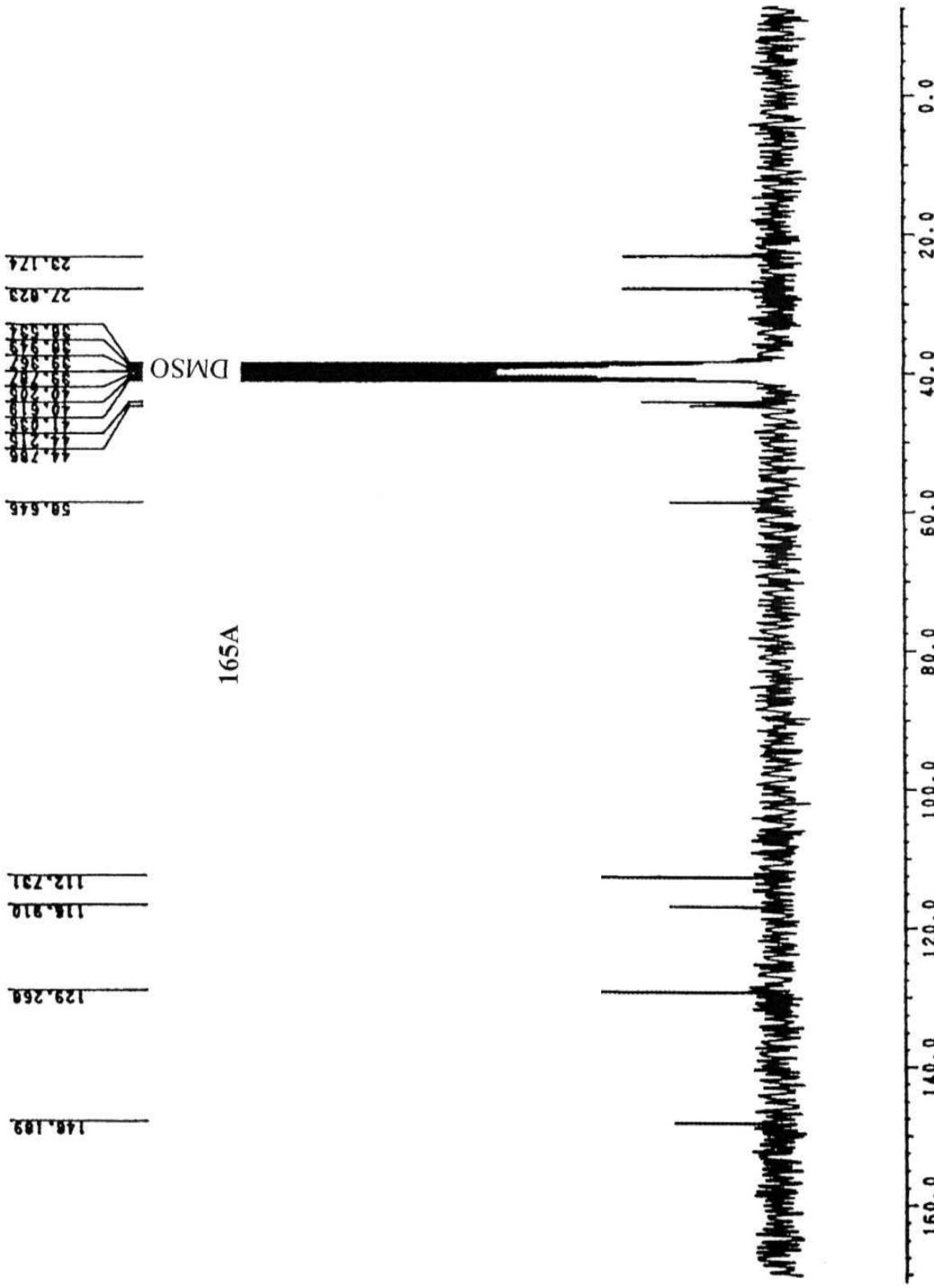
HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 87% ee ***Chromatogram 4***
[obtained *via* the asymmetric reduction of **166b** using 5 mol% chiral source (2*S*, 5*S*)-**165**].

Solvent system, hexanes: IPA / 90:10; flow rate: 1.0 mL / min.



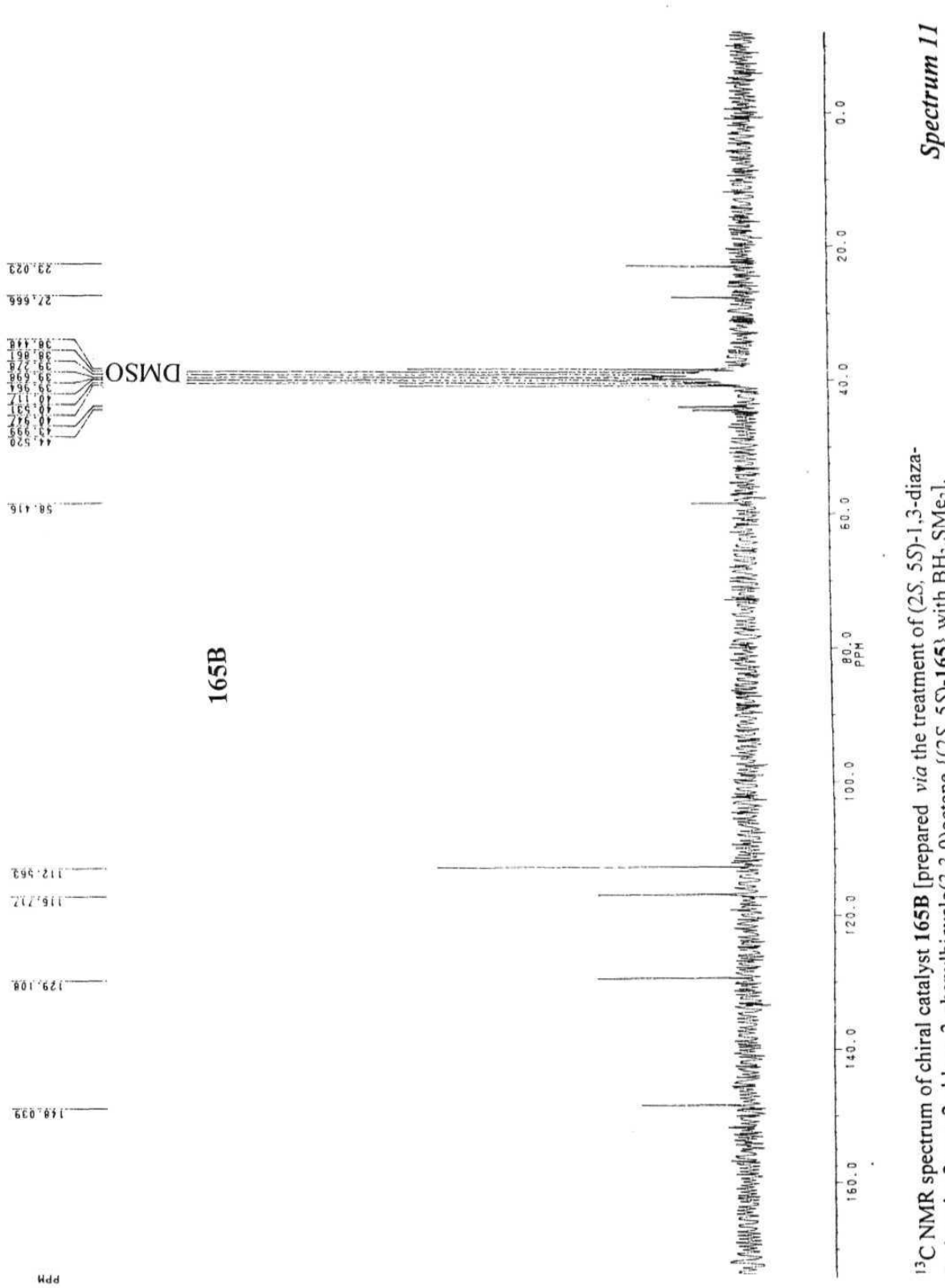
Spectrum 9

^{1}H NMR spectrum of **173** (A) splitting of acetoxy methyl protons ($OCO\underline{CH_3}$) of the molecule (±)-**173** in the presence of Eu(hfc)$_3$ (B) splitting of acetoxy methyl protons ($OCO\underline{CH_3}$) of the molecule (*S*)-**173** [acetate of alcohol (*S*)-**167h**, obtained *via* the asymmetric reduction of **166h** using 5 mol% catalyst (2*S*, 5*S*)-**165**] in the presence of Eu(hfc)$_3$, 91% ee.



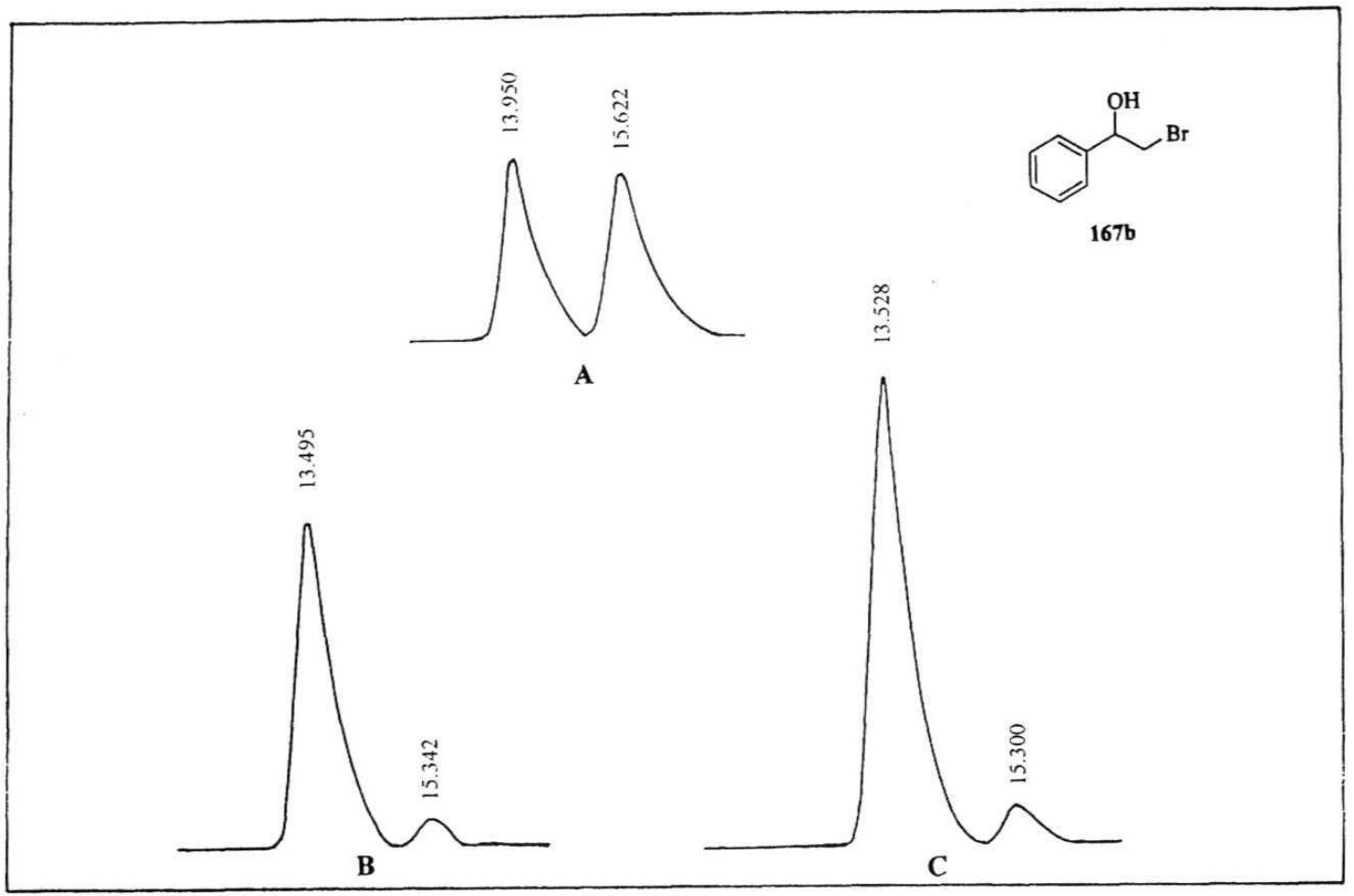
Spectrum 10

^{13}C NMR spectrum of recovered chiral catalyst **165A** [from the (2*S*, 5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane {(2*S*, 5*S*)-**165**)} (5 mol%) catalyzed asymmetric reduction of phenacyl bromide (**166b**) with BH_3.SMe$_2$].

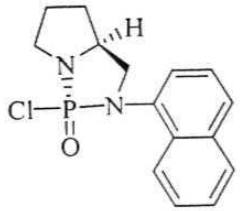


^{13}C NMR spectrum of chiral catalyst **165B** [prepared *via* the treatment of (2*S*, 5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane {(2*S*, 5*S*)-**165**} with BH_3.SMe_2].

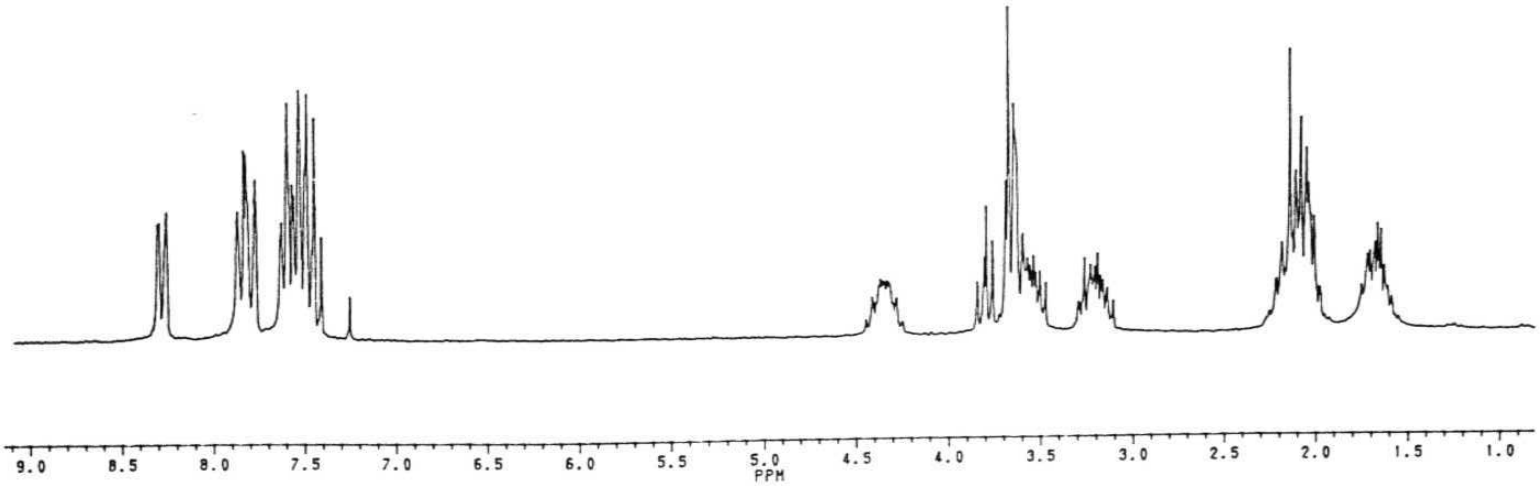
Spectrum 11



HPLC analysis of **167b** (**A**) Chromatogram of (±)-**167b**, (**B**) Chromatogram of (*S*)-**167b**, 85% ee (obtained *via* the asymmetric reduction of **166b** using 12.8 mg catalyst **165A**), (**C**) Chromatogram of (*S*)-**167b**, 82% ee (obtained *via* the asymmetric reduction of **166b** using 12.8 mg catalyst **165B**). Solvent system, hexanes: IPA / 95:05; flow rate: 1.0 mL / min. ***Chromatogram 5***

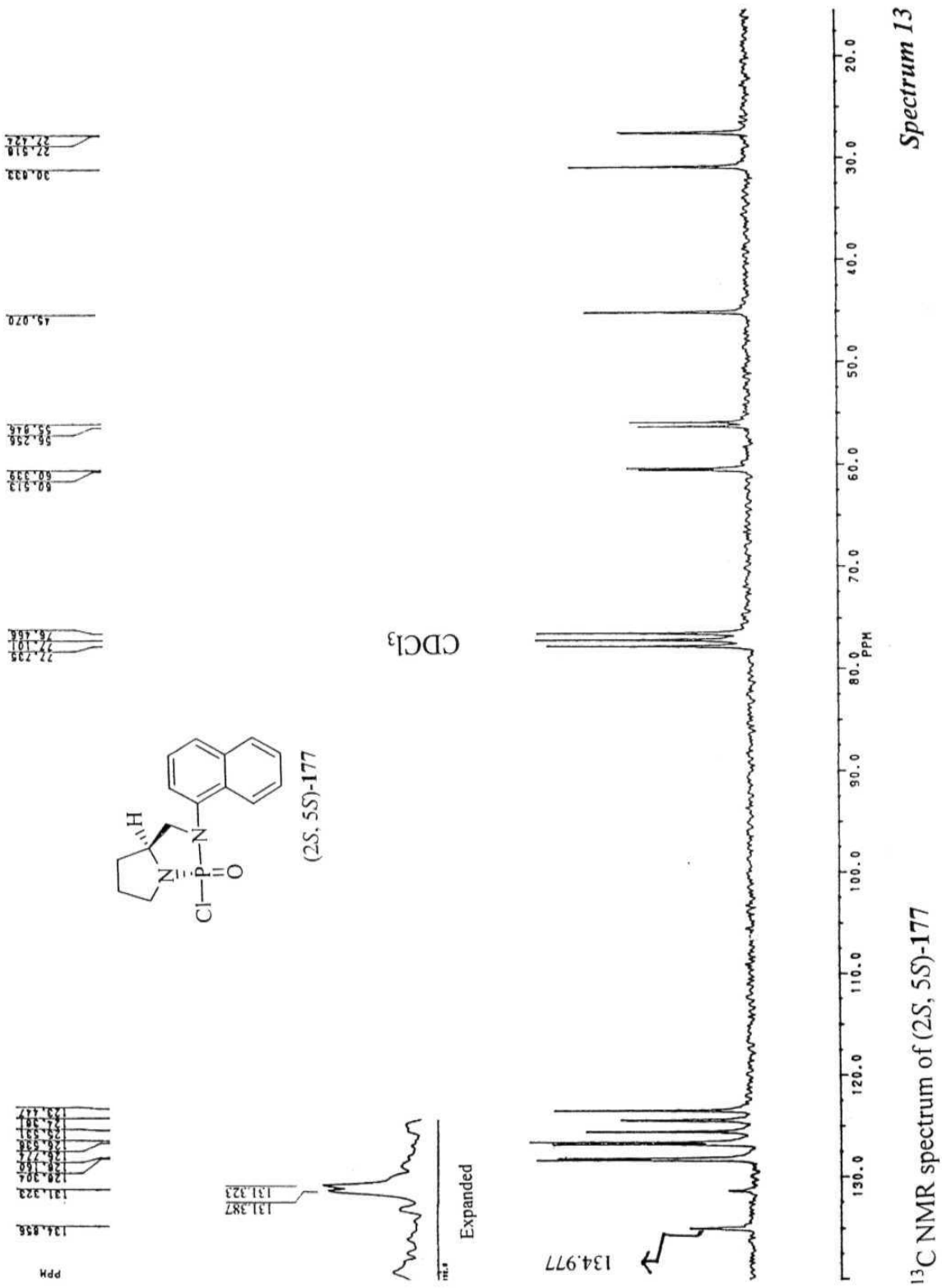


(2*S*, 5*S*)-**177**



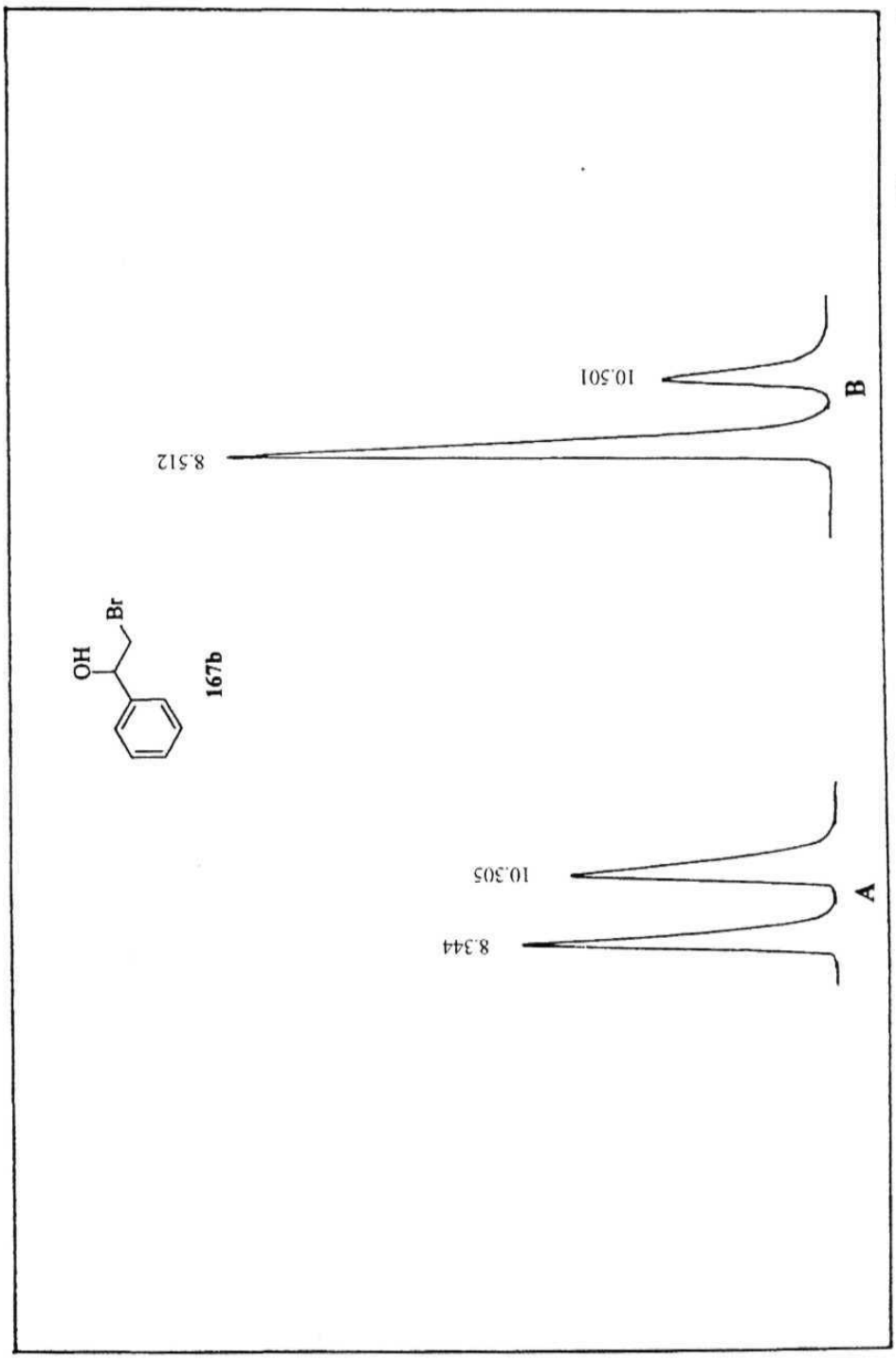
^{1}H NMR spectrum of (2*S*, 5*S*)-**177**

Spectrum 12



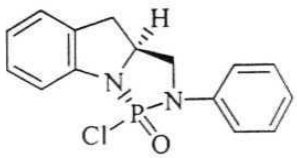
^{13}C NMR spectrum of (2*S*, 5*S*)-**177**

Spectrum 13

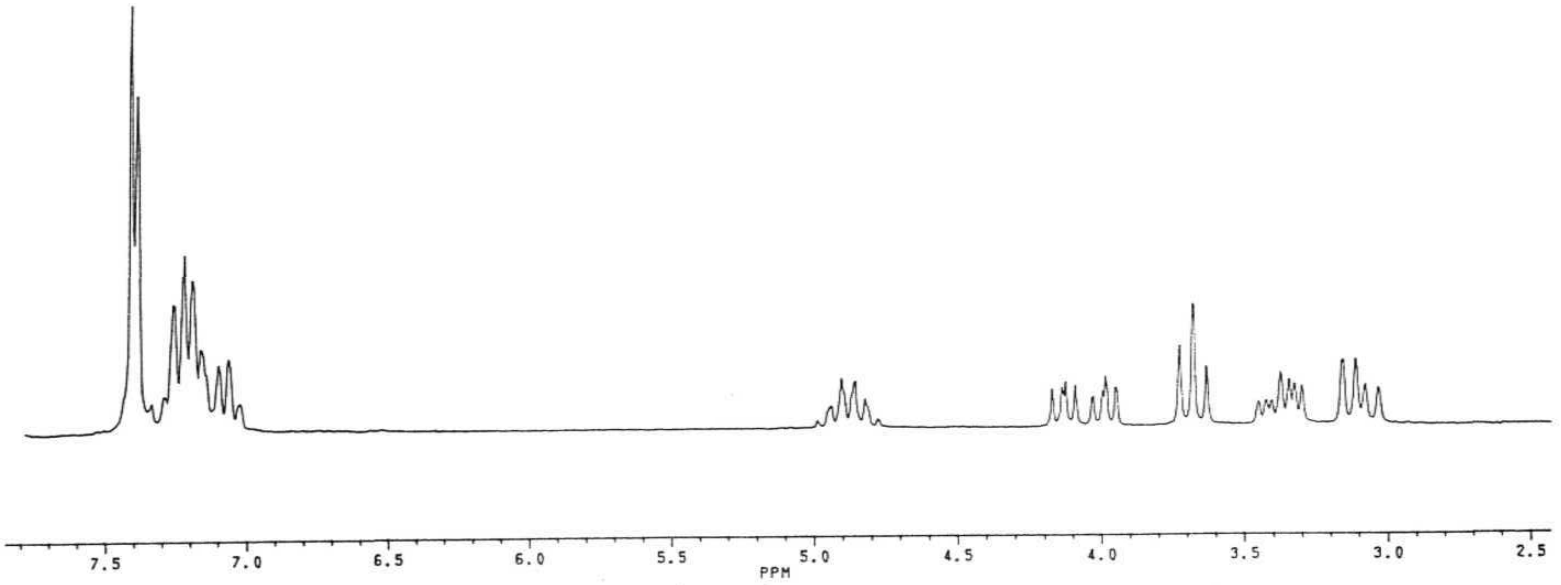


Chromatogram 6

HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 55% ee [obtained *via* the asymmetric reduction of **166b** using 20 mol% catalyst (2*S*, 5*S*)-**177**].

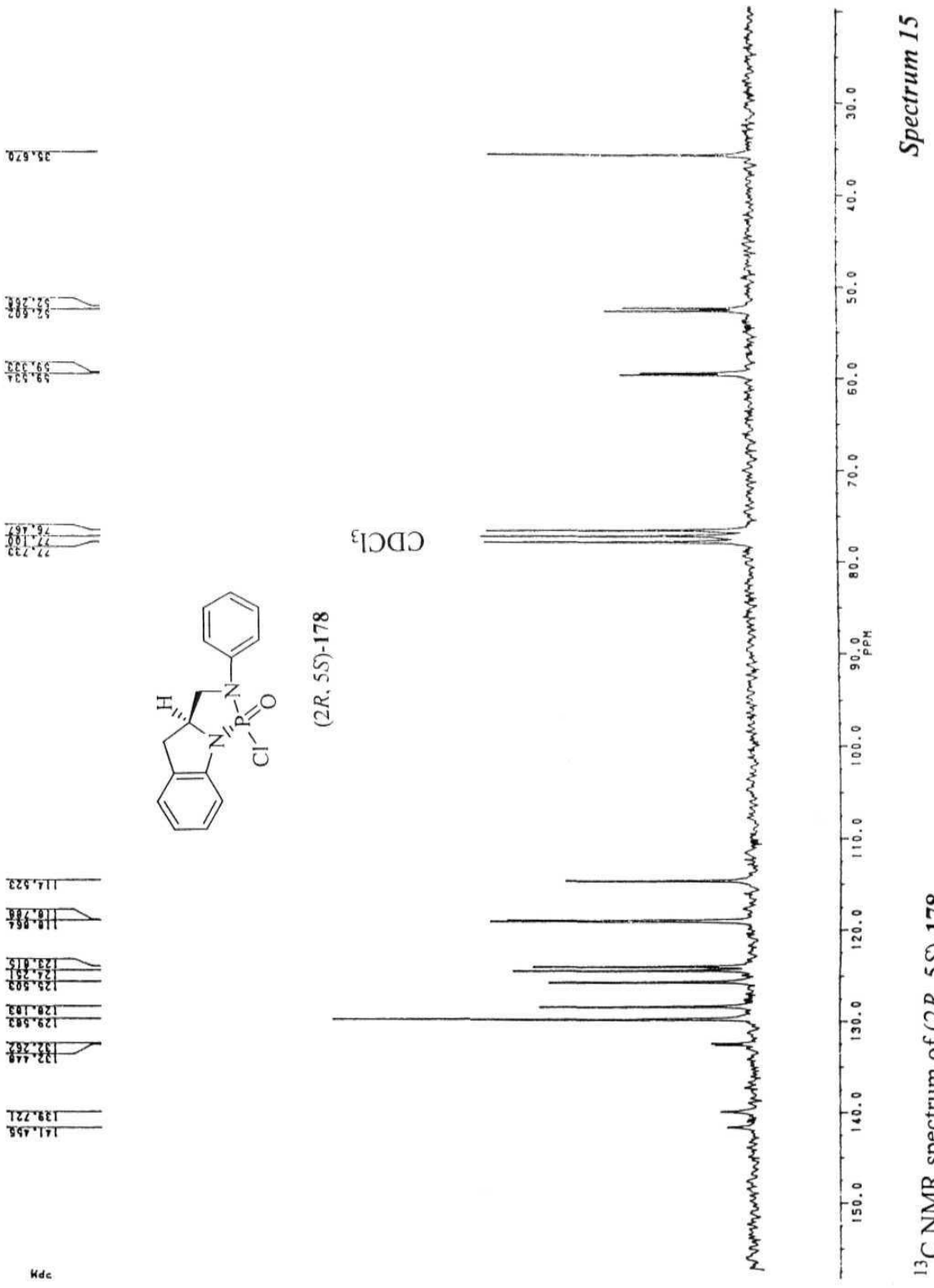


(2*R*, 5*S*)-**178**



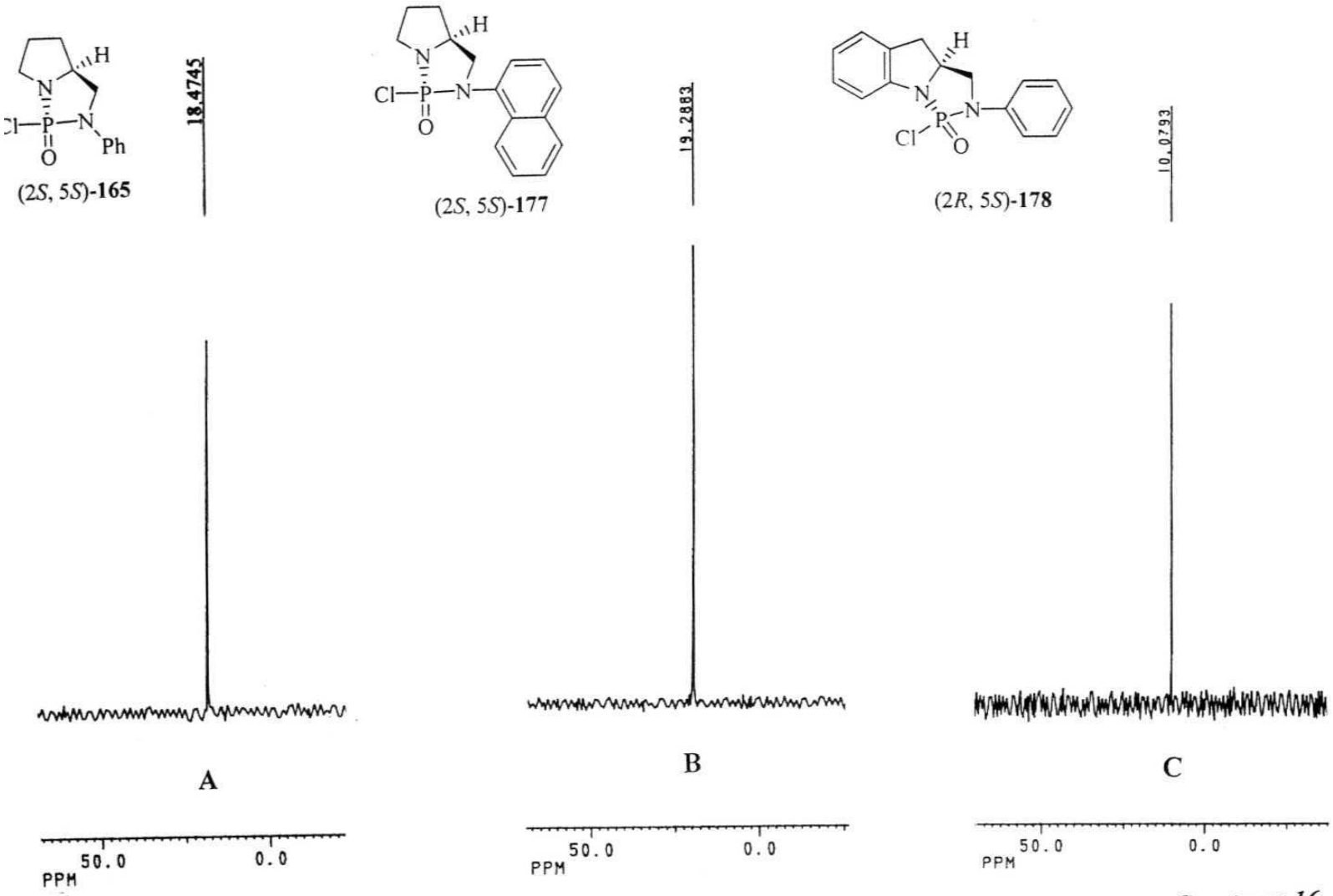
^{1}H NMR spectrum of (2*R*, 5*S*)-**178**

Spectrum 14



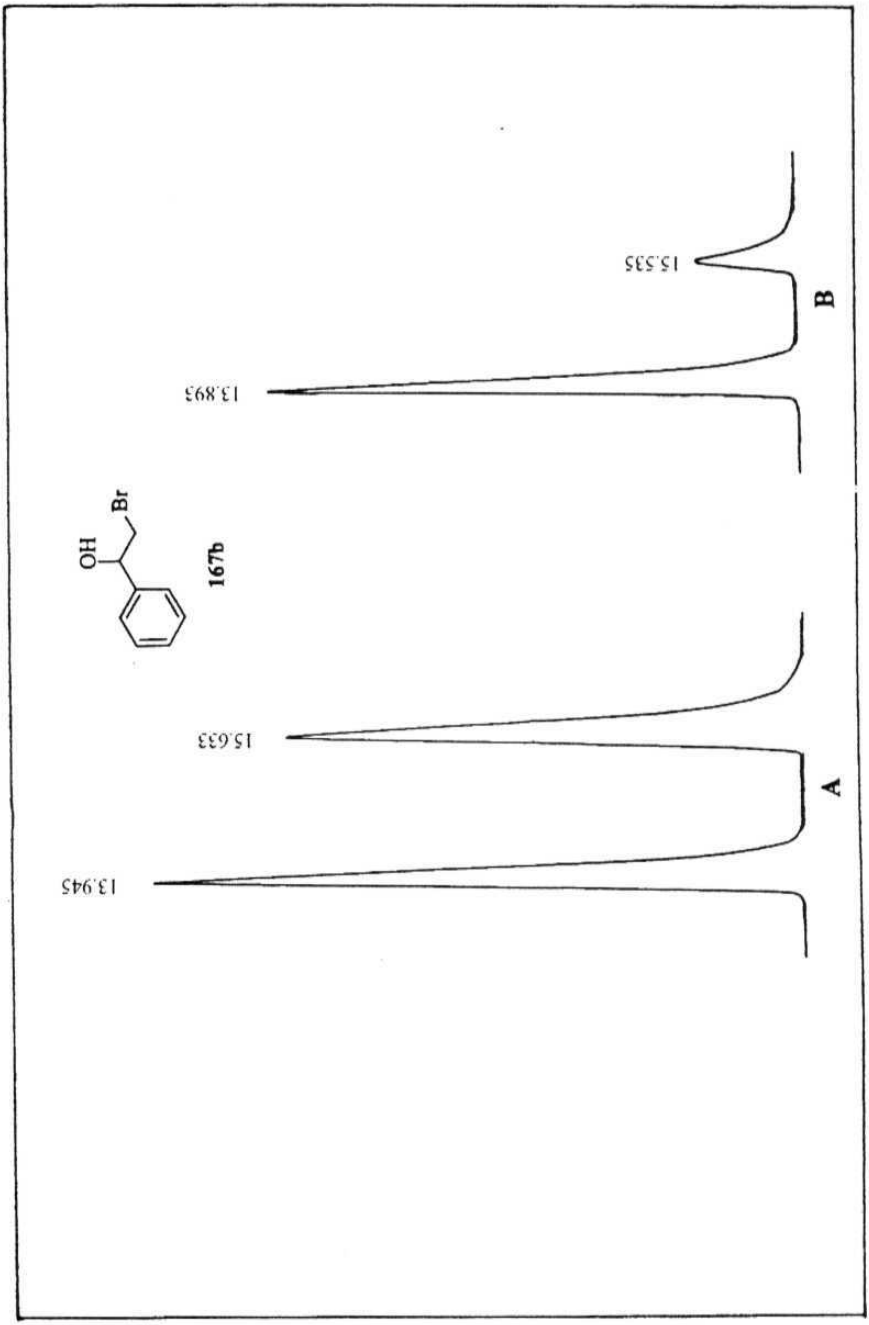
^{13}C NMR spectrum of (2*R*, 5*S*)-**178**

Spectrum 15

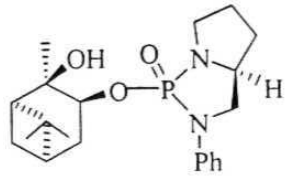


(A) ^{31}P NMR spectrum of (2*S*, 5*S*)-**165** (B) ^{31}P NMR spectrum of (2*S*, 5*S*)-**177**
(C) ^{31}P NMR spectrum of (2*R*, 5*S*)-**178**

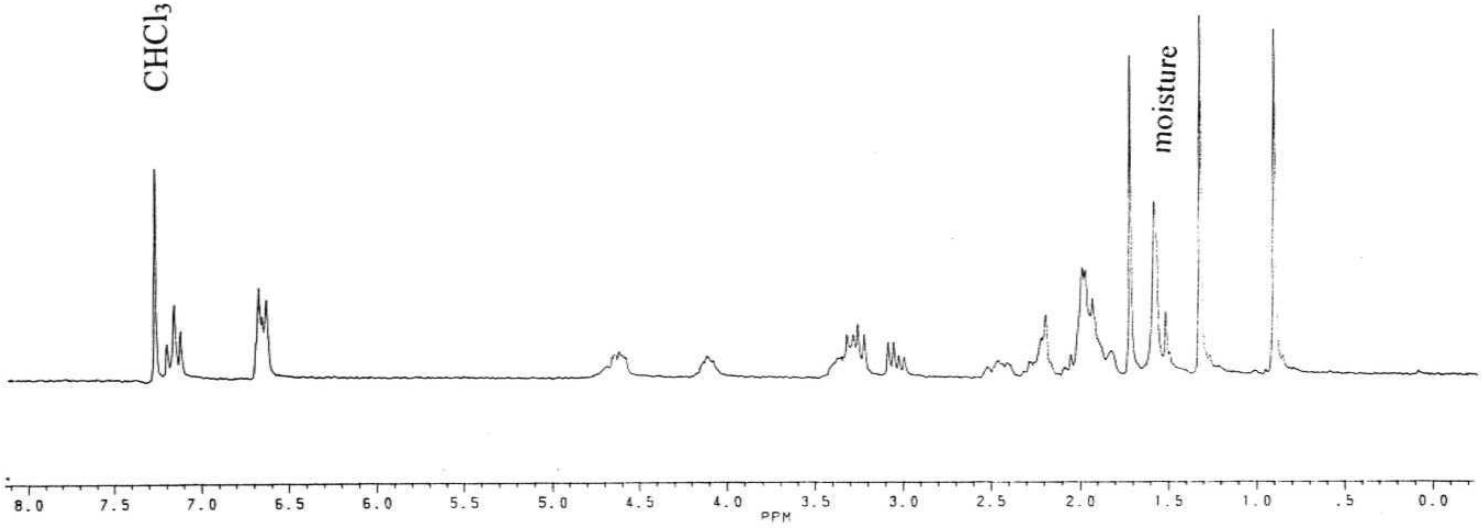
Spectrum 16



HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 65% ee ***Chromatogram 7*** [obtained *via* the asymmetric reduction of **166b** using 10 mol% catalyst (2*R*, 5*S*)-**178**].

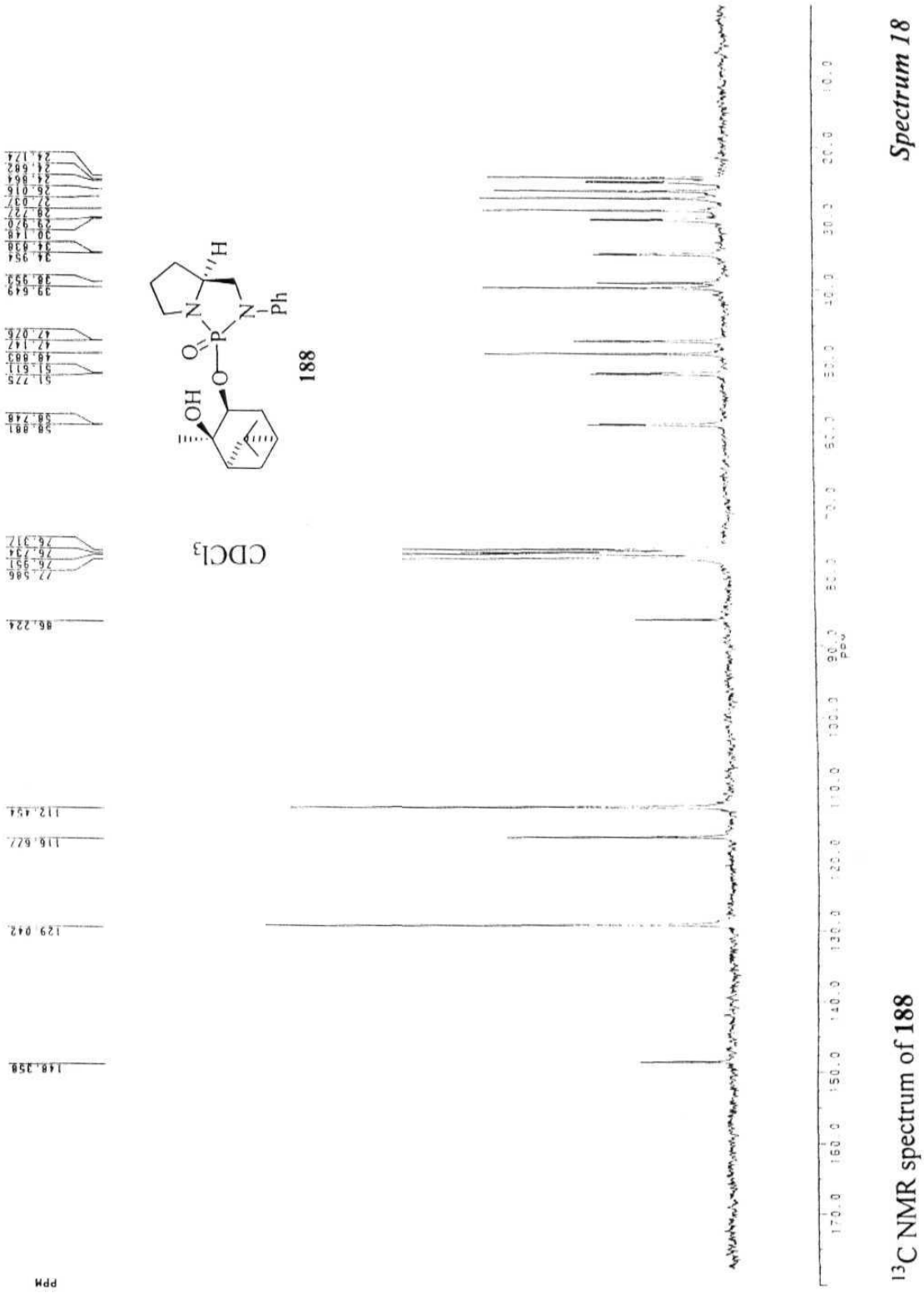


188



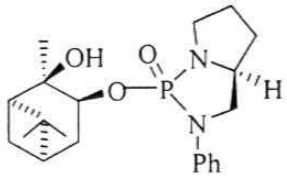
^{1}H NMR spectrum of **188**

Spectrum 17

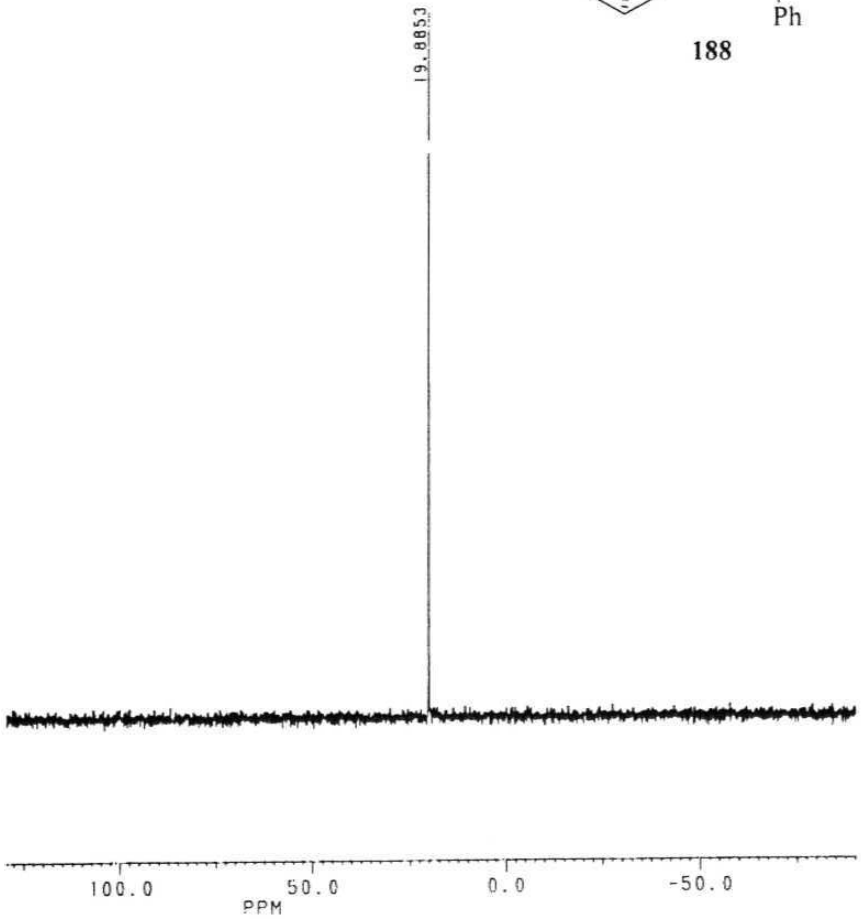


^{13}C NMR spectrum of **188**

Spectrum 18

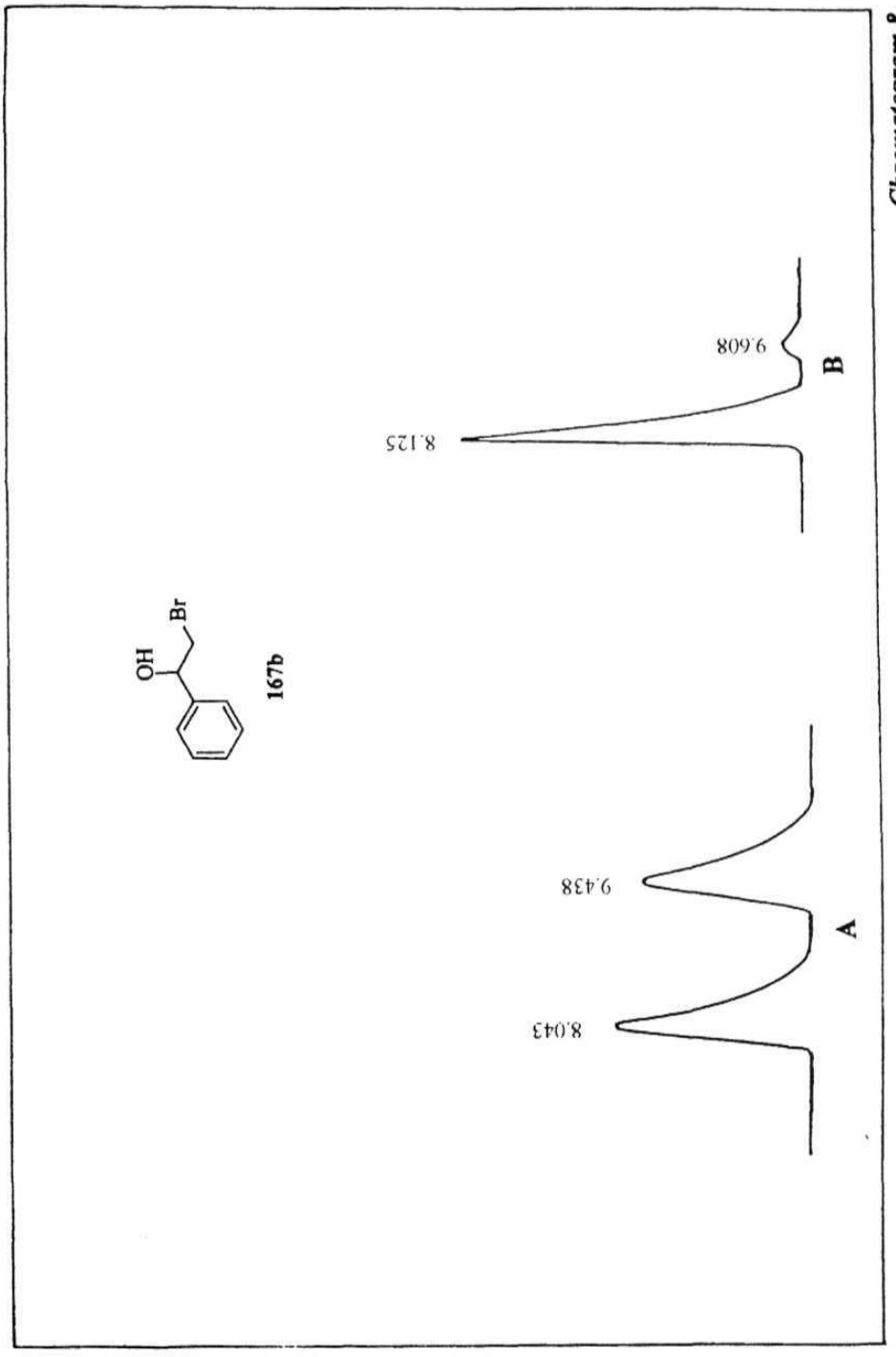


188



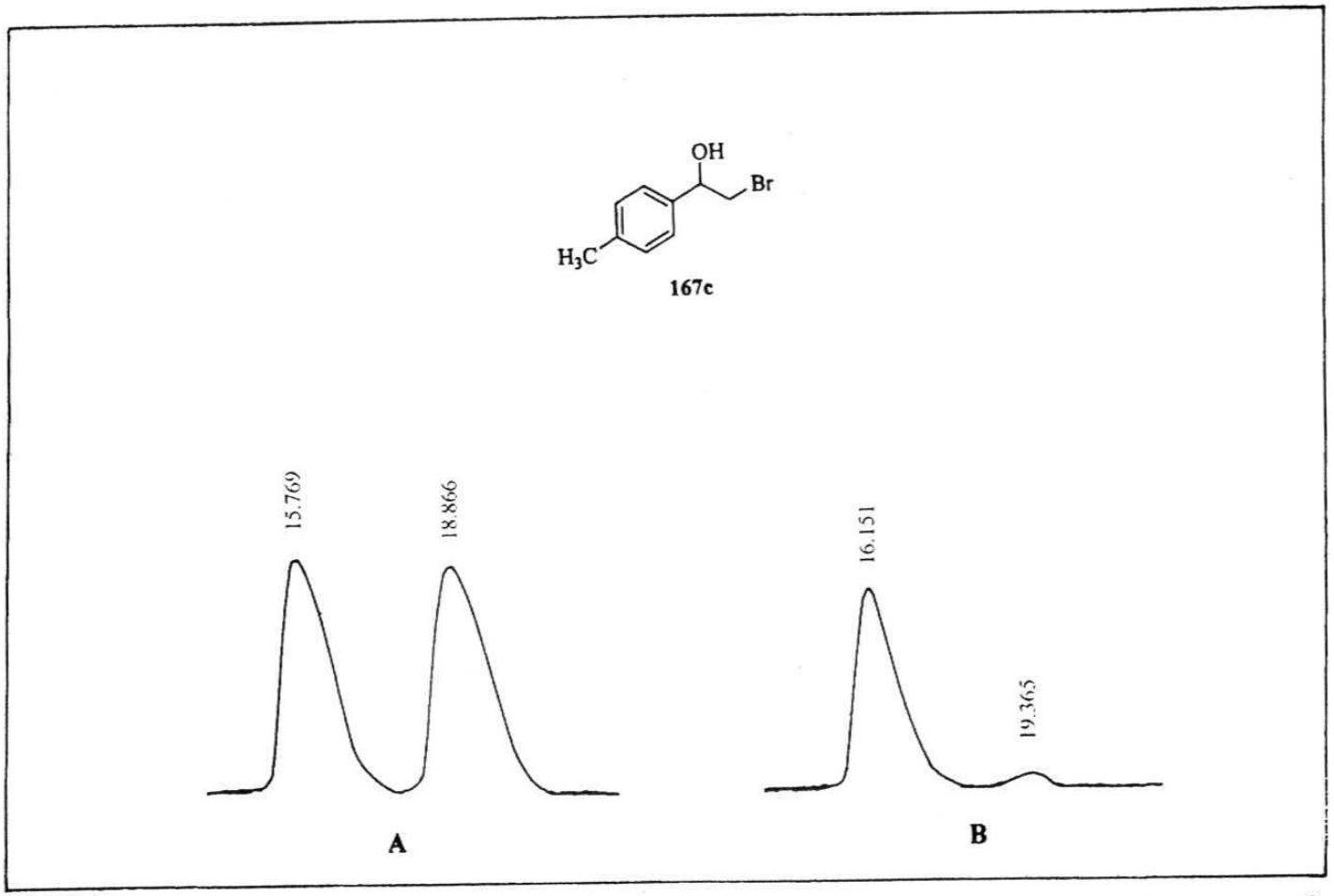
^{31}P NMR spectrum of **188**

Spectrum 19

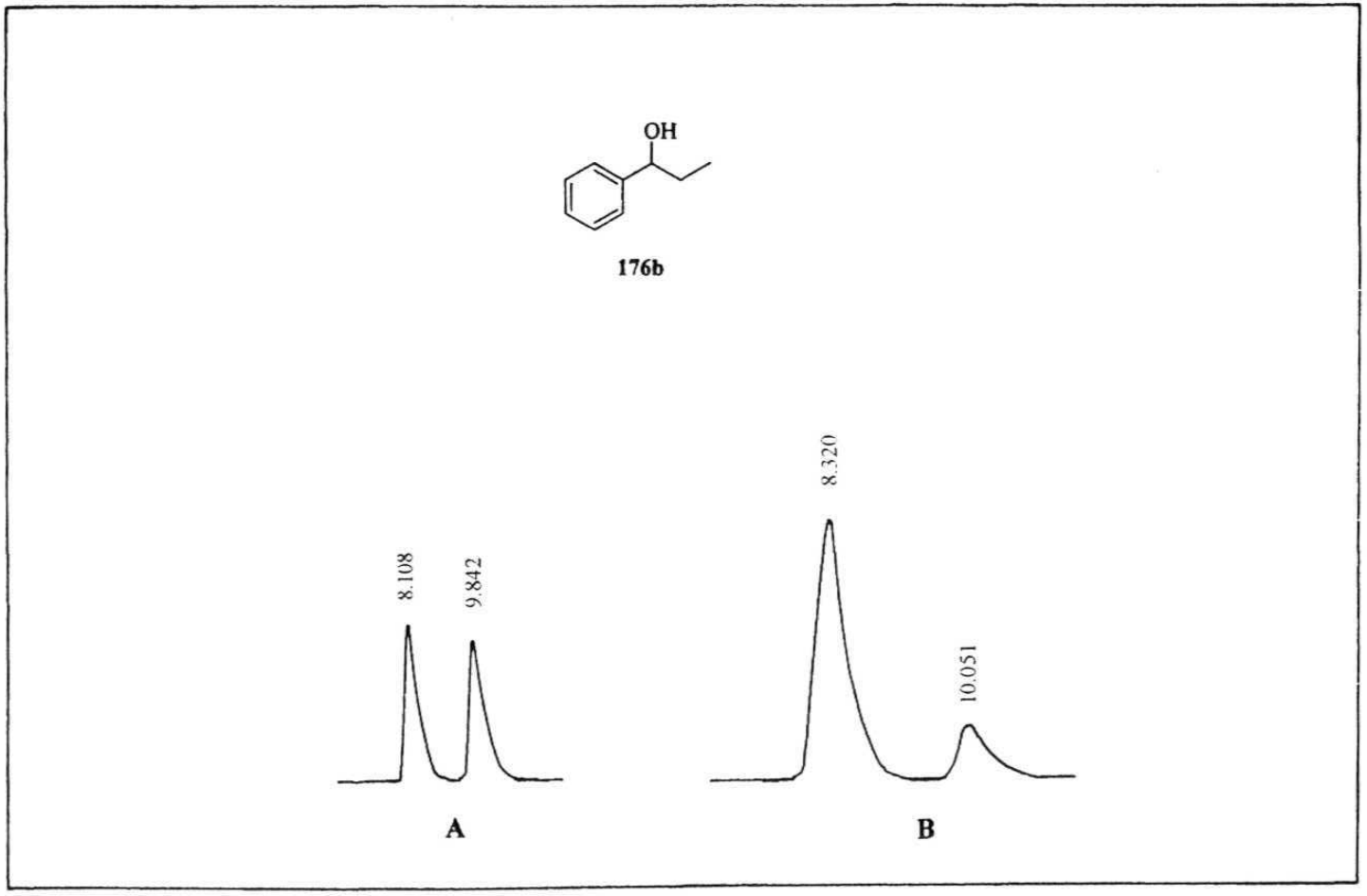


Chromatogram 8

HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 91% ee (obtained *via* the asymmetric reduction of **166b** using 4 mol% catalyst **188**).

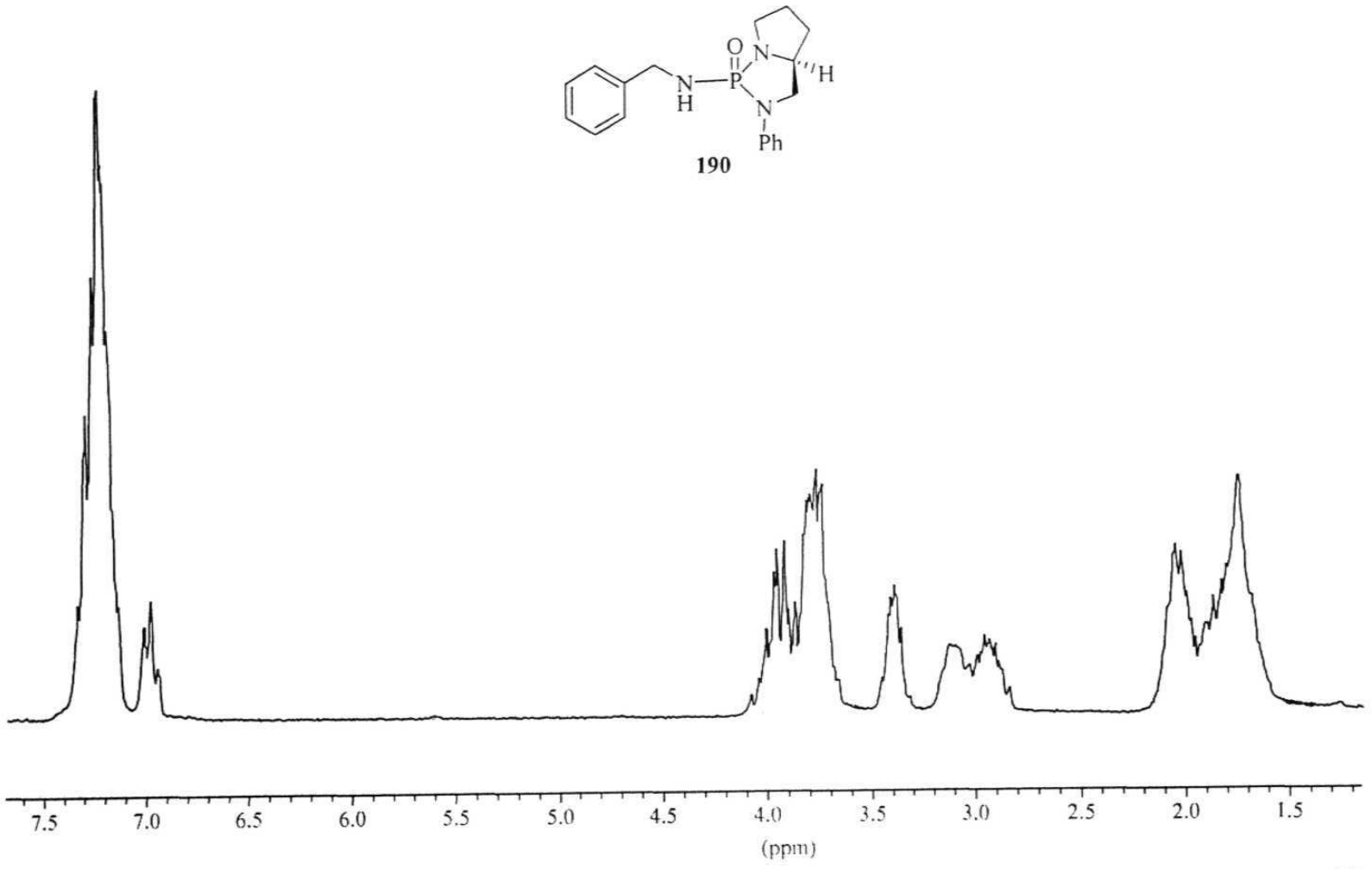


HPLC analysis of **167c** (A) Chromatogram of (±)-**167c**, (B) Chromatogram of (*S*)-**167c**, 91% ee (obtained *via* the asymmetric reduction of **166c** using 4 mol% catalyst **188**). ***Chromatogram 9***



Chromatogram 10

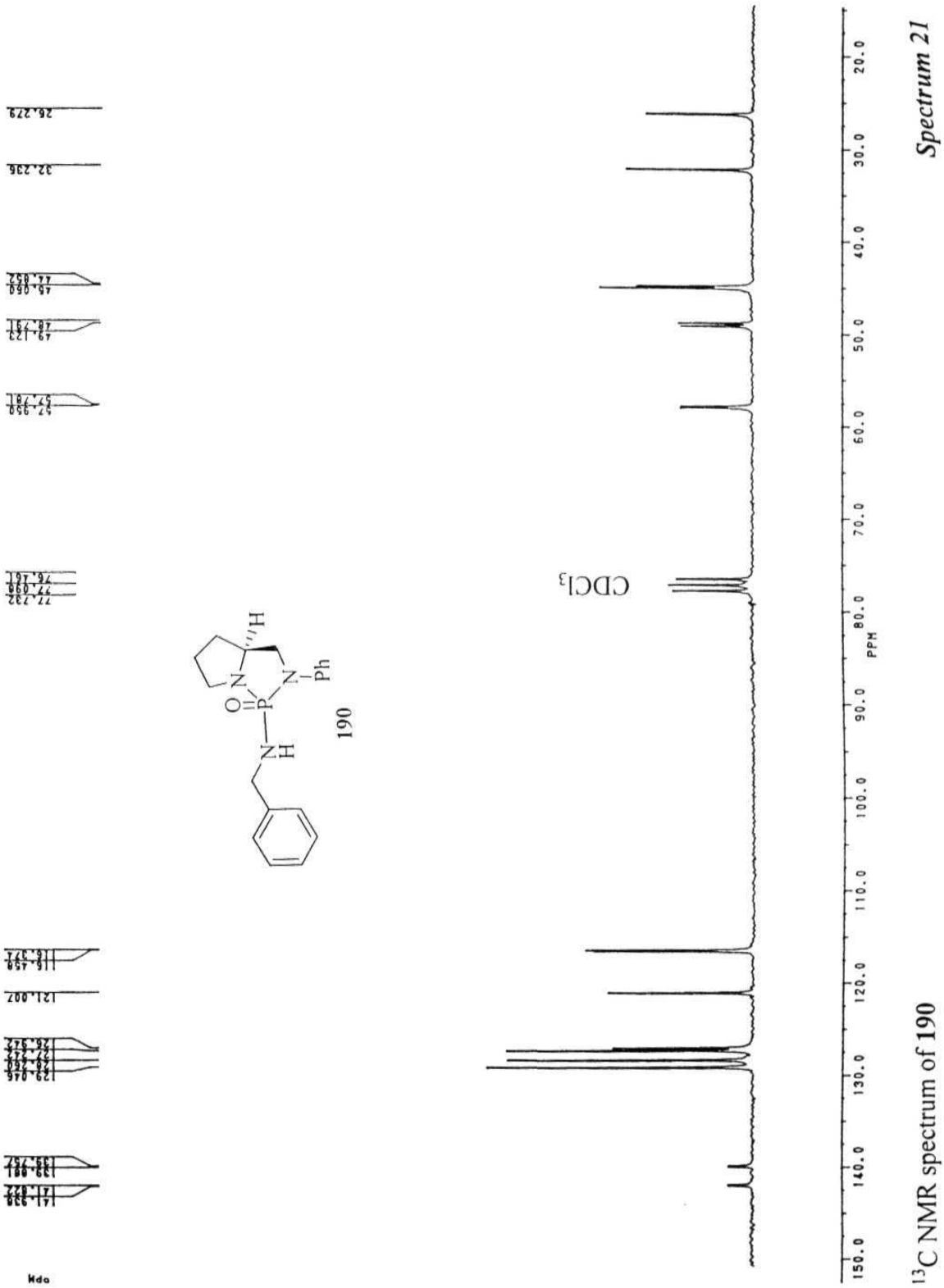
HPLC analysis of **176b** (A) Chromatogram of (±)-**176b**, (B) Chromatogram of (*R*)-**176b**, 67% ee (obtained *via* the asymmetric reduction of **175b** using 4 mol% catalyst **188**).



190

^{1}H NMR spectrum of **190**

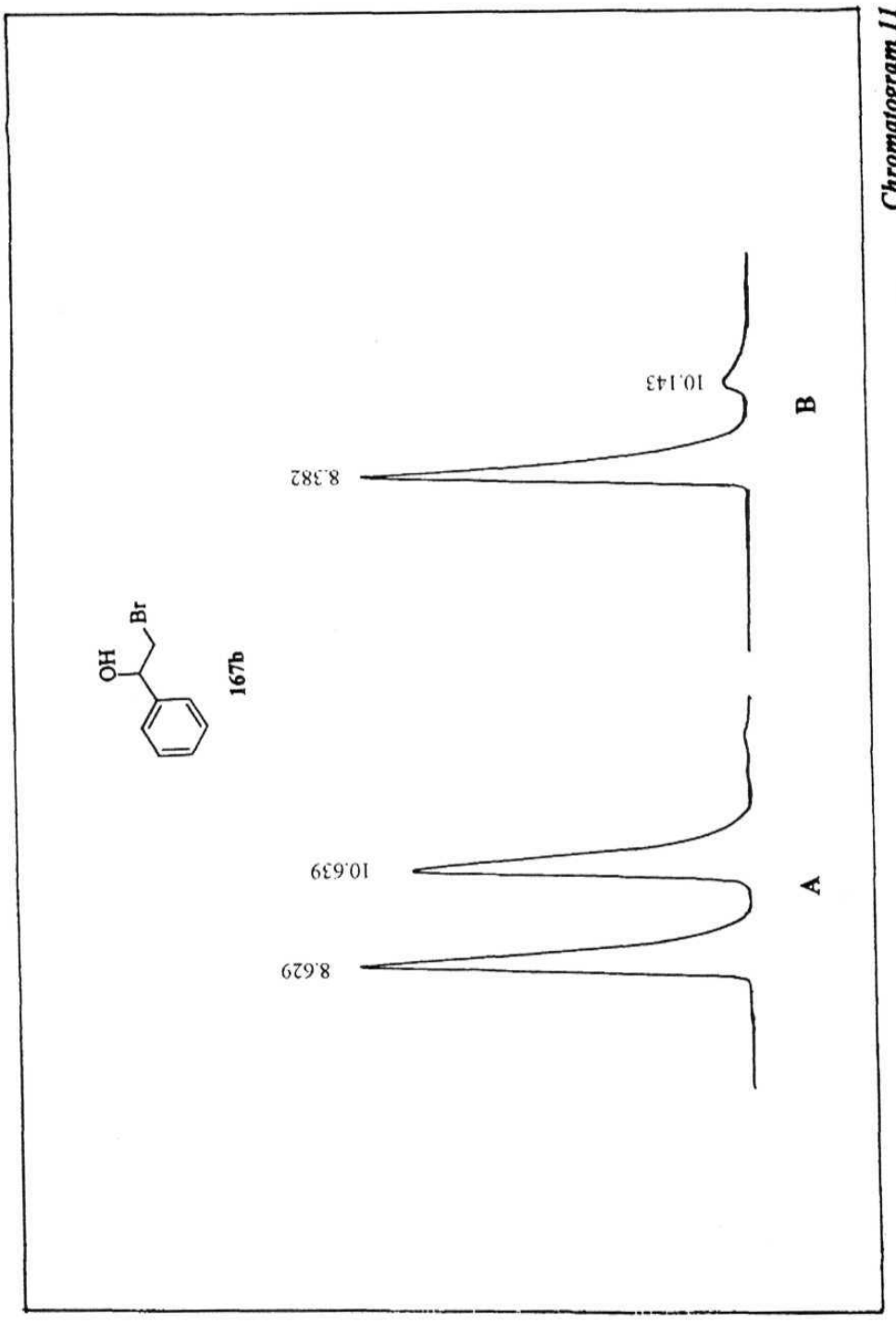
Spectrum 20



190

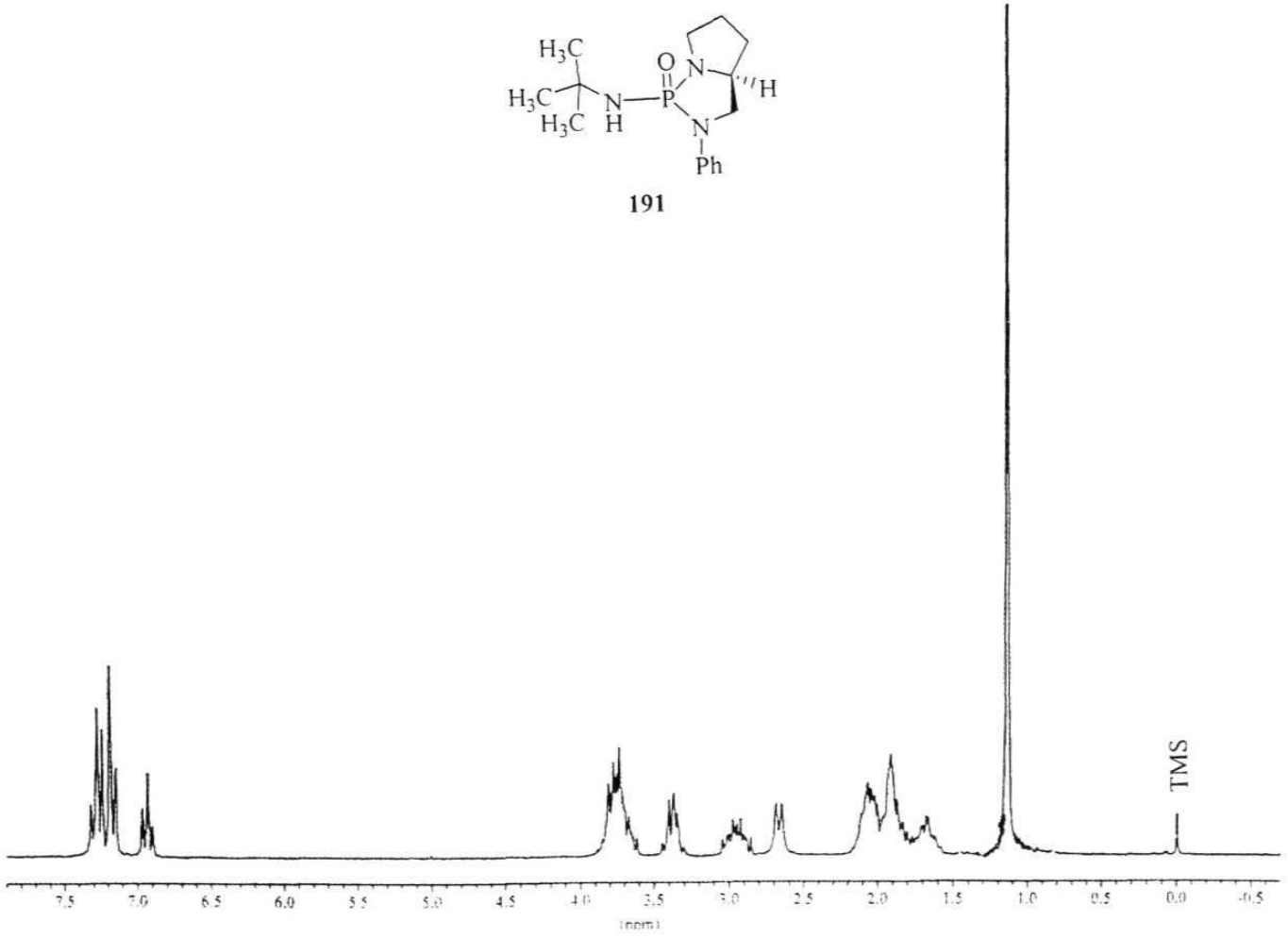
^{13}C NMR spectrum of **190**

Spectrum 21



Chromatogram 11

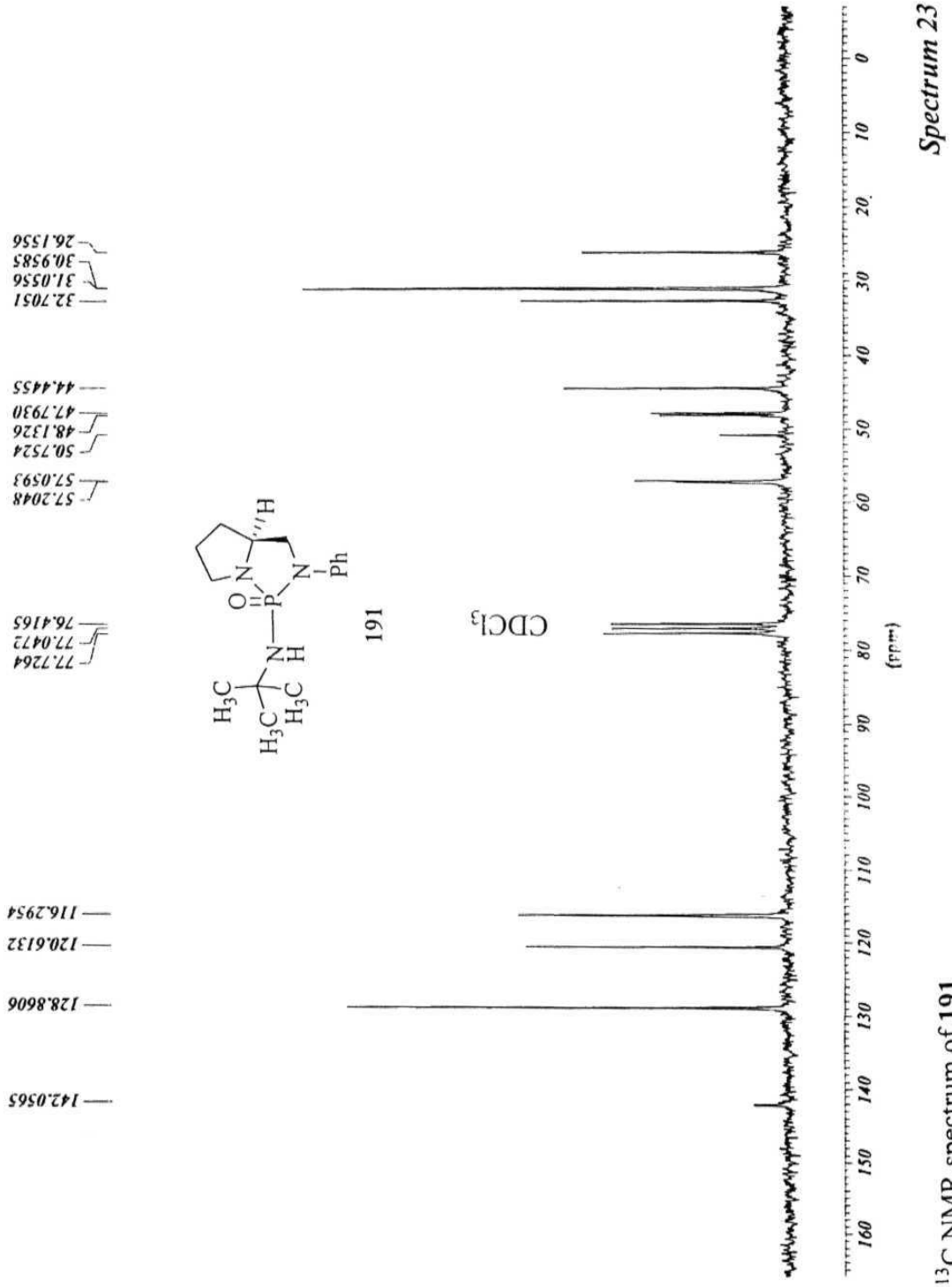
HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 89% ee (obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst **190**).



191

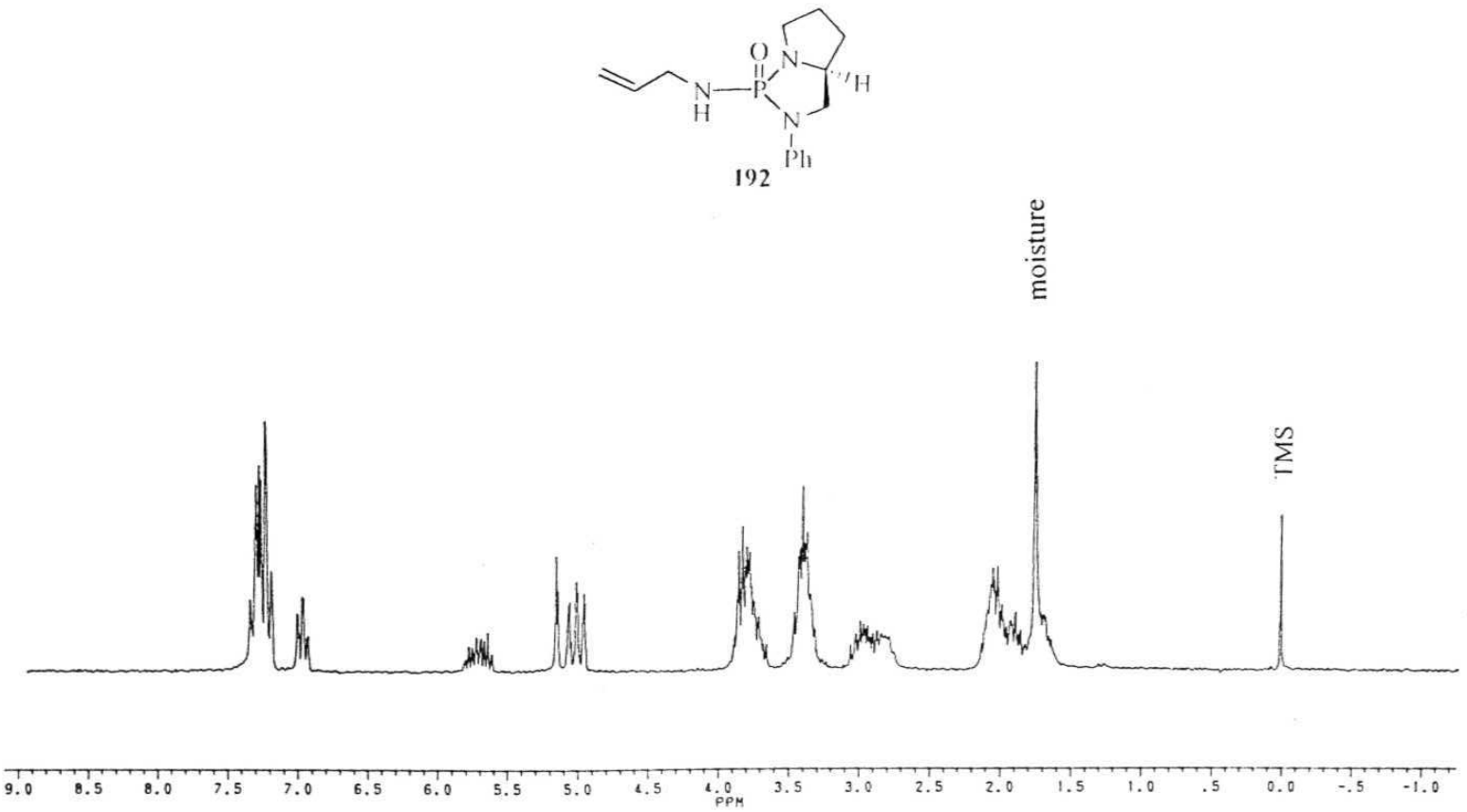
^{1}H NMR spectrum of **191**

Spectrum 22



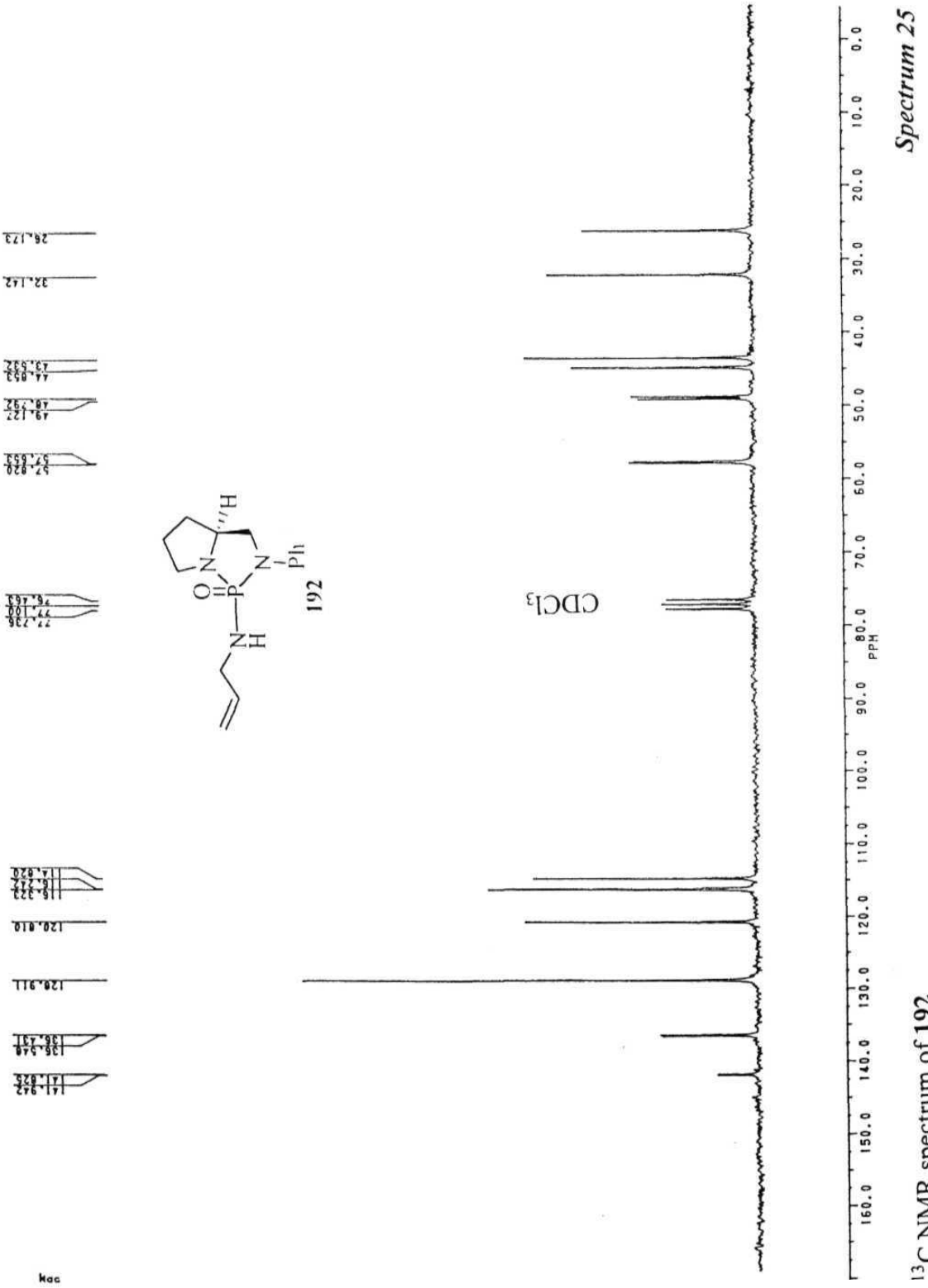
Spectrum 23

^{13}C NMR spectrum of **191**



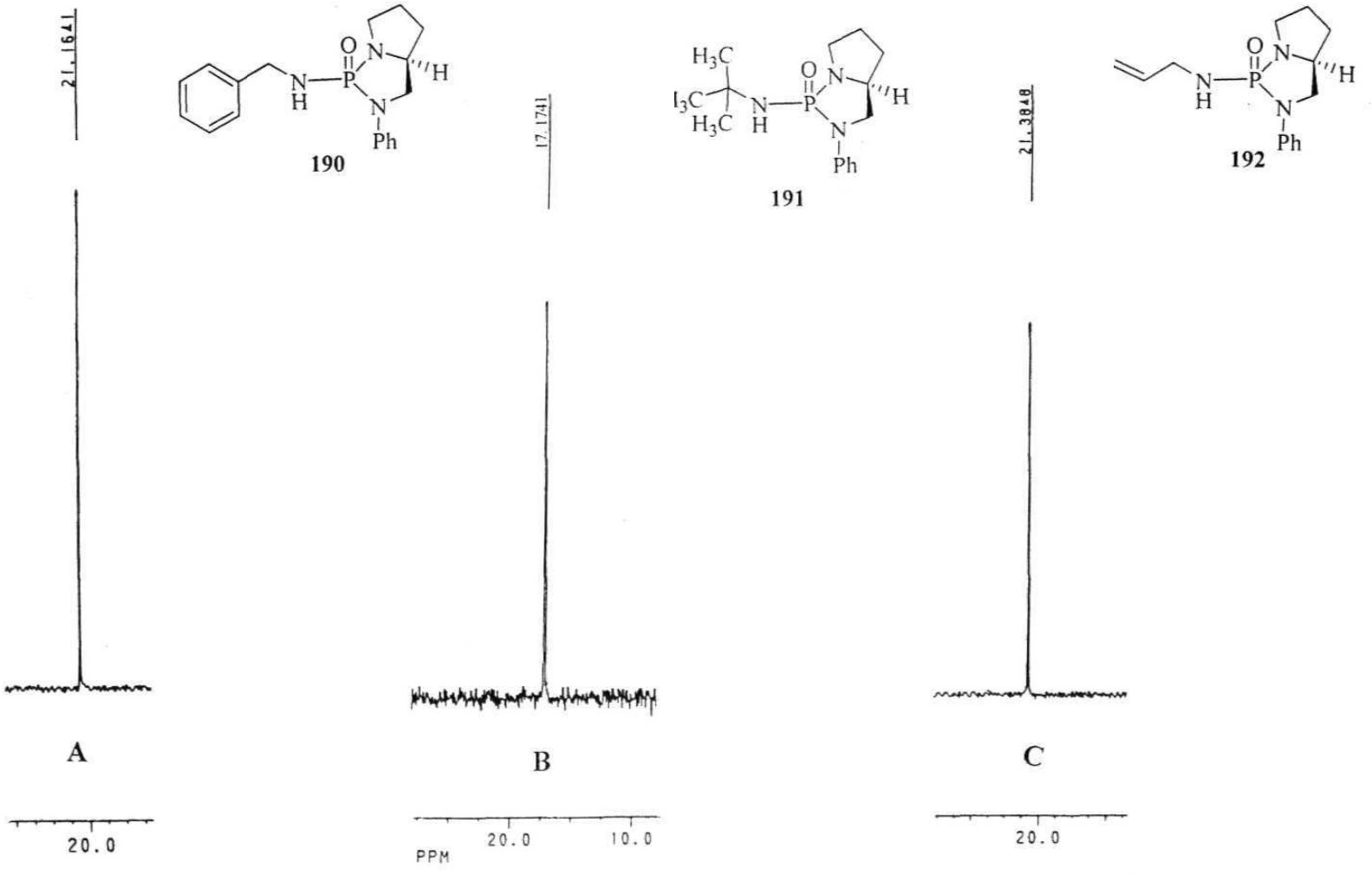
^{1}H NMR spectrum of **192**

Spectrum 24



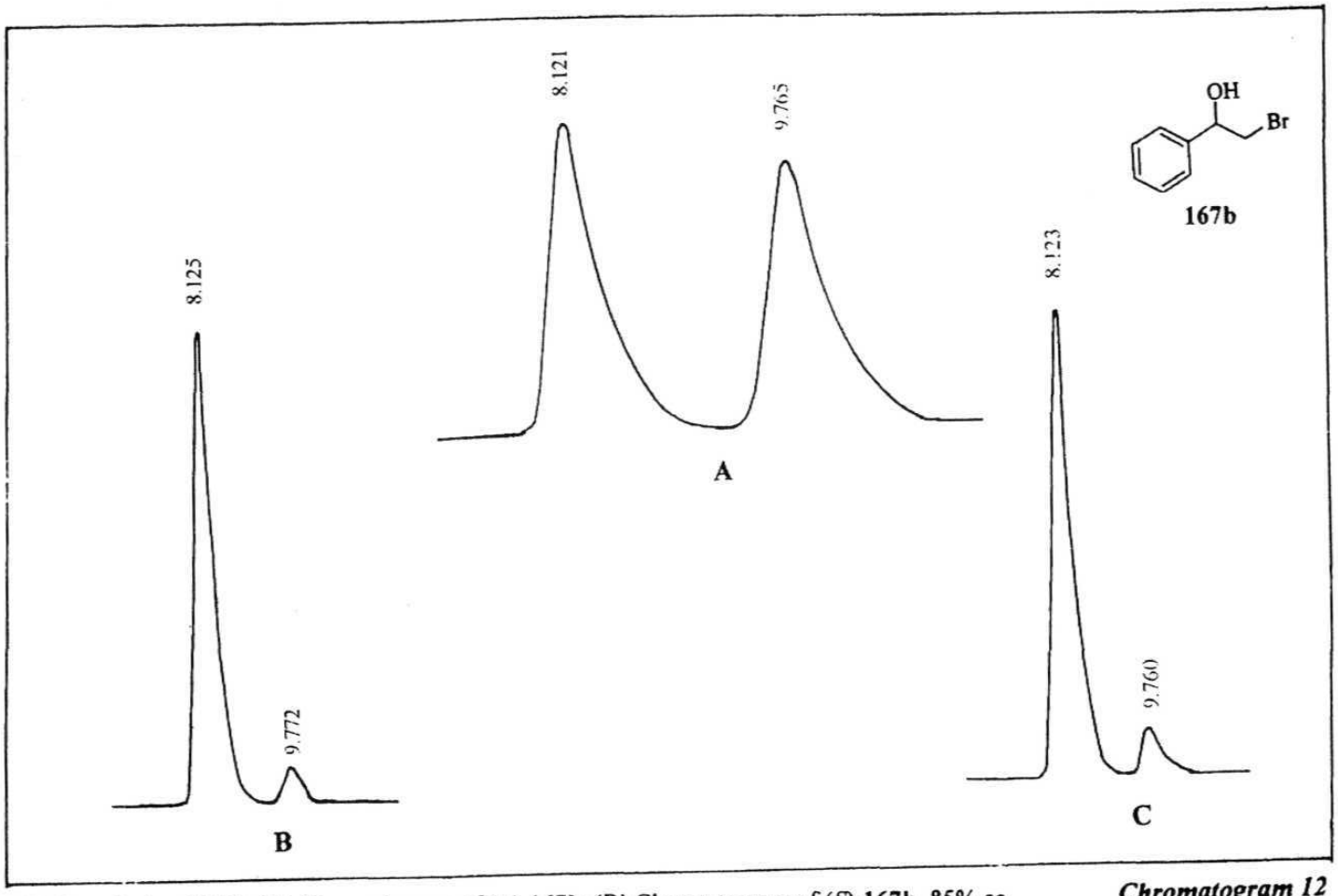
^{13}C NMR spectrum of **192**

Spectrum 25



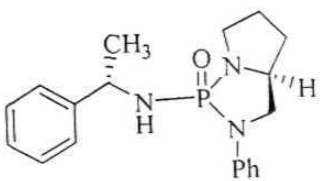
(A) ^{31}P NMR spectrum of **190** (B) ^{31}P NMR spectrum of **191**
(C) ^{31}P NMR spectrum of **192**

Spectrum 26

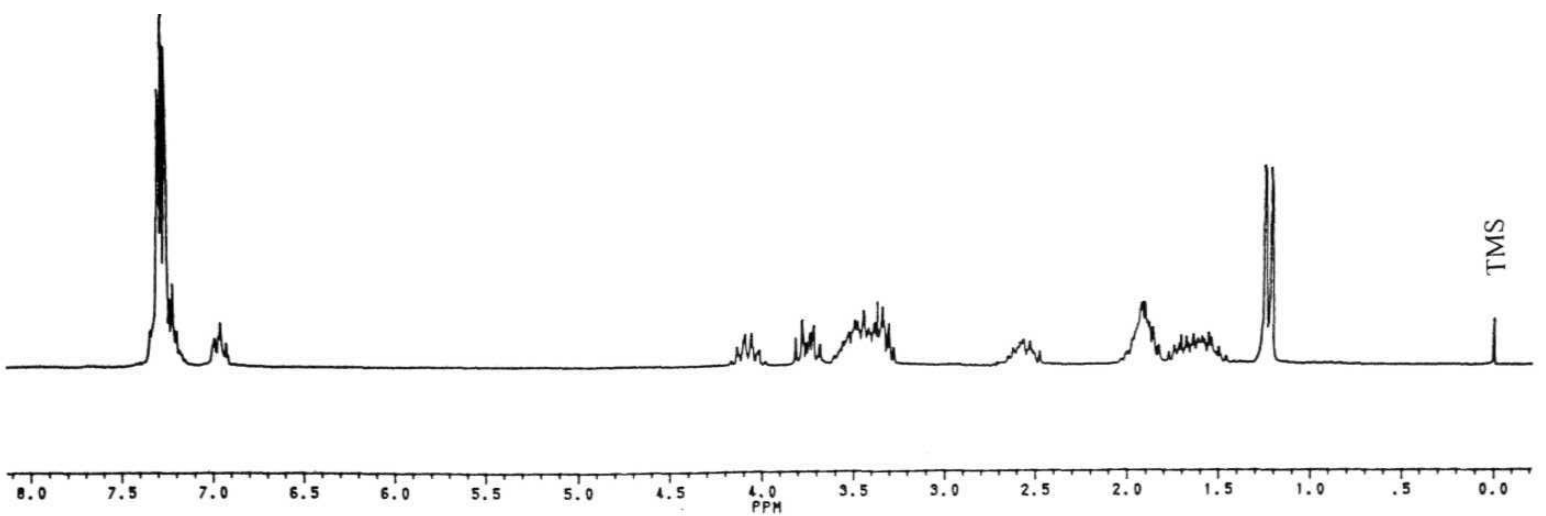


Chromatogram 12

HPLC analysis of **167b** (A) Chromatogram of (±)-**167b**, (B) Chromatogram of (*S*)-**167b**, 85% ee (obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst **191**), (C) Chromatogram of (*S*)-**167b**, 81% ee (obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst **192**).

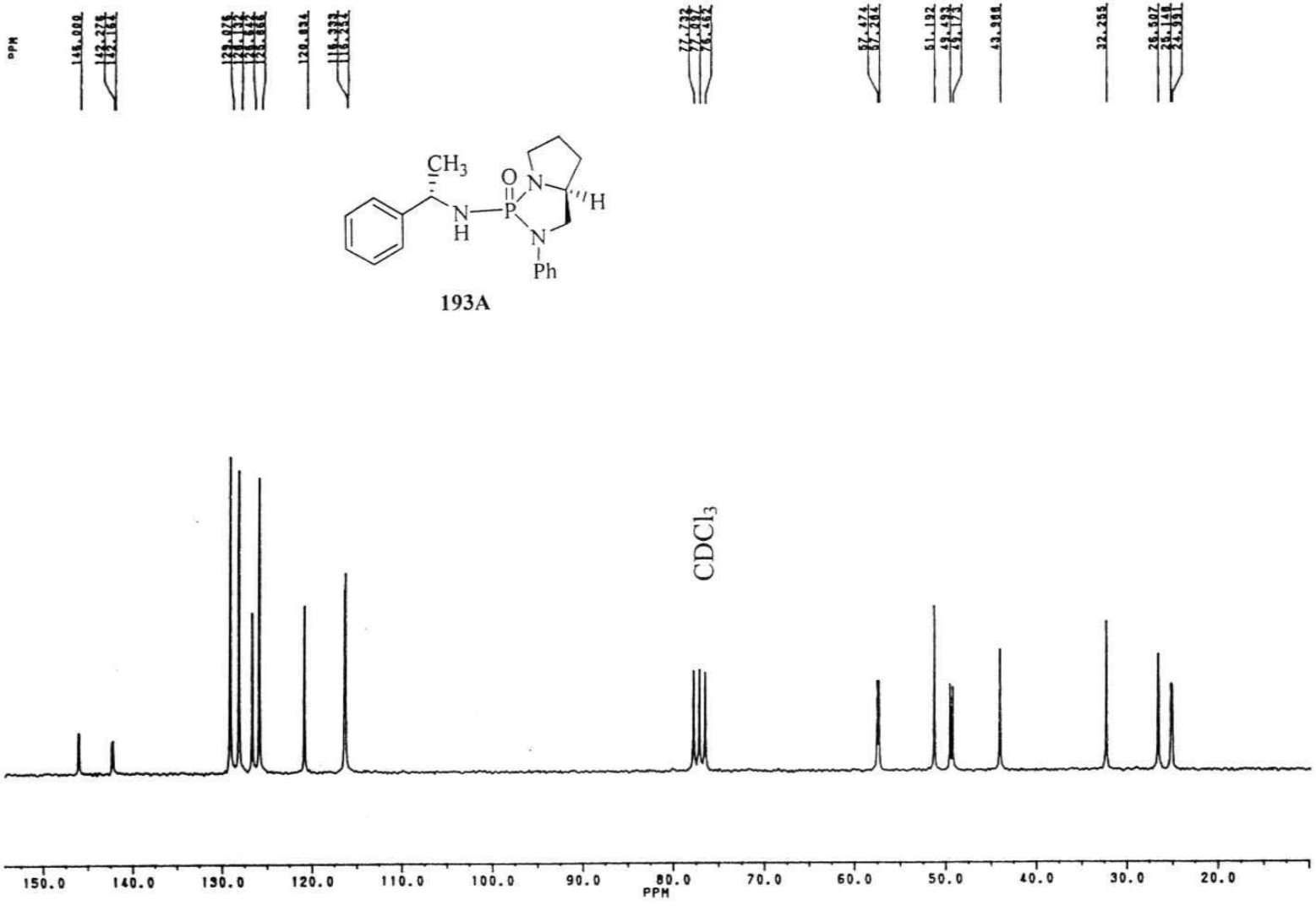


193A



^{1}H NMR spectrum of **193A**

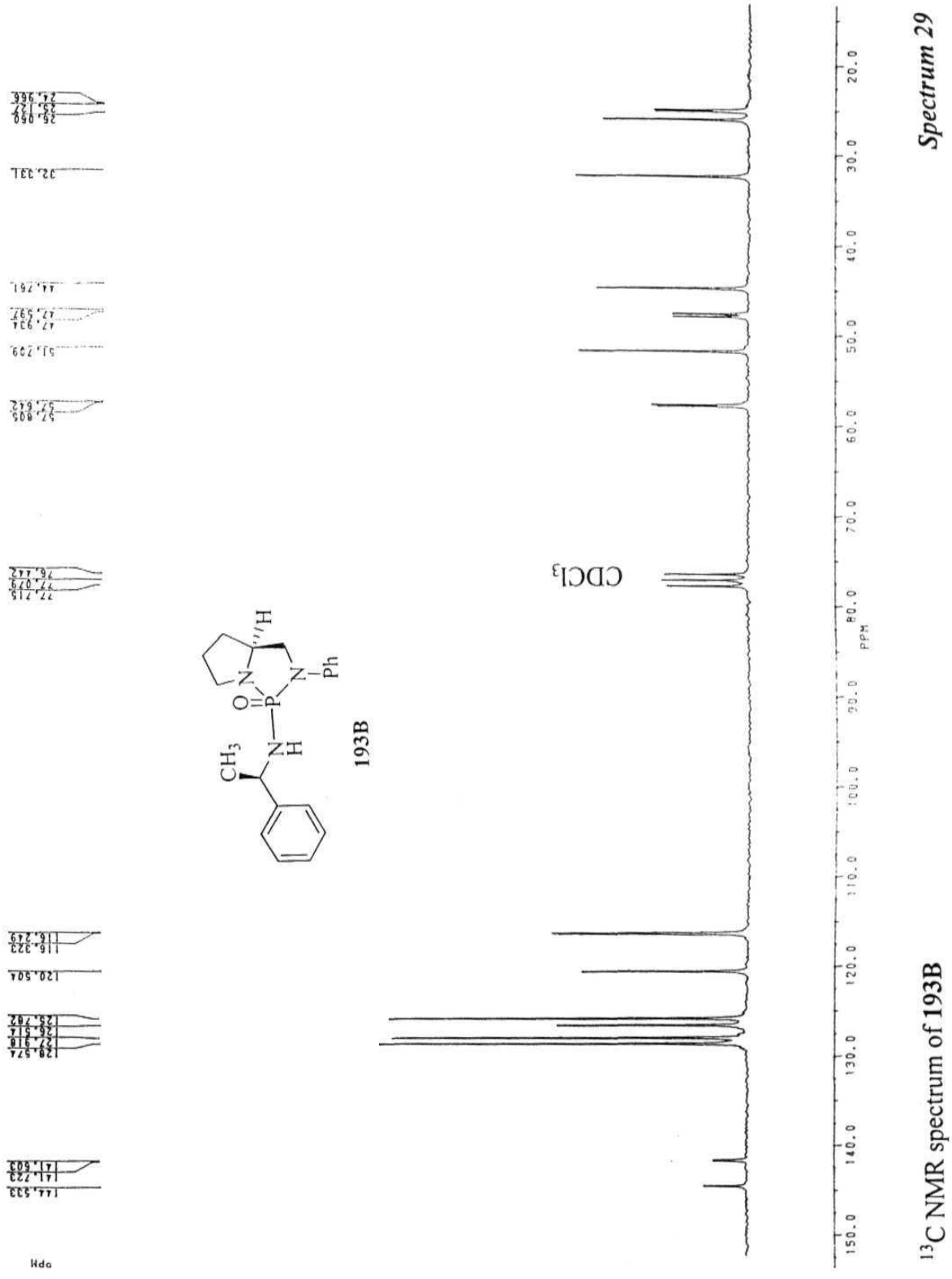
Spectrum 27



193A

^{13}C NMR spectrum of **193A**

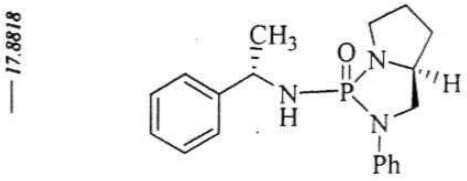
Spectrum 28



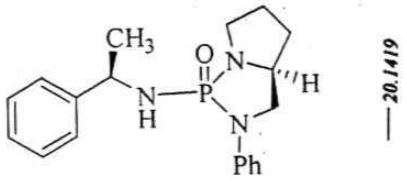
193B

^{13}C NMR spectrum of **193B**

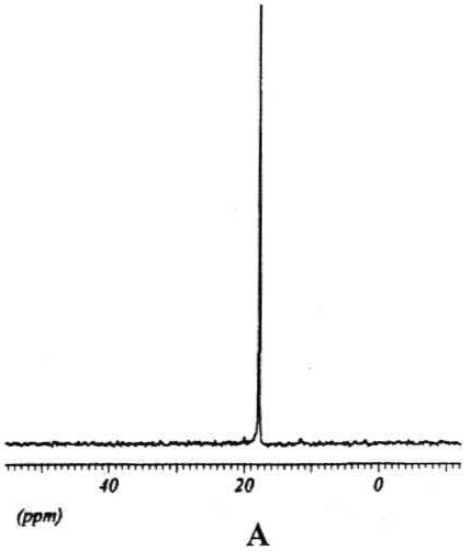
Spectrum 29



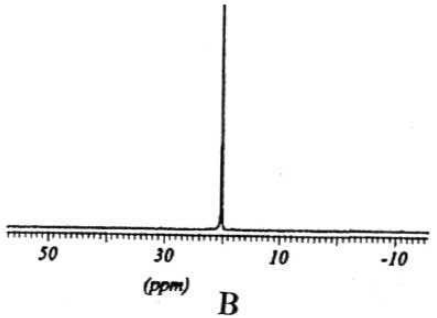
193A



193B



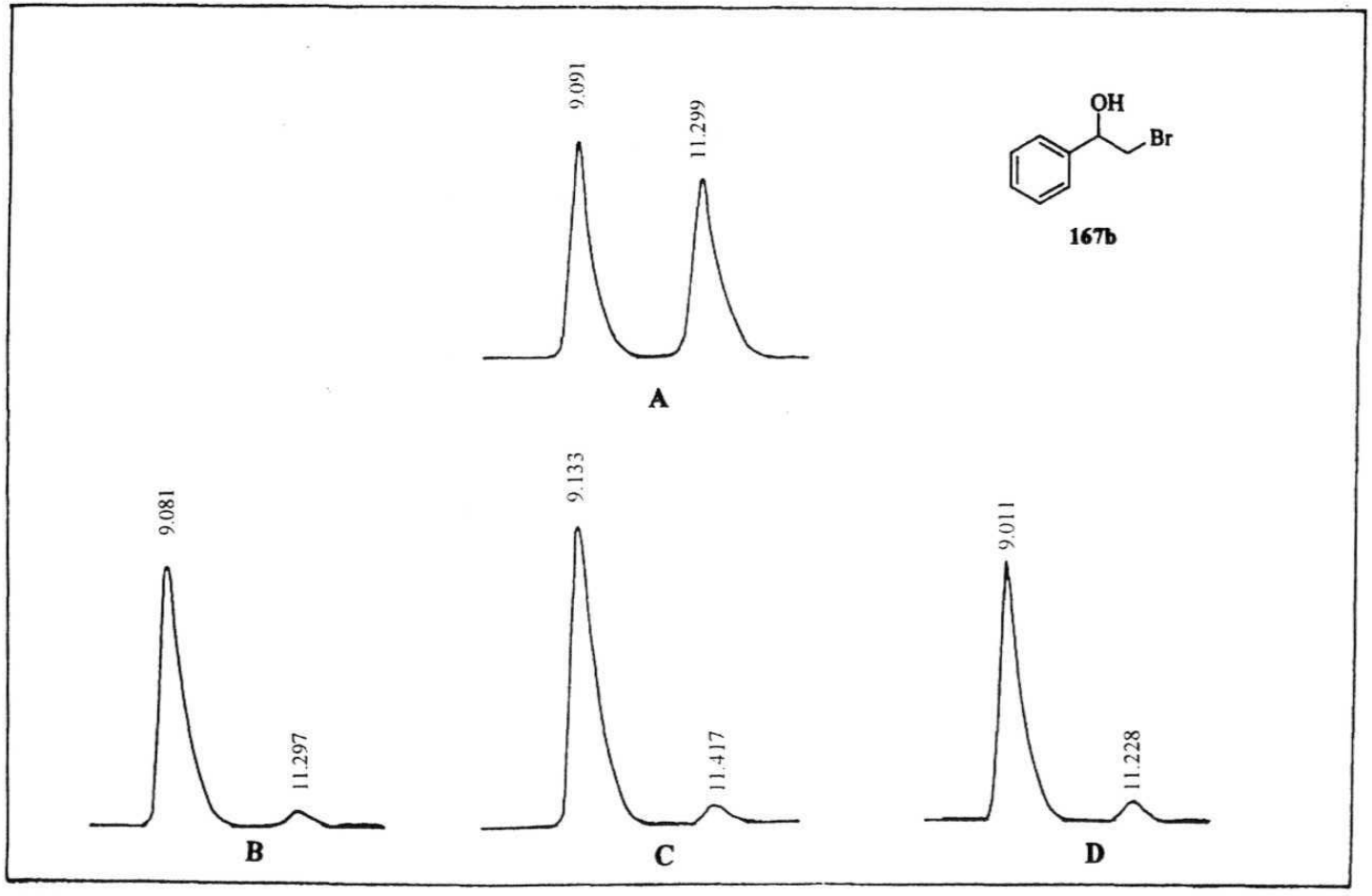
A



B

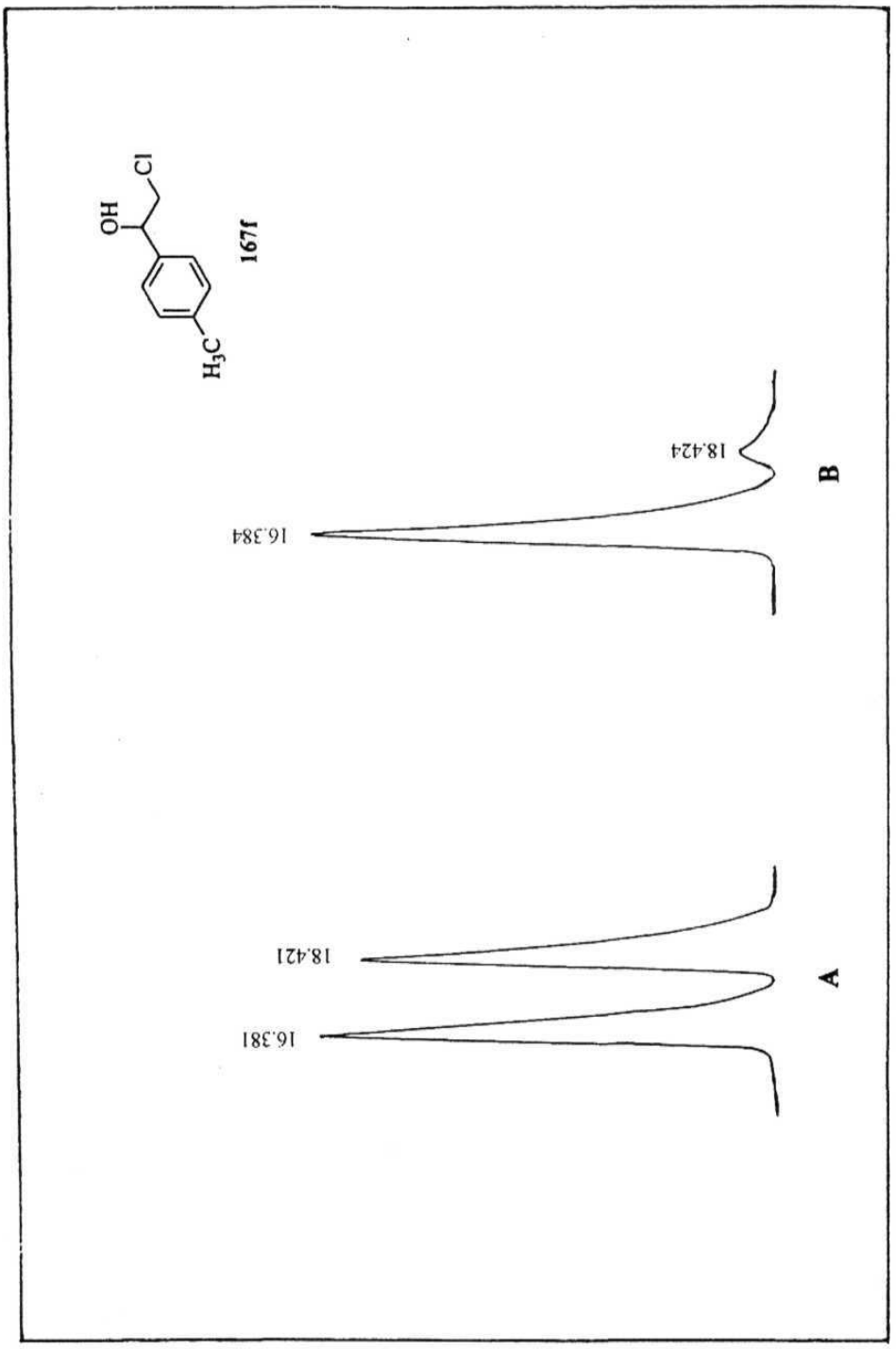
(A) ^{31}P NMR spectrum of **193A** (B) ^{31}P NMR spectrum of **193B**

Spectrum 30

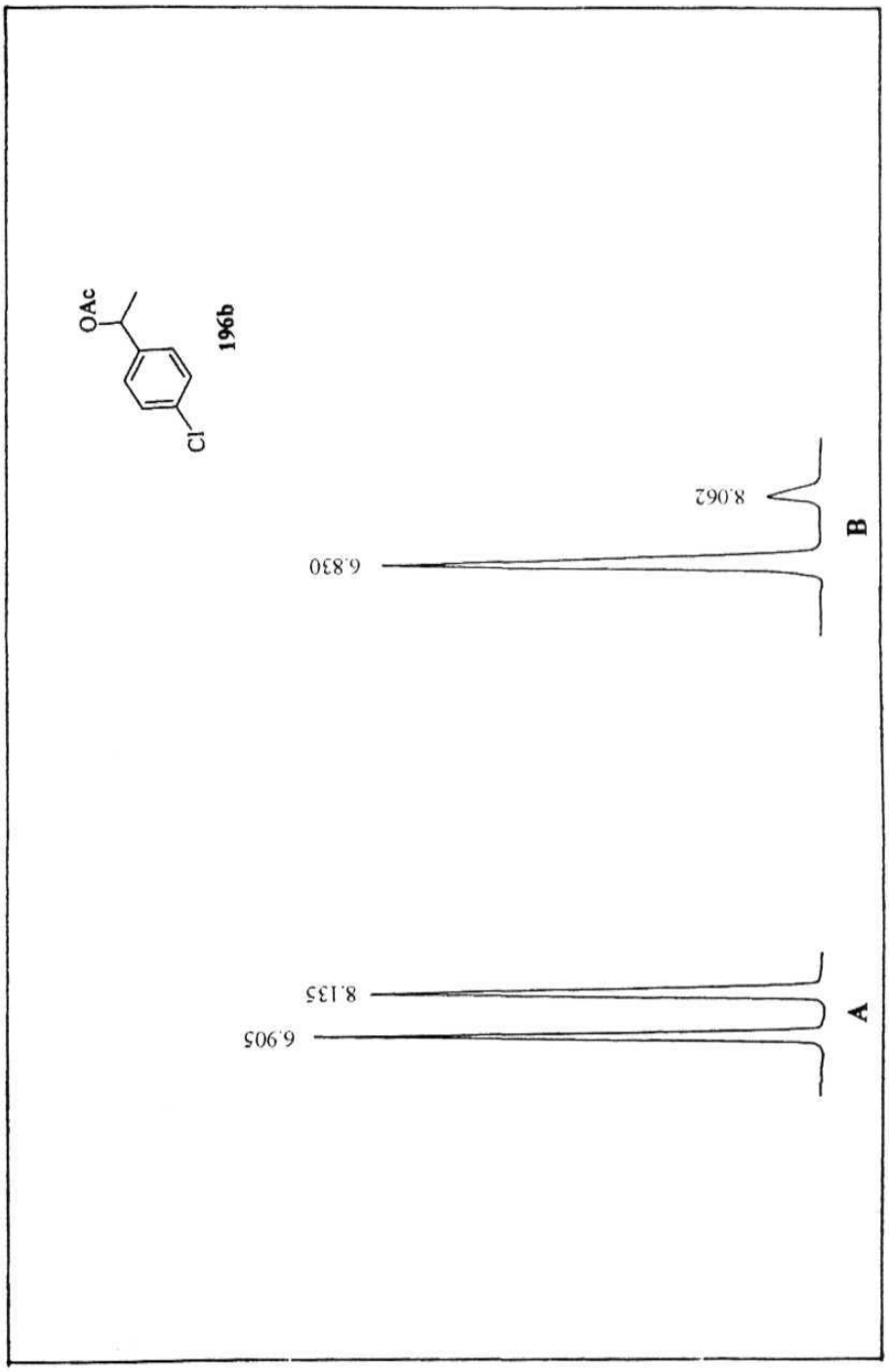


HPLC analysis of **167b** (**A**) Chromatogram of (±)-**167b**, (**B**) Chromatogram of (*S*)-**167b**, 89% ee (obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst **193A**), (**C**) Chromatogram of (*S*)-**167b**, 88% ee (obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst **193B**), (**D**) Chromatogram of (*S*)-**167b**, 85% ee [obtained *via* the asymmetric reduction of **166b** using 5 mol% catalyst (1:1 mixture of catalysts **193A** and **193B**)].

Chromatogram 13

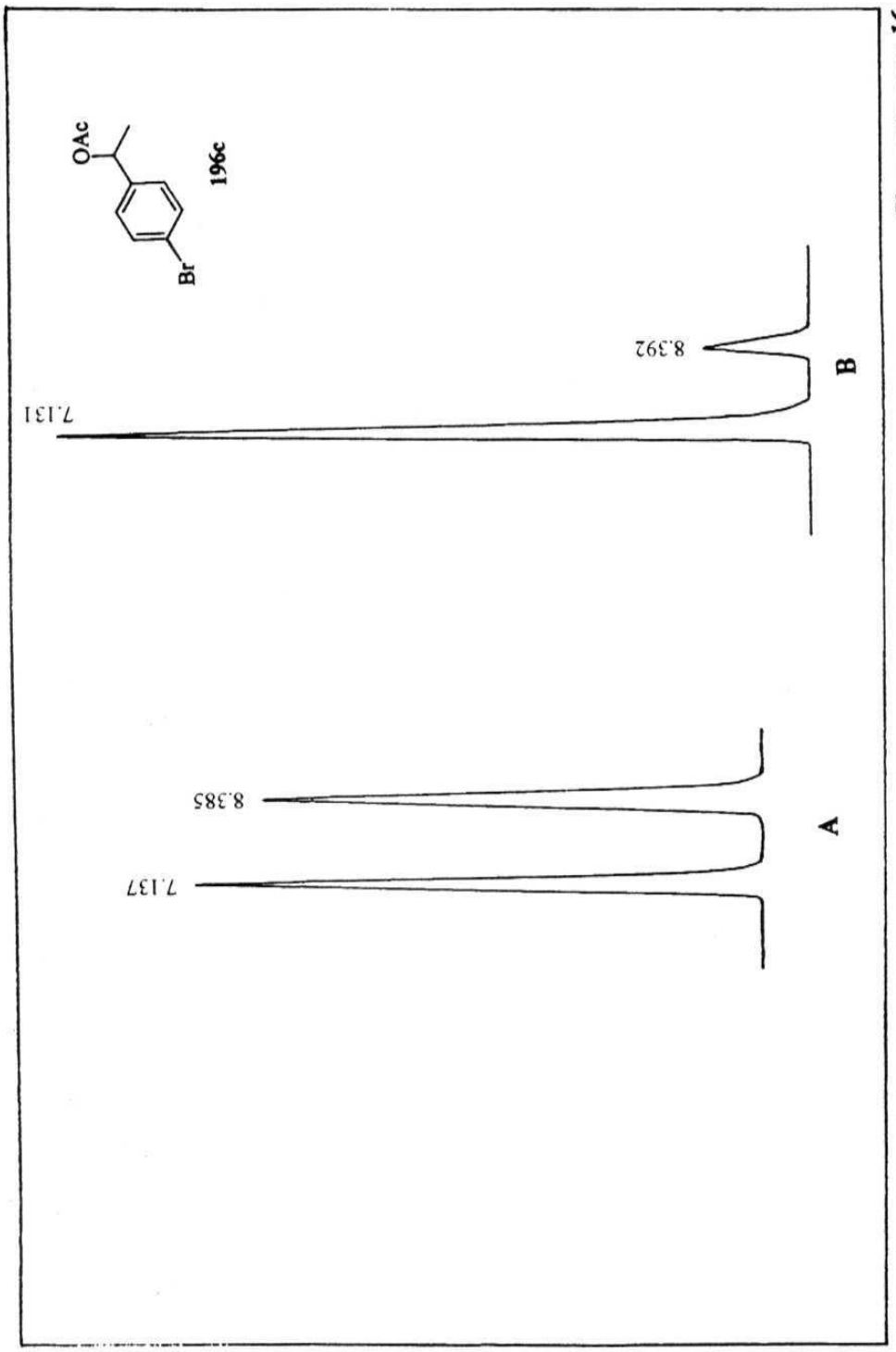


Chromatogram 14 HPLC analysis of **167f** (A) Chromatogram of (±)-**167f**, (B) Chromatogram of (*S*)-**167f**, 89% ee (obtained *via* the asymmetric reduction of **166f** using 5 mol% catalyst **193A**).



Chromatogram 15

HPLC analysis of **196b** (A) Chromatogram of (±)-**196b**, (B) Chromatogram of (*R*)-**196b**, 76% ee



HPLC analysis of **196c** (A) Chromatogram of (±)-**196c**, (B) Chromatogram of (*R*)-**196c**, 74% ee ***Chromatogram 16***

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule *(2S,5S)-165*. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	Y	Z	U(eq)
p	1285(1)	7921(1)	3407(1)	44(1)
Cl	1828(1)	8219(1)	2039(1)	65(1)
N(2)	3124(3)	8462(2)	3978(2)	45(1)
C(6)	3466(4)	9593(2)	4069(2)	43(1)
N(l)	1884(3)	6676(2)	3617(2)	53(1)
0	-685(3)	8310(2)	3595(2)	63(1)
C(7)	5346(4)	9981(2)	4191(2)	54(1)
C(4)	3852(4)	6570(2)	4023(2)	48(1)
C(ll)	1921(5)	10321(3)	4047(2)	60(1)
C(5)	4784(4)	7695(2)	3986(2)	51(1)
C(3)	4769(5)	5666(2)	3468(2)	65(1)
C(8)	5643(5)	11090(3)	4290(2)	66(1)
C(9)	4138(6)	11801(2)	4254(2)	70(1)
C(10)	2278(6)	11422(3)	4132(3)	72(1)
C(l)	1394(6)	5706(2)	3068(3)	77(1)
C(2)	3039(6)	4932(3)	3272(2)	74(1)

Table II: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule (2*S*,5*S*)-**177**. U (eq) is defined as one third of the trace of the orthogonal ized U_{ij} tensor.

	X	Y	Z	U(eq)
P(l)	-13(3)	8566(2)	1778(1)	55(1)
N(l)	1295(8)	9613(5)	1365(2)	49(1)
0(1)	-2242(7)	8380(7)	1685(2)	83(2)
N(2)	851(9)	9154(7)	2396(2)	64(2)
C(l)	1325(11)	9455(7)	736(3)	51(2)
C(2)	2884(12)	8764(7)	471(3)	61(2)
C(3)	2933(13)	8604(8)	-139(3)	71(2)
C(4)	1408(15)	9146(7)	-472(3)	68(2)
C(5)	-1785(15)	10499(8)	-560(4)	75(2)
C(6)	-3291(15)	11219(9)	-314(4)	83(3)
C(7)	-3355(13)	11423(8)	296(4)	78(2)
C(8)	-1894(11)	10838(7)	643(3)	60(2)
C(9)	-274(10)	10067(6)	401(3)	47(2)
C(10)	-200(13)	9886(6)	-220(3)	58(2)
C(ll)	3205(11)	10016(9)	1663(3)	69(2)
C(12)	2605(12)	10106(9)	2309(3)	70(2)
C(13)	4235(15)	9664(14)	2746(4)	113(4)
C(14)	3490(20)	8469(14)	3019(7)	184(8)
C(15)	1225(18)	8364(11)	2928(3)	95(3)
Cl(l)	1306(4)	6725(2)	1671(1)	85(1)

Table III: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule (2*R*,5*S*)-**178**. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
0(1)	-1779(3)	29(3)	1139(1)	56(1)
C(10)	1687(4)	451(3)	249(1)	34(1)
C(15)	-132(5)	-523(4)	126(1)	43(1)
N(2)	1754(4)	1254(3)	684(1)	37(1)
C(13)	1558(6)	-1162(4)	-599(1)	50(1)
C(2)	393(7)	1332(4)	2298(1)	55(1)
C(8)	3087(6)	3098(4)	1267(1)	46(1)
C(ll)	3409(5)	639(4)	-60(1)	47(1)
C(5)	4309(6)	3016(4)	2523(1)	54(1)
C(12)	3308(6)	-169(5)	-481(1)	55(1)
C(l)	1751(5)	1993(4)	1967(1)	42(1)
C(3)	1045(7)	1529(5)	2754(1)	63(1)
N(l)	1384(4)	2003(3)	1486(1)	41(1)
C(14)	-155(6)	-1336(4)	-293(1)	47(1)
C(4)	2933(7)	2376(4)	2865(1)	59(1)
C(7)	4890(6)	3304(5)	1632(1)	57(1)
C(6)	3705(6)	2811(4)	2068(1)	46(1)
C(9)	3695(6)	2268(4)	816(1)	47(1)
P(l)	556(1)	496(1)	1149(1)	36(1)
Cl(l)	2310(2)	1582(1)	1327(1)	58(1)

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