STUDIES IN THE BORANE-MEDIATED ASYMMETRIC REDUCTION OF PROCHIRAL KETONES USING NEW CHIRAL CATALYSTS CONTAINING *N-P=O* STRUCTURAL FRAMEWORK

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

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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

JULY 2006 **V. CHANDRASHAKER**

CERTIFICATE

Certified that the work embodied in this thesis entitled ″**Studies in the Borane-mediated Asymmetric Reduction of Prochiral Ketones Using New Chiral Catalysts Containing *N-P=O* Structural Framework**″ has been carried out by **Mr. V. Chandrashaker**, under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH

(THESIS SUPERVISOR)

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V. Chandrashaker

ABBREVIATIONS

Ac	acetyl
Alpine-Hydride	lithium *B*-3-pinanyl-9-borabicyclo[3.3.1]nonyl hydride
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bp	boiling point
Bu	*n*-butyl
i-Bu or Bu^i	*iso* butyl
t-Bu or Bu^t	*tert*-butyl
t-BuEapBCl	*tert*-Butyl(*iso*-2-ethylapopinocampheyl)chloroborane
Bzl	benzyl
calcd.	calculated
cat.	catalyst
DMSO	dimethyl sulfoxide
DMF	N,N-dimethylformamide
Eapine-Borane	*B*-(*Iso*-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonane
Eap_2BCl	*B*-Chlorobis(*iso*-2-ethylapopinocampheyl)borane
ee	enantiomeric excess
Et	ethyl
equiv.	equivalent
IPA	*iso*-propyl alcohol
K-Glucoride	potassium-9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-gluco-furanosyl)-9-boratabicyclo[3.3.1]nonane
LAH	lithium aluminum hydride
Me	methyl
Mp	melting point

NBS	*N*-bromosuccinimide
Np	naphthyl
Ph	phenyl
Prapine-Borane	*B*-(*Iso*-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]-nonane
Pr	propyl
i-Pr or Pr^i	*iso*-propyl
rt	room temperature
TFA	trifluroacetic acid
THF	tetrahydrofuran
Thx	thexyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
K-Xylide	potassium-9-*O*-(1,2-isopropylidene-5-deoxy-D-xylo-furanosyl)-9-boratabicyclo[3.3.1]nonane

ABSTRACT

Chirality has become an essential dimension in pharmacology in recent years and in fact, occupies a special place in organic and medicinal chemistry as biological/pharmacological activities of many drug molecules depend on the enantiomeric purity of these molecules. Due to this emergence of chirality as a major and important concern in pharmaceutical industry, scientists from both the academic and industrial communities directed their studies on this aspect and have indeed made significant contributions in developing convenient and practical procedures/processes for obtaining various types of enantiomerically pure molecules. Homochiral secondary alcohols represent one such interesting class of molecules and therefore development of simple and highly practical methodologies for obtaining secondary alcohols in enantiomerically pure form *via* the asymmetric reduction of prochiral ketones has been and continues to be an interesting and challenging area in chiral chemistry.

This thesis deals with the studies on the applications of molecules containing *N–P=O* structural framework as catalysts, for the borane-mediated asymmetric reduction of prochiral ketones and it consists of three chapters: 1) Introduction, 2) Objectives, Results & Discussion and 3) Experimental. The first chapter presents the brief/relevant literature survey on asymmetric reduction of prochiral ketones using chiral boron reagents and catalysts.

The second chapter deals with the objectives, results and discussion. With a view to develop simple and convenient methodologies for the synthesis of secondary alcohols in high enantiomeric purities *via* the reduction of prochiral ketones using new class of chiral catalysts containing *N-P=O* structural framework, we have undertaken a major research program with the following objectives.

i) To synthesize chiral molecules (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) and (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**) from easily accessible (2*S*)-2-anilinomethylpyrrolidine and study their applications as possible catalysts in the borane-mediated asymmetric reduction of representative prochiral ketones.

ii) To synthesize 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) and 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**), which contain two *N-P=O* structural units, and study their applications as possible chiral catalysts for asymmetric reduction of prochiral ketones.

iii) To synthesize three diastereomeric pairs of chiral catalysts based on *N-P=O* structural framework, built mainly on (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety (**111**), having different stereochemistry at phosphorus *i.e.,* (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)-octanes (**114** & **114A**), (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes (**177** & **177A**), and (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octanes (**178** & **178A**) and examine the influence of phosphorus chirality in the stereochemical course of reduction process.

iv) To synthesize (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) and study its potential as a possible catalyst for asymmetric reduction of prochiral ketones.

(2*S*,5*S*)-2-[(2*S*)-2-(Anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane as a catalyst

We have synthesized (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) according to Scheme 7 and successfully employed this molecule as a chiral catalyst (1 mol%) for borane-mediated asymmetric reduction of prochiral ketones to obtain the corresponding secondary alcohols with up to (90% *ee*) (eqs. 76-79, 84-88, 90, 91 & Tables 1-3). With a view to understand the influence of hydrogen *Vs* methyl group in directing the stereochemical course of the reduction process, we have also synthesized (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**) according to eq. 94. Subsequently, we have examined the potential this molecule as a catalyst (1 mol%) in the borane-mediated asymmetric reduction of prochiral ketones, to provide the corresponding alcohols up to 74% enantiomeric purities (eq. 95 & 96). These results show that the catalyst **156** with "-*NH*-" group offers better selectivity than the catalyst **168** containing "-*NMe*" group.

Catalysts containing two *N*-*P*=*O* structural frameworks

With a view to understand the influence of two *N*-*P*=*O* structural moieties in the same catalyst, we have designed and synthesized two molecules 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) and 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**)

according to Schemes 9 & 10 respectively. We have then examined their potential as catalysts in the borane-mediated reduction of representative prochiral ketones to provide the resulting secondary alcohols in 60-90% enantiomeric purities (eqs. 97-100 & Tables 5-7). From these studies it may be concluded that catalysts (**169** & **170**), containing two *N-P=O* moieties, are inferior catalysts, as we need to use more catalytic quantities (10 mol%) in these cases to obtain similar selectivities as that of catalyst **156** (where we need only 1 mol% catalyst).

A study toward understanding the role of a phosphorus stereogenic center in (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane derivatives as catalysts in the borane-mediated asymmetric reduction of prochiral ketones

We envisioned that understanding the actual role of stereochemistry at phosphorus center in catalysts, containing chiral *N-P=O* structural framework, built mainly on (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane framework (**111**) in the borane-mediated asymmetric reduction of prochiral ketones would probably (a) throw some light on understanding the mechanism of this reaction as the stereochemistry of the resulting secondary alcohols would provide the stereochemical sense of direction of the reduction process and (b) help us in designing appropriate catalyst(s) which can provide high enantioselectivities. We have, therefore, prepared three representative diastereomeric pairs of catalysts [**114**, **114A** (eq. 103); **177**, **177A** (eq. 106); & **178**, **178A** (eq. 107)] mainly built on the framework **111** and employed in the reduction process using three ketones

160a, **160b**, **163a** (eqs. 104, 108; Schemes 11, 12 & Table 8). The resulting secondary alcohols were obtained with the same absolute configuration and the enantioselectivities are also in the same range (59-84%). These studies demonstrate that the phosphorus chirality has no significant role in directing stereochemical pathway of the reduction process in all these cases.

(2*R*,4*S*,5*S*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholodin-2-one as a catalyst

With a view to understand the influence of "*-N-(P=O,Cl)-O-*" framework as a catalyst in the borane-mediated asymmetric reduction of prochiral ketones we have synthesized (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholodin-2-one (**181**) according to eq. 110. Borane-mediated reduction of prochiral ketones, using this molecule as catalyst provides the resulting secondary alcohols in 56-72% enantiomeric purities (eqs. 111, 112 & Table 9 & 10).

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

LIST OF PUBLICATIONS

(1) A novel and effective chiral phosphoramide catalyst for the borane-mediated asymmetric reduction of prochiral α-halo ketones
Deevi Basavaiah,* Gone Jayapal Reddy, **Vanampally Chandrashekar**
Tetrahedron: Asymmetry **2001**, *12*, 685-689.

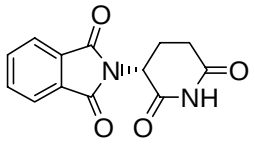
(2) (2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane: a novel chiral source for borane-mediated catalytic chiral reductions
Deevi Basavaiah, Gone Jayapal Reddy, **Vanampally Chandrashekar**
Tetrahedron: Asymmetry **2002**, *13*, 1125-1128.

(3) 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
Deevi Basavaiah, Gone Jayapal Reddy, **Vanampally Chandrashekar**
Tetrahedron: Asymmetry **2004**, *15*, 47-52.

(4) A study toward understanding the role of a phosphorus stereogenic center in (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane derivatives as catalysts in the borane-mediated asymmetric reduction of prochiral ketones
Deevi Basavaiah, **Vanampally Chandrashekar**, Utpal Das and Gone Jayapal Reddy *Tetrahedron: Asymmetry* **2005**, *16*, 3955-3962.

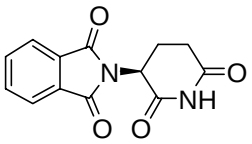
INTRODUCTION

Chirality has become an essential dimension in pharmacology in recent years and in fact occupies a special place in organic and medicinal chemistry as biological/pharmacological activities of many drug molecules depend on the enantiomeric purity of these molecules.[1-3] For example, the (*R*)-enantiomer of thalidomide[4] (**1**) is a drug for morning sickness (for pregnant women) while its (*S*)-enantiomer is teratogenic. (*S*)-Enantiomer of the drug propranolol[2] (**2**) has 100 times of β-andregenic activity compared to its (*R*)-counterpart. (*S,S*)-Ethambutol[2] (**3**) is tuberculostatic while (*R,R*)-isomer causes blindness. (*R,R*)-Enantiomer of chloramphenicol[2] (**4**) is antibacterial while its (*S,S*)-enantiomer is inactive.

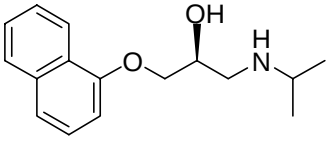


(*R*)-**1**
sedative

Thalidomide (**1**)

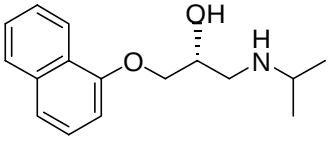


(*S*)-**1**
teratogen

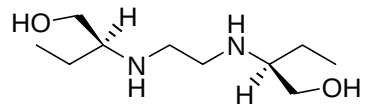


(*S*)-**2**
100 times active than (*R*)-**2**

Propranolol (**2**)

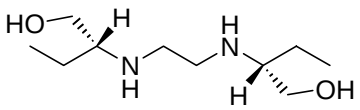


(*R*)-**2**
less active

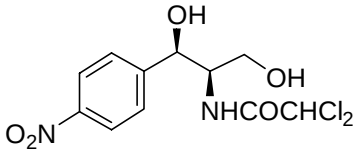


(*S*,*S*)-**3**
tuberculostatic

Ethambutol (**3**)

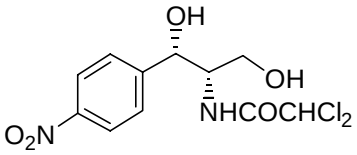


(*R*,*R*)-**3**
causes blindness



(*R*,*R*)-**4**
antibacterial

Chloramphenicol (**4**)



(*S*,*S*)-**4**
inactive

Therefore, in recent years there has been much emphasis on enantiomeric purity of drug molecules as illustrated by the survey of chirality character of the worldwide approved drugs (Fig. 1).[5] Due to this emergence of chirality as a major and important concern in pharmaceutical industry, scientists in both academic and industrial communities directed their research on this aspect, and indeed made significant contributions in developing convenient and practical procedures/processes for obtaining various types of enantiomerically pure molecules.[6,7] Enantiomerically pure secondary alcohols represent one such interesting class of molecules and therefore, development of simple and highly practical methodologies for obtaining secondary alcohols in enantiomerically pure form *via* the asymmetric reduction of prochiral ketones has been and continues to be an interesting and challenging area in chiral chemistry.

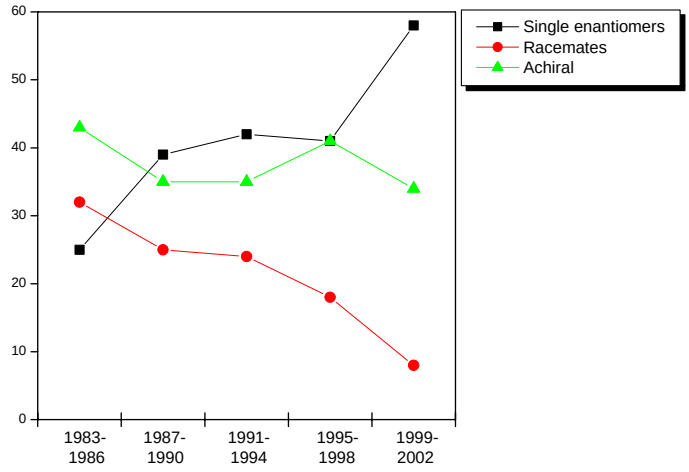


Fig. 1: Distribution of worldwide-approved drugs according to chirality character

Literature survey reveals that various chiral reagents/catalysts based on $LiAlH_4$,[8-13] $LiBH_4$[14] and borane[15-21] have been developed for asymmetric reduction of prochiral ketones to provide the required secondary alcohols with high enantioselectivities. Also, catalytic asymmetric hydrogenation[22-25] and asymmetric transfer hydrogenation reactions[26-28] have been developed for this purpose. In addition to these chemical methods, biocatalytic approaches have also been employed for the asymmetric reduction of prochiral ketones.[29,30] Since, this thesis deals with the studies on the applications of molecules, containing *N–P=O* structural framework, as catalysts for the borane-mediated asymmetric reduction of prochiral ketones, this chapter presents the important known methods from the literature on the reduction of prochiral ketones using chiral boron reagents/catalysts. As there are large number of publications in this area, it will not be possible to present all the literature

methods in this section. However, all attempts were made to present most relevant and recent methodologies.

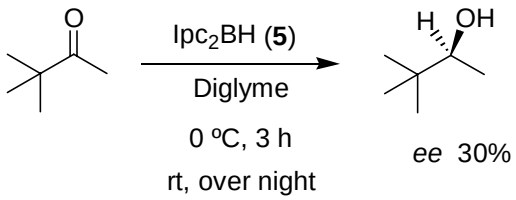
Based on the available literature, boron reagents can be broadly classified into two major classes a) **Stoichiometric reagents** [where an equivalent amount of **chiral reagent** is required for carrying out the reduction process] and b) **Catalytic reagents** [where sub-stoichiometric amount of chiral reagent is sufficient for the same process].

Stoichiometric reagents

Chiral stoichiometric reagents based on boron can be further categorized as 1) monoalkyl/ dialkylboranes (RBH_2/R_2BH), 2) trialkyl/dialkylhaloboranes (R_3B/R_2BX), and 3) chiral borohydrides ($R_3BH^- M^+$), and this section presents relevant applications of these reagents for asymmetric reduction of prochiral ketones.

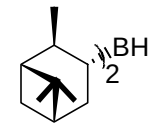
Mono/dialkylboranes

As early as 1961, Brown and Bigley,[31] for the first time, reported the asymmetric reduction of prochiral ketones with diisopinocampheylborane [Ipc_2BH (**5**)] (Chart 1) and obtained a maximum enantiomeric purity of 30% in the case of *t*-butyl methyl ketone (eq. 1).

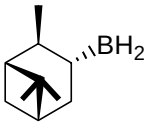


(eq. 1)

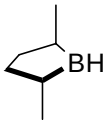
Chart 1



Ipc_2BH (**5**)



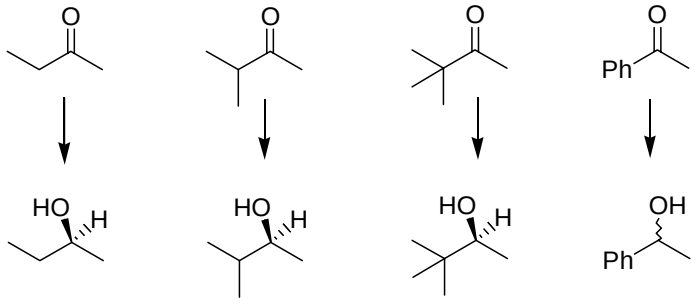
$IpcBH_2$ (**6**)



(*R*,*R*)-2,5-Dimethylborolane (**7**)

In the later years Ipc_2BH (**5**) was used as a reagent for the asymmetric reduction of representative ketones.[32] Brown has also examined the potential of monoisopino-campheylborane [$IpcBH_2$ (**6**)] as a reagent for asymmetric reductions.[33] A comparison between **5** & **6** in performing the asymmetric reduction of representative prochiral ketones is presented in Scheme 1. Although the enantioselectivities are not high, these studies in fact, provided a preliminary understanding of chiral reduction process.

Scheme 1: Enantioselectivities for the reductions carried at 0 °C using **5** & **6**

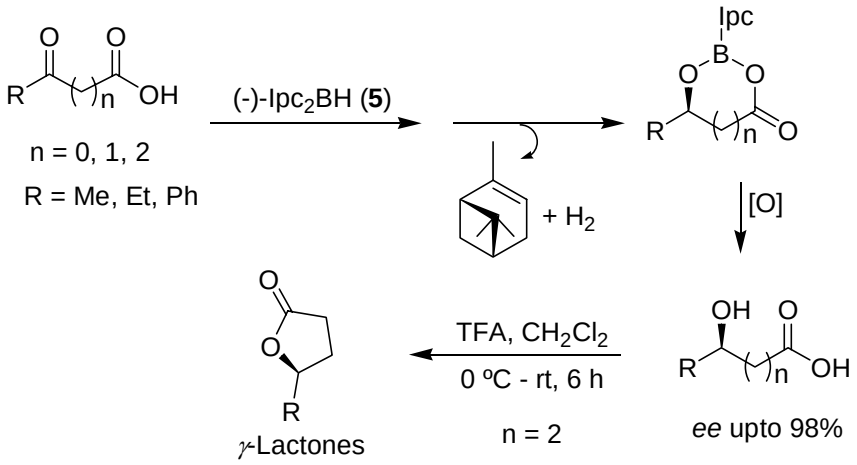


Ipc_2BH (**5**)[32]	13.4% (*S*)	37.0% (*S*)	19.8% (*S*)	9.0% (*R*)
$IpcBH_2$ (**6**)[33]	22.2% (*S*)*	46.3% (*S*)*	21.2% (*S*)	14.9% (*S*)

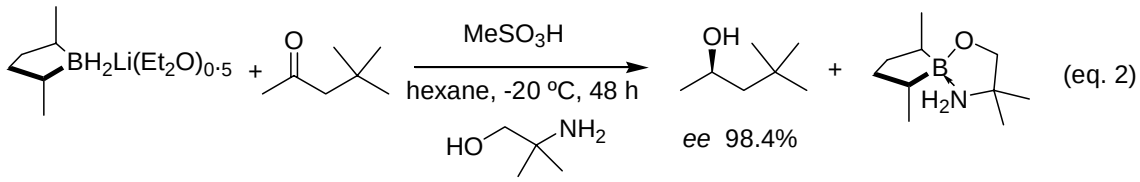
* Reaction carried at -25 °C

Very recently, Ramachandran and Brown[34,35] reported an interesting application of Ipc_2BH (**5**) for the reduction of *α*-, *β*-, and *γ*-keto acids thus obtaining the corresponding alcohols (*γ*-hydroxy acids were further transformed to *γ*-lactones) in high enantiomeric purities (Scheme 2). High enantioselectivities may be attributed to intramolecular asymmetric reduction process.

Scheme 2

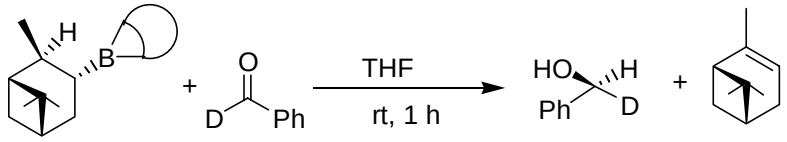


Masamune *et al.*[36] have successfully used, *in situ* generated (2*R*,5*R*)-2,5-dimethylborolane (**7**), for the asymmetric reduction of dialkyl ketones to provide the resulting alcohols in high enantiomeric purities. Representative example is presented in eq. 2.[36]

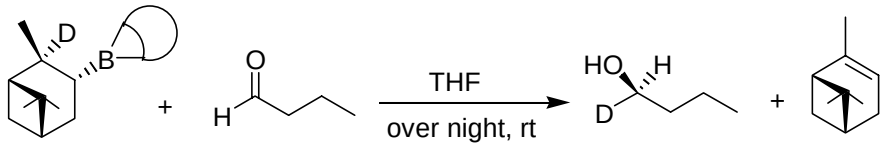


Trialkyl/dialkylhaloborane reagents

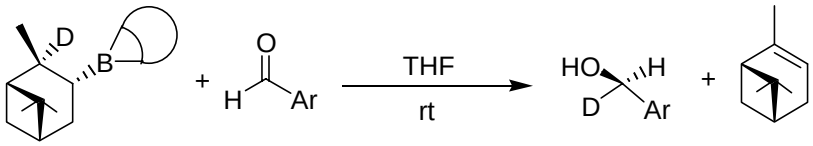
In 1979, Midland used *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane [Alpine-Borane®[1] (**8**)], a trialkylborane, obtained *via* the hydroboration of α-pinene with 9-BBN, for reduction of aldehydes and synthesized series of deuterated primary alcohols in essentially optically pure form (eqs. 3-5).[37]



8 *ee* 97.8% (eq. 3)



ee 100% (eq. 4)

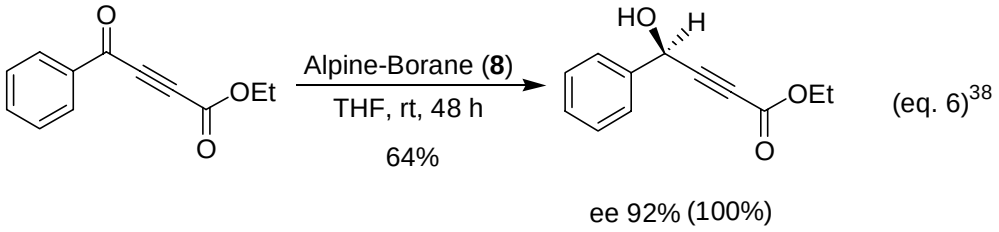


ee 100% when Ar = *p*-ClC_6H_4, *p*-$NO_2C_6H_4$ (eq. 5)

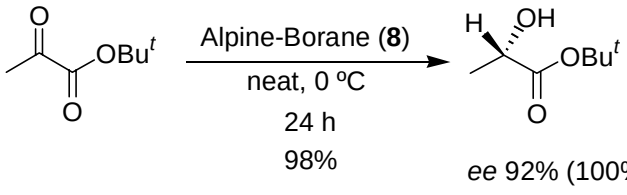
*ee*s mentioned are corrected ones wih respect to Alpine-Borane from 100% optically pure α-pinene

[1] Alpine-Borane is a trademark of Aldrich Chemical Company

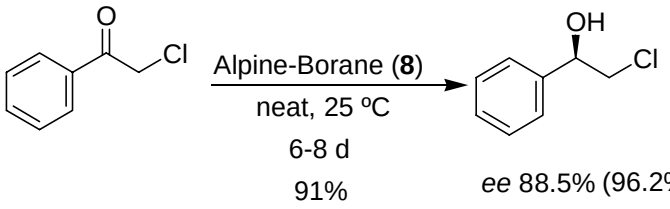
Later, Midland & Brown independently studied the application of Alpine-Borane (**8**) for asymmetric reduction of various prochiral ketones (eqs. 6-9).[38-40]



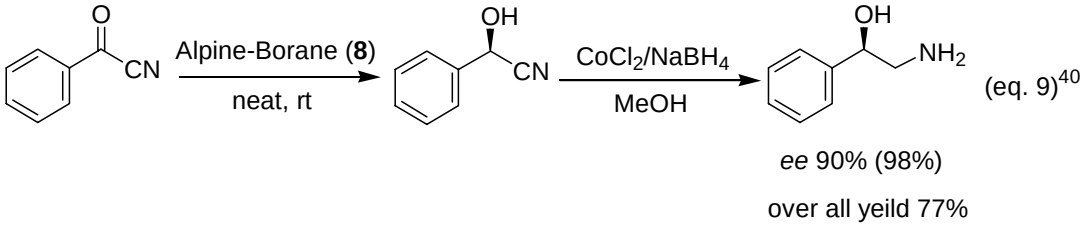
(eq. 6)[38]



(eq. 7)[39]



(eq. 8)[39]

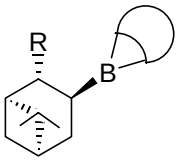


(eq. 9)[40]

Reported *ee*s are due to Alpine-Borane obtained from α-pinene with 92% enantiomeric purity, while *ee*s in parenthesis are corrected ones wih respect to Alpine-Borane from 100% optically pure α-pinene

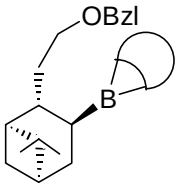
Subsequently several trialkylborane reagents (**9**-**12**) based on pinene (or pinene framework) have been synthesized and their applications have been examined for asymmetric reduction of various prochiral ketones (Chart 2 & eqs. 10-13).[41-43]

Chart 2

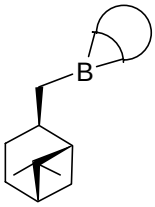


R = Ethyl, Eapine-Borane (**9**)

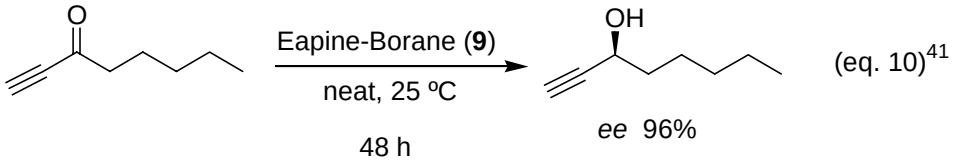
R = Propyl, Prapine-Borane (**10**)



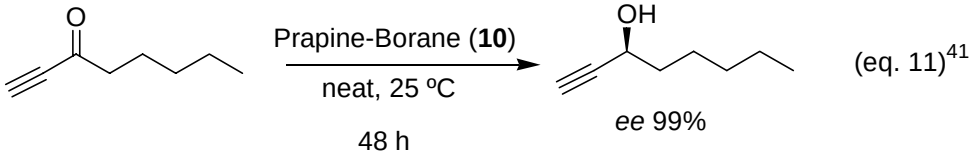
NB-Enantrane (**11**)



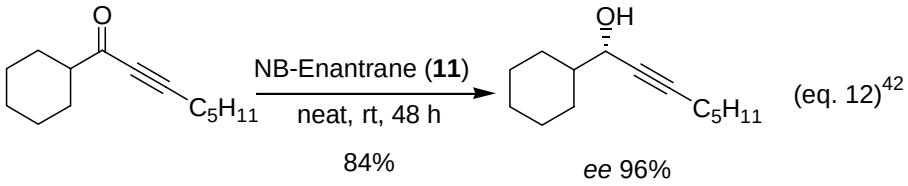
cis-myrtanylborane (**12**)

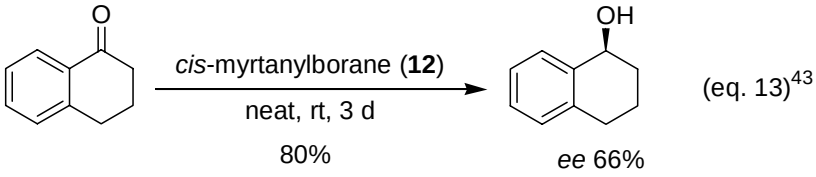


(eq. 10)[41]



(eq. 11)[41]

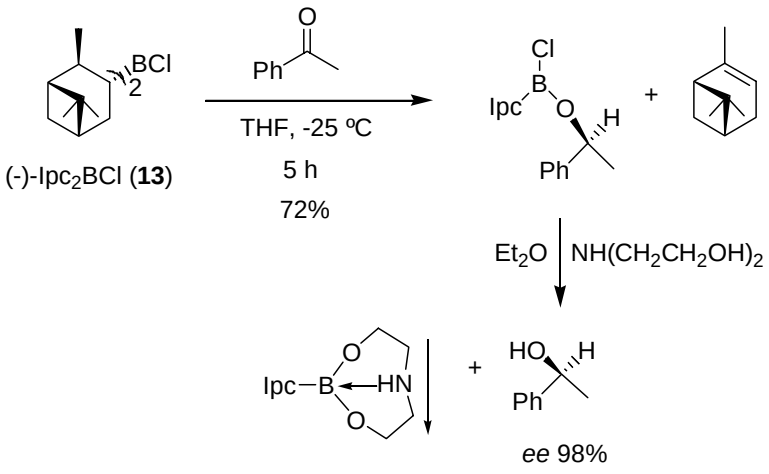




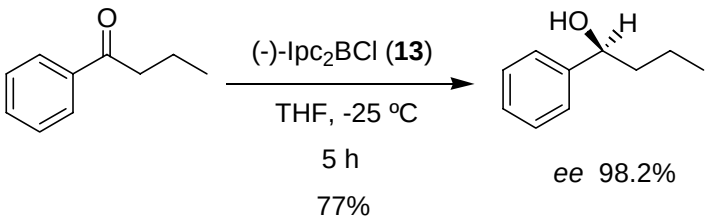
Dialkylchloroborane reagents

Brown and co-workers have successfully employed *B*-chlorodiisopinocampheylborane [Ipc_2BCl (**13**)] (DIP-Chloride^{TM}[2]) for reduction of prochiral ketones.[44] Subsequently this has become a reagent of choice for asymmetric reductions of many prochiral ketones.[44-46] Representative examples have been presented in Scheme 3 & eqs. 14-17.[44-46]

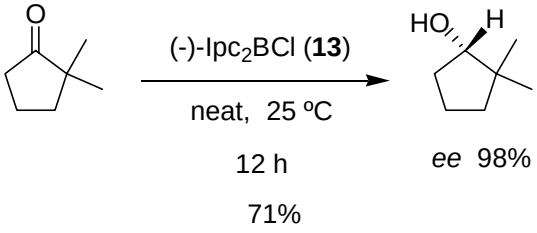
Scheme 3



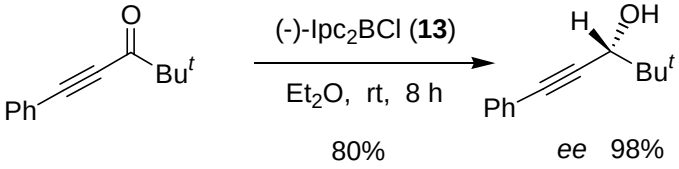
[2] DIP-Chloride is a trademark of Aldrich Chemical Company.



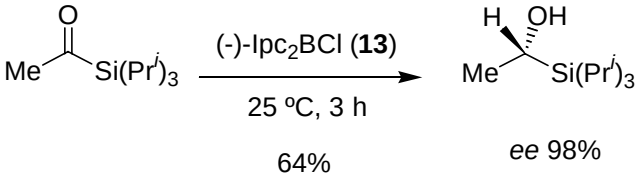
(eq. 14)[44]



(eq. 15)[44]



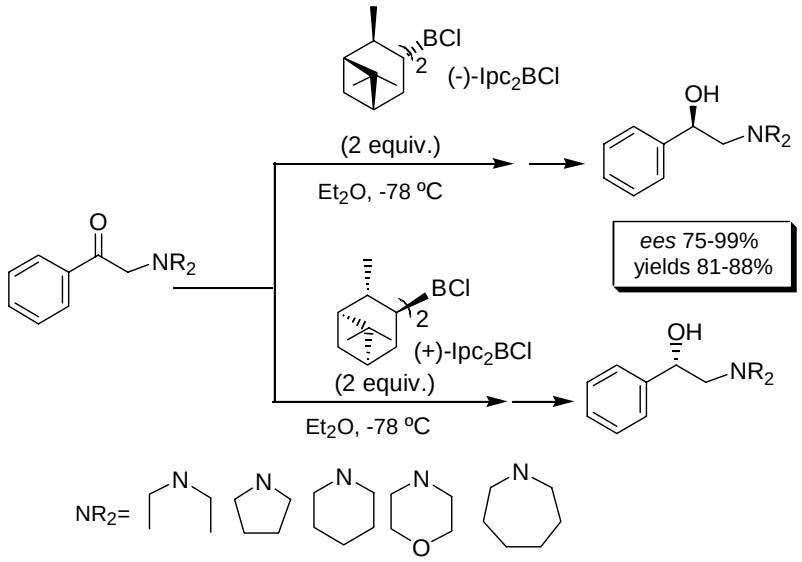
(eq. 16)[45]



(eq. 17)[46]

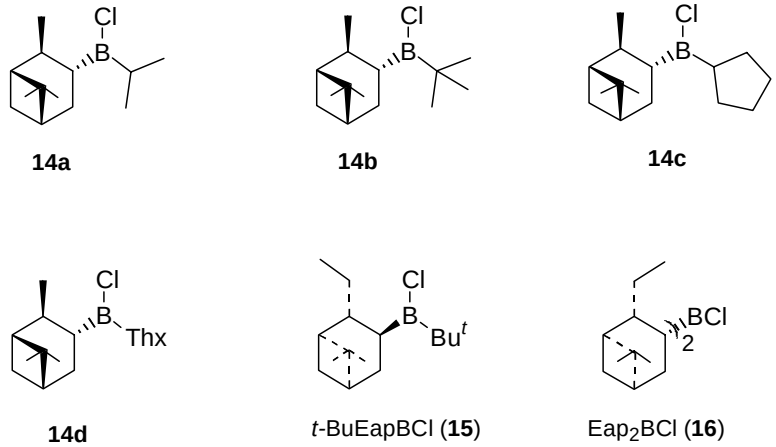
Singaram *et al.* have utilized both the enantiomers of DIP-Chlorides [*i e.* (-)-Ipc_2BCl & (+)-Ipc_2BCl] for the reduction of the α-amino ketones to obtain both the enantiomers of α-amino alcohols in high optical purities (Scheme 4).[47]

Scheme 4

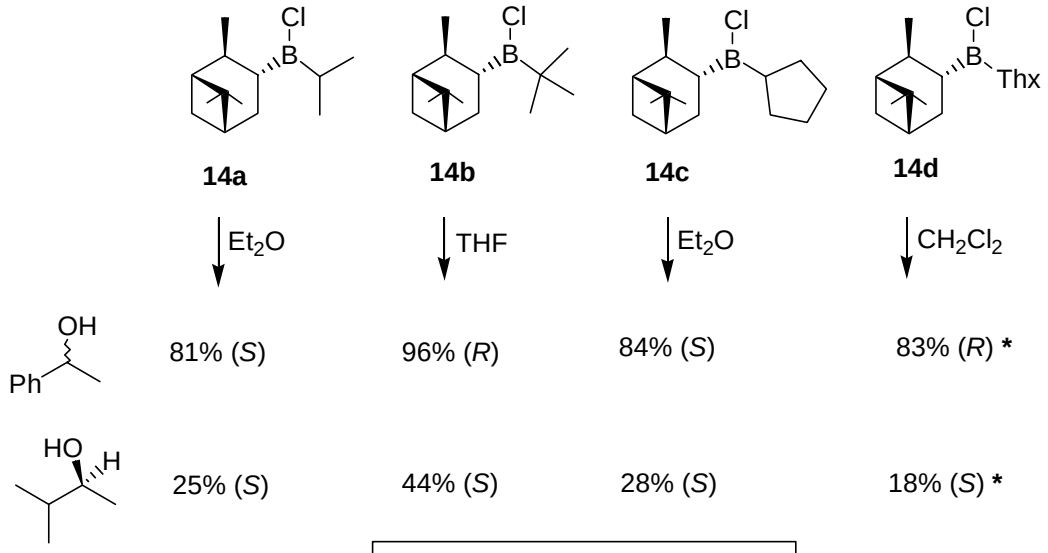


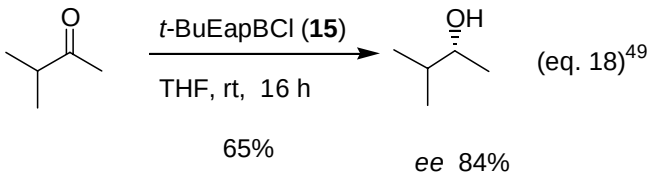
Brown *et al*. also synthesized several chiral chloro-borane reagents based on pinene framework (**14-16**, Chart 3)[48-50] and studied their applications systematically for chiral reduction of various prochiral ketones (Scheme 5, eqs. 18 & 19).[48-50]

Chart 3

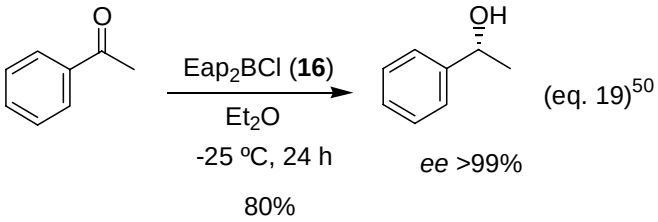


Scheme 5: Enantioselectivities for the reductions of acetophenone & 3-methyl-2-butanone carried out at -25 °C using **14a-14d**[48]





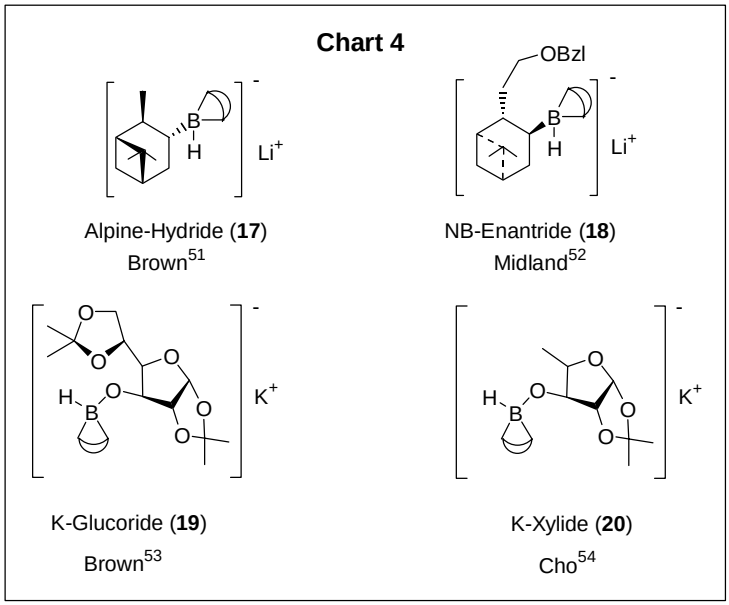
The *ee* mentioned in eq. 18 is the corrected one wih respect to reagent obtained from 100% optically pure ethylapopinene.



Chiral borohydride reagents

Another important class of reagents used for chiral reductions is chiral borohydrides (Chart 4).[51-54] Brown *et al.* used Alpine-Hydride®[3] (**17**) for asymmetric reduction of aliphatic ketones. Representative example is presented in eq. 20.[51]

Chart 4

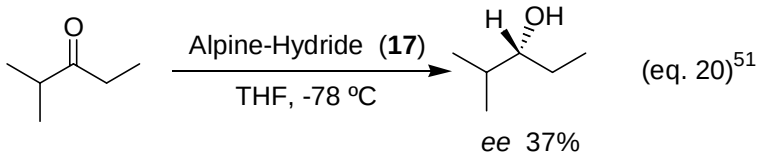


Alpine-Hydride (**17**)
Brown[51]

NB-Enantride (**18**)
Midland[52]

K-Glucoride (**19**)
Brown[53]

K-Xylide (**20**)
Cho[54]

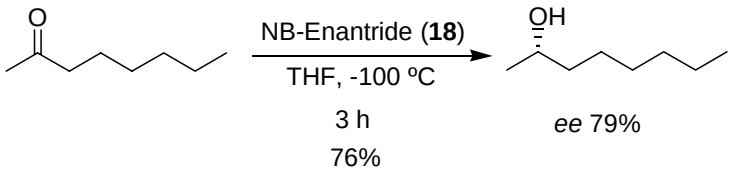


ee 37%

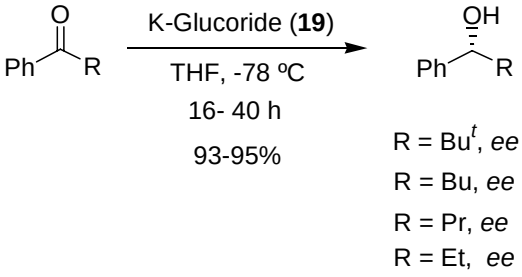
(eq. 20)[51]

In subsequent years, Brown and others have synthesized various chiral borohydrides (Chart 4)[51-54] and employed them as reducing agents in asymmetric reduction of prochiral ketones to provide the resulting secondary alcohols in high enantioselectivities (eqs. 21-23).

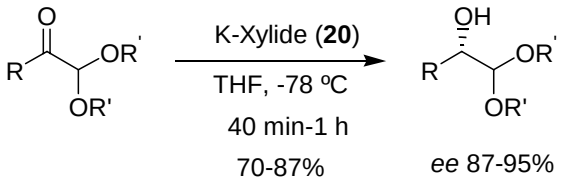
[3] Alpine-Hydride is trademark of Aldrich Chemical Company



(eq. 21)[52]



(eq. 22)[53]



(eq. 23)[54]

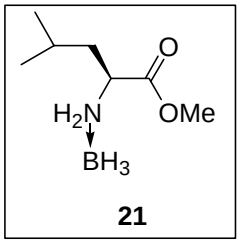
R = Me, Bu, Ph, β-Naphthyl, Pr^i, Bu^t

R' = Me, Et

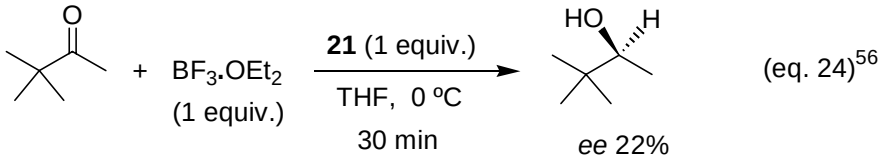
Chiral catalysts

As early as 1969, Kagan *et al.*[55] used chiral amine borane complex derived from ephedrine for reduction of acetophenone and obtained the resulting alcohol up to 5% enantiomeric purity. Later, in the year 1976 Grundon *et al.*[56] used *L-leucine methyl ester borane complex* (**21**) and obtained the maximum *ee* of 22% in the case of *t*-butyl methyl ketone (eq. 24). A major breakthrough was achieved in 1981 by Itsuno *et al.*[57] who reported the effective

asymmetric reduction of aromatic ketones, utilizing stoichiometric amounts of optically active amino alcohol borane complex prepared *in situ, via* the reaction between amino alcohols (Chart 5) and BH_3.THF (eq. 25). Subsequently Itsuno *et al*.[58-60] were able to achieve, 100% enantioselectivity (eq. 26), selecting appropriate amino alcohols and substrates.

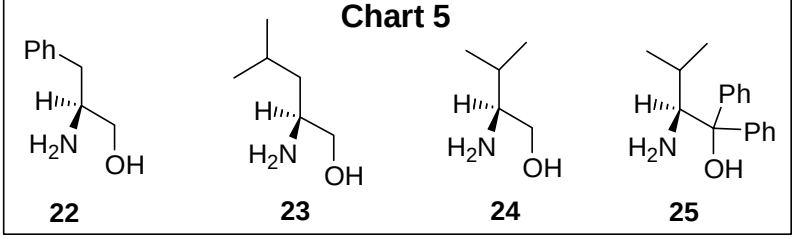


21

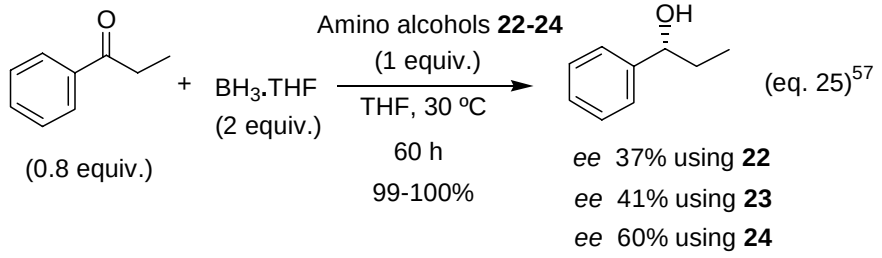


(eq. 24)[56]

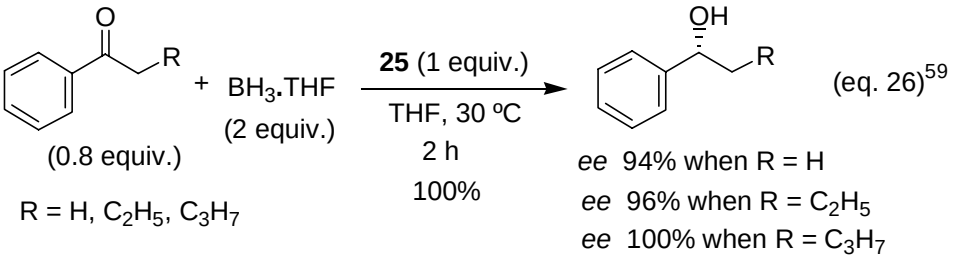
Chart 5



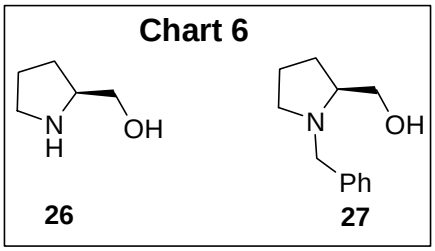
22 **23** **24** **25**

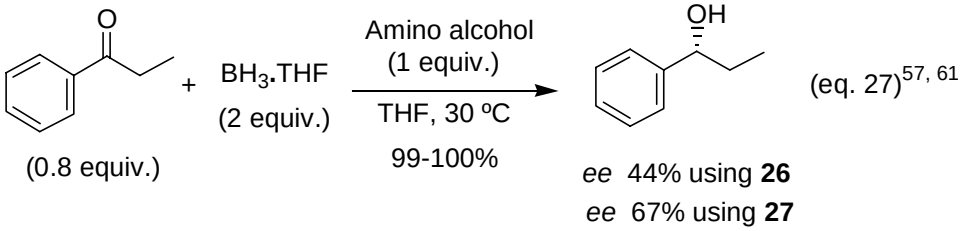


(eq. 25)[57]



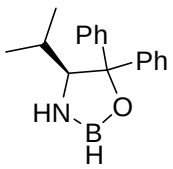
Itsuno also used conformationally rigid system like prolinol (**26**) and its derivative (**27**) (Chart 6) and obtained moderate enantioselectivities in the borane-mediated asymmetric reduction of prochiral ketones (eq. 27).[57,61]



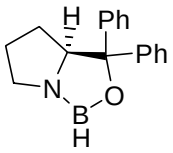


Real break through came in 1987 due to Corey and co-workers,[62] who reported an efficient, catalytic chiral reduction of prochiral ketones using oxazaborolidines (Chemzyme) [**28** & **29**, Chart 7 & eqs. 28-30].

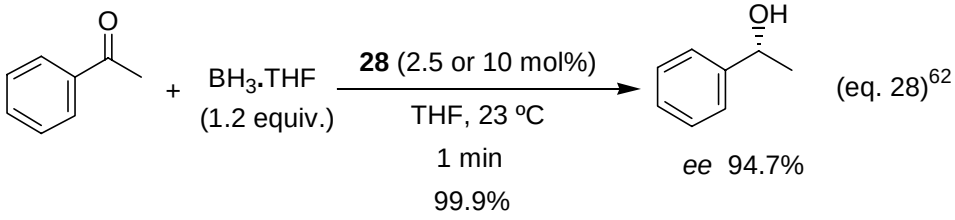
Chart 7



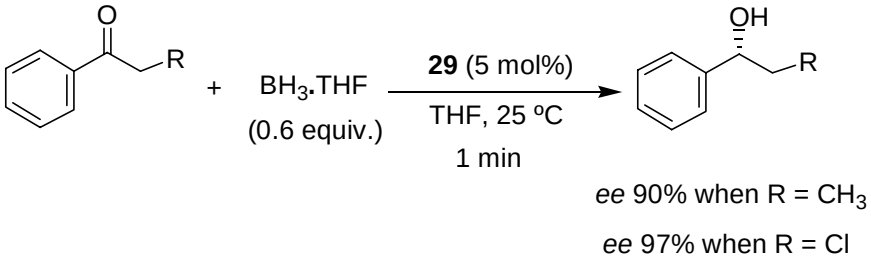
28



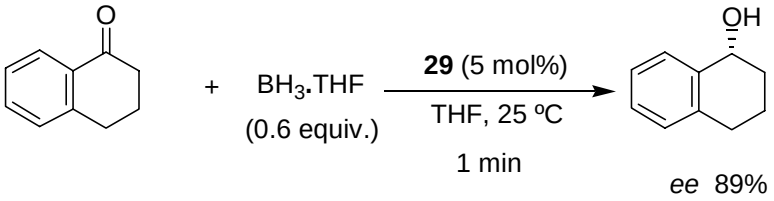
29



(eq. 28)[62]

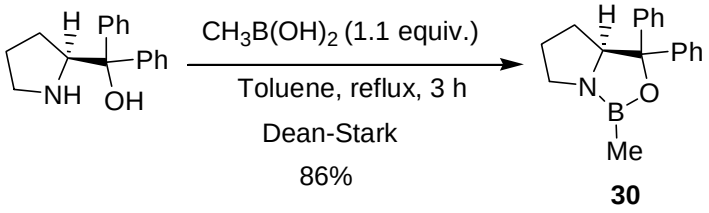


(eq. 29)[62]

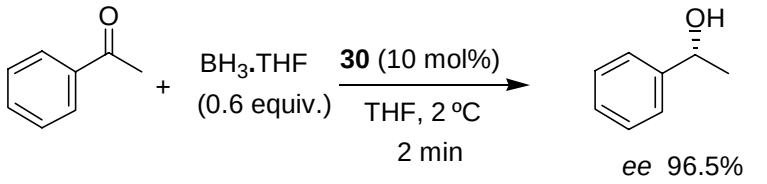


(eq. 30)[62]

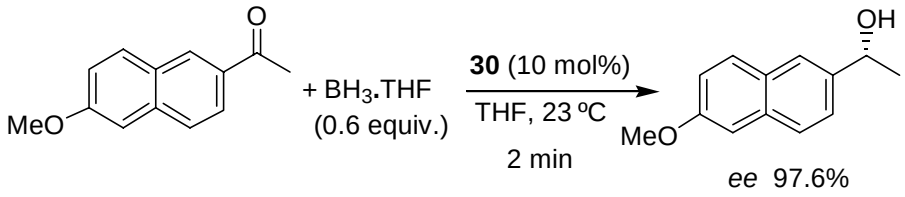
Subsequently Corey *et al.* prepared boron-methylated oxazaborolidine (**30**) according to eq. 31, which was found to be more effective. Representative examples using **30** as a catalyst have been presented in eqs. 32 & 33.[63]



30 (eq. 31)[63]

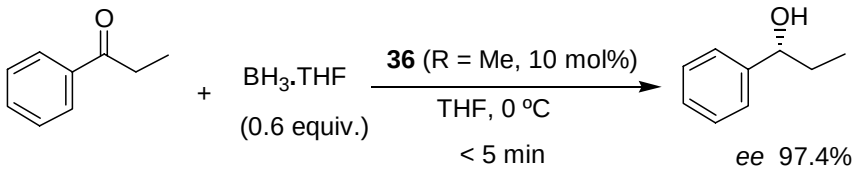


ee 96.5% (eq. 32)[63]



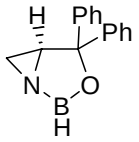
ee 97.6% (eq. 33)[63]

After these elegant reports by Corey *et al*. there was a flood of publications on the synthesis and applications of various oxazaborolidines (Charts 8 & 9)[64-87] derived from variety of amino alcohols. Some significant examples with different oxazaborolidine catalysts are presented in the eqs. 34-39.

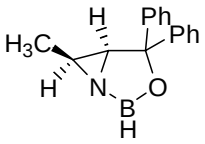


ee 97.4% (eq. 34)[70]

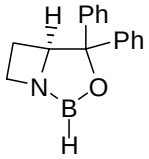
Chart 8



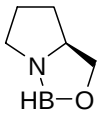
31[64]



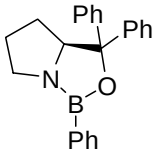
32[64]



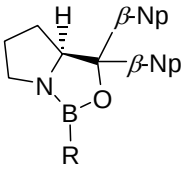
33[65,66]



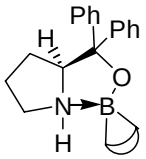
34[67,68]



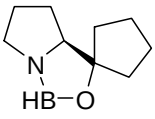
35[69]



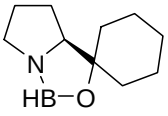
36[70]



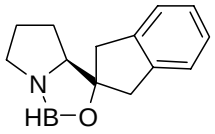
37[71]



38[72]

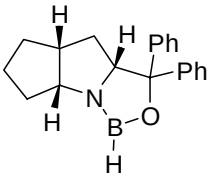


39[72]

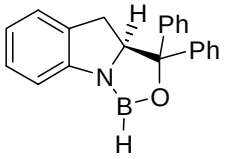


40[72]

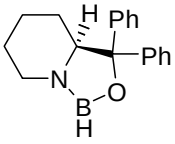
R = H, Me, Bu



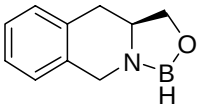
41[73]



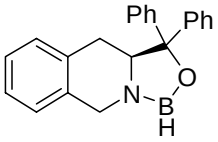
42[74,75]



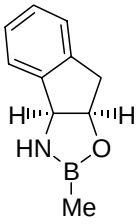
43[76]



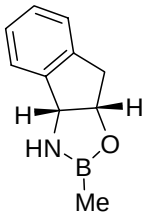
44[77]



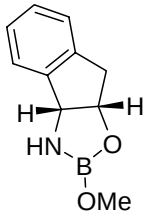
45[77]



46a[78]

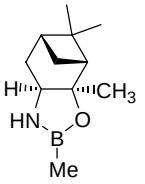


46b[79]

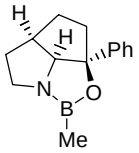


47[80]

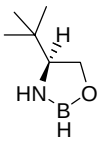
Chart 9



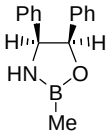
48[81]



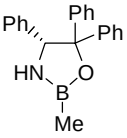
49[82]



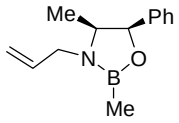
50[66]



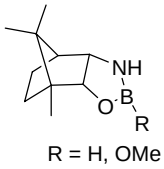
51[83]



52[84]

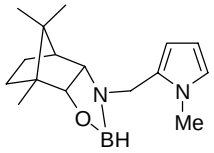


53[85]

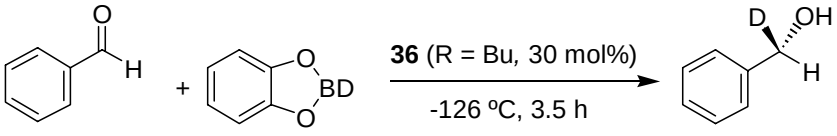


R = H, OMe

54[86]



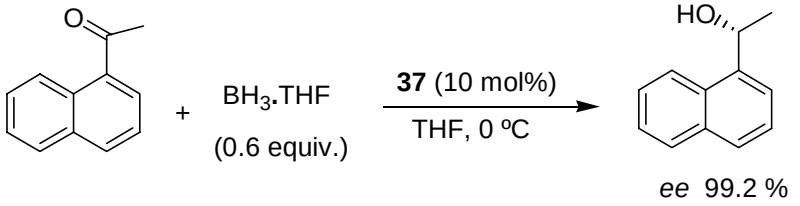
55[87]



(1.5 equiv.)

ee 95%

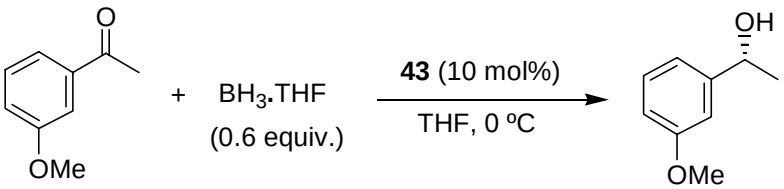
(eq. 35)[70]



(0.6 equiv.)

ee 99.2 %

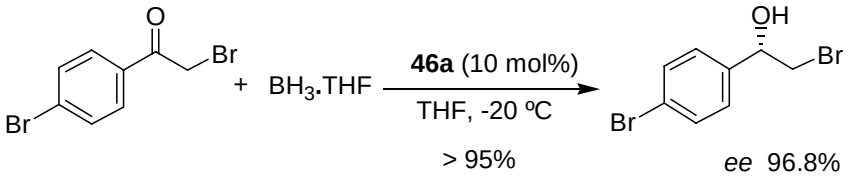
(eq. 36)[71]



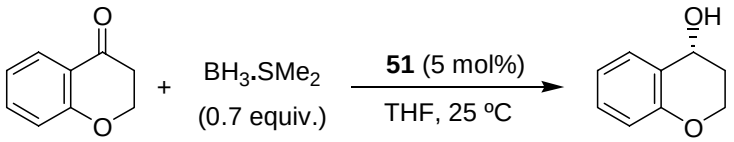
(0.6 equiv.)

ee 92%

(eq. 37)[76]



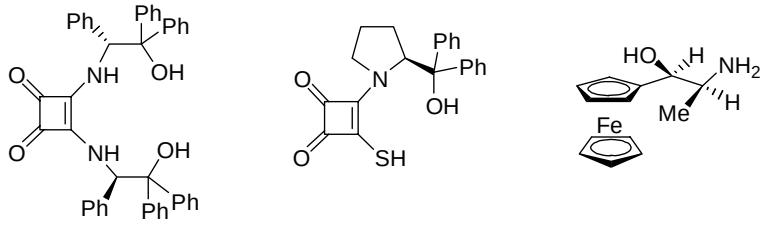
(eq. 38)[78]



(eq. 39)[83]

Recently some interesting amino alcohols (Chart 10) have been employed as catalyst in the borane-mediated reduction of ketones, and representative examples have been presented in the eqs. 40 & 41.

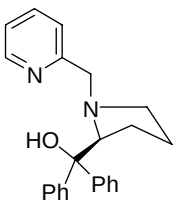
Chart 10



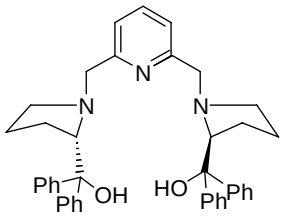
56[88]

57[89]

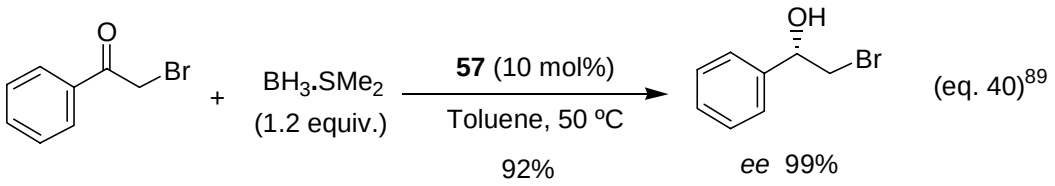
58[90]

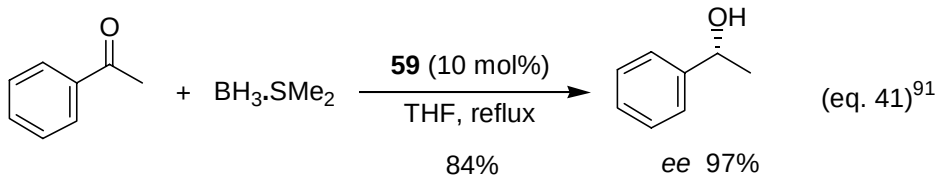


59[91]



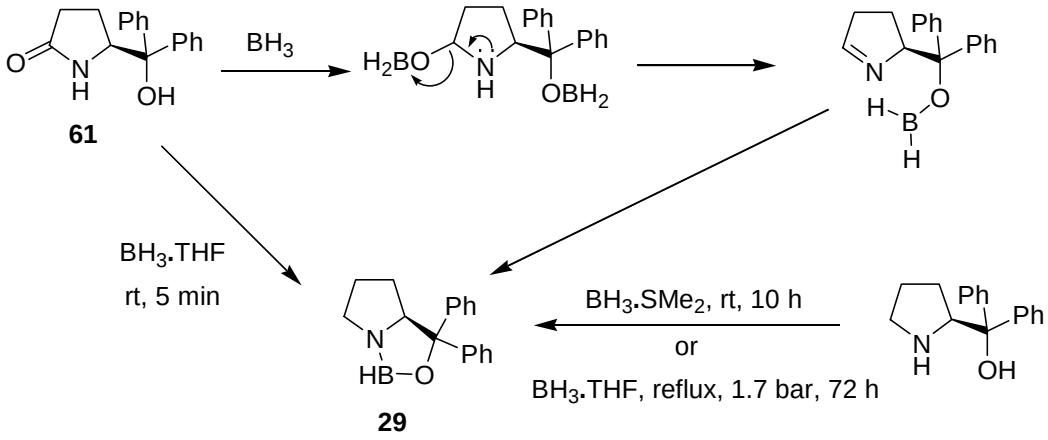
60[91]

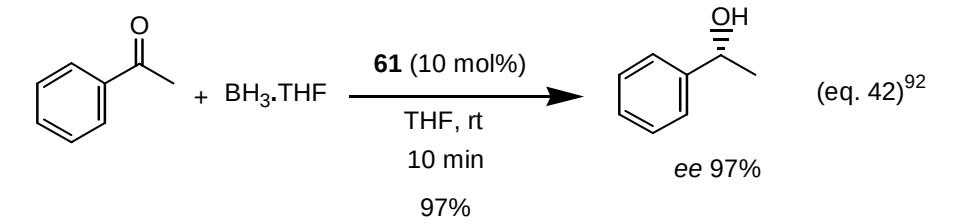


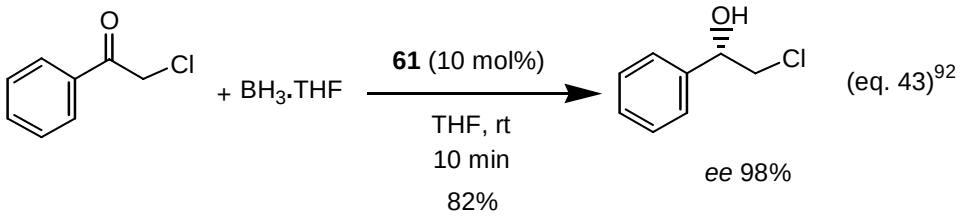


Kawanami *et al.*[92] have used lactam alcohol **61** as a catalytic source (which was reduced to amino alcohol to provide oxazaborolidine **29** *in situ*) to catalyze reduction of the prochiral ketones thus providing the resulting secondary alcohols with high enantiomeric purities (Scheme 6, eqs. 42 & 43).

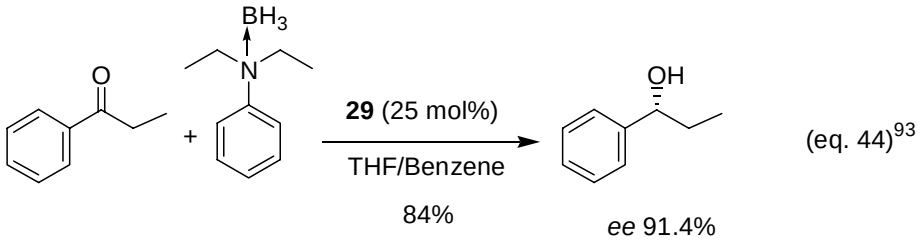
Scheme 6

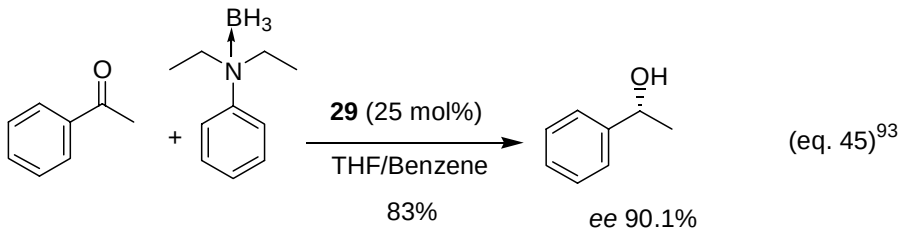






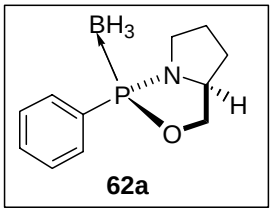
Periasamy *et al*.[93] have developed a convenient procedure for asymmetric reduction of prochiral ketones utilizing oxazaborolidine (**29**) generated *in situ* from *α,α*-diphenyl-pyrrolidinemethanol and diborane in the presence of *N,N*-diethylaniline-BH_3 (*in situ* generated from $NaBH_4/I_2$ and *N,N*-diethylaniline). Representative examples are given in eqs. 44 & 45.



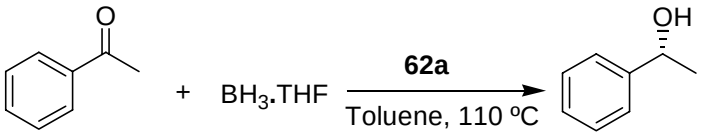


Phosphorus based chiral catalysts

With a view to examine the possible applications of oxazaphospholodine-borane complexes as catalysts Buono *et al.*[94] prepared the molecule **62a** and applied as a catalyst for asymmetric reduction of representative prochiral ketones. High stereoselectivity (*ee* 99%) was achieved when one equivalent of the catalyst was used in the borane-mediated reduction of acetophenone (eq. 46).



62a



(eq. 46)

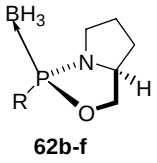
ee 33% with 2 mol%

ee 63% with 16 mol%

ee >99% with 100 mol%.

Subsequently various tricoordinate phosphorus borane complexes have been prepared by Buono,[95] Vasella,[96] Wills,[97] Tang[98] and Muller[99] (Chart 11) and their applications have been examined for asymmetric reduction of number of prochiral ketones. Representative examples with best enantioselectivities have been presented in eq. 47.

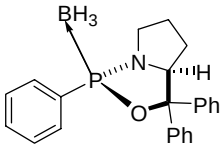
Chart 11



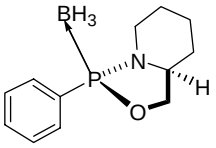
62b-f

R = *o*-methoxyphenyl **62b**
p-tolyl **62c**
β-naphthyl **62d**
phenoxy **62e**
dimethylamino **62f**

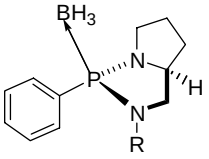
62b-62f, 63-68
Buono[95]



63

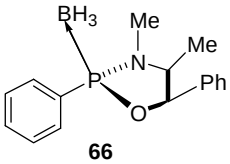


64

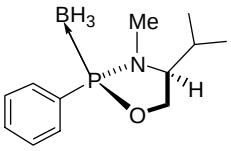


R = phenyl
o-methoxyphenyl
o-tolyl

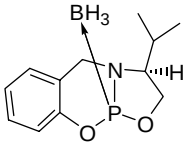
65



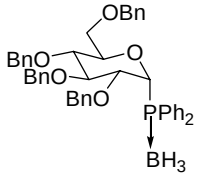
66



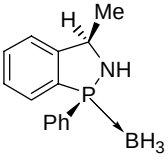
67



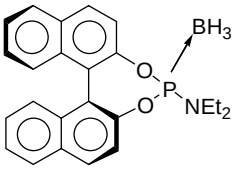
68



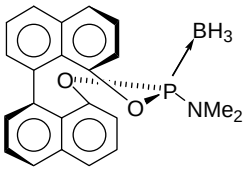
69
Vasella[96]



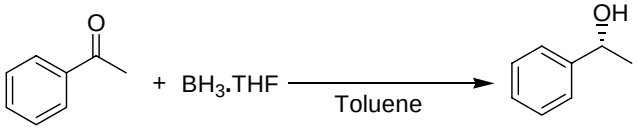
70
Wills[97]



71
Tang[98]



72
Muller[99]



(eq. 47)

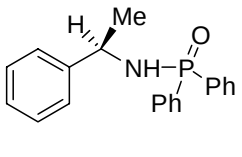
[**62b-62f, 63, 64** (100 mol%), 110 ºC, *ee* >99%][95]

[**71** (6 mol%), 100 ºC, *ee* 98.4%][98]

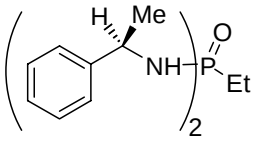
Catalysts with *N-P=O* structural framework

In 1993, Wills and co-workers[100] for the first time prepared a new class of molecules containing *N-P=O* structural framework (**73-75**, Chart 12) and studied their applications as possible catalysts in the borane-mediated reduction of acetophenone. They were able to achieve a maximum enantioselectivity of 35% with the catalyst **74** (2 mol%) (eq. 48).

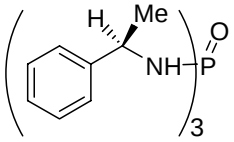
Chart 12



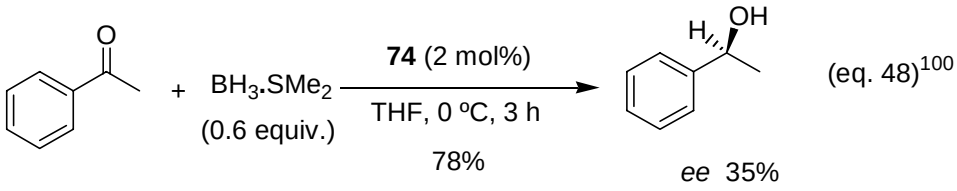
73



74

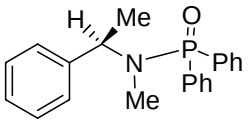


75

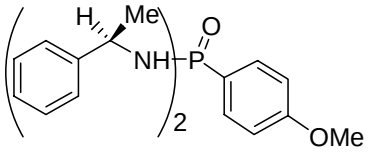


Subsequently Wills *et al.* prepared several catalysts having *N-P=O* structural framework (Charts 13)[101-105] and systematically studied their applications in the asymmetric reduction of prochiral ketones. They obtained best results in the case of catalysts **82**, **83** and **92** (eqs. 49-51).[102,105]

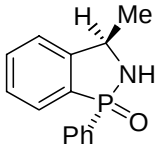
Chart 13



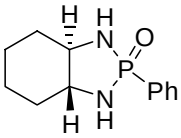
76[101]



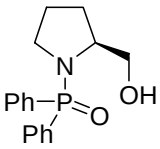
77[101]



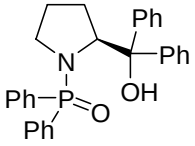
78[101]



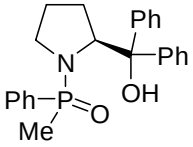
79[101]



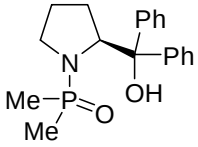
80[102]



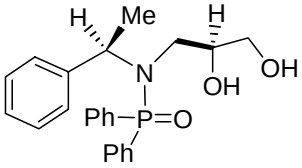
81[102]



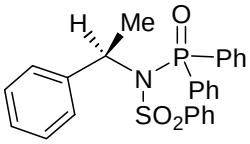
82[102]



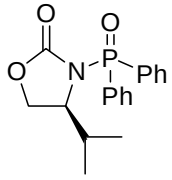
83[102]



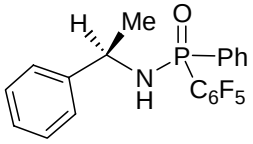
84[103]



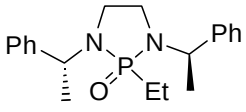
85[104]



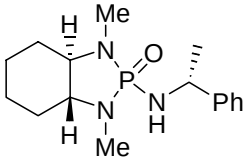
86[104]



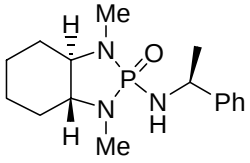
87[104]



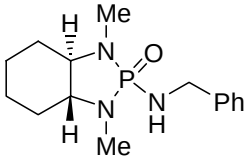
88[104]



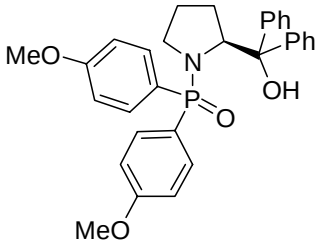
89[104]



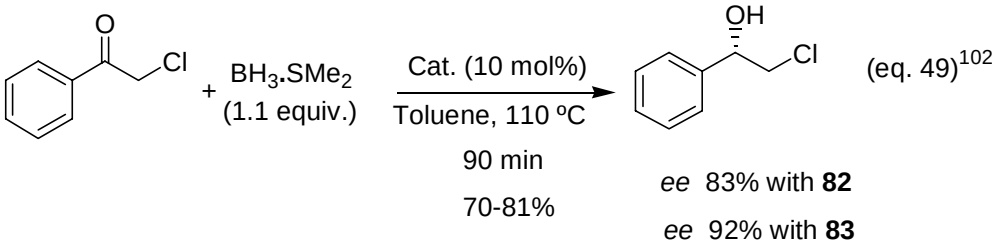
90[104]



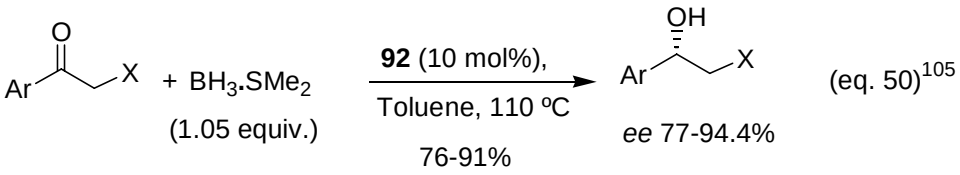
91[104]



92[105]



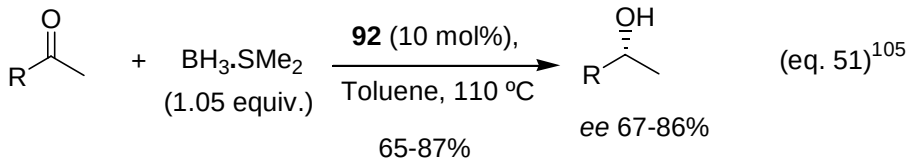
(eq. 49)[102]



(eq. 50)[105]

Ar = Ph, *p*-$OMeC_6H_4$, *β*–naphthyl

X = Br, Cl, Me, H

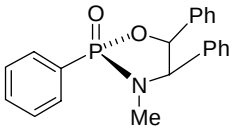


(eq. 51)[105]

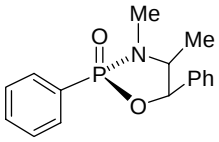
R = Bu^t, cyclohexyl

Subsequently various phosphine oxides (also containing *N-P=O* or *N-P=S* framework) have been prepared by Buono,[106,107] Martens,[108] Kellogs,[109] and Tang[110,111] (Chart 14) and their applications have been examined. A few representative examples with the good enantioselectivities have been presented in eqs. 52-55.

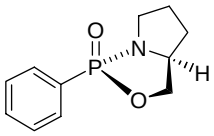
Chart 14



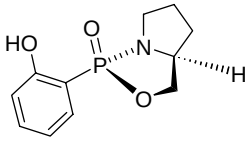
93
Buono[106]



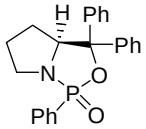
94
Buono[106]



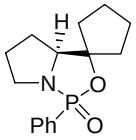
95
Buono[106]



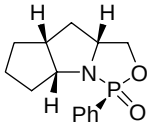
96
Buono[107]



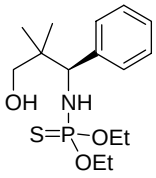
97
Martens[108]



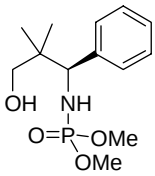
98
Martens[108]



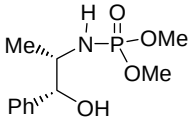
99
Martens[108]



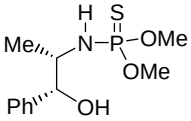
100
Kellogs[109]



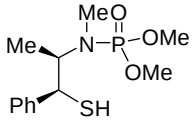
101
Kellogs[109]



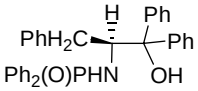
102
Kellogs[109]



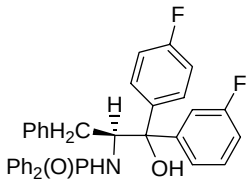
103
Kellogs[109]



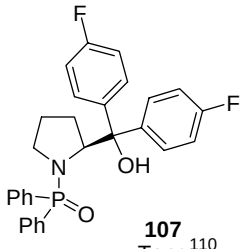
104
Kellogs[109]



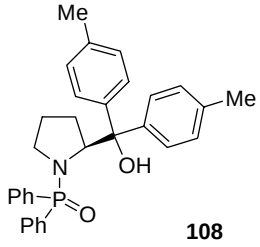
105
Tang[110]



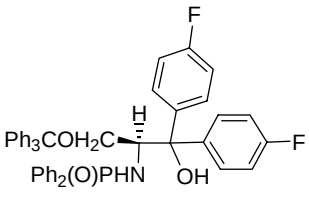
106
Tang[110]



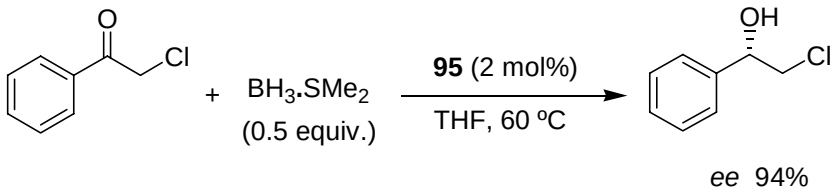
107
Tang[110]



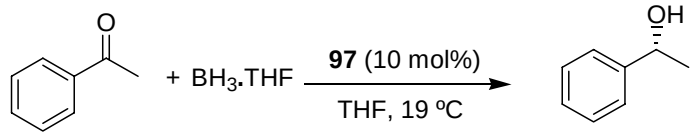
108
Tang[110]



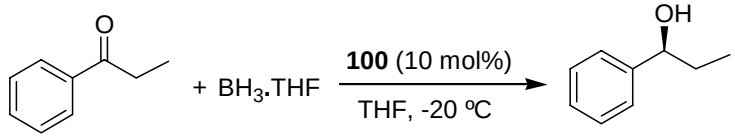
109
Tang[111]



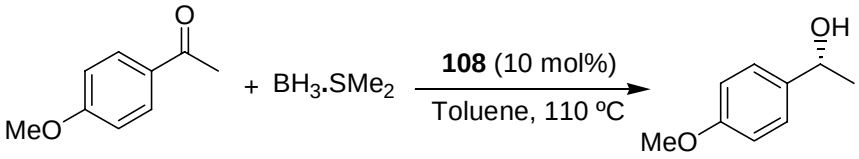
ee 94% (eq. 52)[106]



ee 97% (eq. 53)[108]

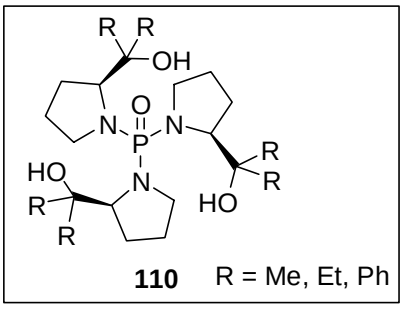


ee 93% (eq. 54)[109]

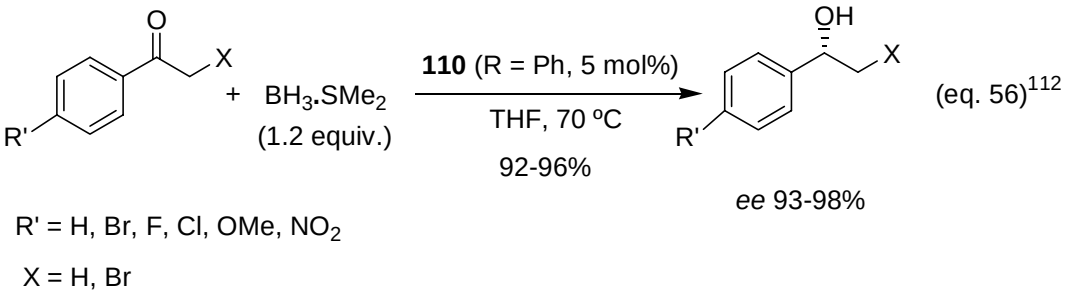


ee 90% (eq. 55)[110]

Very recently, Du and co-workers[112] synthesized a new C_3-symmetric tris(*β*-hydroxy-phosphoramide) catalyst **110** and successfully employed in the borane-mediated asymmetric reduction of prochiral ketones (eq. 56).



110 R = Me, Et, Ph



Our research group has been actively involved in the synthesis and application of molecules containing *N-P=O* structural framework mainly built on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* moiety (**111**, Chart 15) in the borane-mediated asymmetric reduction of prochiral ketones (eqs. 57-59).[113-116]

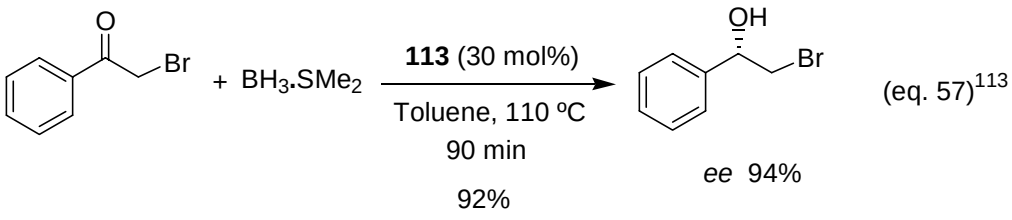
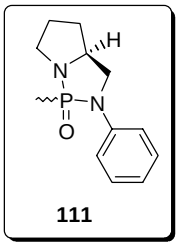
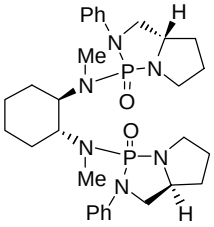


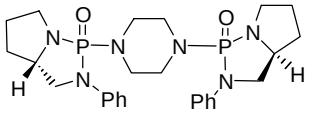
Chart 15



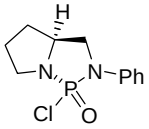
111



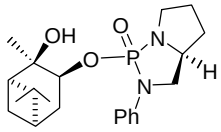
112[113]



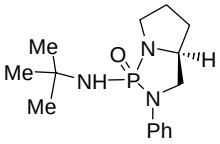
113[113]



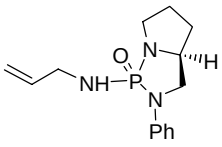
114[114]



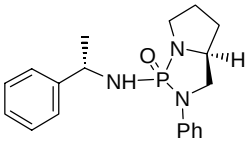
115[115]



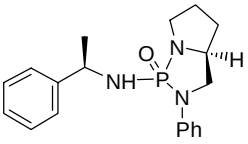
116[116]



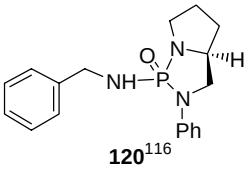
117[116]



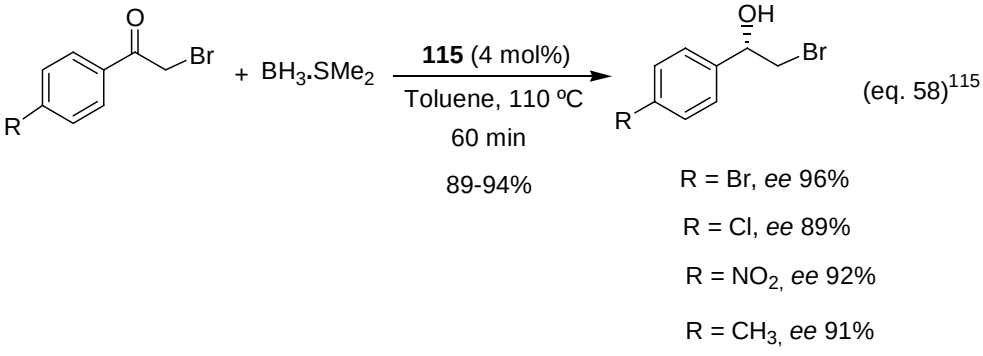
118[116]



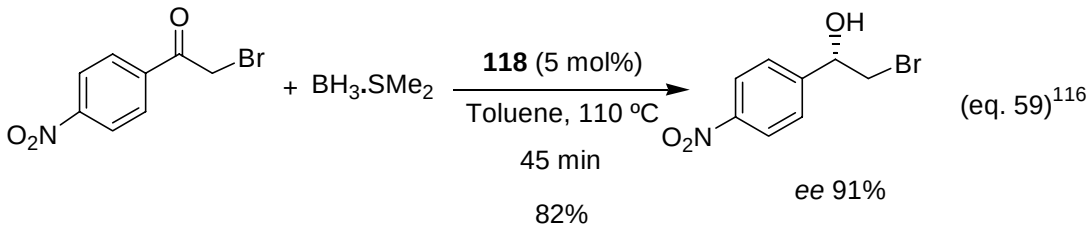
119[116]



120[116]



(eq. 58)[115]

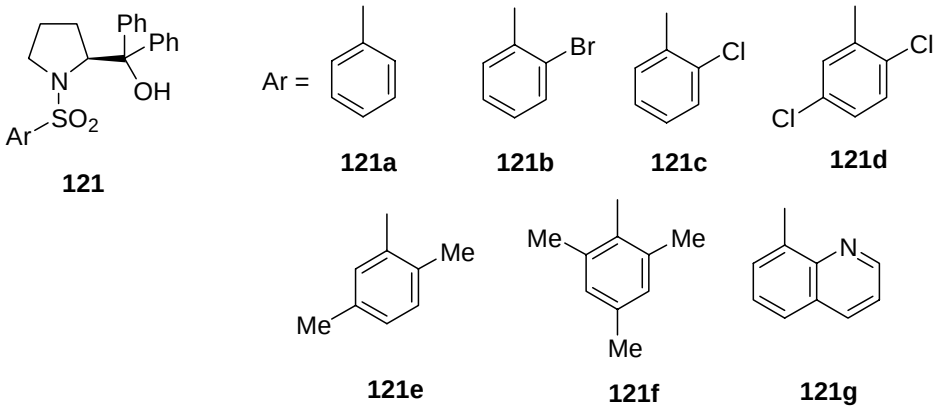


(eq. 59)[116]

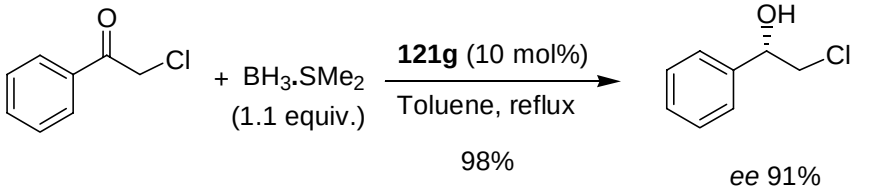
Chiral sulphonamides

Zhao and co-workers[117] utilized chiral sulphonamides (**121**) derived from the (*S*)-2-(diphenylhydroxylmethyl)pyrrolidine (Chart 16) for the borane-mediated reduction of prochiral ketones to provide the corresponding alcohols with good enantioselectivities (eqs. 60 & 61).

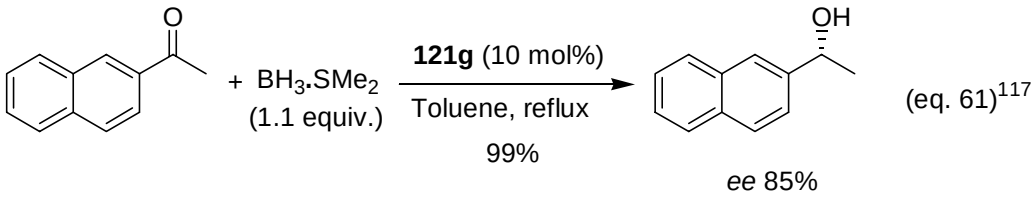
Chart 16



121 **121a** **121b** **121c** **121d** **121e** **121f** **121g**



(eq. 60)[117]

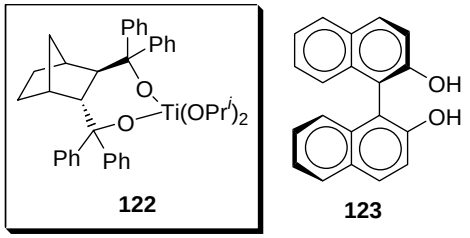


(eq. 61)[117]

Chiral titanium alkoxides as catalysts

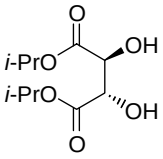
Wandrey and co-workers[118] have reported the application of chiral titanium alkoxide (**122**) as catalyst (Chart 17) for borane-mediated asymmetric reduction of prochiral ketones (one representative example is given in eq. 62). They have also made various chiral titanium alkoxide catalysts from representative chiral diols (Chart 17) and studied their potential as catalysts for borane-mediated reduction of prochiral ketones.[118]

Chart 17

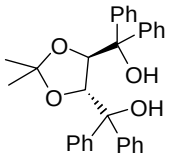


122

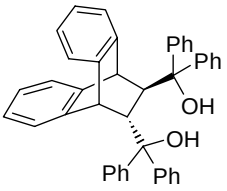
123



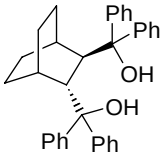
124



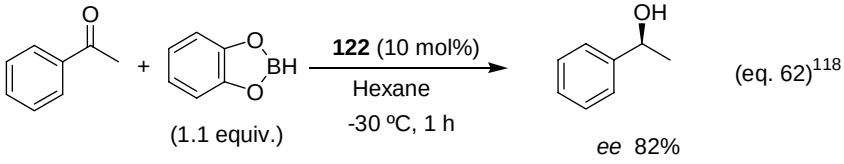
125



126



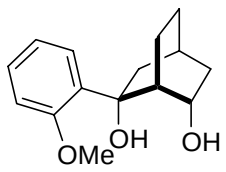
127



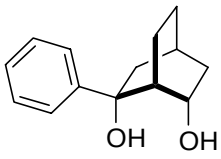
(eq. 62)[118]

Frejd *et al.*[119] have prepared representative titanium catalysts derived from chiral diols (Chart 18) and used them as catalysts for borane-mediated asymmetric reduction of prochiral ketones. Some important examples have been presented in eqs. 63-65.

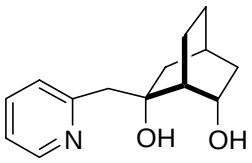
Chart 18



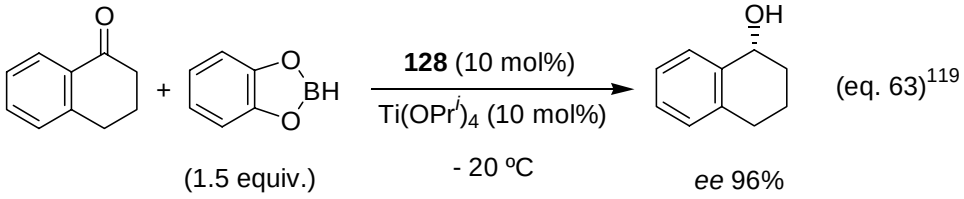
128



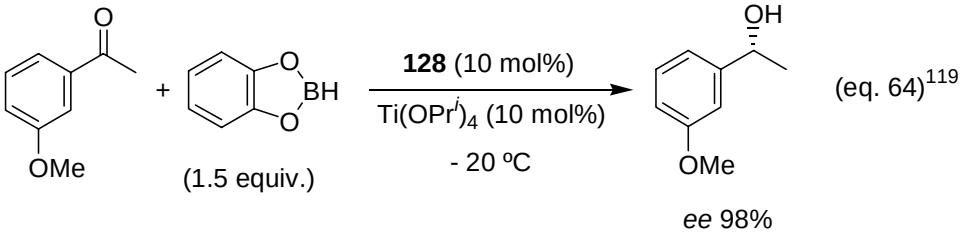
129



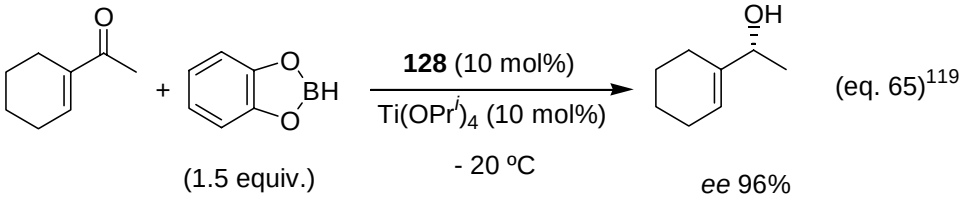
130



(eq. 63)[119]



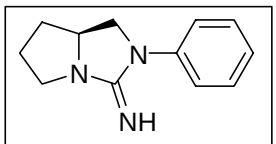
(eq. 64)[119]



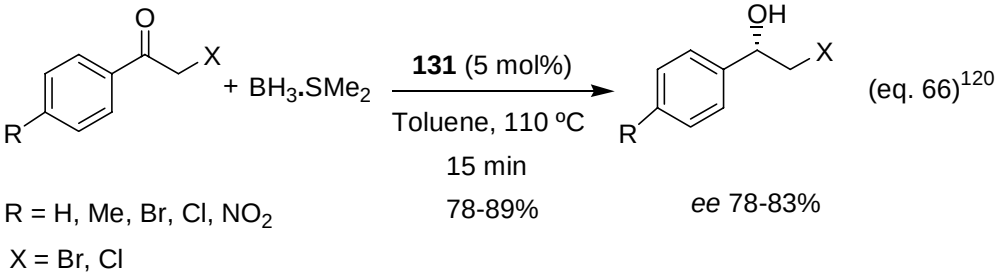
(eq. 65)[119]

Chiral guanidine as a catalyst

Our research group for the first time reported chiral guanidine (**131**) as a novel *in situ* recyclable chiral catalytic source for the borane-mediated asymmetric reduction of prochiral ketones (eq. 66).[120]



131



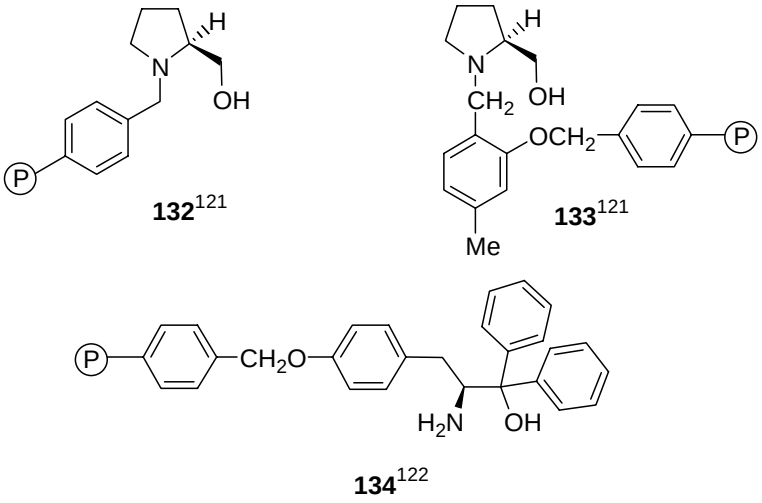
the recyclable ability of catalytic source was tested for four times, the enantioselectivity remained almost same.

Polymer supported chiral catalysts

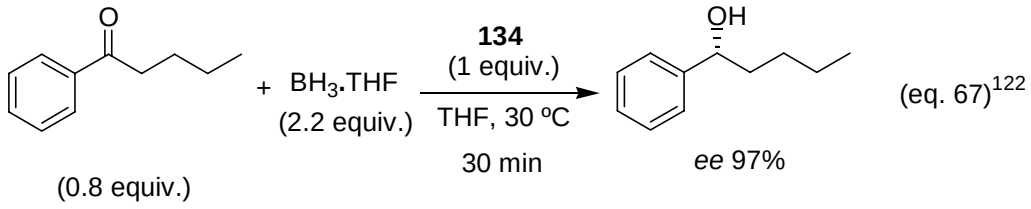
To facilitate the easy recovery of potentially useful catalyst(s) and simplifying the reaction conditions and purification procedures, synthetic chemists also directed their attention to produce heterogeneous catalysts, which can be recoverable and reusable keeping in view the economical and environmental concerns.

Itsuno *et al.*[121-122] have made the polymer supported chiral reagents (**132**-**134**, Chart 19) and examined their potential as possible recoverable and reusable reagents for borane-mediated reduction of prochiral ketones. They used the polymer **134** up to four cycles without any loss in its activity (eq. 67).

Chart 19



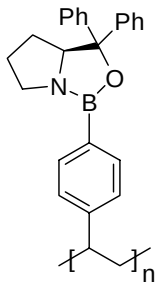
132[121] **133**[121] **134**[122]



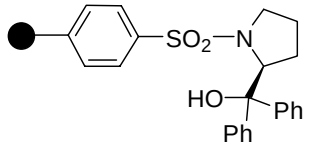
(eq. 67)[122]

Subsequently various polymer supported catalysts (**135**-**137**) have been prepared and their applications in the asymmetric reduction of prochiral ketones have been studied (Chart 20 & eqs. 68-71).[123-127]

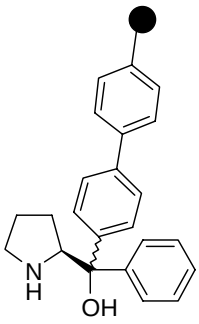
Chart 20



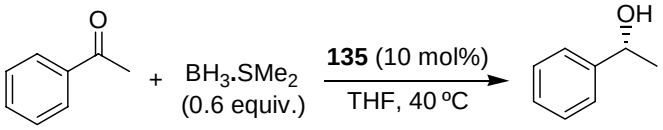
135[123]



136[124]



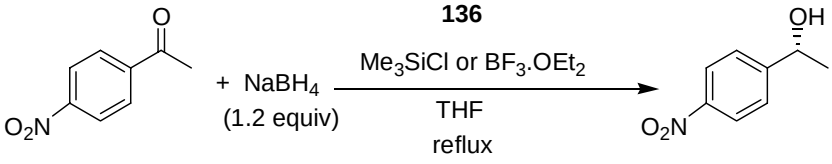
137[125]



(eq. 68)[123]

ee 98%

The catalyst can also be used for the second time without any loss in the acitivity

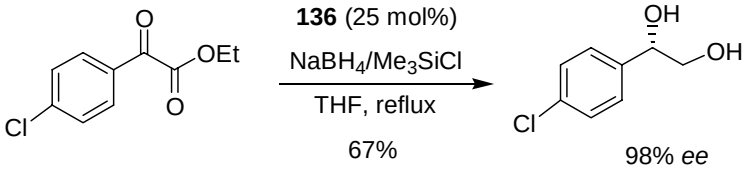


(eq. 69)[124]

136 (25 mol%); Me_3SiCl (1.2 equiv); *ee* 96.6%

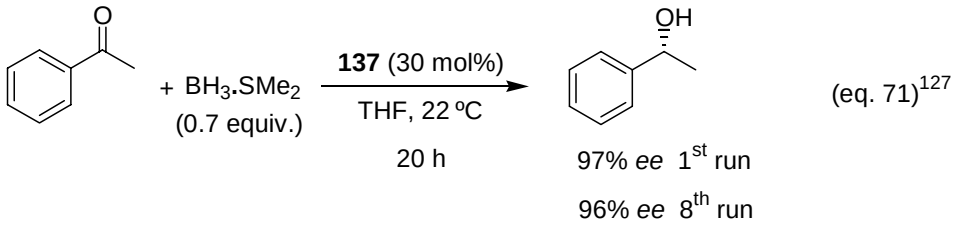
136 (15 mol%); $BF_3.OEt_2$ (1.8 equiv); *ee* 96.0%

The catalyst can be recycled atleast 3 times with little or no loss of performance



(eq. 70)[126]

Catalyst was reused 5 times with little or no loss of performance

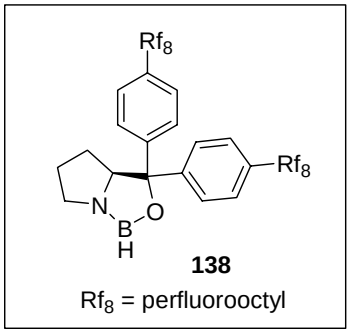


(eq. 71)[127]

The catalyst remains essentially unchanged upto 8 cycles

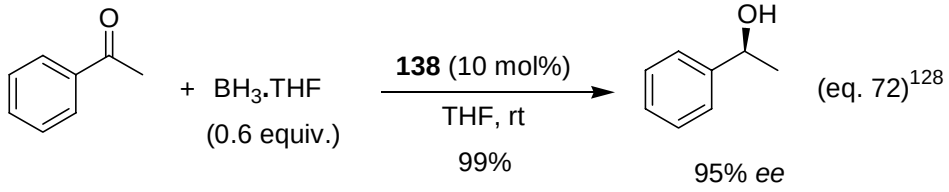
Homogeneous soluble polymers

A different approach for the recovery of catalyst (**138**) was reported up by Soos *et al.*[128] using flourous chemistry[129] as a promising option for catalyst recovery, wherein highly hydrophobic perflouro alkyl group is tagged to the catalyst instead of polymer which makes this flourous molecule highly soluble in flourous phase which can be recovered easily after the reaction using solid phase extraction methodology (eq. 72).



138

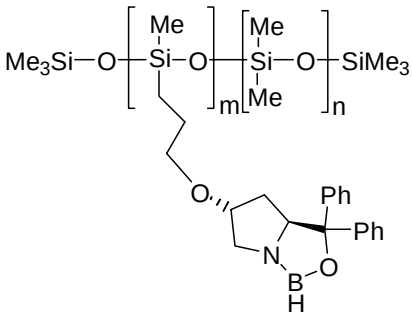
Rf_8 = perfluorooctyl



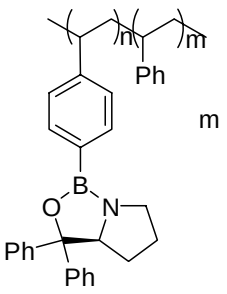
(eq. 72)[128]

Wandrey *et al.*[130] prepared homogeneously soluble polymer catalyst **139** (Chart 21) and employed in the enantioselective borane reduction of prochiral ketones to provide the corresponding chiral alcohols with *ee* up to 97% (eq. 73). Subsequently they employed these (**140** & **141**, Chart 21) homogeneous soluble polymers in the reduction process in a continuously operated membrane reactor equipped with nano filters.[131]

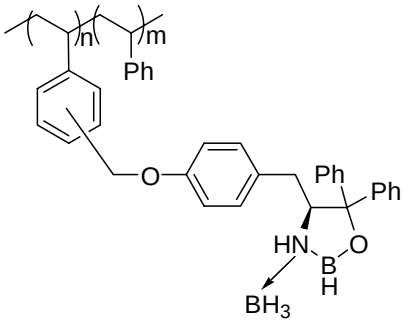
Chart 21



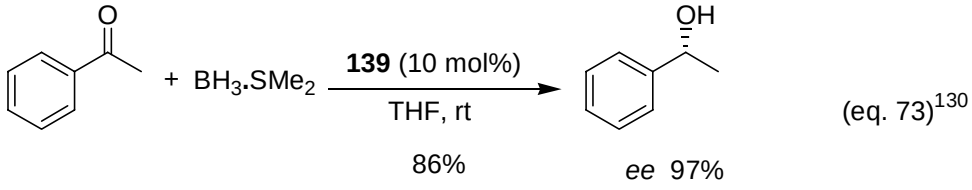
139[130]



140[131]



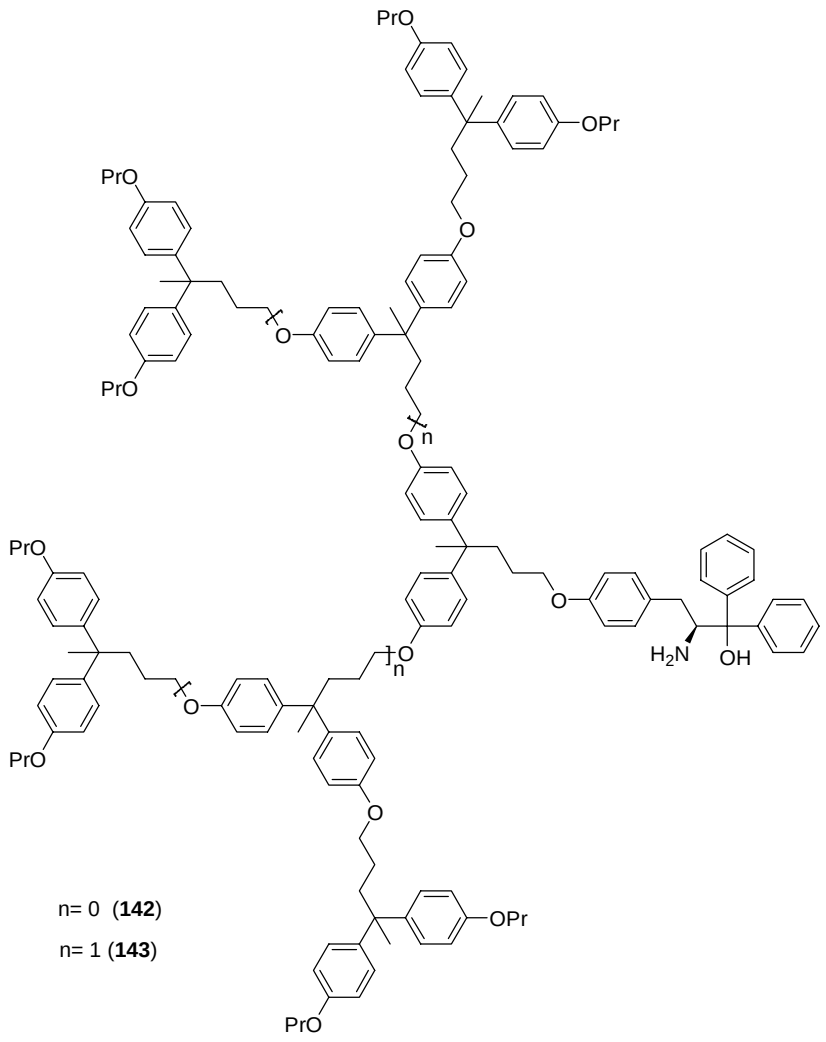
141[131]

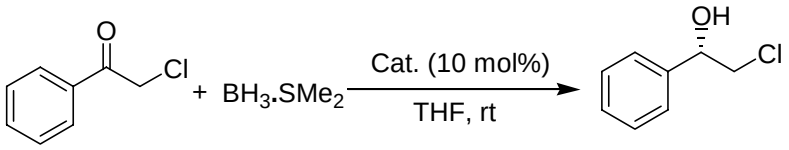


(eq. 73)[130]

Bolm and co-workers reported interesting homogeneous dendritic catalysts **142** & **143** (Chart 22) for the asymmetric borane-mediated reduction of several prochiral ketones (Representative examples is presented in eq. 74).[132]

Chart 22



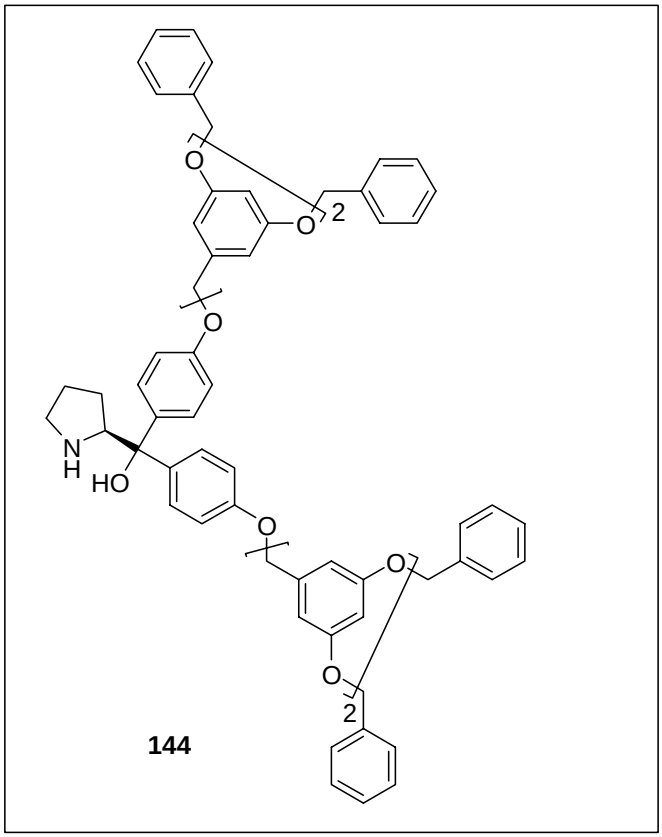


(eq. 74)[132]

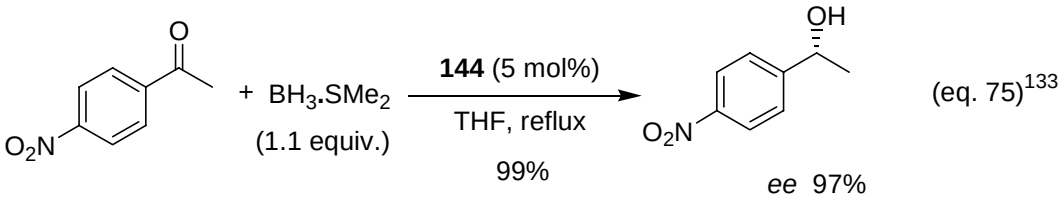
ee 96% with **142**

ee 94% with **143**

More recently Zhao *et al.*[133] used dendritic amino alcohols **144** as a catalyst in the enantioselective borane-mediated reduction of various ketones with high enantiomeric purities (eq. 75). Catalyst **144** can be recycled at least five times with little or no loss of performance.



144



(eq. 75)[133]

OBJECTIVES, RESULTS AND DISCUSSION

Enantiomerically pure secondary alcohols occupy an interesting place in chiral chemistry as some of these molecules are biologically active and also because of their enormous use as synthons for obtaining various biologically active molecules (Chart 23). Due to the importance of homochiral alcohols in organic and medicinal chemistry, development of simple and convenient methods for the synthesis of these molecules represents a challenging and interesting endeavor in chiral chemistry. It is quite clear from the previous section that a large number of catalysts have been prepared and their applications in borane-mediated asymmetric reduction of prochiral ketones have been studied systematically for obtaining a variety of secondary alcohols in high enantiomeric purities.

Our research group has been working for the last few years on the development of chiral catalysts, containing *N-P=O* structural framework, for the borane-mediated asymmetric reduction of prochiral ketones, actually inspired by an elegant original work of Wills[100-105] in this area, with a view to provide an efficient synthetic methodologies for obtaining enantiomerically pure secondary alcohols. This thesis deals with our work towards the design and synthesis of catalysts/catalytic sources, having *N-P=O* structural framework, and study their applications in borane-mediated asymmetric reduction of prochiral ketones with the following objectives.

Objectives

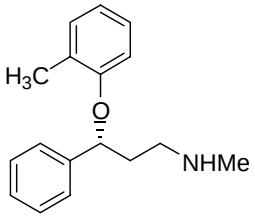
1) To synthesize (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane and (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane from easily accessible (2*S*)-2-anilinomethylpyrrolidine and study their applications as possible catalysts in the borane-mediated asymmetric reduction of representative prochiral ketones.

2) To synthesize 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane and 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane, which contain two *N-P=O* structural units, and study their applications as possible chiral catalysts for asymmetric reduction of prochiral ketones.

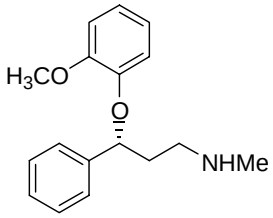
3) To synthesize three diastereomeric pairs of chiral catalysts based on *N-P=O* structural framework, having different stereochemistry at phosphorus *i.e.* (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octanes;(2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes; and (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo-(3.3.0)octanes and examine the influence of phosphorus chirality in the stereochemical course of reduction process.

4) To study the catalytic potential of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one for asymmetric reduction of prochiral ketones.

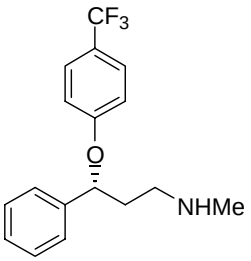
Chart 23



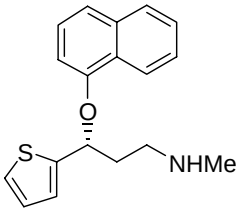
(*R*)-Tomoxetine (**145**)[134]
anti-depressent



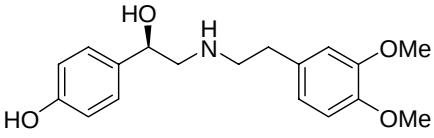
(*R*)-Nisoxetine (**146**)[134]
inhibitor of norepinephrene



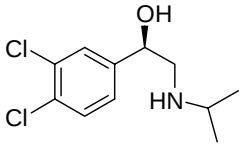
(*R*)-Fluoxetine (**147**)[134]
inhibitor of serotinin uptake



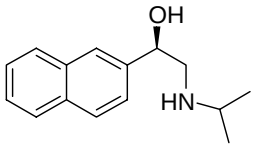
(*R*)-Duloxetine (**148**)[135]
anti-depressant



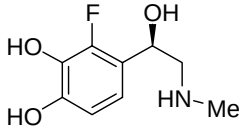
(*R*)-Denopamine (**149**)[136]
drug for congestive heart failure



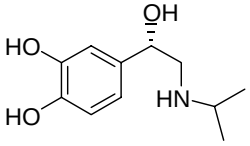
(*R*)-Dichloroisoproterenol (**150**)[137]
drug for asthama, bronchitis, congestive heart failure



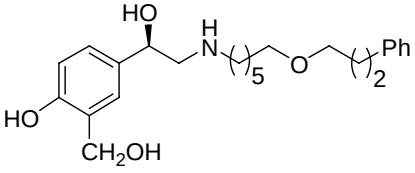
(*R*)-Pronethalol (**151**)[137]
drug for asthama, bronchitis, congestive heart failure



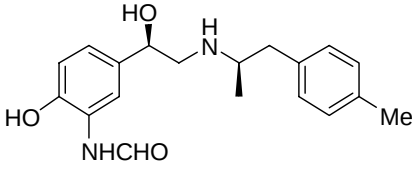
(*R*)-2-Fluoroepinephrine (**152**)[138]
β-andregenic agonist



(*S*)-Isoproterenol (**153**)[139]
drug for asthama



(*R*)-Salmeterol (**154**)[140]
drug for asthama, chronic bronchitis



(*R,R*)-Formeterol (**155**)[141]
drug for asthama, bronchitis

OBJECTIVES, RESULTS AND DISCUSSION

Enantiomerically pure secondary alcohols occupy an interesting place in chiral chemistry as some of these molecules are biologically active and also because of their enormous use as synthons for obtaining various biologically active molecules (Chart 23). Due to the importance of homochiral alcohols in organic and medicinal chemistry, development of simple and convenient methods for the synthesis of these molecules represents a challenging and interesting endeavor in chiral chemistry. It is quite clear from the previous section that a large number of catalysts have been prepared and their applications in borane-mediated asymmetric reduction of prochiral ketones have been studied systematically for obtaining a variety of secondary alcohols in high enantiomeric purities.

Our research group has been working for the last few years on the development of chiral catalysts, containing *N-P=O* structural framework, for the borane-mediated asymmetric reduction of prochiral ketones, actually inspired by an elegant original work of Wills[100-105] in this area, with a view to provide an efficient synthetic methodologies for obtaining enantiomerically pure secondary alcohols. This thesis deals with our work towards the design and synthesis of catalysts/catalytic sources, having *N-P=O* structural framework, and study their applications in borane-mediated asymmetric reduction of prochiral ketones with the following objectives.

Objectives

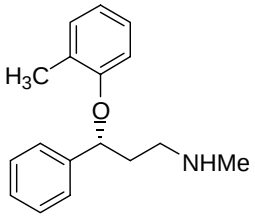
1) To synthesize (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane and (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane from easily accessible (2*S*)-2-anilinomethylpyrrolidine and study their applications as possible catalysts in the borane-mediated asymmetric reduction of representative prochiral ketones.

2) To synthesize 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane and 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane, which contain two *N-P=O* structural units, and study their applications as possible chiral catalysts for asymmetric reduction of prochiral ketones.

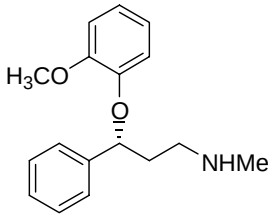
3) To synthesize three diastereomeric pairs of chiral catalysts based on *N-P=O* structural framework, having different stereochemistry at phosphorus *i.e.* (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octanes;(2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes; and (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo-(3.3.0)octanes and examine the influence of phosphorus chirality in the stereochemical course of reduction process.

4) To study the catalytic potential of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one for asymmetric reduction of prochiral ketones.

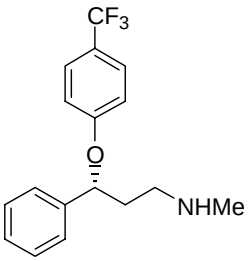
Chart 23



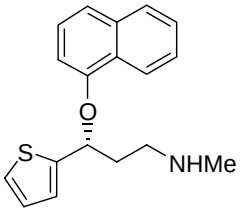
(*R*)-Tomoxetine (**145**)[134]
anti-depressent



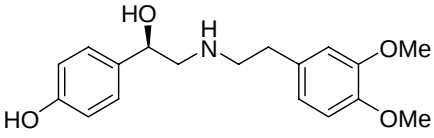
(*R*)-Nisoxetine (**146**)[134]
inhibitor of norepinephrene



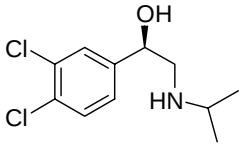
(*R*)-Fluoxetine (**147**)[134]
inhibitor of serotinin uptake



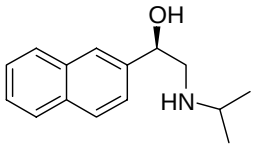
(*R*)-Duloxetine (**148**)[135]
anti-depressant



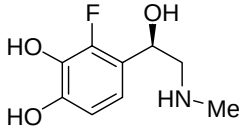
(*R*)-Denopamine (**149**)[136]
drug for congestive heart failure



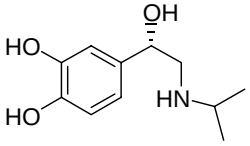
(*R*)-Dichloroisoproterenol (**150**)[137]
drug for asthama, bronchitis, congestive heart failure



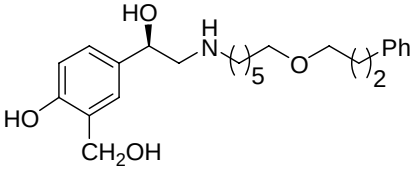
(*R*)-Pronethalol (**151**)[137]
drug for asthama, bronchitis, congestive heart failure



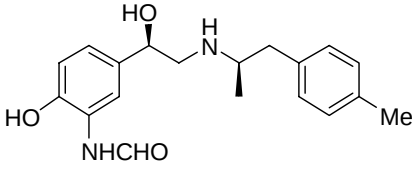
(*R*)-2-Fluoroepinephrine (**152**)[138]
β-andregenic agonist



(*S*)-Isoproterenol (**153**)[139]
drug for asthama



(*R*)-Salmeterol (**154**)[140]
drug for asthama, chronic bronchitis



(*R,R*)-Formeterol (**155**)[141]
drug for asthama, bronchitis

RESULTS AND DISCUSSION

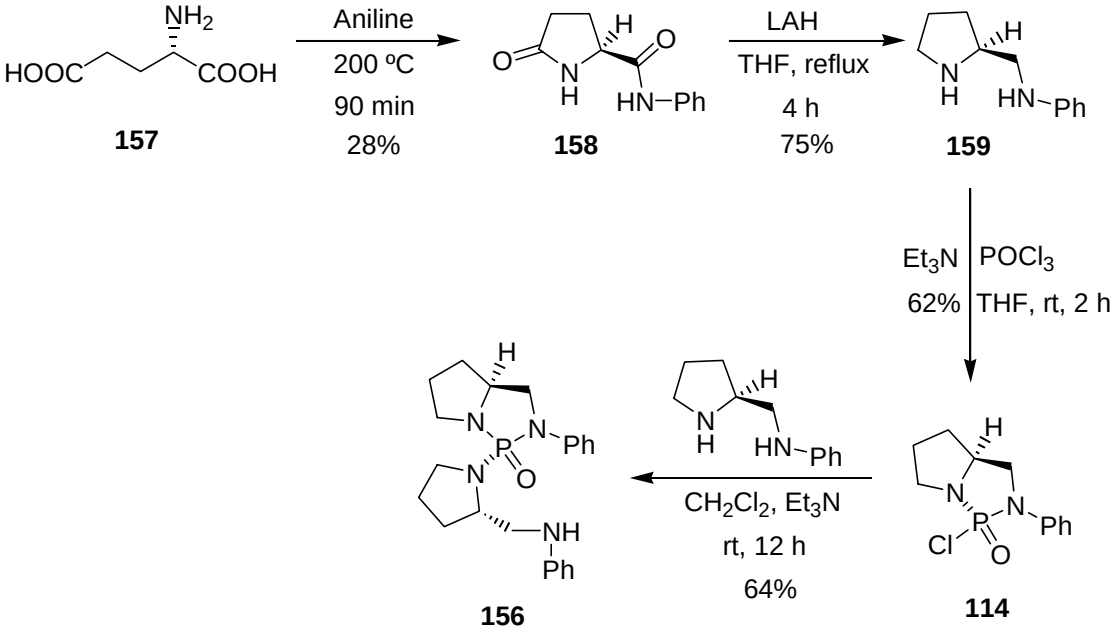
(2*S*,5*S*)-2-[(2*S*)-2-(Anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane as a catalyst

During our efforts in designing catalysts based on the *N-P=O* structural framework for the borane-mediated reduction of prochiral ketones, we have first planned to synthesize (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) and study its potential as a possible catalyst. The required chiral molecule **156** was prepared according to the Scheme 7. Commercially available *L*-glutamic acid (**157**) was converted to (2*S*)-5-oxopyrrolidine-2-carboxanilide (**158**) by treatment with aniline following the literature procedure.[142] This diamide **158** was transformed into (2*S*)-2-anilinomethylpyrrolidine (**159**) *via* treatment with LAH in THF. Treatment of this diamine **159** with $POCl_3$ at room temperature in the presence of triethylamine, following the literature procedure[143] provided (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114**) [this procedure, in fact, provides two diastereomers (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114**) (more polar) and (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114A**)[$] (less polar) in the ratio of 90:10, and these diastereomers are separable using column chromatography] in 62% isolated yield. Structure of this molecule was established by IR,

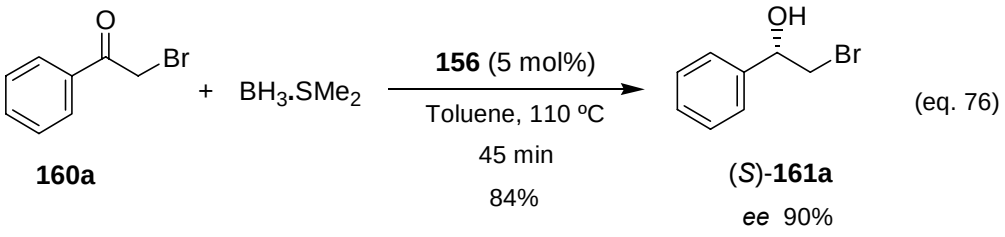
[$] The structure of molecule **114A** and its applications will be discussed on pages 76-79.

^{1}H, ^{13}C & ^{31}P NMR spectral data. Subsequent treatment of **114** with diamine **159** at room temperature in the presence of triethylamine for 12 h provided the desired catalyst, (2*S,*5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane (**156**) in 64% yield after the chromatographic purification (silica gel, 60% ethyl acetate in hexanes). The structure of the molecule was established by ^{1}H (*Spectrum 1*), ^{13}C (*Spectrum 2*), ^{31}P (*Spectrum 3*) NMR spectral data, mass & elemental analysis. We have further confirmed the structure and stereochemistry of this compound by single crystal X-ray data. [The structure refinement of this molecule is presented in Table I and the ORTEP diagram is shown in Figure 2].

Scheme 7



We have then planned to examine the catalytic potential of this molecule **156** for the borane-mediated asymmetric reduction of prochiral ketones. We have first selected phenacyl bromide (**160a**) as a substrate. We have carried out the reduction of phenacyl bromide (**160a**) with catalyst **156** (5 mol%) in the presence of borane-dimethyl sulphide at 110 °C in toluene, which provided the resulting (*S*)-2-bromo-1-phenylethanol [(*S*)-**161a**] in 90% *ee* after chromatographic purification (silica gel, 5% ethyl acetate in hexanes) (eq. 76). Structure of this alcohol was confirmed by spectral data (IR, ^{1}H, & ^{13}C NMR). Enantiomeric purity of this alcohol (*S*)-**161a** was determined by HPLC analysis using chiral column, Chiralcel-ODH with reference to the racemic 2-bromo-1-phenylethanol [(±)-**161a**].



(eq. 76)

With a view to understand the minimum requirement of catalyst for obtaining maximum enantioselectivity, we have carried out the reduction of phenacyl bromide (**160a**) with different catalytic quantities of **156**, ranging from 0.1 mol% to 10 mol% under the same reaction conditions. Enantioselectivities of the resulting (*S*)-2-bromo-1-phenylethanol [(*S*)-**161a**] are given in Table 1. It is clear from the Table 1 that 1 mol% catalyst provides the best results (*Chromatogram 1*).

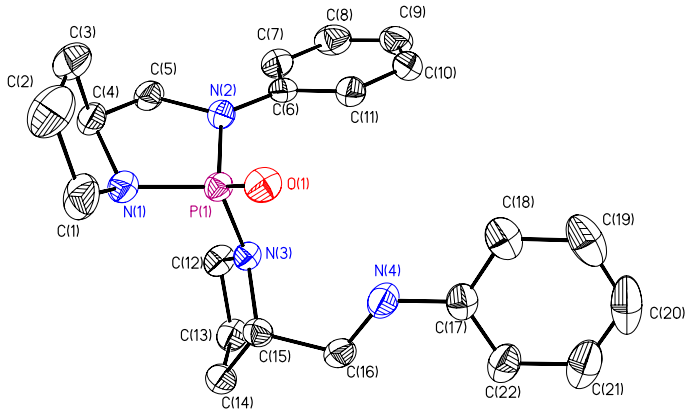


Fig. 2 ORTEP diagram of the compound **156**
(*Hydrogen atoms were omitted for clarity*)

We have therefore performed the reduction of representative prochiral α-haloketones **160b-160g** with 1 mol% catalyst (eq. 77), in order to understand the generality of this methodology. The resulting alcohols (*S*)-**161b-161g** were obtained with enantio-selectivities in the range of 86-90% (Table 2). The structures of the alcohols (*S*)-**161b-161g** were confirmed by IR, ^{1}H, & ^{13}C NMR spectral data. The enantiomeric purities of the alcohols (*S*)-**161b-161d** were determined by HPLC analysis using chiral column, Chiralcel-ODH while the enantiomeric purities of the alcohols (*S*)-**161e** & (*S*)-**161f** with reference to the corresponding racemic alcohols. Our attempts to determine the enantiomeric purity of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [(*S*)-**161g**] using the above mentioned chiral columns were not successful. However, we were able to determine the

Table 1: Asymmetric reduction of phenacyl bromide (160a) with various quantities of the catalyst 156[a]

Entry	Catalyst **156** (mol%)	Yield (%)[b] **161a**	*ee* (%)[c]	Configuration[d]
1	10	87	88	*S*
2	5	84	90	*S*
3	2	84	89	*S*
4	1	79	89	*S*
5	0.5	81	88	*S*
6	0.1	83	54	*S*

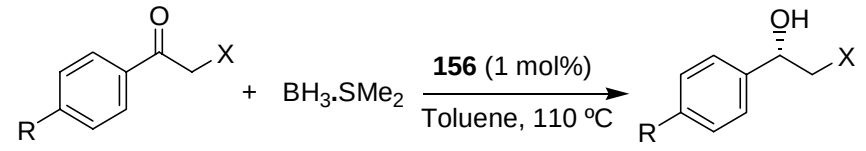
[a] All reactions were carried out on 1 mM scale of phenacyl bromide (**160a**) with one equivalent of BH_3**.**SMe_2 in the presence of **156** in toluene for 45 min at 110 $^{\circ}$C.

[b] Isolated yields of alcohol **161a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[144]

enantiomeric purity of this alcohol (*ee* 89%) by converting into the corresponding acetate, (*S*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-**162g**][Ψ] (eq. 78), as the enantiomers of the acetate are separable in the chiral column, Chiralcel-ODH. With a view to understand the influence of naphthalene ring we have next selected 2-bromoacetylnaphthalene (**160h**) for reduction with the catalyst **156** and the resulting secondary alcohol (*S*)-**161h** was obtained in 89 % *ee* as determined by the HPLC analysis using chiral column, Chiralcel-OJH (eq. 79) (*chromatogram 2*).



160b-160g

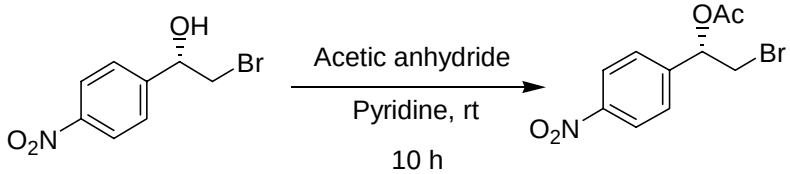
R = H, Me, Br, Cl, NO_2

X = Br, Cl

(*S*)-**161b-161g**

ee 86-90%

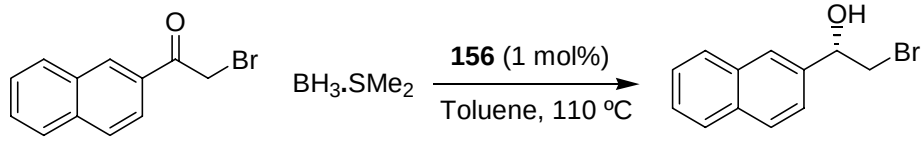
(eq. 77)



(*S*)-**161g**

(*S*)-**162g**

(eq. 78)[144]



160h

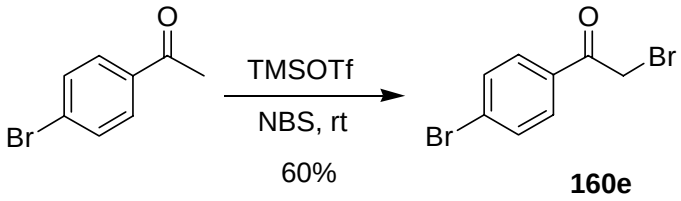
(*S*)-**161h**

ee 89%

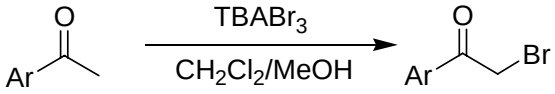
(eq. 79)

[Ψ] For easy understanding and more clarity we have numbered acetate of alcohol (*S*)-**161g** as (*S*)-**162g**

The required *α*-bromo ketones **160e-160h** were prepared *via* the bromination of corresponding ketones according to the reported procedures (eqs. 80-82).[145-147] 4-Methylphenacyl chloride (**160d**) was prepared *via* Friedel-Crafts reaction of toluene with chloroacetyl chloride in the presence of $AlCl_3$ (eq. 83).

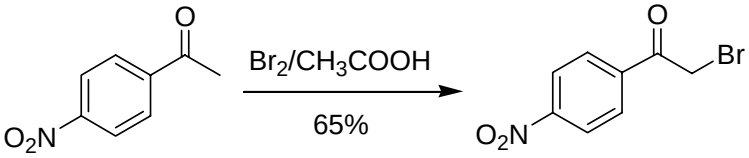


160e (eq. 80)[145]

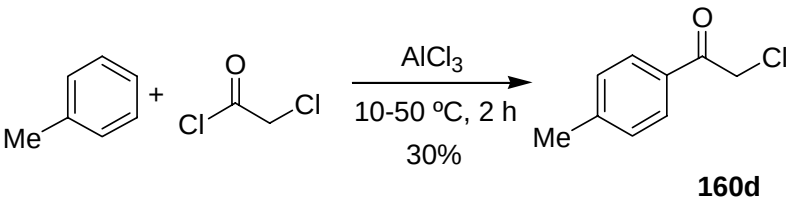


Ar = *p*-ClC_6H_4 (**160f**)

Ar = *β*-naphthyl (**160h**) (eq. 81)[146]



160g (eq. 82)[147]



160d (eq. 83)

Table 2: Asymmetric reduction of *α*-halo ketones 160a-160h with 1 mol% catalyst 156[a]

α-Halo ketone	Product, Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	*Ee* (%)[d]
Phenacyl bromide (**160a**)	**161a**, 79	+39.20 (*c* 1.07, $CHCl_3$)	*S*[144]	89
Phenacyl chloride (**160b**)	**161b**, 82	+44.00 (*c* 1.05, C_6H_{12})	*S*[144]	88
4-Methylphenacyl bromide (**160c**)	**161c**, 85	+39.42 (*c* 1.04, $CHCl_3$)	*S*[113]	90
4-Methylphenacyl chloride (**160d**)	**161d**, 90	+44.14 (*c* 1.01, $CHCl_3$)	*S*[113]	86
4-Bromophenacyl bromide (**160e**)	**161e**, 82	+30.80 (*c* 0.99, $CHCl_3$)	*S*[148]	89[e]
4-Chlorophenacyl bromide (**160f**)	**161f**, 90	+40.20 (*c* 1.00, $CHCl_3$)	*S*[113]	90[e]
4-Nitrophenacyl bromide (**160g**)	**161g**, 88	+31.80 (*c* 0.80, $CHCl_3$)	*S*[114]	89[f]
2-Bromoacetylnaphthalene (**160h**)	**161h**, 84	+27.09 (*c* 0.84, EtOH)	*S*[39]	89[e]

[a] All reactions were carried out on 1 mM scale of *α*-halo ketones **160a-160h** with one equivalent of BH_3**.**SMe_2 in toluene for 45 min at 110 °C.

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

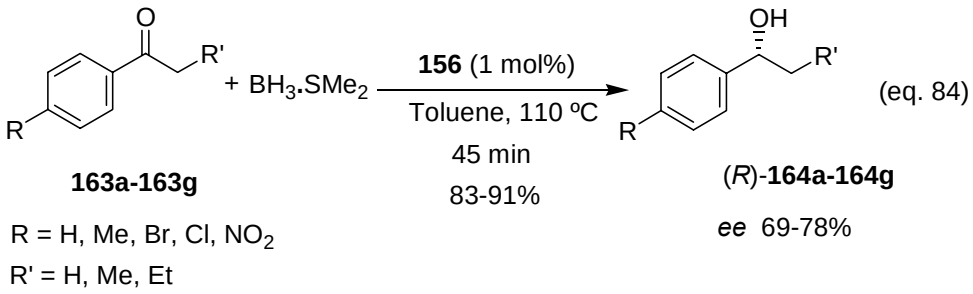
[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.

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

[e] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-OJH.

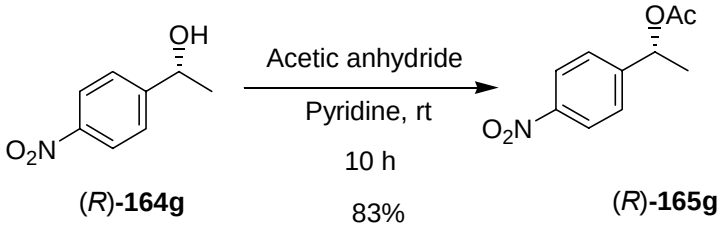
[f] Enantiomeric excess was determined by HPLC analysis of its acetate using chiral column, Chiralcel-ODH.

After achieving good enantioselectivities with aryl α-haloalkyl ketones, we have directed our attention towards the reduction of simple aryl alkyl ketones. We have first selected acetophenone (**163a**) for our study. Reduction of acetophenone (**163a**) was carried out with 1 mol% catalyst **156** to provide the resulting (*R*)-1-phenylethanol [(*R*)-**164a**] in 76% *ee* (eq. 84, Table 3, entry 1). Enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-ODH with reference to the racemic 1-phenylethanol [(±)-**164a**]. With a view to understand the generality of this methodology various aryl alkyl ketones **163b-163g**, having different substitutions on aromatic ring, were subjected to borane-mediated asymmetric reduction under the influence of 1 mol% catalyst **156** (eq. 84). Enantiomeric purities of the resulting secondary alcohols (*R*)-**164b-164g** were in the range of 69-78% (Table 3). The enantiomeric purities of the alcohols (*R*)-**164b** & (*R*)-**164c** were determined by HPLC analysis using chiral column, Chiralcel-ODH while the enantiomeric purities of the alcohols (*R*)-**164d-161f** were determined by HPLC analysis using chiral column, Chiralcel-OJH with reference to their racemic alcohols.



Enantiomeric purity of (*R*)-1-(4-nitrophenyl)ethanol [(*R*)-**164g**] could not be determined directly using these chiral columns. However, we have converted this alcohol into

corresponding acetate (*R*)-1-acetoxy-(4-nitrophenyl)ethane [(*R*)-**165g**][ψ] (eq. 85) following the similar procedure described for (*S*)-**162g** and determined the enantiomeric purity using chiral column, Chiralcel-ODH (as enantiomers of the acetate separated on this column). Enantiomeric purity of the alcohol (*R*)-**165g** was found to be 78% (*Chromatogram 3*).

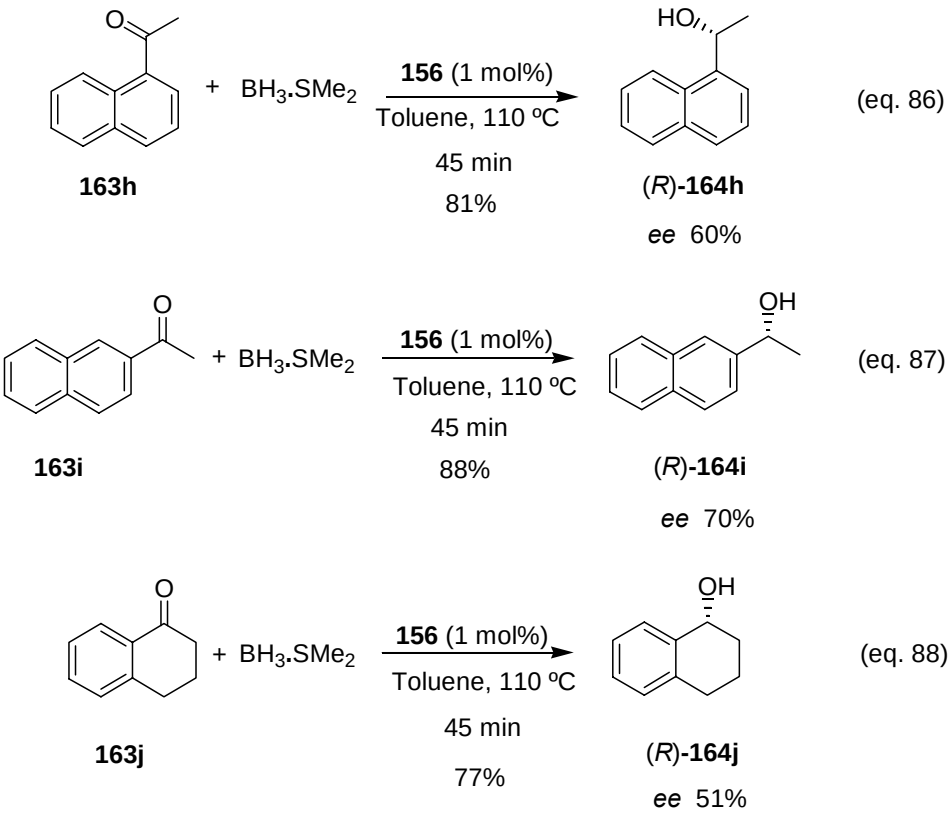


(*R*)-**164g** (*R*)-**165g** (eq. 85)

With a view to understand the influence of naphthalene ring we have selected 1-acetylnaphthalene (**163h**) and 2-acetylnaphthalene (**163i**) as substrates for the asymmetric reductions. We have carried out the reduction of 1-acetylnaphthalene (**163h**) and 2-acetylnaphthalene (**163i**) with 1 mol% catalyst **156** to provide the resulting alcohols (*R*)-**164h** & (*R*)-**164i** in 60% & 70% *ee* respectively (eqs. 86 & 87). The enantiomeric purity of (*R*)-1-(naphth-1-yl)ethanol [(*R*)-**164h**] was determined by HPLC analysis using chiral column, Chiralcel-ODH whereas, *ee* for (*R*)-1-(naphth-2-yl)ethanol [(*R*)-**164i**] was determined by Chiralcel-OJH (*Chromatogram 4*). With a view to further understand the potential of this catalyst we have selected tetralone (**163j**) as a substrate. Borane-mediated reduction of tetralone (**163j**) in the presence of catalyst **156** (1 mol%) provided the

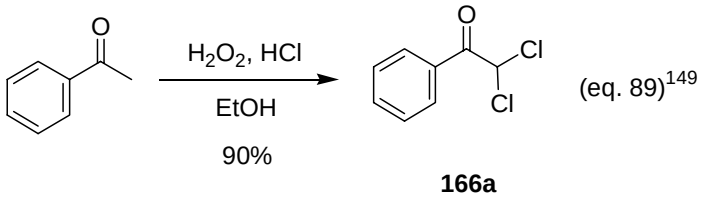
[ψ] For easy understanding and more clarity we have numbered acetate of alcohol (*R*)-**164g** as (*R*)-**165g**

corresponding alcohol (*R*)-**164j** with 51% enantiomeric purity (eq. 88), as determined by HPLC analysis using chiral column, Chiralcel-ODH.



With a view to understand the influence of *α*-chloro groups, we have examined the reduction of 2,2-dichloro-1-phenylethanone (**166a**) and 2,2,2-trichloro-1-phenylethanone (**166b**). Required dichloro ketone **166a** and trichloro ketone **166b** were prepared according to the known procedures (eq. 89 & Scheme 8).[149,150] Borane-mediated reduction of **166a** with 1 mol% catalyst **156** provided the resulting alcohol (*S*)-**167a** in 7% *ee* (eq. 90) as determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to its racemic alcohol (±)-**167a**. Similar reduction of *α*,*α*,*α*-trichloroacetophenone (**166b**) with 1

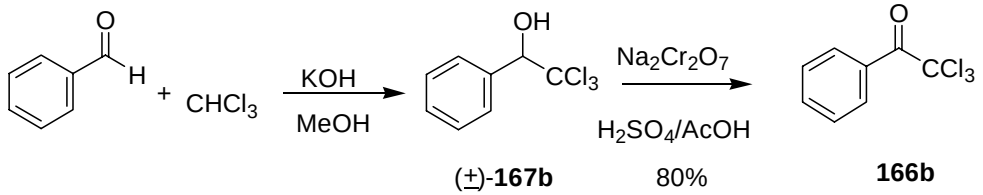
mol% **156** afforded the resulting alcohol (*R*)-**167b** in 39% *ee* (eq. 91). The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to its racemic alcohol (±)-**167b**. Though *ee* is low it is interesting to note that the configuration of the alcohol (*R*)-**167b** is opposite to that normally expected. This may be due to the presence of three chlorines at *α*-position.



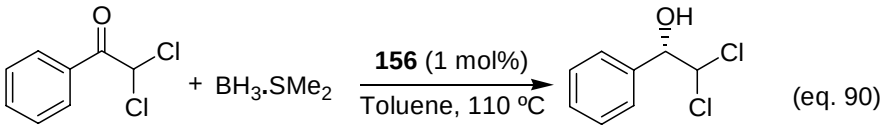
(eq. 89)[149]

166a

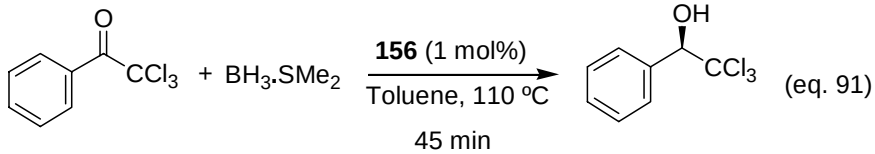
Scheme 8[150]



(±)-**167b** 80% **166b**

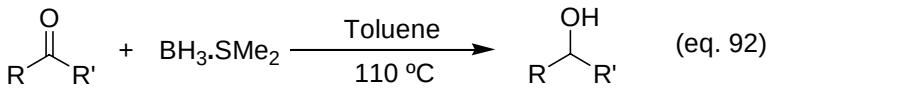


166a (*S*)-**167a** *ee* 7% (eq. 90)



166b (*R*)-**167b** *ee* 39% (eq. 91)

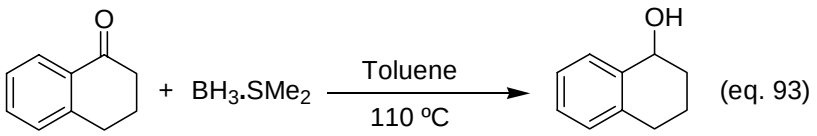
All the required racemic alcohols (±)-**161a-161h**, **164a-164j** & **167a** were obtained by treating corresponding ketones **160a-160h**, **163a-163j** & **166a** with BH_3**.**SMe_2 for 2 h at 110 °C (eqs. 92 & 93), followed by usual purification procedures[ϕ]. The structures of the racemic alcohols (±)-**161a-161h**, **164a-164j**, **167a** & **167b** were confirmed by IR, ^{1}H, & ^{13}C NMR spectral data.



160a-160h, 163a-163i & **166a** (+)-**161a-161h, 164a-164i** & **167a**

R = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, α-naphthyl, β-naphthyl

R' = Me, Et, Pr, CH_2Br, CH_2Cl, $CHCl_2$



163j (±)-**164j**

From this study it is clear that α-haloalkyl aryl ketones offers better selectivity in comparison with simple aryl alkyl ketones. Also our study concludes that α,α-dichloro and α,α,α-trichloroalkyl aryl ketones may not be good substrates in this methodology.

[ϕ] The preparation of racemic alcohol (±)-**167b** is already mentioned in the Scheme 8 page 58

Table 3: Asymmetric reduction of aryl alkyl ketones 163a-163j, 166a & 166b with 1 mol% catalyst 156[a]

Aryl alkyl ketone	Product, Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	*ee* (%)[d]
Acetophenone (**163a**)	**164a**, 83	+33.96 (*c* 0.89, MeOH)	*R*[151]	76
Propiophenone (**163b**)	**164b**, 87	+30.10 (*c* 0.76, $CHCl_3$)	*R*[151]	70
Butyrophenone (**163c**)	**164c**, 84	+34.00 (*c* 0.85, C_6H_6)	*R*[9]	72
4-Methylacetophenone (**163d**)	**164d**, 88	+31.69 (*c* 1.36, MeOH)	*R*[152]	69[e]
4-Bromoacetophenone (**163e**)	**164e**, 91	+31.60 (*c* 0.78, $CHCl_3$)	*R*[152]	78[e]
4-Chloroacetophenone (**163f**)	**164f**, 87	+35.87 (*c* 1.15, Et_2O)	*R*[152]	72[e]
4-Nitroacetophenone (**163g**)	**164g**, 85	+22.50 (*c* 0.82, EtOH)	*R*[153]	78[f]
1-Acetylnaphthalene (**163h**)	**164h**, 81	+50.33 (*c* 1.03, Et_2O)	*R*[154]	60
2-Acetylnaphthalene (**163i**)	**164i**, 88	+26.25 (*c* 0.99, EtOH)	*R*[154]	70[e]
Tetralone (**163j**)	**164j**, 77	-12.00 (*c* 1.05, MeOH)	*R*[151]	51
2,2-Dichloroacetophenone (**166a**)	**167a**, 87	+03.00 (*c* 1.10, CH_2Cl_2)	*S*[155]	07[e]
2,2,2-Trichloroacetophenone (**166b**)	**167b**, 83	-14.04 (*c* 1.22, $CHCl_3$)	*R*[150]	39

[a] All reactions were carried out on 1 mM scale with one equivalent of $BH_3.SMe_2$ in toluene for 45 min at 110 °C.

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

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

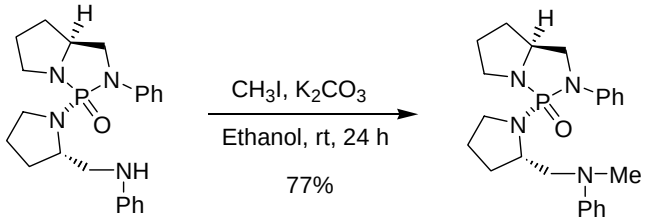
[d] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[e] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-OJH.

[f] Enantiomeric excess was determined by HPLC analysis of its acetate using chiral column, Chiralcel-ODH.

(2*S*,5*S*)-2-[(2*S*)-2-(*N*-Methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane as catalyst

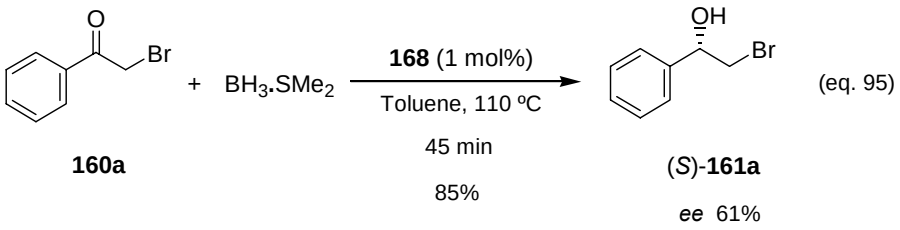
We have next directed our attention towards the application of catalyst (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane (**168**) with a view to understand the influence of hydrogen *Vs* methyl group in directing stereochemical course of the reduction process. Desired molecule **168** was obtained in 77% yield *via* the methylation of "-*NH*-" of molecule **156** using methyl iodide (eq. 94). The structure of the molecule was established by, IR, ^{1}H (*Spectrum 4*), ^{13}C (*Spectrum 5*), ^{31}P (*Spectrum 6*) NMR spectral data, mass and elemental analysis. We have also confirmed the structure and stereochemistry by single crystal X-ray data [the structure refinement of this molecule is presented in Table II and the ORTEP diagram is shown in Figure 3]. We first examined the reduction of phenacyl bromide (**160a**) with 1 mol% of **168** (eq. 95). Resulting secondary alcohol (*S*)-**161a** was obtained in 61% enantiomeric purity (*Chromatogram 5A*).



(eq. 94)

156 **168**

We have also examined the reduction of phenacyl bromide (**160a**) with different quantities of the catalyst **168** with a view to understand the actual quantity of the catalyst necessary to obtain maximum selectivity (Table 4).



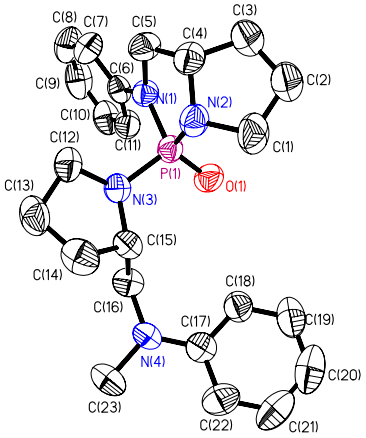
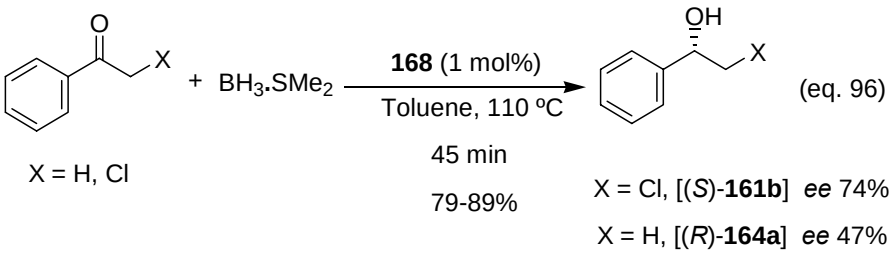


Fig. 3 ORTEP diagram of the compound **168**

(*Hydrogen atoms were omitted and in asymmetric unit of the two molecules present, only one is shown for clarity*)

From the Table 4 it is quite clear that 5 mol% offers the best result thus providing the alcohol in 87% enantiomeric purity (*Chromatogram 5B*). Although 5 mol% provided the best enantioselectivities in the case of catalyst **168**, with a view to have real comparison of the catalyst **168** (containing "-*N*Me" group) with catalyst **156** (having "-*NH*-" group) we have performed asymmetric reduction of representative prochiral ketones like phenacyl chloride (**160b**) & acetophenone (**163a**) with 1 mol% catalyst **168**. Resulting alcohols (*S*)-**161b (***Chromatogram 6*) and (*R*)-**164a** were obtained in 74% and 47% *ee* respectively (eq. 96).



From these results it is possible to conclude that the compound **156** with "-*NH*-" group is a better catalyst than the molecule **168** containing "-*NMe*" group as we need more catalytic quantities of **168** (5 mol%) than that of **156** (1mol%) to obtain similar selectivities.

Table 4: Asymmetric reduction of phenacyl bromide (160a) with various quantities of the catalyst 168[a]

Entry	Catalyst **168** (mol%)	Yield (%)[b] **161a**	*ee* (%)[c]	Configuration[d]
1	10	87	87	*S*
2	5	82	87	*S*
3	1	85	61	*S*
4	0.5	82	37	*S*

[a] All reactions were carried out on 1 mM scale of phenacyl bromide (**160a**) with one equivalent of BH_3**.**SMe_2 in toluene for 45 min at 110 °C.

[b] Isolated yields of the product alcohols after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[144]

Table I: Crystal data and structure refinement for the compound **156**

Empirical formula	$C_{22}H_{29}N_4OP$
Formula weight	396.46
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.748 (2) Å, α = 90˚
	b = 13.985 (3) Å, β = 90˚
	c = 16.881 (4) Å, γ = 90˚
Volume	2065.4 (8) $Å^3$
Z	4
Density calculated	1.275 g/cm^3
Absorption coefficient	0.153 mm^{-1}
F(000)	848
Crystal size	0.48 X 0.28 X 0.24 mm
Theta range for data collection	1.89 to 28.26˚
Index ranges	$-9 \leq h \leq 11$; $-18 \leq k \leq 17$; $-22 \leq l \leq 22$
Reflections collected/unique	12731 / 4857 [R (int) = 0.0272]
Completeness to $\theta = 28.26$	97.3%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	4857 / 0 / 257
Goodness-of-fit on F^2	1.035
Final R indices [I> 2σ (I)]	$R_1 = 0.0489$, $wR_2 = 0.1146$
R indices (all data)	$R_1 = 0.0584$, $wR_2 = 0.1204$
Absolute structure parameter	0.05 (10)
Largest diff. peak and hole	0.298 and -0.201 $eÅ^{-3}$

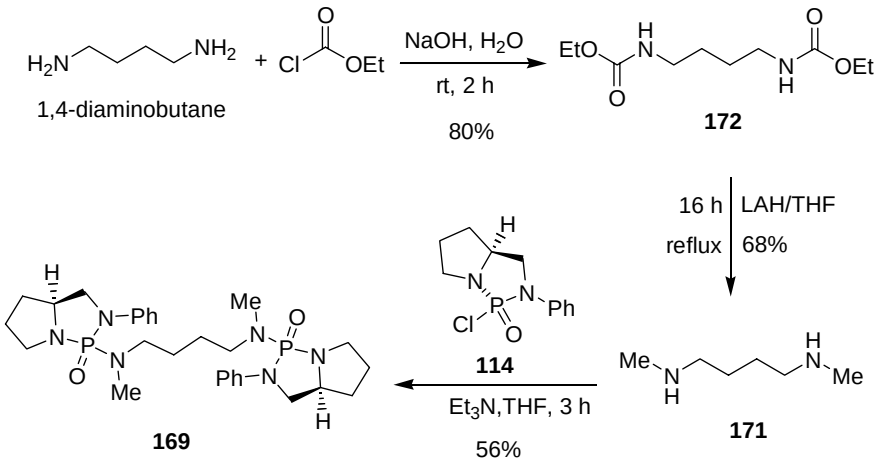
Table II: Crystal data and structure refinement for the compound **168**

Empirical formula	$C_{23}H_{31}N_4OP$
Formula weight	410.49
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 13.3248 (17) Å, α = 90˚
	b = 9.8198 (13) Å, β = 90.768 (2) ˚
	c = 16.855 (2) Å, γ = 90˚
Volume	2205.2 (5) $Å^3$
Z	4
Density calculated	1.236 g/cm^3
Absorption coefficient	0.146 mm^{-1}
F(000)	880
Crystal size	0.44 X 0.14 X 0.12 mm
Theta range for data collection	1.53 to 26.08˚
Index ranges	$-16 \leq h \leq 16$; $-12 \leq k \leq 12$; $-19 \leq l \leq 20$
Reflections collected/unique	13503 / 8469 [R (int) = 0.0253]
Completeness to $\theta = 28.26$	99.0%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	8469 / 1 / 547
Goodness-of-fit on F^2	0.986
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0491$, $wR_2 = 0.1076$
R indices (all data)	$R_1 = 0.0707$, $wR_2 = 0.1194$
Absolute structure parameter	-0.04 (8)
Largest diff. peak and hole	0.192 and -0.197 $eÅ^{-3}$

Catalysts containing two *N-P=O* structural frameworks

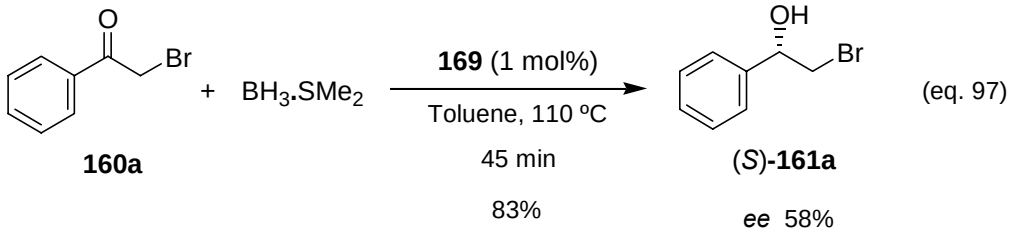
With a view to understand the influence of two *N-P=O structural moieties* in the same catalyst in the reduction process, we have selected catalysts 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) and 1,5-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**) having two *N-P=O* units, for our study. First we have focused on the catalyst **169**. This was prepared *via* the reaction of *N,N′*-dimethyl-1,4-diaminobutane (**171**) with **114** (Scheme 9) in presence of triethylamine at room temperature for 3 h in 56% yield after the chromatographic purification (silica gel, 2% methanol in ethyl acetate). The structure of the molecule[⊗] was established by ^{1}H (*Spectrum 7*), ^{13}C (*Spectrum 8*), ^{31}P (*Spectrum 9*) NMR spectral data, mass and elemental analysis. *N,N′*-Dimethyl-1,4-diaminobutane (**171**) was in turn prepared according to usual synthetic methodology (Scheme 9).

Scheme 9



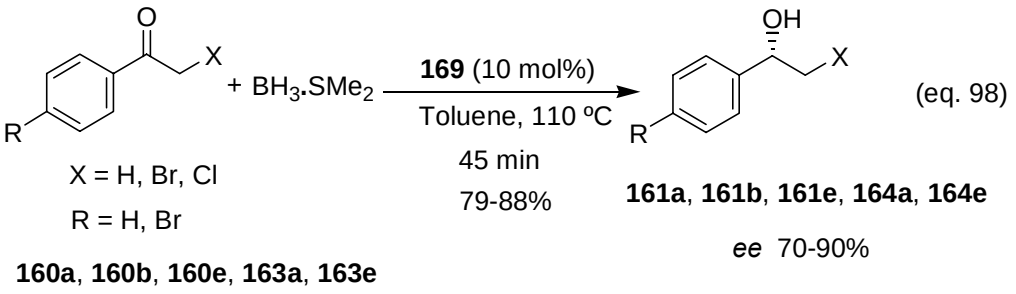
[⊗] Regarding the configuration of phosphorus stereogenic center in **169** & **170**; ^{31}P NMR spectra of these molecules show that they are single diastereomers. Since they are not good solids we could not use crystallographic technique to determine the configuration. However in analogy with molecule **156** (*S*)-configuration may be tentatively assigned to phosphorus chiral center in these molecules **169** & **170**.

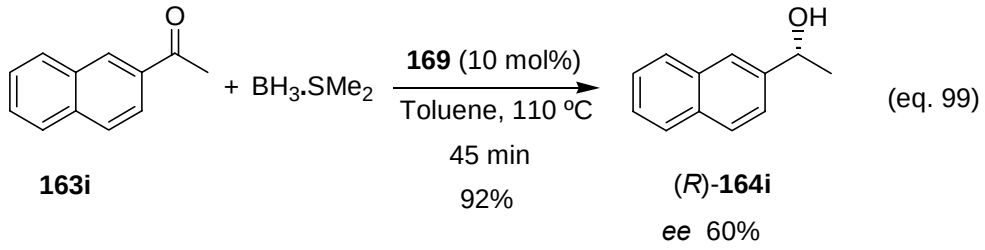
We have first selected phenacyl bromide (**160a**) as a substrate using this catalyst. We have carried out the reduction of this ketone with 1 mol% catalyst **169** in the presence of BH_3**.**SMe_2 at 110 °C (eq. 97). Resulting (*S*)-2-bromo-1-phenylethanol [(*S*)-**161a**] was obtained in 58% enantiomeric purity (eq. 97).



160a (*S*)-**161a** *ee* 58%

In order to understand the actual amount of the catalyst necessary to obtain maximum enantiomeric purity, we have performed the reduction of phenyl bromide (**160a**) in the presence of BH_3**.**SMe_2 at 110 °C using different quantities of the catalyst, 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) and enantiomeric purities are listed in the Table 5. From the Table, it is clear that 10 mol% catalyst offers the best enantioselectivity providing the resulting alcohol in 90% enantiomeric purity. In order to have further understanding the generality of the efficiency of this catalyst, we performed reduction of the representative prochiral ketones **160b**, **160e**, **163a**, **163e** & **163i** employing 10 mol% catalyst **169** (eqs. 98 & 99). The resulting alcohols (*S*)-**161b**, (*S*)-**161e**, (*R*)-**164a**, (*R*)-**164e** and (*R*)-**164i** were obtained in 60–89% enantiomeric purities (Table 6) [see: *Chromatogram 7 & 8* for enantiomeric purity of alcohol (*S*)-**161e** & (*R*)-**164e** respectively].





From these results it is clear that we require 10 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) to obtain similar selectivities as that of (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) where we need only 1 mol% catalyst.

With a view to understand the effect of the length of carbon chain that separates the two *N-P=O* structural frameworks in the asymmetric reduction process, we have selected another catalyst 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethyl-amino]pentane (**170**). Required compound was prepared *via* the reaction of *N,N′*-dimethyl-1,5-diaminopentane (**173**) with molecule **114** in presence of triethylamine at room temperature for 3 h in 49% yield (Scheme 10) after the chromatographic purification (silica gel,

2% methanol in ethyl acetate). The structure of the molecule[⊗] was established by ^{1}H (*Spectrum 10*), ^{13}C (*Spectrum 11*), ^{31}P (*Spectrum 12*) NMR spectral data, mass and elemental analysis. Required *N,N'*-dimethyl-1,5-diaminopentane (**173**) was prepared by the following reaction sequence as mentioned in the Scheme 10.

Table 5: Asymmetric reduction of phenacyl bromide (160a) with varying quantities of catalyst 169[a]

Entry	Catalyst **169** (mol%)	Yield (%)[b] **161a**	*ee* (%)[c]	Configuration[d]
1	20	81	74	*S*
2	10	86	90	*S*
3	5	89	82	*S*
4	1	83	58	*S*

[a] All reactions were carried out on 1 mM scale of phenacyl bromide (**160a**) with one equivalent of $BH_3.SMe_2$ in toluene for 45 min at 110 °C.

[b] Isolated yields of the product alcohols **161a** after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported one.[144]

[⊗] Regarding the configuration of phosphorus stereogenic center in **169** & **170**; ^{31}P NMR spectra of these molecules show that they are single diastereomers. Since they are not good solids we could not use crystallographic technique to determine the configuration. However in analogy with molecule **156** (*S*)-configuration may be tentatively assigned to phosphorus chiral center in these molecules **169** & **170**.

Table 6: Asymmetric reduction of ketones 160a, 160b, 160e, 163a, 163e & 163i with 10 mol% catalyst 169[a]

Ketone	Product, Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	*ee* (%)[d]
Phenacyl bromide (**160a**)	**161a**, 86	+39.59 (*c* 1.17, $CHCl_3$)	*S*[144]	90
Phenacyl chloride (**160b**)	**161b**, 88	+40.00 (*c* 0.91, C_6H_6)	*S*[144]	83
4-Bromophenacyl bromide (**160e)**	**161e**, 84	+30.4 (*c* 0.99, $CHCl_3$)	*S*[148]	89[e]
Acetophenone (**163a**)	**164a**, 79	+31.62 (*c* 0.95, MeOH)	*R*[151]	70
4-Bromoacetophenone (**163e**)	**164e**, 80	+30.40 (*c* 0.95, $CHCl_3$)	*R*[152]	77[e]
2-Acetylnaphthalene (**163i**)	**164i**, 92	+25.01 (*c* 0.94, EtOH)	*R*[154]	60[e]

[a] All reactions were carried out on 1 mM scale with one equivalent of $BH_3.SMe_2$ in toluene for 45 min at 110 °C.

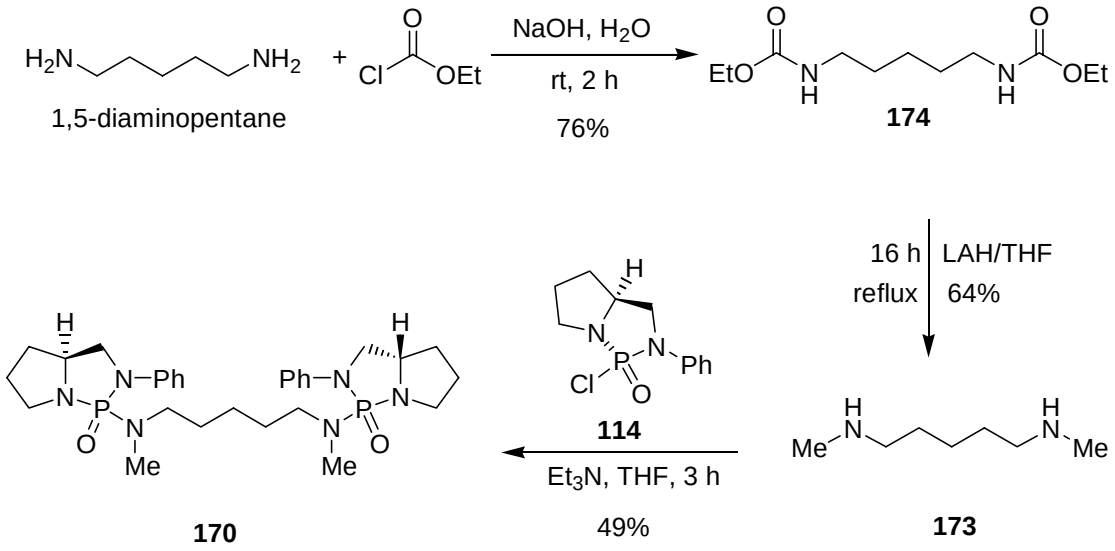
[b] Isolated yields of the product alcohols after chromatographic purification on silica gel column.

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

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

[e] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-OJH.

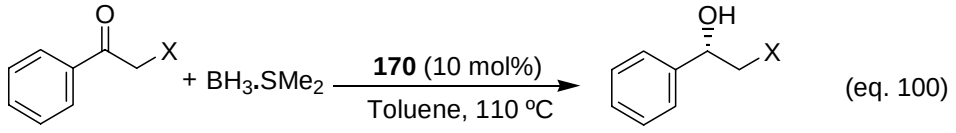
Scheme 10



We have examined the reduction of phenacyl bromide (**160a**) with different quantities of the catalyst and the results are presented in the Table 7, which clearly indicate that 10 mol% catalyst provides the maximum enantiomeric purity thus affording the required alcohol in 89% enantiomeric purity. We have then subjected two more ketones, phenacyl chloride (**160b**) and acetophenone (**163a**) for similar reduction process and the resulting alcohols **161b** (*Chromatogram 9*) and **164a** (*Chromatogram 10*) were obtained with 78% and 74% enantiomeric purities respectively (eq. 100). These results clearly indicate that both catalysts **169** & **170** have similar abilities for directing the reduction process.

From these results it may be concluded that the compound **156** which has only one *N-P=O* structural unit, is a better catalyst than the catalysts **169** and **170** as we need more catalytic

quantities in these cases (10 mol%) than that of **156** (1mol%) to obtain similar selectivities.



160b, **163a**

ee 78% (X = Cl) [(*S*)- **161b**]

ee 74% (X = H) [(*R*)- **164a**]

Table 7: Asymmetric reduction of phenacyl bromide (160a) with varying quantities of catalyst 170[a]

Entry	Catalyst **170** (mol%)	Yield (%)[b] **161a**	*ee* (%)[c]	Configuration[d]
1	20	90	62	*S*
2	10	86	89	*S*
3	5	83	82	*S*
4	1	88	70	*S*

[a] All reactions were carried out on 1 mM scale of phenacyl bromide (**160a**) with one equivalent of $BH_3.SMe_2$ in toluene for 45 min at 110 °C.

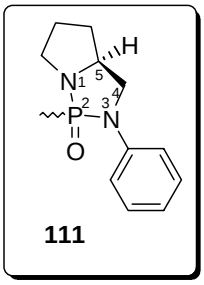
[b] Isolated yields of the product alcohols after chromatographic purification (silica gel, 5% ethyl acetate in hexanes).

[c] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[144]

A study toward understanding the role of a phosphorus stereogenic center in (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane derivatives as catalysts in the borane-mediated asymmetric reduction of prochiral ketones

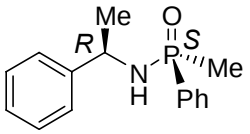
During our studies in our research group it has been established that the real catalytic chiral species, which offers enantioselectivities, is the *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* (**111**) moiety, and it has also been already to some extent established that groups on the phosphorus in the *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* (**111**) moiety has no significant role in directing the stereochemical pathway of the reduction process.[116] Also, our studies on the catalysts **156**, **168-170** (pages 47-72) to some extent support these conclusions. The skeleton *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* (**111**) has two stereogenic centers, one is on the phosphorus at 2-position and, the other center is on the carbon (5-position). However, in all these studies, the influence of phosphorus chiral center in directing the stereochemical pathway of the reduction process has not been studied. Therefore, we thought it would be quite appropriate to understand the influence of phosphorus chirality, if any, in directing the stereoselectivity of the reduction process.



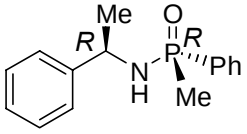
111

We envisaged that understanding the actual role of stereochemistry at the phosphorus center in catalysts, containing chiral *N-P=O* structural framework, in the borane-mediated asymmetric reduction of prochiral ketones would probably (a) throw some light on understanding the mechanism of this reaction as the stereochemistry of the resulting secondary alcohols would provide the stereochemical sense of direction of the reduction process and (b) help us in designing appropriate catalyst(s) which can provide high enantioselectivities. A careful literature survey reveals that there are very few reports in this direction. Wills prepared the catalysts **175** and **175A** (Chart 24) and studied their catalytic potential in the borane-mediated asymmetric reduction of prochiral ketones (eq. 101).[156]

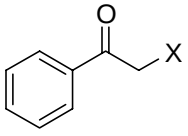
Chart 24



175

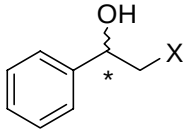


175A



160b, 163a

+ $BH_3.SMe_2$ $\xrightarrow[\text{rt, <1 h}]{\text{Cat. (10 mol\%)}}$

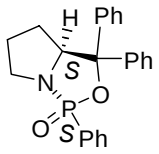


(eq. 101)

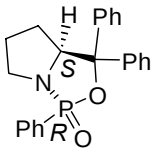
Cat.	X = H	X = Cl
175	50% *ee* (*S*),	42% *ee* (*R*)
175A	5% *ee* (*R*),	4% *ee* (*R*)

Wills and co-workers have also reported that the catalysts **176** and **176A** (Chart 25) provide the same sense of stereoselectivity in the borane-mediated asymmetric reduction of acetophenone, while the catalyst **176** provides better enantioselectivities than **176A** (eq. 102).[105]

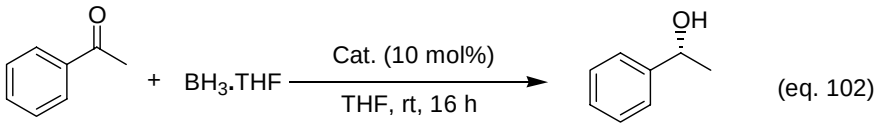
Chart 25



176



176A



163a

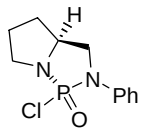
(*R*)-**164a**

95% *ee* (with Cat. **176)**

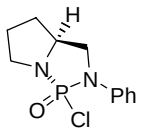
75% *ee* (with Cat. **176A**)

With this background information, we planned to examine the stereochemical sense of direction in the case of three representative diastereomeric pairs of catalysts **114** & **114A**; **177** & **177A** and **178** & **178A** (Chart 26) containing *N-P=O* structural framework, built mainly on skeleton **111**. All these catalysts were prepared from common diamine **159**. The molecule **114** (*already mentioned in pages 47-48*) is already known in the literature[143] and in fact, we have reported[114] the applications of catalyst **114** (5 mol%) in the borane-mediated asymmetric reduction of representative prochiral ketones (Table 8, entry 1).

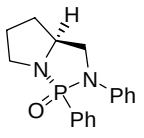
Chart 26



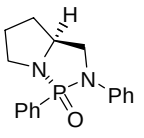
114



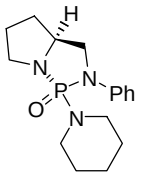
114A



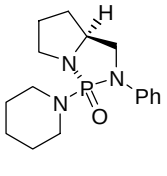
177



177A

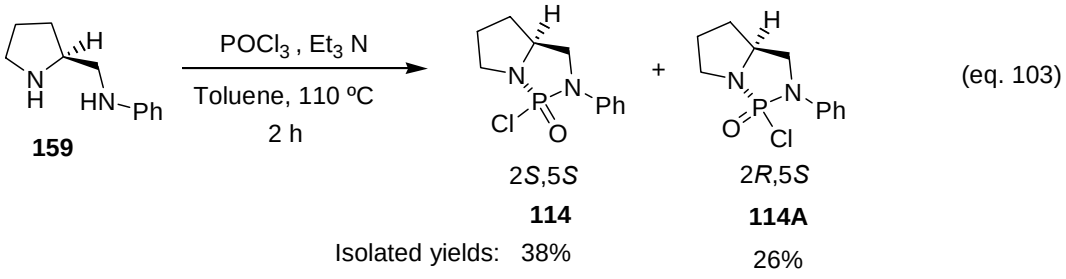


178



178A

With a view to obtain the molecule **114A** in substantial quantities, we treated chiral diamine **159** with $POCl_3$ in toluene at 110 °C and thus obtained both the diastereomers **114**[Ω] & **114A** in 38% and 26% yields respectively, after separation through column chromatography (eq. 103). The structure of molecule **114A** was established by ^{1}H (*Spectrum 13*), ^{13}C (*Spectrum 14*), ^{31}P NMR (*Spectrum 15*) spectral data, mass and elemental analysis. We have further confirmed the structure and stereochemistry by single crystal X-ray data (Figure 4, Table III).



(eq. 103)

[Ω] Spectral data of **114** is already reported[114] and our data is in complete agreement with the reported data.

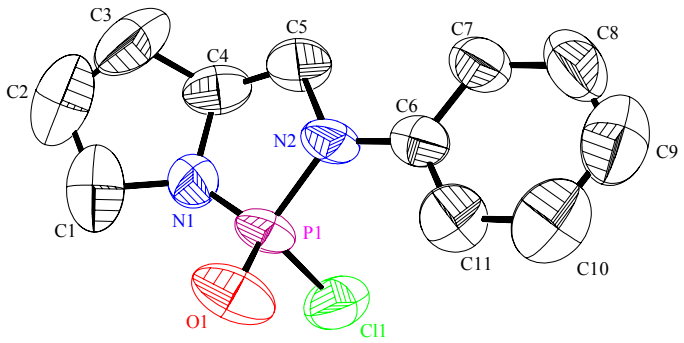
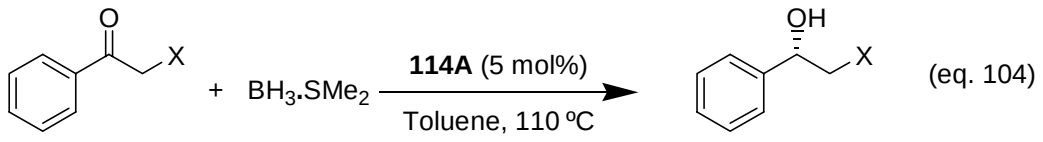


Fig. 4 ORTEP diagram of **114A**

(*Hydrogen atoms were omitted for clarity*)

We have examined the borane-mediated asymmetric reduction of three selected ketones **160a**, **160b**, **163a** using catalyst **114A** (5 mol%) (eq. 104). [We did not make any further attempt to optimize the reaction conditions like the optimum amount of catalyst needed and others conditions normally required to be done in any asymmetric process since we need to perform reduction under similar conditions as in the case of **114** for having a comparison (eq. 105) [114] (Table 8, entry 1)].



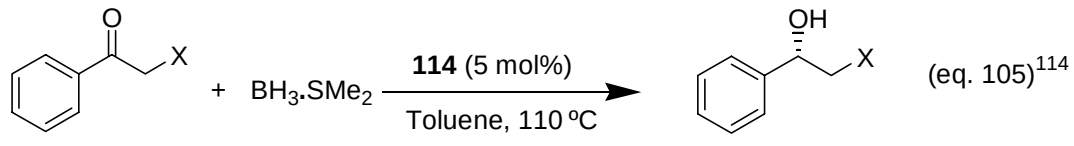
(eq. 104)

160a, **160b** & **163a**

X = Br, Cl, H

161a, **161b** & **164a**

X	*ee*	conf.
Br	84%	(*S*)
Cl	75%	(*S*)
H	66%	(*R*)



160a, **160b** & **163a**

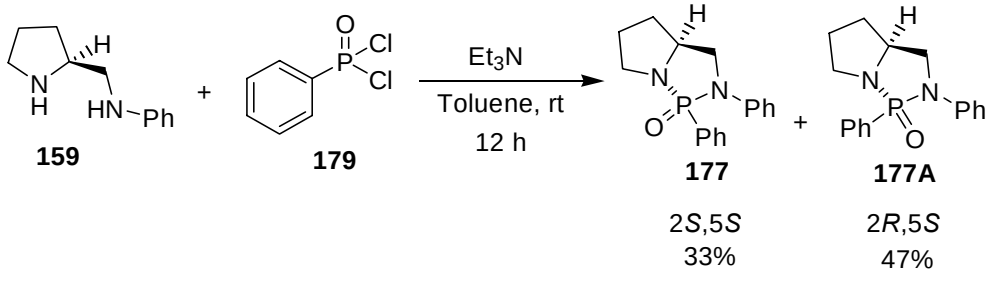
X = Br, Cl, H

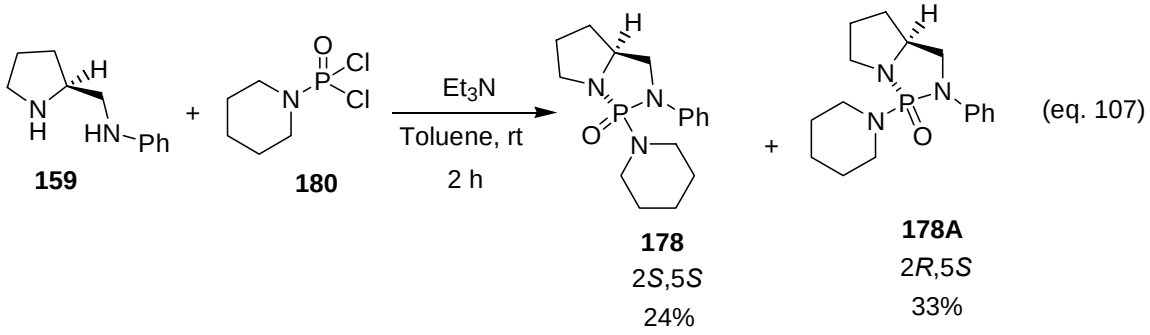
161a, **161b** & **164a**

X	*ee*	conf.
Br	87%	(*S*)
Cl	81%	(*S*)
H	62%	(*R*)

The resulting secondary alcohols **161a**, **161b** & **164a** were obtained in similar enantioselectivities (Table 8, entry 2) as in the case of the catalyst **114**.[114] More interestingly, we noticed that the resulting secondary alcohols (with catalyst **114A**) have the same absolute configuration as in the case of the catalyst **114** (Table 8, entries 1 & 2). We have next prepared the catalysts (diastereomeric pairs) **177** & **177A** and **178** & **178A** in reasonable isolated yields *via* the reaction of diamine **159** with phenylphosphonicdichloride (**179**) and *N*-(dichlorophosphinyl)piperidine (**180**) respectively followed by careful column chromatography (eqs. 106 & 107). The diastereomers **177** & **177A** are reported in the literature.[157] These were prepared *via* the reaction of the diamine **159** with phenylphosphonicdichloride (**179**) in THF at 0 °C for 24 h.[157] The diastereomers **178** & **178A** are also known in the literature and were prepared *via* the reaction of the diamine **159** with *N*-(dichlorophosphinyl)piperidine (**180**) in ethyl acetate at room temperature for 18 h.[158] However, we have prepared these molecules *i.e*. **177** & **177A** and **178** & **178A** *via* the reaction of the diamine **159** with phenylphosphonicdichloride (**179**) and *N*-(dichlorophos-

phinyl)piperidine (**180**) respectively in toluene as solvent at room temperature for 12 & 2 hours respectively, because we have prepared the diastereomers **114** & **114A** *via* the reaction of the diamine **159** with $POCl_3$ in toluene. Since we obtained reasonable amounts of both these diastereomers **177** & **177A** and **178** & **178A**, we did not make any attempt to optimize the yields in both the cases. The structures of the catalyst were established by ^{1}H, ^{13}C, ^{31}P NMR spectral data (*Spectra 16-25*), mass and elemental analysis. The absolute configurations of all the catalysts **177** & **177A** and **178** & **178A** were also established by single crystal X-ray data (Figures 5 & 6, Tables IV-VII).





We have then examined their catalytic potential in the borane-mediated asymmetric reduction of the three representative prochiral ketones **160a**, **160b** & **163a** [see: *Chromatograms 11-13*], (Schemes 11 & 12) (Table 8, entries 3-6). We have also

performed the reduction of phenacyl bromide (**160a**) with a combination of catalysts **178** & **178A** (2.5 mol% + 2.5 mol% = total 5 mol%) with a view to understand the effect (eq. 108), if any, on the stereodirection and we noticed that the resulting alcohol was obtained in almost similar enantioselectivity and with the same configuration (Table 8, entry 7). All these results are presented in the Table 8.

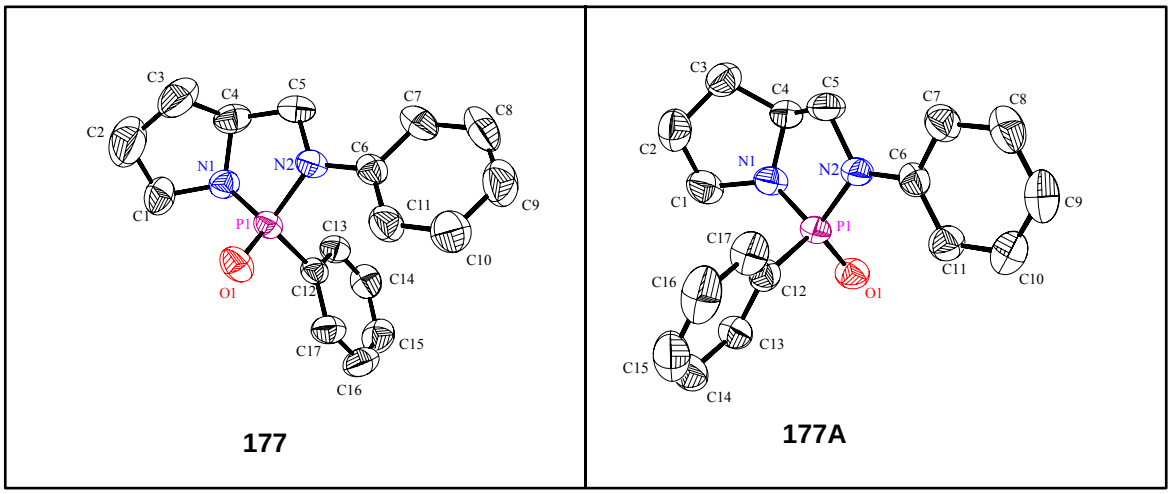
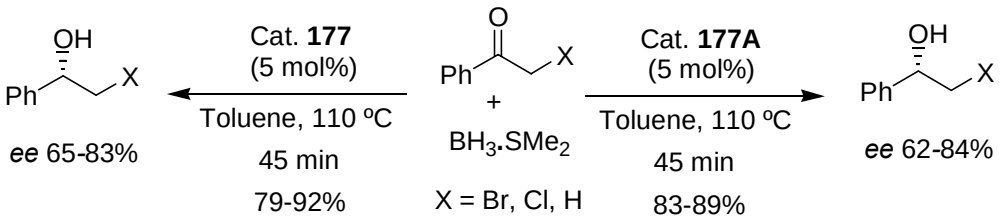


Fig. 5 ORTEP diagrams of **177** & **177A**

(*Hydrogen atoms were omitted for clarity*)

Scheme 11



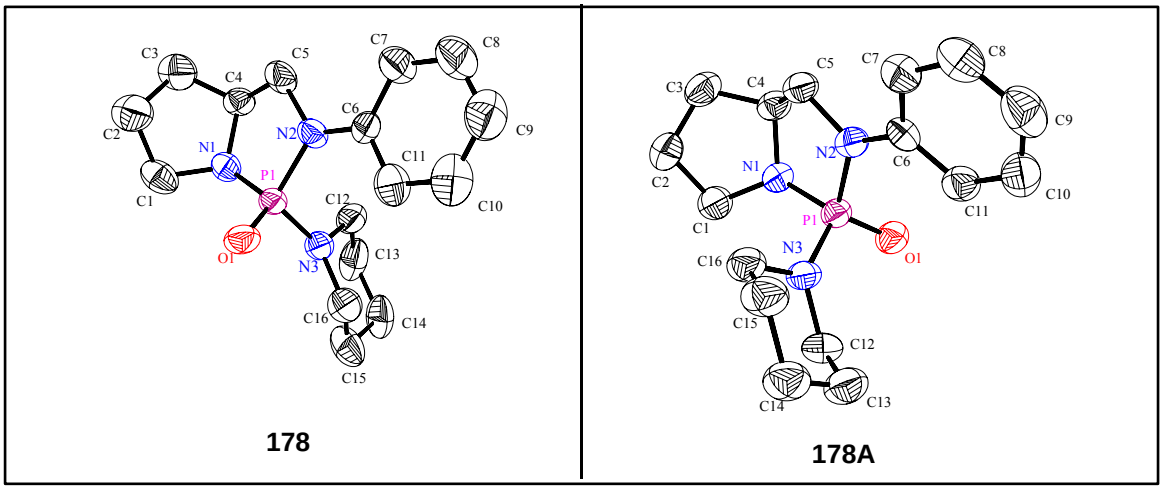
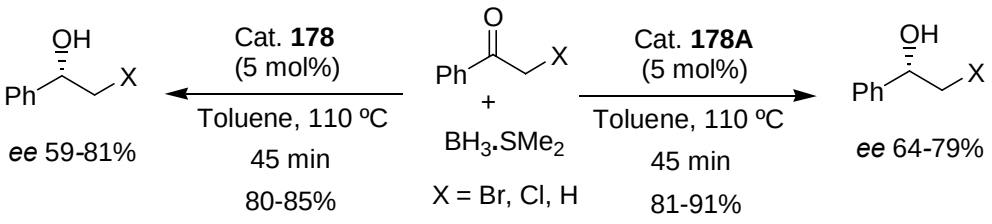


Fig. 6 ORTEP diagrams of **178** & **178A**

(*Hydrogen atoms were omitted for clarity*)

Scheme 12



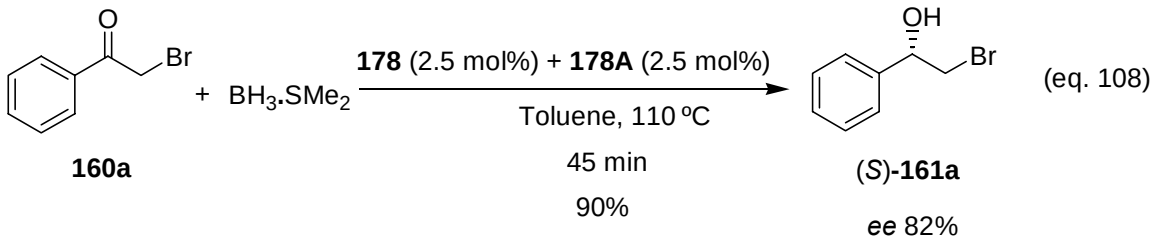


Table 8: Asymmetric reduction of prochiral ketones 160a, 160b, 163a using catalysts 114, 114A, 177, 177A, 178, 178A and 178 + 178A[a]

Entry	Ketone	Catalyst	Conf. at phosphorus	Product	Yield (%)[b]	*ee* (%)[c]	Conf.[d]
1[e]	**160a**	**114**	*S*	**161a**	89	87	*S*
	160b	**114**	*S*	**161b**	93	81	*S*
	163a	**114**	*S*	**164a**	85	62	*R*
2	**160a**	**114A**	*R*	**161a**	91	84	*S*
	160b	**114A**	*R*	**161b**	88	75	*S*
	163a	**114A**	*R*	**164a**	82	66	*R*
3	**160a**	**177**	*S*	**161a**	92	83	*S*
	160b	**177**	*S*	**161b**	90	76	*S*
	163a	**177**	*S*	**164a**	79	65	*R*
4	**160a**	**177A**	*R*	**161a**	89	84	*S*
	160b	**177A**	*R*	**161b**	88	79	*S*
	163a	**177A**	*R*	**164a**	83	62	*R*
5	**160a**	**178**	*S*	**161a**	80	81	*S*
	160b	**178**	*S*	**161b**	85	78	*S*
	163a	**178**	*S*	**164a**	84	59	*R*
6	**160a**	**178A**	*R*	**161a**	91	79	*S*
	160b	**178A**	*R*	**161b**	85	73	*S*
	163a	**178A**	*R*	**164a**	81	64	*R*
7	**160a**	**178+178A (1:1)**	*S+R*	**161a**	90	82	*S*

[a] All reactions were carried out on 1 mM scale of ketone (**160a**, **160b**, **163a**) with 1 mM of $BH_3.SMe_2$ in the presence of catalyst (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] Enantiomeric excess was determined by HPLC analysis using the chiral column, Chiralcel-ODH. [d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules. [e] These results were earlier reported by us.[114]

Fate of the phosphorus stereogenic center: possible explanation

From these results (Table 8) it is quite clear that the diastereomeric pairs of catalysts (**114** & **114A**, **177** & **177A**, and **178** & **178A**) containing *N-P=O* structural framework, built mainly on skeleton **111** provided the resulting secondary alcohols (**161a**, **161b** & **164a**) with the same absolute configuration and also in almost similar enantioselectivities thus, indicating that all the catalysts perform the reduction process with a similar sense of stereoselection. This would mean that both the diastereomeric catalysts (in all the cases) are forming either the same or similar type of species, which essentially direct the reduction process. To understand this aspect we have performed the following experiments using the diastereomeric catalysts **177** & **177A** as a representative case.

1) With a view to understand the effect of temperature on the stability of phosphorus stereogenic center, we heated the catalyst **177** in toluene at 110 $^{\circ}$C for 45 minutes and recorded the ^{31}P NMR spectrum in $CDCl_3$ (after removing toluene), which showed a peak at δ 26.59 (the original catalyst **177** showed peak at δ 26.54). In a similar experiment catalyst **177A** showed a peak at δ 21.16 in the ^{31}P NMR spectrum (the original catalyst **177A** showed peak at δ 21.11). These results clearly indicate that both these catalysts **177** & **177A** are stable at 110 $^{\circ}$C in toluene and that the stereochemistry at the phosphorus stereogenic center remains intact.

2) With a view to examine the stability of these catalysts in the presence of BH_3**.**SMe_2, we first treated the catalyst **177** (5 mol%, 0.030 g, 0.1 mM) in toluene with $BH_3.SMe_2$ (0.152

g, 2 mM) [in the ratio of 1:20 as in the case of reaction conditions] at 110 °C for 45 minutes. The ^{31}P NMR spectrum of this mixture (in toluene containing 20% $CDCl_3$) showed many broad peaks in the region δ 60-140 (the prominent peaks at δ 76.48, 85.29, 133.64 & 138.66).[#] With a view to understand the optical nature of this (actual) catalytic species, we destroyed the BH_3**.**SMe_2 with methanol and the solvent evaporated and recorded the specific rotation of the resulting mixture which had $[\alpha]_D^{25}$: +9.9 (*c* 1.87, MeOH). We also recorded ^{31}P NMR spectrum (of this mixture) in $CDCl_3$, which showed many broad peaks in the region δ 55-110 (the prominent ones at δ 66.76, 84.14, 99.20, 101.50, 106.90 & 107.66).[#] Similar experiments were carried out with **177A**: ^{31}P NMR spectrum (in toluene with 20% $CDCl_3$ after treating with BH_3**.**SMe_2 as in the case of the catalyst **177**) showed many broad peaks in the region δ 60-140 (the prominent ones at δ 78.31, 85.93, 134.48, 135.99 & 138.40)[#] while the ^{31}P NMR spectrum in $CDCl_3$ (after destruction of BH_3**.**SMe_2 using methanol as in the case of the catalyst **177**) showed broad peaks in the region δ 55-110 (the prominent ones at δ 66.36, 84.80, 99.07, 101.96, 107.65 & 108.39)[#] and this mixture (as in the case of **177**) gave $[\alpha]_D^{25}$: +10.75 (*c* 1.60, MeOH). Specific rotations of the original catalysts showed that the catalyst **177**, $[\alpha]_D^{25}$: -31.4 (*c* 1.02, $CHCl_3$), is levorotatory while the catalyst **177A**, $[\alpha]_D^{25}$: +107.6 (*c* 0.98, $CHCl_3$), is dextrorotatory. Although it may not be appropriate (because of the presence of more than one species) the fact that both these diastereomers show the same sense (sign) of optical (dextrorotatory)

[#] Peaks intensities in the case of **177** & **177A** are different in ^{31}P NMR spectra (162 MHz)

rotation may, to some extent, indicate the same configuration of the phosphorus stereogenic center (in the reduction process) in both the cases.

3) With a view to understand the nature of catalyst after the reduction process, we recorded ^{31}P NMR spectrum of the reaction mixture in $CDCl_3$ in the case of the catalyst **177** [after the reduction of phenacyl bromide (**160a**) and destroying the excess BH_3**.**SMe_2 with methanol and removing all the solvents] which showed many broad peaks in the region δ 55-110 [(prominent ones at δ 64.54, 94.43, 97.25 & 102.43) and also showed minor peaks at δ -1.20, -17.05, -58.80]. In a similar experiment ^{31}P NMR spectrum in the case of the catalyst **177A** showed broad peaks in the region δ 55-110 [(prominent peaks at δ 64.85, 94.27, 97.47 & 102.63) and also showed minor peaks at δ -1.24, -58.90].

Although it is difficult to ascertain the actual nature of the catalytic species from these studies, it is quite clear that catalysts are not stable and undergo changes during reduction process. On the basis of ^{31}P NMR spectra and specific rotation studies it may, to some extent, be possible to say that both the catalysts (diastereomeric pairs) may be converting into similar species although we do not have any concrete evidence. It may be possible to speculate that, both the catalysts may be undergoing some changes in the presence of BH_3**.**SMe_2 due to scrambling of the stereochemistry of phosphorus center as shown in the Scheme 13. In conclusion we have demonstrated that the phosphorus stereochemistry, in all these catalysts, containing *N-P=O* structural framework, built mainly on skeleton **111** has no significant role in directing stereochemical pathway of the reduction process. These

results also support, to some extent, our earlier studies that the different groups on the phosphorus, in the catalysts built on the skeleton **111**, have little or no significant influence on the enantioselectivities.[116]

Scheme 13: Possible pathway for scrambling of phosphorus stereogenic center

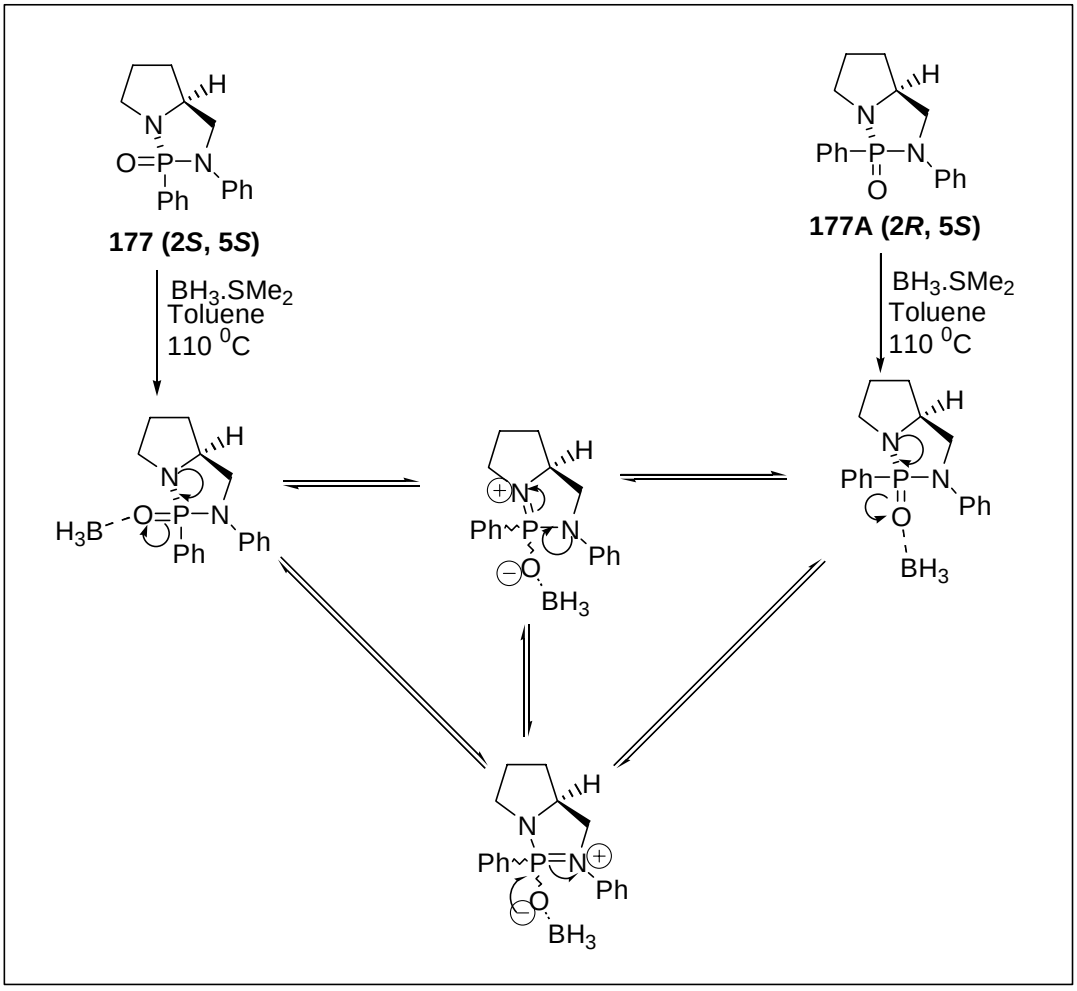


Table III: Crystal data collection and structure refinement for the compound **114A**

Empirical formula	$C_{11}H_{14}N_2OPCl$
Formula weight	256.66
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.7889 (19) Å, α = 90˚
	b = 12.646 (4) Å, β = 90˚
	c = 14.253 (4) Å, γ = 90˚
Volume	1223.6(6) $Å^3$
Z	4
Density calculated	1.393 g/cm^3
Absorption coefficient	0.423 mm^{-1}
F(000)	536
Crystal size	0.52 x 0.22 x 0.20 mm
Theta range for data collection	2.15 to 28.37˚
Index ranges	$-8 \leq h \leq 8$; $-16 \leq k \leq 16$; $-19 \leq l \leq 18$
Reflections collected/unique	13448 / 2896 [R(int) = 0.0737]
Completeness to $\theta = 28.37$	96.9%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	2896 / 0 / 149
Goodness-of-fit on F^2	1.058
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0827$, $wR_2 = 0.1832$
R indices (all data)	$R_1 = 0.1662$, $wR_2 = 0.2306$
Absolute structure parameter	0.1(2)
Largest diff. peak and hole	0.598 and -0.292 $eÅ^{-3}$

Table IV: Crystal data collection and structure refinement for the compound **177**

Empirical formula	$C_{17}H_{19}N_2OP$
Formula weight	298.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Hexagonal
Space group	*P*65
Unit cell dimensions	a = 9.0023 (11) Å, α = 90 (2)˚
	b = 9.0023 (13) Å, β = 90 (18)˚
	c = 33.331 (13) Å, γ = 120 (10)˚
Volume	2338.6 (10) $Å^3$
Z	6
Density calculated	1.271 g/cm^3
Absorption coefficient	0.177 mm^{-1}
F(000)	948
Crystal size	0.60 x 0.52 x 0.52 mm
Theta range for data collection	2.61 to 27.46 ˚
Index ranges	$-11 \leq h \leq -1$ $-9 \leq k \leq 10$; $-43 \leq l \leq 0$
Reflections collected/unique	3618 / 1809 [R(int) = 0.0186]
Completeness to $\theta = 28.27$	99.6%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	1809 / 1 / 191
Goodness-of-fit on F^2	1.058
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0368$, $wR_2 = 0.0870$
R indices (all data)	$R_1 = 0.0464$, $wR_2 = 0.0899$
Absolute structure parameter	0.13(12)
Largest diff. peak and hole	0.266 and -0.164 $eÅ^{-3}$

Table V: Crystal data collection and structure refinement for the compound **177A**

Empirical formula	$C_{17}H_{19}N_2OP$
Formula weight	298.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 16.4550 (9) Å, α = 90˚
	b = 8.5013 (5) Å, β = 90˚
	c = 10.7642 (6) Å, γ = 90˚
Volume	1505.79 (15) $Å^3$
Z	4
Density calculated	1.316 g/cm^3
Absorption coefficient	0.183 mm^{-1}
F(000)	632
Crystal size	0.32 x 0.24 x 0.21 mm
Theta range for data collection	2.26 to 28.26˚
Index ranges	$-18 \leq h \leq 21$; $-11 \leq k \leq 11$; $-12 \leq l \leq 13$
Reflections collected/unique	9570 / 3474 [R (int) = 0.0157]
Completeness to $\theta = 28.26$	95.2 %
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	3474 / 0 / 191
Goodness-of-fit on F^2	1.053
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0356$, $wR_2 = 0.0914$
R indices (all data)	$R_1 = 0.0337$, $wR_2 = 0.0893$
Absolute structure parameter	0.09(8)
Largest diff. peak and hole	0.219 and -0.184 $eÅ^{-3}$

Table VI: Crystal data collection and structure refinement for the compound **178**

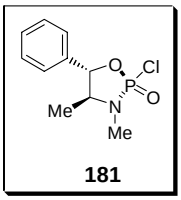
Empirical formula	$C_{16}H_{24}N_3OP$
Formula weight	305.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.6671 (3) Å, α = 90°
	b = 13.4035 (7) Å, β = 90°
	c = 18.0477 (9) Å, γ = 90°
Volume	1612.79(14) $Å^3$
Z	4
Density calculated	1.258 g/cm^3
Absorption coefficient	0.174 mm^{-1}
F(000)	656
Crystal size	0.45 x 0.32 x 0.30 mm
Theta range for data collection	1.89 to 28.21°
Index ranges	$-8 \leq h \leq 8$; $-17 \leq k \leq 17$; $-23 \leq l \leq 23$
Reflections collected/unique	19015 / 3793 [R(int) = 0.0231]
Completeness to $\theta = 28.21$	97.9%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	3793 / 0 / 193
Goodness-of-fit on F^2	1.046
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0446$, $wR_2 = 0.1194$
R indices (all data)	$R_1 = 0.0467$, $wR_2 = 0.1219$
Absolute structure parameter	0.03(10)
Largest diff. peak and hole	0.456 and -0.328 $eÅ^{-3}$

Table VII: Crystal data collection and structure refinement for the compound **178A**

Empirical formula	$C_{16}H_{24}N_3OP$
Formula weight	305.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.9004 (7) Å, α = 90˚
	b = 9.8833 (8) Å, β = 90˚
	c = 17.7994 (15) Å, γ = 90˚
Volume	1565.7(2) Å ^{3}
Z	4
Density calculated	1.295 g/cm^3
Absorption coefficient	0.179 mm^{-1}
F(000)	656
Crystal size	0.27 x 0.24 x 0.13 mm
Theta range for data collection	2.29 to 28.27˚
Index ranges	$-11 \leq h \leq 11$ $-12 \leq k \leq 13$; $-23 \leq l \leq 14$
Reflections collected/unique	10026 / 3692 [R(int) = 0.0351]
Completeness to $\theta = 28.27$	98.3%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	3692 / 0 / 193
Goodness-of-fit on F^2	1.037
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0503$, $wR_2 = 0.1030$
R indices (all data)	$R_1 = 0.0701$, $wR_2 = 0.1110$
Absolute structure parameter	0.00(11)
Largest diff. peak and hole	0.250 and -0.268 eÅ^{-3}

(2*R*,4*S*,5*S*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one as a catalyst

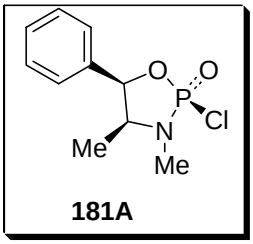
In the earlier sections we have presented our work on the applications of *"-N-(P=O)-N-"* moiety built on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenyl-bicyclo(3.3.0)octane* (**111**) moiety as chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones. Our research group also earlier studied the application of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114**) having *"-N-(P=O,Cl)-N-"* moiety mainly built on **111** and noticed that this molecule can be used as air stable, recoverable and reusable catalytic source and for the borane-mediated asymmetric reduction of prochiral ketones.[114] These results prompted us to examine the application of *"-N-(P=O,Cl)-O-"* moiety as possible recoverable catalyst for asymmetric reduction of prochiral ketones. In this direction we planned to examine the possible application of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as catalyst in the reduction of prochiral ketones.



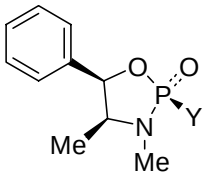
181

Careful literature survey revealed that this compound is reported in the literature and its applications as chiral auxiliary in the synthesis of optically pure olefinic and aliphatic ketone cyanohydrins are also reported.[159] However, the application of this molecule as a

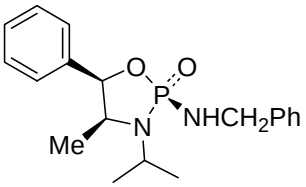
Chart 27



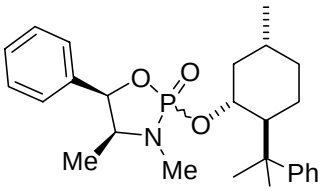
181A



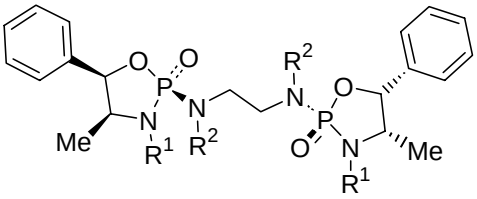
Y = $NHCH_2Ph$, **182a**
$NHNH_2$, **182b**
$N(CH_2)_5$, **182c**
OBu^t, **182d**



183



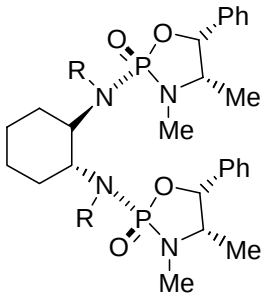
184



R^1 = Me, R^2 = H **185a**

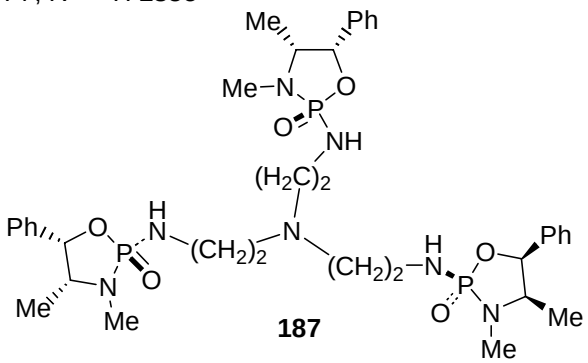
R^1 = Me, R^2 = Me **185b**

R^1 = Pr^i, R^2 = H **185c**



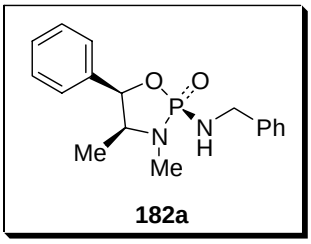
R = H, **186a**

R = Me, **186b**

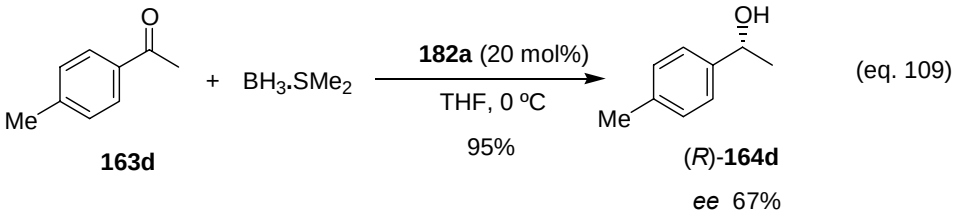


187

catalyst for the asymmetric reduction of prochiral ketones was not reported. It is worth mentioning here that similar molecule **181A** is also known and its various derivatives (**182a-d**, **183**, **184**, **185a-c**, **186a**, **b** & **187**, Chart 27)[160] have been used as catalyst for the borane-mediated asymmetric reduction of prochiral ketones and the best results up to *ee* 67% was obtained in the case of 4-methylacetophenone (**163d**) with **182a** in eq. 109.



182a

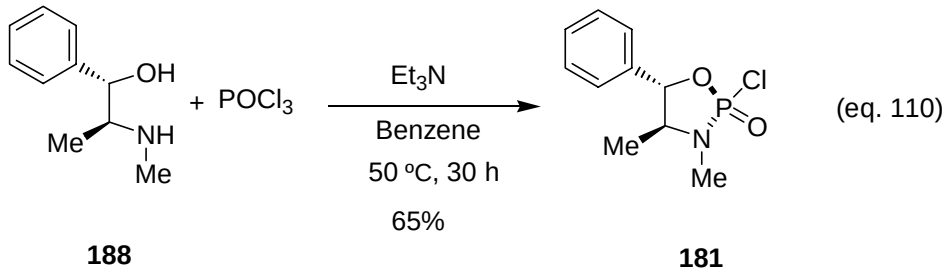


163d (*R*)-**164d** *ee* 67% (eq. 109)

This required catalyst **181**[9] was prepared *via* the reaction of commercially available (+)-(*S,S*)-pseudoephedrine (**188**) with $POCl_3$ in the presence of triethylamine following the reported procedure[159] (eq. 110). The structure of the molecule **181** was established by ^{1}H (*Spectrum 26*), ^{13}C (*Spectrum 27*), ^{31}P (*Spectrum 28*), NMR spectral data, mass and elemental analysis. The spectral data is in agreement with reported data.[159] We have examined the reduction of acetophenone (**163a**) using 10 mol% of the catalyst (**181**) which gave the resulting alcohol in 56% enantiomeric purity (*Chromatogram 14*) (eq. 111). With

[9] The diastereomeric ratio is >99% after chromatographic purification.

a view to understand the minimum quantity of the catalyst required for obtaining high enantioselectivity, we have carried out the reductions with various quantities of this catalyst **181** (Table 9).



188 **181** (eq. 110)

Table 9: Asymmetric reduction of acetophenone (163a) with varying quantities of the catalyst 181[a]

Entry	Catalyst **181** (mol%)	*ee* (%)[b]	Yield (%)[c]	Configuration.[d]
1	30	37	86	*R*
2	20	39	79	*R*
3	10	56	88	*R*
4	5	38	83	*R*

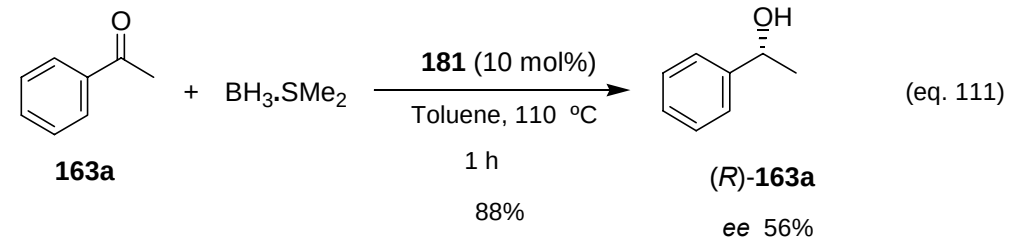
[a] All reactions were carried out on 1 mM scale of acetophenone (**163a**) with one equivalent of BH_3**.**SMe_2 in the presence of **181** in toluene for 60 min at 110 °C.

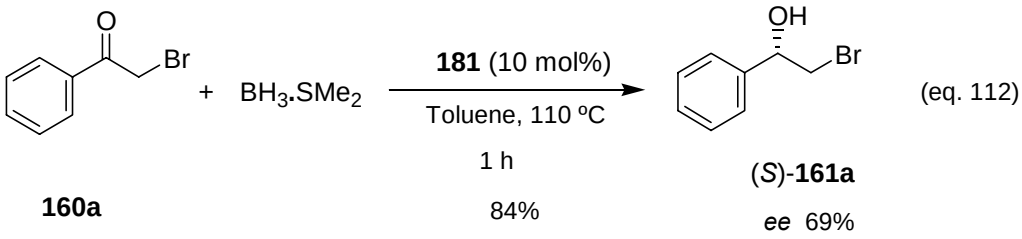
[b] Enantiomeric excess was determined by HPLC analysis using chiral column, Chiralcel-ODH.

[c] Isolated yields of the product alcohols after chromatographic purification.

[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[151]

From the Table 9 it is clear that 10 mol% catalyst provides the best results. We have next carried the reduction of the phenacyl bromide (**160a**) with 10 mol% catalyst and the resulting alcohol was obtained with 69% enantiomeric purity (eq. 112).





We have next subjected various prochiral ketones **160b-160g** to the borane-mediated asymmetric reduction in the presence of catalyst **181** (10 mol%) and the results are tabulated in the (see: *Chromatogram* 15 for enantiomeric purity of (*S*)-**161g**) Table 10. From this table it is clear that the catalyst **181** with "-*N*-*(P=O,Cl)*-*O*-" structural framework offers inferior selectivities in comparison with that of the catalyst **114**[114] with "-*N*-*(P=O,Cl)*-*N*-" structural framework (Table 8). Since, the enantioselectivities are inferior we did not make any attempt to understand the structure of the actual catalytic species in this case.

Table 10: Asymmetric reduction of prochiral ketones 160a-160g & 163a with 10 mol% catalyst 181[a]

α-Halo ketone	Product, Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	*ee* (%)[d]
Phenacyl bromide (**160a**)	**161a**, 84	+28.20 (*c* 1.10, $CHCl_3$)	*S*[144]	69
Phenacyl chloride (**160b**)	**161b**, 92	+33.60 (*c* 1.15, C_6H_{12})	*S*[144]	66
4-Methylphenacyl bromide (**160c**)	**161c**, 90	+29.81 (*c* 1.33, $CHCl_3$)	*S*[113]	68
4-Methylphenacyl chloride (**160d**)	**161d**, 91	+32.00 (*c* 1.4, $CHCl_3$)	*S*[113]	66
4-Bromophenacyl bromide (**160e**)	**161e**, 87	+25.08 (*c* 1.10, $CHCl_3$)	*S*[148]	72[e]
4-Chlorophenacyl bromide (**160f**)	**161f**, 89	+26.50 (*c* 1.20, $CHCl_3$)	*S*[113]	67[e]
4-Nitrophenacyl bromide (**160g**)	**161g**, 80	+24.01 (*c* 1.02, $CHCl_3$)	*S*[114]	72[f]
Acetophenone (**163a**)	**164a**, 83	+25.12 (*c* 1.28, MeOH)	*R*[151]	56

[a] All reactions were carried out on 1 mM scale of prochiral ketones with one equivalent of BH_3**.**SMe_2 in toluene for 60 min at 110 °C.

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

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

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

[e] Enantiomeric excess was determined by determined by HPLC analysis using chiral column, Chiralcel-OJH.

[f] Enantiomeric excess was determined by determined by HPLC analysis of its acetate using chiral column, Chiralcel-ODH.

CONCLUSIONS

We have made considerable progress in achieving the four objectives mentioned in the beginning of this chapter. We have designed and synthesized representative chiral catalysts *i.e.* (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenyl-bicyclo(3.3.0)octane (**156**), (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**), 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) and 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**) and examined their potential as chiral catalysts in the borane-mediated asymmetric reduction of prochiral ketones to provide the resulting secondary alcohols in high enantiomeric purities. We have, also from these studies, established that chiral catalyst **156** having one *N-P=O* structural framework offers, better results than the other two catalysts **169** & **170** having two *N-P=O* structural framework. Also catalyst **156** with *"-NH-"* group provides better selectivity than **168** having *"-NMe"* group. We have also examined the effect of phosphorous stereogenic center by selecting three diastereomeric pairs *i.e.*, (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octanes (**114** & **114A**), (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes (**177** & **177A**), and (2*S*,5*S*) & (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octanes (**178** & 1**78A**) and established to some extent that phosphorus stereochemistry, in all these catalysts, has no significant role in directing stereochemical pathway of the reduction process. We have also utilized catalyst **181** with "*-N-(P=O,Cl)-O-*" structural framework which offers inferior selectivities in comparison with that of the catalyst **114** containing "*-N-(P=O,Cl)-N-*" structural framework.

EXPERIMENTAL

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

Elemental Analyses: Elemental analyses were performed on a Perkin–Elmer 240C-CHN analyzer or on a Thermo Finnigan Flash 1112 analyzer.

Infrared Spectra: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in CH_2Cl_2, peaks are reported in cm^{-1}.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a Bruker-AC-200 spectrometer or Bruker-Avance-400 spectrometer. ^{1}H NMR (200 MHz or 400 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned, with TMS (δ = 0 ppm) as internal standard. ^{13}C NMR (50 MHz or 100 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 reference. ^{31}P NMR (81 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned, using 85% H_3PO_4 (δ = 0 ppm) as external standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale,

(2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, b = broad, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

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

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

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

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

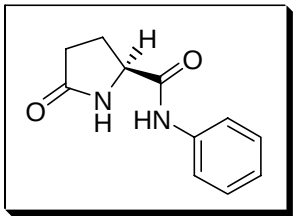
X-Ray Crystallography:

The X-ray diffraction measurements for the respective compounds were carried out at 293 K on an automated Enraf-Nonius MACH3 difractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Measuring the intensity of the three standard reflections after every one and half hour intervals monitored stability of the crystal during the measurement. No appreciable variation of the crystal was detected. X-ray diffraction measurements for the respective compounds were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system. The data were reduced using XTAL 3.4 (or) SAINT program, without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).

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

(2*S*)-5-Oxopyrrolidine-2-carboxanilide (158):

This molecule was prepared according to the known procedure with slight modifications.[142] A mixture of *L*-glutamic acid (**157**) (15 g, 102 mM) and aniline (113 mL) was stirred for 90 min at 200 °C. The reaction mixture was cooled to room temperature. Aniline was distilled off under reduced pressure around 60-70 °C. The hot oily residue, thus obtained was dissolved in hot acetone (60 mL) and filtered while it is hot (the unreacted glutamic acid is insoluble in hot acetone and is filtered out, whereas amide is soluble in hot acetone that comes in filtrate) and cooled to 0 °C. Solid thus obtained was separated by filtration and crystallized from methanol to provide (2*S*)-5-oxopyrrolidin-2-carboxanilide (**158**) as a crystalline solid.



Yield: 5.82 g (28%)

Mp: 183-185 °C (Lit.[142] 189-191 °C)

$[\alpha]_D^{25}$: +18.25 (*c* 1.09, MeOH)

[Lit.[142] $[\alpha]_D^{25}$: +18.6 (*c* 1, MeOH)]

IR (KBr): ν 3325-3050 (multiple bands), 1664 cm^{-1}

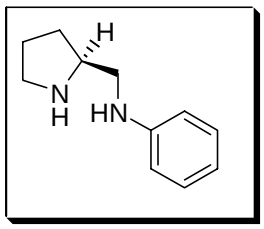
^1H NMR (400 MHz): [20% DMSO-d_6 in $CDCl_3$] δ 2.13-2.50 (m, 4H), 4.23-4.33 (m, 1H), 7.02-7.13 (m, 1H), 7.21-7.35 (m, 2H), 7.57-7.70 (m, 2H), 7.80 (s, 1H), 9.69 (s, 1H)

^{13}C NMR [(50 MHz): [20% DMSO-d_6 in $CDCl_3$] δ 24.31, 28.49, 55.99, 118.76, 122.70, 127.55, 137.46, 169.91, 177.19

(2*S*)-2-Anilinomethylpyrrolidine (159):

This compound was prepared according to the literature procedure.[142]

To a suspension of lithium aluminum hydride (4.75 g, 125 mM) in THF (150 mL) at 0 °C (2*S*)-5-oxopyrrolidin-2-carboxanilide (**158**) (10.2 g, 50.0 mM) was slowly added portion wise. After the addition was complete, the reaction mixture was heated under reflux for 4 h with stirring. Then the reaction mixture was cooled to 5 °C (ice water). Water (6 mL) was added carefully (drop-wise) followed by addition of 2.5 N sodium hydroxide solution and reaction mixture was diluted with dichloromethane and stirred for 5 min. Organic layer was separated and the aluminum salts were washed with dichloromethane (3 x 150 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the oil thus obtained, was distilled under reduced pressure to afford the (2*S*)-2-anilinomethylpyrrolidine (**159**) as a viscous liquid (6.6 g) in 75% yield.



Bp: 118-121 °C/0.4 mm
(Lit.[142] 117-120 °C/0.4 mm)

$[\alpha]_D^{25}$: +18.4 (*c* 2.49, EtOH)
[Lit.[142] $[\alpha]_D^{25}$: +18.5 (*c* 1.087, EtOH)]

IR (neat): ν 3312 cm^{-1}

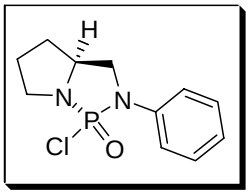
^{1}H NMR (400 MHz): δ 1.36-1.52 (m, 1H), 1.62-2.00 (m, 4H), 2.82-3.03 (m, 3H), 3.10-3.25 (m, 1H), 3.28-3.47 (m, 1H), 4.09 (b, 1H), 6.55-6.75 (m, 3H), 7.10-7.23 (m, 2H)

^{13}C NMR (50 MHz): δ 25.86, 29.65, 46.60, 48.76, 57.79, 113.07, 117.36, 129.27, 148.63

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (114):

This molecule was prepared according to the literature procedure.[143]

To a stirred solution of (2*S*)-2-anilinomethylpyrrolidine (**159**) (5.28 g, 30 mM) and triethyl amine (8.34 mL, 60 mM) in THF (180 mL) at 0 °C was added phosphorusoxy chloride (2.8 mL, 30 mM) in THF (30 mL) drop-wise over 30 min. After stirring for 2 h at room temperature, the salts formed were filtered off and the solvent was evaporated under reduced pressure. The crude product thus obtained, was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide a nice solid which was crystallized from ethyl acetate, hexanes (1:1) to provide the desired (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114**) as colorless needles (4.76 g) in 62% yield.



Mp: 133-134 °C [Lit.[143] 135 °C]

$[\alpha]_D^{25}$: +124.22 (*c* 0.9, $CHCl_3$)

[Lit.[143] $[\alpha]_D^{25}$: +127.2 (*c* 2.1, $CHCl_3$)]

IR (KBr): ν 1599, 1504, 1271, 1172 cm^{-1}

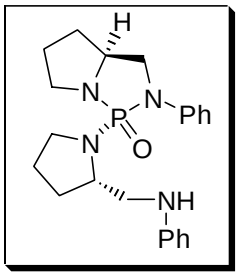
^{1}H NMR (200 MHz): δ 1.56-1.84 (m, 1H), 1.86-2.30 (m, 3H), 3.11-3.32 (m, 1H), 3.44-3.67 (m, 1H), 3.72-4.05 (m, 3H), 7.01-7.17 (m, 1H), 7.21-7.45 (m, 4H)

^{13}C NMR (50 MHz): δ 27.38 (d, J = 4.8 Hz), 31.05, 44.81 (d, J = 2.4 Hz), 50.81 (d, J = 18.2 Hz), 58.64 (d, J = 9.7 Hz), 117.90 (d, J = 4.8 Hz), 123.28, 129.22, 140.07 (d, J = 4.8 Hz)

^{31}P NMR: δ 18.78

(2*S*,5*S*)-2-[(2*S*)-2-(Anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (156):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane (**114**) (0.256 g, 1 mM) and triethylamine (0.14 mL, 1 mM) in dichloromethane (5 mL) was added (2*S*)-2-anilinomethylpyrrolidine (**159**) (0.176 g, 1 mM) at room temperature. After stirring the reaction mixture for 12 h at room temperature, the salts thus formed, were filtered off and the dichloromethane solution was concentrated under reduced pressure. The residue, thus obtained, was purified by column chromatography (silica gel, 60% ethyl acetate in hexanes), to provide a white solid which on recrystalization using ethyl acetate gave the desired (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) as colorless needles (0.254 g) in 64% yield.



Mp: 146-148 °C

$[\alpha]_D^{25}$: +26.18 (*c* 1.1, $CHCl_3$)

IR (KBr): ν 3321, 1602, 1498, 1300, 1211 cm^{-1}

^1H NMR (400 MHz): δ 1.58-1.95 (m, 6H), 1.98-2.12 (m, 2H), 2.80-3.12 (m, 4H), 3.22-3.44 (m, 2H), 3.71-3.97 (m, 4H), 5.59 (b, 1H), 6.55-6.72 (m, 3H), 6.81-6.90 (m, 1H), 6.98-7.07 (m, 2H), 7.11-7.20 (m, 4H)

^{13}C NMR (50 MHz): δ 24.95 (d, J = 6.1 Hz), 26.01, 31.10 (d, J = 7.3 Hz), 32.22, 46.05, 46.56 (d, J = 2.4 Hz), 48.96 (d, J = 17.0 Hz), 49.78, 57.60 (d, J = 3.6 Hz), 58.25 (d, J = 7.3 Hz), 112.32, 116.29, 116.50 (d, J = 3.6 Hz), 121.29, 128.93, 129.03, 141.52 (d, J = 4.8 Hz), 148.80

^{31}P NMR: δ 23.64

LCMS (m/z): 397 $(M + H)^+$

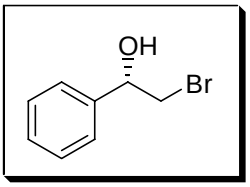
Analysis calcd. for $C_{22}H_{29}N_4OP$: C, 66.65; H, 7.37; N, 14.13

Found: C, 66.78; H, 7.37; N, 13.97

Asymmetric reduction of phenacyl bromide (160a) using 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (156):

To a stirred solution of (2*S,*5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (0.004 g, 0.01 mM) [0.5 mL of 0.02 M standard solution in toluene] in toluene (3 mL) at room temperature was added borane-dimethyl sulfide [0.076 g, 1.0 mM (1.0 mL of 1 M standard solution in toluene)]. Reaction mixture was heated to 110 °C and once the temperature has stabilized at 110 °C, phenacyl

bromide (**160a**) (0.199 g, 1.0 mM) in toluene (2 mL) was added drop-wise over a period of 10 min and stirring 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 (2 mL). 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 (**161a**) as colorless oil.



Yield: 79%

$[\alpha]_D^{25}$: +39.20 (*c* 1.07, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 89% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**]

IR (neat): ν 3377 cm^{-1}

^{1}H NMR (400 Mz): δ 2.67 (d, 1H, *J* = 2.9 Hz), 3.49-3.69 (m, 2H), 4.86-4.99 (m, 1H), 7.28-7.41 (m, 5H)

^{13}C NMR (50 MHz): δ 39.84, 73.72, 125.97, 128.35, 128.59, 140.41

Determination of enantiomeric purity:

Racemic alcohol (±)-**161a** showed two peaks of equal intensity on HPLC analysis [chiral column, Chiralcel-ODH, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.04 min and 8.51 min] due to *S* and *R* enantiomers. The chiral alcohol (*S*)-

161a showed two peaks in the ratio of 94.5:5.5 [retention times: 8.01 min (*S*) and 8.50 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 89%.

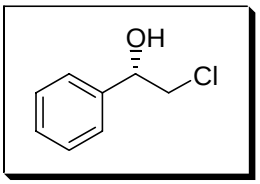
(±)-2-Bromo-1-phenylethanol [(±)-161a]:

To a stirred solution of phenacyl bromide (**160a**) (0.199 g, 1 mM) in toluene (5 mL) was added BH_3**.**SMe_2 (0.076 g, 1mM) and heated under reflux for 2 h. Then the reaction mixture was allowed to cool to room temperature and quenched with methanol (2 ml). 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-bromo-1-phenylethanol [(±)-**161a**] as colorless oil. The spectral data (IR, ^{1}H & ^{13}C NMR) of this molecule are in full agreement with that of the chiral molecule (*S*)-**161a**.

All the racemic alcohols (161b-161g, 164a-164j and 167a) were prepared following the above-mentioned procedure. The spectral data (IR, ^{1}H & ^{13}C NMR) of these molecules are in full agreement with the chiral alcohols.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b]:

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a viscous liquid following the procedure described for the molecule (*S*)-**161a**.



Yield: 82%

$[\alpha]_D^{25}$: +44.00 (*c* 1.05, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 88% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

IR (neat): ν 3395 cm^{-1}

^{1}H NMR (400 MHz): δ 2.66 (d, 1H, *J* = 2.9 Hz), 3.58-3.81 (m, 2H), 4.88-4.96 (m, 1H), 7.29-7.47 (m, 5H)

^{13}C NMR (50 MHz): δ 50.63, 73.99, 126.07, 128.37, 128.59, 140.04

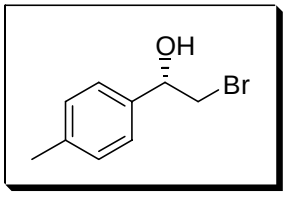
Determination of enantiomeric purity:

Racemic alcohol (±)-**161b** showed two peaks in equal intensity on HPLC analysis [chiral column, Chiralcel-ODH, solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min; retention times: 8.08 min and 8.62 min] arising from *S* and *R* enantiomers. The chiral alcohol (*S*)-**161b** showed two peaks in 94:6 ratios [retention times: 8.04 min (*S*) and 8.62 min (*R*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 88%.

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-161c]:

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

(**160c**) with BH_3**.**SMe_2 in the presence of 1 mol% (2*S,*5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a viscous liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 85%

$[\alpha]_D^{25}$: +39.42 (*c* 1.04, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +41.8 (*c* 1.00, $CHCl_3$), (*S*)-configuration, 95% *ee*]

Enantiomeric purity: 90% (determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161c**)

IR (neat): ν 3350 cm^{-1}

^{1}H NMR (400 MHz): δ 2.35 (s, 3H), 2.58 (b, 1H), 3.48-3.68 (m, 2H), 4.82-4.92 (m, 1H) 7.18 (d, 2H, *J* = 7.8 Hz), 7.26 (d, 2H, *J* = 7.8 Hz)

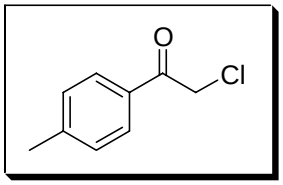
^{13}C NMR (50 MHz): δ 21.13, 39.96, 73.63, 125.90, 129.27, 137.45, 138.15

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-ODH, solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min] of the racemic compound (±)-**161c** showed two peaks at 15.04 min (*S*) and 16.54 min (*R*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol (*S*)-**161c** showed two peaks at 15.03 min (*S*) and 16.56 min (*R*) in the ratio of 95:5 indicating that the reaction is 90% enantioselective.

4-Methylphenacyl chloride (160d):

To a stirred suspension of $AlCl_3$ (0.67 g, 5 mM) in toluene (15 mL) at 10 °C was added, chloroacetyl chloride (2.82 g, 25 mM) drop-wise 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 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained, was recrystalized from ether-hexane mixture (1:5) to provide the 4-methylphenacyl chloride (**160d**) as a white solid.



Yield: 30% (1.26 g)

Mp: 49-51 °C

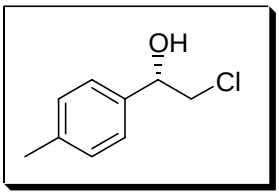
IR (KBr): ν 1699 cm^{-1}

^{1}H NMR (400 MHz): δ 2.43 (s, 3H), 4.68 (s, 2H), 7.29 (d, 2H, J = 7.8 Hz), 7.86 (d, 2H, J = 7.8 Hz)

^{13}C NMR (50 MHz): δ 21.76, 45.88, 128.71, 129.64, 131.89, 145.06, 190.76

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-161d]:

This molecule was prepared by the asymmetric reduction of 4-methylphenacyl chloride (**160d**) with BH_3.SMe_2 under the influence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilino-methyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 90%

$[\alpha]_D^{25}$: +44.14 (*c* 1.01, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*]

Enantiomeric purity: 86% (determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161d**)

IR (neat): ν 3342 cm^{-1}

^{1}H NMR (400 MHz): δ 2.35 (s, 3H), 2.58 (b, 1H), 3.58-3.78 (m, 2H), 4.82-4.93 (m, 1H), 7.18 (d, 2H, *J* = 7.8 Hz), 7.27 (d, 2H, *J* = 7.8 Hz)

^{13}C NMR (50 MHz): δ 21.18, 50.90, 73.99, 126.05, 129.37, 137.11, 138.30

Determination of enantiomeric purity:

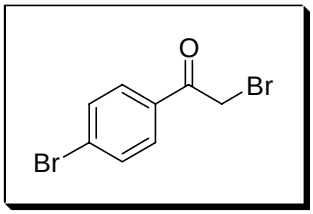
The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-ODH. The racemic alcohol (±)-**161d** showed two peaks at 15.13 min (*S*) and 16.34 min (*R*) in 1:1 ratio [solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min]. Similar HPLC analysis of the chiral alcohol (*S*)-**161d** showed two peaks at 15.12 min (*S*) and 16.42 min (*R*) in the ratio of 93:7 indicating that its enantiomeric purity is 86%.

2-Bromo-1-(4-bromophenyl)ethanone (160e):

This molecule was prepared according to the reported procedure.[145]

To a stirred solution of 4-bromoacetophenone (**163e**) (1.9 g, 10 mM) and NBS (1.96 g, 11 mM) in acetonitrile (60 mL) was added TMSOTf (0.11 g, 0.5mM). After stirring the

reaction mixture at room temperature for 24 h, it was diluted with ether and washed with water. Organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes)



Yield: 60% (1.67 g)

Mp: 108-110 °C [Lit.[146] 107.5-108 °C]

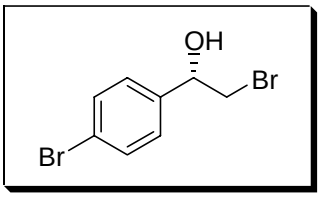
IR (KBr): ν 1697 cm^{-1}

^{1}H NMR (400 MHz): δ 4.40 (s, 2H), 7.65 (d, 2H, J = 6.8 Hz), 7.86 (d, 2H, J = 6.8 Hz)

^{13}C NMR (50 MHz): δ 30.45, 129.27, 130.41, 132.21, 132.67, 190.38

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-161e]:

This molecule was obtained *via* the borane-mediated reduction of 4-bromophenacyl bromide (**160e**) under the catalytic influence of (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)-pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol%) as a white solid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 82%

Mp: 69-71 °C [Lit.[148] 70-72 °C]

$[\alpha]_D^{25}$: +30.80 (*c* 0.99, $CHCl_3$)

[Lit.[148] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*]

Enantiomeric purity: 89% [determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161e**]

IR (KBr): ν 3242 cm^{-1}

^{1}H NMR (400 MHz): δ 2.65 (b, 1H), 3.46-3.66 (m, 2H), 4.85-4.95 (m, 1H), 7.27 (d, 2H, *J* = 8.8 Hz), 7.50 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz): δ 39.67, 73.09, 122.33, 127.70, 131.77, 139.31

Determination of enantiomeric purity:

The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OJH. The racemic alcohol (±)-**161e** showed two peaks at 19.57 min (*R*) and 21.56 min (*S*) in 1:1 ratio [solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min]. Similar HPLC analysis of the chiral alcohol (*S*)-**161e** showed two peaks at 19.70 min (*R*) and 21.50 min (*S*) in the ratio of 5.5:94.5 indicating that its enantiomeric purity is 89%.

Tetrabutylammonium tribromide (TBA Br_3):

This compound was prepared following the literature procedure.[146]

To a stirred solution of tetrabutylammonium bromide (19.4 g, 60 mM) and potassium bromide (2.38 g, 20 mM) in water (120 mL) was added hydrobromic acid (48%, 15 mL) drop-wise at room temperature. After 10 minutes, the orange precipitate formed, was filtered and recrystalized from ether-dichloromethane (1:1) to provide TBA Br_3 as orange crystals.

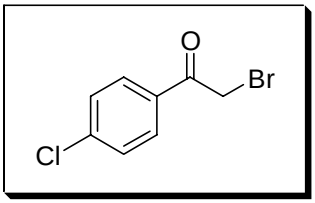
Yield: 95% (13.73 g)

Mp: 73-74 °C (Lit.[146] 74-75 °C)

4-Chlorophenacyl bromide (160f):

This molecule was prepared according to the reported procedure.[146]

To a stirred solution of *p*-chloroacetophenone (**163f**) (1.54 g, 10 mM) in dichloromethane (100 mL) and methanol (40 mL) was added TBA Br_3 (5.30 g, 11 mM) at room temperature. After stirring for 6 h at 35 °C (until the discoloration of the orange solution), the solvent was removed and the residue, thus obtained, was extracted with ether (3 X 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was recrystalized from ethanol-water (1:2) to provide the 4-chlorophenacyl bromide (**160f**) as a white solid.



Yield: 84% (1.97%)

Mp: 95-96 °C (Lit.[146] 97-97.5 °C)

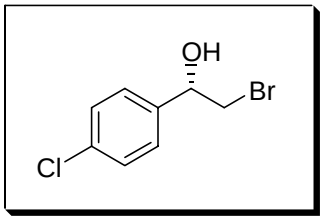
IR (KBr): ν 1695 cm^{-1}

^{1}H NMR (400 MHz): δ 4.40 (s, 2H), 7.47 (d, 2H, J = 8.5 Hz), 7.93 (d, 2H, J = 8.5 Hz)

^{13}C NMR (50 MHz): δ 30.35, 129.27, 130.39, 132.38, 140.55, 190.23

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-161f]:

This compound was obtained as a colorless liquid *via* the borane-mediated reduction of 4-chlorophenacyl bromide (**160f**) in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilino-methyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 90 %

$[\alpha]_D^{25}$: +40.20 (*c* 1.00, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +38.60 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91% *ee*]

Enantiomeric purity: 90% [determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161f**]

IR (neat): ν 3323 cm^{-1}

^{1}H NMR (400 MHz): δ 2.67 (b, 1H), 3.44-3.68 (m, 2H), 4.85-4.95 (m, 1H), 7.29-7.40 (m, 4H)

^{13}C NMR (50 MHz): δ 39.54, 72.97, 127.36, 128.74, 134.05, 138.81

Determination of enantiomeric purity:

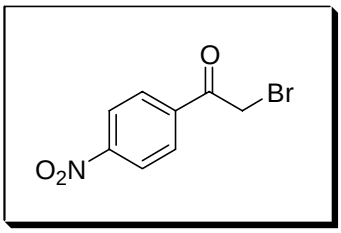
The enantiomeric purity was determined by HPLC analysis using chiral column, Chiralcel-OJH. The racemic alcohol (±)-**161f** showed two peaks at 24.53 min (*R*) and 26.76 min (*S*) in 1:1 ratio [solvent system, hexanes:IPA (95:5); flow rate: 0.75 mL/min]. Similar HPLC analysis of the chiral alcohol (*S*)-**161f** showed two peaks at 24.46 min (*R*) and 26.09 min (*S*) in the ratio of 5:95 indicating that its enantiomeric purity is 90%.

4-Nitrophenacyl bromide (160g):

This molecule was prepared according to the known procedure[147]

To a stirred solution of 4-nitroacetophenone (**163g**) (3.3 g, 20 mM) and glacial acetic acid (15 mL) was slowly added bromine (1.0 mL, 20 mM). Reaction mixture was stirred at

room temperature for over night, diluted with ice-cold water (20 mL), and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was purified by column chromatography to obtain light yellow solid of **160g**.



Yield: 65% (3.2 g)

Mp: 89 °C [lit.[146] 96-96.5 °C]

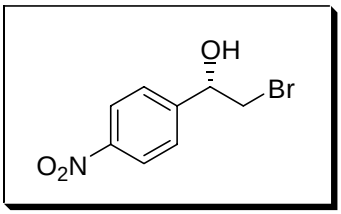
IR (KBr): ν 1703 cm^{-1}

^{1}H NMR (400 MHz): δ 4.45 (s, 2H), 8.16 (d, 2H, J = 8.8 Hz), 8.35 (d, 2H, J = 8.8 Hz)

^{13}C NMR (50 MHz): δ 30.25, 124.06, 130.10, 138.49, 150.76, 189.96

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-161g]:

This compound was prepared *via* the asymmetric reduction of 4-nitrophenacyl bromide (**160g**) with BH_3**.**SMe_2 under the catalytic influence of (2*S*,5*S*)-2-[(2*S*)-2-(anilino-methyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol%) as a white solid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 88%

Mp: 80-82 °C [Lit.[115] 78-80 °C]

$[\alpha]_D^{25}$: +31.80 (*c* 0.80, $CHCl_3$)

[Lit.[114] $[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*]

Enantiomeric purity: 89% [determined by HPLC analysis of acetate (*S*)-**162g** using chiral column, Chiralcel-ODH, with reference to racemic acetate (±)-**162g**]

IR (KBr): ν 3549 cm^{-1}

^{1}H NMR (400 MHz): δ 2.82 (d, 1H, J = 2.9 Hz), 3.45-3.75 (m, 2H), 5.00-5.10 (m, 1H), 7.59 (d, 2H, J = 8.8 Hz), 8.24 (d, 2H, J = 8.8 Hz)

^{13}C NMR (50 MHz): δ 39.16, 72.63, 123.79, 126.99, 147.54, 147.73

Determination of enantiomeric purity:

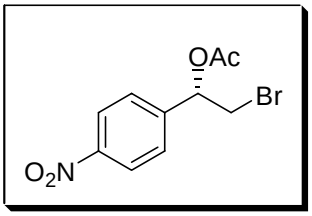
The enantiomeric purity was determined by HPLC analysis of the corresponding acetate *i.e.* 1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane (**162g**) using chiral column, Chiralcel-ODH. The racemic acetate (±)-**162g** showed two peaks at 11.42 min (*R*) and 13.13 min (*S*) in 1:1 ratio [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]. Chiral acetate (*S*)-**162g** showed two peaks at 11.34 min (*R*) and 13.02 min (*S*) in the ratio of 5.5:94.5 in a similar HPLC analysis indicating that its enantiomeric purity of the alcohol is 89%.

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-162g]:

This molecule was prepared according to the known procedure[144]

To a stirred solution of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [(*S*)-**161g**] (0.084 g, 0.34 mM) and acetic anhydride (20 mL) was added pyridine (4 mL) and maintained stirring for 10 h at room temperature, then the reaction mixture was diluted with water (80 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively

with 5% HCl and 10% sodium bicarbonate solution and was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes).



Mp: 101-103 °C [Lit.[115] 102-105 °C]

Yield: 81%

$[\alpha]_D^{25}$: +43.00 (*c* 1.15, $CHCl_3$)

[Lit.[115] $[\alpha]_D^{25}$: +46.6 (*c* 0.9, $CHCl_3$), (*S*)-configuration, 92% *ee*]

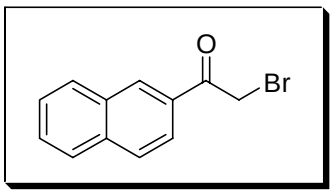
IR (KBr): ν 1751 cm^{-1}

^{1}H NMR (400 MHz): δ 2.17 (s, 3H), 3.58-3.72 (m, 2H), 5.99-6.09 (m, 1H), 7.55 (d, 2H, *J* = 8.8 Hz), 8.25 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz): δ 20.79, 33.41, 73.58, 123.86, 127.65, 144.55, 148.07, 169.51

2-Bromoacetylnaphthalene (160h):

This compound was obtained as a light yellow solid *via* the treatment of 2-acetyl-naphthalene (**163i**) with TBA Br_3 following the similar procedure described for the ketone **160f**.



Time: 6 h

Yield: 72%

Mp: 80-81 °C [Lit.[146] 81-82 °C]

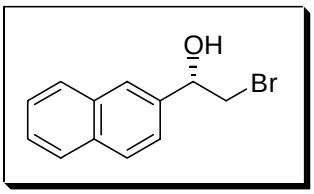
IR (KBr): ν 1691 cm^{-1}

^{1}H NMR (400 MHz): δ 4.58 (s, 2H), 7.54-7.71 (m, 2H), 7.87-8.10 (m, 4H), 8.51 (s, 1H)

^{13}C NMR (50 MHz): δ 31.01, 124.13, 127.04, 127.82, 128.79, 129.01, 129.68, 130.87, 131.33, 132.40, 135.85, 191.20

(*S*)-2-Bromo-1-(naphth-2-yl)ethanol [(*S*)-161h]:

This compound was obtained as a white solid *via* the asymmetric reduction of 2-bromoacetylnaphthalene (**160h**) with BH_3**.**SMe_2 under the catalytic influence of (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octane (**156**) (1 mol%) following the similar procedure described for the molecule (*S*)-**161a**.



Mp: 78-80 °C [Lit.[39] 88-90 °C]

Yield: 84 %

$[\alpha]_D^{25}$: +27.09 (*c* 0.84, EtOH)

[Lit.[39] $[\alpha]_D^{23}$: -25.6 (*c* 4.0, EtOH) (*R*)-configuration, 83% *ee*]

Enantiomeric purity: 89% [determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161h**].

IR (KBr): ν 3304 cm^{-1}

^{1}H NMR (400 MHz): δ 2.73 (d, 1H, *J* = 2.9 Hz), 3.57-3.78 (m, 2H), 5.07-5.16 (m, 1H), 7.44-7.57 (m, 3H), 7.80-7.92 (m, 4H)

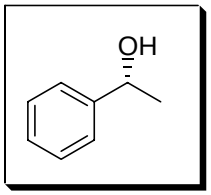
^{13}C NMR (50 MHz): δ 39.91, 73.87, 123.57, 125.17, 126.29, 126.39, 127.72, 128.06, 128.50, 133.18, 137.69

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-OJH, solvent system, hexanes:IPA (80:20); flow rate: 1 mL/min] of the racemic compound (±)-**161h** showed two peaks at 14.55 min (*R*) and 19.20 min (*S*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol (*S*)-**161h** showed two peaks at 14.70 min (*R*) and 19.15 min (*S*) in the ratio of 5.5:94.5 indicating that the reaction is 89% enantioselective.

(*R*)-1-Phenylethanol [(*R*)-164a]:

This compound was obtained as a colorless liquid *via* borane-mediated reduction of acetophenone (**163a**) in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)-pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 83%

$[\alpha]_D^{25}$: +33.96 (*c* 0.89, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 76% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**]

IR (neat): ν 3396 cm^{-1}

^{1}H NMR (400 MHz): δ 1.49 (d, 3H, J = 6.8 Hz), 1.87 (b, 1H), 4.82-4.98 (m, 1H), 7.20-7.42 (m, 5H)

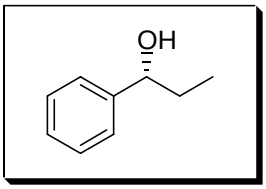
^{13}C NMR (50 MHz): δ 25.16, 70.35, 125.44, 127.45, 128.50, 145.86

Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel-ODH, flow rate: 1 mL/min solvent system, hexanes:IPA (95:05)] of racemic compound (±)-**164a** showed two peaks at 8.35 min (*R*) and 9.72 min (*S*) in 1:1 ratio. Chiral alcohol (*R*)-**164a** showed two peaks at 8.52 min (*R*) and 9.89 min (*S*) in the ratio of 88:12 on similar HPLC analysis indicating that its enantiomeric purity is 76%.

(*R*)-1-Phenylpropan-1-ol [(*R*)-164b]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of propiophenone (**163b**) with BH_3.SMe_2 under the catalytic influence of (2*S,*5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol %), following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 87%

$[\alpha]_D^{25}$: +30.10 (*c* 0.76, $CHCl_3$)

[Lit.[151] $[\alpha]_D^{25}$: +43.0 (*c* 5.1, $CHCl_3$), (*R*)-configuration, 96% *ee*]

Enantiomeric purity: 70% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164b**]

IR (neat): ν 3369 cm^{-1}

^1H NMR (400 MHz): δ 0.92 (t, 3H, J = 7.8 Hz), 1.65-1.91 (m, 3H), 4.54-4.65 (m, 1H), 7.20-7.41 (m, 5H)

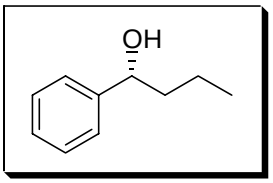
^{13}C NMR (50 MHz): δ 10.22, 31.98, 76.12, 126.05, 127.57, 128.50, 144.68

Determination of enantiomeric purity:

Racemic alcohol (±)-**164b** showed two peaks in equal intensity on HPLC analysis [chiral column, Chiralcel-ODH, solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min; retention times: 8.34 min and 8.98 min arising from *R* and *S* enantiomers]. The chiral alcohol (*R*)-**164b** showed two peaks in 85:15 ratio [retention times: 7.99 min (*R*) and 8.85 min (*S*) respectively] on similar HPLC analysis, indicating that its enantiomeric purity is 70%.

(*R*)-1-Phenylbutan-1-ol [(*R*)-164c]:

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of butyrophenone (**163c**) with BH_3**.**SMe_2 under the catalytic influence of (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol%), following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 84%

$[\alpha]_D^{25}$: +34.00 (*c* 0.85, benzene)

[Lit.[9] $[\alpha]_D^{25}$: -45.2 (*c* 4.81, benzene), (*S*)-configuration, 100% *ee*].

Enantiomeric purity: 72% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164c**].

IR (neat): ν 3315 cm^{-1}

^{1}H NMR (400 MHz): δ 0.93 (t, 3H, *J* = 7.8 Hz), 1.25-1.90 (m, 5H), 4.61-4.69 (m, 1H), 7.25-7.46 (m, 5H)

^{13}C NMR (50 MHz): δ 13.91, 18.95, 41.17, 74.23, 125.90, 127.28, 128.28, 144.99

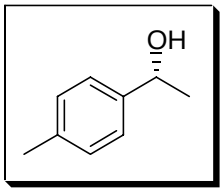
Determination of enantiomeric purity:

HPLC analysis [solvent system, hexanes:IPA (97.5:2.5); flow rate: 1 mL/min] of the racemic alcohol [(±)-**164c**] showed two peaks at 11.91 min (*R*) and 12.73 min (*S*) in 1:1 ratio on chiral column, Chiralcel-ODH. Similar HPLC analysis of the chiral alcohol [(*R*)-**164c**] showed two peaks at 11.80 min (*R*) and 12.73 min (*S*) in the ratio of 86:14 indicating that its enantiomeric purity is 72%.

(*R*)-1-(4-Methylphenyl)ethanol [(*R*)-164d]:

This molecule was obtained *via* the treatment of 4-methylacetophenone (**163d**) with BH_3**.**SMe_2 in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-

diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 88%

$[\alpha]_D^{25}$: +31.69 (*c* 1.36, MeOH)

[Lit.[152] $[\alpha]_D^{26}$: -43.5 (*c* 0.99, MeOH), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 69% [determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164d**]

IR (neat): ν 3377 cm^{-1}

^{1}H NMR (400 MHz): δ 1.47 (d, 3H, *J* = 5.9 Hz), 1.95 (bs, 1H), 2.33 (s, 3H), 4.78-4.89 (m, 1H), 7.15 (d, 2H, *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 7.8 Hz)

^{13}C NMR (50 MHz): δ 21.01, 24.99, 69.99, 125.34, 129.03, 136.86, 142.95

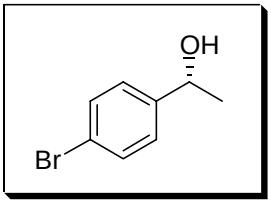
Determination of enantiomeric purity:

The racemic alcohol (±)-**164d** showed two peaks at 13.33 min (*S*) and 15.14 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJH [solvent system, hexanes:IPA (95:05); flow rate: 0.8 mL/min]. The chiral alcohol (*R*)-**164d** showed two peaks at 13.33 min (*S*) and 14.93 min (*R*) in the ratio of 15.5:84.5 on similar HPLC analysis, indicating that its enantiomeric purity is 69%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-164e]:

This molecule was obtained by borane-mediated reduction of 4-bromoacetophenone (**163e**) in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-

phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 91%

$[\alpha]_D^{25}$: +31.60 (*c* 0.78, $CHCl_3$)

[Lit.[152] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*].

Enantiomeric purity: 78% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164e**]

IR (neat): ν 3400 cm^{-1}

^{1}H NMR (400 MHz): δ 1.46 (d, 3H, *J* = 5.9 Hz), 1.99 (bs, 1H), 4.78-4.92 (m, 1H), 7.24 (d, 2H, *J* = 8.8 Hz), 7.46 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz): δ 25.11, 69.53, 121.00, 127.14, 131.43, 144.72

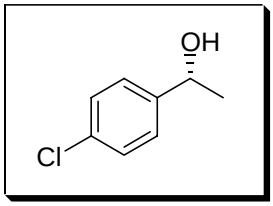
Determination of enantiomeric purity:

The racemic alcohol (±)-**164e** showed two peaks at 14.28 min (*S*) and 15.47 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJH [solvent system, hexanes:IPA (95:05); flow rate: 0.8 mL/min]. The chiral alcohol (*R*)-**164e** showed two peaks at 14.42 min (*S*) and 15.58 min (*R*) in the ratio of 11:89 on similar HPLC analysis, indicating that its enantiomeric purity is 78%.

(*R*)-1-(4-Chlorophenyl)ethanol [(*R*)-164f]:

Asymmetric reduction of 4-chloroacetophenone (**163f**) with BH_3**.**SMe_2 in the presence of 1

mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) provided the chiral alcohol (*R*)-**164f**, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 87%

$[\alpha]_D^{25}$: +35.87 (*c* 1.15, Et_2O)

[Lit.[152] $[\alpha]_D^{25}$: -49.0 (*c* 1.84, Et_2O), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 72% [determined by HPLC analysis of its alcohol using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164f**].

IR (neat): ν 3369 cm^{-1}

^1H NMR (400 MHz): δ 1.46 (d, 3H, *J* = 6.9 Hz), 2.05 (bs, 1H), 4.80-4.92 (m, 1H), 7.20-7.38 (m, 4H)

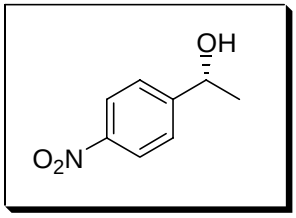
^{13}C NMR (50 MHz): δ 25.14, 69.53, 126.80, 128.50, 132.91, 144.24

Determination of enantiomeric purity:

The racemic alcohol (±)-**164f** showed two peaks at 13.14 min (*S*) and 14.19 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJH [solvent system, hexanes:IPA (95:05); flow rate:0.8 mL/min]. The chiral alcohol (*R*)-**164f** showed two peaks at 13.16 min (*S*) and 14.14 min (*R*) in the ratio of 14:86 on similar HPLC analysis, indicating that its enantiomeric purity is 72%.

(*R*)-1-(4-Nitrophenyl)ethanol [(*R*)-164g]:

This molecule was obtained *via* the borane-mediated reduction of 4-nitroacetophenone (**163g**) in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 85%

$[\alpha]_D^{25}$: +22.50 (*c* 0.82, EtOH)

[Lit.[153] $[\alpha]_D^{24.5}$: -29.7 (*c* 1.0, EtOH), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 78% [determined by HPLC analysis of corresponding acetate (*R*)-**165g** using chiral column, Chiralcel-ODH, with reference to its racemic acetate (±)-**165g**]

IR (neat): ν 3292 cm^{-1}

^{1}H NMR (400 MHz): δ 1.52 (d, 3H, *J* = 6.9 Hz), 2.01 (bs, 1H), 4.95-5.10 (m, 1H), 7.54 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz): δ 25.26, 69.28, 123.57, 126.07, 146.91, 153.31

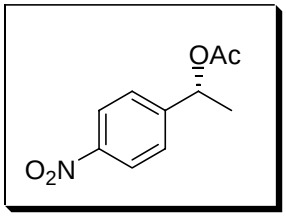
Determination of enantiomeric purity:

The enantiomeric purity was determined by HPLC analysis of the corresponding acetate 1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*R*)-**165g**]. The racemic acetate (±)-**165g** showed two peaks at 21.59 min (*S*) and 23.63 min (*R*) in 1:1 ratio [solvent system,

hexanes:IPA (98:2); flow rate: 0.5 mL/min]. Similar HPLC analysis of the chiral acetate (*R*)-**165g** showed two peaks at 21.51 min (*S*) and 23.42 min (*R*) in the ratio of 11:89 indicating that reaction is 78% enantioselective.

(*R*)-1-Acetoxy-1-(4-nitrophenyl)ethane [(*R*)-165g]:

This compound was prepared as a colorless liquid *via* the reaction of (*R*)-1-(4-nitrophenyl)ethanol [(*R*)-**164g**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule (*S*)-**162g** (pages, 118-119).



Yield: 83 %

Mp: 102-105 °C

$[\alpha]_D^{25}$: +78.03 (*c* 1.1, $CHCl_3$)

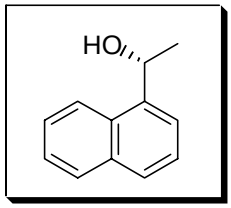
IR (KBr): ν 1739 cm^{-1}

^{1}H NMR (400 MHz): δ 1.55 (d, 3H, *J* = 6.8 Hz), 2.11 (s, 3H), 5.88-5.98 (m, 1H), 7.51 (d, 2H, *J* = 8.8 Hz), 8.21 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz): δ 20.99, 22.10, 71.13, 123.69, 126.68, 147.32, 148.99, 169.90

(*R*)-1-(Naphth-1-yl)ethanol [(*R*)-164h]:

This molecule was obtained by the asymmetric reduction of 1-acetylnaphthalene (**163h**) with $BH_3.SMe_2$ under the catalytic influence of (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)-pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol%) as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 81%

$[\alpha]_D^{25}$: +50.33 (*c* 1.03, Et_2O)

[Lit.[154] $[\alpha]_D^{25}$: -79.6 (*c* 1.02, Et_2O), (*S*)-configuration, 94% *ee*]

Enantiomeric purity: 60% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164h**]

IR (neat): ν 3371 cm^{-1}

^{1}H NMR (400 MHz): δ 1.65 (d, 3H, *J* = 6.8 Hz), 2.02 (bs, 1H), 5.60-5.72 (m, 1H), 7.43-7.57 (m, 3H), 7.66 (d, 1H, *J* = 6.8 Hz), 7.76 (d, 1H, *J* = 7.8 Hz), 7.86 (d, 1H, *J* = 7.8 Hz), 8.10 (d, 1H, *J* = 7.8 Hz)

^{13}C NMR (50 MHz): δ 24.24, 66.71, 121.95, 123.11, 125.34, 125.80, 127.65, 128.74, 130.17, 133.66, 141.38

Determination of enantiomeric purity:

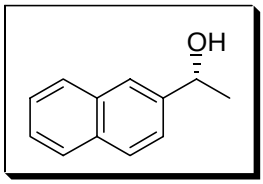
The racemic alcohol (±)-**164h** showed two peaks at 15.51 min (*S*) and 25.45 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-ODH [solvent system, hexanes:IPA (95:5); flow rate: 1 mL/min]. The chiral alcohol (*R*)-**164h** showed two peaks at 15.71 min (*S*) and 25.22 min (*R*) in the ratio of 20.1:79.9 on similar HPLC analysis, indicating that its enantiomeric purity is 60%.

(*R*)-1-(Naphth-2-yl)ethanol [(*R*)-164i]:

This molecule was obtained by the asymmetric reduction of 2-acetylnaphthalene (**163i**)

with BH_3.SMe_2 under the influence of 1mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), as a white solid, following the similar procedure described for the molecule (*S*)-**161a**.

Mp: 68-69 °C



Yield: 88%

$[\alpha]_D^{25}$: +26.25 (*c* 0.99, EtOH)

[Lit.[154] $[\alpha]_D^{25}$: -34.3 (*c* 1.10, EtOH), (*S*)-configuration, 86% *ee*]

Enantiomeric purity: 70% [determined by HPLC analysis of the alcohol using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164i**]

IR (KBr): ν 3339 cm^{-1}

^{1}H NMR (400 MHz): δ 1.57 (d, 3H, *J* = 6.8 Hz), 1.97 (bs, 1H), 5.01-5.12 (m, 1H), 7.41-7.52 (m, 3H), 7.78-7.97 (m, 4H)

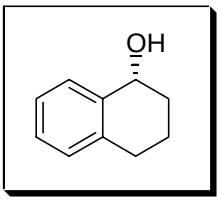
^{13}C NMR (50 MHz): δ 25.11, 70.42, 123.84, 125.75, 126.12, 127.67, 127.94, 128.25, 132.89, 133.30, 143.22

Determination of enantiomeric purity:

The racemic alcohol (±)-**164i** showed two peaks at 9.50 min (*S*) and 11.82 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJH [solvent system, hexanes:IPA (80:20); flow rate: 1 mL/min]. The chiral alcohol (*R*)-**164i** showed two peaks at 9.34 min (*S*) and 11.53 min (*R*) in the ratio of 15:85 on similar HPLC analysis, indicating that the reaction is 70% enantioselective.

(*R*)-1,2,3,4-Tetrahydronaphth-1-ol [(*R*)-164j]:

This product was prepared as a colorless liquid *via* borane-mediated reduction of α-tetralone (**163j**) in the presence of 1 mol% (2*S,5S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 77%

$[\alpha]_D^{25}$: -12.00 (*c* 1.05, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: -23.14 (*c* 1.3, MeOH), (*R*)-configuration, 94% *ee*]

Enantiomeric purity: 51% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164j**]

IR (neat): ν 3369 cm^{-1}

^{1}H NMR (400 MHz): δ 1.65-2.06 (m, 5H), 2.61-2.90 (m, 2H), 4.69-4.82 (m, 1H), 7.06-7.14 (m, 1H), 7.16-7.23 (m, 2H), 7.36-7.47 (m, 1H)

^{13}C NMR (50 MHz): δ 18.83, 29.19, 32.19, 67.95, 126.05, 127.40, 128.62, 128.86, 137.01, 138.83

Determination of enantiomeric purity:

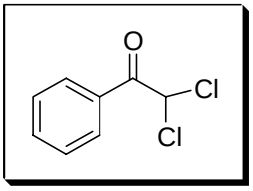
The racemic alcohol (±)-**164j** showed two peaks at 31.32 min (*S*) and 34.23 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-ODH [solvent system, hexanes:IPA (97.5:2.5); flow rate: 0.4 mL/min]. The chiral alcohol (*R*)-**164j** showed two peaks at 31.33

min (*S*) and 34.16 min (*R*) in the ratio of 24.5:75.5 on similar HPLC analysis, indicating that its enantiomeric purity is 51%.

2,2-Dichloro-1-phenylethanone (166a):

This molecule was prepared according to the known procedure.[149]

Acetophenone (**163a**) (0.480 g, 4 mM), was dissolved in a mixture of 31% HCl (20 mL) and EtOH (20 mL) and the mixture was heated to reflux (93-95 °C). A solution of 35% aq. H_2O_2 (0.6 mL, 20 mM) in ethanol (2 mL) was added over 1 min. The reaction mixture was refluxed for 10-15 min and cooled to room temperature then the reaction mixture was diluted with water and the mixture was extracted with $CHCl_3$ (4 x 25 mL). The combined organic extracts were washed with water (4 x 10 mL) dried over anhydrous Na_2SO_4 solvent was evaporated and the crude product thus obtained was column purified using silica gel column with <1% ethyl acetate in hexanes to afford 2,2-dichloro-1-phenylethanone (**166a**) as a viscous oil.



Yield: 90% (0.64 g)

IR (neat): ν 1709 cm^{-1}

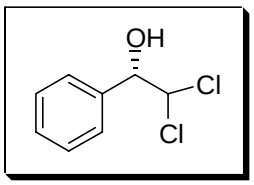
^{1}H NMR (400 MHz): δ 6.68 (s, 1H), 7.47-7.58 (m, 2H), 7.61-7.71 (m, 1H), 8.09 (d, 2H, J = 6.9 Hz)

^{13}C NMR (100 MHz): δ 67.79, 128.92, 129.68, 131.32, 134.57, 185.89

LCMS (m/z): 187 $(M - H)^-$, 189 $(M + 2 - H)^-$, 191 $(M + 4 - H)^-$

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

This molecule was prepared *via* the asymmetric reduction of 2,2-dichloro-1-phenylethanone (**166a**) with BH_3**.**SMe_2 under the catalytic influence of (2*S,*5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**) (1 mol%) following the similar procedure described for the molecule (*S*)-**161a**.



Yield: 87%

$[\alpha]_D^{25}$: +3.00 (*c* 1.10, CH_2Cl_2)

[Lit.[155] $[\alpha]_D^{21}$: -11.8 (*c* 1.26, CH_2Cl_2), (*R*)-configuration, 38% *ee*]

Enantiomeric purity: 7% [determined by HPLC analysis using chiral column, Chiralcel-OJH, with reference to the racemic alcohol (±)-**167a**]

IR (neat): ν 3369 cm^{-1}

^{1}H NMR (400 MHz): δ 2.87 (d, 1H, *J* = 4.0 Hz), 4.94-5.03 (m, 1H), 5.82 (d, 1H, *J* = 5.8 Hz), 7.32-7.45 (m, 5H)

^{13}C NMR (50 MHz): δ 76.39, 78.82, 127.16, 128.52, 129.03, 137.42

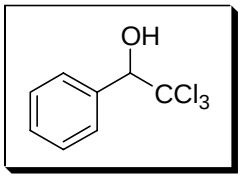
Determination of enantiomeric purity:

The racemic alcohol (±)-**167a** showed two peaks at 21.52 min (*S*) and 22.91 min (*R*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-OJH [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]. The chiral alcohol (*S*)-**167a** showed two peaks at 21.31 min (*S*) and 22.72 min (*R*) in the ratio of 53:46 on similar HPLC analysis, indicating that its enantiomeric purity is 7%.

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

This molecule was prepared according to the known procedure.[150]

A solution of KOH (1.12 g, 20 mM) in MeOH (4 mL) was added drop-wise to a stirred solution of benzaldehyde (2.12 g, 20 mM) and chloroform (3.5 mL, 44 mM) in DMF (15 mL) at -10 °C under an inert atmosphere. After 1 h stirring at the room temperature the reaction mixture was treated with a 1N HCl solution (4 mL) and then diluted in toluene (4 mL). Then the mixture was allowed to warm to room temperature over 30 min, organic phase was collected and washed with water (2 x 4 mL) stirred with active charcoal for 10 min and filtered through celite, then successively washed with a 5% $NaHCO_3$ solution (4 mL) and water (4 mL). Then organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was purified by column chromatography.



Yield: 92% (3.25 g)

IR (neat): ν 3377 cm^{-1}

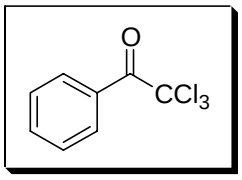
^{1}H NMR (400 MHz): δ 3.28 (d, 1H, J = 4.0 Hz), 5.22 (d, 1H, J = 4.0 Hz), 7.36-7.47 (m, 3H), 7.59-7.68 (m, 2H)

^{13}C NMR (50 MHz): δ 84.44, 103.00, 127.84, 129.22, 129.49, 134.90

2,2,2-Trichloro-1-phenylethanone (166b):

This molecule was prepared according to the reported procedure.[150]

A solution of sodium dichromate dihydrate (2.98 g, 10 mM) and concentrated sulphuric acid (1 mL) in glacial acetic acid (20 mL) was added drop-wise to a stirred solution of racemic (±)-2,2,2-trichloro-1-phenylethanol [(±)-**167b**] (2.25 g, 10 mM) in glacial acetic acid (20 mL). After stirring for 1 h at room temperature, 2-propanol (3 mL) was added and stirred for 10 min. Then a saturated NaCl solution (50 mL) was added to the mixture and was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained was purified by column chromatography.



Yield: 73% (1.64 g)

IR (neat): ν 1712 cm^{-1}

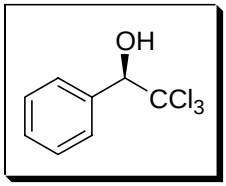
^{1}H NMR (400 MHz): δ 7.45-7.56 (m, 2H), 7.59-7.68 (m, 1H,), 8.26 (d, 2H, J = 7.8 Hz)

^{13}C NMR (50 MHz): δ 95.55, 128.47, 129.32, 131.53, 134.27, 181.33

(*R*)-2,2,2-Trichloro-1-phenylethanol [(*R*)-167b]:

This molecule was prepared *via* the asymmetric reduction of 2,2,2-trichloro-1-phenylethanone (**166b**) with BH_3.SMe_2 in the presence of 1 mol% (2*S*,5*S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), following the similar procedure described for the molecule (*S*)-**161a**.

Yield: 83%



$[\alpha]_D^{25}$: -14.04 (*c* 1.22, $CHCl_3$)

[Lit.[150] $[\alpha]_D^{25}$: -36.0 (*c* 1.00, $CHCl_3$), (*R*)-configuration, >98% *ee*]

Enantiomeric purity: 39% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to the racemic alcohol (±)-**167b**]

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

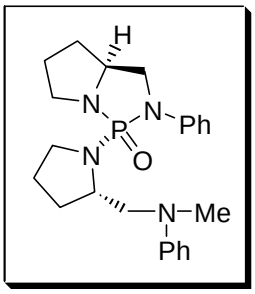
Determination of enantiomeric purity:

The racemic alcohol (±)-**167b** showed two peaks at 8.28 min (*R*) and 11.36 min (*S*) in 1:1 ratio on HPLC analysis using chiral column, Chiralcel-ODH [solvent system, hexanes:IPA (90:10); flow rate: 1 mL/min]. The chiral alcohol (*R*)-**167b** showed two peaks at 8.23 min (*R*) and 11.31 min (*S*) in the ratio of 69.5:30.5 on similar HPLC analysis, indicating that its enantiomeric purity is 39%.

(2*S*,5*S*)-2-[(2*S*)-2-(*N*-Methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (168):

To a stirred solution of (2*S,5S*)-2-[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**156**), (0.198 g, 0.5 mM) in ethanol (2 mL) were added potassium carbonate (0.138 g, 1.0 mM) and methyl iodide (0.284 g, 2.0 mM) at room temperature. After 24 h (monitored by TLC) the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (10 mL). 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 (silica gel, 60% ethyl acetate in hexanes) to afford the desired (2*S*,5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**) as a white solid (0.863 g) in 77% yield this solid was recrystalized from ethyl acetate to afford crystalline solid.



Mp: 102-104 °C

$[\alpha]_D^{25}$: -53.92 (*c* 0.95, $CHCl_3$)

IR (KBr): ν 2947, 2878, 1599, 1359, 1298, 1228 cm^{-1}

^1H NMR (400 MHz): δ 1.47-1.95 (m, 6H), 1.97-2.14 (m, 2H), 2.88-3.15 (m, 6H), 3.29-3.45 (m, 2H), 3.66-3.92 (m, 5H), 6.64-6.71 (m, 1H), 6.76-6.83 (m, 2H), 6.90-7.01 (m, 1H), 7.12-7.35 (m, 6H)

^{13}C NMR (50 MHz): δ 24.22 (d, *J* = 7.3 Hz), 26.08, 29.93 (d, *J* = 6.0 Hz), 32.27, 39.71, 45.61, 46.82, 48.80 (d, *J* = 15.8 Hz), 56.09, 56.50, 58.10 (d, *J* = 7.3 Hz), 111.64, 115.81, 116.76, 121.29, 128.96, 129.18, 141.93, 149.26

^{31}P NMR: δ 21.48

MS (*m/z*): 411 $(M + H)^+$, 433 $(M + Na)^+$

Analysis calcd. for $C_{23}H_{31}N_4OP$: C, 67.30; H, 7.61; N, 13.65

Found: C, 67.30; H, 7.62; N, 13.60

{Spectral data (IR, ^{1}H, ^{13}C) of the chiral alcohols 161a-161g, 164a, 164e, 164i appearing henceforth, obtained by reduction using various catalysts 114A, 168-170, 177, 177A, 178, 178A, 181 were in full agreement with spectral data of the chiral alcohols presented so far. Therefore we have only mentioned their optical rotations and type of analysis}.

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a] (with catalyst 168):

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (**160a**) with BH_3**.**SMe_2 in the presence of 1 mol% (2*S,*5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **156**.

Yield: 85%

$[\alpha]_D^{25}$: +26.9 (*c* 0.98, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 61% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**, following the similar analysis as described in pages 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 168):

This molecule was prepared *via* the borane-mediated reduction of phenacyl chloride (**160b**) under the catalytic influence of (2*S,*5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane (**168**) (1 mol%), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **156**.

Yield: 89%

$[\alpha]_D^{25}$: +36.80 (*c* 1.00, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 74% [determined following the similar HPLC analysis as described in page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 168):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with $BH_3.SMe_2$ under the influence of 1 mol% (2*S,*5*S*)-2-[(2*S*)-2-(*N*-methylanilinomethyl)pyrrolidin-1-yl]-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octane (**168**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **156**.

Yield: 79%

$[\alpha]_D^{25}$: +22.4 (*c* 1.09, MeOH)

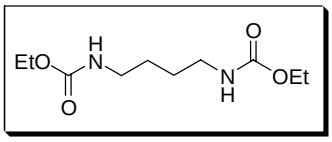
[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 47% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**, following the similar analysis as described in page122]

***N,N'*-Di(ethoxycarbonyl)-1,4-diaminobutane (172):**

To the stirred aq. solution of NaOH [(9.4 g, 235 mM, of NaOH) in 45 mL of water], was added 1,4-diaminobutane (4.4 g, 50 mM) and the resulting mixture was stirred at 0 °C for 10 min. A solution of ethyl chloroformate (9.56 mL, 100 mM) in benzene (45 mL) was added drop-wise over a period of 30 min at 0 °C. The mixture was allowed to warm to room temperature and stirring continued at room temperature for another 2 h. The organic layer was separated and dried over anhydrous Na_2SO_4. Solvent was evaporated to obtain the desired *N,N'*-di(ethoxycarbonyl)-1,4-diaminobutane (**172**) as a white solid.

Yeild: 80% (9.28 g)



Mp: 60-62 °C

IR (KBr): ν 3337, 1685 cm^{-1}

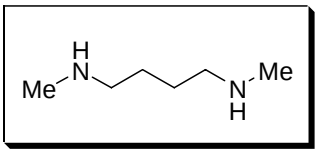
^{1}H NMR (400 MHz): δ 1.23 (t, 6H, J = 6.8 Hz), 1.48-1.62 (m, 4H), 3.09-3.25 (m, 4H), 4.10 (q, 4H, J = 6.8 Hz), 4.81 (b, 2H)

^{13}C NMR (50 MHz): δ 14.51, 27.10, 40.39, 60.48, 156.76

***N,N'*-Dimethyl-1,4-diaminobutane (171):**

To a stirred suspension of LAH (7.6 g, 200 mM) in THF (200 mL) was added *N,N'*-di(ethoxycarbonyl)-1,4-diaminobutane (**172**) (5.8 g, 25 mM) in small portions (using solid addition flask) at 0 °C. Reaction mixture was allowed to warm to room temperature and stirring continued for another 1 h. The reaction mixture was then heated under reflux for 16 h (monitored by TLC). Reaction mixture was cooled to 0 °C, and ice cold water (6 mL)

was carefully added drop-wise, followed by successive addition of 15% NaOH (6 mL) and water (20 mL), and stirring continued for another 1 h at room temperature. The resulting white precipitate (aluminum salts) was filtered and rinsed with warm THF (3 x 50 mL). The filtrates were combined and the solvent was evaporated under reduced pressure. The residue was acidified with 10% HCl to pH~2 and washed with dichloromethane (3 x 50 mL). This acidic aqueous layer was treated with 10% NaOH until basic pH~10, and then extracted with dichloromethane (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude oil was distilled under vacuum to provide *N,N′*-dimethyl-1,4-diaminobutane (**171**) as a colorless liquid.



Yield: 68% (1.9 g)

IR (neat): ν 3281, 1114 cm^{-1}

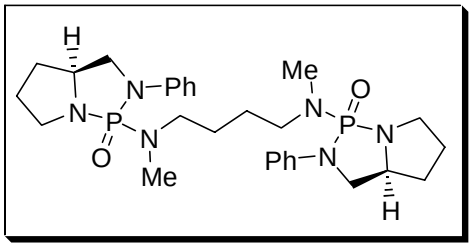
^{1}H NMR (400 MHz): δ 1.35-1.62 (m, 6H), 2.42 (s, 6H), 2.53-2.67 (m, 4H)

^{13}C NMR (50 MHz): δ 27.29, 36.10, 51.65

1,4-Bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethyl-amino]butane (169):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane (**114**) (0.563 g, 2.2 mM) in THF (10 mL) were added triethylamine (0.202 g, 2 mM) and *N,N′*-dimethyl-1,4-diaminobutane (**171**) (0.116 g, 1.0 mM) at room

temperature. After 3 h (monitored by TLC) the reaction mixture was filtered to remove salts and the solvent was removed and the residue, thus obtained, was purified by column chromatography (silica gel, 2% MeOH in ethyl acetate) to afford the desired 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) as viscous liquid.



Yeild: 55.7% (0.345 g)

$[\alpha]_D^{25}$: +20.0 (*c* 1.67, $CHCl_3$)

IR (neat): ν 3429, 1602, 1500, 1300, 1213 cm^{-1}

^1H NMR (400 MHz): δ 1.31-1.47 (m, 4H), 1.61-1.74 (m, 2H), 1.79-1.91 (m, 2H), 1.96-2.09 (m, 4H), 2.50 (s, 3H), 2.53 (s, 3H), 2.76-2.94 (m, 4H), 3.05-3.18 (m, 2H), 3.32-3.43 (m, 2H), 3.60-3.86 (m, 6H), 6.88-6.96 (m, 2H), 7.04 (d, 4H, 7.8 Hz), 7.21- 7.29 (m, 4H)

^{13}C NMR (50 MHz): δ 24.97, 26.08, 32.22, 32.73, 45.08, 48.37, 48.86 (d, J = 17.0 Hz), 57.86 (d, J = 7.3 Hz), 115.91, 120.61, 128.88, 141.91

^{31}P NMR: δ 23.20

LCMS (m/z): 557 $(M+H)^+$

Analysis calcd. for $C_{28}H_{42}N_6O_2P_2$: C, 60.42; H, 7.61; N, 15.10

Found: C, 60.54; H, 7.60; N, 15.07

Asymmetric reduction of phenacyl bromide (160a) using 10 mol% 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (169):

To a stirred solution of 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octan-2-ylmethylamino]butane (**169**) (1.0 mL, 0.1 M standard solution in toluene) in toluene (1 mL) was added borane-dimethyl sulfide solution of toluene (1 mL, 1 M standard solution in toluene) at room temperature and the reaction mixture was heated to 110 °C. And once the temperature has stabilized at 110 °C, phenacyl bromide (**160a**) (0.199 g, 1.0 mM) in toluene (2 mL) was added drop-wise over a period of 10 min and stirring 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 (2 mL). 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*)-**161a**] as colorless oil.

Yield: 86%

$[\alpha]_D^{25}$: + 39.59 (*c* 1.17, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 90% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a** following the similar analysis as described in page 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 169):

This molecule was prepared *via* the borane-mediated asymmetric reduction of phenacyl chloride (**160b**) under the catalytic influence of 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) (10 mol%)**,** following the similar procedure described for the molecule (*S*)-**161a** in page 144.

Yield: 88%

$[\alpha]_D^{25}$: +40.00 (*c* 0.91, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 83% [determined following the similar HPLC analysis as described in page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-161e] (with catalyst 169):

This molecule was obtained *via* borane-mediated reduction of 4-bromophenacyl bromide (**160e**) using BH_3**.**SMe_2, in the presence of 10 mol% 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**) as a white solid, following the similar procedure described for the molecule (*S*)-**161a** [page 144].

Yield: 84 %

Mp: 71-72 °C

$[\alpha]_D^{25}$: +30.4 (*c* 0.99, $CHCl_3$)

[Lit.[148] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*]

Enantiomeric purity: 89% [determined *via* HPLC analysis using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161e**, following the similar analysis as described in page 114]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 169):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3**.**SMe_2 under the influence of 10 mol% 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**), following the similar procedure described for the molecule (*S*)-**161a** [page 144].

Yield: 79 %

$[\alpha]_D^{25}$: +31.62 (*c* 0.95, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 70% [determined following the similar HPLC analysis as described in page 122 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**].

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-164e] (with catalyst 169):

This molecule was obtained by borane-mediated asymmetric reduction of 4-bromomethylacetophenone (**163e**) in the presence 10 mol% 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**), as a colorless

liquid, following the similar procedure described for the molecule (*S*)-**161a** [page 144].

Yield: 80 %

$[\alpha]_D^{25}$: +30.40 (*c* 0.95, $CHCl_3$)

[Lit.[152] $[\alpha]_D^{23}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*]

Enantiomeric purity: 77% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164e**, following the similar analysis as in the case of (*R*)-**164e** [page 126]

(*R*)-1-(Naphth-2-yl)ethanol [(*R*)-164i] (with catalyst 169):

This molecule was obtained by the asymmetric reduction of 2-acetylnaphthalene (**163i**) with $BH_3.SMe_2$ under the influence of 10 mol% 1,4-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]butane (**169**), as a white solid, following the similar procedure described for the molecule (*S*)-**161a** [page 144].

Yield: 92 %

Mp: 67-69 °C

$[\alpha]_D^{25}$: +25.01 (*c* 0.94, EtOH)

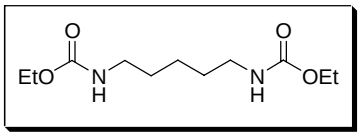
[Lit.[154] $[\alpha]_D^{25}$: -34.3 (*c* 1.10, EtOH), (*S*)-configuration, 86% *ee*]

Enantiomeric purity: 60% [determined by HPLC analysis of alcohol using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**164i**, following the similar analysis as described in page 131]

***N,N'*-Di(ethoxycarbonyl)-1,5-diaminopentane (174):**

To a stirred solution of NaOH (7.5 g, 189 mM) in water (40 mL) at 0 °C was added 1,5-diaminopentane (4.0 g, 40 mM) and the resulting mixture was stirred for 10 min. A solution of ethyl chloroformate (7.64 mL, 80 mM) in benzene (40 mL) was added over a period of 30 min at 0 °C. The mixture was then stirred at room temperature for 2 h. Organic layer was separated, dried over anhydrous Na_2SO_4. Solvent was evaporated to provide the desired *N,N'*-di(ethoxycarbonyl)-1,5-diaminopentane (**174**) as a white solid.

Yeild: 76% (3.04 g)



Mp: 92-94 °C

IR (KBr): ν 3341, 1685, 1541 cm^{-1}

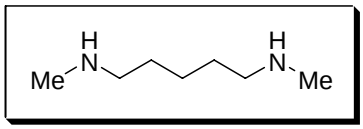
^{1}H NMR (400 MHz): δ 1.23 (t, 6H, J = 6.8 Hz), 1.29-1.42 (m, 2H), 1.46-1.56 (m, 4H), 3.07-3.26 (m, 4H), 4.10 (q, 4H, J = 6.8 Hz), 4.70 (b, 2H)

^{13}C NMR (50 MHz): δ 14.51, 23.61, 29.45, 40.54, 60.43, 156.76

***N,N'*-Dimethyl-1,5-diaminopentane (173):**

To a stirred suspension of LAH (7.6 g, 200 mM) in THF (200 mL) was added *N,N'*-di(ethoxycarbonyl)-1,5-diaminobutane (**174**) (6.15 g, 25 mM) portion wise at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was heated under reflux for 16 h. The resulting gray suspension was cooled to 0 °C, 15% NaOH (6 mL) and water (20 mL) were successively added, and stirring was continued for 1 h at room temperature. The resulting white precipitate (aluminum salts) was filtered off and rinsed with warm THF (3 x

50 mL). The filtrates were combined and the solvent was evaporated under reduced pressure. The residue was acidified 10% HCl (pH~2) and extracted with dichloromethane (3 x 50 mL). The aqueous layer was treated with NaOH (10%) until basic pH (pH~10) and then extracted with dichloromethane (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and distilled under reduced pressure to provide *N,N*′-dimethyl-1,5-diaminopentane (**173**) as a colorless liquid.



Yeild: 64% (3.94 g)

IR (neat): ν 3306, 1473, 1122 cm^{-1}

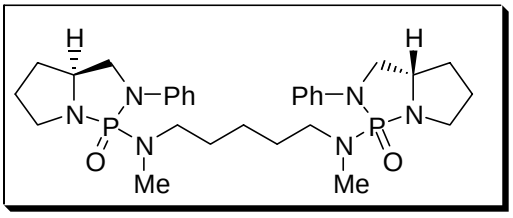
^{1}H NMR (400 MHz): δ 1.08-1.25 (b, 2H), 1.30-1.43 (m, 2H), 1.45-1.57 (m, 4H), 2.42 (s, 6H), 2.56 (t, 4H, J = 6.8 Hz)

^{13}C NMR (50 MHz): δ 24.77, 29.58, 36.25, 51.82

1,5-Bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethyl-amino]pentane (170):

To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane (**114**) (0.563 g, 2.2 mM) in THF (10 mL) were added triethylamine (0.202 g, 2 mM) and *N,N*′-dimethyl-1,5-diaminopentane (**173**) (0.130 g, 1.0 mM) at room temperature. After 3 h (monitored by TLC) the reaction mixture was filtered to remove salts and the solvent was removed under reduced pressure. Residue, thus obtained, was purified by column chromatography (silica gel, 2% MeOH in ethyl acetate) to afford the

desired 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethyl-amino]pentane (**170**) as a viscous liquid.



Yeild: 49%

$[\alpha]_D^{25}$: -22.60 (*c* 1.56, $CHCl_3$)

IR (neat): ν 3449, 2922, 1738, 1601, 1502 cm^{-1}

^1H NMR (400 MHz): δ 1.07-1.20 (m, 2H), 1.26-1.48 (m, 4H), 1.57-1.70 (m, 2H), 1.75-1.89 (m, 2H), 1.91-2.06 (m, 4H), 2.49 (s, 3H), 2.52 (s, 3H), 2.71-2.93 (m, 4H), 2.98-3.12 (m, 2H), 3.28-3.39 (m, 2H), 3.57-3.83 (m, 6H), 6.85-6.93 (m, 2H), 7.01 (d, 4H, *J* = 8.8 Hz), 7.18- 7.26 (m, 4H)

^{13}C NMR (50 MHz): δ 23.66, 25.96, 27.59, 32.07, 32.79 (d, *J* = 3.64 Hz), 44.95, 48.54, 48.71 (d, *J* = 17 Hz),* 57.76 (d, *J* = 7.3 Hz), 115.80 (d, *J* = 3.6 Hz), 120.52, 128.74, 141.86 (d, *J*= 4.9 Hz)

[*It looks one of the pyrrolidine ring carbon doublet merging with *N*-methyl carbon peak and appears as two singlets]

^{31}P NMR: δ 23.10

LCMS (m/z): 571 $(M+H)^+$

Analysis calcd. for $C_{29}H_{44}N_6O_2P_2$: C, 61.04; H, 7.77; N, 14.73

Found: C, 61.26; H, 7.77; N, 14.48

Asymmetric reduction of phenacyl bromide (160a) using 10 mol% 1,5-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (170):

To a stirred solution of 1,5-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)-octan-2-ylmethylamino]pentane (**170**) (1.0 mL, 0.1 M standard solution in toluene) in toluene (1 mL) was added borane-dimethyl sulfide solution of toluene (1 mL, 1 M standard solution in toluene) at room temperature and the reaction mixture was heated to 110 °C. And once the temperature has stabilized at 110 °C, phenacyl bromide (**160a**) (0.199 g, 1.0 mM) in toluene (2 mL) was added drop-wise over a period of 10 min and stirring 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 (2 mL). 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*)-**161a**] as colorless oil.

Yield: 86%

$[\alpha]_D^{25}$: +37.6 (*c* 0.99, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 89% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**, following the similar analysis as described in pages 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 170):

This molecule was prepared *via* the borane-mediated asymmetric reduction of phenacyl chloride (**160b**) in the presence of 10 mol%, 1,5-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**), following the similar procedure described for the molecule (*S*)-**161a** [page 151].

Yield: 82 %

$[\alpha]_D^{25}$: +38.6 (*c* 1.04, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 78% [determined following the similar HPLC analysis as described in page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 170):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3**.**SMe_2 under the catalytic influence of 10 mol% 1,5-bis-[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octan-2-ylmethylamino]pentane (**170**), following the similar procedure described for the molecule (*S*)-**161a** [page 151].

Yield: 80 %

$[\alpha]_D^{25}$: +33.8 (*c* 1.03, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 74% [determined following the similar HPLC analysis as described in page 122 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**]

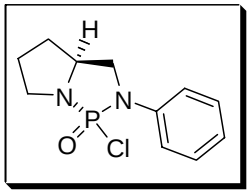
(2*S*,5*S*) and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenybicyclo(3.3.0) octanes (114 and 114A):

To the stirred solution of (2*S*)-2-anilinomethylpyrrolidine (**159**) (1.058 g, 6 mM) and triethylamine (1.214 g, 12 mM) in toluene (20 mL) at 110 °C was added phosphorusoxy chloride (0.920 g, 6 mM). After stirring at the same temperature for 2 h (monitored by TLC), the reaction mixture was cooled to room temperature and filtered to remove the salts. The filtrate was concentrated in *vacuo* and the residue, thus obtained, was purified by column chromatography (silica gel, 15% ethyl acetate in hexanes) to afford less polar (26%) (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane **114A**, and more polar (38%) (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)-octane **114**. (***The spectral data for the molecule* 114 *has been presented in pages* 104-105**).

(2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (114A):

Mp: 126-128 °C (lit.[143] 130 °C)

$[\alpha]_D^{25}$: -145.6 (*c* 1.04, $CHCl_3$)



IR (KBr): ν 2970, 1602, 1502, 1265, 1118 cm^{-1}

^1H NMR (200 MHz): δ 1.61-2.26 (m, 4H), 3.11-3.32 (m, 1H), 3.46-3.65 (m, 1H), 3.70-4.00 (m, 3H), 7.05-7.16 (m, 1H), 7.21-7.45 (m, 4H)

^{13}C NMR (50 MHz): δ 26.03 (d, J = 4.9 Hz), 32.29, 45.78, 47.93 (d, J = 15.8 Hz), 57.07 (d, J = 10.9 Hz), 117.39 (d, J = 4.9 Hz), 123.06, 129.35, 139.84 (d, J = 3.6 Hz)

^{31}P NMR: δ 25.32

LCMS (m/z): 257 $(M + H)^+$, 259 $(M + 2 + H)^+$

Analysis calcd for $C_{11}H_{14}N_2OPCl$: C, 51.47; H, 5.50; N, 10.91

Found: C, 51.51; H, 5.56; N, 10.80

Asymmetric reduction of phenacyl bromide (160a) using the catalyst 114A, Synthesis of (*S*)-2-Bromo-1-phenylethanol [(*S*)-161a]:

To a stirred solution of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane (**114A**) (0.0128 g, 0.05 mM) in toluene (3 mL) was added borane-dimethyl sulfide (0.076 g, 1.0 mM) at room temperature and the reaction mixture was heated to 110 °C. Once the temperature has stabilized at 110 °C, phenacyl bromide (**160a**) (0.199 g, 1.0 mM) in toluene (2 mL) was added drop-wise over 10 min and stirring 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 (2 mL). 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*)-**161a**] as colorless oil.

Yield: 91%

$[\alpha]_D^{25}$: +33.5 (*c* 1.21, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 84% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**, following the similar analysis as mentioned in the pages107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 114A):

This molecule was obtained as a colorless liquid *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of 5 mol% (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114A**) following the similar procedure described for the molecule (*S*)-**161a** in pages 154-155.

Yield: 88%

$[\alpha]_D^{25}$: +34.00 (*c* 0.90, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 75% [determined following the similar HPLC analysis mentioned in the page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 114A):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane (**114A**), following the similar procedure described for the molecule (*S*)-**161a in** pages 154-155.

Yield: 82%

IR (neat): ν 3408 cm^{-1}

$[\alpha]_D^{25}$: +28.06 (*c* 0.95, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

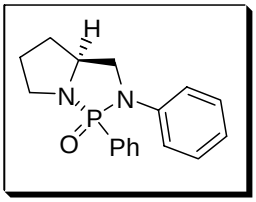
Enantiomeric purity: 66% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**, following the similar analysis as mentioned in the page 122]

(2*S*,5*S*) and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes (177 and 177A):

To a stirred solution of (2*S*)-2-anilinomethylpyrrolidine (**159**) (0.705 g, 4 mM) and triethylamine (0.809 g, 8 mM) in CH_2Cl_2 (10 mL) at room temperature was added phenylphosphonicdichloride (**179**) (0.780 g, 4 mM) drop-wise. After 12 h stirring at room temperature (monitored by TLC) the reaction mixture was filtered to remove the salts. The solvent, from the filtrate, was removed in *vacuo* and the residue, thus obtained, was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford less polar

(2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (**177**) and more polar (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (**177A**). The molecules **177** & **177A** are known in the literature.[157] However, their spectral data were not reported.

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (177):



Yield: 33%

Mp: 162-164 °C

$[\alpha]_D^{25}$: -31.4 (*c* 1.02, $CHCl_3$)

IR(KBr): ν 2964, 1602, 1506, 1261, 1103 cm^{-1}

^1H NMR (200 MHz): δ 1.70-2.28 (m, 4H), 2.85-3.10 (m, 1H), 3.48-3.63 (m, 1H), 3.72-4.17 (m, 3H), 6.78-6.94 (m, 1H), 7.00-7.57 (m, 7H), 7.71-7.94 (m, 2H)

^{13}C NMR (100 MHz): δ 26.39, 32.19, 44.69, 49.19 (d, J = 14.3 Hz), 59.31 (d, J = 5.0 Hz), 116.20 (d, J = 4.0 Hz), 121.00, 128.28 (d, J = 14.5 Hz), 128.93, 131.39, 131.70 (d, J = 9.5 Hz), 133.15 (d, J = 165.8 Hz), 141.68 (d, J = 6.0 Hz)

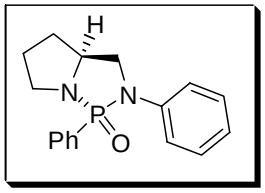
^{31}P NMR: δ 26.59

LCMS (m/z): 299 $(M + H)^+$

Analysis calcd. for $C_{11}H_{14}ClN_2OP$: C, 68.44; H, 6.42; N, 9.39

Found: C, 68.51; H, 6.40; N, 9.47

(2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (177A):



Yield: 47%

Mp: 164-165 °C

$[\alpha]_D^{25}$: +107.6 (*c* 0.98, $CHCl_3$)

IR(KBr): ν 2972, 1601, 1500, 1234, 1122 cm^{-1}

^{1}H NMR (400 MHz): δ 1.61-2.02 (m, 3H), 2.16-2.27 (m, 1H), 2.81-2.94 (m, 1H), 3.08-3.17 (m, 1H), 3.56-3.66 (m, 1H), 4.03-4.13 (m, 1H), 4.24-4.38 (m, 1H), 6.81-6.90 (m, 1H), 7.11-7.22 (m, 4H), 7.39-7.54 (m, 3H), 7.65-7.76 (m, 2H)

^{13}C NMR (50 MHz): δ 26.75 (d, *J* = 6.1 Hz), 31.48 (d, *J* = 3.6 Hz), 44.15 (d, *J* = 7.3 Hz), 54.10 (d, *J* = 9.7 Hz), 57.77 (d, *J* = 9.7 Hz), 115.66 (d, *J* = 4.9 Hz), 120.52, 128.45 (d, *J* = 14.6 Hz), 128.74, 129.12 (d, *J* = 149.2 Hz), 131.75, 132.46 (d, *J* = 10.9 Hz), 142.13 (d, *J* = 7.3 Hz)

^{31}P NMR: δ 21.36

LCMS (*m/z*): 299 $(M + H)^+$

Analysis calcd. for $C_{11}H_{14}ClN_2OP$: C, 68.44; H, 6.42; N, 9.39

Found: C, 68.58; H, 6.41; N, 9.29

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a] (with catalyst 177):

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (**160a**) with

BH_3**.**SMe_2 in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenyl-bicyclo(3.3.0)octane (**177**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 92%

$[\alpha]_D^{25}$: +36.5 (*c* 1.02, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*]

Enantiomeric purity: 83% [determined following similar HPLC analysis as mentioned in pages 107-108 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 177):

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenyl-bicyclo(3.3.0)octane (**177**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 90%

$[\alpha]_D^{25}$: +38.52 (*c* 1.01, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 76% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**, following the similar analysis as mentioned in page 109]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 177):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3.SMe_2 in the presence of 5 mol% (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (**177**) following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in page 154-155.

Yield: 79%

$[\alpha]_D^{25}$: +29.24 (*c* 0.99, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 65% [determined following the similar HPLC analysis mentioned in the page 122 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**]

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a] (with catalyst 177A):

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (**160a**) with BH_3.SMe_2 in the presence of 5 mol% of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenyl-

bicyclo(3.3.0)octane (**177A**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 89%

$[\alpha]_D^{25}$: +36.6 (*c* 0.99, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 84% [determined following similar HPLC analysis as mentioned in the pages 107-108 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 177A):

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of 5 mol% of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenyl-bicyclo(3.3.0)octane (**177A**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 88%

$[\alpha]_D^{25}$: +29.79 (*c* 0.97, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 79% [determined by similar HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**, following the similar analysis as mentioned in the page 109]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 177A):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3**.**SMe_2 in the presence of 5 mol% of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane (**177A**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 83%

$[\alpha]_D^{25}$: +28.94 (*c* 1.08, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

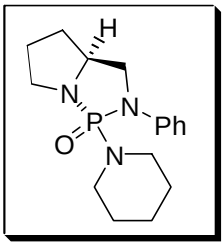
Enantiomeric purity: 62% [determined following similar HPLC analysis mentioned in page 122 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**]

(2*S*,5*S*) and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo-(3.3.0)octanes (178 and 178A):

To a stirred solution of (2*S*)-2-anilinomethylpyrrolidine (**159**) (0.352 g, 2 mM) and triethylamine (0.404 g, 4 mM) in toluene (10 mL) at room temperature was added *N*-(dichlorophosphinyl)piperidine (**180**) (0.505 g, 2.5 mM) slowly. After stirring for 2 h at the same temperature (monitored by TLC) the reaction mixture was filtered to remove the salts. The solvent from the filtrate was removed in *vacuo* and the residue, thus obtained, was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford less

polar (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178**) and more polar (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenyl-bicyclo(3.3.0)octane (**178A**). The molecules **178** & **178A** were reported in the literature.[158]

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (178):



Yield: 24%

Mp: 108-110 °C [lit.[158] 117.6-118.3 °C]

$[\alpha]_D^{25}$: -21.2 (*c* 0.84, $CHCl_3$)

[lit.[158] $[\alpha]_D^{25}$: -21.8 (*c* 1.10, $CHCl_3$)]

IR(KBr): ν 2932, 1601, 1502, 1226, 1122 cm^{-1}

^{1}H NMR (400 MHz): δ 1.20-2.15 (m, 10H), 2.82-3.15 (m, 5H), 3.32-3.47 (m, 1H), 3.60-3.90 (m, 3H), 6.85-6.97 (m, 1H), 7.02-7.18 (m, 2H), 7.20-7.36 (m, 2H)

^{13}C NMR (100 MHz): δ 24.53, 25.99 (d, *J* = 3.9 Hz),* 32.10, 44.92, 44.99, 48.78 (d, *J* = 16.5 Hz), 57.83 (d, *J* = 7.7 Hz), 116.06 (d, *J* = 5.0 Hz), 120.54, 128.77, 142.02 (d, *J* = 6.8 Hz)

[* It looks that one of the pyrrolidine ring carbon and two of the piperidine ring carbons (*β*-to nitrogen) might be merging and appearing as a doublet at δ 25.99 (total three carbons)]

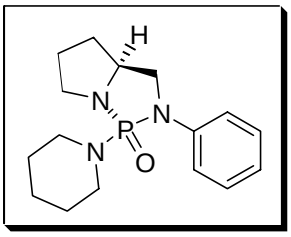
^{31}P NMR: δ 21.00

LCMS (m/z): 306 $(M + H)^+$

Analysis calcd. for $C_{11}H_{14}ClN_2OP$: C, 62.93; H, 7.92; N, 13.76

Found: C, 62.92; H, 8.00; N, 13.65

(2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (178A):



Yield: 33%

Mp: 119-121 °C [lit.[158] 128.5-130.3 °C]

$[\alpha]_D^{25}$: +64.9 (*c* 1.55, $CHCl_3$)

[lit.[158] $[\alpha]_D^{25}$: +66.5 (*c* 1.91, $CHCl_3$)]

IR(KBr): ν 2932, 1599, 1494, 1234, 1122 cm^{-1}

^1H NMR (400 MHz): δ 1.15-2.33 (m, 10H), 2.85-3.47 (m, 7H), 3.62-3.80 (m, 1H), 3.96-4.18 (m, 1H), 6.82-7.00 (m, 1H), 7.09-7.40 (m, 4H)

^{13}C NMR (50 MHz): δ 24.51, 26.18 (d, *J* = 4.9 Hz), 27.48 (d, *J* = 6.1 Hz), 31.64 (d, *J* = 4.9 Hz), 43.79 (d, *J* = 4.9 Hz), 45.46, 52.99 (d, *J* = 12.1 Hz), 56.45 (d, *J* = 13.3 Hz), 115.55 (d, *J* = 4.9 Hz), 120.30, 129.01, 142.89 (d, *J* = 6.1 Hz)

^{31}P NMR: δ 15.34

LCMS (m/z): 306 $(M + H)^+$

Analysis calcd. for $C_{11}H_{14}ClN_2OP$: C, 62.93; H, 7.92; N, 13.76

Found: C, 63.00; H, 7.90; N, 13.88

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a] (with catalyst 178):

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (**160a**) with BH_3**.**SMe_2 in the presence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178**) 5 mol%, following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 80%

$[\alpha]_D^{25}$: +36.07 (*c* 0.93, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 81% [determined by HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**. following the similar analysis as mentioned in the pages 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 178):

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178**) 5 mol%, following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 85%

$[\alpha]_D^{25}$: +37.15 (*c* 1.09, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.10 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 78% [determined by similar HPLC analysis using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**], following the similar analysis as mentioned in page 109]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 178):

This compound was obtained as a colorless liquid by the reduction of acetophenone (**163a**) with BH_3**.**SMe_2 under the catalytic (5 mol%) influence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178**), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 84%

$[\alpha]_D^{25}$: +27.16 (*c* 1.0, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.12 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*].

Enantiomeric purity: 59% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**, following the similar analysis as mentioned in the page 122].

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a](with catalyst 178A):

This molecule was prepared *via* the asymmetric reduction of phenacyl bromide (**160a**) with BH_3**.**SMe_2 in the presence of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178A**) 5 mol%, following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 91%

$[\alpha]_D^{25}$: +34.9 (*c* 0.86, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 79% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**, following the similar analysis as mentioned in the pages 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 178A):

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178A**) 5 mol%, following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 85%

$[\alpha]_D^{25}$: +37.1 (*c* 1.35, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 73% [determined following the similar HPLC analysis mentioned in page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*R*)-1-Phenylethanol [(*R*)-164a] (with catalyst 178A):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3**.**SMe_2 in the presence of (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-(piperidin-1-yl)-3-phenylbicyclo(3.3.0)octane (**178A**) 5 mol%, following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 81%

$[\alpha]_D^{25}$: +27.2 (*c* 0.98, MeOH)

[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 64% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**, following the similar analysis as mentioned in page 122]

(*S*)-2-Bromo-1-phenylethanol [(*S*)-161a] using 2.5 mol% 178 + 2.5 mol% 178A:

This molecule was obtained as a colorless liquid by the borane-mediated asymmetric reduction of phenacyl bromide (**160a**) using 2.5 mol% **178** and 2.5 mol% **178A** (total 5 mol%), following the similar procedure described for the molecule (*S*)-**161a** using the chiral catalyst **114A** in pages 154-155.

Yield: 90%

$[\alpha]_D^{25}$: +36.4 (*c* 1.0, $CHCl_3$)

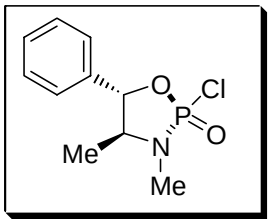
[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 82% [determined following the similar HPLC analysis as mentioned in pages 107-108 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a**]

(2*R*,4*S*,5*S*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (181):

This molecule was prepared following the literature procedure.[159]

To the stirred solution of (+)-pseudoephedrine (**188**) (1.65 g, 10 mM) and triethylamine (3.16 mL, 23 mM) in 50 mL of dry benzene was added phosphorusoxy chloride (0.93 mL, 10 mM) drop by drop. The mixture was stirred for 30 h at 50 °C (monitored by TLC) the salts were filtered. Filtrate was concentrated under reduced pressure. The residue thus obtained was purified by chromatography (silica gel 20% ethyl acetate in hexanes) to afford **181** as colorless oil.



Yield: 65%

IR (neat): ν 1626, 1454 cm^{-1}

$[\alpha]_D^{25}$: +11.96 (*c* 2.5, $CHCl_3$)

^{1}H NMR (400 MHz): δ 1.24 (d, 3H, *J* = 6.1 Hz), 2.68 (d, 3H, *J* = 14.8), 3.23-3.35 (m, 1H), 5.01 (dd, 1H, *J* = 9.3, Hz, *J* = 2.8 Hz,), 7.36-7.48 (m, 5H)

^{13}C NMR (50 MHz): δ 14.74 (d, *J* = 13.3 Hz), 28.58, 61.36 (d, *J* = 10.9 Hz), 87.38, 127.11, 128.91, 129.61, 135.46 (d, *J* = 7.2 Hz)

^{31}P NMR: δ 23.37

LCMS (m/z): 246 $(M + H)$,$^{+}$ 248 $(M + 2 + H)^{+}$

Analysis calcd. for $C_{28}H_{42}N_6O_2P_2$: C, 48.90; H, 5.33; N, 5.70

Found: C, 49.15; H, 5.37; N, 5.55

Asymmetric reduction of phenacyl bromide (160a) using 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (181):

To a stirred solution of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) (0.045 g, 0.1 mM) in toluene (3 mL) was added borane-dimethyl sulfide (0.076 g, 1.0 mM) at room temperature and the reaction mixture was heated to 110 °C. Once the temperature has stabilized at 110 °C, phenacyl bromide (**160a**) (0.199 g, 1.0 mM) in toluene (2 mL) was added drop-wise over a period of 10 min and stirring continued for further 60 min (monitored by TLC). Then the reaction mixture was allowed to cool to room temperature and quenched with methanol (2 mL). 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*)-**161a**] as colorless oil.

Yield: 84%

$[\alpha]_D^{25}$: +28.20 (*c* 1.10, $CHCl_3$)

[Lit.[144] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*]

Enantiomeric purity: 69% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161a]**, following the similar analysis as mentioned in pages 107-108]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-161b] (with catalyst 181):

This molecule was prepared *via* the asymmetric reduction of phenacyl chloride (**160b**) with BH_3**.**SMe_2 in the presence of 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as a viscous liquid following the representative procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 92%

$[\alpha]_D^{25}$: +33.60 (*c* 1.15, cyclohexane)

[Lit.[144] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*]

Enantiomeric purity: 66% [determined following the similar HPLC analysis mentioned in page 109 using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**161b**]

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-161c] (with catalyst 181):

This molecule was prepared *via* the asymmetric reduction of 4-methylphenacyl bromide (**160c**) with BH_3**.**SMe_2 in the presence of 10 mol% of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-

phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as a viscous liquid, following the similar procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 90%

$[\alpha]_D^{25}$: +29.81 (*c* 1.33, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +41.8 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 95% *ee*]

Enantiomeric purity: 68% [determined by HPLC using chiral column, Chiralcel-ODH with reference to racemic alcohol (±)-**161c**, following the similar analysis as mentioned in page 110]

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-161d] (with catalyst 181):

This molecule was prepared by the asymmetric reduction of 4-methylphenacyl chloride (**160d**) with $BH_3.SMe_2$ in the presence of 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as a colorless liquid, following the similar procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 91%

$[\alpha]_D^{25}$: +32.00 (*c* 1.4, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*]

Enantiomeric purity: 66% [determined following the similar HPLC analysis as mentioned in page 112 using chiral column, Chiralcel-ODH. with reference to racemic alcohol (±)-**161d**]

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-161e] (with catalyst 181):

This molecule was obtained *via* the asymmetric reduction of 4-bromophenacyl bromide (**160e**) with BH_3**.**SMe_2, in the presence of 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as a white solid, following the similar procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 87%

Mp: 69-71 °C [Lit.[148] 70-72 °C]

$[\alpha]_D^{25}$: +25.08 (*c* 1.10, $CHCl_3$)

[Lit.[148] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*]

Enantiomeric purity: 72% [determined by HPLC using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161e**, following the similar analysis as mentioned in page 114]

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-161f] (with catalyst 181):

This compound was obtained as a colorless liquid *via* the asymmetric reduction of 4-chlorophenacyl bromide (**160f**) with BH_3**.**SMe_2 in the presence of 10 mol% of (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**), following the similar procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 89 %

$[\alpha]_D^{25}$: +26.50 (*c* 1.20, $CHCl_3$)

[Lit.[113] $[\alpha]_D^{25}$: +38.6 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91% *ee*]

Enantiomeric purity: 67% [determined following the similar HPLC analysis as mentioned in page 116, using chiral column, Chiralcel-OJH, with reference to racemic alcohol (±)-**161f**]

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-161g] (with catalyst 181):

This compound was obtained *via* the asymmetric reduction of 4-nitrophenacyl bromide (**160g**) with BH_3**.**SMe_2 in the presence of 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) as a white solid, following the similar procedure described for the molecule (*S*)-**161a** [page 170].

Yield: 80%

Mp: 80-82 °C [Lit.[115] 78-80 °C]

$[\alpha]_D^{25}$: +24.01 (*c* 1.02, $CHCl_3$).

[Lit.[114] $[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*]

Enantiomeric purity: 72% [determined by converting (*S*)-**161g** into its acetate (*S*)-**162g** and following the similar HPLC analysis of this acetate, as described in page 118, using chiral column, Chiralcel-ODH, with reference to racemic acetate (±)-**162g**]

(*R*)-1-Phenylethanol [(*R*)-164a](with catalyst 181):

This compound was obtained as a colorless liquid by the asymmetric reduction of acetophenone (**163a**) with BH_3**.**SMe_2 in the presence of 10 mol% (2*R*,4*S*,5*S*)-2-chloro-3,4-

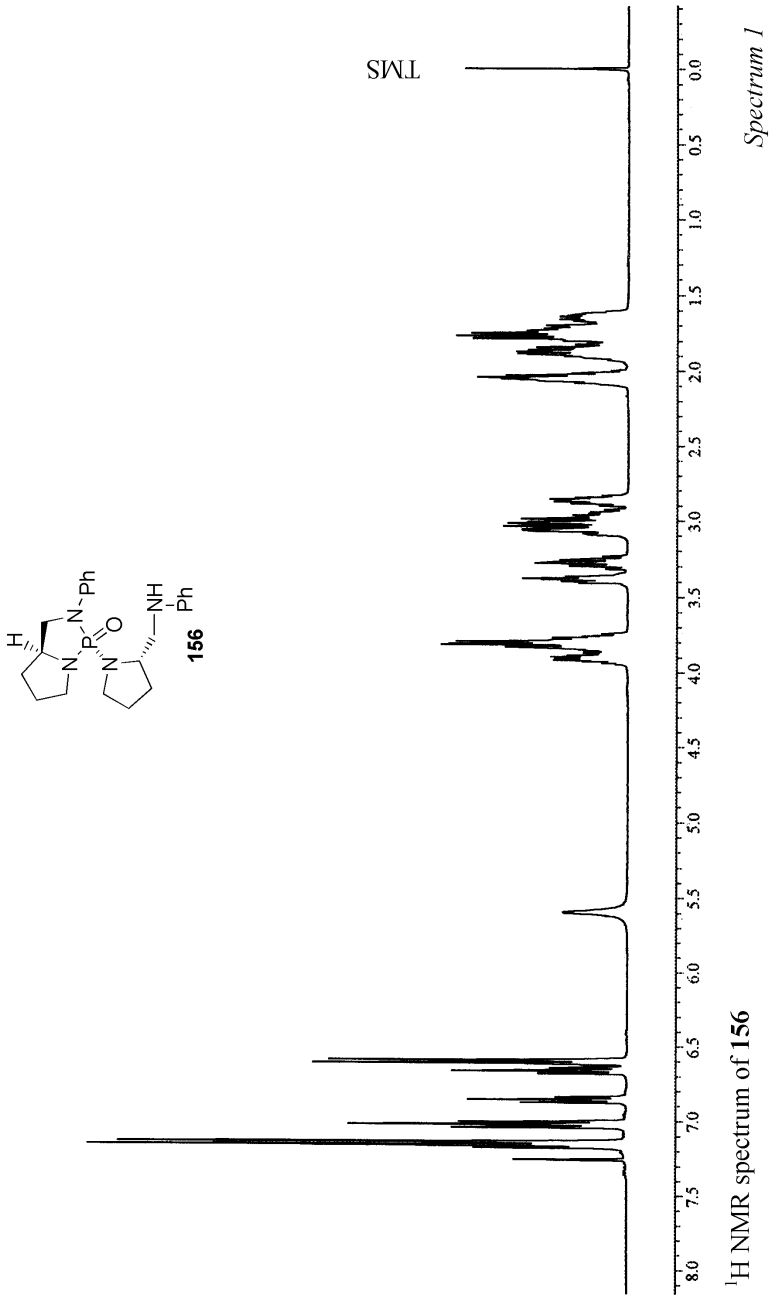
dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**181**) 10 mol%, following the similar procedure described for the molecule (*S*)-**161a [**page 170].

Yield: 83%

$[\alpha]_D^{25}$: +25.12 (*c* 1.28, MeOH)

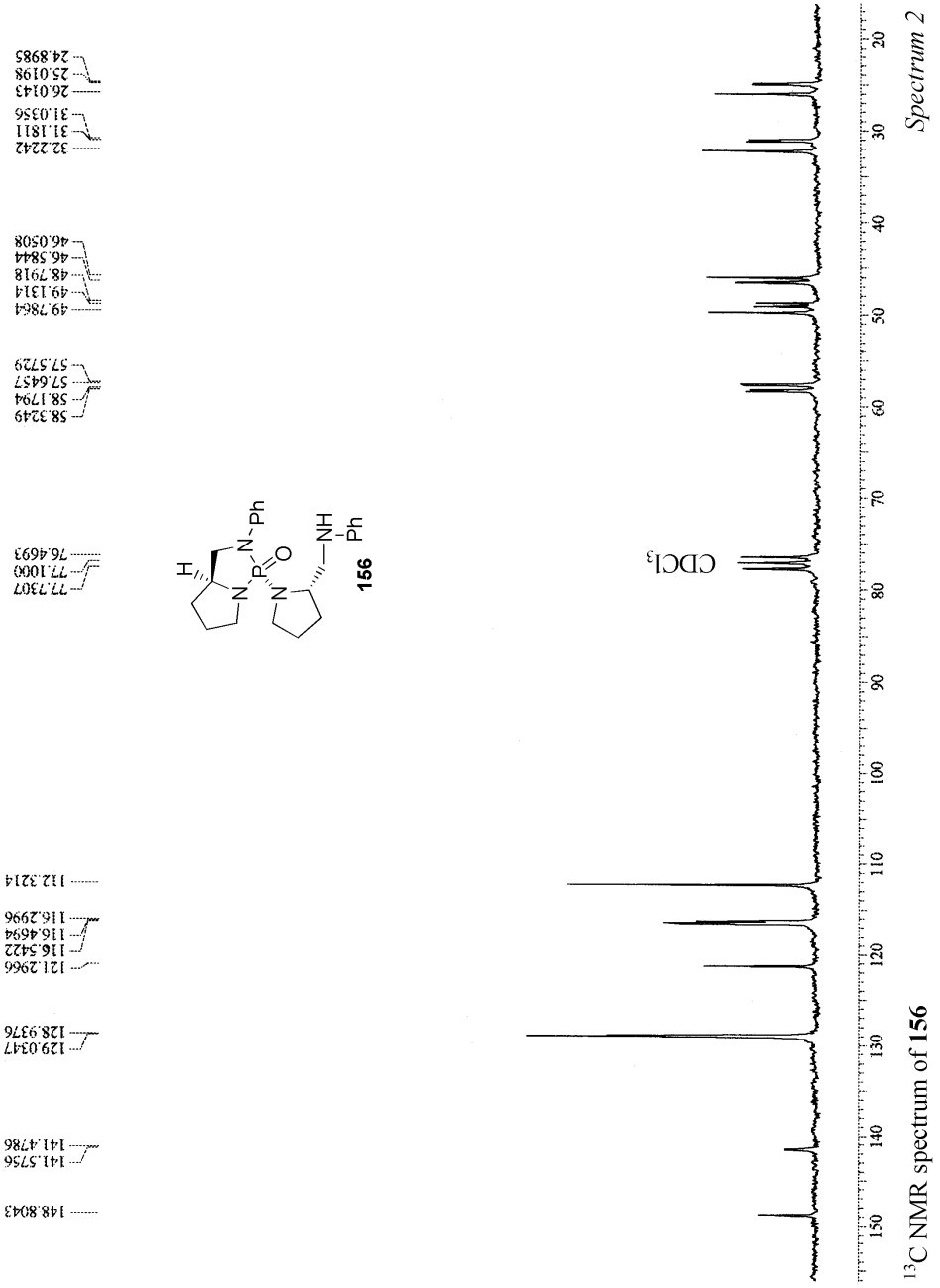
[Lit.[151] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*]

Enantiomeric purity: 56% [determined by HPLC using chiral column, Chiralcel-ODH, with reference to racemic alcohol (±)-**164a**, following the similar analysis as mentioned in page 122]



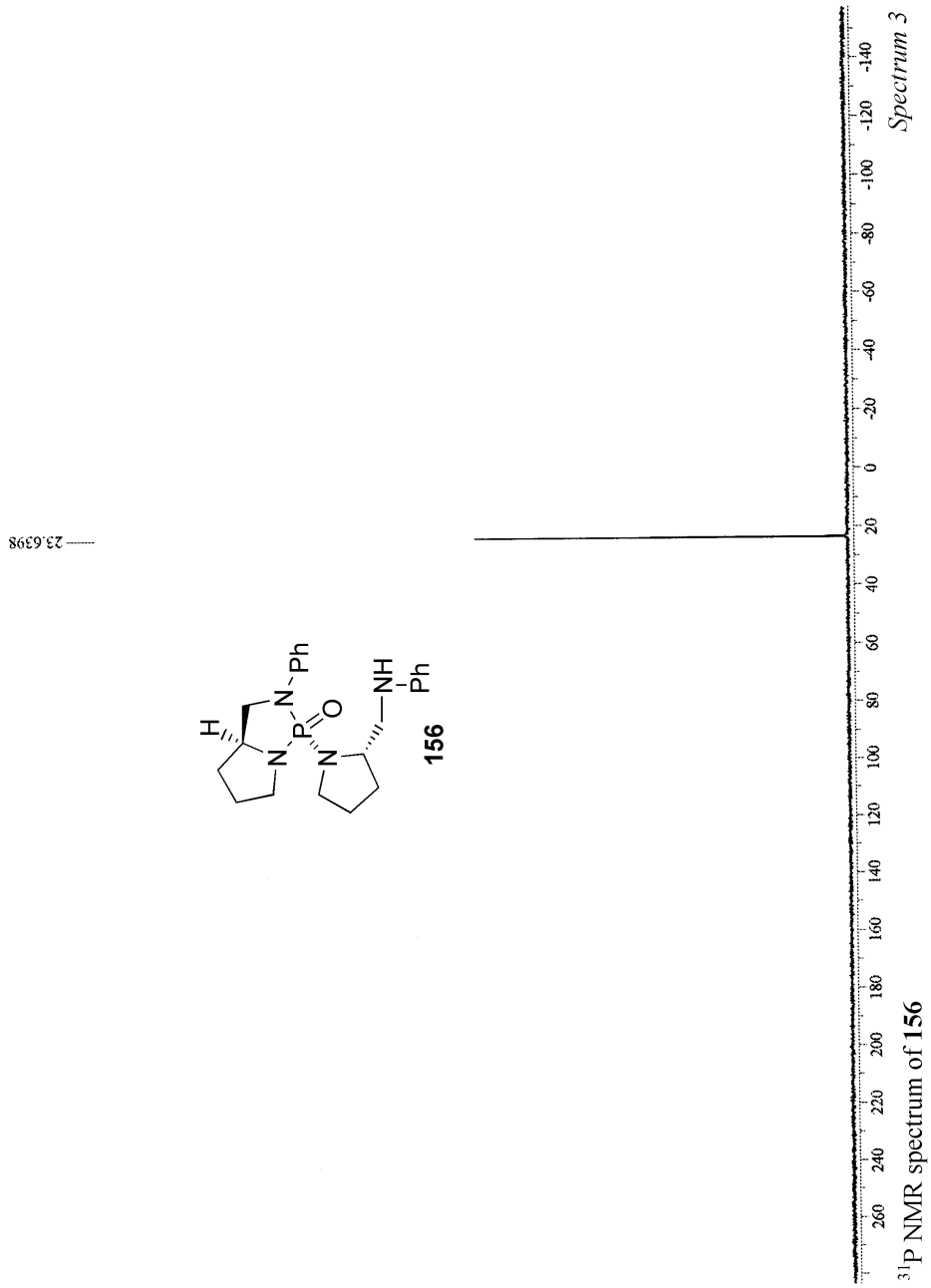
156

^{1}H NMR spectrum of **156**

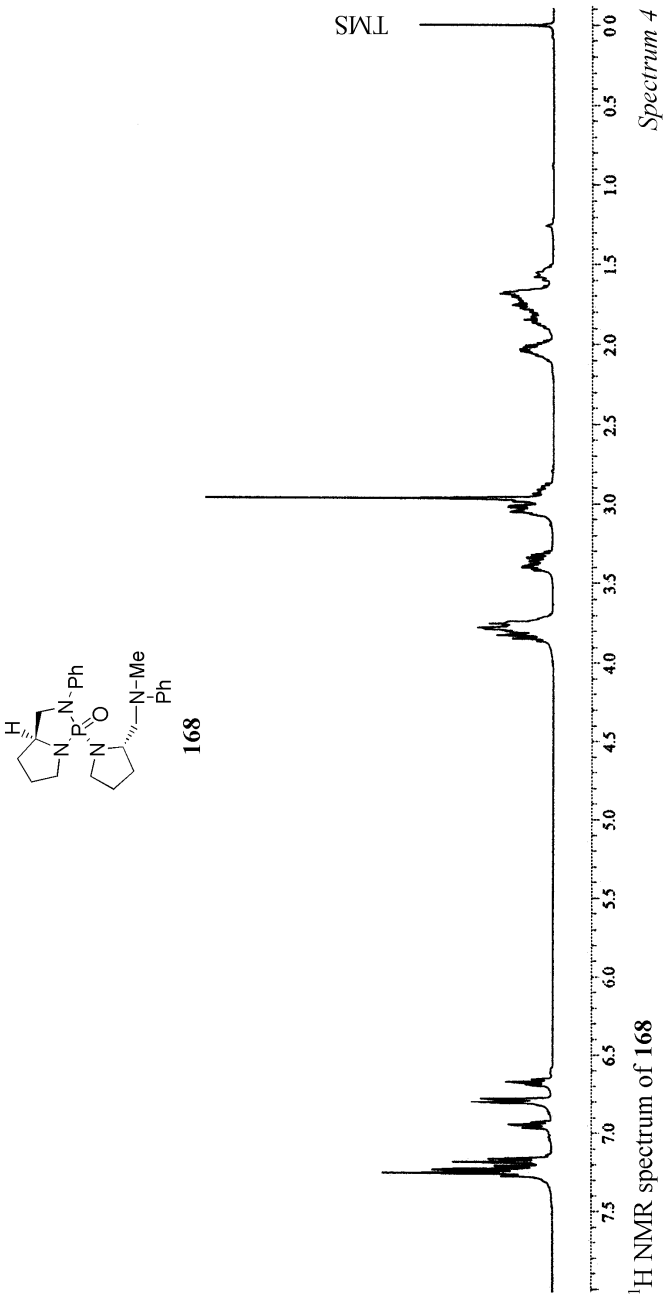


^{13}C NMR spectrum of **156**

Spectrum 2



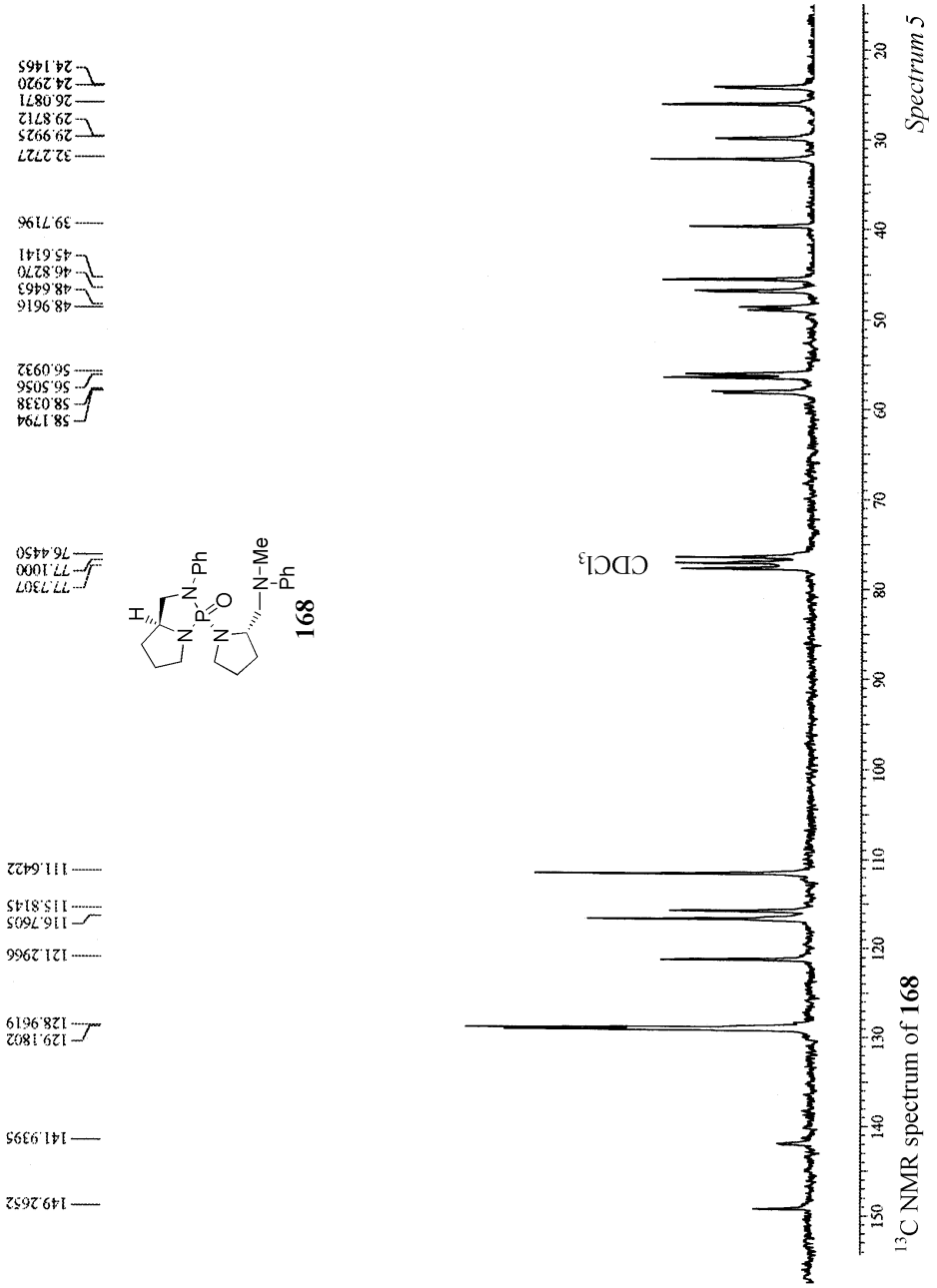
^{31}P NMR spectrum of **156**



168

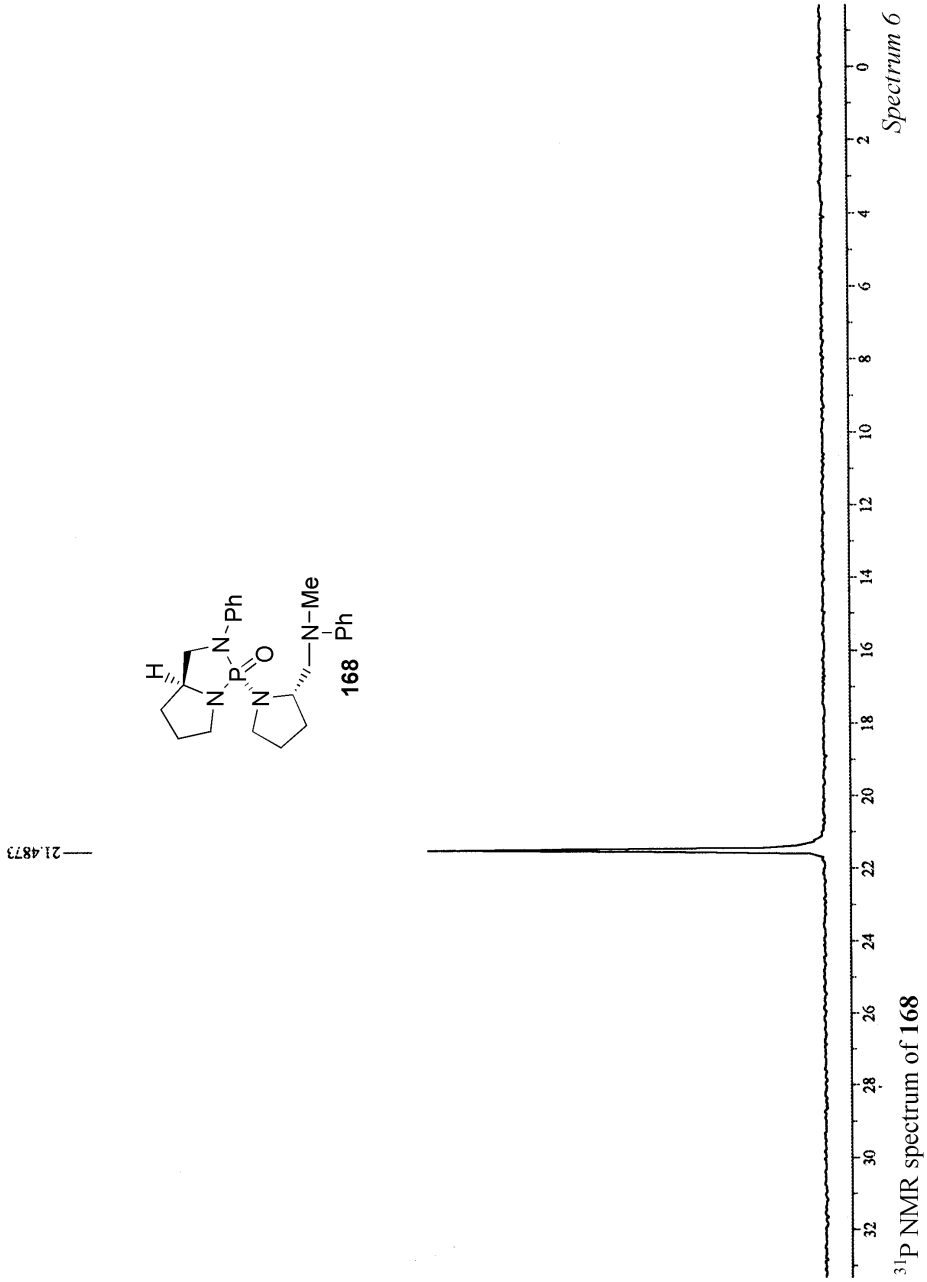
^{1}H NMR spectrum of **168**

Spectrum 4

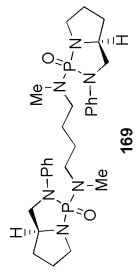


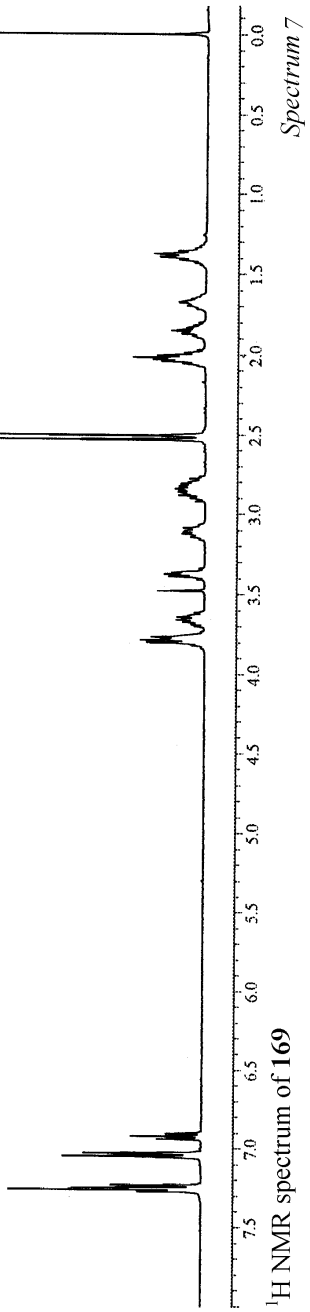
^{13}C NMR spectrum of **168**

Spectrum 5



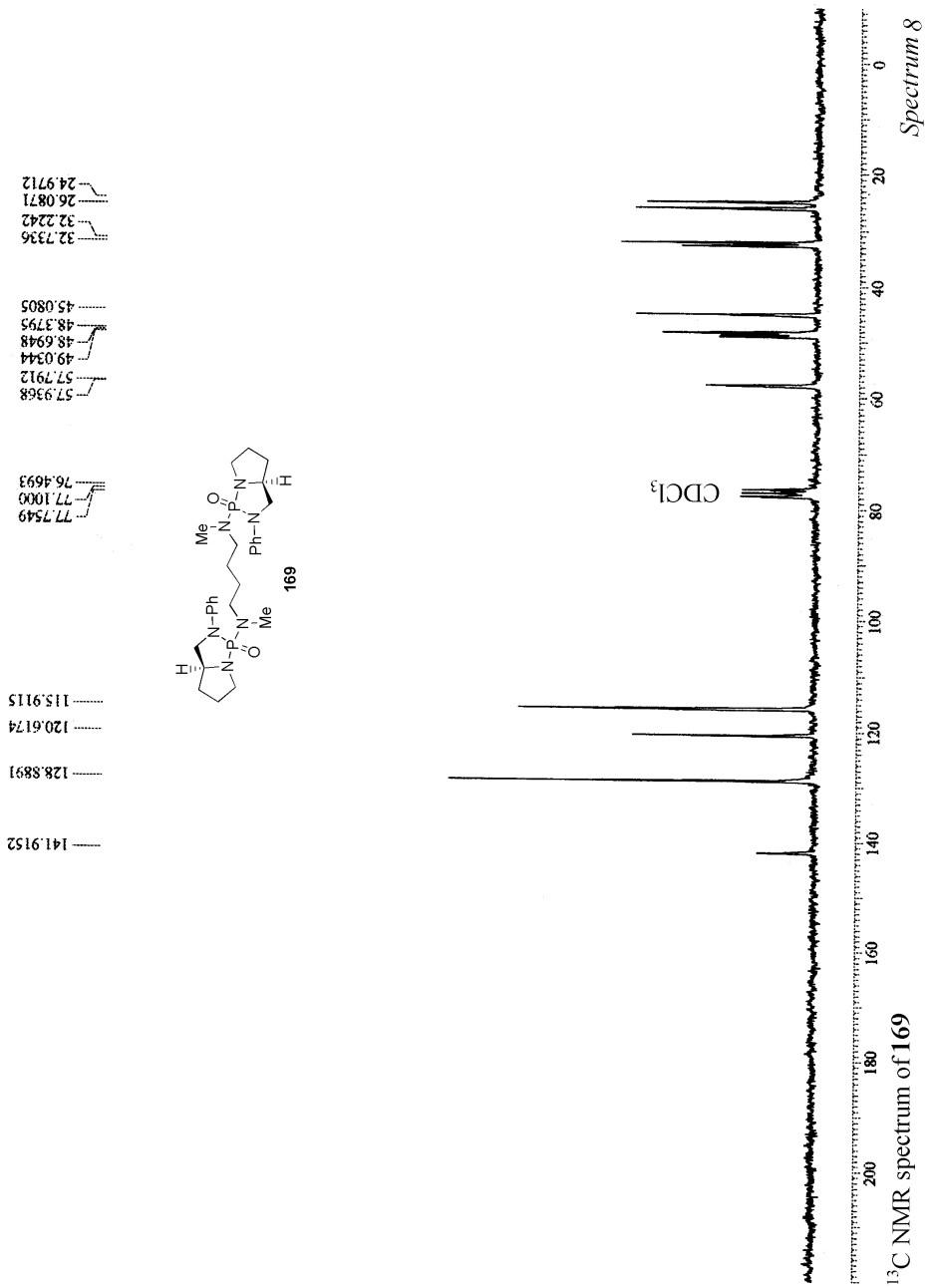
^{31}P NMR spectrum of **168**





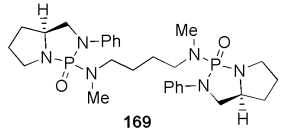
^{1}H NMR spectrum of **169**

Spectrum 7



^{13}C NMR spectrum of **169**

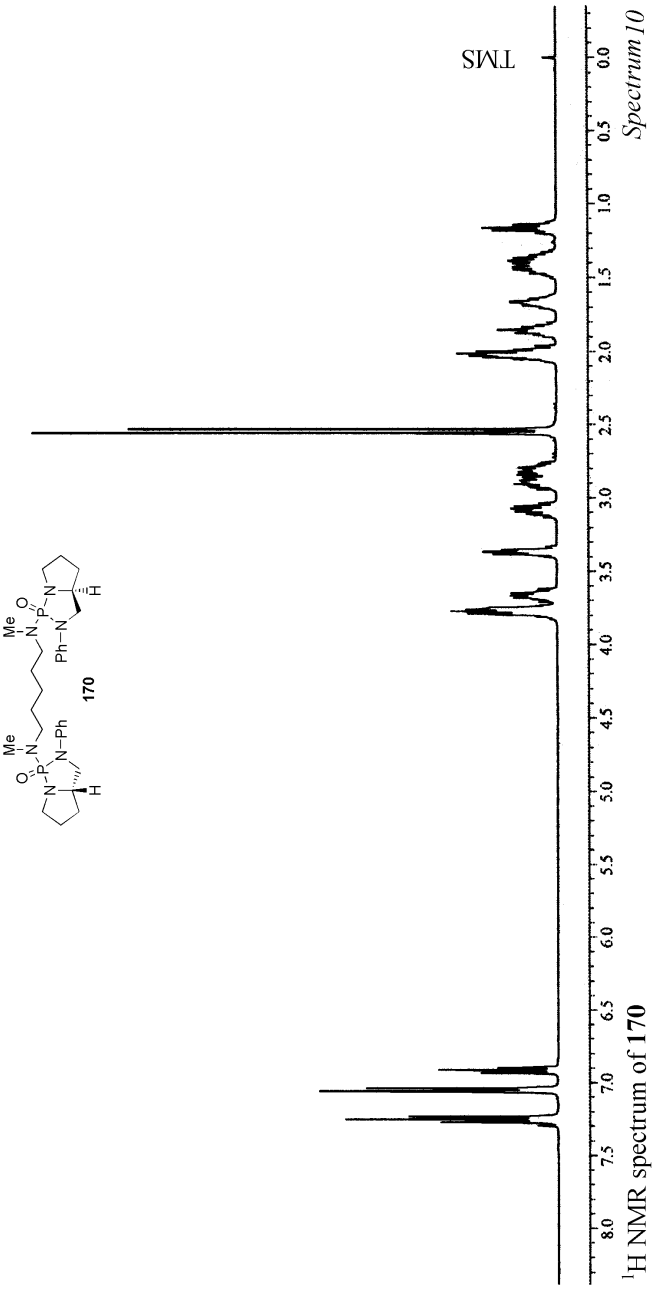
Spectrum 8



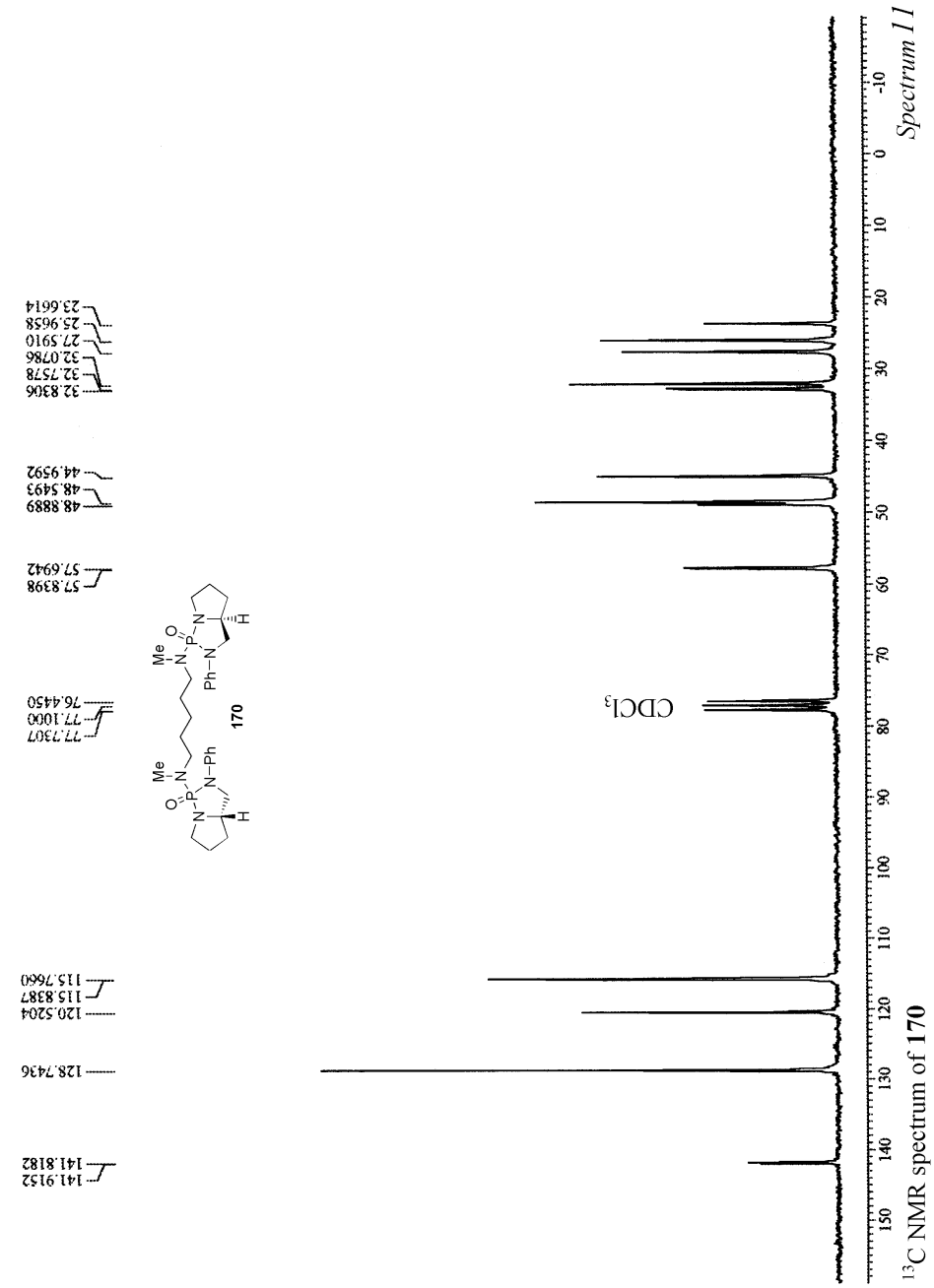
169

^{31}P NMR spectrum of **169**

Spectrum 9

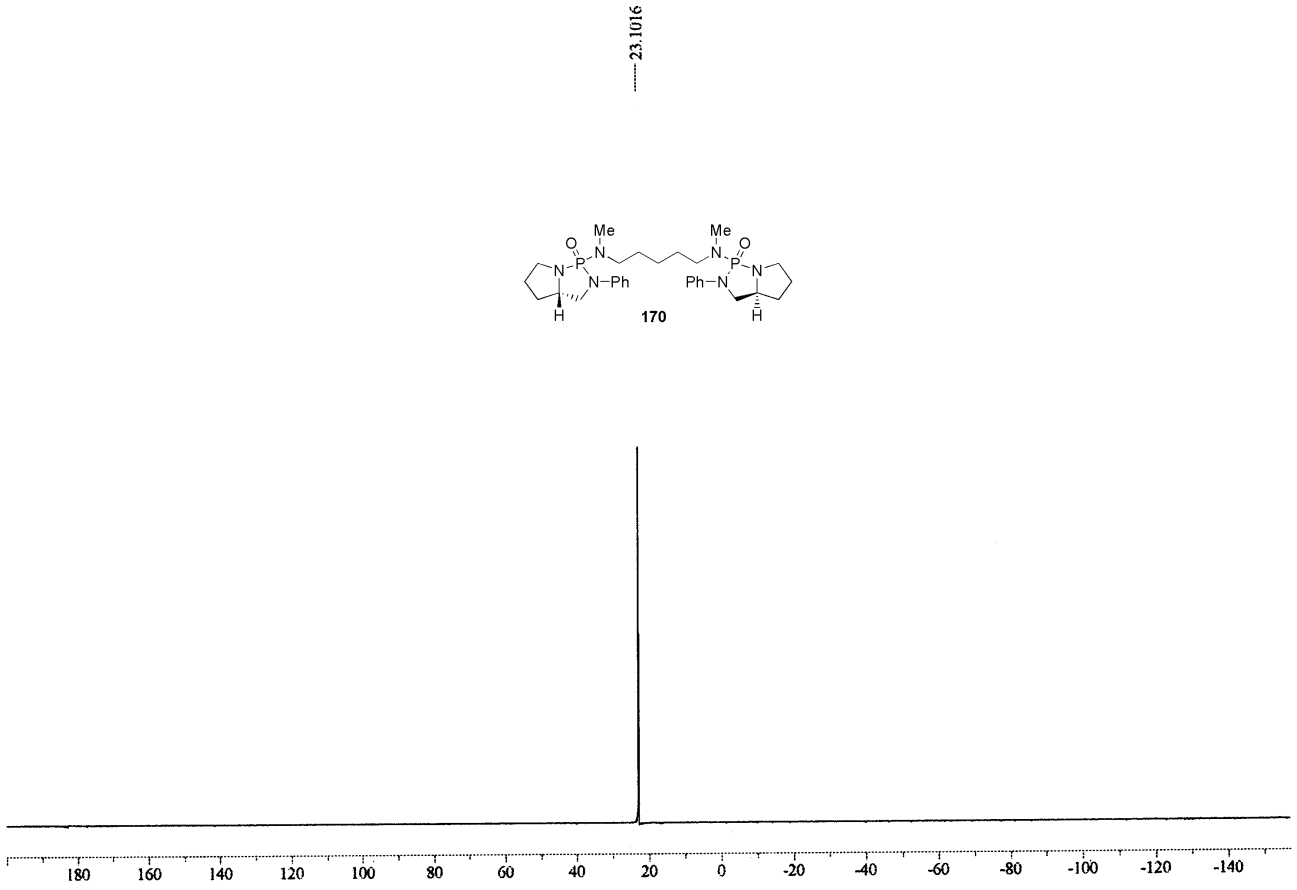


^{1}H NMR spectrum of **170**



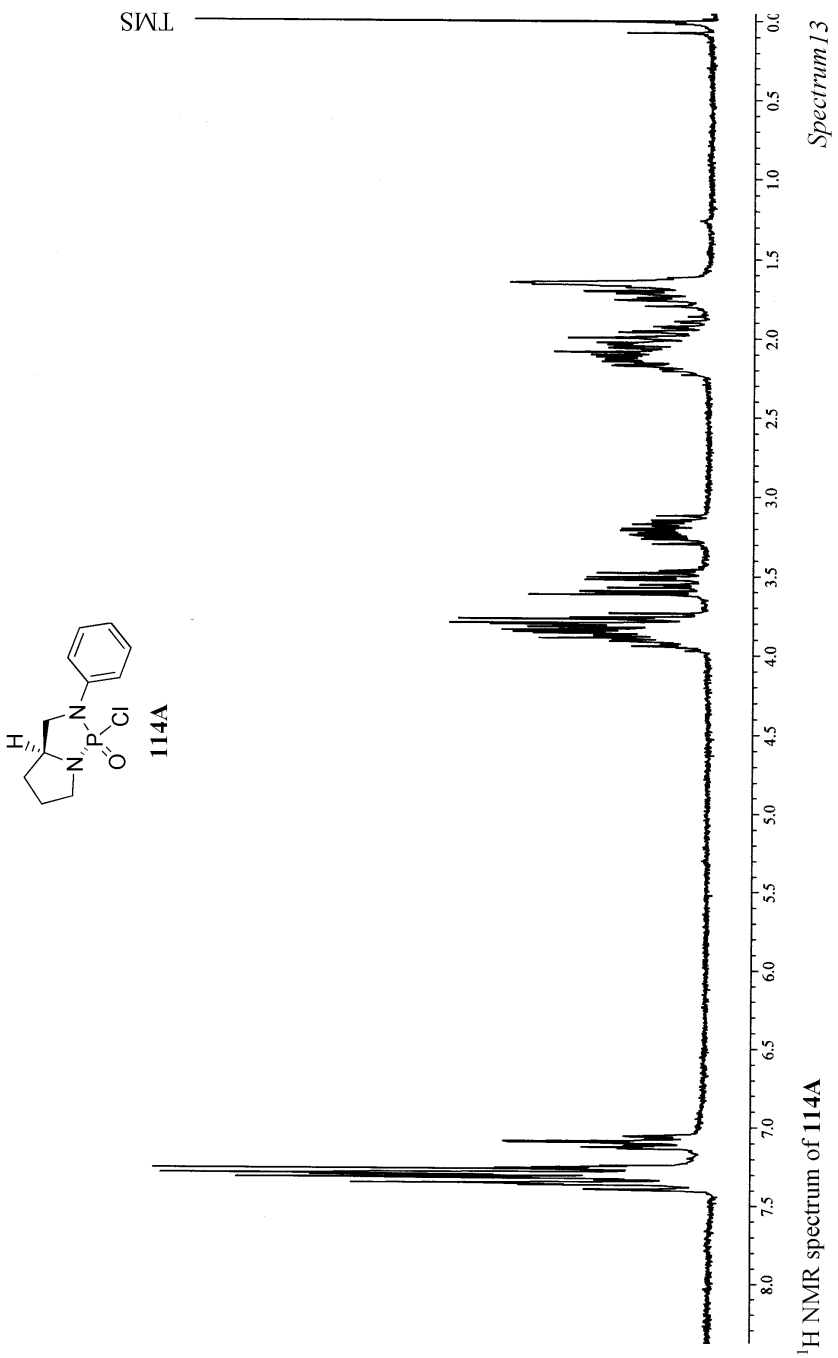
^{13}C NMR spectrum of **170**

Spectrum 11



^{31}P NMR spectrum of **170**

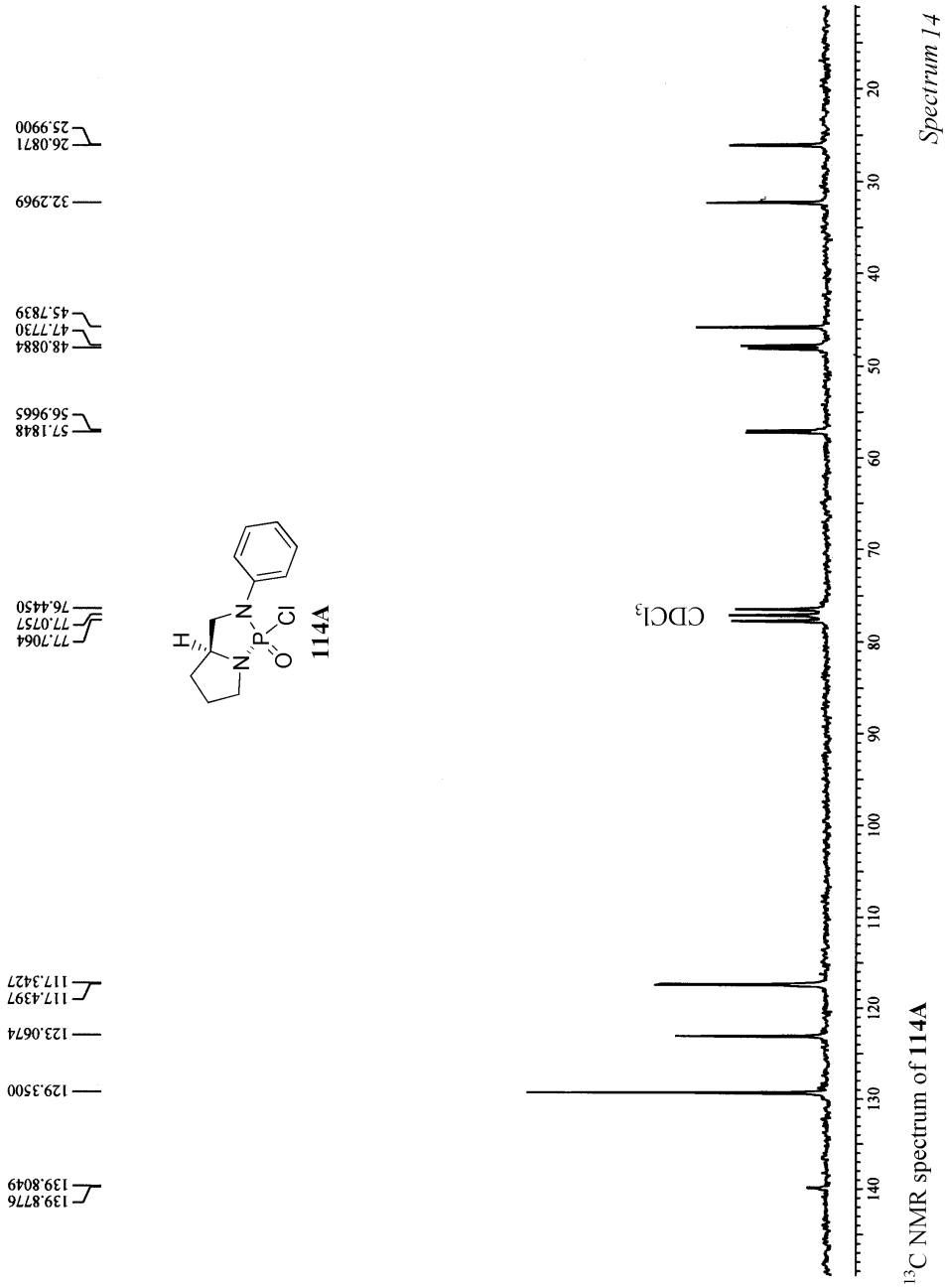
Spectrum 12



114A

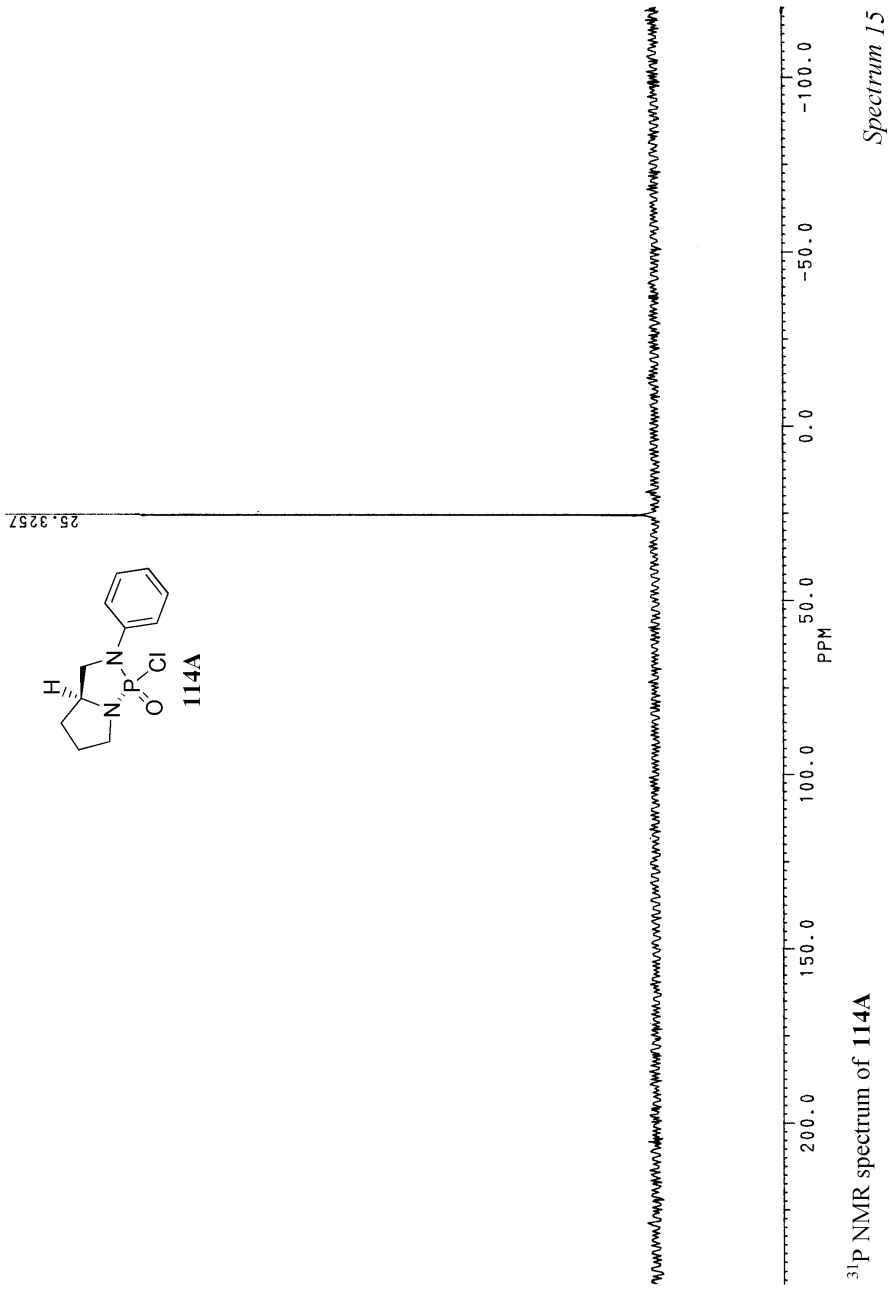
^{1}H NMR spectrum of **114A**

Spectrum 13



^{13}C NMR spectrum of **114A**

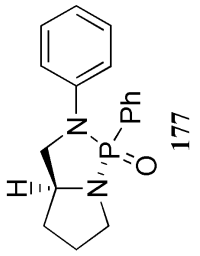
Spectrum 14



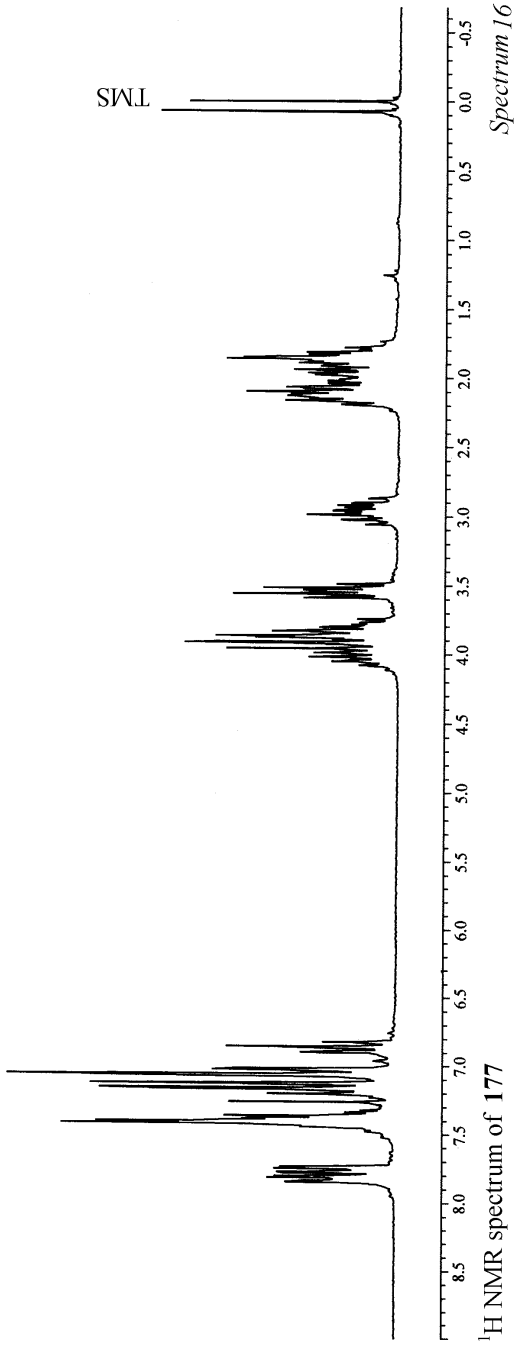
114A

^{31}P NMR spectrum of **114A**

Spectrum 15

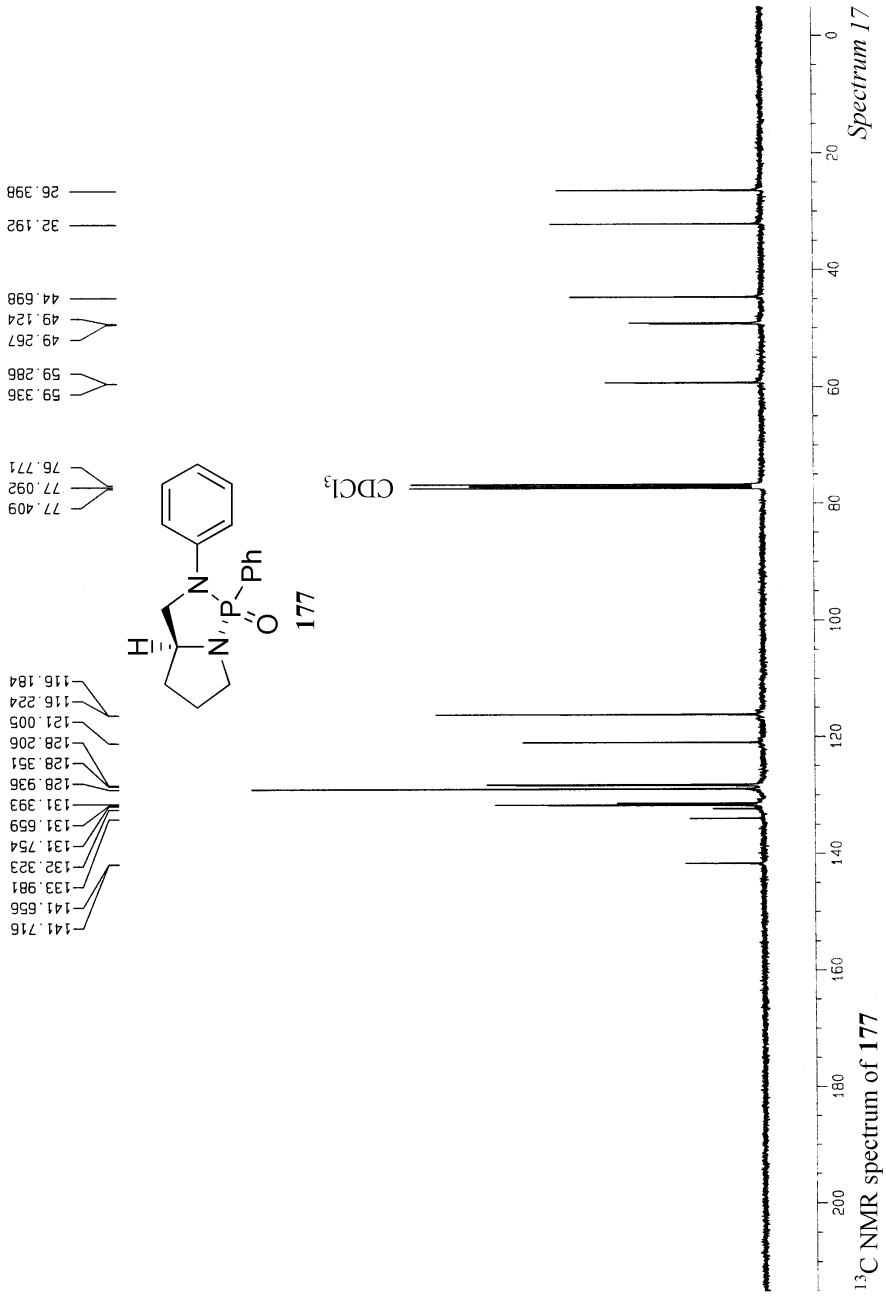


177

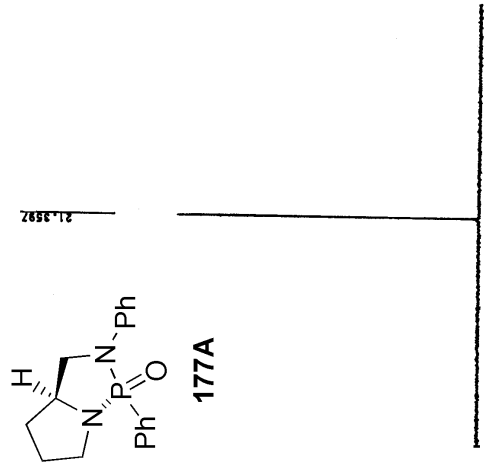


^{1}H NMR spectrum of **177**

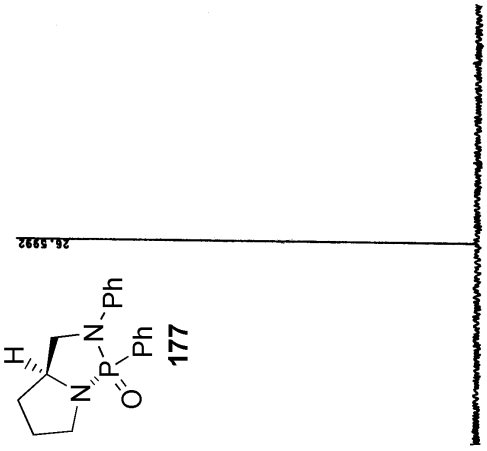
Spectrum 16



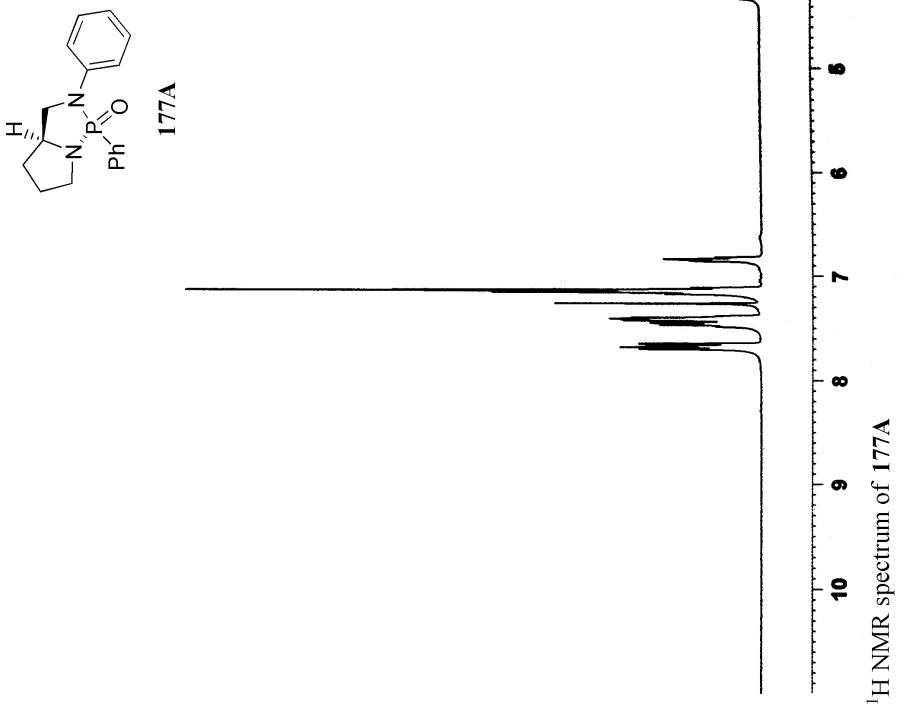
^{13}C NMR spectrum of **177**



Spectrum 18A: ^{31}P NMR of **177A**



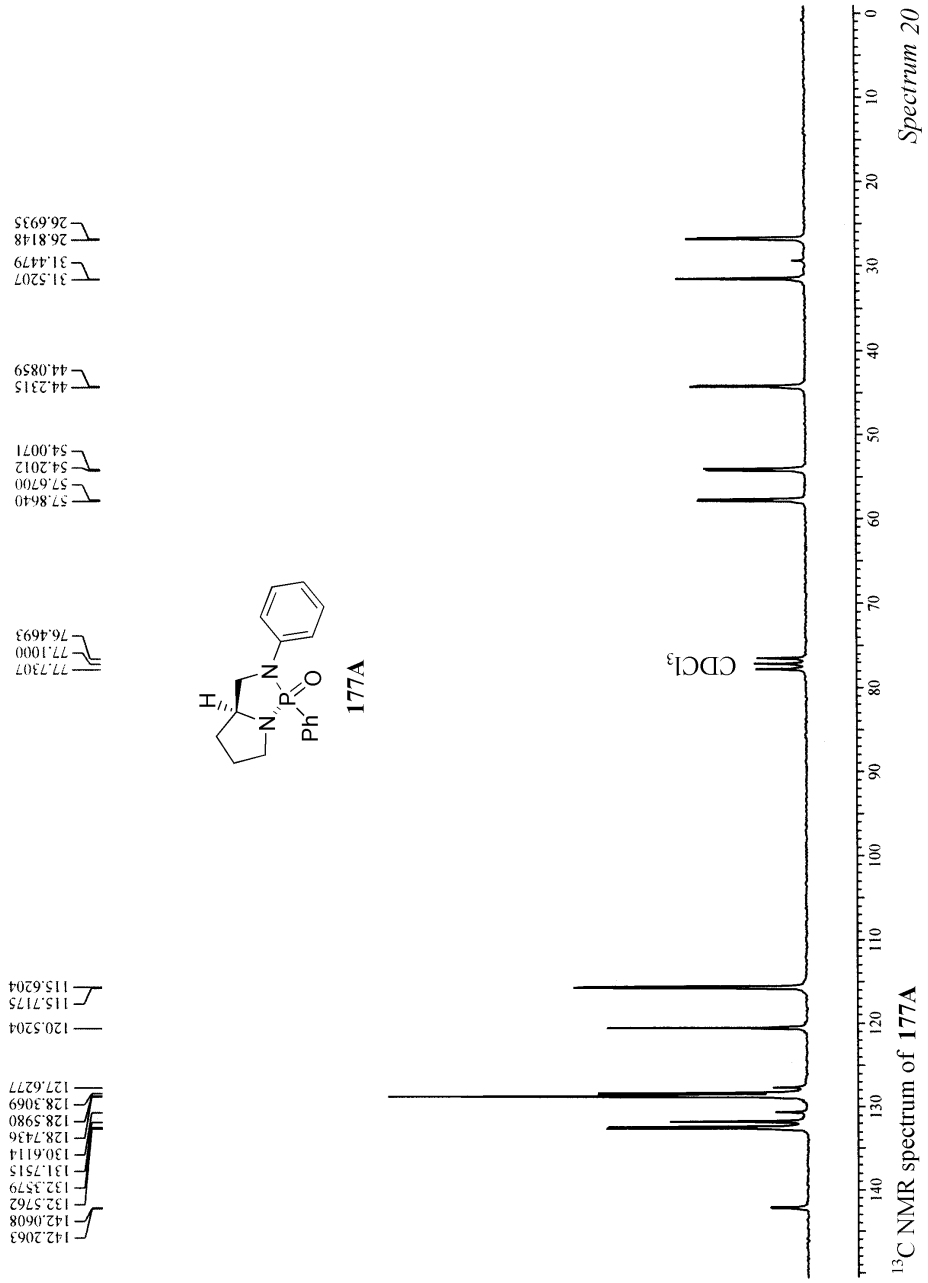
Spectrum 18 : ^{31}P NMR of **177**

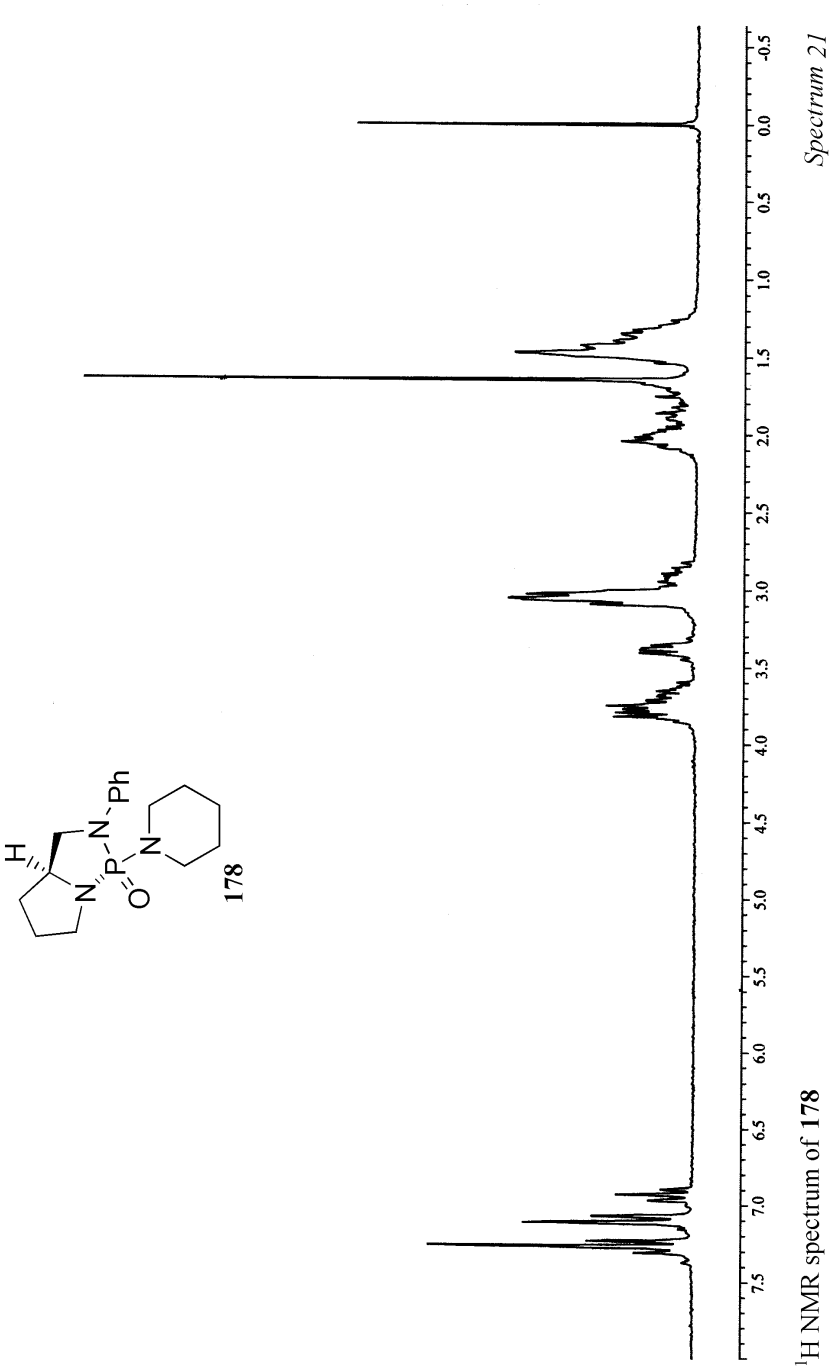


^{1}H NMR spectrum of **177A**

Spectrum 19

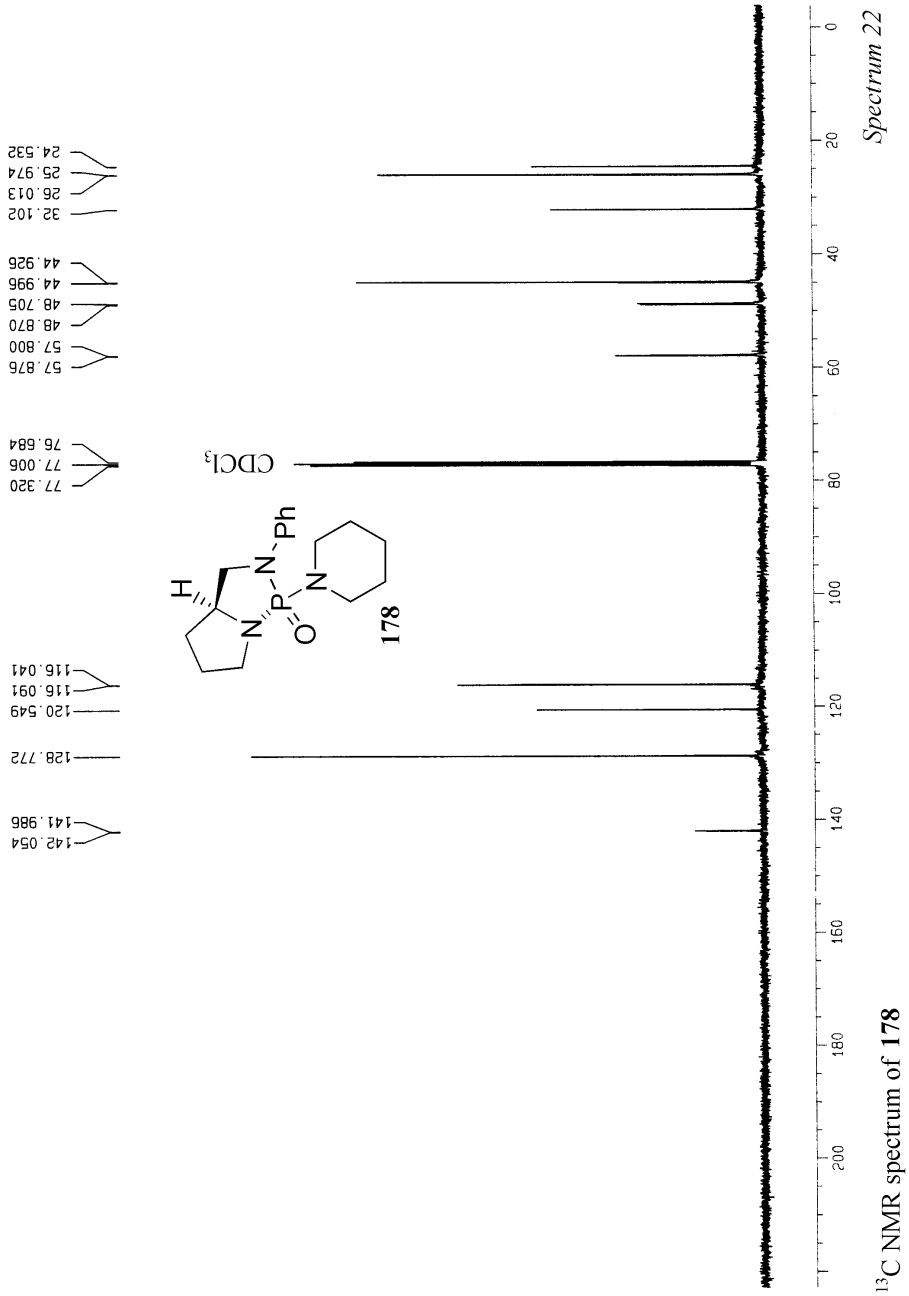
177A


142.2063
142.0608
132.5762
132.3579
131.7515
130.6114
128.7436
128.5980
128.3069
127.6277
120.5204
115.7175
115.6204
77.7307
77.1000
76.4693
57.8640
57.6700
54.2012
54.0071
44.2315
44.0859
31.5207
31.4479
26.8148
26.6935
CDCl3
177A
13C NMR spectrum of 177A
Spectrum 20



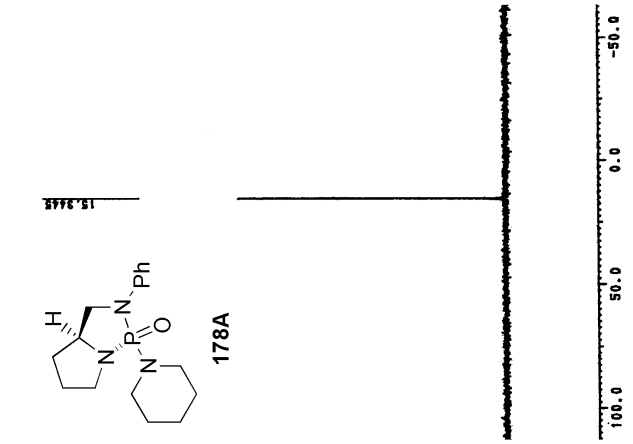
^{1}H NMR spectrum of **178**

Spectrum 21

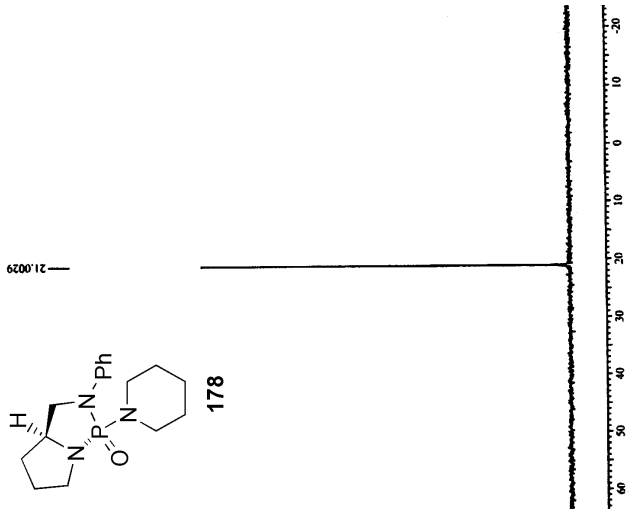


Spectrum 22

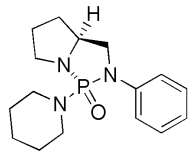
^{13}C NMR spectrum of **178**



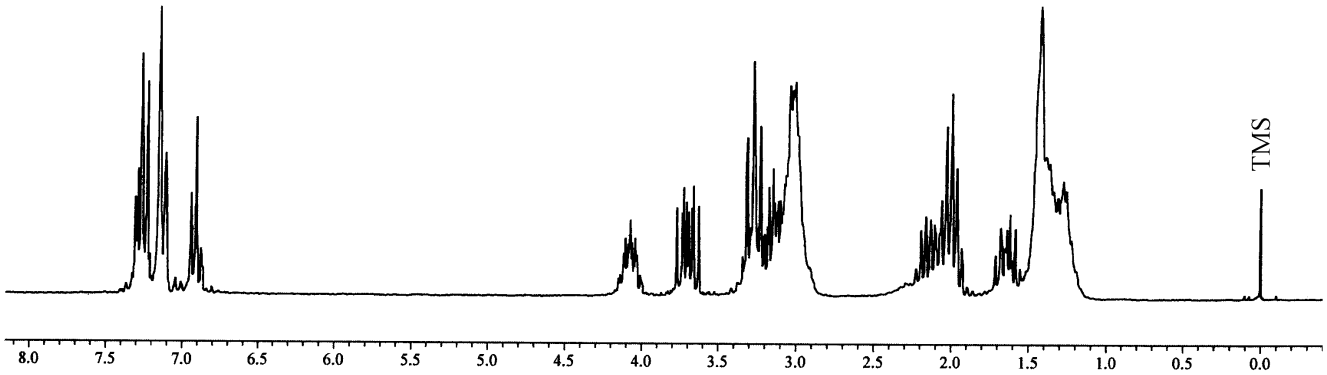
Spectrum 23A: ^{31}P NMR of **178A**



Spectrum 23: ^{31}P NMR of **178**

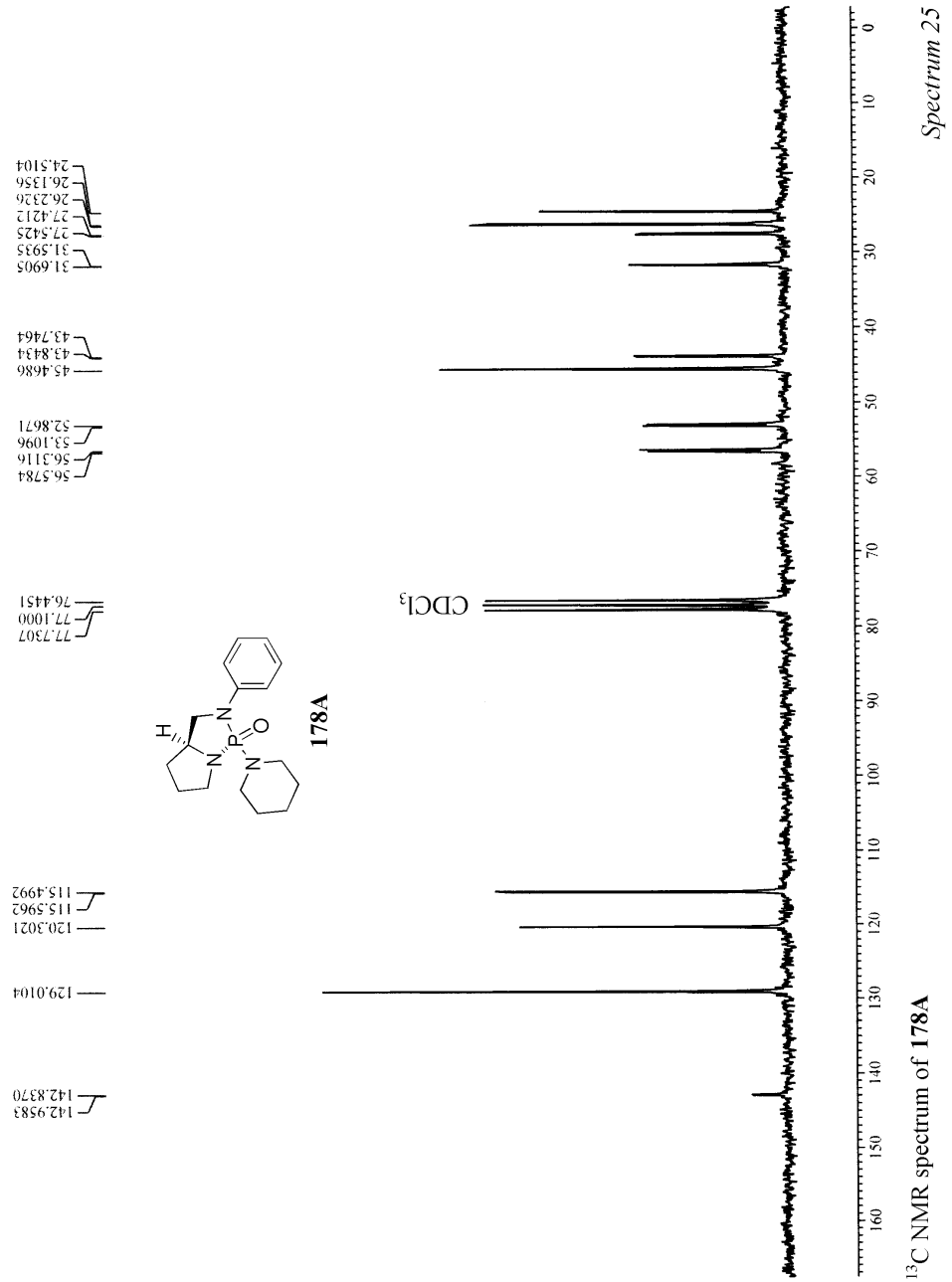


178A



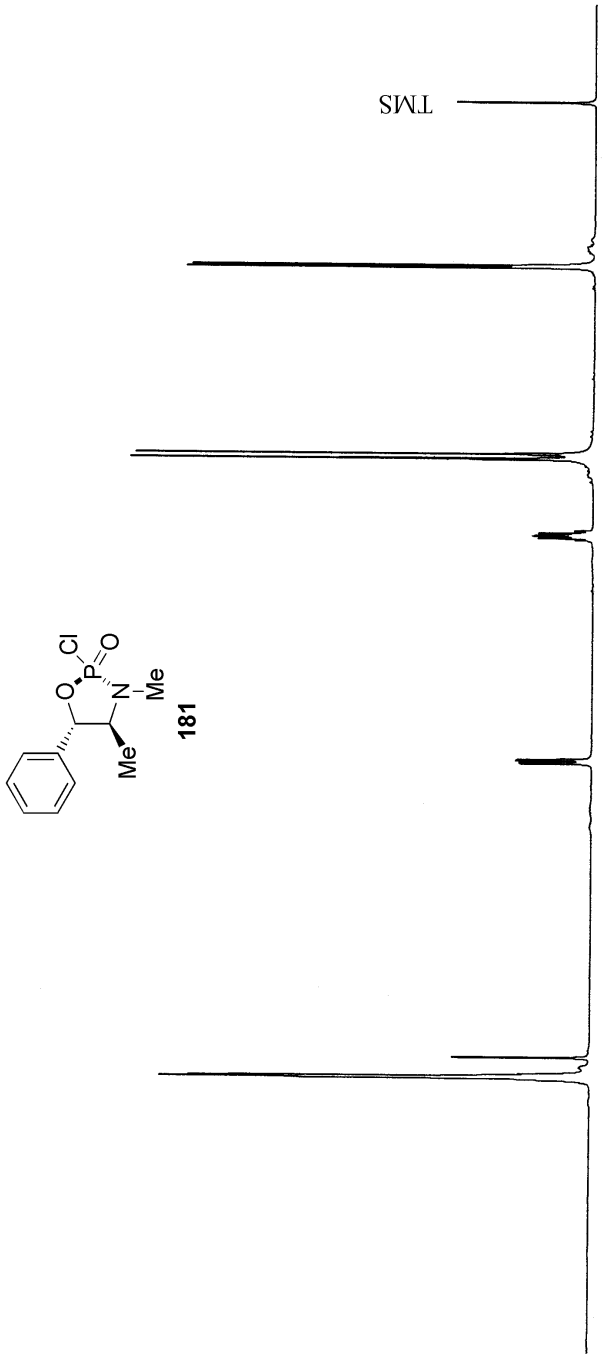
^{1}H NMR spectrum of **178A**

Spectrum 24



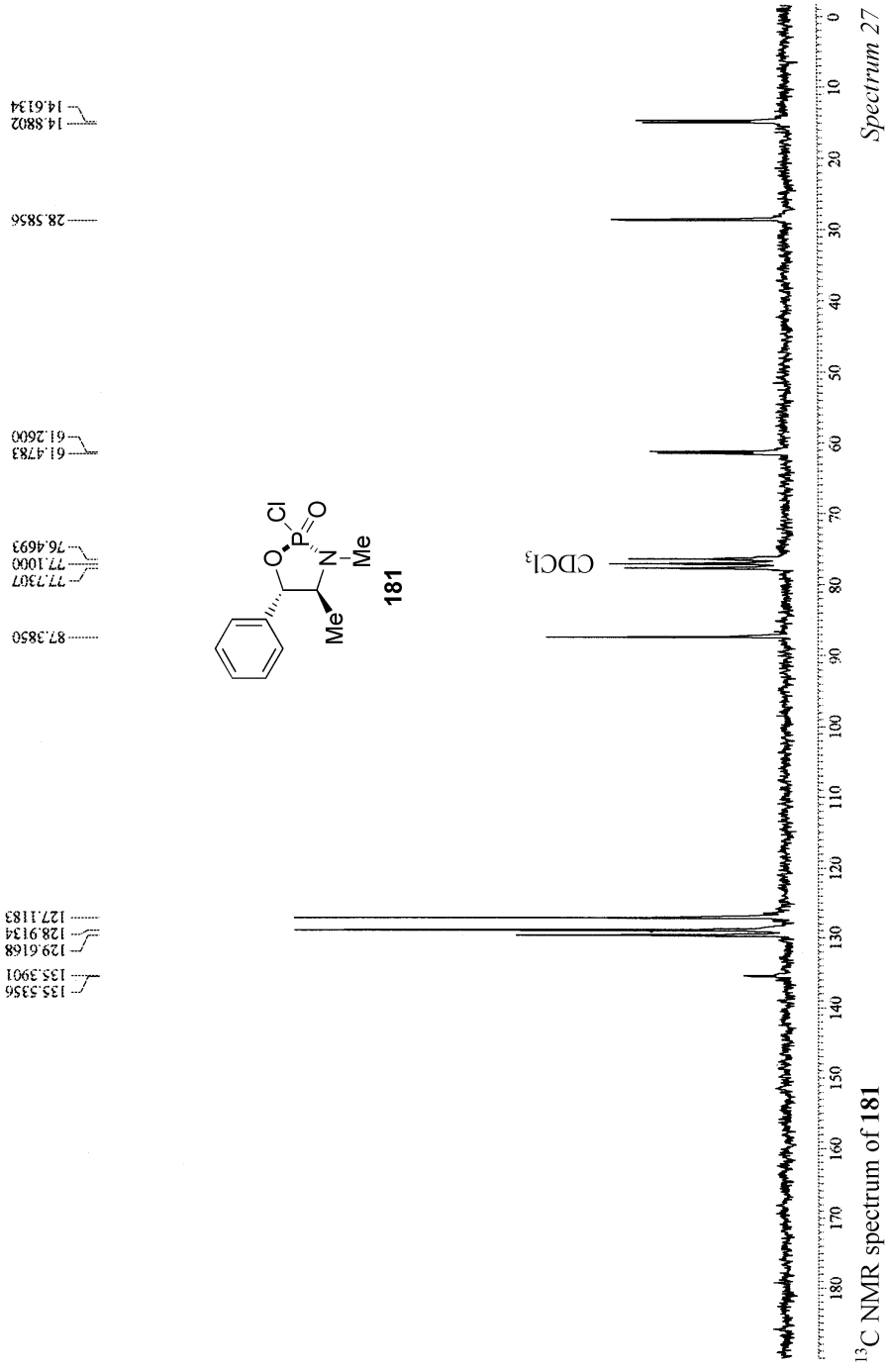
^{13}C NMR spectrum of **178A**

Spectrum 25



^{1}H NMR spectrum of **181**

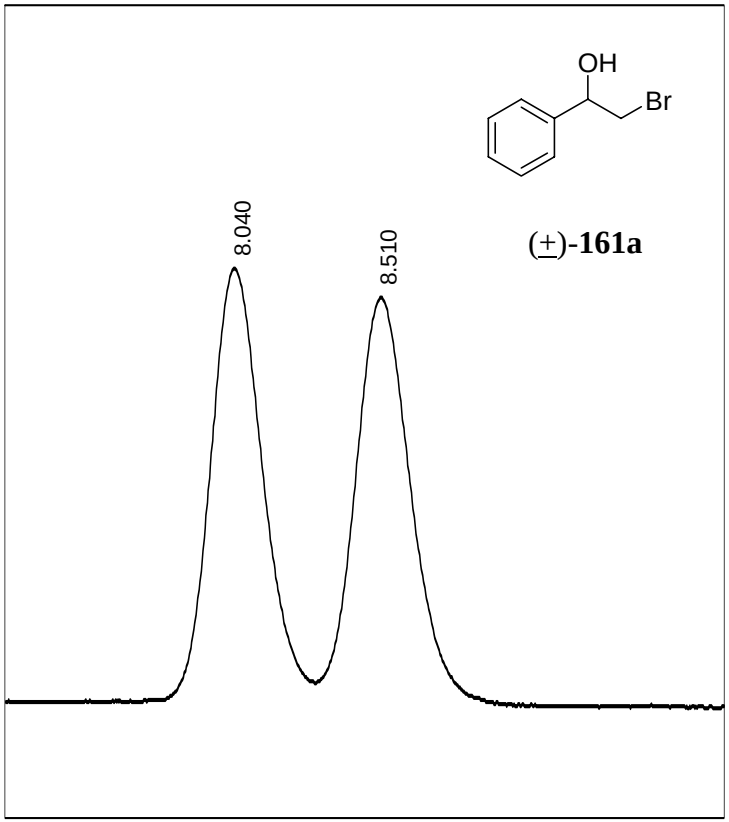
Spectrum 26



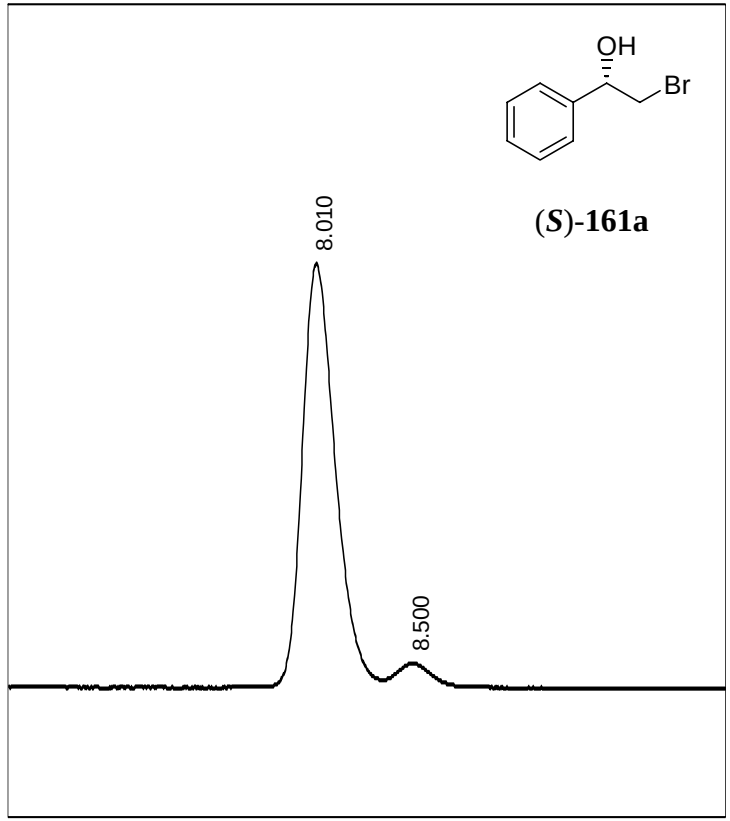
^{13}C NMR spectrum of **181** *Spectrum 27*

^{31}P NMR spectrum of **181**

Spectrum 28



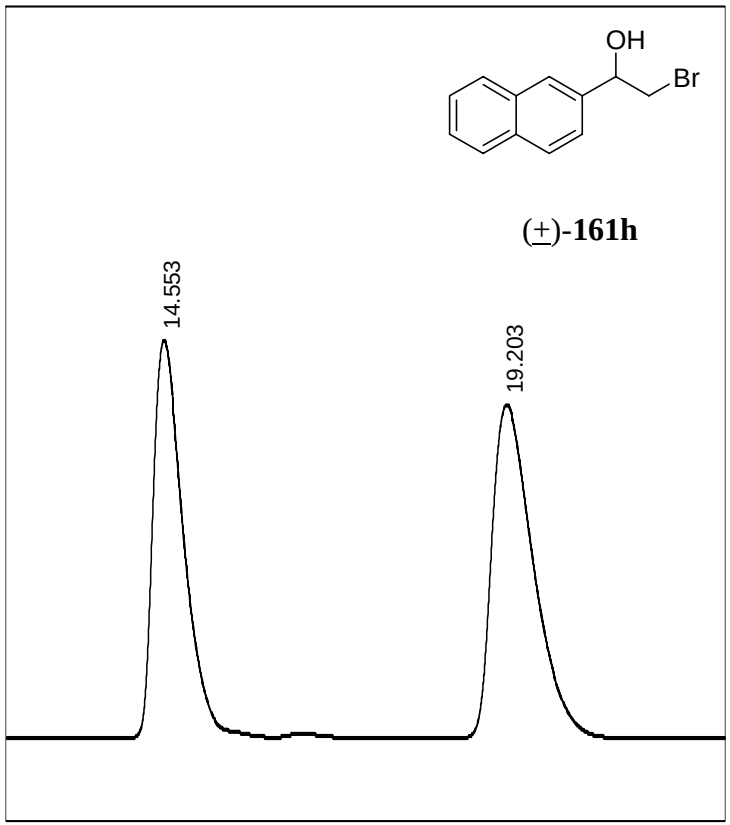
(±)-2-Bromo-1-phenylethanol



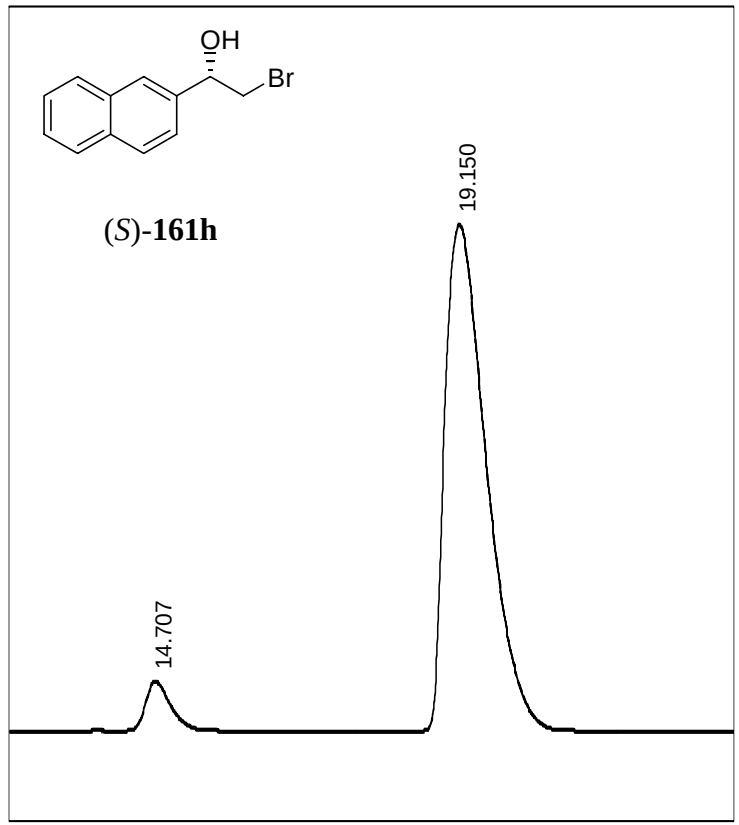
(*S*)- 2-Bromo-1-phenylethanol

(***S***)-**161a** (enantiomeric purity 89%) obtained *via* the reduction of phenacyl bromide (**160a**) using 1 mol% catalyst **156**

HPLC analysis: ***Chromatogram* 1**



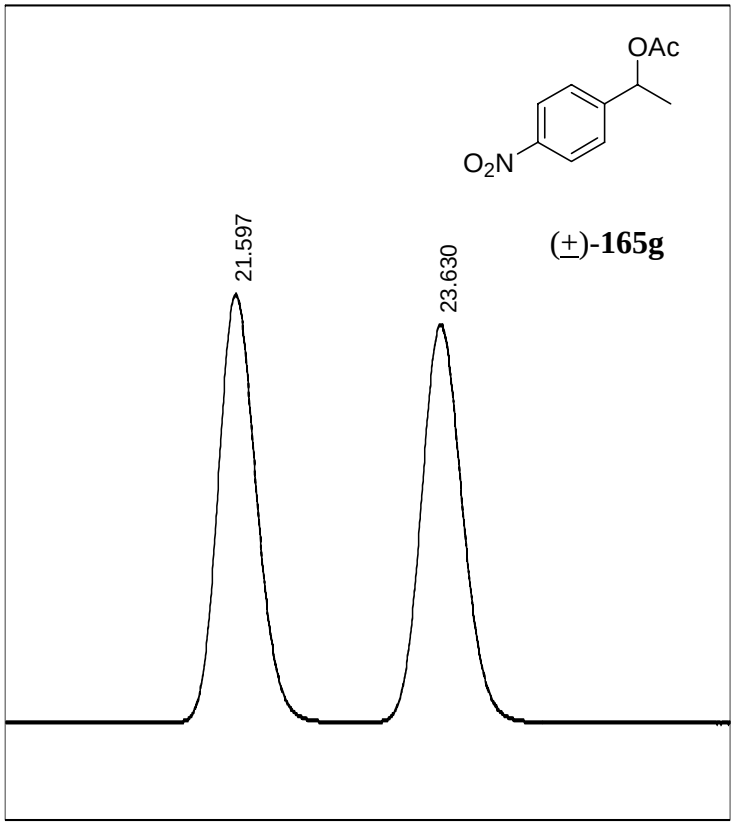
(±)-2-Bromo-1-(naphth-2-yl)ethanol



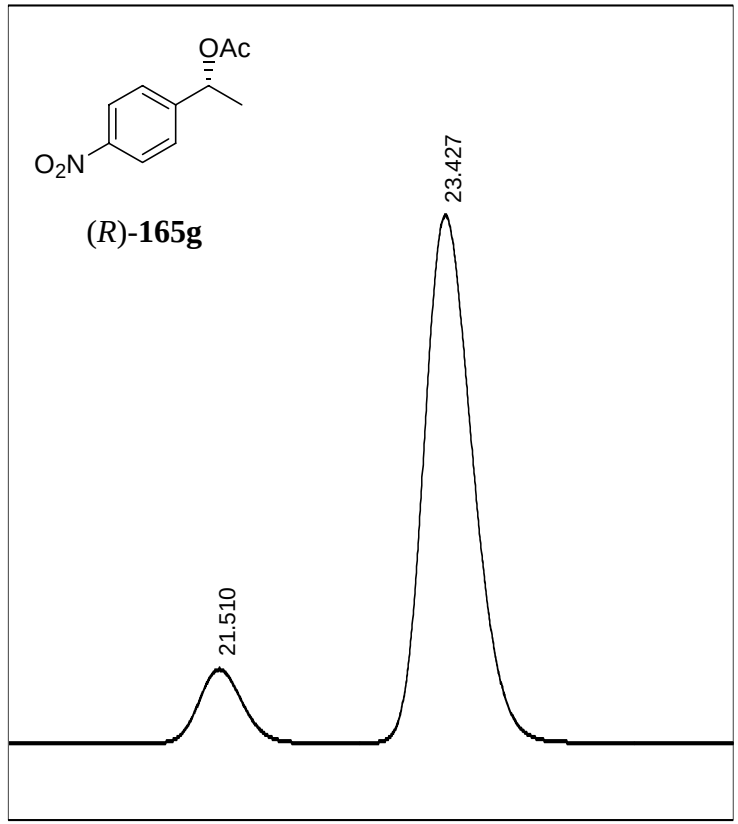
(*S*)-2-Bromo-1-(naphth-2-yl)ethanol

(*S*)-**161h** (enantiomeric purity 89%) obtained *via* the reduction of **160h** using 1 mol% catalyst **156**

HPLC analysis: ***Chromatogram* 2**



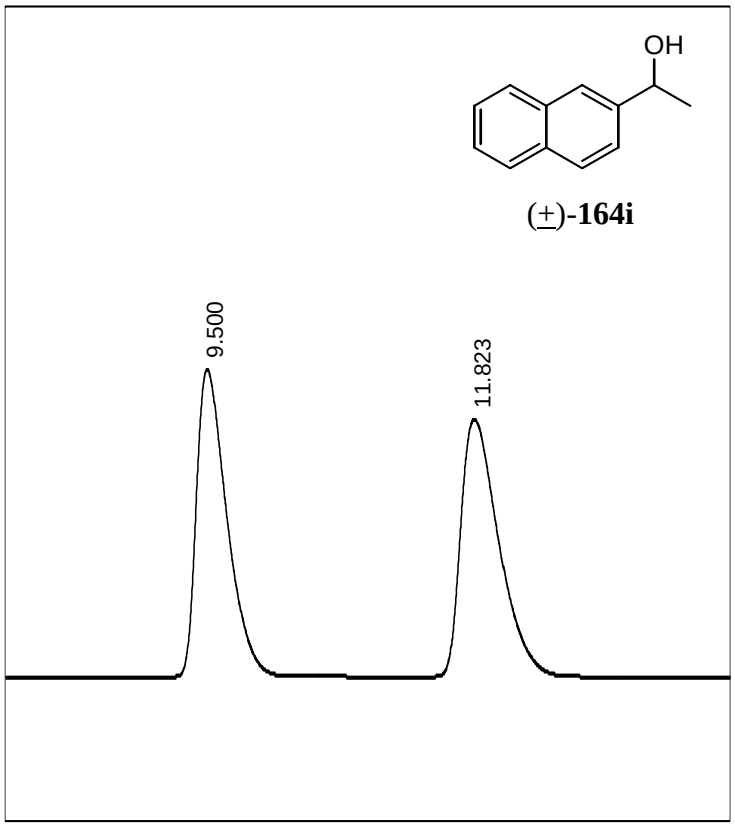
(±)-1-Acetoxy-1-(4-nitrophenyl)ethane



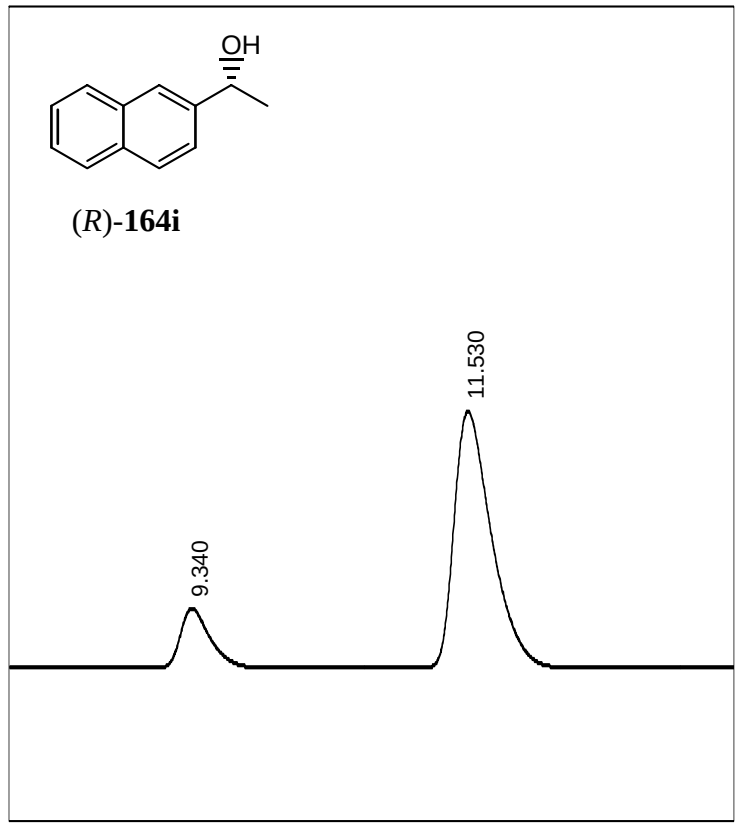
(*S*)-1-Acetoxy-1-(4-nitrophenyl)ethane

(***R***)-**165g** (enantiomeric purity 78%) an acetate derivative of (***R***)-**164g** obtained *via* the reduction of **163g** using 1 mol% catalyst **156**

HPLC analysis: ***Chromatogram* 3**



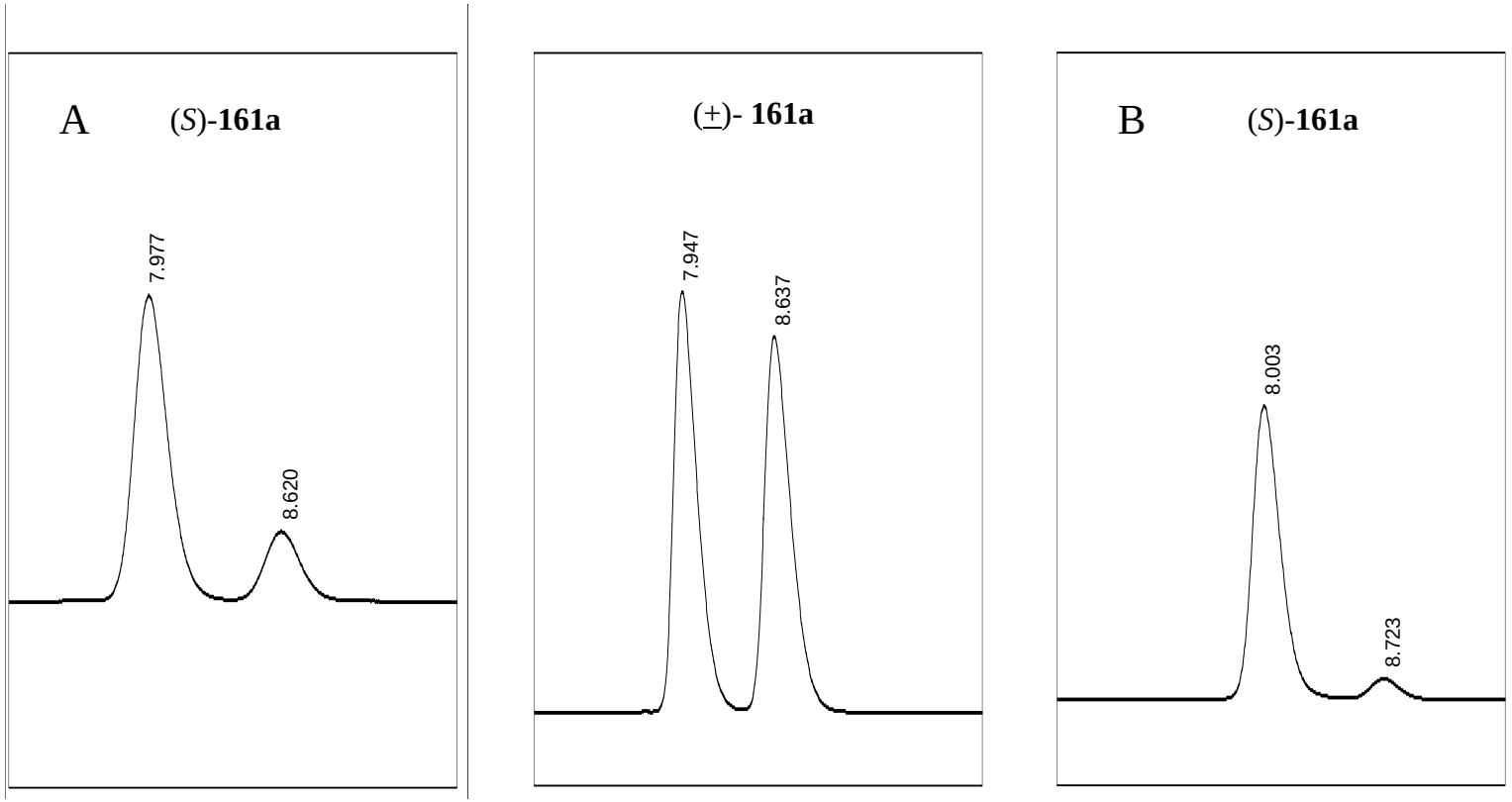
(±)-1-(Naphth-2-yl)ethanol



(*R*)-1-(Naphth-2-yl)ethanol

(***R***)-**164i** (enantiomeric purity 70%) obtained *via* the reduction of **163i** using 1 mol% catalyst **156**

HPLC analysis: ***Chromatogram* 4**

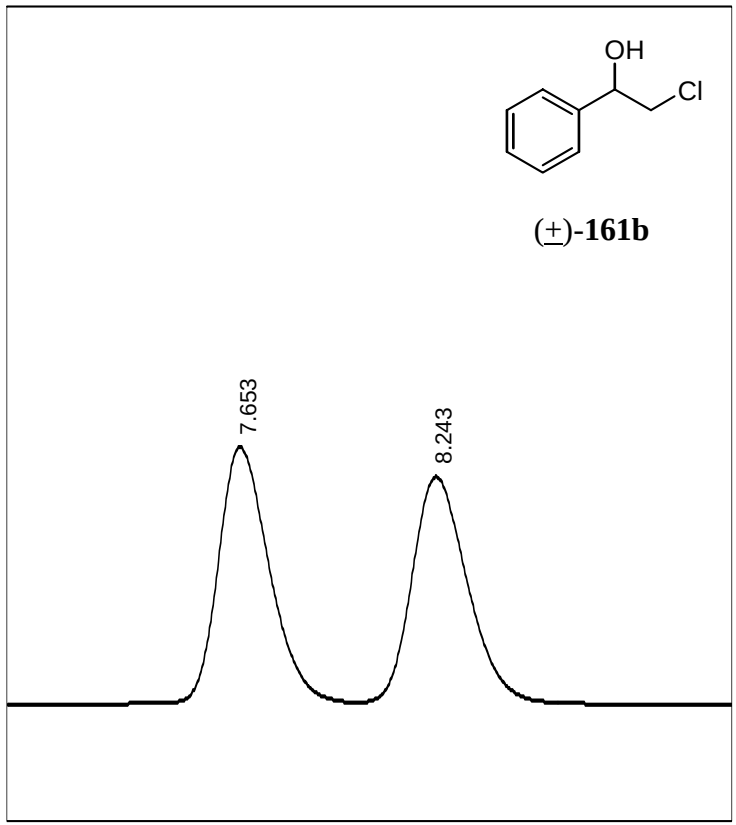


(*S*)-2-Bromo-1-phenylethanol (±)-2-Bromo-1-phenylethanol (*S*)-2-Bromo-1-phenylethanol

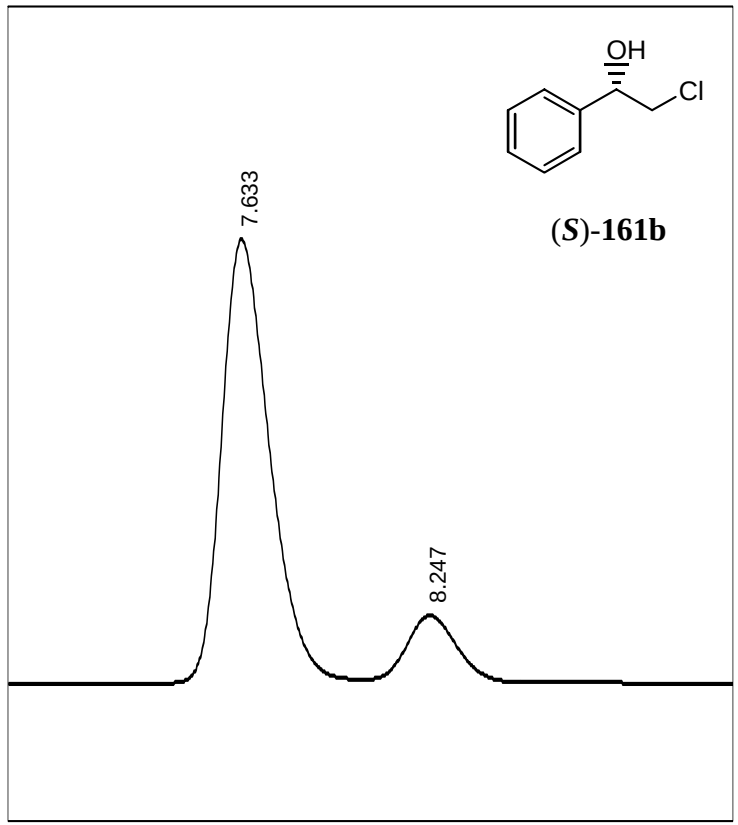
A: (*S*)-**161a** (enantiomeric purity 61%) obtained *via* the reduction of phenacyl bromide (**160a**) using 1 mol% catalyst **168**

B: (*S*)-**161a** (enantiomeric purity 87%) obtained *via* the reduction of phenacyl bromide (**160a**) using 10 mol% catalyst **168**

HPLC analysis: ***Chromatogram* 5**



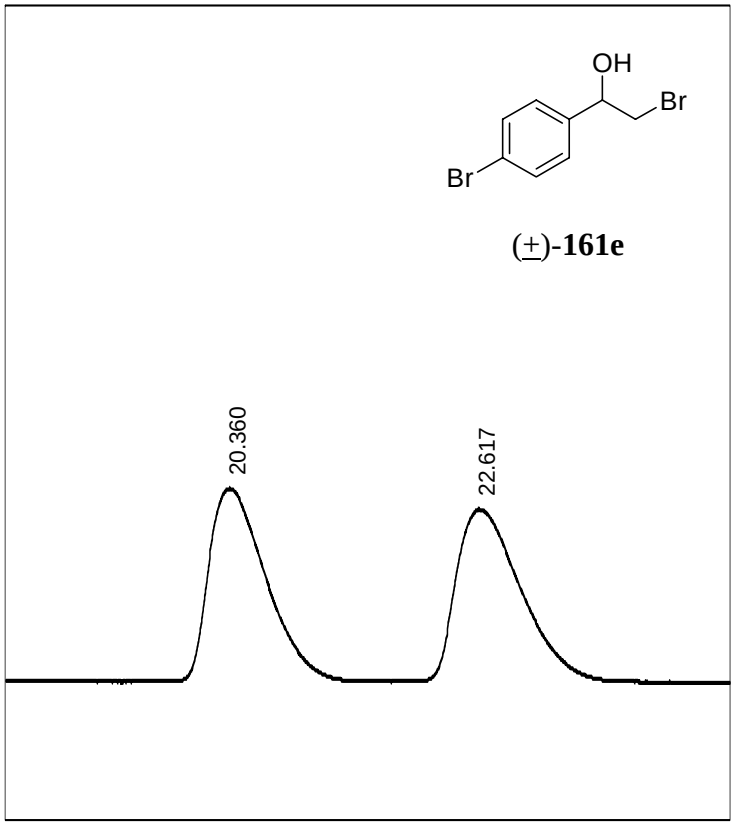
(±)-2-Chloro-1-phenylethanol



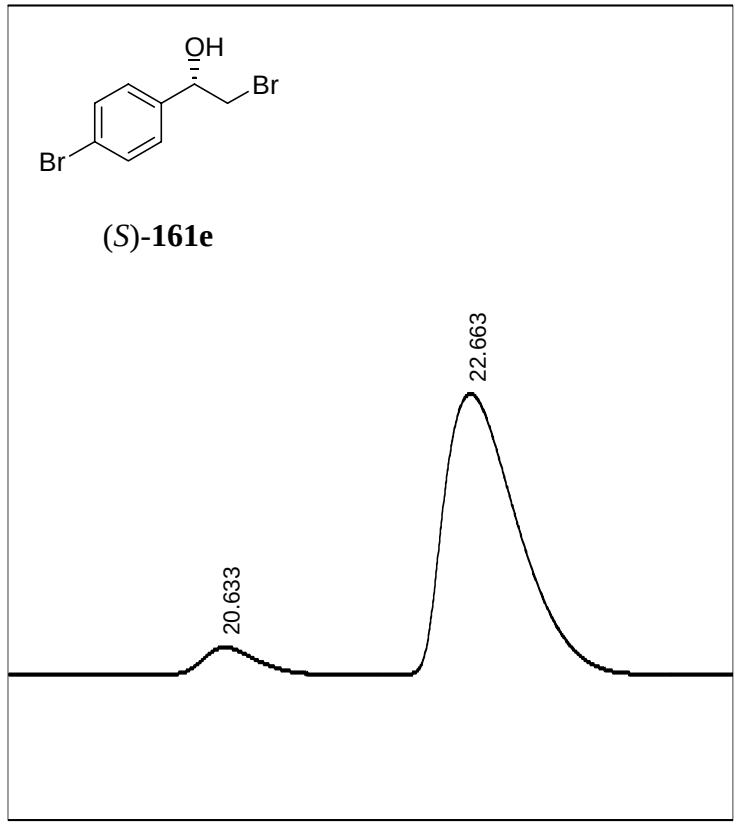
(*S*)-2-Chloro-1-phenylethanol

(*S*)-**161b** (enantiomeric purity 74%) obtained *via* the reduction of phenacyl chloride (**160b**) using 1 mol% catalyst **168**

HPLC analysis: ***Chromatogram* 6**



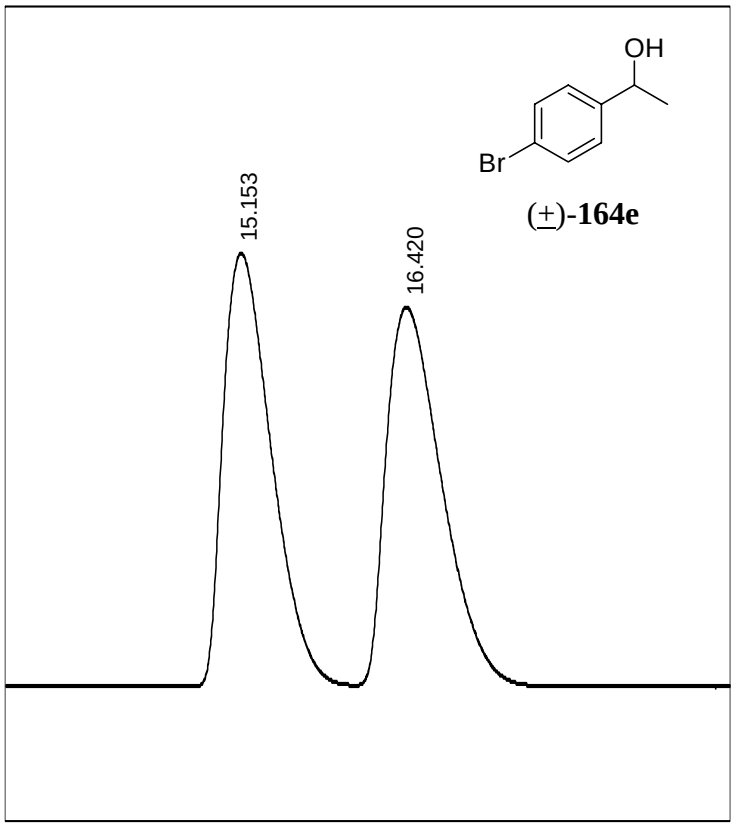
(±)-2-Bromo-1-(4-bromophenyl)ethanol



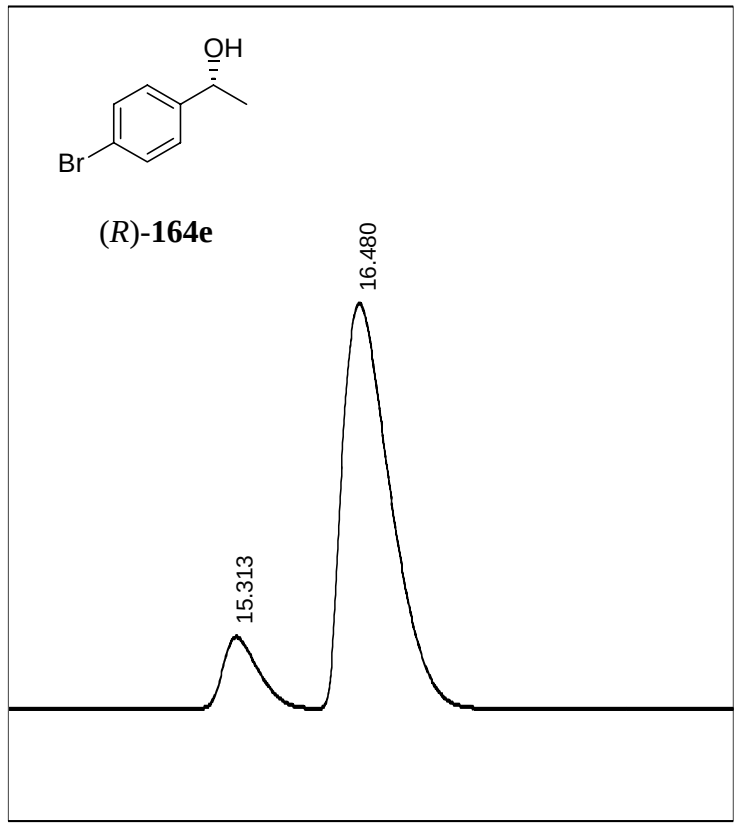
(*S*)-2-Bromo-1-(4-bromophenyl)ethanol

(*S*)-**161e** (enantiomeric purity 89%) obtained *via* the reduction of 4-bromophenacyl bromide (**160e**) using 10 mol% catalyst **169**

HPLC analysis: ***Chromatogram* 7**



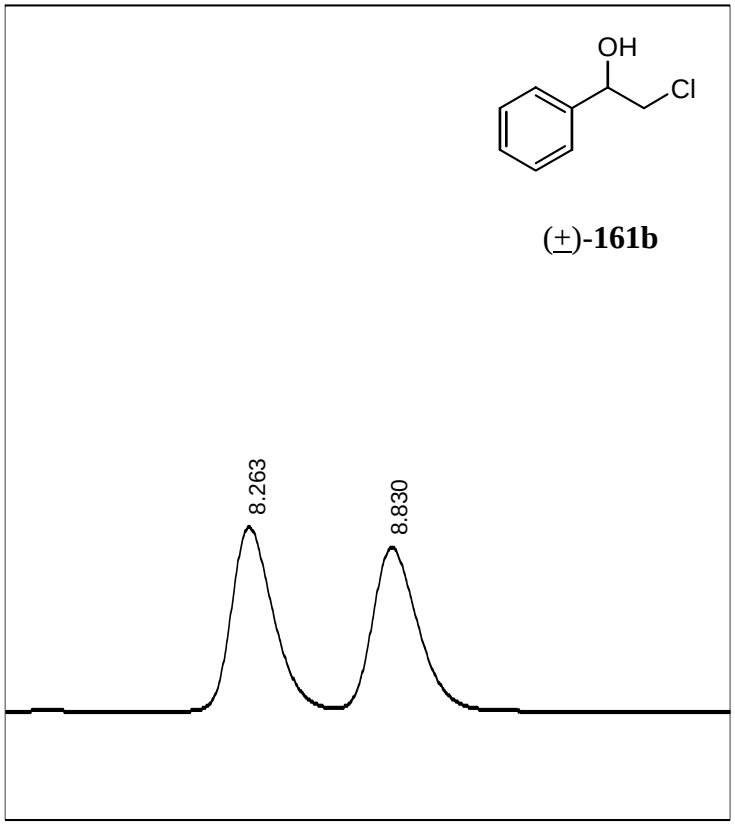
1-(4-Bromophenyl)ethanol



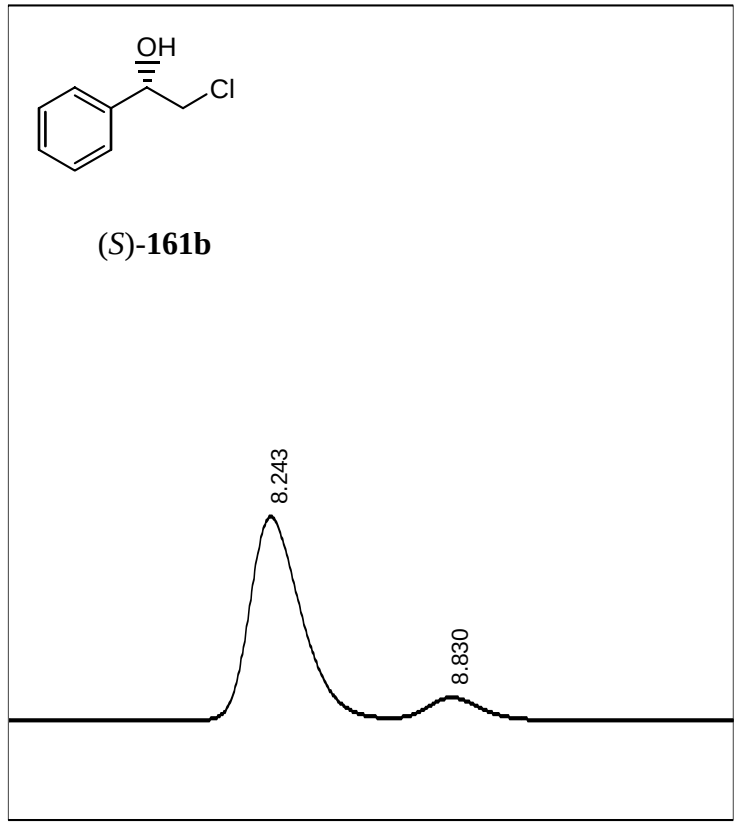
(*R*)-1-(4-Bromophenyl)ethanol

(*R*)-**164e** (enantiomeric purity 77%) obtained *via* the reduction of 4-bromoacetophenone (**163e**) using 10 mol% catalyst **169**

HPLC analysis: ***Chromatogram* 8**



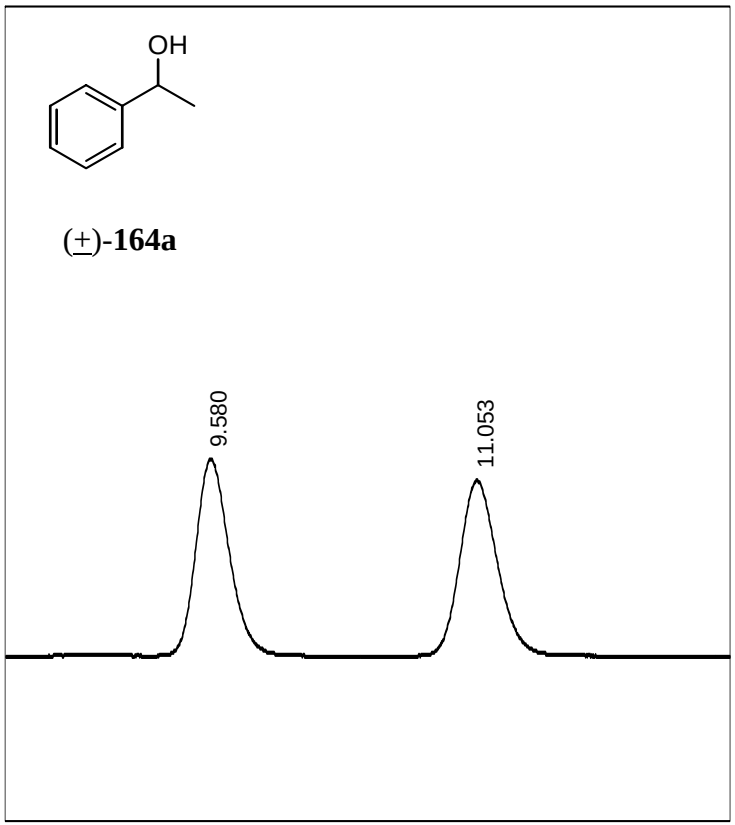
(±)-2-Chloro-1-phenylethanol



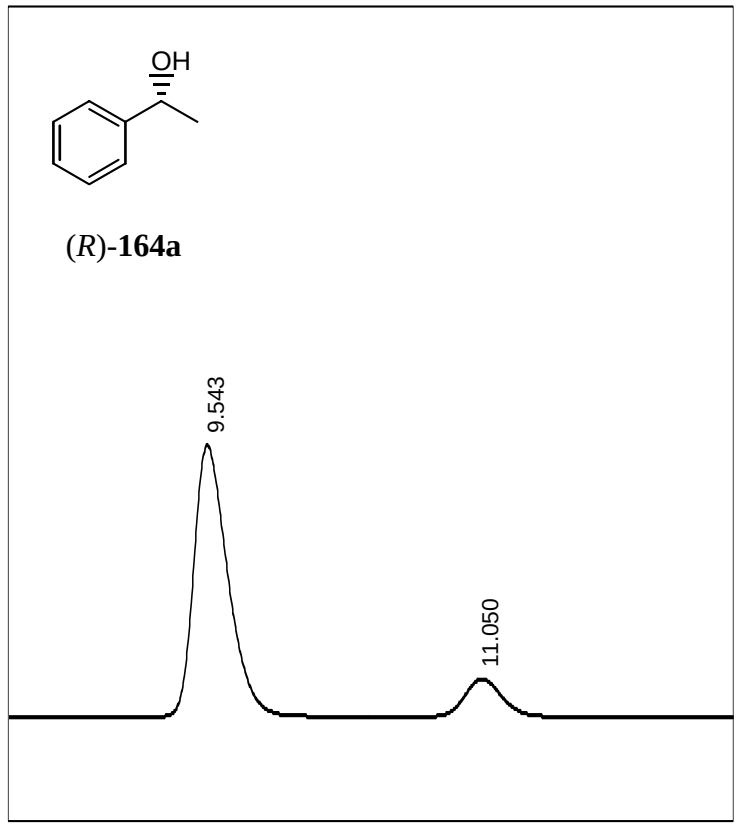
(*S*)-2-Chloro-1-phenylethanol

(*S*)-**161b** (enantiomeric purity 78%) obtained *via* the reduction of phenacyl chloride (**160b**) using 10 mol% catalyst **170**

HPLC analysis: ***Chromatogram* 9**



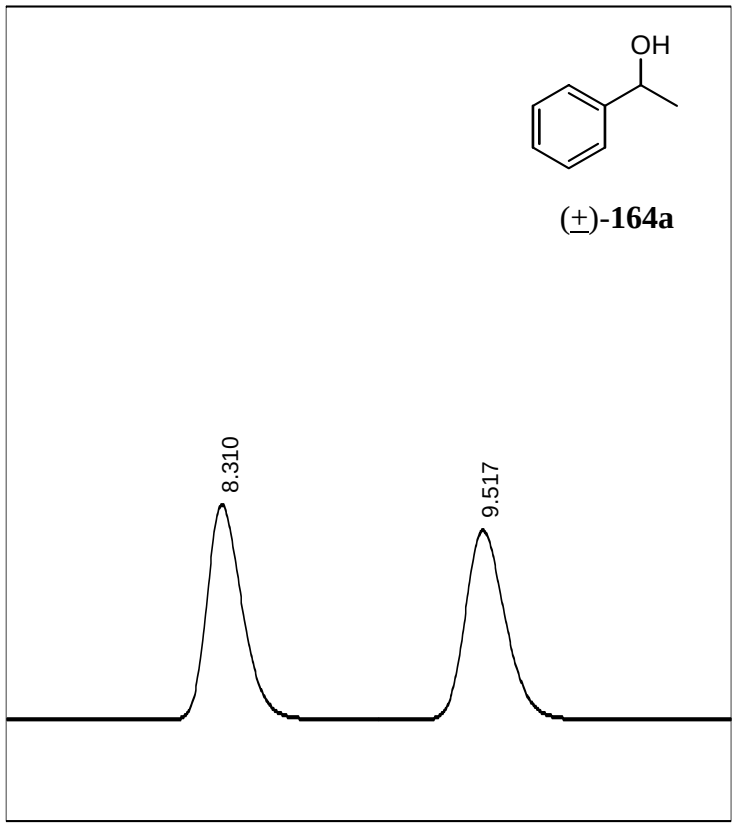
(±)-1-Phenylethanol



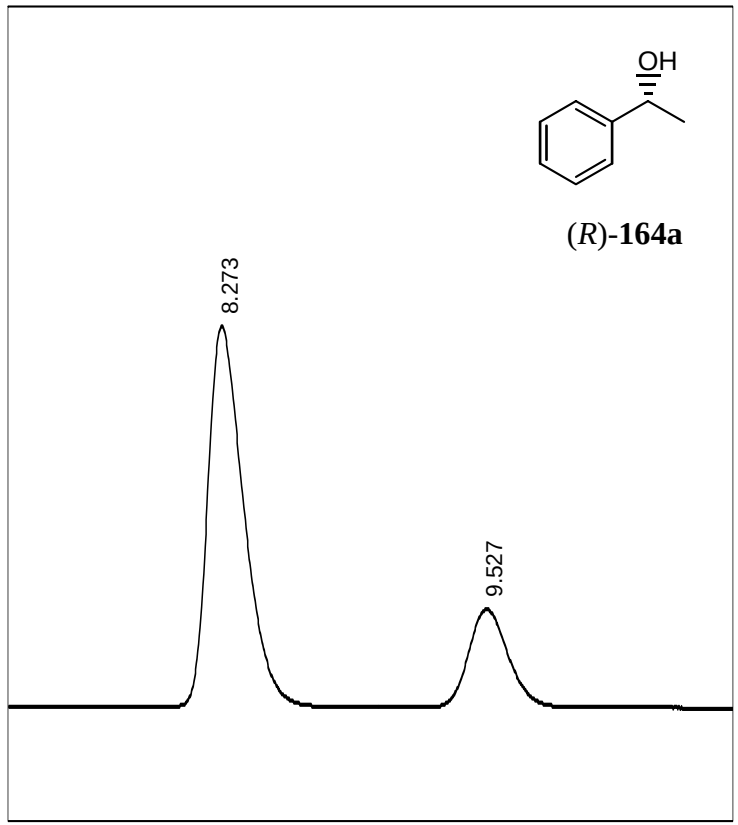
(*R*)-1-Phenylethanol

(*S*)-**164a** (enantiomeric purity 74%) obtained *via* the reduction of acetophenone (**163a**) using 10 mol% catalyst **170**

HPLC analysis: ***Chromatogram* 10**



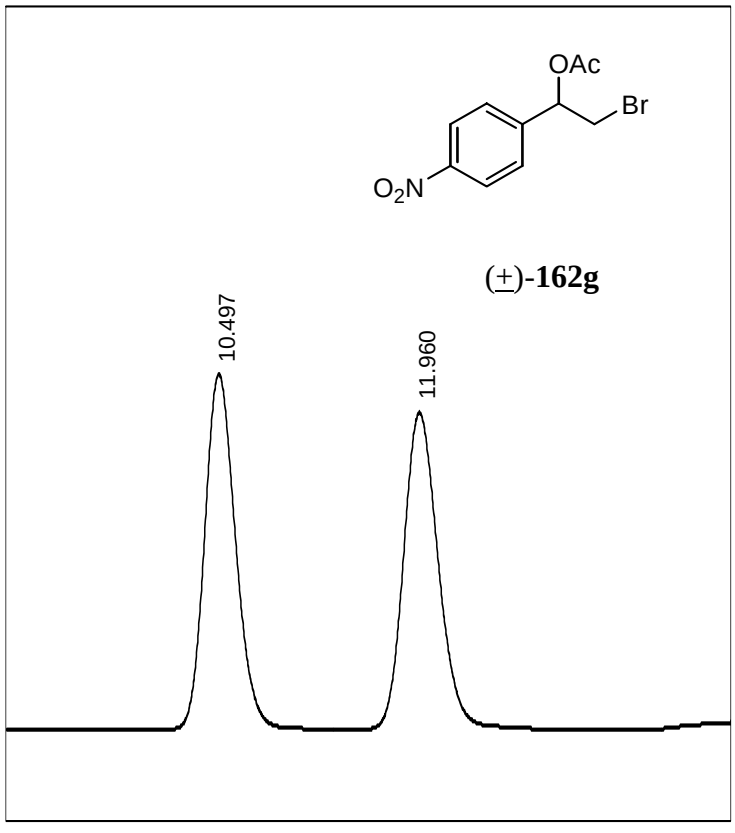
(±)-1-Phenylethanol



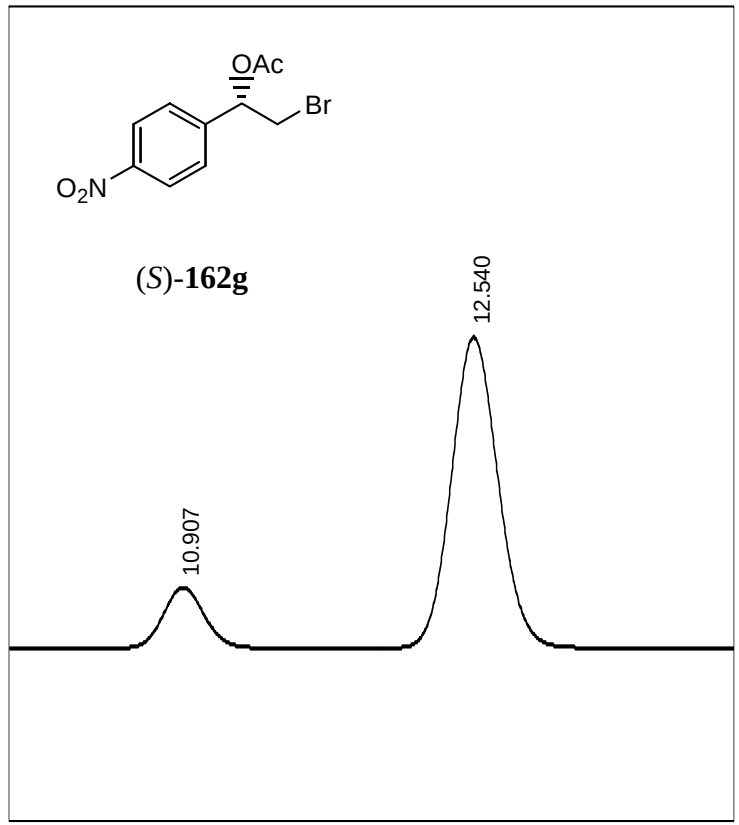
(*R*)-1-Phenylethanol

(*R*)-**164a** (enantiomeric purity 56%) obtained *via* the reduction of acetophenone (**163a**) using 10 mol% catalyst **181**

HPLC analysis: ***Chromatogram* 14**



(±)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane



(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane

(*S*)-**162g** (enantiomeric purity 72%) an acetate derivative of (*S*)-**161g** obtained *via* the reduction of **160g** using 10 mol% catalyst **181**

HPLC analysis: ***Chromatogram* 15**

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **156.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
P(1)	9193(1)	5109(1)	9386(1)	38(1)
O(1)	8392(2)	5349(1)	8648(1)	51(1)
N(1)	8489(2)	5495(1)	10247(1)	43(1)
N(2)	10900(2)	5626(1)	9502(1)	49(1)
N(3)	9304(2)	3941(1)	9469(1)	37(1)
N(4)	7242(3)	3450(2)	8168(1)	55(1)
C(1)	11574(4)	6162(2)	8833(2)	74(1)
C(2)	11329(5)	7204(2)	9021(2)	95(1)
C(3)	10662(4)	7260(2)	9829(2)	74(1)
C(4)	10912(3)	6270(2)	10194(1)	51(1)
C(5)	9689(3)	5910(2)	10755(1)	50(1)
C(6)	7057(2)	5235(1)	10559(1)	41(1)
C(7)	5822(2)	5083(2)	10056(1)	49(1)
C(8)	4400(3)	4863(2)	10364(2)	58(1)
C(9)	4186(3)	4799(2)	11167(2)	65(1)
C(10)	5399(3)	4947(2)	11666(2)	66(1)
C(11)	6833(3)	5164(2)	11374(1)	54(1)
C(12)	9928(3)	3524(2)	10213(1)	47(1)
C(13)	10409(3)	2521(2)	9967(2)	54(1)

C(14)	10955(3)	2661(2)	9126(1)	53(1)
C(15)	9784(2)	3353(1)	8774(1)	41(1)
C(16)	8464(3)	2814(2)	8399(1)	49(1)
C(17)	5863(3)	3147(2)	7880(1)	48(1)
C(18)	5604(3)	2206(2)	7649(2)	62(1)
C(19)	4209(4)	1938(3)	7326(2)	83(1)
C(20)	3058(4)	2579(4)	7235(2)	95(1)
C(21)	3290(3)	3505(3)	7471(2)	81(1)
C(22)	4663(3)	3790(2)	7798(1)	61(1)

Table II Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **163.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
P(1)	4303(1)	8874(1)	1898(1)	49(1)
P(2)	684(1)	1915(1)	7056(1)	46(1)
O(1)	3340(2)	8679(2)	1488(1)	64(1)
O(2)	1671(1)	1964(2)	6685(1)	61(1)
N(1)	4424(2)	10120(2)	2561(1)	49(1)
N(2)	5235(2)	9415(3)	1332(2)	57(1)
N(3)	4614(2)	7489(3)	2391(2)	53(1)
N(4)	2990(2)	4399(3)	2083(2)	57(1)
N(5)	412(2)	607(2)	7636(1)	47(1)
N(6)	-278(2)	1683(3)	6439(1)	57(1)

N(7)	503(2)	3291(3)	7600(1)	51(1)
N(8)	2103(2)	6285(3)	7025(2)	60(1)
C(1)	5088(3)	9531(4)	466(2)	74(1)
C(2)	5000(4)	11049(4)	309(2)	91(1)
C(3)	5263(3)	11771(4)	1042(2)	75(1)
C(4)	5664(2)	10700(3)	1616(2)	58(1)
C(5)	5376(2)	10855(3)	2474(2)	59(1)
C(6)	3890(2)	10218(3)	3276(2)	53(1)
C(7)	4296(3)	10857(4)	3932(2)	69(1)
C(8)	3738(4)	11022(5)	4609(2)	91(1)
C(9)	2786(4)	10564(6)	4639(3)	103(2)
C(10)	2379(3)	9883(5)	4000(3)	93(1)
C(11)	2919(2)	9704(4)	3319(2)	71(1)
C(12)	5541(2)	7440(4)	2870(2)	68(1)
C(13)	5662(2)	5966(4)	3075(2)	72(1)
C(14)	5217(2)	5225(4)	2373(2)	67(1)
C(15)	4364(2)	6112(3)	2080(2)	47(1)
C(16)	3332(2)	5705(3)	2375(2)	51(1)
C(17)	2586(2)	4258(3)	1328(2)	50(1)
C(18)	2464(2)	5376(3)	821(2)	55(1)
C(19)	2067(2)	5210(4)	67(2)	71(1)
C(20)	1774(3)	3952(5)	-200(2)	86(1)
C(21)	1871(3)	2870(4)	286(3)	83(1)
C(22)	2278(2)	2994(3)	1044(2)	67(1)
C(23)	2981(3)	3266(4)	2621(3)	73(1)
C(24)	-121(3)	1735(4)	5569(2)	79(1)
C(25)	-184(4)	294(5)	5287(2)	101(2)

C(26)	-456(3)	-586(4)	5971(2)	79(1)
C(27)	-816(2)	411(4)	6599(2)	60(1)
C(28)	-575(2)	18(4)	7456(2)	58(1)
C(29)	937(2)	209(3)	8333(2)	47(1)
C(30)	486(2)	-600(4)	8900(2)	63(1)
C(31)	1023(3)	-1065(4)	9544(2)	78(1)
C(32)	2008(3)	-742(4)	9645(2)	82(1)
C(33)	2455(3)	80(4)	9096(2)	70(1)
C(34)	1931(2)	553(3)	8444(2)	58(1)
C(35)	-410(3)	3379(4)	8083(2)	66(1)
C(36)	-494(3)	4882(4)	8273(2)	78(1)
C(37)	-136(2)	5551(4)	7520(2)	73(1)
C(38)	710(2)	4630(3)	7229(2)	51(1)
C(39)	1764(2)	5118(3)	7468(2)	54(1)
C(40)	2515(2)	6145(3)	6284(2)	56(1)
C(41)	2612(2)	4853(4)	5933(2)	62(1)
C(42)	3050(3)	4705(5)	5210(2)	85(1)
C(43)	3406(3)	5826(8)	4807(3)	103(2)
C(44)	3313(3)	7070(6)	5130(3)	98(1)
C(45)	2876(3)	7250(4)	5862(2)	78(1)
C(46)	2105(4)	7610(4)	7409(3)	76(1)

Table III Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for (**2*R*,5*S***) **115A**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
Cl	8393(3)	8593(2)	1846(1)	94(1)
P(1)	8283(2)	7986(1)	3170(1)	67(1)
O(1)	10240(6)	8061(5)	3575(4)	105(2)
N(1)	6441(6)	8602(4)	3666(3)	62(1)
N(2)	7285(7)	6851(4)	3081(4)	78(1)
C(1)	8132(18)	5809(7)	3318(7)	124(3)
C(2)	6520(20)	5182(8)	3728(8)	139(4)
C(3)	5140(19)	5947(8)	4029(7)	124(4)
C(4)	5185(10)	6858(7)	3353(5)	83(2)
C(5)	4689(9)	7932(6)	3703(8)	109(3)
C(6)	6328(8)	9683(5)	3844(4)	63(2)
C(7)	4524(11)	10162(6)	4042(5)	88(2)
C(8)	4483(19)	11245(9)	4215(6)	117(3)
C(9)	6070(20)	11845(8)	4186(6)	114(3)
C(10)	7867(17)	11364(8)	4015(6)	107(3)
C(11)	7975(10)	10300(6)	3848(5)	81(2)

Table IV Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **(2*S*,5*S*)-172**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
P(1)	7632(1)	4575(1)	1078(1)	39(1)
O(1)	7862(3)	5221(3)	1492(1)	53(1)
N(1)	7065(3)	5544(3)	735(1)	46(1)
N(2)	9386(3)	4890(3)	833(1)	44(1)
C(1)	6488(5)	6721(5)	875(1)	64(1)
C(2)	7914(7)	8500(6)	780(2)	117(2)
C(3)	9359(5)	8321(5)	597(2)	82(1)
C(4)	8469(4)	6488(4)	444(1)	57(1)
C(5)	9509(4)	5590(5)	432(1)	55(1)
C(6)	10313(3)	4066(4)	939(1)	43(1)
C(7)	11264(4)	3765(5)	655(1)	60(1)
C(8)	12152(5)	2947(6)	767(2)	75(1)
C(9)	12119(5)	2425(5)	1152(2)	75(1)
C(10)	11203(5)	2742(5)	1433(1)	70(1)
C(11)	10328(4)	3563(5)	1332(1)	55(1)
C(12)	6117(3)	2313(3)	1069(1)	40(1)
C(13)	5432(4)	1440(4)	712(1)	48(1)
C(14)	4274(4)	-288(4)	708(1)	62(1)
C(15)	3786(4)	-1164(4)	1067(2)	68(1)
C(16)	4445(4)	-344(5)	1423(1)	65(1)
C(17)	5632(4)	1399(4)	1426(1)	52(1)

Table V Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **(2*R*,5*S*)-172A**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
P(1)	699(1)	4003(1)	4947(1)	40(1)
O(1)	1195(1)	5445(1)	4902(1)	53(1)
N(1)	-157(1)	3966(2)	4154(1)	49(1)
N(2)	262(1)	3577(2)	6304(1)	46(1)
C(1)	-282(1)	3227(3)	2942(2)	66(1)
C(2)	-890(1)	1936(3)	3208(2)	71(1)
C(3)	-1442(1)	2652(2)	4180(2)	60(1)
C(4)	-884(1)	3727(2)	4942(2)	50(1)
C(5)	-587(1)	3052(3)	6167(2)	60(1)
C(6)	651(1)	3492(2)	7465(1)	44(1)
C(7)	249(1)	2864(2)	8492(2)	55(1)
C(8)	629(1)	2813(2)	9641(2)	64(1)
C(9)	1407(1)	3350(2)	9783(2)	65(1)
C(10)	1817(1)	3942(2)	8769(2)	61(1)
C(11)	1448(1)	4026(2)	7615(2)	52(1)
C(12)	1303(1)	2351(2)	4457(2)	45(1)
C(13)	1830(1)	2533(2)	3461(2)	55(1)
C(14)	2283(1)	1270(3)	3028(2)	71(1)
C(15)	2219(1)	-160(3)	3594(2)	79(1)
C(16)	1702(2)	-374(2)	4576(2)	77(1)
C(17)	1233(1)	877(2)	5010(2)	59(1)

Table VI Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **(2*S*,5*S*)-173**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
P(1)	10877(1)	499(1)	511(1)	36(1)
O(1)	12825(2)	1001(1)	428(1)	52(1)
N(1)	9333(2)	980(1)	1125(1)	43(1)
N(2)	9235(2)	583(1)	-194(1)	42(1)
N(3)	11222(2)	-687(1)	703(1)	45(1)
C(1)	9946(4)	1781(2)	1632(1)	61(1)
C(2)	8565(5)	2630(2)	1433(2)	80(1)
C(3)	6708(4)	2174(2)	1181(2)	71(1)
C(4)	7310(3)	1194(2)	827(1)	45(1)
C(5)	7460(3)	1174(2)	-13(1)	50(1)
C(6)	9660(3)	315(1)	-928(1)	44(1)
C(7)	8269(4)	452(2)	-1495(1)	61(1)
C(8)	8745(6)	181(2)	-2216(1)	79(1)
C(9)	10558(6)	-217(2)	-2398(2)	78(1)
C(10)	11929(5)	-356(2)	-1847(2)	72(1)
C(11)	11529(4)	-93(2)	-1118(1)	58(1)
C(12)	9486(4)	-1342(2)	777(2)	58(1)
C(13)	9819(5)	-2109(2)	1378(2)	79(1)
C(14)	11729(5)	-2688(2)	1243(2)	77(1)
C(15)	13482(5)	-1982(2)	1168(2)	75(1)
C(16)	13102(3)	-1209(2)	563(2)	58(1)

Table VII Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **(2*R*,5*S*)-173A**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
P(1)	5611(1)	5328(1)	9801(1)	39(1)
O(1)	4164(2)	4790(2)	9543(1)	51(1)
N(1)	5720(2)	5851(2)	10679(1)	42(1)
N(2)	6947(2)	4233(2)	9637(1)	45(1)
N(3)	6091(2)	6852(2)	9449(1)	43(1)
C(1)	6478(3)	5191(3)	11307(2)	58(1)
C(2)	7599(4)	6262(3)	11571(2)	69(1)
C(3)	6762(3)	7564(3)	11459(2)	59(1)
C(4)	5841(3)	7339(2)	10749(1)	45(1)
C(5)	6567(3)	7818(2)	10027(1)	45(1)
C(6)	6295(3)	7161(2)	8683(1)	41(1)
C(7)	7083(3)	8299(3)	8466(2)	52(1)
C(8)	7228(4)	8639(3)	7716(2)	64(1)
C(9)	6589(4)	7848(4)	7171(2)	70(1)
C(10)	5826(3)	6695(3)	7379(2)	61(1)
C(11)	5679(3)	6345(3)	8124(1)	49(1)
C(12)	6705(3)	2834(2)	9407(2)	53(1)
C(13)	7547(4)	2519(3)	8695(2)	63(1)
C(14)	9195(3)	2847(3)	8773(2)	63(1)
C(15)	9421(3)	4307(3)	9029(2)	63(1)
C(16)	8538(3)	4566(3)	9733(2)	55(1)

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