TOWARDS DEVELOPMENT OF EFFECTIVE CHIRAL CATALYSTS/CATALYTIC SOURCES FOR THE BORANE-MEDIATED ASYMMETRIC REDUCTION OF PROCHIRAL KETONES

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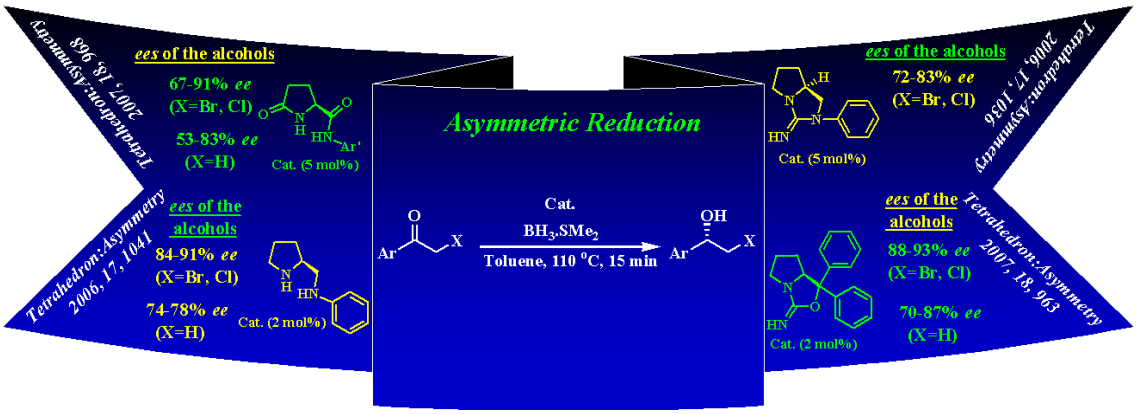
ABBREVIATIONS

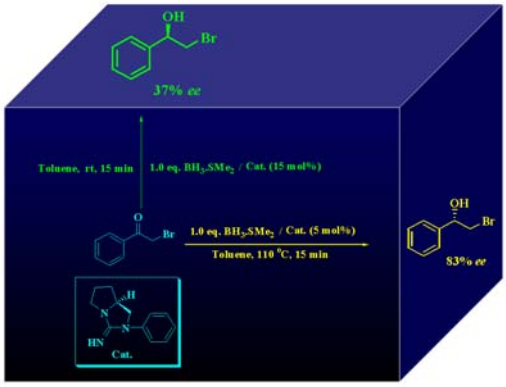
Ac	acetyl
Alpine-Borane	*B*-3-pinanyl-9-borabicyclo[3.3.1]nonane
BAr_F	tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate
Boc	*tert*-butoxycarbonyl
Bp	boiling point
cat.	catalyst
cod	cycloocta-1,5-diene
CPME	cyclopentyl methyl ether
DIP-Chloride	diisopinocampheylchloroborane
DIPEA	*N*,*N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
equiv	equivalents
Ipc_2BH	diisopinocampheylborane
Ipc_2BCl	diisopinocampheylchloroborane
Me	methyl
min	minutes
Mp	melting point
MS	molecular sieves
Ph	phenyl
Pr	propyl
i-Pr or Pr^i	*iso* propyl
rt	room temperature
TBA Br_3	tetrabutylammonium tribromide

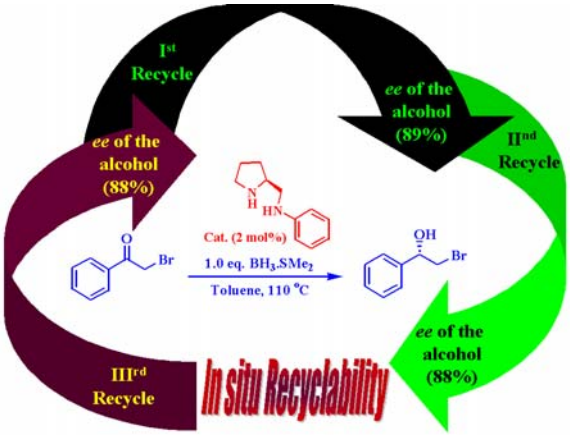
TBHP	*tert*-butyl hydroperoxide
tert-	*tertiary*
THF	tetrahydrofuran
$^{-}$OTf	trifluoromethanesulfonate

Work at a Glance



Enantiomeric Switch





ABSTRACT

Synthesis of enantiomerically pure molecules has been and continues to be one of the most fascinating areas in science of synthesis due to the challenges and attractions involved in such endeavors. More interestingly recent developments in medicinal and pharmaceutical chemistry emphasize the need for obtaining enantiomerically pure molecules in large scale due to the dependence of the biological activity of the most of the drug molecules on the enantiomeric purity of these molecules. The recent survey on "***Trends in the development of chiral drugs***" clearly demonstrates that there is a continuous growth in the worldwide sales of chiral drugs in enantiomerically pure forms. The share of single enantiomer dosage from drugs is 27% in 1996, 29% in 1997, 30% in 1998, 32% in 1999, 34% in 2000, 38% in 2001, 39% in 2002 and the percentage is expected to be higher in the coming years.

This thesis deals with the synthesis and applications of chiral catalysts/catalytic sources containing ***N-(C=NH)-N***, ***N-(C=NH)-O***, ***diamine*** and ***diamide*** structural frameworks, in the borane-mediated asymmetric reduction of prochiral ketones and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter presents very brief literature survey on the applications of some important and recent chiral catalysts in asymmetric synthesis and also brief/relevant literature survey on asymmetric reduction of prochiral ketones using chiral boron reagents and catalysts.

The second chapter deals with studies towards the development of novel and effective chiral catalysts/catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones with the following main objectives.

1. To synthesize (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**), containing the ***N-(C=NH)-N*** structural framework (guanidine framework), and examine its catalytic potential in the borane-mediated enantioselective reduction of prochiral ketones. Our objective is also directed towards understanding the nature of the chiral catalyst and examining its potential for *in situ* recyclability.

2. To synthesize (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**), containing the ***N-(C=NH)-O*** moiety, and study the applications as chiral catalyst/catalytic source in the borane-mediated asymmetric reduction of prochiral ketones.

3. To study the efficiency of (2*S*)-2-anilinomethylpyrrolidine (**134**) as chiral catalytic source in the borane-mediated asymmetric reductions of prochiral ketones and also to study the nature of actual chiral catalyst.

4. To synthesize representative chiral diamides [(2*S*)-5-oxo-2-(arylamino)carbonyl-pyrrolidines] (**137**, **149-156**) derived from abundantly available (*S*)-glutamic/(*S*)-pyroglutamic acids and utilize them as effective chiral catalytic precursors in the borane-mediated asymmetric reduction of prochiral ketones.

(5*S*)-1,3-Diaza-2-imino-3-phenylbicyclo(3.3.0)octane: First Example of Guanidine Based *in situ* Recyclable Chiral Catalytic Source for Borane-Mediated Asymmetric Reduction of Prochiral Ketones

We have synthesized the desired (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) *via* the reaction of the chiral diamine (**134**) with cyanogen bromide according to the general literature procedure (Scheme 10, Page no. 49) and successfully employed, for the first time, as a chiral catalytic source for the borane-mediated asymmetric reduction of prochiral α-halo ketones to provide the corresponding secondary alcohols in high enantiomeric purities (eq. 83, Table 2, Page nos. 53 & 57). Also the potential of the chiral catalytic species **141** [generated *in situ via* the reaction of **135** with $BH_3.SMe_2$ in refluxing toluene (Scheme 11, Page no. 58)] as an *in situ* recyclable chiral catalytic source for the borane-mediated chiral reduction processes has been demonstrated (Table 4, Scheme 13, Page nos. 62 & 63). We have also observed a remarkable reversal of stereo-selectivity (enantiomeric switch) from room temperature (≈30 ^{o}C) to high temperature (110 ^{o}C) in the borane-mediated chiral reduction of phenacyl bromide using (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) as catalyst/catalytic source (eq. 90, Table 3, Page no. 60).

(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane: A Novel Chiral Catalytic Source Containing the *N-(C=NH)-O* Moiety for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones

(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**), a novel chiral catalytic source containing the ***N-(C=NH)-O*** moiety, has been synthesized *via* the

reaction of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**143**) with cyanogen bromide according to the equation 91 (Page no. 65) and successfully utilized, for the first time, as a chiral catalytic source in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene to provide the corresponding secondary alcohols with up-to 93% enantiomeric purities (eqs. 93 & 95, Tables 6 & 7, Page nos. 69 & 72). We have also observed an interesting reversal of stereo-selectivity from room temperature (although the levels of reversal of stereoselectivity is not impressive) to high temperature (110 ^{o}C) in the borane-mediated chiral reduction of phenacyl bromide (eq. 99, Table 8, Page no. 74).

(2*S*)-2-Anilinomethylpyrrolidine: an Efficient *in situ* Recyclable Chiral Catalytic Source for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones in Refluxing Toluene

(2*S*)-2-Anilinomethylpyrrolidine (**134**) was successfully utilized as a chiral catalytic source in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene to provide the corresponding secondary alcohols with up-to 91% enantiomeric purities (eqs. 103 & 105, Tables 10 & 11, Page nos. 81 & 83) and also the potential of the catalytic species **148** [generated *in situ via* the reaction of **134** with $BH_3.SMe_2$ in refluxing toluene (Scheme 16, Page no. 85)] as an *in situ* recyclable chiral catalytic source in the borane-mediated chiral reduction processes has been demonstrated (Table 12, Scheme 18, Page nos. 87 & 88).

Chiral Diamides as Efficient Catalytic Precursors for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones

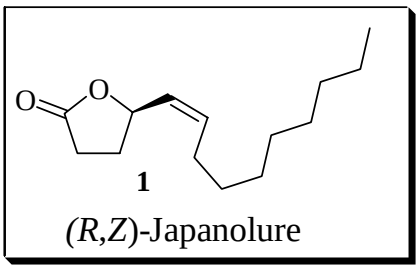
Chiral diamides [(2*S*)-5-oxo-2-(arylamino)carbonylpyrrolidines] (**137**, **149-156**) derived from abundantly available (*S*)-glutamic/(*S*)-pyroglutamic acids were synthesized (Scheme 10 & eq. 108, Page nos. 49 & 95) and successfully utilized as effective chiral catalytic sources in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene to provide the corresponding secondary alcohols with up-to 91% enantiomeric purities (eqs. 109-111, Tables 15-17, Page nos. 101-103).

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

CONTENTS

INTRODUCTION

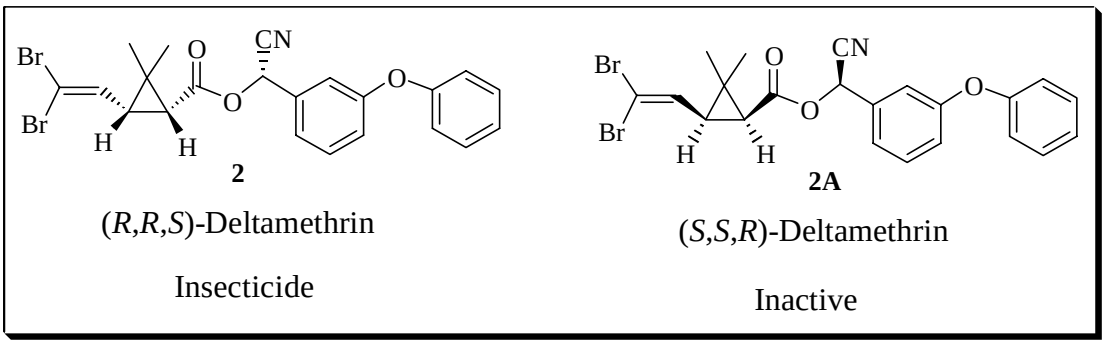
Synthesis of enantiomerically pure molecules has been and continues to be one of the most fascinating areas in science of synthesis due to the challenges and attractions involved in such endeavors.[1-3] More interestingly recent developments in medicinal and pharmaceutical chemistry emphasize the need for obtaining enantiomerically pure molecules in large scale due to the dependence of the biological activity of the most of the drug molecules on the enantiomeric purity of these molecules,[1-3] *i.e.*, 1). biological activity/pharmacology of the drug molecule is often associated with the enantiomeric purity, for example (*R*,*Z*)-japanolure (**1**) is the Japanese beetle pheromone. The presence of even 1% of the other enantiomer reduces 50% activity (Fig. 1).[1,4] 2). Some times only one of the enantiomeric pairs might have the activity of interest and the other might be inactive or might have different type of activity (this activity might be even harmful). For example i). (*R*,*R*,*S*)-deltamethrin (**2**) is a potent insecticide where as its enantiomer (*S*,*S*,*R*)-deltamethrin (**2A**) has no activity (Fig. 2).[1] ii). (*S*,*S*)-Ethambutol (**3**) is a tuberculostatic while (*R*,*R*)-ethambutol (**3A**) causes blindeness (undesired activity) (Fig. 3).[1] 3). Both the enantiomers might have same activity and exhibit different rates of activity. For example i). (*R*)-isoproterenol (**4**) exhibit β-adrenoreceptor activity 90 times more than the corresponding (*S*) enantiomer (**4A**) (Fig. 4).[5] ii) (*S*)-Naproxen (**5**) is 28 times more effective anti inflammatory drug than (*R*)-naproxen (**5A**) (Fig. 5).[6]



1

(R,Z)-Japanolure

Figure 1



2

(*R*,*R*,*S*)-Deltamethrin

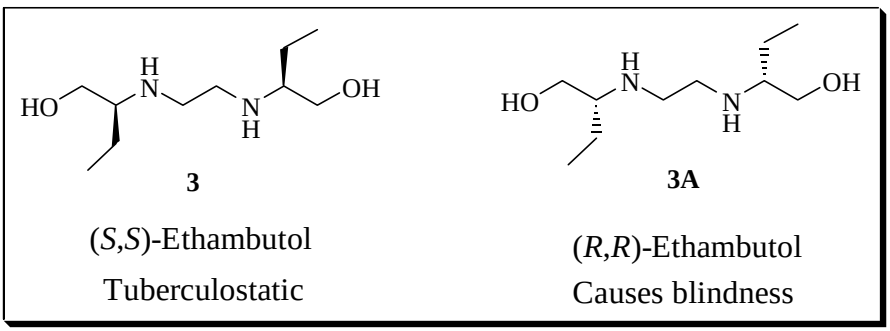
Insecticide

2A

(*S*,*S*,*R*)-Deltamethrin

Inactive

Figure 2



3

(*S*,*S*)-Ethambutol

Tuberculostatic

3A

(*R*,*R*)-Ethambutol

Causes blindness

Figure 3

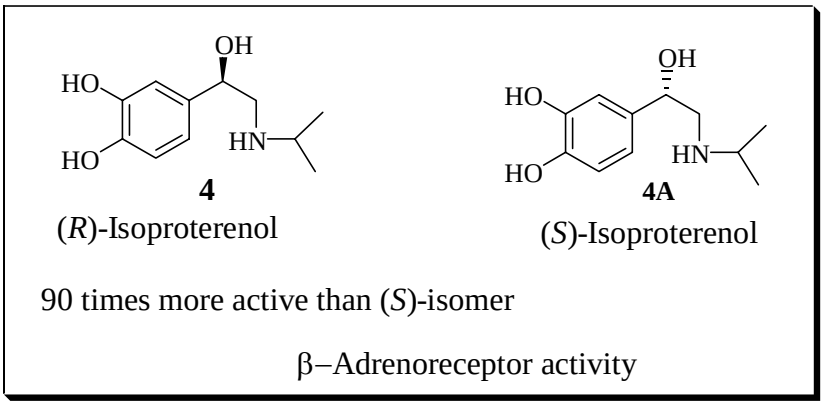


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Figure 4

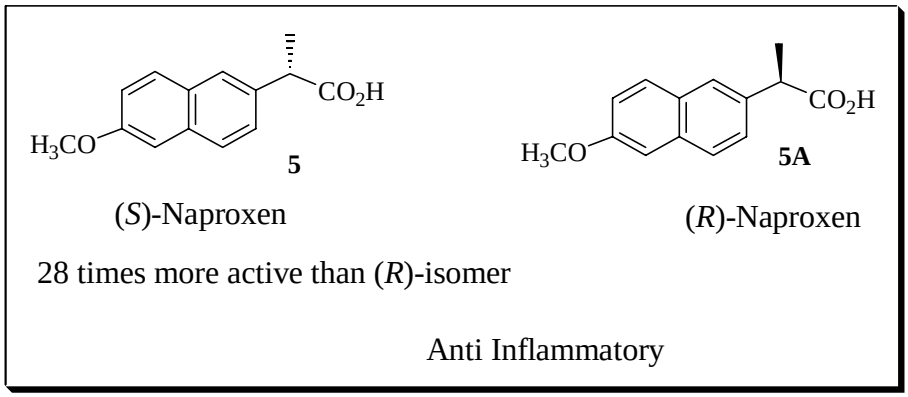
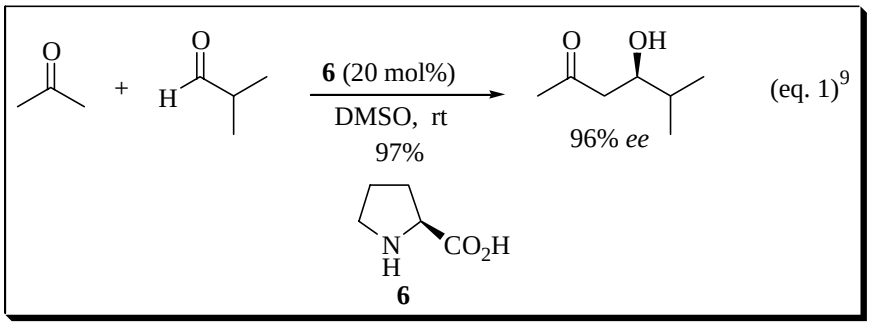


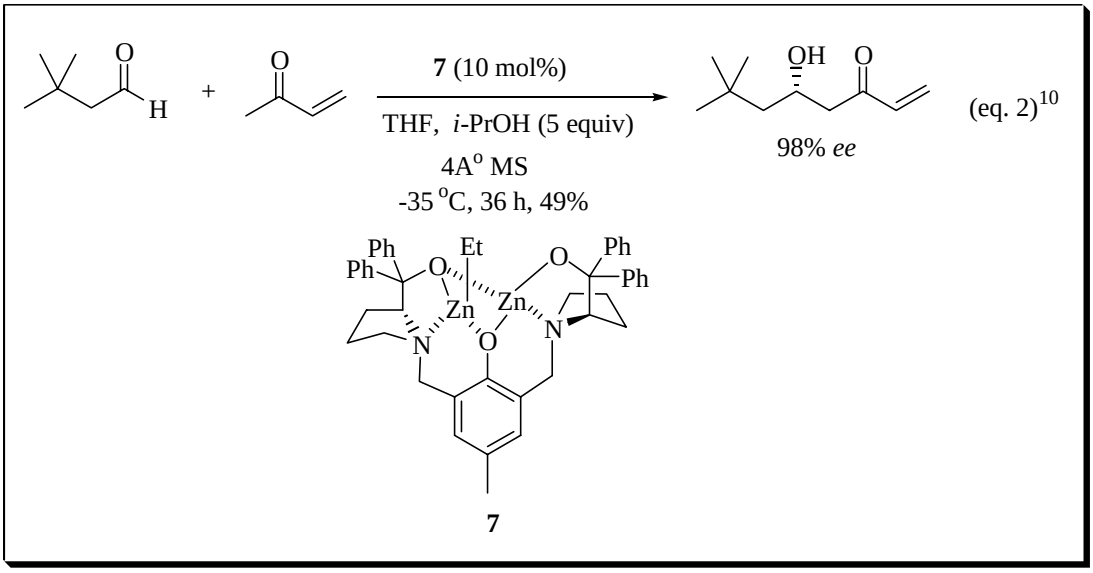
Figure 5

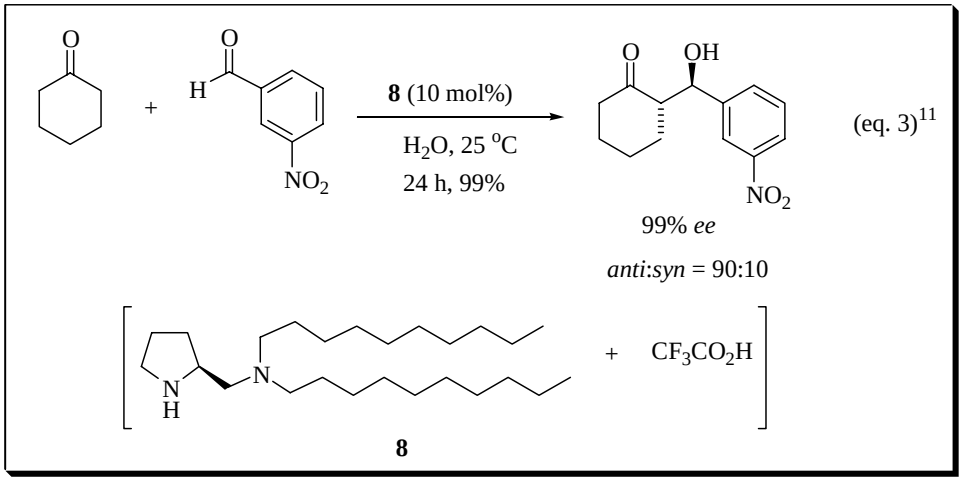
The recent survey on "***Trends in the development of chiral drugs***" clearly demonstrates that there is a continuous growth in the worldwide sales of chiral drugs in enantiomerically pure forms. The share of single enantiomer dosage from drugs is 27% in 1996, 29% in 1997, 30% in 1998, 32% in 1999, 34% in 2000, 38% in 2001, 39% in 2002[3] and the percentage is expected to be higher in the coming years.

To meet the present day requirements several synthetic chemists, all over the world, have focused their efforts in this direction and in fact made original and significant contributions in this area of research. Because of their relentless efforts and dedicated work, now various synthetic concepts based on chiral pool, chiral auxiliary, bio-transformations, and chiral catalysis have been systematically developed for obtaining different classes of enantiomerically pure molecules. However, the continuous increasing demand for enantiomerically pure molecules emphasizes also the need for development of easy, economical, and operationally simple procedures for synthesizing these molecules and ***chiral catalysis***, therefore, has now emerged as a method of choice for this purpose. During the last two decades, several chiral catalysts of different dimensions have been developed, keeping the present day requirements as a major concern, for synthesis of large classes of enantiomerically pure molecules of medicinal importance. Some of such selected, recent & important chiral catalysts and their applications for the asymmetric carbon-carbon bond forming reactions [such as aldol reaction (eqs. 1-3),[7-11] Baylis-Hillman reaction (eqs. 4-6),[12-16] Diels-Alder reaction (eqs. 7-10),[8,17-20] Friedel-Crafts reaction (eqs. 11-13),[21-23] Michael addition (eqs. 14-16)[8,24-26] allylation (eqs. 17 & 18),[27-29] and cyanosilylation (Scheme 1 & eq. 19)[30-32]], C-O bond forming reaction [such as epoxidation (eqs. 20-23)[33-37]] and C-H bond forming reaction [such as hydrogenation (eqs. 24 & 25)[38-40]] *etc*. are presented in equations 1-25.

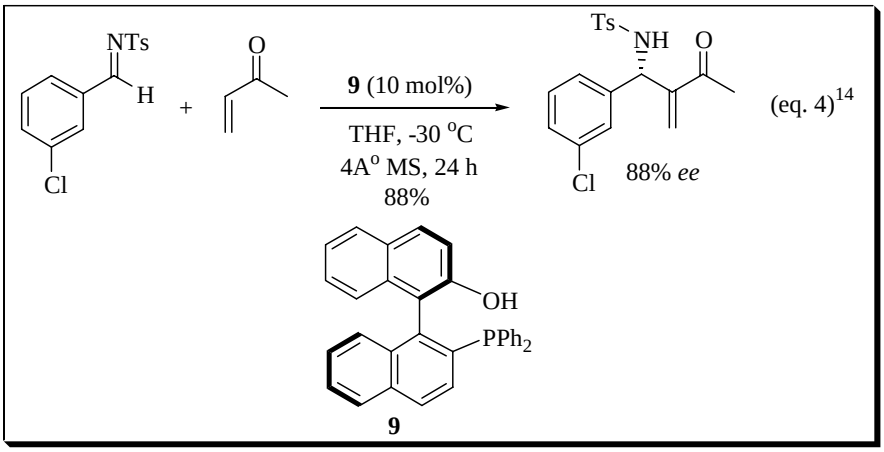
Catalytic Asymmetric Aldol Reaction:[7-11]

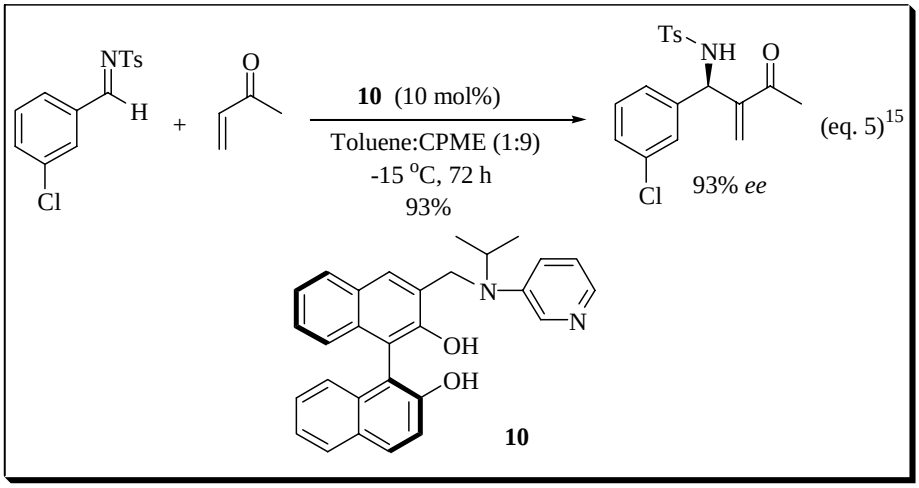


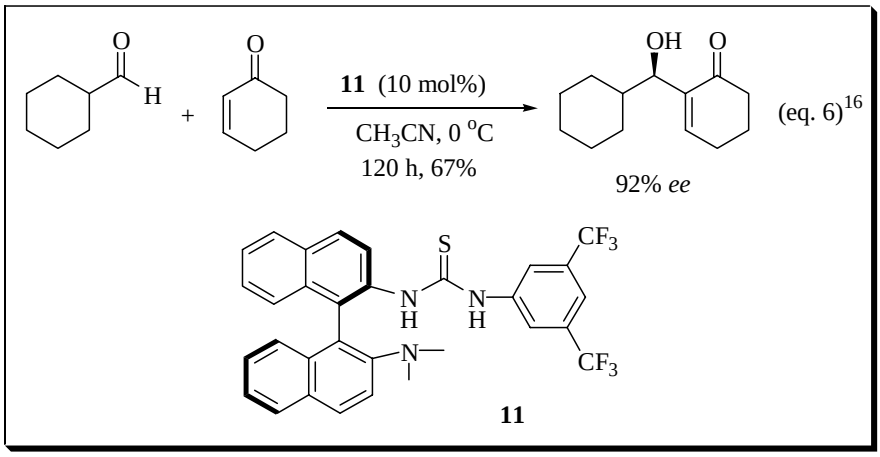




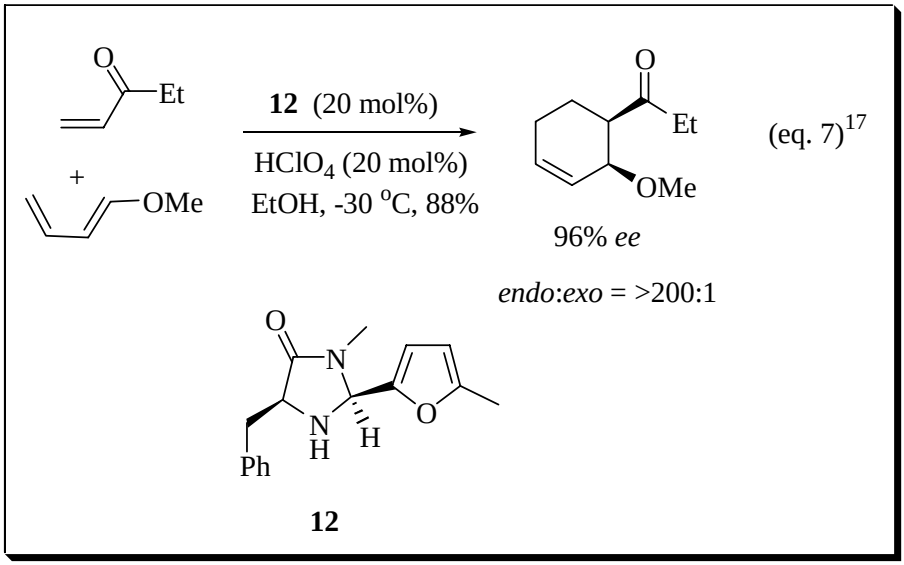
Catalytic Asymmetric Baylis-Hillman Reaction:[12-16]







Catalytic Asymmetric Diels-Alder Reaction:[8,17-20]



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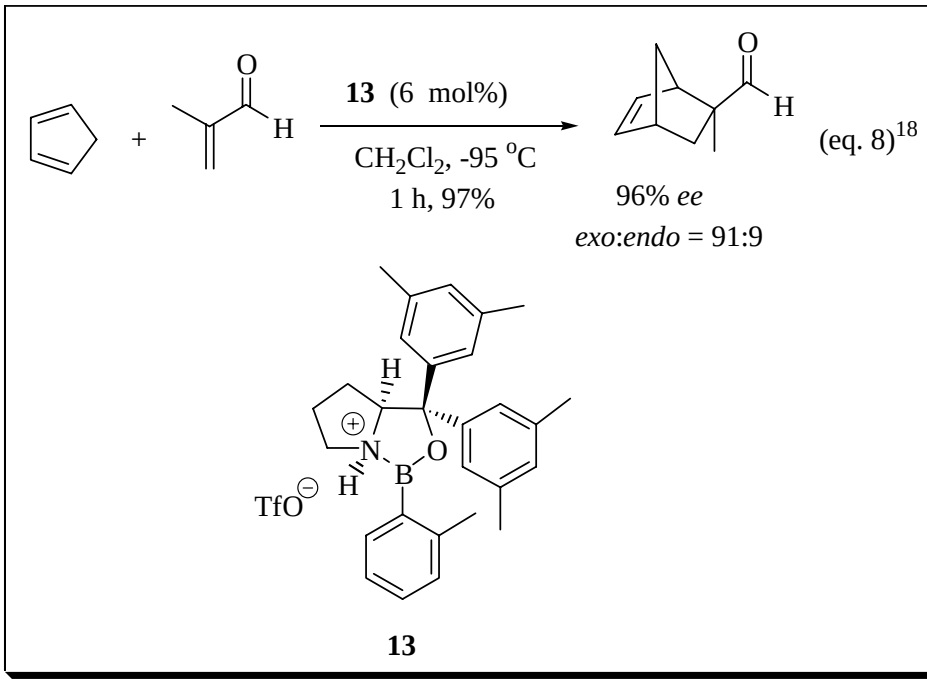

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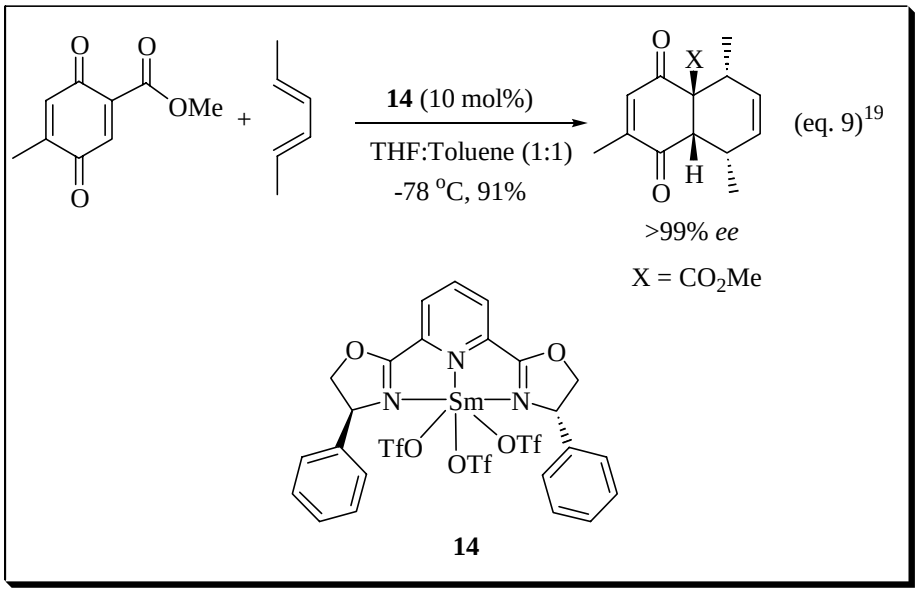
Catalytic Asymmetric Diels-Alder Reaction:[8,17-20]



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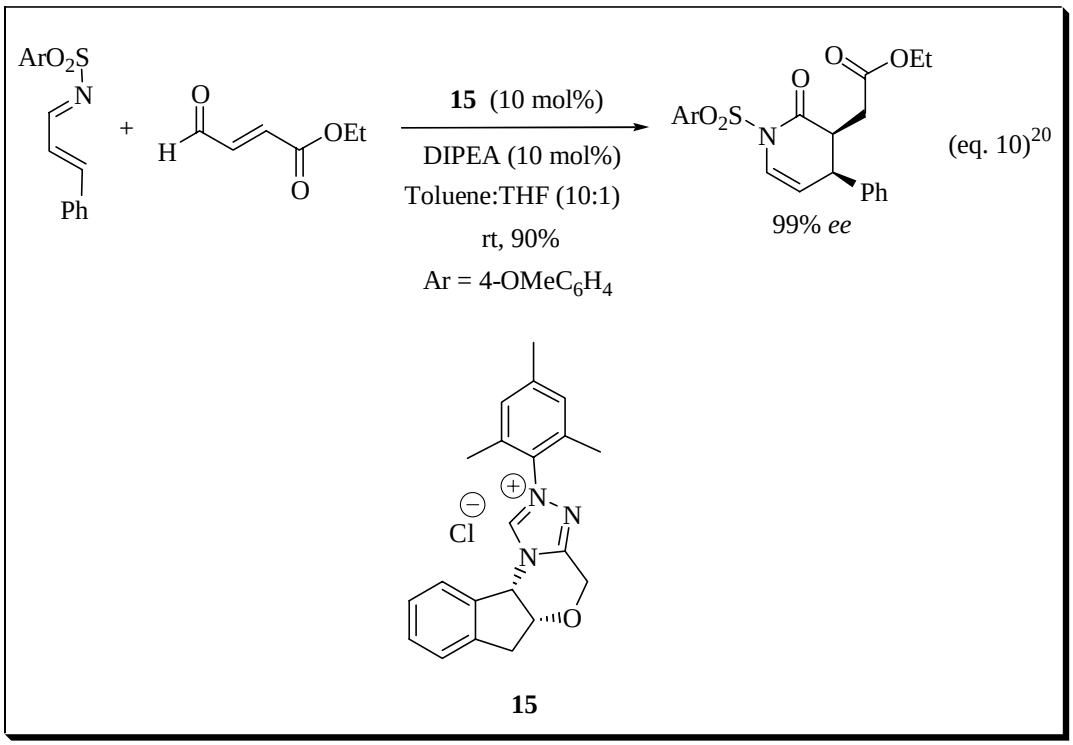

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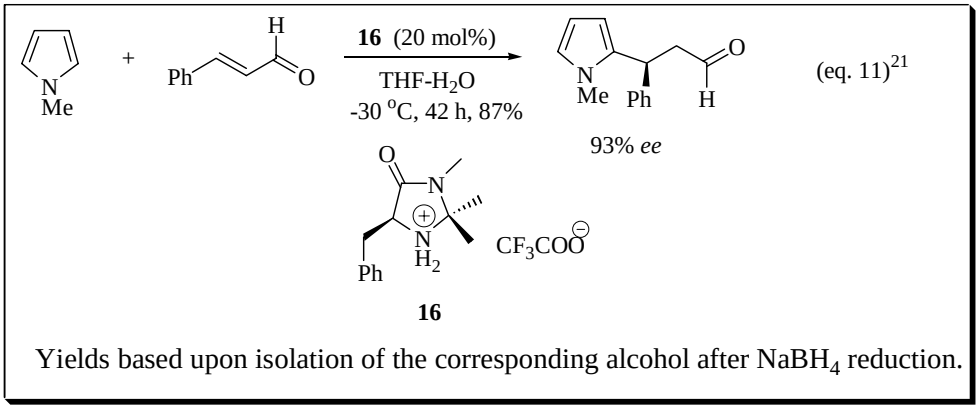
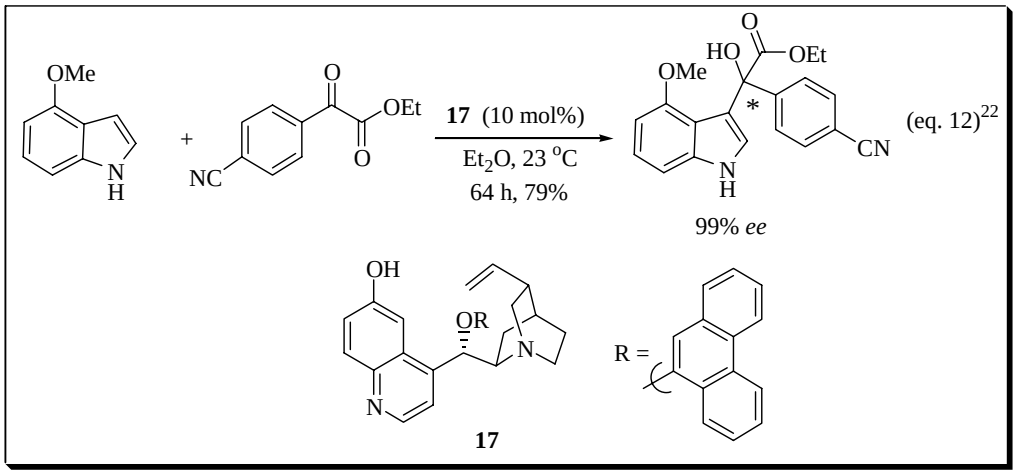
Catalytic Asymmetric Friedel-Crafts Reaction:[21-23]

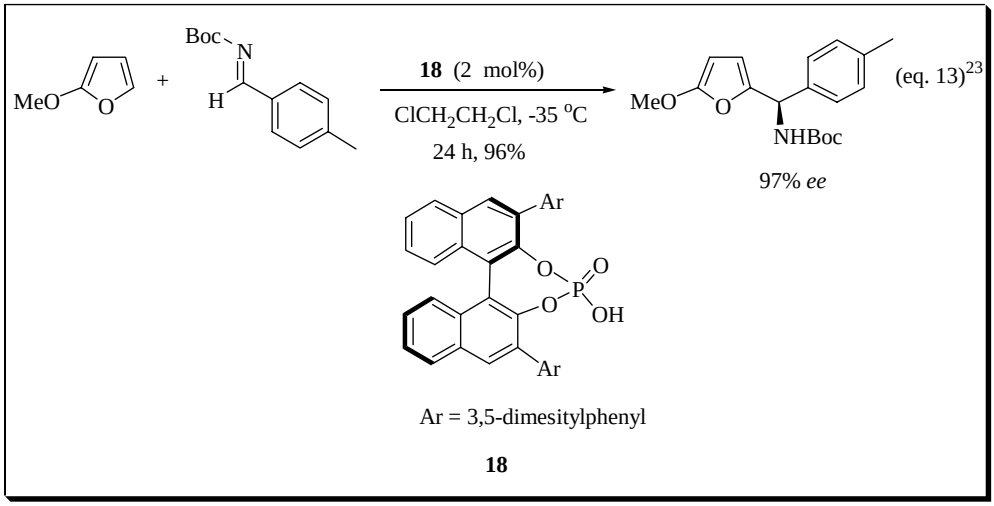


(eq. 11)[21]

Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.

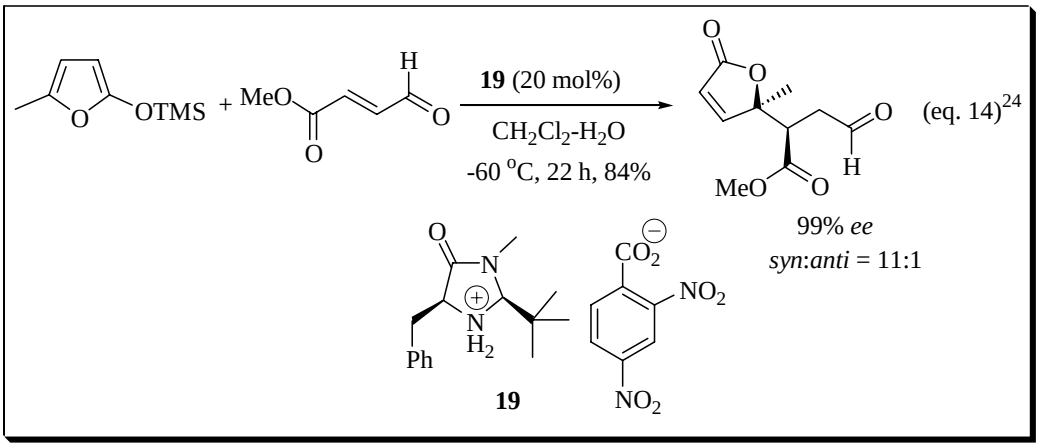


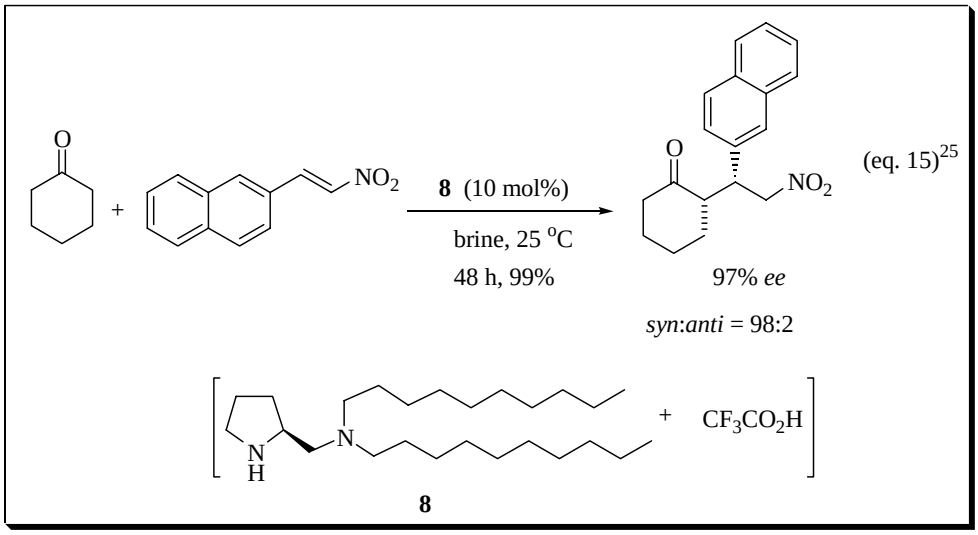
(eq. 12)[22]

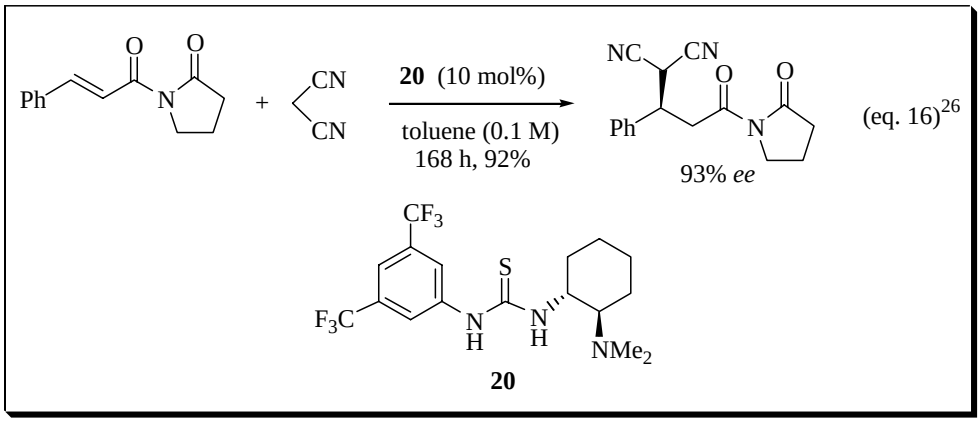


(eq. 13)[23]

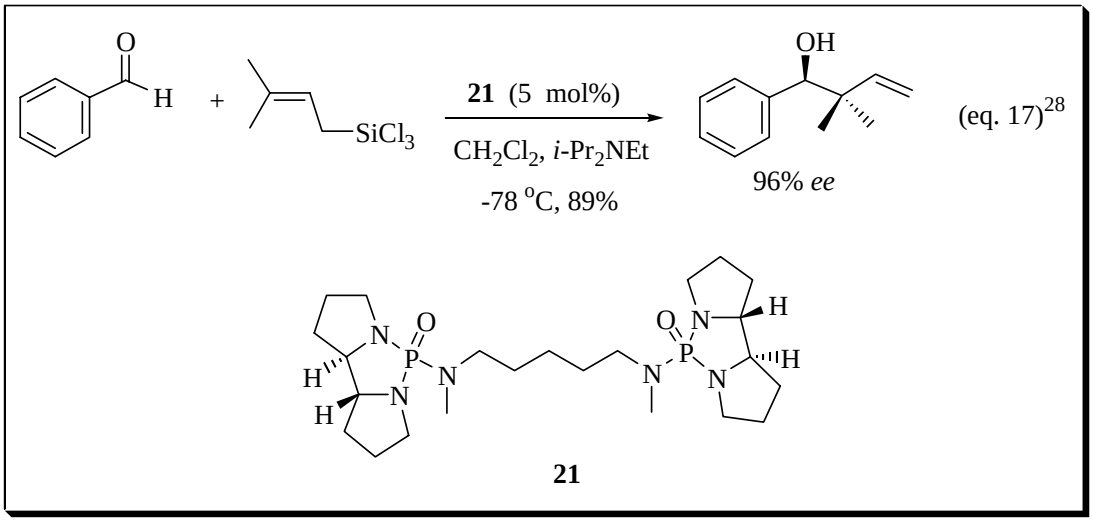
Catalytic Asymmetric Michael Addition:[8,24-26]

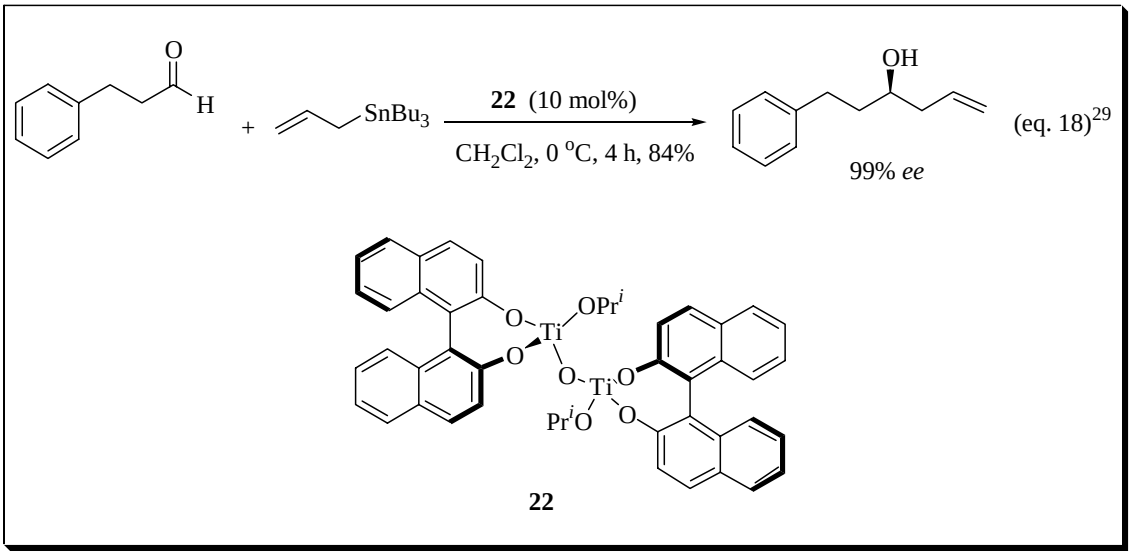




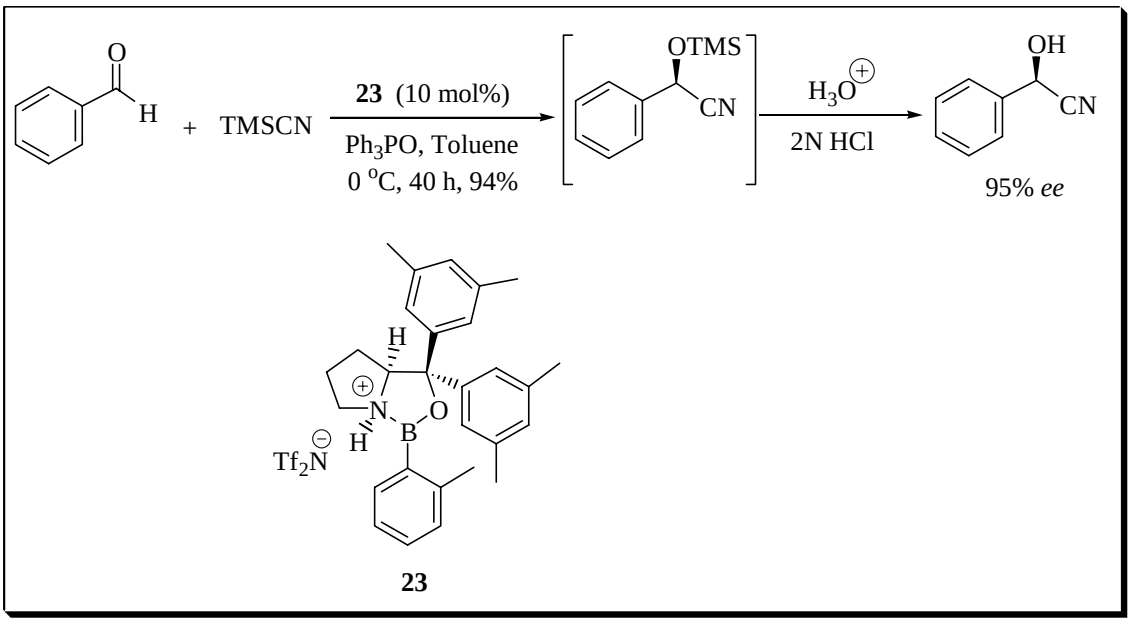


Catalytic Asymmetric Allylation:[27-29]

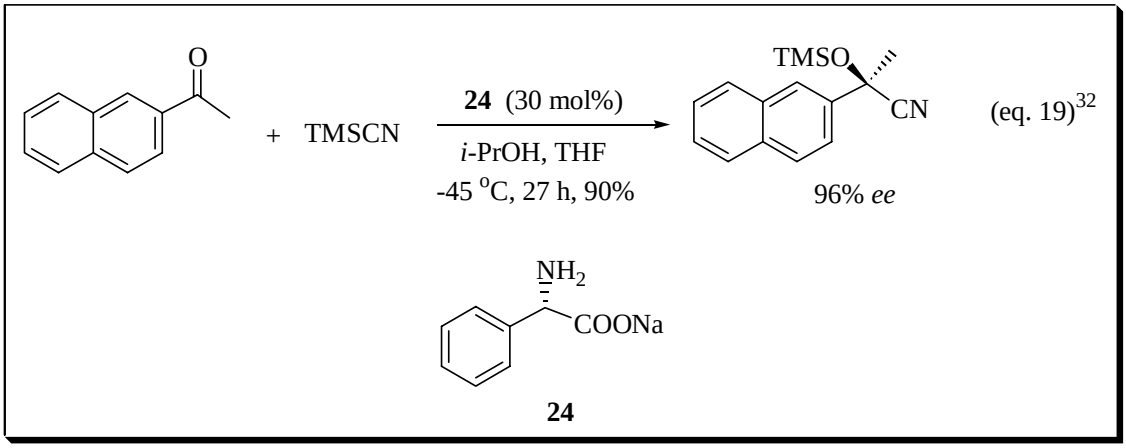




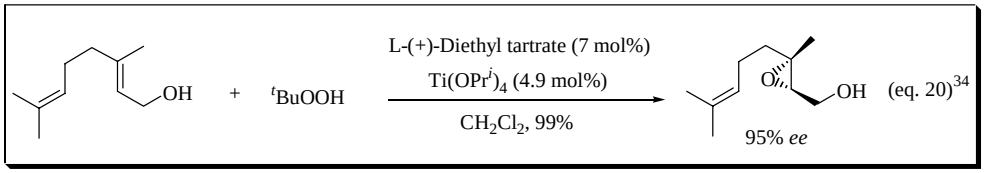
Catalytic Asymmetric Cyanosilylation:[30-32]

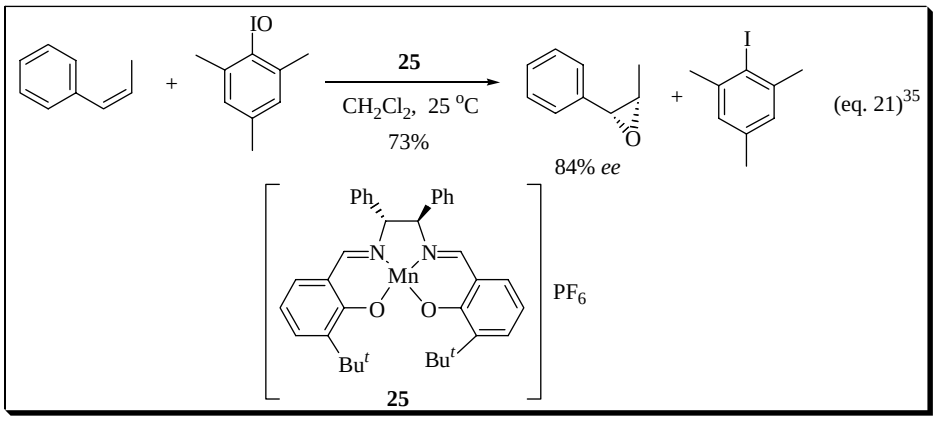


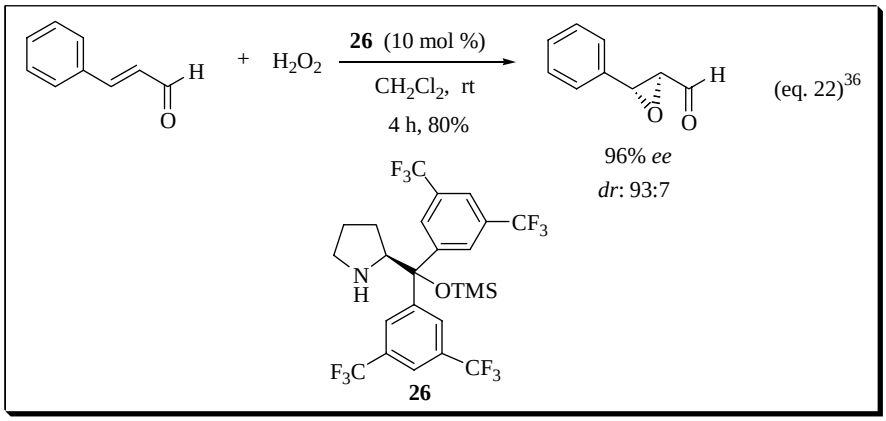
Scheme 1[31]

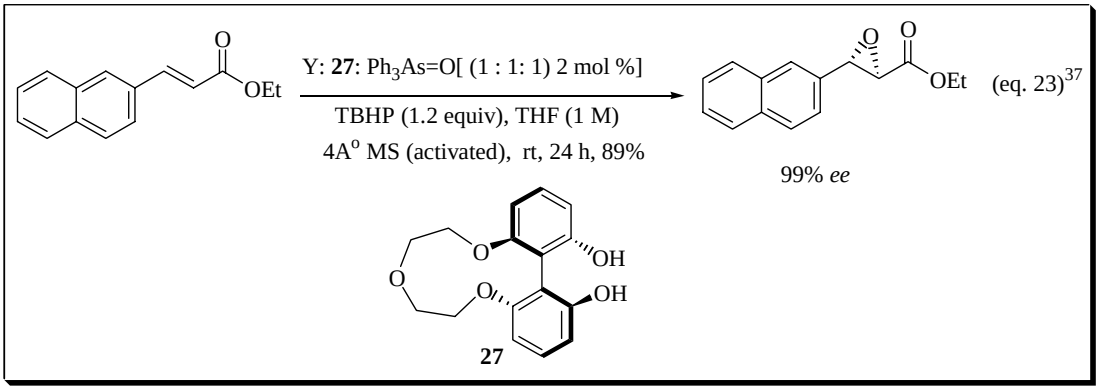


Catalytic Asymmetric Epoxidation:[33-37]

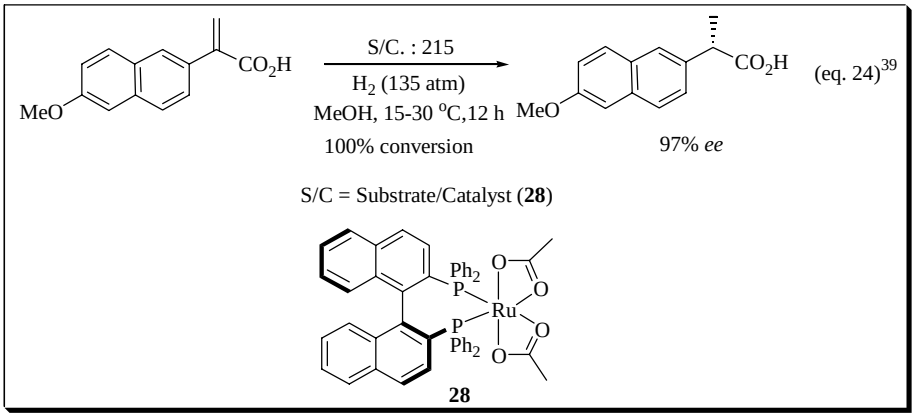


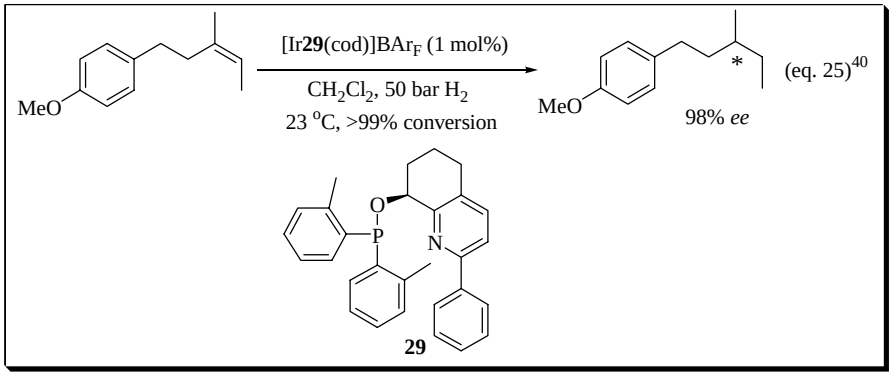






Catalytic Asymmetric Hydrogenation:[38-40]



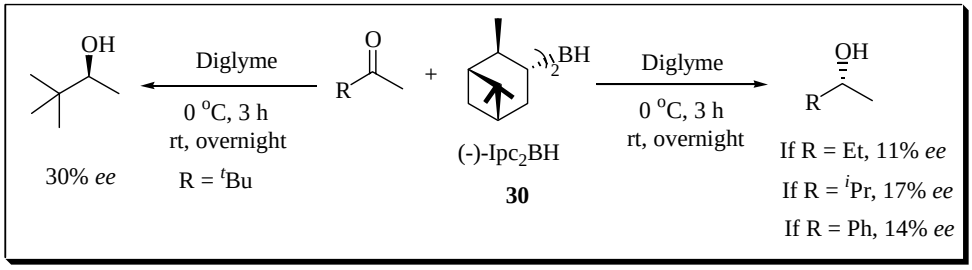


Asymmetric Reduction of Prochiral Ketones:

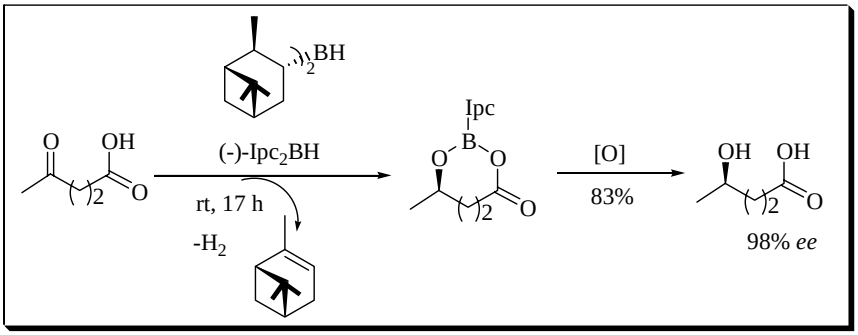
Synthesis of enantiomerically pure secondary alcohols *via* the asymmetric reduction of prochiral ketones represents one of the interesting and challenging areas in chiral chemistry.[38,41-53] Since this thesis deals with the development of recoverable and reusable chiral catalysts/catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones, salient features of recent and relevant literature on the boron based chiral reducing agents and also on the borane-mediated enantioselective reduction of prochiral ketones using chiral catalysts/catalytic sources are presented in this chapter.

Boron Based Chiral Reducing Agents: A Journey from $(Ipc)_2BH$ to $(Ipc)_2BCl$ (an Efficient Chiral Reducing Agent) *via* Alpine Borane

Brown and Bigley[54] have examined, for the first time, the potential of diisopino-campheylborane (**30**) as a chiral reducing agent in the asymmetric reduction of prochiral ketones. The corresponding secondary alcohols were obtained with low enantiomeric purities (Scheme 2). Although the enantioselectivities are low, this work provided the way to search for suitable chiral boron based reagents for asymmetric reduction of prochiral ketones. Recently Ramachandran and coworkers[55] have in fact demonstrated the high potentiality of diisopinocampheylborane (**30**) for the reduction of the α-, β- and γ-keto acids to provide the corresponding hydroxy acids with high enantiomeric purities (one representative example is shown in Scheme 3).



Scheme 2[54]



Scheme 3[55]

Midland and coworkers examined the applications of various chiral trialkylboranes (**31-34**) (Fig. 6) for the reduction of prochiral ketones/deuterated aldehydes.[56,57] They also observed that *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane) (**31**) provides the better enantioselectivities (representative examples are shown in eqs. 26-28).

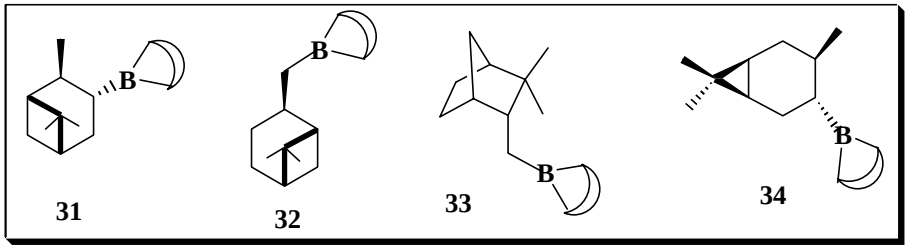
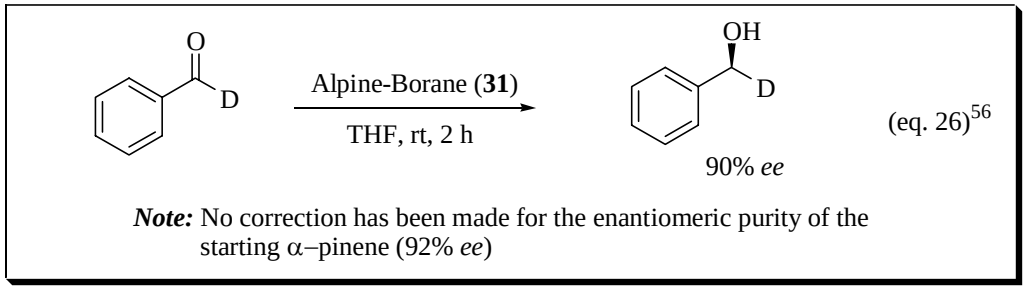
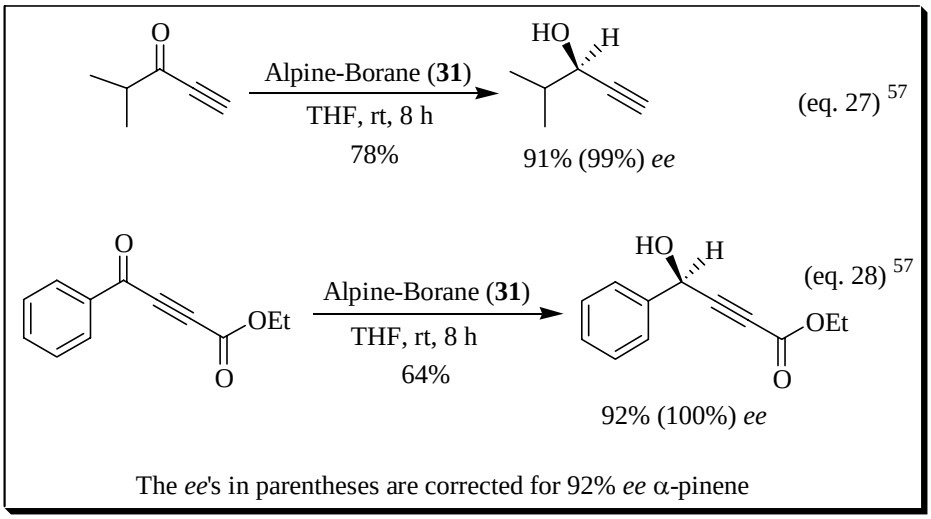
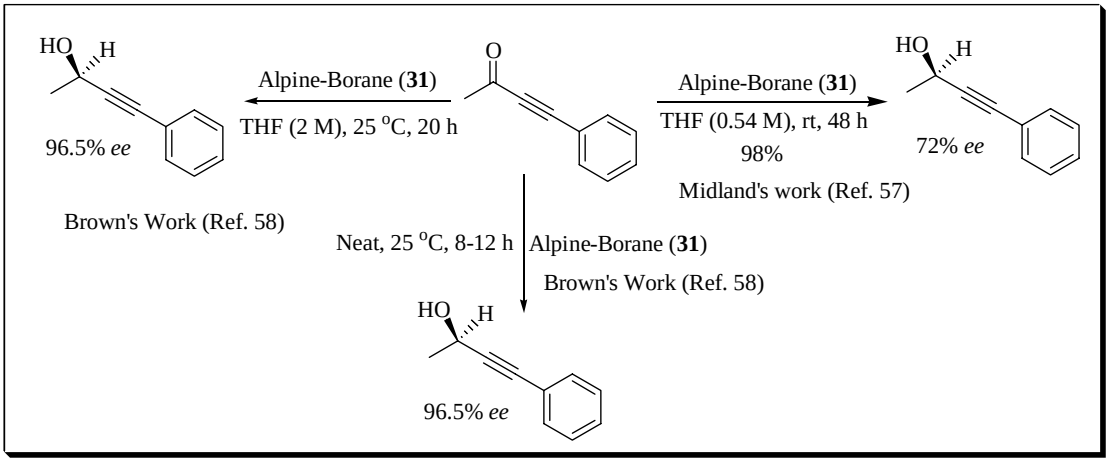


Figure 6

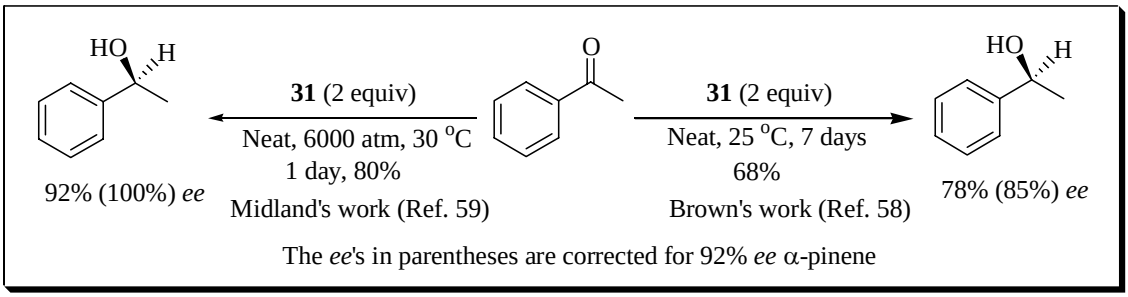




Subsequently Brown and Pai[58] demonstrated that alpine-borane (**31**), under neat/more concentrated conditions, provides the corresponding secondary alcohols with high enantiomeric purities and also at faster reaction rates in the reduction of acetylenic ketones and employed the same methodology for the reduction of aryl alkyl ketones (Schemes 4, 5). Later on Midland and McLoughlin[59] found an interesting influence of high pressure on the rate of the reaction and also on the levels of enantioselectivity (Scheme 5).

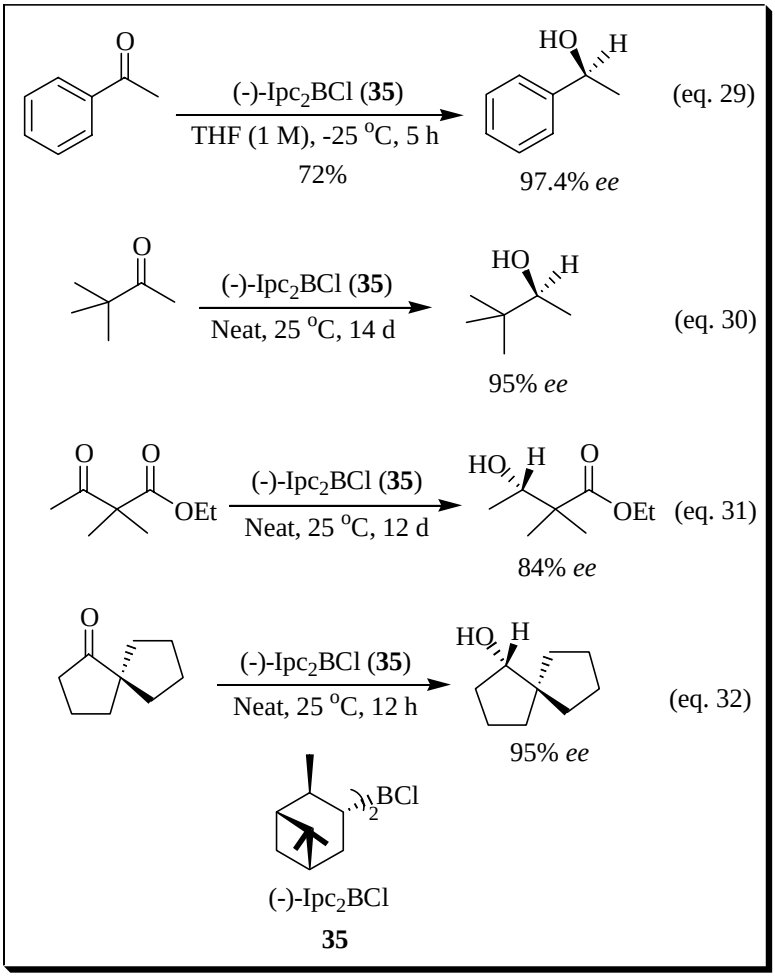


Scheme 4



Scheme 5

During their attempts in search of efficient chiral reducing agents, Brown and coworkers[60] examined various haloborane reagents built on isopinocampheyl moiety and demonstrated that diisopinocampheylchloroborane [Ipc_2BCl or DIP-Chloride (**35**)] is the reagent of choice (representative examples are presented in eqs. 29-32).



A Journey Towards Chiral Catalysts for the Asymmetric Reduction

Hirao and coworkers,[61] in 1981, reported the applications of borane complexes of chiral amino alcohols (**36-39**) (Fig. 7), derived from α-amino acids, as reducing agents for the asymmetric reduction of prochiral ketones. The corresponding secondary alcohols were

obtained with up-to 60% enantiomeric purity. The borane complex of **37** is found to be the better reducing agent (eq. 33).

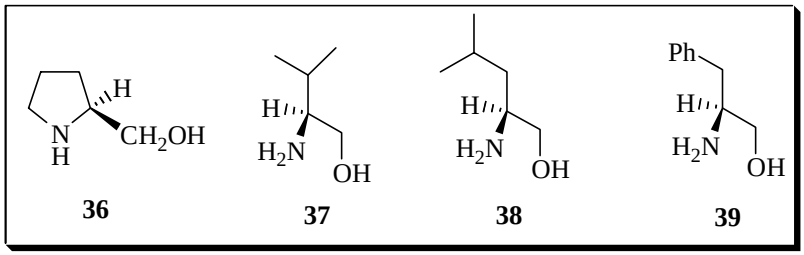
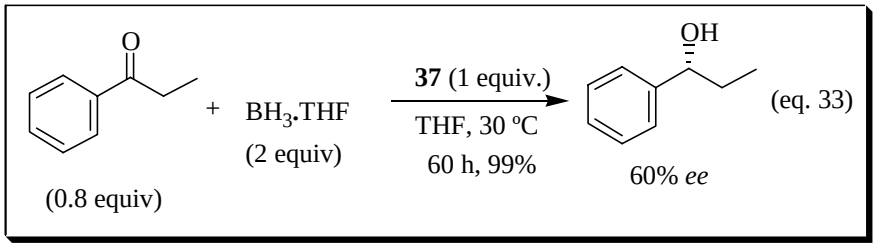
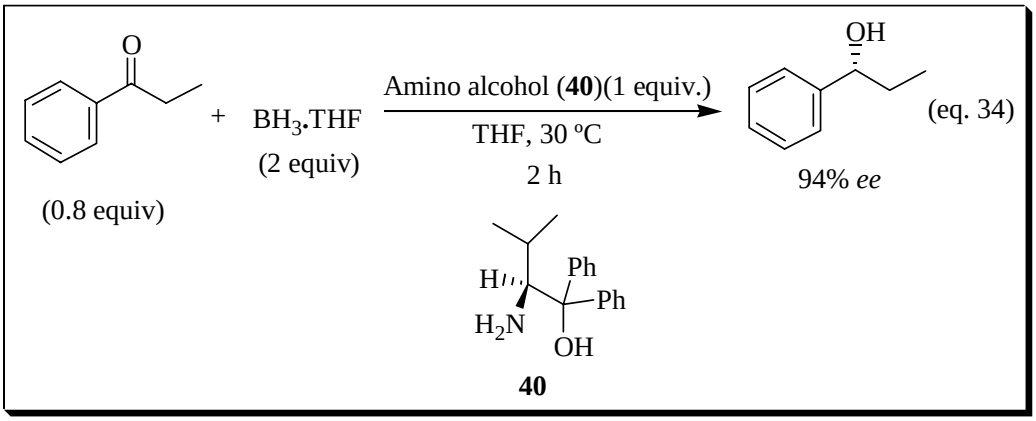


Figure 7

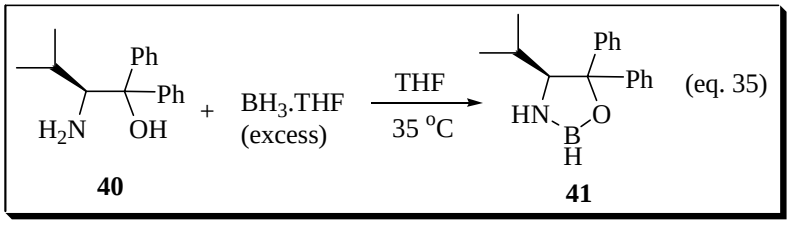


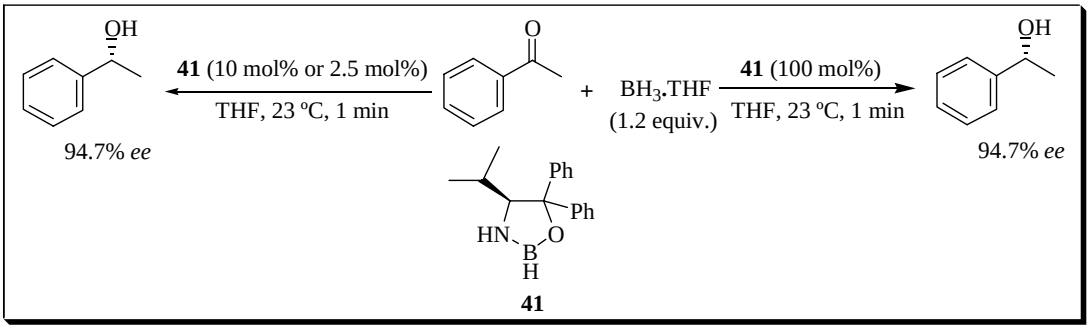
Later on Itsuno and coworkers[62] reported that the complex derived from (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**40**) [prepared from (*S*)-valine] and borane provides better enantioselectivities in the asymmetric reduction of prochiral ketones. One representative example is given in the equation 34.



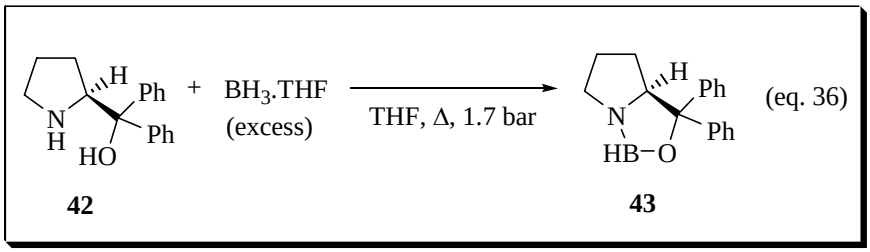
Corey's Ingenious Development of Oxazaborolidines as Efficient Catalysts For the Borane-Mediated Enantioselective Reduction of Prochiral Ketones:

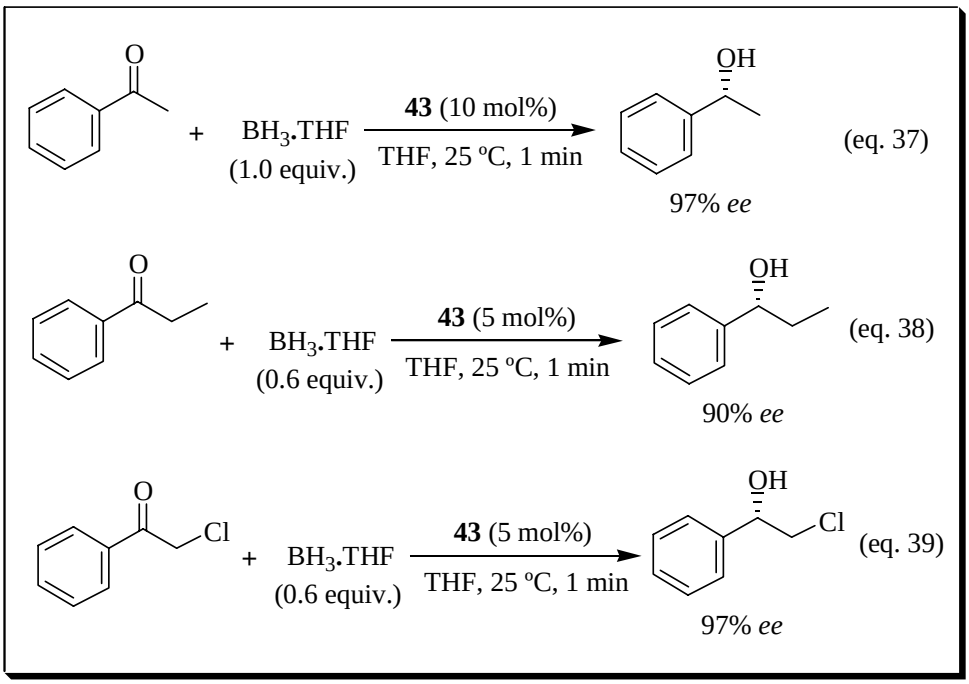
In 1987, for the first time, Corey and coworkers[63] elegantly used oxazaborolidine (**41**), prepared *via* the reaction of amino alcohol [(*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**40**)] with borane (eq. 35), as a catalyst for the borane-mediated reduction of acetophenone (Scheme 6). They also observed that the oxazaborolidine (**43**) derived from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**42**) (eq. 36) offers better selectivity (eqs. 37-39).[63]



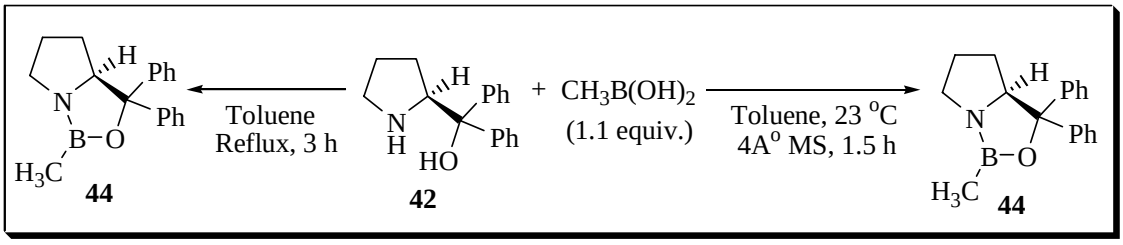


Scheme 6

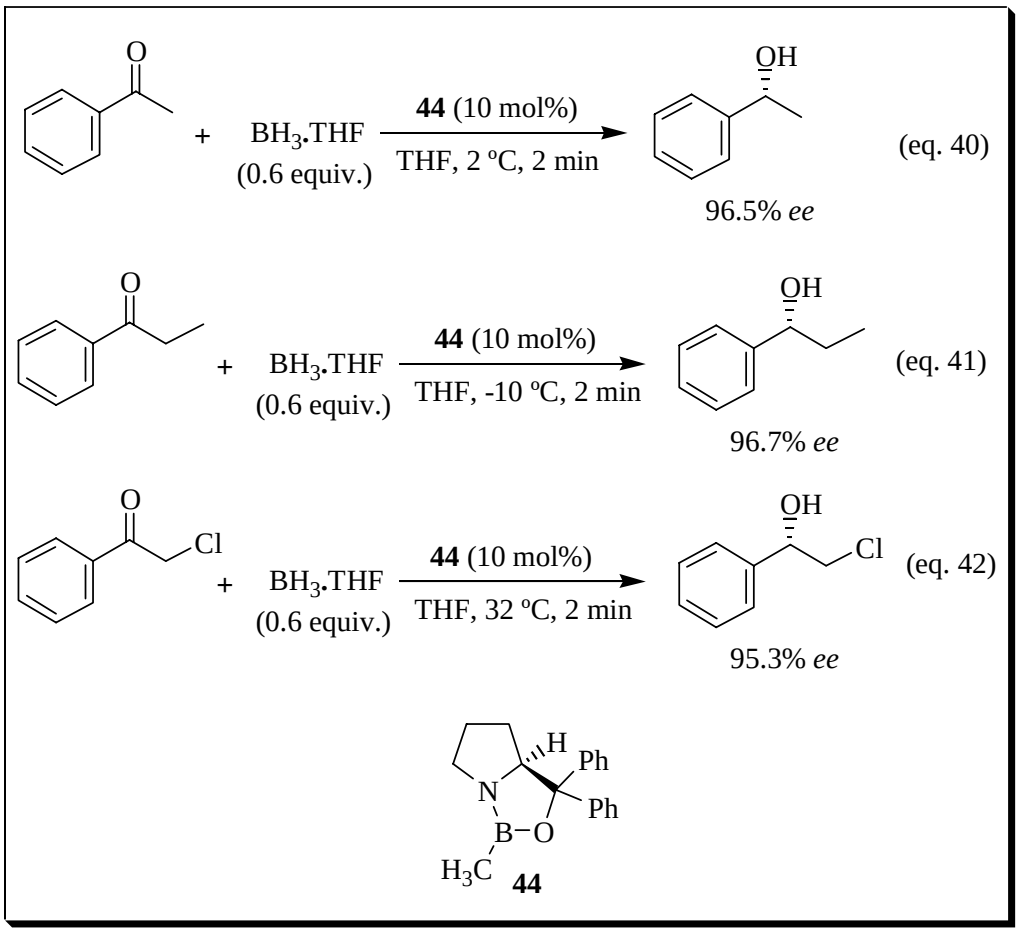




Subsequently Corey and coworkers[64] have prepared the oxazaborolidine (**44**) *via* the reaction of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**42**) with methylboronic acid (Scheme 7) and found that it is even better than the oxazaborolidine **43** (eqs. 40-42).



Scheme 7



Based on the ingenious utilization of oxazaborolidines by Corey and coworkers plethora of oxazaborolidines have been synthesized and systematically applied as catalysts for the borane-mediated asymmetric reduction of various prochiral ketones. Representative list of recent and important catalysts (**45-70**) are given in figure 8 and selected applications are presented in equations 43-46.

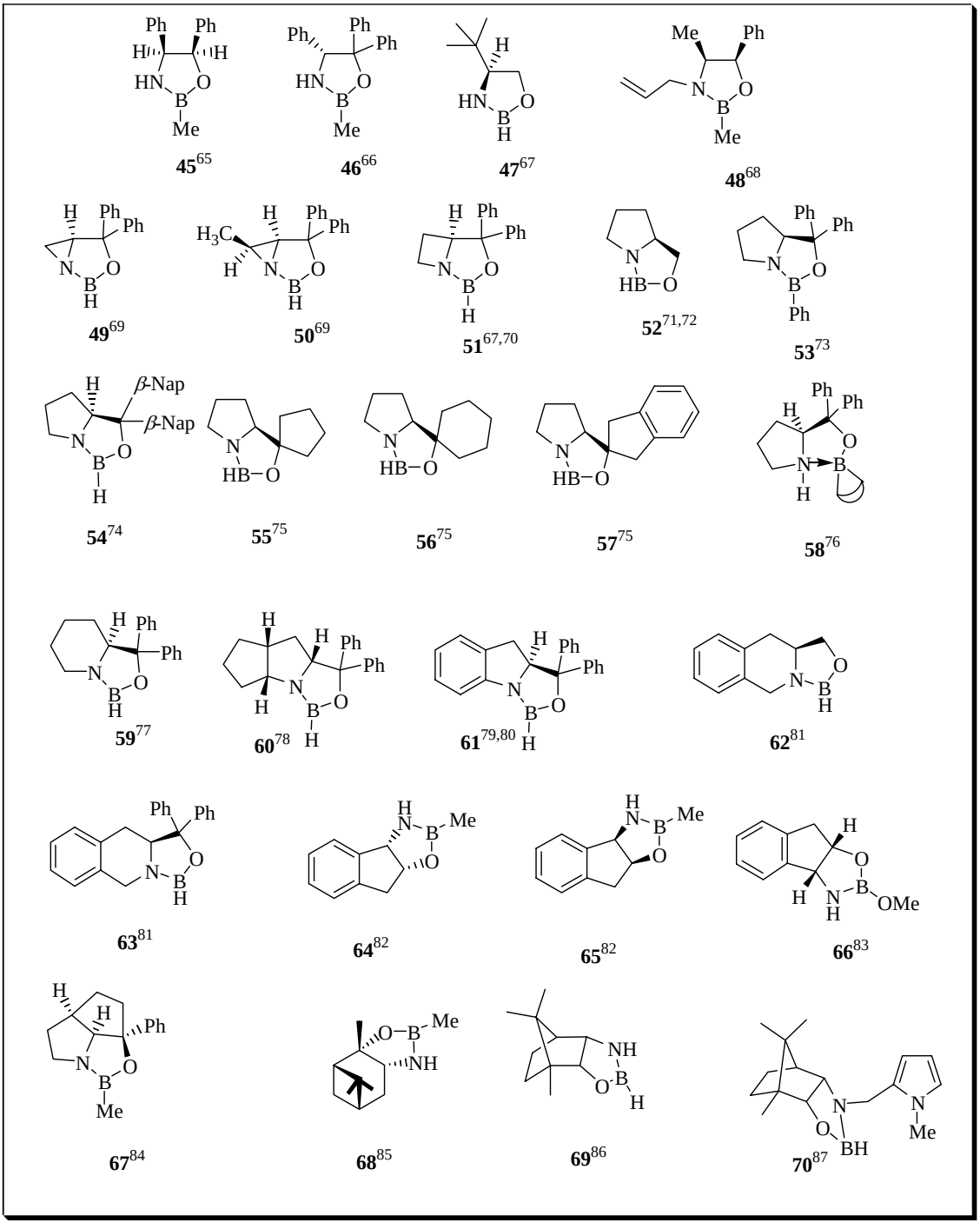
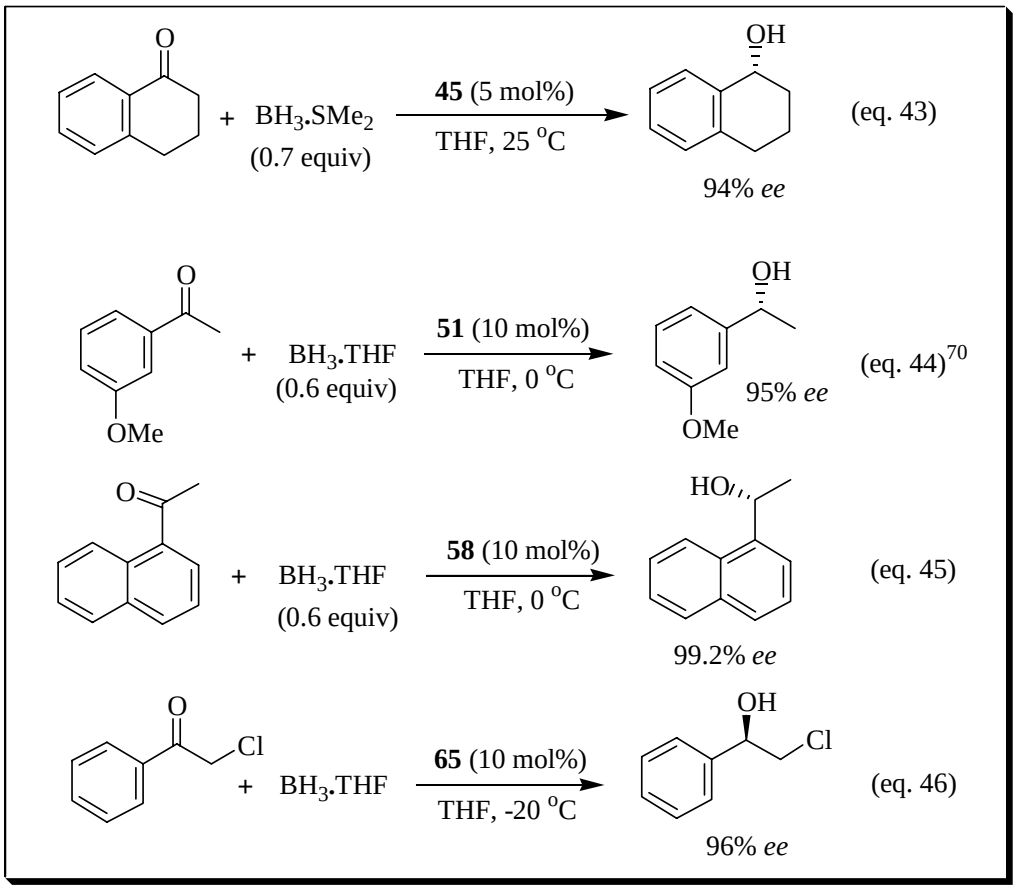
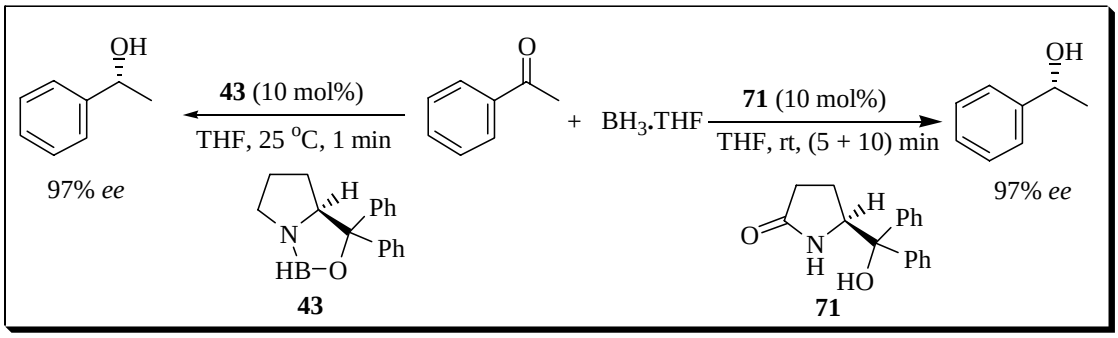

45[65]
46[66]
47[67]
48[68]
49[69]
50[69]
51[67,70]
52[71,72]
53[73]
54[74]
55[75]
56[75]
57[75]
58[76]
59[77]
60[78]
61[79,80]
62[81]
63[81]
64[82]
65[82]
66[83]
67[84]
68[85]
69[86]
70[87]

Figure 8

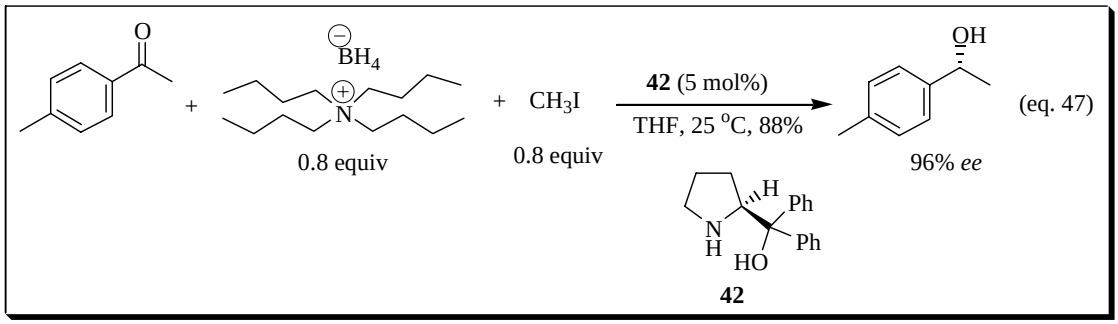


Kawanami and coworkers[88] have recently reported a simple methodology for the asymmetric reduction of prochiral ketones using the *in situ* generated oxazaborolidine **43** [from the chiral lactam alcohol, (*S*)-5-(diphenylhydroxymethyl)pyrrolidin-2-one (**71**) and BH_3.THF]. The enantioselectivities obtained by this methodology are comparable with the enantioselectivities obtained by the isolated oxazaborolidine **43**. One representative example is shown in the scheme 8.



Scheme 8

Very recently Periasamy and Anwar[89] reported a convenient method for the *in situ* generation of oxazaborolidine **43** from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**42**), tetrabutylammonium borohydride and methyl iodide and its application as a catalyst in the borane-mediated asymmetric reduction of prochiral ketones (one representative example is presented in the eq. 47).



Potential of amino alcohols (**72-77**), containing various frameworks [squaric acid,[90,91] ferrocine[92] and pyridine[93] (Fig. 9)] have also been examined as chiral catalysts/catalytic sources in the borane-mediated chiral reductions of prochiral ketones and some representative examples are presented in the equations 48-52.

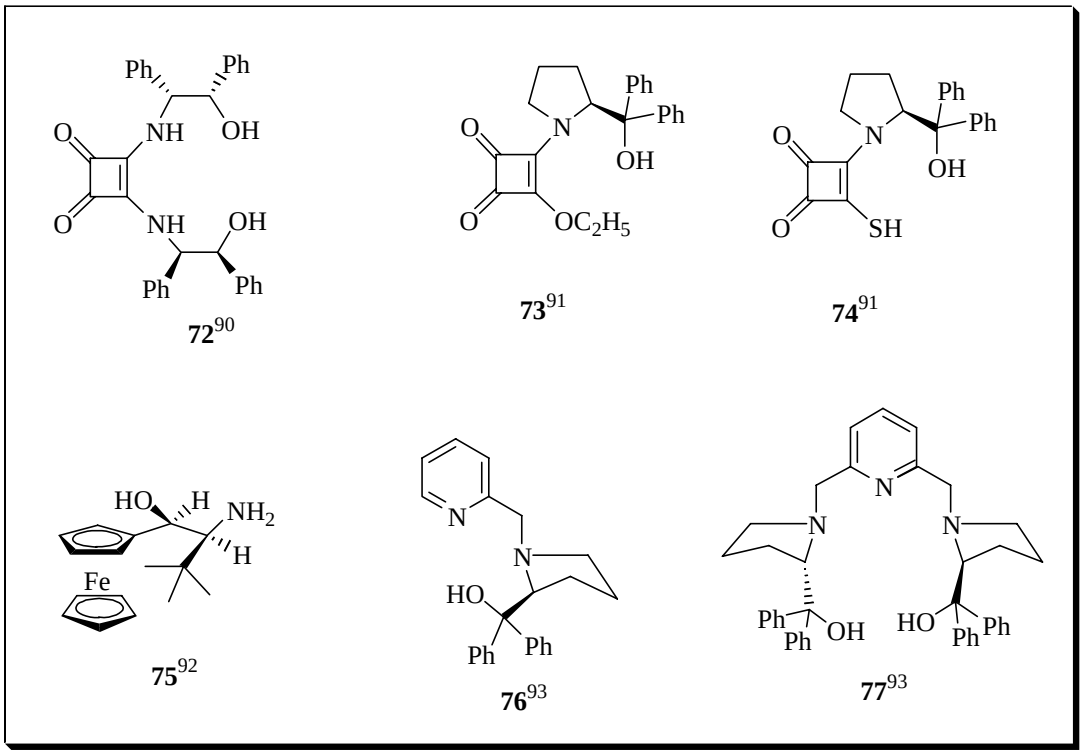
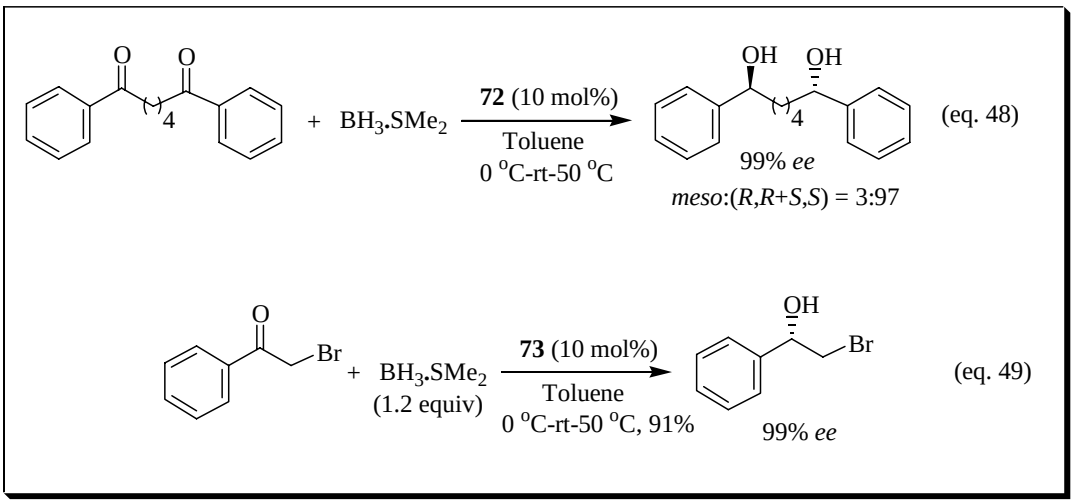
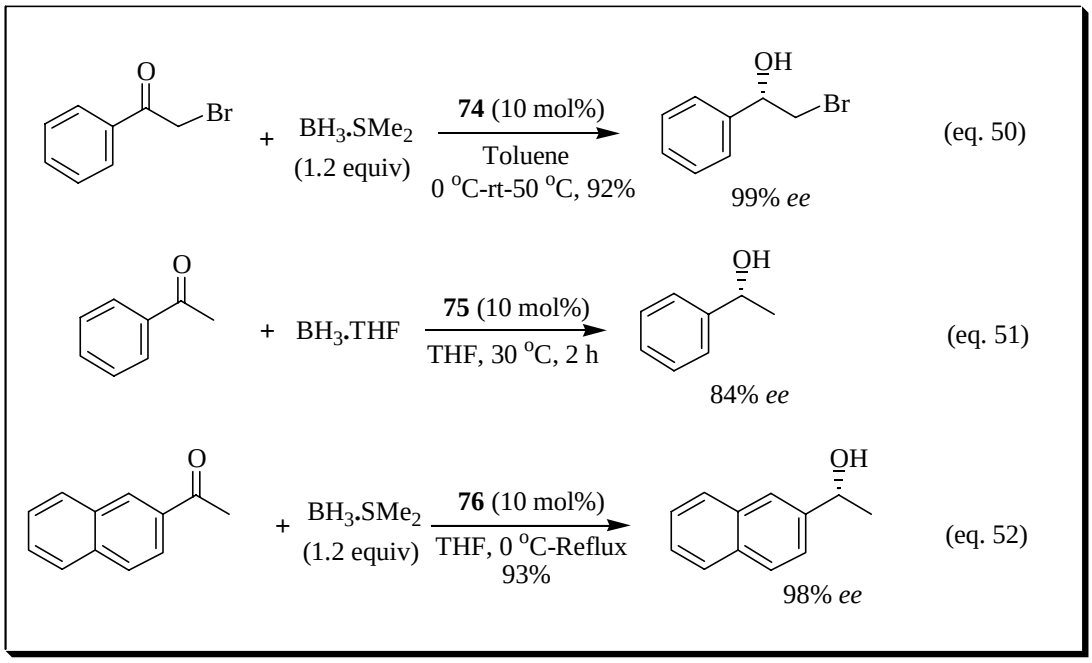

Ph
Ph
O
NH
OH
O
NH
OH
Ph
Ph
72[90]
Ph
Ph
O
N
OH
O
OC2H5
73[91]
Ph
Ph
O
N
OH
O
SH
74[91]
HO
H
NH2
H
Fe
75[92]
N
N
HO
Ph
Ph
76[93]
N
N
N
Ph
Ph
OH
HO
Ph
Ph
77[93]

Figure 9

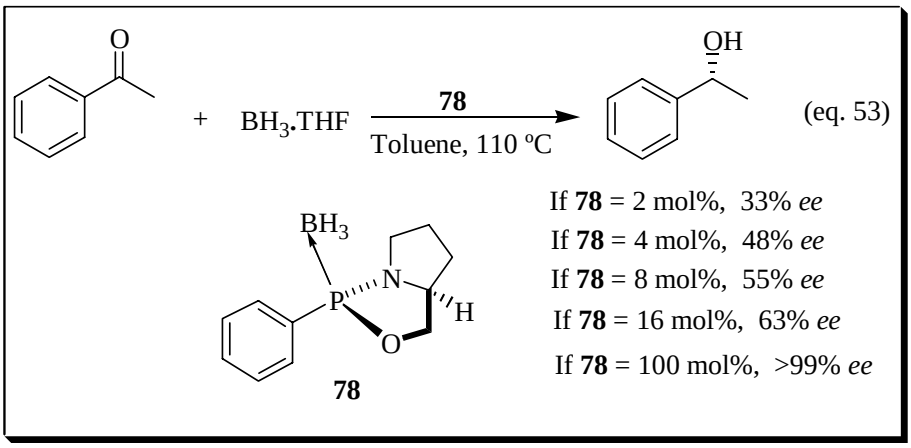

O
O
4
+ BH3.SMe2
72 (10 mol%)
Toluene
0 °C-rt-50 °C
OH
OH
4
99% ee
meso:(R,R+S,S) = 3:97
(eq. 48)
O
Br
+ BH3.SMe2
(1.2 equiv)
73 (10 mol%)
Toluene
0 °C-rt-50 °C, 91%
OH
Br
99% ee
(eq. 49)



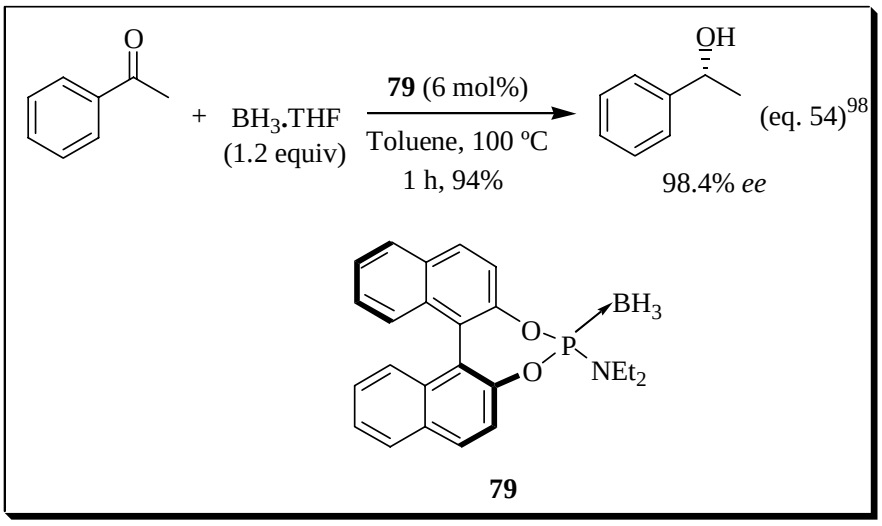
Phosphorus Based Chiral Catalysts:

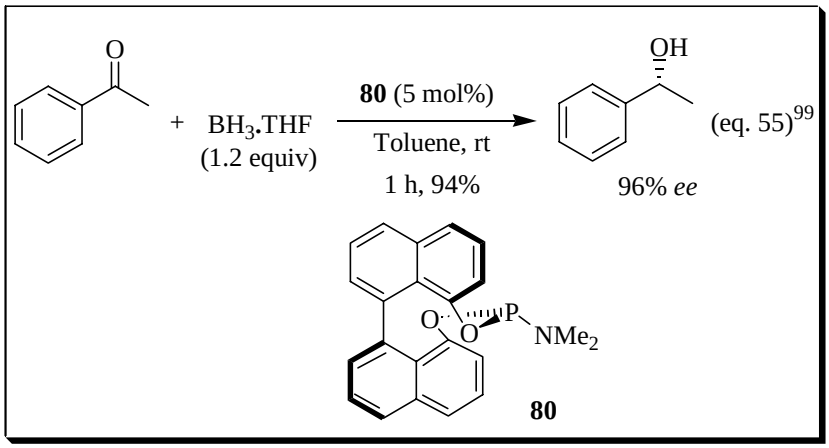
Phosphorus(III) Based Chiral Catalysts:

High applicability of oxazaborolidine as valuable catalysts for the borane-mediated reduction of prochiral ketones prompted organic chemists to examine the possible applications of structurally similar phosphorus based molecules *i. e.*, oxazaphospholidine-borane complexes, as catalysts in the borane-mediated asymmetric reduction of prochiral ketones. In this direction, Buono and co-workers[94] synthesized and studied the catalytic potential of oxazaphospholidine-borane complex (**78**) in the borane-mediated reduction of prochiral ketones. This compound provides >99% enantioselectivity in the borane-mediated reduction of acetophenone when used in molar ratio as that of the ketone. However this compound provides inferior selectivities when used in catalytic amounts in similar reduction (eq. 53).



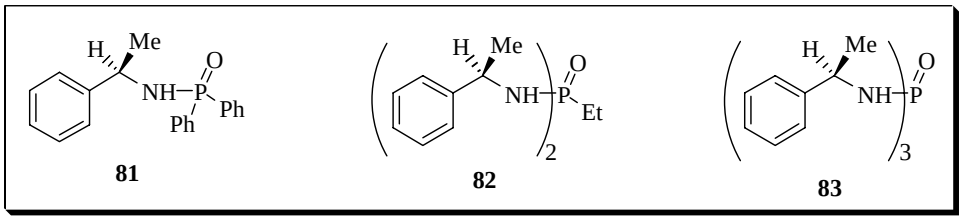
Subsequently the chiral inducing potential of various tricoordinate phosphorus-borane complexes have been examined.[95-97] The complexes derived from chiral binaphthol (**79** & **80**) exhibited high potentiality as catalysts in the borane-mediated asymmetric reduction of prochiral ketones (eqs. 54 & 55).[98,99]





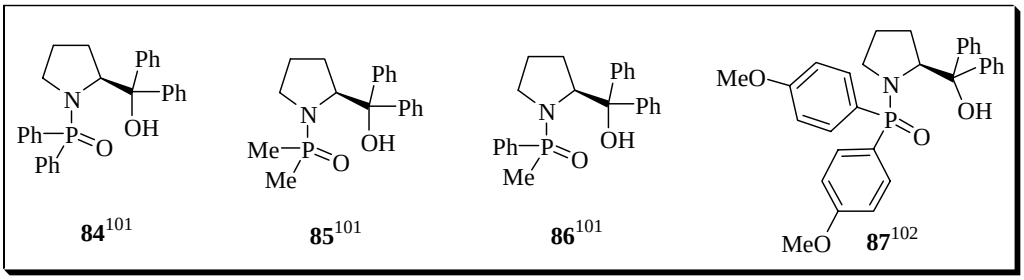
Phosphorus(V) Based Chiral Catalysts: Chiral Catalysts/Catalytic Sources Containing the *N-P=O* Structural Framework

Wills and coworkers for the first time, in 1993,[100] reported the synthesis and the applications of novel classes of molecules having the *N-P=O* structural framework (**81-83**) (Fig. 10) as chiral catalysts in the borane-mediated asymmetric reduction of acetophenone. Although these catalysts provide the corresponding alcohol with low enantiomeric purity [the best result was obtained with the catalyst **82** (eq. 56)], these results are encouraging in the sense that these catalysts can be modified so as to obtain better selectivity. Subsequently Wills and coworkers have designed and synthesized a number of chiral catalysts containing the *N-P=O* structural framework and examined their catalytic potential in the borane-mediated asymmetric reduction of various prochiral ketones. Some of the catalysts (**84-87**) which provided high enantioselectivity are listed in the figure 11 and representative examples have been presented in the eqs. 57-59.[101,102]



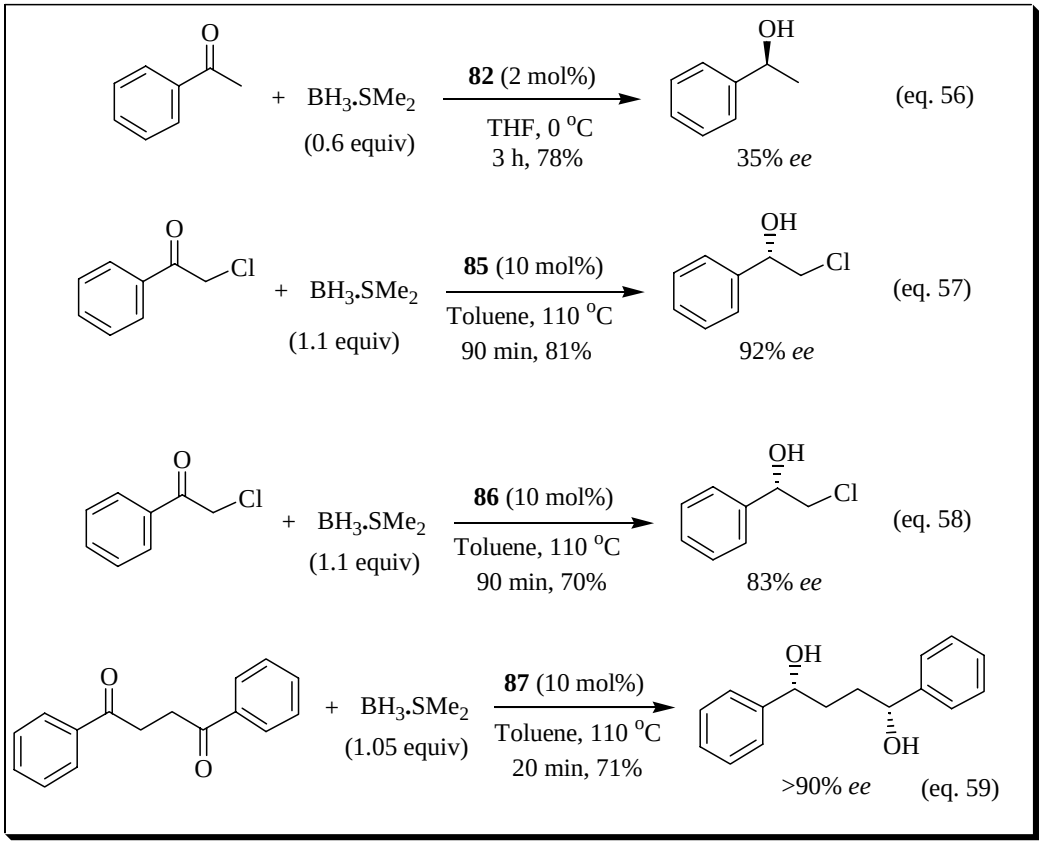
81 **82** **83**

Figure 10



84[101] **85**[101] **86**[101] **87**[102]

Figure 11



Later on various chiral catalysts containing the *N-P=O* and *N-P=S* structural framework have been synthesized by various research groups and their catalytic efficiency in the borane-mediated asymmetric reduction of prochiral ketones has been examined. Some of the effective chiral catalysts (**88-97**) are listed in figure 12 and representative examples are presented in the equations 60-64.[103-107]

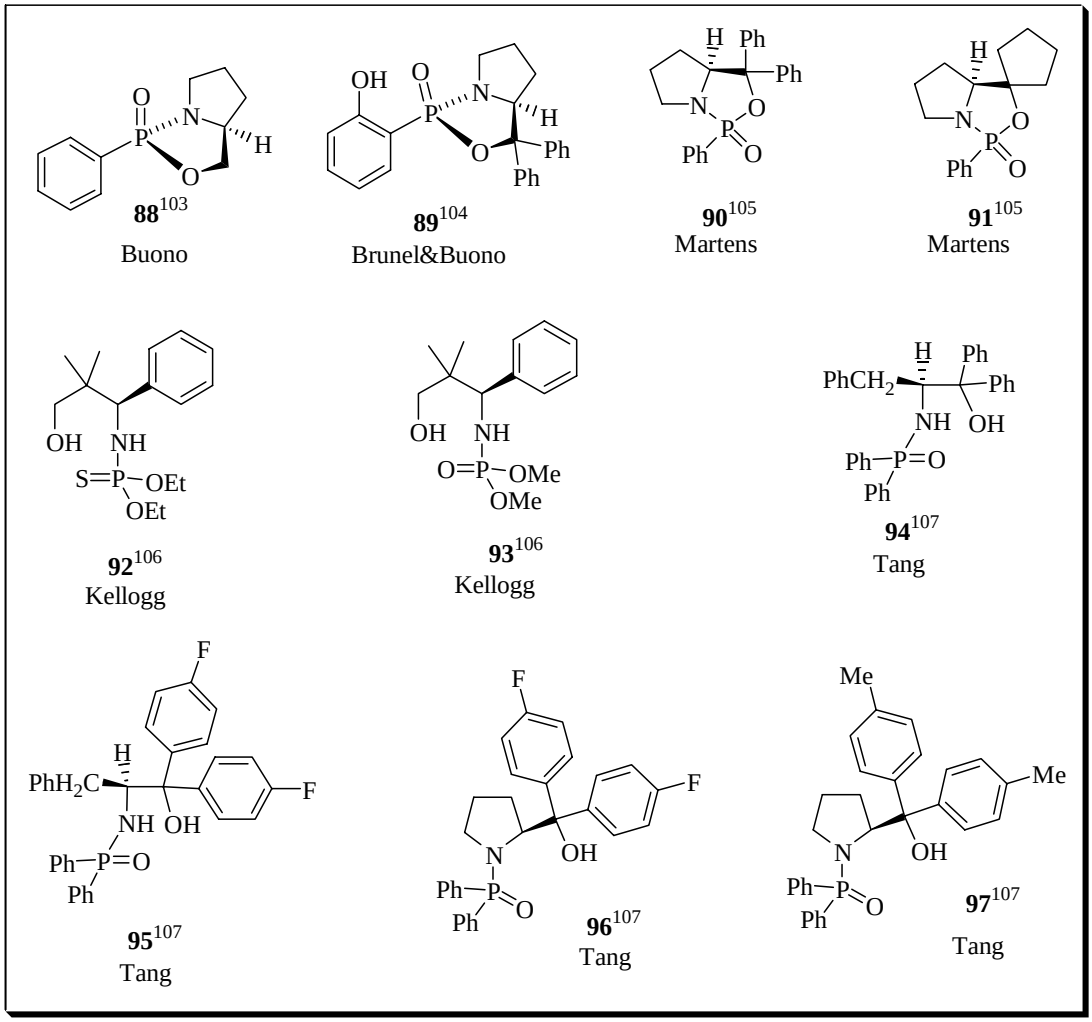
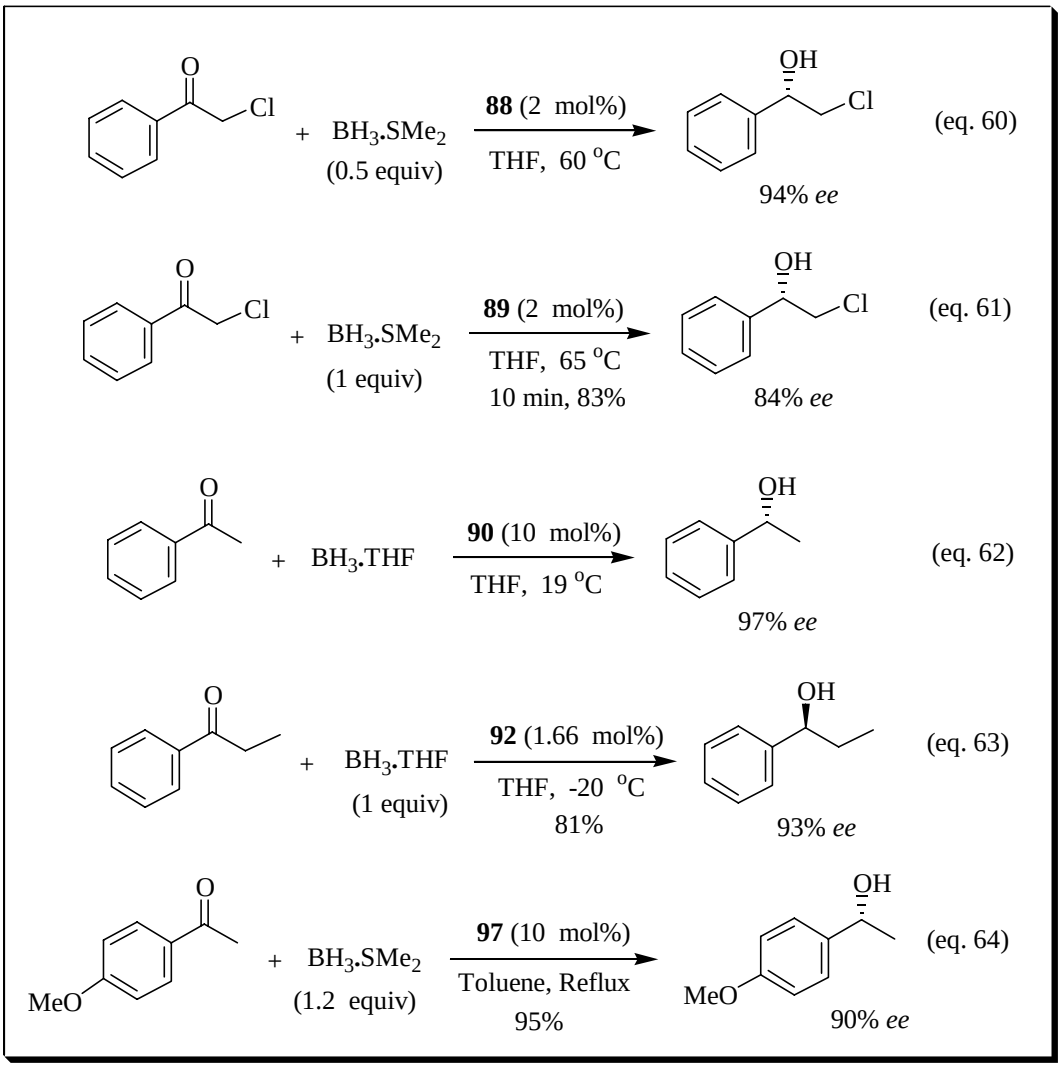
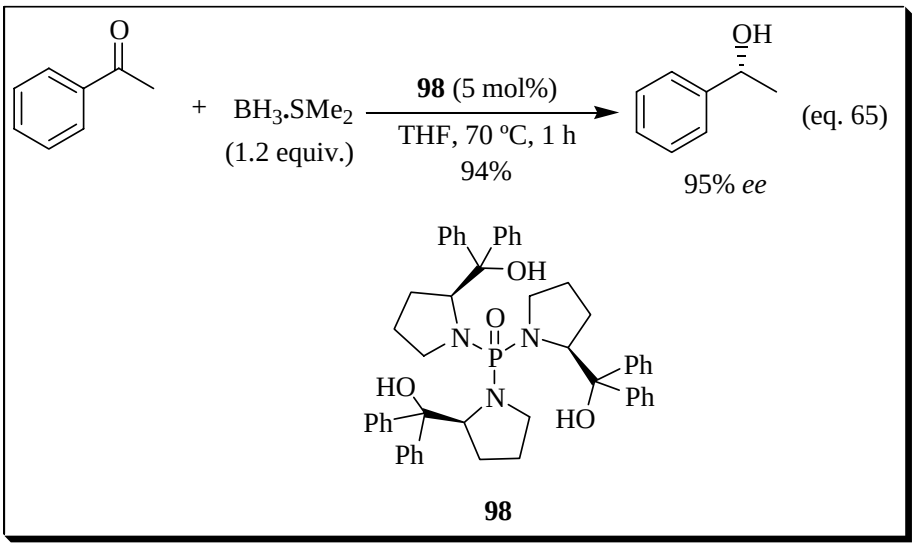


Figure 12



Very recently C_3-symmetric chiral tris(β-hydroxyphosphoramide) (**98**) has been synthesized and successfully employed as catalyst by Du and coworkers for the borane-mediated asymmetric reduction of prochiral ketones (one representative example is presented in the eq. 65).[108]



98

Our research group has been working for the last few years on the development of useful chiral catalysts containing the *N-P=O* structural framework, built mainly on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* moiety (**I**), for the borane-mediated asymmetric reduction of prochiral ketones.[109-113] In this direction, our research group has designed & synthesized a number of chiral catalysts (**99-107**) (Fig. 13) and examined their chiral inducing potential in the borane-mediated asymmetric reduction of prochiral ketones (Some representative examples have been shown in eqs. 66-69). During this study our research group has also designed and synthesized three representative diastereomeric pairs (**101** & **101A**, **108** & **108A**, **109** & **109A**) containing the different stereochemistry at phosphorus with a view to examine the effect of the phosphorus stereochemistry in directing the stereochemical course of the reduction and, in fact, to some extent demonstrated that the stereochemistry of phosphorus have no/little significant role in directing the stereochemical out-come of the reduction process. One representative example is given in the scheme 9.[113]

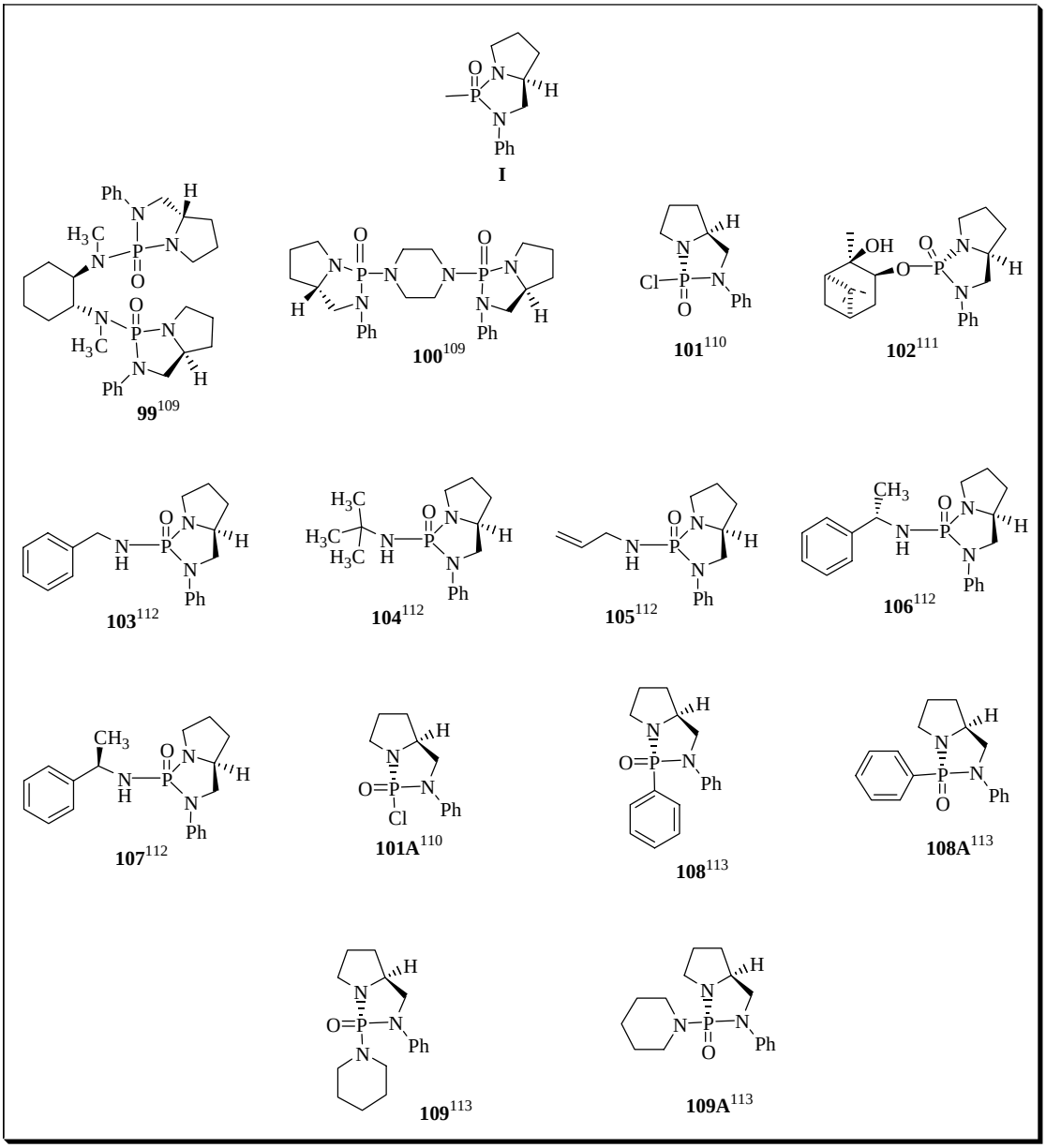
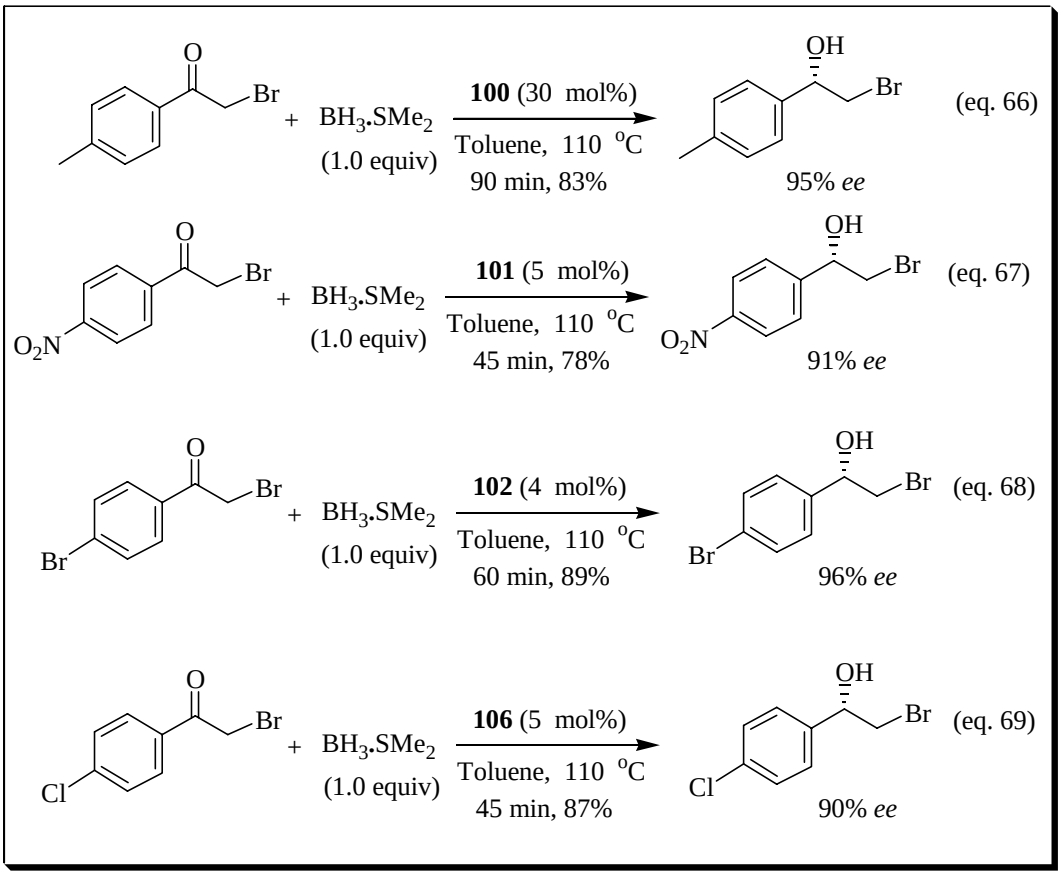
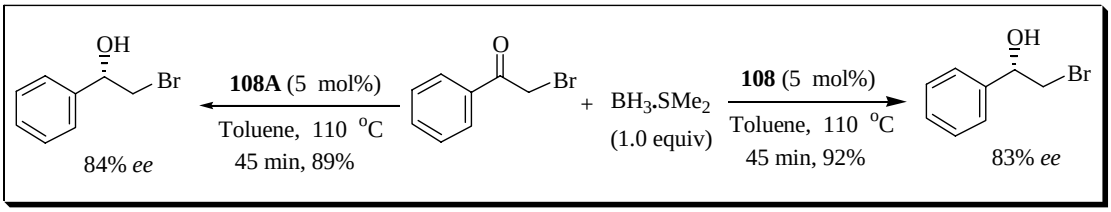

I
99[109]
100[109]
101[110]
102[111]
103[112]
104[112]
105[112]
106[112]
107[112]
101A[110]
108[113]
108A[113]
109[113]
109A[113]

Figure 13



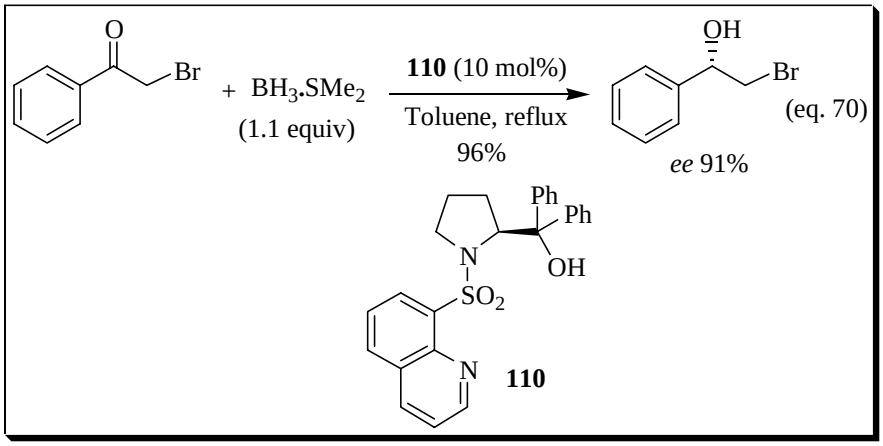


Scheme 9

Other Catalysts

Various other catalysts based on chiral sulfonamide and titanium alkoxide frameworks have been examined for performing the borane-mediated asymmetric reduction of prochiral ketones.

Zhao and coworkers[114] prepared representative chiral sulfonamides based on (*S*)-2-(diphenylhydroxymethyl)pyrrolidine moiety and examined their potential in the borane-mediated asymmetric reduction of prochiral ketones. They have observed that the chiral sulfonamide **110** provided the better selectivity. One representative example is presented in the equation 70.



The potential of chiral titanium alkoxides (derived *via* the reaction between $Ti(O^iPr)_4$ and chiral diols) was also examined as chiral catalysts in the borane-mediated reduction of prochiral ketones. Some of the effective chiral diols (**111-114**) are listed in the figure 14.[115,116] One representative example is shown in the equation 71.

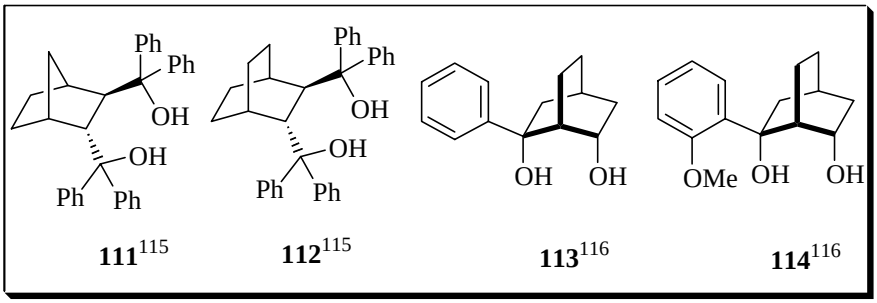
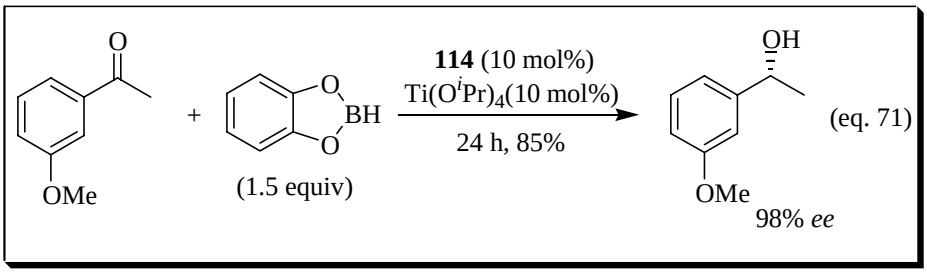


Figure 14



Polymer-Bound Chiral Catalysts/Reagents (Heterogeneous Catalysis)

Since the present day concept of chiral catalysis requires and even demands the easy recovery of the catalyst and isolation of the product, synthetic chemists have focused their efforts in this direction and developed some interesting polymer-bound chiral catalysts/catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones. It is quiet appropriate to mention here that work of Itsuno,[117,118] who in fact made in the year 1984, a number of polymer-bound amino alcohols (**115-117**) (Fig. 15) and studied the applications of these amino alcohol-borane complexes as reducing agents in the asymmetric reductions of prochiral ketones. One representative example is shown in the equation 72. They have also examined the recyclable ability. Although the enantioselectivities are not that high and also catalytic efficiency of these molecules have not been studied, these results are interesting in the sense that these studies provided the necessary understanding to design and develop efficient polymer-supported chiral catalysts/catalytic sources.

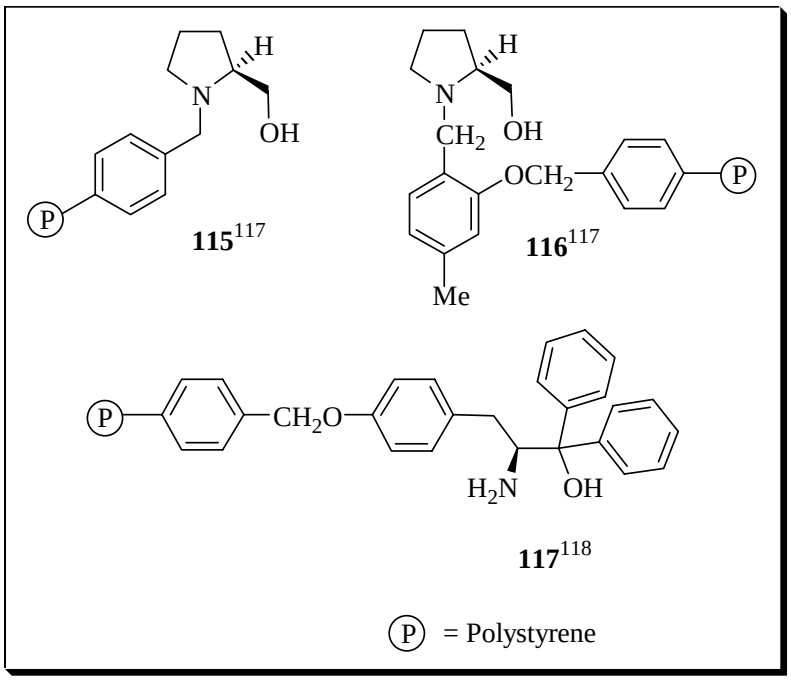
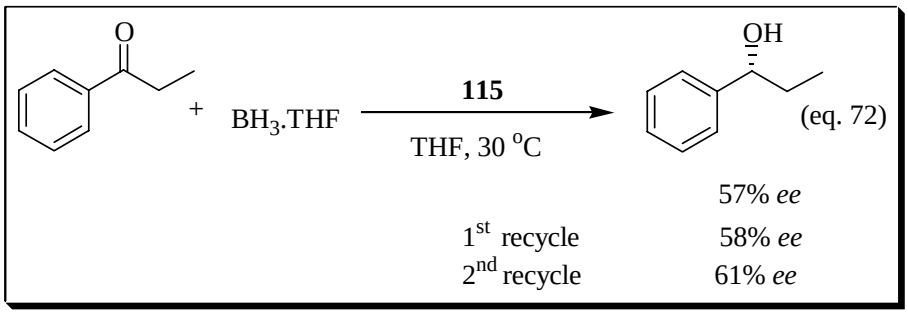
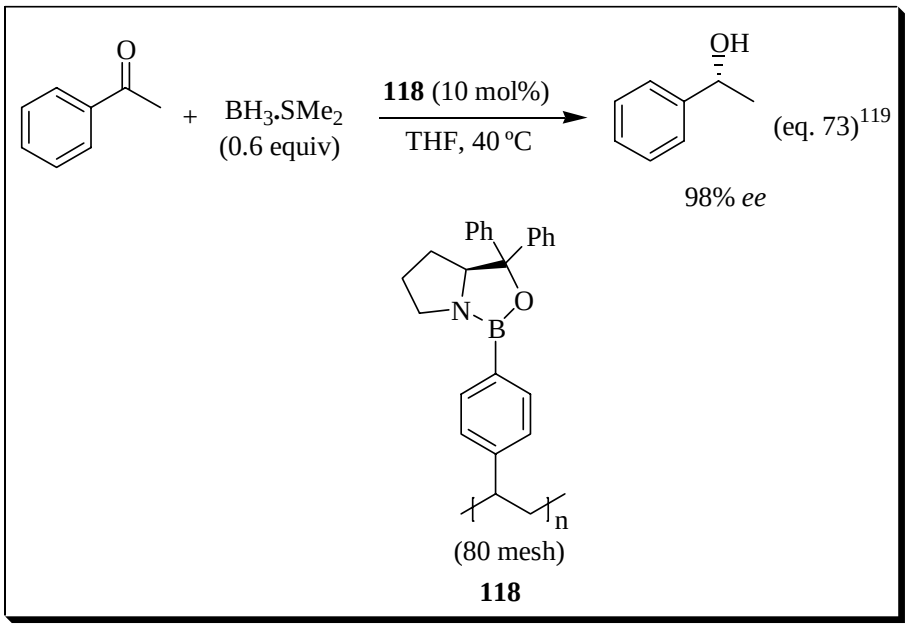
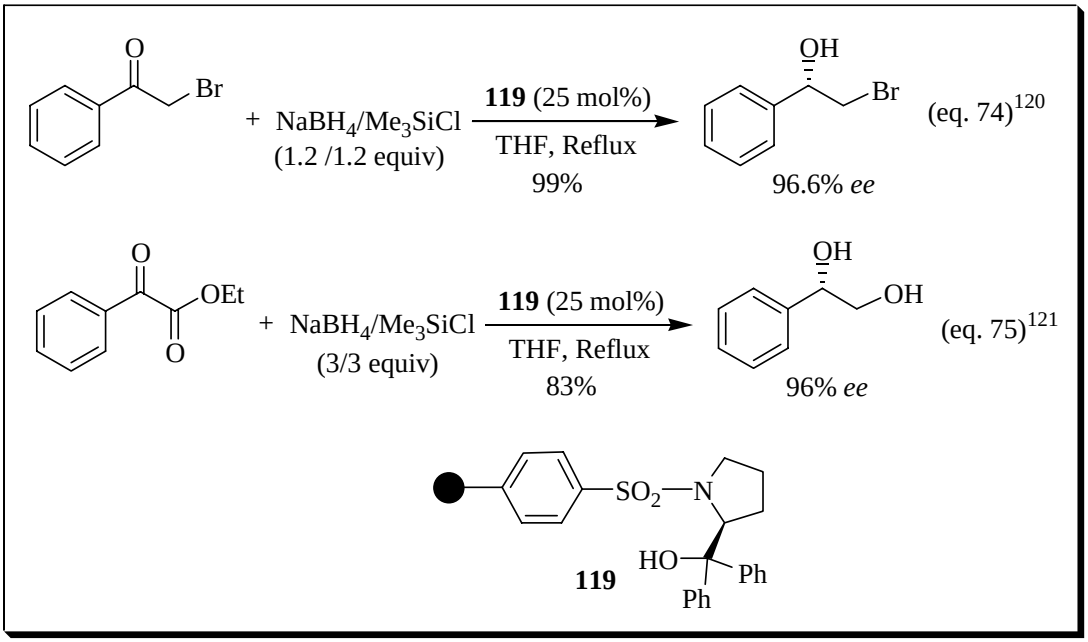


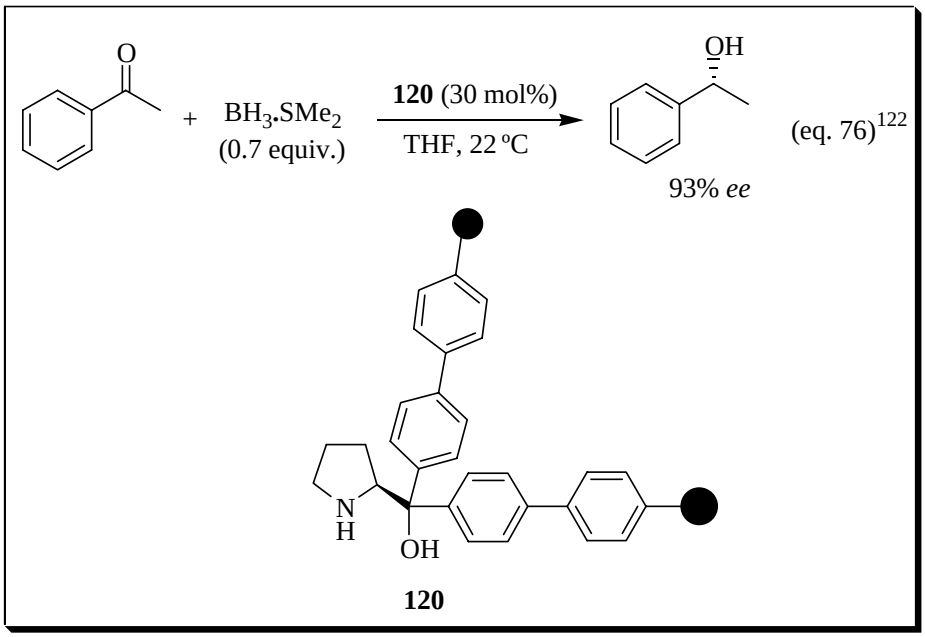
Figure 15



Later on various polymer supported chiral catalysts (**118-120**), built mainly on (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**42**) moiety, have been synthesized and their catalytic potential in the borane-mediated reduction of prochiral ketones has been examined (eqs. 73-76).[119-122]

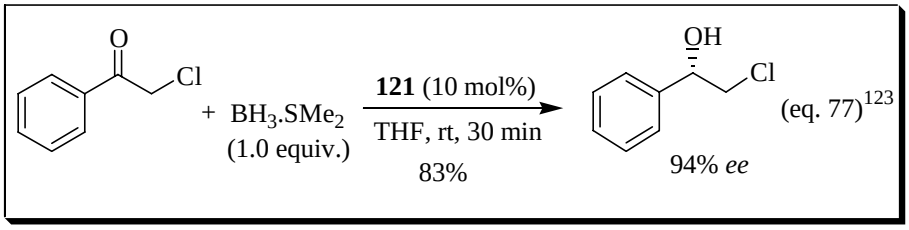

O
+ BH3.SMe2
(0.6 equiv)
118 (10 mol%)
THF, 40 ºC
OH
(eq. 73)119
98% ee
Ph
Ph
N
O
B
n
(80 mesh)
118

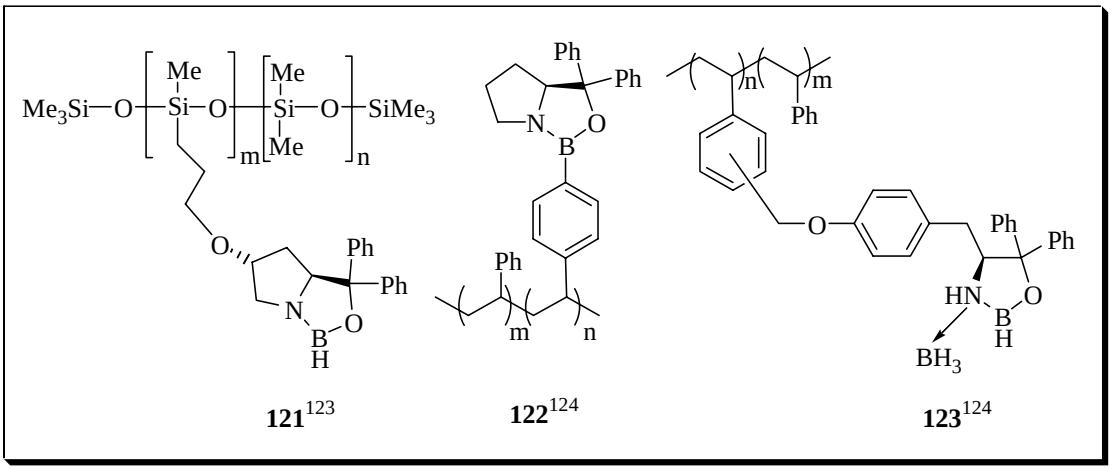

O
Br
+ NaBH4/Me3SiCl
(1.2 /1.2 equiv)
119 (25 mol%)
THF, Reflux
99%
OH
Br
(eq. 74)120
96.6% ee
O
OEt
O
+ NaBH4/Me3SiCl
(3/3 equiv)
119 (25 mol%)
THF, Reflux
83%
OH
OH
(eq. 75)121
96% ee
SO2
N
HO
Ph
Ph
119



Homogeneous Catalysis

In addition to the heterogeneous catalytic methods, various homogeneous catalysts have also been developed for the borane-mediated asymmetric reduction of prochiral ketones. Some recent and interesting homogeneous polymer-enlarged oxazaborolidine catalysts (**121-123**) are listed in the figure 16[123,124] and one representative example is presented in the equation 77.

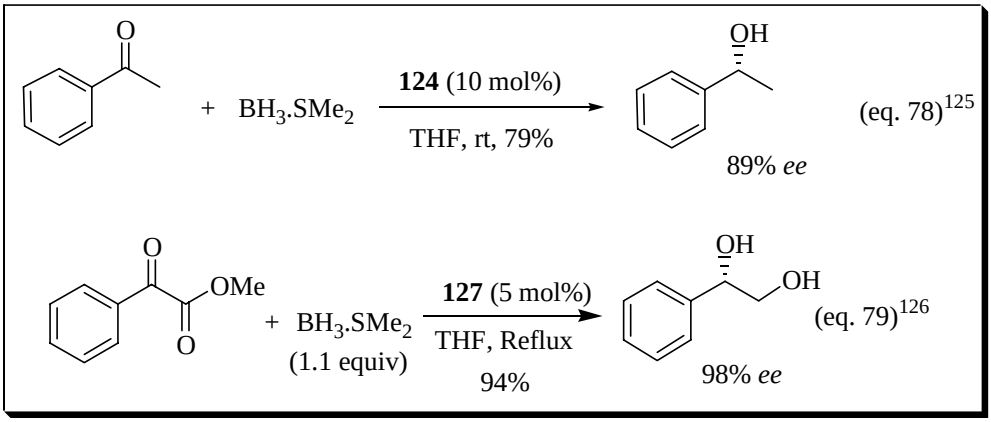


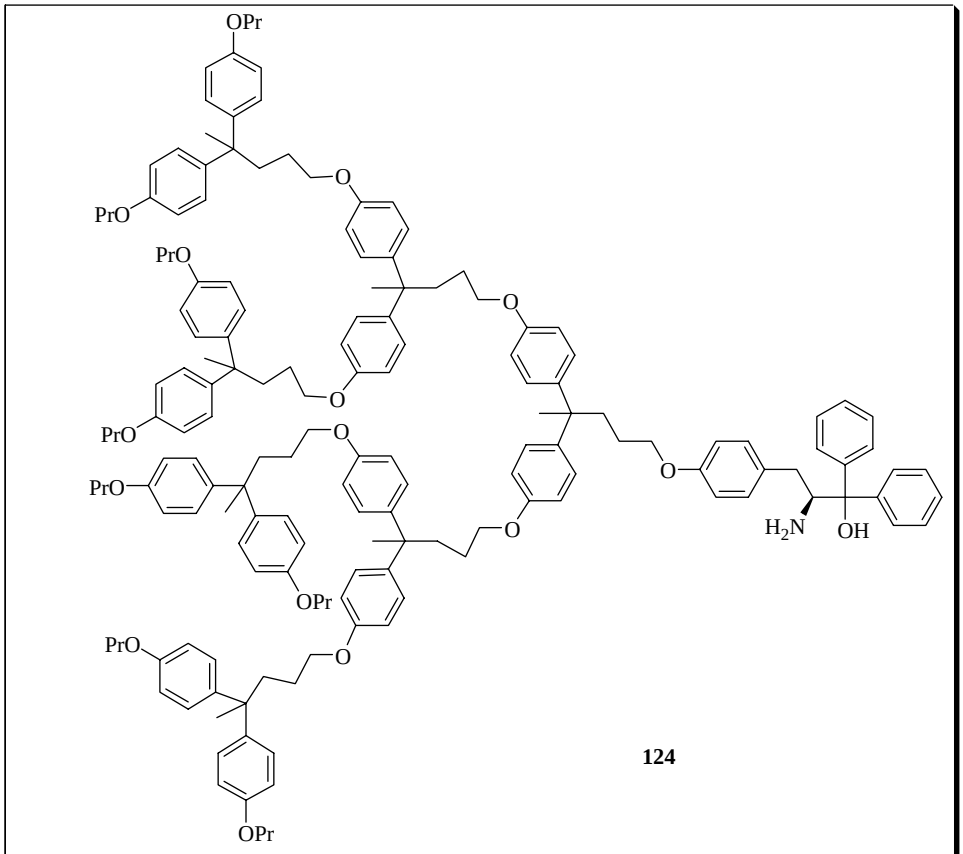


121[123] **122**[124] **123**[124]

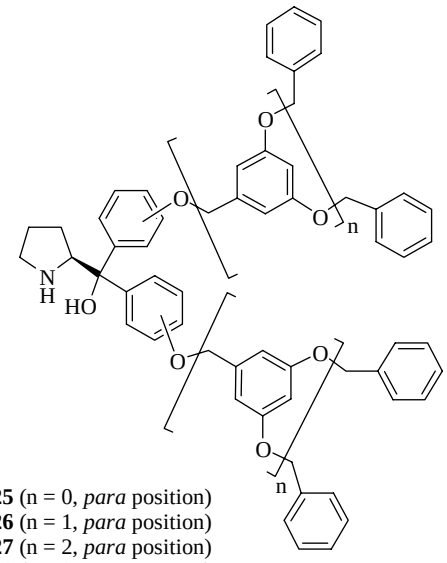
Figure 16

Recently dendritic based chiral amino alcohols (**124-129**) (Fig. 17) have been successfully employed as soluble catalysts/catalytic sources for the borane-mediated reduction of prochiral ketones (eqs. 78&79).[125,126]





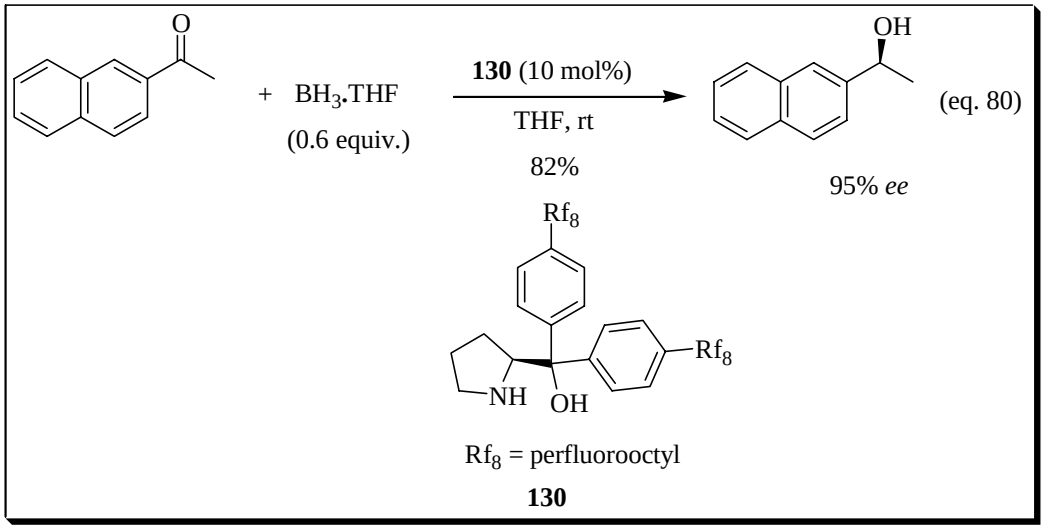
124



125 (n = 0, *para* position)
126 (n = 1, *para* position)
127 (n = 2, *para* position)
128 (n = 3, *para* position)
129 (n = 1, *meta* position)

Figure 17

Very recently Soos and coworkers[127] have developed an operationally simple methodology for the borane-mediated asymmetric reduction of prochiral ketones using the *in situ* generated fluorous oxazaborolidine and also for the easy recovery of the pre-catalyst *i.e*. flourous amino alcohol (**130**). They have also examined the recyclable ability of this recovered pre-catalyst for two times and found that the enantioselectivity remains almost same. One representative example is presented in the equation 80.



OBJECTIVES, RESULTS AND DISCUSSION

From the preceding chapter, it is clear that development of useful and practical chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones for obtaining enantiomerically pure (enriched) secondary alcohols has been and continues to be one of the interesting and fascinating areas in chiral chemistry because of the challenges involved in such endeavors and also due to the enormous applications of homochiral secondary alcohols in organic and medicinal chemistry. For example (*R*,*R*)-isomer of formoterol (**131**) (drug for asthama and chronic bronchitis),[128] is more active than the corresponding (*S*,*S*)-isomer. (*R*)-Isomer of isoproterenol (**4**) (drug for asthama),[5] salmeterol (**132**) (drug for asthama and chronic bronchitis)[129] and denopamine (**133**) (drug for congestive heart failure)[130] are more active than the corresponding (*S*)-enantiomers/racemates as drugs and these can be readily synthesized from the respective enantiomerically pure/enriched secondary alcohols (Figure 18). Our research group has been working for the last few years on the development of recoverable and reusable chiral catalysts/catalytic species (Fig. 13, first chapter, page no. 34) for the borane-mediated asymmetric reduction of prochiral ketones with a view to provide operationally simple procedures for synthesis of secondary alcohols in high enantiomeric purities.[109-113]

Chiral secondary alcohols as synthons for drugs

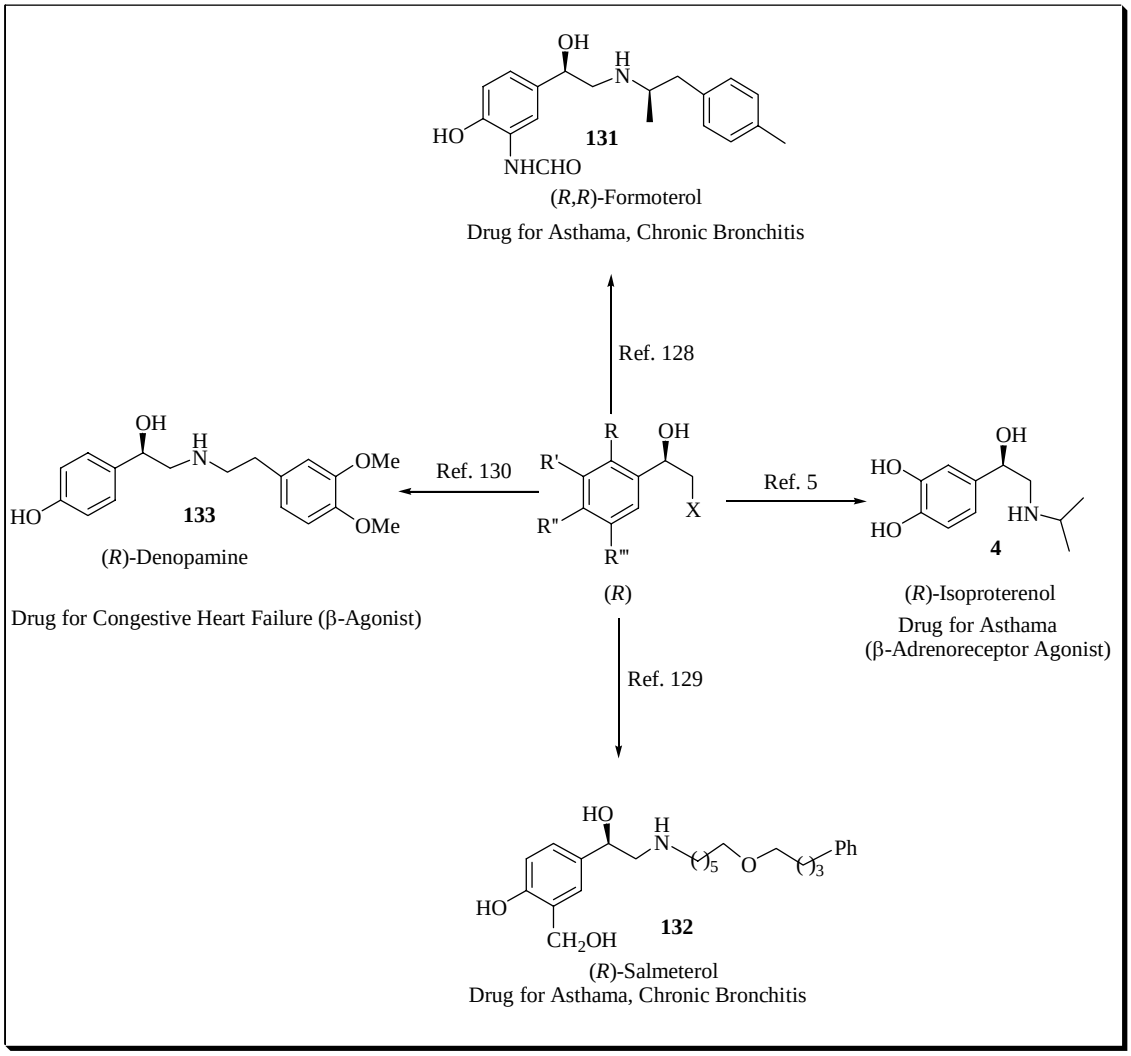


Figure 18

This thesis deals with studies towards the development of novel and effective chiral catalysts/catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones with the following main objectives.

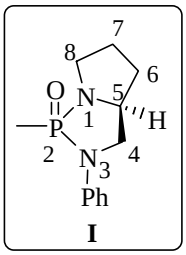
OBJECTIVES

1. To synthesize (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane, containing the ***N-(C=NH)-N*** structural framework (guanidine framework), and examine its catalytic potential in the borane-mediated enantioselective reduction of prochiral ketones. Our objective is also directed towards understanding the nature of the chiral catalyst and examining its potential for *in situ* recyclability.
2. To synthesize (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane, a novel chiral catalytic source containing the ***N-(C=NH)-O*** moiety, and study the applications as chiral catalyst/catalytic source in the borane-mediated asymmetric reduction of prochiral ketones.
3. To study the efficiency of (2*S*)-2-anilinomethylpyrrolidine as chiral catalytic source in the borane-mediated asymmetric reductions of prochiral ketones and also to study the nature of actual chiral catalyst. Also our studies are directed to examine its potential for *in situ* recyclability in the borane-mediated asymmetric reduction of prochiral ketones.
4. To synthesize representative chiral diamides [(2*S*)-5-oxo-2-(arylamino)carbonyl-pyrrolidines] derived from abundantly available (*S*)-glutamic/(*S*)-pyroglutamic acids and utilize them as effective chiral catalytic precursors in the borane-mediated asymmetric reduction of prochiral ketones.

RESULTS AND DISCUSSION

(5*S*)-1,3-Diaza-2-imino-3-phenylbicyclo(3.3.0)octane: First Example of Guanidine Based *in situ* Recyclable Chiral Catalytic Source for Borane-Mediated Asymmetric Reduction of Prochiral Ketones

Our research group has been working for the last few years on the design and synthesis of novel chiral catalysts/catalytic sources (**99-109A**, Page no. 34) containing the *N-P=O* structural framework mainly built on *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* framework **I** with a view to develop recoverable and reusable chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones.



I

During these studies we have also, to some extent, established that the group on the phosphorus in *(5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane* skeleton **I** has no significant role to play in chiral induction process[112] and also the stereochemistry on the phosphorus stereogenic center does not play any role in directing the stereoselectivity of the reduction process.[113] On the basis of these results it

appeared to us that real chiral director in all these studies is the chiral diamine (2*S*)-2-anilinomethylpyrrolidine (**134**) (Fig. 19) from which actually all our catalysts were derived. It, therefore, occurred to us that the guanidine derivative (**135**) (Fig. 19), derived from this wonderful diamine (**134**) (Fig. 19), might provide some interesting guidelines/directions so as to understand the applicability of molecules, containing chiral guanidine framework as possible chiral catalysts or catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones.

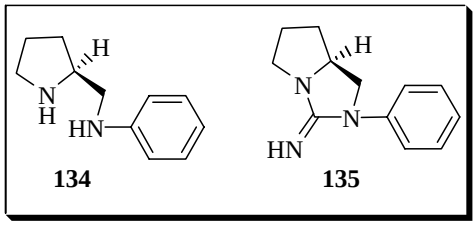
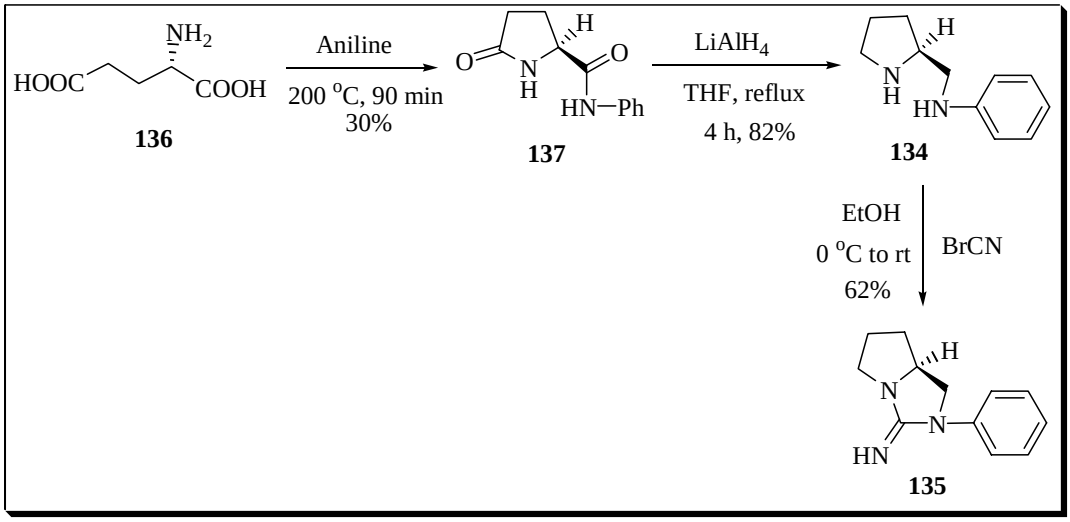


Figure 19

Accordingly we have synthesized the desired (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo-(3.3.0)octane (**135**) *via* the reaction of the chiral diamine (**134**) with cyanogen bromide according to the general literature procedure[131a] {$[\alpha]_D^{25}$:-48.7 (*c* 1.1, $CHCl_3$), 62% yield} (Scheme 10). The structure of this compound (**135**) was confirmed by IR, ^1H (Spectrum 1), ^{13}C NMR (Spectrum 2) spectral data, LC MS and elemental analysis. The structure of this compound (**135**) was also established by the single crystal X-ray data (Fig. 20, Table I). The diamine (**134**) in turn has been synthesized from the easily available and inexpensive (*S*)-glutamic acid (**136**) following the reported procedure (Scheme 10).[131b] The structures of (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**), {$[\alpha]_D^{25}$: +18.4 (c 1.06, MeOH) [Lit.[131b] $[\alpha]_D^{25}$: +18.60 (*c* 1.0, MeOH)]} and (2*S*)-2-

anilinomethylpyrrolidine (**134**) {$[\alpha]_D^{25}$: +19.1 (c 1.1, EtOH) [Lit.[131b] $[\alpha]_D^{25}$: +18.50 (*c* 1.087, EtOH)]} were confirmed by spectral data (IR, ^{1}H and ^{13}C NMR).



Scheme 10

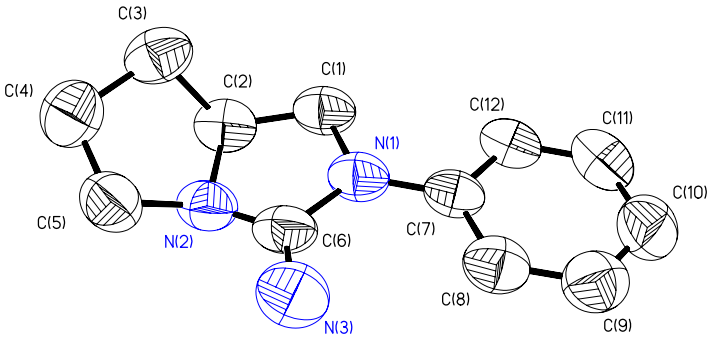


Figure 20: ORTEP diagram of 135[Ψ]
(*Hydrogen atoms were omitted for clarity*)

[Ψ]The single crystal X-ray structure revealed the presence of two molecules in the asymmetric unit. For clarity we have shown one molecule in the ORTEP diagram. Although the sample is enantiomerically pure, having (*S*)-configuration, the asymmetric unit consists of two molecules related by a pseudo-center of symmetry. For similar literature reports please see reference 132.

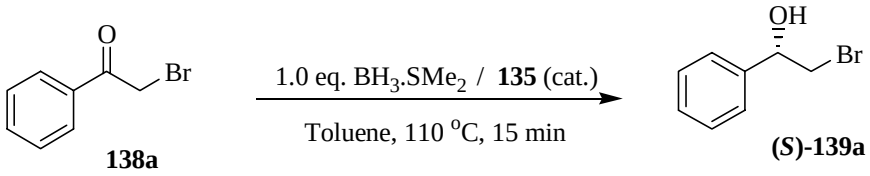
We have first selected phenacyl bromide (**138a**) as a substrate for our study. We have, thus, examined the reduction of phenacyl bromide (**138a**) with different catalytic amounts of guanidine derivative (**135**) with a view to understand the minimum amount of the catalyst required for obtaining higher enantioselectivities (eq. 81, Table 1). The best results were obtained when phenacyl bromide (**138a**) was subjected to the borane-mediated chiral reduction under the influence of (5*S*)-1,3-diaza-2-imino-3-phenyl-bicyclo(3.3.0)octane (**135**) (5 mol%) in refluxing toluene for 15 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 81% yield with 83% enantiomeric excess {$[\alpha]_D^{25}$: +36.5 (*c* 1.1, $CHCl_3$) [Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*]} with (*S*)-configuration (eq. 81, Table 1, entry 3). The structure of the 2-bromo-1-phenylethanol (**139a**) was confirmed by IR, ^1H and ^{13}C NMR spectral data. The enantiomeric purity was determined by HPLC analysis (Chromatogram 1a) using chiral column, Chiralcel OD-H with reference to racemic alcohol (±)-**139a**.

The desired racemic alcohol (±)-**139a** was prepared *via* the reaction of phenacyl bromide (**138a**) with $BH_3.SMe_2$ in refluxing toluene (eq. 82). The spectral data (IR, ^1H & ^{13}C NMR) of this molecule [(±)-**139a**] are in full agreement with that of the chiral molecule **(*S*)-139a**.

Table I: Crystal data and structure refinement for the compound 135

Identification	: **135**
Empirical formula	: $C_{12}H_{15}N_3$
Formula weight	: 201.27
Temperature	: 298 ^oK
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *P* 2_1
Unit cell dimensions	: *a* = 9.5937 (13) Å α = 90.00
	: *b* = 11.6631 (16) Å β = 91.683 (2)
	: *c* = 9.6206 (13) Å γ = 90.00
Volume	: 1076.0 (3) $Å^3$
Z	: 4
Density (calculated)	: 1.242 g/cm^3
Absorption coefficient	: 0.077 mm^{-1}
F (000)	: 432
Crystal size	: 0.45 X 0.32 X 0.14 mm^3
Theta range for data collection	: 2.12 $\leq \varnothing \leq$ 28.29
Index ranges	: $-12 \leq h \leq 12$, $-15 \leq k \leq 15$, $-12 \leq l \leq 12$
Reflections collected	: 2723
Independent reflections	: 1697
Refinement method	: *Full-matrix least-squares on* F^2
Data / restraints / parameters	: 1697 / 1 / 279
Goodness-of-fit on F^2	: 0.934
Final R indices [I> 2 sigma (I)]	: R1 = 0.0378; wR^2 = 0.0814.
R indices (all data)	: R1 = 0.0711, wR^2 = 0.0923
Absolute structure parameters	: 0(10)
Largest diff. Peak and hole	: 0.120 and -0.127 e. A^{-3}

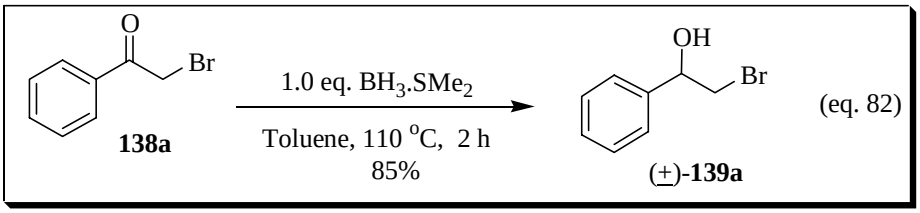
Table 1. Asymmetric reduction of phenacyl bromide (**138a**) at 110 ^{o}C[a]



(eq. 81)

Entry	Catalyst **135** (mol%)	Yield[b] (%) **(139a)**	Enantiomeric purity[c] (%) **(139a)**	Configuration[d]
1	2	82	74	*S*
2	4	84	81	*S*
3	**5**	**81**	**83**	***S***
4	6	86	79	*S*
5	8	88	78	*S*
6	10	80	80	*S*

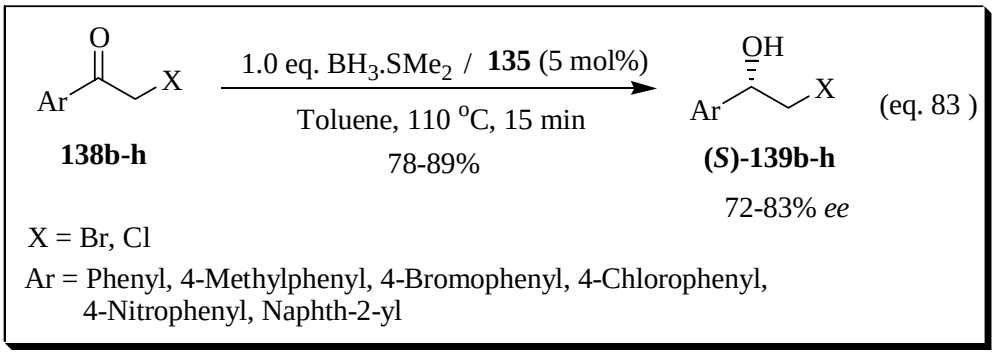
[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with 1 mM of $BH_3.SMe_2$ in the presence of **135** in toluene for 15 min at 110 ^{o}C.
[b]Isolated yields of alcohol **[(*S*)-139a]** after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[133]



(eq. 82)

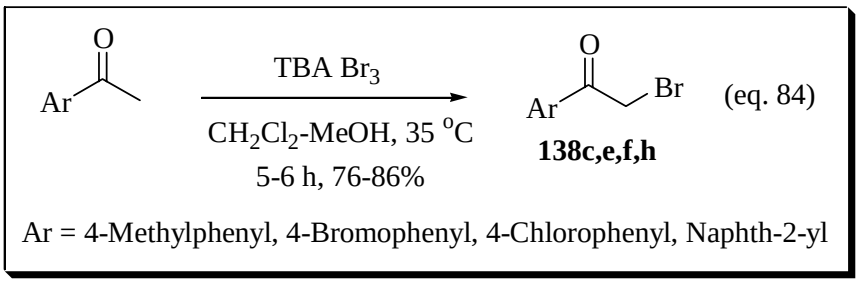
Encouraged by this result and also with a view to understand the generality, we extended this methodology to a representative prochiral α-halo ketones **138b-h**. The resulting secondary alcohols **(*S*)-139b-h** were obtained in 72-83% enantiomeric purities

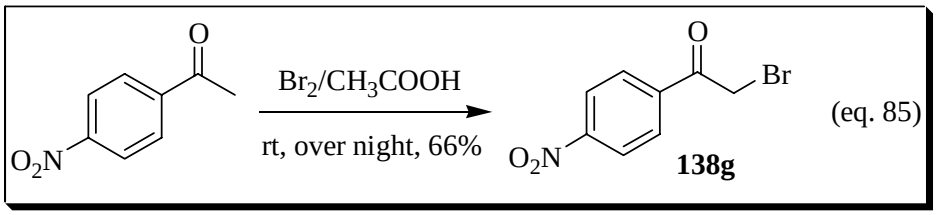
(eq. 83, Table 2). The structures of these molecules **(*S*)-139b-h** were confirmed by IR, ^{1}H and ^{13}C NMR spectral data.

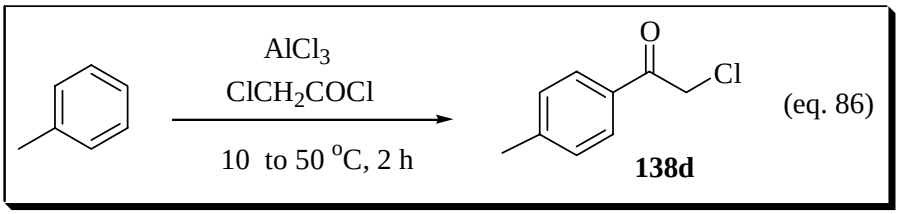


The required α-bromo ketones *i.e.*, 4-methylphenacyl bromide (**138c**), 4-bromophenacyl bromide (**138e**), 4-chlorophenacyl bromide (**138f**), and 2-bromoacetylnaphthalene (**138h**) were prepared by the treatment of TBA Br_3 with the corresponding aryl alkyl ketones[α] according to the literature procedure (eq. 84).[134] 4-Nitrophenacyl bromide (**138g**) was prepared *via* the reaction of 4-nitroacetophenone with Br_2/CH_3CO_2H (eq. 85),[135] while 4-methylphenacyl chloride (**138d**) was synthesized *via* the reaction of toluene with chloroacetyl chloride, in presence of $AlCl_3$ according to the equation 86. The structures of these α-halo ketones were established by spectral data (IR, ^{1}H and ^{13}C NMR).

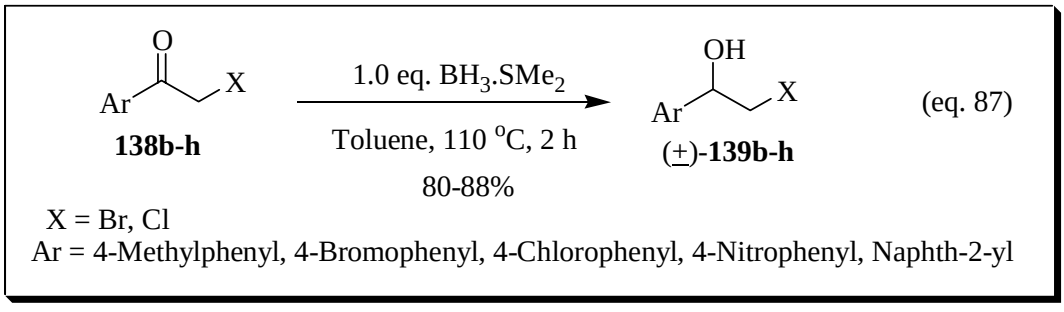
[α]The starting materials (aryl alkyl ketones) are not given numbering in this section for better clarity and also to have continuity.







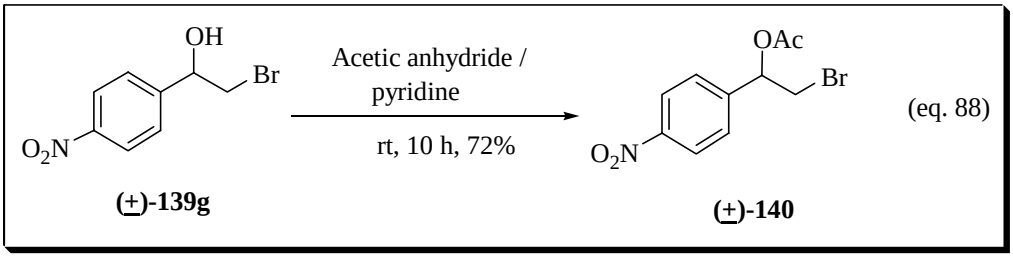
The racemic alcohols (±)-**139b-h** were prepared *via* the treatment of corresponding α-halo ketones **138b-h** with $BH_3.SMe_2$ (eq. 87). The structures of these racemic alcohols [(±)-**139b-h**] were established by IR, ^1H and ^{13}C NMR spectral data.



Determination of Enantiomeric Purities of Alcohols:

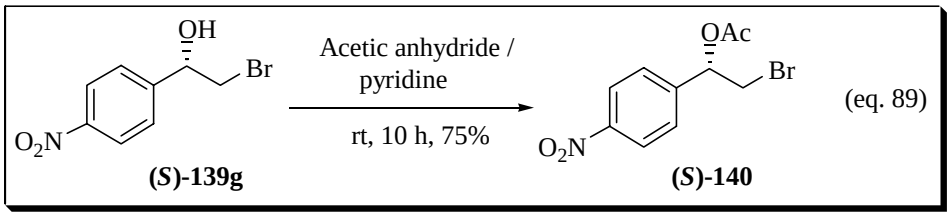
The enantiomeric purities of the alcohols [**(*S*)-139b-d**] were determined by HPLC analyses using the chiral column, Chiralcel OD-H with reference to the corresponding racemic alcohols [**(±)-139b-d**], where as the enantiomeric excesses of the alcohols [**(*S*)-139e,f,h** (Chromatogram 2)] have been determined by HPLC analyses using the chiral column, Chiralcel OJ-H with reference to the corresponding racemic alcohols [**(±)-139e,f,h**].

Determination of enantiomeric purity of the alcohol [**(*S*)-139g**] has been done by the HPLC analysis of the corresponding acetate [**(*S*)-140**] using the chiral column, chiralcel OD-H with reference to the racemic acetate, [**(±)-140**]. The required (±)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(±)-140**] and (*S*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(*S*)-140**] were prepared *via* the reaction of the corresponding racemic [**(±)-139g**] and chiral [**(*S*)-139g**] alcohols respectively with acetic anhydride in the presence of pyridine according to the equations 88 & 89.[β]



(±)-139g **(±)-140**

[β]For continuity and easy understanding acetates derived from **(±)-139g** & **(*S*)-139g** are numbered as **(±)-140** & **(*S*)-140** respectively.



(*S*)-139g **(*S*)-140**

Towards Understanding Catalytic Process:

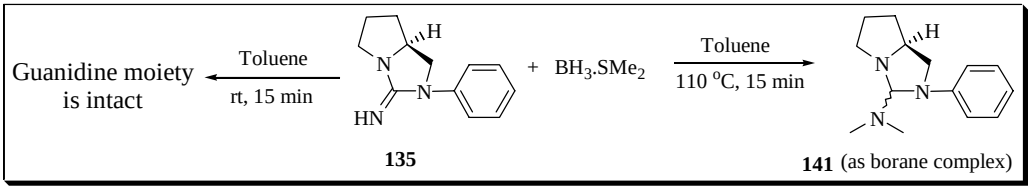
With a view to understand the nature of the actual chiral catalyst/catalytic source we have carried out the following experiments. i) We have performed the reaction between the guanidine derivative (**135**) (0.25 mM) and $BH_3.SMe_2$ (5 mM, 5 mL, 1 M solution in toluene) (in the ratio of 1:20 as in the case of reaction conditions) in refluxing toluene (25 mL) for 15 min and recorded ^1H, ^{13}C, ^{11}B NMR[γ] spectra of this crude mixture (after removal of excess $BH_3.SMe_2$ and toluene under reduced pressure). Although ^1H & ^{13}C NMR spectral data did not provide any indication about the exact structure of the actual catalyst, the presence of a peak at δ 85.02 ppm (along with other peaks) and also absence of the peak at δ 161.69 ppm [present in spectrum of original guanidine (**135**)] in the ^{13}C NMR spectrum (Spectrum 3) indicate the possible reduction of C=N of the guanidine moiety probably leading to the formation of compound **141** (*possibly complexing with borane*) having ***CH*** attached to three different nitrogens (Scheme 11).

[γ] ^{11}B NMR spectrum showed a broad peak at δ 31.7 ppm (in addition to other peaks in the region δ -32 to 3 ppm) probably indicating the presence of N-B-N.

Table 2. Asymmetric reduction of prochiral α-halo ketones[a]

Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)
138a	Phenyl	Br	**139a**	81	+36.5 (*c* 1.1, $CHCl_3$)	*S*[133]	83[d]
138b	Phenyl	Cl	**139b**	80	+40.7 (*c* 1.3, C_6H_{12})	*S*[133]	81[d]
138c	4-Methylphenyl	Br	**139c**	85	+35.3 (*c* 1.2, $CHCl_3$)	*S*[109]	82[d]
138d	4-Methylphenyl	Cl	**139d**	82	+42.0 (*c* 1.1, $CHCl_3$)	*S*[109]	83[d]
138e	4-Bromophenyl	Br	**139e**	78	+27.7 (*c* 1.1, $CHCl_3$)	*S*[136]	81[e]
138f	4-Chlorophenyl	Br	**139f**	89	+37.4 (*c* 1.2, $CHCl_3$)	*S*[109]	83[e]
138g	4-Nitrophenyl	Br	**139g**	84	+26.5 (*c* 1.2, $CHCl_3$)	*S*[110]	78[f]
138h	Naphth-2-yl	Br	**139h**	86	+21.6 (*c* 1.0, EtOH)	*S*[137]	72[e]

[a]All reactions were carried out on 1 mM scale of α-halo ketone with 1 mM of $BH_3.SMe_2$ in the presence of **135** (5 mol%) in toluene for 15 min at 110 ^oC.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.
[f]Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel OD-H.



Scheme 11

ii) With a view to understand the stability of guanidine moiety in the presence of BH_3. SMe_2 at room temperature, we have treated the guanidine derivative (**135**) (0. 25 mM) with $BH_3.SMe_2$ (5 mM, 5 mL, 1 M solution in toluene) (in the ratio of 1:20 as in the case of reaction conditions) in toluene (25 mL) at room temperature (≈30 ^oC) for 15 min and recorded ^1H, ^{13}C, ^{11}B NMR[π] spectra of this crude compound (after removal of excess $BH_3.SMe_2$ and toluene under reduced pressure). ^{13}C NMR spectrum (Spectrum 4) indicated that the guanidine moiety is more or less intact as evidenced by the absence of any peak in the region δ 70-110 ppm (due to the absence of carbon attached to three nitrogens) and the presence of a peak at δ 161.02 (as there is no reduction of C=N) (Scheme 11). Also the ^{13}C NMR spectrum show the presence of all the peaks that are originally present in starting guanidine (**135**) (with little difference in the chemical shift

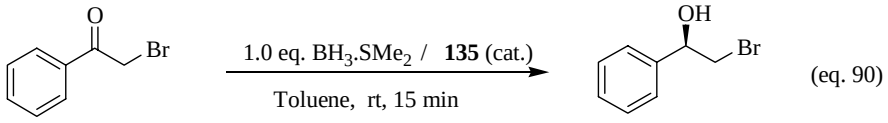
[π] ^{11}B NMR spectrum did not show any peak in the region δ 15- 40 ppm thus indicating the absence of N-B-N moiety and ^{11}B NMR spectrum showed peaks at δ -20.3, -21.4, -29.9 ppm and a minor peak at δ -11.3 ppm indicating the presence of the tetra-coordinated boron (ate complexes). *However it needs more studies to understand the actual nature of the boron species present in the catalytic cycle.*

values) along with the minor peaks (probably arising due to the complexation with borane). We have then performed the asymmetric reduction of phenacyl bromide (**138a**) under the influence of **135** (5 mol%) at room temperature (≈30 ^{o}C) in order to understand its efficiency as catalyst. The resulting secondary alcohol **139a** was obtained with 32% enantiomeric purity, more interestingly with (*R*)-configuration (opposite to the configuration of alcohol obtained at reflux conditions). Although enantioselectivity is low, this has fascinated us because of the reversal of stereo-selection from room temperature to 110 ^{o}C. Thus the same catalytic source operates in two different stereo-directions (as enantiomeric switch) in the reduction of phenacyl bromide (**138a**) thus providing the resulting alcohol with opposite configurations at room temperature and high temperature (110 ^{o}C) due to two different catalytic species actually involved in the reduction path-way. We have also carried out the same reaction with different catalytic amounts of **135** in order to study the influence of amount of catalyst on the asymmetric induction at room temperature. However enantiomeric purity of the resulting alcohol remains almost the same (eq. 90, Table 3) [see Chromatogram 1b for HPLC of entry 5, Table 3].

iii) With a view to understand the stereo-selection of reduced catalytic species **141**, at room temperature, we have carried out the reduction of phenacyl bromide (**138a**) under the influence of catalytic species **141** (5 mol%) (generated *in situ* by the reaction of guanidine moiety (**135**) with $BH_3.SMe_2$ at 110 ^{o}C and cooling back to room temperature) for 30 min

at room temperature and obtained the corresponding (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 44% *ee* (Scheme 12).

Table 3. Asymmetric reduction of phenacyl bromide (**138a**) at room temperature[a]

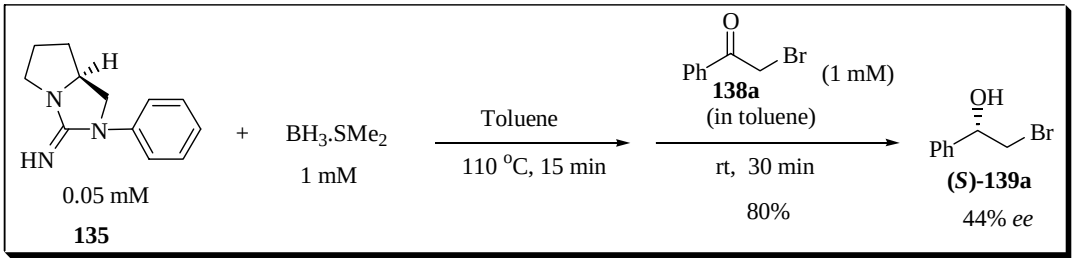


(eq. 90)

138a **(*R*)-139a**

Entry	Catalyst **135** (mol%)	Yield[b] (%) **(139a)**	Enantiomeric purity[c] (%) (**139a**)	Configuration[d]
1	5	87	32	*R*
2	6	85	31	*R*
3	8	85	36	*R*
4	10	84	36	*R*
5	15	83	37	*R*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with 1 mM of $BH_3.SMe_2$ in the presence of **135** in toluene for 15 min at ≈30 ^oC.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[d]Absolute configuration was assigned by comparison of the sign [(-) *i.e.*, (levo rotatory)] of the specific rotation with that of reported molecule.[133]



Scheme 12

This study demonstrates that there is a remarkable difference in the levels of stereo-selectivity from the same catalytic species at 110 ^{o}C and at room temperature probably due to two different path-ways of reduction processes. The coordination of the catalyst with BH_3 and ketone may not be strong enough at room temperature, therefore non catalytic path-way might dominate thus leading to low enantioselectivity.

Recyclable potential of *in situ* generated catalyst/catalytic species:

With a view to examine the *in situ* recyclable potential of the catalytic species (**141**), we first carried out the reduction of phenacyl bromide (**138a**) (1 mM) in usual way at 110 ^{o}C (run 1). $BH_3.SMe_2$ (1 mM) (for run 2) was added to this reaction flask (without work-up), and heated at 110 ^{o}C for 15 min and then a solution of phenacyl bromide (**138a**) (1 mM) in toluene was added slowly drop-wise and stirring was continued at 110 ^{o}C for further 15 min as usual (run 2). We were pleased to obtain the resulting secondary alcohol **(*S*)-139a** (after work-up and purification as usual) in almost the same enantioselectivity. In a similar way we have also examined the recyclable ability of this catalyst for further two times (total four times) and in fact, the enantioselectivity remained almost the same (Table 4, Scheme 13).

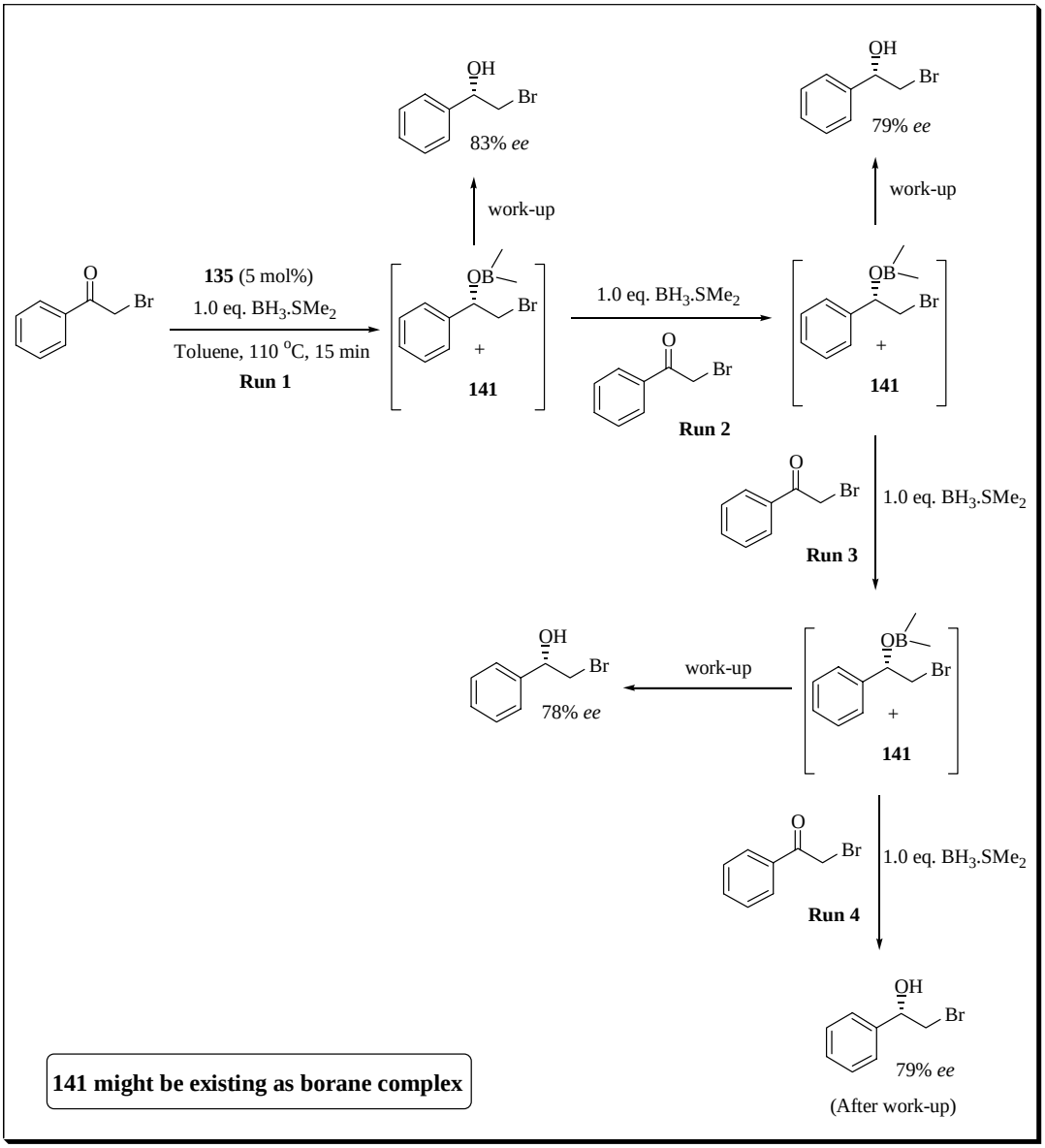
In conclusion, we have, for the first time, developed a novel and *in situ* recyclable chiral catalytic source (**135**) based on guanidine framework for the borane-mediated asymmetric reduction of prochiral α-halo ketones thus providing the secondary alcohols with good

enantiomeric purities. Our study also demonstrates a remarkable reversal of stereo-selectivity from room temperature (≈30 ^{o}C) to high temperature (110 ^{o}C) during the borane-mediated reduction of phenacyl bromide (**138a**) using the guanidine (**135**) as a chiral catalytic source, probably due to two different catalytic species actually involved in the transition state of the reduction process and also we observed an interesting temperature dependant levels of stereo-selectivity from the same catalytic species (**141**) probably due to different path-ways involved in the reduction process. This study also to some extent indicates that it would be in principle possible to design and synthesize appropriate chiral guanidine catalyst/catalytic source, which can indeed act as an enantiomeric switch, to obtain both the enantiomers of the secondary alcohols in homochiral form.

Table 4. *In situ* recyclable ability of catalytic species (**141**) in the asymmetric reduction of phenacyl bromide (**138a**)

Number of runs	Enantiomeric purity (%)[a] [**(*S*)-139a**]
1	83
2	79
3	78
4	79

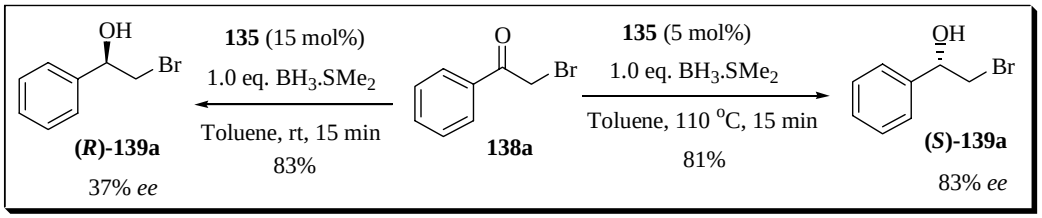
[a]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.



Scheme 13: *In situ* recyclability

(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane: A Novel Chiral Catalytic Source Containing the *N-(C=NH)-O* Moiety for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones

In the previous section, we have described, for the first time, the application of chiral guanidine, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (Fig. 21), as a novel, *in situ* recyclable chiral catalytic source for the borane-mediated asymmetric reduction of prochiral α-halo ketones. During this study we have also noticed that this catalytic source has remarkable potential in directing the borane-mediated reduction of phenacyl bromide (**138a**) at high temperature (110 ^{o}C) (in refluxing toluene) providing (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 83% *ee*, while at room temperature (≈30 ^{o}C) producing (*R*)-2-bromo-1-phenylethanol [**(*R*)-139a**] in 37% *ee*. This remarkable temperature dependant reversal of stereoselectivity (enantiomeric switch) exhibited by the compound **135**, containing the ***N-(C=NH)-N*** framework in the borane-mediated asymmetric reduction of phenacyl bromide (**138a**) (Scheme 14), prompted us to examine whether similar closely related chiral catalytic source (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (Fig. 21), with ***N-(C=NH)-O*** moiety, would also exhibit such kind of temperature dependant reversal of stereoselectivity in similar reduction processes.



Scheme 14: Enantiomeric switch

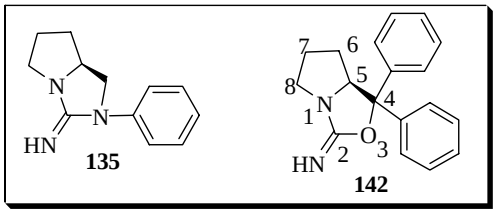
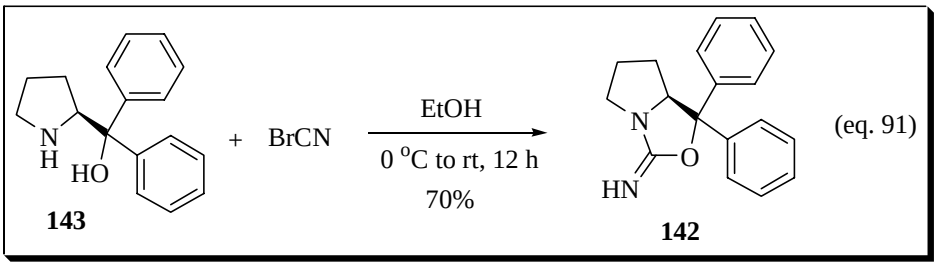


Figure 21

The desired chiral compound, (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) has been synthesized *via* the reaction of the (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine (**143**) with cyanogen bromide[131a] according to the equation 91 {70% yield, $[\alpha]_D^{25}$: -221.9 (*c* 1.14, $CHCl_3$)}. The structure of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenyl-bicyclo(3.3.0)octane (**142**) was established by IR, ^{1}H NMR (Spectrum 5), ^{13}C NMR (Spectrum 6), LC MS and elemental analysis and was also confirmed by the single crystal X-ray data (Fig. 22, Table II).



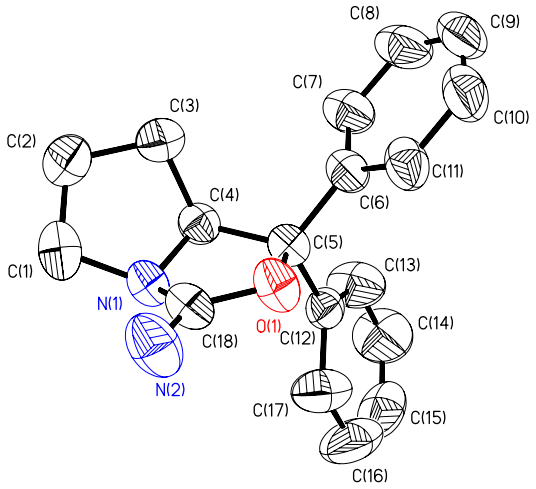


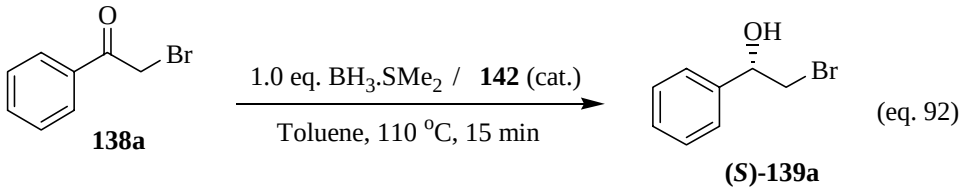
Figure 22: ORTEP diagram of 142
(*Hydrogen atoms were omitted for clarity*)

We have selected phenacyl bromide (**138a**) as a substrate for our study. We have performed the asymmetric reduction of phenacyl bromide (**138a**) with varying catalytic amounts of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) with a view to understand the requirement of minimum amount of the catalyst for obtaining highest selectivity (eq. 92, Table 5). The best results were obtained when phenacyl bromide (**138a**) was treated with $BH_3.SMe_2$ under the influence of **142** (2 mol%) in refluxing toluene for 15 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 85% yield with 92% enantiomeric excess (entry 3, Table 5). The enantiomeric excess of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol [**(±)-139a**].

Table II: Crystal data and structure refinement for the compound 142

Identification	: **142**
Empirical formula	: C18 H18 N2 O
Formula weight	: 278.34
Temperature	: 298 ^{o}K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: *P* 2_1 2_1 2_1
Unit cell dimensions	: *a* = 8.5608(5) Å α = 90.00
	: *b* = 10.1884(6) Å β = 90.00
	: *c* = 16.9703(10) Å γ = 90.00
Volume	: 1480.16(15) Å^3
Z	: 4
Density (calculated)	: 1.249 g/cm^3
Absorption coefficient	: 0.078 mm^{-1}
F (000)	: 592
Crystal size	: 0.35 X 0.30 X 0.28 mm^3
Theta range for data collection	: 2.33 $\leq \varnothing \leq$ 28.27
Index ranges	: -11 $\leq$h $\leq$ 11, -13 $\leq$ k $\leq$ 13, -22 $\leq$ l $\leq$ 22
Reflections collected	: 2062
Independent reflections	: 1680
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1680 / 0 / 194
Goodness-of-fit on F^2	: 1.127
Final R indices [I> 2 sigma (I)]	: R1 = 0.0549; *wR*^{2} = 0.1275
R indices (all data)	: R1 = 0.0687, *wR*^{2} = 0.1339
Absolute structure parameters	: 0(10)
Largest diff. Peak and hole	: 0.177and -0.173 e. A^{-3}

Table 5. Standardization: Asymmetric reduction of phenacyl bromide (**138a**) at 110 ^{o}C[a]



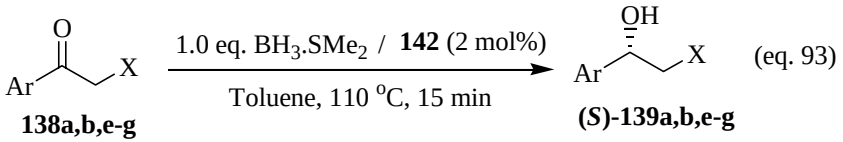
138a **(*S*)-139a** (eq. 92)

Entry	Catalyst **142** (mol%)	Yield[b] (%) (**139a**)	Enantiomeric excess[c] (%) (**139a**)	Configuration[d]
1	0.5	80	87	*S*
2	1	81	90	*S*
3	**2**	**85**	**92**	***S***
4	3	82	90	*S*
5	4	82	91	*S*
6	5	81	92	*S*
7	10	82	92	*S*
8	15	80	92	*S*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (1 mM) in the presence of **142** in toluene for 15 min at 110 ^{o}C.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecule.[133]

With a view to examine the generality of this methodology, we have subjected representative prochiral α-halo ketones **138b,e-g** to the borane-mediated asymmetric reduction using this catalytic source (**142**). The resulting secondary alcohols **(*S*)-139b,e-g** were obtained in 88-93% enantiomeric excess (eq. 93, Table 6).

Table 6. Asymmetric reduction of prochiral α-halo ketones[a]



138a,b,e-g **(*S*)-139a,b,e-g** (eq. 93)

X = Br, Cl

Ar = Phenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Nitrophenyl

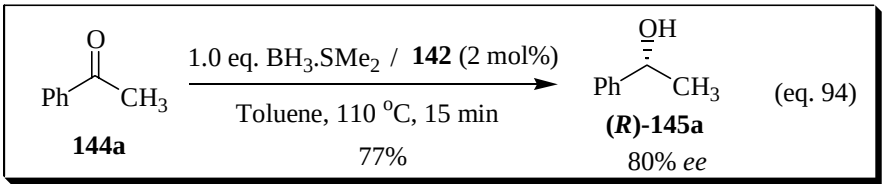
Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)
138a	Phenyl	Br	**139a**	85	+40.1 (*c* 1.8, $CHCl_3$)	*S*[133]	92[d]
138b	Phenyl	Cl	**139b**	87	+44.7 (*c* 1.1, C_6H_{12})	*S*[133]	91[d]
138e	4-Bromophenyl	Br	**139e**	86	+31.9 (*c* 1.2, $CHCl_3$)	*S*[136]	92[e]
138f	4-Chlorophenyl	Br	**139f**	85	+39.3 (*c* 1.0, $CHCl_3$)	*S*[109]	93[e]
138g	4-Nitrophenyl	Br	**139g**	84	+32.3 (*c* 1.3, $CHCl_3$)	*S*[110]	88[f]

[a]All reactions were carried out on 1 mM scale of α-halo ketone with $BH_3.SMe_2$ (1 mM) in the presence of **142** (2 mol%) in toluene for 15 min at 110 °C.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.
[f]Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel OD-H.

Determination of Enantiomeric Purities of Alcohols:

The enantiomeric purity of the (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to the corresponding racemic alcohol, (±)-2-chloro-1-phenylethanol [**(±)-139b**], where as the enantiomeric excesses of (*S*)-2-bromo-1-(4-bromophenyl)ethanol [**(*S*)-139e**] (Chromatogram 3) & (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [**(*S*)-139f**] (Chromatogram 4) have been determined by HPLC analyses using the chiral column, Chiralcel OJ-H with reference to the corresponding racemic alcohols **(±)-139e** & **(±)-139f** respectively. Enantiomeric purity of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [**(*S*)-139g**] has been determined by the HPLC analysis of the corresponding acetate, (*S*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(*S*)-140**] using the chiral column, Chiralcel OD-H with reference to the racemic acetate **(±)-140**.

Encouraged by these results and also with a view to examine the level of selectivity in the case of aryl alkyl ketones, we have first examined the reduction of acetophenone (**144a**) under the influence of **142** (2 mol%). The resulting secondary alcohol **(*R*)-145a** was obtained in 80% enantiomeric purity (eq. 94). The enantiomeric purity was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to (±)-1-phenylethanol [**(±)-145a**].



To understand the generality, we have extended this methodology for the borane-mediated asymmetric reduction of representative aryl alkyl ketones **144b-e**. The resulting secondary alcohols **(*R*)-145b-e** were obtained in 70-87% enantiomeric excess (eq. 95, Table 7).

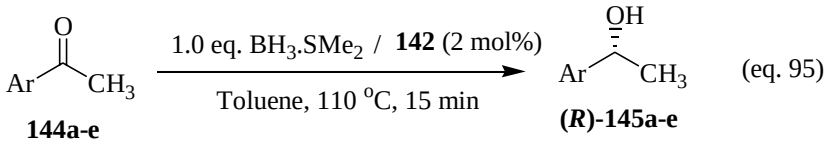
Determination of Enantiomeric Purities of Alcohols:

The enantiomeric purities of (*R*)-1-(4-methylphenyl)ethanol [**(*R*)-145b**], (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-145c**] and (*R*)-1-(4-chlorophenyl)ethanol [**(*R*)-145d**] have been determined by HPLC analyses using the chiral column, Chiralcel OJ-H with reference to (±)-1-(4-methylphenyl)ethanol [**(±)-145b**], (±)-1-(4-bromophenyl)ethanol [**(±)-145c**] and (±)-1-(4-chlorophenyl)ethanol [**(±)-145d**] respectively. The enantiomeric purity of (*R*)-1-(4-nitrophenyl)ethanol [**(*R*)-145e**] (Chromatogram 5) was determined by HPLC analysis of the corresponding acetate [**(*R*)-146**] using the chiral column, Chiralcel OD-H with reference to the corresponding racemic acetate [**(±)-146**].[ε]

The required racemic alcohols **(±)-145a-e** were prepared by the reduction of the corresponding ketones **144a-e** with $BH_3.SMe_2$ in toluene at reflux temperature (eq. 96).

[ε]For continuity and easy understanding acetates derived from **(±)-145e** & **(*S*)-145e** are numbered as **(±)-146** & **(*S*)-146** respectively.

Table 7. Asymmetric reduction of aryl alkyl ketones[a]

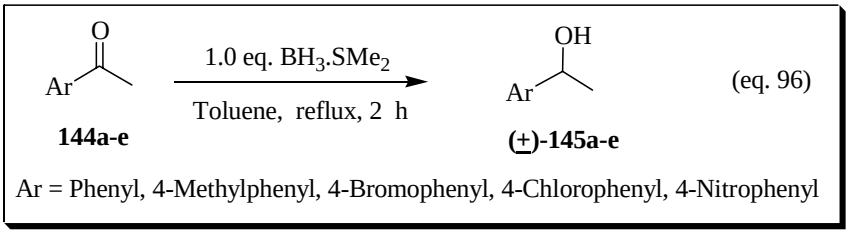


(eq. 95)

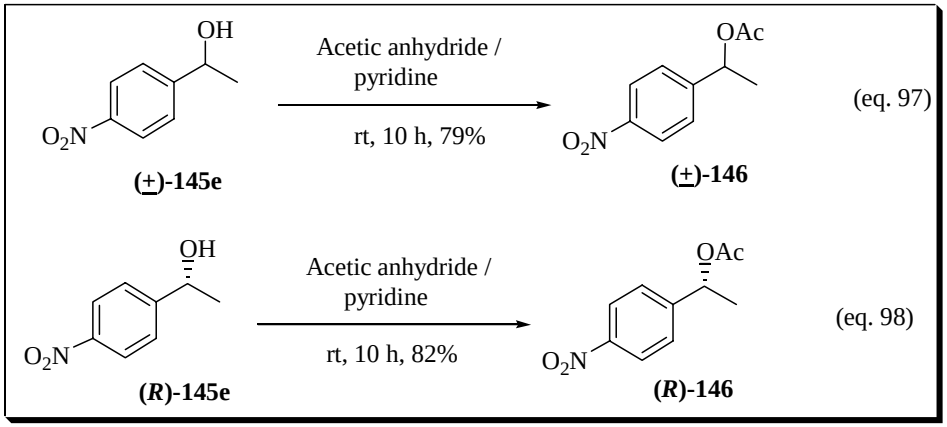
Ar = Phenyl, 4-Methylphenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Nitrophenyl

Substrate	**Ar**	**Product**	**Yield[b] (%)**	**$[\alpha]_D^{25}$**	**Conf.[c]**	**E.e (%)**
144a	Phenyl	**145a**	77	+35.5 (*c* 1.2, MeOH)	*R*[138]	80[d]
144b	4-Methylphenyl	**145b**	82	+29.2 (*c* 1.5, MeOH)	*R*[139]	70[e]
144c	4-Bromophenyl	**145c**	85	+27.5 (*c* 1.1, $CHCl_3$)	*R*[139]	73[e]
144d	4-Chlorophenyl	**145d**	84	+38.5 (*c* 1.3, Et_2O)	*R*[139]	78[e]
144e	4-Nitrophenyl	**145e**	82	+27.2 (*c* 1.2, EtOH)	*R*[140]	87[f]

[a]All reactions were carried out on 1 mM scale of aryl alkyl ketone with $BH_3.SMe_2$ (1 mM) in the presence of **142** (2 mol%) in toluene for 15 min at 110 °C.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules.
[d]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.
[f]Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel OD-H.



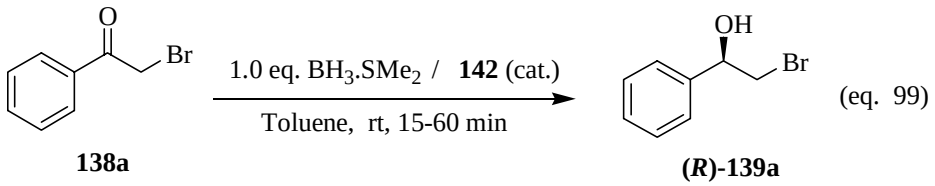
The desired (±)-1-acetoxy-1-(4-nitrophenyl)ethane [**(±)-146**] and (*R*)-1-acetoxy-1-(4-nitrophenyl)ethane [**(*R*)-146**] were synthesized *via* the reaction of the corresponding racemic [**(±)-145e**] and chiral [**(*R*)-145e**] alcohols with acetic anhydride in the presence of pyridine according to the equations 97 & 98.



With a view to further understand the efficiency of this molecule (**142**) as a chiral catalytic source and also to examine the possible reversal of stereoselectivity at room temperature, we have carried out the borane-mediated asymmetric reduction of phenacyl bromide (**138a**) at room temperature under the catalytic influence of **142** (2 mol%). The resulting 2-bromo-1-phenylethanol (**139a**) was obtained in very low (5%) enantiomeric purity, interestingly, with opposite configuration *i. e.*, an (*R*)-configuration (eq. 99, Table 8). In

order to improve the enantioselectivity, we performed the same reaction with varying amounts of the catalytic source **142**. However the enantioselectivity remains almost the same (eq. 99, Table 8). Although the enantioselectivity is not that impressive, this result is still interesting in the sense that this compound (**142**), containing the ***N-(C=NH)-O*** moiety, shows a potential for exhibiting a temperature dependant reversal of stereoselectivity in borane-mediated reduction processes.

Table 8. Asymmetric reduction of phenacyl bromide (**138a**) at room temperature[a]

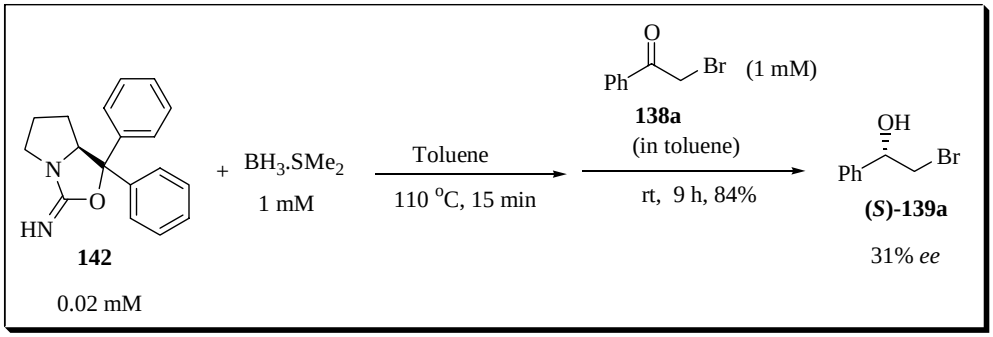


138a **(*R*)-139a** (eq. 99)

Entry	Catalyst **142** (mol%)	Time (min)	Yield[b] (%) (**139a**)	Enantiomeric purity[c] (%) (**139a**)	Configuration[d]
1	2	60	86	5	*R*
2	5	15	81	7	*R*
3	10	15	82	5	*R*
4	15	15	80	4	*R*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (1 mM) in the presence of **142** in toluene at room temperature.
[b]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[d]Absolute configuration was assigned by the comparison of the sign [(-) *i.e.*, (levo rotatory)] of the specific rotation with that of reported molecule.[133] Also intensities of enanatiomeric (*R* and *S*) peaks in HPLC analysis confirm the assignment of configuration.

Next we have directed our studies to examine the potential of the chiral species, generated *in situ* by the reaction of **142** with $BH_3.SMe_2$ in refluxing toluene, in asymmetric reduction at room temperature. Thus, we have treated the compound **142** (2 mol%, 0.02 mM) with $BH_3.SMe_2$ (1 mM) for 15 min in refluxing toluene and cooled to room temperature and performed the reduction of phenacyl bromide (**138a**) (1mM) at room temperature to provide the corresponding 2-bromo-1-phenylethanol (**139a**) in 31% enantiomeric purity with an (*S*)-configuration (Scheme 15). This is an interesting result as it clearly indicates that enantioselectivities are better at higher temperature (110 ^oC) than at room temperature probably due to better coordination of borane and ketone with the catalyst at high temperature than at room temperature. This result is, in fact, consistent with our previous result with chiral guanidine *i.e.*, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**).



Scheme 15

Since the level of reversal of stereoselectivity exhibited by this catalyst/catalytic source (**142**) at room temperature in the borane-mediated reduction of phenacyl bromide (**138a**) is

not impressive, we did not make any attempt towards understanding the nature of catalyst generated *in situ* by the reaction of **142** with $BH_3.SMe_2$ in refluxing toluene.

In conclusion we have developed a novel chiral catalytic source (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**), containing the ***N-(C=NH)-O*** moiety for the borane-mediated asymmetric reduction of prochiral ketones which provides the corresponding secondary alcohols with up-to 93% enantiomeric purity. Although this chiral source (**142**) provides inferior (negligible) enantioselectivities at room temperature when compared to our earlier catalyst, chiral guanidine (**135**), with respect to the reversal of stereo-selectivity, it does give clear indication that an appropriate chiral catalytic source containing the ***N-(C=NH)-O*** moiety might provide high levels of temperature dependant stereo-directionality thus leading to the production of both the enantiomers in high enantioselectivities in the borane-mediated reduction of prochiral ketones.

(2*S*)-2-Anilinomethylpyrrolidine: an Efficient *in situ* Recyclable Chiral Catalytic Source for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones in Refluxing Toluene

In the first section (Page nos. 47-63), we described the application of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (Fig. 23) as the first example of guanidine based chiral catalytic source for the borane-mediated asymmetric reduction of representative prochiral ketones. During our work on the borane-mediated asymmetric reduction of representative prochiral ketones using the chiral guanidine *i.e.*, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) built on the (2*S*)-2-anilinomethylpyrrolidine (**134**) (Fig. 23) framework, as an *in situ* recyclable catalytic source, we observed a remarkable reversal of stereo-selectivity from room temperature (≈30 ^{o}C) to high temperature (110 ^{o}C) probably due to two different catalytic species actually involved in the transition state of the reduction process. We also observed interesting temperature dependant levels of stereo-selectivity from the same catalytic species due to the different pathways involved in the reduction process. This temperature dependant direction and levels of stereo-selectivity have attracted our attention and based on this fact it occurred to us that (2*S*)-2-anilinomethylpyrrolidine (**134**), itself might offer promising enantioselectivities at higher temperature *i.e.*, at 110 ^{o}C in toluene. Asami *et.al.*[141,142] reported during their elegant work on the applications of various chiral diamines as possible catalysts for the borane-mediated asymmetric reduction of prochiral ketones that

the chiral diamine **147** (Fig. 23) as a catalyst, provides high enantioselectivities in the reduction of prochiral ketones at room temperature and at low temperatures (up-to -15 ^{o}C) (they studied up-to -30 ^{o}C), while the catalyst **134** provides inferior selectivity (14% *ee*) at room temperature in the reduction of acetophenone (**144a**) (eqs. 100 & 101). However, to the best of our knowledge, they did not examine the effect of high temperature on the enantioselectivity using those chiral diamines (**134** & **147**), and also there is no report in the literature in this regard. We have, therefore, decided to examine the catalytic potential of (2*S*)-2-anilinomethylpyrrolidine (**134**) in refluxing toluene.

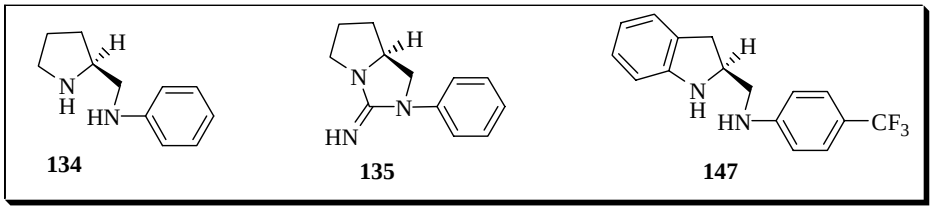
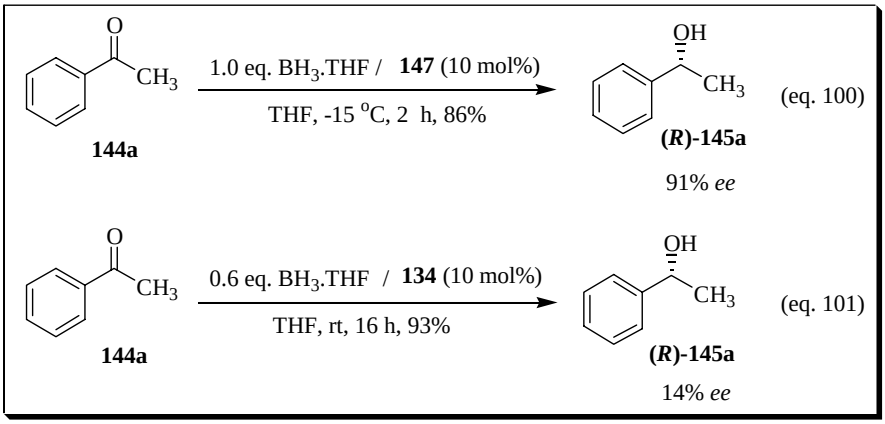


Figure 23



Accordingly we have performed the reduction of phenacyl bromide (**138a**) using 5 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**) in the presence of $BH_3.SMe_2$ at 110 ^{o}C. In fact, we

were pleased to notice that reduction is complete in 15 min and more interestingly the desired secondary alcohol **(*S*)-139a** is obtained in 91% enantiomeric purity. As a result, we thought it would be appropriate to investigate the minimum levels of the catalyst required for the reduction process to achieve maximum possible induction. We, therefore, performed the reduction of phenacyl bromide (**138a**) using different quantities of catalyst (from 0.25 to 10 mol%) and noticed that 2 mol% catalyst also offers almost the same selectivity as that of 3, 4, 5 and 10 mol% catalyst (eq. 102, Table 9). The enantiomeric purity of the (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H (Chromatogram 6) with reference to the corresponding racemic alcohol **(±)-139a**.

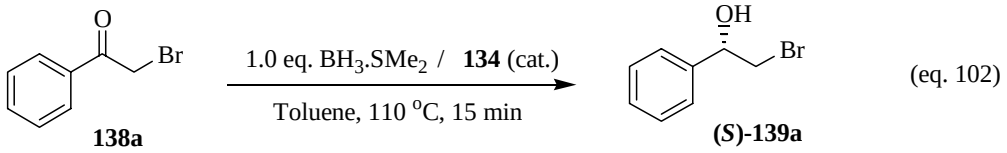
In order to understand the generality of this methodology, we have then carried out reduction of representative prochiral α-halo ketones **138b,d-g** using 2 mol% catalyst (**134**) to provide the resulting secondary alcohols **(*S*)-139b,d-g** in 84-90% enantiomeric purities (eq. 103, Table 10).

Determination of the Enantiomeric Excess:

The enantiomeric purities of the chiral alcohols **(*S*)-139b,d** were determined using the chiral column, Chiralcel OD-H, where as the enantiomeric purities of the alcohols **(*S*)-139e,f** were determined using the chiral column, Chiralcel OJ-H with reference to the corresponding racemic alcohols **(±)-139b,d-f**. The enantiomeric excess of the (*S*)-2-bromo-

1-(4-nitrophenyl)ethanol [**(*S*)-139g**] was determined by the HPLC analysis of the corresponding acetate [**(*S*)-140**] with reference to its racemic acetate [**(±)-140**] using the chiral column, Chiralcel OD-H.

Table 9. Asymmetric reduction of phenacyl bromide (**138a**) with different quantities of the catalyst[a]

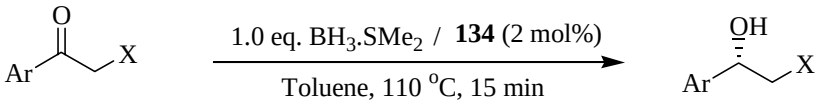


138a **(*S*)-139a** (eq. 102)

Entry	Catalyst **134** (mol%)	Yield[b] (%) (**139a**)	Enantiomeric excess[c] (%) (**139a**)	Configuration[d]
1	0.25	82	69	*S*
2	0.5	80	86	*S*
3	1	82	86	*S*
4	**2**	**82**	**91**	***S***
5	3	80	90	*S*
6	4	78	91	*S*
7	5	79	91	*S*
8	10	82	89	*S*

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with 1 mM of $BH_3.SMe_2$ in the presence of **134** in toluene for 15 min at 110 °C.
[b]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[d]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported.[133]

Table 10. Asymmetric reduction of prochiral α-halo ketones[a]



(eq. 103)

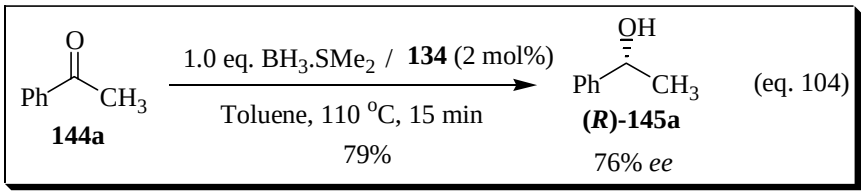
138a,b,d-g **(*S*)-139a,b,d-g**

X = Br, Cl
Ar = Phenyl, 4-Methylphenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Nitrophenyl

Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	E.e. (%)
138a	Phenyl	Br	**139a**	82	+39.8 (*c* 1.2, $CHCl_3$)	*S*[133]	91[d]
138b	Phenyl	Cl	**139b**	80	+43.8 (*c* 1.0, C_6H_{12})	*S*[133]	87[d]
138d	4-Methylphenyl	Cl	**139d**	88	+43.1 (*c* 0.8, $CHCl_3$)	*S*[109]	84[d]
138e	4-Bromophenyl	Br	**139e**	85	+30.5 (*c* 1.0, $CHCl_3$)	*S*[136]	90[e]
138f	4-Chlorophenyl	Br	**139f**	83	+38.9 (*c* 0.9, $CHCl_3$)	*S*[109]	90[e]
138g	4-Nitrophenyl	Br	**139g**	84	+29.9 (*c* 0.8, $CHCl_3$)	*S*[110]	86[f]

[a]All reactions were carried out on 1 mM scale of α-halo ketone with 1 mM of $BH_3.SMe_2$ in the presence of **134** (2 mol%) in toluene for 15 min at 110 °C.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Absolute configuration was assigned by comparison of the sign of specific rotation with that reported.
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.
[f]Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel OD-H.

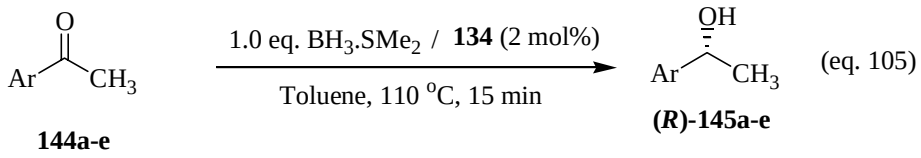
With a view to extend the scope of the application of this catalyst, we have next directed our attention to aryl alkyl ketones. We selected acetophenone (**144a**) first, for our study. Borane-mediated asymmetric reduction of acetophenone (**144a**) with 2 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**) provided the desired alcohol **(*R*)-145a** in 76% enantiomeric purity (eq. 104, Table 11). We have then examined the reduction of representative class of aryl alkyl ketones **144b-e** using 2 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**). The resulting secondary alcohols **(*R*)-145b-e** were obtained in 74–78% enantiomeric purities (eq.105, Table 11).



Determination of the Enantiomeric Purity:

The enantiomeric excess of (*R*)-1-phenylethanol [**(*R*)-145a**] was determined by HPLC analysis using the chiral column, Chiralcel OD-H with reference to (±)-1-phenylethanol [**(±)-145a**]. The enantiomeric purities of the chiral alcohols {(*R*)-1-(4-methylphenyl)-ethanol [**(*R*)-145b**], (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-145c**] (Chromatogram 7), (*R*)-1-(4-chlorophenyl)ethanol [**(*R*)-145d**] (Chromatogram 8)} were determined by HPLC analyses using chiral column, Chiralcel OJ-H with reference to the corresponding racemic alcohols {(±)-1-(4-methylphenyl)ethanol [**(±)-145b**], (±)-1-(4-bromophenylethanol [**(±)-145c**], (±)-1-(4-chlorophenyl)ethanol [**(±)-145d**] respectively}.

Table 11. Asymmetric reduction of aryl alkyl ketones[a]



144a-e **(*R*)-145a-e** (eq. 105)

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

Substrate	**Ar**	**Product**	**Yield[b] (%)**	**$[\alpha]_D^{25}$**	**Conf.[c]**	**E.e (%)**
144a	Phenyl	**145a**	79	+35.2 (*c* 0.9, MeOH)	*R*[138]	76[d]
144b	4-Methylphenyl	**145b**	79	+33.1 (*c* 0.7, MeOH)	*R*[139]	74[e]
144c	4-Bromophenyl	**145c**	87	+30.6 (*c* 1.0, $CHCl_3$)	*R*[139]	78[e]
144d	4-Chlorophenyl	**145d**	78	+37.5 (*c* 0.7, Et_2O)	*R*[139]	77[e]
144e	4-Nitrophenyl	**145e**	83	+22.2 (*c* 0.5, EtOH)	*R*[140]	78[f]

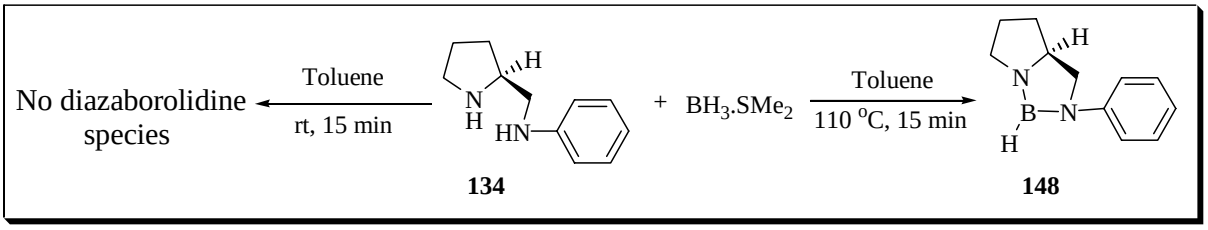
[a]All reactions were carried out on 1 mM scale of aryl alkyl ketone with 1 mM of $BH_3.SMe_2$ in the presence of **134** (2 mol%) in toluene for 15 min at 110 °C.
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c]Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported.
[d]Determined by HPLC analysis using the chiral column, Chiralcel OD-H.
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H.
[f]Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel OD-H.

The enantiomeric purity of (*R*)-1-(4-nitrophenyl)ethanol [**(*R*)-145e**] was determined by HPLC analysis of its acetate [**(*R*)-146**] using the chiral column, Chiralcel OD-H with reference to the corresponding racemic acetate [**(±)-146**].

Towards Understanding the Nature of the Catalytic Species:

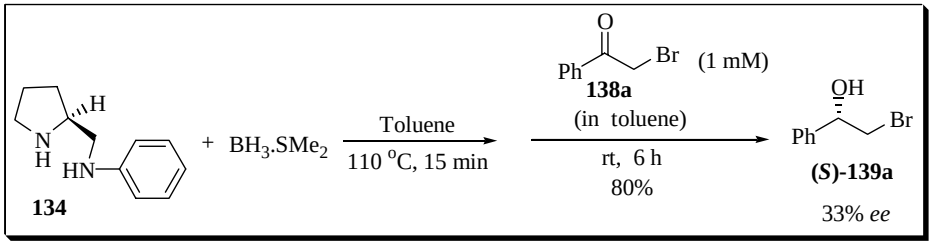
In order to understand the effect of temperature on the enantioselectivity, we examined the efficiency of this diamine **134** (2 mol%) as a chiral source in the asymmetric reduction of phenacyl bromide (**138a**) with $BH_3.SMe_2$ at room temperature (≈30 ^oC) for 7 h and obtained the resulting secondary alcohol **(*S*)-139a** in 8% enantiomeric excess. In an attempt to understand the nature of the catalyst/catalytic species generated *in situ*, we carried out the reaction between **134** (0. 2 mM, 4 mL, 0.05 M solution in toluene) and $BH_3.SMe_2$ (10 mM, 10 mL, 1 M solution in toluene) (in the ratio of 1:50 as in the case of reaction conditions) in refluxing toluene (40 mL) for 15 min and recorded ^{11}B NMR spectrum of this crude mixture (after removal of excess $BH_3.SMe_2$ and toluene under vacuum) and observed a broad peak at δ 33.2 ppm[143] [in addition to other peaks between δ -10 to -30 ppm, arising most likely due to tetra-coordinated boron species (ate-complexes)]. This probably indicates the presence of diazaborolidine moiety (**148**) in the catalyst/catalytic species. However we did not observe any peak in the region δ 20-40 ppm [but contains peaks between δ -10 to -30 ppm, probably due to tetra-coordinated boron species (ate-complexes) *i.e.*, *due to complexation of borane with diamine*] in the ^{11}B NMR

spectrum of the crude compound, when similar reaction was carried out at room temperature (≈30 ^{o}C). These results suggest that there is formation of diazaborolidine species (**148**) at 110 ^{o}C while such a species is not formed at room temperature (Scheme 16).



Scheme 16

In order to understand the potential of the diazaborolidine species (**148**) as a catalyst at room temperature, we have performed the asymmetric reduction of phenacyl bromide (**138a**) under the influence of catalytic species **148** (2 mol%) (generated *in situ* by the reaction of diamine (**134**) with $BH_3.SMe_2$ at reflux temperature and cooling back to room temperature) at room temperature for 6 h and obtained the resulting (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] with 33% *ee* (Scheme 17).



Scheme 17

These results possibly suggest that different path-ways of reduction processes may be operating at high temperature (110 ^{o}C) and at room temperature with the same catalytic species. At room temperature the catalyst coordination with borane and ketone might not be strong there by resulting low enantioselectivity. The plausible mechanism is shown in scheme 19 (Page no. 105).[Ω]

Recyclable Potential of *in situ* Generated Catalyst/Catalytic Species:

With a view to understand the *in situ* recyclable nature of the catalytic species (**148**), we have first carried out the reduction of phenacyl bromide (**138a**) (1 mM scale) in usual way at 110 ^{o}C (run 1). To this reaction mixture (without work-up), $BH_3.SMe_2$ (1 mM) (for run 2) was added and heated at 110 ^{o}C for 15 min and followed by the addition of a solution of phenacyl bromide (1 mM) in toluene drop-wise and stirring was continued at 110 ^{o}C for further 15 min (run 2). It is interesting to note that the resulting (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] (after work-up and purification as usual) has almost the enantiomeric purity (89%). Encouraged by this result, we examined, in a similar way, the recyclable ability of this catalyst for two more times (total four times) and noticed that the enantioselectivity remained almost the same (Table 12, Scheme 18).

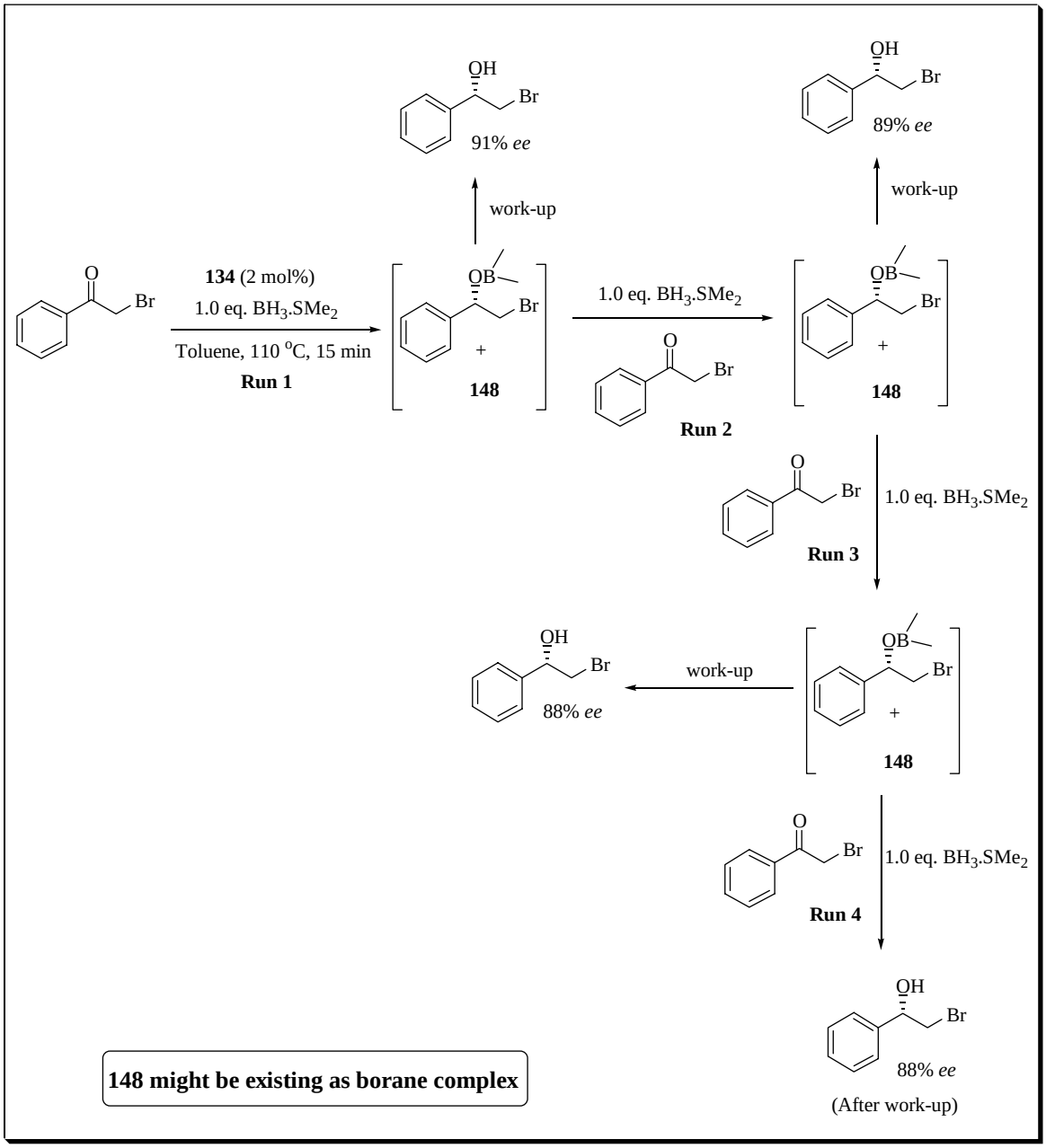
[Ω]We have presented the plausible mechanism for the borane-mediated asymmetric reduction of prochiral ketones using chiral diamides in page no. 105. In this, first step is the formation of diamine.

In order to examine (rule out) the possible auto-catalytic potential of the chiral alkoxyborane, generated in the reaction medium, in inducing the chirality in the asymmetric reduction of phenacyl bromide (**138a**), we have conducted the reduction of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (1 equiv and also with 2 equiv) under the influence of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] (1 equiv, 84% *ee*) (for 30 and 15 min in two separate experiments). In both cases, we obtained (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 42% enantiomeric purity (*i.e*., enantiomeric purity of the alcohol obtained by the reduction is ~ 0%). These experiments clearly indicate that there is no auto-catalysis and (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] (as boron species) has no role in the chiral induction process. Thus, these experiments clearly demonstrate the recyclable potential of the diamine as the chiral catalytic source in the asymmetric reduction processes.

Table 12. *In situ* recyclable ability of catalyst (**148**) in the asymmetric reduction of phenacyl bromide (**138a**)

Number of runs	Enantiomeric purity (%)[a] [**(*S*)-139a**]
1	91
2	89
3	88
4	88

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


134 (2 mol%)
1.0 eq. BH3.SMe2
Toluene, 110 °C, 15 min
Run 1
148
work-up
91% ee
1.0 eq. BH3.SMe2
Run 2
148
work-up
89% ee
1.0 eq. BH3.SMe2
Run 3
148
work-up
88% ee
1.0 eq. BH3.SMe2
Run 4
88% ee
(After work-up)
148 might be existing as borane complex

Scheme 18

In conclusion, we have developed a simple, convenient, and practical methodology for the borane-mediated asymmetric reduction of prochiral ketones employing (2*S*)-2-anilinomethylpyrrolidine (**134**) as an efficient *in situ* recyclable chiral catalytic source in refluxing toluene thus providing the secondary alcohols with high enantiomeric purities. Although, our methodology did not provide 100% enantioselectivities, this study has shown the hidden potential of chiral diamines in directing the enantioselective processes in the borane-mediated asymmetric reduction of prochiral ketones at high temperature and also emphasizes the need for design of appropriate chiral diamines for achieving 100% enantioselectivities.

Chiral Diamides as Efficient Catalytic Precursors for the Borane-Mediated Asymmetric Reduction of Prochiral Ketones

We have reported, in the previous section (Page nos. 77-89), a simple, and convenient methodology for the borane-mediated asymmetric reduction of prochiral ketones employing the chiral diamine, (2*S*)-2-anilinomethylpyrrolidine (**134**) (Fig. 24), as an efficient chiral catalytic source in refluxing toluene thus providing the secondary alcohols with high enantiomeric purities. The reduction of amides using $BH_3.SMe_2$ (THF) to provide the corresponding amines is a well documented and useful synthetic reaction in organic synthesis.[64,144] It therefore occurred to us that the diamide, (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) (Fig. 24), could in principle be reduced *in situ* by $BH_3.SMe_2$ to the corresponding diamine, (2*S*)-2-anilinomethylpyrrolidine (**134**), which could then be as such used, without isolation, as a chiral catalytic precursor (pre catalyst or source) for the reduction of prochiral ketones to produce the corresponding, enantiomerically enriched secondary alcohols. This would mean that the diamide, (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**), can itself directly act as the catalytic precursor for the borane-mediated reduction of prochiral ketones to provide the desired enantiomerically enriched secondary alcohols in a one-pot process.

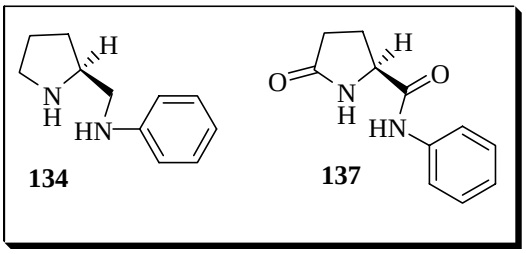
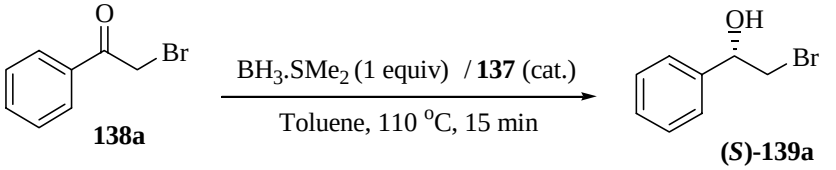


Figure 24

Accordingly we have synthesized (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**), *via* the reaction of (*S*)-glutamic acid with aniline according to the literature procedure (Scheme 10, Page no. 49).[131b] We have examined the potential of this diamide **137**, as a possible chiral catalytic precursor for the borane-mediated reduction of prochiral ketones, first selecting phenacyl bromide (**138a**) as a substrate. The borane-mediated reduction was performed with varying catalytic amounts of (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) (2, 5, 7, & 10 mol%) in order to determine the minimum amount of the catalyst required to obtain the maximum selectivity (eq. 106) and the enantioselectivities are shown in Table 13. From these results it is clear that enantioselectivities are similar in all the cases. However we decided upon using 5 mol% catalyst for further studies as this provide slightly better selectivity (Table 13, entry 2).

Table 13. Asymmetric reduction of phenacyl bromide (**138a**) with varying catalytic amounts of **137**[a,b]



(eq. 106)

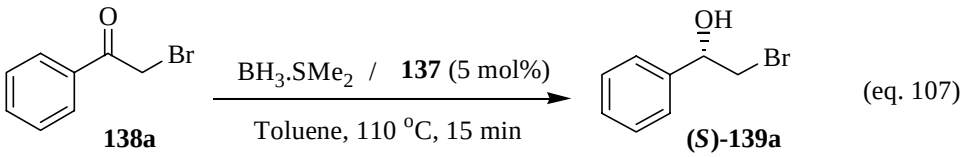
Entry	Catalyst (**137**) (mol%)	Yield [c] (%) [**(*S*)-139a**]	Enantiomeric purity [d](%) [**(*S*)-139a**]
1	2	86	87[e]
2	**5**	**88**	**89**
3	7	83	87
4	10	85	88

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (1 mM) in the presence of **137** in refluxing toluene for 15 min.
[b]The absolute configuration was assigned by comparison of the sign of the specific rotation with that of the reported molecule.[133]
[c]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.
[e]This reaction was carried out on 2 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (2 mM) in the presence of **137** in refluxing toluene for 15 min.

With a view to examine the influence of amount of $BH_3.SMe_2$ on the enantioselectivity and also to understand the appropriate amount of $BH_3.SMe_2$ required to obtain the maximum selectivity, we have carried out the asymmetric reduction of phenacyl bromide (**138a**) using 5 mol% (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) with varying amounts (0.9-

1.8 equiv with respect to prochiral ketone) of $BH_3.SMe_2$ (eq. 107). Although there is not much effect on the enantioselectivity with 1-1.8 equiv of $BH_3.SMe_2$, 1.4 equiv of $BH_3.SMe_2$ provides slightly better enantioselectivity (Table 14, entry 4).

Table 14. Asymmetric reduction of phenacyl bromide (**138**) with varying amounts of the $BH_3.SMe_2$[a,b]



138a **(*S*)-139a** (eq. 107)

Entry	$BH_3.SMe_2$ (equiv)	Yield[c] (%) [**(*S*)-139a**]	Enantiomeric purity[d] (%) [**(*S*)-139a**]
1	0.9	84	81
2	1.0	88	89
3	1.2	84	88
4	**1.4**	**86**	**91**
5	1.6	87	89
6	1.8	85	89

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ in the presence of 5 mol% **137** in refluxing toluene for 15 min.
[b]The absolute configuration was assigned by comparison of the sign of the specific rotation with that of the reported molecule.[133]
[c]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

Encouraged by these results and with a view for understanding the influence of different substitutions with various steric and electronic requirements on the aromatic (phenyl) ring of the diamide, (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**), we selected eight diamides **149-156** (Fig. 25) to study. The required diamides **149-156** were conveniently prepared by the reaction of (*S*)-pyroglutamic acid (**157**) with the corresponding aryl amines according to the equation 108 (no attempts were made to optimize the yields). The structures of these diamides were established by IR, ^{1}H (for compounds **149-156** see spectra 7,9,11,13,15,17,19 and 21 respectively), ^{13}C (for compounds **149-156** see spectra 8,10,12,14,16,18,20 and 22 respectively) NMR spectral data, LC MS and the elemental analyses. The structures of **149**, **151** and **153** were also further confirmed by the single crystal X-ray data (Figs. 26-28, Tables III-V).

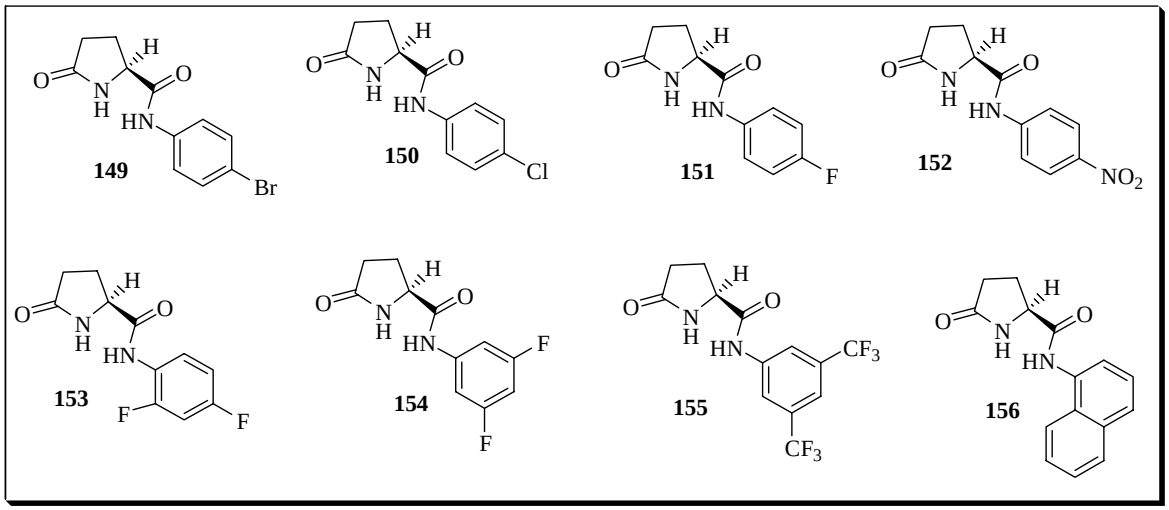
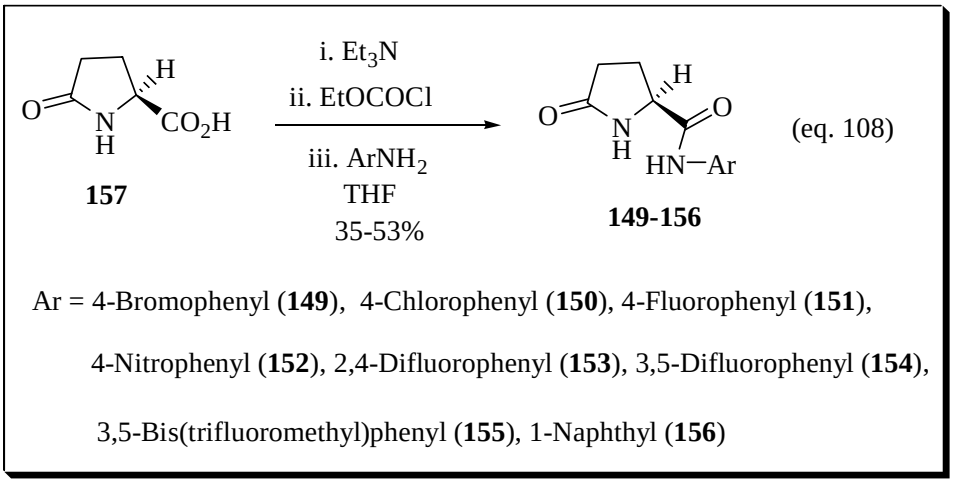


Figure 25



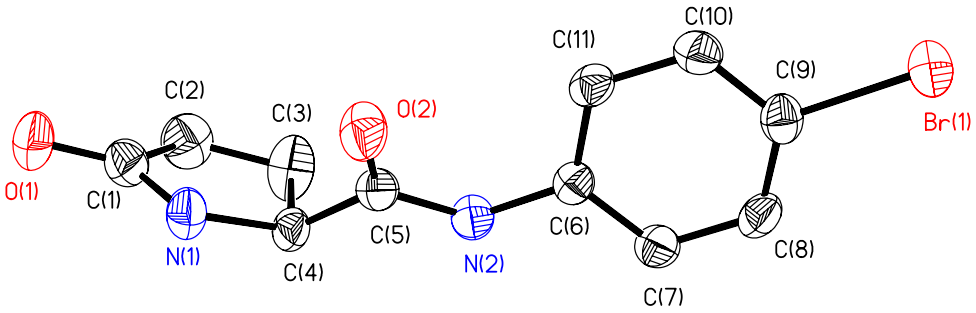


Figure 26: ORTEP diagram of 149
(*Hydrogen atoms were omitted for clarity*)

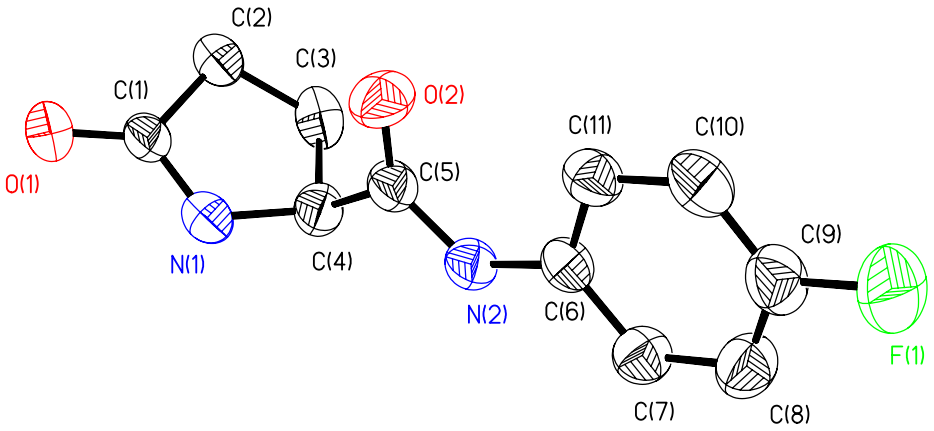


Figure 27: ORTEP diagram of 151
(*Hydrogen atoms were omitted for clarity*)

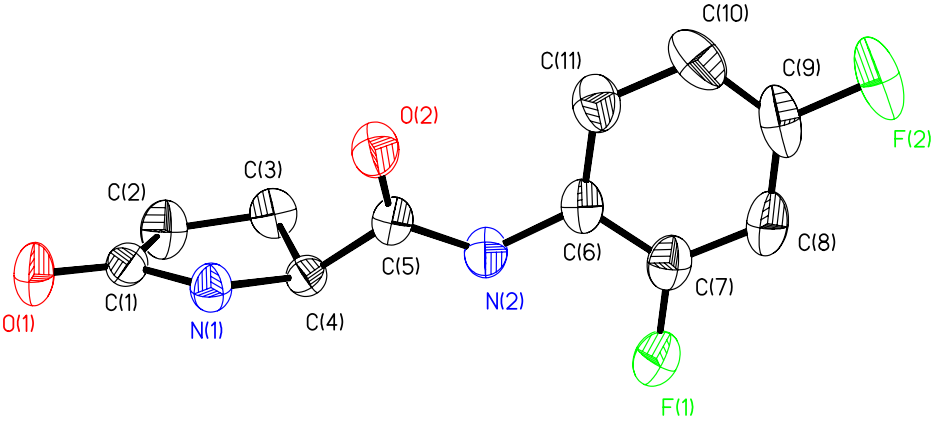


Figure 28: ORTEP diagram of 153
(*Hydrogen atoms were omitted for clarity*)

Table III: Crystal data and structure refinement for the compound 149

Identification	: **149**
Empirical formula	: $C_{11}H_{11}BrN_2O_2$
Formula weight	: 283.13
Temperature	: 298 ^oK
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *P 2₁*
Unit cell dimensions	: a = 5.1189(6) Å α = 90.00
	: b = 7.6470(9) Å β = 97.717(2)
	: c = 14.2151(16) Å γ = 90.00
Volume	: 551.40(11) $Å^3$
Z	: 2
Density (calculated)	: 1.705 g/cm^3
Absorption coefficient	: 3.713 mm^{-1}
F (000)	: 284
Crystal size	: 0.18 X 0.10 X 0.10 mm^3
Theta range for data collection	: 1.45 ≤ ∅ ≤ 28.22
Index ranges	: -6 ≤h ≤ 6, -10 ≤ k ≤ 10, -18 ≤ l ≤ 18
Reflections collected	: 2427
Independent reflections	: 1933
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1933 / 1 / 153
Goodness-of-fit on F^2	: 0.949
Final R indices [I> 2 sigma (I)]	: R1 = 0.0360; wR^2 = 0.0656
R indices (all data)	: R1 = 0.0499, wR^2 = 0.0696
Absolute structure parameters	: 0.009(11)
Largest diff. Peak and hole	: 0.575 and -0.233 e. A^{-3}

Table IV: Crystal data and structure refinement for the compound 151

Identification	: **151**
Empirical formula	: $C_{11}H_{11}FN_2O_2$
Formula weight	: 222.22
Temperature	: 298 ^oK
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *P* 2_1
Unit cell dimensions	: a = 4.9456(8) Å α = 90.00
	: b = 9.8911(15) Å β = 92.151(2)
	: c = 10.4695(16) Å γ = 90.00
Volume	: 511.78(14) $Å^3$
Z	: 2
Density (calculated)	: 1.442 g/cm^3
Absorption coefficient	: 0.113 mm^{-1}
F (000)	: 232
Crystal size	: 0.38 X 0.26 X 0.26 mm^3
Theta range for data collection	: 1.95 $\leq \varnothing \leq$ 28.15
Index ranges	: $-6 \leq h \leq 6$, $-13 \leq k \leq 11$, $-13 \leq l \leq 13$
Reflections collected	: 2023
Independent reflections	: 1890
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1890 / 1 / 153
Goodness-of-fit on F^2	: 1.070
Final R indices [I> 2 sigma (I)]	: R1 = 0.0373; wR^2 = 0.0906
R indices (all data)	: R1 = 0.0401, wR^2 = 0.0927
Absolute structure parameters	: 0.5(10)
Largest diff. Peak and hole	: 0.151 and -0.224 e. A^{-3}

Table V: Crystal data and structure refinement for the compound 153

Identification	: **153**
Empirical formula	: $C_{11}H_{10}F_2N_2O_2$
Formula weight	: 240.21
Temperature	: 298 ^oK
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: $P\ 2_1\ 2_1\ 2_1$
Unit cell dimensions	: a = 4.8924(6) Å α = 90.00
	: b = 8.9735(11) Å β = 90.00
	: c = 23.921(3) Å γ = 90.00
Volume	: 1050.2(2) $Å^3$
Z	: 4
Density (calculated)	: 1.519 g/cm^3
Absorption coefficient	: 0.129 mm^{-1}
F (000)	: 496
Crystal size	: 0.42 X 0.32 X 0.18 mm^3
Theta range for data collection	: 1.70 $\leq \varnothing \leq$ 26.02
Index ranges	: $-6 \leq h \leq 5$, $-9 \leq k \leq 11$, $-23 \leq l \leq 29$
Reflections collected	: 2012
Independent reflections	: 1955
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1955 / 0 / 162
Goodness-of-fit on F^2	: 1.297
Final R indices [I> 2 sigma (I)]	: R1 = 0.0670; wR^2 = 0.1429
R indices (all data)	: R1 = 0.0685, wR^2 = 0.1437
Absolute structure parameters	: 0.3(19)
Largest diff. Peak and hole	: 0.204 and -0.307 e. A^{-3}

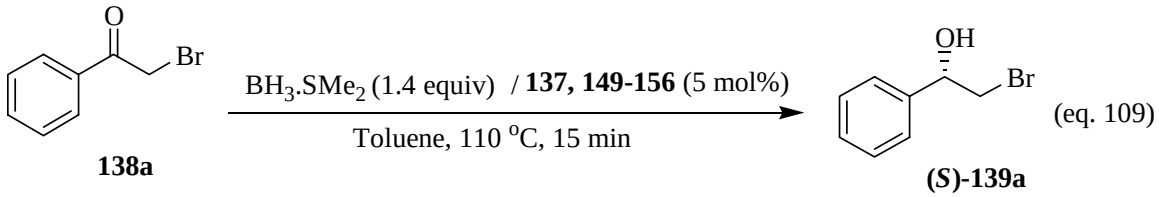
With a view to examining the chiral catalytic potential of these diamides **149-156**, we selected three representative prochiral ketones, phenacyl bromide (**138a**), phenacyl chloride (**138b**) and acetophenone (**144a**), as substrates in the borane-mediated asymmetric reduction. Thus we first carried out the asymmetric reduction of phenacyl bromide (**138a**) in the presence of 5 mol% chiral diamide (**149-156**) with $BH_3.SMe_2$ (1.4 equiv) in refluxing toluene for 15 min. The corresponding secondary alcohol, (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] was obtained with 68-91% enantiomeric purities (eq. 109, Table 15, entries 2-9).

Similar borane-mediated reductions of phenacyl chloride (**138b**) and acetophenone (**144a**) using chiral diamides, **149-156**, as chiral catalytic sources provided (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] and (*R*)-1-phenylethanol [**(*R*)-145a**] in 67-89% (eq. 110, Table 16, entries 1-9) and 53-83% (eq. 111, Table 17, entries 1-9) enantiomeric excesses, respectively.

Determination of the Enantiomeric Purity:

The enantiomeric purities of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] {for HPLC chromatograms of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] obtained *via* the asymmetric reduction under the catalytic influence of **151** & **155** see: Chromatograms 9 & 10 respectively} were determined by HPLC analysis using the chiral column, Chiralcel OD-H

Table 15. Asymmetric reduction of phenacyl bromide (**138a**) using the chiral diamides **137**, **149-156** as chiral catalytic sources[a,b]

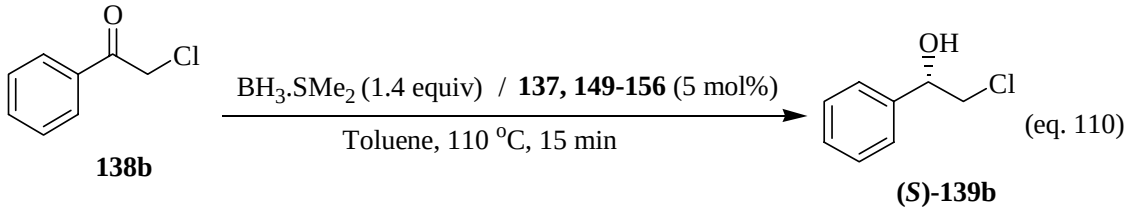


138a **(*S*)-139a** (eq. 109)

Entry	Chiral Diamide	Yield[c] (%) [**(*S*)-139a**]	Enantiomeric purity[d] (%) [**(*S*)-139a**]
1	**137**	86	91
2	**149**	87	90
3	**150**	86	91
4	**151**	82	90
5	**152**	88	88
6	**153**	83	89
7	**154**	84	88
8	**155**	83	90
9	**156**	84	68

[a]All reactions were carried out on 1 mM scale of phenacyl bromide (**138a**) with $BH_3.SMe_2$ (1.4 mM) in the presence of 5 mol% **137, 149-156** in refluxing toluene for 15 min.
[b]The absolute configuration was assigned by comparison of the sign of the specific rotation with that of the reported molecule.[133]
[c]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

Table 16. Asymmetric reduction of phenacyl chloride (**138b**) using the chiral diamides **137, 149-156** as chiral catalytic sources[a,b]

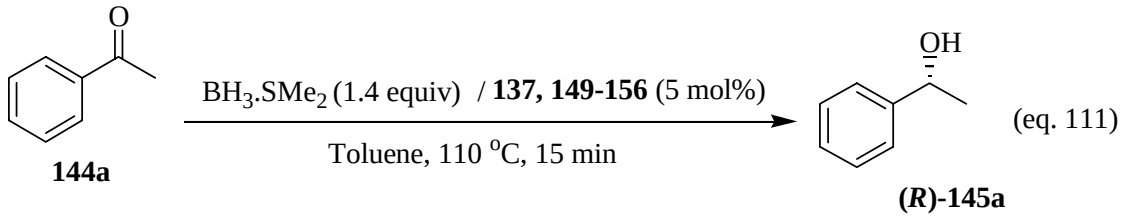


138b **(*S*)-139b** (eq. 110)

Entry	Chiral Diamide	Yield[c] (%) [**(*S*)-139b**]	Enantiomeric purity[d] (%) [**(*S*)-139b**]
1	**137**	83	88
2	**149**	82	87
3	**150**	84	89
4	**151**	80	88
5	**152**	85	86
6	**153**	82	87
7	**154**	83	87
8	**155**	87	89
9	**156**	81	67

[a]All reactions were carried out on 1 mM scale of phenacyl chloride (**138b**) with $BH_3.SMe_2$ (1.4 mM) in the presence of 5 mol% **137, 149-156** in refluxing toluene for 15 min.
[b]The absolute configuration was assigned by comparison of the sign of the specific rotation with that of the reported molecule.[133]
[c]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

Table 17. Asymmetric reduction of acetophenone (**144a**) using the chiral diamides **137, 149-156** as chiral catalytic sources[a,b]



144a **(*R*)-145a** (eq. 111)

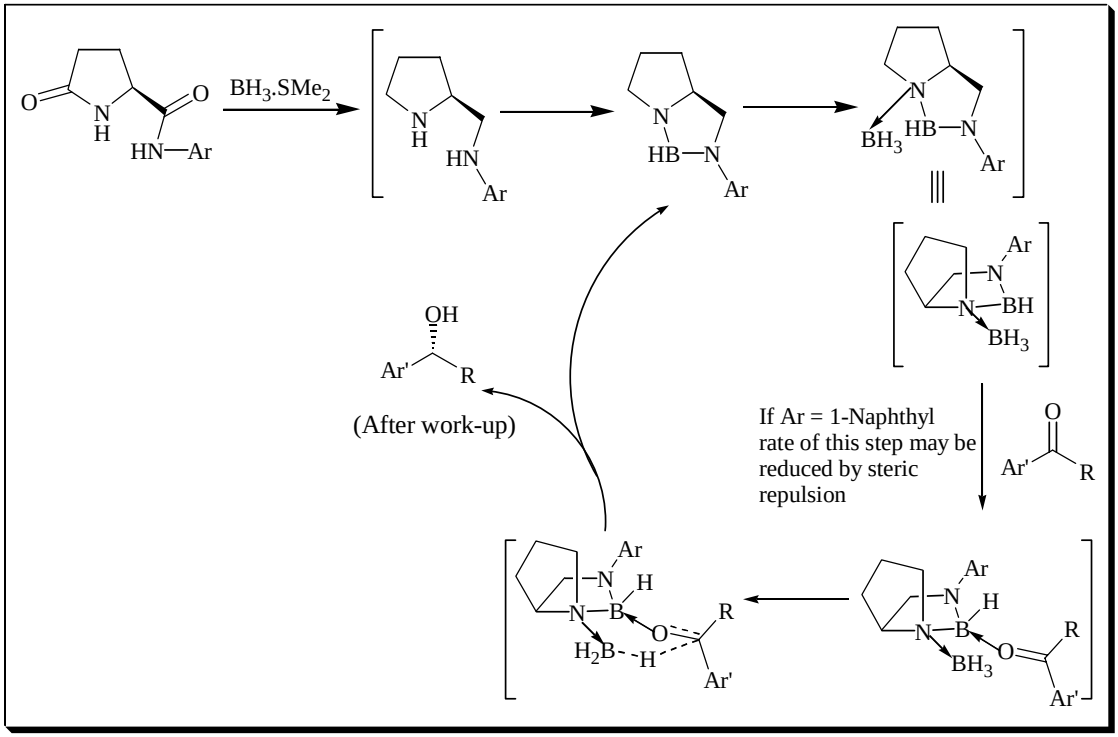
Entry	Chiral Diamide	Yield[c] (%) [**(*R*)-145a**]	Enantiomeric purity[d] (%) [**(*R*)-145a**]
1	**137**	76	82
2	**149**	74	81
3	**150**	72	83
4	**151**	74	79
5	**152**	76	77
6	**153**	74	78
7	**154**	75	82
8	**155**	73	81
9	**156**	77	53

[a]All reactions were carried out on 1 mM scale of acetophenone (**144a**) with $BH_3.SMe_2$ (1.4 mM) in the presence of 5 mol% **137, 149-156** in refluxing toluene for 15 min.
[b]The absolute configuration was assigned by comparison of the sign of the specific rotation with that of the reported molecule.[138]
[c]Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H.

with reference to (±)-2-bromo-1-phenylethanol [**(±)-139a**]. The enantiomeric excesses of (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] {HPLC chromatograms of (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] obtained *via* the asymmetric reduction under the catalytic influence of **137** & **150** are presented in chromatograms 11 & 12 respectively} were determined by the HPLC analysis using the chiral column, Chiralcel OD-H with reference to the corresponding racemic alcohol [**(±)-139b**]. The enantiomeric purities of (*R*)-1-phenylethanol [**(*R*)-145a**] {for HPLC chromatograms of (*R*)-1-phenylethanol [**(*R*)-145a**] resulted *via* the borane-mediated asymmetric reduction under the catalytic influence of **149** & **154** see: Chromatograms 13 & 14 respectively] were determined by the HPLC analysis using the chiral column, Chiralcel OD-H with reference to the racemic alcohol, (±)-1-phenylethanol [**(±)-145a**].

These results to some extent suggest that the substitution on the phenyl group [of (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**)] does not play any significant role with regards to the chiral induction. However, the chiral diamide (2*S*)-5-oxo-2-(1-naphthylamino)-carbonylpyrrolidine (**156**) with a 1-naphthyl moiety provides inferior selectivities in all these cases in comparison with other diamides **137**, **149**-**155**. The lower enantioselectivity in the case of **156** might be attributed to the competitive non-catalytic reduction of prochiral ketone with $BH_3.SMe_2$ as the sterically bulky 1-naphthyl moiety may to some extent disfavor the effective coordination of prochiral ketone with the boron of the

diazaborolidine (which might be forming *in situ*) (A plausible mechanism is presented in the Scheme 19).



Scheme 19

In conclusion, we have successfully demonstrated the potential of the chiral diamides, (2*S*)-5-oxo-2-(arylamino)carbonylpyrrolidines (**137, 149-156**), derived from abundantly available (*S*)-glutamic/(*S*)-pyroglutamic acids, as possible catalytic sources in the borane-mediated asymmetric reduction of prochiral ketones.

CONCLUSION

We have made a considerable success in achieving our objectives mentioned in the beginning of this chapter. We have designed and synthesized two novel chiral catalysts/catalytic sources, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**), containing ***N-(C=NH)-N*** & ***N-(C=NH)-O*** structural frameworks respectively and examined their catalytic efficiency in the borane-mediated asymmetric reduction of prochiral ketones. The corresponding secondary alcohols were obtained with high enantiomeric excesses. In the case of **135**, we have observed a remarkable temperature dependant reversal of stereo-selectivity (enantiomeric switch) from room temperature (≈30 ^{o}C) to high temperature (110 ^{o}C) in the borane-mediated chiral reduction of phenacyl bromide. Also the potential of the chiral catalytic species **141** [generated *in situ via* the reaction of **135** with $BH_3.SMe_2$ in refluxing toluene] as an *in situ* recyclable chiral catalytic source for the borane-mediated chiral reduction processes has been demonstrated. We have also observed an interesting reversal of stereo-selectivity (enantiomeric switch) in the case of **142** from room temperature (although the levels of reversal of stereoselectivity is not impressive) to high temperature (110 ^{o}C) in the borane-mediated chiral reduction of phenacyl bromide. We have demonstrated the potential of (2*S*)-2-anilinomethylpyrrolidine (**134**) as a chiral catalytic source in the asymmetric reduction of prochiral ketones in refluxing toluene thus

providing the resulting secondary alcohols in high enantiomeric purities. Chiral diamides [(2*S*)-5-oxo-2-(arylamino)carbonylpyrrolidines] (**137**, **149-156**) derived from abundantly available (*S*)-glutamic/(*S*)-pyroglutamic acids were synthesized and successfully utilized as effective chiral catalytic sources in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene. This study also demonstrates the hidden potential of chiral diamines/diamides in directing the enantioselective processes in the borane-mediated asymmetric reduction of prochiral ketones at high temperature and also emphasizes the need for designing of appropriate chiral diamines/diamides for achieving 100% enantioselectivities.

EXPERIMENTAL

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

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

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

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on 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 = 77.1 ppm) as internal reference. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of

doublet, brs = broad singlet, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

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

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

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

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

X-Ray Crystallography:

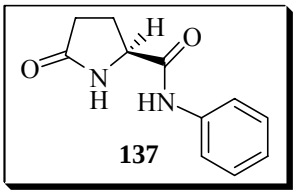
Single crystal X-ray data for the respective compounds were collected on a Bruker SMART APEX CCD area detector system [Mo-Kα (λ = 0.71073 Å)] at 298 ^{o}K, graphite monochromator with a ω scan width 0.3^{o}, crystal detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F^2 was carried out using SHELXS-97.

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

(2*S*)-5-Oxo-2-anilinocarbonylpyrrolidine (137):

This molecule was prepared according to the known procedure with slight modifications.[131b]

A mixture of aniline (150 mL) and *L*-glutamic acid (**136**) (20 g, 136 mM) was heated with stirring at 200 ^{o}C for 90 min. The reaction mixture was cooled to room temperature and the excess aniline was distilled off under reduced pressure at around 60-70 ^{o}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 ^{o}C. Solid thus obtained was separated by filtration and crystallized from methanol to provide (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) as a white crystalline solid.



137

Yield: 8.33 g (30%)

Mp: 182-184 ^{o}C (Lit.[131b] 189-191 ^{o}C)

$[\alpha]_D^{25}$: +18.4 (*c* 1.06, MeOH)

{Lit.[131b] $[\alpha]_D^{25}$: +18.60 (*c* 1.0, MeOH)}

IR (KBr) : 3400-2800 (multiple bands), 1701, 1666 cm^{-1}

^{1}H NMR (400 MHz): δ 2.15-2.52 (m, 4H), 4.19-4.32 (m, 1H), 7.01-7.11 (m, 1H),

($CDCl_3$:DMSO-d_6 = 4:1) 7.24-7.32 (m, 2H), 7.54-7.69 (m, 3 H), 9.51 (s, 1H)

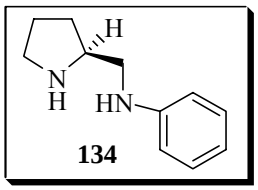
^{13}C NMR (50 MHz) : δ 24.21, 28.36, 55.85, 118.65, 122.58, 127.43, 137.42, 169.83,

($CDCl_3$:DMSO-d_6 = 4:1) 176.96

(2*S*)-2-Anilinomethylpyrrolidine (134):

This compound was prepared according to the literature procedure.[131b]

(2*S*)-5-Oxo-2-anilinocarbonylpyrrolidine (**137**) (6.53 g, 32 mM) was added slowly portion wise to a stirred suspension of lithium aluminum hydride (3.28 g, 86.4 mM) in THF (100 mL) at 0 ^{o}C and the reaction mixture was stirred under reflux for 4 h. Then the reaction mixture was cooled to 5 ^{o}C (ice water) and water (4 mL) was added carefully (drop-wise) followed by the addition of 2.5 N sodium hydroxide solution. The reaction mixture was diluted with CH_2Cl_2 and stirred for 5 min. Organic layer was separated and the aluminum salts were washed with CH_2Cl_2 (3X100 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-anilino-methylpyrrolidine (**134**) as a viscous liquid (4.6 g) in 82% yield.



134

Bp: 123-125 ^{o}C/0.5 mm

(Lit.[131b] 117-120 ^{o}C/0.4 mm)

$[\alpha]_D^{25}$: +19.1 (*c* 1.1, EtOH) {Lit.[131b] $[\alpha]_D^{25}$: +18.50 (*c* 1.087, EtOH)}

IR (Neat) : 3296 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.32-1.58 (m, 1H), 1.60-2.04 (m, 3H), 2.19 (brs, 1H), 2.90-3.10 (m, 3H), 3.16-3.31 (m, 1H), 3.32-3.50 (m, 1H), 4.19 (brs, 1H), 6.60-6.83 (m, 3H), 7.10-7.30 (m, 2H)

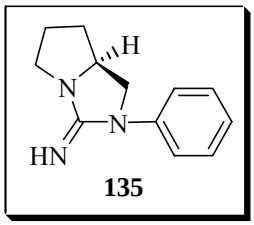
^{13}C NMR (50 MHz) : δ 25.43, 29.24, 46.19, 48.33, 57.40, 112.63, 116.83, 128.86,

148.36

(5*S*)-1,3-Diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135):

This compound was prepared according to the general literature procedure for the preparation of guanidine from diamine.[131a]

To a stirring solution of (2*S*)-2-anilinomethylpyrrolidine (**134**) (1.76 g, 10 mM) in EtOH (3 mL) was carefully added a solution of cyanogen bromide (1.17 g, 11 mM) in EtOH (1 mL) at 0 ^{o}C. After the addition, the reaction mixture was allowed to warm to room temperature (≈10 min) and then heated at 150 ^{o}C for 30 min to completely remove the boiling solvent. The fused reaction mixture was allowed to cool to room temperature and the resulting solid was taken up in hot EtOH (15 mL). The resultant solution was treated with decolorizing charcoal (60 mg) and filtered through Celite. The filtrate was diluted with aqueous 1 N NaOH (20 mL) and extracted with CH_2Cl_2 (3X30mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue, thus obtained, was crystallized (hexanes:EtOAc = 9:1) to provide the desired (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo-(3.3.0)octane (**135**) in 62% (1.25 g) yield.



135

Mp: 58 ^{o}C

$[\alpha]_D^{25}$: -48.7 (*c* 1.1, $CHCl_3$)

IR (KBr): 3316, 1630, 1593 cm^{-1}

^{1}H NMR (400 MHz): δ 1.42-1.54 (m, 1H), 1.84-1.98 (m, 1H), 1.99-2.10 (m, 2H), 3.22-3.29 (m, 1H), 3.50-3.61 (m, 1H), 3.68-3.73 (m, 1H), 3.77-3.86 (m, 1H), 3.91-3.98 (m, 1H), 5.09 (brs, 1H), 7.02-7.10 (m, 1H), 7.32-7.56 (m, 4H)

^{13}C NMR (100 MHz): δ 25.92, 31.37, 48.14, 51.60, 57.48, 120.32, 123.09, 129.09, 141.32, 161.69

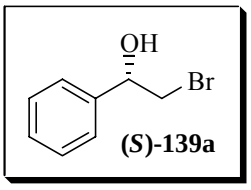
LC MS (m/z): 202 $(M+H)^+$

Anal. calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88

Found: C, 71.66; H, 7.47; N, 20.86

Asymmetric reduction of phenacyl bromide (138a): Synthesis of (*S*)-2-bromo-1-phenylethanol [(*S*)-139a]: Representative procedure:

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at 110 ^oC for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and heating was continued for further 15 min. The reaction mixture was then cooled to room temperature and quenched with MeOH. 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*)-139a**] as a colorless oil.



Yield: 163 mg (81%)

$[\alpha]_D^{25}$: +36.5 (*c* 1.1, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 83% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

IR (Neat) : 3412 cm^{-1}

^1H NMR (400 MHz) : δ 2.67 (d, 1H, *J* = 2.8 Hz), 3.51-3.72 (m, 2H), 4.88-4.97 (m, 1H), 7.28-7.45 (m, 5H)

^{13}C NMR (50 MHz) : δ 39.86, 73.72, 125.97, 128.37, 128.59, 140.41

Determination of enantiomeric purity:

HPLC analysis of (±)-2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks with equal intensity [chiral column: Chiralcel OD-H, solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min] with retention times 7.98 min and 8.51 min due to (*S*) and (*R*) enantiomers. Similar HPLC analysis of chiral alcohol [**(*S*)-139a**] showed two peaks at 7.99 min (*S*) and 8.52 min (*R*) in the ratio of 91.5:8.5 indicating that the enantioselectivity of this reaction is 83%.

(±)-2-Bromo-1-phenylethanol [(±)-139a]:

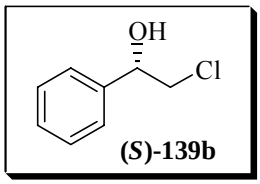
To a stirred solution of phenacyl bromide (**138a**) (0.398 g, 2 mM) in toluene (10 mL) was added $BH_3.SMe_2$ (0.152 g, 2 mM) and heated under reflux for 2 h. Then the

reaction mixture was allowed to cool to room temperature and quenched with methanol. The solvent was removed under reduced pressure and the residue, thus obtained, was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (±)-2-bromo-1-phenylethanol [**(±)-139a**] in 85% (0.342 g) yield 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*)-139a**].

All the racemic alcohols [(±)-139b-h & (±)-145a-e] were prepared following the above-mentioned procedure and their spectral data (IR, ^{1}H & ^{13}C NMR) are in full agreement with the spectral data of corresponding chiral alcohols [(S)-139b-h & (R)-145a-e].

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b]:

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (Page no. 114) *via* borane-mediated asymmetric reduction of phenacyl chloride (**138b**) under the catalytic (5 mol %) influence of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane(**135**).



(*S*)-139b

Yield : 80%

$[\alpha]_D^{25}$: +40.7 (*c* 1.3, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 81% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

IR (Neat) : 3393 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.80 (s, 1H), 3.54-3.78 (m, 2H), 4.81-4.92 (m, 1H), 7.30-7.44 (m, 5H)

^{13}C NMR (50 MHz) : δ 50.89, 74.10, 126.11, 128.49, 128.70, 139.98

Determination of enantiomeric purity:

Racemic alcohol [**(±)-139b**] showed two peaks in 1:1 ratio [retention times 7.99 min (*S*) and 8.64 min (*R*)] on HPLC analysis using chiral column Chiralcel OD-H [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min]. In the case of chiral alcohol [**(*S*)-139b**], we have observed two peaks at 7.80 min and 8.75 min arising from (*S*) and (*R*) enantiomers in 90.5:9.5 ratio on similar HPLC analysis indicating that the enantiomeric purity of the (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] is 81%.

Tetrabutylammonium tribromide (TBA Br_3):

This compound was prepared following the literature procedure.[134]

To a stirred solution of tetrabutylammonium bromide (16.12 g, 50 mM) and sodium bromate (2.52 g, 16.7 mM) in water (100 mL), hydrobromic acid (48%, 11.7 mL) was added drop-wise at room temperature. After 10 minutes, the orange precipitate formed,

was filtered and recrystallized from ether-dichloromethane (1:1) to provide TBA Br_3 as orange crystals.

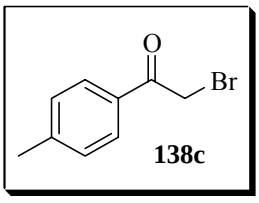
Yield: 93% (22.5 g).

Mp: 72-74 ^oC (Lit.[134] 70-72 ^oC).

4-Methylphenacyl bromide (138c):

This molecule was prepared according to the known procedure.[134]

TBA Br_3 (2.12 g, 4.4 mM) was added to a stirred solution of 4-methylacetophenone (0.54 g, 4 mM) in dichloromethane (50 mL)-methanol (20 mL) at room temperature. After stirring for 5 h at 35 ^oC (until decoloration of the orange solution), the solvent was removed and the residue, thus obtained, was extracted with ether (4X30 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 to provide the 4-methylphenacyl bromide (**138c**) as a colorless solid.



138c

Yield: 76% (0.65 g)

Mp: 48-50 ^oC (Lit.[134] 45-48 ^oC).

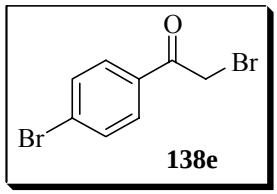
IR (KBr): ν 1695 cm^{-1}

^1H NMR (400 MHz): δ 2.44 (s, 3H), 4.45 (s, 2H), 7.30 (d, 2H, J = 8.0 Hz), 7.90 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 21.79, 30.96, 129.10, 129.61, 131.55, 145.06, 190.98

4-Bromophenacyl bromide (138e):

This product was obtained as colorless needles *via* the treatment of 4-bromoacetophenone with TBA Br_3 following the similar procedure described for the molecule **138c** (Page no. 118).



138e

Time: 6 h

Yield: 80%

Mp: 108-109 ^{o}C (Lit.[134] 107.5-108 ^{o}C)

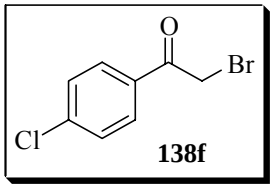
IR (KBr): 1697 cm^{-1}

^{1}H NMR (400 MHz): δ 4.42 (s, 2H), 7.64 (d, 2H, J = 8.5 Hz), 7.86 (d, 2H, J = 8.5 Hz)

^{13}C NMR (50 MHz): δ 30.42, 129.35, 130.49, 132.28, 132.72, 190.45

4-Chlorophenacyl bromide (138f):

This compound was prepared *via* the treatment of 4-chloroacetophenone with TBA Br_3 following the similar procedure described for the molecule **138c** (Page no. 118).



138f

Time: 6 h

Yield: 84%

Mp: 94-96 ^{o}C (Lit.[134] 97-97.5 ^{o}C)

IR (KBr): 1699 cm^{-1}

^{1}H NMR (200 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 30.42, 129.27, 130.41, 132.33, 140.58, 190.23

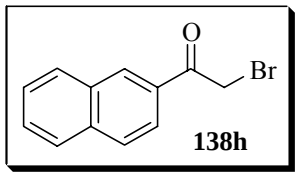
2-Bromoacetylnaphthalene (138h):

This product was synthesized *via* the reaction of 2-acetylnaphthalene with TBA Br_3 following the similar procedure described for the molecule **138c** (Page no. 118).

Time: 6 h

Yield: 86%

Mp: 79-80 ^{o}C (Lit.[134] 81-82 ^{o}C)



138h

IR (KBr): 1693 cm^{-1}

^{1}H NMR (400 MHz): δ 4.58 (s, 2H), 7.51-7.71 (m, 2H), 7.82-8.08 (m, 4H), 8.51 (s, 1H)

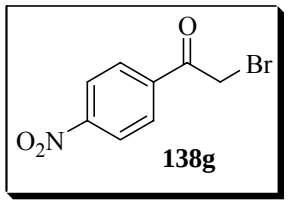
^{13}C NMR (50 MHz): δ 31.03, 124.13, 127.06, 127.84, 128.79, 129.03, 129.68, 130.90, 131.29, 132.38, 135.85, 191.23

4-Nitrophenacyl bromide (138g):

This molecule was prepared according to the known general procedure.[135]

To a stirred solution of 4-nitroacetophenone (3.3 g, 20 mM) in glacial acetic acid (13.3 mL), bromine (1.0 mL, 20 mM) was added slowly and the temperature of the reaction mixture maintained below 20 ^{o}C. Reaction mixture was now stirred at room temperature for over night. The reaction mixture was diluted with ice-cold water (17 mL), and extracted with ethyl acetate (3X25 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 furnish **138g** as a light yellow solid.



138g

Yield: 66% (3.2 g)

Mp: 91 ^{o}C [Lit.[134] 96-96.5 ^{o}C]

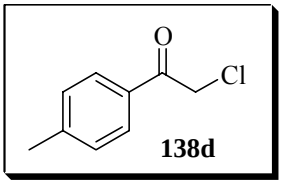
IR (KBr): 1703 cm^{-1}

^{1}H NMR (400 MHz): δ 4.45 (s, 2H), 8.16 (d, 2H, J = 8.7 Hz), 8.35 (d, 2H, J = 8.7 Hz)

^{13}C NMR (50 MHz): δ 38.84, 123.98, 131.04, 135.77, 150.93, 184.60

4-Methylphenacyl chloride (138d):

To a stirred suspension of $AlCl_3$ (0.67 g, 5 mM) in toluene (15 mL) at 10 ^{o}C, chloroacetyl chloride (2.82 g, 25 mM) was added drop-wise over a period of 15 min. The reaction mixture was heated for 2 h at 50 ^{o}C. Then the reaction mixture was cooled to 0 ^{o}C and quenched with ice cooled water (8 mL) and extracted with ether (3X50 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 (**138d**) as a white solid.



138d

Yield: 30% (1.26 g)

Mp: 50-52 ^{o}C

IR (KBr): 1699 cm^{-1}

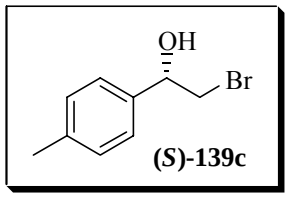
^{1}H NMR (400 MHz): 2.42 (s, 3H), 4.68 (s, 2H), 7.28 (d, 2H, J = 7.9 Hz), 7.85 (d, 2H, J

= 7.9 Hz)

^{13}C NMR (50 MHz): δ 21.79, 45.95, 128.71, 129.64, 131.87, 145.11, 190.76

(*S*)-2-Bromo-1-(4-methylphenyl)ethanol [(*S*)-139c]:

This compound was prepared *via* the asymmetric reduction of 4-methylphenacyl bromide (**138c**) with BH_3.SMe_2 using (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo-(3.3.0)octane (**135**) (5 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 114).



(*S*)-139c

Yield: 85%

Mp: 40-42 ^{o}C

$[\alpha]_D^{25}$: +35.3 (*c* 1.2, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +41.8 (*c* 1.00, $CHCl_3$), (*S*)-configuration, 95% *ee*}

Enantiomeric purity: 82% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139c**]

IR (Neat) : 3337 cm^{-1}

^{1}H NMR (400 MHz): δ 2.38 (s, 3H), 2.70 (d, 1H, *J* = 2.2 Hz), 3.40-3.64 (m, 2H), 4.80-4.94 (m, 1H), 7.21 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz)

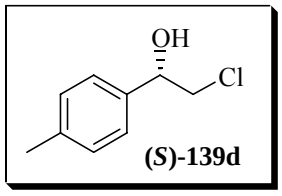
^{13}C NMR (50 MHz): δ 21.16, 40.03, 73.65, 125.90, 129.30, 137.45, 138.17

Determination of enantiomeric purity:

Racemic alcohol [**(±)-139c**] showed two peaks at 16.04 min (*S*) and 17.70 min (*R*) with equal intensity on HPLC analysis [chiral column: Chiralcel OD-H, solvent system: hexanes:IPA (97.5:2.5), flow rate: 1 mL/min], while similar HPLC analysis of chiral alcohol [**(*S*)-139c**] showed two peaks at 15.94 min (*S*) and 17.64 min (*R*) in 91:9 ratio indicating that the enantiomeric purity of (*S*)-2-bromo-1-(4-methylphenyl)ethanol [**(*S*)-139c**] is 82%.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-139d]:

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of 4-methylphenacyl chloride (**138d**) with BH_3**.**SMe_2 in the presence of 5 mol% (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 114).



(*S*)-139d

Yield: 82%

$[\alpha]_D^{25}$: +42.0 (*c* 1.1, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*}

Enantiomeric purity: 83% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139d**]

IR (Neat) : 3395 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.37 (s, 3H), 2.84 (s, 1H), 3.59-3.74 (m, 2H), 4.80-4.90 (m,

1H), 7.19 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz)

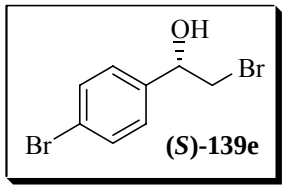
^{13}C NMR (50 MHz) : δ 21.21, 50.92, 74.04, 126.05, 129.39, 137.11, 138.35

Determination of enantiomeric purity:

Enantiomeric purity of (*S*)-2-chloro-1-(4-methylphenyl)ethanol [**(*S*)-139d**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. Racemic alcohol [**(±)-139d**] showed two peaks [flow rate: 0.9 mL/min, solvent system: hexanes:IPA (97.5:2.5)] in equal intensities at 15.62 min (*S*) and 16.82 min (*R*), while chiral alcohol **(*S*)-139d** showed two peaks at 15.67 min and 16.90 min corresponding to (*S*) and (*R*) enantiomers in the ratio of 91.5:8.5 indicating that (*S*)-2-chloro-1-(4-methylphenyl)-ethanol [**(*S*)-139d**] is 83% enantiomerically pure.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-139e]:

This compound was synthesized *via* the borane-mediated asymmetric reduction of 4-bromophenacyl bromide (**138e**) with (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)-octane (**135**) (5 mol%), as a chiral catalyst/catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 114).



(*S*)-139e

Yield: 78%

Mp: 60-62 ^{o}C [Lit.[111] 71-72 ^{o}C]

$[\alpha]_D^{25}$: +27.7 (*c* 1.1, $CHCl_3$)

{Lit.[136] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

Enantiomeric purity: 81% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139e**]

IR (KBr) : 3306 cm^{-1}

^1H NMR (400 MHz) : δ 2.70 (d, 1H, *J* = 3.3 Hz), 3.42-3.64 (m, 2H), 4.83-4.94 (m, 1H), 7.26 (d, 2H, *J* = 8.4 Hz), 7.50 (d, 2H, *J* = 8.4 Hz)

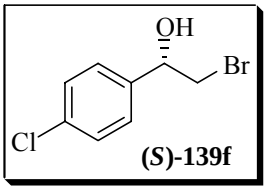
^{13}C NMR (50 MHz) : δ 39.86, 73.21, 122.46, 127.77, 131.92, 139.39

Determination of enantiomeric purity:

HPLC analysis (using chiral column, Chiralcel OJ-H) of (±)-2-bromo-1-(4-bromophenyl)ethanol [**(±)-139e**] showed two peaks at 20.54 min (*R*) and 22.33 min (*S*) in 1:1 ratio [solvent system: hexanes:IPA (95:5), flow rate: 1 mL/min] while chiral 2-bromo-1-(4-bromophenyl)ethanol [**(*S*)-139e**], on similar HPLC analysis, showed two peaks at 20.39 min (*R*) and 22.18 min (*S*) in the ratio of 9.5:90.5 indicating that the reduction is 81% enantioselective.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-139f]:

This compound was prepared (as a solid) following the procedure described for the molecule **(*S*)-139a** (Page no. 114) *via* borane-mediated asymmetric reduction of 4-chlorophenacyl bromide (**138f**) under the catalytic influence of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (5 mol%).



Yield: 89%

Mp: 44-46 ^{o}C

$[\alpha]_D^{25}$: +37.4 (*c* 1.2, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +38.6 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91% *ee*}

Enantiomeric purity: 83% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139f**]

IR (Neat) : 3423 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.71 (s, 1H), 3.42-3.73 (m, 2H), 4.85-4.97 (m, 1H), 7.26-7.48 (m, 4H)

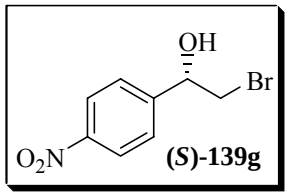
^{13}C NMR (100 MHz) : δ 39.98, 73.12, 127.42, 128.91, 134.27, 138.78

Determination of enantiomeric purity:

HPLC analysis of racemic alcohol **(±)-139f** showed two peaks in equal intensity [chiral column: Chiralcel OJ-H, solvent system: hexanes:IPA (95:5), flow rate: 0.75 mL/min] at 25.18 min and 27.35 min arising due to (*R*) and (*S*) enantiomers. Similar HPLC analysis of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [**(*S*)-139f**] showed two peaks at 24.30 min (*R*) and 26.09 min (*S*) in the ratio of 8.5:91.5 indicating that the enantioselectivity of this reaction is 83%.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-139g]:

This compound was prepared *via* the asymmetric reduction of 4-nitrophenacyl bromide (**138g**) with $BH_3.SMe_2$ using (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (5 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 114).



(*S*)-139g

Yield: 84%

Mp: 88-90 °C [Lit.[111] 78-80 °C]

$[\alpha]_D^{25}$: +26.5 (*c* 1.2, $CHCl_3$)

{Lit.[110] $[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*}

Enantiomeric purity: 78% [determined by HPLC analysis of the corresponding acetate **(*S*)-140** using chiral column, Chiralcel OD-H, with reference to racemic acetate **(±)-140**]

IR (KBr) : 3547 cm^{-1}

^1H NMR (400 MHz) : δ 2.79 (d, 1H, *J* = 3.3 Hz), 3.49-3.71 (m, 2H), 4.98-5.11 (m, 1H), 7.59 (d, 2H, *J* = 8.6 Hz), 8.24 (d, 2H, *J* = 8.6 Hz)

^{13}C NMR (50 MHz) : δ 39.28, 72.70, 123.86, 126.99, 147.39, 147.88

Determination of enantiomeric purity:

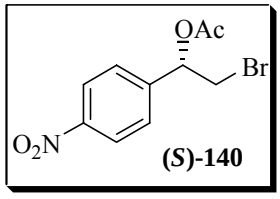
The enantiomeric purity was determined by HPLC analysis of the corresponding acetate *i.e.* 1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(*S*)-140**] using chiral column,

Chiralcel OD-H. The racemic acetate **(±)-140** showed two peaks with equal intensity at 10.52 min and 11.93 min corresponding to (*R*) and (*S*) enantiomers [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min], while similar HPLC analysis of chiral acetate **(*S*)-140** showed two peaks at 10.33 min (*R*) and 11.68 min (*S*) in the ratio of 11:89 indicating that the reduction is 78% selective.

(*S*)-1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane [(*S*)-140]:

This molecule was prepared according to the known procedure.[133]

Pyridine (4.68 mL) was added to a stirred solution of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [**(*S*)-139g**] (0.098 g, 0.4 mM) in acetic anhydride (23.4 mL). After stirring the reaction mixture for 10 h at room temperature, it was diluted with water (80 mL) and extracted with ether (3X20 mL). The combined organic layer was 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).



Yield: 75% (0.0864 g)

Mp: 112 °C [Lit.[111] 102-105 °C]

$[\alpha]_D^{25}$: +40.6 (*c* 1.0, $CHCl_3$)

[Lit.[111] $[\alpha]_D^{25}$: +46.6 (*c* 0.9, $CHCl_3$), (*S*)-configuration, 92% *ee*]

IR (KBr) : 1749 cm^{-1}

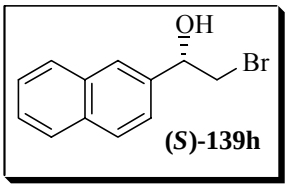
^{1}H NMR (400 MHz) : δ 2.17 (s, 3H), 3.60-3.68 (m, 2H), 5.98-6.07 (m, 1H), 7.55 (d, 2H, J = 8.4 Hz), 8.25 (d, 2H, J = 8.4 Hz)

^{13}C NMR (50 MHz) : δ 20.84, 33.38, 73.65, 123.96, 127.67, 144.55, 148.17, 169.54

Racemic acetate (±)-140 was prepared following the above-mentioned procedure from the corresponding racemic alcohol (±)-139g and its spectral data (IR, ^{1}H & ^{13}C NMR) are in full agreement with the spectral data of (S)-140.

(*S*)-2-Bromo-1-(naphth-2-yl)ethanol [(*S*)-139h]:

This secondary alcohol was obtained as a solid *via* the asymmetric reduction of 2-bromoacetylnaphthalene (**138h**) with BH_3**.**SMe_2 in the presence of 5 mol% (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 114).



(*S*)-139h

Yield: 86%

Mp: 77-79 ^{o}C [Lit.[137] 88-90 ^{o}C]

$[\alpha]_D^{25}$: +21.6 (*c* 1.0, EtOH)

{Lit.[137] $[\alpha]_D^{23}$: -25.6 (*c* 4.0, EtOH) (*R*)-configuration, 83% *ee*}

Enantiomeric purity: 72% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139h**]

IR (KBr) : 3308 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.70 (brs, 1H), 3.51-3.74 (m, 2H), 5.03-5.14 (m, 1H), 7.36-

7.53 (m, 3H), 7.71-7.89 (m, 4H)

^{13}C NMR (100 MHz) : δ 40.11, 73.94, 123.60, 125.21, 126.34, 126.45, 127.77, 128.08, 128.58, 133.23, 133.32, 137.65

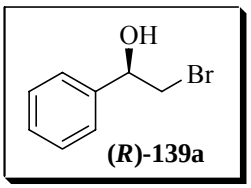
Determination of enantiomeric purity:

HPLC analysis [chiral column, Chiralcel OJ-H, solvent system, hexanes:IPA (80:20); flow rate: 1 mL/min] of the racemic compound **(±)-139h** showed two peaks at 13.61 min (*R*) and 17.76 min (*S*) in 1:1 ratio. Similar HPLC analysis of the chiral alcohol **(*S*)-139h** showed two peaks at 13.76 min (*R*) and 17.77 min (*S*) in the ratio of 14:86 indicating that the reaction is 72% enantioselective.

Reduction of phenacyl bromide (138a) at room temperature (≈30 ^{o}C) in the presence of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135) as catalyst/catalytic source:

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature (≈30 ^{o}C) and the reaction mixture was stirred for 15 min at the same temperature. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued for further 15 min. The reaction mixture was then quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column

chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*R*)-2-bromo-1-phenylethanol [**(*R*)-139a**] as a colorless oil.



(*R*)-139a

Yield: 87% (0.175 g)

$[\alpha]_D^{25}$: -15.1 (*c* 1.4, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 32% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

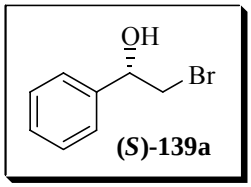
The spectral data (IR, ^1H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

Determination of enantiomeric purity:

Racemic alcohol {(±)-2-bromo-1-phenylethanol [**(±)-139a**]} showed two peaks in 1:1 ratio [retention times: 7.98 min (*S*) and 8.51 min (*R*)] on HPLC analysis using chiral column Chiralcel OD-H [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min]. In the case of chiral alcohol [**(*R*)-139a**], we have observed two peaks at 7.99 min and 8.52 min respectively due to (*S*) and (*R*) enantiomers in 34:66 ratio on similar HPLC analysis indicating that the enantiomeric purity of (*R*)-2-bromo-1-phenylethanol [**(*R*)-139a**] is 32%.

Reduction of phenacyl bromide (138a) at room temperature (≈30 ^{o}C) using the catalytic species 141 (generated *in situ* at 110 ^{o}C):

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at 110 ^{o}C for 15 min. Reaction mixture was cooled to room temperature (≈30 ^{o}C) and a solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued for further 30 min at the same temperature. The reaction mixture was quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] as a colorless oil.



(*S*)-139a

Yield: 80% (0.161 g)

$[\alpha]_D^{25}$: +17.4 (*c* 2.0, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 44% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

The spectral data (IR, ^{1}H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

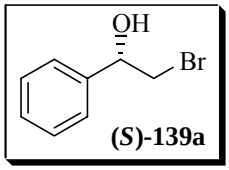
Determination of enantiomeric purity:

Enantiomeric purity of the (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. (±)-2-Bromo-1-phenylethanol [**(±)-139a**] showed two peaks [flow rate: 1 mL/min, solvent system: hexanes:IPA (90:10)] in equal intensities [retention times: 7.82 min (*S*) and 8.27 min (*R*)], while chiral alcohol **(*S*)-139a** showed two peaks at 7.83 min (*S*) and 8.29 min (*R*) (on similar HPLC analysis) in the ratio of 72:28, indicating that (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is 44% enantiomerically pure.

***In situ* recyclability of the catalytic species 141 [generated *in situ* at 110 ^{o}C *via* the reaction of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135) with $BH_3.SMe_2$]: (*S*)-2-Bromo-1-phenylethanol [(*S*)-139a] (*in situ* reusability: run 2):**

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at 110 ^{o}C for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and heating was continued for further 15 minutes (run 1). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 2) was added to this reaction flask (without work-up), and heated at 110 ^{o}C for 15 min and then a solution of

phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued at 110 ^{o}C for further 15 min as usual (run 2). The reaction mixture was now cooled to room temperature quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] as a colorless oil.



(*S*)-139a

Yield: 90% (0.362 g)

$[\alpha]_D^{25}$: +34.0 (c 1.1, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 79% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

The spectral data (IR, ^{1}H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

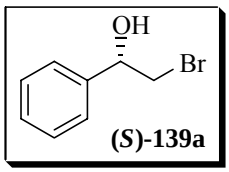
Determination of enantiomeric purity:

HPLC analysis (using chiral column, Chiralcel OD-H) of (±)-2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks in 1:1 ratio [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min] at 8.32 min and 8.83 min due to (*S*) and (*R*) enantiomers. Chiral 2-bromo-1-phenylethanol [**(S)-139a**] showed two peaks at 8.27 min (*S*) and 8.82 min (*R*) in 89.5:10.5 ratio indicating that the reduction is 79% selective.

***In situ* recyclability of the catalytic species 141 [generated *in situ* at 110 ^{o}C *via* the reaction of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135) with $BH_3.SMe_2$]: (*S*)-2-Bromo-1-phenylethanol [(*S*)-139a] (*in situ* reusability: run 3):**

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at 110 ^{o}C for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and heating was continued for further 15 min (run 1). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 2) was added to this reaction flask (without work-up), and heated at 110 ^{o}C for 15 min and then a solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued at 110 ^{o}C for further 15 min as usual (run 2). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 3) was added to this reaction flask (without work-up), and heated at 110 ^{o}C for 15 min and then a solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued at 110 ^{o}C for further 15 min as usual (run 3). The reaction mixture was now cooled to room temperature quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] as a colorless oil.

Yield: 88% (0.531 g)



(*S*)-139a

$[\alpha]_D^{25}$: +33.5 (c 1.4, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (c 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 78% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

The spectral data (IR, ^1H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

Determination of enantiomeric purity:

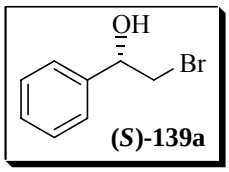
HPLC analysis (using chiral column Chiralcel OD-H) of (±)-2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks in 1:1 ratio [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min] at 8.32 min and 8.83 min due to (*S*) and (*R*) enantiomers. Chiral 2-bromo-1-phenylethanol [**(*S*)-139a**] showed two peaks at 8.28 min (*S*) and 8.85 min (*R*) in 89:11 ratio indicating that the reduction is 78% selective.

***In situ* recyclability of the catalytic species 141 [generated *in situ* at 110 °C *via* the reaction of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135) with $BH_3.SMe_2$]: (*S*)-2-Bromo-1-phenylethanol [(*S*)-139a] (*in situ* reusability: run 4):**[τ]

To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (10.1 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at 110 °C for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was

added slowly drop-wise and heating was continued for further 15 min (run 1). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 2) was added to this reaction flask (without work-up), and heated at 110 ^oC for 15 min and then a solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued at 110 ^oC for further 15 min as usual (run 2). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 3) was added to this reaction flask (without work-up), and heated at 110 ^oC for 15 min and then a solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and stirring was continued at 110 ^oC for further 15 min as usual (run 3). $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) (for run 4) was added to the flask (without work-up), and heated at 110 ^oC for 15 min followed by added solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) drop-wise and stirring was continued at 110 ^oC for further 15 min as usual (run 4). The reaction mixture was now cooled to room temperature quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] as a colorless oil.

Yield: 88% (0.708 g)



(*S*)-139a

[τ]To have clarity, we have given the complete procedure in all the experiments dealing with recyclability.

$[\alpha]_D^{25}$: +34.5 (*c* 1.3, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 79% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

The spectral data (IR, ^{1}H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

Determination of enantiomeric purity:

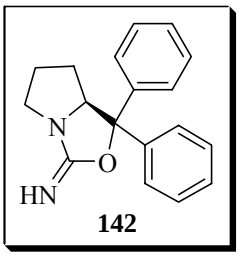
HPLC analysis (using chiral column, Chiralcel OD-H) of (±)-2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks in 1:1 ratio [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min] at 8.32 min and 8.83 min due to (*S*) and (*R*) enantiomers. Chiral 2-bromo-1-phenylethanol [**(*S*)-139a**] showed two peaks at 8.31 min (*S*) and 8.83 min (*R*) in 89.5:10.5 ratio indicating that the reduction is 79% selective.

(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (142):

This molecule was prepared following the general literature procedure for the preparation of guanidine *via* the reaction of diamines with cyanogen bromide, with some modification.[131a]

To a stirred solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**143**) (2.02 g, 8 mM) in EtOH (18 mL) was carefully added a solution of cyanogen bromide (1.694 g, 16

mM) in EtOH (2 mL) at 0 ^{o}C. After stirring the reaction mixture for 12 h at room temperature, it was heated at 100 ^{o}C (about 2 h) to completely remove the boiling solvents. The residue thus obtained was diluted with EtOH (16 mL) and 1N aqueous NaOH solution (16 mL) and was extracted with CH_2Cl_2 (3X30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue, thus obtained, was crystallized (hexanes:EtOAc = 9:1) to provide the desired (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) in 70 % (1.56 g) yield.



142

Mp: 94-96 ^{o}C

$[\alpha]_D^{25}$: -221.9 (*c* 1.14, $CHCl_3$)

IR (KBr): 3341, 1676 cm^{-1}

^{1}H NMR (400 MHz): δ 1.04-1.16 (m, 1H), 1.58-1.69 (m, 1H), 1.74-1.96 (m, 2H), 3.23-3.34 (m, 1H), 3.57-3.68 (m, 1H), 4.48 (dd, 1H, *J* = 5.6 Hz & 10.4 Hz), 5.12 (brs, 1H), 7.21-7.37 (m, 8H), 7.45-7.51 (m, 2H)

^{13}C NMR (50 MHz): δ 25.35, 28.82, 48.52, 70.93, 87.26, 125.66, 126.07, 127.48, 128.06, 128.13, 128.40, 140.70, 143.61, 163.89

LC MS (m/z): 279 $(M+H)^+$

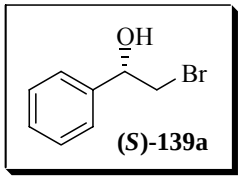
Anal. calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06

Found: C, 77.89; H, 6.53; N, 10.05

Spectral data (IR, ^{1}H & ^{13}C NMR) of the chiral alcohols (S)-139a,b,e-g obtained via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b,e-g in the presence of (5S)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)-octane (142) as a catalyst/catalytic source are in full agreement with the spectral data of the chiral alcohols (S)-139a,b,e-g (IR, ^{1}H & ^{13}C NMR) prepared via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b,e-g in the presence of (5S)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135). Therefore we have not mentioned the spectral data again in the following experiment.

Asymmetric reduction of phenacyl bromide (138a) using 142 as a chiral catalyst/catalytic source: **Synthesis of (*S*)-2-bromo-1-phenylethanol [(*S*)-139a]**: **Representative procedure**:

To a stirred solution of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (0.4 mL, 0.05 M solution in toluene, 0.02 mM) in toluene (4 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated at reflux for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM), in toluene (2 mL), was added slowly drop-wise and heated at reflux for a further 15 min. The reaction mixture was cooled to room temperature and quenched with MeOH. The solvent was removed under a reduced pressure. Residue, thus obtained, was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to furnish the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] in 85% (171 mg) yield as a colorless oil.



(*S*)-139a

$[\alpha]_D^{25}$: +40.1 (*c* 1.8, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 92% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

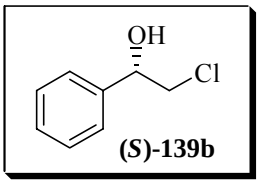
Determination of enantiomeric purity:

HPLC analysis of (±)-2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks with equal intensity (chiral column: Chiralcel OD-H, solvent system: 10% IPA in hexanes, flow rate: 1 mL/min) at 7.92 min and 8.61 min due to (*S*) and (*R*) enantiomers. Similar HPLC analysis of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] showed two peaks at 7.82 min (*S*) and 8.55 min (*R*) in the ratio of 96:4 indicating that the enantioselectivity of this reaction is 92%.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (with 142 as catalyst/catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of phenacyl chloride (**138b**) with (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)-octane (**142**) (2 mol%), as a chiral catalyst/catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).

Yield : 87%



(*S*)-139b

$[\alpha]_D^{25}$: +44.7 (*c* 1.1, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

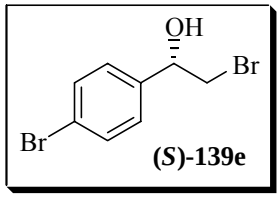
Enantiomeric purity: 91% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

Determination of enantiomeric purity:

Enantiomeric purity of (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. (±)-2-Chloro-1-phenylethanol [**(±)-139b**] showed two peaks (flow rate: 1 mL/min, solvent system: 10% IPA in hexanes) in equal intensities at 7.59 min (*S*) and 8.04 min (*R*), while chiral alcohol **(*S*)-139b**, on similar HPLC analysis, showed two peaks at 7.51 min and 8.01 min in the ratio of 95.5:4.5 corresponding to (*S*) and (*R*) enantiomers indicating that (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] is 91% enantiomerically pure.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-139e] (with 142 as catalyst/catalytic source):

This compound was prepared (as a solid) following the procedure described for the molecule **(*S*)-139a** (Page no. 140) *via* the borane-mediated asymmetric reduction of 4-bromophenacyl bromide (**138e**) under the catalytic influence of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (2 mol%).



(*S*)-139e

Yield : 86%

Mp: 69-71 ^{o}C (Lit.[111] 71-72 ^{o}C)

$[\alpha]_D^{25}$: +31.9 (*c* 1.2, $CHCl_3$)

{Lit.[136] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

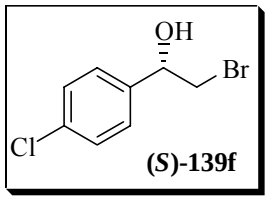
Enantiomeric purity: 92% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139e**]

Determination of enantiomeric purity:

HPLC analysis (using chiral column Chiralcel OJ-H) of racemic alcohol **(±)-139e** showed two peaks in 1:1 ratio (solvent system: 5% IPA in hexanes, flow rate: 1 mL/min) at 20.70 min and 22.97 min arising due to (*R*) and (*S*) enantiomers. Similar HPLC analysis of (*S*)-2-bromo-1-(4-bromophenyl)ethanol [**(*S*)-139e**] showed two peaks at 20.66 min (*R*) and 22.65 min (*S*) in 4:96 ratio indicating that the reduction is 92% selective.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-139f] (with 142 as catalyst/catalytic source):

This compound was prepared *via* the asymmetric reduction of 4-chlorophenacyl bromide (**138f**) with $BH_3.SMe_2$ using (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo-(3.3.0)octane (**142**) (2 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).



Yield: 85%

Mp: 40-42 ^{o}C

$[\alpha]_D^{25}$: +39.3 (*c* 1.0, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +38.6 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91% *ee*}

Enantiomeric purity: 93% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139f**]

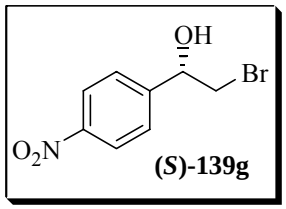
Determination of enantiomeric purity:

Racemic 2-bromo-1-(4-chlorophenyl)ethanol [**(±)-139f**] showed two peaks in 1:1 ratio [retention times: 24.76 min (*R*) and 27.04 min (*S*)] on HPLC analysis using chiral column Chiralcel OJ-H (solvent system: 5% IPA in hexanes, flow rate: 0.75 mL/min). In the case of chiral compound **(*S*)-139f**, we have observed two peaks at 25.45 min and 27.34 min arising due to (*R*) and (*S*) enantiomers, on similar HPLC analysis, in the ratio of 3.5:96.5 indicating that the enantiomeric purity of (*S*)-2-bromo-1-(4-chlorophenyl)ethanol [**(*S*)-139f**] is 93%.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-139g] (with 142 as catalyst/catalytic source):

This secondary alcohol was obtained as a solid *via* the asymmetric reduction of 4-

nitrophenacyl bromide (**138g**) with BH_3**.**SMe_2 in the presence of 2 mol% (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).



(*S*)-139g

Yield: 84%

Mp: 94-96 ^oC

$[\alpha]_D^{25}$: +32.3 (*c* 1.3, $CHCl_3$)

{Lit.[110] $[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*}

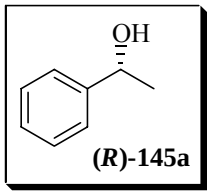
Enantiomeric purity: 88% [determined by HPLC analysis of the corresponding acetate **(*S*)-140** using chiral column, Chiralcel OD-H, with reference to racemic acetate **(±)-140**]

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 [**(*S*)-140**] using chiral column, Chiralcel OD-H. The racemic acetate **(±)-140** showed two peaks with equal intensity at 10.49 min (*R*) and 11.96 min (*S*) (solvent system: 10% IPA in hexanes, flow rate: 1 mL/min). Chiral acetate **(*S*)-140**, on similar HPLC analysis, showed two peaks at 10.61 min (*R*) and 12.10 min (*S*) in the ratio of 6:94 indicating that the reduction is 88% selective.

(*R*)-1-Phenylethanol [(*R*)-145a] (with 142 as catalyst/catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of acetophenone (**144a**) using (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (2 mol%), as a chiral catalyst/catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).



(*R*)-145a

Yield: 77%

$[\alpha]_D^{25}$: +35.5 (*c* 1.2, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 80% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]

IR (Neat) : 3383 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.49 (d, 3H, *J* = 6.4 Hz), 1.99 (brs, 1H), 4.89 (q, 1H, *J* = 6.4 Hz), 7.19-7.40 (m, 5H)

^{13}C NMR (50 MHz) : δ 25.21, 70.47, 125.46, 127.53, 128.57, 145.91

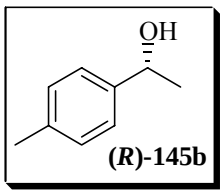
Determination of enantiomeric purity:

HPLC analysis of (±)-1-phenylethanol [**(±)-145a**] showed two peaks with equal intensity (chiral column: Chiralcel OD-H, solvent system: 5% IPA in hexanes, flow rate: 1 mL/min) at 8.54 min (*R*) and 9.73 min (*S*). Similar HPLC analysis of (*R*)-1-phenylethanol [**(*R*)-145a**] showed two peaks at 8.42 min and 9.65 min [corresponding

to (*R*) and (*S*) enantiomers] in the ratio of 90:10 indicating that the enantioselectivity of this reaction is 80%.

(*R*)-1-(4-Methylphenyl)ethanol [(*R*)-145b] (with 142 as catalyst/catalytic source):

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (Page no. 140) *via* borane-mediated asymmetric reduction of 4-methylacetophenone (**144b**) under the catalytic influence of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (2 mol%).



(*R*)-145b

Yield: 82%

$[\alpha]_D^{25}$: +29.2 (*c* 1.5, MeOH)

{Lit.[139] $[\alpha]_D^{26}$: -43.5 (*c* 0.99, MeOH), (*S*)-configuration, >99% *ee*}

Enantiomeric purity: 70% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145b**]

IR (Neat) : 3366 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.48 (d, 3H, *J* = 6.0 Hz), 2.30-2.40 (m, 4H), 4.84 (q, 1H, *J* = 6.0 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz)

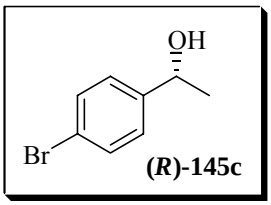
^{13}C NMR (50 MHz) : δ 21.13, 25.14, 70.30, 125.44, 129.22, 137.20, 143.00

Determination of enantiomeric purity:

(±)-1-(4-Methylphenyl)ethanol [**(±)-145b**] showed two peaks in 1:1 ratio [retention times: 14.38 min (*S*) and 16.44 min (*R*)] on HPLC analysis using chiral column Chiralcel OJ-H (solvent system: 5% IPA in hexanes, flow rate: 0.8 mL/min). In the case of chiral compound **(*R*)-145b**, we have observed two peaks at 14.52 min (*S*) and 16.52 min (*R*) (on similar HPLC analysis) in the ratio of 15:85 indicating that the enantiomeric purity of (*R*)-1-(4-methylphenyl)ethanol [**(*R*)-145b**] is 70%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-145c] (with 142 as catalyst/catalytic source):

This compound was prepared *via* the asymmetric reduction of 4-bromoacetophenone (**144c**) with $BH_3.SMe_2$ using (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)-octane (**142**) (2 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).



(*R*)-145c

Yield: 85%

$[\alpha]_D^{25}$: +27.5 (*c* 1.1, $CHCl_3$)

{Lit.[139] $[\alpha]_D^{25}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*}

Enantiomeric purity: 73% [determined by HPLC analysis of alcohol using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145c**]

IR (Neat) : 3358 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.44 (d, 3H, J = 6.4 Hz), 2.26 (brs, 1H), 4.82 (q, 1H, J = 6.4 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz)

^{13}C NMR (100 MHz) : δ 25.25, 69.76, 121.16, 127.20, 131.57, 144.81

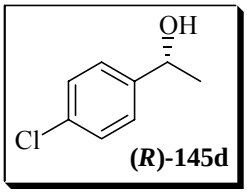
Determination of enantiomeric purity:

Racemic alcohol **(±)-145c** showed two peaks at 14.62 min (*S*) and 15.77 min (*R*) with equal intensity on HPLC analysis using chiral column, Chiralcel OJ-H (solvent system: 5% IPA in hexanes, flow rate: 0.8 mL/min), while similar HPLC analysis of (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-145c**] showed two peaks at 14.75 min and 15.86 min due to (*S*) and (*R*) enantiomers in 13.5:86.5 ratio indicating that the enantiomeric purity of (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-145c**] is 73%.

(*R*)-1-(4-Chlorophenyl)ethanol [(*R*)-145d] (with 142 as catalyst/catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of 4-chloroacetophenone (**144d**) with BH_3**.**SMe_2 in the presence of 2 mol% (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).

Yield: 84%



(*R*)-145d

$[\alpha]_D^{25}$: +38.5 (*c* 1.3, Et_2O)

{Lit.[139] $[\alpha]_D^{25}$: -49.0 (*c* 1.84, Et_2O), (*S*)-configuration, >99% *ee*}

Enantiomeric purity: 78% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145d**]

IR (Neat) : 3368 cm^{-1}

^1H NMR (400 MHz) : δ 1.47 (d, 3H, *J* = 6.4 Hz), 1.87 (d, 1H, *J* = 1.6 Hz), 4.80-4.93 (m, 1H), 7.31 (s, 4H)

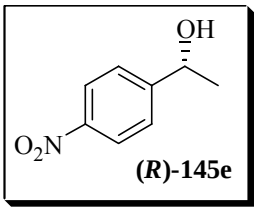
^{13}C NMR (100 MHz) : δ 25.28, 69.76, 126.79, 128.61, 133.01, 144.25

Determination of enantiomeric purity:

HPLC analysis (using chiral column, Chiralcel OJ-H) of (±)-1-(4-chlorophenyl)ethanol [**(±)-145d**] showed two peaks in 1:1 ratio (solvent system: 5% IPA in hexanes, flow rate: 0.8 mL/min) at 13.37 min and 14.28 min [corresponding to (*S*) and (*R*) enantiomers]. Chiral alcohol **(*R*)-145d**, on similar HPLC analysis, showed two peaks at 13.39 min (*S*) and 14.24 min (*R*) in 11:89 ratio indicating that the reduction is 78% enantioselective.

(*R*)-1-(4-Nitrophenyl)ethanol [(*R*)-145e] (with 142 as catalyst/catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of 4-nitroacetophenone (**144e**) with (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)-octane (**142**) (2 mol%), as a chiral catalyst/catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 140).



(*R*)-145e

Yield: 82%

$[\alpha]_D^{25}$: +27.2 (*c* 1.2, EtOH)

{Lit.[140] $[\alpha]_D^{24.5}$: -29.7 (*c* 1.0, EtOH), (*S*)-configuration, >99% *ee*}

Enantiomeric purity: 87% [determined by HPLC analysis of the corresponding acetate **(*R*)-146** using chiral column, Chiralcel OD-H, with reference to its racemic acetate **(±)-146**]

IR (Neat) : 3398 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.52 (d, 3H, *J* = 6.6 Hz), 2.08 (s, 1H), 4.97-5.05 (m, 1H), 7.54 (d, 2H, *J* = 8.4 Hz), 8.19 (d, *J* = 2H, J = 8.4 Hz)

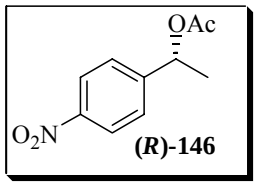
^{13}C NMR (100 MHz) : δ 25.52, 69.52, 123.78, 126.13, 146.80, 153.07

Determination of enantiomeric purity:

The enantiomeric purity was determined by HPLC analysis of the corresponding acetate *i.e.* 1-acetoxy-1-(4-nitrophenyl)ethane [**(*R*)-146**] using chiral column, Chiralcel OD-H. The racemic acetate **(±)-146** showed two peaks at 20.65 min (*S*) and 22.61 (*R*) min in 1:1 ratio [solvent system: 2% IPA in hexanes, flow rate: 0.5 mL/min], while similar HPLC analysis of chiral 1-acetoxy-1-(4-nitrophenyl)ethane [**(*R*)-146**] showed two peaks at 20.61 min (*S*) and 22.45 min (*R*) in the ratio of 6.5:93.5 indicating that the reduction is 87% enantioselective.

(*R*)-1-Acetoxy-1-(4-nitrophenyl)ethane [(*R*)-146]:

This compound was prepared as a colorless liquid *via* the reaction of (*R*)-1-(4-nitrophenyl)ethanol [**(*R*)-145e**] with acetic anhydride in presence of pyridine following the similar procedure as described for the molecule **(*S*)-140** (Page no. 128).



Yield: 82 %

$[\alpha]_D^{25}$: +83.9 (*c* 1.1, $CHCl_3$)

{Lit.[145] $[\alpha]_D^{25}$: +99.2 (c 1.4, $CHCl_3$), (*R*)-configuration, >99% *ee*}

IR (Neat) : 1738 cm^{-1}

^1H NMR (400 MHz) : δ 1.54 (d, 3H, *J* = 6.6 Hz), 2.10 (s, 3H), 5.91 (q, 1H, *J* = 6.6 Hz), 7.50 (d, 2H, *J* = 8.6 Hz), 8.19 (d, 2H, *J* = 8.6 Hz)

^{13}C NMR (50 MHz) : δ 21.16, 22.27, 71.30, 123.89, 126.82, 147.56, 149.04, 170.05

Racemic acetate (±)-146 was also prepared following the similar procedure described for the (S)-140 (Page no. 128) and its spectral data (IR, ^1H & ^{13}C NMR) are in full agreement with the spectral data of (R)-146.

Reduction of phenacyl bromide (138a) at room temperature in the presence of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (142) (2 mol%) as catalyst/catalytic source:

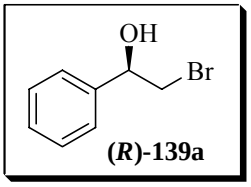
Borane-mediated asymmetric reduction of phenacyl bromide (**138a**) under the catalytic influence of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (**142**) (2

mol%) has been carried out at room temperature following the similar procedure described for the molecule **(*R*)-139a** using the catalyst/catalytic source (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (**135**) (Page nos. 130 & 131).

Time: 60 min

Yield: 86%

$[\alpha]_D^{25}$: -2.1 (*c* 3.5, $CHCl_3$)



(*R*)-139a

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 5% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

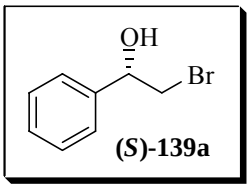
The spectral data (IR, ^1H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

Determination of enantiomeric purity:

Racemic alcohol {(±)-2-bromo-1-phenylethanol [**(±)-139a**]} showed two peaks in 1:1 ratio [retention times: 7.97 min (*S*) and 8.63 min (*R*)] on HPLC analysis using chiral column Chiralcel OD-H [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min]. In the case of chiral alcohol [**(*R*)-139a**], we have observed two peaks at 7.88 min and 8.51 min respectively due to (*S*) and (*R*) enantiomers in 47.5:52.5 ratio on similar HPLC analysis indicating that the enantiomeric purity of (*R*)-2-bromo-1-phenylethanol [**(*R*)-139a**] is 5%.

Reduction of phenacyl bromide (138a) at room temperature using the chiral catalytic species, generated *in situ via* the reaction of 142 with $BH_3.SMe_2$ at 110 ^oC:

Borane-mediated asymmetric reduction of phenacyl bromide (**138a**) at room temperature using the chiral catalytic species, generated *in situ via* the reaction of **142** (2 mol%) with $BH_3.SMe_2$ at 110 ^oC, was carried out following the similar procedure described for the molecule **(*S*)-139a** using the catalytic species **141** (Page no. 132).



(*S*)-139a

Time: 9 h

Yield: 84%

$[\alpha]_D^{25}$: +11.7 (*c* 2.5, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 31% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

The spectral data (IR, ^1H & ^{13}C NMR) of this alcohol are in full agreement with the spectral data of (S)-139a (Page no. 115).

Determination of enantiomeric purity:

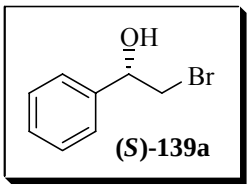
Enantiomeric purity of the (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. (±)-2-Bromo-1-phenylethanol [**(±)-139a**] showed two peaks [flow rate: 1 mL/min, solvent system: hexanes:IPA (90:10)] in equal intensities [retention times: 7.91 min (*S*) and 8.68 min (*R*)], while

chiral alcohol **(*S*)-139a** showed two peaks at 7.84 min (*S*) and 8.61 min (*R*) (on similar HPLC analysis) in the ratio of 65.5:34.5, indicating that (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is 31% enantiomerically pure.

Asymmetric reduction of prochiral ketones in the presence of 2 mol% (2*S*)-2-anilinomethylpyrrolidine (134):

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]: Representative procedure:

To a stirred solution of (2*S*)-2-anilinomethylpyrrolidine (**134**) (0.4 mL, 0.05 M solution in toluene, 0.02 mM) in toluene (4 mL) was added $BH_3.SMe_2$ (1 mL, 1 M solution in toluene, 1 mM) at room temperature and the reaction mixture was heated under reflux for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM), in toluene (2 mL), was then added slowly drop-wise and stirring was continued at reflux for further 15 min. The reaction mixture was cooled to room temperature and quenched with MeOH. 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*)-139a**] in 82% (165 mg) yield as a colorless oil.



(*S*)-139a

$[\alpha]_D^{25}$: +39.8 (*c* 1.2, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 91% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

Determination of enantiomeric purity:

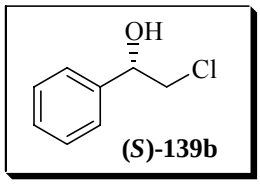
HPLC analysis of racemic 2-bromo-1-phenylethanol [**(±)-139a**] showed two peaks with equal intensity [chiral column: Chiralcel OD-H, solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min] with retention times 8.26 min (*S*) and 8.83 min (*R*). Similar HPLC analysis of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] showed two peaks at 8.19 min and 8.87 min in the ratio of 95.5:4.5 corresponding to (*S*) and (*R*) enantiomers indicating that the enantioselectivity of this reaction is 91%.

Spectral data (IR, ^{1}H & ^{13}C NMR) of the chiral alcohols (S)-139a,b,d-g&(R)-145a-e obtained via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b,d-g & 144a-e in the presence of (2S)-2-anilinomethyl-pyrrolidine (134), as catalytic source, are in full agreement with the spectral data of the chiral alcohols (S)-139a,b,d-g & (R)-145a-e (IR, ^{1}H & ^{13}C NMR) prepared via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b,d-g & 144a-e in the presence of (5S)-1,3-diaza-2-imino-3-phenylbicyclo-(3.3.0)octane (135) and (5S)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (142). Therefore we have not mentioned the spectral data again for any of these compounds.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (with 134 as catalytic source):

This compound was prepared *via* the asymmetric reduction of phenacyl chloride (**138b**) with $BH_3.SMe_2$ using (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%), as a chiral

catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



(*S*)-139b

Yield: 80%

$[\alpha]_D^{25}$: +43.8 (*c* 1.0, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 87% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

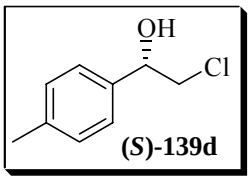
Determination of enantiomeric purity:

Enantiomeric purity of (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. Racemic alcohol **(±)-139b** showed two peaks [flow rate: 1 mL/min, solvent system: hexanes:IPA (90:10)] in equal intensities at 7.56 min (*S*) and 8.10 min (*R*). Chiral compound **(*S*)-139b** showed two peaks at 7.49 min and 8.10 min in the ratio of 93.5:6.5 corresponding to (*S*) and (*R*) enantiomers indicating that (*S*)-2-chloro-1-phenylethanol [**(*S*)-139b**] is 87% enantiomerically pure.

(*S*)-2-Chloro-1-(4-methylphenyl)ethanol [(*S*)-139d] (with 134 as catalytic source):

This compound was prepared (as a solid) following the procedure described for the molecule **(*S*)-139a** (Page no. 155) *via* borane-mediated asymmetric reduction of 4-

methylphenacyl chloride (**138d**) under the influence of 2 mol% (2*S*)-2-anilinomethyl-pyrrolidine (**134**).



(*S*)-139d

Yield: 88%

Mp: 38-40 ^{o}C

$[\alpha]_D^{25}$: +43.1 (*c* 0.8, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +47.2 (*c* 1.1, $CHCl_3$), (*S*)-configuration, 92% *ee*}

Enantiomeric purity: 84% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139d**]

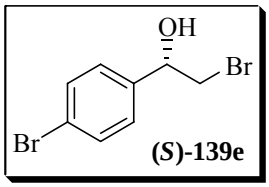
Determination of enantiomeric purity:

Racemic alcohol **(±)-139d** showed two peaks at 15.52 min and 16.72 min [corresponding to (*S*) and (*R*) enantiomers] with equal intensity on HPLC analysis [chiral column: chiralcel OD-H, solvent system: hexanes:IPA (97.5:2.5), flow rate: 0.9 mL/min]. Similar HPLC analysis of chiral alcohol **(*S*)-139d** showed two peaks at 15.57 min (*S*) and 16.80 min (*R*) in 92:8 ratio indicating that the enantiomeric excess of (*S*)-2-chloro-1-(4-methylphenyl)ethanol [**(*S*)-139d**] is 84%.

(*S*)-2-Bromo-1-(4-bromophenyl)ethanol [(*S*)-139e] (with 134 as catalytic source):

This secondary alcohol was obtained as a solid *via* the asymmetric reduction of 4-bromophenacyl bromide (**138e**) with $BH_3.SMe_2$ in the presence of 2 mol% (2*S*)-2-

anilinomethylpyrrolidine (**134**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



(*S*)-139e

Yield: 85%

Mp: 61-63 ^{o}C [Lit.[111] 71-72 ^{o}C]

$[\alpha]_D^{25}$: +30.5 (*c* 1.0, $CHCl_3$)

{Lit.[136] $[\alpha]_D^{25}$: -31.0 (*c* 2.9, $CHCl_3$), (*R*)-configuration, 94% *ee*}

Enantiomeric purity: 90% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139e**]

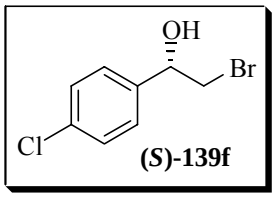
Determination of enantiomeric purity:

HPLC analysis of (±)-2-bromo-1-(4-bromophenyl)ethanol [**(±)-139e**] showed two peaks in equal intensity [chiral column: Chiralcel OJ-H, solvent system: hexanes:IPA (95:5), flow rate: 1 mL/min] with 21.67 min and 24.22 min retention times [corresponding to (*R*) and (*S*) enantiomers]. Similar HPLC analysis of chiral alcohol **(*S*)-139e** showed two peaks at 21.94 min (*R*) and 24.41 min (*S*) in the ratio of 5:95 indicating that the enantioselectivity of this reaction is 90%.

(*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [(*S*)-139f] (with 134 as catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of 4-chlorophenacyl bromide (**138f**) using (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%),

as a chiral catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



(*S*)-139f

Yield: 83%

Mp: 44-46 ^{o}C

$[\alpha]_D^{25}$: +38.9 (*c* 0.9, $CHCl_3$)

{Lit.[109] $[\alpha]_D^{25}$: +38.60 (*c* 1.15, $CHCl_3$), (*S*)-configuration, 91% *ee*}

Enantiomeric purity: 90% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-139f**]

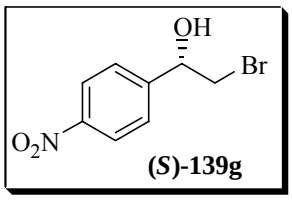
Determination of enantiomeric purity:

HPLC analysis (using chiral column, Chiralcel OJ-H) of racemic alcohol **(±)-139f** showed two peaks in 1:1 ratio [solvent system: hexanes:IPA (95:5), flow rate: 0.75 mL/min] at 26.48 min (*R*) and 28.85 min (*S*). (*S*)-2-Bromo-1-(4-chlorophenyl)ethanol [**(*S*)-139f**], on similar HPLC analysis, showed two peaks at 26.99 min (*R*) and 29.00 min (*S*) in 5:95 ratio indicating that the reduction is 90% selective.

(*S*)-2-Bromo-1-(4-nitrophenyl)ethanol [(*S*)-139g] (with 134 as catalytic source):

This compound was prepared *via* the asymmetric reduction of 4-nitrophenacyl bromide (**138g**) with $BH_3.SMe_2$ using (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-**

139a (Page no. 155).



(*S*)-139g

Yield: 84%

Mp: 90 ^{o}C [Lit.[111] 78-80 ^{o}C]

$[\alpha]_D^{25}$: +29.9 (*c* 0.8, $CHCl_3$)

{Lit.[110] $[\alpha]_D^{25}$: +32.0 (*c* 1.0, $CHCl_3$), (*S*)-configuration, 91% *ee*}

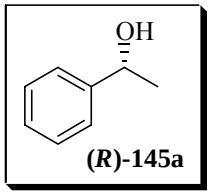
Enantiomeric purity: 86% [determined by HPLC analysis of the corresponding acetate **(*S*)-140** using chiral column, Chiralcel OD-H, with reference to racemic acetate **(±)-140**]

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 [**(*S*)-140**] using chiral column, Chiralcel OD-H. The racemic 1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane [**(±)-140**] showed two peaks in equal intensity (retention times: 10.52 min and 11.93 min) corresponding to (*R*) and (*S*) enantiomers [solvent system: hexanes:IPA (90:10), flow rate: 1 mL/min]. Chiral acetate **(*S*)-140**, on similar HPLC analysis, showed two peaks at 10.46 min (*R*) and 11.83 min (*S*) in the ratio of 7:93 indicating that the enantiomeric purity of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol [**(*S*)-139g**] is 86%.

(*R*)-1-Phenylethanol [**(*R*)-145a**] **(with 134 as catalytic source):**

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (Page no. 155) *via* borane-mediated asymmetric reduction of acetophenone (**144a**) under the catalytic influence of (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%).



(*R*)-145a

Yield: 79%

$[\alpha]_D^{25}$: +35.2 (*c* 0.9, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

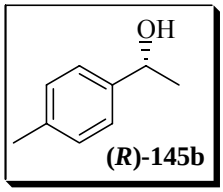
Enantiomeric purity: 76% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]

Determination of enantiomeric purity:

HPLC analysis of (±)-1-phenylethanol [**(±)-145a**] showed two peaks with equal intensity [chiral column: Chiralcel OD-H, solvent system: hexanes:IPA (95:5), flow rate: 1 mL/min] with 8.43 min and 9.89 min retention times [corresponding to (*R*) and (*S*) enantiomers]. Similar HPLC analysis of chiral alcohol **(*R*)-145a** showed two peaks at 8.40 min (*R*) and 9.88 min (*S*) in the ratio of 88:12 indicating that the enantioselectivity of this reaction is 76%.

(*R*)-1-(4-Methylphenyl)ethanol [(*R*)-145b] (with 134 as catalytic source):

This compound was prepared *via* the asymmetric reduction of 4-methylacetophenone (**144b**) with $BH_3.SMe_2$ in the presence of 2 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



Yield: 79%

$[\alpha]_D^{25}$: +33.1 (*c* 0.7, MeOH)

{Lit.[139] $[\alpha]_D^{26}$: -43.5 (*c* 0.99, MeOH), (*S*)-configuration, >99% *ee*}

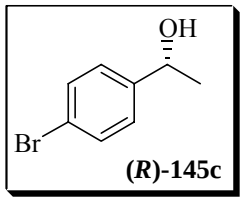
Enantiomeric purity: 74% [determined by HPLC analysis using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145b**]

Determination of enantiomeric purity:

(±)-1-(4-Methylphenyl)ethanol [**(±)-145b**] showed two peaks in 1:1 ratio [retention times: 13.33 min (*S*) and 15.14 min (*R*)] on HPLC analysis using chiral column Chiralcel OJ-H [solvent system: hexanes:IPA (95:5), flow rate: 0.8 mL/min]. In the case of chiral 1-(4-methylphenyl)ethanol [**(*R*)-145b**], we have observed two peaks (on similar HPLC analysis) at 13.33 min and 14.86 min in 13:87 ratio corresponding to (*S*) and (*R*) enantiomers indicating that the enantiomeric purity of (*R*)-1-(4-methylphenyl)-ethanol [**(*R*)-145b**] is 74%.

(*R*)-1-(4-Bromophenyl)ethanol [(*R*)-145c] (with 134 as catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of 4-bromoacetophenone (**144c**) with $BH_3.SMe_2$ in the presence of 2 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



(*R*)-145c

Yield: 87%

$[\alpha]_D^{25}$: +30.6 (*c* 1.0, $CHCl_3$)

{Lit.[139] $[\alpha]_D^{25}$: -37.9 (*c* 1.13, $CHCl_3$), (*S*)-configuration, >99% *ee*}

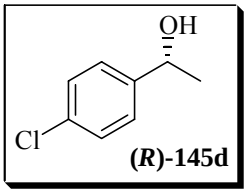
Enantiomeric purity: 78% [determined by HPLC analysis of alcohol using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145c**]

Determination of enantiomeric purity:

HPLC analysis of racemic alcohol **(±)-145c** showed two peaks in equal intensity [chiral column: Chiralcel OJ-H, solvent system: hexanes:IPA (95:5), flow rate: 0.8 mL/min] with 14.85 min and 16.20 min retention times [arising due to (*S*) and (*R*) enantiomers]. Similar HPLC analysis of (*R*)-1-(4-bromophenyl)ethanol [**(*R*)-145c**] showed two peaks at 14.96 min (*S*) and 16.25 min (*R*) in the ratio of 11:89 indicating that the enantioselectivity of this reaction is 78%.

(*R*)-1-(4-Chlorophenyl)ethanol [(*R*)-145d] (with 134 as catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of 4-chloroacetophenone (**144d**) with (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%), as a chiral catalytic source following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



Yield: 78%

$[\alpha]_D^{25}$: +37.5 (*c* 0.7, Et_2O)

{Lit.[139] $[\alpha]_D^{25}$: -49.0 (*c* 1.84, Et_2O), (*S*)-configuration, >99% *ee*}

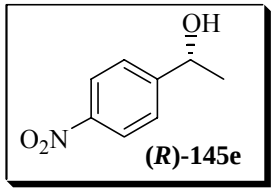
Enantiomeric purity: 77% [determined by HPLC analysis of its alcohol using chiral column, Chiralcel OJ-H, with reference to racemic alcohol **(±)-145d**]

Determination of enantiomeric purity:

HPLC analysis (using chiral column, Chiralcel OJ-H) of (±)-1-(4-chlorophenyl)ethanol [**(±)-145d**] showed two peaks in 1:1 ratio [solvent system: hexanes:IPA (95:5), flow rate: 0.8 mL/min] at 12.58 min (*S*) and 13.60 min (*R*). Chiral alcohol **(*R*)-145d**, on similar HPLC analysis, showed two peaks at 12.17 min and 13.05 min in 11.5:88.5 ratio corresponding to (*S*) and (*R*) enantiomers indicating that the reduction is 77% selective.

(*R*)-1-(4-Nitrophenyl)ethanol [(*R*)-145e] (with 134 as catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of 4-nitroacetophenone (**144e**) with $BH_3.SMe_2$ in the presence of 2 mol% (2*S*)-2-anilinomethylpyrrolidine (**134**) following the similar procedure described for the molecule **(*S*)-139a** (Page no. 155).



(*R*)-145e

Yield: 83%

$[\alpha]_D^{25}$: +22.2 (*c* 0.5, EtOH)

{Lit.[140] $[\alpha]_D^{24.5}$: -29.7 (*c* 1.0, EtOH), (*S*)-configuration, >99% *ee*}

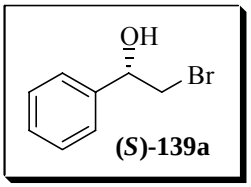
Enantiomeric purity: 78% [determined by HPLC analysis of the corresponding acetate **(*R*)-146** using chiral column, Chiralcel OD-H]

Determination of enantiomeric purity:

The enantiomeric purity was determined by HPLC analysis of the corresponding acetate *i.e.* 1-acetoxy-1-(4-nitrophenyl)ethane [**(*R*)-146**] using chiral column, Chiralcel OD-H. The racemic acetate **(±)-146** showed two peaks at 21.67 min and 23.63 min in 1:1 ratio corresponding to (*S*) and (*R*) enantiomers [solvent system: 2% IPA in hexanes, flow rate: 0.5 mL/min]. Chiral 1-acetoxy-1-(4-nitrophenyl)ethane, [**(*R*)-146**], on similar HPLC analysis, showed two peaks at 21.39 min (*S*) and 23.21 min (*R*) in the ratio of 11:89 indicating that the reduction is 78% selective.

Reduction of phenacyl bromide (138a) at room temperature using the chiral catalytic species 148 (generated *in situ via* the reaction of 134 with $BH_3.SMe_2$ at 110 ^oC):

Borane-mediated asymmetric reduction of phenacyl bromide (**138a**) at room temperature using the chiral catalytic species **148**, generated *in situ via* the reaction of (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%) with $BH_3.SMe_2$ at 110 ^oC, was carried out following the similar procedure described for the molecule **(*S*)-139a** using the catalytic species **141** (Page no. 132).



(*S*)-139a

Time: 6 h

Yield: 80%

Enantiomeric purity: 33% [determined by HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

Determination of enantiomeric purity:

Enantiomeric purity of the (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is determined by HPLC analysis using chiral column, Chiralcel OD-H. (±)-2-Bromo-1-phenylethanol [**(±)-139a**] showed two peaks [flow rate: 1 mL/min, solvent system: hexanes:IPA (90:10)] in equal intensities [retention times: 7.69 min (*S*) and 8.13 min (*R*)], while chiral alcohol **(*S*)-139a** showed two peaks at 7.70 min (*S*) and 8.16 min (*R*) (on similar

HPLC analysis) in the ratio of 66.5:33.5, indicating that (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] is 33% enantiomerically pure.

***In situ* recyclability of the catalytic species 148 [generated *in situ* at 110 ^{o}C *via* the reaction of (2*S*)-2-anilinomethylpyrrolidine (134) with $BH_3.SMe_2$]: (*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:**

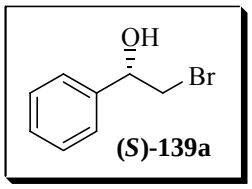
In situ recyclable potential of the catalytic species **148** [generated *in situ* at 110 ^{o}C *via* the reaction of (2*S*)-2-anilinomethylpyrrolidine (**134**) (2 mol%) with $BH_3.SMe_2$] has been examined for four times *via* the borane-mediated asymmetric reduction of phenacyl bromide (**138a**) following the similar procedure described for *in situ* recyclability of **141** (generated *in situ* at 110 ^{o}C *via* the reaction of **135** with $BH_3.SMe_2$) as chiral catalytic source in the reduction of phenacyl bromide (**138a**) (Page nos. 133-137).

Run 1: 91% *ee*

Run 2: 89% *ee*

Run 3: 88% *ee*

Run 4: 88% *ee*



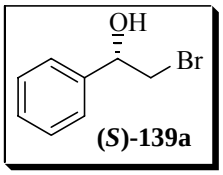
(*S*)-139a

Enantiomeric purity of (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**], for each run, is determined by HPLC analysis using chiral column Chiralcel OD-H as mentioned in page no. 167.

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (137):

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

To a stirred mixture of (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine **(137)** (10.2 mg, 0.05 mM) in toluene (5 mL) was added $BH_3.SMe_2$ (1.4 mL, 1 M solution in toluene, 1.4 mM) at room temperature. Then the reaction mixture was heated under reflux for 15 min. A solution of phenacyl bromide (**138a**) (199 mg, 1 mM) in toluene (2 mL) was added slowly drop-wise and heating was continued under reflux for further 15 min. The reaction mixture was then cooled to room temperature and quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [**(*S*)-139a**] as a colorless oil.



(*S*)-139a

Yield: 86% (173 mg)

$[\alpha]_D^{25}$: +39.2 (*c*1.4, $CHCl_3$)

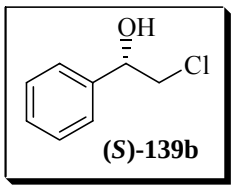
{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), *R*-configuration, 93% *ee*}

Enantiomeric purity: 91% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a** as mentioned in page no. 156].

Spectral data (IR, ^{1}H & ^{13}C NMR) of the chiral alcohols (S)-139a,b & (R)-145a obtained via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b & 144a in the presence of various diamides (137, 149-156) are in full agreement with the spectral data of the chiral alcohols (S)-139a,b & (R)-145a (IR, ^{1}H & ^{13}C NMR) prepared via the borane-mediated asymmetric reduction of the corresponding prochiral ketones 138a,b & 144a in the presence of (5S)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane (135) and (5S)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane (142). Therefore we have not mentioned the spectral data again for any of these alcohols.

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 137 as chiral catalytic source):

This compound was prepared *via* the asymmetric reduction of phenacyl chloride (**138b**) with BH_3**.**SMe_2 using (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) (5 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** (Page no. 169).



(*S*)-139b

Yield: 83%

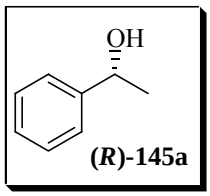
$[\alpha]_D^{25}$: +43.8 (*c* 1.5, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 88% [determined following the similar HPLC analysis as mentioned in page no. 157 using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 137 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of acetophenone (**144a**) with BH_3.SMe_2 in the presence of 5 mol% (2*S*)-5-oxo-2-anilinocarbonylpyrrolidine (**137**) following the similar procedure described for the molecule **(*S*)-139a** (Page no.169).



(*R*)-145a

Yield: 76%

$[\alpha]_D^{25}$: +35.4 (*c* 1.3, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

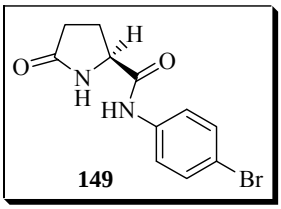
Enantiomeric purity: 82% [determined following the similar HPLC analysis, as mentioned in page no. 162, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]

Synthesis of (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (149):[μ]

Representative procedure[λ]

To a stirred mixture of (*S*)-pyroglutamic acid (**157**) (0.6455 g, 5 mM) in THF (10 mL), was added a solution of Et_3N (0.7 mL, 5 mM) in THF (5 mL) at -15 ^oC. After stirring for 15 min, a solution of ethyl chloroformate (0.53 mL, 5.5 mM) in THF (5 mL) was

added slowly at -15 °C and the reaction mixture was stirred for 15 min. A solution of 4-bromoaniline (0.86 g, 5 mM) in THF (5 mL) was then added at the same temperature to the above reaction mixture and stirred at 0 °C for 1 h followed by 14 h at room temperature. The solvent was removed under reduced pressure and the residue, thus obtained, was diluted with EtOAc (150 mL) and saturated aqueous $NaHCO_3$ solution (30 mL). Organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (3X30 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue, thus obtained was purified by column chromatography (silica gel, EtOAc) to provide the desired (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (**149**) as a white solid (0.75 g) in 53% yield.



149

Mp: 212-214 °C (Lit.[146] 225-227 °C)

$[\alpha]_D^{25}$: +13.0 (*c* 1.09, MeOH)

IR (KBr): ν 3500-3000 (multiple bands), 1693, 1668 cm^{-1}

^1H NMR (400 MHz) : δ 2.06-2.49 (m, 4H), 4.21-4.30 (m, 1H), 7.39 (d, 2H, *J* = 8.8 Hz), 7.59 (d, 2H, *J* = 8.8 Hz), 7.84 (s, 1H), 9.95 (s, 1H)

($CDCl_3$:DMSO-d_6 = 4:1)

[λ]The chiral diamides **149-156** were synthesized following a similar literature procedure for the preparation of 1-(*tert*-butoxycarbonyl)indoline-2-carboxamides with some modification.[142]

[μ]The compound **149** was known and the spectral data were reported.[146] Our spectral data are in agreement with the reported data.

^{13}C NMR (50 MHz) : δ 24.51, 28.70, 56.31, 115.25, 120.78, 130.65, 136.94, 170.24, 177.47

($CDCl_3$:DMSO-d_6 = 4:1)

LC MS (m/z) : 283 $(M+H)^+$, 285 $(M+2+H)^+$

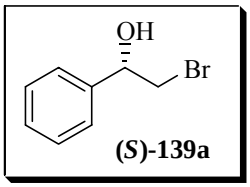
Anal. calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89

Found : C, 46.68; H, 3.92; N, 9.98.

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (149)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was prepared *via* the asymmetric reduction of phenacyl bromide (**138a**) with BH_3**.**SMe_2 using (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (**149**) (5 mol%), as a chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139a

Yield: 87%

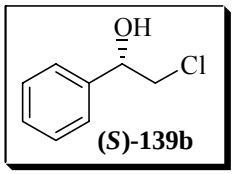
$[\alpha]_D^{25}$: +39.1 (*c* 1.4, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 90% [determined following the similar HPLC analysis, as mentioned in page no. 156, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 149 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of phenacyl chloride (**138b**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (**149**) following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139b

Yield: 82%

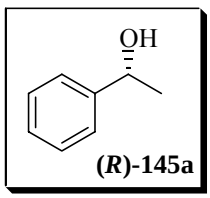
$[\alpha]_D^{25}$: +42.0 (*c* 1.7, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 87% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b** as mentioned in page no. 157]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 149 as chiral catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of acetophenone **(144a)** with 5 mol% (2*S*)-5-oxo-2-(4-bromoanilino)carbonylpyrrolidine (**149**), as a chiral catalytic source following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*R*)-145a

Yield: 74%

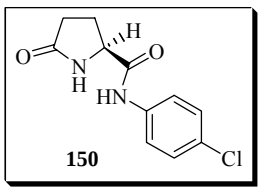
$[\alpha]_D^{25}$: +35.6 (*c* 1.4, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 81% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a** as mentioned in page no. 162]

(2*S*)-5-Oxo-2-(4-chloroanilino)carbonylpyrrolidine (150):

This product was obtained as a white solid *via* the successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 4-chloroaniline (in the presence of triethyl amine) following the similar procedure described for **149** (Page nos. 171 & 172).



150

Time[φ]: 14 h

Yield: 50%

Mp: 194-196 °C

$[\alpha]_D^{25}$: +14.1 (*c* 1.04, MeOH)

IR (KBr): ν 3400-3000 (multiple bands), 1701, 1660 cm^{-1}

^{1}H NMR (400 MHz): δ 2.08-2.49 (m, 4H), 4.23-4.34 (m, 1H), 7.25 (d, 2H, *J* = 8.6 Hz), ($CDCl_3$:DMSO-d_6 = 4:1) 7.64 (d, 2H, *J* = 8.6 Hz), 7.84 (s, 1H), 9.93 (s, 1H)

^{13}C NMR (50 MHz) : δ 24.24, 28.37, 55.93, 120.12, 127.06, 127.37, 136.28, 170.00, ($CDCl_3$:DMSO-d_6 = 4:1) 177.00

LC MS (m/z) : 239 $(M+H)^+$, 241 $(M+2+H)^+$

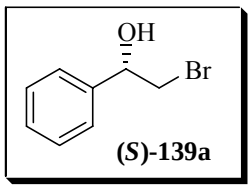
Anal. calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74

Found : C, 55.17; H, 4.64; N, 11.76

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(4-chloroanilino)carbonylpyrrolidine (150)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of phenacyl bromide (**138a**) with BH_3**.**SMe_2 in the presence of 5 mol% (2*S*)-5-oxo-2-(4-chloroanilino)carbonylpyrrolidine (**150**) following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139a

Yield: 86%

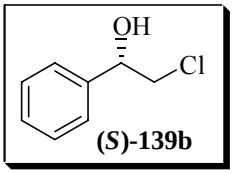
$[\alpha]_D^{25}$: +38.8 (*c* 1.3, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 91% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a** as mentioned in page no. 156]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 150 as chiral catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of phenacyl chloride (**138b**) using (2*S*)-5-oxo-2-(4-chloroanilino)carbonylpyrrolidine (**150**) (5 mol%), as a chiral catalytic source following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139b

Yield: 84%

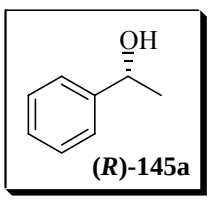
$[\alpha]_D^{25}$: +43.4 (*c* 1.1, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 89% [determined following the similar HPLC analysis, as mentioned in page no. 157, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 150 as chiral catalytic source):

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (with the chiral catalytic source **137**) (Page no. 169) *via* borane-mediated asymmetric reduction of acetophenone (**144a**) under the catalytic influence of (2*S*)-5-oxo-2-(4-chloroanilino)carbonylpyrrolidine (**150**) (5 mol%).



(*R*)-145a

Yield: 72%

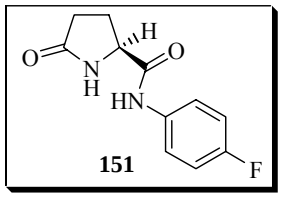
$[\alpha]_D^{25}$: +36.6 (*c* 1.3, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 83% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a** as mentioned in page no. 162]

(2*S*)-5-Oxo-2-(4-fluoroanilino)carbonylpyrrolidine (151):

This compound was prepared *via* the successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 4-fluoroaniline (in the presence of triethyl amine) following the similar procedure described for **149** (Page nos. 171 & 172).



151

Time[φ]: 24 h

Yield: 45%

Mp: 178-180 °C

$[\alpha]_D^{25}$: +14.0 (*c*1.08, MeOH)

IR (KBr): ν 3450-3150 (multiple bands), 1693, 1666 cm^{-1}

^{1}H NMR (400 MHz): δ 2.18-2.52 (m, 4H), 4.22-4.34 (m, 1H), 6.93-7.04 (m, 2H), 7.55-7.71 (m, 3H), 9.65 (s, 1H)
($CDCl_3$:DMSO-d_6 = 4:1)

^{13}C NMR (100 MHz): δ 24.63, 28.80, 56.37, 114.40 (d, *J* = 21.8 Hz), 120.86 (d, *J* = 8.0 Hz), 133.82 (d, *J* = 2.9 Hz), 158.09 (d, *J* = 241.5 Hz), 170.11, 177.65
($CDCl_3$:DMSO-d_6 = 4:1)

LC MS (m/z) : 223 $(M+H)^+$

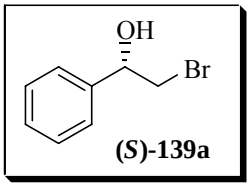
Anal. calcd. for $C_{11}H_{11}FN_2O_2$: C, 59.45; H, 4.99; N, 12.61

Found : C, 59.52; H, 5.01; N, 12.52

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(4-fluoroanilino)carbonylpyrrolidine (151)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (with the chiral catalytic source **137**) (Page no. 169) *via* borane-mediated asymmetric reduction of phenacyl bromide (**138a**) under the catalytic influence of (2*S*)-5-oxo-2-(4-fluoroanilino)carbonylpyrrolidine (**151**) (5 mol%).



(*S*)-139a

Yield: 82%

$[\alpha]_D^{25}$: +39.3 (*c* 1.7, $CHCl_3$)

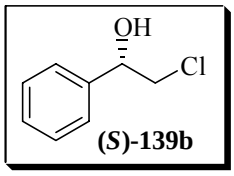
{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 90% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a** as mentioned in page no. 156]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 151 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of

phenacyl chloride (**138b**) with BH_3**.**SMe_2 in the presence of 5 mol% (2*S*)-5-oxo-2-(4-fluoroanilino)carbonylpyrrolidine (**151**) following the similar procedure described for the molecule **(*S*)-139a** using the chiral catalytic source **137** (Page no. 169).



(*S*)-139b

Yield: 80%

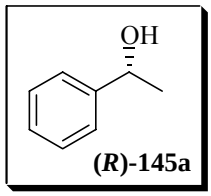
$[\alpha]_D^{25}$: +44.0 (*c* 1.3, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 88% [determined following the similar HPLC analysis, as mentioned in page no. 157, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 151 as chiral catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of acetophenone (**144a**) with 5 mol% (2*S*)-5-oxo-2-(4-fluoroanilino)carbonylpyrrolidine (**151**), as chiral source following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*R*)-145a

Yield: 74%

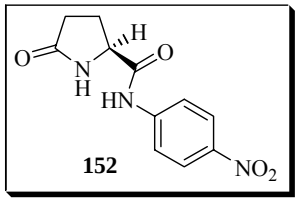
$[\alpha]_D^{25}$: +34.5 (*c* 1.5, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 79% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a** as mentioned in page no. 162]

(2*S*)-5-Oxo-2-(4-nitroanilino)carbonylpyrrolidine (152):

This diamide was synthesized *via* the successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 4-nitroaniline in the presence of triethyl amine following the similar procedure described for **149** (Page nos. 171 & 172).



152

Time[φ]: 24 h

Yield: 38%

Mp: 214-216 ^{o}C

$[\alpha]_D^{25}$: + 21.0 (*c* 0.60, MeOH)

IR (KBr): ν 3400-3000 (multiple bands), 1707, 1682 cm^{-1}

^{1}H NMR (400 MHz): δ 2.16-2.54 (m, 4H), 4.31-4.37 (m, 1H), 7.79 (s, 1H), 7.88 (d, (CDCl$_3$:DMSO-d_6 = 4:1) 2H, *J* = 9.2 Hz), 8.15 (d, 2H, *J* = 9.2 Hz), 10.37 (s, 1H)

^{13}C NMR (50 MHz) : δ 24.34, 28.43, 56.11, 118.27, 123.55, 141.83, 143.83, 170.88, (CDCl$_3$:DMSO-d_6 = 4:1) 177.22

LC MS (m/z) : 248 $(M-H)^+$

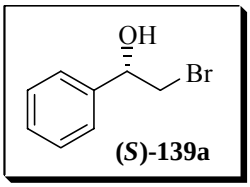
Anal. calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86

Found : C, 53.15; H, 4.44; N, 16.80.

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(4-nitroanilino)carbonylpyrrolidine (152)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was prepared *via* the asymmetric reduction of phenacyl bromide (**138a**) with BH_3**.**SMe_2 using (2*S*)-5-oxo-2-(4-nitroanilino)carbonylpyrrolidine (**152**) (5 mol%), as chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** under the catalytic influence of **137** (Page no. 169).



(*S*)-139a

Yield: 88%

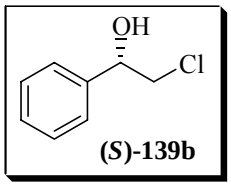
$[\alpha]_D^{25}$: +38.0 (*c* 1.4, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 88% [determined following the similar HPLC analysis, as mentioned in page no. 156, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 152 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of phenacyl chloride (**138b**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*)-5-oxo-2-(4-nitroanilino)carbonylpyrrolidine (**152**) following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139b

Yield: 85%

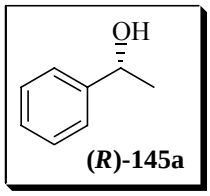
$[\alpha]_D^{25}$: +42.2 (*c* 1.4, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 86% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b** as mentioned in page no. 157]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 152 as the chiral catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of acetophenone (**144a**) with 5 mol% (2*S*)-5-oxo-2-(4-nitroanilino)carbonylpyrrolidine (**152**), as chiral source following the similar procedure described for the molecule **(*S*)-139a** using the chiral catalytic source **137** (Page no. 169).



(*R*)-145a

Yield: 76%

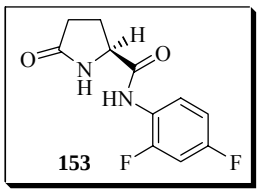
$[\alpha]_D^{25}$: +33.5 (*c* 1.4, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 77% [determined by the similar HPLC analysis, as mentioned in page no. 162, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]

(2*S*)-5-Oxo-2-(2,4-difluoroanilino)carbonylpyrrolidine (153):

Successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 2,4-difluoroaniline in the presence of triethyl amine following the similar procedure described for **149** (Page nos. 171 & 172) provided (2*S*)-5-oxo-2-(2,4-difluoroanilino)-carbonylpyrrolidine (**153**) as a white solid.



153

Time[φ]: 24 h

Yield: 44%

Mp: 138-140 ^{o}C

$[\alpha]_D^{25}$: +12.9 (*c*1.02, MeOH)

IR (KBr): ν 3450-3100 (multiple bands), 1695, 1655 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.18-2.55 (m, 4H), 4.34-4.43 (m, 1H), 6.82-6.96 (m, 2H), 7.72 ($CDCl_3$:DMSO-d_6 = 4:1) (s, 1H), 7.89-8.00 (m, 1H), 9.36 (s, 1H)

^{13}C NMR (100 MHz) : δ 24.19, 28.11, 55.14, 102.48 (dd, *J* = 24.0 and 25.8 Hz), ($CDCl_3$:DMSO-d_6 = 4:1) 109.54 (dd, *J* = 3.6 and 21.1 Hz), 120.93 (dd, *J* = 3.2 and 11.3 Hz), 124.02 (dd, *J* = 2.2 and 9.0 Hz), 152.80 (dd, *J* = 12.4 and 247.3 Hz), 157.57 (dd, *J* = 10.9 and 244.0 Hz), 170.35, 176.84

LC MS (m/z) : 239 $(M-H)^+$

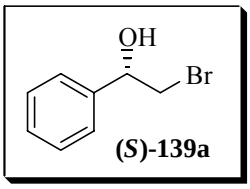
Anal. calcd. for $C_{11}H_{10}F_2N_2O_2$: C, 55.00; H, 4.20; N, 11.66

Found : C, 55.06; H, 4.21; N, 11.73

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(2,4-difluoroanilino)carbonylpyrrolidine (153)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of phenacyl bromide (**138a**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*)-5-oxo-2-(2,4-difluoroanilino)carbonylpyrrolidine (**153**) following the similar procedure described for the molecule **(*S*)-139a** using the chiral catalytic source **137** (Page no. 169).



(*S*)-139a

Yield: 83%

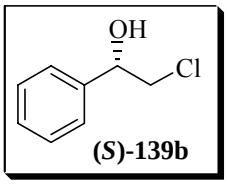
$[\alpha]_D^{25}$: +38.9 (*c* 1.2, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 89% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a** as mentioned in page no. 156]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 153 as chiral catalytic source):

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (with the chiral catalytic source **137**) (Page no. 169) *via* borane-mediated asymmetric reduction of phenacyl chloride (**138b**) under the catalytic influence of 5 mol% (2*S*)-5-oxo-2-(2,4-difluroanilino)carbonylpyrrolidine (**153**).



Yield: 82%

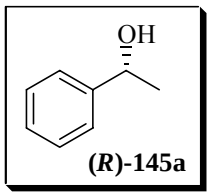
$[\alpha]_D^{25}$: +42.7 (*c* 1.5, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 87% [determined following the similar HPLC analysis, as mentioned in page no. 157, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 153 as chiral catalytic source):

This compound was prepared *via* the asymmetric reduction of acetophenone (**144a**) with $BH_3.SMe_2$ using (2*S*)-5-oxo-2-(2,4-difluoroanilino)carbonylpyrrolidine (**153**) (5 mol%), as chiral catalytic source, following the similar procedure described for the molecule **(*S*)-139a** using the chiral catalytic source **137** (Page no. 169).



Yield: 74%

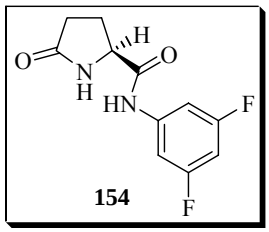
$[\alpha]_D^{25}$: +33.9 (*c* 1.7, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 78% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a** as mentioned in page no. 162]

(2*S*)-5-Oxo-2-(3,5-difluoroanilino)carbonylpyrrolidine (154):

This compound was obtained as a white solid *via* the successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 3,5-difluoroaniline in the presence of triethyl amine following the similar procedure described for **149** (Page nos.171 & 172).



154

Time[φ]: 24 h

Yield: 35%

Mp: 198-200 ^{o}C

$[\alpha]_D^{25}$: +13.4 (*c* 1.08, MeOH)

IR (KBr): ν 3400-3170 (multiple bands), 1697, 1676 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.16-2.53 (m, 4H), 4.23-4.32 (m, 1H), 6.49-6.59 (m, 1H), 7.27-
($CDCl_3$:DMSO-d_6 = 4:1) 7.37 (m, 2H), 7.65 (s, 1H), 10.00 (s, 1H)

^{13}C NMR (100 MHz): δ 24.40, 28.54, 56.18, 97.72 (t, *J* = 25.5 Hz), 101.73 (dd, *J* =
($CDCl_3$:DMSO-d_6 = 4:1) 8.7 and 20.7 Hz), 140.09 (t, *J* = 13.1 Hz), 161.81 (dd, *J* = 14.5
and 243.7 Hz), 170.60, 177.29

LC MS (m/z) : 241 $(M+H)^+$

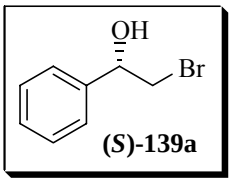
Anal. calcd. for $C_{11}H_{10}F_2N_2O_2$: C, 55.00; H, 4.20; N, 11.66

Found : C, 55.03; H, 4.18; N, 11.76

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(3,5-difluoroanilino)carbonylpyrrolidine (154)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (using the chiral catalytic source **137**) (Page no. 169) *via* borane-mediated asymmetric reduction of phenacyl bromide (**138a**) under the catalytic influence of (2*S*)-5-oxo-2-(3,5-difluoroanilino)carbonylpyrrolidine (**154**) (5 mol%).



(*S*)-139a

Yield: 84%

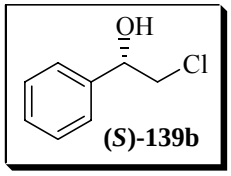
$[\alpha]_D^{25}$: +38.1 (*c* 1.1, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 88% [determined following the similar HPLC analysis, as mentioned in page no. 156, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 154 as chiral catalytic source):

This compound was synthesized *via* the borane-mediated asymmetric reduction of phenacyl chloride (**138b**) with 5 mol% (2*S*)-5-oxo-2-(3,5-difluroanilino)carbonyl-pyrrolidine (**154**), as a chiral source following the similar procedure described for the molecule **(*S*)-139a** under the catalytic influence of **137** (Page no. 169).



Yield: 83%

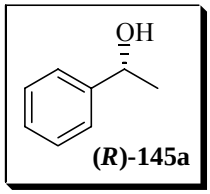
$[\alpha]_D^{25}$: +43.2 (*c* 1.7, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 87% [determined following the similar HPLC analysis, as mentioned in page no. 157, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 154 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of acetophenone (**144a**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*)-5-oxo-2-(3,5-difluoroanilino)carbonylpyrrolidine (**154**) following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



Yield: 75%

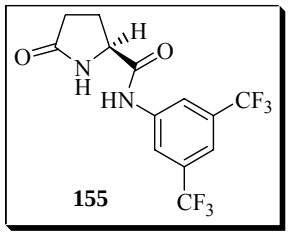
$[\alpha]_D^{25}$: +35.9 (*c* 1.1, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 82% [determined following the similar HPLC analysis, as mentioned in page no. 162, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]

(2*S*)-5-Oxo-2-[3,5-bis(trifluoromethyl)anilino]carbonylpyrrolidine (155):

This compound was prepared *via* the successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 3,5-bis(trifluoromethyl)aniline (in the presence of triethyl amine) following the similar procedure described for **149** (Page nos. 171 & 172).



155

Time[φ]: 24 h

Yield: 45%

Mp: 182-184 ^{o}C

$[\alpha]_D^{25}$: +4.9 (*c* 2.09, MeOH)

IR (KBr): ν 3400-3000 (multiple bands), 1716, 1674 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.20-2.61 (m, 4H), 4.27-4.33 (m, 1H), 7.54 (s, 1H), 7.61 (s,

($CDCl_3$:DMSO-d_6 = 4:1) 1H), 8.27 (s, 2H), 10.26 (s, 1H)

^{13}C NMR (100 MHz): δ 24.67, 28.73, 56.58, 115.85 (sept, *J* = 3.6 Hz), 118.87

($CDCl_3$:DMSO-d_6 = 4:1) (unresolved quartet), 122.49 (q, *J* = 270.6 Hz), 130.89 (q, *J* =

32.7 Hz), 139.64, 171.20, 177.65

LC MS (m/z) : 341 $(M+H)^+$

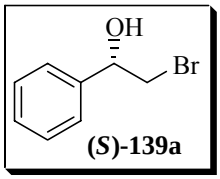
Anal. calcd. for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; N, 8.23

Found : C, 45.71; H, 2.98; N, 8.22

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-[3,5-bis(trifluoromethyl)anilino]carbonylpyrrolidine (155)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was synthesized *via* the borane-mediated asymmetric reduction of phenacyl bromide (**138a**) with (2*S*)-5-oxo-2-[3,5-bis(trifluoromethyl)anilino]carbonyl-pyrrolidine (**155**), as chiral catalytic source following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139a

Yield: 83%

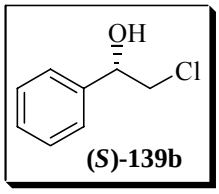
$[\alpha]_D^{25}$: +39.1 (*c* 1.4, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 90% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a** as mentioned in page no. 156]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 155 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of phenacyl chloride (**138b**) with BH_3**.**SMe_2 in the presence of 5 mol% (2*S*)-5-oxo-2-[3,5-bis(trifluoromethyl)anilino]carbonylpyrrolidine (**155**) following the similar procedure described for the molecule **(*S*)-139a** with the chiral catalytic source **137** (Page no. 169).



(*S*)-139b

Yield: 87%

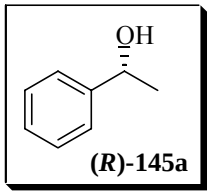
$[\alpha]_D^{25}$: +43.8 (*c* 1.3, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 89% [determined following the similar HPLC analysis, as mentioned in page no. 157, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b**]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 155 as chiral catalytic source):

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (with the chiral catalytic source **137)** (Page no. 169) *via* borane-mediated asymmetric reduction of acetophenone (**144a**) under the influence of 5 mol% (2*S*)-5-oxo-2-[3,5-bis(trifluoromethyl)anilino]carbonylpyrrolidine (**155**).



(*R*)-145a

Yield: 73%

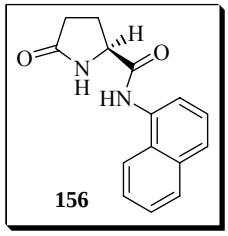
$[\alpha]_D^{25}$: +36.1 (*c* 1.3, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

Enantiomeric purity: 81% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a** as mentioned in page no. 162]

(2*S*)-5-Oxo-2-(1-naphthylamino)carbonylpyrrolidine (156):

Successive treatment of (*S*)-pyroglutamic acid (**157**) with ethyl chloroformate and 1-naphthylamine in the presence of triethyl amine following the similar procedure described for **149** (Page nos. 171 & 172) provided (2*S*)-5-oxo-2-(1-naphthylamino)-carbonylpyrrolidine (**156**) as a white solid.



156

Time[φ]: 24 h

Yield: 36%

Mp: 198-200 °C

$[\alpha]_D^{25}$: +15.0 (*c* 1.09, MeOH)

IR (KBr): ν 3400-3150 (multiple bands), 1722, 1670 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.21-2.61 (m, 4H), 4.42-4.54 (m, 1H), 7.42-7.55 (m, 3H), 7.71 ($CDCl_3$:DMSO-d_6 = 4:1) (d, 2H, *J* = 7.8 Hz), 7.83-7.92 (m, 2H), 8.01-8.07 (m, 1H), 9.75 (s, 1H)

^{13}C NMR (50 MHz) : δ 24.65, 28.70, 56.04, 121.00, 121.44, 124.52, 124.93, 125.05, ($CDCl_3$:DMSO-d_6 = 4:1) 127.28, 131.82, 133.03, 170.85, 177.33

LC MS (m/z) : 253 $(M-H)^+$

Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02

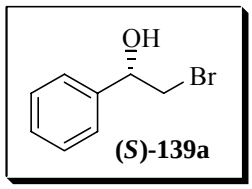
Found : C, 70.66; H, 5.55; N, 11.05

[φ]This refers to the time of stirring at room temperature (after the addition of amine and stirring 1 h at 0 °C).

Asymmetric reduction of prochiral ketones in the presence of 5 mol% (2*S*)-5-oxo-2-(1-naphthylamino)carbonylpyrrolidine (156)

(*S*)-2-Bromo-1-phenylethanol [(*S*)-139a]:

This compound was synthesized *via* the borane-mediated asymmetric reduction of phenacyl bromide (**138a**) with 5 mol% (2*S*)-5-oxo-2-(1-naphthylamino)carbonyl-pyrrolidine **(156)**, as a chiral source following the similar procedure described for the molecule **(*S*)-139a** under the influence of chiral catalytic source **137** (Page no. 169).



(*S*)-139a

Yield: 84%

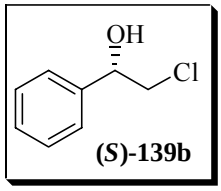
$[\alpha]_D^{25}$: +29.7 (*c* 1.1, $CHCl_3$)

{Lit.[133] $[\alpha]_D^{25}$: -39.0 (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% *ee*}

Enantiomeric purity: 68% [determined following the similar HPLC analysis, as mentioned in page no. 156, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139a**]

(*S*)-2-Chloro-1-phenylethanol [(*S*)-139b] (using 156 as chiral catalytic source):

This compound was prepared (as a colorless oil) following the procedure described for the molecule **(*S*)-139a** (with the chiral catalytic source **137**) (Page no. 169) *via* borane-mediated asymmetric reduction of phenacyl chloride (**138b**) under the catalytic influence of 5 mol% (2*S*)-5-oxo-2-(1-naphthylamino)carbonylpyrrolidine (**156**).



(*S*)-139b

Yield: 81%

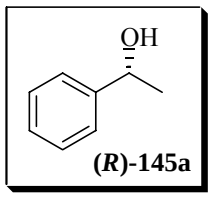
$[\alpha]_D^{25}$: +34.1 (*c* 1.5, cyclohexane)

{Lit.[133] $[\alpha]_D^{25}$: -48.1 (*c* 1.73, cyclohexane), (*R*)-configuration, 100% *ee*}

Enantiomeric purity: 67% [determined following the similar HPLC analysis using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-139b** as mentioned in page no. 157]

(*R*)-1-Phenylethanol [(*R*)-145a] (using 156 as chiral catalytic source):

This secondary alcohol was obtained as a colorless oil *via* the asymmetric reduction of acetophenone (**144a**) with $BH_3.SMe_2$ in the presence of 5 mol% (2*S*)-5-oxo-2-(1-naphthylamino)carbonylpyrrolidine (**156**) following the similar procedure described for the molecule **(*S*)-139a** using the chiral catalytic source **137** (Page no. 169).



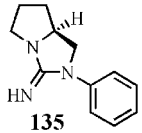
(*R*)-145a

Yield: 77%

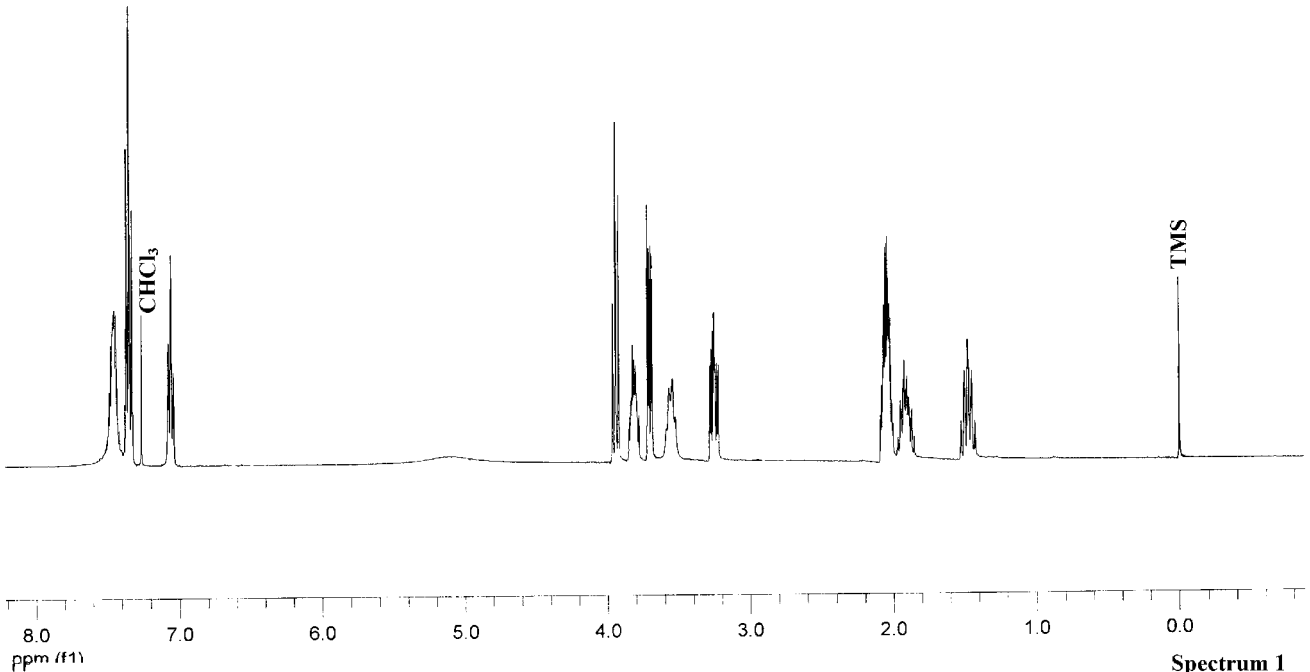
$[\alpha]_D^{25}$: +22.8 (*c* 0.8, MeOH)

{Lit.[138] $[\alpha]_D^{25}$: +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% *ee*}

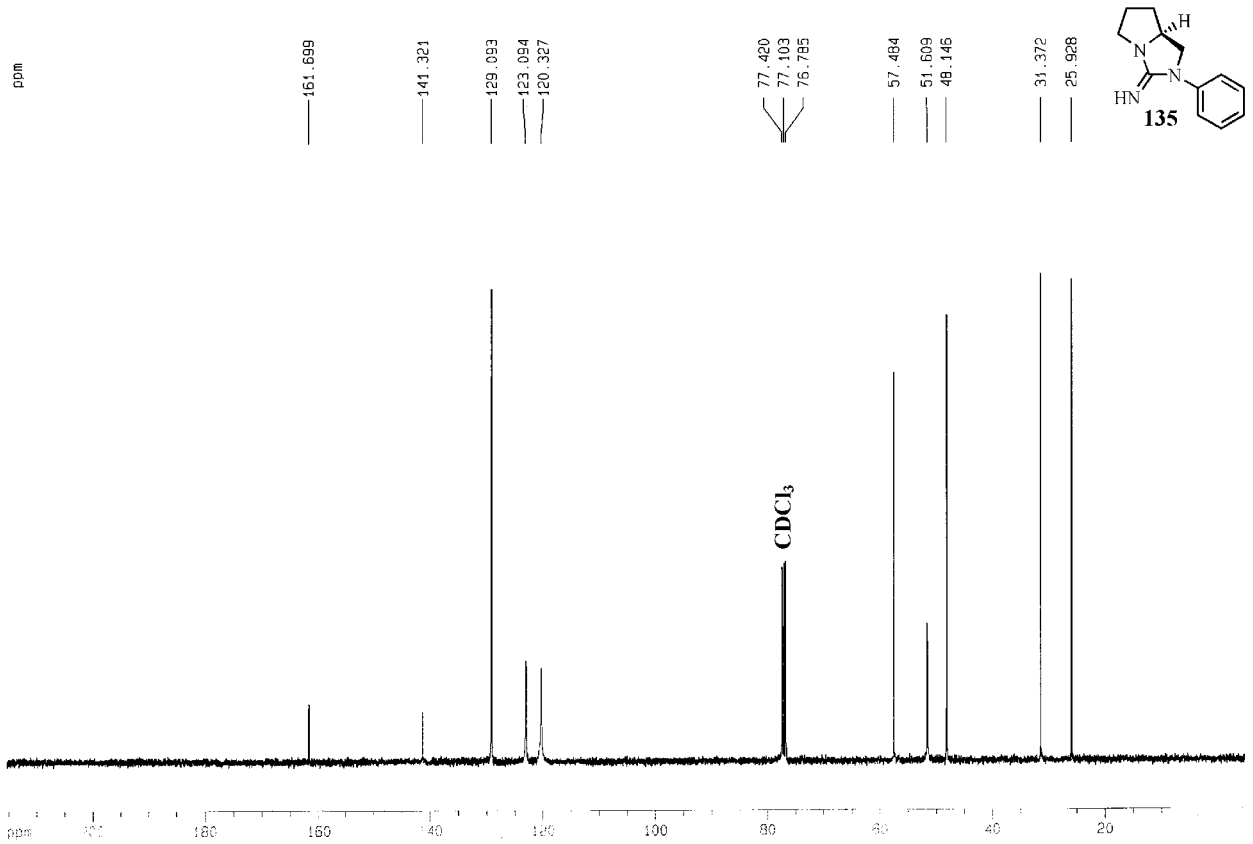
Enantiomeric purity: 53% [determined following the similar HPLC analysis, as mentioned in page no. 162, using chiral column, Chiralcel OD-H, with reference to racemic alcohol **(±)-145a**]



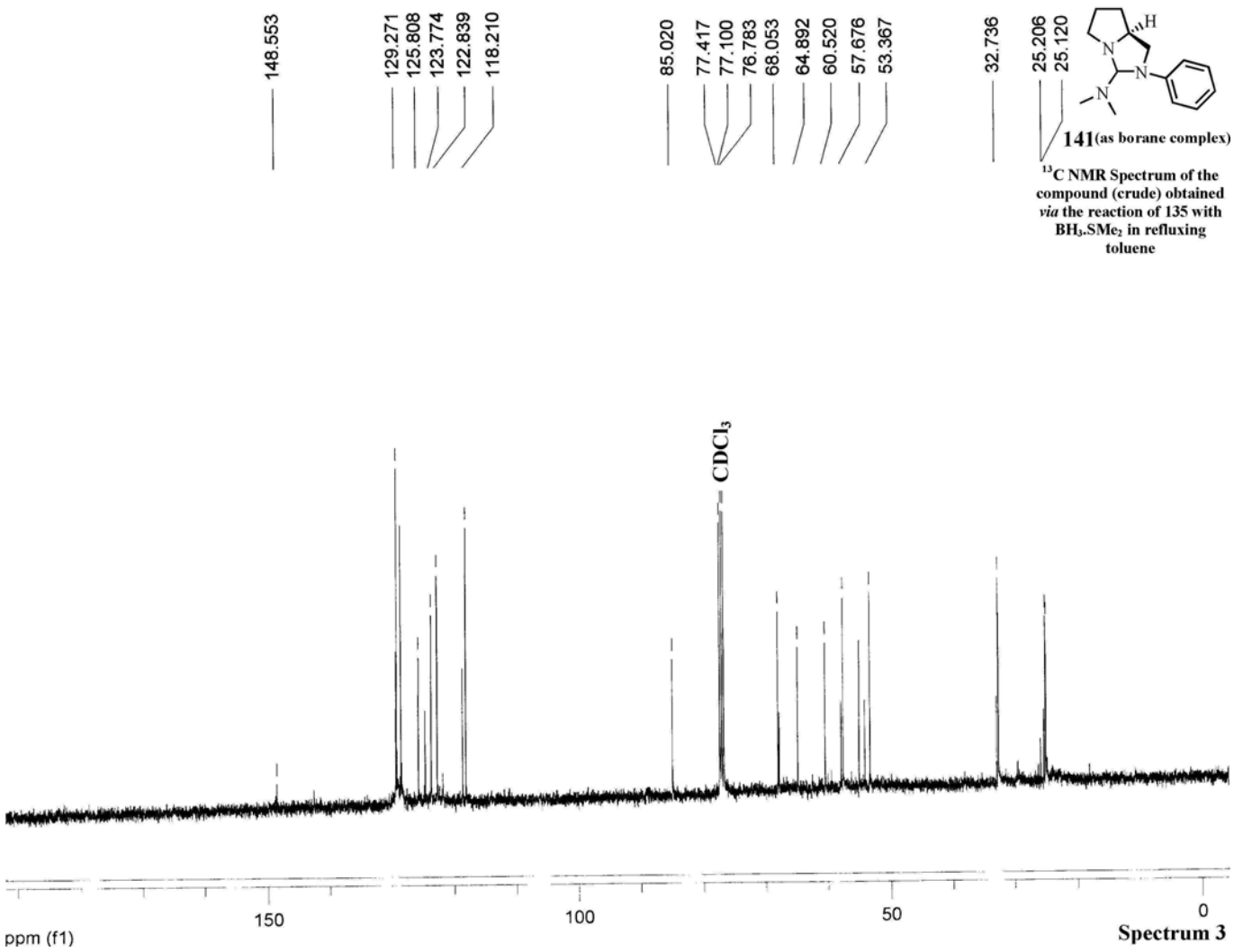
135



^{1}H NMR Spectrum of 135

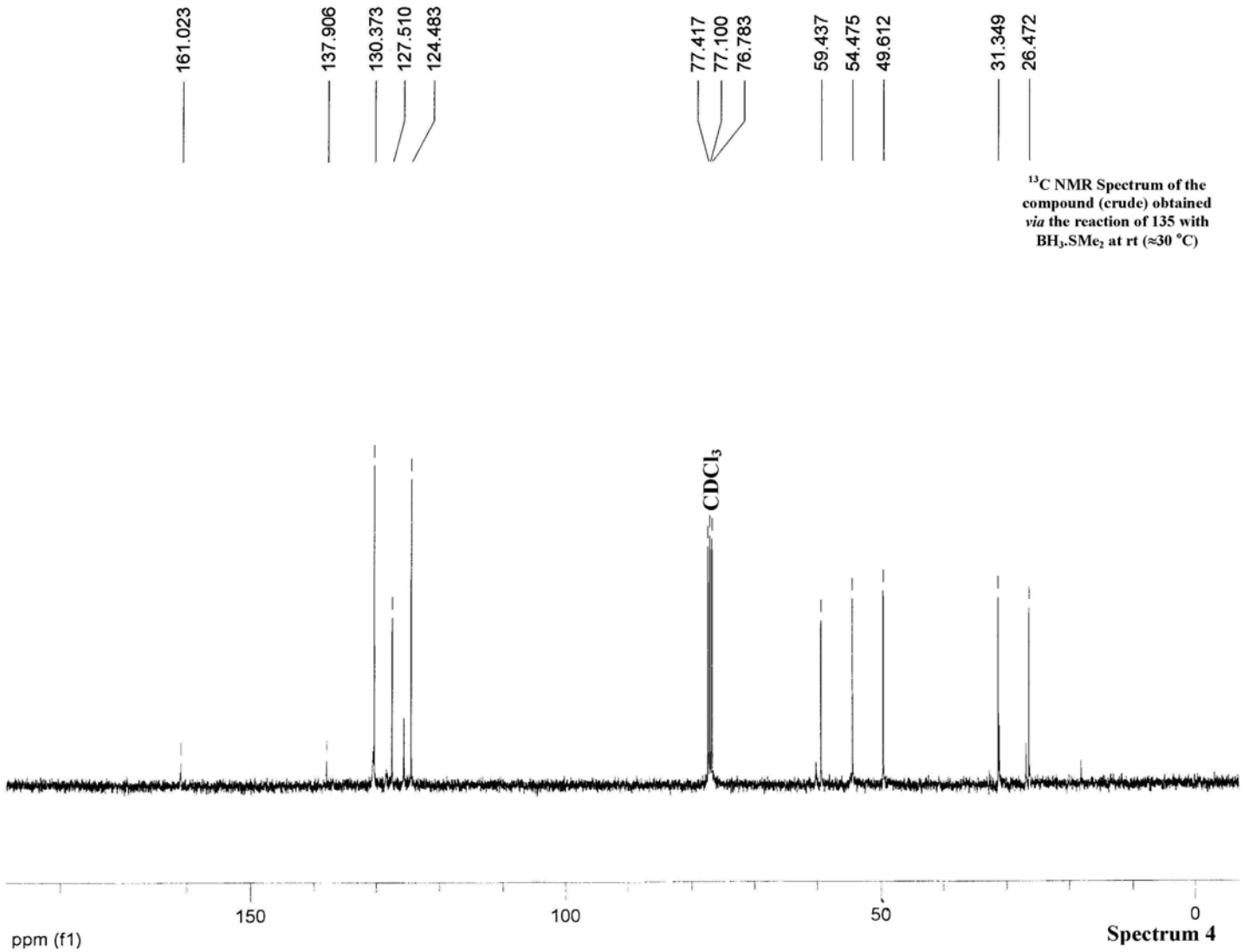


^{13}C NMR Spectrum of 135 **Spectrum 2**

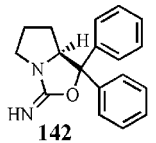


141(as borane complex)

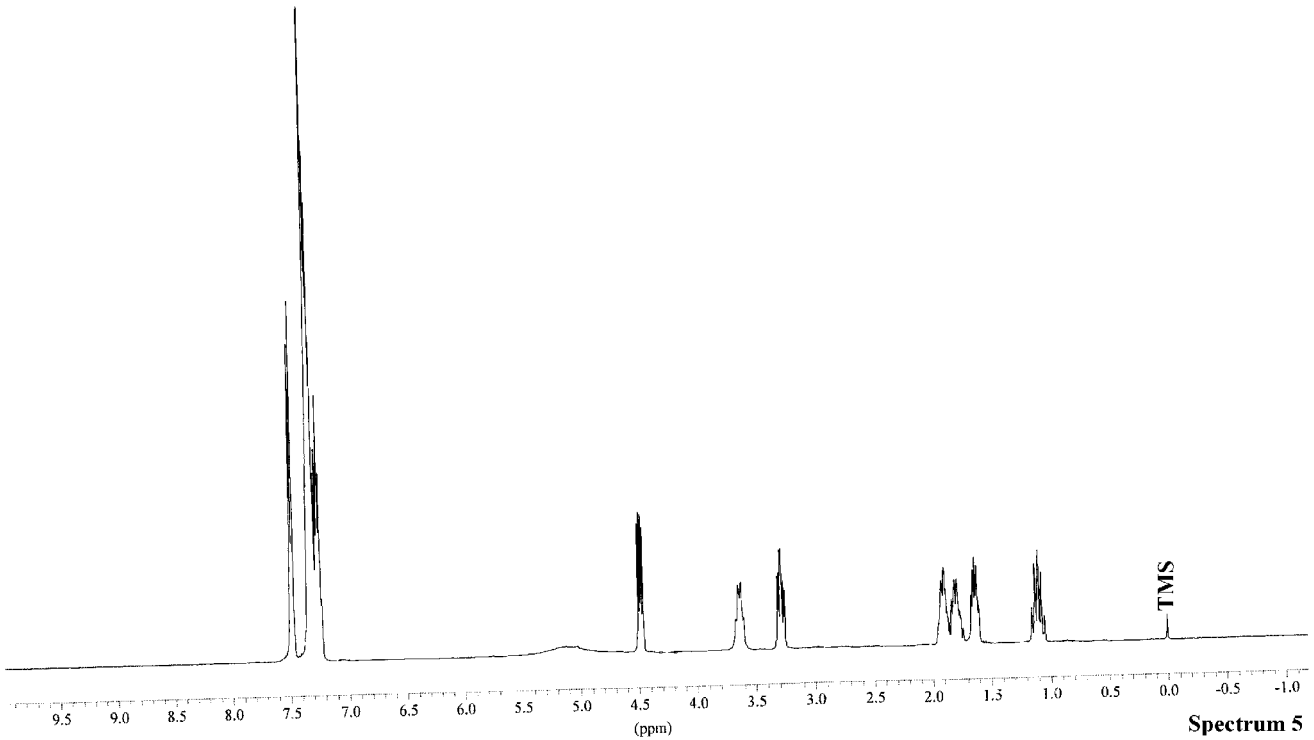
^{13}C NMR Spectrum of the compound (crude) obtained *via* the reaction of 135 with $BH_3.SMe_2$ in refluxing toluene



^{13}C NMR Spectrum of the compound (crude) obtained *via* the reaction of 135 with $BH_3.SMe_2$ at rt (≈30 °C)

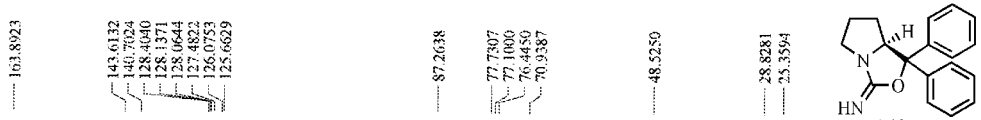


142

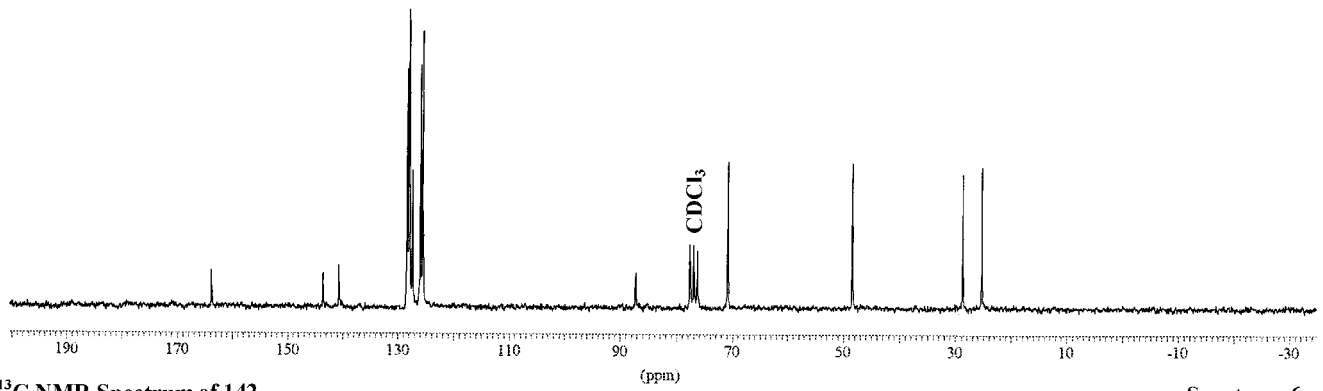


Spectrum 5

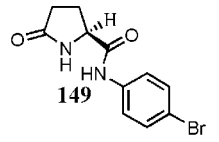
^{1}H NMR Spectrum of 142



142

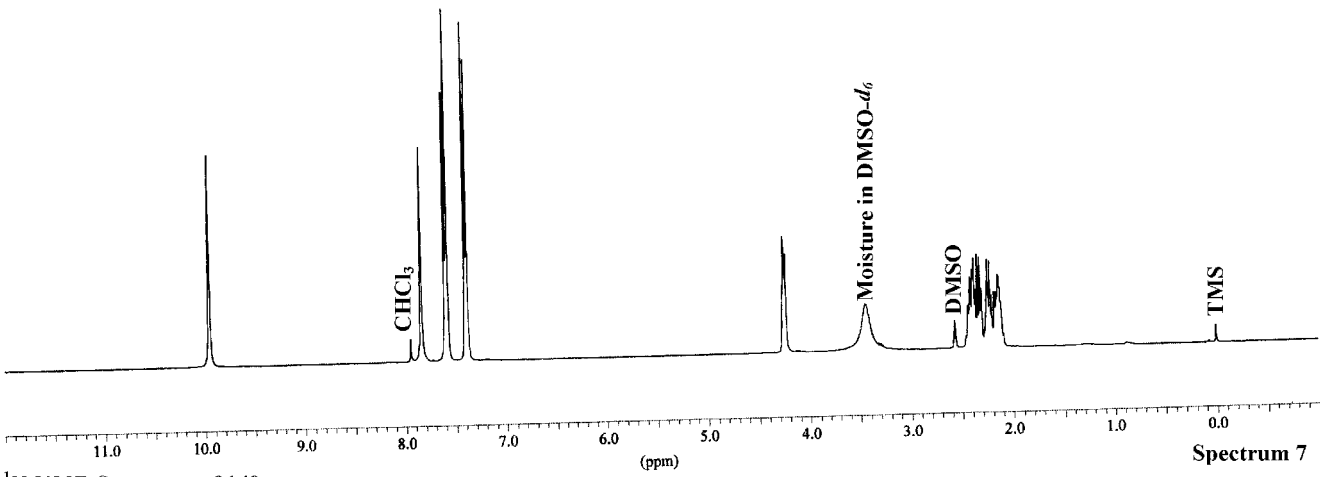


^{13}C NMR Spectrum of 142 **Spectrum 6**



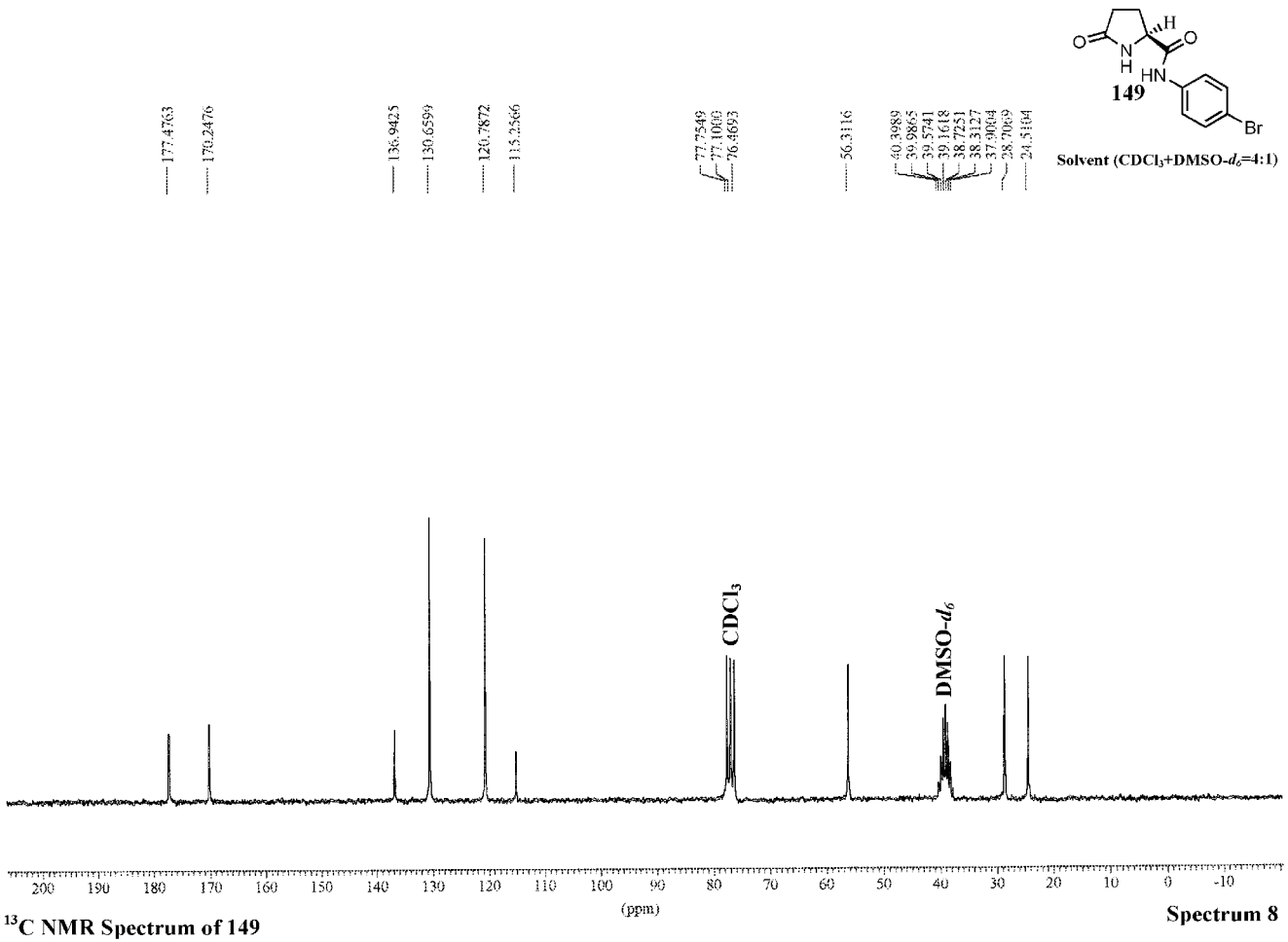
149

Solvent ($CDCl_3$+DMSO-d_6=4:1)



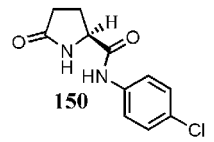
Spectrum 7

^{1}H NMR Spectrum of 149



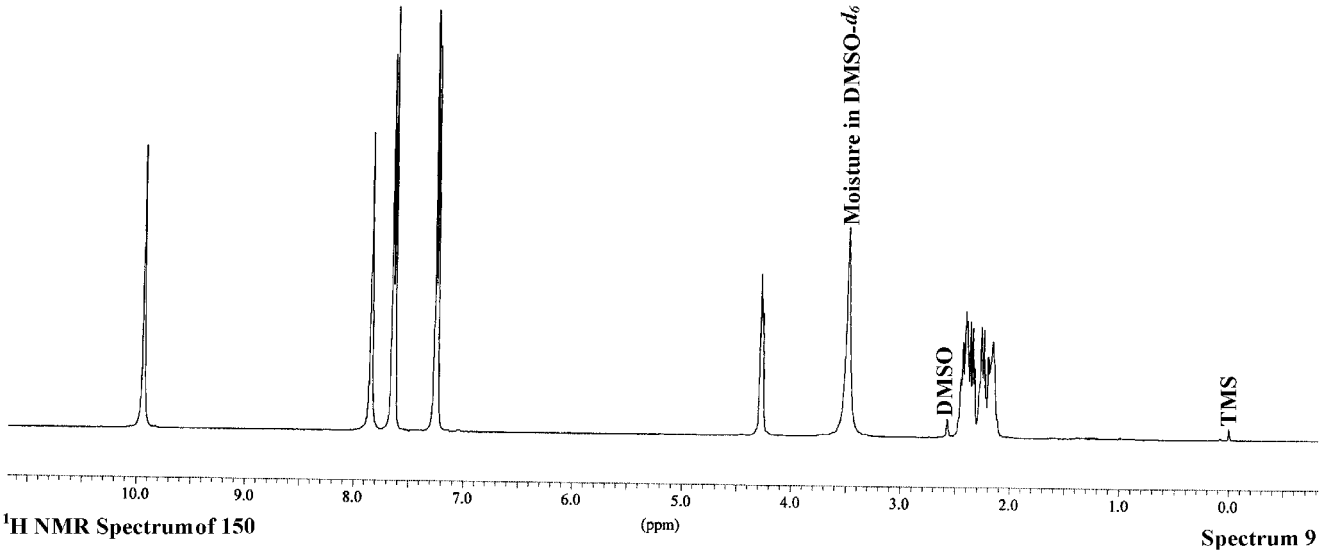
^{13}C NMR Spectrum of 149

Spectrum 8



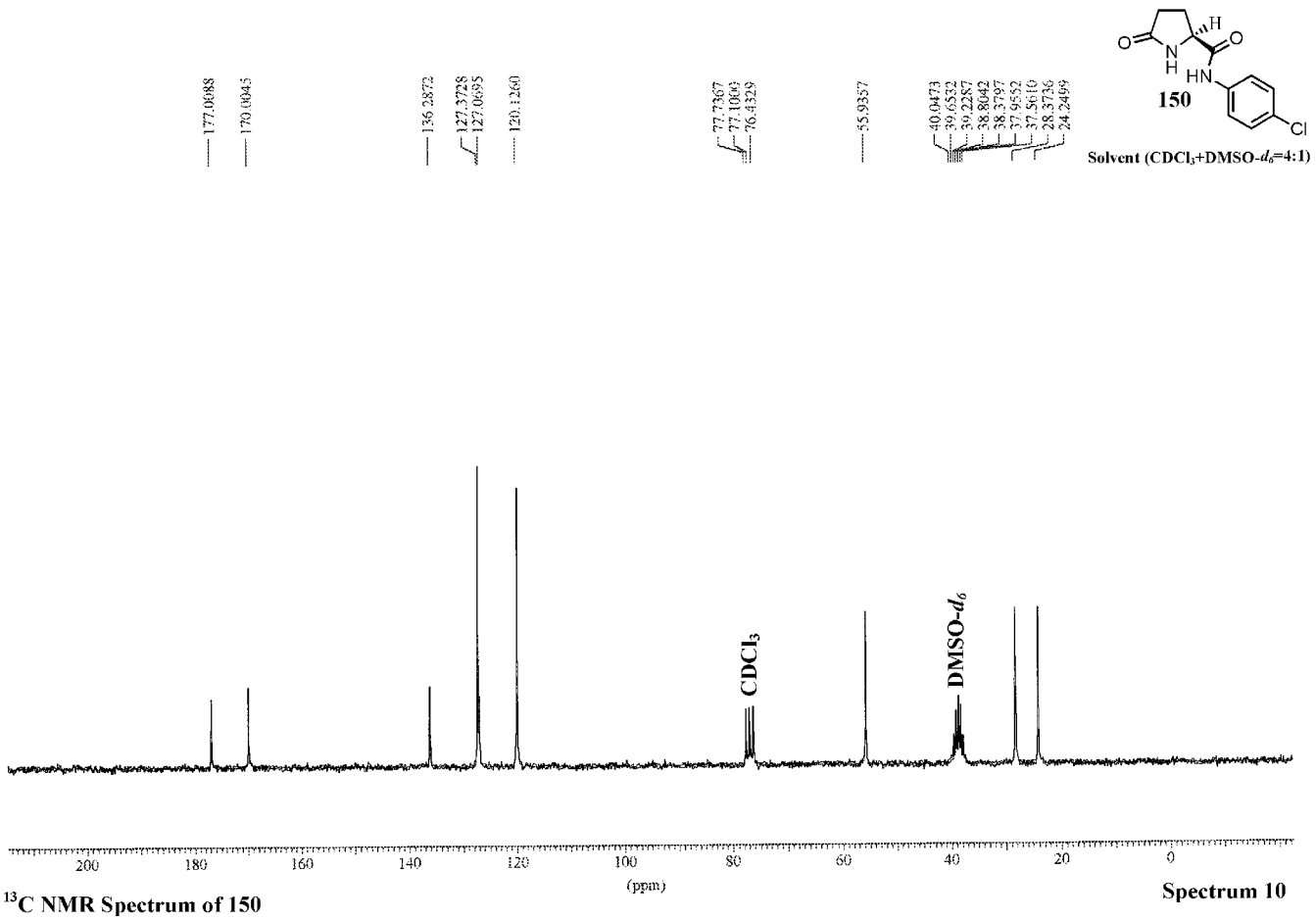
150

Solvent ($CDCl_3$+DMSO-d_6=4:1)



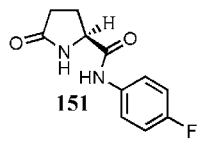
^{1}H NMR Spectrum of 150

Spectrum 9



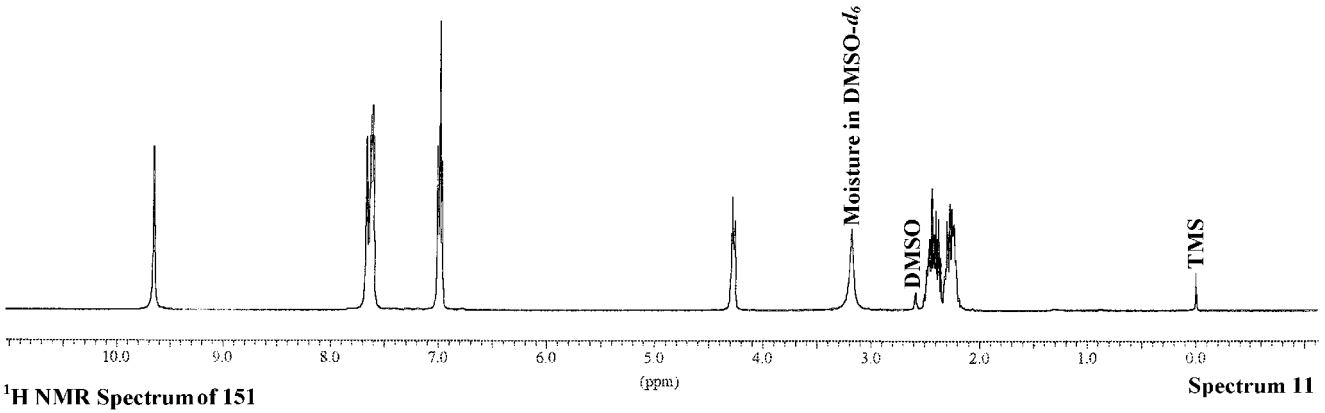
^{13}C NMR Spectrum of 150

Spectrum 10

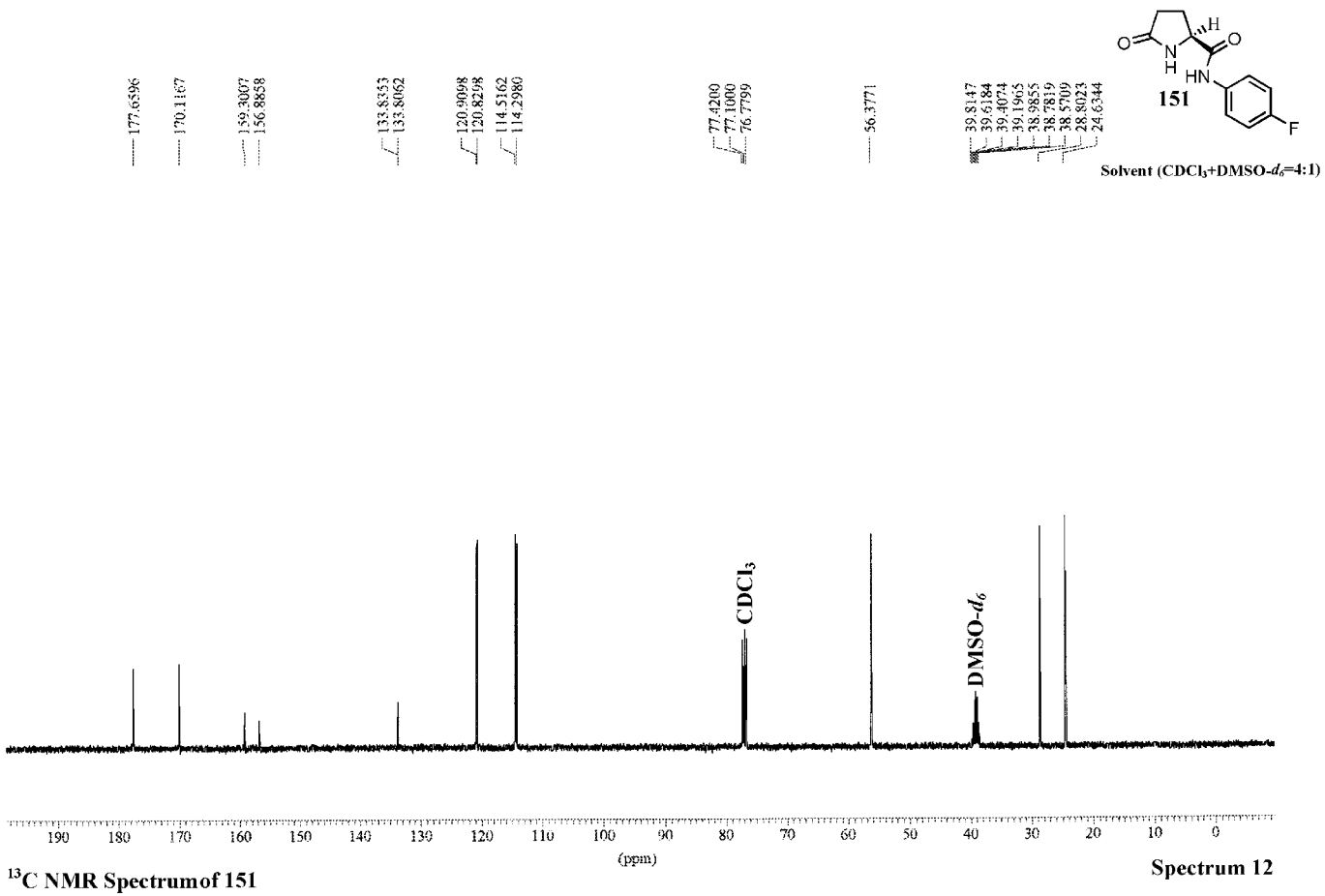


151

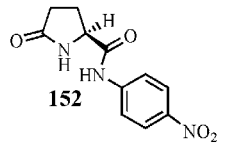
Solvent ($CDCl_3$+DMSO-d_6=4:1)



^{1}H NMR Spectrum of 151 **Spectrum 11**

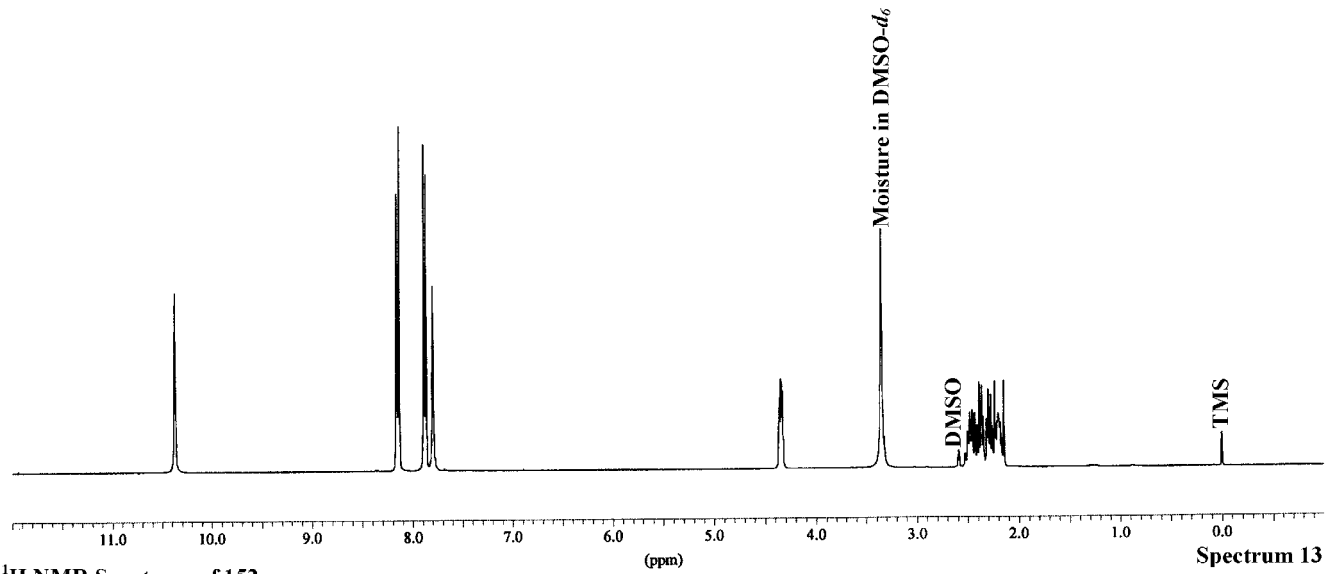


^{13}C NMR Spectrumof 151 **Spectrum 12**

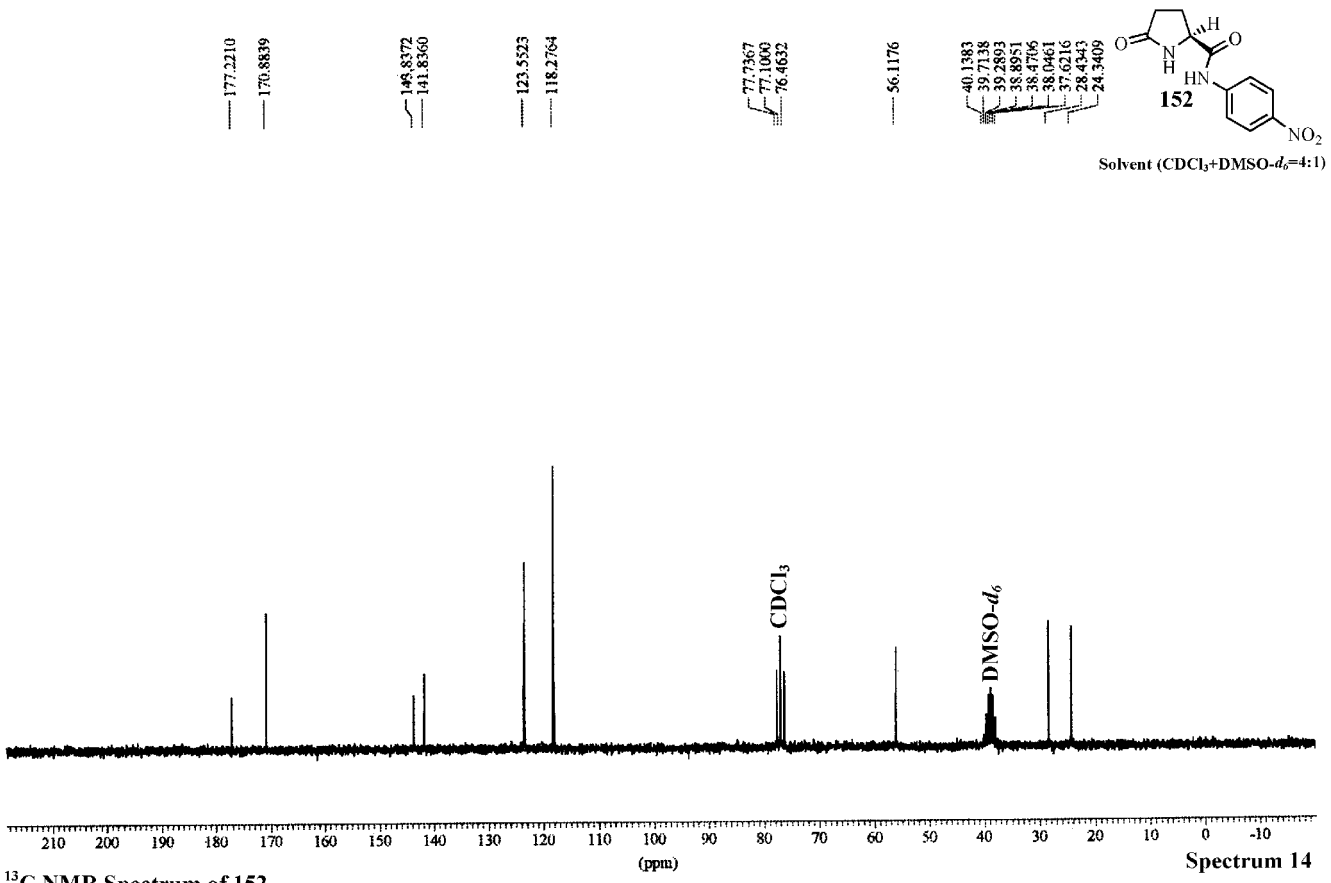


152

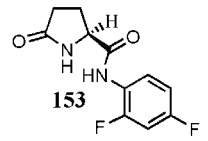
Solvent ($CDCl_3$+DMSO-d_6=4:1)



^{1}H NMR Spectrum of 152

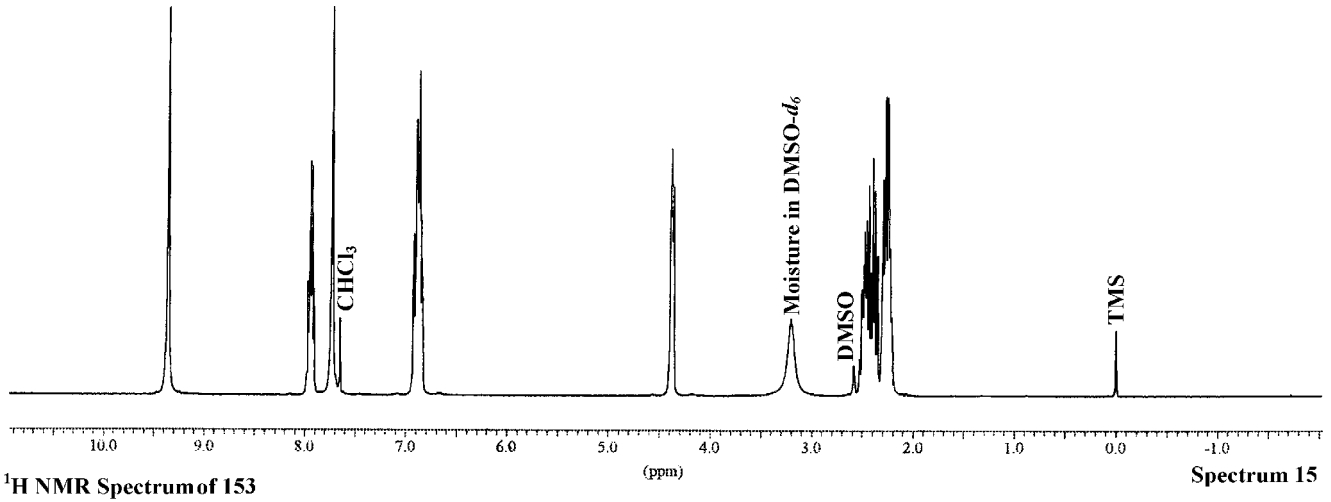


^{13}C NMR Spectrum of 152

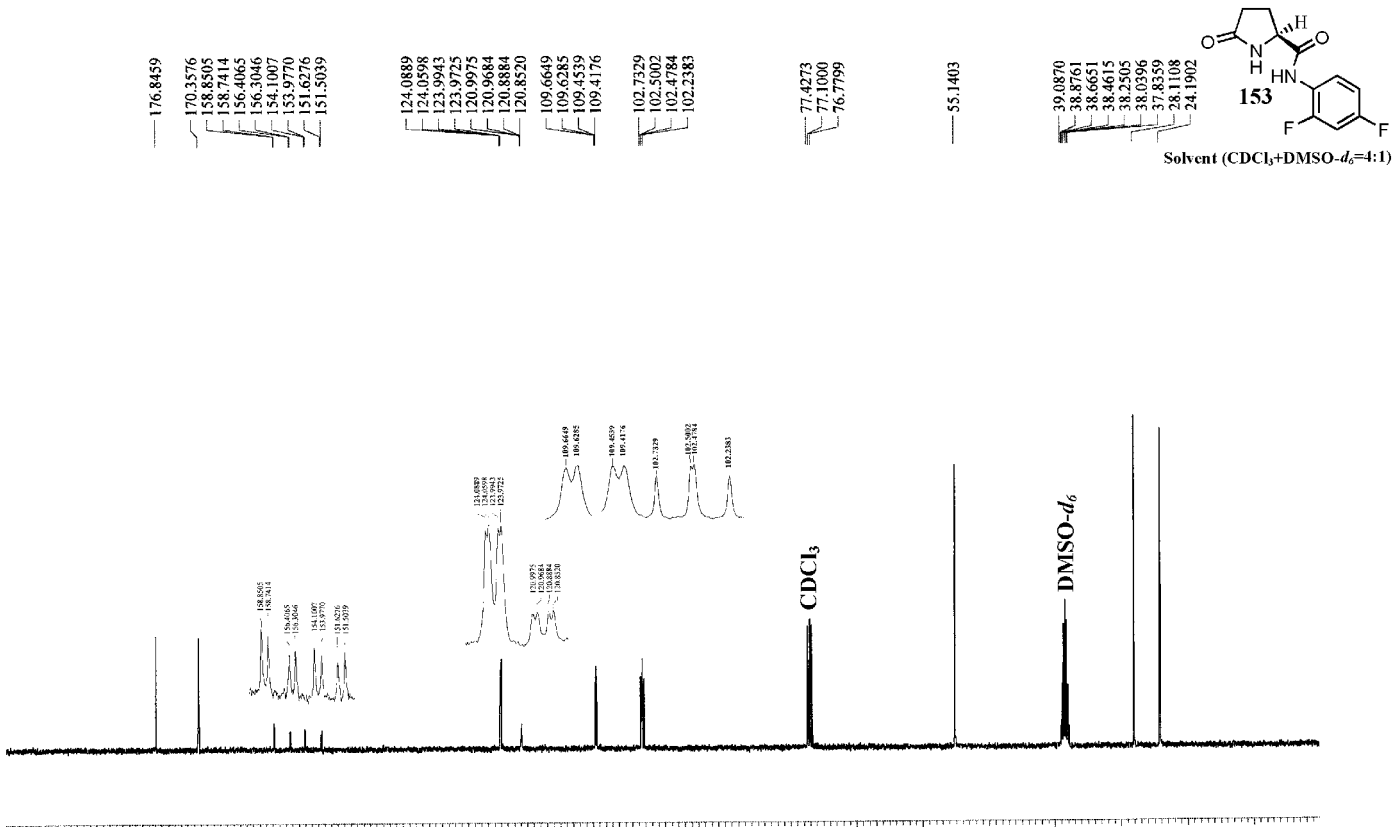


153

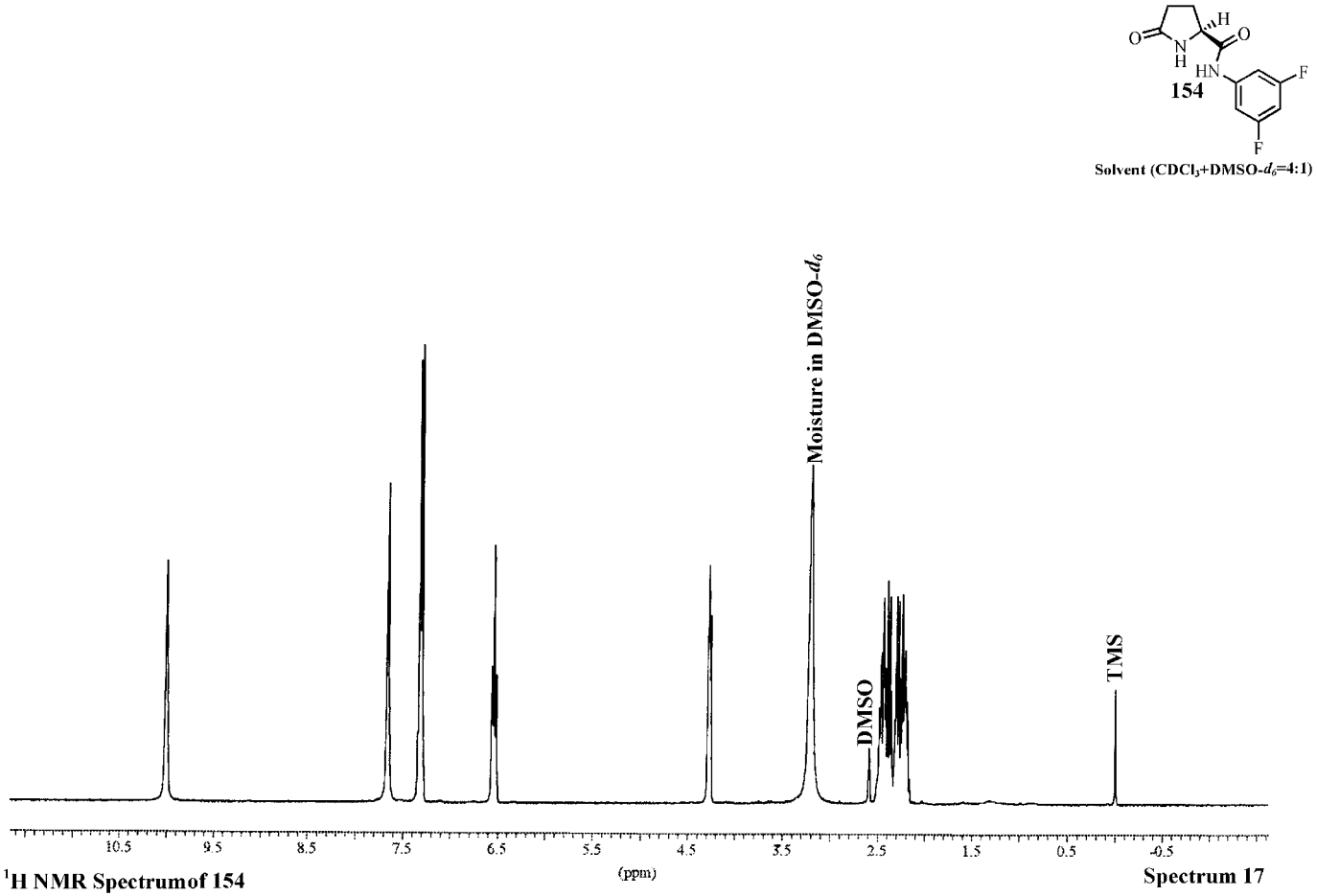
Solvent ($CDCl_3$+DMSO-d_6=4:1)



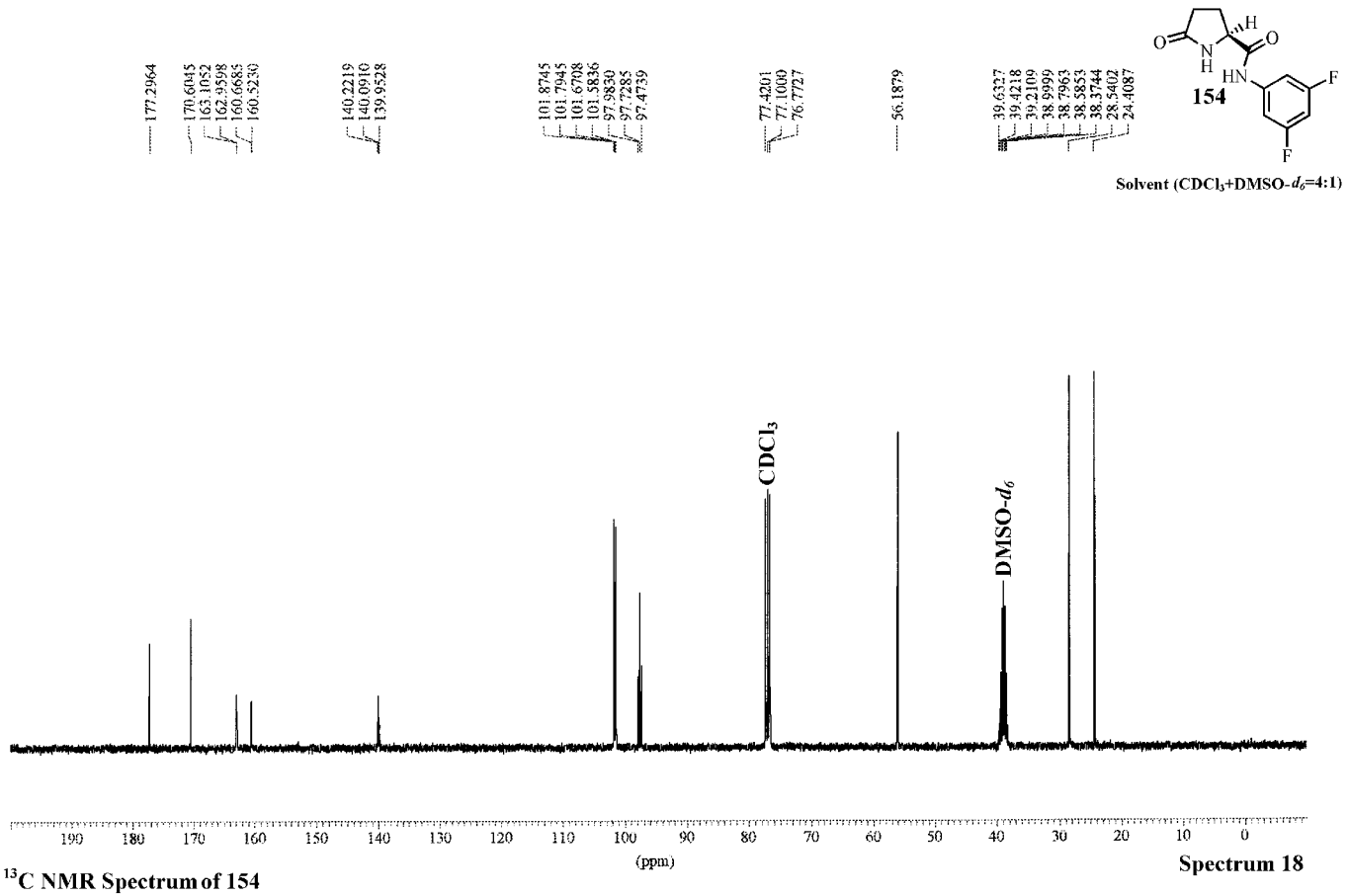
^{1}H NMR Spectrum of 153 **Spectrum 15**



^{13}C NMR Spectrum of 153 **Spectrum 16**

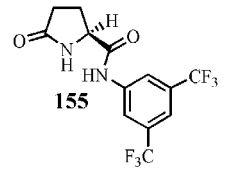


^{1}H NMR Spectrumof 154 **Spectrum 17**



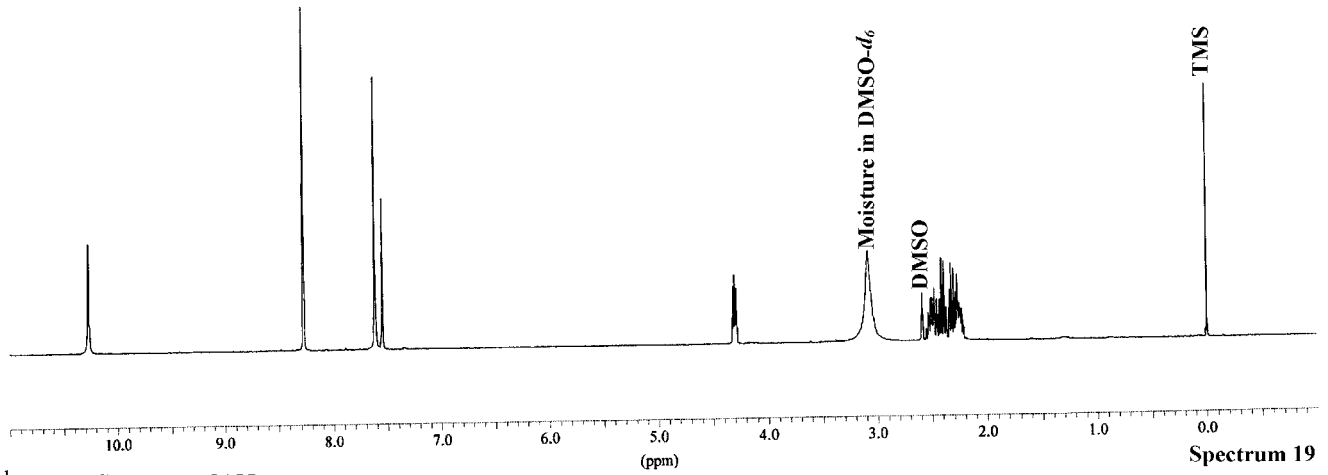
^{13}C NMR Spectrum of 154

Spectrum 18

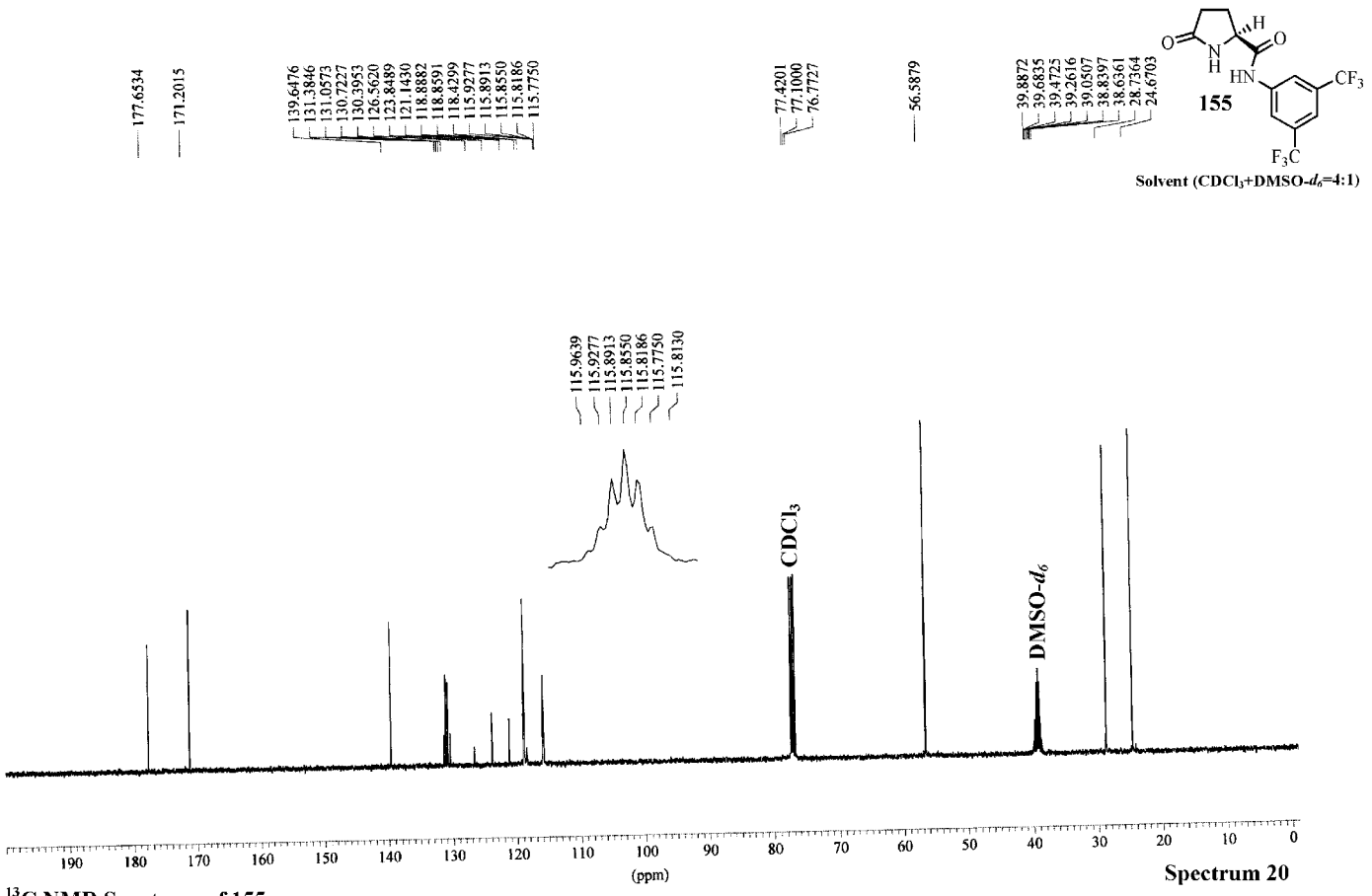


155

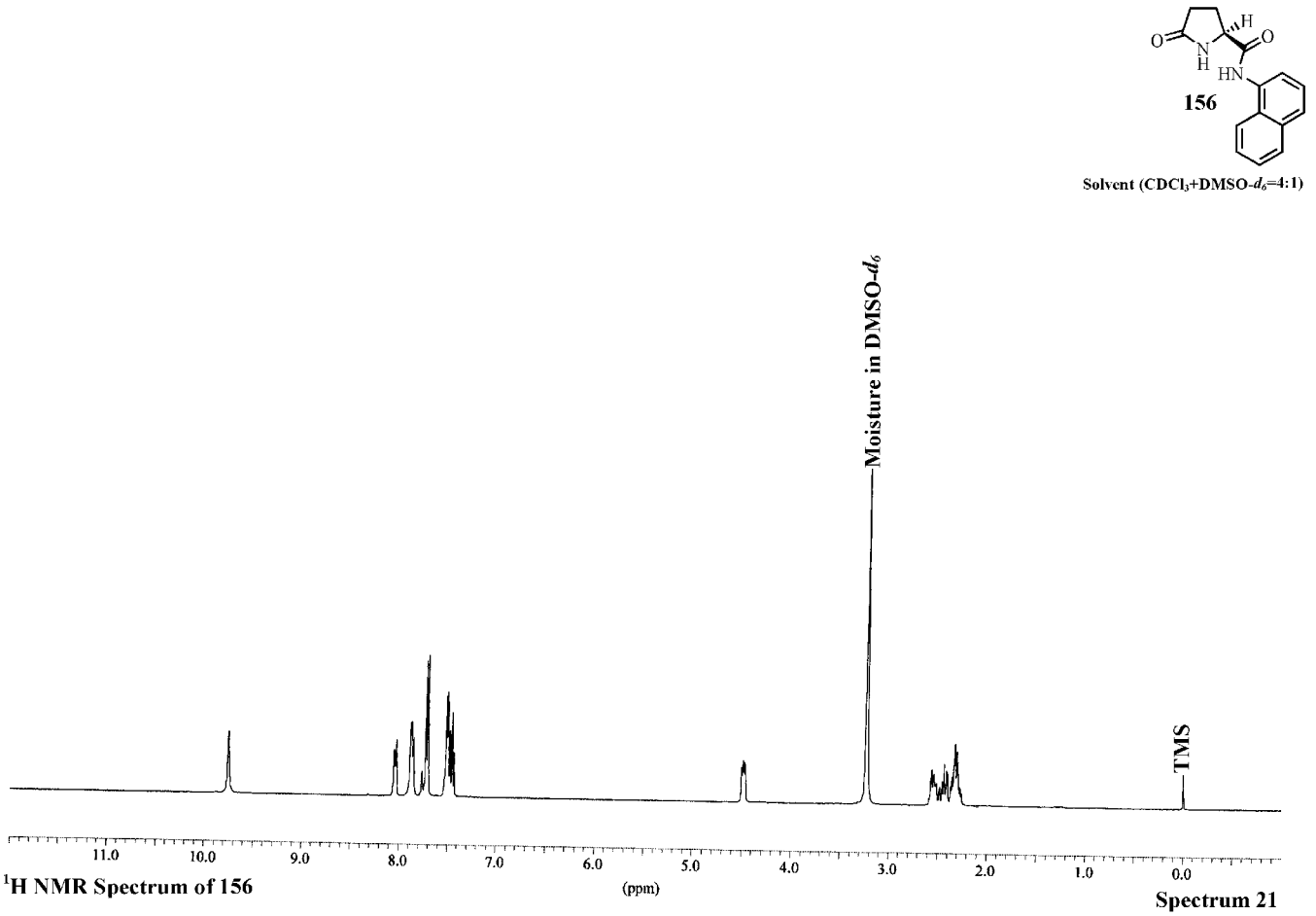
Solvent ($CDCl_3$+DMSO-d_6=4:1)

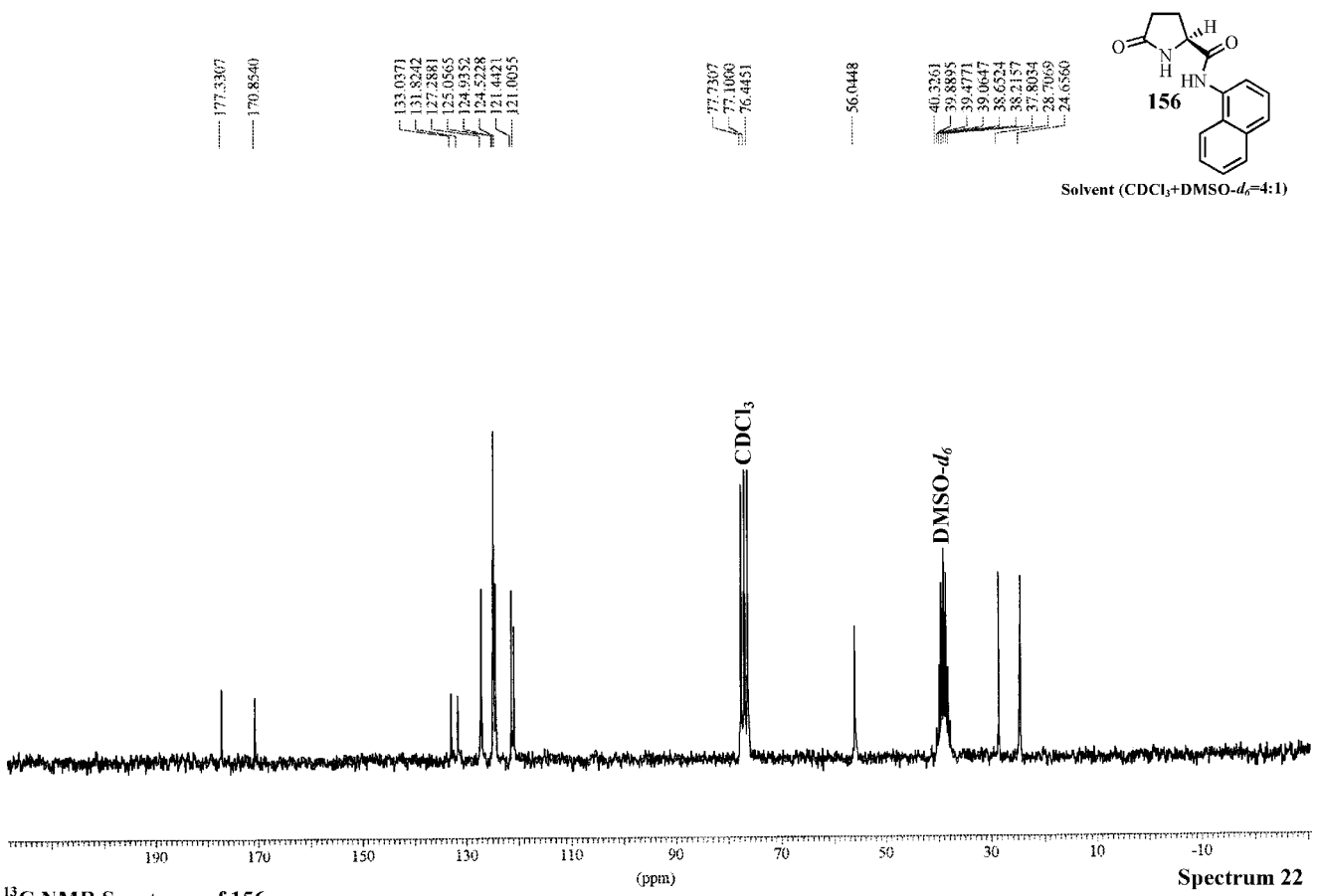


^{1}H NMR Spectrumof 155

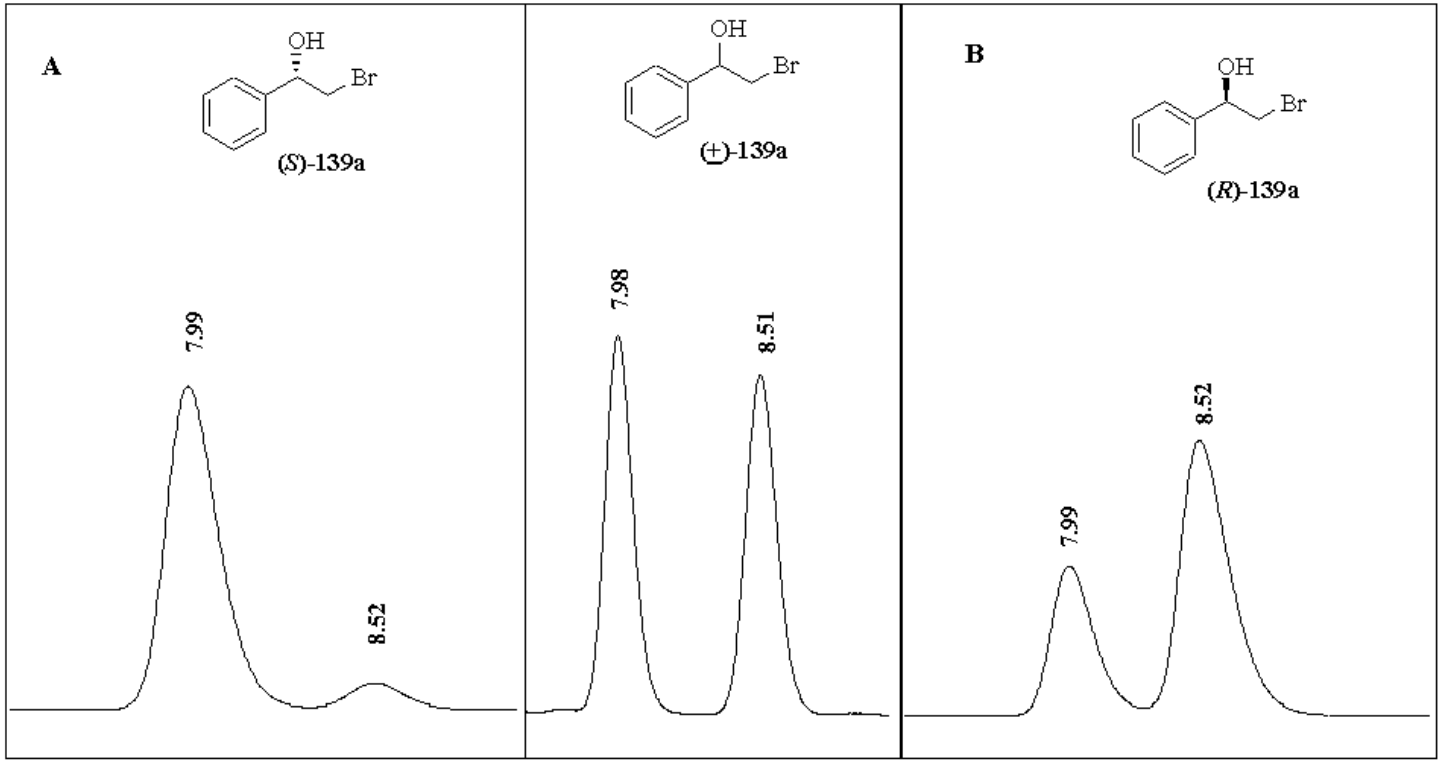


^{13}C NMR Spectrum of 155


156
Solvent (CDCl3+DMSO-d6=4:1)
Moisture in DMSO-d6
TMS
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
1H NMR Spectrum of 156
Spectrum 21

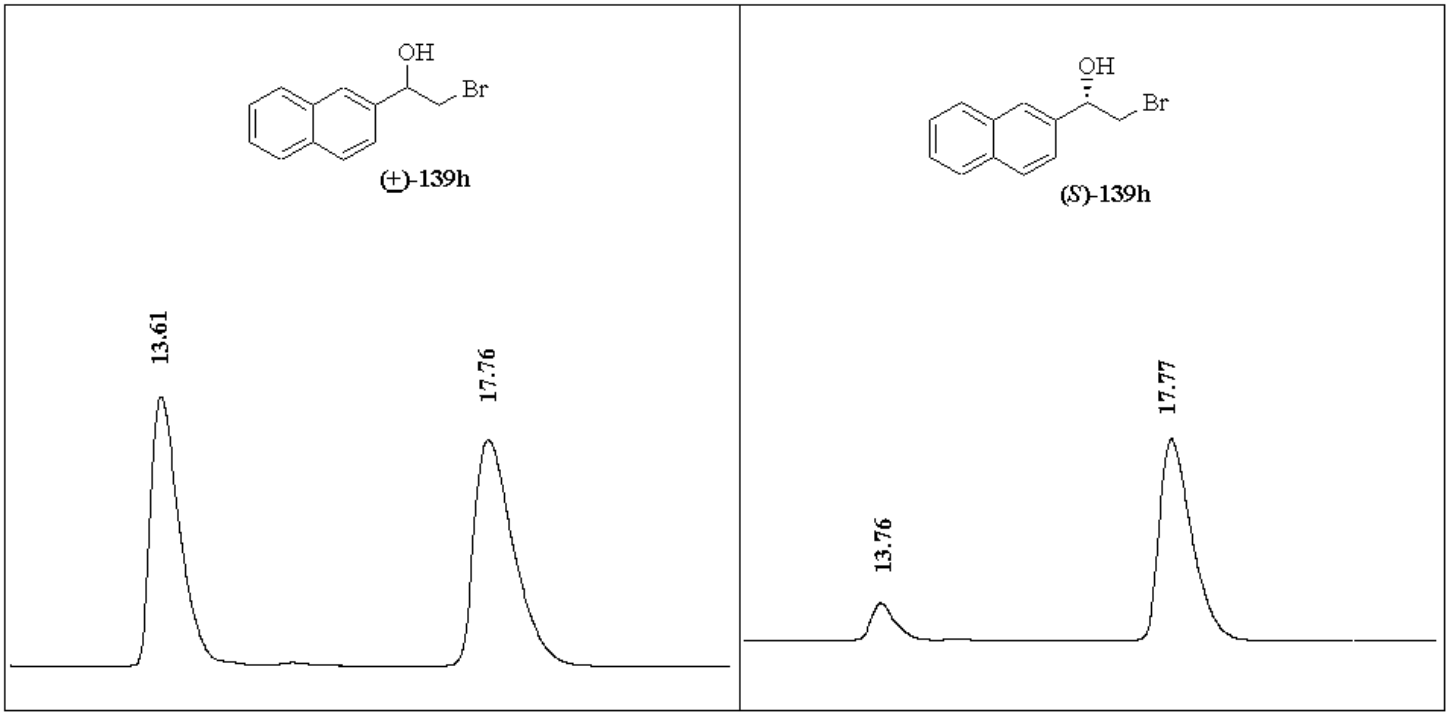


^{13}C NMR Spectrum of 156



A. (***S***)-**139a** (83% *ee*) was obtained *via* the reduction of phenacyl bromide (**138a**) using 5 mol% **135** at reflux temperature.
B. (***R***)-**139a** (37% *ee*) was obtained *via* the reduction of phenacyl bromide (**138a**) using 15 mol% **135** at rt.

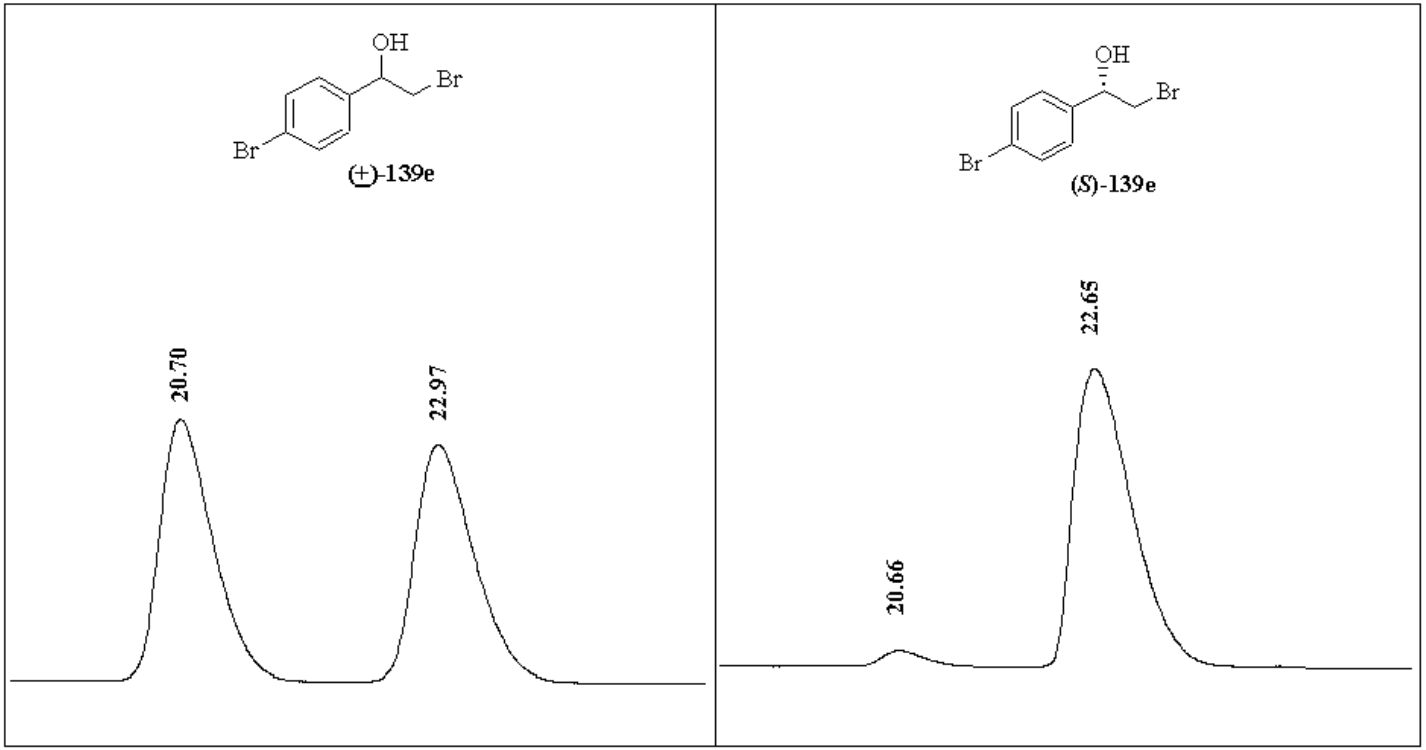
HPLC analysis: Chromatogram 1



(±)-2-Bromo-1-(naphth-2-yl)ethanol **(*S*)-2-Bromo-1-(naphth-2-yl)ethanol**

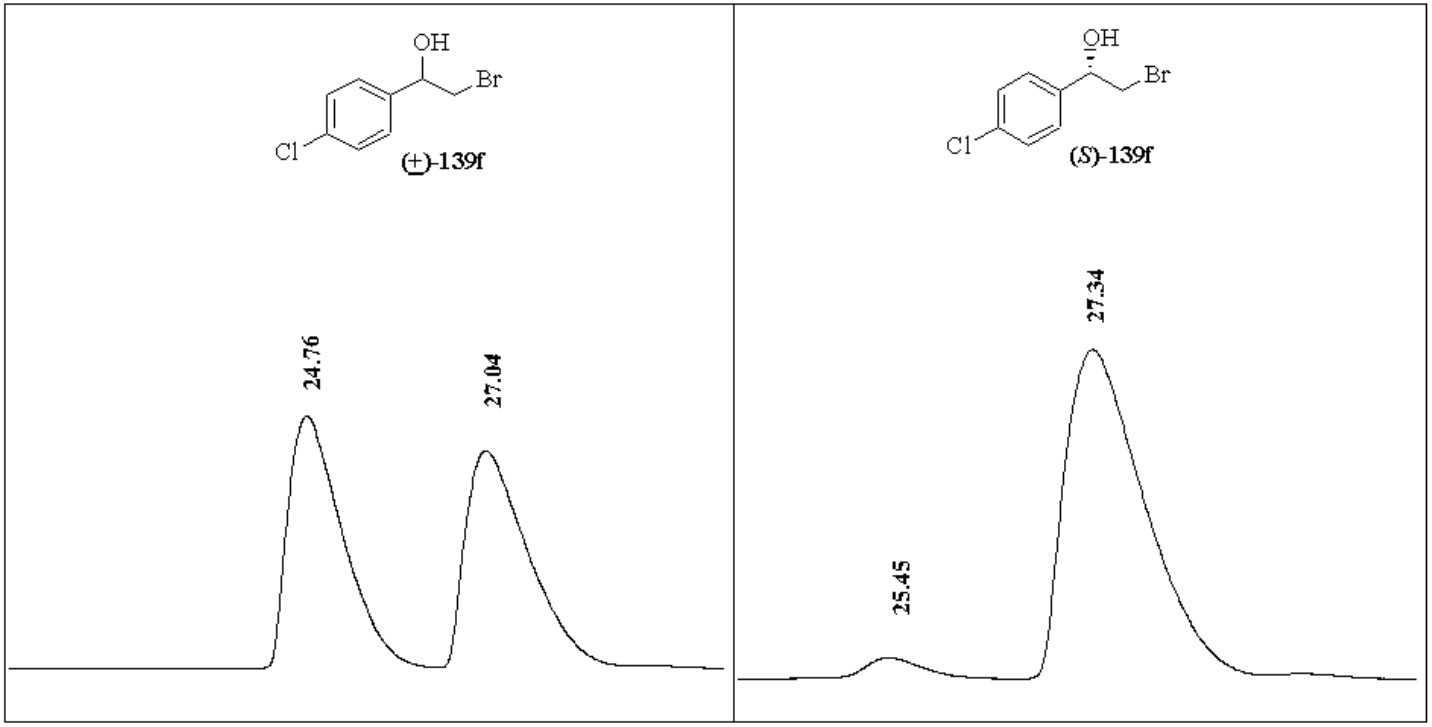
(***S***)-**139h** (72% *ee*) was obtained *via* the reduction of 2-bromoacetylnaphthalene (**138h**) using 5 mol% **135** at reflux temperature.

HPLC analysis: Chromatogram 2



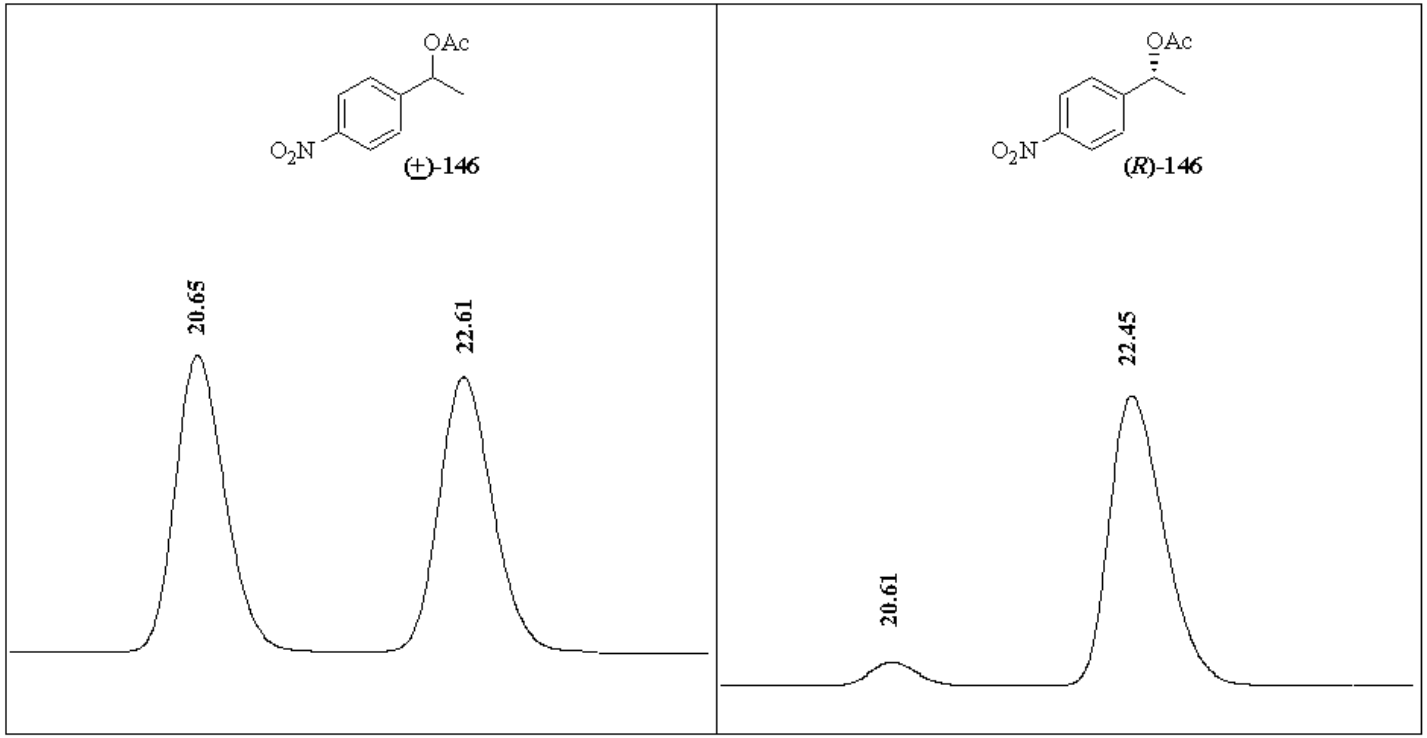
(***S***)-**139e** (92% *ee*) was obtained *via* the reduction of 4-bromophenacyl bromide (**138e**) using 2 mol% **142** at reflux temperature.

HPLC analysis: Chromatogram 3



(***S***)-**139f** (93% *ee*) was obtained *via* the reduction of 4-chlorophenacyl bromide (**138f**) using 2 mol% **142** at reflux temperature.

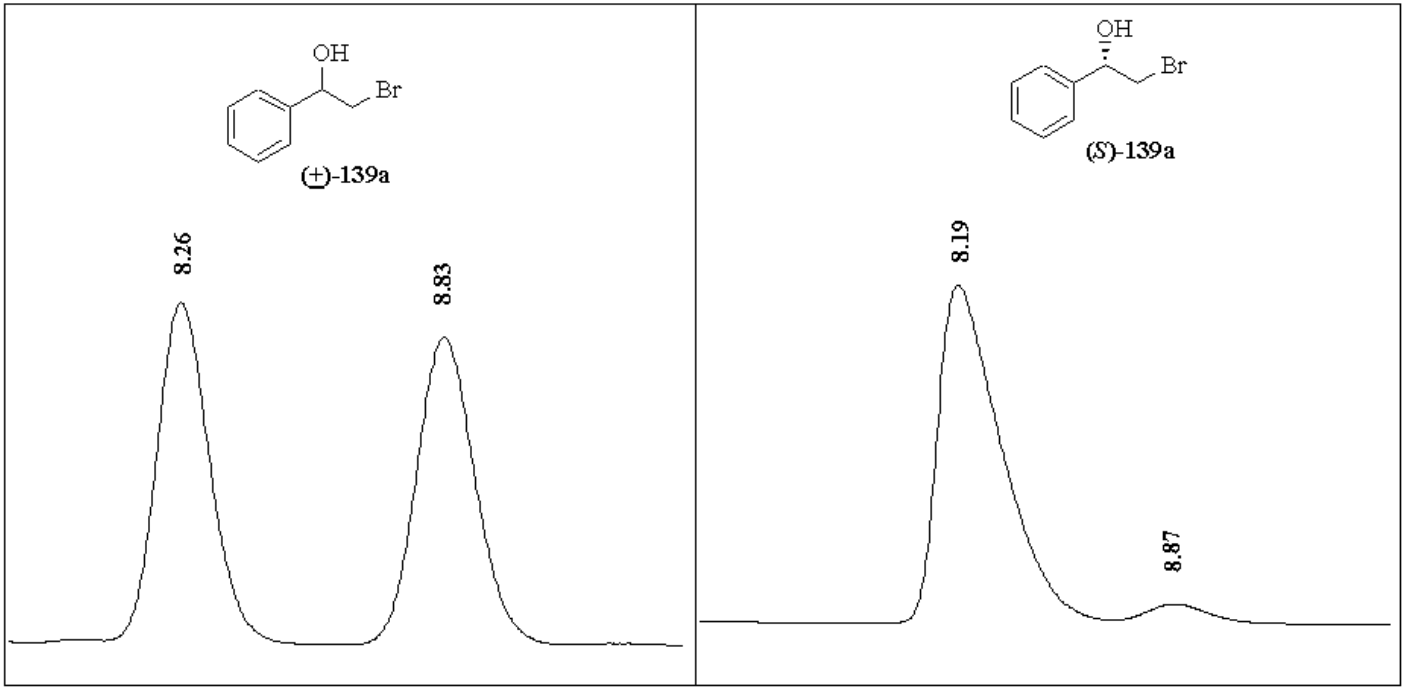
HPLC analysis: Chromatogram 4



(±)-1-Acetoxy-1-(4-nitrophenyl)ethane **(*R*)-1-Acetoxy-1-(4-nitrophenyl)ethane**

(***R***)-**146** (87% *ee*) an acetate derivative of (***R***)-**145e** [obtained *via* the reduction of 4-nitroacetophenone (**144e**) using 2 mol% **142** at reflux temperature].

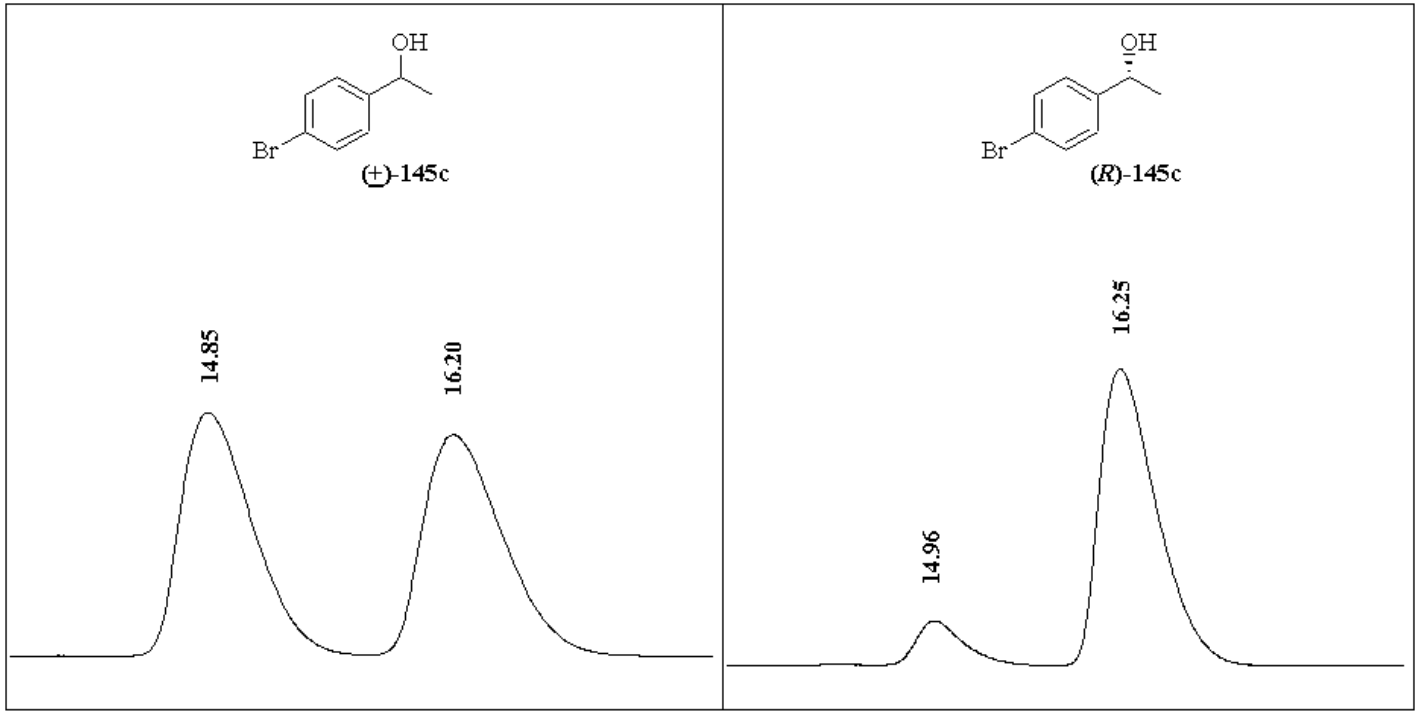
HPLC analysis: Chromatogram 5



(±)-2-Bromo-1-phenylethanol **(*S*)-2-Bromo-1-phenylethanol**

(***S***)-**139a** (91% *ee*) was obtained *via* the reduction of phenacyl bromide (**138a**) using 2 mol% **134** at reflux temperature.

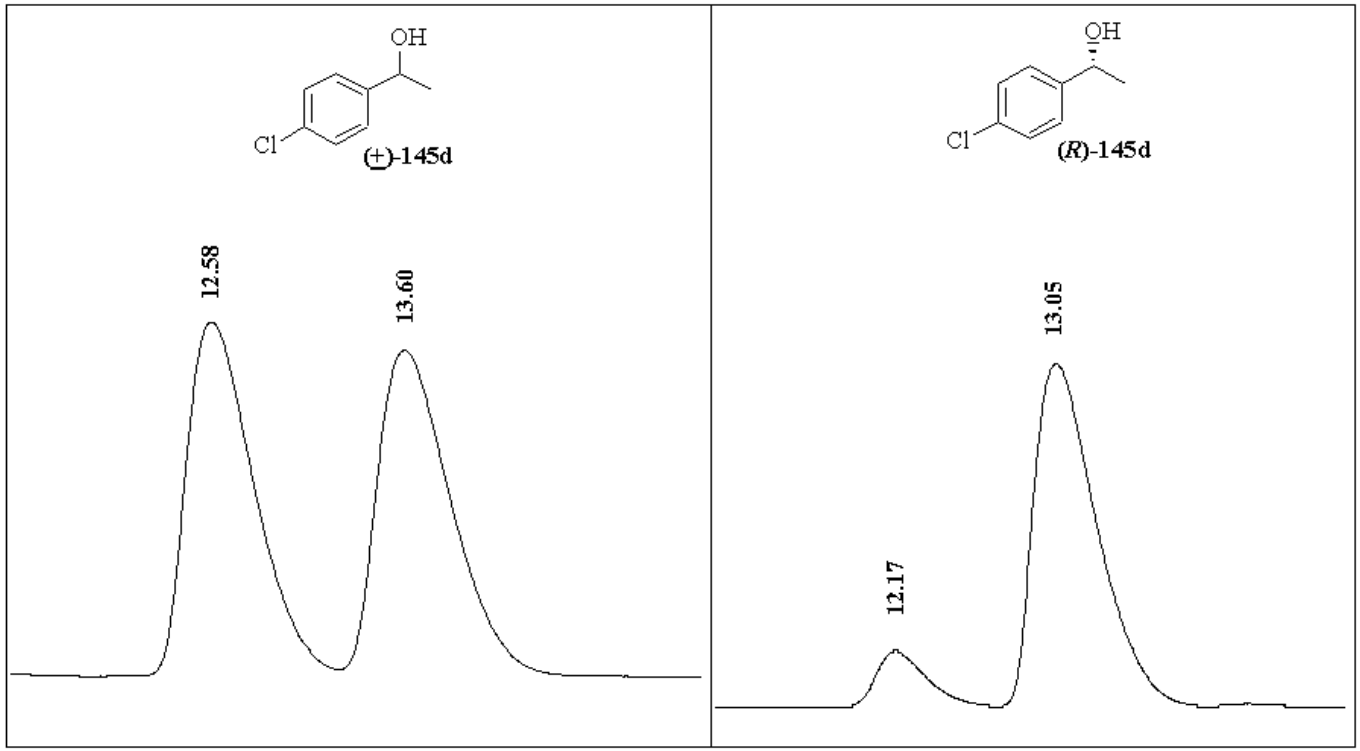
HPLC analysis: Chromatogram 6



(±)-1-(4-Bromophenyl)ethanol **(*R*)-1-(4-Bromophenyl)ethanol**

(***R***)-**145c** (78% *ee*) was obtained *via* the reduction of 4-bromoacetophenone (**144c**) using 2 mol% **134** at reflux temperature.

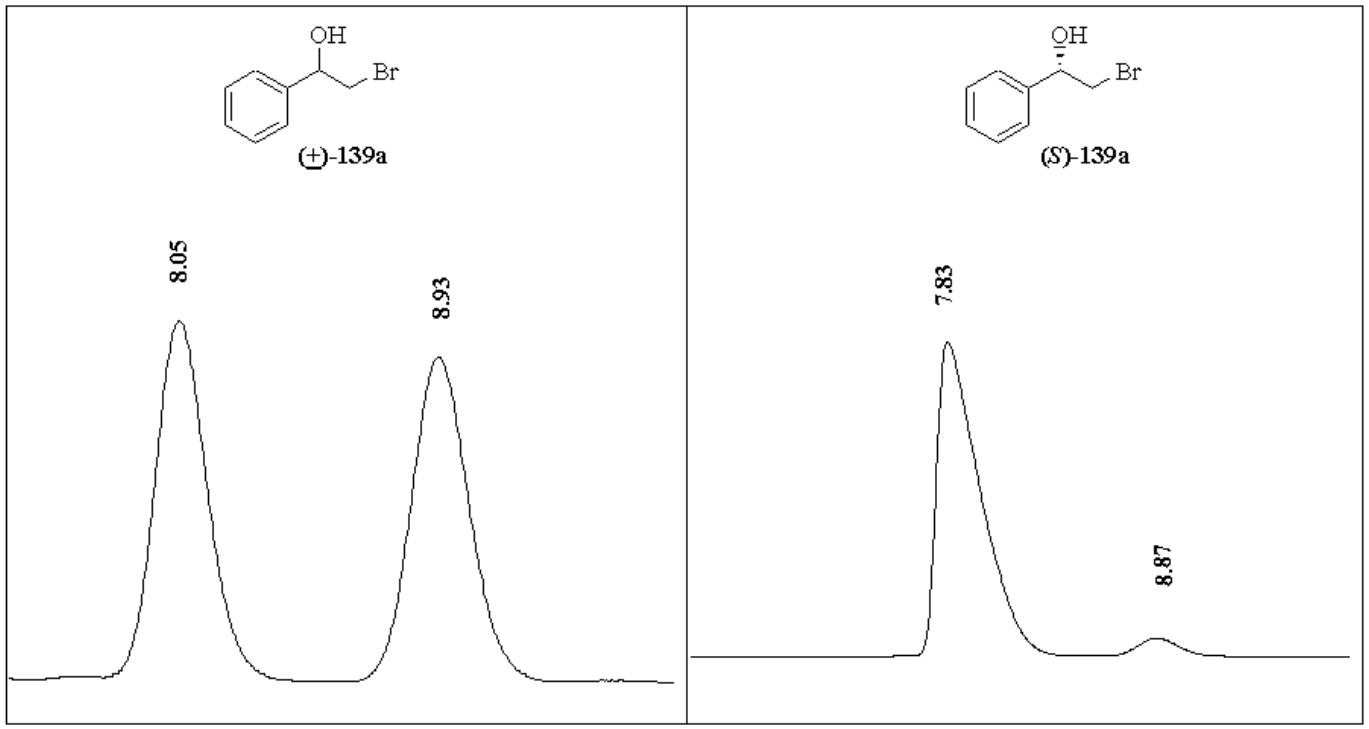
HPLC analysis: Chromatogram 7



(±)-1-(4-Chlorophenyl)ethanol **(*R*)-1-(4-Chlorophenyl)ethanol**

(***R***)-**145d** (77% *ee*) was obtained *via* the reduction of 4-chloroacetophenone (**144d**) using 2 mol% **134** at reflux temperature.

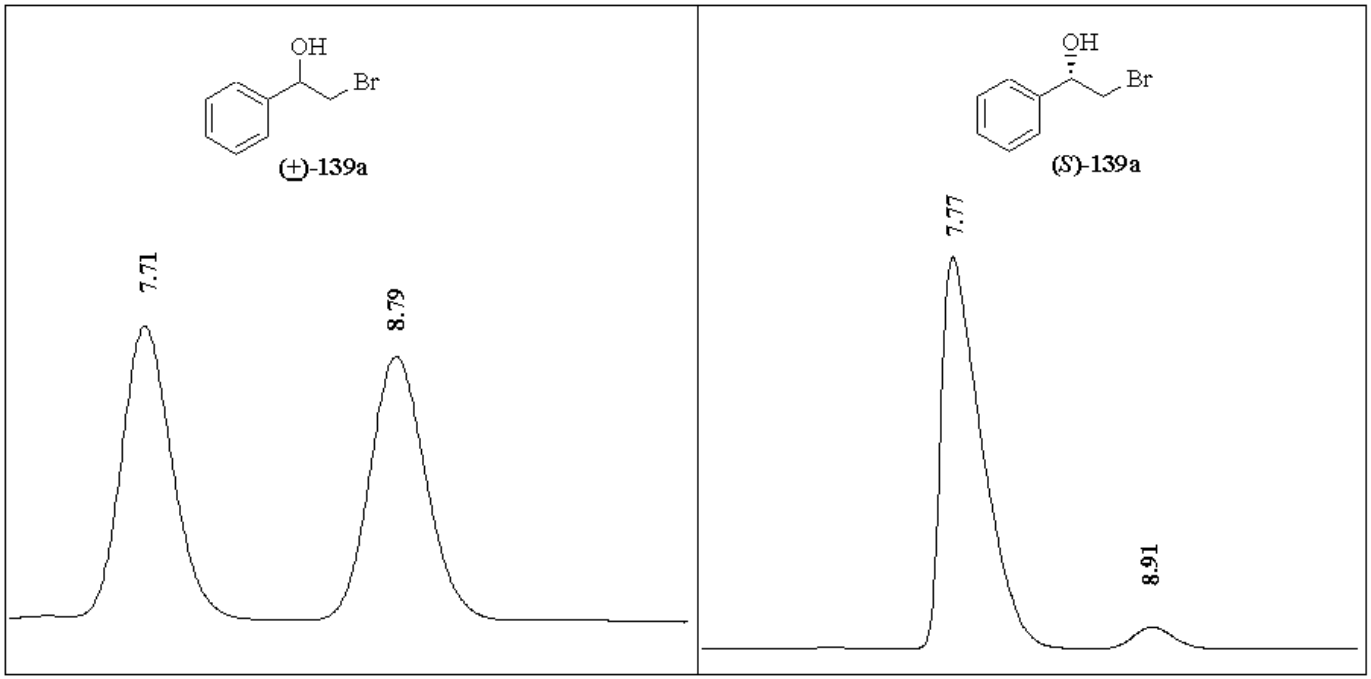
HPLC analysis: Chromatogram 8



(±)-2-Bromo-1-phenylethanol **(*S*)-2-Bromo-1-phenylethanol**

(***S***)-**139a** (90% *ee*) was obtained *via* the reduction of phenacyl bromide (**138a**) using 5 mol% **151** at reflux temperature.

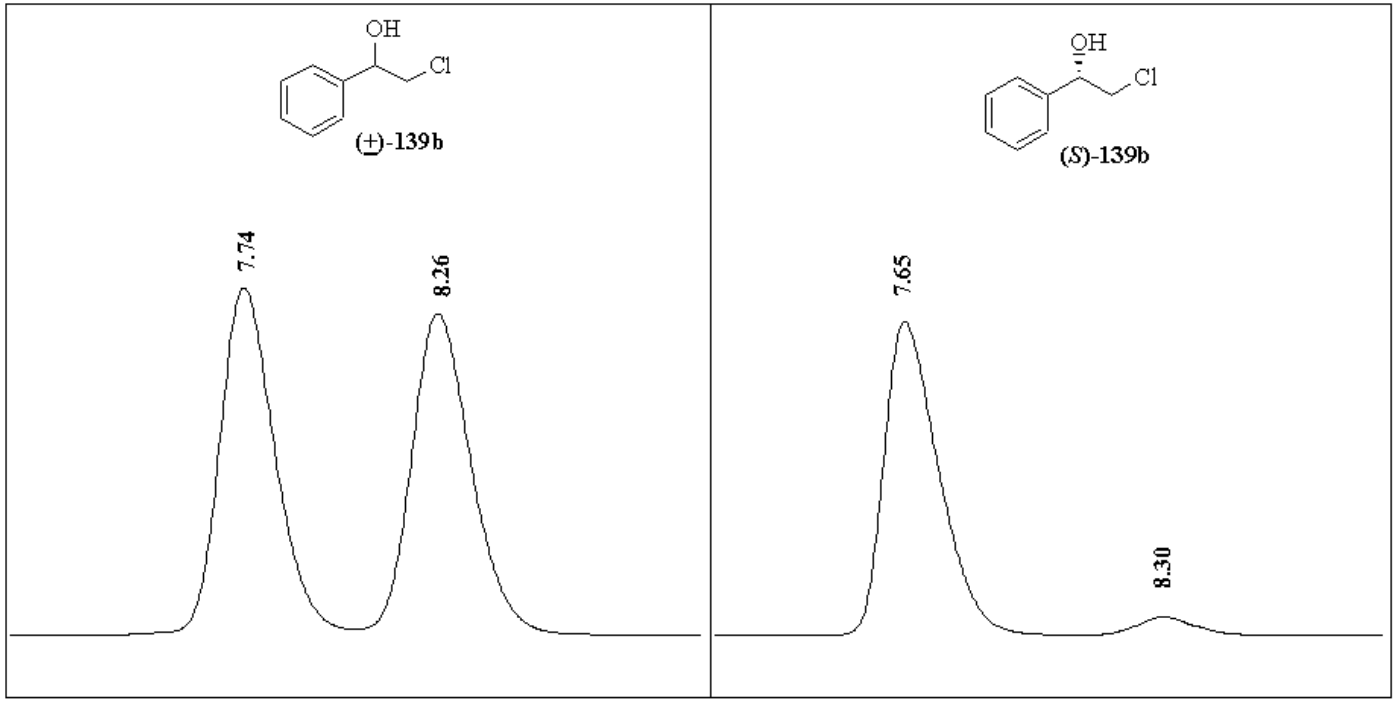
HPLC analysis: Chromatogram 9



(±)-2-Bromo-1-phenylethanol **(*S*)-2-Bromo-1-phenylethanol**

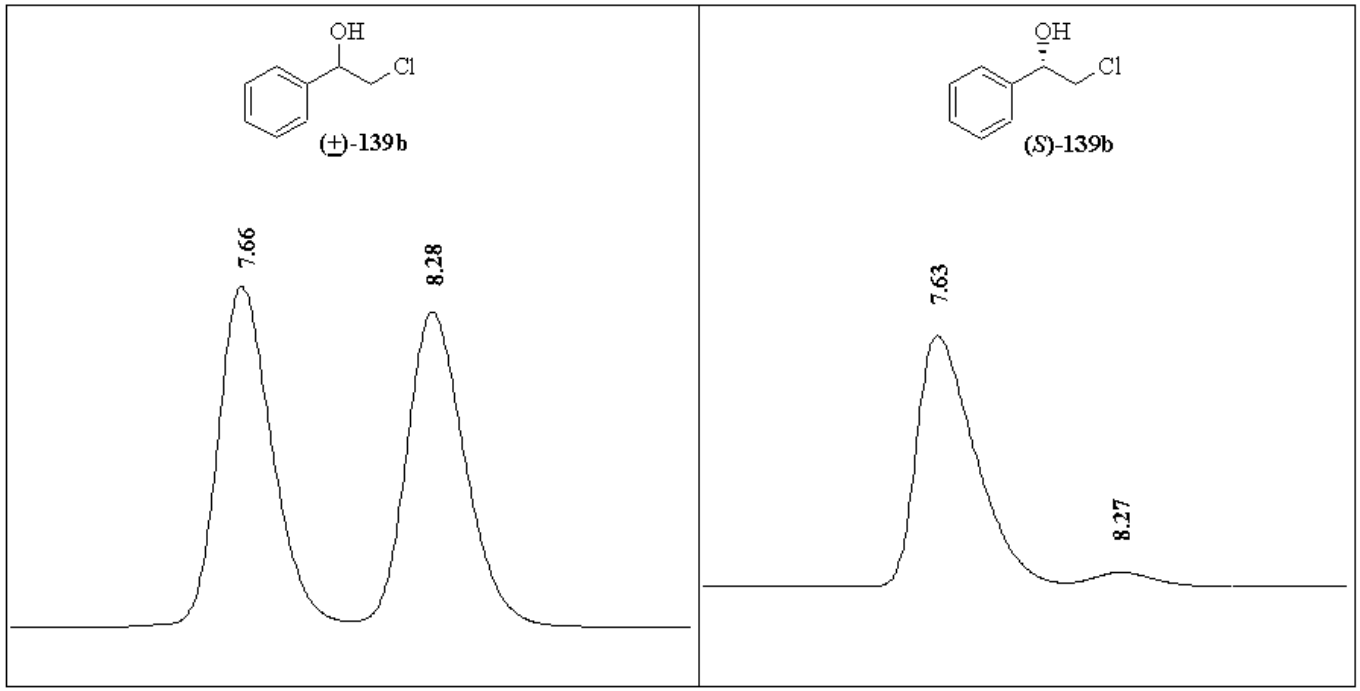
(***S***)-**139a** (90% *ee*) was obtained *via* the reduction of phenacyl bromide (**138a**) using 5 mol% **155** at reflux temperature.

HPLC analysis: Chromatogram 10



(***S***)-**139b** (88% *ee*) was obtained *via* the reduction of phenacyl chloride (**138b**) using 5 mol% **137** at reflux temperature.

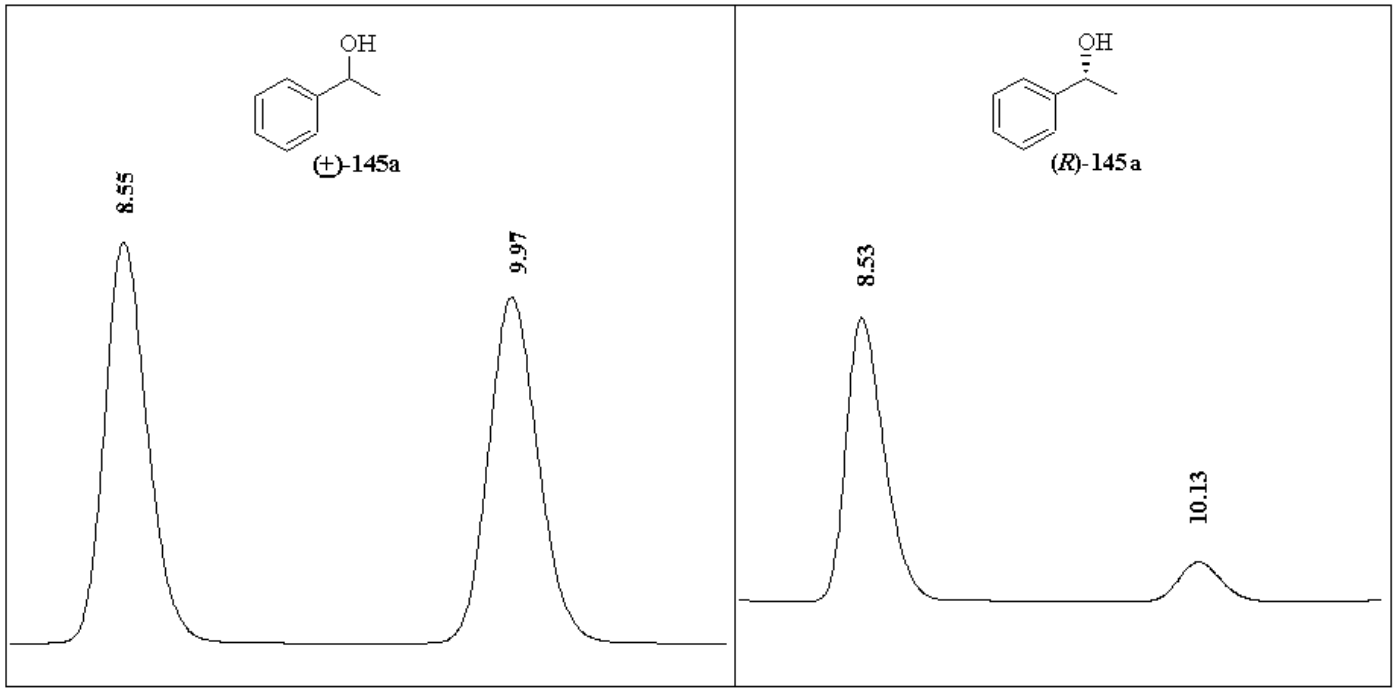
HPLC analysis: Chromatogram 11



(±)-2-Chloro-1-phenylethanol **(*S*)-2-Chloro-1-phenylethanol**

(***S***)-**139b** (89% *ee*) was obtained *via* the reduction of phenacyl chloride (**138b**) using 5 mol% **150** at reflux temperature.

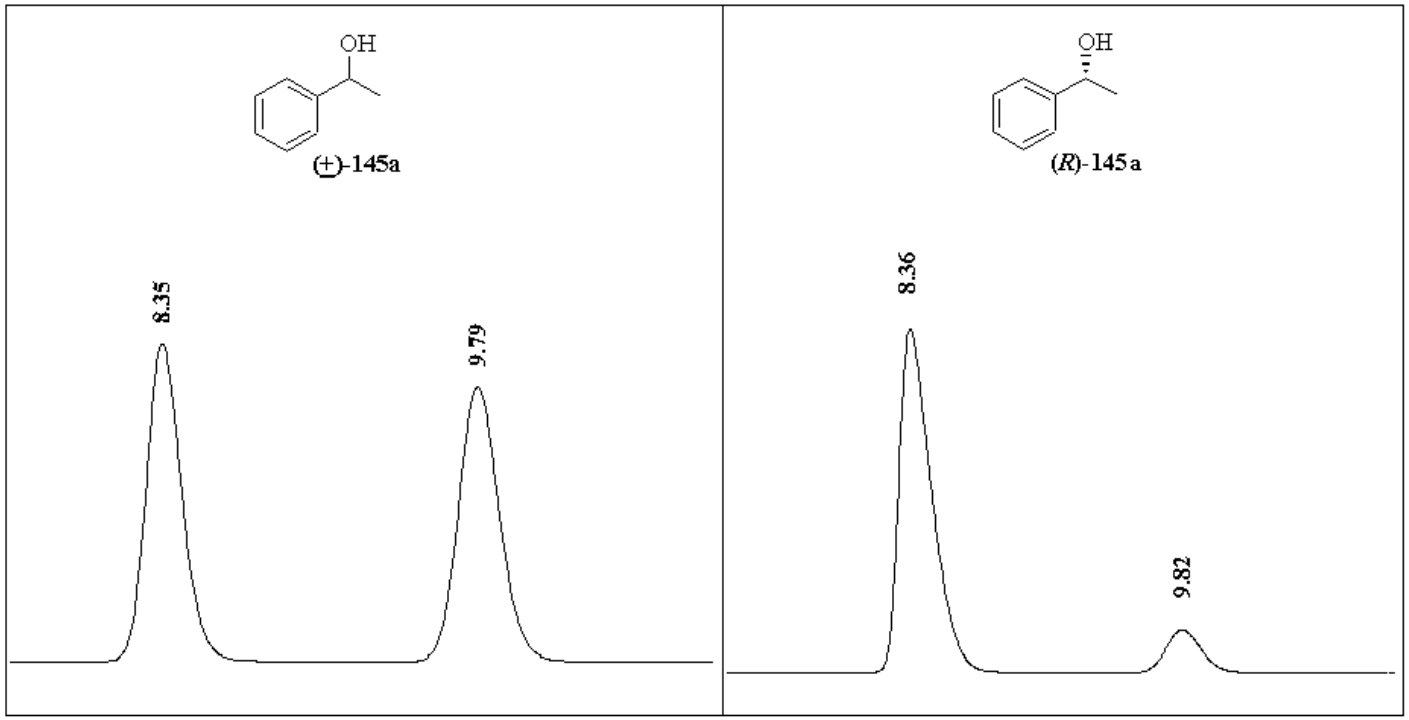
HPLC analysis: Chromatogram 12



(±)-1-Phenylethanol **(*R*)-1-Phenylethanol**

(*R*)-145a (81% *ee*) was obtained *via* the reduction of acetophenone (**144a**) using 5 mol% **149** at reflux temperature.

HPLC analysis: Chromatogram 13



(±)-1-Phenylethanol **(*R*)-1-Phenylethanol**

(*R*)-145a (82% *ee*) was obtained *via* the reduction of acetophenone (**144a**) using 5 mol% **154** at reflux temperature.

HPLC analysis: Chromatogram 14

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I: Atomic coordinates and equivalent isotropic displacement parameters for molecule **135**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	Y	Z	U(eq)
N(1)	0.59503(19)	0.22824(14)	0.5256(2)	0.0663(5)
N(2)	0.6991(2)	0.15412(16)	0.3407(2)	0.0719(5)
N(3)	0.4767(3)	0.0832(2)	0.4012(3)	0.1064(9)
C(1)	0.7169(2)	0.3009(2)	0.5070(2)	0.0718(6)
C(2)	0.7825(2)	0.2556(2)	0.3772(2)	0.0713(6)
C(3)	0.7771(3)	0.3254(2)	0.2458(2)	0.0856(7)
C(4)	0.7825(3)	0.2323(2)	0.1344(3)	0.0913(8)
C(5)	0.6895(3)	0.1391(2)	0.1896(3)	0.0847(7)
C(6)	0.5812(3)	0.14900(19)	0.4186(2)	0.0697(6)
C(7)	0.5187(2)	0.23222(17)	0.6469(2)	0.0617(6)
C(8)	0.4043(2)	0.1620(2)	0.6700(3)	0.0745(7)
C(9)	0.3379(3)	0.1664(2)	0.7945(3)	0.0859(8)
C(10)	0.3805(3)	0.2403(3)	0.8981(3)	0.0928(8)
C(11)	0.4909(3)	0.3115(3)	0.8752(3)	0.0891(8)
C(12)	0.5599(2)	0.3082(2)	0.7517(3)	0.0713(6)

Table II: Atomic coordinates and equivalent isotropic displacement parameters for molecule **142**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	**Y**	**Z**	**U(eq)**
O(1)	0.9057(2)	0.54242(18)	0.14069(11)	0.0563(5)
N(1)	0.8419(3)	0.6639(2)	0.03583(13)	0.0521(5)
N(2)	1.0359(4)	0.7398(3)	0.1220(2)	0.0759(9)
C(1)	0.9068(4)	0.7221(3)	-0.03674(17)	0.0707(9)
C(2)	0.9198(5)	0.6110(3)	-0.0944(2)	0.0881(11)
C(3)	0.8893(4)	0.4858(3)	-0.04799(18)	0.0657(8)
C(4)	0.7822(3)	0.5328(2)	0.01765(15)	0.0463(6)
C(5)	0.7872(3)	0.4667(2)	0.10012(15)	0.0446(5)
C(6)	0.8384(3)	0.3238(2)	0.10079(17)	0.0496(6)
C(7)	0.7807(4)	0.2338(3)	0.0475(2)	0.0644(8)
C(8)	0.8258(5)	0.1038(3)	0.0513(3)	0.0815(11)
C(9)	0.9306(5)	0.0620(3)	0.1067(3)	0.0846(12)
C(10)	0.9884(4)	0.1494(4)	0.1590(2)	0.0776(11)
C(11)	0.9437(3)	0.2799(3)	0.15723(18)	0.0603(7)
C(12)	0.6309(3)	0.4841(3)	0.14363(14)	0.0486(6)
C(13)	0.5088(4)	0.4019(4)	0.1303(2)	0.0802(10)
C(14)	0.3676(5)	0.4191(5)	0.1673(3)	0.1039(14)
C(15)	0.3441(5)	0.5167(5)	0.2181(2)	0.0953(14)
C(16)	0.4634(6)	0.6027(5)	0.2320(2)	0.1040(15)
C(17)	0.6070(5)	0.5873(4)	0.1947(2)	0.0808(10)
C(18)	0.9360(3)	0.6557(3)	0.10065(18)	0.0537(6)

Table III: Atomic coordinates and equivalent isotropic displacement parameters for molecule **149**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	**Y**	**Z**	**U(eq)**
Br(1)	0.36676(7)	0.44067(7)	1.26368(2)	0.05415(14)
O(1)	0.4790(6)	0.3512(4)	0.46955(18)	0.0556(8)
O(2)	0.5621(4)	0.4797(4)	0.78805(16)	0.0456(9)
N(1)	0.3613(6)	0.4953(4)	0.5972(2)	0.0397(9)
N(2)	0.1551(5)	0.5015(4)	0.83417(19)	0.0329(8)
C(1)	0.3441(8)	0.3636(5)	0.5350(3)	0.0426(10)
C(2)	0.1368(8)	0.2383(6)	0.5574(3)	0.0545(11)
C(3)	0.0591(8)	0.2972(6)	0.6500(3)	0.0559(12)
C(4)	0.1828(6)	0.4818(5)	0.6678(2)	0.0339(10)
C(5)	0.3243(6)	0.4899(4)	0.7683(2)	0.0307(9)
C(6)	0.2174(6)	0.4906(4)	0.9345(2)	0.0283(8)
C(7)	0.0475(7)	0.5696(5)	0.9898(2)	0.0343(8)
C(8)	0.0940(7)	0.5575(5)	1.0872(2)	0.0361(9)
C(9)	0.3082(6)	0.4665(6)	1.1295(2)	0.0342(9)
C(10)	0.4795(7)	0.3895(4)	1.0756(2)	0.0358(10)
C(11)	0.4356(6)	0.4002(4)	0.9775(2)	0.0321(9)

Table IV: Atomic coordinates and equivalent isotropic displacement parameters for molecule **151**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	**Y**	**Z**	**U(eq)**
F(1)	0.0547(3)	0.07233(17)	0.29918(12)	0.0855(5)
O(1)	0.9538(3)	0.42573(15)	1.19208(15)	0.0616(4)
O(2)	0.3873(3)	0.28662(15)	0.87067(13)	0.0589(4)
N(1)	0.9007(3)	0.27822(19)	1.02611(16)	0.0520(4)
N(2)	0.6016(3)	0.11839(16)	0.76529(14)	0.0429(3)
C(1)	0.8342(3)	0.33234(19)	1.13756(17)	0.0447(4)
C(2)	0.5882(4)	0.2595(2)	1.18278(18)	0.0495(4)
C(3)	0.5693(4)	0.1324(2)	1.10139(18)	0.0527(5)
C(4)	0.7399(4)	0.1630(2)	0.98487(18)	0.0487(4)
C(5)	0.5575(3)	0.19702(18)	0.86728(16)	0.0425(4)
C(6)	0.4537(3)	0.11249(18)	0.64726(15)	0.0399(4)
C(7)	0.5306(4)	0.01415(19)	0.56153(18)	0.0487(4)
C(8)	0.3969(4)	0.0006(2)	0.44418(19)	0.0572(5)
C(9)	0.1871(4)	0.0869(2)	0.41463(18)	0.0573(5)
C(10)	0.1063(4)	0.1850(2)	0.4959(2)	0.0548(5)
C(11)	0.2400(4)	0.19853(19)	0.61455(18)	0.0472(4)

Table V: Atomic coordinates and equivalent isotropic displacement parameters for molecule **153**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	X	**Y**	**Z**	**U(eq)**
F(1)	1.4036(6)	0.5593(3)	0.35536(11)	0.0606(7)
F(2)	1.1135(7)	0.3414(3)	0.52294(12)	0.0796(9)
O(1)	0.5392(7)	1.2893(3)	0.25141(12)	0.0523(8)
O(2)	0.6240(5)	0.8841(3)	0.37534(11)	0.0436(7)
N(1)	0.7173(6)	1.0704(3)	0.28272(12)	0.0346(7)
N(2)	1.0508(7)	0.7886(3)	0.36511(14)	0.0387(8)
C(1)	0.7009(7)	1.2189(4)	0.27982(15)	0.0358(8)
C(2)	0.9179(9)	1.2831(4)	0.31693(18)	0.0492(10)
C(3)	1.0234(8)	1.1525(4)	0.35127(16)	0.0423(9)
C(4)	0.9406(7)	1.0149(4)	0.31663(14)	0.0325(8)
C(5)	0.8503(7)	0.8879(4)	0.35504(14)	0.0316(7)
C(6)	1.0491(7)	0.6740(4)	0.40533(15)	0.0367(8)
C(7)	1.2371(9)	0.5593(4)	0.40016(17)	0.0415(9)
C(8)	1.2623(10)	0.4471(4)	0.43853(18)	0.0508(11)
C(9)	1.0877(10)	0.4496(4)	0.48363(19)	0.0532(12)
C(10)	0.8955(9)	0.5570(5)	0.49059(17)	0.0538(11)
C(11)	0.8752(8)	0.6703(5)	0.45119(17)	0.0470(10)

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