Synthesis and Applications of Chiral Amines Containing *trans*-1,2-Diaminocyclohexane and 2,3-Diphenylpiperazine Moieties

A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

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Dedicated to

My Bapa and Bou

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled "**Synthesis and Applications of Chiral Amines Containing *trans*-1,2-Diaminocyclohexane and 2,3-Diphenylpiperazine Moieties**" has been carried out by Ms. **Manasi Dalai** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

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Manasi

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
Ac	acetyl
anhyd.	anhydrous
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tertiary*-butoxycarbonyl
BOX	bis(oxazoline)
br	broad (in spectroscopy)
BSA	bis-(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
COD	cyclooctadiene
conf.	configuration
cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
d	doublet (in spectroscopy)
dba	dibenzylideneacetone
de	diastereomeric excess
DHQ-CLB	dihydroquinine-(4-chlorobenzoylether)
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
h	hour(s)
hex	hexane
HPLC	high performance liquid chromatography
^{i}Pr	isopropyl
IPA	2-propanol
IR	infrared

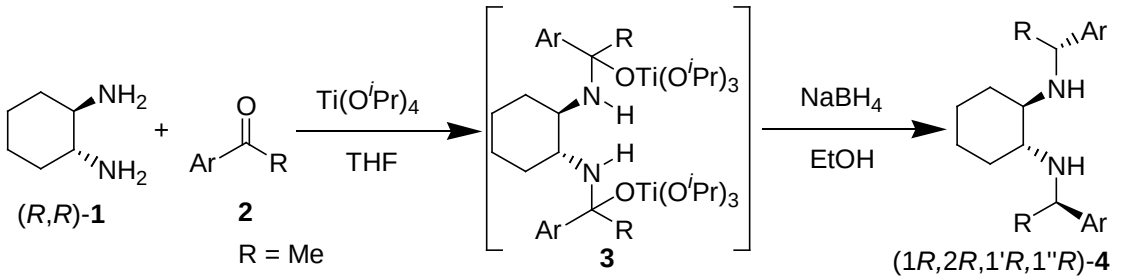
J	coupling constant (in NMR spectroscopy)
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature
m	multiplet (in spectroscopy)
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
min.	minute(s)
mp	melting point
MS	mass spectrum
Ms	methanesulfonyl
MS	molecular sieves
MSA	methanesulfonic acid
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Np	naphthyl
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Pent	pentyl
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet (in spectroscopy)
ref	reference number
rt	room temperature
s	singlet (in spectroscopy)
sat.	saturated
sec	secondary
T	temperature
t	tertiary
t	triplet (in spectroscopy)
TBDMS	*tertiary*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultraviolet

Abstract

This thesis describes studies on the "**Synthesis and Applications of Chiral Amines Containing *trans*-1,2-Diaminocyclohexane and 2,3-Diphenylpiperazine Moieties**". It comprises of four chapters. Each chapter is subdivided into four parts namely, **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**. The work described in this thesis is exploratory in nature.

The first chapter describes a convenient method for the synthesis of C_2-symmetric chiral diamines (**4a**-**4i**) containing (*R*,*R*)-*trans*-1,2-diaminocyclohexane moiety through diastereoselective reductive *N*-alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **1** with prochiral ketones **2** using the $Ti(O^iPr)_4/NaBH_4$ reagent system *via* the intermediate **3** in a single pot operation (Scheme 1).

Scheme 1



a: Ar = Ph
b: Ar = 4-NO_2-C_6H_4
c: Ar = 4-Cl-C_6H_4
d: RCOAr = tetralone
e: Ar = 2-thiophenyl
f: Ar = 2-naphthyl
g: Ar = 2-pyridyl
h: Ar = 4-Me-C_6H_4
i: Ar = 4-MeO-C_6H_4

up to 95% yield
up to 23:1:1 dr

The absolute configuration at the newly formed stereogenic centres of the major diastereomer **4c** was confirmed to be (1*R*,2*R*,1'*R*,1''*R*) by single crystal X-ray analysis.

The second chapter describes details of investigations on the use of the readily accessible chiral C_2-symmetric diamines **4a** and **4d** containing *trans*-1,2-diaminocyclohexyl moiety as chiral solvating agents (CSAs) for determination of the enantiomeric excess of mandelic acid **5**, 2,3-diphenylsuccinic acid **6** and *N*-Ts-phenylglycine **7** (Figure 1). The enantiomeric composition of different carboxylic acids estimated herein by the ^{1}H NMR method, based on the integration of the corresponding methine proton ($C^{\alpha}H$) signals are in excellent correlation with that determined using HPLC method. The data are in accordance with the formation of multimolecular diastereomeric complexes in solution, which render good splitting of NMR signals for the enantiomers of representative carboxylic acids.

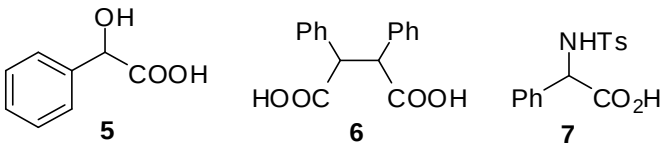


Figure 1. Structure of the carboxylic acids

Studies undertaken on the hydroboration reaction of olefins using chiral amine borane complexes **8**-**11** (Figure 2) and aminoborane complex **12a** are described in Chapter 3.

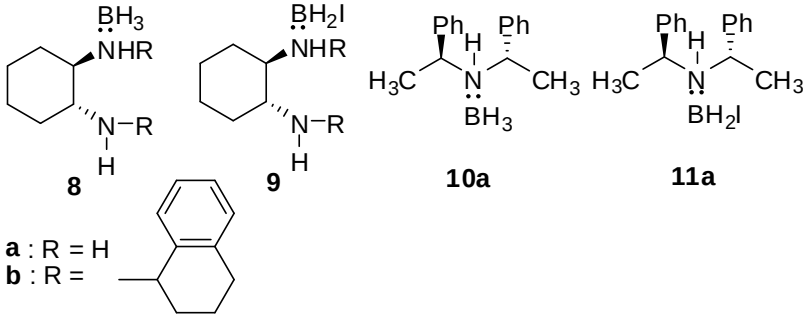
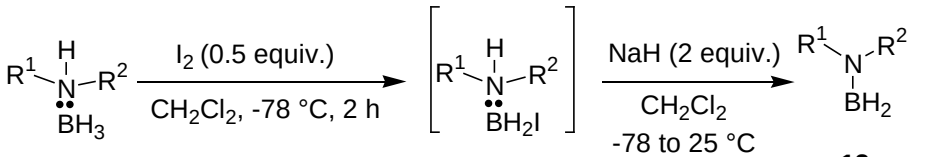


Figure 2. Chiral amine-BH_3 and BH_2I complexes

Hydroboration oxidation of α-methylstyrene, *cis* and *trans*-stilbene using these complexes (Figure 3) gave the corresponding alcohols in up to 75% yields with only 5% ee. Mechanistic implications of these results are briefly discussed.

A convenient one pot method for the synthesis of aminoboranes **12** with up to 100% conversion by the reaction of the corresponding secondary amine-BH_2I complexes **11** with NaH at 25 °C was developed (Scheme 2).

Scheme 2



10

a: $R^1 = R^2 =$ (*S*)-Ph(Me)C*****H

b: $R^1 = R^2 = {}^i$Pr

c: $R^1 = {}^i$Pr, R^2 = (*S*)-Ph(Me)C*****H

11

100% conversion

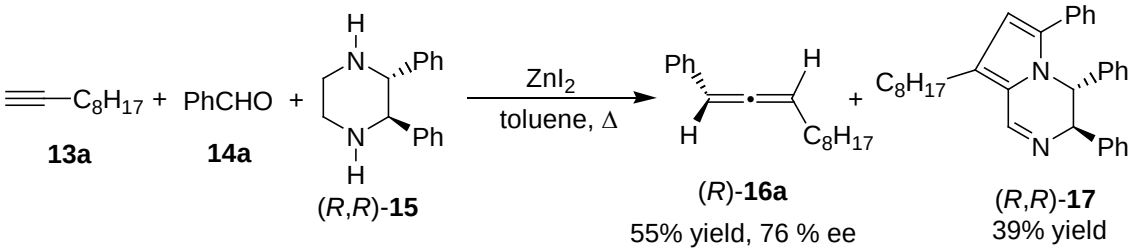
12

up to 100% conversion

Hydroboration of α-methylstyrene takes place only at 120 °C, using the chiral (*S*,*S*)-bis-(1-phenyl-ethyl)-aminoborane **12a**, giving only the racemic product 2-phenylpropanol in 43% yield after H_2O_2/OH^- oxidation.

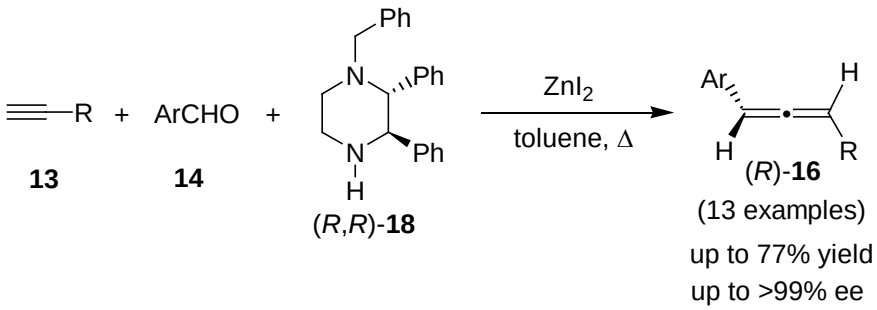
Studies on the applications of (*R*,*R*)-2,3-diphenylpiperazine derivatives toward enantioselective synthesis of chiral allenes are described in Chapter 4. A convenient one pot method has been developed for the enantioselective synthesis of chiral allenes **16** using the readily accessible terminal alkynes **13**, arylaldehydes **14** and chiral (*R*,*R*)-2,3-diphenylpiperazine derivatives **15** and **18** in the presence of zinc iodide. The reaction using the (*R*,*R*)-2,3-diphenylpiperazine **15** as chiral auxiliary, gave the (*R*)-allene **16a** in 76% ee and 55% yield along with the bicyclic product **17** (Scheme 3).

Scheme 3



Fortunately, the use of (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **18** gave the (*R*)-allene **16** in up to 77% yield and >99% ee (Scheme 4).

Scheme 4



Several experiments were performed to understand the intermediates and mechanisms involved in this transformation. The results are discussed comparing the reports on similar transformations in the literature.

Note: Scheme numbers and compound numbers given in this abstract are different from those given in the chapters. Also different set of numbers for Schemes, Tables, compounds, Figures and references etc. are given in different chapters.

Chapter 1

Studies on reductive N-alkylation of (R,R)-trans-1,2-diaminocyclohexane

1.1 Introduction

Amines and their derivatives are highly versatile building blocks for the synthesis of various organic molecules and essential precursors for the synthesis of a variety of biologically active compounds. Among the amine family, compounds incorporating the chiral 1,2-diamines functionality are currently of immense research interest. For instance, chiral 1,2-diamine moiety is present in many natural products with notable biological properties such as biotin (**1**),[1] also referred as vitamin H or B_7 and penicillins (**2**),[2a] well known antibiotics. Several synthetic pharmaceuticals such as oxaliplatin (**3**),[2a] an anticancer drug; Tamiflu (**4**),[2b] an anti-viral drug and U-50,488 (**5**),[3] a highly selective κ-opioid agonist contain a chiral 1,2-diamine moiety. In catalysis, enantiomerically pure 1,2-diamines and their derivatives are used in the development of various metal complexes, used in organic syntheses,[4] like Grubbs chiral metathesis catalyst (**6**),[5] Jacobsen epoxidation catalyst (**7**)[6] and Maruoka organocatalyst (**8**)[7] (Figure 1).

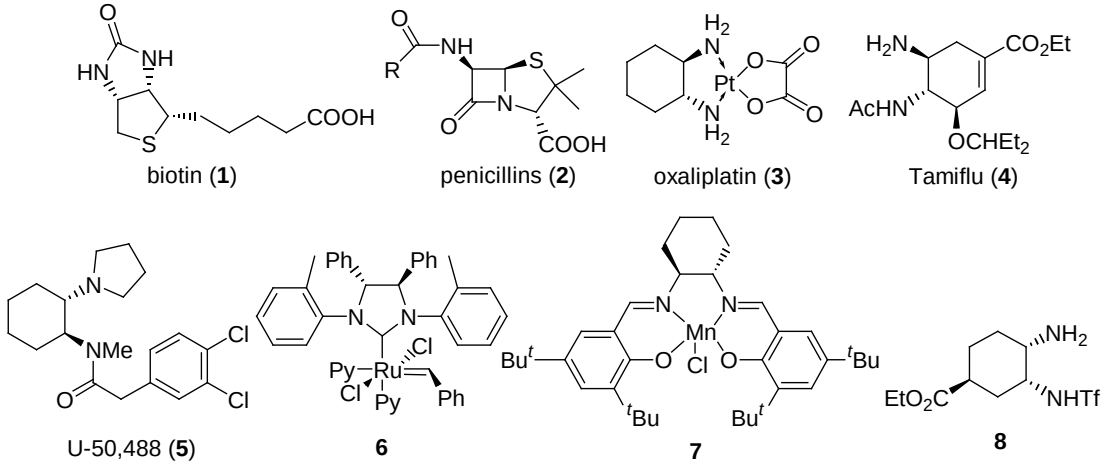


Figure 1

We have envisaged the synthesis of a series of C_2-symmetric 1,2-diamines starting from (*R*,*R*)-*trans*-1,2-diaminocyclohexane *via* a Ti(IV)-isopropoxide mediated reductive *N*-alkylation reaction. A brief review of various methods available for the synthesis of chiral 1,2-diamines will be useful for the discussion.

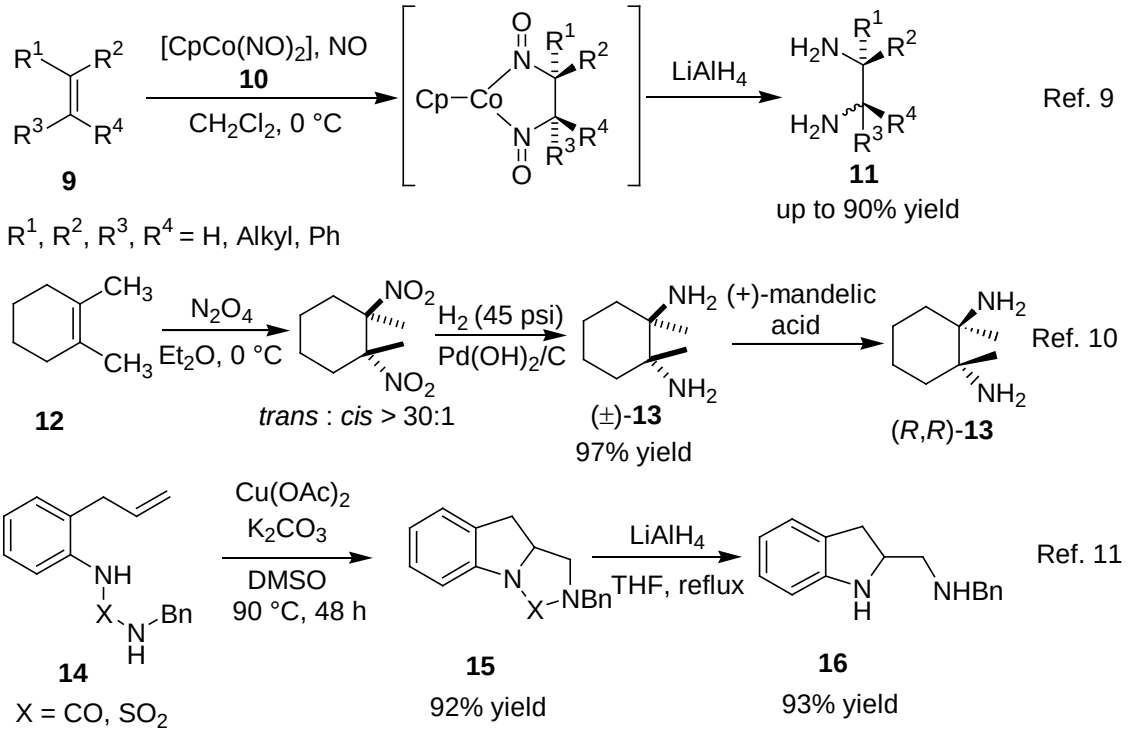
1.1.1 Synthesis of chiral 1,2-diamines

Although enantiopure chiral 1,2-diamines have been obtained through resolution of the racemates,[8] several diastereo- and enantioselective methods are employed increasingly for their synthesis. An overview on the reported synthesis of 1,2-diamines, with emphasis on the stereoselective methods is outlined here.

1.1.1.1 Synthesis of chiral 1,2-diamines from olefins

Different methods of preparation of chiral 1,2-diamines from olefins by inter or intramolecular diamination reactions are given in Chart 1.

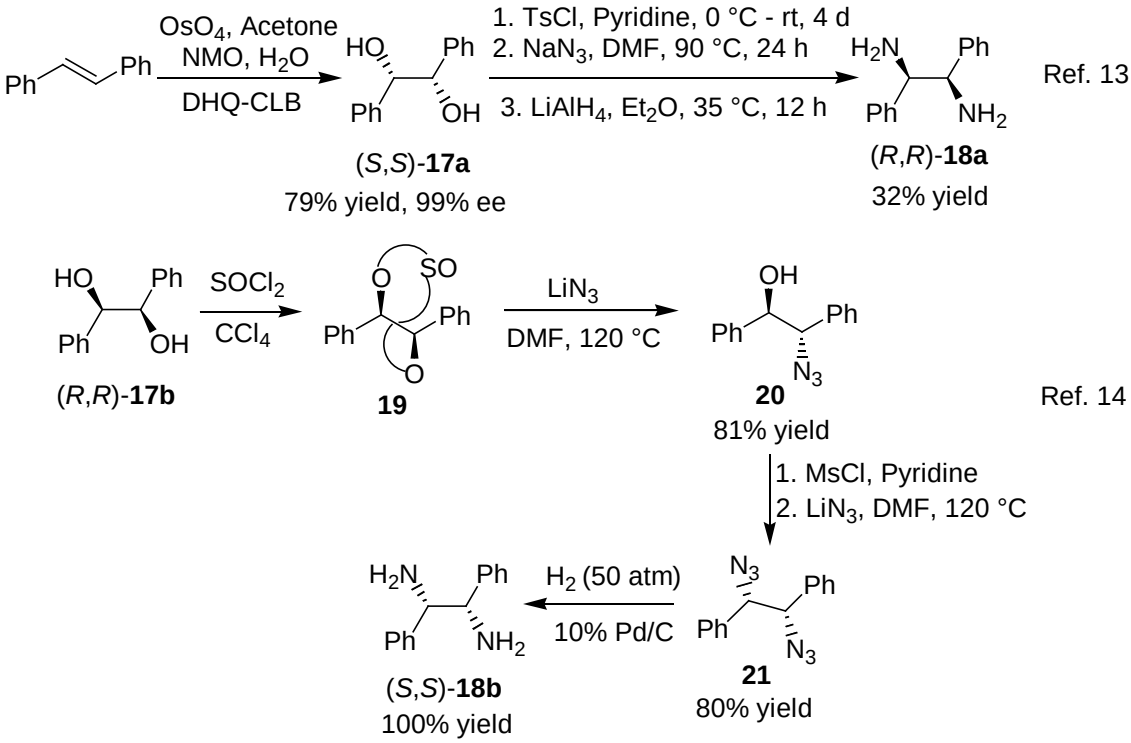
Chart 1



1.1.1.2 Synthesis of chiral 1,2-diamines from 1,2-diols

The efficiency of osmium catalyzed asymmetric dihydroxylation[12] allows access to various enantiomerically pure 1,2-diols that can be converted by several methods into enantiopure vicinal diamines (Chart 2).

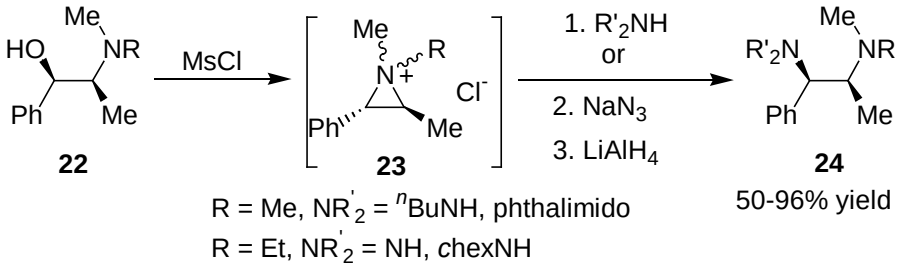
Chart 2



1.1.1.3 Synthesis of chiral 1,2-diamines from 1,2-amino alcohols

A stereo- and regioselective route to chiral diamines from (-)-ephedrine and (-)-pseudoephedrine was reported (Scheme 1).[15] This strategy relied on the transformation of the chiral 1,2-amino alcohol **22** into aziridinium ion **23**, which was then treated with various nitrogen nucleophiles to afford the corresponding diamines **24**, after $LiAlH_4$ reduction.

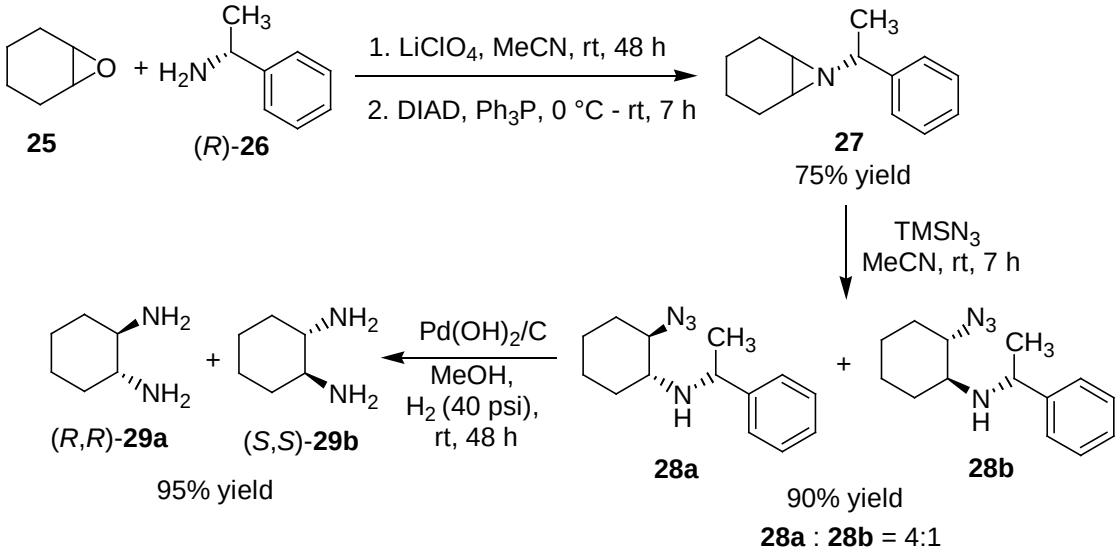
Scheme 1



1.1.1.4 Synthesis of chiral 1,2-diamines from aziridines

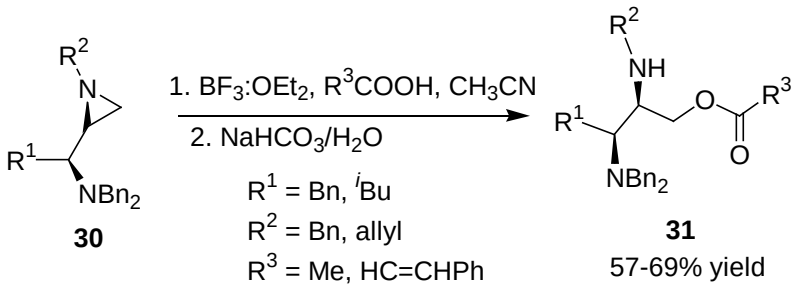
Synthesis of chiral 1,2-diaminocyclohexanes **29** starting from the chiral aziridine **27** has been reported.[16] The chiral aziridine **27** synthesized from cyclohexene oxide **25** and (*R*)-1-phenylethylamine **26**, was opened with TMS azide in acetonitrile to give two separable diastereomers **28a** and **28b** in 4:1 ratio. Hydrogenation of the diastereomers yielded the corresponding (*R*,*R*)-1,2-diaminocyclohexane **29a** and (*S*,*S*)-1,2-diaminocyclohexane **29b** (Scheme 2).

Scheme 2



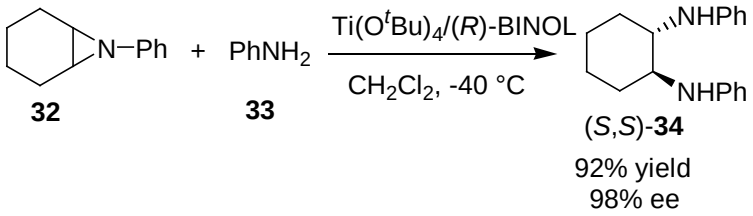
The *O*-acylated 2,3-diaminoalkanol **31** was synthesized by the ring opening of the unactivated aziridine **30** using carboxylic acid in the presence of BF_3:OEt_2 (Scheme 3).[17]

Scheme 3



Recently, Schneider *et al.*[18] reported the first highly enantioselective ring opening of *meso* aziridines **32** by titanium binolate catalyzed reaction using aniline **33** to furnish the valuable 1,2-diamine **34** with excellent optical purities in one step (Scheme 4).

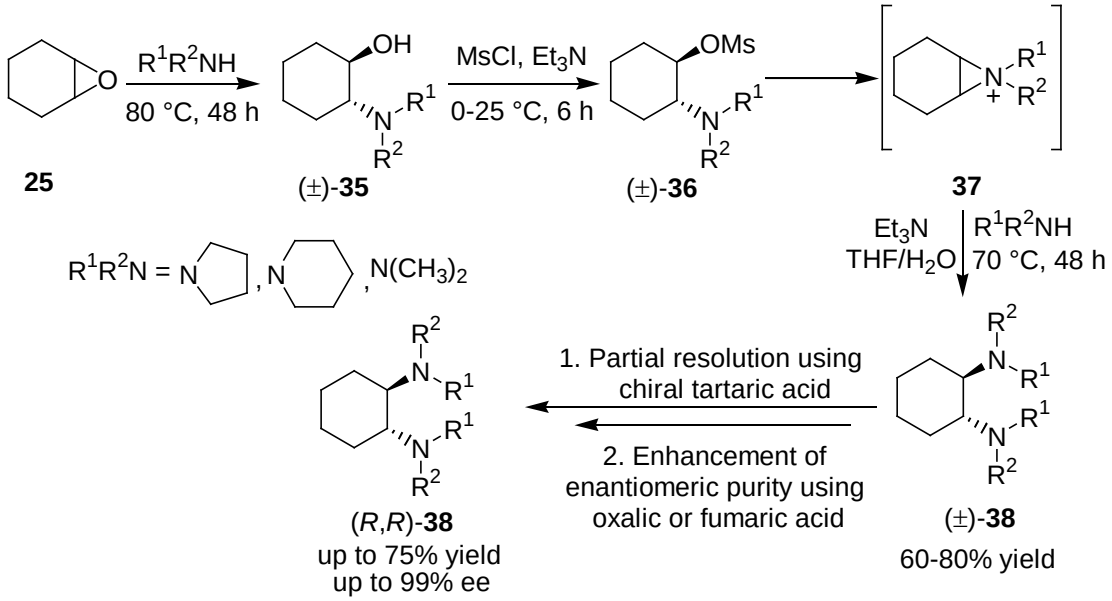
Scheme 4



From this laboratory, a method of synthesis of C_2-symmetric 1,2-diaminocyclohexane derivatives **38** involving the nucleophilic ring opening of the aziridinium ion intermediates **37**, prepared *in situ* from the mesylates **36** of the 1,2-amino alcohols **35**, which in turn were prepared by the ring opening of cyclohexene oxide **25** with various amine nucleophiles was developed (Scheme 5).[19a] Some of these amine derivatives were readily resolved by using chiral tartaric acid derivatives and

enriched to obtain enantiomerically pure diamines *via* preparation of homo- or hetero-chiral aggregates using achiral carboxylic acid like oxalic or fumaric acid (Scheme 5).[19b]

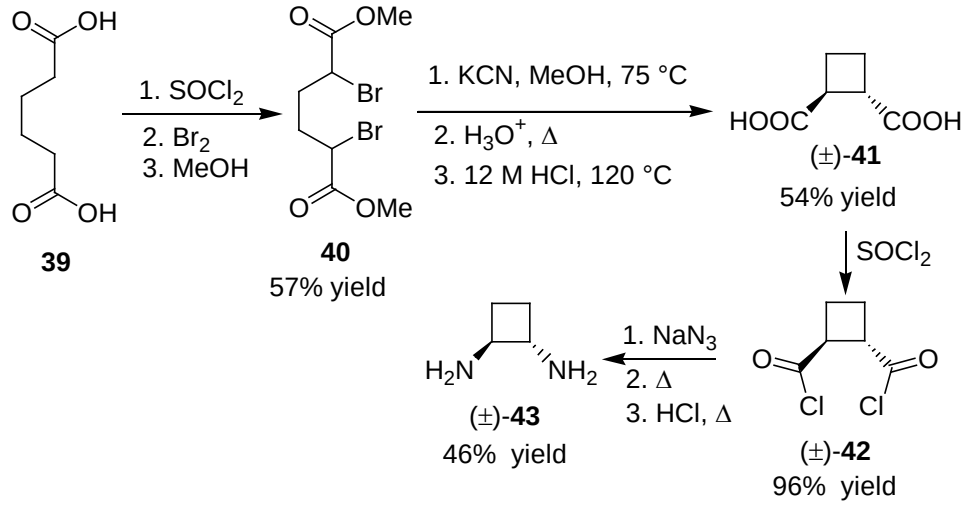
Scheme 5



1.1.1.5 Synthesis of chiral 1,2-diamines from dicarboxylic acids

The synthesis of the racemic *trans*-1,2-diaminocyclobutane **43** starting from adipic acid **39** was reported (Scheme 6).[20] Finally, resolution of the racemic diamine **43** using L-(+)-tartaric acid yielded the enantiopure (+)-1,2-diaminocyclobutane **43**.

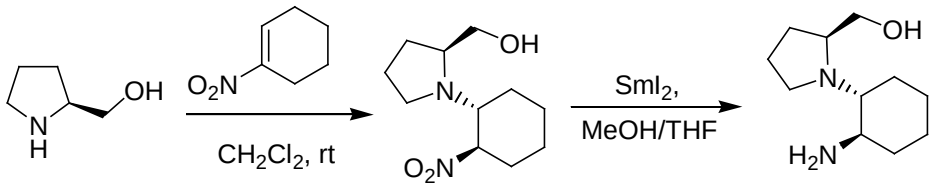
Scheme 6



1.1.1.6 Synthesis of chiral 1,2-diamines from nitroalkenes

Michael type addition of (*S*)-2-pyrrolidinylmethanol **44** to 1-nitro-1-cyclohexene afforded a single adduct **45** in excellent yield and stereoselectivity (Scheme 7).[21] The reduction of the nitro group with samarium diiodide in methanol-THF mixture yielded the corresponding diamine **46**.

Scheme 7



(*S*)-**44** **45** 95% yield **46** 90% yield

1.1.1.7 Synthesis of chiral 1,2-diamines from amino acids and their derivatives

Methods have been reported for the conversion of amino acids and their derivatives to enantiopure vicinal diamines (Chart 3).

Chart 3

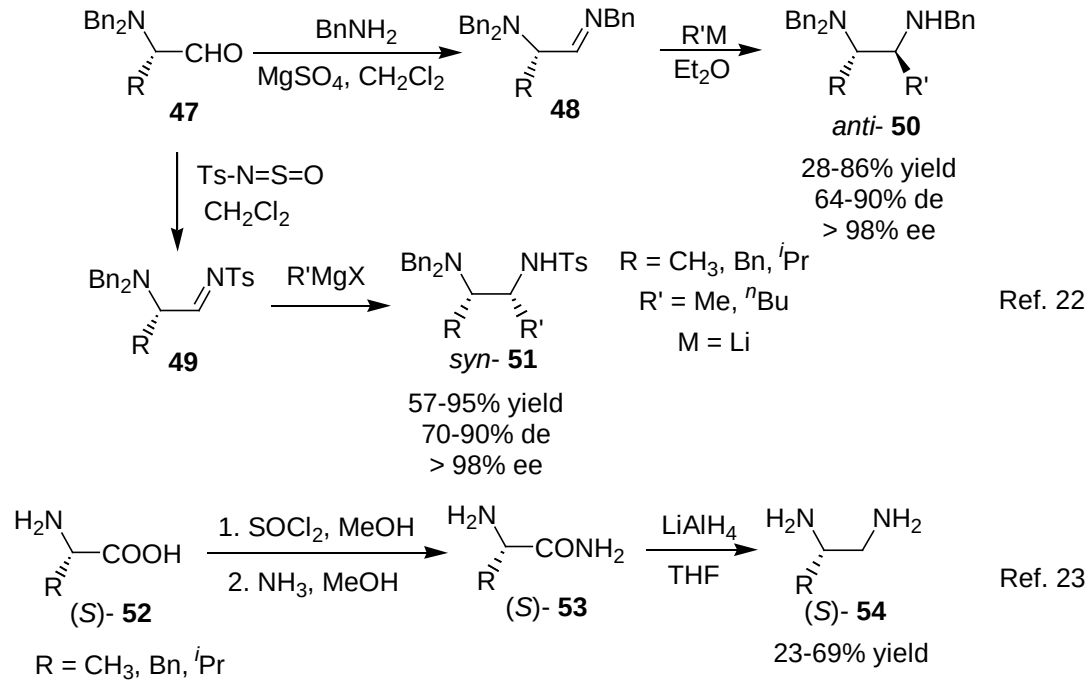
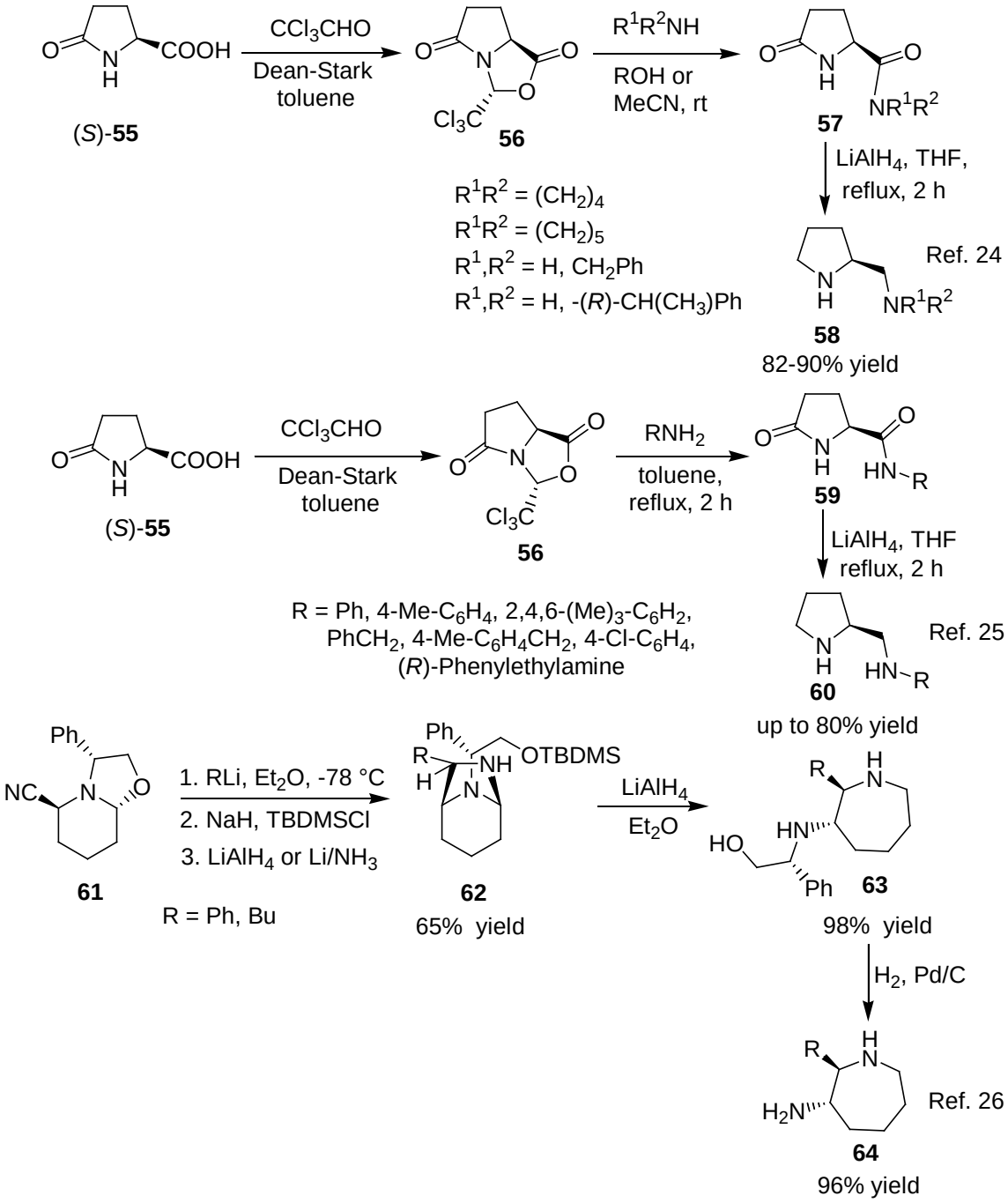


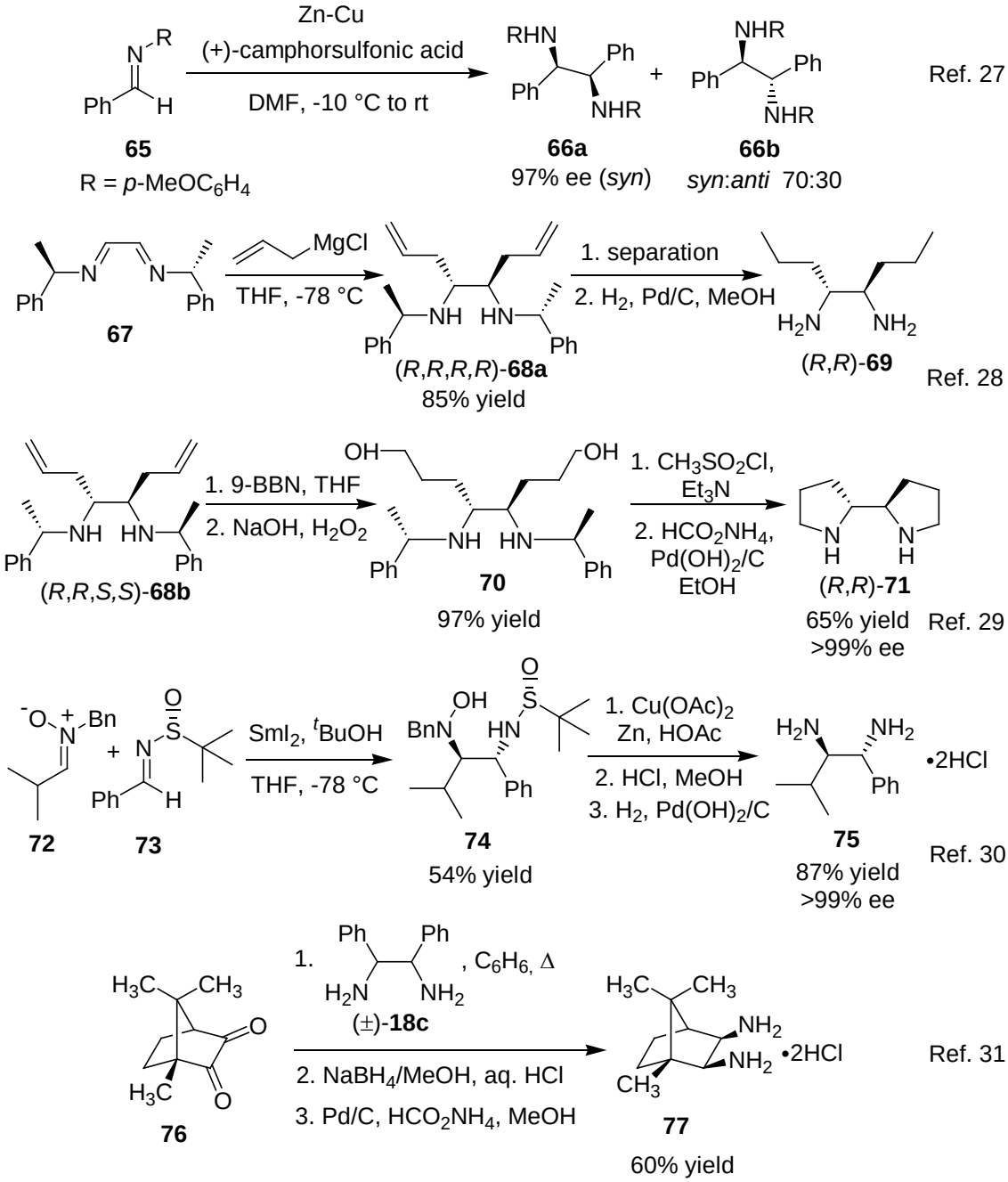
Chart 3 continued…



1.1.1.8 Synthesis of chiral 1,2-diamines from imines

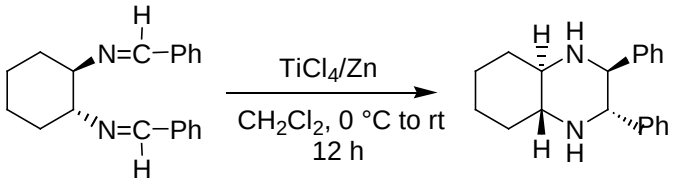
In principle, the reductive coupling of imines with the help of a metal or metallic complex is a simple way to prepare 1,2-diamines. Several enantioselective and diastereoselective reductive coupling of imines have been reported (Chart 4).

Chart 4



It has been reported from this laboratory that the chiral 3,4-disubstituted 2,5-diazabicyclo[4.4.0]decane **79** can be readily prepared by the intramolecular coupling of the bis-imine **78** using a low-valent titanium species (Scheme 8).[32]

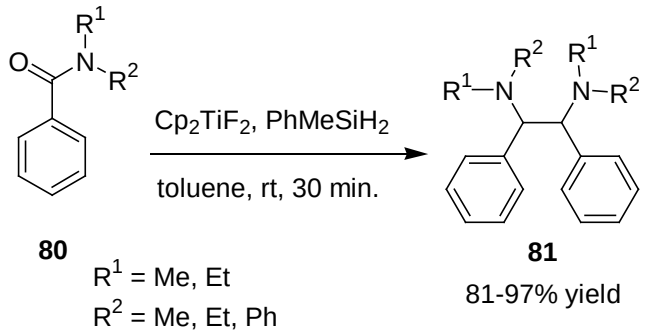
Scheme 8



1.1.1.9 Synthesis of chiral 1,2-diamines from amides

The titanocene catalyzed coupling of the amides **80** in the presence of organosilanes give a *meso*/racemic mixture of 1,2-diamines **81** (Scheme 9).[33]

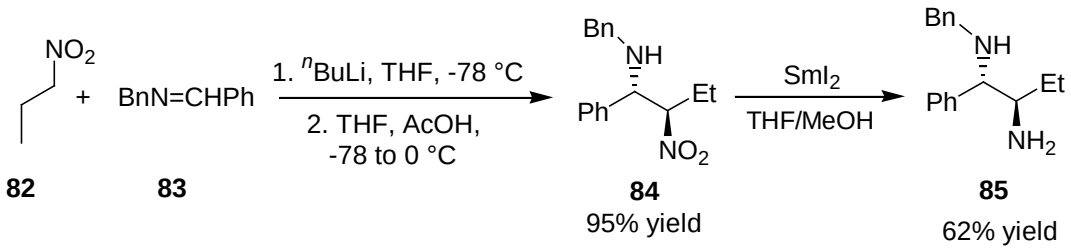
Scheme 9



1.1.1.10 Synthesis of chiral 1,2-diamines from nitroalkanes

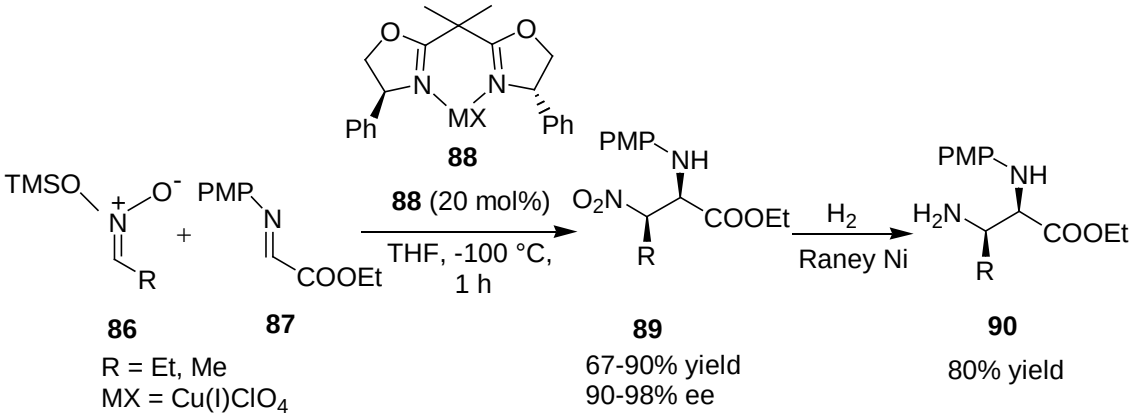
Addition of the nitropropane **82** to the imine **83** (nitro-Mannich reaction) provides the corresponding β-nitroamine **84** which on reduction with SmI_2 gives the 1,2-diamine **85** in high yield and good diastereoselectivity (Scheme 10).[34]

Scheme 10



Addition of the trimethylsilyl nitronate **86** to *N*-protected α-imino esters **87** catalyzed by the (*S*)-Ph-BOX-copper catalyst **88** afforded the β-nitro-α-amino esters **89**. Amino esters **89** were reduced to the synthetically useful α,β-diamino esters **90** in 80% yield using Raney Ni/H_2 reagent system (Scheme 11).[35]

Scheme 11



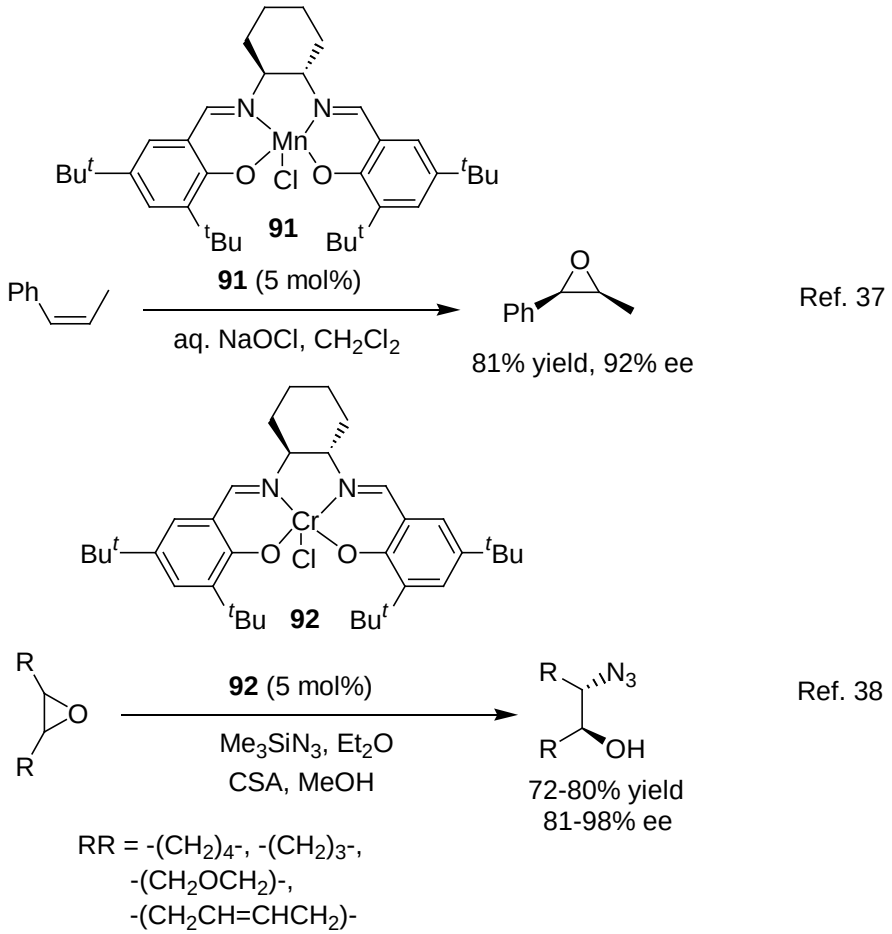
1.1.2 Synthetic applications of chiral 1,2-diamine derivatives

Enantiomerically pure C_2-symmetrical 1,2-diamines and their derivatives are particularly useful as chiral auxiliaries or ligands. These derivatives have found tremendous application in stereoselective syntheses.[2,36] In this field, several C_2-symmetric chiral 1,2- diamines and their derivatives containing 1,2-cyclohexyl moiety offer especially great promise in a variety of asymmetric organic transformations. A brief overview on the applications of these derivatives is summarized below.

1.1.2.1 Salen complexes

The Mn(salen) complex **91** and Cr(salen) complex **92** have been used in the asymmetric epoxidation of variety of olefins and asymmetric epoxide opening reactions, respectively (Chart 5).

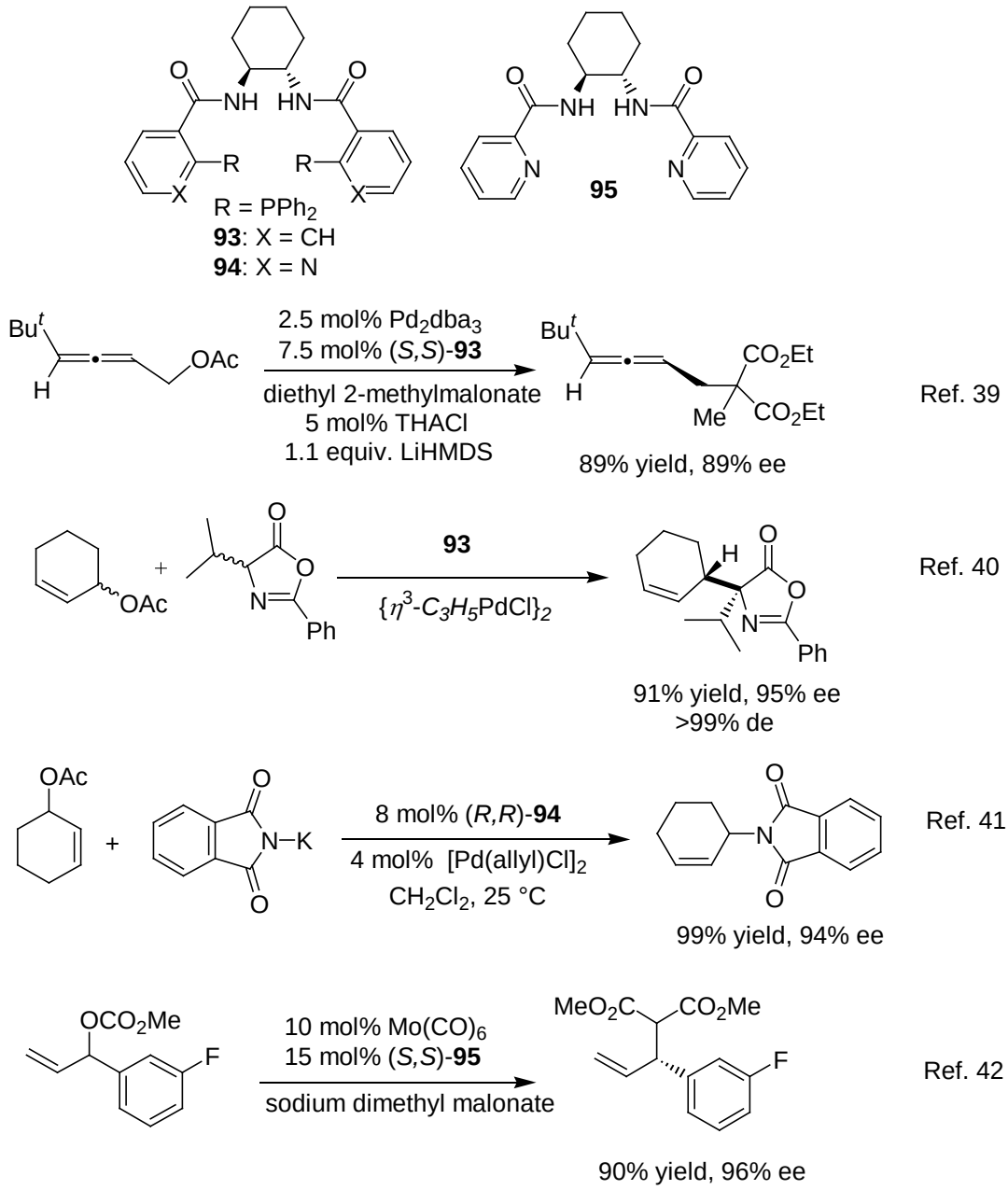
Chart 5



1.1.2.2 Chiral 1,2-diamides

Several C_2-symmetric chiral 1,2-diamide derivatives have been prepared and used as ligands in transition metal catalyzed asymmetric C-C and C-N bond forming reactions (Chart 6).

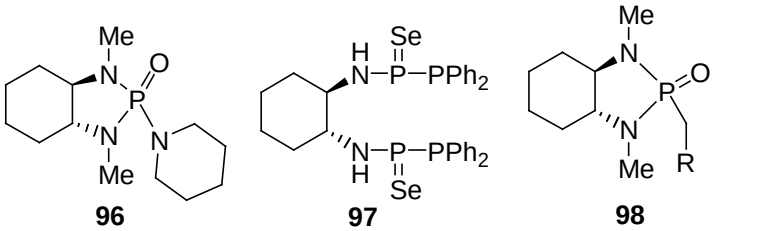
Chart 6

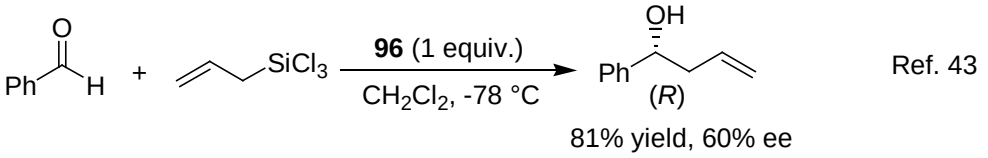


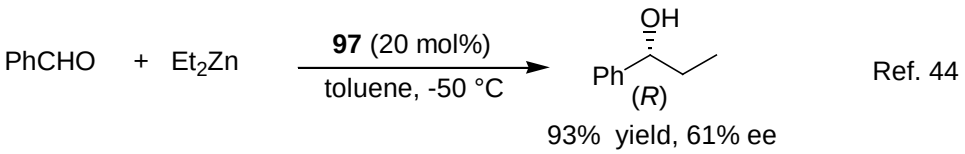
1.1.2.3 Chiral phosphoramides

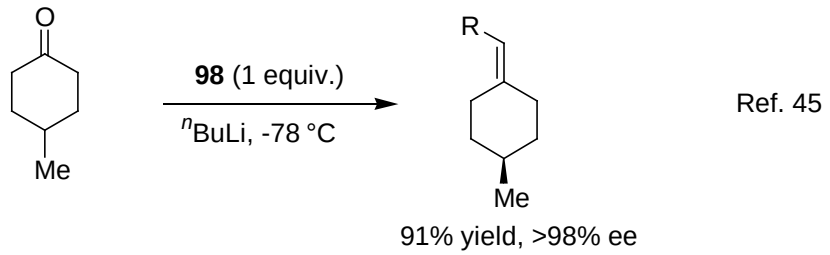
Chiral phosphoramides of C_2-symmetric 1,2-diamines have been used as reagents and catalysts in allylation of aldehydes, diethylzinc addition, asymmetric olefination of ketones and trichlorosilyl enolate addition to aldehydes (Chart 7).

Chart 7









1.1.2.4 Chiral sulfonamides

Bis-sulfonamides have been demonstrated for use as catalysts in diethylzinc addition to various aldehydes, ketones and in the C-C bond forming reactions (Chart 8).

Chart 8

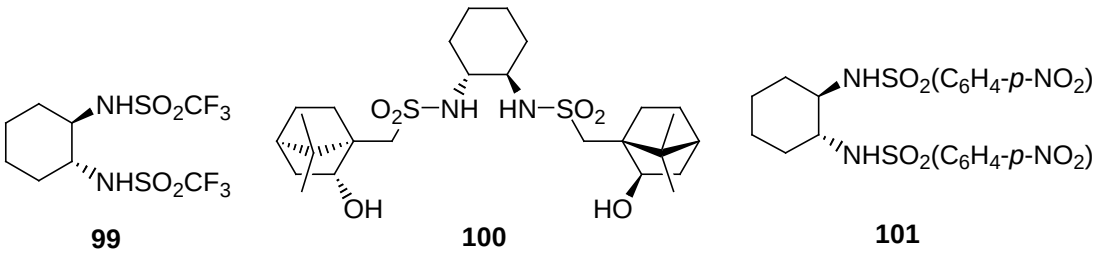
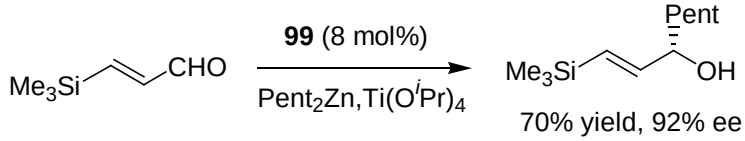
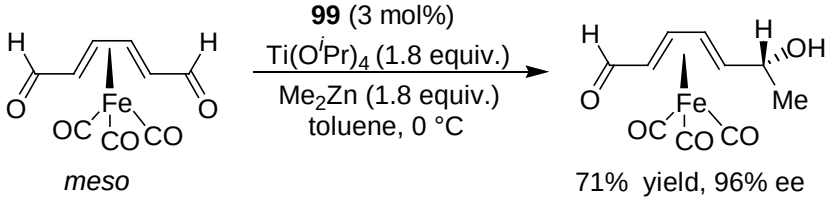


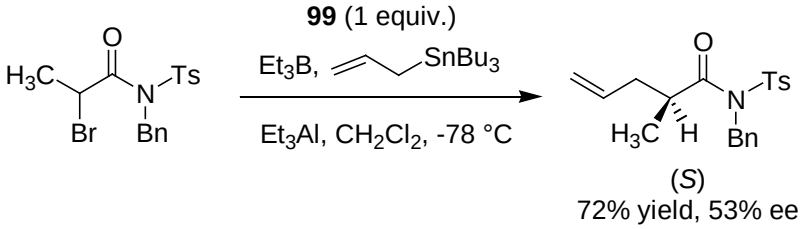
Chart 8 continued…



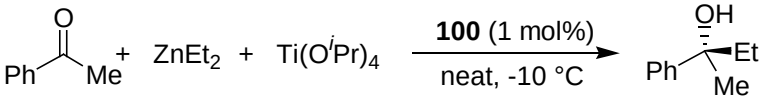
Ref. 46



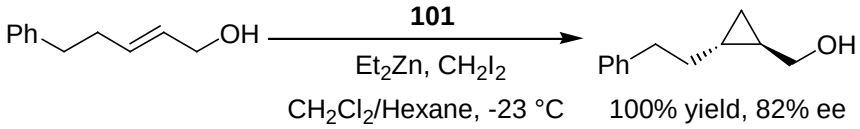
Ref. 47



Ref. 48



Ref. 49

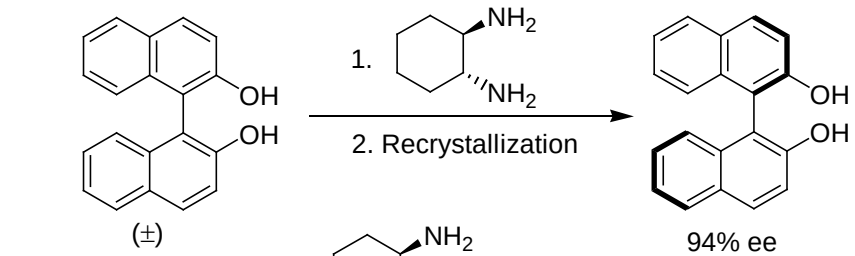


Ref. 50

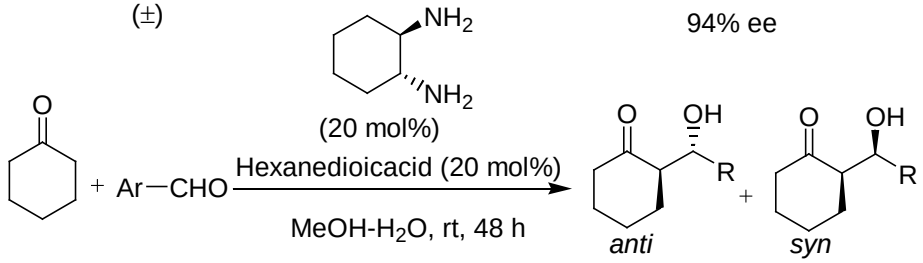
1.1.2.5 Chiral 1,2-diamines

Chiral C_2-symmetrical 1,2-diamines containing (*R*,*R*)-*trans*-(1,2)-diaminocyclohexane moiety have been used in the resolution of racemic BINOL, enantioselective aldol reactions, asymmetric pinacol coupling and dihydroxylation of alkenes (Chart 9).

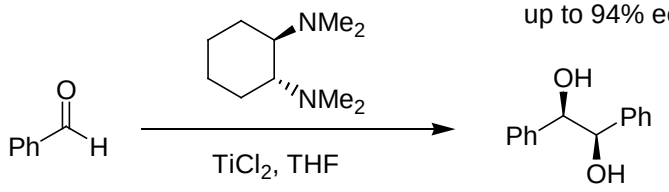
Chart 9



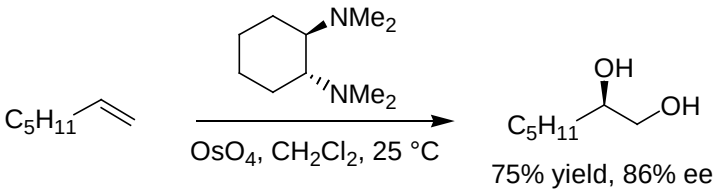
Ref. 51



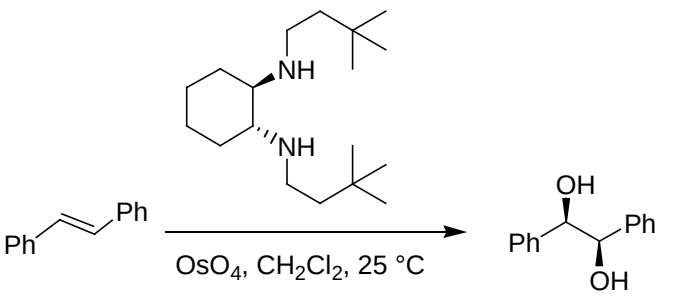
Ref. 52



Ref. 53



Ref. 54

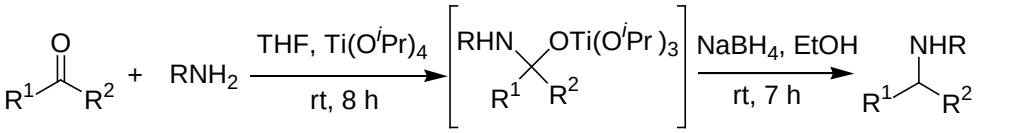


Ref. 55

There have been continued interest in this laboratory on the synthesis and applications of various chiral secondary amines as outlined in the Schemes 5 and 8.[19,32]

The reductive *N*-alkylation of amine is a convenient and important tool for chemists to target synthesis of primary, secondary and tertiary amines. Recently, there have been reports on the reductive mono *N*-alkylation of primary amines **103** with ketones **102** using the $Ti(O^iPr)_4/NaBH_4$ reagent system to obtain the corresponding *N*-alkylated product **105** (Scheme 11).[56-60]

Scheme 11



102 **103** **104** **105**

R^1 = aryl, R^2 = alkyl

up to 84% yield

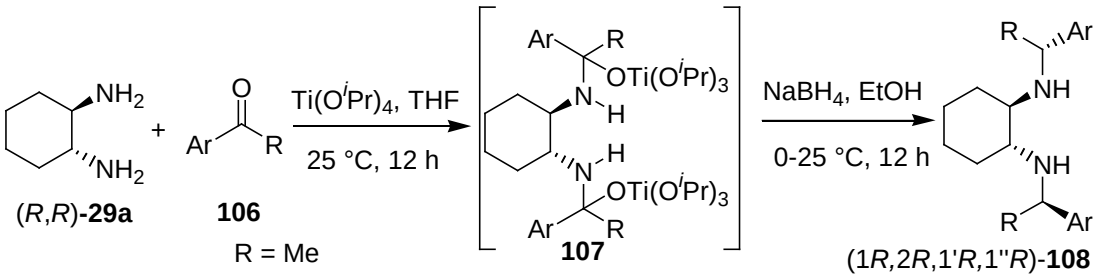
We have undertaken studies to explore this reductive *N*-alkylation methodology to access chiral C_2-symmetric 1,2-diaminocyclohexane derivatives. The results are discussed in the next section.

1.2 Results and Discussion

1.2.1 *N*-Alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane using $Ti(O^iPr)_4/NaBH_4$ system

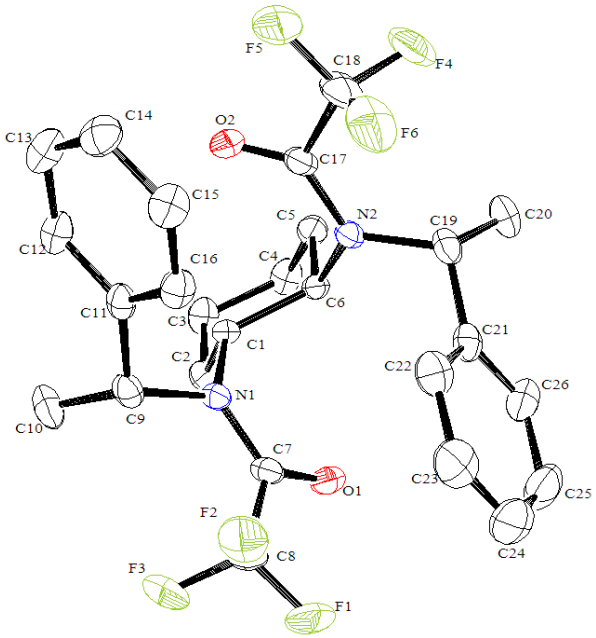
Initially, we have examined the titanium(IV) mediated reductive *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **29a** with acetophenone **106a** using the $Ti(O^iPr)_4/NaBH_4$ system (Scheme 12). Acetophenone **106a** was reacted with the chiral (*R*,*R*)-diamine **29a** and $Ti(O^iPr)_4$ and the intermediate **107** was reduced *in situ* using $NaBH_4$ under ambient conditions to obtain the product **108** in 8:1:1 diastereomeric ratio (Table 3, entry 1).

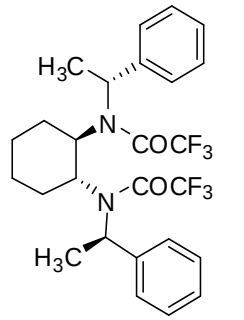
Scheme 12



The major diastereomer **108a** was readily isolated in 61% yield by flash column chromatography (silica gel, 230-400 mesh, hexanes/EtOAc- 97/3). The configuration of this major diastereomer was assigned as (1*R*,2*R*,1'*R*,1''*R*) by comparison with the reported optical rotation value.[61] The absolute configuration at the newly formed stereogenic centres of the major diastereomer **108a** was further confirmed by single crystal X-ray analysis of its trifluoroacetamide derivative **109** (Figure 2, Table 1). Also, the absolute configuration at the newly formed stereogenic centres of the major

diastereomer **108c** was confirmed to be (1*R*,2*R*,1'*R*,1''*R*) by single crystal X-ray analysis (Figure 3, Table 2).





(1*R*,2*R*,1'*R*,1''*R*)-**109**

Figure 2. ORTEP diagram of the compound **109** (Thermal ellipsoids are drawn at 30% probability)

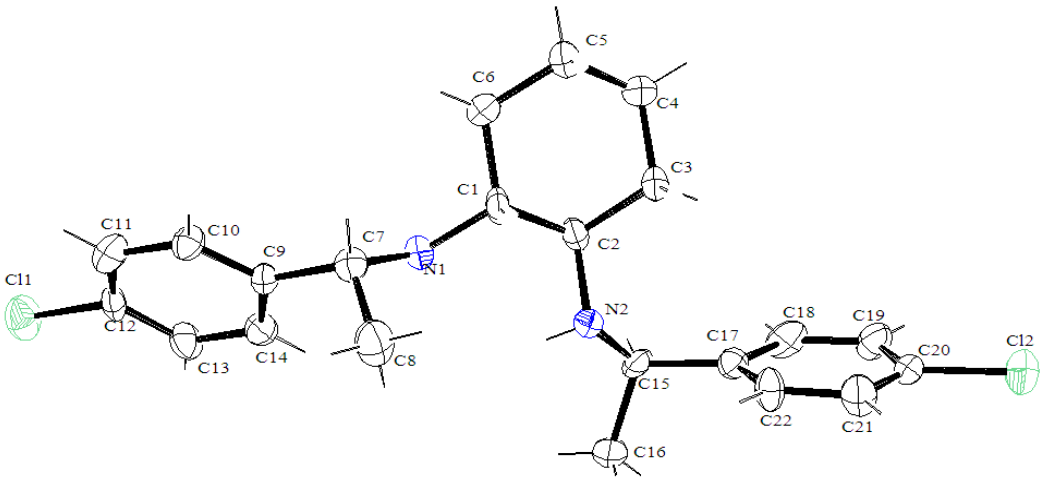


Figure 3. ORTEP diagram of the compound **108c** (Thermal ellipsoids are drawn at 30% probability)

Table 1. Crystal data and structure refinement for compound 109	
Identification code	**109**
Empirical formula	$C_{26}H_{28}F_6N_2O_2$
Formula weight	514.50
Temperature	298 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Trigonal, P3(1)
Unit cell dimensions	a = 9.7315 (3) Å, α = 90 ° b = 9.7315 (3) Å, β = 90 ° c = 22.5776 (17) Å, γ = 120 °
Volume	1851.69 (16) $Å^3$
Z, Calculated density	3, 1.384 Mg M^{-3}
Absorption coefficient	0.118 mm^{-1}
F(000)	804
Crystal size	0.42 x 0.38 x 0.32 mm
Theta range for data collection	2.42 to 25.91°
Limiting indices	-11≤h≤11, -11≤k≤11, -27≤l≤27
Reflections collected / unique	13570 / 4787 [R(int) = 0.0198]
Completeness to θ	25.91, 100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4787 / 1/ 327
Goodness-of-fit on F^2	1.102
Final R indices [I>2σ (I)]	R1 = 0.0451, wR2 = 0.1034
R indices (all data)	R1 = 0.0510, wR2 = 0.1068
Largest diff. peak and hole	0.141 and -0.197 e. $Å^{-3}$

Table 2. Crystal data and structure refinement for compound 108c	
Identification code	**108c**
Empirical formula	$C_{22}H_{28}Cl_2N_2$
Formula weight	391.36
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.7190 (11) Å, α = 90 ° b = 16.311(3) Å, β = 90 ° c = 23.291(5) Å, γ = 90 °
Volume	2172.5(7) $Å^3$
Z, Calculated density	4, 1.197 Mg M^{-3}
Absorption coefficient	0.307 mm^{-1}
F(000)	832
Crystal size	0.20 x 0.10 x 0.08 mm
Theta range for data collection	1.52 to 28.21°
Limiting indices	$-7\leq h\leq 7$, $-7\leq k\leq 20$, $-28\leq l\leq 16$
Reflections collected / unique	6359 / 4630 [R(int) = 0.1134]
Completeness to θ	28.21, 90.3%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4630 / 0 / 245
Goodness-of-fit on F^2	0.429
Final R indices [I>2σ (I)]	R1 = 0.0414, wR2 = 0.0530
R indices (all data)	R1 = 0.3372, wR2 = 0.0997
Largest diff. peak and hole	0.111 and -0.126 e. $Å^{-3}$

Then, we have examined the titanium(IV) mediated reductive *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **29a** with various prochiral ketones **106**. The results are summarized in Table 3. In all the cases, three diastereomeric product mixture **108** were obtained as expected (Table 3).

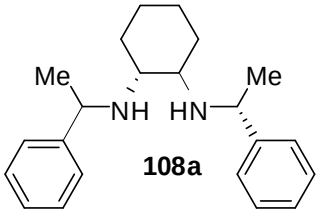
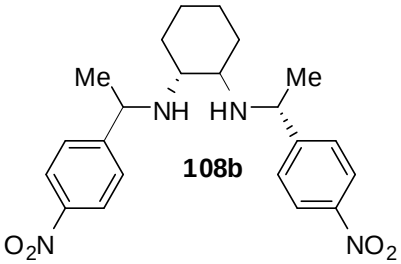
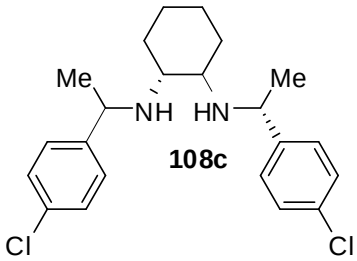
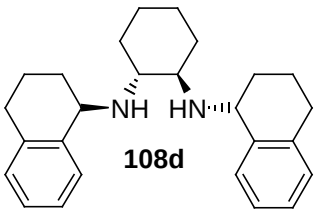
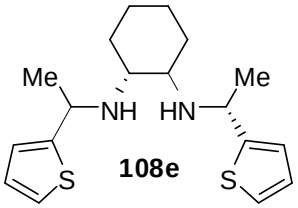
In the case of 4-nitro and 4-chloroacetophenones **106b** and **106c**, the corresponding *N*-alkylated products **108b** and **108c** were obtained in 4:1:1 and 7:1:1 dr, respectively (Table 3, entries 2 and 3). In these cases, the major diastereomers were isolated in pure form by column chromatography.

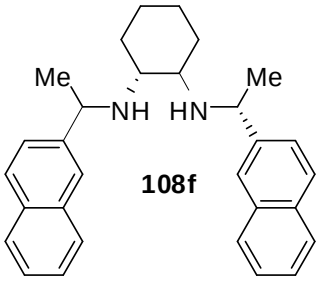
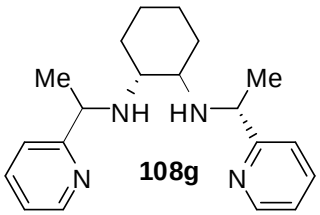
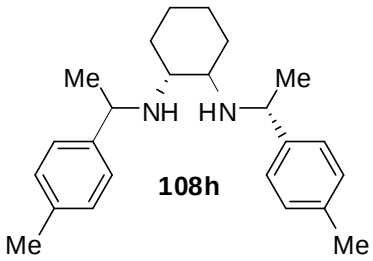
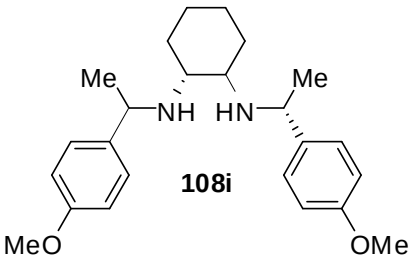
In the reaction of chiral amine **29a** with α-tetralone **106d**, the corresponding *N*-alkylated product **108d** was obtained in 13:1:1 diastereomeric ratio (Table 3, entry 4). The major and two minor diastereomers of the *N*-alkylated product **108d** were separated by column chromatography. The diastereoselectivity was very high in the case of reaction with 2-acetylthiophene **106e** in up 23:1:1 dr (Table 3, entry 5). The major diastereomer of **108e** was isolated in 84% yield by column chromatography.

In the reactions using ketones such as 2-acetylnaphthalene **106f**, 4-methylacetophenone **106h** and 4-methoxyacetophenone **106i**, only the major diastereomers were obtained in pure form by column chromatography besides the mixture of other two diastereomers. In the reaction with 2-acetylpyridine **106g**, the major diastereomer could not be isolated in pure form by column chromatography and the diastereoselectivity for this reaction was poor (Table 3, entry 7).

The configurations of the major diastereomers of the *N*-alkylated products **108b, 108d** and **108e**) were assigned as (1*R*,2*R*,1'*R*,1"*R*) by comparison with the specific rotation value of the diamine **108a**.[61]

Table 3. $Ti(O^iPr)_4$ mediated reductive *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane 29a with various prochiral ketones 106[a]

Entry	Ketone			Product Amine (**108**)[b]	Yield (%)[c]	dr[d]
	106	Ar	R			
1	**106a**	Ph	Me	 **108a**	87	8:1:1
2	**106b**	4-NO_2-C_6H_4	Me	 **108b**	80	4:1:1
3	**106c**	4-Cl-C_6H_4	Me	 **108c**	89	7:1:1
4	**106d**	α-tetralone		 **108d**	94	13:1:1
5	**106e**	2-thiophenyl	Me	 **108e**	89	23:1:1

6	**106f**	2-naphthyl	Me	 **108f**	76	7:1:1
7	**106g**	2-pyridyl	Me	 **108g**	90	2:1:0[e]
8	**106h**	4-Me-C_6H_4	Me	 **108h**	95	4:1:0
9	**106i**	4-MeO-C_6H_4	Me	 **108i**	79	8:1:1

[a]All the reactions were carried out using diamine **29a** (1.0 mmol), ketone **106** (2.2 mmol), $Ti(O^iPr)_4$ (4.0 mmol) in THF (5.0 mL) at 25 °C for 12 h and for the *in situ* reduction, $NaBH_4$ (5.0 mmol) and absolute EtOH (5.0 mL) were used at 25 °C and stirred for 12 h.
[b]Products were identified using spectroscopic data (IR, ^1H and ^{13}C NMR).
[c]Yields are of the isolated product correspond to the three diastereomers.
[d]Diastereomeric ratio (dr) was determined by ^1H NMR analysis of the crude product mixture. The major diastereomers were isolated in pure form by column chromatography of the crude diastereomeric products **108a**, **108b**, **108c**, **108d** and **108e**.
[e]A mixture containing the major diastereomer (87.5%) and the minor diastereomer (12.5%) was isolated by column chromatography for spectral analysis.

We have also studied the effect of solvent and temperature on the reductive *N*-alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **29a** with α-tetralone **106d** using the $Ti(O^iPr)_4/NaBH_4$ reagent system (Scheme 13). The results are summarized in Table 4.

When the reaction was carried out in MeOH at 25 °C, the yield and diastereoselectivity of the product diamine **108d** decreased (Table 4, entry 1). Using EtOH as solvent, the yield of the product **108d** increased to 73% (Table 4, entry 2). When CH_2Cl_2 was used as solvent, there was a significant decrease in the yield to 41% (Table 4, entry 4). Finally, in THF, the reaction proceeded well and the product diamine **108d** was obtained in 94% yield with 13:1:1 dr (Table 4, entry 3). When the reaction was carried out at -78 ºC in THF, both yield as well as diastereoselectivity decreased (Table 4, entry 5).

Scheme 13

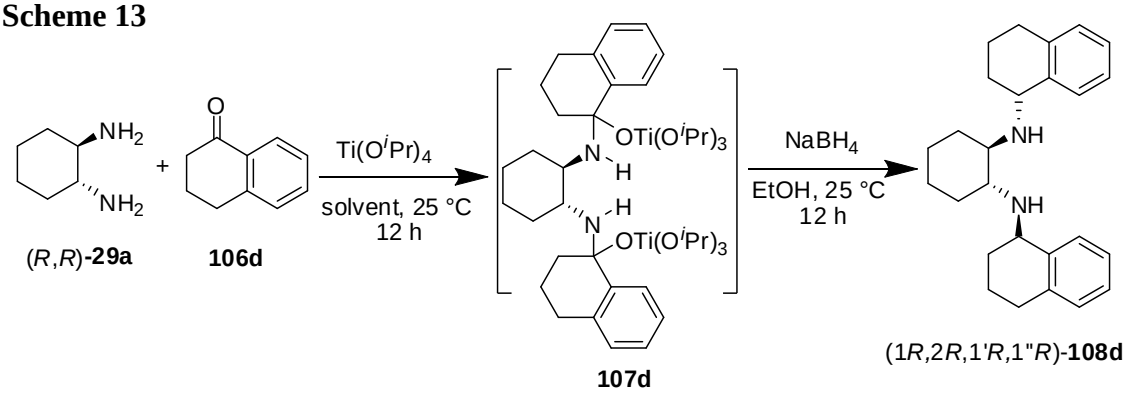


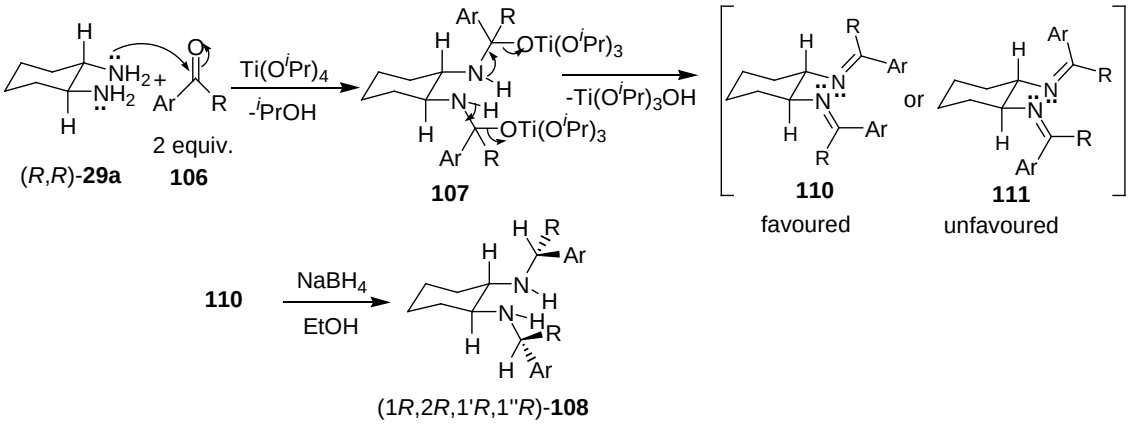
Table 4. $Ti(O^iPr)_4$ mediated reductive *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane 29a with α-tetralone 106d under various experimental conditions[a]

Entry	Solvent	Temp. (°C)	Product[b]	Yield (%)[c]	dr[d]
1	MeOH	25	**108d**	64	12:1:1
2	EtOH	25	**108d**	73	13:1:1
3	THF	25	**108d**	94	13:1:1
4	CH_2Cl_2	25	**108d**	41	12:1:1
5	THF	-78	**108d**	66	12:1:1

[a]All the reactions were carried out using diamine **29a** (1.0 mmol), α-tetralone **106d** (2.2 mmol), $Ti(O^iPr)_4$ (4.0 mmol) in dry solvent (5.0 mL) at 25 °C for 12 h and for the *in situ* reduction, $NaBH_4$ (5.0 mmol) and absolute EtOH (5.0 mL) were used at 25 °C and stirred for 12 h.
[b]The product was identified using spectroscopic data (IR, ^1H and ^{13}C-NMR).
[c]Yields are of the isolated product correspond to the three diastereomers.
[d]Diastereomeric ratio (dr) was determined by ^1H NMR analysis of the crude product mixture.

The transformation reported here may be rationalized by considering the steps and stereochemical models shown in Scheme 14 and Figure 4. The initially formed titanium(IV) complex **107** (Schemes 12, 13 and 14) would undergo further elimination to give the chiral diimine intermediates **110** or **111**.[57] The (*E*,*E*) intermediate **110** is expected to be more favorable in which the aryl group is far away from the cyclohexyl moiety. Since the *re* face is more sterically hindered, the borohydride would prefer to approach the intermediate **110** through the *si* face leading to the formation of the major product (1*R*,2*R*,1'*R*,1"*R*)-**108** (Figure 4).

Scheme 14



Also, the formation of a titanium complex of the diimine intermediate **112** before reduction cannot be ruled out (Figure 4). However, such an intermediate would be also expected to give the same stereochemical outcome.

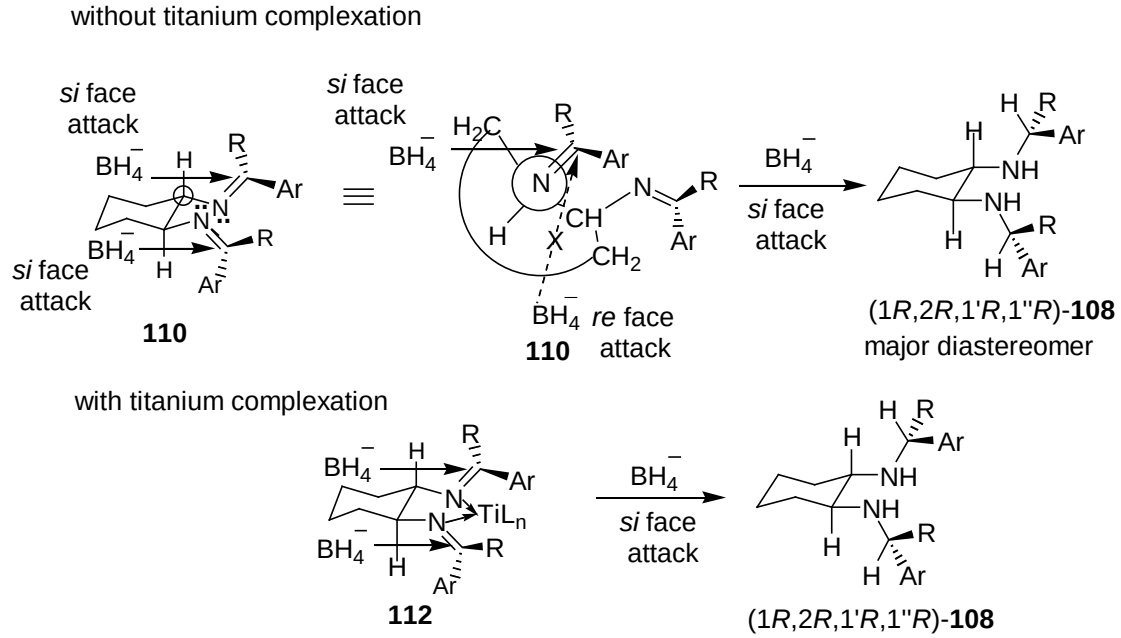
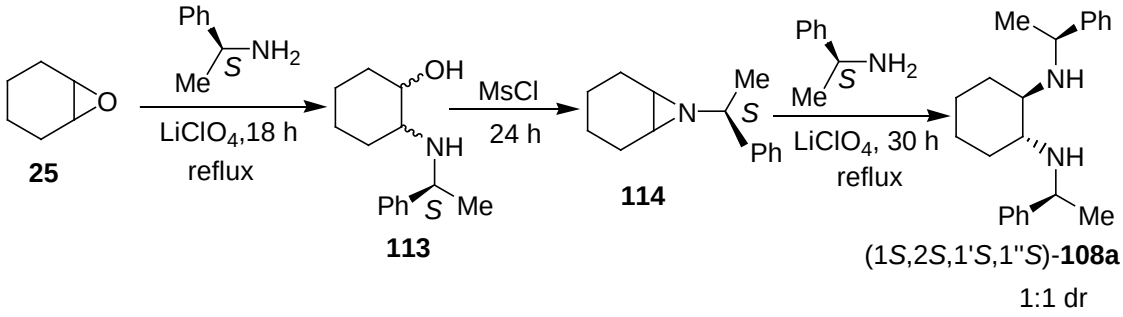


Figure 4. Stereochemical models

Previously, the C_2-symmetric *trans*-1,2-diaminocyclohexane derivative **108a** containing chiral *N*-α-methylbenzylamine moiety was prepared by the opening of an aziridine **114** with (*S*)-α-methylbenzylamine catalyzed by lithium perchlorate in a three step reaction sequence with moderate chemical yield and diastereoselectivity (Scheme 15).[61]

Scheme 15



However, following the one pot diastereoselective reductive *N*-alkylation methodology described here, these chiral C_2-symmetric diamines **108a**–**108i** were synthesized in good yields and diastereoselectivities.

1.3 Conclusions

In conclusion, we have developed a convenient one pot method for the synthesis of C_2-symmetric chiral diamines **108a**-**108i** through $Ti(O^iPr)_4$ mediated reductive *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **29a** with prochiral ketones **106** in good to excellent yields and diastereoselectivities. The major diastereomers were isolated by flash column chromatography in up to 85% yields. Easy access to these chiral diamines **108a-108i** following the method described here, compared to the three steps available method[61] for the preparation of **108a** should be helpful for further synthetic exploitation of these derivatives.

1.4 Experimental Section

1.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) and IR (neat) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz), ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker-AC-200, Bruker-Avance-400 and Bruker-Avance-500 spectrometers, respectively with chloroform-d as solvent. Chemical shifts (δ ppm) were determined with tetramethylsilane (TMS) as internal reference (δ = 0 ppm). Coupling constants *J* are in Hz. Mass spectra were determined on a LCMS-2010A mass spectrometer. Elemental analyses were carried out on a Flash EA 1112 series analyzer. Optical rotations were measured in an AUTOPOL-IV automatic polarimeter (readability ±0.001). The condition of the polarimeter was checked by measuring the optical rotation of (*R)*-(+)-α-methylbenzylamine {$[\alpha]_D^{25}$ = +30.2 (*c* 10, EtOH)} supplied by Fluka.

Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250mμ acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's or E-Merck's silica gel (100-200 mesh and 230-400 mesh).

All the glasswares were pre-dried at 140 ^{o}C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless otherwise mentioned,

all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive reagents and organometallic compounds. Reagents prepared *in situ* in solvents were transferred using a double-ended stainless steel (Aldrich) needle under a pressure of nitrogen whenever required.

In all of the experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler was used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ or Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All the yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy.

Dichloromethane, 1,2-dichloroethane were distilled over CaH_2 and dried over molecular sieves. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Triethylamine was distilled over CaH_2 and stored over KOH pellets. $Ti(O^iPr)_4$ was supplied by Sigma Aldrich, USA. $NaBH_4$ was supplied by E-Merck (India). Commercially available ketones were used after further distillation under reduced pressure.

The X-ray diffraction measurements for the respective compounds were carried out at 293 or 100 K on Bruker-Nonius SMART APEX CCD area detector system. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. The data were reduced using SAINT

program,[62] without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).[63]

1.4.2 Resolution of 1,2-diaminocyclohexane 29

A reported procedure was followed.[64] In a 250 mL beaker, L(+)-tartaric acid (37.5 g, 250 mmol) and water (100 mL) were taken. The mixture was stirred at room temperature until complete dissolution occurred. At this point, a mixture of *cis/trans*-1,2-diaminocyclohexane **29** (60 mL, 500 mmol) was added at a rate such that the reaction temperature was below 70 °C. To the resulting solution, glacial acetic acid (25 mL) was added at a rate such that the reaction temperature was below 90 °C. The precipitate was formed immediately upon the addition of glacial acetic acid and the slurry was vigorously stirred. It was cooled to 25 °C over a period of 2 h. The mixture was cooled to 5 °C for 2 h and the precipitate was collected by suction filtration. The wet cake was washed with cooled water (25 mL) followed by cold methanol until the cake turned to white solid. The product (*R,R*)-*trans*-1,2-diammoniumcyclohexane mono-(+)-tartrate salt was dried in air.

Yield: 111 g (85%)

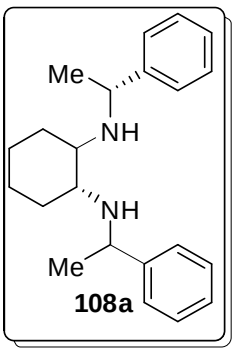
The (*R,R*)-*trans*-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (42 g, 159 mmol) was taken in a separating funnel. Approximately, 30 g of KOH dissolved in water (20 mL) was added. The contents were shaken well and the amine layer was separated. The (*R,R*)-*trans*-1,2-diaminocyclohexane **29a** was distilled under reduced pressure.

1.4.3 General procedure for the *N*-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane 29a

To a stirred solution of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **29a** (0.12 mL, 1 mmol) in dry THF (5 mL), ketone **106** (2.2 mmol) and $Ti(O^iPr)_4$ (1.2 mL, 4 mmol) were added and stirred at 25 °C for 12 h under N_2 atmosphere. To this, absolute EtOH (5 mL) and $NaBH_4$ (0.19 g, 5 mmol) were added at 0 °C under N_2 atmosphere and the resulting mixture was stirred for an additional 12 h at 25 °C. The reaction mixture was quenched with water (1 mL). The solvent was evaporated and residue was stirred with diethyl ether (15 mL) for 15 min. The resulting inorganic precipitate was filtered and washed with diethyl ether (10 mL). Water (10 mL) was added to the filtrate and the organic layer was separated and the remaining aqueous layer was extracted with diethyl ether (10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel. The reaction when carried out in a larger scale (5-10 mmol), also gave the product **108** in similar yields and diastereoselectivity.

(1*R*,2*R*,1'*R*,1''*R*) -*N*,*N*'-Di(1-phenylethyl)-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 8:1:1. The mixture containing three diastereomeric products was isolated in 87% yield by flash column chromatography. The major diastereomer (1*R*,2*R*,1'*R*,1''*R*)-**108a** was isolated in pure form by flash column chromatography (silica gel; 230-400 mesh, hexanes/EtOAc-97/3) as a colourless liquid.



108a

Yield 0.196 g (61%)

IR (neat) (cm^{-1}) 3308, 3061, 2926, 1602, 1493, 1448, 1122, 700

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.29-7.10 (m, 10H), 3.76 (q, *J* = 6.6 Hz, 2H), 2.23-2.17 (m, 2H), 1.77-1.74 (m, 4H), 1.51-1.48 (m, 2H), 1.26 (d, *J* = 6.6 Hz, 6H), 1.06-1.02 (m, 2H), 0.88 – 0.78 (m, 2H) (**Spectrum No. 1**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 147.6, 128.3, 126.7, 126.6, 60.4, 56.1, 32.6, 25.0, 24.0 (**Spectrum No. 2**)

$[\alpha]_D^{25}$ -40.4 (*c* 1.1, $CHCl_3$) [lit.[61] for (1*S*,2*S*,1'*S*,1"*S*) isomer = + 40.5 (*c* 1.0, $CHCl_3$]

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(4-nitrophenyl)ethyl]-1,2-cyclohexanediamine

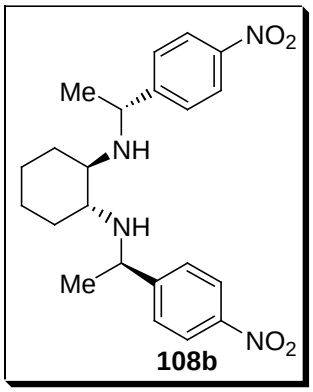
^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 4:1:1. The mixture containing three diastereomeric products was isolated in 80% yield by column chromatography. The major diastereomer (1*R*,2*R*,1'*R*,1"*R*)-**108b** was isolated in pure form by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc - 90/10) as a colourless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using hexanes/EtOAc-85/15 as eluent in 19% yield.

Yield 0.329 g (80%)

IR (neat) (cm^{-1}) 3306, 3930, 1601, 1516, 1344, 1109, 856

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.22 (d, *J* = 8.4 Hz, 4H), 7.48 (d, *J* = 8.4 Hz, 4H), 4.00 (q, *J* = 6.6 Hz , 2H), 2.17 (br s, 2H), 1.82-1.84 (m, 4H), 1.63-

1.50 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 6H), 1.12-0.96 (m, 2H), 0.92- 0.81 (m, 2H)



108b

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 155.5, 146.8, 127.4, 123.6, 60.8, 55.9, 32.6, 24.8, 24.1

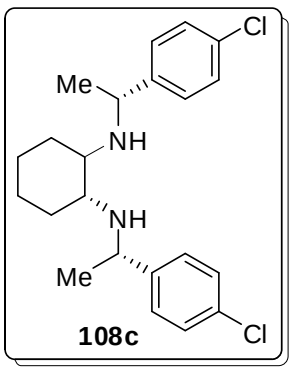
$[\alpha]_D^{25}$ -21.0 (*c* 1.0, $CHCl_3$)

LCMS *m/z* 413 (M+1)

Analysis calculated for $C_{22}H_{28}N_4O_4$: C, 64.06%; H, 6.84%; N, 13.58%; O, 15.52%; found: C, 64.07%; H, 6.91%; N, 13.60%; O, 15.51%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(4-chlorophenyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 7:1:1. The mixture containing three diastereomeric products was isolated in 89% yield by column chromatography. The major diastereomer (1*R*,2*R*,1'*R*,1"*R*)-**108c** was isolated in 69% yield in pure form by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc-93/7) as a colourless liquid which solidifies slowly. The two minor diastereomers were obtained together as a 1:1 mixture using hexanes/EtOAc-85/15 as eluent in 20% yield.



108c

Yield 0. 269 g (69%)

mp 70-72 ºC

IR (KBr) (cm^{-1}) 3306, 2924, 1595, 1489, 1369, 1091, 829

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.30-7.25 (m, 8H), 3.79 (q, *J* = 6.6 Hz, 2H), 2.26-2.22 (m, 2H),

1.79-1.75 (m, 2H), 1.56-1.54 (m, 2H), 1.46 (br s, 1H), 1.44 (br s, 1H), 1.28 (d, *J* = 6.6 Hz, 6H), 1.12-1.07 (m, 2H), 0.92-0.83 (m, 2H) (**Spectrum No. 7**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.2, 132.2, 128.5, 128.4, 127.9, 126.8, 60.5, 55.6, 32.7, 24.9, 24.1

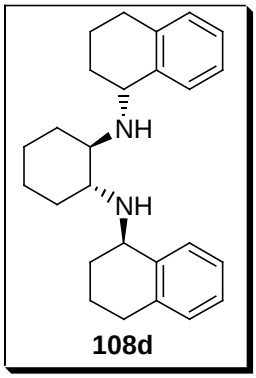
$[\alpha]_D^{25}$ -17.5, (*c* 1.0, $CHCl_3$)

LCMS *m/z* 392 (M+1)

Analysis calculated for $C_{22}H_{28}Cl_2N_2$: C, 67.51%; H, 7.21%; Cl, 18.12%; N, 7.16%; found: C, 67.41%; H, 7.32%; Cl, 18.32%; N, 7.06%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2-cyclohexane-diamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 13:1:1. The mixture containing three diastereomeric products was isolated in 94% yield by column chromatography. The major diastereomer (1*R*,2*R*,1'*R*,1''*R*)-**108d** was isolated in pure form in 85% yield by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc-90/10) as a colourless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using hexanes/EtOAc-85/15 as eluent in 9% yield.



108d

Yield 0.318 g (85%)

IR (neat) (cm^{-1}) 3301, 3059, 2930, 2855, 1603, 1578, 1489, 739

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.34 (d, *J* = 6.6 Hz, 2H), 7.14-7.10 (m, 4H), 7.04 (d, *J* = 6.6 Hz, 2H),

3.77 (br s, 2H), 2.77-2.60 (m, 4H), 2.33-2.30 (m, 4H), 1.86-1.66 (m, 10H), 1.33-1.12 (m, 6H) (**Spectrum No. 3**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 140.3, 137.4, 129.2, 128.8, 126.3, 125.7, 59.2, 51.8, 32.6, 29.3, 28.0, 25.3, 18.5 (**Spectrum No. 4**)

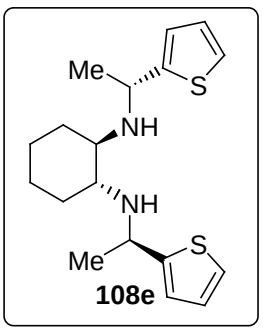
$[\alpha]_D^{25}$ -115.1 (*c* 1.0, $CHCl_3$)

LCMS *m/z* 375 (M+1)

Analysis calculated for $C_{26}H_{34}N_2$: C, 83.37%; H, 9.15%; N, 7.48%; found: C, 83.23%; H, 9.12%; N, 7.81%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(2-thienyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 23:1:1. The mixture containing three diastereomeric products was isolated in 89% yield by column chromatography. The major diastereomer (1*R*,2*R*,1'*R*,1''*R*)-**108e** was isolated in pure form in 84% yield by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc-90/10) as a colourless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using hexanes/EtOAc-85/15 as eluent in 5% yield.



108e

Yield 0.280 g (84%)

IR (neat) (cm^{-1}) 3299, 3073, 2969, 2926, 2855, 1510, 1449

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.18-7.16 (m, 2H), 6.95-6.93 (m, 4H), 4.20 (q, *J* = 6.4 Hz, 2H), 2.33 -2.31 (m, 2H), 2.00 (br s, 2H), 1.92-1.89 (m, 2H), 1.65-1.62 (m, 2H), 1.43 (d, *J* = 6.4 Hz, 6H), 1.20-1.15 (m, 2H), 1.05-1.00 (m, 2H) (**Spectrum No. 5**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 152.7, 126.4, 123.4, 122.5, 60.1, 51.5, 32.5, 25.0, 24.4 (**Spectrum No. 6**)

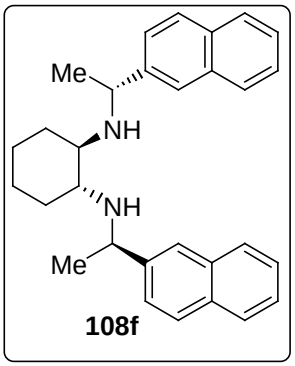
$[\alpha]_D^{25}$ -27.9 (*c* 1.0, $CHCl_3$)

LCMS *m/z* 335 (M+1)

Analysis calculated for $C_{18}H_{26}N_2S_2$: C, 64.62%; H, 7.83%; N, 8.37%; S, 19.17%
found: C, 64.42%; H, 7.93%; N, 8.48%; S, 19.26%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(2-naphthyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 7:1:1. The mixture of three diastereomeric products **108f** was isolated by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc-90/10) in 76% yield. A small quantity (0.030 g) of the major isomer (1*R*,2*R*,1'*R*,1''*R*)-**108f** was obtained in pure form as a colourless liquid which solidified on standing.



108f

Yield 0.320 g (76%)

mp 73-75 ºC

IR (KBr) (cm^{-1}) 3306, 3053, 2926, 2854, 1601, 1508, 1367, 746

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.87 (d, *J* = 8.4 Hz, 6H), 7.83 (s, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.50 (m, 4H), 4.06 (q, *J* = 6.4 Hz, 2H), 2.43-2.37 (m, 2H), 1.89 (br s, 1H), 1.85 (br s, 1H), 1.62-1.53 (m, 4H), 1.48 (d, *J* = 6.4 Hz, 6H), 1.16-1.11 (m, 2H), 1.02-0.91 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 147.7, 136.2, 135.4, 130.7, 130.4, 130.3, 128.5, 128.0, 127.9, 127.5, 63.3, 59.1, 35.4, 27.6, 26.8

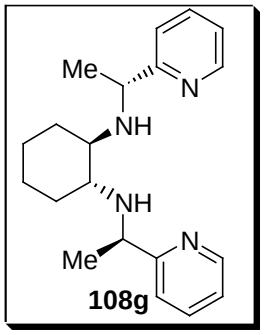
$[\alpha]_D^{25}$ -9.1 (*c* 0.5, $CHCl_3$)

LCMS *m/z* 423 (M+1)

Analysis calculated for $C_{30}H_{34}N_2$: C, 85.26%; H, 8.11%; N, 6.63%; found: C, 85.11%; H, 8.23%; N, 6.71%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(2-pyridyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 2:1:0. The mixture of three diastereomeric products **108g** was isolated in 90% yield by column chromatography (silica gel; 100-200 mesh, $CHCl_3$/MeOH-98/2) as a brownish liquid, which solidified slowly on standing. Upon further purification, a small quantity (0.050 g) of the product containing major diastereomer (1*R*,2*R*,1'*R*,1"*R*)-**108g** (88%) and the minor diastereomer (12%) was obtained.



108g

Yield 0.290 g (90%)

mp 88-90 °C (For the mixture of diastereomeric product, dr = 87.5:12.5:0)

IR (KBr) (cm^{-1}) 3294, 2934, 1593, 1375, 856, 787

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.40 (d, *J* = 4.6 Hz, 2H), 7.58-7.54 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.10-7.07 (m, 2H), 4.16 (q, *J* = 6.8 Hz, 2H), 2.57-2.55 (m, 2H), 1.67-1.64 (m, 2H), 1.5 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.13-1.06 (m, 2H), 1.03-0.95 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 161.1, 148.8, 136.9, 122.6, 121.5, 59.1, 56.1, 30.2, 24.2, 21.1 (**Spectrum No. 8**)

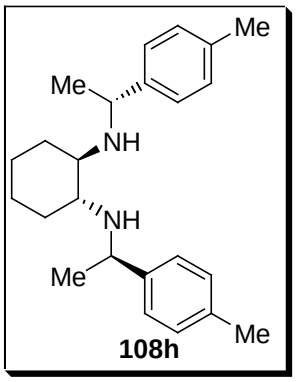
$[\alpha]_D^{25}$ -10.3 (*c* 1.0, $CHCl_3$) (For the mixture of diastereomeric product, dr = 87.5:12.5:0)

LCMS *m/z* 325 (M+1)

Analysis calculated for $C_{20}H_{28}N_4$: C, 74.03%; H, 8.70%; N, 17.27%; found: C, 74.11%; H, 8.72%; N, 17.4%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(4-methylphenyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 4:1:0. A mixture of two diastereomeric products **108h** was isolated by column chromatography (silica gel; 100-200 mesh, hexanes/EtOAc-90/10) as a colourless liquid. A small quantity (0.065 g) of the major diastereomer (1*R*,2*R*,1'*R*,1''*R*)-**108h** was obtained in pure form.



108h

Yield 0.332 g (95%)

IR (neat) (cm^{-1}) 3306, 3015, 2961, 2924, 2857, 1613, 1514, 1447, 1109, 818

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.24 (d, *J* = 8.0 Hz, 4H), 7.12 (d, *J* = 8.0 Hz, 4H), 3.8 (q, *J* = 6.4 Hz, 2H), 2.33 (s, 6H), 2.27-2.21 (m, 2H), 1.85 (br s, 1H), 1.81 (br s, 1H), 1.59-1.55 (m, 4H), 1.30 (d, *J* = 6.4 Hz, 6H), 1.14-1.08 (m, 2H), 0.95-0.83 (m, 2H) (**Spectrum No. 9**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 144.6, 136.2, 129.0, 126.5, 60.4, 55.8, 32.7, 25.0, 24.0, 21.1 (**Spectrum No. 10**)

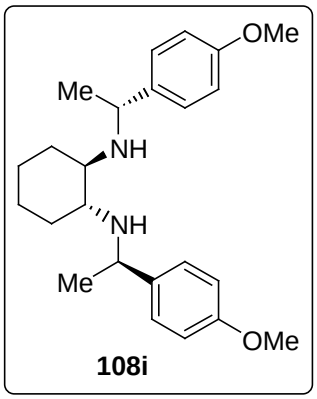
$[\alpha]_D^{25}$ -29.2 (*c* 1.2, $CHCl_3$)

LCMS *m/z* 351 (M+1)

Analysis calculated for $C_{24}H_{34}N_2$: C, 82.23%; H, 9.78%; N, 7.99%; found: C, 82.30%; H, 9.72%; N, 7.63%

(1*R*,2*R*,1'*R*,1''*R*)-*N*,*N*'-Di[1-(4-methoxyphenyl)ethyl]-1,2-cyclohexanediamine

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 8:1:1. A mixture of three diastereomeric products **108i** was isolated by column chromatography (silica gel; 100-200 mesh, $CHCl_3$/MeOH-98/2) as a colourless liquid in 79% yield. A small quantity (0.035 g) of the major diastereomer (1*R*,2*R*,1'*R*,1"*R*)-**108i** was obtained in pure form.



108i

Yield 0. 30 g (79%)

IR (neat) (cm^{-1}) 3293, 2932, 2857, 1610, 1512, 1248, 1033, 833

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.27 (d, *J* = 8.8 Hz, 4H), 6.86 (d, *J* = 8.8 Hz, 4H), 3.8 (s, 8H), 2.28-2.20 (m, 2H), 1.97 (br s, 2H), 1.86-1.77 (m, 2H), 1.59-1.54 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 6H), 1.16-1.09 (m, 2H), 0.97-0.85 (m, 2H) (**Spectrum No. 11**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 158.5, 139.7, 127.6, 113.8, 60.4, 55.5, 55.3, 32.7, 25.1, 24.0 (**Spectrum No. 12**)

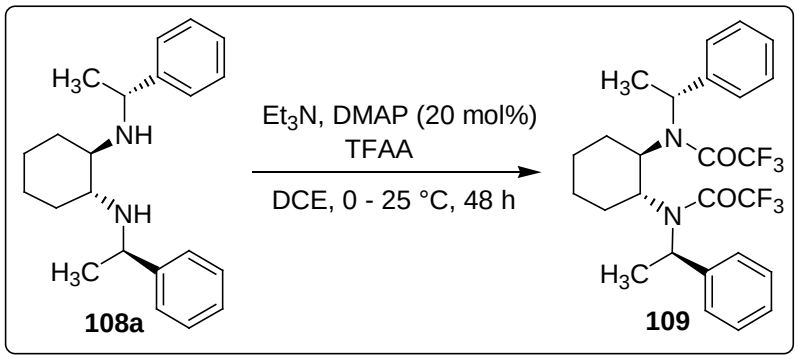
$[\alpha]_D^{25}$ +10.7 (*c* 0.6, $CHCl_3$)

LCMS *m/z* 383 (M+1)

Analysis calculated for $C_{24}H_{34}N_2O_2$: C, 75.35%; H, 8.96%; N, 7.32%; O, 8.36%
found: C, 75.14%; H, 8.98%; N, 7.52%; O, 8.41%

1.4.4 Representative procedure for the synthesis of (1*R*,2*R*,1'*R*,1''*R*)-2,2,2-trifluoro-*N*-(1-phenyl-ethyl)-*N*-{2-[(1-phenyl-ethyl)-(2,2,2-trifluoro-acetyl)-amino]-cyclohexyl}-acetamide 109

To a stirred solution of the diamine (1*R*,2*R*,1'*R*,1"*R*)-**108a** (0.32 g, 1 mmol) in DCE (5 mL), Et_3N (0.3 mL, 2.1 mmol) and DMAP (0.024 g, 0.2 mmol) were added under N_2 atmosphere. To this, excess amount of trifluoroacetic anhydride (TFAA) (2 mL) was added slowly at 0 ºC and the reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was quenched with water (10 mL) and CH_2Cl_2 (10 mL) was added to it. The aqueous layer was separated and washed with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, 100-200 mesh, hexanes/EtOAc-99/1). The product (1*R*,2*R*,1'*R*,1"*R*)-**109** was obtained as a colourless solid.

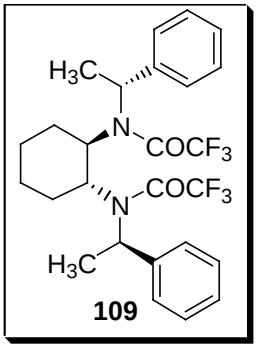


Yield 0.350 g (68%)

mp 150-152 ºC

IR (KBr) (cm^{-1}) 3065, 2984, 2937, 1699, 1442, 1140, 744

^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.43-7.30 (m, 10H),



	4.92 (q, *J* = 8.0 Hz, 2H), 4.27 (q, *J* = 4.1 Hz, 2H), 2.30-2.28 (m, 2H), 1.69-1.66 (m, 4H), 1.54 (d, *J* = 8.0 Hz, 6H), 1.33-1.28 (m, 2H) (**Spectrum No. 13**)
^{13}C NMR	(100 MHz, $CDCl_3$, δ ppm): 155.6 (q, *J* = 34.0 Hz), 137.1, 128.7, 128.6, 128.4, 116.0 (q, *J* = 288.1 Hz), 56.5, 55.4, 29.0, 24.9, 18.4 (**Spectrum No. 14**)
$[\alpha]_D^{25}$	+34.7 (*c* 1.2, $CHCl_3$)
LCMS	*m/z* 515 (M+1)
Analysis	calculated for $C_{26}H_{28}F_6N_2O_2$: C, 60.70%; H, 5.49%; F, 22.16%; N, 5.44%; O, 6.22% found: C, 60.82%; H, 5.37%; F, 22.13%; N, 5.35%; O, 6.34%

1.5 References

1. (a) Eisenberg, M. A. In *Escherichia coli and Salmonella typhimurium*; F. C. Neidhardt, Ed.; American Society for Microbiology: Washington DC, **1987**, *1*, 544. (b) Marquet, A. *Pure Appl. Chem*. **1993**, *65*, 1249.
2. (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Cardona, F.; Goti, A. *Nature Chem.* **2009**, *1*, 269.
3. (a) Szmuszkovicz, J.; Von voigtlander, P. F. *J. Med. Chem*. **1982,** *25*, 1125. (b) Cheney, B. V.; Szmuszkovicz, J.; Lathi, R. A.; Zichi, D. A. *J. Med. Chem*. **1985,** *28*, 1853.
4. (a) Bennani, Y.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
5. (a) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (b) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591. (c) Fournier, P. A.; Collins, S. K. *Organometallics* **2007**, *26*, 2945.
6. (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett*. **1997**, *38*, 773. (c) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
7. Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 17666.
8. (a) Dwyer, F. P.; Garvan, F. L.; Shulman, A. *J. Am. Chem. Soc*. **1959**, *81*, 290. (b) Asperger, R. G.; Liu, C. F. *Inorg. Chem*. **1965**, *4*, 1492. (c) Pikul, S.; Corey, E. J. *Org. Synth*. **1992**, *71*, 22. (d) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa,

M. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 931. (e) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

9. (a) Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc*. **1980**, *102*, 5676. (b) Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787.
10. Zhang, W.; Jacobsen, E. N. *Tetrahedron Lett*. **1991**, *32*, 1711.
11. Zabawa, T. D.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc*. **2005**, *127*, 11250.
12. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.
13. Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023.
14. (a) Oi, R.; Sharpless, K. B. *Tetrahedron Lett*. **1991**, *32*, 999. (b) Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett*. **1995**, *36*, 9241.
15. Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.
16. Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett*. **2000**, 41, 10079.
17. Concellon, J. M.; Riego, E.; Suarez, J. R. *J. Org. Chem.* **2003**, *68*, 9242.
18. Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4849.
19. (a) Periasamy, M.; Seenivasaperumal, M.; Padmaja, M.; Rao, V. D. *Arkivoc* **2004**, (*viii*), 4. (b) Periasamy, M.; Sivakumar, S.; Reddy, M. N.; Padmaja, M. *Org. Lett.* **2004**, *6*, 265.
20. Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127.
21. Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett*. **1993**, *34*, 4743.
22. Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 103.

23. Brunner, H.; Schmidt, M.; Unger, G.; Schonenberger, H. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 509.
24. Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229.
25. Kohn, U.; Schramm, A.; Klob, F.; Gorls, H.; Arnold, E.; Anders, E. *Tetrahedron: Asymmetry* **2007**, *18*, 1735.
26. Cutri, S.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2003**, *68*, 2645.
27. Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609.
28. Neumann, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett*. **1991**, *32*, 5865.
29. Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093.
30. Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953.
31. Busacca, C. A.; Campbell, S.; Dong, Y.; Grossbach, D.; Ridges, M.; Smith, L.; Spinelli, E. *J. Org. Chem.* **2000**, *65*, 4753.
32. Periasamy, M.; Srinivas, G.; Suresh, S. *Tetrahedron Lett*. **2001**, *42*, 7123.
33. Selvakumar, K.; Harrod, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2129.
34. Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.
35. Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.
36. Whitesell, J. K. *Chem. Rev*. **1989**, *89*, 1581.
37. (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng,

L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.

38. (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773. (c) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
39. Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.
40. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.
41. Sinou, D.; Percina-Pichon, N.; Konovets, A.; Iourtchenko, A. *Arkivoc* **2004**, (*xiv*), 103.
42. Palucki, M.; Um, J. M.; Yasuda, N.; Conlon, D. A.; Tsay, F.-R.; Hartner, F. W.; Hsiao, Y.; Marcune, B.; Karady, S.; Hughes, D. L.; Dormer, P. G.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5508.
43. Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
44. (a) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319. (b) Shi, M.; Sui, W.-S. *Chirality* **2000**, *12*, 574. (c) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 835.
45. (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Org. Chem.* **1984**, *49*, 5754. (b) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837. (c) Hanessian, S.; Bennani, Y. L.; Delorme, D. *Tetrahedron Lett.* **1990**, *31*, 6461. (d) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465.
46. Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231.

47. (a) Takemoto, Y.; Baba, Y.; Honda, A.; Nakao, S.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron* **1998**, *54*, 15567. (b) Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. *Tetrahedron Lett.* **1996**, *37*, 3345.

48. Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071.

49. Jeon, S. J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

50. (a) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett*. **1992**, *33*, 2575. (b) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013. (c) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett*. **1994**, *35*, 7045.

51. (a) Kawashima, M.; Hirayama, A. *Chem. Lett*. **1990**, 2299. (b) Tanaka, K.; Moriyama, A.; Toda, F. *J. Org. Chem.* **1997**, *62*, 1192.

52. Liu, Y.; Wang, J.; Sun, Q.; Li, R. *Tetrahedron Lett*. **2011**, *52*, 3584.

53. (a) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411. (b) Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503.

54. Tokles, M.; Snyder, J. K. *Tetrahedron Lett*. **1986**, *27*, 3951.

55. Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J. Y.; Bennani, Y. L. *J. Org. Chem.* **1993**, *58*, 1991.

56. Kumpaty, H. J.; Bhattacharyya, S.; Rehr, E. W.; Gonzalez, A. M. *Synthesis* **2003**, *14*, 2206.

57. Salmi, C.; Letourneux, Y.; Brunel, J. M. *Lett. Org. Chem.* **2006**, *3*, 396.

58. Salmi, C.; Letourneux, Y.; Brunel, J. M. *Lett. Org. Chem.* **2006**, *3*, 384.

59. Loncle, C.; Salmi, C.; Letourneux, Y.; Brunel, J. M. *Tetrahedron* **2007**, *63*, 12968.

60. Tanuwidjaya, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.

61. Parrodi, C. A.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093.

62. (a) Hall, S. R.; King, G. S. D.; Stewart, J. M.; Eds.; *Xtal 3.4 User's manual;* Xtal system, University of Western Australia, 1995 (b) *SAINT* Version 6.2.

63. (a) Sheldrick, G. M. *SHELX-97*, University of Göttingen, Göttingen, Germany, 1997 (b) *SHELXTL* Version 6.14, Bruker AXS.

64. Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.

Chapter 2

Studies on application of chiral C_2- symmetric 1,2-diamines as chiral solvating agents

2.1 Introduction

The utility of enantiomerically pure *trans*-1,2-diaminocyclohexane derivatives as chiral reagents and ligands in the field of asymmetric synthesis has been described in the introductory section of Chapter 1. We have made efforts to explore the application of various chiral diamines containing enantiomerically pure *trans*-1,2-diaminocyclohexane moiety prepared *via* the method described in Chapter 1, for application as chiral solvating agents for carboxylic acids. A brief review of the available reports on these topics will be helpful for discussion.

2.1.1 Enantiomeric recognition of chiral compounds by synthetic receptors

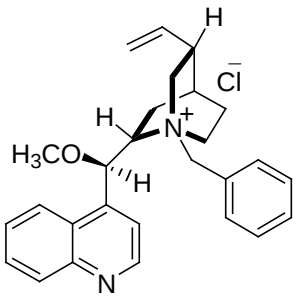
In view of the importance of chiral organic compounds in biological and pharmaceutical chemistry,[1-4] there is increasing requirement for fast and accurate methodologies for the determination of the enantiomeric composition of these chiral compounds. Among the various available methods, NMR spectroscopy has the advantages of easy performance and accessibility[5] with no need for special equipment apart from the common NMR spectrometers. As enantiomers cannot be distinguished in an achiral environment, these techniques require the modification of the substrate with a chiral auxiliary, which would convert the mixture of enantiomers into a mixture of diastereomeric molecular (covalent, chiral derivatizing agent, CDA) or supramolecular (non-covalent, chiral solvating agents, CSA) complexes.[6] Ideally, these diastereomeric species show chemical shift non-equivalence of some of their NMR signals, allowing the determination of the enantiomeric composition of the substrate by the direct integration of these bands.[7] The advantage of using non-covalent chiral solvating agents

relies on the possibility of carrying out the experiment *in situ*, without purification steps.[8,9] Besides the starting chiral materials, analytes and CSA could be easily recovered after the measurement.

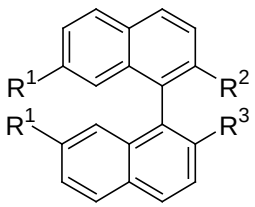
The first realization of this phenomenon was reported by Pirkle,[10] who observed separate ^{19}F NMR resonances for the enantiomers of (trifluoromethyl)phenylcarbinol in optically active 1-phenylethylamine solvent. This technique has recently emerged as a facile alternative for determining enantiomeric purity and absolute configuration. A brief review of the available reports will be helpful for the discussion.

2.1.1.1 Chiral acyclic amine derivatives as chiral solvating agents

The enantiomeric recognition by acyclic chiral amine derivatives as chiral solvating agents has been extensively studied by the ^1H NMR spectroscopy. Salvadori *et al.*[11] reported the use of quinine **1** as a chiral solvating agent for the enantiomeric purity determination of binaphthyl derivatives **2** and alkylarylcarbinols **3** by ^1H and ^{19}F-NMR spectroscopy.

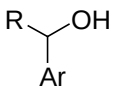


1



2

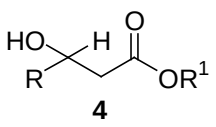
R^1 = H, OMe
R^2 = OH, OMe, O^{i}Pr, OCOMe, OCO^{t}Bu
R^3 = OH, NH_2, NHMe



3

R = Me, ^{t}Bu, CF_3, ^{i}Pr, CH_2OH
Ar = Ph, *p*-$MeOC_6H_4$, 9-anthryl, 1-naphthyl, *m*-MeC_6H_4

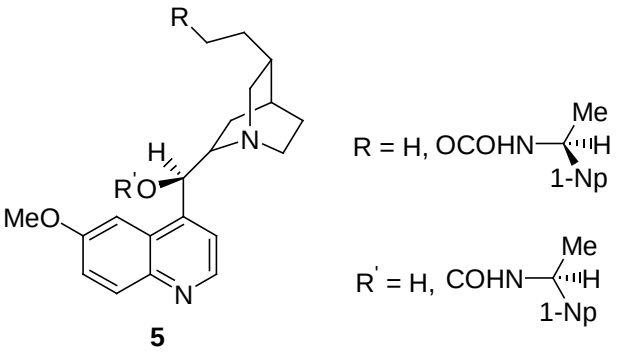
Later, the same group demonstrated the use of quinine **1** as a chiral solvating agent for the enantiomeric purity determination of β-hydroxyesters **4**.[12]



4

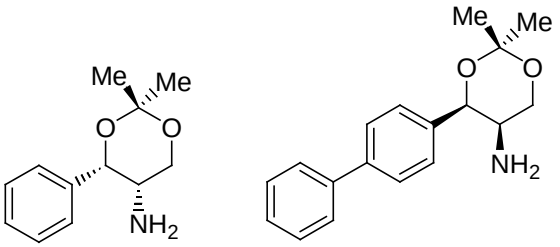
R^1 = ^{t}Bu, Et, Me
R = Ph, *p*-MeC_6H_4, *p*-$CF_3C_6H_4$,
2-naphthyl, 1-naphthyl, cyclohexyl

In 2003, the same group synthesized the simple carbamate derivatives of quinine **5**, by derivatization of the double bond, which behaves as chiral solvating agent for acids, alcohols, amine derivatives and for very simple amino acid derivatives.[13]



5

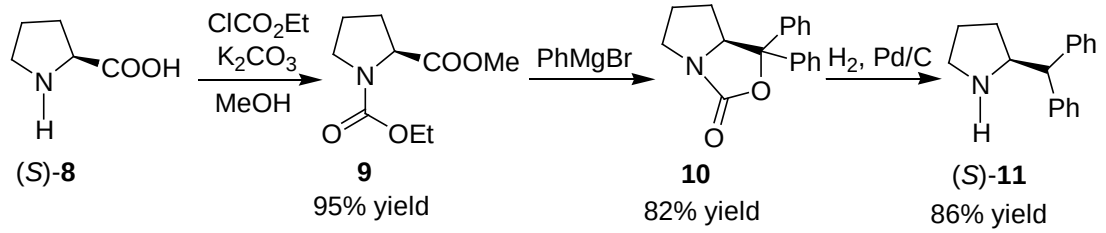
The use of (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan **6** (ADPD) and (4*R*,5*R*)-5-amino-(4'-biphenyl)-2,2-dimethyl-1,3-dioxan **7** (ABDD) as chiral solvating agents for the enantiomeric purity determination of compounds bearing an acidic proton by means of ^{1}H NMR spectroscopy was demonstrated.[14]



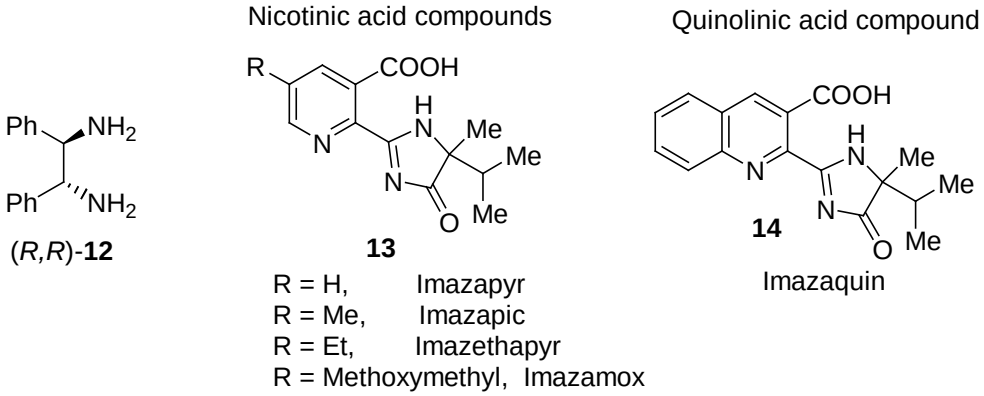
(*S*,*S*)-ADPD-**6** (*R*,*R*)-ABDD-**7**

A three step synthesis of (*S*)-2-(diphenylmethyl)pyrrolidine **11** (Scheme 1) and its use as a chiral solvating agent for the enantiomeric excess determination of chiral carboxylic acids such as 3-phenylbutyric, 2-bromopropionic, mandelic, 2-phenoxypropionic, 2-phenylpropionic acids and Mosher's acid was reported.[15]

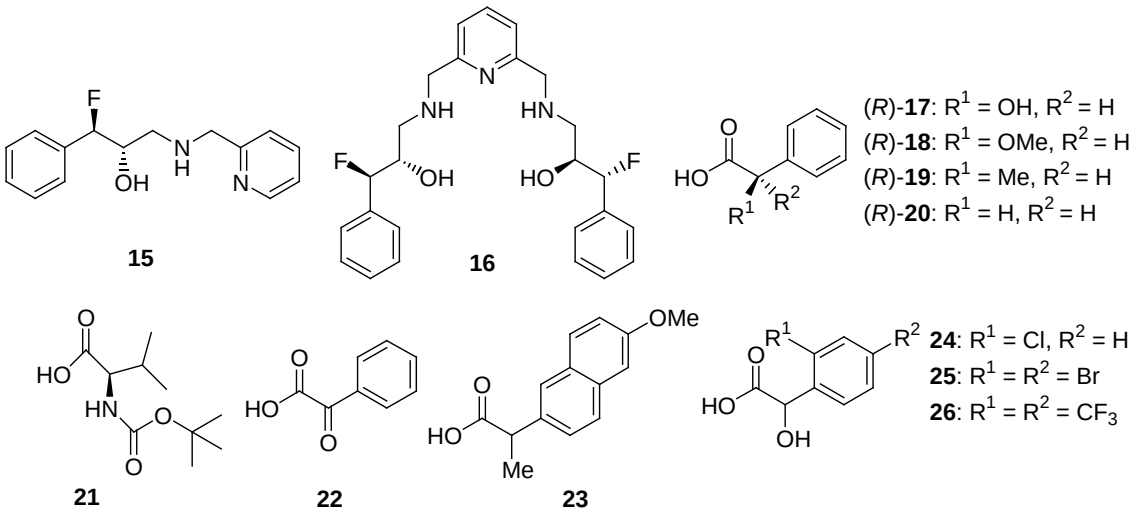
Scheme 1



A fast, direct and routine method has been developed for the measurement of the enantiomeric composition of imidazolinone herbicides (nicotinic and quinolinic carboxylic acid compounds) **13** and **14** containing a free carboxylic acid group, by using (*R*,*R*)-1,2-diphenylethane-1,2-diamine **12** as a chiral solvating agent.[16]

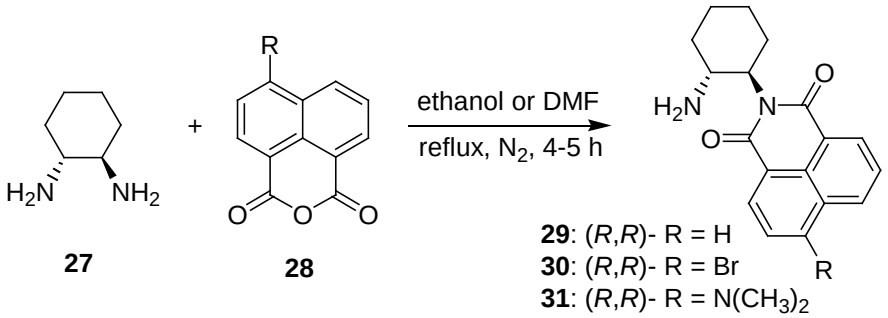


Two flexible receptors **15** and **16** for carboxylic acids, based on 1-amino-3-fluoro-2-alcohol functional arrays and built on aminomethylpyridine platforms have been described.[17] The C_2-symmetric compound **16** has been shown to be an efficient CSA due to its ability to form geometrically different diastereomeric complexes enabling the discrimination between the enantiomers of a series of carboxylic acids **17**-**26** in their ^{1}H NMR spectra.

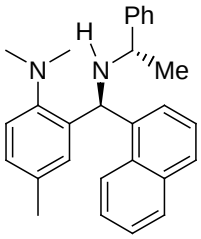


A series of compounds **29**-**31** have been synthesized from (*R*,*R*)-1,2-diaminocyclohexane **27** (Scheme 2), which exhibited better enantiodiscriminating ability toward a variety of chiral carboxylic acids such as naproxen, ibuprofen, ketoprofen, phthalyl alanine and amino acid derivatives.[18]

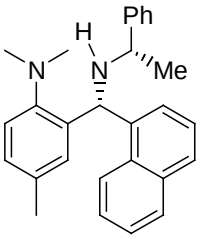
Scheme 2



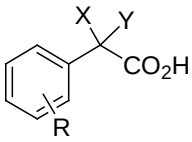
The diastereomeric chiral auxiliaries **32a** and **32b** were synthesized from (*S*)-α-phenylethylamine (PEA).[19] Compared to (*S*)-PEA, these new chiral auxiliaries **32a** and **32b** have been proved to be efficient chiral NMR solvating agents for the carboxylic acids **33**-**36**.



32a

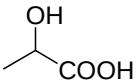


32b

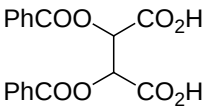


33

R = H, *p*-Cl, *o*-Cl, *p*-OMe, *o*-Me
X = OH, OMe
Y = H



34



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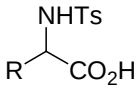
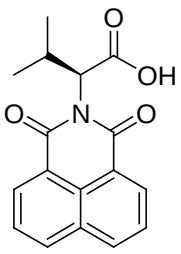


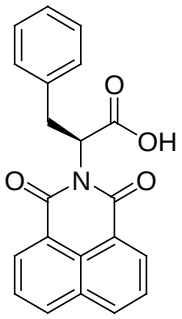
36

R = Ph, ^{i}Pr, CH_3, $CH_2CH(CH_3)_2$

The compounds **37** and **38** were synthesized from natural amino acids and 1,8-naphthalic anhydride which were found to be effective chiral solvating agents for chiral α-arylalkylamines **39** and **40**.[20]



37



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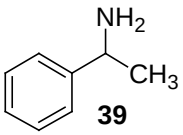
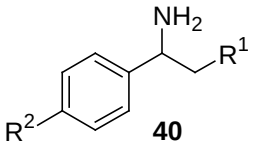


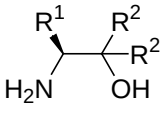
39



40

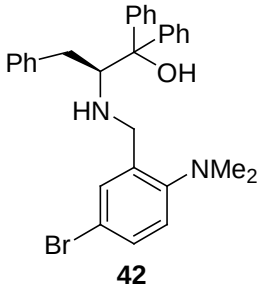
R^1 = H, CH_3, C_2H_5
R^2 = OCH_3, NO_2, H,

Several chiral amino alcohols **41**-**43** were synthesized starting from natural amino acids, which have been shown to be efficient CSAs for the determination of enantiomeric composition of chiral carboxylic acids.[21]

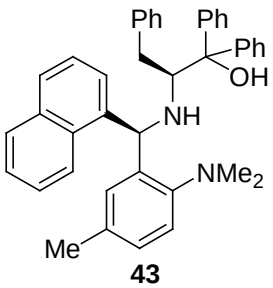


41

R^1 = ^{i}Pr, $PhCH_2$
R^2 = Ph, H

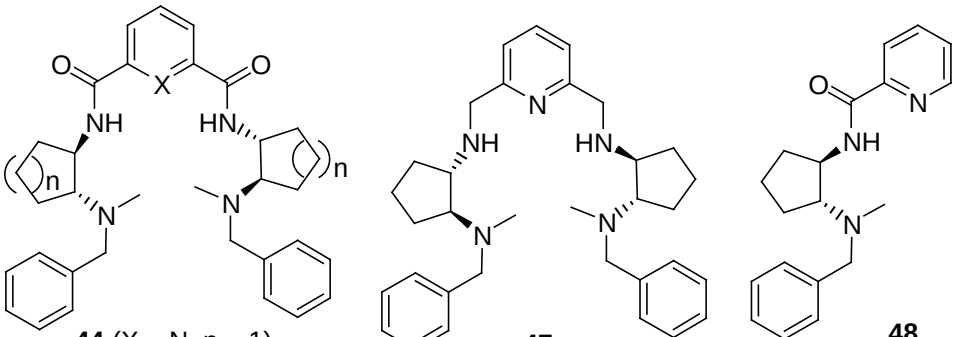


42



43

In 2008, a family of pincer-like receptors **44-48** have been synthesized and tested as efficient CSA for different chiral carboxylic acids.[22]

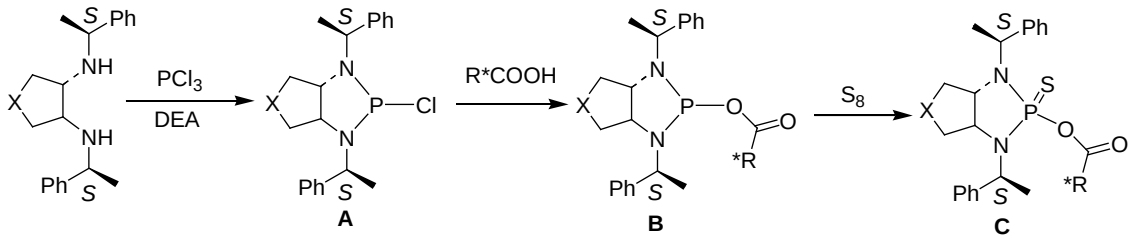


44 (X = N, n = 1)
45 (X = CH, n = 1)
46 (X = N, n = 2)

47 **48**

The P(III) and P(V) organophosphorus derivatizing agents (**A**, **B**, **C**) prepared from C_2-symmetric (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-*N*,*N*'-bis-[(*S*)-α-phenylethyl]-cyclohexane-1,2-diamines **49** and **50**, as well as (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-*N*,*N*'-bis-[(*S*)-α-phenylethyl]-4-cyclohexene-1,2-diamines **51** and **52** were used for the determination of enantiomeric composition of chiral carboxylic acids by ^{31}P NMR (Scheme 3).[23]

Scheme 3

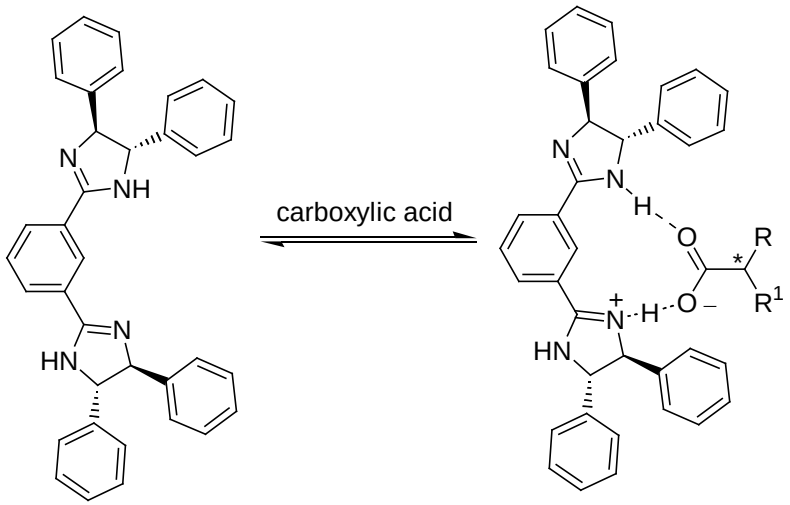


A **B** **C**

49 (1*R*, 2*R*) and **50** (1*S*, 2*S*) : X = -CH_2-CH_2-
51 (1*R*, 2*R*) and **52** (1*S*, 2*S*) : X = -CH=CH-

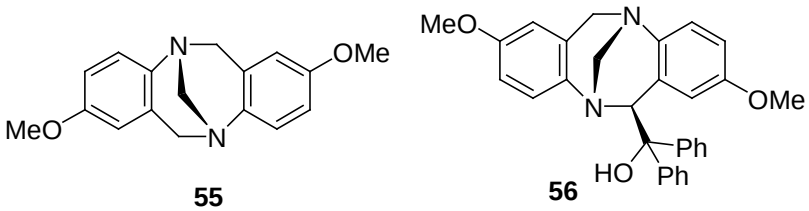
A bis-imidazoline compound **53** starting from isophthalaldehyde and (*S*,*S*)-1,2-diphenylethylene-1,2,-diamine was synthesized and used as a chiral solvating agent for

carboxylic acids.[24] In the presence of one equivalent of this reagent, carboxylic acid racemates show ^{1}H NMR chemical shift non-equivalences large enough for the discrimination of the enantiomers.



53 **54**

Recently, from this laboratory the chiral methoxy Tröger's base **55** and the corresponding α,α'-diphenyl carbinol derivative **56** have been reported to exhibit good chiral recognition ability towards carboxylic acids.[25]

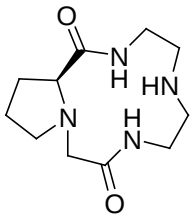


55 **56**

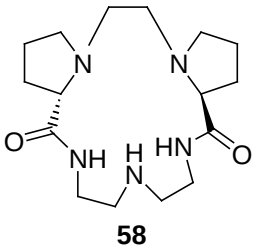
2.1.1.2 Chiral macrocyclic amine derivatives as chiral solvating agents

Chiral macrocyclic compounds have been demonstrated to be very effective in enantiomeric recognitions by NMR spectroscopy. For instance, Fu *et al.*[26] synthesized the L-proline derived chiral macrocyclic dioxopolyamines **57** and **58**, which exhibited

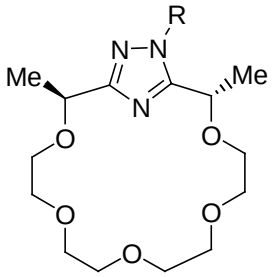
chiral recognition toward the enantiomers of racemic carboxylic acids like substituted mandelic acids and dibenzoyltartaric acid.



57



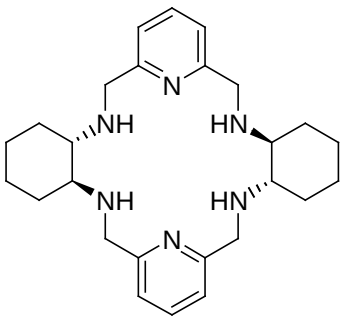
58



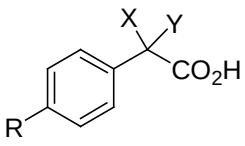
59 : R = CH_2COOcholesteryl
60 : R = ^{n}dodecyl

The use of the chiral triazole-18-crown-6-ligands **59** and **60** with lipophilic side arms, for the chiral recognition of the enantiomers of [1-(1-naphthyl)ethyl]ammonium cation and [1-phenylethyl]ammonium cation has been reported.[27] The (*S*,*S*) chiral host recognizes preferentially the (*R*)-enantiomer of the ammonium salt over the (*S*) enantiomer.

In 2006, the use of an azamacrocyclic receptor **61** as a chiral solvating agent for the determination of enantiomeric excess of different carboxylic acids **62**-**64** was demonstrated.[28]

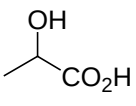


61

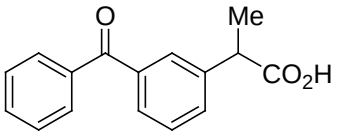


R = H, Cl, OMe
X = OH, OMe, Me, NHBoc
Y = H, CF_3

62

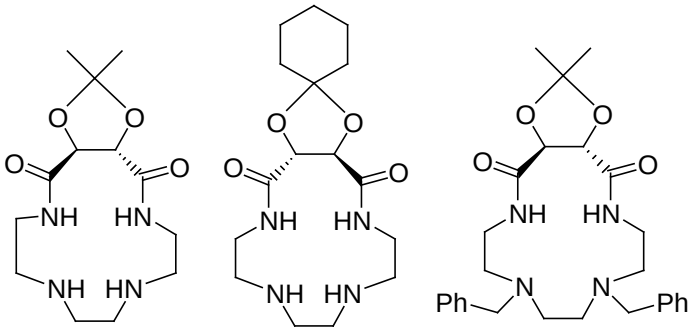


63



64

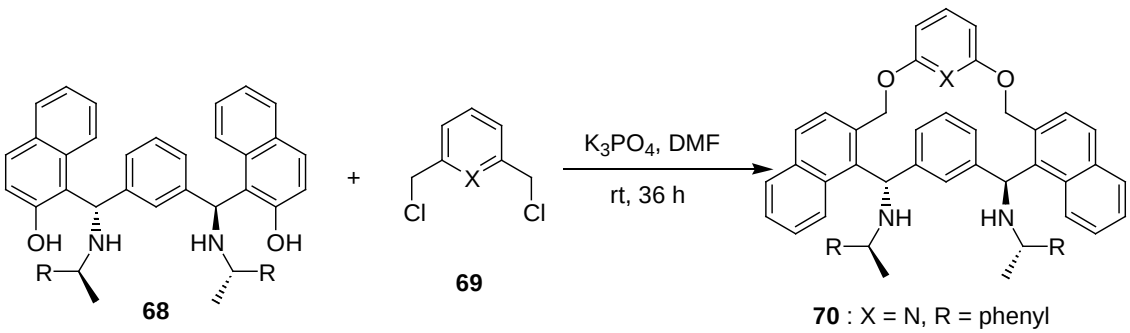
The use of chiral macrocyclic polyamides **65**-**67** derived from L/D-tartaric acid as chiral solvating agents towards carboxylic acids has been investigated.[29] All the macrocycles exhibited ability to recognise enantiomers of racemic carboxylic acids like mandelic acid derivatives and dibenzoyltartaric acid.



65 **66** **67**

In 2007, Ma and coworkers[30] synthesized a novel chiral macrocyclic compound **70** from C_2-symmetric aminonaphthol **68** (Scheme 4), followed by the synthesis of similar macrocyclic compounds[31] **71** and **72** that shows excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids such as mandelic acid derivatives and aminoacid derivatives by ^{1}H NMR spectroscopy. The same group also reported these macrocyclic compounds **71** and **72** as chiral solvating agents for phosphinic, phosphonic, and phosphoric acids by ^{1}H NMR and ^{31}P NMR spectroscopy.[32]

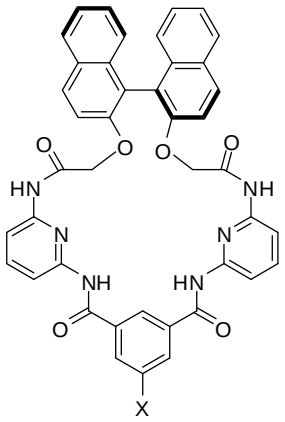
Scheme 4



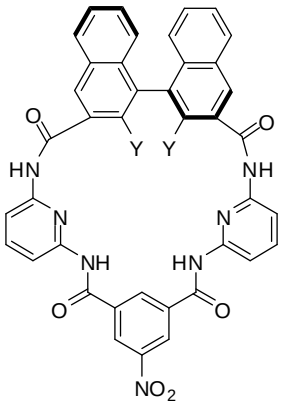
68 **69**

70 : X = N, R = phenyl
71 : X = N, R = 2-naphthyl
72 : X = CH, R = phenyl

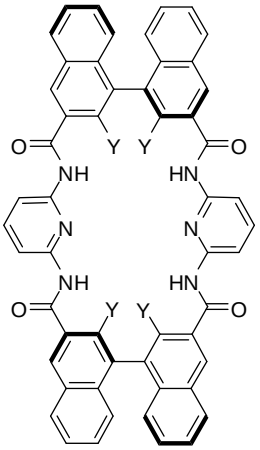
NMR studies of the bifunctional macrocycles **73**-**76** demonstrated that, among them, the receptor (*R*)-**73** functions as the best chiral solvating solvent for a wide range of chiral compounds having a carboxyl group, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate and epoxide functionality.[33]



(*R*)-**73** : X = NO_2
(*R*)-**74** : X = H

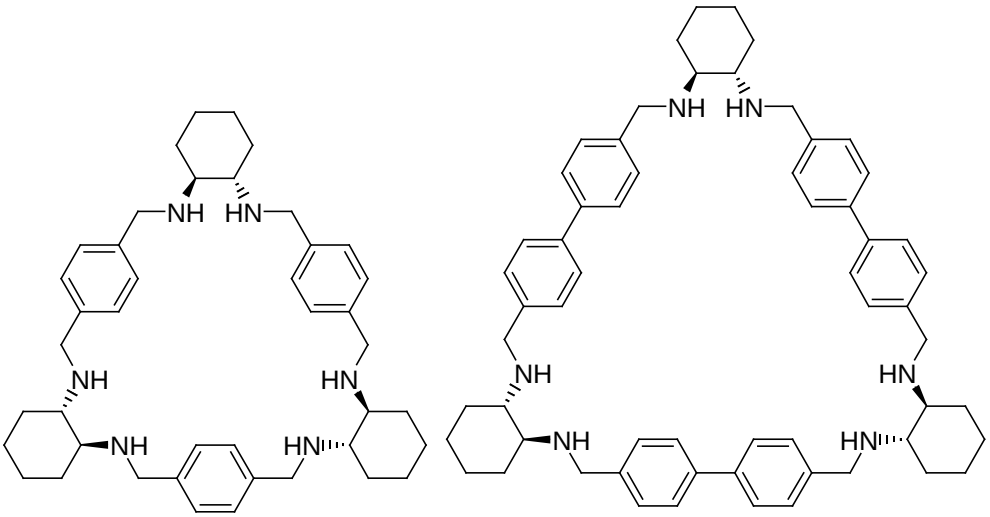


(*R*)-**75** : Y = OMe



(*R*)-**76** : Y = OMe

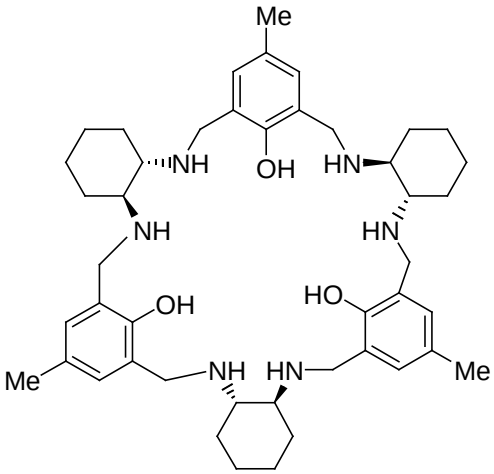
Tanaka *et al*.[34] reported that the chiral macrocyclic amines **77** and **78** function as highly sensitive chiral shift reagents for several kind of secondary alcohols, cyanohydrins and propargyl alcohols.



77 **78**

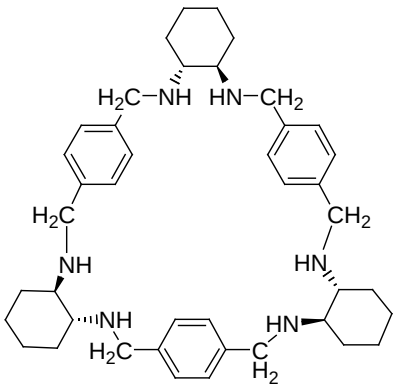
However, these macrocycles are not useful as chiral shift reagents for carboxylic acids for multiple binding with the carboxylic acids without the introduction of both hydrogen bond acceptor and donor group in the host macrocycles.[34] Another calixarene-like chiral amine macrocycle **79** containing both hydrogen bond acceptor (NH) and donor group (OH), which functions as a new chiral shift reagent for the determination of

the enantiomeric excess and absolute configuration of several kinds of carboxylic acid and amino acid derivatives has been reported.[35]

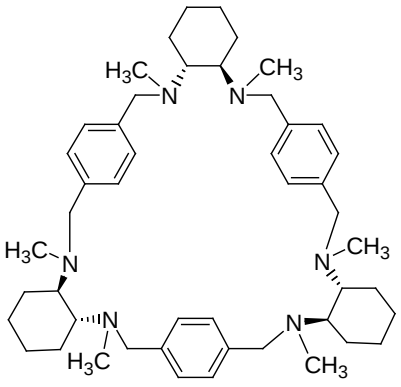


79

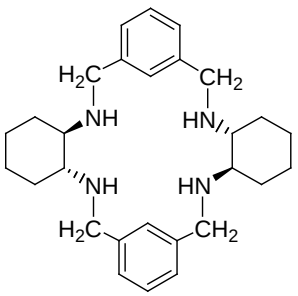
During research efforts from this laboratory on the synthesis and application of chiral macrocycles[36] **80-82**, it was found that they are efficient chiral solvating agent for the determination of enantiomeric excess of carboxylic acids **85** and **86** by ^{1}H NMR spectroscopy.[37]



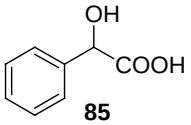
80



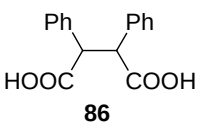
81



82



85



86

In continuation of our research efforts toward the synthesis of chiral *N*-alkylated C_2-symmetric diamines containing (*R*,*R*)-*trans*-1,2-diaminocyclohexane moiety[38] as discussed in Chapter 1, we have examined the use of some of these derivatives as chiral solvating agents for the determination of enantiomeric excess of carboxylic acids and amino acid derivatives by ^{1}H NMR spectroscopy. The results are discussed in the next section 2.2.

2.2 Results and Discussion

2.2.1. Application of chiral C_2-symmetric diamines as chiral solvating agents for carboxylic acids

As discussed in the introductory section 2.1, chiral macrocyclic as well as acyclic amines are useful in chiral recognition studies. Accordingly, we have examined the application of the readily accessible chiral *N*-alkylated C_2-symmetric diamines **83** and **84** (Chapter 1, Section 1.2) for the enantiomeric recognition of carboxylic acids. It was expected that the presence of the protonable chiral amine groups would lead to the formation of corresponding diastereomeric salts with the enantiomers of carboxylic acids.[39] As a result, the methine proton ($C^{\alpha}H$) signal of the carboxylic acids is expected to split. Accordingly, we have evaluated the chiral recognition ability of the secondary amines **83** and **84** towards the carboxylic acids **85-92** (Figure 1) by ^{1}H-NMR spectroscopy.

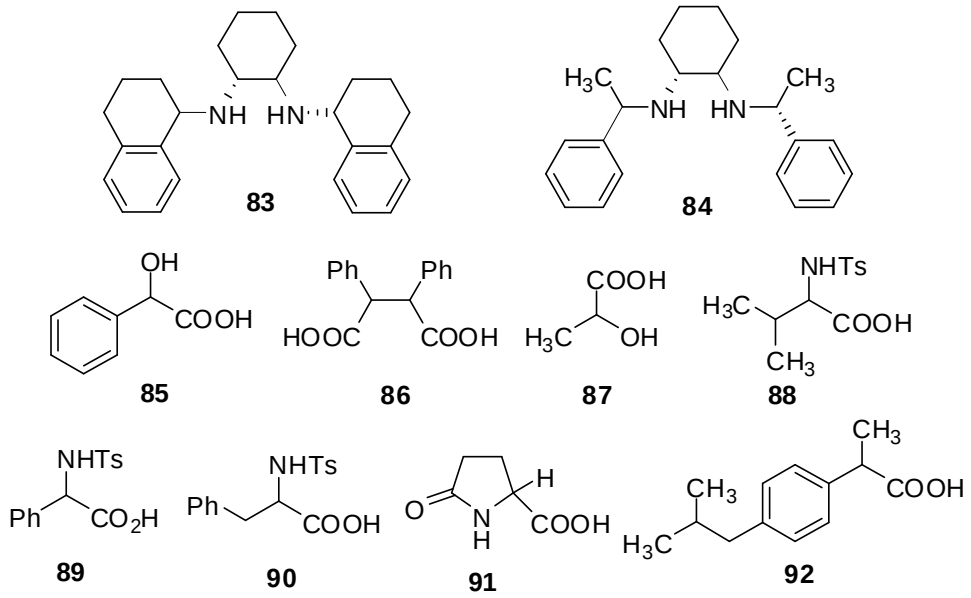


Figure 1. Structures of the receptor amines **83-84** and carboxylic acids **85-92**

Initially, the ^{1}H NMR experiments were carried out by incrementally adding solution of racemic mandelic acid **85** in $CDCl_3$ (2.5 mM) to a solution of chiral amine **83** in $CDCl_3$ (2.5 mM). Immediately after each addition, the ^{1}H NMR spectrum was acquired in a 400 MHz spectrometer at 25 ºC. Due to the difference in the interaction of the enantiomers of carboxylic acids with chiral amines, the methine proton ($C^{\alpha}H$) of mandelic acid **85**, 2,3-diphenylsuccinic acids **86** and *N*-Ts-phenylglycine **89** were split into two singlets. The splitting values between methine proton ($C^{\alpha}H$) signals corresponding to each enantiomer of acid **85** ($\Delta\Delta\delta$), after addition of the receptor **83** with different molar ratio, are summarized in Table 1.

Table 1. Measurement of the chemical shift non-equivalence (ΔΔδ) of the mandelic acid 85 in the presence of chiral amine receptor (1*R*,2*R*,1'*R*,1''*R*)-83 by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$ with different amine:acid molar ratio[a]

Entry	Amine **83**:Acid **85**	ΔΔδ (Hz)
1	1: 1.6	13.2
2	1: 1.8	13.6
3	1:1.9	15.2
4	1:2.0	16.4
5	1:2.5	17.2
6	1:2.8	17.8
7	1:3.0	18.0
8	1:3.5	17.2
9	1:4.0	16.8
10[b]	1:3.0	16.0

[a]Typical conditions: concentration of the acid and the receptor was 2.5 mM in 0.5 mL of $CDCl_3$, and the spectra were recorded at 25 ºC.

[b]Sample in the NMR tube was subjected to ultra sonication for 30 min. and the spectrum was recorded at 25 ºC.

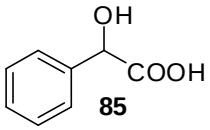
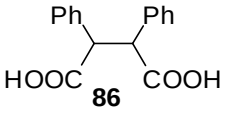
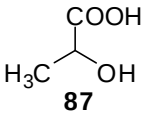
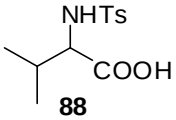
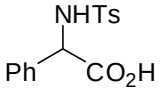
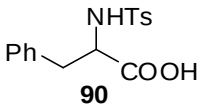
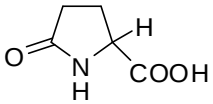
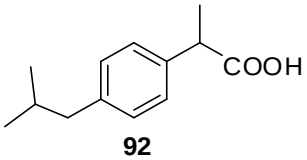
When the receptor amine **83** to mandelic acid **85** molar ratio is 1:3, maximum non-equivalence (18.0 Hz) of the $C^{\alpha}H$ proton of the acid was observed at 2.5 mM of total molar concentration (Table 1, entry 7). When the same sample was subjected to ultra sonication for 30 min, ΔΔδ decreases from 18.0 Hz to 16.0 Hz (Table 1, entry 10). We have observed that increase or decrease in the molar ratio between amine **83** and mandelic acid **85** from 1:3, the non-equivalences of the $C^{\alpha}H$ proton of the acid **85** decreases (Table 1).

According to the theory of chemical equilibrium, upon increasing the concentration of reactants, mole fraction decreases for a combination reaction. So, it can be predicted that at a larger concentration of reactants, the fractional population of free acid will be smaller and the chemical shift non-equivalence (ΔΔδ) would be larger. Accordingly, in the presence of receptor **83**, the chemical shift non-equivalences (ΔΔδ) of the strong acid **85** increases from 18.0 Hz to 53.6 Hz, as the total molar concentration increases from 2.5 mM to 100 mM (Table 2).

Table 2. Concentration variation of ^{1}H NMR chemical shift non-equivalence (ΔΔδ) of acid 85 in the presence of receptor amine 83 with amine:acid molar ratio of 1:3

Entry	Total molar conc. (mM)	ΔΔδ (Hz)
1	2.5	18
2	5	20.4
3	15	37.6
4	25	41.2
5	100	53.6

Table 3. Measurement of the chemical shift non-equivalences (ΔΔδ) of the racemic acids 85-92 in the presence of chiral amine receptor (1*R*,2*R*,1'*R*,1''*R*)-83 by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$[a]

Entry	Acid	Proton	Amine:Acid	ΔΔδ (Hz)
1	 **85**	α-H	1:3	53.6
2	 **86**	α-H	1:1	69.0
3	 **87**	α-H	1:1-1:3	0.0
4	 **88**	α-H CH_3(Ts) NH	1:1-1:3	0.0 0.0 0.0
5	 **89**	α-H CH_3(Ts) NH	1:3	118.0 3.2 68.7
6	 **90**	α-H CH_3(Ts) NH	1:1-1:3	0.0 0.0 0.0
7	 **91**	α-H	1:1-1:3	0.0
8	 **92**	α-H	1:1-1:3	0.0

[a]Typical conditions: concentration of the acid and the receptor amine **83** was 100 mM in 0.5 mL of $CDCl_3$ and the spectra were recorded at 25 ºC

Then, we examined the chiral recognition ability of chiral amine (1*R*,2*R*,1'*R*,1"*R*)-**83** towards different racemic carboxylic acids **85**-**92** at 100 mM concentration. The maximum chemical shift non-equivalence (ΔΔδ) observed at different amine:acid molar ratio is summarized in Table 3. In the presence of receptor amine **83**, the chemical shift non-equivalences of at least one of the protons of acids **85**, **86** and **89** are large enough to give base line resolution on a 400 MHz NMR spectrometer at 25 ºC.

When the receptor amine **83** to mandelic acid **85** ratio was 1:3, maximum non-equivalence of the $C^{\alpha}H$ proton (53.6 Hz) was obtained (Table 3, entry 1). A partial ^{1}H NMR spectrum of the racemic mandelic acid **85** in the presence of chiral amine receptor **83** is shown in Figure 2. In the case of 2,3-diphenylsuccinic acid **86**, the maximum non-equivalence of the $C^{\alpha}H$ proton (69.0 Hz) was observed at amine to acid molar ratio of 1:1 (Table 3, entry 2).

When the amine **83** to *N*-Ts-phenylglycine **89** ratio was 1:3, excellent non-equivalence of the $C^{\alpha}H$ proton (118.0 Hz) was obtained (Table 3, entry 5). In this case, the NH proton also shows good non-equivalence (68.7 Hz), whereas the CH_3 (Ts) proton shows poor non-equivalence might be due to the presence of CH_3 group far away from the chiral centre. A partial ^{1}H NMR spectrum of the racemic *N*-Ts-phenylglycine **89** in the presence of chiral amine receptor (1*R*,2*R*,1'*R*,1"*R*)-**83** is shown in Figure 3.

In the case of racemic carboxylic acids **87**, **88**, **90**, **91** and **92** the splitting of the corresponding $C^{\alpha}H$ proton was not observed. Presumably, the presence of bulky groups

attached to the $C^{\alpha}H$ proton centre may disturb the interaction between the chiral amine **83** and the racemic carboxylic acids.

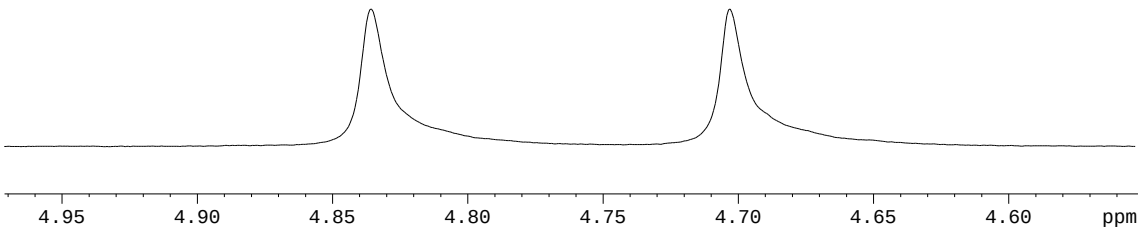


Figure 2. Partial ^{1}H NMR spectrum of racemic mandelic acid **85** in the presence of chiral amine receptor **83**

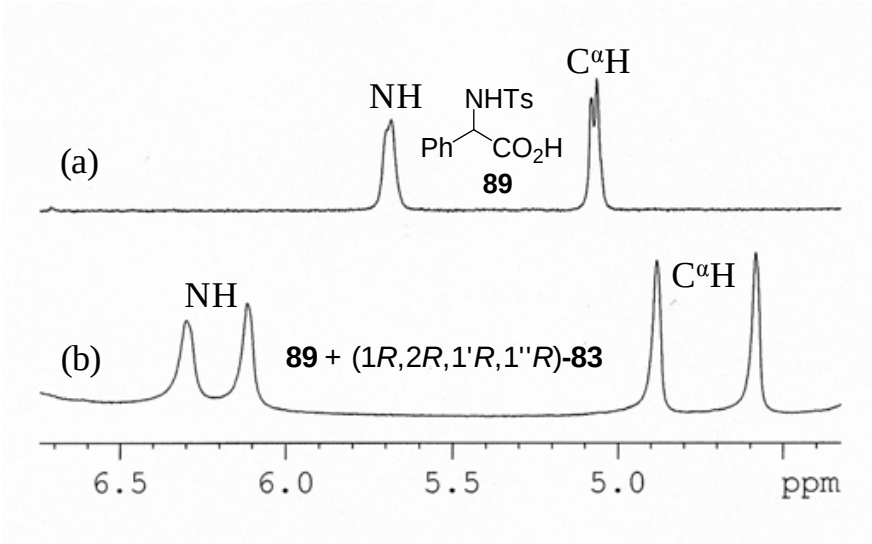
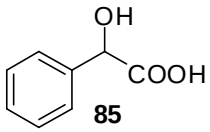
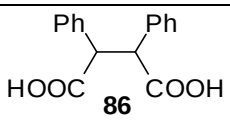
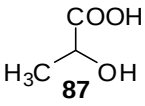
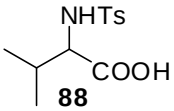
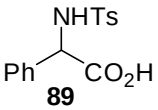
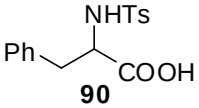
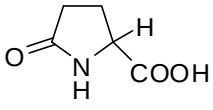
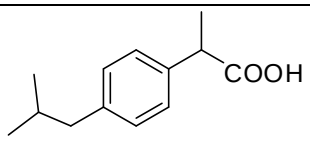


Figure 3. Partial ^{1}H NMR spectra showing $C^{\alpha}H$ and NH signals for the racemic *N*-Ts-phenylglycine **89** (100 mM, $CDCl_3$, 400 MHz, 25 ºC) (a) in the absence and (b) in the presence of 0.33 equiv. of (1*R*,2*R*,1'*R*,1''*R*)-**83**

Then, we examined the chiral recognition ability of chiral amine **84** towards different racemic carboxylic acids **85-92** at 100 mM concentration. Maximum chemical shift non-equivalence ($\Delta\Delta\delta$) observed at different amine:acid molar ratio is summarized in Table 4. When the receptor amine **84** to mandelic acid **85** ratio was 1:2.3, maximum non-equivalence of the $C^{\alpha}H$ proton (48.0 Hz) was obtained (Table 4, entry 1). In the

case of 2,3-diphenylsuccinic acid **86**, maximum non-equivalence of the $C^{\alpha}H$ proton (55.2 Hz) was obtained at amine:acid molar ratio of 1:2 (Table 4, entry 2).

Table 4. Measurement of the chemical shift non-equivalences (ΔΔδ) of the racemic acids 85-92 in the presence of chiral receptor amine (1*R*,2*R*,1'*R*,1''*R*)-84 by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$[a]

Entry	Acid	Proton	Amine:Acid	ΔΔδ (Hz)
1	 **85**	α-H	1:2.3	48.0
2	 **86**	α-H	1:2	55.2
3	 **87**	α-H	1:1-1:3	0.0
4	 **88**	α-H CH_3(Ts) NH	1:1-1:3	0.0 0.0 0.0
5	 **89**	α-H CH_3(Ts) NH	1:3	28.6 2.9 0.0
6	 **90**	α-H CH_3(Ts) NH	1:1-1:3	0.0 0.0 0.0
7	 **91**	α-H	1:1-1:3	0.0
8	 **92**	α-H	1:1-1:3	0.0

[a]Typical conditions: concentration of the acid and the receptor amine **84** was 100 mM in 0.5 mL of $CDCl_3$ and the spectra were recorded at 25 ºC.

A partial ^{1}H NMR spectrum of the racemic 2,3-diphenylsuccinic acid **86** in the presence of chiral amine (1*R*,2*R*,1'*R*,1"*R*)- **84** is shown in Figure 4.

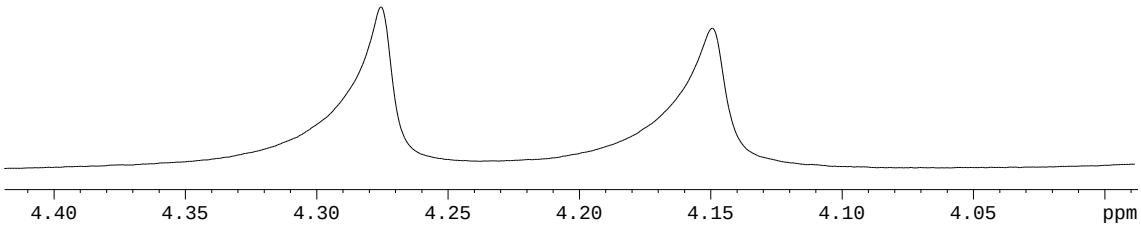


Figure 4. Partial ^{1}H-NMR spectrum of racemic 2,3-diphenylsuccinic acid **86** in the presence of chiral amine (1*R*,2*R*,1'*R*,1"*R*)-**84**

When the receptor amine **84** to *N*-Ts-phenylglycine **89** ratio was 1:3, maximum non-equivalence of the $C^{\alpha}H$ proton (28.6 Hz) was observed (Table 4, entry 5), which shows less splitting compared to that observed by using chiral amine **86** (Table 3, entry 5).

For racemic carboxylic acids **87**, **88**, **90**, **91** and **92**, the splitting of the corresponding $C^{\alpha}H$ proton was not observed (Table 4), might be due to the presence of bulky groups attached to the $C^{\alpha}H$ proton centre which may disturb the interaction between chiral amine **84** and the racemic carboxylic acids as observed in the case of the amine **83** (Table 3).

Some interesting observations have been made during these studies. First of all, the signals from the acids move upfield ($\Delta\delta<0$), suggesting a deprotonation of carboxylic group. Only, the NH proton from *N*-Ts-phenylglycine **89** resonates at lower field upon addition of the receptor, which can be interpreted as formation of a stronger intramolecular hydrogen bond with the carboxylate anion thus formed. Concomitantly,

signals from the receptor move downfield, which clearly indicates the proton transfer from the acid to the receptor, leading to the corresponding diastereomeric salts. These salts are expected to form intimate ionic pairs in $CDCl_3$.

The stoichiometry of the complex formed between the amine **83** and mandelic acid **85** was evaluated by carrying out the Job's titration between the amine **83** and both (*R*)-and (*S*)-mandelic acids in different ratios. The product (ΔδX) of the difference in chemical shift (Δδ) and the mole fraction of the acid (X) was plotted against the mole fraction of the acid to obtain the Job's plot (Table 5, Figure 5). A maximum was observed when the mole fraction of the (*R*) or (*S*)-mandelic acid was 0.75, indicating that the amine **83** forms a 1:3 complex with (*R*) or (*S*)-mandelic acid **85**. From the plot (Figure 5), it is evident that the chemical shift changes of the (*S*)-mandelic acid is greater when compared to the (*R*)-mandelic acid.

Table 5. Job's plot of the chiral amine 83 with (*R*) and (*S*)-mandelic acids 85

Entry	Mole fraction of the acid **85** (X)	(*S*)-Mandelic acid **85**		(*R*)-Mandelic acid **85**	
		Δδ[a]	ΔδX	Δδ[a]	ΔδX
1	0.1	0.310	0.031	0.310	0.031
2	0.2	0.311	0.062	0.311	0.062
3	0.3	0.312	0.094	0.312	0.094
4	0.4	0.316	0.126	0.316	0.126
5	0.5	0.323	0.162	0.323	0.162
6	0.6	0.436	0.262	0.364	0.218
7	0.65	0.459	0.298	0.368	0.239
8	0.7	0.472	0.330	0.368	0.258
9	0.75	0.425	0.319	0.325	0.244
10	0.8	0.377	0.301	0.285	0.228
11	0.9	0.207	0.186	0.157	0.141

[a]The change in the chemical shift (Δδ) of the acid **85** in the presence of amine **83** was calculated with

reference to the methine ($C^{\alpha}H$) proton signal of the acid at 5.257 δ ppm in the absence of **83**.

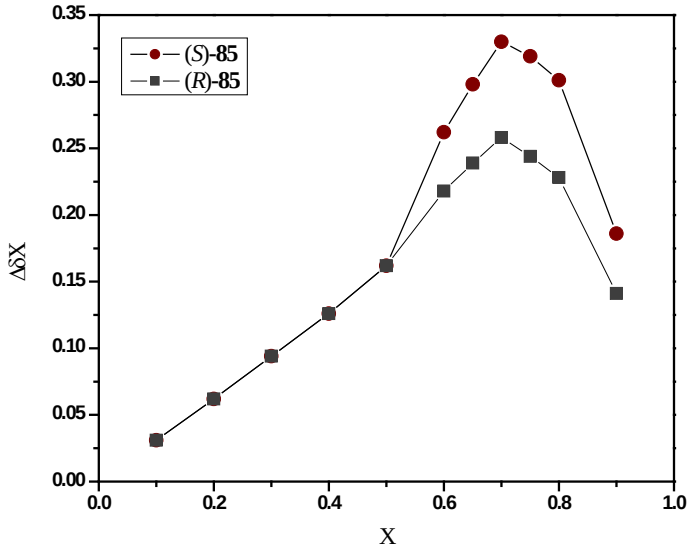


Figure 5. Job's plot of chiral receptor amine **83** with (*R*) and (*S*)-mandelic acids **85** [X = mole fraction of the acid; Δδ = change in the chemical shift of the $C^{\alpha}H$ proton signal of (*R*)- and (*S*)- mandelic acid **85**]

Finally, we have examined the practical applicability of this method for the measurement of enantiomeric excess of carboxylic acids. With this objective, samples containing different proportions of both the enantiomers of mandelic acid **85 (**100 mM in 5 mL $CDCl_3$) were prepared and analyzed with ^1H NMR method using the receptor amine **83** (100 mM in 5 mL $CDCl_3$) with amine:acid molar ratio of 1:3. Integration of the corresponding $C^{\alpha}H$ ^1H NMR signals shows an excellent linear correlation of the observed % ee values with that of expected % ee values based on HPLC method (Figure 6).[40]

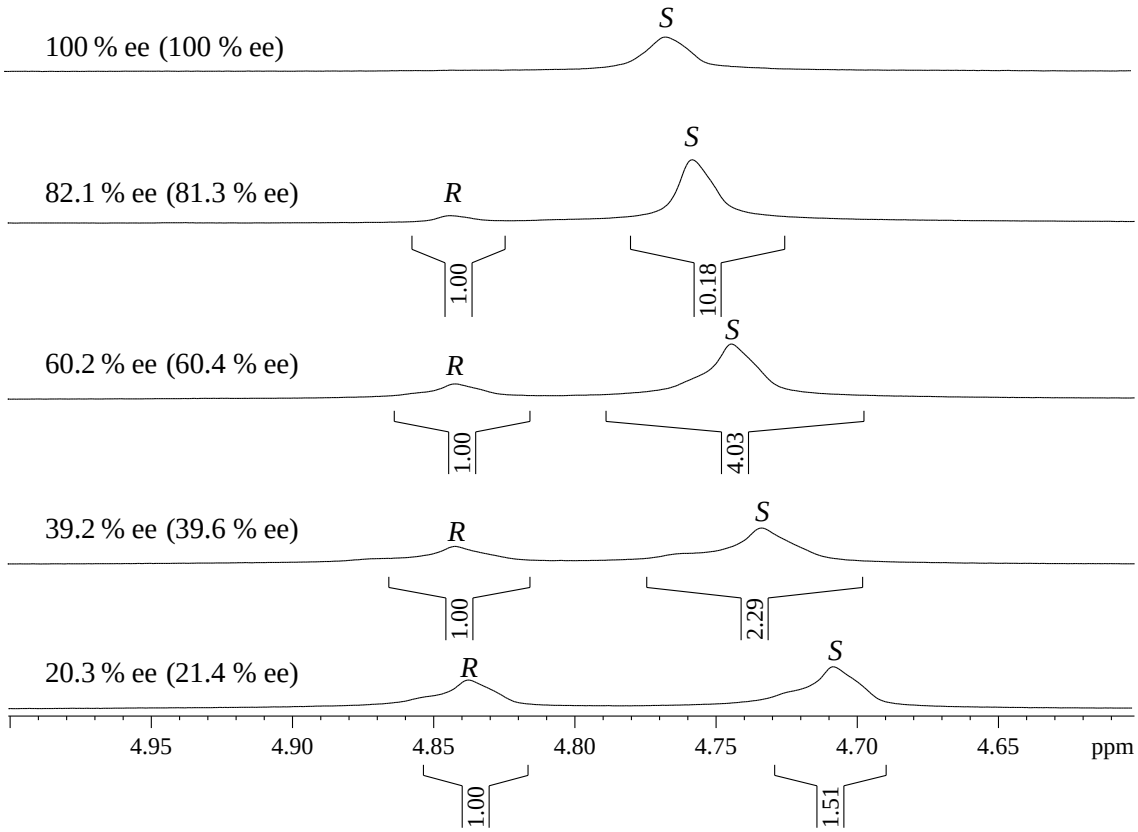


Figure 6. Selected region of the ^{1}H NMR (400 MHz) spectra of mandelic acid **85** (100 mM) with various enantiomeric purities in the presence of (1*R*,2*R*,1'*R*,1"*R*)-**83** (100 mM) in $CDCl_3$ at 25 ºC. The % ee values were obtained from the integration of the $C^{\alpha}H$ signals. The % ee values obtained by HPLC analysis are given in parentheses.

From these results, it is evident that the readily accessible chiral C_2-symmetric diamines **83** and **84** are useful chiral solvating agents for the carboxylic acids **85**, **86** and *N*-Ts-phenylglycine derivative **89**.

2.3 Conclusions

The use of the readily accessible chiral C_2-symmetric acyclic diamines **83** and **84** containing *trans*-1,2-diaminocyclohexane moiety as chiral solvating agents (CSAs) for the determination of enantiomeric excess of representative carboxylic acids **85**, **86** and an amino acid derivative **89** is illustrated. The enantiomeric composition of different carboxylic acids estimated herein by the ^{1}H NMR method, based on the integration of the corresponding methine proton ($C^{\alpha}H$) signals are in excellent correlation with that determined using HPLC method. The data are in accordance with the formation of multimolecular diastereomeric complexes in solution, which render good splitting of the NMR signals for the enantiomers of representative carboxylic acids **85** and **86** as well as for *N*-Ts-phenylglycine **89** (up to $\Delta\Delta\delta$ = 0.295 ppm, 118.0 Hz). The high symmetry and simple ^{1}H NMR spectrum of these chiral amines reduce the possibility of large overlapping with signals of the substrates. The easy accessibility of the chiral amine receptors **83** and **84** from commercially available 1,2-diaminocyclohexane should make this methodology very attractive for practical application as chiral solvating agents (CSAs) for carboxylic acids.

2.4 Experimental Section

2.4.1 General Information

Several information given in the section 1.4 are also applicable for the experiments outlined in this section. The racemic 2,3-diphenylsuccinic acid **86** was synthesized following a reported procedure.[41] The *N*-Ts-amino acid derivatives **88-90** were synthesized following a reported procedure.[42] The racemic mandelic acid **85** supplied by Sigma-Aldrich, USA and the (*S*)-(+)-mandelic acid supplied by E-Merck (Germany) were used. Ultrasonication was carried out in a Sonorex washing bath (BANDELIN electronic, type RK31H, 120W, 35 kHz).

2.4.2 ^{1}H-NMR shift experiments

^{1}H NMR shift experiments were performed on a 400 MHz NMR spectrometer at 25 °C by mixing the chiral amines **83** or **84** with the acids **85-92** in varying ratios in $CDCl_3$, until maximum splitting of the signals were observed.

2.4.3 Evaluation of stoichiometry of the complex formed between the amine 83 and (*R*)- or (*S*)-mandelic acid 85 by Job's method

The stoichiometry of the complex formed between **83** and **85** was determined according to Job's method of continuous variations. Equimolar amounts of **83** (25 mM) and (*R*) or (*S*)-**85** (25 mM) were prepared in $CDCl_3$ (5 mL). These solutions were distributed among ten NMR tubes in such a way that the mole fractions of **85** in the resulting solutions increased from 0.1 to 0.9. The complexation induced shifts of the methine ($C^{\alpha}H$) signal ($\Delta\delta$) were multiplied by the mole fraction of the acid **85** (X) (Table 5, Section 2.2.1) and plotted against X to obtain the Job's plot (Figure 5, Section 2.2.1).

2.5 References

1. Lin, J.; Hu, Q.-S.; Xu, M.-H.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 2088.
2. Pu, L. *Chem. Rev.* **2004**, *104*, 1687.
3. Lin, J.; Rajaram, A. R.; Pu, L. *Tetrahedron* **2004**, *60*, 11277.
4. Valentine, D. Jr.; Johnson, K. K.; Priester, W.; Sun, R. C.; Toth, K.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 3698.
5. (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (b) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256. (c) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
6. (a) Uccello-Barretta, G.; Balzano, F.; Sicoli, G.; Scarselli, A.; Salvadori, P. *Eur. J. Org. Chem.* **2005**, 5349. (b) Uccello-Barretta, G.; Balzano, F.; Martinelli, J.; Berni, M. G.; Villani, C.; Gasparrini, F. *Tetrahedron: Asymmetry* **2005**, *16*, 3746.
7. Ema, T.; Tanida, D.; Sakai, T. *J. Am. Chem. Soc.* **2007**, *129*, 10591.
8. (a) Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609. (b) Chin, J.; Kim, D. C.; Kim, H. J., Panosyan, F. B.; Kim, K. M. *Org. Lett.* **2004**, *6*, 2591.
9. Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, *9*, 4249.
10. Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837.
11. Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4579.

12. Uccello-Barretta, G.; Pini, D.; Mastantuono, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1965.

13. Uccello-Barretta, G.; Mirabella, F.; Balzano, F.; Salvadori, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1511.

14. Enders, D.; Thomas, C. R.; Runsink, J. *Tetrahedron: Asymmetry* **1999**, *10*, 323.

15. Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149.

16. Rajamoorthi, K.; Stockton, G. W. *Spectrosc. Lett.* **2001**, *34*, 255.

17. Cuevas, F.; Ballester, P.; Perics, M. A. *Org. Lett*. **2005**, *7*, 5485.

18. Yang, X.; Wang, G.; Zhong, C.; Wu, X.; Fu, E. *Tetrahedron: Asymmetry* **2006**, *17*, 916.

19. Wang, W.; Ma, F.; Shen, X.; Zhang, C. *Tetrahedron: Asymmetry* **2007**, *18*, 832.

20. Luo, Z.; Li, B.; Fang, X.; Hu, K.; Wu, X.; Fu, E. *Tetrahedron Lett.* **2007**, *48*, 1753.

21. Wang, W.; Shen, X.; Ma, F.; Li, Z.; Zhang, C. *Tetrahedron: Asymmetry* **2008**, *19*, 1193.

22. Peña, C.; González-Sabìn, J.; Alfonso, I.; Rebolledo, F.; Gotor, V. *Tetrahedron* **2008**, *64*, 7709.

23. Mastranzo, V. M.; Quintero, L.; Parrodi, C. A. D. *Chirality* **2007**, *19*, 503.

24. Kim, S.-M.; Choi, K. *Eur. J. Org. Chem.* **2011**, 4747.

25. Satishkumar, S.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2257.

26. Yang, X.; Wu, X.; Fang, M.; Yuan, Q.; Fu, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2491.

27. Li, Y.; Echegoyen, L. *J. Org. Chem*. **1991**, *56*, 4193.

28. González-Álvarez, A.; Alfonso, I.; Gotor, V. *Tetrahedron Lett.* **2006**, *47*, 6397.

29. Li, B.; Yang, X.; Wu, X.; Luo, Z.; Zhong, C.; Fu, E. *Supramol. Chem.* **2006**, *18*, 507.

30. Ma, F.; Ai, L.; Shen, X.; Zhang, C. *Org. Lett*. **2007**, *9*, 125.

31. Ma, F.; Shen, X.; Ming, X.; Wang, J.; Ou-Yang, J.; Zhang, C. *Tetrahedron: Asymmetry* **2008**, *19*, 1576.

32. Ma, F.; Shen, X.; Ou-Yang, J.; Zhang, C. *Tetrahedron: Asymmetry* **2008**, *19*, 31.

33. Ema, T.; Tanida, D.; Sakai, T. *J. Am. Chem. Soc.* **2007**, *129*, 10591.

34. Tanaka, K.; Fukuda, N.; Fujiwara, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2657.

35. Tanaka, K.; Fukuda, N. *Tetrahedron: Asymmetry* **2009**, *20*, 111.

36. Padmaja, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437.

37. (a) Padmaja, M. Ph.D. Thesis **2005**, School of Chemistry, University of Hyderabad. (b) Periasamy, M.; Dalai, M.; Padmaja, M. *J. Chem. Sci*. **2010**, *122*, 561.

38. Dalai, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1247.

39. González-Álvarez, A.; Alfonso, I.; Díaz, P.; García-España, E.; Gotor, V. *Chem. Commun*. **2006**, 1227.

40. Ebbers, E. J.; Ariaans, G. J. A.; Bruggink, A.; Zwanenburg, B.; *Tetrahedron: Asymmetry* **1999**, *10*, 3701.

41. Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809.

42. Li, G.-I.; Zhao, G. *Org. Lett*. **2006**, *8*, 633.

Chapter 3

Studies on hydroboration of olefins using chiral amine-borane and aminoborane complexes

3.1 Introduction

Boron reagents have become increasingly important for use in catalytic and stoichiometric transformations in the synthesis of highly complex functionalized molecules. Some of the highlights include asymmetric hydroboration and reductions (Ipc_2BH and CBS), Suzuki-Miyaura cross-coupling and the introduction of functional groups such as alcohols and amines. Because of their unique properties and high selectivities, these reagents have become a valuable part of the organic chemistry tool box and found their way into a number of commercial applications. Amine-borane adducts have attracted increasing attention as reagents and hydrogen storage materials. For example, studies on the ammonia-borane as a potential portable hydrogen storage material has attracted a surge of interest as a result of high hydrogen content (19.6 wt %) in this complex.

We have made efforts to explore the application of the borane complexes of various chiral diamines containing enantiomerically pure *trans*-1,2-diaminocyclohexane moiety prepared *via* the methods described in Chapter 1. It is of interest to briefly review the reported studies in this area.

3.1.1 Hydroboration of prochiral olefins with chiral amine-borane complexes

The hydroboration reaction is one of the most widely studied reactions in organic synthesis, discovered by H. C. Brown and B. C. SubbaRao in 1956.[1] Borane adducts of Lewis bases such as tetrahydrofuran (THF), dimethyl sulfide (DMS) and some aromatic and hindered amines have been used effectively for the hydroboration of double and triple bonds, as well as in reduction of the functional groups such as

aldehydes, ketones, carboxylic acids, amides, lactams and Schiff bases. Also, the oxazaborolidine catalyzed enantioselective reduction of prochiral ketones have been widely used in synthesis.[2]

The pyridine-borane and trimethyl amine-borane complexes hydroborate olefins at elevated temperature.[3] The *N*-alkyl substituted anilines form more reactive amine-borane complexes.[4] The order of reactivity among the amine-borane complexes is closely related to their stability. The less basic aniline derivatives form weaker and hence more reactive adducts with borane.

Previously, hydroboration studies using *N*,*N*-diethylaniline iodoborane complexes have been reported from this laboratory.[5] It was found that appropriate amount of I_2 gives the corresponding BH_2I, BHI_2 and BI_3 complexes (Chart 1). Among these, the BHI_2 complex **3** has been used for the hydroboration of alkenes, including in some selective hydroboration reactions (Chart 2).

Chart 1

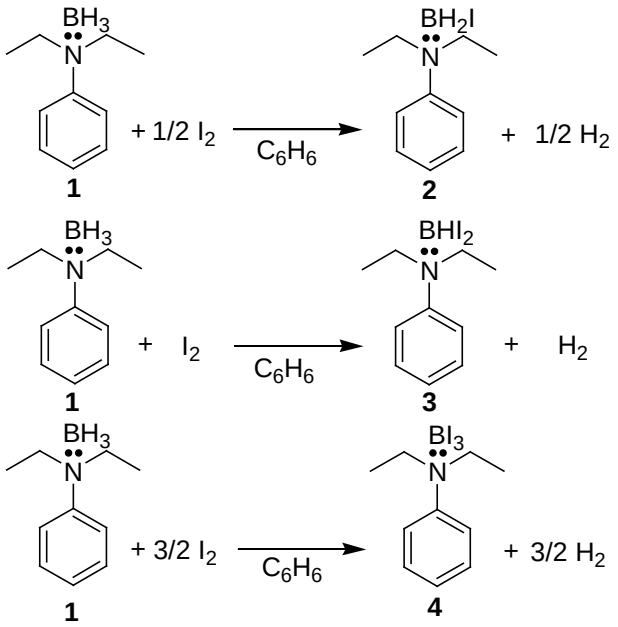
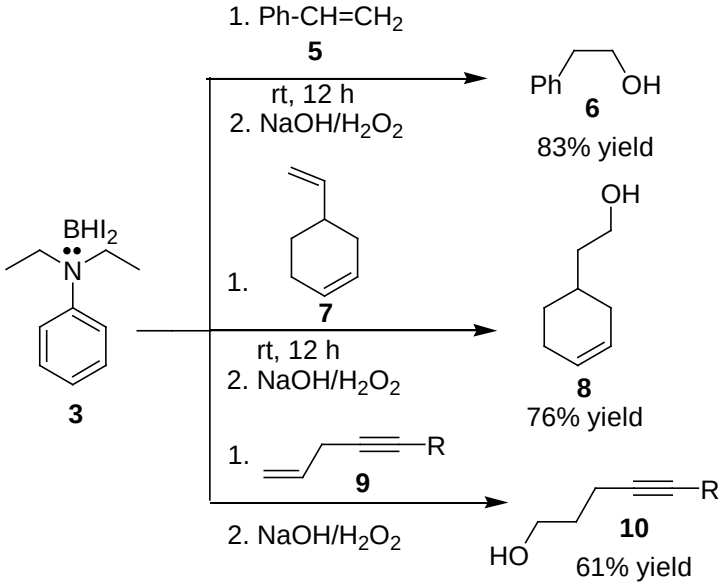
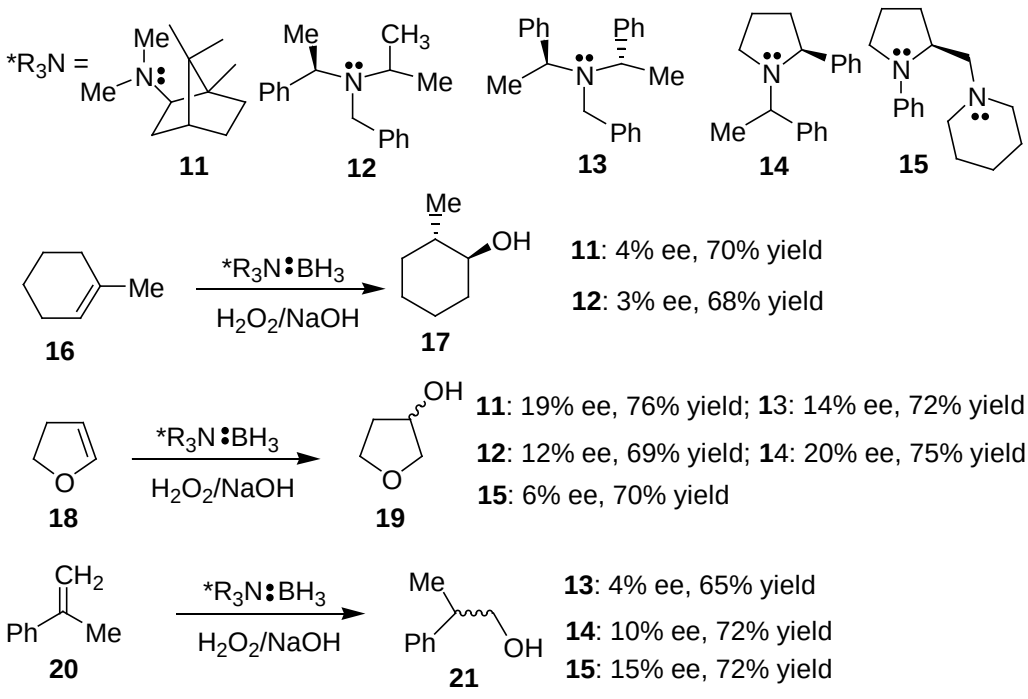


Chart 2



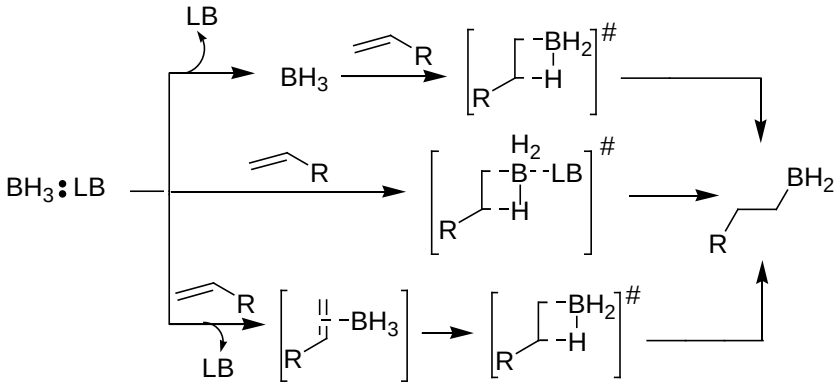
It has been reported from this laboratory that the hydroboration of representative prochiral olefins **16**, **18** and **20** using chiral tertiary amine-borane complexes of amines **11-15** gave the corresponding alcohols with up to 20% ee (Chart 3).[6]

Chart 3



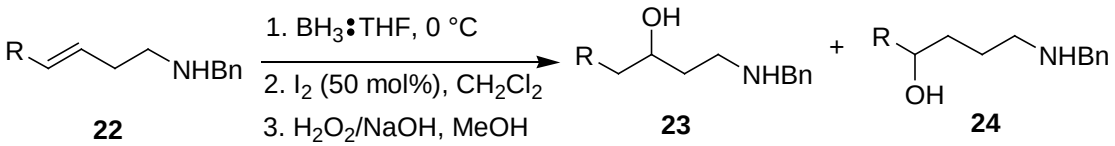
The selectivities realized in these reactions are low, as the amine moiety is expected to leave before or during formation of the hydroboration reaction transition state as outlined in Scheme 1.

Scheme 1



Recently, Vedejs *et al.*[7] reported the intramolecular hydroboration of homoallylic amines and phosphine borane complexes using I_2 as activating agent (Scheme 2).

Scheme 2



22

R = Me, Et, Ph, H

23

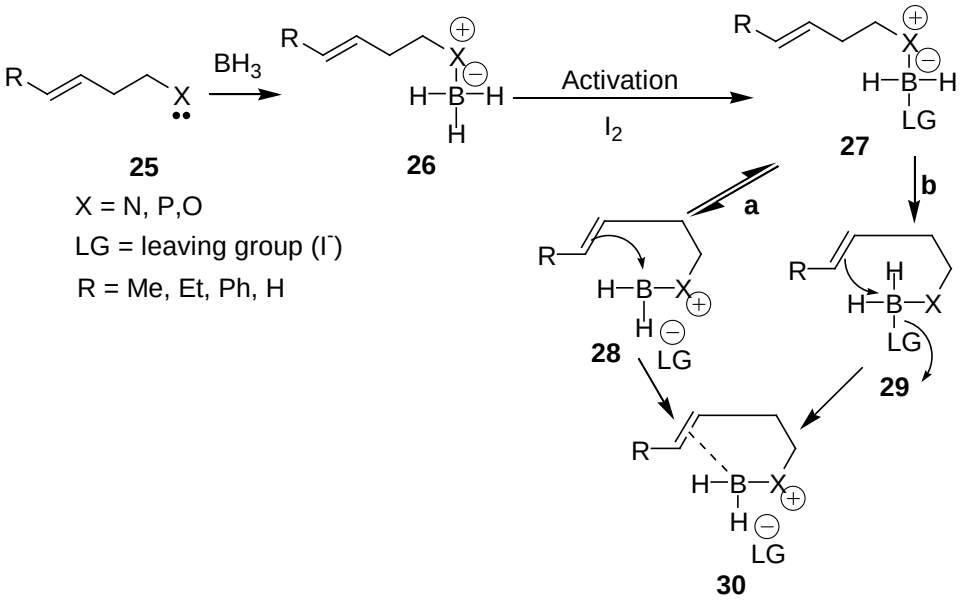
24

23:**24** = >20-1:1-3

79-90% yield

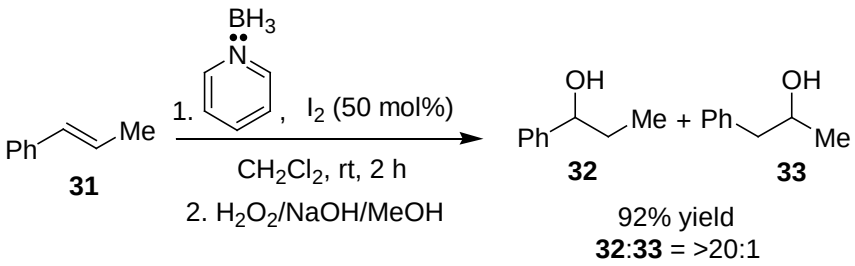
The proposed mechanistic pathway indicates that the reaction goes through an S_N1 like mechanistic pathway *via* the transition state **28** or S_N2 like mechanistic pathway *via* the transition state **29**, where the iodide (I^-) acts as a leaving group (Scheme 3).

Scheme 3



Also, Vedejs *et al.*[8] reported the intermolecular hydroboration of β-methylstyrene **31** using pyridine-BH_3 complex and 50 mol% I_2 at room temperature (Scheme 4).

Scheme 4

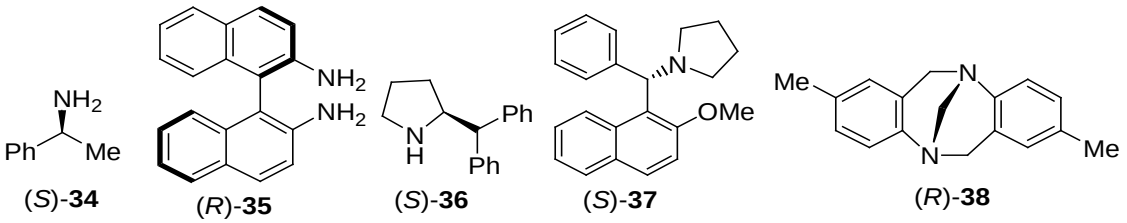


Since the amine moiety is anchored on the boron centre in these iodine activated borane complexes with iodide behaving like leaving group, it was of our interest to prepare the chiral amine-BH_2I complexes to examine the enantioselectivity in the hydroboration of prochiral olefins. Hydroboration studies reveal that the reactivity order is $RNH_2{:}BH_3 > R_2NH{:}BH_3 > R_3N{:}BH_3$ for iodine activated hydroboration reaction of

α-methylstyrene **20** (Chart 4).[9] When the hydroboration reaction of α-methylstyrene **20** was carried out in the presence of primary amines such as α-methylbenzylamine **34** or (*R*)-BINAM **35** borane complexes under 50 mol% iodine activation, the product **21** was obtained in up to 13% ee and 11% ee respectively (Chart 4).

Chart 4

Chiral Amines



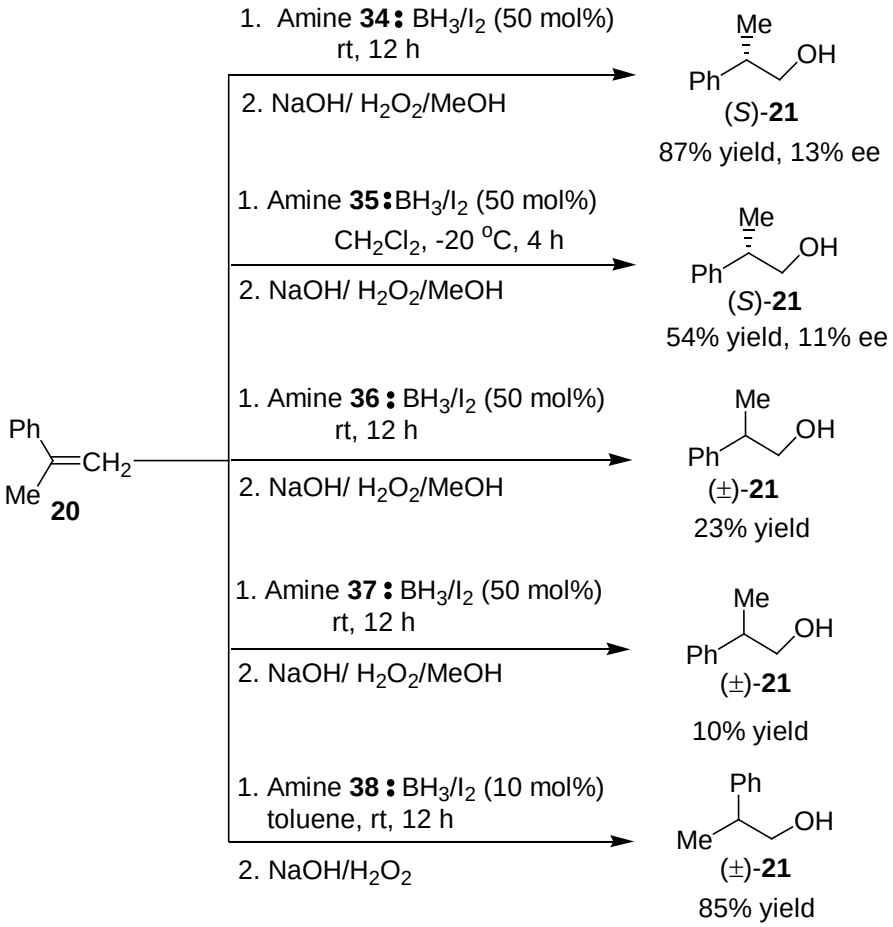
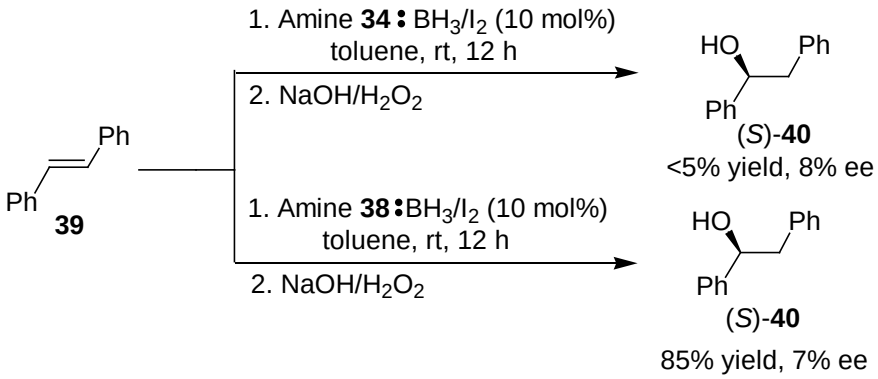


Chart 4 continued…



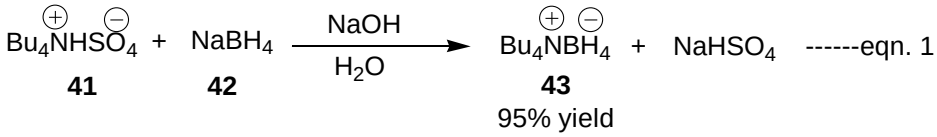
When the hydroboration reaction of α-methylstyrene **20** was carried out in the presence of the borane complexes of secondary or tertiary amines **36**, **37** and **38** under iodine activation, only racemic product **21** was obtained (Chart 4). However, the hydroboration reaction of *trans*-stilbene **39** using chiral tertiary amine Tröger base **38**-borane complex with catalytic amount of iodine (10 mol%) gave the corresponding alcohol **40** with up to 7% ee. When the hydroboration reaction of *trans*-stilbene **39** was carried out in the presence of α-methylbenzylamine **34**-borane complex with catalytic amount of iodine (10 mol%), the alcohol **40** was obtained in <5% yield with up to 8% ee (Chart 4).

We became interested in examining the stereochemical outcome of the hydroboration reaction of prochiral olefins with chiral amine-boranes derived from (*R*,*R*)-*trans*-1,2-diaminocyclohexane derivatives, readily accessed through the method outlined in Chapter 1. The results are discussed in the next section.

3.2 Results and Discussion

3.2.1 Hydroboration of prochiral olefins using borane complexes of *trans*-(*R*,*R*)-1,2-diaminocyclohexane derivatives

The tetrabutylammonium borohydride **43** in combination with methyl iodide or I_2 or $PhCH_2Cl$ reagent is useful for the generation of diborane gas which facilitates several organic and asymmetric transformations.[10] Earlier, sodium borohydride **42** was used for the generation of diborane gas.[11] As sodium borohydride exhibits poor solubility in common organic solvents, diglyme is the preferred solvent for the generation of diborane gas using sodium borohydride. Due to the presence of lengthy alkyl chains, the tetrabutylammonium borohydride **43** is soluble in toluene and other common organic solvents. Moreover, the tetrabutylammonium borohydride **43** is less moisture sensitive compared to sodium borohydride. It can be conveniently prepared in quantitative yields by the reaction of sodium borohydride **42** and tetrabutylammonium hydrogen sulphate **41** (Eqn 1).[12]



Accordingly, we have prepared the chiral amine-borane complexes from chiral diamines **44** and **45** containing *trans*-(*R*,*R*)-1,2-diaminocyclohexane moiety using tetrabutylammonium borohydride **43** for hydroboration of α-methylstyrene **20** (Scheme 5). The results are summarized in Table 1.

Scheme 5

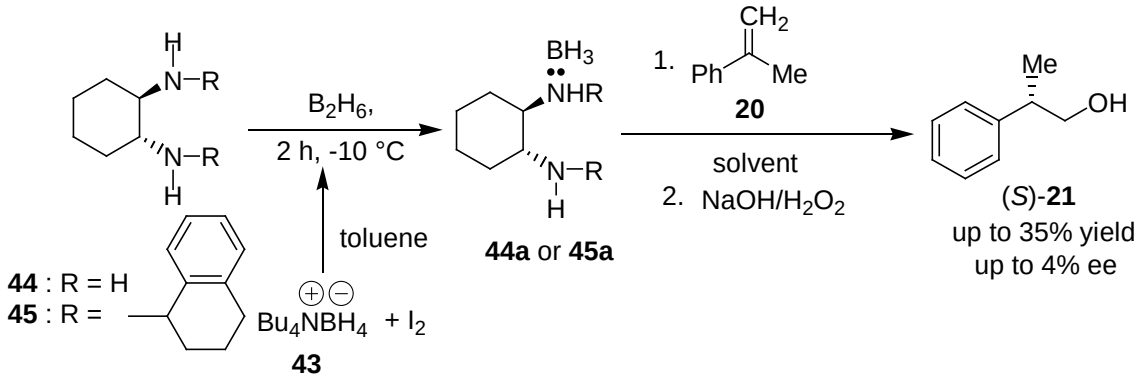


Table 1. Hydroboration-oxidation reaction of α-methylstyrene 20 using chiral amine-borane complexes 44a or 45a[a]

Entry	Amine	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**44**	CH_2Cl_2	25	24	---	---
2	**44**	DCE	80	24	12	2
3	**44**	toluene	120	24	16	4
4	**45**	toluene	25	19	35	0
5	**45**	toluene	0	24	19	0

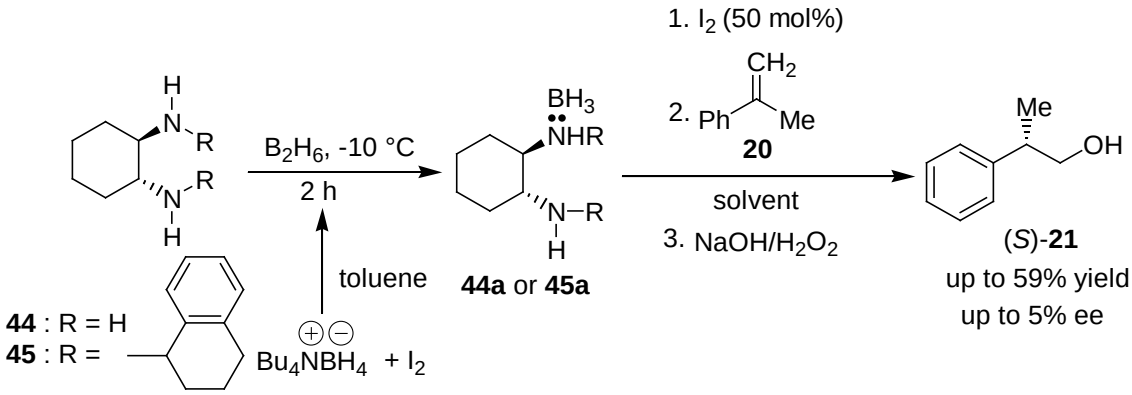
[a]Unless otherwise noted all the reactions were carried out by purging excess diborane gas through a solution of amine **44** or **45** (2.5 mmol) in toluene or DCE, CH_2Cl_2 for 2 h at -10 °C. The α-methylstyrene **20** (2.5 mmol) was added after the formation of amine-borane.
[b]Yields are for the isolated products.
[c]Determined by HPLC analysis using the chiral column OB-H; n-Hexane:*i*PrOH-97:3, 0.3 mL/min. The chiral alcohol **21** obtained in all the cases have *S*-absolute configuration.

The more basic *trans*-(*R*,*R*)-1,2-diaminocyclohexane **44** forms stronger complex with borane. After optimization of the reaction condition for hydroboration oxidation of α-methylstyrene **20**, we have observed that the product 2-phenylpropanol **21** was obtained in 16% yield with 4% ee at 120 °C in toluene (Table 1, entry 3).

The less basic and more sterically hindered secondary amine **45** derived from *trans*-(*R*,*R*)-1,2-diaminocyclohexane **44** forms a weaker complex with boron. As a result, the hydroboration-oxidation reaction of α-methylstyrene **20** takes place at 25 °C, giving only racemic alcohol **21** in 35% yield (Table 1, entry 4).

We have also examined the hydroboration-oxidation reaction of α-methylstyrene **20** with the amine-borane complexes **44a** and **45a** under I_2 activation at different conditions (Scheme 6). The results are summarized in Table 2.

Scheme 6



After optimization of the reaction conditions, we have observed that the product (*S*)-**21** was obtained in 59% yield with 5% ee at 120 °C in toluene by using chiral amine-borane complex **44a** under 50 mol% I_2 activation (Table 2, entry 4). When the reaction was carried out using secondary amine-borane complex **45a**, under I_2 activation (50 mol%) at 25 °C for 12 h, only racemic product **21** was obtained in 62% yield (Table 2, entry 6).

Table 2. Hydroboration-oxidation reaction of α-methylstyrene 20 using chiral amine-borane complexes 44a or 45a under I_2 activation[a]

Entry	Amine	Solvent	I_2 (mol%)	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**44**	CH_2Cl_2	10	25	24	---	---
2	**44**	CH_2Cl_2	50	25	24	15	2
3	**44**	DCE	50	80	20	52	2
4	**44**	toluene	50	120	20	59	5
5	**44**	toluene	50	120	4	19	4
6	**45**	toluene	50	25	12	62	0

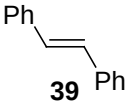
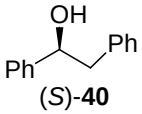
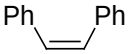
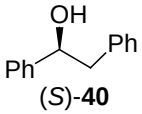
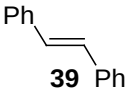
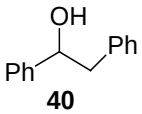
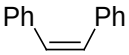
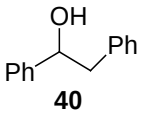
[a]Unless otherwise noted, all the reactions were carried out by purging excess diborane gas through a solution of chiral amine **44** or **45** (2.5 mmol) in toluene or DCE, CH_2Cl_2 for 2 h at -10 °C. The amine-borane complexes were activated with 1.25 mmol of I_2. The α-methylstyrene **20** (2.5 mmol) was added after the activation of amine-borane with iodine.

[b]Yields are for the isolated products.

[c]Determined by HPLC analysis using the chiral column OB-H; n-Hexane:^{i}PrOH-97:3, 0.3 mL/min. The chiral alcohol obtained in all the cases have *S*-absolute configuration.

The hydroboration reaction of 1,2-substituted prochiral olefins **39** and **46** were also examined using the amine-borane complexes **44a** and **45a** at 120 °C. The alcohol **40** was formed in 61-75% yields upon hydroboration-oxidation reaction of *trans*- and *cis*-stilbene **39** and **46** with very poor selectivity (Table 3).

Table 3. Hydroboration-oxidation reaction of *trans*- and *cis*-stilbene 39 and 46 using chiral amine-borane complexes 44a and 45a under I_2 activation[a]

Entry	Substrate	Amine	Time (h)	Product	Yield (%)[b]	ee (%)[c]
1	 **39**	**44**	12	 (*S*)-**40**	61	2
2	 **46**	**44**	12	 (*S*)-**40**	67	3
3	 **39**	**45**	12	 **40**	72	0
4	 **46**	**45**	12	 **40**	75	0

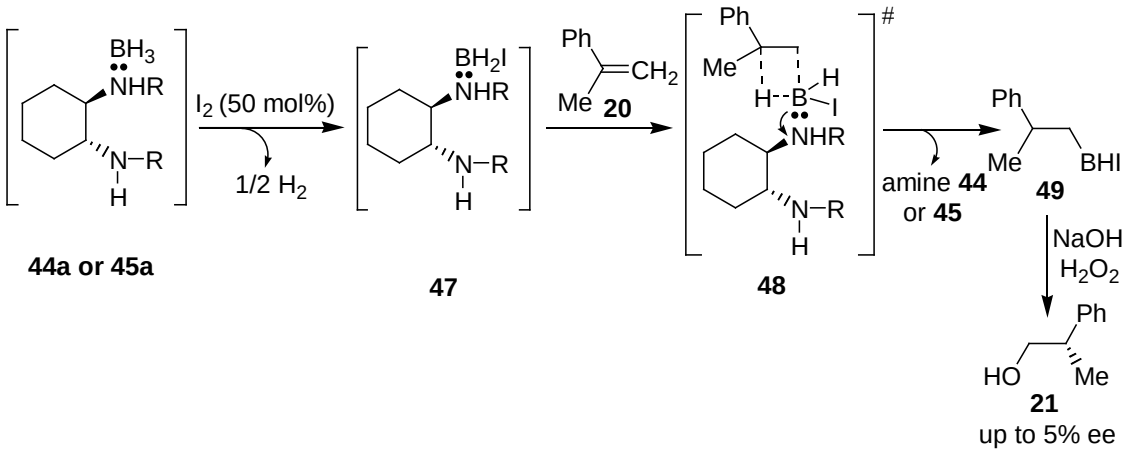
[a]All the reactions were carried out by purging excess B_2H_6 through a solution of **44** or **45** (2.5 mmol) in toluene at -10 °C. The amine-borane was activated with 1.25 mmol of I_2. Substrate olefin **39** or **46** (2.5 mmol) was added after the activation of iodine and the reaction mixture was warmed to 25 °C and further stirred for 12 h at 120 °C.

[b]Yields are for the isolated products.

[c]Determined by HPLC analysis using the chiral column, Chiralcel OD-H; n-hexane:^{i}PrOH-90:10, 0.3 mL/min.

Presumably, the products were obtained in poor selectivities because of the crowded nature of the amine-borane complexes **44a** and **45a**. Thus, the amine **44** or **45** might depart during the reaction instead of the iodide as outlined in Scheme 7.

Scheme 7

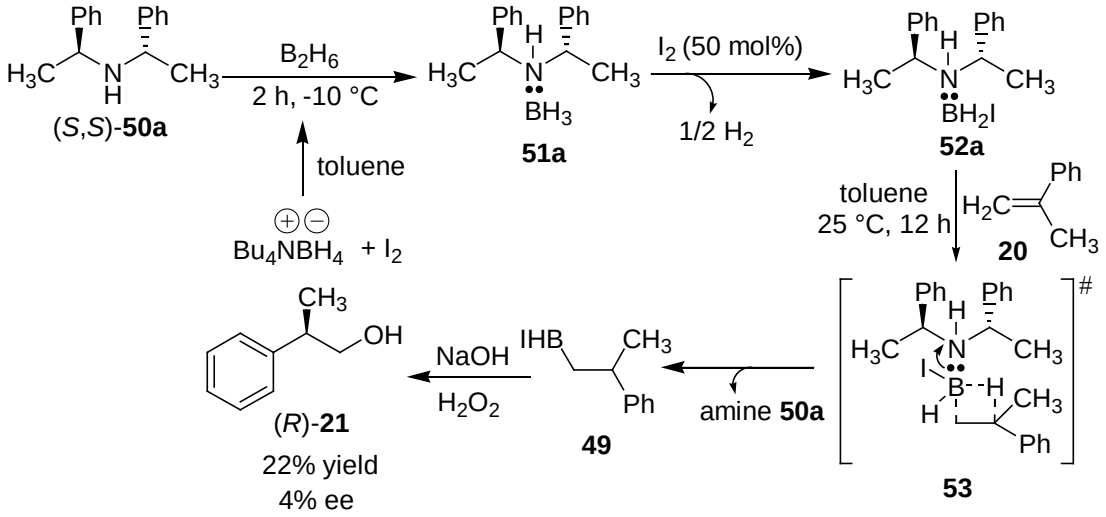


3.2.2 Hydroboration using chiral amine-borane and aminoborane prepared from (*S*,*S*)-bis-(1-phenyl-ethyl)-amine 50a

Since only negligible asymmetric inductions were realized in the hydroboration reaction of olefins **20**, **39** and **46** as summarized in Tables 1, 2 and 3 by using the amine-borane complexes **44a** and **45a**, we decided to examine the hydroboration reaction using the C_2-symmetrical chiral amine **50a**, as better enantioselectivity (up to 13% ee) was realized in the hydroboration reaction using the borane complex of amine **34** containing α-methylbenzyl moiety under I_2 activation (Section 3.1.1, Chart 4).

Accordingly, we have carried out the hydroboration of α-methylstyrene **20** using amine-borane complex **51a** derived from the amine (*S*,*S*)-**50a** under I_2 (50 mol%) activation. However, the corresponding product **21** was obtained only in 4% ee with 22% yield (Scheme 8).

Scheme 8

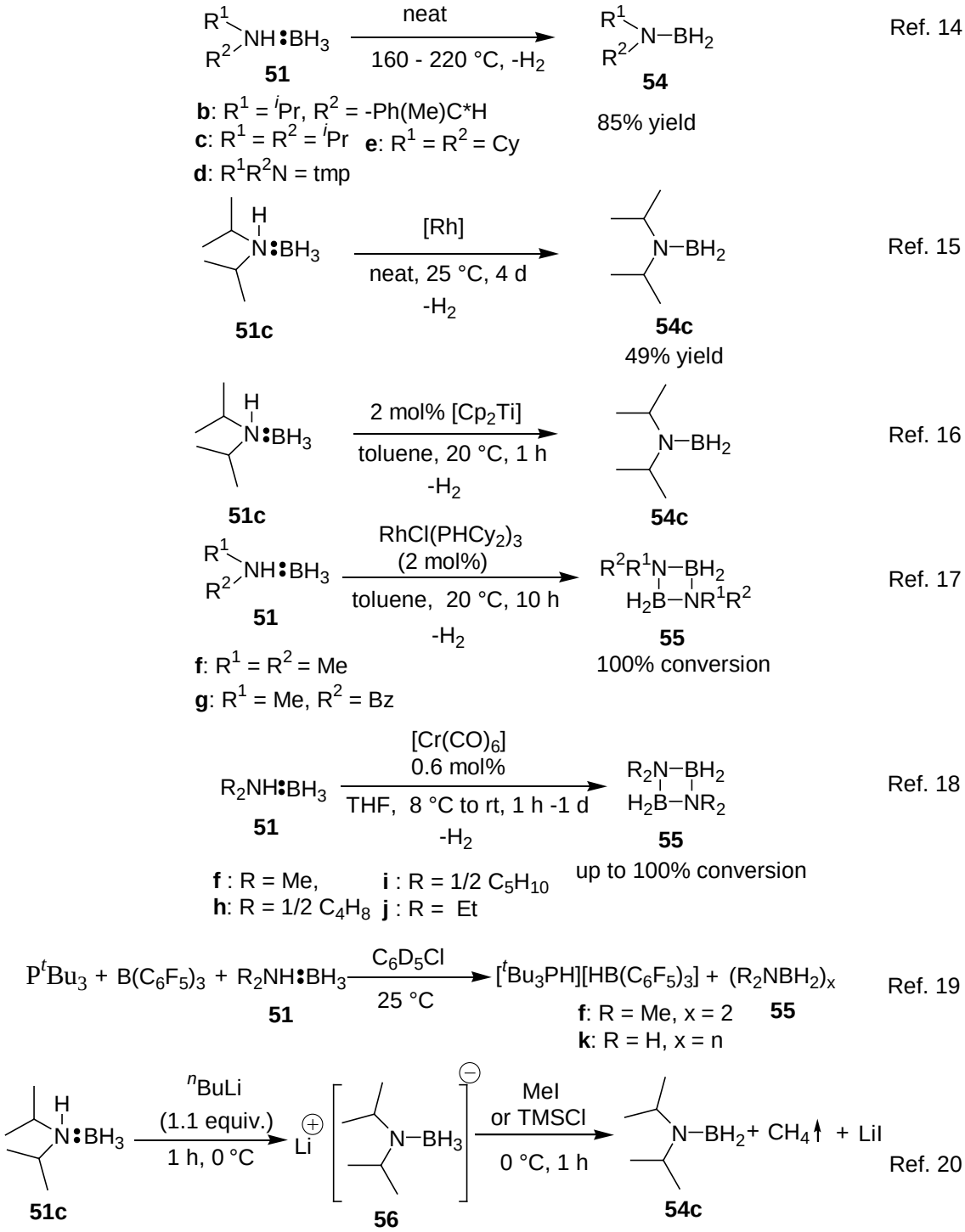


Presumably, the poor asymmetric induction realized might be due to the poor chiral discriminating ability of this amine system or crowded nature of the transition state favoring the departure of chiral amine **50a** instead of iodide during the reaction as outlined in Scheme 8.

3.2.2.1 Synthesis of aminoboranes

Aminoboranes (R_1R_2N-BR_3R_4) are well known as precursors for the preparation of BN-based ceramics.[13] Amino-dihydridoboranes (R_1R_2N-BH_2) have not been studied much for the applications in organic synthesis. These complexes are expected to remain in their more reactive monomeric form, if the alkyl groups hinder dimerization. Previous reports on the synthesis of aminoboranes are outlined in Chart 5.

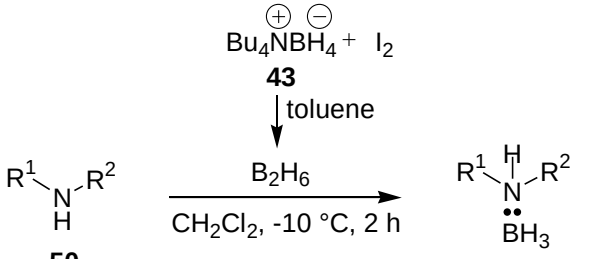
Chart 5


neat
160 - 220 °C, -H2
51
54
Ref. 14
b: R1 = iPr, R2 = -Ph(Me)C*H
c: R1 = R2 = iPr
e: R1 = R2 = Cy
d: R1R2N = tmp
85% yield
[Rh]
neat, 25 °C, 4 d
-H2
51c
54c
49% yield
Ref. 15
2 mol% [Cp2Ti]
toluene, 20 °C, 1 h
-H2
Ref. 16
RhCl(PHCy2)3
(2 mol%)
toluene, 20 °C, 10 h
-H2
Ref. 17
f: R1 = R2 = Me
g: R1 = Me, R2 = Bz
100% conversion
[Cr(CO)6]
0.6 mol%
THF, 8 °C to rt, 1 h -1 d
-H2
Ref. 18
f : R = Me,
h: R = 1/2 C4H8
i : R = 1/2 C5H10
j : R = Et
up to 100% conversion
PtBu3 + B(C6F5)3 + R2NH:BH3
C6D5Cl
25 °C
[tBu3PH][HB(C6F5)3] + (R2NBH2)x
Ref. 19
f: R = Me, x = 2
k: R = H, x = n
nBuLi
(1.1 equiv.)
1 h, 0 °C
Li
MeI
or TMSCl
0 °C, 1 h
+ CH4 + LiI
Ref. 20
56

The reported procedures for the synthesis of aminoboranes involve harsh reaction conditions such as high temperature, expensive transition or rare transition metal catalysts and use of highly moisture sensitive reagents such as ^{n}BuLi. We have developed a convenient method for the synthesis of aminoborane **54** by the reaction of corresponding amine-BH_2I complex **52** with NaH. The results are discussed in the following sections.

The tetrabutylammonium borohydride **43** and iodine reagent system was used for the *ex situ* generation of diborane gas for reaction with amine **50** to afford the amine-borane **51** in 99% yields (Scheme 9).

Scheme 9



a: $R^1 = R^2$ = (*S*)-Ph(Me)C***H**
b: $R^1 = {}^{i}Pr$, R^2 = (*S*)-Ph(Me)C***H**
c: $R^1 = R^2 = {}^{i}Pr$

	yield (%)
51a	99
51b	99
51c	99

When the solution of amine-borane **51** in CH_2Cl_2 was treated with 0.5 equivalent of molecular I_2, the corresponding amine-BH_2I complex **52** was obtained in quantitative yields. Subsequent addition of NaH to the solution of amine-BH_2I complex **52** gave the corresponding aminoborane **54** in quantitative yields (Scheme 10).

Scheme 10

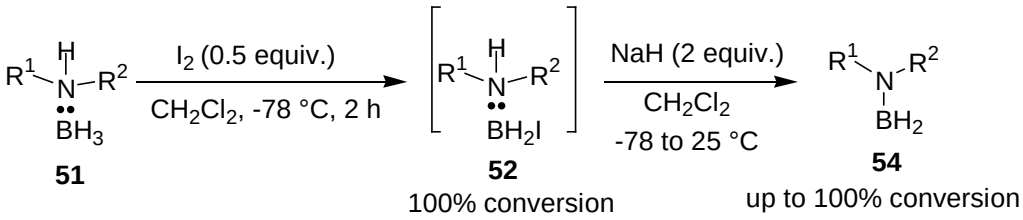
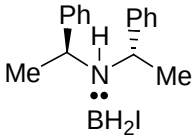
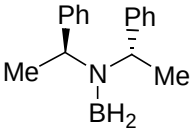
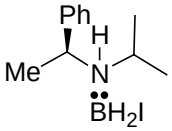
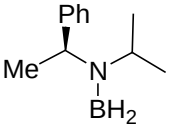
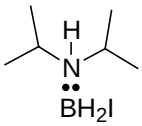
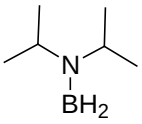


Table 4. Reaction of amine-BH_2I complexes 52 with NaH (2 equiv.) at 25 °C[a]

Entry	BH_2I complex	Time (h)	Aminoborane	Conversion (%)[b]
1	 (*S*,*S*)-**52a**	35	 (*S*,*S*)-**54a**	100
2	 (*S*)-**52b**	18	 (*S*)-**54b**	80
3	 **52c**	10	 **54c**	68

[a] All the reactions were carried out in 5 mmol scale at 25 °C.

[b] % of Conversion was determined from the integration of the corresponding signals in ^{11}B NMR spectrum at 25 °C.

The conversions of the amine-BH_2I complexes **52a-52c** to the corresponding aminoboranes **54a-54c** are summarized in Table 4. When the amine-BH_2I complex (*S*,*S*)-**52a** was reacted with NaH, the corresponding aminoborane (*S*,*S*)-**54a** was obtained with 100% conversion in 35 h (Table 4, entry 1). In the case of amine-BH_2I complex (*S*)-**52b**, the corresponding aminoborane (*S*)-**54b** was obtained with 80% conversion in 18 h (Table 4, entry 2). When the amine-BH_2I complex **52c** was reacted

with NaH, the corresponding aminoborane **54c** was obtained with 68% conversion in 10 h (Table 4, entry 3). Presumably, the lower in conversion to the aminoboranes **54b** and **54c** might be due to the formation the amine-borane complexes **51b** and **51c** by the reaction of NaH with the corresponding amine-BH_2I complexes **52b** and **52c**, which was confirmed by the ^{11}B NMR spectroscopy.

The aminoborane **54a** exists as monomer due to the high steric requirement of the alkyl and aryl groups. Aminoboranes can potentially serve as hydroborating agents. However, so far only 1-pyrrolylborane has been used for hydroboration reaction.[21,22] It monohydroborates alkenes and alkynes at ambient temperatures due to the delocalization of the nitrogen lone pair in aromaticity of pyrrole and hence weakening the strength of N-B bond for hydroboration reaction.

The hydroboration-oxidation reaction of α-methylstyrene **20** using the chiral aminoborane **54a** under different conditions is summarized in Scheme 11 and Table 5. Initially, we have examined the hydroboration-oxidation reaction of α-methylstyrene **20** at 25 °C for 24 h using the aminoborane **54a**. The reaction did not take place under these conditions (Table 5, entry 1). However, when the reaction was carried out at 120 °C for 24 h, only the racemic alcohol **21** was obtained in 43% chemical yield (Table 5, entry 2).

Scheme 11

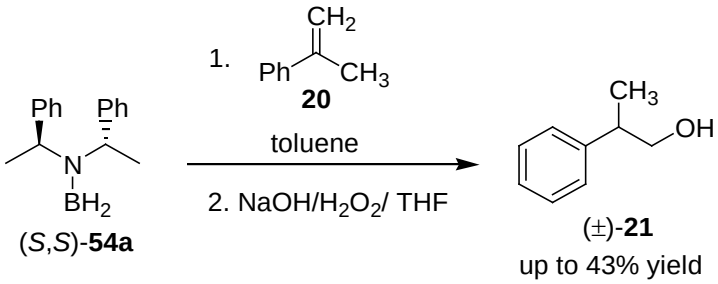


Table 5. Hydroboration reaction of α-methylstyrene 20 in the presence of the aminoborane (*S,S*)-54a with or without activation by acids[a]

Entry	Activation	Temp. (°C)	Time (h)	Yield (%)[c]	ee (%)[d]
1	---	25	24	---	---
2	---	120	24	43	0
3[b]	BF_3:OEt_2	-78	36	---	---
4[b]	BF_3:OEt_2	25	24	22	0
5[b]	*p*-TsOH	25	24	---	---

[a]All the reactions were carried out in 5 mmol scale.

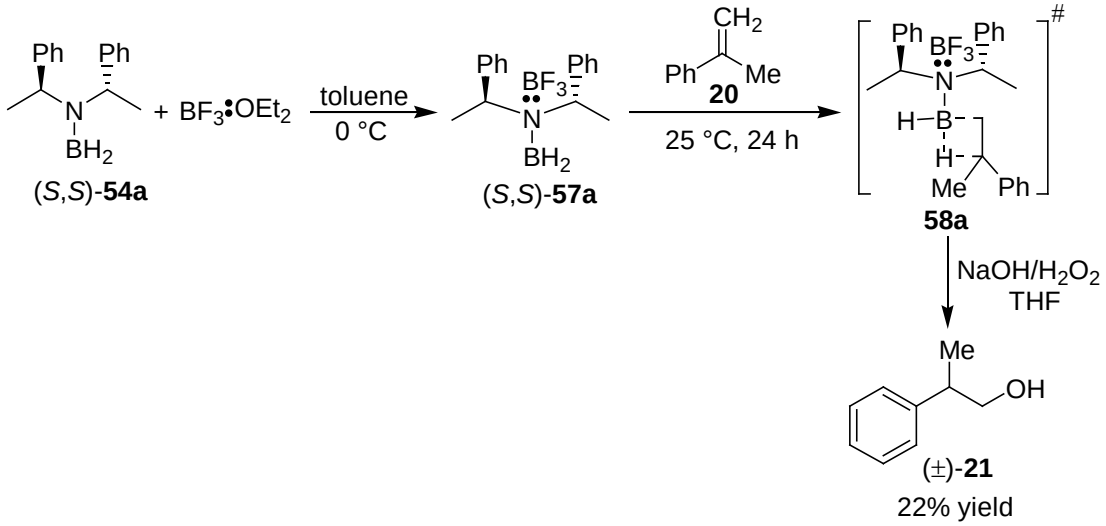
[b]Acid (BF_3:OEt_2 or *p*-TsOH) was added at 0 °C after the 100% formation of the aminoborane **54a** by ^{11}B NMR spectroscopy followed by the addition of α-methylstyrene **20** (5 mmol) at 25 °C.

[c]Yields are for the isolated products.

[d]Determined by HPLC analysis using the chiral column OB-H; Hex:*i*PrOH-97:3, 0.3 mL/min.

We have also examined the effect of Lewis or Brønsted acid in activating the chiral aminoborane **54a** for hydroboration of α-methylstyrene **20**. When the reaction was carried out at 25 °C for 24 h in the presence of BF_3:OEt_2, only the racemic product **21** was obtained after oxidation as outlined in Scheme 12 (Table 5, entry 4). Use of Brønsted acid such as anhydrous *p*-toluenesulfonic acid instead of BF_3:OEt_2 at 25 °C for 24 h, led to the decomposition of aminoborane **54a** (Table 5, entry 5).

Scheme 12



(*S*,*S*)-**54a**

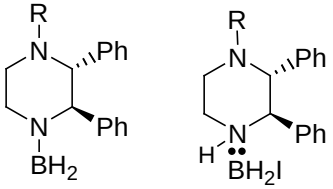
(*S*,*S*)-**57a**

(±)-**21**

22% yield

Presumably, only racemic product **21** was obtained in all cases as the α-methylbenzyl groups in aminoborane **54a** are highly hindered. Further coordination of BF_3 with the nitrogen may slow down the reaction, resulting in poor conversion to the racemic product without any selectivity (Scheme 12).

Systematic studies using less hindered chiral secondary amines such as (*R*,*R*)-2,3-diphenyl piperazine derivatives **59** and **60 (**Figure 1), readily accessible *via* methods described in the Chapter 4 may give more fruitful results.



59 **60**

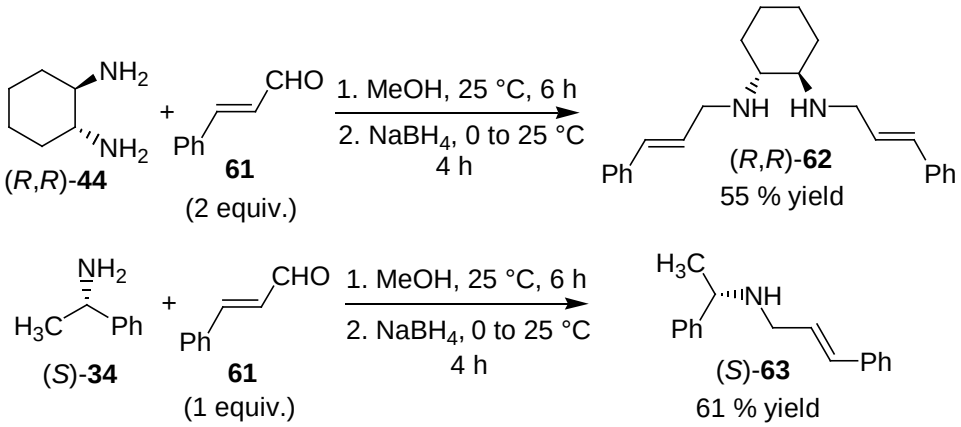
R = H, CH_2Ph, COOR

Figure 1

3.2.3 Attempted intramolecular hydroboration

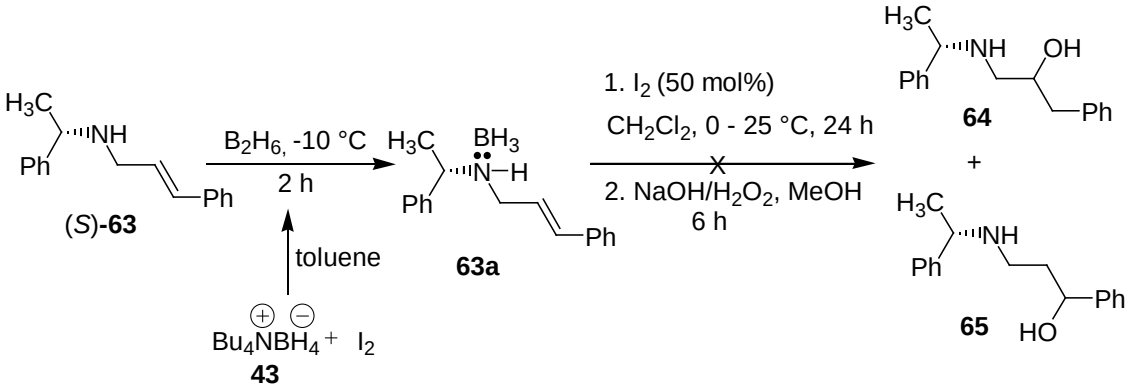
We have undertaken efforts toward the synthesis of chiral *N*-allylic amines (*R*,*R*)-**62** and (*S*)-**63** for the intramolecular asymmetric hydroboration studies. The *N*-allylic amines **62** and **63** were synthesized by *in situ* reduction of the corresponding imine derivatives using $NaBH_4$/MeOH reagent system as shown in Scheme 13.

Scheme 13



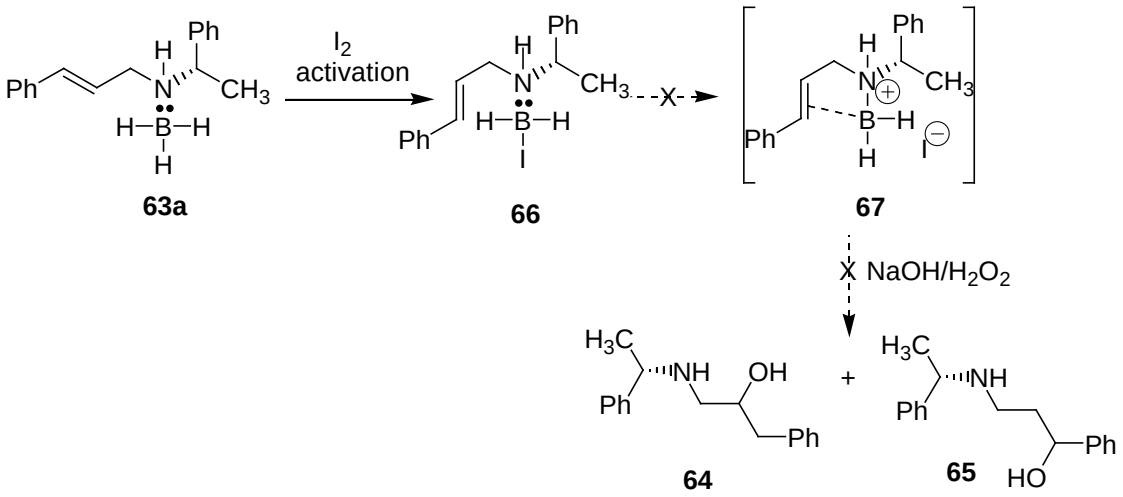
We have examined the intramolecular hydroboration reaction of the allylic amine-borane complex (*S*)-**63a** with I_2 (50 mol%) activation as shown in Scheme 14. Similar experiment was also carried out in the presence of amine (*R*,*R*)-**62** instead of amine (*S*)-**63**. Unfortunately, in both the cases the intramolecular hydroboration reaction did not take place and the starting chiral amines **62** and **63** were recovered. Increasing the reaction temperature to 120 °C for 12 h in toluene also did not help in achieving the hydroboration reaction.

Scheme 14



Presumably, the five membered cyclic transition state **67** (Scheme 15) expected for the present cases of intramolecular hydroboration (Scheme 14) might not be favored compared to the reported six-membered transition state **30** for the reaction outlined in the introductory section (Scheme 3).[7]

Scheme 15



3.3 Conclusions

The hydroboration reaction of prochiral olefins such as α-methylstyrene **20**, *trans*-stilbene **39** and *cis*-stilbene **46** were carried out with chiral amine-borane complexes prepared using *trans*-(*R*,*R*)-1,2-diaminocyclohexane derivatives **44** and **45**. Only in the case of *trans*-(*R*,*R*)-1,2-diaminocyclohexane-borane complex **44a**, the product 2-phenylpropanol **21** was obtained in 5% ee, indicating that the reaction is highly sensitive to steric effects.

A simple and convenient one pot method for the synthesis of aminoboranes **54** by the reaction of corresponding secondary amine-BH_2I complexes **52** with NaH at 25 °C in up to 100% conversion has been developed. When the hydroboration-oxidation reaction of α-methylstyrene **20** was carried out in the presence of chiral aminoborane such as (*S*,*S*)-bis-(1-phenyl-ethyl)-aminoborane **54a**, only the racemic product 2-phenylpropanol **21** was obtained in 43% yield at 120 °C. In the presence of BF_3:OEt_2 as activating agent for the chiral aminoborane **54a**, the hydroboration-oxidation reaction of α-methylstyrene **20** takes place at 25 °C with the formation of racemic product **21** in 22% yield. Though, some of the results described in this chapter are not synthetically useful, they serve to illustrate the scope of such reactions and the need to avoid the steric crowding while designing the Lewis base-borane complexes for asymmetric hydroboration studies.

3.4 Experimental Section

3.4.1 General Information

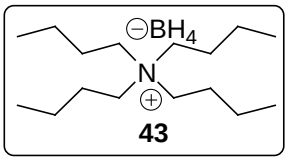
Several information given in the section 1.4 are also applicable for the experiments outlined in this section. The tetrabutylammonium hydrogen sulphate **41** was purchased from Loba Chemie (Pvt), Ltd., India. The sodium borohydride was purchased from E-Merck, India. NaH (60% suspension in mineral oil) supplied by Sigma-Aldrich, USA was used. Aminoboranes were not isolated but were characterized and used in solutions. All the reactions were analyzed by ^{11}B NMR spectroscopy and were recorded at 128.3 MHz. ^{11}B NMR chemical shifts are reported relative to the external standard BF_3:OEt_2 (δ = 0 ppm).

3.4.2 Asymmetric hydroboration of prochiral olefins with chiral amines **44** or **45**

3.4.2.1 Preparation of tetrabutylammonium borohydride 43

In a round bottom flask, tetrabutylammonium hydrogen sulphate **41** (33.95 g, 100 mmol) was dissolved in water (20 mL). To this, 5M NaOH (25 mL) was added and the mixture was cooled to 25 °C. A solution of $NaBH_4$ (4.18 g, 110 mmol) dissolved in water (10 mL) was added to it and the reaction mixture was allowed to stir for 15 min. The reaction mixture was extracted with CH_2Cl_2 (50 mL) i.e. upper phase. The organic layer was separated and the aq. layer was again extracted with CH_2Cl_2 (2 x 25 mL) i.e. lower phase. The combined organic extract was dried over anhydrous K_2CO_3, filtered and evaporated under reduced pressure at 25 °C to obtain tetrabutylammonium borohydride **43** as white amorphous solid.

Yield 24.5 g (95%)



43

mp 126-131 °C

IR (KBr) (cm^{-1}) 2962, 2876, 2282, 2208, 2137, 1602, 1074

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.29 (t, *J* = 8.1 Hz, 2H), 1.62 (m, 2H), 1.46 (m, 2H), 0.99 (t, *J* = 8.1 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 58.8, 24.0, 19.5, 13.5

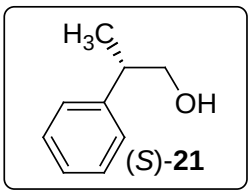
^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -39.93

3.4.2.2 General procedure for the hydroboration reaction of olefins using *ex situ* generation of the diborane gas

The diborane gas was generated *ex situ* by the slow addition of molecular iodine (1.4 g, 5.5 mmol) in dry toluene (15 mL) to a dispersion of tetrabutylammonium borohydride (10 mmol, 2.57 g) in dry toluene (10 mL) at 25 °C under nitrogen atmosphere. The diborane gas generated was purged to a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane **44** (0.3 mL, 2.5 mmol) in toluene (10 mL) at 0 °C for 2 h. After completion, the bubbler was replaced with a stopper and the reaction mixture was warmed to 25 °C. Then iodine (0.316 g, 1.25 mmol) in toluene (6 mL) was added drop wise at 25 °C through a syringe over a period of 5 minutes. The reaction mixture was stirred at the same temperature for further 15 minutes. Olefin (2.5 mmol) in toluene (5 mL) was then slowly added through a syringe over a period of 5 minutes. The reaction mixture was refluxed at 120 °C for 20 h. The reaction mixture was quenched with methanol (10 mL) and the oxidation was carried out by adding 3N NaOH (10 mL) and H_2O_2 solution (30% solution, 5 mL) to the reaction mixture and stirred at 25 °C for 6 h.

It was extracted with Et_2O (3 x 20 mL) and the combined organic extract was washed with water (20 mL), brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (230-400 mesh) using hexanes/EtOAc as eluent.

(*S*)-2-Phenylpropan-1-ol



(*S*)-**21**

Yield 0.20 g (59%)

$[\alpha]_D^{25}$ -2.0 (*c* 1.0, $CHCl_3$), {Lit.[23] $[\alpha]_D^{25}$ -16.1 (*c* 0.51, $CHCl_3$)}

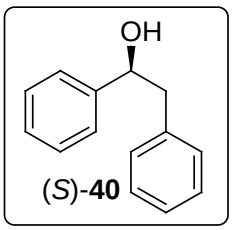
IR (neat) (cm^{-1}) 3375, 3050, 2950, 1603, 1057

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.20-7.46 (m, 5H), 3.62 (d, *J* = 6.5 Hz, 2H), 2.86-3.12 (m, 1H), 1.88 (br s, 1H), 1.22 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 143.9, 128.3, 127.3, 126.3, 68.1, 42.1, 17.4

ee 5% [HPLC analysis: Chiralcel OB-H column, n-Hexane:IPA-95:5; Flow rate 0.3 mL/min., 254 nm, Retention time: 24.9 min. (*S* isomer) and 26.8 min. (*R* isomer)]

(*S*)-1,2-Diphenylethan-1-ol



(*S*)-**40**

Yield 0.33 g (67%)

mp 61-63 °C (lit.[24] 63-64 °C)

IR (KBr) (cm^{-1}) 3319, 3084, 2922, 1039, 696

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.19-7.36 (m, 10H), 4.88-4.91 (m, 1H), 2.96-3.03 (m, 2H), 1.96 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 143.8, 138.1, 129.5, 128.5, 128.4, 127.6, 126.6, 125.9, 75.3, 46.1

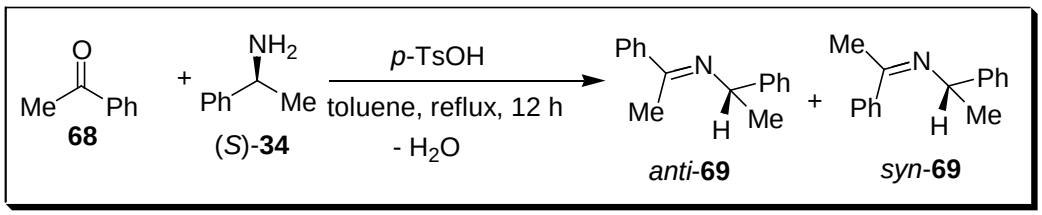
ee 3% [HPLC analysis: Chiralcel OD-H column, n-hexane:IPA-90:10; Flow rate 0.3 mL/min., 254 nm, Retention time: 26.66 min. (*R* isomer) and 30.27 min. (*S* isomer)]

3.4.3 Procedure for the synthesis of chiral amines

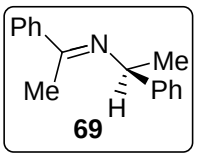
3.4.3.1 Procedure for the synthesis of (*S*,*S*)-bis-(1-phenyl-ethyl)-amine 50a

Modification of a three steps reported procedure[25] for the preparation of (*S*,*S*)-bis-(1-phenyl-ethyl)-amine **50a** is given below.

Acetophenone **68** (11.60 mL, 100 mmol), (*S*)-α-methylbenzylamine **34** (12.8 mL, 100 mmol) and *p*-toluenesulfonic acid (1.9 g, 10 mmol) were taken in dry toluene (40 mL) and refluxed at 120 °C for 12 h under nitrogen atmosphere with continuous removal of water by means of Dean-Stark trap. The contents were brought to 0 ºC and aq. sodium bicarbonate solution (30 mL), toluene (50 mL) were added and stirred for 5 min. The organic layer was separated and washed with cold brine (30 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting oily residue was used as such without purification. The imines *anti*-**69** and *syn*-**69** were found to be in 7:1 ratio.



(1-Phenyl-ethyl)-(1-phenyl-ethylidene)-amine



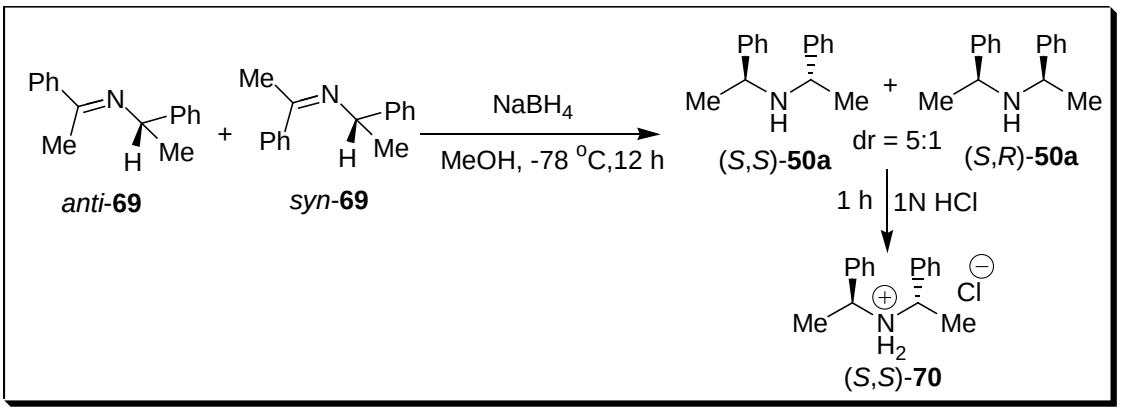
Yield 22.6 g (95%)

Syn:*anti* 1:7

IR (neat) (cm^{-1}) 3059, 1635, 1601, 1448, 1026

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) *Syn*-**69**: 8.10-7.00 (m, 10H), 4.00 (q, *J* = 6.3 Hz, 1H), 2.49 (s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), *anti*-**69**: 8.10-7.00 (m, 10H), 4.73 (q, *J* = 6.3 Hz, 1H), 2.17 (s, 3H), 1.50 (d, *J* = 6.1 Hz, 3H),

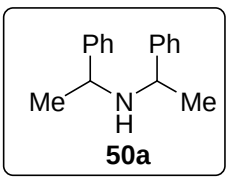
To a 500 mL two necked round bottom flask equipped with a magnetic stirrer, crude imine residue **69** (22.6 g, 95 mmol) and MeOH (200 mL) were taken and cooled at -78 ºC under N_2 atmosphere. To it $NaBH_4$ (5.7 g, 150 mmol) was added in portions from a solid addition flask and stirred at -78 ºC for 12 h. The solvent was evaporated under reduced pressure. Water (50 mL) and Et_2O (50 mL) were added and stirred for 15 min. The organic layer was separated and the aqueous layer was extracted again using Et_2O (2 x 30 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. A pale yellow oily residue containing two diastereomers (*S*,*S*)-**50a** and (*S*,*R*)-**50a** was obtained.



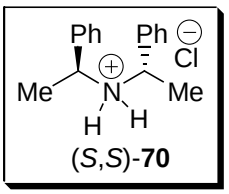
Yield 20.5 g (96%)

dr 1:5

IR (neat) (cm^{-1}) 3327, 3061, 1493, 1452, 1024



The crude oily residue was treated with 1N HCl (250 mL). The white residue was filtered and washed once with ice cold Et_2O (20 mL). The resulting solid compound was recrystallized from water affording colourless crystalline solid (*S*,*S*)-**70**.



(*S*,*S*)-**70**

Yield 15.9 g (67%)

mp >300 ºC

IR (KBr) (cm^{-1}) 3030, 2949, 1597, 1375, 1072

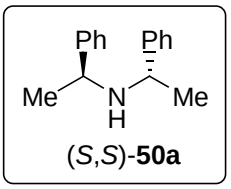
$[\alpha]_D^{25}$ -84.3 (*c* 3, EtOH)

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 10.48 (s, 1H), 7.2-7.5 (m, 5H), 3.86 (q, *J* = 6.0 Hz, 1H), 1.91 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 136.3, 129.2, 129.1, 128.2, 57.1, 21.5

Then the crystals were partly dissolved in water (100 mL) and Et_2O (100 mL) and subsequently powdered NaOH (5 g) was slowly added at 0 °C until the solution became basic. The reaction mixture was stirred at 25 °C for 30 min. The aqueous layer was extracted with Et_2O (50 mL) and the combined organic extract was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and evaporated, affording a colorless oil (*S*,*S*)-**50a** in pure form.

(*S*,*S*)-Bis-(1-phenyl-ethyl)-amine



(*S*,*S*)-**50a**

Yield 13.05 g (95%)

IR (neat) (cm^{-1}) 3327, 3061, 1493, 1452, 1024

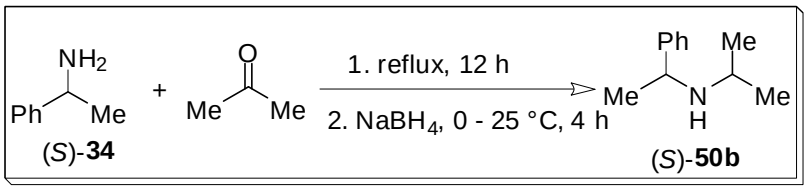
$[\alpha]_D^{25}$ -157.0 (*c* 2.4, EtOH)

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.21-7.35 (m, 10H), 3.50 (q, *J* = 6.4 Hz ,2H), 1.91 (s, 1H), 1.27 (d, *J* = 6.4 Hz, 6H) (**Spectrum No. 15**)

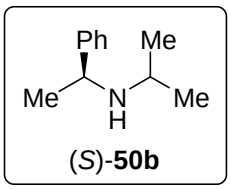
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 145.8, 128.3, 126.7, 126.6, 55.0, 25.0, (**Spectrum No. 16**)

3.4.3.2 Procedure for the synthesis of (*S*)-*N*-(1-phenylethyl)-1-methylethylamine 50b

The amine (*S*)-**50b** was synthesized as described below following a reported procedure.[26] The (*S*)-α-methylbenzylamine **34** (3.86 mL, 30 mmol) was taken in acetone (150 mL) and refluxed for 12 h. The solvent was evaporated under reduced pressure and the oily residue was dissolved in methanol (150 mL). To it $NaBH_4$ (2.2 g, 60 mmol) was added in portions at 0 °C and the reaction mixture was stirred at 25 °C for 4 h. The solvent was evaporated under reduced pressure. To it water (30 mL) and CH_2Cl_2 (30 mL) were added and stirred for 5 min. The organic layer was separated and the aqueous layer was extracted again using CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The product (*S*)-**50b** was obtained as colourless oil in pure form.



(*S*)-*N*-(1-Phenylethyl)-1-methylethylamine



Yield 4.67 g (95%)

IR (neat) (cm^{-1}) 3315, 2962, 1451, 1169, 761, 701

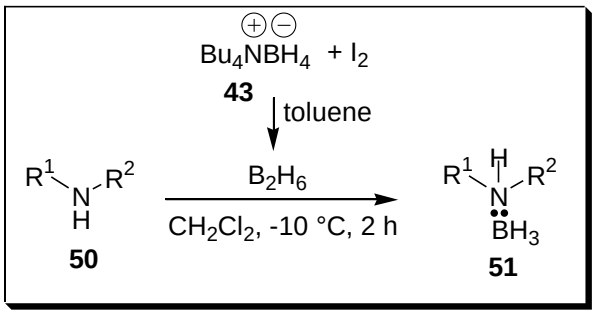
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.35-7.22 (m, 5H), 3.90 (q, *J* = 6.2 Hz, 1H), 2.63 (sept, *J* = 6.2 Hz, 1H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 8.1 Hz, 3H), 1.01 (d, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 146.1, 128.4, 126.7, 126.4, 55.1, 45.5, 24.9, 24.1, 22.2

3.4.4 Procedure for the synthesis of amine-boron complexes

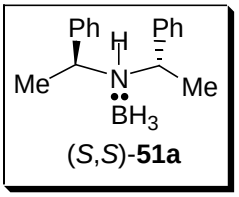
3.4.4.1 Procedure for the synthesis of amine-boranes (*S*,*S*)-51a, (*S*)-51b and 51c

To a stirred solution of tetrabutylammonium borohydride **43** (5.14 g, 20 mmol) in dry toluene (20 mL), iodine (2.53 g, 10 mmol) dissolved in dry toluene (30 mL) was added dropwise at 25 °C over a period of 2 h. The generated diborane gas was bubbled through a side tube using a bubbler into another reaction flask containing amine **50** (5 mmol) in dry CH_2Cl_2 (20 mL) at -10 ºC until the complete addition of iodine took place. The reaction mixture was further stirred at 0 ºC for 1 h. The solvent was evaporated under reduced pressure to get pure amine-borane complex **51**.



(*S*,*S*)-Bis-(1-phenyl-ethyl)-amine-borane

Colourless solid



(*S*,*S*)-**51a**

Yield 1.2 g (99%)

mp 84-87 °C

IR (KBr) (cm^{-1}) 3204, 3063, 2405, 2341, 2289, 1494, 1454

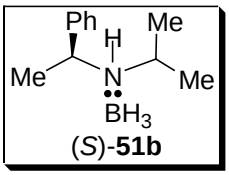
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.42 (m, 4H), 7.28 (m, 4H), 6.95 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.63 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 141.5, 138.0, 129.0, 129.0, 128.9, 128.6, 128.3, 127.0, 61.8, 57.9, 19.4, 15.8

^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -19.59 (q, J_{BH} = 110.2 Hz)

(*S*)-*N*-(1-Phenylethyl)-1-methylethylamine-borane

Colourless solid



(*S*)-**51b**

Yield 0.885 g (99%)

mp 122-125 °C

IR (KBr) (cm^{-1}) 3208, 3053, 2399, 2341, 2289, 1494, 1454

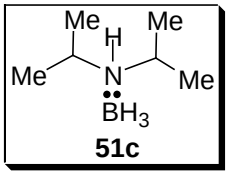
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.42-7.25 (m, 5H), 3.93 (sept, 1H), 3.46 (s, 1H), 2.96 (q, *J* = 6.4 Hz, 1H), 1.67 (d, *J* = 8.0 Hz, 3H), 1.20 (d, *J* = 4.1 Hz, 3H), 1.14 (d, *J* = 4.2 Hz, 3H) (**Spectrum No. 17**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 141.4, 129.4, 128.4, 126.5, 62.4, 51.5, 21.5, 21.3, 15.1 (**Spectrum No. 18**)

^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -22.7 (q, J_{BH} = 117.1 Hz) (**Spectrum No. 19**)

Diisopropylamine-borane

Colourless oil



51c

Yield 0.575 g (99%)

IR (neat) (cm^{-1}) 3209, 2976, 2361, 1471, 1388, 1124, 825

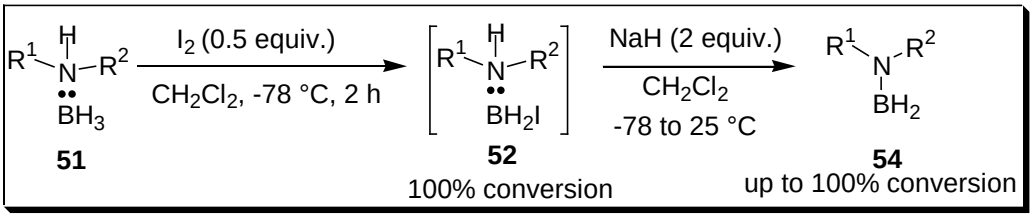
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.23 (sept, 2H), 2.93 (br s, 1H), 1.31 (d, J = 3.0 Hz, 12H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 52.3, 21.3, 19.2

^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -21.6 (q, J_{BH} = 97.1 Hz)

3.4.4.2 Procedure for the synthesis of aminoboranes 54a-54c

To the stirred solution of amine-borane **51** (5 mmol) in dry CH_2Cl_2 (25 mL), powdered solid iodine (0.632 g, 2.5 mmol) was added slowly at -78 ºC and stirred for 2 h. The 100% conversion to the corresponding amine-BH_2I complex **52** was confirmed by ^{11}B NMR spectroscopy recorded at 128.3 MHz at 25 °C. The ^{11}B NMR signal values corresponding to the amine-BH_2I complexes **52a**-**52c** are given below.



^{11}B NMR (**52a**) (128.3 MHz, CH_2Cl_2, δ ppm) -17.5 Hz

^{11}B NMR (**52b**) (128.3 MHz, CH_2Cl_2, δ ppm) -18.2 Hz (**Spectrum No. 20**)

^{11}B NMR (**52c**) (128.3 MHz, CH_2Cl_2, δ ppm) -17.6 Hz

To the above reaction mixture, sodium hydride (0.240 g, 10 mmol) [washed with hexane and dried under N_2 atmosphere] was added slowly at -78 ºC. The reaction mixture was warmed to 25 °C and stirred until complete conversion to the aminoborane **54** took place. The solvent was removed by continuous N_2 flow through the reaction flask and the residue aminoborane **54a** was used as such for hydroboration reaction as mentioned in sections 3.4.5 and 3.4.6. The ^{11}B NMR signal values corresponding to the aminoboranes **54a**-**54c** are given below.

(*S*,*S*)-Bis-(1-phenyl-ethyl)-aminoborane 54a

Conversion 100%

^{11}B NMR (128.3 MHz, CH_2Cl_2, δ ppm) +34.6 (**Spectrum No. 22**)

(*S*)-*N*-(1-Phenylethyl)-1-methylethylaminoborane 54b

Conversion 80%

^{11}B-NMR (128.3 MHz, CH_2Cl_2, δ ppm) +34.9 (t, J_{BH} = 118.0 Hz)

(**Spectrum No. 21**)

Diisopropylaminoborane 54c

Conversion 68%

^{11}B NMR (128.3 MHz, CH_2Cl_2, δ ppm) +34.2 (t, J_{BH} = 121.0 Hz); [lit.[15] δ 34.7 (t, J_{BH} = 123.0 Hz)]

3.4.5 Procedure for the hydroboration reaction of α-methylstyrene 20 using chiral aminoborane 54a

To a 25 mL reaction flask with side septum containing aminoborane **54a** (5 mmol), dry toluene (10 mL) was added. To this, α-methylstyrene **20** (0.6 mL, 5 mmol) was added slowly at 25 °C. The reaction mixture was refluxed at 120 °C for 24 h. It was quenched with THF (5 mL) and the oxidation was carried out by adding 3N NaOH (10 mL) and H_2O_2 solution (30% solution, 10 mL) to it. The reaction mixture was stirred at 25 °C for 6 h. It was extracted with Et_2O (3 x 20 mL) and the combined organic extract was washed with water (1 x 20 mL), brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (100-200 mesh) using hexanes/EtOAc (95/5) as eluent, affording the racemic product **21** in 43% yield (0.292 g).

3.4.6 Procedure for the hydroboration reaction of α-methylstyrene 20 by using chiral aminoborane 54a under BF_3:OEt_2 activation

To a 25 mL reaction flask with side septum containing aminoborane **54a** (5 mmol), dry toluene (10 mL) was added. To it, BF_3:OEt_2 (0.6 mL, 2.5 mmol) was added at 0 °C followed by the addition of α-methylstyrene **20** (0.6 mL, 5 mmol). The reaction mixture was stirred at 25 °C for 24 h. It was quenched with MeOH (5 mL) and the oxidation was carried out by adding 3N NaOH (10 mL) and H_2O_2 solution (10 mL, 30% solution) to the reaction mixture. The reaction mixture was stirred at 25 °C for 6 h. The procedure outlined in the section 3.4.5 was followed to purify the racemic product **21**.

Yield 0.149 g (22%)

3.5 References

1. (a) Brown, H. C.; SubbaRao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694. (b) Brown, H. C.; SubbaRao, B. C. *J. Org. Chem.* **1957**, *22*, 1135.
2. (a) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1519. (b) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523.
3. (a) Hawthorne, M. F. *J. Org. Chem.* **1958**, *23*, 1788. (b) Davies, K. M.; Dewar, M. J. S.; Rona, P. *J. Am. Chem. Soc*. **1967**, *89*, 6294.
4. Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V. *Organometallics* **1998**, *17*, 4202.
5. Reddy, Ch. K.; Periasamy, M. *Tetrahedron* **1992**, *48*, 8329.
6. (a) Periasamy, M.; Narayana, C. *J. Chem. Soc. Chem. Commun.* **1987**, 1857. (b) Kanth, J. V. B. Ph.D. Thesis **1993**, School of Chemistry, University of Hyderabad. (c) Reddy, Ch. K. Ph.D. Thesis **1993**, School of Chemistry, University of Hyderabad.
7. (a) Scheidman, M.; Shapland, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 10502. (b) Shapland, P.; Vedejs, E. *J. Org. Chem.* **2004**, *69*, 4094. (c) Rarig, R. A. F.; Scheidman, M.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 9182. (d) Scheidman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 8669.
8. Clay, M.; Vedejs, E. *J. Am. Chem. Soc.* **2005**, *127*, 5766.
9. (a) Anwar, S. Ph. D. Thesis, **2009**, School of Chemistry, University of Hyderabad. (b) Selva Ganesan, S. Ph. D. Thesis, **2009**, School of Chemistry, University of Hyderabad. (c) Satishkumar, S. Ph. D. Thesis, **2009**, School of Chemistry, University of Hyderabad.

10. (a) Anwar, S.; Periasamy, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3244. (b) Periasamy, M.; Muthukumaragopal, G. P.; Sanjeevakumar, N. *Tetrahedron Lett.* **2007**, *48*, 6966. (c) Periasamy, M.; Ramani, G. B.; Muthukumaragopal, G. P. *Synthesis* **2009**, *10*, 1739. (d) Narasimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Indian. J. Chem., Sec. B*: **1998**, *37B*, 1189.

11. (a) Brown, H. C.; SubbaRao, B. C. *J. Am. Chem. Soc.* **1959**, *81*, 6428. (b) Brown, H. C.; Korytnyk, W. *J. Am. Chem. Soc.* **1960**, *82*, 3866.

12. Brandstrom, A.; Junggren, U.; Lamm, B. *Tetrahedron Lett.* **1972**, *31*, 3173.

13. Thevent, F.; Doche, C.; Mongeot, H.; Guilhon, F.; Miele, P.; Cornu, D.; Bonnetot, B. *J. Solid State Chem.* **1997**, *133*, 164.

14. Euzenat, L.; Horhant, D.; Ribourdouille, Y.; Duriez, C.; Alcaraz, G.; Vaultier, M. *Chem. Commun.* **2003**, 2280.

15. Jaska, C. A.; Temple, K.; Lough, A. J.; Manners, I. *J. Am. Chem. Soc.* **2003**, *125*, 9424.

16. Clark, T. J.; Russell, C. A.; Manners, I. *J. Am. Chem. Soc.* **2006**, *128*, 9582.

17. Sloan, M. E.; Clark, T. J.; Manners, I. *Inorg. Chem.* **2009**, *48*, 2429.

18. Kawano, Y.; Uruichi, M.; Shimoi, M.; Taki, S.; Kawaguchi, T.; Kakizawa, T.; Ogino, H. *J. Am. Chem. Soc.* **2009**, *131*, 14946.

19. Miller, A. J. M.; Bercaw, J. E. *Chem. Commun.* **2010**, *46*, 1709.

20. Pasumansky, L.; Haddenham, D.; Clary, J. W.; Fisher, G. B.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2008**, *73*, 1898.

21. (a) Ioffe Sz. L.; Lyashenko, A. A.; Shitov, O. P.; Negrebetskii, V. V. *Khim. Geterotsil. soedin.* **1971**, *7*, 1056. (b) Gyori, B.; Emri, J.; Szarvas, P. *Acta Chim. Acad. Sci. Hung.* **1975**, *86*, 235.

22. (a) Anez, M.; Uribe, G.; Mendoza, L.; Contreras, R. *Synthesis* **1981**, 214. (b) Wrackmeyer, B.; Schwarze, B.; Milius, W. *Inorg. Chim. Acta* **1996**, *241*, *87*. (c) Wrackmeyer, B.; Schwarze, B. *J. Organomet .Chem.* **1997**, *534*, 207.

23. Toda, A.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053.

24. Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074.

25. Eleved, M. B.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1986**, *51*, 3635.

26. Leleu, S.; Papamicaël, C.; Marsais, F.; Dupas, G.; Levacher, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3919.

Chapter 4

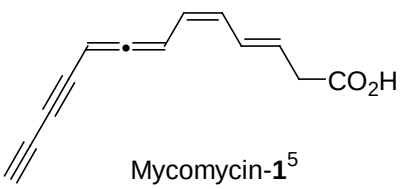
Studies on enantioselective synthesis of chiral allenes

4.1 Introduction

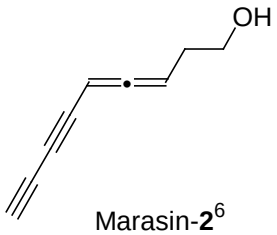
Since the first prediction by van't Hoff in 1875,[1] and later by Burton and von Pechmann in 1887,[2] chiral allenes have transformed from a laboratory curiosity to a versatile and unique reactive functional group.[3] For a long time, allenes were considered highly unstable, which retarded the development of the chemistry of allenes. However, during the last 10-15 years, allenes have been shown to exhibit excellent reactivities as well as selectivities. The C=C bond of allenes is around 10 kcal mol^{-1} less stable than that of simple alkenes, rendering them significantly more reactive.[4] Chiral allenes are highly valuable synthetic precursors in organic chemistry due to the presence of orthogonal π bond and ability to undergo a variety of transformations. Many natural products and pharmaceuticals (around 150) with an allene or cumellene moiety have been reported (Charts 1 and 2).

Chart 1: Allenic Natural Products

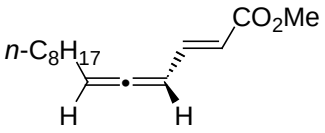
Linear Allenes



Mycomycin-**1**[5]

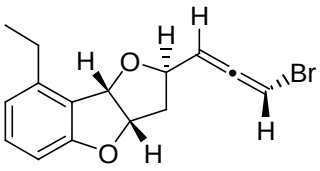


Marasin-**2**[6]

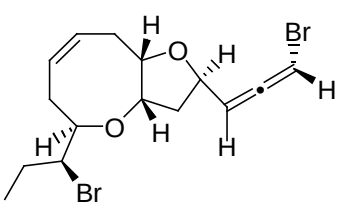


Insect pheromone-**3**[7]

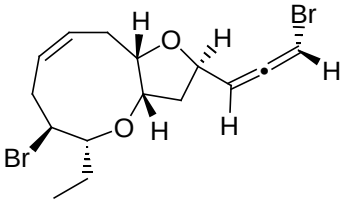
Naturally Occurring Bromoallenes



Panacene-**4**[8]



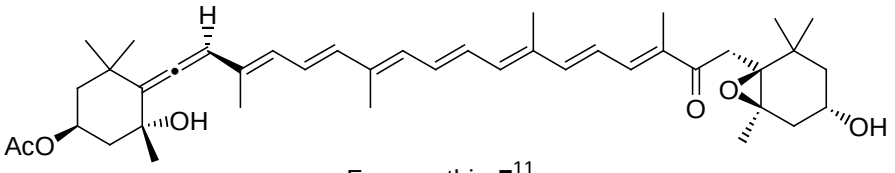
Laurallene-**5**[9]



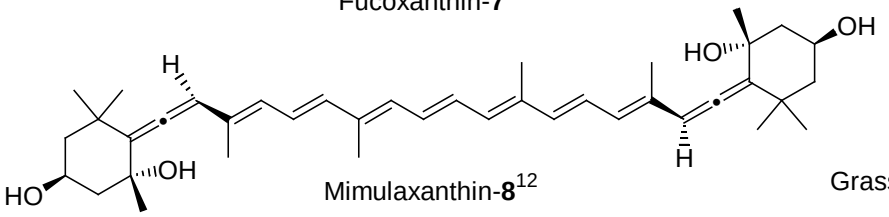
Isolaurallene-**6**[10]

Chart 1 continued…

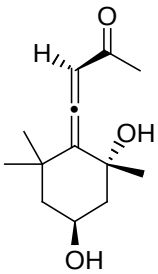
Allenic Carotinoids and Terpenoids



Fucoxanthin-**7**[11]



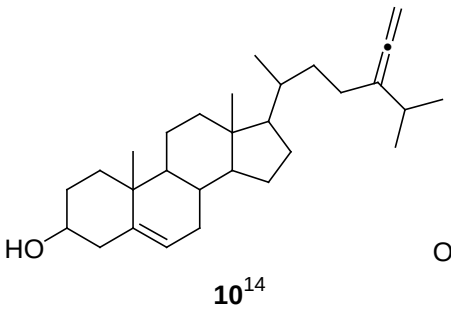
Mimulaxanthin-**8**[12]



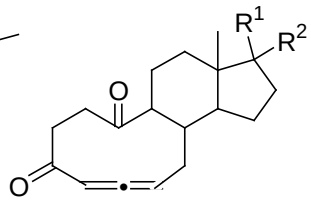
Grasshopper ketone-**9**[13]

Chart 2: Pharmacologically Active Allenes

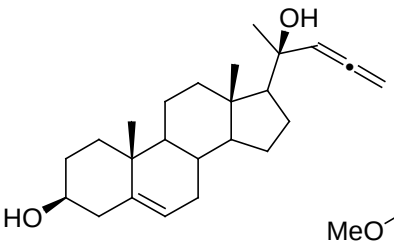
Allenic Steroids



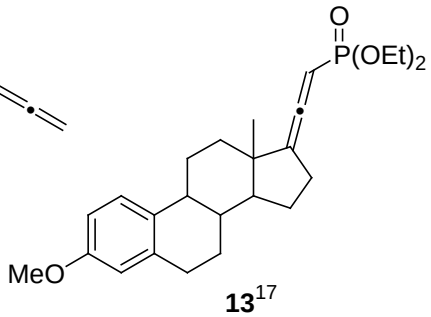
10[14]



11[15]



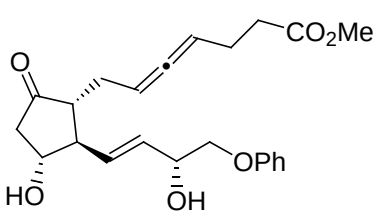
12[16]



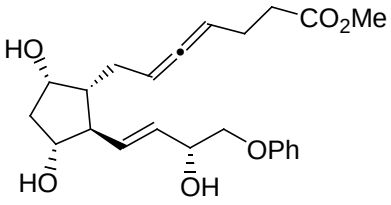
13[17]

Chart 2 continued…

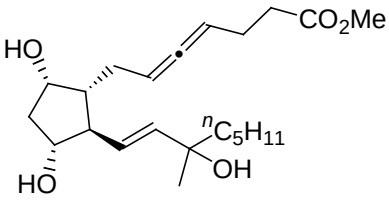
Allenic Prostaglandins and Carbacyclins



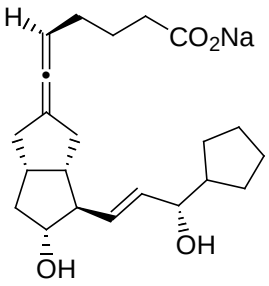
Enprostil-**14**[18]



Fenprostalene-**15**



Prostalene-**16**



Carbacyclin-**17**[18]

Therefore, there have been immense interests on the development of synthetic methods for chiral allenes. In continuation of our efforts on the synthetic applications of readily accessible chiral amines, we have undertaken studies on the enantioselective synthesis of chiral allenes. Accordingly, a brief review on various methods available for the synthesis of chiral allenes will facilitate the discussion.

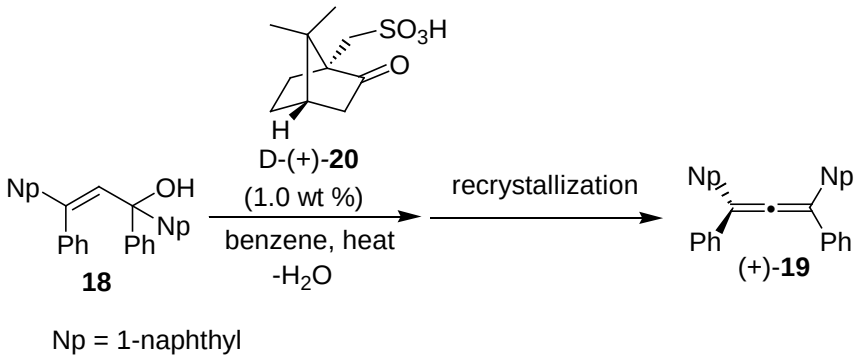
4.1.1 Enantioselective synthesis of axially chiral allenes

4.1.1.1 Synthesis of chiral allenes from allylic compounds

Dehydration of allylic alcohols:

In 1935, Maitland and Mills described the first synthesis of an optically active dissymmetric allene **19** and proved van't Hoff's prediction.[19a] This enantioselective synthesis was attained by dehydration of the racemic allylalcohol **18** in the presence of catalytic amount of (+)-camphor-10-sulfonic acid **20** (Scheme 1).[19b]

Scheme 1

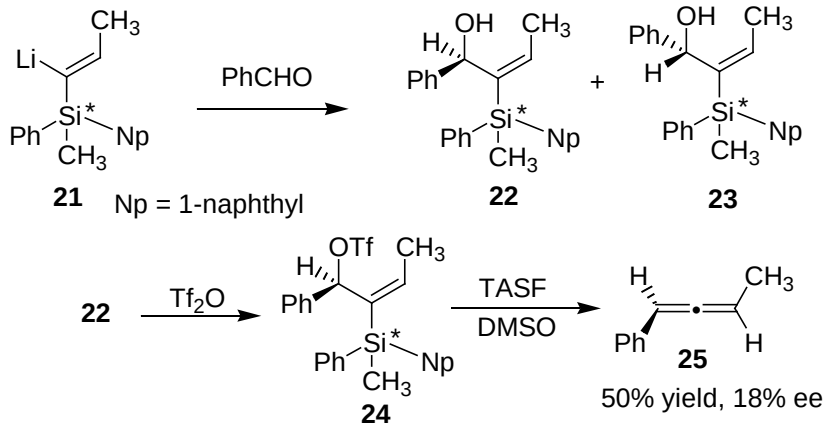


Np = 1-naphthyl

Chirality transfer from allylic position by elimination reaction:

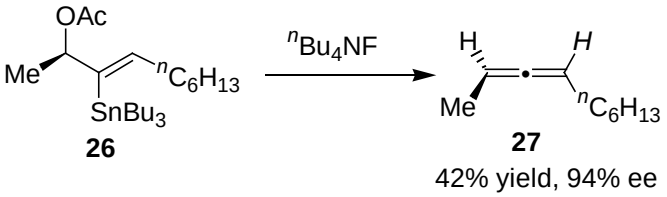
Chiral allylic silyl trifluoromethanesulfonate **24** prepared by the reaction of **21** with benzaldehyde followed by the triflation of **22**, upon fluoride ion-induced elimination gave the 1-phenyl-1,2-butadiene **25** with 18% ee and 50% yield (Scheme 2).[20] The poor ee was ascribed to low *anti*-selectivity in the elimination step.

Scheme 2



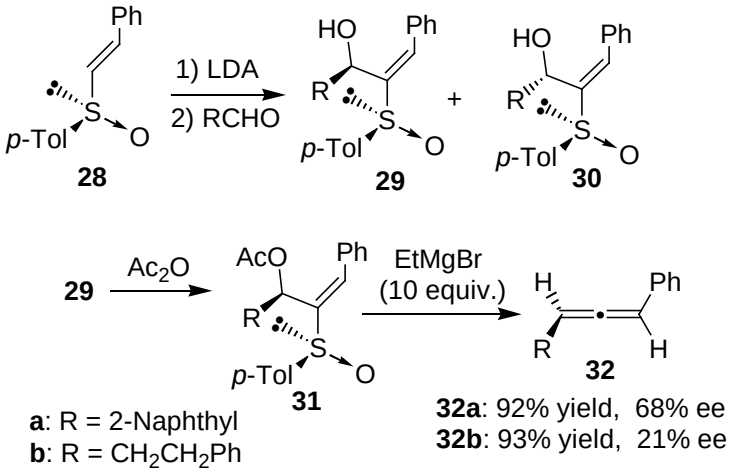
On the other hand, a highly stereoselective fluoride ion induced deoxystannylation of the optically active β-stannyl allylic acetate **26** gave the allene **27** in 42% yield and 94% ee (Scheme 3).[21]

Scheme 3



Chiral allylic sulfinyl acetate **31a** prepared through a sequence of reactions outlined in Scheme 4, upon reaction with excess of EtMgBr leads to a stereospecific *anti*-elimination of a β-acetoxysulfoxide to give the corresponding allene **32a** in 92% yield and 68% ee. The reaction using **31b** afforded the allene **32b** in 93% yield and only 21% ee (Scheme 4).[22]

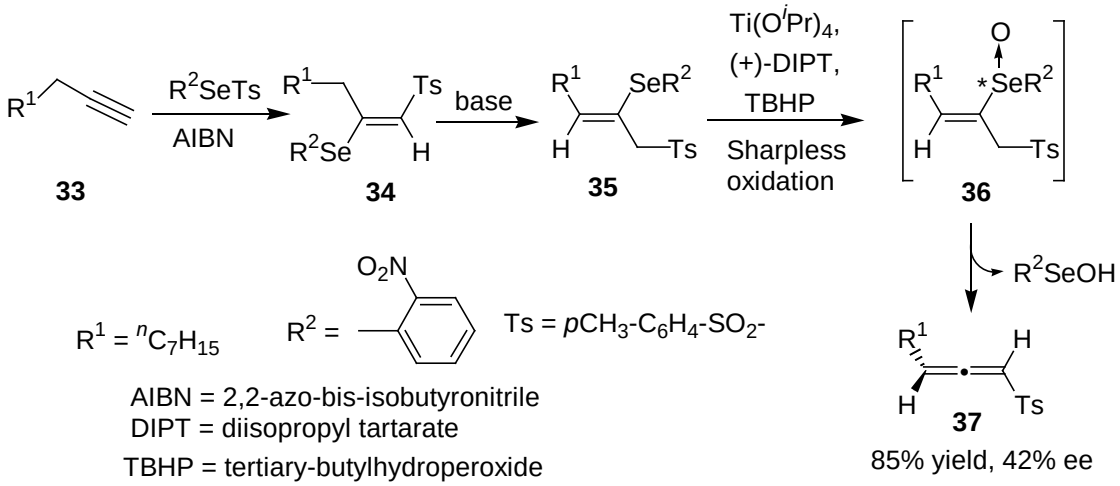
Scheme 4



Elimination reactions of allylic compounds having a chiral leaving group:

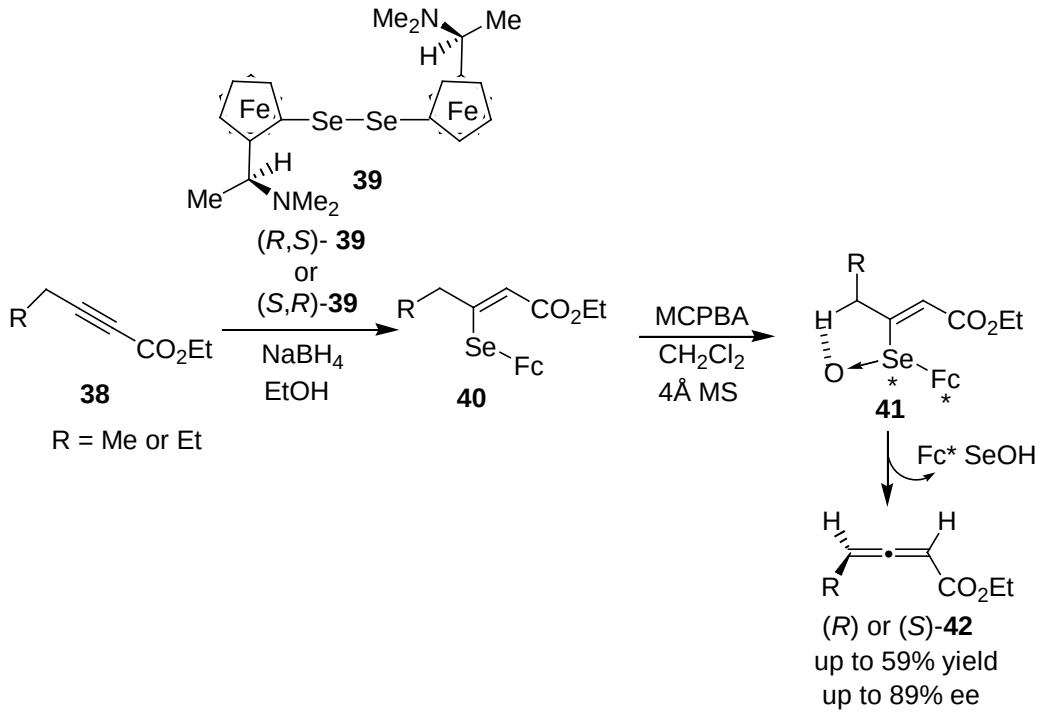
A new synthetic route to chiral allenes **37** has been reported using an asymmetric oxidation of aryl vinyl selenide **35** to **36** using Sharpless or Davis oxidants (Scheme 5).[23] The axial chirality in the resulting allenic sulfone is derived from optically active selenoxide leaving groups.

Scheme 5



Enantioselective elimination reaction of chiral intermediate selenoxides **41** prepared by the sequence of reactions shown in Scheme 6, in the presence of (*R*,*S*)-**39** or (*S*,*R*)-**39**, gave the corresponding chiral allenecarboxylates (*R*)-**42** or (*S*)-**42**, respectively in up to 89% ee (Scheme 6).[24]

Scheme 6

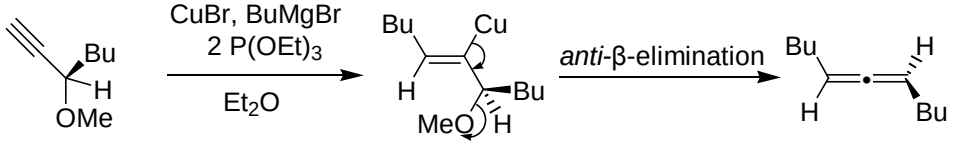


4.1.1.2 Chirality transfer from propargylic compounds

Organocopper-mediated alkylation of propargyl alcohol derivatives:

An interesting copper mediated S_N2' substitution reaction of chiral propargyl ether **43** (37-58% ee) gave the corresponding chiral allene (*S*)-**45** in 96% ee through *anti*-β-elimination of the intermediate **44** (Scheme 7).[25]

Scheme 7



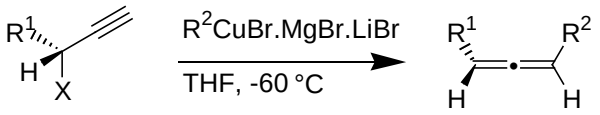
43
37-58% ee

44

(*S*)-**45**
95% yield, 96% ee

The reaction of chiral propargyl mesylates or sulfinates **46** with organocopper(I) reagent at low temperatures in THF gave the chiral 1,3-dialkylallenes **47** with high enantiomeric purity (Scheme 8).[26]

Scheme 8

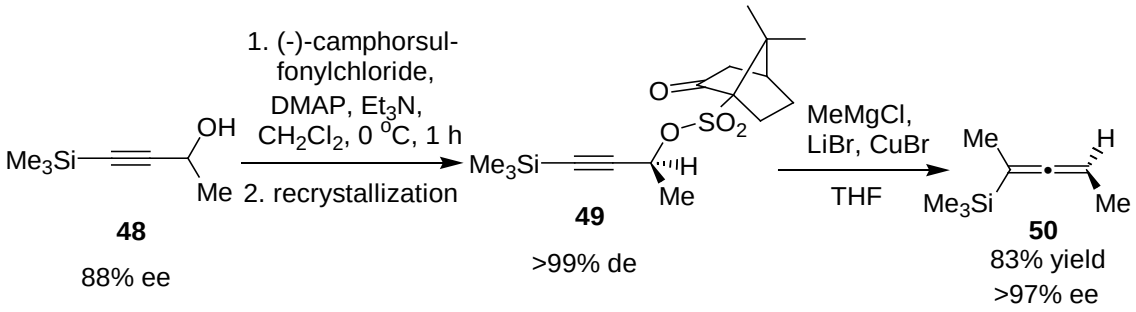


46
R^1 = Ph, ^{t}Bu, octyl, Me
X = OS(O)Me or OSO_2Me
R^2 = Me, Et, Ph, ^{n}Bu, ^{n}Pr

(*S*)-**47**
70-96% yield

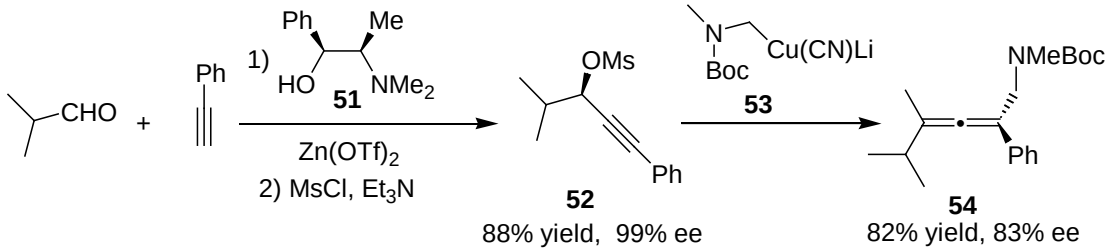
The chiral allene **50** (>97% ee) was synthesized by the synthetic protocol outlined in Scheme 9 involving the reaction of MeMgCl and copper bromide with the camphorsulfonate **49**.[27]

Scheme 9



Reaction of phenylacetylene with isobutyraldehyde in the presence of $Zn(OTf)_2$ and **51** followed by MsCl treatment afforded the propargyl alcohol derivative **52** in 88% yield with 99% ee, which on reaction with the cyanocuprate **53** gave the desired allene **54** in 83% ee (Scheme 10).[28]

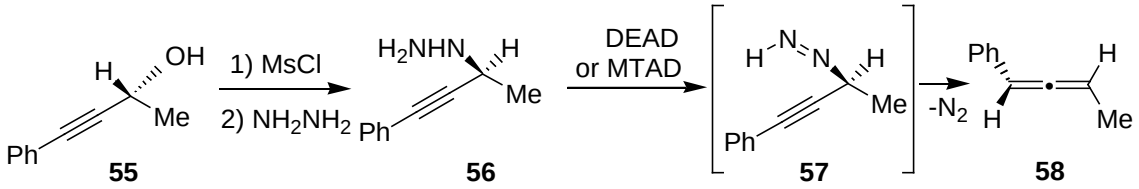
Scheme 10



Rearrangement of propargyl alcohol derivatives:

An interesting synthesis of allenes from alkynyl hydrazines was reported (Scheme 11).[29] In this method, the hydrazine derivative **56** underwent a smooth oxidative rearrangement with diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), presumably *via* a propargyldiazene intermediate **57** to form the allene **58** in 75% ee.

Scheme 11



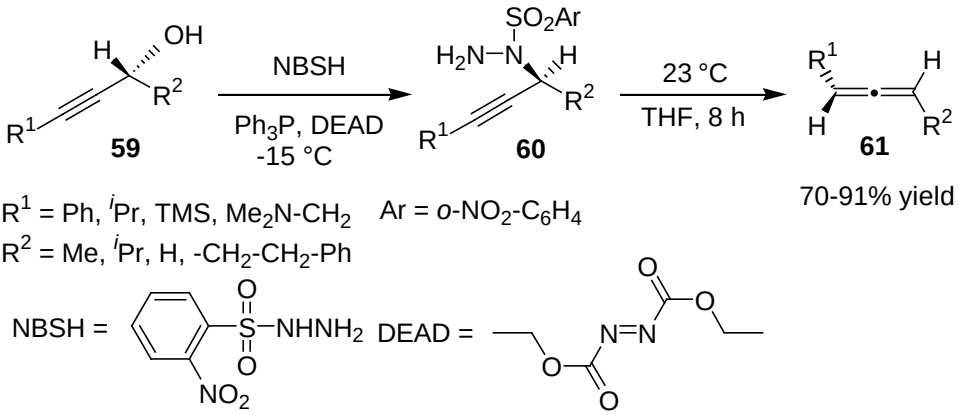
55 **56** **57** **58**

76% ee

81% yield
75% ee

A highly efficient method has been subsequently reported for the stereospecific synthesis of chiral allenes **61** in a single pot operation from chiral propargyl alcohols **59** (Scheme 12).[30]

Scheme 12



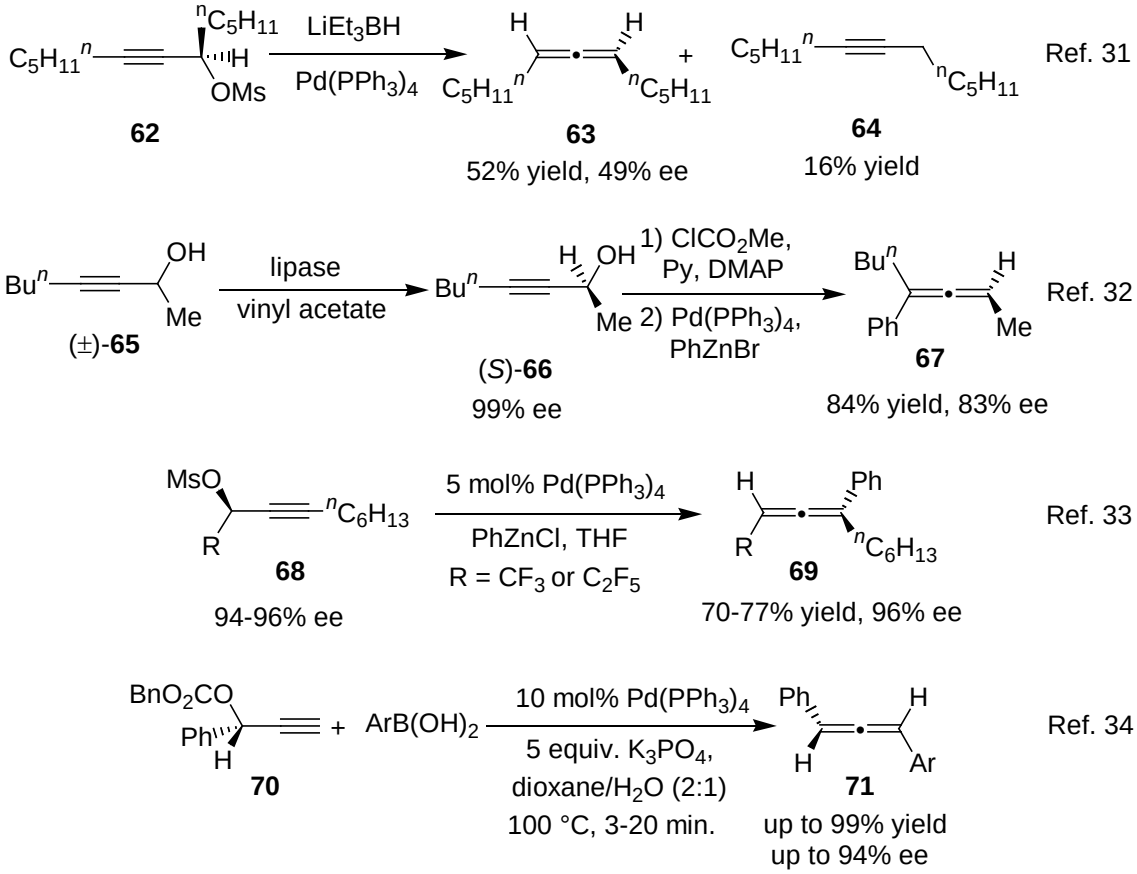
59 **60** **61**

70-91% yield

Palladium(0)-catalyzed reactions of propargyl alcohol derivatives:

Methods reported for the synthesis of chiral allenes by palladium(0)-catalyzed reaction of propargyl alcohol derivatives are summarized in Chart 3.

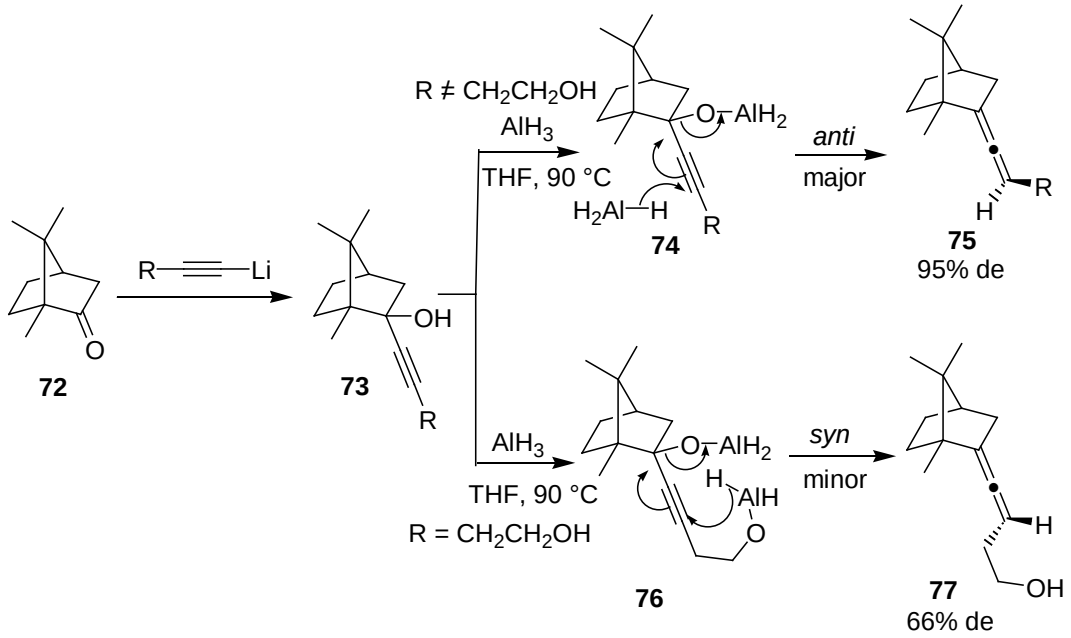
Chart 3



S_N2' Reduction of propargyl alcohol derivatives:

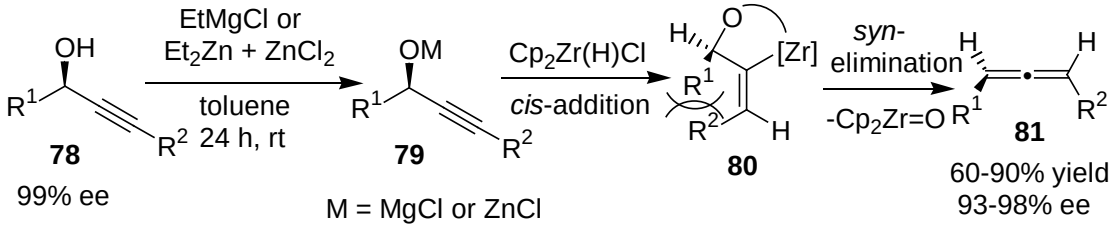
Propargyl alcohol derivatives **73** prepared from chiral camphor **72**, upon AlH_3 reduction gave the corresponding allenes **75** and **77** *via* intermediates **74** and **76**, respectively (Scheme 13).[35]

Scheme 13



Recently, a stereospecific synthesis of chiral allenes **81** has been reported by reduction of propargyl alcohol derivatives **79** with Schwartz reagent [$Cp_2Zr(H)Cl$] followed by elimination of the resulting vinyl metal species **80** (Scheme 14).[36]

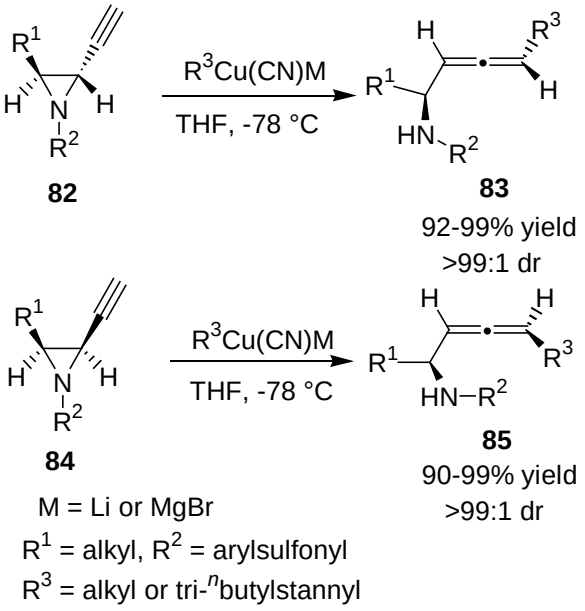
Scheme 14



Ring-opening reactions of propargyl compounds:

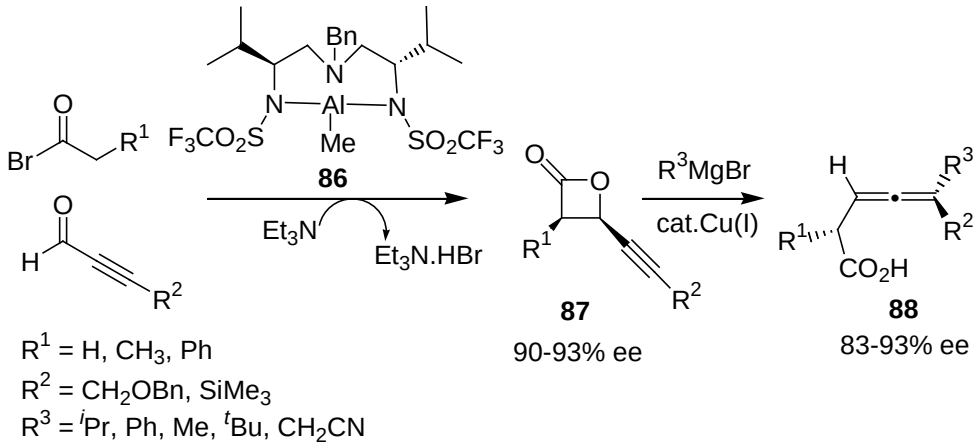
Stereoselective synthesis of chiral α-aminoalkylallenes **83** and **85** by RCu(CN)M -mediated *anti*-S_N2' substitution of chiral 2-ethynylaziridines **82** and **84** have been reported (Scheme 15).[37]

Scheme 15



A series of optically active alkynyl-substituted β-lactones **87** (90–93% ee) were prepared by asymmetric acyl halide–aldehyde cyclocondensation reactions (AAC reactions) catalyzed by Al(III) catalyst **86**, which on subsequent copper-catalyzed ring opening gave the β-allenic acids **88** with 83-93% ee (Scheme 16).[38]

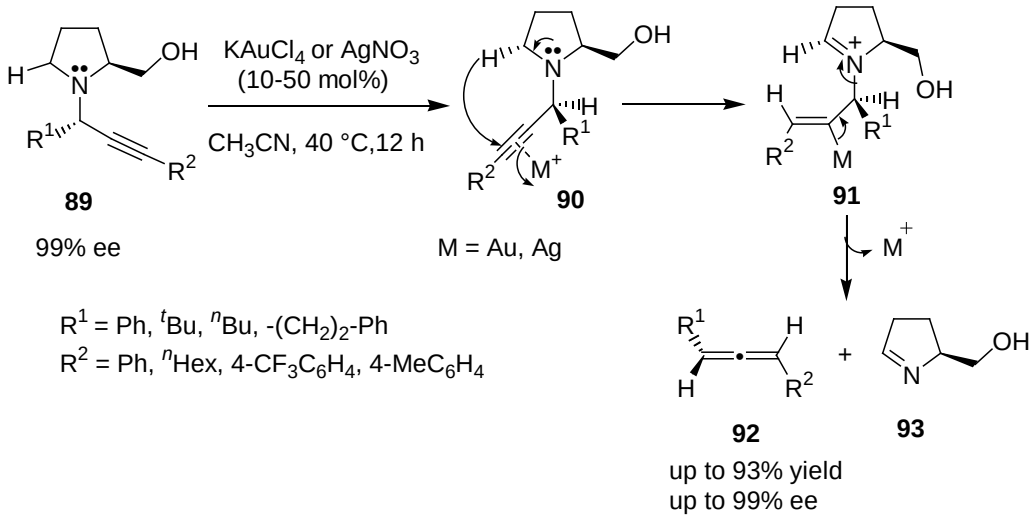
Scheme 16



Chirality transfer from propargylamines by elimination reaction:

An interesting one pot method has been reported for the synthesis of axially chiral allenes **92** *via* $KAuCl_4$ or silver(I) salts mediated stereospecific transformation of propargylamines **89** with excellent enantioselectivities (Scheme 17).[39]

Scheme 17

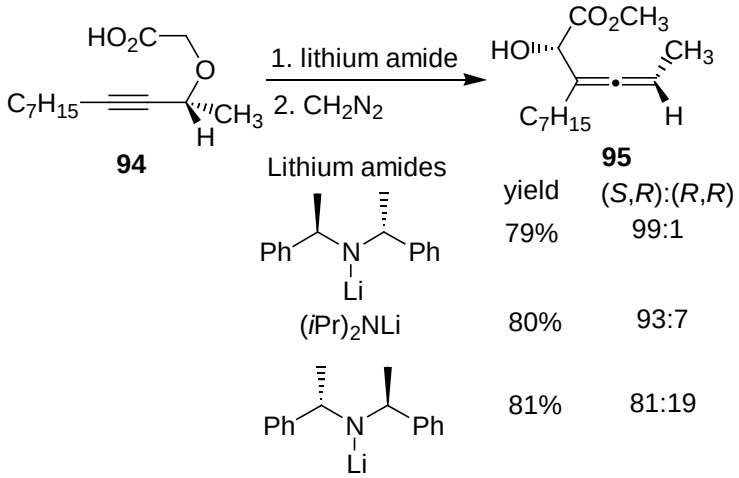


4.1.1.3 Synthesis of chiral allenes using chiral reagents

Enantioselective deprotonation-protonation of alkynes:

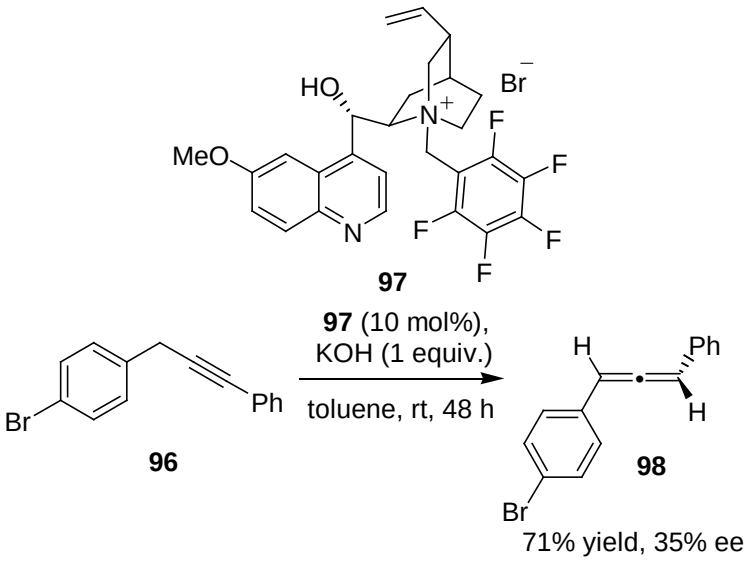
The [2,3]-Wittig rearrangement of chiral α-(propargyloxy)acetic acid **94** (90-92% ee) with chiral (*R,R*)- and (*S,S*)-lithium amide gave the allene **95** in 99:1 and 81:19 dr respectively, indicating the dependence of the selectivity on the configuration of the lithium amide (Scheme 18).[40]

Scheme 18



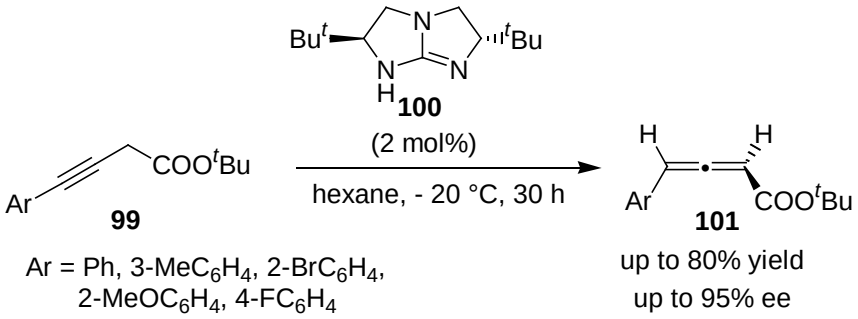
A catalytic asymmetric synthesis of allene **98** by isomerization of the alkyne **96** using a chiral phase transfer catalyst **97** has been reported (Scheme 19).[41]

Scheme 19



Recently, it has been reported that the chiral bicyclic guanidine **100** catalyzes the isomerization of 3-alkynoates **99** to chiral allenoates **101** with up to 95% ee (Scheme 20).[42]

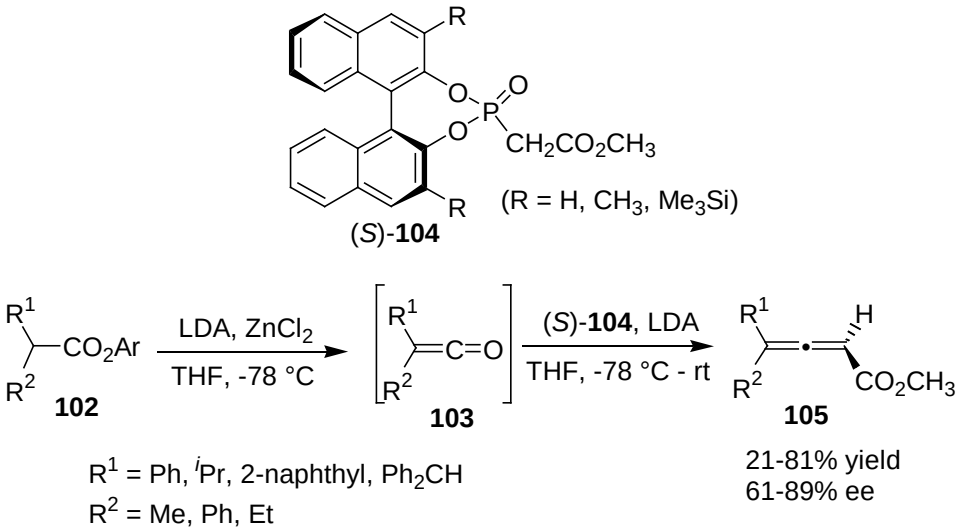
Scheme 20



Enantioselective Horner-Wadsworth-Emmons (HWE) and related reactions:

A variety of optically active 4,4-disubstituted allene carboxylates **105** were synthesized by HWE reaction of disubstituted ketene **103** with homochiral HWE reagents **104** (Scheme 21).[43] The ketene **103** was prepared *in situ* from α,α-disubstituted phenyl or 2,6-di-*tert*-butyl-4-methylphenyl acetate **102**.[44]

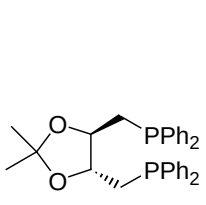
Scheme 21



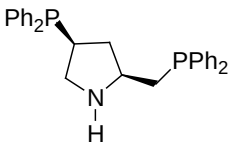
4.1.1.4 Direct enantioselective synthesis of allenes using an external chiral catalyst

Several methods have been reported for the synthesis of chiral allenes using an external chiral catalyst (Chart 4).

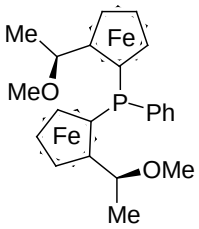
Chart 4



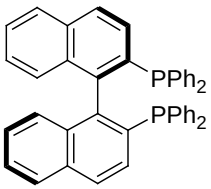
(*R*,*R*)-DIOP-**106**



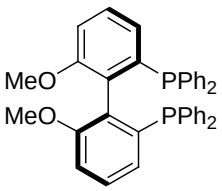
(*S*,*S*)-PPM-**107**



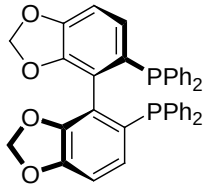
(*S*,*R*)-bisPPFOMe-**108**



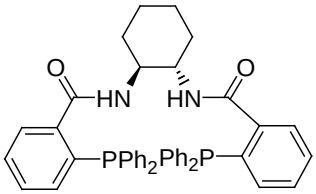
(*R*)-BINAP-**109**



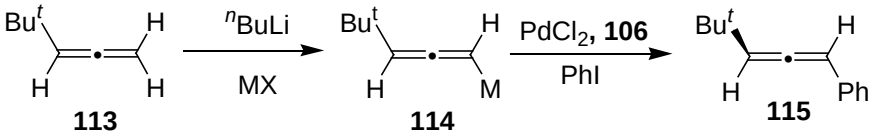
(*R*)-MeOBIPHEP-**110**



(*R*)-segphos-**111**



(*S*,*S*)-Trost's Ligand-**112**

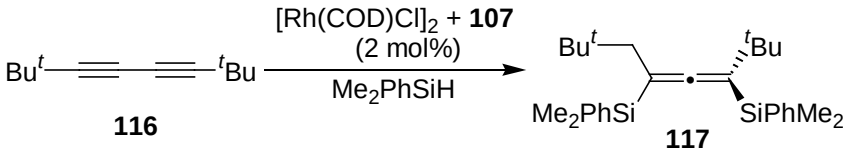


113 **114** **115**

(M = ZnCl, MgCl or Cu)

25% ee

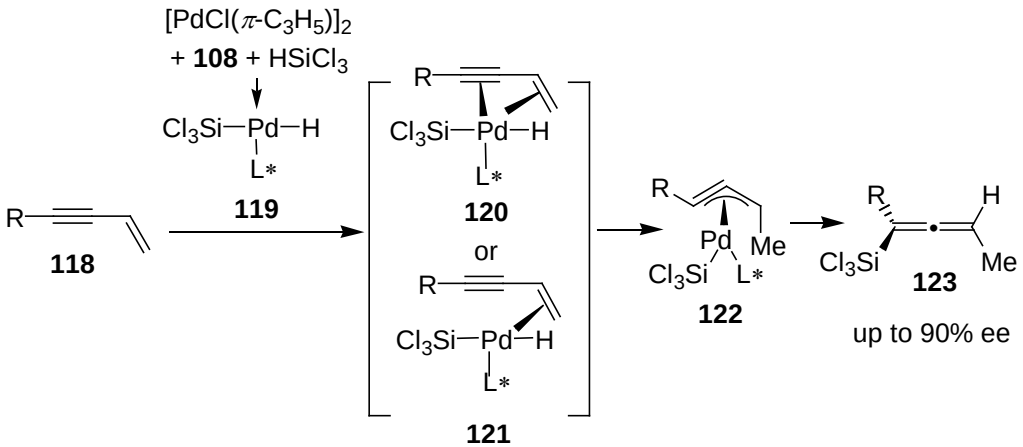
Ref. 45



116 **117**

up to 27% ee

Ref. 46

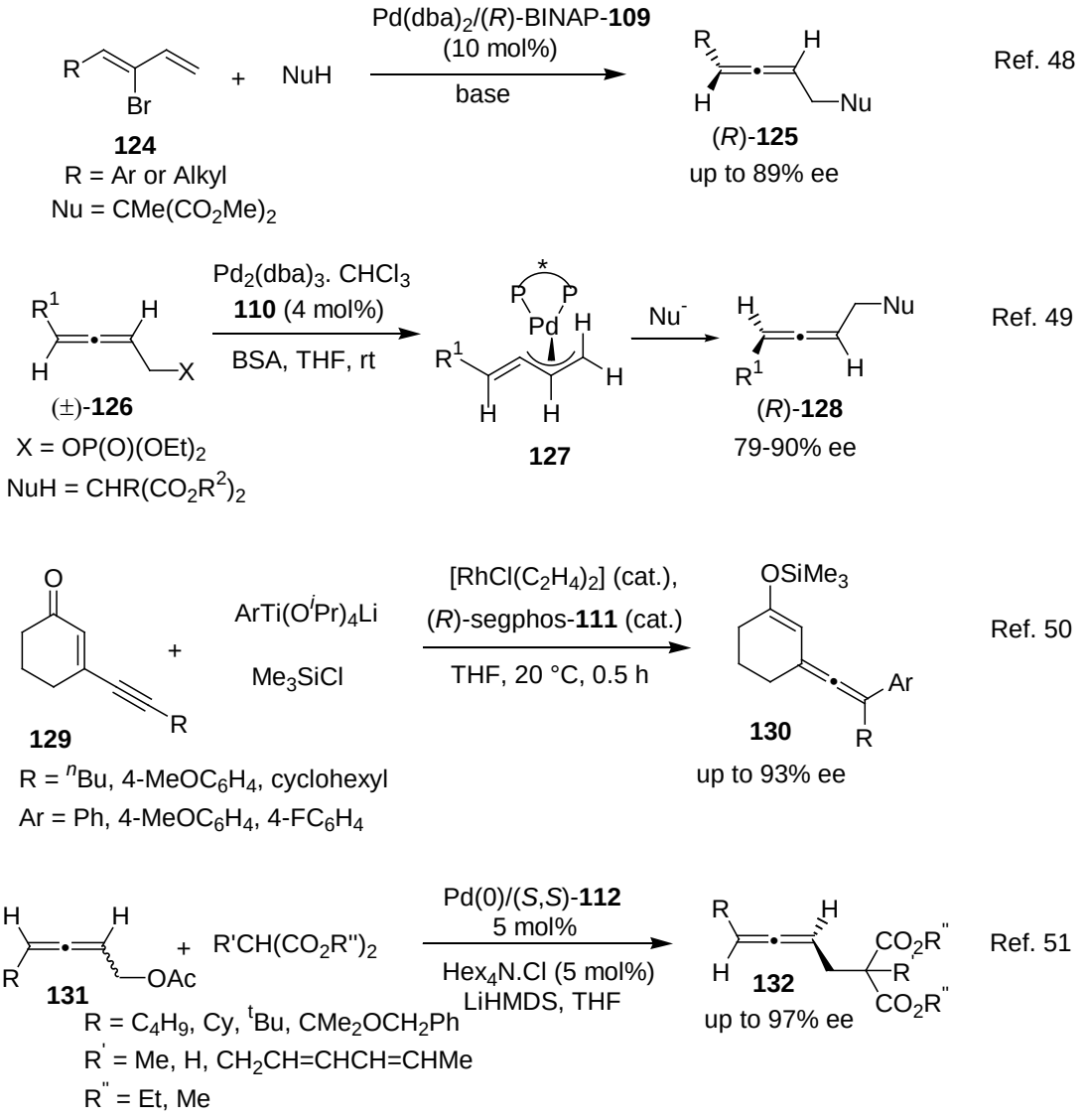


118 **119** **120** **121** **122** **123**

up to 90% ee

Ref. 47

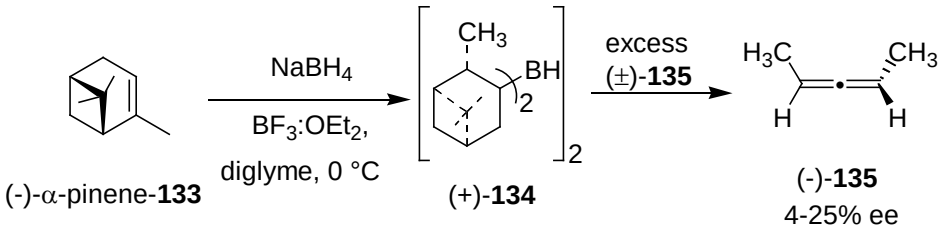
Chart 4 continued …



4.1.1.5 Synthesis of enantiomerically enriched allenes by kinetic resolution of racemic allenes

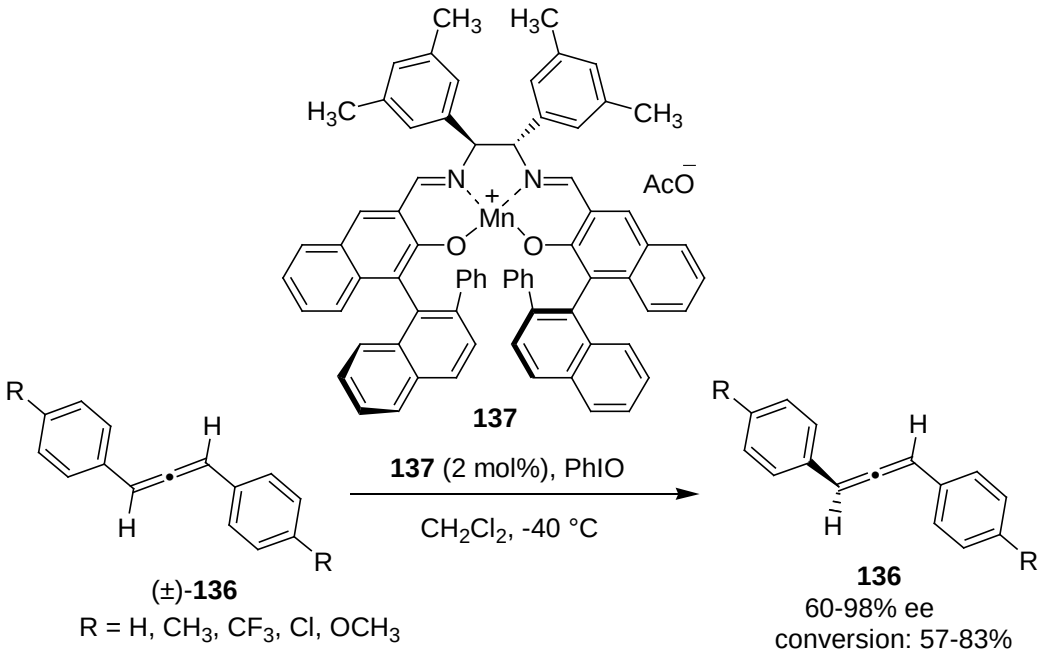
A simple one-step method for the partial resolution of racemic allenes based on the asymmetric hydroboration reaction has been reported (Scheme 22).[52-54]

Scheme 22



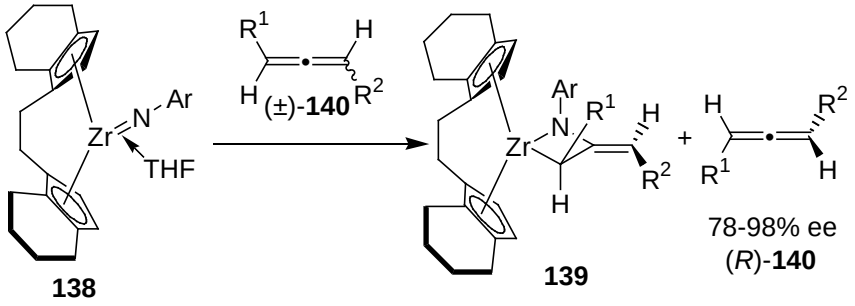
Kinetic resolution of racemic allenes **136** by enantiomer-differentiating catalytic asymmetric epoxidation using a chiral salen-Mn(III) complex **137** has been reported (Scheme 23).[55]

Scheme 23



A method for the kinetic resolution of racemic allene **140** using a chiral zirconocene–imido complex **138** has been reported (Scheme 24).[56]

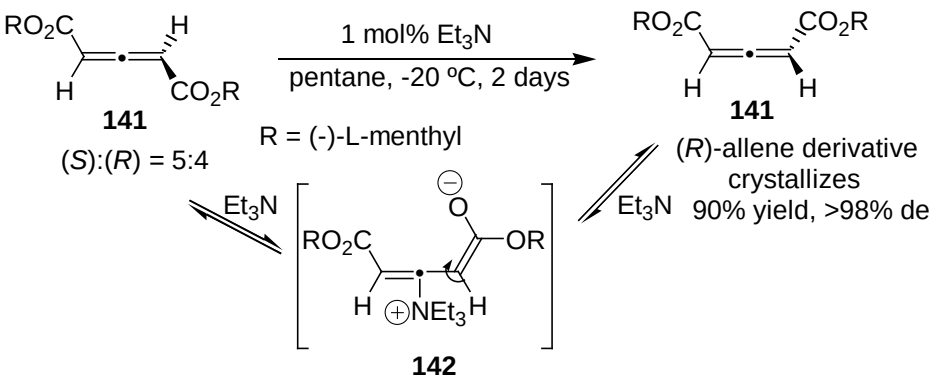
Scheme 24



R^1, R^2 = C_3H_5, Ph, Me, Et, cyclohexyl

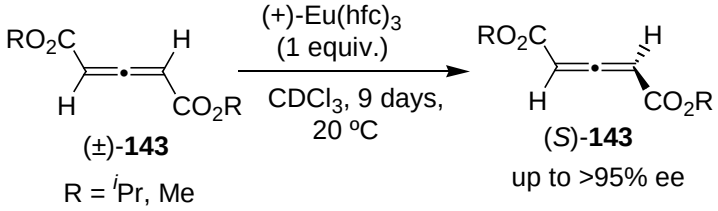
The diastereomeric mixture of **141** has been converted to the corresponding chiral allene dicarboxylate (*R*)-**141** with > 98% de by an epimerization-crystallization method through the intermediate **142** with the assistance of a catalytic amount of Et_3N (Scheme 25).[57]

Scheme 25



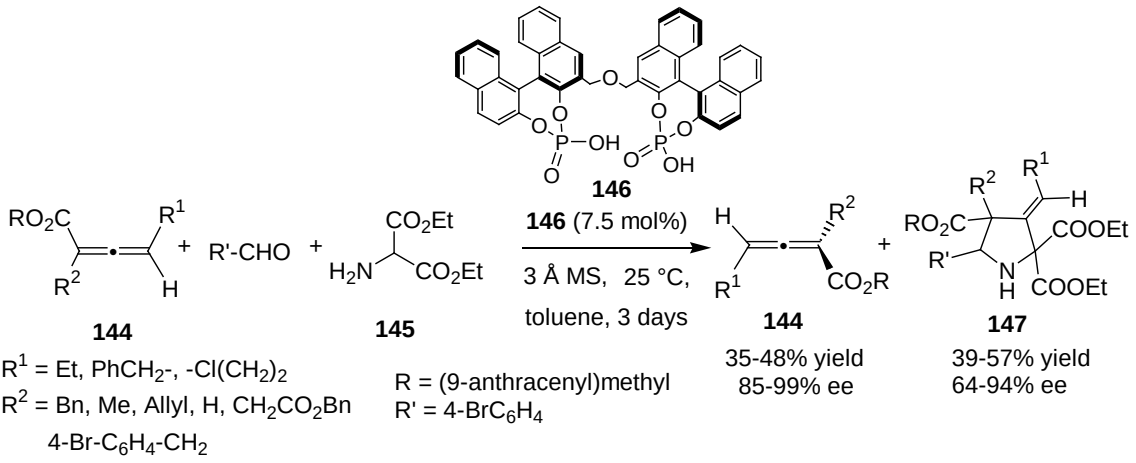
Reaction of racemic dialkylallene-1,3-dicarboxylate **143** with a chiral organoeuropium reagent (+)-Eu(hfc)$_3$, gave the corresponding optically active allene **143** in up to >95% ee (Scheme 26).[58] However, the chiral allene **143** could not be isolated from the reaction mixture because of the difficulty in removing the europium reagent.

Scheme 26



A method for kinetic resolution of racemic 2,3-allenoates **144** *via* 1,3-dipolar cycloaddition by using a bisphosphoric acid catalyst **146**, has been reported (Scheme 27).[59]

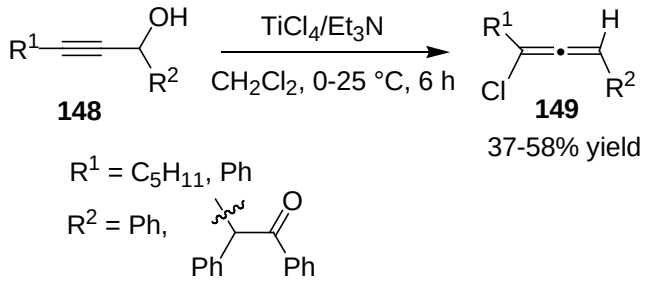
Scheme 27



4.1.2. Previous work on the synthesis of racemic allenes

Previously, a convenient method for the synthesis of racemic chloroallenes **149** from propargylic alcohol **148** and $TiCl_4/Et_3N$ reagent system has been reported in up to 58% yield (Scheme 28).[60]

Scheme 28

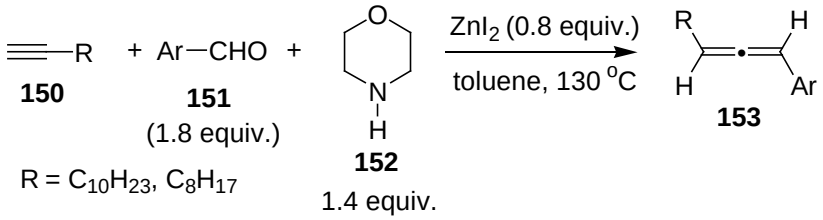


As described in this introductory section, the methods available for the synthesis of chiral allenes, involve a multistep synthetic protocol. Surprisingly a single pot method for the synthesis of chiral allenes is not available. Accordingly, we have undertaken efforts toward the enantioselective synthesis of chiral allenes in a single pot operation from readily available starting materials. The results are discussed in the next section.

4.2 Results and Discussion

Recently, it has been reported that ZnI_2 promote the formation of racemic allenes **153** from readily available terminal alkynes **150**, arylaldehydes **151**, and morpholine **152** (Scheme 29).[61]

Scheme 29

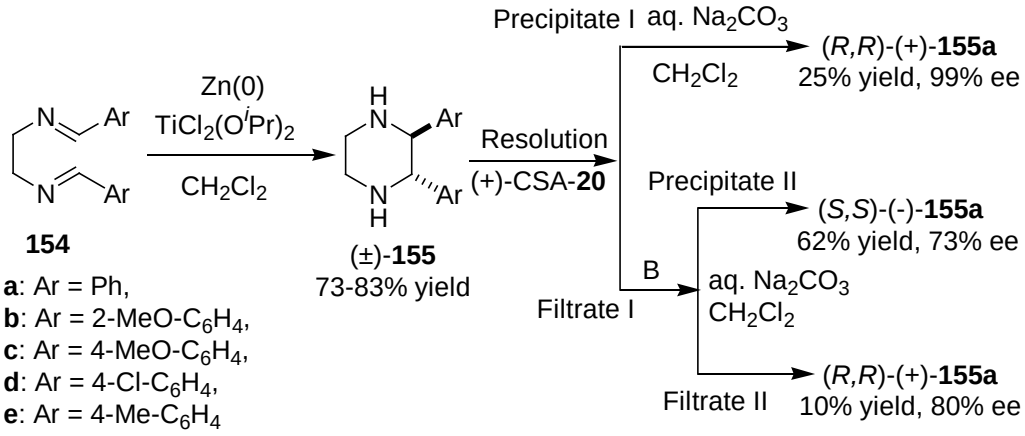


It was of interest to us to explore the use of chiral morpholines or similar type of compounds containing a cyclic secondary amine moiety for this transformation so as to develop a enantioselective method for the synthesis of chiral allenes. Previously, methods have been developed in this laboratory for the synthesis and applications of 2,3-diarylpiperazines **155**.[62-64] Accordingly, we decided to examine the use of these derivatives in the enantioselective synthesis of chiral allenes in the presence of Lewis acids like ZnX_2.

4.2.1 Synthesis of (*R*,*R*)-2,3-diarylpiperazines

Previously, it was reported from this laboratory that intramolecular reductive coupling of the diimines **154** promoted by the $TiCl_2(O^iPr)_2$/Zn reagent system gave the (±)-2,3-diphenylpiperazines **155** with >99% *dl*:*meso* ratio (Scheme 30).[62] The (±) 2,3-diphenylpiperazine **155a** obtained in this way was easily resolved using (1*S*)-(+)-10-camphorsulfonic acid **20** (Scheme 30). The enantiomerically pure (*R*,*R*)-2,3-diphenylpiperazine **155a** was obtained with 99% ee and 25% yield in a single step.[63]

Scheme 30

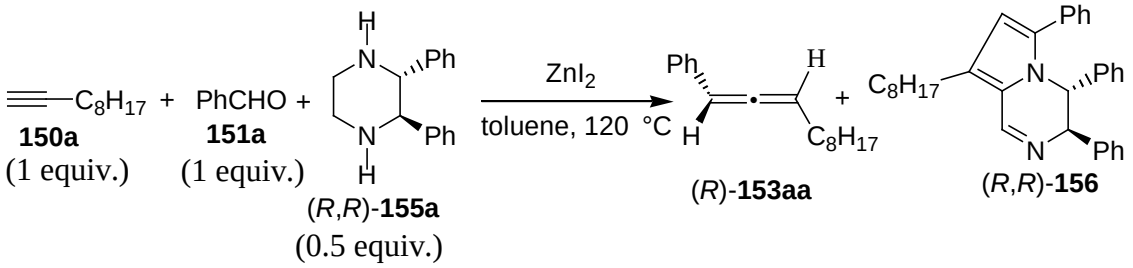


B: the volume of the solvent was reduced to half and then stirred at 25 °C for 12 h

4.2.2 Reaction of (*R*,*R*)-2,3-diphenylpiperazine 155a with 1-decyne 150a, benzaldehyde 151a and ZnI_2

We have examined the enantioselective synthesis of chiral allene **153aa** by the reaction of 1-decyne **150a**, benzaldehyde **151a** with (*R*,*R*)-2,3-diphenylpiperazine **155a** using different amounts of ZnI_2 by varying the reaction time (Scheme 31). The results are summarized in Table 1.

Scheme 31



When the reaction was carried out for 4 h, using ZnI_2 (0.8 equiv.) the corresponding (*R*)-allene **153aa** was obtained in 43% yield and 59% ee (Table 1, entry 1). Using 0.6 equivalent of ZnI_2, the enantioselectivity of allene **153aa** increased to 65% in 4 h (Table 1, entry 2). With increase in reaction time to 8 h, the corresponding allene

153aa was obtained with 76% ee and 55% yield (Table 1, entry 3). Surprisingly, with further increase in reaction time to 20 h, the enantioselectivity decreases to 65% with 58% yield.

Table 1. Synthesis of allene 153aa from benzaldehyde 151a, 1-decyne 150a and (*R*,*R*)-2,3-diphenylpiperazine 155a in the presence of ZnI_2[a]

Entry	ZnI_2 (equiv.)	Time (h)	Yield[b] of **153aa** (%)	(%) ee[c] of **153aa**	Yield[b] of **156** (%)
1	0.8	4	43	59	32
2	0.6	4	40	65	39
3	0.6	8	55	76	35
4	0.6	20	58	65	42

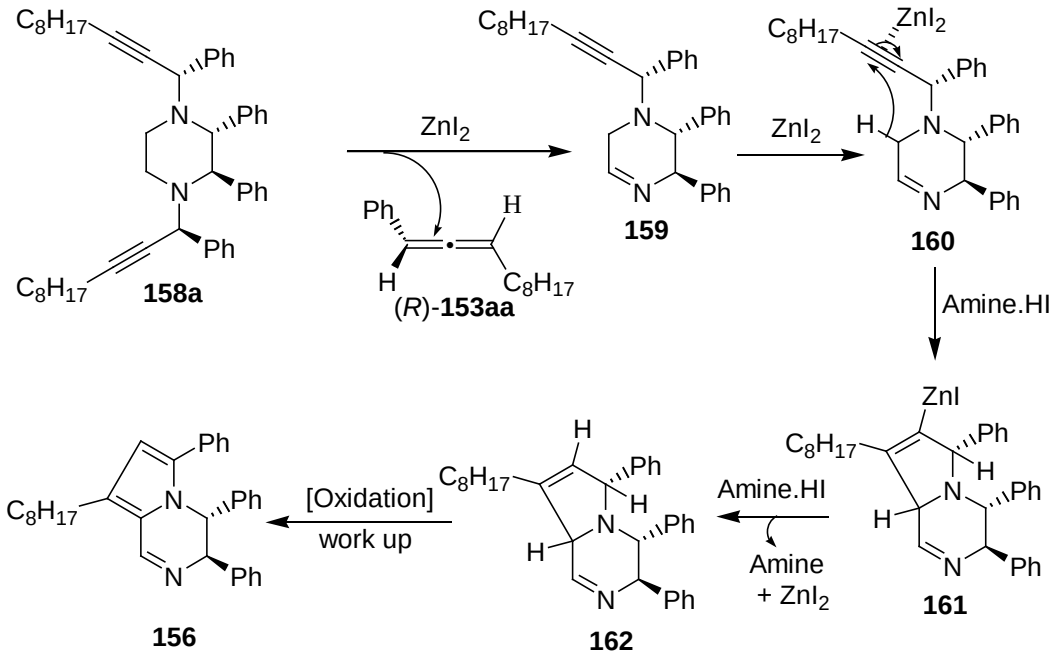
[a]The reactions were carried out in 1 mmol scale in 5 mL of dry toluene.
[b]Isolated yield by column chromatography.
[c]Determined by HPLC using Chiralcel-OD-H column.

In all these experiments, we have observed the formation of an intramolecular bicyclic byproduct **156** in up to 42% yield (Scheme 31). In a separate run, we have isolated the initially formed dipropargylamine intermediate **158a** and shown that upon reaction with ZnI_2, the chiral allene **153aa** was obtained in 55% ee besides the bicyclic product **156** in 39% yield. The results are discussed later (Scheme 41). Presumably, with increase in time, the dipropargylamine **158a** would be formed in more amounts leading to lower enantioselectivity of the allene **153aa** in 20 h reaction time (Table 1, entry 4).

Based on the previous understanding of a zinc(II) catalyzed ring closure reaction,[65] a mechanism for the formation of the bicyclic byproduct **156** can be proposed, *via* generation of the dipropargylamine intermediate **158a** *in situ* from (*R*,*R*)-2,3-diphenylpiperazine **155a**, 1-decyne **150a** and benzaldehyde **151a** (Scheme 32). The

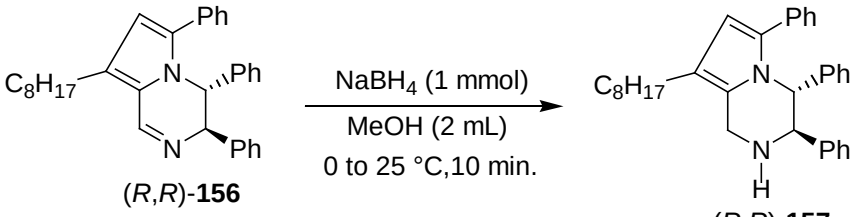
ZnI_2 would complex with one of the €C bonds in the intermediate **158a** to give the (*R*)-allene **153aa** and the cyclic imine **159**, following the similar mechanistic pathway as outlined in the Scheme 44 (see latter). The C≡C bond of propargylamine **159** would then form complex **160** with ZnI_2, which on deprotonation induced cyclization would give the cyclized product **161**. Protodemetallation of **161** would form the dihydropyrrole derivative **162,** which upon air oxidation during work up would result the aromatized product **156**.

Scheme 32. Plausible mechanism for the formation of bicyclic product 156



The bicyclic product **156** could be readily transformed to the corresponding (*R*,*R*)-2,3-diphenylpiperazine derivative **157** in 95% yield (Scheme 33).

Scheme 33



(*R*,*R*)-**156**

(*R*,*R*)-**157**

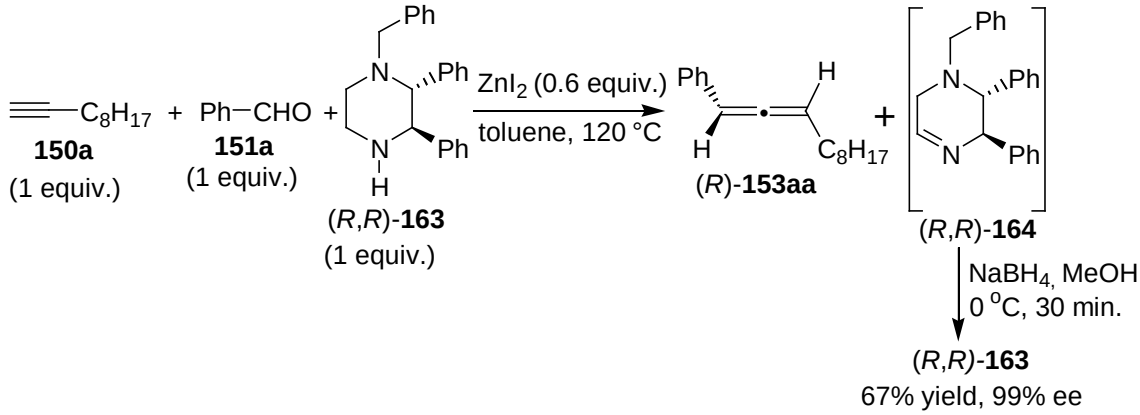
95% yield

It was thought that protection of one of the secondary amine moieties in the (*R*,*R*)-2,3-diphenylpiperazine **155a** would prevent the formation of the dipropargylamine intermediate **158a** as well as the bicyclic byproduct **156**. Accordingly, we have synthesized the chiral (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** for use in this transformation.

4.2.3 Reaction of (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163 with 1-alkynes 150, arylaldehydes 151 and ZnI_2

Initially, we have examined the reaction of (*R*,*R*)-1-benzyl-2,3-diphenyl piperazine **163**, 1-decyne **150a** and benzaldehyde **151a** with ZnI_2 (0.6 equiv.) at 120 °C for 8 h. In this run, the corresponding (*R*)-allene **153aa** was obtained in 71% yield and 94% ee (Table 2, entry 1). When the reaction was carried out for 4 h, the chiral allene **153aa** was obtained in 65% yield and 95% ee (Table 2, entry 3). Unfortunately, the isolation of the expected imine byproduct **164** was found to be somewhat difficult. However, when the crude product mixture containing the imine **164** was reduced with the $NaBH_4$/MeOH reagent, the starting chiral amine (*R*,*R*)-**163** was recovered in 67% yield for reuse without any loss of optical activity, which was confirmed by HPLC analysis (Scheme 34).

Scheme 34



Under the same experimental conditions, a variety of axially chiral (*R*)-allenes **153** were synthesized from 1-heptyne **150b** and substituted benzaldehydes (**151a-k**) in up to 77% yields and >99% ee. The results are summarized in Table 2.

With benzaldehyde **151a**, the allene **153ba** was obtained in 65% yield and 94% ee (entry 4). With the electron donating *p*-methyl substituted benzaldehyde **151b**, the corresponding allene **153bb** was obtained in 61% yield and 90% ee (entry 5).

In case of *p*-chloro and *p*-bromo substituted benzaldehydes **151c** and **151d**, the corresponding (*R*)-allenes **153bc** and **153bd** were obtained in 71% and 77% yields with >99% ee, respectively (entries 6 and 7). The chiral allene **153be** was obtained in 57% yield and 92% ee by using *m*-bromo substituted benzaldehyde **151e** (entry 8). In case of *o*-bromo substituted benzaldehyde **151f**, the chiral allene **153bf** was obtained in 66% yield and 90% ee (entry 9).

Table 2. ZnX_2 promoted reactions of various 1-alkynes 150 with aldehydes 151 in the presence of (*R*,*R*)-1-benzyl-2,3-diphenyl-piperazine 163[a]

Entry	Alkyne **150** R	Aldehyde **151** Ar	ZnX_2	Time (h)	Allene[b] **153**	Yield[c] (%)	% ee[d] (*R*)
1	C_8H_{17} (**a**)	Ph (**a**)	ZnI_2	8	**153aa**	71	94
2	C_5H_{11} (**b**)	Ph (**a**)	ZnI_2	8	**153ba**	65	91
3	C_8H_{17} (**a**)	Ph (**a**)	ZnI_2	4	**153aa**	65	95
4	C_5H_{11} (**b**)	Ph (**a**)	ZnI_2	4	**153ba**	65	94
5	C_5H_{11} (**b**)	*p*-Me-Ph (**b**)	ZnI_2	4	**153bb**	61	90
6	C_5H_{11} (**b**)	*p*-Cl-Ph (**c**)	ZnI_2	4	**153bc**	77	>99
7	C_5H_{11} (**b**)	*p*-Br-Ph (**d**)	ZnI_2	4	**153bd**	71	>99
8	C_5H_{11} (**b**)	*m*-Br-Ph (**e**)	ZnI_2	4	**153be**	57	92
9	C_5H_{11} (**b**)	*o*-Br-Ph (**f**)	ZnI_2	4	**153bf**	66	90
10	C_5H_{11} (**b**)	*p*-MeO-Ph (**g**)	ZnI_2	4	**153bg**	58	76
11	C_5H_{11} (**b**)	*m*-MeO-Ph (**h**)	ZnI_2	4	**153bh**	55	90
12	C_5H_{11} (**b**)	*o*-MeO-Ph (**i**)	ZnI_2	4	**153bi**	56	84
13	C_5H_{11} (**b**)	1-Naphthyl (**j**)	ZnI_2	4	**153bj**	45	90
14	C_5H_{11} (**b**)	2-Naphthyl (**k**)	ZnI_2	4	**153bk**	51	91
15	Ph (**c**)	Ph (**a**)	ZnI_2	12	**153ca**	48	94
16	C_8H_{17} (**a**)	Ph (**a**)	$ZnBr_2$	8	**153aa**	54	94
17	C_8H_{17} (**a**)	Ph (**a**)	$ZnCl_2$	8	**153aa**	47	94

[a]All the reactions were carried out in 0.5 mmol scale. [b]Allenes **153** were identified using physical constant and spectroscopic data (IR, ^1H, ^{13}C-NMR and mass spectral data) [c]Yields are of isolated product obtained from column chromatography. [d]The % ee was confirmed by HPLC analysis on chiralcel OD-H or OJ-H column.

Using *para* and *ortho*-methoxy substituted benzaldehydes **151g** and **151i**, the corresponding allenes **153bg** and **153bi** were obtained in 76% ee and 84% ee, respectively (entries 10 and 12). The enantioselectivities are somewhat poor in these cases. Presumably, due to the (+M)-resonance effect of the *ortho* and *para* methoxy groups, the addition of the alkynyl zinc compound **168** with the iminium ion is expected to be slower, leading to relatively poor enantioselectivity.

Using 1-naphthaldehyde **151j**, the allene **153bj** was obtained in 45% yield and 90% ee (entry 13). Similarly, in case of 2-naphthaldehyde **151k**, the allenes **153bk** was obtained in 51% yield with 91% ee (entry 14).

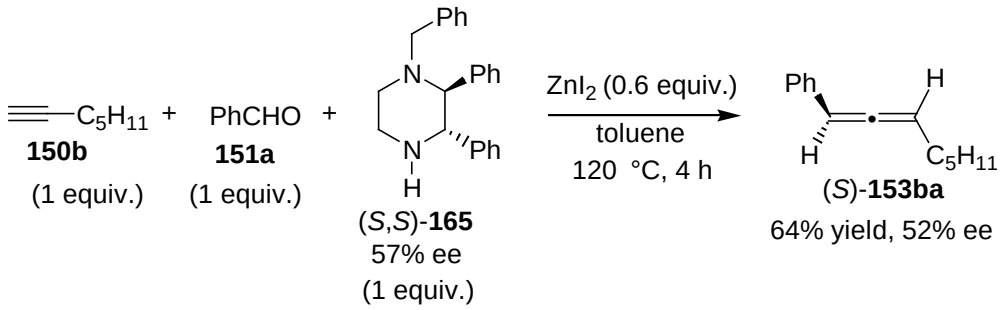
When the reaction was carried out using phenylacetylene **150c** and benzaldehyde **151a**, a longer reaction time of 12 h was required for the formation of allene **153ca** in 48% yield and 94% ee (entry 15).

When $ZnBr_2$ and $ZnCl_2$ were used in the place of ZnI_2, the (*R*)-allene **153aa** was obtained in 94% ee with 54% and 47% yields, respectively (entries 16 and 17). Presumably, the lower in yield of (*R*)-allene **153aa** might be due to the slow reaction with less polarizable Zn-Cl and Zn-Br bonds compared to that of more polarizable and reactive Zn-I bond of ZnI_2.

All the optically active allenes **153** obtained by using chiral (*R*,*R*)-2,3-diphenylpiperazine derivatives **155a** and **163** are levorotatory and thus, the absolute configurations of the major enantiomer of the allenes **153** could be readily assigned as *R* by considering Lowe-Brewster rule[66] and also by comparison with reported sign of the optical rotation values.[67] As expected, use of the opposite enantiomer (*S*,*S*)-1-benzyl-

2,3-diphenylpiperazine **163** (57% ee) in this transformation resulted in the formation of (*S*)-allene **153ba** in 52% ee and 64% yield (Scheme 35).

Scheme 35

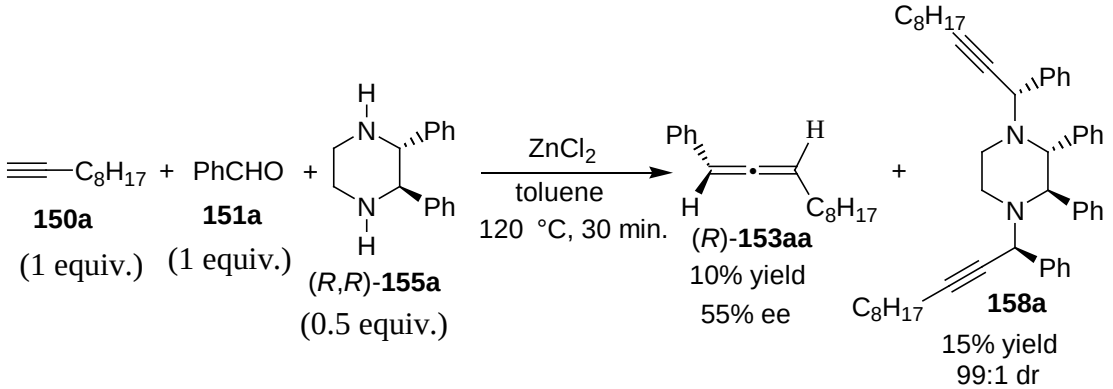


4.2.4 Synthesis of chiral propargylamine derivatives

4.2.4.1 Chiral propargylamines from (*R*,*R*)-2,3-diphenylpiperazine 155a

Since $ZnCl_2$ is less reactive compared to ZnI_2 for the formation of allene **153**, we have used $ZnCl_2$ instead of ZnI_2 in the reaction for the isolation of propargylamine intermediates. The dipropargylamine **158a** was isolated in 15% yield with 99:1 dr along with (*R*)-allene-**153aa** in 10% yield and 55% ee by using $ZnCl_2$ and carrying out the reaction for 30 min. at 120 °C in toluene (Scheme 36).

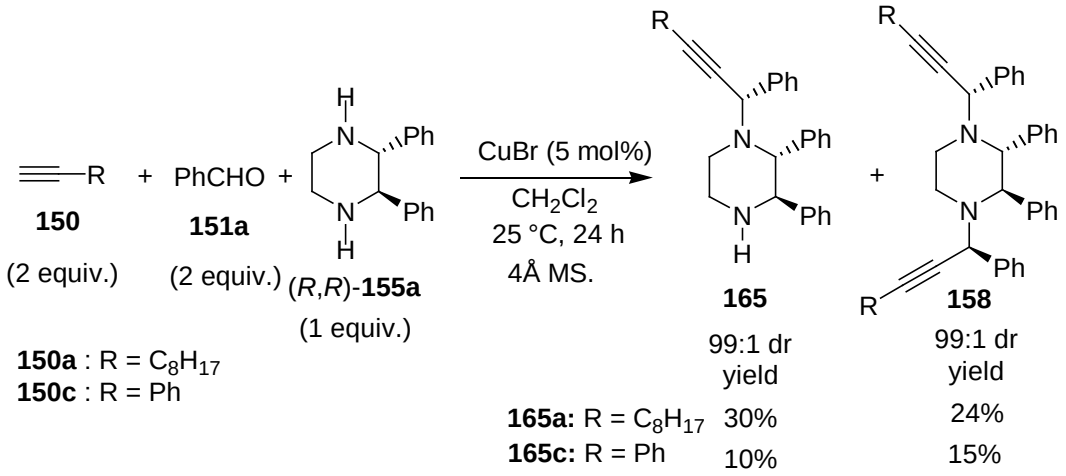
Scheme 36



Previously, the formation of propargylamines in CuBr catalyzed reaction of 1-alkynes, aldehydes and secondary amines has been reported.[68] We have observed that

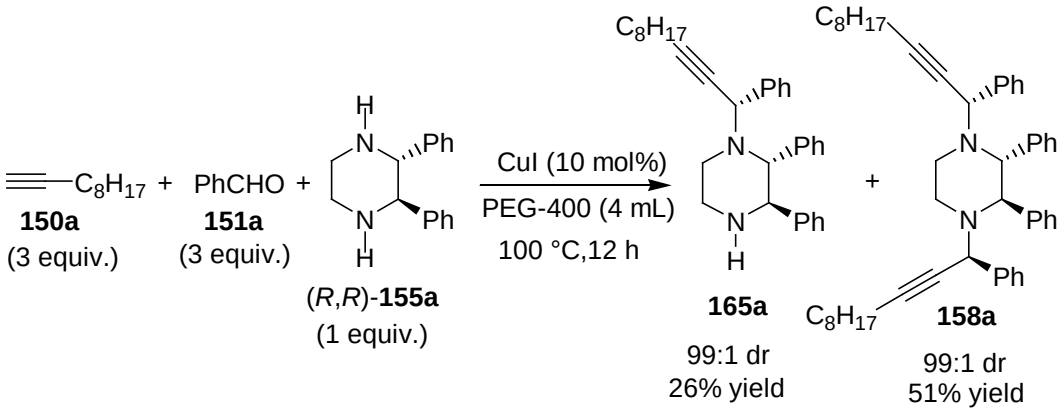
when the reaction of 1-decyne **150a**, benzaldehyde **151a** and (*R*,*R*)-2,3-diphenylpiperazine **155a** was carried out in the presence of CuBr (5 mol%) in CH_2Cl_2 at 25 °C for 24 h, the corresponding monopropargylamine **165a** and dipropargylamine **158a** were obtained in 30% and 24% yields, respectively with 99:1 dr (Scheme 37). When the reaction was carried out using phenylacetylene **150c** instead of 1-decyne **150a**, the corresponding propargylamines **165c** and **158c** were obtained in 10% and 15% yields, respectively (Scheme 37).

Scheme 37



We have also carried out the reaction using CuI (10 mol%)/PEG-400 reagent system with 1-decyne **150a**, benzaldehyde **151a** and (*R*,*R*)-2,3-diphenylpiperazine **155a** following a reported method for the synthesis of propargylamines.[69] In this case, the monopropargylamine **165a** and dipropargylamine **158a** derivatives were obtained in 26% and 51% yields, respectively with 99:1 dr (Scheme 38).

Scheme 38



Crystals suitable for the single crystal X-ray analysis were obtained by crystallization of **158c** from CH_3CN solvent. The absolute configuration at the newly formed chiral centres of the dipropargylamine **158c** was found to be (*S*) by single crystal X-ray analysis. The ORTEP diagram of the dipropargylamine derivative **158c** is shown in Figure 1.

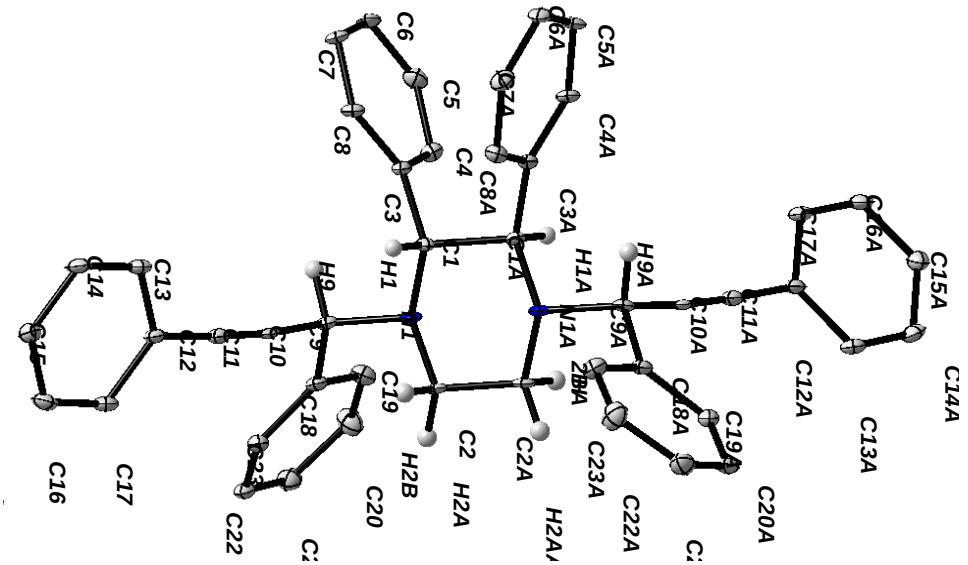


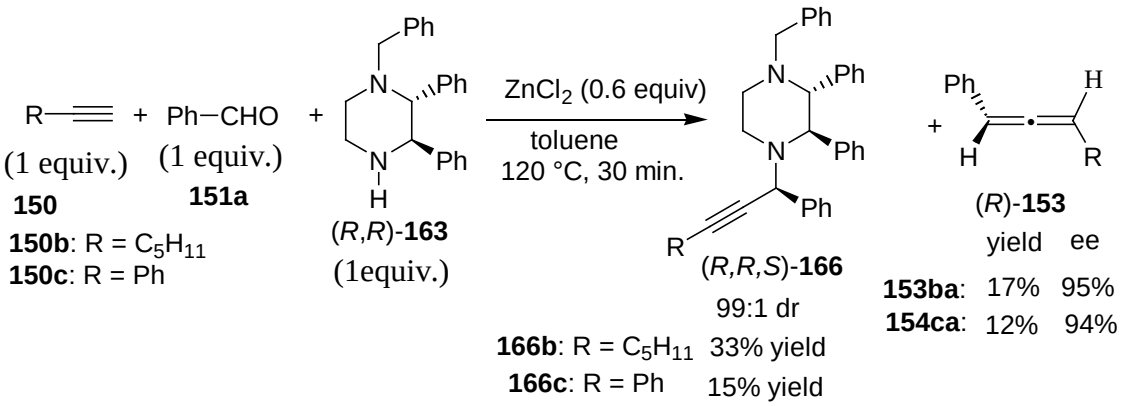
Figure 1. ORTEP diagram of the dipropargylamine amine **158c**. Thermal ellipsoids are drawn at 30% probability. Another molecule **158c** and hydrogen atoms on the benzene rings have been omitted for clarity.

Table 3. Crystal data and structure refinement for compound 158c	
Identification code	**158c**
Empirical formula	$C_{46}H_{38}N_2$
Formula weight	618.78
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	C2, Monoclinic
Unit cell dimensions	a = 23.819(6) Å, α = 90 ° b = 9.560(2) Å, β = 115.828(3) ° c = 16.851(4) Å, γ = 90 °
Volume	3453.8(14) $Å^3$
Z, Calculated density	2, 1.190 Mg M^{-3}
Absorption coefficient	0.069 mm^{-1}
F(000)	1312
Crystal size	0.25 x 0.21 x 0.11 mm
Theta range for data collection	1.34 to 26.14 °
Limiting indices	-29≤h≤29, -11≤k≤11, -20≤l≤20
Reflections collected / unique	17680 / 6799 [R(int) = 0.0686]
Completeness to θ	26.14, 99.2%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6799 / 1 / 445
Goodness-of-fit on F^2	1.136
Final R indices [I>2σ (I)]	R1 = 0.0717, wR2 = 0.1737
R indices (all data)	R1 = 0.0765, wR2 = 0.1776
Largest diff. peak and hole	0.547 and -0.347 e. $Å^{-3}$

4.2.4.2 Chiral propargylamines from (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163

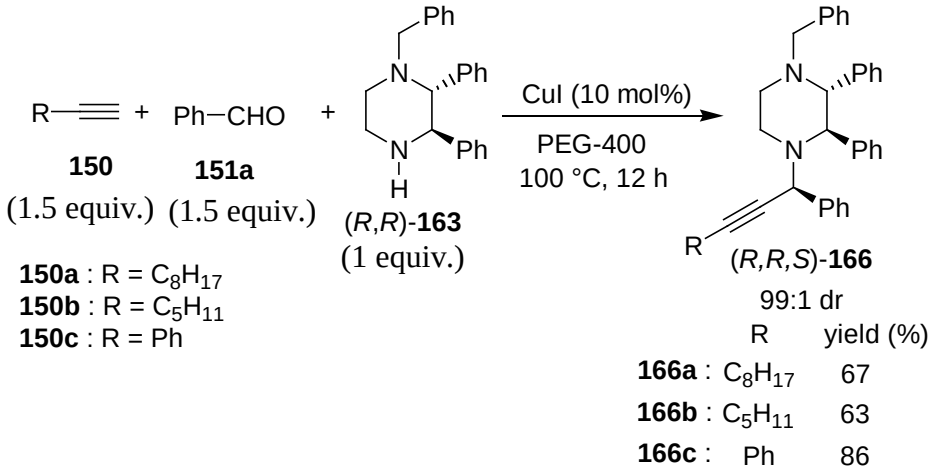
We have observed that the chiral propargylamines **166b** and **166c** were isolated only in 33% and 15% yields, respectively with 99:1 dr along with (*R*)-allenes **153** in up to 17% yield and 95% ee, when the reaction was carried out using $ZnCl_2$ at 120 °C for 30 min. in toluene (Scheme 39).

Scheme 39



Also, in the reaction of CuI (10 mol%)/PEG-400 reagent system[69] with 1-decyne **150a** and benzaldehyde **151a** at 100 °C for 12 h, the corresponding propargylamine **166a** was obtained in 67% yield with 99:1 dr. Using 1-heptyne **150b**, the corresponding propargylamine **166b** was obtained in 63% yield (99:1 dr). When the reaction was carried out using phenylacetylene **150c** under these conditions, the corresponding propargylamine **166c** was obtained in 86% yield with 99:1 dr (Scheme 40).

Scheme 40



Crystals suitable for single crystal X-ray analysis were obtained after recrystallization from CH_3CN/MeOH (1:1) solvent mixture. The absolute configuration at the newly formed chiral centre of propargylamine **166c** was found to be (*S*) by single crystal X-ray analysis. The ORTEP diagram of the propargylamine **166c** is shown in Figure 2.

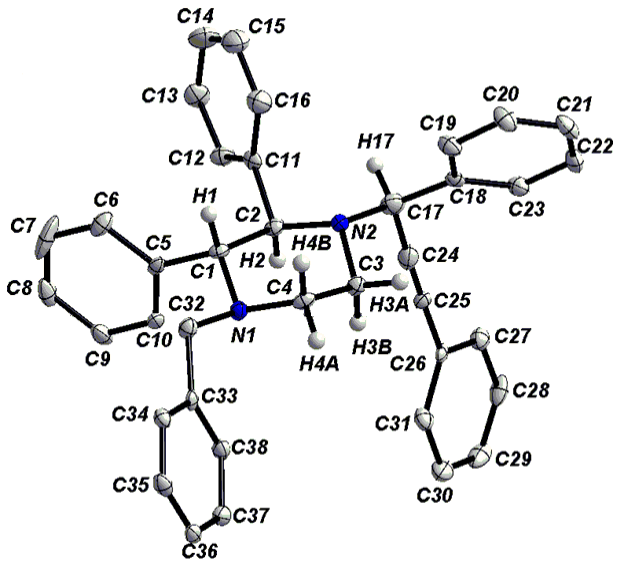


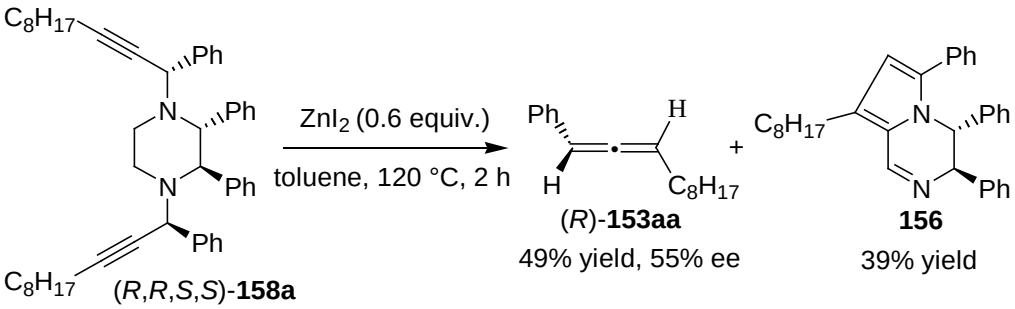
Figure 2. ORTEP diagram of **166c** showing thermal ellipsoid drawn at 30% probability. Another molecule **166c** and hydrogen atoms on the benzene rings have been omitted for clarity.

Table 4. Crystal data and structure refinement for compound 166c	
Identification code	**166c**
Empirical formula	C_{38} H_{34} N_2
Formula weight	518.67
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 15.001(3) Å, α = 90 ° b = 13.206(3) Å, β = 102.30(3) ° c = 15.517(3) Å, γ = 90 °
Volume	3003.5(10) $Å^3$
Z, Calculated density	4, 1.147 Mg M^{-3}
Absorption coefficient	0.066 mm^{-1}
F(000)	1104
Crystal size	0.40 x 0.30 x 0.20 mm
Theta range for data collection	1.34 to 25.00°
Limiting indices	-17≤h≤17, -15≤k≤15, -18≤l≤18
Reflections collected / unique	26544 / 10442 [R(int) = 0.0922]
Completeness to θ	25, 99.6%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10442 / 1 / 745
Goodness-of-fit on F^2	1.070
Final R indices [I>2σ (I)]	R1 = 0.0657, wR2 = 0.1604
R indices (all data)	R1 = 0.0915, wR2 = 0.1123
Largest diff. peak and hole	0.234 and -0.206 e. $Å^{-3}$

4.2.5 Chiral allenes from chiral propargylamines

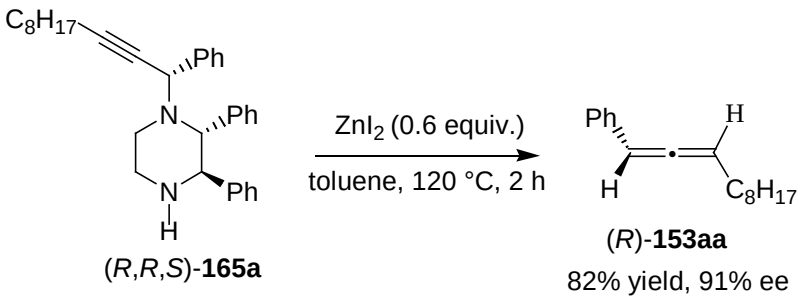
When a solution of the chiral dipropargylamine **158a** and ZnI_2 (0.6 equiv.) in toluene was refluxed at 120 °C under N_2 atmosphere for 2 h, the chiral (*R*)-allene **153aa** was obtained in 49% yield and 55% ee along with the intramolecular bicyclic product **156** in 39% yield (Scheme 41). This observation is in accordance with the mechanism of *in situ* formation of the bicyclic product **156** as outlined in Scheme 32.

Scheme 41



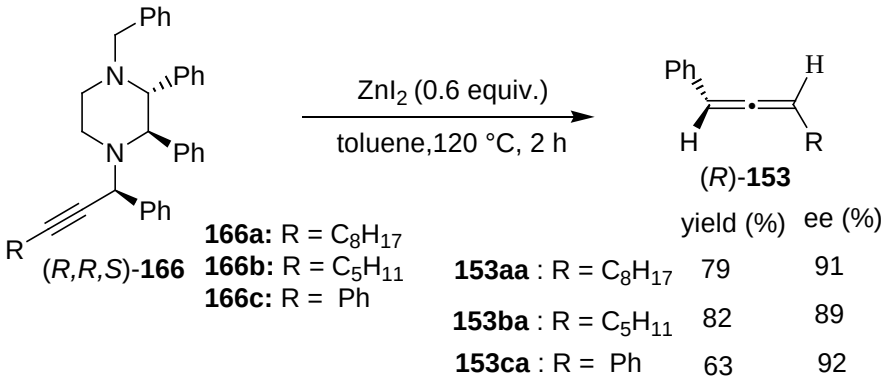
Also, when a solution of monopropargylamine (*R*,*R*,*S*)-**165a** and ZnI_2 (0.6 equiv.) in toluene was refluxed at 120 °C under N_2 atmosphere for 2 h, the chiral (*R*)-allene **153aa** was obtained in 82% yield and 91% ee without any bicyclic byproduct **156** as expected (Scheme 42).

Scheme 42



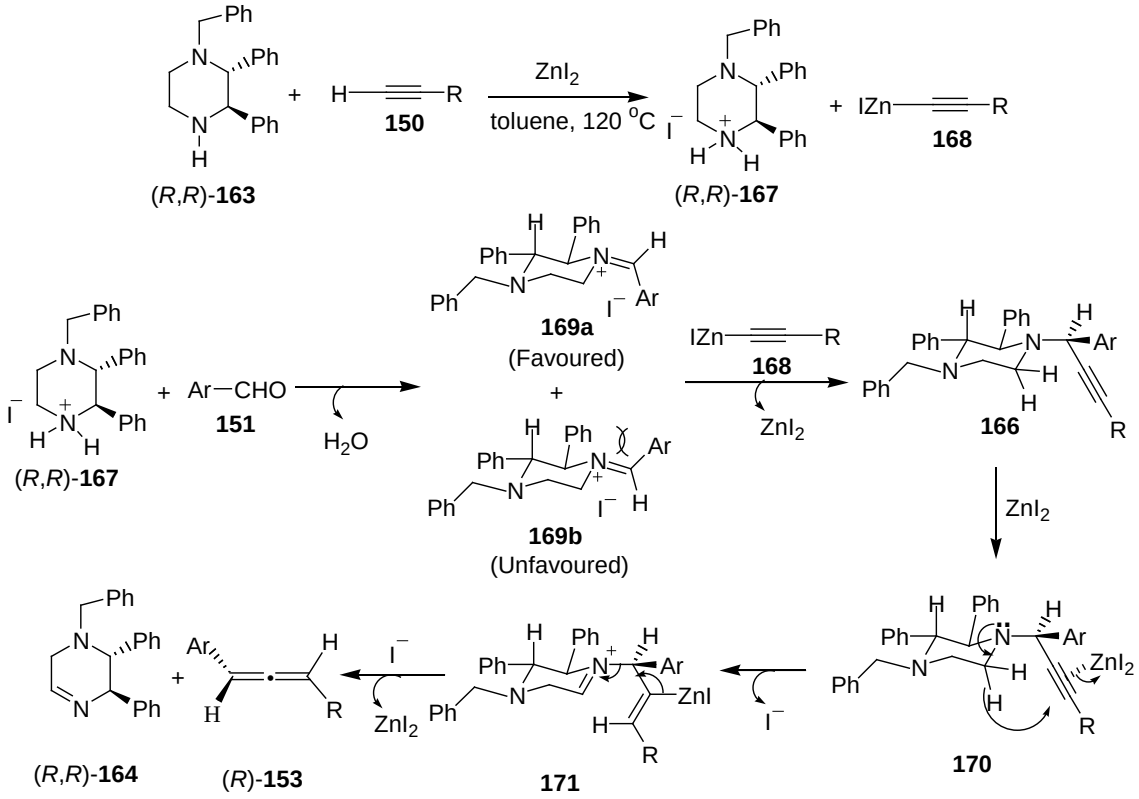
When a solution of the propargylamine (*R*,*R*,*S*)-**166a** and ZnI_2 (0.6 equiv.) in toluene was refluxed at 120 °C under N_2 atmosphere for 2 h, the chiral (*R*)-allene **153aa** was obtained in 79% yield and 91% ee (Scheme 43). Using the propargylamine (*R*,*R*,*S*)-**166b** and ZnI_2, the chiral (*R*)-allene **153ba** was obtained in 82% yield and 89% ee. Similarly, in the reaction using the propargylamine (*R*,*R*,*S*)-**166c**, the chiral (*R*)-allene **153ca** was obtained in 63% yield and 92% ee (Scheme 43).

Scheme 43



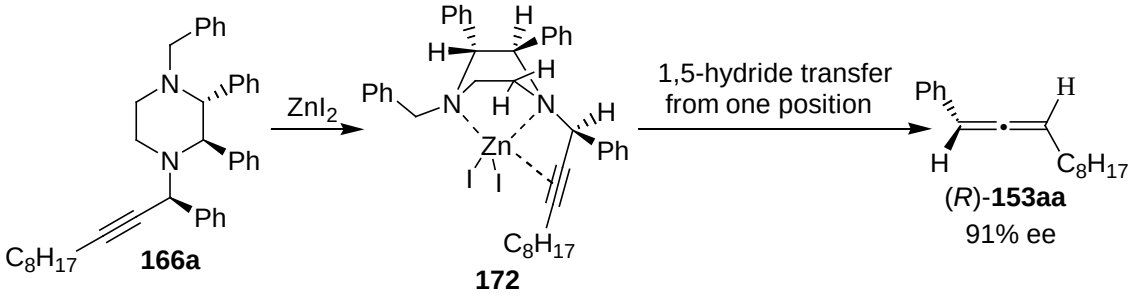
Based on the relative configuration of the chiral propargylamines (*R*,*R*,*S*,*S*)-**158c** and (*R*,*R*,*S*)-**166c** and previous understanding of this type of reactions,[39,61,70] a mechanism for the formation of the propargylamine and subsequent conversion to the chiral allene **153** could be considered as outlined in Scheme 44. The initially formed alkynyl zinc species **168** is expected to react with the most favoured *trans*-iminium ion **169a** formed *in situ*, in which the aryl group is far away from the phenyl group attached at the C3 position of **163,** to yield the corresponding propargylamine (*R*,*R*,*S*)-**166** and regenerate ZnI_2. Subsequently, the ZnI_2 complexation to the C≡C bond of (*R*,*R*,*S*)-**166** to form the intermediate **170** followed by a 1,5-hydride transfer[71] *via* a six membered transition state and β-elimination would afford the (*R*)-allene-**153** and tetrahydropyrazine **164**.

Scheme 44. Plausible reaction mechanism for the formation of (*R*)-allene 153



In this mechanistic pathway, the formation of (*R*)-allene **153** was explained by considering the propargylamine intermediate **166** with chair conformation (Scheme 44). However, the propargylamine intermediate with boat conformation **172** cannot be ruled out. In such a conformation, interaction of ZnI_2 with the C≡C bond and nitrogen centers of the propargylamine moiety **166a** is expected in the transition state **172** (Scheme 45).

Scheme 45

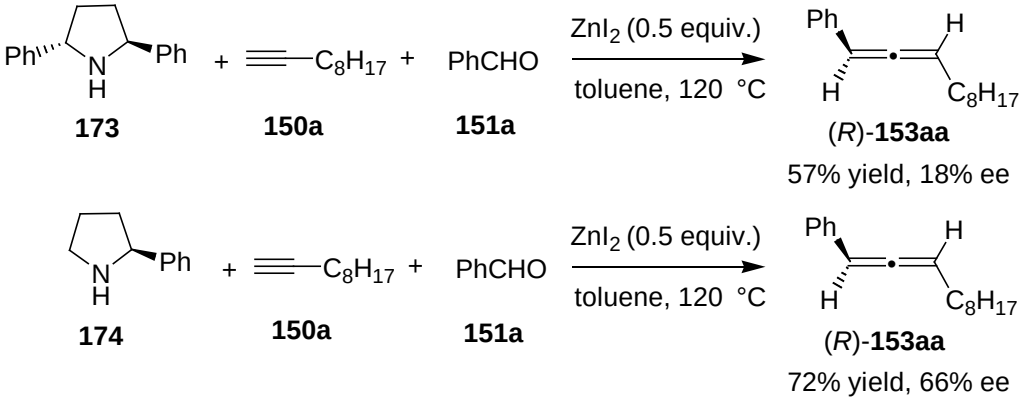


As discussed earlier, the chiral dipropargylamine **158a** gives the chiral (*R*)-allene **153aa** only in 55% ee upon reaction with ZnI_2 (Scheme 41) compared to the formation of allene **153aa** in 91% ee from the 1-benzyl-propargylamine **166a** (Scheme 43) as well as using the monopropargylamine **165a** (Scheme 42). Presumably, in the case of dipropargylamine intermediate **158a**, the corresponding transition state **172** may be in higher energy due to the greater steric requirement of the additional propargyl moiety, leading to the poor ee of the (*R*)-allene **153aa**.

We have also made efforts to prepare and characterize the ZnI_2-(*R*,*R*)-2,3-diphenylpiperazine **155a** complex. Though, a colourless solid material was isolated in the experiment, crystals suitable for the single crystal X-ray analysis could not be obtained.

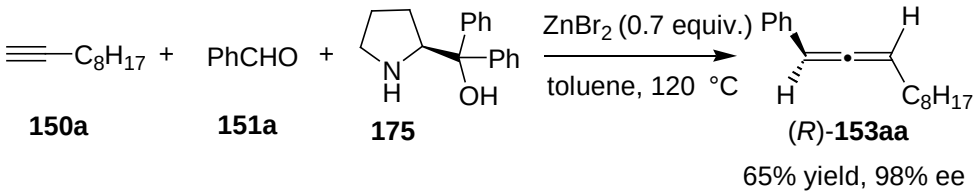
It has been observed in this laboratory that chiral pyrrolidine systems **173** and **174**, which do not have the second amine moiety give the allene **153aa** with poor enantioselectivity (Scheme 46).[72a]

Scheme 46



Also, it was found that the chiral allene **153aa** was obtained in 98% ee and 65% yield using $ZnBr_2$, 1-decyne **150a**, benzaldehyde **151a** and (*S*)-DPP **175** (Scheme 47).[72b]

Scheme 47



Presumably, the hydroxyl group present in the (*S*)-DPP **175** might help in interaction with $ZnBr_2$ and plays the role similar to that by the second nitrogen in the 1-benzyl-propargylamine **166a** (Scheme 45).

Further research efforts on the isolation of intermediate ZnI_2 complexes formed are necessary to understand the mechanism involved in this transformation.

4.3 Conclusions

We have developed a convenient and one pot method for the enantioselective synthesis of chiral allenes **153** by the reaction of commercially available terminal alkynes **150** and arylaldehydes **151** using readily accessible chiral (*R,R*)-2,3-diphenylpiperazine derivatives (**155a**, **163**) and zinc halides. When the reaction was carried out using (*R,R*)-1-benzyl-2,3-diphenylpiperazine **163**, the corresponding chiral allenes (*R*)-**153** were obtained up to 77% yield and >99% ee. As expected, when the opposite enantiomer (*S,S*)-1-benzyl-2,3-diphenylpiperazine **163** (57% ee) was used, the (*S*)-allene **153ba** was formed in 52% ee. The results are in accordance with the mechanism that, the reaction proceeds through the formation of propargylamine intermediates with creation of a new asymmetric centre and subsequent chirality transfer *via* an intramolecular hydride shift to produce chiral allenes with high enantiomeric purity.

The propargylamine intermediates **158c** and **166c** were isolated and the relative configuration at the newly formed chiral centres were found to be (*S*) by single crystal X-ray analysis. Since this reaction procedure involves an enantioselective synthesis of chiral allenes *via* a single pot synthetic operation in short reaction time, by using readily accessible chiral reagents such as (*R,R*)-2,3-diphenylpiperazine derivatives and commercially available starting materials like 1-alkynes, arylaldehydes and ZnX_2, this methodology has considerable potential for further synthetic exploitation, especially for use as building blocks for the synthesis of new chiral molecular skeletons.

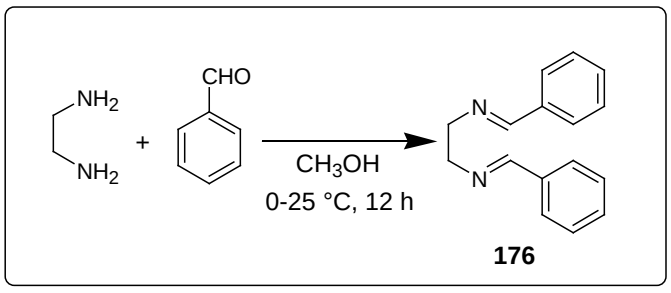
4.4 Experimental Section

4.4.1 General Information

Several details given in the experimental section 1.4 of Chapter 1 are also applicable for the experiments outlined in this section. Analytical grade $ZnCl_2$, ZnI_2, CuBr, CuI reagents were purchased from Sigma-Aldrich. PEG-400 was purchased from E-Merck, India.

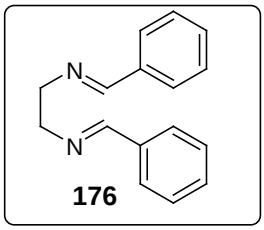
4.4.2 Preparation of diimine 176

To a solution of benzaldehyde (10.14 mL, 100 mmol) in methanol (80 mL) ethylenediamine (3.61 g, 4.0 mL, 60 mmol) was slowly added at 0 °C in 10 min. The contents were brought to 25 °C and stirred for 12 h. The solvent and the excess ethylenediamine were evaporated under reduced pressure. To the residue, CH_2Cl_2 (100 mL) was added, dried using anhydrous K_2CO_3 and filtered. The solvent was evaporated from the filtrate under reduced pressure. The diimine **176** obtained in this way was used in further reactions.



176

***N,N'*-Dibenzylidineethane-1,2-diamine**



176

Yield 11.3 g (95%)

mp 38-40 °C (lit.[73] 37-39 °C)

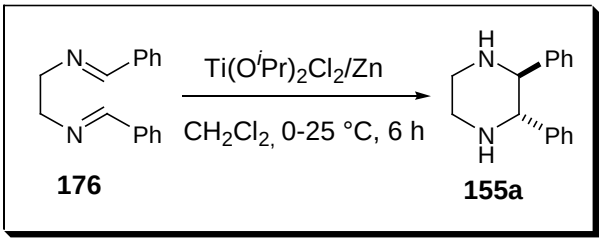
IR (KBr) (cm^{-1}) 3028, 2914, 2856, 1649, 1597

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 8.29 (s, 2H), 7.66-7.72 (m, 4H), 7.35-7.40 (m, 6H), 3.97 (s, 4H)

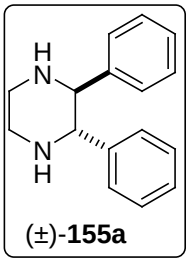
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 162.7, 136.2, 130.6, 128.6, 128.1, 61.7

4.4.3 Procedure for the intramolecular reductive coupling of diimine 176 using Zn and $Ti(O^iPr)_2Cl_2$

To a $TiCl_4$ (1.04 g, 0.60 mL, 5.5 mmol) solution in CH_2Cl_2 (40 mL), $Ti(O^iPr)_4$ (1.56 g, 5.5 mmol) was added under nitrogen atmosphere and stirred for 10-15 min. To this, activated zinc powder (1.65 g, 25.0 mmol) was added in three portions and the stirring was continued for another 1 h. The diimine **176** (1.18 g, 5.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added in drops through a dropping funnel at 0 °C for 20 min. After the addition was completed, the reaction mixture was stirred at 25 °C for 5-6 h. It was poured into saturated aqueous K_2CO_3 solution at 0 °C and filtered. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with water, brine and dried over anhydrous K_2CO_3. The solvent was evaporated and the product **155a** was purified by flash column chromatography (Silica gel, 100-200 mesh, $CHCl_3$ and then $CHCl_3$:CH_3OH-90:10).



(±)-2,3-Diphenylpiperazine



Yield 83% (0.99 g)

mp 94-96 °C (lit.[74] 96-98 °C)

IR (KBr) (cm^{-1}) 3318, 3280, 3030, 2949, 2820, 1603

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.02-7.12 (m, 10H), 3.72 (s, 2H), 3.15 (s, 4H), 2.00 (br s, 2H) (**Spectrum No. 23**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 149.7, 123.0, 129.3, 128.1, 67.7, 46.9 (**Spectrum No. 24**)

MS (EI) *m/z* 238 (M+1)

4.4.4 Resolution of (±)-2,3-diphenylpiperazine 155a using (1*S*)-(+)-10-camphorsulfonic acid 20

The (1*S*)-(+)-10-camphorsulfonic acid **20** (4.64 g, 20 mmol) and (±)-2,3-diphenylpiperazine **155a** (2.4 g, 10 mmol) were taken in CH_2Cl_2 (100 mL) and the contents were stirred at 25 °C for 24 h and filtered. The precipitate (I) obtained in this way was suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enantio-enriched (*R*,*R*)-**155a**. The filtrate was concentrated to reduce its volume to 50

mL and stirred for another 12 h and filtered. The precipitate (II) obtained in this way was suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enantio-enriched (*S*,*S*)-**155a**. The filtrate was stirred with aq. Na_2CO_3 (2M) for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enantio-enriched (*R*,*R*)-**155a**.

After decomposition

From precipitate (I)

(*R*,*R*)-2,3-Diphenylpiperazine

Yield 0.60 g (25%)

ee 99%, HPLC analysis (Chiralcel OD-H column, Hexane:IPA = 90:10, Flow rate: 0.5 mL/min, 254 nm, Retention time for the enantiomer of (±)-2,3-diphenylpiperazine is 11.88 min. (*S*,*S*) and 14.7 min. (*R*,*R*) isomer.

From precipitate (II)

(*S*,*S*)-2,3-Diphenylpiperazine

Yield 1.50 g (63%)

ee 73% ee (by HPLC analysis)

From filtrate (II)

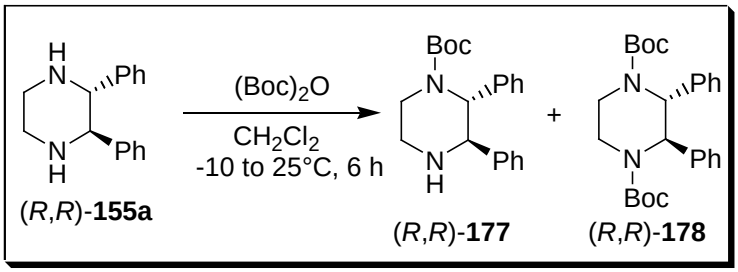
(*R*,*R*)-2,3-Diphenylpiperazine

Yield 0.24 g (10%)

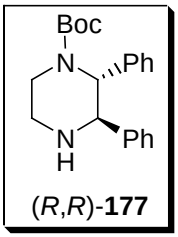
ee 80% ee (by HPLC analysis)

4.4.5 Synthesis of (*R*,*R*)-*tert*-butyl 2,3-diphenyl-1-piperazinecarboxylate 177

To a solution of (*R*,*R*)-2,3-diphenylpiperazine **155a** (2.40 g, 10 mmol) in CH_2Cl_2 (40 mL), di-*tert*-butyldicarbonate (1.8 mL, 8 mmol) was added at -10 °C (ice-salt bath) slowly for 10 min using a syringe under N_2 atmosphere. The reaction mixture was brought to 25 °C slowly and further stirred for 6 h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. The desired product **177** was purified by column chromatography on silica gel (100-200 mesh) using hexanes/EtOAc (50/50) as eluent to obtain a colourless viscous liquid. The product **178** was isolated as colourless solid by using hexanes/EtOAc (80/20) as eluent.



***tert*-Butyl-(2*R*,3*R*)-2,3-diphenyl-1-piperazinecarboxylate**



Yield 2.67 g (79%)

$[\alpha]_D^{25}$ +14.0 (*c* 1.1, $CHCl_3$)

IR (neat) (cm^{-1}) 3337, 2974, 1684, 1413, 1167, 698

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.41 (d, *J* = 7.5 Hz, 2H), 7.34-7.22 (m, 8H),

5.43 (d, *J* = 3.5 Hz, 1H), 4.39 (d, *J* = 3.5 Hz, 1H), 3.96-3.93 (m, 1H), 3.35-3.29 (m, 1H), 3.02-2.97 (m, 1H), 2.81-2.78 (m, 1H), 1.88 (s, 1H), 1.38 (s, 9H) (**Spectrum No. 25**)

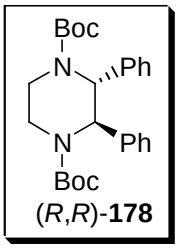
^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 155.5, 141.2, 140.8, 128.3, 128.27, 127.7, 127.2, 126.8, 126.79, 80.0, 59.4, 58.0, 40.3, 40.1, 28.2 (**Spectrum No. 26**)

LCMS *m/z* 339 (M+1)

Analysis calculated for $C_{21}H_{26}N_2O_2$: C, 74.52%; H, 7.74%; N, 8.28%; O, 9.45%; Found: C, 74.46%; H, 7.68%; N, 8.15%; O, 9.71%

Di-(*tert*-Butyl)-(2*R*,3*R*)-2,3-diphenyl-1,4-piperazinedicarboxylate

Yield 0.350 g (8%)



(*R*,*R*)-**178**

mp 108-109 °C

$[\alpha]_D^{25}$ -60.0 (*c* 1.03, $CHCl_3$)

IR (neat) (cm^{-1}) 3061, 2974, 2876, 1693, 1413, 698

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.43-7.29 (m, 10H), 6.08-5.82 (m, 2H), 3.89-3.62 (m, 2H), 3.16-2.94 (m, 2H), 1.45-1.43 (m, 18H)

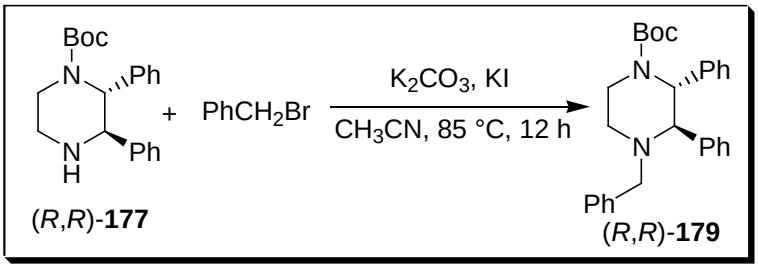
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 154.8, 139.4, 128.7, 127.3, 126.7, 80.4, 56.1, 39.7, 28.3

LCMS *m/z* 439 (M+1)

Analysis calculated for $C_{26}H_{34}N_2O_4$: C, 71.21%; H, 7.81%; N, 6.39%; O, 14.59%; Found: C, 71.32%; H, 7.78%; N, 6.45%; O, 14.45%

4.4.6 Procedure for the synthesis of (*R*,*R*)-*tert*-butyl-4-benzyl-2,3-diphenyl-1-piperazinecarboxylate 179 from (*R*,*R*)-177

To a solution of (*R*,*R*)-*tert*-butyl-2,3-diphenyl-1-piperazinecarboxylate **177** (3.38 g, 10 mmol) in dry acetonitrile (50 mL), benzyl bromide (1.3 mL, 11 mmol), K_2CO_3 (2.8 g, 20 mmol) and KI (200 mg) were added. The mixture was stirred at 85 °C for 12 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The product was extracted with CH_2Cl_2 (2 X 40 mL) and water (20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and purification of the residue by column chromatography on silica gel (100-200 mesh) using hexane/EtOAc (95/5) as eluent afforded the product (*R*,*R*)-**179** as colourless viscous liquid.



(*R*,*R*)-**177** (*R*,*R*)-**179**

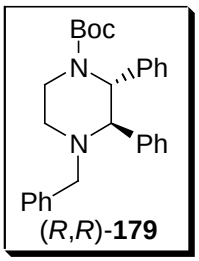
(*R*,*R*)-*tert*-butyl-4-benzyl-2,3-diphenyl-1-piperazinecarboxylate

Yield 4.06 g (95%)

$[\alpha]_D^{25}$ +20.0 (*c* 0.52, $CHCl_3$)

IR (neat) (cm^{-1}) 3061, 2974, 1693, 1365, 864, 700

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.51-7.49 (m, 2H), 7.36-



(*R*,*R*)-**179**

7.23 (m, 13H), 5.32-5.26 (m, 1H), 4.14-4.13 (m, 1H), 4.03-3.99 (m, 1H), 3.51-3.40 (m, 2H), 3.35-3.29 (m, 1H), 2.95-2.89 (m, 1H), 2.52-2.48 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 9H) (**Spectrum No. 27**)

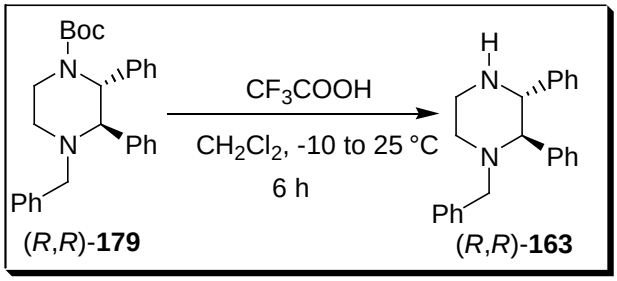
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 155.4, 141.9, 138.9, 138.6, 129.2, 128.7, 128.2, 128.0, 127.5, 127.0, 126.8, 80.0, 65.2, 59.3, 59.1, 45.3, 40.6, 28.3 (**Spectrum No. 28**)

LCMS *m/z* 429 (M+1)

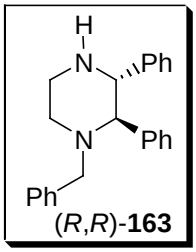
Analysis calculated for $C_{28}H_{32}N_2O_2$: C, 78.47%; H, 7.53%; N, 6.54%; O, 7.47%; Found: C, 78.42%; H, 7.62%; N, 6.48%; O, 7.49%

4.4.7 Procedure for the synthesis of (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163

To a solution of (*R*,*R*)-*tert*-butyl-4-benzyl-2,3-diphenyl-1-piperazinecarboxylate **179** (4.28 g, 10 mmol) in dry CH_2Cl_2 (25 mL) in a round bottomed flask, excess trifluoroacetic acid (25 mL) was added slowly using a syringe for 15 min under N_2 atmosphere. The resulting mixture was stirred at 25 °C for 6 h. The reaction mixture was evaporated and then poured to premixed solid sodium bicarbonate with few pieces of ice. The product was extracted with CH_2Cl_2 (2 X 40 mL) and water (20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated and purification of the residue by column chromatography on silica gel (100-200 mesh) using hexanes/EtOAc (50/50) as eluent afforded the (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** as colourless solid.



(*R*,*R*)-1-benzyl-2,3-diphenylpiperazine



Yield 3.05 g (93%)

mp 128-129 °C

$[\alpha]_D^{25}$ +81.0 (*c* 0.71, $CHCl_3$)

IR (KBr) (cm^{-1}) 3285, 3030, 2941, 1601, 1321, 760, 698

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.28-7.01 (m, 15H), 3.79-3.75 (m, 2H), 3.27-3.25 (m, 1H), 3.13-3.03 (m, 2H), 2.96-2.87 (m, 2H), 2.37-2.31 (m, 1H), 1.99 (s, 1H) (**Spectrum No. 29**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 141.6, 140.6, 139.2, 128.7, 128.1, 128.0, 127.8, 127.7, 127.1, 126.9, 126.6, 74.6, 68.7, 59.5, 52.3, 46.3 (**Spectrum No. 30**)

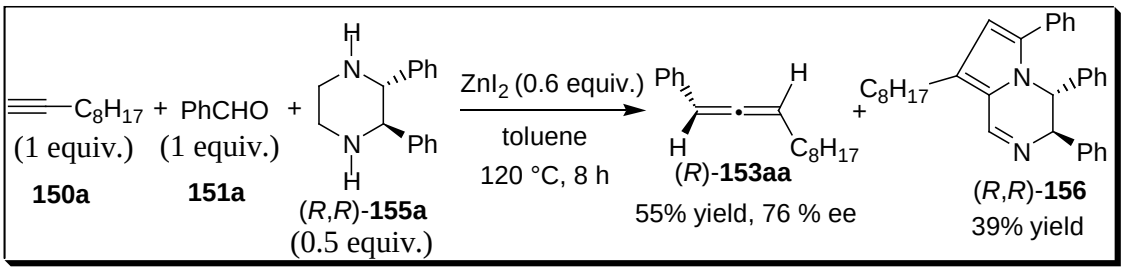
LCMS *m/z* 329 (M+1)

Analysis calculated for $C_{23}H_{24}N_2$: C, 84.11%; H, 7.37%; N, 8.53%; Found: C, 84.21%; H, 7.29%; N, 8.45%

ee >99%, HPLC analysis (Chiralcel OD-H column, Hexane:IPA = 80:20, Flow rate: 0.3 mL/min, 254 nm, Retention time for the enantiomer of (±)-1-benzyl-2,3-diphenylpiperazine **163** : 14.57 min. (*S*,*S*) and 18.38 min. (*R*,*R*) isomer

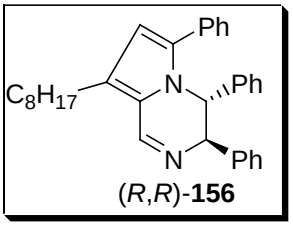
4.4.8 Reaction of (*R*,*R*)-2,3-diphenylpiperazine 155a, 1-decyne 150a and benzaldehyde 151a with ZnI_2 : Isolation of bicyclic product 156

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (5 mL), ZnI_2 (192 mg, 0.6 mmol), 1-decyne **150a** (0.18 mL, 1 mmol) and (*R*,*R*)-2,3-diphenylpiperazine **155a** (0.119 g, 0.5 mmol) were placed under N_2 atmosphere and stirred at 120 °C for 10-15 min. The reaction mixture was cooled to 25 °C and benzaldehyde **151a** (0.10 mL, 1 mmol) was added using a syringe. The reaction mixture was further stirred at 120 °C for 8 h. It was cooled to 25 °C under N_2 atmosphere. The product (*R*)-1,3-disubstituted allene **153aa** was purified directly by column chromatography on silica gel (100-200 mesh) using hexanes as eluent in 55% yield (0,125 g) and 76% ee (by HPLC analysis). The bicyclic byproduct **156** was isolated using hexanes/EtOAc (85/15) as eluent as colourless viscous liquid.



(3*R*,4*R*)-8-Octyl-3,4,6-triphenyl-3,4-dihydropyrrolo[1,2-a]pyrazine

Yield 0.179 g (39%)



$[\alpha]_D^{25}$ +45.0 (*c* 0.25, $CHCl_3$)

IR (neat) (cm^{-1}) 3059, 3026, 1604, 1462, 1379, 1030

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 8.52 (s, 1H), 7.31-7.19 (m, 11H), 7.0 (d, *J* = 4.2 Hz, 2H), 6.8 (d, *J* = 8.0 Hz, 2H), 6.23 (s, 1H), 5.45 (s, 1H), 5.38 (s, 1H), 2.74 (t, *J* = 6.2 Hz, 2H), 1.72-1.67 (m, 2H), 1.42-1.30 (m, 10H), 0.93-0.88 (m, 3H) (**Spectrum No. 31**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 150.3, 141.5, 140.6, 137.5, 131.2, 128.7, 128.6, 128.4, 128.2, 127.6, 127.5, 127.4, 126.8, 125.3, 123.2, 111.1, 68.3, 60.2, 31.8, 31.5, 29.4, 29.3, 29.28, 25.2, 22.7, 14.1 (**Spectrum No. 32**)

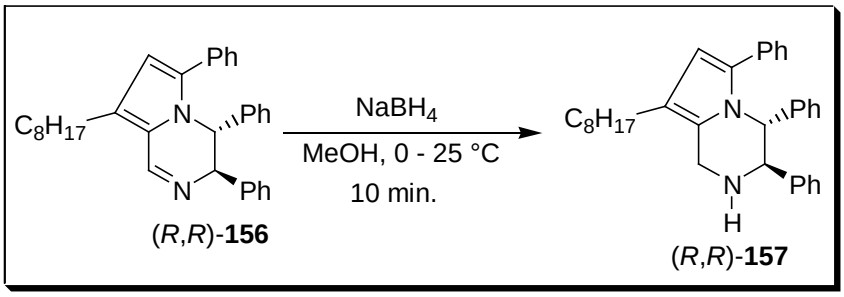
LCMS *m/z* 461 (M+1)

Analysis calculated for $C_{33}H_{36}N_2$: C, 86.04%; H, 7.88%; N, 6.08%; Found: C, 86.21%; H, 7.81%; N, 5.90%

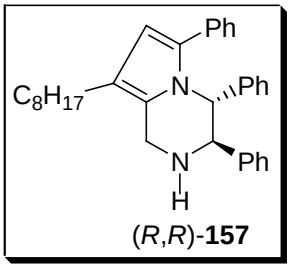
4.4.9 Reduction of (3*R*,4*R*)-8-octyl-3,4,6-triphenyl-3,4-dihydropyrrolo[1,2-a]pyrazine 156 using the $NaBH_4$/MeOH reagent system

To a stirred solution of (*R*,*R*)-**156** (230 mg, 0.5 mmol) in methanol (5 mL) in a 25 mL round bottomed flask, $NaBH_4$ (0.038 g, 1 mmol) was added slowly at 0 °C. The reaction mixture was further stirred at 25 °C for 10 min. It was quenched with water (10 mL). The solvent was evaporated under reduced pressure. To the residue, EtOAc (15 mL) and water (10 mL) were added and stirred for 15 min. The organic layer was separated and the remaining aqueous layer was extracted with EtOAc (10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated at reduced pressure. The crude residue

was purified by column chromatography on silica gel (100-200 mesh) using hexanes/EtOAc (95/5) as eluent to isolate the product (*R*,*R*)-**157** as colourless viscous liquid.



(3*R*,4*R*)-8-Octyl-3,4,6-triphenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine



Yield 0.219 g (95%)

$[\alpha]_D^{25}$ +82.6 (*c* 0.12, $CHCl_3$)

IR (neat) (cm^{-1}) 3271, 2920, 1604, 1450, 908, 698

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.26-7.21 (m, 6H), 7.05-7.02 (m, 7H), 6.60-6.59 (m, 2H), 6.09 (s, 1H), 5.53-5.51 (m, 1H), 4.11-4.07 (m, 2H), 3.99-3.95 (m, 1H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.08 (br s, 1H), 1.60-1.56 (m, 2H), 1.31-1.28 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H)

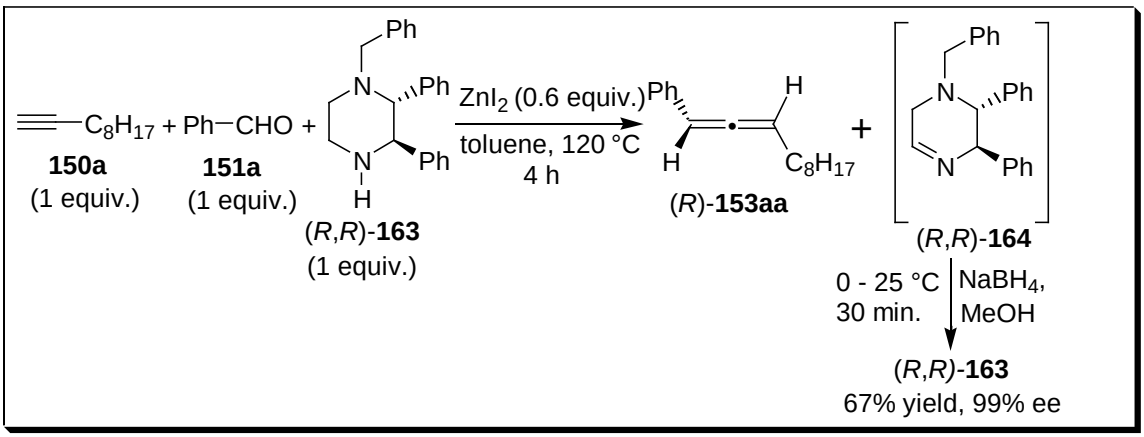
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 142.6, 140.3, 133.9, 132.9, 128.7, 128.5, 128.1, 127.9, 127.8, 127.7, 127.0, 126.6, 126.1, 124.8, 118.1, 109.7, 64.8, 61.4, 40.4, 32.0, 30.9, 29.6, 29.57, 29.5, 25.7, 22.8, 14.2

LCMS *m/z* 461 (M-1)

Analysis calculated for $C_{33}H_{38}N_2$: C, 85.67%; H, 8.28%; N, 6.05%; Found: C, 85.87%; H, 7.25%; N, 5.90%

4.4.10 Reduction of the imine byproduct 164 formed *in situ* in the reaction of (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163 with 1-decyne 150a, benzaldehyde 151a and ZnI_2

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (5 mL), ZnI_2 (0.192 g, 0.6 mmol), 1-decyne **150a** (0.18 mL, 1 mmol) and (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** (0.328 g, 1 mmol) were taken under N_2 atmosphere and stirred at 120 °C for 10 min. The mixture was brought to 25 °C and benzaldehyde **151a** (0.10 mL, 1 mmol) was added using a syringe. The reaction mixture was further stirred at 120 °C for 4 h. It was brought to 0 °C. Methanol (5 mL) and $NaBH_4$ (0.038 g, 1 mmol) was added to it and stirred for 30 min. at 25 °C. The reaction mixture was chromatographed directly on a silica gel (100-200 mesh) column to isolate the allene (*R*)-**153aa** in 65% yield (0.148 g) and 95% ee (by HPLC analysis) using hexanes as eluent. The starting amine (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** was isolated using hexanes/EtOAc (50/50) as eluent in 67% yield (0.221 g) without any significant change in its enantiomeric purity (HPLC analysis).

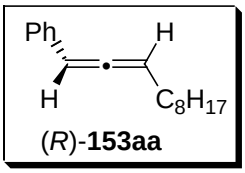


4.4.11 Reaction of (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163 with 1-alkynes 150, arylaldehydes 151 and ZnI_2 : Synthesis of chiral (*R*)-allenes 153

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (2.5 mL), ZnI_2 (0.096 g, 0.3 mmol), 1-alkyne **150** (0.5 mmol) and (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** (0.164 g, 0.5 mmol) were taken under N_2 atmosphere and the contents were stirred at 120 °C for 10-15 min. The reaction mixture was cooled to 25 °C and aryl aldehyde **151** (0.5 mmol) was added using a syringe. It was further stirred at 120 °C for the required time (Table 2, Section 4.2) and the reaction mixture was brought to 25 °C. The product (*R*)-allene **153** was isolated directly by column chromatography on a silica gel (100-200 mesh) column using hexanes or hexanes/EtOAc as eluent. The % ee was determined by HPLC analysis using either Chiralcel-OD-H or OJ-H column using IPA/n-hexane as eluent. The yields and spectral data of the (*R*)-allenes **153** are summarized below.

(*R*)-1-Phenyl-1,2-undecadiene

Colourless oil (eluent: silica gel 100-200 mesh, hexanes)



(*R*)-**153aa**

Yield 0.081 g (71%)

$[\alpha]_D^{25}$ -146.5 (*c* 0.78, EtOH)

IR (neat) (cm^{-1}) 2926, 2853, 1950, 1597, 1028, 690

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.29-7.28 (m, 4H), 7.20-7.15 (m, 1H), 6.13-6.10 (m, 1H), 5.58-5.53 (m, 1H), 2.15-2.09 (m, 2H), 1.52-1.44 (m, 2H), 1.29-1.25 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.1, 135.1, 128.5, 126.6, 126.5, 95.1, 94.5, 31.8, 29.4, 29.3, 29.2, 29.1, 28.7, 22.7, 14.1

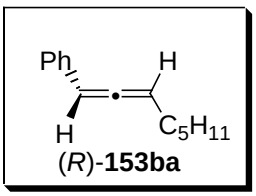
LCMS *m/z* 227 (M-1)

Analysis calculated for $C_{17}H_{24}$: C 89.41%; H, 10.59%; Found: C, 89.32%; H, 10.71%

ee 95%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 13.1 min. (*R* isomer) and 14.8 min. (*S* isomer)

(*R*)-1-Octa-1,2-dienyl-benzene

Colourless oil (eluent: silica gel 100-200 mesh, hexanes)



(*R*)-**153ba**

Yield 0.06 g (65%)

$[\alpha]_D^{25}$ -198.2 (*c* 0.4, $CHCl_3$)

IR (neat) (cm^{-1}) 3067, 2957, 2928, 2856, 1948, 1599, 1460, 775

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.30-7.29 (m, 4H), 7.21-7.15 (m, 1H), 6.13-6.10 (m, 1H), 5.59-5.54 (m, 1H), 2.16-2.09 (m, 2H), 1.51-1.45 (m, 2H), 1.37-1.27 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) (**Spectrum No. 33**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.2, 135.2, 128.5, 126.8, 126.6, 95.1, 94.5, 31.4, 28.9, 28.7, 22.4, 14.0 (**Spectrum No. 34**)

LCMS *m/z* 185 (M-1)

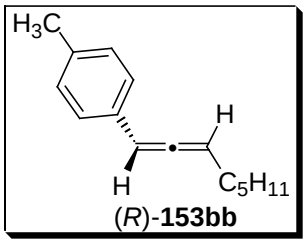
Analysis calculated for $C_{14}H_{18}$: C, 90.26%; H, 9.74%. Found: C, 90.50%; H, 9.79%

ee 94%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 10.4 min. (*R* isomer) and 11.7 min. (*S* isomer)

(*R*)-1-Methyl-4-(1,2-octadienyl)-benzene

Colourless oil (eluent: hexanes)

Yield 0.061 g (61%)



(*R*)-**153bb**

$[\alpha]_D^{25}$ -234.0 (*c* 0.41, $CHCl_3$)

IR (neat) (cm^{-1}) 3022, 2926, 1948, 1512, 1464, 819

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.17 (d, *J* = 10 Hz, 2H), 7.08 (d, *J* = 10.1 Hz, 2H), 6.10-6.07 (m, 1H), 5.55-5.48 (m, 1H), 2.31 (s, 3H), 2.13-2.08 (m, 2 H), 1.50-1.44 (m, 2H), 1.37-1.30 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) (**Spectrum No. 35**)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 204.9, 136.2, 132.2, 129.2, 126.5, 94.9, 94.3, 31.4, 28.8, 28.79, 22.4, 21.1, 14.0 (**Spectrum No. 36**)

LCMS *m/z* 201 (M+1)

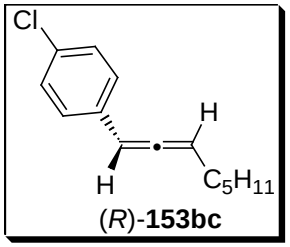
Analysis calculated for $C_{15}H_{20}$: C, 89.94%, H, 10.06%; Found: C, 89.87%; H, 9.98%

ee 90%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 19.1 min. (*R* isomer) and 21.4 min. (*S* isomer)

(*R*)-1-Chloro-4-(1,2-octadienyl)-benzene

Colourless oil (eluent: hexanes)

Yield 0.085 g (77 %)



(*R*)-**153bc**

$[\alpha]_D^{25}$ -185.5 (*c* 0.5, $CHCl_3$)

IR (neat) (cm^{-1}) 3030, 2856, 1950, 1491, 877

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.25-7.19 (m, 4H), 6.08-6.06 (m, 1H), 5.59-5.55 (m, 1H), 2.14-2.09 (m, 2H), 1.50-1.44 (m, 2H), 1.35-1.28 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 205.2, 133.7, 132.1, 128.6, 127.7, 95.5, 93.7, 31.4, 28.8, 28.6, 22.4, 14.0

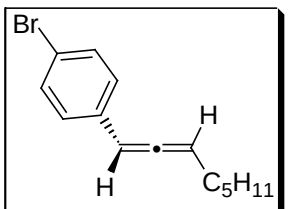
LCMS *m/z* 221 (M+1)

Analysis calculated for $C_{14}H_{17}Cl$: C, 76.18%, H, 7.76%, Cl, 16.06%. Found: C, 76.25%; H, 7.73%; Cl, 15.89%

ee >99%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 10.2 min. (*R* isomer) and 12.7 min. (*S* isomer)

(*R*)-1-Bromo-4-(1,2-octadienyl)-benzene

Colourless oil (eluent: hexanes)



(*R*)-**153bd**

Yield 0.094 g (71 %)

$[\alpha]_D^{25}$ -150.0 (*c* 0.5, $CHCl_3$)

IR (neat) (cm^{-1}) 2924, 1948, 1487, 1589, 1385, 1010

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.41-7.39 (m, 2H), 7.15-7.13 (m, 2H), 6.07-6.04 (m, 1H), 5.58-5.54 (m, 1H), 2.14-2.09 (m, 2H), 1.50-1.44 (m, 2H), 1.35-1.30 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 205.3, 134.3, 131.6, 128.1, 120.1, 95.6, 93.8, 31.4, 28.8, 28.6, 22.4, 14.0

LCMS *m/z* 266 (M+1)

Analysis calculated for $C_{14}H_{17}Br$: C, 63.41%; H, 6.46%; Br, 30.13%; Found: C, 63.31%; H, 6.53%; Br, 30.16%

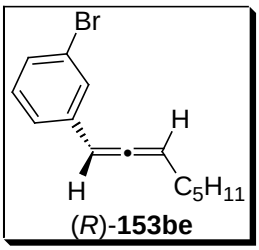
ee >99%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 14.7 min. (*R* isomer) and 19.9 min. (*S* isomer)

(*R*)-1-Bromo-3-octa-1,2-dienyl-benzene

Colourless oil (eluent: hexanes)

Yield 0.075 g (57 %)

$[\alpha]_D^{25}$ -79.0 (*c* 0.48, $CHCl_3$)



(*R*)-**153be**

IR (neat) (cm^{-1}) 2959, 2858, 1950, 1589, 1068, 883, 785

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.43 (s, 1H), 7.42-7.28 (m, 1H), 7.20-7.12 (m, 2H), 6.06-6.03 (m, 1H), 5.62-5.57 (m, 1H), 2.16-2.10 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.29 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) (**Spectrum No. 37**)

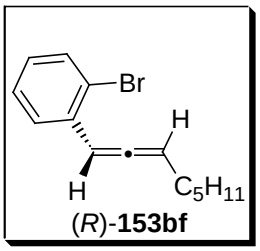
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.4, 137.6, 130.0, 129.5, 129.3, 125.1, 122.7, 95.7, 93.5, 31.4, 28.7, 28.6, 22.4, 14.1 (**Spectrum No. 38**)

LCMS *m/z* 266 (M+1)

Analysis calculated for $C_{14}H_{17}Br$: C, 63.41%; H, 6.46%; Br, 30.13%; Found: C, 63.31%; H, 6.53%; Br, 30.16%

ee 92%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 12.3 min. (*R* isomer) and 13.9 min. (*S* isomer)

(*R*)-1-Bromo-2-octa-1,2-dienyl-benzene



(*R*)-**153bf**

Colourless oil (eluent: hexanes)

Yield 0.087 g (66 %)

$[\alpha]_D^{25}$ -81.0 (*c* 0.5, $CHCl_3$)

IR (neat) (cm^{-1}) 3061, 2926, 1950, 1473, 1022, 760

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.51 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.04-7.0 (m, 1H), 6.58-6.55 (m, 1H), 5.62-5.57 (m, 1 H), 2.16-2.10 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.29 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) (**Spectrum No. 39**)

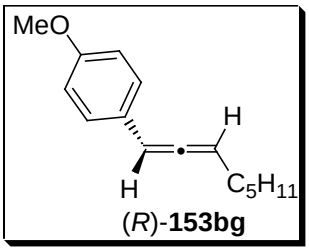
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 206.1, 134.5, 132.9, 128.2, 127.9, 127.3, 122.3, 95.3, 93.6, 31.4, 28.8, 28.5, 22.4, 14.1 (**Spectrum No. 40**)

LCMS *m/z* 266 (M+1)

Analysis calculated for $C_{14}H_{17}Br$: C, 63.41%; H, 6.46%; Br, 30.13%; Found: C, 63.31%; H, 6.53%; Br, 30.16%

ee 90%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, Flow rate: 0.5 mL/min, 254 nm, Retention time: 13.5 min. (*R* isomer) and 16.9 min. (*S* isomer)

(*R*)-1-Methoxy-4-(1,2-octadienyl)-benzene



(*R*)-**153bg**

Colourless oil (eluent: hexanes/EtOAc-99.75/0.25)

Yield 0.062 g (58%)

$[\alpha]_D^{25}$ -130.7 (*c* 0.48, $CHCl_3$)

IR (neat) (cm^{-1}) 2928, 2856, 1946, 1606, 1510, 1246, 833

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 7.22 (d, *J* = 5.1 Hz, 2H), 6.85 (d, *J* = 4.1 Hz, 2H), 6.09-6.07 (m, 1H), 5.56-5.52 (m, 1H), 3.80 (s, 3H), 2.13-2.08 (m, 2H), 1.50-1.43 (m, 2H), 1.36-1.29 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H)

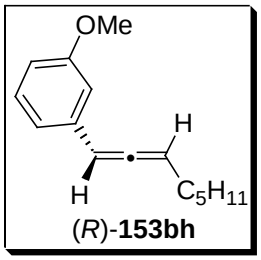
^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 204.5, 158.5, 127.6, 127.5, 114.1, 95.0, 93.9, 55.3, 31.4, 28.9, 22.5, 14.0

LCMS *m/z* 217 (M+1)

Analysis calculated for $C_{15}H_{20}O$: C, 83.28%; H, 9.32%; O, 7.40%; Found: C, 83.32%; H, 9.21%; O, 7.47%

ee 76%, HPLC analysis (Chiralcel OJ-H column, n-Hexane:IPA = 99.75:0.25, Flow rate: 0.4 mL/min, 254 nm, Retention time: 28.7 min. (*R* isomer) and 32.2 min. (*S* isomer)

(*R*)-1-Methoxy-3-octa-1,2-dienyl-benzene



(*R*)-**153bh**

Colourless oil (eluent: hexanes)

Yield 0.059 g (55%)

$[\alpha]_D^{25}$ -87.0 (*c* 0.42, $CHCl_3$)

IR (neat) (cm^{-1}) 2928, 2856, 1948, 1599, 1491, 1466, 1047, 883

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.28-7.22 (m, 1H), 6.92-6.88 (m, 2H), 6.78-6.76 (m, 1H), 6.14-6.11 (m, 1H), 5.60-5.59 (m, 1H), 3.83 (s, 3H), 2.19-2.12 (m, 2H), 1.58-1.48 (m, 2H), 1.40-1.34 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H)

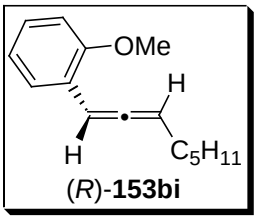
^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 205.2, 159.9, 136.7, 129.5, 119.3, 112.4, 111.7, 95.2, 94.5, 55.2, 31.4, 28.9, 28.7, 22.5, 14.1

LCMS *m/z* 217 (M+1)

Analysis calculated for $C_{15}H_{20}O$: C, 83.28%; H, 9.32%; O, 7.40%; Found: C, 83.32%; H, 9.21%; O, 7.47%

ee 90%, HPLC analysis (Chiralcel OJ-H column, n-Hexane:IPA = 99.75:0.25, Flow rate: 0.4 mL/min, 254 nm, Retention time: 19.6 min. (*R* isomer) and 22.2 min. (*S* isomer)

(*R*)-1-Methoxy-2-octa-1,2-dienyl-benzene



(*R*)-**153bi**

Colourless oil (eluent: hexanes)

Yield 0.060 g (56%)

$[\alpha]_D^{25}$ -167.0 (*c* 0.5, $CHCl_3$)

IR (neat) (cm^{-1}) 3001, 2928, 1948, 1597, 1583, 1464, 1246

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.38 (d, *J* = 10.1 Hz, 1H), 7.17-7.13 (m, 1H), 6.92-6.89 (m, 1H), 6.85 (d, *J* = 5.2 Hz, 1H), 6.53-6.52 (m, 1H), 5.54-5.50 (m, 1H), 3.83 (s, 3H), 2.14-2.09 (m, 2H), 1.51-1.45 (m, 2H), 1.36-1.29 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H)

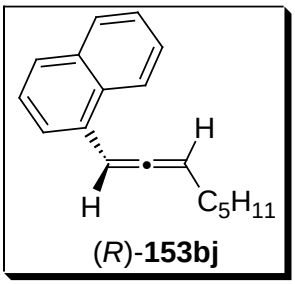
^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 205.5, 155.9, 127.6, 127.5, 123.6, 120.7, 110.9, 94.3, 88.2, 55.5, 31.4, 28.9, 28.8, 22.4, 14.0

LCMS *m/z* 217 (M+1)

Analysis calculated for $C_{15}H_{20}O$: C, 83.28%; H, 9.32%; O, 7.40%; Found: C, 83.32%; H, 9.21%; O, 7.47%

ee 94%, HPLC analysis (Chiralcel OJ-H column, n-Hexane:IPA = 99.75:0.25, Flow rate: 0.4 mL/min, 254 nm, Retention time: 36.6 min. (*R* isomer) and 43.7 min. (*S* isomer)

(*R*)-1-Octa-1,2-dienyl-naphthalene



(*R*)-**153bj**

Colourless oil (eluent: hexanes)

Yield 0.053 g (45%)

$[\alpha]_D^{25}$ -161.0 (*c* 0.33, $CHCl_3$)

IR (neat) (cm^{-1}) 3059, 2928, 2858, 1948, 1693, 1591, 873, 777

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 8.23 (d, *J* = 8.2 Hz, 1H), 7.84-7.82 (m, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 10.0 Hz, 1H), 7.51-7.41 (m, 3H), 6.82-6.80 (m, 1H), 5.62-5.57 (m, 1H), 2.20-2.15 (m, 2H), 1.55-1.49 (m, 2H), 1.39-1.28 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H) (**Spectrum No. 41**)

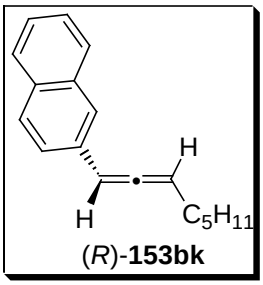
^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 206.7, 134.0, 131.3, 130.9, 128.6, 127.1, 125.8, 125.6, 125.1, 123.6, 94.1, 91.1, 31.5, 28.9, 28.8, 22.5, 14.1 (**Spectrum No. 42**)

LCMS *m/z* 237 (M+1)

Analysis calculated for $C_{18}H_{20}$: C, 91.47%; H, 8.53%. Found: C, 91.38%; H, 8.61%

ee 90%, HPLC analysis (Chiralcel OJ-H column, n-Hexane:IPA = 99:1, Flow rate: 0.5 mL/min, 254 nm, Retention time: 15.0 min. (*S* isomer) and 22.7 min. (*R* isomer)

(*R*)-2-Octa-1,2-dienyl-naphthalene



(*R*)-**153bk**

Colourless oil (eluent: hexanes)

Yield 0.060 g (51%)

$[\alpha]_D^{25}$ -122.0 (*c* 0.51, $CHCl_3$)

IR (neat) (cm^{-1}) 3055, 2928, 2856, 1946, 1695, 1599, 893

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.78-7.74 (m, 3H), 7.63 (s, 1H), 7.50-7.38 (m, 3H), 6.31-6.28 (m, 1H), 5.66-5.59 (m, 1H), 2.19-2.13 (m, 2H), 1.55-1.46 (m, 2H), 1.39-1.30 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.7, 133.7, 132.71, 132.52, 128.1, 127.7, 127.6, 126.1, 125.4, 125.2, 124.7, 95.3, 94.9, 31.4, 28.8, 28.7, 22.5, 14.0

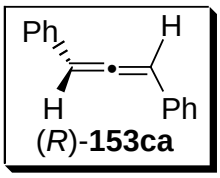
LCMS *m/z* 237 (M+1)

Analysis calculated for $C_{18}H_{20}$: C, 91.47%; H, 8.53%. Found: C, 91.38%; H, 8.61%

ee 91%, HPLC analysis (Chiralcel OJ-H column, n-Hexane:IPA = 99:1, Flow rate: 0.5 mL/min, 254 nm, Retention time: 19.5 min. (*R* isomer) and 26.9 min. (*S* isomer)

(*R*)-1,3-Diphenyl-propane-1,2-diene

Colourless crystal (eluent: hexanes)



(*R*)-**153ca**

Yield 48% (0.046 g)

mp 50-52 °C (lit.[34] 48-50 °C)

$[\alpha]_D^{25}$ -864.4 (*c* 0.59, $CHCl_3$)

IR (KBr) (cm^{-1}) 3061, 3028, 1936, 1597, 1493, 1450, 758

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.36-7.30 (m, 8H), 7.25-7.21 (m, 2H), 6.60 (s, 2H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 207.8, 133.6, 128.7, 127.3, 127.0, 98.4

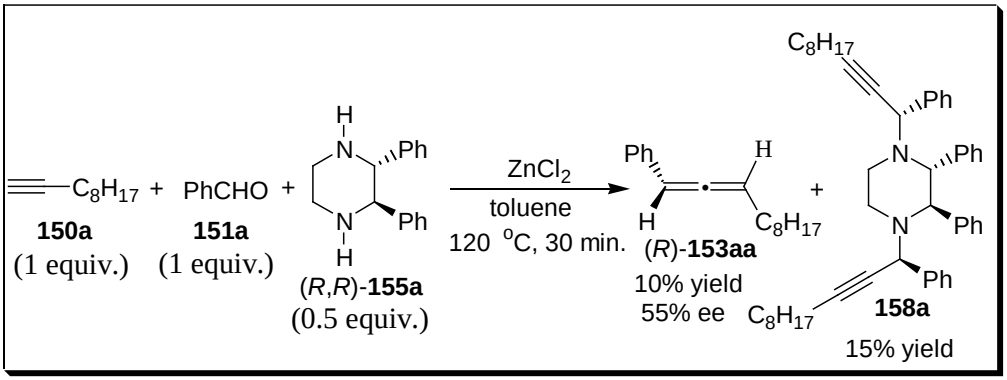
LCMS *m/z* 193 (M+1)

ee 94%, HPLC analysis (Chiralcel OD-H column, n-Hexane:IPA = 99:1, Flow rate: 0.5 mL/min, 254 nm, Retention time: 11.3 min. (*R* isomer) and 26.9 min. (*S* isomer)

(The spectral data of the compound showed 1:1 correspondence with the reported data.[34])

4.4.12 Synthesis of chiral dipropargylamine 158a from (*R*,*R*)-2,3-diphenylpiperazine 155a using $ZnCl_2$

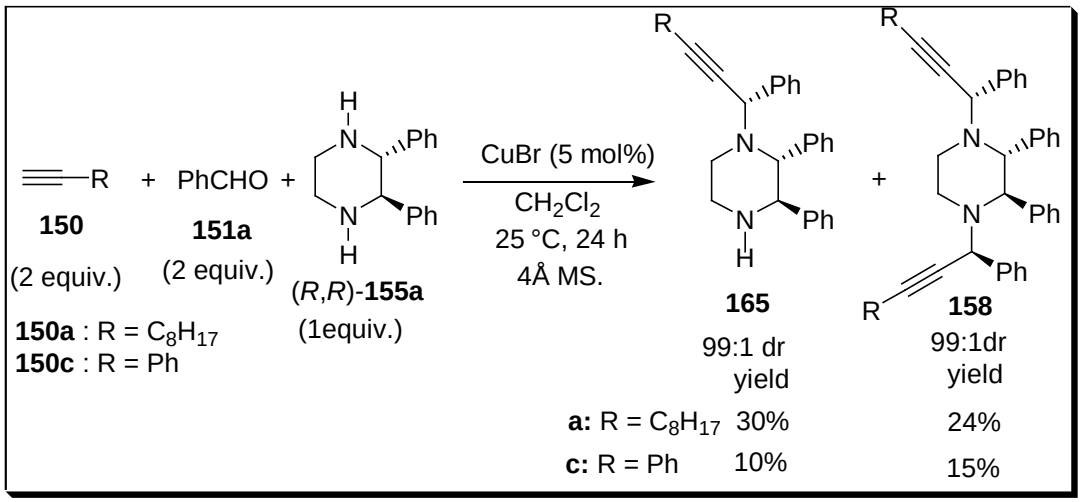
In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (5 mL), $ZnCl_2$ (0.081 g, 0.6 mmol), 1-decyne **150a** (1 mmol) and (*R*,*R*)-2,3-diphenylpiperazine **155a** (0.119 g, 0.5 mmol) were taken under N_2 atmosphere and stirred at 120 ^oC for 10-15 min. The reaction mixture was cooled to 25 °C and benzaldehyde **151a** (0.10 mL, 1 mmol) was added using a syringe. It was further stirred at 120 °C for 30 min. The reaction mixture was cooled to 25 °C and the mixture was chromatographed directly on a silica gel (100-200 mesh) column. The product (*R*)-allene **153aa** was isolated using hexanes as eluent in 10% yield and 55% ee (from HPLC analysis). The chiral dipropargylamine (*R*,*R*,*S*,*S*)-**158a** was isolated in 15% yield (0.052 g) using hexanes/EtOAc (99.75/0.25) as eluent.



4.4.13 Synthesis of chiral propargylamines 165 and 158 from (*R*,*R*)-2,3-diphenylpiperazine 155a using CuBr [68]

The (*R*,*R*)-2,3-diphenylpiperazine **155a** (0.476 g, 2 mmol), 4 Å molecular sieves (2.4 g) and 1-decyne **150a** (0.72 mL, 4 mmol) were taken in dry CH_2Cl_2 (10 mL) in a 25 mL round bottomed flask under N_2 atmosphere at 25 °C. Then, CuBr (0.014 g, 0.2 mmol) and benzaldehyde **151a** (0.48 mL, 4 mmol) were added at 25 °C. The reaction mixture was stirred at 25 °C for 24 h. It was quenched with water (10 mL) and CH_2Cl_2 (20 mL) was added to it and stirred for 5 min. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extract was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel (100-200 mesh) column. The dipropargylamine (*R*,*R*,*S*,*S*)-**158a** was isolated using hexanes/EtOAc (98/2) as eluent in 24% yield (0.335 g) as yellowish viscous liquid. The corresponding monopropargylamine (*R*,*R*,*S*)-**165a** was isolated using hexanes/EtOAc (90/10) as eluent in 30% yield (0.278 g) as yellowish viscous liquid. The diastereomeric ratio (dr) of the propargylamines **158a** and **165a** were obtained from the ^{1}H NMR analysis of the crude product. When the reaction was

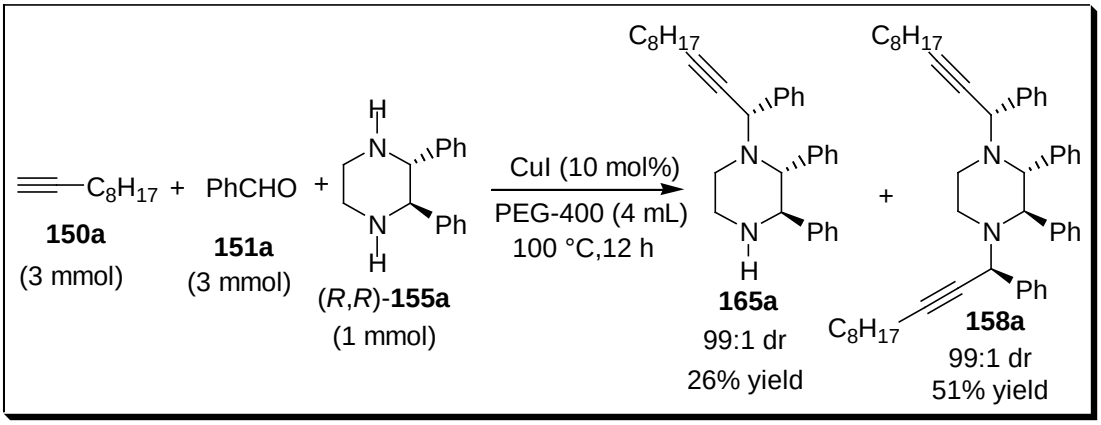
carried out using phenylacetylene **150c** instead of 1-decyne **150a**, the corresponding propargylamines **158c** and **165c** were obtained in 15% and 10% yields respectively.



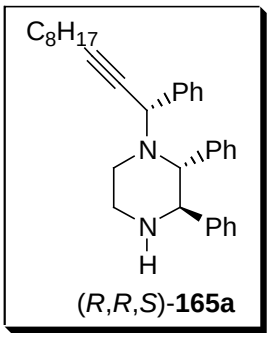
4.4.14 Synthesis of chiral propargylamines 165a and 158a from (*R*,*R*)-2,3-diphenylpiperazine 155a using CuI/PEG-400 reagent system[69]

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, PEG-400 (4 mL), CuI (0.040 g, 0.2 mmol), 1-decyne **150a** (0.54 mL, 3 mmol), benzaldehyde **151a** (0.30 mL, 3 mmol) and (*R*,*R*)-2,3-diphenylpiperazine **155a** (0.238 g, 1 mmol) were placed under N_2 atmosphere and stirred at 100 °C for 12 h. The reaction mixture was cooled to 25 °C. It was diluted with EtOAc (20 mL) and water (10 mL) and stirred for 10 min. The organic layer was separated and aqueous layer was extracted with EtOAc (10 mL). The combined organic extract was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the residue was chromatographed on a silica gel (100-200 mesh) column as mentioned in the section 4.4.13. The

dipropargylamine (*R*,*R*,*S*,*S*)-**158a** was obtained in 51% yield (0.352 g) and the corresponding monopropargylamine (*R*,*R*,*S*)-**165a** was obtained in 26% yield (0.120 g). The diastereomeric ratio (dr) of the propargylamines **158a** and **165a** were obtained from the ^{1}H NMR analysis of the crude product. Using phenylacetylene **150c** (3 mmol), instead of 1-decyne **150a** resulted in the formation of dipropargylamine **158c** in 20% yield. The yields and spectral data of the propargylamines are given below.



(2*R*,3*R*)-2,3-Diphenyl-1-[(1*S*)-1-phenyl-2-undecynyl]-piperazine



Yield 0.120 g (26%)

$[\alpha]_D^{25}$ -37.0 (*c* 0.53, $CHCl_3$)

IR (neat) (cm^{-1}) 3321, 3030, 2723, 2355, 2224, 1454, 760

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.58 (d, *J* = 7.6 Hz, 2H), 7.31-7.28 (m, 3H), 7.23-7.19 (m, 2H), 7.09-7.07 (m, 8H), 4.5 (s, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.67 (d, *J* = 9.2 Hz, 1H), 3.05-3.03 (m, 2H), 2.79-2.72 (m, 1H), 2.49-2.46 (m, 1H), 2.38-2.34 (m, 2H), 1.87 (s, 1H), 1.66-1.59 (m, 2H), 1.54-1.50 (m, 2H), 1.34-1.31 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H) (**Spectrum No. 43**)

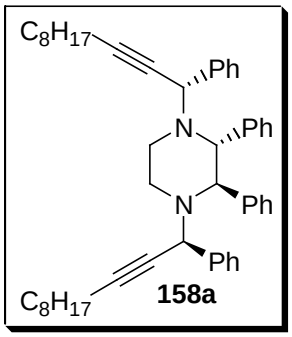
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 141.9, 140.0, 139.6, 128.1, 128.07, 127.9, 127.8, 127.7, 127.1, 127.0, 126.9, 88.9, 74.3, 71.9, 68.4, 56.4, 46.3, 45.7, 31.9, 29.3, 29.2, 29.0, 22.7, 18.8, 14.1 (**Spectrum No. 44**)

LCMS *m/z* 465 (M+1)

Analysis calculated for $C_{33}H_{40}N_2$: C, 85.30%; H, 8.68%; N, 6.03%. Found: C, 85.12%; H, 8.79%; N, 6.09%

dr 99:1 (calculated from ^{1}H NMR analysis of the crude product mixture)

(2*R*,3*R*)-2,3-Diphenyl-1,4-di[(1*S*)-1-phenyl-2-undecynyl]piperazine



158a

Yield 0.352 g (51%)

$[\alpha]_D^{25}$ -38.0 (*c* 0.53, $CHCl_3$)

IR (neat) (cm^{-1}) 3061, 2928, 2729, 2256, 1601, 700

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.84 (s, 2H), 7.56-7.54 (m, 4H), 7.36 (s, 2H), 7.29-7.26 (m, 4H), 7.21-7.18 (m, 2H), 7.12-7.08 (m, 2H), 6.88 (s, 2H), 6.52 (s, 2H), 4.48 (s, 2H), 3.80 (s, 2H), 2.64-2.62 (m, 2H), 2.39-2.35 (m, 6H), 1.65-1.59 (m, 8H), 1.38-1.32 (m, 16H), 0.91-0.88 (m, 6H) (**Spectrum No. 45**)

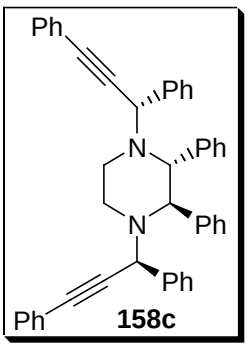
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.7, 139.6, 128.1, 127.7, 127.0, 126.9, 88.8, 74.4, 72.0, 56.4, 45.1, 32.0, 29.3, 29.26, 29.25, 29.0, 22.7, 18.8, 14.1 (**Spectrum No. 46**)

LCMS *m/z* 692 (M+1)

Analysis calculated for $C_{50}H_{62}N_2$: C, 86.90%; H, 9.04%; N, 4.05%. Found: C, 86.85%; H, 9.12%; N, 4.11%

dr 99:1 (calculated from ^{1}H NMR analysis of the crude product mixture)

(2*R*,3*R*)-1,4-Di[(1*S*)-1,3-diphenyl-2-propynyl]-2,3-diphenylpiperazine



Colourless solid (eluent: hexanes/EtOAc-98/2)

Yield 0.123 g (20%)

mp 166-168 °C

IR (KBr) (cm^{-1}) 3059, 2835, 1599, 1491, 1450, 756

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 7.88 (br s, 2H), 7.61 (d, *J* = 8.2 Hz, 4H), 7.59-7.57 (m, 4H), 7.40-7.36 (m, 8H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.23 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 2H), 6.92 (br s, 2H), 6.61 (br s, 2H), 4.76 (s, 2H), 3.92 (s, 2H), 2.77 (d, *J* = 7.7 Hz, 2H), 2.54 (d, *J* = 8.2 Hz, 2H) (**Spectrum No. 47**)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 140.3, 138.8, 131.9, 128.4, 128.2, 128.1, 127.9, 127.2, 123.5, 88.7, 84.6, 72.4, 56.8, 45.5 (**Spectrum No. 48**)

LCMS *m/z* 619 (M+1)

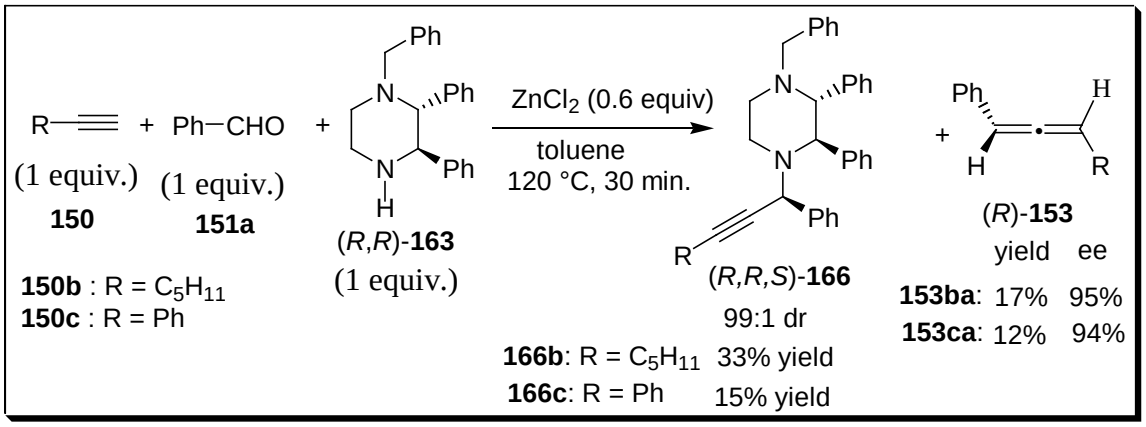
Analysis calculated for $C_{46}H_{38}N_2$: C, 89.28%; H, 6.19%; N, 4.53% Found: C, 89.41%; H, 6.05%; N, 4.54%

dr 99:1 (calculated from ^{1}H NMR analysis of the crude product mixture)

4.4.15 Synthesis of chiral propargylamines (*R*,*R*,*S*)-166b and (*R*,*R*,*S*)-166c from (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163 using $ZnCl_2$

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (5 mL), $ZnCl_2$ (0.081 g, 0.6 mmol), 1-heptyne **150b** (0.12 mL, 1 mmol) and (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** (0.328 g, 1 mmol) were taken under N_2 atmosphere and stirred at 120 ^{o}C for 10-15 min. The reaction mixture was cooled to 25 °C and benzaldehyde

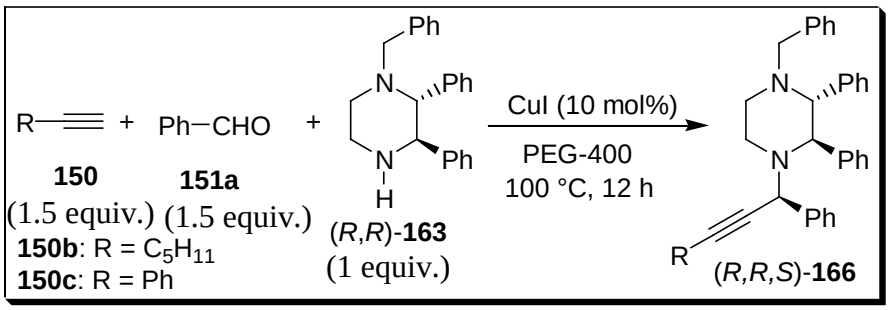
151a (0.10 mL, 1 mmol) was added using a syringe. It was further stirred at 120 °C for 30 min. The reaction mixture was cooled to 25 °C and chromatographed directly on a silica gel (100-200 mesh) column. The product (*R*)-allene **153ba** was isolated using hexanes as eluent in 17% yield and 95% ee (from HPLC analysis). The corresponding propargylamine (*R*,*R*,*S*)-**166b** was isolated in 33% yield (0.169 g) by using hexanes/EtOAc (99.75/0.25) as eluent. When the reaction was carried out using phenylacetylene **150c** instead of 1-heptyne **150b**, the product (*R*)-allene **153ca** was isolated using hexanes as eluent in 12% yield and 94% ee (from HPLC analysis). The corresponding propargylamine (*R*,*R*,*S*)-**166c** was isolated in 15% yield (0.078 g) by using hexanes/EtOAc (99.5/0.5) as eluent.



4.4.16 Synthesis of chiral propargylamines (*R*,*R*,*S*)-166b and (*R*,*R*,*S*)-166c from (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine 163 using CuI/PEG-400 reagent system[69]

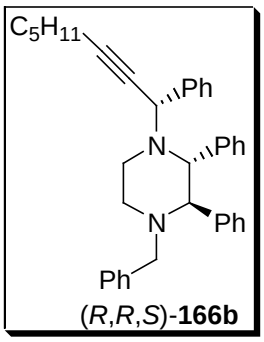
In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, PEG-400 (4 mL), CuI (0.040 g, 0.2 mmol), 1-heptyne **150b** (0.36 mL, 3 mmol), benzaldehyde **151a** (0.30 mL, 3 mmol) and (*R*,*R*)-1-benzyl-2,3-diphenylpiperazine **163** (0.656 g, 2 mmol) were taken under N_2

atmosphere and stirred at 100 °C for 12 h. The reaction mixture was cooled to 25 °C. It was diluted with EtOAc (20 mL) and water (10 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extract was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the residue was chromatographed on a silica gel (100-200 mesh) column to isolate the propargylamine (*R*,*R*,*S*)-**166b** using hexanes/EtOAc (99.75/0.25) as eluent. When the reaction was carried out in the presence of phenylacetylene **150c** (3 mmol) instead of 1-heptyne **150b**, the corresponding propargylamine (*R*,*R*,*S*)-**166c** was isolated by column chromatography on silica gel (100-200 mesh) using hexanes/EtOAc (99.5/0.5) as eluent. The yields and the spectral data of the propargylamines **166b** and **166c** are given below.



(2*R*,3*R*)-1-Benzyl-2,3-diphenyl-4-[(1*S*)-1-phenyl-2-octynyl]-piperazine

Colourless viscous liquid



Yield 0.645 g (63%)

$[\alpha]_D^{25}$ -19.0 (*c* 0.54, $CHCl_3$)

IR (neat) (cm^{-1}) 3030, 2932, 2841, 2300, 1602, 1493, 1028

^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.73 (br s, 1H), 7.49-7.47 (m, 2H), 7.30-7.01 (m, 15H), 6.8 (br s, 1H), 6.4 (br s, 1H), 4.42 (s,

1H), 3.67-3.62 (m, 2H), 3.33-3.31 (m, 1H), 2.79-2.76 (m, 2H), 2.67-2.63 (m, 1H), 2.34-2.27 (m, 3H), 2.21-2.16 (m, 1H), 1.59-1.53 (m, 2H), 1.51-1.43 (m, 2H), 1.39-1.31 (m, 2H), 0.93-0.89 (m, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 141.4, 140.5, 139.6, 139.1, 128.8, 128.1, 128.0, 127.8, 127.1, 126.9, 126.8, 126.6, 88.9, 74.8, 74.3, 72.3, 59.4, 56.4, 51.7, 45.1, 31.2, 28.9, 22.3, 18.8, 14.1

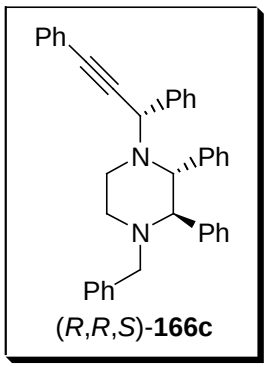
LCMS *m/z* 514 (M+1)

Analysis calculated for $C_{37}H_{40}N_2$: C, 86.67%; H, 7.86%; N, 5.46%. Found: C, 86.51%; H, 7.82%; N, 5.37%

dr 99:1 (calculated from ^{1}H NMR analysis of the crude product mixture)

(2*R*,3*R*)-1-Benzyl-4-[(1*S*)-1,3-diphenyl-2-propynyl]-2,3-diphenyl-piperazine

Colourless solid



(*R*,*R*,*S*)-**166c**

Yield 0.890 g (86%)

mp 154-155 ^{o}C

$[\alpha]_D^{25}$ -102.0 (*c* 0.6, $CHCl_3$)

IR (KBr) (cm^{-1}) 3059, 3030, 2791, 1952, 1599, 1446, 758

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.82 (br s, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.57-7.54 (m, 2H), 7.38-7.29 (m, 6H), 7.23-7.08 (m, 12H), 6.93 (br s, 1H), 6.56 (br s, 1H), 4.76 (s, 1H), 3.82 (d, *J* = 9.2 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 2.89-2.79 (m, 3H), 2.54-2.50 (m, 1H), 2.32-2.27 (m, 1H) (**Spectrum No. 49**)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 141.2, 140.2, 139.0, 138.9, 131.9, 128.8, 128.3, 128.1, 128.09, 128.0, 127.8, 127.2, 126.9, 126.64, 123.4, 88.7, 84.4, 74.7, 72.5, 59.5, 56.8, 51.7, 45.4 (**Spectrum No. 50**)

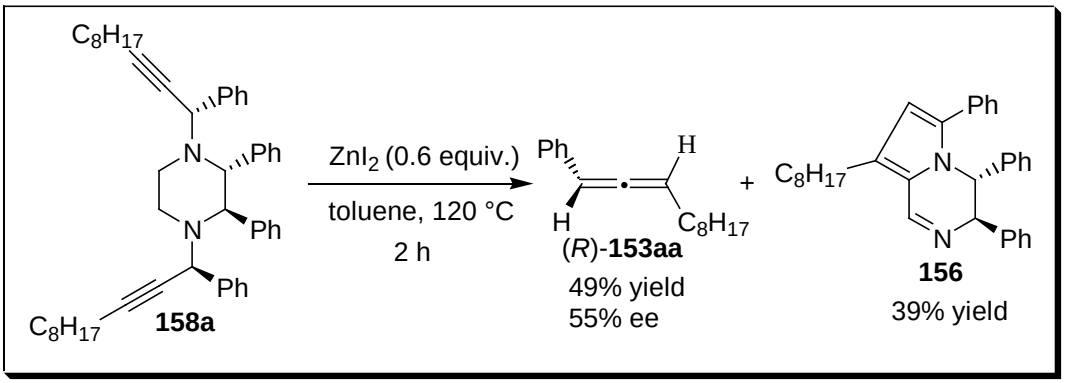
LCMS *m/z* 519 (M+1)

Analysis calculated for $C_{38}H_{34}N_2$: C, 87.99%; H, 6.61%; N, 5.40% Found: C, 87.85%; H, 6.68%; N, 5.35%

dr 99:1 (calculated from ^{1}H NMR analysis of the crude product mixture)

4.4.17 Procedure for the synthesis of chiral allenes (*R*)-153aa from chiral dipropargylamine (*R*,*R*,*S*,*S*)-158a

In a 25 mL round bottomed flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, dry toluene (2.5 mL), ZnI_2 (0.096 g, 0.3 mmol), and dipropargylamine (*R*,*R*,*S*,*S*)-**158a** (0.345 g, 0.5 mmol) were placed under N_2 atmosphere and stirred at 120 ^{o}C for 2 h. The reaction mixture was cooled to 25 °C and chromatographed on a silica gel (100-200 mesh) column. Using hexanes as eluent, the allene (*R*)-**153aa** was isolated in 49% yield (0.055 g) with 55% ee (from HPLC) and the bicyclic byproduct **156** was isolated in 39% yield (0.089 g) using hexanes/EtOAc (85/15) as eluent as colourless viscous liquid.



The experimental procedure as outlined in the section 4.4.17 was followed for the preparation of chiral allenes (*R*)-**153** from other propargylamines (*R*,*R*,*S*)-**165** and (*R*,*R*,*S*)-**166** instead of the dipropargylamine (*R*,*R*,*S*,*S*)-**158a**, in the presence of ZnI_2 (0.6 equiv.) as mentioned in the results and discussion section 4.2.5.

4.5 References

1. van't Hoff, J. H. *La Chimie dans L'Espace*, Bazendijk, Rotterdam, **1875**.
2. Burton, B. S.; Pechmann, H. V. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.
3. (a) *The Chemistry of the Allenes* (ed. Landor, S. R.), Academic Press, London, **1982**; (b) *Modern Allene Chemistry* (ed. Krause. N.; Hashmi, A. S. K.), Wiley-VCH, Weinheim, **2004**.
4. Padwa, A.; Filipkowski, M. A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 588.
5. (a) Johnson, E. A.; Burdon, K. L. *J. Bacteriol.* **1947**, *54*, 281. (b) Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 1870. (c) Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 2245. (d) Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 3838.
6. (a) Bendz, G. *Arkiv. Kemi.* **1959**, *14*, 305. (b) Bendz, G. *Arkiv. Kemi* **1959**, *14*, 475. (c) Cambie, R. C.; Hirschberg, A.; Jones, E. R. H.; Lowe, G. *J. Chem. Soc.* **1963**, 4120. (d) Bohlmann, F.; Herbst, P.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 948. (e) Evans, R. J. D.; Landor, S. R.; Regan, J. P. *J. Chem. Soc. Perkin Trans. 1* **1974**, 552. (f) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 557. (g) de Graaf, W.; Smits, A.; Boersma, J.; van Koten, G.; Hoekstra, W. P. *Tetrahedron* **1988**, *44*, 6699.
7. Horler, D. F. *J. Chem. Soc. C* **1970**, 859.
8. Kinnel, R.; Duggan, A. J.; Eisner, T.; Meinwald, J. *Tetrahedron Lett.* **1977**, *18*, 3913.

9. (a) Fukuzawa, A.; Kurosawa, E. *Tetrahedron Lett.* **1979**, *20*, 2797. (b) Suzuki, M.; Koizumi, K.; Kikuchi, H.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 715. (c) Wright, A. D.; Koenig, G. M.; Sticher, O. *J. Nat. Prod.* **1991**, *54*, 1025.

10. Kurata, K.; Furusaki, A.; Suehiro, K.; Katayama, C.; Suzuki, T. *Chem. Lett.* **1982**, *11*, 1031.

11. (a) Willstätter, R.; Page, H. J.; Liebigs, *J. Ann. Chem.* **1914**, *404*, 237. (b) Bonnett, R.; Spark, A. A.; Tee, J. L.; Weedon, B. C. L. *Proc. Chem. Soc. London* **1964**, 419.

12. (a) Goodwin, T. W.; Thomas, D. M. *Phytochemistry* **1964**, *3*, 47. (b) Nitsche, H.; *Z. Naturforsch. C* **1973**, *28*, 481.

13. (a) Meinwald, J.; Erickson, K.; Hartshorn, M.; Meinwald, Y. C.; Eisner, T. *Tetrahedron Lett*. **1968**, *9*, 2959. (b) DeVille, T. E.; Hursthouse, M. B.; Russell, S. W.; Weedon, B. C. L. *J. Chem. Soc. Chem. Commun.* **1969**, 754.

14. (a) Theobald, N.; Shoolery, J. N.; Djerassi, C.; Erdman, T. R.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5574. (b) Morisaki, M.; Awata, N.; Fujimoto, Y.; Ikekawa, N. *J. Chem. Soc. Perkin Trans. 1* **1975**, 362. (c) Fujimoto, Y.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc. Perkin Trans. 1* **1975**, 2302.

15. (a) Covey, D. F.; Robinson, C. H. *J. Am. Chem. Soc.* **1976**, *98*, 5038. (b) Batzold, F. H.; Covey, D. F.; Robinson, C. H. *Cancer Treat. Rep.* **1977**, *61*, 255.

16. (a) Burger, A.; Roussel, J.-P.; Hetru, C.; Hoffmann, J. A.; Luu, B. *Tetrahedron* **1989**, *45*, 155. (b) Roussell, J.-P.; Burger, A.; Hetru, C. *Arch. Int. Physiol. Biochim.* **1990**, *98*, 253.

17. Beach, D. H.; Chen, F.; Cushion, M. T.; Macomber, R. S.; Krudy, G. A.; Wyder, M. A.; Kaneshiro, E. S. *Antimicrob. Agents Chemother.* **1997**, *41*, 162.

18. Collins, P.W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

19. (a) Maitland, P.; Mills, W. H. *Nature* **1935**, *135*, 994. (b) Maitland, P.; Mills, W. H. *J. Chem. Soc.* **1936**, 987.

20. Torres, E.; Larson, G. L.; McGarvey, G. J. *Tetrahedron Lett.* **1988**, *29*, 1355.

21. Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093.

22. (a) Satoh, T.; Kuramochi, Y.; Inoue, Y. *Tetrahedron Lett.* **1999**, *40*, 8815. (b) Satoh, T.; Hanaki, N.; Kuramochi, Y.; Inoue, Y.; Hosoya, K.; Sakai, K. *Tetrahedron* **2002**, *58*, 2533.

23. Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 3697.

24. (a) Nishibayashi, Y.; Singh, J. D.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 3115. (b) Nishibayashi, Y.; Singh, J. D.; Fukuzawa, S.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4114.

25. (a) Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5499. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant. J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

26. Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726.

27. Buckle, M. J. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383.

28. Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855.

29. Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747.

30. Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

31. Colas, Y.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 845.

32. Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083.

33. Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360.

34. Yoshida, M.; Okada, T.; Shishido, K. *Tetrahedron* **2007**, *63*, 6996.

35. Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1308.

36. Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874.

37. (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811.

38. Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470.

39. (a) Lo, V. K. Y.; Wong, M.-K.; Che, C.-M. *Org. Lett*. **2008**, *10*, 517. (b) Lo, V. K.Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun*. **2010**, 213.

40. Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 2747.

41. Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* **2000**, 493.

42. Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212.

43. (a) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735. (b) Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669.

44. (a) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276.

45. de Graaf, W.; Boersma, J.; van Koten, G.; Elsevier, C. J. *J. Organomet. Chem.* **1989**, *378*, 115.

46. (a) Tillack, A.; Michalik, D.; Koy, C.; Michalik, M. *Tetrahedron Lett.* **1999**, *40*, 6567. (b) Tillack, A.; Koy, C.; Michalik, D.; Fischer, C. *J. Organomet. Chem.* **2000**, *603*, 116.

47. Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915.

48. Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

49. Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S. *Chem. Lett.* **2002**, 140.

50. Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett*. **2004**, 6, 305.

51. Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.

52. (a) Waters, W. L.; Caserio, M. C. *Tetrahedron Lett.* **1968**, *9*, 5233. (b) Waters, W. L.; Linn, W. S.; Caserio, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6741.

53. Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc*. **1964**, *86*, 1071.

54. Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc*. **1964**, *86*, 393.

55. Noguchi, Y.; Takiyama, H.; Katsuki, T. *Synlett* **1998**, 543.

56. Sweeney, Z. K.; Salsman, J. L.; Andersen, R. A.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2339.

57. Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S. *Chem. Commun.* **1998**, 2363.

58. (a) Naruse, Y.; Watanabe, H.; Inagaki, S. *Tetrahedron: Asymmetry* **1992**, *3*, 603. (b) Naruse, Y.; Watanabe, H.; Ishiyama, Y.; Yoshida, T. *J. Org. Chem.* **1997**, *62*, 3862.

59. Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett*. **2010**, *12*, 4050.

60. Karunakar, G. V.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 7463.

61. Kuang, J.; Ma, S. *J. Am. Chem. Soc*. **2010**, *132*, 1786.

62. Vairaprakash, P.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 3636.

63. Vairaprakash, P.; Periasamy, M. *J. Chem. Sci*. **2008**, *120*, 175.

64. Periasamy, M.; Vairaprakash, P.; Dalai, M. *Organometallics* **2008**, *27*, 1963.

65. Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331.

66. (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1.

67. Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726.

68. Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

69. Zhang, Q.; Chen, J.-X.; Gao, W.-X.; Ding, J.-C.; Wu, H.-Y. *Appl. Organomet. Chem.* **2010**, *24*, 809.

70. (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun*. **1979**, 859. (b) Kazmaier, U.; Lucas, S.; Klein, M. *J. Org. Chem*. **2006**, *71*, 2429. (c) Kuang, J.; Ma, S. *J. Org. Chem*. **2009**, *74*, 1763. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497.

71. Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416.

72. (a) Gurubrahamam, R. Unpublished results (b) Sanjeevakumar, N. Ph.D. Thesis **2011**, School of Chemistry, University of Hyderabad.

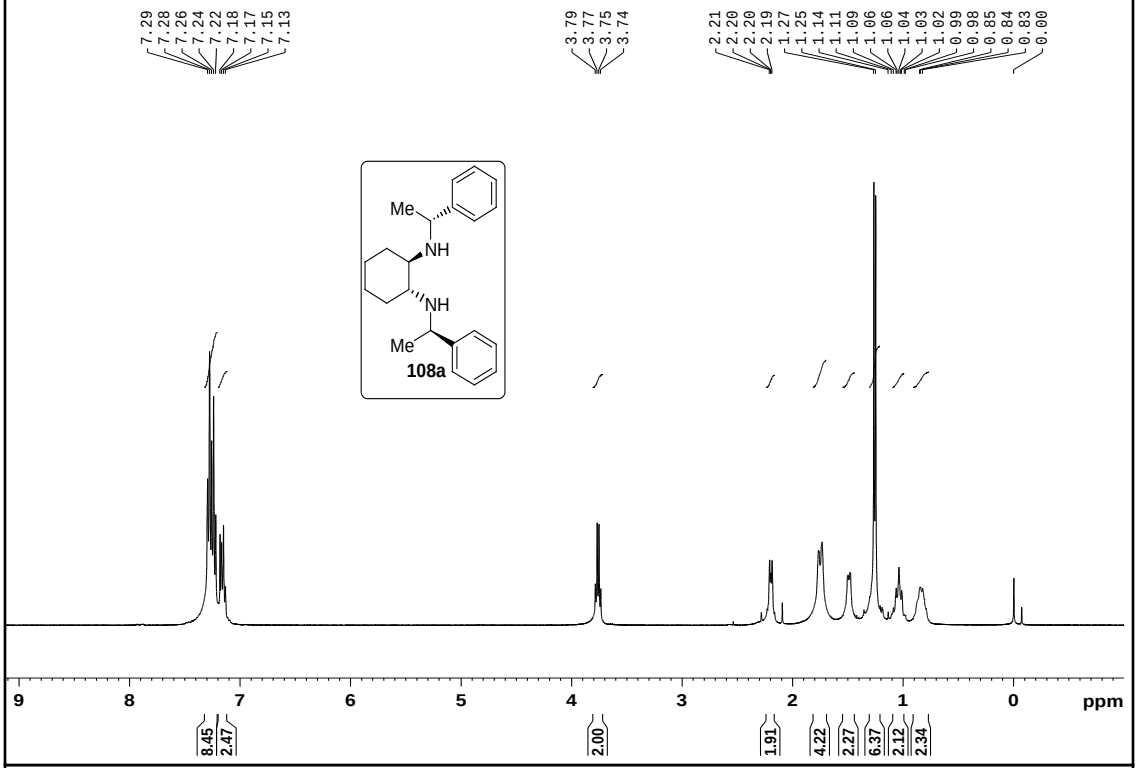
73. Kouznetsov, V. V.; Amado, D. F.; Bahsas, A.; Amaro-Luis, J. *J. Heterocycl. Chem.* **2006**, *43*, 447.

74. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063.

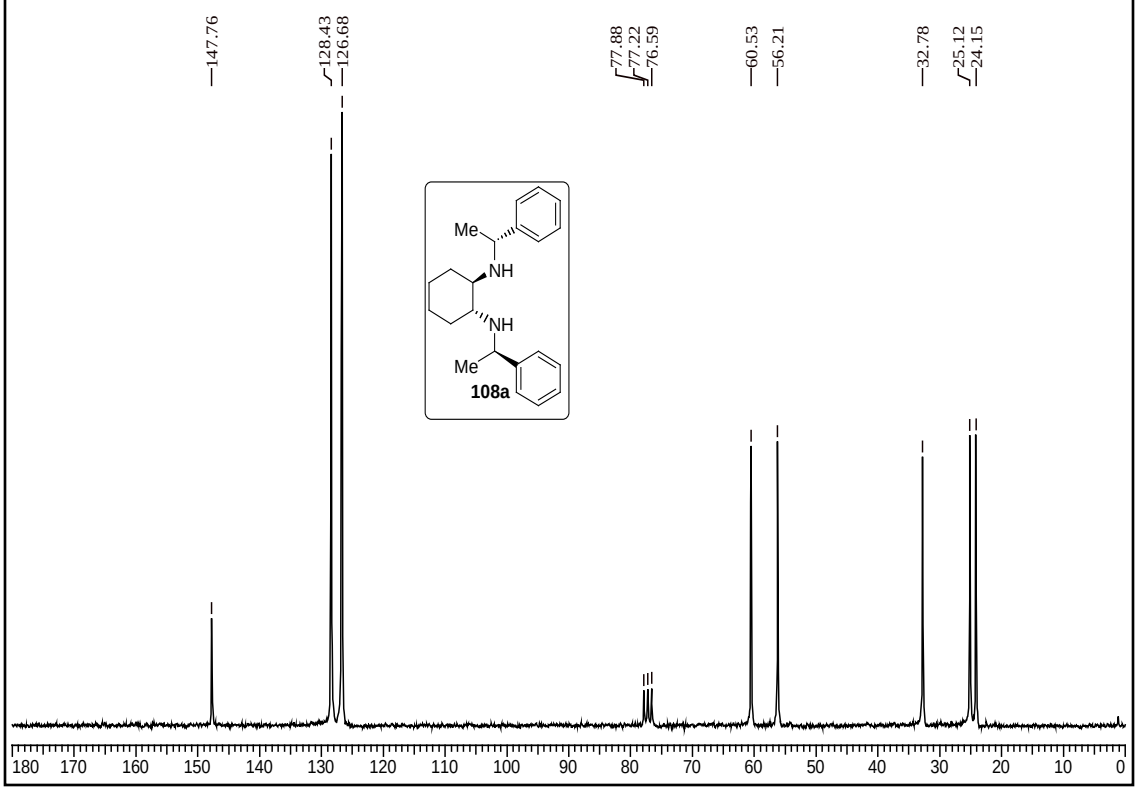
Appendix I

(Representative Spectra)

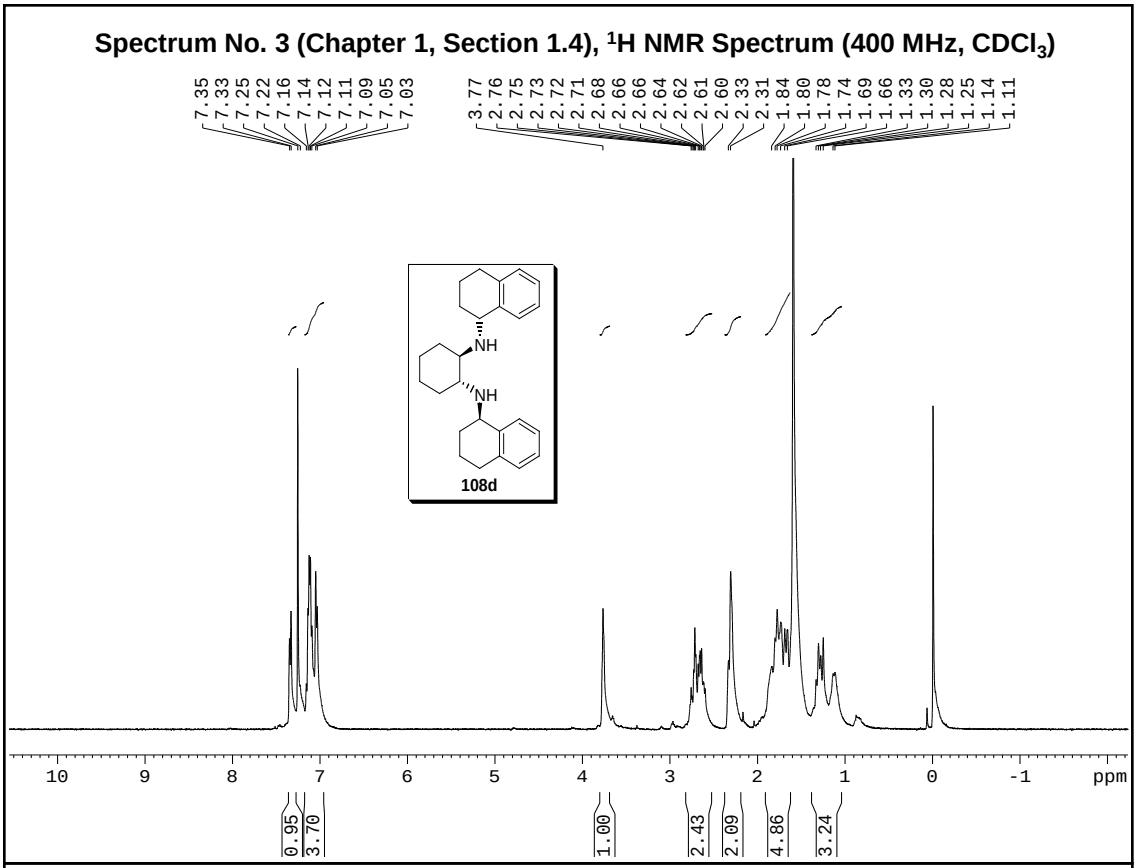
Spectrum No. 1 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



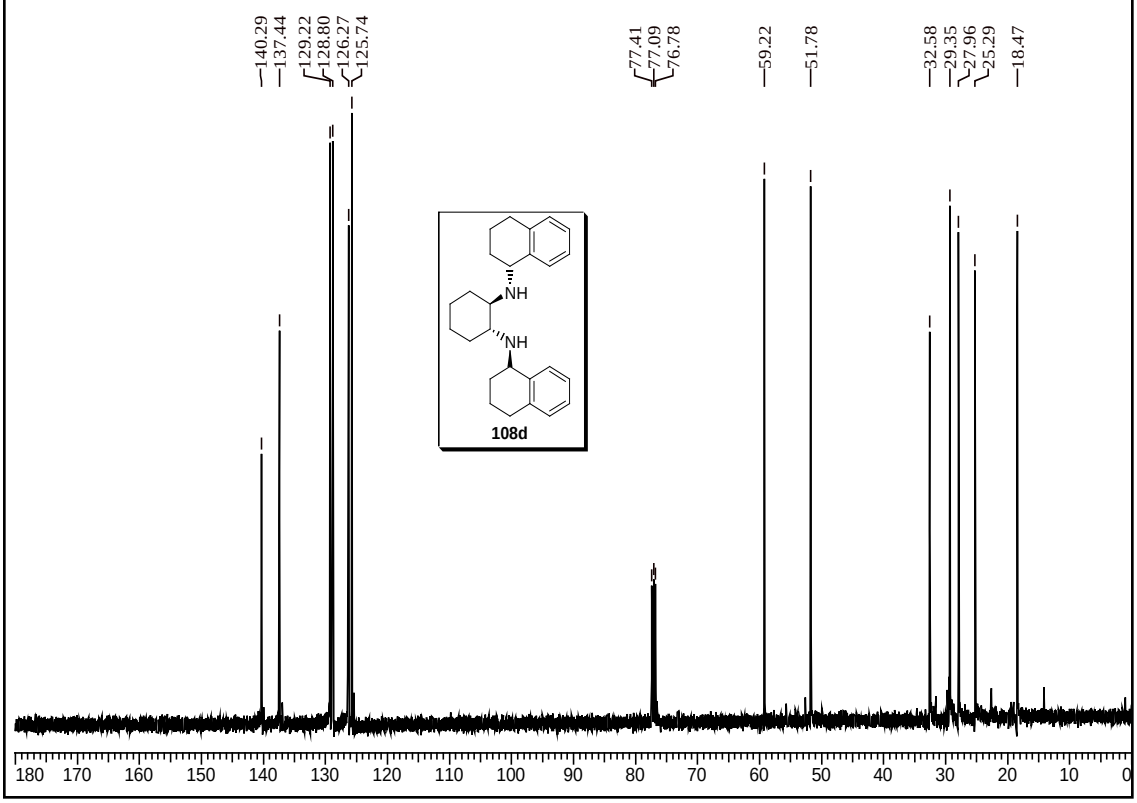
Spectrum No. 2 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



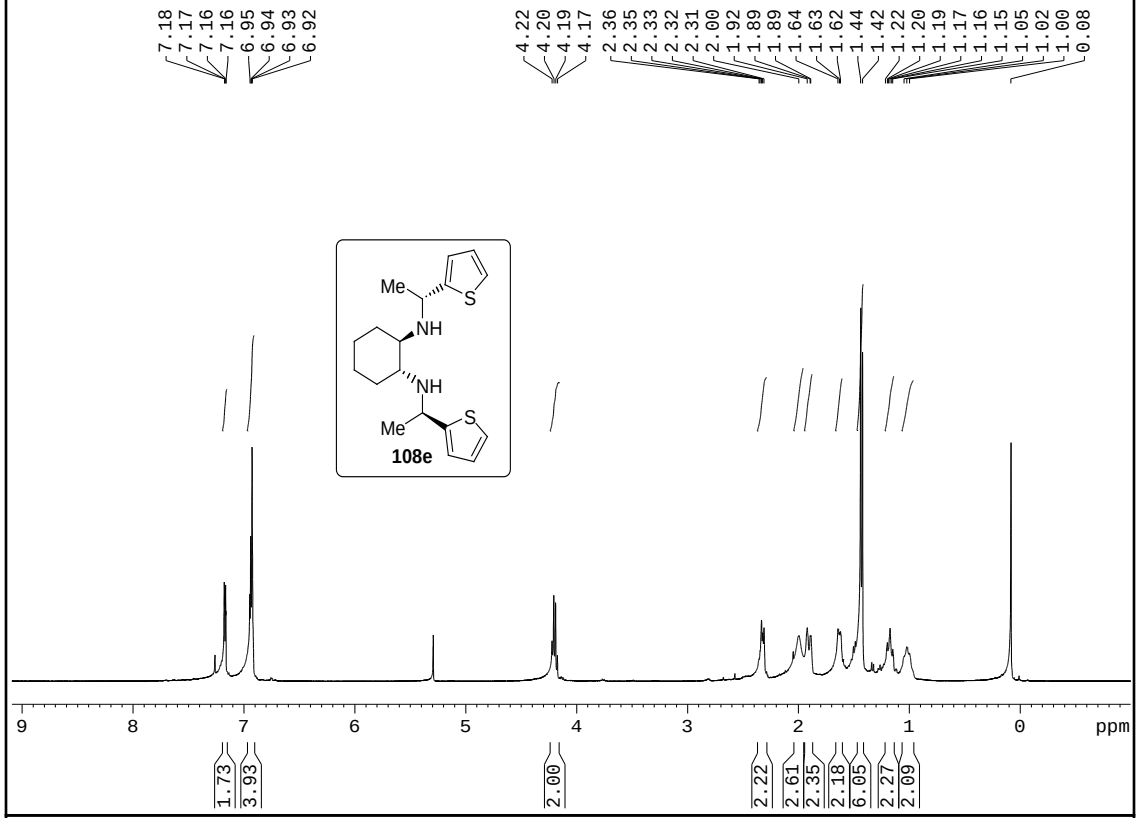
Spectrum No. 3 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



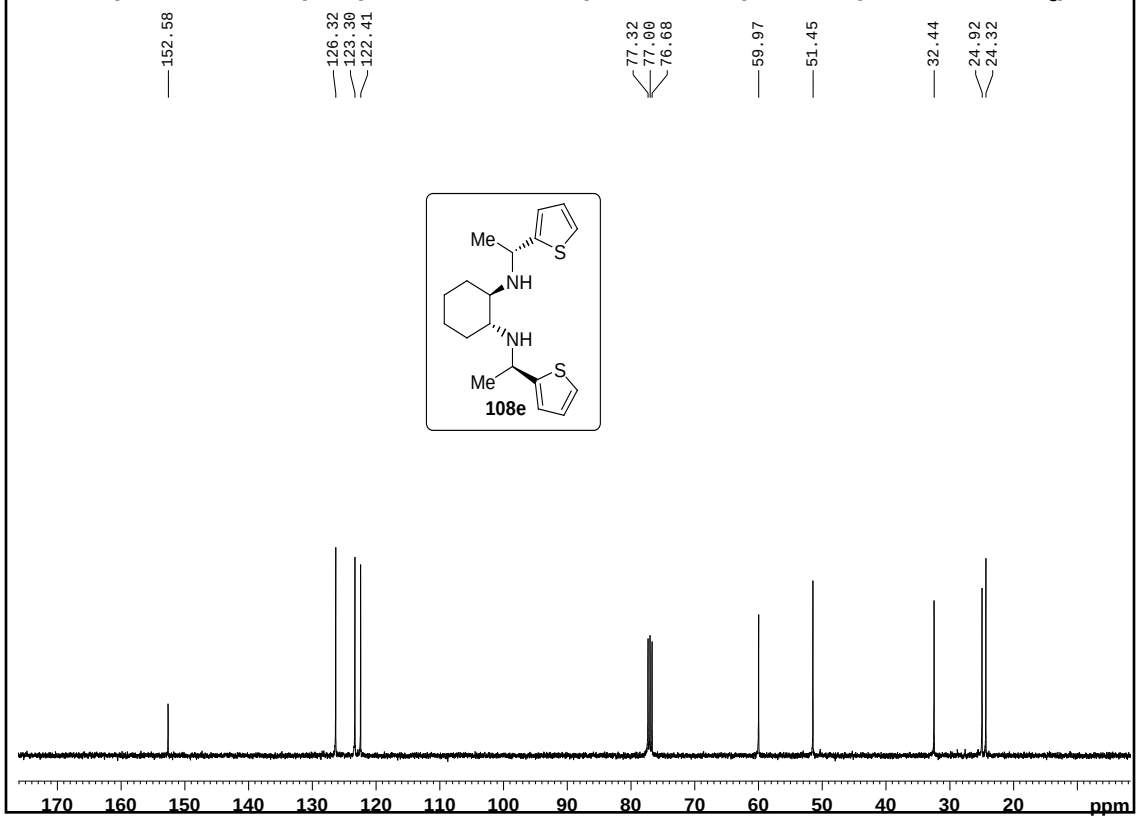
Spectrum No. 4 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



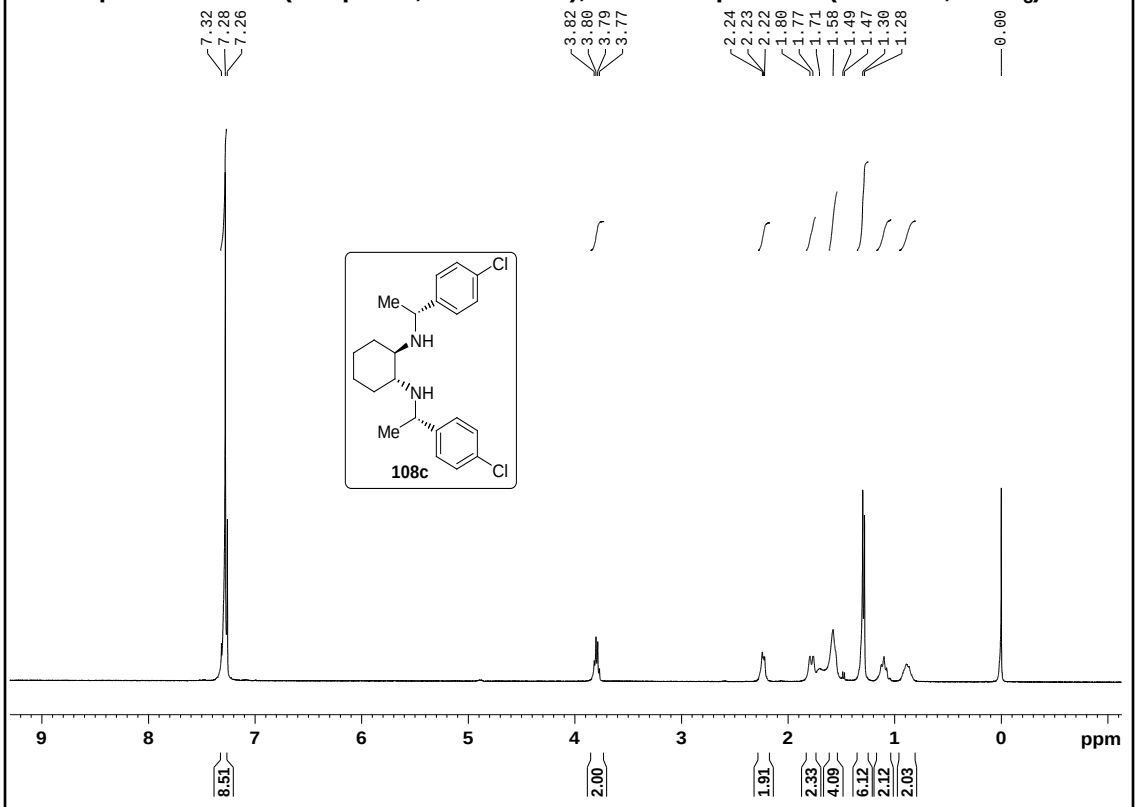
Spectrum No. 5 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



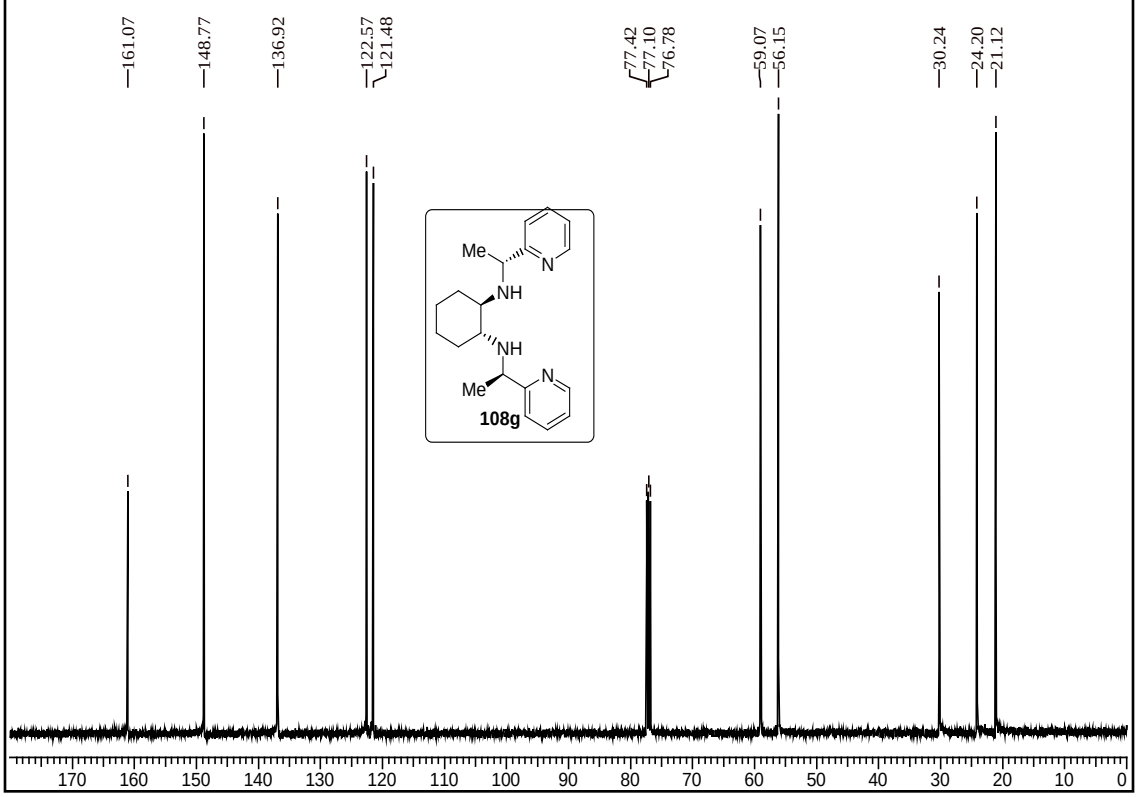
Spectrum No. 6 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



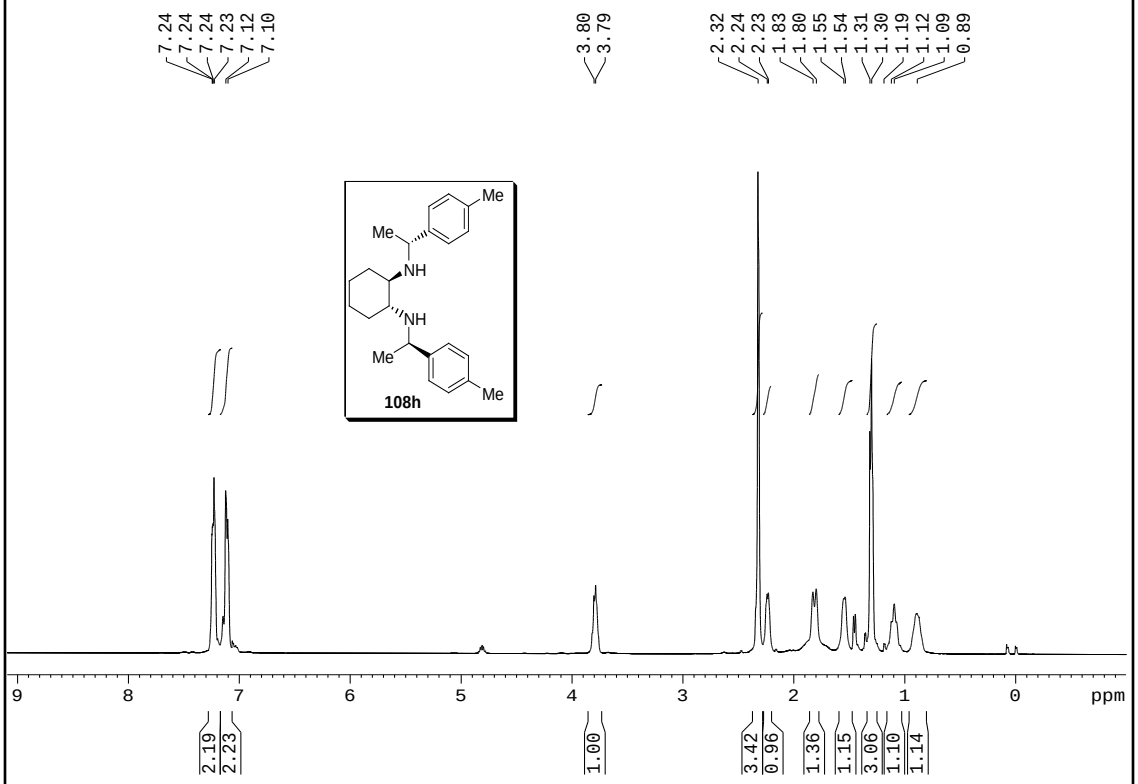
Spectrum No. 7 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



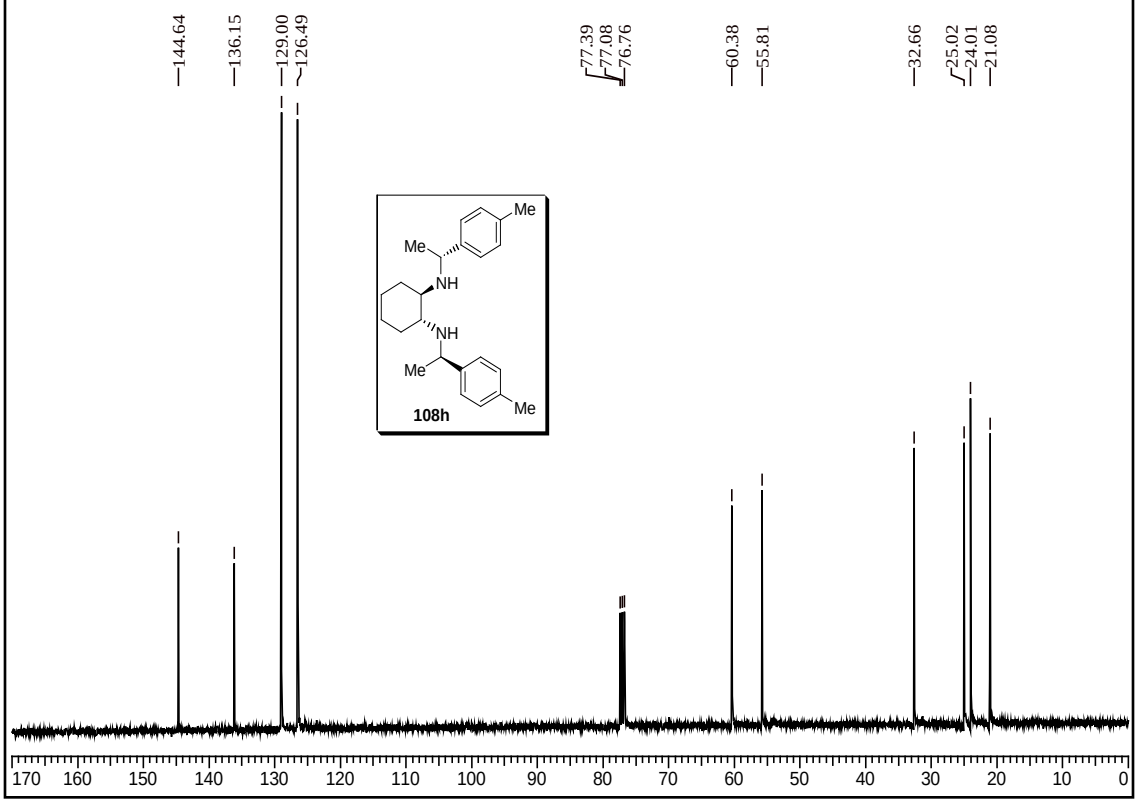
Spectrum No. 8 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



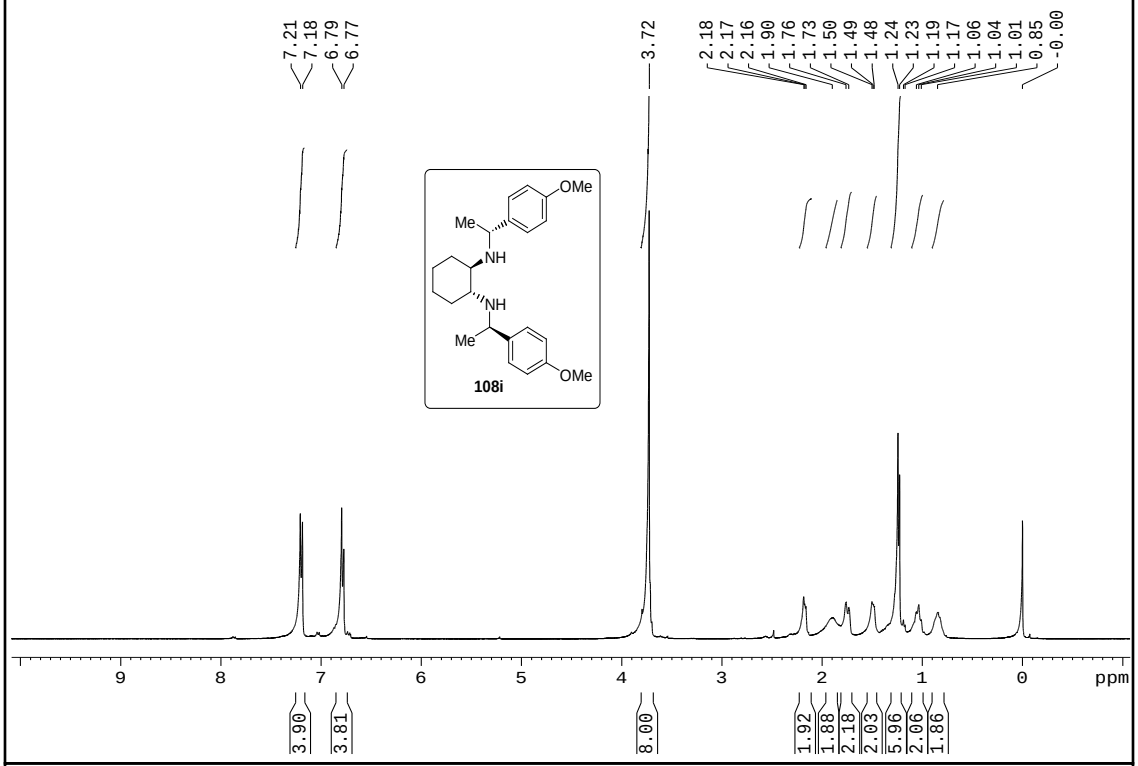
Spectrum No. 9 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



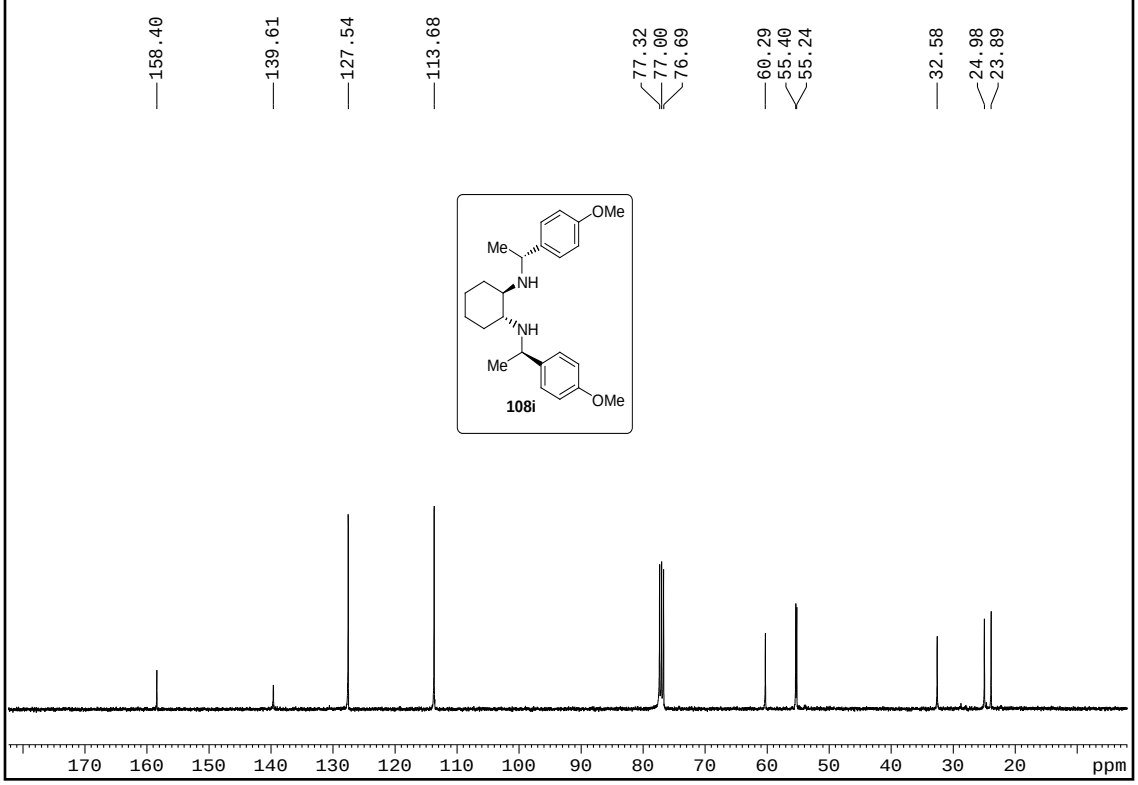
Spectrum No. 10 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



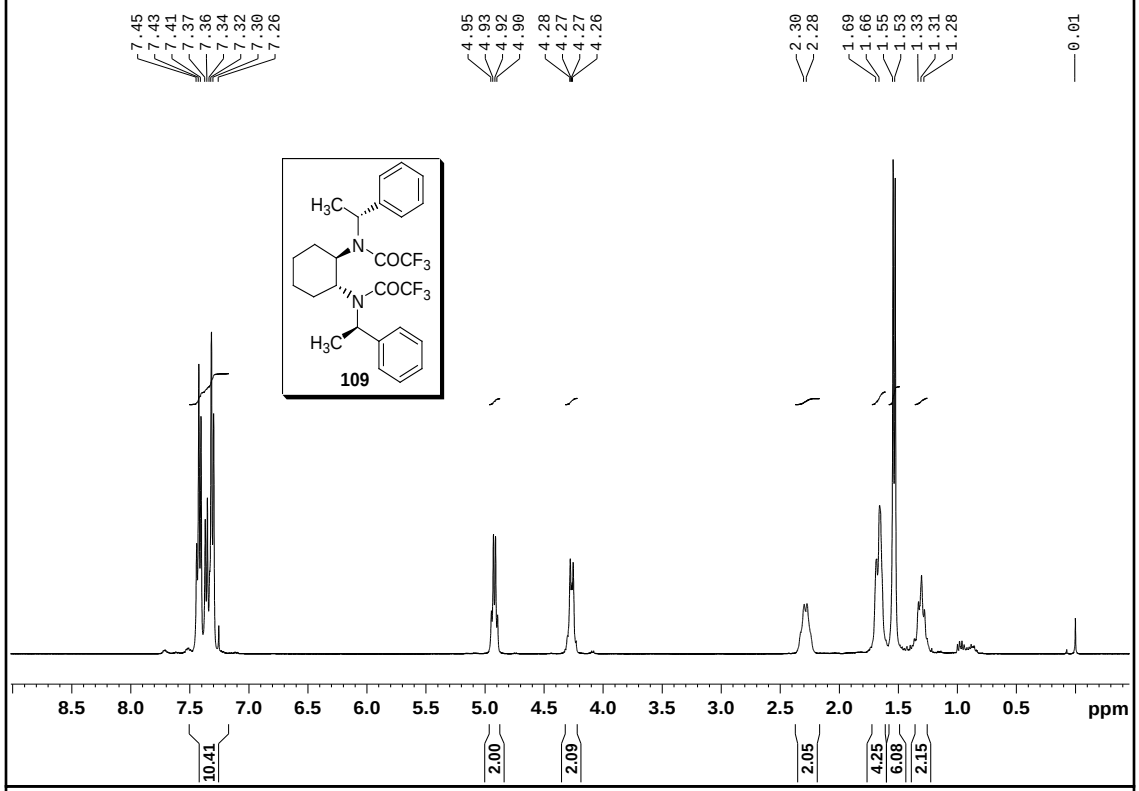
Spectrum No. 11 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



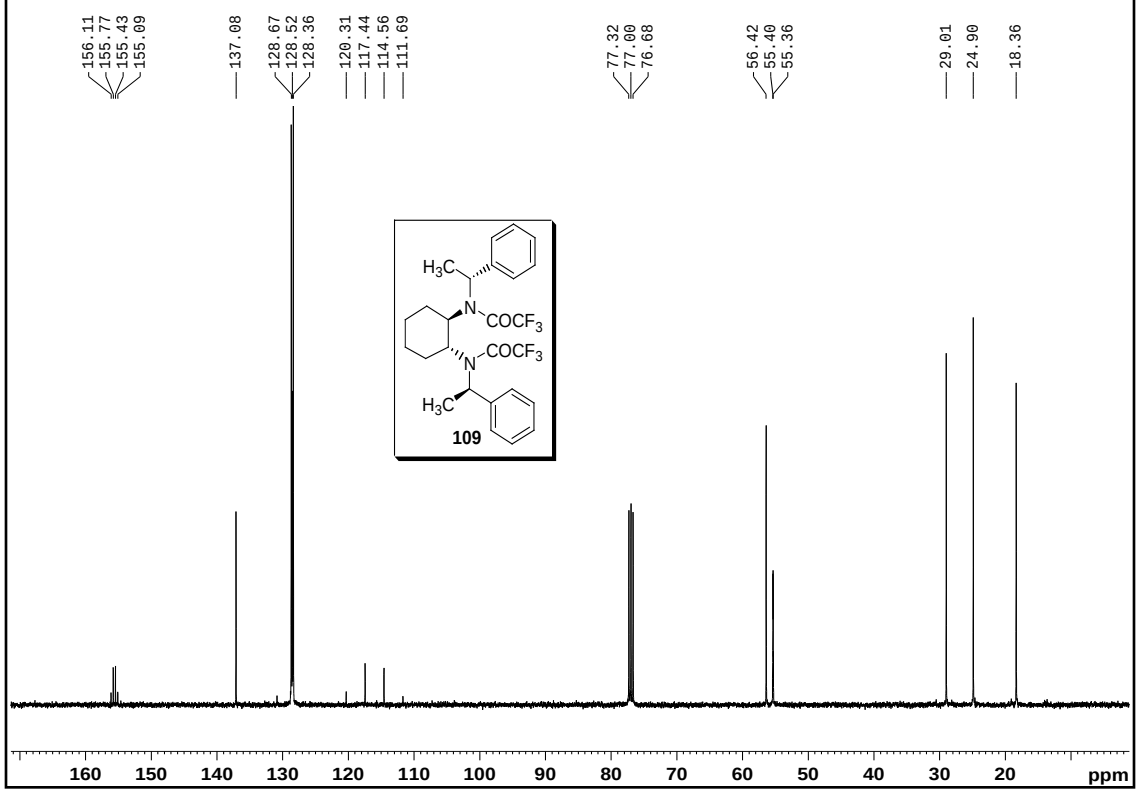
Spectrum No. 12 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



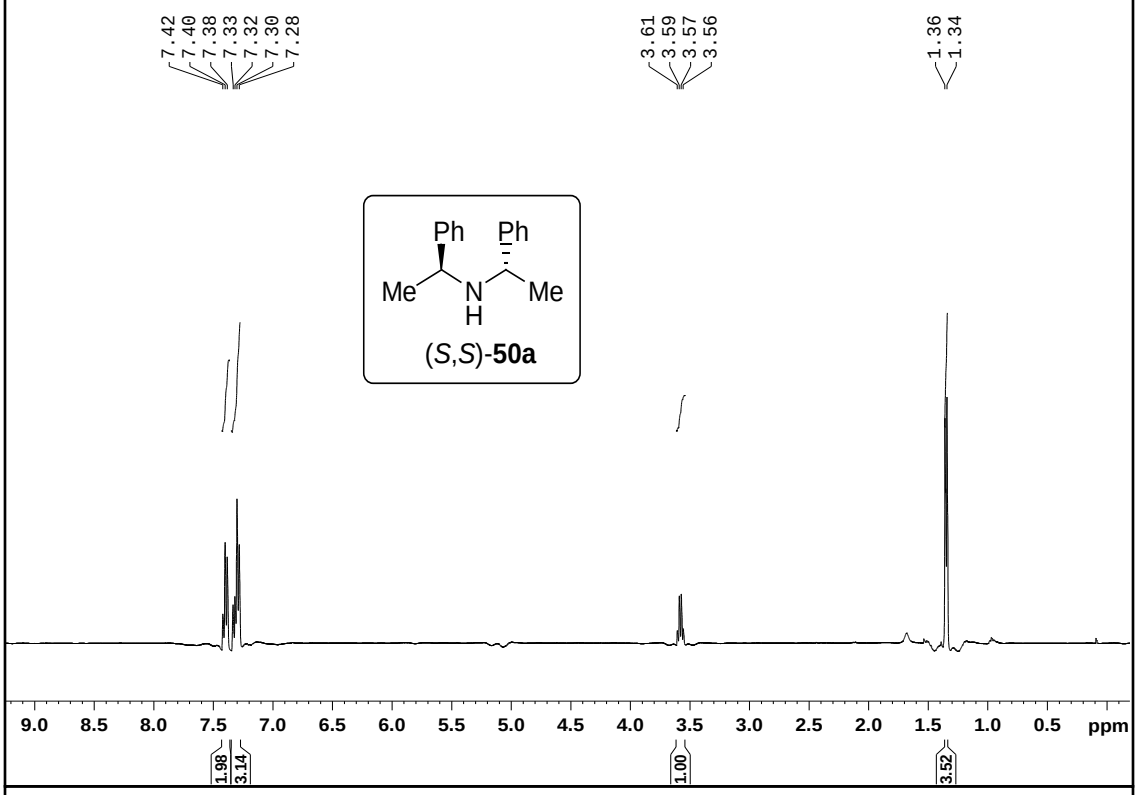
Spectrum No. 13 (Chapter 1, Section 1.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



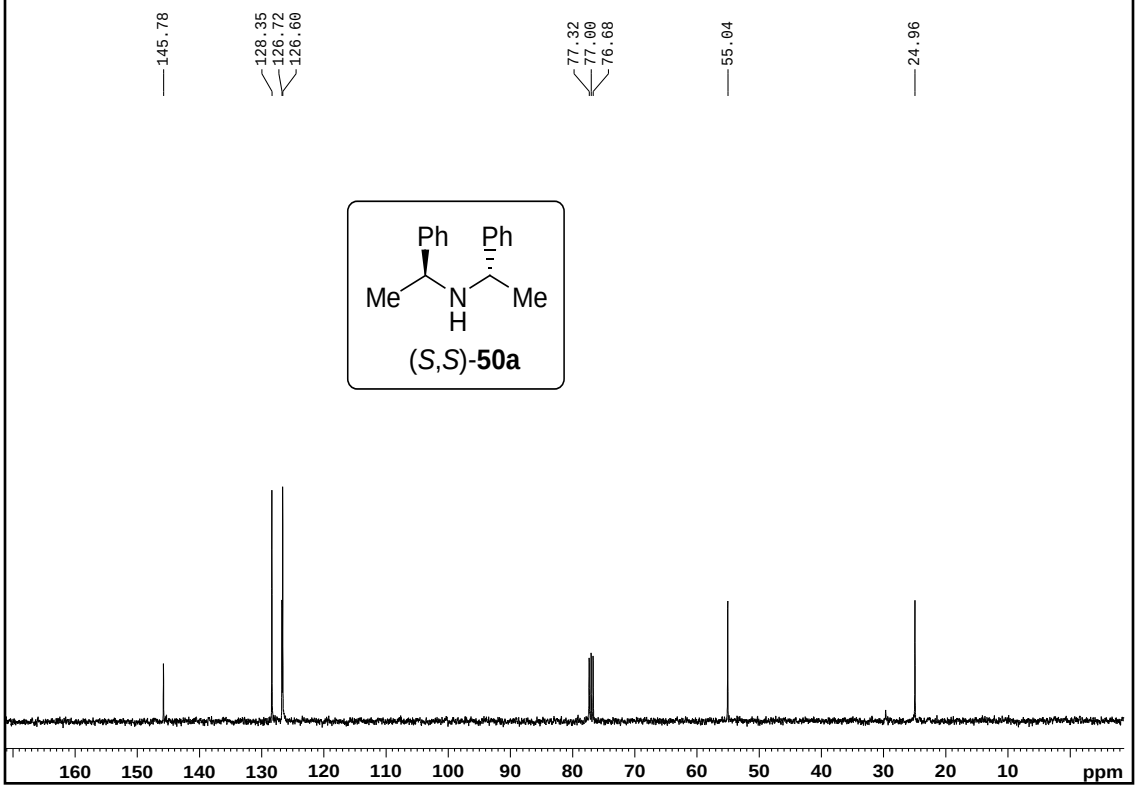
Spectrum No. 14 (Chapter 1, Section 1.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



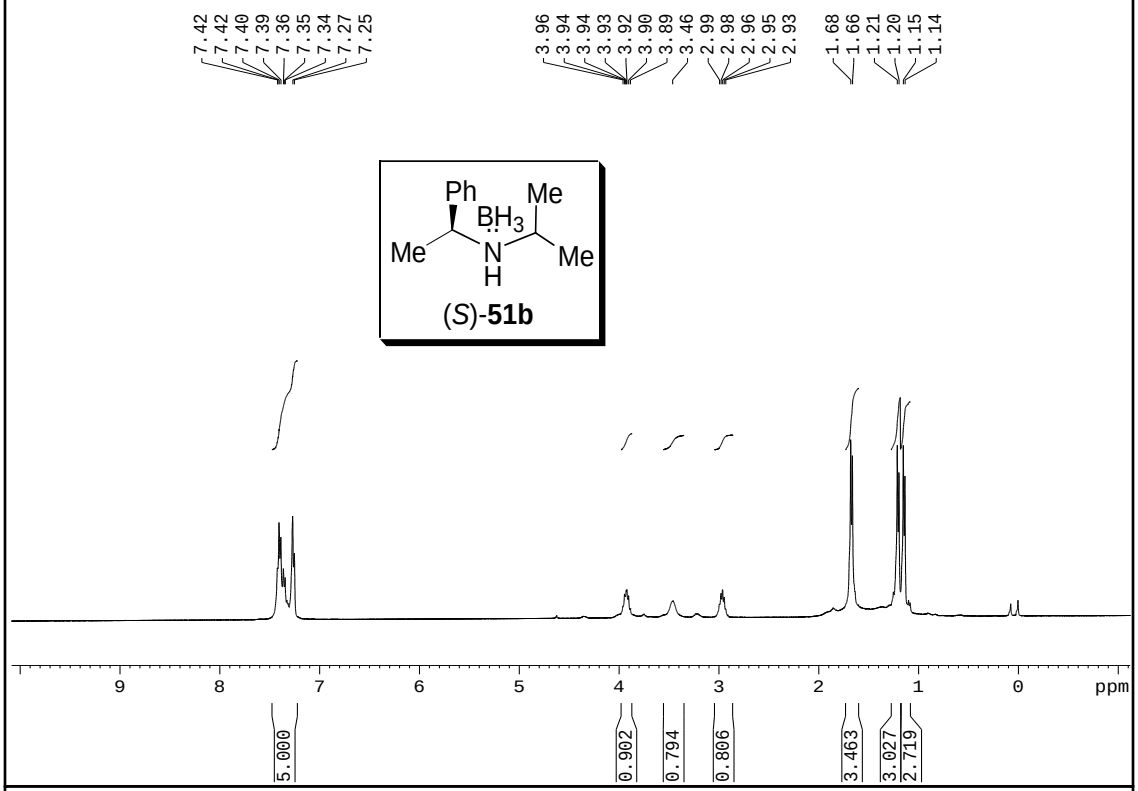
Spectrum No. 15 (Chapter 3, Section 3.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



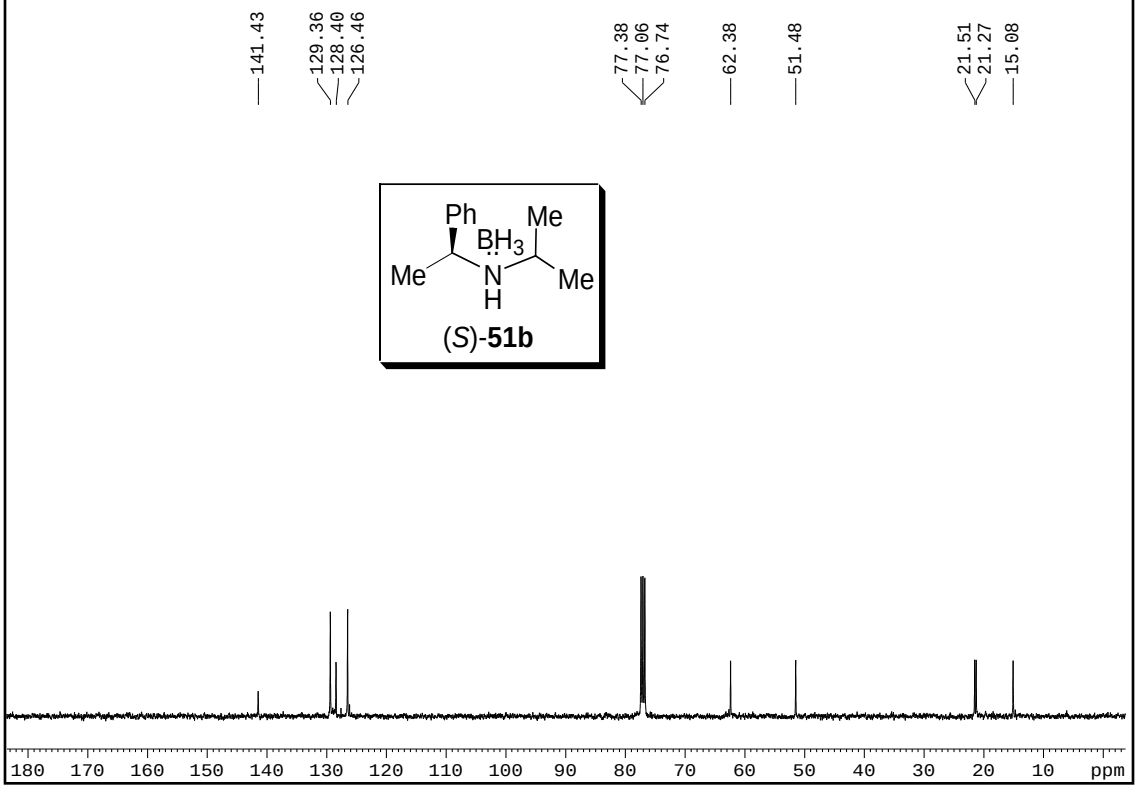
Spectrum No. 16 (Chapter 3, Section 3.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



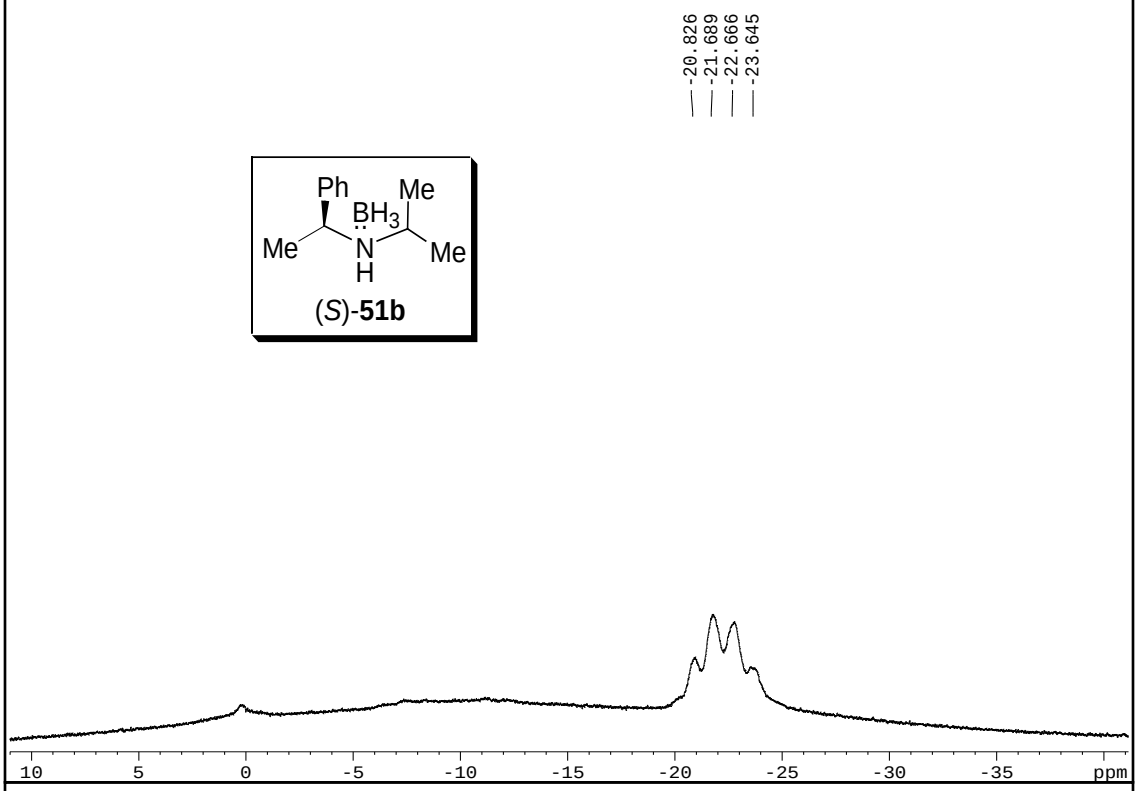
Spectrum No. 17 (Chapter 3, Section 3.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



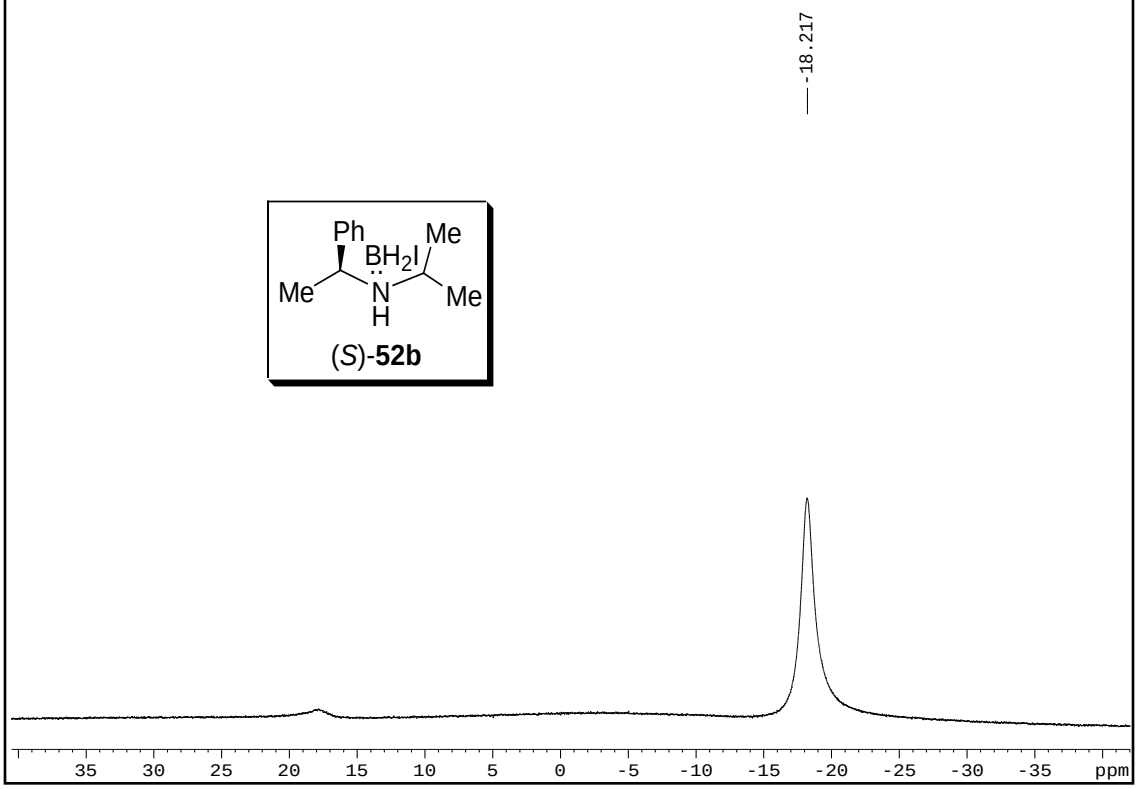
Spectrum No.18 (Chapter 3, Section 3.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



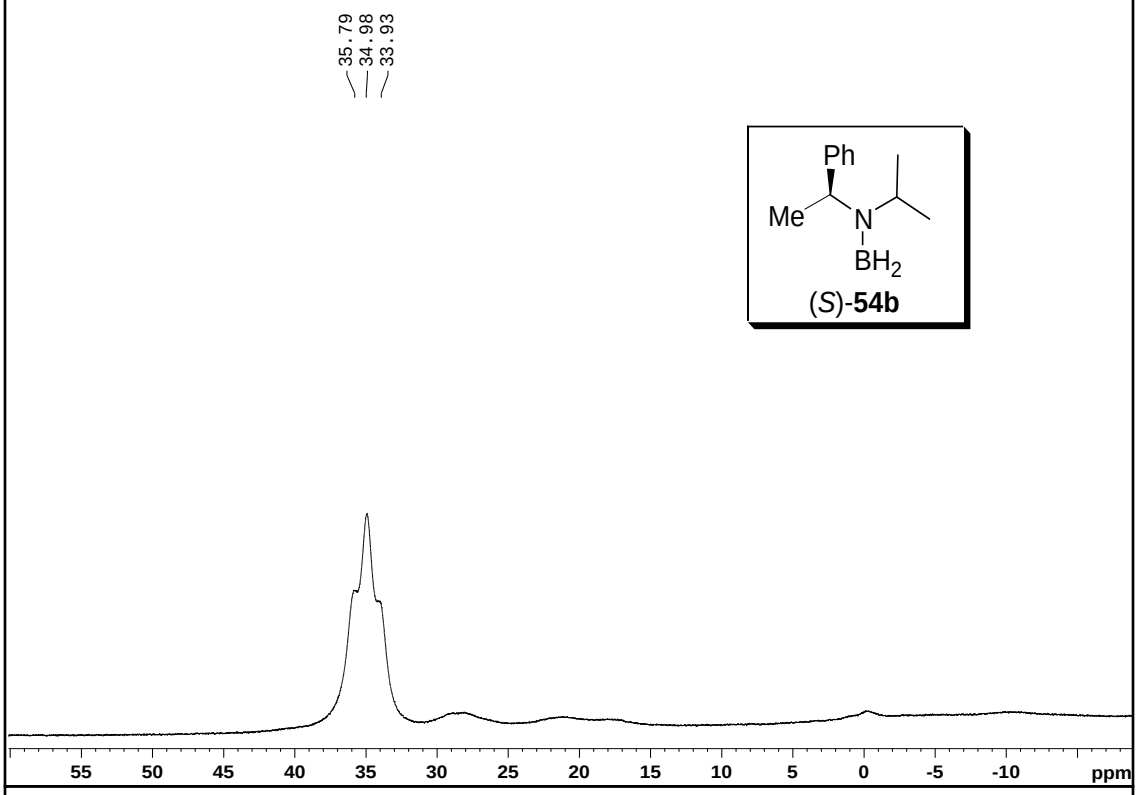
Spectrum No. 19 (Chapter 3, Section 3.4), ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



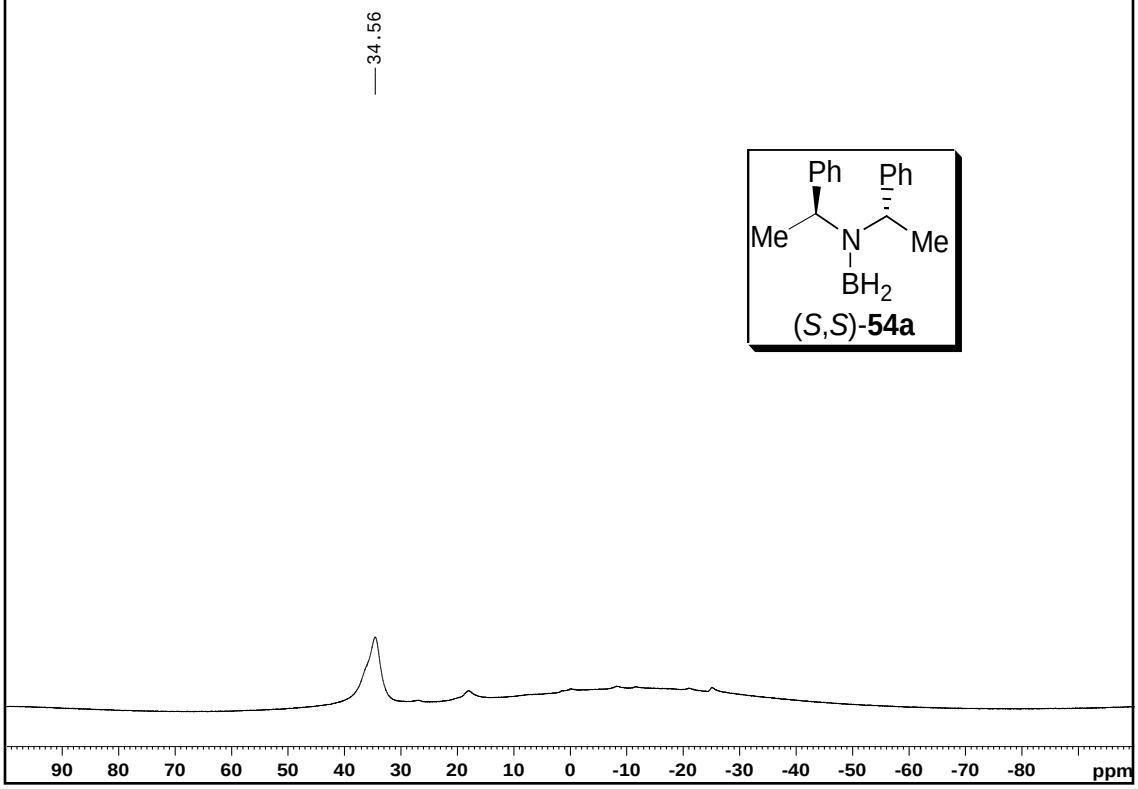
Spectrum No. 20 (Chapter 3, Section 3.4), Decoupled ^{11}B NMR Spectrum (128.3 MHz, CH_2Cl_2)



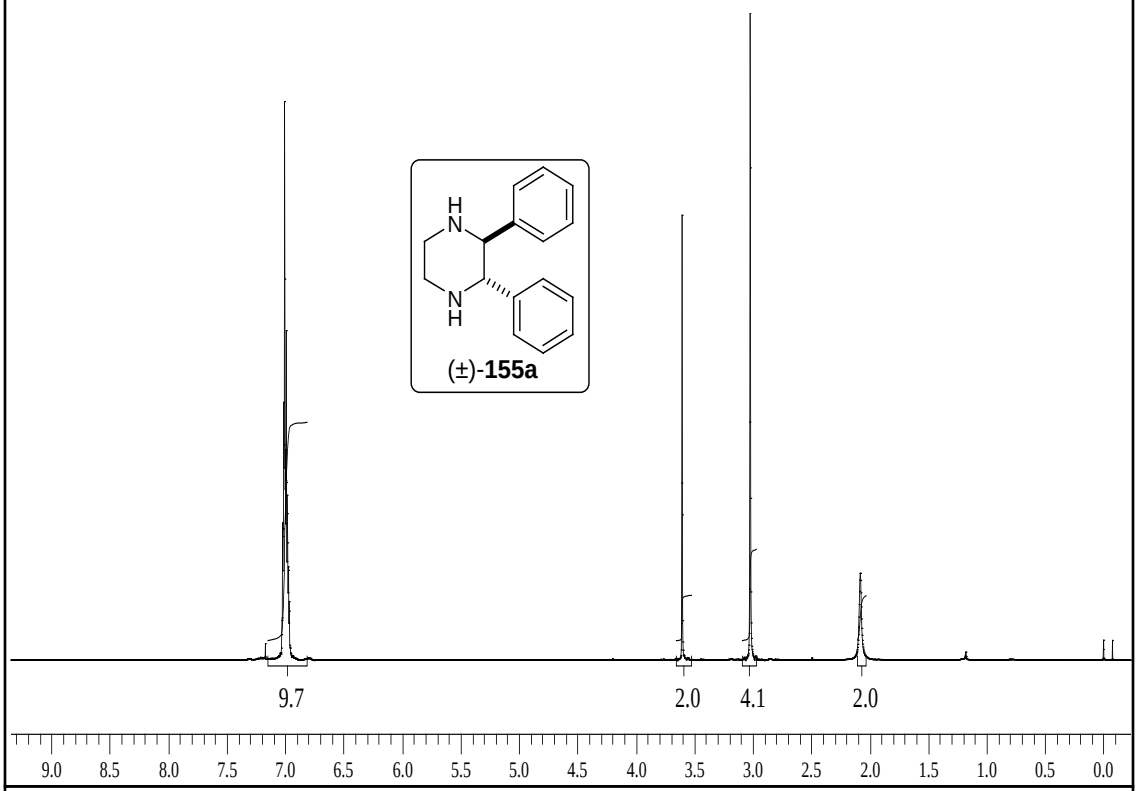
Spectrum No. 21 (Chapter 3, Section 3.4), ^{11}B NMR Spectrum (128.3 MHz, CH_2Cl_2)



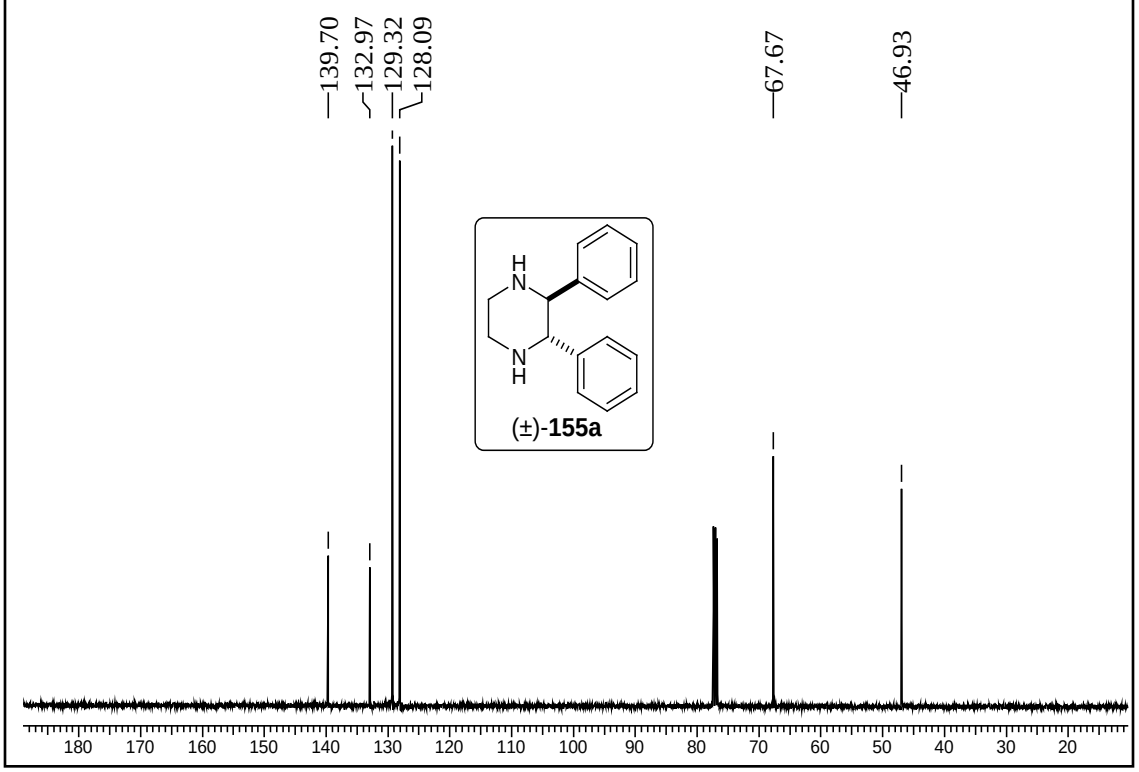
Spectrum No. 22 (Chapter 3, Section 3.4), Decoupled ^{11}B NMR Spectrum (128.3 MHz, CH_2Cl_2)



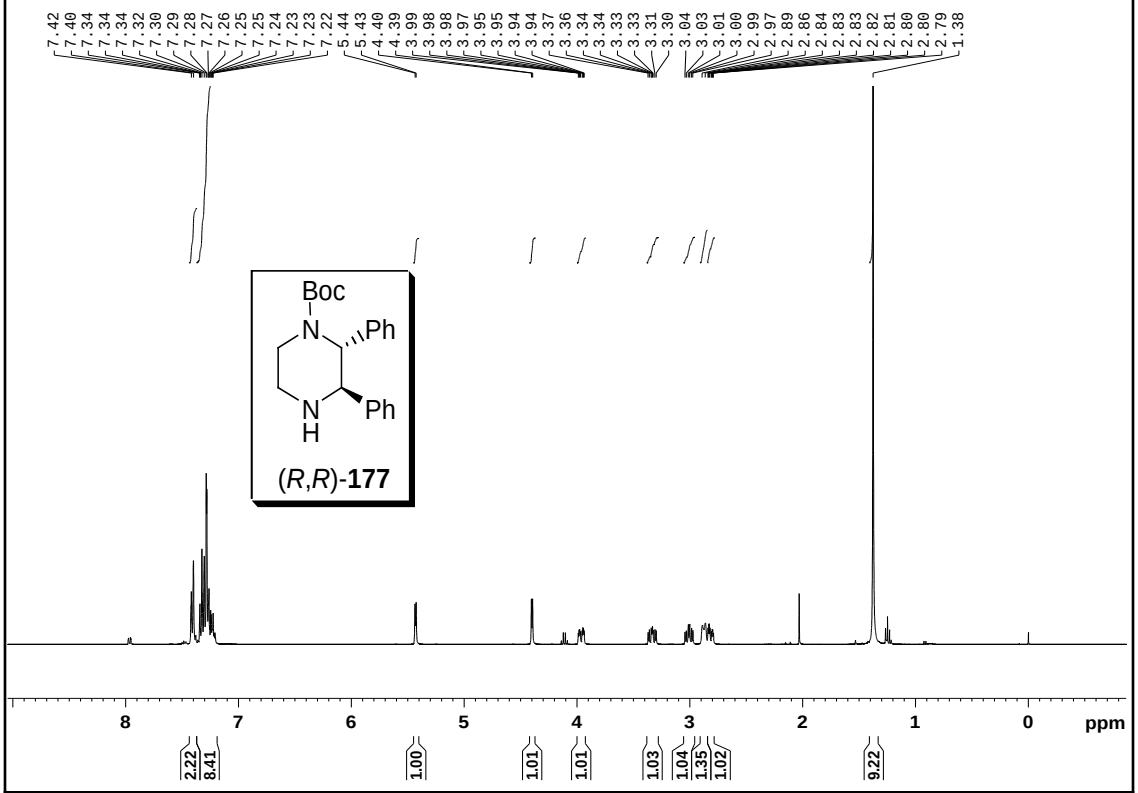
Spectrum No. 23 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



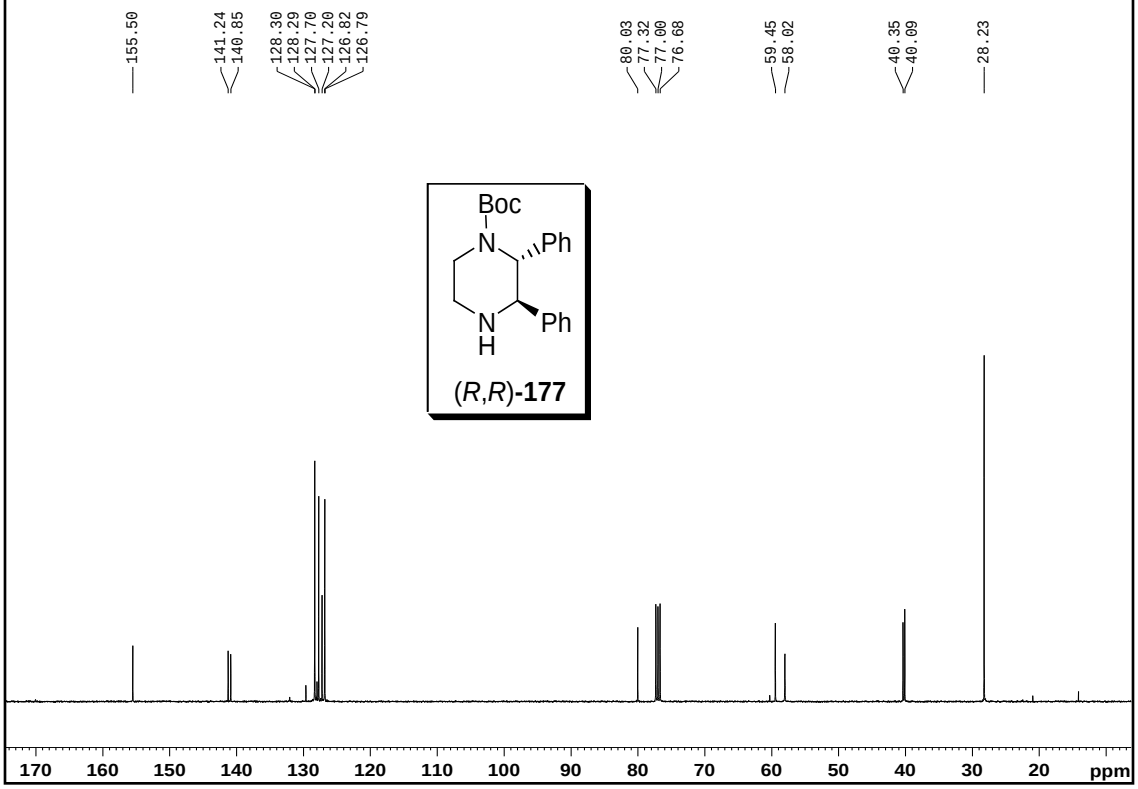
Spectrum No. 24 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



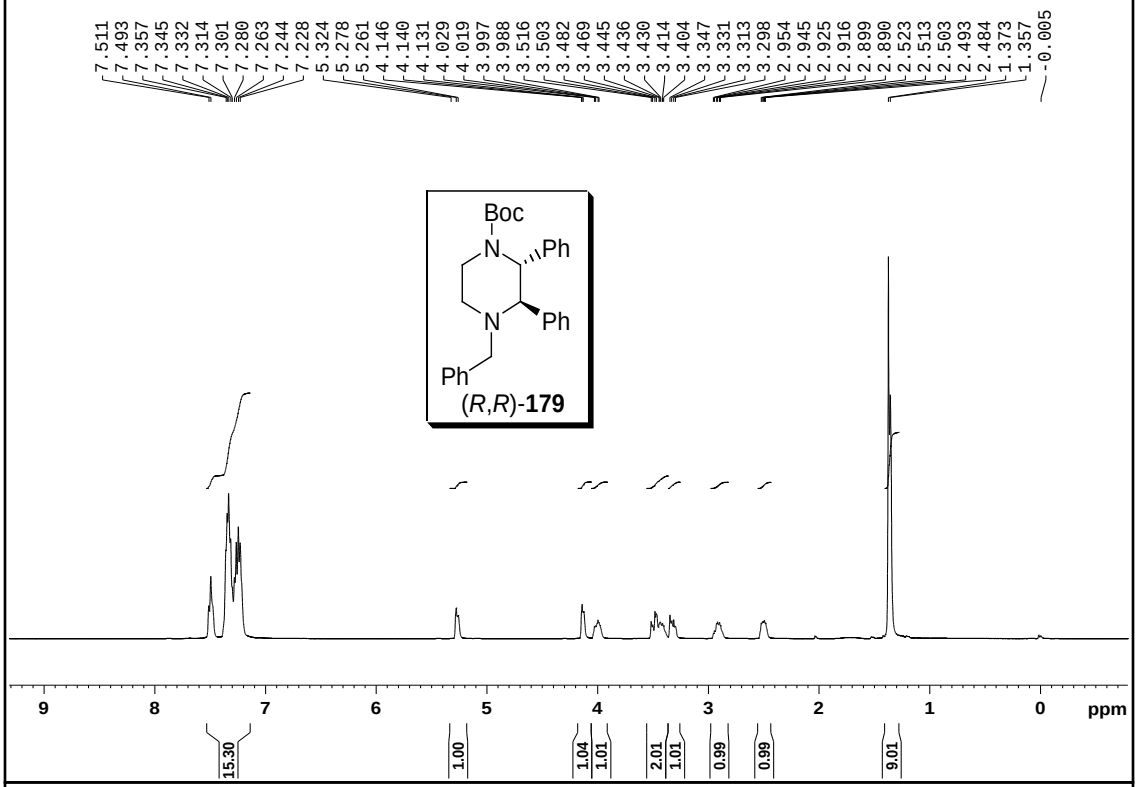
Spectrum No. 25 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



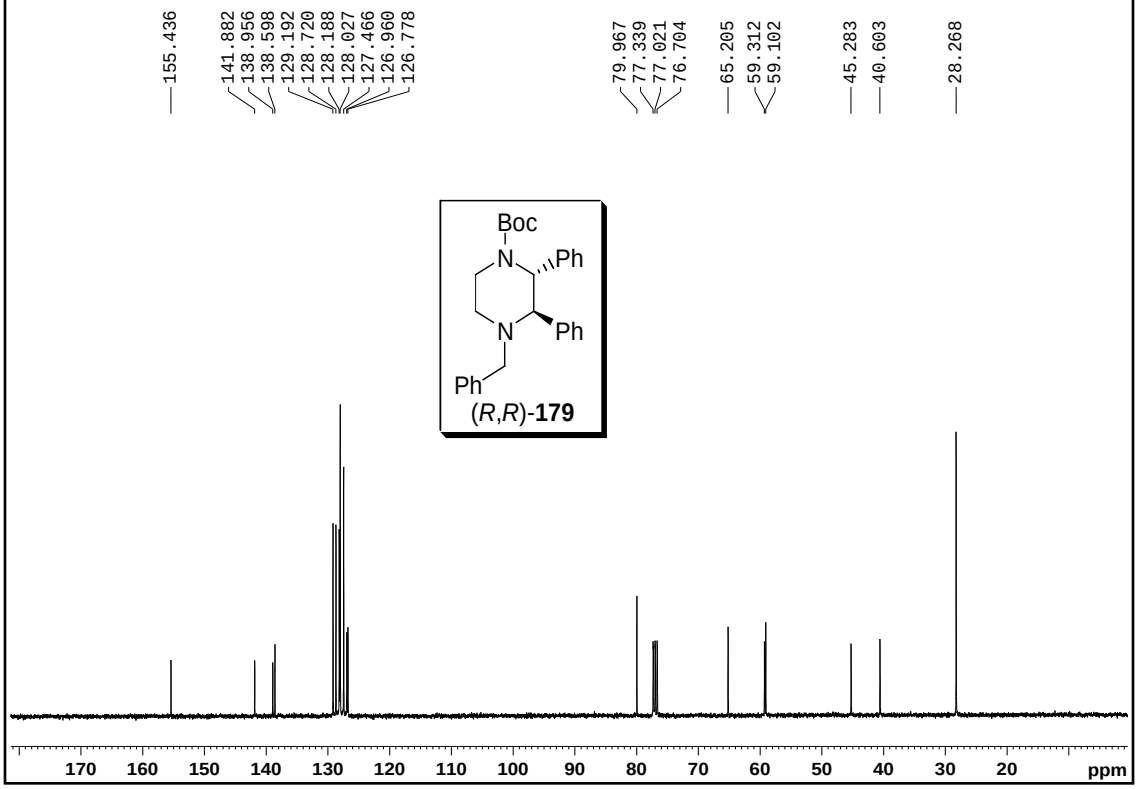
Spectrum No. 26 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



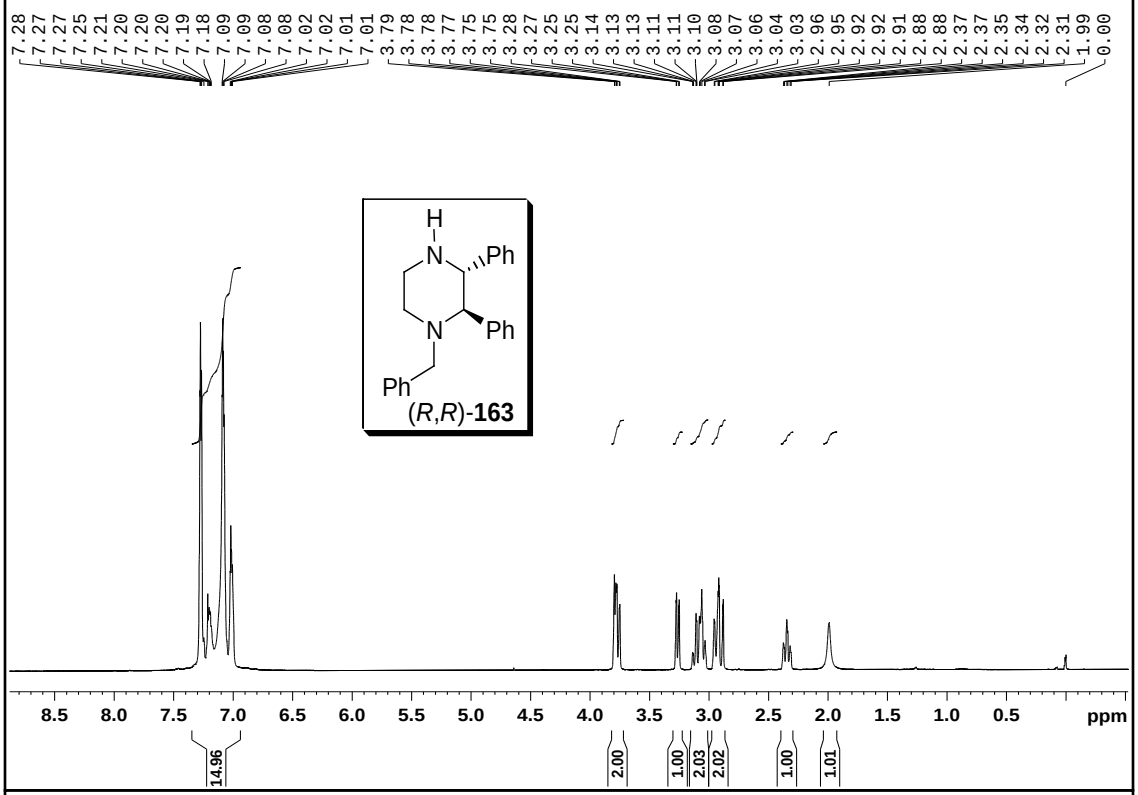
Spectrum No. 27 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



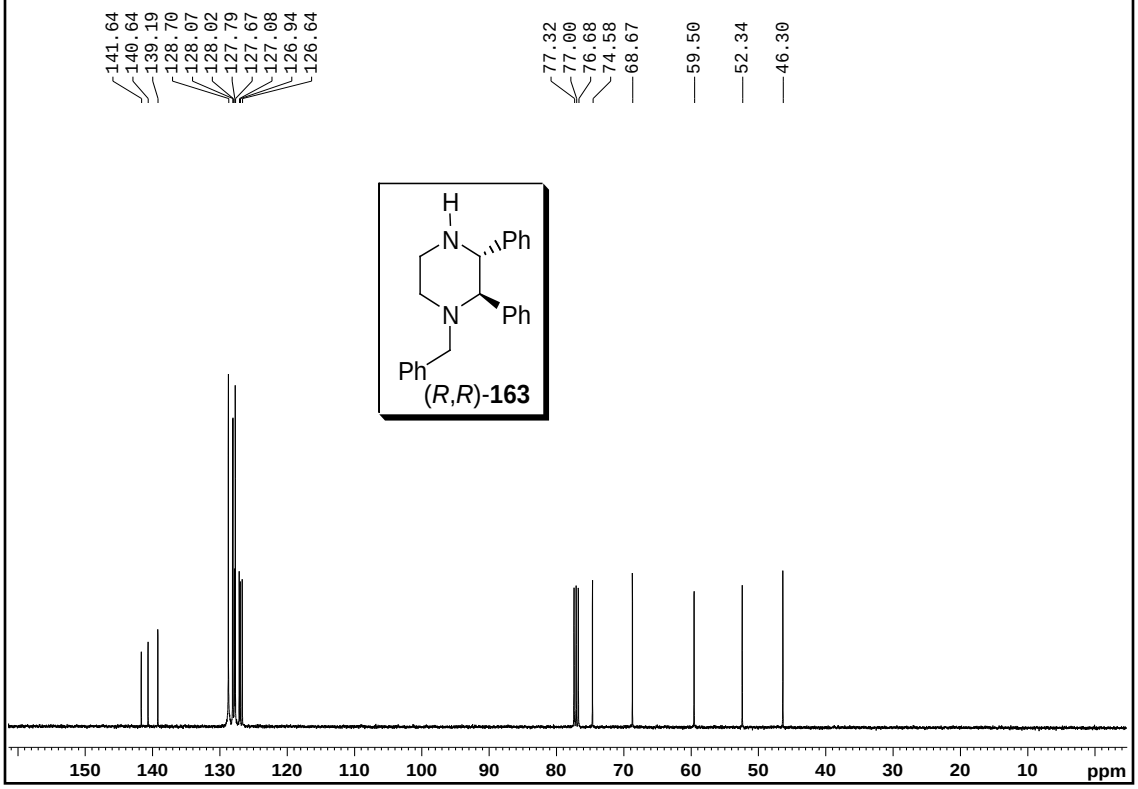
Spectrum No. 28 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



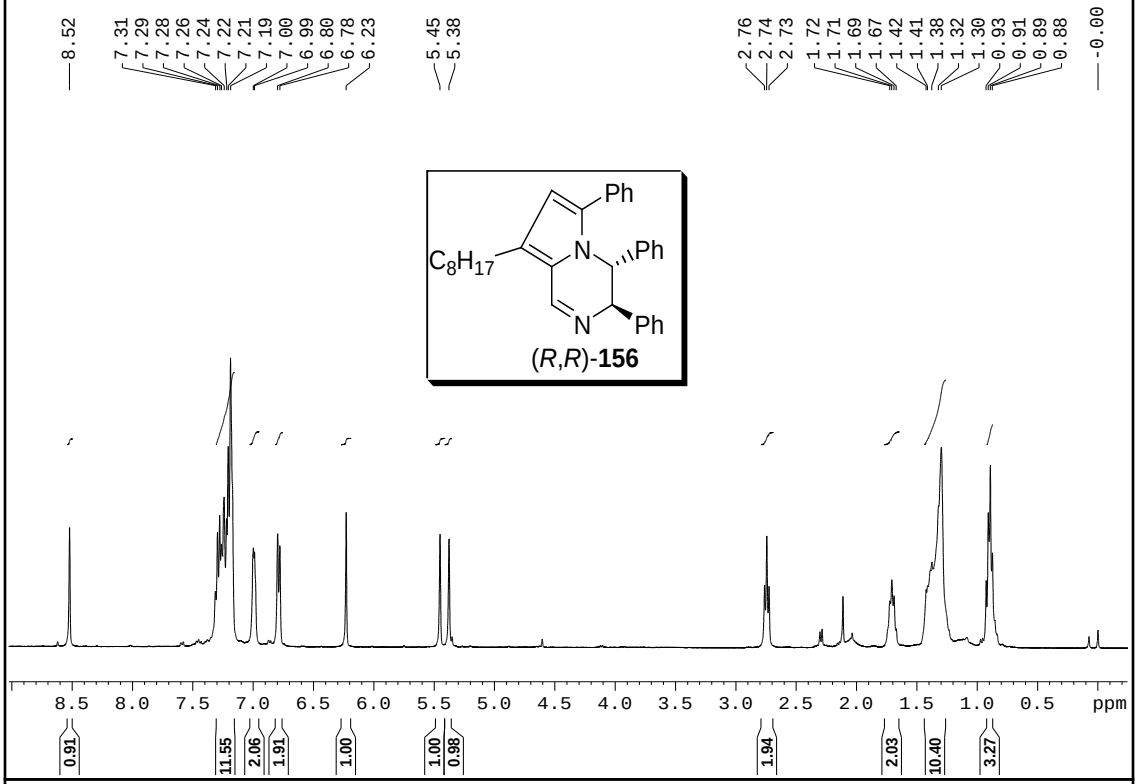
Spectrum No. 29 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



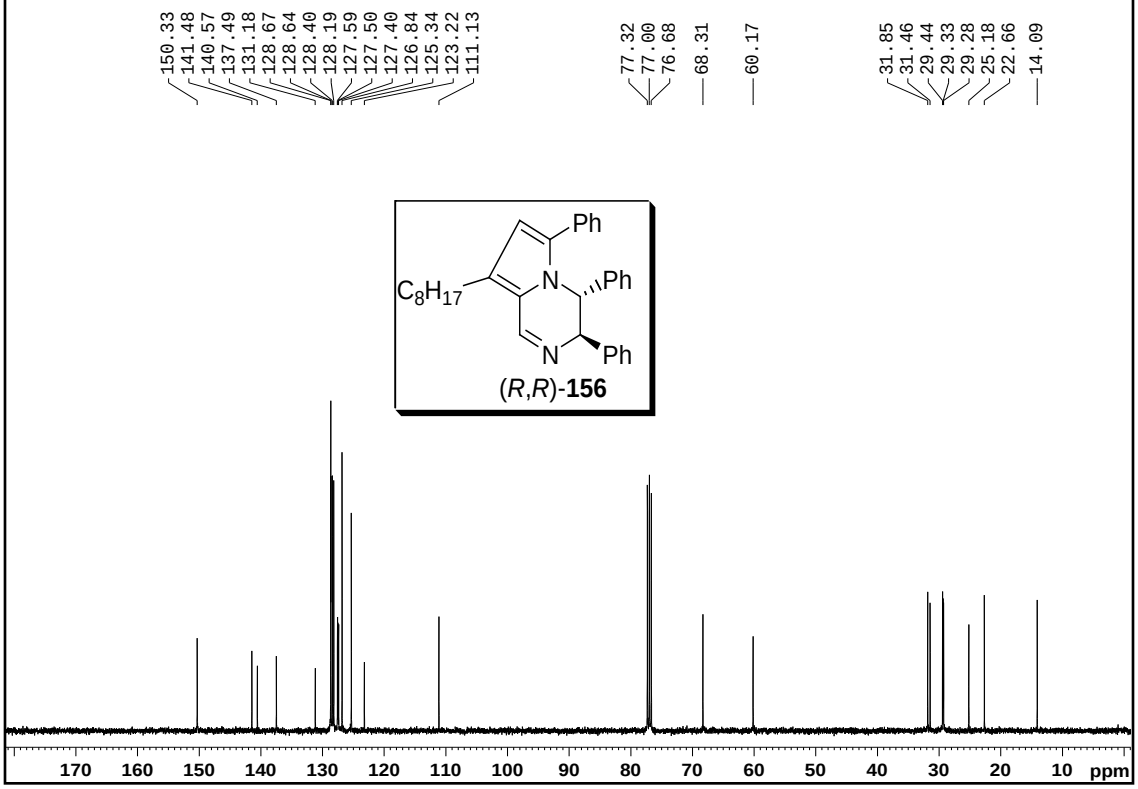
Spectrum No. 30 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



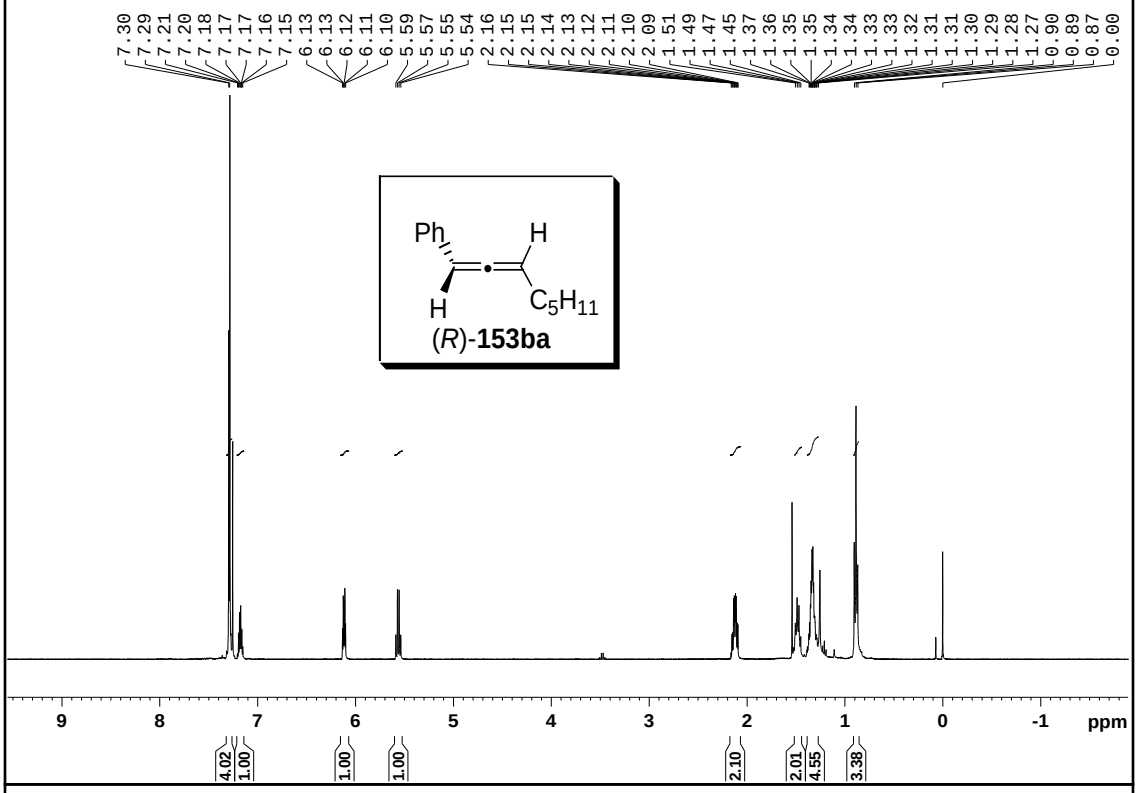
Spectrum No. 31 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



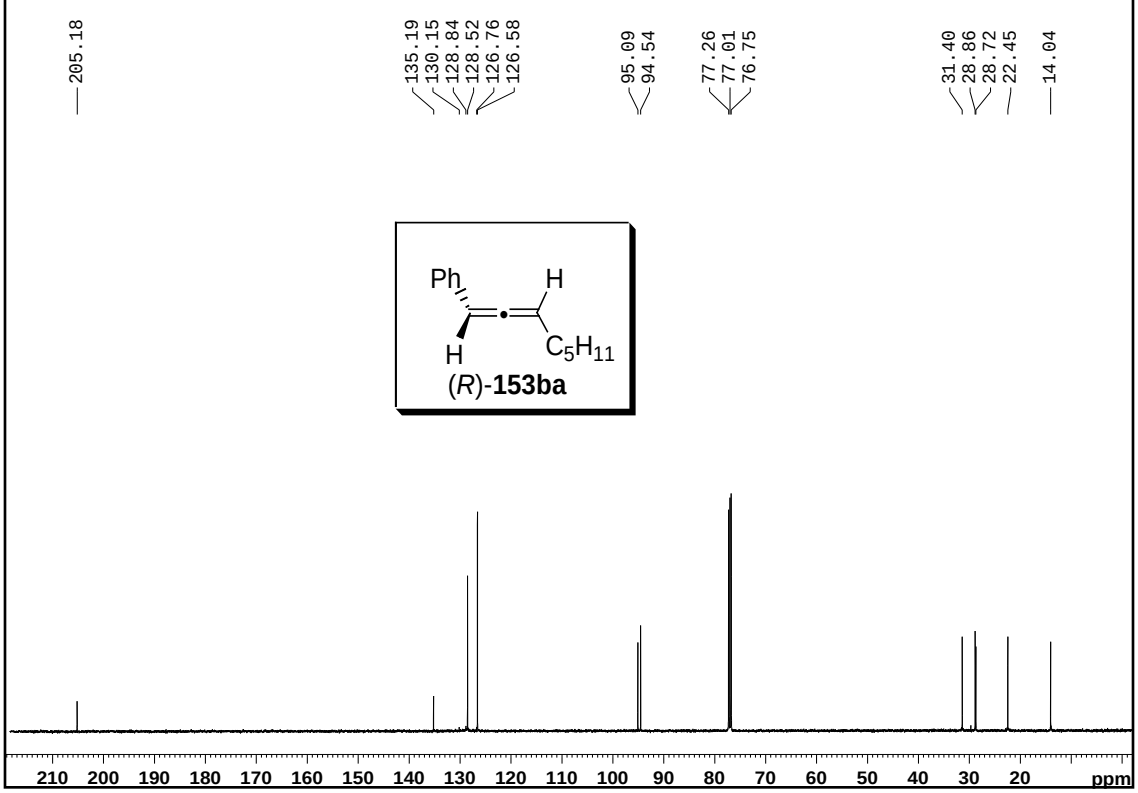
Spectrum No. 32 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



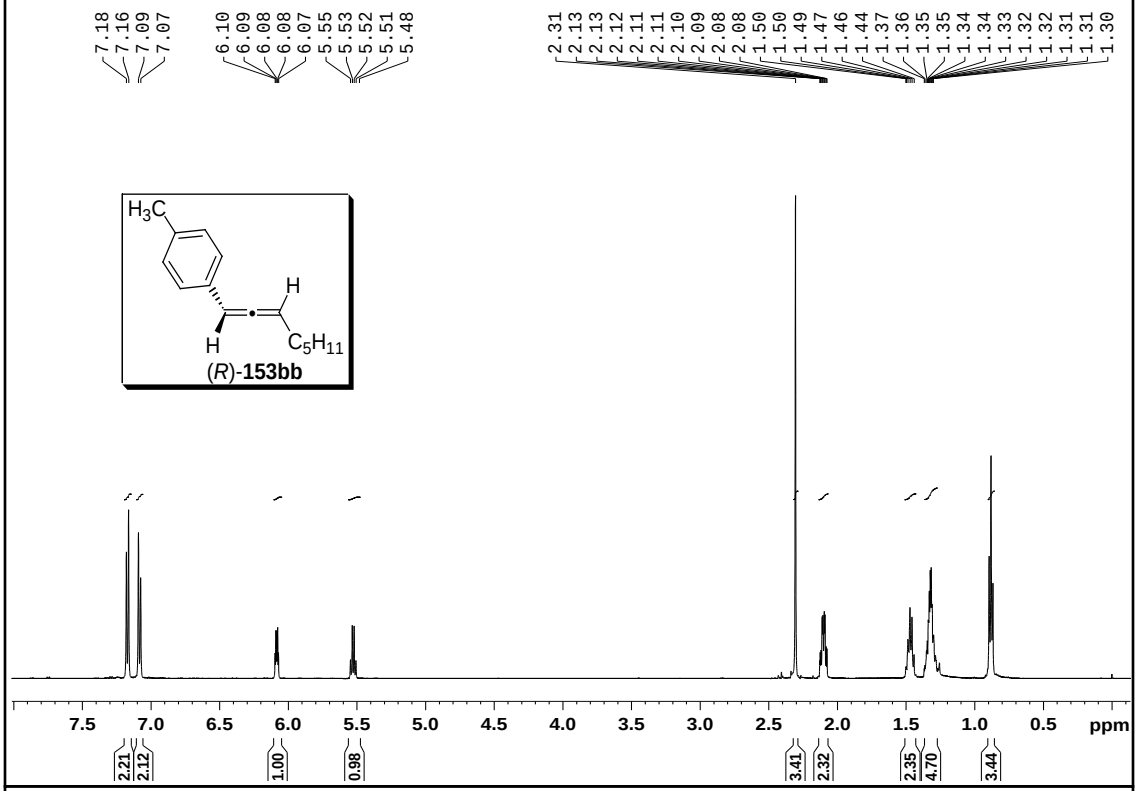
Spectrum No. 33 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



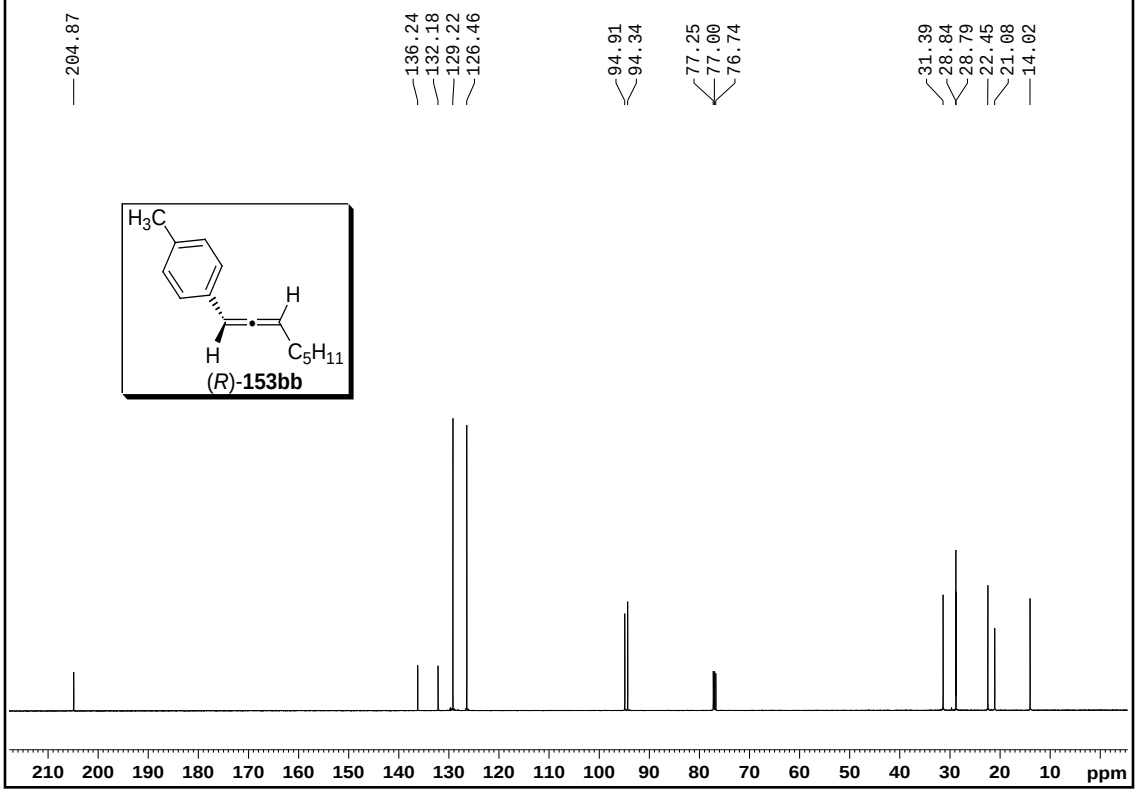
Spectrum No. 34 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



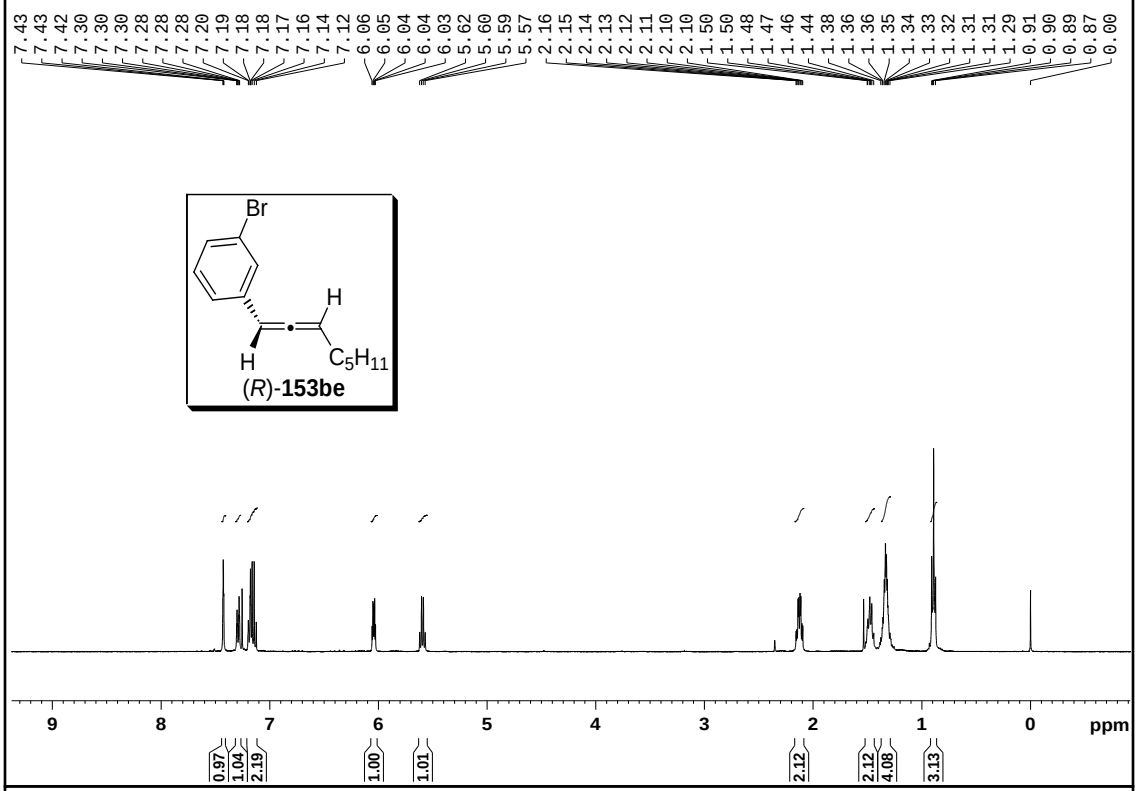
Spectrum No. 35 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



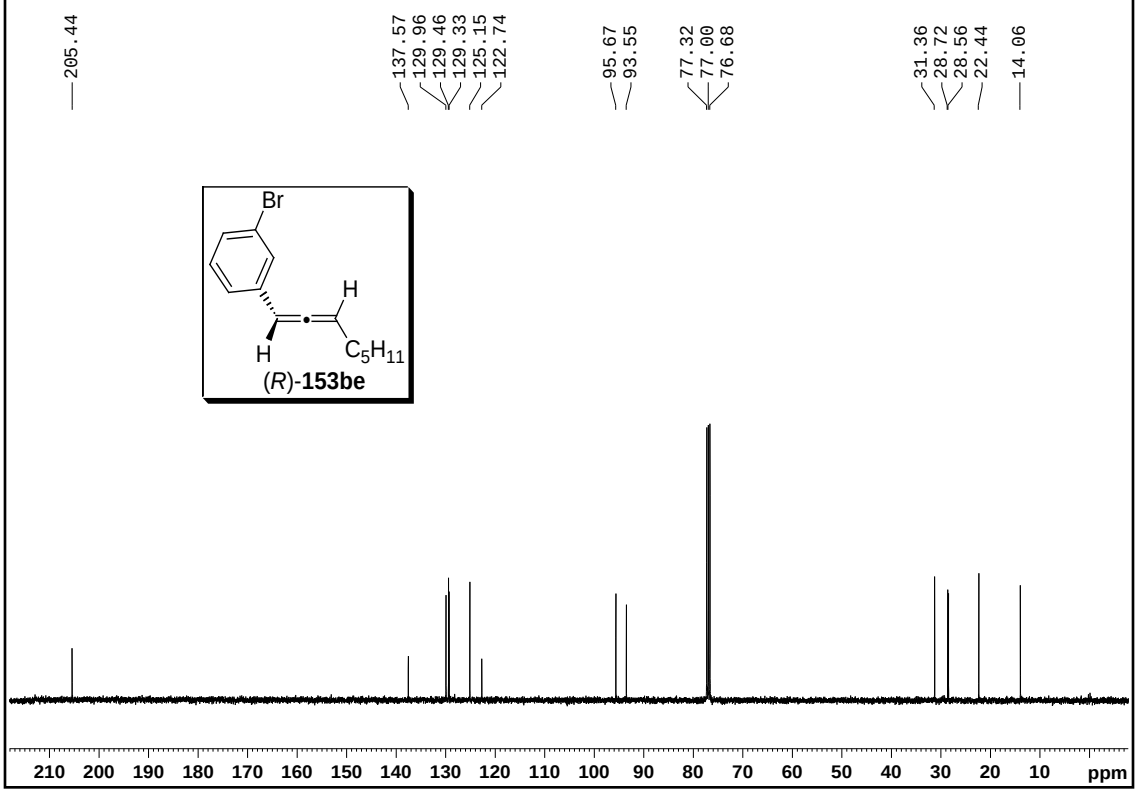
Spectrum No. 36 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



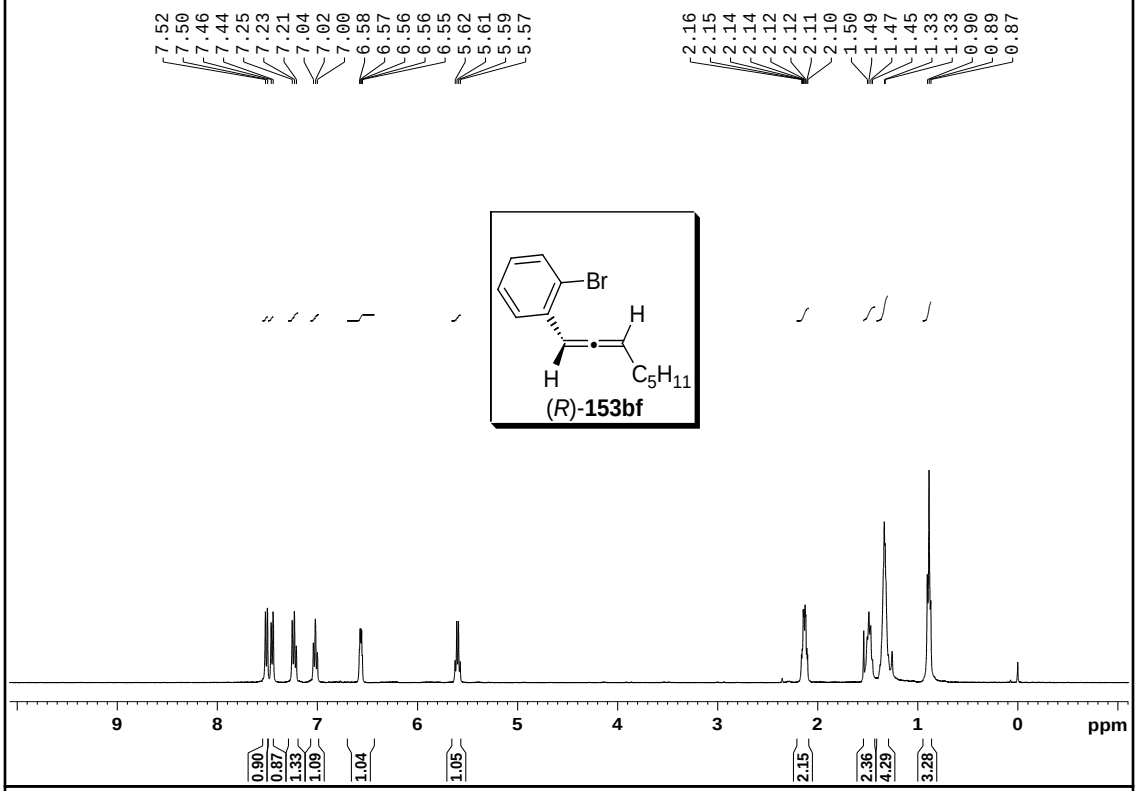
Spectrum No. 37 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



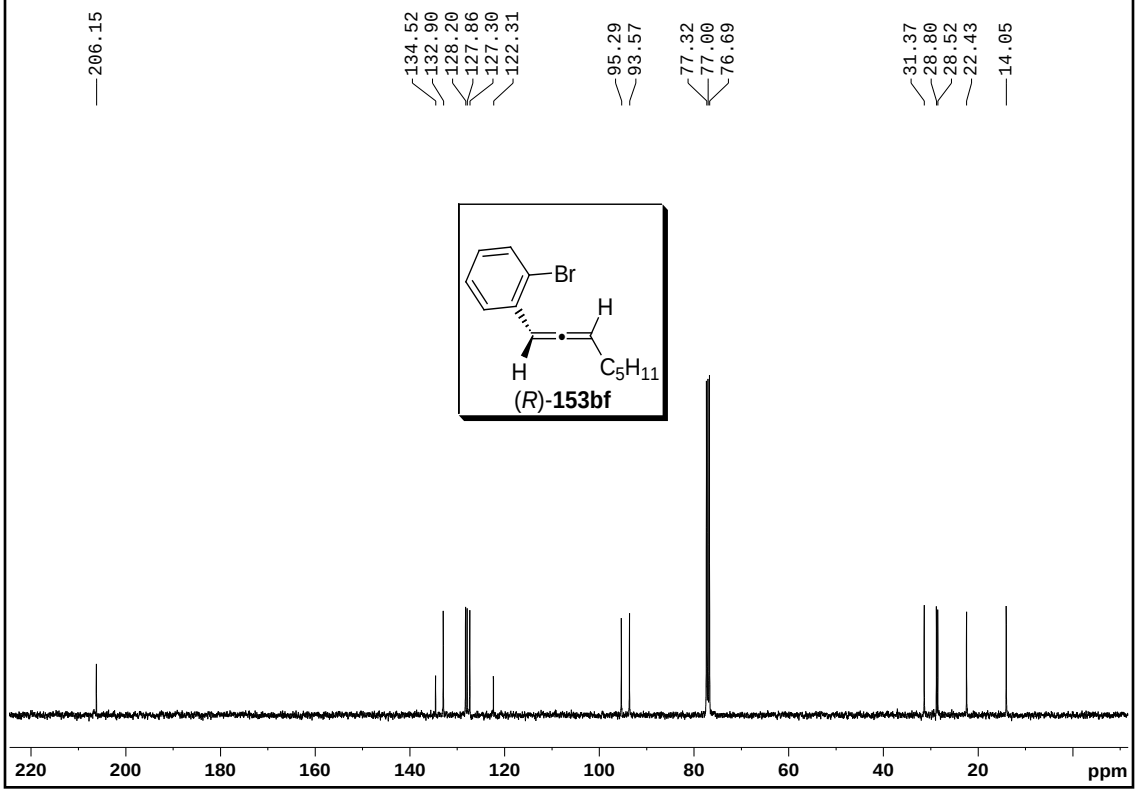
Spectrum No. 38 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



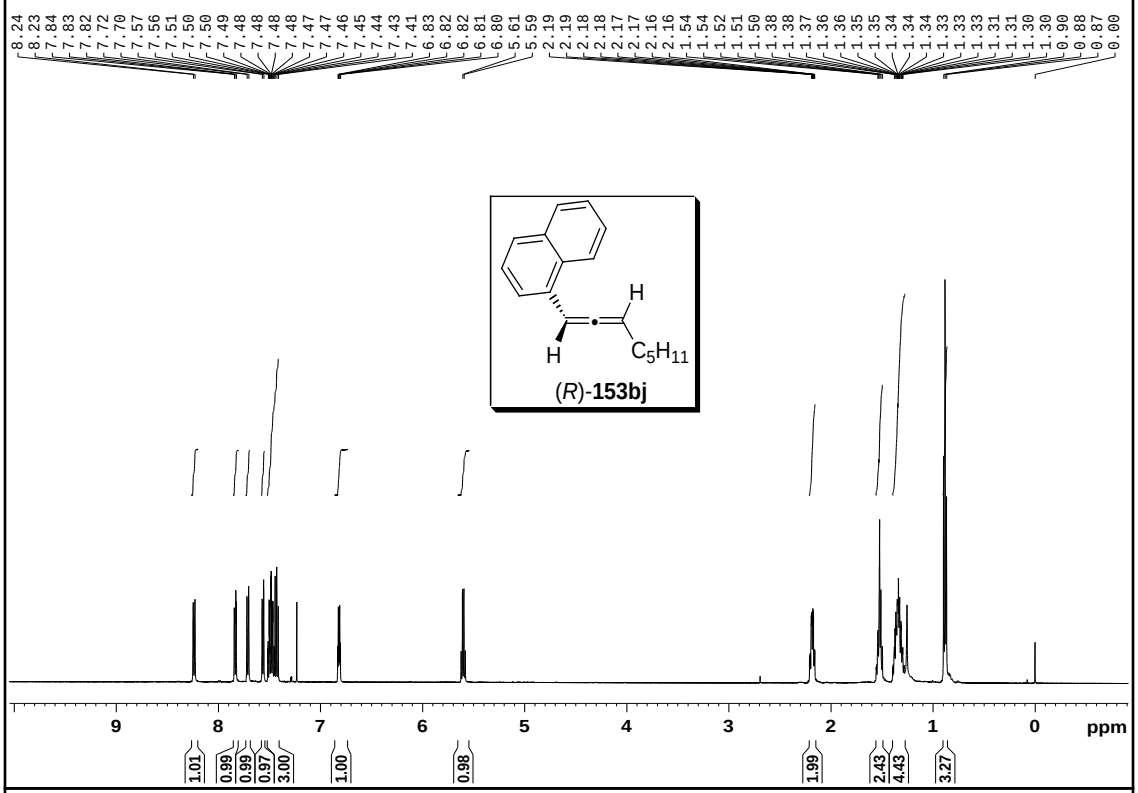
Spectrum No. 39 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



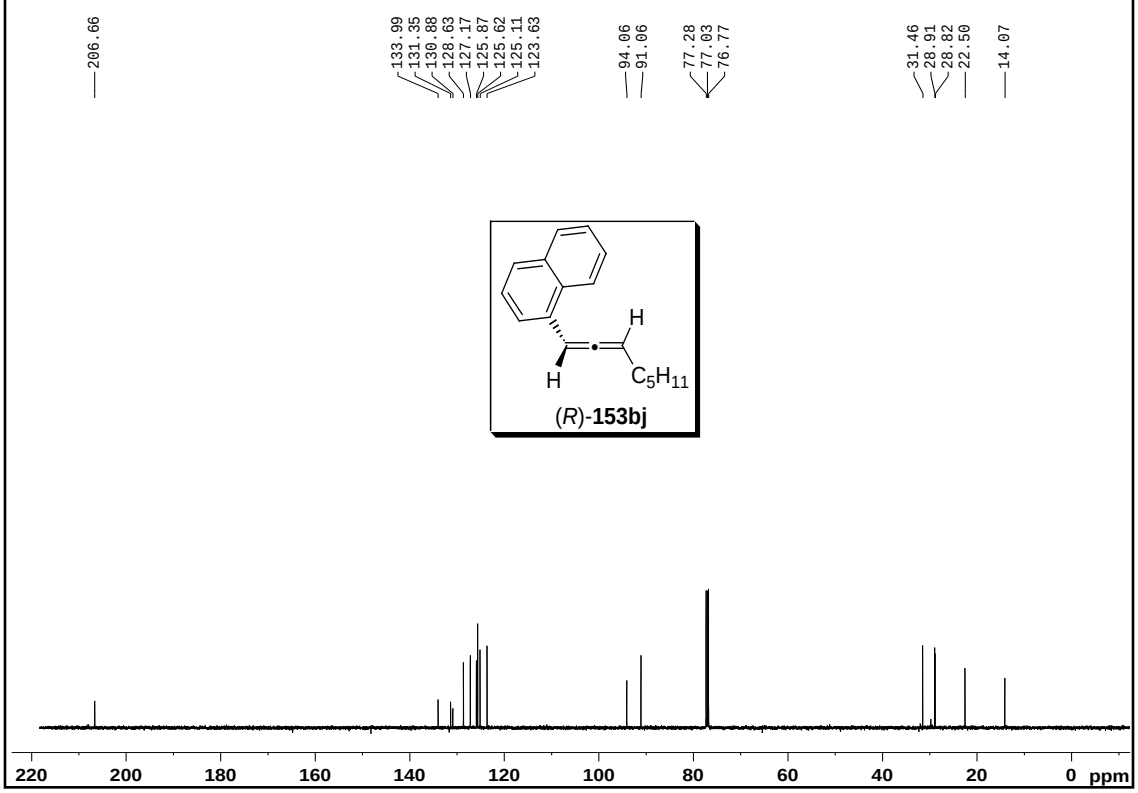
Spectrum No. 40 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



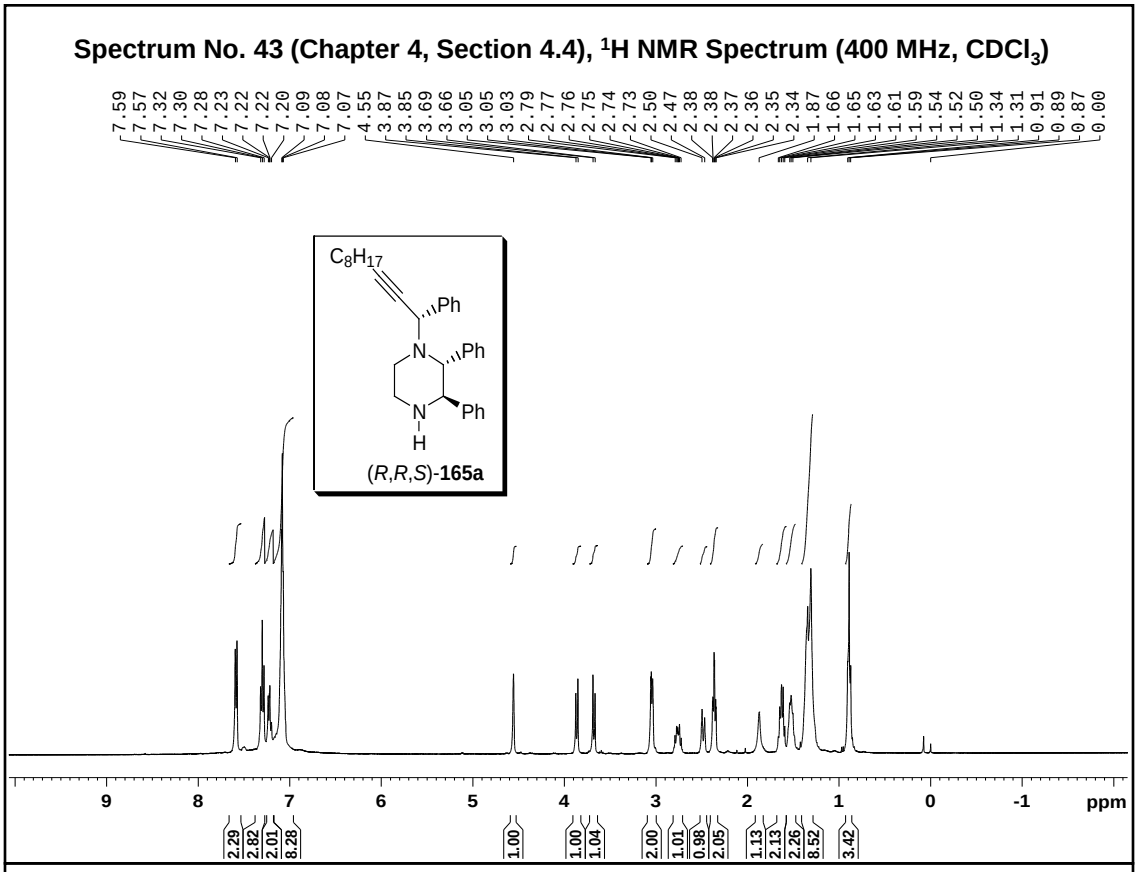
Spectrum No. 41 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



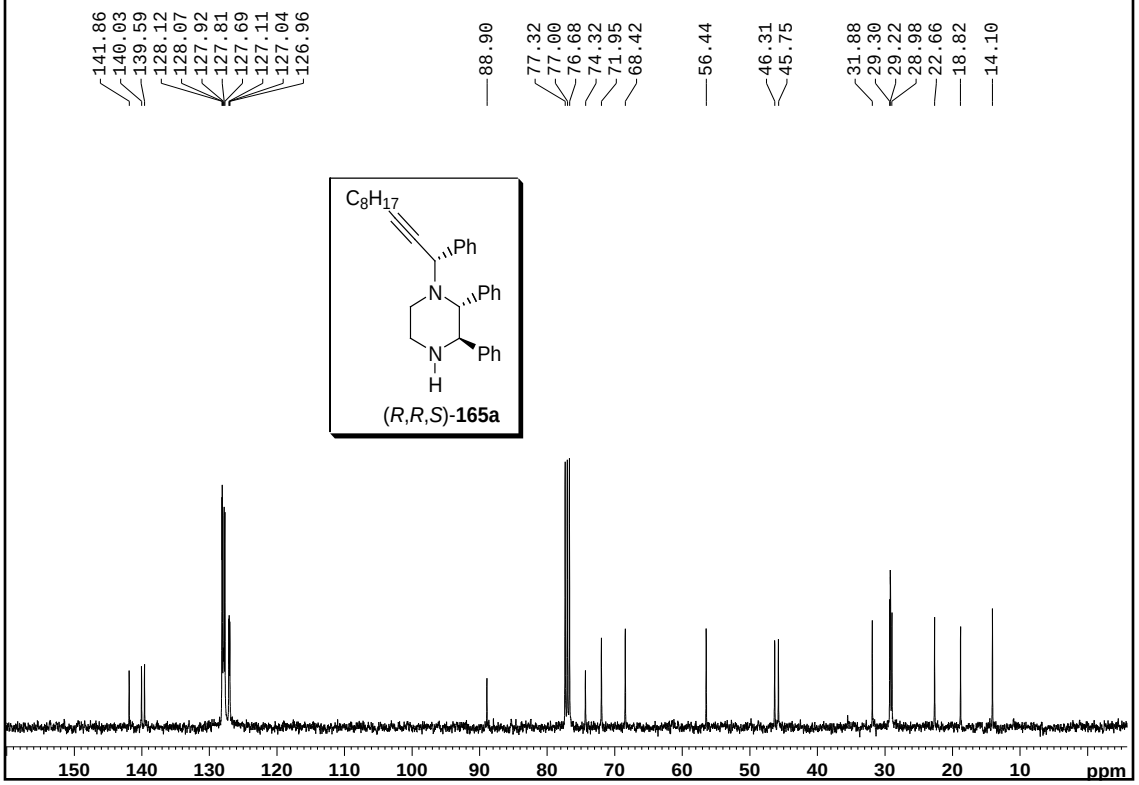
Spectrum No. 42 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



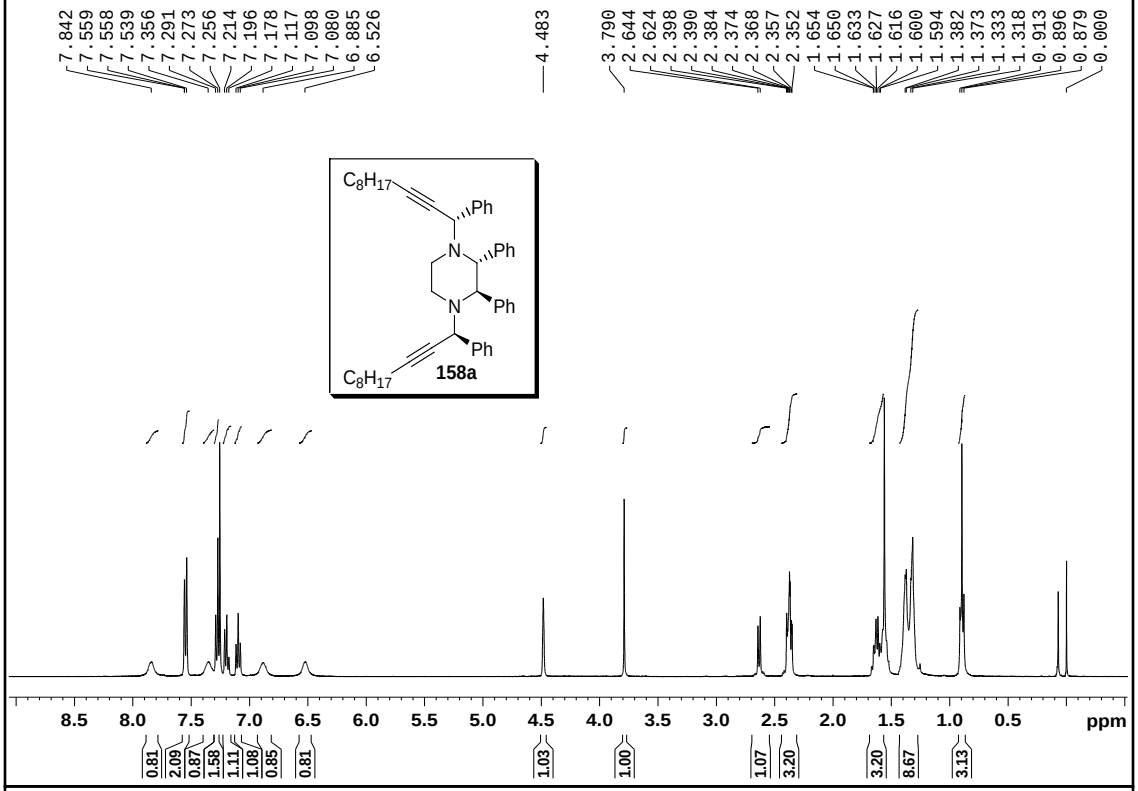
Spectrum No. 43 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



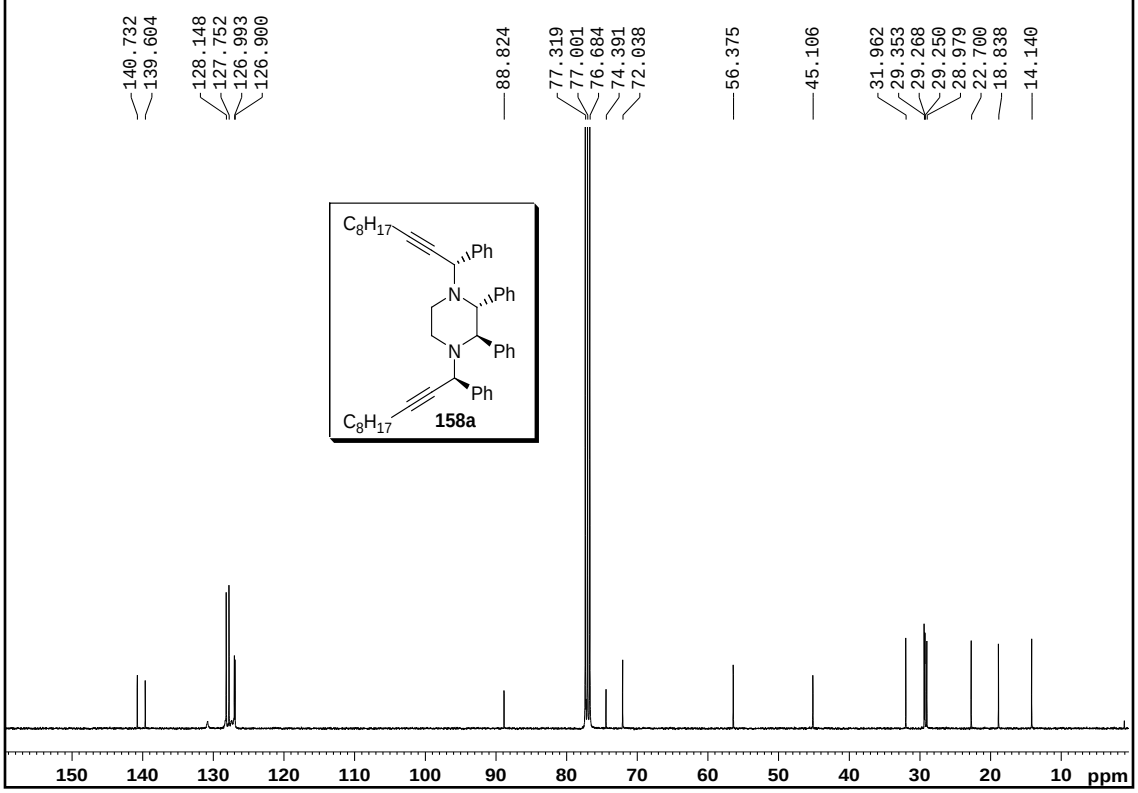
Spectrum No. 44 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



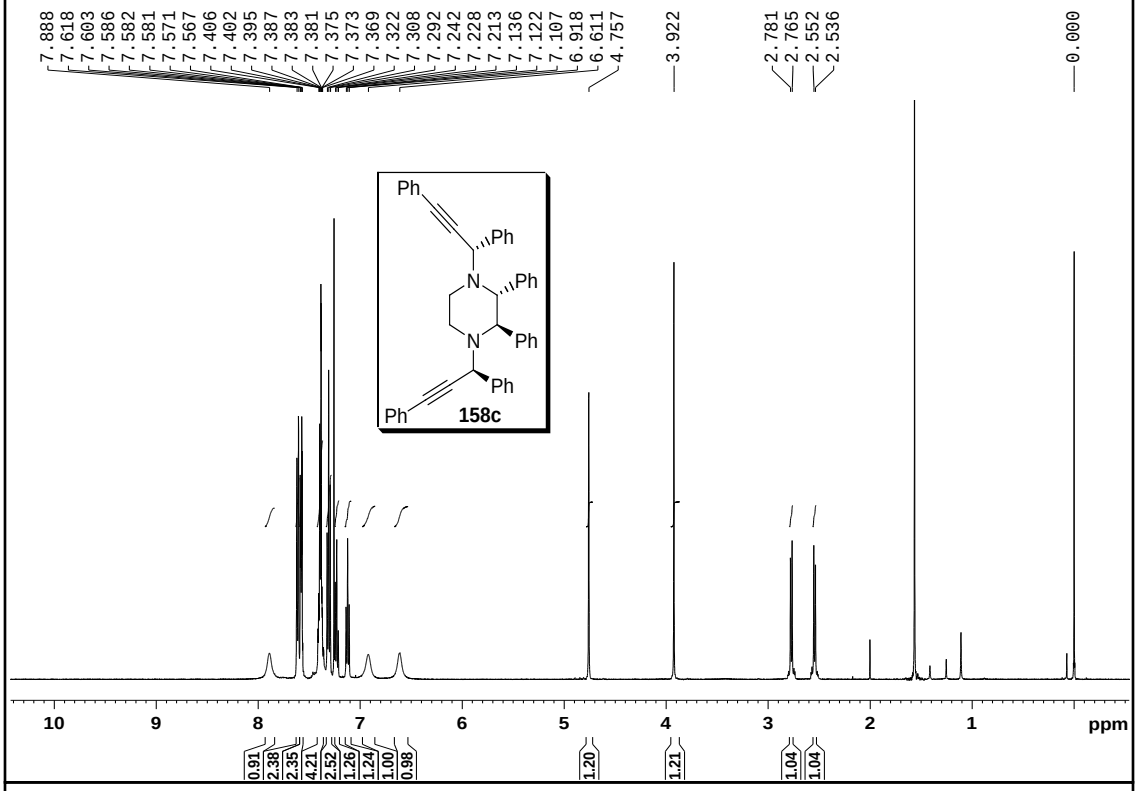
Spectrum No. 45 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



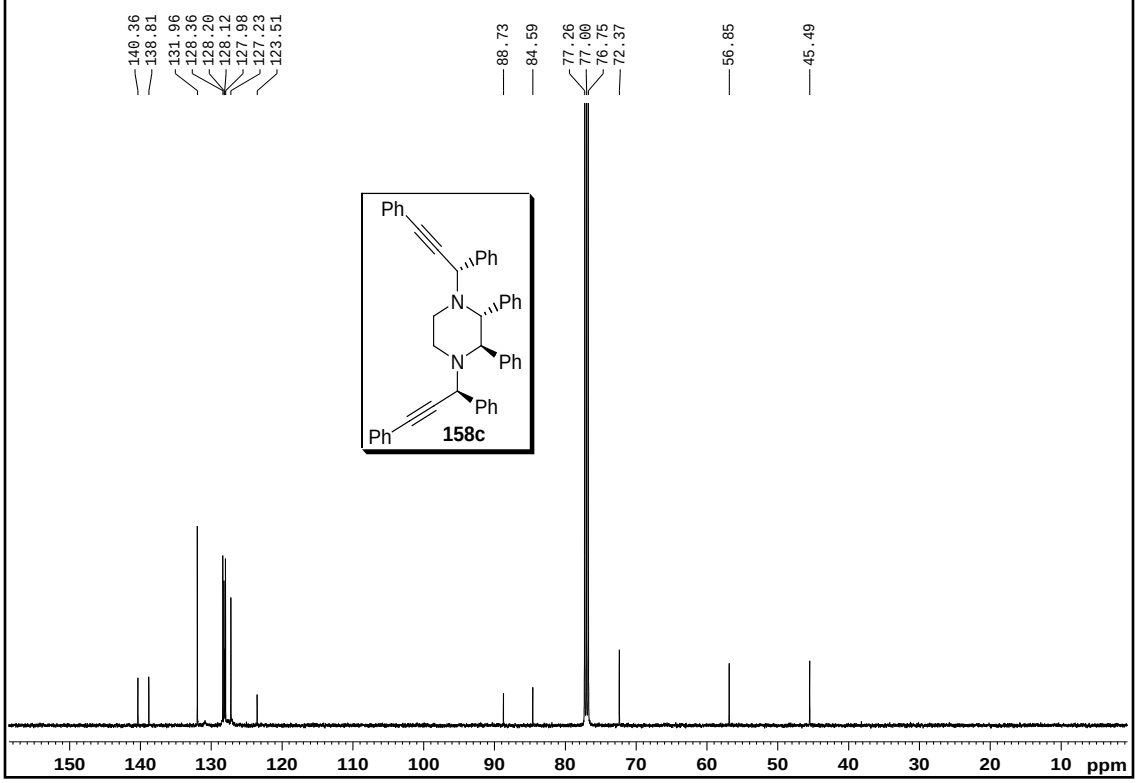
Spectrum No. 46 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



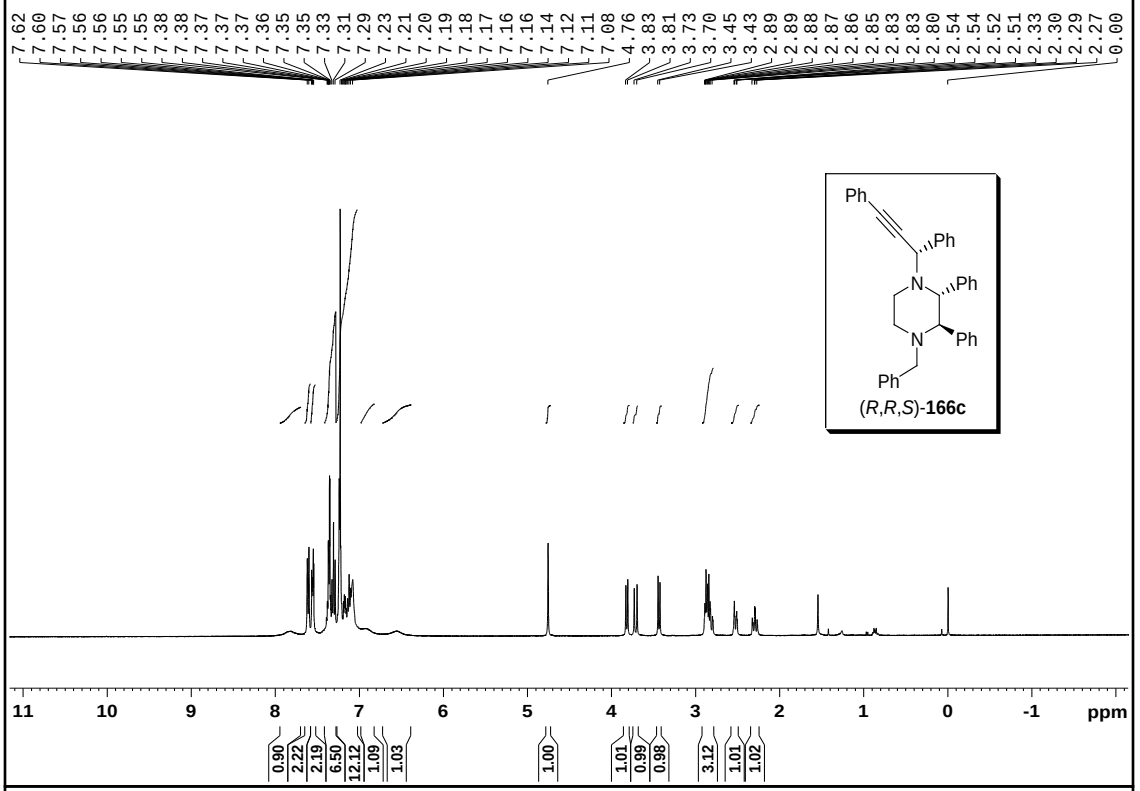
Spectrum No. 47 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



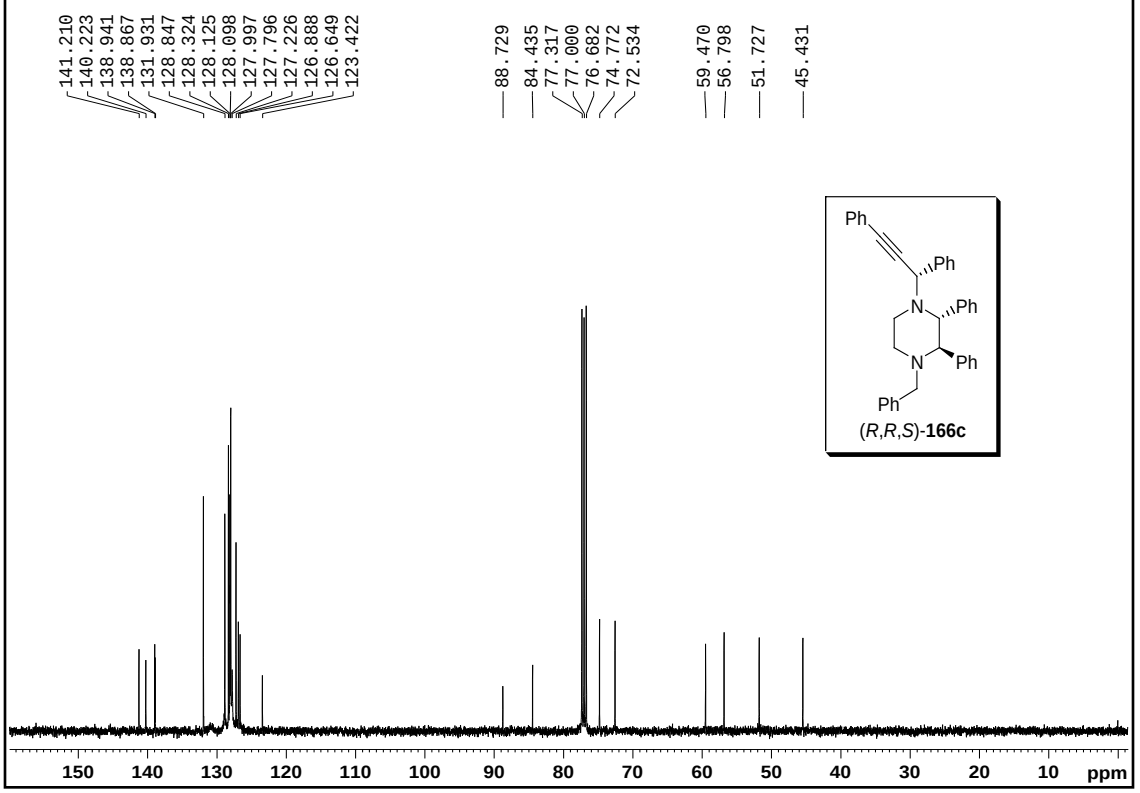
Spectrum No. 48 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



Spectrum No. 49 (Chapter 4, Section 4.4), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 50 (Chapter 4, Section 4.4), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the chiral diamine derivative **109** (**Chapter 1, Section 1.2.1**). U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	3662(2)	8613(2)	2743(1)	43(1)
C(2)	5483(3)	9601(3)	2794(1)	58(1)
C(3)	6257(3)	8594(4)	2802(1)	68(1)
C(4)	5862(3)	7641(4)	2234(1)	68(1)
C(5)	4086(3)	6646(3)	2164(1)	60(1)
C(6)	3215(2)	7606(2)	2171(1)	42(1)
C(7)	3418(3)	10843(3)	2418(1)	57(1)
C(8)	3022(5)	12169(3)	2543(2)	89(1)
C(9)	2305(3)	9656(3)	3413(1)	59(1)
C(10)	3591(4)	10229(4)	3891(1)	84(1)
C(11)	834(3)	8089(3)	3548(1)	55(1)
C(12)	769(3)	7092(4)	3996(1)	68(1)
C(13)	-625(4)	5728(4)	4138(1)	82(1)
C(14)	-1985(4)	5359(4)	3832(1)	78(1)
C(15)	-1938(3)	6328(4)	3388(1)	75(1)
C(16)	-556(3)	7674(3)	3248(1)	65(1)
C(17)	689(3)	5369(3)	2462(1)	66(1)
C(18)	-1027(6)	4073(4)	2323(2)	109(1)
C(19)	899(3)	6511(3)	1451(1)	63(1)
C(20)	1613(4)	5885(4)	1001(1)	84(1)
C(21)	1043(3)	8087(3)	1288(1)	62(1)
C(22)	106(3)	8575(4)	1577(1)	78(1)
C(23)	132(4)	9946(5)	1421(2)	99(1)
C(24)	1084(6)	10875(5)	976(2)	116(1)
C(25)	1996(5)	10404(5)	685(2)	109(1)
C(26)	1982(4)	9015(4)	826(1)	83(1)
F(1)	3444(3)	13139(2)	2081(1)	132(1)
F(2)	1507(3)	11675(3)	2645(1)	112(1)
F(3)	3835(3)	13044(2)	3011(1)	115(1)

F(4)	-1054(3)	3159(2)	1875(1)	136(1)
F(5)	-1646(3)	3138(2)	2789(1)	154(1)
F(6)	-2009(3)	4598(3)	2186(1)	133(1)
N(1)	2965(2)	9659(2)	2812(1)	47(1)
N(2)	1487(2)	6536(2)	2066(1)	50(1)
O(1)	4145(2)	10992(2)	1967(1)	66(1)
O(2)	1211(2)	5231(2)	2932(1)	76(1)

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the chiral diamine **108c** (**Chapter 1, Section 1.2.1**). U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	3605(12)	9902(5)	7613(3)	69(3)
C(2)	5371(13)	9784(4)	8093(3)	62(2)
C(3)	4801(14)	10337(4)	8599(3)	77(3)
C(4)	4687(15)	11237(4)	8420(3)	88(3)
C(5)	2906(15)	11358(4)	7957(3)	104(3)
C(6)	3425(14)	10824(4)	7441(3)	98(3)
C(7)	2267(14)	9117(5)	6760(3)	66(2)
C(8)	1136(12)	8352(4)	7040(3)	109(3)
C(9)	3108(15)	8922(5)	6148(3)	55(2)
C(10)	1793(13)	9142(4)	5688(4)	66(2)
C(11)	2463(16)	8982(5)	5129(4)	85(3)
C(12)	4484(17)	8573(5)	5057(3)	66(3)
C(13)	5873(14)	8314(4)	5502(4)	80(3)
C(14)	5124(16)	8493(4)	6055(4)	79(3)
C(15)	7430(16)	8637(4)	8564(3)	78(3)
C(16)	7831(18)	7722(4)	8444(3)	132(4)
C(17)	7245(18)	8738(5)	9218(3)	63(2)
C(18)	9022(16)	9101(5)	9530(5)	91(3)
C(19)	8892(17)	9173(5)	10130(5)	90(3)
C(20)	7030(20)	8858(5)	10396(3)	71(3)
C(21)	5271(15)	8492(5)	10101(4)	86(3)
C(22)	5372(15)	8457(5)	9514(4)	79(3)
Cl(1)	5537(4)	8357(1)	4360(1)	108(1)
Cl(2)	6983(5)	8953(1)	11144(1)	126(1)

N(1)	4233(17)	9388(5)	7105(3)	63(2)
N(2)	5359(14)	8914(5)	8258(3)	75(2)

Table A3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the chiral dipropargylamine **158c** (**Chapter 4, Section 4.2.4**). U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	341(1)	6244(3)	356(2)	19(1)
C(2)	332(1)	3757(3)	348(2)	23(1)
C(3)	447(1)	7563(3)	899(2)	20(1)
C(4)	156(1)	7769(3)	1438(2)	24(1)
C(5)	214(1)	9037(3)	1872(2)	28(1)
C(6)	568(1)	10094(3)	1761(2)	28(1)
C(7)	872(1)	9887(3)	1248(2)	29(1)
C(8)	815(1)	8627(3)	819(2)	23(1)
C(9)	1089(1)	4991(3)	1623(2)	20(1)
C(10)	1591(1)	4906(3)	1338(2)	22(1)
C(11)	2012(1)	4940(3)	1142(2)	22(1)
C(12)	2540(1)	5042(3)	952(2)	21(1)
C(13)	2653(1)	6265(3)	588(2)	26(1)
C(14)	3156(1)	6375(3)	413(2)	29(1)
C(15)	3578(1)	5288(3)	604(2)	26(1)
C(16)	3469(1)	4071(3)	957(2)	28(1)
C(17)	2966(1)	3940(3)	1132(2)	25(1)
C(18)	1150(1)	3936(3)	2331(2)	21(1)
C(19)	740(1)	4001(3)	2701(2)	28(1)
C(20)	822(1)	3182(4)	3420(2)	33(1)
C(21)	1321(1)	2273(3)	3761(2)	30(1)
C(22)	1717(1)	2162(3)	3374(2)	26(1)
C(23)	1637(1)	2978(3)	2661(2)	22(1)
C(24)	4640(1)	3599(3)	4776(2)	18(1)
C(25)	4650(1)	1099(3)	4778(2)	24(1)
C(26)	4411(1)	4917(3)	4244(2)	21(1)
C(27)	4427(1)	5077(3)	3452(2)	29(1)
C(28)	4253(2)	6327(3)	2992(2)	34(1)
C(29)	4053(1)	7418(3)	3344(2)	35(1)
C(30)	4030(1)	7268(3)	4131(2)	33(1)

C(31)	4207(1)	6010(3)	4583(2)	25(1)
C(32)	3741(1)	2303(3)	3735(2)	21(1)
C(33)	3434(1)	2078(3)	4317(2)	24(1)
C(34)	3263(1)	1975(3)	4880(2)	24(1)
C(35)	3050(1)	1898(3)	5551(2)	26(1)
C(36)	2690(1)	774(3)	5593(2)	28(1)
C(37)	2465(1)	750(4)	6208(2)	35(1)
C(38)	2597(1)	1825(4)	6815(2)	35(1)
C(39)	2972(1)	2924(4)	6795(2)	34(1)
C(40)	3192(1)	2947(3)	6175(2)	29(1)
C(41)	3547(1)	1305(3)	2959(2)	23(1)
C(42)	3907(1)	1169(3)	2517(2)	26(1)
C(43)	3703(2)	391(3)	1752(2)	29(1)
C(44)	3130(2)	-262(3)	1432(2)	31(1)
C(45)	2773(1)	-154(3)	1874(2)	31(1)
C(46)	2977(1)	623(3)	2645(2)	25(1)
N(1)	455(1)	4995(2)	905(1)	20(1)
N(2)	4420(1)	2336(2)	4231(1)	20(1)

Table A4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for monopropargyl amine **166c** (**Chapter 4, Section 4.2.4**). U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	8342(2)	2965(2)	3486(2)	24(1)
C(2)	7529(2)	2590(2)	3891(2)	25(1)
C(3)	7290(2)	1236(2)	2801(2)	26(1)
C(4)	7988(2)	1687(2)	2332(2)	27(1)
C(5)	9073(2)	3352(2)	4250(2)	24(1)
C(6)	9246(2)	4369(3)	4395(2)	36(1)
C(7)	9891(3)	4695(3)	5137(3)	49(1)
C(8)	10353(2)	4009(3)	5734(3)	46(1)
C(9)	10191(2)	2989(3)	5605(3)	42(1)
C(10)	9554(2)	2677(3)	4864(2)	34(1)
C(11)	7119(2)	3502(2)	4259(2)	22(1)
C(12)	7339(2)	3737(3)	5156(2)	33(1)
C(13)	7025(2)	4628(3)	5481(3)	42(1)
C(14)	6458(2)	5266(3)	4906(3)	42(1)

C(15)	6223(2)	5024(3)	4013(3)	36(1)
C(16)	6546(2)	4150(2)	3689(2)	29(1)
C(17)	6118(2)	1632(3)	3635(2)	24(1)
C(18)	5288(2)	1345(2)	2919(2)	23(1)
C(19)	5080(2)	1882(3)	2123(2)	34(1)
C(20)	4303(2)	1680(3)	1474(2)	40(1)
C(21)	3729(2)	922(3)	1629(3)	42(1)
C(22)	3921(2)	372(3)	2414(3)	39(1)
C(23)	4696(2)	585(3)	3055(2)	32(1)
C(24)	6405(2)	797(3)	4291(2)	24(1)
C(25)	6627(2)	102(3)	4785(2)	24(1)
C(26)	6881(2)	-762(2)	5370(2)	22(1)
C(27)	6330(2)	-1088(3)	5940(2)	32(1)
C(28)	6574(2)	-1931(3)	6480(2)	41(1)
C(29)	7373(3)	-2434(3)	6451(2)	46(1)
C(30)	7923(2)	-2128(3)	5889(3)	45(1)
C(31)	7671(2)	-1291(3)	5344(2)	33(1)
C(32)	9425(2)	2575(2)	2556(2)	28(1)
C(33)	10057(2)	1778(2)	2312(2)	24(1)
C(34)	10562(2)	1975(3)	1671(2)	26(1)
C(35)	11179(2)	1268(3)	1478(2)	32(1)
C(36)	11293(2)	350(3)	1923(2)	30(1)
C(37)	10795(2)	159(3)	2575(2)	32(1)
C(38)	10182(2)	870(3)	2761(2)	29(1)
C(39)	7011(2)	8538(2)	1486(2)	21(1)
C(40)	7649(2)	7887(2)	1038(2)	21(1)
C(41)	7918(2)	6793(2)	2333(2)	24(1)
C(42)	7296(2)	7441(3)	2762(2)	25(1)
C(43)	6284(2)	9025(2)	764(2)	19(1)
C(44)	5555(2)	8455(3)	310(2)	25(1)
C(45)	4905(2)	8879(3)	-376(2)	34(1)
C(46)	4987(2)	9890(3)	-606(2)	37(1)
C(47)	5707(2)	10444(3)	-166(2)	33(1)
C(48)	6355(2)	10030(2)	507(2)	25(1)
C(49)	8069(2)	8531(2)	411(2)	16(1)
C(50)	7767(2)	8475(2)	-508(2)	24(1)
C(51)	8122(2)	9101(3)	-1080(2)	31(1)
C(52)	8797(2)	9793(2)	-728(2)	28(1)
C(53)	9108(2)	9857(2)	186(2)	28(1)
C(54)	8746(2)	9232(2)	752(2)	24(1)
C(55)	9022(2)	6805(2)	1362(2)	22(1)
C(56)	9871(2)	6587(2)	2066(2)	19(1)
C(57)	9997(2)	5688(2)	2535(2)	24(1)
C(58)	10790(2)	5527(3)	3166(2)	34(1)
C(59)	11465(2)	6244(3)	3325(2)	36(1)
C(60)	11353(2)	7141(3)	2846(2)	35(1)

C(61)	10555(2)	7313(3)	2225(2)	27(1)
C(62)	8633(2)	5866(3)	898(2)	22(1)
C(63)	8372(2)	5087(3)	543(2)	21(1)
C(64)	8113(2)	4122(2)	132(2)	21(1)
C(65)	8782(2)	3417(3)	48(2)	29(1)
C(66)	8551(2)	2485(3)	-327(2)	35(1)
C(67)	7659(2)	2250(3)	-657(3)	46(1)
C(68)	6990(2)	2952(3)	-602(3)	56(1)
C(69)	7215(2)	3876(3)	-199(2)	41(1)
C(70)	5959(2)	8459(2)	2529(2)	25(1)
C(71)	5299(2)	7758(2)	2847(2)	22(1)
C(72)	4908(2)	6965(3)	2317(2)	34(1)
C(73)	4256(2)	6353(3)	2560(3)	39(1)
C(74)	3994(2)	6518(3)	3359(3)	42(1)
C(75)	4396(3)	7277(3)	3910(3)	49(1)
C(76)	5046(2)	7890(3)	3658(2)	40(1)
N(1)	8715(2)	2172(2)	2991(2)	25(1)
N(2)	6857(2)	2034(2)	3231(2)	22(1)
N(3)	6594(2)	7906(2)	2089(2)	22(1)
N(4)	8352(1)	7406(2)	1740(2)	19(1)

List of publications

1. New Diimine-Copper Complexes: An Efficient and Simple Catalyst System for Buchwald *N*-Arylation of Indole**;** Periasamy, M.; Vairaprakash, P.; **Dalai, M**. *Organometallics* **2008**, *27*, 1963.
2. Diastereoselective reductive *N*-alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane with prochiral ketones using the $Ti(O^{i}Pr)_4/NaBH_4$ system; **Dalai, M**.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*,1247.
3. Chiral *trans*-1,2-diaminocyclohexane derivatives as chiral solvating agents for carboxylic acids**;** Periasamy, M.; **Dalai, M**.; Padmaja, M. *J. Chem. Sci*. **2010**, *122*, 561.
4. Highly Enantioselective Synthesis of Chiral Allenes by Sequential Asymmetric Synthesis and Chirality Transfer in a Single Pot Operation; Periasamy, M.; Sanjeevakumar, N.; **Dalai**, **M.**; Gurubrahamam, R.; Reddy, P.O. (*communicated*).
5. Highly diastereoselective synthesis of chiral propargylamines containing (*R*,*R*)-2,3-diphenylpiperazine moiety using CuI/PEG-400 reagent system; Periasamy, M.; **Dalai**, **M.** (to be communicataed)

POSTERS/PRESENTATIONS

1. Presented a poster in the *"Chemfest 2008"* 5^{th} in house symposium held at School of Chemistry, University of Hyderabad, Hyderabad, 1^{st} to 2^{nd} March **2008**; Title: New Diimine-Copper Complexes: An Efficient and Simple Catalyst System for Buchwald *N*-Arylation of Indole.

2. Oral presentation in the “Junior National Organic Trust Conference” held at School of Chemistry, University of Hyderabad, Hyderabad, 28th to 31th January **2011**; Title: Diastereoselective Synthesis and Application of Chiral *trans*-1,2-Diaminocyclohexane Derivatives as Chiral Solvating Agents for Carboxylic Acids.
3. Oral presentation and presented a poster in the *“Chemfest 2011”* 8th in house symposium held at University of Hyderabad, Hyderabad, 25th to 26th February **2011**; Title: Diastereoselective Synthesis and Application of Chiral *trans*-1,2-Diaminocyclohexane Derivatives as Chiral Solvating Agents for Carboxylic Acids.