Synthesis of Chiral Amine Derivatives Using D-(+)-Camphor and Their Application in Asymmetric Transformations

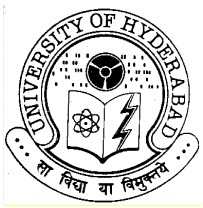
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

NALLURI SANJEEVA KUMAR



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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 of Chiral Amine Derivatives Using D-(+)-Camphor and Their Application in Asymmetric Transformations"** has been carried out by **Mr. N. Sanjeeva kumar** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN
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Dedicated to

My Grand Mother

And

My Parents

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Nalluri Sanjeeva Kumar

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g. dm, are understood]
aq.	aqueous
Ac	acetyl
Bn	benzyl
Bz	benzoyl
bp	boiling point
br s	broad singlet (spectral)
Bu	butyl
^{t}Bu	*ter*-butyl
^{o}C	degree Celsius
conc.	concentrated
CSA	camphor sulphonic acid
Cat.	catalytic
cm^{-1}	wavenumber
δ	chemical shift in parts per million downfield from tetramethyl silane
DCM	dichloromethane
DBU	1,8-diazabicyclo(5,4,0)undec-7-ene
DIEA	diisopropylethylamine
DIPEDA	diphenylethylenediamine
DME	dimethoxyethane
dr	diastereomeric ratio
dt	doublet of triplet (spectral)
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol
equiv.	equivalent
eqn.	equation

g	gram (s)
h	hour (s)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
Hz	hertz
^{i}Pr	isopropyl
IR	infrared
J	coupling constant (in NMR Spectrometry)
KHMDS	potassium bis(trimethylsilyl)amide
lit.	literature
LDA	lithium diisopropyl amide
m	multiplet (spectral)
Me	methyl
MW	molecular weight
MHz	megahertz
min.	minute(s)
mmol	millimolar
mp	melting point
MS	molecular sieves
NMP	N-methyl pyrrolidone
NMR	nuclear magnetic resonance
n-	primary
Nu	nucleophile
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
q	quartet (in spectroscopy)
RT	room temperature
THF	tetrahydrofuran
TMS-Cl	trimethylsilyl chloride
TFA	trifluoroacetic acid
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine

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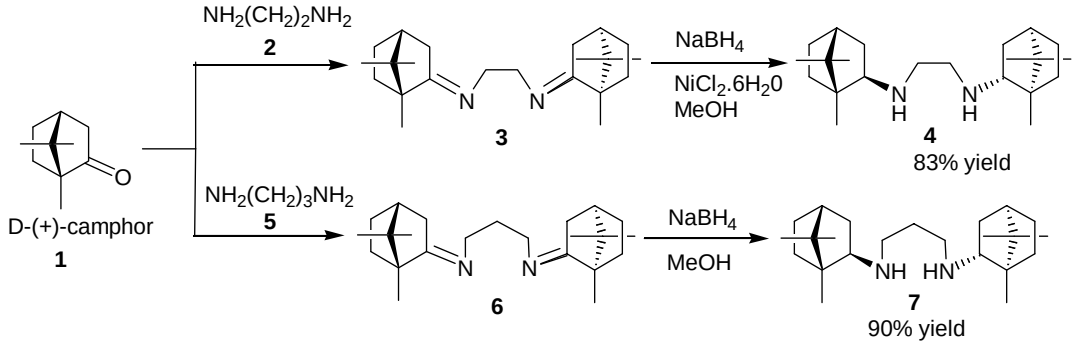
Abstract

This thesis entitled "**Synthesis of Chiral Amine Derivatives using D-(+)-Camphor and their Application in Asymmetric Transformations**" comprises of three chapters. Each chapter is subdivided into four sections 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 investigations on the synthesis of chiral amine derivatives using D-(+)-camphor **1**, D-(-)-camphorquinone **14** and various amine sources. In the introductory section, a brief review on the synthesis and application of various chiral amines and amino alcohols containing camphanyl moiety is presented.

The *bis*-imines **3** and **6** prepared *in situ* using D-(+)-camphor **1** and diamines **2** and **5** upon reduction gave the corresponding C_2-symetrical diamines **4** and **7** in 83% and 90% yields respectively, with good exo, exo selectivity after $NaBH_4$ reduction (Scheme **1**).

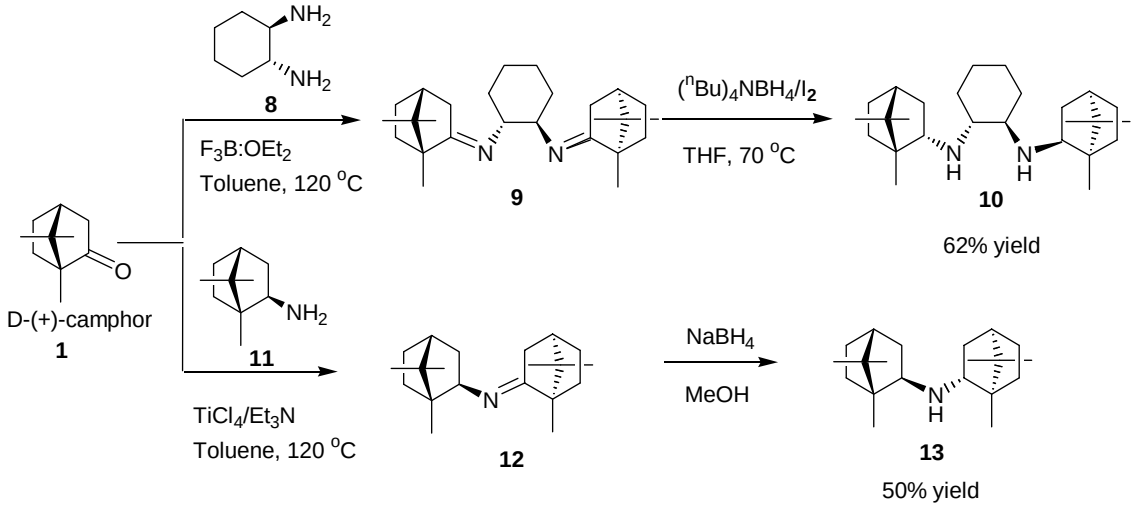
Scheme 1



The use of certain chiral amines to prepare chiral amine derivatives containing camphanyl moiety has been also investigated. It has been observed that the chiral amine **8**

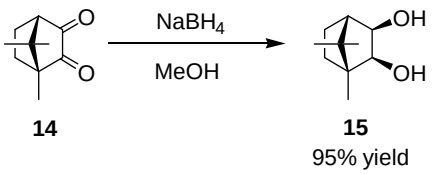
and **11** react with D-(+)-camphor **1** to give the imines **9** and **12** respectively. Subsequent reduction using $(^nBu)_4NBH_4/I_2$ and $NaBH_4$/MeOH reagent systems gave the corresponding C_2-symetrical diamines **10** and **13** in 62% and 50% yields respectively with excellent selectivity (Scheme **2)**. The structure of the diamine **10** was characterized by single crystal X-ray analysis of the corresponding *bis*-trifluoro acetamide derivative.

Scheme 2



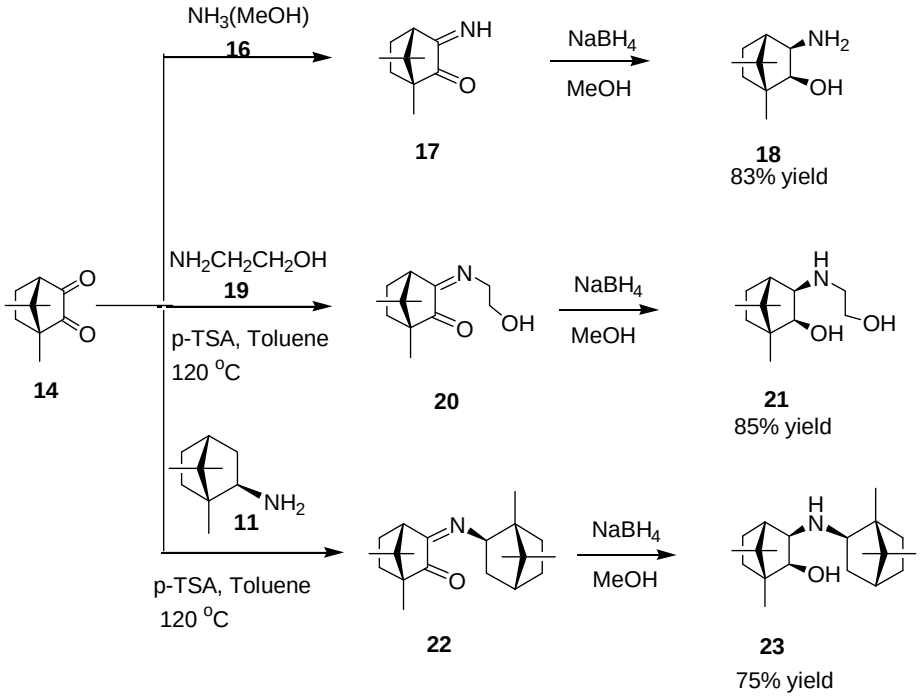
We have found that D-(-)-camphorquinone **14** undergoes selective reduction using $NaBH_4$/MeOH reagent system at 0 °C gave diol **15** in 95% yield with exo, exo selectivity (Scheme **3)**.

Scheme 3



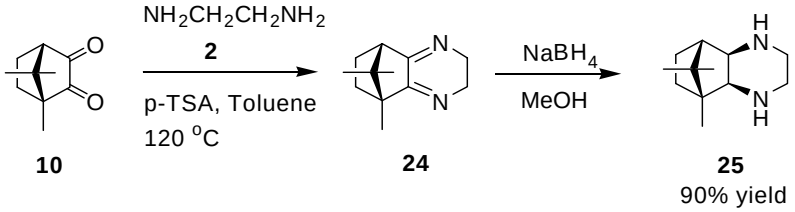
We have also observed that various imines **17**, **20**, **22** prepared *in situ* using D-(-)-camphorquinone **14** and different amines **16**, **19**, **11** gave amino alcohols **18**, **21**, **23** upon $NaBH_4$ reduction in 75-85% yields with exo, exo selectivity (Scheme **4**). The structure of the amino alcohol **18** was characterized by single crystal X-ray analysis of the corresponding acetamide derivative.

Scheme 4



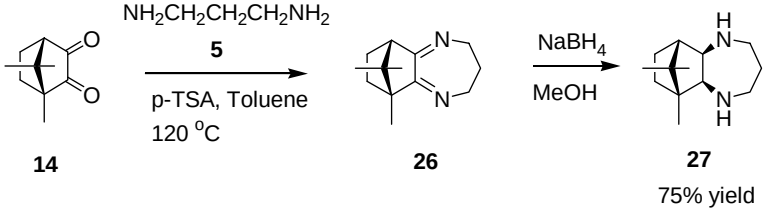
We have also prepared the quinazoline derivative **25** in 90% yield by the reaction of D-(-)-camphorquinone **14** with diamine **2**, followed by reduction of the corresponding imine **24** with $NaBH_4$/MeOH with exo, exo selectivity (Scheme **5**).

Scheme 5



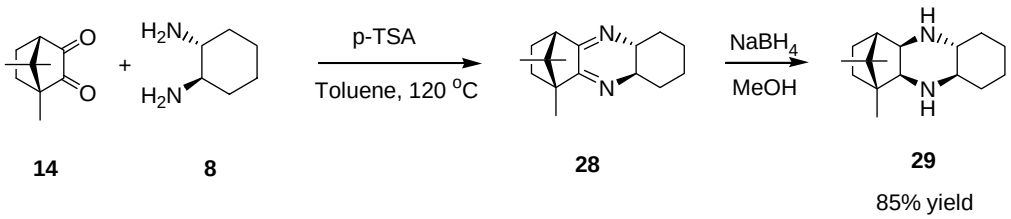
We have also prepared the azepine derivative **27** in a similar way with exo, exo selectivity (Scheme **6**).

Scheme 6



We have also prepared phenazine derivative **29** in 85% yield in this way using D-(-)-camphorquinone **14** with exo, exo selectivity (Scheme **7**).

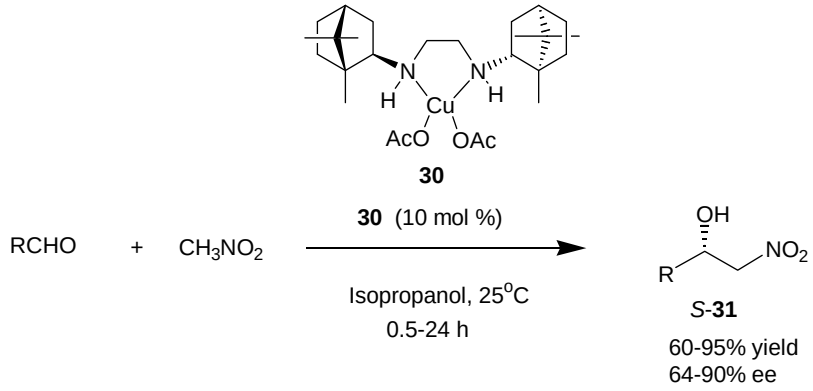
Scheme 7



Investigations carried out on the use of some camphanyl amines prepared in Chapter **1** for asymmetric Henry reaction and chiral allenes synthesis are discussed in Chapter **2** and Chapter **3** respectively. A brief review of reports on the chiral catalyst based

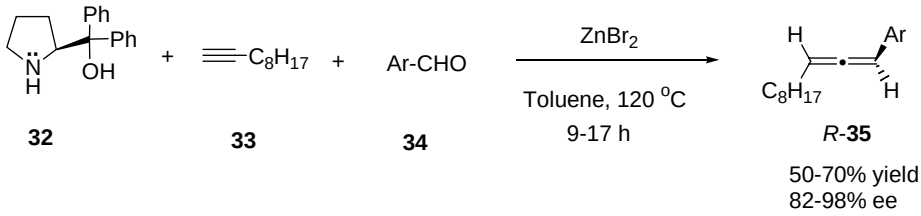
Henry (nitroaldol) reaction is discussed in the introductory section of Chapter **2**. The copper complex **30** was prepared by the reaction of diamine **4** with $Cu(OAc)_2.H_2O$. The structure of the complex **30** was confirmed by single crystal X-ray analysis. The copper complex **30** catalysed the nitroaldol reaction of nitromethane and various aldehydes to give the corresponding β-nitro compound **31** in 60-95% yield with 64-90% ee (Scheme **8**). Results obtained on the effect of solvent, catalyst loading and reactivity with various aldehydes are discussed.

Scheme 8



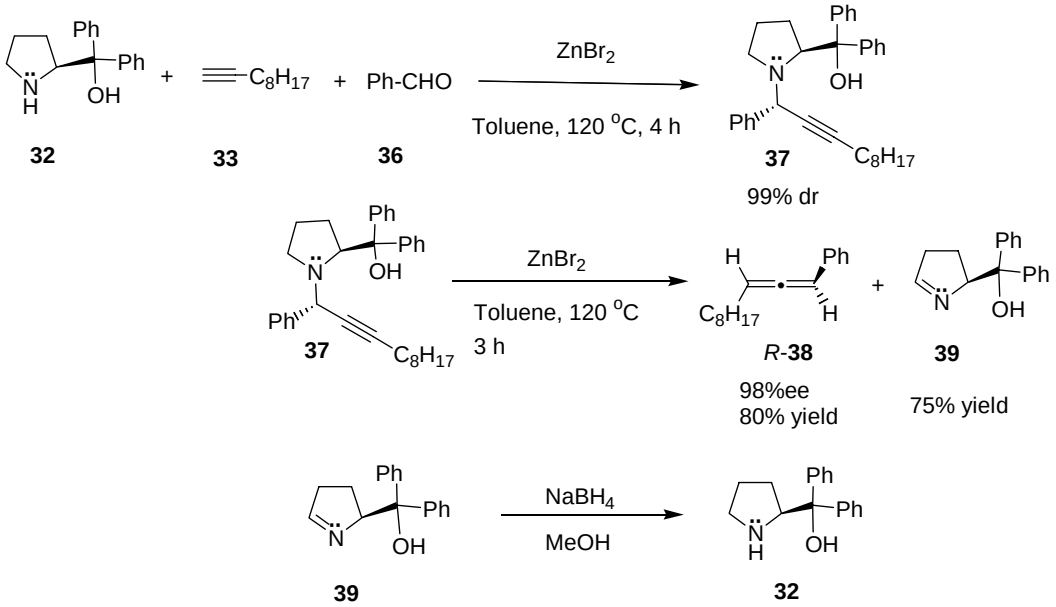
Results of investigations on the preparation of chiral allenes using the readily accessible chiral cyclic secondary amine derivatives are described in chapter **3**. In the introductory section, a brief review on the methods reported for the synthesis of chiral allenes is described to facilitate the discussion. The reaction of (*S*)-α,α-diphenylprolinol **32**, 1-decyne **33** and various aromatic aldehydes **34** in the presence of $ZnBr_2$ gave the corresponding chiral allenes **35** in 50-70% yield with 82-98% ee (Scheme **9**).

Scheme 9



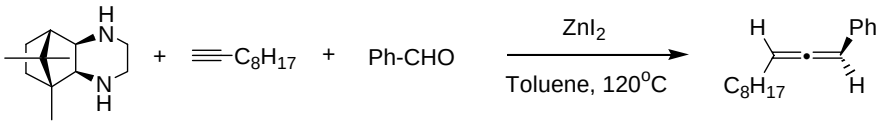
The chiral propargyl amine intermediate **37** has been isolated by carrying out the reaction at 120 ^{o}C for 4 h. Subsequent reaction of the chiral propargyl amine **37** with $ZnBr_2$ gave chiral allene **38** in 80% yield with 98% ee and the imine **39** in 75% yield (Scheme **10**). The imine **39** has been converted back to the starting (*S*)-DPP **32** for reuse by simple $NaBH_4$/MeOH reduction.

Scheme 10



We have also examined the use of the quinazoline **40** prepared in chapter **1** for the allene synthesis. We have observed that the reaction using 1-decyne **33,** benzaldehyde **36** and quinazoline **40** in the presence of ZnI_2 gave the corresponding chiral allene **38** in 75% yield with up to 65% ee (Scheme **11**).

Scheme 11



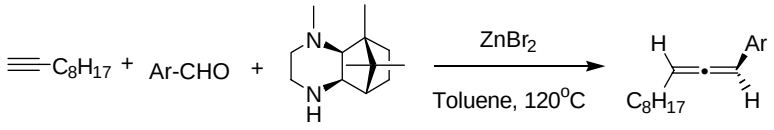
40 **33** **36**

R-**38**

75% yield
65% ee

Further, we have found that one pot enantioselective synthesis of chiral allenes using 1-decyne **33**, aromatic aldehydes **34** and amine **41** in the presence of $ZnBr_2$ gave the corresponding chiral allenes in 63-75% yield with up to 99% ee (*R*) (Scheme **12**).

Scheme 12



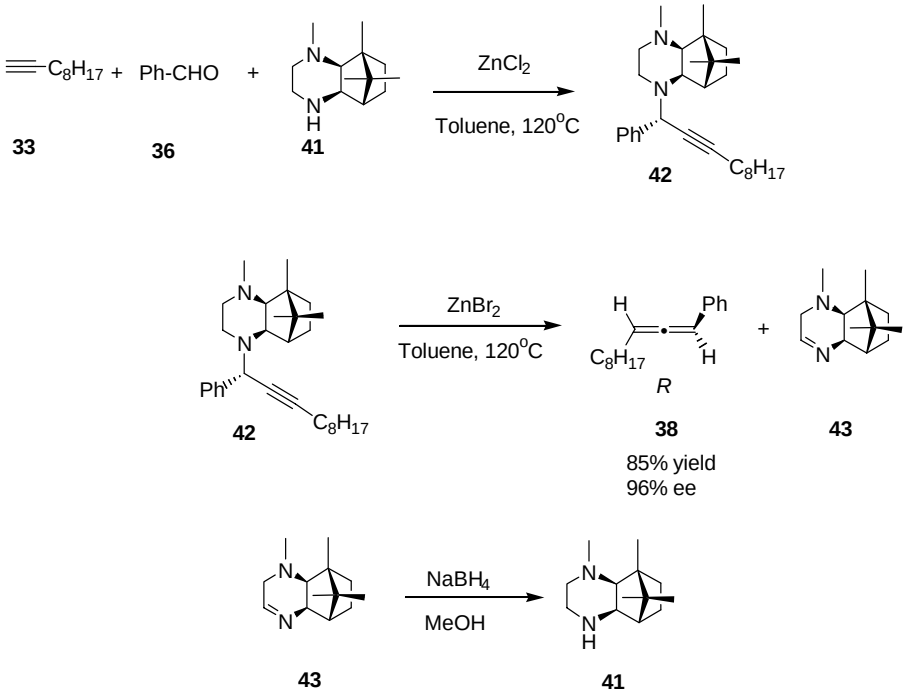
33 **34** **41**

R-**35**

63-75% yield
90-99% ee

We have isolated the chiral propargyl amine intermediate **42** using 1-decyne **33**, benzaldehyde **36** and amine **41** in the presence of $ZnCl_2$ at 120 ^oC for 5 h. The reaction of chiral propargyl amine **42** with $ZnBr_2$ gave chiral allene **38** in 85% yield with 98% ee and imine **43**, which upon reduction with $NaBH_4$/MeOH gave amine **41** without loss of optical activity (Scheme **13**).

Scheme 13



The results reported in this thesis are discussed considering mechanisms, intermediates involved in these transformations and comparison with literature reports.

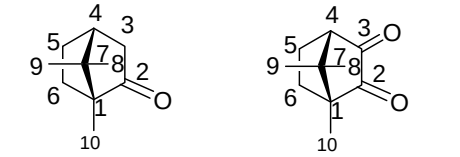
Note: Scheme numbers and compound numbers given in this abstract are different from those given in chapters.

Chapter 1

Synthesis of New Chiral Amines and Amino Alcohol Derivatives Using D-(+)-Camphor and D-(-)-Camphorquinone

1.1 Introduction

D-(+)-Camphor **1** is available in nature in optically pure form. A large number of D-(+)-camphor derivatives have been prepared and widely used as chiral auxiliaries or chiral ligands in asymmetric organic transformations.[1] The successful exploitation of this chiral natural product in asymmetric synthesis is due to its rigid [2.2.1] bicyclic framework. The importance of this camphor based chiral pool has been further increased interest by ready conversion of D-(+)-camphor **1** to D-(-)-camphorquinone **2**. Also, introduction of functionalities at C-2, C-3, C-5, C-8, C-9, and C-10 provides interesting variations for these derivatives in various asymmetric transformations.[2]



D-(+)-Camphor **1** D(-)-Camphorquinone **2**

Figure 1

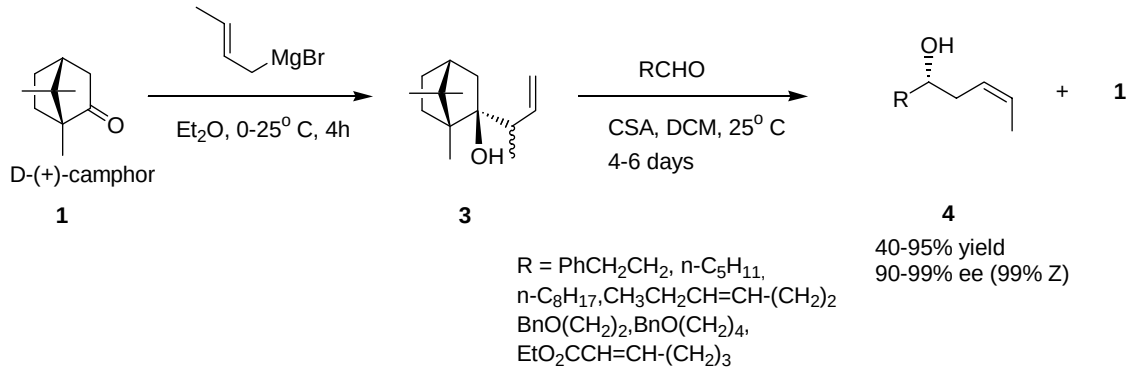
Chiral amine derivatives play a central role in the expanding area of asymmetric synthesis.[3] Although a variety of chiral amines have been synthesized and utilized extensively in the development of asymmetric transformations, it has always been a challenge to synthesize these optically active compounds in good yields and selectivities.[4] In recent years, there has been a renewed interest in the use of chiral skeletons containing camphanyl moiety in organic synthesis,[5] because the starting D-(+)-camphor is inexpensive

and readily available for the preparation of enantiomerically pure compounds. It may be of interest to briefly review the reports on the use of chiral camphor and its derivatives in asymmetric transformations.

1.1.1 D-(+)–Camphor 1 as chiral auxiliary

D-(+)-Camphor is generally used in conversion to other useful ligands for use in asymmetric transformations. However, it has been also used as a chiral auxiliary. For example, the use of D-(+)-camphor **1** as auxiliary for the enantioselective synthesis of *cis*-linear homoallylic alcohols **4** with 90-99% ee has been reported (Scheme **1**).[6]

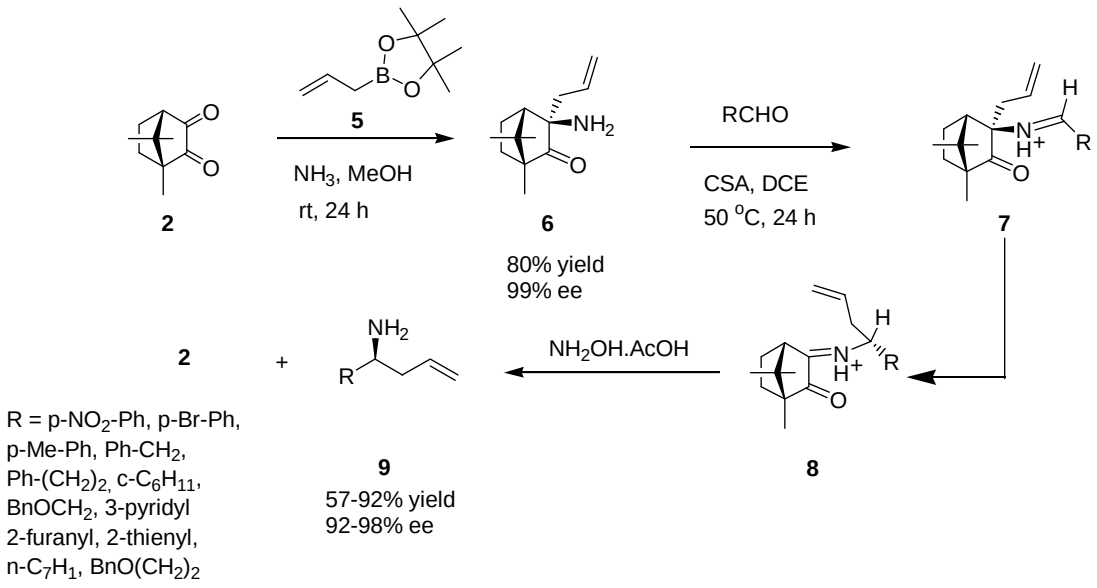
Scheme 1



1.1.2 D-(-)–Camphorquinone 2 as chiral auxiliary

D-(-)-Camphorquinone **2** has been also used as chiral auxiliary. For example, the chiral allyl amine **6** prepared using D-(-)-camphorquinone **2** and allyl boronic esters **5**, reacts with various aldehydes to yield the homo allylic primary amines **9** with 92-98% ee (Scheme **2**).[7]

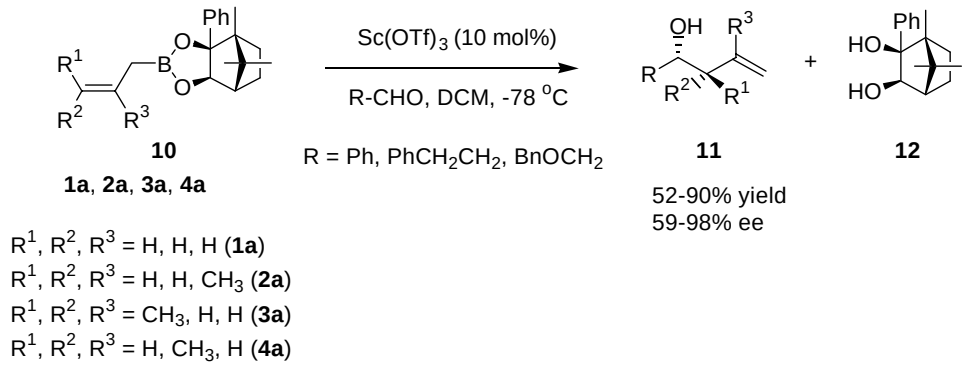
Scheme 2



1.1.3 Chiral camphanyl derivatives as auxiliaries in asymmetric transformations

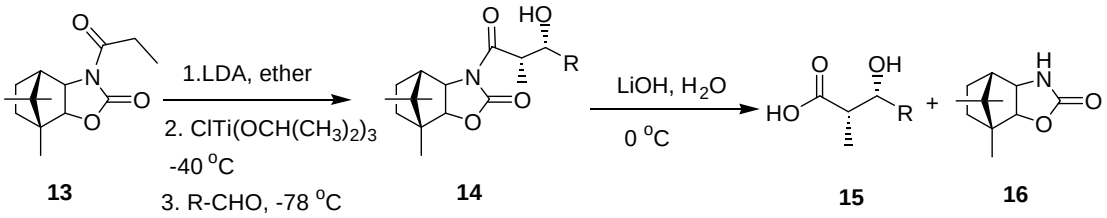
Stereoselective allylation of various aldehydes using stable chiral allyl boronates **10** under $Sc(OTf)_3$ catalysis to give the homo allylic alcohols **11** with 59-98% ee has been reported (Scheme **3**).[8]

Scheme 3



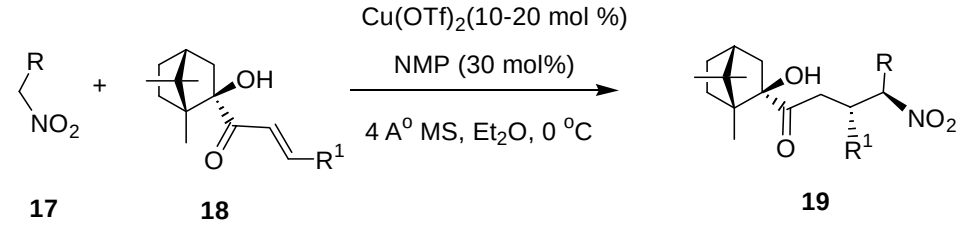
In the presence of LDA and $ClTi(OCH(CH_3)_2)_3$ reagent system, the camphor derived N-propionyloxazolidinone **13** reacts with various aldehydes to produce *syn*-selective aldol products **14**, which on base hydrolysis give β-hydroxy-α-methyl carboxylic acids **15** in 92-99% ee (Scheme **4**).[9]

Scheme 4



Conjugate addition of prochiral nitroalkanes **17** to substituted chiral Michael acceptors **18** in the presence of $Cu(OTf)_2$ gives the 1,4-addition products **19** with 96:4 *anti/syn* selectivities (Scheme **5**).[10]

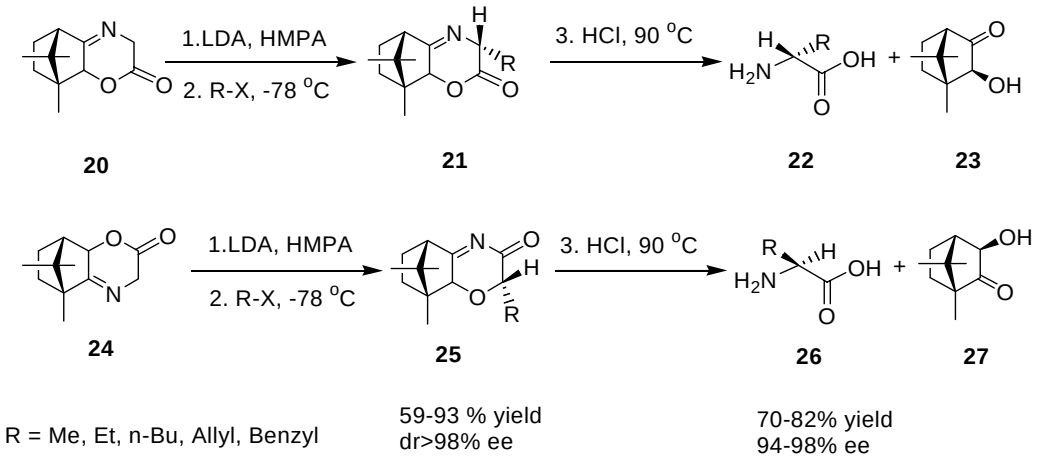
Scheme 5



Alkylation of iminolactones **20** and **24** provided the iminolactones **21** and **25** in high yields with excellent diastereoselectivities (>98% ee). Hydrolysis of the alkylated

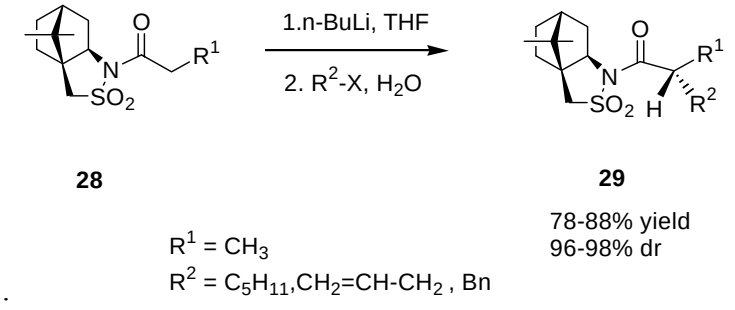
iminolactones furnished the desired α-substituted α-amino acids **22** and **26** in 70-82% yields with 94-98% ee (Scheme **6**).[11]

Scheme 6



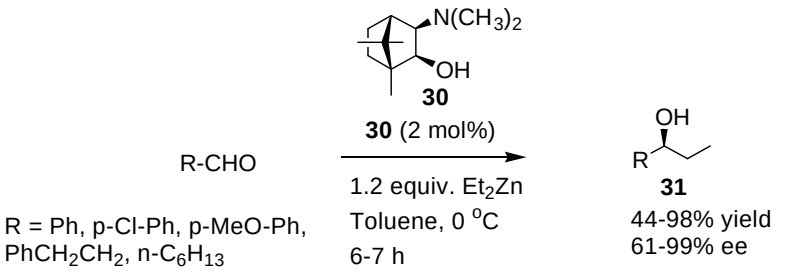
The Oppolzer camphorsultam is a versatile chiral auxiliary useful in the diastereoselective C-C bond forming reactions. Enolates generated *in situ* using the N-acyl camphorsultam **28** and n-butyllithium react with various alkyl halides to give the α-substituted amide derivatives **29** in 78-88% yield with high stereoselectivities (Scheme **7**).[12]

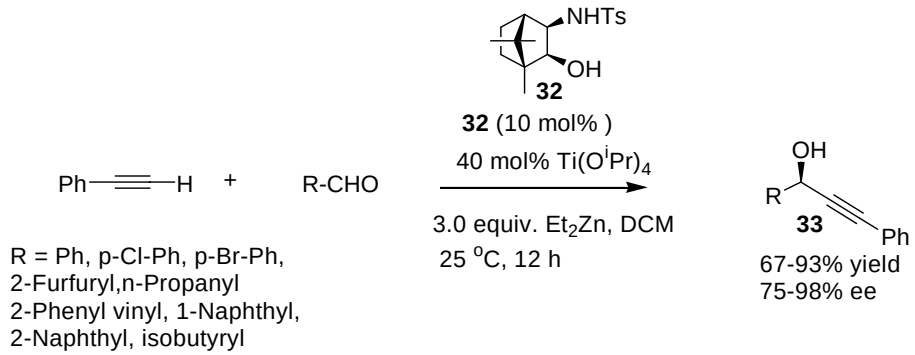
Scheme 7

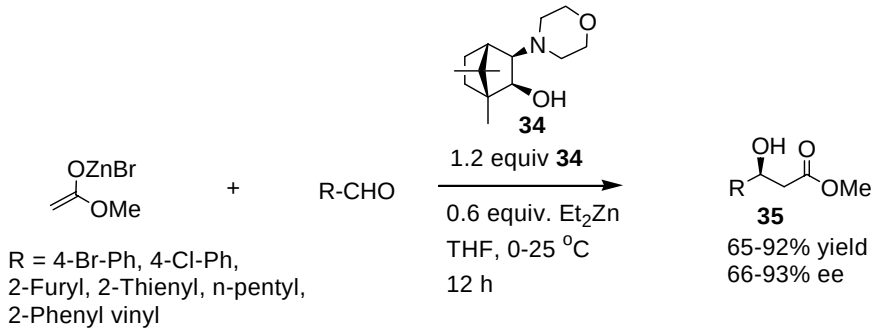


1.1.4 Applications of chiral camphanyl ligands in asymmetric transformations

Several camphanyl amino alcohol and diamine ligands have been used in asymmetric transformations.[13] The reported results are summarized below.







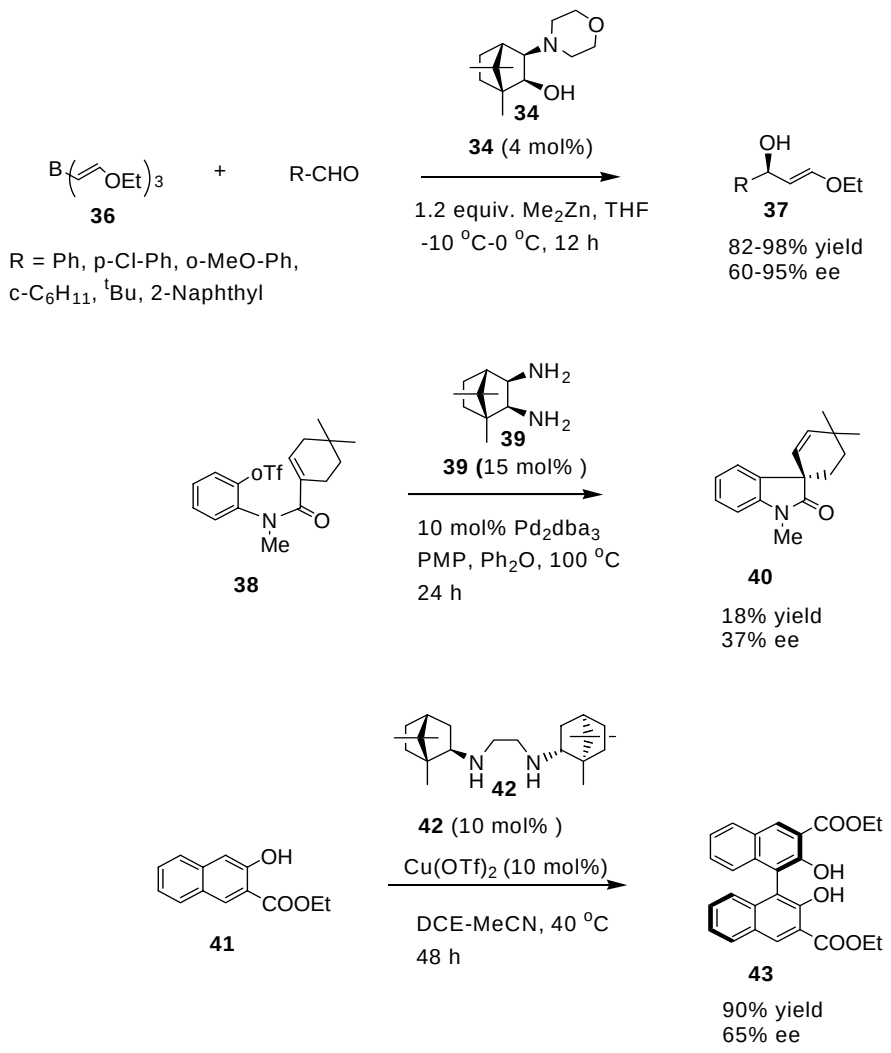
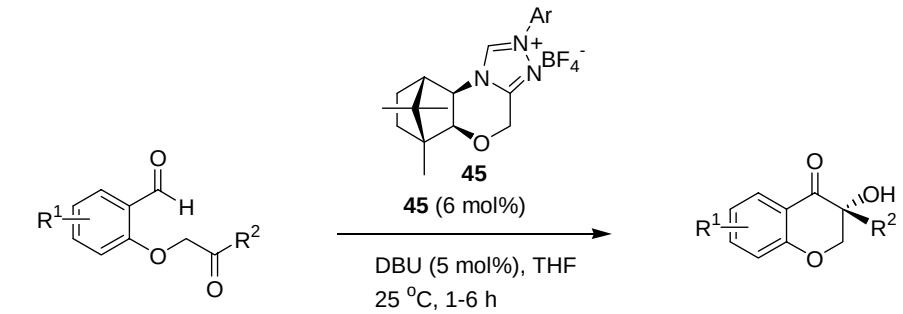


Figure.2

1.1.5 N-Heterocyclic carbenes (NHC) containing chiral camphanyl moiety

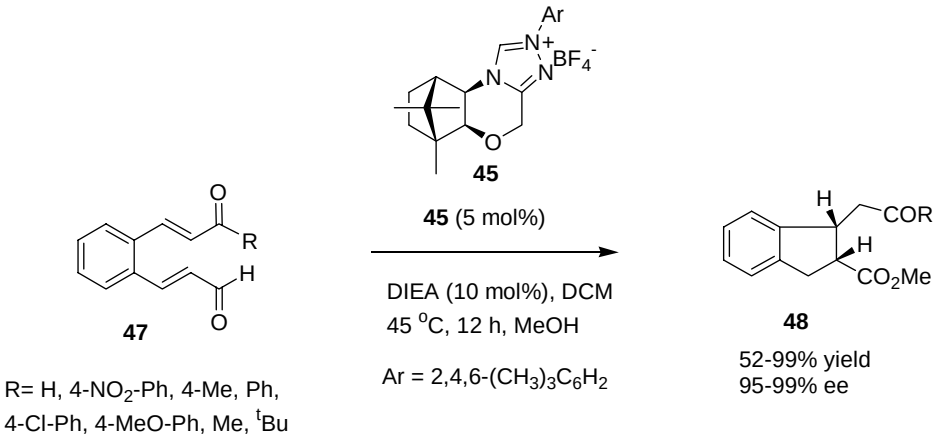
In recent years, several NHC derivatives containing camphanyl moiety were prepared for use in asymmetric transformations. For example, the chiral NHC catalyst **45**-DBU combination is found to be efficient for intramolecular cyclization of **44** to give the α-ketols **46** in excellent yields with up to 93% ee (Scheme **8**).[14]

Scheme 8



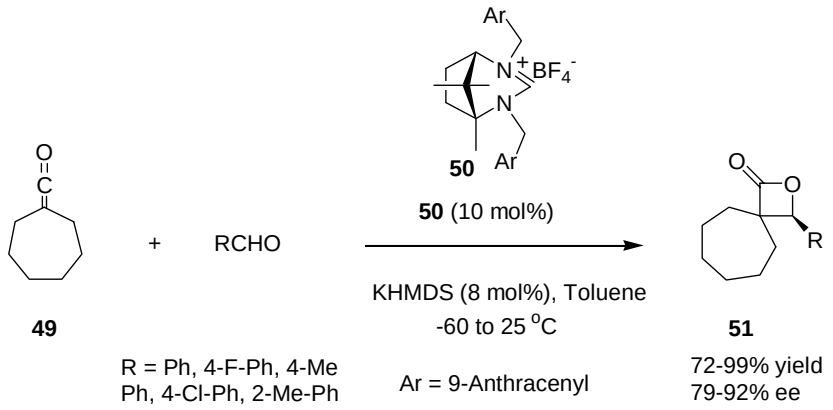
The chiral triazolium salt **45** containing camphanyl moiety has been found to be highly efficient for asymmetric intramolecular Michael reaction of **47** to give the desired product **48** in 52-99% yields with 95-99% ee (Scheme **9**).[15]

Scheme 9



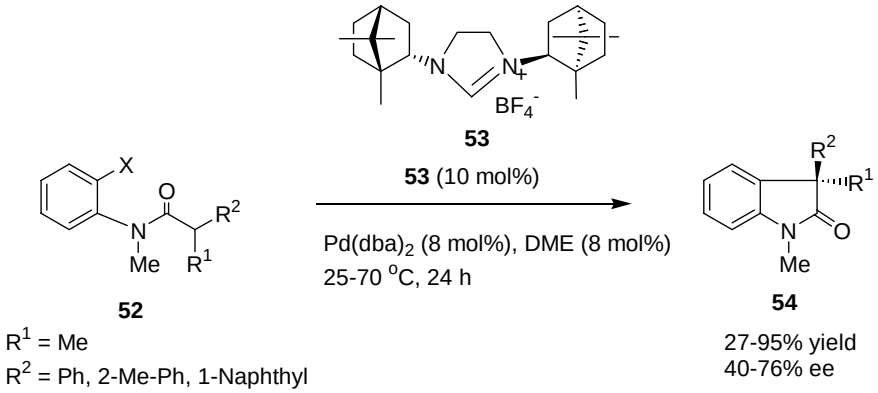
Chiral β-lactones **51** were synthesized by the reaction of cyclic ketene **49** and different aldehydes under chiral NHC **50** catalysis *via* a formal [2+2] addition reaction (Scheme **10**).[16]

Scheme 10



Chiral NHC **53** catalyzed formation of α, α-disubstituted oxindoles **54** by α-arylation of N-aryl substituted amide derivativies **52** results in 27-95% yields with 40-76% ee under mild conditions (Scheme **11**).[17]

Scheme 11

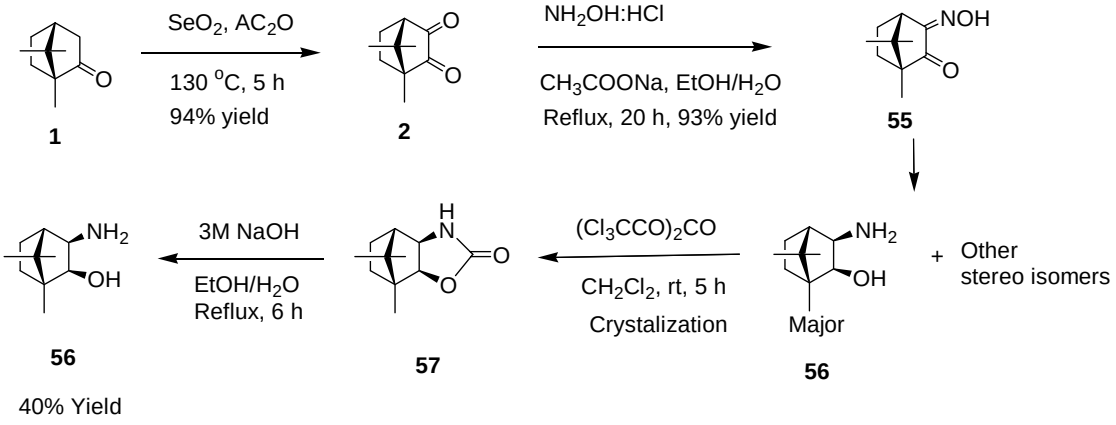


1.1.6 Synthesis of chiral amine derivativies containing camphanyl moiety

We have undertaken studies to synthesize chiral amines and amino alcohols containing camphanyl moiety for use in asymmetric transformations. Accordingly, it is of

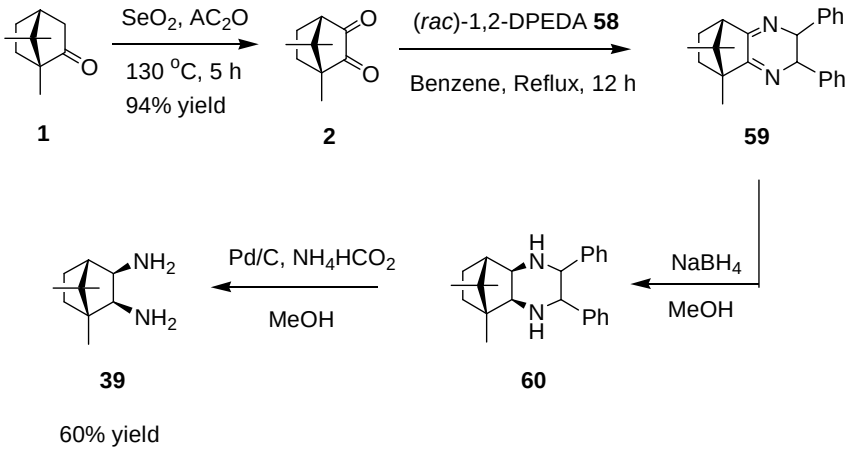
interest to briefly review the synthetic methods reported to access derivatives. A diastereoselective multistep synthesis of the chiral amino alcohol **56** involves the use of D-(+)-camphor as starting material (Scheme **12**).[18]

Scheme 12



Synthesis of (*R*)-camphanyldiamine **39** from D-(+)-camphor **1** and *rac*-1,2-diphenylethylenediamine **58** *via* $NaBH_4$/MeOH reduction has been reported (Scheme **13**).[19]

Scheme 13



(+)-*cis*-1,2,2-Trimethylcyclopentane-1,3-diamine **62** was prepared by the reaction of (1*R*,4*S*)-(+)-camphoric acid **61** with sodium azide in the presence of concentrated sulfuric acid (Scheme **14**).[20]

Scheme 14

1 **61** **62**

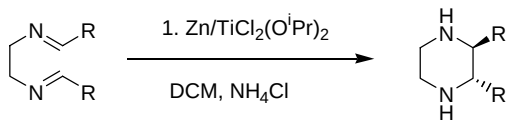
65% yield

1.1.7 Previous work from this laboratory

Several new convenient methods for the synthesis of chiral amines and amino alcohol derivatives have been reported from this laboratory.[21] Some of these methods involve selective reductions using $NaBH_4$ and $NaBH_4/I_2$ reagent system in crucial steps.[22] Very recently, the $(^nBu)_4NBH_4/PhCH_2Cl$ and $(^nBu)_4NBH_4/I_2$ reagent systems have been developed for reduction of various carbonyl compounds and hydroboration of alkenes.[23]

Diastereomerically pure (±)-2,3-diarylpiperazines **64** were readily prepared in 73-83% yields by intramolecular reductive coupling of diimines **63** using the $Zn/Ti(O^iPr)_2Cl_2$ reagent system (Scheme **15**).[24]

Scheme 15

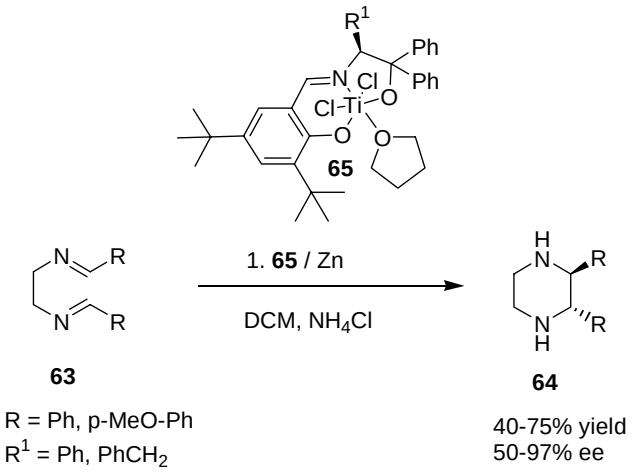


63 (±)-**64**

73-83% yield

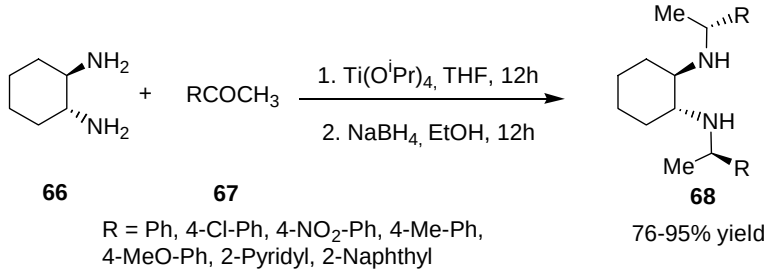
Enantioselective intramolecular reductive coupling of diimines **63** by chiral titanium complex **65** and zinc gives the *trans*-2,3-diarylpiperazines **64** in 40-75% yield with up to 97% ee (Scheme **16**).[25]

Scheme 16



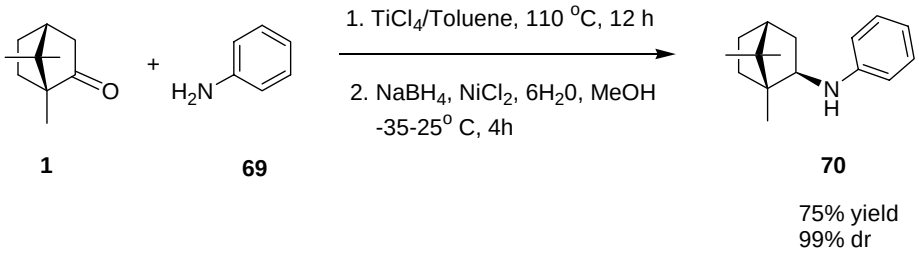
Reductive N-alkylation of *trans*-(*R,R*)-1,2-diaminocyclohexane **66** by prochiral ketones **67** using the $Ti(O^iPr)_4/NaBH_4$ has been reported to give the corresponding alkyl amine derivatives **68** in 76–95% yields with good diastereoselectivity (23:1:1) (Scheme **17**).[26]

Scheme 17



Previously, synthesis of isobornyl aniline **70** *via* condensation of D-(+)-camphor **1** and aniline **69** followed by selective reduction with $NaBH_4/NiCl_2.6H_2O$ reagent system was reported (Scheme **18**).[27]

Scheme 18



Though, such synthetic methods look somewhat simple, they result from systematic investigations. Accordingly, we have undertaken efforts to synthesize various amines and amino alcohol derivatives using D-(+)-camphor **1** and D-(-)-camphorquinone **2**. Also, it is of interest to understand the stereochemical outcome of the reactions involved in the synthesis. The results of these studies are discussed in the next section.

1.2 Results and Discussion

1.2.1 Synthesis of chiral camphanyl amine and amino alcohol derivatives

Chiral camphor analogs are powerful molecular elements for creating optically active compounds. As outlined in the introductory section, D-(+)–camphor **1**, D-(-)-camphorquinone **2** and their derivatives have been widely used as chiral auxiliaries and ligands in various asymmetric transformations. We have chosen the readily available naturally occurring D-(+)–camphor **1** as chiral precursor for preparing various chiral camphanyl amine derivatives using different amine sources *via* reduction of intermediates using $NaBH_4$ along with some additives. The results are discussed here.

1.2.2 Synthesis of new C_2-symmetrical diamines using D-(+)-Camphor

We have followed a protocol similar to that previously used for the conversion of D-(+)-camphor to isobornyl aniline in this laboratory (Scheme **16**).[27] D-(+)-camphor **1** was first reacted with ethylene diamine **71** in the presence of BF_3:OEt_2 (5 mol%) to obtain the *bis*-imine **72**. Subsequent reduction of this imine **72** with $NaBH_4$ at 0-25 ^oC gave the diamine **42** with dr ratio 80:20. The reaction at -78 ^oC gave the product with dr ratio 85:15. Earlier, it was observed in this laboratory that the use of $NaBH_4$ – $NiCl_2.6H_2O$ reagent system (nickel boride prepared *in situ*) for the reduction of camphor-anil into isobornyl aniline gave 75% yield (Scheme **16**).[27] We have observed that the reduction of the *bis*-imine **72** in the presence of nickel boride [generated *in situ* using

$NiCl_2.6H_2O$ (1.0 equiv.) and $NaBH_4$ (1.0 equiv.)] in MeOH at -30 °C resulted in 90% yield of diamine **42** with 95:5 selectivity (by ^1H NMR). The diastereomeric mixture of **42** is readily enriched to obtain samples with dr up to 99% by recrystalization of the diamine hydrochloride salt from ethanol. The absolute configuration of the newly formed stereogenic centers of the diamine **42** was assigned as 2*R,* 2'*R* by comparison with reported data (Scheme **19**).[13g]

Scheme 19

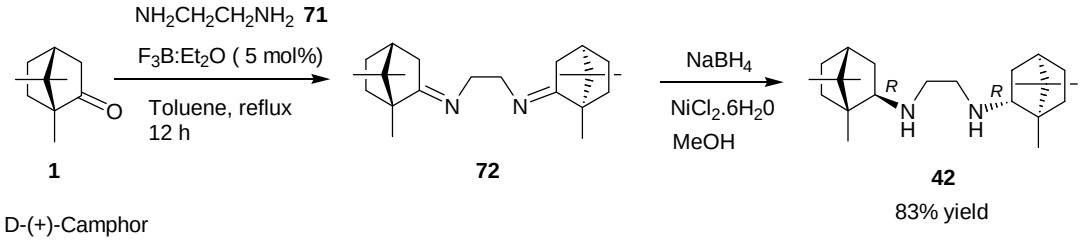


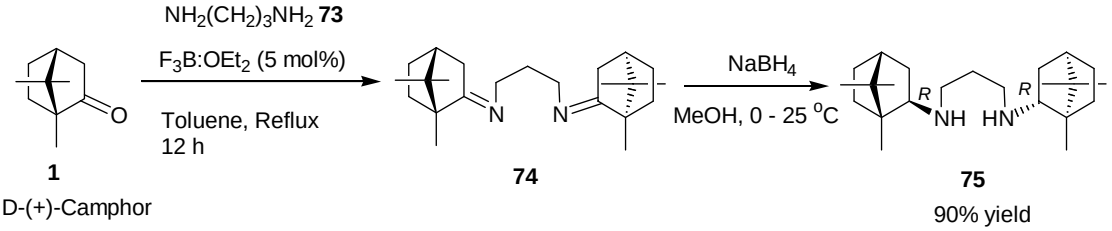
Table 1 Reduction of diimine **72**

Entry	Reduction Source	Yield (%)	dr of **42**
1	$NaBH_4$/MeOH at 0 ^oC	93	80:20
2	$NaBH_4$MeOH at -78 ^oC	84	80:15
3	$NaBH_4/NiCl_2.6H_2O$/ MeOH at -30 ^oC	90	95:5

Similarly, the diimine **74** is readily prepared by the reaction of D-(+)-camphor **1** with propylene diamine **73** in the presence of $F_3B:OEt_2$ (5 mol%) in toluene under reflux conditions. This *bis*-imine **74** is easily reduced using $NaBH_4$/MeOH to obtain the diamine **75** in 90% yield. The absolute configuration at the newly formed chiral centers

of diamine **75** is assigned as 2*R, 2'R* by comparison with reported data for **42** (Scheme **20**).[13g]

Scheme 20



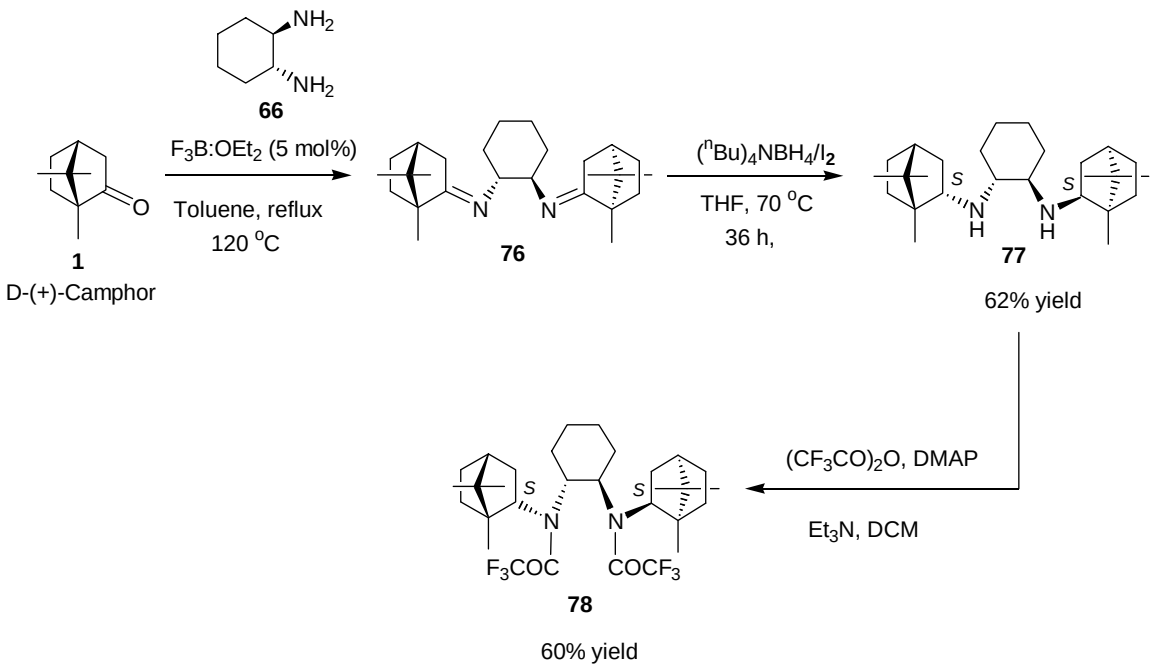
For the diamines **42** and **75**, the $[\alpha]_D^{25}$ values in ethanol have same sign and are almost same i.e -107.6 and -104.6, respectively. These values compare well with the reported $[\alpha]_D^{25}$ value of diamine **42** [-107.7].[13g]

1.2.3 Synthesis of new C_2-symmetrical amines using chiral camphor and chiral amines

Previously, methods for the synthesis of various chiral amines and macrocycles containing the *trans*-(*R,R*)-1,2-diaminocyclohexane **66** moiety have been reported from this laboratory.[28] We have first examined the use of the *trans*-1,2-diaminocyclohexane **66** and D-(+)–camphor **1** to obtain the corresponding chiral amine system. The *bis*-imine **76** is readily accessed by the reaction of D-(+)–camphor **1** with *trans*-(*R,R*)-1,2-diaminocyclohexane **66** in the presence of $F_3B{:}OEt_2$ (5 mol%). Unfortunately, the *bis*-imine **76** failed to undergo reduction using $NaBH_4$/MeOH or $NaBH_4/NiCl_2.6H_2O$/MeOH under the conditions discussed in the previous section. Fortunately, the *bis*-imine **76** underwent reduction using diborane prepared using the $(^nBu)_4NBH_4/I_2$ reagent system.[23]

After completion of the reaction, the diamine **77** was isolated in 62% yield. Among the three expected diastereomeric products, only one diastereomeric product **77** was obtained exclusively. The absolute configuration of the compound **77** at newly formed stereogenic centers was assigned as 2*S*, 2'*S* indicating only the endo, endo product, i.e *trans*-(*R,R*)-*N,N'*-bis(bornyl)-1,2-diaminocyclohexane **77** is formed in this reaction (Scheme **21**). The crystal structure analysis of the amide derivative **78** clearly confirms this stereochemical assignment (Figure **3**).

Scheme 21



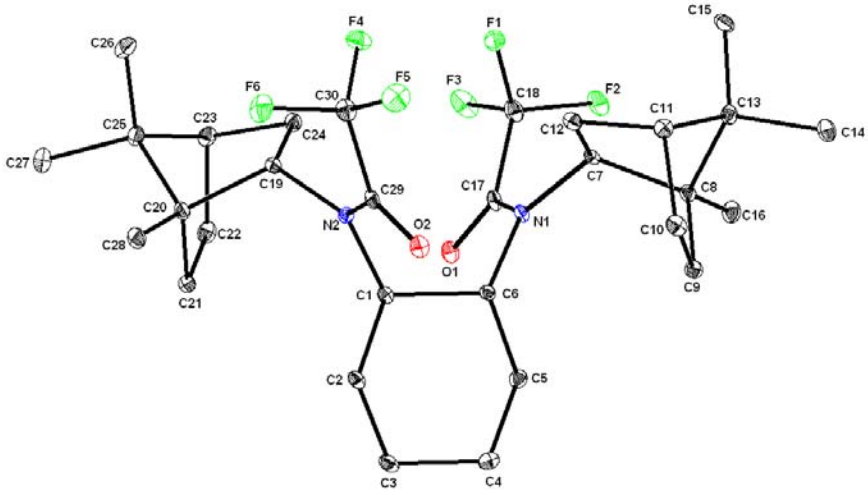
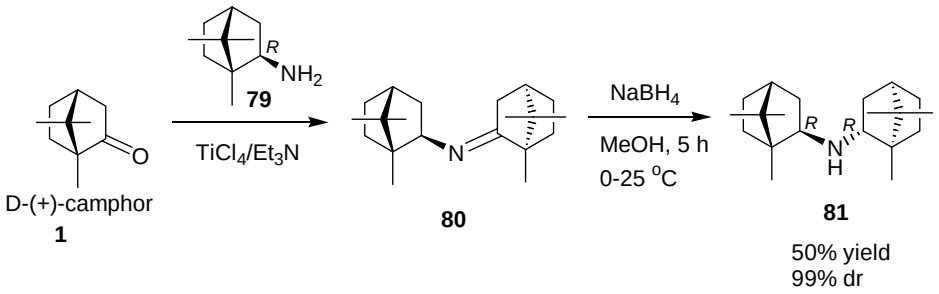


Figure 3

Figure.3 ORTEP representation of **78** (All the H-atoms were removed for clarity and thermal elipsoids were drawn with 25% probability).

We have also examined the use of exo-(-)-bornylamine **79** for the synthesis of the isobornyl C_2-symmetrical amine **81** following a simillar synthetic sequence. We have observed that the reaction of D-(+)-camphor **1** with exo-(-)-bornylamine **79** in the presence of $TiCl_4/Et_3N$ gave the imine **80** in 60% yield. Subsequent reduction with $NaBH_4$/MeOH under ambient conditions gave the amine **81** (Scheme **22**). After work up and coloumn chromatography, the C_2-symmetrical amine **81** was obtained in 50% yield. Interestingly, among the three diastereomeric products expected, only one product **81** was obtained in this reaction. The absolute configuration at the newly formed stereogenic centers was assigned as 2*R,* 2*'R* by comparison of the $[\alpha]_D^{25}$ value with the value reported for **81** (Scheme **22**).[29]

Scheme 22

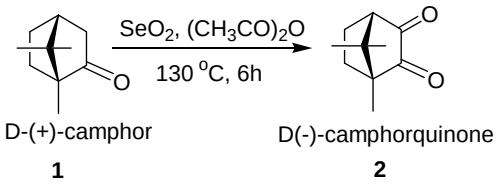


Previously, the imine **80** was prepared using D-(+)-camphor and excess of the chiral amine **79**. We have used stochiometric quantity of D-(+)-camphor, *exo*-bornyl amine **79** and Et_3N was used instead of more amount of **79**. The $[\alpha]_D^{25}$ value observed for **81** in chloroform solvent compares well with the reported $[\alpha]_D^{25}$ value.[29]

1.2.4 Synthesis of various chiral D-(-)-Camphorquinone derivatives

The highly reactive D-(-)-camphorquinone **2** is readily accessed by the reaction of D-(+)–camphor **1** with SeO_2 in acetic anhydride (Scheme **23**).[18]

Scheme 23

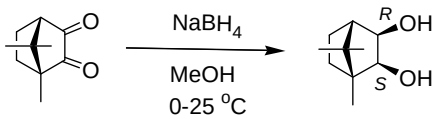


We have decided to undertake systematic studies towards the synthesis of various derivatives of the D-(-)-camphorquinone **2**.

1.2.5 Synthesis of new chiral camphanyl diol and amino alcohol derivatives

The D-(-)-camphorquinone **2** undergoes selective reduction with $NaBH_4$ in MeOH under ambient conditions. Among the four diastereomeric products expected, only one diastereomer **82** was obtained in 95% yield. The absolute configuration of the newly formed stereogenic centers was assigned as 2*S*, 3*R* by comparison with reported optical rotation values (Scheme **24**).[30]

Scheme 24



2 **82**

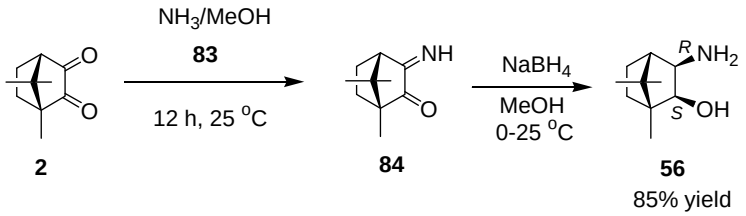
95% yield

It should be pointed out that the D-(-)-camphorquinone **2** undergoes reduction using hydrogen and Raney nickel to give a mixture of isomeric products.[30] Whereas the reduction using the inexpensive $NaBH_4$/MeOH reagent system leads to formation of the 2,3-exo,exo-diol **82** in 95% yield with 99% dr selectivity.[30]

As outlined in the introductory section, the amino alcohol **56** based ligands have been successfully used in certain chiral transformations.[13] However, only multistep methods were reported for the synthesis of **56** with low overall yields.[18] We have observed that the reaction of D-(-)-camphorquinone **2** with methanolic ammonia **83** gives the imine **84**. This imine **84** intermediate is unstable for isolation, but upon reduction

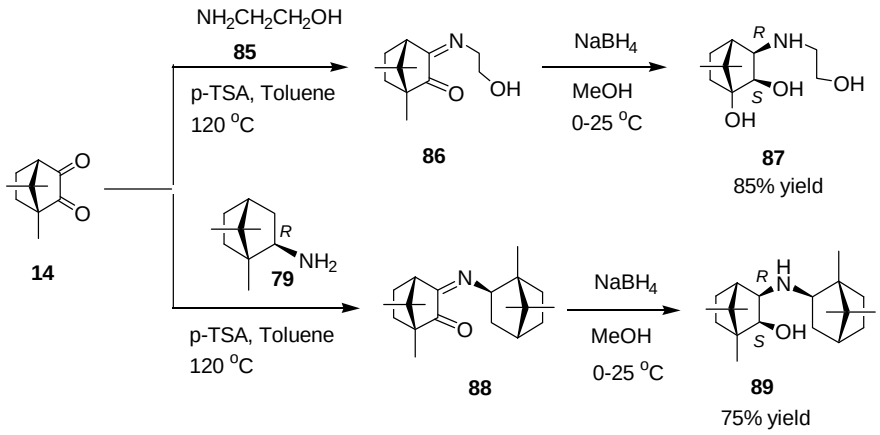
with $NaBH_4$ under ambient conditions afforded **56** as the only product in 85% yield. The absolute configuration of the newly formed stereogenic centers was assigned as 2*S*,3*R* by comparision of the $[\alpha]_D^{25}$ of this compound with repoted data for **56** (Scheme **25**).[18]

Scheme 25



Following a similar synthetic protocol, the substituted amino alcohol derivatives **87** and **89** were obtained in 75-85% yields by using D-(-)-camphorquinone **2** *via* the preparation of the corresponding imine **86**, **88** derivatives using ethanol amine **85** and exo-(-)-bornyl amine **79**, followed by reduction using $NaBH_4$ in methanol under ambient conditions. Among the four diastereomeric products expected, only the diastereomeric products **87** and **89** were obtained. The absolute configuration of the newly formed stereogenic centers of **87** was assigned as 2*S*, 3*R* by comparision with reported for **56**. The configuration of the product **89** was also assigned as 2*S*, 3*R,* assuming endo, endo attack on the ketimine **88** by $NaBH_4$ (Scheme **26**).[18]

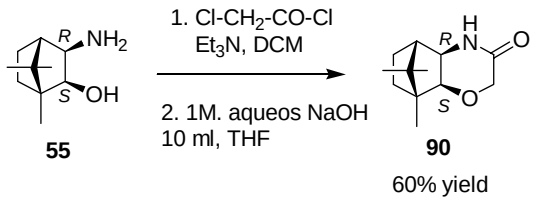
Scheme 26



In all above cases, the amino alcohols were prepared in two steps in one pot operation succesfully. However, the methods reported in the literature for the synthesis of amino alcohol **56** involves multistep synthetic operation.[18] Accordingly, the methods developed for the synthesis of the amino alcohols **56**, **87** and **89** have considerable potential for further exploitation.

The amide derivative **90** is easily accessed by the reaction of chiral amino alcohol **56** with chloro acetyl chloride and Et_3N, followed by NaOH treatment (Scheme **27**). The crystal structure analysis of the amide derivative **90** clearly confirms the stereochemical assignment of **56** (Figure **4**).

Scheme 27



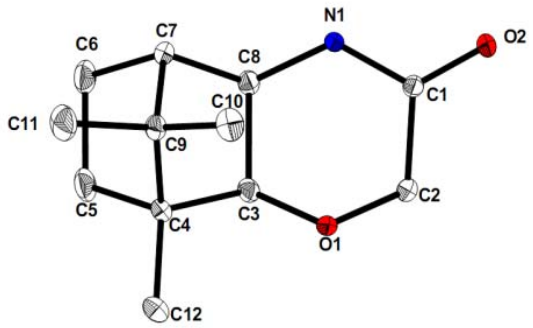


Figure.4

Figure.4 ORTEP representation of **90** (All the H-atoms were removed for clarity and thermal elipsoids were drawn with 25% probability).

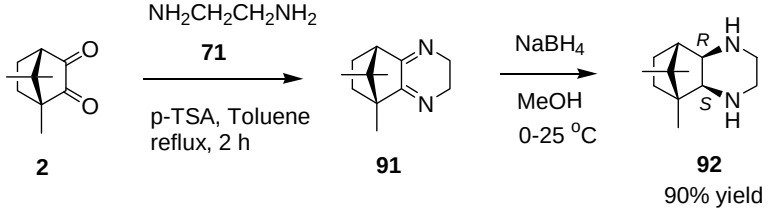
1.2.6 Synthesis of new chiral camphanyl diamine derivatives

As outlined in the introductory section, methods for the synthesis of chiral piperazines have been reported from this laboratory.[24] It was of interest to synthesize D-(-)-camphorquinone **2** derived chiral piperazine derivatives. As the presence of substituents on piperazine skeletons at the C_2, C_3, C_5 and C_6 positions of the ring has a significant influence on the biological activity of such derivatives, development of methods for the synthesis of different substituted piperazines are also of important to biological chemistry.[31]

We have observed that the reaction of D-(-)-camphorquinone **2** with ethylene diamine **71** in the presence of p-TSA (5 mol%) gives the dihydropyrazine **91** derivative. Subsequent, reduction of **91** with $NaBH_4$/MeOH at 0 ^oC afforded the substituted quinazoline **92** in 90% yield. Again, among the four diastereomeric products expected, only one diastereomer **92**

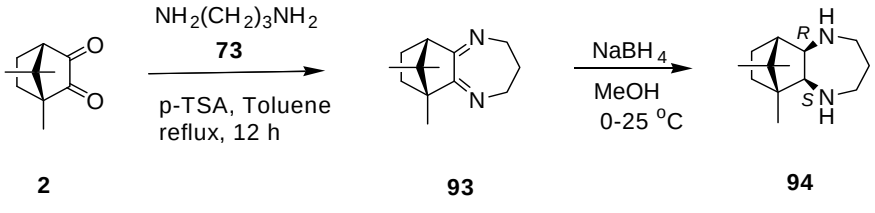
was obtained. The absolute configuration of the newly formed stereogenic centers was assigned as *S, R* by comparison with the data reported for the diamine **39** (Scheme **28**).[19]

Scheme 28



We have further observed that the reaction of D-(-)-camphorquinone **2** with propylene diamine **73** and p-TSA (10 mol%) under refluxing condition in toluene gave the diazepine **93** derivative, which on $NaBH_4$/MeOH reduction at 0 ^oC afforded the diamine **94** in 75% yield. Again, among the four isomeric products expected, only one diastereomer **94** with exo, exo selectivity was obtained. The absolute configuration of the newly formed stereogenic centers was assigned as *S, R* by comparision with the reported data for the diamine **39** (Scheme **29**).[19]

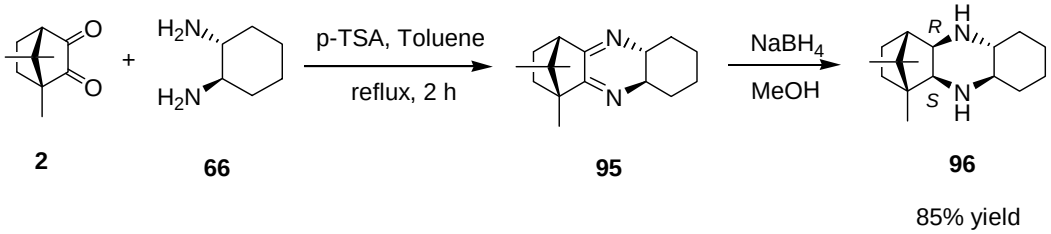
Scheme 29



We have also observed that the D-(-)-camphorquinone **2** reacts with *trans*-(*R,R*)-1,2-diaminocyclohexane **66** in the presence of p-TSA (5 mol%) in toluene under reflux to give the

phenazine derivative **95**, which undergoes reduction with $NaBH_4$ in methanol under ambient conditions to afford the highly substituted phenazine **96**. Again, among the four diastereomeric products expected, only one product **96** with exo, exo selectivity was obtained in 85% yield (Scheme **30**).[19] The absolute configuration of the newly formed stereogenic centers in the compound **96** was assigned as *S, R* by assuming reduction of the diimine only from the endo side as observed in other borohydride reductions studied so far with camphorquinone derived imine derivatives (Scheme **24**, **25**, **26**, **28** and **29**).

Scheme 30



2 **66** **95** **96**

85% yield

We have undertaken studies on the use of some of the chiral amines synthesized, following the procedure developed above for asymmetric transformations like Henry (nitroaldol) reaction and for the synthesis of chiral allenes using certain 1-alkynes and aldehydes. The results are described in Chapter **2** and Chapter **3**.

1.3 Conclusions

Convenient methods were developed for accessing several chiral amines and amino alcohols in moderate to good yields with good selectivities using D-(+)–camphor **1**, D-(-)-camphorquinone **2** and various amine derivatives to prepare the corresponding imines followed by $NaBH_4$ reduction. The configurations of the newly formed chiral centers of the camphor analogs were determined by single crystal X-ray analysis in some cases. These chiral derivatives has considerable potential for use in asymmetric transformations. We have investigated the use of some of these derivatives in asymmetric nitroaldol reaction (Chapter **2**) and in the synthesis of chiral allenes from aromatic aldehydes and 1-alkynes (chapter **3**). Some structurally related chiral camphanyl amines have been previously used in antiproliferative studies of the enantiomers of cis-[(1,2-camphordiamine) dichloro]platinum(II) complexes.[32] Hence, the methods described here have potential for use in the preparation of biologically active molecules containing such skeletons.

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) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. The neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (200 MHz), ^{13}C-NMR (50 MHz) and ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and TMS as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Liquid Chromatography (LC) and mass analysis (LC-MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electro Spray Ionization (ESI) techniques. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV.

Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{o}$) and AUTOPOL-IV (readability $\pm 0.001^{o}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard

solution of (*S)*-(+)-α,α–diphenylprolinol {$[\alpha]_D^{25}$ = +67.2 (*c* 0.52, $CHCl_3$)} supplied by Gerchem Laboratory (Pvt) Ltd., India.

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 silica gel (100-200) and neutral alumina.

All the glassware were pre-dried at 140 ^oC 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 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 were 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 yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy.

Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Ethylene diamine, propylene diamine, (*R,R*)-1,2-cyclohexyl diamine, ethanol amine supplied by Lancaster Synthesis, Ltd., England were used as purchased. The D-(+)-Camphor was supplied by Aldrich, USA. Iodine was supplied by Spectrochem, India. All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents before use. $NaBH_4$ was supplied by E-Merck (India). HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. The ee values were determined using CHIRALCEL OD-H column (4.6 x 250 mm) with eluents: hexane, 2-propanol, at a rate 0.5 mL/min, with the monitoring wave length 254 nm.

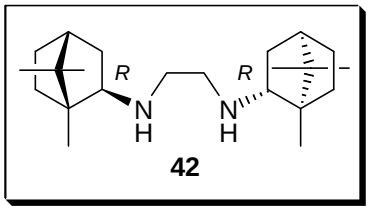
The X-ray diffraction measurements for the respective compounds were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system. The data were reduced using XTAL 3.4 (or) SAINT program, without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).

N,N′-Bis(1,7,7–trimethyl-bicyclo[2.2.1]hept-2-yl)–ethane–1,2-diamine 42

To a stirred solution of D-(+)-camphor **1** (1.52 g, 10 mmol) and ethylene diamine **71** (0.3 g, 5 mmol) in dry toluene (15 mL), BF_3:OEt_2 (0.01 mL, 5 mol%) or p-TSA (0.01 g, 5 mol%) was added carefully and the reaction mixture was refluxed for 12 h using a Dean-Stark apparatus. The mixture was brought to 25 ^oC. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated to obtain the *bis*-imine **72**. To this *bis*-imine **72** in MeOH (50 mL), $NiCl_2.6H_2O$ (2.37 g, 10 mmol) was added and the contents were cooled to -30 ^oC. $NaBH_4$ (1.90 g, 50 mmol) was added in portions from a solid addition flask over a period of 1 h and the contents were stirred further for 12h at -30-25 ^oC. 3N. Aqueous NaOH (20 mL) was added, followed by diethyl ether (30 mL) and the black precipitate was filtered off. The layers were separated. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The diamine **42** was isolated in 90% yield (95:5, exo/exo selectivity) by column chromatography on silica gel 100-200 (hexane and ethyl acetate 9:1). It was further enriched to obtain optically pure sample by recrystalisation of its dihydrochloride salt from ethanol with excellent recovery, followed by neutralization of the salt with aqueous NaOH.

Yield : 1.38 g (83%)

mp : 95-98 ^oC



42

$[\alpha]_D^{25}$: -107.6 (*c* 0.42, EtOH), [lit.$[\alpha]_D^{20}$ = -107.7 (*c* 0.65, EtOH, 99% ee)][13g]

IR (neat) : (cm^{-1}) 3435, 3032, 2920, 1552, 1379, 1066

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 2.65-2.64 (m, 2H), 2.52-2.49 (m, 4H), 1.67-1.49 (m, 8H), 1.06-1.04 (m, 6H), 0.99 (s, 6H), 0.86 (s, 6H), 0.80 (s, 6H).

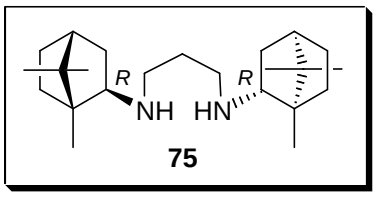
^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 66.7, 48.3, 48.2, 46.6, 45.2, 39.0, 36.9, 27.3, 20.6, 20.5, 12.2.

LCMS : m/z 333 (M+1)

N,N′-Bis(1,7,7–Trimethyl-bicyclo[2.2.1]hept-2-yl)propane–1,3-diamine 75

To a stirred solution of D-(+)-camphor **1** (1.52 g, 10 mmol) and propylene diamine **73** (0.37 g, 5 mmol) in dry toluene (15 mL), BF_3:OEt_2 (0.01 mL, 5 mol%) or p-TSA (0.01 g, 5 mol%) was added carefully and the reaction mixture was refluxed for 12 h using a Dean-Stark apparatus. The mixture was brought to 25 ^oC. The toluene layer was separated, dried (Na_2SO_4) and the solvent was removed to obtain the *bis*-imine **74**. It was taken in MeOH (50 mL) and cooled to 0 ^oC. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 1 h and the contents were stirred further for 6 h at 0-25 ^oC. 3N. Aqueos NaOH (10 mL) was added, followed by addition of diethyl ether (20 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After purification of residue by column chromatography on silica gel (100-200)

using hexane and ethyl acetate (9:1) as eluent, the product **75** was isolated in 90% yield. Comparison of the $[\alpha]_D^{25}$ value with the value reported for the diamine **42** indicated the exo,exo-selectivity in this reaction.[13g]



75

Yield : 1.55 g (90%)

$[\alpha]_D^{25}$: -104.6 (*c* 0.50, EtOH)

IR (neat) : (cm^{-1}) 3317, 2949, 1475, 1452, 1386, 1367, 1022

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 2.57-2.50 (m, 2H), 2.50- 2.47 (m, 4H), 1.67-1.49 (m, 12H), 1.06-1.04 (m, 4H), 1.01 (s, 6H), 0.86 (s, 6H), 0.80 (s, 6H)

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 67.0, 48.3, 47.3, 46.6, 45.2, 39.0, 36.9, 31.0, 27.4, 20.6, 20.6, 12.2.

LCMS : m/z 347 (M+1)

Analysis : for $C_{23}H_{42}N_2$

calcd: C, 79.70%; H, 12.21%; N, 8.08%

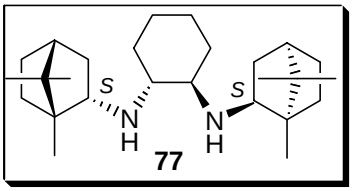
found: C, 79.65%; H, 12.16%; N, 8.15%

N,N'-Bis(1,7,7–trimethyl-bicyclo[2.2.1]hept-2-yl)–*trans*-(*R,R*) cyclohexane–1,2-diamine, 77

To a stirred solution of D-(+)-camphor **1** (1.52 g, 10 mmol) and *trans*-(*R,R*)-1,2-diaminocyclohexane **66** (0.57 g, 5 mmol) in dry toluene (15 ml), BF_3:OEt_2 (0.01 mL, 5 mol%) was added carefully. The reaction mixture was refluxed for 4 h using a Dean-Stark apparatus. The mixture was brought to 25 ^oC. The toluene layer was separated, dried (Na_2SO_4) and the solvent was removed to obtain **76**. The *bis*-imine **76** obtained was taken in THF (50 mL), cooled to 0 ^oC under N_2 atmosphere and $NaBH_4$ (0.76 g, 20 mmol) was added. Iodine (2.54 g, 10 mmol) in THF (15 mL) was added slowly during 15 min. The reaction mixture was further stirred for 1 h at 25 ^oC and refluxed for 36 h. It was carefully quenched with 3N. aqueous NaOH (20 mL) at 0 ^oC and diethyl ether (30 mL) was added. The organic layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After purification by column chromatography on silica gel (100-200) using hexane and ethyl acetate (8:2) as eluent, the diamine **77** was obtained. The structure analysis of the *bis*-trifluoroacetamide derivative revealed the endo, endo-selectivity in this reaction with configuration at the newly formed chiral centers as *S, S*.

Yield **:** 1.20 g (62%)

Mp **:** 95-100 ^oC



77

$[\alpha]_D^{25}$ **:** +5.06 (*c* 0.50, EtOH)

IR (neat) **:** (cm^{-1}) 3304, 2945, 2876, 1462, 1386, 1124

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 2.76-2.74 (m, 2H), 2.29-2.24 (m, 2H), 2.16-2.14 (m, 2H), 2.05-2.01 (m, 2H), 1.83-1.77 (m, 2H), 1.69-1.66 (m, 4H), 1.59-1.58 (m, 2H), 1.29-1.16 (m, 6H), 1.03-0.99 (m 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.86 (s, 6H)

^{13}C NMR **:** (100 MHz, $CDCl_3$,δ ppm) 64.5, 62.5, 49.6, 47.8, 45.3, 41.2, 33.7, 28.4, 27.3, 25.2, 19.8, 18.6, 14.4.

LCMS **:** m/z 388 (M+1)

Analysis **:** for $C_{26}H_{48}N_2$

calcd: C, 80.76%; H, 11.99%; N, 7.25%

found: C, 80.55%; H, 11.86%; N, 7.21%

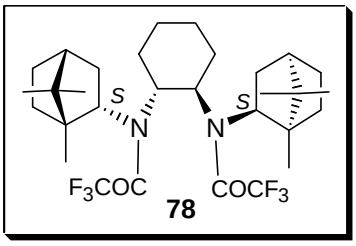
2,2,2–Trifluoro–N–{2–[(2,2,2–trifluoroacetyl)–(1,7,7–trimethyl–bicyclo[2.2.1]hept--2–yl)–amino]-cyclohexyl}–N–(1,7,7-trimethyl bicyclo[2.2.1]hept–yl)–acetamide, 78

To a stirred solution of the diamine **77** (0.387 g, 1 mmol) in dry DCE (5 mL), Et_3N (0.3 mL, 2.1 mmol) and DMAP (0.02 g, 0.2 mmol) were added under N_2 atmosphere, and

the contents were stirred for 5 min. Trifluoroacetic anhydride (2 mL) was added slowly at 0 ^{o}C and the contents were stirred at room temperature for 48 h. The reaction mixture was quenched with water (2 mL) and DCM (10 mL) was added. The organic layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200) using hexane and ethyl acetate (7:3) as eluent, the trifluoro acetamide **78** was isolated. It was crystalised from hexane and ethyl acetate to obtain cryatals suitable for single crystal X-ray analysis.

Yield : 0.33 g (60%)

Mp : 225-230 ^{o}C



78

$[\alpha]_D^{25}$: -11.3 (*c* 0.50, $CHCl_3$)

IR (KBr) : (cm^{-1}) 2955, 1682, 1456, 1195, 1136

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 4.53-4.51 (m, 2H), 4.10-4.06 (m, 2H), 2.70-2.66 (m, 2H), 2.29-2.24 (m, 2H), 2.16-2.14 (m, 2H), 2.05-2.01 (m, 2H), 1.95-1.69 (m, 6H), 1.54-1.35 (m, 6H), 1.03-0.93 (m, 2H) 0.92 (s, 6H), 0.88 (s, 6H), 0.86 (s, 6H)

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 158.7, 118.2, 61.7, 54.8, 50.5, 49.0, 43.2,

31.6, 29.1, 28.8, 27.5, 24.3, 19.6, 18.3, 13.3.

LCMS : m/z 483 (M^+-$COCF_3$)

Analysis : for $C_{30}H_{48}N_2O_2F_6$

calcd: C, 62.27%; H, 7.66%; F, 19.70%; N, 4.84%; O, 5.53%

found: C, 62.37%; H, 7.58%; F, 19.67%; N, 4.75%; O, 5.48%

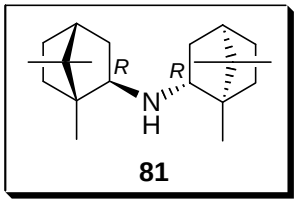
Preparation of Bis(1,7,7–trimethyl-bicyclo[2.2.1]hept-2-yl)-amine, 81

To a stirred solution of D-(+)-camphor **1** (1.52 g, 10 mmol), exo-(-)-bornylamine **79** (1.54 g, 10 mmol) and Et_3N (30 mmol, 4mL) in dry toluene (15 mL), $TiCl_4$ (0.50 mL, 5 mmol) in toluene (10 ml) was added slowly during 15 min. under N_2 atmosphere at 0 ^oC. The reaction mixture was further stirred for 0.5 h at 25 ^oC and refluxed for 12 h. The reaction was carefully quenched with aqueous K_2CO_3 solution (20 mL) at 0 ^oC and diethyl ether (20 mL) was added. The organic layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was removed. After column chromatography on silica gel (100-200) using hexane as eluent, the imine **80** was isolated. It was taken in MeOH (30 mL) and cooled to 0 ^oC and $NaBH_4$ (0.380 g, 10 mmol) was added in portions from a solid addition flask over a period of 0.5 h and stirred further for 6 h at 0-25 ^oC. The reaction mixture was quenched with water (10 mL) and diethyl ether (20 mL) was added. The diethyl ether layer was washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200) using hexane

as eluent, the amine **81** was isolated. The configuration at the newly formed chiral centers was assigned as *R, R* by comparision with repoted data.[29]

Yield : 1.45 g (50%)

mp : 55-60 ^{o}C



81

$[\alpha]_D^{25}$: -144.6 (*c* 0.50, $CHCl_3$), [$[\alpha]_D^{20}$ = -140.0 (*c* 1.0, $CHCl_3$)][29]

IR (KBr) : (cm^{-1}) 3435, 3032, 2920, 1552, 1379, 1066

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 2.46 (m, 2H), 1.65-1.50 (m, 12H), 1.05-1.03 (t, 4H), 0.96 (s, 6H), 0.80 (s, 6H), 0.79 (s, 6H)

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 64.2, 48.0, 46.5, 45.2, 39.2, 36.9, 27.3, 20.6, 20.5, 12.5.

LCMS : m/z 290 (M+1)

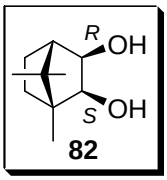
(*1R,2S,3R,4S*)-(+)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2,3-exo,exo-diol 82

D-(+)-Camphorquinone **2** (1.66 g, 10 mmol)) was taken in MeOH (50 mL) and cooled to 0 ^{o}C. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 0.5 h and stirred further for 0.5 h at 25 ^{o}C. Methanol was removed under reduced pressure. Water (10 mL) and ethyl acetate (20 mL) were added. The organic layer

was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was removed. After column chromatography on silica gel (100-200) using hexane and ethyl acetate (8:2) as eluent, the diol **82** was isolated. The configuration at the newly formed chiral centers was assigned as *S*, *R* by comparision with reported data.[30]

Yield : 1.62 g (95%)

mp : 255-257 ^{o}C



82

$[\alpha]_D^{25}$: -17.3 (*c* 0.52, EtOH), [$[\alpha]_D^{20}$ = -17.5 (*c* 6.0, EtOH)][31]

IR (KBr) : (cm^{-1}) 3331, 2955, 1481, 1460, 1392, 1130, 1091, 1053

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.81-3.80 (d, *J* = 4.0 Hz, 1H), 3.58-3.57 (d, *J* = 4.0 Hz, 1H), 3.17 (s, 1H), 3.03 (s, 1H), 1.64-1.60 (m, 2H),1.46-1.40 (m, 2H), 1.4 (s, 3H), 0.92 (s, 3H), 0.94 (s, 1H), 0.78 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$,δ ppm) 79.8, 76.0, 51.4, 48.7, 46.4, 33.1, 24.0, 21.8, 21.0, 11.1

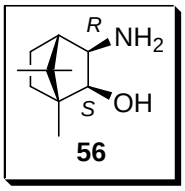
LCMS : m/z 170 (M+1)

(*1R,2S,3R,4S*)-(-)–3–Amino-1,7,7-Trimethyl bicyclo[2.2.1]heptan-2-ol, 56

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) in MeOH (5 mL) and 1M solution of NH_3 (MeOH) **83** (15 mL) was added carefully and the reaction mixture was stirred for 12 h at 25 ^oC. MeOH (30 mL) was added and cooled to 0 ^oC. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 1 h and stirred further for 2 h at 0-25 ^oC. Methanol was removed under reduced pressure. Water (10 mL) and DCM (20 mL) were added. The organic layer was separated, washed with saturated NaCl solution and dried (Na_2SO_4). After evaporation of DCM, the crude product was washed with hexane and the product **56** was isolated. The configuration at the newly formed chiral centers were assigned as *S*, *R* by comparision with reported data.[18]

Yield : 1.402 g (83%)

Mp : 210-215 ^oC



56

$[\alpha]_D^{25}$: -8.1 (*c* 0.52, MeOH) [$[\alpha]_D^{20}$ = -8.2 (*c* 1.15, CH_3OH)][18]

IR (KBr) : (cm^{-1}) 3414, 2953, 2876, 1575, 1456, 1385, 1095

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.38-3.37 (d, *J* = 4.0 Hz, 1H), 3.06-3.04 (d, *J* = 8.0 Hz, 1H), 1.70-1.69 (m, 2H),1.56-1.55 (d, *J* = 4.0

Hz, 1H), 1.45-1.43 (s, 1H), 1.03 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 79.0, 57.3, 53.4, 48.7, 46.6, 33.1, 26.9, 21.9, 21.2, 11.4

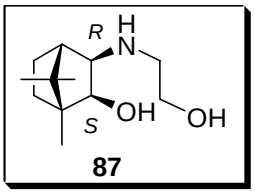
LCMS : m/z 170 (M+1)

(*1R,2S,3R,4S*)-(+)–3–(2-Hydroxy-ethylamino)-1,7,7-trimethyl-bicyclo[2.2.1] heptan-2-ol, 87

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) and ethanol amine **85** (1.11 mL, 10 mmol) in dry toluene (15 mL), p-TSA (0.01 g, 5 mol%) was added carefully. The reaction mixture was refluxed for 6 h using a Dean-Stark apparatus. The mixture was brought to 25 ^{o}C. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated. The imine residue was taken in MeOH (50 mL) was added and the contents were cooled to 0 ^{o}C. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 1 h and stirred further for 4 h at 0-25 ^{o}C. The MeOH was removed under reduced pressure. Water (10 mL) and ethyl acetate (25 mL) were added. The organic layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200) using ethyl acetate as eluent, the product **87** was isolated. The configuration at the newly formed chiral centers was assigned as *S*, *R* by comparision with reported data for compound **55**.[18]

Yield : 1.82 g (85%)

Mp : 45-50 ^{o}C



87

$[\alpha]_D^{25}$: +6.1 (*c* 0.60, $CHCl_3$)

IR (KBr) : (cm^{-1}) 3414, 2953, 2876, 1575, 1456, 1385, 1095

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.68-3.66 (m, 2H), 3.46-3.44 (d, *J* = 8.0 Hz, 1H), 3.06-2.90 (br, 2H), 2.92-2.89 (m, 1H), 2.73-2.71 (m, 2H), 1.71-1.64 (m, 2H),1.46-1.44 (m, 1H), 1.05 (s, 3H), 1.03-1.02 (m, 2H), 0.94 (s, 3H), 0.78 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 78.9, 66.3, 61.6, 52.6, 51.6, 48.2, 46.5, 32.9, 27.1, 21.9, 21.2, 11.3

LCMS : m/z 215 (M+1)

Analysis : for $C_{12}H_{23}NO_2$

calcd: C, 67.57%; H, 10.87%; N, 6.57%; O, 15.00%

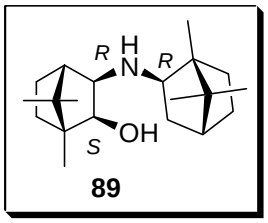
found: C, 67.54%; H, 10.82%; N, 6.65%; O, 14.95%

(*1R,2S,3R,4S*)-(-)–1,7,7–Trimethyl-3–(1,7,7–trimethyl–bicyclo[2.2.1] hept–2–ylamino)-bicyclo[2.2.1]hept–2–ol, 89

To a stirred solution of D-(+)-camphorquinone **2** (0.836 g, 5 mmol), and exo-(-)-bornylamine **79** (0.77 g, 5 mmol) in dry toluene (15 mL), p-TSA (0.01 g, 5 mol%) was added carefully and the reaction mixture was refluxed for 6 h using a Dean-Stark apparatus. The contents were brought to 25 ^{o}C. The toluene layer was separated, dried (Na_2SO_4) and the solvent was removed. The imine residue **88** was taken in MeOH (25 mL) and cooled to 0 ^{o}C. $NaBH_4$ (0.57 g, 15 mmol) was added in portions from a solid addition flask over a period of 1 h and stirred further for 3h at 0-25 ^{o}C. MeOH was removed under reduced pressure. Water (10 mL) and ethyl acetate (20 mL) were added. The organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200) using hexane and ethyl acetate (9:1) as eluent, the product **89** was isolated. The configuration at the newly formed chiral centers was assigned as *S*, *R* by assuming endo, endo attack on the ketimine **88** by $NaBH_4$.[18]

Yield : 1.14 g (75%)

Mp : 115-120 ^{o}C



89

$[\alpha]_D^{25}$: -60.1 (*c* 0.53, $CHCl_3$)

IR (KBr) : (cm^{-1}) 3356, 3260, 2951,2876, 1479, 1450, 1386, 1369, 1114, 1057, 960

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.33-3.32 (d, *J* = 4.0 Hz, 1H), 2.69 (s, 1H), 2.67–2.66 (d, *J* = 4.0 Hz, 1H), 1.70-1.40 (m, 9H), 1.07–1.04 (m, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.77 (s, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$,δ ppm) 78.8, 67.7, 65.5, 51.3, 48.7, 48.4, 46.6, 44.9, 38.6, 36.9, 33.0, 27.2, 27.2, 21.9, 21.2, 20.6, 20.5, 12.1, 11.2.

LCMS : m/z 305 (M+1)

Analysis : for $C_{20}H_{35}NO$

calcd: C, 78.63%; H, 11.55%; N, 4.58%; O, 5.24%

found: C, 78.60%; H, 11.63%; N, 4.52%; O, 5.33%

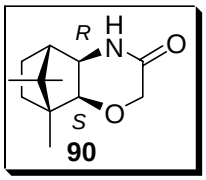
Procedures for the preparation of cyclic amide 90

To a stirred solution of amino alcohol **56** (0.154 g, 1 mmol), triethyl amine (0.21 mL, 1 mmol) in dry THF (5 mL) was added carefully chloro acetyl chloride (0.12 g, 1.1 mmol). The contents were stirred for 6 h and were brought to 0 ^{o}C. 1N. Aqueous NaOH (3

mL) was added and stirred for 2 h at 25 ^{o}C. DCM (10 mL) was added and the organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200) using hexane and ethyl acetate as eluent, the product **90** was isolated.

Yield : 0.12 g (60 %)

Mp : 45-50 ^{o}C



90

$[\alpha]_D^{25}$: +70.1 (*c* 0.60, $CHCl_3$)

IR (KBr) : (cm^{-1}) 3414, 2953, 2876, 1575, 1456, 1385, 1095

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 6.93 (s, 1H), 4.11-4.07 (d, *J* = 16.0 Hz, 1H), 3.77-3.74 (d, *J* = 12.0 Hz, 1H), 3.64-3.63 (d, *J* = 4.0 Hz, 1H), 3.35-3.33 (d, *J* = 8.0 Hz, 1H), 1.74-1.70 (m, 2H),1.58-1.55 (m, 1H), 1.10 (s, 3H), 1.06-1.03 (m, 2H), 0.97 (s, 3H), 0.83 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$,δ ppm) 170.8, 83.7, 66.2, 58.4, 50.5, 49.1, 47.5, 32.9, 25.9, 22.0, 20.5, 11.1

LCMS : m/z 210 (M+1)

Analysis : for $C_{12}H_{19}NO_2$

calcd: C, 68.87%; H, 9.15%; N, 6.69%; O, 15.29%

found: C, 68.81%; H, 9.23%; N, 6.73%; O, 15.32%

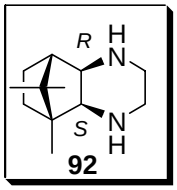
Procedure for the preparation of camphanyl diamine 92

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) and ethylene diamine **71** (0.60 g, 10 mmol) in dry toluene (10 mL), p-TSA (0.01 g, 5 mol%) was added carefully. The reaction mixture was refluxed for 2 h using a Dean-Stark apparatus. The mixture was brought to 25 ^{o}C. The toluene layer was separated and dried (Na_2SO_4) and the solvent was removed. The *bis*-imine **91** was taken in MeOH (50 mL) and cooled to 0 ^{o}C. $NaBH_4$ (1.14 g, 30 mmol) was added in portions from a solid addition flask over a period of 1 h and stirred further for 5 h at 25 ^{o}C. MeOH was removed under reduced pressure. Water (10 mL) and DCM (25 mL) were added. The DCM layer was separated and washed with saturated NaCl solution and dried (Na_2SO_4). After column chromatography on silica gel (100-200) using chloroform and methanol (9:1) as eluent, the product **92** was isolated. The configuration at the newly formed chiral centers was assigned as *S*, *R* by comparison with reported data for the diamine **39**.[19]

(+)-(*5R,13S,12R,8S*)5,9,9–Trimethyl–decahydro-5,8–methano-quinazoline92

Yield : 1.75 g (90%)

$[\alpha]_D^{25}$: +5.6 (*c* 0.52, $CHCl_3$)



92

IR (neat) : (cm^{-1}) 3281, 3076, 2934, 1554, 1485, 1415, 1379, 1147, 1055, 808, 692

^{1}H NMR :` (400 MHz, $CDCl_3$, δ ppm) 2.96-2.91 (m, 2H), 2.94-2.92 (d, *J* = 10.0 Hz, 1H), 2.70-2.68 (d, *J* = 8.0 Hz, 1H), 2.62-2.61 (m, 3H), 1.79-161 (m, 4H),1.46 (s, 3H), 1.09-1.02 (m, 2H), 0.85 (s, 3H), 0.80 (s, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 68.2, 63.4, 50.2, 47.9, 47.1, 42.0, 41.7, 35.8, 27.0, 22.6, 21.3, 11.3.

LCMS : m/z 195 (M+1)

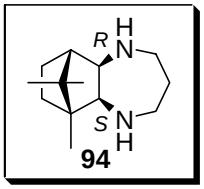
Analysis : for $C_{12}H_{22}N_2$

calcd: C, 74.17%; H, 11.41%; N, 14.42%

found: C, 74.05%; H, 11.45%; N, 14.55%

(+)-(*6R,14S,13R,9S*)6,10,10–Trimethyl–decahydro-6,9–methano–benzo(1, 4) diazepine 94

The procedure outlined as above was also followed for the preparation of azepine **94** starting from D-(-)-camphorquinone **2** and propylene diamine **73** (**Scheme 29**). The configuration of newly formed chiral centers of azepine **94** was assigned as *S, R*, by comparison of reported data for the compound **39**.[19]



94

Yield : 1.56 g (75%)

$[\alpha]_D^{25}$: +4.1 (*c* 0.65, $CHCl_3$)

IR (KBr) : (cm^{-1}) 3281, 3076, 2934, 1554, 1485, 1415, 1379, 1147, 1055. 808, 692.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.33-3.30 (m, 2H), 2.82-2.80 (d, *J* = 8.0 Hz,1H), 2.68-2.66 (d, *J* = 8.0 Hz, 1H), 2.39-2.30 (m, 2H), 1.93-1.76 (m, 4H), 1.75-1.66 (m, 4H),1.53-1.46 (m, 2H), 1.26 (s, 3H), 1.18-1.32 (m, 2H), 0.87 (s, 3H), 0.78 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ 75.5, 71.5, 52.4, 51.6, 51.5, 49.1, 46.4,

36.1, 34.4, 27.2, 21.7, 21.7, 12.2.

LCMS : m/z 208 (M+1)

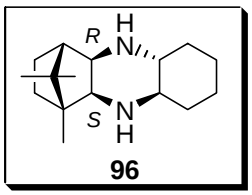
Analysis : for $C_{13}H_{24}N_2$

calcd: C, 74.94%; H, 11.61%; N, 13.45%

found: C, 74.85%; H, 11.55%; N, 13.21%

(+)-(*1R,2S,3R,4S*)1,11,11-Trimethyl–tetradecahydro-1,4–methano-phenazine96

The procedure was outlined for the synthesis of **92** was also followed for the preparation of phenazine **96** starting from D-(-)-camphorquinone **2** and *trans*-1,2-diamino cyclohexane **66** (**Scheme 30**). The configuration of newly formed chiral centers of phenazine **96** was assigned as *S, R*, by comparison of reported data for the compound **39**.[19]



96

Yield : 2.11g (85%)

$[\alpha]_D^{25}$: +11.5 (*c* 0.50, $CHCl_3$)

IR (neat) : (cm^{-1}) 3489, 2928, 1583, 1460, 1140, 1047

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 4.01-5.80 (bs, 2H), 3.49-3.47 (d, *J* = 8.0

Hz, 1H), 3.21-3.18 (d, *J* = 8.0 Hz, 1H), 3.11-3.07 (t, *J* = 16.0 Hz, 1H), 2.49-2.45 (t, *J* = 16.0 Hz, 1H), 2.12-2.11 (d, *J* = 4.0 Hz, 1H), 2.02-2.00 (d, *J* = 4.0 Hz, 1H), 1.81-1.72 (m, 5H), 1.50-1.22 (m, 9H), 1.11-1.02 (m, 2H), 0.90 (s, 3H), 0.83 (s, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 67.6, 58.0, 56.4, 55.8, 50.1, 48.4, 47.2, 34.9, 31.9, 30.9, 26.5, 24.8, 24.2, 21.5, 20.7, 11.0

LCMS : m/z 249 (M+1)

Analysis : for $C_{16}H_{30}N_2$

calcd: C, 77.36%; H, 11.36%; N, 11.28%

found: C, 77.21%; H, 11.41%; N, 11.15%

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Chapter 2

Highly Enantioselective Henry Reaction Catalyzed by Chiral C_2-Symmetric N,N′-bis(isobornyl)ethylenediamine-Copper Complex

2.1 Introduction

The nitroaldol (Henry) reaction is one of the atom economical reactions useful to prepare β-nitro alcohols from carbonyl compounds and nitroalkanes. The resulting nitro alcohol products are widely used as intermediates in organic synthesis, because of the many possible transformations of the nitro group into other functional groups.[1] Hence, the Henry reaction represents a powerful C–C bond forming tool as the resulting nitro alcohol products can be transformed into a number of nitrogen and oxygen containing derivatives (e.g. amino alcohols, amino acids etc.).

Enantiomerically pure β-amino alcohols are useful building blocks for the synthesis of several moieties that are present in many potent drugs.[2] For example, one of the best-known molecules that contain β-amino alcohol moiety is taxol **1**, which is composed of a polyoxygenated diterpene and (2*R*, 3*S*)-phenylisoserine.[3] Amastatin **2** and bestatin **3**[4] are β-amino alcohol containing moieties used as immunological response modifiers. Some other molecules that contain β-amino alcohol moiety are bevantolol **4**, propranolol **5** and denopamine **6**, which have been shown to be effective therapeutic agents in the treatment of heart disease. Also, numerous biologically active molecules such as isoproterenol **7**, sotalol **8**, formoterol **9**, miconazole **10** and cytoxazone **11** contain β-amino alcohol moieties (Figure **1**).[5]

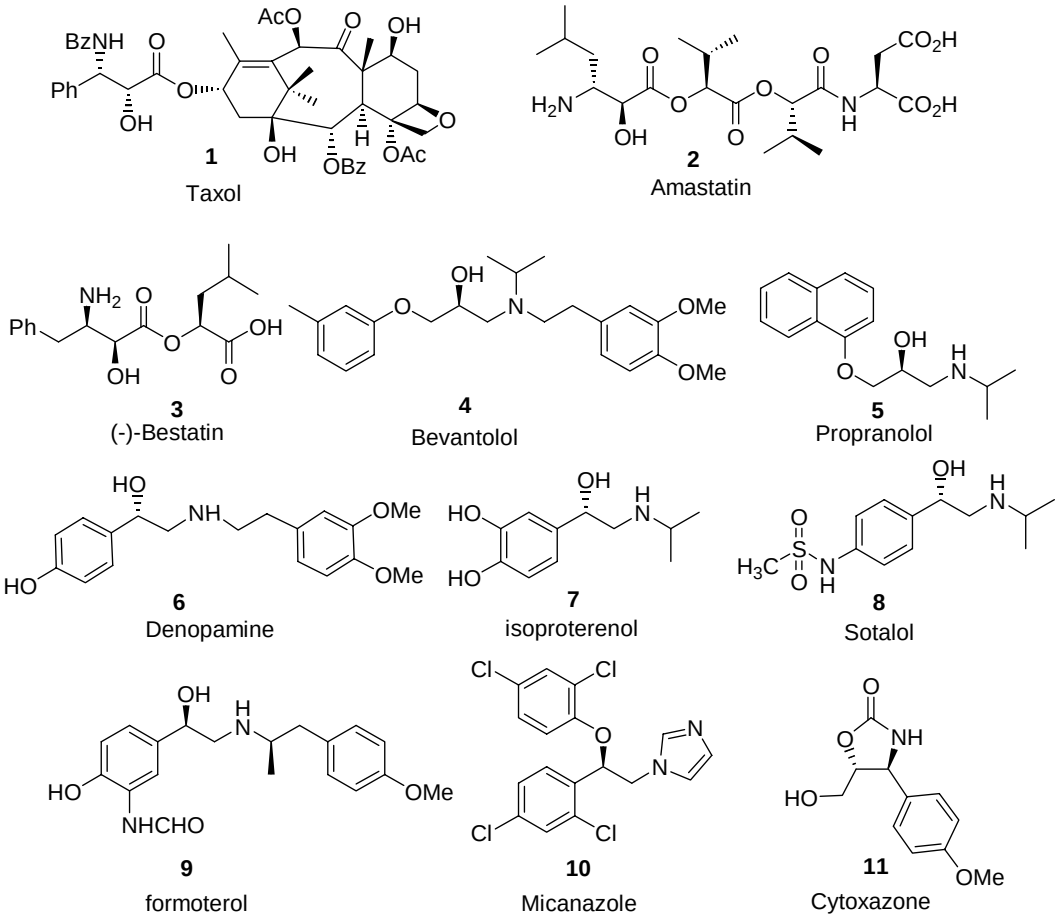


Figure 1

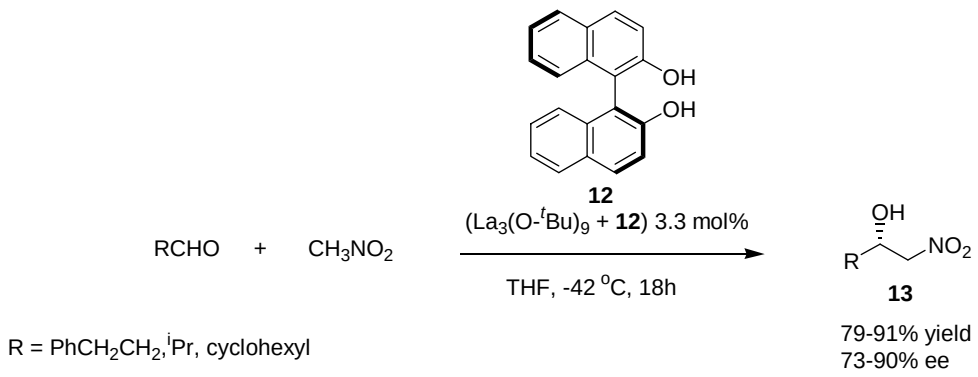
Over the years, several methods have been developed for the preparation of β-amino alcohol derivatives.[6] The enantiopure nitro alcohols obtained by asymmetric Henry reaction and can be easily reduced to access chiral amino alcohols. In recent years, numerous research efforts have been devoted to develop asymmetric versions of the nitroaldol reaction. Stereo control of the nitroaldol reaction remains challenging. The design and development of the chiral ligand plays a pivotal role in the development of efficient metal-catalyzed asymmetric reactions. The use of chiral catalysts has

advantages over substrate or auxiliary controlled reactions, since lower loadings of the expensive chiral non racemic inductors are required. Three reviews on catalytic asymmetric Henry reactions have already appeared.[7, 8] However, a brief review of the reports on the asymmetric nitroaldol reactions of various carbonyl compounds would facilitate the discussion.

2.1.1 Lanthanum reagents promoted nitroaldol reaction

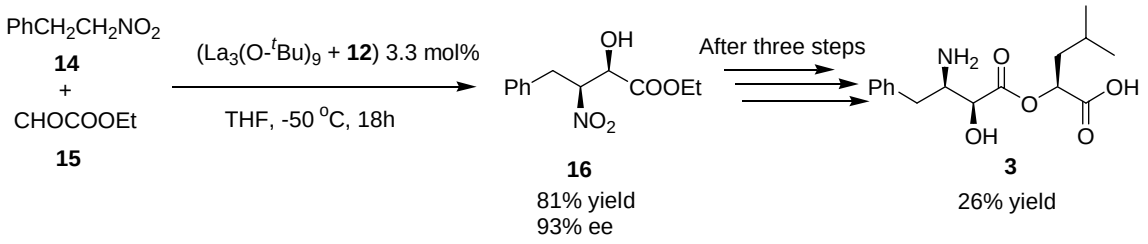
The first asymmetric nitroaldol reaction was reported by M. Shibasaki *et al*[9] in the reaction between various aldehydes and nitromethane gives the nitroaldol products **13** with up to 90% ee using the chiral bi-2-naphthol **12** and a lanthanum complex (Scheme **1**).

Scheme 1



A total synthesis of the potent amino peptidase inhibitor (-)-bestatin **3** has been achieved using asymmetric Henry reaction catalyzed by an optically active rare earth lanthanum and (*R*)-binol complex in a crucial step (Scheme **2**).[4]

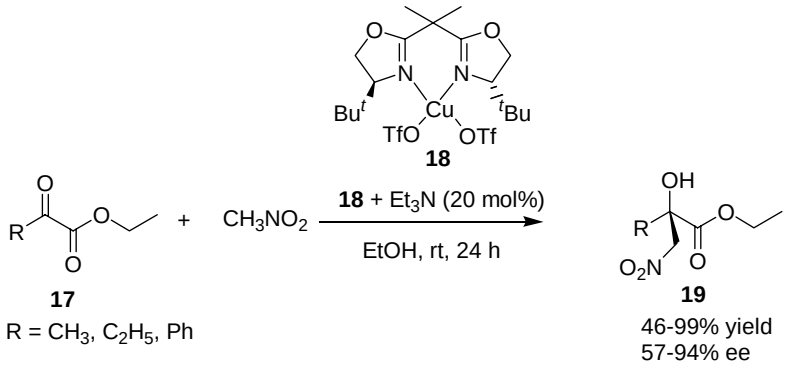
Scheme 2



2.1.2 Copper complexes mediated nitro aldol reactions

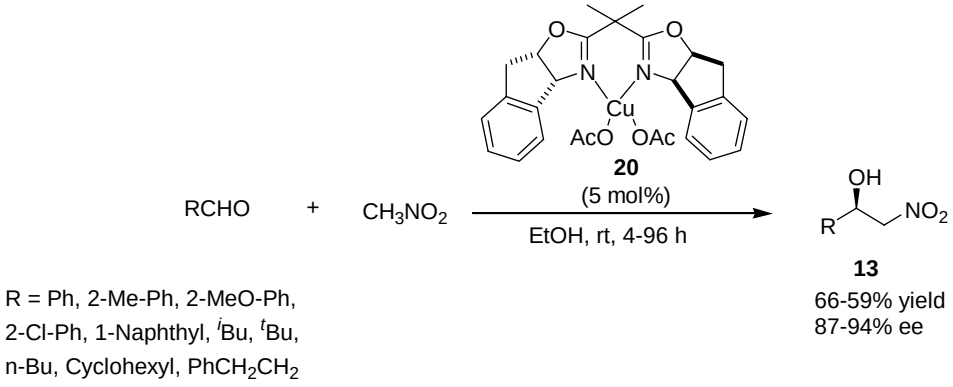
The reaction between nitromethane and different α-keto esters **17** in the presence of chiral Cu(II) complex **18** and triethylamine as the co-catalyst leads to nitro alcohol products **19** containing quaternary stereocentre with 57-94% ee (Scheme **3**).[10]

Scheme 3



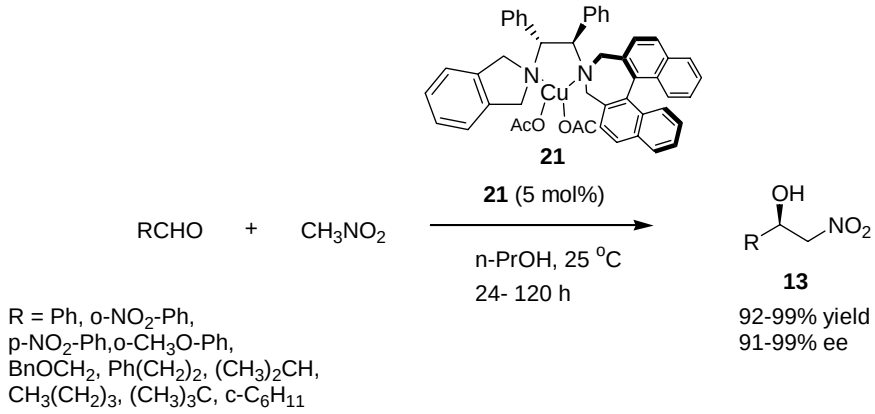
A more efficient Cu(II) catalyst **20** at loading levels of 5 mol%, has been described by Evans *et al*[11] for nitroaldol reaction of nitromethane with various aldehydes to β-nitro alcohols **13**. This method is quite general for a range of both aliphatic and aromatic aldehydes and works under mild reaction conditions (Scheme **4**).

Scheme 4



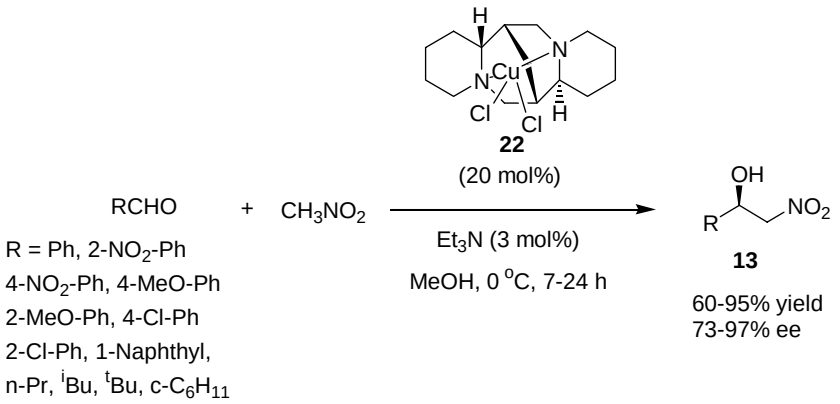
A diamine and Cu(II) catalytic system **21** has been reported for the reaction between nitromethane and aldehydes to give the corresponding β–nitro alcohols **13** with 91-99% ee (Scheme **5**).[12]

Scheme 5



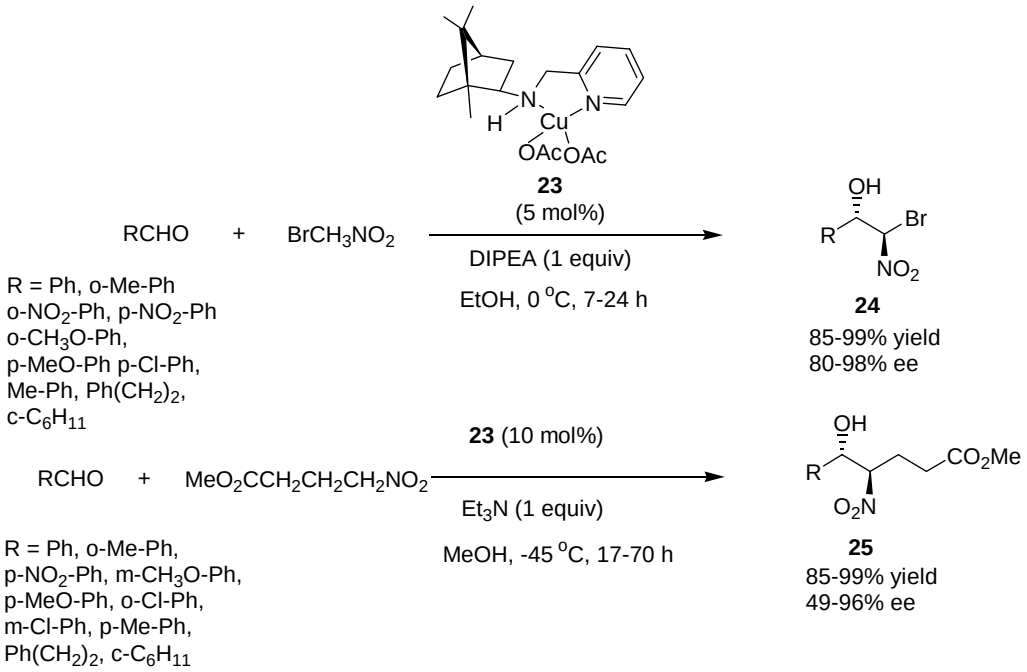
A $CuCl_2$–(–)-sparteine complex **22** is reported to be inefficient in promoting the nitroaldol reaction. However, a smooth reaction takes place in the presence of triethylamine (3 mol%) to give the products **13** with 73-97% ee (Scheme **6**).[13]

Scheme 6



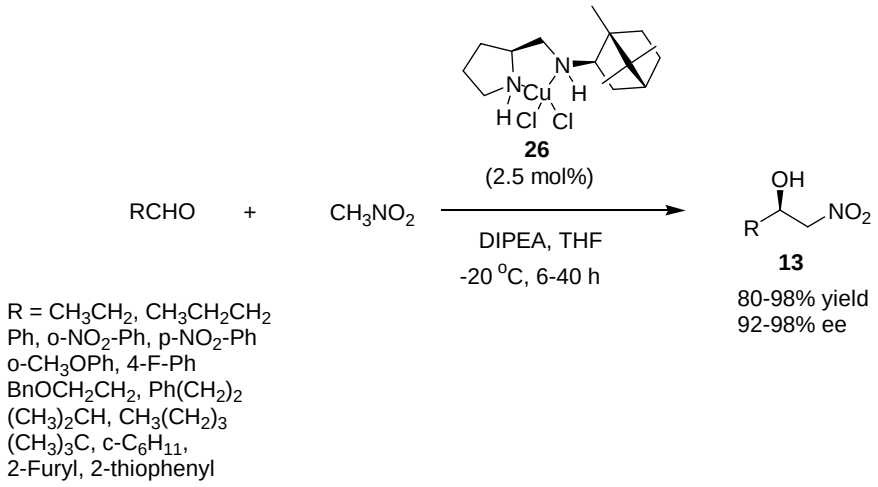
The nitroaldol reaction between different nitroalkanes and aldehydes by a Cu(II) complex **23** obtained using a chiral aminopyridine ligand gives the β-nitro compounds **24**, **25** with 80-98% ee and 49-96% ee (Scheme **7**).[14a, b]

Scheme 7



Very recently, a new chiral Cu(II)–diamine complex **26** has been reported to be an efficient catalyst in the nitroaldol reaction giving the products **13** in 80-98% yield and 92-98% ee (Scheme **8**).[15]

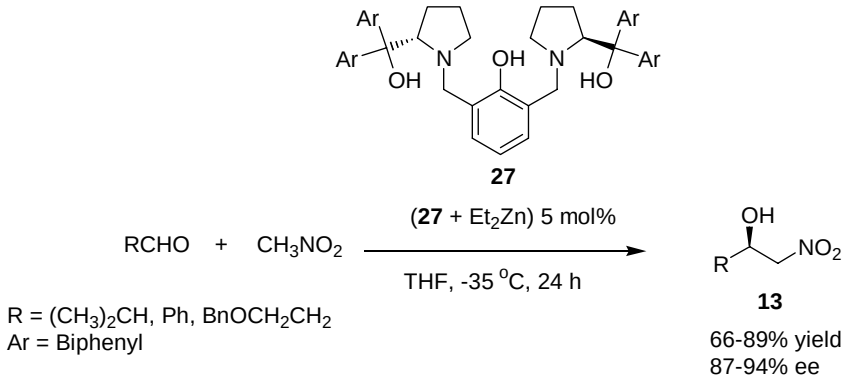
Scheme 8



2.1.3 Zinc complex mediated nitro aldol reactions

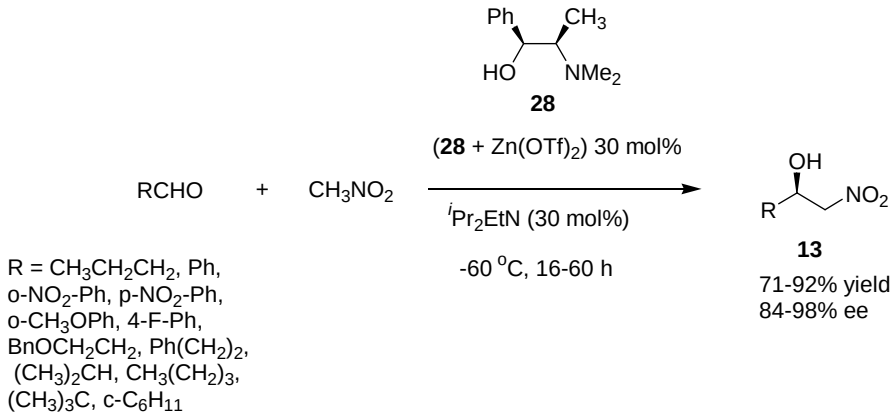
A nitroaldol reaction catalysed by the Trost ligand **27** and Et_2Zn (5 mol%) gives the products **13** in 66-89% yield and 87-94% ee (Scheme **9**).[16]

Scheme 9



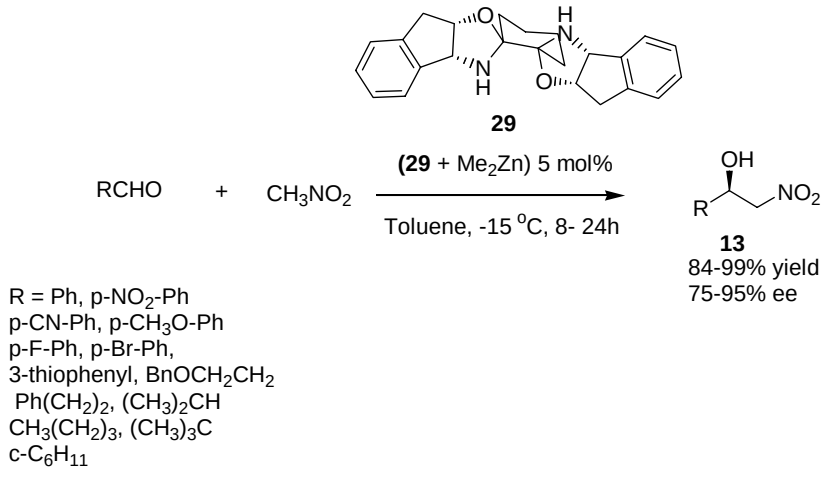
A practical catalyst system that combines Zn(II) triflate salt, a chiral amino alcohol **28** and a base has been reported to give nitroaldol products **13** with 94-98% ee (Scheme **10**).[17]

Scheme 10



An effective catalyst consisting of a zinc complex of the C_2-symmetric bisoxazolidine **29** gives products **13** with 84-99% yield and 75-95% ee (Scheme **11**).[18]

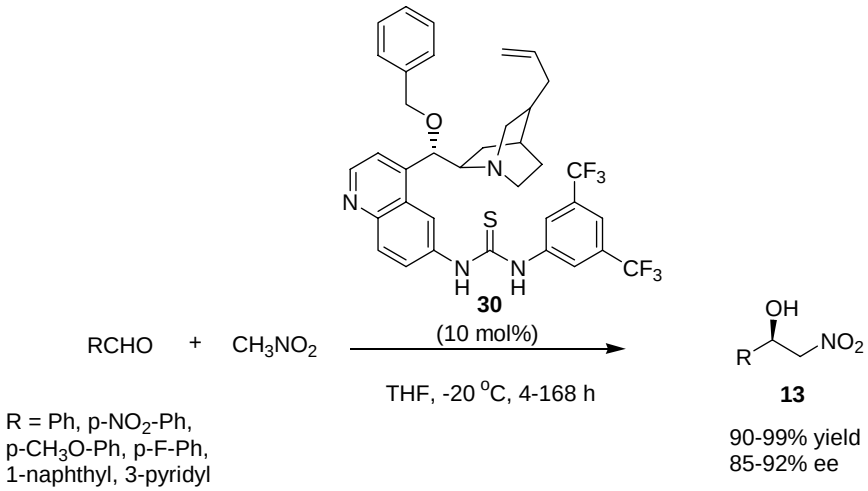
Scheme 11



2.1.4 Nitro aldol reaction catalysed by organo catalysts

The catalyst **30** containing cinchona alkaloid moiety was found to be an efficient system for the nitroaldol reaction of nitromethane and various aromatic aldehydes providing the products **13** in 90-99% yield and 85-92% ee (Scheme **12**).[19]

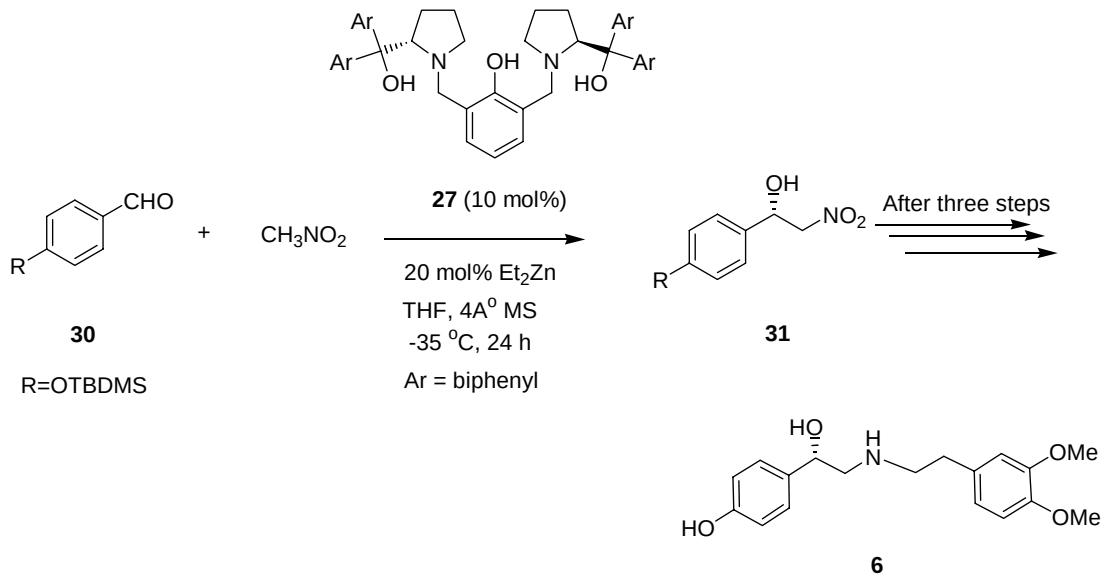
Scheme 12



2.1.5 Synthesis of some representative bioactive molecules *via* nitroaldol reaction

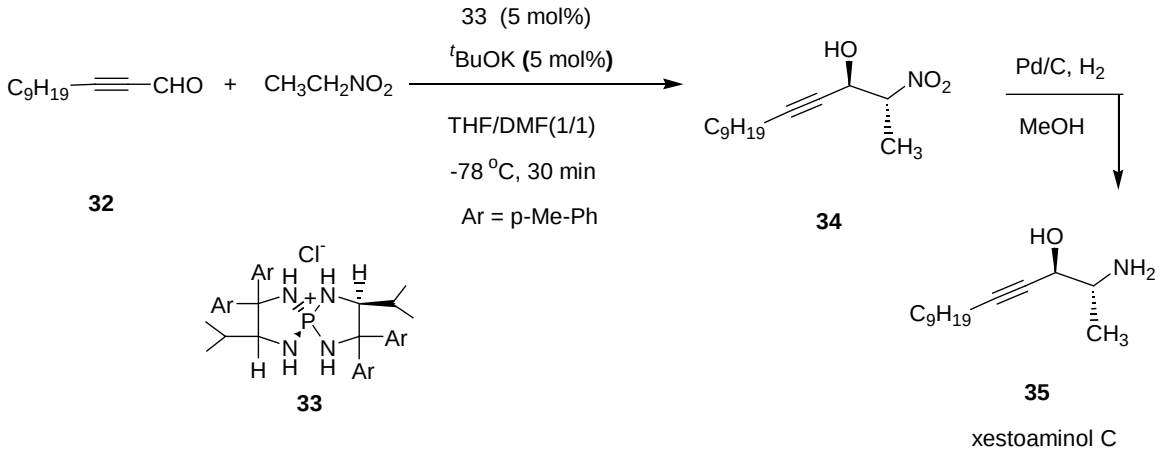
Synthesis of several bioactive molecules and natural products have been achieved *via* nitroaldol reaction in crucial steps. For example, asymmetric nitroaldol reaction between aldehyde **30** and nitromethane in the presense of **27** directly gives the β-nitro alcohol **31**. This intermediate has been utilized in the synthesis of the denopamine **6** (Scheme **13**).[16]

Scheme 13



The nitroaldol reaction sequence is also useful for the synthesis of xestoaminol C **35** using alkynal **32** and niroethane in the presence of the phosphonium salt **33** as shown in Scheme **14**.[20]

Scheme 14

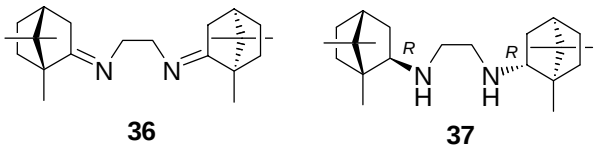


We have examined the use of diamines **36** and **37** readily accessible using the methods described in Chapter **1** for the reaction of nitromethane with various aldehydes. The results are discussed in the next section.

2.2 Results and Discussion

2.2.1 Chiral diamine containing camphanyl moiety for use in asymmetric nitroaldol reaction

The chiral ligands play a central role in the development of efficient metal complexes catalyzed asymmetric reactions. We have chosen the chiral ligands **36** and **37** readily accessible by methods developed in Chapter **1** for use in the development of a new catalyst system for asymmetric Henry reaction (Fig.**2**).



36 **37**

Figure 2

2.2.2 Selection of metal complex partners

Initially, we have examined the asymmetric nitroaldol reaction using the compounds **36** and **37**. The compound **35** did not react with nitromethane and 4-nitrobenzaldehyde even after 24 h. The reaction was also carried out using the more basic amine **36,** but again there was no reaction. Clearly, the basicity of chiral ligands **36** and **37** are not enough to generate the nitronate species *in situ* for reaction with aldehydes. It is well-known that metal acetate promote the nitroaldol reactions with or without using an external base.[11, 12, 14] Accordingly, it was thought that a metal acetate complexed with diamine ligands **36** and **37** would help in

the development of the asymmetric version of this reaction. Therefore, we have examined the nitroaldol reaction using the ligand **36** with different readily accesible acetates like $Cu(OAc)_2.H_2O$, $Zn(OAc)_2.2H_2O$, $Ni(OAc)_2.4H_2O$, $Mn(OAc)_2.H_2O$. In all these cases, the reaction with nitromethane and 4-nitrobenzaldehyde afforded the nitroaldol products. Among the metal acetates examined, copper(II) acetate mediated transformation gave the product in 90% yield with 36% ee (Scheme **15**). The other metal acetates gave only the racemic products (Table **1**).

Scheme 15

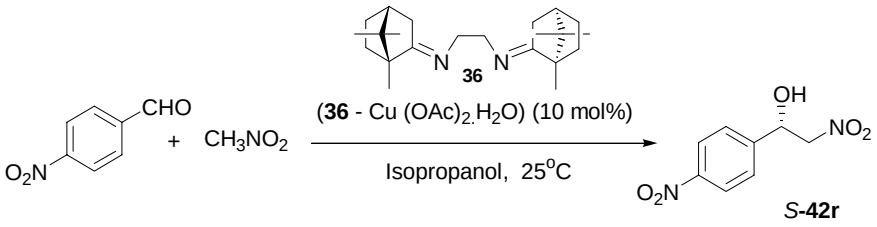


Table 1 Enantioselective Henry reaction of nitromethane with 4-nitrobenzaldehyde using different metal complexes with compound **36**.[a]

S.No	Metal acetate	Time (h)	Yield (%)[b]	Ee (%)[c]
1	$Zn(OAc)_2.2H_2O$	2.5	80	0
2	$Ni(OAc)_2.4H_2O$	5.0	83	0
3	$Mn(OAc)_2.2H_2O$	3.0	78	0
4	$Cu(OAc)_2.H_2O$	2.0	90	36

[a]In this reaction, ligand **36** (0.12 mmol) and metal acetate (0.10 mmol) were stirred for 3 h in isopropanol (1 mL) for complex formation. All the reactions were carried out using 4-nitrobenzaldehyde (1.0 mmol), isopropanol (1 mL) and nitromethane (10 mmol) at 25 °C. [b]isolated yield of product **42 r**. [c]Determined by HPLC analysis (Chiralcel OD-H) using hexane and isopropanol as eluent.

The diimine **36**-copper complex may be formed under the reaction condition. As outlined in the introductory section, some chiral oxazoline–Cu(II) complexes in nitroaldol reaction giving nitroalcohol products with up to 99% ee (Scheme **4**).[11] Unfortunately, the diimine **36**-$Cu(OAc)_2.H_2O$ gave the product in 90% yield but only with 36% ee.

We have then examined the use of the amine **37**, which is expected to be more basic and hence is expected to bind stronger with metal acetates. A series of divalent metal acetates and triflates in combination with the chiral bidentate ligand **37** were screened as catalysts for the nitroaldol reaction between nitromethane and 4-nitrobenzaldehyde in isopropanol solvent. The results are summarized in Table **2**. The nitro alcohol was obtained in 90% yield with 50% ee using the $Cu(OAc)_2.H_2O$ (Entry **4**, Table **2**). Some other metal acetates are capable of producing good chemical yields but the asymmetric inductions were poor (Table **2**). Accordingly, we have further examined the reactions of the copper complex prepared from ligand **37** and $Cu(OAc)_2.H_2O$.

Scheme 16

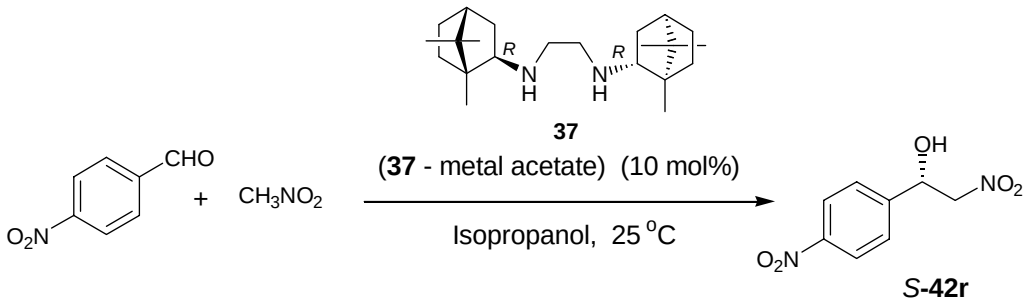


Table 2 Enantioselective Henry reaction of nitromethane with 4-nitrobenzaldehyde using different metal complexes of ligand **37** prepared *in situ* in isopropanol.[a]

S.No	Metal acetate	Time (h)	Product	Yield (%)[b]	Ee (%)[c]
1	$Zn(OAc)_2.2H_2O$	0.75	**42r**	70	2
2	$Ni(OAc)_2.4H_2O$	0.50	**42r**	85	5
3	$Mn(OAc)_2.2H_2O$	0.50	**42r**	75	0
4	$Cu(OAc)_2.H_2O$	0.50	**42r**	90	50
5	$Cu(OTf)_2$	13	**42r**	80	6

[a]In this reaction, ligand **37** (0.12 mmol) and metal acetate (0.10 mmol) were stirred for 3 h in isopropanol (1 mL) for complex formation. All the reactions were carried out using 4-nitrobenzaldehyde (1.0 mmol), isopropanol (1 mL) and nitromethane (10 mmol) at 25 ^{o}C. [b]Isolated yield of product **42r**. [c]Determined by HPLC analysis (Chiralcel OD-H) using hexane and isopropanol as eluent

2.2.3 Effect of solvents on the nitroaldol reaction

We have then examined the effect of different solvents on the nitroaldol reaction (Table **3**). Initially, the reaction was caried out in the aprotic solvent DCM. The nitro alcohol was obtained in 53% yield with 60% ee. We have found that the amine **38** and copper acetate forms the copper complex **38** in DCM solvent, which was easily isolated as a good crystaline compound with molecular formula $C_{26}H_{48}CuN_2O_5$. This complex **38** has been characterized by single crystal X-ray analysis (Fig.**3**).

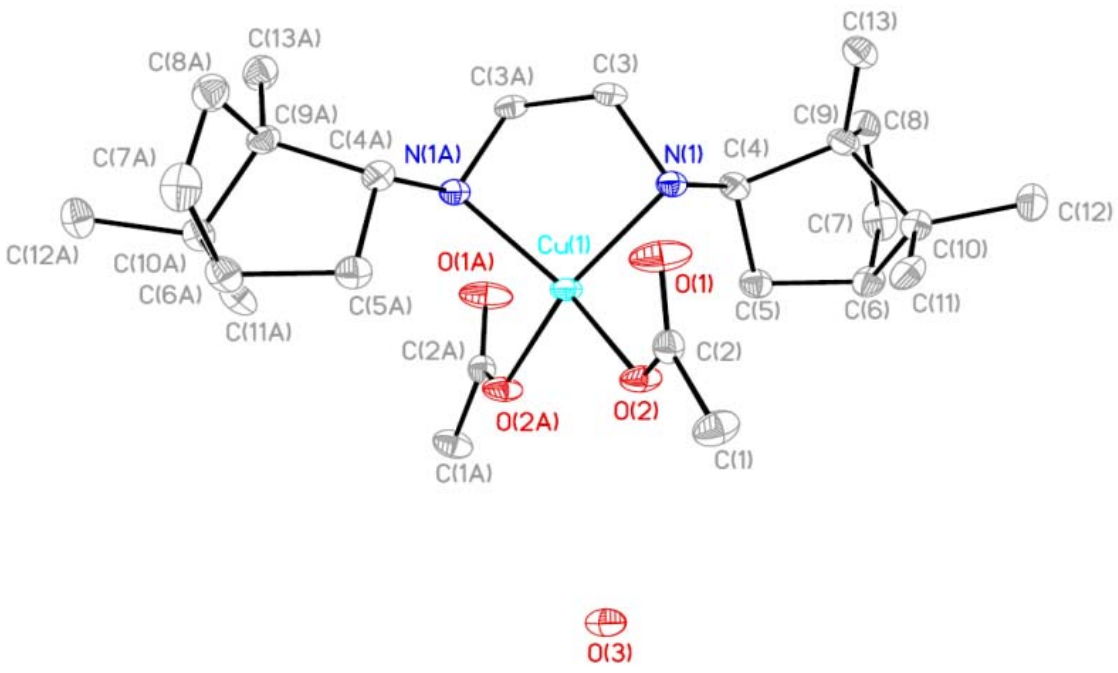
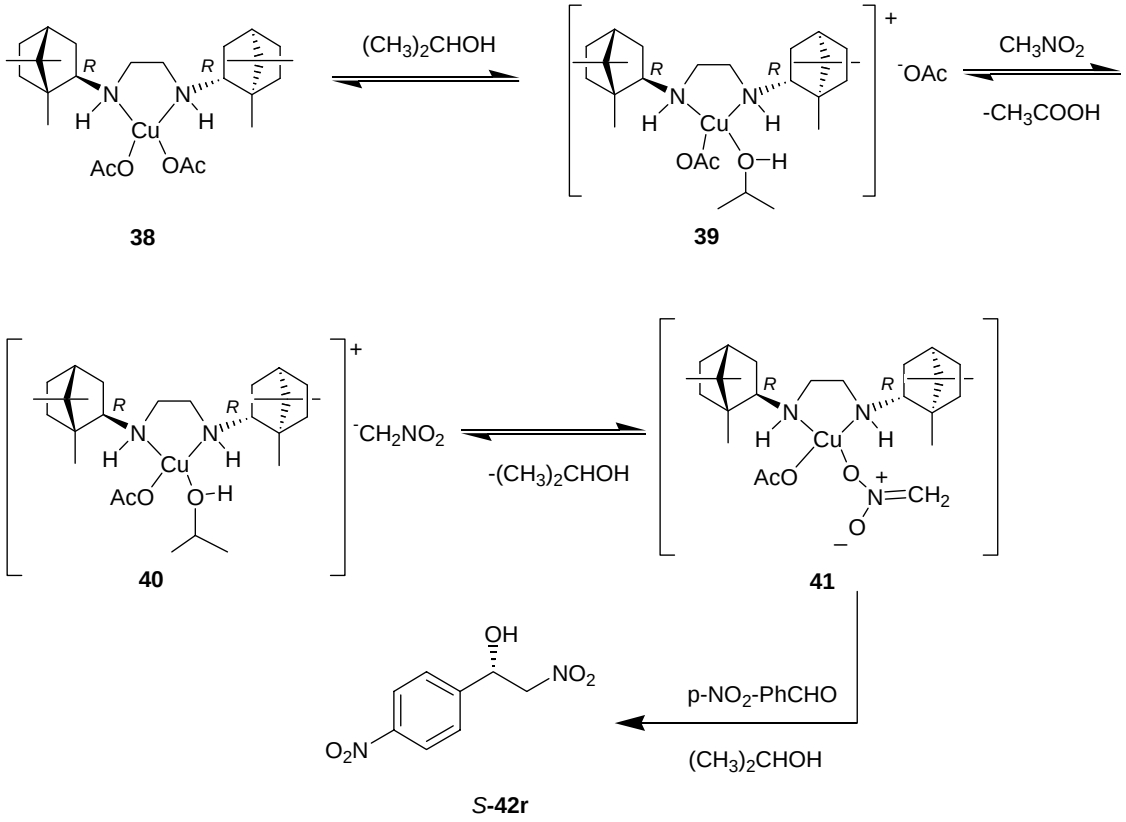


Figure 3. ORTEP representation of the *N, N′*-bis(isobornyl)ethylenediamine-Cu(OAc)$_2$.H$_2$O complex **38** (All the H-atoms were removed for clarity and thermal elipsoids were drawn with 25% probability).

When the copper complex was prepared in DCM (1 mL) and the nitroaldol reaction was carried out after the addition of isopropanol (1 mL) to the reaction mixture, the enantiomeric excess obtained was the same (60% ee). When the copper complex **38** was prepared in DCM and the isopropanol was added after removal of DCM, the product was obtained in 95% yield with 74% ee (Table **3**, entry **4**). Presumbly, the alcoholic solvents form weak coordination complex like **39** upon reaction with the complex **38** (Scheme **17**) resulting in better reactivity and enantioselectivities in alcoholic solvents compared to aprotic solvents (Table **3**).

Scheme 17



Scheme 18

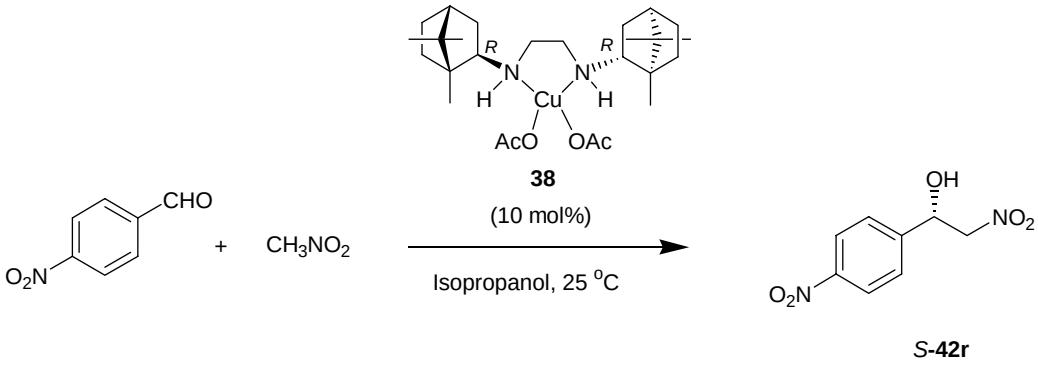


Table 3. Effect of solvent on the enantioselective Henry reaction between nitromethane and 4-nitrobenzaldehyde using complex **38**.[a]

Entry	Solvent	Time/h	Product	Yield[b](%)	Ee (%)[c]
1	MeOH	0.50	**42r**	90	62
2	EtOH	0.50	**42r**	88	60
3	n-PrOH	0.50	**42r**	92	68
4	^{i}PrOH	0.50	**42r**	95	74
5	^{t}BuOH	0.50	**42r**	90	30
6	CH_2Cl_2	20	**42r**	53	60
7	MeCN	12	**42r**	70	20
8	Toluene	24	**42r**	50	60
9	CH_2Cl_2 + ^{i}PrOH	1	**42r**	85	60
10	THF	12	**42r**	80	54

[a]The compound **38 (**0.12 mmol) and $Cu(OAc)_2.H_2O$ (0.10 mmol) in CH_2Cl_2 were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using 4-nitrobenzaldehyde (1 mmol), isopropanol (1 mL) and nitromethane (10.0 mmol) at 25^{o} C. [b]Isolated yield of product **42r**. [c]Determined by HPLC analysis (Chiralcel OD-H) using hexane and isopropanol as eluent.

Interestingly, the enantioselectivity increased in the order MeOH < EtOH < ^{n}PrOH < ^{i}PrOH, but in the case of ^{t}BuOH the ee decreased. Probably, the low enantioselectivity in the case of ^{t}BuOH may be due to steric hindrance of bulky tertiary butyl group, which may hinder the reaction of the metal complex with the aldehyde leading to non catalysed reaction to more extent, resulting in low enantioselectivity (Table **3**).

2.2.4 Optimization of catalyst loading

A series of experiments were carried out to assess the catalyst loading for optimum results. We found that 10 mol% of the catalyst is sufficient to provide the nitroalcohol product in 95% yield with 74% ee (Table **4**, entry **3**). The reaction can be performed with lower catalyst loading 1-5 mol% of complex **48** (Entry **1**-**3**, Table **4**), but the product is obtained only in 60-70% yield with 72-74% ee under these conditions. When the catalyst loading increased to 15-30 mol%, the reaction is completed in 0.5 h with 91-93% yield but only with 30-58% ee (Entry **4**-**6**, Table **4**). This observation indicates that increase in catalyst loading decreases the enantioselectivity of the nitroaldol reaction. Presumbly, at higher catalyst loading, more amount of acetate ion may be present in the reaction medium leading to formation of uncoordinated nitronate to more extent, resulting in the formation of racemic nitroaldol to more extent. Also, less reactive dimeric copper complexes which could have formed at higher catalyst loading would lead to less enantioselectivity. We have observed that 10 equiv. of nitromethane is required to complete the reaction smoothly in 0.5 h to 2 h.

Table 4. Different quantities of $Cu(OAc)_2.H_2O$ and the diamine **37**[a]

Entry	**37** (mmol)	$Cu(OAc)_2.H_2O$	mol%	Time/h	Yield (%)[b]	Ee (%)[c]
1	0.012	0.010	1	2	60	72
2	0.052	0.050	5	0.75	70	72
3	0.12	0.10	10	0.50	95	74
4	0.17	0.15	15	0.50	92	58
5	0.22	0.20	20	0.50	91	40
6	0.30	0.30	30	0.50	93	30

[a]Diamine **37** and $Cu(OAc)_2.H_2O$ were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using 4-nitrobenzaldehyde (1 mmol), in isopropanol (1 mL) and nitromethane (10 mmol) at 25 °C. [b]isolated yield of **42r**. [c]Determined by HPLC analysis (Chiralcel OD-H) using hexane and isopropanol as eluent.

2.2.5 Structural effects of various aldehydes

In order to examine the scope of this transformation, we have carried out experiments using several substrates (Table **5**). A variety of aldehydes provided nitroaldol products with enantiomeric excesses in the range of 64-90% at 25 ^{o}C (Table **4**). Aliphatic aldehydes were smoothly converted to nitroaldols in good yields with high enantioselectivity (86-88% ee). Most of the aromatic aldehydes gave the corresponding nitroaldols in 80-90% ee. Some aromatic aldehydes, especially those containing electron with drawing substituents gave the nitroaldols in the range 64-78% ee. The heteroaromatic aldehyde (entry **15**, Table **4**) also gave enantioselectivity with up to 88% ee. In some cases, along with the expected nitroaldol product, small amount (5-10%) of the corresponding eliminaton product was also obtained (entry **19**, Table **4**). It may be of interest to note that the nitroaldol product **42s** was obtained in 72% yield with 80% ee is a precursor in the synthesis of the biologically active (*S*)-Norphenylephrine (entry **19**, Table **4**).[21]

Scheme 19

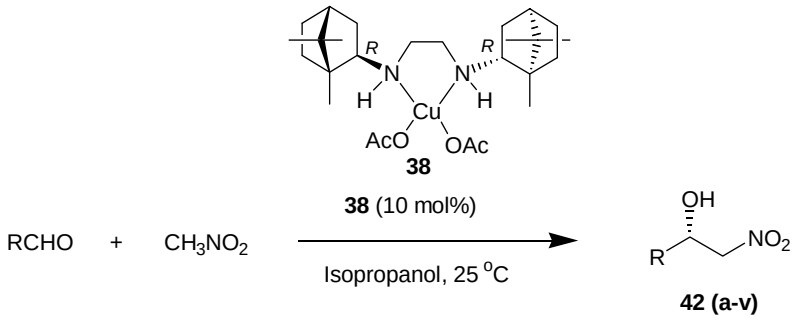


Table 5. Enantioselective Henry reaction of various aldehydes with nitromethane catalyzed by the complex **38.**[a]

Entry	Substrate	Time/h	Product(**42**)	Yield (%)[b]	Ee (%)[c]
1	Ph-	11	**42a**	70	84(*S*)
2	o-MeO-C_6H_4	13	**42b**	75	90(*S*)
3	m-MeO-C_6H_4	12	**42c**	80	88(*S*)
4	m-Me-C_6H_4	12	**42d**	85	88(*S*)
5	p-Me-C_6H_4	24	**42e**	60	78(*S*)
6	o-Cl-C_6H_4	7	**42f**	70	86(*S*)
7	m-Cl-C_6H_4	15	**42g**	75	78
8	p-Cl-C_6H_4	24	**42h**	60	68(*S*)
9	o-Br-C_6H_4	15	**42i**	75	70
10	m-Br-C_6H_4	12	**42j**	78	64
11	p-Br-C_6H_4	16	**42k**	70	86(*S*)
12	p-F-C_6H_4	4	**42l**	80	82(*S*)
13	1-naphthyl	12	**42m**	72	72(*S*)
14	2-naphthyl	12	**42n**	70	82(*S*)
15	2-furfuryl	13	**42o**	81	88(*S*)
16	o-NO_2-C_6H_4	0.5	**42p**	83	84(*S*)
17	m-NO_2-C_6H_4	0.5	**42q**	85	78(*S*)
18	p-NO_2-C_6H_4	0.5	**42r**	95	74(*S*)
19	m-OH-C_6H_4	15	**42s**	72	80
20	Cyclohexyl	7	**42t**	90	88(*S*)
21	Isopropyl	8	**42u**	90	86(*S*)
22	Isobutyl	10	**42v**	90	88(*S*)

[a]The ligand **37** (0.12 mmol) and $Cu(OAc)_2.H_2O$ (0.10 mmol) in CH_2Cl_2 were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using the aldehydes (1 mmol), isopropanol (1 mL) and nitromethane (10 mmol) at 25 ^oC. [b]Isolated yield of products **42 (a-v)** [c]Determined by HPLC analysis (Chiralcel OD-H, AD-H, OJ-H) using hexane and isopropanol as eluent

2.2.6 Mechanism of the Cu(II) catalysed nitroaldol reaction

The nitroaldol reaction may be rationalised by the mechanistic pathway and intermediates outlined in Figure **4**. The reaction would probably involve copper complex mediated dual activation of the nitronate and the aldehyde substrates.

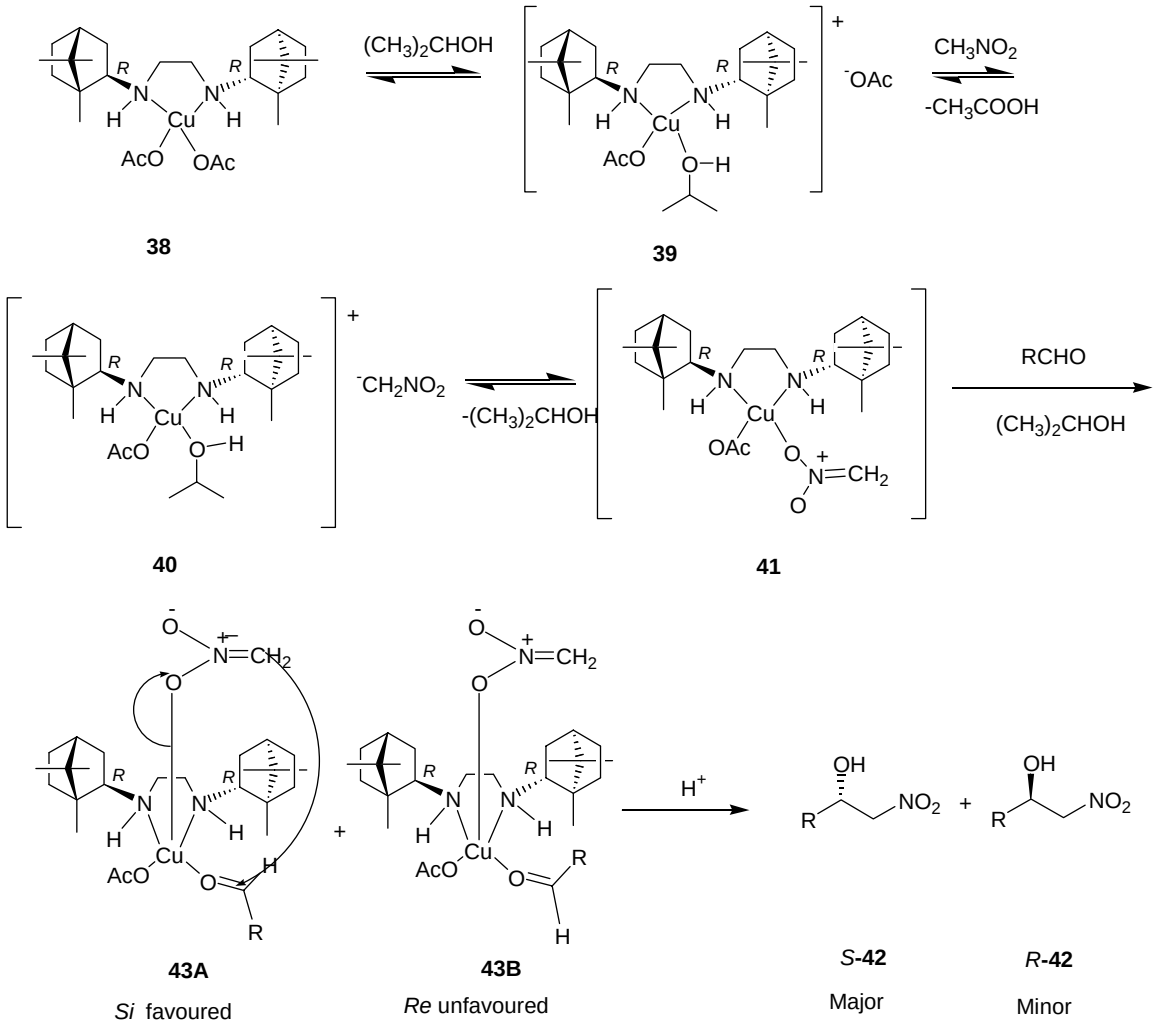


Figure 4

In this mechanism, the alcoholic solvents could initially form weak coordination complex like **39** displacing the acetate ion from complex **38**. Subsequently, the displaced

acetate ion reacts with nitromethane to give the nitronate species which coordinate with Cu(II) in the chiral complex **41** displacing the alcohol. Coordination of the aldehydes with this complex followed by intarmolecular C-C bond formation from the *Si* face of the aldehyde **43A** would lead to *S* nitroaldol **42** as the major product (Figure **4**). Presumbly, the *Re* face C-C bond formation is not favoured due to unfavourable non-bonding interactions between the aromatic group or longer chain of the corresponding aldehyde with chiral camphor moiety of the C_2-symmetric *N, N′*-bis(isobornyl)ethylenediamine ligand **37**.

The present nitroaldol synthesis using the ligand **37**-Cu(II) complex **38** has some advantages. In this method, use of external base is not required and the reaction is completed in shorter time. Moreover, the reaction is performed without the need for dry conditions or inert atmosphere. Also, the ligand **37** can be easily accessed using simple bench top chemicals starting from D-(+)-camphor. Therefore, the method described here has considerable potential for further synthetic exploitation.

2.3 Conclusions

In summary, the readily accessible C_2-symmetrical *N, N′*- bis(isobornyl) ethylenediamine ligand **46** and $Cu(OAc)_2.H_2O$ is usefull for the preparation of the chiral copper complex **47** in CH_2Cl_2. The complex **47** prepared in this way is useful for the asymmetric nitroaldol reaction between nitromethane and aldehydes in isopropanol at 25 ^oC. The nitroaldol adducts **48 (a-v)** have ben obtained in good yields (60-95%) with high enantioselectivities (64-90% ee). In addition, the present procedure for the Henry reaction has several advantages including air-tolerance, relatively short reaction time and high stereochemical control with a wide range of substrates. The β-hydroxy nitroalkanols derivatives are useful intermediates in the synthesis of β-receptor agonists (-)-denopamine and (-) arbutamine,[16] the β-blockers (*S*)-metoprolol, (*S*)-propanolol and (*S*)-pindolol.[5] Therefore, the results described here have significant potential for further synthetic exploitation.

2.4 Experimental Section

General Information

The informations given in the experimental section **1.4** are also applicable for the experiments outlined in this section. Nitromethane was purchased from Merck chemicals (P) Ltd., india. The $Cu(OAc)_2.H_20$ was purchased from Loba chemie (P) Ltd, India.

2.4.1 General procedure for the preparation of copper complex 38

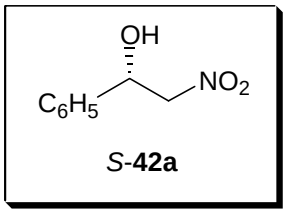
To a oven-dried 25 mL round-bottomed flask, a solution of ligand **37** (0.696 g, 2.1 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.360 g, 2.0 mmol) in the CH_2Cl_2 (10 mL) was added and stirred for 6 h at 25 ^oC. The resulting blue solution in CH_2Cl_2 was left untill most of the DCM solvent evaporated. The crystals obtained were suitable for single cryatal X-ray structural analysis

2.4.2 General procedure for the enantioselective Henry reaction

To a oven-dried 10 mL round-bottomed flask, the complex **38** (0.050 g, 10 mol%)**,** isopropanol (1 mL) and nitromethane (0.510 g, 10 mmol) were added and stirred for 30 min. The aldehyde (1 mmol) was added and the reaction mixture was stirred at 25 ^oC until the reaction was complete (disappearance of aldehyde by TLC). After evaporation of the solvent, the residue was purified by column chromatography on silica gel 100-200 using hexane and ethyl acetate to isolate the nitroaldol product **42(a-v)**.

(*S*)-2-Nitro-1-phenylethanol 42a

Yield **:** 0.12 g (70%)



$[\alpha]_D^{25}$ **:** +32.6 (*c* 0.42, CH_2Cl_2, 84% *ee*), $[[\alpha]_D^{25}$ = +36.8 (*c* 4.04, CH_2Cl_2, 95% *ee* (*S*))]^{23}

IR (neat) **:** (cm^{-1}) 3435, 3032, 2920, 1552, 1379, 1066

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.36-7.42 (m, 5H) 5.42-5.44 (d, *J* = 8.0 Hz, 1H), 4.47-4.62 (m, 2H), 3.08 (s, 1H).

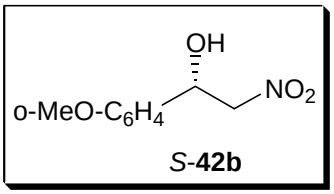
^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 138.1, 129.1, 128.9, 125.9, 81.2, 71.

Enantiomeric purity 84% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254 nm, retention times 11.9 min. (*R*) and 14.1 min. (*S*)].

The above procedure was followed for the conversion of other aldehydes in 1mmol scale to corresponding nitroaldol products **42 (b-v**).

(*S*)-2-Nitro-1-(2-methoxyphenyl)ethanol 42b

Yield : 0.15 g (75%)



$[\alpha]_D^{25}$: +35.50 (*c* 0.40, CH_2Cl_2, 90% *ee*), [lit. $[\alpha]_D^{25}$ = +33.2 (*c* 7.06, CH_2Cl_2, 85% *ee*(*S*))][23]

IR (neat) : (cm^{-1}) 3543, 3011, 2943, 2841, 1554, 1379, 1072

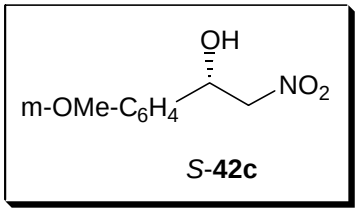
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.43-7.45 (d, *J* = 8.0 Hz,1H), 7.31-7.35 (t, *J* = 16.0 Hz, 1H), 6.99-7.03 (t, *J* =16.0 Hz, 1H), 6.90-6.92 (d, *J* = 8.0 Hz, 1H), 5.61-5.65 (m, 1H), 3.88 (s, 3H), 4.54-4.67 (m, 2H),3.13-3.15 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 156.0,129.8, 127.2, 125.9 121.1, 110.5, 79.8, 67.8, 55.4.

Enantiomeric purity 90% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254 nm, retention times 14.3 min. (*R*) and 16.6 min. (*S*)].

(*S*)-2-Nitro-1-(3-methoxyphenyl)ethanol 43c

Yield **:** 0.16 g (80%)



$[\alpha]_D^{25}$ **:** +30.80 (*c* 0.44, CH_2Cl_2, 88% *ee*), [lit. $[\alpha]_D^{25}$ = -33.2 (*c* 0.27, CH_2Cl_2, 95% *ee* (*R*))][17]

IR (neat) **:** (cm^{-1}) 3483, 3011, 2943, 2839, 1556, 1157, 1039

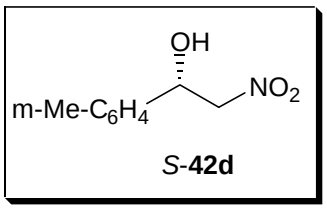
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.25-7.33 (m, 2H) 6.88-6.97 (m, 2H), 4.49-4.63 (m, 2H), 5.46 (s, 1H), 3.38-3.84 (d, *J* = 8.0 HZ, 3H), 2.79 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm), 160.0, 139.8, 130.1, 118.0, 114.3, 81.2, 70.9, 55.3

Enantiomeric purity 88% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/90:10; flow rate 1.0 mL/min., 254 nm, retention times 21.6 min. (*R*) and 29.2 min. (*S*)].

(*S*)-2-Nitro-1-(3-methylphenyl)ethanol 42d

Yield **:** 0.15 g (85%)



$[\alpha]_D^{25}$ **:** +31.1 (*c* 0.46, CH_2Cl_2, 88% *ee*), [lit. $[\alpha]_D^{25}$ = +31.8 (*c* 5.82, CH_2Cl_2, 91% *ee*(*S*))][22]

IR (neat) **:** (cm^{-1}) 3531, 3109, 2972, 1633, 1556, 1340, 1089

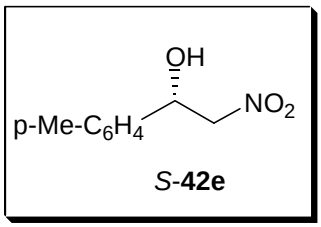
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.16-7.31 (m, 4H) 5.42-5.45 (t, *J* = 12.0 Hz, 1H), 4.49-4.64 (m, 2H), 2.74-2.75 (d, *J* = 4.0 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 138.6, 138.1, 129.6, 128.9, 126.6, 123.0,81.2, 71.0, 21.3.

Enantiomeric purity 88% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254 nm, retention times 10.3 min. (*R*) and 11.7 min. (*S*)].

(*S*)-2-Nitro-1-(4-methylphenyl)ethanol 42e

Yield **:** 0.12 g (60%)



$[\alpha]_D^{25}$ **:** +12.90(*c* 0.50, EtOH, 78% *ee*), [lit. $[\alpha]_D^{25}$ = +15.2 (*c* 3.62, EtOH, 90% *ee* (*S*))][22]

IR (neat) **:** (cm^{-1}) 3537, 2922, 1614, 1554, 1379, 1078

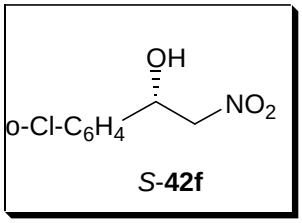
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.27-7.29 (d, *J* = 8.0 Hz, 2H), 7.20-7.22 (d, *J* = 8.0 Hz, 2H) 5.41-5.43 (d, *J* = 8.0 Hz, 1H), 4.47-4.63 (m, 2H), 2.36 (s, 3H), 2.84(s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm,) 138.9, 135.1, 129.6, 125.8, 81.2, 70.9, 21.1.

Enantiomeric purity 78% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254 nm, retention times 11.9 min. (*R*) and 14.4 min. (*S*)].

(*S*)-2-Nitro-1-(2-chlorophenyl)ethanol 42f

Yield **:** 0.14 g (70%)



$[\alpha]_D^{25}$ **:** +50.10 (*c* 0.40, CH_2Cl_2, 86% *ee*), [lit. $[\alpha]_D^{23}$ = -52.7 (*c* 1.21, CH_2Cl_2, 91% *ee* (*R*))[11]

IR (neat) **:** (cm^{-1}) 3530, 2924, 1556, 1379, 1087.

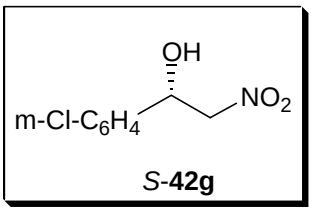
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.65-7.66 (d, *J* = 4.0 Hz, 1H) 7.28-7.39 (m, 3H), 5.82-5.85 (d, *J* = 12.0 Hz, 1H), 3.10 (s, 1H), 4.42-4.68 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 135.5, 131.4, 129.9, 129.7, 127.6, 127.5, 79.3, 67.8.

Enantiomeric purity 86% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/98:2; flow rate 1.0 mL/min., 254 nm, retention times 27.8 min. (*R*) and 29.7 min. (*S*)].

(*S*)-2-Nitro-1-(3-chlorophenyl)ethanol 42g

Yield **:** 0.15 g (75%)



$[\alpha]_D^{25}$ **:** +16.3 (*c* 0.34, $CHCl_3$, 78% *ee*)

IR (neat) **:** (cm^{-1}) 3450, 3069, 2922, 1556, 1379, 1076

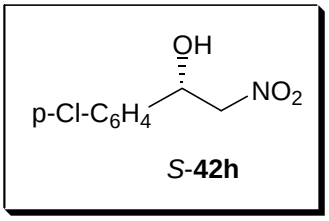
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm)7.27-7.43 (m, 4H) ,5.44-5.46 (d, *J* = 8.0 Hz, 1H), 4.49-4.61 (m, 2H), 3.0-3.0 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm), 140.0,135.0, 130.3, 129.1, 126.2, 124.0, 80.9, 70.2.

Enantiomeric purity 78% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times 12.9 min. (*R*) and 16.0 min. (*S*)].

(*S*)-2-Nitro-1-(4-chlorophenyl)ethanol 42h

Yield **:** 0.12 g (60%)



$[\alpha]_D^{25}$ **:** +27.6(*c* 0.42, CH_2Cl_2, 68% *ee*), [lit. $[\alpha]_D^{25}$ = +36.7 (*c* 4.42, CH_2Cl_2, 91% *ee*(*S*))][22]

IR (neat) **:** (cm^{-1}) 3543, 2922, 1552, 1379, 1089.

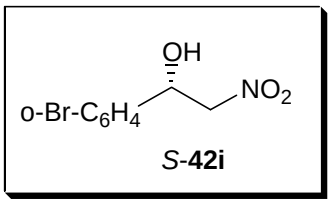
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.34-7.43 (m, 4H), 5.44- 5.46 (d, *J* = 8.0 Hz, 1H), 4.47-4.60 (m, 2H), 2.96 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δ ppm) 136.6, 134.9, 129.3, 127.4, 81.0, 70.3.

Enantiomeric purity 68% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254 nm, retention times 11.5 min. (*R*) and 13.9 min. (*S*)].

(*S*)-2-Nitro-1-(2-bromophenyl)ethanol 42i

Yield : 0.18 g (75%)



$[\alpha]_D^{25}$: +23.6 (*c* 0.72, $CHCl_3$, 70% *ee*)

IR (neat) : (cm^{-1}) 3520, 2922, 1554, 1377, 1084

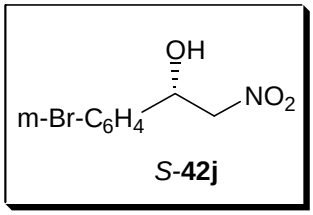
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.64-7.66 (d, *J* = 8.0 Hz, 1H), 7.55-7.57 (d, *J* = 8.0 Hz, 1H), 7.38-7.45 (m, 1H), 7.21-7.25 (m, 2H), 5.78-5.81 (m, 1H), 4.40-4.70 (m, 2H), 3.12-3.13 (d, *J* = 4.0 Hz, 1H), 3.10 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm),137.1,133.0, 130.2, 128.2, 127.8, 121.4, 79.370.8.

Enantiomeric purity 70% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/97:3; flow rate 1.0 mL/min., 254 nm, retention times 24.0 min. (*R*) and 26.0 min. (*S*)].

(*S*)-2-Nitro-1-(3-bromophenyl)ethanol 42j

Yield **:** 0.19 g (78%)



$[\alpha]_D^{25}$ **:** +15.2 (*c* 0.46, $CHCl_3$, 64 % *ee*).

IR (neat) **:** (cm^{-1}) 3443, 3065, 2922, 1556, 1379, 1072

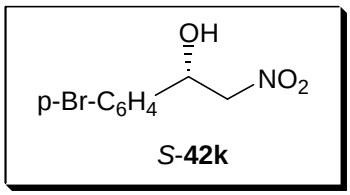
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.27- 7.60 (m, 4H) 5.45 (s, 1H), 4.50-4.62 (m, 2H), 2.97 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.2, 132.0, 130.6, 129.1, 124.5, 123.1, 80.9, 70.2.

Enantiomeric purity 64% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/90:10; flow rate 1.0 mL/min., 254 nm, retention times 15.7 min. (*R*) and 20.6 min. (*S*)].

(*S*)-2-Nitro-1-(4-bromophenyl)ethanol 42k

Yield : 0.17 g (70%)



$[\alpha]_D^{25}$: +66.5 (*c* 0.50, $CHCl_3$, 86 % *ee*), [lit. $[\alpha]_D^{23}$ = -68.6 (*c* 1.40, $CHCl_3$, 89% *ee*(*R*))][23]

IR (neat) : (cm^{-1}) 3431, 2926, 1552, 1381, 1072

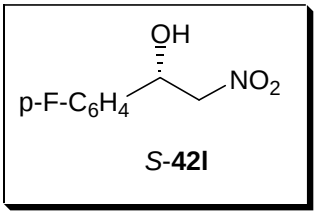
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.50-7.54 (m, 2H), 7.24-7.29 (m, 2H), 5.41-5.44 (m, 1H), 4.45-4.60 (m, 2H), 2.95 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 137.0,132.1, 127.6, 122.9, 80.9, 70.3.

Enantiomeric purity 86% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times 13.8 min. (*R*) and 17.4 min. (*S*)].

(*S*)-2-Nitro-1-(4-fluorophenyl)ethanol 42l

Yield **:** 0.15 g (80%)



S-**42l**

$[\alpha]_D^{25}$ **:** +31.0 (*c* 0.56, EtOH, 82% *ee*), [lit. $[\alpha]_D^{25}$ = +34.0 (*c* 6.74, CH_2Cl_2, 91% *ee* (*S*))][22]

IR (KBr) **:** (cm^{-1}) 3431, 2924, 1556, 1379, 1224

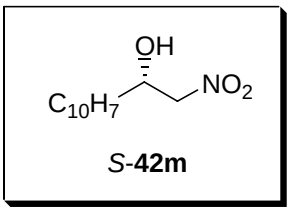
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.36-7.40 (m, 2H), 7.06-7.15 (m, 2H), 5.42-5.45 (m, 1H), 4.46-4.60 (m, 2H), 3.08 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 164.1, 161.6, 127.8, 116.1, 81.1, 70.3.

Enantiomeric purity 82% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/90:10; flow rate 0.8 mL/min., 215 nm, retention times 14.5 min. (*R*) and 16.9 min. (*S*)].

(*S*)-2-Nitro-1-(1-naphthyl)ethanol 42m

Yield : 0.16 g (72%)



S-**42m**

$[\alpha]_D^{25}$: +13.8 (*c* 0.42, CH_2Cl_2, 72% *ee*), [lit. $[\alpha]_D^{25}$ = +17.67 (*c* 2.41, CH_2Cl_2, 93% *ee* (*S*))][23]

IR (KBr) : (cm^{-1}) 3431, 2924, 1556, 1379, 1224

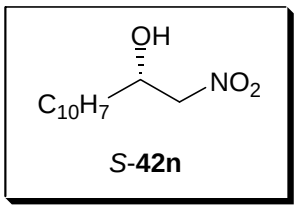
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 8.04 (d, *J* = 8.0 Hz, 1H), 7.91-7.93 (d, *J* = 8.0 Hz, 1H), 7.86-7.88 (d, *J* = 8.0 Hz, 1H), 7.77-7.79 (d, *J* = 8.0 Hz, 1H), 7.51-7.62 (m, 3H), 6.28-6.30 (m, 1H), 4.68-4.73 (m, 2H), 2.85-2.86 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 133.7, 133.5, 129.5, 129.4, 129.3, 127.0, 126.1, 125.5, 123.8, 121.8, 80.8, 68.3.

Enantiomeric purity 72% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 1.0 mL/min., 254nm, retention times 11.5 min. (*R*) and 17.1 min. (*S*)].

(*S*)-2-Nitro-1-(2-naphthyl)ethanol 42n

Yield : 0.15 g (70%)



S-**42n**

$[\alpha]_D^{25}$: +30.0 (*c* 0.46, CH_2Cl_2, 82% *ee*), [lit. $[\alpha]_D^{25}$ = +31.0 (*c* 3.08, CH_2Cl_2, 86% *ee(S)*)][22]

IR (KBr) : (cm^{-1}) 3460, 2926, 1552, 1377, 1080

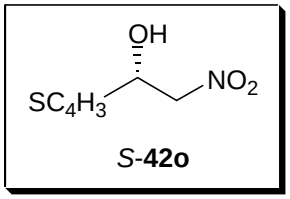
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.84-7.88 (m, 4H) . 7.44-7.54 (m, 3H), 5.59-5.62 (d, *J* = 12.0 Hz, 1H), 4.56-4.70 (m, 2H), 3.04-3.05 (d, *J* = 4.0, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 135.4, 133.4, 133.1, 129.0, 128.0, 127.8, 126.7, 126.6, 125.3, 123.2, 81.9, 71.1.

Enantiomeric purity 82% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 1.0 mL/min., 215nm, retention times 21.5 min. (*R*) and 35.1 min. (*S*)].

(*S*)-2-Nitro-1-(1-furfuryl)ethanol 42o

Yield **:** 0.13 g (80%)



$[\alpha]_D^{25}$ **:** +33.5 (*c* 0.42, CH_2Cl_2, 84% *ee*), [lit. $[\alpha]_D^{25}$ = -37.1 (*c* 0.24, CH_2Cl_2, 98% *ee* (*R*))][23]

IR (KBr) **:** (cm^{-1}) 3447, 3126, 2926, 1556, 1381, 1068

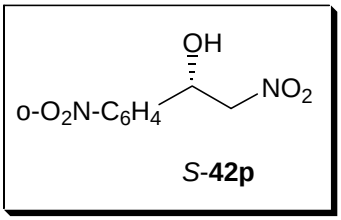
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.42-7.43 (m, 1H), 6.38-6.41 (m, 2H), 5.46-5.51 (m, 1H), 4.64-4.82 (m, 2H), 2.76-2.78 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 150.7, 143.2, 110.7, 108.2, 78.4, 64.9.

Enantiomeric purity 88% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/90:10; flow rate 1.0 mL/min., 215 nm, retention times 22.8 min. (*R*) and 27.2 min. (*S*)].

(*S*)-2-Nitro-1-(2-nitrophenyl)ethanol 42p

Yield : 0.18 g (83%)



$[\alpha]_D^{25}$: -210.9 (*c* 0.64, CH_2Cl_2, 90% *ee*), [lit. $[\alpha]_D^{25}$ = -230.9 (*c* 1.81, CH_2Cl_2, 92% *ee*)][22]

IR (KBr) : (cm^{-1}) 3530, 1610, 1556, 1346, 1097

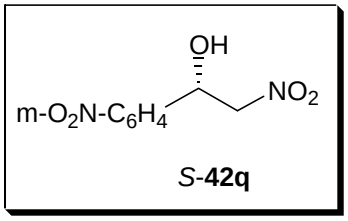
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 8.05-8.07 (d, *J* = 8.0 Hz, 1H), 7.93-7.95 (d, *J* = 8.0 Hz, 1H), 7.72-7.76 (t, *J* = 16.0 Hz, 1H), 7.52-7.56 (t, *J* = 16.0, 1H), 6.02-6.05 (d, *J* =12.0 Hz, 1H), 4.52-4.87 (m, 2H), 3.28 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 147.1, 134.3, 134.0, 129.6, 128.6, 125.0, 80.0, 66.8.

Enantiomeric purity 84% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times 11.8 min. (*R*) and 12.7 min. (*S*)].

(*S*)-2-Nitro-1-(3-nitrophenyl)ethanol 42q

Yield **:** 0.18 g (85%)



$[\alpha]_D^{25}$ **:** +28.1 (*c* 0.46, CH_2Cl_2, 78 % *ee*), [lit. $[\alpha]_D^{20}$ = +24.0 (*c* 1.65, CH_2Cl_2, 67% *ee*(*S*))][24]

IR (KBr) **:** (cm^{-1}) 3545, 3092, 2924, 1556, 1527, 1354, 1072

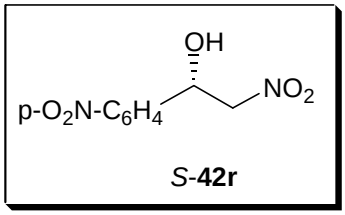
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 8.33 (s, 1H), 8.22-8.24 (d, *J* = 8.0 Hz, 1H), 7.76-7.78 (d, *J* = 8.0 Hz, 1H), 7.59-7.63 (m, 1H), 5.60-5.61 (d, *J* = 4.0 Hz, 1H), 4.56-4.66 (m, 2H), 3.13 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 148.5, 140.2, 132.0, 130.1, 123.8, 121.1, 80.6, 69.8.

Enantiomeric purity 78% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times 18.5 min. (*R*) and 20.5 min. (*S*)].

(*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 42r

Yield **:** 0.20 g (95%)



$[\alpha]_D^{25}$ **:** +26.1 (*c* 0.60, CH_2Cl_2, 74% *ee*), [lit. $[\alpha]_D^{25}$ = +29.4 (*c* 2.36, CH_2Cl_2, 85% *ee*(*S*))[22]

IR (KBr) **:** (cm^{-1}) 3543, 1556, 1520, 1381, 1082

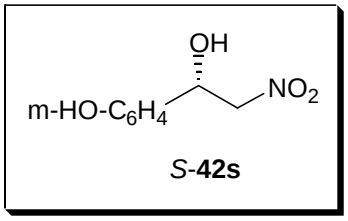
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 8.21-8.23 (d, *J* = 8.0 Hz, 2H), 7.60-7.62 (d, *J* = 8.0 Hz, 2H), 5.60 (s, 1H), 4.56-4.64 (m, 2H), 3.43 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 148.0, 145.2, 127.0, 124.1, 80.6, 69.9.

Enantiomeric purity 74% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times : 19.5 min. (*R*) and 23.7 min. (*S*)].

(*S*)-2-Nitro-1-(3-hydroxyphenyl)ethanol 42s

Yield : 0.13 g (72%)



$[\alpha]_D^{25}$: +8.1 (*c* 0.55, EtOH, 80% *ee*)

IR (KBr) : (cm^{-1}) 3543, 1556, 1520, 1381, 1082

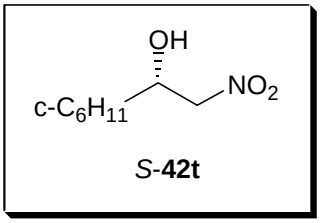
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.18-7.23 (m, 1H), 6.87-6.89 (m, 2H), 6.76-6.78 (m, 1H), 5.32-5.36 (m, 1H), 4.56-4.57 (m, 2H), 3.34 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 161, 144.8, 133.6, 120.9, 119.2, 116.5, 85.5, 74.5.

Enantiomeric purity 80% ee [determined by HPLC using chiral column, chiralcel AD-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 254nm, retention times 13.4 min. (*R*) and 14.4 min. (*S*)].

(*S*)-2-Nitro-(1-cyclohexyl)ethanol 42t

Yield **:** 0.15 g (90%)



$[\alpha]_D^{25}$ **:** +15.5 (*c* 0.6, CH_2Cl_2, 84% *ee*), [lit. $[\alpha]_D^{25}$ = +16.7 (*c* 4.13, CH_2Cl_2, 91% *ee(S)*)[22]

IR (neat) **:** (cm^{-1}) 3431, 2928, 2854, 1554, 1385, 1097

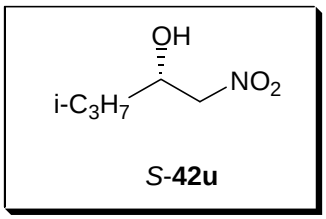
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 4.38-4.49 (m, 2H), 4.08 (s, 1H), 2.52 (s, 1H), 1.65-1.84 (m, 5H), 1.42-1.51 (m, 1H), 1.23-1.30 (m, 5H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δ ppm) 79.3, 72.8, 41.4, 28.8, 27.9, 26.0, 25.8, 25.7.

Enantiomeric purity 88% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes : ^{i}PrOH/97:3; flow rate 0.8 mL/min., 215 nm, retention times 40.9 min. (*R*) and 43.8 min. (*S*)].

(*S*)-3-Methyl-1-nitrobutan-2-ol 42u

Yield **:** 0.121 g (90%)



$[\alpha]_D^{25}$ **:** +19.5 (*c* 0.5, $CHCl_3$, 84% *ee*), [lit. $[\alpha]_D^{25}$ = +20.4 (*c* 1.0, $CHCl_3$, 91% *ee (S)*)][22]

IR (neat) **:** (cm^{-1}) 3431, 2968, 1552, 1385, 1070

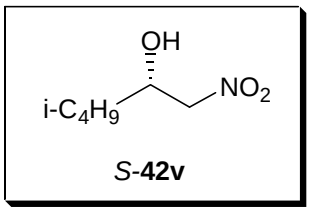
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 4.37-4.48 (m, 2H), 4.10 (s, 1H), 2.57 (s, 1H), 1.77-1.81 (m, 1H), 0.97-1.00 (m, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 79.2, 73.2, 31.7, 18.4, 17.4.

Enantiomeric purity 86% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/97:3; flow rate 0.6 mL/min., 220 nm, retention times 27.6 min. (*R*) and 30.0 min. (*S*)].

(*S*)-4-Methyl-1-nitropentan-2-ol 42v

Yield **:** 0.13 g (90%)



S-**42v**

$[\alpha]_D^{25}$ **:** -2.17 (*c* 0.42, CH_2Cl_2, 88% *ee*), [lit. $[\alpha]_D^{25}$ = -2.17 (*c* 1.95, CH_2Cl_2, 87% *ee* (*S*))][11]

IR (neat) **:** (cm^{-1}) 3414, 2961, 1556, 1386, 1089

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 4.33-4.43 (m, 2H), 0.90-0.98 (m, 6H), 2.50 (s, 1H), 1.81-1.86 (m, 1H), 1.48-1.55 (m, 1H), 1.02-1.27 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 80.9, 66.9, 42.4, 24.3, 23.1, 21.7.

Enantiomeric purity 88% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:^{i}PrOH/85:15; flow rate 0.8 mL/min., 215 nm, retention times 29.9 min. (*R*) and 32.1 min. (*S*)].

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Chapter 3

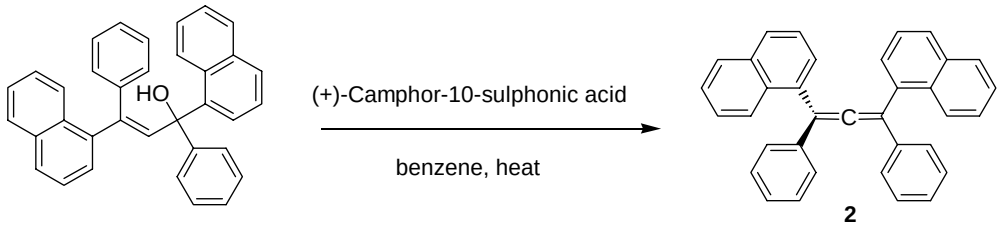
Synthesis of Chiral Allenes Using Aromatic aldehydes and 1-Alkynes by Chirality Transfer from Chiral Secondary Amine Derivatives

3. 1 Introduction

3.1.1 Chiral Allenes

In 1875, Jacobus Henricus van't Hoff predicted the existence of an asymmetrically substituted allene in two enantiomeric forms.[1] In 1935, P. Maitland and W. H. Mills proved this by dehydration of allylic alcohol **1** in the presence of (+)-camphor-10-sulfonic acid to obtain the chiral allene **2** (scheme **1**).[2]

Scheme 1



1 **2**

$[\alpha]_D^{25}$ = +437 (benzene)

3.1.2 Naturally occurring chiral allenes

The first naturally occuring allene pyrethrolone **3** was characterized by H. Staudinger and L. Ruzicka.[3] Occurrence of allenic structures in a variety of natural products and pharmacologically active compounds have inspired ample interest on chiral allenes among organic and medicinal chemists.[4] In the last few years, many natural products containing chiral allene moiety have been isolated (Fig. **1)**.[5]

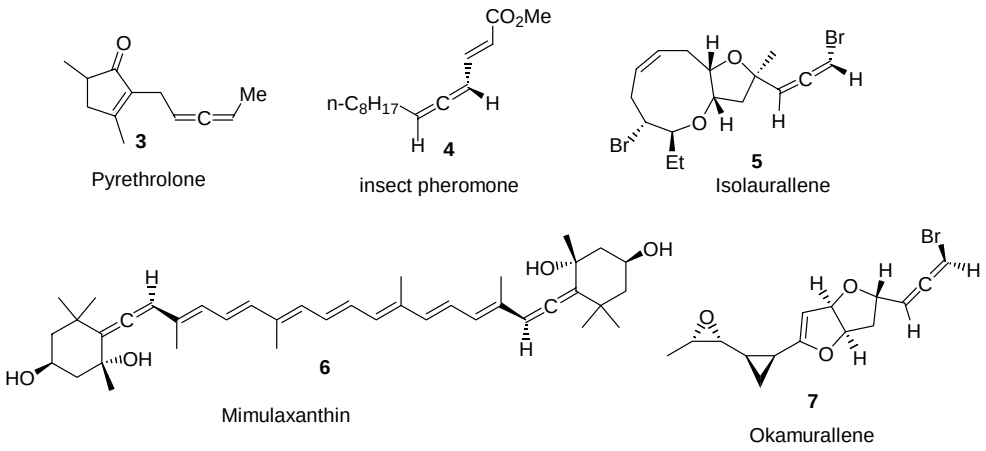
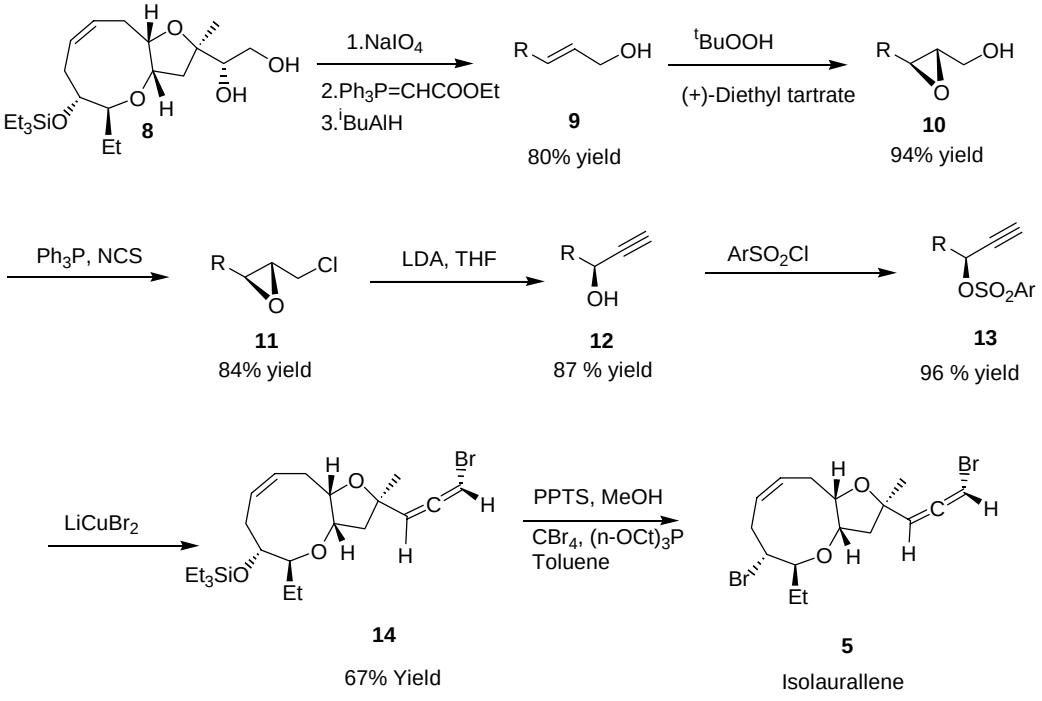


Figure 1

Many of these naturally occurring allenes have also been prepared synthetically. For example, the isolaurallene **5** has been prepared *via* multistep sequence shown below.[6]

Scheme 2



3.1.3 Biologically active chiral allenes

Allenic derivatives not only occur in nature but also have considerable potential as phormacologically active molecules. For example, the compounds scorodonin **15**, nemotin **16** and phomallenic acid **17** have inhibiting effects on the growth of bacteria, yeasts and filamentous fungi. Other allenic moieties with such inhibiting effects are sterol biosynthesis inhibitor **18**, gastric acid inhibitor **19**, HIV inhibitor **20** and hepatitis B replication inhibitor **21** (Figure **2**).[5, 7]

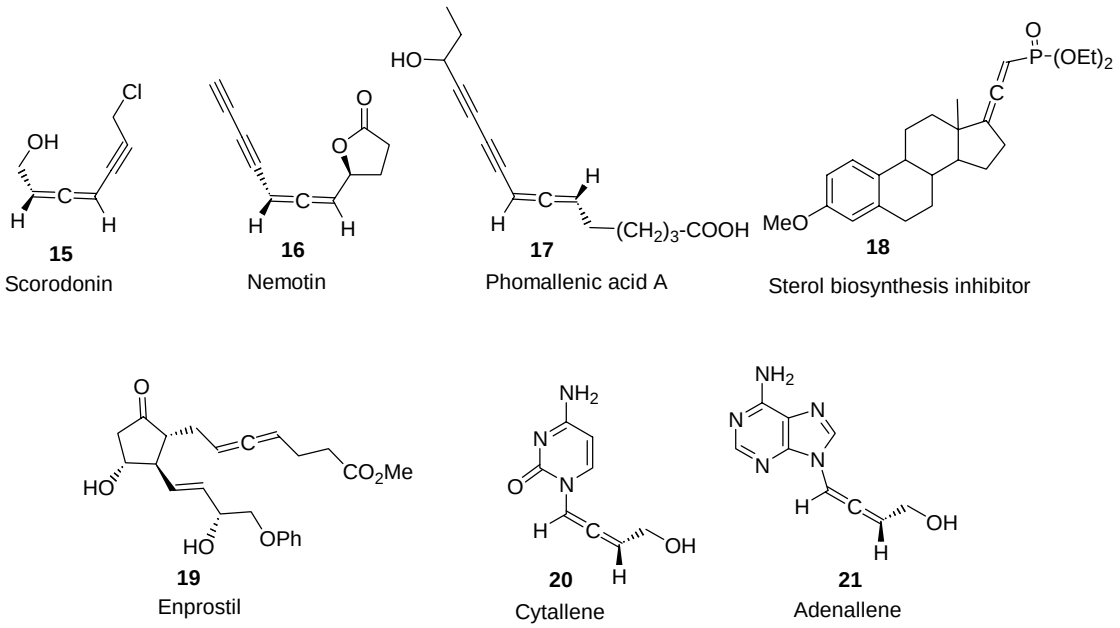
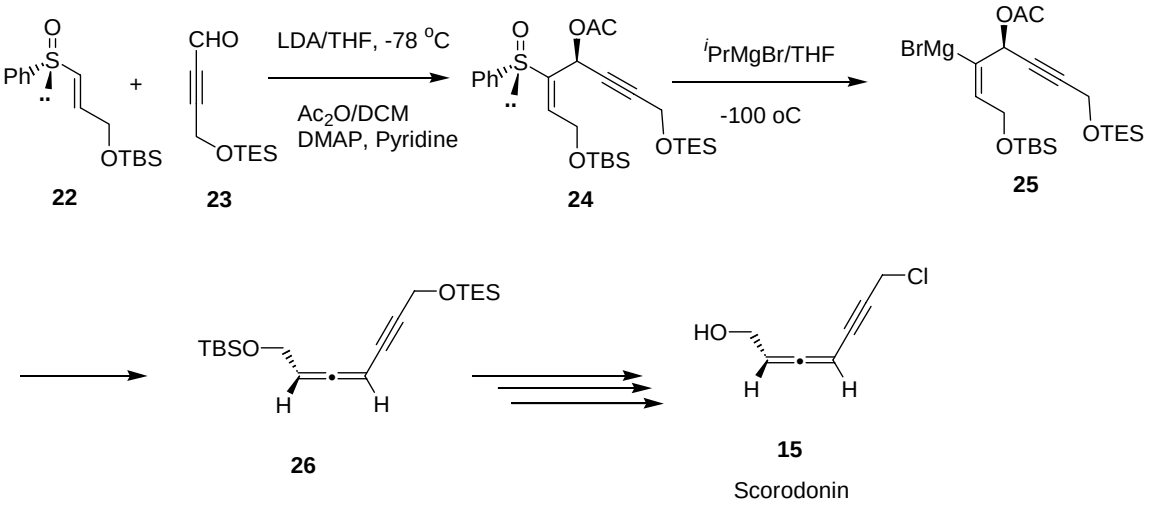


Figure 2

Constructions of allene moiety in the synthesis of some of these bioactive molecules are outlined here.

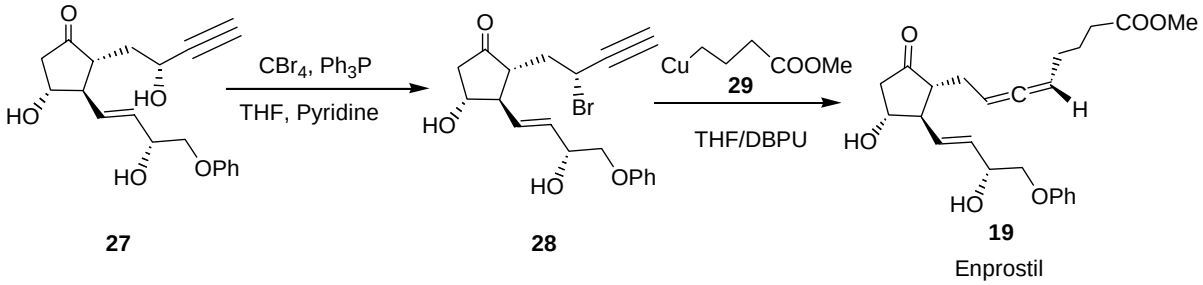
The first step in the preparation of scorodonin **15** is the formation of Baylis-Hilman adduct **24** from unsaturated chiral sulphoxide **22** and alkynal **23**, which gave the crucial intermediate for the synthesis of scorodonin **15**.[8]

Scheme 3



Another interesting moiety enprostil **19** has been made by a sequence of steps using chiral propargylic alcohol **27** as starting material involving an S_N^2-type substitution in crucial steps to get the allenic skeleton.[9]

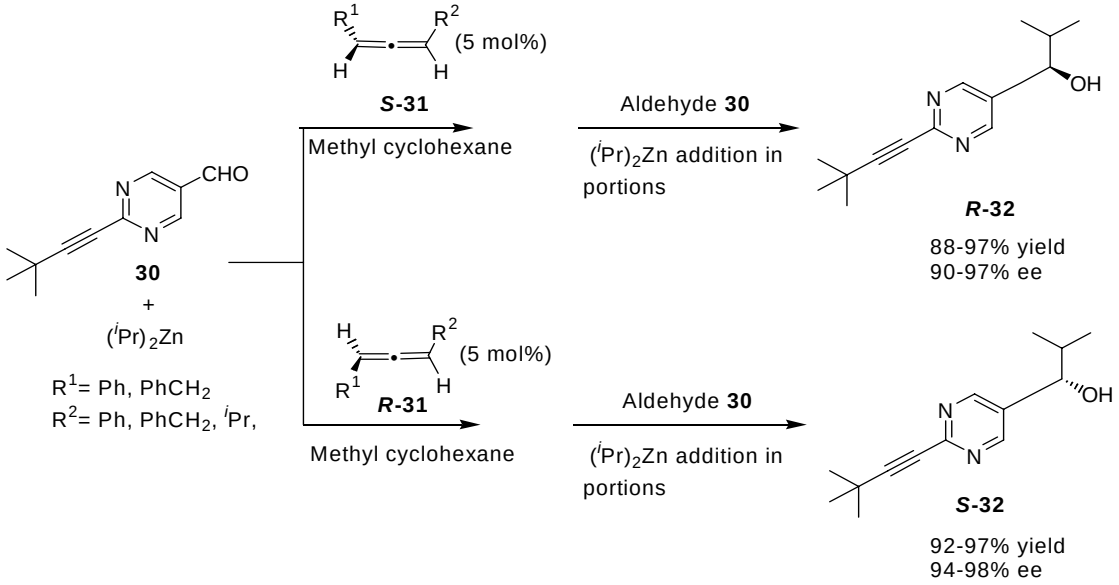
Scheme 4



3.1.4 Chiral allenes induced asymmetric transformation

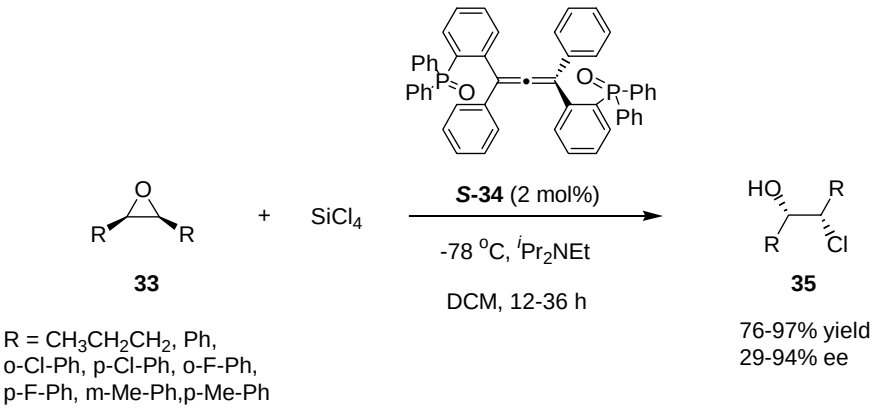
1,3-Disubstituted chiral allenes *S*-**31** or *R*-**31** without any heteroatoms act as chiral initiators in the addition of $(^{i}Pr)_2Zn$ to pyrimidine-5-carbaldehyde **30** to afford the chiral pyrimidin-5-yl alkanols **32**. Subsequent autocatalysis by the resulting products *R*-**32** or *S*-**32** leads to the formation of chiral pyrimidin-5-yl alkanols with up to 98% ee (Scheme **5**).[10]

Scheme 5



cis-Stilbene oxides **33** react with $SiCl_4$ and $^{i}Pr_2NEt$ in the presence of chiral allene containing *bis*-phosphine oxide moiety **34** to give the corresponding chlorohydrins **35** in 97% yield with up to 94% ee (Scheme **6**).[11]

Scheme 6

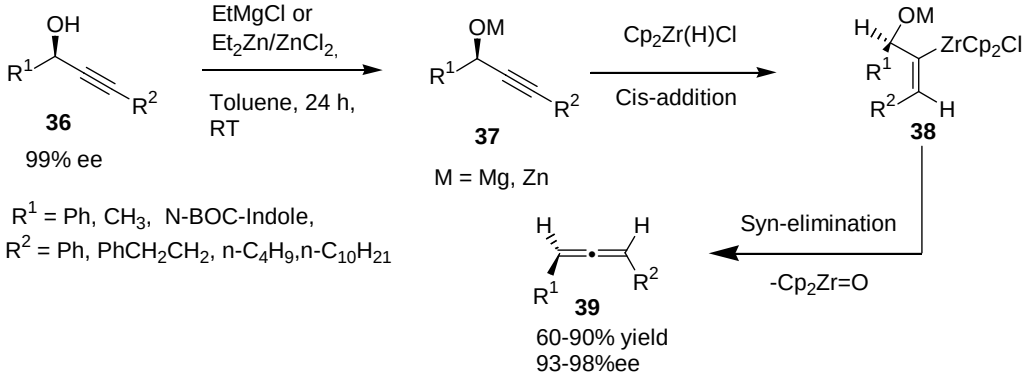


3.1.5 Methods to synthesize of chiral allenes

All the classical reaction types like addition, elimination, substitution, rearrangement have been followed for the synthesis of allenes.[12] The most widely used reaction is the direct S_N^2-type substitution using various nucleophilic sources with propargylic derivatives.

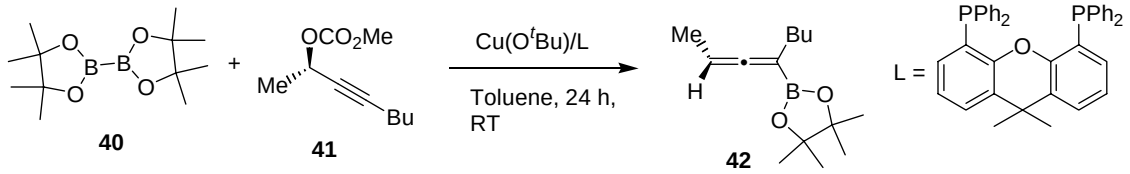
Hydrozirconation of propargylic derivatives **36** by *in situ* generated zinc or magnesium alkoxides of propargylic alcohols **37** by $Cp_2Zr(H)Cl$ furnishes the allenes **39** in good yields with high optical purities (Scheme **7**).[13]

Scheme 7



The Cu(O^{t}Bu)/ligand reagent system is useful for the stereoselective substitution of propargylic carbonates **41** with bis(pinacolato)diboron **40** to give the boroallene **42** with 96% ee (Scheme **8**).[14]

Scheme 8



40 **41** **42**

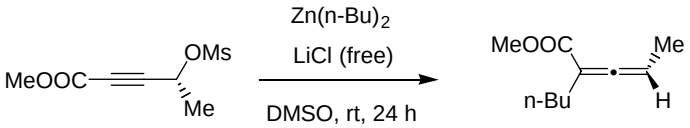
99% ee

60% yield
96% ee

.

The S_N^2 reaction of propragyl mesylates **43** with organozinc reagents in DMSO as solvent gives the chiral allene **44** in 87% yield with up to 98% ee (Scheme **9**).[15]

Scheme 9



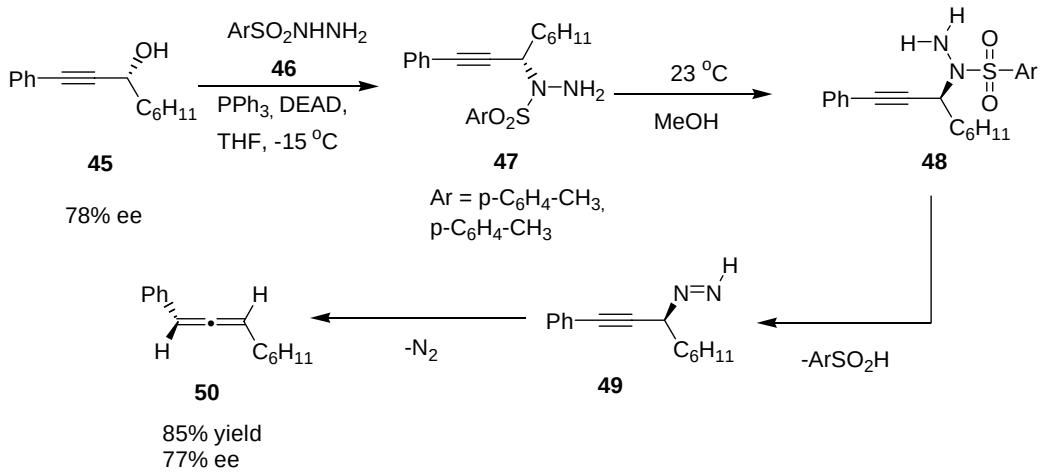
43 **44**

99% ee

87% yield
98% ee

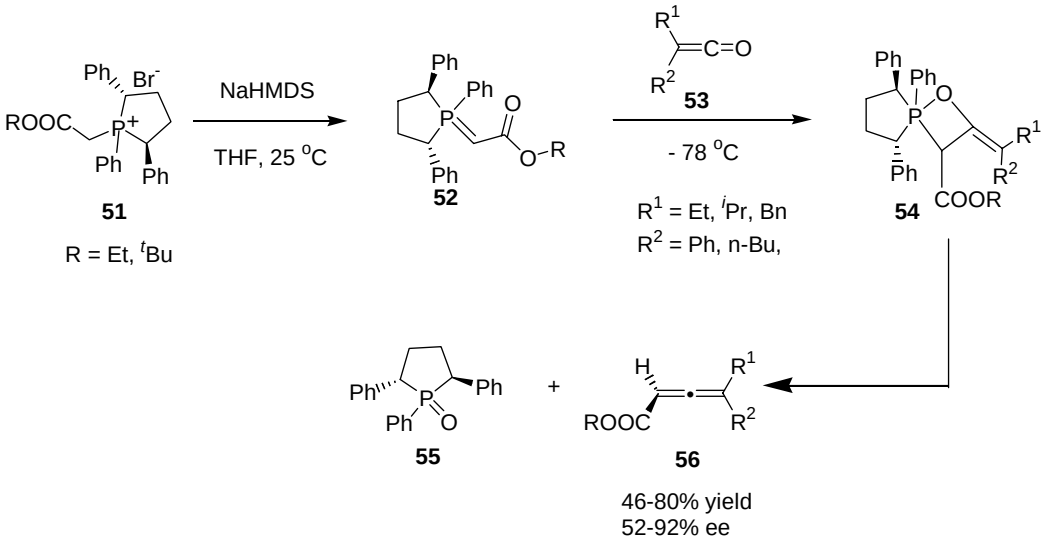
A representative method for the preparation of axially chiral allene **50** (77% ee) from the chiral propargylic alcohol **45** (78% ee) by using aryl sulphonamide **46** under Mistunubu reaction conditions has been reported (Scheme **10**).[16]

Scheme 10



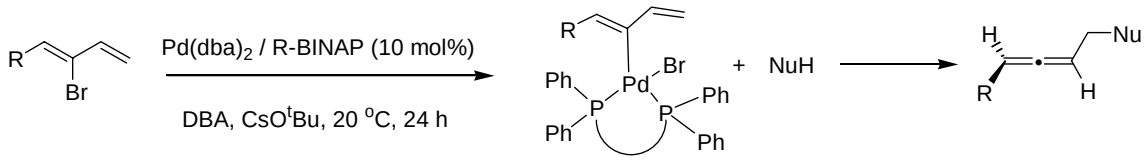
Highly enantioselective synthesis of allenic esters **56** by the condensation of pseudo C_2-symmetrical chiral phosphorus ylides **51** with various ketenes **53** using NaHMDS as base at -78 °C has been reported.[17] The chiral phosphine oxide **55** was recovered without losing its chirality (Scheme **11**).

Scheme 11



A novel route to the enantiomerically enriched axially chiral allenes **59** was reported using achiral conjugated dienes **57**, nuchleophiles and palladium-BINAP complex as a chiral catalytic system (Scheme **12**).[18]

Scheme 12



57

R = Ph, n-C_8H_{17}, Ferrocenyl
Nu = $CMe(COOMe)_2$

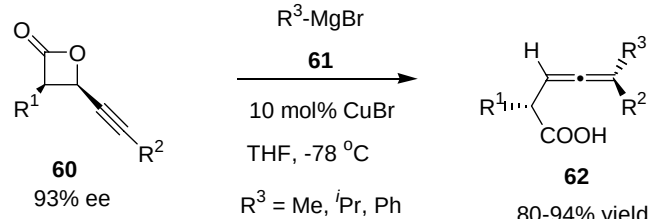
58

59

59-78% yield
41-89% ee

The S_N^2 ring opening reaction of β-lactones **60** provides an efficient and operationally simple enantioselective synthesis of *di*- and *tri*-substituted allene derivatives **62** using various Grignard reagents **61** (Scheme **13**).[19]

Scheme 13

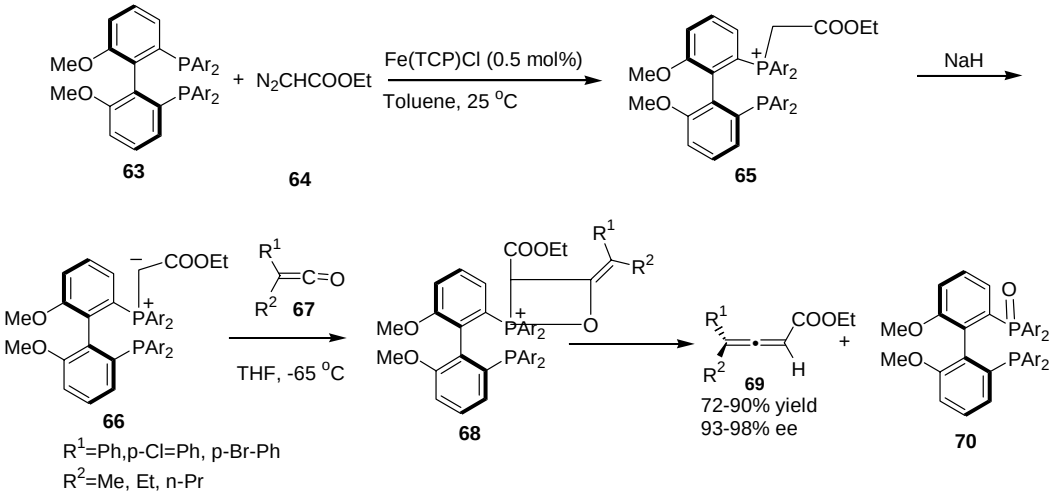


60
93% ee
R^1 = H, CH_3, $PhCH_2$
R^2 = CH_2OCH_2Ph, $SiMe_3$

62
80-94% yield
83-93% ee

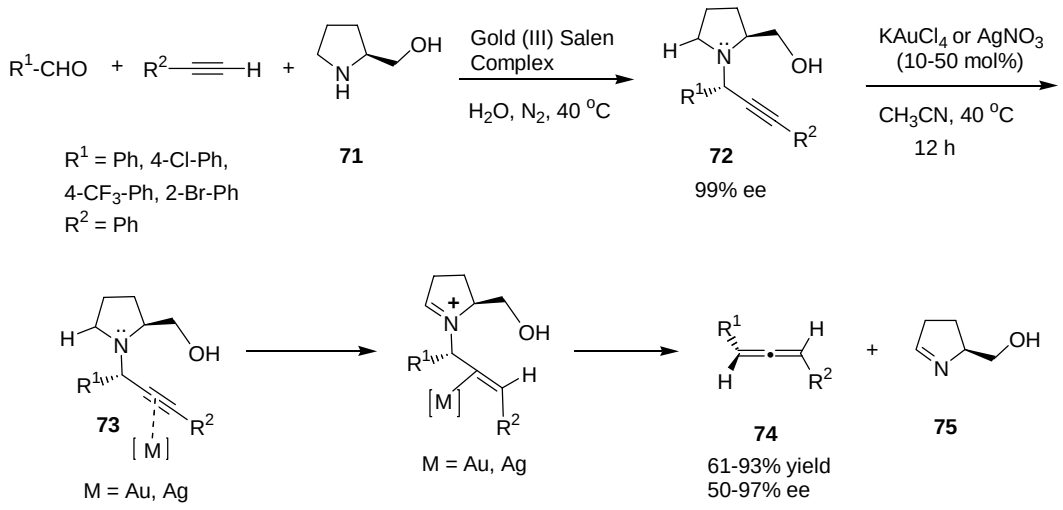
An efficient method for the synthesis of chiral allenes **69** under neutral conditions by olefination of ketenes **67** with ethyl diazoacetate (EDA) **64** in the presence of chiral phosphine **63**-Fe(TCP)-Cl catalyst system has been reported (Scheme **14**).[20]

Scheme 14



Chiral propargyl amines **72**, prepared using various aldehydes, 1-alkynes and chiral amine **71** using a gold(III)-salen complex, have been reported to yield axially chiral allenes **74** (50-97% ee) under $KAuCl_4$ or $AgNO_3$ catalysis in CH_3CN at 40 °C (Scheme **15**).[21]

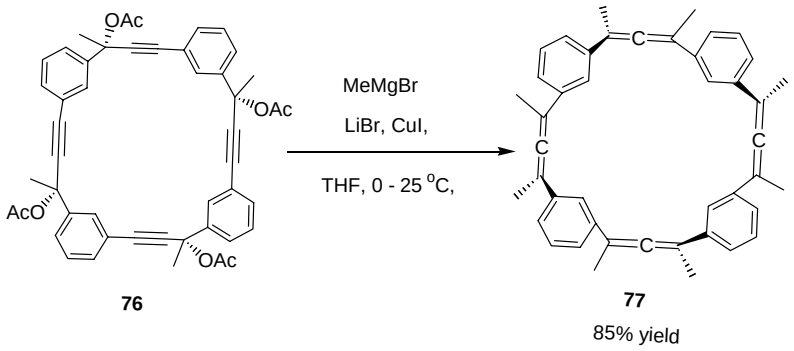
Scheme15



3.1.6 Synthesis of chiral allenophane macrocycles

These allenyl macrocycles are useful as chiral ligands and as hosts for metal ions and small guest molecules. The chiral allenophanes **77** was prepared by organocuprate mediated S_N2 coupling reaction with optical active cyclic propargyl acetates **76** (Scheme **16**).[22]

Scheme 16



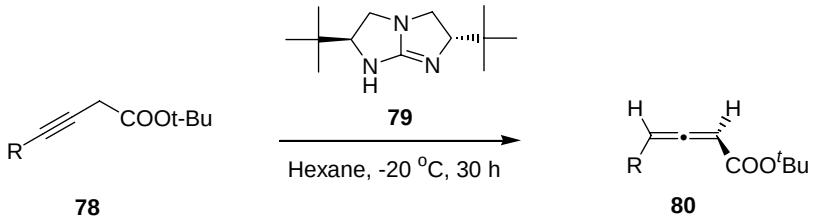
76 **77**

85% yield

3.1.7 Preparation of chiral allenes using organo catalytic methods

Chiral bicyclic guanidine **79** has been reported to catalyze the isomerization of highly reactive alkyne derivatives **78** to chiral allenoates **80** with 79-95% ee (Scheme **17**).[23]

Scheme 17



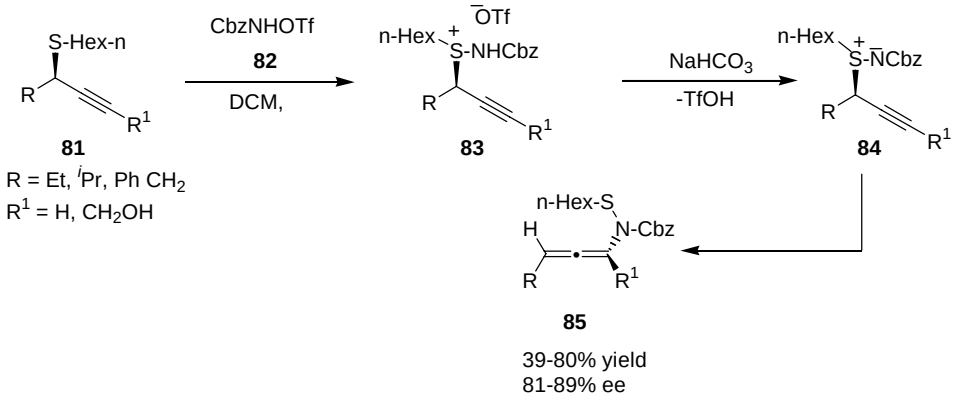
78 **80**

R = Ph, 3-Me-Ph, 2-Br-Ph,
2-MeO-Ph, 4-F-Ph,

39-80% yield
79-95% ee

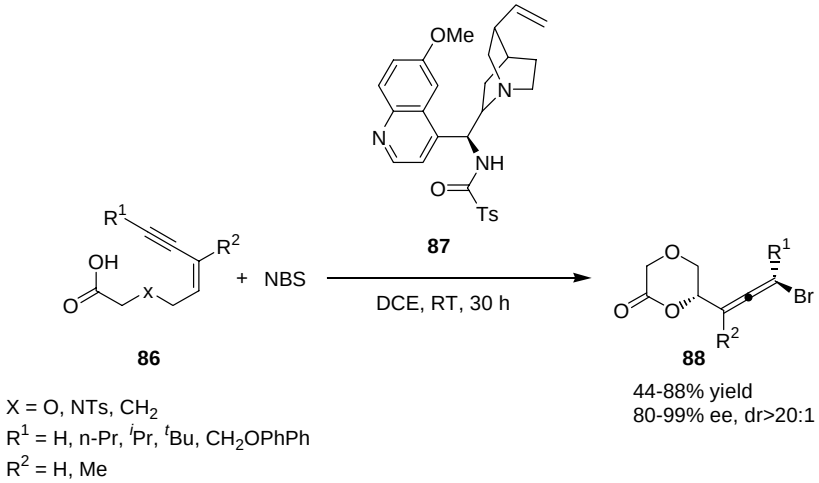
Chiral allenamides **85** were prepared with high levels of enantiomeric purity by [2,3]-sigmatropic rearrangement of propargylic sulfides **81** and the amide derivative **82** (Scheme **18**).[24]

Scheme 18



The bifunctional cinchonidine catalyst **87** promoted the highly enantioselective bromolactonization of conjugated (*Z*)-enynes **86** for the preparation of versatile bromoallenes **88** containing lactone heterocycles moiety with high optical purity (Scheme **19**).[25]

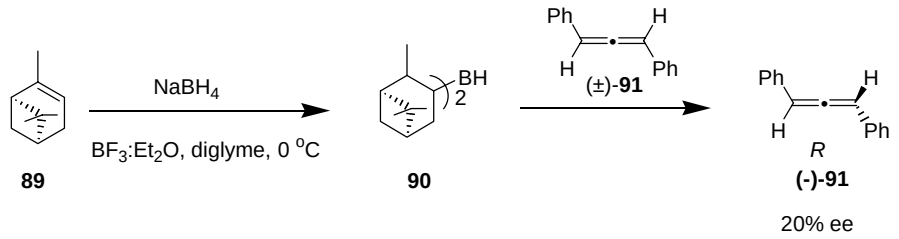
Scheme 19



3.1.8 Synthesis of enantiomerically enriched chiral allenes by kinetic resolution

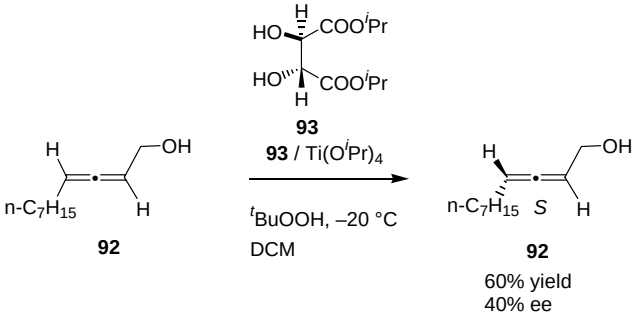
Kinetic resolutions of racemic allenes using asymmetric catalysts is an alternative method to access enantiomerically pure allenes. Hydroboration of (-)-α-pinene **89**, $NaBH_4$ and BF_3:Et_2O in diglyme leads to (+)-$(Ipc)_2BH$ **90**, which has been shown to be a highly stereoselective hydroborating agent. It hydroborates (±)-allenes **91** to give the (-)-allene **91** with low optical purity in 3 h (Scheme **20**).[26]

Scheme 20



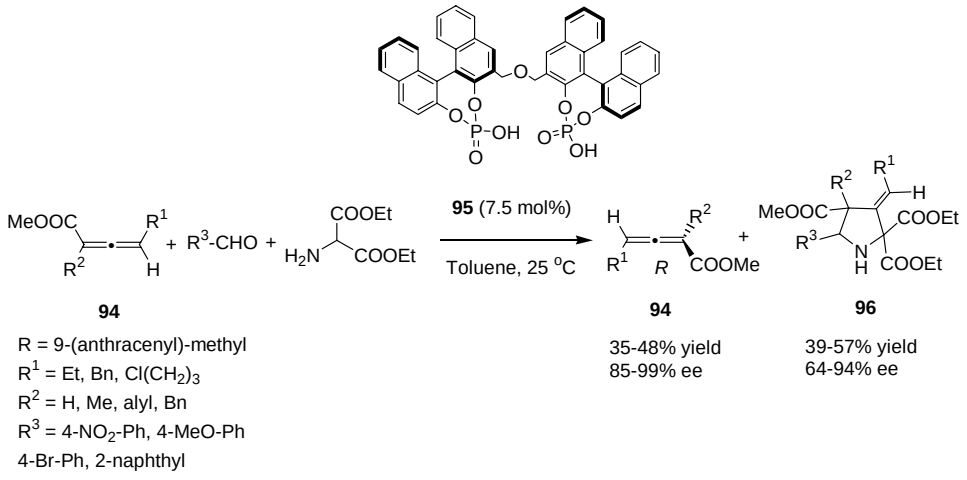
An example of the titanium-catalyzed epoxidation of racemic allenic alcohol was described briefly in 1983.[27] Oxidation of racemic allene **92** under the well-known Sharpless epoxidation conditions, i.e with $Ti(O^iPr)_4$, (+)-diisopropyl tartrate **93** [(+)-DIPT], and ^{t}BuOOH, gave the (*S*)-(+)-allene **92** with 40% ee (Scheme **21**).

Scheme 21



Very recently, chiral bisphosphoric acid **95** catalyzed kinetic resolution of racemic 2,3-allenoates **94** via 1,3-dipolar cycloaddition has been reported. In this way, optically active 2,3-allenoates **94** with (*R*)-configuration are obtained in 35-48% yield with 85-99% ee, besides the 3-methylene pyrrolidine derivative **96** (Scheme **22**).[28]

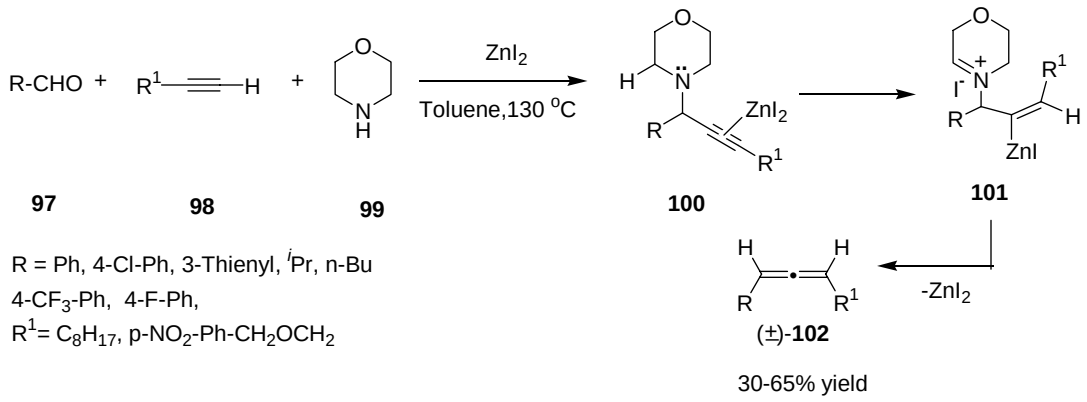
Scheme 22



3.1.9 Synthesis of racemic allenes using 1-alkynes, aldehydes and cyclic amine

Recently, it has been reported that racemic allenes are formed in the reaction of aldehydes **97**, 1-alkynes **98**, morpholine **99** and ZnX_2 in toluene at 130 ^oC (Scheme **23**).[29]

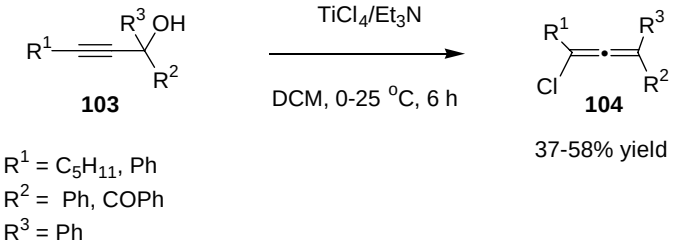
Scheme 23



3.1.10 Previous work from this laboratory

Previously, efforts were undertaken in this laboratory towards the synthesis of allenes. It was found that the reaction of propargylic alcohol **103** with $TiCl_4/Et_3N$ gave the corresponding racemic chloroallenes **104** (Scheme **24**).[30]

Scheme 24



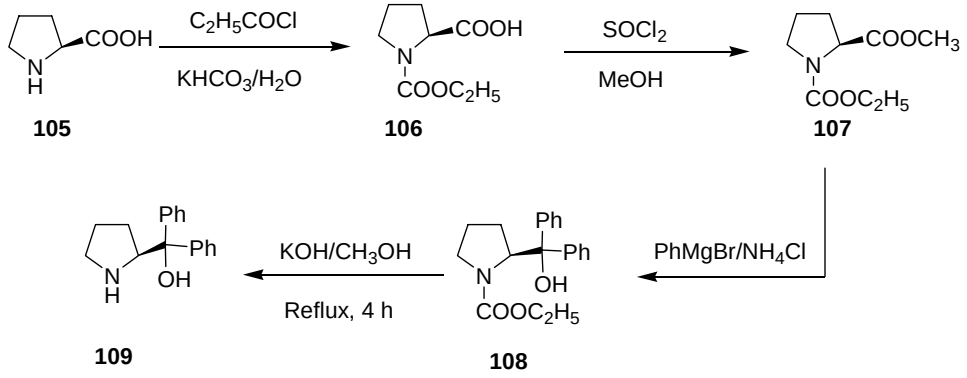
However, methods for accesing optically pure allenes are still very few and often involve expensive reagents. Also, in the reported procedures, several steps are required to make various chiral propargylic derivatives. Therefore, preparation of optically pure allenes by using easily accessible reagents is still a challenging research topic. We were looking for simple, convenient one-pot methods for enantiopure allene synthesis. The results of these studies are discussed in the next section.

3.2 Results and Discussion

3.2.1 Chiral Allenes from 1-Alkynes, Aromatic aldehydes and (*S*)-diphenylprolinol

As outlined in the introductory section, racemic allenes can be readily accessed from 1-alkynes, aldehydes, certain secondary amines and ZnX_2 in toluene at 130 ^oC (Scheme **23**).[29] As discussed in Chapter **1**, several convenient methods have been doveloped in this laboratory to access chiral amines. For example, the (*S*)-α,α-diphenylprolinol (*S*-DPP, 109) can be readily accesed by the method developed in this laboratory (Scheme **25**).[31]

Scheme 25



Accordingly, we have examined the utility of the (*S*)-α,α-diphenylprolinol (*S*-DPP) **109** for the reaction of 1-decyne **110** and benzaldehyde **111a** in the presence of promoters like $ZnCl_2$, $ZnBr_2$ and ZnI_2. The corresponding chiral *R*-allene **112a** was obtained in 50%

yield with up to 94% ee using $ZnCl_2$ (1.0 mmol) in toluene at 120 ^oC after 17 h (Scheme **26**, Table.**1**). Whereas the use of $ZnBr_2$ (0.7 mmol) in this transformation gave the allene in 65% yield and 98% ee, the reaction using ZnI_2 (0.5 mmol) gave the allene product in 57% yield and 84% ee (**Table 1)**. Results of optimization of this transformation using various amounts zinc halides are summarized in Table **1**.

Scheme 26

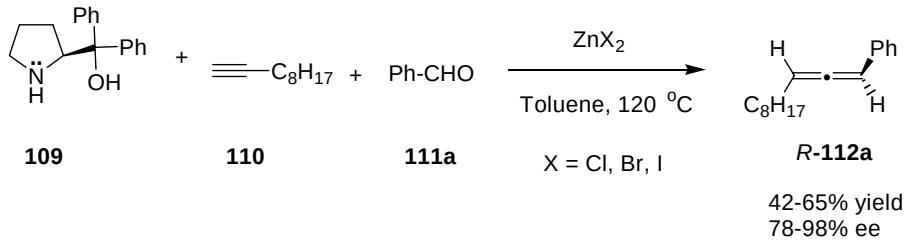


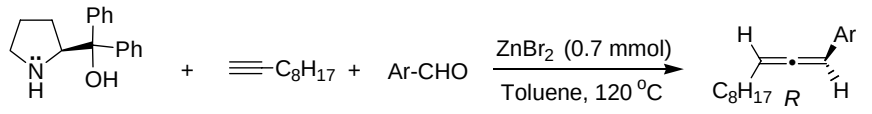
Table.1 Optimization of the reaction condition[a]

Entry	Lewis acid	mmol	Time(h)	Yield[b](%)	% ee[c]
1	$ZnCl_2$	1	12	50	94
2	$ZnCl_2$	0.8	12	47	94
3	$ZnCl_2$	0.6	14	45	94
4	$ZnCl_2$	0.5	17	42	94
5	$ZnBr_2$	0.8	10	66	92
6	$ZnBr_2$	0.7	10	65	98
7	$ZnBr_2$	0.5	13	52	94
8	ZnI_2	0.8	5	66	78
9	ZnI_2	0.6	5	63	84
10	ZnI_2	0.5	6	57	84

[a] All the reactions were carried out with *S*-DPP **109** (1 mmol), 1-decyne **110** (1 mmol), zinc halide at 120^{o}C in toluene (3 mL) for 15min. followed by addition of benzaldehyde **112a** (1 mmol) at 25 ^{o}C and further stirring at 120 ^{o}C. [b]Isolated yield of **112a**. [c]The configuration of the allene **112a** is assigned as *R* by comparison of the $[\alpha]_D$ with the reported value[32] and the % ee was determined by HPLC analysis (chiralcel OD-H column) using hexane as eluent.

As evident from Table **1**, $ZnBr_2$ (0.7 mmol) in toluene gave optimum results. Therefore, we have carried out the reactions of different aryl aldehydes using $ZnBr_2$ (0.7 mmol) to obtain the corresponding chiral allenes in good yields and high enantioselectivities (Scheme **27**, Table **2**). The substituted benzaldehyde derivatives having both electron donating and withdrawing groups afforded good results.

Scheme 27



109 **110** **111 (a-h)** ***R*-112 (a-h)**

50-70% yield
82-98% ee

Table 2 $ZnBr_2$ promoted reaction of 1-decyne with various aldehydes using **109**[a]

Entry	Ar	Allene	Time(h	Yield[b](%)	% ee[c]	Configuration
1	Ph	**112a**	10	65	98	(*R*)
2	p-F-Ph	**112b**	9	70	90	(*R*)
3	p-Cl-Ph	**112c**	14	65	90	(*R*)
4	p-Br-Ph	**112d**	14	68	90	(*R*)
5	P-CF_3-Ph	**112e**	13	60	82	(*R*)
6	m-Me-Ph	**112f**	12	60	90	(*R*)
7	m-MeO-Ph	**112g**	13	58	94	(*R*)
8	p-Me-Ph	**112h**	17	50	90	(*R*)

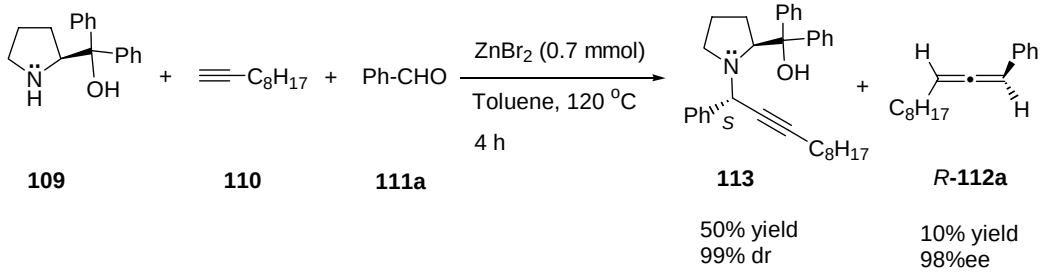
[a]All the reactions were carried out with *S*-DPP **109** (1 mmol), 1-Decyne **110** (1 mmol), $ZnBr_2$ at 120 °C in toluene for 15 min. followed by addition of aldehydes **111** (**a-h**) (1 mmol) at 120 °C. [b]Isolated yield of **112 (a-h)**. [c]The % ee was confirmed by HPLC analysis on chiralcel OD-H, OJ-H and OB-H column using hexane as eluent.

All the optically active allenes obtained by using (*S*)-DPP **109** are levorotatory, from which the absolute configurations of the major enantiomer of the allenes can be assigned as *R* by considering the Lowe-Brewster rules.[33] Comparison of $[\alpha]_D^{25}$ values with reported values confirms this stereochemical assignment.[32]

3.2.2 Isolation of chiral propargyl amine intermediate

To study the mechanistic pathway of this reaction, we have stopped the reaction using $ZnBr_2$ after 4 h at 120 ^oC. In this run, the propargyl amine intermediate **113** was isolated in 50% yield besides the *R*-allene **112a** in 10% yield with 98% ee. This propargyl amine **113** derivative was found to be with 99% dr and the new chiral center at the propargylic position is assigned *S* configuration based on comparison of $[\alpha]_D^{25}$ value with value reported for similar derivatives (Scheme **28)**.[34]

Scheme 28

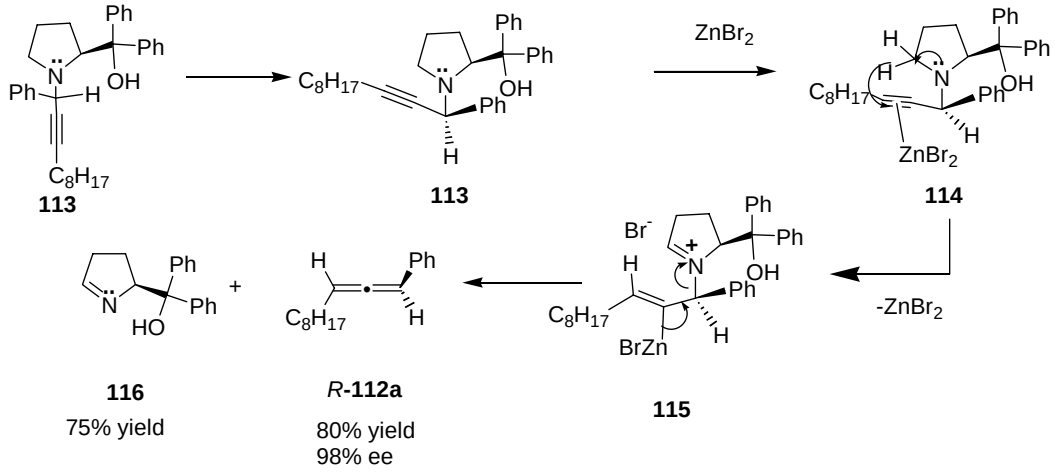


3.2.3 Isolation of chiral imine 116 intermediate in allene transformation from chiral propargyl amine 113

In experiments that gave allene products (Scheme **26**, **27**), the imine **116** has been isolated in 40-50% yields. This imine should have formed in the conversion of propargyl

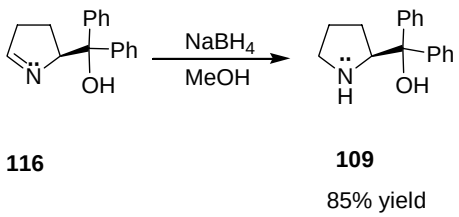
amine **113** to chiral allene. In order to confirm this, we have carried out the reaction of intermediate **113** (1.0 mmol) with $ZnBr_2$ (0.5 mmol) in toluene (3 mL) for 3 h at 120 ^oC. In this run, the *R*-allene **112a** has obtained in 80% yield with 98% ee besides the imine **116** in 75% yield without loss of its chirality (Scheme **29)**.

Scheme 29



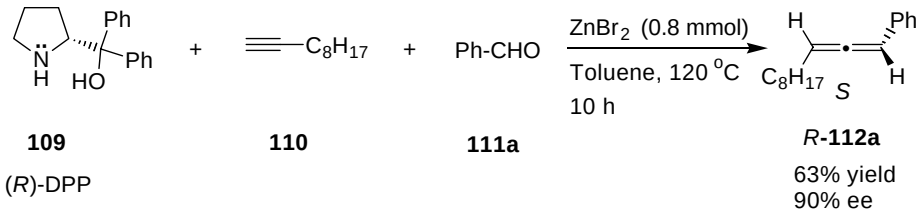
The imine **116** was converted back to the (*S*)-DPP **109** in quantitative yield for reuse by simple reduction using $NaBH_4$/MeOH without any change in optical purity (Scheme **30)**.

Scheme 30



As expected, in an experiment using (*R)*-DPP **109**, the (*S*)-allene **112a** was isolated in 63% yield with up to 90% ee using $ZnBr_2$ (0.8 mmol) at 120 ^oC (Scheme **31**).

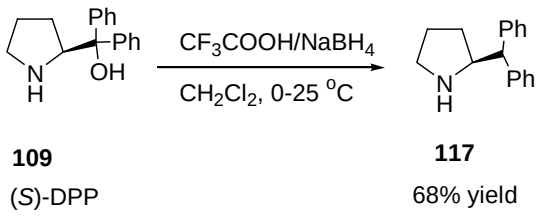
Scheme 31



3.2.4 Chirality transfer from other pyrrolidine systems

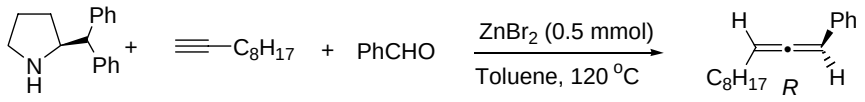
A simple method has been reported for synthesis of (*S*)-2-diphenylmethanopyrrolidine **117** starting from the commercially available (*S*)-diphenylprolinol **109** by reaction with trifluoroacetic acid and sodium borohydride with retention of configuration (Scheme **32**).[35]

Scheme 32



We have examined the $ZnBr_2$ promoted reaction of 1-decyne **110** and benzaldehyde **111a** using the amine **11**7. In this experiment, the *R*-allene was obtained in 68% yield and 66% ee (Scheme **33**).

Scheme 33



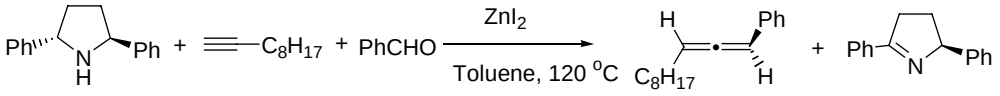
117 **110** **111a** ***R*-112a**

68% yield
66% ee

.

Presumably, the hydroxyl group present in the (*S*)-DPP leads to better chiral discrimination. Recently, it has been observed in this laboratory that the use of the amines **118** and **120** leads to chiral allenes with lower selectivity (Scheme **34**).

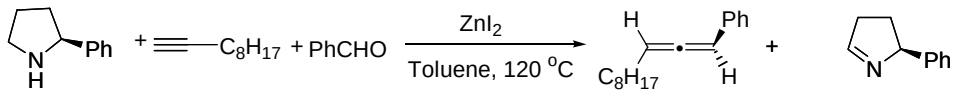
Scheme 34



118 **110** **111a** ***R*-112a** **119**

57% yield
18% ee

52%y



120 **110** **111a** ***R*-112a** **121**

72% yield
66%ee

56% y

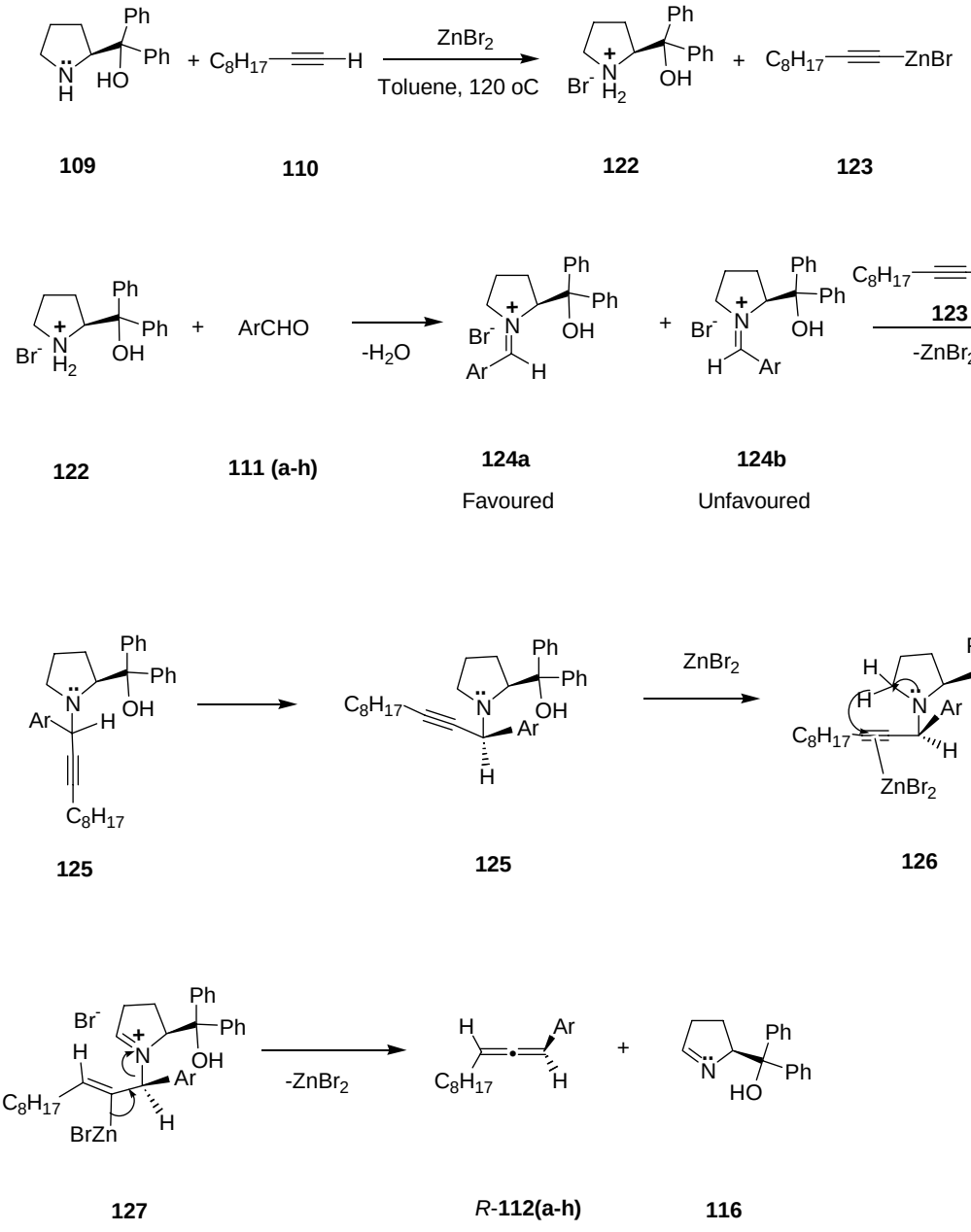
It has been also shown that the low selectivity observed in these transformations is due to formation of mixture of diastereomers of the propargyl amine intermediates before conversion to allenes.[36]

3.2.5 Plausible mechanistic pathway for the allene formation

The formation of chiral allenes can be explained by considering a tentative mechanism as outlined in **Scheme 35**. The initially formed alkynyl zinc intermediate **123** intermediate [37] would react with the favoured conformation of iminium ion **124A** derived from various aromatic aldehydes and (*S*)-α,α-diphenylprolinol **109** to give the corresponding propargylamine intermediate **125.** The propargylamine intermediate **125** would then undergo an intramolecular hydride shift from the pyrrolidine skeleton of (*S*)-DPP **126** to the $ZnBr_2$ complexed acetylinic moiety leading to alkenyl zinc complex **127**. Subsequently, cleavage of C-N bond would lead to the chiral allene **112 (a-h)** and the imine **116** of (*S*)-DPP.

The results using various chiral amines (**109**, **117**, **118**, **120**) in these reactions indicates that the amine **109** has given the best results. Probably, the reason for this may the presence of hydroxylic group in amine **109**, which may help in interaction of $ZnBr_2$ in complex **126** with the hydroxylic group leading to increased chiral discrimination.

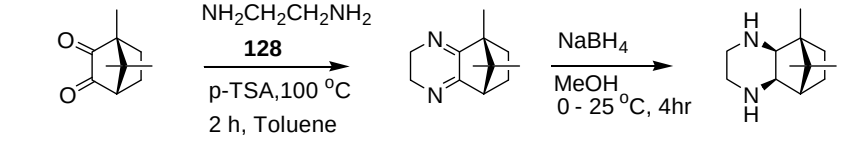
Scheme 35


Ph
Ph
HO
N
H
+ C8H17
H
ZnBr2
Toluene, 120 oC
Br-
H2
OH
ZnBr
109
110
122
123
ArCHO
-H2O
Ar
124a
Favoured
124b
Unfavoured
-ZnBr2
111 (a-h)
125
126
127
BrZn
R-112(a-h)
116

3.2.6 Synthesis of chiral allenes using chiral diamine containing camphanyl moiety

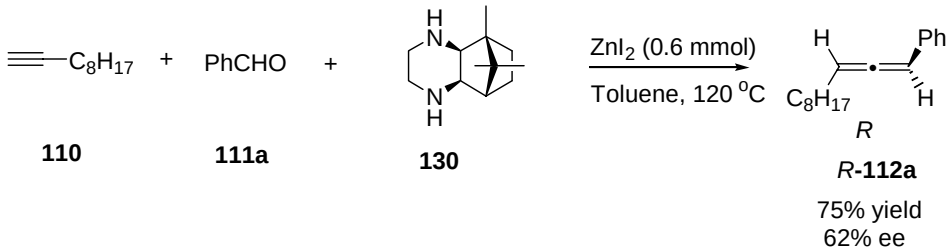
We have developed convenient methods for the synthesis of various chiral amine derivatives containing camphanyl moiety in chapter **1**. We have examined the use of a copper(II) complex of C_2-symmetric diamine in the nitroaldol reaction in Chapter **2**. We have decided to examine the use of the chiral cyclic secondary amine **130** for the preparation of chiral allenes using aromatic aldehydes, 1-alkynes and zinc halides.

Scheme 36



We have observed that the reaction of 1-decyne **110**, benzaldehyde **111a** and diamine **130** using ZnI_2 at 120 °C gave the *R*-allene in 75% yield with 62% ee (Scheme **37**).

Scheme 37

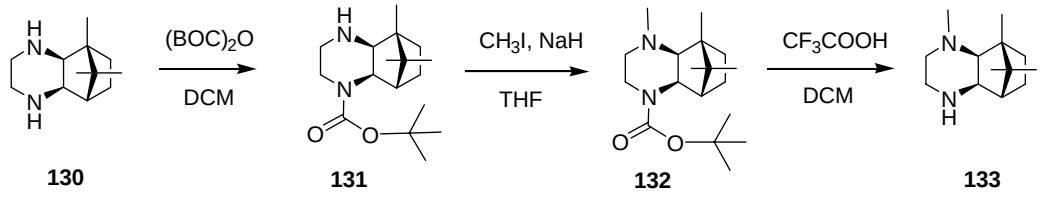


A probable reason for relatively low enantioselectivity realized using the diamine **130** may be because of different chiral discrimination abilities of the two secondary amine moieties present in the chiral diamine **130**. Perhaps, blocking one of the secondary amine moieties in the chiral amine **130** would give better results.

3.2.6.1 Synthesis of chiral cyclic diamine 133 containing camphanyl moiety 130

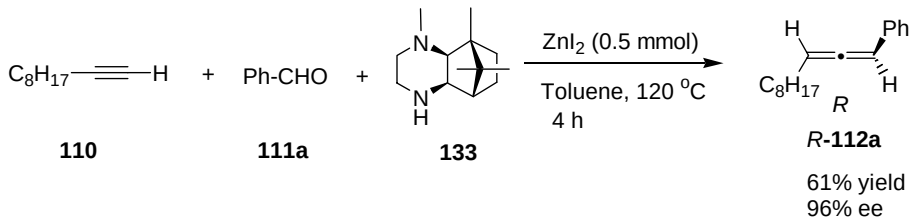
We have prepared the diamine **133** from the chiral amine **130** in three steps as outlined in scheme **38**.

Scheme 38



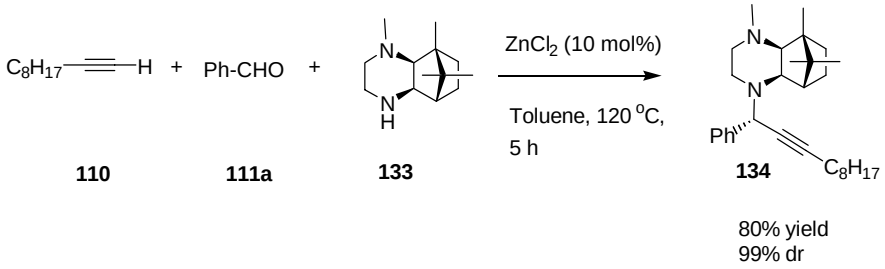
We have observed that the reaction between 1-decyne **110**, benzaldehyde **111a**, the diamine **133** and ZnI_2 (0.5 mmol) leads to formation of *R*-allene **112a** in 61% yield with up to 96% ee in 4 h at 120 ^oC (Scheme **39**).

Scheme 39



In this case, we have isolated the propargyl amine intermediate **134** in 80% yield with 99% dr using 1-decyne **110**, benzaldehyde **111a**, the amine **133** and $ZnCl_2$ (10 mol%) at 120 ^oC after 5 h (Scheme **40**). Clearly, blocking of one of the secondary amine as tertiary amine leads to the chiral *R*-allene and the corresponding propargyl amine with high enantiomeric purities. Indeed, the chiral propargyl amine isolated had *S* configuration at the propargylic position of the amine, which was also confirmed by X-ray crystal structure analysis.[38]

Scheme 40



3.2.6.2 Effect of various zinc halides using camphanyl diamine 133 in chiral allene formation

The reaction of the 1-decyne **110**, benzaldehyde **111a** and diamine **133** was also performed using $ZnCl_2$, $ZnBr_2$ and ZnI_2 (Scheme **41**, Table **3**).

Scheme 41

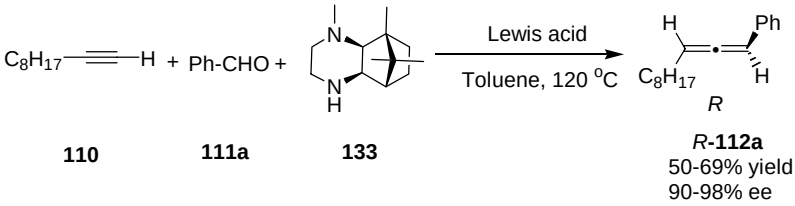


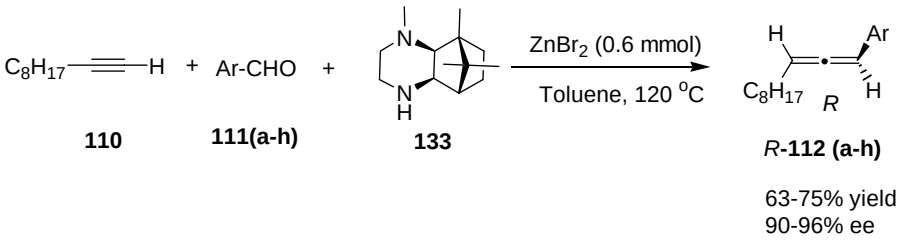
Table 3 Reaction of the 1-decyne, benzaldehyde and chiral amine **133**[a] by various zinc halides

Entry	Zinc halides	mmol	Time(h)	Yield[b] %	% ee[c]
1	$ZnCl_2$	1	6	55	96
2	$ZnCl_2$	0.7	7	50	98
3	$ZnBr_2$	0.8	4	69	94
4	$ZnBr_2$	0.6	4	65	98
5	$ZnBr_2$	0.5	6	60	98
6	ZnI_2	0.8	4	68	90
7	ZnI_2	0.6	4	60	94
8	ZnI_2	0.5	4	61	96

[a]all the reactions were carried out with amine **133** (1 mmol), 1-Decyne **110** (1 mmol), Zinc halide at 120 ^oC in toluene for 15 min. followed by addition of benzaldehyde **111a** (1 mmol) at 120 ^oC. [b]% Isolated yield of product **112a**. [c] % ee was confirmed by HPLC analysis (chiralcel OD-H column) using hexane as eluent and the compared with reported $[\alpha]_D^{25}$ value.[32]

It is evident from the Table **3**, $ZnBr_2$ (0.6 mmol) (Table **3**, Entry **4**) gave optimum results. Therefore, we have carried out the reactions with different aryl aldehydes using $ZnBr_2$ (0.6 mmol) to obtain the corresponding chiral allenes in good yields and high enantioselectivities (**Table 4**). All the optically active allenes obtained by using **133** are levorotatory, from which the absolute configurations of the major enantiomer of the allenes are assigned as *R* by the Lowe-Brewster rule and also by comparison with reported $[\alpha]_D^{25}$ values (Scheme **42**).[32, 33]

Scheme 42



110 **111(a-h)** **133**

***R*-112 (a-h)**

63-75% yield
90-96% ee

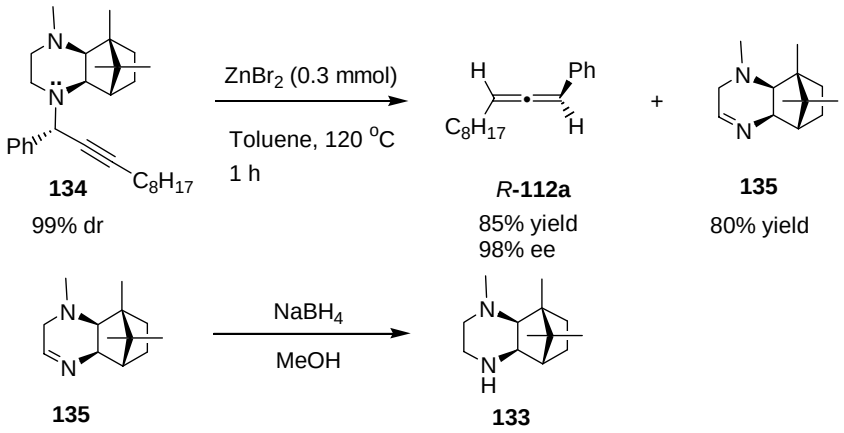
Table 4: Scope of the reaction condition with various aldehydes using **133**[a]

Entry	Ar	product	time(h)	yield[b](%)	% ee[c]
1	Ph	**112a**	5	68	98
2	p-F-Ph	**112b**	4	75	96
3	p-Cl-Ph	**112c**	4	71	90
4	p-Br-Ph	**112d**	5	72	97
5	P-CF_3-Ph	**112e**	6	70	98
6	m-Me-Ph	**112f**	7	67	90
7	m-MeO-Ph	**112g**	10	65	98
8	p-Me-Ph	**112h**	9	63	99

[a] all the reactions were carried out with **133** (1 mmol), 1-Decyne **110** (1 mmol), lewis acid at 120 °C in toluene for 15 min. followed by addition of aromatic aldehydes **111 (a-h)** (1 mmol) at 120 °C. [b]Isolated yield of products **112 (a-h).** [c] The % ee was confirmed by HPLC analysis (chiralcel OD-H, OJ-H, OB-H column) using hexane as eluent.

The propargyl amine **134** isolated in the reaction using $ZnCl_2$ at 120 °C after 5 h was found to be with 99% dr. This propargyl amine intermediate **134** (1.0 mmol) upon reaction with $ZnBr_2$ (0.3 mmol) in toluene (3 mL) for 1 h at 120 °C gave the *R*-allene in 85% yield with up to 98% ee (Scheme **43**). In this experiment, the imine **136** was also isolated in 80% yield.

Scheme 43



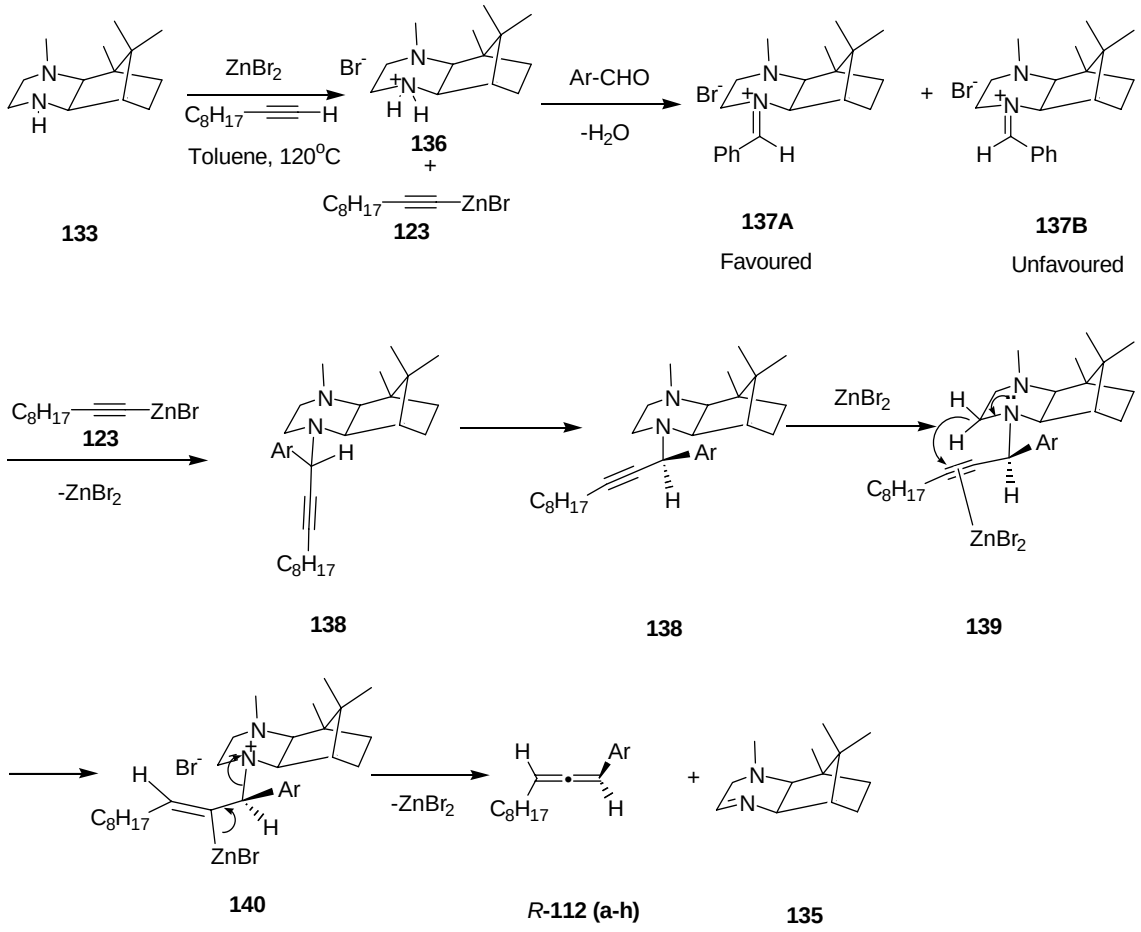
It could be converted back to the amine **133** for reuse in quantitative yield by simple reduction using $NaBH_4$/MeOH without any change in optical purity (Scheme **43**).

3.2.6.3 Tentative mechanistic pathway for the allene formation

The formation of chiral allenes can be explained by considering a tentative mechanism as outlined in **Scheme 44**. The initially formed alkynyl zinc intermediate **123** would react with the favoured conformer **137A** of the iminium ion derived from various aromatic aldehydes **111** (**a-h**) and diamine **133** to give selectively the corresponding propargylamine intermediate **138**. Thus, the formation of the single isomer is mainly due to the exclusive formation of the favoured conformer of the iminium ion **137A** compared to **137B**, because of steric repulsions with the bridged bicyclic system in the crucial step of the addition of the alkynl zinc reagent.[37] The corresponding zinc halide complexed propargylamine intermediate would then undergo intramolecular hydride shift from the camphanyl skeleton to the acetylinic moiety **139** leading to the

alkenyl zinc intermediate **140**. Subsequently, cleavage of C-N bond in intermediate **140** would result in the formation the allene **112 (a-h)** and the imine **135** (Scheme **44**).

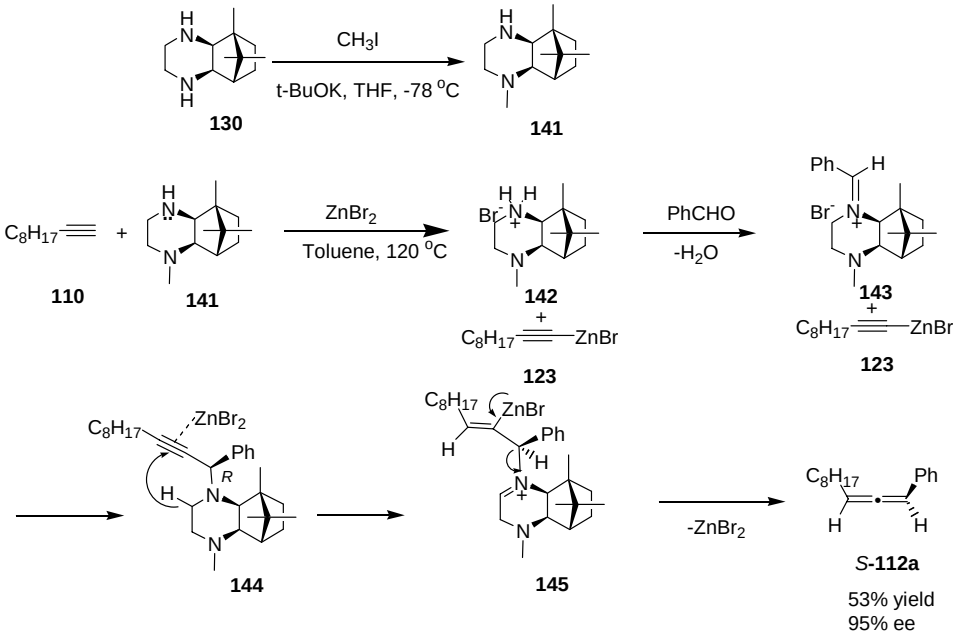
Scheme 44



Again, the creation of asymmetric center in the propargylamine intermediate and subsequent chirality transfer *via* the hydride shift from the camphanyl skeleton takes place with very high selectivity, even though the transformations are carried out at higher temperature.

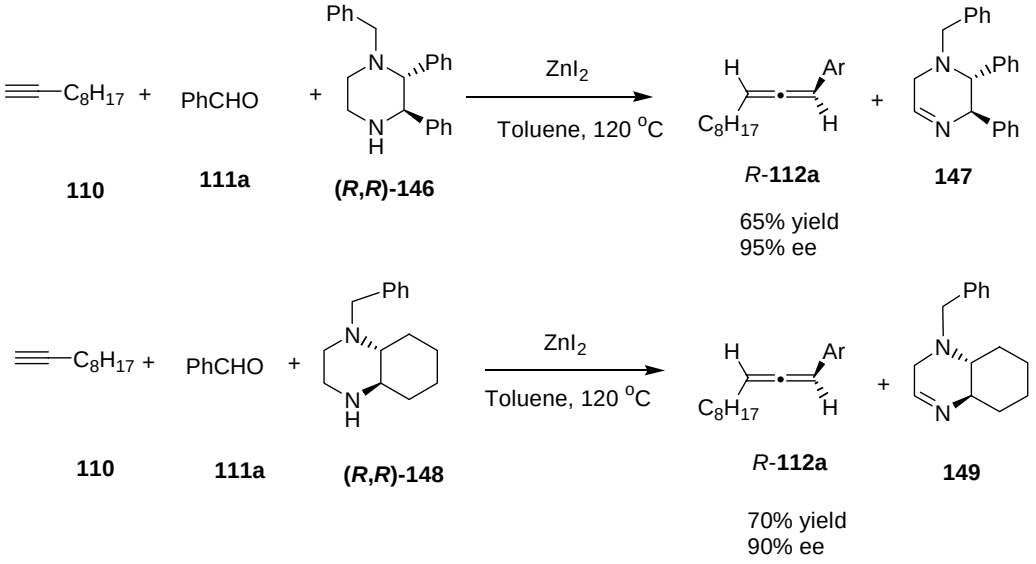
As discussed earlier, the chiral discrimination ability of the diamine **130** is relatively poor. Probably, because the two NH moieties present in the diamine **130** may have opposite chiral discriminating effect. The improvement in the results upon methylation of one of the NH in **130** confirms this. Recently, the regioisomeric diamine **141** has been prepared in this laboratory by alkylation of the less hindered NH with CH_3I.[38] As anticipated, the reaction of benzaldehyde **110**, 1-decyne **111a**, the diamine **141** and ZnI_2 (0.5 mmol) gave the *S*-allene **112a** in 53% yield with up to 95% ee, as in this case the iminium ion formed *in situ* is expected to give the propargyl amine with *R* configuration leading to *S*-allene (Scheme **45**). Indeed, the chiral propargyl amine isolated had *R* configuration at the propargylic position of the amine, which was also confirmed by X-ray crystal structure analysis.[39]

Scheme 45



It has been observed in this laboratory that the readily accessible (*R*,*R*)-2,3-diphenyl piperazine system also give similar results in the allene synthesis . For example, the reaction of 1-decyne **110**, benzaldehyde **111a** and piperazine **146** using ZnI_2 gave *R*-allene in 65% yield and 95% ee of (*R*)-allene **112a**. The transformation using the piperazine **148** also gave the (*R*)-allene **112a** in 70% yield with 90% ee (Scheme **46**).[40, 41]

Scheme 46

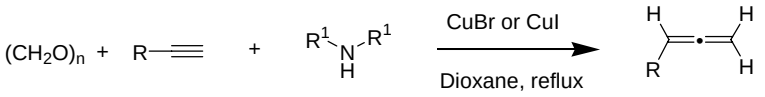


Clearly, the transformations involving creation of an asymmetric center in the intermediate propargyl amine and subsequent chirality transfer to the corresponding chiral allene is a general transformation observed in the ZnX_2 promoted reaction of 1-alkynes and aryl aldehydes with various chiral cyclic secondary amines investigated so far.

3.2.7 Copper halides using aldehyde, 1-alkyne and amine 141

It has been reported that the reaction of paraformaldehyde, 1-alkynes and secondary amines using CuBr or CuI gives the corresponding allenes in very low yields (Scheme **47**). [42]

Scheme 47

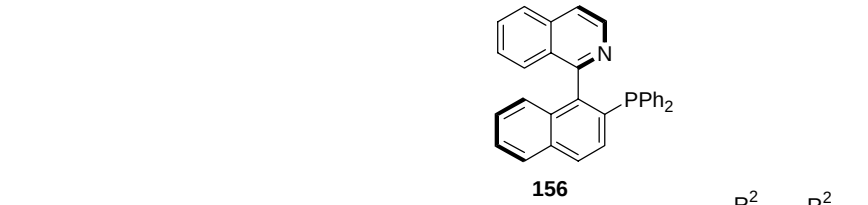


150 **151** **152**

R = C_8H_{17}, C_8H_{19}, p-C_6H_4-C_6H_4
p-NO_2-$PhCH_2OCH_2$, p-Et-PhCH(OH)CH_2
p-Cl-PhCH(OH)CH_2, p-Br-PhCH(OH)CH_2
o-Cl-PhCH(OH)CH_2
R^1 = ^{i}Pr, Cyclohexyl

Recently, it has been reported that the reaction of 1-alkyne **153**, aldehyde **154** and secondary amines **155** using CuBr in the presence of the chiral ligand **156** gives the corresponding chiral propargyl amine **157** derivatives (Scheme **48**).[34]

Scheme 48



153 **154** **155** **156** **157**

43-98% yield
32-96% ee

R^1 = Ph, n-Bu, $SiMe_3$, p-Br-Ph
R^2 = ^{i}Pr, ^{i}Bu, Ph, p-MeO-Ph, p-Br-Ph
R^3 = Bn, Allyl

We have observed that the reaction of the readily accessible CuBr and CuI with 1-decyne **110**, benzaldehyde **111a** and amine **133** in toluene at 120 ^{o}C gives *R*-allene **112a** in 30-47% yield with 96-98% ee, besides the corresponding propargyl amine in 32-45% yield with 99% dr (Scheme **49**, Table **5**).

Scheme 49

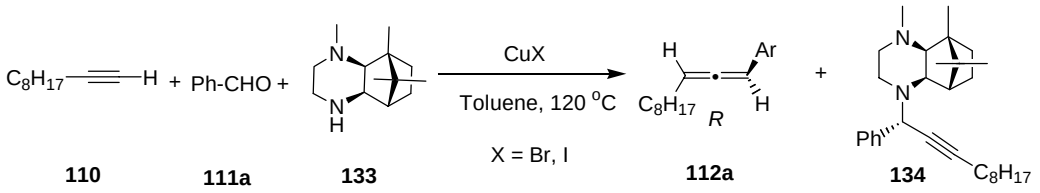


Table 5 Reaction of CuX with 1-decyne and benzaldehyde and amine **133**[a]

Entry	CuX	mmol	Time(h)	Yield[b] (%) (**112a**)	% ee[c]	Yield[d] (%) (**134**)	% dr[e]
1	CuBr	0.5	24	30	98	45	99
2	CuBr	1.0	20	41	98	35	99
3	CuI	0.5	18	35	96	40	99
4	CuI	1.0	14	47	96	32	99

[a]all the reactions were carried out with 1-decyne **110** (1 mmol), benzaldehyde **111a** (1 mmol) and amine **141** (1 mmol) at 120 ˚C using CuX. [b]Isolated yield of chiral allene **112a.** [c] The % ee was confirmed by HPLC analysis (chiralcel OD-H column) using hexane as eluent. [d]Isolated yield of chiral product **134**. [d]Isolated yield of chiral allene **134**. [e]The % dr was confirmed by using ^{1}H and ^{13}C nmr.

Also, it is of interest to note that use of lesser quantity of CuBr or CuI (Table **5**, entry **1** and 3) leads to the formation of the corresponding propargyl amine **134** in higher yields with 99% dr. Systematic studies of the effect of temperature, time and quantity of copper halides on this transformation would give more fruitful results.

3.4 Experimental Section

General Information

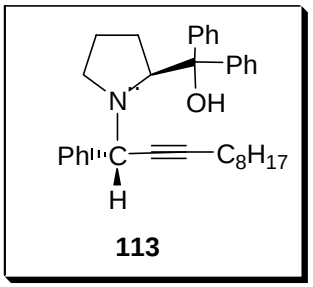
Several informations given in the section **1.4** are also applicable for the experiments described in this section. The *S*-(+)-DPP and *R*-(-)-DPP were purchased from Gerchem Labs (P) Ltd. Hyderabad. Analytical grade $ZnCl_2$ was purchased from E-Merck and the CuBr, CuI, $ZnBr_2$, ZnI_2 and D-(+)-camphor were purchased from Sigma Aldrich.

Synthesis of dipheny-[l-(1-phenyl-undec-2-ynyl)pyrrolidin-2-yl]-methanol 113

To a stirred suspension of *S*-(+)-DPP **109** (0.253 g, 1 mmol), $ZnBr_2$ (0.161 g, 0.7 mmol) and 1-decyne **110** (0.152 g, 1.1 mmol) in toluene (3 mL) was added and heated to 120 ^oC in 15 min. Freshly distilled benzaldehyde **111a** (0.105 g, 1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 ^oC room temperature after 4 h. The solvent was removed and the water (5 mL) was added . The reaction mixture was extracted with ethyl acetate (25 mL), was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100-200) using hexane and ethyl acetate (98:2) as eluent. The propargyl amine **113** was isolated in 50% yield besides the corresponding chiral allene **112a** in 10% yied (0.024 g).

Yield : 0.25 g (50%)

$[\alpha]_D^{25}$: -53.8 (*c* 1.8, $CHCl_3$)



113

IR (KBr) : (cm^{-1}) 3431, 2924, 1556, 1379, 1224

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.83-7.81 (d, *J* = 8.0 Hz, 2H), 7.64-7.62 (d, *J* = 8.0 Hz, 2H), 7.33-7.11 (m, 11H), 4.75 (s, 1H), 4.46-4.42 (m, 1H), 4.03 (s, 1H), 2.84-2.82 (m, 1H), 2.52-2.50 (m, 1H), 2.40-2.36 (m, 2H), 1.90-1.87 (m, 1H), 1.75-1.74 (m, 1H), 1.67-1.53 (m, 7H), 1.38-1.33 (m, 10H), 0.93-0.89 (m, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 148.0, 146.6, 139.8, 128.2, 128.0, 127.9, 127.1, 126.5, 126.1, 125.4, 87.7, 77.8, 75.8, 67.8, 57.3,49.1, 31.8, 29.8, 29.3, 29.2, 29.1, 28.9, 24.2, 22.6, 18.8, 14.4.

LCMS : m/z 483 (M+1)

Analysis : for $C_{34}H_{41}NO$

calcd: C, 85.13%; H, 8.61%; N, 2.92%; 0, 3.34%

found: C, 85.26%; H, 8.57%; N, 2.85%; 0, 3.32%

The configuration at the newly formed asymmetric center of the propargylic position in the compound **113** was assigned as *S* by comparison of the optical rotation value with the reported for similar compounds.[21], [34a, b]

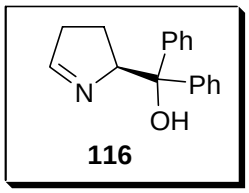
Synthesis of chiral imine 116 and allene 112a using 113

A mixture of $ZnBr_2$ (0.058 g, 0.25 mmol), propargyl amine **113** (0.240 g 0.5 mmol) in toluene (3 mL) was stirred at 120 ^oC for 3 h under N_2 atmosphere. Toluene was removed and the residue was washed with hexane (2 X 10 mL). The hexane washings were combined and the solvent was evaporated to isolate the allene **112a** (0.092 g, 80 % yield). The residue was washed with ethyl acetate (2 X 10 mL). The ethyl acetate washings were combined and concentrated under reduced pressure to isolate the required imine **116**.

(3,4-dihydro-2H-2-yl)-diphenyl-methanol 116

Yield **:** 0.09 g (75%)

$[\alpha]_D^{25}$ **:** -63.12 (*c* 0.52, $CHCl_3$)



116

IR (KBr) **:** (cm^{-1}) 3329, 2926, 1633, 1493, 1358, 748, 700

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.80-7.71 (m, Hz, 2H), 7.59 (s, 1H), 7.50-7.45 (m, 2H), 7.42-7.38 (m, 2H), 7.29-7.20 (m, 4H), 7.17-

7.12 (m, 1H), 5.10 (s, 1H), 4.26 (s, 1H), 2.77-2.51 (m, 2H), 1.83-1.72 (m, 2H)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 179.2, 145.9, 144.4, 129.0, 128.3, 127.0, 126.8, 125.4, 125.2, 79.0, 78.5, 37.5, 21.0.

LCMS **:** m/z 252 (M+1)

Analysis **:** for $C_{17}H_{17}NO$

calcd: C, 81.24%; H, 6.82%; N, 5.57%; 0, 6.37%

found: C, 81.35%; H, 6.73%; N, 5.48%; 0, 6.44%

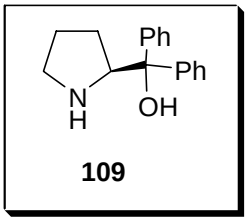
General procedure for the reduction of imine 116

To a stirred suspension of imine **116** (0.13 g, 0.5 mmol) in methanol (10 mL) was added $NaBH_4$ (0.08 g, 2 mmol) during 5 min. at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 0.5 h. Methanol was removed. Water (5 mL) and DCM (10 mL) were added. The DCM layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to isolate the *S*-DPP **109**.[31]

(*S*)-α, α-diphenylprolinol 109

Yield **:** 0.11 g (85%)

$[\alpha]_D^{25}$ **:** +66.5 (*c* 0.51, $CHCl_3$)

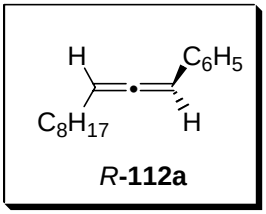


109

General procedure for the synthesis of chiral allenes using (*S*)-DPP 109

A stirred suspension of *S*-(+)- DPP **106** (0.25 g, 1 mmol), $ZnBr_2$ (0.16 g, 0.7 mmol) and 1-decyne **110** (0.152 g, 1.1 mmol) in toluene (3 mL) was heated to 120 ^oC during 15 minutes. Freshly distilled aromatic aldehyde **111 (a-h)** (1 mmol) was added at 25 ^oC to this mixture and the contents were refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 ^oC after the required time. After evaporation of toluene, column chromatography of the residue on silica gel (100-200) using hexane as eluent to afforded the chiral allenes **112 (a-h)**.

(*R*)-1-Phenyl-1,2-undecadiene 112a



***R*-112a**

Yield : 0.15 g (65 %)

$[\alpha]_D^{25}$: -225.1 (*c* 0.50, $CHCl_3$, 98% ee), [lit. $[\alpha]_D^{20}$ = +298.8 (*c 0*.60, EtOH, 99% *ee*(*S*))][32]

IR (KBr) : (cm^{-1}) 2926, 2854, 1950, 1599, 1460, 773

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.34-7.28 (m, 4H), 7.24-7.20 (m, 1H), 6.19-6.14 (m, 1H), 5.64-5.58 (m, 1H), 2.19-2.15 (m, 2H), 1.56-1.51 (m, 2H), 1.41-1.32 (m, 12H), 0.95-0.91 (m, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 205.1, 135.1, 128.5, 126.5, 95.5, 94.5,

31.8, 29.4, 29.3, 29.1, 28.7, 22.6, 14.1

LCMS : m/z 229 (M+1)

Analysis : for $C_{17}H_{24}$

calcd: C, 89.41%; H, 10.59%

found: C, 89.32%; H, 10.51%

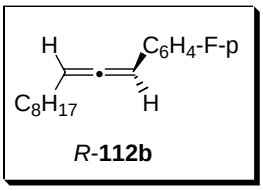
Enantiomeric purity 98% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 4.7 min. (*R*) and 5.2 min. (*S*)].

The above procedure was followed for the preparation of other allenes **112(b-h)**.

(*R*)-1-(4-Fluorophenyl)-1,2-undecadiene 112b

Yield : 0.17 g (70%)

$[\alpha]_D^{25}$: -146.5 (*c* 0.50, $CHCl_3$)



R-**112b**

IR (KBr) : (cm^{-1}) 2926, 2854, 1950, 1602, 1508, 1228, 837

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.26-7.22 (m, 2H), 7.01-6.96 (m, 2H), 6.11-6.08 (m, 1H), 5.57-5.56 (m, 1H), 2.15-2.09 (m, 2H), 1.50-

1.44 (m, 2H), 1.37-1.28 (m, 10H), 0.98-0.89 (m, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 204.9, 162.9, 160.5, 131.1, 127.9, 127.8, 115.5, 115.3, 95.3, 93.9, 31.8, 29.4, 29.3, 29.2, 29.1, 28.7, 22.6, 14.1

LCMS : m/z 247 (M+1)

Analysis : for $C_{17}H_{23}F$

calcd: C, 82.88%; H, 9.41%; F, 7.71%

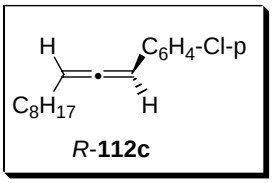
found: C, 82.65%; H, 9.36%; F, 7.99%

Enantiomeric purity 92% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 4.4 min. (S) and 4.8 min. (*R*)].

(*R*)-1-(4-Chlorophenyl)-1,2-undecadiene 112c

Yield : 0.17 g (65%)

$[\alpha]_D^{25}$: -167.8 (*c* 0.50, $CHCl_3$)



R-**112c**

IR (KBr) : (cm^{-1}) 2926, 2854, 1950,1491, 831

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.27-7.20 (m, 4H), 6.09-6.06 (m, 1H), 5.60-

5.55 (m, 1H), 2.16-2.09 (m, 2H), 1.51-1.44 (m, 2H), 1.37- 1.26 (m, 10H), 0.92-0.87 (m, 3H)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.2, 133.7, 132.1, 128.6, 127.7, 95.5, 93.7, 31.8, 29.3, 29.3, 29.1, 28.6, 22.6, 14.1

LCMS **:`** m/z 263 (M+1)

Analysis **:** for $C_{17}H_{23}Cl$

calcd: C, 77.69%; H, 8.82%; Cl, 13.49%

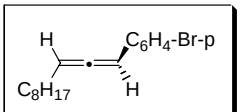
found: C, 77.52%; H, 8.76%; Cl, 13.72%

Enantiomeric purity 92% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 3.3 min. (*S*) and 4.2 min. (*R*)].

(*R*)-1-(4-Bromophenyl)-1,2-undecadiene 112d

Yield **:** 0.21 g (68%)

$[\alpha]_D^{25}$ **:** -139.2 (*c* 0.50, $CHCl_3$)



R-**112d**

IR (KBr) **:** (cm^{-1}) 2926, 2858, 1950, 1599, 1487, 829

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.44-7.41 (m, 2H), 7.18-7.15 (m,

2H), 6.10-6.07 (m, 1H), 5.61-5.56 (m, 1H), 2.17-2.11 (m, 2H), 1.51-1.46 (m, 2H), 1.39-1.28 (m, 10H), 0.92-0.89 (m, 3H)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.2, 134.2, 131.6, 128.0, 120.1, 95.6, 93.7, 31.8, 29.3, 29.3, 29.1, 29.1, 28.6, 22.6, 14.1

LCMS **:** m/z 307 (M+1)

Analysis **:** for $C_{17}H_{23}Br$

calcd: C, 66.45%; H, 7.54%; Br, 26.0%

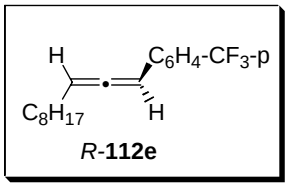
found: C, 66.32%; H, 7.51%; Br, 26.17%

Enantiomeric purity 92% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 3.5 min. (S) and 4.6 min. (*R*)].

(*R*)-1-(4-Trifluoromethylphenyl)-1,2-undecadiene 112e

Yield **:** 0.18 g (60%)

$[\alpha]_D^{25}$ **:** -142.5 (*c* 0.55, $CHCl_3$)



R-**112e**

IR (KBr) **:** (cm^{-1}) 2928, 2856, 1950, 1616, 1325, 844

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.55-7.52 (d, *J* = 12.0 Hz, 2H), 7.38-

7.36 (d, J = 8.0 Hz, 2H), 6.16-6.13 (m, 1H), 5.66-5.62 (m, 1H), 2.18-2.12 (m, 2H), 1.54-1.45 (m, 2H), 1.38-1.27 (m, 10H), 0.89-0.88 (m, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 206.1, 139.1, 131.6, 126.6, 125.6, 125.4, 125.4, 95.6, 93.8, 31.8, 29.3, 29.2, 29.1, 29.0, 28.5, 22.6, 14.0

LCMS : m/z 296 (M+1)

Analysis : for $C_{18}H_{23}F_3$

calcd: C, 72.95%; H, 7.82%; F, 19.23%

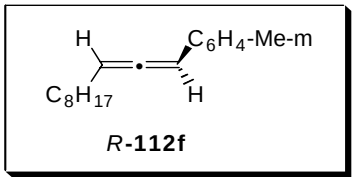
found: C, 72.85%; H, 7.76%; F, 19.39%

Enantiomeric purity 82% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 15.4 min. (*S*) and 17.0 min. (*R*)].

(*R*)-1-(3-Methylphenyl)-1,2-undecadiene 112f

Yield : 0.14 g (60%)

$[\alpha]_D^{25}$: -125.3 (*c* 0.50, $CHCl_3$)



R-**112f**

IR (KBr) : (cm^{-1}) 2957, 2926, 1950, 1599, 1494, 690

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.28-7.22 (m, 1H), 7.16-7.14 (d, J = 8.0

Hz, 2H), 7.05-7.04 (d, J = 4 Hz, 1H), 6.16-6.13 (m, 1H), 5.62- 5.57 (m, 1H), 2.38 (s, 3H), 2.20-2.15 (m, 2H), 1.56-1.52 (m, 2H), 1.43-1.32 (m, 10H), 0.94-0.92 (t, J = 8.0 Hz, 3H)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.1, 138.1, 135.0, 128.4, 127.4, 127.2, 123.7, 94.9, 94.5, 31.9, 29.4, 29.3, 29.2, 28.8, 22.7, 21.4, 14.1

LCMS **:** m/z 243 (M+1)

Analysis **:** for $C_{18}H_{26}$

calcd: C, 89.19%; H, 10.81%

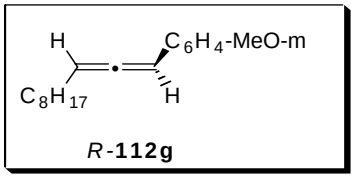
found: C, 89.06%; H, 10.75%

Enantiomeric purity 90% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.0 mL/min., 254 nm, retention times : 5.8 min. (*R*) and 8.3 min. (*S*)].

(*R*)-1-(3-Methoxy-phenyl)-1,2-undecadiene 112g

Yield **:** 0.15 g (58%)

$[\alpha]_D^{25}$ **:** -193.5 (c 0.33, $CHCl_3$)



R-**112g**

IR (KBr) : (cm^{-1}) 3055, 2926, 2854, 1946, 1508, 1325, 817, 746

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.24-7.20 (m, 1H), 6.90-6.86 (m, 2H), 6.76-6.74 (m, 1H), 6.12-6.10 (m, 1H), 5.58-5.57 (m, 1H), 3.81 (s, 3H), 2.17-2.12 (m, 2H), 1.53-1.46 (m, 2H), 1.39-1.28 (m, 10H), 0.91-0.87 (t, J = 12.0 Hz, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 205.2, 159.8, 136.7, 129.4, 119.3, 112.4, 111.7, 95.2, 94.5, 55.1, 31.8, 29.4, 29.3, 29.2, 28.7, 22.6, 14.1

LCMS : m/z 259 (M+1)

Analysis : for $C_{18}H_{26}O$

calcd: C, 83.67%; H, 10.14%; O, 6.19%

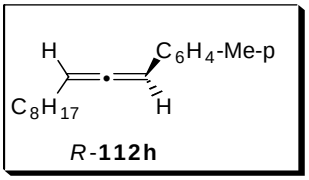
found: C, 83.45%; H, 10.06%; O, 6.49%

Enantiomeric purity 90% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:^{i}PrOH/100:0; flow rate 1.0 mL/min., 254 nm, retention times : 7.3 min. (*R*) and 9.5 min. (*S*)].

(*R*)-1-(4-Methyl-phenyl)-1,2-undecadiene 112h

Yield : 0.122 g (50%)

$[\alpha]_D^{25}$: -151.5 (*c* 0.51, $CHCl_3$)



R-**112h**

IR (KBr) : (cm^{-1}) 2924, 2854, 1948, 1512, 1464, 821

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.20-7.18 (d, *J* = 8.0 Hz, 2H), 7.12-7.10 (d, *J* = 8.0 Hz, 2H), 6.12-6.09 (m, 1H), 5.55-5.54 (m, 1H), 2.36 (s, 3H), 2.15-2.10 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.27 (m, 10H), 0.94-0.90 (m, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 204.8, 136.3, 132.1, 129.2, 126.4, 95.0, 94.3, 31.8, 29.4, 29.3, 29.2, 28.8, 22.7, 21.1, 14.1

LCMS : m/z 243 (M+1)

Analysis : for $C_{18}H_{26}$

calcd: C, 89.19%; H, 10.81%

found: C, 89.26%; H, 10.26%

Enantiomeric purity 90% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, heptane:^{i}PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times : 5.1 min. (*R*) and 5.7 min. (*S*)]

General procedure for the synthesis of chiral allene using *R*-DPP 109

A stirred suspension of (*R*)-DPP **116** (0.253 g, 1 mmol), $ZnBr_2$ (0.116 g, 0.8 mmol) and 1-decyne **110** (0.152 g, 1.1 mmol) in toluene (3 mL) was heated to 120 ^oC during 15 minutes. Freshly distilled benzaldehyde **111a** (0.105 g, 1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 oC after required time. After evaporation of the toluene, the column chromatography of the residue on silica gel 100-200 using hexane as eluent afforded the chiral allene **112 a**.

(*S*)-1-Phenyl-1,2-undecadiene 112a

Yield **:** 0.132 g, (60%)

$[\alpha]_D^{25}$ **:** +205.5 (*c* 0.5, $CHCl_3$, 90% ee), [lit. $[\alpha]_D^{20}$ = +298.8 (*c 0*.60, EtOH, 99% *ee*(*S*))][32]

General procedure for the synthesis of chiral allenes using diamine 130

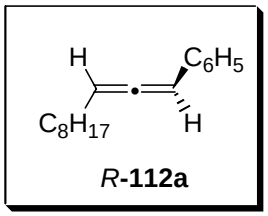
To a stirred suspension of diamine **130** (0.194 g, 1 mmol), $ZnBr_2$ (0.162 g 0.7 mmol) and 1-decyne **110** (0.152 g, 1.1 mmol) in toluene (3 mL) was heated to 120 ^oC about 15 minutes. Freshly distilled benzaldehyde **111a** (0.105 g, 1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 ^oC after 12 h. After evaporation of the toluene, the column chromatography of the residue on silica gel (100-200) using hexane as eluent afforded the chiral allene **112 a**.

(*R*)-1-phenyl-1,2-undecadiene 112a

Yield **:** 0.171 g, (75%)

$[\alpha]_D^{25}$: -142.5 (*c* 0.55, $CHCl_3$, 62% ee),

[lit. $[\alpha]_D^{20}$ = +298.8 (*c 0*.60, EtOH, 99% *ee*(*S*))][32]



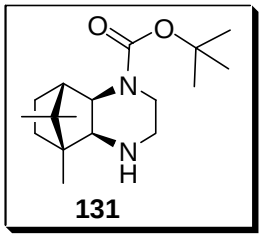
***R*-112a**

Preparation of 5,9,9-Trimethyl-octahydro-5,8-methano-quinzoline-1-carboxylic acid tert- butyl ester 131

To a stirred solution of diamine **130** (1.94 g, 10 mmol) in dry DCM (20 ml) at 0 ^oC, $(BOC)_2O$ (1.09 g, 5 mmol) dry DCM (10 mL) was added carefully over a period of 0.5 h and the contents were stirred further for 12 h at 25 ^oC. The DCM was evaporated under reduced pressure and the amide **131** was isolated by column chromatography on silica gel (100-200) using hexane and ethyl acetate (1:1) as eluent.

Yield 2.51g (85%)

$[\alpha]_D^{25}$ -68.2 (*c* 0.55, $CHCl_3$)



131

IR (KBr) : (cm^{-1}) 3335, 2953, 1689, 1369, 1172, 1032, 777

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.56-3.53 (d, *J* = 12.0 Hz,1H), 3.44-3.41(d, *J* = 12.0 Hz, 1H), 3.18-3.17 (m, 1H), 3.03-2.96 (m, 2H), 2.67-2.63 (m, 1H), 2.06 (s, 1H), 1.67-1.65 (m, 1H),1.53-1.52 (m,

1H), 1.47 (s, 9H), 1.15 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$,δ ppm) 156.2, 79.3, 66.1, 58.7, 48.4, 45.5, 43.0, 35.5, 28.5, 26.6, 22.0, 21.3, 11.6.

LCMS : m/z 295 (M+1)

Analysis : for $C_{17}H_{30}N_2O_2$

calcd: C, 69.35; H, 10.27; N, 9.51, 0, 10.87

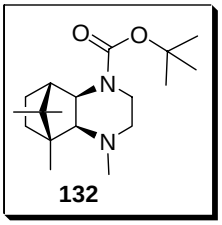
found: C, 69.21; H, 10.35; N, 9.45, 0, 10.99

4,5,9,9-Trimethyl-octahydro-5,8-methano-quinzoline-1-carboxylic acid tertiary butyl ester 132

To a stirred solution of amide **131** (2.94 g, 10 mmol) and NaH (0.360 g, 15 mmol) in dry THF (20 mL) at 0 ^{o}C, CH_3I (2.1 g, 15 mmol) in dry THF (10 mL) was added carefully and the contents were stirred further for 2 h at 25 ^{o}C. Water (5 mL) was added followed by diethyl ether (30 mL). The organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The amine **132** was isolated in 90% yield by column chromatography on silica gel (100-2000 using hexane and ethyl acetate (9:1) as eluent.

Yield : 2.80 g (90%)

$[\alpha]_D^{25}$: -61.2 (*c* 0.52, $CHCl_3$)



132

IR (KBr) : (cm^{-1}) 2953, 1695, 1454, 1367, 1170, 869, 775

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.69-3.60 (m, 2H), 3.35-3.32 (m, 1H), 2.67-2.65 (m, 1H), 2.24 (s, 3H), 1.87 (s, 1H), 1.67 (s, 1H), 1.45 (s, 9H), 1.04 (s, 5H), 0.99 (s, 3H), 0.77 (s, 3H)

^{13}C NMR : (100 MHz, $CDCl_3$,δ ppm) 156.0, 79.4, 74.8, 59.0, 54.5, 53.3, 49.8, 48.5, 45.6, 41.8, 36.2, 28.5, 26.6, 22.1, 20.4, 14.6.

LCMS : m/z 309 (M+1)

Analysis : for $C_{18}H_{32}N_2O_2$

calcd: C, 70.09; H, 10.46; N, 9.08; 0, 10.37

found: C, 70.21; H, 10.35; N, 9.16; 0, 10.28

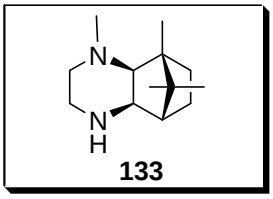
(+)-1, 8, 9, 9–Tetramethyl–decahydro-5, 8–methano-quinazoline 133

To a stirred solution of amide **132** (3.90 g, 10 mmol) in dry DCM (10 mL) at 0 ^oC, CF_3COOH (5 mL) was added carefully and the contents were stirred further for 12 h at 25

^{o}C. Saturated aqueous $NaHCO_3$ (10 mL) was carefully added followed by DCM (25 mL). The DCM layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The amine **133** was isolated in 93% yield by column chromatography of the residue on silica gel (100-200) using chloroform and methanol (9:1) as eluent.

Yield **:** 1.95 g (93%)

$[\alpha]_D^{25}$ **:** +22.7 (*c* 0.53, $CHCl_3$)



133

IR (KBr) **:** (cm^{-1}) 3281, 3076, 2934, 1554, 1485, 1415, 1379, 692

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 3.12-3.09 (m, 1H), 2.77-2.73 (m, 2H), 2.64-2.58 (m, 1H), 2.25 (s, 3H), 1.91-1.63 (m, 6H), 1.41 (s, 3H), 1.25-1.11(m, 3H), 1.06 (s, 3H), 0.83 (s, 3H)

^{13}C NMR **:** (100 MHz, $CDCl_3$,δ ppm) 79.8, 61.6, 54.9, 50.3, 50.0, 47.2, 46.1, 41.9, 37.4, 27.2, 22.2, 21.0, 15.8.

LCMS **:** m/z 209 (M+1)

Analysis **:** for $C_{13}H_{24}N_2$

calcd: C, 74.94; H, 11.61; N, 13.45

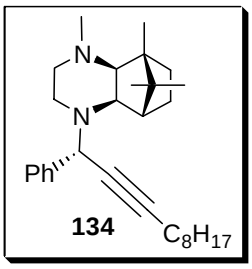
found: C, 74.85; H, 11.56; N, 13.56

4,5,9,9–Tetramethyl–1-(1-phenyl-undec-2-ynyl)-decahydro-5,8–methano quinazoline 134

A stirred suspension of amine **133** (0.21 g, 1 mmol), $ZnCl_2$ (0.01 g, 0.1 mmol) and 1-decyne **110** (0.15 g, 1.1 mmol) in toluene (3 mL) was heated to 120 ^oC for 15 min. Freshly distilled benzaldehyde **111a** (0.11 g, 1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 ^oC after 5 h. Toluene was removed, water (5 mL) was added and the extracted with DCM (25 mL). The DCM layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product **134** was purified by column chromatography of the residue on silica gel (100-200) using hexane:ethyl acetate (95:5) as eluent.

Yield **:** 0.352g (80%)

$[\alpha]_D^{25}$ **:** -26.7 (*c* 0.35,$CHCl_3$)



IR (KBr) **:** (cm^{-1}) 2953, 2930, 2235, 1599, 1452, 1390, 709

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.63 (d, *J* = 8.0 Hz, 2H), 7.31-7.23 (m, 3H), 4.99 (s, 1H), 3.03-3.01 (d, *J* = 8.0 Hz, 1H), 2.73-2.68 (m, 1H), 2.51-2.49 (m, 1H), 2.40-2.31 (m, 3H), 2.27 (s, 3H), 2.20-2.18 (d, *J* = 4.0 Hz, 1H), 1.92-1.91 (d, *J* = 4.0 Hz, 1H) 1.80-1.71 (m, 1H), 1.61-1.56 (m, 4H), 1.52-1.48 (m, 6H), 1.48-1.30 (m, 9H), 1.21-1.12 (m, 3H), 1.09 (s, 3H), 0.98-0.90 (m, 4H), 0.85 (s, 3H)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δ ppm) 139.7, 128.2, 127.9, 126.9, 88.0, 78.2, 75.8, 65.5, 57.7, 54.5, 50.3, 48.2, 47.4, 47.3, 42.6, 37.2, 31.9, 29.3, 29.1, 28.9, 26.2, 22.7, 22.2, 21.2, 18.7, 10.8, 10.6.

LCMS **:** m/z 436 (M+1)

Analysis **:** for $C_{30}H_{46}N_2$

calcd: C, 82.89; H, 10.67; N, 6.44

found: C, 82.75; H, 10.56; N, 6.53

Preparation of chiral imine 135 and allene 112a using 134

A mixture of $ZnBr_2$ (0.069 g, 0.3 mmol), propargyl amine **134** (0.436 g, 1.0 mmol) in toluene (3 mL) was stirred at 120 ^oC for 1 h under N_2 atmosphere. The contents were brought to 25 ^oC and toluene was removed. The residue was washed with hexane (2 X 10 mL). The hexane washings were concentrated to isolate the allene **112a** (0.192 g, 85 % yield) with 98% ee. The residue was washed with ethyl acetate (2 X 10 mL) and the combined ethyl acetate layers were concentrated under reduced pressure to obtain the imine **135**.

General procedure for the reduction of imine 135

To a stirred suspension of imine **135** (0.11 g, 0.5 mmol) in methanol (10 mL) at 0 ^oC, $NaBH_4$ (0.08 g, 2 mmol) was added for about 5 min. The reaction mixture was stirred at 25 ^oC for 1.5 h. Methanol was removed. Water (5 mL) and DCM (5 mL) were added. The DCM layer was separated and dried over anhydrous Na_2SO_4, filtered and the DCM layer was concentrated under reduced pressure. The diamine **133** was isolated in 75% yield by column chromatography of the residue on silica gel (100-200) using chloroform and methanol (99:1) as eluent.

Yield **:** 0.08 g (75%)

$[\alpha]_D^{25}$ **:** +20.2 (*c* 0.53,$CHCl_3$)

General procedure for the synthesis of chiral allenes using the diamine 133

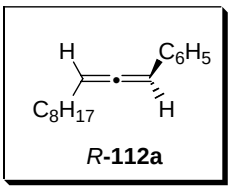
A stirred suspension of diamine **133** (0.21 g, 1 mmol), $ZnBr_2$ (0.14 g 0.6 mmol) and 1-decyne **110** (0.15 g, 1.1 mmol) in toluene (3 mL) was heated to 120 ^oC for 15 minutes. Freshly distilled aromatic aldehyde **111(a-h)** (1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 ^oC under nitrogen atmosphere. The reaction mixture was brought to 25 ^oC after required time. After evaporation of toluene, column chromatography of the residue on silica gel (100-200) using hexane as eluent afforded the chiral allenes **112 (a-h)**.

(*R*)-1-Phenyl-1,2-undecadiene 112a

Yield : 0.159 g (69%)

$[\alpha]_D^{25}$: -225.1 (*c* 0.50, $CHCl_3$, 98% ee),

[lit. $[\alpha]_D^{20}$ = +298.8 (*c* 0.60, EtOH,99% *ee*(*S*))][32]

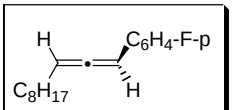


R-**112a**

(*R*)-1-(4-Fluoro-phenyl)-1,2-undecadiene 112b

Yield : 0.187 g (75%)

$[\alpha]_D^{25}$: -156.3 (*c* 0.52, $CHCl_3$, 96% ee)

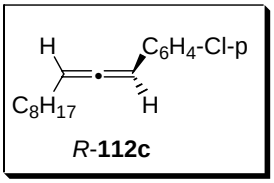


R-**112b**

(*R*)-1-(4-Chloro-phenyl)-1,2-undecadiene 112c

Yield : 0.188 g (71%)

$[\alpha]_D^{25}$: -167.3 (*c* 0.65, $CHCl_3$, 90% ee)

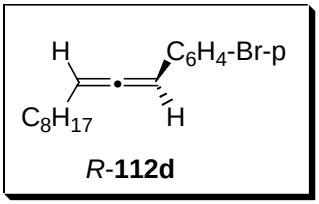


R-**112c**

(*R*)-1-(4-Bromo-phenyl)-1,2-undecadiene 112d

Yield : 0.221 g (72%)

$[\alpha]_D^{25}$: -150.3 (*c* 0.56, $CHCl_3$, 98% ee)

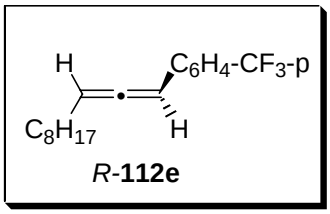


R-**112d**

(*R*)-1-(4-Trifluoromethane-phenyl)-1,2-undecadiene 112e

Yield : 0.211 g (70%)

$[\alpha]_D^{25}$: -170.1(*c* 0.45, $CHCl_3$, 98%ee)

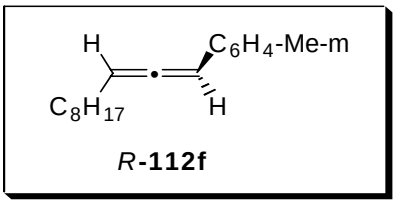


R-**112e**

(*R*)-1-(3-Methyl-phenyl)-1,2-undecadiene 112f

Yield : 0.163 g (67%)

$[\alpha]_D^{25}$: -125.3 (*c* 0.51, $CHCl_3$, 90% ee)

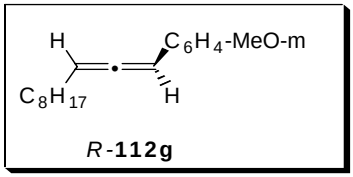


R-**112f**

(*R*)-1-(3-Methoxy-phenyl)-1,2-undecadiene 112g

Yield : 0.171 g (65%)

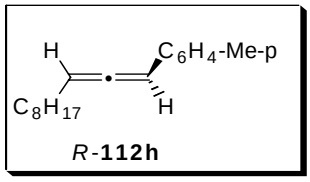
$[\alpha]_D^{25}$: -202.7 (*c* 0.53, $CHCl_3$, 98% ee)



(*R*)-1-(4-Methyl-phenyl)-1,2-undecadiene 112h

Yield : 0.154 g (63%)

$[\alpha]_D^{25}$: -168.4 (*c* 0.53, $CHCl_3$, 99% ee)



The physical constants and spectral data were identical to the data of samples obtained in the previous experiments.

Representative procedure for the synthesis of chiral allenes using copper halides

To a stirred suspension of diamine **133** (0.21 g, 1 mmol), CuBr (0.07 g, 5 mmol) and 1-decyne **110** (0.15 g, 1.1 mmol) in toluene (3 mL), freshly distilled benzaldehyde **111a** (0.105 g, 1 mmol) was added at 25 ^oC. The contents were stirred at 50 ^oC for 4 h and refluxed at 120 ^oC for 24 h. The reaction mixture was brought to 25 ^oC. Toluene was removed, water (5 mL) and DCM (15 mL) were added. The DCM layer was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (100-200) coiumn using hexane and ethyl acetate (9:1) as

eluent to isolate the chiral allene **112a** (yield : 0.07 g, 30% and 98% ee) and the propargyl amine **134** (yield : 0.21 g, 45% and 99% dr) (Table **5**, entry **1**).

The physical constants and spectral data were identical to the data of samples obtained in previous section.

3.5 References

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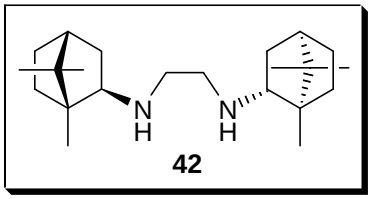
Appendix I

Representative Spectra

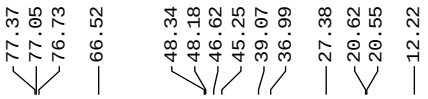
Spectrum No. 1 (Chapter I, Section 1.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

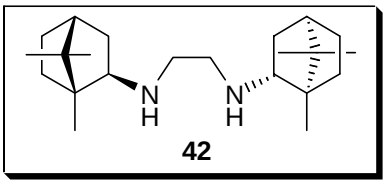


42

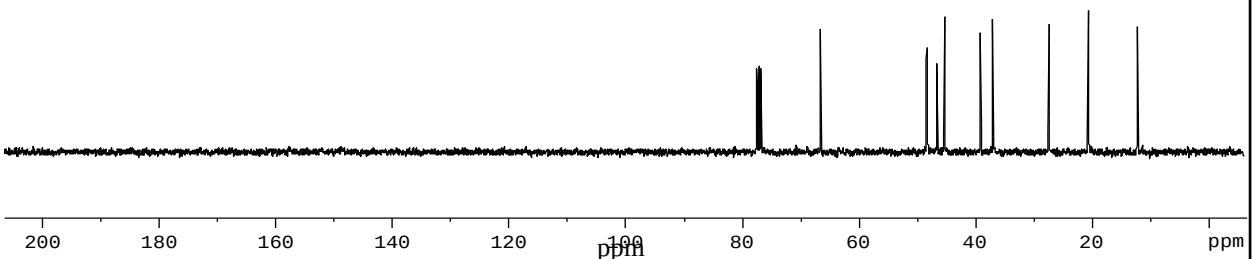
ppm

Spectrum No. 2 (Chapter I, Section 1.2.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



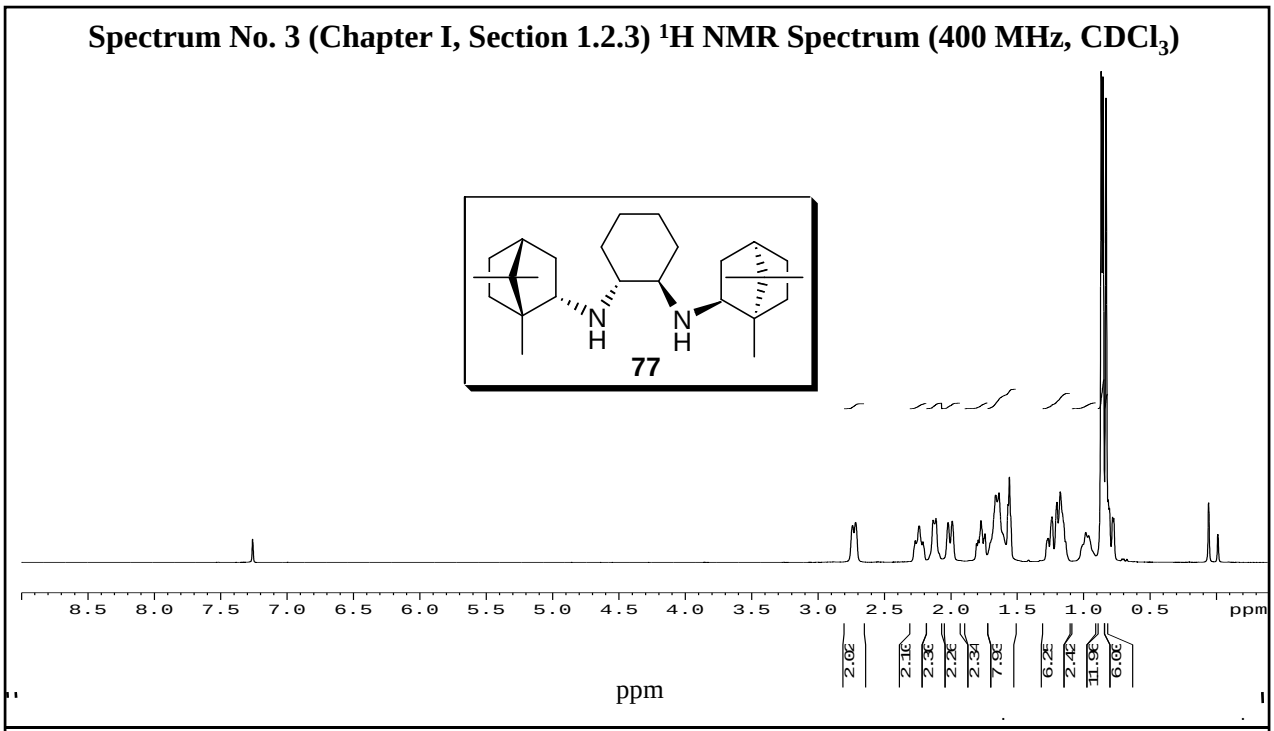


42

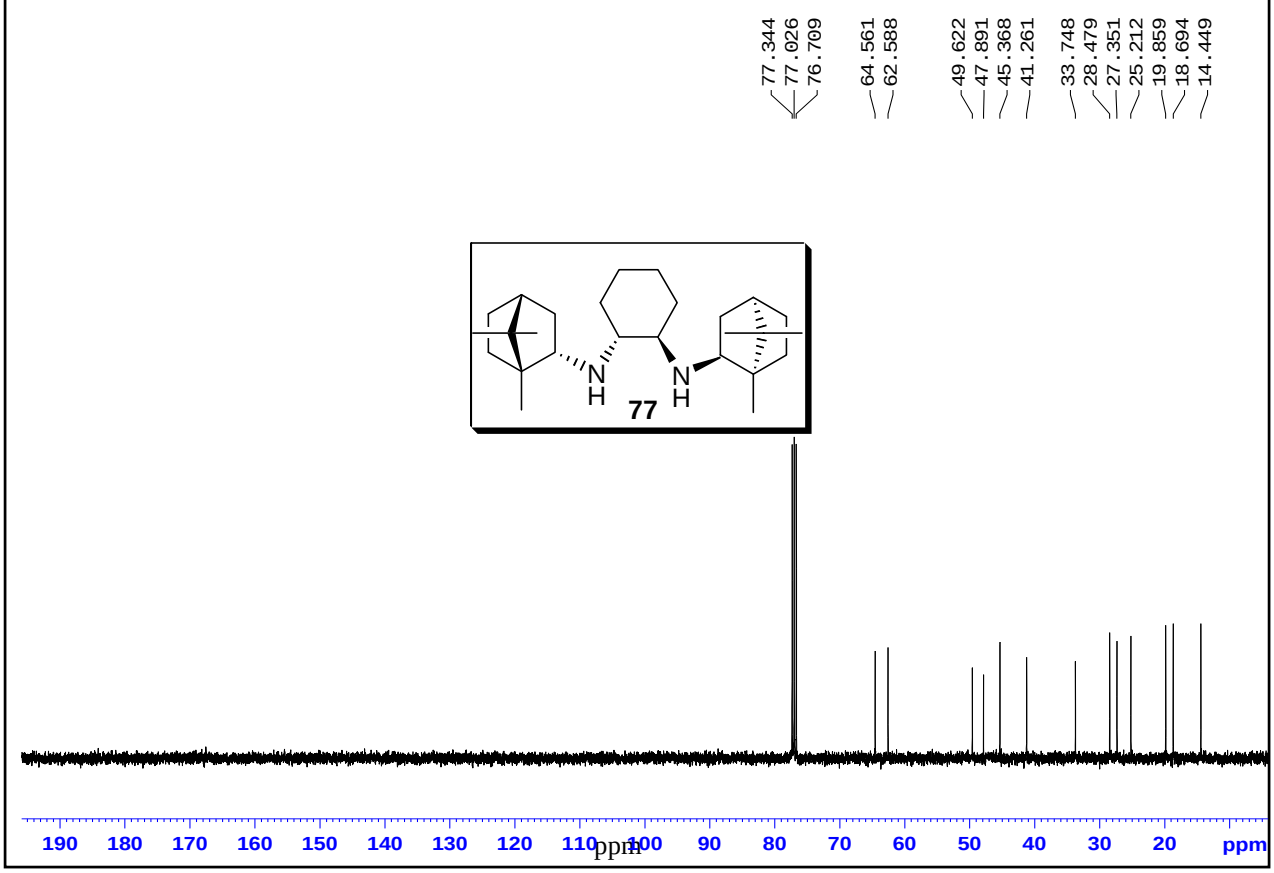


ppm

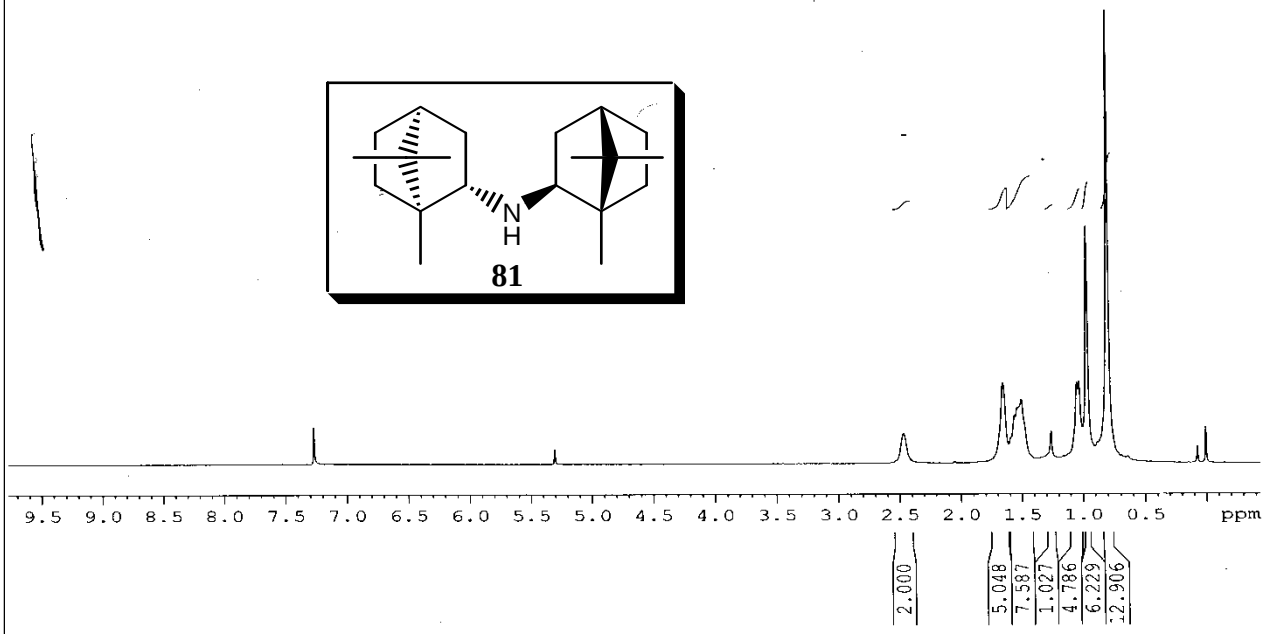
Spectrum No. 3 (Chapter I, Section 1.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 4 (Chapter I, Section 1.2.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

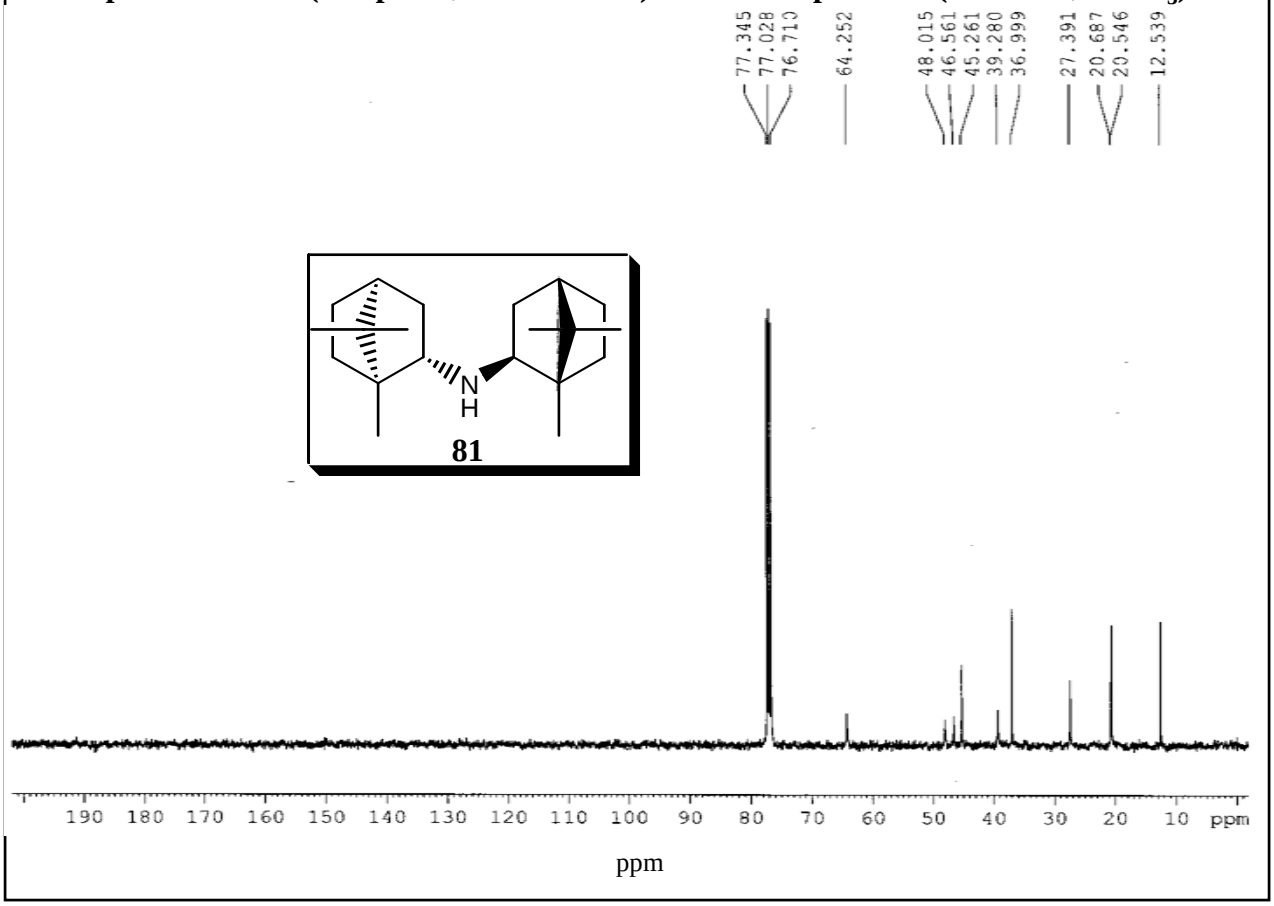


Spectrum No. 5 (Chapter I, Section 1.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



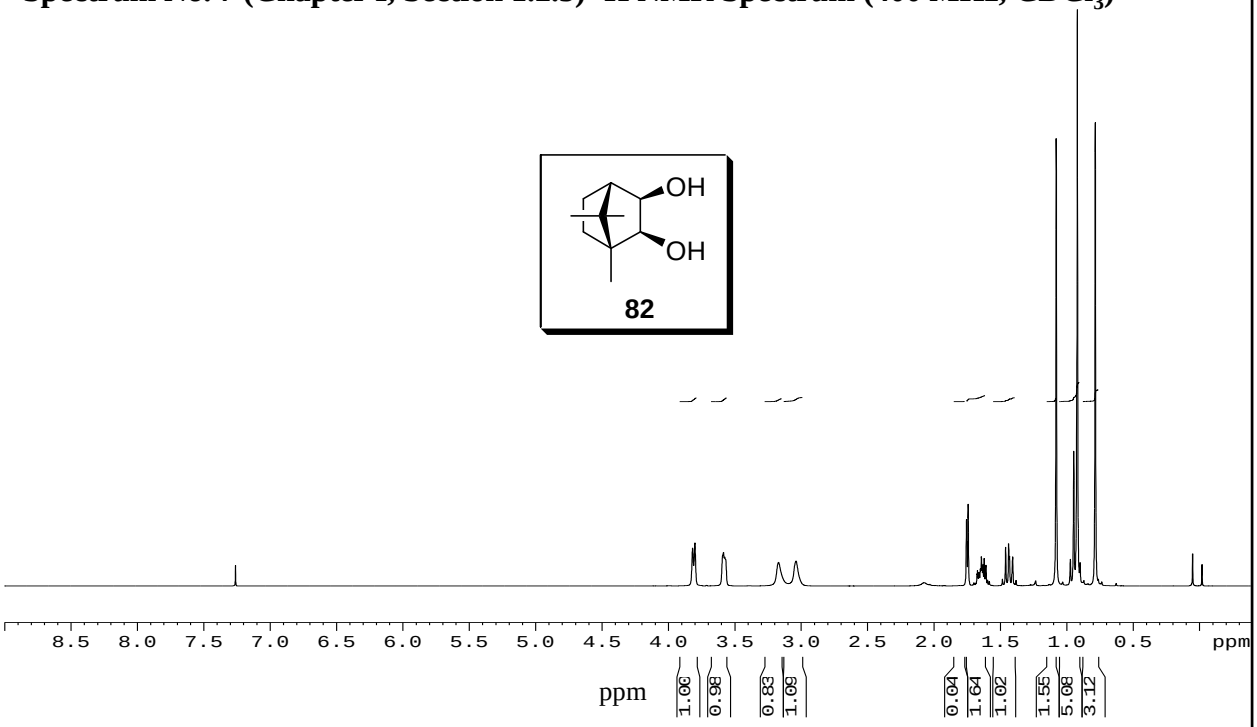
ppm

Spectrum No. 6 (Chapter I, Section 1.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

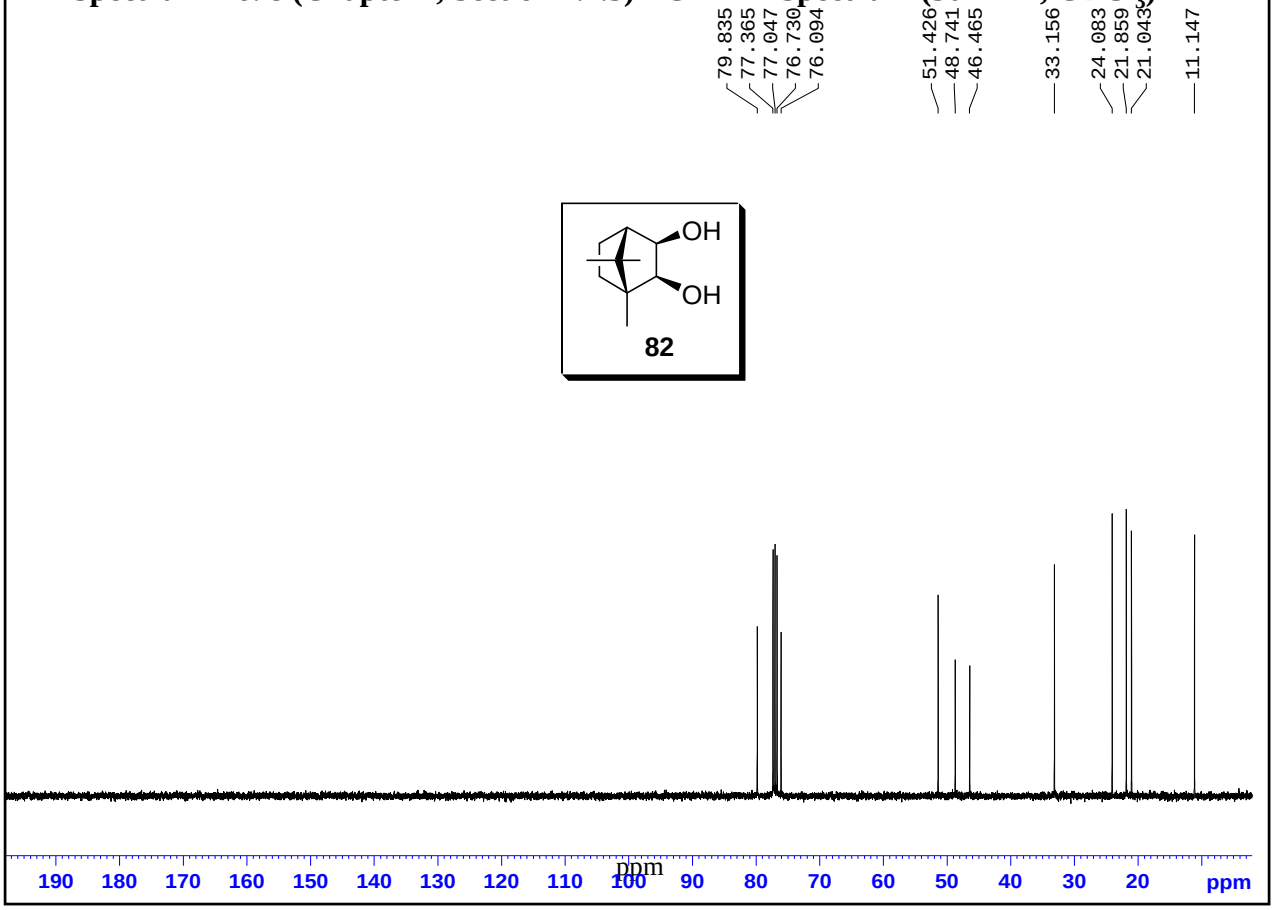


ppm

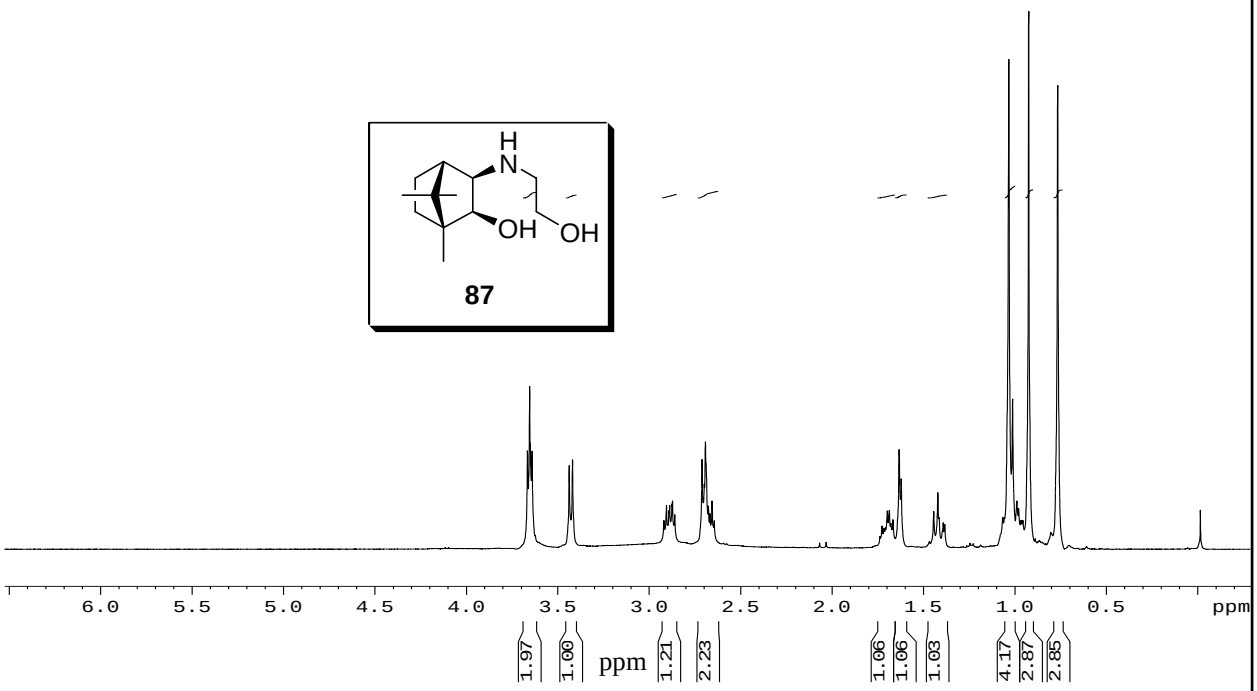
Spectrum No. 7 (Chapter I, Section 1.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



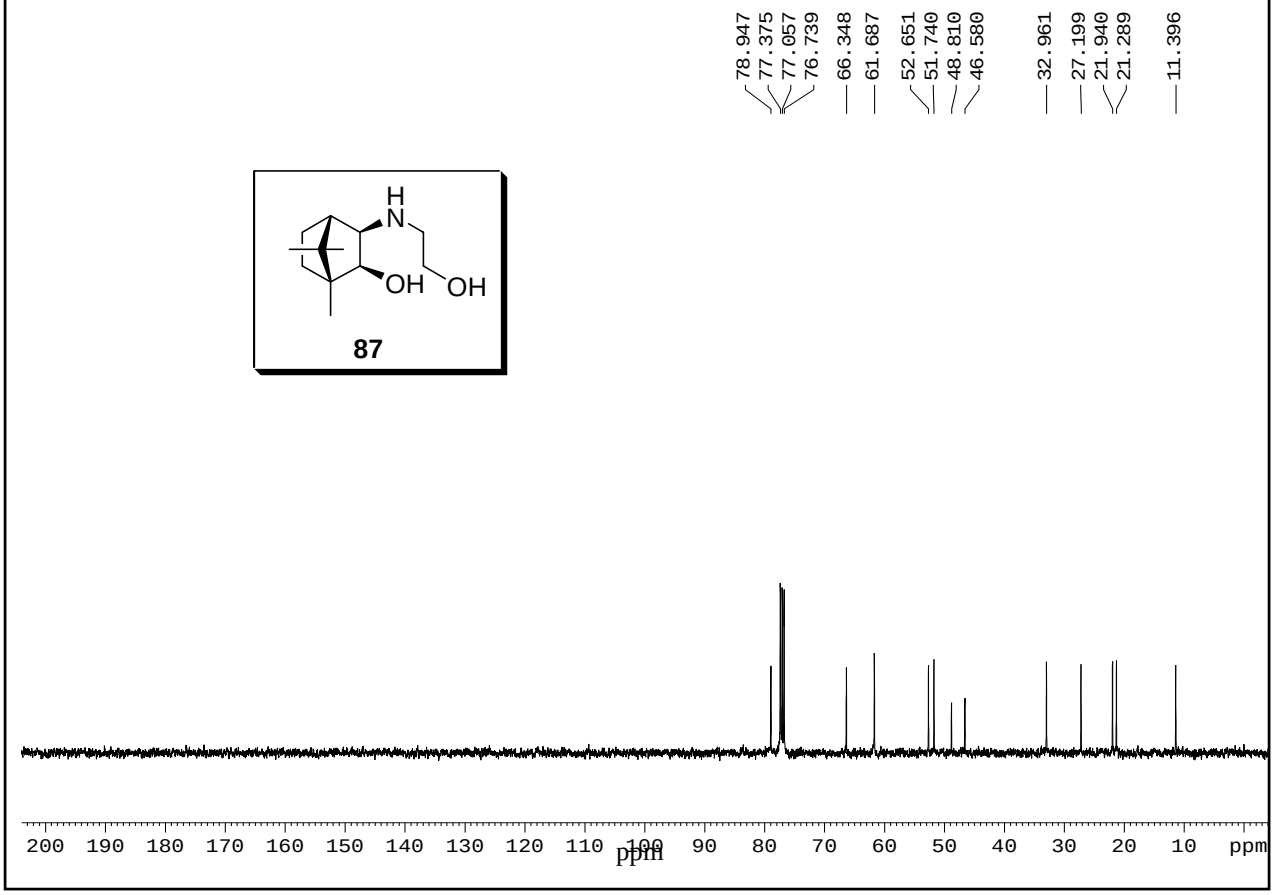
Spectrum No. 8 (Chapter I, Section 1.2.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



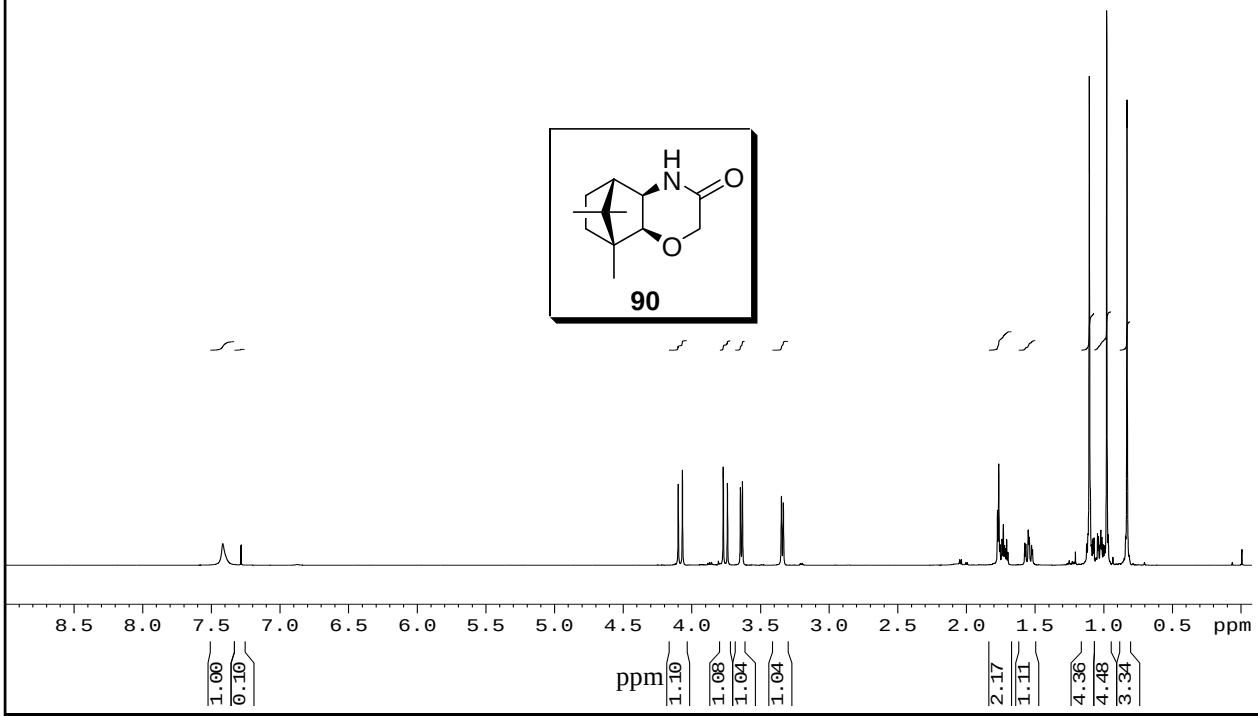
Spectrum No. 9 (Chapter I, Section 1.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



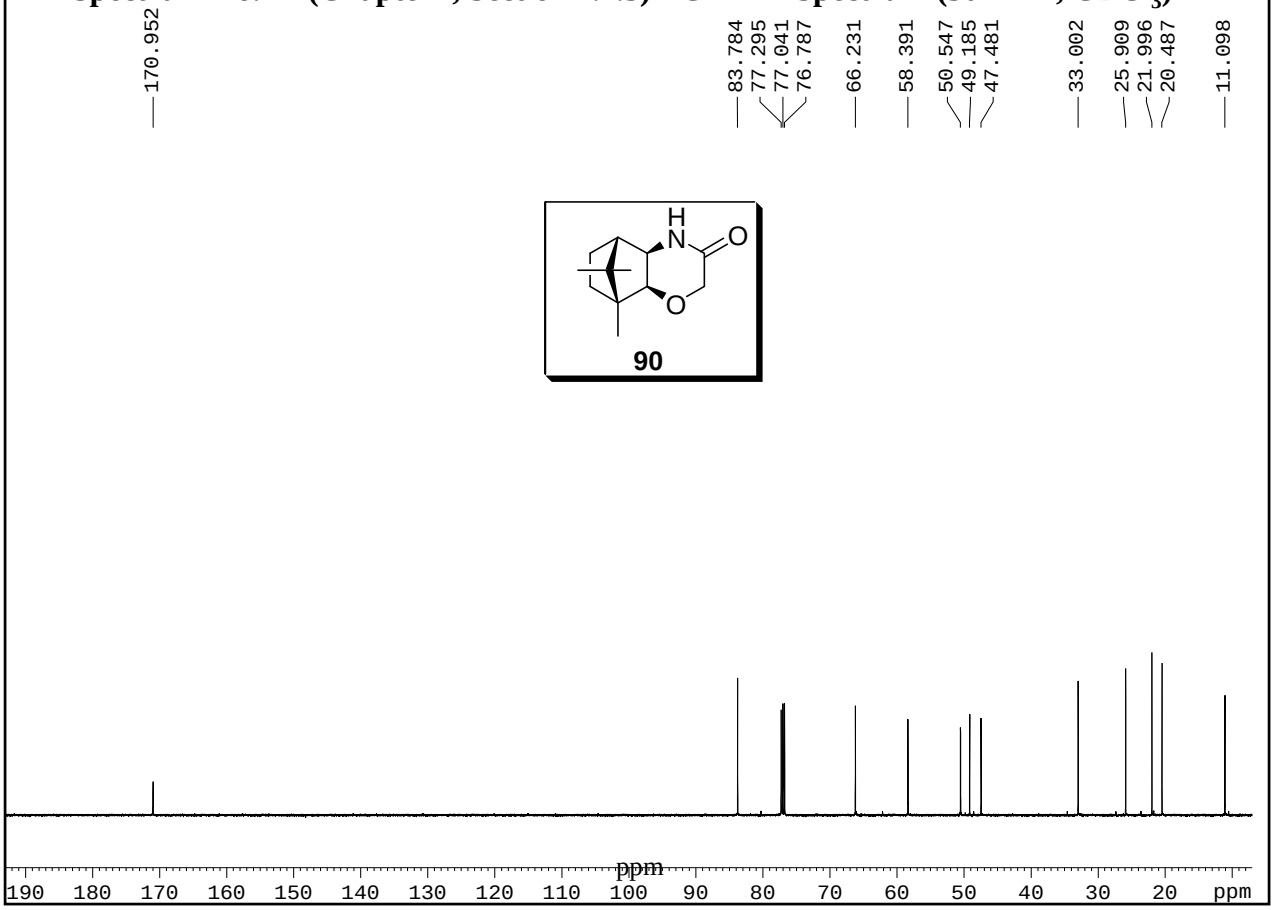
Spectrum No. 10 (Chapter I, Section 1.2.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



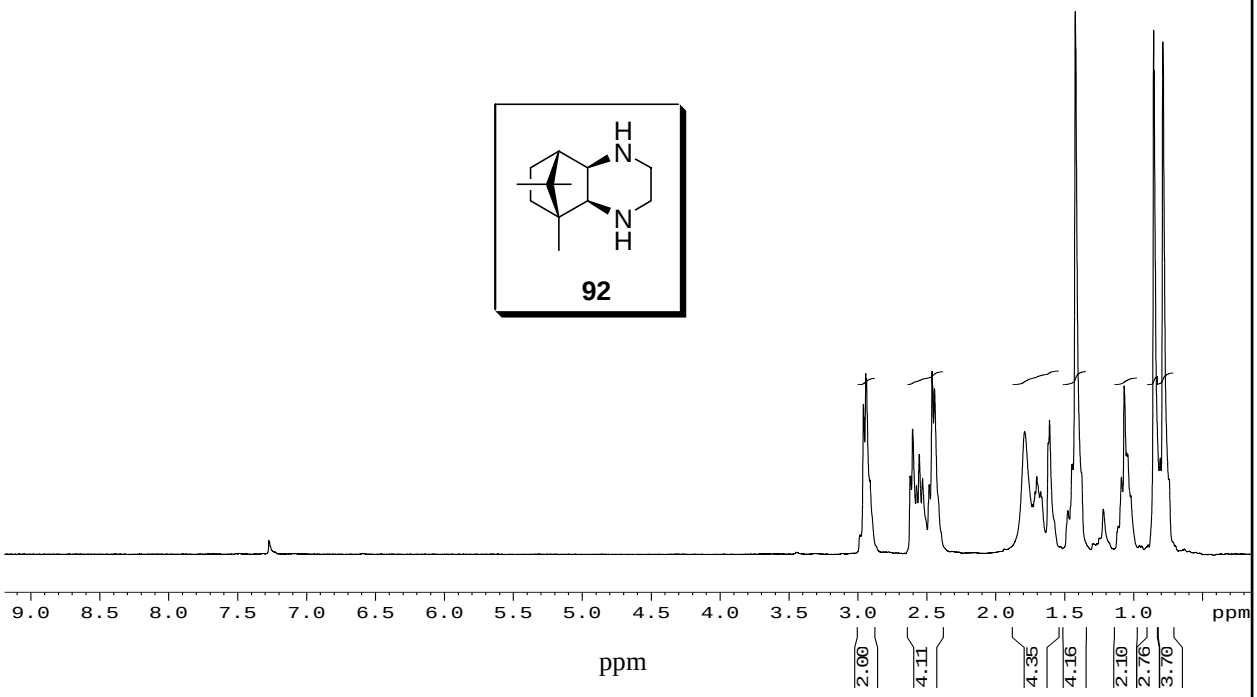
Spectrum No. 11 (Chapter I, Section 1.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



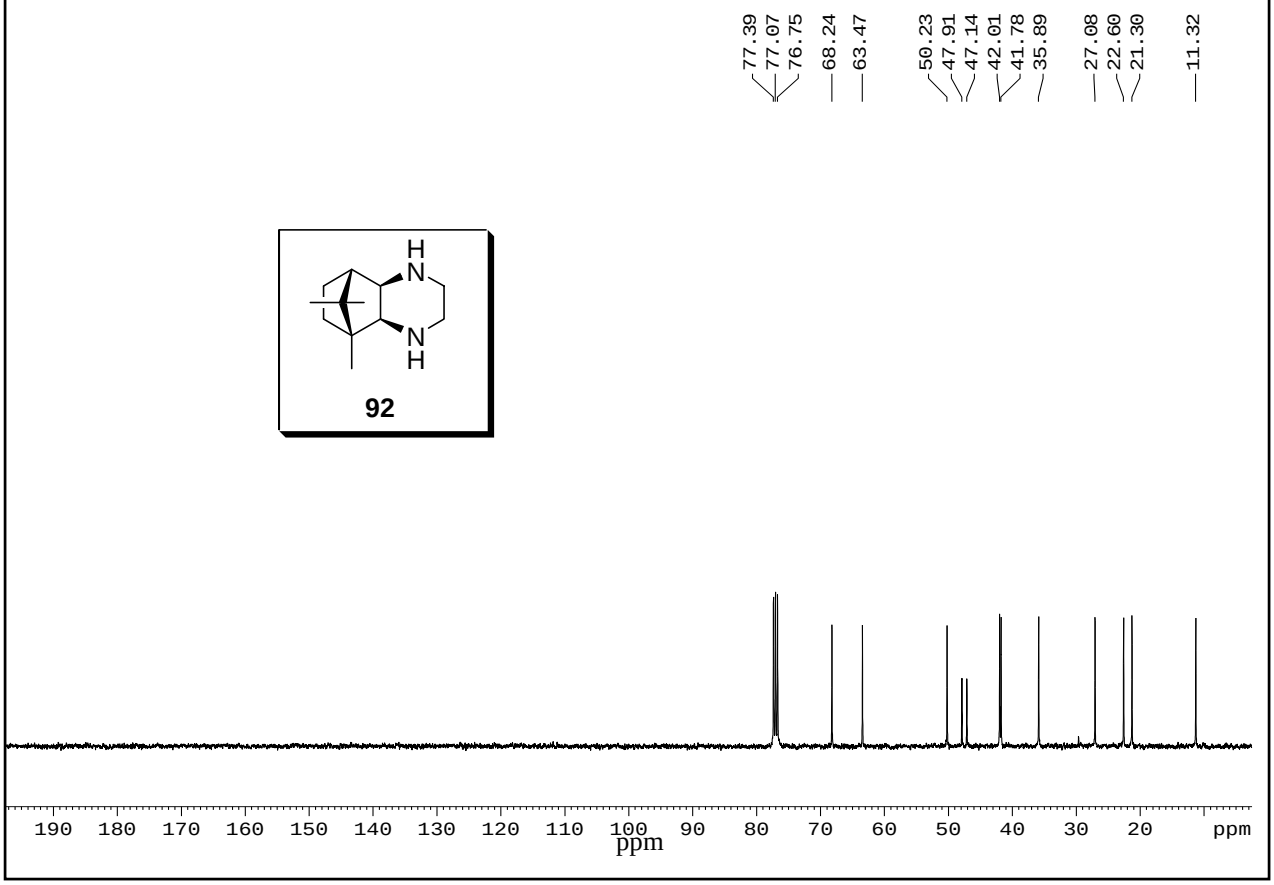
Spectrum No. 12 (Chapter I, Section 1.2.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



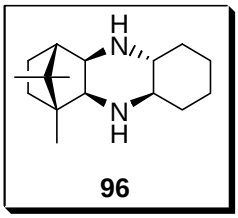
Spectrum No. 13 (Chapter I, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 14 (Chapter I, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



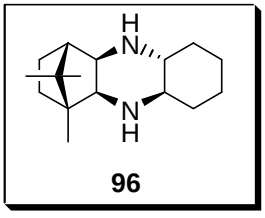
Spectrum No. 15 (Chapter I, Section 1.2.6) ^{1}H NMR Spectrum (400 Hz, $CDCl_3$)



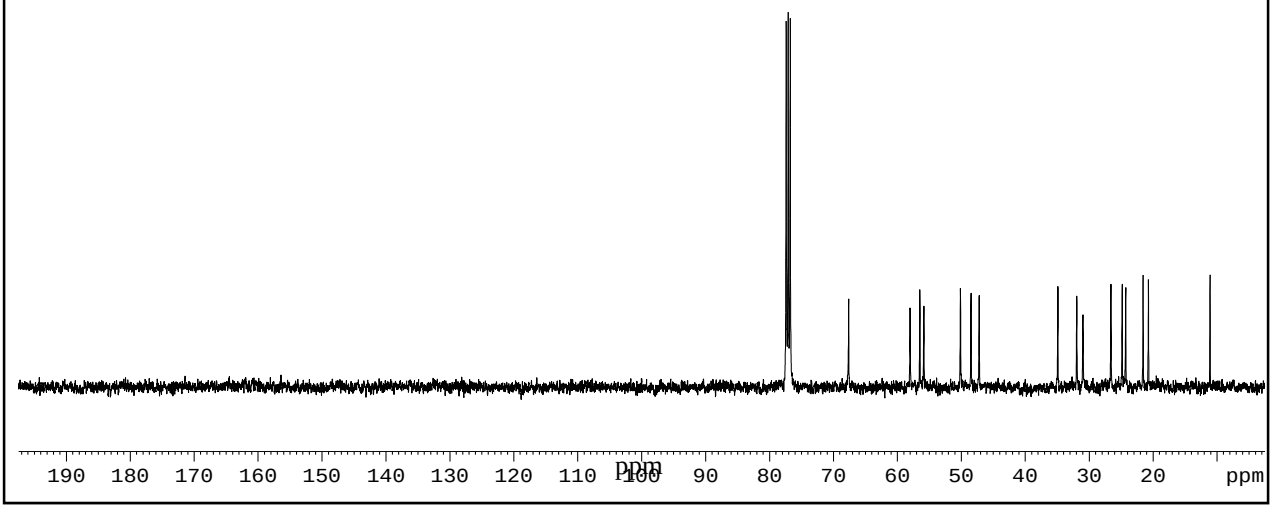
96

Spectrum No. 16 (Chapter I, Section 1.2.6) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

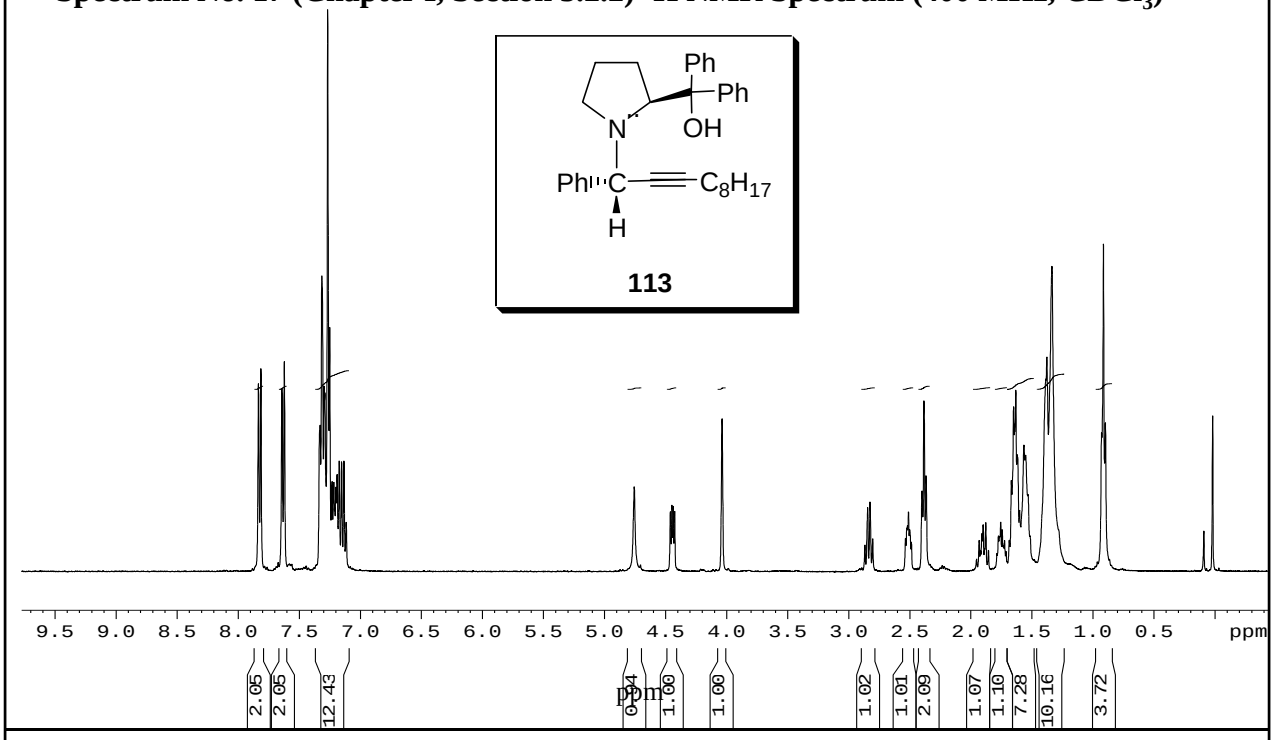
77.40
77.08
76.76
67.63
58.02
56.50
55.87
50.15
48.49
47.21
34.91
31.95
30.98
26.60
24.84
24.29
21.57
20.74
11.09



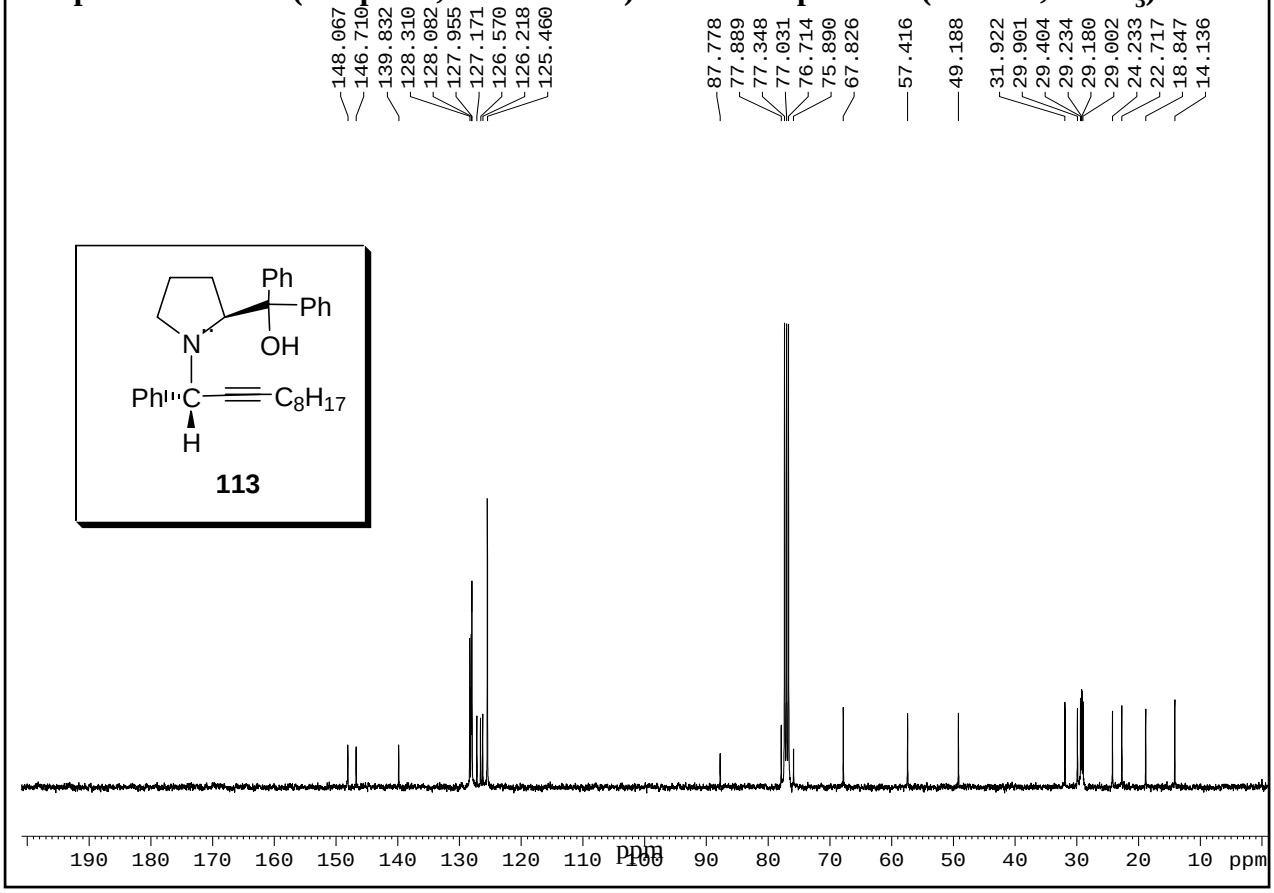
96



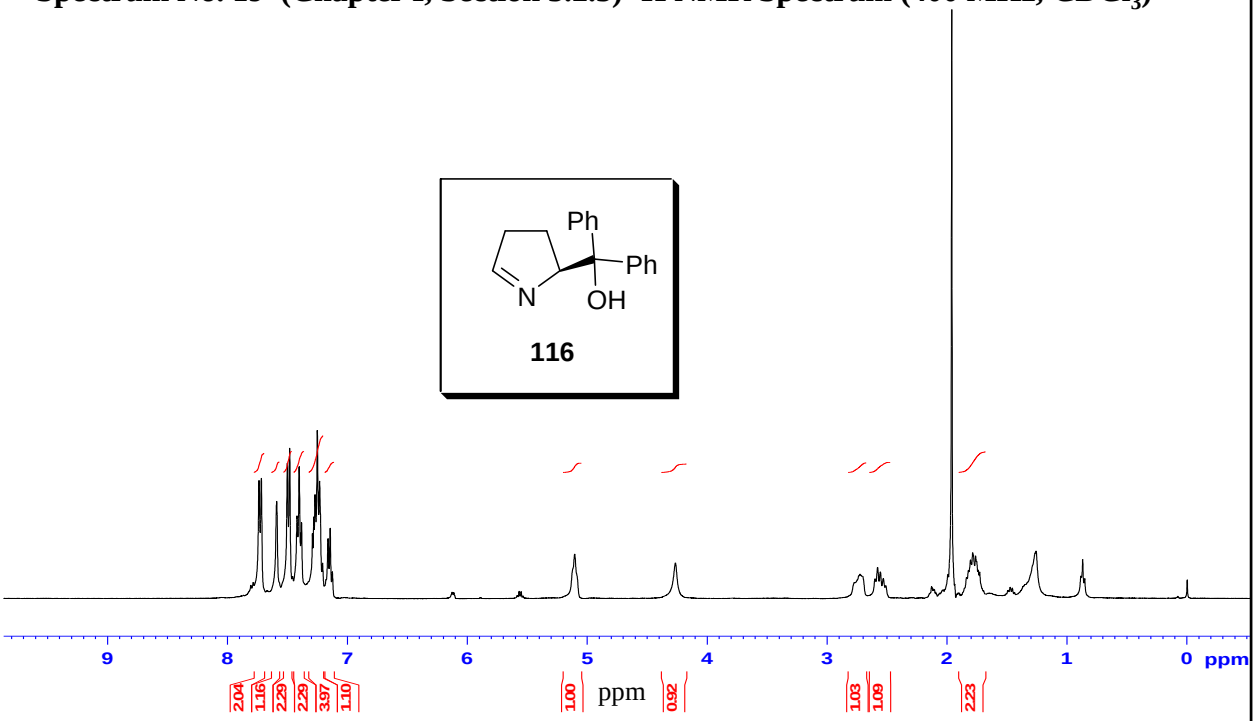
Spectrum No. 17 (Chapter I, Section 3.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



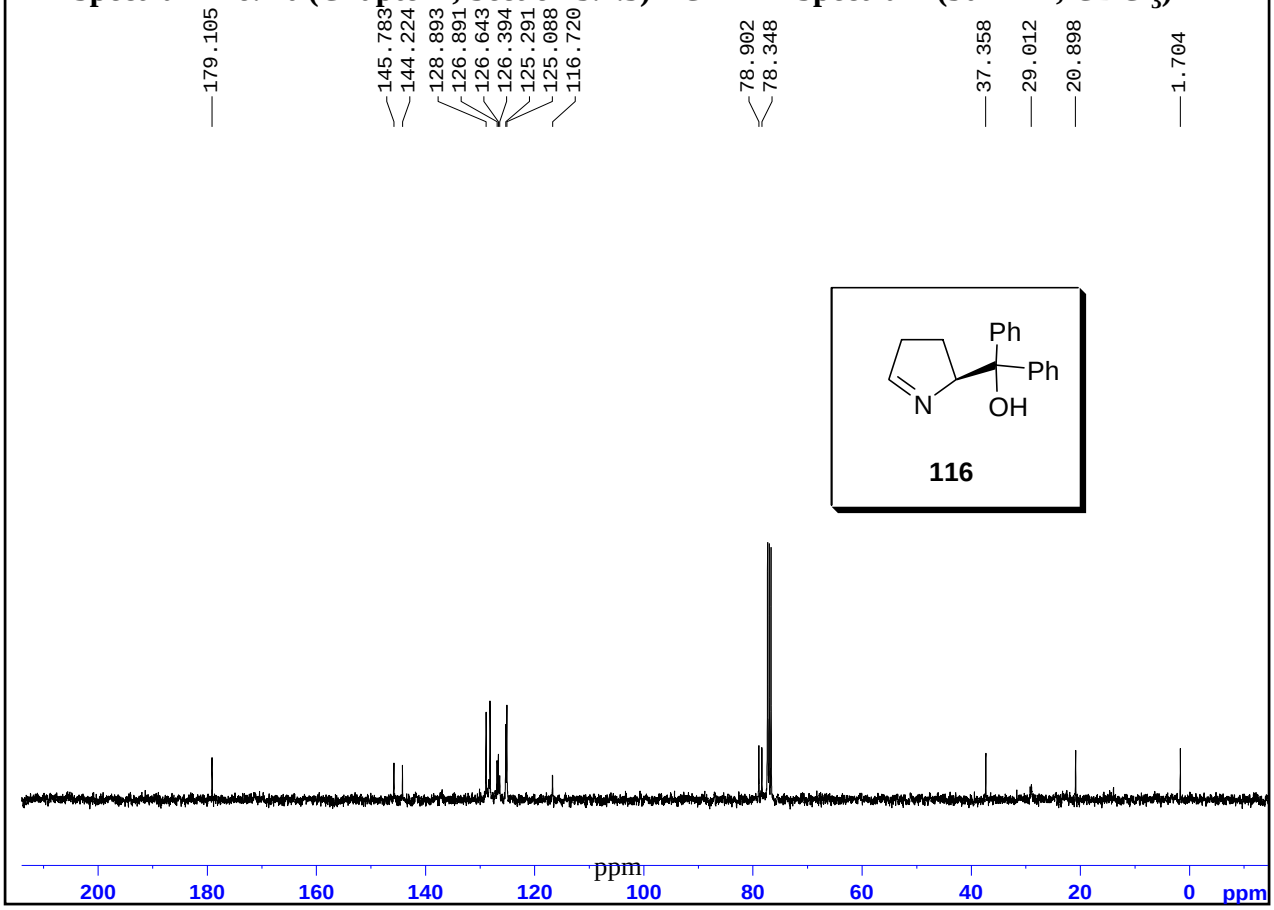
Spectrum No. 18 (Chapter I, Section 3.2.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



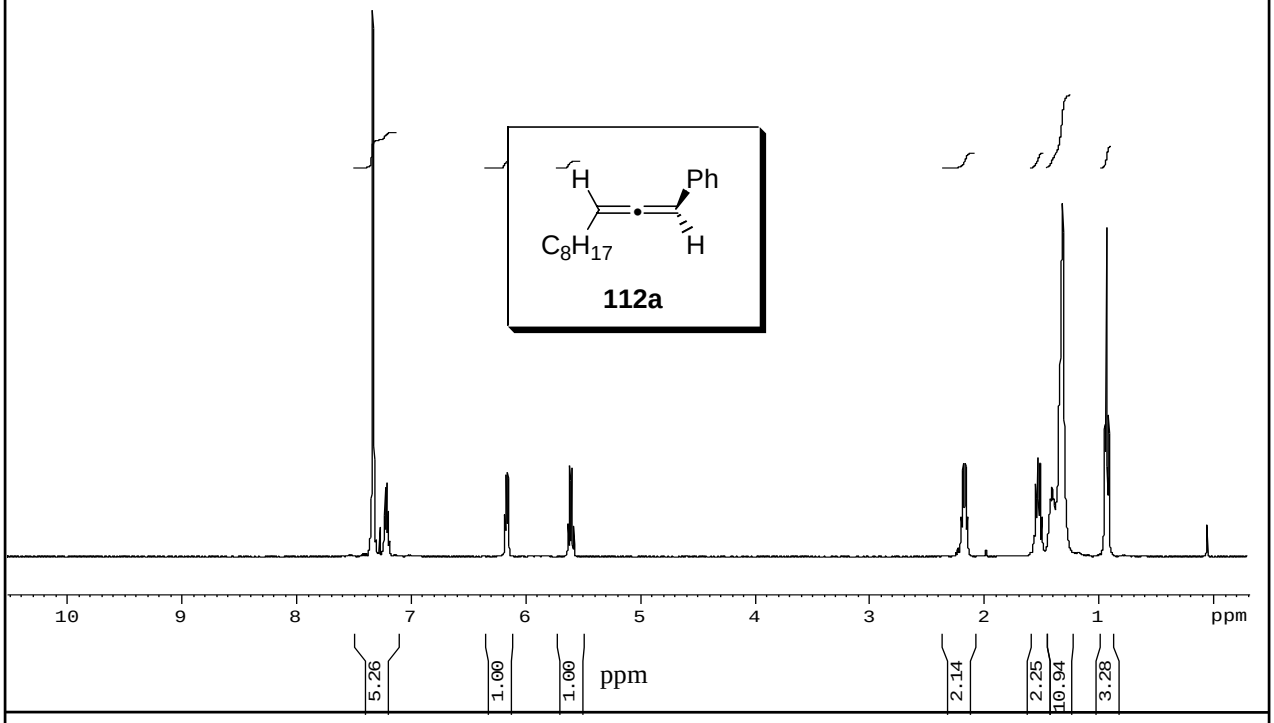
Spectrum No. 19 (Chapter I, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



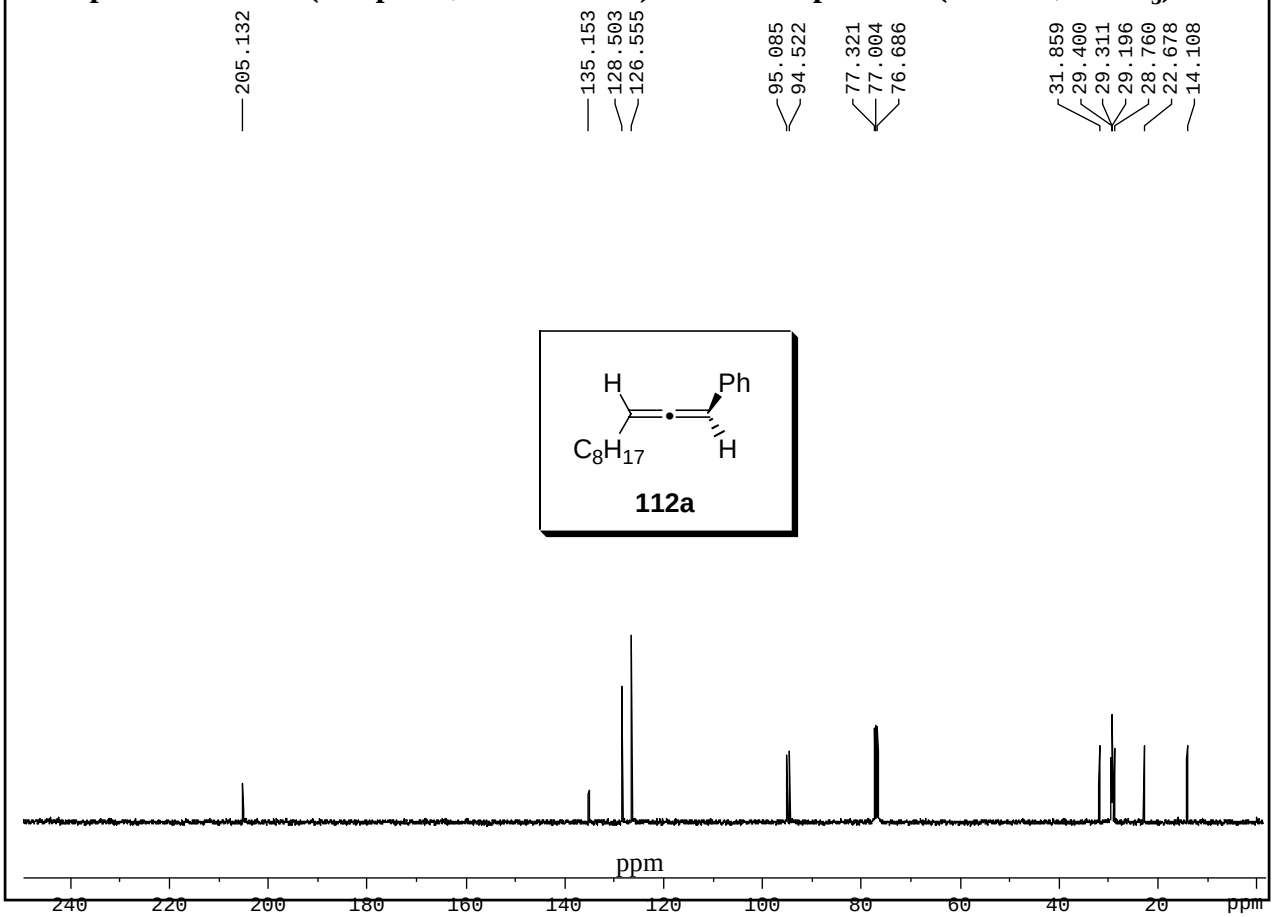
Spectrum No. 20 (Chapter I, Section 3.2.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



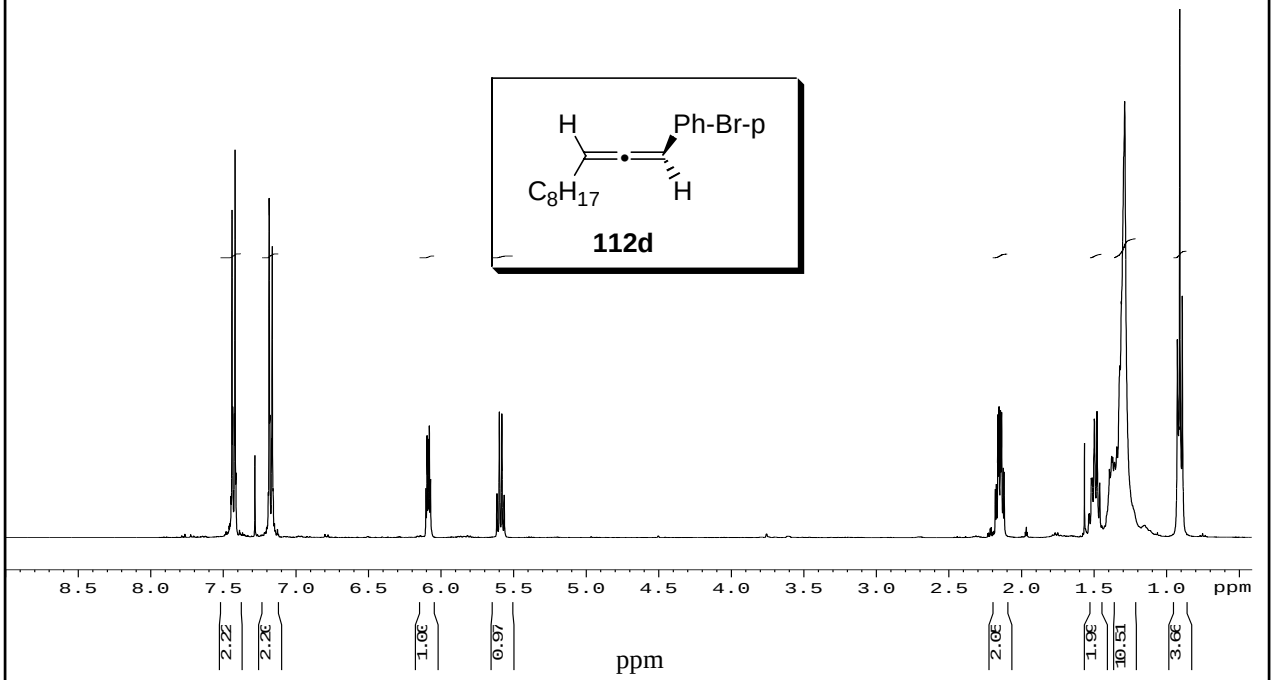
Spectrum No. 21 (Chapter I, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



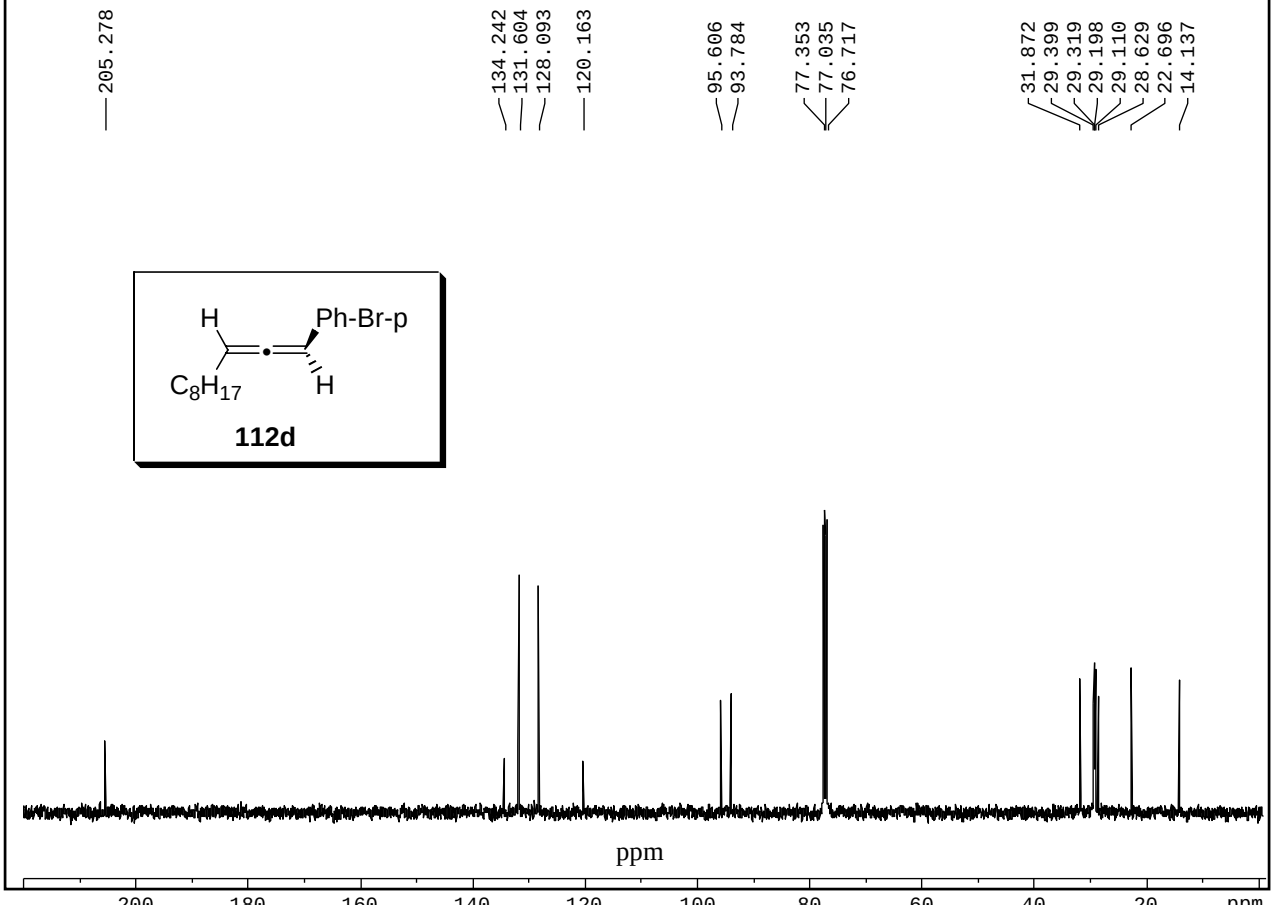
Spectrum No. 22 (Chapter I, Section 3.2.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



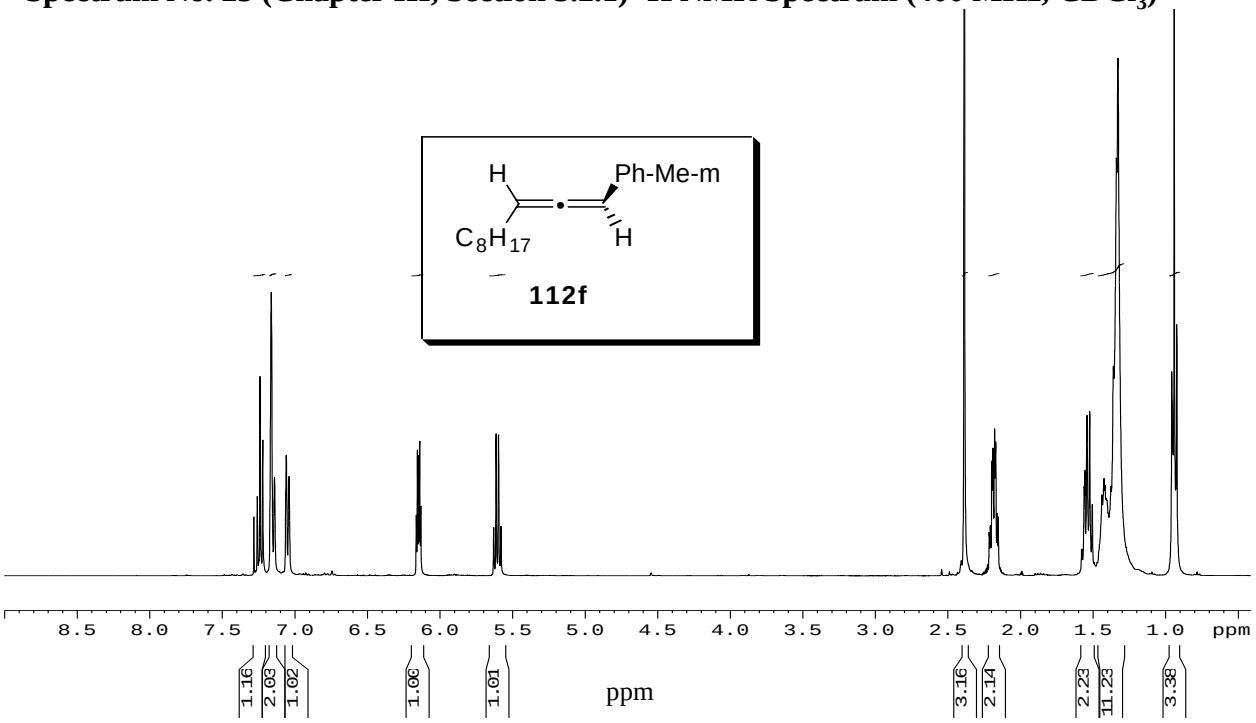
Spectrum No. 23 (Chapter III, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



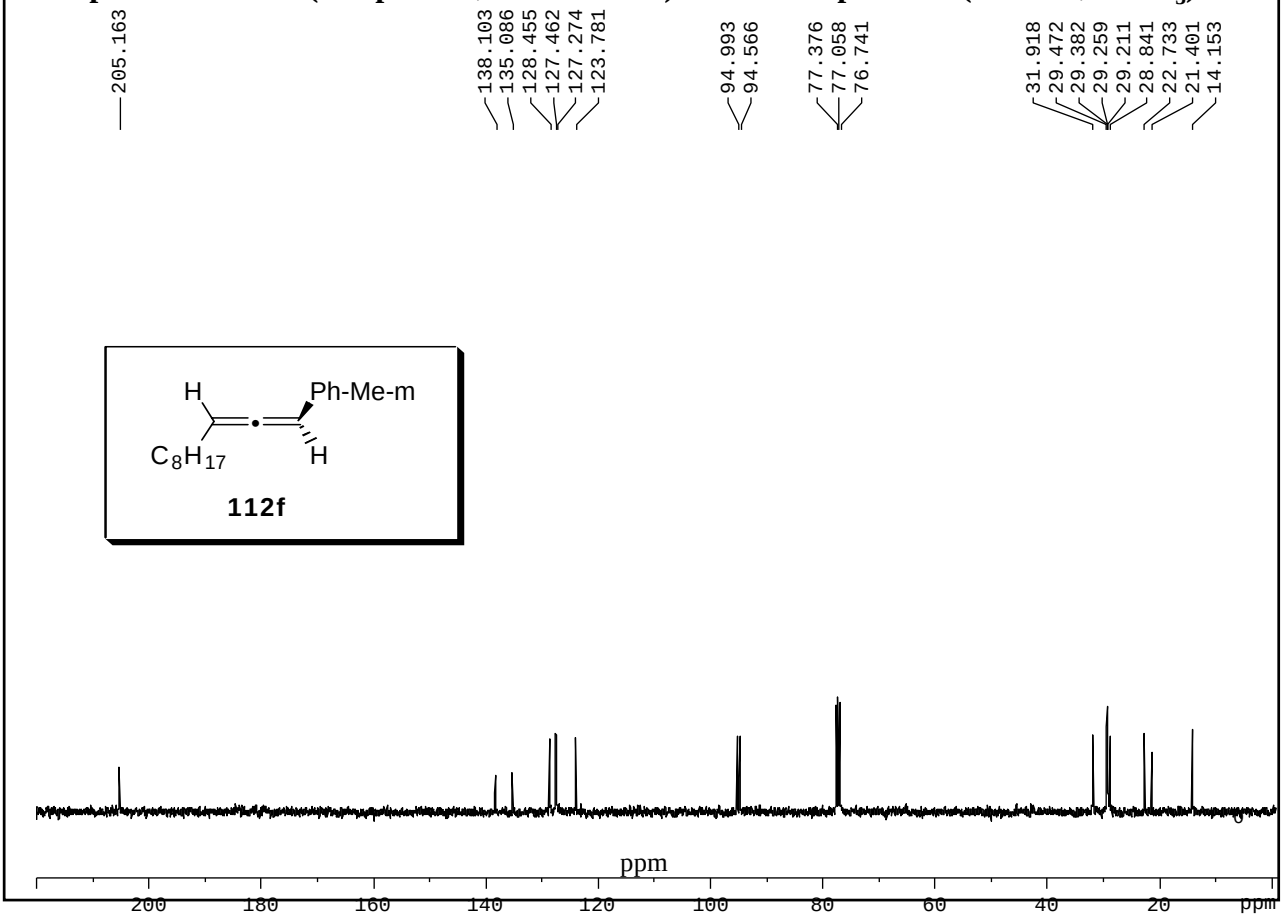
Spectrum No. 24 (Chapter III, Section 3.2.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



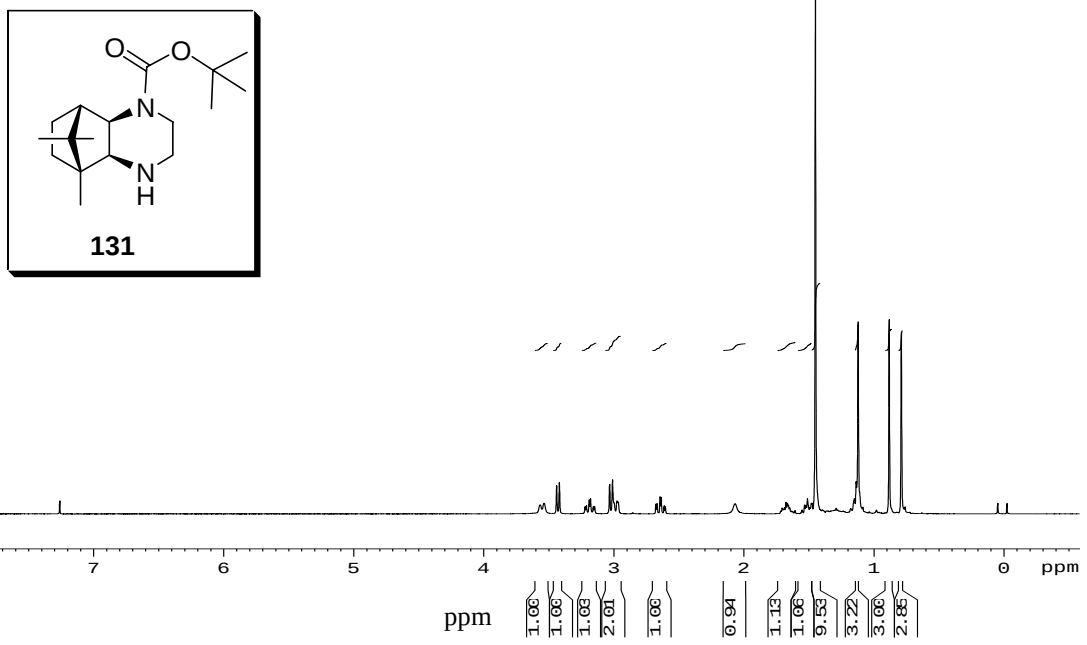
Spectrum No. 25 (Chapter III, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



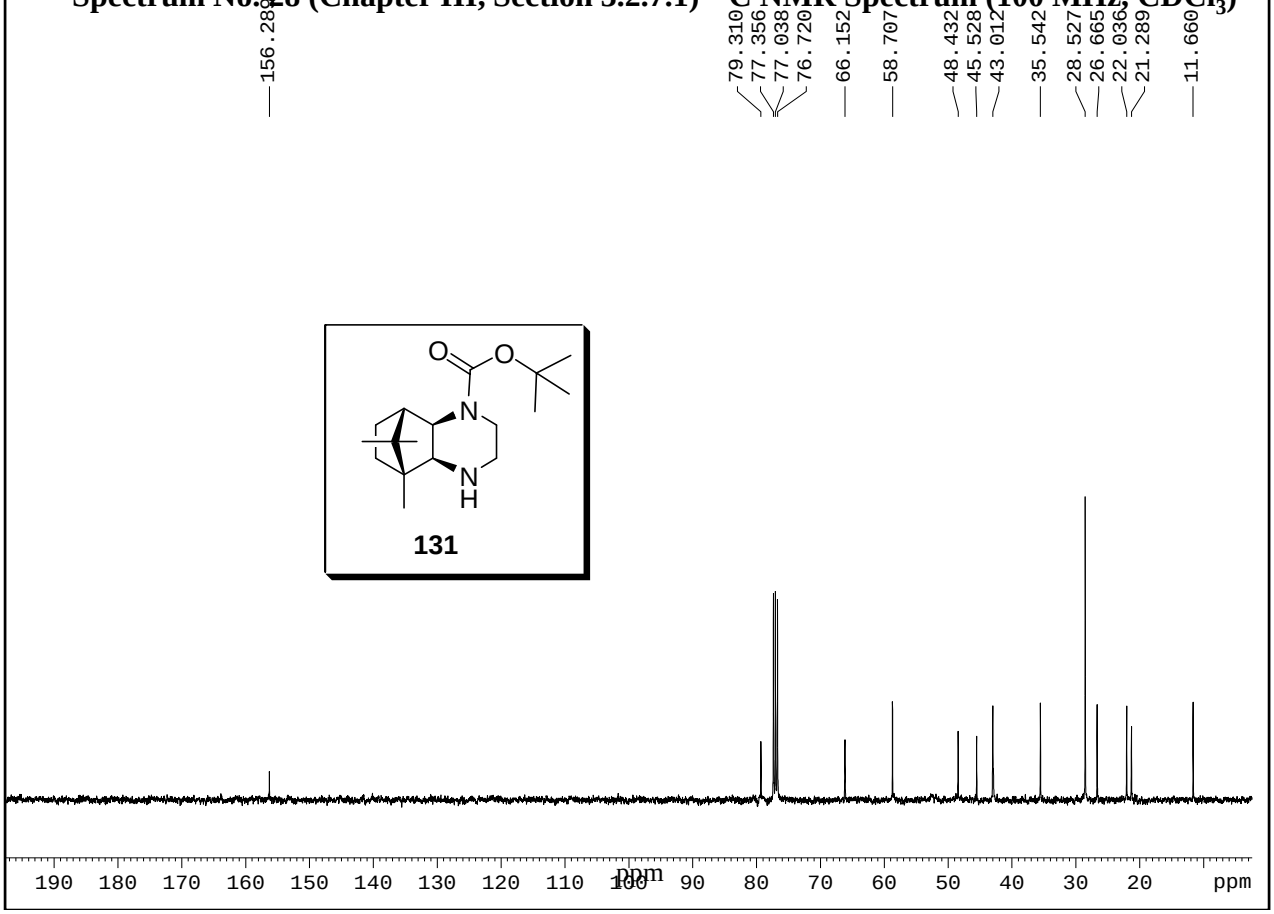
Spectrum No. 26 (Chapter III, Section 3.2.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



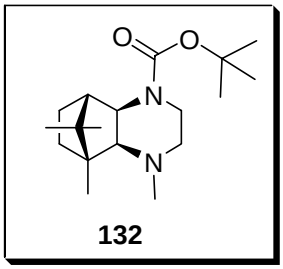
Spectrum No. 27 (Chapter III, Section 3.2.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 28 (Chapter III, Section 3.2.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 29 (Chapter III, Section 3.2.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



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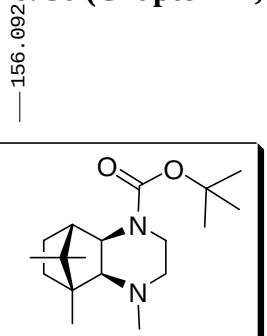
Spectrum No. 30 (Chapter III, Section 3.2.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



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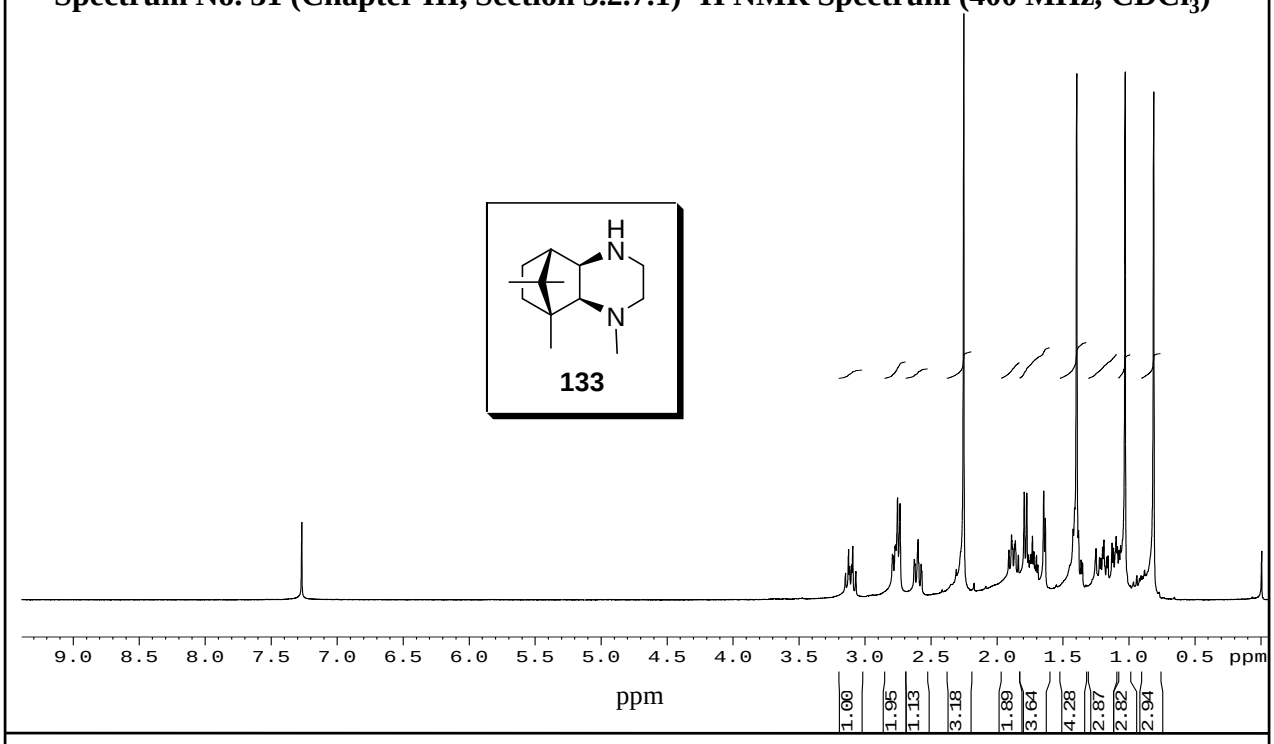
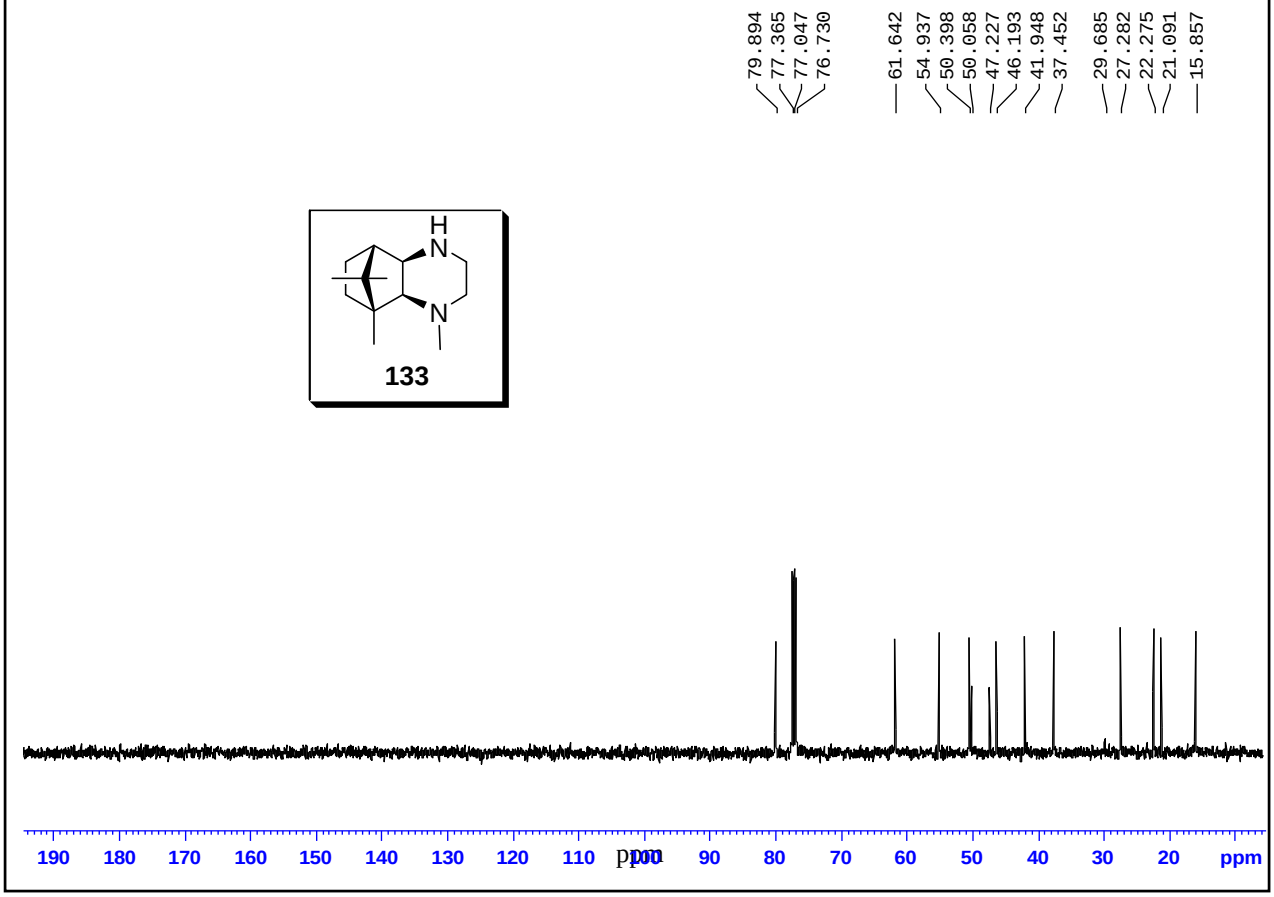
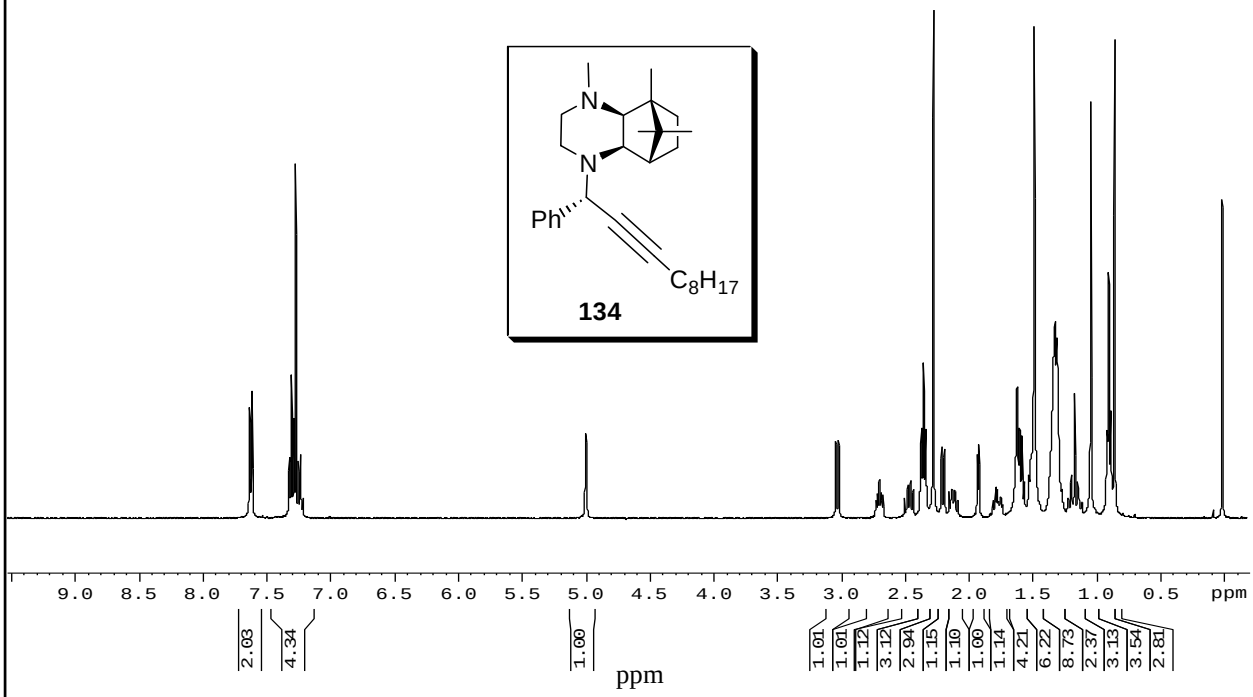
Spectrum No. 31 (Chapter III, Section 3.2.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



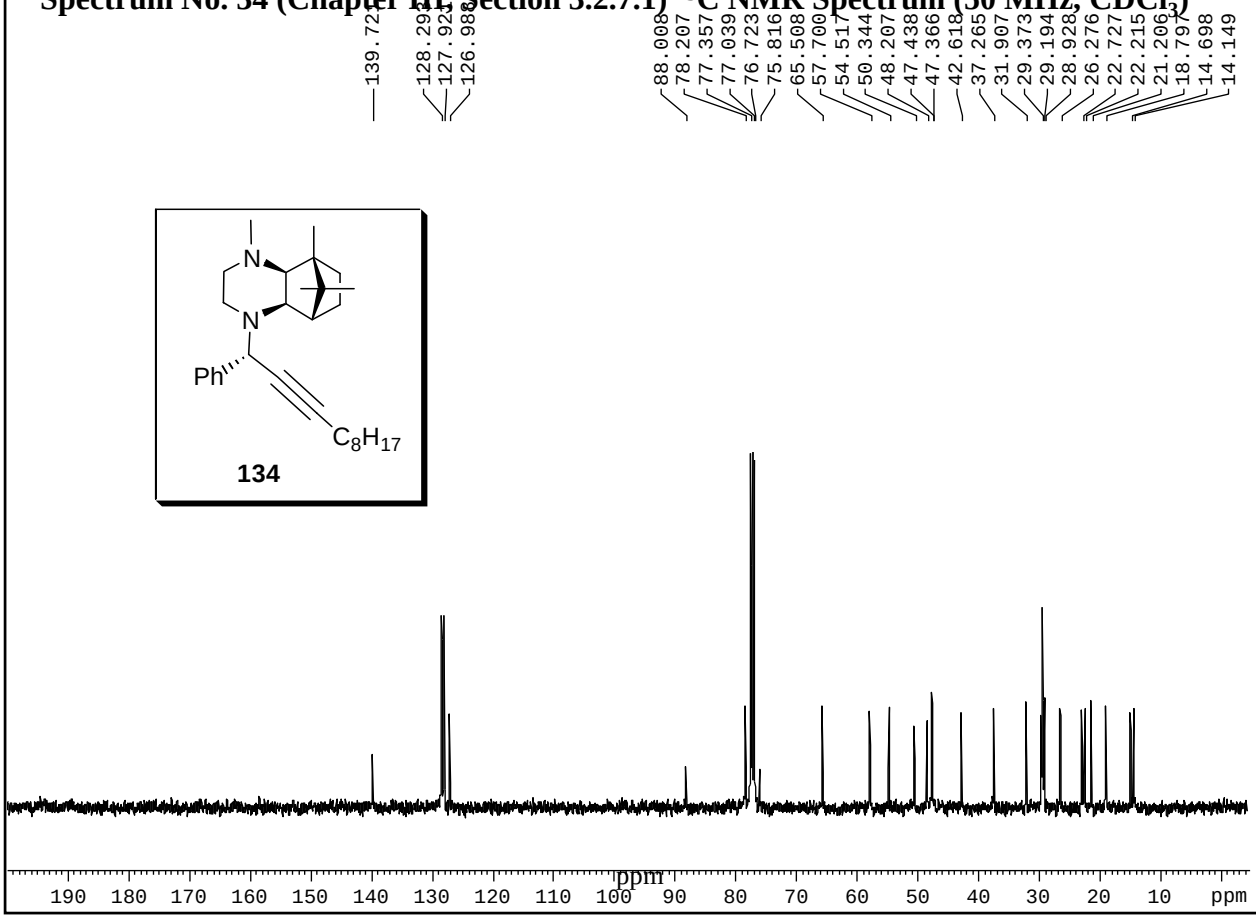
Spectrum No. 32 (Chapter III, Section 3.2.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Spectrum No. 33 (Chapter III, Section 3.2.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 34 (Chapter III, Section 3.2.7.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Appendix II

X-Ray Crystallographic Data

Table 1 X-ray data collection and structure refinement for the amide derivative 78 (Chapter 1, Section 1.2.3)

Empirical Formula	$C_{30}\ H_{44}\ F_6\ N_2\ O_2$
Formula weight F_w	578.67
Temperature T (K)	298(2)
Wavelength λ (Å)	1.54184
Crystal system, Space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	
a (Å), α (°)	9.8272(8), 90
b (Å), β (°)	10.1021(8), 90
c (Å), γ (°)	28.819(2), 90
Volume V (Å^3)	2861.0(4)
Z	4
Calculated density ρ_{calcd} mg/M^3	1.343
Absorption coefficient μ (mm^{-1})	0.932
F (000)	1232
Crystal Size (mm)	0.46 x 0.28 x 0.12 mm
θ for data collection range/deg	4.64 to 64.83deg
Limiting indices	-7<=h<=11, -11<=k<=11, -
Reflections collected/unique	9459 / 4751 [R(int) = 0.0597]
Completeness to θ	64.83, 99.4 %
Max. and min. transmission	0.8964 and 0.6737
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4751 / 0 / 367
Goodness-of-fit on GOF (F^2)	0.959
Final R indices *R1*, *wR2 [I>2σ(I)]*	*R1* = 0.0523, *wR2* = 0.1232
R indices (all data) *R1*, *wR2*	*R1* = 0.0663, *wR2* = 0.1295
Largest diff. Peak and hole (e·Å^{-3})	0.288 and -0.368

Table A1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the complex **78 (Chapter 1, Section 1.2.3)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	Z	U(eq)
C(1)	1386(3)	2082(3)	928(1)	14(1)
C(2)	973(3)	3372(3)	690(1)	17(1)
C(3)	1270(3)	3378(3)	172(1)	20(1)
C(4)	553(4)	2214(3)	-59(1)	23(1)
C(5)	977(3)	930(3)	165(1)	18(1)
C(6)	672(3)	884(3)	689(1)	14(1)
C(7)	-47(3)	-1372(3)	1050(1)	15(1)
C(8)	-931(3)	-2079(3)	680(1)	16(1)
C(9)	-1887(3)	-1096(3)	430(1)	18(1)
C(10)	-2908(3)	-661(3)	807(1)	22(1)
C(11)	-2434(3)	-1453(3)	1233(1)	20(1)
C(12)	-1103(3)	-820(3)	1401(1)	19(1)
C(13)	-1962(3)	-2780(3)	1024(1)	19(1)
C(14)	-3075(4)	-3559(4)	770(1)	28(1)
C(15)	-1335(4)	-3729(3)	1378(1)	23(1)
C(16)	-141(3)	-2981(3)	355(1)	23(1)
C(17)	2354(3)	-776(3)	879(1)	18(1)
C(18)	2831(3)	-2002(3)	1164(1)	23(1)
C(19)	2325(3)	2291(3)	1767(1)	16(1)
C(20)	3247(3)	3548(3)	1745(1)	17(1)
C(21)	4107(3)	3599(3)	1297(1)	19(1)
C(22)	5094(3)	2410(3)	1345(1)	22(1)
C(23)	4734(3)	1846(3)	1821(1)	19(1)
C(24)	3360(3)	1140(3)	1772(1)	17(1)
C(25)	4362(3)	3096(3)	2102(1)	20(1)
C(26)	3859(4)	2826(3)	2596(1)	26(1)
C(27)	5551(4)	4087(4)	2153(1)	27(1)
C(28)	2498(4)	4816(3)	1861(1)	22(1)
C(29)	-144(3)	2318(3)	1587(1)	16(1)
C(30)	-464(4)	2183(4)	2113(1)	24(1)
N(1)	1036(3)	-420(2)	891(1)	14(1)
N(2)	1163(2)	2171(2)	1442(1)	13(1)
O(1)	3269(2)	-179(2)	679(1)	19(1)
O(2)	-1133(2)	2471(2)	1339(1)	21(1)
F(1)	2361(2)	-2012(2)	1601(1)	25(1)
F(2)	2492(2)	-3054(2)	965(1)	28(1)
F(3)	4182(2)	-1993(2)	1195(1)	36(1)
F(4)	151(2)	1147(2)	2314(1)	30(1)
F(5)	-1788(2)	2009(2)	2167(1)	37(1)
F(6)	-119(2)	3263(2)	2357(1)	36(1)

Table 2 X-ray data collection and structure refinement for Amide derivative 90 (Chapter 1, Section 1.2.5)

Empirical Formula	C_{12} H_{19} N O_2
Formula weight F_w	209.28
Temperature T (K)	293(2) K
Wavelength λ (Å)	0.71073
Crystal system, Space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	
a (Å), α (^{o})	7.2717(5), 90
b (Å), β (^{o})	12.0988(12), 90
c (Å), γ (^{o})	13.5408(10), 90
Volume V (Å^3)	1191.30(17)
Z	4
Calculated density ρ_{calcd} mg/M^3	1.167
Absorption coefficient μ (mm^{-1})	0.079
F (000)	456
Crystal Size (mm)	0.40 x 0.30 x 0.20
θ for data collection range/deg	3.01 to 24.71
Limiting indices	-8<=h<=8, -14<=k<=13, -15<=l<=14
Reflections collected/unique	3100 / 1946 [R(int) = 0.0138]
Completeness to θ	24.71, 99.8 %
Max. and min. transmission	0.9844 and 0.9692
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1946 / 0 / 143
Goodness-of-fit on GOF (F^2)	1.063
Final R indices $R1$, $wR2$ $[I>2\sigma(I)]$	$R1$ = 0.0430 $wR2$ = 0.0993
R indices (all data) $R1$, $wR2$	$R1$ = 0.0519 $wR2$ = 0.1054
Largest diff. Peak and hole (e·Å^{-3})	0.154 and -0.149

Table A2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for amide **90** (**Chapter 1, Section 1.2.5**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	X	y	Z	U(eq)
C(1)	36(3)	3211(2)	5602(1)	45(1)
C(2)	-1519(3)	3787(2)	6121(2)	55(1)
C(3)	413(3)	4650(2)	7265(2)	50(1)
C(4)	1149(3)	4646(2)	8326(2)	56(1)
C(5)	2502(4)	5629(2)	8352(2)	82(1)
C(6)	4203(4)	5218(3)	7774(2)	86(1)
C(7)	3587(3)	4071(2)	7438(2)	59(1)
C(8)	2107(3)	4300(2)	6650(2)	49(1)
C(9)	2498(3)	3652(2)	8330(2)	55(1)
C(10)	1609(4)	2513(2)	8198(2)	76(1)
C(11)	3679(5)	3594(3)	9284(2)	96(1)
C(12)	-352(4)	4697(3)	9105(2)	98(1)
N(1)	1692(2)	3377(2)	5989(1)	49(1)
O(1)	-1113(2)	3928(1)	7140(1)	54(1)
O(2)	-221(2)	2605(2)	4884(1)	60(1)

Table A3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for copper complex **47** (**Chapter 2, Section 2.2.3**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	Z	U(eq)
C(1)	9163(1)	5561(3)	13321(3)	23(1)
C(2)	9401(1)	4010(3)	12377(3)	17(1)
C(3)	9713(1)	-1156(3)	10305(3)	18(1)
C(4)	9085(1)	463(3)	8003(3)	16(1)
C(5)	8993(1)	2404(4)	7120(2)	19(1)
C(6)	8351(1)	2402(4)	6419(2)	21(1)
C(7)	8259(1)	946(4)	5020(3)	27(1)
C(8)	8341(1)	-937(3)	5975(3)	25(1)
C(9)	8468(1)	-352(3)	7820(3)	18(1)
C(10)	8090(1)	1438(3)	7825(3)	18(1)
C(11)	8166(1)	2555(5)	9441(2)	22(1)
C(12)	7448(1)	1040(4)	7375(3)	24(1)
C(13)	8366(1)	-1925(3)	8998(3)	25(1)
N(1)	3445(2)	1159(2)	-145(1)	58(1)
O(1))	9415(1)	2389(3)	12888(2)	30(1)
O(2)	9582(1)	4517(2)	11031(2)	19(1)
Cu(II)	10000(1)	2629(1)	10000(2)	15(1)

Table 3 X-ray data collection and structure refinement for copper complex 47

(**Chapter 2, Section 2.2.3**)

Empirical Formula	C_{26} H_{48} Cu N_2 O_5
Formula weight F_w	532.20
Temperature T (K)	373(2) K
Wavelength λ (Å)	0.71073
Crystal system, Space group	Monoclinic, C2
Unit cell dimensions	
a (Å), α (^{o})	23.7871(17), 90
b (Å), β (^{o})	7.1236(5), 98.8440(10)
c (Å), γ (^{o})	8.1621(6), 90
Volume V (Å^3)	1366.62(17)
Z	2
Calculated density ρ_{calcd} mg/M^3	1.293
Absorption coefficient μ (mm^{-1})	0.836
F (000)	574
Crystal Size (mm)	0.40 x 0.20 x 0.12
θ for data collection range/deg	1.73 to 26.10
Limiting indices	-29<=h<=29, -8<=k<=8, -10<=l<=10
Reflections collected/unique	7136 / 2705 [R(int) = 0.0289]]
Completeness to θ	26.10, 99.9 %
Max. and min. transmission	0.905 and 0.716
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2705 / 1 / 163
Goodness-of-fit on GOF (F^2)	1.045
Final R indices *R1*, *wR2 [I>2σ(I)]*	*R1* = 0.0272, *wR2* = 0.0616
R indices (all data) *R1*, *wR2*	*R1* = 0.0280, *wR2* = 0.0619
Largest diff. Peak and hole (e·Å^{-3})	0.500 and -0.229

LIST OF PUBLICATIONS

1. A simple and convenient method for the preparation of diborane from tetrabutylammonium borohydride and benzyl chloride for application in organic synthesis; Periasamy, M.; Muthukumaragopal, G. P.; **Sanjeevakumar**, **N**. *Tetrahedron Lett.* 2007, *48*, 6966.
2. Highly enantioselective Henry reaction catalyzed by a new chiral C_2 - symmetric *N*,*N'*-bis(isobornyl)ethylenediamine-copper complex; Periasamy, M.; **Sanjeevakumar, N**. *Tetrahedron: Asymmetry* 2009, *20*, 1842.
3. 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.; Obula Reddy, P. *communicated.*
4. Convenient methods for the synthesis of new chiral amines and amino alcohols using D-(+)-camphor and D-(-)-camphorquinone; Periasamy, M.; **Sanjeevakumar**, **N**.; Obula Reddy, P. *To be communicated*.
5. Highly enantioselective synthesis of both isomers of chiral Allenes using a single chiral D-(+)-camphor based diamine; Periasamy, M.; **Sanjeevakumar**, **N**.; Obulareddy, P. (*manuscript under preparation*).

POSTERS/PAPERS PRESENTED IN SYMPOSIA

1. Oral presentation in the *"Chemfest 2010"* in house symposium held at University of Hyderabad, Hyderabad, March 1-2, **2010**; Title: Synthesis and application of chiral camphor amines and its applications.
2. Presented a poster in the *"Chemfest 2010"* in house symposium held at University of Hyderabad, Hyderabad, March 1-2, **2010**; Title: Synthesis and application of of chiral camphor amines and its applications.