Synthesis of Chiral C_1- and C_2-Symmetric Nitrogen and Sulfur Heterocycles for Application in Asymmetric Transformations

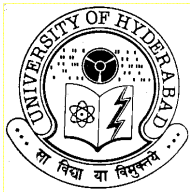
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

GURU BRAHAMAM RAMANI



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HYDERABAD 500 046
INDIA

July 2012

Dedicated to

my mother

Late. Smt. Sivanagulu

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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 C_1- and C_2-Symmetric Nitrogen and Sulfur Heterocycles for Application in Asymmetric Transformations"** has been carried out by Mr. **Guru Brahamam Ramani**, under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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GURU BRAHAMAM RAMANI

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
9-BBN	9-borabicyclononane
BINOL	1,1'-bi-2-naphthol
bp	boiling point
brs	broad singlet (spectral)
Bu	butyl
^{s}Bu	*sec*-butyl
cat.	catalytic
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
dr	diastereomeric ratio
de	diastereomeric excess
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Ee	enantiomeric excess
EI	electron impact (in mass spectrometry)
eq.	equation
equiv.	equivalent
Et	ethyl
h	hour(s)
HPLC	high-performance liquid chromatography

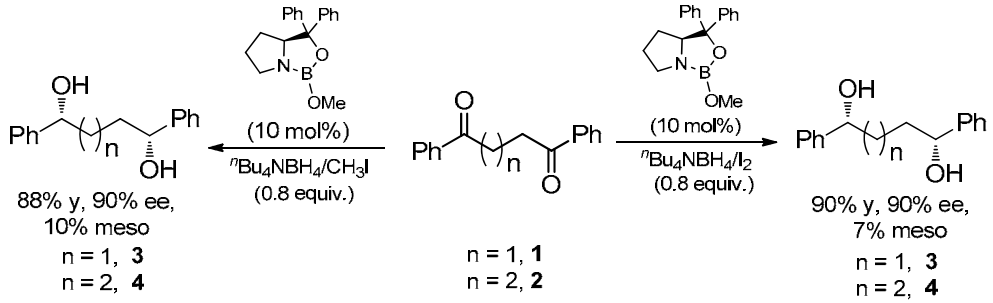
IR	infrared
J	coupling constant (in NMR spectroscopy)
O^{i}Pr	isopropyloxy
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
liq.	liquid
Lit.	literature
m	multiplet (spectral)
Me	methyl
MHz	megahertz
mp	melting point
Ms	methanesulfonyl
n-	primary
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Ph	phenyl
Py	pyridine
PTSA	*p*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet
t-	tertiary
TBAI	tetrabutylammonium iodide
THF	tetrahydrofuran
TMS	tetramethylsilane
Tol	tolyl
Ts	toluenesulfonyl
X	halide
y	yield

Abstract

This thesis entitled "**Synthesis of Chiral C_1- and C_2-Symmetric Nitrogen and Sulfur Heterocycles for Application in Asymmetric Transformations**" comprises of four 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.

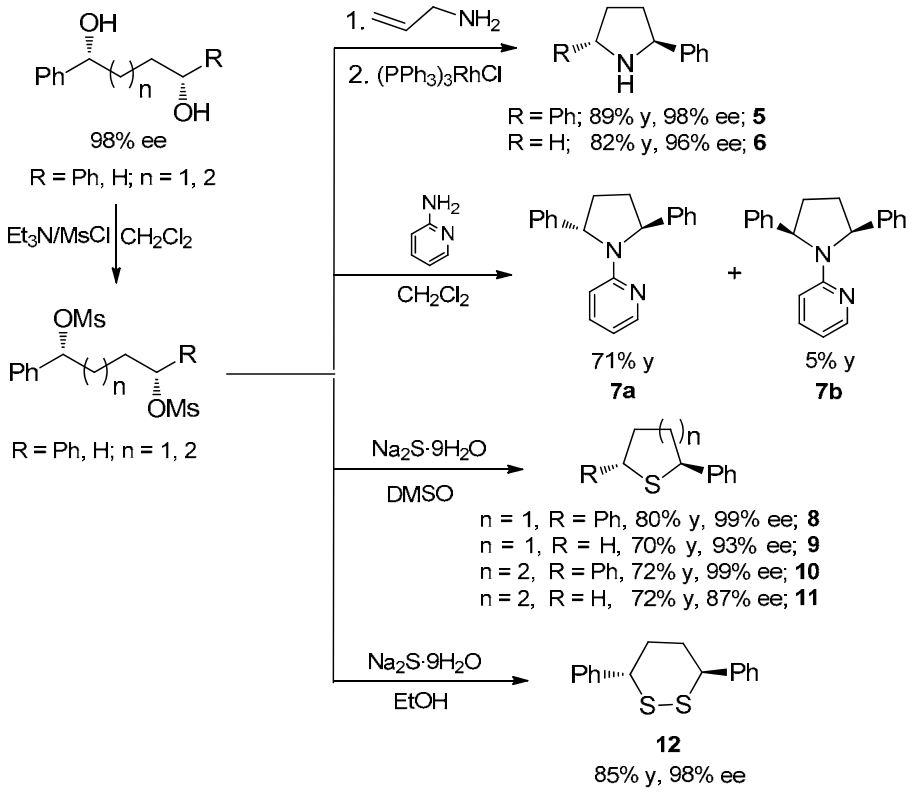
The first chapter deals with development of methods for the synthesis of chiral C_1- and C_2-symmetric phenyl substituted nitrogen and sulfur heterocycle derivatives. A brief review on the methods available for the synthesis of chiral heterocyclic amines and sulfides is presented in the introductory section. We have developed methods for asymmetric reduction of 1,4-diphenylbutan-1,4-dione **1** and 1,5-diphenylpentan-1,5-dione **2** using the chiral oxazaborolidine catalyst and the modified $^{n}Bu_4NBH_4/I_2$ and $^{n}Bu_4NBH_4/CH_3I$ reagent systems (Scheme 1).

Scheme 1



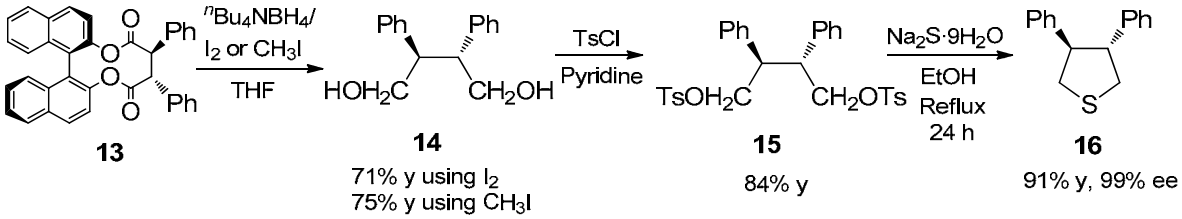
The chiral diols prepared in this way were converted to the (2*S*,5*S*)-2,5-diphenylpyrrolidine **5**, (2*S*)-phenylpyrrolidine **6,** (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **8**, (2*S*)-phenyltetrahydrothiophene **9,** (2*S*,6*S*)-2,6-diphenyltetrahydrothiopyran **10** and (2*S*)-phenylthiopyran **11** in 71-89% yields with 87-99% ee (Chart 1).

Chart 1



We have also developed methods for the synthesis of the chiral sulfide **16** *via* reduction of diester **13** using the $^{n}Bu_4NBH_4$ based borane reagent system (Scheme 2).

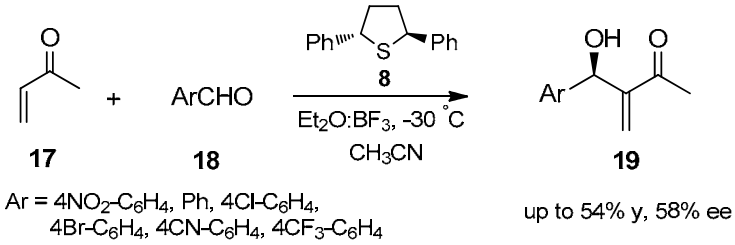
Scheme 2



The second chapter deals with the studies undertaken towards the use of chiral sulfide borane complexes in the reduction of prochiral ketones and in the hydroboration of prochiral olefins.

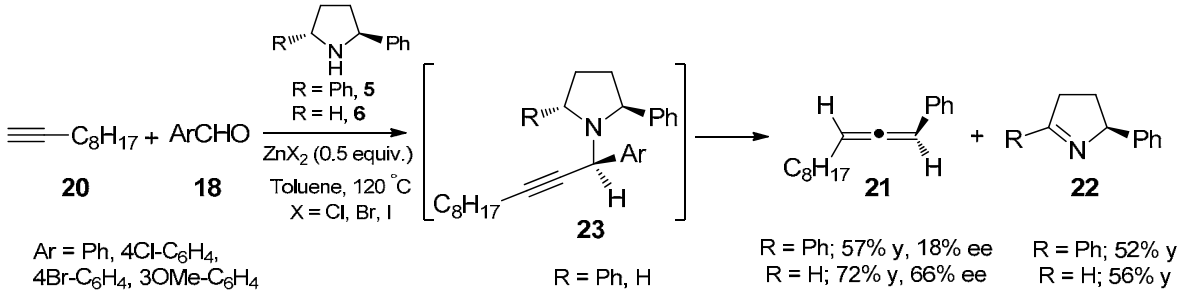
Results of studies on the asymmetric Baylis-Hillman reaction promoted by the C_2-symmetric chiral sulfide **8** in the presence of $Et_2O{:}BF_3$ are described in chapter 3 (Scheme 3).

Scheme 3



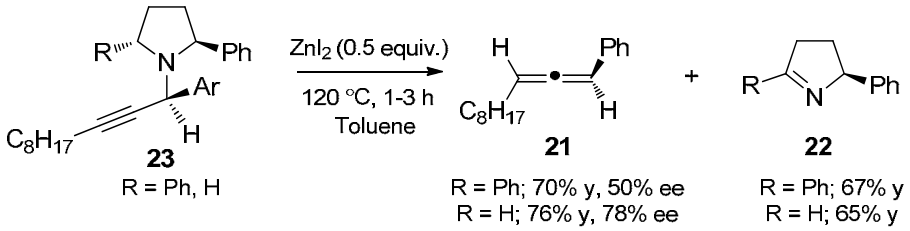
Studies on the application of the chiral C_2-, C_1-symmetric nitrogen heterocycles **5** and **6** in the enantioselective synthesis of chiral allenes *via* creation of a stereogenic center and subsequent chirality transfer are described in chapter 4 (Scheme 4).

Scheme 4



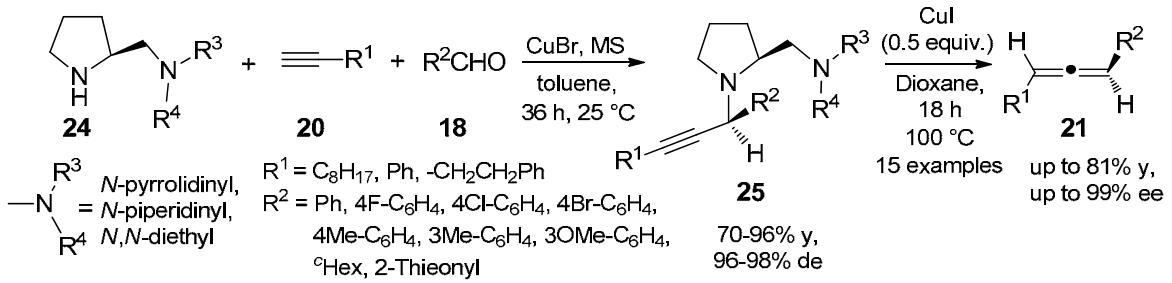
The propargylamine intermediates were isolated by carrying out the reaction at 90 ˚C and converted to the chiral allenes at 120 ˚C (Scheme 5).

Scheme 5



A two step method involving the CuBr promoted reaction of the (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine **24**, 1-alkynes **20** and aldehydes **18** for the preparation of the propargylamine intermediates **25** and subsequent conversion to chiral allenes **21** using CuI in dioxane afforded the chiral allenes with up to 81% yields and 99% ee (Scheme 6).

Scheme 6



The results are discussed by considering mechanistic pathways with appropriate stereochemical models.

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

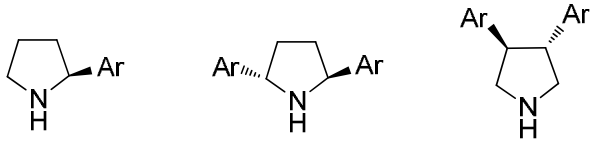
Chapter I

Synthesis of C_1- and C_2-symmetric chiral nitrogen and sulfur heterocycles

1.1 Introduction

1.1.1 Synthesis and applications of chiral C_2-symmetric nitrogen heterocyclic systems

Chiral C_2-symmetric molecules are widely used as auxiliaries and ligands in asymmetric tranformations.[1] The C_2-symmetric derivatives such as 2,5-disubstituted pyrrolidines,[2] borolanes,[3] thiolanes,[4] and phospholanes[5] have been used extensively in various asymmetric organic transfomations. Chiral C_2-symmetric 2,5-disubstituted pyrrolidine derivatives are important class of chiral auxiliaries and are widely used in variety of asymmetric transformations including alkylation, radical cyclizations, Michael addition, enantioselective deprotonation, Claisen rearrangements, Diels-Alder reactions, allylic substitutions, reduction of prochiral ketones and in other asymmetric hydrogenation reactions. Chiral C_2-symmetric 3,4-disubstituted pyrrolidines are useful in dihydroxylations of olefins, asymmetric addition of organometallics to carbonyl compounds and palladium catalysed asymmetric alkylations.



1 **2** **3**

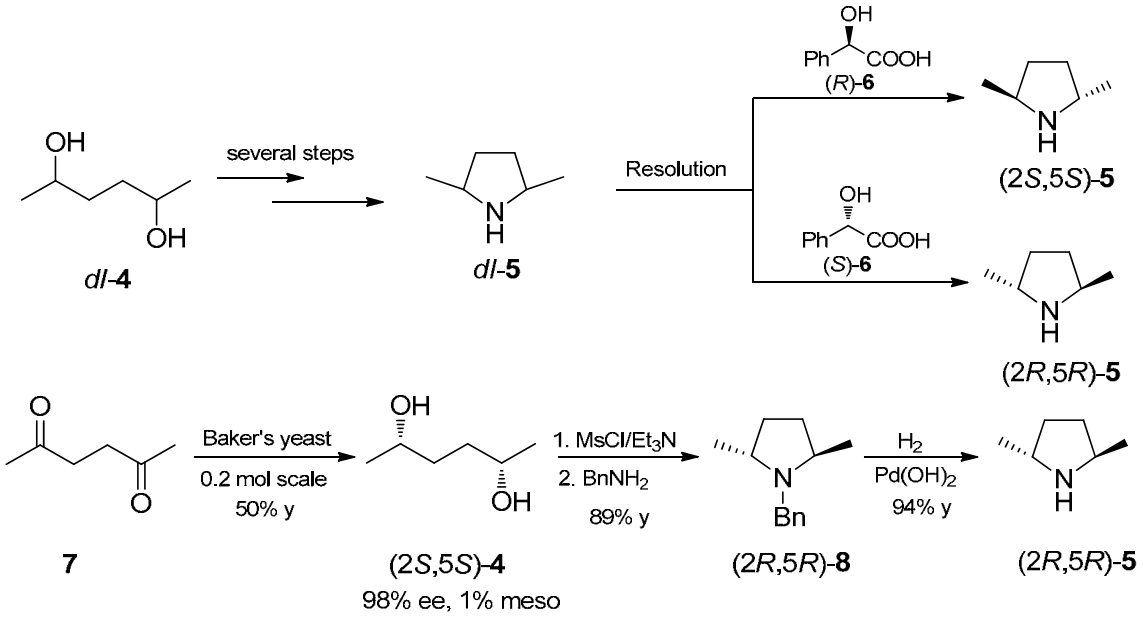
Figure 1

Saturated nitrogen heterocycles including pyrrolidines and piperidines occur in a wide variety of natural products, alkaloids and biologically active compounds.[6] There have been numerous reports on the syntheses of substituted pyrrolidines and other heterocycles in the literature.[7] We have undertaken research efforts towards the synthesis and applications of (*S*)-2-phenylpyrrolidine **1** and *trans*-(2*S*,5*S*)-2,5-diphenylpyrrolidine **2** systems. A brief review on the

synthesis and applications of 2-arylpyrrloidine **1** and 2,5-diarylpyrrolidine **2** systems (Figure 1) would facilitate the discussion.

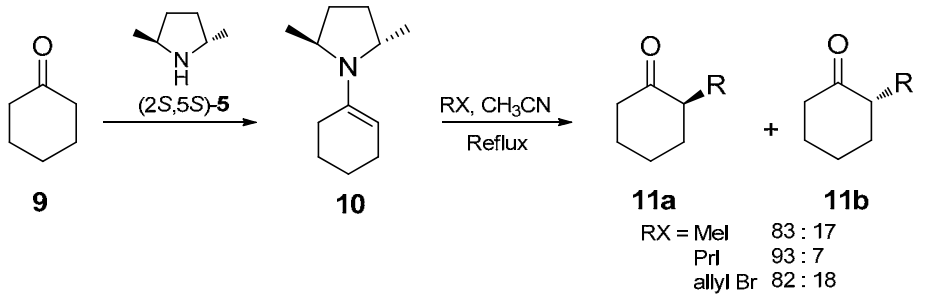
The chiral C_2-symmetric 2,5-dimethylpyrrolidine **5** was first introduced in 1977 by Whitesell and co-workers.[8] This amine has been accessed by catalytic reduction of the corresponding *N*-amino derivative followed by resolution by forming the salt using mandelic acid **6**. Later, a convenient route involving asymmetric Baker's yeast reduction of 2,5-hexanedione **7** followed by mesylation, cyclization using benzylamine and debenzylation has been reported to obtain the enantiomerically pure amine (+)-(2*S*,5*S*)-**5** (Scheme 1).[9]

Scheme 1



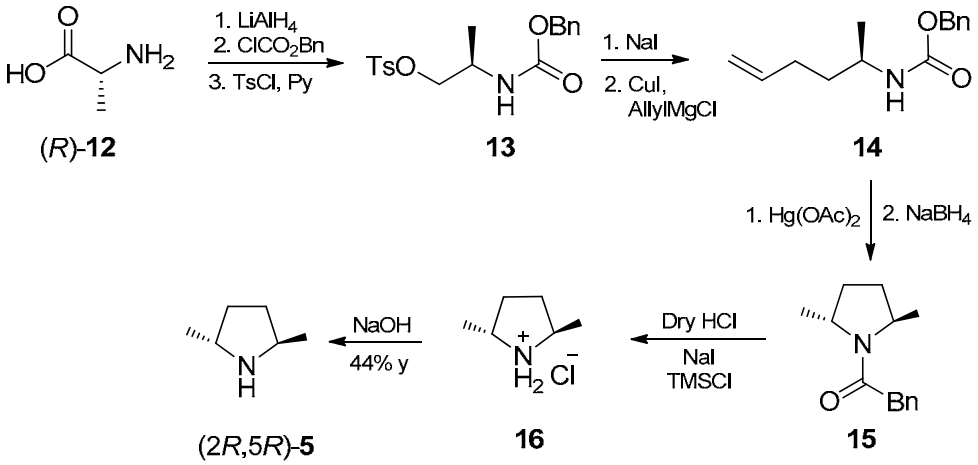
The cyclohexanone enamine **10** derivative of the chiral *trans*-2,5-dimethylpyrrolidine was used in asymmetric alkylations with akyl halides. The corresponding alkylated product **11** was obtained with good enantioselectivity (up to 80% ee) in 50-80% yield (Scheme 2). Whereas, the use of optically pure 2-methylpyrrolidine gave only 50% ee of the alkylated product **11a**.[8,10]

Scheme 2



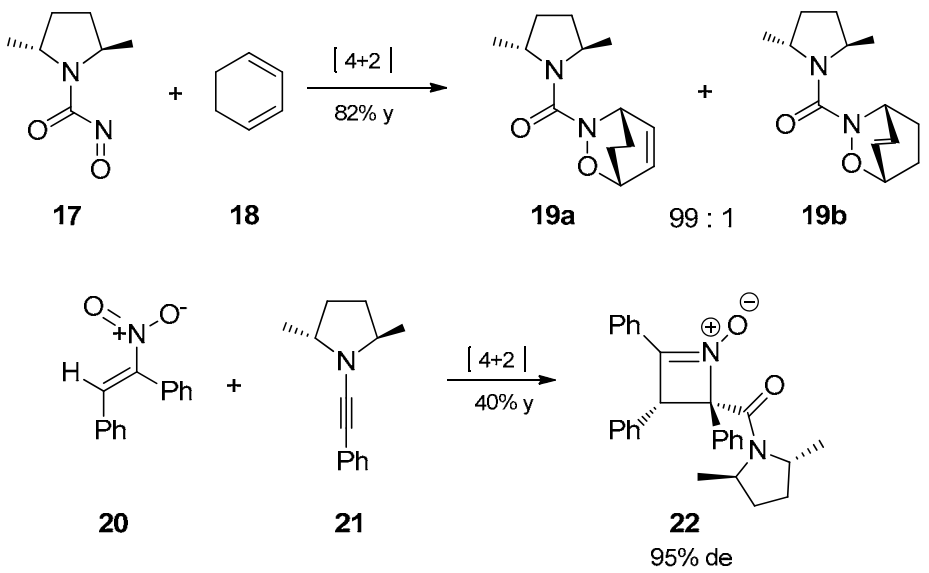
An efficient method for accessing both the optically pure enantiomers of *trans*-2,5-dimethylpyrrolidine **5** starting from D- or L-alanine **12** was reported. This procedure involves the mercury (II) promoted intramolecular amidomercuration method to form the pyrrolidine derivative **15**.[11] The enantiomerically pure product was isolated as its hydrochloride salt in 44% overall yield (Scheme 3).[12]

Scheme 3



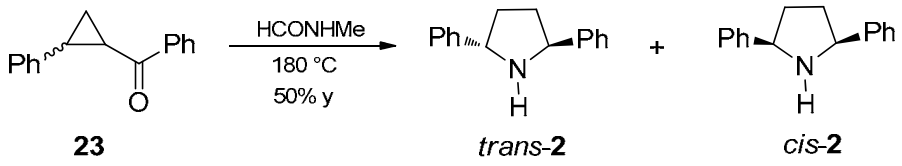
The carbamoyl nitroso dienophile derivative of chiral (-)-*trans*-2,5-dimethylpyrrolidine **17** was used in asymmetric Diels-Alder cycloadditions with the diene **18**. The corresponding cycloadduct **19** was obtained in 82% yield and 98% diastereomeric excess.[13] Similarly, chiral ynamine dienophiles **21** have been utilized in asymmetric [4+2] cycloadditions with α,β-unsaturated nitroalkenes **20** to prepare nitronic esters **22** (Scheme 4).[14]

Scheme 4



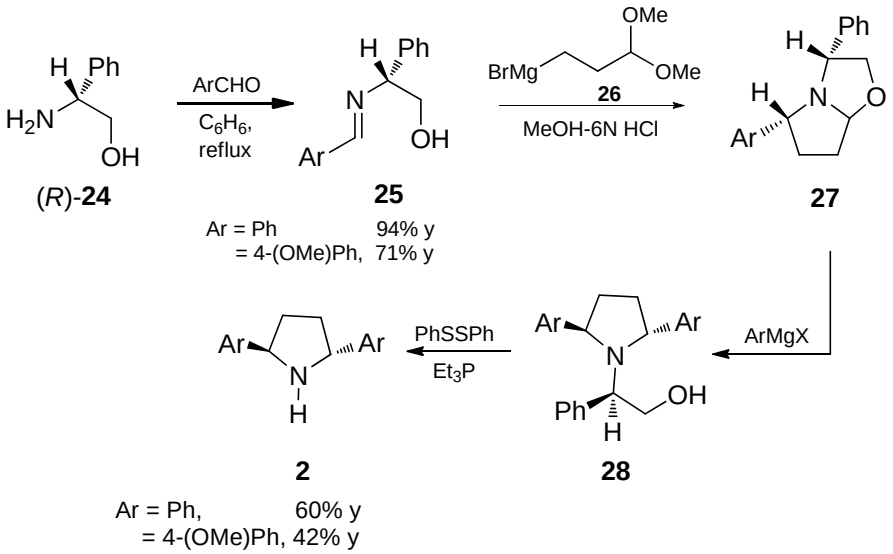
The formation of the mixture of 2,5-diphenylpyrrolidine **2** derivatives by Leuckart reaction using *cis* and *trans*-1-benzoyl-2-phenylcyclopropane **23** *via* opening of the cyclopropane ring with *N*-methylformamide at 180 ˚C was reported (Scheme 5).[15]

Scheme 5



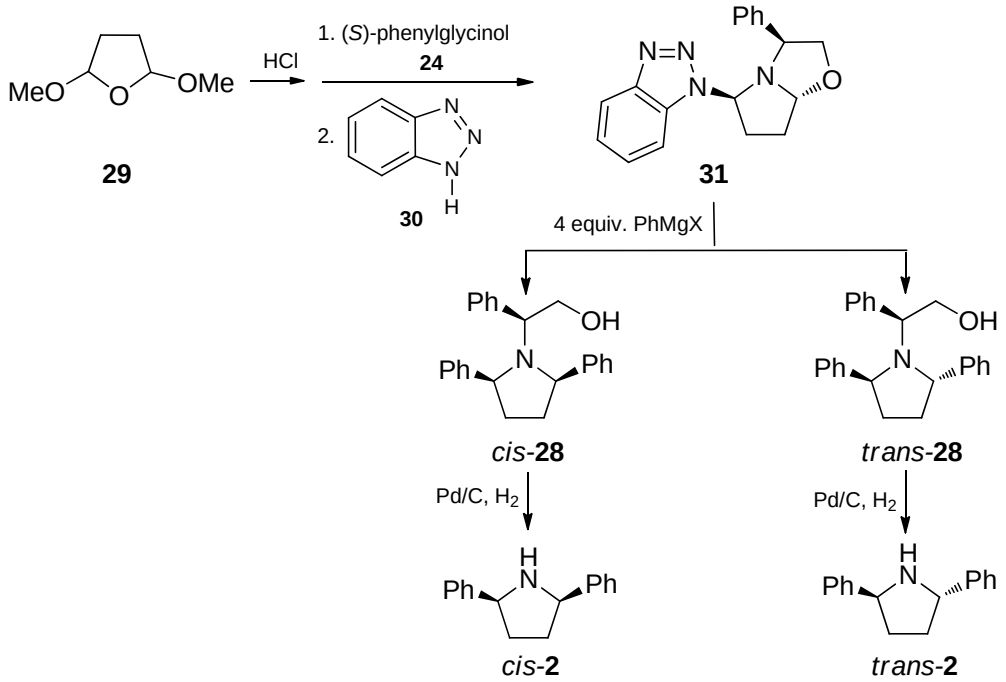
Methods for the synthesis of 2,5-diarylpyrrolidines **2** and 2-arylpyrrolidines **1** derivatives involving diastereoselective addition of Grignard reagents to chiral imines **25** and 1,3-oxazolidines **27** were reported (Scheme 6).[16]

Scheme 6



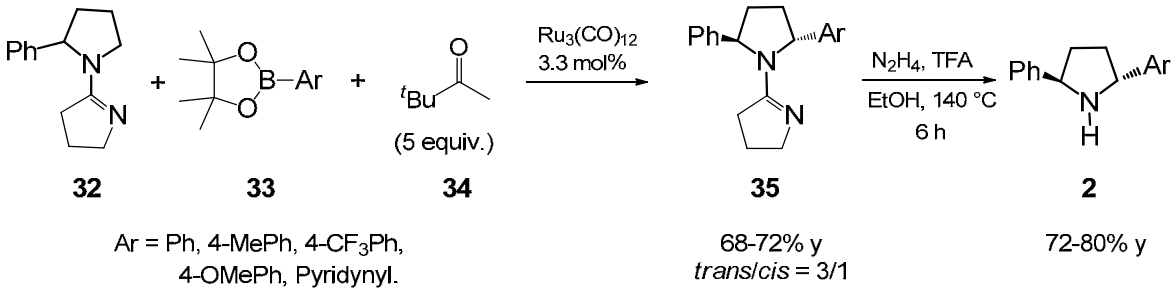
A method for asymmetric synthesis of 2,5-diphenylpyrrolidine **2** from (4*S*,5*R*)-5-(benzotriazol-1-yl)-4-phenyl-[1,2-a]oxazopyrrolidine **31** *via* the phenylglycinol derivative of 2,5-diphenylpyrrolidine **28** was reported (Scheme 7).[17]

Scheme 7



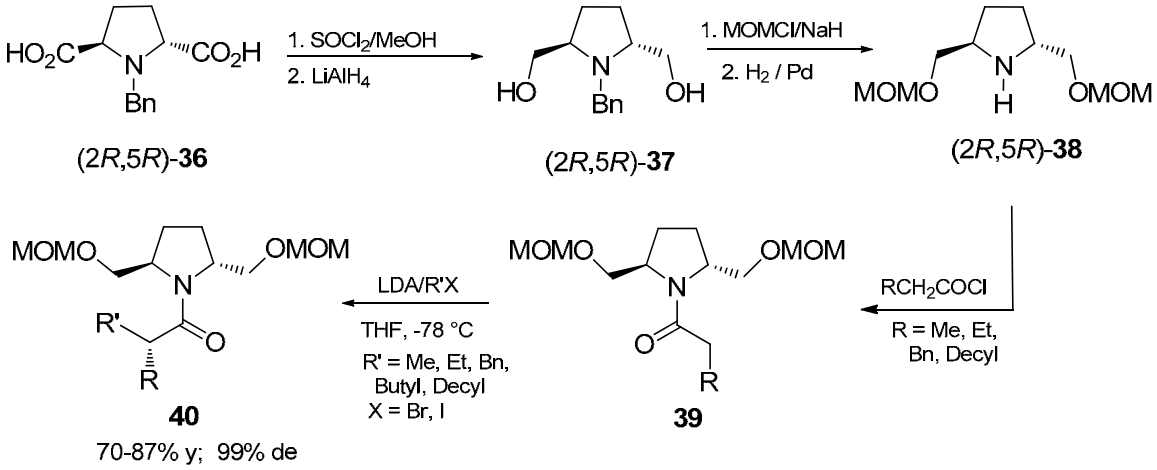
A synthetic protocol for accessing pyrrolidine and piperidine derivatives by arylation of sp^3 C-H bonds directed by amidine protecting group *via* transmetallation with arylboronates **33** in the presence of the ruthenium catalyst (3.3 mol%) and ketone was reported (Scheme 8).[18]

Scheme 8



Synthesis of *trans*-2,5-bis(methoxymethyl)-pyrrolidine **38** was reported from *dl-N*-benzyl-2,5-pyrrolidine dicarboxylic acid **36** which can be readily resolved using D-(-)-threo-(*p*-nitrophenyl)-2-amino-1,3-propanediol.[19] The amine **38** played a prominent role in many asymmetric processes including amide alkylations, acylations, radical additions and Diels-Alder reactions (Scheme 9).[20]

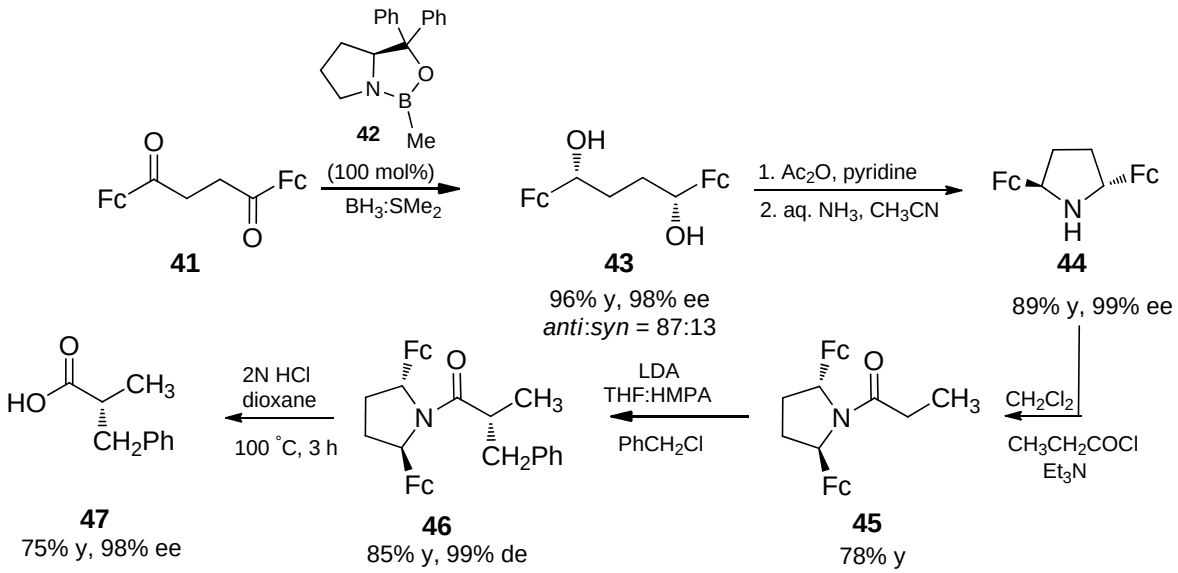
Scheme 9



The new C_2-symmetrical ferrocenyl amine **44**, prepared from the diferrocenyl-1,4-diketone **41** through the CBS reduction, has been used in the diastereoselective alkylations of the

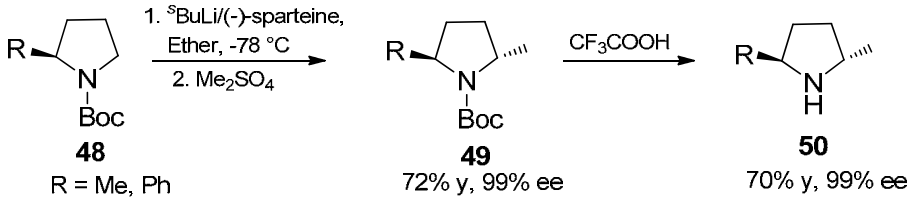
amide **45**.[21] The ferrocenyl group shows better discrimination to give the alkylated product in 85% yield and 99% de (Scheme 10).

Scheme 10



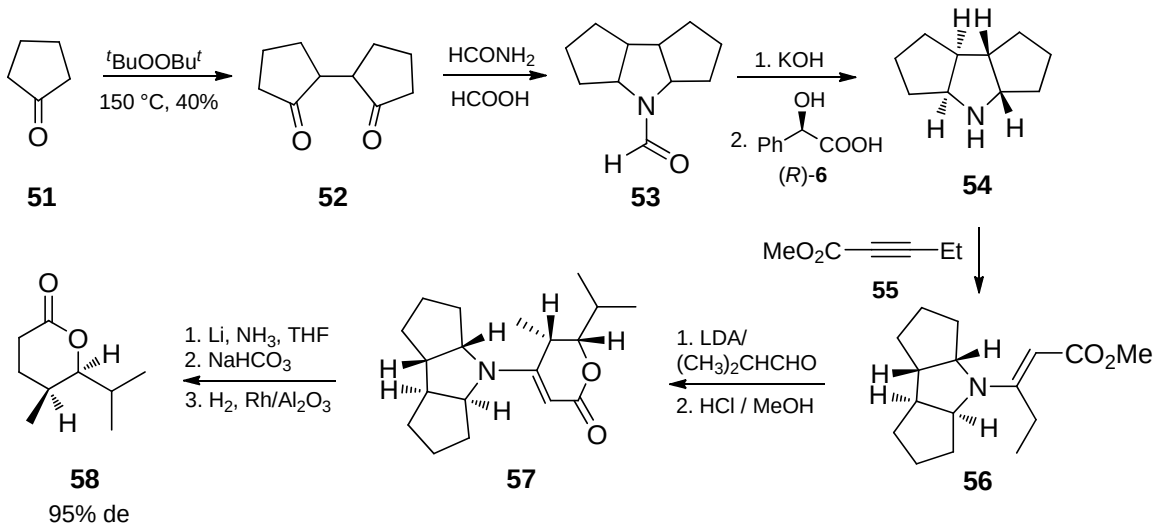
The chiral 2,5-disubstituted pyrrolidine derivatives **50** were synthesized by asymmetric deprotonation of *N*-boc-pyrrolidines **48** using ^{s}BuLi/(-)-sparteine and dimethylsulfate with high enantioselectivity (Scheme 11).[22]

Scheme 11



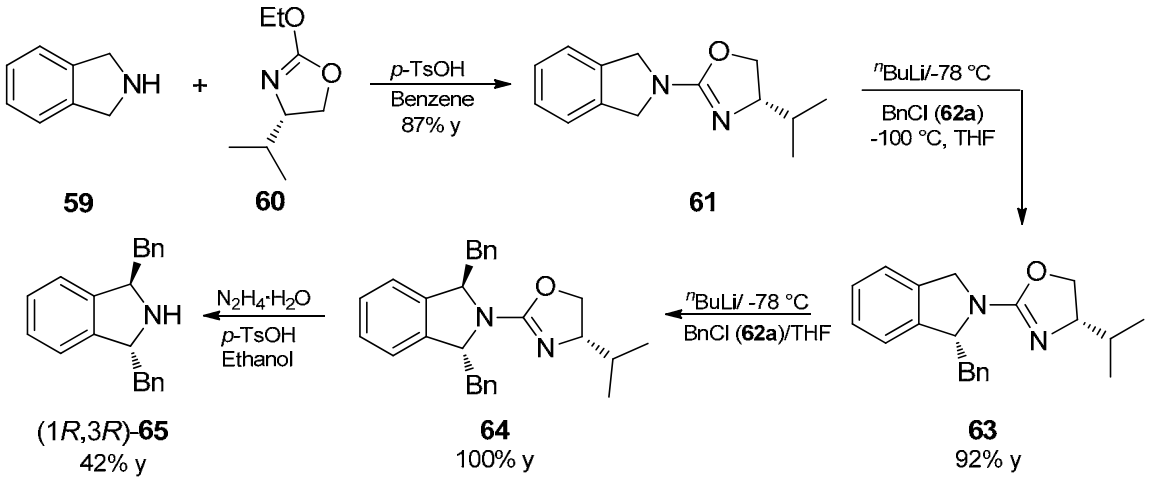
The C_2-symmetric chiral amine **54** was prepared from cyclopentanone **51**, followed by resolution using chiral mandelic acid (*R*)-**6**. The utility of this amine **54** has been demonstrated in the synthesis of a six membered ring lactone **58** with diastereomeric purity up to 95% de (Scheme 12).[23]

Scheme 12



The synthesis of chiral C_2-symmetric (*R*,*R*)-1,3-dibenzylisoindoline **65** involves condensation of isoindoline **59** with ethoxyoxazoline **60** to afford isoindolyloxazoline **61** in 87% yield. Subsequent asymmetric alkylation using benzyl chloride give the mono alkylated product **63** which upon reaction with benzyl chloride affords the dibenzylated product **65** in 89% de**.** After removal of the oxazoline group, the product **65** was obtained in 42% yield (Scheme 13).[24]

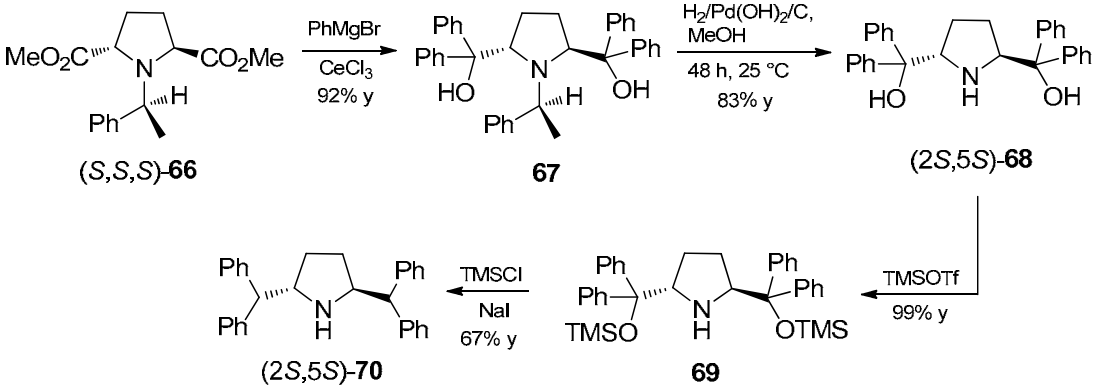
Scheme 13



The highly hindered C_2-symmetric *trans*-(2*S*,5*S*)-(1,1-diphenylmethyl)pyrrolidine **70** was prepared through the nucleophilic addition of PhMgBr to the ester **66** promoted by cerium (III)

chloride, followed by sequence of reactions involving reductive debenzylation, silylation and reduction (Scheme 14).[25]

Scheme 14



The chiral C_2-symmetric lithium amide has been useful in several asymmetric transformations. Also this chiral amine **2** has been useful in asymmetric organocatalytic transformations (Chart 1).

Chart 1.

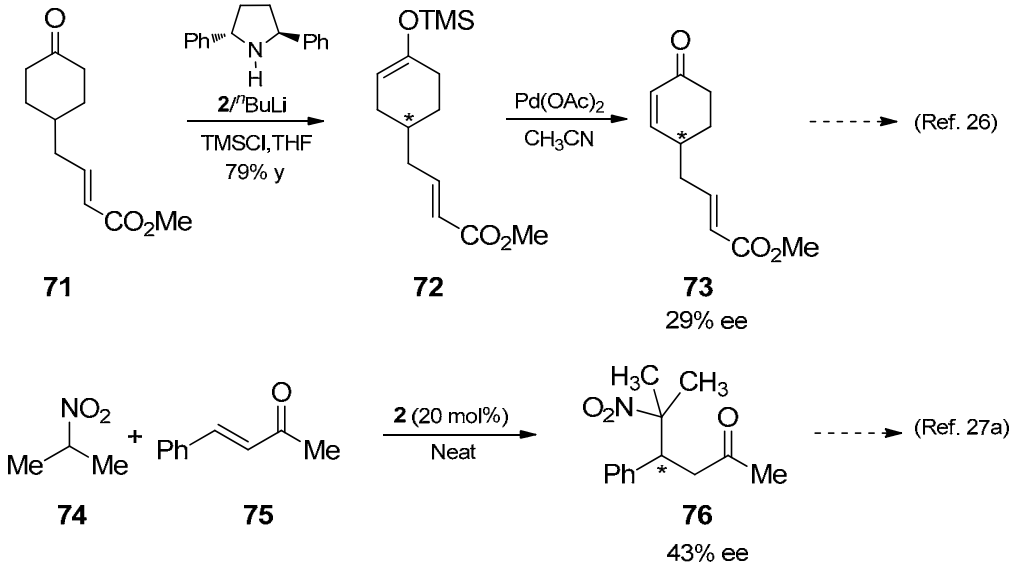
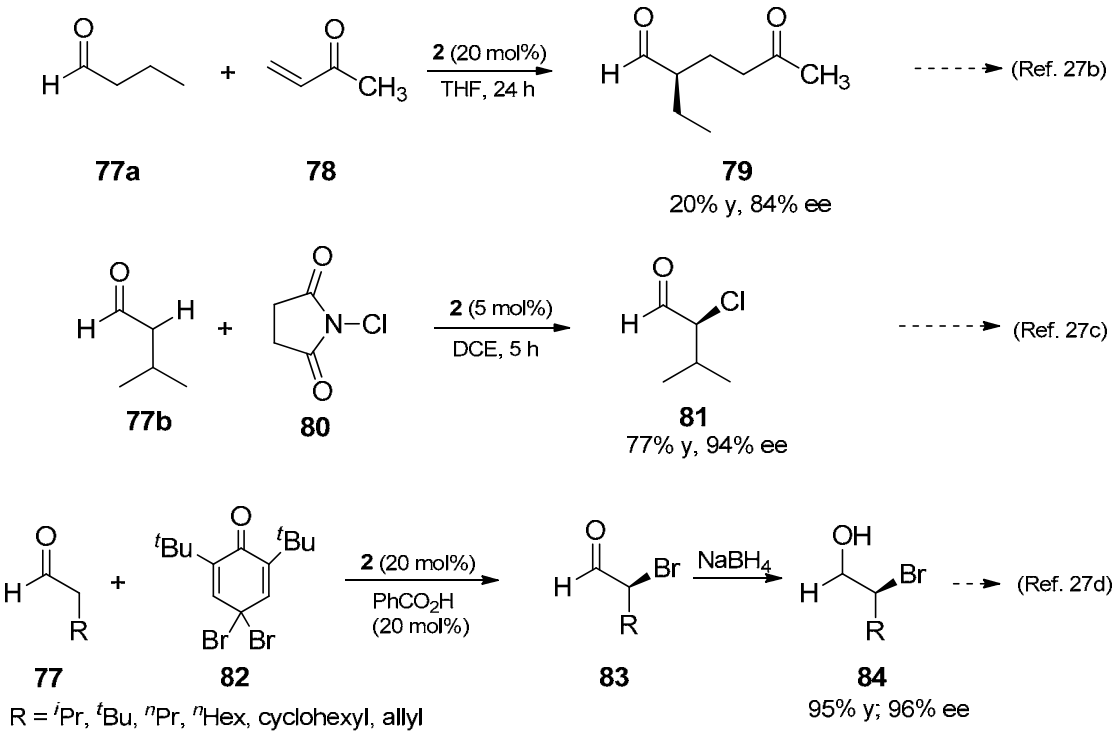
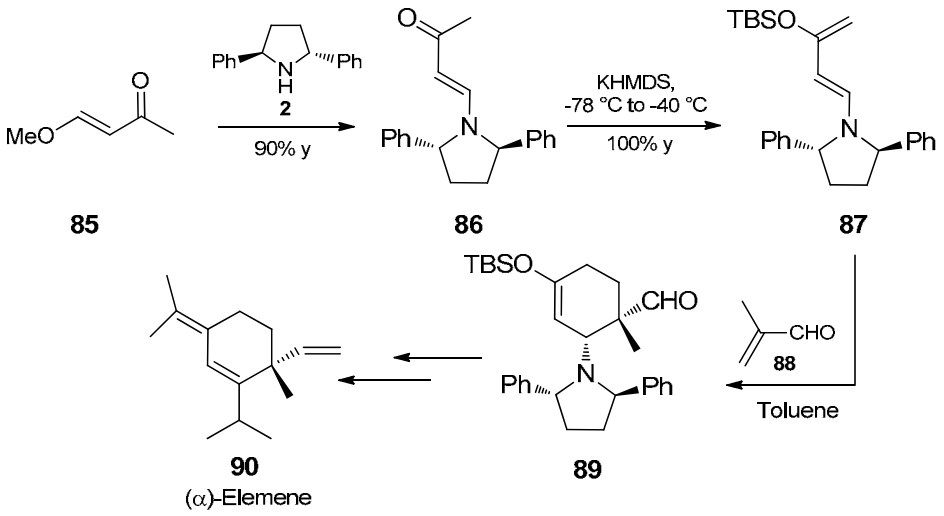


Chart 1 contd…



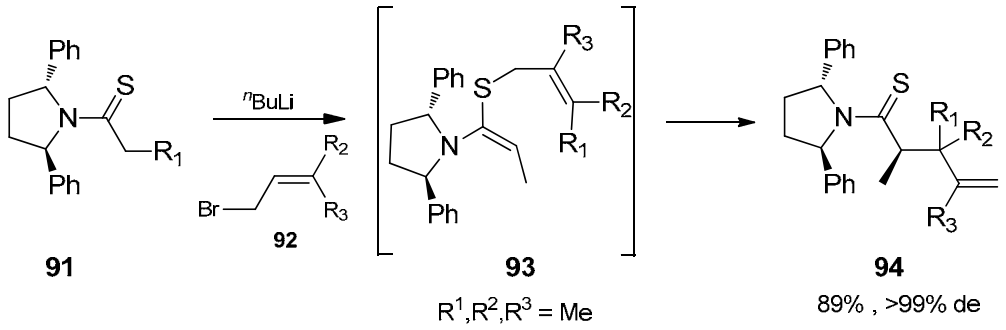
The chiral C_2-symmetric (+)-*trans*-2,5-diphenylpyrrolidine moiety was used in asymmetric Diels-Alder reaction to prepare chiral 1-amino-3-siloxy-1,3-butadiene **87**. It is an important precursor for the enantioselective synthesis of (-)-α-elemene **90** (Scheme 15).[28]

Scheme 15



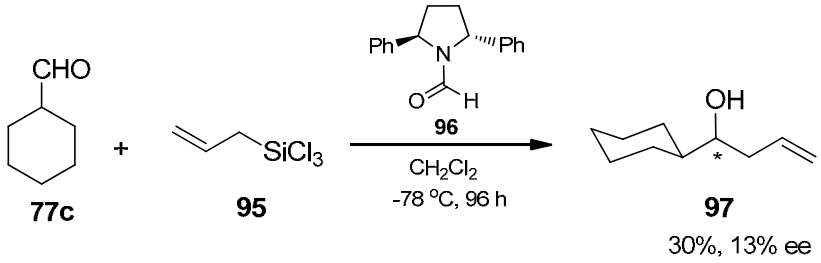
The 2,5-diphenylpyrrolidine thioamide derivative **91** undergoes thio-Claisen rearrangement in the presence of ^{n}BuLi and allylic bromide **92** to give the adduct **94** in 89% yield with 99% de (Scheme 16).[29]

Scheme 16



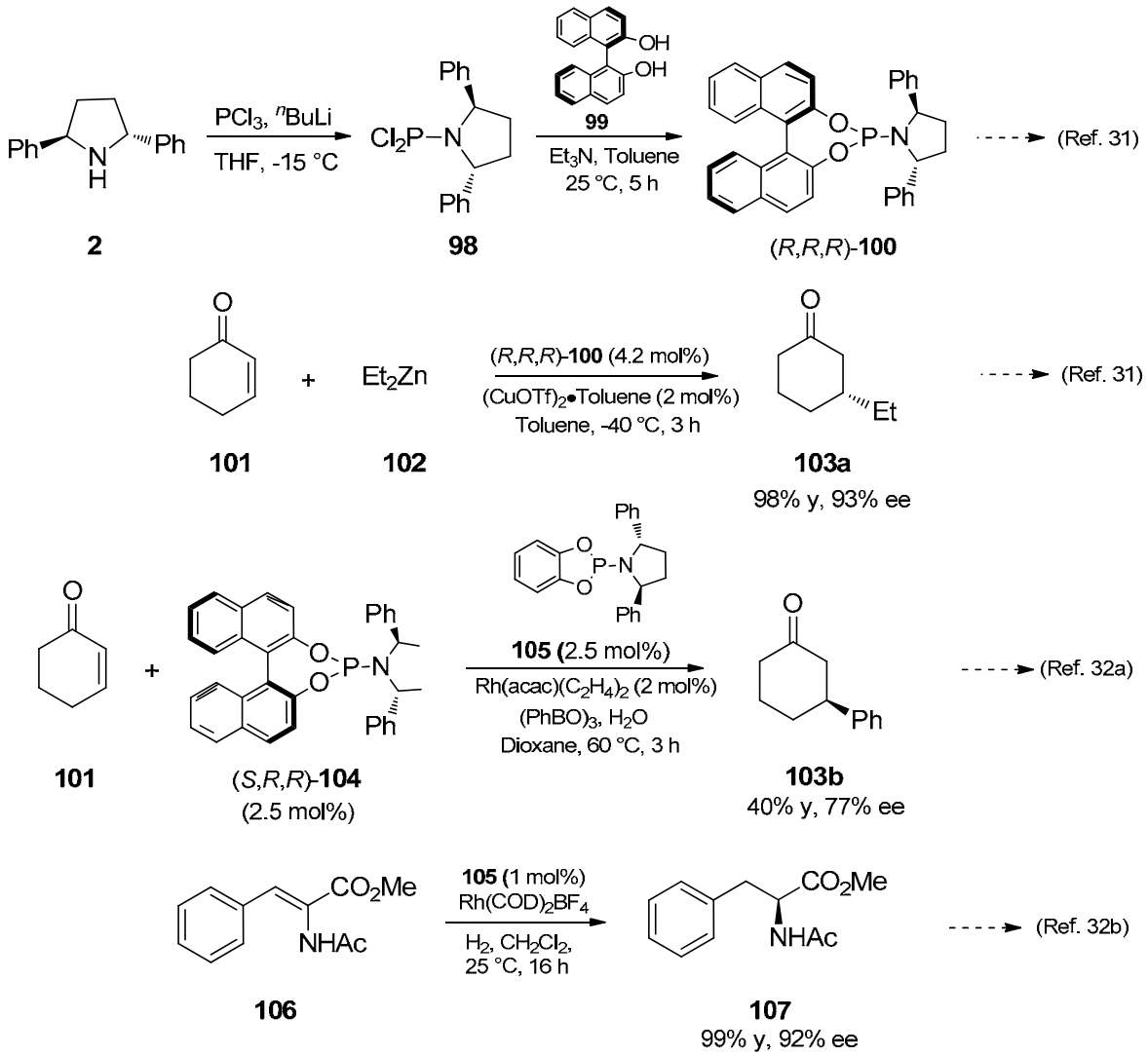
The chiral 2,5-disubstituted pyrrolidine formamide derivative **96** catalyses the asymmetric allylation reaction between aldehyde **77** and trichloroallylsilane **95** to give the allylic alcohol **97** in 13% ee (Scheme 17).[30]

Scheme 17



Recently, the preparation of chiral phosphoramidite ligand **100** has been reported using the C_2-symmetric amine moiety **2** and chiral 1,1'-bi-2-naphthol **99**. It is useful for copper-catalyzed asymmetric conjugate addition reactions (Chart 2).

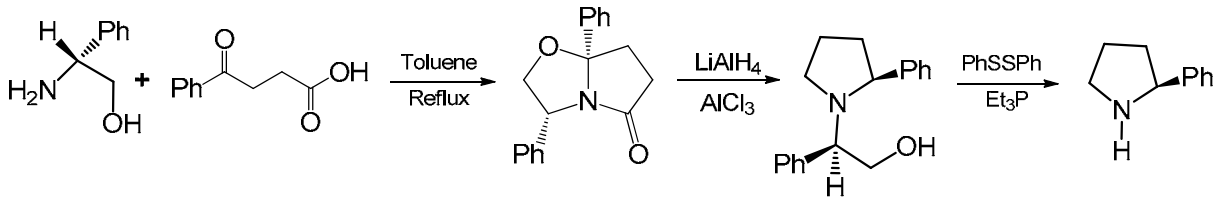
Chart 2.



1.1.2 Synthesis and applications of chiral C_1-symmetric nitrogen heterocyclic systems

Asymmetric synthesis of enantiomerically pure 2-substituted pyrrolidines from γ-keto acid **108** and (*R*)-phenylglycinol **24** has been reported.[33] The *N*-substituted pyrrolidinone **109** obtained was reduced to the *N*-glycinol pyrrolidine derivative **110** using alane which upon reaction with diphenyl disulfide and triethylphosphine gave the 2-phenylpyrrolidine **1** (Scheme 18).

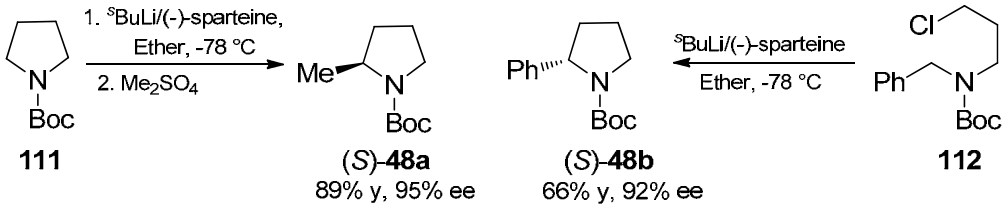
Scheme 18



(*R*)-**24** **108** **109** **110** **1**

A method for the synthesis of chiral C_1-symmetric 2-substituted pyrrolidines **48** was reported *via* asymmetric deprotonation of *N*-boc-pyrrolidines **111** and arylmethyl-3-chloro propyl-boc-amines **112** using ^{s}BuLi/(-)-sparteine with high enantioselectivity (Scheme 19).[22]

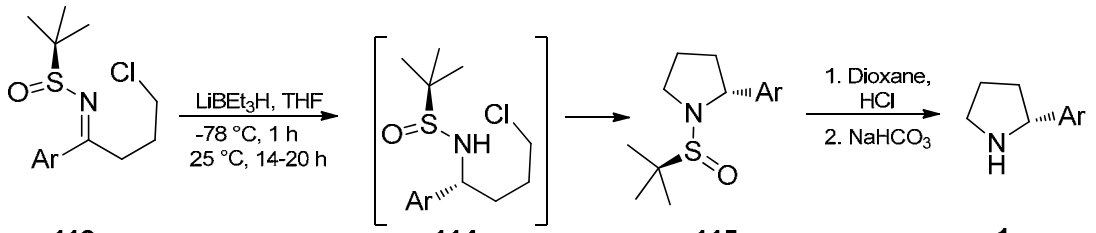
Scheme 19



111 (*S*)-**48a** 89% y, 95% ee (*S*)-**48b** 66% y, 92% ee **112**

Enantioselective reductive cyclization of γ-chloro *N*-(tert-butanesulfinyl)ketimines **113** using $LiBEt_3H$ gives (S_s,*R*)-2-aryl-1-(^{t}butanesulfinyl)pyrrolidines **115** which after deprotection using HCl afforded the 2-arylpyrrolidine **1** in 84% yield (Scheme 20).[34]

Scheme 20



113 **114** **115** **1**

Ar = Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-OMe-C_6H_4

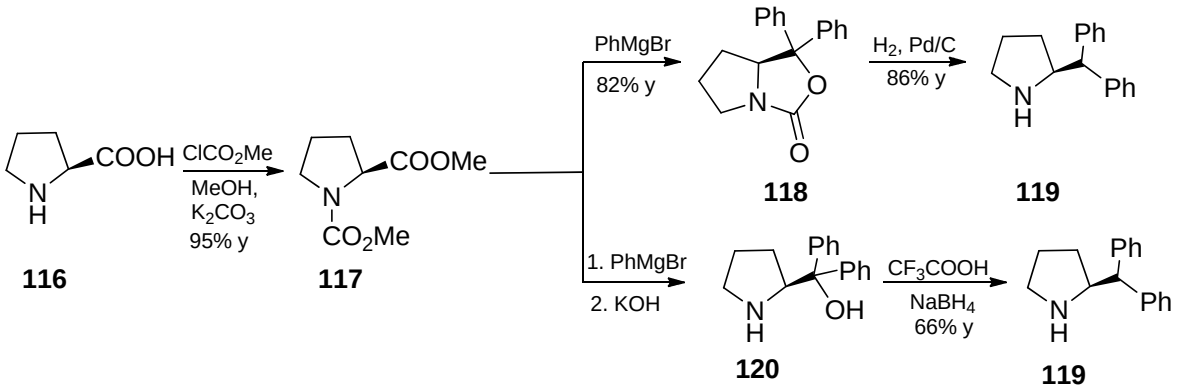
Ar = Ph, 82% y

Ar = Ph, 84% y

The (*S*)-2-(diphenylmethyl)pyrrolidine **119** has been used as a chiral solvating agent for the NMR analysis of chiral carboxylic acids and some secondary alcohols.[35] The synthesis of

119 invoves the hydrogenation of **118** on Pd/C. In this laboratory, a slightly different method involving $NaBH_4/CF_3CO_2H$ for the reduction of (*S*)-α,α'-diphenylprolinol **120** was followed to obtain the chiral amine **119** in 66% yield (Scheme 21).[36]

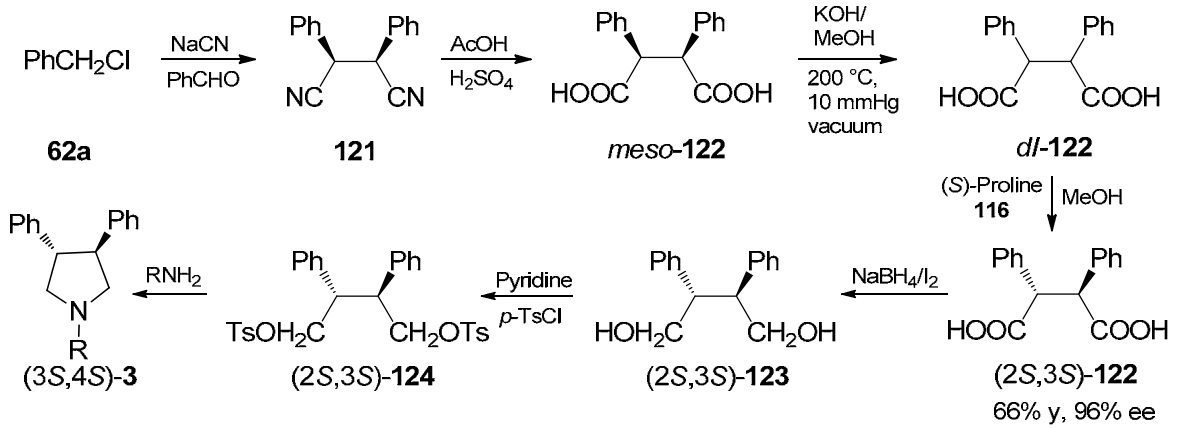
Scheme 21



1.1.3 Synthesis and applications of chiral 3,4-diphenylpyrrolidine systems

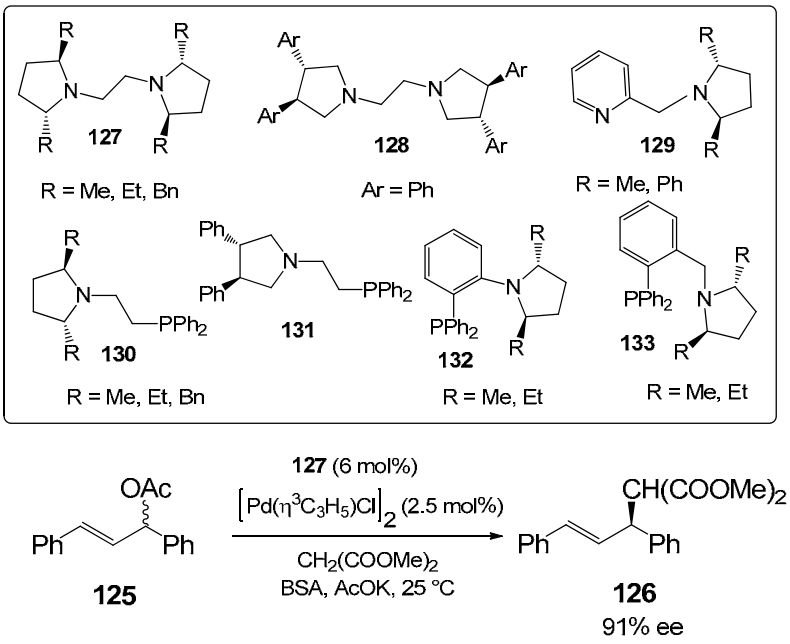
The chiral 3,4-diphenylpyrrolidine system has found extensive use as a chiral ligand in asymmetric synthesis. Synthesis of the chiral amine **3** was reported starting from 2,3-diphenylsuccinic acid **122** (Scheme 22).[37-40]

Scheme 22



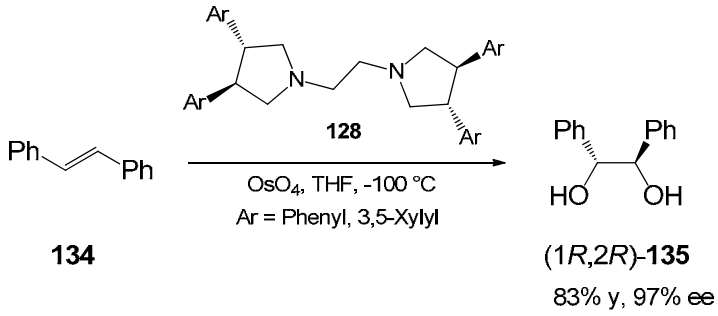
The chiral C_2-symmetric 2,5- and 3,4-disubstituted pyrrolidine derivatives **127**-**133** were used in enantioselective palladium-catalyzed alkylations (Scheme 23).[41]

Scheme 23



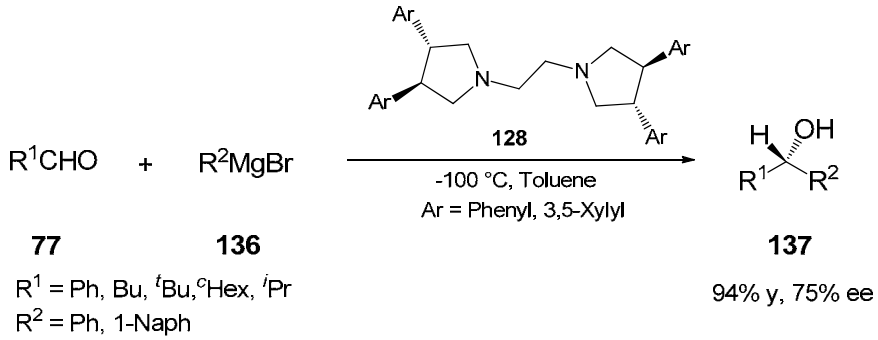
The chiral 3,4-diphenyl pyrrolidine system **128** has been also utilized in stoichiometric amounts for asymmetric osmylation of olefin **134** to obtain the corresponding chiral diol **135** in high enantioselectivity (up to 97% ee) (Scheme 24).[42]

Scheme 24



Also, the use of the chiral diamines **128** in asymmetric addition of Grignard reagent to the carbonyl compound resulted in the formation of the chiral carbinols **137** in 94% yield with 75% ee (Scheme 25).[43]

Scheme 25

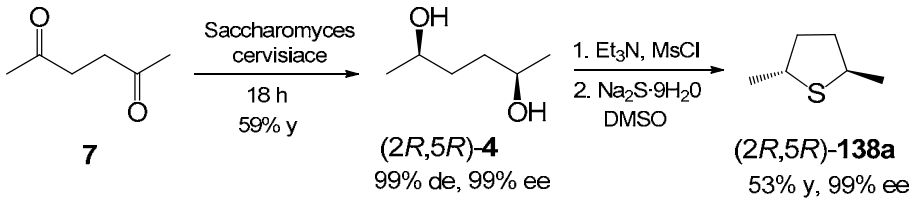


1.1.4 Synthesis and applications of chiral sulfur heterocyclic systems

Chiral ligands containing sulfide moieties are useful in many asymmetric transformations like asymmetric epoxidation, catalytic cyclopropanation of electron deficient alkenes,[44] electrophilic sulfenylation of unsaturated carbon-carbon bonds[45] and aziridination of imines.[46] The chiral sulfides are also useful for the synthesis of chiral alcohols and amines from organo boranes,[47] synthesis of carbocycles[48] and functionalized *N*-heterocycles.[49]

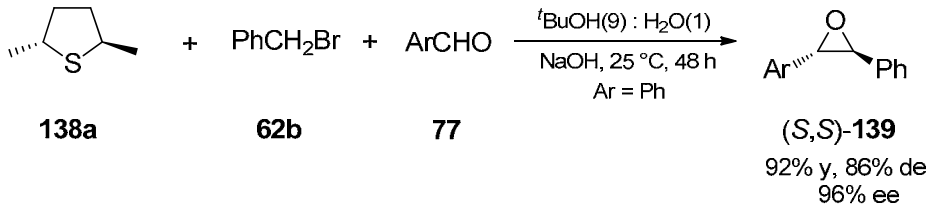
The chiral C_2-symmetric sulfide (+)-(2*R*,5*R*)-*trans*-2,5-dimethylthiolane **138a** was synthesized from (+)-(2*S*,5*S*)-2,5-dimethylhexanediol **4** with 99% de and 99% ee (Scheme 26).[50]

Scheme 26



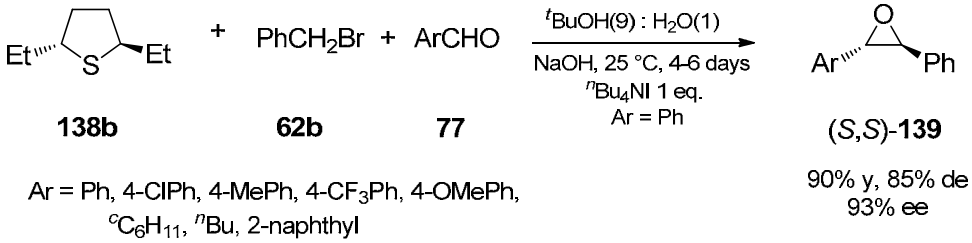
The chiral sulfide (+)-(2*R*,5*R*)-*trans*-2,5-dimethylthiolane **138a** was used in stochiometric amounts for one-pot asymmetric synthesis of chiral epoxides **139** from various aldehydes with benzyl bromide **62b** and NaOH (Scheme 27).[51a-d]

Scheme 27



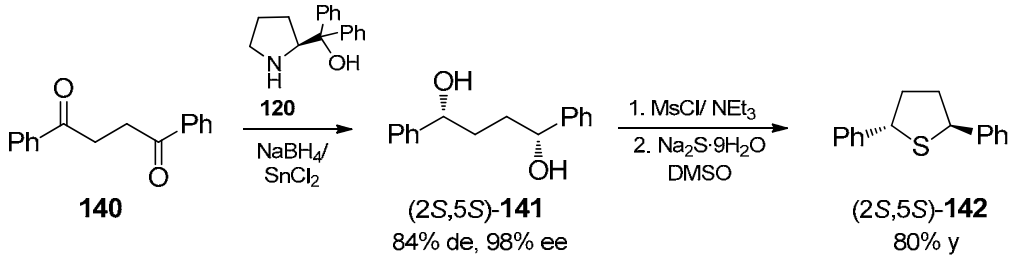
Also, a catalytic cycle was reported using $^{n}Bu_4NI$ as phase transfer catalyst to access various chiral oxiranes **139** up to 97% yield and 93% ee (Scheme 28).[51e]

Scheme 28



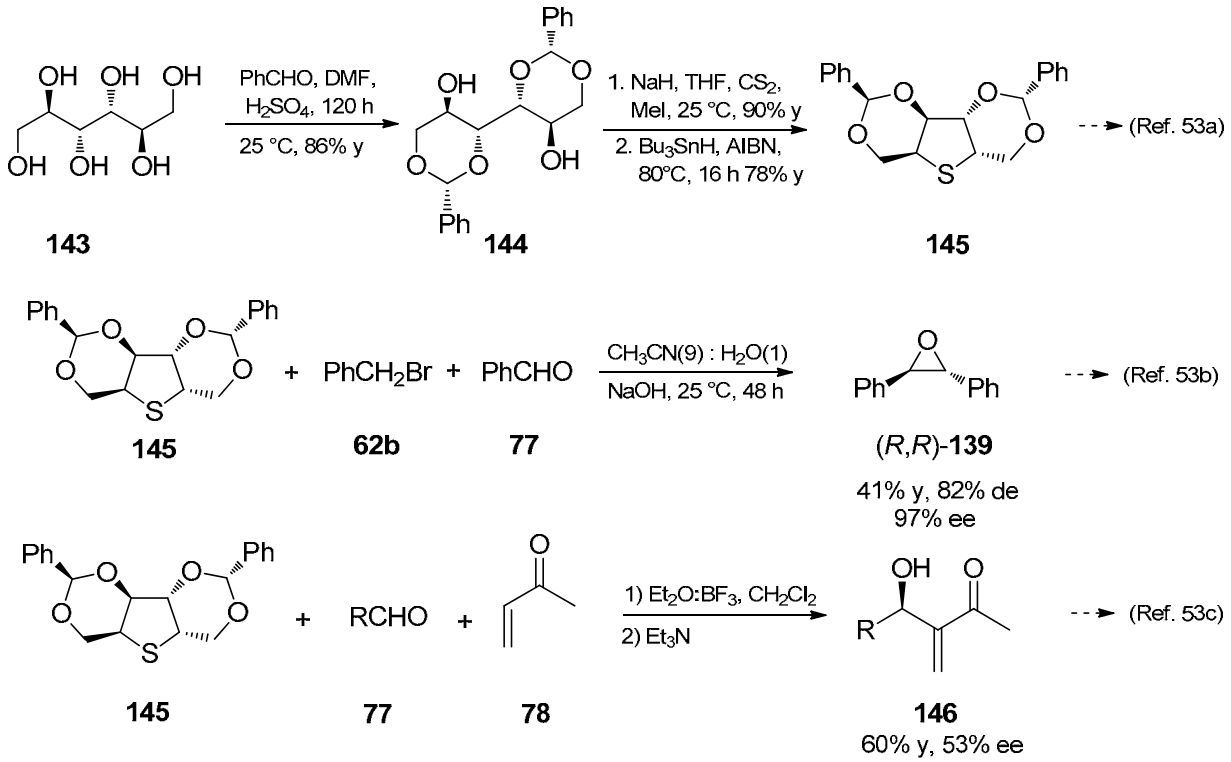
Synthesis of the chiral C_2-symmetric (2*S*,5*S*)-*trans*-2,5-diphenyltetrahydrothiophene **142** involving asymmetric reduction of diketone **140** using borane reagent $NaBH_4/SnCl_2$ in the presence of (*S*)-DPP **120** was reported. After mesylation of the chiral diol **141** (>98% ee) and cyclization with sodium sulfide, the chiral thiolane (+)-(2*S*,5*S*)-**142** was obtained in 80% yield (Scheme 29).[52]

Scheme 29



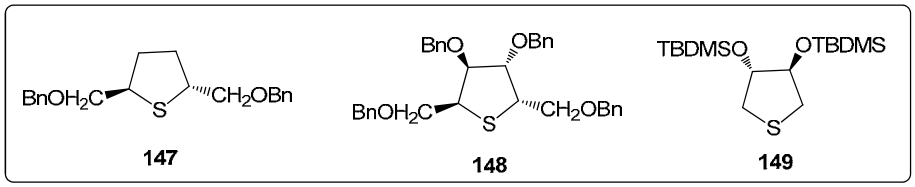
Synthesis of chiral C_2-symmetric tricyclic sulfide **145** from D-mannitol **143** has been reported. It has been used in asymmetric epoxidation and in Baylis-Hillman reactions (Chart 3).

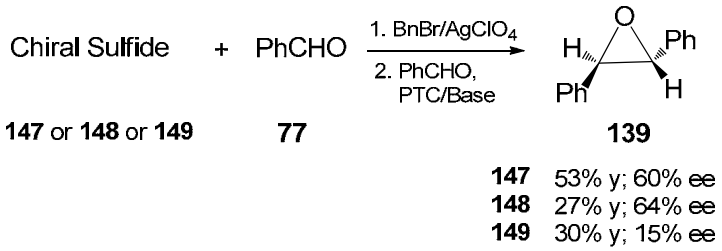
Chart 3



The chiral C_2-symmetrical 2,5- and 3,4-disubstituted sulfides (**147**-**149**) were also used in asymmetric epoxidation with arylaldehyde in presence of a phase transfer catalyst (PTC) and mineral base. The stilbene epoxides **139** were obtained in 27-94% yields with up to 64% ee (Scheme 30).[54]

Scheme 30





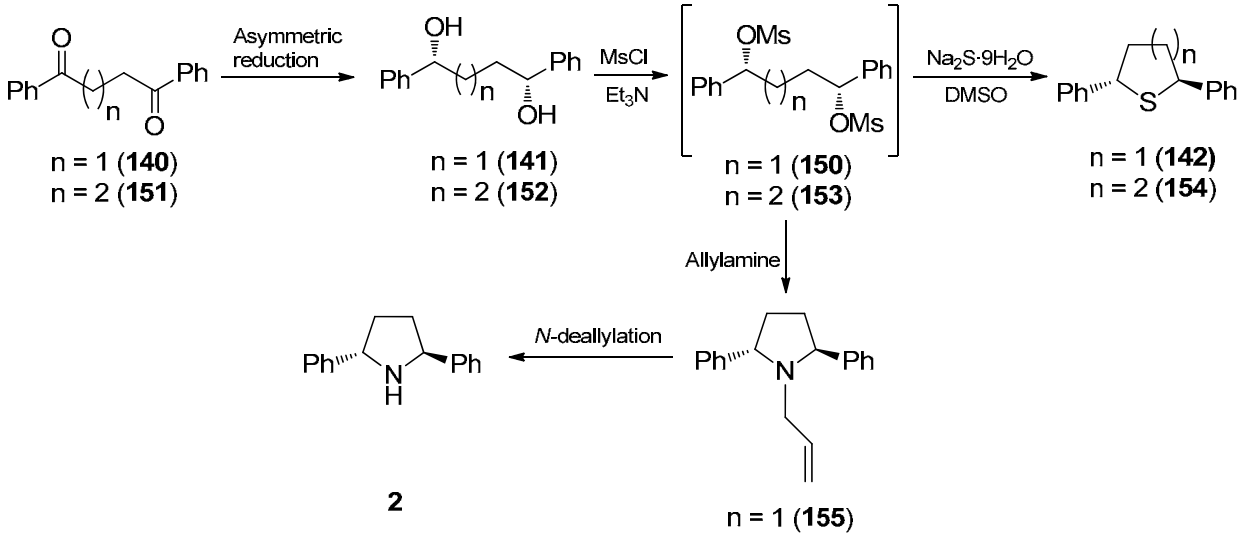
We have undertaken studies on the synthesis of 2,5-diphenyl, 2-phenyl, 2,6-diphenyl and 3,4-diphenyl substituted five and six membered nitrogen and sulfur heterocycles. The results are discussed in the next section.

1.2 Results and Discussion

1.2.1 Synthesis of disubstituted pyrrolidine, tetrahydrothiophene and tetrahydrothiopyran

As outlined in the introductory section, the chiral *trans*-2,5-dimethylpyrrolidine was introduced for applications in organic synthesis by Whitesell and co-workers.[1] In this case, the recovery and recycling of the chiral auxiliary is somewhat difficult. The corresponding 2,5-diphenylpyrrolidine derivative is a non-volatile compound and hence, it can be readily recovered after use. Therefore, we have decided to develop methods to synthesize C_1- and C_2-symmetric chiral nitrogen and sulfur heterocyclics with phenyl substituent by following methods developed in this laboratory. The synthetic strategies and the reactions involved are outlined in Scheme 31.

Scheme 31

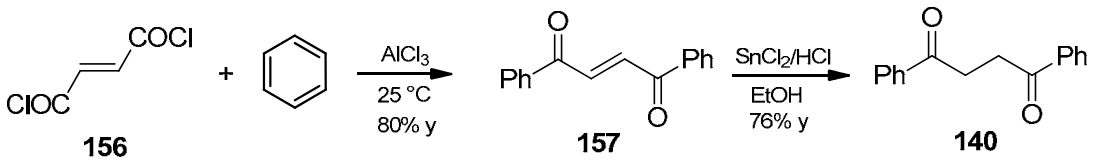


1.2.2 Preparation of 1,4-diphenylbutan-1,4-dione

The required 1,4-diphenylbutan-1,4-dione **140** was prepared in large quantities by following a well established protocol through Friedel-Crafts acylation of benzene in the presence of Lewis acid $AlCl_3$ with fumaryl chloride to get 1,4-diphenylbut-2-ene-1,4-dione **157** and

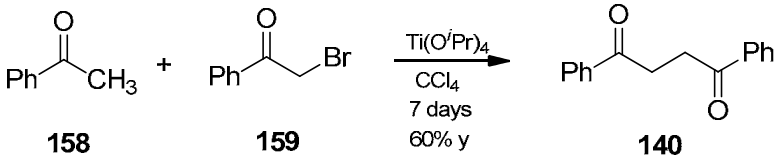
subsequent reduction using the $SnCl_2$/HCl reagent system to obtain the 1,4-diphenylbutan-1,4-dione **140** (Scheme 32).[55,56]

Scheme 32



The 1,4-diphenylbutan-1,4-dione **140** can also prepared in one step through the reaction of phenacylbromide **159** with acetophenone **158** in the presence of $Ti(O^iPr)_4$ (Scheme 33).[57]

Scheme 33

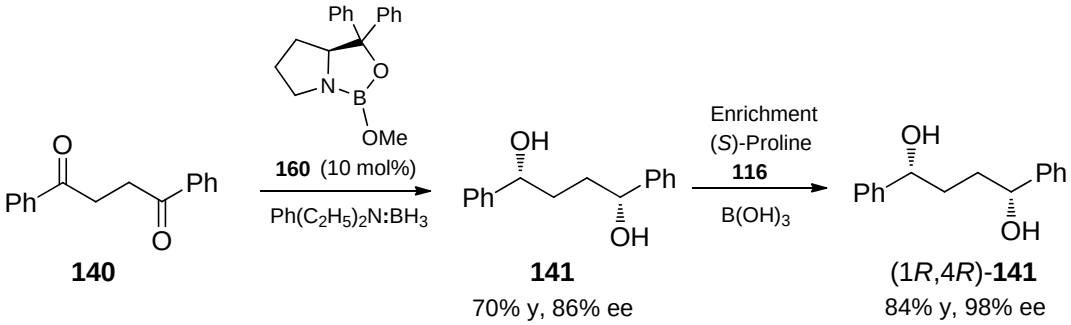


1.2.3 Asymmetric reduction of 1,4-diphenylbutan-1,4-dione

In 1995, Chong *et al*.[58] reported the asymmetric reduction of 1,4-diphenylbutan-1,4-dione **140** using the reagent (-)-diisopinocampheylchloro-borane Ipc_2BCl in stoichiometric amounts. However, the disadvantage of this method is the requirement of removal of the chiral auxiliary which is tedious. Later, Quallich[59] and Steel[60] reported methods to reduce 1,4-diketones with oxazaborolidine catalyst with BH_3**:**THF and BH_3**:**$S(CH_3)_2$. Although these methods gave good enantioselectivity, they involve handling of highly moisture sensitive reagents like BH_3**:**THF. Also, this borane complex is thermally unstable reagent, needs storing below 4 ˚C. A convenient route to synthesize chiral diols has been developed using *N,N*-diethylaniline-borane which is relatively stable, less moisture sensitive and easier to prepare and store without loss of hydride.[61]

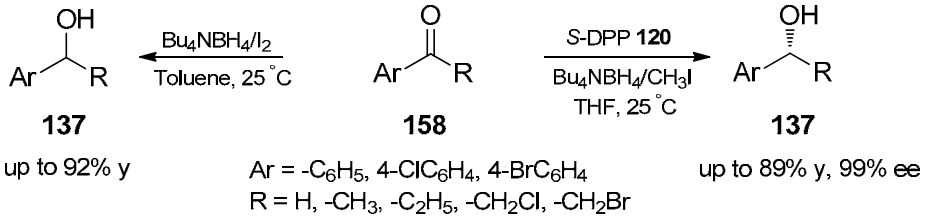
Recently, it was reported from this laboratory that asymmetric reduction of 1,4-diphenylbutan-1,4-dione **140** using *B*-methoxyoxazaborolidine (10 mol%) prepared *in situ* using (*S*)-α,α'-diphenylpyrrolidinemethanol, $B(OMe)_3$ and *N*,*N*-diethylaniline**:**borane complex gave the chiral diol **141** in good enantioselectivity (86% ee) besides 10% meso (Scheme 34).[62] Later, Zhao *et al*.[52] reported a method for reduction of diketones using borane reagent $NaBH_4/SnCl_2$ in the presence of catalyst (*S*)-DPP **120**.

Scheme 34



More recently, methods have developed based on the use of $^{n}Bu_4NBH_4$ reagent in combination with I_2 or CH_3I or benzylchloride in THF.[63] Also, the use of this reagent combination in the oxazaborolidine catalyzed asymmetric reduction of prochiral ketones gave the corresponding chiral secondary alcohols with up to 99% ee (Scheme 35).[64]

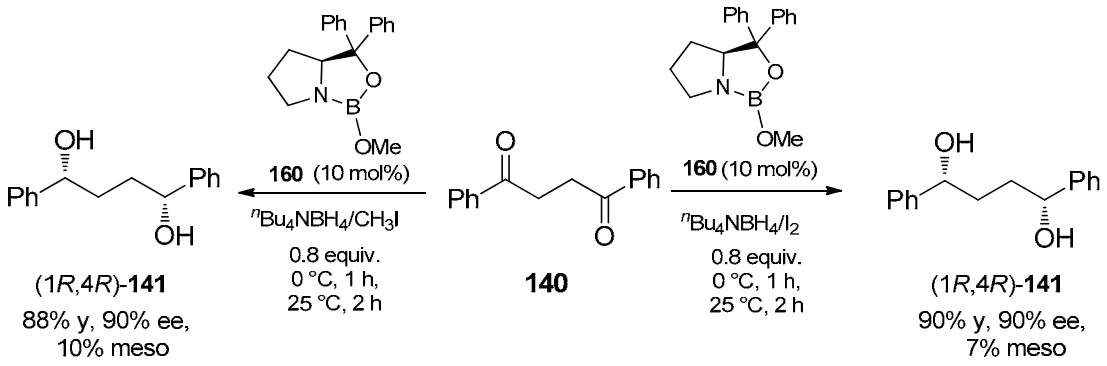
Scheme 35



We envisaged the utility of this modified borohydride $^{n}Bu_4NBH_4$ in combination with I_2 and iodomethane for the reduction of 1,4-diketone in the presence of oxazaborolidine **160** (10

mol%). We have observed that in this case the chiral (+)-(1*R*,4*R*)-1,4-diphenylbutan-1,4-diol **141** is formed in 90% yield (90% ee, 7% meso) using 0.8 equivalent of $^{n}Bu_4NBH_4/I_2$. We have also found that the use of the $^{n}Bu_4NBH_4/CH_3I$ (0.8 equiv.) reagent system for the reduction of 1,4-diketone **140** gave the diol **141** in 88% yield (90% ee, 10% meso) (Scheme 36).

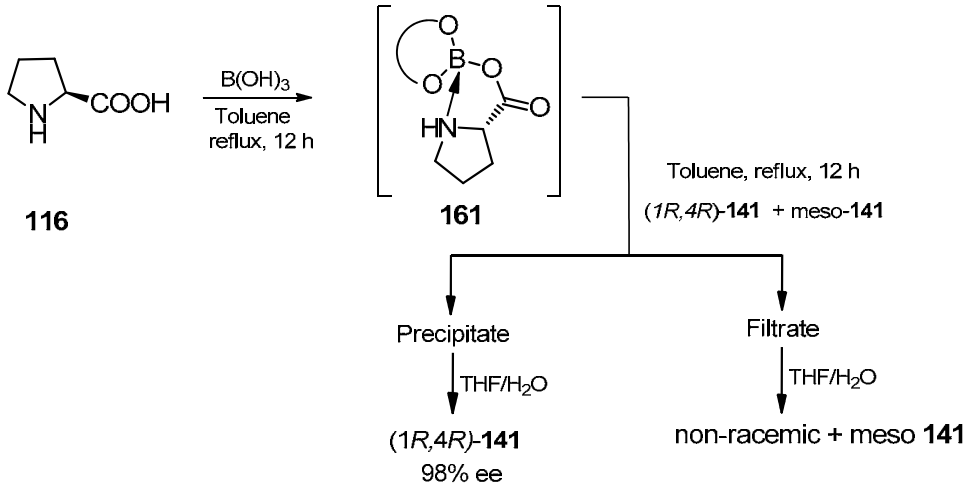
Scheme 36



1.2.4 Enrichment of (1*R*,4*R*)-1,4-diphenylbutan-1,4-diol using (*S*)-proline/B(OH)$_3$

The chiral diol prepared in this way contains small amounts (7-10%) of the corresponding *meso*-diol. However, this mixture of non-racemic (1*R,*4*R*)-diol and *meso*-diol can be readily purified using (*S*)-proline/B(OH)$_3$ to obtain the optical pure diol-**141**, with up to 98% ee (Scheme 37). [65]

Scheme 37

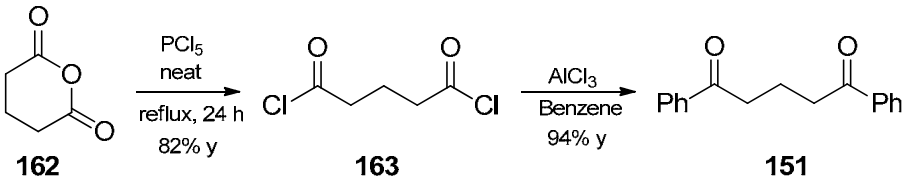


The enriched chiral 1,4-diol **141** (98% ee) was used for the preparation of 2,5-disubstituted pyrrolidines, thiolanes and pyridine derivatives.

1.2.5 Preparation of 1,5-diphenylpentan-1,5-dione

The 1,5-diphenylpentan-1,5-dione **151** was readily prepared from the commercially available glutaric anhydride. The reaction of glutaric anhydride **162** with PCl_5 at reflux conditions gave pentanedioyl dichloride **163** in 82% yield. The subsequent Friedel-Crafts acylation of **163** with benzene afforded the 1,5-diphenylpentan-1,5-dione **151** in 94% yield (Scheme 38).

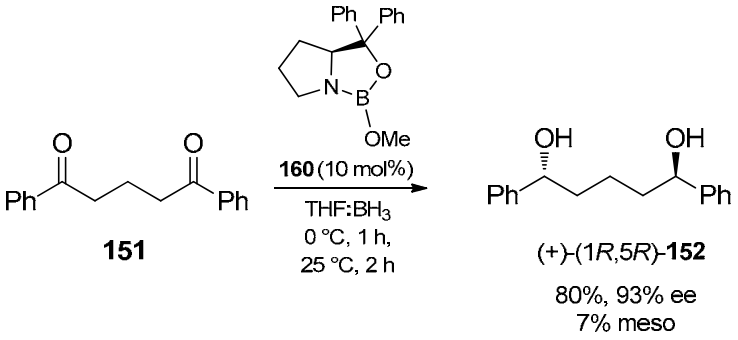
Scheme 38



1.2.6 Asymmetric reduction of 1,5-diphenylpentan-1,5-dione

We extended the asymmetric reduction methodology described earlier for the reduction of 1,4-diketone to 1,5-diketone as well. Thus, the 1,5-diphenylpentan-1,5-dione **151** was reduced using the *B*-methoxy oxazaborolidine **160** (10 mol%) reagent prepared *in situ* along with THF:BH_3 (2M) to obtain the chiral (+)-(1*R*,5*R*)-1,5-diphenylpentan-1,5-diol **152** in good yield (80%) and with good diastereomeric ratio (93:7). The asymmetric induction observed for 1,5-diketone **151** was comparable to that observed in the reduction of 1,4-diketone **140**, indicating that longer carbon chain length has little effect on the diastereoselectivity (Scheme 39). The chiral 1,5-diol **152** obtained from this method was recrystallized from ethyl acetate and hexane mixture to obtain optically pure sample (>99% ee) with 68% overall yield.

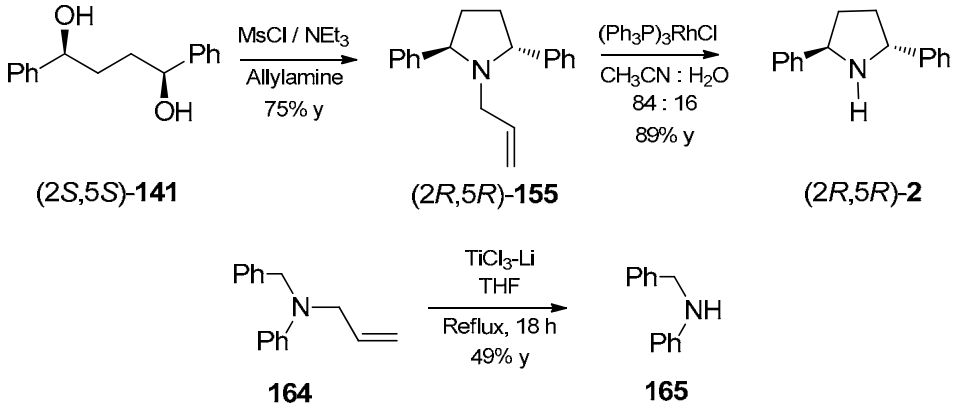
Scheme 39



1.2.7 Synthesis of (-)-(2*S*,5*S*)-2,5-diphenylpyrrolidine

Previously, the (+)-(2*R*,5*R*)-2,5-diphenylpyrrolidine **2** was prepared from the diol (2*S*,5*S*)-**141** *via* the cyclization of the corresponding dimesylates with allylamine to the *trans*-(2*R*,5*R*)-*N*-allyl-2,5-diphenylpyrrolidine **155** followed by deallylation using the Wilkinson's catalyst (Scheme 40).[58,60,52] Since, the Wilkinson's catalyst is expensive, we were looking for *N*-deallylation using inexpensive reagents. Banerji *et al.*[66] reported a method for *N*, *O*-deallylation and *N*, *O*-debenzylation using low-valent titanium reagent system (Scheme 40).

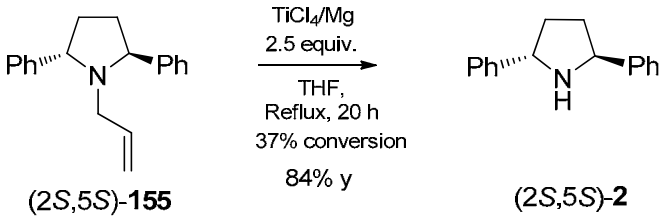
Scheme 40



Low valent titanium reagents were prepared earlier in this laboratory using the $TiCl_4/NEt_3$, $TiCl_4$/Mg and $TiCl_4$/Zn reagent systems for coupling of aldehydes, aldimines, amino esters and esters.[67] The reaction of the $TiCl_4$/Mg reagent system with the *trans*-(2*S*,5*S*)-*N*-allyl-

2,5-diphenylpyrrolidine **155** in anhydrous THF gave the product **2** in 84% yield but unfortunately the conversion was only to the extent of 37% (Scheme 41).

Scheme 41



(2*S*,5*S*)-**155** (2*S*,5*S*)-**2**

Since in this method the percentage of conversion is poor, we have adapted the *N*-deallylation of **155** using the Wilkinson's catalyst (Scheme 40).[58]

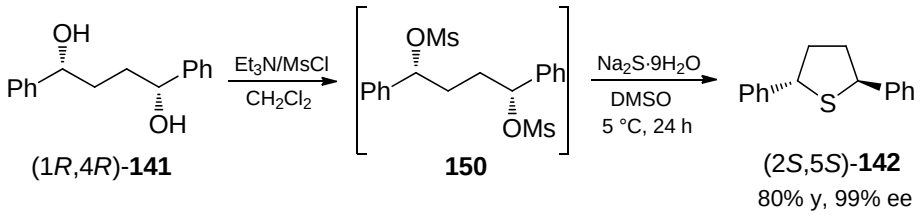
1.2.8 Synthesis of (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene

As outlined in the introductory section, the C_2-symmetric sulfur heterocycles and chiral sulfides were used as chiral auxiliaries in asymmetric epoxidation,[51,53,54] cyclopropanation,[44] sulfenylation of unsaturated carbon-carbon bonds[45] and asymmetric Baylis-Hillman reactions.[53c] Several methods have been reported for the synthesis of chiral 2,5-dialkyl substituted thiolane derivatives.[50, 51, 53] We have envisaged that compounds with bulky substituent like phenyl group would provide the better facial discrimination in asymmetric transformations with prochiral substances. Accordingly, we have extended our work for the preparation of sulfur analogues of the nitrogen heterocycles.

We have observed that the (+)-(2*S,*5*S*)-2,5-diphenylthiolane **142** can be readily prepared from the optically pure chiral (+)-(1*R,*4*R*)-1,4-diphenylbutan-1,4-diol (**141**, 98% ee) *via* preparation of the corresponding dimesylate using Et_3N/MsCl in dry dichloromethane. Further,

reaction with the sodium sulfide nonahydrate ($Na_2S{\cdot}9H_2O$) dissolved in dimethylsulfoxide (DMSO) gave the chiral thiolane **142** in 80% yield and 99% ee (Scheme 42).

Scheme 42



(1*R*,4*R*)-**141** **150** (2*S*,5*S*)-**142**

80% y, 99% ee

The (2*S*,5*S*)-2,5-diphenylthiolane **142** was crystallized from hexane to obtain crystals suitable for X-ray structural analysis. The configuration of the *trans*-(+)-2,5-diphenylthiolane was confirmed as (2*S*,5*S*). The ORTEP diagram of the (+)-(2*S*,5*S*)-2,5-diphenylthiolane **142** is shown in Figure 2. The crystal structural data of the compound **142** is summarized in Table 1.

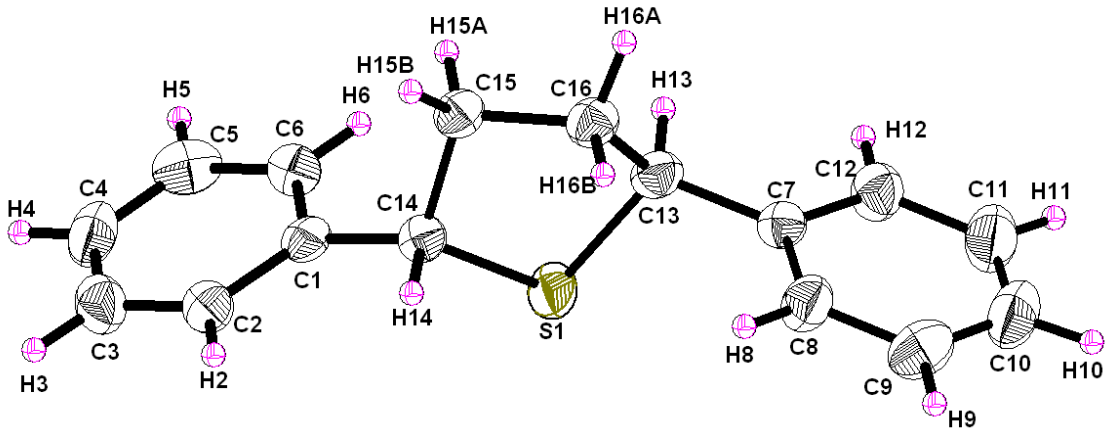


Figure 2. ORTEP representation of the crystal structure **142** (Thermal ellipsoids are drawn at 30% probability, the presence of other molecule is omitted in unit cell for clarity).

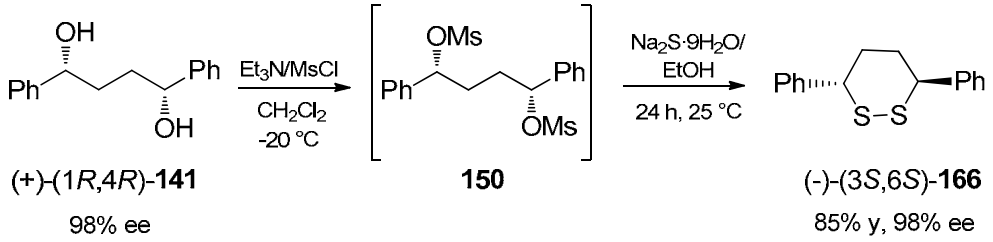
Table 1. Crystal data and structure refinement for compound 142

Empirical formula	$C_{16}H_{16}S$
Formula weight	240.35
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 13.453(4) Å, α = 90˚
	b = 5.7139(18) Å, β = 99.66(5)˚
	c = 17.416(5) Å, γ = 90˚
Volume	1319.8(7) $Å^3$
Z	4
Calculated density	1.210 mg/m^3
Absorption coefficient	0.220 mm^{-1}
F(000)	512
θ Range for data collection	1.19 to 26.22˚
Limiting indices	-16<=h<=16, -7<=k<=7, -21<=l<=21
Reflections collected/unique	13432 / 5181 [R(int) = 0.0668]
Completeness to *θ* = 26.22	98.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5181 / 1 / 307
Goodness-of-fit on F^2	1.056
Final *R* indices [I> 2σ (I)]	R1 = 0.0805, wR2 = 0.2008
R indices (all data)	R1 = 0.1168, wR2 = 0.2153
Largest diff. peak and hole	0.488 and -0.199 $eÅ^{-3}$

1.2.9 Synthesis of (-)-(3*S*,6*S*)-diphenyl-1,2-dithiane

Surprisingly, the (-)-(3*S*,6*S*)-diphenyl-1,2-dithiane **166** was formed when the reaction was carried out in EtOH solvent instead of DMSO in 85% yield (Scheme 43). The structure of the dithiane **166** was further confirmed by X-ray structural analysis and the crystal structure data of the compound **166** are summarized in Table 2. The ORTEP diagram of the (-)-(3*S*,6*S*)-diphenyl-1,2-dithiane **166** is shown in Figure 3.

Scheme 43



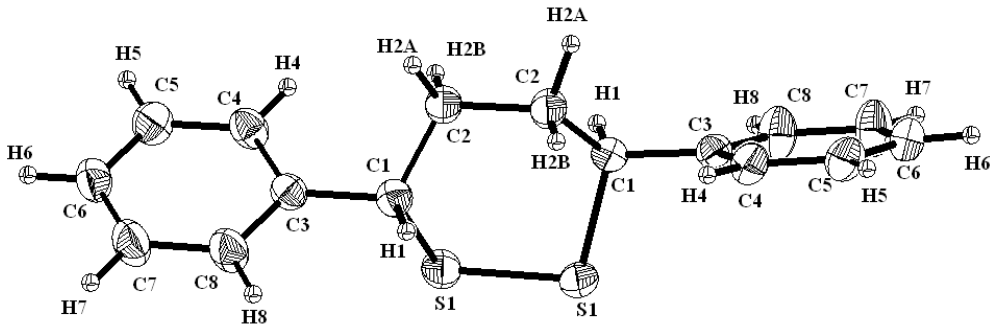


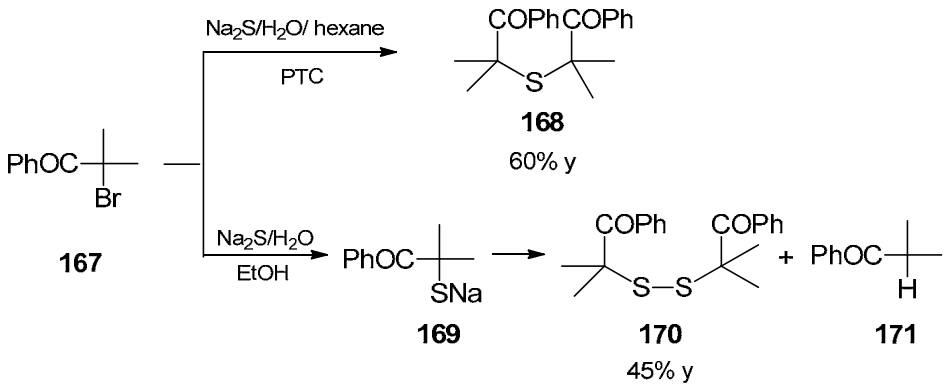
Figure 3. ORTEP representation of the crystal structure **166** (Thermal ellipsoids are drawn at 20% probability and all the hydrogens are omitted for clarity).

Earlier, formation of sulfur-sulfur bond containing compounds were reported in the reaction of bromo ketones and sodium sulfide in ethanol.[68] For example, bromo isobutyrophenone **167** reacts with sodium sulfide to give the monosulfide **168** and disulfide **170** in hexane and ethanol, respectively (Scheme 44).

Table 2. Crystal data and structure refinement for compound 166

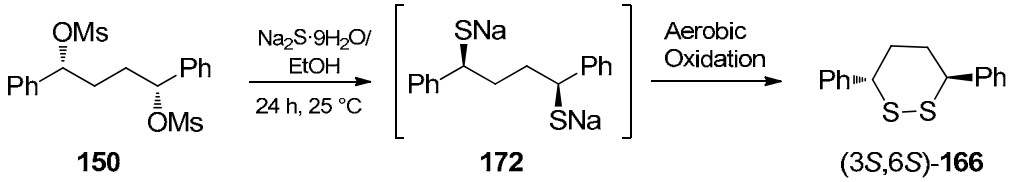
Empirical formula	C16 H16 S2
Formula weight	272.41
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Trigonal
Space group	$P3_1$ 21
Unit cell dimensions	a = 9.2159(14) Å, α = 90˚
	b = 9.2159(14) Å, β = 90˚
	c = 14.647(5) Å, γ = 120˚
Volume	1077.3(4) $Å^3$
Z	3
Calculated density	1.260 mg/m^3
Absorption coefficient	0.350 mm^{-1}
F(000)	432
θ Range for data collection	2.55 to 25.89˚
Limiting indices	-8<=h<=11, -11<=k<=11, -18<=l<=17
Reflections collected/unique	6010 / 1401 [R(int) = 0.0326]
Completeness to *θ* = 26.22	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1401 / 0 / 82
Goodness-of-fit on F^2	1.033
Final *R* indices [I> 2σ (I)]	R1 = 0.0412, wR2 = 0.1092
R indices (all data)	R1 = 0.0495, wR2 = 0.1137
Largest diff. peak and hole	0.211 and -0.173 $eÅ^{-3}$

Scheme 44



Presumably, the dimesylate **150** reacts with sodium sulfide in ethanol to give the diphenyl dithiolate **172**, which in turn undergoes aerobic oxidation to give the dithiane compound **166** (Scheme 45).[68c]

Scheme 45

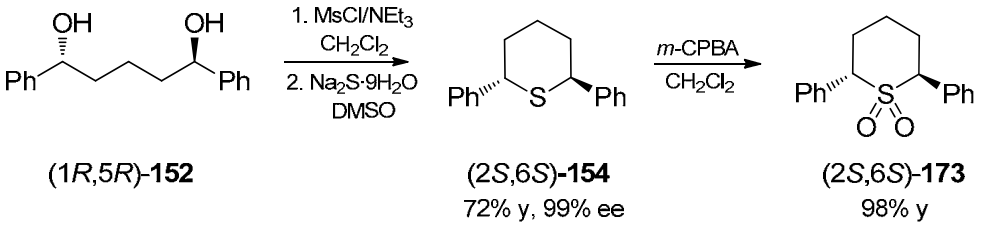


The dithiane product **166** has potential for further applications in organic synthesis as the sulfur-sulfur bond can be cleaved by both nucleophiles and electrophiles.[69]

1.2.10 Synthesis of (+)-(2*S*,6*S*)-2,6-diphenyltetrahydrothiopyran

We have observed that the reaction of (+)-(1*R,5R*)-1,5-diphenylpentan-1,5-diol **152** with MsCl/NEt_3 followed by $Na_2S{\cdot}9H_2O$ treatment in dimethylsulfoxide gives the cyclized product (+)-(2*S,*6*S*)-2,6-diphenyltetrahydrothiopyran **154** in 72% yield with 99% ee (Scheme 46).

Scheme 46



(1*R*,5*R*)-**152** (2*S*,6*S*)-**154** 72% y, 99% ee (2*S*,6*S*)-**173** 98% y

We confirmed the absolute stereochemistry of the compound **154** using single crystal X-ray structural analysis of the sulfone obtained after *m*-CPBA oxidation (Scheme 46). The ORTEP diagram of its sulfone **173** is given in Figure 4.

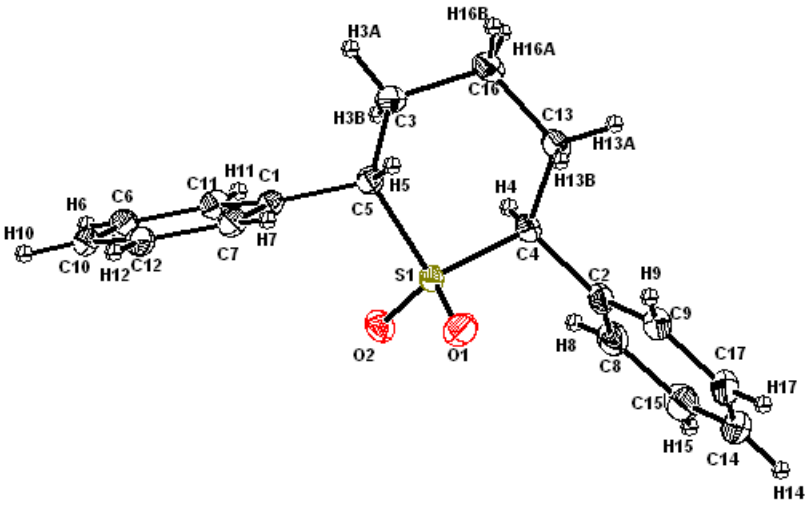


Figure 4. ORTEP representation of the crystal structure of compound **173.** (Thermal ellipsoids are drawn at 30% probability).

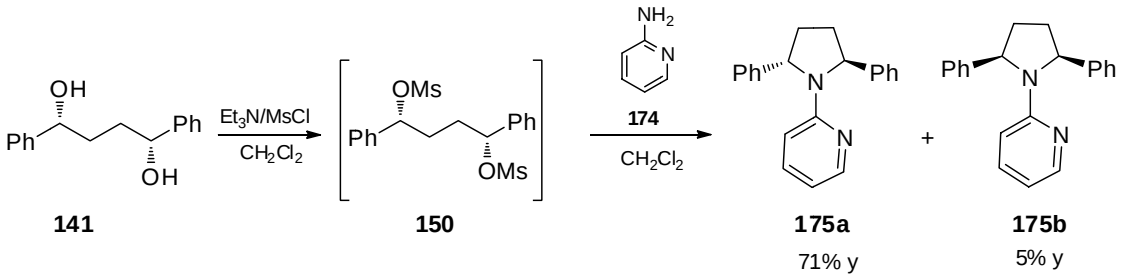
1.2.11 Synthesis of (2*S*,5*S*)-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine

We have also made efforts to synthesize the chiral pyridine derivative **175** from the chiral diol **141**. We have observed that the dimesylate of the chiral diol produced *in situ* can be cyclized using 2-aminopyridine **174** (Scheme 47). The *syn* isomer of the 2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine **175b** was obtained in 5% yield besides the chiral *trans*-(-)-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine **175a** in 71% yield (Scheme 47).

Table 3. Crystal data and structure refinement for compound 173

Empirical formula	C17 H18 O2 S
Formula weight	286.40
Temperature	298(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.71939(17) Å, α = 90°
	b = 13.8298(4) Å, β = 90°
	c = 18.0499(5) Å, γ = 90°
Volume	1427.71(7) $Å^3$
Z	4
Calculated density	1.332 mg/m^3
Absorption coefficient	1.994 mm^{-1}
F(000)	608
θ Range for data collection	4.03 to 72.16°
Limiting indices	-4<=h<=6, -14<=k<=16, -21<=l<=21
Reflections collected/unique	4586 / 2709 [R(int) = 0.0232]
Completeness to *θ* = 26.22	97.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2709 / 0 / 187
Goodness-of-fit on F^2	1.098
Final *R* indices [I> 2σ (I)]	R1 = 0.0491, wR2 = 0.1550
R indices (all data)	R1 = 0.0547, wR2 = 0.1746
Largest diff. peak and hole	0.218 and -0.496 $eÅ^{-3}$

Scheme 47



141 **150** **175a** 71% y **175b** 5% y

The configuration of the *syn*-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine isomer **175b** was further confirmed by single crystal X-ray structural analysis and the ORTEP diagram is given in Figure 5.

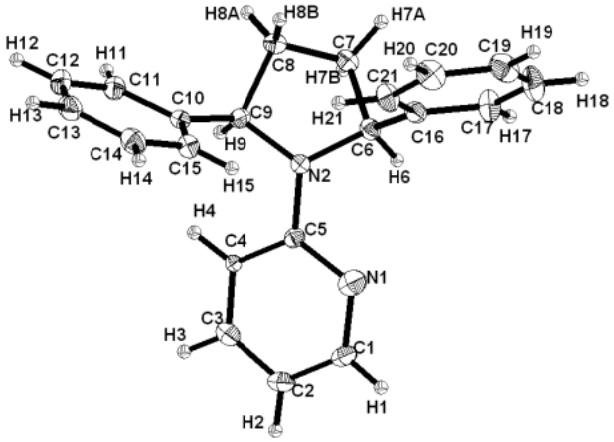


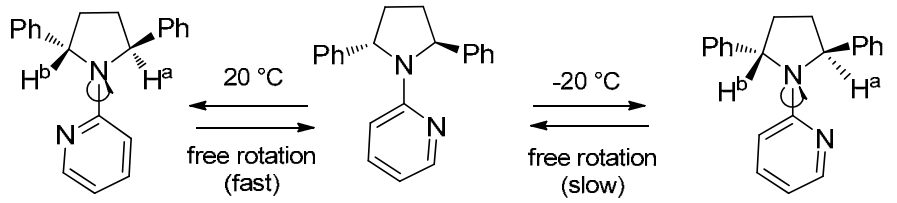
Figure 5. ORTEP representation of the crystal structure of compound **175b.** (Thermal ellipsoids are drawn at 20% probability).

We have noticed some interesting spectral characteristics for the *trans* isomer **175a**. In this case, the methine proton attached to the phenyl substituted carbon gave a broad singlet at 5.486 ppm in 400 MHz at 20 ˚C but appeared as two doublets at 5.8096 ppm (J = 4.8 Hz) and 5.2091 (J = 5.4 Hz), when the experiment was carried out at -20 ˚C. This can be explained considering restricted rotation about the marked C-N bond (Scheme 48, Figure 6).

Table 4. Crystal data and structure refinement for compound 175b

Empirical formula	C21 H20 N2
Formula weight	300.39
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.073(3) Å, α = 90°
	b = 7.2763(15) Å, β = 93°
	c = 18.357(4) Å, γ = 90°
Volume	1610.0(6) $Å^3$
Z	4
Calculated density	1.239 mg/m^3
Absorption coefficient	0.073 mm^{-1}
F(000)	640
θ Range for data collection	1.69 to 25.00°
Limiting indices	-14<=h<=14, -8<=k<=8, -21<=l<=21
Reflections collected/unique	14827 / 2835 [R(int) = 0.0466]
Completeness to *θ* = 26.22	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2835 / 0 / 208
Goodness-of-fit on F^2	1.078
Final *R* indices [I> 2σ (I)]	R1 = 0.0655, wR2 = 0.1946
R indices (all data)	R1 = 0.0814, wR2 = 0.2062
Largest diff. peak and hole	0.522 and -0.562 $eÅ^{-3}$

Scheme 48



H^a and H^b are equal with respect to nitrogen of pyridine ring

175a

H^a and H^b are not equal with respect to nitrogen of pyridine ring and H^a is more desheilded compare to H^b.

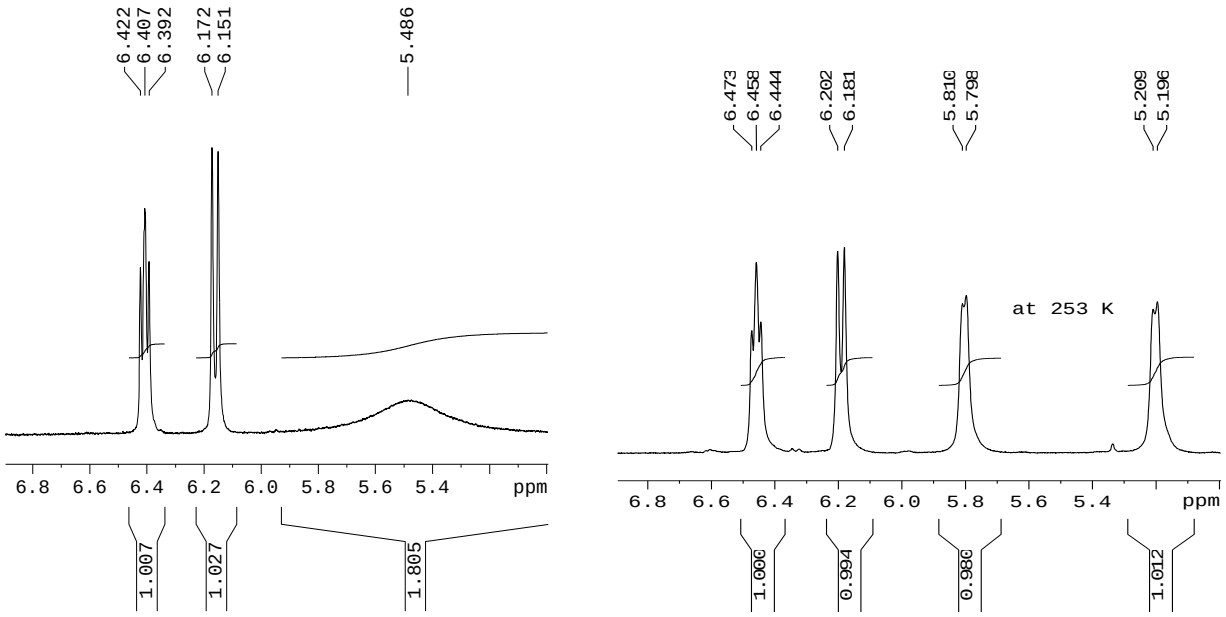
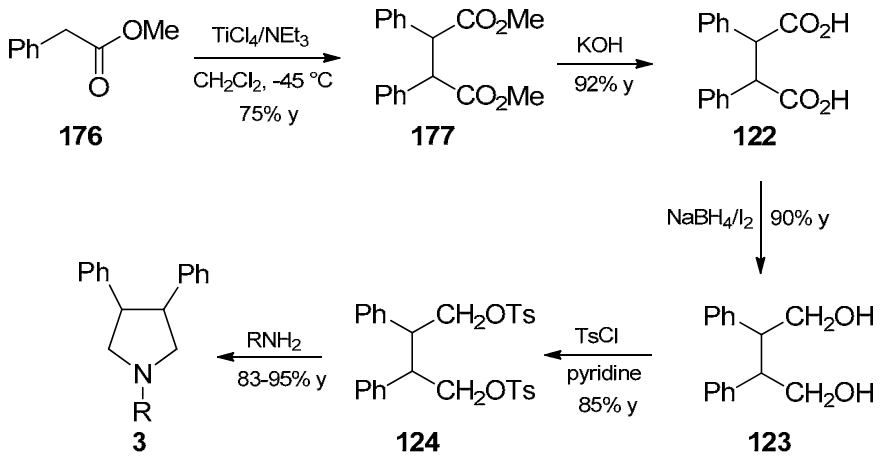


Figure 6

1.2.12 Synthesis of *dl*-3,4-diphenyltetrahydrothiophene

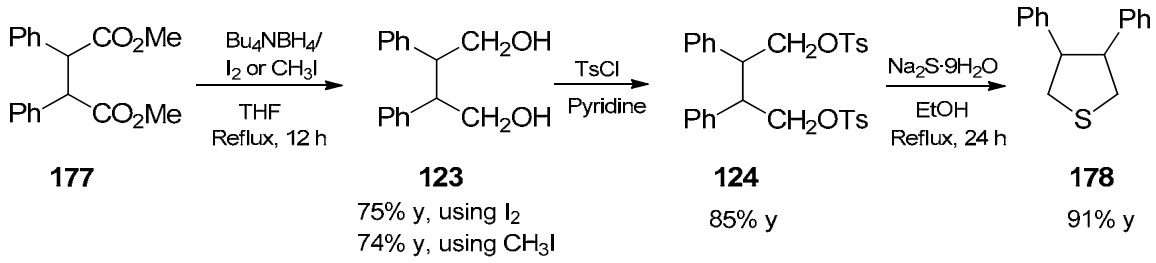
Previously, convenient synthetic methods were reported from this laboratory to access C_2-symmetric racemic 3,4-diphenylpyrrolidine derivatives **3** *via* oxidative coupling of methyl phenyl acetate using the $TiCl_4/NEt_3$ combination to obtain the coupled ester **177** (Scheme 49).[70]

Scheme 49



We have undertaken efforts to examine the utility of the borane reagent systems $^{n}Bu_4NBH_4/I_2$ and $^{n}Bu_4NBH_4/CH_3I$ for the reduction of the *dl*-dimethyl-2,3-diphenylsuccinate diester. We have observed that the $^{n}Bu_4NBH_4/I_2$ and $^{n}Bu_4NBH_4/CH_3I$ systems are useful for the reduction of the diester **177** to obtain the *dl*-2,3-diphenylbutan-1,4-diol **123** in 75% and 74% yields, respectively (Scheme 50).

Scheme 50

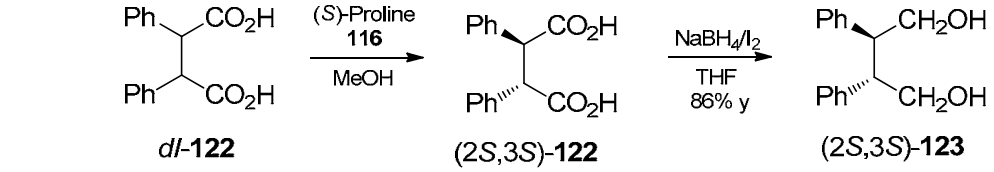


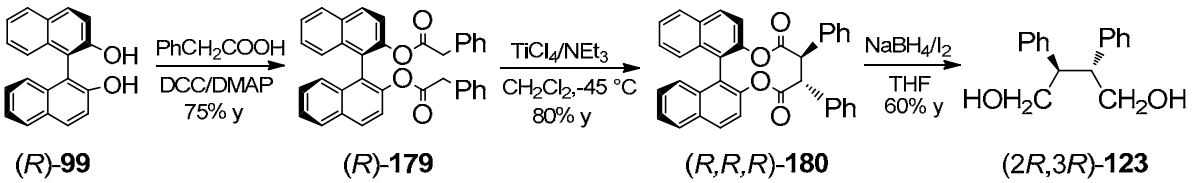
Further conversion to the corresponding ditosylate **124** with TsCl/pyridine, followed by cyclization with $Na_2S{\cdot}9H_2O$ in refluxed EtOH gave the *dl*-3,4-diphenyltetrahydrothiophene **178** in 91% yield (Scheme 50)**.**

1.2.13 Synthesis of (-)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene (-)-178

Previously, methods to access the chiral 2,3-diphenylbutan-1,4-diol have been reported from this laboratory (Scheme 51).[38c,71]

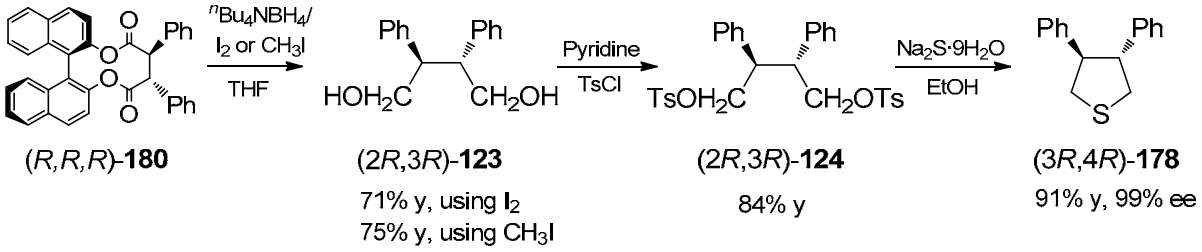
Scheme 51





We have adapted the same methodology to prepare the chiral (-)-(2*R*,3*R*)-2,3-diphenylbutan-1,4-diol **123** by intramolecular oxidative coupling of (*R*)-(+)-1,1′-bi-2-naphthol ester **179** of phenyl acetic acid using $TiCl_4/NEt_3$ to access the coupled diester (-)-(*R*,*R*,*R*)-**180**. The reduction of coupled diester using the borane reagent systems $^{n}Bu_4NBH_4/I_2$ and $^{n}Bu_4NBH_4/CH_3I$ in dry THF gave the (-)-(2*R*,3*R*)-2,3-diphenylbutan-1,4-diol **123** in 71% and 75% yields, respectively with >98% ee. It is of interest to point out that these borohydride reagent systems give better results compare to the $NaBH_4/I_2$ system. We need to perform direct reduction of **180** since the hydrolysis of (-)-(*R*,*R*,*R*)-**180** using KOH/MeOH leads to racemization of the 2,3-diphenylsuccinic acid. The chiral diol **123** was tosylated with TsCl/pyridine and cyclized with $Na_2S{\cdot}9H_2O$ in EtOH to obtain the (-)-(3*R*,4*R*)-diphenyltetrahydrothiophene **178** in 91% yield and 99% ee (Scheme 52).

Scheme 52



The structure of the product **178** was further confirmed by X-ray structural analysis and the ORTEP diagram is given in Figure 7.

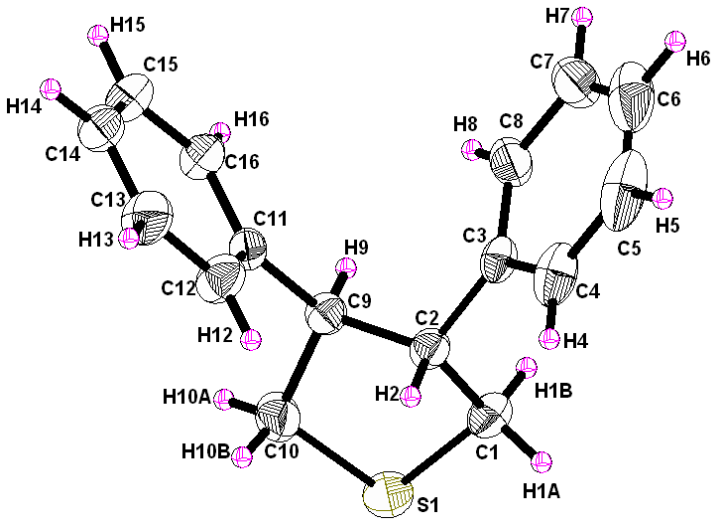


Figure 7. ORTEP representation of the crystal structure **178** (Thermal ellipsoids are drawn at 20% probability).

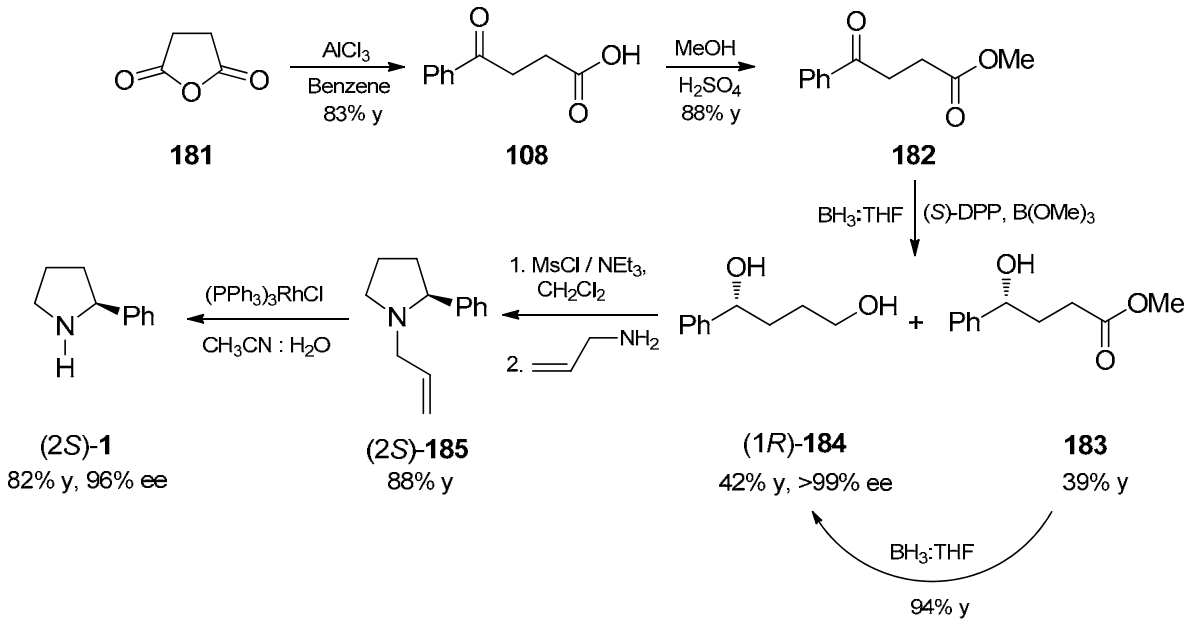
Table 5. Crystal data and structure refinement for compound 178

Empirical formula	C16 H16 S
Formula weight	240.36
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 10.363(2) Å, α = 90˚
	b = 8.6732(19) Å, β = 91˚
	c = 14.857(3) Å, γ = 90˚
Volume	1335.0(5) Å ^{3}
Z	2
Calculated density	1.196 mg/m^3
Absorption coefficient	0.218 mm^{-1}
F(000)	512
θ Range for data collection	1.37 to 25.98˚
Limiting indices	-12<=h<=12, -10<=k<=10, -18<=l<=18
Reflections collected/unique	13820 / 5194 [R(int) = 0.0301]
Completeness to *θ* = 26.22	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5194 / 1 / 307
Goodness-of-fit on F^2	1.053
Final *R* indices [I> 2σ (I)]	R1 = 0.0487, wR2 = 0.1107
R indices (all data)	R1 = 0.0742, wR2 = 0.1231
Largest diff. peak and hole	0.160 and -0.192 eÅ^{-3}

1.2.14 Synthesis of (-)-(2*S*)-phenylpyrrolidine 1

As outlined in the introductory section, several methods have been reported for the preparation of (2*S*)-phenylpyrrolidine **1**. We have used the CBS method for the reduction of methyl 4-benzoylpropionate **182** to get the chiral (1*R*)-phenylbutan-1,4-diol **184** using THF**:**BH_3 (2M). We have observed that the chiral diol **184** is formed in 42% yield with 99% ee along with the (4*R*)-hydroxy-4-phenyl methyl butyrate **183** and lactone mixture in 39% yield. This hydroxy ester **183** and lactone mixture was converted to chiral diol **184** in 94% yield using THF**:**BH_3 (2M). The chiral diol **184** obtained in this way was mesylated using MsCl/NEt_3. The crude dimesylate was cyclized using allylamine to obtain the (2*S*)-*N*-allyl-2-phenylpyrrolidine **185** in 88% yield. After *N*-deallylation using Wilkinson's catalyst, the (2*S*)-phenylpyrrolidine **1** was obtained in 82% yield with 96% ee (Scheme 53).

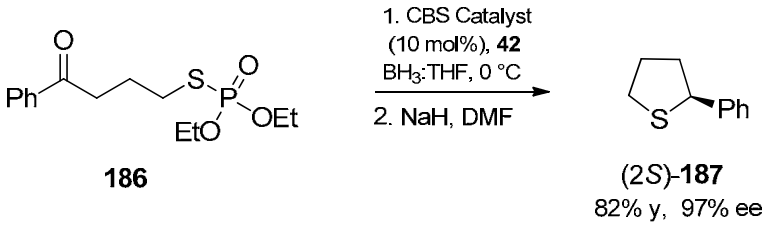
Scheme 53



1.2.15 Synthesis of (+)-(2*S*)-phenyltetrahydrothiophene 187

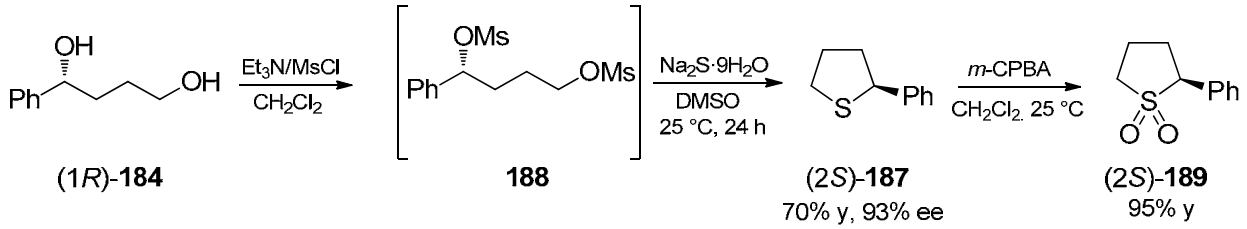
Recently, the C_1-symmetric chiral (2*S*)-phenyltetrahydrothiophene **187** was synthesized *via* CBS reduction of ketophosphorothioate ester **186** followed by reaction with NaH in DMF (Scheme 54). This procedure involves many steps and expensive reagents. Also, this method suffers racemization when the phenyl ring possess electron withdrawing groups.[72]

Scheme 54



We have developed a convenient procedure for the synthesis of (+)-(2*S*)-phenyltetra hydrothiophene **187** using inexpensive reagents. The chiral (1*R*)-phenylbutan-1,4-diol (>99% ee) **184** was dimesylated using MsCl/NEt_3 in CH_2Cl_2 and the crude dimesylate was further cyclized using sodium sulfide nonahydrate $Na_2S{\cdot}9H_2O$ in DMSO to obtain the (+)-(2*S*)-phenyl tetrahydrothiophene **187** in 70% yield with 93% ee (Scheme 55).

Scheme 55



We have confirmed the absolute stereochemistry of **187** by single crystal X-ray structural analysis of the sulfone **189** obtained after *m*-CPBA oxidation. The ORTEP diagram of its sulfone **189** is given in Figure 8.

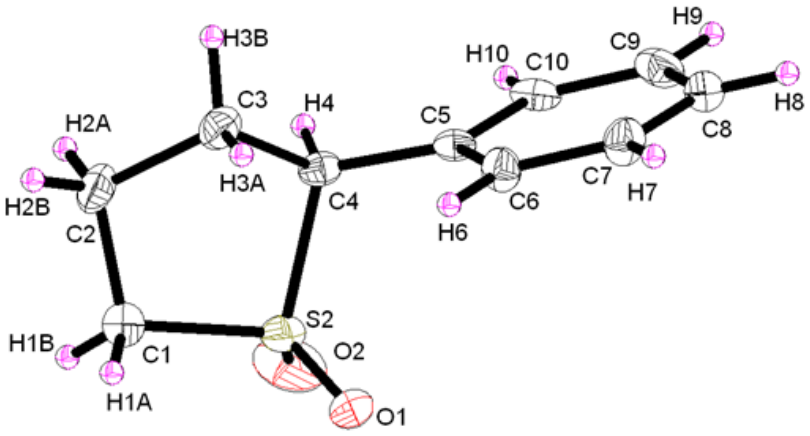


Figure 8. ORTEP representation of the crystal structure of compound **189** (Thermal ellipsoids are drawn at 20% probability).

1.2.16 Synthesis of (*S*)-2-((2-phenylpyrrolidin-1-yl)methyl)pyridine 191

The crude dimesylate **188** obtained in the reaction of chiral (1*R*)-phenylbutan-1,4-diol (>99% ee) **184** with MsCl/Et_3N was also used for cyclization with 2-aminomethylpyridine **190** to obtain the C_1-symmetric pyridine derivative (*S*)-2-((2-phenylpyrrolidin-1-yl)methyl)pyridine **191** in 66% yield (Scheme 56).

Scheme 56

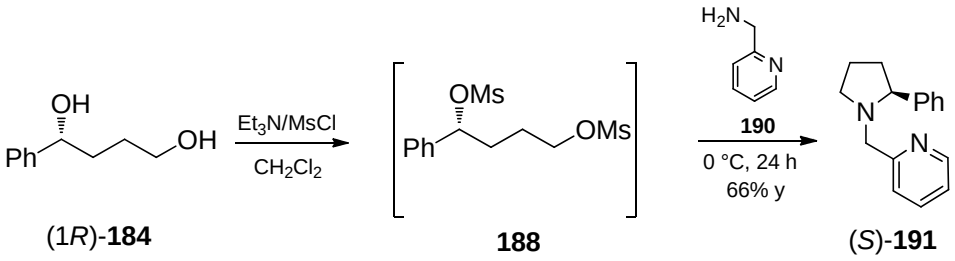


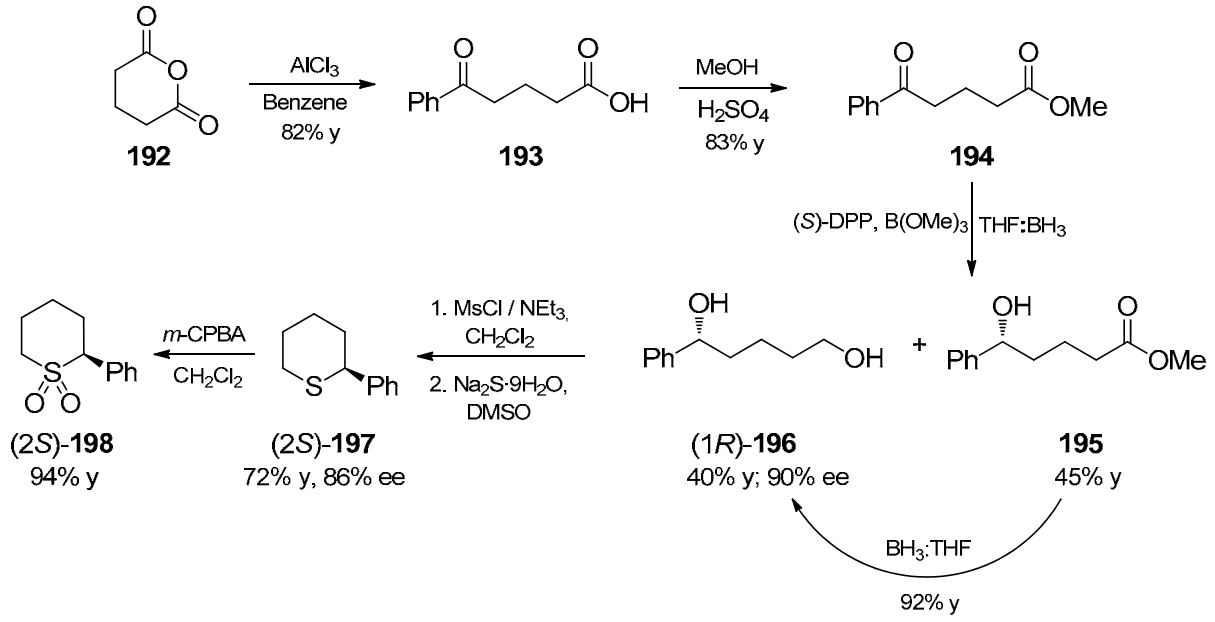
Table 6. Crystal data and structure refinement for compound 189

Empirical formula	C10 H12 O2 S
Formula weight	196.26
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic,
Space group	P 21 21 21
Unit cell dimensions	a = 5.8362(7) Å, α = 90˚
	b = 10.8236(10) Å, β = 90˚
	c = 15.4677(17) Å, γ = 90˚
Volume	977.07(18) $Å^3$
Z	4
Calculated density	1.334 mg/m^3
Absorption coefficient	0.295 mm^{-1}
F(000)	416
θ Range for data collection	2.63 to 26.37˚
Limiting indices	-6<=h<=7, -6<=k<=13, -19<=l<=17
Reflections collected/unique	2544 / 1682 [R(int) = 0.0333]
Completeness to *θ* = 26.22	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1682 / 0 / 118
Goodness-of-fit on F^2	0.855
Final *R* indices [I> 2σ (I)]	R1 = 0.0447, wR2 = 0.0732
R indices (all data)	R1 = 0.0860, wR2 = 0.0818
Largest diff. peak and hole	0.157 and -0.203 $eÅ^{-3}$

1.2.17 Synthesis of (-)-(2*S*)-phenylthiopyran 197

The chiral (-)-(2*S*)-phenylthiopyran **197** was prepared by following a protocol similar to that followed for (+)-(2*S*)-phenyltetrahydrothiophene **187** (Scheme 53). Friedel-Crafts acylation of benzene with glutaric anhydride **192** gives 4-benzoylbutanoic acid **193** in 82% yield, which was esterified with MeOH to give the methyl 5-oxo-5-phenylpentanoate **194** in 83% yield (Scheme 57).

Scheme 57



The keto ester **194** on asymmetric reduction using CBS catalyst (10 mol%) gives (5*R*)-methyl 5-hydroxy-5-phenylpentanoate **195** and lactone in 45% yield. The chiral (1*R*)-phenylpentan-1,5-diol **196** was obtained in 40% yield with 90% ee. The isolated (5*R*)-methyl 5-hydroxy-5-phenylpentanoate and lactone mixture was converted to chiral diol **196** using THF:BH_3 in 92% yield. The chiral diol **196** was dimesylated using MsCl/NEt_3 in CH_2Cl_2. The

crude dimesylate was further cyclized using sodium sulfide nonahydrate $Na_2S{\cdot}9H_2O$ in DMSO to obtain (-)-(2*S*)-phenylthiopyran **197** in 72% yield with 86% ee.

The chiral sulfide was converted to the corresponding sulfone **198** in 94% yield by *m*-CPBA oxidation but suitable crystals for X-ray structural analysis could not be obtained.

The utility of these chiral sulfides were examined in asymmetric hydroboration of prochiral olefins and reduction of prochiral ketones. The results are discussed in **Chapter II**. Also, studies on the use of these chiral sulfides in asymmetric Baylis-Hillman reaction are described in **Chapter III**. The application of the chiral secondary amines prepared was examined in the one-pot three component chiral allene synthesis and the results are described in **Chapter IV**.

1.3 Conclusions

Convenient methods were developed for the preparation of C_2-symmetric (-)-(2*S*,5*S*)-2,5-diphenylpyrrolidine **2**, (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **142**, (+)-(2*S*,6*S*)-2,6-diphenyltetrahydrothiopyran **154** and *trans*-(-)-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine **175a** *via* CBS reduction of 1,4-diphenylbutan-1,4-dione and 1,5-diphenylpentan-1,5-dione using the modified borane reagent systems $^{n}Bu_4NBH_4/I_2$ and $^{n}Bu_4NBH_4/CH_3I$. Also, syntheses of corresponding C_1-symmetric heterocyclic derivatives (-)-(2*S*)-phenylpyrrolidine **1**, (+)-(2*S*)-phenyltetrahydrothiophene **187**, (*S*)-2-((2-phenylpyrrolidin-1-yl)methyl)pyridine **191**, and (-)-(2*S*)-phenylthiopyran **197** were achieved. The racemic and chiral 3,4-diphenyltetrahydro thiophenes **178** were synthesized using low valent titanium reagent in crucial steps. These chiral heterocycles have scope for use in several asymmetric organic transformations and our studies towards these objectives are described in Chapter 2-4.

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 and the neat IR spectra were recorded on SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on Bruker-Avance-400 spectrometer 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. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured in an AUTOPOL-II automatic polarimeter (readability ± 0.01^{o}). 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 mesh) or neutral alumina.

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless, otherwise mentioned, all the operations and transfer of reagents were carried out using standard syringe, septum technique recommended for handling air sensitive 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 by a long tube to the atmosphere. 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 Na_2SO_4 and concentrated on Heidolph-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_2 before use. Diglyme was distilled over sodium-benzophenone ketyl under reduced pressure. Toluene and benzene were distilled over sodium-benzophenone ketyl. THF and sodium borohydride supplied by E-Merck, India. THF was kept over sodium-benzophenone ketyl and freshly distilled before use. Triethylamine was distilled over CaH_2 and stored over KOH pellets. Methanesulfonyl chloride was supplied by Loba chemie (P) Ltd, India were used after distillation. Sodium sulfide nonahydrate was supplied by Loba chemie (P) Ltd, India were used after recrystallization from ethanol. *p*-Toluenesulfonyl chloride, boric acid supplied by Sisco Chemical (P) Ltd., India and (*S*)-α,α-diphenylprolinol [(*S*)-DPP] was supplied by Gerchem labs, India, (*S*)-proline supplied by Lancaster Synthesis Ltd., UK were used.

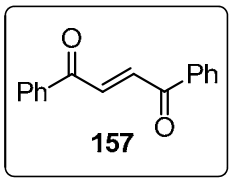
The X-ray diffraction measurements for the compounds were carried out at 298 K on Bruker-Nonius SMART APEX CCD area detector system using graphite monochromated, Mo-Kα (λ = 0.71073 A^o) radiation. Primary unit cell constants were determined with a set of 25

narrow frame scans. Intensity data were collected by the ω scan mode. The data were reduced using SAINT program, without applying absorption correction. The refinement for structure was made by full-matrix least-squares on F^2 (SHELX 97).

1.4.2 Preparation of (2*S*,5*S*)-2,5-diphenylpyrrolidine

1.4.2a Procedure for the preparation of *trans*-1,2-dibenzoylethylene 159

To a mixture of finely powdered aluminium chloride (32 g, 235 mmol) in benzene (250 mL), the fumaryl chloride (18 g, 117 mmol) was added dropwise during 15 min. The stirring was continued for 2 h at 25 ˚C and the mixture was decomposed by pouring into ice. The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with aqueous sodium bicarbonate solution (25 mL), dried over $MgSO_4$ and evaporated to obtain reddish brown solid. It was recrystallized from ethyl alcohol.



157

Yield 20 g (74%).

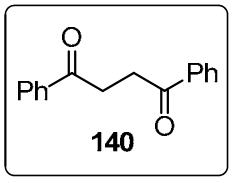
mp 110-111 ˚C (*Lit.*[55] 111 ˚C).

IR (KBr) (cm^{-1}) 1647, 1593, 1575, 1446, 1323, 1292, 1192, 1016, 763, 704, 679, 632.

^1H NMR (400 MHz, $CDCl_3$, ppm) 7.51-7.83 (m, 6H), 8.02-8.30 (m, 6H).

1.4.2b Procedure for the selective reduction of 1,2-dibenzoylethylene

In a hot suspension of stannous chloride (25 g, 131 mmol) in 8N HCl (38 mL) and 95% ethanol (13 mL), a hot solution of *trans*-dibenzoylethylene (25 g, 105 mmol) in 95% ethanol (25 mL) was poured with stirring. The contents were then diluted with H_2O (12 mL), cooled, filtered and recrystallized from methanol.



140

Yield 16 g (76%).

mp 145 ˚C (*Lit.*[56] 145-147 ˚C).

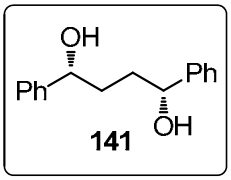
IR (KBr) (cm^{-1}) 2905, 1678, 1593, 1446, 1354, 1222, 989, 775, 736, 692.

^1H NMR (400 MHz, $CDCl_3$, ppm) 8.13-8.01 (d, *J* = 6 Hz, 4H), 7.64-7.42 (m, 6H), 3.60 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 198.6, 136.9, 133.1, 128.6, 128.1, 32.6.

1.4.2c Procedure for the reduction of 1,2-dibenzoylethane with $^nBu_4NBH_4/I_2$ or CH_3I and (*S*)-α,α-diphenyl prolinol (10 mol%)/$B(OMe)_3$ system

The $^nBu_4NBH_4$ (7.6 mmol, 1.89 g) was taken in 100 mL three neck round bottom flask under N_2 atmoshpere in 20 mL dry THF. To this I_2 (3.68 mmol, 0.93 g) in 30 mL dry THF was added under N_2 at 0 ˚C during 1 h using pressure equalizer. The diborane generated *in situ* was trapped as BH_3**:**THF complex. To this reagent a solution of *B*-methoxy oxazaborolidine [prepared using (*S*)-DPP (0.8 mmol), trimethyl borate (1 mmol) in THF (8 mL)] was added and stirred for 10 min at 25 ˚C. To this reaction mixture 1,4-dibenzoylethane (1 g, 4.6 mmol) dissolved in THF (25 mL) was added slowly with a pressure equalizer during 1 h. at 0 ˚C and further stirred at 25 ˚C for 1 h. The reaction was carefully quenched with 2N HCl (15 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2 x 20 mL). The combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated and the product was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (75:25) as eluent.



141

Yield 1.0 g (90%).

mp 63-65 ˚C.

IR (KBr) (cm^{-1}) 3339, 3025, 1207, 990.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.51-7.04 (m, 10H), 4.75-4.53 (m, 2H), 3.52 (bs, 2H), 2.05-1.67 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.7, 128.4, 127.4, 125.9, 74.4, 74.0, 35.9, 35.0.

HPLC 90% ee of (1*R*,4*R*), enantiomeric excess was determined by HPLC with Chiralcel OB-H column (hexane**:**2-propanol=8**:**2, V:V, flow rate =1.0 mL/min.). t_r(*S*,*S*)=7.8 min, t_r(*R*,*R*)=16.5 min. 7% of meso isomer t_r(*R*,*S*)= 11.9 min.

$[\alpha]_D^{25}$ +52.6 (c 0.25, $CHCl_3$); {*Lit.*[58] $[\alpha]_D^{25}$ = -58.5 (c 1.01, $CHCl_3$, >98% ee) for (1*S*,4*S*)}.

In the reaction using Bu_4NBH_4/CH_3I:

Yield 0.97 g (88%).

HPLC 90% ee of (1*R*,4*R*) enantiomeric excess was determined by HPLC with Chiralcel OB-H column (hexane**:**2-propanol=8**:**2, V:V, flow rate =1.0 mL/min.). t_r(*S*,*S*)=9.1 min, t_r(*R*,*R*)=16.5 min. 10% of meso isomer t_r(*R*,*S*)= 12.2 min.

$[\alpha]_D^{25}$ +52.68 (c 0.47, $CHCl_3$); {*Lit.*[58] $[\alpha]_D^{25}$ = -58.5 (c 1.01, $CHCl_3$, >98% ee) for (1*S*,4*S*)}.

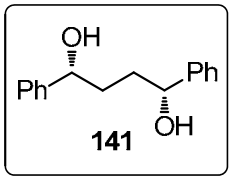
1.4.2d Procedure for the purification of the non-racemic diol 141 using (*S*)-proline and boric acid

(*S*)-Proline (0.26 g, 2.2 mmol) and boric acid (0.13 g, 2.2 mmol) were taken in dry benzene (16 mL) and refluxed for 12 h and the water produced was removed using a Dean-Stark apparatus. The non-racemic diol **141** (0.48 g, 2 mmol, $[\alpha]_D^{25}$ = +50.6) dissolved in dry benzene

(16 mL) was added to the reaction mixture under nitrogen atmosphere through a cannula. The slurry becomes homogeneous and precipitation starts after 3 h. The contents were further refluxed for 9 h and brought to 25 ˚C. The precipitate was filtered in hot condition and was decomposed using a 1:1 mixture of THF and water (20 mL). 3N HCl (10 mL) was added and stirred at 25 ˚C for 5 h. The mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed successively with water (10 mL), brine (10 mL) and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by column chromatography on a silica gel using hexane:ethyl acetate (75:25) as eluent, the (1*R*,4*R*)-diphenylbutane-1,4-diol **141** was obtained in 98% ee.

After decomposition:

From precipitate after decomposition:



141

Yield 0.4 g (84%).

mp 68-70 ˚C.

IR (KBr) (cm^{-1}) 3339, 3025, 1207, 990.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.51-7.04 (m, 10H), 4.75-4.53 (m, 2H), 3.52 (bs, 2H), 2.05-1.67 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.7, 128.4, 127.3, 125.9, 74.2, 35.9.

HPLC 98% ee of (1*R*,4*R*), enantiomeric excess was determined by HPLC with Chiralcel OB-H column (hexane**:**2-propanol=8**:**2, V:V, flow rate =1.0 mL/min.). t_r(*S*,*S*)=7.8 min, t_r(*R*,*R*)=16.5 min.

$[\alpha]_D^{25}$ +58 (c 0.11, $CHCl_3$); {*Lit.*[58] $[\alpha]_D^{21}$: -58.5 (c 1.01, $CHCl_3$) >98% ee) for (1*S*,4*S*)-(-)-**141**}.

^{13}C-NMR spectrum of the sample revealed that the sample did not contain meso isomer.

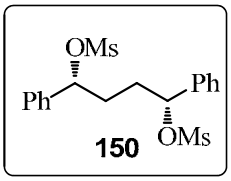
The filtrate obtained was evaporated and decomposed using THF/water mixture. After workup, the diol sample was isolated that was essentially the meso isomer.

Diol from filtrate after decomposition:

Yield 0.038 g (8%).

1.4.2e Procedure for the preparation of *(1R,4R)*-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane 150[60]

To methanesulfonyl chloride (0.4 mL, 5.3 mmol) in dichloromethane (20 mL) at –20 ˚C, a solution of (1*R*,4*R*)-1,4-diphenylbutan-1,4-diol (0.5 g, 2.06 mmol, 98% ee) and triethylamine (0.87 mL, 6.2 mmol) in dichloromethane (20 mL) were added. The mixture was stirred for 1.5 h at –20 ˚C and quenched with saturated NH_4Cl solution (2 mL). The mixture was warmed to 25 ˚C and the solvent was concentrated to approximately 17 mL. The solution was diluted with ethyl acetate (80 mL) and washed successively with saturated sodium bicarbonate (20 mL), water (10 mL) and brine (10 mL). It was dried over Na_2SO_4, filtered through celite pad and concentrated to approximately 8 mL and then the solution was cooled to 0 ˚C. The crude dimesylate was precipitated out by dropwise addition of hexane (80 mL) and the resulting solid was filtered and dried.



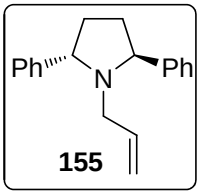
150

^{1}H NMR (400 MHz, C_6D_6, ppm) 7.21-7.0 (m, 10H), 5.74-5.70 (m, 2H), 2.05-1.84 (m, 4H), 2.01 (s, 6H).

1.4.2f Procedure for the preparation of (2*S*,5*S*)-*N*-allyl-2,5-diphenylpyrrolidine 155

Allyl amine (25 mL, 0.33 mol) was added to a cooled flask (0 ˚C) containing the dimesylate (0.670 g, 1.68 mmol) and the resultant solution was stirred at this temperature for 14 h. After warming to 25 ˚C, the excess allyl amine was removed in vacuo and the residue dissolved in ether (70 mL). The organic layer was washed with satd. $NaHCO_3$ (2 x 25 mL), brine

(20 mL), dried over anhyd. Na_2SO_4 and concentrated to afford the crude product as a yellow oil. Flash chromatography on silica gel (230-400 mesh) using hexane:ethylacetate (95:5) elutes to get the diastereomerically pure title amine as a colourless oil.



155

Yield 0.33 g (75%).

IR (neat) (cm^{-1}) 3070, 2967, 2817, 1640, 1071, 916.

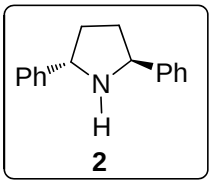
^1H NMR (400 MHz, $CDCl_3$, ppm) 7.41-7.20 (m, 10H), 5.7-5.55 (m, 1H), 4.92-4.87 (m, 2H), 4.32-4.30 (m, 2H), 2.95-2.68 (m, 2H), 2.60-2.45 (m, 2H), 2.01-1.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.6, 137.2, 128.5, 128.2, 127.1, 115.9, 65.9, 50.2, 33.5

$[\alpha]_D^{25}$ -115 (c 0.85, $CHCl_3$) {*Lit.*[58] +115.1 (c 1.40, $CHCl_3$) for (*R*,*R*) isomer}.

1.4.2g Procedure for the preparation of (2*S*,5*S*)-2,5-diphenylpyrrolidine 2

(2*S*,5*S*)-*N*-allyl-*trans*-2,5-diphenylpyrrolidine **155** (1.28 g, 4.96 mmol) and $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, 22 mg, 0.047 mmol) were dissolved in 13 mL of 84:16 w/w CH_3CN:H_2O mixture and placed in a 50 mL three-necked flask fitted with distillation head. The mixture was purged with nitrogen gas and heated to boiling for 5 h. The reaction was then cooled to 25 ˚C and diluted with ether. The layers were separated and the organic layer was washed with brine, and the combined aqueous washes were back extracted with ether. The combined organic extracts were dried (over Na_2SO_4) and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (100-200 mesh) using hexane:ethylacetate (90:10) to yield the desired amine as a yellow oil which solidified on standing overnight.



2

Yield 0.98 g (89%)

mp 44-45 ˚C (*Lit.*[58] 43 ˚C).

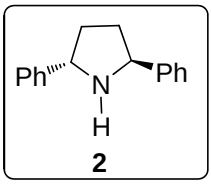
IR (KBr) (cm^{-1}) 3367, 3061, 3026, 2956, 2925, 2853, 1602, 1492, 1451, 751.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.26-7.50 (m, 10H), 4.56-4.61(m, 2H), 2.39-2.49 (m, 2H), 2.14 (s, 1H), 1.91-1.99 (m, 2H) **(Spectrum No. 1)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 145.7, 128.2, 126.5, 126.1, 62.1, 35.3 **(Spectrum No. 2)**.

$[\alpha]_D^{25}$ -106.1 (c 0.75 $CHCl_3$) {*Lit.*[58] $[\alpha]_D^{25}$ -108.2 (c 0.45, $CHCl_3$)}.

1.4.2h Procedure for the preparation of (2*S*,5*S*)-2,5-diphenylpyrrolidine (2) using $TiCl_4$/Mg



2

To an oven dried reaction flask, magnesium turnings (0.240 g, 10 mmol) in dry THF (30 mL) was added. To this reaction mixture, $TiCl_4$ (0.6 mL, 5 mmol) was slowly added drop by drop at 0 ˚C and stirred for 30 min. at 25 ˚C. To this (2*S*,5*S*)-*N*-allyl-*trans*-2,5-diphenyl pyrrolidine **155** (0.526 g, 2 mmol) in dry THF (10 mL) was added and allowed to reflux for 20 h. The reaction mixture was quenched with aq. K_2CO_3 (4 mL) and the aqueous layer was extracted with ether (10 mL x 2). The combined organic extracts were washed with brine (10 mL x 1), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel (100-200 mesh). The hexane:ethyl acetate (90:10) mixture elutes the desired product (-)-(2*S*,5*S*)-**2.**

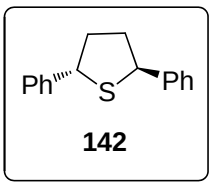
(2*S*,5*S*)-**155** : 0.33 g (63%).

(2*S*,5*S*)-**2** : 0.14 g (84% yield with respect to percentage of conversion).

The IR, ^{1}H NMR, ^{13}C NMR and optical rotational data show 1:1 correspondence with the data of the compound previously obtained in reaction using Wilkinson's catalyst.

1.4.3 Procedure for the preparation of (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene 142

The dimesylate (1.99 g, 5 mmol) prepared using the (+)-(1*R*,4*R*) diol **141** (98% ee), was taken in DMSO (15 mL) and sodium sulfide nonahydrate (freshly recrystallized from EtOH, 4.8 g, 20 mmol) was added and stirred at 5 ˚C for 24 h. Water (10 mL) was added and the contents were extracted with diethyl ether. The combined extracts were concentrated and the product was purified by column chromatography on silica gel (230-400 mesh) using hexane as eluent.



142

Yield 0.96 g (80%).

mp 78 ˚C.

IR (KBr) (cm^{-1}) 3026, 2941, 1597, 1487, 1450, 754, 698.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.47-7.46 (m, 4H), 7.34-7.22 (m, 6H), 4.86-4.82 (m, 2H), 2.62-2.58 (m, 2H), 2.16-2.11 (m, 2H). **(Spectrum No. 3)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 142.5, 128.4, 127.2, 54.3, 41.0 **(Spectrum No. 4)**.

HPLC 99% ee (Daicel Chiralcel OJ-H, ^{i}PrOH:Hexane 20:80, flow rate 1.0 mL/min, 254 nm, t_R(*S*,*S*)=28.8 min, t_R(*R*,*R*)=42.5 min).

$[\alpha]_D^{25}$ +22 (c, 0.5, $CHCl_3$) {(*Lit.*[52] +15.76 (c, 1.0, $CHCl_3$}.

MS (EI) m/z 241 $(M+1)^+$.

Analytical data calculated for $C_{16}H_{16}S$ C, 79.95; H, 6.71.

Found C, 79.99; H, 6.74.

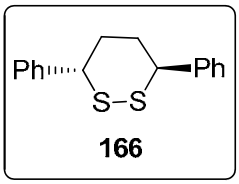
1.4.4 Procedure for the preparation of (–)-(3*S*,6*S*)-3,6-diphenyl-1,2-dithiane 166

The dimesylate (1.99 g, 5 mmol) prepared using the (+)-(1*R*,4*R*) diol **141** (98% ee) was taken in ethanol (20 mL) and sodium sulfide nonahydrate (freshly recrystallized from EtOH, 4.8 g, 20

mmol) was added and stirred at 25 ˚C for 24 h. Water (10 mL) was then added and the mixture was extracted with diethyl ether. The combined extracts were concentrated and the product purified by column chromatography on silica gel (230-400 mesh) using hexane as eluent.

Yield 1.16 g (85%).

mp 69-70 ˚C.



166

IR (KBr) (cm^{-1}) 3026, 1599, 1489, 754, 698.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.36-7.22 (m, 10H), 4.86-4.82 (m, 2H), 2.61-2.53 (m, 2H), 2.15-2.0 (m, 2H). **(Spectrum No. 5)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 142.5, 128.5, 127.6, 127.5, 54.3, 41.0 **(Spectrum No. 6)**.

HPLC (98% ee based on the enantiomeric excess of the diol precursor **142**. However, the X-Ray structure data revealed the absence of the other enantiomer). Unfortunately, the corresponding racemic mixture could not be resolved in HPLC using the chiral columns OD, OB, OJ and AD).

$[\alpha]_D^{25}$ -4.2 (c 0.6, $CHCl_3$).

MS (EI) m/z 273 $(M+1)^+$.

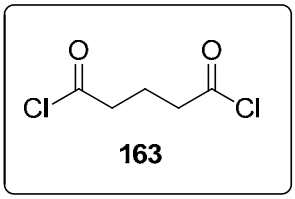
Analytical data calculated for $C_{16}H_{16}S_2$ C, 70.54; H, 5.92.

Found C, 70.56; H, 5.94.

1.4.5 Preparation of (2*S*,6*S*)-*trans*-2,6-diphenyltetrahydrothiopyran 154

1.4.5a Procedure for the preparation of pentanedioyl dichloride 163

To the glutaric anhydride (23 g, 200 mmol) was added PCl_5 (45.8 g, 220 mmol) and refluxed for 24 h. The phosphorous oxychloride ($POCl_3$) was removed. The crude product was distilled out to afford pentanedioyl dichloride under reduced pressure.



163

Yield 28 g (82%).

IR (neat) (cm^{-1}) 1799, 1298.

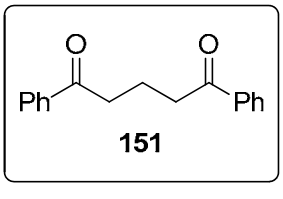
^1H NMR (400 MHz, $CDCl_3$, δ ppm) 3.04-2.98 (m, 4H), 2.11-2.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 172.9, 45.0, 20.3.

1.4.5b Procedure for the preparation of 1,5-diphenylpentane-1,5-dione 151

To a mixture of finely powdered aluminium chloride (16 g, 120 mmol) in benzene (150 mL), was added pentanedioyl dicholride (7 mL, 54 mmol) in benzene (50 mL) dropwise during 30 min. The stirring was continued for 2 h at 25 ˚C and the mixture was decomposed by pouring it upon ice. The benzene layer was separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 25 mL), water (25 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain the product as a pale white solid. It was recrystallized from hexane.

Yield 2.8 g (94%).



151

mp 59-61 ˚C.

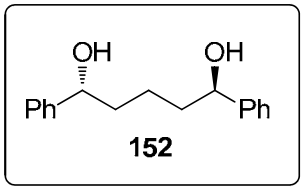
IR (KBr) (cm^{-1}) 3065, 2970, 2889, 1680, 1597, 731, 688.

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.96-7.95 (m, 4H), 7.56-7.26 (m, 6H), 3.12 (m, 4H), 2.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 199.7, 136.9, 133.0, 128.0, 37.6, 18.7

1.4.5c Procedure for the reduction of 1,5-diphenylpentan-1,5-dione with THF:BH_3 using *B*-methoxy oxazaborolidine (10 mol%) system

To a stirred solution of (*S*)-α,α'-diphenylpyrrolidinemethanol (0.25 g, 1 mmol) in THF (10 mL) at 25 ˚C, $B(OMe)_3$ (0.15 mL, 1.25 mmol) was added and stirred for 1 h. The reaction mixture was cooled to 0 ˚C and a solution of THF**:**BH_3 complex (1M, 10 mL, 10 mmol) was added. To this 1,5-diphenylpentan-1,5-dione (1.26 g, 5 mmol) dissolved in THF (25 mL) was added to this suspension at 0 ˚C during 1 h and the reaction mixture was brought to 25 ˚C, stirred further for 1 h. The reaction was carefully quenched with 2N HCl (5 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2 x 25 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, the crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane:ethyl acetate (70:30) as eluent to obtain the 1,5-diol **152**.



152

Yield 0.99 g (80%).

mp 100-101 ˚C {*Lit.*[60] 101-102 ˚C}.

IR (KBr) (cm^{-1}) 3246, 3026, 2941, 2862, 1602, 1454, 758, 698.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.34-7.25 (m, 10H), 4.64 (m, 2H), 2.19 (bs, 2H), 1.95-1.47 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 144.8, 128.5, 127.5, 125.8, 74.4, 38.8, 22.3.

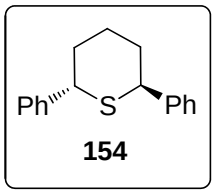
$[\alpha]_D^{25}$ +21.0 (c, 0.94, MeOH) {*Lit.*[60] $[\alpha]_D^{25}$ = -22.8 (c, 1.0, MeOH, 99% ee for (1*S*,5*S*)}.

^{13}C-NMR spectrum of the sample revealed that the sample did not contain meso isomer.

1.4.5d Procedure for preparation of (+)-(2*S*,6*S*)-*trans*-2,6-diphenyltetrahydrothiopyran 154

In an identical fashion to that described in **1.4.2e** above (1*R*,5*R*)-1,5-diphenylpentan-1,5-diol was converted to (*R*,*R*)-1,5-bis(methanesulfonyloxy)-1,5-diphenylpentane. To this

dimesylate (not isolated), sodium sulfide nonahydrate ($Na_2S·9H_2O$) (2.4 g, 10 mmol) dissolved in DMSO (10 mL) was added at 0 ˚C. The reaction temperature brought to 25 ˚C and stirring continued for 36 h. The solvents were removed under reduced pressure and the crude was dissolved in ether (50 mL), washed several times with H_2O to remove any trace of DMSO. The organic layer was treated with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified on silica gel (230-400 mesh) using hexanes as an eluent to obtain the *trans*-2,6-diphenyltetrahydrothiopyran **154**.



154

Yield 0.91 g (72%).

IR (neat) (cm^{-1}) 3059, 3026, 2932, 1597, 1493, 756.

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.54-2.24 (m, 10H), 4.09-4.06 (m, 2H), 2.35-2.18 (m, 4H), 1.76-1.70 (m, 2H) **(Spectrum No. 7)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 142.1, 128.4, 127.7, 126.7, 43.6, 32.9, 21.6. **(Spectrum No. 8)**.

$[\alpha]_D^{25}$ +36.896 (c 1.04 $CHCl_3$)

HPLC >99% ee (Daicel Chiralcel OJ-H, ^{i}PrOH:Hexane 15:85, flow rate 1.0 mL/min, 254 nm, t_R(*S*,*S*)=17.8 min, t_R(*R*,*R*)=26.3 min).

MS (EI) m/z 255 (M^+).

1.4.5e Procedure for the preparation of (-)-(2*S*,6*S*)-2,6-diphenyltetrahydro-2*H*-thiopyran-1,1-dioxide 173

The chiral sulfone **173** was prepared by treating the chiral sulfide **154** (0.5 mmol, 0.13 g), with *m*-CPBA (0.18 g, 1.0 mmol) in CH_2Cl_2 (4 mL) at 25 ˚C for 6 h. The reaction was quenched with aqueous $NaHCO_3$ and washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified using haxane:ethyl acetate (80:20).

Yield 0.14 g (98%).

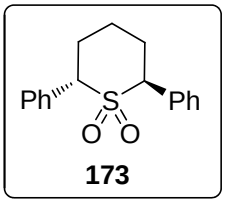
mp 128-130 ˚C.

IR (KBr) (cm^{-1}) 3063, 3034, 2943, 1493, 1452, 1296, 1118, 773, 698.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.54-7.52 (m, 4H), 7.42-7.36 (m, 6H), 4.29-4.25 (m, 2H), 2.74-2.65 (m, 2H), 2.58-2.51 (m, 2H), 2.16-2.10 (m, 2H). **(Spectrum No. 9)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 132.0, 129.7, 128.64, 128.61, 64.6, 29.7, 21.5. **(Spectrum No. 10)**.

$[\alpha]_D^{25}$ -41.394 (c 0.39, $CHCl_3$).



173

MS (EI) m/z 287 (M^+).

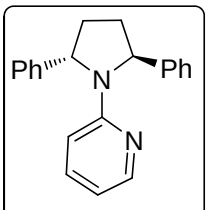
Anal. Calcd for $C_{17}H_{18}O_2S$ C, 71.30; H, 6.34.

Found C, 71.45; H, 6.28.

1.4.6 Procedure for the preparation of (2*S*,5*S*)-diphenyl-*N*-(2-pyridyl)pyrrolidine 175

To the dimesylate (*1R,4R*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane (1.99 g, 5 mmol) in dry DCM (30 mL) was added to 2-aminopyridine (1.88 g, 20 mmol) and was allowed to stir at 25 ˚C for 24 h. The organic solvent was evaporated and the crude product was purified on silica gel (100-200 mesh) to afford the desired *trans*-(2*S*,5*S*)-diphenyl-*N*-(2-pyridyl) pyrrolidine **175a** along with minor amount of its *syn* isomer **175b**.

***trans*-(2*S*,5*S*)-diphenyl-*N*-(2-pyridyl)pyrrolidine 175a**



175a

Yield 1.07 g (71%).

mp 177 ˚C.

IR (KBr) (cm^{-1}) 3020, 1593, 1483, 1440, 771, 746, 698.

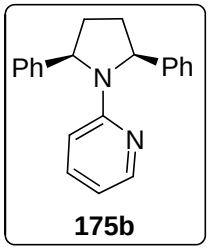
^{1}H NMR (400 MHz, $CDCl_3$, ppm) 8.01-7.99 (m, 1H), 7.32-7.21 (m, 11H), 6.43-6.40 (m, 1H), 6.18 (d, *J* = 8.4 Hz, 1H), 5.48 (bs, 2H), 2.56-2.53 (m, 2H), 1.85-1.83 (m, 2H). **(Spectrum No. 11)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 155.8, 148.3, 144.0, 136.5, 128.4, 126.5, 126.0, 111.7, 108.4, 62.0, 32.1. **(Spectrum No. 12)**.

$[\alpha]_D^{25}$ -34.459 (c 0.4 $CHCl_3$).

MS (EI) m/z 301 $(M+1)^+$.

***syn*-2,5-diphenyl *N*-(2-pyridyl)-pyrrolidine 175b:**



175b

Yield 0.08 g (5%).

mp 124-126 ˚C.

IR (KBr) (cm^{-1}) 3030, 1595, 1475, 1435, 808, 752, 700.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 8.11 (m, 2H), 7.48 (d, *J* = 7.72 Hz, 4H), 7.37-7.33 (t, *J* = 7.28 Hz, 4H), 7.31-7.23 (m, 3H), 6.57-6.55 (m, 1H), 6.29 (d, *J* = 8.52 Hz, 1H), 5.18 (m, 1H), 2.44 (m, 2H), 2.14-2.08 (m, 2H) **(Spectrum No. 13)**.

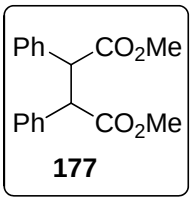
^{13}C NMR (100 MHz, $CDCl_3$, ppm) 158.8, 148.0, 144.3, 136.5, 128.4, 126.6, 126.4, 113.0, 108.3, 65.9, 34.3 **(Spectrum No. 14)**.

MS (EI) m/z 301 $(M+1)^+$.

1.4.7 Peparation of *dl*-3,4-diphenyltetrahydrothiophene 178

1.4.7a Procedure for the preparation of *dl*-dimethyl-2,3-diphenylsuccinate 177

Methyl phenylacetate (4.50 g, 30 mmol) was taken in dry dichloromethane (100 mL) and $TiCl_4$ (7.2 mL, 66 mmol) was added with a syringe at -45 ˚C with stirring. After 30 min, triethylamine (9.2 mL, 66 mmol) was added and the solution was stirred at -45 ˚C for 2 h. The solution was quenched with saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The crude product **177** was purified by column chromatography on silica gel using hexane:ethylacetate (98:2) as eluent.



177

Yield 3.6 g (80%)

mp 164-165 ˚C (*Lit.*[70b] 163-164 ˚C).

IR (KBr) (cm^{-1}) 3030, 2990, 2950, 1730, 1601, 1435, 1305, 1250, 1155, 740, 700.

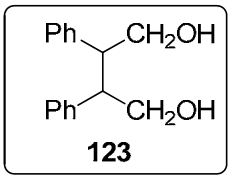
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.20-7.08 (m, 6H), 7.08-6.95 (m, 4H), 4.28 (s, 2H), 3.70 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 173.7, 135.6, 128.5, 128.4, 127.5, 54.7, 52.4.

1.4.7b Procedure for the preparation of *dl*-2,3-diphenylbutane-1,4-diol using tetrabutyl ammoniumborohydride/Iodine

The diester **177** (1.49 g, 5 mmol) and Bu_4NBH_4 (6.17 g, 24 mmol) were taken in anhydrous THF (60 mL) under N_2 in a two-necked septum capped round bottom flask. I_2 (3.05 g, 12 mmol) dissolved in anhydrous THF (30 mL) was added under N_2 at 0 ˚C during 1 h, stirred at 25 ˚C for 4 h and refluxed for 12 h. The contents were cooled to 25 ˚C and the excess hydride

was carefully quenched with 3N HCl (10 mL). After the gas evolution ceased, the reaction mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (15 mL), water (10 mL), brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed and the product **123** was purified by column chromatography on silica gel (100-200 mesh) using hexane:ethyl acetate (80:20) as eluent and recrystallized from hexane.



123

Yield 0.9 g (75%).

mp 100-101 ˚C.

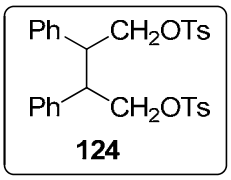
IR (KBr) (cm^{-1}) 3290, 3060, 1601.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.2-7.0 (m, 6H), 6.95-6.8 (m, 4H), 4.1-3.8 (m, 4H), 3.4-3.1 (m, 2H), 2.2 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.6, 128.6, 128.1, 126.5, 65.5, 51.0.

1.4.7c Procedure for the preparation of *dl*-2,3-diphenyl-1,4-butanediol ditosylate 124

Anhydrous pyridine (30 mL, 380 mmol) was added slowly to a mixture of 2,3-diphenyl 1,4-butanediol (4.84 g, 20 mmol) and *p*-toluenesulfonyl chloride (15.2 g, 80 mmol) at -15 ˚C. The mixture was stirred at -10 ˚C for 4 h and then kept at 0 ˚C for 24 h. After pouring into ice, the resulting oil solidified. This product **124** was filtered and washed consecutively with water, 2% HCl, 2% NaOH, and water. It was further purified by recrystallisation from benzene-hexane mixture.



124

Yield 8.94 g (85%).

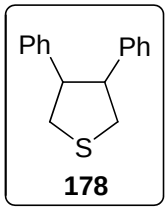
mp 138-140 ˚C.

IR (KBr) (cm^{-1}) 1350, 1180.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.72 (d, *J* = 8 Hz, 4H), 7.40-7.04 (m, 10H), 6.6 (d, *J* = 8 Hz, 4H), 4.23-4.1 (m, 4H), 3.48-3.4 (m, 2H), 2.46 (s, 6H).

1.4.7d Procedure for the preparation of *dl*-3,4-diphenyltetrahydrothiophene 178

To *dl*-ditosylate **124** (2.63 g, 5 mmol) in EtOH (40 mL), sodium sulfide nonahydrate (freshly recrystallized from EtOH, 4.8 g, 20 mmol) was added and it was refluxed for 24 h. Water (10 mL) was then added and the contents were extracted with diethyl ether (2 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **178** was purified by column chromatography on silica gel (230-400 mesh) using hexane as eluent.



178

Yield 1.09 g (91%).

mp 109-110 ˚C.

IR (KBr) (cm^{-1}) 3024, 1601, 1493, 761, 696.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.26-7.1 (m, 10H), 3.5-3.48 (m, 2H), 3.32-3.28 (m, 2H), 3.17-3.12 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.5, 128.5, 127.4, 126.8, 55.8, 38.6.

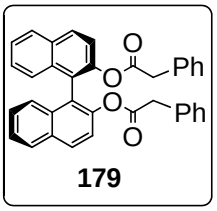
MS (EI) m/z 241 $(M+1)^+$.

1.4.8 Preparation of (-)-(3*R*,4*R*)-diphenyltetrahydrothiophene 178

1.4.8a Procedure for the preparation of (*R*)-(+)-1,1'-bi-2-naphthol ester of phenylacetic acid 179

Dicyclohexylcarbodiimide (12 mmol, 2.47 g) and phenylacetic acid (12 mmol, 1.63 g) were taken in dry CH_2Cl_2 (75 mL) and stirred at 0 ˚C for 30 min. (*R*)-(+)-1,1'-bi-2-naphthol (5 mmol, 1.43 g) and DMAP (0.14 g) were added at 0 ˚C and the contents were stirred at 25 ˚C for

24 h. The solvent was evaporated under reduced pressure and ethyl acetate (75 mL) was added. The precipitate was removed by filtration. The organic layer was washed with 5% HCl solution (25 mL), H_2O (15 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product **179** was purified on silica gel column using hexane:ethylacetate (98:2) as eluent.



179

Yield 1.95 g (75%).

mp 98-100 ˚C.

$[\alpha]_D^{25}$ +11.5 (c 0.872, $CHCl_3$).

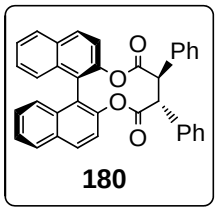
IR (KBr) (cm^{-1}) 3063, 3032, 1757.

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.95 (t, J = 7 Hz, 4H), 6.8-7.6 (m, 18H), 3.4 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 169.8, 146.8, 133.4, 133.1, 131.6, 129.5, 129.1, 128.3, 128.0, 126.8, 126.1, 125.8, 123.4, 121.8, 40.9.

1.4.8b Procedure for the oxidative coupling of 179 with $TiCl_4/Et_3N$

To a solution of (*R*)-(+)-**179** (2 mmol, 1.04 g) in dry CH_2Cl_2 (30 mL) was added dropwise $TiCl_4$ (8.8 mmol, 0.96 mL) in CH_2Cl_2 (10 mL) at -45 ˚C and the solution was stirred for 30 min. Triethyl amine (8.8 mmol, 1.22 mL) in CH_2Cl_2 (10 mL) was added and the solution was stirred at -45 ˚C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with water (10 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain a white solid. The solid was chromatographed on silica gel using hexane:ethyl acetate (98:2) as eluent to isolate the product **180**.



180

Yield 0.83 g (80%).

mp 228-230 ˚C.

IR (KBr) (cm^{-1}) 3065, 3035, 1768, 1620, 1589, 1224, 1130, 764, 748, 733, 709.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 8.2-7.9 (m, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.52 (t, *J* = 6.8 Hz, 2H), 7.4-7.2 (m, 4H), 7.2-7.0 (m, 12H), 4.5 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 169.5, 148.0, 133.6, 133.4, 131.7, 130.3, 128.6, 128.3, 128.1, 127.1, 126.8, 125.9, 121.9, 121.0, 56.7.

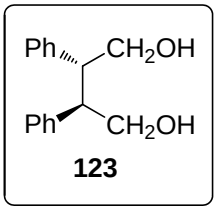
$[\alpha]_D^{25}$ -102.45 (c 0.24, $CHCl_3$).

1.4.8c Procedure for the preparation of (-)-(2*R*,3*R*)-2,3-diphenylbutane-1,4-diol 123

The reaction was performed with **180** by following the procedure described in the experiment **1.4.6b**. The crude product was purified by column chromatography on silica gel. The hexane:ethylacetate (90:10) mixture eluted (*R*)-(+)-1,1'-bi-2-naphthol and hexane:ethylacetate (75:25) mixture eluted (-)-(2*R*,3*R*)-2,3-diphenylbutan-1,4-diol **123**. This chiral diol **123** was recrystallised from hexane.

(*R*)-(+)-1,1'-bi-2-naphthol 0.51 g (90%).

(2*R*,3*R*)-(-)-**123** 0.9 g (75%).



123

mp 101 ˚C (*Lit.*[40] 101-102 ˚C).

IR (KBr) (cm^{-1}) 3290, 3060, 1602.

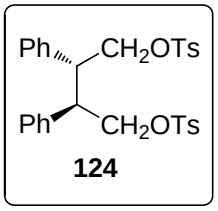
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.2-7.05 (m, 6H), 7.0-6.8 (m, 4H), 4.1-3.8 (m, 4H), 3.35-3.15 (m, 2H), 2.2 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.7, 128.6, 128.1, 126.5, 65.5, 51.0.

$[\alpha]_D^{25}$ -48.0 (c, 0.27, $CHCl_3$) {*Lit.*[40] -48.2 (c, 0.25, $CHCl_3$)}.

1.4.8d Procedure for the preparation of (2*R*,3*R*)-2,3-diphenylbuta-1,4-ditosylate 124

The (2*R*,3*R*)-2,3-diphenylbuta-1,4-ditosylate **124** was prepared by following the procedure described in **1.4.7c**.



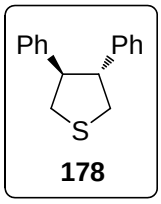
124

Yield 2.2 g (84%).

$[\alpha]_D^{25}$ -8 (c 0.41, C_6H_6); {*Lit.*[40] $[\alpha]_D^{25}$: -8.1 (c 0.234, C_6H_6)}.

1.4.8e Procedure for the preparation of (-)-(3*R*,4*R*)-diphenyltetrahydrothiophene 178

This compound was prepared from the corresponding ditosylate **(-)-124** by following the procedure described in **1.4.7d.**



178

Yield 1.09 g (91%).

mp 109-110 ˚C.

IR (KBr) (cm^{-1}) 3024, 1601, 1493, 761, 696.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.26-7.1 (m, 10H), 3.5-3.48 (m, 2H), 3.32-3.28 (m, 2H), 3.17-3.12 (m, 2H) **(Spectrum No. 15)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.5, 128.5, 127.4, 126.8, 55.8, 38.6. **(Spectrum No. 16)**.

$[\alpha]_D^{25}$ -205 (c 1.08, $CHCl_3$).

HPLC 99% ee; (Daicel Chiralcel OB-H, *i*-PrOH-hexane 5:95, flow rate 1.0 mL/min, 254 nm): t_R(*R*,*R*)=7.7 min, t_R(*S*,*S*)=12.3 min).

MS (EI) m/z 241 $(M+1)^+$.

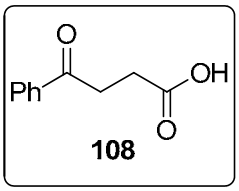
Anal. Calcd for $C_{16}H_{16}S$ C, 79.95; H, 6.71.

Found C, 79.85; H, 6.78.

1.4.9 Preparation of (2*S*)-phenylpyrrolidine 1

1.4.9a Procedure for the preparation of 3-benzoylpropionic acid 108

Dry benzene (100 mL) and succinic anhydride (17 g, 170 mmol) were placed in a one litre three necked flask equipped with an efficient reflux condenser. The top of the condenser was connected to a calcium chloride guard tube. The mixture was stirred and powdered anhydrous aluminium chloride (50 g, 375 mmol) was added all at once. The reaction started immediately, hydrogen chloride was evolved and the mixture became hot. The reaction mixture was refluxed for 2 h. It was allowed to cool in a bath of cold water and water (50 mL) was slowly added. HCl (13N, 25 mL) was added and the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, 3-benzoylpropionic acid was isolated.



108

Yield 50 g (83%).

mp 113 ˚C (*Lit.*[73] 115 ˚C).

IR (KBr) (cm^{-1}) 1680, 1600, 760, 680.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 8.02-7.99 (m, 2H), 7.62-7.58 (m, 1H), 7.51-7.47 (m, 2H), 3.34 (t, J = 6.6 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 197.9, 179.1, 136.4, 133.4, 128.7, 128.1, 33.2, 28.1.

1.4.9b Procedure for the preparation of methyl 4-benzoylpropionate 182

To a stirred solution of 3-benzoylpropionic acid (17.8 g, 100 mmol) in methanol (80 mL) was added catalytic amount of conc. H_2SO_4 and refluxed for 12 h at 78 ˚C. Methanol was

evaporated and diluted with ether (80 mL), washed successively with satd. $NaHCO_3$ (20 mL), water (20 mL) and brine (15 mL). The organic extract was dried over anhydrous Na_2SO_4. The crude product was distilled out under reduced pressure to afford methyl 4-benzoylpropionate.

Yield 16.9 g (88%).

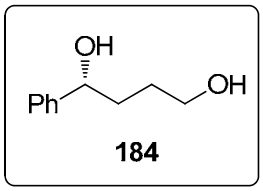
IR (Neat) (cm^{-1}) 2953, 1738, 1687, 1597, 1448, 750, 692.

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.99 (d, *J* = 8 Hz, 2H), 7.58-7.46 (m, 3H), 3.72 (s, 3H), 3.34 (t, *J* = 8 Hz, 2H), 2.78 (t, *J* = 8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 198.1, 173.4, 136.5, 133.3, 128.6, 128.0, 51.9, 33.4, 28.0.

1.4.9c Procedure for the preparation of (1*R*)-phenyl-butane-1,4-diol 184

To a stirred solution of (*S*)-α,α-diphenylpyrrolidinemethanol (5.06 g, 20 mmol) in THF (20 mL) at 25 ˚C, trimethyl borate (2.8 mL, 25 mmol) was added and stirred for 1 h. To this, THF: BH_3 (100 mL, 2M) was added at 0 ˚C. The ketoester (38.4 g, 200 mmol) dissolved in THF (100 mL) was added to this suspension at 0 ˚C during 1 h. The reaction mixture was further stirred at 25 ˚C for 1 h. The reaction was carefully hydrolysed with 2N HCl (20 mL) and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic extract was washed with brine (10 mL) and dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified on silica gel (100-200 mesh). The solvent mixture hexane:ethylacetate (85:15) elutes the methyl (4*R*)-hydroxy-4-phenyl methyl butyrate and its lactone (yield 39%). The chiral diol (1*R*)-phenyl-butane-1,4-diol was eluted in hexane:ethylacetate (50:50).



184

Yield 13.94 g (42%).

mp 83 ˚C (*Lit.*[74] 82-83 ˚C)

IR (KBr) (cm^{-1}) 3333, 3036, 1496, 1446, 947

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.26-7.34 (m, 5H), 4.67-4.70 (m, 1H), 3.58-3.68 (m, 2H), 3.09 (bs, 2H), 1.86-1.81 (m, 2H), 1.61-1.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.7, 128.3, 127.3, 125.8, 74.1, 62.5, 36.3, 29.1.

$[\alpha]_D^{25}$ +31.5 (c 0.97 CH_3OH) {*Lit.*[52] $[\alpha]_D^{25}$ = +27.5 for 91% ee, c 0.75, CH_3OH)}.

HPLC 99% ee, Chiralcel OB-H Hexane (90): Isopropanol (10). Flowrate 1.0 mL/min t_S(9.6 min), t_R(18.7 min).

MS (EI) m/z 167 $(M+1)^+$.

Analysis for $C_{10}H_{14}O_2$ calculated C, 72.26; H, 8.49.

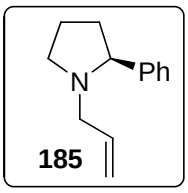
Found C, 72.31; H, 8.42.

The isolated (4*R*)-methyl 4-hydroxy-4-phenylbutanoate **183** and its lactone (39% yield) mixture was also converted to (1*R*)-phenyl-butan-1,4-diol **184** by reducing with THF:BH_3 in 94% yield.

1.4.9d Procedure for the preparation of (2*S*)-*N*-Allyl-2-phenylpyrrolidine 185

To methanesulfonyl chloride (4.6 mL, 60 mmol) in dichloromethane (70 mL) at -10 ˚C was added a solution of (1*R*)-phenylbutan-1,4-diol (4.15 g, 25 mmol, 99% ee) and triethylamine (10.4 mL, 75 mmol) in dichloromethane (25 mL). The mixture was stirred for 2 h. at -10 ˚C and then quenched with saturated NH_4Cl (5 mL). The mixture was warmed to 25 ˚C. The organic

layer was washed with water (5 mL), saturated $NaHCO_3$ (10 mL) and brine solution (10 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to approximately 5 mL. The crude dimesylate was added to allylamine (30 mL) at 0 ˚C and stirred for 24 h. The reaction mixture was warmed to 25 ˚C and the excess allyl amine was removed under reduced pressure. The residue was dissolved in ether (75 mL) and washed successively with saturated $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). The organic extract was dried over anhyd. Na_2SO_4 and concentrated to afford the residue as a yellow oil. The crude product was purified on silica gel (100-200 mesh) using hexane:ethylacetate (95:5) as eluent to obtain the pure product **185** as colourless liquid.



185

Yield 4.12 g (88 %).

IR (Neat) (cm^{-1}) 3072, 3028, 2968, 2789, 916, 756.

^1H NMR (400 MHz, $CDCl_3$, ppm) 7.24-7.37 (m, 5H), 5.85-5.86 (m, 1H), 5.12 (d, *J* = 17.08 Hz, 1H), 5.04 (d, *J* = 10.12 Hz, 1H), 3.23-3.28 (m, 3H), 2.60-2.63 (m, 1H), 2.1-2.2 (m, 2H), 1.92-1.94 (m, 1H), 1.73-1.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 143.5, 136.2, 128.3, 127.5, 126.9, 116.4, 69.5, 56.9, 53.5, 34.9, 22.3.

$[\alpha]_D^{25}$ -130.22 (c 0.85 $CHCl_3$).

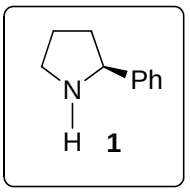
MS (EI) m/z 188 $(M+1)^+$.

Analysis for $C_{13}H_{17}N$ calculated C, 83.37; N, 7.48; H, 9.21.

Found C, 83.25; N, 7.41; H, 9.21.

1.4.9e Procedure for the preparation of (2*S*)-phenylpyrrolidine 1

(2*S*)-*N*-Allyl-2-phenylpyrrolidine (4.0 g, 21 mmol) and $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, 0.1 g, 0.11 mmol) were dissolved in 40 mL of 84:16 w/w acetonitrile:water mixture and placed in a 50 mL three-necked flask fitted with distillation head and dropping funnel. The mixture was purged with nitrogen gas and heated to boiling. The solvent level was maintained *via* the dropping funnel and the reaction heated for 5 h. The reaction was then cooled to 25 ˚C and diluted with ether (75 mL). The layers were separated and the organic layer was washed with brine (2 X 20 mL), and the combined aqueous washes were back extracted with ether (20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product **1** was purified on basic alumina column using hexane:ethylacetate (75:25) as eluent.



1

Yield 2.54 g (82 %).

IR (Neat) (cm^{-1}) 3335, 3028, 2964, 1602, 1493, 1068, 756, 700.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.43-7.15 (m, 5H), 4.12 (t, J = 7.7 Hz, 1H), 3.21 (m, 1H), 3.02 (m, 1H), 2.27-1.61 (m, 4H).

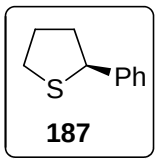
^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.7, 128.3, 126.8, 126.5, 62.6, 47.0, 34.3, 25.6.

$[\alpha]_D^{25}$ -21.9 (c 0.97 MeOH) {*Lit.*[33] $[\alpha]_D^{25}$ = -22.0 (c, 0.3 MeOH)}.

1.4.10 Procedure for the preparation of (+)-(2*S*)-phenyltetrahydrothiophene 187

The chiral diol (1*R*)-Phenyl-butane-1,4-diol (0.830 g, 5 mmol, 99%ee) was dimesylated by following the procedure described in **1.4.8d**. This dimesylate was cyclized using $Na_2S{\cdot}9H_2O$ as outlined in **1.4.3** to get the product **187**.

Yield 0.58 g (70%).



187

IR (Neat) (cm^{-1}) 3060, 3024, 2943, 1599, 1491, 1440, 758, 698.

^1H NMR (400 MHz, $CDCl_3$, ppm) 7.44-7.21 (m, 5H), 4.54-4.51 (m, 1H), 3.17-3.0 (m, 2H), 2.43-2.37 (m, 2H), 2.04-1.95 (m, 2H) **(Spectrum No. 17)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 142.9, 128.4, 127.6, 126.9, 52.7, 40.5, 33.5, 31.1 **(Spectrum No. 18)**.

$[\alpha]_D^{25}$ +28.2 (c 2.0, CH_2Cl_2) {*Lit.*[72] $[\alpha]_D^{25}$ = +28.9 (c 1.6, CH_2Cl_2) for 97% ee}.

HPLC 93% ee; (Daicel Chiralcel OJ-H, hexane:^{i}PrOH 85:15, flow rate 1.0 mL/min, 254 nm): t_R(7.0 min), t_S(7.7 min).

MS (EI) m/z 165 (M^+).

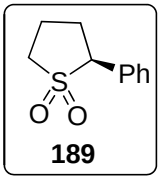
Analysis for $C_{10}H_{12}S$ calculated C, 73.12; H, 7.36.

Found C, 73.26; H, 7.41.

1.4.10a Procedure for the preparation of (2*S*)-phenyltetrahydrothiophene-1,1-dioxide 189

This compound was prepared from **187**, following the procedure described in **1.4.5e.**

Yield 0.09 g (95%).



189

mp 88-90 ˚C.

IR (KBr) (cm^{-1}) 3032, 2947, 1697, 1494, 1444, 1300, 1242, 1122, 763, 723, 696.

^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.42-7.40 (m, 5H), 4.20-4.15 (dd, J_1 = 6.96 Hz, J_2 = 12 Hz, 1H), 3.34-3.28 (m, 1H), 3.21-3.13 (m, 1H), 2.58-2.33 (m, 3H), 2.28-2.16 (m, 1H). **(Spectrum No. 19)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 130.3, 129.1, 128.9, 128.7, 66.6, 50.5, 28.6, 19.6. **(Spectrum No. 20)**.

$[\alpha]_D^{25}$ -24.667 (c 0.58, $CHCl_3$).

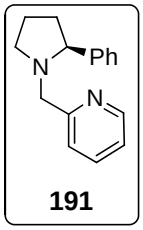
MS (EI) m/z 197 (M^+).

Anal. Calcd for $C_{10}H_{12}O_2S$ C, 61.20; H, 6.16.

Found C, 61.09; H, 6.23.

1.4.11 Procedure for the preparation of (*S*)-2-((2-phenylpyrrolidin-1-yl)methyl)pyridine 191

The reaction was performed using **184** by following the procedure described in **1.4.6.**



191

Yield 0.79 g (66%).

IR (Neat) (cm^{-1}) 3061, 2966, 2800, 1682, 1589, 1433, 758, 700.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 8.50-8.48 (m, 1H), 7.63-7.59 (m, 1H), 7.47-7.41 (m, 3H), 7.35-7.31 (m, 2H), 7.26-7.21 (m, 1H), 7.12-7.09 (m, 1H), 3.95 (d, *J* =13.96 Hz, 1H), 3.47 (t, *J* = 7.92 Hz, 1H), 3.32 (d, *J* = 13.96 Hz, 1H), 3.20-3.15 (m, 1H), 2.33 (q, *J* = 8.88 Hz, 1H), 2.26-2.17 (m, 1H), 1.96-1.73 (m, 3H) **(Spectrum No. 21)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 160.1, 148.8, 143.7, 136.3, 128.4, 127.6, 127.0, 122.8, 121.7, 69.9, 60.1, 53.8, 35.1, 22.6. **(Spectrum No. 22)**.

$[\alpha]_D^{25}$ +23.322 (c 0.86 $CHCl_3$).

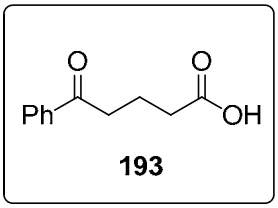
MS (EI) m/z 239 $(M+1)^+$.

Analysis for $C_{16}H_{18}N_2$ calculated C, 80.63; H, 7.61; N, 11.75.

Found C, 80.47; H, 7.68; N, 11.68.

1.4.12 Preparation of (2*S*)-phenylthiopyran 197

1.4.12a Procedure for the preparation of 4-benzoylbutanoic acid 193



193

Dry benzene (100 mL) and glutaric anhydride (19.38 g, 170 mmol) were placed in a one litre three necked flask equipped with an efficient reflux condenser. The top of the condenser was connected to a calcium chloride guard tube. The mixture was stirred and powdered anhydrous aluminium chloride (50 g, 375 mmol) was added all at once. The reaction started immediately, hydrogen chloride was evolved and the mixture became hot. The reaction mixture was refluxed for 2 h. It was allowed to cool in a bath of cold water and water (50 mL) was slowly added. HCl (13N, 25 mL) was added and the organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, 4-benzoylbutanoic acid was isolated.

Yield 26.76 g (82%).

mp 126 ˚C (*Lit.*[75] 126-129 ˚C).

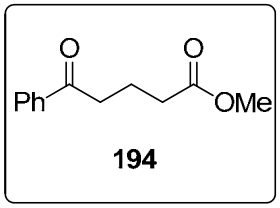
IR (KBr) (cm^{-1}) 3057, 2966, 1695, 1678, 1450, 1412, 1288, 734, 690.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.99-7.95 (m, 2H), 7.59-7.55 (m, 1H), 7.48-7.44 (m, 2H), 3.15-3.07 (m, 2H), 2.51 (t, J = 7.08 Hz, 2H), 2.12-2.05 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 199.4, 179.4, 136.7, 133.2, 128.6, 128.0, 37.3, 33.1, 19.0.

1.4.12b Procedure for the preparation of methyl 5-benzoylbutyrate 194

The product **194** was prepared from the compound **193** by following the procedure described in **1.4.9b.**



194

Yield 17.01 g (83%).

IR (Neat) (cm^{-1}) 2953, 1734, 1685, 1597, 1581, 1448, 748, 692.

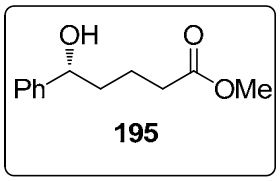
^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.98 (d, J = 8.12 Hz, 2H), 7.58-7.44 (m, 3H), 3.68 (s, 3H), 3.06 (t, J = 7.12 Hz, 2H), 2.46 (t, J = 7.16 Hz, 2H), 2.08 (q, J = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 199.4, 173.7, 136.8, 133.1, 128.6, 128.0, 51.6, 37.4, 33.1, 19.3.

1.4.12c Procedure for the preparation of (1*R*)-phenyl-pentane-1,5-diol 196

The product **195** was prepared from the compound **194** by following the procedure described in **1.4.9c**.

(+)-(5*R*)-methyl-5-hydroxy-5-phenylpentanoate 195:



195

Yield 1.87 g (45%).

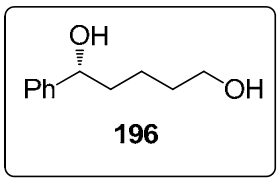
IR (Neat) (cm^{-1}) 3429, 3028, 2951, 1734, 1726, 1440, 763, 702.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.36-7.28 (m, 5H), 4.70-4.69 (m, 1H), 3.66 (s, 3H), 2.37-2.34 (m, 2H), 2.0 (bs, 1H), 1.84-1.62 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 174.2, 144.7, 128.4, 127.4, 125.9, 73.8, 51.5, 38.3, 33.7, 21.2.

$[\alpha]_D^{25}$ +35.69 (c 1.2, $CHCl_3$).

(1*R*)-phenylpentan-1,5-diol 196:



Yield 1.44 g (40%).

IR (Neat) (cm^{-1}) 3294, 3061, 3030, 1448, 1028, 700.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.37-7.29 (m, 5H), 4.7 (t, *J* = 6.24 Hz, 1H), 3.65 (t, *J* = 6.44 Hz, 2H), 1.99 (bs, 1H), 1.87-1.37 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 144.7, 128.4, 127.5, 125.8, 74.5, 62.6, 38.6, 32.4, 22.0.

$[\alpha]_D^{25}$ +44.028 (c 1.0 $CHCl_3$) {*Lit.*[77] $[\alpha]_D^{25}$= -25.4 (c 1.28 benzene) for 65% ee of *S* isomer}.

HPLC 88% ee, Chiral OB-H; Hexane:Isopropanol (90:10). Flow rate 1.0 mL/min t_S(11.2 min), t_R(15.0 min).

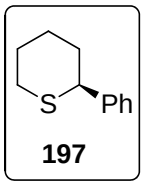
The isolated (5*R*)-hydroxy-5-phenyl methyl pentanoate **195** and its lactone (45% yield) mixture was also converted to (1*R*)-phenyl-pentane-1,5-diol **196** by reducing with THF:BH_3 in 92% yield.

1.4.12d Procedure for the preparation of (-)-(2*S*)-2-phenyltetrahydro-2*H*-thiopyran 197

The reaction was performed with **196** by following the procedure described in **1.4.10.**

Yield 0.64 g (72%).

IR (Neat) (cm^{-1}) 3028, 2926, 1599, 1489, 1435, 756, 696.



197

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.33-7.23 (m, 5H), 4.01 (t, J = 8 Hz, 1H), 3.10 (m, 1H), 2.77 (m, 1H), 2.35 (m, 2H), 2.22 (m, 1H), 2.05 (m, 2H), 1.77 (m, 1H). **(Spectrum No. 23)**.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 143.4, 128.6, 127.3, 126.8, 57.6, 40.0, 37.6, 30.6, 25.8. **(Spectrum No. 24)**.

$[\alpha]_D^{25}$ -31.152 (c 0.84 $CHCl_3$).

HPLC 86% ee; (Daicel Chiralcel OJ-H, hexane:^{i}PrOH 85:15, flow rate 1.0 mL/min, 254 nm): t_S(8.4 min), t_R(9.6 min).

MS (EI) m/z 179 $(M+1)^+$.

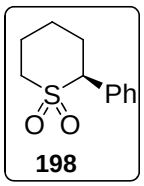
Anal. Calcd for $C_{11}H_{14}S$ C, 74.10; H, 7.91.

Found C, 74.25; H, 7.85.

1.4.12e Procedure for the preparation of 2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide 198

This compound was prepared from **197** following the procedure described in **1.4.5e.**

Yield 0.1 g (94%).



198

mp 145-147 ˚C.

IR (KBr) (cm^{-1}) 3032, 2934, 1494, 1454, 1307, 1284, 1118, 866, 761, 727.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.47-7.39 (m, 5H), 4.04 (dd, J_1 = 2.96 Hz, J_2 = 12.84 Hz, 1H), 3.28-3.22 (m, 1H), 3.11-3.03 (m, 1H), 2.58-2.47 (m, 1H), 2.29-2.18 (m, 3H), 2.11-2.05 (m, 1H), 1.69-1.57 (m, 1H). **(Spectrum No. 25)**

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 130.5, 129.9, 129.0, 128.6, 67.5, 52.7, 31.0, 25.1, 24.6. **(Spectrum No. 26)**

$[\alpha]_D^{25}$ +11.143 (c 0.20 $CHCl_3$).

MS (EI) m/z 211 $(M+1)^+$.

Analysis for $C_{11}H_{14}O_2S$ calculated C, 62.83; H, 6.71.

Found C, 62.75; H, 6.79.

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Chapter II

Studies on hydroboration of olefins and reduction of carbonyl compounds

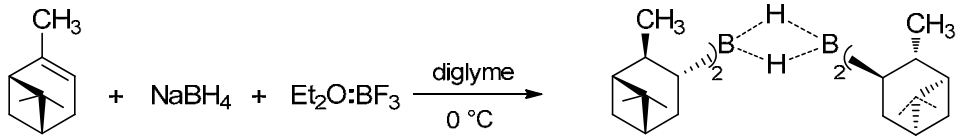
2.1 Introduction

The hydroboration reaction using sodium borohydride and aluminium chloride in diglyme was discovered by Brown and Subba Rao in 1956.[1a] The asymmetric hydroboration using the diisopinocampheyl borane (Ipc_2BH) was reported in 1961.[1b] A brief review on reports on transformations would facilitate the discussion.

2.1.1 Asymmetric hydroboration using chiral alkyl boranes:

Brown *et al*.[1,2] introduced chiral diisopinocampheyl borane **1** (Ipc_2BH) for asymmetric hydroboration with a variety of substrates. The reagent Ipc_2BH was conventionally prepared by the reaction of α-pinene and sodium borohydride in diglyme with boron trifluoride etherate at 0 ˚C in stoichiometric quantities (Scheme 1). The reaction involves formation of B_2H_6 *in situ* and catalysis of hydroboration of α-pinene by diglyme.

Scheme 1

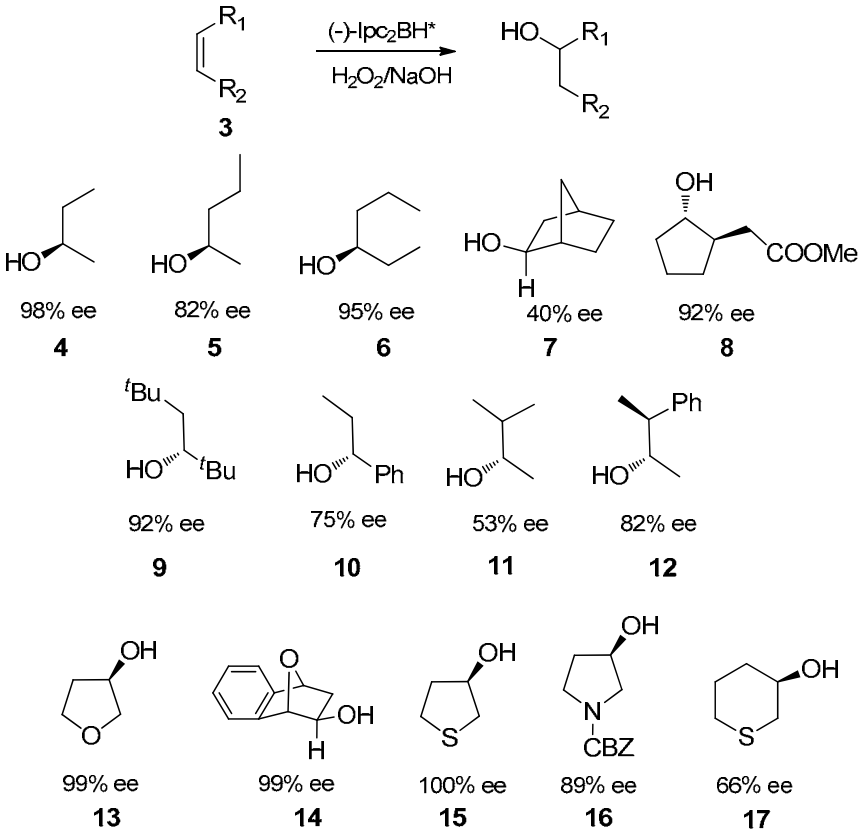


2 **1**

The Ipc_2BH reagent has been used for the synthesis of many chiral products, such as alcohols, halides, amines, ketones, hydrocarbons and amino acids. It has also been used for the reduction of prochiral ketones to chiral alcohols,[3] kinetic resolution of racemic alkenes,[4] dienes[5] and allenes.[6] The asymmetric hydroboration using this Ipc_2BH with different unhindered *cis* olefins give the chiral alcohols with very high enantioselectivity (up to >99% ee) (Chart 1). Pure

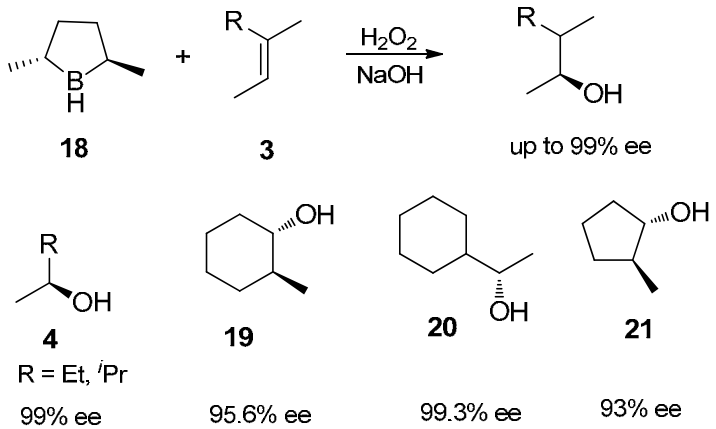
enantiomers of Ipc_2BH **1** are readily accessible since both the enantiomers of α-pinene **2** commercially available. Hence, a variety of enantiomerically enriched alcohols can be accessed *via* hydroboration-oxidation (Chart 1).[7]

Chart 1



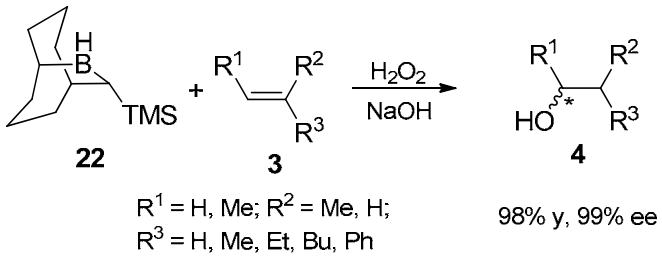
Chiral C_2-symmetric *trans*-(2*R*,5*R*)-dimethyl borolane **18** has been used for asymmetric hydroboration of prochiral olefins. It gives uniformly high enantioselectivities for all olefins except for 1,1-disubstituted and hindered *trans* olefinic substrates (Scheme 2).[8]

Scheme 2



More recently, Soderquist *et al.*[9] reported that the chiral bicyclic 9-borabicyclo[3.3.2]decane **22** reagent hydroborates a variety of prochiral hindered and trisubstituted olefinic substrates. The corresponding alcoholic products were obtained with up to 98% yield and 99% ee (Scheme 3).

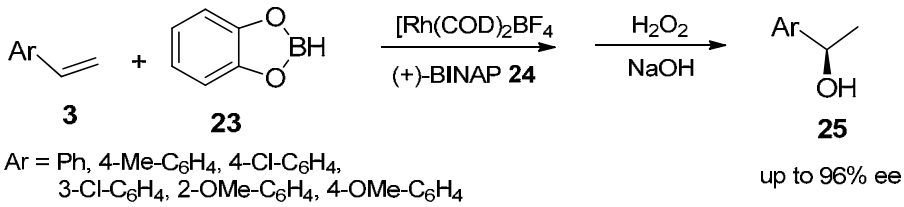
Scheme 3



2.1.2 Asymmetric hydroboration catalysed by chiral BINAP-rhodium complexes:

Asymmetric synthesis of chiral alcohols was reported through asymmetric hydroboration of styrenes catalysed by a cationic rhodium chiral BINAP complex-catechol borane **23** combination. The corresponding chiral alcohols were obtained with up to 96% ee after H_2O_2/NaOH oxidation (Scheme 4).[10]

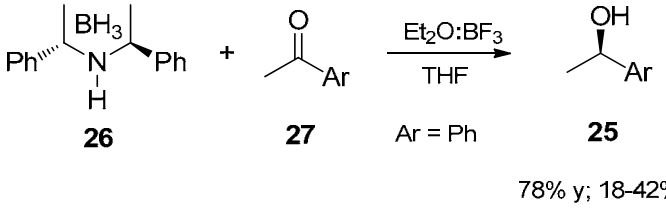
Scheme 4



2.1.3 Asymmetric reduction and hydroboration using chiral amine borane complexes:

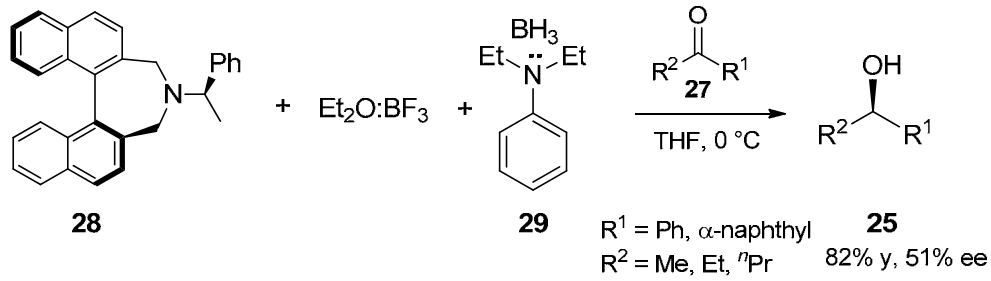
Hogeveen *et al.*[11] reported the use of (*S*,*S*)-α,α'-dimethyldibenzylamine borane **26** in asymmetric reduction of prochiral ketones **27** in the presence of borane and Et_2O**:**BF_3. The corresponding alcohols were obtained with up to 42% ee and 78% yield (Scheme 5).

Scheme 5



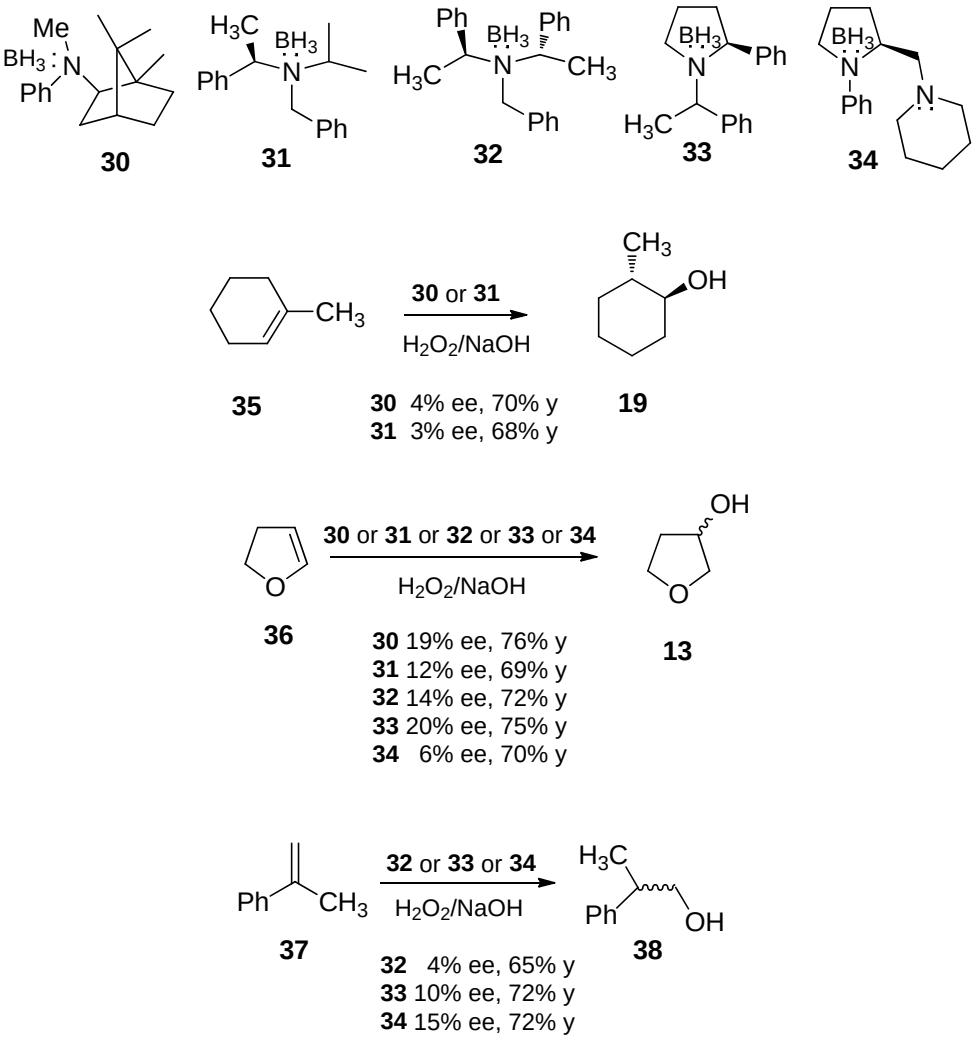
The utility of the chiral binaphthyl amine **28** in asymmetric reduction of prochiral ketones has been reported from this laboratory.[12] The corresponding alcohols were obtained in up to 51% ee and 82% yield (Scheme 6).

Scheme 6



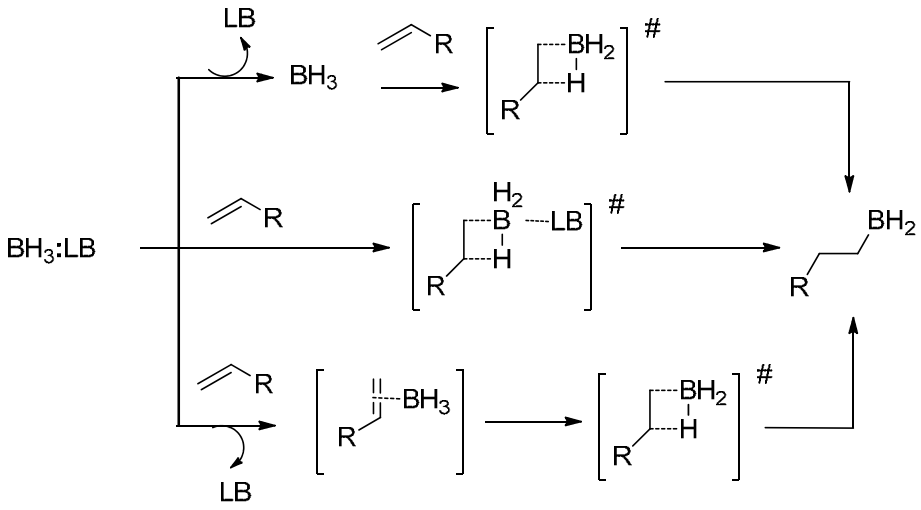
Previously, it has been reported that hydroboration of representative prochiral olefins using chiral tertiary amine borane complexes **30-34** gave the corresponding alcohols with up to 20% ee after H_2O_2/NaOH oxidation (Chart 2).[13]

Chart 2



The selectivities realized in these reactions are low, as the amine moiety is expected to leave before or during formation of the hydroboration reaction transition state as outlined in Scheme 7.[13b-c]

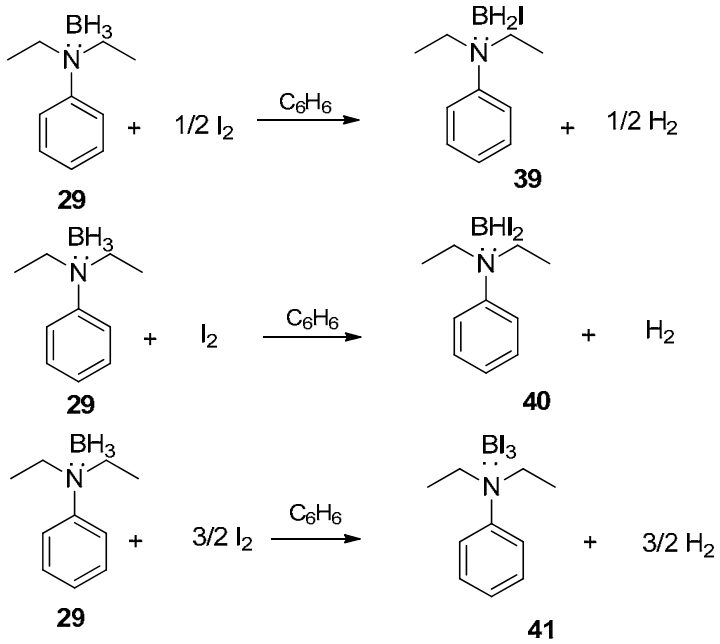
Scheme 7



2.1.4 Hydroboration using iodoborane complexes

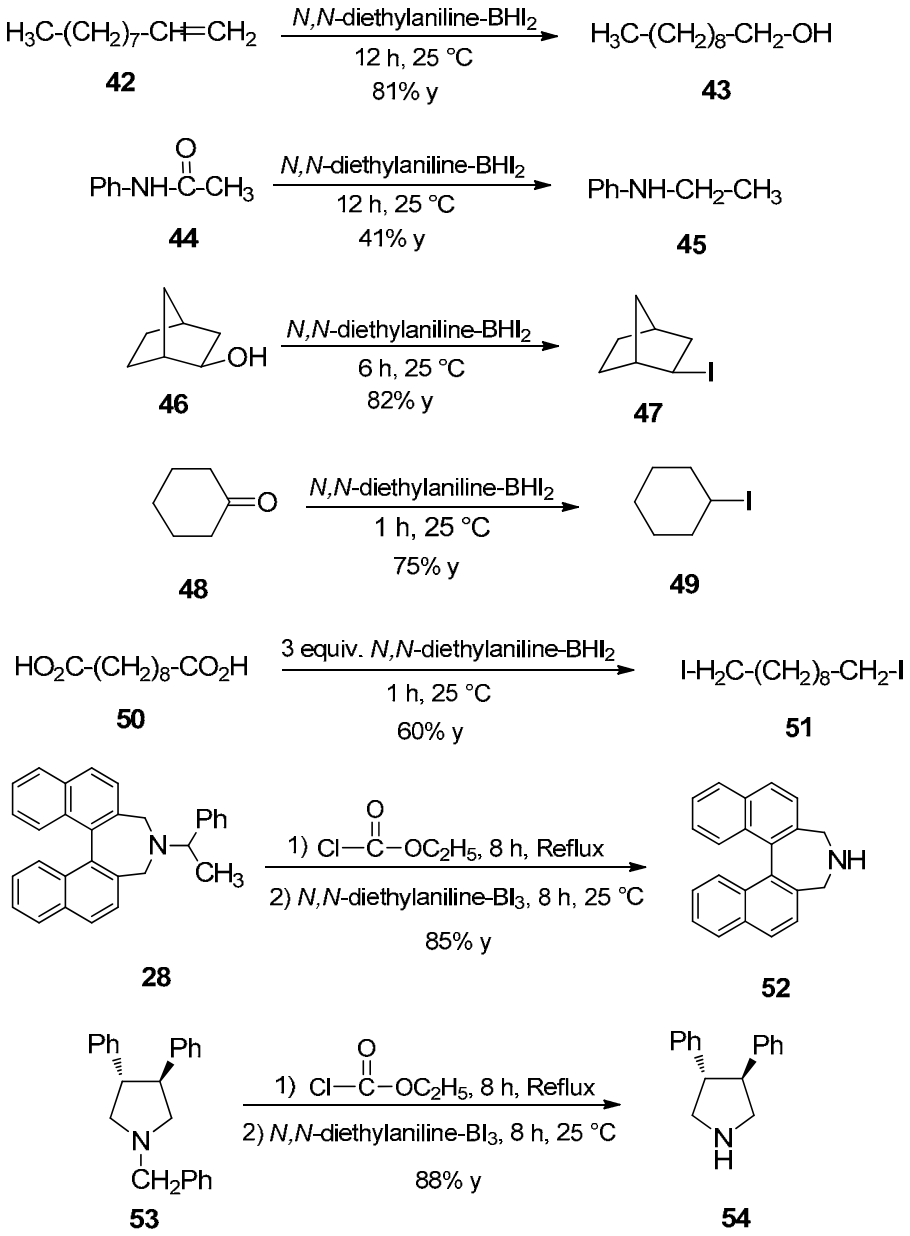
Previously, hydroboration studies using *N*,*N*-diethylaniline iodoborane complexes have been reported from this laboratory (Scheme 8).[14]

Scheme 8



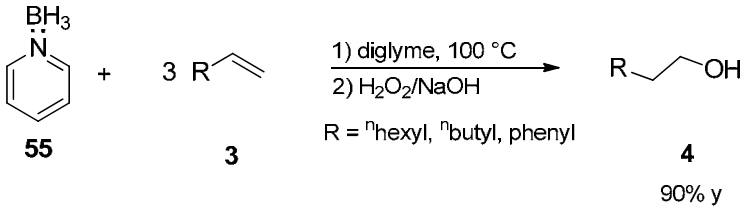
These complexes have been used for hydroborations of alkenes, reduction of amides, iodination of alcohols, reductive iodination of carbonyl compounds and *N*-debenzylation of tertiary amines (Chart 3).[14]

Chart 3



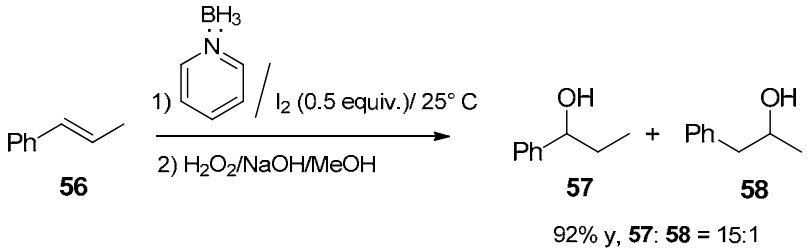
Pyridine borane (Py:BH_3) hydroborates a variety of olefins at 100 ˚C in diglyme and the corresponding alcohols were obtained in up to 90% yield after H_2O_2/NaOH oxidation (Scheme 9).[15]

Scheme 9



Vedejs. *et al*.[16] reported that the intermolecular hydroboration of β-methylstyrene **56** using pyridine borane complex at room temperature under iodine activation (Scheme 10).

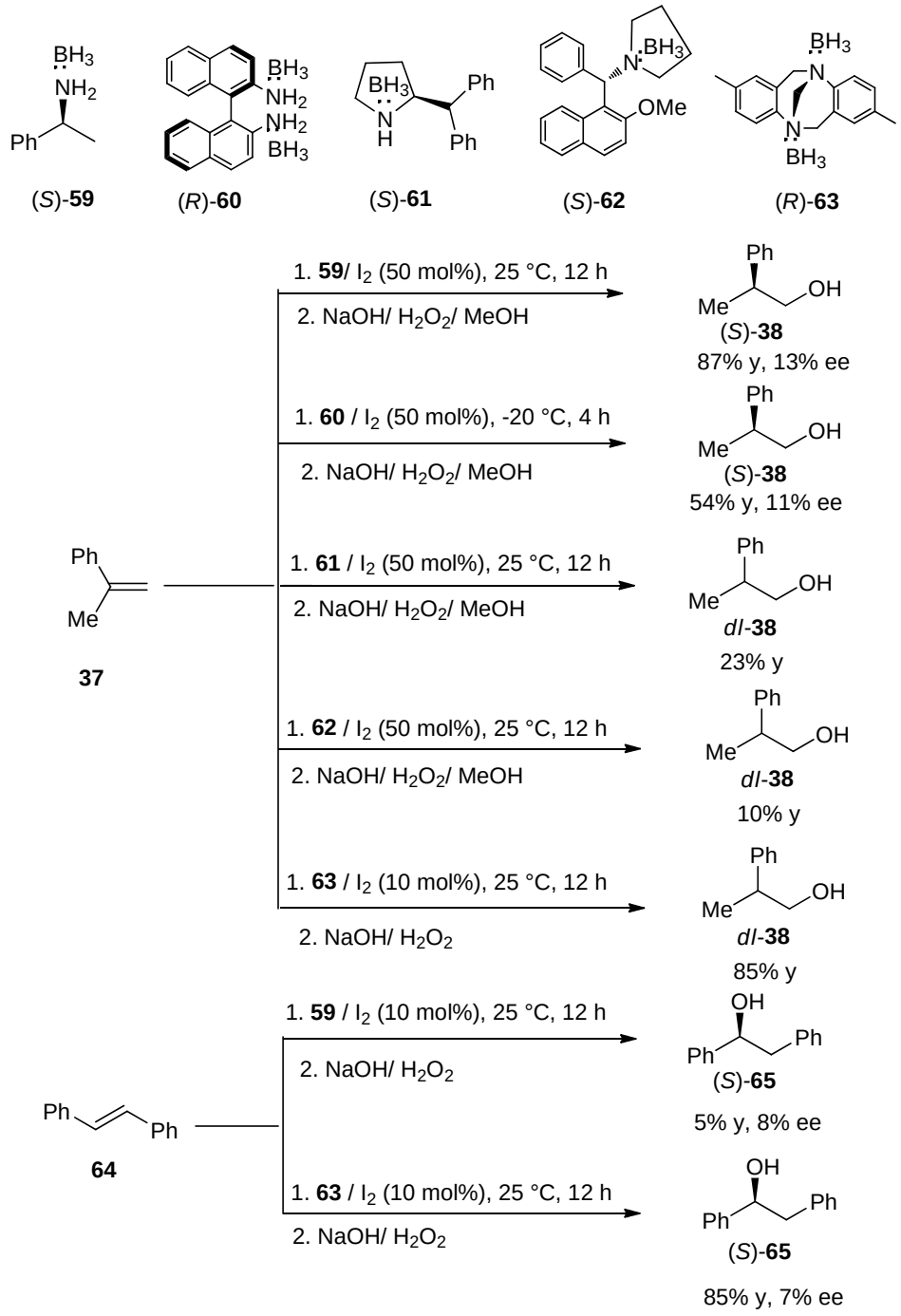
Scheme 10



The iodine activated hydroboration goes through initial formation of the iodoborane complexes. Since the amine moiety is anchored on the boron centre in these iodoborane complexes and the iodide behaving like a leaving group, it was of interest to us to prepare chiral amine-BH_2I complexes to examine the asymmetric hydroboration of prochiral olefins. Previous, studies revealed that the reactivity order is RNH_2:BH_2I > R_2NH:BH_2I > R_3N:BH_2I for iodine activated hydroboration reaction of α-methylstyrene **37** (Chart 4). Whereas the borane complexes of primary amines like *α*-methylbenzylamine **59** and (*R*)-BINAM **60** hydroborate the α-

methylstyrene **37** under 50 mol% iodine activation to give the product **38** in 13% ee and 11% ee, respectively after H_2O_2/NaOH oxidation (Chart 4), the secondary amine **61** and tertiary amine **62** gave only racemic products under these conditions.[17]

Chart 4



When the hydroboration reaction of α-methylstyrene was carried out in the presence of the borane complexes of secondary or tertiary amines **61**, **62** and **63** under iodine activation, only racemic product **38** was obtained (Chart 4). However, the hydroboration reaction of *trans*-stilbene **64** using the Troger base **63**-borane complex with catalytic amount of iodine (10 mol%) gave the corresponding alcohol **65** with up to 7% ee. When the hydroboration reaction of *trans*-stilbene **64** was carried out in the presence of α-methylbenzylamine **59**-borane complex with catalytic amount of iodine (10 mol%), the alcohol **65** was obtained in 5% yield with up to 8% ee (Chart 4).

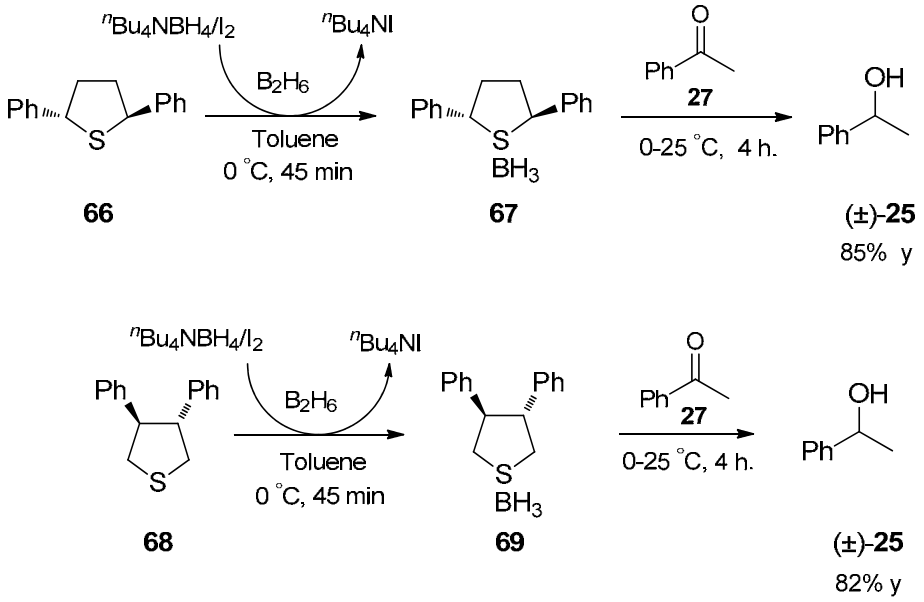
We became interested in examining the hydroboration reaction of prochiral olefins with chiral sulfide-boranes, readily accessed through the methods outlined in Chapter 1. The results are discussed in the next section.

2.2 Results and Discussion

2.2.1 Asymmetric reductions using borane complexes of (+)-(2*S*,5*S*)-2,5-diphenyl tetrahydrothiophene 66 and (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene 68

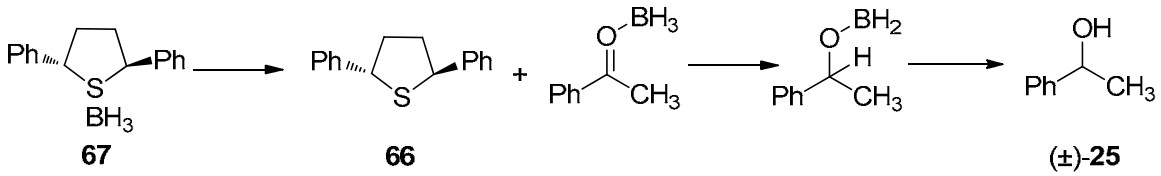
We have examined the use of the borane complexes of (+)-(2*S*,5*S*)-2,5-diphenyl tetrahydrothiophene **66** and (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene **68** derivatives prepared by the reaction of diborane generated using $^{n}Bu_4NBH_4$ and I_2 for asymmetric reduction of acetophenone **27**. The product 1-phenylethanol **25** was formed in 82-85% yield but it was found to be only racemic (Scheme 11).

Scheme 11



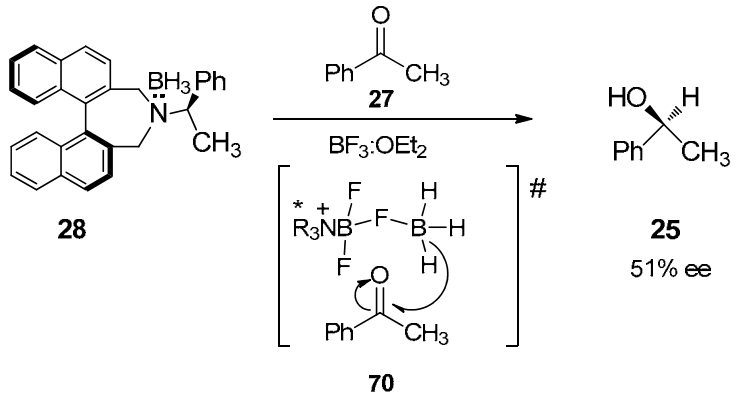
Presumably, the reaction may take place *via* the mechanism in which the chiral sulfide borane is displaced by the ketone before the reduction step, leading to the racemic product (Scheme 12).

Scheme 12



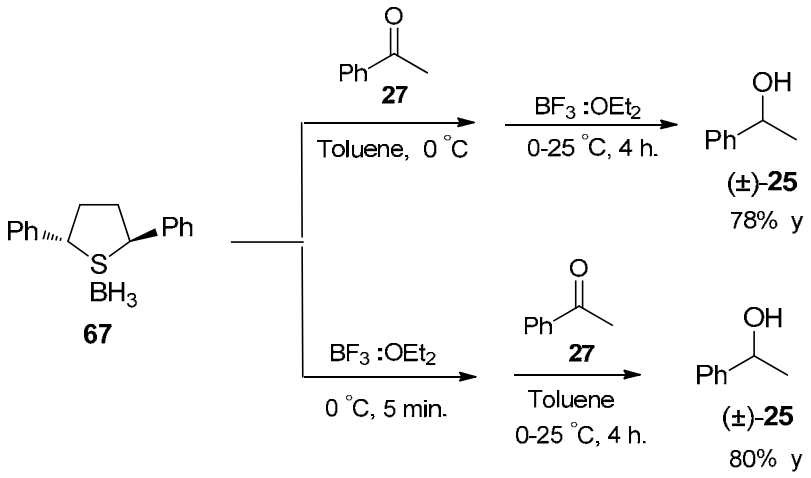
Previous report on the chiral binaphthyl system **28** revealed that the reduction of prochiral ketones **27** utilizing the chiralamine borane **28**-BF_3 catalyst in combination with achiral reagents such as *N*,*N*-diethylaniline-BH_3, triethylamine-BH_3 or B_2H_6 itself, give the alcoholic product with 51% ee. The results were explained by considering a cyclic transition state **70** outlined in Scheme 13.[12]

Scheme 13



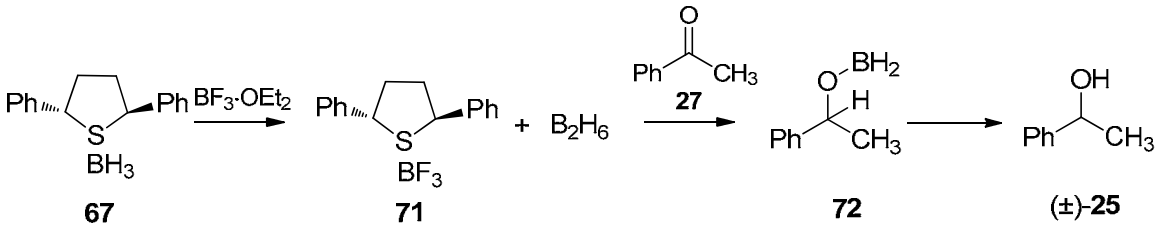
Accordingly, we have examined this reduction under Et_2O**:**BF_3 catalysis but the reduced product 1-phenylethanol was found to be only racemic under different conditions (Scheme 14).

Scheme 14



Presumably, instead of leading to the transition state like **70**, the BF_3 may replace BH_3 resulting in the racemic product (Scheme 15).

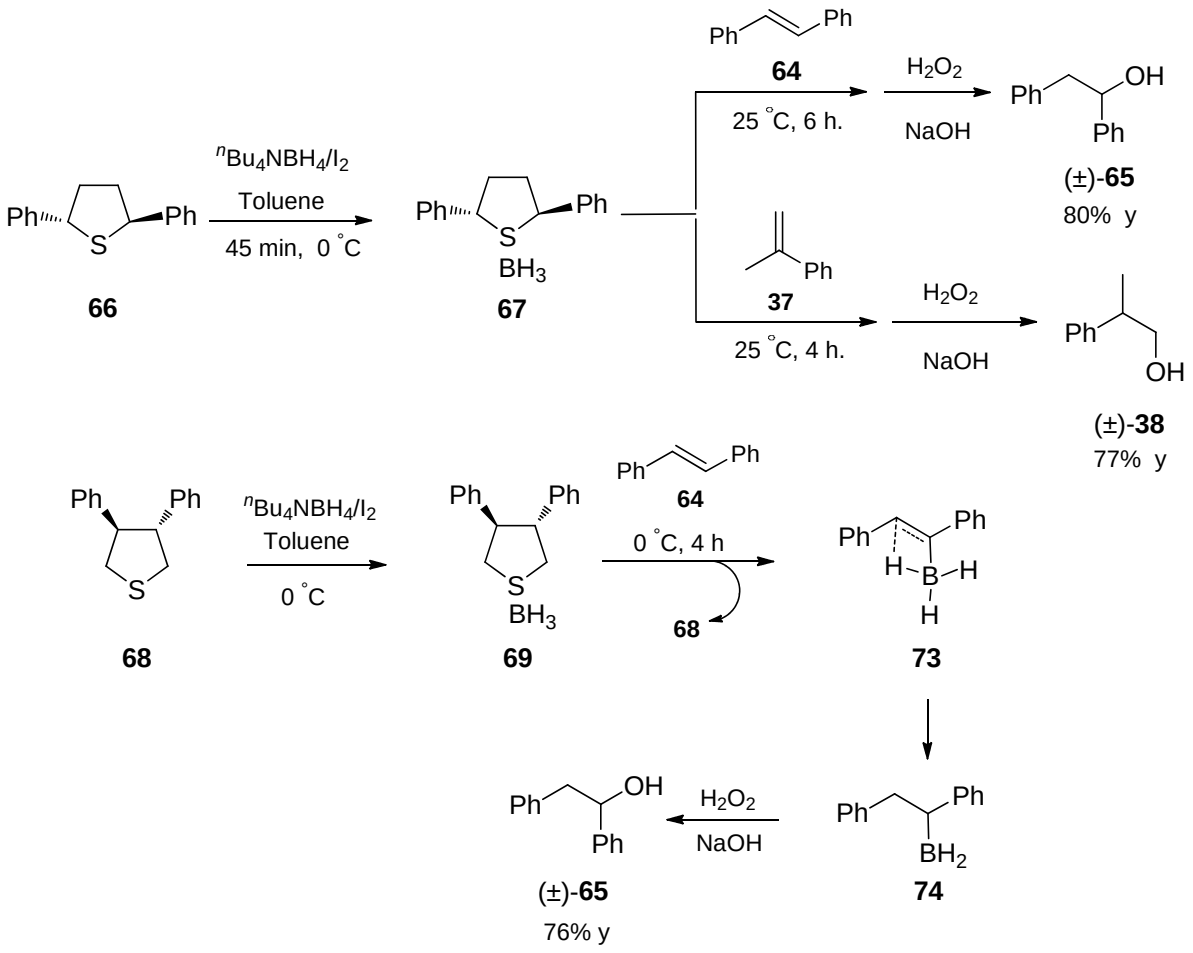
Scheme 15



2.2.2 Hydroboration of prochiral olefins using borane complexes of (2*S*,5*S*)-2,5-diphenyl tetrahydrothiophene 66 and (3*R*,4*R*)-3,4-diphenyltetrahydrothiophene 68

The borane-methyl sulfide complex hydroborates numerous olefins at 25 °C.[18] Accordingly, we have examined the use of borane complexes of the chiral C_2-symmetric sulfides **66** and **68** for hydroboration of prochiral olefins *trans*-stilbene and α-methyl styrene but the alcohol products obtained after oxidation were found to be only racemic (Scheme 16).

Scheme 16



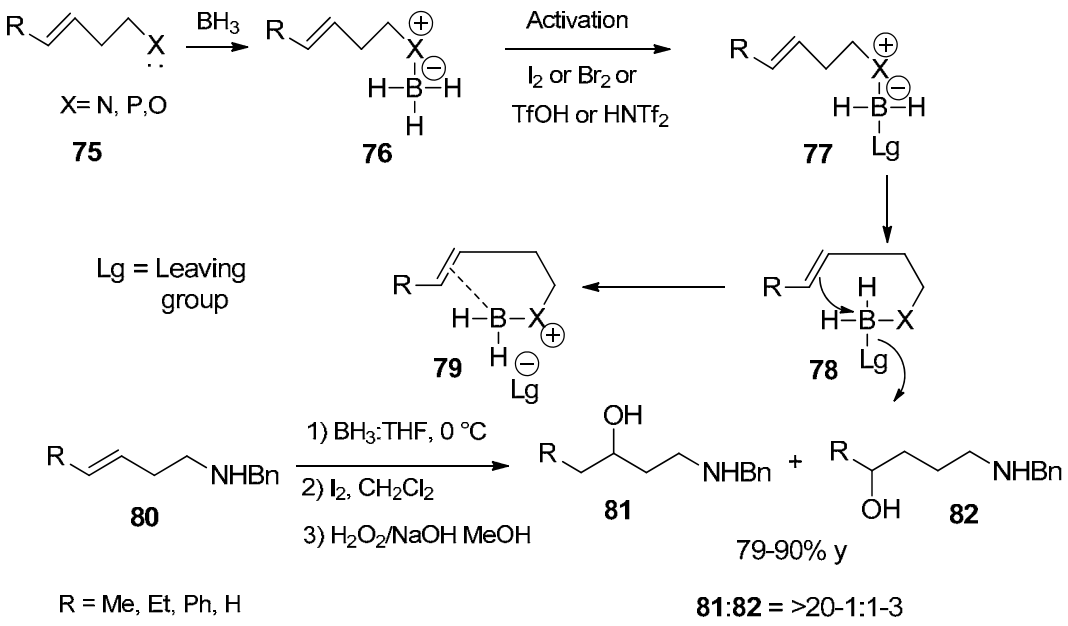
Presumably, the poor asymmetric induction realized may be due to the poor chiral discriminating ability of these chiral sulfide systems or the hydroboration reaction takes place after the chiral sulfide is displaced by the olefin.

2.2.3 Hydroboration of prochiral olefins using iodoborane complexes of (3*R*,4*R*)-3,4-diphenyltetrahydrothiophene 68 and (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene 66

Recently, Vedejs *et al.*[19] reported that the intramolecular hydroboration of homoallylic amine boranes and phosphine boranes takes place at 25 ˚C through activating agents like I_2, Br_2, TfOH and $HNTf_2$. It was suggested that such iodine activated hydroborations would go through a

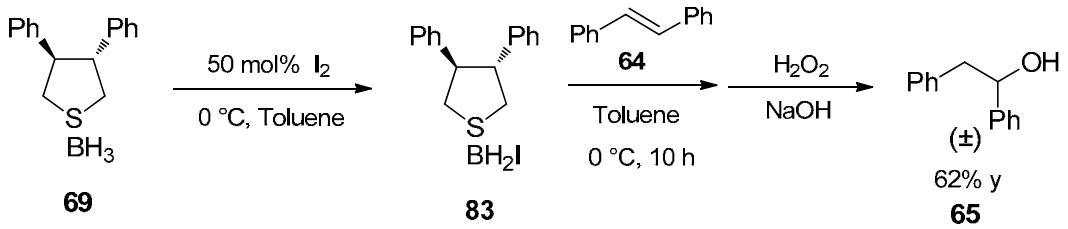
mechanistic pathway in which the iodide would behave like a leaving group and the chiral sulfide or amine are anchored to the boron throughout the course of the reaction (Scheme 17).

Scheme 17



We have examined the iodine activated hydroborations using the borane complexes of chiral sulfide **68** in reaction with *trans*-stilbene at 0 ˚C but the alcohol product obtained after oxidation was found to be only racemic (Scheme 18).

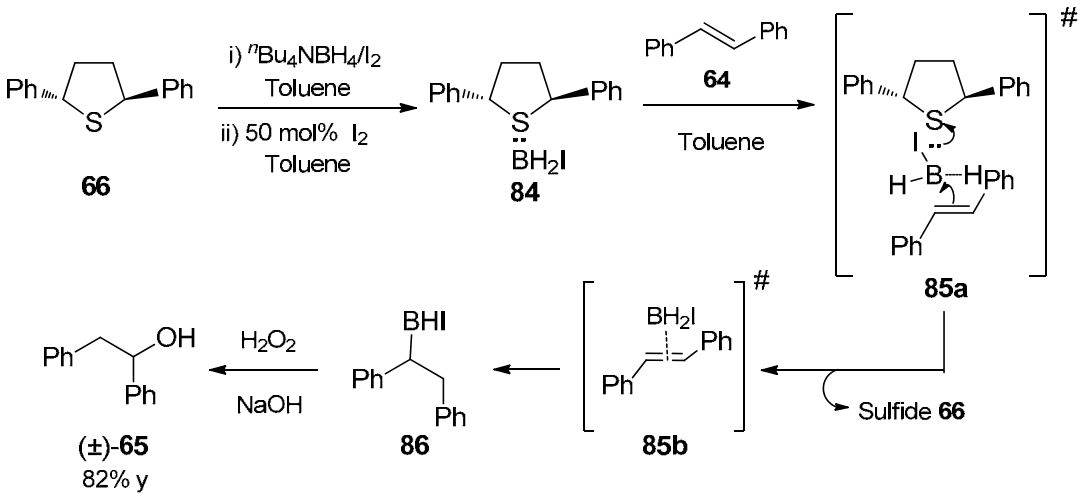
Scheme 18



The poor asymmetric induction realized might be due to the poor chiral discriminating ability of these chiral sulfide systems because the chiral centers are far away from the reaction

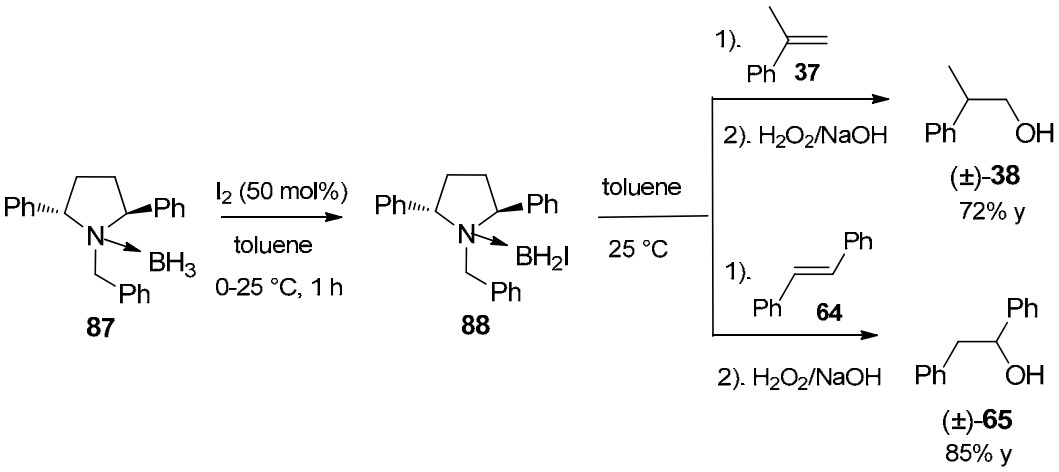
centre. Surprisingly, the (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **66** system also gave only racemic product (Scheme 19).

Scheme 19



Previously, hydroboration of the prochiral olefins *trans*-stilbene and α-methylstyrene using the (2*S*,5*S*)-*N*-benzyl-2,5-diphenylpyrrolidine borane complex **87** was carried out in this laboratory. The hydroboration-oxidation products were obtained in this reaction in 70-85% yield but were also found to be only racemic (Scheme 20).[20]

Scheme 20

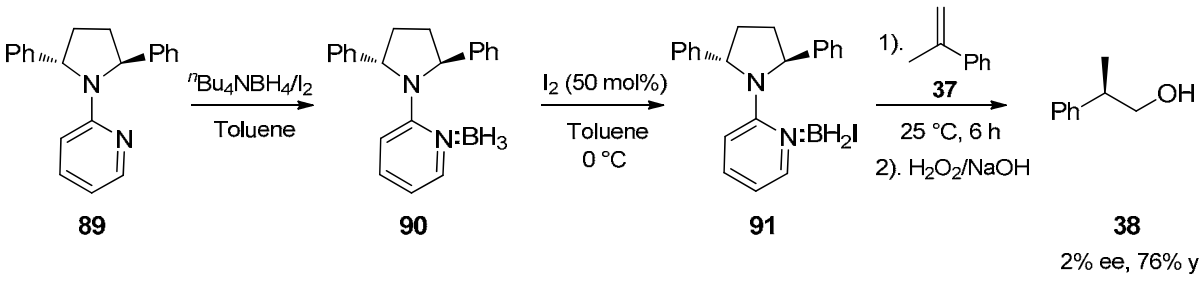


Presumably, the olefin may displace the chiral amine before hydroboration because of steric hindrance of the phenyl groups at C2 and C5 carbons of the chiral amine **87** (Scheme 20) and the sulfide **66** (Scheme 19).

2.2.4 Hydroboration of prochiral olefins using iodoborane complexes of chiral pyridine derivative *trans*-(-)-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine 89

Since pyridine-BH_3 hydroborates olefins at 25 ˚C under iodine activation, we have examined the utility of the chiral pyridine derivative *trans*-(-)-2,5-diphenyl-*N*-(2-pyridyl) pyrrolidine **89** containing pyridine moiety synthesized by the method described in Chapter 1. We made the corresponding borane complex **90** using the $^{n}Bu_4NBH_4/I_2$ reagent system. The corresponding iodoborane complex **91** was obtained using 50 mol% of iodine at 0 ˚C. The reaction of this chiral iodoborane complex **91** and prochiral α-methylstyrene at 25 ˚C gave the hydroboration-oxidation product with 76% yield but only in 2% ee (HPLC analysis, Scheme 21).

Scheme 21

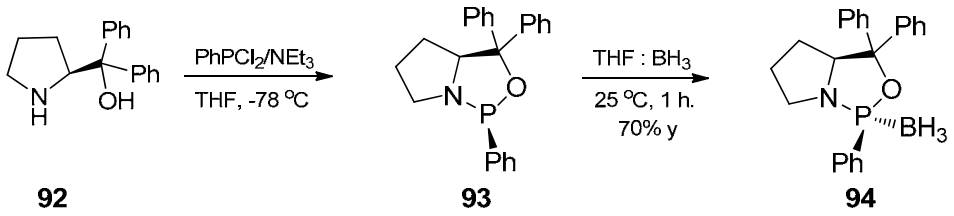


In this case, the poor chiral discrimination is realized as the reaction center is far away from the chiral substituent. Presumably, larger groups like anthracenyl moiety in the place of the phenyl group in the complex **91** would give better chiral recognition.

2.2.5 Hydroboration of prochiral olefins using iodoborane complexes of chiral oxazaphospholidine borane complex 94

Intramolecular hydroboration of homoallylic phosphine boranes has been reported by triflic acid activation at 0 ˚C. We have examined the utility of chiral oxazaphospholidine **93** derived from (*S*)-α,α-diphenylprolinol **92**. We have synthesized the (*S*)-α,α-diphenylprolinol derived chiral oxazaphospholidine ligand **93** by following a literature procedure.[22] It was then reacted with BH_3**:**THF complex to obtain the oxazaphospholidine borane complex **94** (Scheme 22).

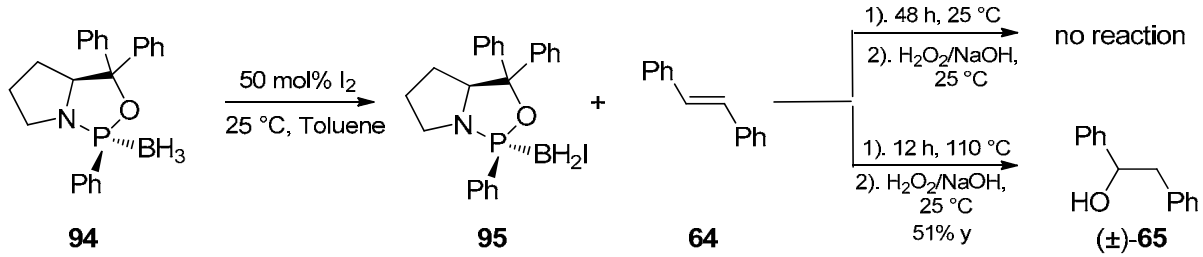
Scheme 22



92 **93** **94**

We have examined this complex **94** for asymmetric hydroboration of olefins at 25 ˚C with iodine activation but unfortunately, there was no reaction even after 48 h. When the reaction carried out at 110 ˚C for 12 h in toluene, the alcoholic product was obtained in 51% yield after H_2O_2/NaOH oxidation but it was found to be racemic (Scheme 23).

Scheme 23



94 **95** **64** **(±)-65**

As outlined in the introductory section, sterically less hindered complexes like primary amine borane, pyridine borane and Tröger base borane complexes lead to asymmetric induction in hydroboration reaction under iodine activation but with poor enantiomeric selectivity at ambient conditions (Chart 4). Accordingly, further studies on the synthesis and application of new primary amine derivative **96** or pyridine borane derivative **97** or DABCO like derivative **98** with large aryl groups should give more fruitful results (Figure 1).

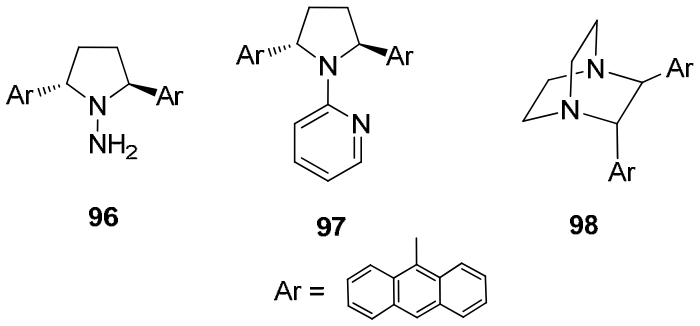


Figure 1

2.3 Conclusions

We have examined the utility of (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **66,** (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene **68** borane complexes in asymmetric reduction of acetophenone and in the asymmetric hydroboration of prochiral olefins *trans*-stilbene and α-methylstyrene. We have also examined the utility of the chiral pyridine derivative *trans*-(-)-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine-borane complex **90** and the chiral oxazaphospholidine borane complex **94** for asymmetric hydroboration of *trans*-stilbene under iodine activation. Though, the alcoholic products obtained were only racemic in most cases, the studies should help in designing new chiral amine skeletons for such studies.

2.4 Experimental Section

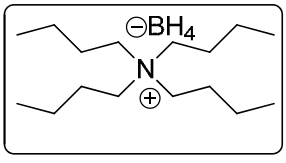
2.4.1 General Information

The information given in the section **1.4** is also applicable for the experiments outlined in this section. The tetrabutylammonium hydrogen sulphate was purchased from Loba Chemie (Pvt) Ltd., India. The sodium borohydride was purchased from E-Merck, India. Chiral sulfide boranes are not isolated but were made and used in solutions. Chiral diphenylprolinol derived oxazaphospholidine borane complex **94** was prepared by following the literature procedure.[22] The ^{11}B NMR was recorded at 128.3 MHz and the chemical shifts are reported relative to the external standard $Et_2O{:}BF_3$.

2.4.2 Preparation of tetrabutylammonium borohydride[23]

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

Yield 25.32 g (98%).



mp 126-131 ˚C.

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

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

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

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 58.8, 24.0, 19.5, 13.5.

2.4.3 General procedure for synthesis of chiral sulfide borane complexes (67 and 69) using tetrabutylammonium borohydride and iodine

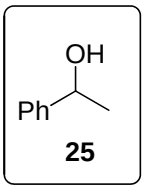
Diborane gas (12 mmol) generated by the slow addition of iodine (1.524 g, 6 mmol) in toluene (20 mL) to tetrabutylammonium borohydride (3.21 g, 12 mmol) in toluene (5 mL) at 25 ˚C was passed through the toluene solution (25 mL) of chiral sulfide **66** (1.2 g, 5 mmol) at 0 ˚C. The reaction flask was closed under nitrogen and the solution was transferred through cannula under nitrogen and stored at 0 ˚C. This solution was used for further reactions.

^{11}B-NMR (128.3 MHz, $PhCH_3$, δ ppm) -18.8.

2.4.4 Asymmetric reduction of acetophenone using the chiral sulfide borane complex 67 without $BF_3{\cdot}Et_2O$

The chiral sulfide borane complex **67** (2 mmol, 10 mL) was taken in 25 mL reaction flask under nitrogen at 0 ˚C. Acetophenone (0.24 g, 2 mmol) dissolved in toluene (10 mL) was added to the reaction flask drop by drop at 0 ˚C for 30 min. The reaction mixture was brough to 25 ˚C and further stirred for 4 h at the same temperature. The reaction mixture was quenched with

water (5 mL), and organic layer was separated. The aqueous layer was washed with ether (2 x 10 mL) and the combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified on silica gel (100-200 mesh). Pure hexane eluted the chiral sulfide and hexane:ethyl acetate (95:5) eluted the reduced product 1-phenylethanol.



25

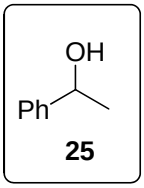
Yield 0.21 g (85%).

IR (neat) (cm^{-1}) 3348, 3030, 2974, 1602, 1078, 760.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.39-7.25 (m, 5H), 4.9 (q, *J* = 6.4 Hz, 1H), 1.89 (br, 1H), 1.49 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 145.8, 128.3, 127.2, 125.3, 70.0, 25.0.

2.4.5 Asymmetric reduction of acetophenone using the chiral sulfide borane complex 67 in the presence of $Et_2O:BF_3$



25

The chiral sulfide borane complex in toluene (2 mmol, 10 mL) was taken in 25 mL reaction flask under nitrogen at 0 ˚C. To this, $Et_2O:BF_3$ (0.28 g, 2 mmol) was added and acetophenone (0.24 g, 2 mmol) dissolved in toluene (10 mL) was added to the reaction flask drop by drop at 0 ˚C for 30 min. The reaction mixture was brought to 25 ˚C and further stirred for 4 h at the same temperature. The reaction mixture was quenched with water (5 mL), and organic layer was separated. The aqueous layer was washed with ether (2 x 10 mL) and the combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified on silica gel (100-200 mesh). Pure

hexane eluted the chiral sulfide and hexane:ethyl acetate (95:5) eluted the product 1-phenylethanol.

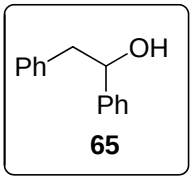
Yield 0.195 g (80%)

The spectral data of this compound showed 1:1 correspondence with the data of the product obtained in the earlier experiment.

2.4.6 General procedure for Hydroboration/oxidation of *trans*-stilbene 64 using chiral sulfide borane complex 67

The chiral sulfide borane complex **67** (2 mmol, 10 mL) was taken in 25 mL reaction flask under nitrogen at 0 ˚C. To this, *trans*-stilbene (2 mmol) dissolved in toluene (10 mL) was added drop by drop at 0 ˚C for 30 min. The reaction mixture was brought to 25 ˚C and further stirred for 6 h at the same temperature. The reaction mixture was quenched with methanol (1 mL). The organoborane was oxidized using 3N NaOH (4 mL), H_2O_2 (30 %, 4 mL) and stirred for about 4 h. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The solvent was evaporated and the crude product was purified on silica gel column. Pure hexane eluted the chiral sulfide and hexane:ethyl acetate (95:5) eluted the reduced product.

Yield 0.32 g (80%).



65

mp 63-64 ˚C (*lit.*[24] 63-64 ˚C).

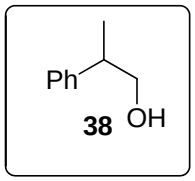
IR (KBr) (cm^{-1}) 3319, 3084, 2922, 1039, 696.

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

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

α-methylstyrene:

Yield 0.21 g (77%).



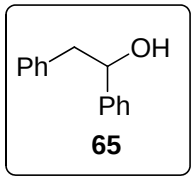
38

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

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.46-7.20 (m, 5H), 3.72-3.52 (m, 2H), 3.12-2.76 (m, 1H), 1.88 (s, 1H), 1.32-1.12 (m, 3H).

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

2.4.7 General procedure for Hydroboration/oxidation of *trans*-stilbene 64 using chiral sulfide borane complex 67 system activated by iodine



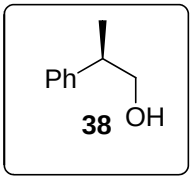
65

The chiral sulfide borane complex (2 mmol, 10 mL) was taken in 25 mL reaction flask under nitrogen at 0 ˚C. To this iodine (0.254 g., 1.0 mmol) dissolved in toluene (10 mL) was added drop by drop for 30 min at 0 ˚C. To this reaction mixture *trans*-stilbene (2 mmol) dissolved in toluene (5 mL) was added drop by drop at 0 ˚C for 30 min. The reaction mixture was brought to 25 ˚C and further stirred for 12 h at the same temperature. The reaction mixture was quenched with methanol (1 mL). The organoborane was oxidized using 3N NaOH (4 mL), H_2O_2 (30 %, 4 mL) and stirred for about 4 h. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The solvent was evaporated and the crude product was purified on silica gel (100-200 mesh). Pure hexane eluted the chiral sulfide and hexane:ethyl acetate (95:5) eluted the reduced product.

Yield 0.33 g (82%).

The spectral data of this compound showed 1:1 correspondence with the data of the product obtained in the earlier experiment.

2.4.8 General procedure for hydroboration/oxidation of α-methylstyrene using chiral pyridine borane complex 90



38

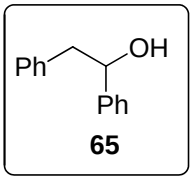
The chiral pyridine borane complex **90** was prepared by following the procedure described in **2.4.3.** The hydroboration with iodine activation was done as described in **2.4.7**.

Yield 0.21 g (76%).

Enantiomeric purity: 2% ee (determined by HPLC using chiral column, chiralcel OB-H, solvent system, hexane:^{i}PrOH: 95:5; flow rate 0.3 mL/min., 254 nm, retention times: 24.9 min for (*S*) and 26.8 min. for (*R*) isomer).

The spectral data of this compound showed 1:1 correspondence with the data of the product obtained in the earlier experiment.

2.4.9 General procedure for Hydroboration/oxidation of *trans*-stilbene using oxazaphospholidine borane complex 94



65

The chiral oxazaphospholidine borane complex **94** (2 mmol, 10 mL) was taken in 25 mL reaction flask under nitrogen at 0 ˚C. To this iodine (1.0 mmol) dissolved in toluene (10 mL) was added drop by drop for 30 min at 0 ˚C. The reaction mixture was brought to 25 ˚C and stirred further for 1 h at the same temperature. To this, *trans*-stilbene (2 mmol) dissolved in toluene (5 mL) was added to the reaction flask drop by drop at 0 ˚C for 30 min. The reaction mixture was brought to 25 ˚C and refluxed for 12 h at 110 ˚C. The

reaction mixture was quenched with methanol (1 mL). The organoborane was oxidized using 3N NaOH (4 mL), H_2O_2 (30 %, 4 mL) and stirred for about 4 h. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The solvent was evaporated and the crude product was purified on silica gel (100-200 mesh). Pure hexane eluted the chiral sulfide and hexane:ethyl acetate (95:5) eluted the reduced product.

Yield 0.20 g (51%).

The spectral data of this compound showed 1:1 correspondence with the data of the product obtained in the earlier experiment.

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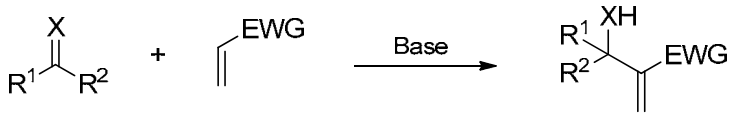
Chapter III

Studies on asymmetric Baylis-Hillman reaction using chiral sulfur heterocycles

3.1 Introduction

The Baylis-Hillman reaction is a three step transformation involving sequential Michael, aldol and elimination processes.[1] It may be broadly defined as a reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing electron withdrawing group under the influence of a catalyst (tertiary amine or phosphine or Lewis acid) and producing multifunctional molecules (Scheme 1).[2]

Scheme 1



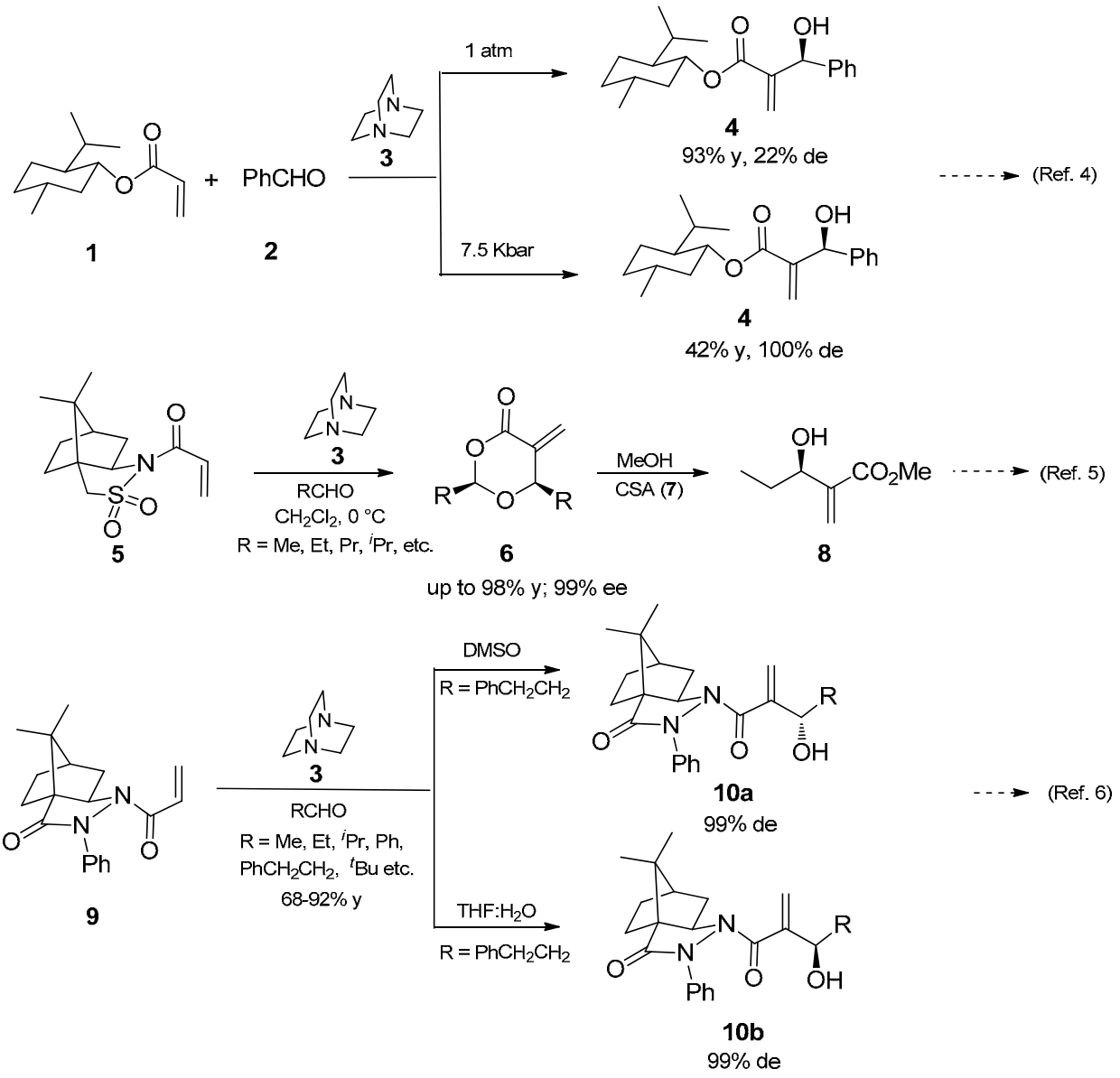
R^1 = aryl, alkyl, R^2 = H, alkyl ; X = O, NTs, NCOOR, etc.; Base = tertiary amine, phoshine, Lewis acid, MX_n
EWG = electron withdrawing group: CHO, COR, CO_2R, CN, $PO(OEt)_2$, SO_3Ph, etc.

As chiral Baylis-Hillman adducts are useful intermediates in natural product and bioactive molecule synthesis, numerous enantioselective versions of this reaction involving chiral environment have been reported. The reaction can be carried out by incorporating chirality in any one of the three components, in electrophile or activated alkene or the catalyst leading to the formation of enantiopure or enantioenriched multifunctional molecules. A brief discussion on these three aspects would facilitate further discussion.

3.1.1 Asymmetric Baylis-Hillman reactions involving chiral activated alkenes

Asymmetric Baylis-Hillman reactions containing chiral menthyl acrylates and camphanyl acrylamide derivatives using achiral DABCO **3** have been reported.[3] The effect of the solvent and pressure on the diastereoselectivity of the reaction were examined (Chart 1).

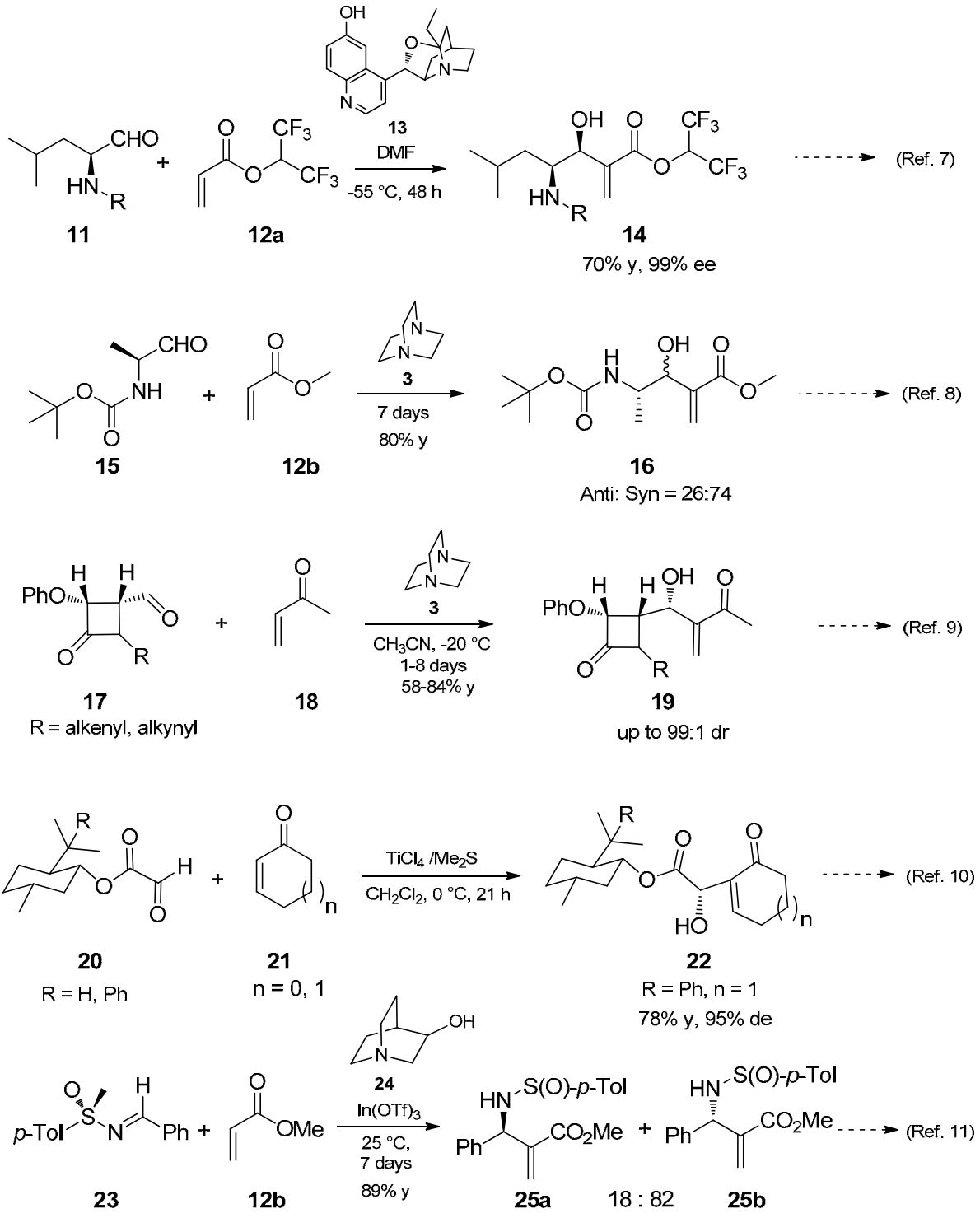
Chart 1



3.1.2 Asymmetric Baylis-Hillman reactions involving chiral electrophiles

Asymmetric Baylis-Hillman reactions directed by chiral electophiles **11**, **15**, **17** and **20** containing aldehydes and imines have also been reported (Chart 2).[2d] Also, enantiomerically pure *N*-*p*-toluenesulfinimines **23** as electrophile with methyl acrylate **12** gave the product with diastereoselectivity up to 18:82 (Chart 2).

Chart 2


OH
13
DMF
-55 °C, 48 h
11
12a
14
70% y, 99% ee
(Ref. 7)
15
12b
3
7 days
80% y
16
Anti: Syn = 26:74
(Ref. 8)
17
R = alkenyl, alkynyl
18
3
CH3CN, -20 °C
1-8 days
58-84% y
19
up to 99:1 dr
(Ref. 9)
20
R = H, Ph
21
n = 0, 1
TiCl4 /Me2S
CH2Cl2, 0 °C, 21 h
22
R = Ph, n = 1
78% y, 95% de
(Ref. 10)
24
In(OTf)3
25 °C,
7 days
89% y
23
12b
25a
18 : 82
25b
(Ref. 11)

3.1.3 Asymmetric Baylis-Hillman reactions involving chiral amine nucleophiles

The asymmetric Baylis-Hillman reactions directed by chiral catalysts like derivatives of chiral amines and chiral phosphines have been extensively studied. Reports on such chiral amine directed asymmetric Baylis-Hillman reactions are briefly outlined in Chart 3.

Chart 3

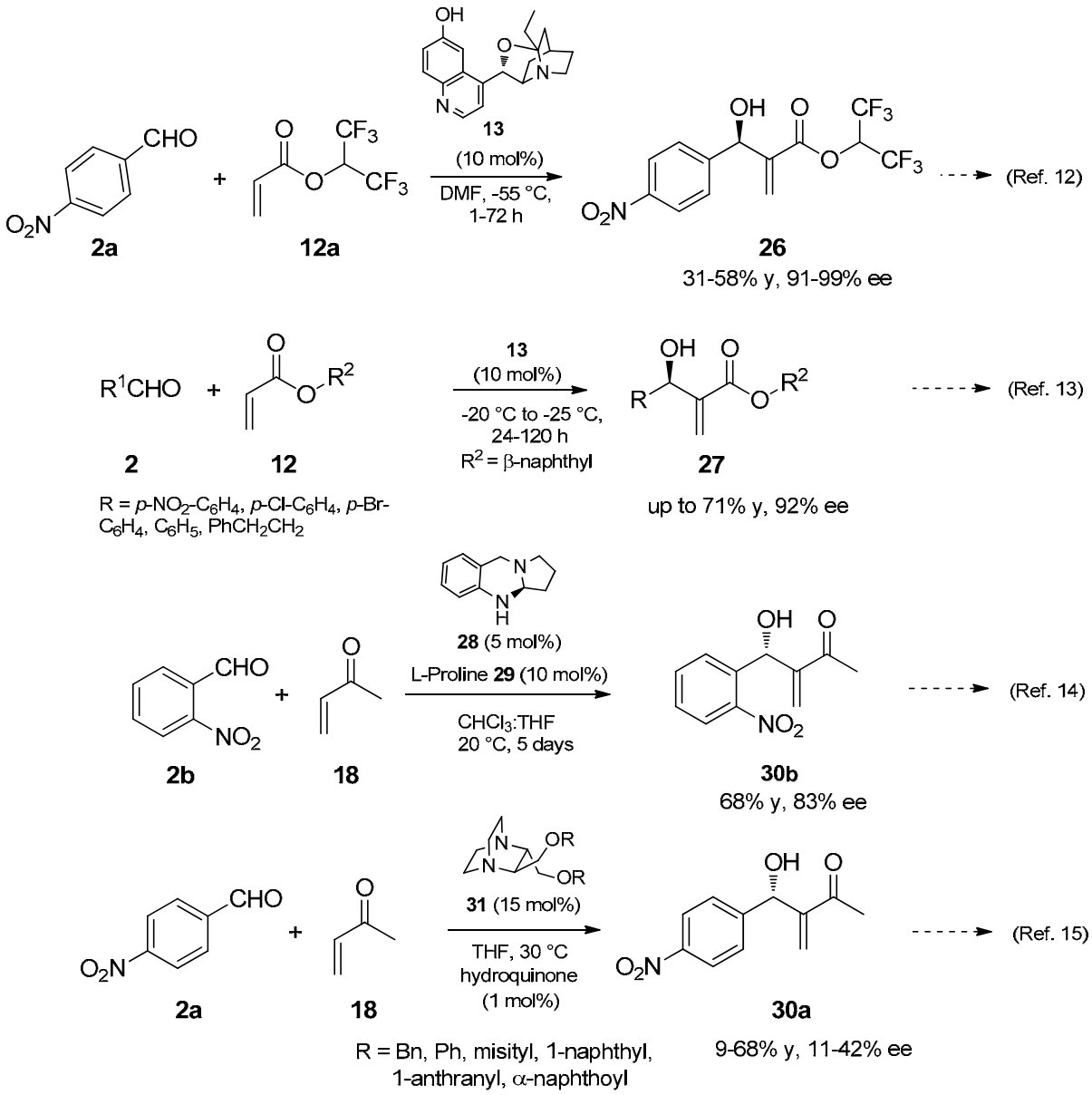
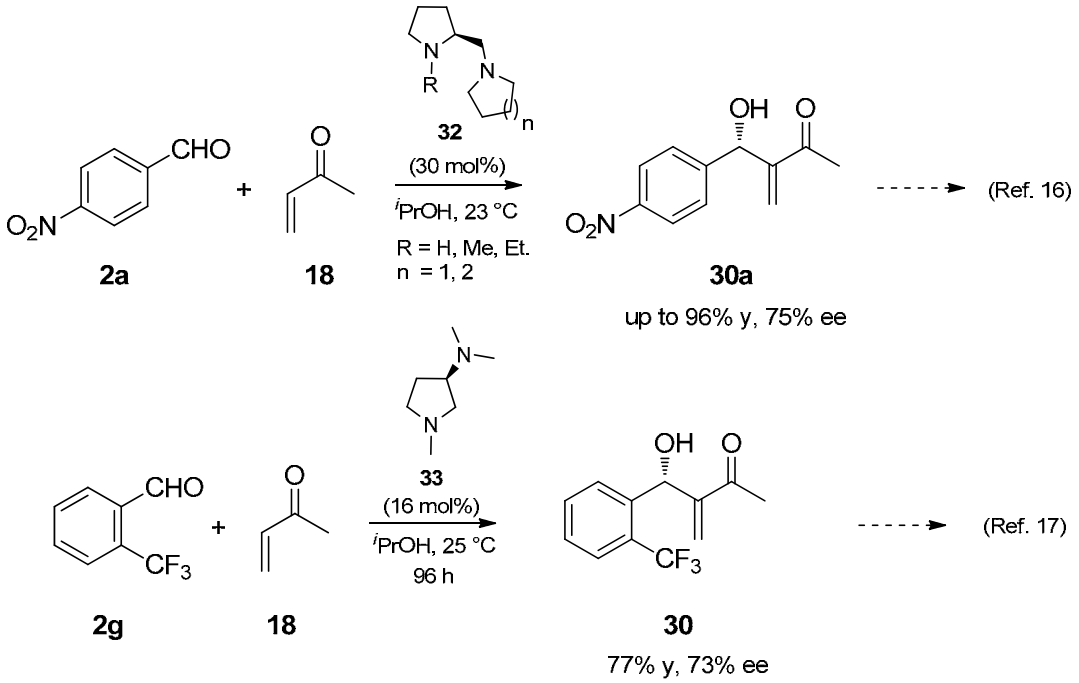


Chart 3 (continued)



3.1.4 Asymmetric Baylis-Hillman reactions involving chiral phosphorous nucleophiles

The chiral phosphorous ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl **35** (BINAP) was utilized in asymmetric Baylis-Hillman reactions.[18] The influence of Lewis acids $ZrCl_4$ and BCl_3 along with BINAP on the selectivity was also examined (Chart 4).[19] Catalytic asymmetric reaction was also studied by using tributylphosphine as cooperative catalyst along with chiral BINOL derived calcium catalyst **38** (Chart 4).[20]

Chart 4

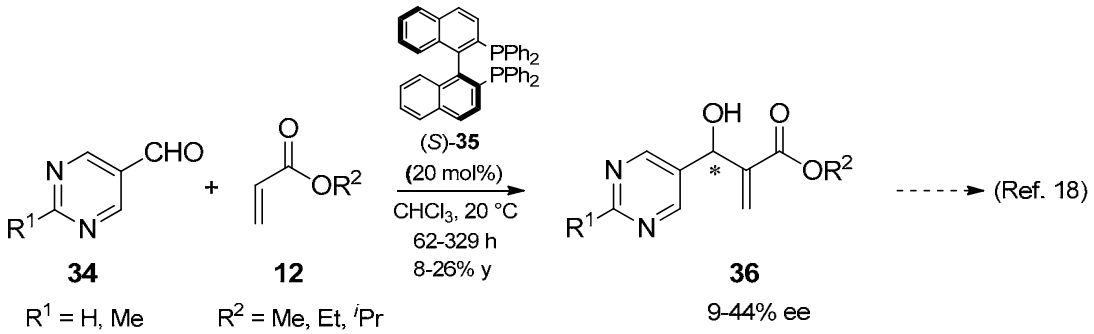
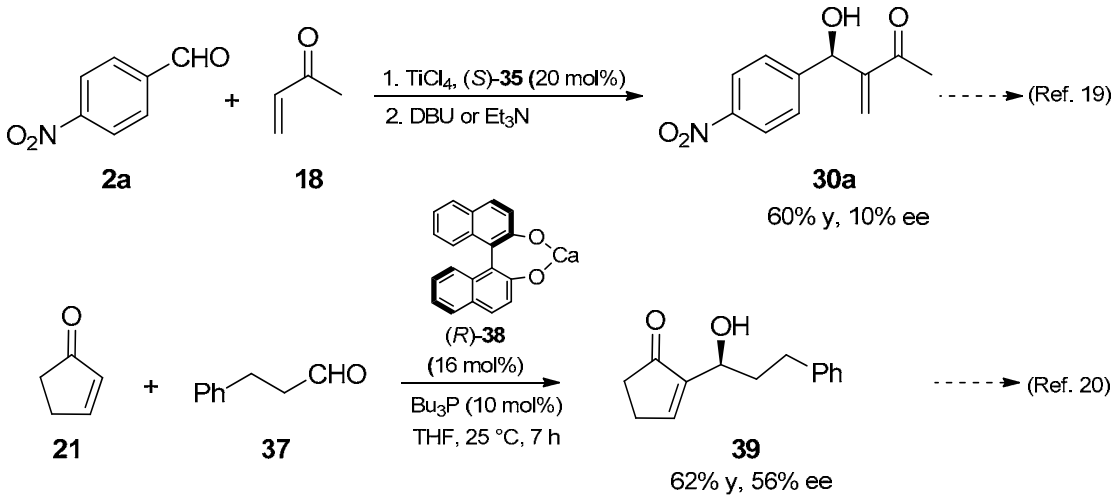


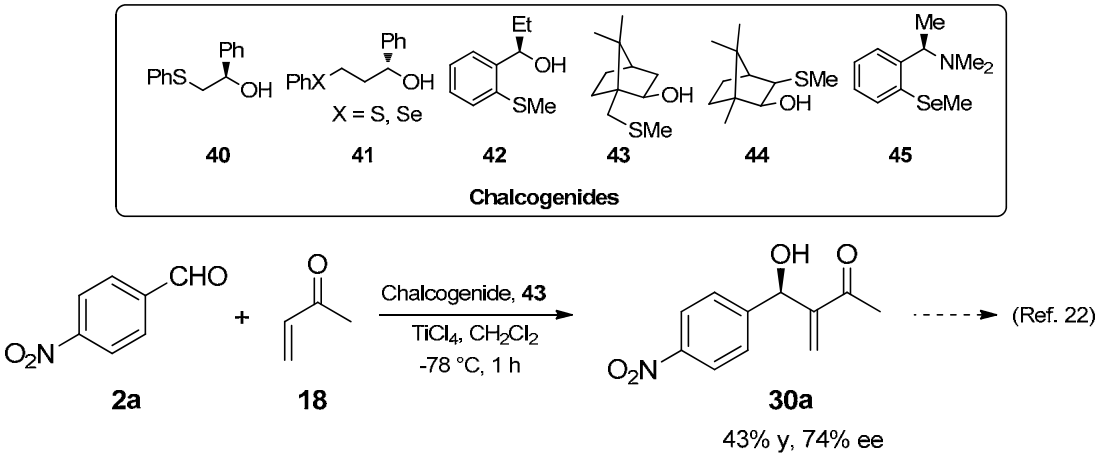
Chart 4 (continued)



3.1.5 Asymmetric Baylis-Hillman reactions directed by chiral chalcogenides

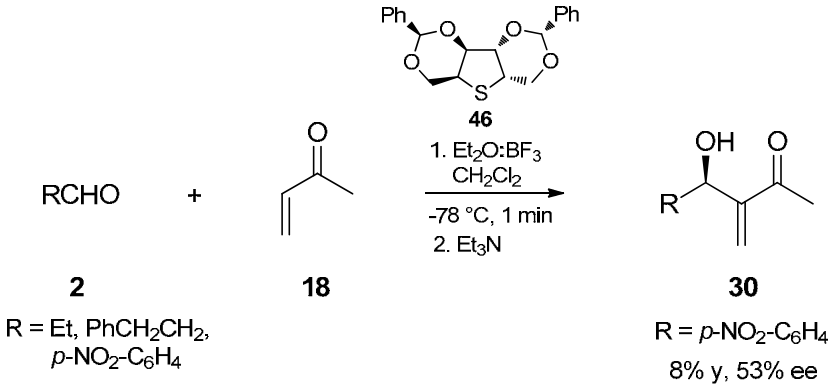
Reports on the reaction between vinyl ketones and various aldehydes catalysed by sulfides or selinides in the presence of $TiCl_4$ are summarized in Chart 5.[21-22]

Chart 5



The chiral C_2-symmetric tricyclic sulfide **46** derived from D-mannitol has been utilized in asymmetric Baylis-Hillman reaction. In this case, the adduct was obtained in 53% ee with 8% yield in the presence of Lewis acid $Et_2O{:}BF_3$ in CH_2Cl_2 (Scheme 2).[23]

Scheme 2

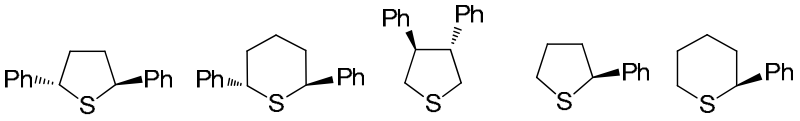


As outlined in the Chapter 1, we have developed methods to access chiral thiolane derivatives. We have examined the use of some of these derivatives for the preparation of chiral Baylis-Hillman adducts. The results are discussed in the next section.

3.2 Results and Discussion

3.2.1 Asymmetric Baylis-Hillman reaction directed by chiral sulfide and Lewis acid

It was of interest to examine the utility of chiral C_2 and C_1-symmetric sulfides (**47-51**, Figure 1) available through methods described in Chapter 1 in the asymmetric Baylis-Hillman reactions.



47 **48** **49** **50** **51**

Figure 1

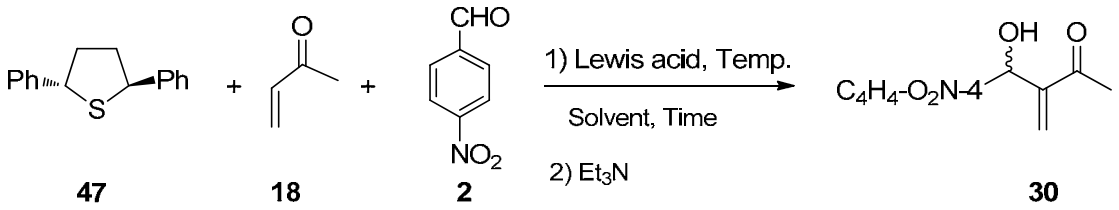
3.2.2 Optimization of the reaction using chiral sulfide 47, MVK and *p*-nitrobenzaldehyde

We have carried out the asymmetric Baylis-Hillman reaction with chiral sulfide **47**, methyl vinyl ketone (MVK) and *p*-nitrobenzaldehyde in the presence of Lewis acid in CH_2Cl_2 at 0 ˚C for 30 min (Scheme 3). In this case, the *S* isomer of the adduct was obtained with only 13% ee (Table 1, entry 1). The adduct was obtained in 38% ee when the reaction temperature was lowered to -78 ˚C (Table 1, entry 2).

The reaction was carried out in various solvents at different temperature and the results are summarized in Table 1. The reaction using CH_3CN as solvent at 0 ˚C for 45 min gave the *R* isomer with 44% ee and 66% yield (Table 1, entry 3). When the reaction time was reduced to 30 min, optical purity was enhanced to 52% ee with slightly lower yield (62%) (Table 1, entry 4).

We have observed better asymmetric induction in CH_3CN with up to 54% ee and 58% yield at -30 ˚C under Et_2O**:**BF_3 catalysis (Table 1, entry 5). We made an effort to further lowering the temperature but freezing of the contents prevented further improvement.

Scheme 3



47 **18** **2** **30**

Table 1: Screening of various conditions for optimization[a]

S. No.	Chiral Sulfide	Acid	Solvent	Temperature	Time (min.)	Yield (%)[b]	Ee[c,d] (%)
1.	**47**	Et_2O**:**BF_3	CH_2Cl_2	0˚C	30	54	13 (*S*)
2.	**47**	Et_2O**:**BF_3	CH_2Cl_2	-78˚C	30	50	38 (*S*)
3.	**47**	Et_2O**:**BF_3	CH_3CN	0˚C	45	66	44 (*R*)
4.	**47**	Et_2O**:**BF_3	CH_3CN	0˚C	30	62	52 (*R*)
5.	**47**	Et_2O**:**BF_3	CH_3CN	-30˚C	30	58	54 (*R*)
6.[e]	**47**	Et_2O**:**BF_3	THF	-30˚C	30	0	-
7.	**47**	Et_2O**:**BF_3	Toluene	0˚C	60	26	13 (*S*)
8.[e]	**47**	TfOH	CH_3CN	-30˚C	30	0	-
9.[e]	**47**	TMSOTf	CH_3CN	-30˚C	30	0	-
10.	**48**	Et_2O**:**BF_3	CH_3CN	-30˚C	30	70	0
11.	**49**	Et_2O**:**BF_3	CH_3CN	-30˚C	30	62	0
12.	**50**	Et_2O**:**BF_3	CH_3CN	-30˚C	30	68	0
13.	**51**	Et_2O**:**BF_3	CH_3CN	-30˚C	30	65	0

[a]All the reactions were carried out by using 1.2 mmol of chiral sulfide **47-51**, 1.0 mmol of 4-nitro benzaldehyde, 3.0 mmol of MVK, 1.5 mmol of Lewis acid in 5 mL of solvent. [b]Isolated yield. [c]Determined by chiral HPLC analysis using Chiralcel OD-H column. [d]Absolute configuration was assigned by comparision with reported optical rotational value.[24] [e]No reaction.

With the other chiral sulfides **48**, **49**, **50**, **51** only racemic products were obtained under these conditions (Table 1, entry 10-13). There was no reaction in THF (Table 1, entry 6). Also, the reaction did not take place using additives such as TfOH and TMSOTf in CH_3CN (Table 1, entry 8-9).

3.2.3 Asymmetric B-H Reaction using chiral sulfide 47, MVK and aromatic aldehydes

We have also examined other aromatic aldehydes (1.0 equiv) in this reaction using chiral sulfide (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **47** (1.2 equiv.) in the presence of Lewis acid Et_2O**:**BF_3 (1.2 equiv.) at -30 ˚C in CH_3CN for 30 min (Scheme 3). The (*R*)-enantiomeric products **30** were obtained in 14% to 55% ee (Table 2). In all cases, the chiral sulfide **47** was recovered in 85% yield without loss in its optical purity and reused in these studies.

Table 2: Asymmetric Baylis-Hillman reaction of MVK with various aldehydes using sulfide **47**[a]

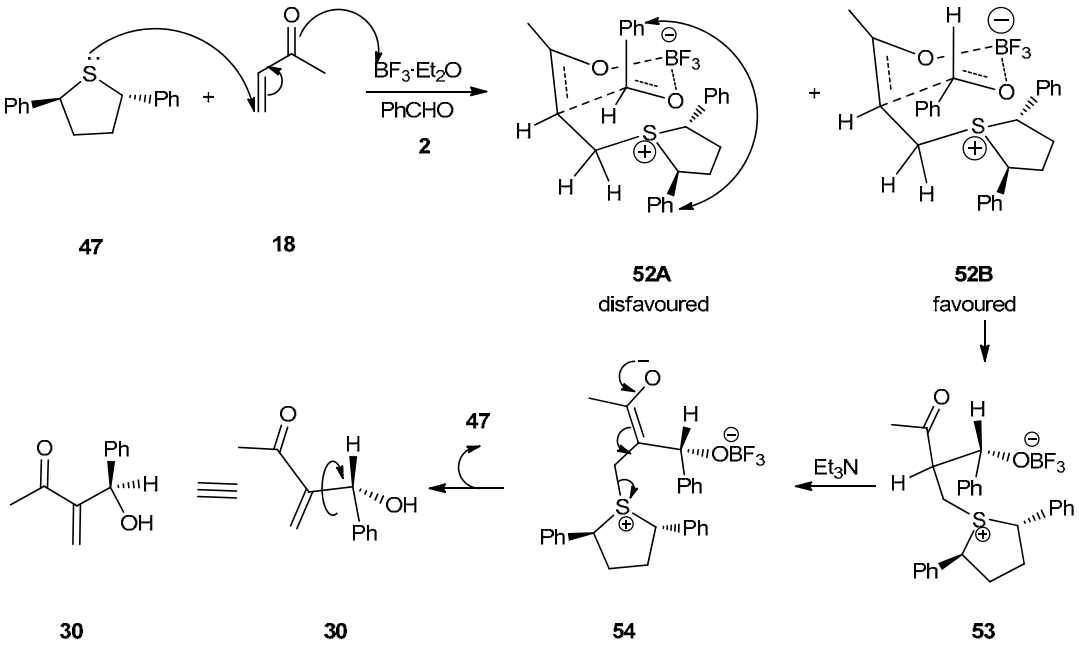
S.No.	Ar	Product	Yield (%)[b]	Ee[c,d] (%)
1.	4-NO_2-C_6H_4	**30a**	58	54
2.	2-NO_2-C_6H_4	**30b**	47	22
3.	3-NO_2-C_6H_4	**30c**	52	37
4.	4-Cl-C_6H_4	**30d**	68	24
5.	4-Br-C_6H_4	**30e**	59	42
6.	4-CN-C_6H_4	**30f**	52	55
7.	4-CF_3-C_6H_4	**30g**	41	32
8.	C_6H_5	**30h**	45	48
9.	Furyl	**30i**	46	14

[a]All the reactions were carried out by using 1.2 mmol of chiral sulfide **47**, 1.0 mmol of benzaldehyde, 3.0 mmol of MVK, 1.5 mmol of Et_2O**:**BF3 in 5 mL of CH_3CN. [b]Isolated yield. [c]Determined by chiral HPLC analysis using Chiralcel AS-H column. [d]Absolute configuration was assigned as *R* by comparision with reported optical rotational value.[24]

3.2.4 Mechanistic aspect of asymmetric Baylis-Hillman reaction directed by chiral sulfide and Lewis acid

The Baylis-Hillman reaction proceeds *via* Michael attack of the sulfide **47** on the activated alkene **18** to give the Z-enolate.[23] The reaction is likely go through a transition state in which the positively charged sulfur and the negatively charged boron are closer in space. Further, the transition state **52B** may be the favoured as it would have less steric interactions between the phenyl group of the chiral auxiliary and phenyl group of the aldehyde in the conformation compared to the other transition state **52A** which would have more steric interactions between phenyl group of the auxiliary and axial phenyl group of aldehyde as outlined in Scheme 5. This would lead to the adduct **53** which upon Et_3N treatment gives the (*R*)-**30** as major enantiomeric product.

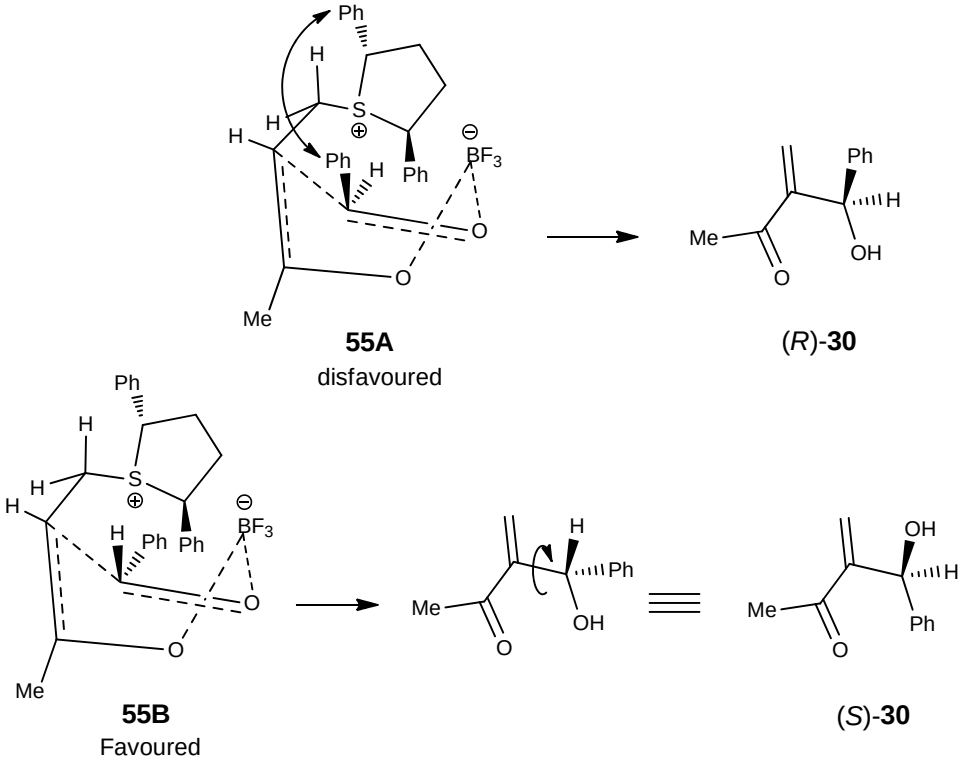
Scheme 5



However, the mechanism suggested in Scheme 5 still does not explain the formation of the (*S*)-**30** enantiomer as major product in the CH_2Cl_2 and toluene solvents (Table 1, entries 1, 2

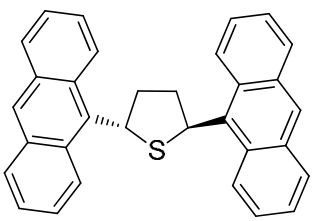
and 7). Whereas in the relatively more polar solvent CH_3CN, the solvent dipole could occupy the space around the charges in transition state **52A** and **52B**, but that may not be the case in the less polar CH_2Cl_2 or toluene solvents. Hence, in the less polar solvents the transition states may adapt a boat like conformation (Scheme 6), in which the positive and negative charges on sulfur and boron could come closer for stability. In such a conformation the transition state **55B** would be favored than the transition state **55A**, which would lead to the opposite enantiomer (*S*)-**30** as major product. However, further systematic studies may be required to understand the solvent effect observed in this transformation.

Scheme 6

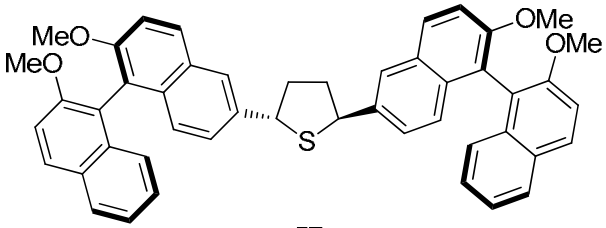


The C_2-symmetric chiral sulfide (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **47** gave asymmetric induction with only up to 55% ee with Et_2O**:**BF_3 catalysis. Presumably, this is due to

the fact that the developing stereogenic center is far away from the chiral moiety in the transition state. Further studies using sulfur derivatives with bulky substituents which are expected to have long range interactions may give more fruitful results (Figure 2).



56



57

Figure 2

3.3 Conclusions

Chiral C_2-symmetric diphenyltetrahydrothiophenes (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **47**, (2*S*,6*S*)-2,6-diphenyltetrahydro-2*H*-thiopyran **48**, (3*R*,4*R*)-3,4-diphenyltetrahydrothiophene **49**, and C_1-symmetric derivatives (2*S*)-phenyltetrahydrothiophene **50**, (2*S*)-phenyltetrahydro-2*H*-thiopyran **51** prepared by methods described in Chapter 1 were examined for use in asymmetric Baylis-Hillman reaction in the presence of Lewis acids. The chiral (2*S*,5*S*)-2,5-diphenyltetrahydrothiophene **47** with MVK and *p*-cyanobenzaldehyde gave asymmetric induction up to 55% ee to give the (*R*)-enantiomer in presence of Et_2O**:**BF_3. Other chiral sulfides failed to give any asymmetric induction. Further studies using larger groups like naphthyl, binaphthyl, anthracenyl and ferrocenyl groups at C2 and C5 positions in the chiral sulfide ligand **47** are expected to give more fruitful results.

3.4 Experimental Section

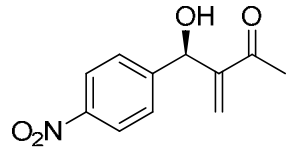
3.4.1 General Information

Several informations given in the section **1.4** are also applicable for the experiments outlined in this section. Procedures for synthesis of chiral sulfides **47-51** were given in Chapter 1 (Section **1.4**). Methyl vinyl ketone (MVK) was purchased from ACROS chemicals, UK.

3.4.2 General Procedure for asymmetric Baylis Hillman reactions:

To a solution of aldehyde (1 mmol), methyl vinyl ketone (0.25 mL, 3 mmol) and chiral sulfide (1.2 mmol) in CH_3CN (5 mL) at -30 ˚C was added Et_2O**:**BF_3 (0.18 mL, 1.5 mmol). After stirring the reaction mixture for 30 min at this temperature, Et_3N (0.14 mL, 1 mmol) was added and the mixture was further stirred for 10 min while warming to 25 ˚C. The solution was washed with dilute HCl, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product. The chiral sulfide was recovered eluting with hexane. The Baylis-Hillman product was eluted using hexane:ethylacetate (70:30) on silica gel (100-200 mesh). The spectral data of the Baylis Hillman products **30a-30i** showed 1:1 correspondance with the previously reported data.[24]

(*R*)-3-[Hydroxy-(4-nitro-phenyl)-methyl]-but-3-en-2-one (30a)



30a

Yield 0.12 g (58%).

IR (Neat) (cm^{-1}) 3479, 1950, 1657, 1601, 1516, 1348, 1041, 974, 738.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 8.20 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 6.28 (s, 1H), 6.04 (s, 1H), 5.69 (d, *J* = 5.6 Hz, 1H), 3.32 (d, *J* = 5.6 Hz, 1H), 2.37 (s, 3H).

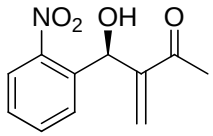
^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.0, 149.1, 147.3, 127.7, 127.3, 123.6, 72.0, 26.3.

HPLC 54% ee (Daicel Chiralcel OD-H, λ = 254 nm, eluent: hexane/2-propanol = 95/5, flow rate: 1.0 mL/min): t_R = 24 min (major), 26 min (minor).

$[\alpha]_D^{25}$ - 9.3 (*c* 0.4, $CHCl_3$); {*Lit.*[24b] $[\alpha]_D^{25}$ = -16.0 (*c* 0.5, $CHCl_3$) for 94% ee}.

(*R*)-3-[Hydroxy-(2-nitro-phenyl)-methyl]-but-3-en-2-one (30b)

Yield 0.10 g (47%).



30b

IR (Neat) (cm^{-1}) 3440, 1666, 1530.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.98 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.23 (s, 1H), 6.18 (s, 1H), 5.80 (s, 1H), 3.49 (s, 1H), 2.39 (s, 3H).

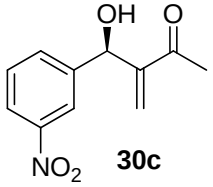
^{13}C NMR (100 MHz, ppm, $CDCl_3$) 199.9, 148.9, 148.0, 136.5, 133.5, 128.9, 128.5, 126.6, 124.7, 67.4, 26.0.

HPLC 22% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 24 min (minor), 28 min (major).

$[\alpha]_D^{25}$ -35.2 (*c* 0.25, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -151.0 (*c* 0.5, $CHCl_3$) for 92% ee}.

(*R*)-3-[Hydroxy-(3-nitro-phenyl)-methyl]-but-3-en-2-one (30c)

Yield 0.12 g (52%).



30c

IR (Neat) (cm^{-1}) 3416, 1668, 1531, 1350, 1047, 976.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 8.23 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 6.29 (s, 1H), 6.09 (s, 1H), 5.68 (s, 1H), 3.32 (s, 1H), 2.37 (s, 3H).

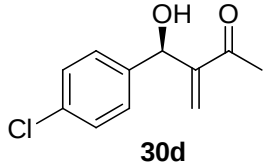
^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.1, 148.9, 148.3, 143.9, 132.7, 129.3, 127.8, 122.6, 121.4, 72.1, 26.4.

HPLC 37% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 85/15, flow rate: 1.0 mL/min): t_R = 10 min (major), 21 min (minor).

$[\alpha]_D^{25}$ -9.2 (*c* 0.38, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -25.0 (*c* 0.5, $CHCl_3$) for 94% ee}.

(*R*)-3-[Hydroxy-(4-chloro-phenyl)-methyl]-but-3-en-2-one (30d)

Yield 0.14 g (68%).



30d

IR (Neat) (cm^{-1}) 3468, 1911, 1658.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.30 (s, 4H), 6.21 (s, 1H), 5.98 (d, *J* = 1.1 Hz, 1H), 5.58 (d, *J* = 5.2 Hz, 1H), 3.15 (d, *J* = 5.2 Hz, 1H), 2.35 (s, 3H).

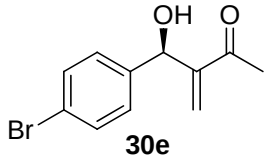
^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.3, 149.7, 140.1, 133.4, 128.5, 127.9, 126.9, 72.2, 26.4.

HPLC 24% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 85/15, flow rate: 1.0 mL/min): t_R = 6.9 min (major), 8.4 min (minor).

$[\alpha]_D^{25}$ -9.0 (*c* 1.06, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -34.8 (*c* 0.23, $CHCl_3$) for 90% ee}.

(*R*)-3-[Hydroxy-(4-bromo-phenyl)-methyl]-but-3-en-2-one (30e)

Yield 0.15 g (59%).



30e

IR (Neat) (cm^{-1}) 3354, 1911, 1666, 1012.

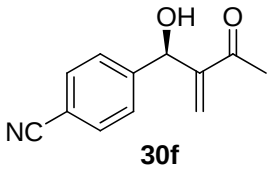
^{1}H NMR (400 MHz, ppm, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 5.98 (s, 1H), 5.57 (d, *J* = 5.2 Hz, 1H), 3.13 (d, *J* = 5.2 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.3, 149.6, 140.6, 131.5, 128.3, 127.0, 121.6, 72.3, 26.5.

HPLC 42% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 9.5 min (major), 11.9 min (minor).

$[\alpha]_D^{25}$ -16.8 (*c* 0.46, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -22.4 (*c* 0.38, $CHCl_3$) for 92% ee}.

(*R*)-3-[Hydroxy-(4-cyano-phenyl)-methyl]-but-3-en-2-one (30f)



30f

Yield 0.11 g (52%).

IR (Neat) (cm^{-1}) 3477, 2229, 1930, 1676, 1606, 1502.

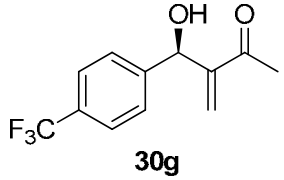
^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.63 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 6.26 (s, 1H), 6.02 (s, 1H), 5.63 (s, 1H), 3.31 (s, 1H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.1, 149.1, 147.0, 132.2, 127.6, 127.2, 118.7, 111.4, 72.3, 26.4.

HPLC 55% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 85/15, flow rate: 1.0 mL/min): t_R = 16.7 min (major), 20.2 min (minor).

$[\alpha]_D^{25}$ -13.9 (*c* 0.27, $CHCl_3$) {Lit.[24b] $[\alpha]_D^{25}$ = -24.2 (*c* 0.31, $CHCl_3$) for 90% ee}.

(*R*)-3-[Hydroxy-(4-trifluoromethyl-phenyl)-methyl]-but-3-en-2-one (30g)



30g

Yield 0.10 g (41%).

IR (Neat) (cm^{-1}) 3443, 1680, 1622, 1327.

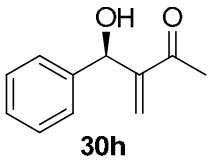
^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.59 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 1H), 6.01 (d, *J* = 1.2 Hz, 1H), 5.65 (d, *J* = 5.4 Hz, 1H), 3.34 (d, *J* = 5.4 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.2, 149.4, 145.6, 127.4, 126.8, 125.3, 125.3, 72.4, 26.4.

HPLC 32% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 6.9 min (major), 8.1 min (minor).

$[\alpha]_D^{25}$ -6.3 (*c* 0.5, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -19.0 (*c* 0.5, $CHCl_3$) for 92% ee}.

(*R*)-3-[Hydroxy-phenyl-methyl]-but-3-en-2-one (30h)



30h

Yield 0.08 g (45%).

IR (Neat) (cm^{-1}) 3433, 1668, 1493.

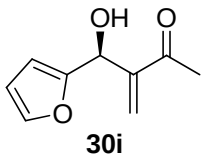
^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.38-7.30 (m, 5H), 6.21 (s, 1H), 5.99 (s, 1H), 5.63 (d, *J* = 4.8 Hz, 1H), 3.10 (d, *J* = 4.4 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 200.4, 149.9, 141.6, 128.4, 127.7, 126.7, 126.5, 72.7, 26.5.

HPLC 48% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 9.0 min (major), 10.8 min (minor).

$[\alpha]_D^{25}$ -12.0 (*c* 0.40, $CHCl_3$) {*Lit.*[24b] $[\alpha]_D^{25}$ = -25.0 (*c* 0.30, $CHCl_3$) for 90% ee}.

(*R*)-3-(furan-2-yl(hydroxy)methyl)but-3-en-2-one (30i)



30i

Yield 0.08 g (46%).

IR (Neat) (cm^{-1}) 3437, 1674, 1624, 1502, 742.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.35 (s, 1H), 6.32-6.10 (m, 4H), 3.39 (d, J = 6.4 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 199.9, 154.3, 147.3, 142.2, 127.3, 110.4, 107.2, 67.0, 26.3.

HPLC 14% ee (Daicel Chiralcel AS-H, λ = 254 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 12.6 min (major), 14.9 min (minor).

$[\alpha]_D^{25}$ -2.8 (*c* 0.40, $CHCl_3$). {*Lit.*[24c] $[\alpha]_D^{25}$ = -6.5 (*c* 0.31, $CHCl_3$) for 63% ee}.

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Chapter IV

Studies on enantioselective synthesis of chiral propargylamines and chiral allenes

4.1 Introduction

4.1.1 Chiral Allenes

The structure of dissymmetric allenes as well as their expected chirality was first predicted by Van't Hoff in 1875.[1] The first naturally occuring allene, pyrethrolone was characterized by H. Staudinger and L. Ruzicka in 1924.[1] The first synthesis of enantiomerically enriched allene was reported in 1935 by P. Maitland and W. H. Mills by dehydration of allylic alcohol in the presence of (+)-camphor-10-sulfonic acid.[2] Occurrence of allenic structures in a variety of natural products and in pharmacologically active compounds have inspired immense interest among organic and medicinal chemists.[3] In the last few years, many natural products containing allene moiety have been isolated (Figure 1**)**.[4]

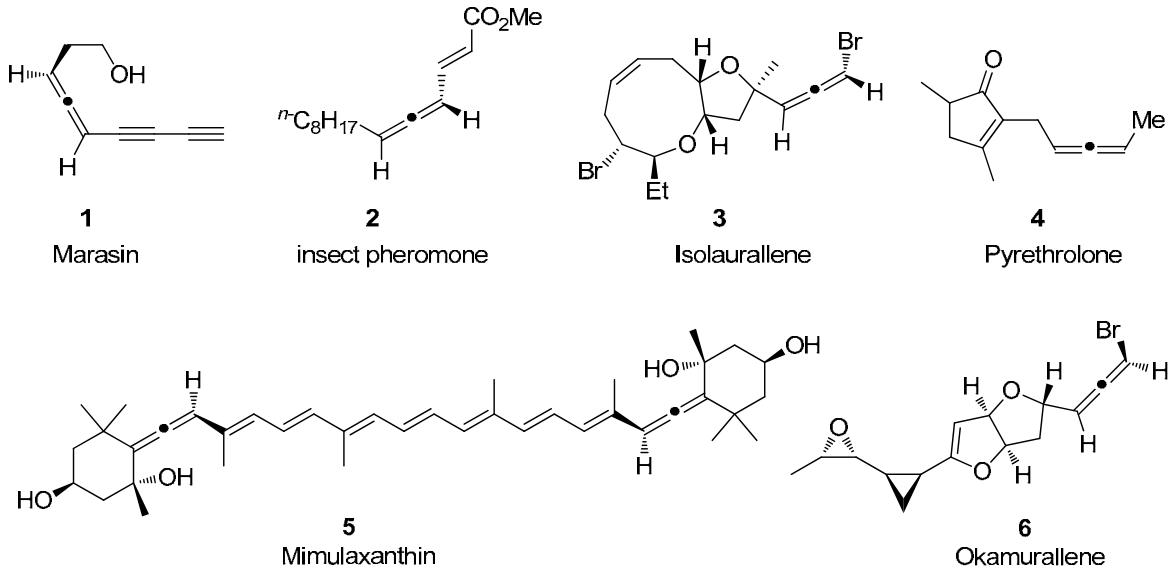


Figure 1

4.1.2 Biologically active chiral allenes

Allenic derivatives not only occur in nature but also have considerable potential as pharmacologically active molecules. For example, the compounds scorodonin **7**, nemotin **8** and phomallenic acid **9** have inhibiting effects on the growth of bacteria, yeasts and filamentous fungi. Other allenic moieties with such inhibiting effects are sterol biosynthesis inhibitor **10**, gastric acid inhibitor **11**, HIV inhibitor **12** and hepatitis B replication inhibitor **13** (Figure 2).[5]

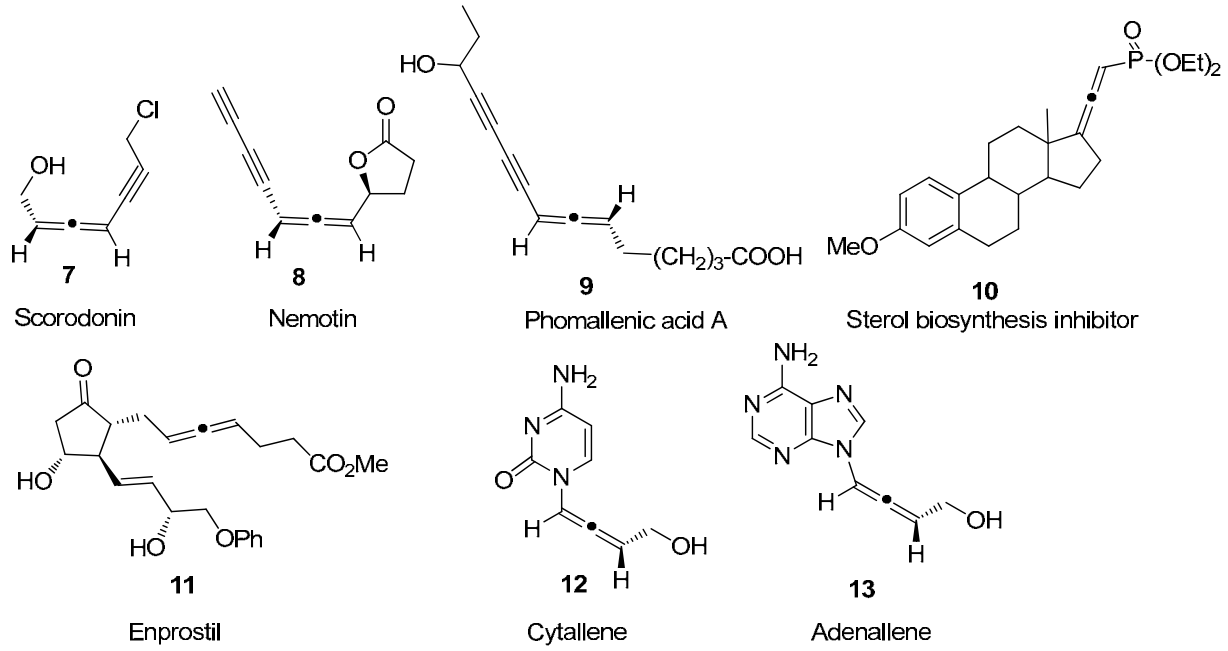
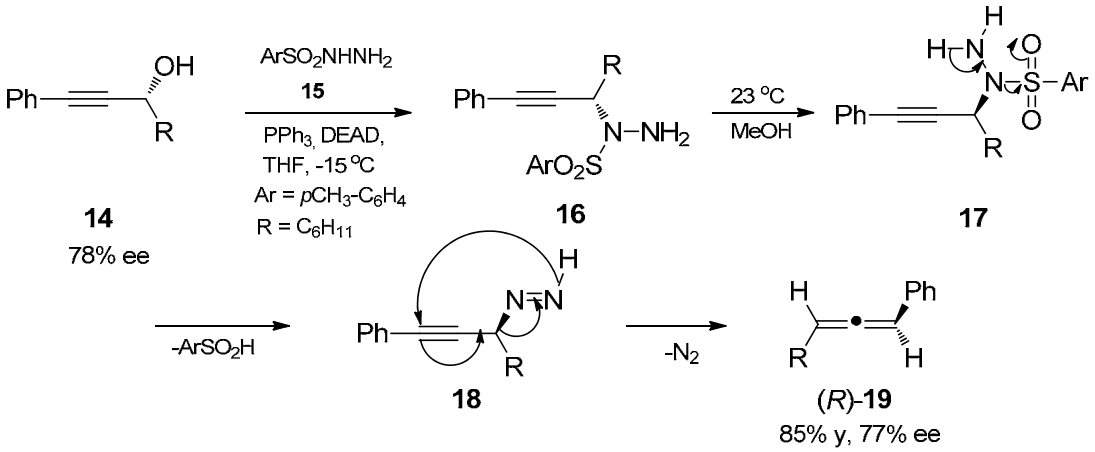


Figure 2

4.1.3 Methods for the synthesis of chiral allenes

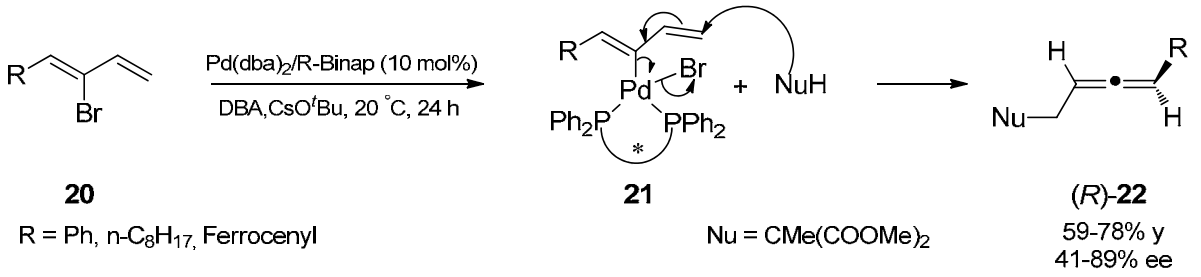
All the classical reaction types like addition, elimination, substitution, rearrangement have been followed for the synthesis of allenes.[4] The most widely used reaction is the direct S_N2'-type substitution of various nucleophilic sources with propargylic derivatives. A representative method reported for the preparation of axially chiral allene **19** (77% ee) from the chiral propargylic alcohol **14** (78% ee) by using aryl sulphonamide **16** under Mistunubu reaction conditions is outlined in Scheme 1.[6]

Scheme 1



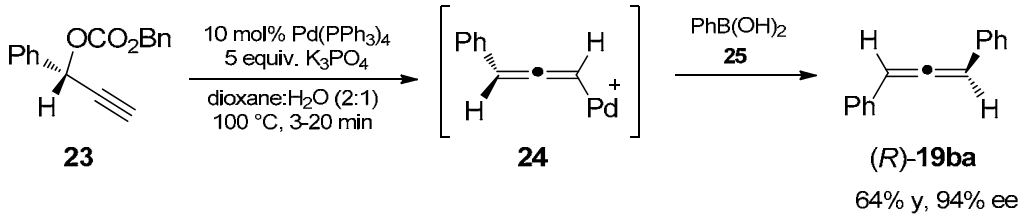
A novel route to enantiomerically enriched axially chiral allenes **22** was reported using achiral conjugated dienes **20**, nuchleophiles and palladium-BINAP complex as a chiral catalytic system (Scheme 2).[7]

Scheme 2



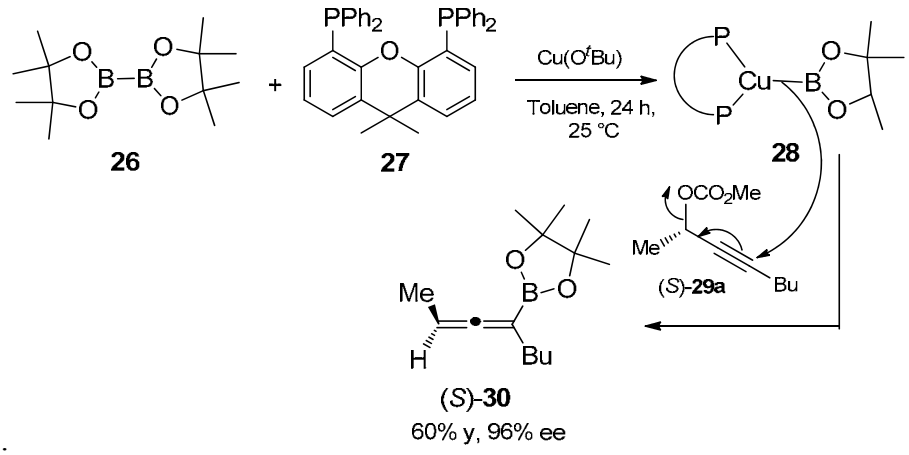
Optically active (-)-(*R*)-1,3-diphenylpropadiene **19ba** has been prepared by enantiospecific coupling of the propargylic carbamate **23** with phenylboronic acid **25** using a palladium catalyst under aqueous basic conditions (Scheme 3).[8]

Scheme 3



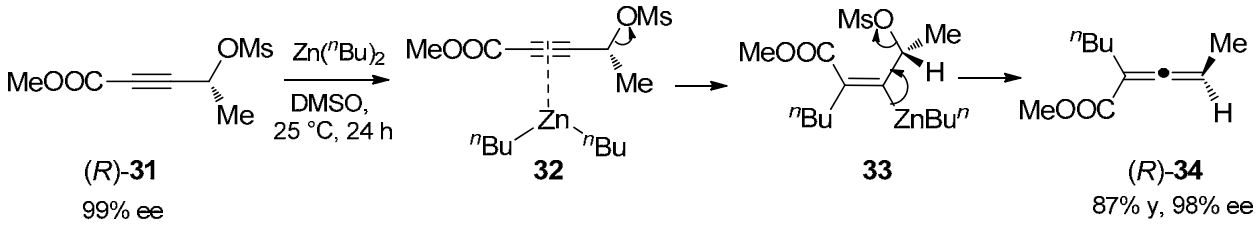
The Cu(O^{t}Bu)/ligand system has been used for the stereoselective substitution of propargylic carbonate **29** with bis(pinacolato)diborate **26** to give the corresponding allene **30** with 96% ee (Scheme 4).[9]

Scheme 4



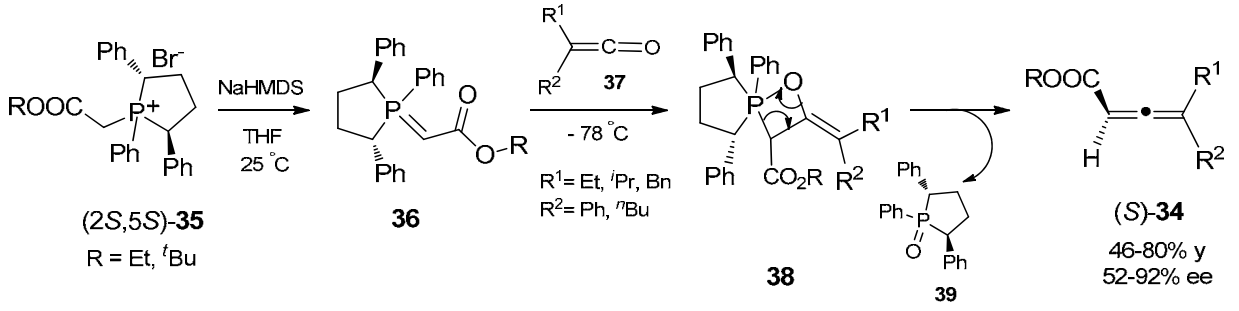
The S_N2' reaction of propragyl mesylates **31** with organozinc reagents in DMSO as solvent gives the chiral allene **34** in 87% yield with up to 98% ee (Scheme 5).[10]

Scheme 5



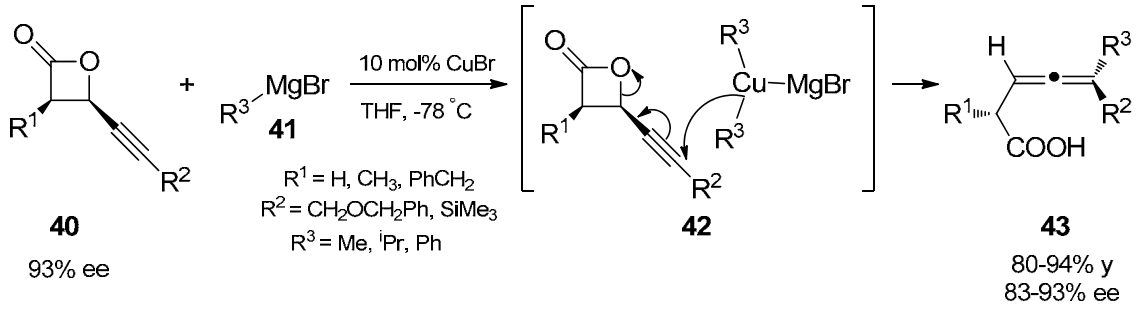
Highly enantioselective synthesis of allenic esters **34** by the condensation of pseudo C_2-symmetrical chiral phosphorus ylides **35** with various ketenes **37** using NaHMDS as base at -78 ˚C has been reported. The chiral phosphine oxide **39** was recovered without loss in optical purity (Scheme 6).[11]

Scheme 6



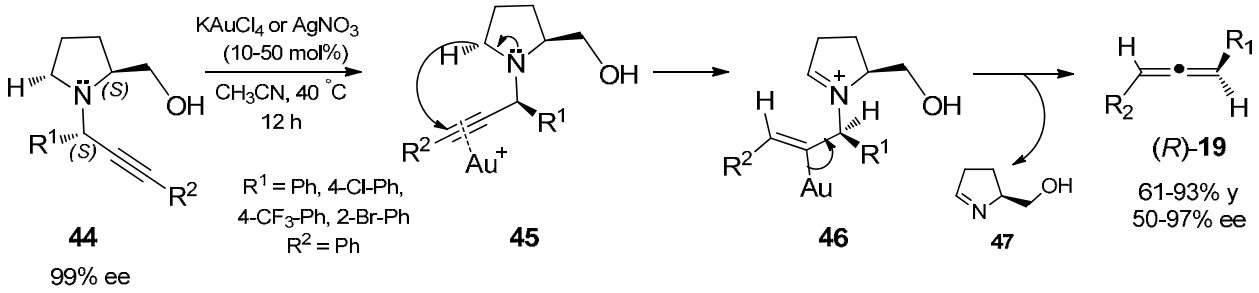
The $S_N^{2'}$ ring opening reaction of β-lactones **40** provides an efficient and operationally simple enantioselective synthesis of di- and trisubstituted allene derivatives **43** using various Grignard reagents **41** (Scheme 7).[12]

Scheme 7



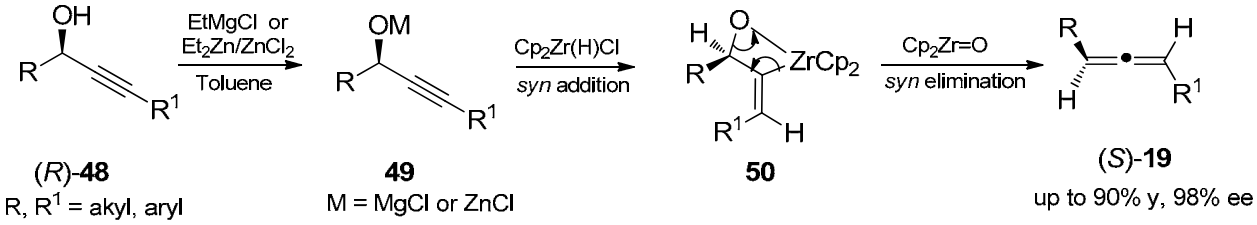
Chiral propargyl amines **44** were prepared using various aldehydes, 1-alkynes and chiral amino alcohol using a gold (III)-salen complex. These chiral propargylamines afforded axially chiral allenes **19** (50-97% ee) under $KAuCl_4$ or $AgNO_3$ catalysis in CH_3CN (Scheme 8).[13]

Scheme 8



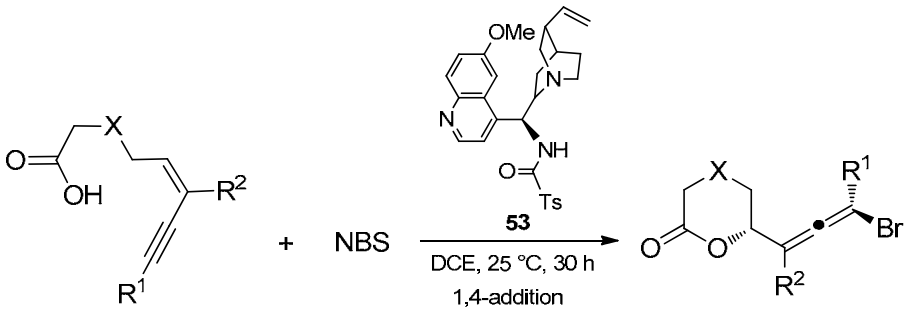
Recently, $Cp_2Zr(H)Cl$ has been used for the anti-S_N2'-type reductive substitution of the *in situ* generated zinc or magnesium alkoxides **49** of propargylic alcohols furnishing allenes **19** in good yields and high optical purities (Scheme 9).[14]

Scheme 9



The bifunctional cinchonidine catalyst **53** promoted the highly enantioselective bromolactonization of conjugated (*Z*)-enynes **51** for the preparation of versatile bromoallenes **54** containing a lactone heterocyclic moiety with high optical purities (Scheme 10).[15]

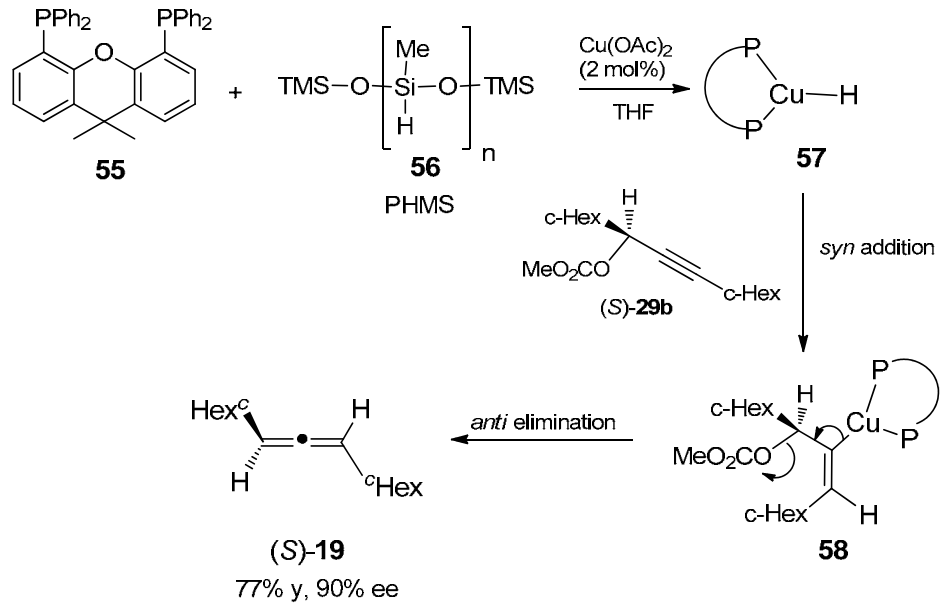
Scheme 10



Copper(I)-catalyzed anti-S_N2'-type reduction of propargylic carbonates **29** with hydrosilanes **56** to various di- and trisubstituted allenes in presence of phosphine ligands **55** to stabilize the corresponding CuH complexes has been reported.[16] These reactions have good

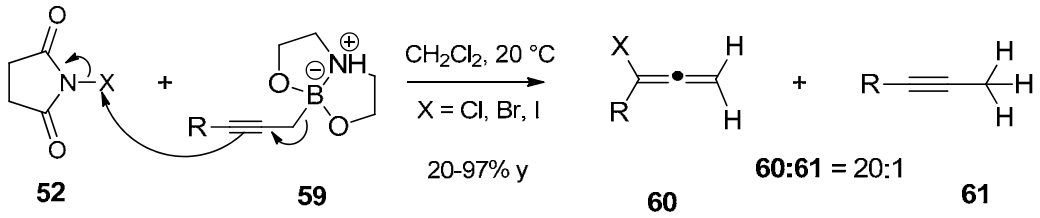
tolerance to various functional groups and work efficiently for the synthesis of optically active allenes (Scheme 11).[16]

Scheme 11



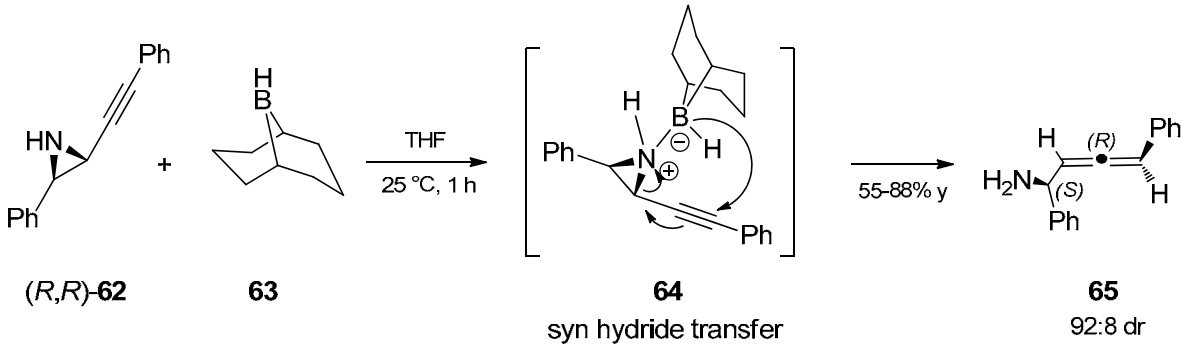
A method to synthesize haloallenes **60** in high yields with good regioselectivity from propargyl boronates involves the reaction of propargyl diethanolamine boronates **59** with *N*-halosuccinimides **52** (Scheme 12).[17]

Scheme 12



Alknylaziridines **62** were converted to unprotected α-amino allenes **65** *via* a highly diastereoselective *syn* hydride migration **64** without any alkyne hydroborated byproducts upon reaction with 9-BBN **63** (Scheme 13).[18]

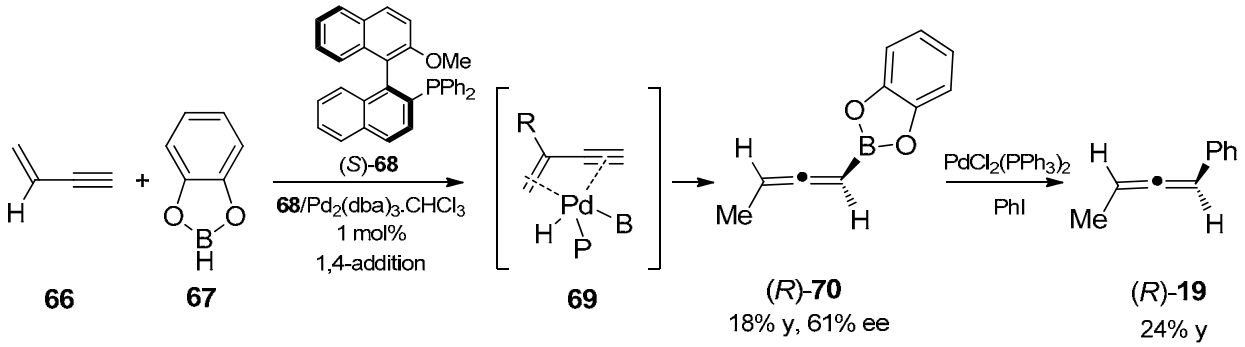
Scheme 13



(*R*,*R*)-**62** **63** **64** syn hydride transfer **65** 92:8 dr

The Pd-catalyzed asymmetric hydroboration of conjugated enynes **66** with catecholborane **67** was reported in 1993.[19] When the chiral monodentate phosphine (*S*)-MeO-MOP **68** is used as a chiral ligand for the palladium catalyst, the axially chiral allenylboranes **70** were obtained in up to 61% ee and 18% yield. The cross-coupling reaction of allenylborane **70** with iodobenzene in the presence of $PdCl_2(PPh_3)_2$ gave 24% yield of chiral allene (*R*)-l-phenylbuta-1,2-diene **19** (Scheme 14).[19]

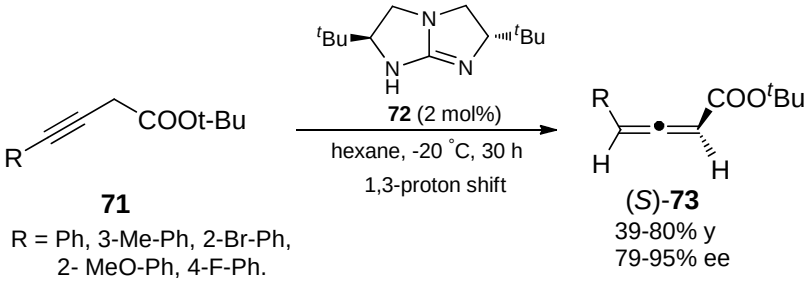
Scheme 14



66 **67** **69** (*R*)-**70** 18% y, 61% ee (*R*)-**19** 24% y

Chiral bicyclic guanidine **72** is found to catalyze the isomerization of highly reactive alkyne derivatives **71** to chiral allenoates **73** with 79-95% ee (Scheme 15).[20]

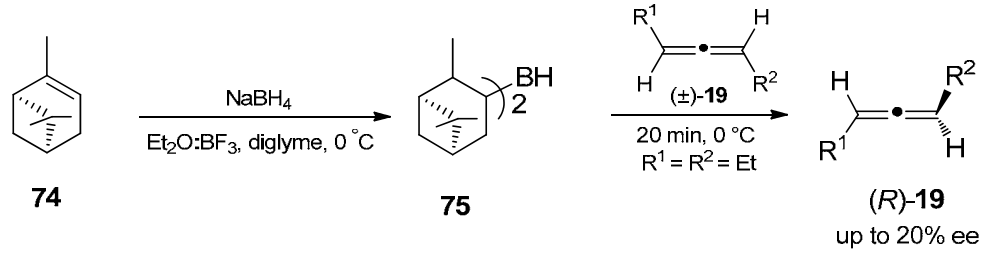
Scheme 15



4.1.4 Synthesis of enantiomerically enriched chiral allenes by kinetic resolution

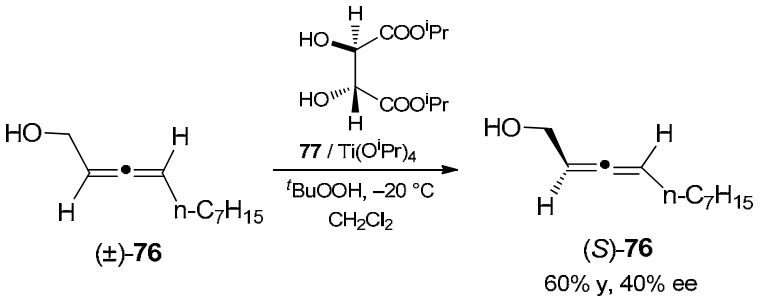
Kinetic resolution of racemic allenes using asymmetric compounds is an alternative method to access enantiomerically pure allenes. Hydroboration of (-)-α-pinene **75** using $NaBH_4$ and $Et_2O{:}BF_3$ in diglyme leads to $(+)\text{-}(Ipc)_2BH$ **76**, which has been shown to be a highly stereoselective hydroborating agent. It selectiviely hydroborates (±)-allenes **19** to give the (-)-allene **19** with low optical purity (Scheme 16).[21]

Scheme 16



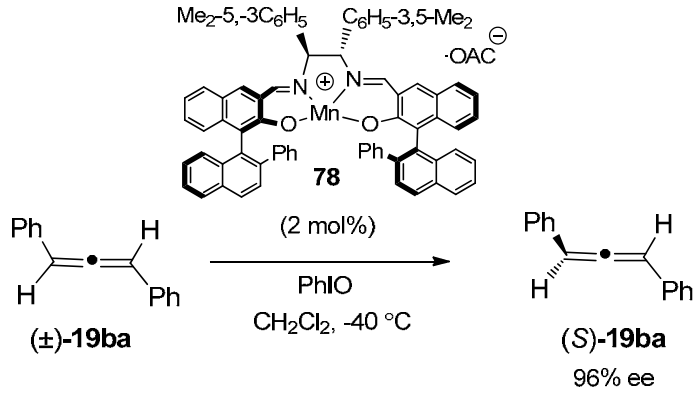
Oxidation of racemic allene **76** under the well-known Sharpless epoxidation conditions, i.e with $Ti(O^iPr)_4$, (+)-diisopropyl tartrate **77** [(+)-DIPT], and ^{t}BuOOH, gave the (*S*)-(+)-allene **76** with 60% yield and 40% ee (Scheme 17).[22]

Scheme 17



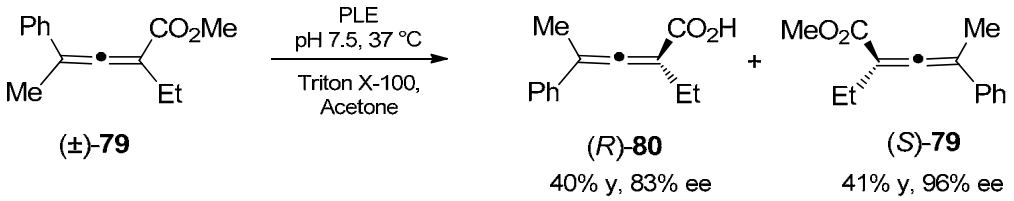
Kinetic resolution of racemic allenes **19** has been reported using an enantiomer-differentiating manganese-catalyzed oxidation. Reaction of racemic **19ba** with 1 equiv. of PhIO and 2 mol% of the Mn-salen* complex **78** in the presence of 4-phenylpyridine *N*-oxide results in partial asymmetric oxidation, which leads to the recovery of enantioenriched allenes (*S*)-**19ba** (Scheme 18).[23]

Scheme 18



It has been reported that the pig liver esterase (PLE) enzyme promotes the hydrolysis of variously substituted racemic methyl allenylcarboxylates **79** with predictable enantiomeric selectivity (73% ee and 42% yield). Whereas the corresponding carboxylic acid **80** is obtained in 63% ee and 52% yield. Later, this reaction was optimized to obtain allenic ester **79** with 96% ee in 41% yield and the corresponding carboxylic acid with 83% ee in 40% yield (Scheme 19).[24]

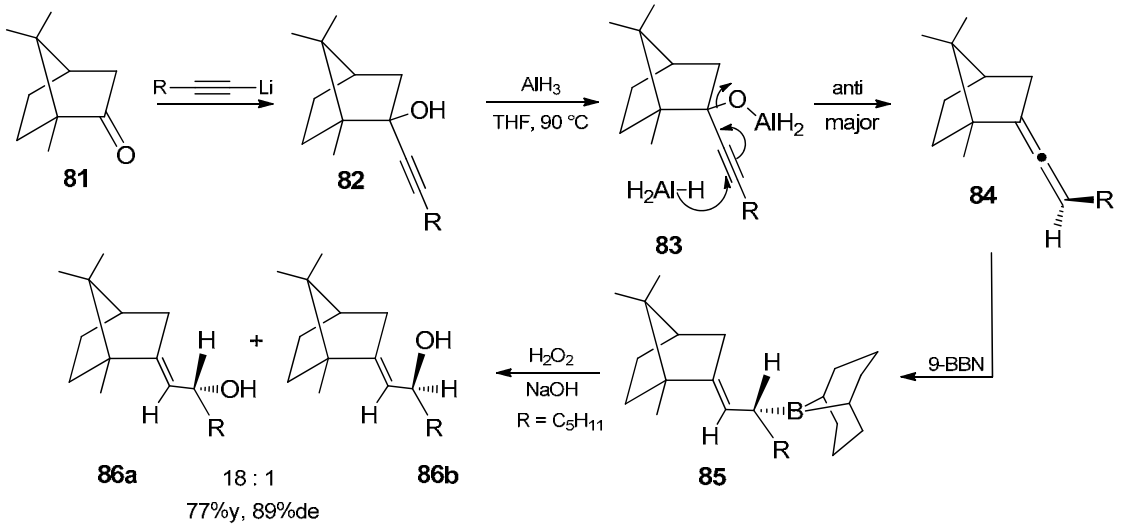
Scheme 19



(±)-**79** (*R*)-**80** 40% y, 83% ee (*S*)-**79** 41% y, 96% ee

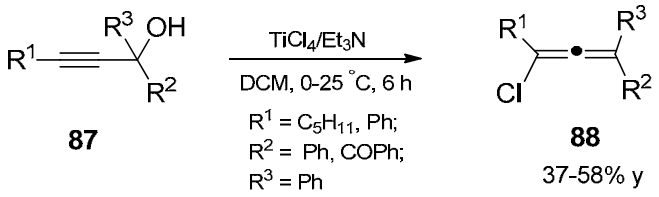
A method to prepare (1*R*)-(+)-camphor based allene **84** in high diastereoselectivity and its hydroboration-oxidation reaction has been reported. The diastereoselectivity of the product allylic alcohol mixture (*E*,*R*) and (*E*,*S*) isomers (**86a:86b**) were in a ratio of 6:1 to 18:1 was observed (Scheme 20).[25]

Scheme 20



Previously, efforts were undertaken in this laboratory towards the synthesis of allenes. It was found that the reaction of propargylic alcohol **87** with $TiCl_4/Et_3N$ gave the corresponding racemic chloroallenes **88** (Scheme 21).[26]

Scheme 21



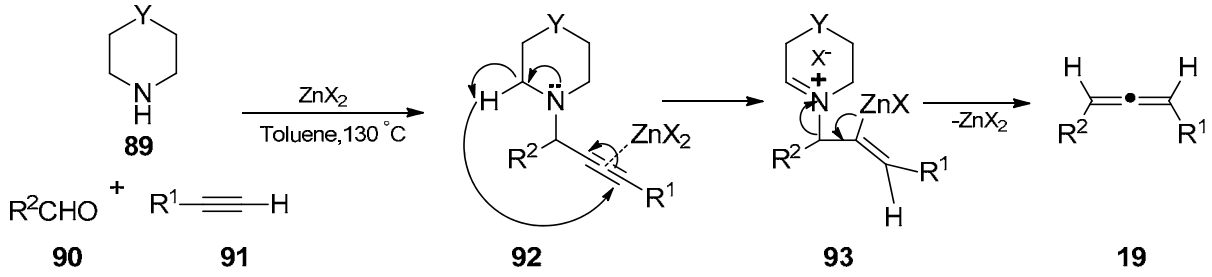
Methods for accesing optically pure allenes are still very few and often involve expensive reagents. In the repoted procedures, several steps are required to make chiral allenes by chirality transfer from chiral propargylic derivatives. Preparation of optically pure allenes by using easily accessible reagents is still challenging. We were interested to develop simple, convenient one-pot methods for enantiopure allene synthesis. The results of these studies are discussed in the next section.

4.2 Results and Discussion

4.2.1 Effort towards the synthesis of chiral allenes

As outlined in the introductory section, generally chiral propargylic alcohol derivatives are used as starting materials for the preparation of chiral allenes by an appropriate chirality transfer process. Recent reports indicate that propargyl amines serve as useful precursors for the preparation of allenes.[4] For example, Ma *et al.*[27] reported a method to access racemic allenes **19** from cyclic secondary amines **89**, aldehydes **90** and terminal alkynes **91** in presence of zinc halides through formation of corresponding propargylamine intermediate derivatives **92** (Scheme 22).

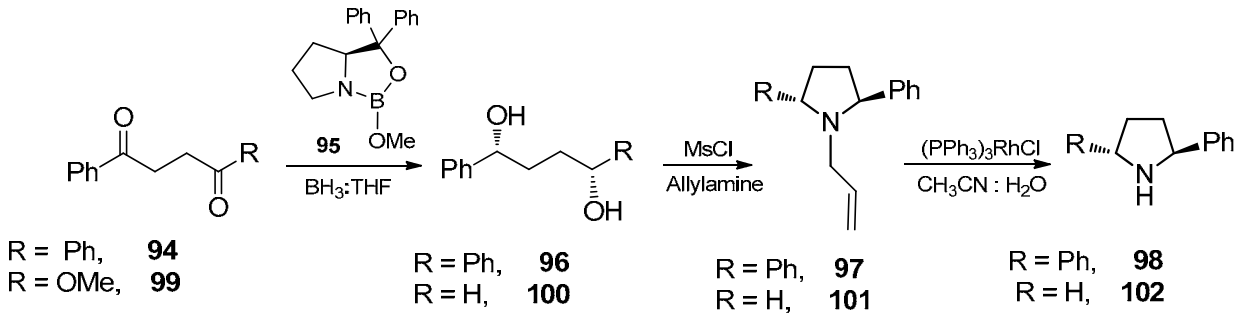
Scheme 22



4.2.2 Chiral allenes from 1-alkynes, aromatic aldehydes using chiral pyrrolidine motifs

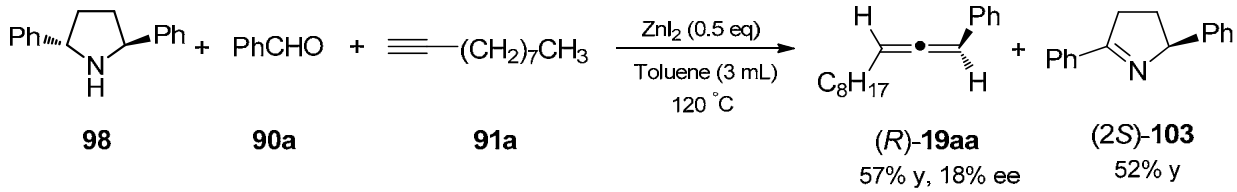
As discussed in Chapter **I**, several convenient methods have been developed in this laboratory to access chiral C_2 and C_1 pyrrolidine derivatives. The chiral C_2-symmetric (-)-(2*S*,5*S*)-2,5-diphenylpyrrolidine **98** and C_1-symmetric (2*S*)-phenylpyrrolidine **102** can be readily accessed following the methods described in chapter **I** (Scheme 23).

Scheme 23



We have examined the use of the C_2-symmetrical chiral (2*S*,5*S*)-2,5-diphenylpyrrolidine **98** (1 equiv.) for one-pot three component chiral allene synthesis using benzaldehyde **90a** (1 equiv.), 1-decyne **91a** (1 equiv.) and ZnI_2 (0.5 equiv.) in 1 mmol scale reaction in toluene (3 mL). Unfortunately, the (*R*)-allene **19aa** was obtained in 57% yield with only 18% ee after 6 h reaction at 120 ˚C along with the imine side product **103** in 52% yield (Scheme 24).

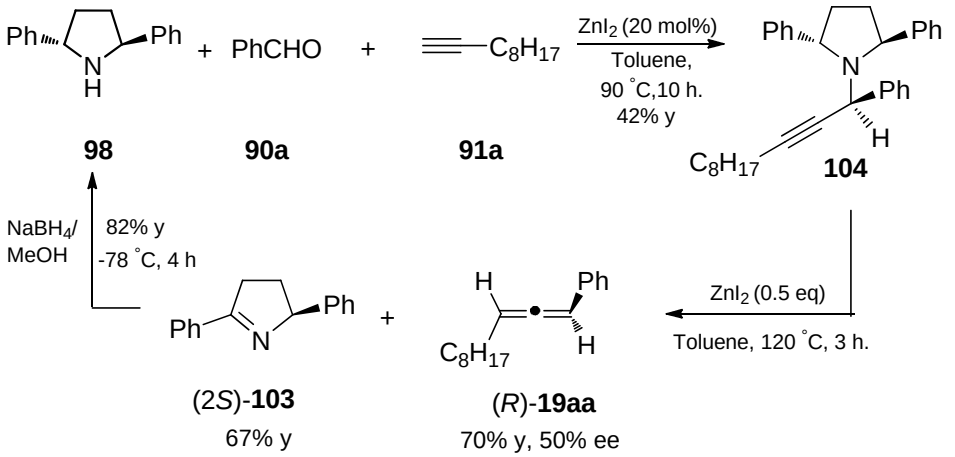
Scheme 24



As it is expected that the chiral allenes were obtained through the corresponding intermediate propargylamines, we made an attempt to isolate the intermediate propargylamine for subsequent conversion to the corresponding allene. The intermediate propargylamine was prepared by carrying out the one-pot three component (amine, aldehyde, alkyne) reaction at 90 ˚C for 10 h in toluene using 20 mol% ZnI_2. The propargylamine mixture was obtained in 76% yield with very low diastereoselectivity (57:43 based on ^{1}H NMR analysis). Clearly, the low optical yield of allene **19aa** is due to low selectivity in the chiral propargylamine formation in this allene transformation. Fortunately, the major diastereomeric propargylamine product **104**

(with *S* configuration at the propargylic position) could be readily separated by chromatography and transformed to (*R*)-allene in 70% yield with 50% ee using ZnI_2 (0.5 equiv.) along with the imine **103** byproduct in 67% yield (Scheme 25).

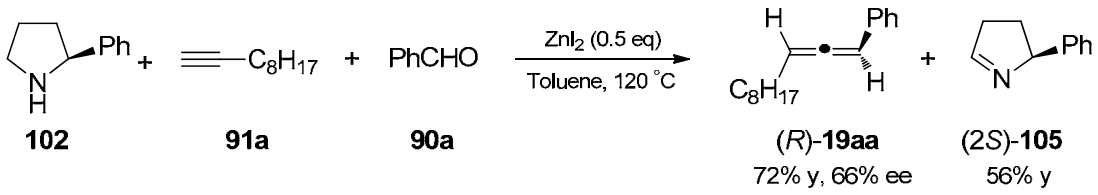
Scheme 25



The imine byproduct **103** was converted back to chiral amine **98** by using $NaBH_4$/MeOH at -78 ˚C for 4 h in 82% yield with out loss in its optical purity (Scheme 25).

The use of the C_1-symmetric (2*S*)-phenylpyrrolidine **102** gave better results in this one-pot three component (amine, aldehyde, 1-alkyne) allene transformation. In this case, we carried out the reaction using chiral amine **102** (1 equiv.), 1-decyne (**91a**, 1.1 equiv.) and benzaldehyde (**90a**, 1 equiv.) in toluene (3 mL) with Lewis acid ZnI_2 (0.5 equiv.) at 120 ˚C for 2 h. We have observed the (*R*)-allene **19aa** in 72% yield with 66% ee along with the side product imine **105** in 56% yield (Scheme 26).

Scheme 26



We have also screened the other Lewis acid promoters like $ZnCl_2$ and $ZnBr_2$. When the reaction was carried out with $ZnCl_2$, the (*R*)-allene **19aa** was obtained in 64% yield with 60% ee, whereas with $ZnBr_2$, the (*R*)-allene **19aa** was obtained in 65% yield with 58% ee. Similar results were also obtained with other aryl aldehydes (Table 1).

Table 1.Reaction of 1-alkynes and aldehydes with chiral amine **102** promoted by Zinc halides[a, b]

S. No	ZnX_2	1-alkyne	aldehyde	Time (h)	allene	Yield (%)[c]	ee (%)[d]
1	$ZnCl_2$	C_8H_{17}, **91a**	PhCHO, **90a**	2	**19aa**	64	60
2	$ZnBr_2$	**91a**	PhCHO, **90a**	2	**19aa**	65	58
3	ZnI_2	**91a**	PhCHO, **90a**	2	**19aa**	72	66
4	ZnI_2	**91a**	4Cl-C_6H_4CHO, **90b**	2	**19ab**	68	52
5	ZnI_2	**91a**	4Br-C_6H_4CHO, **90c**	2	**19ac**	71	52
6	ZnI_2	**91a**	3MeO-C_6H_4CHO,**90d**	3	**19ad**	65	38
7	ZnI_2	Ph, **91b**	PhCHO, **90a**	3	**19ba**	48	46

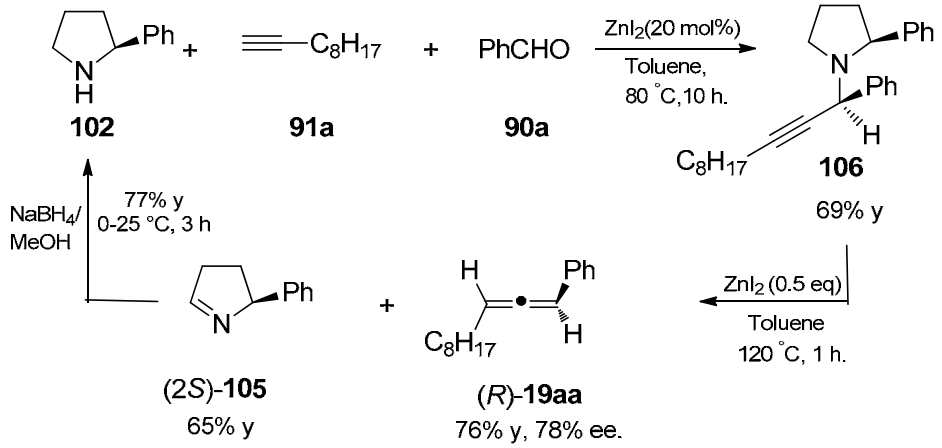
[a]The reactions were carried out by taking amine **102 (**1.0 mmol), and 1-alkyne (1.1 mmol) in toluene (3 mL) and heating at 120 ˚C for 10 min, adding aldehyde (1 mmol) at 25 ˚C and heating at 120 ˚C for the required time. [b]0.5 equiv. of ZnI_2 is used. [c]Isolated yield. [d]The % ee was determined by HPLC analysis on chiralcel OD-H or OJ-H column.

4.2.3 Isolation of chiral propargylamine intermediate 106

We have isolated the corresponding propargylamine intermediate **106** in 69% yield and 82% de (91:9 dr based on ^{1}H NMR) by carrying out the reaction using ZnI_2 (0.2 mmol) at 80 ˚C for 10 h. The configuration at the propargylic position of this intermediate was found to be *S*. The results indicate that the propargylamine intermediate **106** is obtained with better diastereoselectivity (82% de) in the case of C_1-symmetric amine **102** compared to the C_2-

symmetric amine **98**. The higher diastereomeric excess (82%) of intermediate propargylamine **106** compared to that of C_2-symmetric derivative **104** (14%) is the reason for difference in enantiomeric excess in their transformation to the chiral allene **19aa** (66% ee *vs* 18% ee). The major diastereomer **106** was separated by column chromatography. The reaction of this diastereomerically pure propargylamine **106** with ZnI_2 (0.5 mmol) at 120 ˚C gave the (*R*)-allene in 76% yield and 78% ee along with the byproduct imine **105** in 65% yield (Scheme 27).

Scheme 27



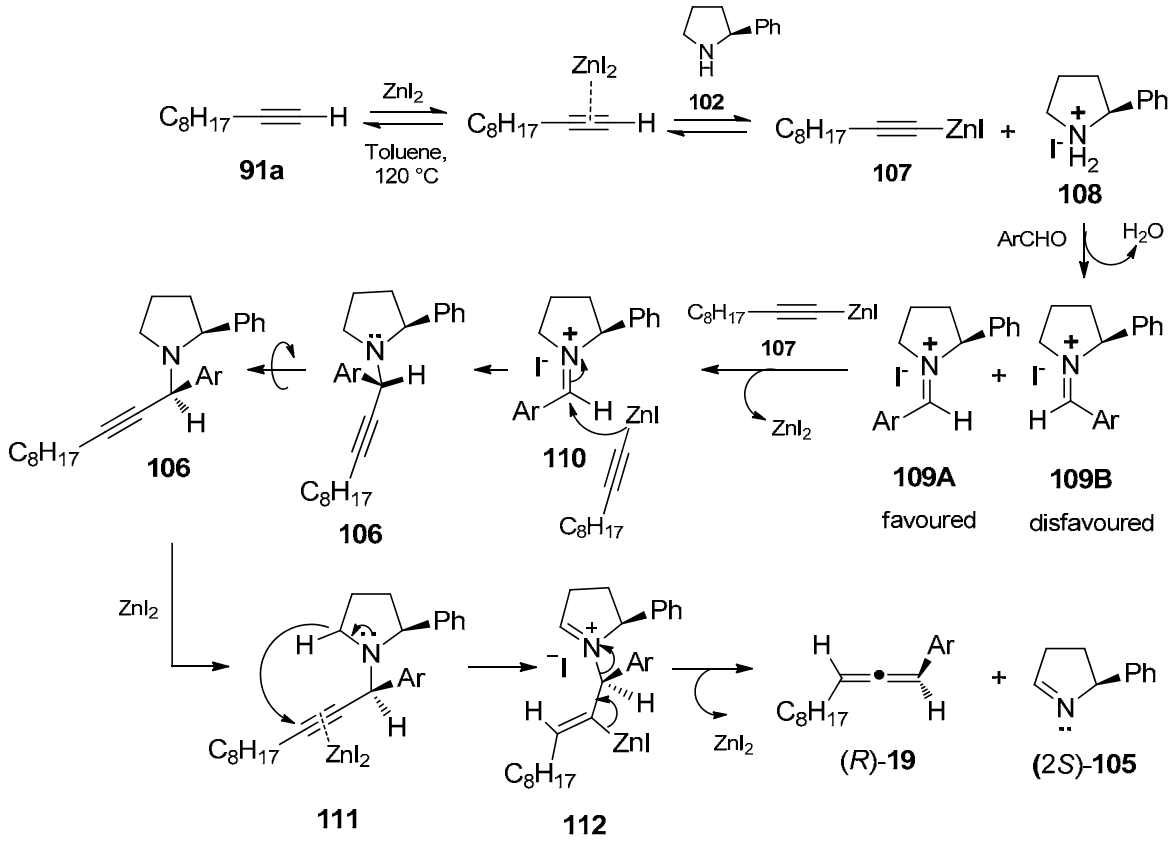
The imine **105** byproduct isolated was be readily converted back to (2*S*)-phenylpyrrolidine **102** in quantitative yield without loss in its optical purity by reduction using $NaBH_4$/MeOH (Scheme 27).

4.2.4 Possible mechanistic pathway for the formation of intermediate propargylamine and allene

The formation of chiral allenes can be explained by considering a tentative mechanism outlined in Scheme 28. The initially formed alkynyl zinc intermediate **107**[28] would react with the favoured iminium ion **109A** derived from various aromatic aldehydes and (*S*)-phenylpyrrolidine **102** to give the corresponding propargylamine intermediate **106.** The propargylamine intermediate **106** would then undergo an intramolecular hydride shift from the

pyrrolidine skeleton of (*S*)-phenylpyrrolidine to the ZnI_2 complexed acetylinic moiety leading to alkenyl zinc complex **111**. Subsequently, cleavage of C-N bond would lead to the chiral allene **19** and the imine **105** (Scheme 28).

Scheme 28

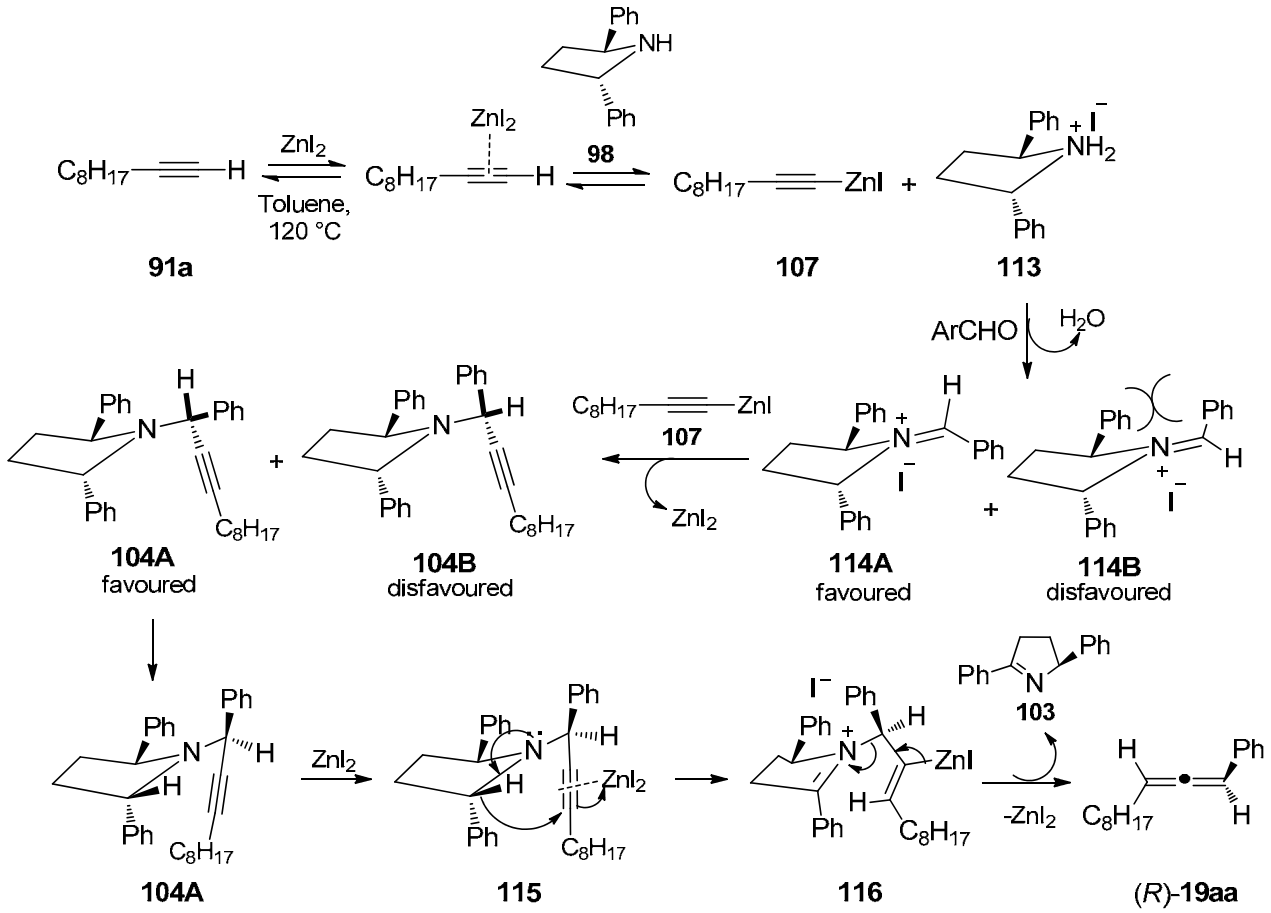


4.2.5 Explanation for poor results for C_2-symmetric amine 98

As outlined in the introductory section, C_2-symmetric chiral amine (2*S*,5*S*)-2,5-diphenyl pyrrolidine **98** systems generally give higher asymmetric induction in various transformations. Though, the chiral amine **98** has the C_2-symmetry, it is expected to give only racemic allene since both the *re*-face and *si*-face attacks are probable if the intermediate iminium ion is planar.

However, as outlined in Scheme 29, the propragylamine would be formed with some selection since the five membered pyrrolidinium ring could adopt an envelope confirmation.

Scheme 29



The iminium ion formed **114A** would be more favoured than **114B** as in the envelope confirmation the phenyl-phenyl steric interactions in iminium ion **114B** would be more than in **114A**. The alkynyl zinc species **107** then would attack from bottom side of the favoured iminium ion **114A** leading to *S* stereogenic center at the propargylamine centre in **104A**. The propargylamine **104A** would lead to (*R*)-allene **19aa** as outlined in Scheme 29. Presumably, this

difference in reactivity leads to 14% de in the propargylamine **104** formation and 18% ee in (*R*)-allene **19aa** formation.

4.2.6 Chirality transfer from other moieties developed in this laboratory

Recently, the (*S*)-diphenylprolinol **119** has been used in this laboratory for this one pot three component (chiral secondary amine **119**, aldehyde, and 1-alkyne) synthesis of chiral allenes in good yields (42-65%) with excellent enantioselectivities (78-98%).[29] Also, it was found that the use of (*S*)-2-diphenylmethanopyrrolidine **117** gave the (*R*)-allene **19aa** only in 68% yield with 66% ee.[30] The readily accessible (*R*,*R*)-2,3-diphenylpiperazine **121** system gave (*R*)-allene **19aa** in 95% ee and 65% yield using ZnI_2[31] and the piperazine **123** derived from (1*R*,2*R*)-cyclohexyldiamine gave the (*R*)-allene **19aa** in 70% yield with 90% ee.[32] Whereas the chiral camphanyl derivatives **125** and **127** gave the opposite isomers of allenes **19aa** with 53-61% yields with up to 96% ee (Chart 1).[33]

Chart 1

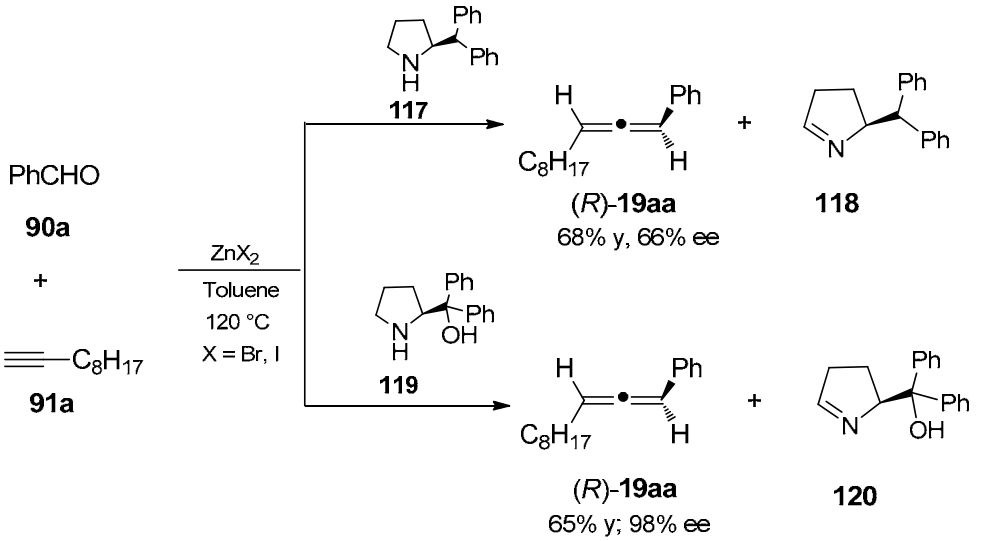
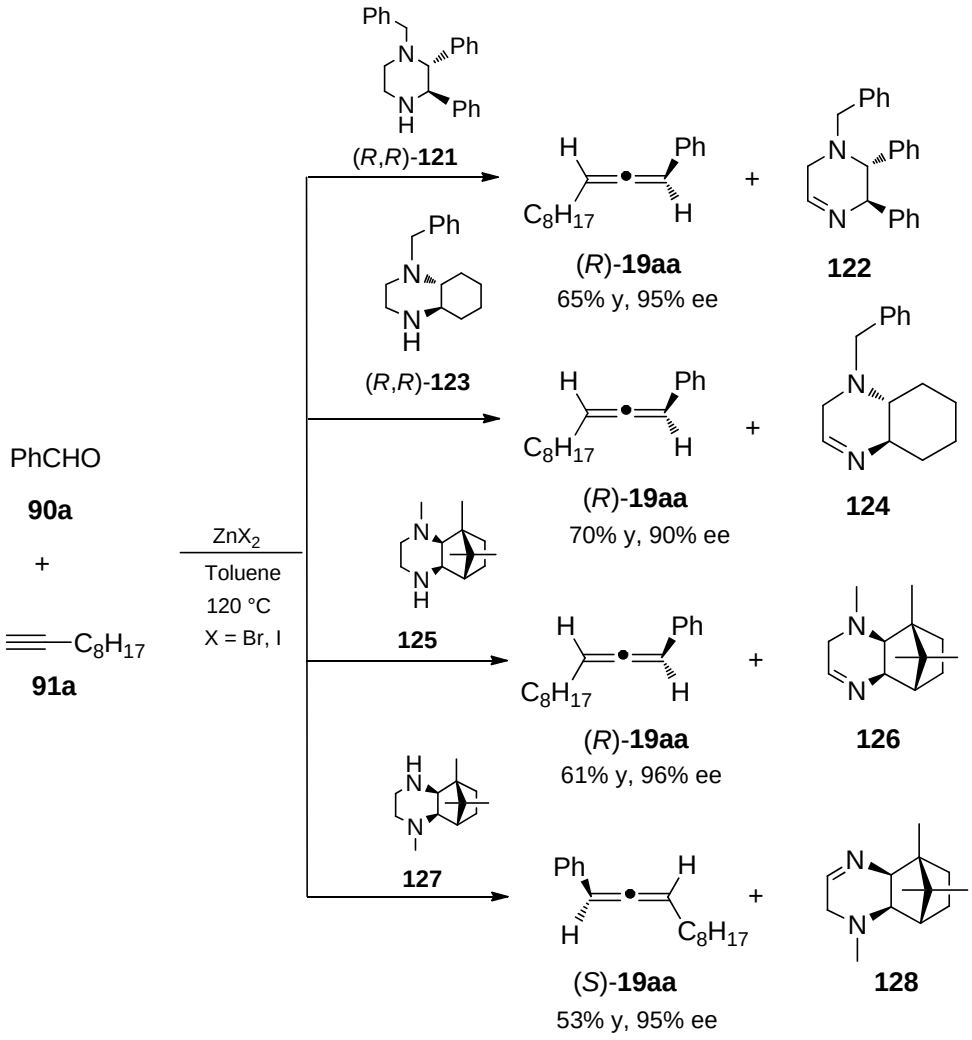
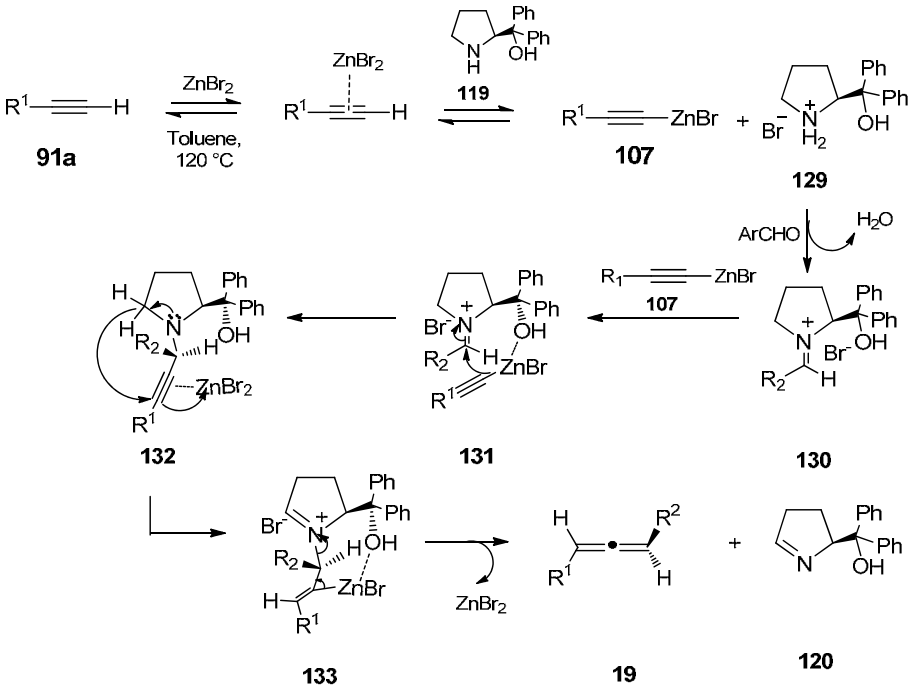


Chart 1 (continued)



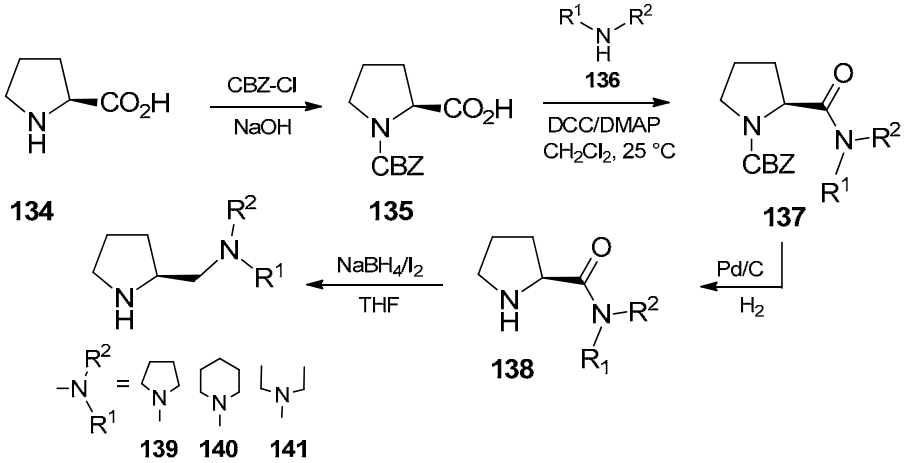
Comparision of the experimental results of the transformations involving creation of new stereogenic center in the intermediate propargyl amine and subsequent chirality transfer to the corresponding chiral allene for various chiral cyclic secondary amines investigated so far indicates that the additional coordinating hydroxyl group or amine moiety present in the derivatives **119**, **121**, **123**, **125** and **127** play a major role while alkynyl addition on to the iminium ion **131** and in allene formation as outlined in Scheme 30. Therefore, it is not surprising that the chiral amines **98**, **102**, and **117** gave poor results (18% ee to 66% e) as there is no additional coordinating group in these amines (Scheme 28 and Scheme 29).

Scheme 30



Accordingly, we have decided to examine the use of chiral diamines **139-141** containing such additional amine moiety. These chiral diamine derivatives have been prepared following a simple protocol starting from L-proline as outlined in Scheme 31.[34]

Scheme 31

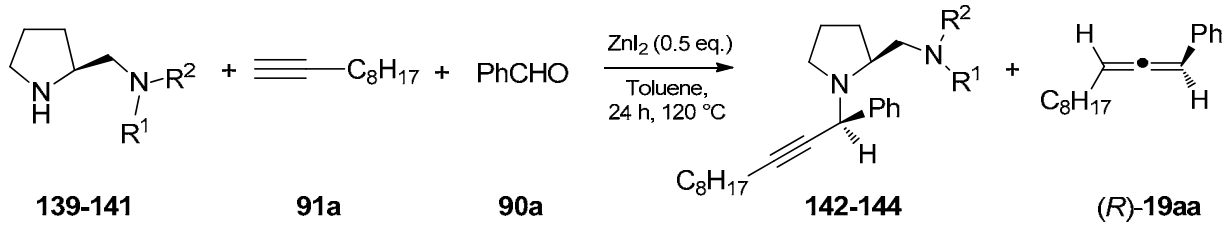


4.2.7 Synthesis of chiral propargylamines using 1-decyne, benzaldehyde and the chiral diamines 139-141

We have first examined the utility of proline diamine derivative **139** in this three component one pot allene transformation. When the reaction was carried out using the chiral diamine **139**, benzaldehyde **90a**, 1-decyne **91a** and ZnI_2, the allene (*R*)-**19aa** was obtained with 94% ee but only in 4% yield along with the corresponding propargylamine intermediate **142aa** in 88% yield with 96% de (Table 2, entry 1). Clearly, the intermediate propargylamine seems to be stable under the reaction conditions.

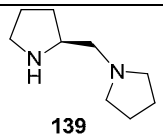
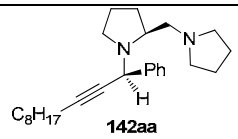
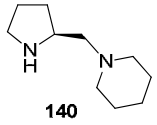
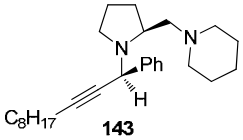
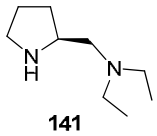
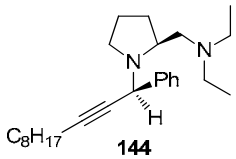
We have also examined the other proline derivatives **140** and **141** for use in this one-pot allene transformation. Whereas the chiral diamine **140** gave the chiral allene **19aa** in 7% yield with 90% ee along with the corresponding propargylamine derivative **143** in 82% yield and 96% de, the chiral diamine **141** gave the chiral allene **19aa** in 11% yield with 90% ee along with the propargylamine derivative **144** in 50% yield and 80% de (Table 2, entry 2-3).

Scheme 32



139-141 **91a** **90a** **142-144** (*R*)-**19aa**

Table 2.Reaction of 1-decyne and benzaldehyde with chiral diamines **139-141** using ZnI_2[a, b]

S. No.	Chiral diamine	(*R*)-Allene **19aa**		Propargylamine		
		Yield (%)[c]	Ee%[d]		Yield (%)[c]	de%[e]
1	 **139**	4	94	 **142aa**	88	96
2	 **140**	7	90	 **143**	82	96
3	 **141**	11	90	 **144**	50	80

[a]The reactions were carried out by taking amine **(**1.0 mmol), 1-alkyne (1.1 mmol), and aldehyde (1 mmol) in toluene (3 mL) and heating at 120 ˚C for 24 h.[b]0.5 equiv. of ZnI_2 was used. [c]Isolated yield. [d]The % ee was determined by HPLC analysis on chiralcel OD-H column. [e] ^{1}H NMR analysis of crude product.

When the mixture of the diamine **139** (1 mmol), 1-decyne **91a** (1.1 mmol) and ZnI_2 (0.5 mmol) were heated in toluene for 10 min at 120 ˚C and cooled to 25 ˚C, a crystalline material **145** precipitated which was found to be a 1:1 complex of the chiral diamine **139** and ZnI_2. The ORTEP diagram of this product **145** is given in Figure 4.

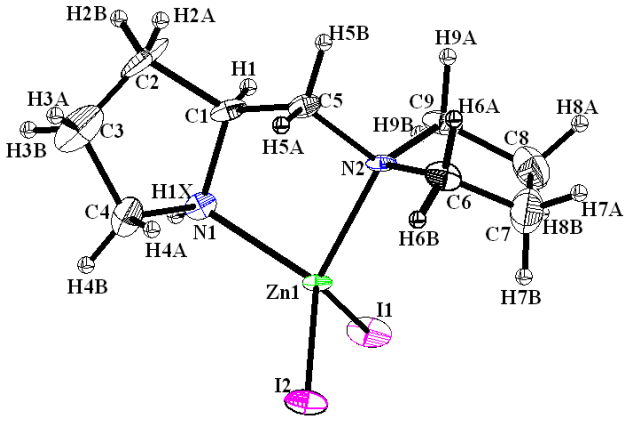


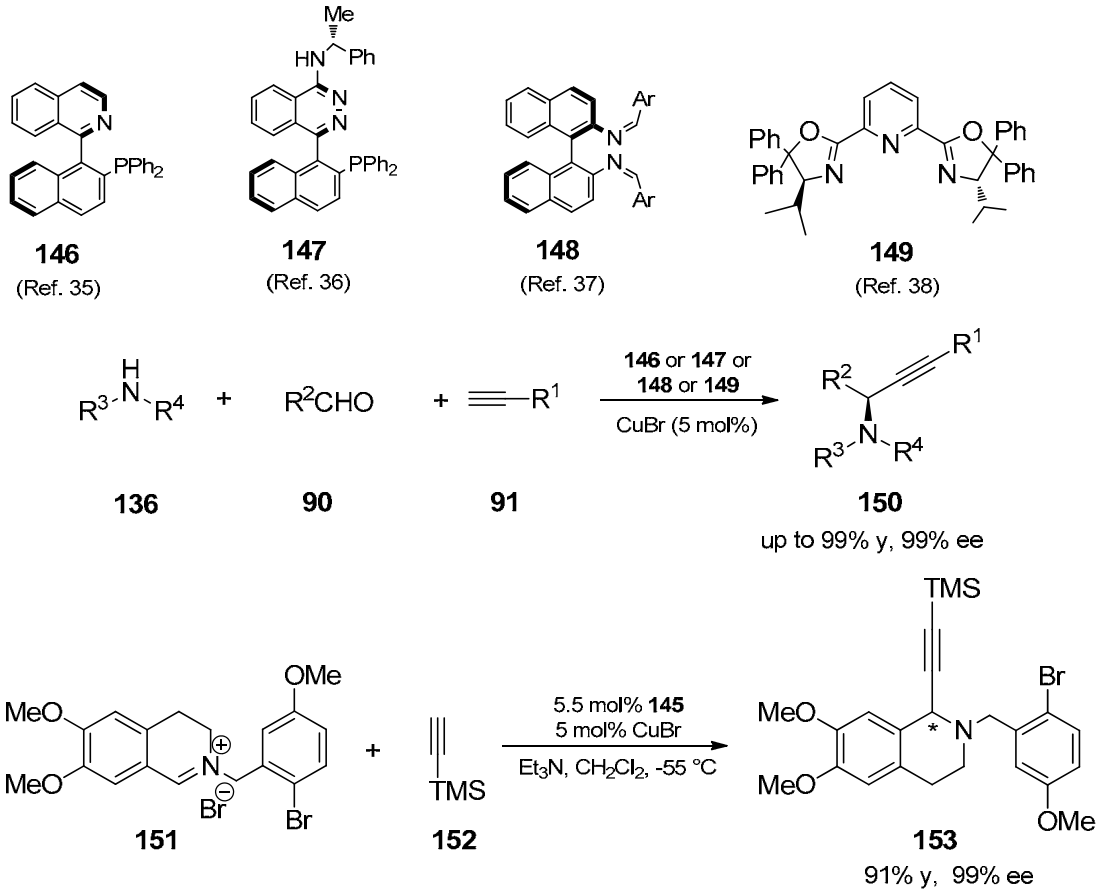
Figure 4. ORTEP representation of the crystal structure **145** (Thermal ellipsoids are drawn at 20% probability)

Table 3. Crystal data and structure refinement for compound 145

Empirical formula	C9 H18 I2 N2 Zn
Formula weight	473.42
Temperature	298(2) K
Wavelength	1.54184 Å
Crystal system	Tetragonal
Space group	P 41 21 2
Unit cell dimensions	a = 8.47990(10) Å, α = 90°
	b = 8.47990(10) Å, β = 90°
	c = 40.7085(18) Å, γ = 90°
Volume	2927.30(14) $Å^3$
Z	8
Calculated density	2.148 mg/m^3
Absorption coefficient	35.215 mm^{-1}
F(000)	1776
θ Range for data collection	5.33 to 71.84°
Limiting indices	-8<=h<=9, -9<=k<=10, -42<=l<=49
Reflections collected	14197
Independent Reflections	2785 [R(int) = 0.0756]
Completeness to *θ* = 71.84	97.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2785 / 0 / 131
Goodness-of-fit on F^2	1.017
Final *R* indices [I> 2σ (I)]	R1 = 0.0597, wR2 = 0.1484
R indices (all data)	R1 = 0.0707, wR2 = 0.1579
Largest diff. peak and hole	1.611 and -1.430 $eÅ^{-3}$

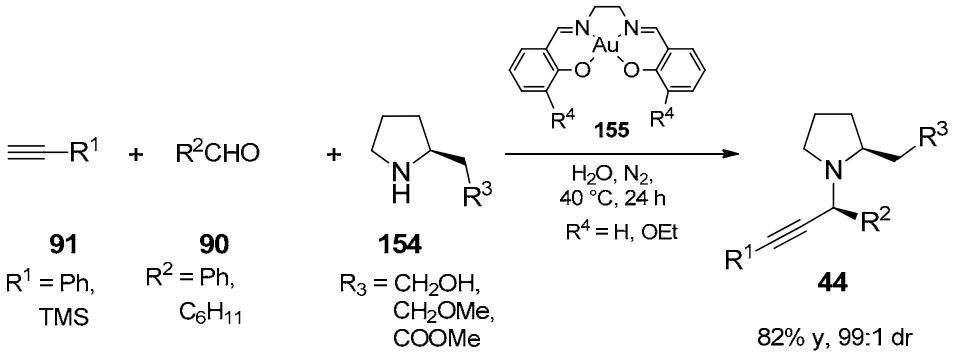
Previously, methods have been reported for enantioselective synthesis of propargylamines **150** by copper (I)-catalyzed three component reaction of amine **136**, aldehyde **90**, and terminal alkyne **91** using the chiral catalysts (*R*)-QUINAP **146,** BINAM derived bisimine **148** and pybox ligand **149** (Chart 2).

Chart 2



Formation of chiral prolinol based propargylamines **44** have been reported using gold (III) salen **155** complex catalyzed three component coupling reaction of aldehydes, amines, and alkynes in water in excellent yields at 40 ˚C in 67-89% yields with 84:16 to 99:1 dr (Scheme 33).[39]

Scheme 33



We have examined the relatively inexpensive CuBr in the three component (A^3) coupling of aldehyde, amine, and alkyne. We have observed various propargylamines **142** can be prepared in good yields (70-96%) and diastereoselectivities (96-98%) using CuBr (20 mol%) at 25 ˚C (Scheme 34). The results are summarized in Table 3.

Scheme 34

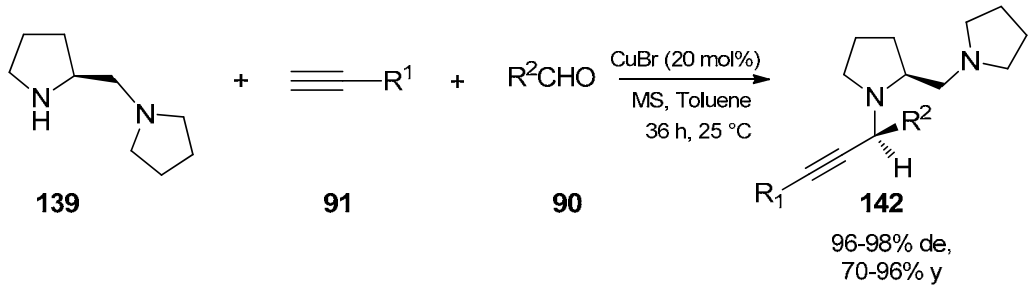
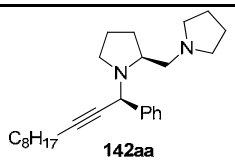
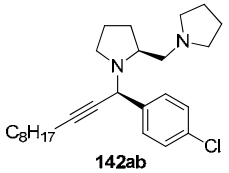
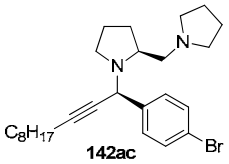
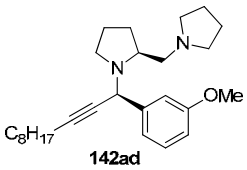
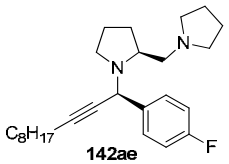
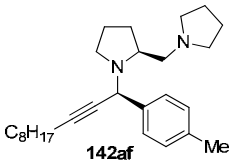
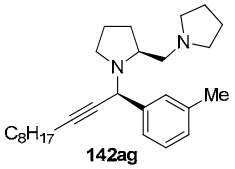
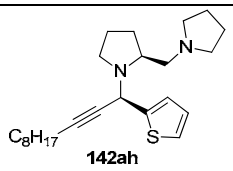
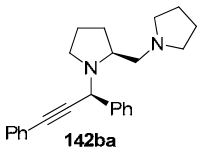
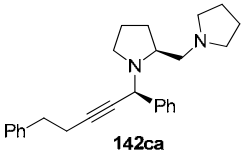
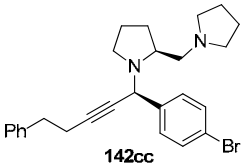
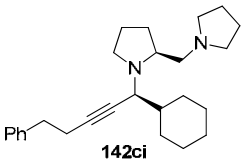
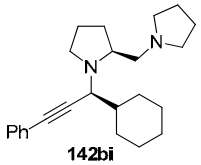
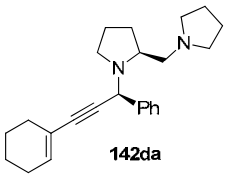
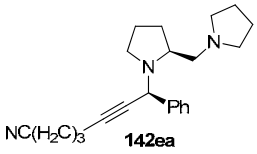


Table 3: Synthesis of different propargylamine derivatives of proline diamine **139**[a]

S. No	R^1	R^2	Product	Yield (%)[c]	de[b]
1	C_8H_{17} (**91a**)	Ph (**90a**)	 **142aa**	92	97
2	C_8H_{17} (**91a**)	4Cl-C_6H_4 (**90b**)	 **142ab**	84	98
3	C_8H_{17} (**91a**)	4Br-C_6H_4 (**90c**)	 **142ac**	86	97
4	C_8H_{17} (**91a**)	3OMe-C_6H_4 (**90d**)	 **142ad**	75	97
5	C_8H_{17} (**91a**)	4-F-C_6H_4 (**90e**)	 **142ae**	95	98
6	C_8H_{17} (**91a**)	4-Me-C_6H_4 (**90f**)	 **142af**	90	96
7	C_8H_{17} (**91a**)	3-Me-C_6H_4 (**90g**)	 **142ag**	82	96

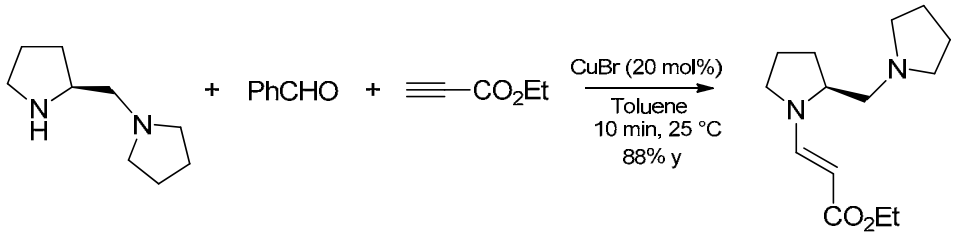
8	C_8H_{17} (**91a**)	2-Thiophenyl (**90h**)	 **142ah**	70	98
9	Ph (**91b**)	Ph (**90a**)	 **142ba**	94	97
10	CH_2CH_2Ph (**91c**)	Ph (**90a**)	 **142ca**	89	97
11	CH_2CH_2Ph (**91c**)	4-Br-C_6H_4 (**90c**)	 **142cc**	78	97
12	CH_2CH_2Ph (**91c**)	Cyclohexyl (**90i**)	 **142ci**	96	97
13	Ph (**91b**)	Cyclohexyl (**90i**)	 **142bi**	96	97
14	1-cyclohexenyl (**91d**)	Ph (**90a**)	 **142da**	88	98
15	$CH_2CH_2CH_2CN$ (**91e**)	Ph (**90a**)	 **142ea**	91	96

[a]The reactions were carried out by taking amine **139 (**2.0 mmol), 1-alkyne (2.2 mmol) and aldehyde (2.0 mmol) in toluene (4 mL) with CuBr (0.4 mmol) and MS (1.0 g, 4Å) at 25 °C for 24 h. [b]dr ratio based on ^{1}H NMR analysis of crude product mixtures. [c]Isolated yield.

4.2.8 Further scope of the reaction using sensitive substrates

Since this transformation using the CuBr takes place under relatively mild conditions, we have examined the reaction of the chiral diamine **139** and ethyl propiolate **156**. However, in this case only the corresponding Michael adduct **157** was obtained in quantitative yield (Scheme 35).

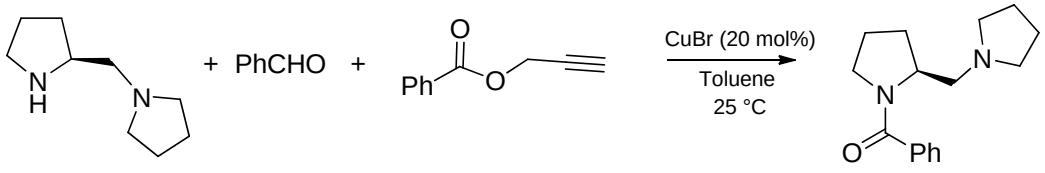
Scheme 35



139 **90a** **156** **157**

When the reaction was carried out using propargyl alcohol only a complex mixture of unidentified products were obtained under these conditions. Also, the reaction using the benzoyl ester of propargyl alcohol **158** gave only the corresponding *N*-benzoyl derivative of the diamine **159** (Scheme 36).

Scheme 36

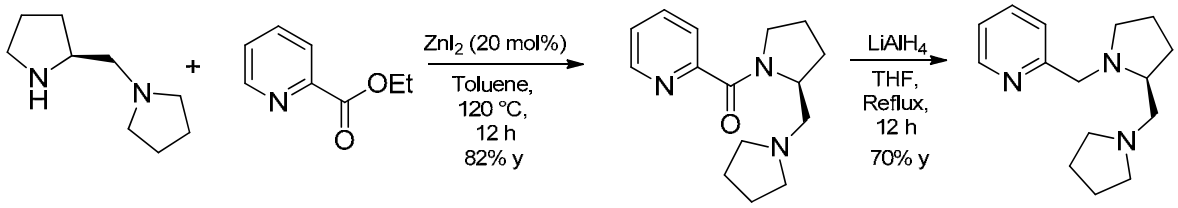


139 **90a** **158** **159**

4.2.9 Attempt towards the catalytic synthesis of chiral propargylamines containing achiral amine moiety

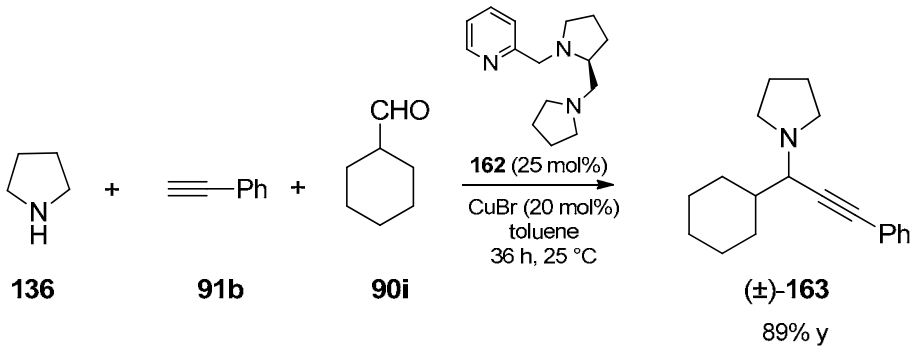
We have also synthesized the chiral tertiary triamine derivative **162** to prepare the corresponding chiral copper complex for use in the synthesis of chiral propargylamines using achiral amines. The chiral diamine **139** was condensed with ethyl picolinate **160** using ZnI_2 (20 mol%) to obtain the amide **161** in 82% yield. The amide was reduced with $LiAlH_4$ in THF under reflux to obtain the (*S*)-2-((2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)pyridine **162** in 70% yield (Scheme 37).

Scheme 37



When the chiral triamine **162** was used in catalytic amounts (25 mol%) along with CuBr (20 mol%) in the reaction of pyrrolidine **136**, cyclohexyl carboxaldehyde **90i** and 1-phenyl acetylene **91b**, only the racemic product **163** was obtained (Scheme 38). Presumably, the reaction may be going through the uncatalysed pathway involving uncomplexed CuBr.

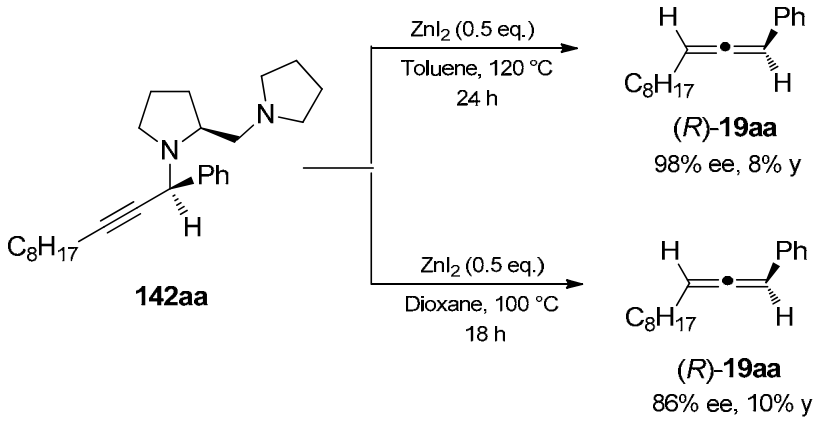
Scheme 38



4.2.10 Conversion of chiral propargylamine derivatives 142aa to chiral allenes

We have observed that the reaction of the propargylamine derivative **142aa** with ZnI_2 gave the chiral allene **19aa** in 98% ee but only in 8% yield. The starting propargylamine **142aa** was recovered in 70% yield under these conditions. The conversion to allene was also poor using dioxane solvent (Scheme 39).

Scheme 39



Therefore, we have examined this conversion using other metal salts like $AgNO_3$ and copper halides. As outlined in the introductory section, $AgNO_3$ reacts with certain propargylamines to give chiral allenes.[25b] We have examined the use of $AgNO_3$ for the

conversion of propargylamine **142aa** to allene in CH_3CN solvent. In this case, the chiral allene **19aa** was obtained in 99% ee but only in 14% yield (Table 4, entry 1).

Scheme 40

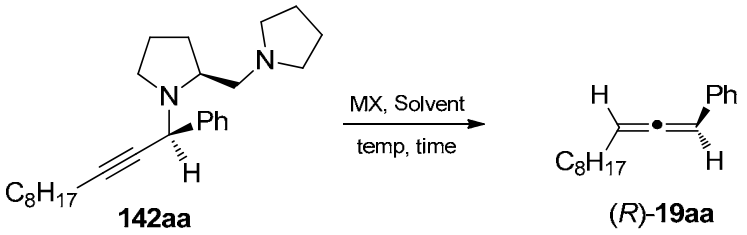


Table 4: Reaction of propargylamine **142aa** with $AgNO_3$ and CuX[a]

S. No.	Solvent	Temp	MX	Equiv.	Time	Yield (%)[b]	Ee(%)[c]
1	CH_3CN	50	$AgNO_3$	0.5	24	14	99
2	Toluene	120	CuI	0.5	2	18	92
3	Toluene	120	CuI	0.5	5	35	76
4	Dioxane	100	CuI	0.25	18	33	99
5	Dioxane	100	CuI	0.5	18	62	99
6	Dioxane	100	CuI	0.5	24	68	98
7	Dioxane	100	CuI	0.75	18	65	99
8	Dioxane	100	CuI	1.0	18	70	98
9	Dioxane	100	CuCl	0.5	18	22	92
10	Dioxane	100	CuBr	0.5	18	30	90

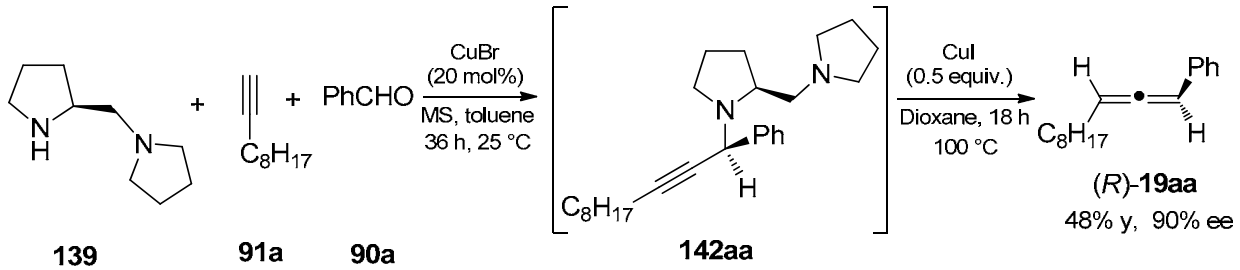
[a]The reactions were carried out by taking amines **142aa** (0.5 mmol) in solvent (2 mL). [b]Isolated yield [c]The % ee was determined by HPLC analysis on chiralcel OD-H column.

We have observed that the reaction at 120 ˚C using CuI (0.5 equiv.) gave the (*R*)-allene in 92% ee with 18% yield (Table 4, entry 2). When the reaction time was increased to 5 h, the (*R*)-allene obtained in 35% yield but only in 76% ee (Table 4, entry 3). When the reaction was

carried out in dioxane solvent at 100 ˚C for 18 h using CuI (0.25 equiv.), the (*R*)-allene was obtained in 33% yield with 99% ee (Table 4, entry 4). When the same reaction reaction was carried out using more amount of CuI (0.5 equiv.), the yield was improved to 62% with 99% ee (Table 4, entry 5). Further increase in amount of CuI (either 0.75 or 1.0 equiv.) did not improve the yield (Table 4, entries 7 and 8). We have also observed that the use of other copper halides CuCl and CuBr led to lower yields (22-30%) and enantioselectivity (90-92% ee) (Table 4, entries 9 and 10).

We have also examined the utility of this chiral diamine **139** system for one-pot chiral allene transformation using CuBr for preparation of propargylamine derivative *in situ* followed by addition of CuI (in dioxane) for chiral (*R*)-allene formation. In this case, we have obtained the chiral (*R*)-allene **19aa** with 48% yield and 90% ee (Scheme 41).

Scheme 41



Since, this one pot procedure gave poor results compared to the two step method (Table 2, entry 1 and Table 4, entry 5), we have followed the two step method for chiral allene synthesis with other propargylamine derivatives (**142ab-142ea**) using CuI (0.5 equiv.) in dioxane at 100 ˚C. The chiral allenes (**19aa-ah**) were obtained in moderate to good yields (58-68% yield) with good enantioselectivities (94-99% ee, Table 5; entries 2-8).

Scheme 42

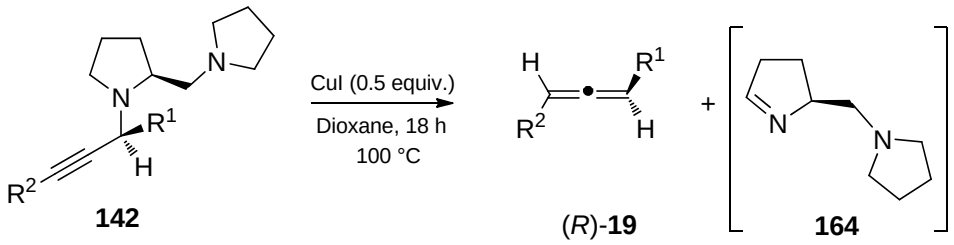
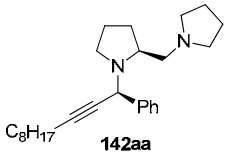
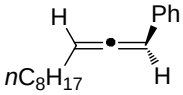
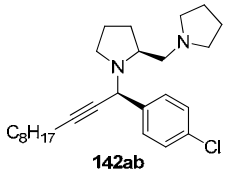
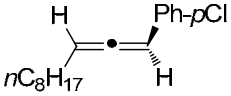
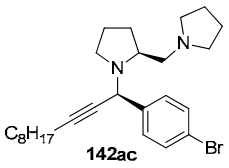
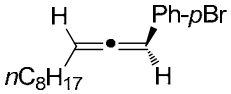
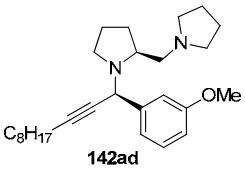
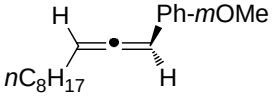
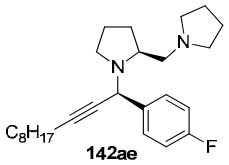
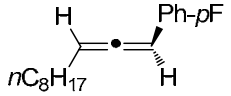
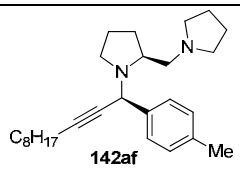
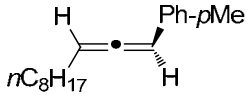
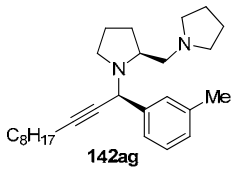
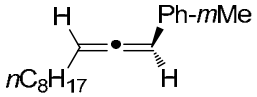
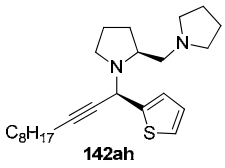
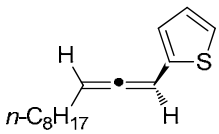
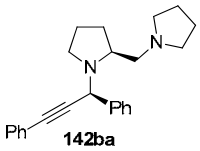
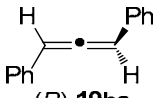
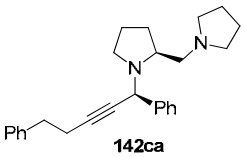
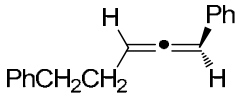
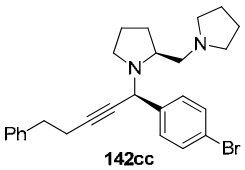
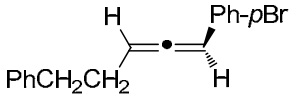
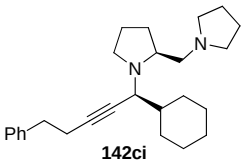
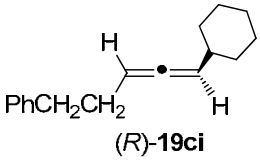
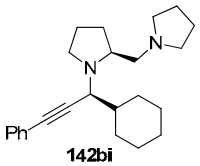
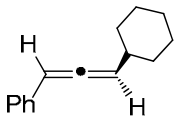
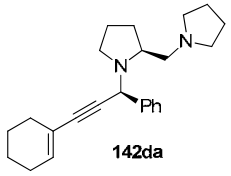
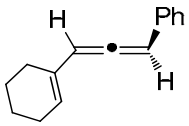
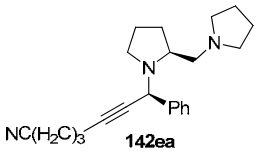
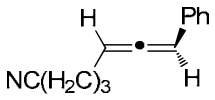


Table 5: Conversion of chiral propargylamines to chiral allenes

S. No.	propargylamine	Product	Yield (%)[b]	Ee (%)[c]
1	 **142aa**	 (*R*)-**19aa**	62	99
2	 **142ab**	 (*R*)-**19ab**	65	98
3	 **142ac**	 (*R*)-**19ac**	68	96
4	 **142ad**	 (*R*)-**19ad**	62	94
5	 **142ae**	 (*R*)-**19ae**	67	98

6	 **142af**	 (*R*)-**19af**	66	98
7	 **142ag**	 (*R*)-**19ag**	59	96
8	 **142ah**	 (*R*)-**19ah**	58	94
9	 **142ba**	 (*R*)-**19ba**	56	85
10	 **142ca**	 (*R*)-**19ca**	64	97
11	 **142cc**	 (*R*)-**19cc**	61	96
12	 **142ci**	 (*R*)-**19ci**	60	98
13	 **142bi**	 (*R*)-**19bi**	65	99

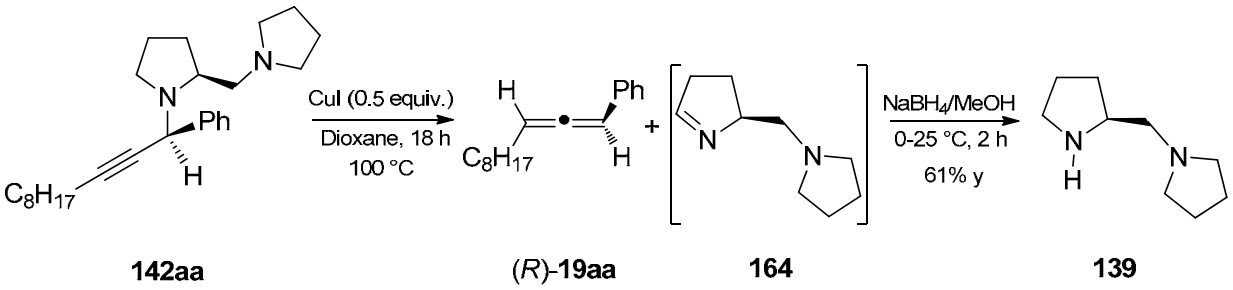
14	 **142da**	 (*R*)-**19da**	58	97
15	 **142ea**	 (*R*)-**19ea**	81	89

[a]The reactions were carried out by taking amines **142 (**0.5 mmol), CuI (0.25 mmol) in dioxane (2 mL). [b]Isolated yield. [c]The % ee was determined by HPLC analysis on chiralcel OD-H or OB-H or OJ-H column.

The propagylamine **142ba** prepared from the diamine **139**, benzaldehyde **90a** and phenyl acetylene **91b**, gave the chiral allene **19ba** in 56% yield and 85% ee (Table 5, entry 9). The propargylamines (**142ca-ci**) prepared using the diamine **139**, 4-phenyl-1-butyne **91c** afforded the corresponding chiral allenes (**19ca-ci**) in 60-64% yield and 96-97% ee (Table 5, entry 10-12). Whereas the propargylamine **142bi** prepared from cyclocarboxaldehyde and phenyl acetylene gave the corresponding chiral allene **19bl** in 65% yield and 99% ee (Table 5, entry 13), the propargylamine **142da** prepared using cyclohexenylethyne **91d** and benzaldehyde **90a** gave the chiral allene in 58% yield and 97% ee (Table 5, entry 14). The propargylamine **142ea** prepared using benzaldehyde **90a** and 5-hexynenitrile **91e** afforded the corresponding chiral allene **19ea** in 81% yield and 89% ee (Table 5, entry 15).

The imine intermediate **164** formed during the reaction was converted back *in situ* to proline diamine using $NaBH_4$/MeOH in 61% yield without loss in optical purity (Scheme 43).

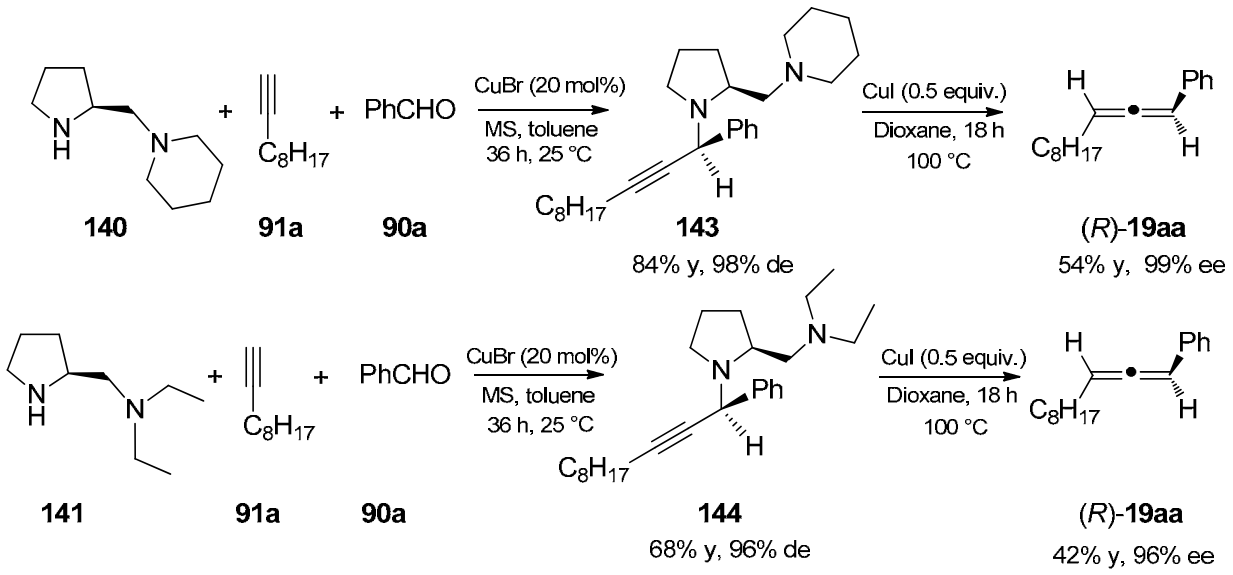
Scheme 43



4.2.11 Chiral allenes using chiral diamines containing diethylamine and piperidine moieties

To study the structural effects of the diamine derivatives in this transformation, we have prepared the diamines containing piperidine and diethylamine moieties (Scheme 31). The corresponding propargylamines **143** and **144** were prepared using CuBr (20 mol%), 1-decyne **91a** and benzaldehyde **90a** and their conversion to the allenes were examined. Whereas the propargylamine **143** gave chiral (*R*)-allene **19aa** in 54% yield and 99% ee, the propargylamine **144** gave the chiral (*R*)-allene **19aa** in 42% yield and 96% ee (Scheme 44).

Scheme 44

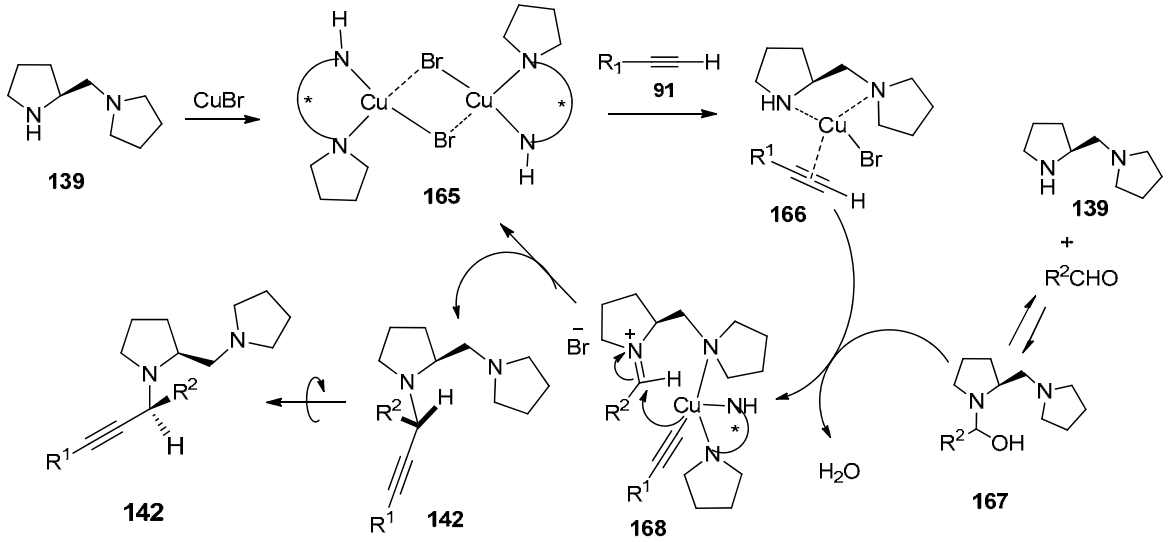


Clearly, the chiral diamine containing pyrrolidine moiety **139** gives relatively better results (Table 5) compared to the propargylamine containing diethylamine and piperidine moieties.

4.2.12 Mechanistic pathway for the propargylamine and chiral allene formation

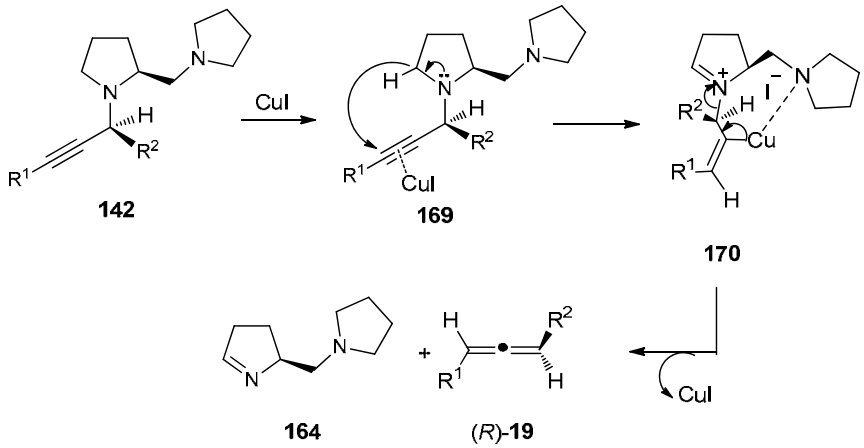
A mechanistic pathway similar to that proposed for the reported copper catalysed propargylamine formation[35c] using the chiral diamines **139**, **140** and **141** as outlined in the Scheme 45. Initially, chiral diamine **139** would form the dimeric coper complex **165** on reaction with CuBr, which complex to 1-alkyne leading to give the complex **166**. The complex **166** would then react with the intermediate aminal **167**, obtained by the reaction of chiral diamine and aldehyde, to afford the iminium copper diamine complex **168**. This intermediate **168** would deliver the alkynyl group from bottom face of the iminium group leading the new (*S*)-stereogenic center at the propargylamine **142**.

Scheme 45



A mechanism similar to that proposed earlier (Scheme 30) for allene synthesis using (*S*)-diphenylprolinol can be considered for the conversion of of chiral propargylamines **142** to chiral allenes (*R*)-**19** (Scheme 46). The propargylamine **142** would complex with CuI to give **169** which could undergo a hydride shift to give the chiral allene (*R*)-**19** *via* the intermediate **170** (Scheme 46).

Scheme 46



The chiral diamine **139** is more easily accessed from commercially available starting materials (Scheme 31) compared to the chiral (*S*)-diphenylprolinol or other diamine derivatives like **121**, **123**, **125** and **127** and give comparable or better results in this propargylamine or allene synthesis. Therefore, the results described here have good potential for further exploitation.

4.3 Conclusions

The utility of chiral C_2 and C_1 symmetric amines (2*S*,5*S*)-2,5-diphenylpyrrolidine **98** and C_1-symmetric (2*S*)-phenylpyrrolidine **102** were examined in the one pot three component chiral allene synthesis using ZnI_2. The C_2-symmetric amine **98** gives the chiral allene in 57% yield and 18% ee. Whereas the C_1-symmetric amine **102** gave the chiral allene in 72% yield with 66% ee. When the reaction was carried out with C_1-symmetric chiral propargylamine **106**, the chiral allene was obtained in 76% yield and 78% ee. The use of chiral C_1-symmetric (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine **139** prepared from (*S*)-proline in two pot chiral allene synthesis with various alkynes and aldehydes using Cu (I) halide gave the chiral allenes up to 99% ee and 68% yield. The mechanistic pathway for the chiral propargylamine from (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine **139**, benzaldehyde **90a** and 1-decyne **91a** with *S* configuration at the newly formed stereogenic center and subsequent chirality transfer to form the corresponding *R*-allene **19aa** is readily rationalized by considering appropriate models based on mechanisms reported for similar transformations.

4.4 Experimental Section

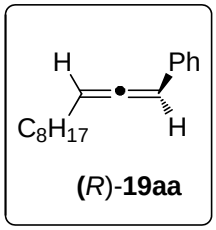
4.1 General Information

Several informations given in the section **1.4** are also applicable for the experiments outlined in this section. Analytical grade $ZnCl_2$ was purchased from E-Merck and CuBr, CuI, $ZnBr_2$ and ZnI_2 were purchased from Sigma Aldrich. Synthesis of chiral secondary amines (2*S*,5*S*)-2,5-diphenylpyrrolidine **98** and (2*S*)-phenylpyrrolidine **102** was described in Chapter 1. Chiral L-proline derived diamines **139-141** were prepared by following the literature procedure.[34]

4.2 Reaction of aldehydes, alkyne, amine 102 with ZnI_2: Synthesis of Chiral Allenes 19aa-ae

A stirred suspension of chiral amine **102** (0.15 g, 1 mmol), ZnI_2 (0.16 g, 0.5 mmol) and 1-alkyne (1.1 mmol) in toluene (3 mL) was heated at 120 ˚C for 10 min. Freshly distilled aldehyde (1 mmol) was added at 25 ˚C and the contents were refluxed at 120 ˚C under nitrogen atmosphere for the required time (Table 1). The mixture was brought to 25 ˚C and chromatographed on a silica gel (100-200) using hexane as eluent to isolate the chiral allene **19**.

(*R*)-1-phenyl-1,2-undecadiene (19aa):



(*R*)-19aa

Yield 0.16 g (72%).

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

^1H NMR (400 MHz, ppm, $CDCl_3$) 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, 10H), 0.95-0.91 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 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.

HPLC 66% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*R*)= 3.9 min, t_R(*S*)= 4.3 min).

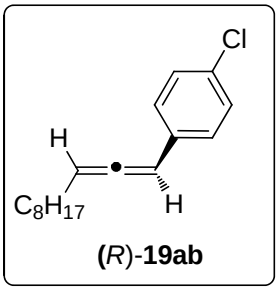
$[\alpha]_D^{25}$ -151.8 (c, 0.70, $CHCl_3$).

MS (EI) m/z 229 $(M+1)^+$.

Analytical data calculated for $C_{17}H_{24}$ C, 89.41; H, 10.59.

Found C, 89.32; H, 10.51.

(*R*)-1-(4-chloro-phenyl)-1,2-undecadiene (19ab):



(*R*)-19ab

Yield 0.18 g (68%).

IR (Neat) (cm^{-1}) 2926, 2854, 1950, 1491, 831.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.24 (dd, J_1 = 8.52 Hz, J_2 = 11.72 Hz, 4H), 6.11-6.08 (m, 1H), 5.59 (q, J = 6.6 Hz, 1H), 2.17-2.11 (m, 2H), 1.52-1.45 (m, 2H), 1.38- 1.28 (m, 10H), 0.90 (t, J = 6.96 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.3, 133.8, 132.1, 128.7, 127.7, 95.6, 93.7, 31.9, 29.4, 29.3, 29.2, 29.1, 28.7, 22.7, 14.1.

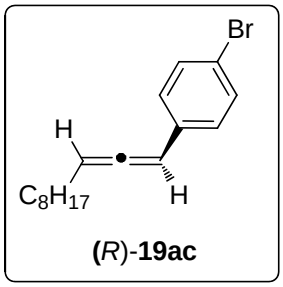
HPLC 52% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 3.0 min, t_R(*R*)= 3.6 min).

$[\alpha]_D^{25}$ -96.7 (c, 0.66, $CHCl_3$).

Analytical data calculated for $C_{17}H_{23}Cl$ C, 77.69; H, 8.82.

Found C, 77.52; H, 8.76.

(*R*)-1-(4-bromo-phenyl)-1,2-undecadiene (19ac):



(*R*)-19ac

Exact Mass: 306.10

Yield 0.22 g (71%).

IR (Neat) (cm^{-1}) 2926, 2858, 1950, 1599, 1487, 829.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.41 (d, *J* = 8.36 Hz, 2H), 7.15 (d, *J* = 8.32 Hz, 2H), 6.08-6.05 (m, 1H), 5.56 (q, *J* = 6.68 Hz, 1H), 2.15-2.09 (m, 2H), 1.49-1.43 (m, 2H), 1.36-1.26 (m, 10H), 0.88 (t, *J* = 6.96 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.2, 134.2, 131.6, 128.0, 120.1, 95.5 93.7, 31.8, 29.3, 29.3, 29.1, 29.1, 28.6, 22.6, 14.1.

HPLC 52% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 3.5 min, t_R(*R*)= 5.3min).

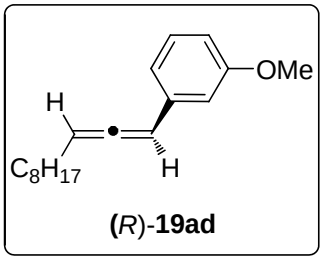
$[\alpha]_D^{25}$ -80.1 (c, 0.60, $CHCl_3$).

MS (EI) m/z 307 $(M+1)^+$.

Analytical data calculated for $C_{17}H_{23}Br$ C, 66.45; H, 7.54.

Found C, 66.32; H, 7.51.

(*R*)-1-(3-methoxy-phenyl)-1,2-undecadiene (19ad):.



(*R*)-19ad

Yield 0.17 g (65%).

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

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 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 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 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.

HPLC 38% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 0.5 mL/min, 254 nm, t_R(*R*)= 8.8 min, t_R(*S*)= 10.2 min).

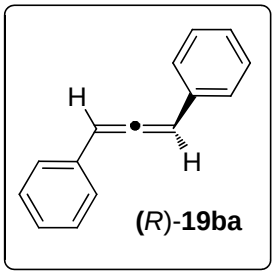
$[\alpha]_D^{25}$ -88.5 (c, 0.60, $CHCl_3$).

MS (EI) m/z 259 $(M+1)^+$.

Analytical data calculated for $C_{18}H_{26}O$ C, 83.67; H, 10.14.

Found C, 83.45; H, 10.06.

(*R*)-1,3-diphenyl-propane1,2-diene (19ba):



(*R*)-**19ba**

Yield 0.09 g (48%).

Mp 50 ˚C.

IR (KBr) (cm^{-1}) 3061, 3028, 1936, 1597, 1493, 1450, 758.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.36-7.30 (m, 8H), 7.25-7.21 (m, 2H), 6.60 (s, 2H)

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 207.8, 133.6, 128.7, 127.3, 127.0, 98.4.

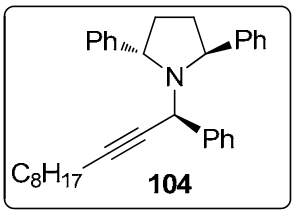
HPLC 46% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.0 mL/min, 254 nm, t_R(*R*)= 11.0 min, t_R(*S*)= 14.4 min).

$[\alpha]_D^{25}$ -205.6 (c, 0.40, $CHCl_3$).

MS (EI) m/z 193 $(M+1)^+$.

4.3 Isolation of (2*S*,5*S*)-Diphenyl-1-(1*S*-phenyl-undec-2-ynyl)-pyrrolidine (104):

To a suspension of ZnI_2 (0.13 g., 0.4 mmol) in dry toluene (5 mL), a solution of chiral amine **98** (0.45 g, 2 mmol), 1-decyne (0.44 mL, 2.2 mmol) and benzaldehyde (0.2 mL, 0.2 mmol) was added under nitrogen atmosphere. The mixture was heated to 90 ˚C and stirred further for 10 h. The solvent was removed in vacuo and propargylamine **104** was chromatographed on a silica gel column using hexane.



104

Yield 0.38 g (42%).

IR (Neat) (cm^{-1}) 3063, 3028, 2926, 1601, 1493, 1454, 754, 698.

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.40 (d, J = 6.96 Hz, 2H), 7.21-7.30 (m, 13H), 4.57 (s, 1H), 4.37 (bs, 2H), 2.57-2.59 (m, 2H), 1.90-1.93 (m, 3H), 1.56 (s, 2H), 1.30 (s, 11H), 0.91 (t, J = 6.92 Hz, 3H) **(Spectrum No. 27)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 144.6, 139.3, 128.6, 128.4, 127.9, 127.7, 126.9, 126.8, 87.9, 76.3, 63.2, 51.6, 33.3, 31.9, 29.3, 29.2, 29.0, 28.8, 22.7, 18.8, 14.2 **(Spectrum No. 28)**.

$[\alpha]_D^{25}$ -111.27 (c 2.06 $CHCl_3$).

MS (EI) m/z 450 $(M+1)^+$.

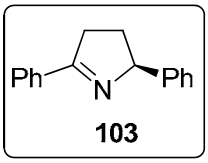
Analytical data calculated for $C_{33}H_{39}N$ C, 88.14; H, 8.74; N, 3.11.

Found C, 88.06; H, 8.81; N, 3.18.

4.4 Isolation of (2*S*)-2,5-Diphenyl-3,4-dihydro-2H pyrrole (103):

A mixture of ZnI_2 (0.25 mmol, 0.08 g), propargyl amine **104** (0.5 mmol, 0.25 g) in toluene (3 mL) were stirred at 120 ˚C for 3 h under N_2 atmosphere and solvent was removed under high

vacuum. The crude product was purified on silica. Hexane eluted the *R*-allene in 70% yield (0.080 g.) with 50% ee and 5% EtOAc in hexane eluted the imine **103**.



103

Yield 0.07 g (67%).

IR (Neat) (cm^{-1}) 3061, 3030, 1614, 1454, 761.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.96-7.97 (d, *J* = 6.72 Hz, 2H), 7.25-7.48 (m, 8H), 5.33 (t, *J* = 7.52 Hz, 1H), 3.19-3.10 (m, 1H), 3.02-3.05 (m, 1H), 2.60-2.63 (m, 1H), 1.89-1.92 (m, 1H) **(Spectrum No. 29)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 173.6, 144.6, 134.4, 130.6, 128.4, 127.9, 126.8, 126.5, 76.1, 35.6, 32.5 **(Spectrum No. 30)**.

$[\alpha]_D^{25}$ -28.4 (c 0.5 $CHCl_3$).

MS (EI) m/z 222 $(M+1)^+$.

Analytical data calculated for $C_{16}H_{15}N$ C, 88.64; H, 6.83; N, 6.33.

Found C, 86.69; H, 6.75; N, 6.41.

4.5 Reduction of (2*S*)-2,5-diphenyl-3,4-dihydro-2H-pyrrole:

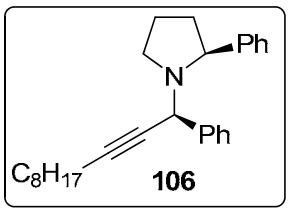
To the imine **103** (0.13 g, 0.6 mmol) in CH_3OH (10 mL), $NaBH_4$ (0.08 g, 2 mmol) was added portion wise using solid additional funnel at -78 ˚C and stirred for 4 h. The contents were brought to 25 ˚C and concentrated to dryness under vacuo. The crude product was dissolved in water (5 mL) : ether (20 mL) mixture. The aqueous layer was extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crude product was purified on a silica gel column using 10% EtOAc in hexane.

Yield 0.11 g (82%).

The spectral data showed 1:1 correspondence with the reported data.[41]

4.6 Isolation of (2*S*)-phenyl-1-(1*S*-phenyl-undec-2-ynyl)-pyrrolidine (106):

To a solution of chiral amine **102** (0.29 g, 2 mmol), 1-decyne (0.44 mL, 2.4 mmol), ZnI_2 (0.13 g, 0.4 mmol) in dry toluene (5 mL), benzaldehyde (0.2 mL, 2.0 mmol) was added under nitrogen atmosphere. The mixture was brought to 90 ˚C and stirred further at same temperature for 10 h. Solvent was removed in vacuo and the propargylamine **106** was eluted using hexane on silica gel (100-200 mesh).



106

Yield 0.52 g (69%).

IR (Neat) (cm^{-1}) 3389, 3059, 3030, 2928, 1602, 1491, 1452, 910, 758.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.60-7.66 (dd, *J* = 7.4 Hz, 8.04 Hz, 4H), 7.31-7.47 (m, 6H), 4.69 (s, 1H), 3.91 (t, *J* = 7.96 Hz, 1H), 2.73-2.79 (m, 2H), 2.42-2.46 (m, 2H), 2.27-2.30 (m, 1H), 1.83-1.95 (m, 3H), 1.67-1.74 (m, 2H), 1.60-1.62 (m, 2H), 1.33 (m, 8H), 0.99 (t, *J* = 6.48 Hz, 3H) **(Spectrum No. 31)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 143.7, 140.5, 128.5, 128.0, 127.8, 127.2, 127.0, 88.2, 75.1, 66.4, 54.8, 46.2, 35.1, 31.9, 29.4, 29.3, 29.2, 29.0, 22.8, 22.4, 18.9, 14.2 **(Spectrum No. 32)**.

$[\alpha]_D^{25}$ -110.17 (c 0.7 $CHCl_3$).

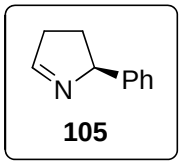
MS (EI) m/z 374 $(M+1)^+$.

Analytical data calculated for $C_{27}H_{35}N$ C, 86.81; H, 9.44; N, 3.75.

Found C, 86.75; H, 9.51; N, 3.68.

4.7 Isolation of (2*S*)-Phenyl -3,4-dihydro-2H pyrrole (105):

A mixture of ZnI_2 (0.25 mmol, 0.08 g), propargyl amine **106** (0.5 mmol, 0.19 g) in toluene (3 mL) were stirred at 120 ˚C for 1 h under N_2 atmosphere. The solvent was removed under high vacuum. The residue was washed with hexane and the solvent was removed to isolate the (*R*)-allene (*R*)-**19aa** in 76% yield (0.087 g.) with 78% ee. The remaining residue was stirred with ethyl acetate (5 mL), filtered and the filtrate was concentrated under reduced pressure to obtain the imine **105**.



105

Yield 0.05 g (65%).

IR (Neat) (cm^{-1}) 2928, 1651, 1371, 761.

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.96 (s, 1H), 7.29 (m, 3H), 7.04 (m, 2H), 4.88 (m, 1H), 2.83 (m, 1H), 2.76 (m, 1H), 2.34 (m, 1H), 1.68 (m, 1H) **(Spectrum No. 33)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 176.3, 141.7, 128.8, 127.9, 126.6, 76.8, 37.6, 29.3 **(Spectrum No. 34)**.

$[\alpha]_D^{25}$ +11.0 (c 0.95 $CHCl_3$).

MS (EI) m/z 146 $(M+1)^+$.

Analytical data calculated for $C_{10}H_{11}N$ C, 82.72; H, 7.64; N, 9.65.

Found C, 82.65; H, 7.59; N, 9.72.

4.8 Reduction of (2*S*)-phenyl-3,4-dihydro-2*H*-pyrrole:

To the imine **105** (0.07 g, 0.5 mmol) in CH_3OH (10 mL), $NaBH_4$ (0.08 g, 2 mmol) was added portion wise using a solid additional funnel at 0 ˚C and stirred for 3 h at 25 ˚C. The solvent was

removed under vacuo and the crude product was taken in water (5 mL): ether (20 mL) mixture. The ether layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhyd. Na_2SO_4. The solvent was evaporated and chromatographed on basic alumina using 25% EtOAc in hexane to isolate the product without any change in optical purity of sample used in preparation of the propargylamine **106.**

Yield 0.06 g (77 %)

The spectral data showed 1:1 correspondence with the reported data.[42]

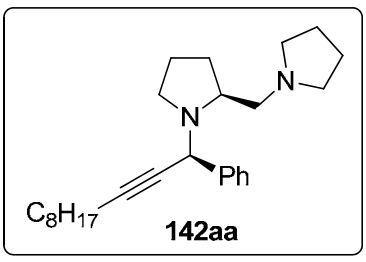
4.9 General procedure for synthesis of (*S*)-proline derived chiral propargylamines

To an oven dried 10 mL flask, copper (I) bromide (29 mg, 20 mol%) and 2-(pyrrolidin-1-ylmethyl)pyrrolidine **139** (0.31 g, 2 mmol) were added in dry toluene (3 mL). Frshly distilled aldehyde (2 mmol), 4 Å MS (1.0 g) and 1-alkyne (2.2 mmol) were added and stirred at 25 ˚C for 36 h. The 4Å MS were removed by filtration and washed with Et_2O. The crude product was concentrated in vacuo and purified by chromatography on basic alumina. The product was eluted in 98:2 mixture of hexane: ethylacetate.

(*S*)-1-((*S*)-1-phenylundec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142aa):

Yield 0.57 g (75%).

IR (Neat) (cm^{-1}) 3061, 3028, 2928, 1601, 1493, 1450, 700.



142aa

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.58 (d, J = Hz, 2H), 7.31-7.23 (m, 3H), 5.20 (s, 1H), 3.10-3.03 (m, 1H), 2.69 (dd, J_1 = 5.04 Hz, J_2 = 11.88 Hz, 1H), 2.62-2.44 (m, 6H), 2.34-2.30 (m, 2H), 2.01-1.94 (m, 1H), 1.81-1.77 (m, 5H), 1.69-1.54 (m, 5H),

1.48-1.44 (m, 2H), 1.31-1.29 (m, 8H), 0.89 (t, J = 6.88 Hz, 3H) **(Spectrum No. 35)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.6, 128.2, 127.9, 126.9, 87.6, 76.1, 62.3, 59.5, 56.5, 54.9, 47.5, 31.8, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.7, 18.8, 14.1 **(Spectrum No. 36)**.

$[\alpha]_D^{25}$ -89.295 (c, 0.68, $CHCl_3$).

MS (EI) m/z 381 $(M+1)^+$.

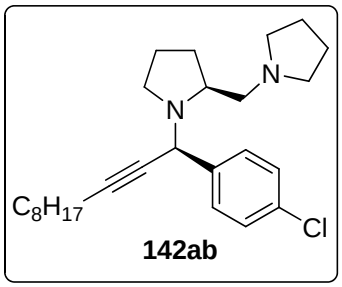
Analytical data calculated for $C_{26}H_{40}N_2$ C, 82.05; H, 10.59; N, 7.36.

Found C, 82.15; H, 10.59; N, 7.31.

(*S*)-1-((*S*)-1-(4-chlorophenyl)undec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ab):

Yield 0.7 g (84%).

IR (Neat) (cm^{-1}) 2928, 2785, 1487, 1460, 1089, 1016.



142ab

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.52 (d, J = 8.24 Hz, 2H), 7.27 (d, J = 8.28 Hz, 2H), 5.21 (s, 1H), 3.10-3.05 (m, 1H), 2.70 (dd, J_1 = 5.36 Hz, J_2 = 11.92 Hz, 1H), 2.60-2.47 (m, 7H), 2.32 (t, J = 6.84 Hz, 2H), 1.99-1.94 (m, 1H), 1.77 (bs, 4H), 1.68-1.53 (m, 5H), 1.47-1.45 (m, 2H), 1.29 (s, 8H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 139.3, 132.6, 129.5, 128.0, 88.0, 75.8, 62.4, 59.4, 55.9, 54.9, 47.5, 31.9, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.6, 18.8, 14.1.

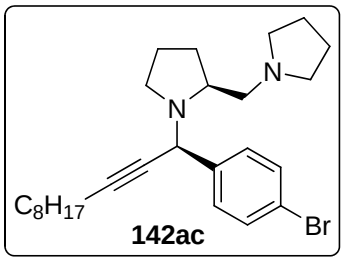
$[\alpha]_D^{25}$ -79.478 (c, 0.75, $CHCl_3$).

MS (EI) m/z 415 (M^+).

Analytical data calculated for $C_{26}H_{39}ClN_2$ C, 75.24; H, 9.47; N, 6.75.

Found C, 75.11; H, 9.56; N, 6.68.

(*S*)-1-((*S*)-1-(4-bromophenyl)undec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ac):



142ac

Yield 0.79 g (86%).

IR (Neat) (cm^{-1}) 3435, 2926, 2858, 1658, 1587, 1483, 1012, 856, 723.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.47-7.41 (m, 4H), 5.18 (s, 1H), 3.07-3.03 (m, 1H), 2.68 (dd, J_1 = 5.16 Hz, J_2 = 11.88 Hz, 1H), 2.58-2.46 (m, 6H), 2.31 (t, J = 6.68 Hz, 2H), 1.99-1.93 (m, 2H), 1.77 (s, 4H), 1.68-1.53 (m, 5H), 1.46-1.44 (m, 2H), 1.29 (s, 8H), 0.88 (t, J = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 139.8, 130.9, 129.9, 120.7, 88.1, 75.6, 62.3, 59.4, 55.9, 54.9, 47.4, 31.8, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.6, 18.7, 14.1.

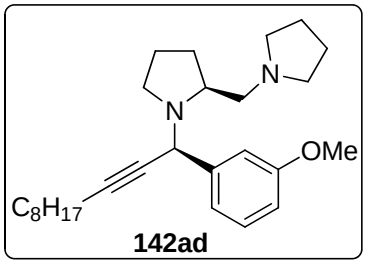
$[\alpha]_D^{25}$ - 64.597 (c, 0.85, $CHCl_3$).

MS (EI) m/z 459 (M^+), 461 $(M+2)^+$.

Analytical data calculated for $C_{26}H_{39}BrN_2$ C, 67.96; H, 8.55; N, 6.10.

Found C, 67.85; H, 8.51; N, 6.15.

(*S*)-1-((*S*)-1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl) pyrrolidine (142ad):



142ad

Yield 0.56 g (75%).

IR (Neat) (cm^{-1}) 2925, 2448, 2777, 1599, 1484, 1314, 1424, 1045, 755, 689.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.23 (d, J = 8.04 Hz, 1H), 7.18-7.17 (m, 2H), 6.78 (d, J = 8.12 Hz, 1H), 5.18 (s, 1H), 3.82 (s, 3H), 3.08-3.04 (m, 1H), 2.68 (dd, J_1 = 5.28 Hz, J_2 = 11.96 Hz, 1H), 2.62-2.47 (m, 6H), 2.31 (t, J = 6.84 Hz, 2H), 1.99-1.97 (m, 1H), 1.77 (s, 4H), 1.68-1.53 (m, 6H), 1.45-1.44 (m, 2H), 1.29 (bs, 8H), 0.89 (t, J = 7.08 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 159.4, 142.4, 128.9, 120.7, 114.0, 112.1, 87.5, 76.2, 62.4, 59.5, 56.4, 55.1, 55.0, 47.6, 31.9, 30.6, 29.3, 29.2, 28.9, 23.5, 22.8, 22.7, 18.8, 14.1.

$[\alpha]_D^{25}$ -82.118 (c, 1.03, $CHCl_3$).

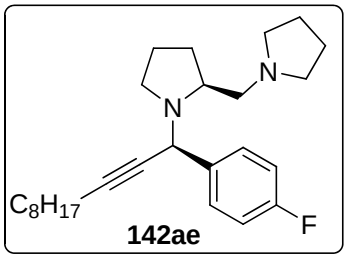
Analytical data calculated for $C_{25}H_{42}N_2O$ C, 80.17; H, 8.07; N, 7.48.

Found C, 80.06; H, 8.15; N, 7.41.

MS (EI) m/z 375 $(M+1)^+$.

(*S*)-1-((*S*)-1-(4-fluorophenyl)undec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ae):

Yield 0.75 g (75%).



142ae

IR (Neat) (cm^{-1}) 2930, 2858, 1604, 1506, 1458, 1221, 781

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.55-7.52 (m, 2H), 6.99 (t, J = 8.56 Hz, 2H), 5.20 (s, 1H), 3.08-3.03 (m, 1H), 2.68 (dd, J_1 = 5.4 Hz, J_2 = 11.88 Hz, 1H), 2.59-2.41 (m, 7H), 2.33-2.30 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 4H), 1.69-1.53 (m, 5H), 1.49-1.45 (m, 2H), 1.30 (s, 8H), 0.89 (t, J = 6.76 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 163.1, 160.7, 136.5, 129.7, 129.6, 114.7, 114.5, 87.8, 76.1, 62.5, 59.3, 55.8, 54.9, 47.5, 31.9, 30.6, 29.3, 29.2, 28.9, 23.5, 22.7, 18.8, 14.1.

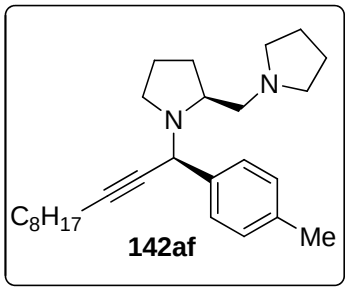
$[\alpha]_D^{25}$ -83.852 (c, 1.03, $CHCl_3$).

MS (EI) m/z 400 $(M+1)^+$.

Analytical data calculated for $C_{26}H_{39}FN_2$ C, 78.34; H, 9.86; N, 7.03.

Found C, 78.25; H, 9.79; N, 7.12.

(*S*)-2-(pyrrolidin-1-ylmethyl)-1-((*S*)-1-(p-tolyl)undec-2-yn-1-yl)pyrrolidine (142af):



142af

Yield 0.71 g (90%).

IR (Neat) (cm^{-1}) 2928, 2858, 2791, 1510, 1460, 1350, 1141, 831, 765.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.47 (d, J = 7.96 Hz, 2H), 7.13 (d, J = 7.84 Hz, 2H), 5.17 (s, 1H), 3.09-3.06 (m, 1H), 2.70 (dd, J_1 = 5 Hz, J_2 = 11.92 Hz, 1H), 2.62-2.46 (m, 7H), 2.34-2.30 (m, 5H), 2.02-1.96 (m, 1H), 1.78 (s, 4H), 1.69-1.55 (m, 5H), 1.49-1.48 (m, 2H), 1.31 (s, 8H), 0.91(t, J = 6.84 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 137.7, 136.5, 128.6, 128.1, 87.4, 76.4, 62.3, 59.5, 56.2, 54.9, 47.6, 31.9, 30.7, 29.3, 29.2, 29.1, 28.9, 23.5, 22.8, 22.7, 21.1, 18.8, 14.1.

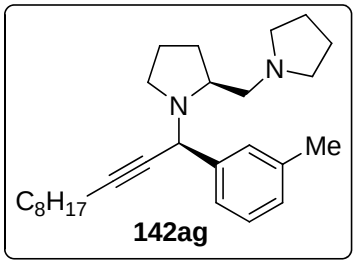
$[\alpha]_D^{25}$ - 81.859 (c, 1.19, $CHCl_3$).

MS (EI) m/z 395 $(M+1)^+$.

Analytical data calculated for $C_{27}H_{42}N_2$ C, 82.17; H, 10.73; N, 7.10.

Found C, 82.21; H, 10.81; N, 7.03.

(*S*)-2-(pyrrolidin-1-ylmethyl)-1-((*S*)-1-(m-tolyl)undec-2-yn-1-yl)pyrrolidine (142ag):



142ag

Yield 0.65 g (82%).

IR (Neat) (cm^{-1}) 2926, 2858, 2785, 1608, 1460, 1143, 754.

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.39-7.37 (m, 2H), 7.21 (t, J = 7.44 Hz, 1H), 7.05 (d, J = 7.28 Hz, 1H), 5.15 (s, 1H), 3.08-3.05 (m, 1H), 2.69 (dd, J_1 = 4.92 Hz, J_2 = 11.92 Hz, 1H),2.63-2.46 (m, 7H), 2.39-2.30 (m, 5H), 2.02-1.97 (m, 1H), 1.78 (s, 4H), 1.70-1.54 (m, 5H), 1.49-1.47 (m, 2H), 1.31-1.30 (m, 8H), 0.89 (t, J = 6.88 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.5, 137.5, 128.9, 127.9, 127.7, 125.3, 87.5, 76.3, 62.3, 59.6, 56.5, 55.0, 47.6, 31.9, 30.7, 29.3, 29.2, 28.9, 23.5, 22.73,22.70, 21.5, 18.8, 14.1.

$[\alpha]_D^{25}$ -80.183 (c, 0.7, $CHCl_3$).

MS (EI) m/z 395 $(M+1)^+$.

Analytical data calculated for $C_{27}H_{42}N_2$ C, 82.17; H, 10.73; N, 7.10.

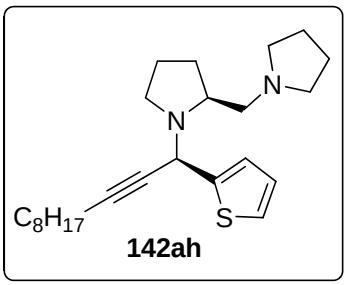
Found C, 82.06; H, 10.65; N, 7.18.

(*S*)-1-((*R*)-3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ah):

Yield 0.47 g (67%).

IR (Neat) (cm^{-1}) 2928, 1460, 1352, 1228, 1143, 696.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.21 (d, *J* = 5.04 Hz, 1H), 7.13-7.12 (m, 1H), 6.93-6.91 (m, 1H), 5.38 (s, 1H), 3.03 (q, *J* = 6.76 Hz, 1H), 2.73-2.46 (m, 8H), 2.32-2.28 (m, 2H), 1.99-1.93 (m, 1H), 1.76-1.53 (m, 9H), 1.47-1.43 (m, 2H), 1.29 (s, 8H), 0.89 (t, *J* = 6.88 Hz, 3H) **(Spectrum No. 37)**.



142ah

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 146.5, 126.0, 124.7, 86.6, 76.2, 62.3, 59.4, 55.0, 52.6, 48.0, 31.9, 30.6, 29.3, 29.2, 29.1, 28.9, 23.6, 22.9, 22.7, 18.7, 14.2 **(Spectrum No. 38)**.

$[\alpha]_D^{25}$ -119.72 (c, 1.09, $CHCl_3$).

MS (EI) m/z 351 $(M+1)^+$.

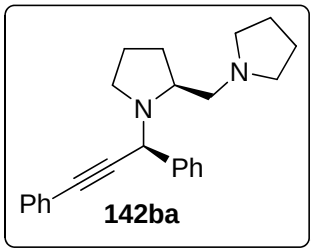
Analytical data calculated for $C_{22}H_{38}N_2S$ C, 74.55; H, 9.91; N, 7.25.

Found C, 74.39; H, 9.83; N, 7.35.

(*S*)-1-((*S*)-1,3-diphenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ba):

Yield 0.65 g (94%).

IR (Neat) (cm^{-1}) 3437, 3061, 3030, 1599, 1489, 1448, 756, 692.



142ba

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.66 (d, *J* = 7.56 Hz, 2H), 7.54-7.52 (m, 2H), 7.38-7.28 (m, 6H), 5.57 (s, 1H), 3.23-3.18 (m, 1H), 2.79 (dd, J_1 = 5.56 Hz, J_2 = 11.96 Hz, 1H), 2.73 (t, *J* = 8.56 Hz, 1H), 2.65-2.52 (m, 6H), 2.05-2.0 (m, 1H), 1.79 (s, 4H), 1.74-1.62 (m, 3H) **(Spectrum No. 39)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.0, 131.9, 128.4, 128.25, 128.2, 128.1, 127.3, 123.5, 87.6, 86.5, 62.3, 59.5, 57.0, 54.9, 47.9, 30.8, 23.6, 22.9 **(Spectrum No. 40)**.

$[\alpha]_D^{25}$ -120.79 (c, 0.91, $CHCl_3$).

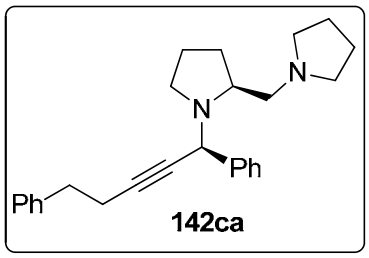
MS (EI) m/z 346 $(M+1)^+$.

Analytical data calculated for $C_{24}H_{28}N_2$ C, 83.68; H, 8.19; N, 8.13.

Found C, 83.56; H, 8.12; N, 8.25.

(*S*)-1-((*S*)-1,5-diphenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ca):

Yield 0.66 g (89%).



142ca

IR (Neat) (cm^{-1}) 3057, 3030, 2964, 1600, 1490, 1441, 695.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.52 (d, *J* = 7.32 Hz, 2H), 7.35-7.24 (m, 8H), 5.21 (s, 1H), 3.04-2.97 (m, 1H), 2.93 (t, *J* = 7.32 Hz, 2H), 2.71-2.66 (m, 3H), 2.58-2.42 (m, 8H), 1.98-1.91 (m, 1H), 1.79 (bs, 4H), 1.67-1.57 (m, 2H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.8, 140.5, 128.6, 128.4, 128.2, 128.0, 127.0, 126.2, 86.7, 62.4, 59.5, 56.4, 55.0, 47.5, 35.4, 30.6, 23.5, 22.7, 20.8.

$[\alpha]_D^{25}$ -87.702 (c, 0.12, $CHCl_3$).

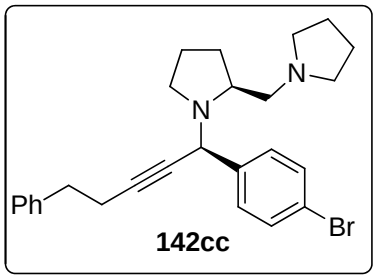
MS (EI) m/z 373 $(M+1)^+$.

Analytical data calculated fo $C_{26}H_{32}N_2$ C, 83.82; H, 8.66; N, 7.52.

Found C, 83.91; H, 8.72; N, 7.45.

(*S*)-1-((*S*)-1-(4-bromophenyl)-5-phenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142cc):

Yield 0.70 g (78%).



142cc

IR (Neat) (cm^{-1}) 3030, 2962, 2868, 2789, 1604, 1485, 1010, 744, 698.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.41-7.22 (m, 9H), 5.16 (s, 1H), 2.98-2.95 (m, 1H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.69-2.64 (m, 3H), 2.58-2.43 (m, 6H), 2.39-2.34 (m, 1H), 1.94-1.89 (m, 1H), 1.79-1.75 (m, 4H), 1.63-1.55 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.6, 139.6, 130.1, 129.9, 128.6, 128.4, 126.3, 120.7, 87.1, 76.6, 62.4, 59.3, 55.9, 55.0, 47.4, 35.3, 30.5, 23.5, 22.7, 20.7.

$[\alpha]_D^{25}$ - 56.560 (c, 0.1, $CHCl_3$).

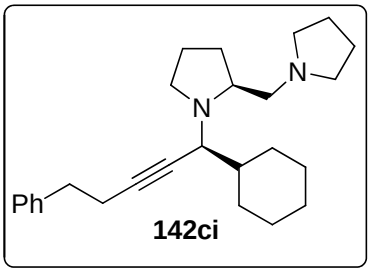
MS (EI) m/z 451 (M^+).

Analytical data calculated for $C_{26}H_{31}BrN_2$ C, 69.17; H, 6.92; N, 6.21.

Found C, 69.05; H, 6.87; N, 6.28.

(*S*)-1-((*R*)-1-cyclohexyl-5-phenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142ci):

Yield 0.73 g (96%).



142ci

IR (Neat) (cm^{-1}) 3063, 3028, 2922, 2851, 2785, 1670, 1604, 1496, 1450, 744, 698.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.32-7.20 (m, 5H), 3.30 (d, *J* = 10 Hz, 1H), 2.85-2.80 (m, 3H), 2.70-2.66 (m, 1H), 2.57-2.48 (m, 7H), 2.43-2.32 (m, 2H), 1.97-1.96 (m,

2H), 1.89-1.85 (m, 1H), 1.76-1.55 (m, 10H), 1.34-1.14 (m, 4H), 0.93-0.85 (m, 2H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.9, 128.5, 128.2, 126.1, 84.4, 78.8, 62.1, 59.9, 58.6, 54.9, 46.8, 41.3, 35.7, 31.4, 30.5, 30.4, 26.9, 26.2, 26.0, 23.5, 23.3, 20.8.

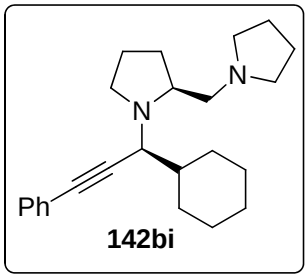
$[\alpha]_D^{25}$ -93.978 (c, 1.02 $CHCl_3$).

MS (EI) m/z 380 $(M+1)^+$.

Analytical data calculated for $C_{26}H_{38}N_2$ C, 82.48; H, 10.12; N, 7.40.

Found C, 82.36; H, 10.18; N, 7.31.

(*S*)-1-((*R*)-1-cyclohexyl-3-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (142bi):



142bi

Yield 0.67 g (96%).

IR (Neat) (cm^{-1}) 3435, 2924, 2787, 1599, 1489, 1446, 754, 690.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.43-7.41 (m, 2H), 7.31-7.27 (m, 3H), 3.61 (d, *J* = 10.04 Hz, 1H), 3.03-2.96 (m, 1H), 2.84-2.79 (m, 1H), 2.72 (q, *J* = 8.44 Hz, 1H), 2.53-2.37 (m, 6H), 2.12-1.92 (m, 3H), 1.76-1.48 (m, 13H), 1.30-1.19 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 131.7, 128.2, 127.6, 123.9, 88.5, 85.6, 62.1, 60.2, 59.1, 55.0, 47.2, 41.3, 31.5, 30.6, 30.5, 26.9, 26.2, 26.0, 23.6, 23.5.

$[\alpha]_D^{25}$ -142.06 (c, 0.83, $CHCl_3$).

MS (EI) m/z 352 $(M+1)^+$.

Analytical data calculated for $C_{24}H_{34}N_2$ C, 82.23; H, 9.78; N, 7.99.

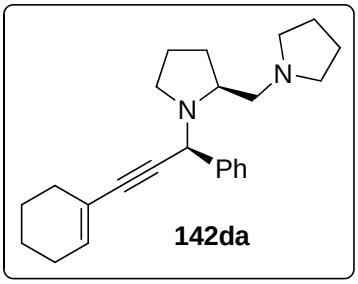
Found C, 82.15; H, 9.86; N, 7.91.

(*S*)-1-((*S*)-3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl) pyrrolidine (142da):

Yield 0.61 g (88%).

IR (Neat) (cm^{-1}) 3061, 3028, 2930, 2785, 1491, 1448, 1136, 702.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.58 (d, J = 7.48 Hz, 2H), 7.34-7.21 (m, 4H), 6.16-6.14 (m, 1H), 5.37 (s, 1H), 3.12-3.07 (m, 1H), 2.72 (dd, J_1 = 5.4 Hz, J_2 = 12 Hz, 1H), 2.65-2.47 (m, 6H), 2.22-2.11 (m, 4H), 2.01-1.96 (m, 1H), 1.77-1.58 (m, 11H).



142da

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.4, 134.0, 128.2, 128.0, 127.0, 120.8, 89.4, 83.3, 62.4, 59.6, 56.9, 55.0, 47.7, 30.6, 29.8, 25.6, 23.6, 22.8, 22.4, 21.6.

$[\alpha]_D^{25}$ -115.58 (c 1.18, $CHCl_3$).

MS (EI) m/z 350 $(M+1)^+$.

Analytical data calculated for $C_{24}H_{32}N_2$ C, 82.71; H, 9.25; N, 8.04.

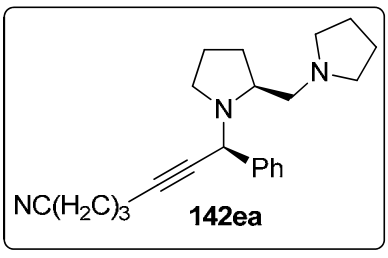
Found C, 82.65; H, 9.21; N, 8.12.

(*S*)-7-phenyl-7-((*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)hept-5-ynenitrile (142ea):

Yield 0.52 g (78%).

IR (Neat) (cm^{-1}) 3059, 3030, 2922, 2868, 2797, 2247, 1493, 1450, 702, 665.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.54 (d, J = 7.4 Hz,



142ea

2H), 7.35-7.31 (m, 2H), 7.25-7.23 (m, 1H), 5.27 (s, 1H), 3.04-2.99 (m, 1H), 2.71 (dd, J_1 = 5.36 Hz, J_2 = 12 Hz, 1H), 2.57-2.48 (m, 11H), 1.98-1.90 (m, 3H), 1.77 (s, 4H), 1.68-1.61 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.1, 128.1, 128.0, 127.2, 119.1, 84.4, 78.6, 62.3, 59.6, 56.4, 55.0, 47.8, 30.6, 25.0, 23.5, 22.8, 18.0, 16.2.

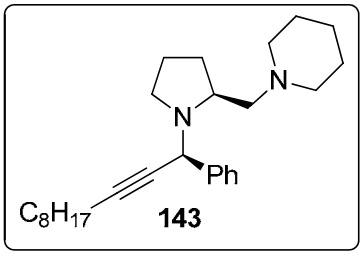
$[\alpha]_D^{25}$ -104.22 (c, 0.96 $CHCl_3$).

MS (EI) m/z 336 $(M+1)^+$.

Analytical data calculated for $C_{22}H_{29}N_3$ C, 78.76; H, 8.71; N, 12.53.

Found C, 78.85; H, 8.65; N, 12.45.

1-(((*S*)-1-((*S*)-1-phenylundec-2-yn-1-yl)pyrrolidin-2-yl)methyl)piperidine (143):



143

Yield 0.57 g (68%).

IR (Neat) (cm^{-1}) 3061, 3028, 1726, 1602, 1493, 1450, 1124, 725, 700.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.58 (d, J = 7.4 Hz, 2H), 7.33-7.21 (m, 3H), 5.42 (s, 1H), 3.13-3.08 (m, 1H), 2.62 (dd, J = 8.64 Hz, 17.16 Hz, 1H), 2.65-2.30 (m, 8H), 2.17 (s, 1H), 1.94-1.88 (m, 1H), 1.65-1.43 (m, 13H), 1.30 (s, 8H), 0.89-0.88 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.9, 128.2, 127.9, 126.9, 87.4, 76.4, 65.8, 57.4, 56.6, 55.4, 47.7, 31.9, 30.6, 29.3, 29.2, 29.1, 28.9, 26.2, 24.6, 22.73, 22.70, 18.8, 14.1.

$[\alpha]_D^{25}$ -76.043 (c 0.81, $CHCl_3$).

MS (EI) m/z 396 $(M+1)^+$.

Analytical data calculated for $C_{27}H_{42}N_2$ C, 82.17; H, 10.73; N, 7.10.

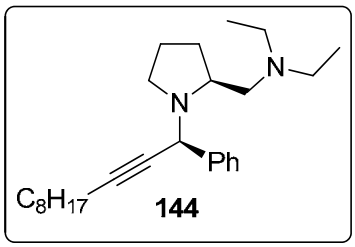
Found C, 82.35; H, 10.62; N, 7.18.

***N*-ethyl-*N*-(((*S*)-1-((*S*)-1-phenylundec-2-yn-1-yl)pyrrolidin-2-yl)methyl)ethanamine (144)**:

Yield 0.47 g (61%).

IR (Neat) (cm^{-1}) 3061, 2959, 2928, 1493, 1450, 1383, 1327, 698.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.58 (d, *J* = 7.4 Hz, 2H), 7.33-7.23 (m, 3H), 5.33 (s, 1H), 3.08-3.06 (m, 1H), 2.61-2.41 (m, 8H), 2.33-2.30 (m, 2H), 1.98-1.91 (m, 1H), 1.66-1.54 (m, 5H), 1.47-1.46 (m, 2H), 1.29 (s, 8H), 1.06 (t, *J* = 6.92 Hz, 6H), 0.89 (t, *J* = 6.88 Hz, 3H).



144

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 140.8, 128.2, 127.9, 126.9, 87.5, 76.3, 59.5, 58.4, 56.6, 48.0, 47.9, 31.9, 30.6, 29.4, 29.3, 29.0, 22.8, 22.6, 18.8, 14.2, 12.1.

$[\alpha]_D^{25}$ -89.278 (c 1.15, $CHCl_3$).

MS (EI) m/z 383 $(M+1)^+$.

Analytical data calculated for $C_{26}H_{42}N_2$ C, 81.61; H, 11.06; N, 7.32.

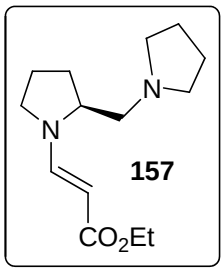
Found C, 81.49; H, 11.15; N, 7.21.

4.10 Procedure for the synthesis of (*S,E*)-ethyl 3-(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)acrylate (157):

To the chiral diamine 2-(pyrrolidin-1-ylmethyl)pyrrolidine **138** (0.31 g, 2.0 mmol) in dry toluene (3 mL) was added ethylpropiolate (0.2 g, 2.0 mmol) at 25 ˚C slowly and stirred further for 15

min. Toluene was removed under reduced pressure and the crude product was purified on basic aumina. The enamine adduct **155** was eluted using hexane: ethylacetate (80:20).

Yield 0.44 g (88%).



IR (Neat) (cm^{-1}) 3503, 2972, 2791, 1685, 1608, 1460, 787, 733.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.75-7.72 (m, 2H), 4.47 (d, *J* = 12.84 Hz, 1H), 4.12-4.07 (m, 2H), 3.64-3.62 (m, 1H), 3.18-3.11 (m, 2H), 2.53-2.42 (m, 5H), 1.96-1.74 (m, 8H), 1.25-1.21 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 169.7, 148.6, 84.9, 60.6, 58.7, 58.6, 54.6, 29.6, 23.5, 23.2, 14.7.

$[\alpha]_D^{25}$ -43.918 (c 0.58, $CHCl_3$).

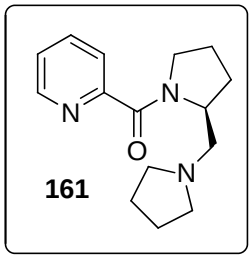
MS (EI) m/z 253 $(M+1)^+$.

Analytical data calculated for $C_{14}H_{24}N_2O_2$ C, 66.63; H, 9.59; N, 11.10.

Found C, 66.51; H, 9.52; N, 11.21.

4.11 Synthesis of (*S*)-2-((2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)pyridine (162)

4.11a (*S*)-pyridin-2-yl(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methanone (161):



To an oven dried round bottom flask, ZnI_2 (0.4 mmol) and ethyl picolinate (0.3 g, 2 mmol) in dry tolene (4 mL) was added to the 2-(pyrrolidin-1-ylmethyl)pyrrolidine **139** (0.31 g, 2 mmol) under N_2 atmosphere. The contents were refluxed at 110 ˚C for 12 h. The volatile contents were removed under reduced pressure and the crude product was purified on basic alumin using 1:1 mixture of hexane and ethylacetate.

Yield 0.42 g (82%).

IR (Neat) (cm^{-1}) 3495, 3057, 2964, 2797, 1626, 1410, 1149, 812, 750.

^1H NMR (400 MHz, ppm, $CDCl_3$) 8.56 (s, 1H), 7.78 (s, 2H), 7.33 (s, 1H), 4.83-4.48 (m, 1H), 3.87-3.57 (m, 2H), 2.86-2.32 (m, 5H), 2.05-1.58 (m, 9H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 166.1, 166.0, 154.4, 154.2, 147.4, 147.1, 136.2, 124.1, 124.0, 123.5, 123.2, 58.9, 57.6, 56.8, 56.4, 54.0, 53.7, 48.8, 45.9, 28.9, 28.1, 24.2, 23.0, 22.9, 20.8.

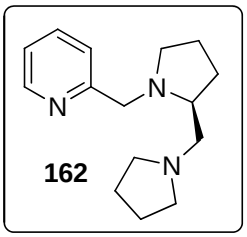
$[\alpha]_D^{25}$ -117.21 (c 0.61, $CHCl_3$).

MS (EI) m/z 260 $(M+1)^+$.

Analytical data calculated for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20.

Found : C, 69.32; H, 8.09; N, 16.31.

4.11b (*S*)-2-((2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)pyridine (162):



162

To an oven dried reaction flask, (*S*)-pyridin-2-yl(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methanone **161** (0.52 g, 2.0 mmol) dissolved in dry THF (10 mL) was added to the suspension of $LiAlH_4$ (0.15 g, 4.0 mmol) in dry THF (10 mL) at 0 ˚C. The contents were refluxed for 12 h. and cooled to 25 ˚C. The contents were poured on saturated Na_2SO_4 (10 mL) and washed the insoluble contents with ethylacetate (2 X 20 mL). Precipitates were removed and the contents were evaporated under reduced pressure. The crude product was purified on basic alumina using 1:1 mixture of hexane and ethylacetate.

Yield 0.34 g (70%).

IR (Neat) (cm^{-1}) 3055, 2961, 2789, 1589, 1570, 1433, 758.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 8.54-8.53 (m, 1H), 7.64 (t, *J* = 7.64 Hz, 1H), 7.42 (d, *J* = 7.72 Hz, 1H), 7.14 (t, *J* = 6.88 Hz, 1H), 4.27 (d, *J* = 13.72 Hz, 1H), 3.50 (d, *J* = 13.76 Hz, 1H), 2.98-2.94 (m, 1H), 2.69-2.64 (m, 2H), 2.52-2.47 (m, 4H), 2.28-2.21 (m, 2H), 1.75 (bs, 8H). **(Spectrum No. 41)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 160.1, 148.9, 136.2, 123.0, 121.6, 63.2, 61.8, 61.2, 54.8, 54.6, 30.4, 23.4, 22.7. **(Spectrum No. 42)**.

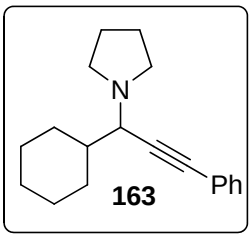
$[\alpha]_D^{25}$ -126.05 (c 0.44, $CHCl_3$).

MS (EI) m/z 246 $(M+1)^+$.

Analytical data calculated for $C_{15}H_{23}N_3$ C, 73.43; H, 9.45; N, 17.13.

Found C, 73.57; H, 9.38; N, 17.06.

4.12 Procedure for the preparation of one pot three component preparation of propargylamine 1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)pyrrolidine (163):



163

To an oven dried round bottom flask, CuBr (57 mg, 0.4 mmol) and chiral amine **162** (0.12 g, 0.5 mmol) in toluene (4 mL) was added and stirred at 25 ˚C for 15 min under N_2 atmosphere. To this mixture, pyrrolidine (0.14 g, 2.0 mmol) and cyclohexyl cabroxaldehyde (0.22 g, 2.0 mmol) was added in dry toluene (4 mL). The oven dried molecular sieves (1.0 g, 4 Å) and phenyl acetylene (0.20 g, 2.0 mmol) were added and stirred for 36 h at 25 ˚C. The volatile contents were removed under reduced pressure and the crude product was purified on basic alumina using hexane as eluent.

Yield 0.48 g (89%)

IR (Neat) (cm^{-1}) 3055, 2925, 2852, 2193, 1598, 1489, 1448, 1260, 1130, 755, 691.

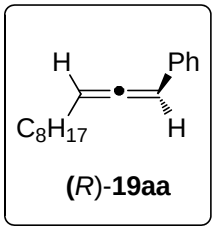
^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.46-7.41 (m, 2H), 7.31-7.25 (m, 3H), 3.36 (d, *J* = 10.4 Hz, 1H), 2.81-2.71 (m, 2H), 2.70-2.62 (m, 2H), 2.14-2.06 (m, 2H), 2.01-1.93 (m, 2H), 1.84-1.73 (m, 4H), 1.72-1.64 (m, 1H), 1.64-1.53 (m, 1H), 1.31-0.86 (m, 5H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 131.9, 128.4, 127.9, 123.9, 88.1, 86.0, 61.5, 50.2, 41.5, 30.9, 30.5, 26.9, 26.48, 26.46, 23.8.

4.4.13 Synthesis of chiral allenes from chiral proline derived propargylamines

The chiral propargylamine **142** (0.5 mmol) was added to a stirred suspension of CuI (48 mg, 0.25 mmol) in dry dioxane (2 mL) and the contents were refluxed for 18 h at 100 ˚C under nitrogen atmosphere. Dioxane was removed under reduced pressure and the crude product was purified on silica gel (100-200) using hexane as eluent to isolate the chiral allene (-)-(*R*)-**19**.

(*R*)-1-phenyl-1,2-undecadiene (19aa):



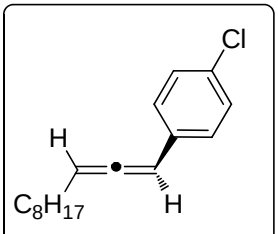
(*R*)-19aa

Yield 0.07 g (62%).

HPLC 99% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*R*)= 3.9 min, t_R(*S*)= 4.3 min).

$[\alpha]_D^{25}$ -227.10 (c, 0.4, $CHCl_3$).

(*R*)-1-(4-chloro-phenyl)-1,2-undecadiene (19ab):



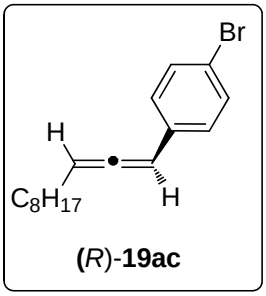
(*R*)-19ab

Yield 0.08 g (65%).

HPLC 98% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 3.3 min, t_R(*R*)= 4.2 min).

$[\alpha]_D^{25}$ -215.0 (c, 0.4, $CHCl_3$).

(*R*)-1-(4-bromo-phenyl)-1,2-undecadiene (19ac):



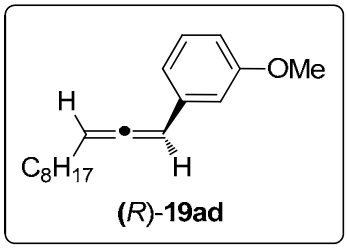
(*R*)-19ac

Yield 0.22 g (71%).

HPLC 96% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 3.5 min, t_R(*R*)= 5.3 min).

$[\alpha]_D^{25}$ -189.89 (c, 0.60, $CHCl_3$).

(*R*)-1-(3-methoxy-phenyl)-1,2-undecadiene (19ad):



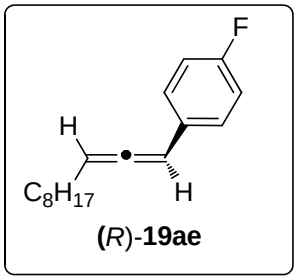
(*R*)-19ad

Yield 0.08 g (62%).

HPLC 94% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 0.5 mL/min, 254 nm, t_R(*R*)= 8.8 min, t_R(*S*)= 10.2 min).

$[\alpha]_D^{25}$ -201.1 (c, 0.60, $CHCl_3$).

(*R*)-1-(4-fluoro-phenyl)-1,2undecadiene (19ae):



(*R*)-19ae

Yield 0.08 g (67%).

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

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.26-7.23 (m, 2H), 7.01-6.97 (m, 2H), 6.11- 6.09 (m, 1H), 5.58 (q, *J* = 6.64 Hz, 1H), 2.16-2.10 (m, 2H), 1.52-1.45 (m, 2H), 1.37-1.28 (m, 10H), 0.89 (t, *J* = 7.08 Hz, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 204.9, 162.9, 160.5, 131.1, 127.9, 127.8, 115.5, 115.3, 95.4, 93.6, 29.4, 29.3, 29.2, 29.1, 28.8, 22.7, 14.1.

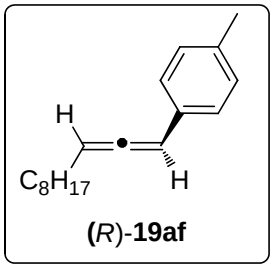
HPLC 98% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 4.4 min, t_R(*R*)= 4.8 min).

$[\alpha]_D^{25}$ -146.58 (c, 0.49, $CHCl_3$).

Analytical data calculated for $C_{17}H_{23}F$ C, 82.88; H, 9.41.

Found C, 82.65; H, 9.36.

(*R*)-1-(4-methyl-phenyl)-1,2-undecadiene (19af):



(*R*)-19af

Yield 0.08 g (66%).

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

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.21 (d, *J* = 8.04 Hz, 2H), 7.12 (d, *J* = 7.92 Hz, 2H), 6.13-6.11 (m, 1H), 5.56 (q, *J* = 6.6 Hz, 1H), 2.35 (s, 3H), 2.17-2.10 (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, ppm, $CDCl_3$) 204.9, 136.3, 132.2, 129.3, 126.5, 95.0, 94.3, 31.9, 29.4, 29.3, 29.2, 28.9, 22.7, 21.1, 14.1.

HPLC 98% ee (Daicel Chiralcel OJ-H, Heptane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*R*)= 4.9 min, t_R(*S*)= 5.5 min).

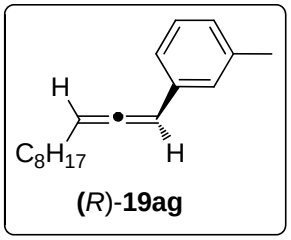
$[\alpha]_D^{25}$ -147.40 (c, 0.41, $CHCl_3$).

MS (EI) m/z 243 $(M+1)^+$.

Analytical data calculated for $C_{18}H_{26}$ C, 89.19; H, 10.81.

Found C, 89.26; H, 10.76.

(*R*)-1-(3-Methyl-phenyl)-1,2-undecadiene (19ag):



(*R*)-19ag

Yield 0.07 g (59%).

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

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.28-7.22 (m, 1H), 7.16-7.14 (d, *J* = 8 Hz, 2H), 7.05-7.04 (d, *J* = 4.0 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 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.1, 138.1, 135.1, 128.4, 127.4, 127.2, 123.8, 94.9, 94.5, 31.9, 29.4, 29.3, 29.2, 29.1, 28.8, 22.7, 21.4, 14.1.

HPLC 96% ee (Daicel Chiralcel OJ-H, Hexane:^{i}PrOH 100:0, flowrate 1.0 mL/min, 254 nm, t_R(*R*)= 5.8 min, t_R(*S*)= 8.3 min).

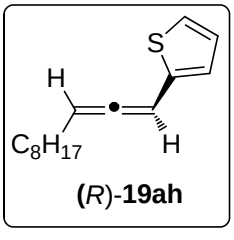
$[\alpha]_D^{25}$ -147.11 (c, 0.31, $CHCl_3$).

MS (EI) m/z 243 $(M+1)^+$.

Analytical data calculated for $C_{18}H_{26}$ C, 89.19; H, 10.81.

Found C, 89.06; H, 10.75.

(*R*)-1-(2-thienyl)undeca-1,2-diene (19ah):



(*R*)-19ah

Yield 0.07 g (58%).

IR (Neat) (cm^{-1}) 3068, 2925, 2848, 1950, 1456, 1374, 1265, 1034, 854.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.15 (d, *J* = 4.88 Hz, 1H), 6.96-6.94 (m, 1H), 6.90-6.88 (m, 1H), 6.37-6.34 (m, 1H), 5.57 (q, *J* = 6.6 Hz, 1H), 2.16-2.10 (m, 2H), 1.53-1.46 (m, 2H), 1.39-1.28 (m, 10H), 0.91-0.88 (m, 3H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 204.5, 139.8, 127.3, 124.2, 124.1, 95.5, 89.0, 31.9, 29.4, 29.3, 29.2, 29.0, 28.9, 22.7, 14.1.

HPLC 94% ee (Daicel Chiralcel OB-H, Hexane:^{i}PrOH 100:0, flowrate 0.3 mL/min, 254 nm, t_R(*S*)= 16.3 min, t_R(*R*)= 18.0 min).

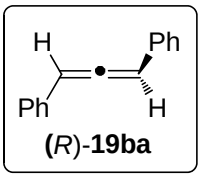
$[\alpha]_D^{25}$ -205.39 (c, 0.3, $CHCl_3$).

MS (EI) m/z 235 $(M+1)^+$.

Analytical data calculated for $C_{15}H_{22}S$ C, 76.86; H, 9.46.

Found C, 76.95; H, 9.38.

(*R*)-1,3-diphenyl-propane1,2-diene (19ba):



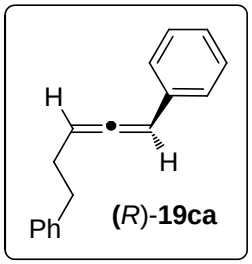
(*R*)-19ba

Yield 0.05 g (56%).

HPLC 85% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.0 mL/min, 254 nm, t_R(*R*)= 11.0 min, t_R(*S*)= 14.4 min).

$[\alpha]_D^{25}$ -390.4 (c, 0.3, $CHCl_3$).

(*R*)-1,5-Diphenyl-penta-1,2-diene (19ca):



(*R*)-19ca

Yield 0.07 g (64%).

IR (Neat) (cm^{-1}) 2928, 2856, 1945, 1698, 1325, 844.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.32-7.16 (m, 10H), 6.14-6.11 (m, 1H), 5.60 (q, *J* = 6.6 Hz, 1H), 2.86-2.79 (m, 2H), 2.51-2.43 (m, 2H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.3, 141.6, 134.9, 128.6, 128.5, 128.4, 126.7, 126.6, 125.9, 95.0, 94.4, 35.4, 30.6.

HPLC 97% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*R*)= 9.6 min, t_R(*S*)= 11.1 min).

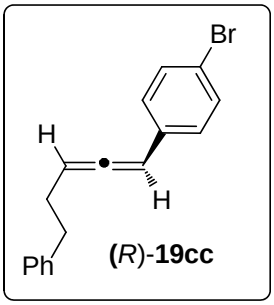
$[\alpha]_D^{25}$ -238.45 (c, 0.48, $CHCl_3$).

MS (EI) m/z 221 (M^+).

Analytical data calculated for $C_{17}H_{16}$ C, 92.68; H, 7.32.

Found C, 92.48; H, 7.38.

(*R*)-1-(4-bromophenyl),5-phenyPenta-1,2-diene (19cc):



(*R*)-19cc

Yield 0.09 g (61%).

IR (Neat) (cm^{-1}) 2928, 2856, 1951, 1616, 1325, 844.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.36 (d, *J* = 8.36 Hz, 2H), 7.29-7.20 (m, 5H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.07-6.04 (m, 1H), 5.58 (q, *J* = 6.68 Hz, 1H), 2.84-2.76 (m, 2H), 2.52-2.42 (m, 2H). **(Spectrum No. 43)**.

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.4, 141.4, 133.9, 131.6, 128.6, 128.4, 128.2, 126.0, 120.2, 94.8, 94.1, 35.3, 30.4. **(Spectrum No. 44)**.

HPLC 96% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 100:0, flowrate 1.5 mL/min, 254 nm, t_R(*S*)= 11.1 min, t_R(*R*)= 13.7 min).

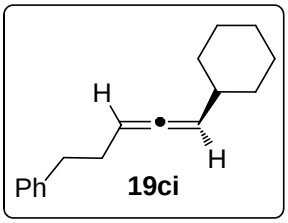
$[\alpha]_D^{25}$ -175.54 (c, 0.67, $CHCl_3$).

MS (EI) m/z 300 $(M+2)^+$.

Analytical data calculated for $C_{17}H_{15}Br$ C, 68.24; H, 5.05.

Found C, 68.36; H, 5.12.

(*R*)-5-(Cyclohexyl)-1-phenyl-penta-3,4-diene (19ci):



Yield 0.07 g (60%).

IR (Neat) (cm^{-1}) 3026, 2924, 2851, 1959, 1728, 1450, 1057

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.32-7.20 (m, 5H), 5.19-5.17 (m, 1H), 5.12-5.10 (m, 1H), 2.76-2.72 (m, 2H), 2.34-2.32 (m, 2H), 1.92-1.84 (m, 1H), 1.73-1.63 (m, 4H), 1.38-1.26 (m, 6H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 202.8, 142.0, 128.5, 128.4, 128.2, 125.8, 97.6, 91.7, 37.2, 35.5, 33.0, 32.9, 30.8, 29.7, 26.2, 26.0.

HPLC 98% ee (Daicel Chiralcel OJ-H, Hexane:^{i}PrOH 100:0, flowrate 0.3 mL/min, 215 nm, t_R(*S*)= 18.8 min, t_R(*R*)= 19.8 min).

$[\alpha]_D^{25}$ -195.0 (c, 0.45, $CHCl_3$).

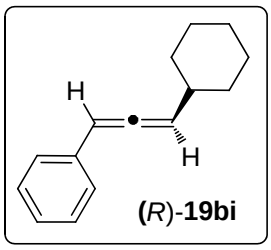
MS (EI) m/z 226 (M^+).

Analytical data calculated for $C_{17}H_{22}$ C, 90.20; H, 9.80.

Found C, 90.35; H, 9.71.

(*R*)-(3-cyclohexylpropa-1,2-dien-1-yl)benzene (19bi):

Yield 0.06 g (65%).



IR (Neat) (cm^{-1}) 3032, 2923, 2851, 1940, 1722, 1593, 1490, 1443, 765, 682.

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.31-7.28 (m, 4H), 7.21-7.18 (m, 1H), 6.17 (dd, *J* = 6.4 Hz, 2.8 Hz, 1H), 5.59 (t, *J* = 6.4 Hz, 1H), 2.19-2.09 (m, 1H), 1.87-1.73 (m, 5H), 1.30-1.20 (m, 5H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 204.1, 135.2, 128.5, 126.6, 126.4, 101.1, 95.4, 37.6, 33.2, 26.1.

HPLC 99% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 99:1, flow rate 0.3 mL/min).

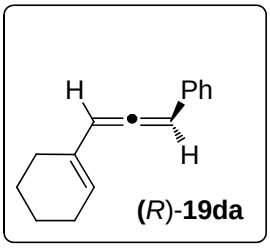
$[\alpha]_D^{25}$ -176.62 (c, 0.38, $CHCl_3$).

MS (EI) m/z 199 $(M+1)^+$.

Analytical data calculated for $C_{15}H_{18}$ C, 90.85; H, 9.15.

Found C, 90.76; H, 9.23.

(*R*)-3-(Cyclohex-1-enyl)-1-phenylpropan-1,2-diene (19da):



Yield 0.06 g (58%).

IR (Neat) (cm^{-1}) 3028, 2924, 2858, 2858, 1930, 1599, 1493, 1074.

^1H NMR (400 MHz, ppm, $CDCl_3$) 7.39-7.28 (m, 4H), 7.23-7.18 (m, 1H), 6.41-6.40 (d, *J* = 4 Hz, 1H), 6.27-6.26 (d, *J* = 4 Hz, 1H), 5.78 (s, 1H), 2.15-2.00 (m, 4H), 1.66-1.54 (m, 4H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 206.4, 142.0, 128.5, 128.4, 128.2, 125.8, 97.6, 91.7, 37.2, 35.5, 33.0, 32.9,30.8, 29.7, 26.2, 26.0.

HPLC 97% ee (Daicel Chiralcel OD-H, Hexane:^{i}PrOH 99:1, flow rate 0.3 mL/min, 215 nm, t_R(*S*)= 14.0 min, t_R(*R*)= 16.6 min).

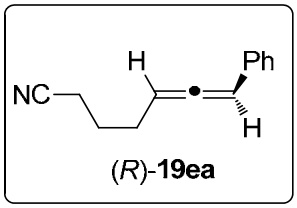
$[\alpha]_D^{25}$ -192.43 (c, 0.42 $CHCl_3$).

MS (EI) m/z 197 $(M+1)^+$.

Analytical data calculated for $C_{15}H_{16}$ C, 91.78; H, 8.22.

Found C, 91.65; H, 8.31.

(*R*)-7-Phenyl-1-cyano-heptan-5,6-diene (19ea):



(*R*)-**19ea**

Yield 0.07 g (81%).

IR (Neat) (cm^{-1}) 3296, 2941, 2247, 1950, 1597, 1494, 1263, 1074, 881.

^{1}H NMR (400 MHz, ppm, $CDCl_3$) 7.34-7.21 (m, 5H), 6.23-6.21 (m, 1H), 5.61- 5.56 (d, *J* = 8.0 Hz, 1H), 2.53-2.39 (m, 2H), 2.0-1.96 (m, 2H), 1.92-1.87 (m, 2H).

^{13}C NMR (100 MHz, ppm, $CDCl_3$) 205.3, 134.3, 128.7, 127.1, 126.5, 95.8, 93.0, 27.3, 24.5, 17.5.

HPLC 89% ee; Chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1 mL/min., 254 nm, retention times: t_R(*S*) = 19.6 min. and t_R(*R*) = 22.1 min.

$[\alpha]_D^{25}$ -126.5 (c, 0.4 $CHCl_3$).

MS (EI) m/z 184 $(M+1)^+$.

Analytical data calculated for $C_{13}H_{13}N$ C, 85.21; H, 7.15; N, 7.64.

Found C, 85.36; H, 7.21; N, 7.54.

4.5. References

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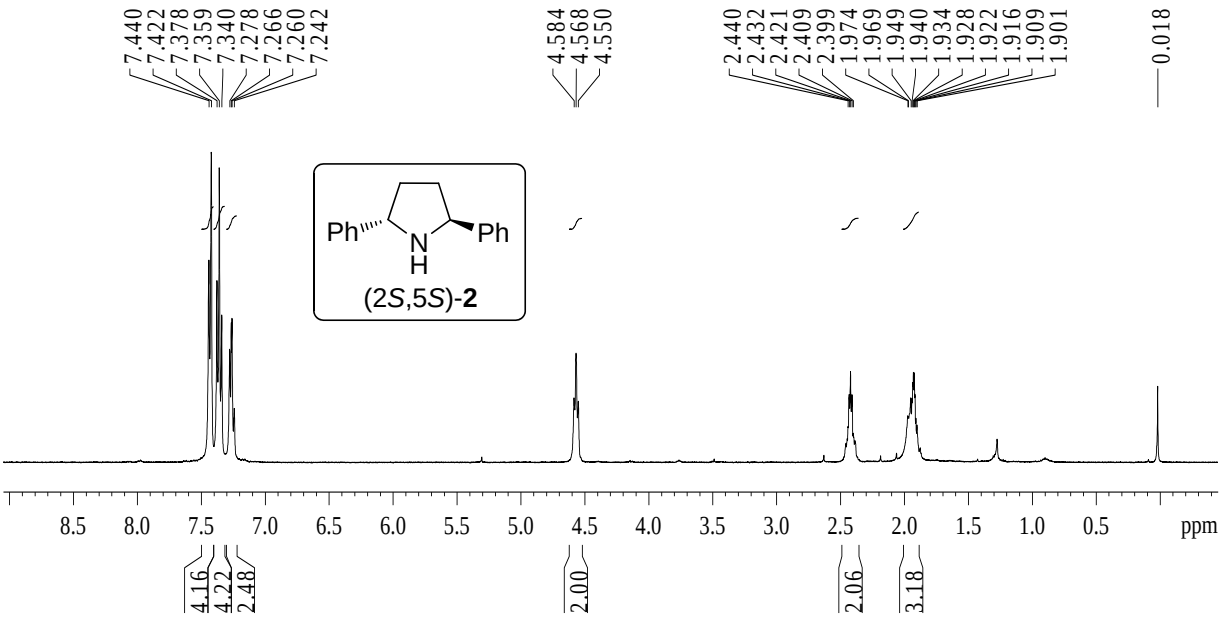
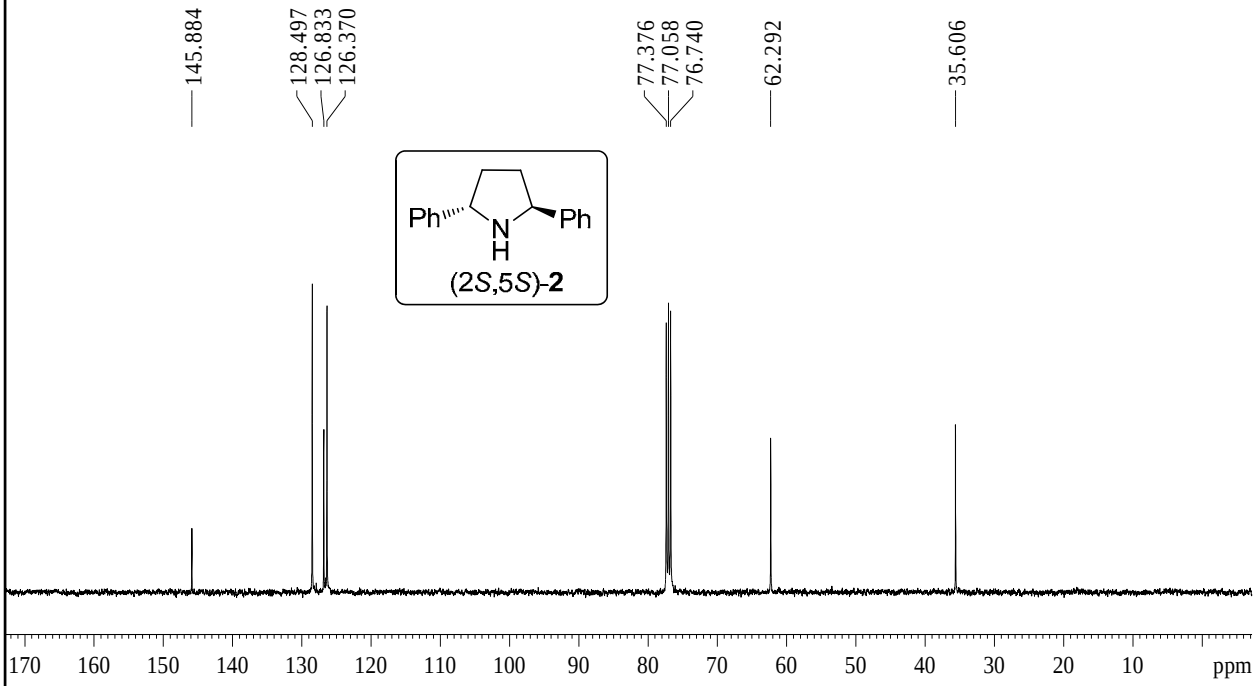
Appendix I

(Representative Spectra)

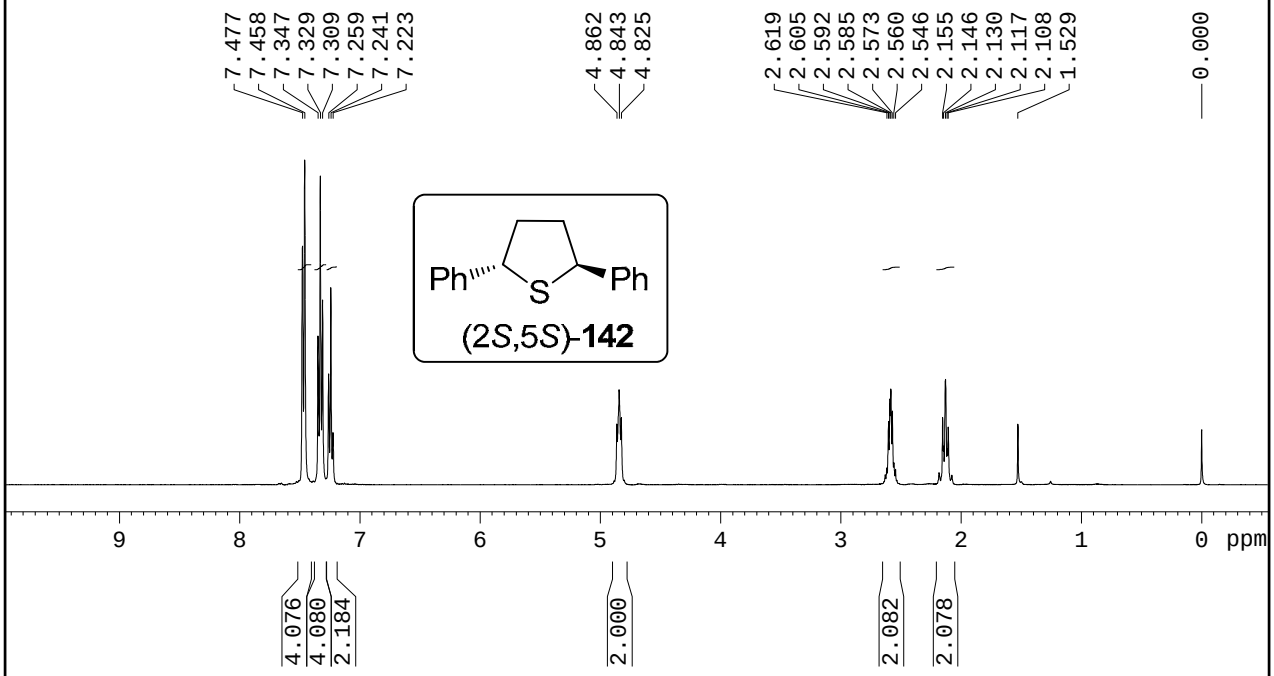
Spectrum No. 1 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



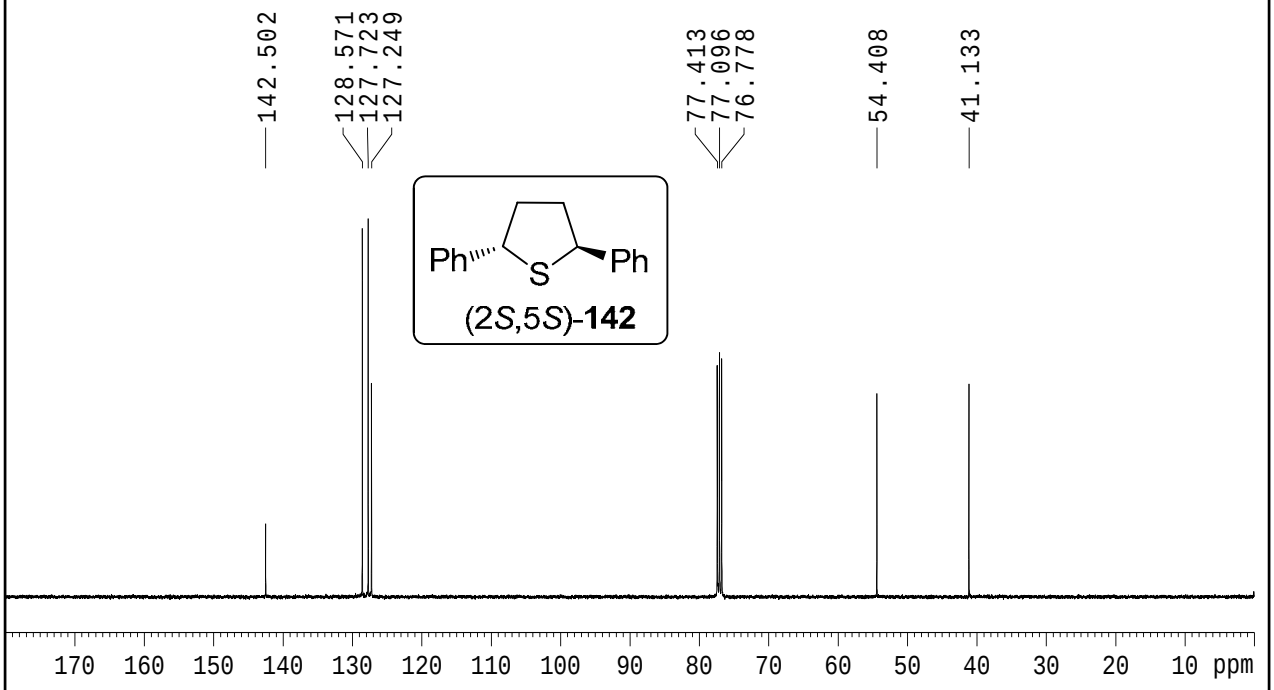
Spectrum No. 2 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



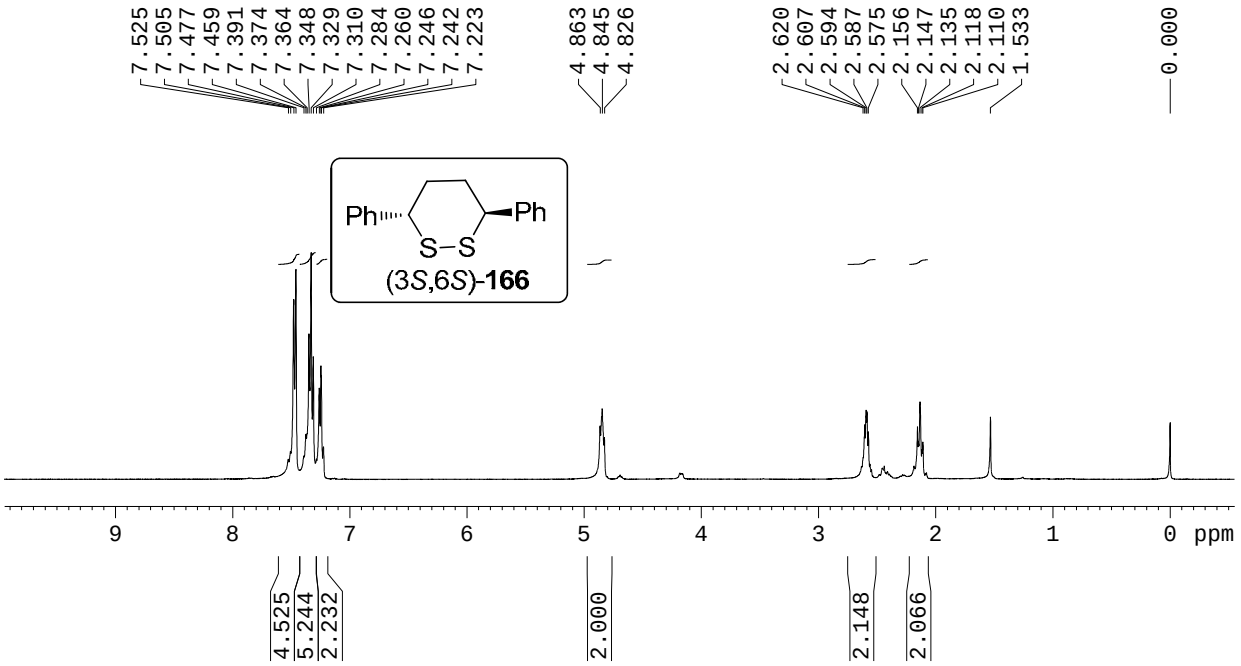
Spectrum No. 3 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



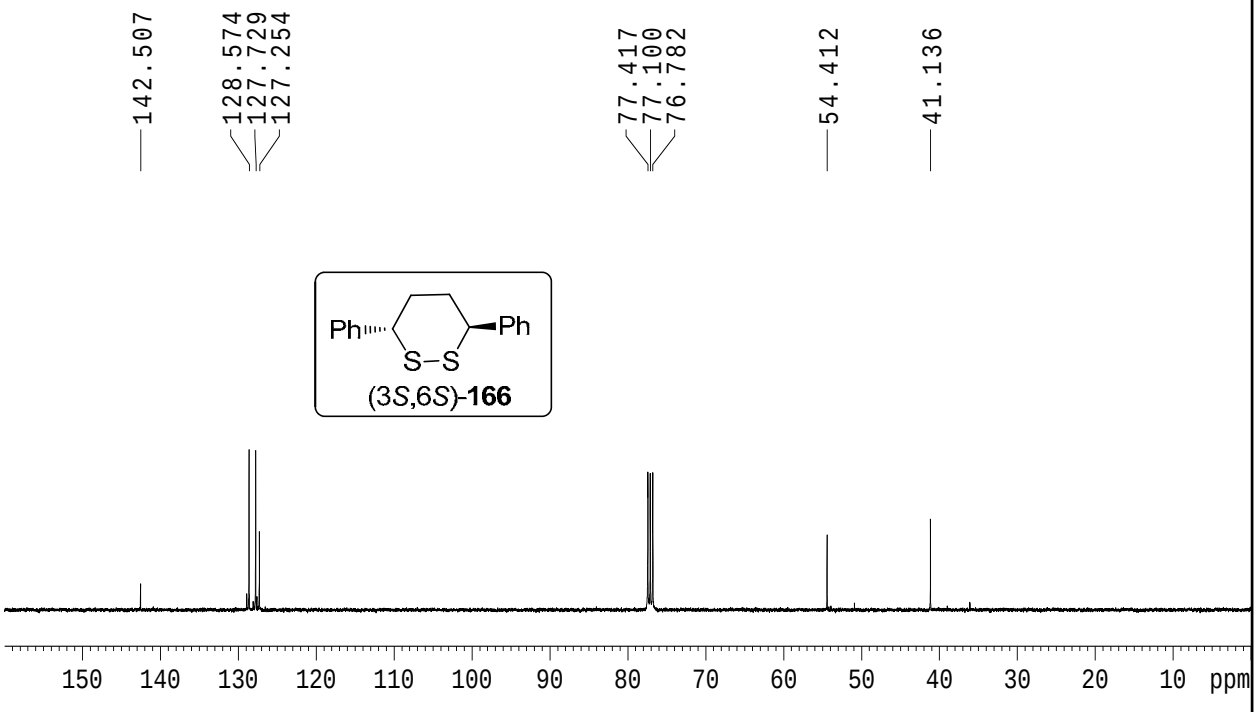
Spectrum No. 4 (Chapter 3, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



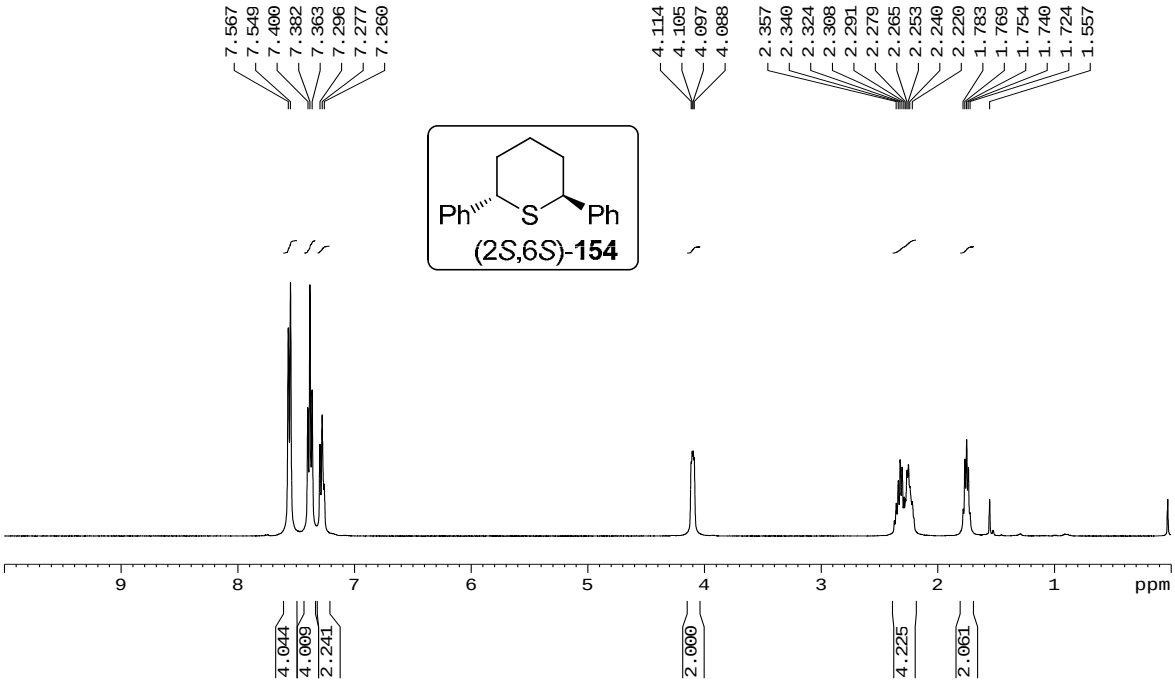
Spectrum No. 5 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



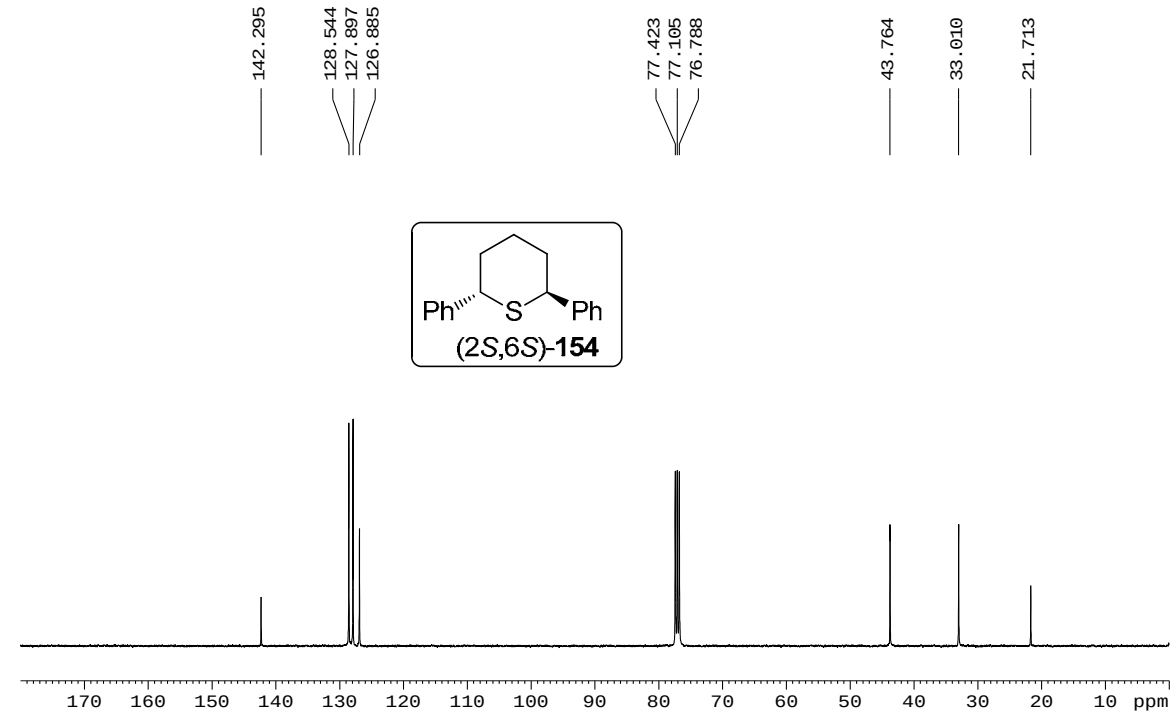
Spectrum No. 6 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 7 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

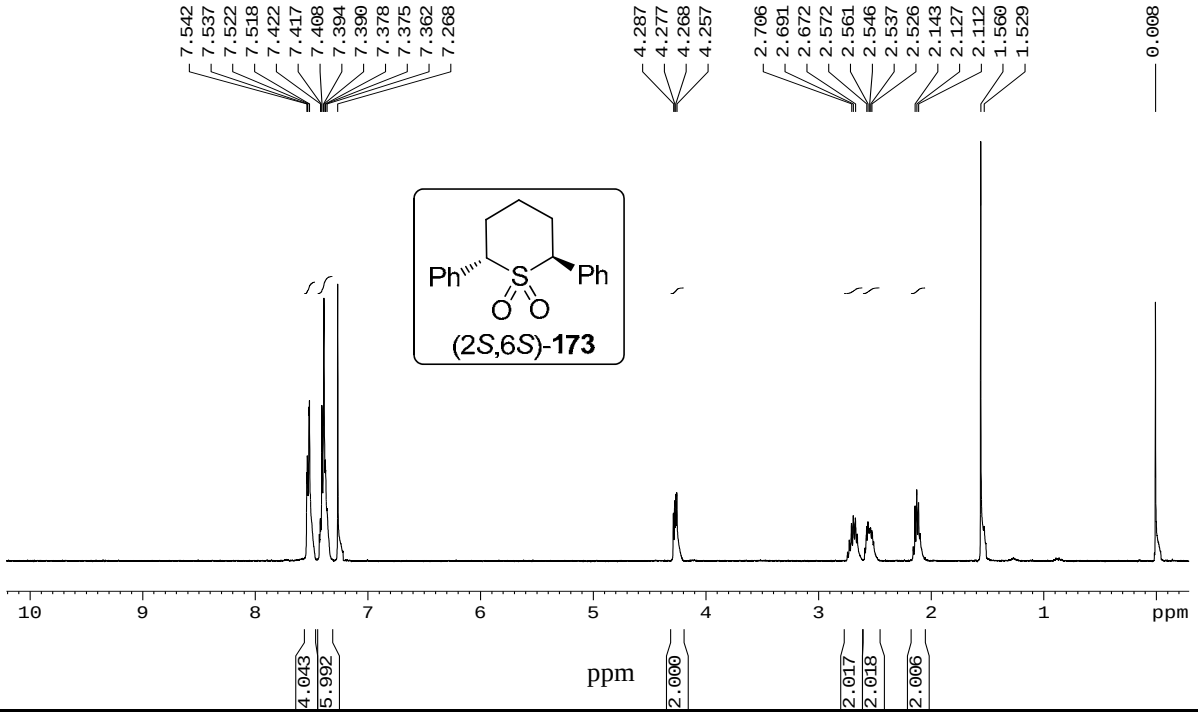


Spectrum No. 8 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

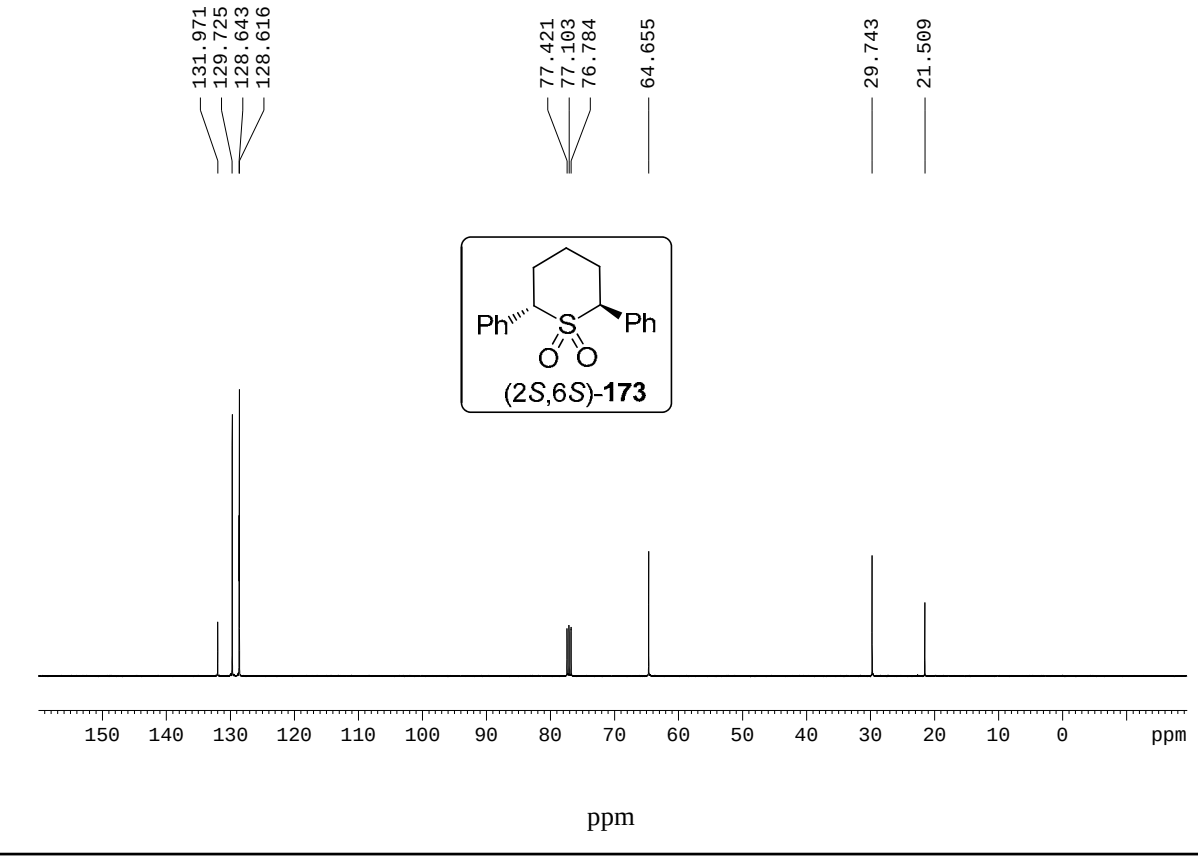


ppm

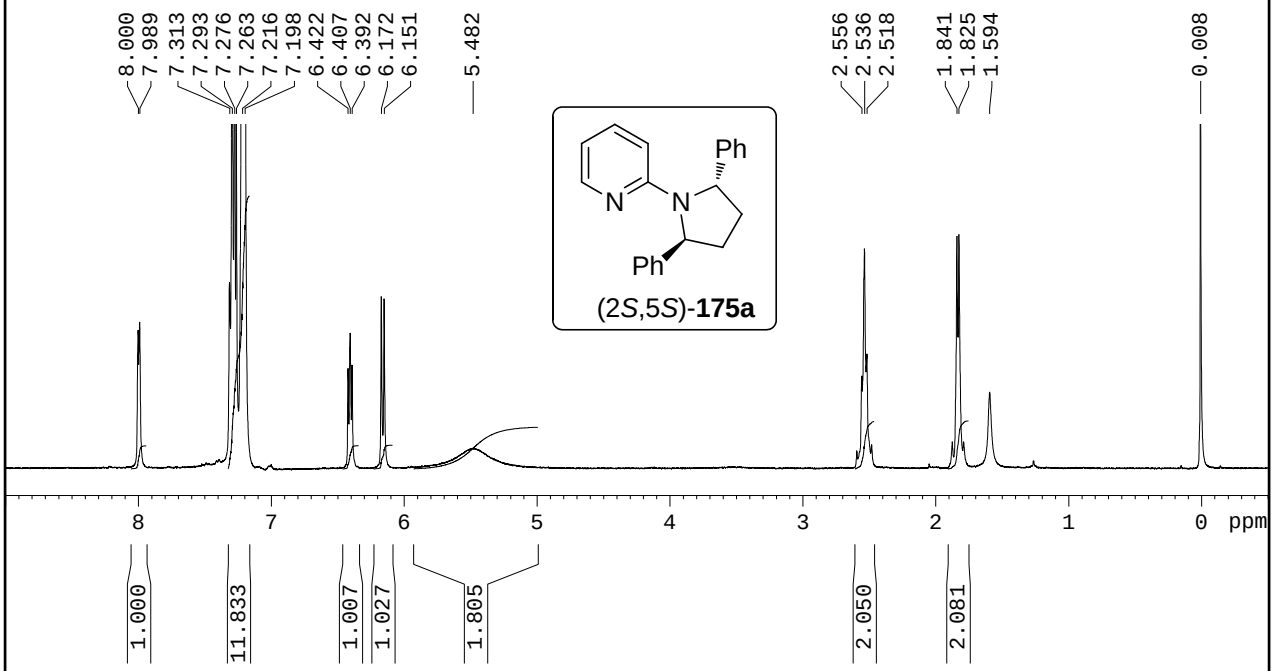
Spectrum No. 9 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



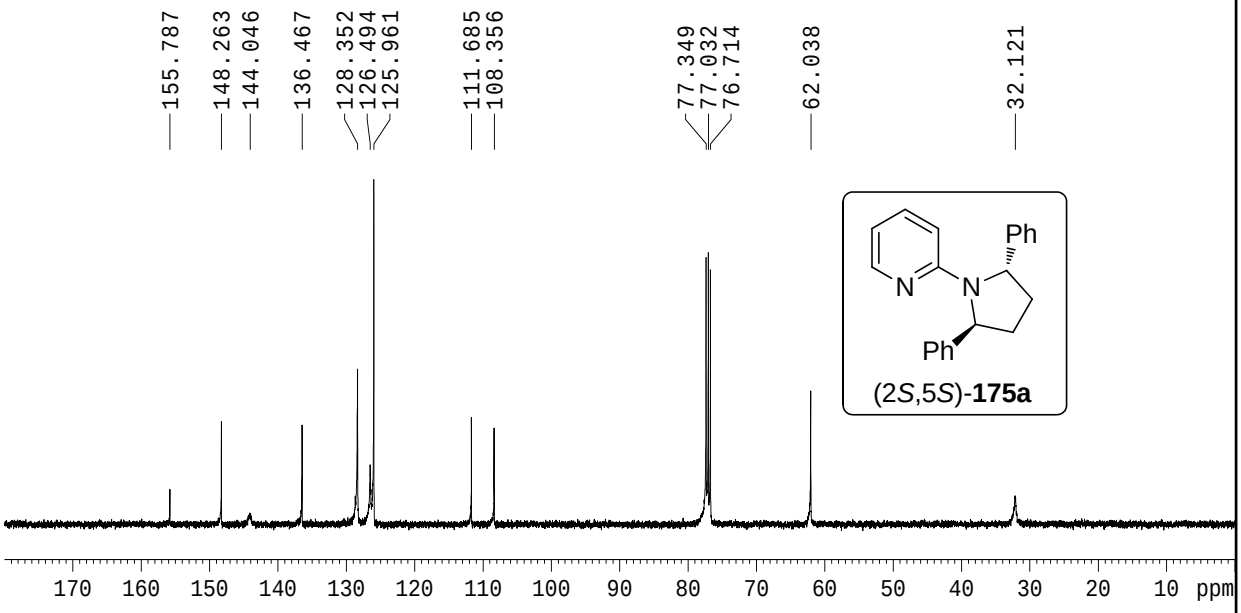
Spectrum No. 10 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



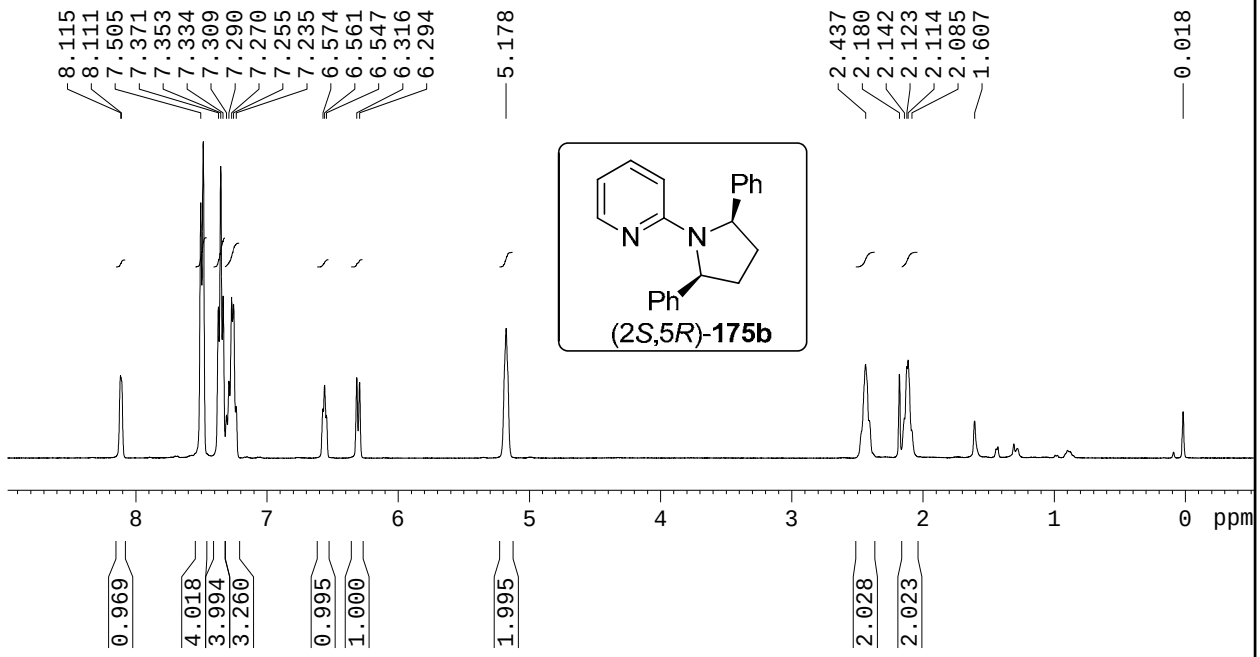
Spectrum No. 11 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



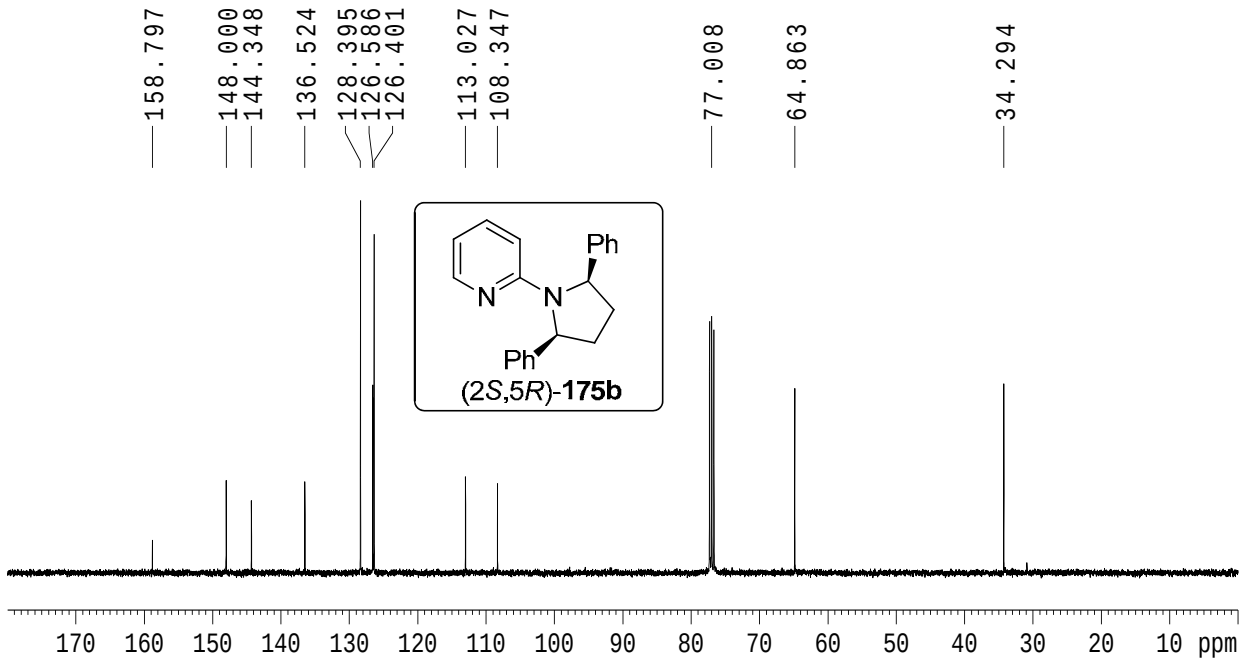
Spectrum No. 12 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



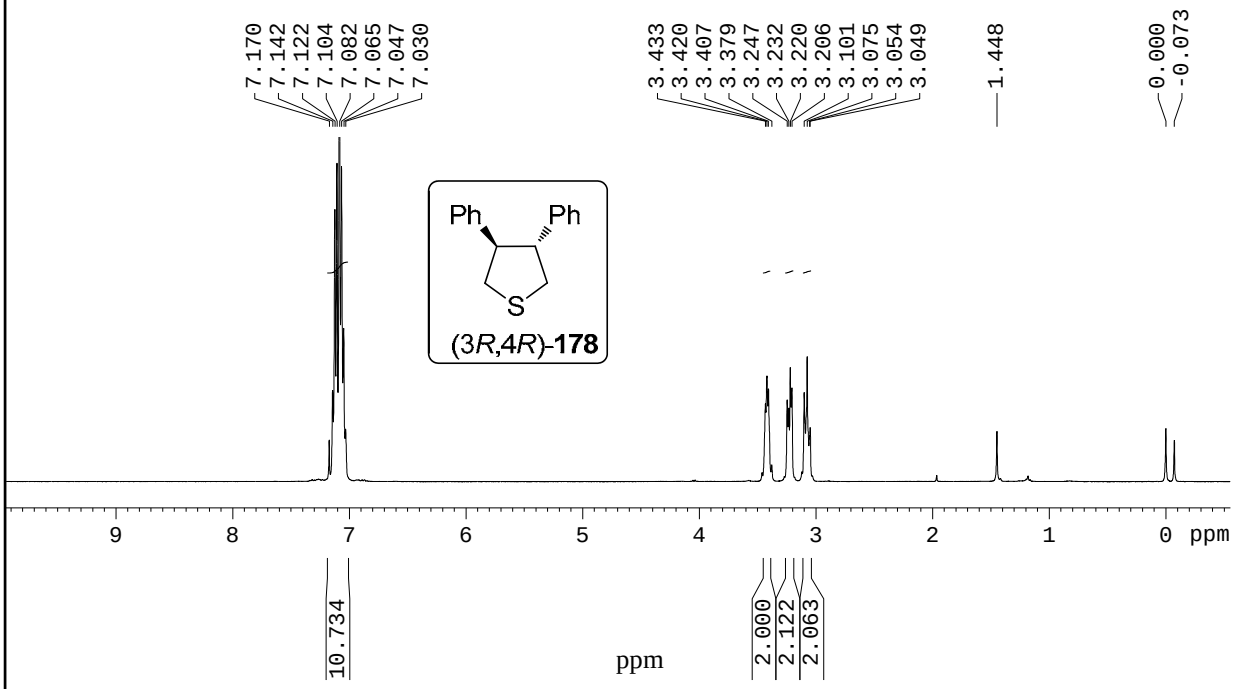
Spectrum No. 13 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



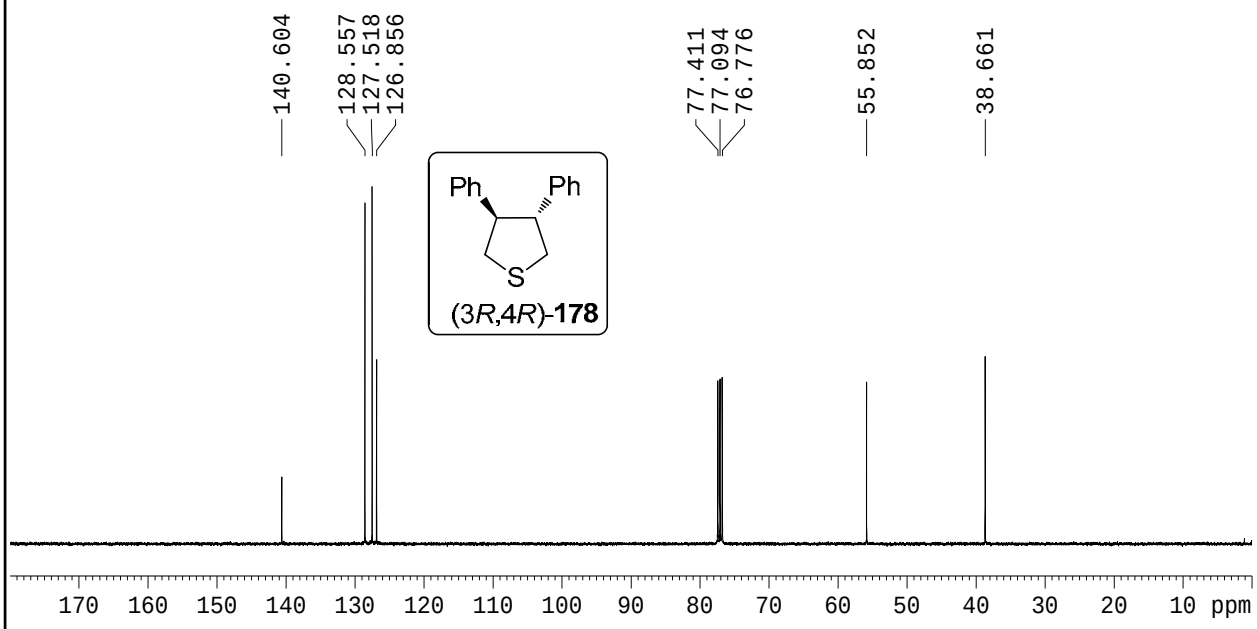
Spectrum No. 14 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



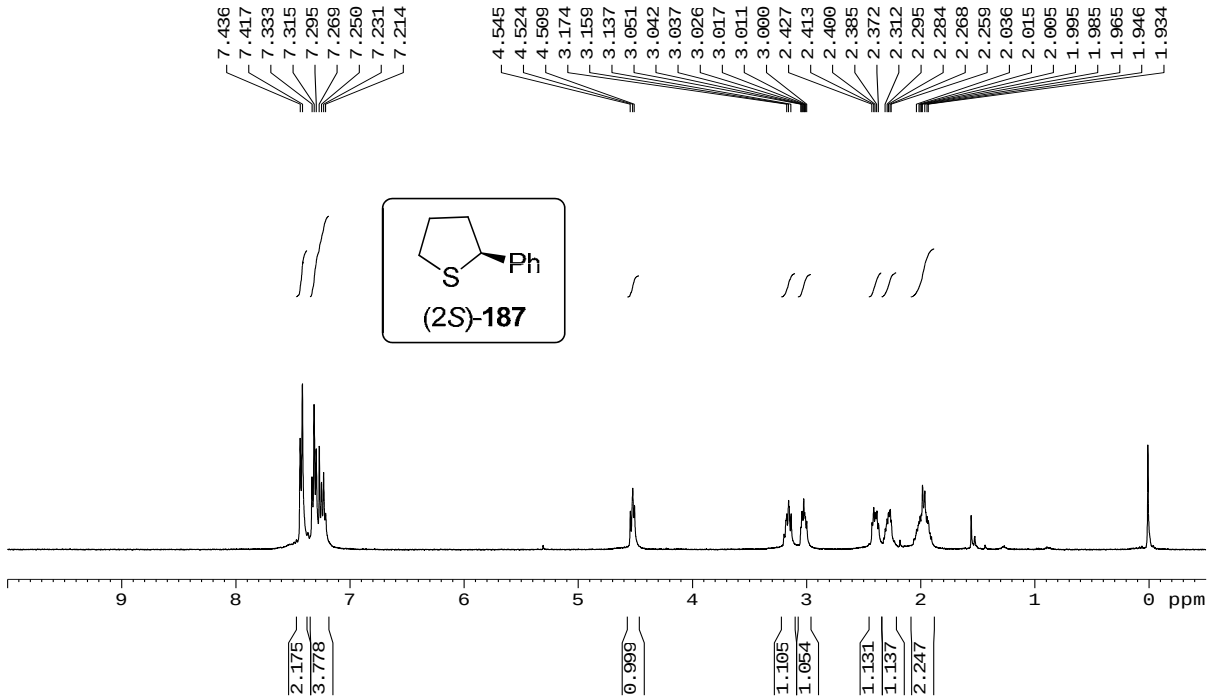
Spectrum No. 15 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



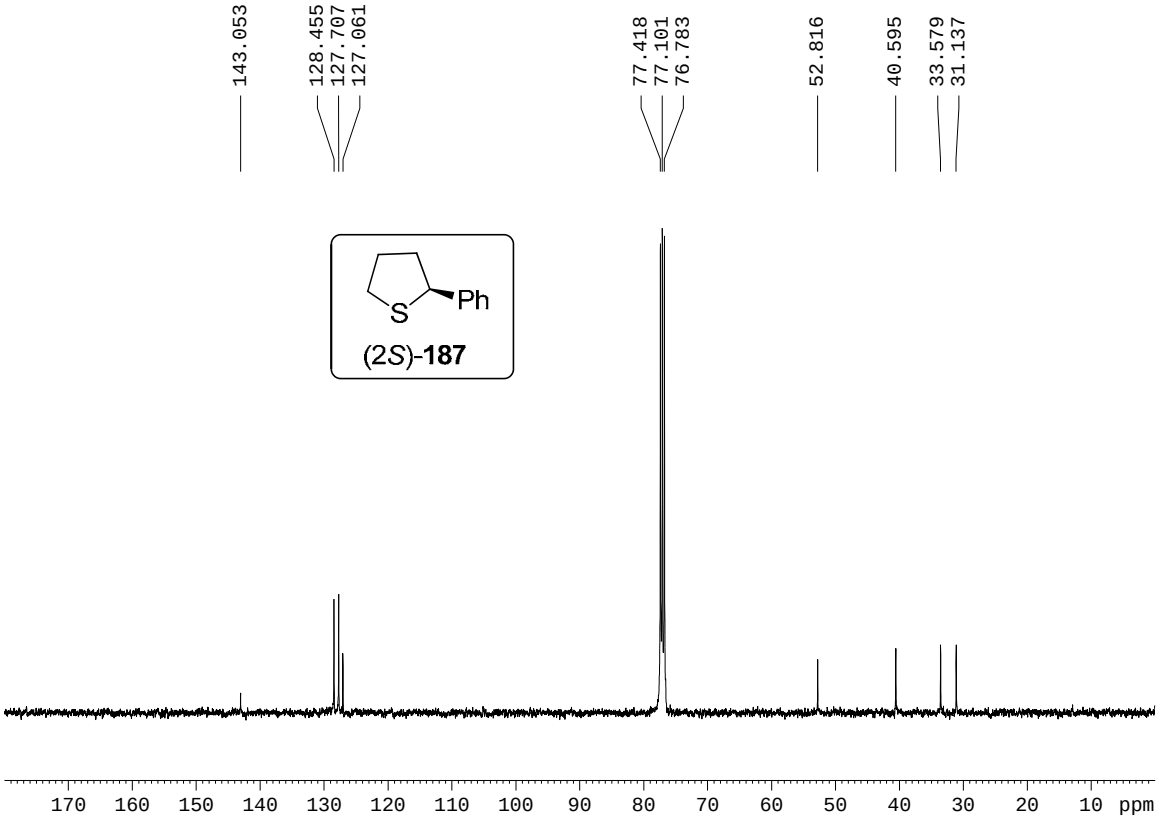
Spectrum No. 16 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



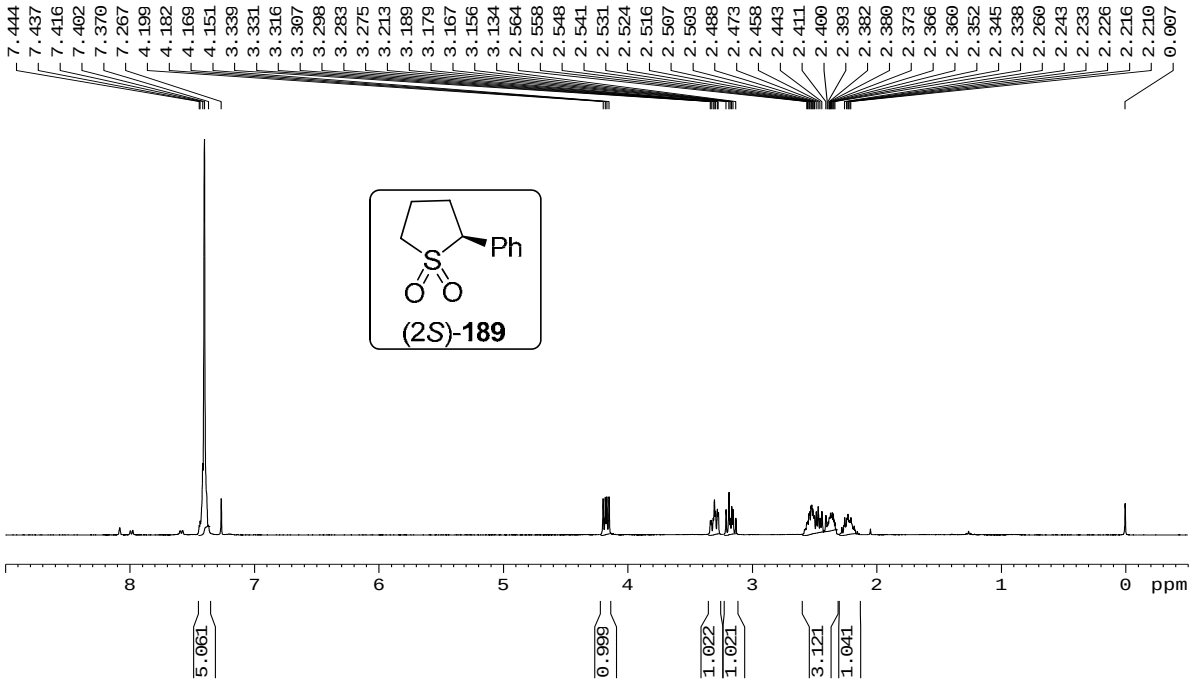
Spectrum No. 17 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



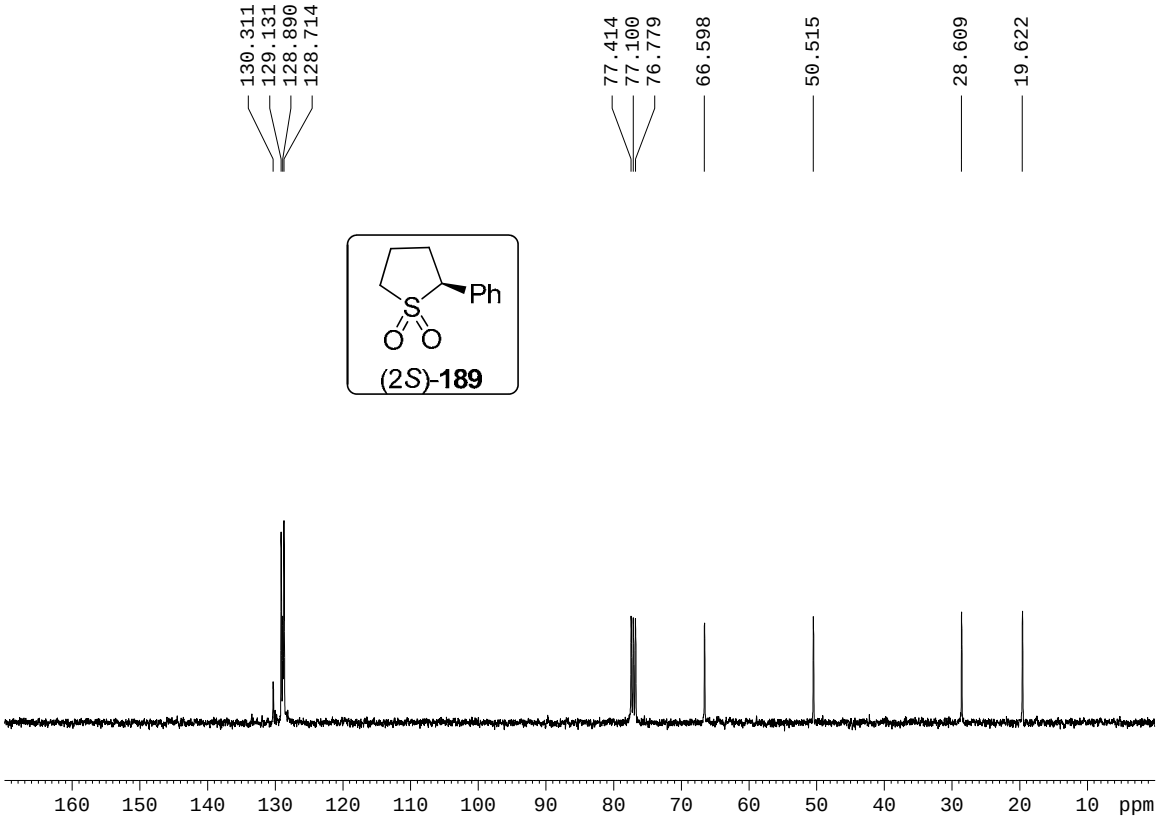
Spectrum No. 18 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



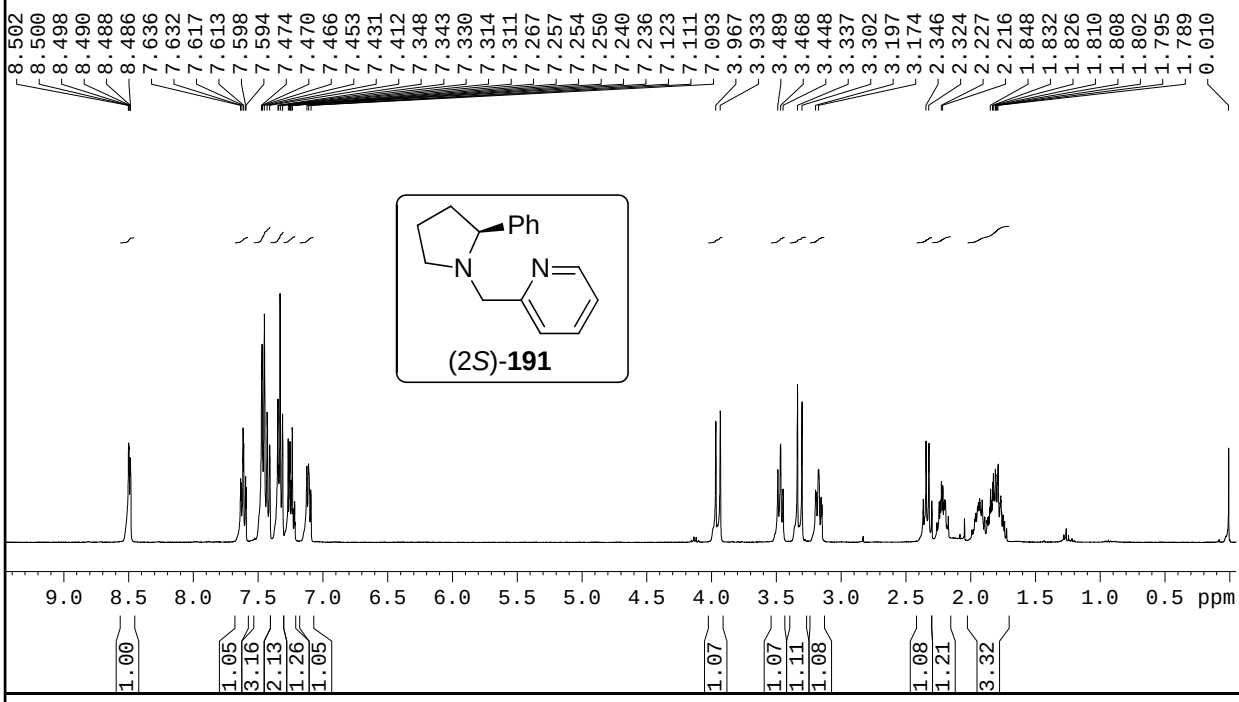
Spectrum No. 19 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



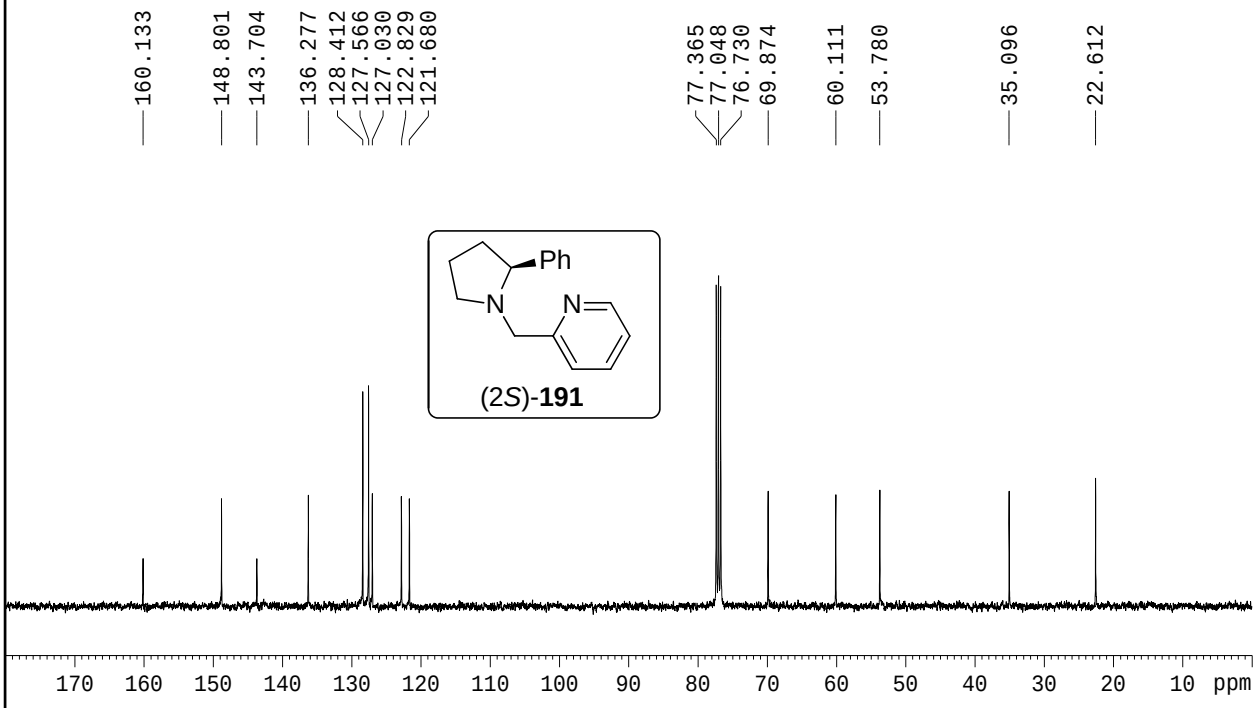
Spectrum No. 20 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



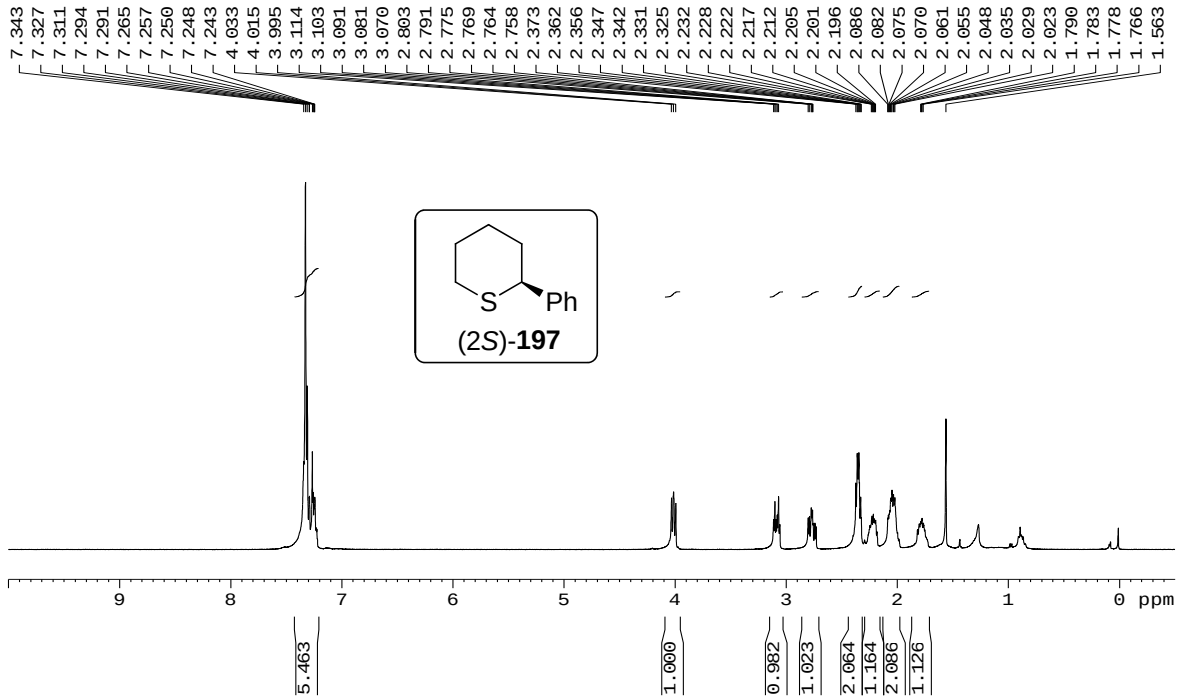
Spectrum No. 21 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



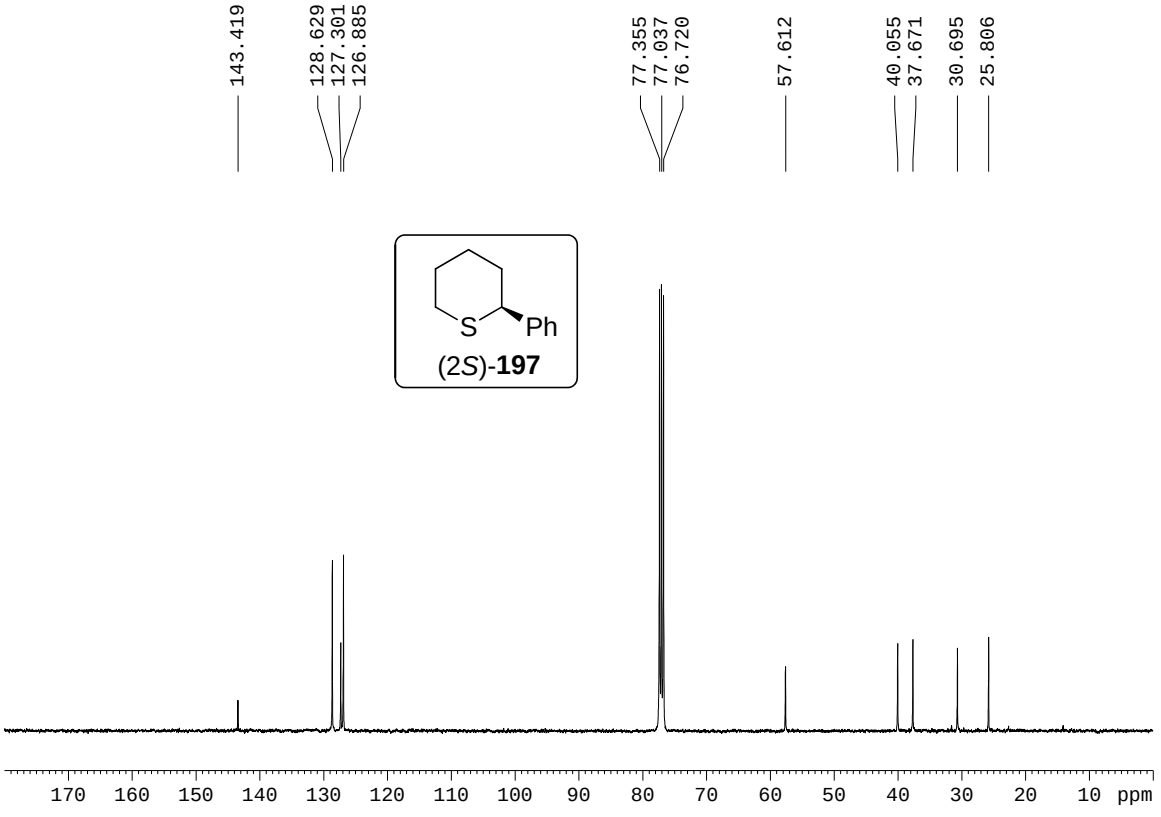
Spectrum No. 22 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



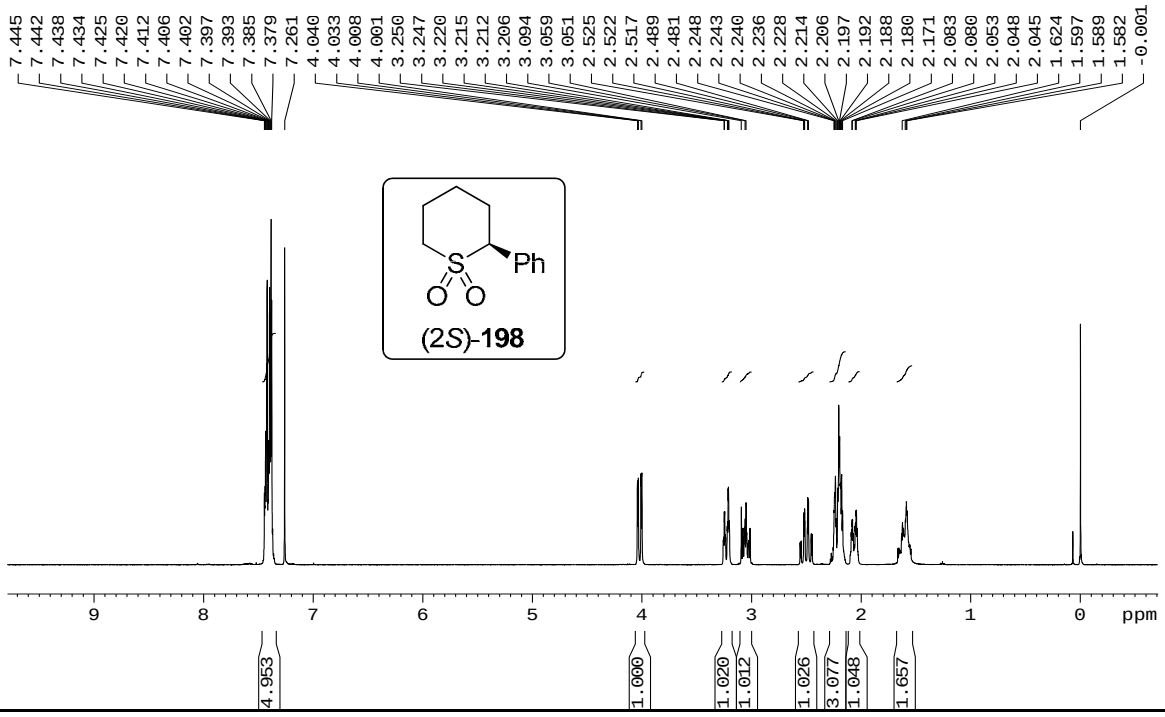
Spectrum No. 23 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



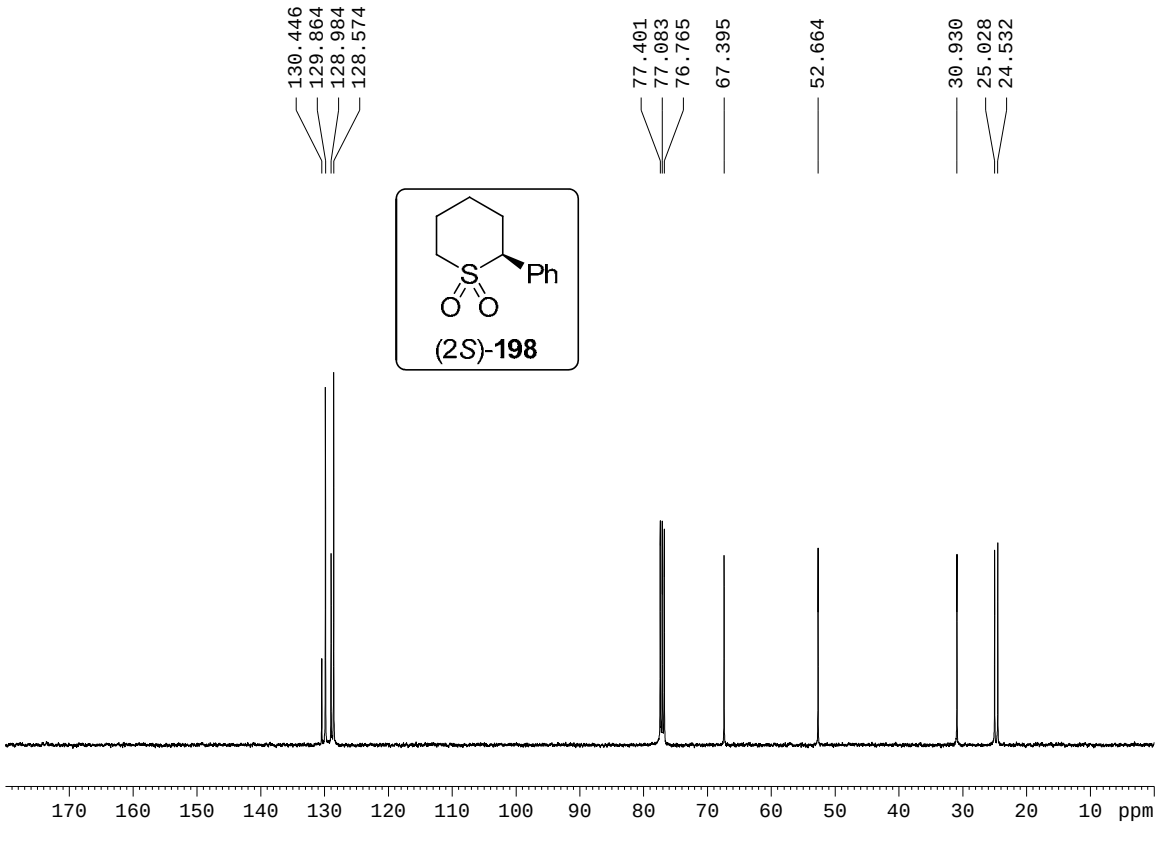
Spectrum No. 24 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



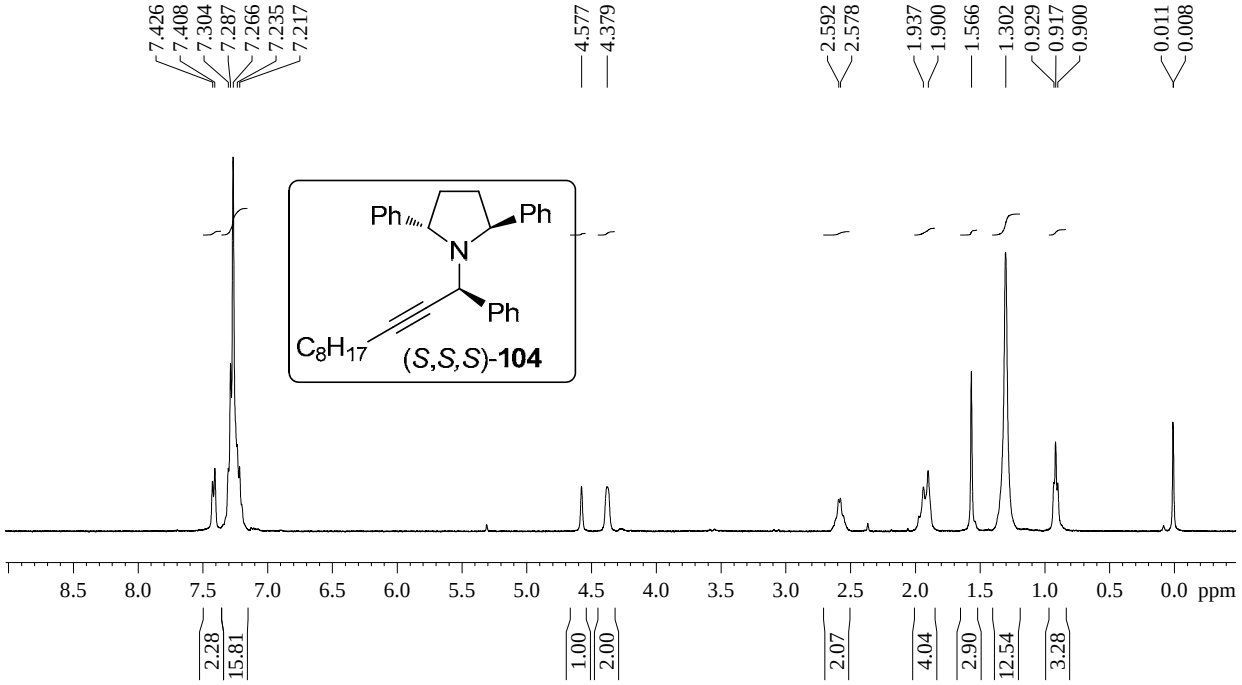
Spectrum No. 25 (Chapter 1, Section 1.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



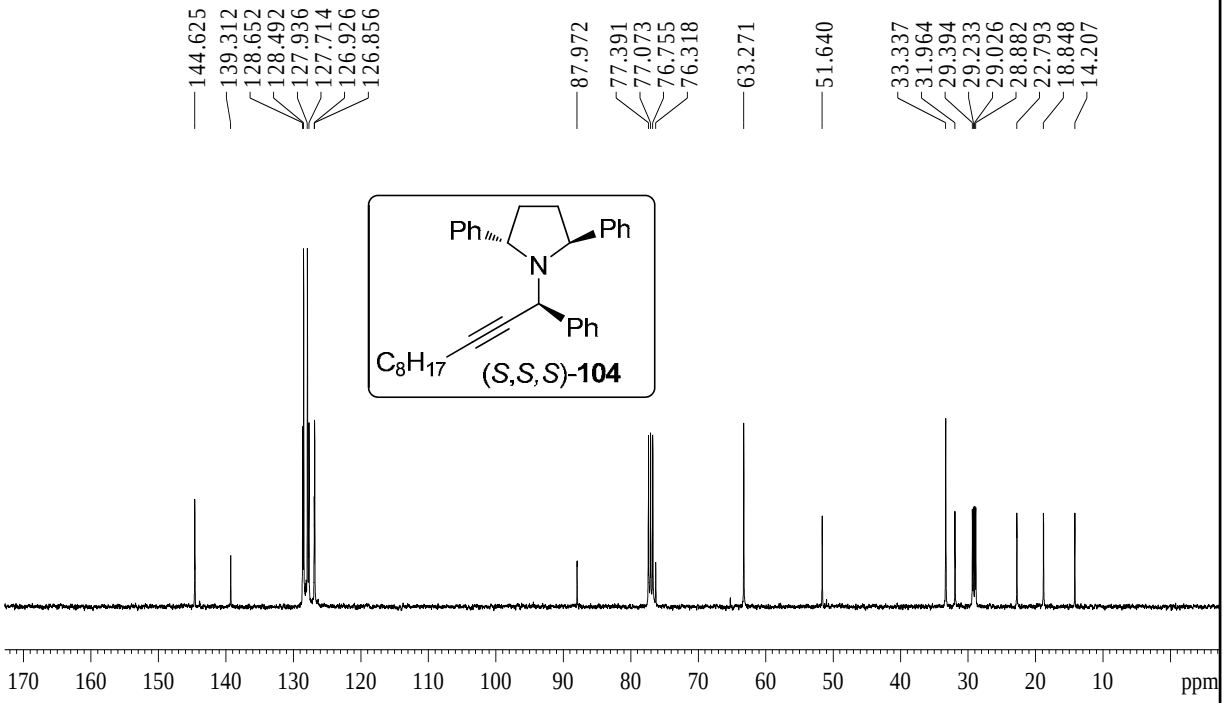
Spectrum No. 26 (Chapter 1, Section 1.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



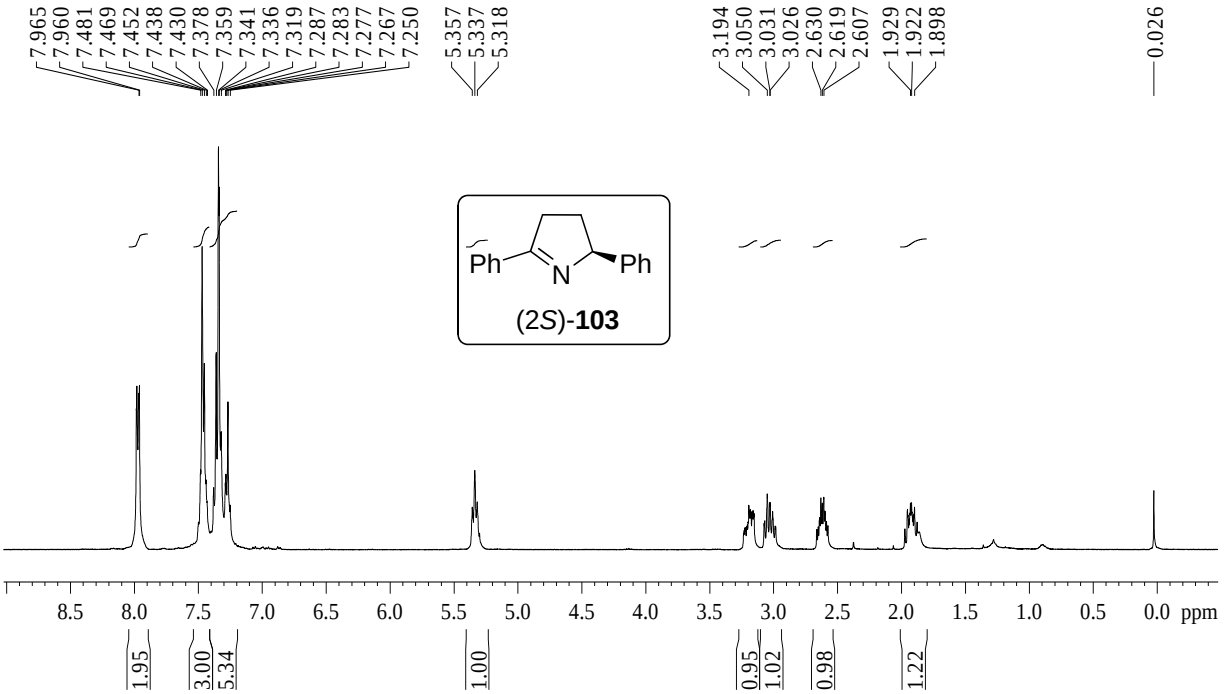
Spectrum No. 27 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



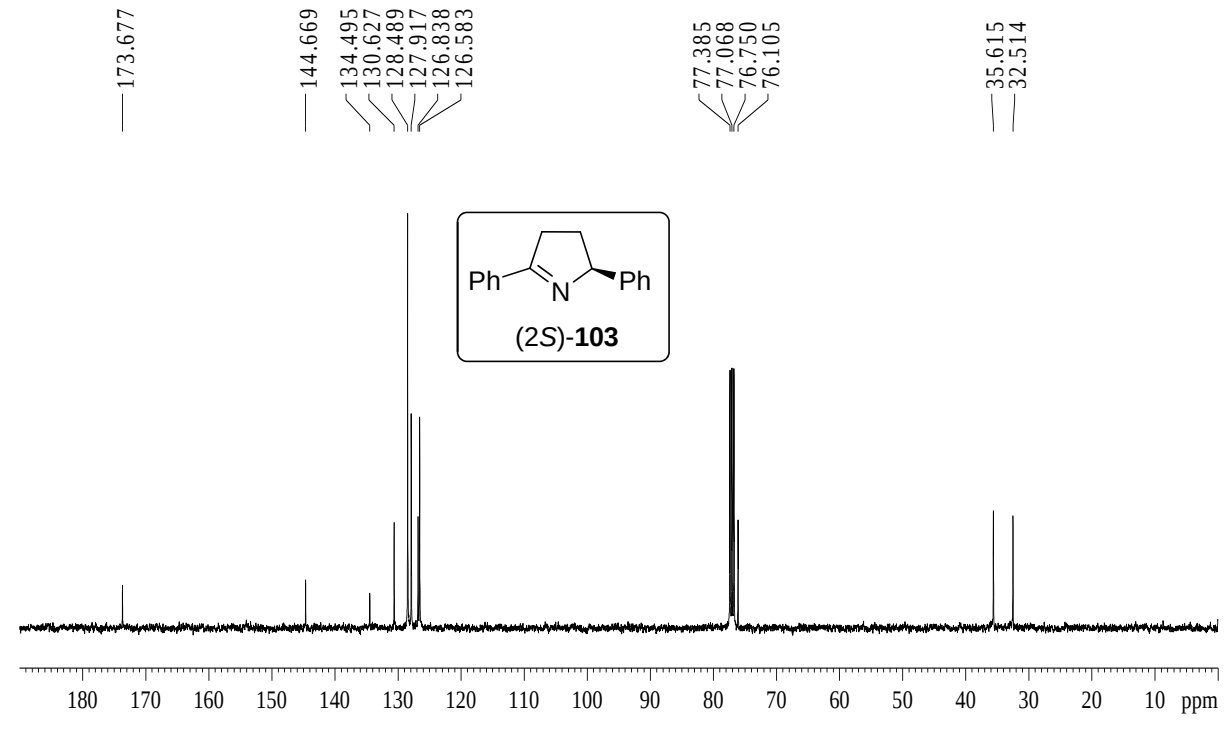
Spectrum No. 28 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 29 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

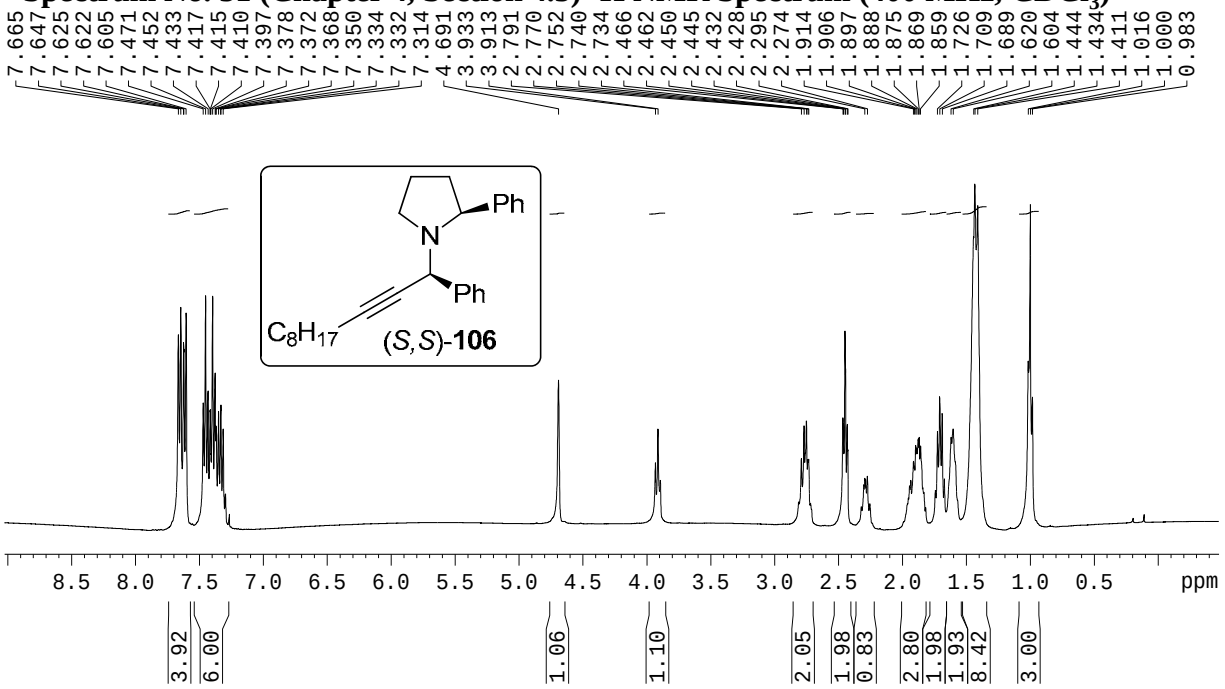


Spectrum No. 30 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

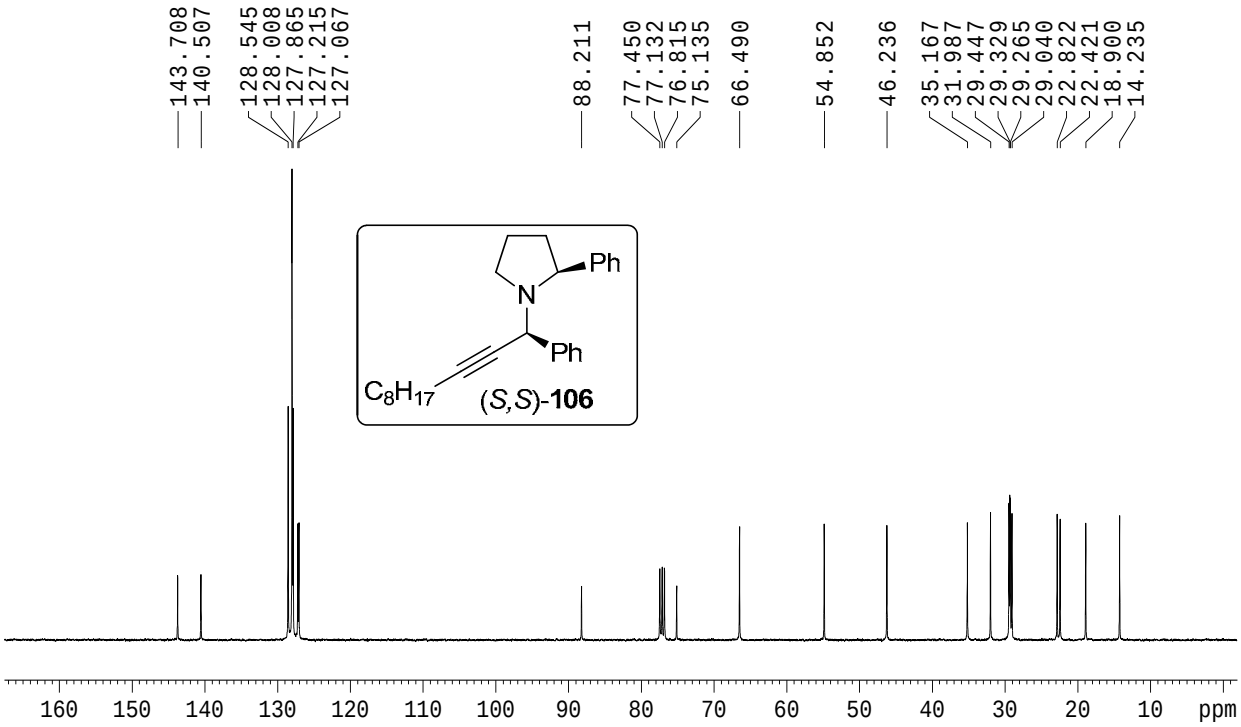


ppm

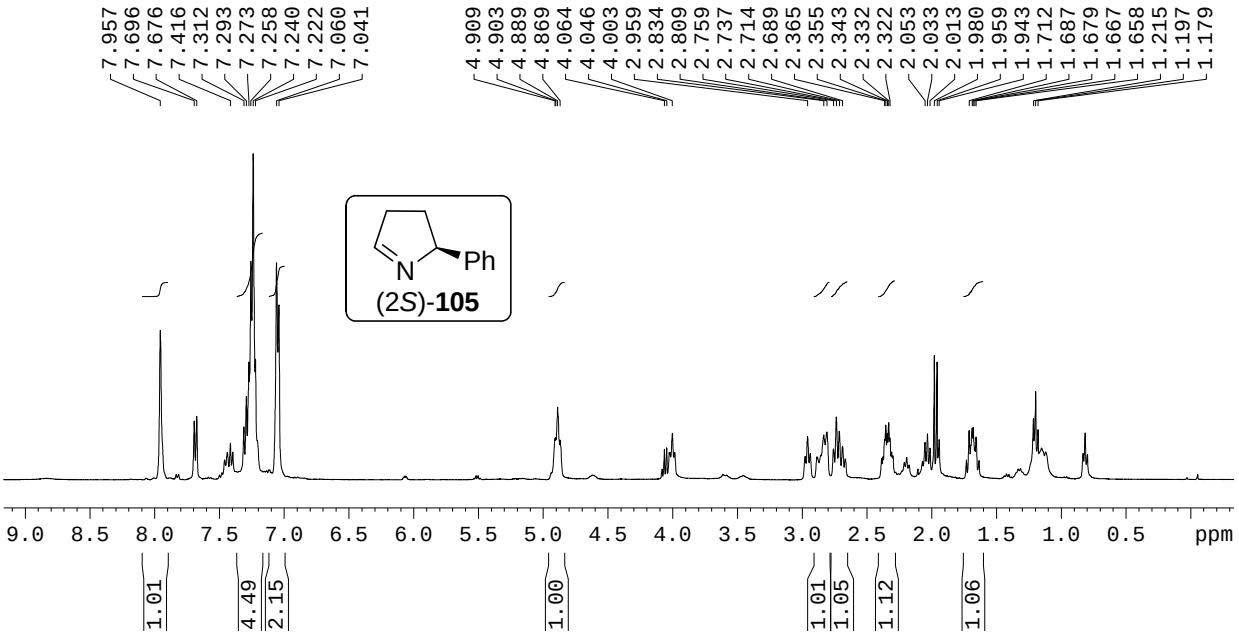
Spectrum No. 31 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



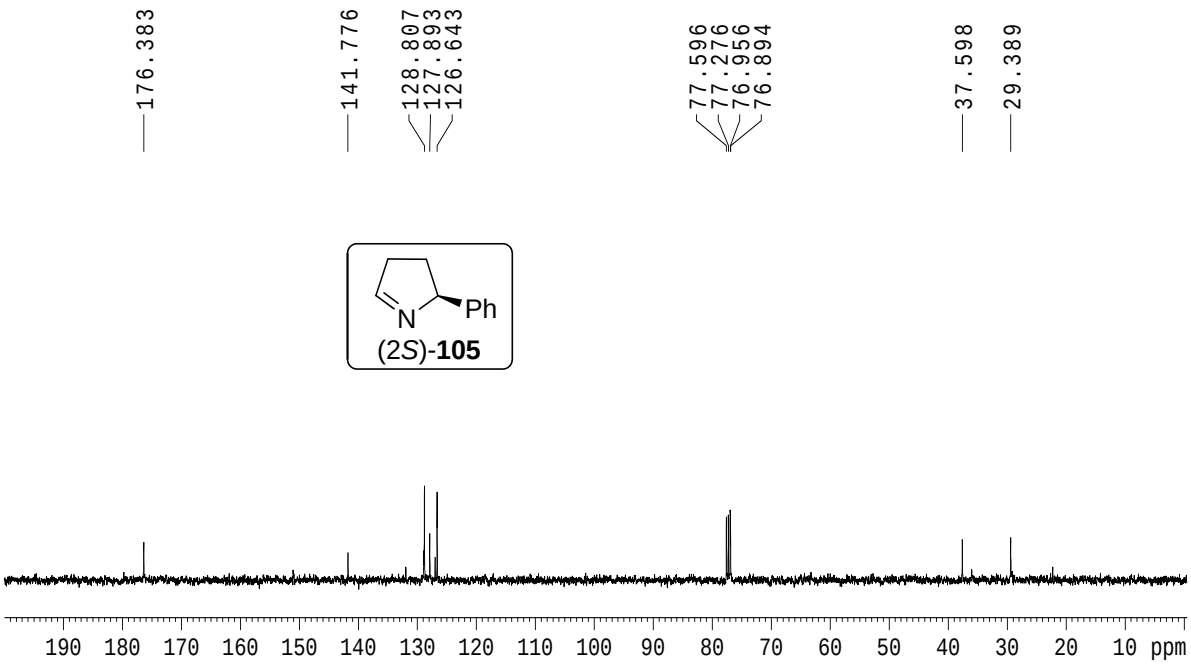
Spectrum No. 32 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



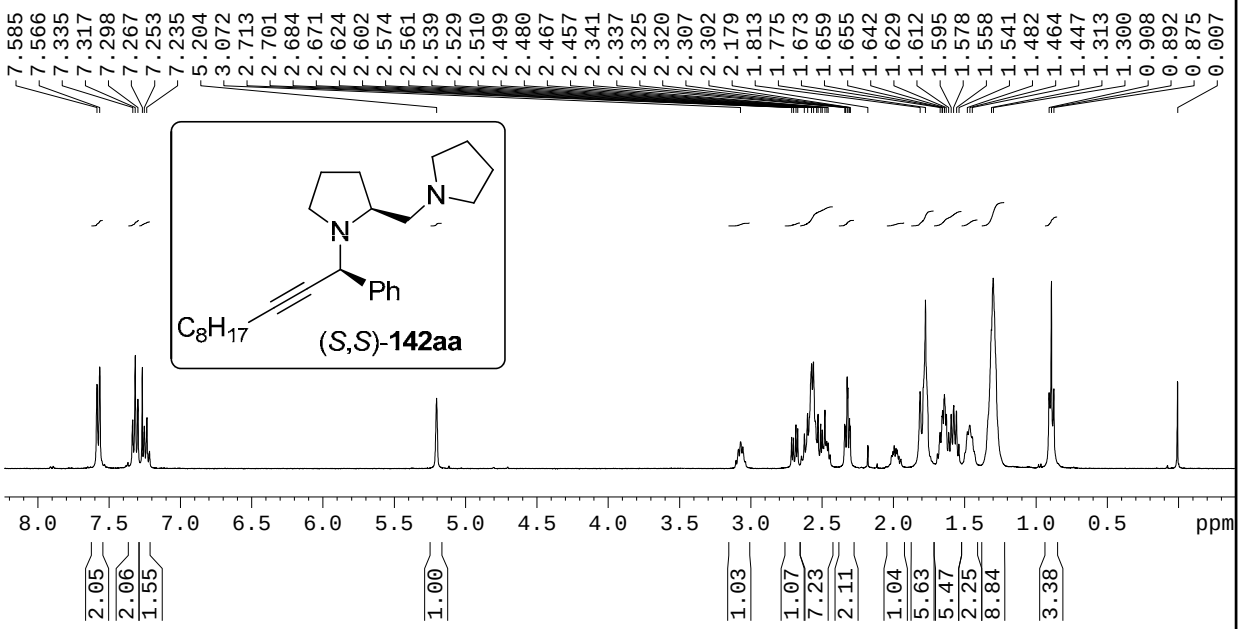
Spectrum No. 33 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



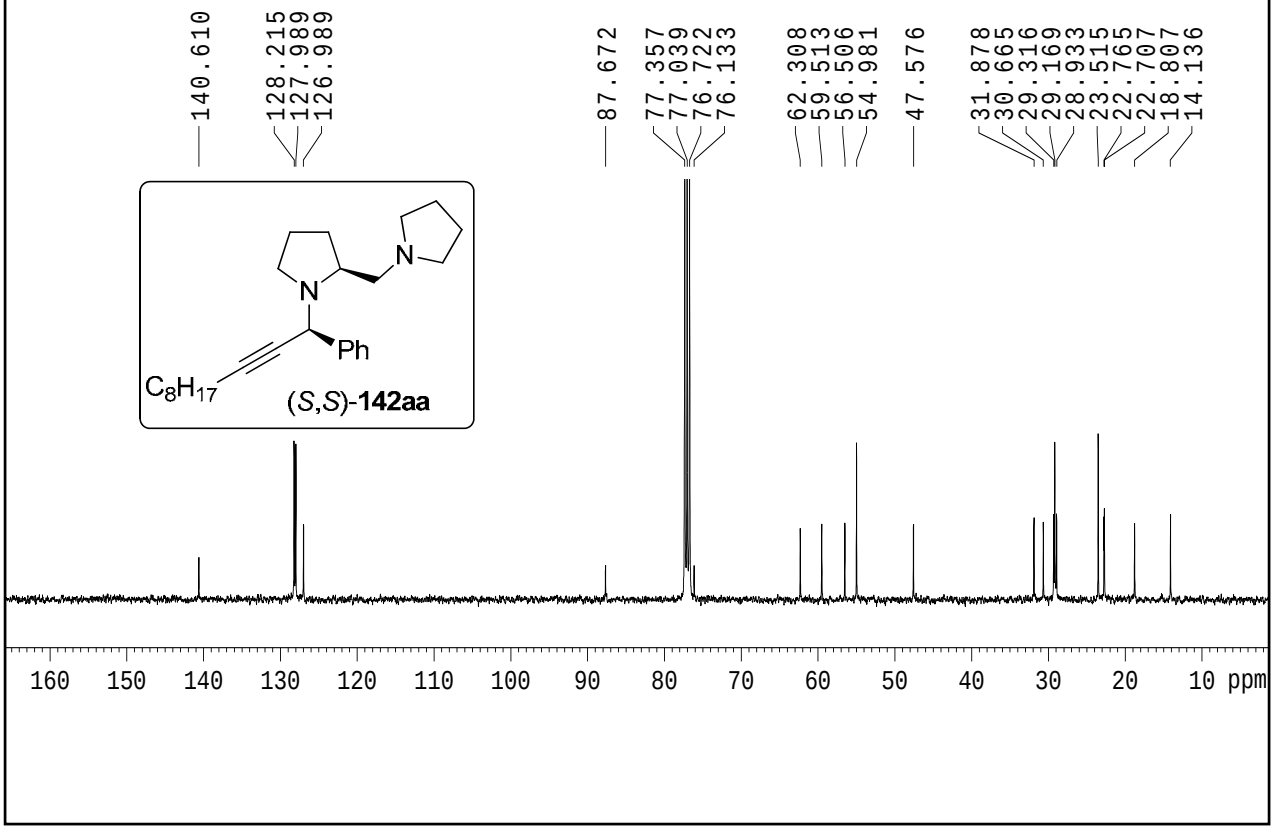
Spectrum No. 34 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



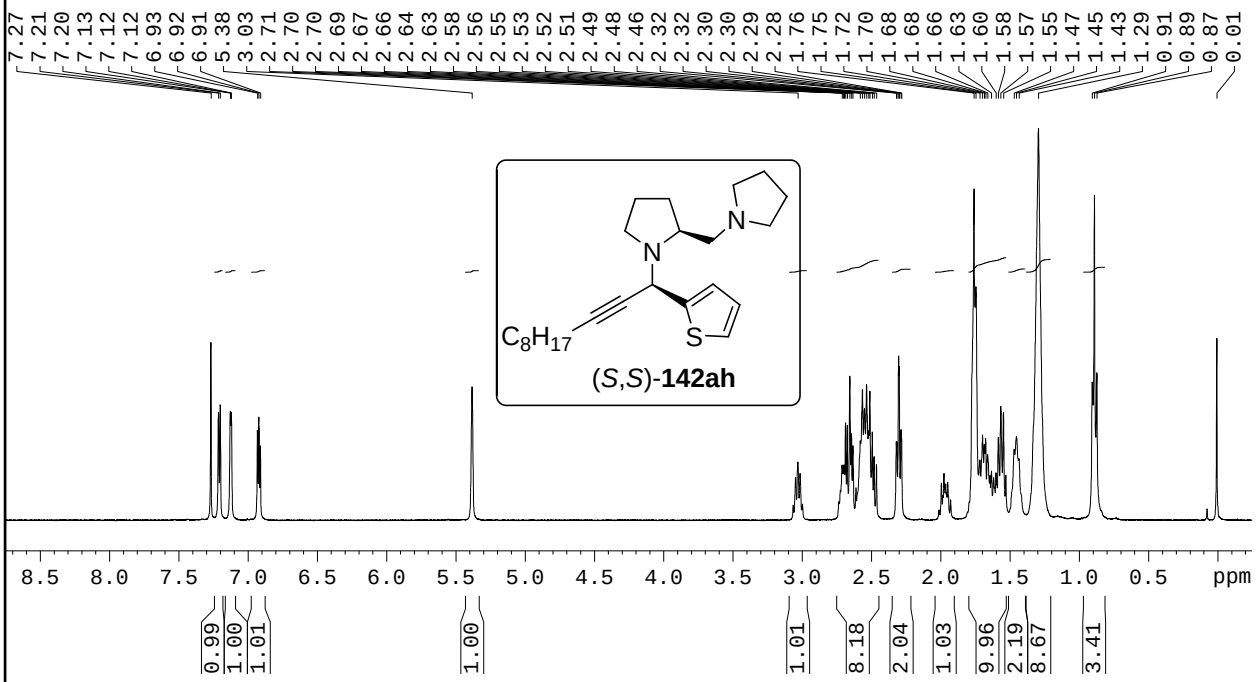
Spectrum No. 35 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



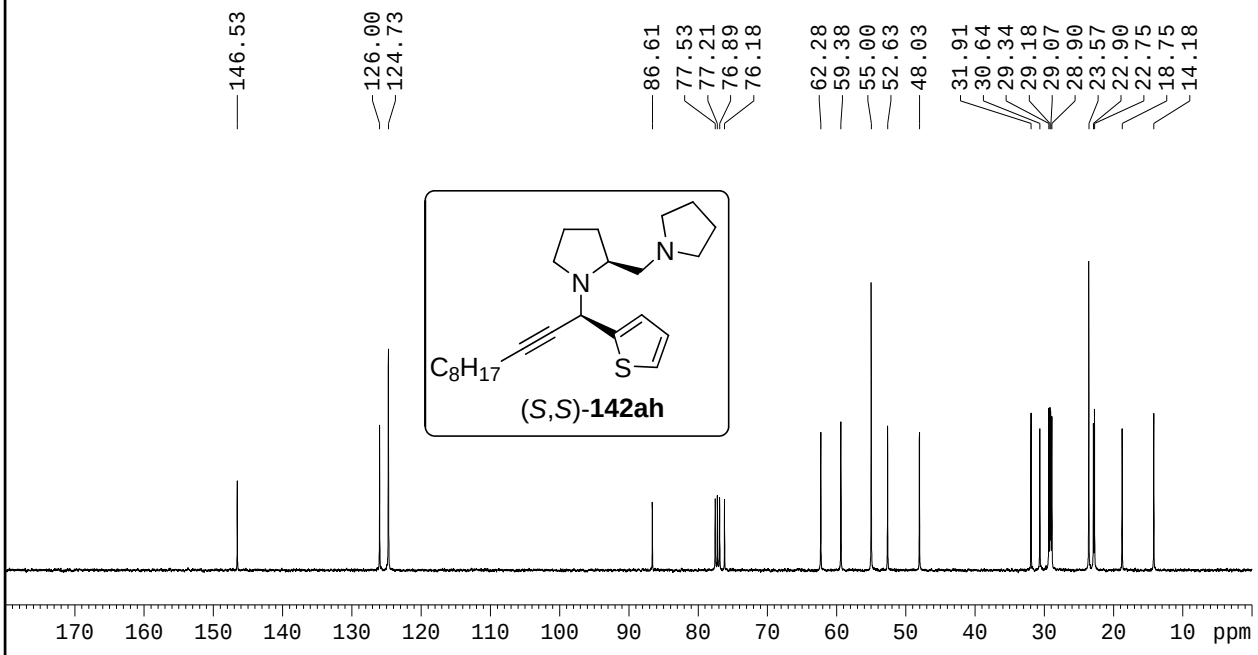
Spectrum No. 36 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



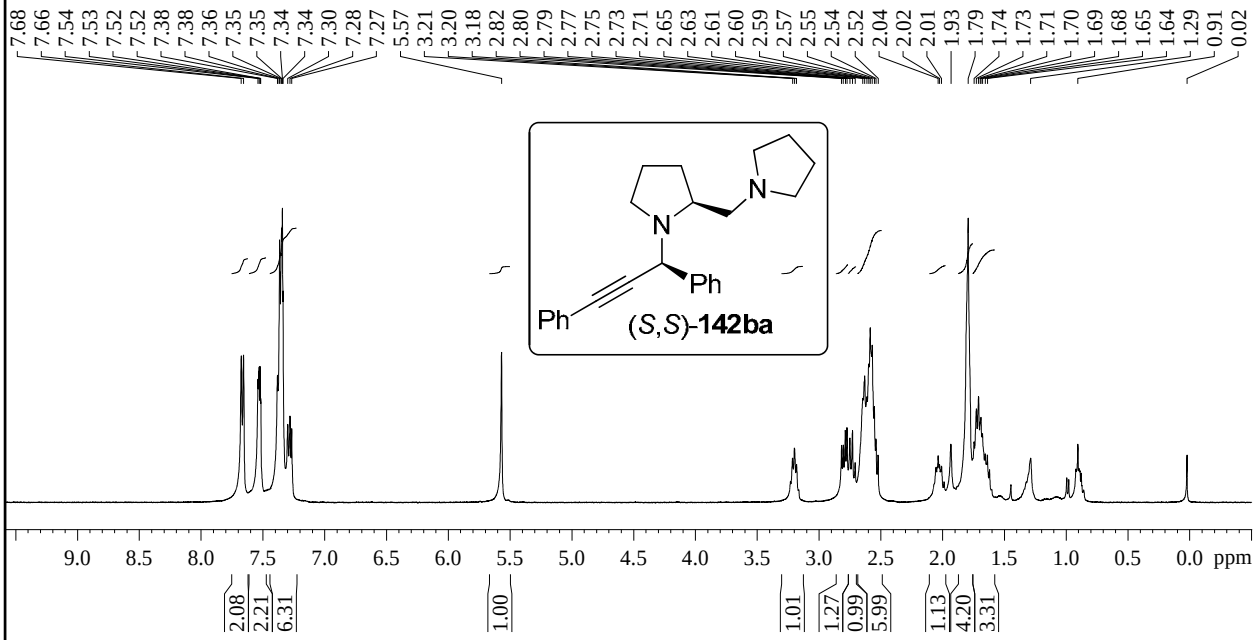
Spectrum No. 37 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



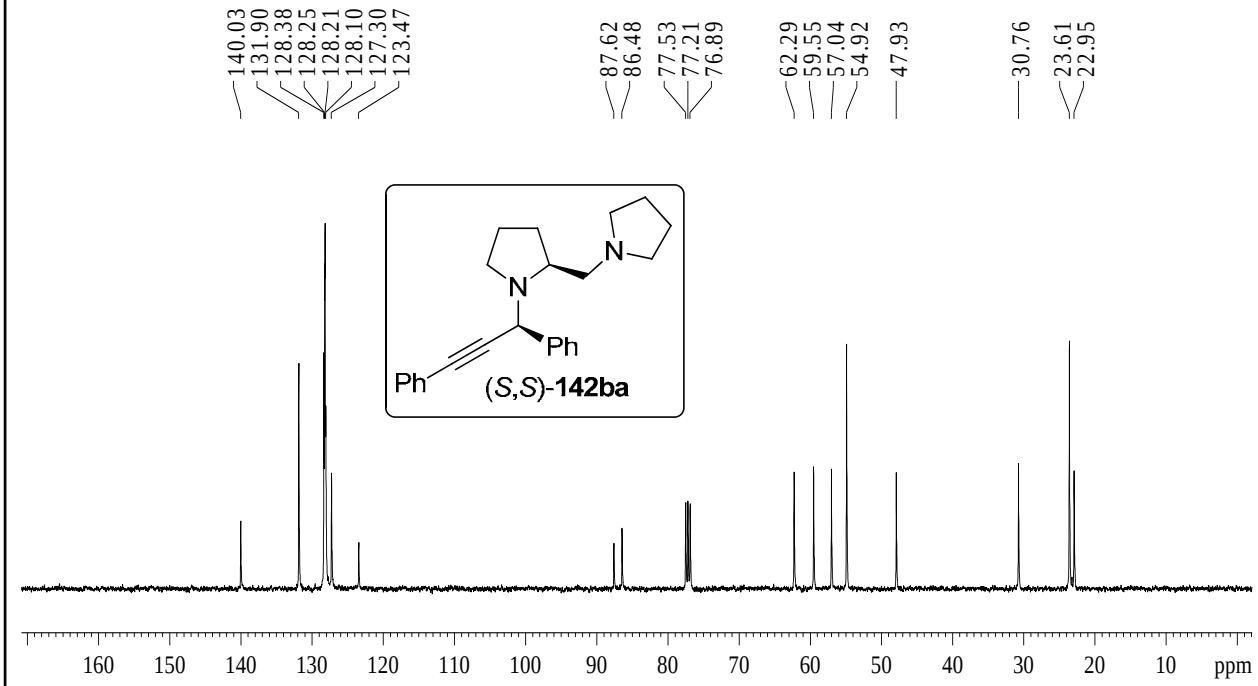
Spectrum No. 38 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



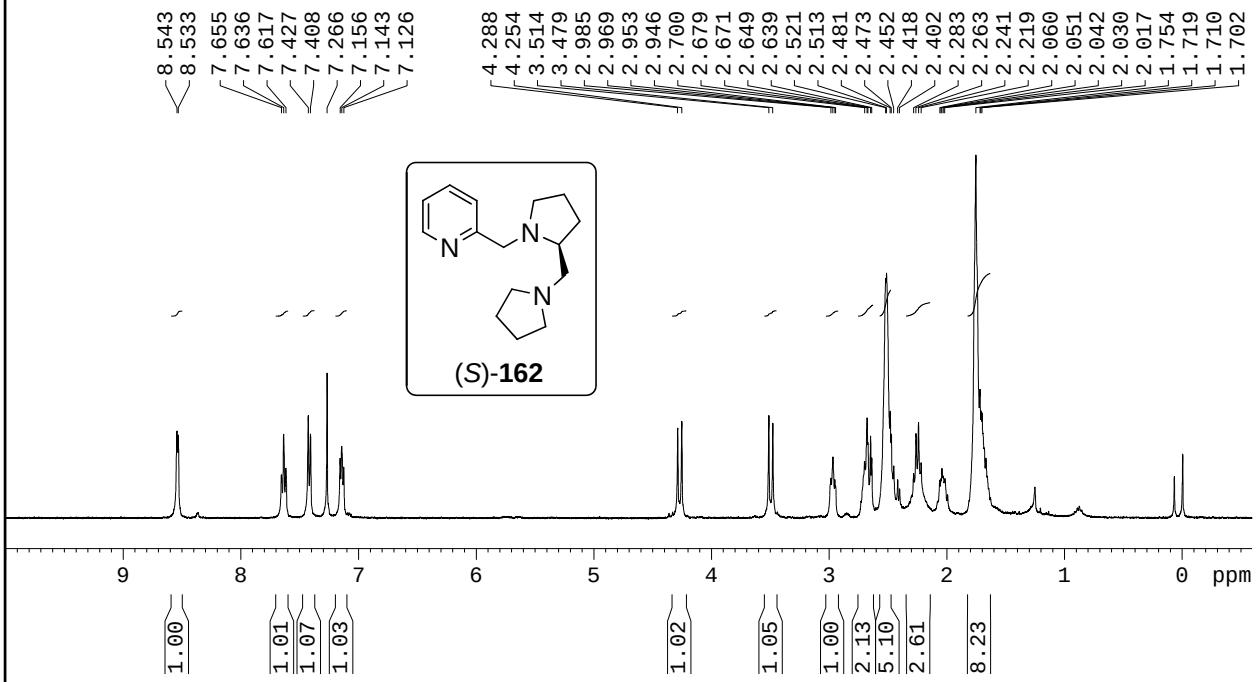
Spectrum No. 39 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



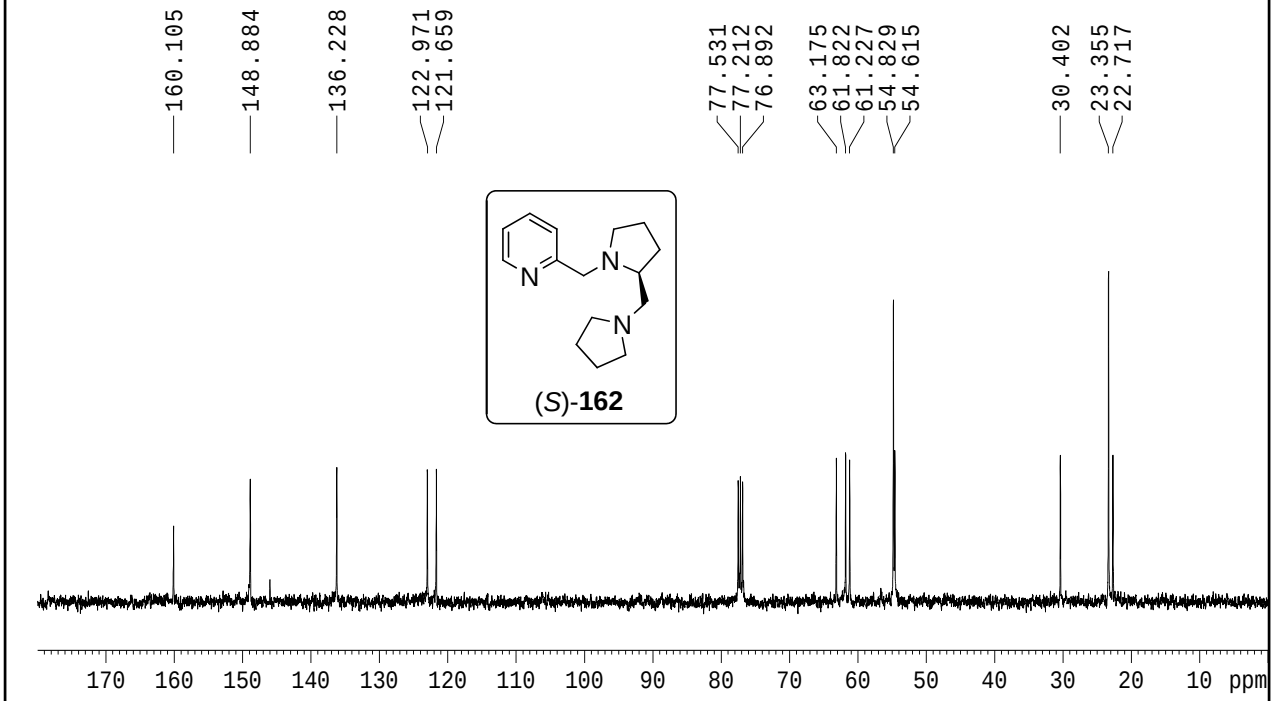
Spectrum No. 40 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



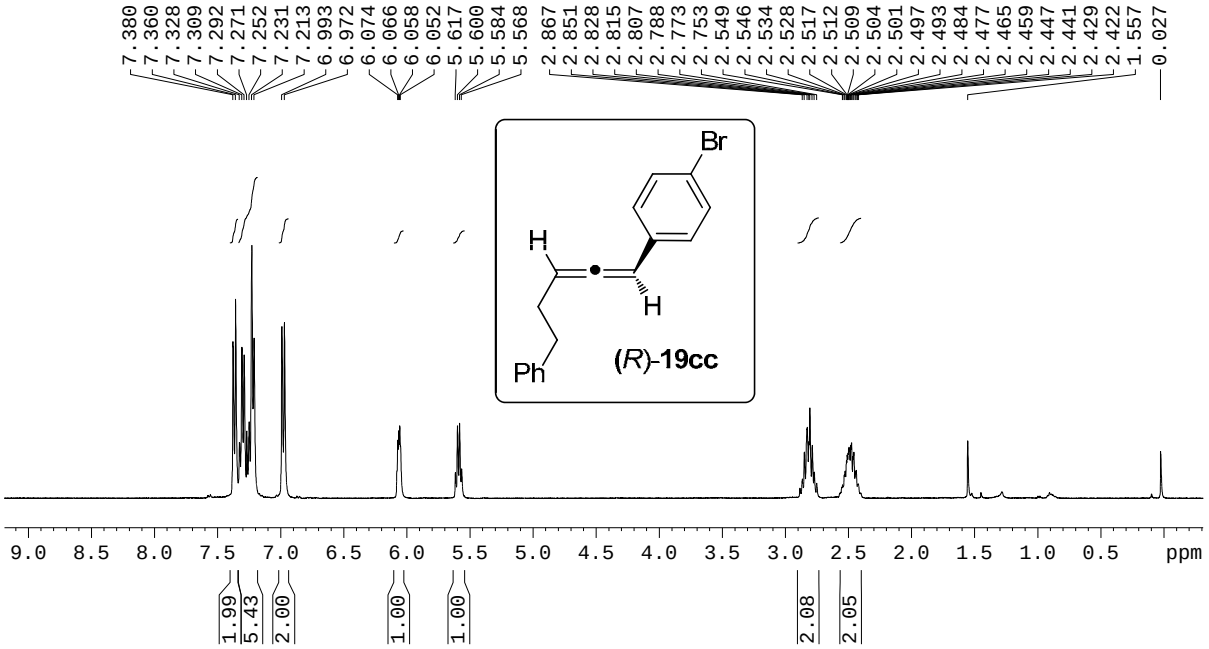
Spectrum No. 41 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



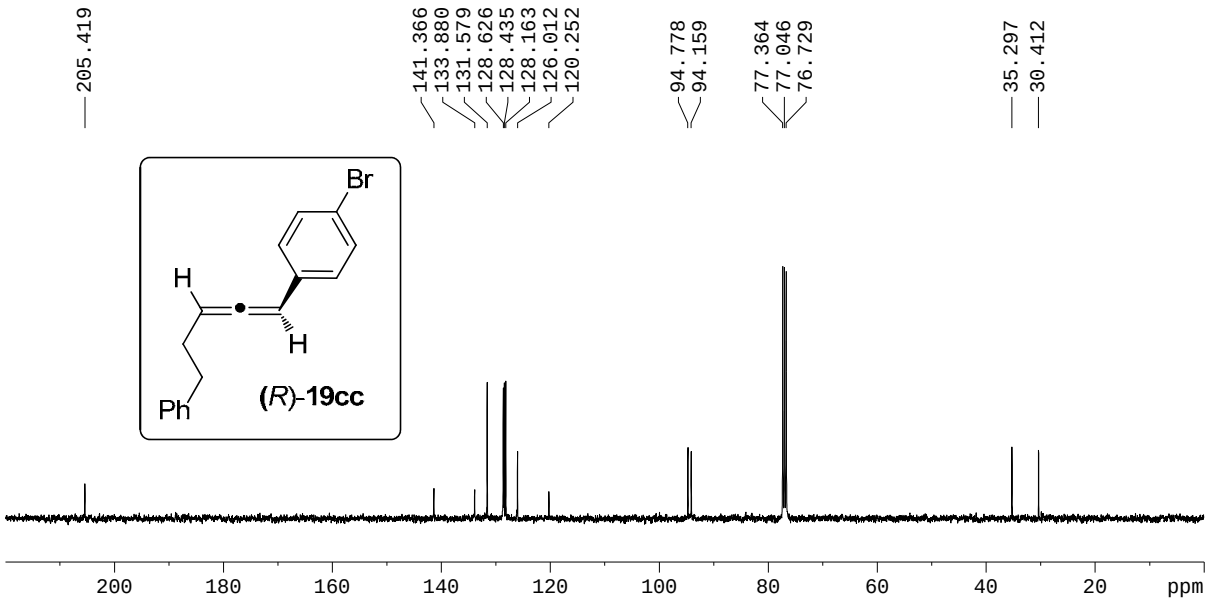
Spectrum No. 42 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 43 (Chapter 4, Section 4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 44 (Chapter 4, Section 4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (+)-(2*S*,5*S*)-2,5-diphenylthiolane **142**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(1)	5051(4)	3661(11)	3868(3)	50(1)
C(2)	4357(4)	4451(10)	4303(3)	56(2)
C(3)	3503(5)	3188(14)	4354(4)	73(2)
C(4)	3354(4)	1126(15)	3971(4)	75(2)
C(5)	4017(5)	294(11)	3542(4)	72(2)
C(6)	4870(4)	1556(10)	3494(3)	57(1)
C(7)	8870(4)	5083(10)	3607(3)	48(1)
C(8)	9176(4)	7006(12)	4043(3)	66(2)
C(9)	10175(6)	7521(13)	4293(4)	81(2)
C(10)	10893(5)	6101(16)	4090(4)	84(2)
C(11)	10611(5)	4140(16)	3670(4)	86(2)
C(12)	9611(4)	3645(13)	3416(4)	67(2)
C(13)	7776(4)	4556(10)	3334(3)	56(1)
C(14)	5969(4)	5133(10)	3787(3)	47(1)
C(15)	6039(4)	5815(10)	2954(3)	52(1)
C(16)	7126(4)	6527(10)	2952(3)	56(1)
C(17)	4478(4)	3427(9)	1044(3)	47(1)
C(18)	4999(4)	1462(10)	1361(3)	55(1)
C(19)	6040(4)	1363(11)	1375(3)	61(2)
C(20)	6534(4)	3152(12)	1075(3)	62(2)
C(21)	6019(5)	5066(12)	765(3)	65(2)
C(22)	4996(5)	5210(10)	742(3)	56(1)
C(23)	814(5)	919(11)	1492(4)	62(2)
C(24)	442(6)	-772(12)	1935(4)	80(2)
C(25)	-541(8)	-1579(17)	1752(6)	114(3)
C(26)	-1161(6)	-629(19)	1128(6)	107(3)
C(27)	-798(5)	1070(20)	687(5)	103(3)
C(28)	185(5)	1735(16)	861(4)	88(2)
C(29)	3362(4)	3734(10)	1057(3)	51(1)
C(30)	3156(5)	4737(11)	1812(4)	64(2)
C(31)	2055(5)	4256(11)	1848(4)	69(2)
C(32)	1900(5)	1660(11)	1691(4)	67(2)
S(1)	7149(1)	3562(3)	4139(1)	66(1)
S(2)	2621(1)	1034(3)	920(1)	66(1)

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (-)-(3*S*,6*S*)-diphenyl-1,2-dithiane **166**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(1)	4989(1)	5078(1)	696(1)	85(1)
C(1)	7368(3)	6306(3)	1982(2)	63(1)
C(2)	7224(3)	6276(3)	956(2)	66(1)

C(3)	7306(4)	7437(4)	3447(2)	86(1)
C(4)	7152(4)	7419(4)	2515(2)	76(1)
C(5)	7746(5)	5219(4)	2418(2)	95(1)
C(6)	7913(5)	5273(5)	3364(2)	103(1)
C(7)	7985(4)	7975(3)	524(2)	94(1)
C(8)	7710(4)	6369(4)	3869(2)	86(1)

Table A3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for (2*S*,6*S*)-2,6-diphenyltetrahydro-2*H*-thiopyran 1,1-dioxide **173**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(1)	2581(1)	4950(1)	1192(1)	41(1)
O(1)	5082(5)	5086(2)	1197(1)	61(1)
O(2)	1473(5)	4820(2)	487(1)	58(1)
C(1)	1892(5)	3006(2)	1362(2)	39(1)
C(2)	2167(6)	6897(2)	1365(2)	45(1)
C(3)	-335(7)	4139(2)	2224(2)	55(1)
C(4)	1177(5)	5957(2)	1664(2)	43(1)
C(5)	1913(6)	3933(2)	1808(2)	41(1)
C(6)	-42(7)	1897(2)	536(2)	52(1)
C(7)	3774(6)	2380(2)	1392(2)	46(1)
C(8)	886(8)	7424(2)	857(2)	56(1)
C(9)	4296(7)	7248(2)	1604(2)	57(1)
C(10)	1843(7)	1281(2)	570(2)	54(1)
C(11)	-36(6)	2756(2)	930(2)	45(1)
C(12)	3759(7)	1517(2)	993(2)	54(1)
C(13)	1427(8)	5804(2)	2497(2)	61(1)
C(14)	3833(10)	8647(3)	829(2)	78(1)
C(15)	1729(10)	8310(3)	596(2)	81(1)
C(16)	-131(9)	4980(2)	2776(2)	66(1)
C(17)	5123(9)	8124(3)	1337(2)	73(1)

Table A4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for *syn*-2,5-diphenyl-*N*-(2-pyridyl)pyrrolidine isomer **175b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(5)	6632(2)	1901(3)	3200(1)	35(1)
N(2)	6889(2)	3125(3)	3759(1)	36(1)
C(4)	5944(2)	536(3)	3331(1)	26(1)
C(3)	5644(2)	-595(4)	2785(2)	47(1)
C(9)	6416(2)	2847(3)	4466(1)	36(1)
C(8)	6581(2)	4744(3)	4826(1)	41(1)
C(7)	6429(2)	6056(3)	4191(1)	41(1)
C(16)	8228(2)	5717(3)	3552(1)	40(1)
C(15)	7942(2)	508(4)	4774(2)	46(1)

N(1)	7096(2)	2125(4)	2520(1)	63(1)
C(1)	6763(2)	917(4)	1971(1)	49(1)
C(10)	6939(2)	1308(3)	4916(1)	37(1)
C(6)	7033(2)	5089(3)	3584(1)	37(1)
C(14)	8416(3)	-802(4)	5236(2)	56(1)
C(13)	7905(3)	-1313(4)	5853(2)	63(1)
C(2)	6011(2)	-447(4)	2098(2)	49(1)
C(11)	6413(3)	726(4)	5529(2)	52(1)
C(12)	6892(3)	-553(4)	5994(2)	63(1)
C(19)	10350(3)	7203(5)	3568(2)	68(1)
C(21)	9094(2)	4921(4)	3960(2)	54(1)
C(17)	8452(3)	7246(4)	3141(2)	62(1)
C(20)	10145(3)	5666(5)	3973(2)	66(1)
C(18)	9509(3)	7978(5)	3151(2)	76(1)

Table A5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (3*R*,4*R*)-3,4-diphenyltetrahydrothiphene **178**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(1)	7680(2)	3559(4)	7953(2)	81(1)
C(2)	6246(2)	4013(3)	7931(2)	65(1)
C(3)	5402(2)	2751(3)	7558(2)	66(1)
C(4)	5025(3)	2745(5)	6657(2)	98(1)
C(5)	4264(4)	1504(8)	6308(3)	140(2)
C(6)	3928(4)	341(7)	6882(4)	144(2)
C(7)	4286(3)	342(5)	7750(3)	124(2)
C(8)	5012(3)	1530(4)	8083(2)	90(1)
C(9)	5981(2)	4520(3)	8888(2)	65(1)
C(10)	7016(3)	5694(4)	9111(2)	94(1)
C(11)	4635(2)	5089(3)	9063(2)	64(1)
C(12)	4021(3)	6117(4)	8510(2)	92(1)
C(13)	2783(3)	6638(4)	8698(3)	105(1)
C(14)	2166(3)	6136(4)	9437(3)	99(1)
C(15)	2757(3)	5100(5)	9976(2)	102(1)
C(16)	3980(3)	4571(4)	9795(2)	83(1)
C(17)	12648(2)	4261(4)	3181(2)	83(1)
C(18)	11213(2)	4198(3)	3429(2)	62(1)
C(19)	10360(2)	4982(3)	2733(2)	58(1)
C(20)	10252(2)	4422(4)	1863(2)	75(1)
C(21)	9528(3)	5184(5)	1214(2)	93(1)
C(22)	8898(3)	6508(4)	1422(2)	93(1)
C(23)	8960(3)	7079(4)	2280(3)	95(1)
C(24)	9694(2)	6310(3)	2930(2)	75(1)
C(25)	10929(2)	2488(3)	3586(2)	64(1)
C(26)	12004(3)	1921(4)	4221(2)	95(1)
C(27)	9607(2)	2134(3)	3916(2)	61(1)
C(28)	9066(3)	2895(4)	4635(2)	82(1)
C(29)	7857(3)	2527(4)	4946(2)	92(1)
C(30)	7158(3)	1375(5)	4532(2)	95(1)
C(31)	7685(3)	604(5)	3844(3)	118(1)
C(32)	8895(3)	978(4)	3535(2)	98(1)

S(1)	8511(1)	4953(1)	8670(1)	95(1)
S(2)	13487(1)	2810(1)	3841(1)	98(1)

Table A6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*S*)-2-phenyltetrahydrothiophene 1,1-dioxide **189**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(2)	303(2)	1635(1)	3309(1)	53(1)
C(5)	374(5)	1812(2)	1509(2)	37(1)
O(1)	1162(5)	411(2)	3189(2)	83(1)
C(7)	1709(6)	367(3)	437(2)	55(1)
C(10)	-1573(5)	1979(3)	1017(2)	47(1)
C(4)	716(5)	2536(2)	2330(2)	42(1)
C(6)	2002(6)	982(3)	1213(2)	49(1)
C(8)	-253(7)	543(3)	-46(2)	55(1)
C(3)	3046(6)	3127(3)	2480(2)	56(1)
O(2)	-1991(4)	1782(3)	3621(2)	105(1)
C(9)	-1902(7)	1353(3)	247(2)	56(1)
C(1)	2287(6)	2470(3)	3962(2)	62(1)
C(2)	3104(7)	3542(3)	3425(2)	63(1)

Table A7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for proline diamine ZnI_2 complex **145**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(1)	9812(12)	5318(11)	875(3)	45(2)
C(2)	11150(20)	5770(20)	1115(5)	103(7)
C(3)	11140(20)	4541(19)	1369(5)	96(6)
C(4)	10109(17)	3241(14)	1252(3)	62(4)
C(5)	10538(10)	4645(12)	557(2)	40(2)
C(6)	10052(13)	3021(14)	74(3)	50(3)
C(7)	8820(20)	2860(20)	-172(4)	98(6)
C(8)	7870(20)	4410(20)	-150(4)	86(5)
C(9)	8477(13)	5238(12)	143(3)	51(3)
I(1)	4999(1)	3534(1)	608(1)	62(1)
I(2)	8572(1)	-173(1)	687(1)	58(1)
N(1)	8958(9)	4005(9)	1032(2)	36(2)
N(2)	9334(7)	4012(8)	336(2)	28(2)
Zn(1)	7877(1)	2753(1)	660(1)	27(1)

LIST OF PUBLICATIONS

1. Convenient methods for synthesis of C_2-symmetric tetrahydrothiophenes. Periasamy, M.; **Gurubrahamam, R.**; Muthukumaragopal, G. P. ***Synthesis*** **2009**, 1739.

2. Highly enantioselective synthesis of chiral allenes by sequential creation of asymmetric center and chirality transfer in a single pot operation. Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; **Gurubrahamam, R.**; Reddy, P. O. ***Org. Lett.*****, 2012,** *14*, 2932.

3. Convenient method for the synthesis of chiral sulfides and its application in asymmetric Baylis Hillman reactions. **Gurubrahamam, R.**; Periasamy, M. (manuscript under preparation).

4. Copper (I) halide catalysed synthesis of highly enantioselective functionalised chiral allenes using chiral C_1-symmetric proline derived diamines. **Gurubrahamam, R.**; Periasamy, M. (to be communicated).

POSTERS/PAPERS PRESENTED IN SYMPOSIA

1. Presented a poster in the "Junior National Organic Trust Conference" held at School of Chemistry, University of Hyderabad, Hyderabad, 28th to 31st January **2011**; Title: Convenient methods for synthesis of C_2-symmetric tetrahydrothiophenes.

2. Oral presentation and presented a poster in the "Chemfest 2011" 8th in house symposium held at University of Hyderabad, Hyderabad, 25th to 26th February **2011**; Title: Convenient methods for synthesis of chiral sulphur and nitrogen heterocyclics.