Synthesis and Applications of Chiral Camphanyl Amines

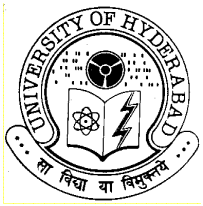
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

POLIMERA OBULA REDDY



SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD 500 046
INDIA
May 2014

Dedicated to

My Parents

Contents

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled **"Synthesis and Applications of Chiral Camphanyl Amines"** has been carried out by Mr. **Polimera Obula Reddy** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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Acknowledgements

I wish to express my deep sense of gratitude and indebtedness with profound respect to my mentor **Prof. M. Periasamy** for his inspiring guidance, teaching, constant encouragement and personal motivation throughout my tenure here.

I thank present and former deans school of chemistry, Prof M. Durga Prasad, Prof. M. V. Rajashekaran, and Prof. D. Basavaiah and all the faculty members of the school of chemistry for their timely help and cooperation.

It is a great privilege to express my heartfelt regards to my teachers Mr.yenimireddy Srinivasa reddy, who taught the basics of science in my school days.

I wish to extend my deep sense of gratitude to my seniors Dr. N. Sanjeevakumar, Dr. M. Nagaraju and Dr. R. Gurubrahmam for their timely help and extreme cooperation for carrying out some of the experiments during my thesis work. I also thank to my colleague Mr. S. Suresh, Mr. M. ShanmugaRaja, Mr. B. Venkanna for their help in this tenure.

I also thank my past and present labmates, Dr. S. Satish Kumar, Dr. B. Mallesh, Dr. M. Dalai, Dr. A. Laxman, Mr. A. Edukondalu, Mr. M. Ramusagar, Mr. V. Harish, Mr. G. Anandarao, Mr. B. Udaykumar, Mr. I. Satyanarayana, Mr. L. Mohan, Mr. E. Ramesh, Mr. K. Thirumurthy, Mr. Yesu and Mr. Srinivas for creating a pleasant working atmosphere.

I thank my friends Mr. Sashank, Mr. A. Srinivas, Mr. Ramaraju, Mr. Srinivasa reddy, Mr. Madhavachary, Mr. N. Ramana Mr. Madhusudan Reddy, Mr. Siva Ramakrishna, for their support in school of chemistry unforgettable.

All the research scholars of the school of chemistry have been extremely helpful and I thank them all. Dr. Mallikarjuna reddy, Dr. Nagarjuna reddy, Mr. Muralikrishna, Mr. Krishna reddy, Mr. Suresh, Mr Naidu, Mr. gangadhar, Dr. Ramesh, Mr. Lee, Dr. Nagaraju, Mr.Chandrashekar reddy, Mr. Satish, Mr. Krishnachary, Mr. Saianna, Mr. Ragavaih, Dr. Santosh, Mr. Konda reddy, Mr.Karthik, Dr. Sheshadri, Mr. Siva reddy Dr. Venu, Mr. R. Ravindra Babu, Dr. Srinivas, Mr. Thirupathi reddy, Mr. Naveen, Mr. Sreedhar reddy. Mr. Trn Prasad, Mr. Obaiah, Mr. Nagaprasad reddy, Mr. Manojveer, Dr. Murali A……Z are to mention.

I thank Dr. P. Raghavaiah for his help in X-ray data collection. All the non-teaching staff of the School has been helpful, I thank them all. Mr. Shetty, Mr. S.

Satyanarayana, Mrs. Vijaya Lakshmi, Mr. V. Bhaskar Rao, Mrs. Asia Parwez, Mr. Vijaya Bhaskar, Mr. K. R. B. V. Prasad, Mr. Ramana, Mr. Joseph, Mr. Santoshand, Mr. Sambasiva Rao are a few to mention.

It is beyond this book to acknowledge the contributions of my parents Mr. P. Venkateswara reddy, Mrs. P. Kumari, my sister Mrs. B. Madhavi mutha reddy and my brothers Mr. P. Sivanagadhara reddy Mr. Kalluri Rajashekarreddy at each and every stage of my life

I wish to extend my sincere thanks to the University authorities for providing all the necessary facilities for this work. The X-ray crystallographic data were collected in the National Single Crystal X-ray facility funded by DST, New Delhi.

Finally I would like to thank the CSIR New Delhi for the financial support during my tenure. Also, financial assistance from the DST-J.C BOSE fellowship research grant of Prof. M. Periasamy is gratefully acknowledged.

Polimera Obula Reddy

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

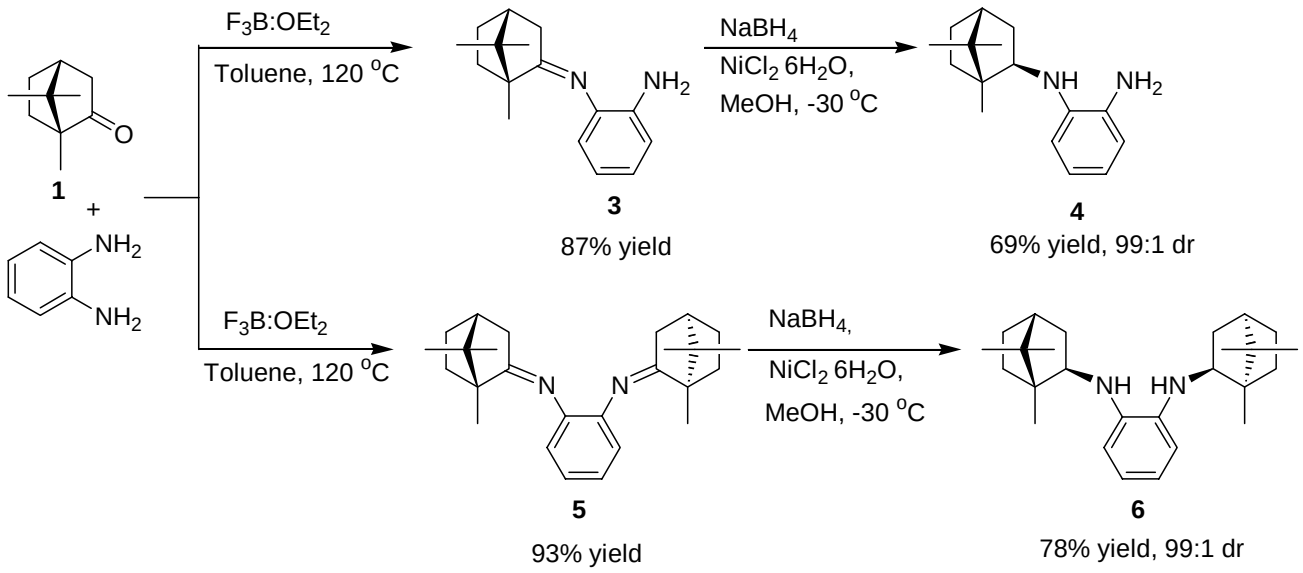
Abstract

This thesis entitled "**Synthesis and Applications of Chiral Camphanyl Amines**" comprises of three chapters. Each chapter is subdivided into four sections namely **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**. The work described in this thesis is exploratory in nature

The first chapter describes studies on the synthesis of chiral amine derivatives using D-(+)-camphor **1**, D-(-)-camphorquinone **2** and various amine sources. In the introductory section, a brief review on the synthesis and applications of various chiral amines containing camphanyl moiety is presented.

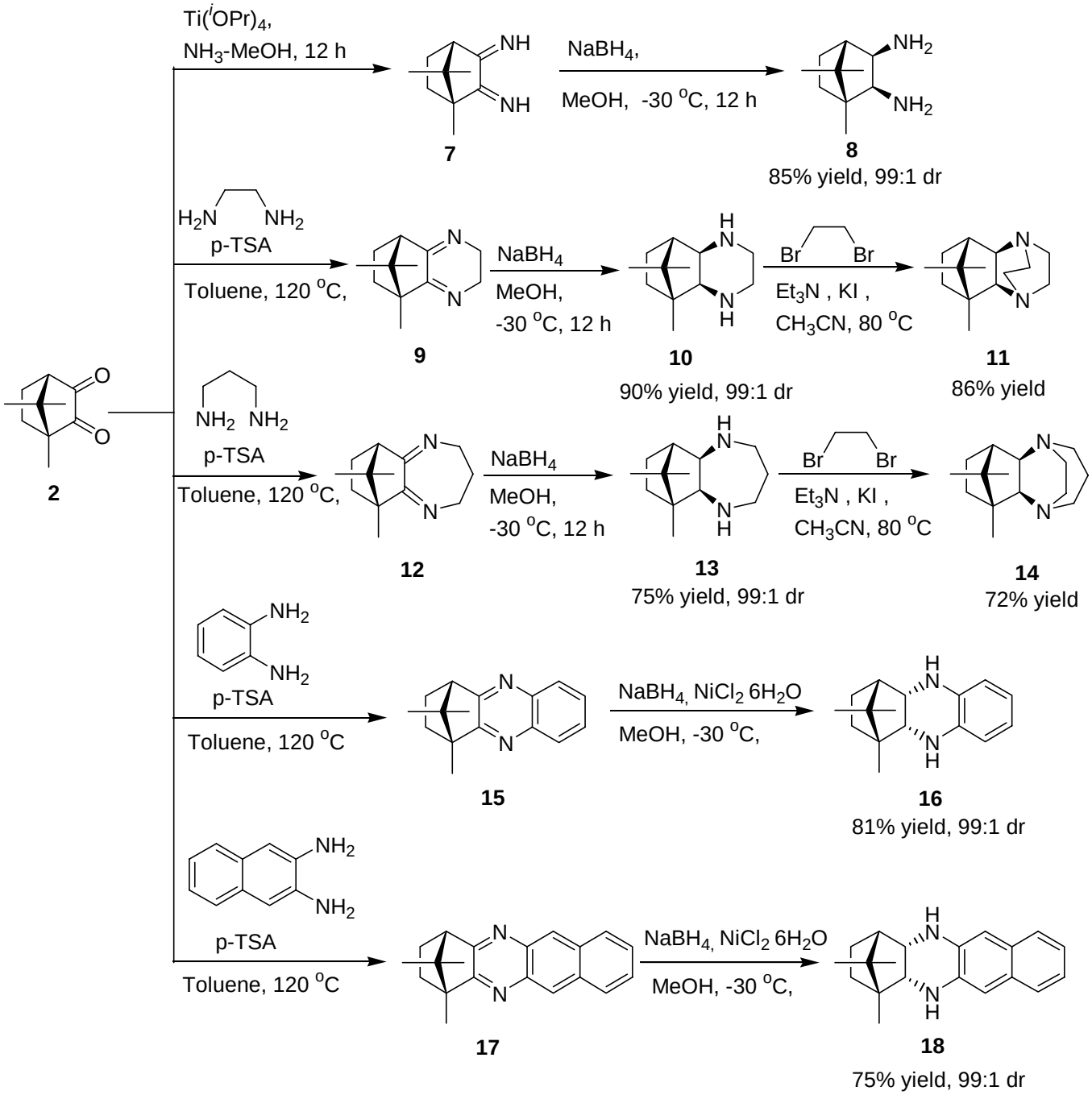
Chiral camphanyl amines have been synthesized via the corresponding imine derivatives of D-(+)-camphor **1** and D-(-)-camphorquinone **2** by reduction using the $NaBH_4/NiCl_2$, $NaBH_4/I_2$, and $(^nBu)_4NBH_4/PhCH_2Cl$ reagent systems. For example, the imine derivatives **3** and **5,** prepared from camphor upon reduction using the $NaBH_4/NiCl_2$ reagent system give the corresponding chiral amines **4** and **6** in good yields (Chart 1**).**

Chart 1



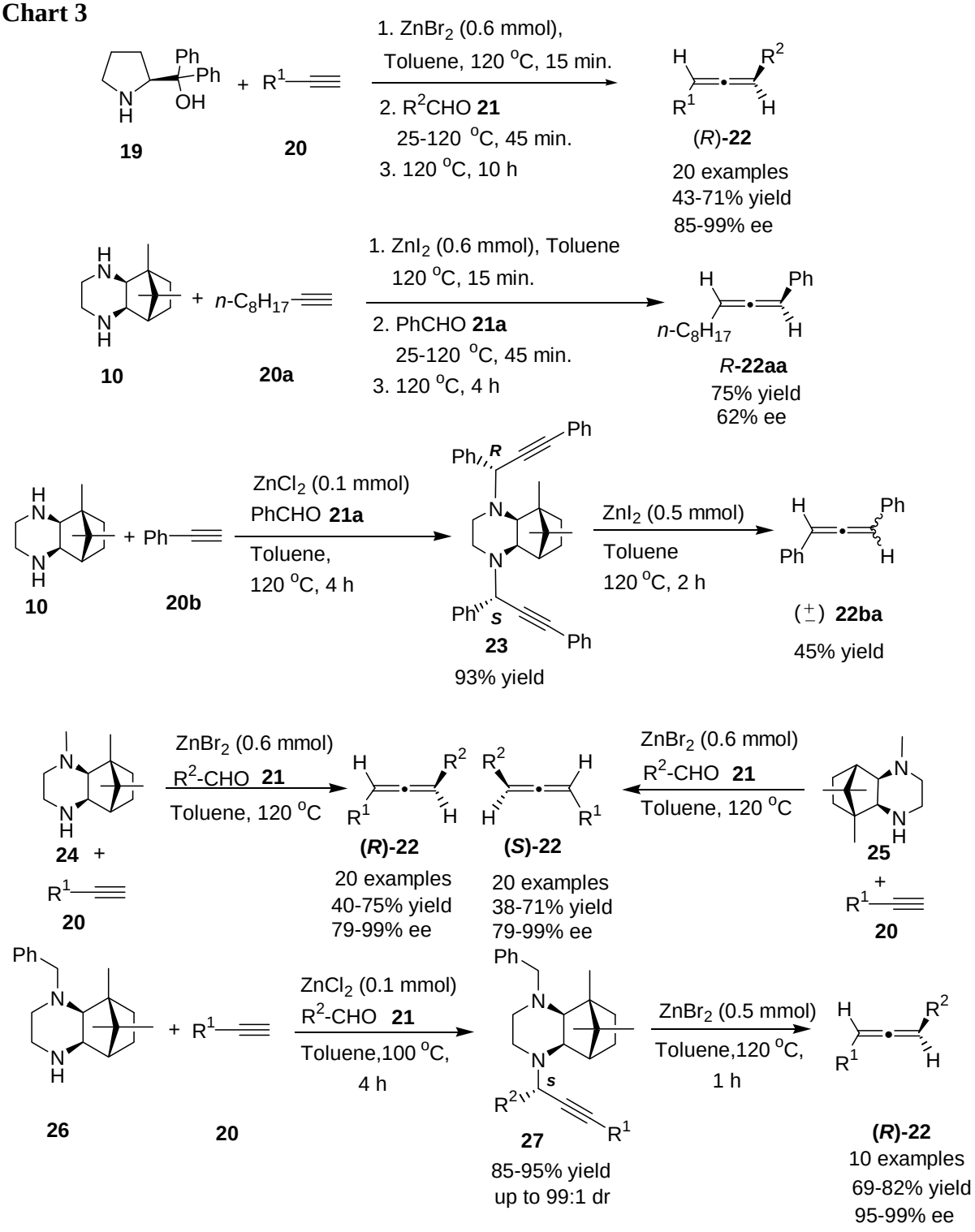
A series of chiral diamines, piperazines and DABCO derivatives have been synthesized via the corresponding imines prepared by condensation of camphorquinone **2** with various diamines followed by $NaBH_4$ reduction under different conditions (Chart 2).

Chart 2



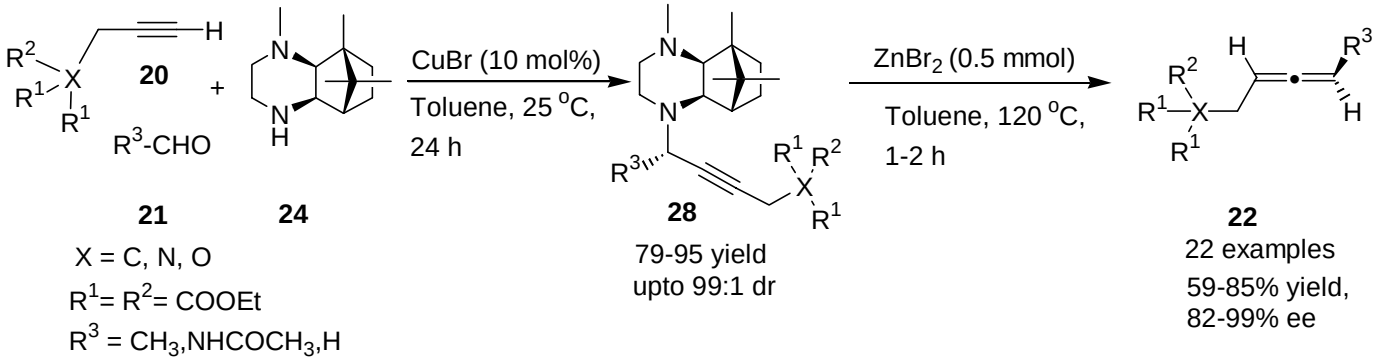
Studies undertaken to examine the scope of the $ZnBr_2$ promoted chiral allene synthesis using (*S*)-diphenylprolinol **19** and camphanyl piperazines **10** are described in Chapter 2 (Chart 3).

Chart 3



In chapter 3**,** results of studies on the development of a methodology to access chiral allenes containing sensitive functional groups including some naturally occurring allenes are described (Scheme 1).

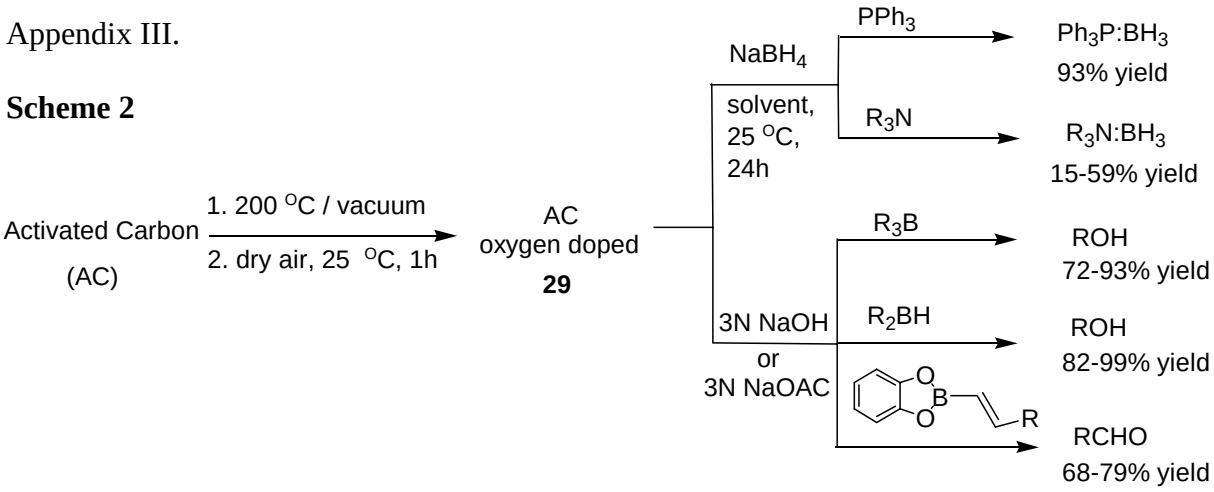
Scheme 1



Representative ^{1}H-NMR, ^{13}C-NMR spectra and HPLC analysis profiles are presented in Appendix-I and X-ray crystallographic data are listed in Appendix-II.

As extension to development of synthetic methods based on borohydride reagents, we have briefly studied the development of new synthetic methods using oxygen doped activated charcoal **29** and borane reagents **(**Scheme 2). Results of these studies are described in the Appendix III.

Scheme 2



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

Chapter 1

Synthesis of Chiral Camphanyl Amines Using D-(+)-Camphor and D-(-)-Camphorquinone

1.1 Introduction

Asymmetric synthesis has become an important area of research in organic chemistry, because it is always a challenging task to synthesize optically active compounds with high selectivities**.** It is well-known that Nature induced chiral transformations and transfer of chiral information from one molecule to another molecule are highly stereospecific.[1] Inspired by Nature, synthetic chemists seek to develop new highly selective synthetic methodology to access natural and unnatural enantiopure biologically active molecules which resulted in the development of new chiral building blocks and chiral catalysts for use in asymmetric organic synthesis.

Chiral starting materials are generally selected from chiral pool of molecules available from natural sources, like amino acids, carbohydrates, alkaloids and terpenoids.[2] Among these four class of chiral molecules, D-(+)-camphor **1** is a unique monoterpenoid available in optically pure form. A large number of D-(+)-camphor derivatives have been prepared and widely used as chiral auxiliaries and chiral ligands in asymmetric organic transformations.[3] The successful exploitation of this chiral natural product in asymmetric synthesis is due to its rigid [2.2.1] bicyclic framework with steric bulk being provided by the 8-,9-and 10-methyl groups. Also, in recent years, there has been a renewed interest in the use of chiral skeletons containing camphanyl moiety in chemistry because the D-(+)-camphor is inexpensive and it has structural diversity at C_3, C_4, C_5, C_6, C_8, C_9 and C_{10} positions (Figure **1**). Furthermore, the cleavage of the C_1-C_2, C_2-C_3, and C_1-C_7 bonds provides a variety of chiral derivatives.[4] Accordingly, it is of our interest to briefly review the reports on the

synthetic methods to access chiral organic derivatives from camphor and its derivatives like camphorquinone (Figure **1**).

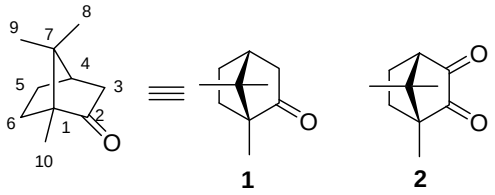
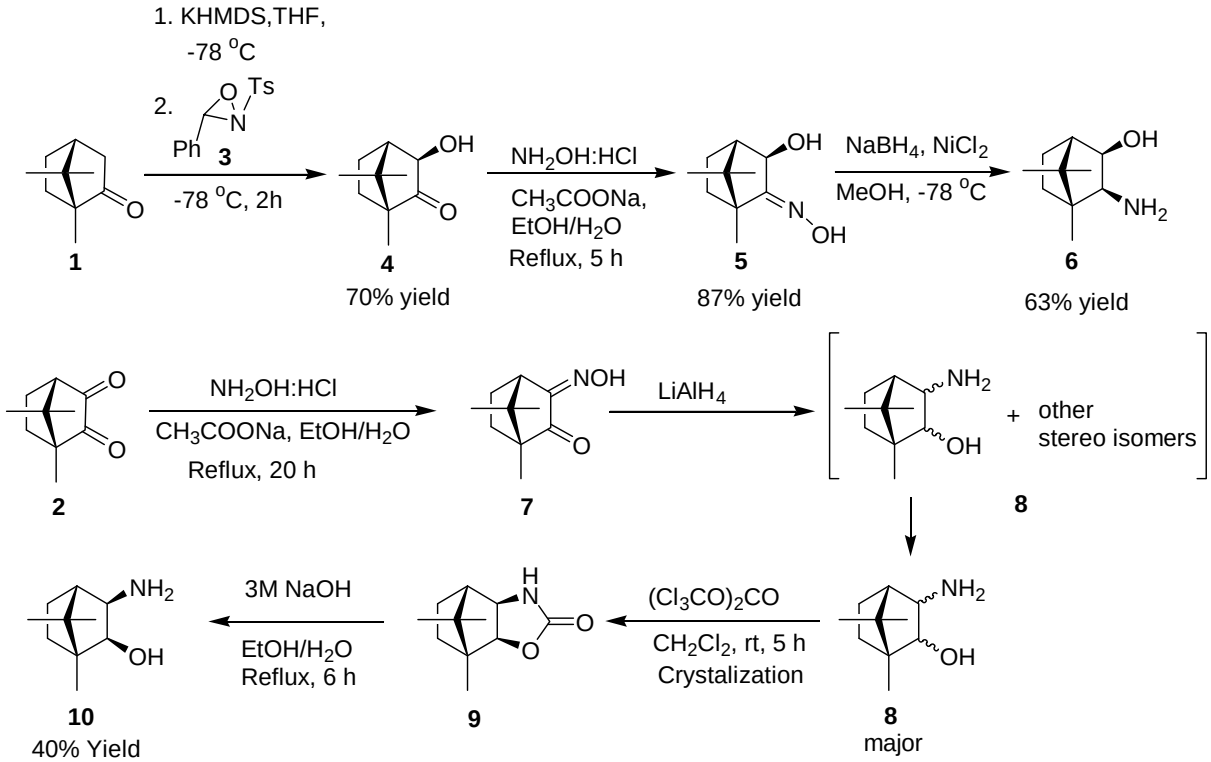


Figure 1

1.1.1 Synthesis of chiral amine derivatives containing camphanyl moiety

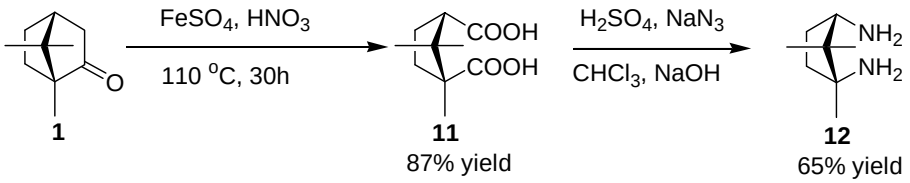
The camphanyl amines and camphanyl amino alcohols play a central role in the expanding the area of asymmetric synthesis. It has always been a challenge to synthesize these optically active compounds in good yields and selectivity. A diastereoselective multistep synthesis of chiral camphanyl amino alcohol derivatives **6** and **10** involves the use of D-(+)-camphor as starting material as outlined in Scheme **1**.[5]

Scheme 1



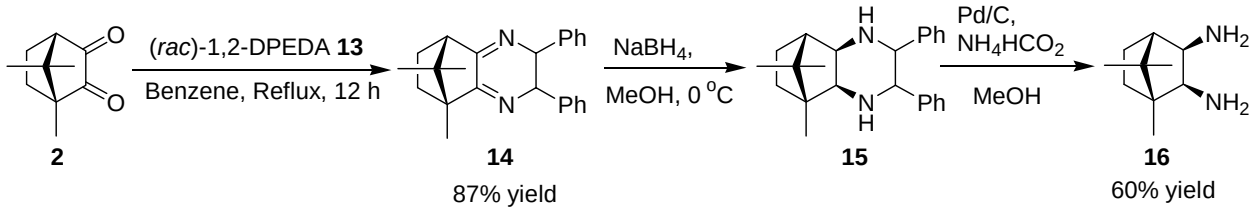
The (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine **12** was prepared by the reaction of (1*R*,4*S*)-(+)-camphoric acid **11** with sodium azide in the presence of concentrated sulfuric acid (Scheme **2**).[6]

Scheme 2



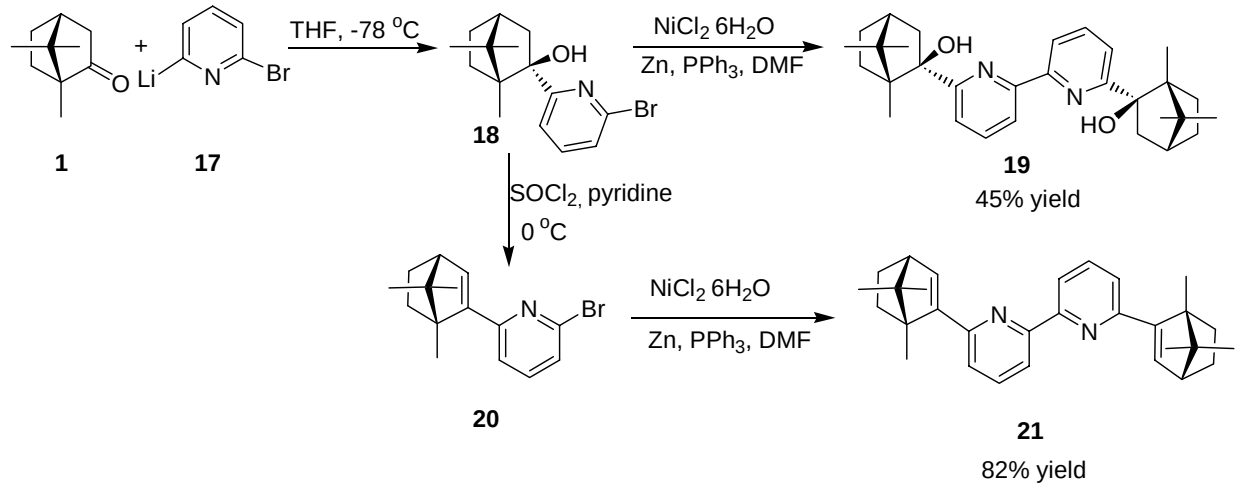
Synthesis of (*R*)-camphanyldiamine **16** from D-(+)-camphor **1** and *rac*-1,2-diphenylethylenediamine **13** *via* $NaBH_4$/MeOH reduction has been reported (Scheme **3**).[7]

Scheme 3



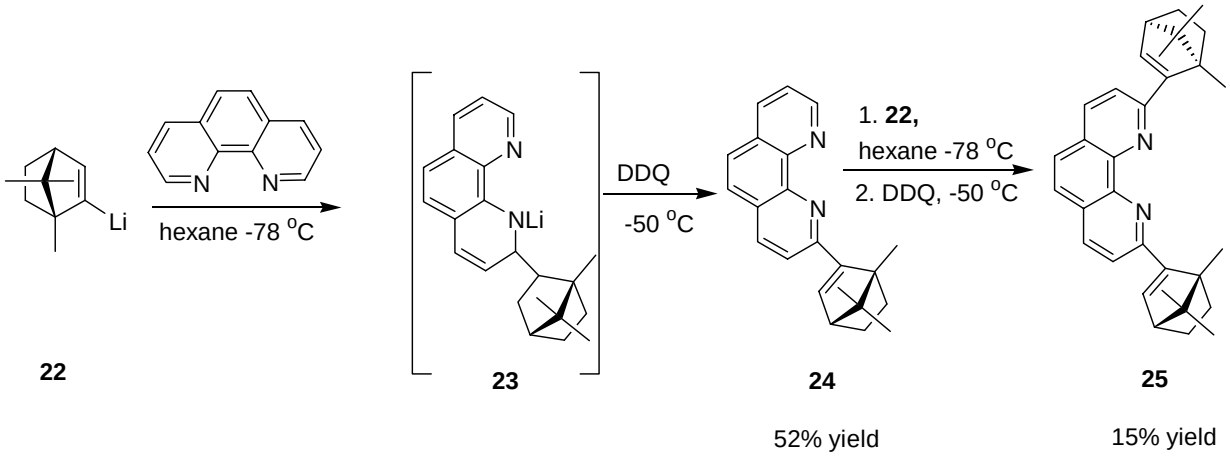
Camphor based 2,2'-bipyridyl systems were exploited as chelating ligands in coordination chemistry due to its redox stability.[8, 9] The bipyridyl ligands **19** and **21** have been prepared from the readily accessible pyridyl-carbinol **18** by the reaction of 2-lithio-6-bromopyridine **17** with (+)-camphor followed by nickel(0)-mediated homocoupling reaction of the compounds **18** and **20** (Scheme **4**).[10]

Scheme 4



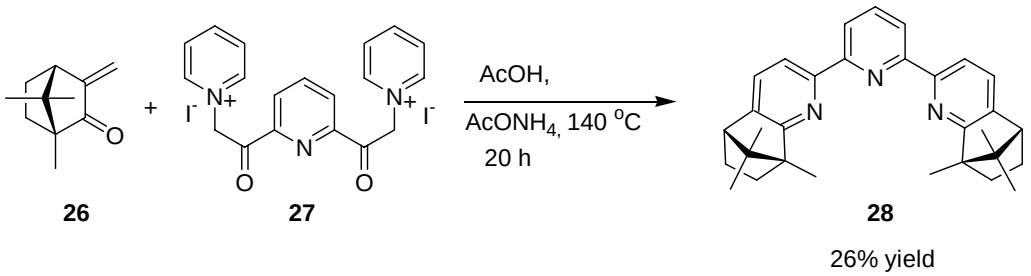
Addition of the camphanyl lithium derivative **22** to phenanthroline followed by DDQ-induced aromatization gave the phenanthroline derivative **24** in 52% yield. Further additionof the bornenyllithium **22** to **24**, followed by aromatization gave the bis(bornenyl)phenanthroline **25** in 15% yield (Scheme **5**).[11]

Scheme 5



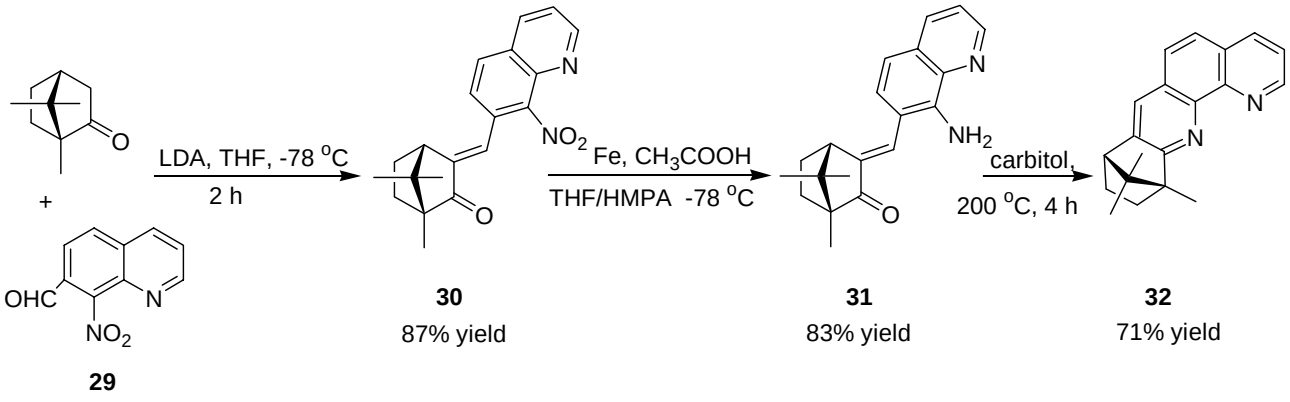
The C_2-symmetric terpyridine **28** was obtained by the reaction of 3-methylene camphor **26** with 2,6-bis(pyridinioacetyl)pyridine iodide **27** in 26% yield (Scheme **6**).[12]

Scheme 6



The enolate anion of (+)-camphor reacts with nitroaldehyde **29** to give the condensed product **30**. The nitro group was then reduced to the amine **31** in 83% yield by refluxing with powdered iron in acetic acid/ethanol/water (2:2:1). Subsequent intramolecular condensation by refluxing **31** in a degassed carbitol solution, afforded the phenanthroline **32** in 71% overall yield from (+)-camphor (Scheme **7**).[13]

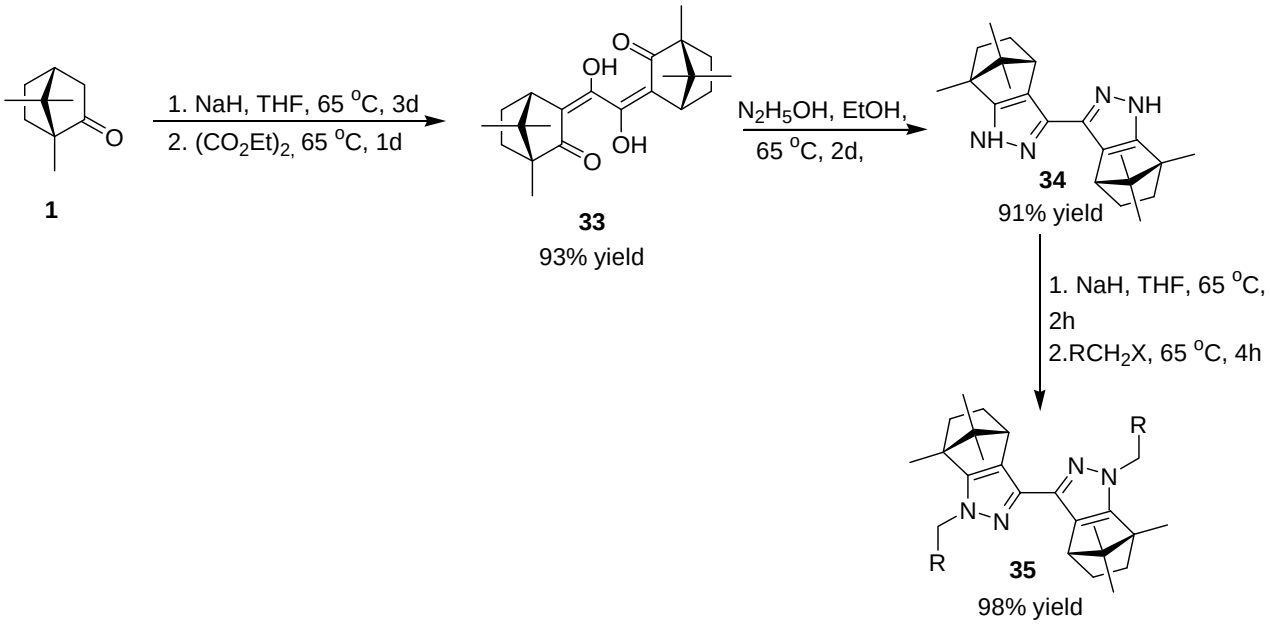
Scheme 7



The camphor based chiral 3,3'-bipyrazole derivatives **35** have been investigated as potential ligands for copper-free Wacker oxidation of alkenes.[25] It was prepared in 98% yield, starting from 1,3,4,6-tetraketone **33,** available in two tautomeric enol forms by double Claisen condensation of (+)-camphor with diethyl oxalate. A second tandem condensation

with hydrazine hydrate furnished the key intermediate 3,3-bicamphorpyrazole(bcpz) **34** as an insoluble powder in 91% yield. Further reaction with alkyl halide gave the chiral 3,3'-bipyrazoles **35** in 98% yield (Scheme **8**).[14]

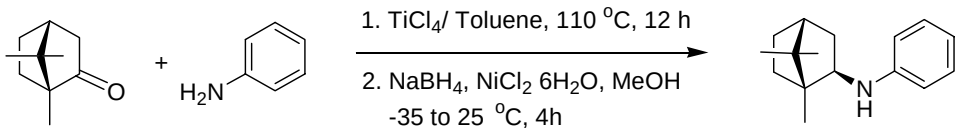
Scheme 8



1.1.2 Previous work from this laboratory

Several new convenient methods to access chiral amines and amino alcohol derivatives have been reported from this laboratory.[15] Some of these methods involve selective reductions using $NaBH_4$ and $NaBH_4/I_2$ reagent system in crucial steps.[16] For example, a method for the synthesis of isobornyl aniline **37** was developed *via* condensation of D-(+)-camphor **1** and aniline **36** followed by selective reduction with $NaBH_4/NiCl_2$ $6H_2O$ reagent system (Scheme **9**).[17]

Scheme 9



1 **36** **37**

75% yield
99% dr

We have undertaken efforts to synthesize various amines and amino alcohol derivatives using D-(+)-camphor **1** and D-(-)-camphorquinone **2**. The results of these studies are described in the next section.

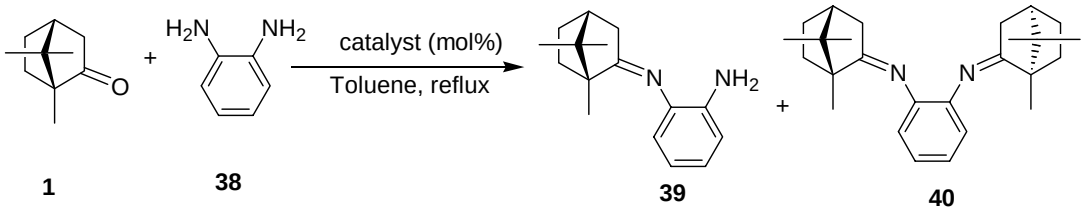
1.2 Results and Discussion

1.2.1 Synthesis of chiral N,N-dicamphanyl derivatives

We have chosen the commercially available naturally occurring D-(+)–camphor **1** and the easily accessible D-(-)-camphorquinone **2** as chiral precursors for the preparation of camphanyl nitrogen heterocycles. We have observed that the chiral aromatic nitrogen heterocycles and dihydroquinoxalines are readily accessed by reduction of the corresponding imine intermediate using the $NaBH_4/NiCl_2.6H_2O$ reagent system (nickel boride formed *in situ*) reduction. Initially, the D-(+)-camphor **1** was reacted with *o*-phenylenediamine **38** in the presence of $F_3B{:}OEt_2$ (10mol %) to obtain the monoimine **39** (54% yield) along with the diimine **40 (**34% yield). We have found that the nature of acid catalyst and amount of substrate influence this transformation. The results are summarized in (Table **1**).

We examined the condensation of camphor **1** with phenylenediamine **38** using $TiCl_4$, in toluene at 120 °C. In this case, the desired product imines **40** was obtained in only moderate yields and it was somewhat difficult to purify the product. The unreacted ketone remained when reaction was carried out using $Ti(^{i}OPr)_4$. Among all acid catalysts were examined, the $F_3B{:}OEt_2$ (20 mol%) gave better results in terms of yields and selectivities. We have observed that the reaction of camphor (1equiv.) and phenylenediamine **38** (1.5 equiv) in the presence of $F_3B{:}OEt_2$ (10 mol%) gave the monoimine **39** in 87% yield (Table **1**, entry **3**). Whereas, the reaction of camphor **1** (1.5 equiv.) with phenylenediamine **38** (0.5 equiv.)] in presence of $F_3B{:}OEt_2$ (20 mol%) gave the diimine **40** in 93% yield (Table **1**, entry **4**).

Table 1. Reaction of D-(+)-camphor **1** and phenylenediamine **38** in toluene promoted by acid catalysts.[a,b]



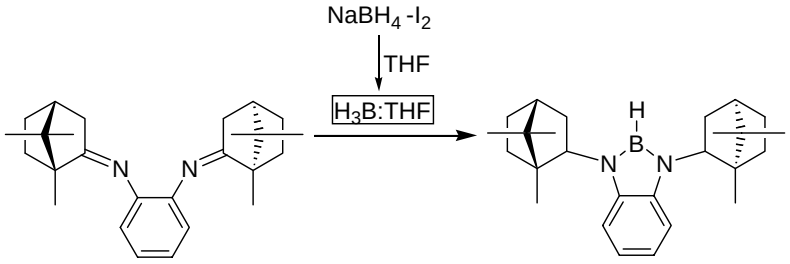
1 **38** **39** **40**

S No	Camphor (mmol)	Phenylene diamine 38 (mmol)	catalyst	Mol%	Time (h)	Monoimine 39 Yield (%)	Diimine 40 Yield (%)
1	10	5	TSOH	10	24	-	-
2	10	5	$F_3B{:}OEt_2$	10	24	54	34
3	10	15	$F_3B{:}OEt_2$	10	12	87	8
4	15	5	$F_3B{:}OEt_2$	20	24	4	93
5	10	30	$TiCl_4$	10	24	-	56
6	10	5	$Ti(O^iPr)_4$	10	24	-	45

[a]The reactions were carried out by using amine **38 (**5.0 mmol), camphor **(**10.0 mmol)) in toluene (20 mL) at 120 °C. [b]Isolated yield.

Next, we turned towards the reduction of the diimine **40** with various hydride sources. First, we performed the reduction using $NaBH_4$ in different solvents (MeOH, EtOH, ^{i}PrOH) but did not get the desired product. When the reduction was carried out using $NaBH_4/I_2$, or $^nBu_4NBH_4/PhCH_2Cl$ at -30 °C, the borolidine **41** was obtained in 90% yield with up to 70:30 dr (Scheme **10**).

Scheme 10

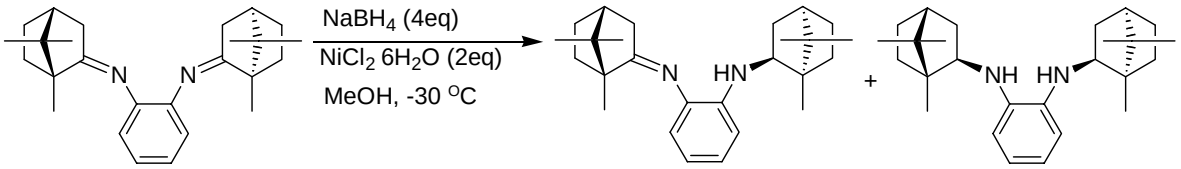


40 **41**

90% yield,
70:30 dr

Previously, a method for the synthesis of isobornylaniline by the reduction of camphor-anil with $NaBH_4/NiCl_2.6H_2O$ was reported from this laboratory.[17] When we performed the reduction of the diimine **40** in the presence of nickel boride [generated *in situ* from $NiCl_2.6H_2O$ (2 equiv) and $NaBH_4$ (4 equiv)] in MeOH at -30 °C, the partially reduced imine **42** was obtained in 67% yield along with the diamine **43** in 16% yield and 99:1 dr (by ^1H NMR). Using, $NiCl_2.6H_2O$ (4 equiv.) and $NaBH_4$ (10 equiv) in MeOH at -30 °C, the diamine **43** was obtained in 56% yield along with the imine **42** in 35% yield. When a large excess of $NiCl_2.6H_2O$ (4 equiv.) and $NaBH_4$ (20 equiv.) were used in MeOH at -30 °C, the diamine **43** was obtained in 78% yield along with the imine **42** in 8% yield (Table **2**).

Table 2. Reduction of diimine **40** with $NaBH_4/NiCl_2.6H_2O$ reagent system.[a]



40 **42** **43**

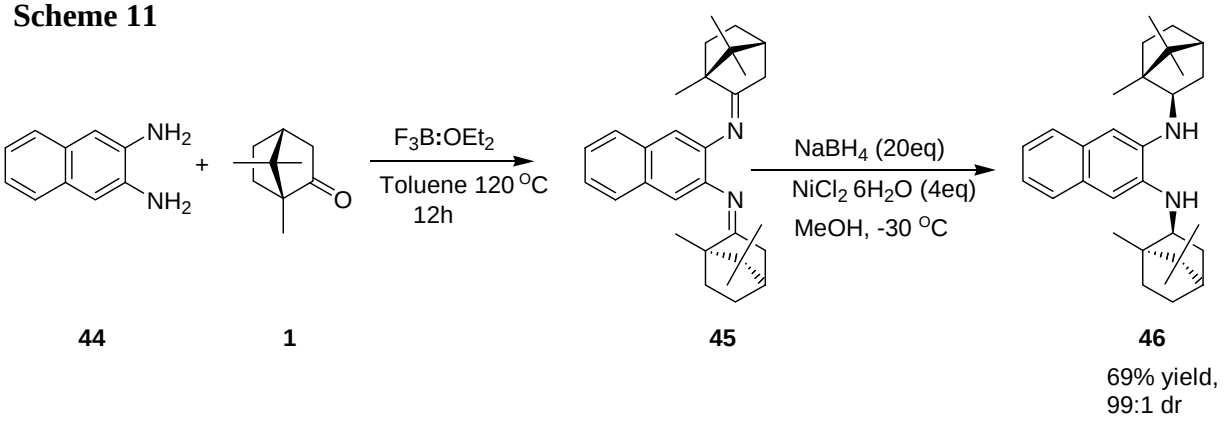
S. No	Diimine 40 (mmol)	$NaBH_4$ (mmol)	$NiCl_2\,6H_2O$ (mmol)	Time(h)	42 Yield (%)[a]	43 Yield (%)[a]
1	1	30	0	6	-	-
2	1	4	2	6	67	16
3	1	10	2	6	35	56
4	1	10	4	6	19	62
5	1	20	4	12	8	78

[a]The reactions were carried out by using diimine **40 (**1.0 mmol), in methanol (3 mL) at -30 °. [b]Isolated yield. [c]The dr was determined by ^1H-NMR analysis of amine **43.**

The configurations at the newly formed stereogenic centers of the diamine **43** were assigned as 2*S*, 2'*S* with exo, exo stereochemistry by the single crystal X-ray structure analysis. Similarly, the diimine **45** is readily prepared by the reaction of D-(+)-camphor **1** with naphthalene diamine **44** in the presence of $F_3B{:}OEt_2$ (20 mol%) in toluene under reflux

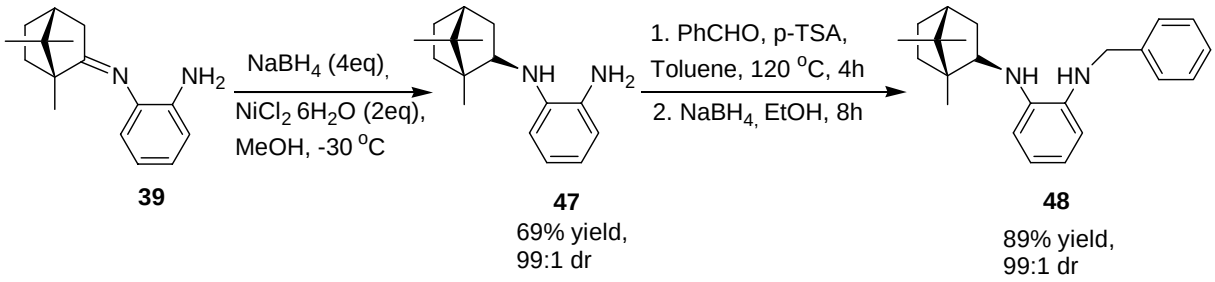
conditions. This diimine **45** was further reduced to the diamine **46** using standard conditions (Table **2**, entry **5**) in 69% yield with 99:1 dr (Scheme **11**).

Scheme 11



Next, we have carried out the converstion of the imine **39** to the N-camphanyl phenylenediamine **47** by the reduction of imine **39** in the presence of $NiCl_2.6H_2O$ (2 equiv.) and $NaBH_4$ (4 equiv.) in MeOH at -30 °C in 69% yield with 99:1 dr. Condensation of the amine **47** with benzaldhyde in the presence of p-TSA, followed by reduction with $NaBH_4$ in EtOH gave the unsymmetrical diamine **48** in 89% yield with 99:1 dr (Scheme **12**).

Scheme 12

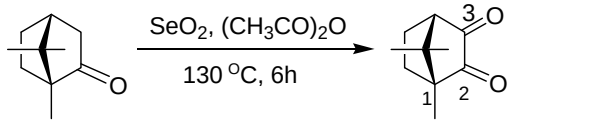


1.2.2 Synthesis of new chiral camphanyldiamine and amino alcohol derivatives from D-(-)-camphorquinone

D-(-)-Camphorquinone **2** is a versatile reagent which can be advantageously used for the synthesis of new chiral ligands because it has special unique property, with one of the

carbonyl groups is highly reactive. The D-(-)-camphorquinone **2** is readily accessed by the reaction of D-(+)–camphor **1** with SeO_2 in acetic anhydride at 130 °C (Scheme **13**).

Scheme 13



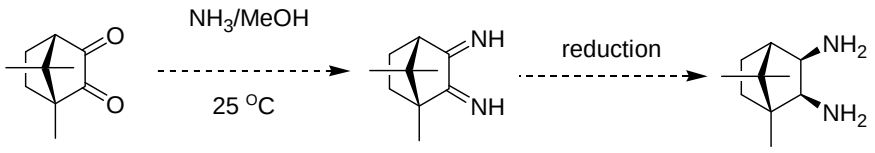
D-(+)-camphor **1** D(-)-camphorquinone **2**

We have undertaken efforts towards the synthesis of various camphanyl derivatives using the D-(-)-camphorquinone **2**.

1.2.2.1 Synthesis of camphanyldiamine 16 derivatives

As outlined in the introductory section, the (*R*)-camphanyldiamine **16** has been successfully used in asymmetric transformations. However, synthesis of camphanyldiamine **16** requires multistep operations and also the overall yield is very less.[7] Therefore, we were looking a simple and convenient, one pot method of synthesis of the diamine **16** from D-(-)-camphorquinone **2.** The synthetic strategy is outlined in Scheme **14** which involve condensation with ammonia to obtain the diimine **49** followed by reduction with $NaBH_4$

Scheme 14

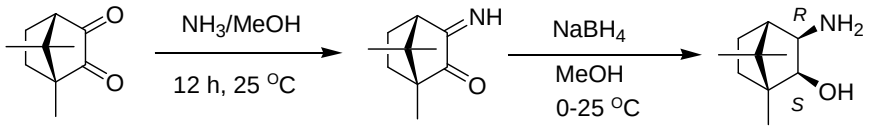


2 **49** **16**

We have observed that the reaction of D-(-)-camphorquinone **2** with methanolic ammonia at room temperature for 12h, followed by $NaBH_4$ reduction did not give the expected diamine product **16**. But interestingly, gave the amino alcohol **10** in 83% yield. The configurations of the newly formed stereogenic centers were assigned as 2*S*,3*R* by

comparison of the $[\alpha]_D^{25}$ value of this product with data reported for the compound **16** (Scheme **15**).[19]

Scheme 15

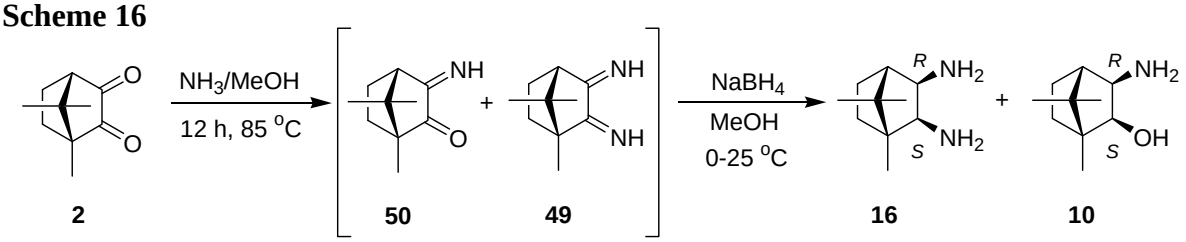


2 **50** **10**

83% yield

We have observed that the reaction at reflux conditions (85 ºC) for 12h followed by reduction with $NaBH_4$ under ambient conditions afforded a mixture of the diamine **16** (12% yield) along with the amino alcohol **10** in 67% yield (Scheme **16**).

Scheme 16

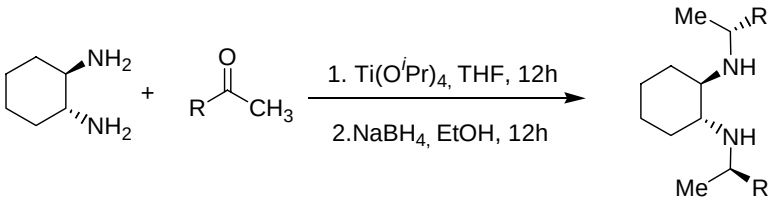


2 **50** **49** **16** **10**

12% yield 67% yield

Previously, it has been reported from this laboratory that reductive N-alkylation of *trans*-(*R,R*)-1,2-diaminocyclohexane **51** by prochiral ketones **52** using the $Ti(O^iPr)_4/NaBH_4$ system gives the corresponding alkylamine derivatives **53** in 76–95% yields with good diastereoselectivity (23:1:1) (Scheme **17**).[20]

Scheme 17



51 **52** **53**

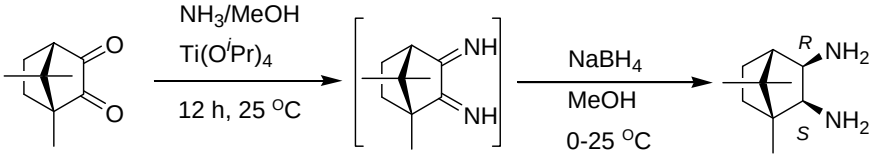
R= Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-Me-Ph, 4-MeO-Ph, 2-Pyridyl, 2-Naphthyl

76-95% yield

We followed this methodology for the synthesis of camphanyldiamine **16**. We have observed that the D-(-)-camphorquinone **2** reacts with methanolic ammonia and $Ti(^iOPr)_4$ to

give the diimine intermediate **49** which upon *in situ* reduction with $NaBH_4$ affords the diamine **16** in 85% yield. The configurations of the newly formed stereogenic centers were assigned as 2*S*,3*R* by comparison of the optical rotation value of this corresponding hydrochloride with data reported for the dihydrochloride salt of **16 (**Scheme **18**) [7]**.**

Scheme 18

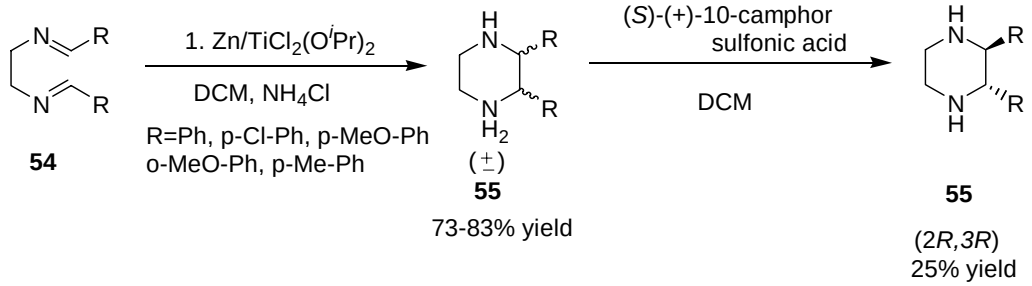


The methods developed for the syntheses of the diamine **16**, and amino alcohols **10** have considerable potential for further exploitation in asymmetric synthesis.

1.2.3 Synthesis of new chiral camphanyl piperazine derivatives

Previously, a simple method has been developed in this laboratory for the synthesis of diastereomerically pure (±)-trans 2,3-diarylpiperazines **55** in 73-83% yield by intramolecular reductive coupling of diimines **54** using the $Zn/Ti(O^iPr)_2Cl_2$ reagent system (Scheme **19**).[21] The racemic product can be readily resolved using (1*S*)-(+)-10-camphorsulfonic acid to obtain the chiral 2*R*,3*R* piperazine **55.**

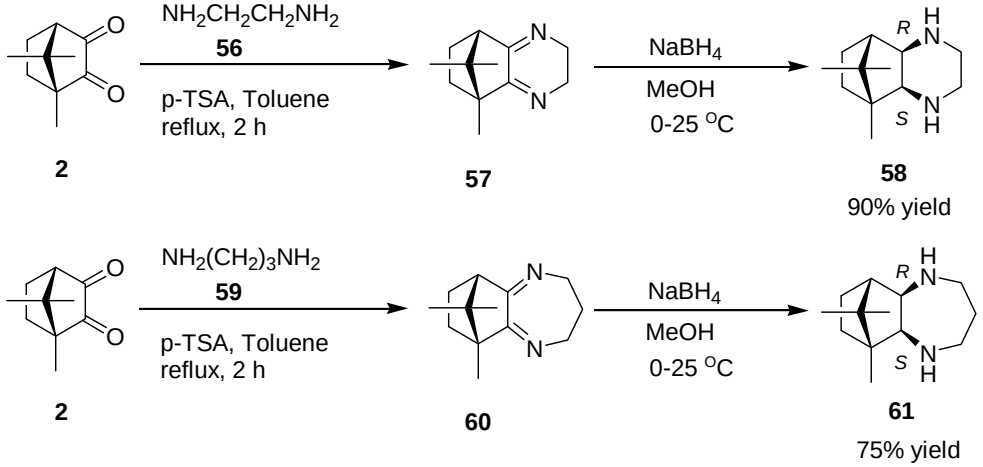
Scheme 19



It was of our interest to synthesize chiral camphanyl piperazine derivatives from D-(-)-camphorquinone **2** as the resulting secondary amine could have *cis* or *trans* relationship

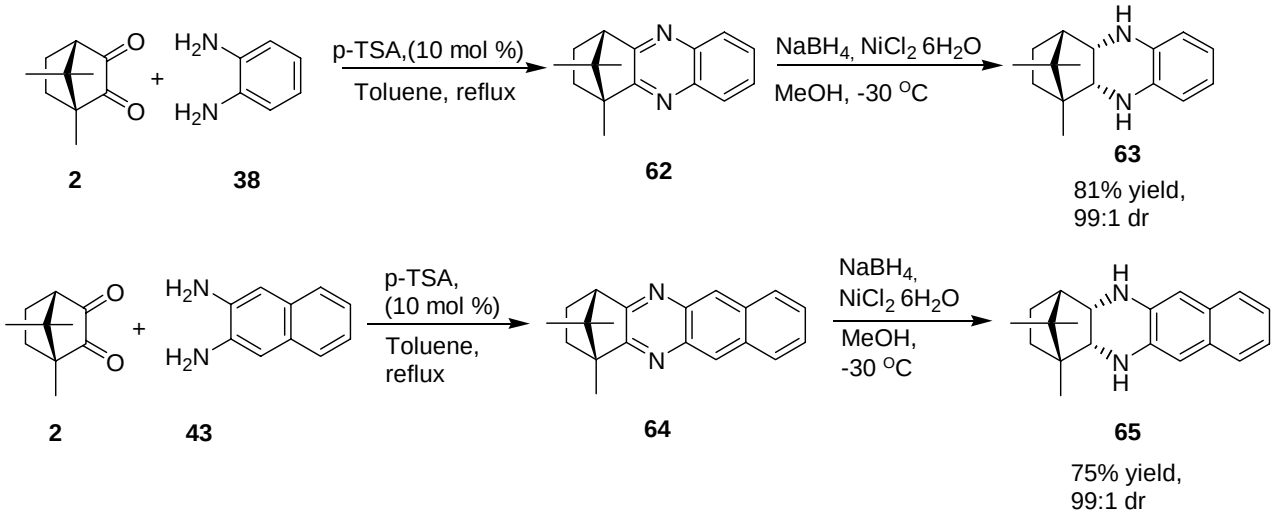
with each other. We have observed that the reaction of D-(-)-camphorquinone **2** with aliphatic diamine (**56** or **59)** in the presence of p-TSA (5 mol%) gives the corresponding dihydropyrazine **57** and **60** derivatives. Subsequent reduction of the compounds **57** and **60** with $NaBH_4$/MeOH at 0 °C afforded the substituted quinazoline **58** and **61** in 90 and 75% yields, respectively. Four diastereomeric products were expected in this reaction but selectively only one diastereomeric product **58** was obtained from the compound **57**. Also, in the case of **60**, the $NaBH_4$ reduction gave only one product **61.** The configurations of the newly formed stereogenic centers were assigned as 2*S*,3*R* by comparison with the data reported for the diamine **16** (Scheme **20**).[18]

Scheme 20



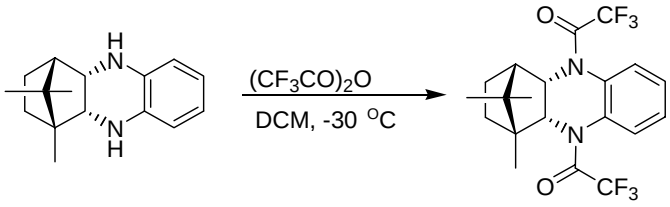
Further, we have extended this methodology for the synthesis of other aromatic diamines. When the D-(-)-camphorquinone was reacted with aromatic diamines (**38** or **43**) in the presence of p-TSA (10 mol%) under refluxing conditions in toluene, the benzodiazepine derivatives (**62** or **64)** were obtained which on reduction with $NaBH_4/NiCl_2$ $6H_2O$ in MeOH at -30 °C afforded the dihydroquinoxalines **63** or **65** in 75-81% yield with 99:1 dr (Scheme **21**).

Scheme 21



Single crystal X-ray structure analysis of the amide derivative **66** of dihydroquinoxaline **63** indicated that the configuration of the newly formed stereogenic centers of **63** and **65** were 2*R*,3*S* with endo, endo stereochemistry **(**Scheme **22,** Figure **2**).

Scheme 22



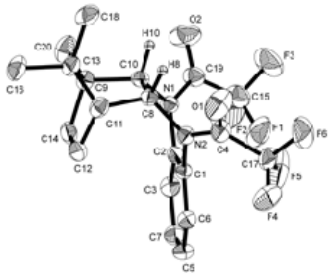


Figure 2. ORTEP representation of the crystal structure **66** (Thermal ellipsoids are drawn at 50% probability the presence of other molecule is omitted in unit cell for clarity).

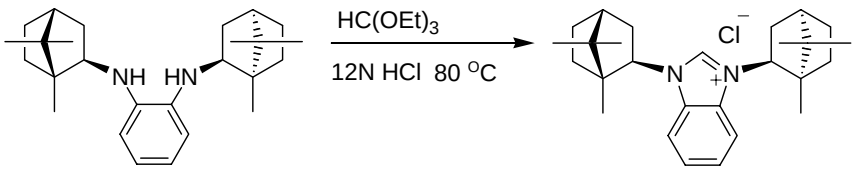
This is an interesting observation since the newly formed stereogenic centers in the simple $NaBH_4$ reduction of the related dihydropyrazine **57** and **60** gave the products **58** and

61 with 2*S*,3*R* configuration. The difference may be due to steric effects of the aromatic system which leads to reduction from the exo face.

1.2.4 Synthesis of chiral imidazolium salts

We have also undertaken studies towards the synthesis of chiral NHC ligands from the chiral camphanyldiamines as the chiral diamines **43** and **48** are expected to the usefull in the synthesis of chiral imidazolium salts which are NHC precursors. We have observed that when N,N dicamphanyl aromatic diamine **43** reacts with triethyl orthoformate in the presences of 12N HCl to give the benzimidazolium salts **67,** in 86% yield (Scheme **23**, Figure **3**).[18]

Scheme 23



43 **67**

86% yield,

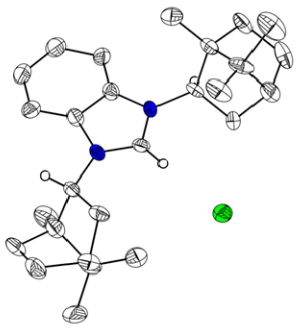
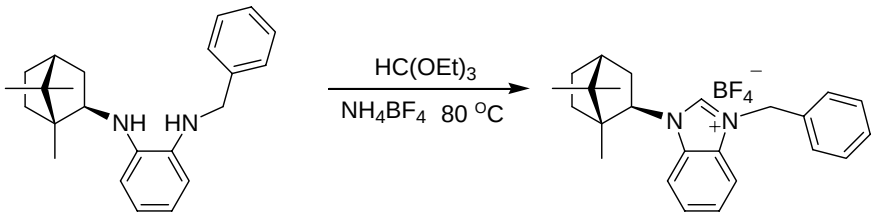


Figure 3. ORTEP representation of the crystal structure **67** (Thermal ellipsoids are drawn at 50% probability the presence of other molecule is omitted in unit cell for clarity).

Similarly, the reaction of chiral diamine **48** with triethyl orthoformate in the presence of NH_4BF_4 gave the corresponding benzimidazolium salt **68** in 91% yield (Scheme **24**).

Scheme 24

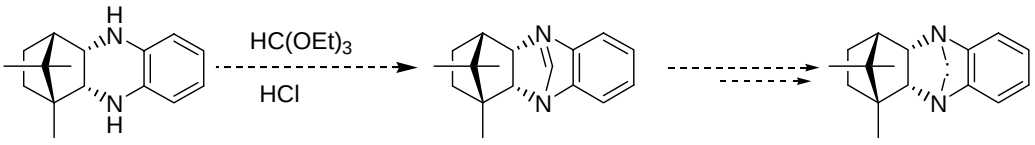


48 **68**

91% yield,

Next, we envisaged the utility of the camphanyl dihydroquinoxalines **63** in the synthesis of chiral imidazolium salts because such derivatives would be useful precursor to access the strained carbenes as outlined in Scheme **25**.

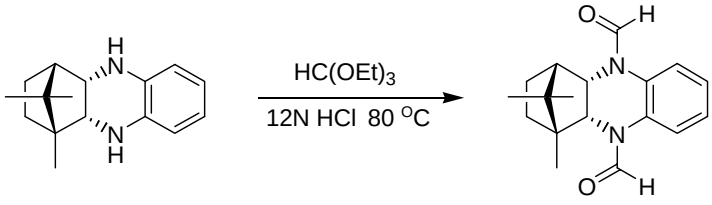
Scheme 25



63 **69**

Unfortunately, the reaction of dihydroquinoxaline **63** with triethyl orthoformate in the presence of HCl gave only the diamide **70** in 95% yield (Scheme **26**). The structure of the diamide **70** was further confirmed by X-ray structural analysis (Figure **4**).

Scheme 26



63 **70**

95% yield,

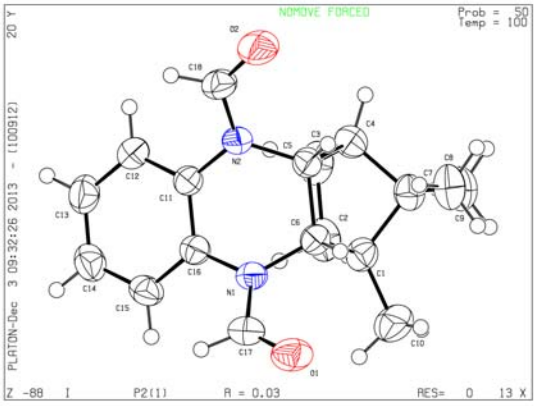
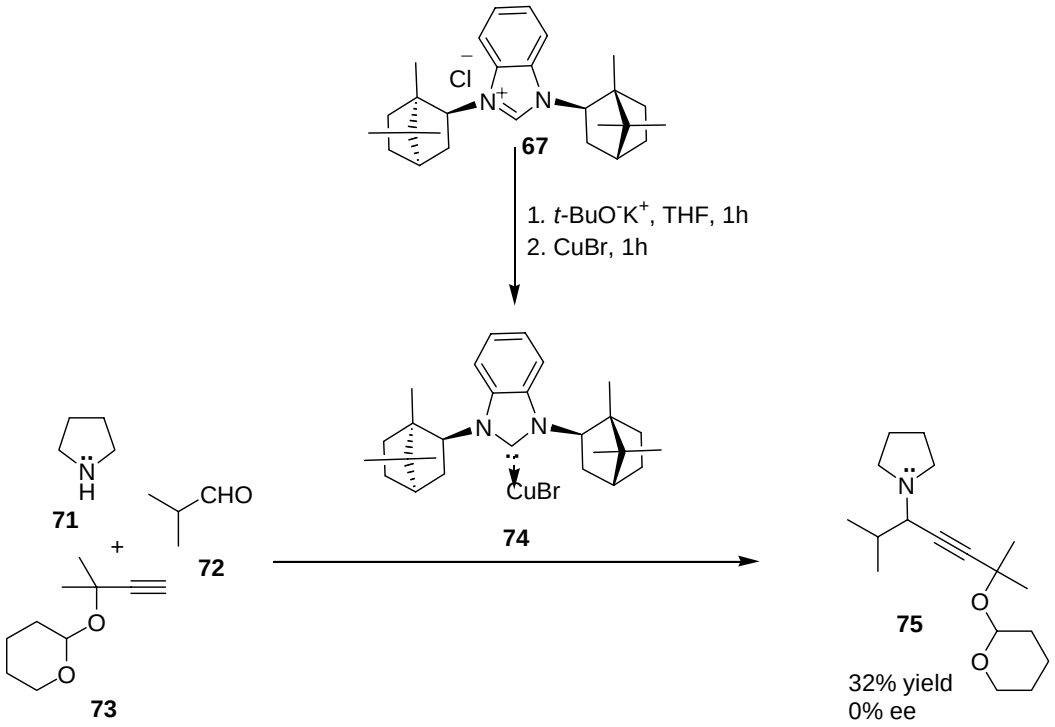


Figure 4. ORTEP representation of the crystal structure **70** (Thermal ellipsoids are drawn at 50% probability the presence of other molecule is omitted in unit cell for clarity).

We have briefly examined the use of the benzimidazolium salt **67** for synthetic transformations like CuBr catalyzed enantioselective three-component reaction of aldehydes, amines and alkynes using benzimidazolium salts as a ligand (Scheme **27)**.[22]

Scheme 27



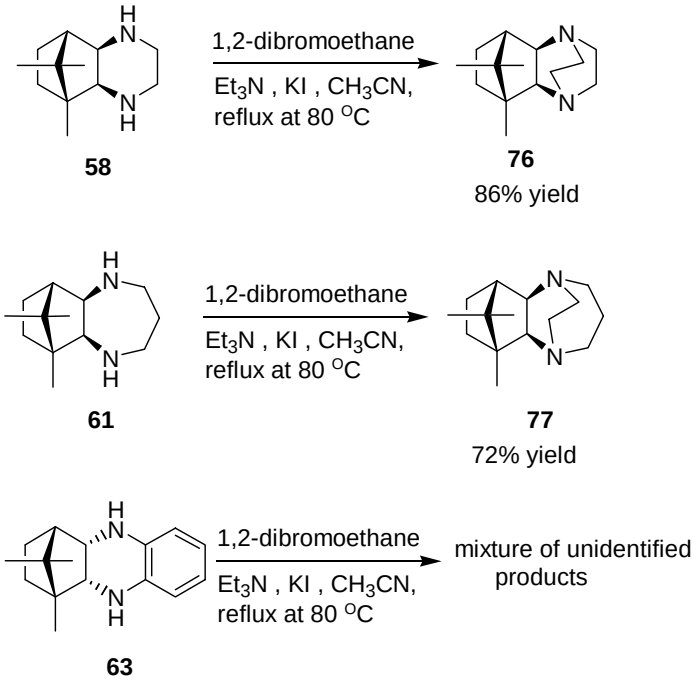
Unfortunately, the chiral carbene complex **74** generated *in situ* does react with alkyne, aldehyde and achiral amine to give the propargylamine **75** in 32% yield but without any asymmetric induction. (Scheme **27).**[23]

1.2.5 Synthesis of chiral camphanyl DABCO derivatives

It was also of interest to us to develop a convenient procedure for the synthesis of chiral DABCO derivatives containing chiral camphanyl moiety. The DABCO is one of the widely used as ligand in organocatalysis. For example, chiral 2,3-disubstituted DABCO derivatives have been synthesized and utilized as a chiral ligand for the osmium catalysed asymmetric dihydroxylation of olefins.[24]

We have found that the camphanyl piperazine **58** reacts with 1,2-dibromoethane in the presence of triethylamine to give the chiral DABCO derivative **76** in 86% yield (Scheme **28**). Similarly the camphanyl piperazine **61** was converted to the chiral DABCO **77** in 72% yield. Whereas, the camphanyl dihydroquinoxalines **63** failed to furnish the desired product **(**Scheme **28**).

Scheme 28



We have undertaken detailed studies on the utilization of some of the chiral camphanyl piperazine derivatives for the synthesis of chiral propargylamines and conversion to allenes. These results are described in Chapter **2** and Chapter **3**.

1.3 Conclusions

Convenient methods were developed for accessing several chiral amines and amino alcohols in moderate to good yields with good selectivities using D-(+)–camphor **1** and D-(-)-camphorquinone **2.** The configurations of the newly formed chiral centers of the camphor analogs were determined by single crystal X-ray analysis in some cases. These chiral derivatives have considerable potential for use in asymmetric transformations. We have briefly investigated the use of some of these derivatives in the synthesis of benzimidazolium salts, for use as chiral ligand for enantioselective reactions. Some of the chiral piperazine derivatives are readily converted to chiral camphanyl derivatives containing the important DABCO moiety. Hence, the methods described here to access chiral camphanyl amine derivatives have enormous potential for use in asymmetric transformations.

1.4. Experimental Section

1.4.1 General Information

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

Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{o}$) and AUTOPOL-IV (readability $\pm 0.001^{o}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*S)*-(+)-α,α–diphenylprolinol {$[\alpha]_D^{25}$ = +67.2 (*c* 0.52, $CHCl_3$)} supplied by Gerchem Laboratory (Pvt) Ltd., India.

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

All the glassware were pre-dried at 120 °C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless otherwise mentioned, all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive reagents and organometallic compounds. Reagents prepared *in situ* in solvents were transferred using a double-ended stainless steel (Aldrich) needle under a pressure of nitrogen whenever required.

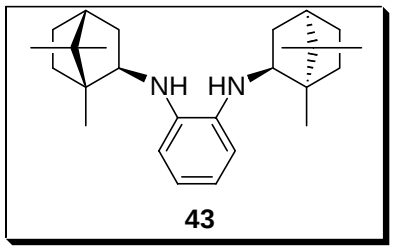
In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents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

Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Ethylene diamine, propylene diamine, supplied by Lancaster

Synthesis, Ltd., England were used as purchased. The D-(+)-Camphor was supplied by Aldrich, USA. Iodine was supplied by Spectrochem, India. All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents before use. $NaBH_4$ was supplied by E-Merck (India).

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

1.4.2. Preparation of N,N'-Bis-(1,7,7-trimethyl-bicyclo [2.2.1] hept-2-yl)-benzene-1, 2-diamine (43):



43

To a stirred solution of D-(+)-camphor **1** (1.824 g, 10 mmol) and phenylenediamine **38** (0.54 g, 5 mmol) in dry toluene (15 mL), $F_3B{:}OEt_2$ (0.283 mL, 20 mol %) was added carefully and the reaction mixture was refluxed for 24 h using a Dean-Stark apparatus. The mixture was brought to 25 °C. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated to obtain the diimine **40**. To this diimine **40** in MeOH (50 mL), $NiCl_2.6H_2O$ (4.69 g, 20 mmol) was added and the contents were cooled to -30 °C. $NaBH_4$ (7.6 g, 200 mmol) was added in portions from a solid addition flask over a period of 1h and the contents were stirred further for 12h at -30 to 25 °C. 3N Aqueous NaOH (20 mL) was added, followed by diethyl ether (30 mL) and the black precipitate was filtered off. The layers were separated. The organic layer was washed with saturated NaCl

solution, dried (Na_2SO_4) and concentrated. After purification by column chromatography on silica gel (100-200 mesh) using hexane as eluent, the amine **43** was obtained as white solid.

Yield : 2.967 g (78%).

$[\alpha]_D^{25}$: -12.4 (*c* 0.64, $CHCl_3$).

IR (KBr) : 3342, 2986, 2947, 2876, 1600, 1512, 1473, 1386, 1364, 1364, 1254, 1123, 1079, 1052 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 6.77-6.75 (d, *J*=8.0Hz, 1H), 6.65-6.62 (q, *J*=12.0Hz , 1H), 3.48 (s, 1H), 3.24-3.21 (q, *J*=8.0Hz, 1H), 1.89-1.62 (m, 5H), 1.33-1.19 (m, 2H), 1.13(s, 3H), 0.97 (s, 3H), 0.90 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 136.7, 118.3, 111.1, 61.1, 48.3, 47.2, 45.5, 40.0, 36.8, 27.6, 20.7, 20.6, 12.2.

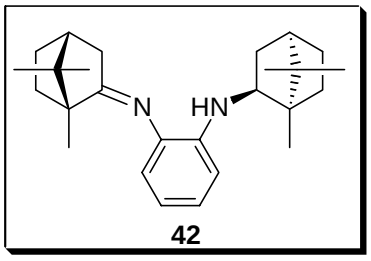
HRMS : (ESI) $C_{25}H_{37}N_2$ calcd 380.3191 found 381.3235.

1.4.3. Preparation of N-(1,7,7-Trimethyl-bicyclo[2.2.1]hept-2-yl)-N'-(1,7,7-trimethyl-icyclo[2.2.1]hept-ylidene)-benzene-1,2-diamine (42):

Yield : 0.30 g (8%), white solid.

$[\alpha]_D^{25}$: -15.3 (*c* 0.20, $CHCl_3$);

IR (KBr) : 3408, 2947, 2871, 1676, 1589, 1506, 1452, 1326, 1057, 739 cm^{-1}



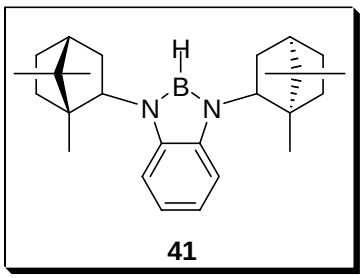
42

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 6.97-6.93 (t, *J*=16.0Hz, 1H), 6.62-6.54 (m, 3H), 4.33 (s, 1H), 3.27 (s, 1H), 2.32-2.26 (t, *J*=24.0Hz, 1H), 1.98 (s, 1H), 1.94-1.86 (m, 3H), 1.82-1.69 (m, 4H), 1.65-1.58 (m, 1H), 1.51-1.43 (m, 3H), 1.30-1.10 (m, 4H), 1.10 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.90, (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 185.5, 140.5, 136.2, 124.7, 118.4, 115.3, 109.7, 104.9, 61.2, 54.5, 48.6, 47.2, 47.0, 45.2, 43.8, 40.7, 36.7, 36.5, 32.3, 27.4, 20.6, 20.4, 19.6, 19.0, 12.3, 11.5.

HRMS : (ESI) $C_{26}H_{38}N_2$: 378.3035 [M+H^+]; found: 379.3176.

1.4.4. Preparation of 1,3-Bis-(1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl)-2,3-dihydro-1H-benzo1,3,2 diazaborole (41)



41

To a stirred solution of D-(+)-camphor **1** (1.824 g, 10 mmol) and phenylenediamine (0.54 g, 5 mmol) in dry toluene (15 mL), $F_3B{:}OEt_2$ (0.283 mL, 20 mol %) was added carefully and the reaction mixture was refluxed for 24h using a Dean-Stark apparatus. The mixture was brought to 25 °C. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated to obtain the diimine **40**. The diimine **40** obtained was taken in THF (50 mL), cooled to 0 °C under N_2 atmosphere and $NaBH_4$ (0.76 g, 20 mmol) was added. Iodine (2.54 g, 10 mmol) in THF (15 mL) was added slowly during 15 min. The reaction mixture was further stirred for 10h at 25 °C. It was carefully quenched with methanol and water at 0 °C diethyl ether (30 mL) was added. The organic layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After purification by column chromatography on silica gel (100-200 mesh) using hexane as eluent, the amine **41** was obtained as white solid.

Yield : 3.510 g (90%).

$[\alpha]_D^{25}$: -14.1 (*c* 0.40, $CHCl_3$).

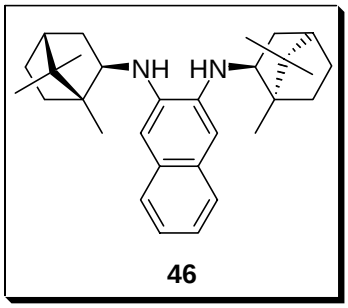
IR (KBr) : 2953, 2870, 2606, 1599, 1477, 1367, 1282, 1186, 1028, 837 cm^{-1}

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.08-7.05 (d, *J*=12.0Hz, 2H), 7.00-7.97 (m, *J*=12.0Hz, 2H), 4.04-4.00 (t, *J*=16.0Hz, 1H), 2.38-2.34 (m, 1H), 1.98-1.85 (m, 3H), 1.73-1.66 (m, 1H), 1.47-1.45 (t, *J*=8.0Hz, 1H), 1.35-1.30 (t, *J*=20.0Hz, 1H), 1.08 (s, 3H), 1.88 (s, 3H), 0.77 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 139.2, 118.1, 110.5, 62.1, 49.8, 47.6, 44.9, 38.3, 37.5, 27.3, 21.4, 20.3, 12.3.

HRMS : (ESI) $C_{26}H_{39}BN_2$: 390.3206 [M+H^+]; found: 391.3123.

1.4.5. Preparation of N,N'-Bis-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-naphthalene-2,3-diamine (46)



46

To a stirred solution of D-(+)-camphor **1** (1.54 g, 10 mmol) and 1,2-diamine naphthalene (0.54 g, 5 mmol) in dry toluene (15 mL), $F_3B{:}OEt_2$ (0.283 mL, 20 mol %) was added carefully and the reaction mixture was refluxed for 24h using a Dean-Stark apparatus. The mixture was brought to 25 °C. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated to obtain the diimine **45**. To this diimine **45** in MeOH (50 mL), $NiCl_2.6H_2O$ (4.69 g, 20 mmol) was added and the contents were cooled to -30 °C. $NaBH_4$ (7.6 g, 200 mmol) was added in portions from a solid addition flask over a period of 1 h and the contents were stirred further for 12h at -30 to 25 °C. 3N Aqueous NaOH (20 mL) was added, followed by diethyl ether (30 mL) and the black precipitate was filtered off. The layers were separated. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. After purification by column chromatography on silica gel (100-200 mesh) using hexane and ethyl acetate (100:0) as eluent, the amine **46** was obtained as white solid.

Yield : 2.96 g, 69%.

$[\alpha]_D^{25}$: -82.2 (*c* 0.29, $CHCl_3$).

IR (KBr) : 3358, 2947, 2870, 1626, 1517, 1489, 1391, 1363, 1259, 1199, 1029, 941, 848, 739, 618 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.61-7.60 (m, 1H), 7.21-7.20 (m, 1H), 6.83 (s, 1H), 3.75 (s, 1H), 3.36-3.35 (d, *J*=4.0Hz, 1H), 2.02-1.97 (q, *J*=20.0Hz, 2H), 1.83- (s, 3H), 1.72-1.66 (m, 1H), 1.56 (s, 1H), 1.39-1.29 (m, 4H), 1.15 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H).

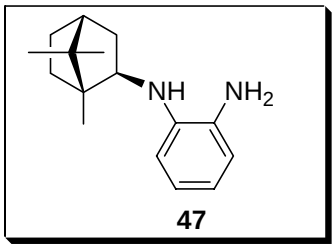
^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 137.7, 128.8, 125.7, 122.5, 105.7, 61.0, 48.4, 47.3, 45.5, 39.9, 36.8, 27.6, 20.7, 20.5, 12.1.

HRMS : (ESI) $C_{30}H_{42}N_2$: 430.3348 [M+H^+]; found: 431.3427.

1.4.6. Preparation of N-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-benzene-1,2-diamine (47):

To a stirred solution of D-(+)-camphor **1** (1.54 g, 10 mmol) and phenylenediamine (1.620 g, 15 mmol) in dry toluene (15 mL), $F_3B{:}OEt_2$ (0.141 mL, 10 mol %) was added carefully and the reaction mixture was refluxed for 12h using a Dean-Stark apparatus. The mixture was brought to 25 °C. The toluene layer was dried (Na_2SO_4) and the solvent was evaporated to obtain the monoimine **39**. To this monoimine **39** in MeOH (50 mL), $NiCl_2.6H_2O$ (2.37 g, 20 mmol) was added and the contents were cooled to -30 °C. $NaBH_4$ (1.90 g, 50 mmol) was added in portions from a solid addition flask over a period of 1h and the contents were stirred further for 12h at -30 to 25 °C. 3N Aqueous NaOH (20 mL) was added, followed by diethyl ether (30 mL) and the black precipitate was filtered off. The layers were separated. The organic layer was washed with saturated NaCl solution, dried

(Na_2SO_4) and concentrated. After purification by column chromatography on silica gel (100-200 mesh) using hexane and ethyl acetate (95:5) as eluent, the amine **47** was obtained as white solid.



47

Yield : 1.68 g, 69%.

$[\alpha]_D^{25}$: -62.9 (*c* 0.45, $CHCl_3$).

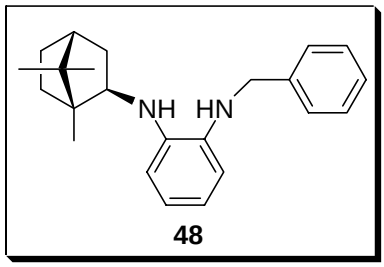
IR (KBr) : 3391, 2953, 2876, 1605, 1512, 1457, 1265, 734 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 6.93-6.89 (m, 1H), 6.79-6.73 (m, 3H), 3.38-3.35 (m, 3H), 2.02-197 (q, *J*=20.0Hz, 1H), 1.87-1.73 (m, 5H), 1.38-1.29 (m, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 137.8, 134.1, 120.8, 117.7, 116.7, 111.7, 61.8, 48.6, 47.3, 45.4, 40.6, 40.6, 36.9, 27.1, 20.8, 20.7, 12.4.

HRMS : (ESI) $C_{16}H_{24}N_2$: 244.1939 [M+H^+]; found: 245.2036.

1.4.7. Preparation of N-benzyl-N'-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-benzene-1,2-diamine (48):



48

To a stirred solution of diamine **47** (0.244 g, 1 mmol), and benzylaldehyde (0.11 g, 1 mmol) in dry toluene (1 mL), p-TSA (0.01 g, 5 mol%) was added carefully and the reaction mixture was refluxed for 6h using a Dean-Stark apparatus. The contents were brought to 25 °C. The toluene layer was separated, dried (Na_2SO_4) and the solvent was removed. The imine residue was taken in EtOH (5 mL) and cooled to 0 °C. $NaBH_4$ (0.170 g, 5 mmol) was added in portions from a solid addition flask over a period of 1h and stirred further for 3h at 0-25 °C. EtOH was removed under reduced pressure. Water

(10 mL) and ethyl acetate (20 mL) were added. The organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200 mesh) using hexane and ethyl acetate (99:1) as eluent, the product **48** was isolated as white solid.

Yield : 0.297 g, 89%.

$[\alpha]_D^{25}$: -58.8 (*c* 0.21, $CHCl_3$)

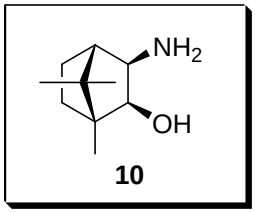
IR (KBr) : 3353, 3062, 3029, 2985, 2870, 1604, 1511, 1451, 1248, 1122, 1045, 1029, 739, 700 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.43-7.31 (m, 4H), 6.85-6.71 (m, 3H), 4.33 (s, 2H), 3.32-3.29 (q, *J*=8.0Hz, 2H), 1.95-1.65 (m, 5H), 1.34-1.22 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 139.7, 137.4, 136.7, 128.6, 127.5, 127.1, 119.9, 118.1, 113.0, 111.6, 61.4, 48.9, 48.5, 47.2, 45.4, 40.4, 36.8, 27.5, 20.7, 20.6, 12.3.

HRMS : (ESI) $C_{23}H_{30}N_2$: 334.2409 [M+H^+]; found: 335.2488.

1.4.8. Preparation of (*1R,2S,3R,4S*)-(-)–3–Amino-1,7,7-trimethyl bicyclo[2.2.1]heptan2-ol (10):



10

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) in MeOH (5 ml) and 1M solution of NH_3 (MeOH) **49** (15 ml) was added carefully and the reaction mixture was stirred for 12 h at 25 °C or 3h at 70 °C in round bottom flask closed with stopper. The contents were brought to 25 °C. MeOH (30 ml) was added and cooled to 0 °C. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 1h and stirred

further for 2h at 0-25 °C. Methanol was removed under reduced pressure. Water (10 ml) and DCM (20 ml) were added. The DCM layer was separated, washed with saturated NaCl solution and dried (Na_2SO_4). After evaporation of DCM, the crude product was washed with hexane and the product **10** was isolated.

Yield : 1.402 g, 83%, gummy liquid.

$[\alpha]_D^{25}$: -8.1 (*c* 0.52, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = -8.2 (*c* 1.15, CH_3OH)][18].

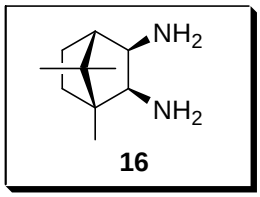
IR (KBr) : 3414, 2953, 2876, 1575, 1456, 1385, 1095 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.38-3.37 (d, J=4Hz, 1H), 3.06-3.04(d, J=8Hz,1H), 1.70-1.69 (m, 2H),1.56-1.55(d, J=4Hz, 1H), 1.45-1.43 (s, 1H), 1.03 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H).

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

LCMS : m/z 170 (M+1)

1.4.9. Preparation of (*1R,2S,3R,4S*)-(-)–1,7,7-trimethyl bicyclo[2.2.1]heptan-2,3-diamine (16)



16

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) in MeOH (5 mL) and 1M solution of NH_3 (MeOH) (30 mL) was added carefully. To this reaction mixture Ti(^{i}OPr)$_4$ (15 mmol) was added and stirred for 12 h at 25 °C. MeOH (15 mL) was added and cooled to 0 °C. $NaBH_4$ (0.95 g, 25 mmol) was added in portions from a solid addition flask over a period of 1h and stirred further for 12h at 0-25 °C. Methanol was removed under reduced pressure. 1N aqueous NaOH (20 ml) and DCM (20 mL) were added. The organic layer was separated, washed with saturated NaCl solution and dried (Na_2SO_4). After evaporation of DCM, the

crude product was washed with hexane and the product **16** was isolated. The configurations at the newly formed chiral centers were assigned as *S*,*R* by comparison with reported data.

Yield **:** 1.445 g, 85%, gummy liquid.

$[\alpha]_D^{25}$ **:** -32.1 (*c* 0.75, CH_3OH) [$[\alpha]_D^{20}$ = -30.6 (*c* 1.03, CH_3OH)][11].

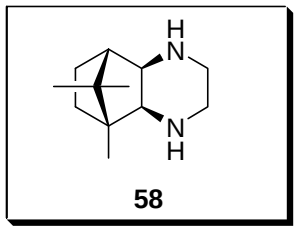
IR (KBr) **:** 3315, 2951, 2876, 1585, 1450, 1386, 1091 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 2.92-2.91 (d, *J* = 4.0 Hz, 1H), 2.84-2.82 (d, *J* = 8.0 Hz, 1H), 1.64-1.56 (m, 4H),1.54-1.52 (d, *J* = 8.0 Hz,1H), 1.14 (s, 3H), 1.05-1.00 (m, 2H), 0.86 (s, 3H), 0.85-0.84 (m, 2H), 0.80 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 69.0, 58.6, 53.7, 50.4, 48.8, 46.7, 36.7, 26.7, 23.4, 21.6, 12.1.

LCMS **:** m/z 170 (M+1).

1.4.10. Preparation of (+)-(*5R,13S,12R,8S*)5,9,9–trimethyl–decahydro-5,8–methano-quinazoline (58):



58

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) and ethylene diamine **56** (0.60 g, 10 mmol) in dry toluene (10 ml), p-TSA (0.01 g, 5 mol%) was added carefully. The reaction mixture was refluxed for 2h using a Dean-Stark apparatus. The mixture was brought to room temperature. The toluene layer was seperated and dried (Na_2SO_4) and the solvent was removed. The diimine **57** was taken in MeOH (50 ml) and cooled to 0 °C. $NaBH_4$ (1.14 g, 30 mmol) was added in portions from a solid addition flask over a period of 1h and stirred further for 5h at 25 °C. MeOH was removed under reduced pressure. Water (10 ml) and DCM (25 mL) were added. The

DCM layer was seperated and washed with saturated NaCl solution and dried (Na_2SO_4). After column chromatography on silica gel (100-200 mesh), using chloroform and methanol (9:1) as eluent the product **58** was isolated. The configuration at the newly formed chiral centers was assigned as *S*,*R* by comparison with reported data for the diamine **16**.[18]

Yield : 1.750 g, 90%, yellow liquid

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

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

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 2.96-2.91 (m, 2H), 2.94-2.92 (d, *J* = 10.0Hz, 1H), 2.70-2.68 (d, 1H2), 2.62-2.61 (m, 3H), 1.79-161 (m, 4H),1.46 (s, 3H),1.09-1.02 (m, 2H), 0.85 (s, 3H), 0.80 (s, 3H).

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

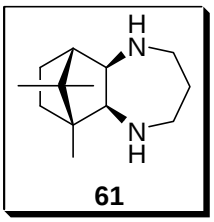
LCMS : m/z 195 (M+1),

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

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

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

1.4.11. Preparation of (+)-(*6R,14S,13R,9S*) 6,10,10–trimethyl–decahydro-6,9–methano–benzo(1,4) diazepine (61):



61

The same procedure followed for the preparation of azepine **60** starting from D-(-)-camphorquinone **2** and propylene diamine **59**.

Yield : 1.56 g (75%).

$[\alpha]_D^{25}$: 4.1 (*c* 0.65, CH_3OH).

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

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

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 75.5, 71.5, 52.4, 51.6, 51.5, 49.1, 46.4, 36.1, 34.4, 27.2, 21.7, 21.7, 12.2.

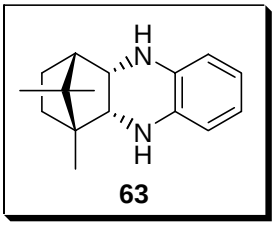
LCMS : m/z 208 (M+1)

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

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

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

1.4.12. Preparation of (1,11,11)-trimethyl-1,2,3,4,4a,5,10,10a-octahydro-1,4-methano-phenazine (63):



63

To a stirred solution of D-(+)-camphorquinone **2** (1.66 g, 10 mmol) and phelenediamine **38** (1.08 g, 10 mmol) in dry toluene (10 mL), p-TSA (0.18 g, 10 mol%) was added carefully. The reaction mixture was refluxed for 2h using a Dean-Stark apparatus. The mixture was brought to 25 °C. The toluene layer was separated and dried (Na_2SO_4) and the solvent was removed. To this diimine **62** in MeOH (50 mL), $NiCl_2.6H_2O$ (4.69 g, 20 mmol) was added and the contents were cooled to -30 °C. $NaBH_4$ (7.60 g, 200 mmol) was added in portions from a solid addition flask over a period of 1h and the contents were stirred further for 12h at -30 to 25 °C. 3N Aqueous NaOH (20 mL) was added, followed by diethyl ether (30 mL) and the black precipitate was filtered off. The layers were separated. After column chromatography

on silica gel (100-200 mesh) using hexane: ethylacetate (99:1) as eluent, the product **63** was isolated as white solid.

Yield : 1.960 g, 81%

$[\alpha]_D^{25}$: 22.6 (*c* 0.54, $CHCl_3$).

IR (KBr) : 3347, 2991, 2942, 2860, 1600, 1523, 1298, 1473, 1386, 1117, 734 cm^{-1}.

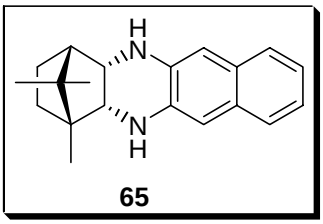
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 6.64-6.59 (m, 4H), 3.88-3.85 (d, *J*=12.0Hz 1H), 3.46-3.44 (s, *J*=8.0Hz 1H), 2.06-2.01 (s, *J*=20.0Hz, 2H), 1.77-1.75 (t, *J*=8.0Hz 1H), 1.44-1.41 (m, 1H), 1.22-1.17 (m, 1H), 1.00 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 135.23, 134.9, 118.6, 113.6, 60.3, 54.4, 50.4, 49.5, 47.0, 26.7, 20.4, 19.2, 18.5, 14.1.

HRMS : (ESI) $C_{16}H_{22}N_2$: 242.1783 [M+H^+]; found: 243.1861.

1.4.13. Preparation of 1,13,13-trimethyl-1,2,3,4,4a,5,12,12a-octahydro-1,4-methanobenzo[b]phenazine (65):

The procedure outlined as above was also followed for the preparation of azepine **64** starting from D-(-)-camphorquinone **2** and naphthalene diamine **65**.



65

Yield : 1.810 g, 75%, white solid.

$[\alpha]_D^{25}$: 15.5 (*c* 0.35, $CHCl_3$).

IR (KBr) : 3386, 2953, 2871, 1627, 1457, 1386, 1287, 1265, 1068, 1002 cm^{-1}.

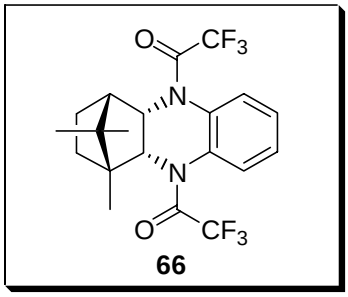
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 7.5 (s, 2H), 7.18-7.15 (m, 2H), 6.90-6.86 (d, *J*=12.0Hz, 2H), 3.99-3.96 (m, 1H), 3.57-3.54 (d, *J*=12.0Hz, 2H),

2.00-1.97 (m, 2H), 1.82-1.80 (t, *J*=12.0Hz, 1H), 1.43-1.46 (m, 1H), 1.25-1.22 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 136.5, 136.3, 129.2, 125.2, 122.3, 107.3, 107.2, 59.5, 53.7, 50.8, 49.9, 47.5, 27.1, 20.4, 19.8, 18.5, 14.1.

HRMS **:** (ESI) $C_{16}H_{22}N_2$: 242.1783 [M+H^+]; found: 243.1861.

1.4.14. Preparation of 2,2,2-trifluoro-1-[1,11,11-trimethyl-10-(2,2,2-trifluoro-acetyl)-2,3,4,4a,10,10a-hexahydro-1H-1,4-methano-phenazin-5-yl]-ethanone (66):



66

To a stirred solution of the diamine **63** (0.242 g, 1 mmol) in dry DCM (5 mL), Et_3N (0.3 mL, 2.1 mmol) and DMAP (0.02 g, 0.2 mmol) were added under N_2 atmosphere, and the contents were stirred for 5 min. Trifluoroacetic anhydride (2 mL) was added slowly at 0 °C and the contents were stirred at room temperature for 48h. The reaction mixture was quenched with water (2 mL) and DCM (10 mL) was added. The organic layer was separated and washed with saturated NaCl solution, dried over (Na_2SO_4) and the solvent was evaporated. After column chromatography on silica gel (100-200 mesh) using hexane as eluent, the trifluoro acetamide **66** was isolated as white solid. It was crystallized from acetonitrile to obtain crystals suitable for single crystal X-ray analysis

Yield **:** 0.412 g, 95%,

$[\alpha]_D^{25}$ **:** -21.6 (*c* 0.34, $CHCl_3$).

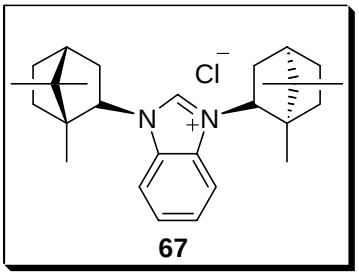
IR (KBr) **:** 3079, 2980, 2942, 2904, 2871, 1693, 1588, 1506, 1430, 1380, 1380, 1199, 1178, 980, 767, 723 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 7.27-7.26 (s, 4H), 5.23-5.18 (d, *J*=20.0Hz, 2H), 2.18 (s, 1H), 1.43-1.40 (t, *J*=12.0Hz, 1H), 1.28 (s, 3H), 1.96 (s, 3H), 0.87 (s, 4H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 158.4, 133.0, 132.4, 128.2, 127.3, 126.0, 117.7, 115.0, 65.2, 61.1, 51.3, 49.6, 29.0, 21.5, 18.6, 18.2, 14.3.

HRMS **:** (ESI) $C_{20}H_{20}F_6N_2O_2$: 434.1429, [M+H^+]; found: 435.1508.

1.4.15. Preparation of 1,3-Bis-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-3H-benzoimidazol-1-ium chloride (67):



67

In a 50 mL round bottomed flask, N,N'-Bis-(1,7,7-trimethyl-bicyclo [2.2.1] hept-2-yl)-benzene-1,2-diamine (0.381g, 1.0 mmol) was dissolved in $CH(OEt)_3$ (10 ml), and 12.N HCl (0.12 ml, 1.5 mmol) added dropwise over 5 min. The resulting solution was stirred at room temperature for 30 min under nitrogen and then heated to 80°C until condensation was observed on the neck of the flask. At this point the rubber septum was removed and the solution was allowed to stir open to the air for 4h. After cooling to room temperature, apply high vacuum for 1h, completely remove ethanol. The suspension obtained was diluted with dry diethyl ether (100ml) and allowed to crystallization. The obtained off white solid **67** was washed with diethyl ether and the residual solvents removed under high vacuum.

Yield **:** 0.365 g, 86%,

$[\alpha]_D^{25}$ **:** –32.1 (*c* 0.56, $CHCl_3$).

IR (KBr) **:** 3472, 3353, 3260, 3019, 2958, 2876, 1638, 1550, 1457, 1320, 1243, 1084, 1052, 1024, 805, 761 cm^{-1}.

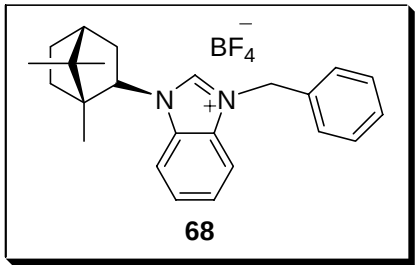
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 10.2 (s, 1H), 7.82 (s, 3H), 7.59 (s, 1H), 4.83 (s, 1H), 3.42 (s, 1H), 3.12 (s, 1H), 2.20-2.10 (m, 2H), 1.85-1.69 (m, 3H), 1.37 (s, 1H), 1.04 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 141.2, 132.6, 127.0, 115.2, 67.6, 51.3, 50.2, 48.0, 37.1, 36.0, 26.8, 20.9, 13.2.

HRMS **:** (ESI) $C_{27}H_{39}ClN_2$: 426.2802, [*M*-H^+]; found: 425.2744.

1.4.16. Preparation of 1-benzyl-3-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-3H-benzoimidazol-1-ium (68):

In a 25 mL round bottomed flask, a mixture of diamine **48** (0.334 g, 1.0 mmol) and NH_4BF_4 (100 mg, 1.0 mmol) and triethyl orthoformate (6 mL) two drops of formic acid were added to under nitrogen. The reaction mixture was heated at 80 °C for 3h. Upon cooling to room temperature, Et_2O (100 mL) was added, and the resulting precipitate was collected by filtration, and washed with Et_2O (10 mL) and apply high vacuum to give product **68** as white solid.



68

Yield **:** 0.394 g, 91%.

$[\alpha]_D^{25}$ **:** 21.6 (*c* 0.22, $CHCl_3$).

IR (KBr) **:** 3150, 3084, 2964, 2876, 1720, 1561, 1479, 1446, 1265, 1210, 1084, 1057, 800, 756 $cm^{-1.}$

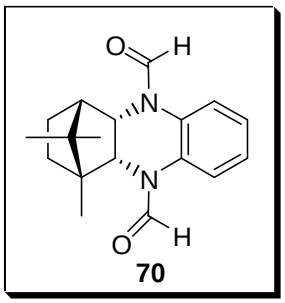
^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 9.61-9.59 (s, 1H), 7.73-7.71 (d, *J*=8.0Hz, 1H), 7.66-7.64 (d, *J*=8.0Hz, 1H), 7.60-7.50 (d, *J*=8.0Hz, 1H), 7.38-7.37 (d, *J*=4.0Hz, 2H), 7.30-7.26 (q, *J*=16.0Hz, 3H), 5.76-5.64 (q, *J*=24.0Hz, 2H), 4.62-4.58 (t, *J*=16.0Hz, 1H), 3.49-3.44 (q, *J*=20.0Hz, 1H), 2.68-2.65 (m, 1H), 2.23-2.17 (m, 1H), 2.06 (s, 1H), 1.92-1.86 (t,

J=24.0Hz, 1H), 1.77-1.76 (m, 1H), 1.54-1.53 (m, 1H), 1.41-1.37 (m, 1H), 1.22-1.17 (m, 2H), 1.03 (s, 3H), 0.89 (s, 3H), 0.74 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.2, 133.2, 133.0, 131.0, 129.3, 129.0, 128.2, 127.5, 114.4, 113.9, 66.6, 65.8, 51.6, 51.3, 50.9, 48.0, 44.7, 37.2, 36.1, 26.5, 21.0, 19.7, 15.2, 12.6.

HRMS **:** (ESI) $C_{24}H_{29}BF_4N_2$: 432.2360, [M+H^+]; found: 433.2436.

1.4.17. Preparation of 1,11,11-Trimethyl-1,2,3,4,4a,10a-hexahydro-1,4-methano-phenazine-5,10-dicarbaldehyde (70):



70

Yield **:** 0.282 g, 95%.

$[\alpha]_D^{25}$ **:** 26.4 (*c* 0.48, $CHCl_3$).

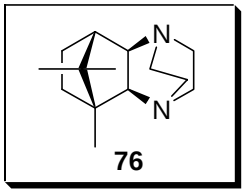
IR (KBr) **:** 3351, 2958, 2893, 1671, 1589, 1506, 1386, 1336, 1260, 1095, 1019, 860, 805, 761 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δ ppm) 8.65-8.63 (d, *J*=8.0Hz 2H), 7.25-7.18 (m, 4H), 5.24-5.21 (d, *J*=12.0Hz, 1H), 5.11-5.08 (d, *J*=12.0Hz, 1H), 2.13-2.11 (t, *J*=8.0Hz, 1H), 1.44 (m, 1H), 1.15 (s, 3H), 1.11-1.07 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 162.2, 161.1, 132.7, 132.2, 126.4, 126.2, 120.2, 119.1, 58.2, 58.9, 51.8, 53.8, 51.8, 49.9, 49.8, 29.2, 21.4, 18.8, 18.4, 14.2.

1.4.18 Preparation of Chiral DABCO derivative (76):

In a 25 mL round bottomed flask, dry CH_3CN (80 mL), camphanyl piperazine **58** (1.950 g, 10 mmol), 1,2-dibromoethane (3.40 mL, 40 mmol) and KI (2 mmol) were placed under N_2 atmosphere and stirred at 80 °C for 10h. The reaction mixture was cooled to 25 °C and filtered. The solid residue was further washed with ethylacetate (20 mL). The filtrate was evaporated under reduced preassure. After purification by column chromatography on silica gel (100-200 mesh) using ethyl acetate:MeOH (95:5) as eluent, the chiral DABCO **76** was obtained as white solid.



76

Yield : 1.9 g, 86%.

$[\alpha]_D^{25}$: -22.3 (*c* 0.57, $CHCl_3$).

IR (KBr) : 3065, 2961, 2893, 2698, 1651, 1560, 1483, 1452, 1415, 1396, 1284, 1153, 1111, 1074, 1051, 902, 661, 613 cm^{-1}.

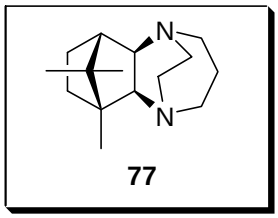
^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.82-3.77 (q, *J*=20.0Hz, 3H), 3.40-3.35 (m, 2H), 3.21-3.14 (m, 2H), 3.12-3.04 (m, 2H), 2.75-2.68 (q, *J*=28.0Hz, 1H), 2.62-2.60 (d, *J*=8.0Hz, 1H), 2.42-2.35 (q, *J*=28.0Hz, 1H), 2.06-2.05 (d, *J*=4.0Hz, 1H), 1.84-1.78 (m, 1H), 1.66-1.59 (m, 1H), 1.48 (s, 3H), 1.25 (s, 3H), 1.12-1.05 (m, 1H), 0.86 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 68.6, 64.0, 55.3, 49.0, 47.5, 46.4, 45.4, 39.7, 35.1, 27.9, 26.1, 21.8, 21.3, 12.3.

HRMS : (ESI) $C_{14}H_{24}N_2$: 220.1939 [M+H^+]; found: 221.2021.

1.4.19 Preparation of Chiral DABCO (77)

The procedure outlined as above was also followed for the preparation of **61** starting from 6,10,10–trimethyl–decahydro-6,9–methano–benzo(1,4) diazepine (**77**).



77

Yield : 1.68 g, 72%.white solid.

$[\alpha]_D^{25}$: -32.2 (*c* 0.36, $CHCl_3$).

IR (KBr) : 2951, 2824, 1730, 1668, 1604, 1454, 1386, 1309, 1257, 1213, 1174, 1130, 1111, 1010, 935, 896 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δ ppm) 3.43-3.38 (m, 2H), 3.33-3.21 (m, 1H), 3.19-3.00 (m, 3H), 2.59-2.57 (q, *J*=8.0Hz, 2H), 2.40-2.33 (m, 3H), 1.92-1.91 (d, *J*=4.0Hz, 1H), 1.75-1.65 (m, 3H), 1.26 (s, 2H), 1.12 (s, 3H), 0.87 (s, 3H), 0.75 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 74.6, 74.3, 58.3, 57.1, 50.7, 49.0, 47.8, 46.7, 36.4, 32.2, 28.6, 27.2, 21.7, 20.5, 13.1.

HRMS : (ESI) $C_{15}H_{26}N_2$: 234.2096 [M+H^+]; found: 235.2174.

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Chapter 2

Synthesis of Chiral Allenes via Chiral Propargylamines by Chirality Transfer from Chiral Secondary Amine Derivatives

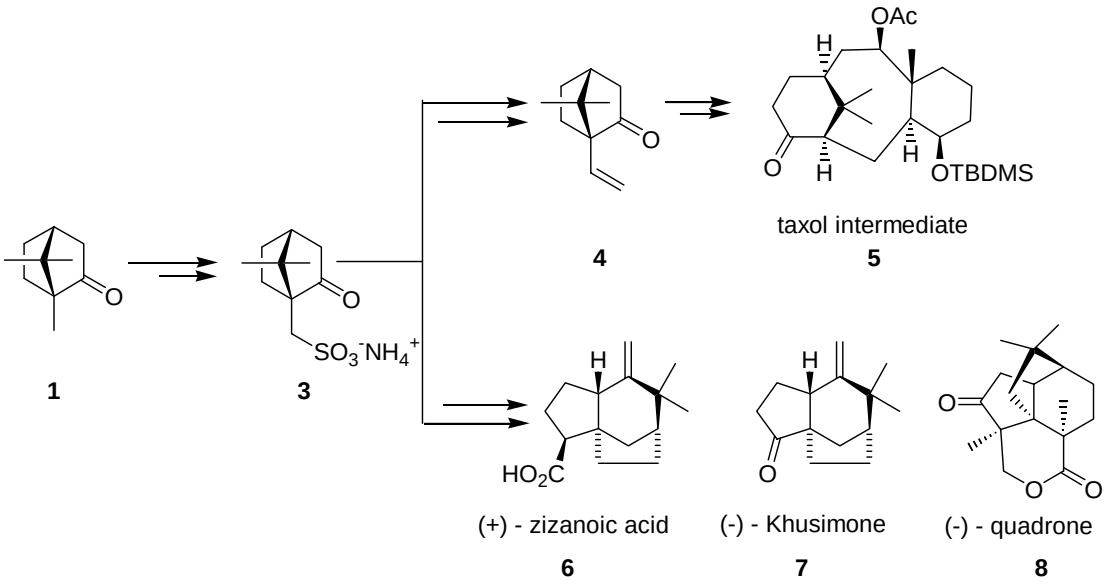
2. 1 Introduction

The camphanyl amine derivatives have proven applications in organic synthesis. We have undertaken efforts towards the application of these valuable chiral auxiliaries for the synthesis of chiral allenes. Accordingly, it will be helpful to briefly review the literature on the application of camphanyl amines in organic transformations and previously reported synthetic methods for accessing chiral allenes.

2.1.1 D-(+)–Camphor 1 and camphorquinone 2 as chiral pool reagents

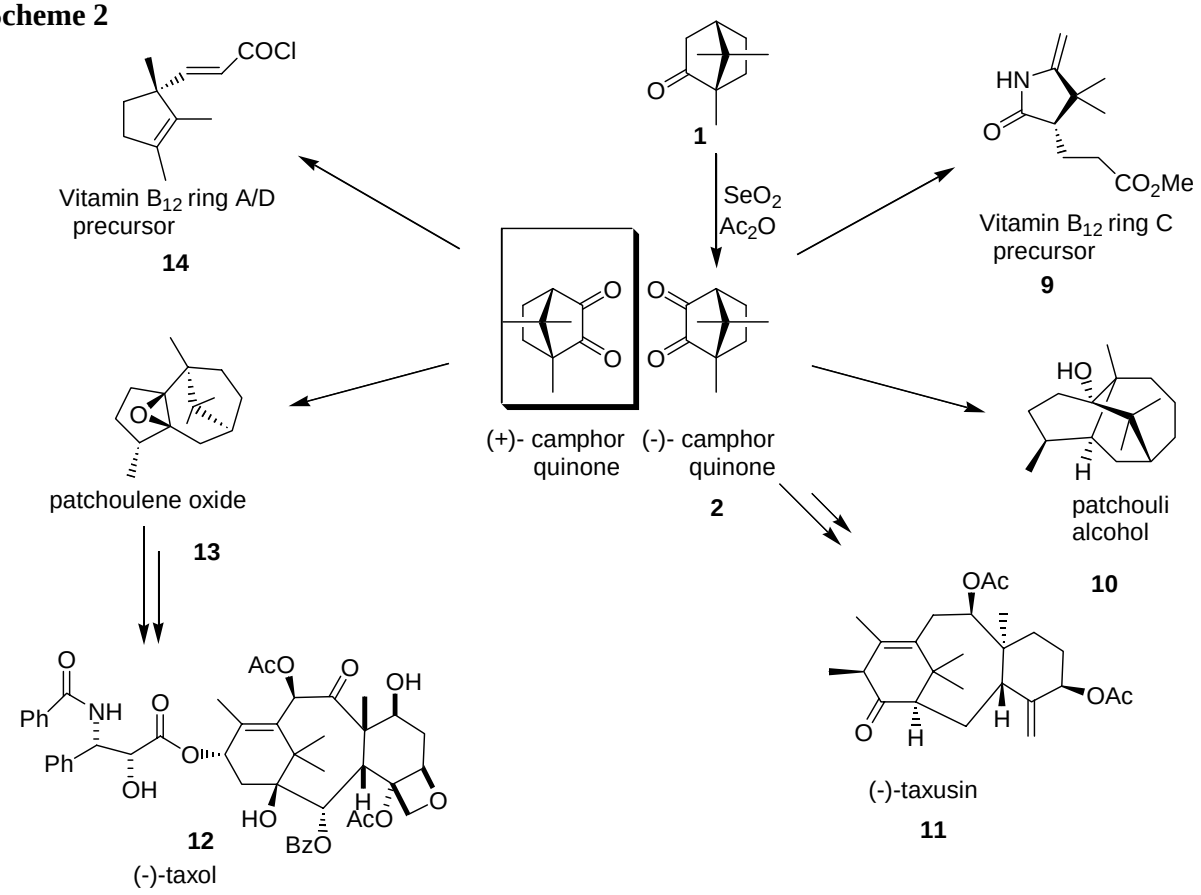
D-(+)-Camphor has been widely used as a chiral pool reagent for the synthesis of natural products. In these syntheses, the camphor moiety is modified to products in which overall stereochemistry is directly influenced by the existing chiral centers in the camphor molecule as illustrated in Scheme **1** with a few representative examples**.**[1, 2]

Scheme 1



The readily accessible camphorquinone enantiomers are also useful for the synthesis of natural products as outlined in Scheme **2**.[3,4,5]

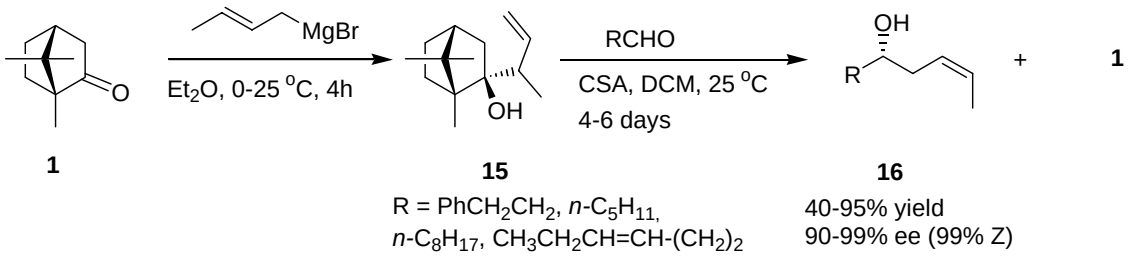
Scheme 2



2.1.2 D-(+)–Camphor 1 and its derivatives as chiral auxiliaries

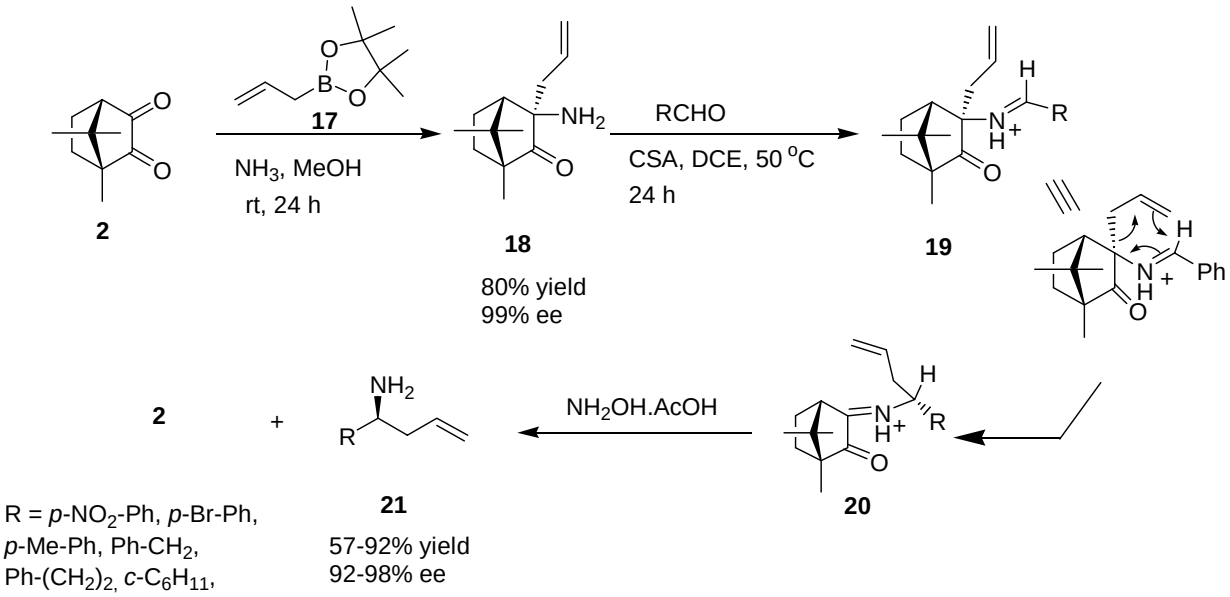
D-(+)-Camphor **1** has been widely used as chiral auxiliary because of availability of procedures for easy attachment to the prochiral substrate and its capacity to induce a high degree of stereoselectivity. For example, the use of D-(+)-camphor **1** as auxiliary for the enantioselective synthesis of *cis*-linear homoallylic alcohols **16** with 90-99% ee has been reported (Scheme **3**).[6]

Scheme 3



D-(-)-Camphorquinone **2** has been also widely used as chiral auxiliary. For example, the chiral allyl amine **21,** prepared using D-(-)-camphorquinone **2** and allyl boronic ester **17**, reacts with various aldehydes to give the homo allylic amines **21** in 57-92% yield with 92-98% ee (Scheme **4**).[7]

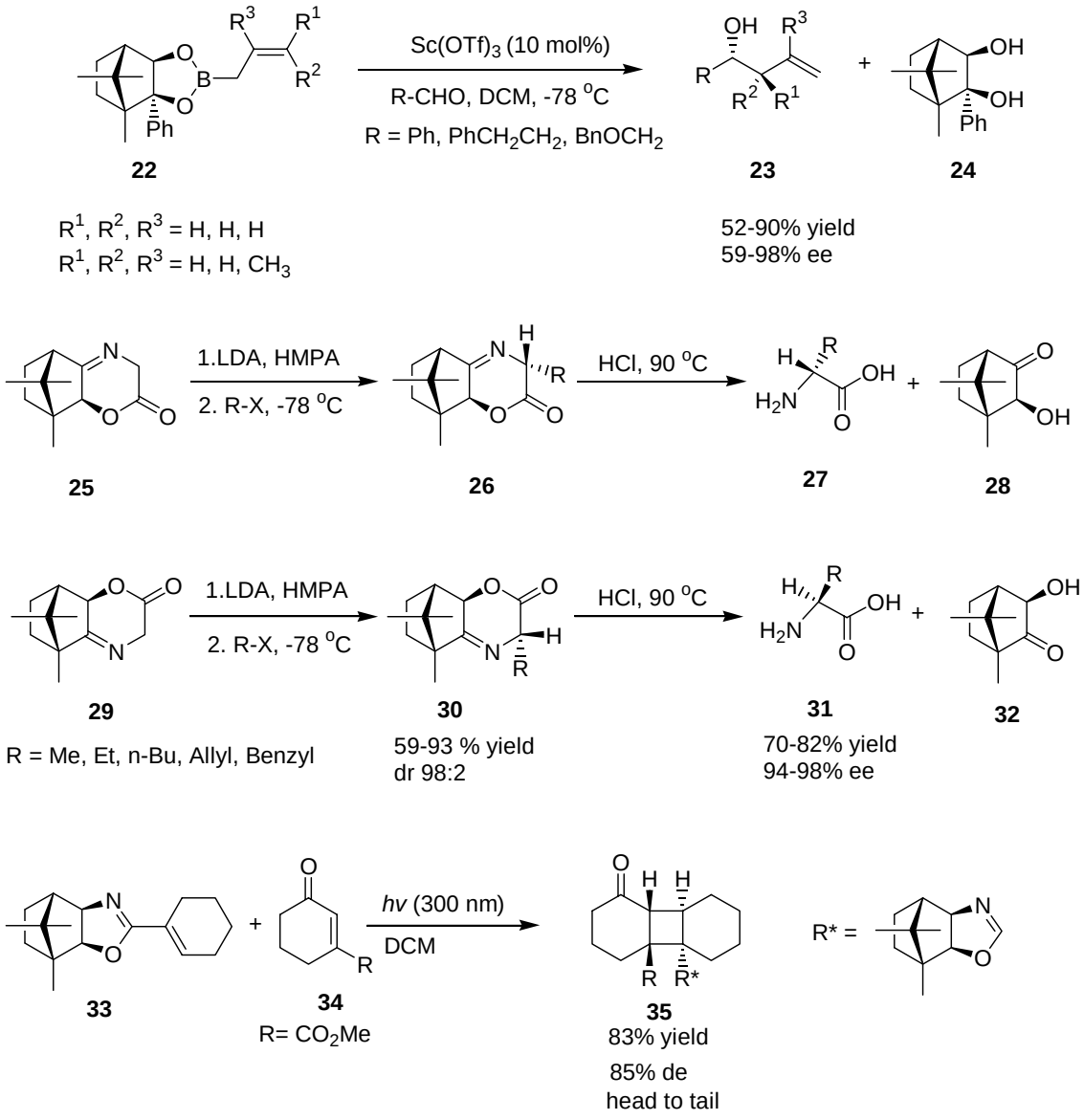
Scheme 4



2.1.3 D-(+)–Camphor 1 and its derivatives as chiral reagents

In this chiral camphanyl reagent approach, stereocontrol is obtained through the use of stoichiometric quantities of the reagent containing camphanyl moiety. Several camphanyl reagents have been used in asymmetric transformations as outlined in Chart **1**.[8,]

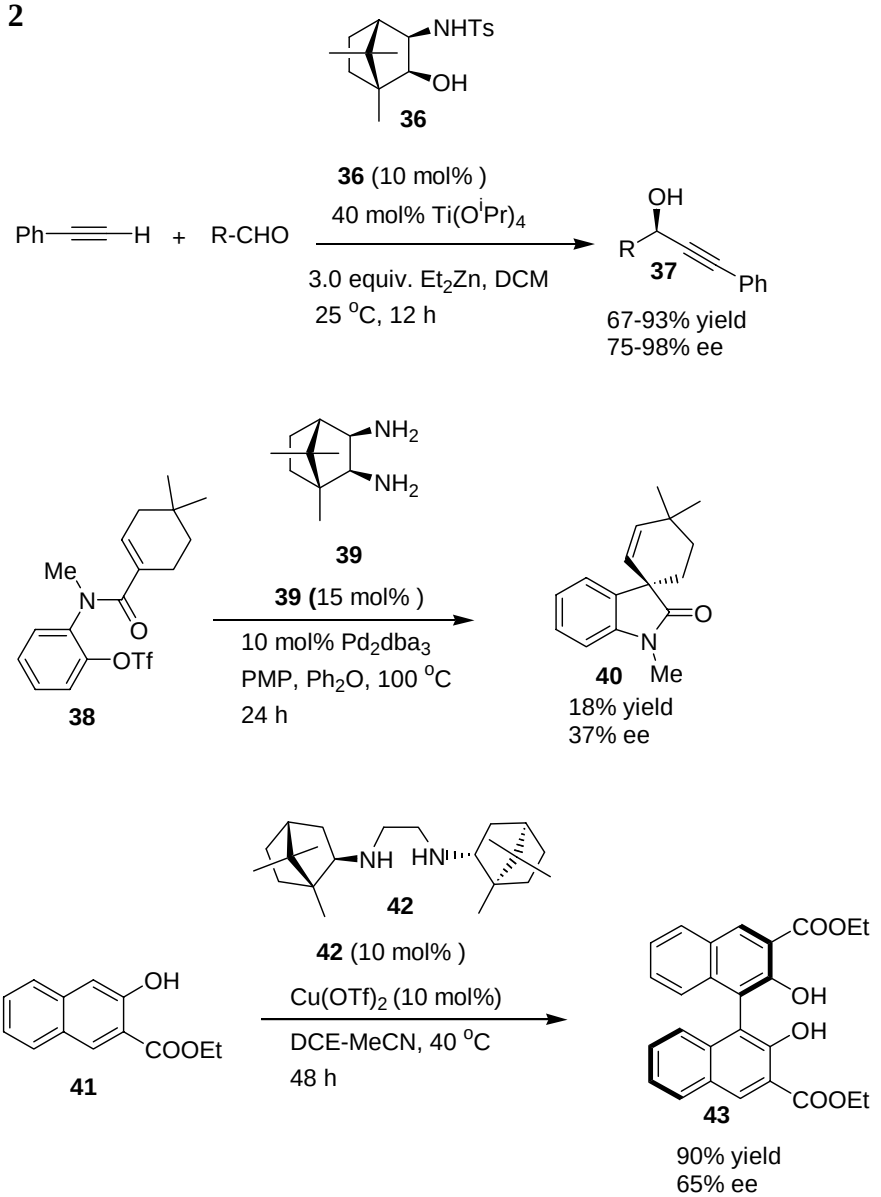
Chart 1

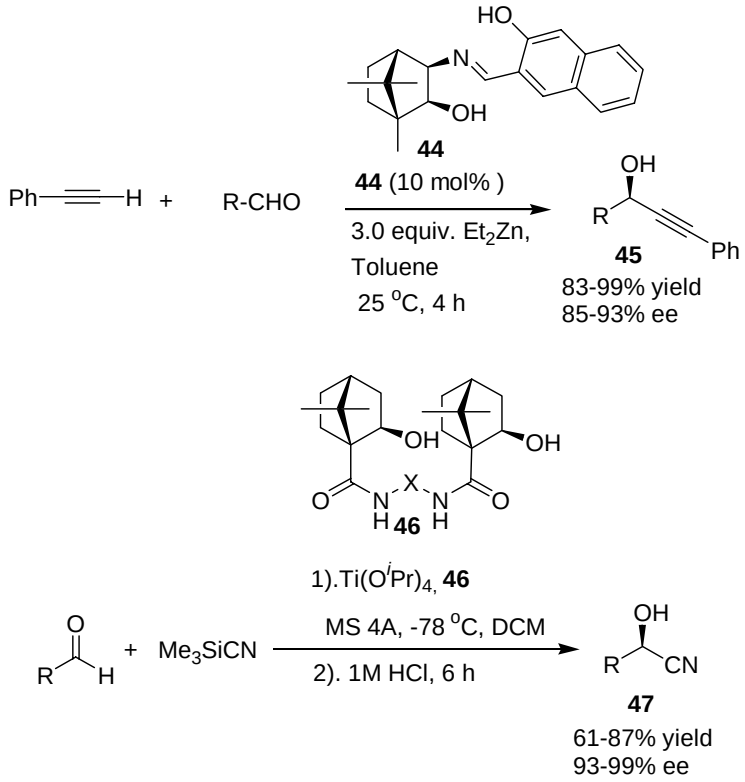


2.1.4 D-(+)–Camphor 1 and its derivatives as chiral catalyst

In this approach, camphor based catalysts are coordinated to a metal which may be covalently attached to the substrate, forming an intermediate in the catalytic cycle, or may act in an intermolecular manner, inducing asymmetry in a single pot operation. Several camphanyl ligands have been used in such asymmetric transformations.[9] The reported results are summarized in Chart **2**.

Chart 2

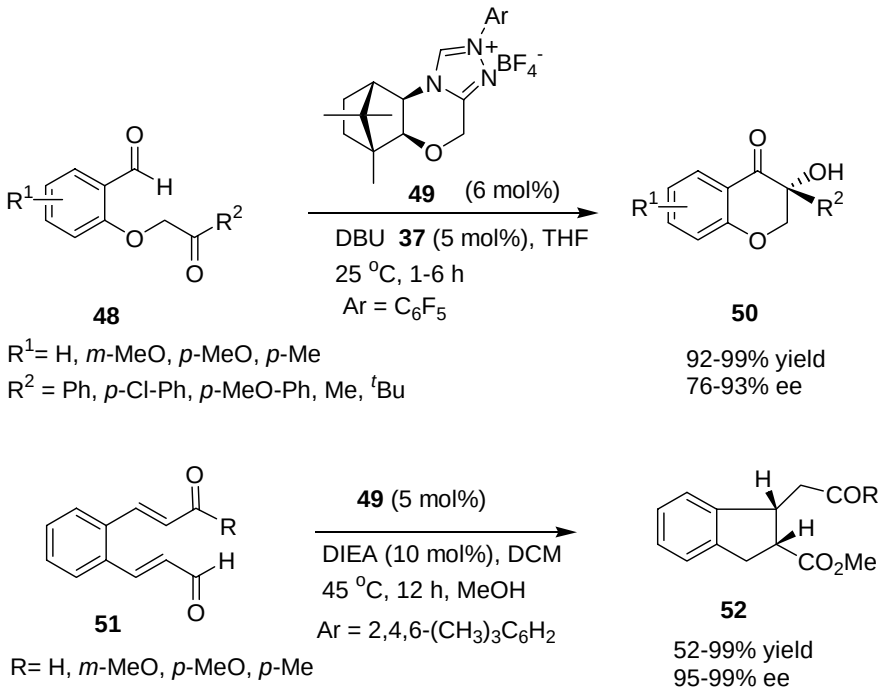


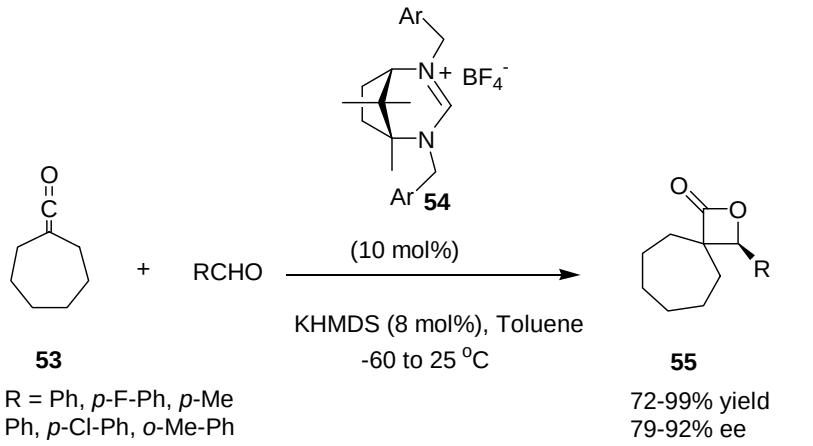


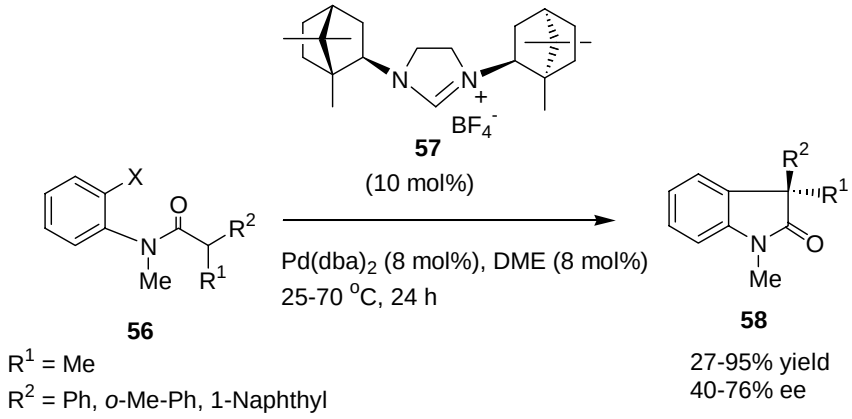
2.1.5 N-Heterocyclic carbenes (NHC) containing chiral camphanyl moiety

Camphanyl triazolium salt and camphanyl imidazole salts are useful as NHC precursors in asymmetric transformations.[10] The reported results are summarized in Chart **3**.

Chart 3

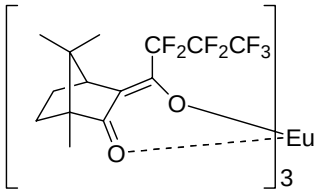






2.1.6 D-(+)–Camphor 1 and its derivatives as chiral shift agents

Polymer supported chiral selectors are useful for chiral discrimination of enantiomers in gas chromatography. Rare earth metal complexes of camphanyl *β*-diketonates have been used as chiral discrimination reagents.[11] Europium tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] $Eu(hfu)_3$ **59** has been used as ^1H NMR shift reagent for discrimination of enantiomers (Figure **1**).

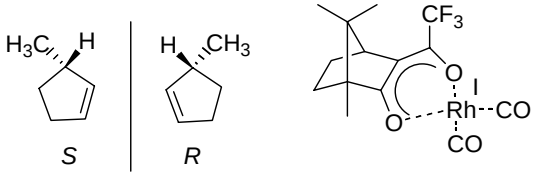


59

$Eu(hfu)_3$

Figure 1

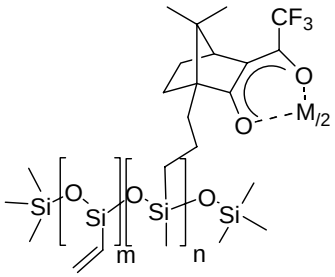
Recently, rhodium(I) 3-(trifluoroacyl)-(1*R*)-camphorate **60** enclosed in a squalane matrix frame work has been reported to separate racemic 3-methylcyclopentene in gas chromatography (Figure **2**) [12]



60

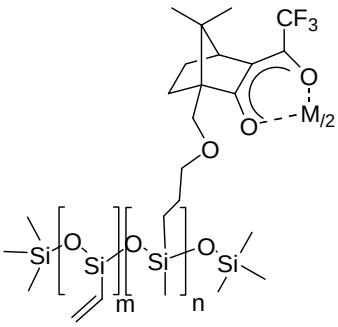
Figure 2

Very recently, chemically bonded chiral camphanyl stationary phases (CSPs) have been reported to be successful in discrimination of enantiomers in gas chromatography. Some representative immobilized chiral stationary phase materials containing camphanyl moiety are given below Figure **3**.[13]



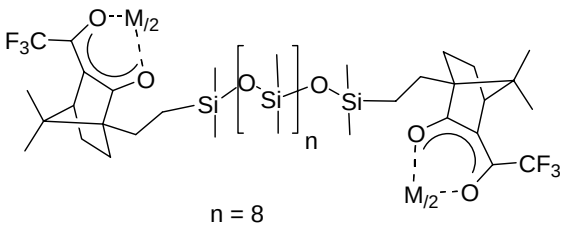
n = 1
m = 7

61



n = 3%, 10.2%, 20%
m = 1-n

62



n = 8

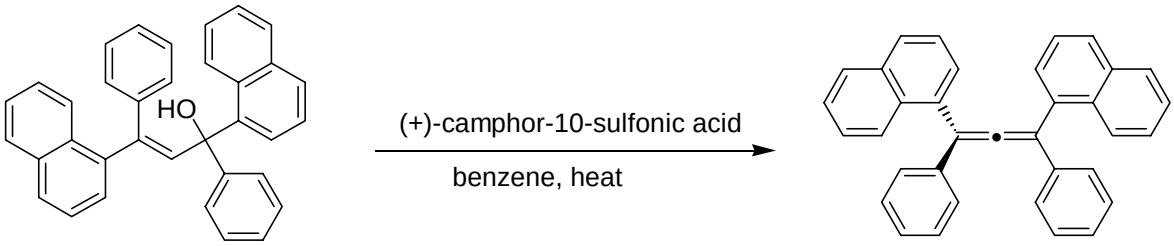
63

Figure 3

2.1.7 Synthesis of chiral allenes

van't Hoff first predicted the existence of two enantiomeric forms for unsymmetrically substituted allene in 1875.[15] Though, the first allene was prepared by Burton and Pechmann in 1887,[14] van't Hoff's prediction of allene chirality was not confirmed until 1935 when Maitland and Mills synthesized the first optically active allene **65** by dehydrating racemic allylic alcohol **64** with (+)-camphor-10-sulfonic acid (Scheme **5**).[16]

Scheme 5



64 **65**

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

So far, more than 150 natural products having allenic structure were reported which clearly indicates that allenes are not simple chemical curiosities. Almost all allenic natural products are chiral and were isolated in non-racemic forms.[17] Allenic derivatives have been also widely used as synthetic precursors in total synthesis of biological active molecules. Chiral allenes have been also used in asymmetric synthesis for amplification of chirality in liquid-crystalline phases, and materials for use as chiral sensor,[18] as redox triggered chiral switches,[19] as chiral magnets,[20, 21, 22] as nonplanar pushpull chromophores,[23] and liquid crystal materials.[24] In continuation of our efforts on the synthetic applications of readily accessible chiral amines, we have undertaken studies on the enantioselective synthesis of 1,3-

disubstituted chiral allenes. Accordingly, a brief review on various methods available in the literature for the synthesis of chiral allenes would facilitate the discussion.

2.1.7.1 Chirality transfer from propargylic position

Nucleophilic substitution reaction at propargylic position is one of the most convenient methods for synthesis of chiral allene because of the availability of propargyl alcohols in enantiomerically pure form. In this process, the central chirality at propargylic position is transfered to axial chirality of the allene. Methods reported for synthesis of chiral allenes by nucleophilic substitution reaction at propargylic position with various leaving groups are summarized in Chart **4**.[25, 26]

Chart 4

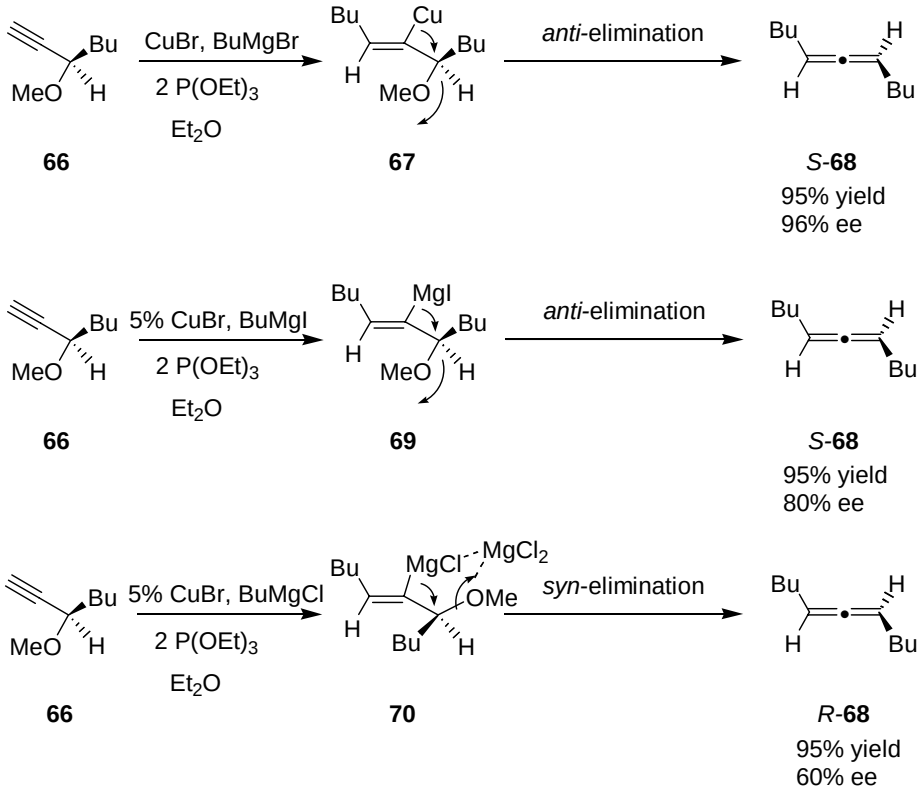
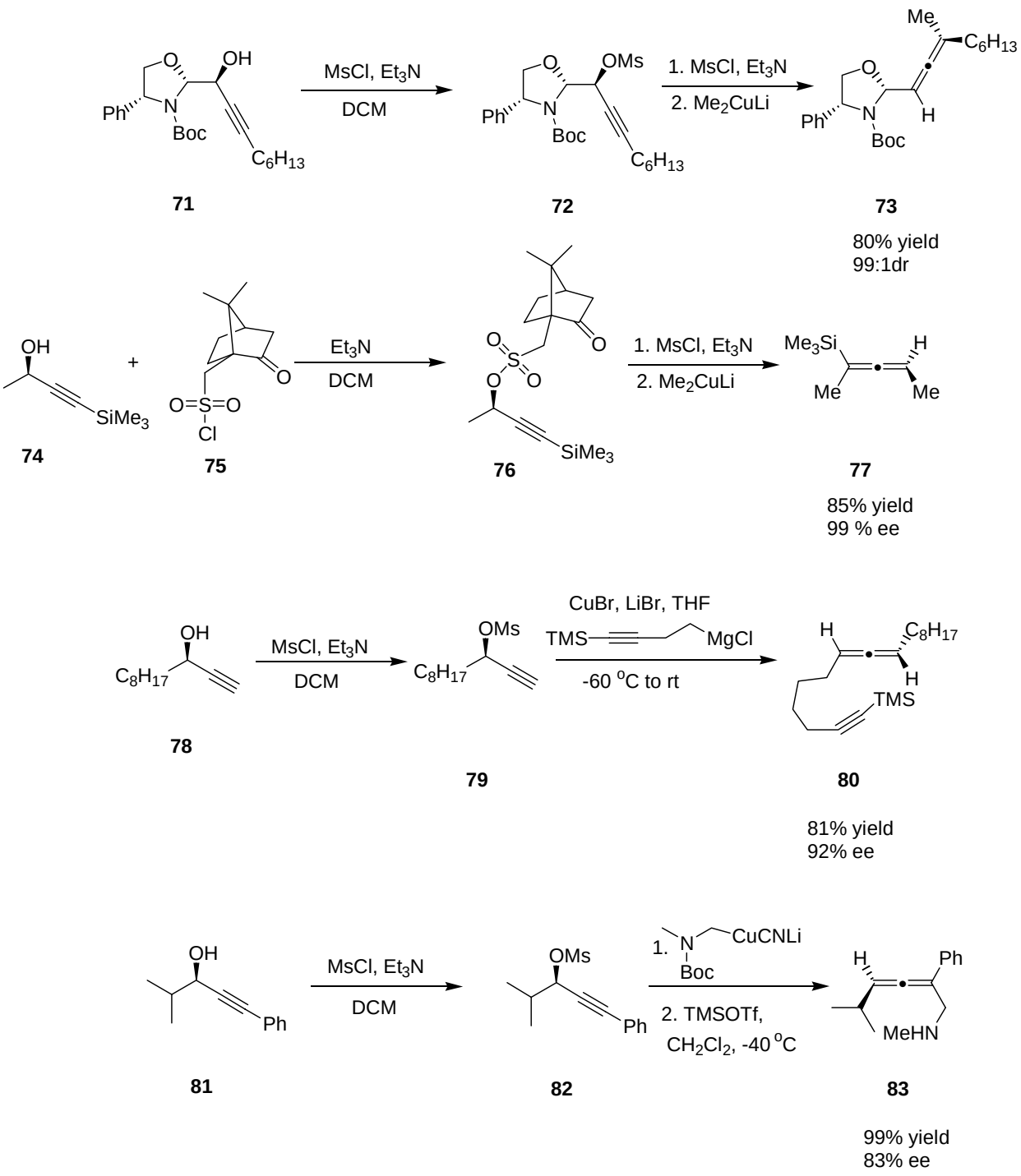
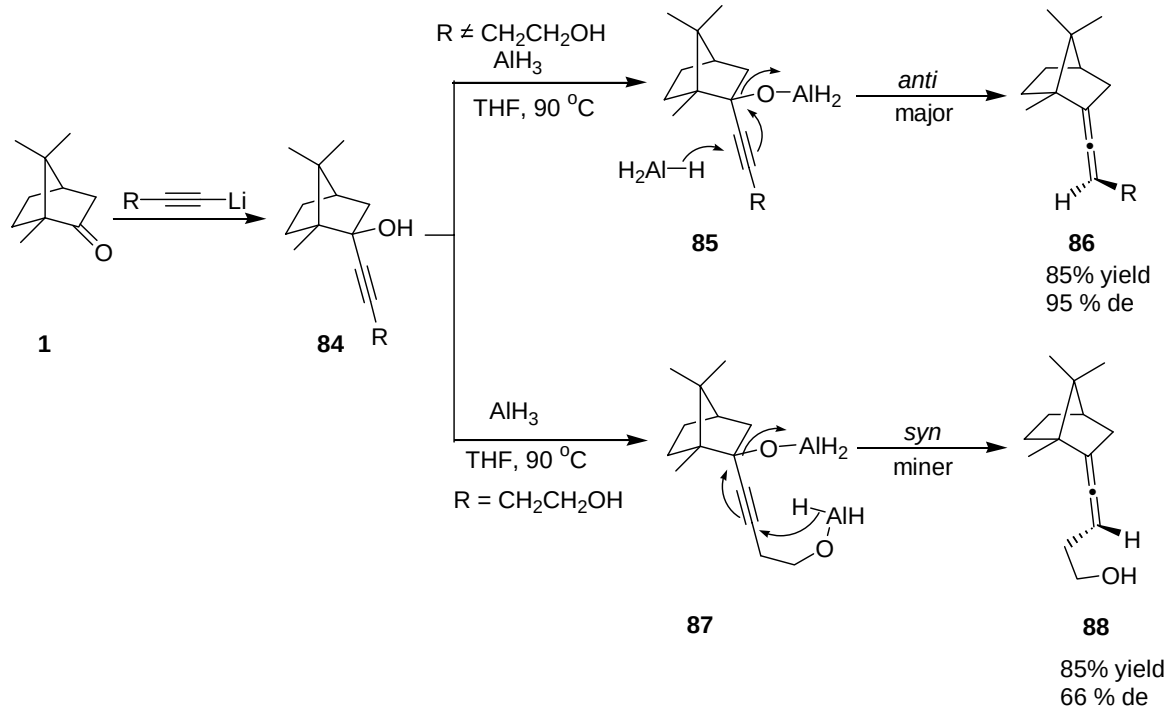


Chart 4 continued……



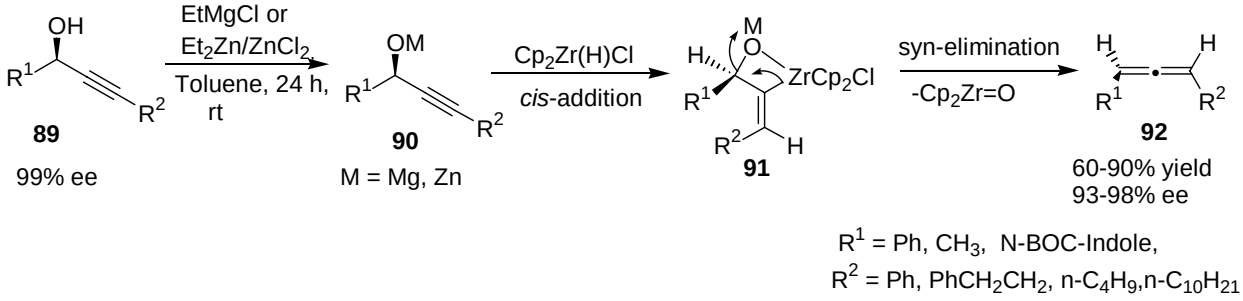
Propargyl alcohol obtained from camphor upon reduction with AlH_3 give the corresponding allenes **86** and **88 (**Scheme **6).**[27]

Scheme 6



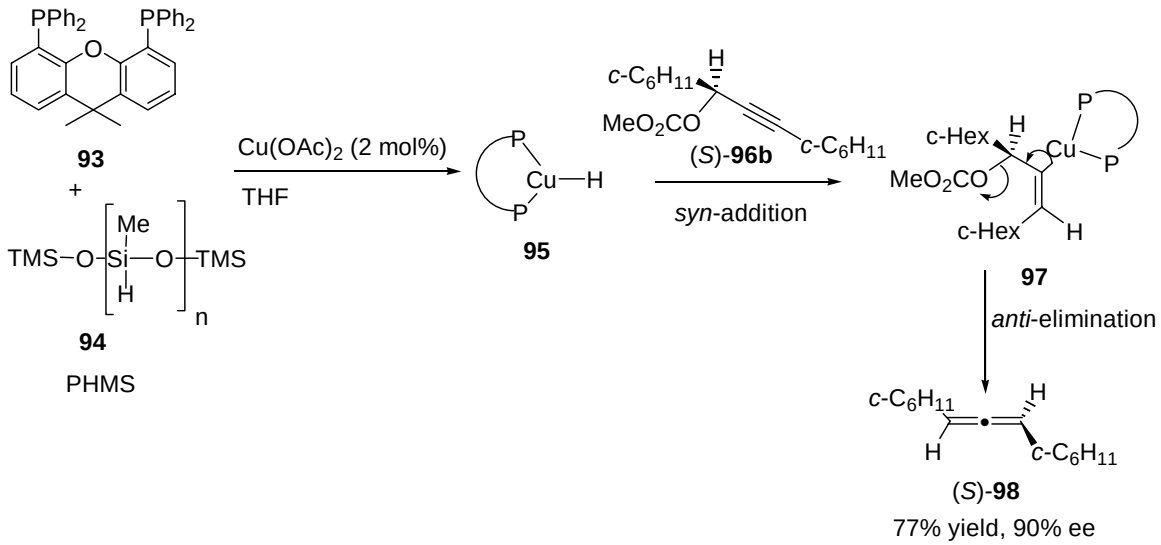
Hydrozirconation of propargylic derivatives **90** by *in situ* generated zinc or magnesium alkoxides of propargylic alcohols **89** by $Cp_2Zr(H)Cl$ furnishes the allenes **92** in good yields with high optical purities (Scheme **7**).[28]

Scheme 7



Synthesis of various di and trisubstituted allenes by copper(I)-catalyzed anti-S_N2'-type reduction of propargylic carbonates **96b** with hydrosilanes **94** in the presence of phosphine ligands **93** to stabilize the corresponding CuH complexe **95** has been reported. These reactions have good tolerance to various functional groups and work efficiently for the synthesis of optically active allenes (Scheme **8**).[29]

Scheme 8



2.1.8 Chirality transfer from allylic position by elimination reactions

Chiral allylic silyl trifluoromethane sulfonates **101,** prepared by the reaction of **99** with aldehyde followed by triflation of **100** upon fluoride ion-induced elimination gave the chiral allene **102** with 18% ee and 50% yield.[30] Several elimination reactions of this type have been reported (Chart **5)**.[31]

Chart 5

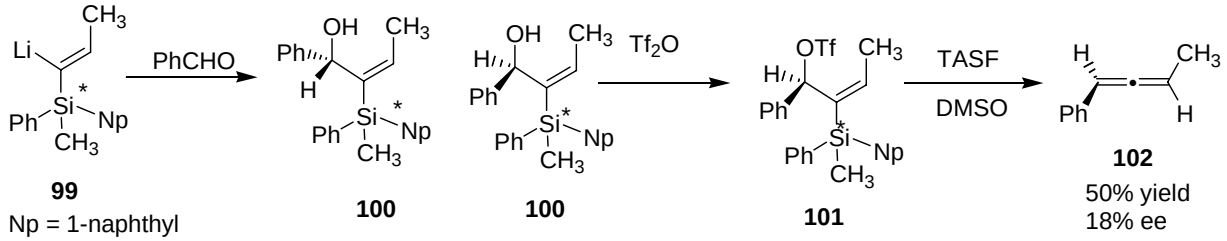
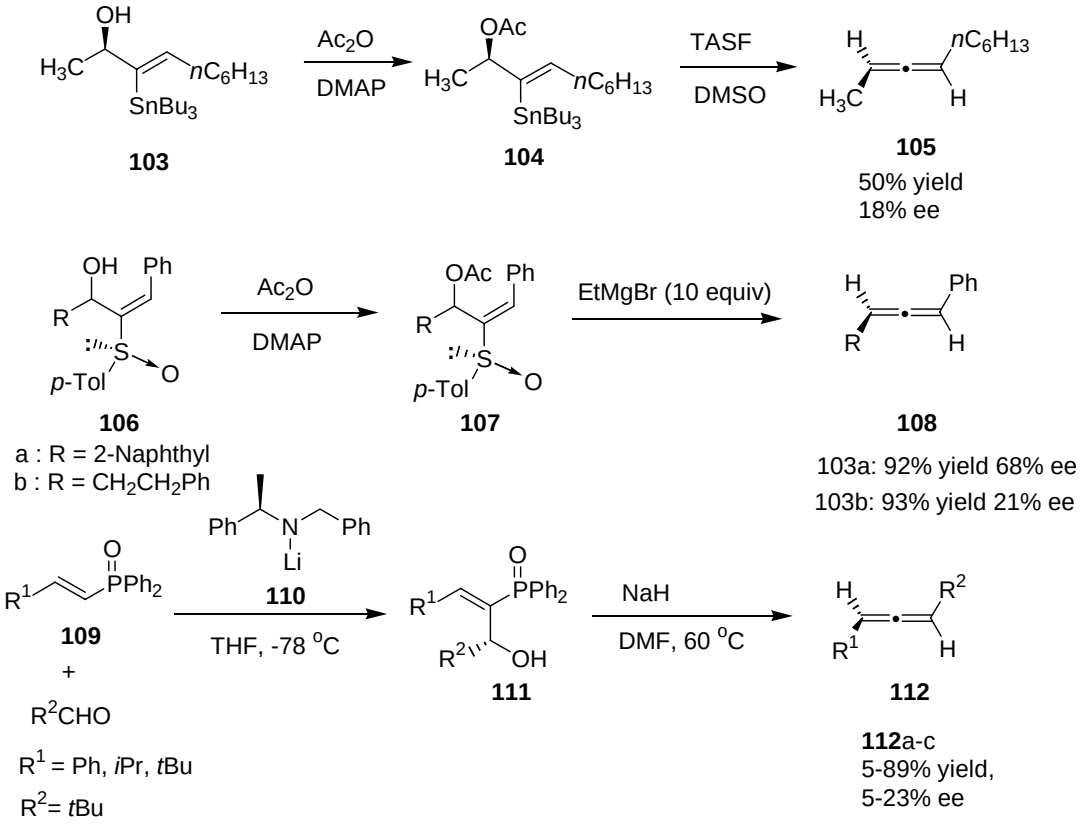


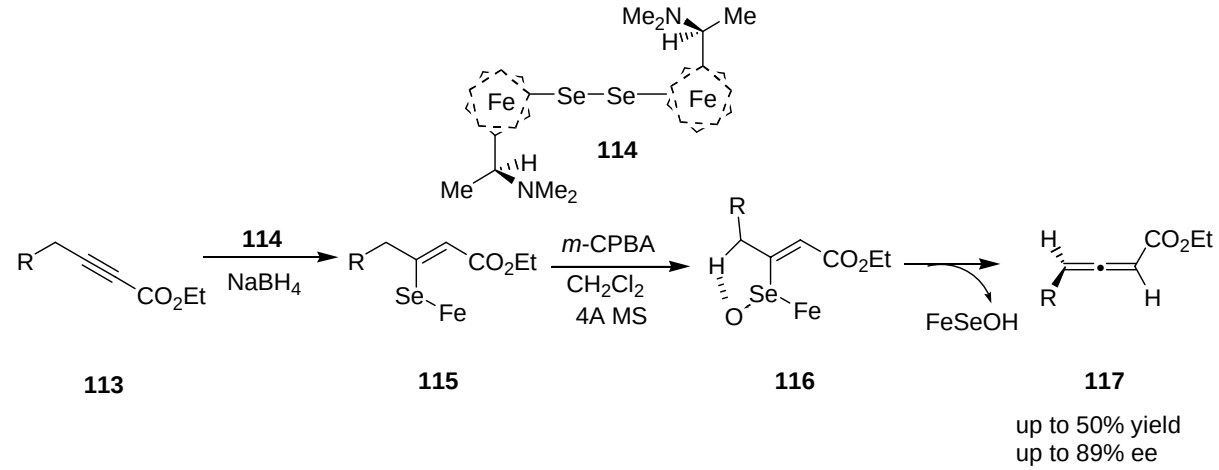
Chart 5 continued……..



2.1.8.1 Chirality transfer from allylic compounds having a chiral leaving group

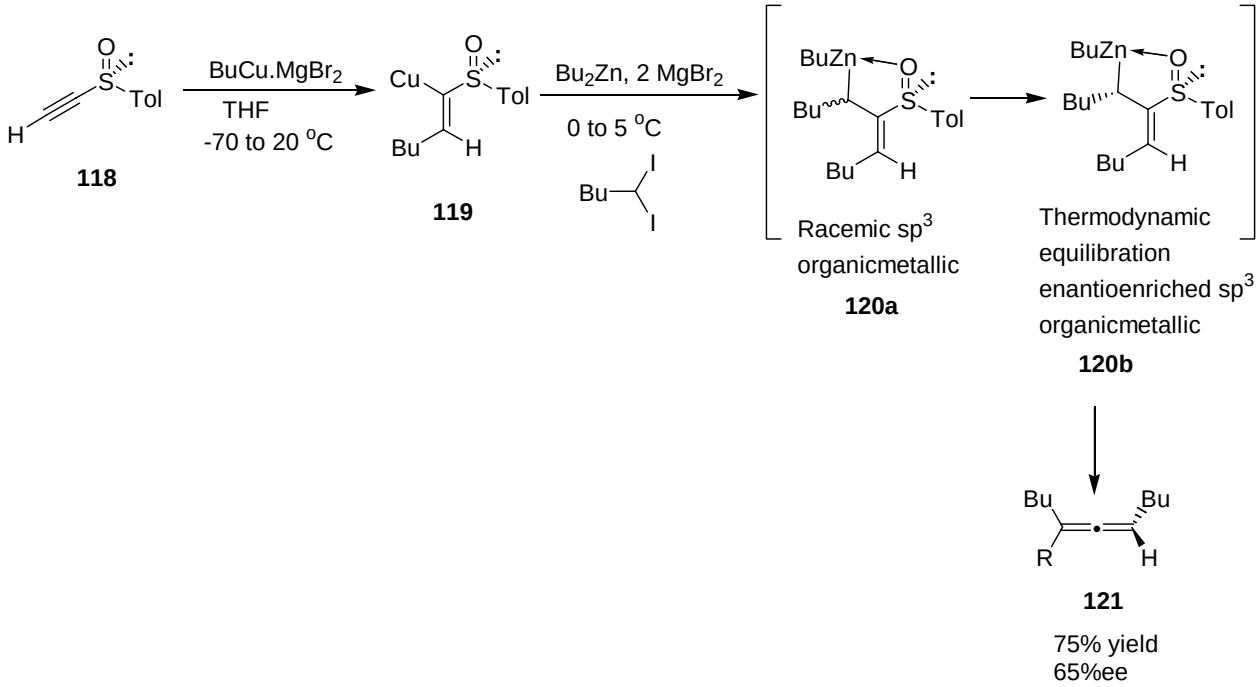
The readily accessible chiral selenoxides **116** act as chiral leaving group, in the oxidation with *m*-CPBA to give the corresponding chiral allenylcarboxylates (*R*)-**117** or (*S*)-**117** in up to 50% yield with 89% ee (Scheme **9**).[32]

Scheme 9



The allylic zinc intermediate **120a,** prepared as outlined in Scheme **10** undergoes an epimerization into the most stable intermediate **120b** in which the tosyl and the butyl groups are *anti* to each other, leads to *syn* β-elimination to give the allene **121** in 75% yield with 65% ee (Scheme **10**). [33]

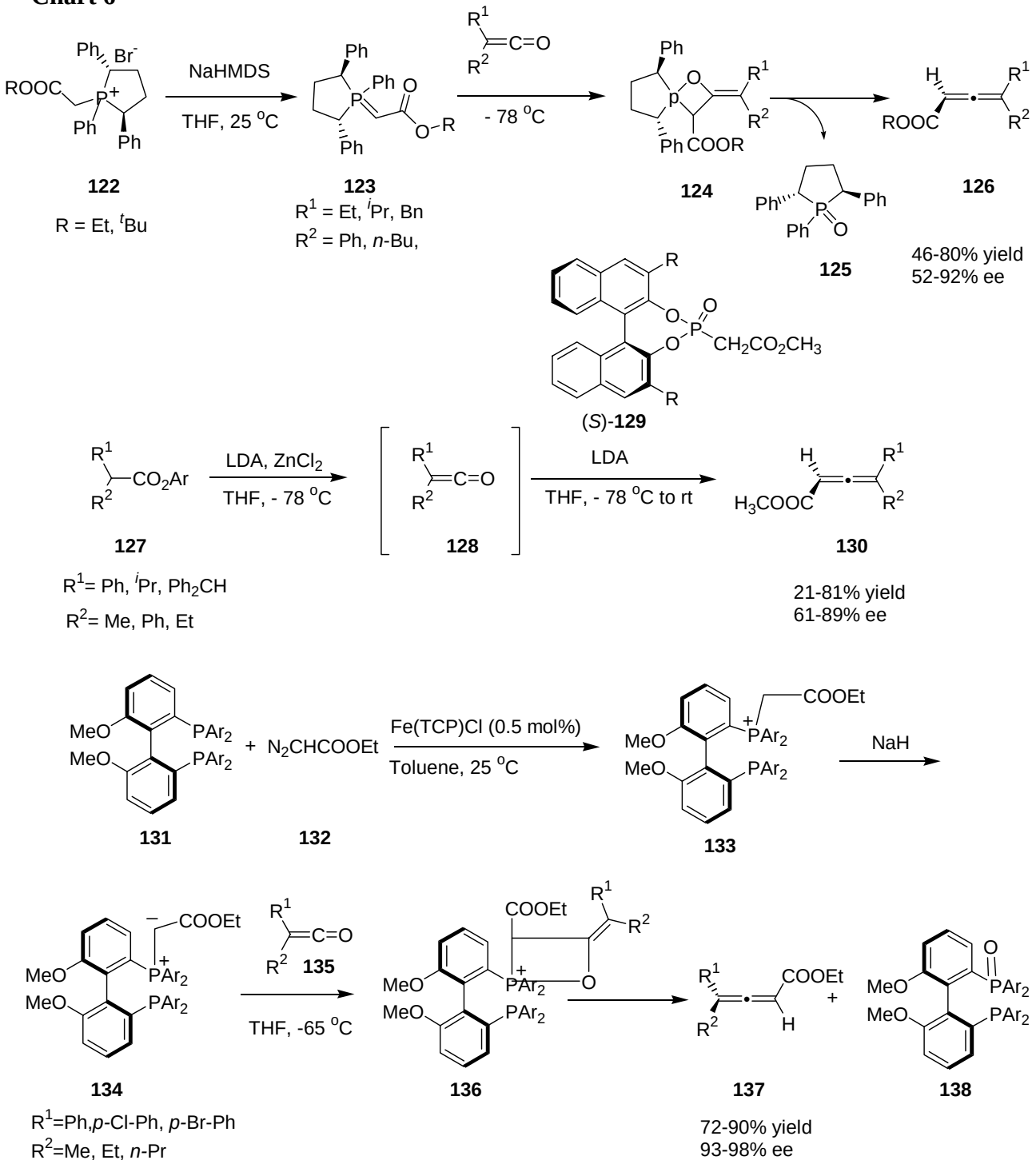
Scheme 10



2.1.9 Chirality transfer by Wittig-type reactions

Synthesis of chiral allenes by Wittig-type reactions using ketene with organophosphate reagents have been reported (Chart **6**). [34, 35, 36]

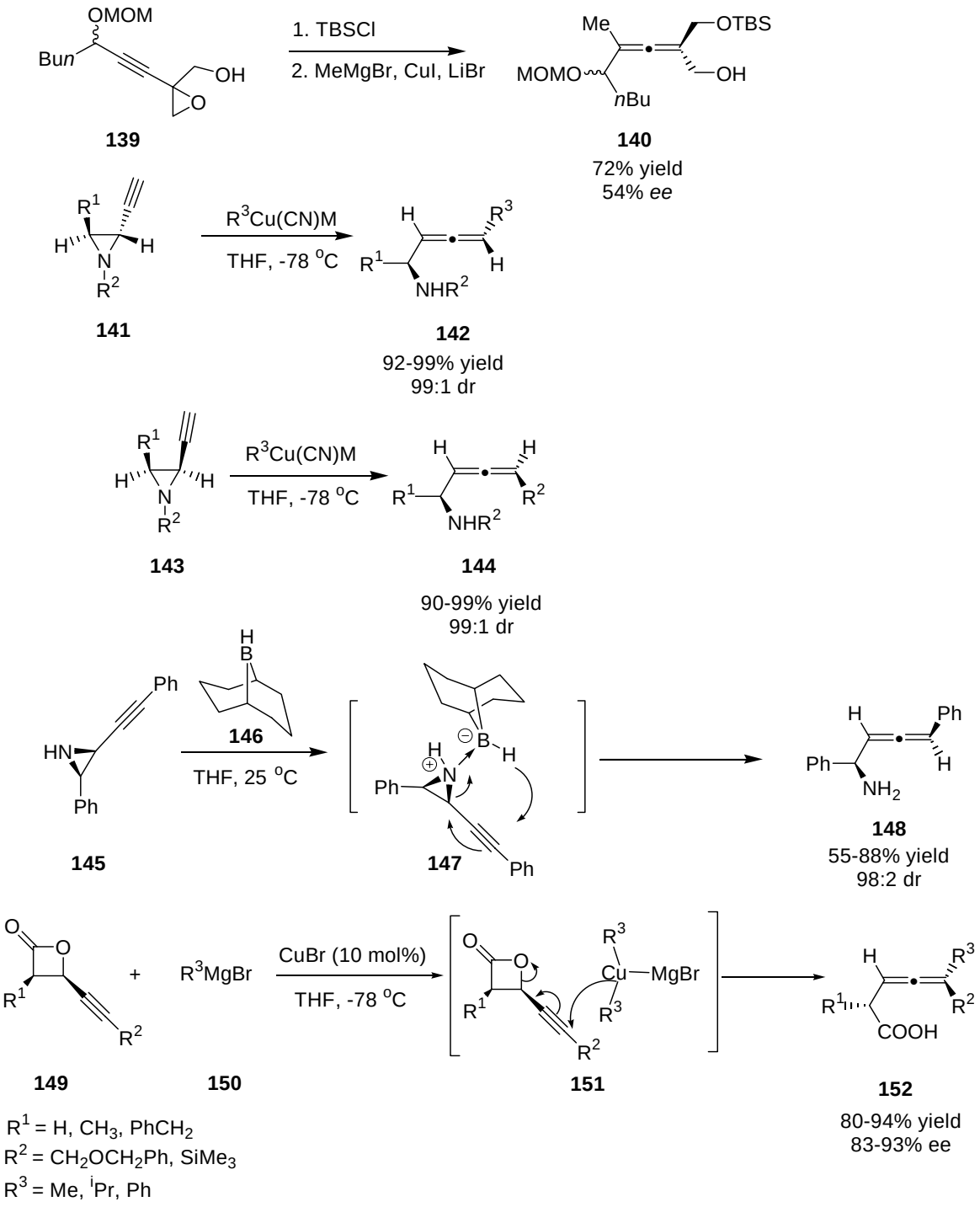
Chart 6



2.1.10 Chirality transfer by ring opening reactions

Synthesis of chiral allenes by S_N2' ring opening of epoxides, aziridines, or β-lactones with organometallic reagents have been reported (Chart **7**).[37]

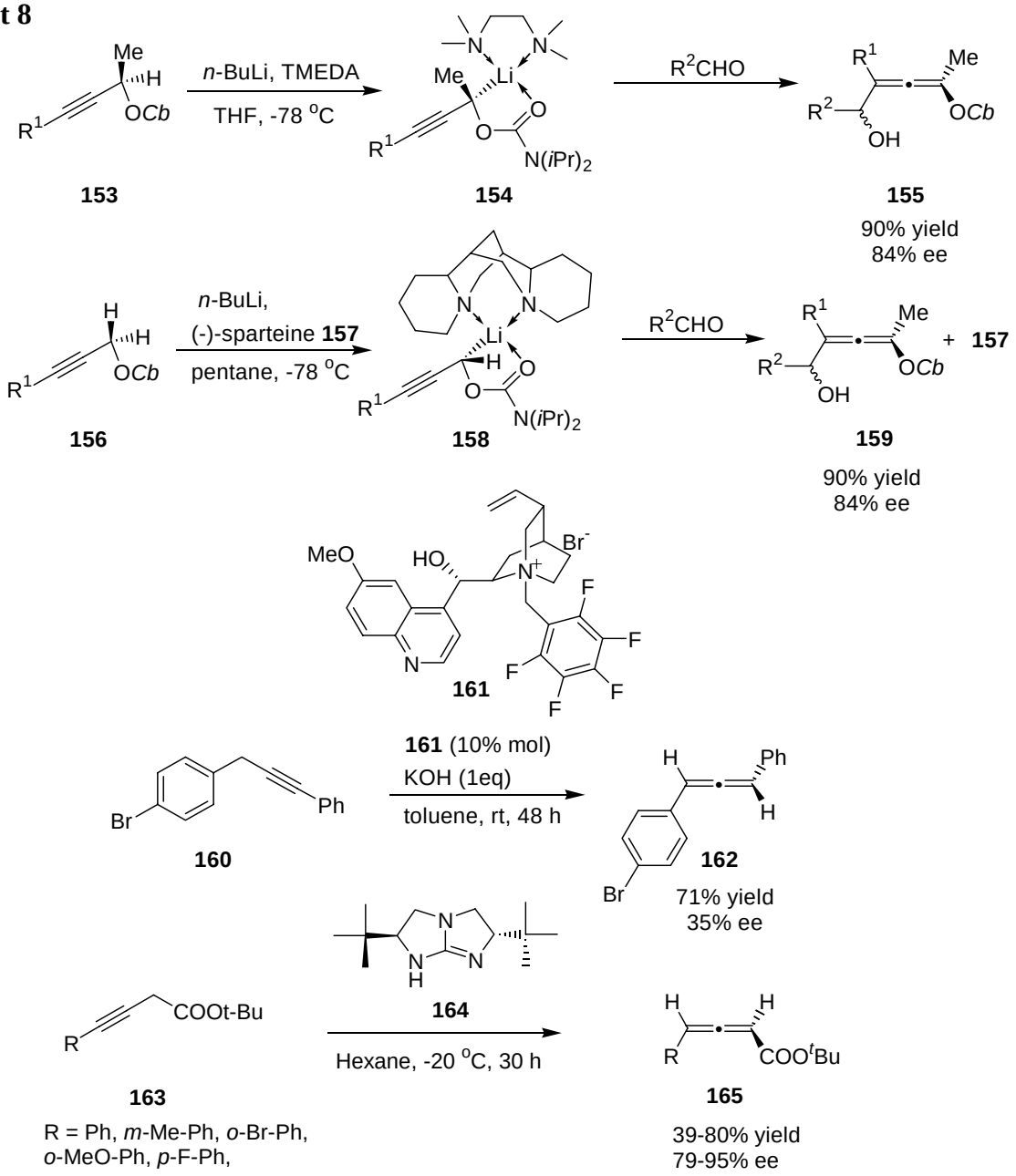
Chart 7



2.1.11 Chirality transfer by prototropic rearrangements

Lithiation of the compounds **153** with *n*-BuLi in the presence of TMEDA or chiral sparteine **157** afforded the configurationally stable lithium intermediates **154** which upon nucleophilic addition to an aldehyde followed by elimination gave the chiral allenes with good enantioselectivity (Chart **8)**. Similar prototropic rearrangements involving the chiral salt **161** and chiral guanidine **164** have been reported (Chart **8**).[38, 39, 40, 41]

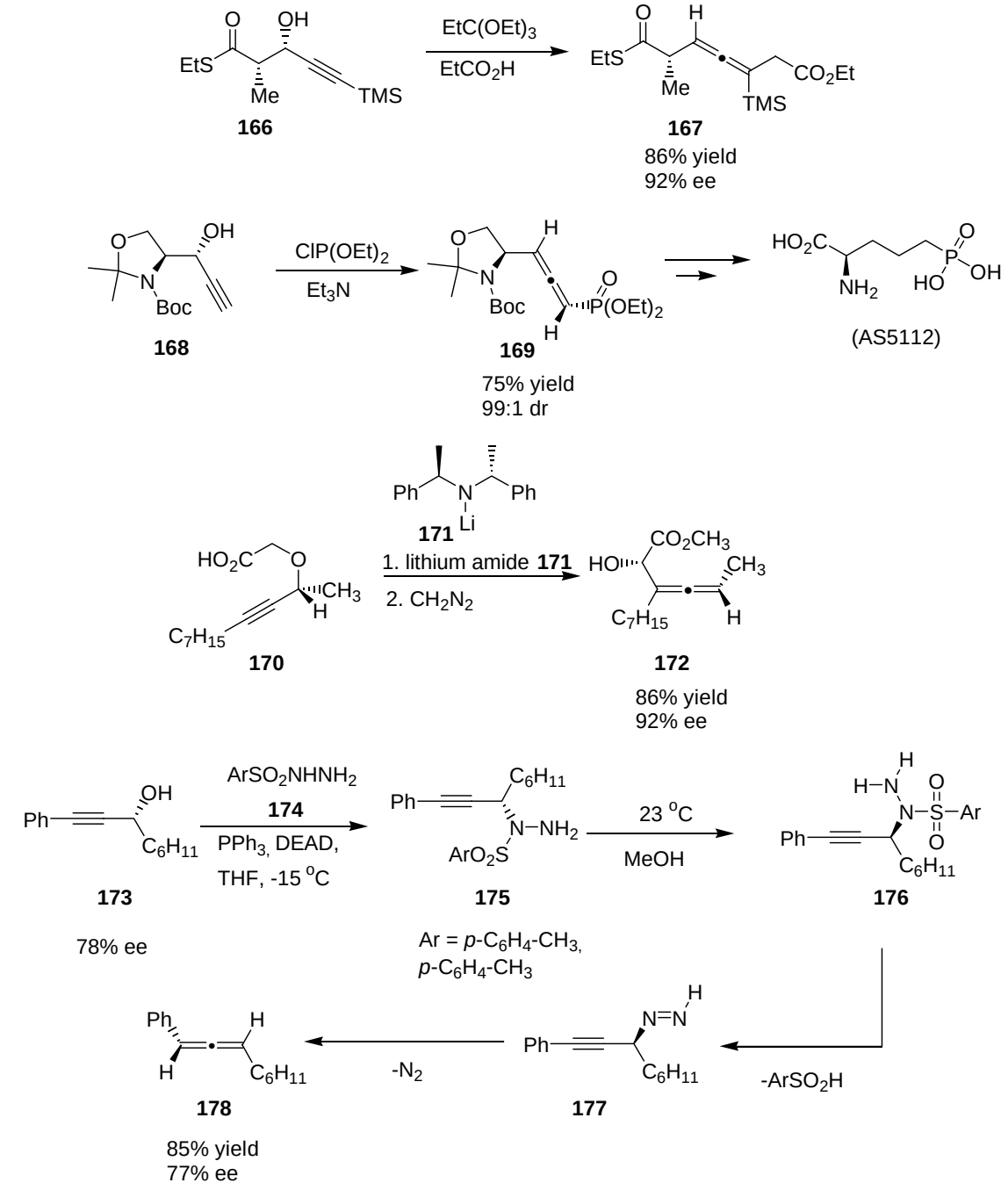
Chart 8



2.1.12 Chirality transfer by sigmatropic rearrangements

Several chiral propargyl alcohols were reported to undergo Claisen rearrangement to give the corresponding chiral allenes (Chart **9**).[42, 43, 44, 45]

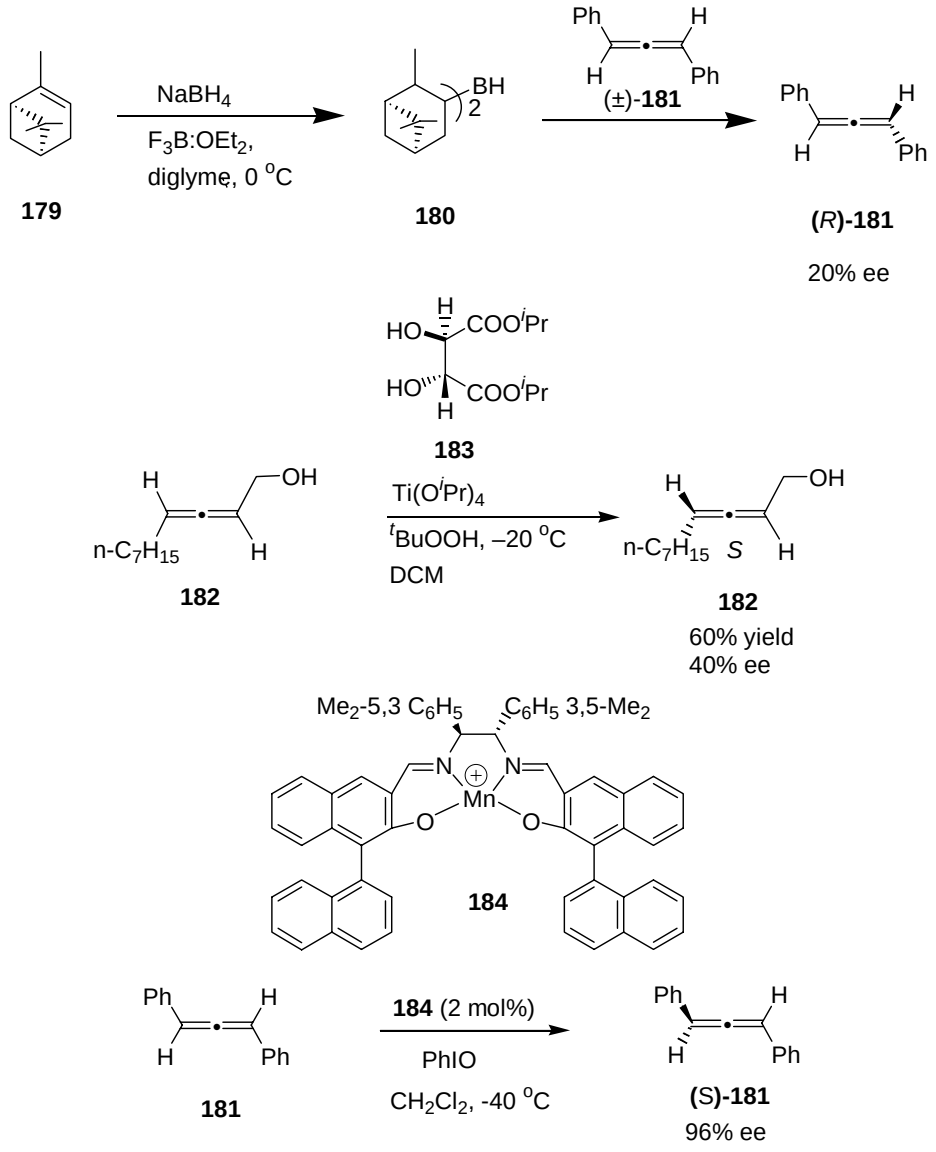
Chart 9



2.1.13 Chirality transfer by kinetic resolution

The kinetic resolution of racemic allenes by selective reaction of one of the enantiomers is an alternative method to access enantiomerically enriched allenes. Methods such as asymmetric hydroboration and asymmetric epoxidation have been reported (Chart **10)**.[46, 47, 48, 49]

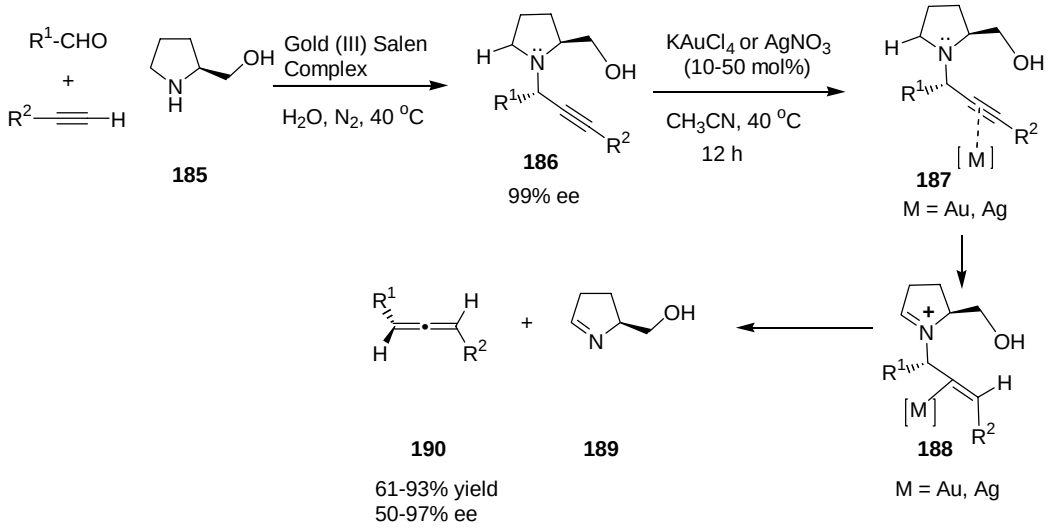
Chart 10



2.1.14 Chirality transfer by Crabbe homologative allenylation

Recently, it has been reported that the chiral propargylamine derivatives **186**, prepared using various aldehydes, 1-alkynes and chiral amino alcohol **185** using a gold(III)-salen as catalyst, yield chiral allenes **190** in 50-97% ee under $KAuCl_4$ or $AgNO_3$ catalysis in CH_3CN at 40 °C (Scheme **11**).[50]

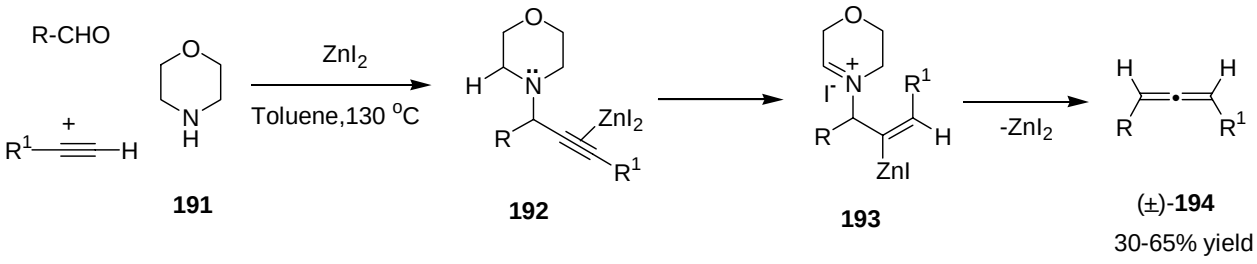
Scheme 11



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

More recently, it has been reported that racemic allenes **194** are formed in 30-65% yield in the reaction of aldehydes, 1-alkynes, morpholine **191** and ZnX_2 in toluene at 130 °C (Scheme **12**).[51]

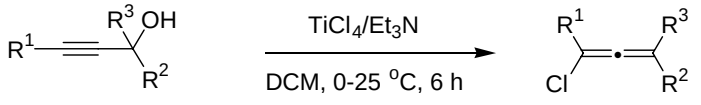
Scheme 12



2.1.16 Previous work from this laboratory

Previously, efforts were undertaken in this laboratory towards the synthesis of allenes. It was found that the reaction of propargylic alcohol **195** with $TiCl_4/Et_3N$ gave the corresponding racemic chloroallenes **196** in 37-58% yield (Scheme **13**).[52]

Scheme 13



195

$R^1 = C_5H_{11}$, Ph

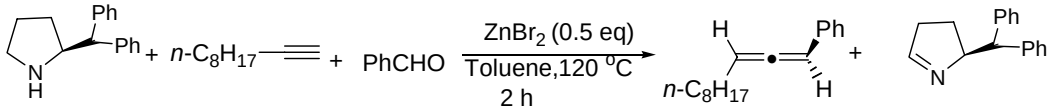
R^2 , R^3= Ph,

196

37-58% yield

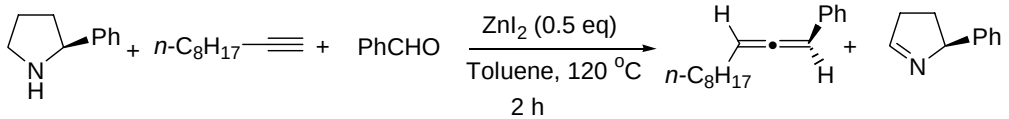
Very recently, methods have been developed for the enantioselective synthesis of chiral allenes via ZnX_2 promoted reaction of 1-alkyne **198** and arylaldehyde **199** using several chiral amine systems (Scheme **14**).[53]

Scheme 14



197 **198a** **199a** (*R*)-**200aa** **201**

65% yield, 66% ee

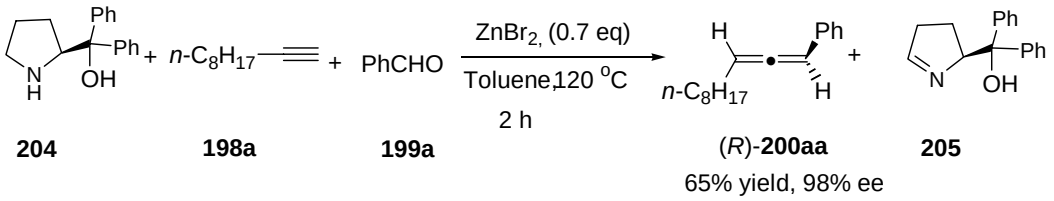


202 **198a** **199a** (*R*)-**200aa** **203**

72% yield, 66% ee

Enantioselective synthesis of chiral allenes via $ZnBr_2$ promoted reaction of 1-decyne **198a** and benzaldehyde **199a** using the diphenylprolinol (*S*)-DPP **204** system gave very high selectivity (Scheme **15)**.[54]

Scheme 15



204 **198a** **199a** (*R*)-**200aa** **205**

65% yield, 98% ee

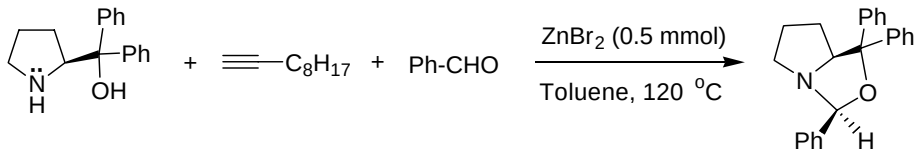
We have undertaken studies to examine the scope of the $ZnBr_2$ promoted chiral allene synthesis using (*S*)-DPP **204**. We have also examined the use of chiral camphanyl piperazine derivatives for this transformation. The results are described in the next section.

2.2 Results and Discussion

2.2.1 Enantioselective synthesis of chiral allenes from 1-alkynes, aldehydes and (*S*)-diphenylprolinol

As outlined in the introductory section, methods were reported on the enantioselective synthesis of chiral allenes via $ZnBr_2$ promoted reaction of 1-decyne **198a** and benzaldehyde **199a** using (*S*)-DPP **204** system (Scheme **16**).[54] We have observed that the enantioselectivity is also affected by the sequence of addition of reagents. For instance, when the amine **204**, 1-decyne **198a**, and benzaldehyde **199a** were heated with $ZnBr_2$ in toluene at 120 °C only for 15 min, the oxazolidine **206** was isolated in 30% yield (Scheme **16**).[55]

Scheme 16

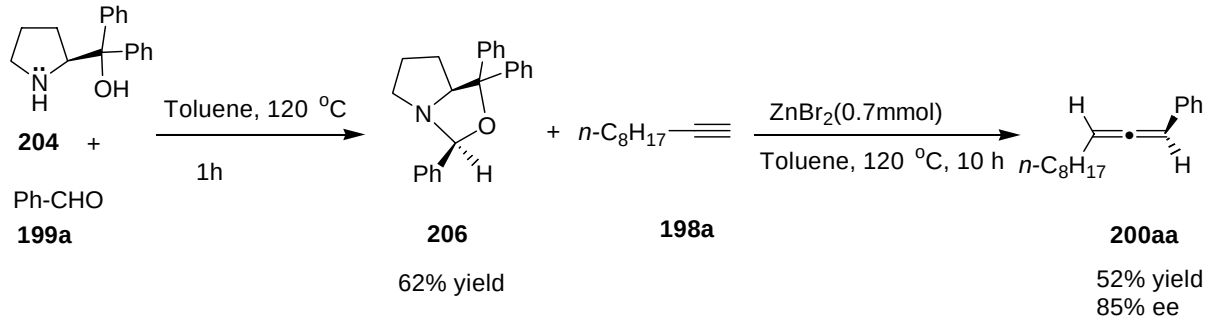


204 **198a** **199a** **206**

30% yield

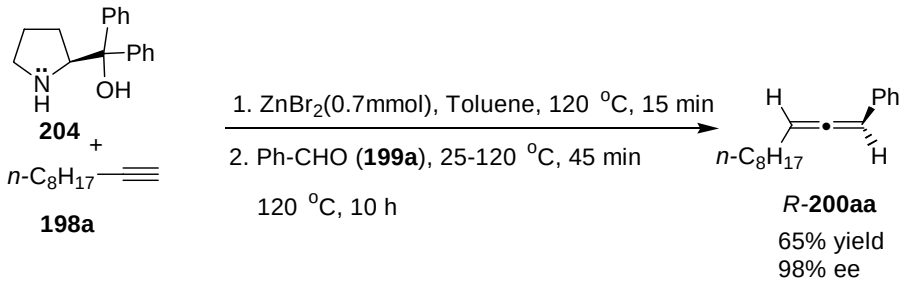
The oxazolidine **206** was also obtained in 62% yield by heating the amine **204** and benzaldehyde **199a** in toluene at 120 °C for 1h which further illustrates the ease of formation of this intermediate upon heating. Unfortunately, this oxazolidine intermediate **206** reacts with 1-decyne and $ZnBr_2$ at 120 °C to give the allene **200aa** only in 85% ee and 52% yield (Scheme **17**).

Scheme `17



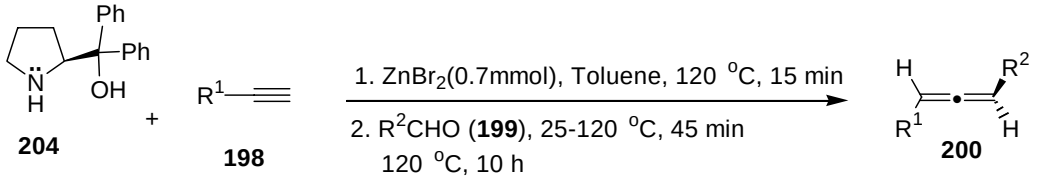
Whereas, heating the chiral amine (*S*)-DPP **204,** $ZnBr_2$ and 1-decyne **198a** in toluene for 10 min at 120 °C followed by addition of the aldehyde **199a** at 25 °C and further stirring at 120 °C for 10h, gave the (*R*)-allene **200aa** in 65% yield and 98% ee (Scheme **18**).

Scheme 18

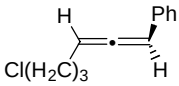


Therefore, we have carried out the reactions of different aldehydes using $ZnBr_2$ (0.7 mmol) using the conditions outlined in Scheme **18** to obtain the corresponding chiral allenes in good yields and high enantioselectivities. The substituted benzaldehyde derivatives having both electron donating and withdrawing groups afforded good results in terms of yield and ee's. The chloro and cyano substituted alkynes **198d** and **198e** react with benzaldehyde **199a** to give the allenes (*R*)-**200da** and (*R*)-**200ea** in 62% and 69% yields, 93% and 99% ee, respectively (Table **1**). Whereas the unprotected propargyl alcohol reacts with benzaldehyde **199a** to give only a complex mixture of products under these conditions, the corresponding benzoyl ester leads to the

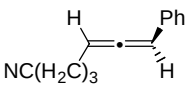
Table-1



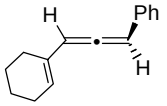
R^1	R^2	
198a = nC_8H_{17},	**199a** = Ph,	**199h** = Ph-*p*CH_3,
198b = Ph,	**199b** = Ph-*p*Br,	**199i** = 2-thiophnyl,
198c = $PhCH_2CH_2$,	**199c** = Ph-*p*Cl,	**199j** = 2-Furanyl,
198d = $Cl(CH_2)_3$,	**199d** = Ph-*p*F,	**199k** = nC_4H_9,
198e = $NC(CH_2)_3$,	**199e** = Ph-*p*CF_3,	**199l** = Cyclohexyl,
198f = 1-cycloHexenyl,	**199f** = Ph-*m*OCH_3,	**199m** = iC_3H_7
198g = *p*-$NO_2PhCH_2OCH_2$,	**199g** = Ph *m*CH_3,	



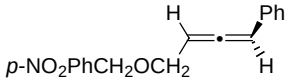
200da, 4h,
62% y, 93% ee



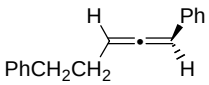
200ea, 4h,
69% y, 99% ee



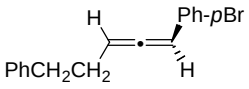
200fa, 4h,
51% y, 99% ee



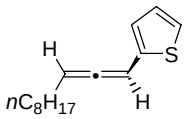
200ga, 10h,
64% y, 99% ee



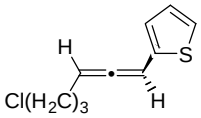
200ca, 4h,
61% y, 93% ee



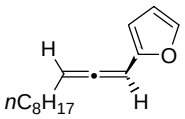
200cb, 4h,
55% y, 88% ee



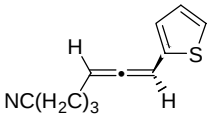
200ai, 4h,
62% y, 92% ee



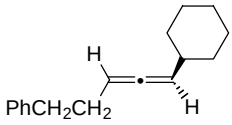
200di, 4h,
52% y, 88% ee



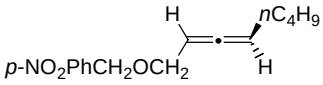
200aj, 2h,
35% y, 86% ee



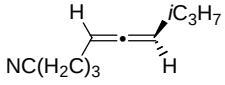
200ei, 4h,
52% y



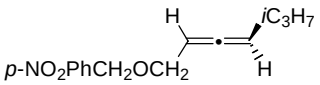
200cl, 4h,
51% y, 84% ee



200gk, 10h,
59% y, 98% ee



200em, 10h,
59% y,



200gm, 10h,
48% y, 99%ee

[a]The reactions were carried out by using amine **204 (**1.0 mmol), $ZnBr_2$ **(**0.7 mmol) and 1-alkyne (1.1 mmol) in toluene (3 mL) at 25 °C following the sequence of addition of reagents as outlined under Table **1**. [b]Isolated yield. [c]The % ee was determined by HPLC analysis on chiralcel OD-H, OJ-H or OB-H column.

formation of the N-benzoyl derivative of the (*S*)-DPP **204** and the corresponding allene was not formed. Fortunately, the *p*-nitrobenzyl ether derivative **198g** gave the allene (*R*)-**200ga** in 64% yield and 99% ee. Also, the enyne **198f** gave the allene (*R*)-**200fa** in 51% yield and 79% ee (Table **1**).

Thiophene-2-aldehyde **199i** also reacts with alkynes **198a**, **198d** and **198e** to give the corresponding allenes (*R*)-**200ai**, (*R*)-**200di** and (*R*)-**200ei** in reasonable yields and selectivity. The allene (*R*)-**200aj** is obtained in 35% yield and 86% ee after 2h in the reaction of furfural **199j** and alkyne **198a** with $ZnBr_2$ at 120 °C, but only a complex mixture of unidentifiable products remained after 4h reaction. The aliphatic aldehydes **199k**, **199l** and **199m**, react with the 4-phenyl-1-butyne **198c**, cyano substituted alkyne **198e** and *p*-nitrobenzyl propargyl ether **198g** to give the allenes (*R*)-**200cl**, (*R*)-**200em,** (*R*)-**200gk** and (*R*)-**200gm** in 48% to 59% yield and 92%-99% ee.

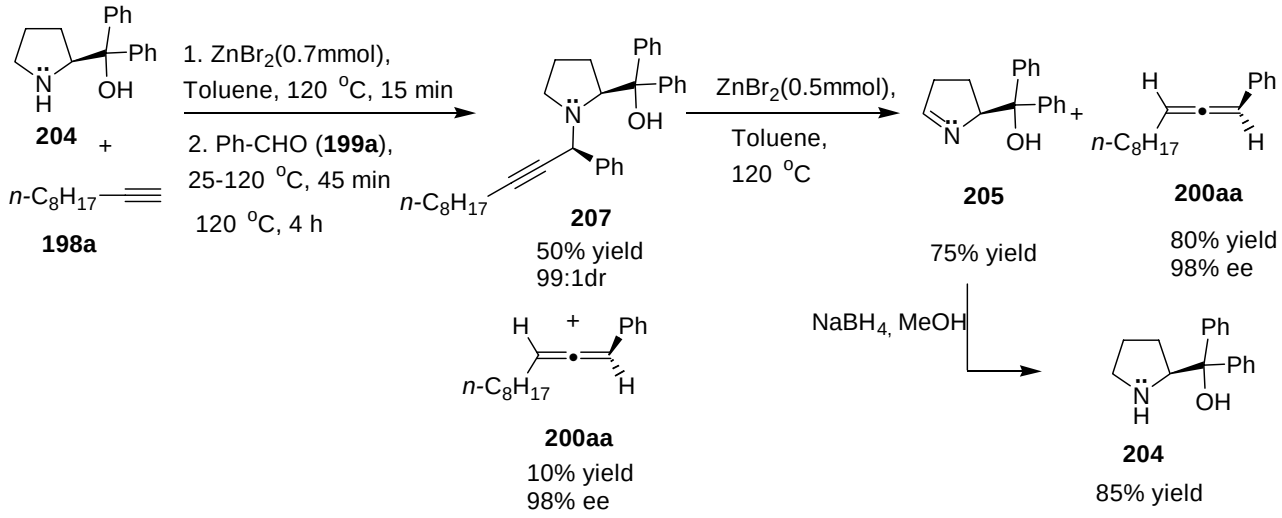
Simple alkynes like **198a** react with the aliphatic aldehydes but chromatographic separation of the mixtures containing the allenic products was somewhat difficult in the absence of chromophoric groups in these cases. The use of ethyl propiolate leads to a complex mixture of products in the reaction with benzaldehyde **199a** with the chiral amine **204**. Also, substrates like cinnamaldehyde, N-methyl-2-formylindole and acetophenone gave only complex mixtures of unidentifiable products in reaction with 1-decyne under the reaction conditions.

All the optically active allenes obtained by using (*S*)-DPP **204** are levorotatory, from which the absolute configurations of the major enantiomer of the allenes can be assigned as *R* by considering the Lowe-Brewster rules.[56] Comparison of $[\alpha]_D^{25}$ values with reported values confirms this stereochemical assignment.

2.2.2 Isolation of chiral propargylamine intermediate and isolation of chiral imine

To study the mechanistic pathway of this reaction, we have carried out the reaction using $ZnBr_2$ only for 4h at 120 °C. In this run, the propargylamine intermediate **207** was isolated in 50% yield besides the *R*-allene **200aa** in 10% yield with 98% ee. This propargylamine **207** derivative was found to be with 99:1 dr and the new chiral center at the propargylic position is assigned as *S* configuration based on comparison of $[\alpha]_D^{25}$ value with reported value for similar derivatives. We have observed that further reaction of intermediate **207** (1.0 mmol) with $ZnBr_2$ (0.5 mmol) in toluene (3 mL) for 3h at 120 °C gives the (*R*)-allene **200aa** in 80% yield with 98% ee besides the imine **205** in 75% yield without loss of its chirality (Scheme **19)**. The imine **205** was converted back to the (*S)*-DPP **204** in quantitative yield for reuse by simple reduction using $NaBH_4$/MeOH without any change in optical purity (Scheme **19)**

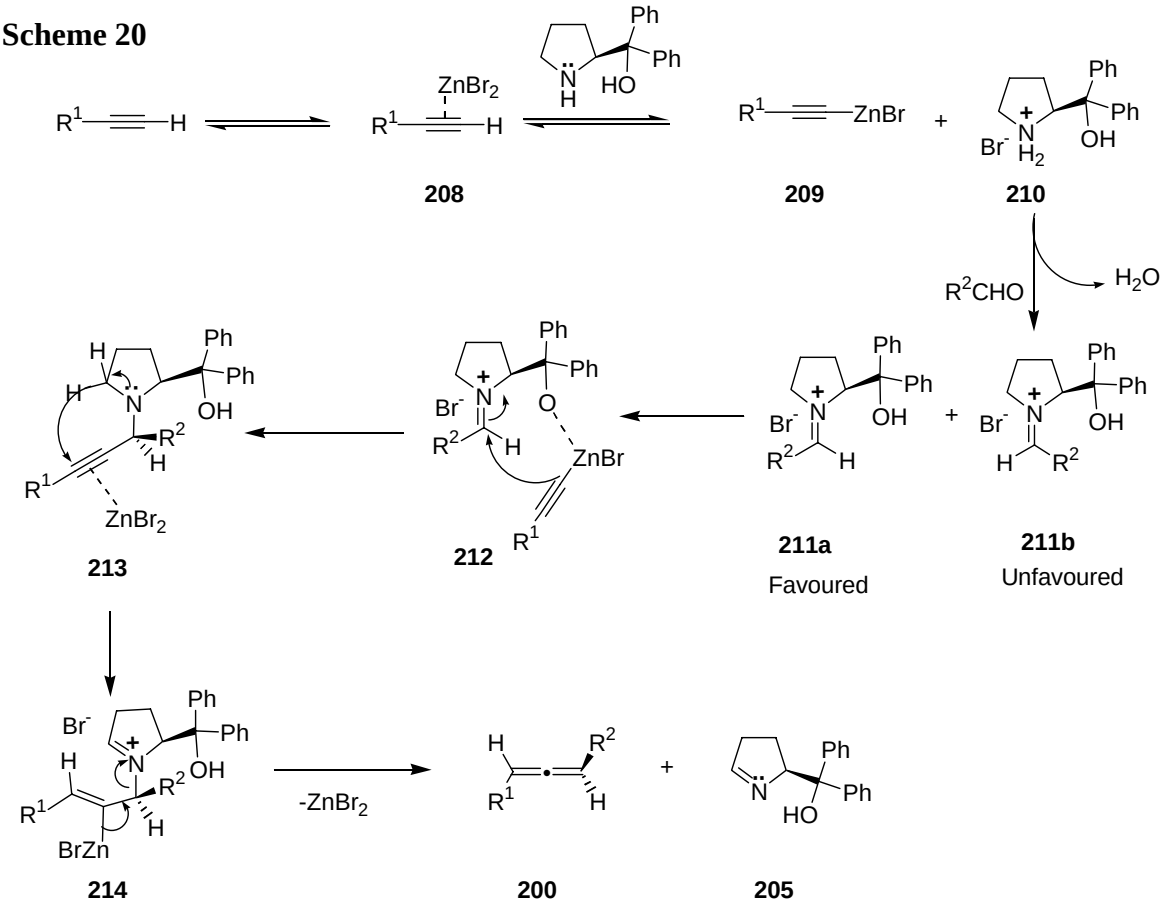
Scheme 19



2.2.3 Plausible mechanistic pathway for the allene formation

The formation of chiral allenes can be explained by considering the mechanism as outlined in Scheme **20**. The initially formed alkynyl zinc intermediate **209**[57] would react with the favoured conformation of iminium ion **211a** derived from various aromatic aldehydes and (*S*)-diphenylprolinol **204** to give the corresponding propargylamine intermediate **213.** The propargylamine intermediate **213** would then undergo an intramolecular hydride shift from the pyrrolidine skeleton of (*S*)-DPP **213** to the $ZnBr_2$ complexed acetylinic moiety leading to alkenyl zinc complex **214**. Subsequently, cleavage of C-N bond by *anti*-elimination would lead to the chiral allene **200** and the imine **205** of (*S*)-DPP.

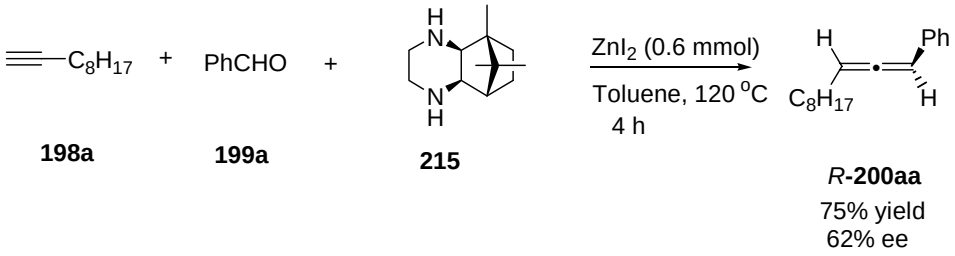
Scheme 20



2.2.4 Synthesis of chiral allenes using chiral amine containing camphanyl moiety

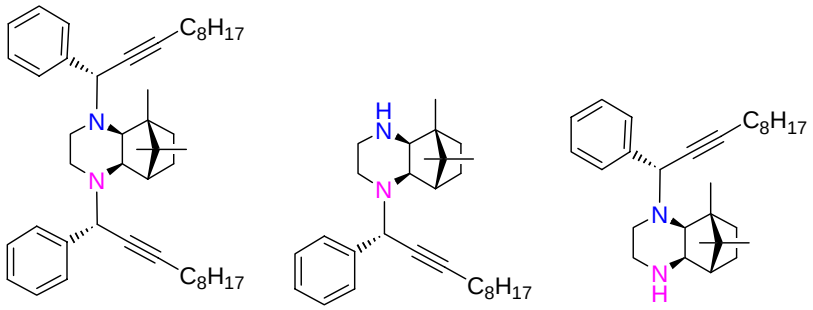
We have then explored the use of the chiral camphanyl piperazines (Chapter **1)**[58] for the synthesis of enantiopure allenes to expand the scope of this "chiral amine approach". We have observed that the reaction of 1-decyne **198a**, benzaldehyde **199a** and camphanyl piperazine **215** using ZnI_2 at 120 °C gave the (*R*)-allene **200aa** in 75% yield with 62% ee (Scheme **21**).

Scheme 21



198a **199a** **215** ***R*-200aa**
75% yield
62% ee

We performed several experiments to understand the probable reason for relatively low enantioselectivity realized using the chiral camphanyl piperazine **215** compared to (*S*)-DPP **204**. It was thought that different chiral discrimination abilities of the two secondary amine moieties present in the chiral camphanyl piperazine **215** would lead to the formation of a mixture of chiral propargylamine intermediates **216, 217** and **218** (Figure **4**), leading to the formation (*R*)-allene **200aa** in only in 62% ee.



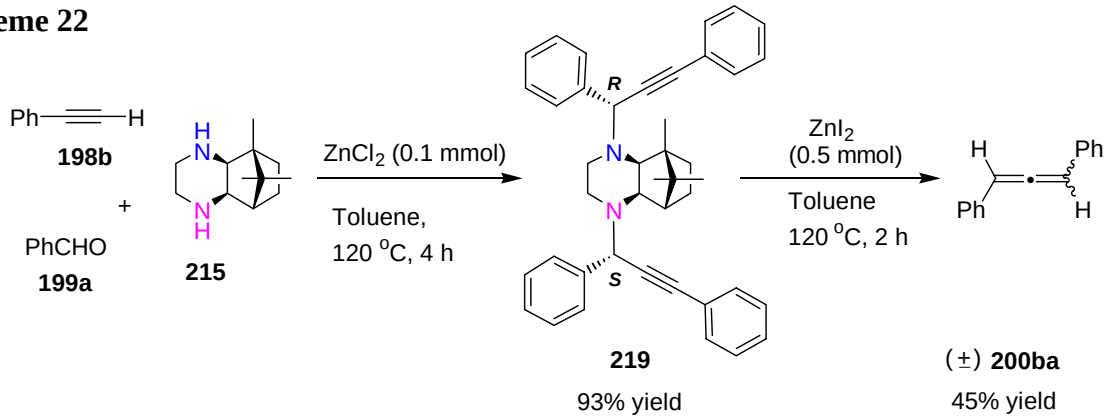
216 **217** **218**

Figure 4

2.2.5 Isolation of dipropargylamine intermediate 219

To examine this, we have carried out the reaction of phenylacetylene **198b**, with benzaldehyde **199a** and the piperazine **215** using $ZnCl_2$ (0.1 mmol) at 120 °C for 4h to isolate the dipropargylamine intermediate **219** in 93% yield. Interestingly, the dipropargylamine **219** reacts with ZnI_2 (0.5 mmol) to give only the racemic allene **200ba** in 45% yield (Scheme **22**).

Scheme 22



The configurations at the newly formed stereogenic centers were assigned as *R*,*S* in the dipropargylamine **219** by X-ray crystal structure analysis (Figure **5**).

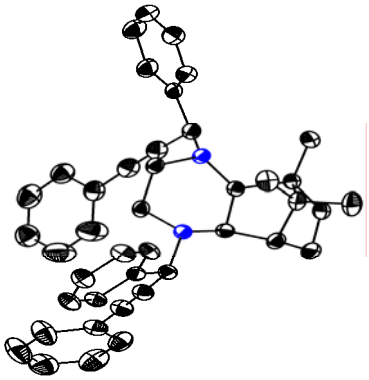


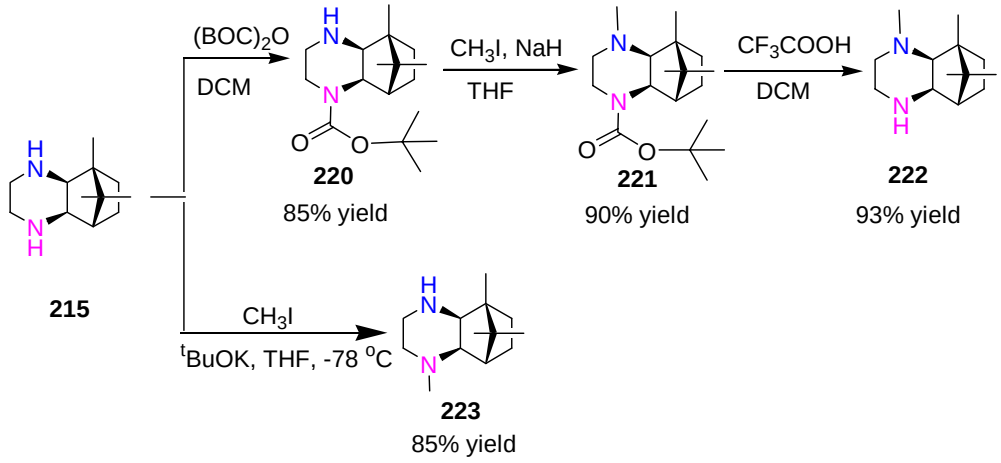
Figure 5. ORTEP representation of the dipropargylamine **219** (All the H-atoms were removed for clarity and thermal ellipsoids were drawn with 30% probability).

Presumably, presence of the dipropargylamine **216** (Figure **4**) in the reaction mixture during the allene transformation outlined in Scheme **21** leads to lower ee.

2.2.6 Synthesis of N-methylcamphanyl piperazine derivatives:

It occurred to us that blocking of one of the secondary amine moieties in the chiral piperazine **215** would give better selectivity in this allene transformation. To examine this, we have developed methods of synthesis for the N-methylcamphanyl piperazine derivatives **222** and **223** from the chiral camphanyl piperazine **215**. Whereas ^{t}BOC protection followed by methylation and ^{t}BOC deprotection gives the N-methylpiperazine **222** in 93% yield, direct methylation using $^{t}BuO^{-}K^{+}$ followed by reaction with methyl iodide at -78 °C gave the N-methylcamphanyl piperazine **223** in 85% yield (Scheme **23**).

Scheme 23

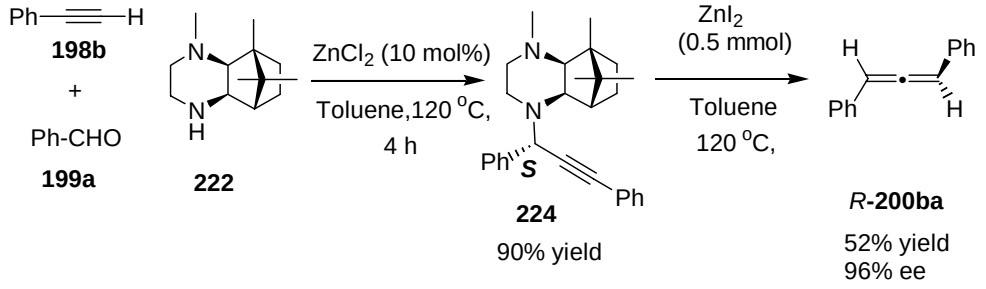


2.2.7 Isolation of chiral propargylamine intermediate

We have then carried out the reaction of phenylacetylene **198b**, benzaldehyde **199a**, N-methylcamphanyl piperazine **215** and $ZnCl_2$ (10 mol%) at 120 °C for 4h obtain the propargylamine intermediate **224** in 90% yield with 99:1 dr (Scheme **24**). Further, the chiral

propargylamine **224** upon reaction with ZnI_2 (0.5 mmol) gives the (*R*)-allene **200ba** in 52% yield with 96% ee.

Scheme 24



Indeed, as marked in the dipropargylamine structure **224,** the configuration of the newly formed stereogenic center in the chiral propargylamine **224** has '*S*' configuration as revealed by X-ray single crystal structure analysis (Figure **6**).

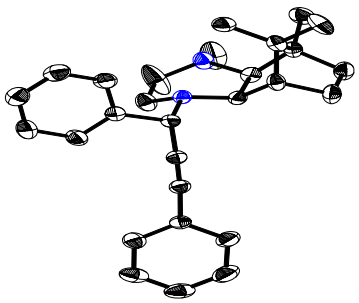
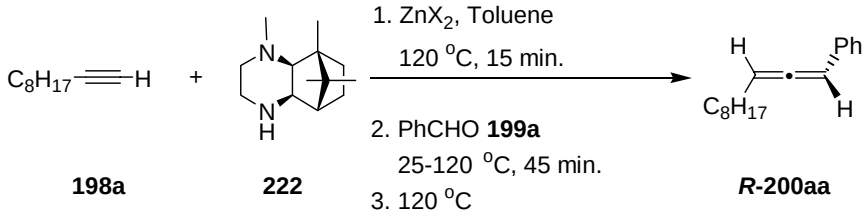


Figure 6. ORTEP representation of the propargylamine **224** (All the H-atoms were removed for clarity and thermal elipsoids were drawn with 30% probability).

We have carried out this chiral allene transformation under various reaction conditions using different zinc halides with 1-decyne **198a**, benzaldehyde **199a** and piperazine **222**. The use of $ZnBr_2$ (0.6 mmol) (Table **2**, entry **5**) gives optimum results.

Table 2. Reaction of 1-decyne **198a** and aldehyde **199a** with piperazine **222** promoted by zinc halide.[a,]



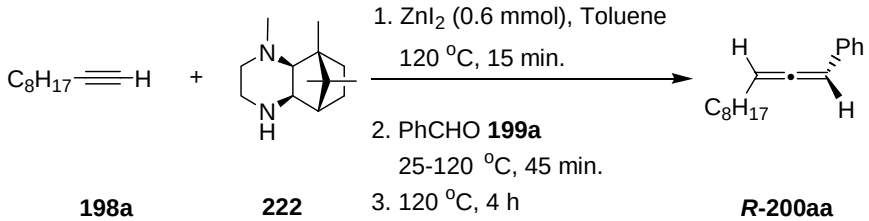
198a **222** ***R*-200aa**

Entry	Zinc halides	mmol	Time(h)	Yield [b]%	% ee[c]
1	$ZnCl_2$	1	4	28	99
2	$ZnCl_2$	0.8	4	17	99
3	$ZnCl_2$	0.6	6	11	99
3	$ZnBr_2$	1	4	71	91
4	$ZnBr_2$	0.8	4	69	94
5	$ZnBr_2$	0.6	6	65	98
6	ZnI_2	1	4	54	87
7	ZnI_2	0.8	4	68	90
8	ZnI_2	0.6	4	61	96

[a]The reactions were carried out by using piperazine **222 (**1.0 mmol), and 1-decyne (1.1 mmol) in toluene (3 mL) at 25 °C.[*b*]Isolated yield. [*c*]The % ee was determined by HPLC analysis .

After optimization of reaction conditions, we have carried out the reaction of 1-decyne **198a**, benzaldehyde **199a** and the chiral piperazine **222** using $ZnBr_2$ (0.6 mmol). In this run, the *R*-allene **200aa** in 61% yield with 96% ee in 4h at 120 °C (Scheme **25**).

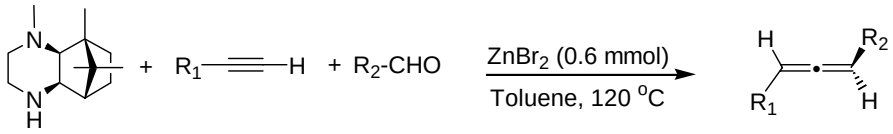
Scheme 25



198a **222** ***R*-200aa**

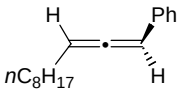
61% yield
96% ee

Table 3. Reaction of 1-alkyne **198** and aldehyde **199** with chiral piperazine **222** promoted by zinc bromide. [a,b,c]

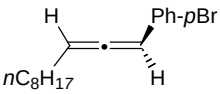


222 **198** **199** **(*R*)-200**

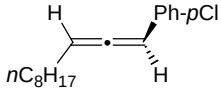
R_1	R_2	R_2
198a = nC_8H_{17},	**199a** = Ph,	**199h** = Ph-*p*CH_3,
198b = Ph,	**199b** = Ph-*p*Br,	**199i** = 2-thiophnyl,
198c = $PhCH_2CH_2$,	**199c** = Ph-*p*Cl,	**199j** = 2-Furanyl,
198d = $Cl(CH_2)_3$,	**199d** = Ph-*p*F,	**199k** = nC_4H_9,
198e = $NC(CH_2)_3$,	**199e** = Ph-*p*CF_3,	**199l** = Cyclohexyl,
198f = 1-cycloHexenyl,	**199f** = Ph-*m*OCH_3,	**199m** = iC_3H_7
198g = *p*-$NO_2PhCH_2OCH_2$,	**199g** = Ph *m*CH_3,	



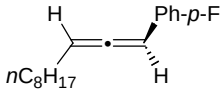
200aa, 5h,
68% y, 98% ee



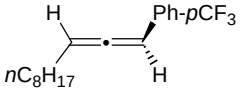
200ab, 4h,
72% y, 97% ee



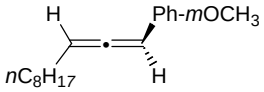
200ac, 5h,
71% y, 92% ee



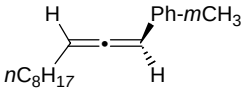
200ad, 4h,
75% y, 98% ee



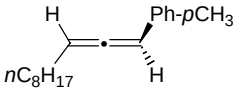
200ae, 6h,
70% y, 99% ee



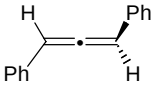
200af, 6h,
65% y, 97% ee



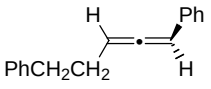
200ag, 10h,
67% y, 90% ee



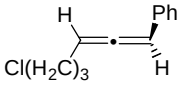
200ah, 9h,
63% y, 99% ee



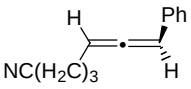
200ba, 4h,
42% y, 79% ee



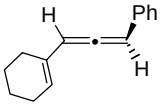
200ca, 4h,
72% y, 98% ee



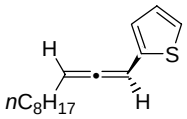
200da, 4h,
68% y, 98% ee



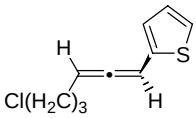
200ea, 4h,
68% y, 99% ee



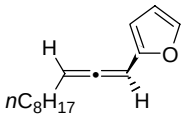
200fa, 4h,
64% y, 79% ee



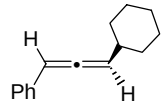
200ai, 4h,
74% y, 91% ee



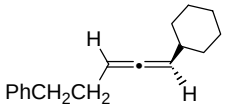
200di, 4h,
66% y, 99% ee



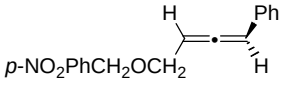
200aj, 2h,
40% y, 86% ee



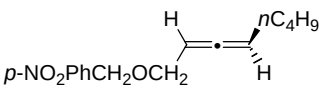
200bl, 4h,
68% y, 83% ee



200cl, 4h,
70% y, 99% ee



200ga, 10h,
62% y, 99% ee



200gk, 10h,
75% y, 99% ee

[a]The reactions were carried out by using piperazine **222 (**1.0 mmol), $ZnBr_2$ **(**0.6 mmol) and 1-alkyne (1.1 mmol) in toluene (3 mL) at 25 °C.[b]Isolated yield.. [c]The % ee was determined by HPLC analysis .

2.2.8 Reaction using various alkyne and aldehyde substrates

We have also carried out the reaction using various aldehydes and 1-alkynes containing functional groups (Table **3**). A broad range of aldehydes and 1-alkynes were converted to the corresponding chiral allenes in high yields and enantiomeric purities (Table **2**). Substituted benzaldehydes react with 1-decyne to give the corrsponding chiral allenes **200aa**-**200ah** in 63-75% yield with up to 90-99% ee (Table **3**). The reaction between benzaldehyde **199a** and phenylacetylene **198b** yields the product **200ba** in 42% with 79% ee. Alkynes like 1-phenylbutyne **198c** reacts with benzaldehyde **199a** to give the corresponding allenes **200ca** in 72% with 98% ee (Table **3**).

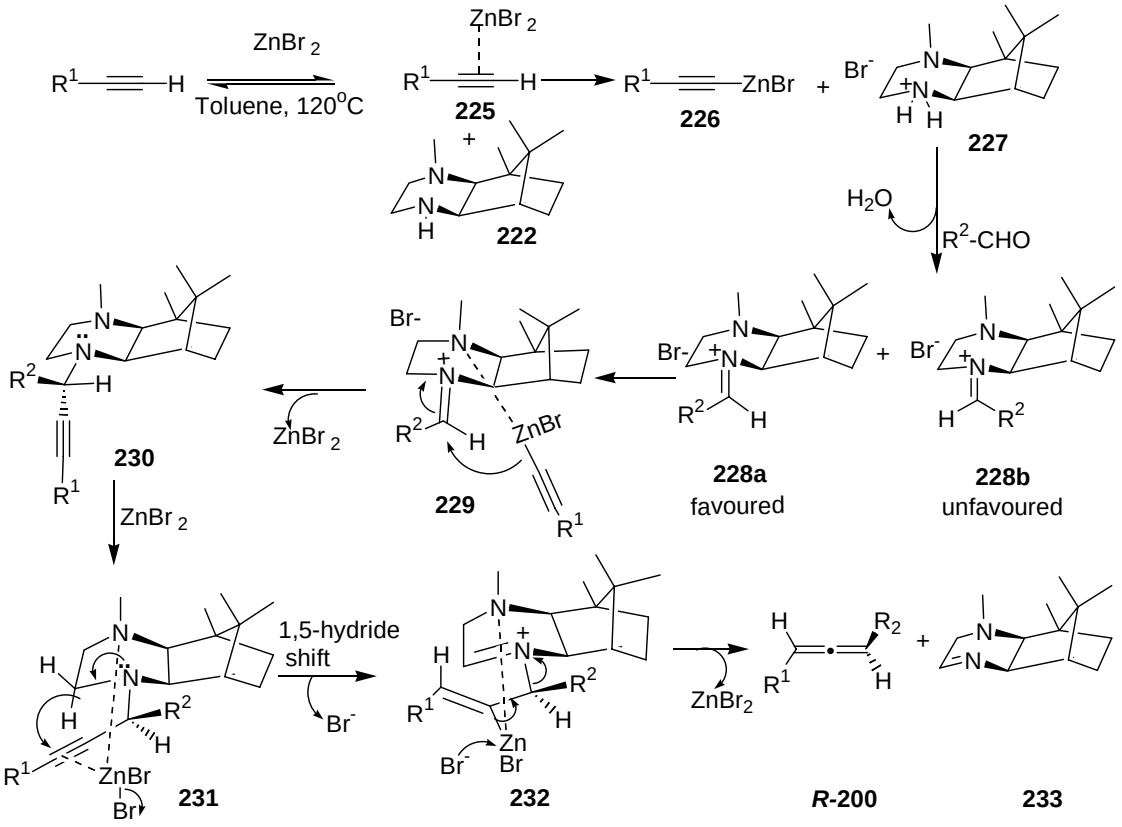
The reaction is also applicable to aliphatic alkynes as illustrated by reactions using the alkynes **198d, 198e** and **198f** react with the benzaldehyde **199a.** The corresponding chiral allenes **200da, 200ea** and **200fa** were obtained in 62-68%, yield and 79-99% ee (Table **3**). We have observed that the reaction of simple propargyl alcohol with benzaldehyde **199a** under these reaction conditions leads to only a complex mixture of products. Whereas, the protected propargyl alcohol like *p*-nitrobenzyl ether derivative **198g** reacts with aldehydes like **199a** and **199k** to give the corresponding chiral allenes **200ga** and **200gk** in 62-75% yield with up to 99% ee (Table **3**). Thiophene-2-aldehyde **199i** also reacts with 1-alkynes **198a** and **198d** to give the corresponding allenes (*R*)-**200ai** and (*R*)-**200di** in reasonable yields and selectivity (Table **3**).

All the optically active allenes obtained by using **222** are levorotatory, from which the absolute configurations of the major enantiomer of the allenes are assigned as *R* by the Lowe-Brewster rule and also by comparison with reported $[\alpha]_D^{25}$ values.[56] The formation of

chiral allenes in this transformation can be explained by considering the mechanism outlined in Scheme **26**.

2.2.9 Mechanism for the formation of (*R*)-allene using the piperazine 222.

Scheme 26

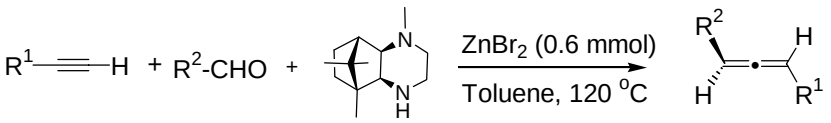


Previously, formation of alkynyl zinc intermediate was reported in the reaction of 1-alkyne, triethylamine and zinc triflate.[57] Also, alkynylzinc addition to iminium ion intermediates has been reported. Accordingly, the initially formed alkynyl zinc intermediate **226** would react with the favoured conformer **228a** of the iminium ion derived from various aldehydes **199** and the chiral piperazine **222** to give selectively the corresponding propargylamine **230 (**Scheme **26)**. Thus, the formation of the single isomer of the intermediate **230** is mainly due to the exclusive formation of the favoured conformer of the

iminium ion intermediate **228A** prior to the alkynlzinc reagent addition which is directed by coordination with the other nitrogen. The corresponding zinc bromide complex of propargylamine intermediate **231** would then undergo an intramolecular hydride shift to give the alkenyl zinc intermediate **232** which would then undergo elimination of zinc bromide and the imine via *anti*-periplanar cleavage of C-N bond in the intermediate **232** to give the chiral allenes **200** and the corresponding chiral camphanyl imine **233**. Such hydrogen shifts were previously considered in the gold, and silver catalysed conversion of propargylamine derivatives to chiral allenes.[59] We have found that the imine byproduct **233** could be easily converted to the starting chiral piperazine **222** by simple borohydride reduction without any change in enantiomeric purity.

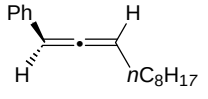
We have then examined the use of the isomeric N-methylcamphanyl piperazine **223** in this chiral allene synthesis. We have observed that the reaction of the 1-decyne **198a**, benzaldehyde **199a** and piperazine **223** using $ZnBr_2$ (0.6mmol) leads to *S*-allene in 53% yield with 95% ee with reverse selectivity as expected (Table **4**). This transformation is also generally applicable for different aldehydes and 1-alkynes. The corresponding chiral 1,3-disubstituted allenes were obtained in 38-71% yields with high enantioselectivities 79-99% (Table **4**).

Table 4. Reaction of 1-alkyne **198** and aldehyde **199** with chiral piperazine **223** promoted by zinc bromide[a,b,c,]

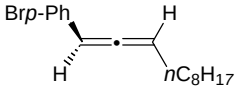


198 **199** **223** **(*S*)-200**

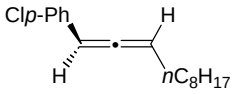
R_1	R_2	R_2
198a = nC_8H_{17},	**199a** = Ph,	**199h** = Ph-*p*CH_3,
198b = Ph,	**199b** = Ph-*p*Br,	**199i** = 2-thiophnyl,
198c = $PhCH_2CH_2$,	**199c** = Ph-*p*Cl,	**199j** = 2-Furanyl,
198d = $Cl(CH_2)_3$,	**199d** = Ph-*p*F,	**199k** = nC_4H_9,
198e = $NC(CH_2)_3$,	**199e** = Ph-*p*CF_3,	**199l** = Cyclohexyl,
198f = 1-cycloHexenyl,	**199f** = Ph-*m*OCH_3,	**199m** = iC_3H_7
198g = *p*-$NO_2PhCH_2OCH_2$,	**199g** = Ph *m*CH_3,	



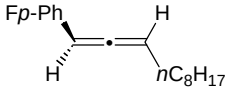
200aa, 5h,
53% y, 95% ee



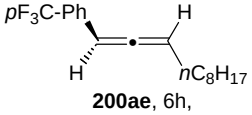
200ab, 4h,
64% y, 99% ee



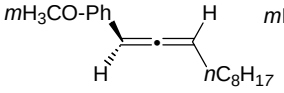
200ac, 5h,
60% y, 98% ee



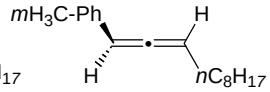
200ad, 4h,
65% y, 96% ee



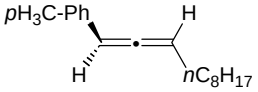
200ae, 6h,
67% y, 96% ee



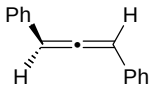
200af, 6h,
61% y, 97% ee



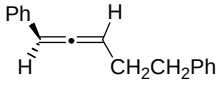
200ag, 10h,
58% y, 90% ee



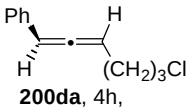
200ah, 9h,
62% y, 95% ee



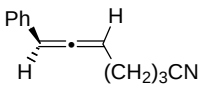
200ba, 4h,
38% y, 79% ee



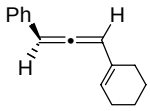
200ca, 4h,
64% y, 96% ee



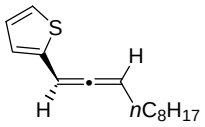
200da, 4h,
59% y, 98% ee



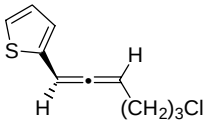
200ea, 4h,
58% y, 97% ee



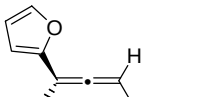
200fa, 4h,
58% y, 80% ee



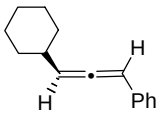
200ai, 4h,
71% y, 99% ee



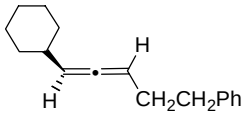
200di, 4h,
64y, 99% ee



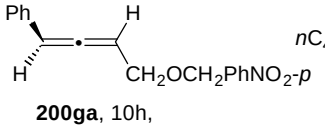
200aj, 2h,
38% y, 85% ee



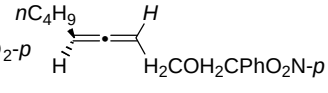
200bl, 4h,
62% y, 91% ee



200cl, 4h,
68% y, 97% ee



200ga, 10h,
58% y, 97% ee



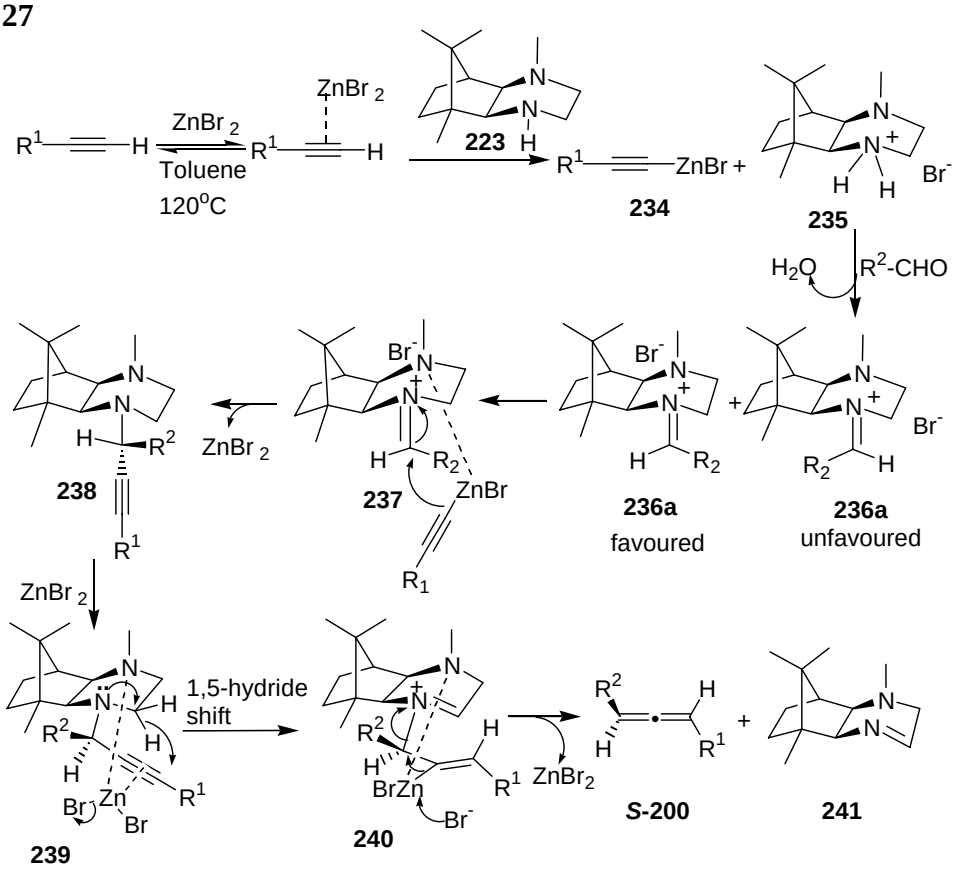
200gk, 10h,
68% y, 98% ee

[a]The reactions were carried out by using piperazine **223 (**1.0 mmol), $ZnBr_2$ **(**0.6 mmol) and 1-alkyne (1.1 mmol) in toluene (3 mL) at 25 °C.[b]Isolated yield.. [c]The % ee was determined by HPLC analysis

Again, all the optically active allenes obtained by using N-methylcamphanyl piperazine **223** are dextrorotatory from which the absolute configurations of the major enantiomer of the chiral allenes are assigned as *S* by the Lowe-Brewster rule and also by

comparison with reported $[\alpha]_D^{25}$ values. The formation of chiral *S* allenes using the N-methylcamphanyl piperazine **223** can be explained by considering a mechanism outlined in (Scheme **27).**

Scheme 27

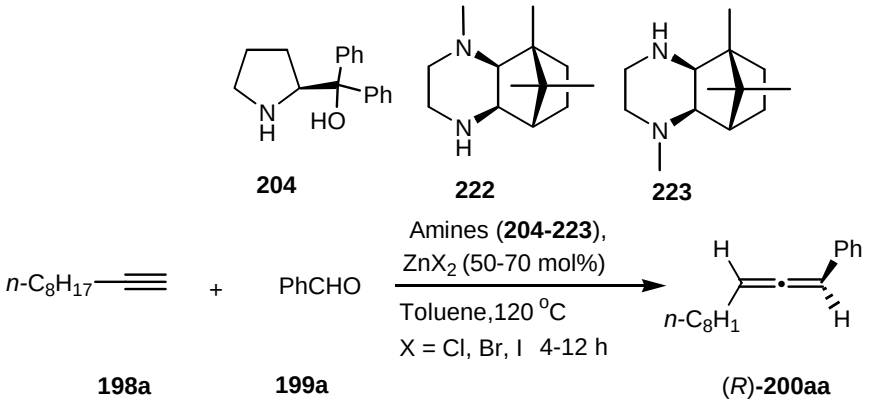


In this case, the favoured iminium ion intermediate **236a** would give the propargylamine intermediate **238** that has *R* configuration at the newly formed stereogenic centre in contrast to the *S* propargylamine intermediate **238** formed using the regioisomeric chiral piperazine **223**. Thus, the corresponding zinc bromide complex of **239** is expected to undergo an intramolecular hydride shift from the camphanyl skeleton to the acetylinic moiety leading to the alkenyl zinc intermediate **240** which after cleavage of the C-N bond via an anti-periplanar transition state would result in the formation of *S* allene besides zinc bromide and the chiral camphanyl imine **241** byproduct.

2.2.10 Effort towards the recovery of chiral amines

We developed "chiral amine approach" for highly enantioselective synthesis of chiral allenes using terminal alkynes, aldehydes and chiral amines promoted by zinc halides in a single pot operation.[60] Thus, the zinc halide promoted reaction of chiral secondary amines (**204-223**), 1-decyne **198a** and benzaldehyde **199a** at 120 °C (Scheme **28**) has been developed to access the chiral allenes **200aa** in very high enantioselectivity up to 99% ee.

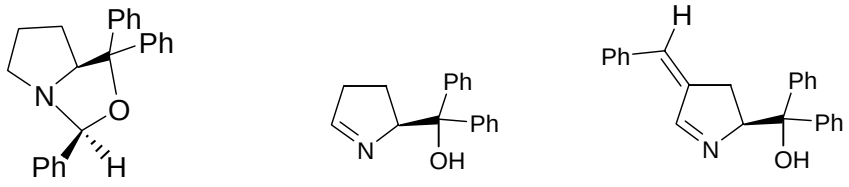
Scheme 28



This reaction has a few limitations. The easily accessible and commercially available chiral amino alcohol **204** yielded the chiral allene **200aa** in 98% ee and the reaction has been generalized for a variety of aldehydes and alkynes. However, as discussed previously, the results are highly dependent on the sequential addition of the reactants and inadvertent formation of the oxazolidine intermediate **206** could lower the enantioselctivity of the allene to 86% ee.

The imine byproduct **205** could be isolated and recycled back to the chiral diphenylprolinol **204** in 85% yield by $NaBH_4/CH_3OH$ reduction.[60a] However, careful analysis of the imine **205** product mixture indicated the formation of the product **242** (5-10%

yield) formed by condensation of the imine byproduct **205** with the benzaldehyde present in the medium (Figure **7**).

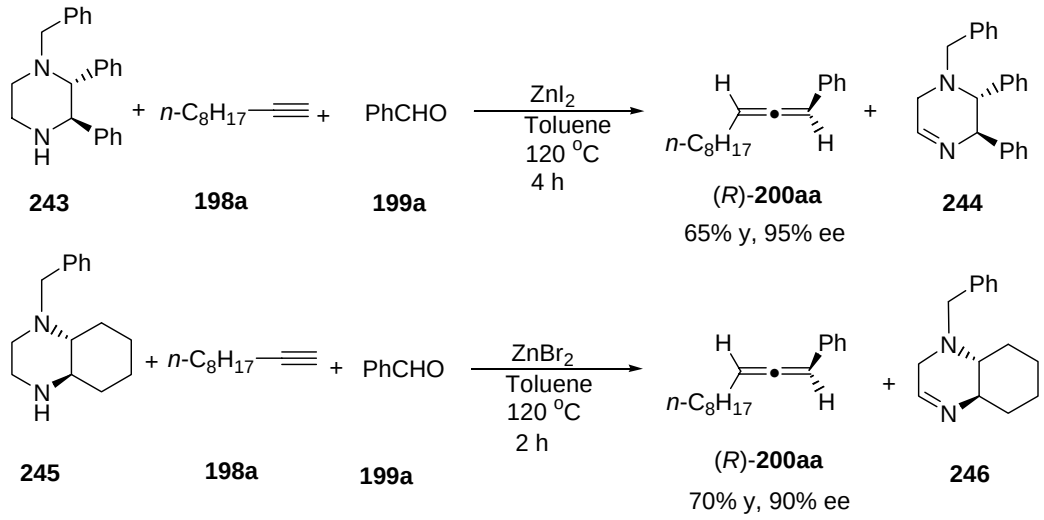


206 **205** **242**

Figure 7

Also, methods were reported from this laboratory for the enantioselective synthesis of chiral allenes via ZnX_2 promoted reaction of 1-alkyne and arylaldehyde using chiral N-benzyl piperazines systems (Scheme **29**).

Scheme 29

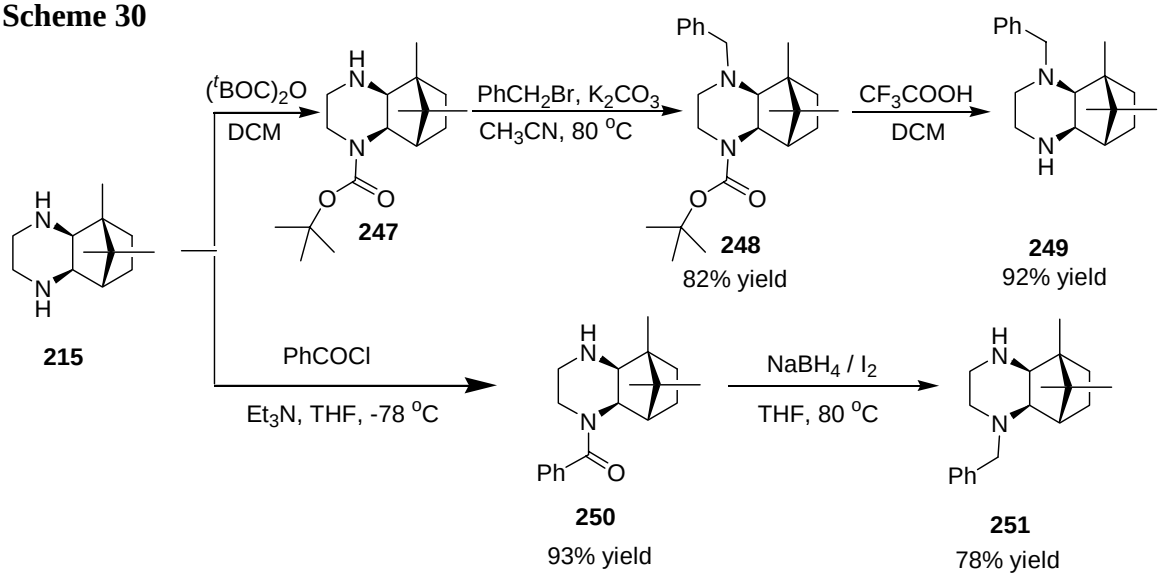


The N-benzylpiperazine derivative **243, 245** gave the chiral allene **200aa** in 90-95% ee without formation of such unwanted side products. Whereas in case of chiral N-methylcamphanyl piperazines (**222, 223)**, it is somewhat difficult to recover chiral piperazine from imine products. Therefore, we have decided to prepare different chiral N-benzylpiperazine derivatives (Scheme **30)** for application in this transformation, especially

for the two step conversion *via* the corresponding propargylamine as this would avoid the presence of the aldehyde substrate that could react with the corresponding cyclic imine byproduct.

2.2.11 Synthesis of N-benzylcamphanyl piperazine derivatives

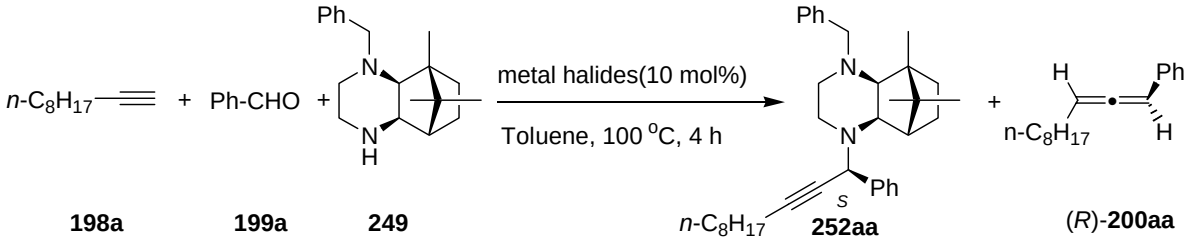
Scheme 30



Initially, ^{t}BOC protection followed by benzylation and ^{t}BOC deprotection of the parent camphanyl piperazine **215** gives the N-benzylcamphanyl piperzine **249** in 92% yield. Whereas, direct benzoylation of the camphanyl piperazine **215** at -78 °C followed by reduction with H_3B:THF prepared *in situ* using $NaBH_4/I_2$ at 80 °C gave the N-benzylcamphanyl piperazine **251** in 78% yield.

We have then carried out detailed studies on the synthesis of chiral piperazines and their conversion to chiral allenes. We have eventually found that the chiral propargylamine **252aa** is obtained in 98% yield with 99:1 dr in the zinc chloride catalyzed reaction of 1-decyne **198a**, aldehyde **199a** and the chiral piperazine derivative **249** at 100 °C (Table **5**). The chiral propargylamine **252aa** was obtained in slightly lower yield using other metal halides like $ZnBr_2$, CuBr and CuI under this reaction conditions (Table **5**).[61]

Table 5. Synthesis of chiral propargylamine **252aa** using 1-decyne **198a**, benzaldehyde **199a** and the chiral piperazine **249** using metal salts.[a, b, c]



198a **199a** **249** **252aa** (*R*)-**200aa**

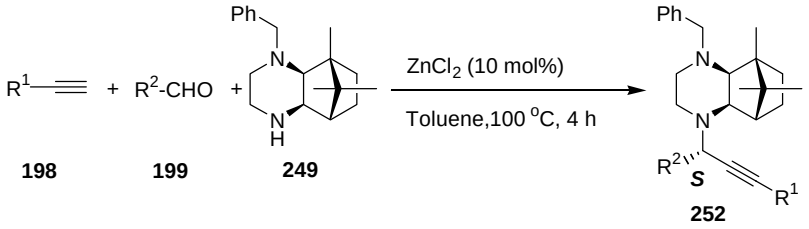
S.No.	Metal halides	Mol%	Time (h)	252aa, yield (%)[b]	dr	200aa	ee(%)[d]
1	$ZnCl_2$	10%	4h	98	99:1	-	-
2	$ZnBr_2$	10%	4h	85	99:1	10	**99**
3	CuBr	10%	4h	90	98:2	8	**99**
4[e]	CuBr	10%	24h	95	99:1	-	-
5	CuI	10%	4h	87	97:3	15	**99**

[a]The reactions were carried out by using piperazine **249 (**1.0 mmol), 1-alkyne (1.1 mmol) and aldehyde (1.0 mmol) in toluene (3 mL) at 100 °C for 4 h. [b]dr ratio based on crude ^{1}H NMR. [c]Isolated yield. [d] ee of allene **200aa** was determined by chiral HPLC analysis. [e] The reactions were carried out by using chiral piperazine **249 (**1.0 mmol), 1-alkyne (1.1 mmol) and aldehyde (1.0 mmol) in toluene (3 mL) at 25 °C for 24 h.

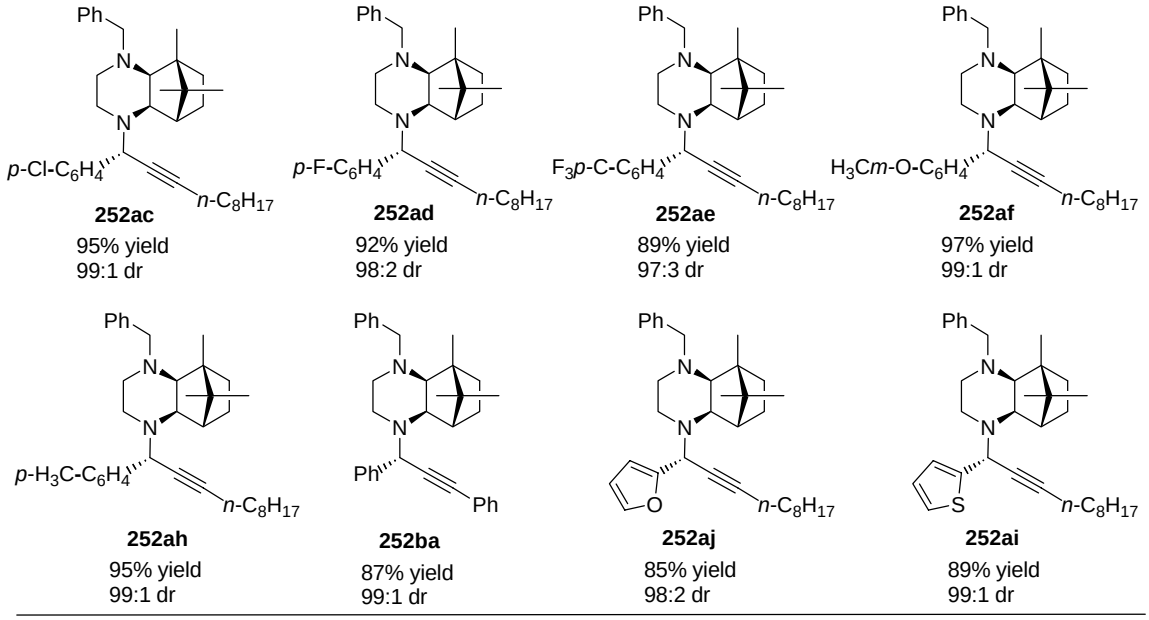
2.2.12 Synthesis of chiral allenes using chiral diamine containing camphanyl moiety

We next investigated the synthesis of various chiral propargylamine derivatives **252** from the corresponding chiral piperazine **249**. The results are summarized in Table **6**. The arylaldehydes, which have an electron-donating group such as methoxy **199f** and methyl **199g**, underwent this reaction to give the corresponding propargylamines **252af** and **252ah** in 95-97% yields with 99:1 dr. Not only the electron-rich aryl aldehydes but also the electron-deficient aryl aldehydes **199b-199e** are smoothly transformed into the desired propargylamine products.

Table 6. $ZnCl_2$ promoted Synthesis of chiral propargylamine **252** using aldehydes, **199a** 1-alkynes **198a** and the chiral piperazine **249.**



R_1	R_2	R_2
198a = nC_8H_{17},	**199a** = Ph,	**199h** = Ph-pCH$_3$,
198b = Ph,	**199b** = Ph-pBr,	**199i** = 2-thiophnyl,
198c = $PhCH_2CH_2$,	**199c** = Ph-pCl,	**199j** = 2-Furanyl,
198d = $Cl(CH_2)_3$,	**199d** = Ph-pF,	**199k** = nC_4H_9,
198e = $NC(CH_2)_3$,	**199e** = Ph-pCF$_3$,	**199l** = Cyclohexyl,
198f = 1-cycloHexenyl,	**199f** = Ph-mOCH$_3$,	**199m** = iC_3H_7
198g = p-$NO_2PhCH_2OCH_2$,	**199g** = Ph mCH$_3$	

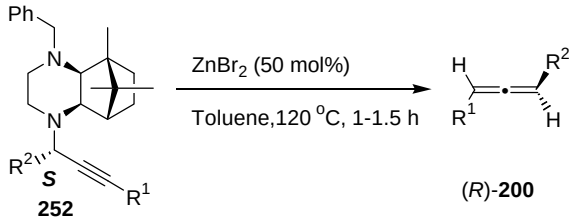


[a]The reactions were carried out by using chiral piperazines (1.0 mmol), 1-alkyne (1.1 mmol) and aldehyde (1.0 mmol) in toluene (3 mL) at 100 °C for 4h. [b]dr ratio based on crude ^{1}H NMR. [c]Isolated yield.

Thiophene-2-aldehyde **199i** reacts with alkyne **198a**, to give the corresponding propargylamines **252ai** in reasonable yields and good selectivity. The propargylamine **252aj** was obtained in 85% yield with 98:2 dr within 3h in the reaction of furfural **199j** and 1-decyne **198a** with $ZnCl_2$ at 100 °C (Table **6**).

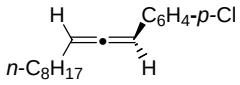
Next, we have turned our attention toward the conversion of the chiral propargylamines to the corresponding chiral allenes. We have observed that the reaction of chiral propargylamine **252aa**, with $ZnBr_2$ (0.5 mmol) at 120 °C gave the chiral allene **200aa** in upto 89% yield with 99% ee. The same procedure was followed for the conversion of other diastereomerically pure propargylamines to the corresponding chiral allenes (Table **7)**.

Table 7. $ZnBr_2$ promoted Synthesis of chiral allenes from chiral propargylamines. [a, b, c]

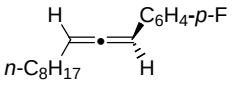


252 (*R*)-**200**

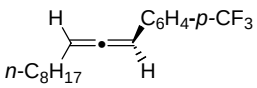
252ac = (R^1 = nC_8H_{17}, R^2 = Ph), **252ah**= (R^1= nC_8H_{17}, R^2 = C_6H_4- pCH_3),
252ad = (R^1 = nC_8H_{17}, R^2 = C_6H_4-*p*F), **252ba** = (R^1 = Ph, R^2 = Ph),
252ae = (R^1 = nC_8H_{17}, R^2 = C_6H_4-*P*CF_3), **252aj** = (R^1 = nC_8H_{17}, R^2 = C_4H_3O),
252af = (R^1 = nC_8H_{17}, R^2 = C_6H_4-*m*OCH_3), **252ai** = (R^1 = nC_8H_{17}, R^2 = C_4H_3S),



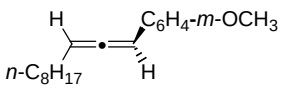
200ac
1h, 76% y, 99% ee



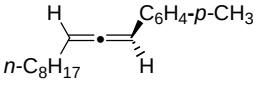
200ad
1h, 69% y, 98% ee



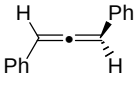
200ae
1h, 71% y, 99% ee



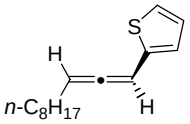
200af
1.5h, 82% y, 97% ee



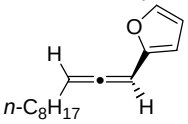
200ah
1.5h, 75% y, 99% ee



200ba
1h, 71% y, 93% ee



200ai
1h, 73% y, 99% ee



200aj
1h, 69% y, 99% ee

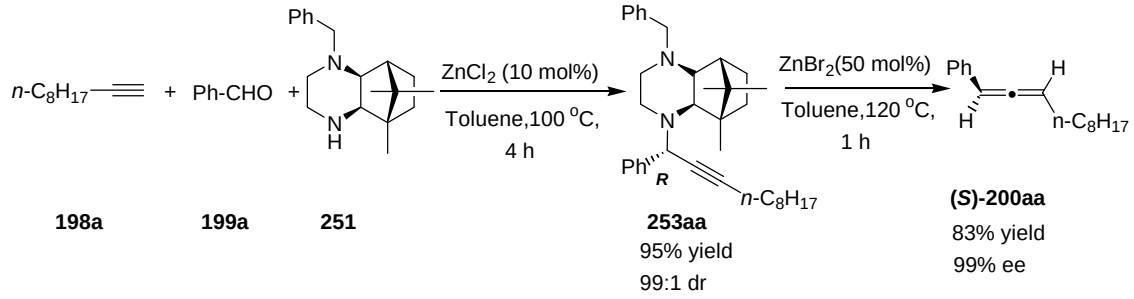
[a]The reactions were carried out by using propargylamine **252** (1 mmol) in toluene (3 mL) with $ZnBr_2$ (0.5 mmol).. [b]Isolated yield. [c] ee determine by using chiral HPLC

The results are summarized in Table **7**. The chiral propargylamines **252af-252ah** substituted with methoxy, methyl groups afforded the corresponding chiral allenes **200af, 200ah** in 75–82% yields with up to 99% ee. Propargylamines having chloro, flouro, triflouro substituents were also compatible with the reaction condition affording the corresponding axially chiral aryl substituted allenes **200ac-200ae** in 69-76% with up to

99% ee. The propargylamines containing heteroaromatic groups **252ai, 252aj** with $ZnBr_2$ (0.5 mmol) at 120 °C gave the chiral allenes **200ai** and **200aj** in 69-73% yields with up to 99% ee.

It should be noted that all the present experiments require shorter reaction times for the formation of chiral allenes compared to other procedures (see Scheme **28**). We have also carried out the allene synthesis by using the chiral propargylamine **253aa** with *R* configuration at the propargylic stereogenic centre. As expected, the *S* chiral allene **200aa** is obtained in 83% yield and 99% ee in this reaction (Scheme **31**).[24]

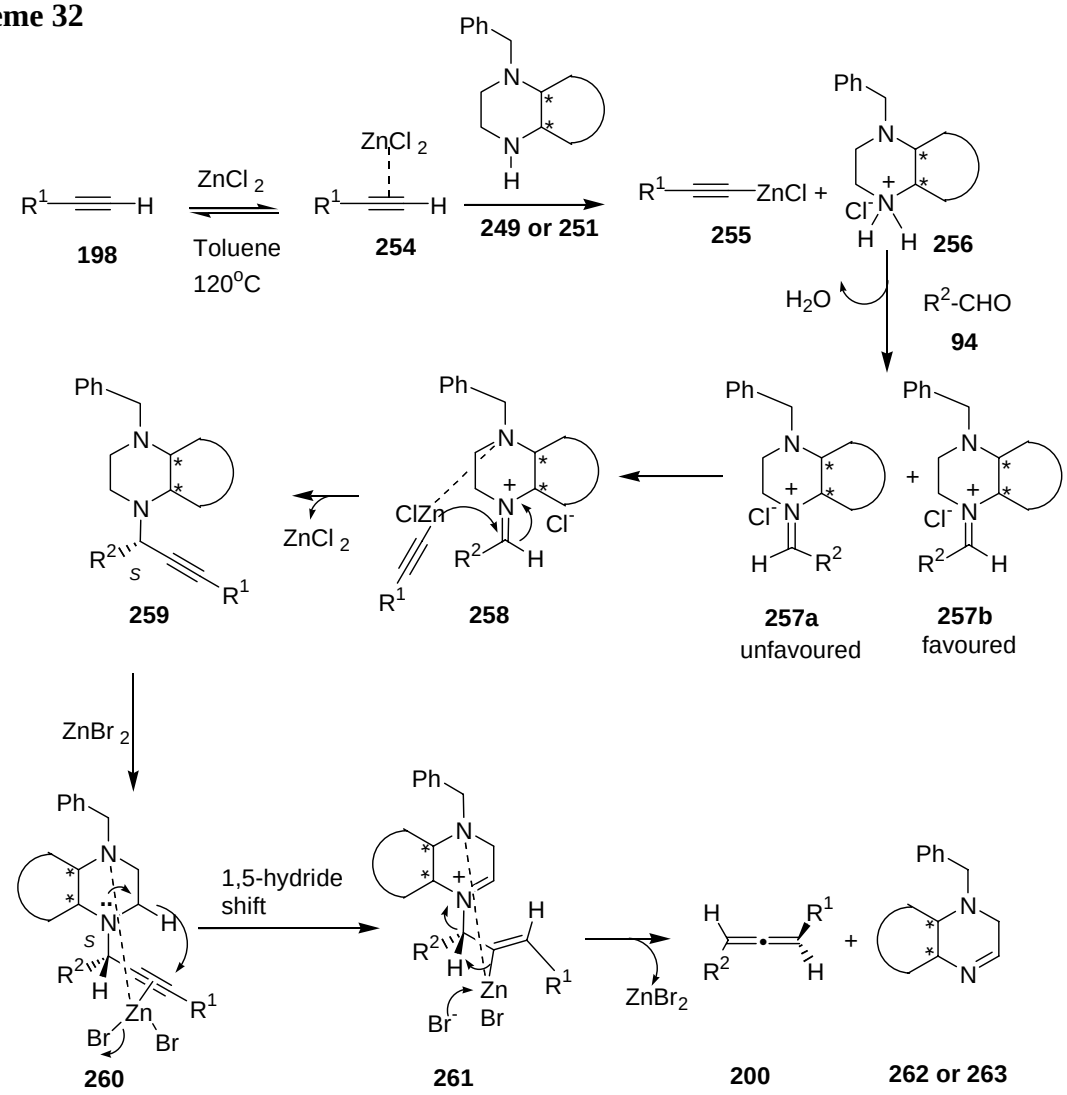
Scheme 31



2.2.13 Plausible mechanistic pathway for the allene formation

The formation of chiral propargylamines and their conversion to chiral allenes can be rationalized by the mechanism outlined in Scheme **32**. The initially formed alkynyl zinc intermediate[14] **255** would react with the favoured conformer **257b** of the iminium ion derived from aldehyde **199** and chiral piperazine (**249** or **251)** to give selectively the corresponding propargylamine **259**. The corresponding zinc bromide complex of **260** would then undergo intramolecular hydride shift from the piperazine skeleton to the acetylinic moiety leading to the formation of alkenyl zinc intermediate **261**. Subsequently, cleavage of C-N bond in the intermediate **261** releases the chiral allenes **200** and the imine (**262 or 263)** byproduct.

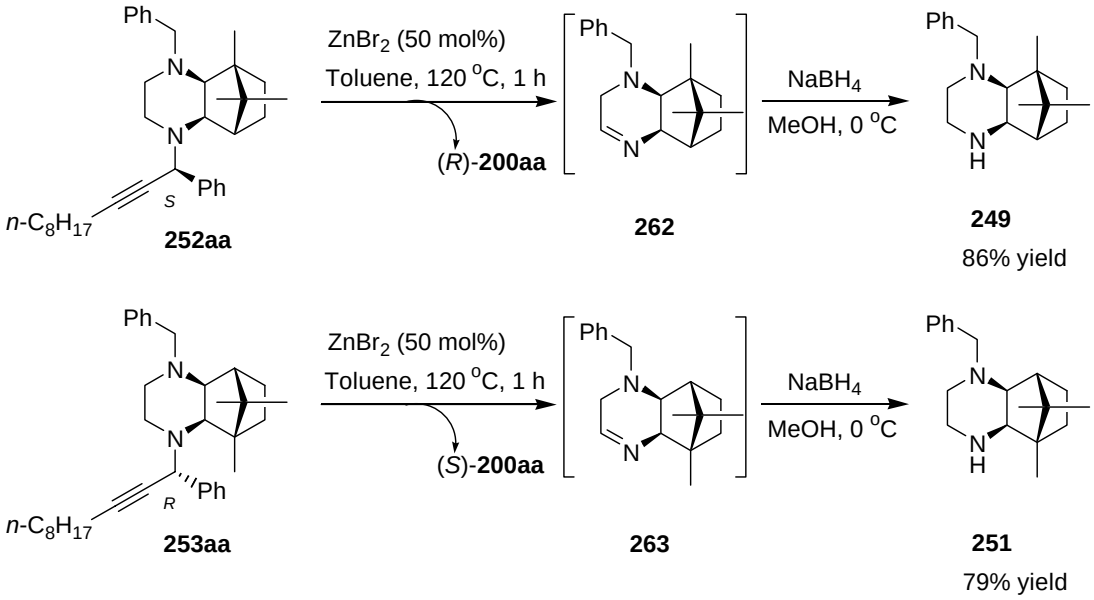
Scheme 32



All the optically active allenes obtained by using chiral piperazine derivatives **249** are levorotatory from which the absolute configurations of the major enantiomer assigned as *R* (Table **7**), whereas the optically active allene (*S*)**-200aa** obtained using the chiral N-benzylcamphanyl piperazine **251** is dextrorotatory from which the absolute configuration of the major enantiomer assigned as *S* by the Lowe-Brewster rule and also by comparison with reported $[\alpha]_D^{25}$ values.[24] We have also found that the imine byproducts **262** and **263** could be easily converted *in situ* to the corresponding chiral piperazines **249** and **251** in 79-86% yield by simple sodium borohydride reduction (Scheme **33**).

2.2.14 Isolation of chiral piperazines from propargylamines using reduction with $NaBH_4$

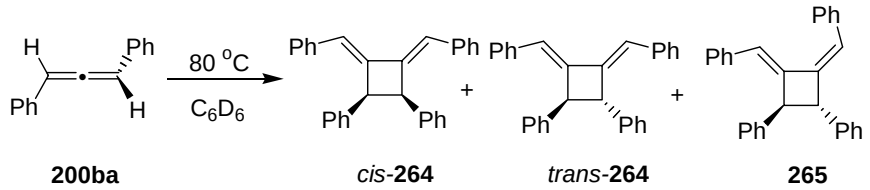
Scheme 33



2.2.15 Cyclodimerization of chiral allenes

We have observed that the chiral allenes containing aryl substituents are not stable and readily undergo cyclodimerization under neat ambient conditions. Previously, it was reported that the 1,3-diphenyl allene **200ba** undergoes dimerization at 80 °C in benzene-d^6 (Scheme **34**).[62]

Scheme 34



Surprisingly, we have observed that even at 25 °C under neat condition the 1,3-diphenyl allene **200ba** undergoes cyclodimerization in 24h. Whereas, the freshly prepared pure chiral allene **200ba** sample exhibits an $[\alpha]_D^{25}$ -830 (c 0.53, $CHCl_3$), the value becomes

zero when the product was kept 25 °C for 72h. The ^{13}C NMR spectrum of the product mixture indicates the presence of the cyclodimerized products.[22e] We have also found that when the freshly prepared pure chiral 1,3-diphenylallene **200ba** was stored in $CDCl_3$ solution, new signals corresponding to the cyclodimerized products started appearing in the ^{13}C NMR spectrum in 24h at 25 °C.

We have also observed that the aryl, alkyl substituted allenes also undergo slow cyclodimerisation to give a complex mixture of products under neat conditions at 25 °C within a week as indicated by ^{13}C NMR spectral analysis. Periodic analysis of optical rotations of chiral aryl substituted allenes indicated that in 14 days the optical rotation values of the samples become zero. However, when the aryl substituted allenes **200ac** or **200af** were stored in hexane or $CDCl_3$ solutions, there was no change in optical rotation and ^{13}C NMR spectral signal values even after 14 days. The facile cyclodimerization of aryl substituted allenes under neat ambient conditions is not clearly understood at this stage. Previouly, cyclodimerizations were reported with some loss in optical activity were reported for chiral allenes at >100 °C and the reaction has been reported to go through a stepwise mechanism.[63] The finding that cyclodimerization takes place even at 25 °C in the case of aryl substituted allenes illustrates the hidden difficulties involved in storing and handling of chiral allenes.

The 1,3-disubstituted chiral allenes have been widely used in recent years in asymmetric transformations,[64] synthesis of allenic macrocycles,[65] redox switchable[66] and donor acceptor molecules[67] (Chart **11** and Chart **12).**

Chart 11

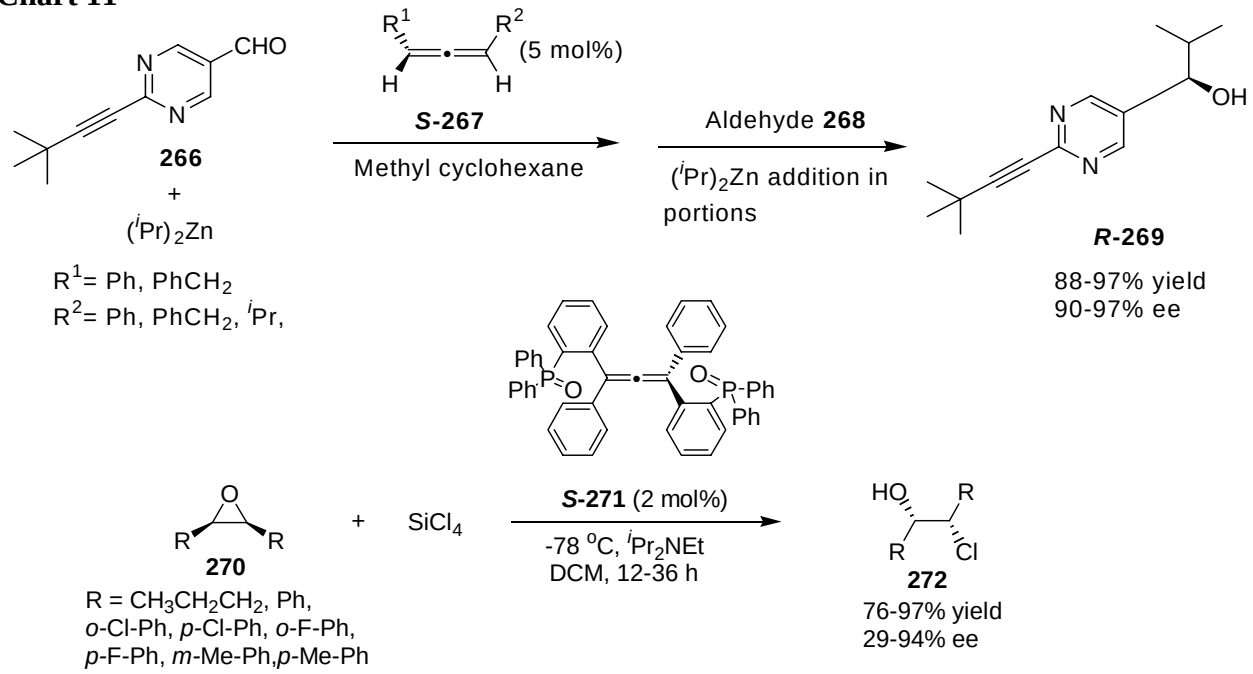


Chart 12

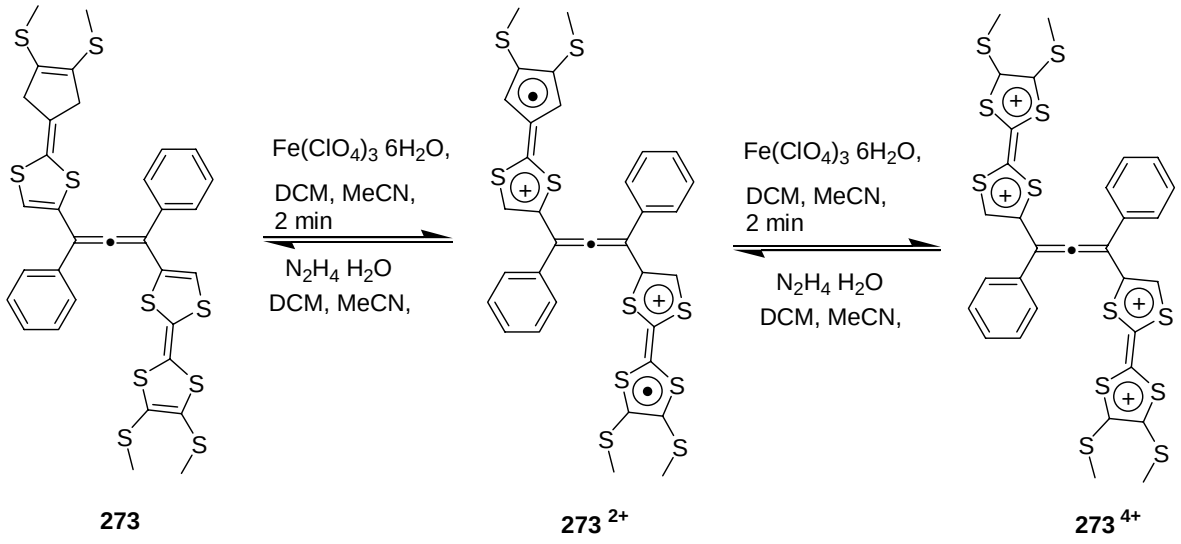
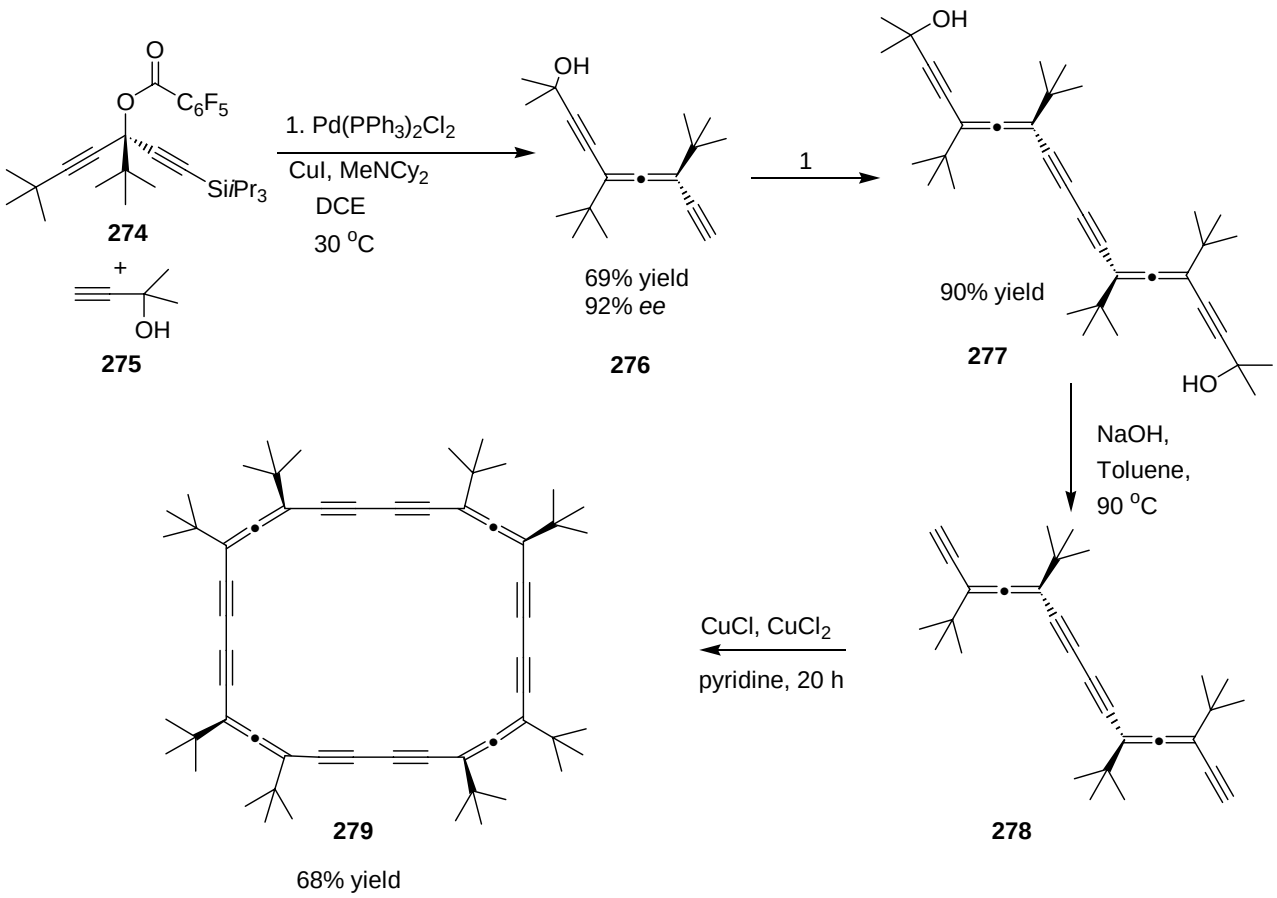


Chart 12 continued



Therefore, easy access to chiral allenes via the methods described here would stimulate further research efforts in the development of functional materials containing chiral allenyl moiety.

2.4 Conclusions

A convenient method for the synthesis of chiral allenes **200** in 50-70% yield and 82-98% ee using *S*-DPP **204**, 1-alkyne **198** and aldehydes **199** using $ZnBr_2$ in toluene at 120 °C has been developed. The enantioselectivity is affected by the sequential of addition of reagents. Heating the *S*-DPP **204,** $ZnBr_2$ and 1-alkyne **198** in toluene for 10 min at 120 °C followed by addition of the aldehyde **199** at 25 °C and further stirring at 120 °C for 10h, gave optimum results.

We have also developed a versatile and efficient stereoselective synthesis of both enantiomers of several chiral 1,3-disubstituted allenes in high enantiomeric purities exploiting the chiral discrimination abilities of the regioisomers of chiral N-methylcamphanyl piperazine derivatives **222** and **223** in a $ZnBr_2$ promoted transformation. The chiral N-methylcamphanyl piperazine derivatives **222** and **223** synthesized by simple methylation of one or the other NH moieties present in the piperazine **215**. Since the chiral piperazine derivatives **222** and **223** are easily recoverable for reuse without loss in optical purity, the method described here has considerable potential for further synthetic exploitation.

We have developed a simple, practical and inexpensive method for the diastereoselective synthesis of chiral propargylamines using chiral piperazines (**249, 251)** and their enantioselective conversion to chiral allenes upon reaction with $ZnBr_2$. The surprisingly facile cyclodimerization reactions observed with some aryl substituted allenes illustrates the hidden difficulties in handling and storing of chiral allenes.

2.4 Experimental Section

2.4.1 General information

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

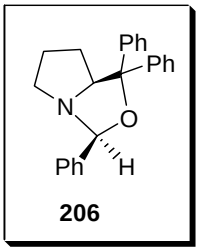
Analytical grade of CuBr, $Cu(OTf)_2$, $AgNO_3$ and ZnI_2 were purchased from Sigma-Aldrich. $ZnBr_2$ was purchased from E-Merck. Toluene supplied by E-Merck, India was freshly distilled over sodium-benzophenone ketyl before use. Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250mμ E-Merck and 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 E-Merck and acme's silica gel (100-200 or 230-400 mesh) and neutral alumina.

Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability ±0.01^{o}) and AUTOPOL-IV (readability ±0.001^{o}) automatic polarimeters. HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. The ee values were determined using various chiral columns e.g., CHIRALCEL OD-H column (4.6 x 250 mm) with eluents: hexane, 2-propanol, ethanol and heptane at a rate 0.5-1 mL/min, with the monitoring wave length 254 nm.

2.4.2. Isolation of oxazolidine intermediate 206 and its reaction with 1-decyne and $ZnBr_2$

2.4.3 Reaction of 1-decyne 198a, benzaldehyde 199a and amine 204 with $ZnBr_2$: Isolation of oxazolidine (206)



206

A flame–dried 25 ml reaction flask was charged with (*S*)-DPP **204** (0.258 g, 1 mmol) in toluene (3 mL) and $ZnBr_2$ (0.16 g, 0.7 mmol), 1-decyne **198a** (0.138g, 1.1 mmol) and freshly distilled aldehyde **199a** (0.110 g, 1 mmol) were added at 25 °C. The contents were heated at 120 °C for 15 min. The mixture was brought to 25 °C, toluene was evaporated under reduced pressure and the residue was chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (90:10) as eluent to isolate oxazolidine **206**.

Yield **:** 0.110 g, 30%, colorless liquid.

$[\alpha]_D^{25}$ **:** -84.1 (*c* 0.50, acetone).

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.61-7.17 (m, 15H), 5.55 (s, 1H), 4,53-4.49 (t, 1H), 3.13-2.86 (m, 2H), 1.86-1.68 (m, 4H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 146.9, 144.3, 141.2, 128.3, 128.2, 128.0, 127.9, 127.3, 126.9, 126.7, 126.5, 126.3, 98.2, 89.1, 51.0, 28.2, 24.5.

2.4.4. Reaction of benzaldehyde 199a and amine 204 at 120 °C: Formation of Oxazolidine (206).

A flame–dried 25 ml reaction flask was charged with (*S*)-DPP **204** (0.258 g, 1 mmol) in toluene (3 mL) and freshly distilled aldehyde **199a** (0.110 g, 1 mmol) was added at 25 °C. The contents were heated at 120 °C for 1h. The mixture was brought to 25 °C, toluene was

evaporated under reduced pressure and the residue was chromatographed on silica gel (100-200 mesh) using hexane/ethyl acetate (90:10) as eluent to isolate oxazolidine **206**.

Yield : 0.220g, 62%

$[\alpha]_D^{25}$: -84.1 (*c* 0.050, acetone).

The spectral data showed 1:1 correspondence with the sample obtained in the previous experiment.

2.4.5 Reaction of oxazolidine 206 with 1-decyne 198a and $ZnBr_2$: Synthesis of Chiral Allenes (200aa).

The oxazolidine **206** (0.361g, 1 mmol) in toluene (3 mL) was taken in a flame–dried 25 ml reaction flask. $ZnBr_2$ (0.160 g, 0.7 mmol), alkyne **198** (0.138g, 1.1 mmol) were added 25 °C. The contents were gradually heated to 120 °C in 45 min and stirred at 120 °C for 10h. The mixture was brought to 25 °C. After evaporation of toluene under reduced pressure, column chromatography of the residue on silica gel (100-200 mesh) using hexane as eluent afforded the chiral allene **200aa** as colorless oil.

Yield **:** 0.118g, 52%.

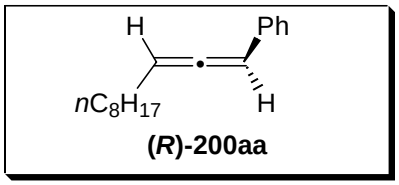
$[\alpha]_D^{25}$ **:** -193.1 (*c* 0.47, $CHCl_3$, 85% ee).

Enantiomeric purity: 85% ee, HPLC analysis was carried out using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min., 254nm, retention times:4.7 min. (*R*) and 5.2 min (*S*) . The spectral data showed 1:1 correspondence with data obtained in previous experiments.

2.4.6 Reaction of 1-alkyne, aldehyde and the amine 204 with $ZnBr_2$: Synthesis of chiral Allenes (200)

To a stirred suspension of (*S*)-DPP **204** (0.25 g, 1 mmol) in toluene (3 mL) and $ZnBr_2$ (0.16 g, 0.7 mmol), alkyne **198** (1.1 mmol) was added and heated at 120 °C for 10 min. Freshly distilled aldehyde **199** (1 mmol) was added at 25 °C and the contents were heated at 120 °C under nitrogen atmosphere. The mixture was brought to 25 °C after the required time (Table 1). After evaporation of toluene, column chromatography on silica gel (100-200 mesh) using hexane as eluent afforded the chiral allene **200**.

(*R*)-1-(phenyl)-1,2-undecadiene (200aa):



(*R*)-200aa

Yield : 0.148 g, 65%, colorless liquid.

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

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

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

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 14.1, 22.6, 28.7, 29.1, 29.3, 29.4, 31.8, 94.5, 95.5, 126.5, 128.5, 135.1, 205.1.

LCMS : m/z 229 (M+1).

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

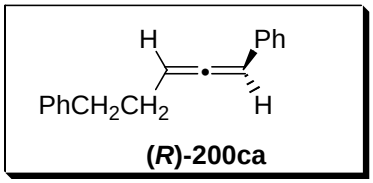
calcd: C, 89.41%; H, 10.59%.

found: C, 89.32%; H, 10.51%.

Enantiomeric purity: 98% ee, determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.5 mL/min, 254 nm, retention times: 3.5 min. (*S*) and 4.6 min. (*R*).

The above procedure was followed for the preparation of other allenes

(*R*)- 1,5-Diphenyl-penta-1,2-diene (200ca):



(*R*)-200ca

Yield : 0.134 g, 61%, colorless liquid.

$[\alpha]_D^{25}$: -195.1 (*c* 0.50, $CHCl_3$, 93% ee).

IR (neat) : 2928, 2856, 1945, 1698, 1325, 844 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.31-7.28 (m, 4H), 7.25-7.16 (m,6H), 6.14-6.11 (d, J=8Hz, 1H), 5.62-5.57 (m, 1H), 2.84-2.79 (m, 2H), 2.51-2.43 (m, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 205.3, 141.5, 134.8, 128.6, 128.5, 128.4, 126.7, 126.6, 125.9, 95.0, 94.3, 35.4, 30.6.

LCMS : m/z 221 (M+1).

Analysis : for $C_{17}H_{16}$

calcd: C, 92.68%; H, 7.32%

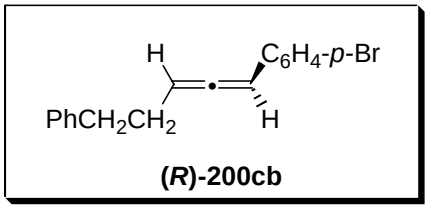
found: C, 92.48%; H, 7.38%

Enantiomeric purity: 93% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:9.6 min. (*R*) and 11.1 min. (*S*).

(*R*)-1-(4-bromophenyl),5-pheny Penta-1,2-diene (200cb):

Yield : 0.163 g, 55%, colorless liquid.

$[\alpha]_D^{25}$ **:** -165.1 (*c* 0.50, $CHCl_3$, 88% ee).



(*R*)-200cb

IR (neat) **:** 2928, 2856, 1951, 1616, 1325, 844 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.38-7.36 (m, 2H), 7.32-7.27(m, 2H), 7.25-7.21(m, 3H), 6.99-6.05(m, 2H), 6.07-6.05 (m, 1H), 5.61-5.56 (m, 1H), 2.86-2.75 (m, 2H), 2.54-2.42 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.4, 141.3, 133.8, 131.5, 128.6, 128.4, 128.1, 126.0, 120.2, 94.7, 94.1, 35.2, 30.4.

LCMS **:** m/z 300 (M+2).

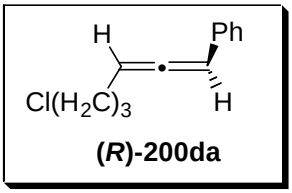
Analysis **:** for $C_{12}H_{13}Cl$

calcd: C, 74.80%; H, 6.80,

found: C, 74.95 % H, 6.71

Enantiomeric purity: 88% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:11.1 min. (*S*) and 13.7 min. (*R*).

(*R*)-1-(Phenyl)-6-chloro-hexa-1,2–diene (200da):



(*R*)-200da

Yield **:** 0.130 g, 62%, colorless liquid.

$[\alpha]_D^{25}$ **:** -262.1 (*c* 0.50, $CHCl_3$, 93% ee).

IR (neat) **:** 3063, 3030, 2957, 1950, 1599, 1494, 1275, 1078, 877 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.34-7.32 (m, 1H), 7.23-7.20 (m, 2H),6.21-6.19 (d, *J* = 8.0 Hz, 1H), 5.62- 5.57 (d, *J* = 8.0 Hz, 1H), 3.64-3.61 (t, *J* = 12Hz, 2H), 2.34-2.30 (m, 2H), 2.0-1.96 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.2, 134.6, 128.6, 126.9, 126.6, 95.4, 93.6, 44.4, 30.2, 25.8.

LCMS **:** m/z 211 (M+1).

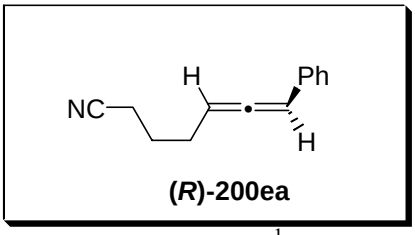
Analysis **:** for $C_{12}H_{13}Cl$

calcd: C, 74.80%; H, 6.80,

found: C, 74.95 % H, 6.71

Enantiomeric purity: 93% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1 mL/min.,254 nm, retention times: 9.78 min. (*S*) and 11.5 min (*R*).

(*R*)-7-Phenyl-1-cyano-hepta-5,6-diene (200ea):



(*R*)-200ea

Yield **:** 0.126 g, 69%, colorless liquid.

$[\alpha]_D^{25}$ **:** -198.1 (*c* 0.50, $CHCl_3$, 98% ee).

IR (neat) **:** 3296, 2941, 2247, 1950, 1597, 1494, 1263, 1074, 881 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.34-7.32 (m, 1H), 7.23-7.20 (m, 2H),6.23-6.20 (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, $CDCl_3$, δppm) 205.3, 134.3, 128.7, 127.1, 126.5, 95.8, 93.0, 27.3, 24.5, 17.5.

LCMS **:** m/z 184 (M+1).

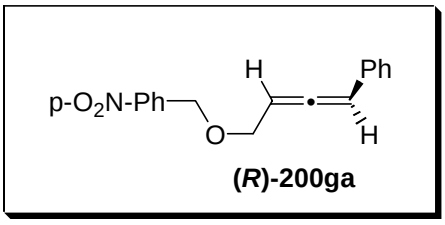
Analysis **:** for $C_{13}H_{13}N$

calcd: C, 84.17%; H, 7.65%, N, 8.18%

found: C, 85.36%; H, 7.21% N,7.54%

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1 mL/min., 254 nm, retention times: 19.6 min. (*S*) and 22.1 min (*R*).

(*R*)-1-(4-Nitrobenzyloxy)-4-phenylbuta-2,3-diene (200ga):



(*R*)-200ga

Yield : 0.180 g, 64%, yellow liquid.

$[\alpha]_D^{25}$: -196.7 (*c* 0.33, $CHCl_3$, 99% ee).

IR (neat) : 2922, 2858, 2362, 1952, 1605, 1520, 1087, 775 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 8.20-8.18 (d, *J* = 8.0 Hz, 2H), 7.51-7.49 (d, *J* = 8.0 Hz, 2H), 7.35-7.22 (m, 4H), 6.31-6.29 (m, 1H), 5.75- 5.70 (m, 1H), 4.66 (s, 2H), 4.22-4.12 (m, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 206.2, 145.8, 133.6, 128.7, 127.8, 126.9, 123.6, 95.9, 92.1, 70.6, 68.5.

LCMS : m/z 282 (M+1)

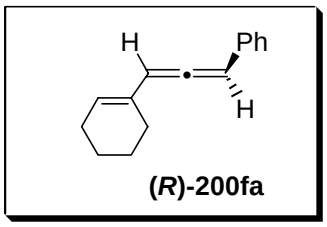
Analysis : for $C_{17}H_{15}NO_3$

calcd: C, 72.58%; H, 5.37, N, 4.98%,

found: C, 72.45%; H, 5.37% N, 4.89%,

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OB-H, hexanes:i-PrOH(85:15); flow rate 0.3 mL/min.,254 nm, retention times:73.3 min. (*R*) and 76.7 min (*S*).

(*R*)-3-(Cyclohex-1-enyl)-1-phenylpropa-1,2-diene (200fa):



(*R*)-200fa

Yield : 0.100 g, 51%, yellow liquid.

$[\alpha]_D^{25}$: -162.7 (*c* 0.50, $CHCl_3$, 99% ee).

IR (neat) : 3028, 2924, 2858, 2858, 1930, 1599, 1493, 1074 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.39-7.28 (m, 4H), 7.23-7.18 (m, 1H), 6.41-6.40 (d, *J*=4Hz, 1H), 6.27-6.26 (d, *J*=4Hz, 1H), 5.78 (s, 1H), 2.15-2.00 (m, 4H), 1.66-1.54 (m, 4H).

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

LCMS : m/z 197 (M+1)

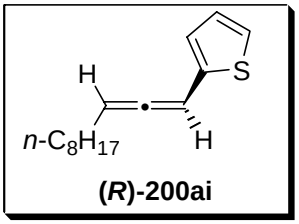
Analysis : for $C_{15}H_{16}$

calcd: C, 91.78%; H, 8.22%.

found: C, 91.65%; H, 8.31%.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/99:1; flow rate 0.3 mL/min.,215 nm, retention times:14.0 min. (*S*) and 16.6 min (*R*).

(*R*)-1-(2-Thienyl)-undeca-1,2-diene (200ai):



(*R*)-200ai

Yield : 0.145 g, 62%, colorless liquid.

$[\alpha]_D^{25}$: -232.3 (*c* 0.46, $CHCl_3$, 92% ee).

IR (neat) : 3068, 2925, 2848, 1950, 1456, 1374, 1265, 1034 854 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.19-7.14 (m, 1H),6.96-6.88 (m,2H), 6.36-6.34 (m, 1H), 5.58- 5.56 (dd, 1H), 2.37 (s, 1H), 2.14-2.09 (m, 2H), 1.57-1.52 (m, 2H), 1.43-1.32 (m, 10H), 0.94-0.92 (t, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 204.5, 139.8, 127.4, 124.1, 124.0, 95.5, 88.9, 31.8, 29.7, 29.3, 29.2, 28.8, 22.6, 21.4, 14.1.

LCMS **:** m/z 235 (M+1)

Analysis **:** for $C_{15}H_{22}S$

calcd: C, 76.86%; H, 9.46%,

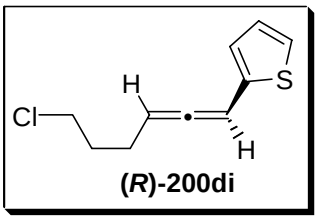
found: C, 76.95%; H, 9.38%.

Enantiomeric purity: 92% ee, HPLC using chiral column, chiralcel OB-H, heptane:i-PrOH/100:0; flow rate 0.3mL/min.,254 nm, retention times:16.3min. (*S*), and 18.0 min (*R*).

(*R*)-1-(2-Thiophenyl)-6-chloro-hexa-1,2-diene (200di)

Yield **:** 0.102 g, 52%, colorless liquid.

$[\alpha]_D^{25}$ **:** -175.5 (*c* 0.35, $CHCl_3$, 89% ee).



(*R*)-200di

IR (neat) **:** 2955, 2926, 2854, 1950, 1738, 1442, 1261, 1039, 875 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.17-7.15(d, *J* = 8.0 Hz, 1H), 6.96-6.90 (m, 2H),6.42-6.40 (m, 1H), 5.62- 5.57 (m, 1H), 3.64-3.61 (m, 2H), 2.36-2.24 (m, 2H), 2.05-1.94 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 204.7, 139.1, 127.4, 124.6, 124.4, 94.0, 89.9, 44.3, 31.5, 25.9.

LCMS **:** m/z 199 (M+1)

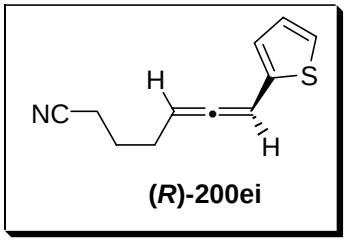
Analysis **:** for $C_{10}H_{11}ClS$

calcd: C, 80.44%; H, 5.55%

found: C, 80.27%; H, 5.61%

Enantiomeric purity: 89% ee, HPLC using chiral column, chiralcel OB-H, hexanes:i-PrOH/95:5; flow rate 0.5 mL/min.,254 nm, retention times: 13.6 min (*S*) and 14.2 min (*R*).

(*R*)-7-(2-Thiophenyl)-1-cyano-hepta-5,6 di ene (200ei):



(*R*)-200ei

Yield : 0.102 g, 52%, colorless liquid.

$[\alpha]_D^{25}$: -175.5 (*c* 0.35, $CHCl_3$).

IR (neat) : 2932, 2247, 1948, 1423, 1265, 1039, 877 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.18-7.16(d, *J* = 8.0 Hz, 1H), 6.97-6.90 (m, 2H),6.45-6.42 (m, 1H), 5.60- 5.57 (m, 1H), 2.46-2.43 (m, 2H), 2.32-2.27 (m, 2H), 1.94-1.85 (m, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 204.8, 138.6, 127.5, 124.8, 124.6, 93.4, 90.3, 27.5, 24.4, 16.5.

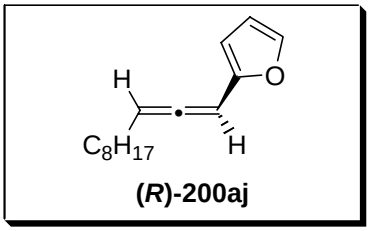
LCMS : m/z 190 (M+1)

Analysis : for $C_{11}H_{11}NS$

calcd: C, 69.80%; H, 5.86%, N,7.40%,

found: C, 69.72%; H, 5.82%, N, 7.51.

(*R*)-1-(2-Furanyl)-undeca-1,2-diene (200aj):



(*R*)-200aj

Yield **:** 0.076 g, 35%, colorless liquid.

$[\alpha]_D^{25}$ **:** -175.5 (*c* 0.35, $CHCl_3$, 86% ee).

IR (neat) **:** 3115, 2926, 2824, 1952, 1585, 1464, 1344, 1079, 925 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.35 (s, 1H), 6.38-6.37 (s, 1 H), 6.19 (s, 1H), 6.14-6.11 (m, 1H), 5.62- 5.58 (d, 1H), 4.64 (s, 2H), 2.15-2.11 (m, 3H), 1.54-1.09 (m, 13H), 0.90-0.87 (m, 7H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 204.4, 149.0, 141.7, 111.3, 106.6, 95.7, 85.4, 31.9, 31.8, 29.4, 29.3, 29.0, 28.8, 27.1, 22.7, 14.1.

LCMS **:** m/z 219 (M+1)

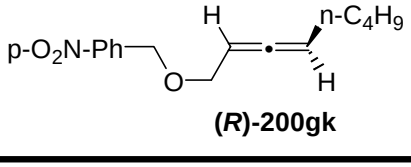
Analysis **:** for $C_{15}H_{22}O$

calcd: C, 82.52%; H, 10.16%,

found: C, 82.45%; H, 10.21%.

Enantiomeric purity: 86% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 0.5 mL/min.,254 nm, retention times: 11.1min. (*R*) and 12.5 min. (*S*).

(*R*)-1-(4-Nitrobenzyloxy)-octan-2,3-diene (200gk):



(*R*)-200gk

Yield **:** 0.153 g, 59%, colorless liquid.

$[\alpha]_D^{25}$ **:** -49.7. (*c* 0.50, $CHCl_3$, 99% ee).

IR (neat) **:** 2957,2928, 2859, 2362, 2336, 1969, 1605 cm^{-1}.

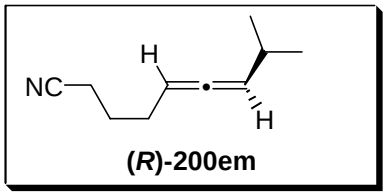
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 8.20-8.18 (d, *J* = 8.0 Hz, 2H), 7.59-7.49 (d, *J* = 8.0 Hz, 2H), 5.25- 5.20 (m, 2H), 4.62 (s, 2H), 4.09-4.07 (m, 2H), 2.05-1.99 (m, 2H), 1.43-1.32 (m, 4H), 0.90-0.89 (t, *J* = 12.0 Hz, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.2, 147.3, 146.1, 127.7, 123.5, 92.2, 87.8, 70.4, 69.3, 31.2, 28.2, 22.1, 13.9.

LCMS **:** m/z 261.5 (M+1)

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:29.8 min. (*R*) and 34.1 min. (*S*).

(*R*)-8-(Methyl)-1-cyano-nona-5,6-diene (200em):



(*R*)-200em

Yield **:** 0.087 g, 59%, colorless oil.

$[\alpha]_D^{25}$ **:** -15.5 (*c* 0.70, $CHCl_3$).

IR (neat) **:** 2926, 2247, 1959, 1738, 1660, 1493, 1462, 1188, 823 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 5.19- 5.15 (m 1H), 5.12-5.11 (m, 1H) 2.41-2.37 (m, 2H), 2.0-1.96 (m, 2H), 2.38-2.35 (m, 1H),2.16-2.13(m, 2H), 1.80-1.75 (q, *J* = 16.0 Hz, 2H), 1.01-1.00 (d, *J* = 4.0 Hz, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 202.6, 128.2, 119.6, 99.7, 90.0, 27.9, 27.7, 24.7, 22.5, 16.4.

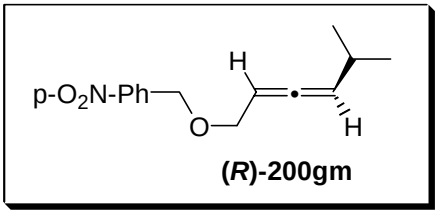
LCMS **:** m/z 149 (M+1)

Analysis **:** for $C_{10}H_{15}N$

calcd: C, 80.48%; H, 10.13%, N, 9.39%

found: C, 80.32%; H, 10.18%, N, 9.31 ;

(*R*)-1- (4-Nitrobenzyloxy)-5-methylhexa-2,3-diene (200gm):



(*R*)-200gm

Yield **:** 0.118 g, 48%, colorless liquid.

$[\alpha]_D^{25}$ **:** -36.9 (*c* 0.50, $CHCl_3$, 99% ee).

IR (neat) **:** 2961, 2924, 1959, 1606, 1344, 800 cm^{-1}.

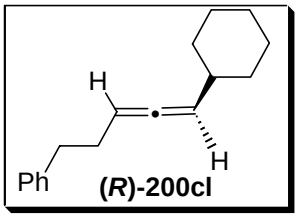
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 8.22-8.20 (d, *J* = 8.0 Hz, 2H), 7.53-7.51(d, *J* = 8.0 Hz, 2H), 5.31- 5.26 (m, 2H), 4.64 (s, 2H), 4.11-4.09 (d, *J* = 8.0Hz 2H), 2.33 (m, 1H), 1.04-1.02 (d, *J*=8Hz, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 203.8, 147.3, 146.1, 127.7, 123.5, 99.7, 89.2, 70.2, 69.4, 27.8, 22.4.

LCMS **:** m/z 247 (M)

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,215 nm, retention times:17.6 min. (*R*) and 19.7 min. (*S*).

(*R*)-5-(Cyclohexyl)-1-phenyl-penta-3, 4-diene (200cl)



(*R*)-200cl

Yield **:** 0.115 g, 51%, colorless liquid.

$[\alpha]_D^{25}$ **:** -62.5 (*c* 0.51, $CHCl_3$, 82% ee).

IR (neat) **:** 3026, 2924, 2851, 1959, 1728, 1450, 1057 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 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, 6H), 1.38-1.26 (m, 8H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 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.

LCMS **:** m/z 226 (M+1)

Analysis **:** for $C_{17}H_{22}$

calcd: C, 90.20%; H, 9.80%.

found: C, 90.35%; H, 9.71%

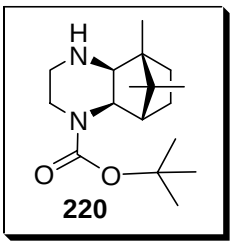
Enantiomeric purity: 82% ee, HPLC using chiral column, chiralcel OJ-H, hexanes:i-PrOH/100:0; flow rate 0.3 mL/min.,215 nm, retention times:18.8 min. (*S*) and 19.8 min. (*R*).

2.4.7 Recovery of the *S*-DPP 204 by $NaBH_4$ reduction

Conversion of propargylamine 207 to allene 200aa and *S*-DPP (204)

A flame dried 25 mL reaction flask was charged with propargylamine **207** (0.480 g, 1 mmol). $ZnBr_2$ (0.160 g, 0.5 mmol) followed by toluene (3 mL). The contents of the flask were stirred in a preheated oil bath at 120 °C for 2 h. The reaction mixture was slowly brought to 25 °C under N_2. Then, $NaBH_4$ and methanol were added to the mixture and stirred for 12 h at room temperature. The residue was column chromatography on silica gel (100-200 mesh) using hexane as eluent to afford the *R*-allene **200aa** in 80% yield and 98% ee. The *S*-DPP **204** [0.190 g (75%)] was isolated by using ethyl acetate as eluent.

2.4.8 Preparation of 5,9,9-Tetramethyl-octahydro-5,8-methano-quinzoline-1-carboxylic acid tert-butyl ester (220)



220

To a stirred solution of piperazine **215** (1.940g, 10 mmol) in dry DCM (20 ml) at 0 °C (^{t}Boc)$_2$O (1.090 g, 5 mmol) in 10 ml dry DCM was added carefully over a period of 0.5 h and the contents were stirred further for 12h at 25 °C. The DCM layer was removed under reduced pressure and the amide **220** was isolated by column chromatography on silica gel (100-200 mesh) hexane and ethyl acetate (1:1) as eluent.

Yield **:** 2.513g (85%), colorless liquid.

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

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

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 3.56-3.53 (d, 1H), 3.44-3.41(d, 1H), 3.18-3.17 (t, 1H), 3.03-2.96 (m, 2H), 2.67-2.63 (m,1H), 2.06 (s, 1H), 1.67-1.65 (m, 1H),1.53-1.52 (m, 1H), 1.47(s, 9H), 1.15 (s, 3H), 1.13 (s, 3H), 1.12(s, 3H).

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

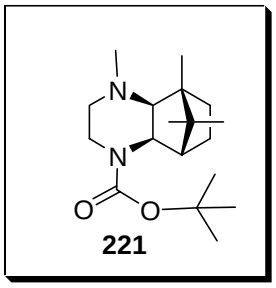
LCMS **:** m/z 295 (M+1).

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

calcd: C, 69.35; H, 10.27; N, 9.51.

found: C, 69.21; H, 10.35; N, 9.45.

2.4.9 Preparation of 4,5,9,9-Tetramethyl-octahydro-5,8-methano-quinzoline-1-carboxylic acid tertiary butyl ester (221):



221

To a stirred solution of amide **220** (2.941g, 10 mmol) and NaH (0.36 g, 15 mmol) in dry THF (20 ml) at 0 °C, MeI (2.100 g, 15 mmol) in dry THF (10 mL) was added carefully and the contents were stirred further for 2h at 25 °C. Water (5 ml) was added followed by diethyl ether (30 mL). The diethyl ether layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The amine **221** was isolated by column chromatography on silica gel (100-200 mesh) hexane and ethyl acetate (9:1) as eluent.

Yield : 2.799g (90%), colorless liquid.

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

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

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

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

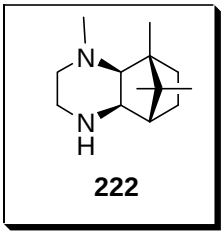
LCMS : m/z 309 (M+1).

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

calcd: C, 70.09; H, 10.46; N, 9.08.

found: C, 70.21; H, 10.35; N, 9.16.

2.4.10 Preparation of 1,8,9,9-Tetramethyl-decahydro-5, 8-methano-quinazoline (222)



222

To a stirred solution of amide **221** (3.900g, 10 mmol) in dry DCM (10 mL) at 0 °C, CF_3COOH (5 mL) was added carefully and the contents were stirred further for 12h at 25 °C. The CF_3COOH (5 mL) was removed under reduced pressure and saturated aqueous $NaHCO_3$ (10 mL) and DCM (25 mL) was added. The DCM layer was separated and washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. The piperazine **222** was isolated by column chromatography on silica gel (100-200 mesh) chloroform and methanol (9:1) as eluent.

Yield **:** 1.943g (93%), yellow liquid.

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

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

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

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

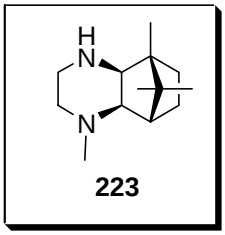
LCMS **:** m/z 209 (M+1).

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

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

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

2.4.11 Preparation of 1,8,9,9-tetramethyl-decahydro-5,8-methano-quinazoline (223):



223

An oven-dried 100 ml reaction flask was flushed with dry nitrogen, $^{t}BuO^{-}K^{+}$ (1.940g, 10 mmol) in 20 ml dry THF was kept at -78 °C, followed by addition of piperazine **215** (1.94g, 10mmol) in 10 ml of dry THF and stirred for 0.5 h at -78 °C. To this reaction mixture MeI (0.66ml, 10 mmol) in 5 ml dry THF was added about 15 min., quenched with water and added diethyl ether. Then organic layer was washed with NaCl solution and dried with Na_2SO_4 followed by column chromatography (basic alumina) using hexane as eluent gives the optically pure piperazine **223**.

Yield : 1.773g (85%), yellow liquid.

$[\alpha]_D^{25}$: -24.6 (*c* 0.45, $CHCl_3$).

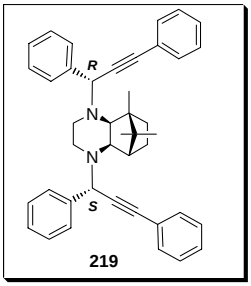
IR (neat) : 3281, 3076, 2934, 1554, 1485, 1415, 1379, 1147. 692 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 3.13-3.08 (m, 1H), 2.68-2.61 (m, 2H), 2.54-2.52 (d, J=8.0 Hz, 1H), 2.17 (s, 3H), 1.90-1.89 (d, J=4.0 Hz, 1H), 1.75-1.65 (m, 4H), 1.54-1.47 (m, 2H), 1.36 (s, 3H), 1.19-1.11 (m, 3H), 0.95 (s, 3H), 0.81 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 74.5, 67.1, 52.6, 47.7, 46.9, 46.5, 43.0, 41.8, 36.5, 26.5, 22.6, 20.3, 12.0.

HRMS : (ESI): calcd for $C_{13}H_{24}N_2+H^+$: 209.2118 [M+H^+]; found: 209.2131.

2.4.12 Preparation of 1, 4-Bis-(1,3-diphenyl-prop-2-ynyl)-5,9,9-Trimethyl-decahydro-5,8-methano quinazoline (219)



219

To a stirred suspension of piperazine **215** (0.194g, 1 mmol), $ZnCl_2$ (0.010 g 0.1 mmol) and phenylacetylene **198b** (0.102g, 1 mmol) in toluene (3 mL) was heated to 120 °C for 15 minutes. Freshly distilled benzaldehyde **199a** (0.110 g, 1 mmol) was added at 25 °C to this mixture and refluxed at 120 °C under nitrogen atmosphere. The reaction mixture was brought to room temperature after 4h. Toluene was removed, water (5 mL) was added and the extracted with DCM (25 mL). The DCM layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product **219** was purified by column chromatography on silica gel (100-200 mesh) hexane: ethyl acetate 95:5 as eluent gives optically pure amine **219**.

Yield **:** 0.533g (93%) brown solid.

$[\alpha]_D^{25}$ **:** +43 (*c* 1.62, $CHCl_3$)

IR (KBr) **:** 3076, 2934, 1554, 1485, 1415, 1379, 1147 869 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.79-7.74 (t, *J*=20.0Hz, 4H), 7.52-7.48 (t, *J*=16.0Hz, 4H), 7.40-7.26 (m, 10H), 7.21-7.17 (t, *J*=16Hz, 2H),5.24 (s, 1H), 5.04 (s, 1H), 3.46-3.38 (m, 2H), 2.93-2.85 (m, 1H), 2.70-2.64 (m, 2H), 2.33-2.28 (m, 2H), 1.89-1.82 (m, 1H), 1.59 (s, 3H), 1.38-1.28 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 139.6, 139.4, 131.9, 131.8, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.3, 123.3, 123.2,88.9, 88.5, 85.2,

85.0,68.6, 67.3, 62.4, 58.4, 51.2, 48.1, 47.1, 45.8, 44.0, 36.1, 26.6, 22.2, 20.8, 13.6.

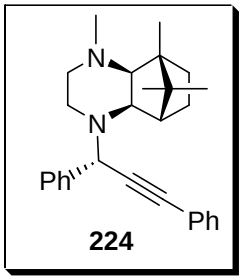
LCMS : m/z 575 (M+1).

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

calcd: C, 87.76; H, 7.36; N, 4.87.

found: C, 87.58; H, 7.41; N, 4.79.

2.4.13 Preparation of 1-(1,3–diphenyl-prop-2-ynyl)-4,5,9,9–Tetramethyl-decahydro-5,8–methano quinazoline (224)



224

To a stirred suspension of piperazine **222** (0.208g, 1 mmol), $ZnCl_2$ (0.01 g 0.1 mmol) and phenylacetylene **198b** (0.102g, 1 mmol) in toluene (3 mL) was heated to 120 °C for 15 minutes. Freshly distilled benzaldehyde **199a** (0.11 g, 1 mmol) was added at 25 ^oC to this mixture and refluxed at 120 °C under nitrogen atmosphere. The reaction mixture was brought to room temperature after 4h. Toluene was removed, water (5 mL) was added and the extracted with DCM (25 mL). The DCM layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product **224** was purified by column chromatography on silica gel (100-200 mesh) hexane: ethyl acetate (95:5) as eluent gives optically pure amine **224**.

Yield : 0.358g (90%), brown soild.

$[\alpha]_D^{25}$: -74.7 (*c* 0.52, $CHCl_3$);

IR (KBr) : 3061, 3026, 2951, 2870, 2831, 2756, 1599, 1489, 1488, 1388, 1365, 1064 842, 694 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.70-7.68 (d, *J* = 8 Hz, 2H), 7.56-7.54 (d, *J* = 8 Hz, 2H), 7.38-7.26-(m, 6H), 5.25 (s, 1H), 3.15-3.12 (d, *J* = 12 Hz,

1H), 2.59-2.57 (m, 1H), 2.49-2.48 (m, 1H), 2.26-1.23 (m, 5H) 1.99-1.63 (m, 1H), 1.52 (s, 3H), 1.30-1.25 (m, 3H), 1.06 (s, 3H), 0.83 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 138.9, 132.0, 128.3, 128.2, 127.2, 123.3, 87.8, 86.0, 78.1, 65.6, 58.2, 54.2, 50.3, 48.2, 47.5, 47.4, 42.9, 37.2, 26.3, 22.2, 21.2, 14.7.

LCMS **:** m/z 399 (M+1).

Analysis **:** for $C_{28}H_{34}N_2$

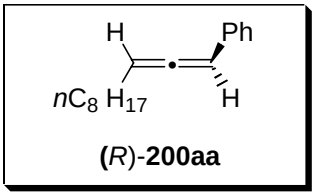
calcd: C, 84.31; H, 8.60; N, 7.03.

found: C, 84.21; H, 8.51; N, 7.12.

2.4.14. General procedure for the preparation of chiral allenes using amines

A flame–dried 25 ml reaction flask was charged with amine (**222** or **223**) (0.209 g, 1 mmol) in toluene (3 mL) under N_2 atmosphere. $ZnBr_2$ (0.135 g, 0.6 mmol) and alkyne **198** (1.1 mmol) were added and stirred at 120 °C for 10 min in a preheated oil bath. After 10 minutes, the reaction flask was lifted from the oil bath and brought to room temperature under nitrogen. Freshly distilled aldehyde **199** (1 mmol) was added to the reaction mixture at 25 °C. The contents were gradually heated to 120 °C in about 45 min and stirred for the time as given in Table **3** and **4**. The mixture was brought to 25 °C after evaporation of toluene. Column chromatography of the residue on silica gel (100-200 mesh) using hexane as eluent afforded the chiral allene.

1-Phenyl-undeca-1,2-diene 200aa:

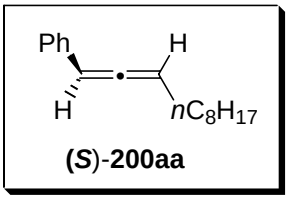


(*R*)-200aa

For (*R*)-200aa:

Yield **:** 0.155 g (68%), colorless oil.

$[\alpha]_D^{25}$ **:** -225.2 (*c* 0.50, $CHCl_3$, 98% ee);



(*S*)-200aa

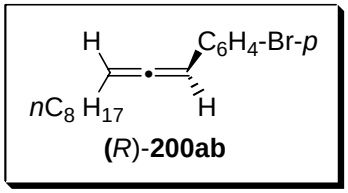
For (*S*)-200aa:

Yield **:** 0.120 g (53%), colorless oil

$[\alpha]_D^{25}$ **:** +215.7 (*c* 0.50, $CHCl_3$ 95% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254nm, retention times:4.7 min. (*R*) and 5.2 min (*S*).

1-(4-Bromo-phenyl)-undeca-1,2-diene 200ab :

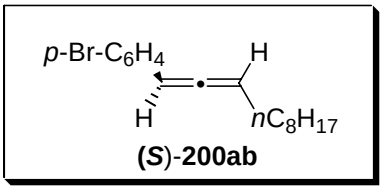


(*R*)-200ab

For (*R*)-200ab:

Yield **:** 0.220g (72%), colorless oil

$[\alpha]_D^{25}$ **:** -148.4 (*c* 0.50, $CHCl_3$ 97% ee).



(*S*)-200ab

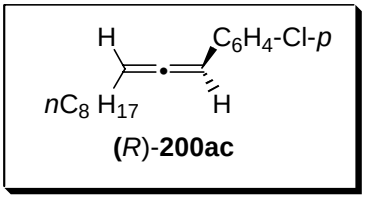
For (*S*)-200ab:

Yield **:** 0.196g (64%), colorless oil

$[\alpha]_D^{25}$ **:** +154.7 (*c* 0.50, $CHCl_3$ 99% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:3.5 min. (*S*) and 4.6 min.(*R*).

1-(4-Chloro-phenyl)-undeca-1,2-diene 200ac:



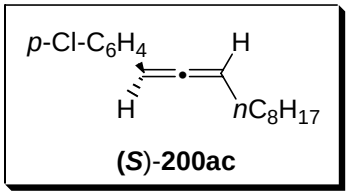
(*R*)-200ac

For (*R*)-200ac:

Yield **:** 0.533g (71%) colorless oil.

$[\alpha]_D^{25}$ **:** -215.5 (*c* 0.45, $CHCl_3$ 92% ee).

For (*S*)-200ac:



(*S*)-200ac

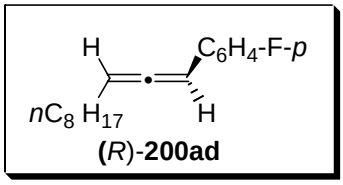
Yield **:** 0.162g (60%) colorless oil.

$[\alpha]_D^{25}$ **:** +223.5 (*c* 0.50, $CHCl_3$ 98% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:3.3 min.(*S*) and 4.2 min. (*R*).

1-(4-Fluoro-phenyl)-undeca-1,2-diene 200ad:

For (*R*)-200ad:

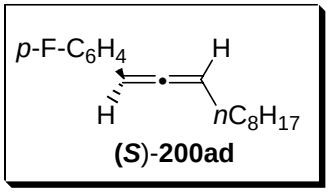


(*R*)-200ad

Yield **:** 0.175g (75%) colorless oil.

$[\alpha]_D^{25}$ **:** -162.7 (*c* 0.45, $CHCl_3$ 98% ee);

For (*S*)-200ad:



(*S*)-200ad

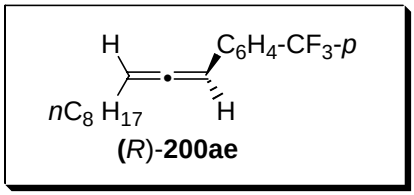
Yield **:** 0.150g (65%) colorless oil.

$[\alpha]_D^{25}$ **:** +157.3 (*c* 0.45, $CHCl_3$ 96% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times:4.4min.(*S*) and 4.8min.(*R*

1-(4-Trifluoromethyl)-phenyl)-undeca-1,2-diene 200ae:

For (*R*)-200ae:

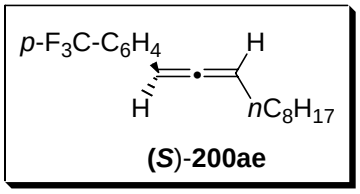


(*R*)-200ae

Yield **:** 0.210g (70%) colorless oil.

$[\alpha]_D^{25}$ **:** -175.6 (*c* 0.60, $CHCl_3$ 99% ee);

For (*S*)-200ae:



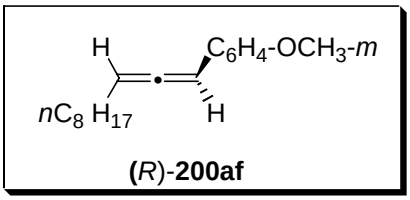
(*S*)-200ae

Yield **:** 0.201g (67%) colorless oil.

$[\alpha]_D^{25}$ **:** +169.2 (*c* 0.60, $CHCl_3$ 96% ee);

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:15.4 min. (*S*) and 17.0 min. (*R*);

1-(3-Methoxy-phenyl)-undeca-1,2-diene 200af:

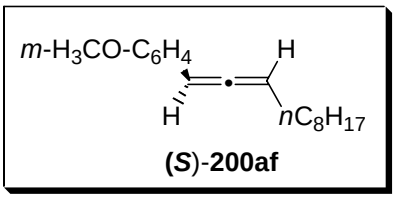


(*R*)-200af

For (*R*)-200af:

Yield **:** 0.167g (65%) colorless oil.

$[\alpha]_D^{25}$ **:** -201.7 (*c* 0.50, $CHCl_3$ 97% ee).



(*S*)-200af

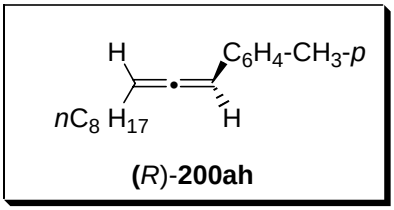
For (*S*)-200af:

Yield **:** 0.157g (61%) colorless oil.

$[\alpha]_D^{25}$ **:** +201.2 (*c* 0.50, $CHCl_3$ 97% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OJ-H, hexanes:i-PrOH/100:0; flow rate 1.0 mL/min.,254 nm, retention times:7.3 min. (*R*) and 9.5 min. (*S*);

1-(4-Methyl-phenyl)-undeca-1,2-diene 200ah :

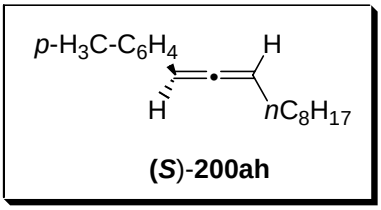


(*R*)-200ah

For (*R*)-200ah:

Yield **:** 0.152g (63%) colorless oil.

$[\alpha]_D^{25}$ **:** -225.2 (*c* 0.59, $CHCl_3$ 99% ee).



(*S*)-200ah

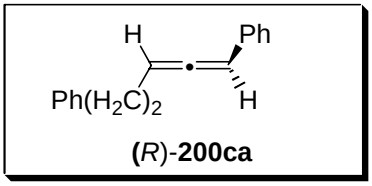
For (*S*)-200ah:

Yield **:** 0.150g (62%) colorless oil.

$[\alpha]_D^{25}$ **:** +210.8 (*c* 0.51, $CHCl_3$ 95% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OJ-H, solvent system, heptane:i-PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times 4.9 min. (*R*) and 5.5 min. (*S*).;

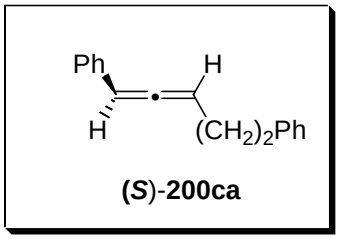
1,5-Diphenyl-penta-1,2-diene 200ca:



For (*R*)-200ca:

Yield **:** 0.159g (72%) colorless oil.

$[\alpha]_D^{25}$ **:** -210.1 (*c* 0.45, $CHCl_3$ 98% ee).



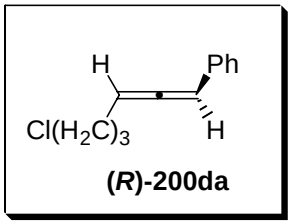
For (*S*)-200ca:

Yield **:** 0.143g (64%) colorless oil.

$[\alpha]_D^{25}$ **:** +206.9 (*c* 0.45, $CHCl_3$ 96% ee)

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:9.6 min. (*R*) and 11.1 min. (*S*);

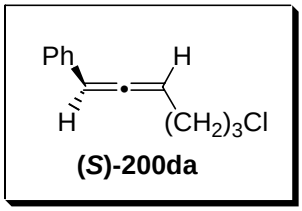
1-Phenyl-6-chloro-hexa-1,2–diene 200da:



For (*R*)-200da:

Yield **:** 0.142g (68%) colorless oil.

$[\alpha]_D^{25}$ **:** -152.3 (*c* 0.65, $CHCl_3$ 98% ee).



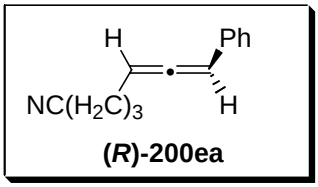
For (*S*)-200da:

Yield **:** 0.126g (59%) colorless oil.

$[\alpha]_D^{25}$ **:** +256.5 (*c* 0.65, $CHCl_3$ 98% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1 mL/min.,254 nm, retention times: 9.78 min. (*S*) and min.11.5 (*R*); ..

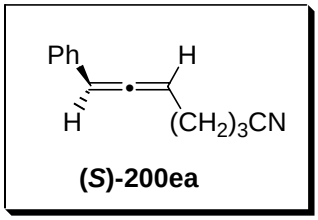
7-Phenyl-1-cyano-hepta-5,6-diene 200ea:



For (*R*)-200ea:

Yield **:** 0.113g (62%), colorless oil.

$[\alpha]_D^{25}$ **:** -201.2 (*c* 0.75, $CHCl_3$ 99% ee).



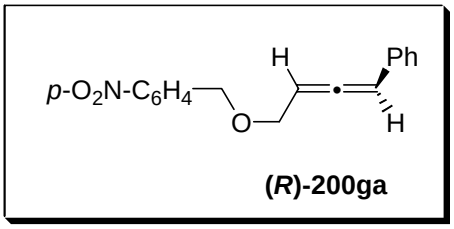
For (*S*)-200ea:

Yield **:** 0.107g (58%) colorless oil.

$[\alpha]_D^{25}$ **:** +190.6 (*c* 0.51, $CHCl_3$ 97% ee,).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1 mL/min., 254 nm, retention times: 19.6 min. (*S*) and min.22.1 (*R*).

1- (4-Nitrobenzyloxy)-4-phenylbuta-2,3-diene 200ga:

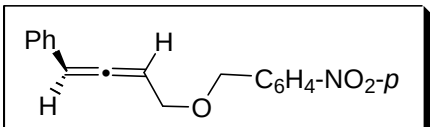


(*R*)-200ga

For (*R*)-200ga:

Yield **:** 0.174g (62%) colorless oil.

$[\alpha]_D^{25}$ **:** -196.1 (*c* 0.50, $CHCl_3$ 99% ee).



(*S*)-200ga

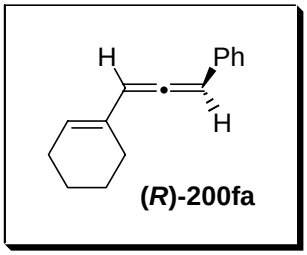
For (*S*)-200ga:

Yield **:** 0.162g (58%) colorless oil.

$[\alpha]_D^{25}$ **:** +192.8 (*c* 0.50, $CHCl_3$ 97% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OB-H, hexanes:i-PrOH(85:15); flow rate 0.3 mL/min.,254 nm, retention times:73.3 min. (*R*) and 76.7min. (*S*)

3-(Cyclohex-1-enyl)-1-phenylpropa-1,2-diene 200fa:

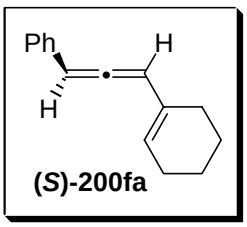


(*R*)-200fa

For (*R*)-200fa:

Yield **:** 0.125g (93%) colorless oil.

$[\alpha]_D^{25}$ **:** -143.6 (*c* 0.50, $CHCl_3$ 79% ee).



(*S*)-200fa

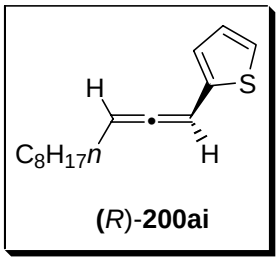
For (*S*)-200fa:

Yield **:** 0.113g (58%) colorless oil.

$[\alpha]_D^{25}$ **:** +145.1 (*c* 0.50, $CHCl_3$ 80% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/99:1; flow rate 0.3 mL/min.,215 nm, retention times:14.0 min. (*S*) and 16.6 min. (*R*).

1-(2-Thienyl)-undeca-1,2-diene 200ai:



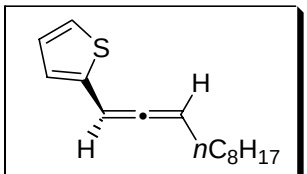
(*R*)-200ai

For (*R*)-200ai:

Yield **:** 0.173g (74%) colorless oil.

$[\alpha]_D^{25}$ **:** -198.3 (*c* 0.45, $CHCl_3$ 91% ee).

For (*S*)-200ai:



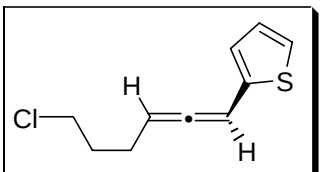
(*S*)-**200ai**

Yield **:** 0.164g (71%) colorless oil.

$[\alpha]_D^{25}$ **:** +215.1 (*c* 0.45, $CHCl_3$ 99% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OB-H,heptane:i-PrOH/100:0; flow rate 0.3mL/min.,254 nm, retention times:16.3min. (*S*) and 18.0 min .(*R*);

1-(2-Thiophenyl)-6-chloro-hexa-1,2-diene 200di:



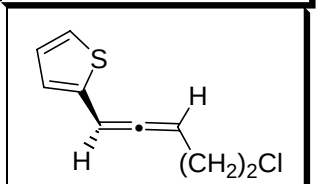
(*R*)-200di

For (*R*)-200di:

Yield **:** 0.130g (66%) colorless oil.

$[\alpha]_D^{25}$ **:** -182.1 (*c* 0.55, $CHCl_3$ 99% ee).

For (*S*)-200di:



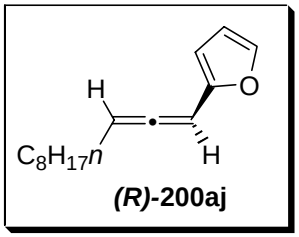
(*S*)-200di

Yield **:** 0.126g (64%) colorless oil.

$[\alpha]_D^{25}$ **:** +184.7 (*c* 0.55, $CHCl_3$ 99% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OB-H, hexanes:i-PrOH/95:5; flow rate 0.5 mL/min.,254 nm, retention times: 13.6min. (*S*) and 14.2 min. (*R*).

1-(2-Furanyl)-undeca-1,2-diene 200aj:



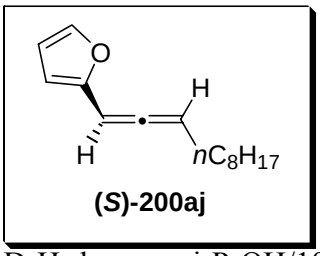
***(R)*-200aj**

For (*R*)-200aj:

Yield **:** 0.087g (40%) colorless oil.

$[\alpha]_D^{25}$ **:** -204.7 (*c* 0.29, $CHCl_3$ 85% ee).

For (*S*)-200aj:



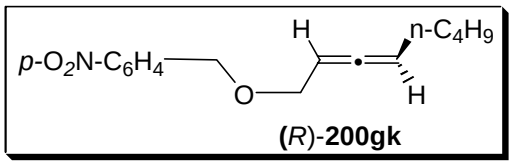
Yield **:** 0.083g (38%) colorless oil.

$[\alpha]_D^{25}$ **:** +200.2 (*c* 0.29, $CHCl_3$ 85% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 0.5 mL/min.,254 nm, retention times: 11.1min. (*R*) and 12.5 min. (*S*).

1-(4-Nitrobenzyloxy)-octan-2,3-diene 200gk:

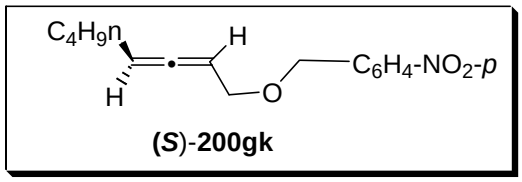
For (*R*)-200gk:



Yield **:** 0.195g (75%) colorless oil.

$[\alpha]_D^{25}$ **:** -48.8 (*c* 0.60, $CHCl_3$ 99% ee).

For (*S*)-200gk:



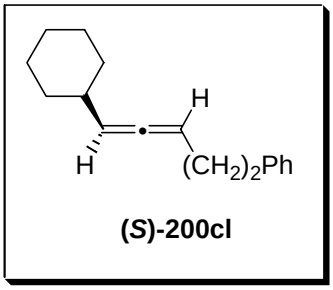
Yield **:** 0.176g (68%) colorless oil.

$[\alpha]_D^{25}$ **:** +48.1 (*c* 0.60, $CHCl_3$ 98% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel AD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254 nm, retention times:29.8 min. (*R*) and 34.1 min. (*S*);

5-(Cyclohexyl)-1-phenyl-penta-3,4-diene 200cl:

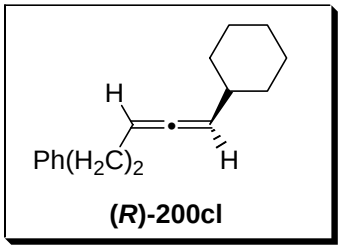
For (*R*)-200cl:



Yield **:** 0.157g (70%) colorless oil.

$[\alpha]_D^{25}$ **:** +194.2 (*c* 0.70, $CHCl_3$ 99% ee).

For (*S*)-200cl:

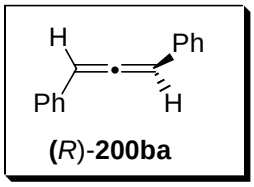


Yield **:** 0.153g (68%) colorless oil.

$[\alpha]_D^{25}$ **:** +194.2 (*c* 0.70, $CHCl_3$ 97% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OJ-H, hexanes:i-PrOH/100:0; flow rate 0.3 mL/min.,215 nm, retention times:18.8 min. (*S*) and 19.8 min. (*R*).

1, 3-Diphenyl-propan-1,2-diene 200ba:

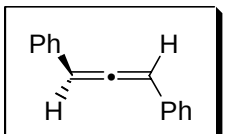


(*R*)-200ba

For (*R*)-200ba:

Yield **:** 0.081g (42%) colorless oil.

$[\alpha]_D^{25}$ **:** -723.1 (*c* 0.65, $CHCl_3$ 79% ee).



(*S*)-200ba

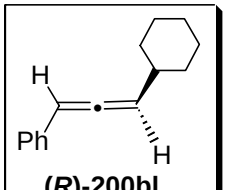
For (*S*)-200ba:

Yield **:** 0.073g (38%) colorless oil.

$[\alpha]_D^{25}$ **:** +726.7 (*c* 0.65, $CHCl_3$ 79% ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/99:1; flow rate 0.5 mL/min.,254 nm, retention times:11.0 min. (*R*) and 14.4 min. (*S*);

3-Cyclohexyl-1-phenyl-1,2-propadiene 200bl:

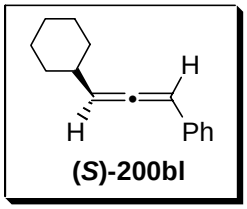


(*R*)-200bl

For (*R*)-200ba:

Yield **:** 0.134g (68%) colorless oil.

$[\alpha]_D^{25}$ **:** -260.1 (*c* 0.70, $CHCl_3$, 83% ee).



(*S*)-200bl

For (*S*)-200ba:

Yield **:** 0.122g (62%) colorless oil.

$[\alpha]_D^{25}$ **:** +310 (c = 0.70, $CHCl_3$, 91 % ee).

Enantiomeric purity: HPLC using chiral column, chiralcel OD-H, heptane:i-PrOH/100:0; flow rate 1 mL/min.,214 nm, retention times:5.4 min. (*R*) and 7.2 min.(*S*).

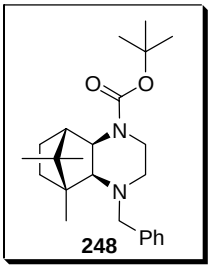
2.4.15 Recovery of the chiral piperazine 222 by $NaBH_4$ reduction

Conversion of propargylamine 224 to allene 200ba and chiral piperazine (222)

A flame dried 25 mL reaction flask was charged with chiral cyclic mono-propargylamine **224** (0.48 g, 1 mmol). $ZnBr_2$ (0.160 g, 0.5 mmol) was added followed by toluene (3 mL). The contents of the flask mixture were stirred in a preheated oil bath at 120 °C for 2 h. The reaction mixture was slowly brought to 25 °C under N_2. Then, $NaBH_4$ and methanol were to the mixture and stirred for 12 h at room temperature. The residue was column chromatography on silica gel (100-200 mesh) using hexane as eluent to afford the *R*-allene **200ba** in 70% yield and 90% ee. The chiral piperazine **222** [0.14 g (67%)] was isolated by using ethyl acetate as eluent.

Preparation of 4-Benzyl-5,9,9-trimethyl-octahydro-5,8-methano-quinazoline-carboxylic acid tert-butyl ester (248):

To the chiral piperazine **215** (1.940g, 10 mmol) solution in DCM (100 mL), di-*t*-butyldicarbonate (2.2 mL, 10 mmol) was added at 0 °C slowly (for 10 min) through a syringe under N_2 atmosphere. The reaction mixture was brought to room temperature slowly and further stirred for 6 h. After the completion of the reaction monitored by TLC, the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (100-200 mesh) using hexane/EtOAc (50:50) afforded 5,9,9-trimethyl-octahydro-5,8-methano-quinzoline-1-carboxylic acid tert-butyl ester **247** as colorless viscous liquid. To this solution of **247** (2.941g, 10 mmol) in dry acetonitrile (30 mL) was added benzyl bromide (0.83 mL, 10 mmol), K_2CO_3 (1.79 g, 13 mmol), KI (0.498 g) and the mixture was stirred under reflux for 12 h. It was cooled to room temperature and filtered off to remove K_2CO_3 and the solvent was evaporated



248

under reduced pressure. The residue was extracted with DCM (80 mL) and water (20 mL). The combined organic extract was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and purification of the residue by column chromatography using ethyl acetate as eluent afforded 4-benzyl-5,9,9-trimethyl-octahydro-5,8-methano-quinazoline-1-carboxylic acid tert-butyl ester **248**.

Yield **:** 3.148 g, 82%, yellow liquid.

$[\alpha]_D^{25}$ **:** 21.6 (*c* 0.70, $CHCl_3$).

IR (neat) **:** 2953, 2887, 2814, 2781, 1691, 1602, 1477, 1452, 1371, 1294, 1232, 1174, 1143, 1109, 1080, 1032, 987 cm^{-1}.

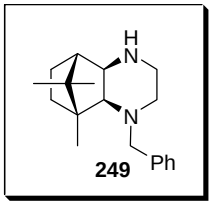
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.39-7.25 (m, 5H), 4.18-4.14 (d, *J*=16.0Hz, 1H), 3.71-3.65 (m, 1H), 3.32-3.25 (m, 2H), 2.90-2.86 (d, *J*=16.0Hz, 1H), 2.72-2.60 (m, 2H), 2.05-2.03 (m, 1H), 1.70 (s, 2H), 1.48-1.45 (s, 9H), 1.30 (s, 3H), 1.16 (s, 2H), 1.07 (s, 3H), 0.84 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 156.5, 139.5, 128.3, 127.9, 126.8, 79.5, 72.4, 71.9, 63.2, 59.2, 53.6, 50.6, 50.0, 45.8, 43.1, 36.0, 28.5, 26.8, 22.3, 20.5, 20.2, 14.5.

HRMS **:** (ESI): calcd for $C_{24}H_{36}N_2O_2$: 384.2777 [M+H^+]; found: 385.2854

Preparation of 1-Benzyl-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (249):

To a solution of 4-benzyl-5,9,9-trimethyl-octahydro-5,8-methano-quinazoline-1-carboxylic acid tert-butyl ester **248** (3.072 g, 8.0 mmol) in 1,4-dioxane (20 mL), 6M HCl (5 mL) was added slowly through a syringe for 15 min. under N_2 atmosphere. The resulting mixture was stirred at room temperature



249

for 12 h. The solvent was evaporated and the residue was neutralized with 6N NaOH solution and the organic layer was extracted with DCM. The combined organic extract was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue on column chromatography using ethyl acetate as eluent afforded the 1-benzyl-5,9,9-trimethyl-decahydro-5, 8-methano-quinazoline **249** as yellow liquid.

Yield **:** 2.090 g, 92%, yellow liquid.

$[\alpha]_D^{25}$ **:** 11.1 (*c* 0.44, $CHCl_3$).

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

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.36-7.23 (m, 3H), 4.34-4.30 (d, *J*=16.0Hz, 1H), 2.94-2.91 (m, 2H), 2.80-2.74 (m, 2H), 2.64-2.60 (m, 1H), 2.25-2.23 (d, *J*=8.0Hz, 1H), 1.82-1.78 (m, 2H), 1.71-1.70 (d, *J*=4.0Hz, 1H), 1.56 (s, 3H), 1.46-1.44 (m, 1H), 1.23-1.18 (m, 2H), 1.09 (s, 3H), 0.86 (s, 3H).

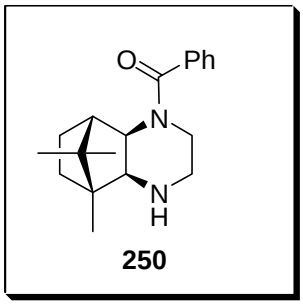
^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.2, 128.4, 128.2, 128.1, 126.6, 76.2, 61.1, 61.0, 50.9, 50.4, 50.1, 47.4, 41.6, 37.0, 27.1, 22.3, 21.1, 15.5.

HRMS **:** (ESI): calcd for $C_{19}H_{28}N_2$: 284.2252 [M+H^+]; found: 284.2329.

Preparation of Phenyl-(5,9,9-trimethyl-octahydro-5,8-methano-quinazolin-1-yl)-methanone (250):

To solution of chiral piperazine **215** (1.940g, 10 mmol) and trimethylamine (1.36 ml, 10.0 mmol) in DCM (100 mL), benzoyl chloride (1.27 mL, 10 mmol) was added at -78 °C slowly (for 30 min) through a syringe under N_2 atmosphere. The reaction mixture was brought to room temperature slowly and further stirred for 12 h. After the completion of the reaction

monitored by TLC, the solvent was evaporated under reduced pressure and washed with $NaHCO_3$. Purification of the residue on column chromatography using ethyl acetate as eluent afforded the phenyl-(5,9,9-trimethyl-octahydro-5,8-methano-quinazolin-1-yl)-methanone **250** as brown soild.



250

Yield : 2.771 g, 93%, brown soild.

$[\alpha]_D^{25}$: 38.6 (*c* 0.60, $CHCl_3$).

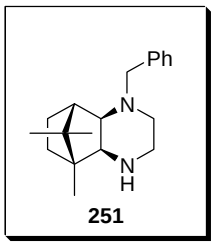
IR (KBr) : 3314, 3079, 3062, 3024, 2947, 2887, 2739, 1610, 1577, 1445, 1402, 1237, 1160, 1122, 1023, 793 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.38-7.28 (m, 5H), 4.02-3.98 (q, *J*=16.0Hz, 1H), 3.80-3.78 (d, *J*=12.0Hz, 1H), 3.50-3.45 (t, *J*=20.0Hz, 1H), 3.08-3.06 (d, *J*=8.0Hz, 2H), 2.82-2.79 (d, *J*=12.0Hz, 1H), 2.57-2.48 (m, 2H), 1.92 (s, 1H), 1.47-1.45 (t, *J*=12.0Hz, 1H), 1.20 (s, 4H), 1.10-1.04 (m, 2H), 0.84 (s, 3H), 0.74 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 173.0, 137.2, 131.7, 129.6, 128.2, 127.9, 127.1, 66.2, 60.2, 58.4, 51.2, 48.6, 48.0, 45.8, 42.9, 35.4, 26.5, 21.8, 20.8, 14.1, 11.4.

HRMS : (ESI): calcd for $C_{19}H_{26}N_2O$: 298.2045 [M+H^+]; found: 299.2123.

Preparation of 1-Benzyl-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (251):



251

To a suspension of $NaBH_4$ (1.9 g, 50 mmol) in THF (50 mL) was added a solution of I_2 (6.32 g, 25 mmol) in THF (40 mL) at 0 °C under N_2 atmosphere over 30 min. The imide **250** (2.982 g, 10 mmol) was added

to the generated diborane and refluxed for 24-36 h. The reaction was brought to room temperature and quenched with methanol and the solvents were evaporated. The residue was refluxed with 10N KOH for 6h and resultant mixture was extracted with DCM (2 X 30 mL). The combined organic extract was evaporated to obtain the decahydroquinazoline **251**. The crude amine was chromatography and isolate the 1-benzyl-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline **251** as yellow liquid.

Yield **:** 2.215 g, 78%, yellow liquid.

$[\alpha]_D^{25}$ **:** 18.9 (*c* 0.46, $CHCl_3$);

IR (neat) **:** 3377, 3030, 2955, 2879, 2802, 2752, 2687, 2310, 1653, 1604, 1483, 1452, 1388, 1265, 1143, 1109, 1072, 1010, 895 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.31-7.24 (m, 3H), 4.19-4.16 (d, *J*=12.0Hz, 1H), 3.03-3.01 (m, 1H), 2.91-2.88 (d, *J*=12.0Hz, 1H), 2.69-2.63 (m, 2H), 2.11-2.06 (m, 2H), 1.76 (m, 1H), 1.64-1.58 (m, 1H), 1.54 (s, 3H), 1.26 (s, 2H), 0.95 (s, 3H), 0.85 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 139.2, 128.8, 128.1, 126.8, 97.0, 59.2, 48.8, 48.1, 47.1, 46.6, 41.6, 36.4, 29.7, 26.5, 22.6, 20.7, 12.1

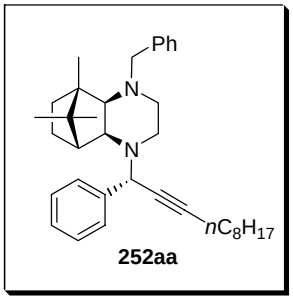
HRMS **:** (ESI): calcd for $C_{19}H_{28}N_2$: 284.2252 [*M*+H^+]; found: 284.2329.

2.4.16 General procedure for the preparation of chiral propargylamines

In a 25 mL reaction flask $ZnCl_2$ (0.014 g, 10 mol %), chiral piperazine **249** (0.283 g, 1 mmol), 1-alkyne **198** (0.150 g, 1.1 mmol) and aldehydes **199** were added in toluene (3 mL) and the mixture was heated to 100 °C for 4 h. The mixture was brought to 25 °C, toluene was evaporated under reduced pressure and the residue was chromatography on silica gel

(100-200 mesh) using hexane/ethyl acetate (90:10) as eluent to isolate the chiral propargyl amine **252.**

4-Benzyl-5,9,9-trimethyl-1-(1-phenyl-undec-2-ynyl)-decahydro-5,8-methano-quinazoline (252aa)



252aa

Yield : 0.499 g, 98%, yellow liquid.

$[\alpha]_D^{25}$: 16.5 (*c* 0.71, $CHCl_3$).

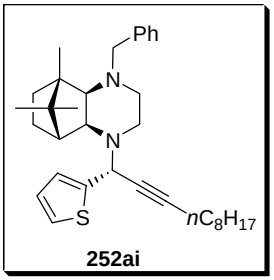
IR (neat) : 3079, 3057, 3024, 2926, 2856, 1600, 1484, 1441, 1380, 1347, 1326, 1254, 1123, 1024, 964 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.64-7.63 (d, *J*=4.0Hz, 2H), 7.36-7.19 (m, 8H), 4.94 (s, 1H), 4.08-4.05 (d, *J*=12.0Hz, 1H), 3.25-3.17 (m, 1H), 2.76-2.74 (d, *J*=12.0Hz, 2H), 2.36-2.28 (m, 4H), 2.15 (s, 1H), 1.90-1.76 (m, 3H), 1.55 (s, 6H), 1.32 (s, 9H), 1.20-1.18 (d, *J*=12.0Hz, 2H), 1.04 (s, 5H), 0.89 (s, 5H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 140.5, 140.1, 128.2, 128.1, 127.8, 126.9, 126.3, 87.8, 75.8, 72.9, 65.9, 63.6, 58.0, 50.6, 50.4, 48.1, 47.2, 42.8, 36.4, 31.9, 29.3, 29.1, 28.9, 26.3, 22.7, 22.3, 21.0, 18.8, 14.1, 13.8.

HRMS : (ESI): calcd for $C_{36}H_{50}N_2$: 510.3974 [M+H^+]; found: 511.4053.

4-Benzyl-5,9,9-trimethyl-1-(1-thiophen-2-yl-undec-2-ynyl)-decahydro-5,8-methano-quinazoline (252ai)



252ai

Yield : 0.459 g, 89%, yellow liquid.

$[\alpha]_D^{25}$: 11.05(*c* 0.61, $CHCl_3$).

IR (neat) : 2920, 2854, 2356, 1720, 1642, 1457, 1129, 1067, 956 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.39-7.37 (d, *J*=4.0Hz, 2H), 7.31-7.27 (m, 2H), 7.22-7.18 (m, 2H), 7.14 (s, 1H), 6.91-6.89 (t, *J*=8.0Hz, 1H), 4.99 (s, 1H), 4.06-4.02 (d, *J*=16.0Hz, 1H), 3.29-3.26 (d, *J*=12.0Hz, 1H), 3.10-3.08 (d, *J*=12.0Hz, 1H), 2.76-2.74 (d, *J*=12.0Hz, 1H), 2.50-2.31 (m, 4H), 2.18-2.14 (m, 1H), 1.83-1.74 (m, 2H), 1.66-1.51 (m, 1H), 1.51 (s, 4H), 1.32-1.31 (m, 9H), 1.17-1.15 (d, *J*=12.0Hz, 2H), 1.03 (s, 3H), 0.91-0.86 (s, 10H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 146.2, 140.5, 128.1, 127.9, 126.4, 125.1, 125.0, 86.8, 75.6, 72.7, 65.7, 63.6, 54.5, 50.5,50.1, 48.3, 47.1, 43.2, 36.3, 31.8, 29.3, 29.1, 29.0, 28.8, 26.2, 22.7, 22.2, 20.8, 18.7, 14.1, 13.7.

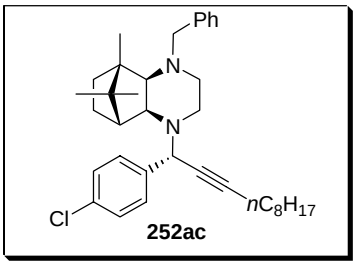
HRMS : (ESI): calcd for $C_{34}H_{48}N_2S$: 516.3538 [M+H^+]; found: 517.3617.

4-Benzyl-1-[1-(4-chloro-phenyl)-undec-2-ynyl]-5,9,9-trimethyl-decahydro-5, 8-methano-quinazoline (252ac)

Yield : 0.516 g, 95%, yellow liquid.

$[\alpha]_D^{25}$: 46.05(*c* 0.52, $CHCl_3$).

IR (neat) : 3084, 3058, 3030, 2958, 2931, 2860, 1649, 1600, 1490, 1452, 1260, 1128, 1084, 1013, 767 cm^{-1}.



252ac

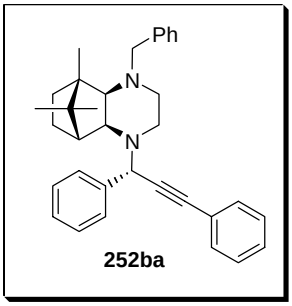
^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.57-7.55 (m, 2H), 7.37-7.35 (m, 1H), 7.30-7.25 (m, 3H), 7.20-7.19 (m, 1H), 4.89 (s, 1H), 4.09-4.05 (d, *J*=16.0Hz, 1H), 3.29-3.26 (m, 2H), 2.76-2.73 (m, 2H), 2.37-2.32 (m, 4H), 2.18-

2.14 (m, 1H), 1.87-1.81 (m, 2H), 1.66-1.57 (m, 3H), 1.52 (s, 5H), 1.33-1.32 (m, 9H), 1.20-1.18 (d, *J*=8.0Hz, 2H), 1.05-1.04 (s, 3H), 0.91-0.86 (s, 6H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 140.4, 138.6, 132.6, 129.5, 128.1, 128.0, 127.9, 126.4, 88.2, 75.4, 72.9, 65.9, 63.5, 57.5, 50.6, 50.3, 48.1, 47.2, 42.8, 36.4, 31.9, 31.6, 29.3, 29.2, 29.1, 28.9, 26.3, 22.7, 22.2, 21.0, 18.7, 14.1, 13.8.

HRMS : (ESI): calcd for $C_{36}H_{49}ClN_2$: 544.3584 [M+H^+]; found: 545.3662.

4-Benzyl-1-(1,3-diphenyl-prop-2-ynyl)-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (252ba)



252ba

Yield : 0.412 g, 87%, yellow liquid.

$[\alpha]_D^{25}$: 40.65 (*c* 0.35, $CHCl_3$).

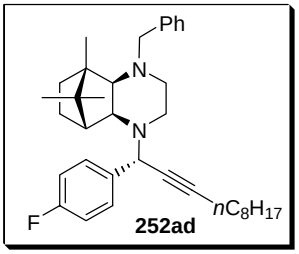
IR (neat) : 3068, 3024, 2953, 2870, 2810, 1599, 1489, 1456, 1396, 1254, 1122, 1100, 1073, 1023, 760 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.74-7.21 (d, *J*=12.0Hz, 2H), 7.59-7.57 (m, 2H), 7.40-7.35 (m, 6H), 7.30-7.25 (m, 2H), 7.23-7.22 (m, 1H), 5.23 (s, 1H), 4.12-4.08 (d, *J*=16.0Hz, 1H), 3.22-3.24 (m, 2H), 2.85-2.80 (m, 2H), 2.50-2.42 (m, 2H), 2.20-2.16 (m, 1H), 2.00-1.98 (d, *J*=8.0Hz, 1H), 1.85-1.81 (m, 1H), 1.60-1.58 (m, 4H), 1.28-1.23 (m, 3H), 1.08 (s, 3H), 0.94 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.5, 139.3, 131.9, 128.3, 128.2, 128.1, 127.9, 127.2, 126.4, 123.3, 87.7, 86.1, 73.0, 66.1, 63.5, 58.6, 50.6, 50.4, 48.2, 47.3, 43.1, 36, 29.5, 26.3, 22.3, 21.1, 13.9.

HRMS **:** (ESI): calcd for $C_{34}H_{38}N_2$: 474.3035 [M+H^+]; found: 475.3114.

4-Benzyl-1-[1-(4-fluoro-phenyl)-undec-2-ynyl]-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (252ad)



252ad

Yield **:** 0.480 g, 89%, yellow liquid.

$[\alpha]_D^{25}$ **:** 50.11 (*c* 0.33, $CHCl_3$);

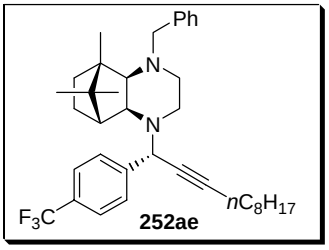
IR (neat) **:** 3068, 3024, 2953, 2870, 2810, 1599, 1489, 1456, 1396, 1254, 1122, 1100, 1073, 1023, 760 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.61-7.57 (t, *J*=16.0Hz, 2H), 7.37-7.35 (d, *J*=8.0Hz, 2H), 7.30-7.35 (m, 2H), 7.21-7.18 (m, 1H), 7.01-6.96 (t, *J*=20.0Hz, 1H), 4.90 (s, 1H), 4.09-4.05 (d, *J*=16.0Hz, 1H), 3.24-3.15 (m, 2H), 2.81-2.74 (m, 2H), 2.37-2.34 (m, 3H), 2.29-2.20 (m, 1H), 2.13-2.07 (m, 1H), 1.88-1.87 (d, *J*=4.0Hz, 1H), 1.79-1.77 (m, 1H), 1.66-1.59 (m, 2H), 1.53 (s, 4H), 1.34-1.32 (m, 9H), 1.23-1.18 (d, *J*=20.0Hz, 1H), 1.05 (s, 3H), 0.91 (s, 7H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 163.1, 160.7, 140.5, 135.7, 129.6, 128.1, 127.9, 126.4, 114.7, 114.4, 88.1, 75.7, 72.9, 65.9, 63.5, 57.4, 50.6, 50.3, 48.1, 47.2, 36.4, 31.9, 29.3, 29.1, 28.9, 26.3, 22.7, 22.3, 21.0, 18.7, 14.1, 13.8.

HRMS **:** (ESI): calcd for $C_{36}H_{49}N_2$: 528.3880 [M+H^+]; found: 529.3957.

4-Benzyl-5,9,9-trimethyl-1-[1-(4-trifluoromethyl-phenyl)-undec-2-ynyl]-decahydro-5,8-methano-quinazoline (252ae)



252ae

Yield : 0.514 g, 89%, yellow liquid.

$[\alpha]_D^{25}$: 42.32(*c* 0.68, $CHCl_3$);

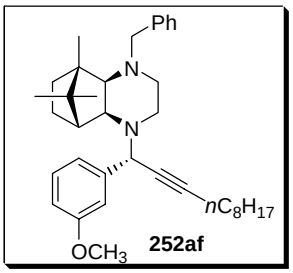
IR (neat) : 2953, 2926, 2854, 1704, 1676, 1621, 1320, 1172, 1128, 1063 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.76-7.74 (d, *J*=8.0Hz, 2H), 7.57-7.55 (d, *J*=8.0Hz, 2H), 7.37-7.35 (d, *J*=8.0Hz, 2H), 7.30-7.25 (t, *J*=20.0Hz, 1H), 7.21-6.19 (t, *J*=12.0Hz, 1H), 4.96 (s, 1H), 4.09-4.06 (d, *J*=12.0Hz, 1H), 3.23-3.17 (t, *J*=20.0Hz, 2H), 2.78-2.74 (m, 2H), 2.38-2.32 (m, 3H), 2.25-2.19 (m, 1H), 2.13-2.09 (m, 1H), 1.88-1.87 (d, *J*=4.0Hz, 1H), 1.80-1.77 (m, 1H), 1.53 (s, 3H), 1.34-1.31 (m, 9H), 1.23-1.15 (m, 3H), 1.05 (s, 3H), 0.90 (s, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 144.2, 140.4, 129.4, 129.1, 128.4, 128.1, 127.9, 126.4, 125.4, 124.8, 122.9, 88.5, 75.1, 73.0, 65.8, 63.5, 57.9, 50.6, 50.2, 48.2, 47.2, 42.9, 36.4, 34.6, 31.8, 31.6, 29.3, 29.1, 29.0, 28.9, 26.2, 25.2, 22.2, 21.0, 18.7, 14.1, 13.8.

HRMS : (ESI): calcd for $C_{37}H_{49}F_3N_2$: 578.3848 [M+H^+]; found: 529.3957.

4-Benzyl-1-[1-(3-methoxy-phenyl)-undec-2-ynyl]-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (252af)



252af

Yield : 0.521 g, 97%, yellow liquid.

$[\alpha]_D^{25}$: 38.12(*c* 0.23, $CHCl_3$).

IR (neat) : 3062, 3024, 2956, 2925, 2854, 1604, 1583,

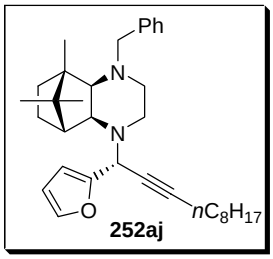
1489, 1451, 1325, 1259, 1128, 1051, 1029, 728 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.39-7.37 (d, *J*=8.0Hz, 2H), 7.31-7.19 (m, 6H), 6.80-6.78 (d, *J*=8.0Hz, 1H), 4.94 (s, 1H), 4.10-4.06 (d, *J*=16.0Hz, 1H), 3.86 (s, 3H), 3.27-3.18 (m, 2H), 2.85-2.75 (m, 2H), 2.39-2.30 (m, 4H), 2.16-2.14 (m, 1H), 1.91-1.89 (d, *J*=8.0Hz, 1H), 1.83-1.77 (m, 1H), 1.66-1.60 (m, 1H), 1.55 (s, 3H), 1.35-1.33 (m, 9H), 1.22-1.20 (d, *J*=8.0Hz, 3H), 1.06 (s, 3H), 0.92 (s, 6H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 159.4, 141.9, 140.5, 128.8, 128.1, 127.9, 126.4, 120.5, 113.6, 112.6, 87.7, 75.9, 72.9, 65.8, 63.6, 58.0, 55.6, 50.4, 48.2, 47.2, 42.9, 36.4, 31.9, 29.4, 29.2, 28.9, 26.3, 22.7, 22.3, 21.0, 18.8, 14.1, 13.9.

HRMS : (ESI): calcd for $C_{37}H_{52}N_2O$: 540.4080 [M+H^+]; found: 541.4159.

4-Benzyl-1-(1-furan-2-yl-undec-2-ynyl)-5,9,9-trimethyl-decahydro-5,8-methano-quinazoline (252aj)



252aj

Yield : 0.425 g, 85%, yellow liquid.

$[\alpha]_D^{25}$: 35.43(*c* 0.81, $CHCl_3$).

IR (neat) : 3090, 3068, 3029, 2947, 2920, 2854, 1599, 1495, 1451, 1391, 1352, 1330, 1128, 1073, 1007, 810, 733 cm^{-1}.

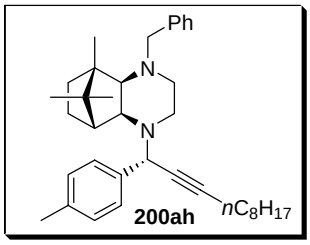
^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.39-7.37 (d, *J*=8.0Hz, 3H), 7.31-7.27 (t, *J*=16.0Hz, 2H), 7.22-7.19 (t, *J*=12.0Hz, 1H), 6.33-6.29 (d, *J*=16.0Hz, 2H), 4.90 (s, 1H), 4.10-4.06 (d, *J*=16.0Hz, 1H), 3.19-3.15 (d, *J*=16.0Hz, 1H), 3.08-3.06 (d, *J*=8.0Hz, 1H), 2.83-2.77 (m, 1H), 2.70-2.68 (d, *J*=8.0Hz, 1H), 2.53-2.43 (m, 2H), 2.32-2.09 (m, 2H), 2.15-

2.09 (m, 1H), 1.89-1.87 (d, *J*=8.0Hz, 1H), 1.81-1.76 (m, 1H), 1.59-1.56 (m, 3H), 1.47 (s, 3H), 1.33 (s, 9H) 1.20-1.15 (m, 2H), 1.04 (s, 3H), 0.92-0.88 (m, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 153.3, 142.0, 140.5, 128.1, 127.9, 126.4, 109.8, 107.9, 86.1, 74.4, 73.3, 65.1, 63.4, 52.6, 50.4, 50.3, 48.0, 47.1, 43.1, 36.5, 31.9, 29.3, 29.1, 29.0, 28.8, 26.1, 22.7, 22.3, 20.6, 18.7, 14.1, 13.8.

HRMS **:** (ESI): calcd for $C_{34}H_{48}N_2O$: 500.3767 [M+H^+]; found: 501.3846.

4-Benzyl-5,9,9-trimethyl-1-(1-p-tolyl-undec-2-ynyl)-decahydro-5,8-methano-quinazoline (200ah)



Yield **:** 0.497 g, 95%, yellow liquid.

$[\alpha]_D^{25}$ **:** 41.23(*c* 0.72, $CHCl_3$).

IR (neat) **:** 3040, 2958, 2931, 2860, 1687, 1605, 1452, 1216, 1172, 1024, 854, 816, 756 cm^{-1}.

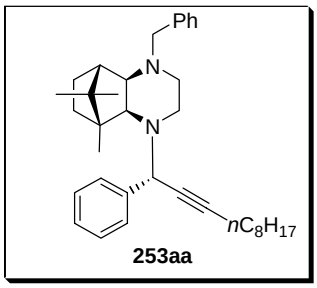
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.57-7.55 (d, *J*=8.0Hz, 2H), 7.42-7.40 (d, *J*=8.0Hz, 2H), 7.34-7.30 (t, *J*=16.0Hz, 2H), 7.25-7.21 (t, *J*=12.0Hz, 1H), 7.17-7.15 (d, *J*=8.0Hz, 2H), 4.97 (s, 1H), 4.13-4.09 (d, *J*=16.0Hz, 1H), 3.29-3.21 (m, 2H), 2.87-2.78 (m, 2H), 2.42-2.31 (m, 4H), 2.17-2.12 (m, 1H), 1.95-1.94 (d, *J*=4.0Hz, 1H), 1.85-1.80 (m, 1H), 1.69-1.65 (m, 2H), 1.59 (s, 6H), 1.38 (s, 9H), 1.27-1.20 (m, 2H), 1.09 (s, 3H), 0.96-0.94 (m, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.6, 137.1, 136.5, 128.6, 128.1, 127.9, 126.4, 87.6, 76.1, 73.0, 66.1, 63.6, 57.8, 50.6, 50.5, 48.2, 47.2, 42.7,

42.7, 36.5, 31.9, 29.4, 29.2, 28.9, 26.3, 22.8, 22.4, 21.0, 18.8, 14.2, 13.9.

HRMS : (ESI): calcd for $C_{37}H_{52}N_2$: 524.4130 [M+H^+]; found: 525.4209.

1-Benzyl-5,9,9-trimethyl-4-(1-phenyl-undec-2-ynyl)-decahydro-5,8-methano-quinazoline (253aa)



253aa

Yield : 0.484 g, 95%, yellow liquid.

$[\alpha]_D^{25}$: 41.20(c 0.72, $CHCl_3$).

IR (neat) : 3065, 3035, 2926, 2854, 2800, 2756, 1704, 1600, 1492, 1452, 1391, 1205, 1128, 1030, 745 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.69-7.67 (d, J=8.0Hz, 2H), 7.34-7.22 (m, 9H), 4.76 (s, 1H), 4.12-4.08 (d, J=16.0Hz, 1H), 3.23-3.21 (d, J=16.0Hz, 2H), 2.93-2.83 (m, 2H), 2.64-2.62 (d, J=16.0Hz, 1H), 2.50-2.41 (m, 2H), 2.35-2.32 (m, 2H), 1.92-1.91 (d, J=4.0Hz, 1H), 1.50 (s, 6H), 1.33-1.32 (m, 9H), 1.05 (s, 3H), 0.91-0.86 (m, 4H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 140.3, 139.9, 128.5, 128.1, 128.0,127.9, 126.8, 126.5, 85.0, 78.8, 71.1, 68.0, 61.8, 61.3, 50.9, 49.4, 48.4, 46.8, 45.4, 36.1, 31.9, 29.4, 29.2, 29.0, 28.9, 26.5, 22.7, 22.1, 20.1, 18.8, 14.1, 13.3.

HRMS : (ESI): calcd for $C_{36}H_{50}N_2$: 510.3974 [M+H^+]; found: 510.3974.

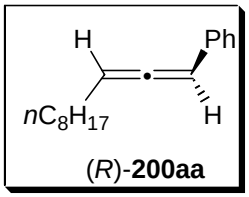
2.4.17 General procedure for the preparation of chiral propargylamines

The chiral propargylamine **252** or **253** (1 mmol) was added to a stirred suspension of $ZnBr_2$ (0.113 g, 0.5 mmol) in dry toluene (3 mL) and the contents were refluxed for 1-2 h at 120 °C under nitrogen atmosphere. Toluene was removed under reduced pressure and the crude

product was purified on silica gel (100-200 mesh) column using hexane as eluent to isolate the chiral allenes. The spectral data showed 1:1 correspondence with reported data.[10a]

1-Phenyl-undeca-1, 2-diene (200aa):

For (*R*)-200aa:

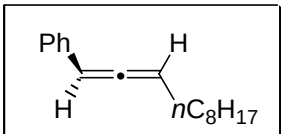


(*R*)-**200aa**

Yield : 0.155g 68% colorless liquid

$[\alpha]_D^{25}$: -225.2 (*c* 0.50, $CHCl_3$ 98%ee)

For (*S*)-200aa:

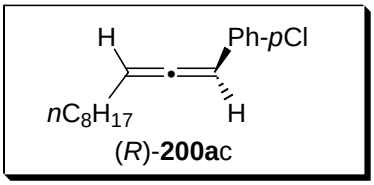


(***S***)-**200aa**

Yield : 0.120g 53% colorless liquid

$[\alpha]_D^{25}$: +215.7 (*c* 0.50, $CHCl_3$, 99%ee).

(*R*)-1-(4-chloro-phenyl)-1,2-undecadiene (200ac):



(*R*)-**200a**c

Yield : 0.204 g, 76%, colorless liquid.

$[\alpha]_D^{25}$: -218.1 (*c* 0.38, $CHCl_3$, 99% ee).

IR (neat) : 2926, 2854, 1950, 1491, 831, 773 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.27-7.20 (m, 4H), 6.09-6.06 (m, 1H), 5.60-5.55 (m, 1H), 2.16-2.09 (m, 2H), 1.51-1.44 (m, 2H), 1.37-1.26 (m, 10H), 0.92-0.87 (t, 3H).

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

LCMS : m/z 264 (M+1).

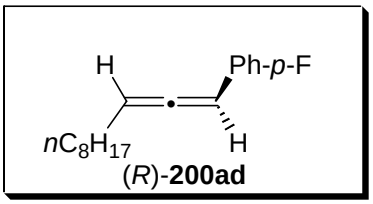
Analysis : for $C_{17}H_{23}Cl$

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

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

Enantiomeric purity: 99% ee, determined by HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254nm, retention times:3.3 min. (*S*) and 4.2 min. (*R*).

(*R*)-1-(4-fluoro-phenyl)-1,2undecadiene (200ad):



(*R*)-**200ad**

Yield : 0.169 g, 69%, colorless liquid.

$[\alpha]_D^{25}$: -203.1 (*c* 0.66, $CHCl_3$, 98% ee).

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

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.26-7.22 (m, 2H), 7.01-6.96 (m, 2H), 6.11-6.08 (m, 1H), 5.57-5.56 (m, 1H), 2.15-2.09 (m, 2H), 1.50-1.44 (m, 2H), 1.37-1.28 (m, 10H), 0.98-0.89 (t, 3H).

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

LCMS : m/z 229 (M+1).

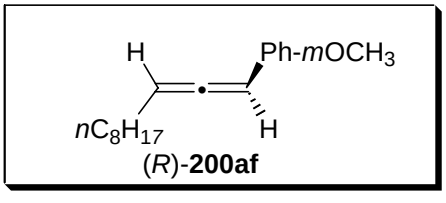
Analysis : for $C_{17}H_{23}F$

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

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

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254nm, retention times:4.4 min. (*S*) and 4.8 min. (*R*).

(*R*)-1-(3-methoxy-phenyl)-1, 2-undecadiene (200af):



(*R*)-**200af**

Yield : 0.211 g, 82%, colorless liquid.

$[\alpha]_D^{25}$: -213.4 (*c* 0.71, $CHCl_3$, 97% ee).

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

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

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

LCMS **:** m/z 259 (M+1).

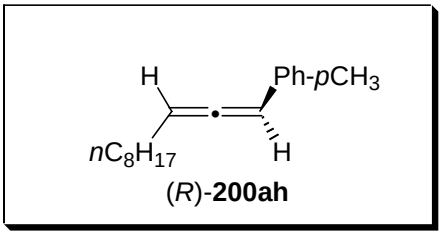
Analysis **:** for $C_{18}H_2O$

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

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

Enantiomeric purity: 97% ee, HPLC using chiral column, chiralcel OJ-H, hexanes:i-PrOH/100:0; flow rate 1.0 mL/min.,254nm, retention times:7.3 min. (*R*) and 9.5 min. (*S*).

(*R*)-1-(4-methyl-phenyl)-1,2-undecadiene (200ah):



(*R*)-**200ah**

Yield **:** 0.182 g, 75%, colorless liquid.

$[\alpha]_D^{25}$ **:** -225.2 (*c* 0.59, $CHCl_3$, 99% ee).

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

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.20-7.18 (d, J=8Hz, 2H), 7.12-7.10 (d, J=8Hz, 2H), 6.12-6.09 (m, 1H), 5.55-5.54 (m, 1H), 2.36 (s, 3H), 2.15-2.10 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.27 (m, 10H), 0.94-0.90 (t, 3H).

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

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

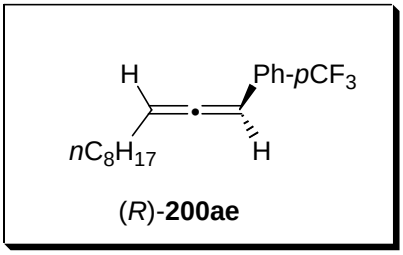
Analysis : for $C_{18}H_{26}$

calcd: C, 89.19%; H, 10.81

found: C, 89.26%; H, 10.76%;

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OJ-H, solvent system, heptane:i-PrOH/100:0; flow rate 1.5 mL/min., 254nm, retention times 4.9 min. (*R*) and 5.5 min. (*S*).

(*R*)-1-(4-Trifluoromethyl-phenyl)-1, 2-undecadiene (200ae):



(*R*)-**200ae**

Yield : 0.210 g, 71%, colorless liquid.

$[\alpha]_D^{25}$: -181.3 (*c* 0.41, $CHCl_3$, 99% ee).

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

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.55-7.52 (d, J=12Hz, 2H), 7.38-7.36 (d, J=8Hz, 2H), 6.16-6.13 (m, 1H), 5.66-5.62 (m, 1H), 2.18-2.12 (m, 2H), 1.54-1.45 (m, 2H), 1.38-1.27 (m, 10H), 0.89-0.88 (t, 3H).

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

LCMS : m/z 301 (M+1).

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

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

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

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.,254nm, retention times:15.4 min. (*S*) and 17.0 min. (*R*).

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Chapter 3

Synthesis of Highly Functionalized and Biologically Active Chiral Allenes

3. 1 Introduction

3.1.1 Functionalized chiral allenes

In recent years, allenes became highly valuable intermediates for target-oriented synthesis because they have proven application in various transformations with high levels of chirality transfer.[1] Hence, 1,3-disubstituted chiral allenes containing functional groups play a significant role in organic synthesis, as they can be converted under mild conditions into biologically active compounds.[2]

All natural and biological active allenes have functional groups, and their synthesis require multistep synthetic operations (Figure **1)**. It is of our interest to examine the use of methods developed in this laboratory to access functionalized 1,3-disubstituted chiral allenes. A brief review of reports based on the synthesis of functionalized 1,3-disubstituted chiral allenes and their application in organic synthesis would facilitate the discussion.

The allenic natural products (Figure **1)** exhibit interesting biological activities. For example, the compounds Scorodonin **1**, Marasin **2** and Phomallenic acid **3** have inhibiting effects on the growth of bacteria, yeast and filamentous fungi.[3] Other allenic moieties with inhibiting effects are sterol biosynthesis inhibitor **4**, gastric acid inhibitor **5**, HIV inhibitor **8** and hepatitis B replication inhibitor **7**.[4-6] Therefore, introduction of allene as a functional group into the existing backbone of the pharmacologically active compounds could be expected to result in interesting new biological properties.

3.1.2 Naturally occurring and biologically active chiral allenes

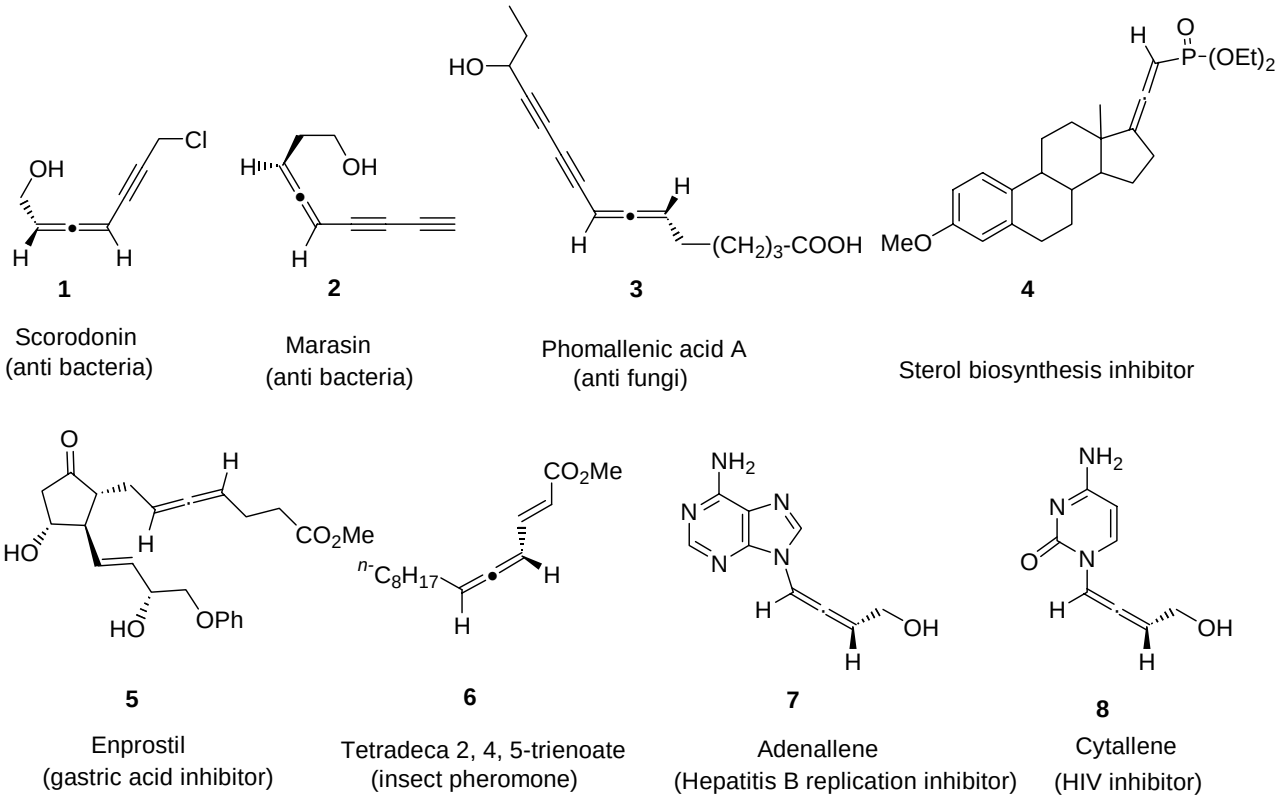
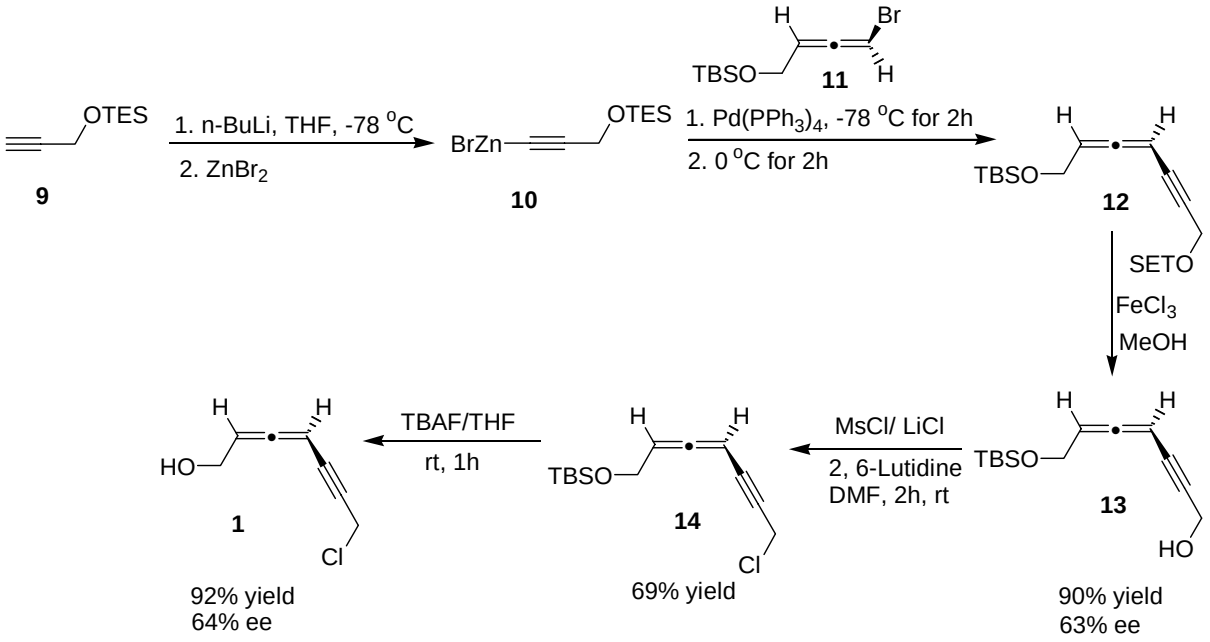


Figure 1

3.1.3 Total synthesis of functionalized chiral allenes

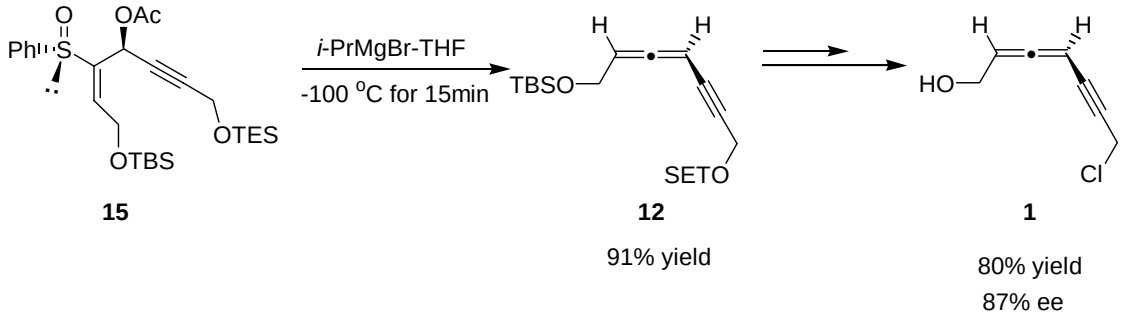
Scorodonin **1** is a natural allenyne, which has significant antibacterial and antifungal activities. The synthesis of Scorodonin **1** was reported using Negishi cross coupling reaction of alkynylzinc **10** with bromoallene **11** followed by several synthetic operations to obtain Scorodonin **1** in 92% yield with 64% ee. The main drawback of this route is the configuration of the chiral allene axis was inverted during the process (Scheme **1)**.[7]

Scheme 1



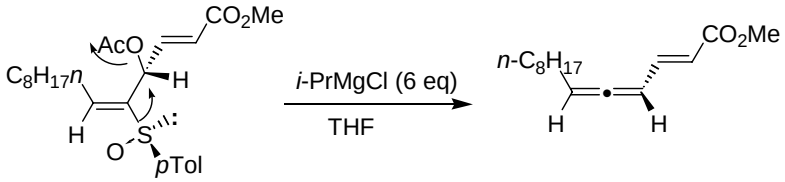
In another approach, the synthesis of Scorodonin **1** was achieved using 1,2-elimination of optically active sulfoxide-allylic acetates **15** (Scheme **2**).[8]

Scheme 2



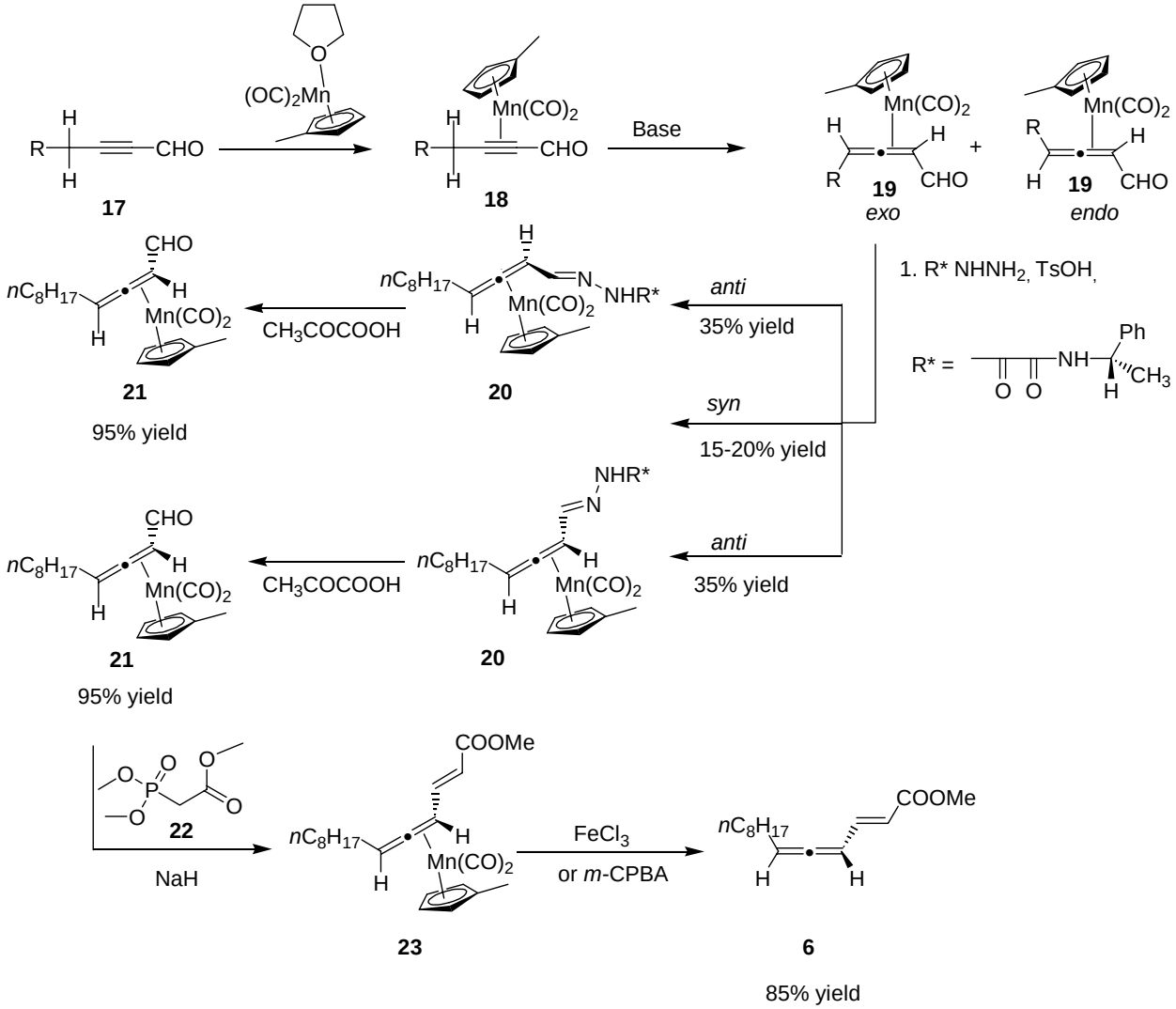
A stereoselective sulfoxide–magnesium exchange of chiral β-acetoxy sulfoxide **16** with isopropylmagnesium chloride, followed by elimination gave insect pheromone methyl (*R*,E) tetradeca 2,4,5-trienoate **6** in 95% yield and 81% ee (Scheme **3**).[9]

Scheme 3



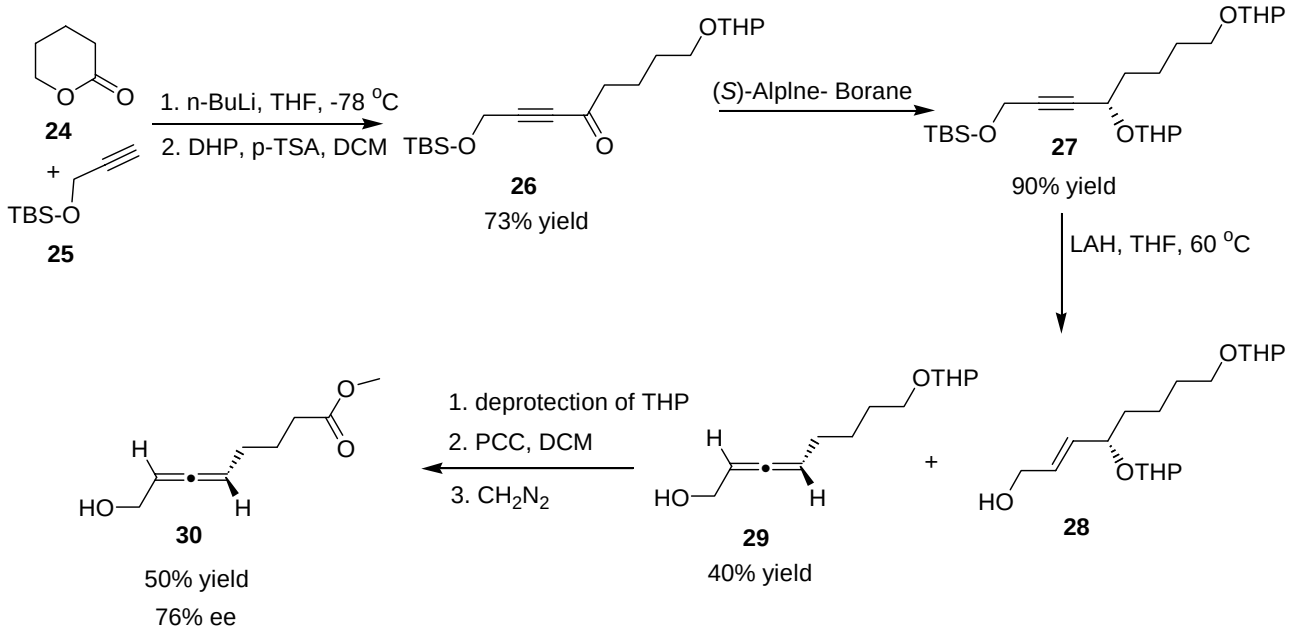
The synthesis of chiral allene **6** was also attained via the manganese intermediate as outlined in Scheme **4**.[10]

Scheme 4



Sapium japonicum **30** is a antifungal agent and its homologue is useful for the synthesis of allenyl prostaglandins.[11] Reduction of propargyl ether **27** with excess of lithium aluminium hydride at 60°C afforded the allenic alcohol **29** which upon reaction with PCC followed by esterification with diazomethane gave the Sapium japonicum **30** in 50% yield with 76% ee (Scheme **5**).

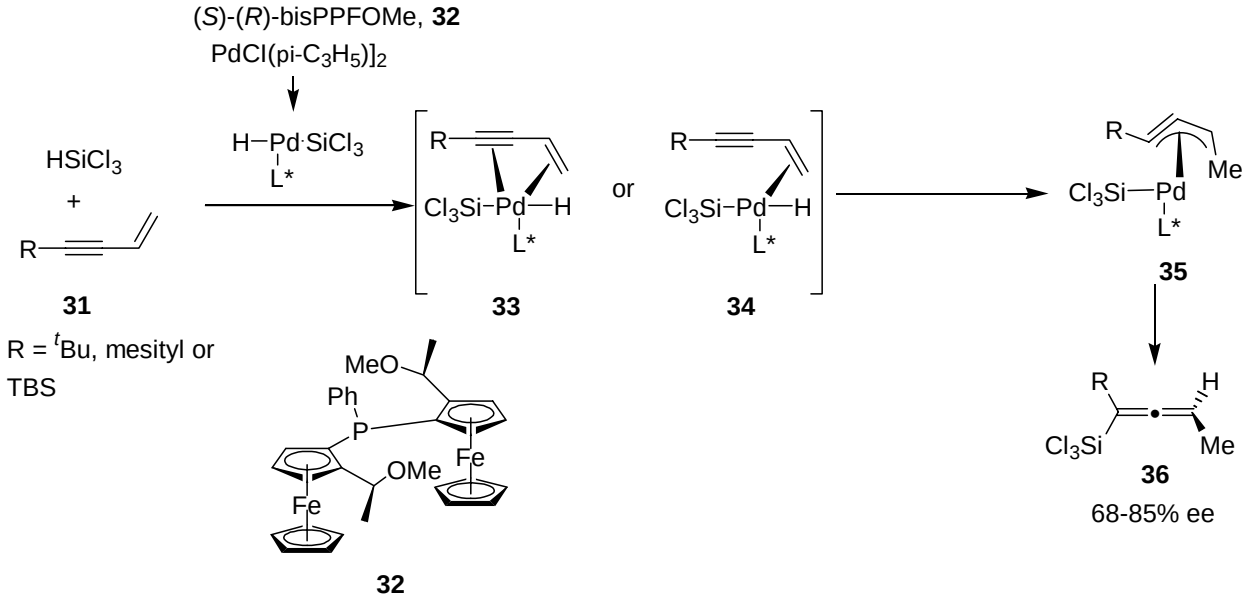
Scheme 5



3.1.4 Synthesis of highly functionalized chiral allenes using a chiral catalyst

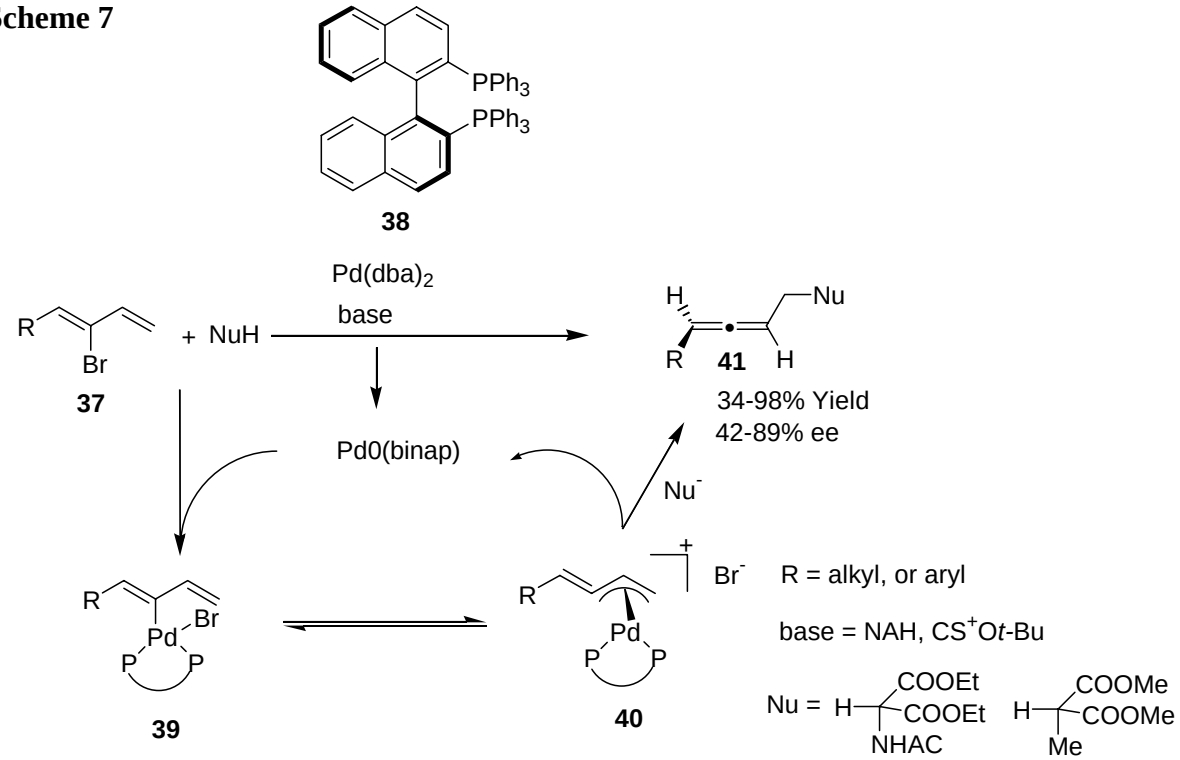
An interesting method for the synthesis of chiral allenylsilanes *via* palladium catalyzed asymmetric hydrosilylation of 1,3-enynes has been reported (Scheme **6)**.[12]

Scheme 6



Another approach involves a palladium catalyzed formal S_N2 reaction of achiral conjugated dienes as outlined in Scheme **7**.[13]

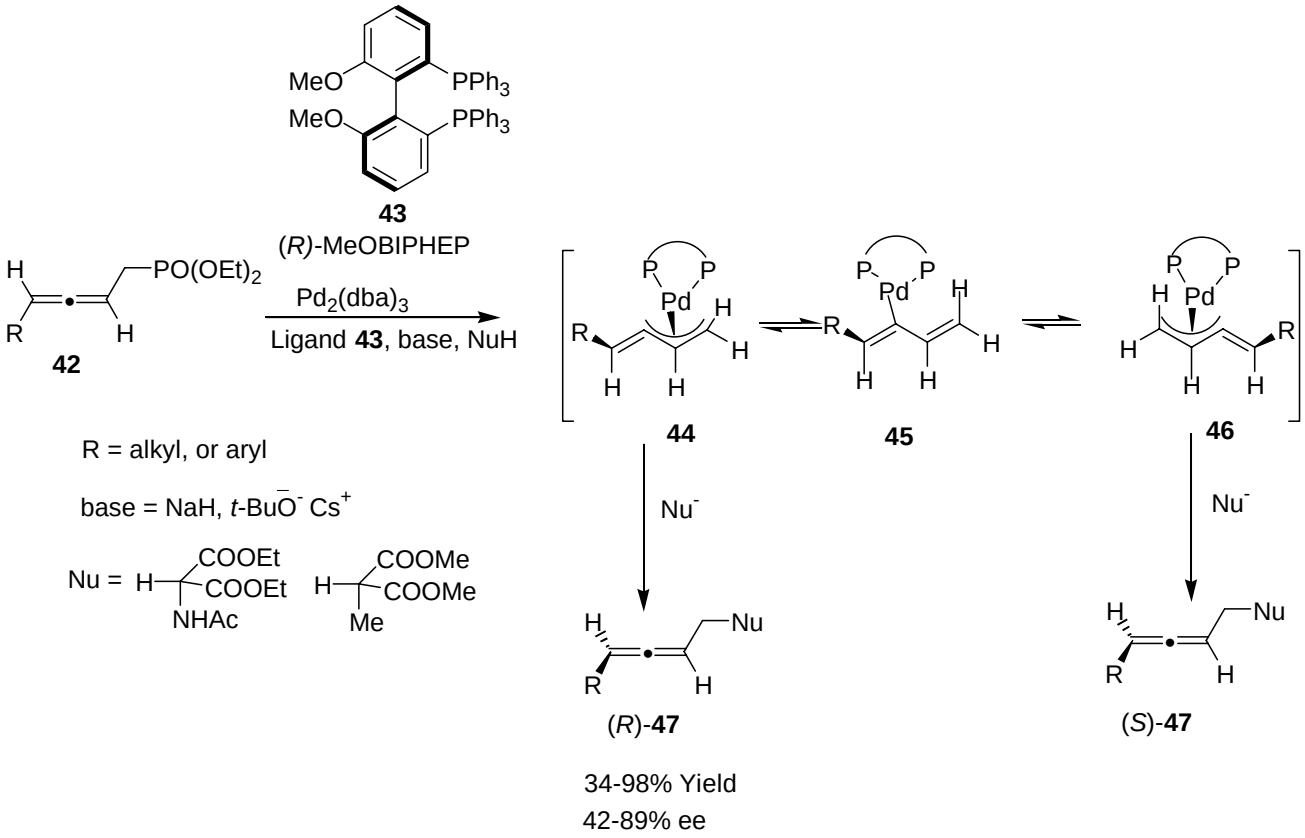
Scheme 7



3.1.5 Palladium catalysed kinetic resolution of racemic allenes

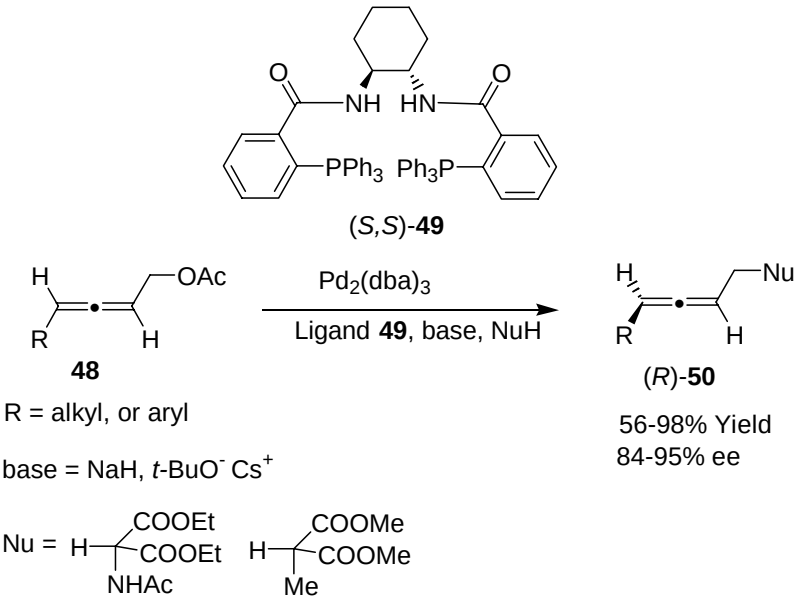
In this approach, first racemic allenes were synthesized and transformed into axially chiral allenes by a catalytic dynamic kinetic asymmetric transformation (DYKAT). For example, reaction of racemic alkadienyl phosphates **42** with soft nucleophiles in the presence of $Pd_2(dba)_3$ (1 mol%), chiral ligand **43** (4 mol%) and base gave the allenic product (*R*)-**47** in 34-98% yield with up to 89% ee. It was proposed that nucleophilic attack occurs preferentially on intermediate **44** from the opposite face on the palladium complex to give the optically active allenes (*R*)-**47**.[14]

Scheme 8



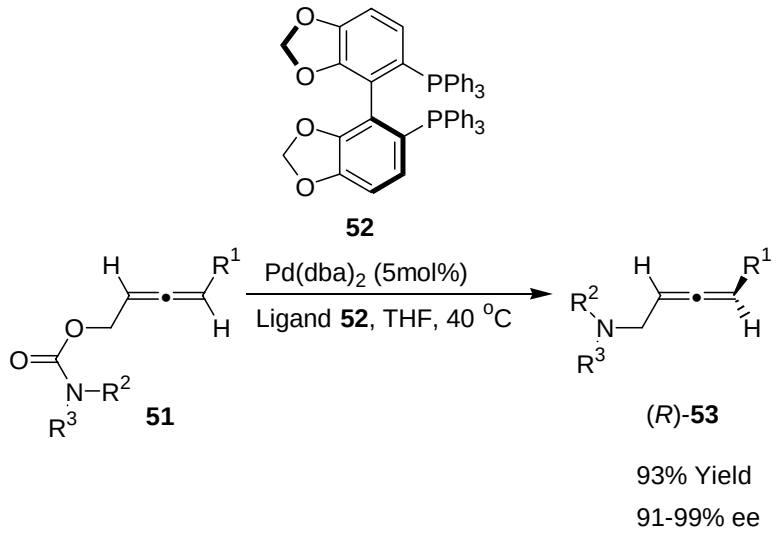
Reaction of racemic allenic acetates **48** with Pd(0) (2.5 mol%) and chiral ligand **(*S*,*S*)-49** (7.5 mol%) in the presence of a soft nucleophile and base gives the allenes **50** in high yields with good enantioselectivity (Scheme **9**).[15]

Scheme 9



Enantioselective decarboxylative amination is another approach for the synthesis of functionalized chiral allenyl amines **53** with up to 93% yield with 99% ee (Scheme **10)**.[16]

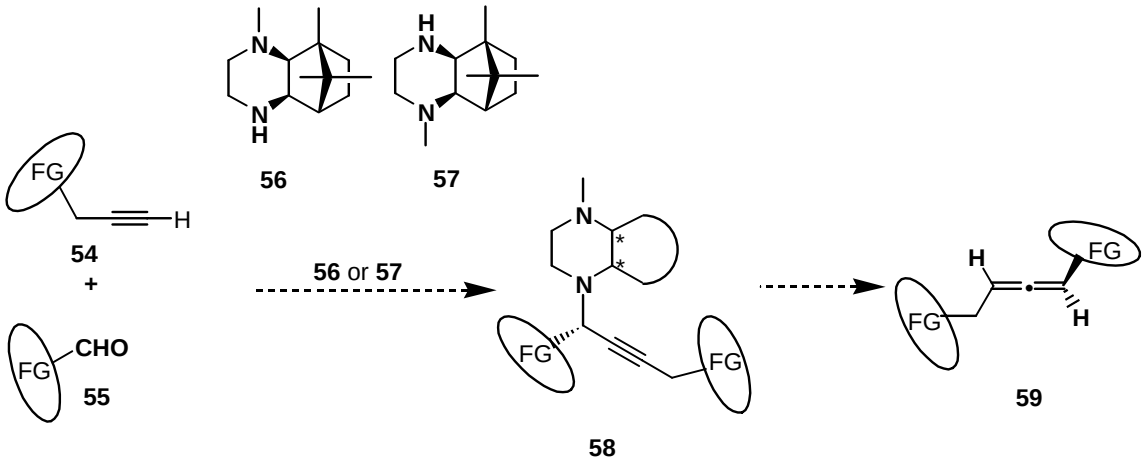
Scheme 10



These approaches give the chiral allenes in reasonable yields and enantioselectivities but they still require synthesis of the racemic allene and hence require extra steps.

Reports on the synthesis of functionalized chiral allenes are still limited and the reported methods involve multistep operation using expensive reagents. Therefore, it is highly desirable to develop an efficient and a simple method for synthesis of functionalized chiral allene. We have undertaken efforts towards the synthesis of highly functionalized chiral allenes through the chiral propargylamine intermediates by using N-methylcamphanyl piperazine templates as shown in Scheme **11**.

Scheme 11

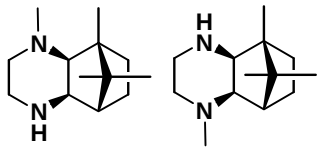


The results are described in the next section.

3.2 Results and Discussion

3.2.1 Efforts toward the synthesis of highly functionalized chiral allenes

We have extended our "chiral amine approach" (chapter **2**) to synthesize highly functionalized chiral allenes through readily accessible chiral propargylamines using chiral N-methylcamphanyl piperazine templates (**56, 57**).

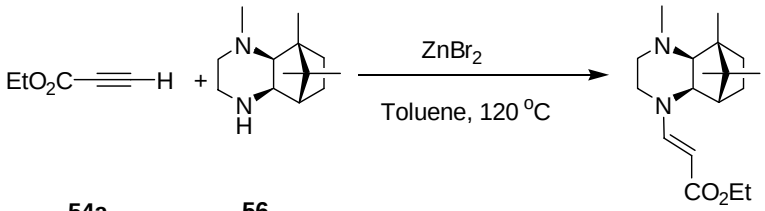


56 **57**

Figure 2

We have observed that the reaction between alkyne like ethyl propiolate **54a** and piperazine **56** gave the Michael addition products **60** in 99% yield (Scheme **12).**[17]

Scheme 12

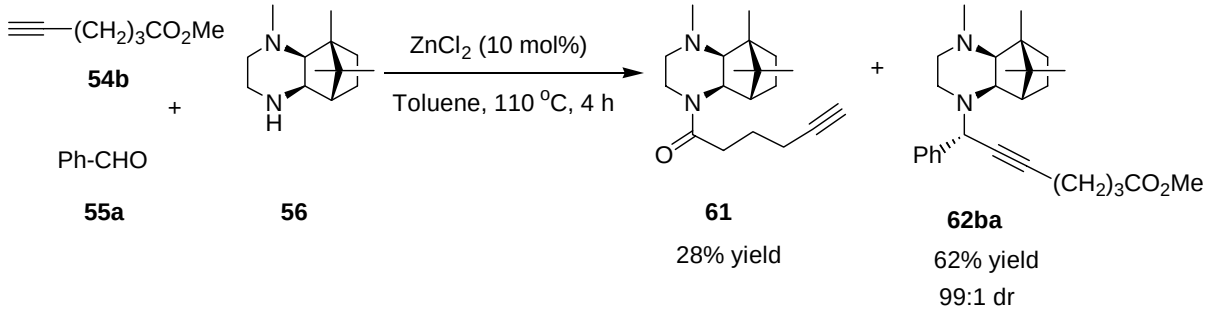


54a **56** **60**

99% yield

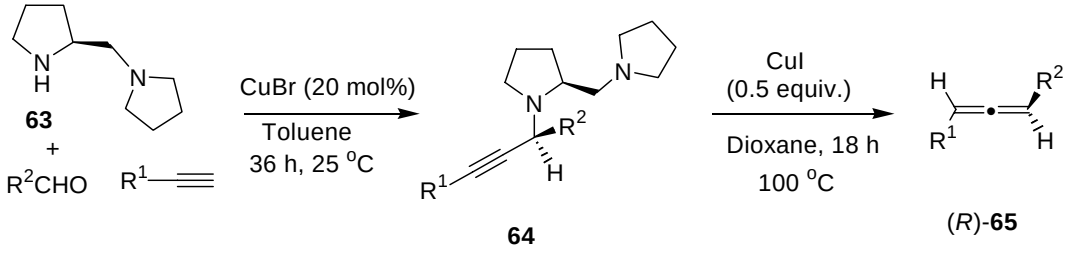
The formation of Michael addition product **60** is due to the conjugation between ester group and triple bond. It occurred to us that if the ester group is far away from the triple bond, the reaction may lead to formation of the desired propargylamine product. To examine this, we have chosen methyl-5-hexynoate as the alkyne **54b** partner for this reaction. However, in this reaction we have isolated the amide derivative **61** of chiral piperazine **56** and alkyne **54b** in 28% yield along with propargylamine **62ba** in 62 % yield with 99:1 dr (Scheme **13**).

Scheme 13



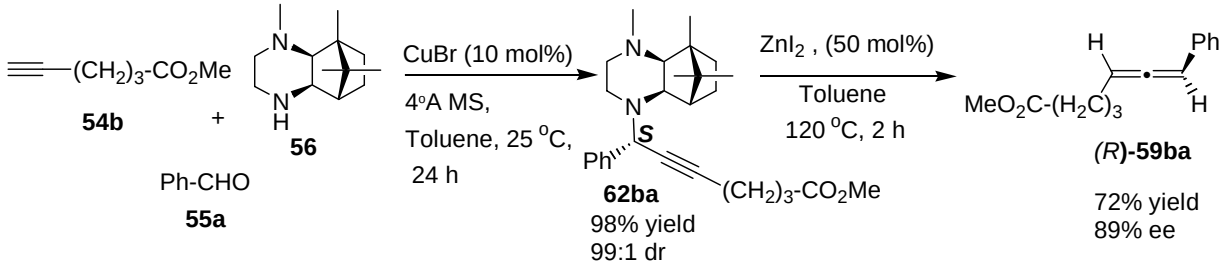
Very recently, in this laboratory, a CuBr promoted method has been reported for the diastereoselective synthesis of chiral propargylamines **64** which upon reaction with CuI gave the corresponding chiral allenes **65** (Scheme **14**).[18]

Scheme 14



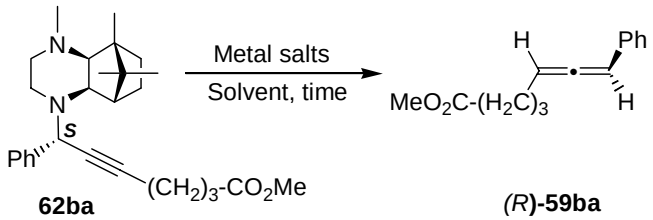
Therefore, we have decided to pursue the CuBr methodology to synthesize the chiral propargylamine from N-methylcamphanyl piperazine templates (**56**, **57**). We have observed that the reaction between methyl-5-hexynoate **54b**, benzaldehyde **55a** and chiral piperazine **56** using CuBr (0.1 mmol) gave the propargylamine **62ba** in 98% yield with 99:1 dr (Scheme **15**).

Scheme 15



When the ZnI_2 (0.5 mmol) was used as metal salt for the conversion of chiral propargylamine **62ba** in toluene, the expected allene product (*R*)-**59ba** was obtained in 75% yield with 89% ee (Scheme **15**). Encouraged by this result, we optimized the reaction conditions by examining the effect of the various metal salts and solvent for the conversion of chiral propargylamine to chiral allene (*R*)-**59ba.**[19, 20]

Table 1. Reaction of propargylamine **62ba** with different metal salts for formation allene (*R*)-**59ba**[a]



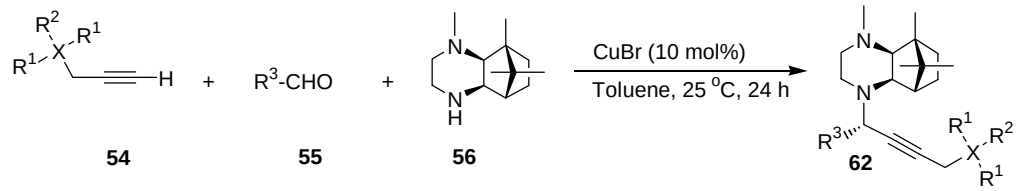
62ba *(R)*-**59ba**

S.No.	Solvent	Temp	MX_n	Equiv.	Time	Yield(%)[b]	Ee(%
1	Toluene	120	ZnI_2	0.5	1	75	89
2	Toluene	120	$ZnBr_2$	0.5	2	72	93
3	Toluene	120	$ZnCl_2$	0.5	12	51	99
4	CH_3CN	50	$AgNO_3$	0.5	24	35	99
5	Toluene	120	CuI	0.5	12	25	98
6	Toluene	120	CuBr	0.5	12	19	99
7	Toluene	120	CuCl	0.5	12	5	99
8	Dioxane	100	CuI	0.5	18	39	99

[a]The reactions were carried out by using propargylamines **62ba** (1 mmol) in solvent (3 mL). [b]Yields are isolated [c]The % ee was confirmed by HPLC analysis on chiralcel AS-H.

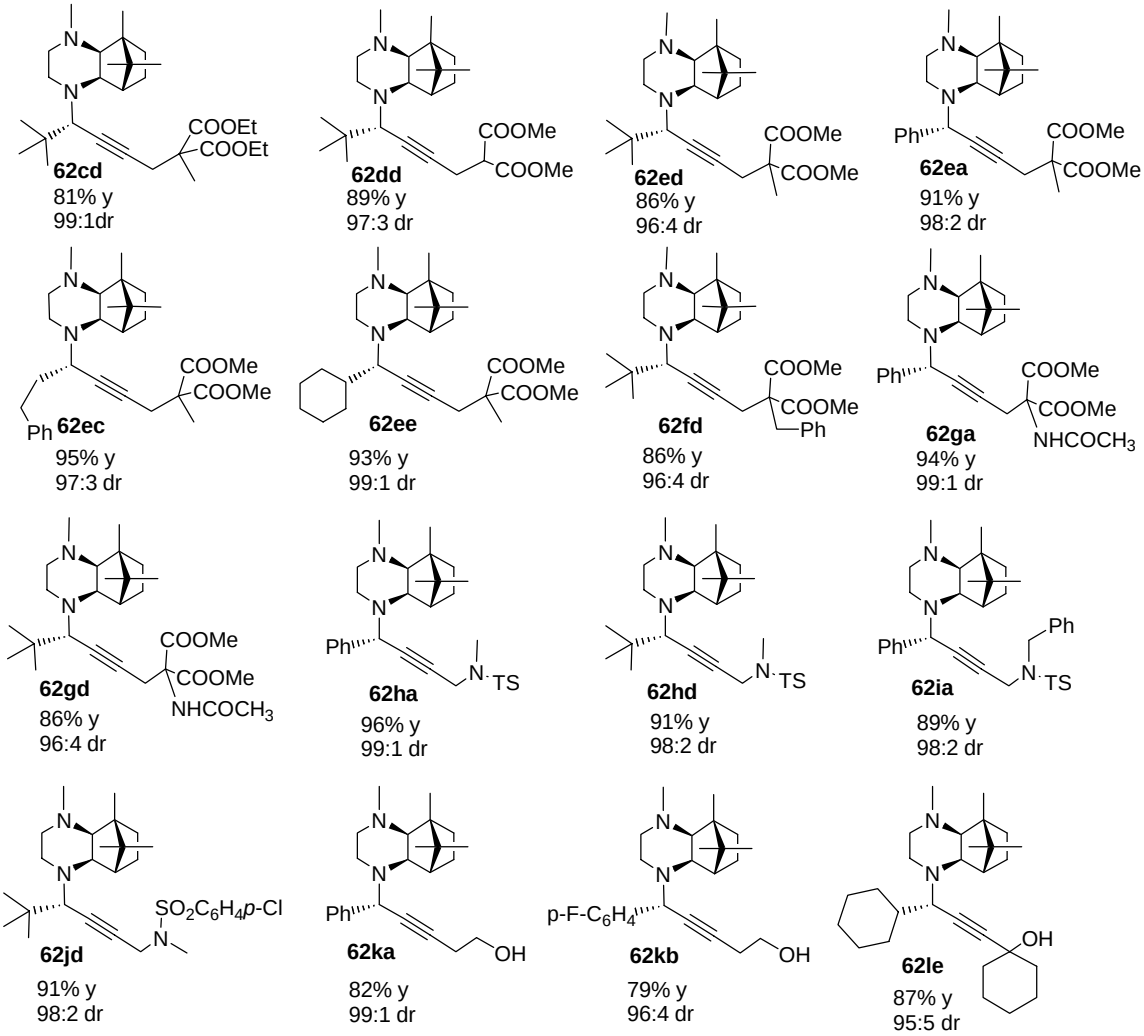
We have also observed that poor substrate conversion using CuCl, CuBr and CuI. In these cases, the (*R*)-**59ba** allene was obtained only in 5-39% yield with 99% ee. Similarly, the allene (*R*)-**59ba** was obtained in 35% yield with 99% ee when $AgNO_3$ used. The zinc halides gave the allene in 51-79% yield with 89-99% ee. It is evident from the Table **1**, that $ZnBr_2$ (0.5 mmol) gave optimum results (72% yield with 93% ee). Following this optimized reaction condition (Table **1**, entry **2**), we have synthesized various functionalized propargylamines. The results are summarized in Table **2**.

Table 2 Diastereoselective synthesis of propargylamines **62** using chiral amine **56**, with different aldehydes **55**, and 1-alkynes **54** in the presence of copper bromide.[a, b, c]



54 **55** **56** **62**

54c = (X= C, R^1 = COOEt, R^2 = Me)
54d= (X= C, R^1 = COOMe, R^2 = H)
54e= (X= C, R^1 = COOMe, R^2 = Me)
54f = (X= C, R^1 = COOMe, R^2 = benzyl)
54g= (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$)
54h= (X= N, R^1 = tosyl, R^2 = Me)
54i= (X= N, R^1 = tosyl, R^2 = benzyl)
54j= (X= N, R^1 = $SO_2C_6H_4$-*p*-Cl, R^2 = Me)
54k= (X= C, R^1 = H, R^2 = OH)
54l = (X= C, R^1 = $-(CH_2)_5-$, R^2 = OH)
55a = PhCHO
55b = *p*-F-C_6H_4CHO
55c = $PhCH_2CH_2CHO$
55d = *t*-BuCHO
55e = *c*-$C_6H_{11}CHO$



[a]The reactions were carried out by using amine **56 (**1.0 mmol), 1-alkyne (1.1 mmol) and aldehyde (1.0 mmol) in toluene (3 mL) with CuBr (0.1 mmol) and MS (1.0 g, 4Å) at 25°C for 24 h. [b]dr ratio based on crude ^{1}H NMR. [c]Isolated yield.

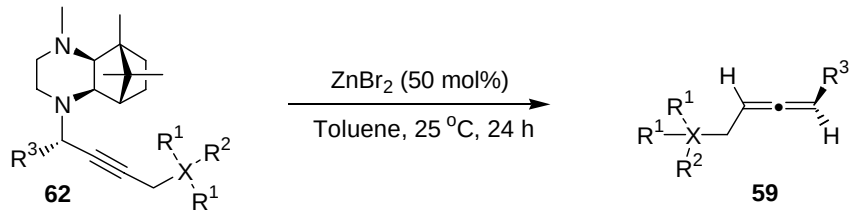
3.2.2 Further scope of the reaction using sensitive substrates

The alkynes containing ester, amides and alcohols groups are compatible with the present reaction conditions **(54c–54l**). The chiral piperazine **56** reacted with diethyl 2-(prop-2-ynyl)malonate **54c** and *t*-butyraldehyde **55d** to give the corrsponding propargylamine **62cd** in 81% yield with up to 99:1dr (Table **2**). The reaction of chiral piperazine **56** with *t*-butyraldehyde **55d** and dimethyl propargylmalonate **54d** yielded the product **62dd** in 89% with 97:3 dr. The reaction is also applicable to substituted dimethyl propargylmalonate as illustrated by reactions using the alkynes **54e, 54f** which react with the aldehydes like **55a, 55c, 55d,** and **55e** to give the corresponding chiral propargylamines **62ea, 62ec, 62ed** and **62ee** in 85-92% yields with excellent diasteroselectivity (Table **2**). The 1-alkyne like diethyl 2-acetamido-2-propargylmalonate **54g** reacts with the aldehydes like **55a, 55d** to give the corresponding propargylamine **62ga, 62gd** in 86-94% yields with 96:4, 99:1 dr ratio respectively. We have observed that the reaction of N-tosyl alkyne **54h** reacts with the aldehydes like **55a, 55d** to give the corresponding propargylamines **62ha, 62hd** in 91-96% yields with good diastereoselectivity (Table **2**).

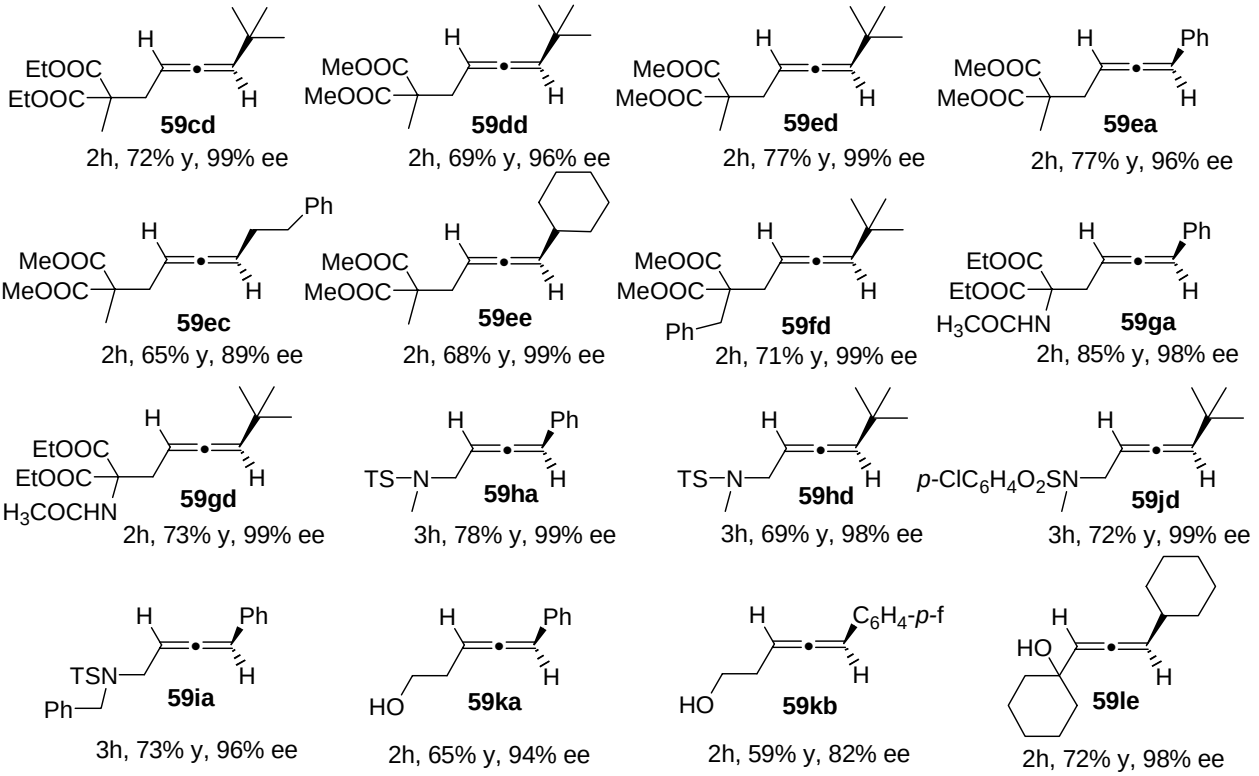
Next, we have examined the conversion of the propargylamine derivatives to the chiral allenes by following the conditions optimised for **62ba** (Table **1**, entry **2**). We have observed that the reaction of ester derivatives of propargylamines (**62cd-62fd**) with $ZnBr_2$ gave the (*R*)-allene **59cd-59fd** in 65-77% yields with 90-99% ee (Table **3**). Similar results were observed with amide derivatives of propargylamines **62ga** and **62gd** in 73-85% yields with 99% ee. Moderate yields and ee's were realized in the reaction with alcohol derivatives (Table **3**). All the optically active allenes obtained by using N-methylcamphanyl piperazine **56** are levorotatory, from which the absolute configurations of the major enantiomer of the

allenes are assigned as *R* by the Lowe-Brewster rule and also comparison with reported $[\alpha]_D^{25}$ values.[21]

Table **3**. $ZnBr_2$ promoted synthesis of chiral allenes from chiral propargylamines.[a,b,c,]



62cd = (X= C, R^1 = COOEt, R^2 = Me, R^3 = *t*-BuCHO)
62dd = (X= C, R^1 = COOMe, R^2 = H, R^3 = *t*-BuCHO)
62ed = (X= C, R^1 = COOMe, R^2 = Me, R^3 = *t*-BuCHO)
62ea = (X= C, R^1 = COOMe, R^2 = Me, R^3 = PhCHO)
62ec = (X= C, R^1 = COOMe, R^2 = Me, R^3 = $Ph(CH_2)_2CHO$)
62ee = (X= C, R^1 = COOMe, R^2 = Me, R^3 = *c*-$C_6H_{11}CHO$)
62fd = (X= C, R^1 = COOMe, R^2 = benzyl, R^3 = *t*-BuCHO))
62ga = (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$, R^3 = PhCHO)
62gd = (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$, R^3 = *t*-BuCHO)
62ha = (X= N, R^1 = tosyl, R^2 = Me, R^3 = PhCHO)
62hd = (X= N, R^1 = tosyl, R^2 = Me, R^3 = *t*-BuCHO)
62jd = (X= N, R^1 = $SO_2C_6H_4$-*p*-Cl, R^2 = Me, R^3 = *t*-BuCHO)
62ia = (X= N, R^1 = tosyl, R^2 = benzyl, R^3 = Ph)
62ka = (X= C, R^1 = H, R^2 = CH_2OH, R^3 = PhCHO)
62kb = (X= C, R^1 = H, R^2 = CH_2OH, R^3 = *p*-F-C_6H_4CHO)
62le = (X= C, R^1 = -$(CH_2)_5$-, R^2 = OH, R^3 = *c*-$C_6H_{11}CHO$)

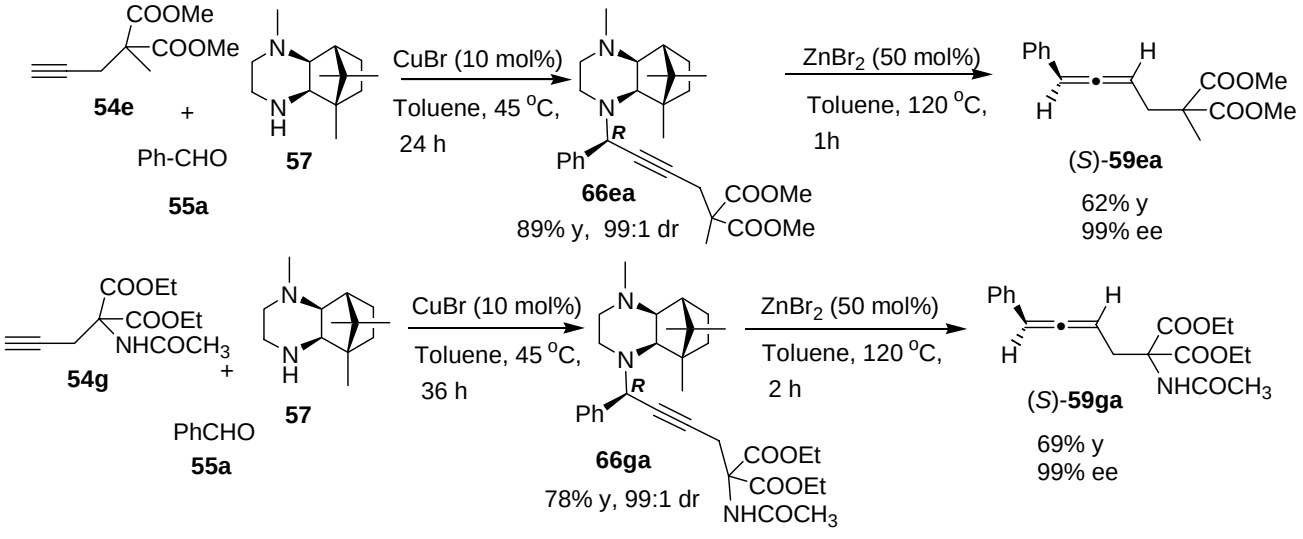


[a]The reactions were carried out by using propargylamine **62** in toluene (3 mL) with $ZnBr_2$ (0.5 mmol)..
[b]Isolated yield. [c] ee determine by using chiral HPLC.

However, when the reaction was performed with chiral piperazine **57**, with diethyl 2-acetamido-2-propargylmalonate **54g** and benzaldehyde **55a,** the desired propargylamine **66ga** was isolated only in 27% yield even after prolonged reaction time 48h. Also, it was noticed that the chiral piperazine **57** reacts with a substituent alkyne **54e** and aldehyde **55a** to give the corresponding propargylamine **66ea** with very low yield. From these observations, it is apparent that the lower reactivity may be due to the steric hindrance between the $\mathbf{C_{10}}$ methyl group of camphanyl piperazine **57** and the substituent groups in the alkyne partner. Fortunately, this surprise seems to be correct as when the reaction mixture was heated at 45 °C for 24 hours and the propargylamine product **66ea** was obtained in 89% yield in 99:1 dr (Scheme **16**).

We have also carried out the conversion of chiral propargylamine derivatives **66ga** which obtained from piperazine **57** to the corresponding chiral allenes (*S*)-**59ga.** The results are summarized in Scheme **16**. The optically active allenes obtained by using the N-methylcamphanyl piperazine **57** were dextrorotatory from which the absolute configurations of the major enantiomer of the chiral allenes are assigned as *S* by the Lowe-Brewster rule and also comparison with reported $[\alpha]_D^{25}$ values.[21]

Scheme 16



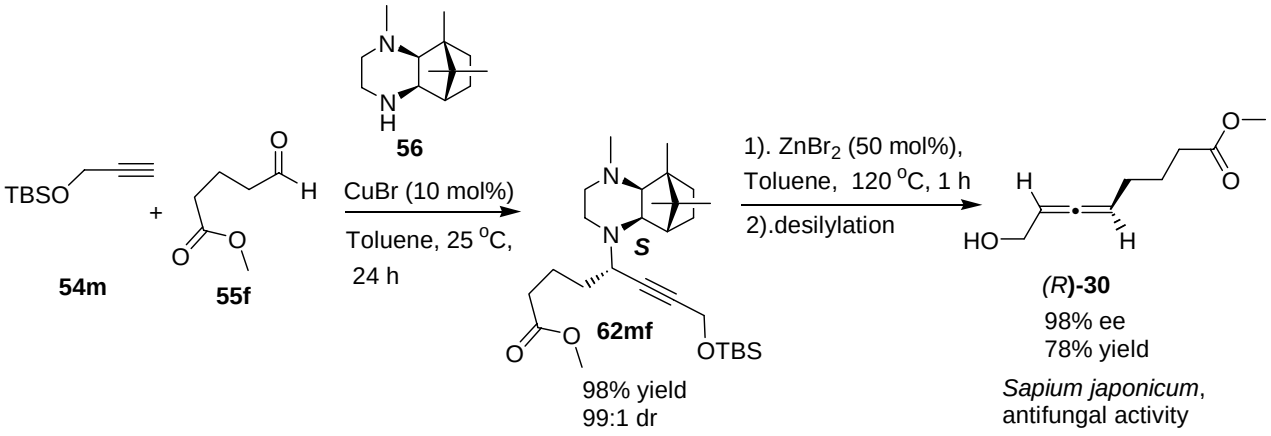
3.2.3 Effort towards the synthesis of biologically active chiral allenes

A). Synthesis of Sapium japonicum **30**:

As outlined in the introduction section, some of the naturally occurring 1,3-disubstituted functionalized chiral allenic compounds are highly biologically active. Therefore, we turned our attention towards the synthesis of naturally occurring allenes by applying our methodology. So far, none of the biologically active allenes were synthesized using chiral propargylamine as precursors. Initially, we have chosen Sapium japonicum as an antifungal agent.[9] There are several synthetic approaches reported for synthesis of this allene in racemic as well as in enantiomerically pure form involving S_N2 reaction, Claisen rearrangement and 1,2-elimination of alkenyl halides (Scheme **5**).

We have observed that the chiral piperazine **56** reacts with 5-oxo-pentanoic acid methyl ester **55f** and TBS alkyne **54m** in the presence of 10mol% CuBr to give the chiral propargylamine derivate **62mf** in 98% yield with 99:1 dr which upon reaction with $ZnBr_2$ followed by desilylation afforded the (*R*)-**30** in 78% yield with 98% ee. (Scheme **17)**.

Scheme 17

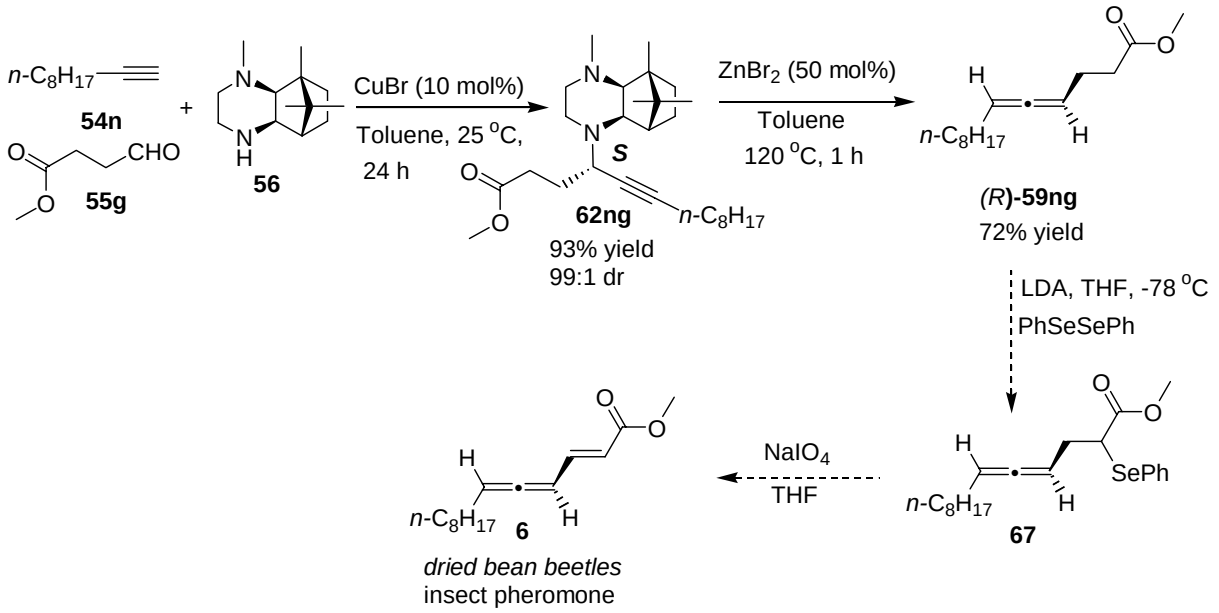


It is of interest to note that the compound (*R*)-**30** has been previously synthesized by a multistep operation with low enantioselectivity.[11f]

B). Synthesis of methyl (*R*,*E*)-2,4,5-tetradecatrienoate **6**:

Methyl (*R*,*E*)-2,4,5-tetradecatrienoate **6** is a pheromone component of the male dried bean beetle. We have observed that the chiral piperazine **56** reacts with 1-decyne **54n** and 4-oxo-butyric acid methyl ester **55g** in presence of CuBr in toluene to give the chiral propargylamine derivative **62ng** in 93% yield with 99:1 dr. This propargylamine intermediate **62ng** does react with $ZnBr_2$ to give the (*R*)-**59ng** allene in 72% yield (Scheme **18)**. Unfortunately, chiral HPLC columns available with us failed to separate the enantiomers of **59ng**. However, comparison of the optical rotation of $[\alpha]_D^{25}$ =-61.5 (c 0.73, hexane) observed for the product (*R*)-**59ng** (Scheme **18**) with the reported rotation of $[\alpha]_D^{25}$ = -63.3 (c 2.07, hexane) indicates that its purity in ≤ 93% ee. The chiral allene (*R*)-**59ng** has been previously converted to the pheromone **6** in two steps (Scheme **18**).[11e]

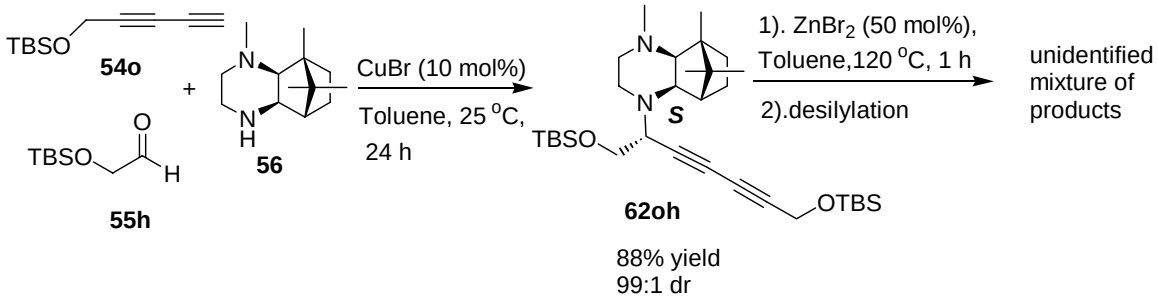
Scheme 18



c). Attempted synthesis of Scorodonin analogue **1**:

Scorodonin **1** a natural allenyne has significant antibacterial and antifungal activities. The reported synthetic approach for this allene involves the cross coupling between the alkynylzinc **10** with bromoallene **11,** and 1,2-elimination of optically-active sulfoxide-allylic acetates (Scheme **1** and Scheme **2**). We have envisaged the synthesis via chiral camphanyl propargylamine synthesis as outlined in Scheme **19**. Indeed, we have observed that the chiral piperazine **56** reacts with the TBS aldehyde **55h** and TBS alkyne **54o** in the presence of 10mol% CuBr in toluene to give chiral propargylamine derivate **62oh** in 88% yield with 99:1 dr. Unfortunately, the reaction of propargylamine **62oh** reacts with $ZnBr_2$ at 120 °C gave only unidentified mixture of products (Scheme **19).**[7c]

Scheme 19



Further systematic studies on the conversion of the intermediate **62oh** at lower temperatures may give fruitful results.

3.3 Conclusions

We have developed a method for the synthesis of highly functionalized chiral allenes from chiral propargylamine derivatives, obtained in the CuBr promoted diastereoselective synthesis of chiral N-methylcamphanyl piperazine derivatives **56** and **57**. These chiral propargylamine derivatives are converted into chiral allenes using zinc bromide in high enantiomeric purities.

We have synthesized naturally occurring functionalized chiral allene (*R*)-**30** by using our "chiral amine approach". The methods described here have considerable potential in accessing biologically active chiral allenes via the corresponding chiral propargylamines.

3.4 Experimental Section

3.4.1 General information

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

Analytical grade of CuBr, Cu(OTf) and ZnI_2 were purchased from Sigma-Aldrich. $ZnBr_2$, $ZnCl_2$ was purchased from E-Merck. Toluene supplied by E-Merck, India was freshly distilled over sodium-benzophenone ketyl before use. Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250mμ E-Merck and acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized

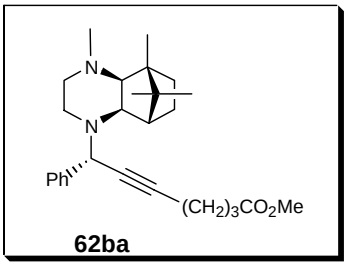
by short exposure to iodine vapour or UV light. Column chromatography was carried out using E-Merck and acme's silica gel (100-200 or 230-400 mesh) and neutral alumina.

Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{o}$) and AUTOPOL-IV (readability $\pm 0.001^{o}$) automatic polarimeters. HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument.

3.4.2. Reaction of 1-alkyne, aldehyde and amine 56 with CuBr: Synthesis of chiral propargylamine 62

To a stirred suspension of chiral piperazine **56** (0.210 g, 1 mmol), CuBr (0.015 g, 10 mmol) and 1-alkyne **54** (1.1 mmol) in toluene (3 mL), freshly distilled aldehyde **55** (1 mmol) was added at 25 °C. The contents were stirred at 25 °C for 24 h. Toluene was removed; water (5 mL) and DCM (15 mL) were added. The DCM layer was washed with saturated NaCl solution, dried with (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (100-200 mesh) using hexane and ethyl acetate (9:1) as eluent to isolate the propargyl amine **62**

7-Phenyl-7-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hept-5-ynoic acid ethyl ester (62ba):



62ba

Yield **:** 0.413 g, 98%, yellow liquid.

$[\alpha]_D^{25}$ **:** -51.2 (*c* 0.43, $CHCl_3$).

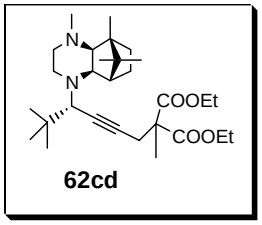
IR (neat) **:** 2951, 2874, 2793, 2762, 2704, 1739, 1660, 1601, 1531, 1493, 1450, 1338, 1367, 996, 773 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.61-7.59 (d, *J*=7.0Hz, 2H), 7.32-7.23 (m, 3H), 5.00 (s, 1H), 3.70-3.69 (s, 3H), 3.0-2.98 (d, *J*=8.0Hz, 1H), 2.72-2.66 (m, 1H), 2.55-2.41 (m, 5H), 2.27 (s, 3H), 2.14-2.17 (m, 2H), 1.94-1.91 (m, 3H), 1.80-1.73 (m, 2H), 1.43 (s, 3H), 1.26-1.16 (m, 3H), 1.03 (s, 3H), 0.85 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 171.4,139.0, 129.7, 129.0, 128.2, 127.9, 127.1, 82.4, 79.0, 78.2, 65.3, 57.5, 54.3, 53.5, 52.8, 48.1, 47.3, 47.2, 42.5, 37.2, 26.5, 26.1, 22.2, 20.2, 14.7.

HRMS **:** (ESI): calcd for $C_{27}H_{38}N_2O_4$: 422.2933 [M+H^+]; found: 423.3085.

2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-2-methyl-malonic acid diethyl ester (62cd):



62cd

Yield **:** 0.396 g, 81%, yellow liquid.

$[\alpha]_D^{25}$ **:** -52.1 (*c* 0.35, $CHCl_3$).

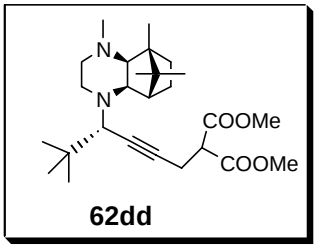
IR (neat) **:** 2951, 2879, 2793, 2798, 1738 1599, 1456, 1365, 1294, 1246, 1194, 1107, 1022, 996, 891 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 4.21-4.16 (m, 1H), 3.07 (s, 1H), 2.80-2.58 (m, 6H), 2.24(s, 3H), 2.18-2.10 (m, 2H), 1.55 (m, 5H), 1.25-1.23 (m, 10H), 0.96 (s, 3H), 0.93 (s, 9H), 0.76 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 171.0, 80.9, 79.9, 66.3, 65.9, 61.7, 61.4, 54.4, 53.4, 49.9, 49.6, 48.8, 47.0, 45.7, 36.9, 36.1, 28.3, 26.2, 25.8, 22.0, 20.6, 19.9, 14.2, 14.0.

HRMS **:** (ESI): calcd for $C_{29}H_{48}N_2O_4$: 488.3614 [M+H^+]; found: 489.3692.

2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester (62dd):



62dd

Yield : 0.383 g, 89%, yellow liquid.

$[\alpha]_D^{25}$ **:** -43.6 (*c* 0.40, $CHCl_3$).

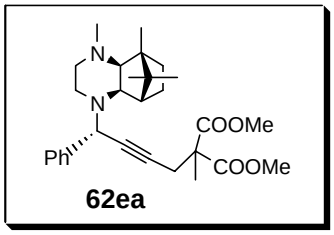
IR (neat) **:** 2953, 2874, 1743, 1437, 1450, 1388, 1365, 1325, 1292, 1211, 1057, 804 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 3.76 (s, 6H), 3.07 (s, 3H) 3.02-3.01 (d, *J*=4Hz, 2H), 2.92-2.80 (m, 2H), 2.79-2.68 (m, 2H), 2.62-2.57 (m, 2H), 2.25 (s, 3H), 2.19-2.13 (m, 2H), 2.04-2.02 (t, *J*=5.3Hz, 1H), 1.58-1.53 (m, 2H), 1.46-1.40(m, 1H), 1.24 (s, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.77 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 169.3, 81.6, 78.9, 78.5,77.7,71.6, 66.3, 66.0, 56.7, 54.5, 53.0, 49.9, 49.6,48.8, 47.0, 45.8, 36.9, 36.1, 28.2, 25.8, 23.1,22.8, 22.0, 20.0, 14.3.

HRMS **:** (ESI): calcd for $C_{26}H_{42}N_2O_4$: 446.3145 [M+K^+]; found: 485.3374

2-Methyl-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid dimethyl ester (62ea):



62ea

Yield : 0.436 g, 91%, yellow liquid.

$[\alpha]_D^{25}$ **:** -50.7 (*c* 0.52, $CHCl_3$).

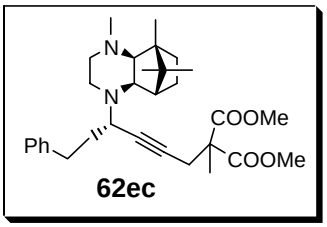
IR (neat) **:** 2953, 2878, 2798, 2798, 2766, 2704, 1738 1668, 1601, 1537, 1452, 1388, 1292, 1249, 1203, 1109, 1028, 997, 856 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.57-7.54 (d, *J*=12.0Hz, 2H), 7.30-7.23 (m, 3H), 4.99 (s, 1H), 3.76-3.70 (s, 6H), 2.98-2.94 (d, *J*=16.0Hz, 3H), 2.48-2.42 (m, 1H), 2.27-2.18 (m, 6H), 1.63 (m, 3H), 1.47-1.43 (m, 4H), 1.20-1.13 (m, 2H), 1.03 (s, 3H), 0.84 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 171.4, 139.0, 129.7, 129.0, 128.1, 127.9, 82.3, 79.0, 78.2, 65.3, 57.5, 54.3, 53.5, 52.8, 50.3, 48.1, 47.3, 47.2, 42.5,37.2, 26.4, 26.1, 22.2, 21.2, 20.2, 14.6.

HRMS **:** (ESI): calcd for $C_{29}H_{40}N_2O_4$: 480.2988 [M+H^+]; found: 481.3066.

2-Methyl-2-[6-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester (62ec):



62ec

Yield : 0.482 g, 95%, yellow liquid.

$[\alpha]_D^{25}$ **:** -48.1 (*c* 0.60, $CHCl_3$).

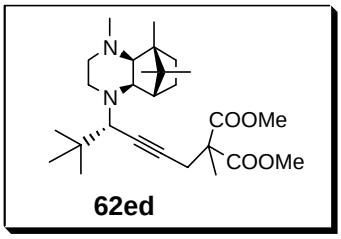
IR (neat) **:** 3296, 2951, 2874, 2795, 1743, 1666, 1533, 1454, 1388, 1365, 1288, 1248, 1211, 1132, 1066, 1018, 966 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.29-7.27 (m, 2H), 7.19-7.17 (m, 3H), 3.59-3.55 (t, *J*=16.0Hz, 1H), 2.82 (s, 2H), 2.79-2.57 (m, 5H), 2.28 (s, 3H), 2.19-2.09 (m, 2H), 1.86-1.80 (q, *J*=24.0Hz, 2H), 1.73-1.61 (m, 3H), 1.55 (s, 3H), 1.46-1.39 (m, 2H), 1.26 (s, 3H), 1.15-1.05 (m, 2H), 0.99 (s, 3H), 0.76 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 171.4, 142.1, 128.4, 128.3, 125.7, 81.9, 79.1, 78.7, 64.7, 54.5, 53.5,53.3, 52.8, 50.0, 48.2, 47.3, 47.1, 42.0, 37.2, 35.5, 32.8, 26.3, 25.8, 22.1, 20.9, 20.0, 14.6.

HRMS **:** (ESI): calcd for $C_{31}H_{44}N_2O_4$: 508.3301 [M+H^+]; found: 509.3652.

2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-2-methyl-malonic acid dimethyl ester (62ed):



62ed

Yield : 0.396 g, 86%, yellow liquid.

$[\alpha]_D^{25}$: -39.7 (*c* 0.32, $CHCl_3$).

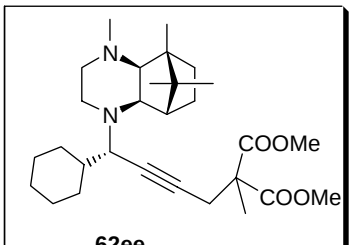
IR (neat) : 3306, 2951, 2874, 2795, 2762, 1739, 1666, 1533, 1454, 1388, 1365, 1294, 1249, 1203, 1111, 1018, 997, 871 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 3.73 (s, 6H), 3.07 (s, 1H), 2.86 (s, 2H), 2.80-2.70 (m, 3H), 2.63-2.53 (m, 2H), 2.25 (s, 2H), 2.19-2.09 (m, 3H), 1.72-1.69 (m, 2H), 1.57 (s, 3H), 1.25 (s, 3H), 1.08-1.01 (m, 2H), 0.96 (s, 1H), 0.93 (s, 9H), 0.76 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 171.5, 81.0, 79.7, 77.7, 66.3, 65.9, 54.5, 53.5, 52.7, 49.9, 49.6, 48.8, 47.0, 45.7, 36.9, 36.1, 28.2, 26.4, 25.8, 22.6, 22.0, 20.6, 20.1, 14.2.

HRMS : (ESI): calcd for $C_{27}H_{44}N_2O_4$: 460.3301 [M+H^+]; found: 461.3378.

2-[4-Cyclohexyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-2-methyl-malonic acid dimethyl ester (62ee):



62ee

Yield : 0.451 g, 93%, yellow liquid.

$[\alpha]_D^{25}$: -36.923 (*c* 0.54, $CHCl_3$).

IR (neat) : 3302, 2947, 2851, 2795, 2764, 2702, 1739, 1657, 1535, 1450, 1388, 1377, 1317, 1292, 1249, 1201, 1109, 1022, 997, 817 cm^{-1}.

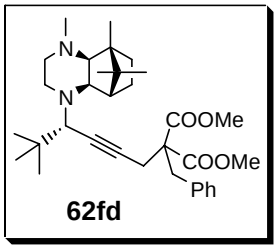
^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 3.72 (s, 6H), 3.13-3.10 (d, J=12.0Hz, 1H), 2.82-2.66 (m, 5H), 2.51-2.46 (m, 1H), 2.25 (s, 3H), 2.16-1.88 (m, 3H),

1.72-1.69 (m, 2H), 1.54 (s, 3H), 1.43-1.41 (d, *J*=8.0Hz, 2H), 1.25-1.23 (m, 7H), 1.14-1.08 (m, 3H), 0.97 (s, 1H), 0.89-0.83 (m, 4H), 0.76 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 171.5, 81.7, 79.2, 78.5, 64.6, 60.2, 54.5, 53.5, 52.7, 50.0, 48.4, 47.6,47.1, 42.2, 40.6, 37.2, 34.6, 31.6, 30.5, 26.7, 26.3, 26.2, 25.9, 22.6, 22.1, 20.9, 20.1, 14.6.

HRMS **:** (ESI): calcd for $C_{29}H_{46}N_2O_4$: 486.3458 [M+H^+]; found: 487.3536.

2-Benzyl-2-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester (62fd):



62fd

Yield : 0.469 g, 86%, yellow liquid.

$[\alpha]_D^{25}$ **:** -39.7 (*c* 2.5, $CHCl_3$).

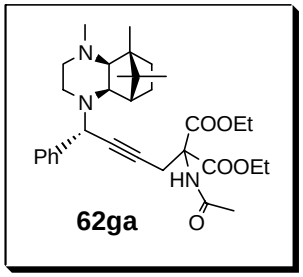
IR (neat) **:** 2951, 2874, 2795, 1743, 1666, 1533, 1454, 1388, 1377, 1365, 1288, 1248, 1211, 1132, 1066, 1018, 966, 889 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.27-7.24 (t, *J*=12.0Hz, 3H), 7.18-7.16 (d, *J*=8.0Hz, 2H), 3.73 (s, 6H), 3.42 (s, 2H), 3.18 (s, 1H), 3.10-2.93 (dd, *J*=24.0Hz, 1H), 2.83-2.79 (m, 3H), 2.26 (s, 2H), 2.60-2.58 (m, 3H), 2.26 (s, 3H), 1.72-1.53 (m, 3H), 1.47-1.41 (m, 2H), 1.27 (s, 3H), 1.00 (s, 9H) 0.78 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 170.2, 135.7, 129.8, 128.4, 127.1, 82.0, 79.9, 77.8, 66.3, 66.0, 58.5, 54.6, 52.6, 50.0, 49.6,48.8, 47.0, 45.8, 37.6, 36.9, 36.2, 28.4, 25.9, 22.6, 22.0, 14.6.

HRMS **:** (ESI): calcd for $C_{33}H_{48}N_2O_4$: 536.3614 [M+H^+]; found: 537.3691.

2-Acetylamino-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid diethyl ester (62ga):



62ga

Yield : 0.517 g, 94%, yellow liquid.

$[\alpha]_D^{25}$: -19.2 (*c* 0.53, $CHCl_3$).

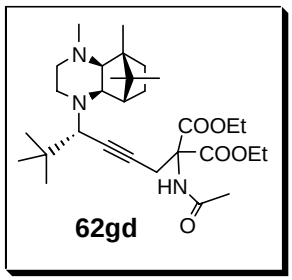
IR (neat) : 3420, 3302, 3061, 2951, 2876, 2795, 2760, 1749, 1684, 1601, 1494, 1450, 1388, 1369, 1302, 1205, 1128, 1057, 854, 734 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.53-7.52 (d, *J*=4.0Hz, 2H), 7.32-7.20 (m, 2H), 6.98 (m, 1H), 4.95 (s, 1H), 4.30-4.25 (q, *J*=20.0Hz, 4H), 4.13-4.08 (m, 1H), 2.92-2.90 (d, *J*=8.0Hz, 1H), 2.72-2.62 (m, 1H), 2.47-2.40 (m, 1H), 2.26 (s, 3H), 2.18-2.16 (d, *J*=8.0Hz, 1H), 2.07 (s, 3H), 2.03-2.02 (d, *J*=4.0Hz, 3H), 1.87-1.86 (d, *J*=4.0Hz, 1H), 1.45 (s, 3H), 1.29-1.23 (m, 12H), 1.02 (s, 3H), 0.83 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 169.1,166.8, 138.8, 129.0, 128.0, 127.9, 127.2, 81.4, 79.2, 78.2, 65.5, 65.3, 62.9, 60.3, 57.5, 54.4, 50.3, 48.2, 47.3, 42.5, 37.2, 26.3, 24.2, 23.0, 22.1, 14.6, 14.2, 14.0.

HRMS : (ESI): calcd for $C_{32}H_{45}N_3O_5$: 551.3359 [M+H^+]; found: 552.3447.

2-Acetylamino-2-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid diethyl ester (62gd):



62gd

Yield : 0.456 g, 86%, yellow liquid.

$[\alpha]_D^{25}$: -16.5 (*c* 0.45, $CHCl_3$).

IR (neat) : 3498, 3298, 2953, 2874, 2795, 2764, 1736,

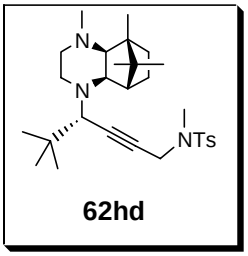
1689, 1653, 1535, 1456, 1388, 1377, 1367, 1294, 1246, 1194, 1024, 862 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 6.91 (s, 1H), 4.29-4.25 (m, 4H), 3.15-3.02 (m, 2H), 3.03-3.01 (m, 1H), 2.92-2.82 (m, 1H), 2.76-2.59 (m, 3H), 2.25 (s, 3H), 2.17-2.08 (m, 2H), 2.06 (s, 3H), 1.66-1.60 (m, 1H), 1.57-1.56 (m, 1H), 1.47-143 (m, 1H), 1.29-1.24 (m, 10H), 0.97 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 168.9, 166.9, 81.2, 78.7, 77.7, 66.2, 65.6, 62.9,62.8, 54.6, 49.9, 49.5, 48.8, 47.0, 45.7, 36.9, 36.0, 28.2, 25.8, 24.1, 23.0, 22.1, 20.6, 14.2.

HRMS : (ESI): calcd for $C_{30}H_{49}N_3O_5$: 531.3672 [M+H^+]; found: 532.3750.

N-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-4,N-dimethyl-benzenesulfonamide (62hd):



62hd

Yield : 0.454 g, 91%, yellow liquid.

$[\alpha]_D^{25}$: -40.8 (*c* 0.40, $CHCl_3$).

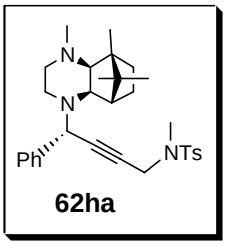
IR (neat) : 2947, 2794, 1600, 1457, 1353, 1167, 926, 821, 754 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.72-7.70 (d, *J*=8.0Hz, 2H), 7.30-7.28 (d, *J*=8.0Hz, 2H), 4.12 (s, 1H), 2.94 (s, 1H), 2.86 (s, 3H), 2.67-2.65 (d, *J*=8.0Hz, 1H), 2.57-2.49 (m, 2H), 2.41 (s, 3H), 2.31 (s, 3H), 2.14-2.11 (d, *J*=12.0Hz, 1H), 2.06-1.98 (m, 2H), 1.68-1.59 (m, 1H), 1.51-1.50 (d, *J*=4.0Hz, 1H), 1.44-1.40 (m, 1H), 1.21 (s, 3H), 0.82 (s, 9H), 0.76 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 143.4, 134.5, 129.6, 127.7, 84.3, 77.5, 66.2, 66.0, 54.5, 49.5, 49.5, 48.7, 45.7, 40.1, 36.8, 36.0, 34.3, 31.6, 28.2, 25.8, 22.6, 22.0, 21.5, 20.6.

HRMS **:** (ESI): calcd for $C_{29}H_{45}N_3O_2S$: 499.3232[M+H^+]; found: 500.3302.

4,N-Dimethyl-N-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-benzenesulfonamide (62ha):



62ha

Yield : 0.498 g, 96%, yellow liquid.

$[\alpha]_D^{25}$ **:** -54.2 (*c* 0.45, $CHCl_3$).

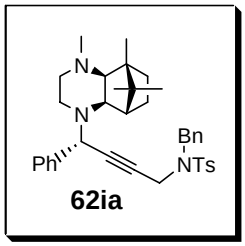
IR (neat) **:** 3057, 3030, 2958, 2871, 1665, 1600, 1446, 1446, 1336, 1167, 1084, 1024, 926, 816, 734 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.71-7.69 (d, J=8.0Hz, 2H), 7.36-7.34 (m, 2H), 7.33-7.21 (m, 3H), 7.19-7.17 (d, J=8.0Hz, 2H), 4.80 (s, 1H), 4.21 (s, 2H), 2.89 (s, 3H), 2.78-2.76 (d, J=8.0Hz, 1H), 2.71-2.66 (m, 1H), 2.41 (s, 1H), 2.28 (s, 5H), 2.18-2.16 (d, J=8.0Hz, 1H), 2.06-1.96 (m, 2H), 1.78 (s, 2H), 1.44-142 (m, 6H), 1.24-1.22 (m, 2H), 1.19-1.09 (m, 3H), 1.03 (s, 4H), 0.82 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 143.5, 138.2, 134.3, 129.5, 128.5, 128.0, 127.9, 127.8, 127.2, 126.9, 82.2, 79.8, 78.1, 65.4, 57.5, 54.2, 52.9, 50.3, 48.0, 47.3, 47.1, 46.6, 4.9, 44.8, 42.6, 40.2, 37.1, 34.4, 32.4, 26.2, 24.5, 22.1, 21.5, 21.1, 20.4, 17.5, 14.6.

HRMS **:** (ESI): calcd for $C_{31}H_{41}N_3O_2S$: 519.2919 [M+H^+]; found: 550.2953

N-Benzyl-4-methyl-N-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-benzenesulfonamide (62ia):



62ia

Yield : 0.549 g, 89%, yellow liquid.

$[\alpha]_D^{25}$: -42.7 (*c* 0.80, $CHCl_3$).

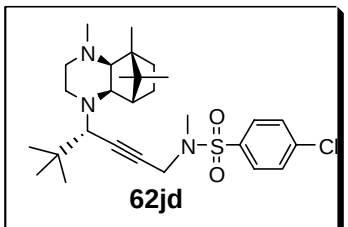
IR (neat) : 3063, 3030, 2953, 2876, 1704, 1600, 1493, 1452, 1374, 1167, 1096, 926, 898, 739 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.82-7.80 (d, *J*=8.0Hz, 2H), 7.42-7.32 (m, 6H), 7.28-7.26 (m, 3H) 7.18-7.16 (d, *J*=8.0Hz, 2H), 4.79 (s, 1H), 4.47-4.45 (d, *J*=8.0Hz, 2H), 4.19-4.17 (d, *J*=8.0Hz, 2H), 2.82-2.81 (d, *J*=4.0Hz, 1H), 2.65-2.58 (m, 1H), 2.36-2.31 (m, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.15-2.13 (d, *J*=8.0Hz, 1H), 2.03-1.98 (m, 2H), 1.76 (s, 2H), 1.44 (s, 3H), 1.21-1.14 (m, 1H), 1.03 (s, 3H), 0.85 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 143.5, 138.2, 134.3, 129.5, 128.0, 127.9, 127.8, 127.2, 126.9, 82.2, 79.8, 78.1, 65.4, 57.5, 54.2, 52.8, 50.3, 48.0, 47.3, 47.1, 46.6, 44.9, 44.8, 42.6, 37.1, 34.4, 32.0, 26.2, 24.5, 22.1, 21.5, 21.1, 20.4, 14.6.

HRMS : (ESI): calcd for $C_{37}H_{45}N_3O_2S$: 595.3232 [*M*+Na^+]; found: 618.3133.

4-Chloro-N-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-N-methyl-benzenesulfonamide (62jd):



62jd

Yield : 0.472 g, 91%, yellow liquid.

$[\alpha]_D^{25}$: -31.7 (*c* 0.40, $CHCl_3$).

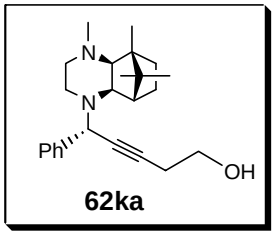
IR (neat) **:** 2942, 2876, 2794, 1589, 1479, 1397, 1353, 1161, 1095, 1013, 980, 926, 767, 728 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.79-7.78 (d, *J*=4.0Hz, 2H), 7.49-7.48 (d, *J*=4.0Hz, 2H), 4.61 (s, 1H), 4.15 (s, 2H), 2.93 (s, 1H), 2.88 (s, 3H), 2.84-2.79 (m, 1H), 2.66-2.61 (m, 4H), 2.53-2.48 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H), 2.04-1.98 (m, 2H), 1.72-1.63 (m, 1H), 1.52-1.51 (d, *J*=4.0Hz, 2H), 1.48-1.41 (m, 1H), 1.21(s, 3H), 0.97 (s, 4H), 0.82 (s, 9H), 0.76 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 139.2, 137.3, 136.1, 129.4, 129.3, 129.1, 128.7, 77.3, 66.4, 65.9, 54.4, 50.0, 49.4, 48.7, 47.0, 45.7, 40.1, 36.8, 36.0, 34.2, 29.3, 28.2, 25.9, 21.9, 20.6, 14.2.

HRMS **:** (ESI): calcd for $C_{28}H_{42}ClN_3O_2S$: 519.2686 [M+H^+]; found: 520.2764.

4-Phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-yn-1-ol (62ka):



62ka

Yield : 0.299 g, 82%, yellow liquid.

$[\alpha]_D^{25}$ **:** -49.4 (*c* 0.80, $CHCl_3$).

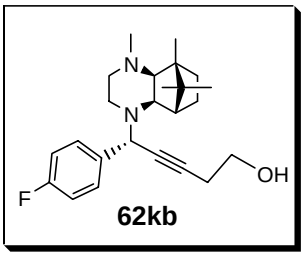
IR (neat) **:** 3300, 2953, 2878, 2795, 1893, 1743, 1655, 1604, 1506, 1451, 1368, 1365, 1332, 1222, 1155, 1128, 1095, 1041, 966, 923, 844 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.61-7.59 (d, *J*=8.0Hz, 2H), 7.32-7.26 (m, 3H), 5.03 (s, 1H), 3.82-3.79 (t, *J*=12.0Hz, 2H), 2.98-2.96 (d, *J*=8.0Hz, 1H), 2.73-2.69 (m, 3H), 2.52-2.45 (m, 1H), 2.35-2.30 (m, 1H), 2.27 (s, 3H), 2.22-2.19 (t, *J*=12.0Hz, 1H), 2.14-2.07 (m, 1H), 1.93-1.77 (m, 3H), 1.47 (m, 4H), 1.27-1.09 (m, 3H), 1.04(s, 3H), 0.85 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7.

HRMS **:** (ESI): calcd for $C_{24}H_{34}N_2O$: 366.2671 [M+H^+]; found: 367.2749.

4-(4-Fluoro-phenyl)-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-yn-1-ol (62kb):



62kb

Yield : 0.303 g, 79%, yellow liquid.

$[\alpha]_D^{25}$ **:** -29.9 (*c* 1.12, $CHCl_3$);

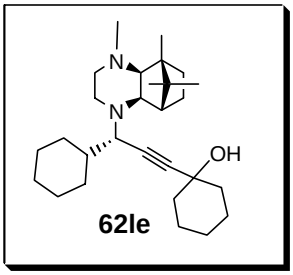
IR (neat) **:** 3300, 2953, 2878, 2795, 1893, 1743, 1655, 1604, 1506, 1451, 1368, 1365, 1332, 1222, 1155, 1128, 1095, 1041, 966, 923, 844 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.56-7.53 (t, J=12.0Hz, 2H), 7.02-6.96 (m, 2H), 4.97 (s, 1H), 4.65 (s, 1H), 3.81-3.77 (t, J=16.0Hz, 2H), 2.95-2.93 (d, J=8.0Hz, 1H), 2.73-2.61 (m, 3H), 2.31-2.26 (m, 4H), 2.20-2.18 (d, J=8.0Hz, 1H), 2.14-2.04 (m, 1H), 1.93-1.89 (m, 3H), 1.80-1.73 (m, 1H), 1.45 (s, 3H), 1.27-1.23 (m, 1H), 1.03 (s, 3H), 0.83 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7.

HRMS **:** (ESI): calcd for $C_{24}H_{33}FN_2O$: 384.2577 [M+H^+]; found: 385.2654.

1-[3-Cyclohexyl-3-(5,9,9-trimethyl-octahydro-5,8-methano-quinazolin-1-yl)-prop-1-ynyl]-cyclohexanol (62le):



62le

Yield : 0.369 g, 87%, yellow liquid.

$[\alpha]_D^{25}$: -49.3 (*c* 0.80, $CHCl_3$).

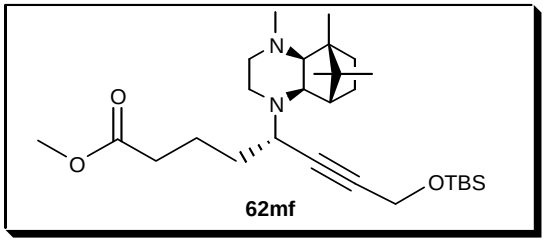
IR (neat) : 3398, 2930, 2852, 2795, 2770, 1757, 1635, 1148, 1390, 1257, 1168, 964 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 3.21-3.19 (d, *J*=8.0Hz, 1H), 2.87-2.85 (d, *J*=8.0Hz, 2H), 2.77-2.66 (m, 1H), 2.66-2.55 (m, 1H), 2.25 (s, 3H), 2.14-2.09 (m, 2H), 2.04-1.96 (m, 3H), 1.93-1.80 (m, 2H), 1.74-1.64 (m, 7H), 1.59-1.51 (m, 5H), 1.47-1.37 (m, 3H), 1.24 (s, 6H), 1.17-1.08 (m, 3H), 0.97 (s, 4H), 0.77 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7.

HRMS : (ESI): calcd for $C_{27}H_{44}N_2O$: 426.3610 [M+H^+]; found: 427.3688.

8-(tert-Butyl-dimethyl-silanyloxy)-5-(4,5,9,9-etramethyl-octahydro-5,8-methano-quinazolin-1-yl)-oct-6-ynoic acid methyl ester (62mf):



62mf

Yield : 0.480 g, 98%, yellow liquid.

$[\alpha]_D^{25}$: -37.4 (*c* 0.46, $CHCl_3$).

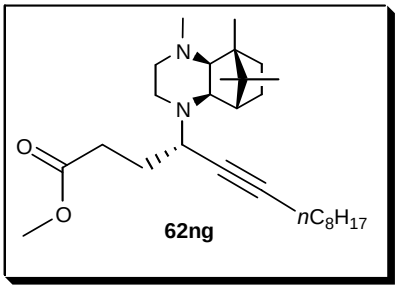
IR (neat) : 2947, 2931, 2854, 1473, 1391, 1358, 1249, 1090, 1002, 936, 843, 772 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 4.33 (s, 2H), 3.66-3.65 (s, 3H), 2.88-2.83 (m, 2H), 2.78-2.66 (m, 1H), 2.57-2.52 (m, 1H), 2.34-2.57 (m, 5H), 2.18-2.11 (m, 2H), 1.75-1.55 (m, 6H), 1.42-1.41 (m, 1H), 1.23 (s, 2H), 1.06-1.03 (m, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.77 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 173.9, 83.6, 83.1, 78.3, 64.7, 54.4, 53.3, 51.8, 51.4, 50.0, 48.2, 47.5, 47.1, 41.9, 37.1, 33.7, 32.7, 25.8, 22.1, 20.8, 18.3, 14.5.

HRMS **:** (ESI): calcd for $C_{28}H_{50}N_2O_3Si$: 490.3591, [M+H^+]; found: 491.3669.

4-(4, 5, 9, 9-Tetramethyl-octahydro-5, 8-methano-quinazolin-1-yl)-tetradec-5-ynoic acid methyl ester (62ng):



62ng

Yield : 0.412 g, 93%, yellow liquid.

$[\alpha]_D^{25}$ **:** -45.5 (*c* 0.62, $CHCl_3$).

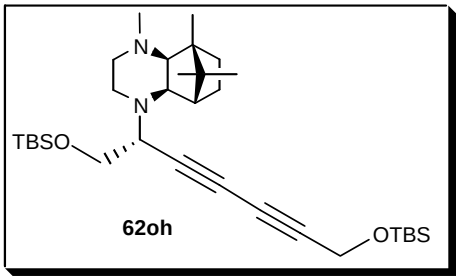
IR (neat) **:** 2947, 2931, 2854, 1655, 1473, 1391, 1358, 1249, 1090, 1002, 936, 843, 772 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 3.64 (s, 3H), 3.59-3.57 (t, *J*=8.0 Hz, 1H), 2.83-2.80 (m, 2H), 2.74-2.71 (m, 1H), 2.58-2.54 (m, 1H), 2.41-2.38 (t, *J*=12.0 Hz, 2H), 2.26 (s, 3H), 1.86-1.81 (q, *J*=20.0 Hz, 6H), 1.67-1.59 (m, 2H), 1.48-1.38 (m, 5H), 1.27 (s, 9H), 1.22 (s, 3H), 0.97 (s, 3H), 0.88-0.85 (t, *J*=20.0 Hz, 4H), 0.75 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 174.0, 84.8, 78.1, 64.7, 54.4, 52.9, 51.4, 50.0, 48.3, 47.8, 47.0, 41.7, 37.1, 31.8, 30.7, 29.3, 29.0, 28.7, 25.9, 22.6, 22.0, 20.7, 18.5, 14.4, 14.1.

HRMS **:** (ESI): calcd for $C_{28}H_{48}N_2O_2$: 444.3716, [M+H^+]; found: 445.3785

1-[6-(tert-Butyl-dimethyl-silanyloxy)-1-(tert-butyl-dimethyl-silanyloxymethyl)-hexa-2,4-diynyl]-4,5,9,9-tetramethyl-decahydro-5,8-methano-quinazoline (62oh):



Yield : 0.491 g, 88%, yellow liquid.

$[\alpha]_D^{25}$: -79.2 (*c* 0.53, $CHCl_3$).

IR (neat) : 2947, 2931, 2854, 1473, 1391, 1358, 1246, 1090, 1002, 936, 843 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 4.38 (s, 2H), 3.79 (s, 1H), 3.68-3.65 (m, 2H), 2.84-2.82 (m, 2H), 2.68 (m, 1H), 2.26 (s, 3H), 2.15-2.13 (m, 2H), 1.69-1.65 (m, 4H), 1.26 (s, 4H), 0.99 (s, 3H), 0.94-0.90 (m, 20H), 0.78 (s, 3H), 0.15-0.13 (m, 6H), 0.09-0.07 (m, 7H).

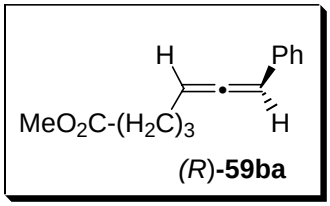
^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 78.9, 78.1, 75.1, 69.7, 69.3, 64.8, 64.4, 57.4, 54.1, 52.1, 50.0, 48.2, 47.8, 47.1, 43.6, 37.0, 25.9, 25.8, 25.7, 22.9, 18.4, 18.3, 14.2, -5.17.

HRMS : (ESI): calcd for $C_{32}H_{58}N_2O_2Si_2$: 558.4037, [M+H^+]; found: 559.4115.

3.4.3 General procedure for the preparation of chiral allenes from propargylamines

The chiral propargylamines **62** (1 mmol) were added to a stirred suspension of $ZnBr_2$ (0.113 g, 0.5 mmol) in dry toluene (3 mL) and the contents were refluxed for 1-2 h at 120 °C under nitrogen atmosphere. Toluene was removed under reduced pressure and the crude product was purified on silica gel (100-200 mesh) column chromatography using hexane as eluent to isolate the chiral allenes. The spectral data showed 1:1 correspondence with reported data.[12-16]

(*R*)-8-Phenyl-octa-6, 7-dienoic acid ethyl ester (59ba):



Yield : 0.262 g, 72%, colorless liquid.

$[\alpha]_D^{25}$: 214.7 (*c* 0.57, $CHCl_3$, 99% ee).

IR (neat) : 3030, 2951, 2854, 1948, 1738, 1597, 1494, 1437, 1363, 1315, 1242, 1155, 1072, 1026, 991, 912 cm^{-1}.

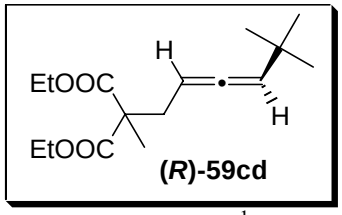
^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.22-7.20 (m, 4H), 7.21-7.17 (m, 1H), 6.18-6.15 (t, *J* = 12.0 Hz, 1H) 5.59- 5.54 (q, *J* = 20.0 Hz, 1H), 3.67 (s, 3H), 2.42-2.38 (t, *J* = 16.0 Hz, 2H), 2.22-2.15 (m, 2H), 1.87-1.82 (q, *J* = 20.0 Hz, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 205.2, 173.9, 134.7, 128.8, 128.5, 126.7, 126.6, 126.2, 95.1, 94.1, 51.5, 33.4, 28.1, 24.2.

HRMS : (ESI): calcd for $C_{14}H_{16}O_2$: 216.1150 [*M*+Na^+]; found: 239.0947

Enantiomeric purity: 99% ee HPLC using chiral column, chiralcel OB-H, hexanes:i-PrOH/97:3; flow rate 0.5 mL/min, 254 nm, retention times: 28.3 min. (*R*) and 29.7 min. (*S*).

(R)- 2-(5,5-Dimethyl-hexa-2,3-dienyl)-2-methyl-malonic acid diethyl ester (59cd):



Yield : 0.203 g, 72%, colorless liquid.

$[\alpha]_D^{25}$: -56.8 (*c* 0.61, $CHCl_3$, 99% ee).

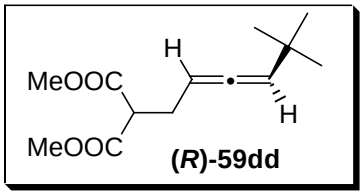
IR (neat) : 2962, 2906, 2868, 1961, 1734, 1462, 1377, 1365, 1298, 1242, 1190, 1107, 1026, 946, 862, cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 5.20- 5.14 (m, 2H), 3.74-3.73 (s, 6H), 3.51-3.47 (t, *J*=16.0 Hz, 1H), 2.61-2.57 (m, 2H), 1.00 (s, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 205.9, 171.9, 171.8, 90.7, 85.1, 61.1, 53.8, 35.9, 31.3, 28.4, 22.2, 19.6, 14.0, 13.8.

Enantiomeric purity: 99% ee HPLC using chiral column, chiralcel AD-H, heptane:i-PrOH/99.5:0.5; flow rate 1.0 mL/min, 210 nm, retention times: 6.7 min. (*R*) and 7.2 min. (*S*).

(*R*)- 2-(5,5-Dimethyl-hexa-2,3-dienyl)-malonic acid dimethyl ester (59dd):



Yield : 0.165 g, 69%, colorless liquid.

$[\alpha]_D^{25}$: -80.8 (*c* 0.70, $CHCl_3$, 96% ee).

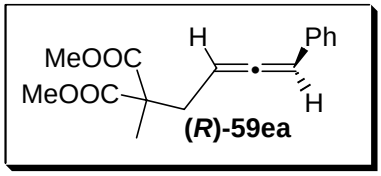
IR (neat) : 2959, 2866, 1961, 1739, 1437, 1388, 1340, 1232, 1078, 1041, 881, 844, 738 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 5.10-5.08 (m, 1H), 5.01-4.96 (q, *J*=20.0 Hz, 1H), 3.72 (s, 6H), 2.64-2.53 (m, 2H), 1.64 (s, 1H), 1.44 (s, 3H), 1.01 (s, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 201.1, 169.4, 169.3, 104.8, 89.2, 52.5, 52.5, 51.2, 31.7, 29.9, 28.2.

Enantiomeric purity: 96% ee HPLC using chiral column, chiralcel AS-H, hexanes:i-PrOH/99:1; flow rate 0.4 mL/min, 220 nm, retention times:13.2 min. (*R*) and 14.7 min. (*S*).

(*R*)- 2-Methyl-2-(4-phenyl-buta-2, 3-dienyl)-malonic acid dimethyl ester (59ea):



Yield : 0.210 g, 77%, colorless liquid.

$[\alpha]_D^{25}$: -205.9 (*c* 0.65, $CHCl_3$, 96% ee).

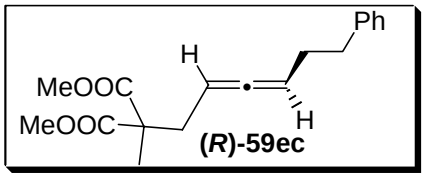
IR (neat) : 3036, 2997, 2953, 2849, 1950, 1734, 1597, 1494, 1458, 1435, 1379, 1290, 1244, 1203, 1109, 985, 914 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.33-7.25 (m, 4H), 7.21-7.17 (m, 1H), 6.16-6.13 (m, 1H), 5.49- 5.43 (q, *J*=24.0 Hz, 1H), 3.75-3.71 (d, *J*=16.0 Hz, 6H), 2.73-2.70 (d, *J*=12.0 Hz, 2H), 1.58 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 206.9, 172.1, 134.1, 128.5, 126.9, 126.8, 94.6, 89.3, 53.7, 52.6, 35.5, 19.9.

Enantiomeric purity: 96% ee, HPLC using chiral column, chiralcel chiralcel AD-H, hexanes:i-PrOH/99:1; flow rate 0.5 mL/min, 254 nm, retention times:20.2 min. (*R*) and 21.5 min. (*S*).

(*R*)- 2-Methyl-2-(6-phenyl-hexa-2,3-dienyl)-malonic acid dimethyl ester (59ec):



Yield : 0.196 g, 65%, colorless liquid.

$[\alpha]_D^{25}$ **:** -69.9 (*c* 0.45, $CHCl_3$, 89% ee).

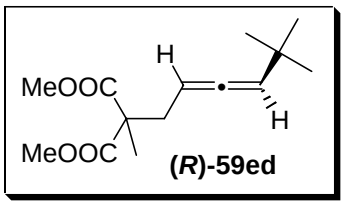
IR (neat) **:** 3086, 3063, 3026, 2999, 2951, 1963, 1736, 1604, 1531, 1496, 1454, 1435, 1246, 1203, 1156, 1111, 985 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.28-7.26 (m, 1H), 7.21-7.17 (m, 4H), 5.16-5.10 (m, 1H), 5.00-4.93 (m, 1H), 3.72 (s, 6H), 2.71-2.68 (t, *J*=12.0 Hz, 2H), 2.54-2.52 (m, 2H), 2.32-2.25 (m, 2H), 1.42 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 206.0, 172.2, 141.6, 128.4, 128.3, 125.8, 90.2, 85.6, 53.8, 52.5, 35.8, 35.4, 30.5, 19.7, 14.1.

Enantiomeric purity: 89% ee, HPLC using chiral column, chiralcel chiralcel AD-H, hexanes:i-PrOH/99:1; flow rate 0.5 mL/min, 210 nm, retention times:17.5 min. (*R*) and 18.2 min. (*S*).

(*R*)-21-2-(5,5-Dimethyl-hexa-2,3-dienyl)-2-methyl-malonic acid dimethyl ester (59ed):



Yield : 0.182 g, 77%, colorless liquid.

$[\alpha]_D^{25}$: -61.9 (*c* 0.45, $CHCl_3$, 99% ee).

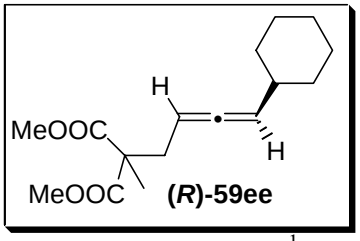
IR (neat) : 2959, 2868, 1961, 1738, 1458, 1435, 1377, 1363, 1296, 1246, 1201, 1109, 1020, 935, 877 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 5.09-5.08 (m, 1H), 5.01-4.98 (q, *J*=12.0 Hz, 1H), 3.71 (s, 6H), 2.60-2.56 (m, 2H), 1.44 (s, 3H), 1.01 (s, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 203.1, 172.4, 172.3, 102.9, 86.9, 53.8, 52.8, 52.5, 36.3, 31.7, 30.1, 19.8.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AS-H, heptane:i-PrOH/100:0; flow rate 0.25 mL/min, 230 nm, retention times:37.2 min. (*R*) and 42.7 min. (*S*).

(*R*)-2-(4-Cyclohexyl-buta-2,3-dienyl)-2-methyl-malonic acid dimethyl ester (59ee):



Yield : 0.190 g, 68%, colorless liquid.

$[\alpha]_D^{25}$: -57.2 (*c* 0.55, $CHCl_3$, 99% ee).

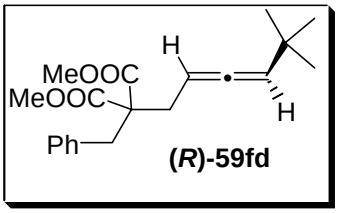
IR (neat) : 2993, 2926, 2852, 1961, 1736, 1618, 1450, 1377, 1290, 1244, 1201, 1159, 1111, 985, cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 5.08-5.06 (m, 1H), 4.98-4.96 (q, *J*=8.0 Hz, 1H), 3.72 (s, 6H), 2.59-2.57 (m, 2H), 1.94-1.93 (m, 1H), 1.72-1.71 (m, 4H), 1.44 (s, 3H), 1.38-1.22 (m, 4H), 1.04-1.00 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 204.7, 172.3, 96.9, 85.9, 53.8, 52.5, 37.1, 36.2, 33.0, 26.1, 25.9, 22.6, 19.8.

Enantiomeric purity: 99% ee, HPLC using, chiralcel AD-H, hexanes:i-PrOH/99.5:0.5; flow rate 0.5 mL/min, 210 nm, retention times: 37.2 min. (*R*) and 42.7 min. (*S*).

(*R*)-2-Benzyl-2-(5,5-dimethyl-hexa-2,3-dienyl)-malonic acid dimethyl ester (59fd):



Yield : 0.234 g, 71%, colorless liquid.

$[\alpha]_D^{25}$: -64.1 (*c* 0.55, $CHCl_3$, 99% ee).

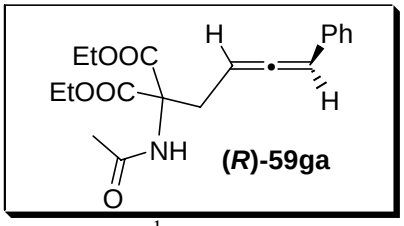
IR (neat) : 3078, 2959, 2906, 2866, 1961, 1738, 1641, 1439, 1361, 1325, 1282, 1246, 1211, 1076, 922 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.28-7.24 (m, 1H), 7.18-7.14 (m, 2H), 5.71-5.61 (m, 1H), 5.13-5.09 (m, 3H), 4.99-4.93 (q, *J*=24.0 Hz, 1H), 3.72 (s, 6H), 2.71-2.69 (d, *J*=8.0 Hz, 2H), 2.63-2.60 (m, 2H), 2.36 (s, 2H), 1.02 (s, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 203.1, 171.2, 132.3, 129.1, 128.2, 125.3, 119.2, 103.1, 86.4, 57.9, 52.4, 52.3, 36.7, 32.8, 31.6, 30.1.

Enantiomeric purity: 99% ee, HPLC using chiralcel AS-H, hexanes:i-PrOH/99.8:0.2; flow rate 0.5 mL/min, 210 nm, retention times: 11.2 min. (*R*) and 12.0 min. (*S*).

(*R*)-2-Acetylamino-2-(4-phenyl-buta-2,3-dienyl)-malonic acid diethyl ester (59ga):



Yield : 0.293 g, 85%, colorless liquid.

$[\alpha]_D^{25}$: -192.3 (*c* 0.55, $CHCl_3$, 98% ee).

IR (neat) : 3310, 2982, 1950, 1743, 1653, 1518, 1460, 1371, 1309, 1192, 1093, 1062, 1014, 887 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.32-7.28 (m, 2H), 7.25-7.18 (m, 3H), 6.83 (s, 1H), 6.13-6.11 (m, 1H), 5.38-5.32 (q, *J*=12.0 Hz, 1H), 4.28-4.11

(m, 4H), 3.18-3.15 (dd, *J*=12.0 Hz, 2H), 1.91 (s, 3H), 1.28-1.25 (t, *J*=12.0 Hz, 4H), 1.21-1.17 (t, *J*=16.0 Hz, 3H).

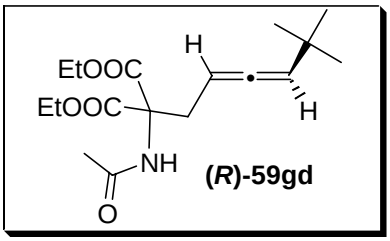
^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 207.1, 169.1, 167.5, 134.0, 128.6, 127.1, 126.7, 94.8, 88.1, 66.3, 62.7, 32.1, 22.9, 14.0, 13.9.

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min, 254 nm, retention times: 17.9 min. (*R*) and 28.1 min. (*S*).

2-Acetylamino-2-(5,5-dimethyl-hexa-2,3-dienyl)-malonic acid diethyl ester (59gd):

Yield : 0.237 g, 73%, colorless liquid.

$[\alpha]_D^{25}$: -66.3 (*c* 0.46, $CHCl_3$, 99% ee).



IR (neat) : 3382, 3312, 2962, 2905, 2868, 1961, 1743, 1682, 1502, 1440, 1367, 1304, 1278, 1201, 1093, 1060, 1018, 946 cm^{-1}.

^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 6.79 (s, 1H), 5.06-5.03 (q, *J*=12.0 Hz, 1H), 4.92-4.85 (q, *J*=28.0 Hz, 4H), 4.28-4.21 (m, 4H), 3.04-3.01 (d, *J*=12.0 Hz, 2H), 2.02 (s, 3H), 1.27-1.23 (m, 6H), 0.99 (s, 9H).

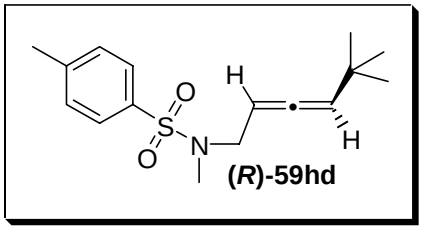
^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 203.1, 168.9, 167.7, 167.6, 103.1, 85.6, 66.3, 62.6, 62.5, 33.1, 31.5, 30.1, 23.1, 13.9.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AD-H, hexanes:i-PrOH/95:5; flow rate 0.5 mL/min, 210 nm, retention times: 22.8 min. (*R*) and 26.2 min. (*S*).

(*R*)- N-(5,5-Dimethyl-hexa-2,3-dienyl)-4, N-dimethyl-benzenesulfonamide (59hd):

Yield : 0.202 g, 69%, colorless liquid.

$[\alpha]_D^{25}$: -92.8 (*c* 0.79, $CHCl_3$, 98% ee).



IR (neat) **:** 2959, 2923, 2897, 2861, 1955, 1593, 1464, 1345, 1303, 1164, 1089, 1086, 977 cm^{-1}.

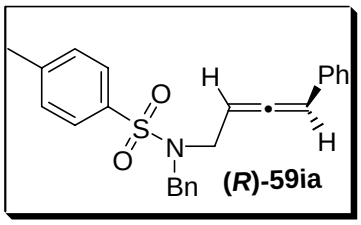
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.69-7.67 (d, *J*=12.0 Hz, 2H), 7.33-7.31 (d, *J*=12.0 Hz, 2H), 5.18- 5.16 (m, 1H), 5.05-5.00 (q, *J*=20.0 Hz, 1H), 3.72-3.56 (m, 2H), 2.73 (s, 3H), 2.43 (s, 3H), 1.00 (s, 9H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 202.7, 143.3, 134.6, 129.7, 127.4, 104.6, 88.3, 50.4, 34.2, 31.9, 30.1, 21.5.

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel OJ-H, hexanes:i-PrOH/ 90:10; flow rate 0.5 mL/min, 210 nm, retention times: 15.8 min. (*R*) and 16.2 min. (*S*);

(*R*)- N-Benzyl-4-methyl-N-(4-phenyl-buta-2,3-dienyl)-benzenesulfonamide (59ia):

Yield : 0.283 g, 73%, colorless liquid.



(*R*)-59ia

$[\alpha]_D^{25}$ **:** -220.3 (*c* 0.45, $CHCl_3$, 99% ee).

IR (neat) **:** 3058, 3021, 2923, 1955, 1650, 1598, 1490, 1459, 1340, 1091, 910 cm^{-1}.

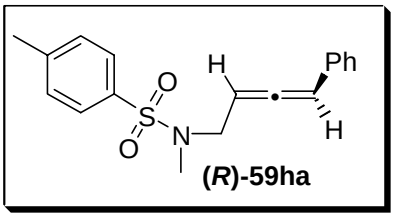
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.78-7.76 (d, *J*=8.0 Hz, 2H), 7.33-7.13 (m, 13H), 6.04-6.02 (m, 1H), 5.28-5.23 (q, *J*=20.0 Hz, 1H), 4.41 (s, 2H), 3.90-3.88 (m, 2H), 2.44 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 206.2, 143.4, 137.5, 135.8, 133.4, 129.8, 129.8, 128.7, 128.5, 128.1, 127.9, 127.8, 127.3, 126.9, 95.9, 90.0, 50.3, 45.7, 21.5.

HRMS **:** (ESI): calcd for $C_{24}H_{23}NO_2S$: 389.1449 [*M*+H]; found: 390.1526.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AS-H, hexanes:i-PrOH/85:15; flow rate 0.5 mL/min, 254 nm, retention times: 27.8 min. (*R*) and 29.8 min. (*S*);

(*R*)- 4, N-Dimethyl-N-(4-phenyl-buta-2,3-dienyl)-benzenesulfonamide (59ha):



(*R*)-59ha

Yield : 0.244 g, 78%, colorless liquid.

$[\alpha]_D^{25}$: -252.2 (*c* 0.50, $CHCl_3$ 99% ee).

IR (neat) : 3058, 3021, 2923, 1955, 1650, 1598, 1490, 1459, 1340, 1091, 967, 910 cm^{-1}.

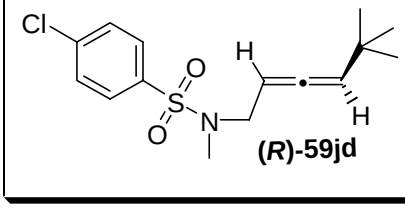
^{1}H NMR : (400 MHz, $CDCl_3$, δppm) 7.70-7.68 (d, *J*=8.0 Hz, 2H), 7.32-7.28 (m, 5H), 7.23-7.21 (m, 2H), 6.19-6.17 (m, 1H), 5.48-5.43 (q, *J*=20.0 Hz, 1H), 3.81-3.77 (m, 2H), 2.78 (s, 3H), 2.42 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$, δppm) 206.4, 143.5, 134.6, 133.4, 129.7, 129.1, 128.7, 128.2, 127.3, 127.3, 126.8, 96.1, 90.6, 49.6, 34.4, 21.5.

HRMS : (ESI): calcd for $C_{24}H_{34}N_2O$: 313.1136 [*M*+Na^+]; found: 336.1042.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel AS-H, hexanes:i-PrOH/85:15; flow rate 0.5 mL/min, 254 nm, retention times: 30.4 min. (*R*) and 33.6 min. (*S*).

(*R*)- 4-Chloro-N-(5,5-dimethyl-hexa-2,3-dienyl)-N-methyl-benzenesulfonamide (59jd):



(*R*)-59jd

Yield : 0.225 g, 72%, colorless liquid.

$[\alpha]_D^{25}$: -86.2 (*c* 0.42, $CHCl_3$, 99% ee).

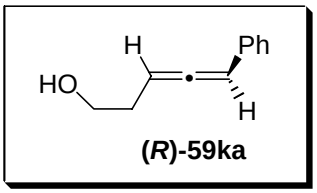
IR (neat) : 3095, 2958, 2898, 2860, 1961, 1589, 1479, 1402, 1347, 1161, 1013, 987 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.33-7.32 (d, *J* = 8.0 Hz, 4H), 5.27- 5.22 (q, *J*=8.0 Hz, 1H), 5.16-5.13 (m, 1H), 3.59-3.50 (q, *J*=36.0 Hz, 2H), 3.14-3.01 (m, 2H), 2.24 (s, 3H), 1.04 (s, 9H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 202.8, 139.1, 136.3, 129.4, 128.8, 104.8, 88.1, 50.3, 34.2, 31.9, 30.1.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/98:2; flow rate 0.5 mL/min, 250 nm, retention times: 16.7 min. (*R*) and 17.3 min. (*S*).

(*R*) - 5-Phenyl-penta-3, 4-dien-1-ol (59ka):



(*R*)-59ka

Yield : 0.104 g, 65%, colorless liquid.

$[\alpha]_D^{25}$ **:** -219.7 (*c* 0.59, $CHCl_3$, 99% ee).

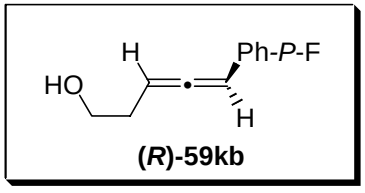
IR (neat) **:** 3350, 3063, 3030, 2928, 2879, 1950, 1753, 1701, 1597, 1494, 1458, 1311, 1299, 1203, 1049, 912, 877 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.32-7.30 (m, 4H), 7.23-7.18 (m, 1H), 6.22-6.18 (q, *J*=16.0 Hz, 1H), 5.63- 5.58 (q, *J*=20.0 Hz, 2H), 3.80-3.78 (t, *J*=8.0 Hz, 2H), 2.44-2.38 (m, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.7, 134.4, 128.6, 126.9, 126.6, 95.1, 91.5, 61.9, 32.1.

Enantiomeric purity: 99% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/97:3; flow rate 0.5 mL/min, 254 nm, retention times: 34.1 min. (*R*) and 38.0 min. (*S*).

(R)- 5-(4-Fluoro-phenyl)-penta-3,4-dien-1-ol (59kb):



(*R*)-59kb

Yield : 0.105 g, 59%, colorless liquid.

$[\alpha]_D^{25}$ **:** -184.73 (*c* 0.55, $CHCl_3$, 82% ee).

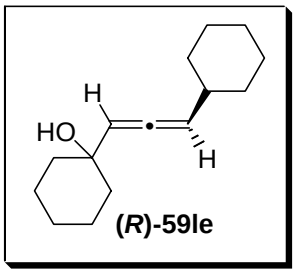
IR (neat) **:** 3351, 3043, 2928, 2958, 1951, 1738, 1232, 1203, 1153, 912, 750 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.27-7.24 (m, 2H), 7.01-6.99 (t, *J*=8.0 Hz, 2H), 6.18-6.16 (m, 1H), 5.63-5.58 (m, 1H), 3.80-3.76 (t, *J*=16.0 Hz, 2H), 2.43-2.37 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 205.5, 160.6, 130.3, 128.1, 128.0, 115.7, 115.9, 94.1, 91.7, 61.9, 32.0.

Enantiomeric purity: 82% ee, HPLC using chiral column, chiralcel OD-H, hexanes:i-PrOH/98:2; flow rate 0.6 mL/min, 254 nm, retention times: 24.1 min. (*R*) and 29.0 min. (*S*).

(R)- 1-(3-Cyclohexyl-propa-1,2-dienyl)-cyclohexanol (59le):



Yield : 0.158 g, 72%, colorless liquid.

$[\alpha]_D^{25}$ **:** -121.7 (*c* 0.55, $CHCl_3$ 98% ee);

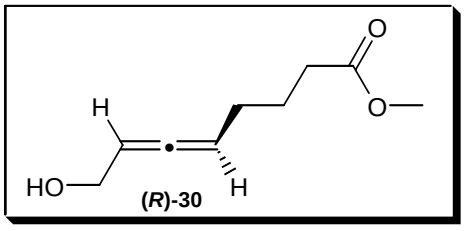
IR (neat) **:** 3313, 2923, 2849, 1962, 1446, 1399, 1355, 1320, 1264, 1247, 1144, 1100, cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 5.32-5.31 (d, *J*=4.0 Hz, 2H), 2.02-1.97 (m, 1H), 1.78-1.71 (m, 2H), 1.65-1.59 (m, 7H), 1.52-1.47 (m, 4H), 1.36-1.26 (m, 4H), 1.10-1.04 (m, 3H), 0.90-0.85 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 199.9, 101.3, 101.0, 70.5, 38.5, 38.3, 37.2, 33.2, 33.1, 25.5, 22.5.

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel AD-H, hexanes:i-PrOH/95:5; flow rate 0.5 mL/min 214 nm, retention times: 10.6 min. (*R*) and 11.2 min. (*S*).

8-Hydroxy-octa-5,6-dienoic acid methyl ester (30):



Yield : 0.132 g, 78%, colorless liquid.

$[\alpha]_D^{25}$ **:** -67.5 (*c* 0.45, $CHCl_3$, 98% ee).

IR (neat) **:** 3448, 2951, 2869, 1963, 1736, 1439, 1201, 1154, 1054 cm^{-1}.

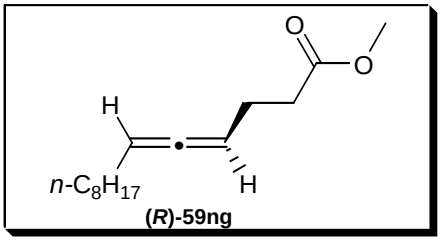
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 5.34- 5.32 (m, 1H), 5.25-5.22 (m, 1H), 4.11-4.09 (d, *J*=8.0 Hz, 2H), 3.66 (s, 3H), 2.38-2.34 (t, *J*=16.0 Hz, 2H), 2.06-2.03 (m, 3H), 1.78-1.73 (m, 2H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 203.3, 174.1, 92.5, 92.4, 60.6, 60.4, 51.6, 33.2, 27.8, 24.0.

HRMS **:** (ESI): calcd for $C_9H_{14}O_3$: 170.0943 [M+H^+]; found: 171.1022.

Enantiomeric purity: 98% ee, HPLC using chiral column, chiralcel AS-H, hexanes:i-PrOH/95:5; flow rate 0.8 mL/min 214 nm, retention times: 20.3 min. (*R*) and 23.8 min. (*S*).

Pentadeca-4, 5-dienoic acid methyl ester (59ng):



(*R*)-59ng

Yield : 0.188 g, 72%, colorless liquid.

$[\alpha]_D^{25}$ **:** -63.5 (*c* 0.73, $CHCl_3$,).

IR (neat) **:** 3008, 2900, 2840, 2644, 1960, 1710, 1430, 1280, 1250, 1210, 1170 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 5.25- 5.11 (m, 2H), 3.70-3.67 (s, 3H), 2.45-2.41 (t, *J*=16.0 Hz, 2H), 2.32-2.28 (m, 2H), 1.97-1.93 (m, 2H), 1.59 (s, 2H), 1.27 (s, 11H), 0.94-0.86 (t, *J*=16.0 Hz, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 203.6, 173.6, 92.6, 89.4, 51.5, 33.2, 31.8, 29.6, 29.4, 29.2, 29.1, 28.8, 23.8, 22.6, 14.0.

HRMS **:** (ESI): calcd for $C_{15}H_{26}O_2$: 238.1933 [M+H^+]; found: 239.2012.

The ^{13}C NMR data showed 1:1 correspondence with the reported data (Ref. **11**).

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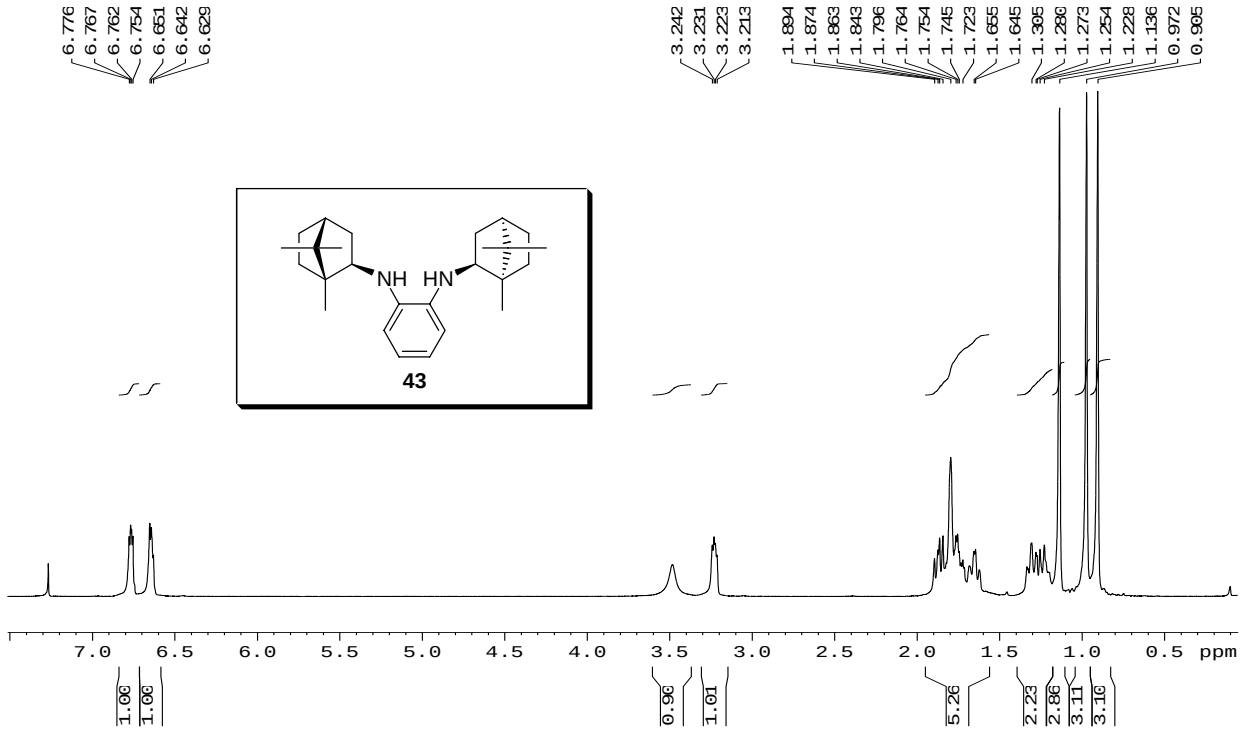
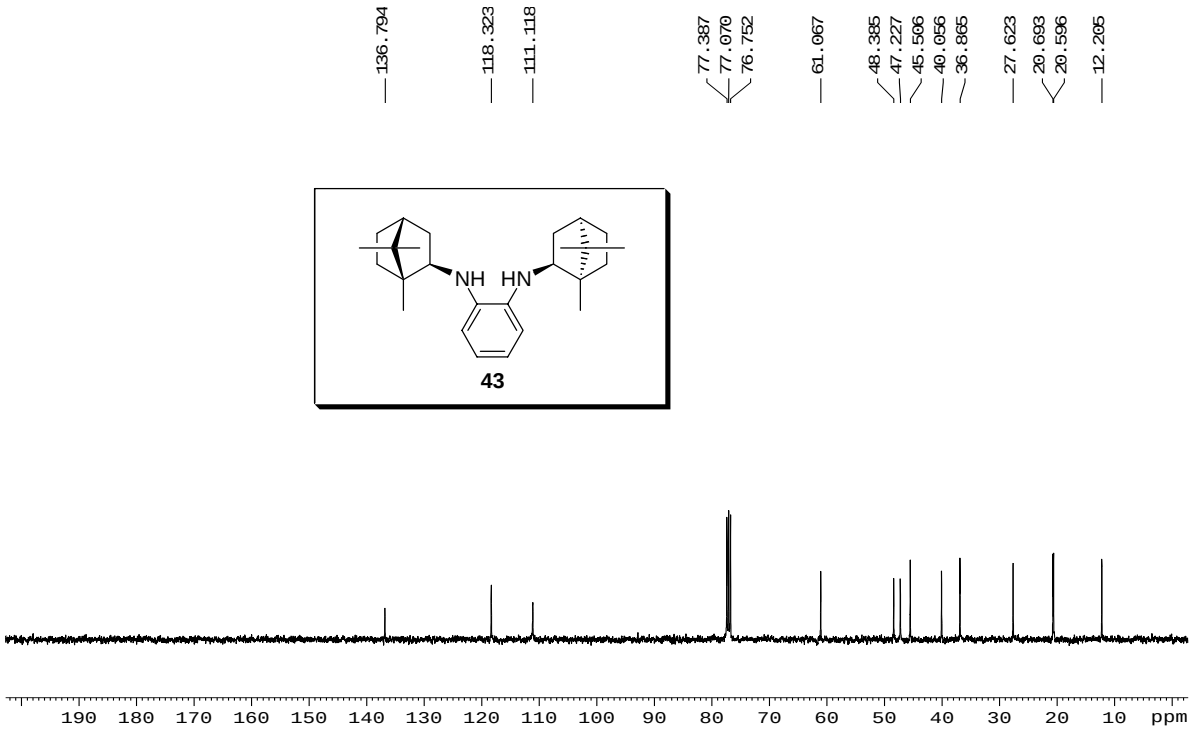
Appendix I

Representative Spectra

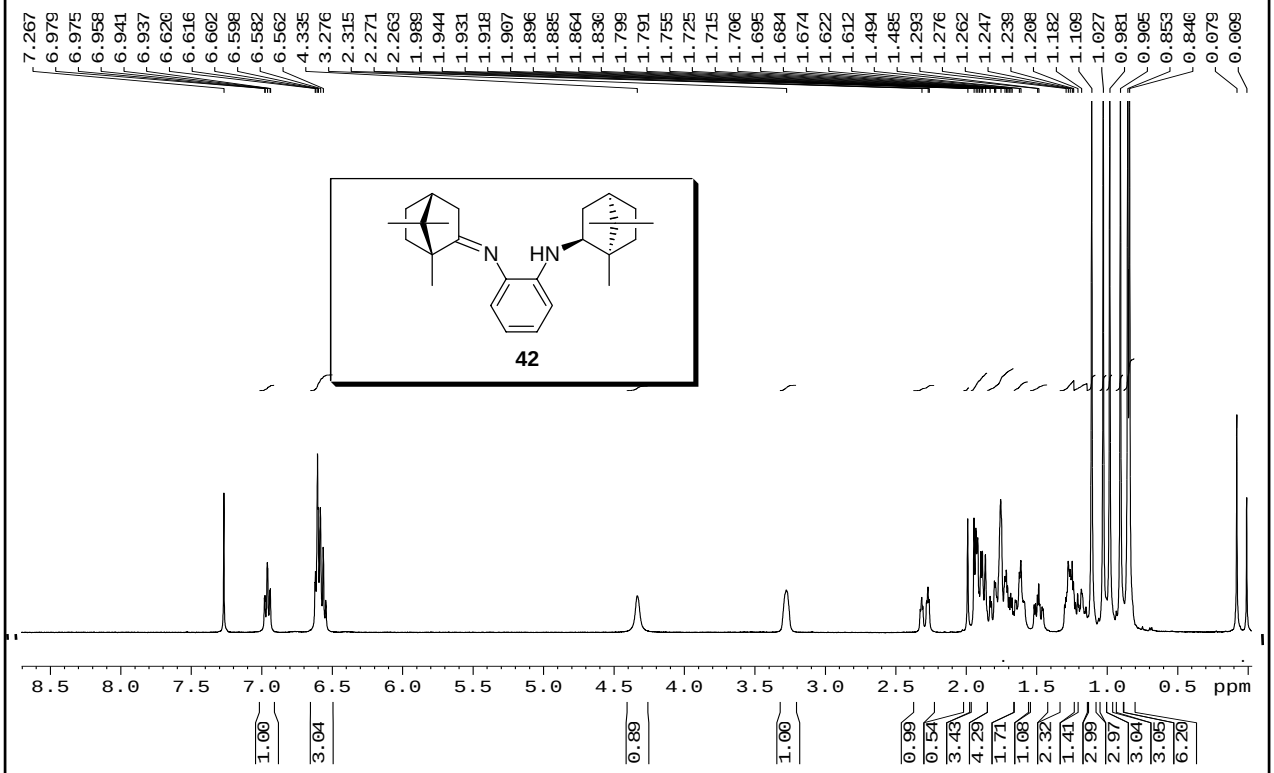
Spectrum No. 1 (Chapter 1, Section 1.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



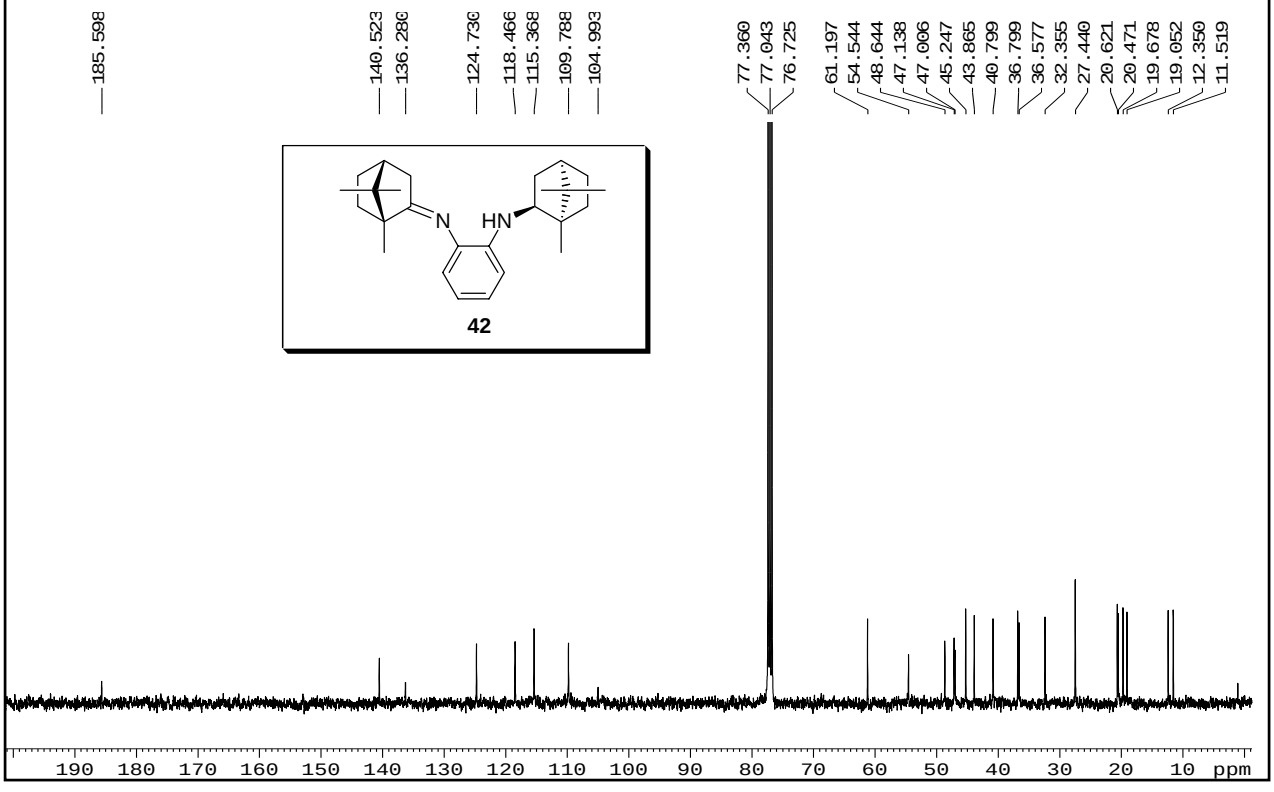
Spectrum No. 2 (Chapter 1, Section 1.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



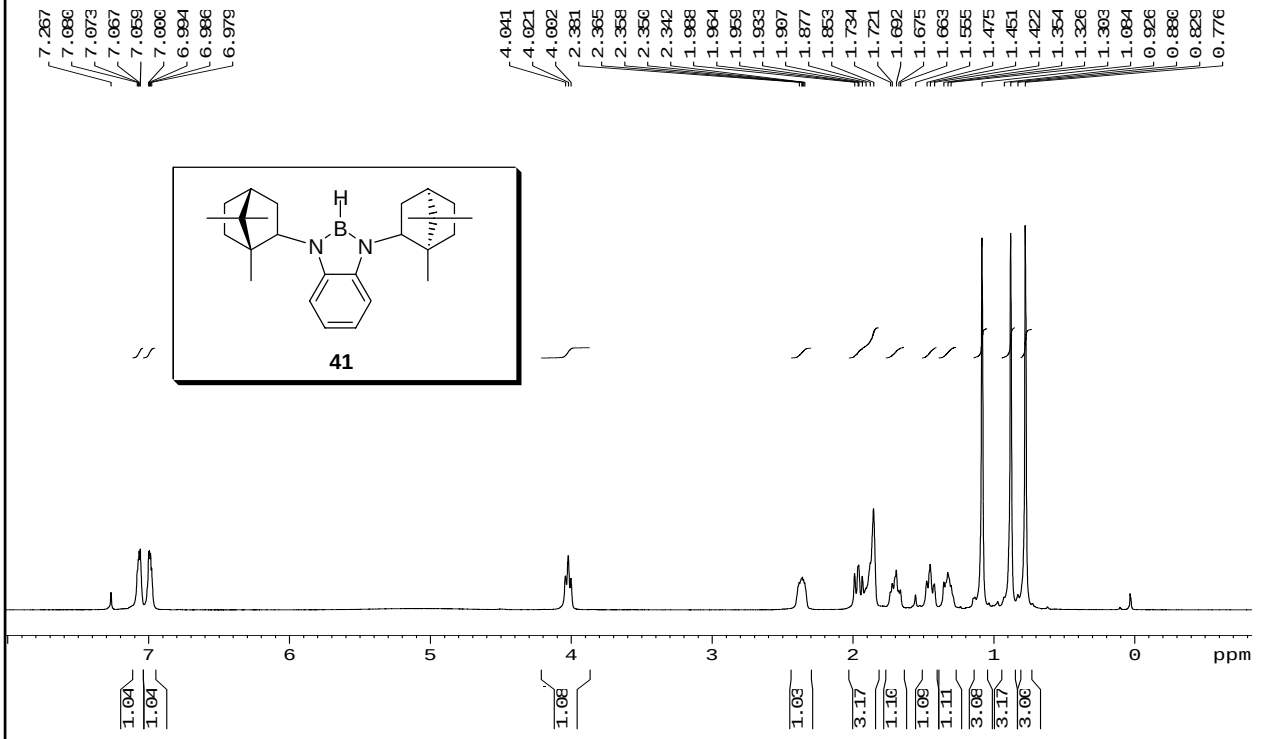
Spectrum No. 3 (Chapter 1, Section 1.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



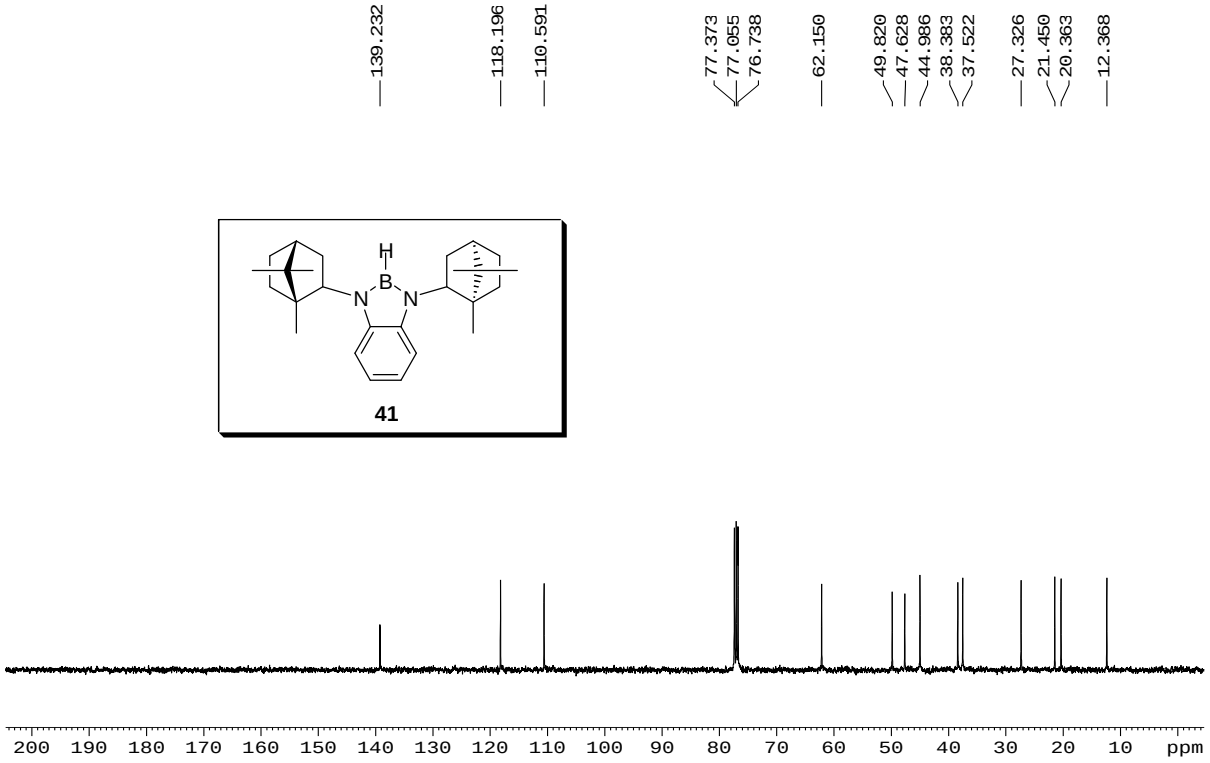
Spectrum No. 4 (Chapter 1, Section 1.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



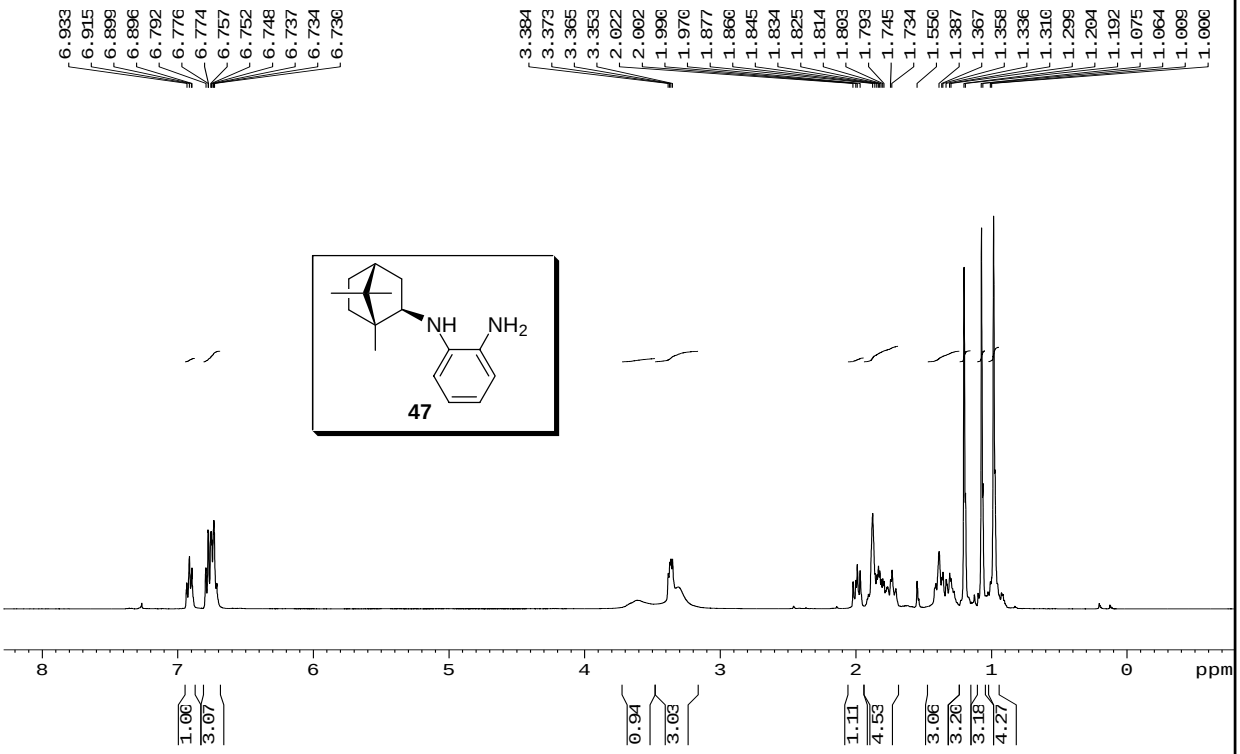
Spectrum No. 5 (Chapter 1, Section 1.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



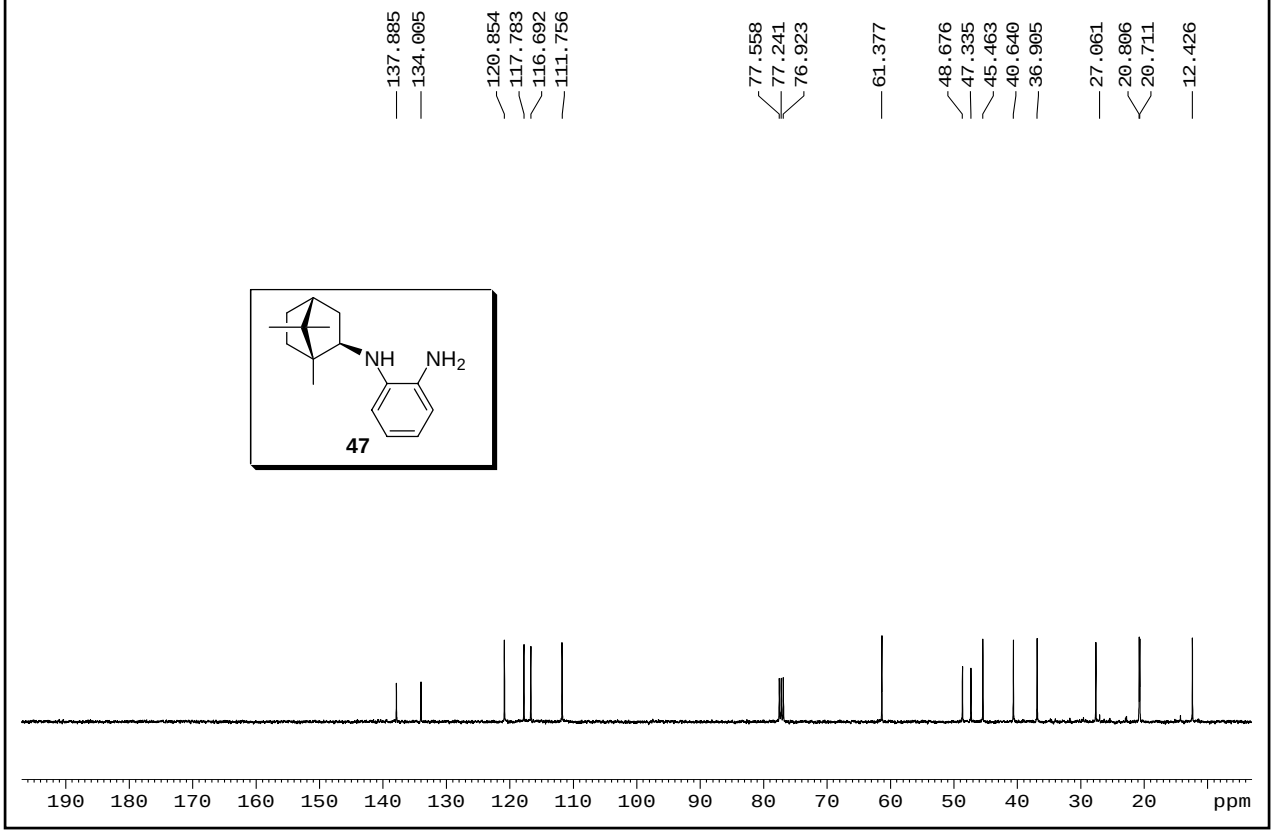
Spectrum No. 6 (Chapter 1, Section 1.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



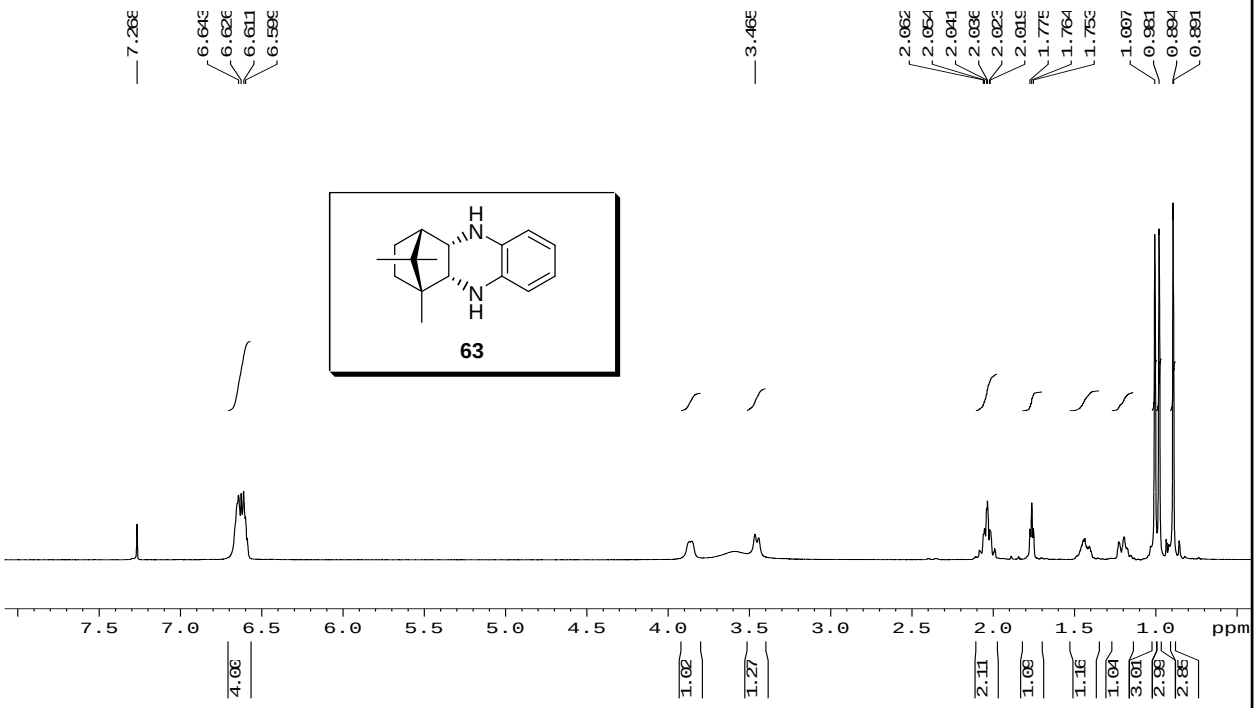
Spectrum No. 7 (Chapter 1, Section 1.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



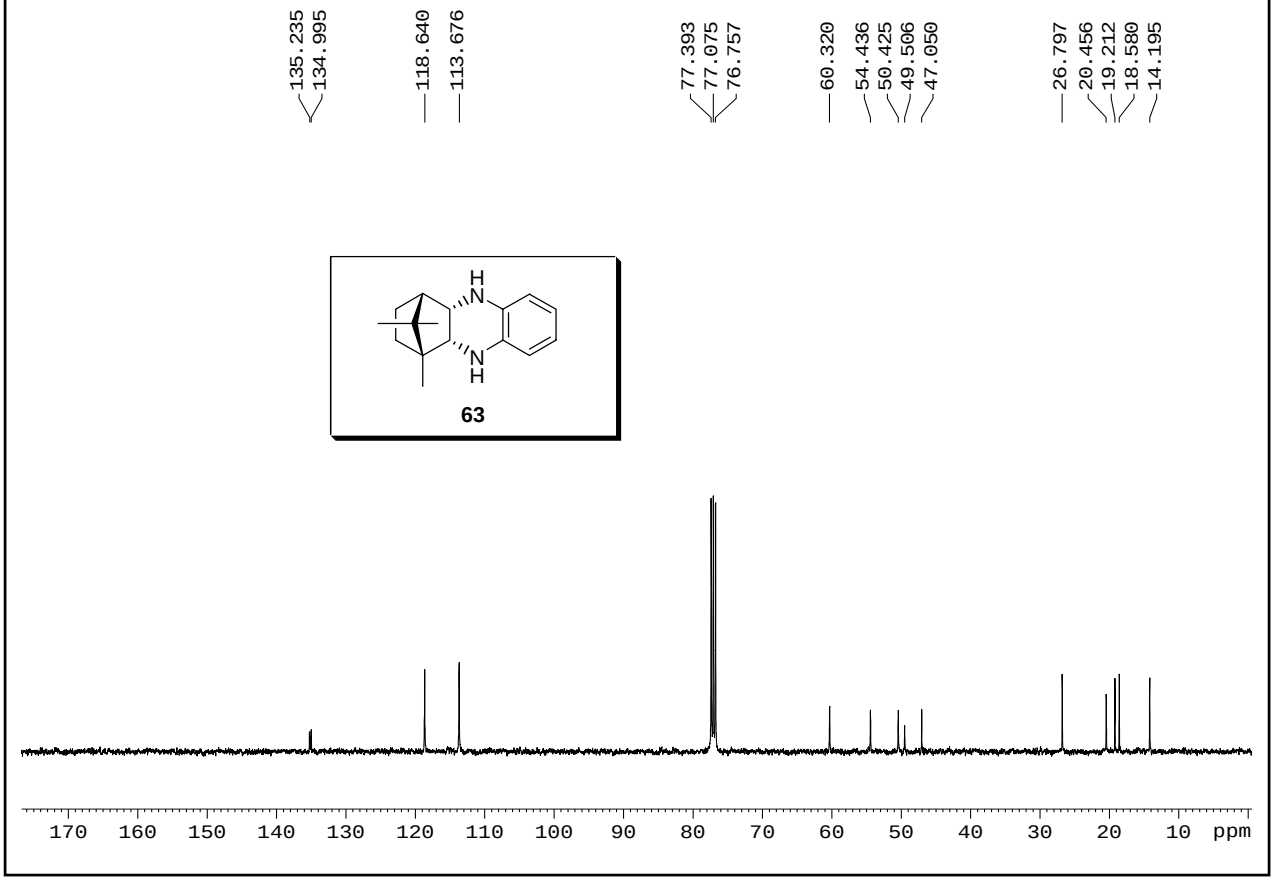
Spectrum No. 8 (Chapter 1, Section 1.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



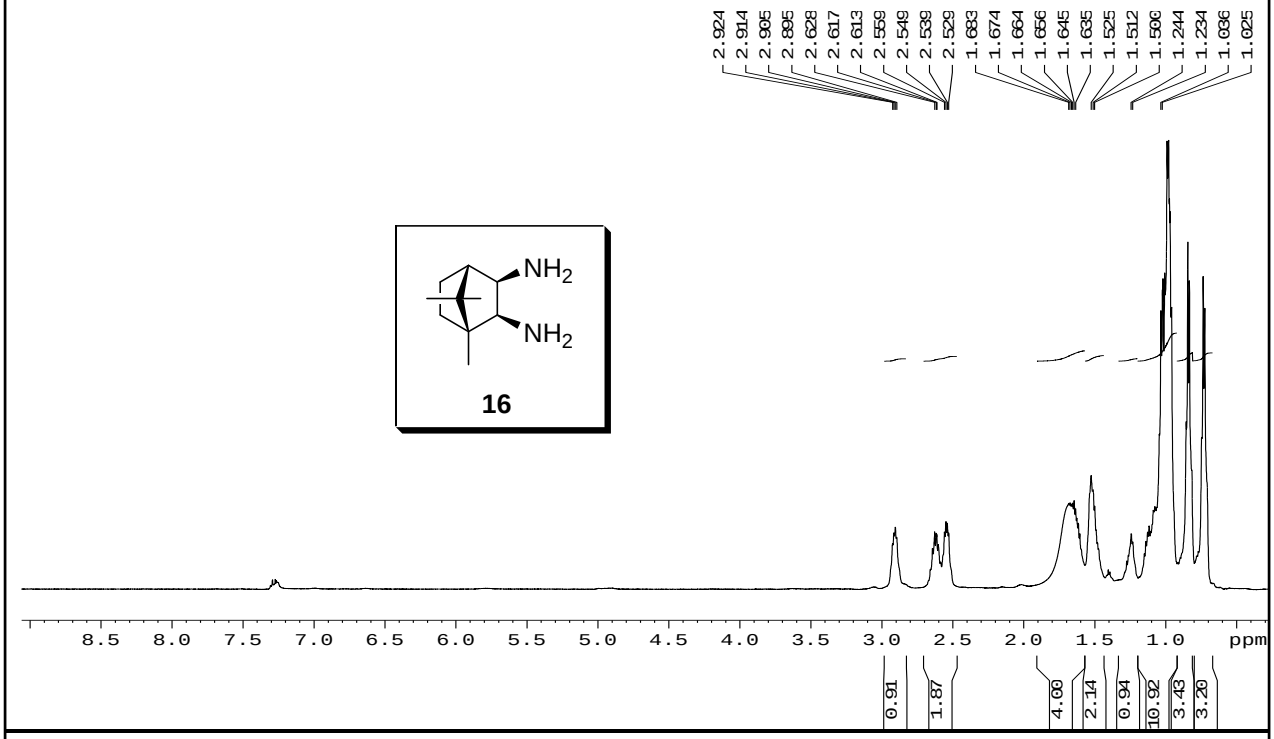
Spectrum No. 9 (Chapter 1, Section 1.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



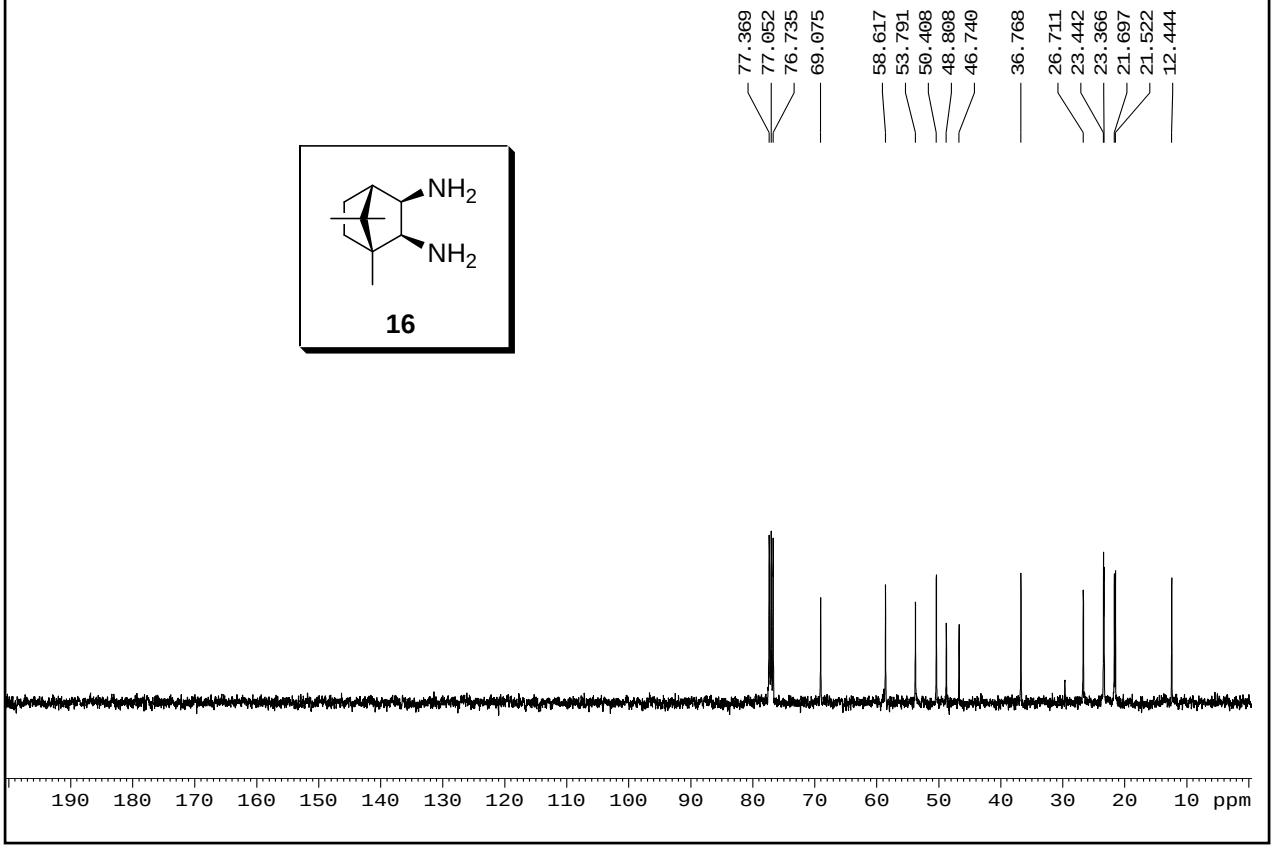
Spectrum No. 10 (Chapter 1, Section 1.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



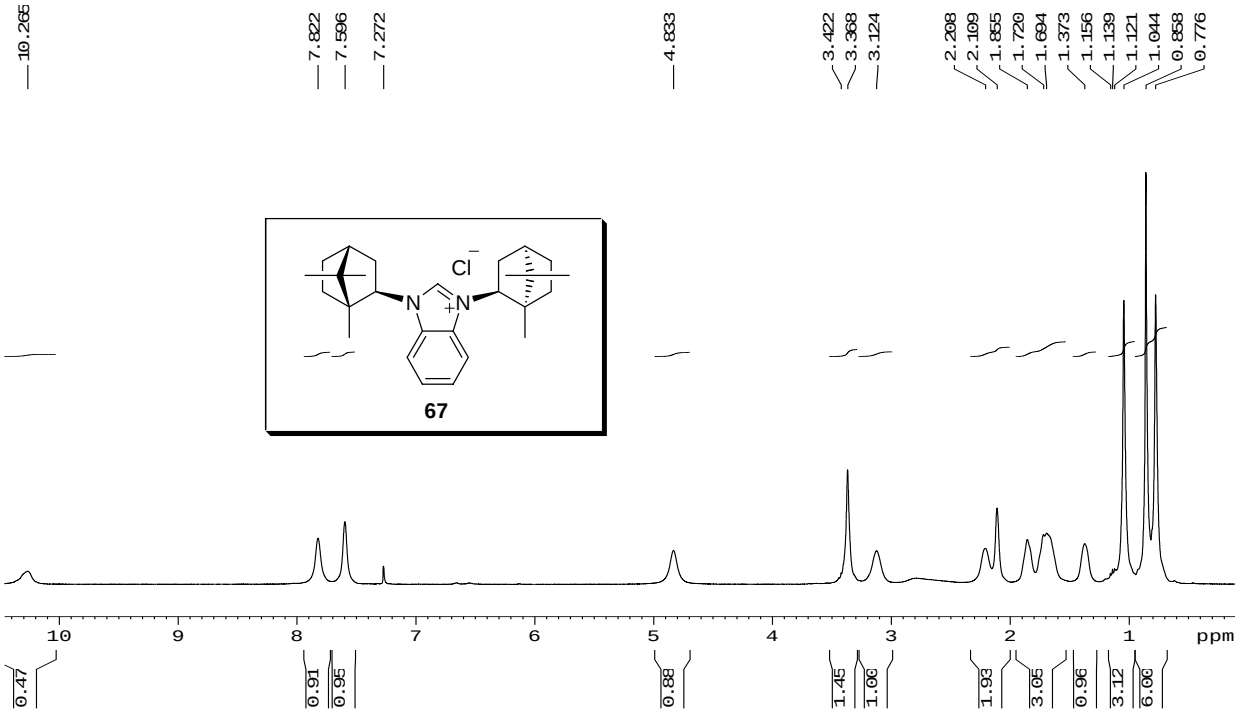
Spectrum No. 11 (Chapter 1, Section 1.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



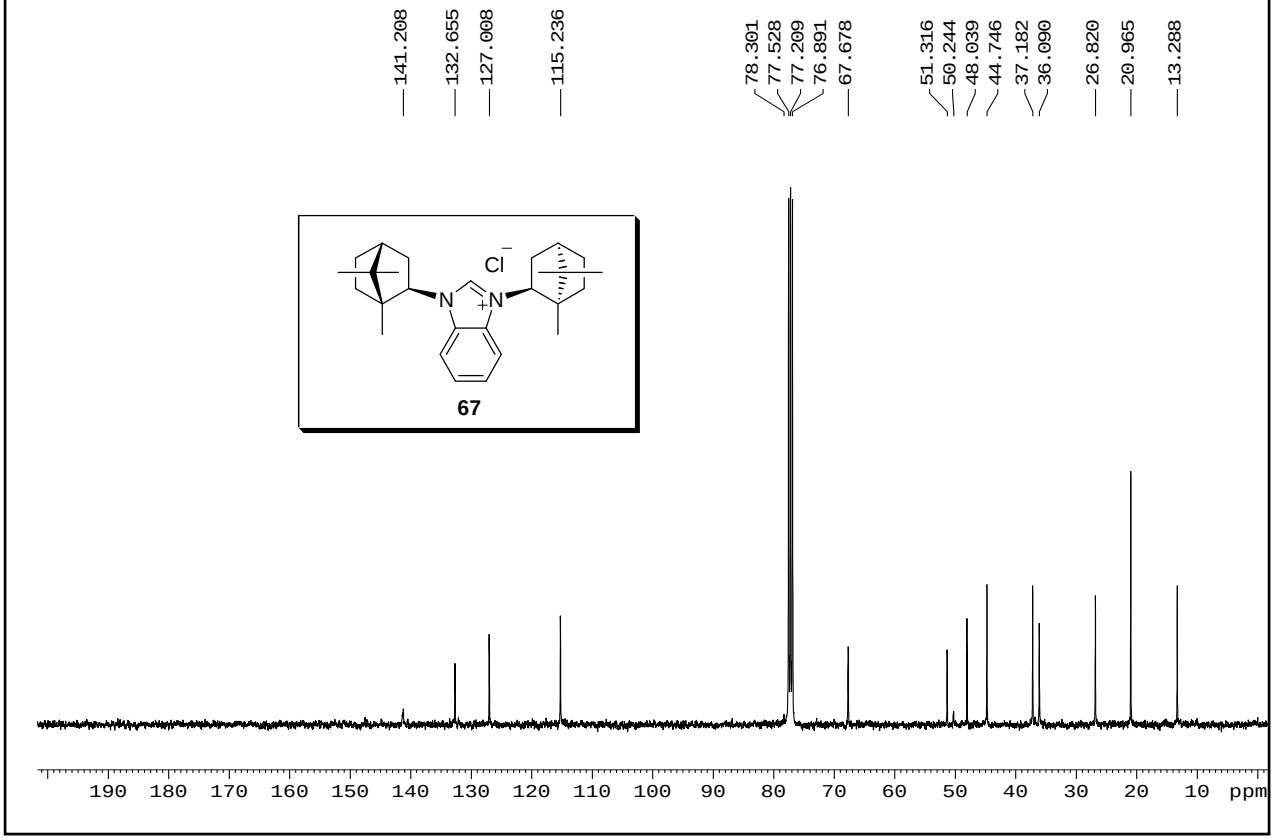
Spectrum No. 12 (Chapter 1, Section 1.2.3) ^{13} C NMR Spectrum (100 MHz, $CDCl_3$



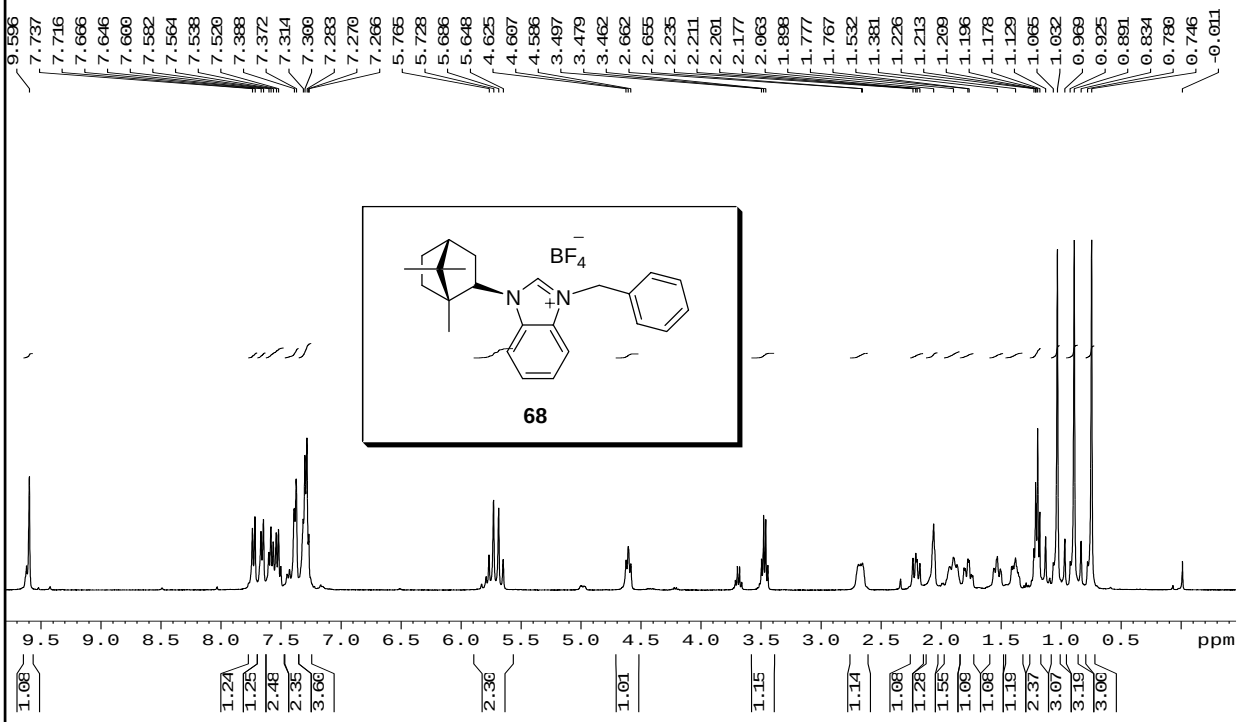
Spectrum No. 13 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



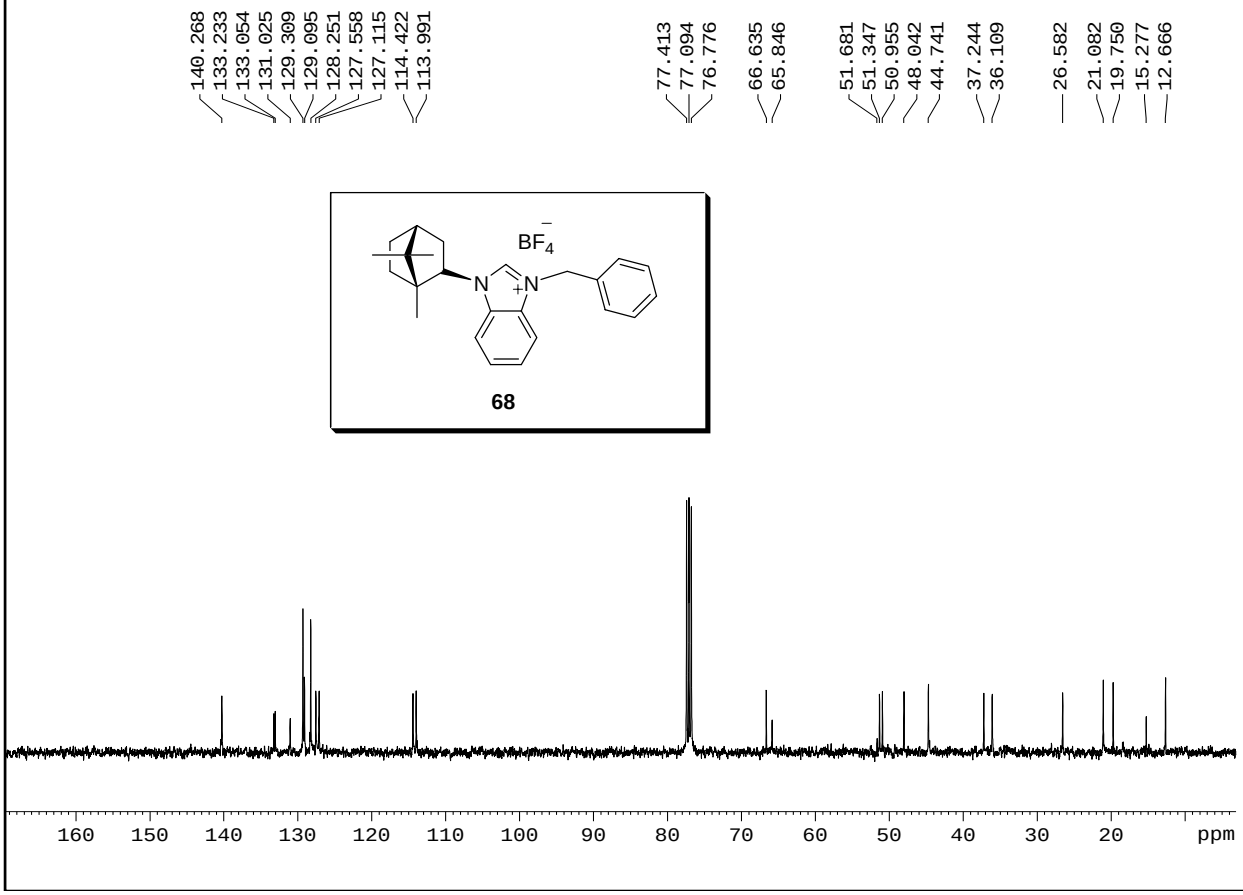
Spectrum No. 14 (Chapter 1, Section 1.2.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



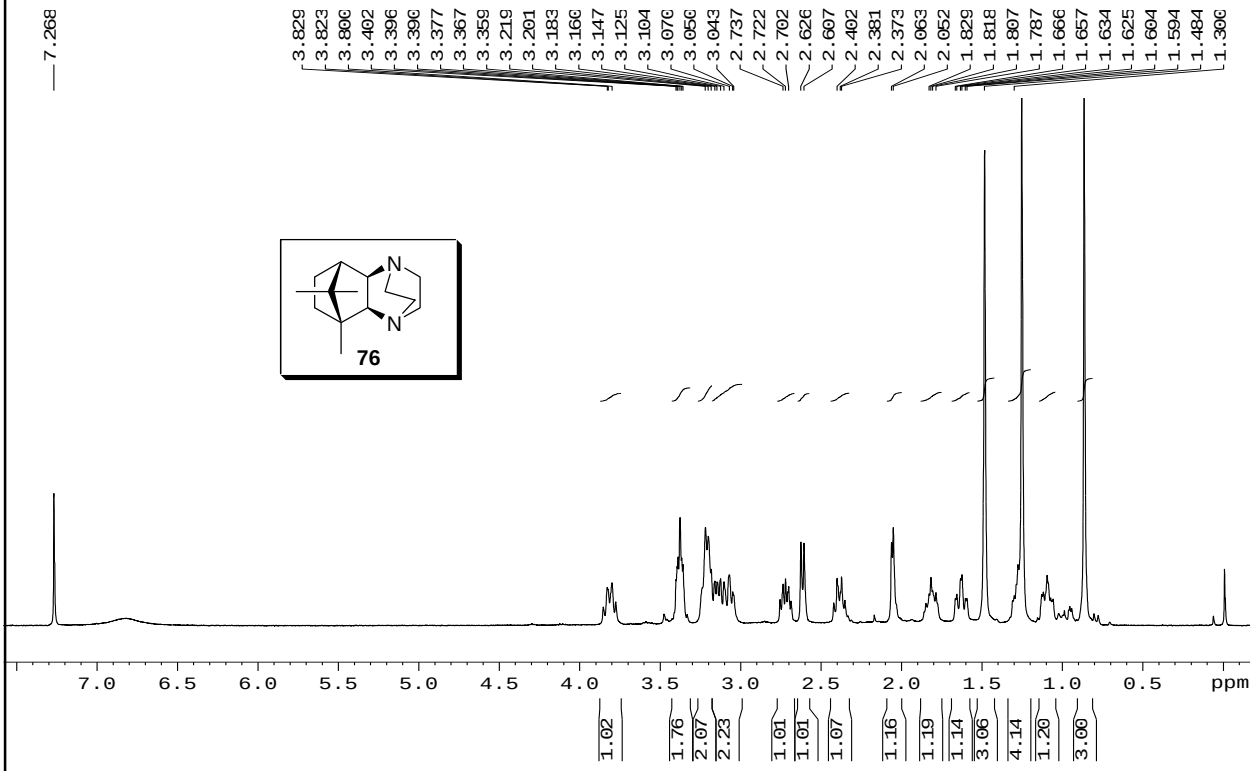
Spectrum No. 15 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



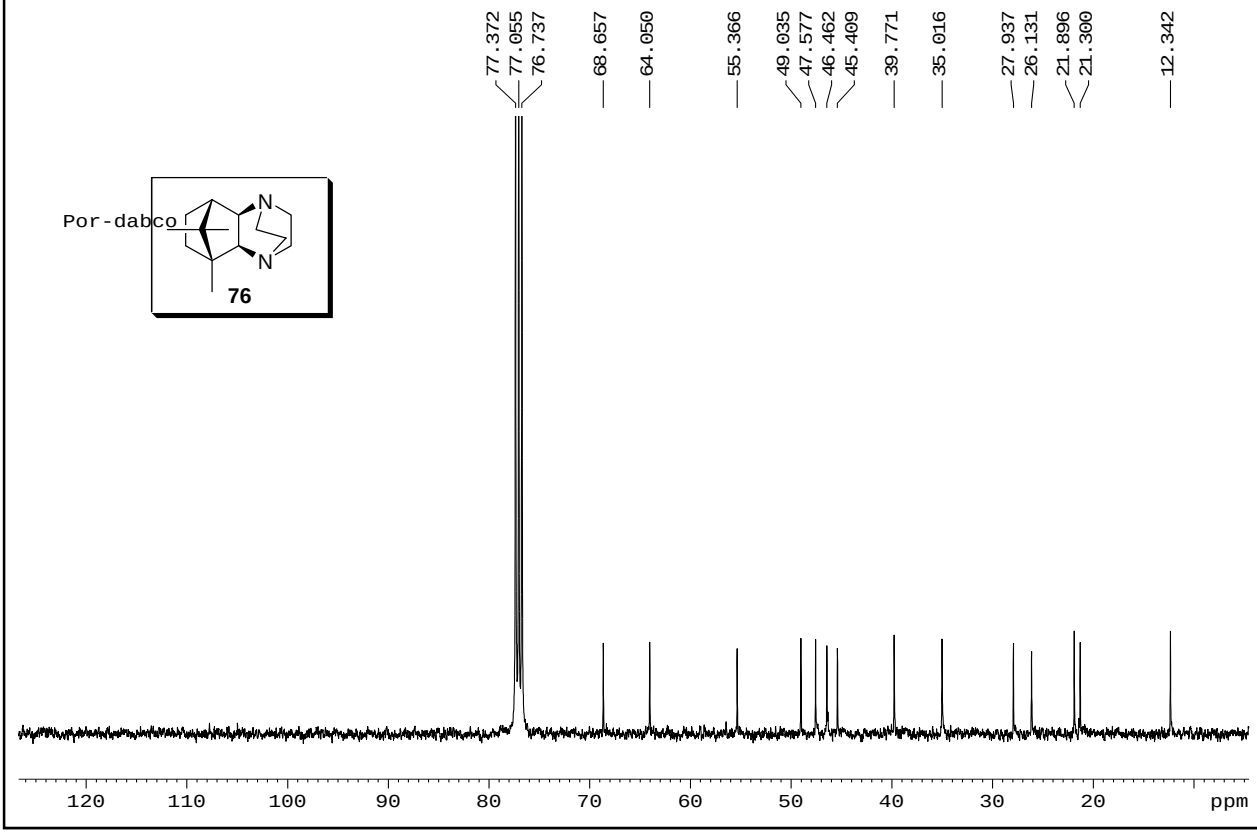
Spectrum No. 16 (Chapter 1, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



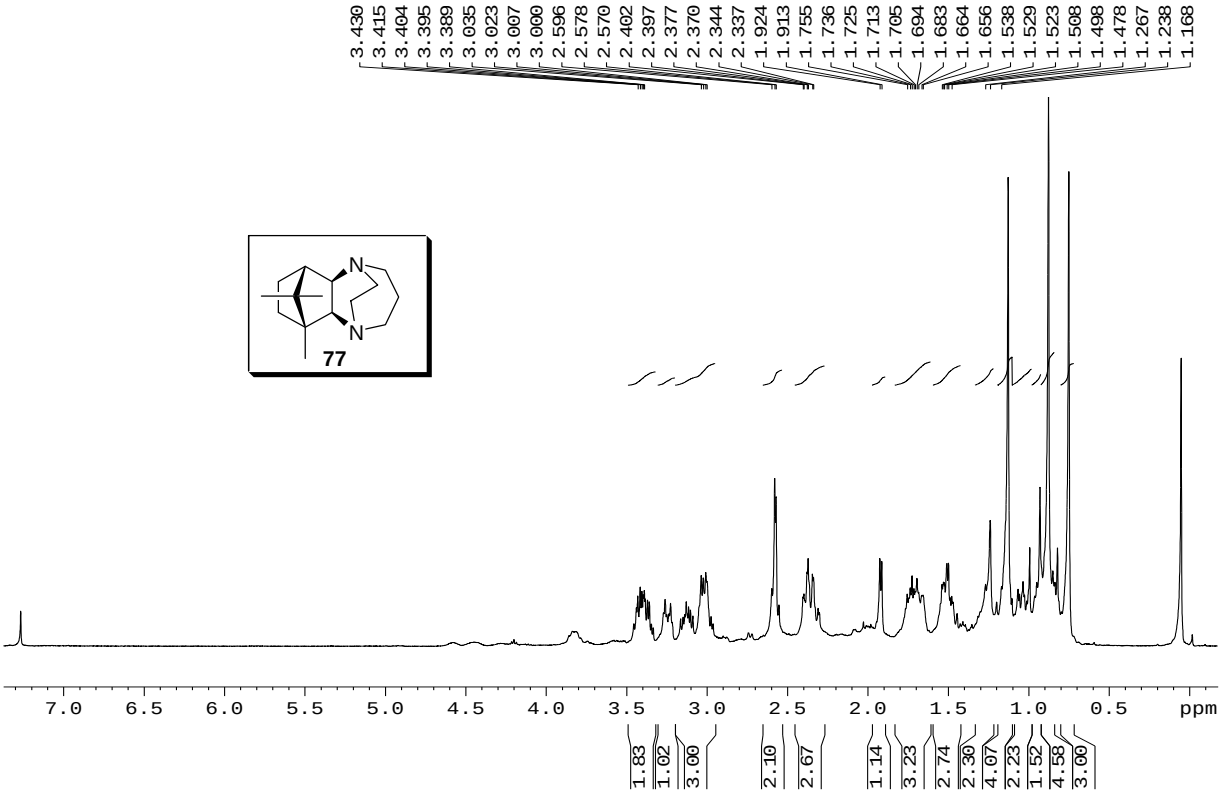
Spectrum No. 17 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 Hz, $CDCl_3$)



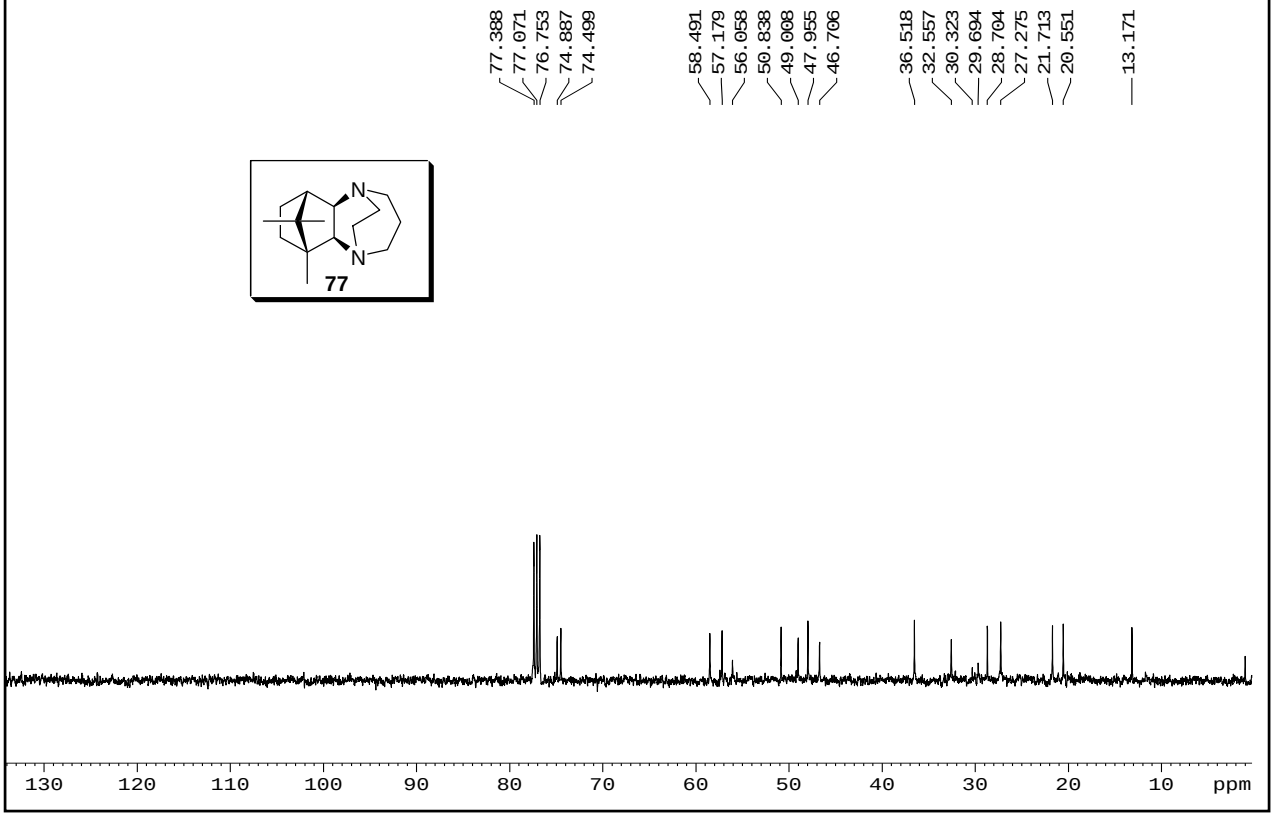
Spectrum No. 18 (Chapter 1, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



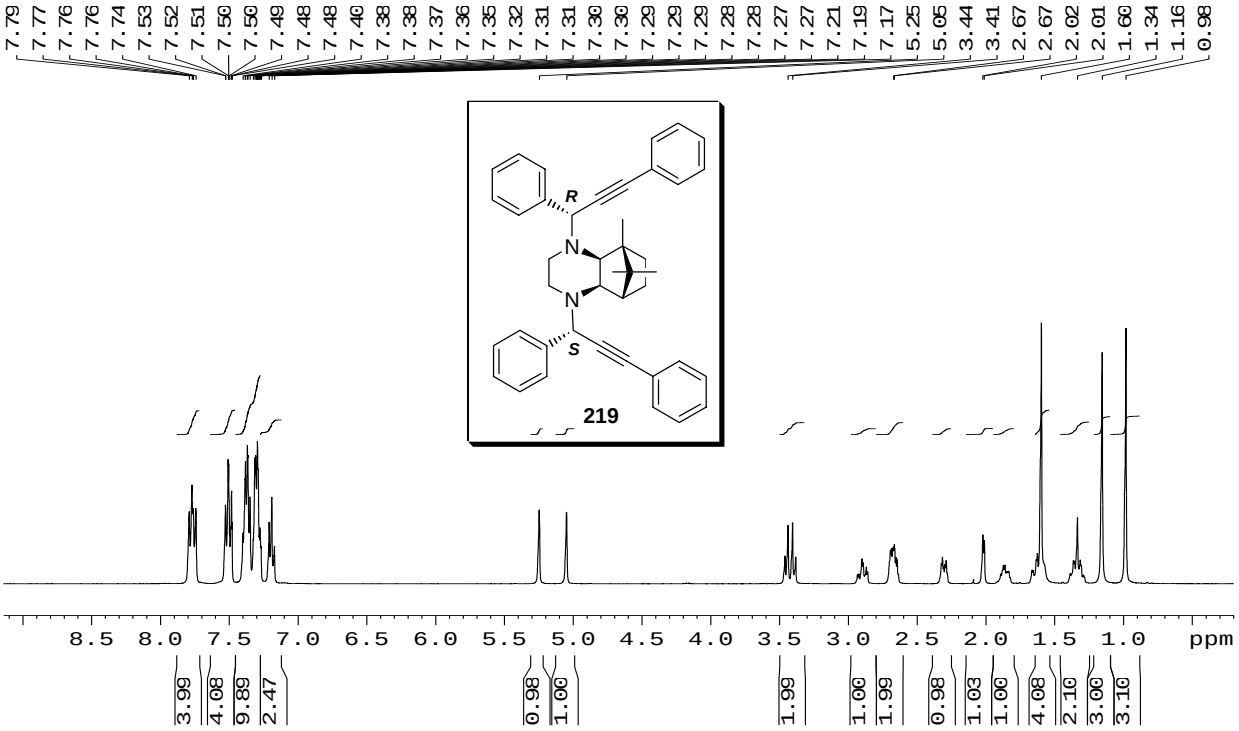
Spectrum No. 19 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



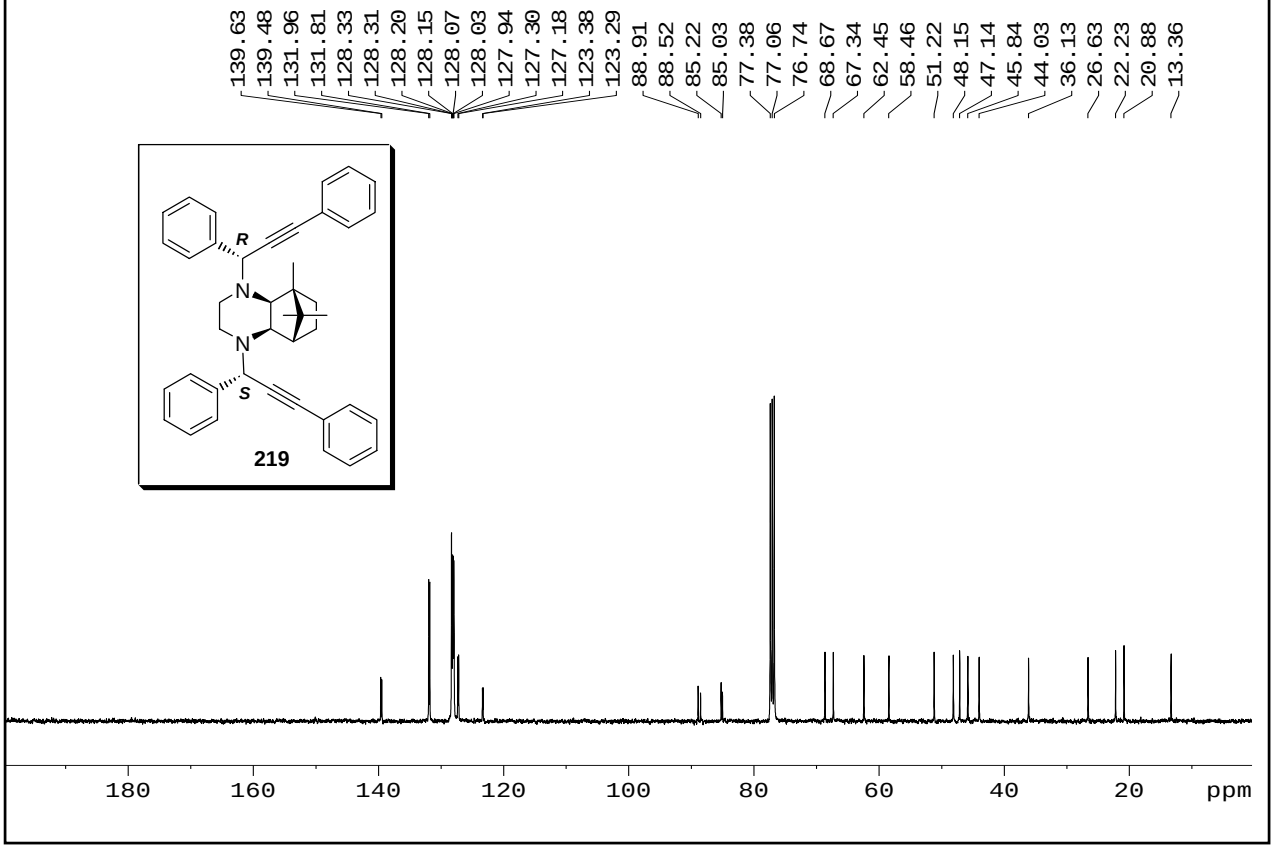
Spectrum No. 20 (Chapter 1, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



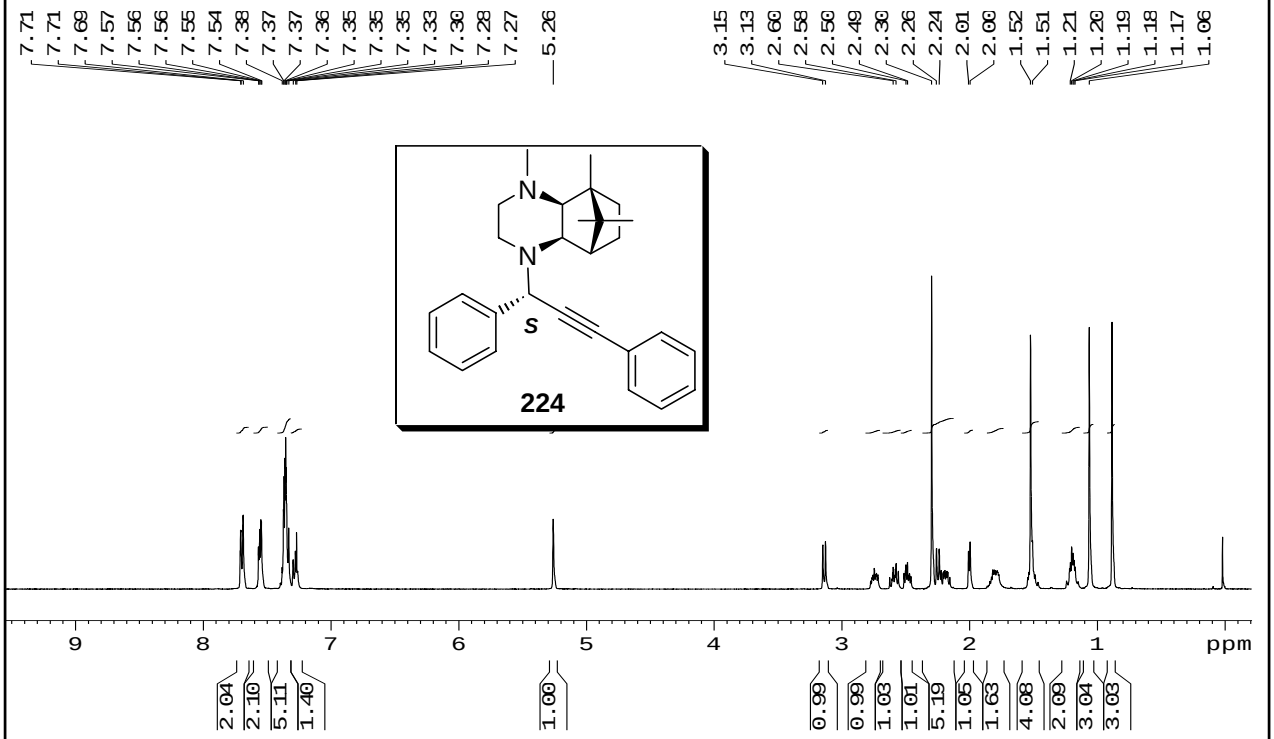
Spectrum No. 21 (Chapter 2, Section 2.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



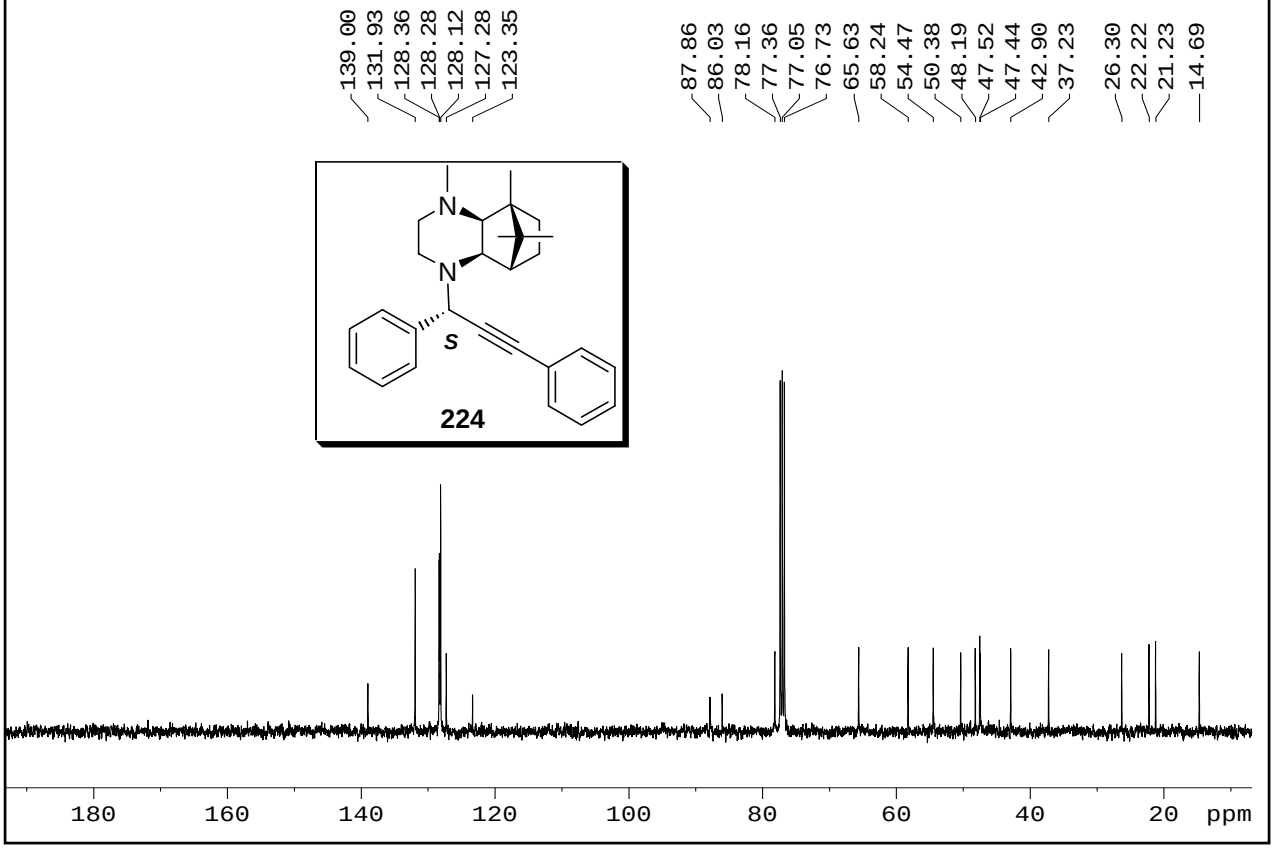
Spectrum No. 22 (Chapter 2, Section 2.2.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



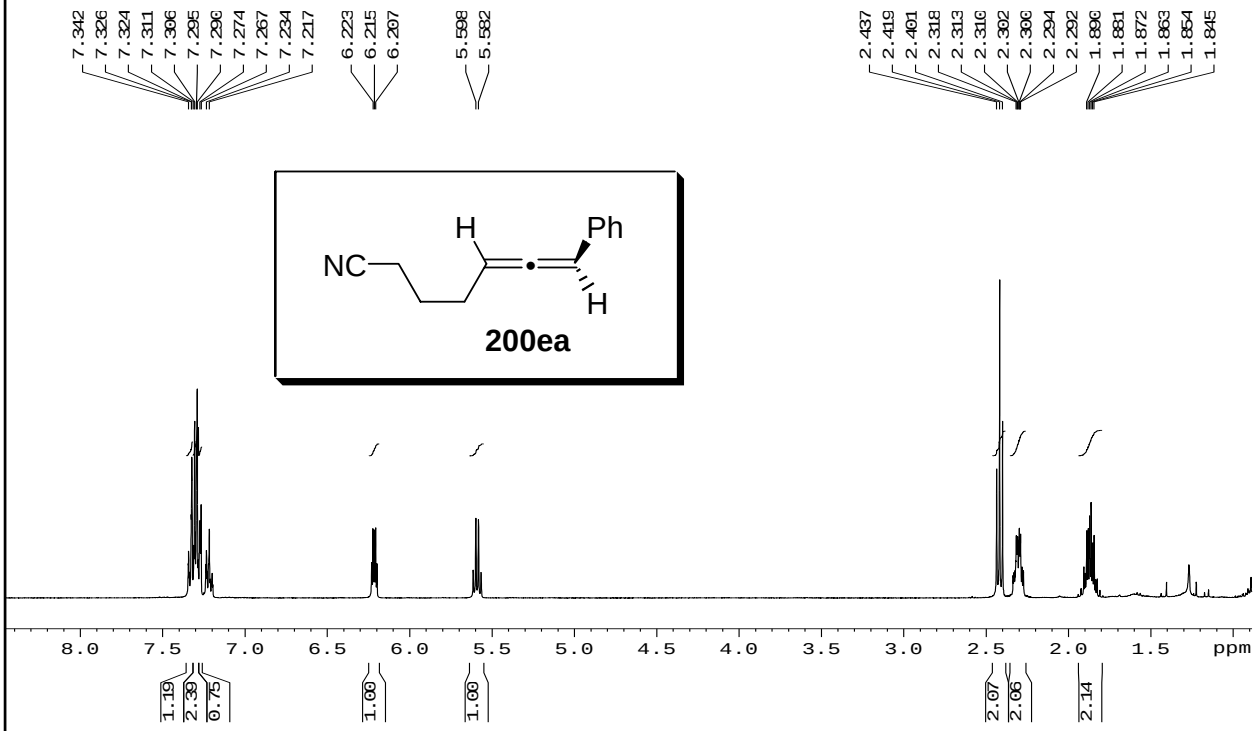
Spectrum No. 23 (Chapter 2, Section 2.2.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



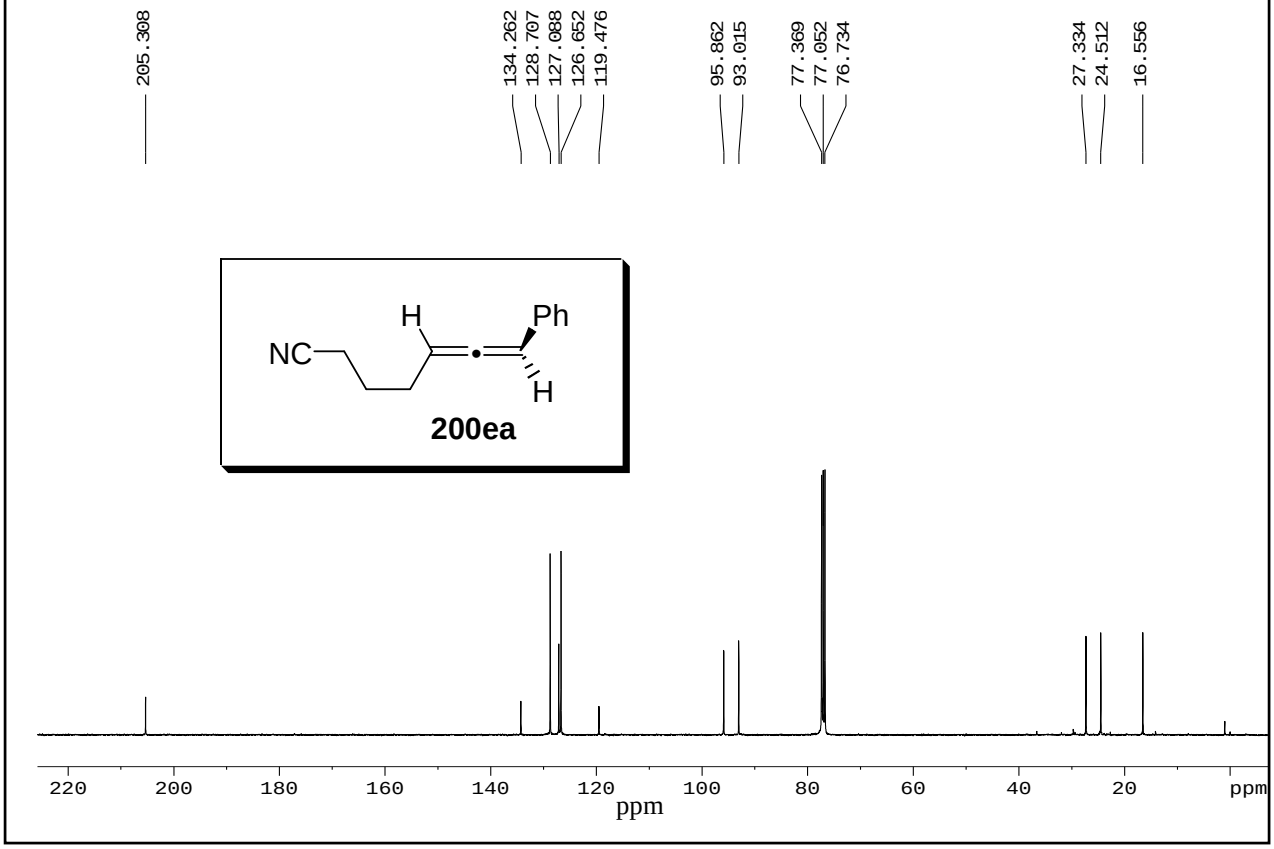
Spectrum No. 24 (Chapter 2, Section 2.2.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



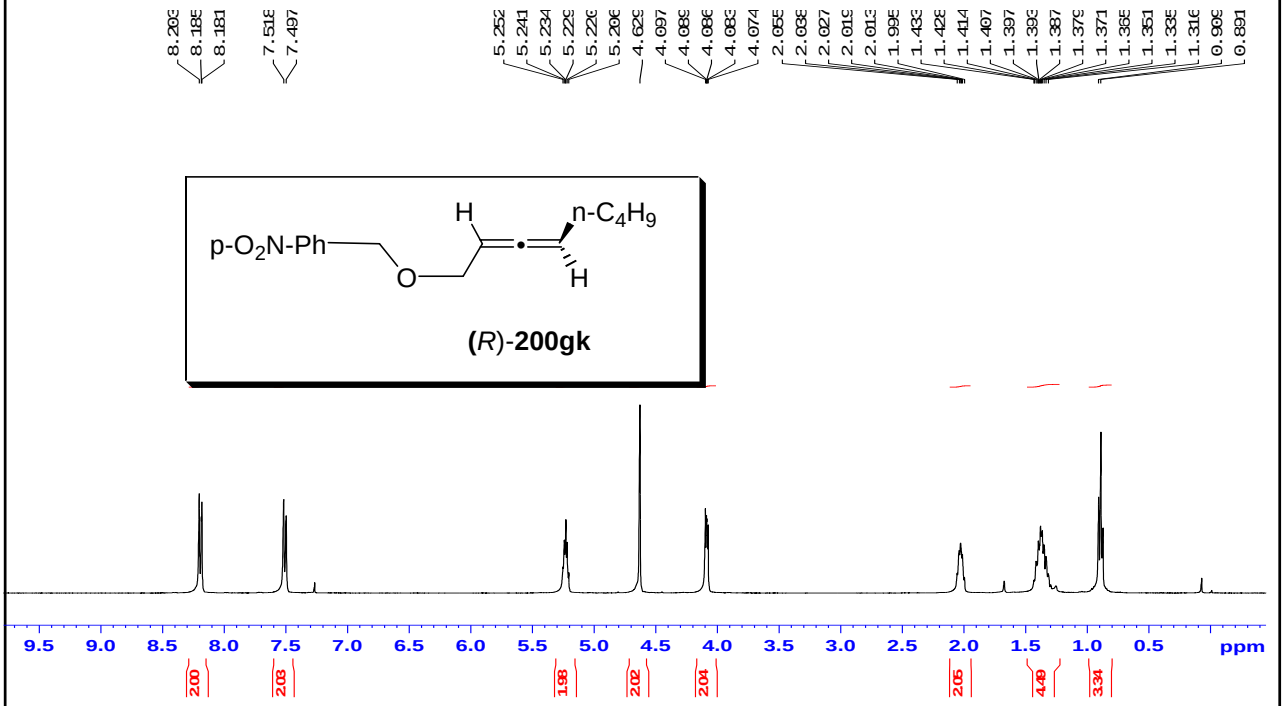
Spectrum No. 25 (Chapter 2, Table 3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



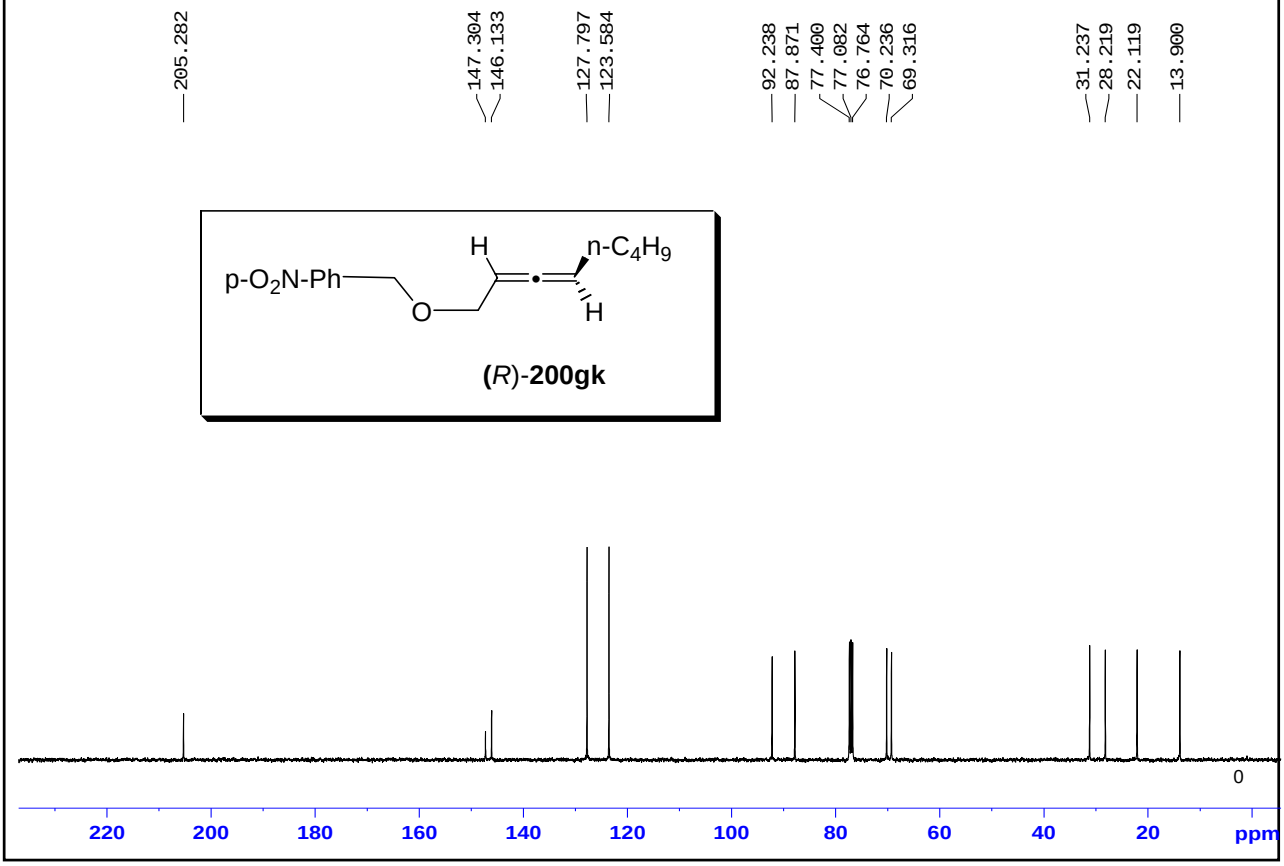
Spectrum No. 26 (Chapter 2, Table 3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



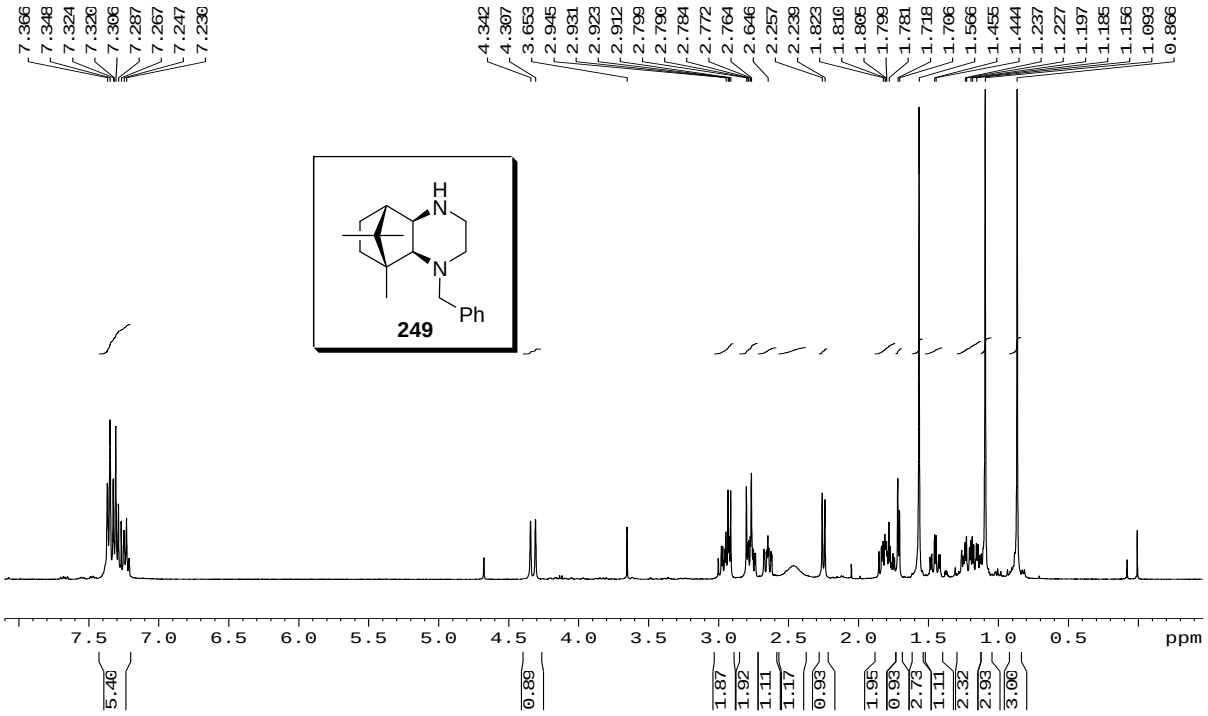
Spectrum No. 27 (Chapter 2, Section 2.2.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



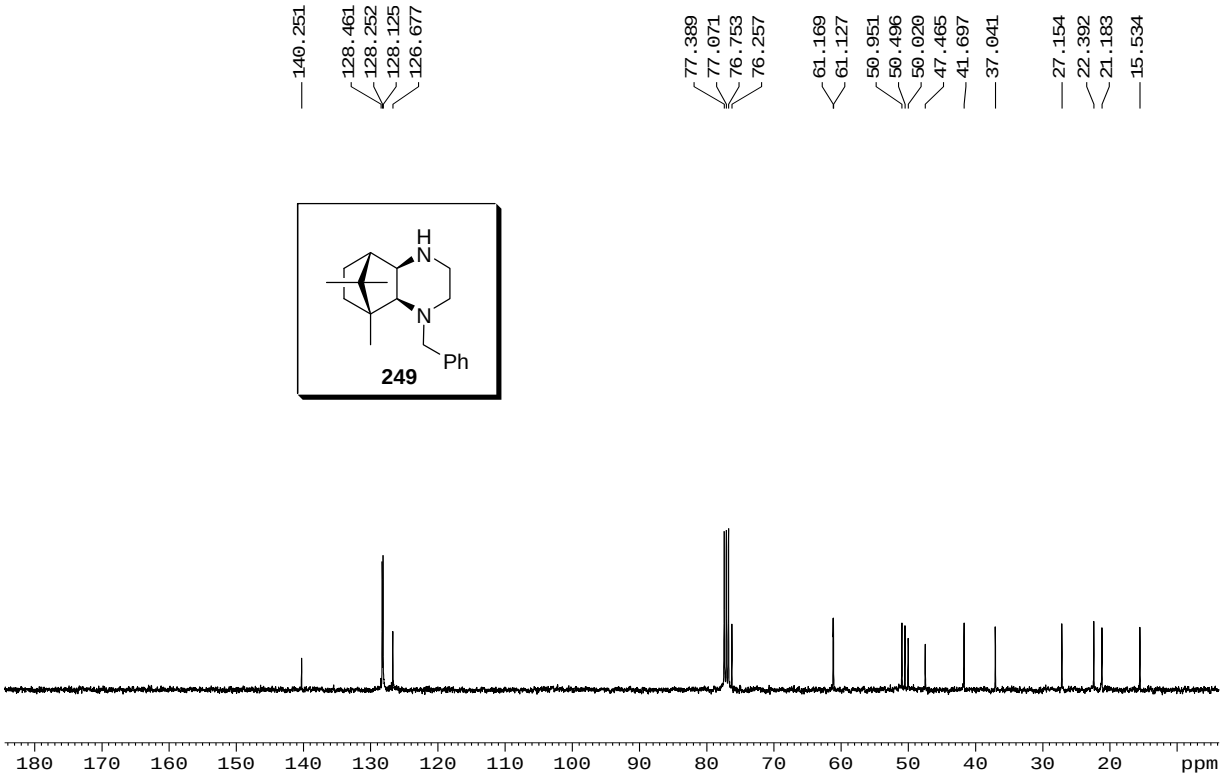
Spectrum No. 28 (Chapter 2, Section 2.2.8) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



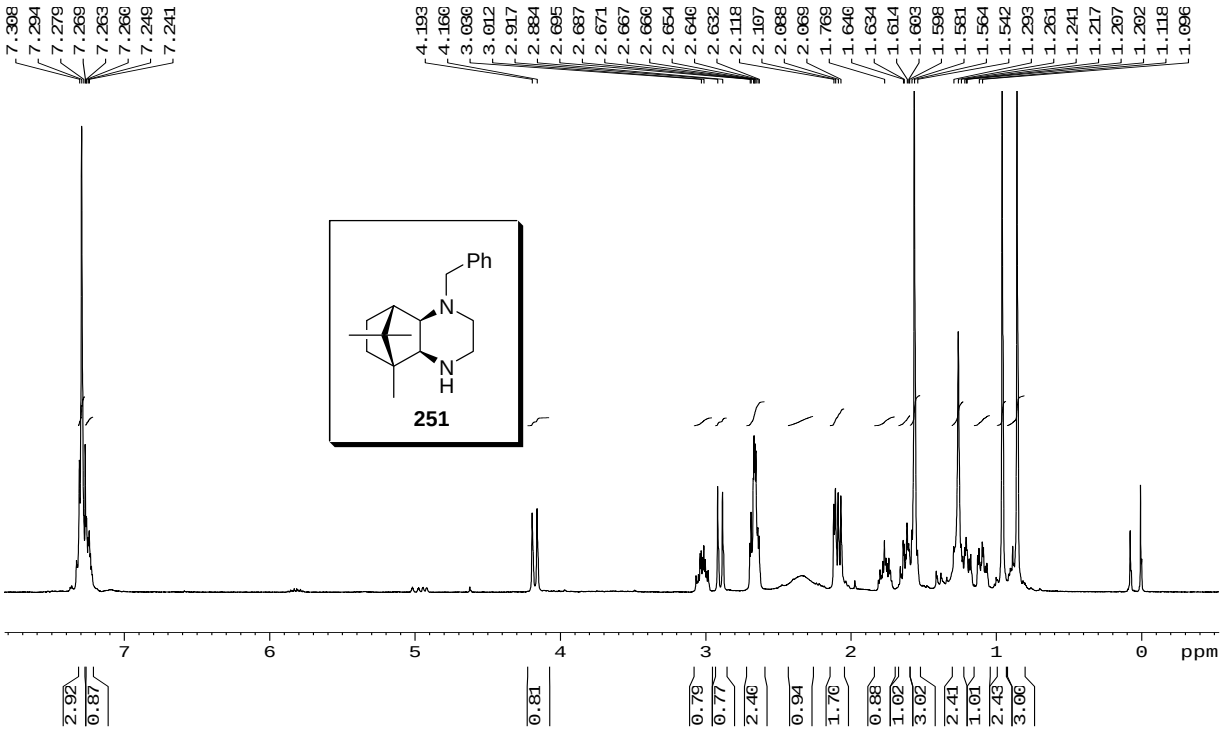
Spectrum No. 29 (Chapter 2, Section 2.2.11) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



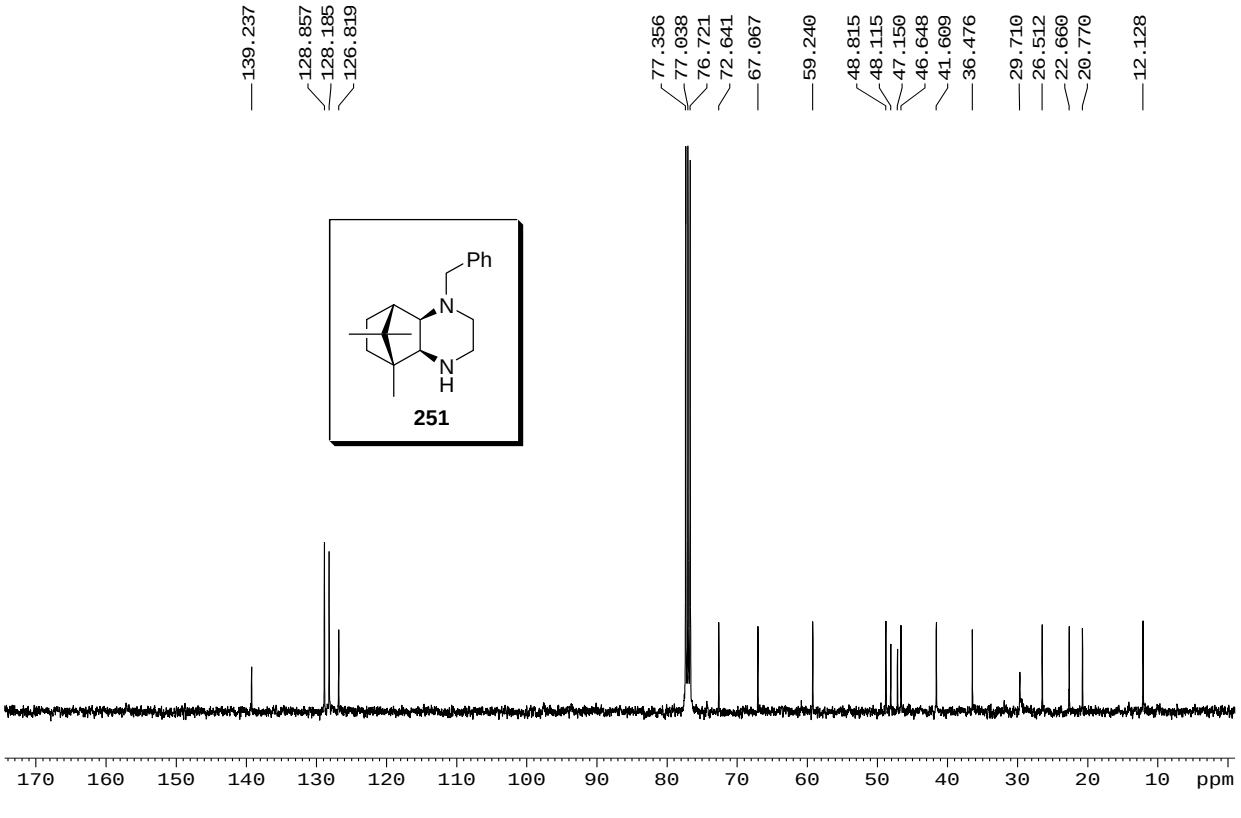
Spectrum No. 30 (Chapter 2, Section 2.2.11) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



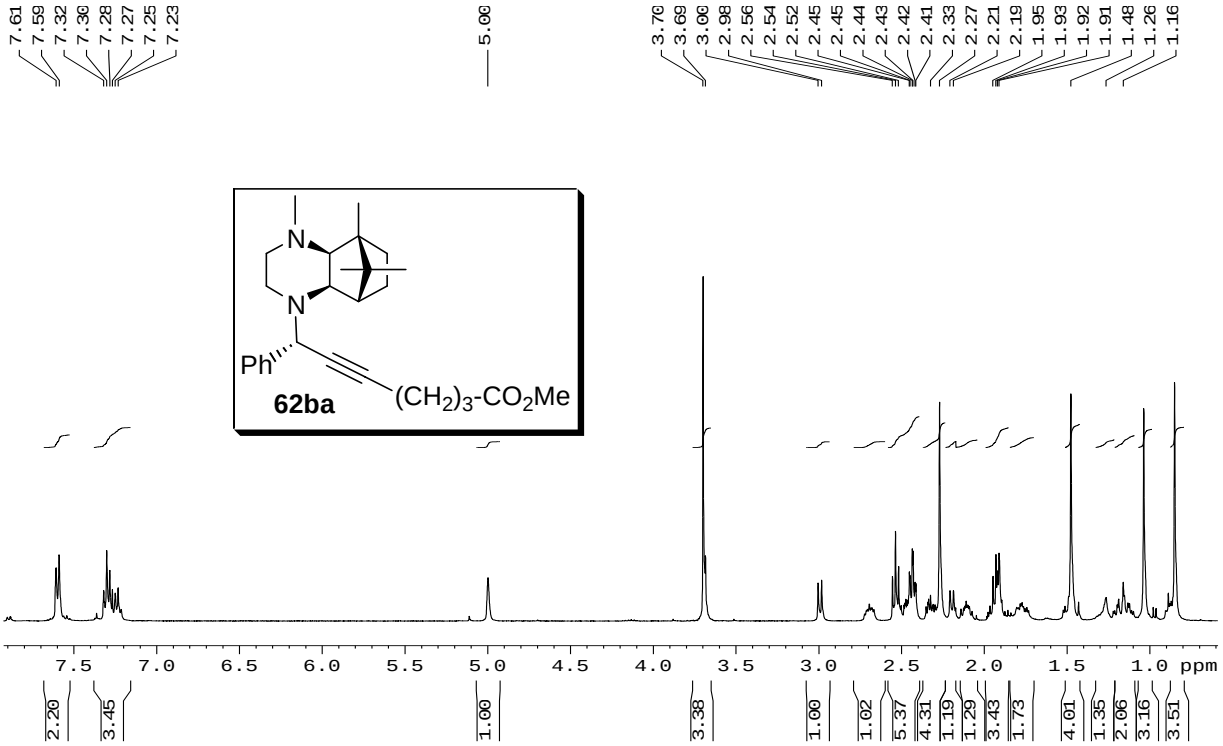
Spectrum No. 31 (Chapter 2, Section 2.2.11) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



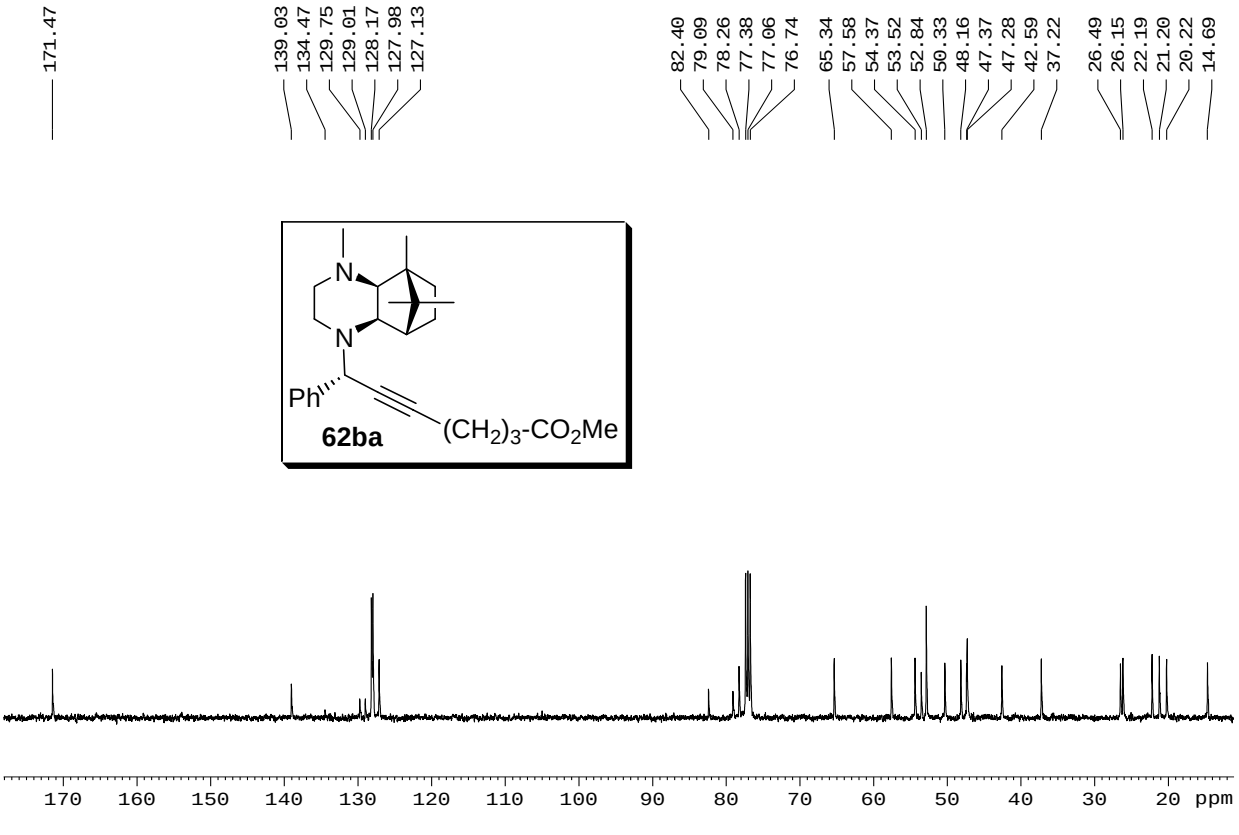
Spectrum No. 32 (Chapter 2, Section 2.2.11) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



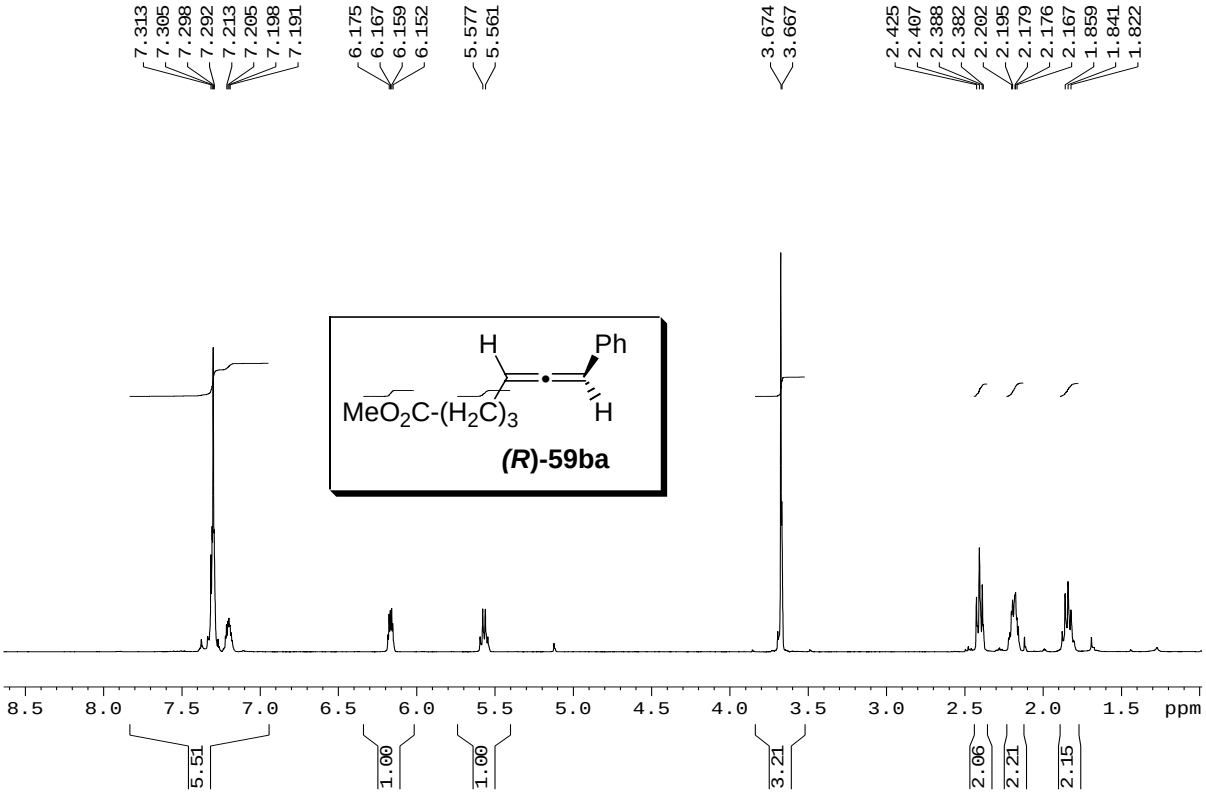
Spectrum No. 33 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



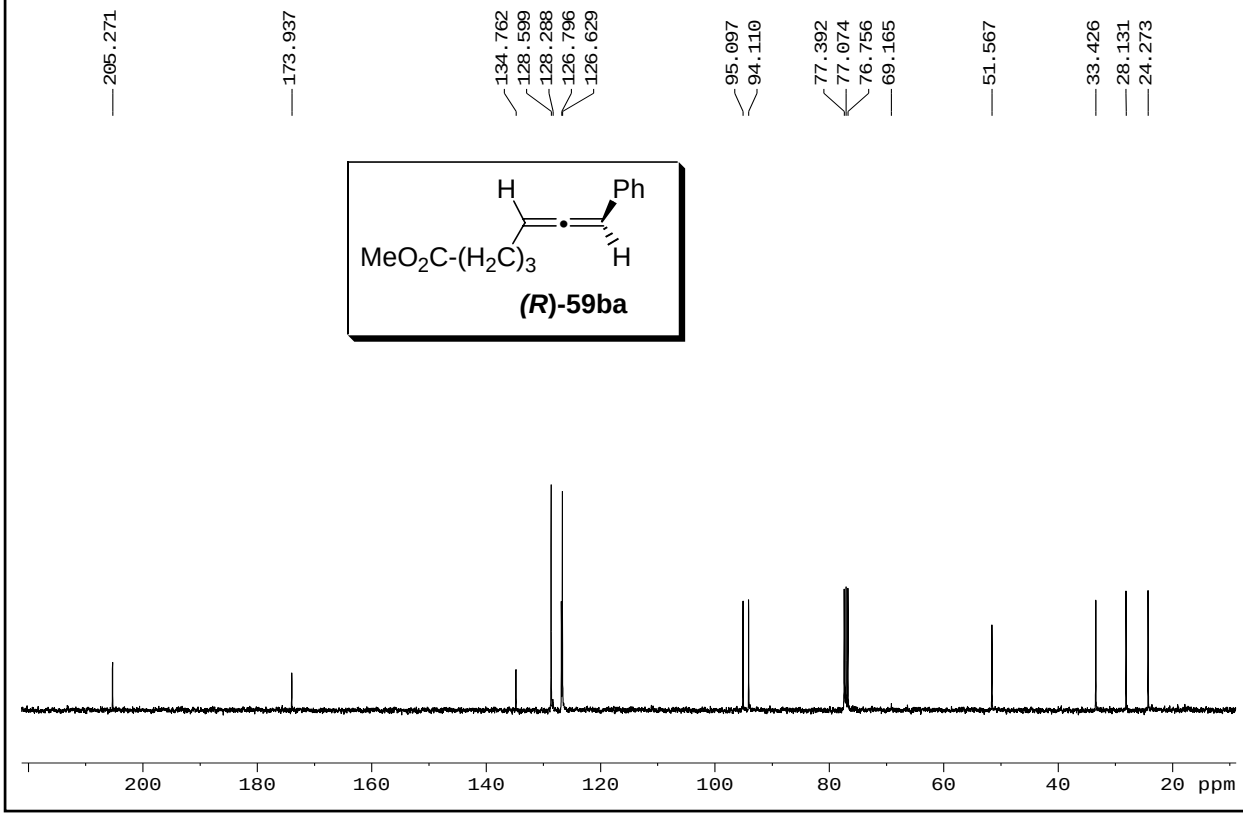
Spectrum No. 34 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



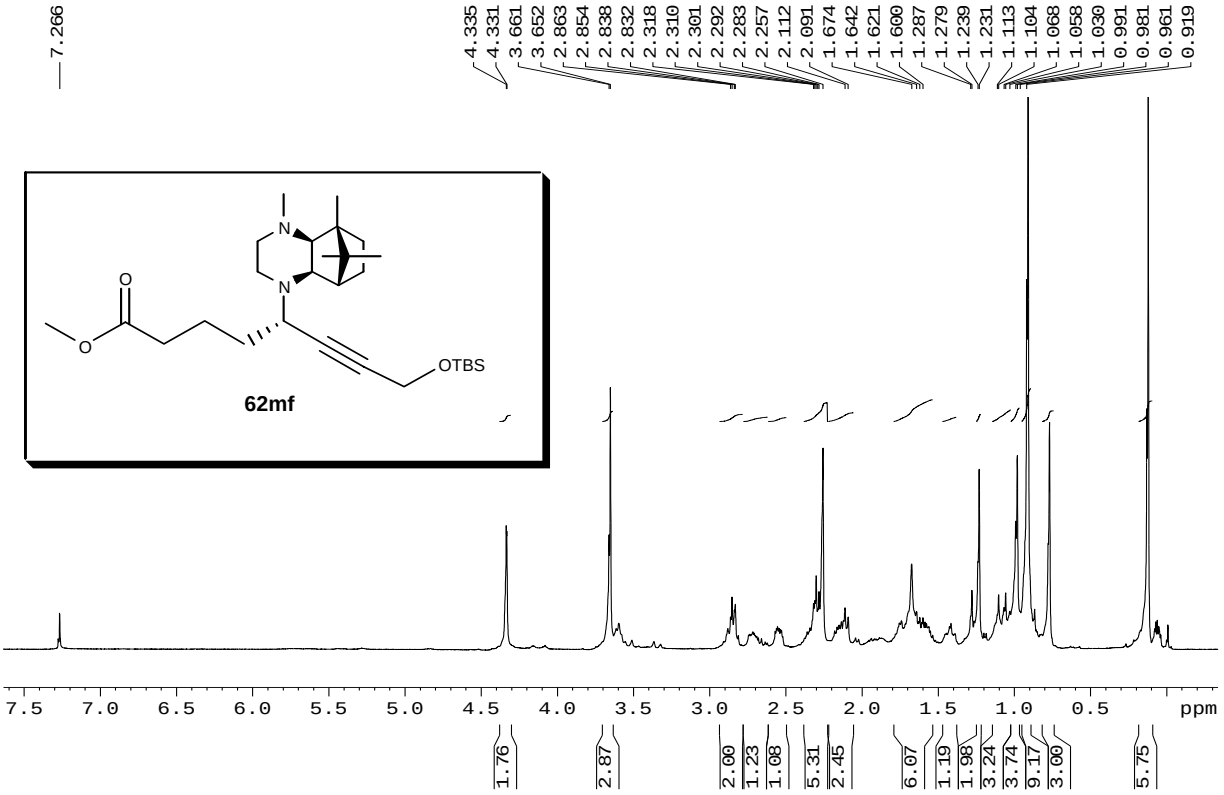
Spectrum No. 35 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



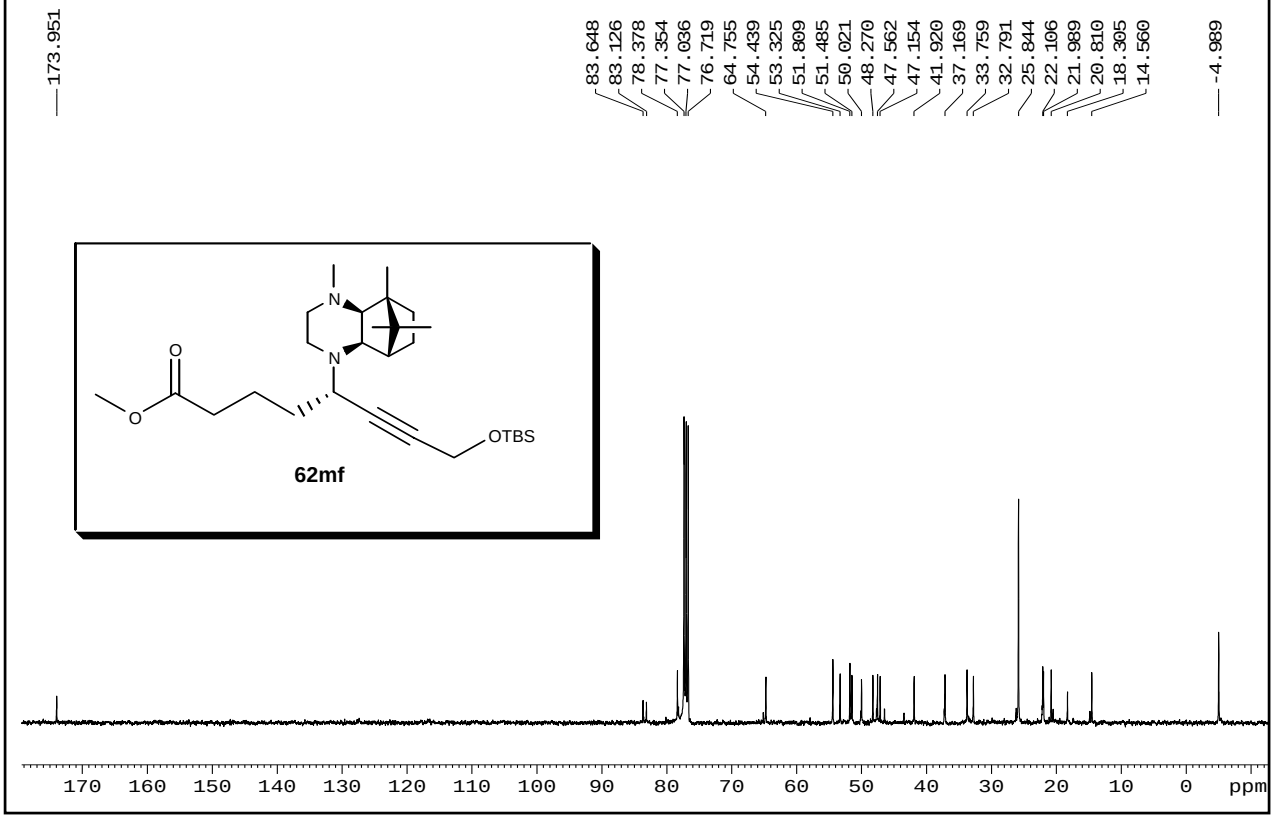
Spectrum No. 36 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



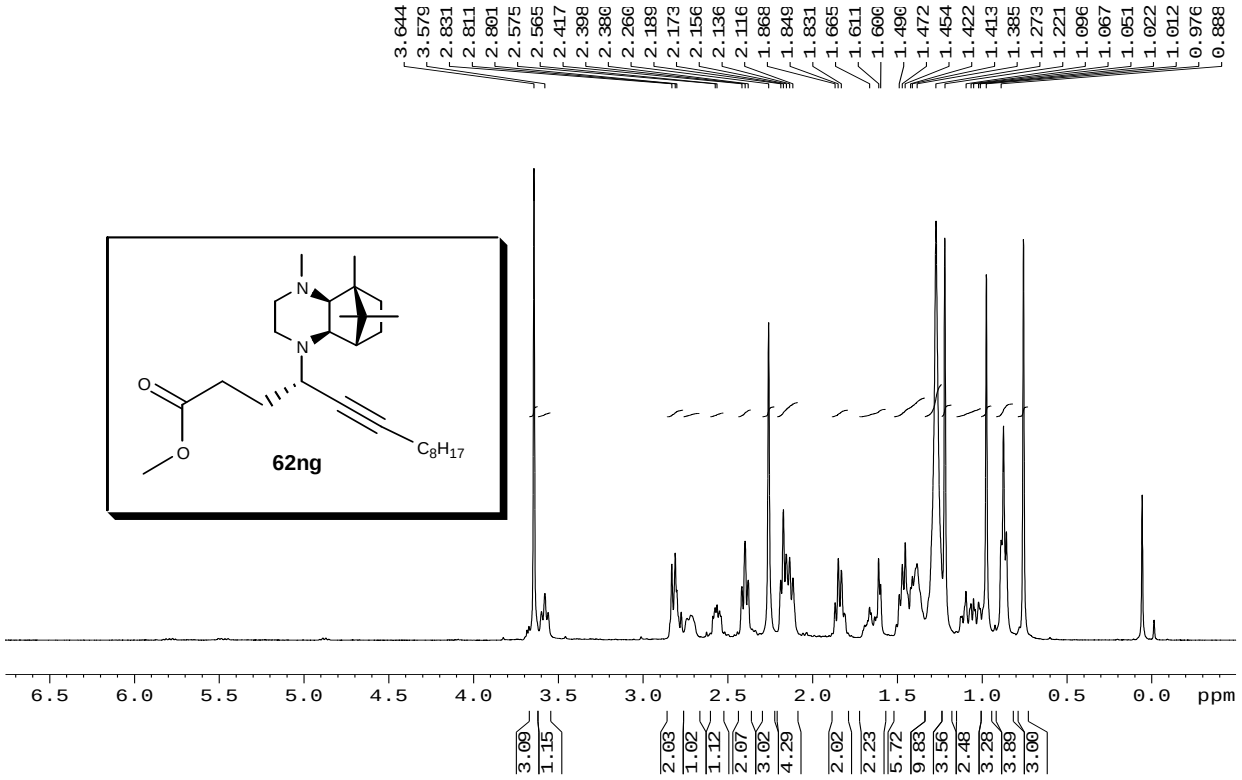
Spectrum No. 37 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



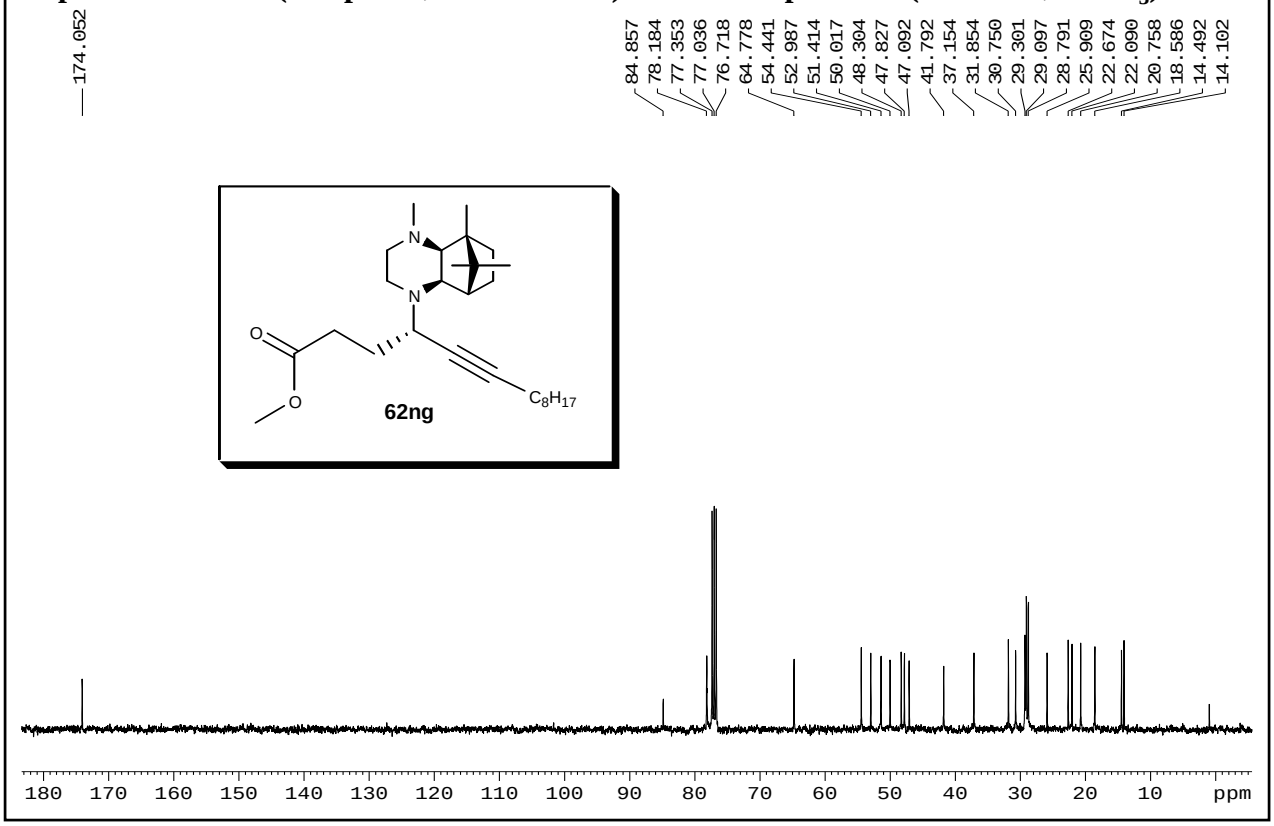
Spectrum No. 38 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



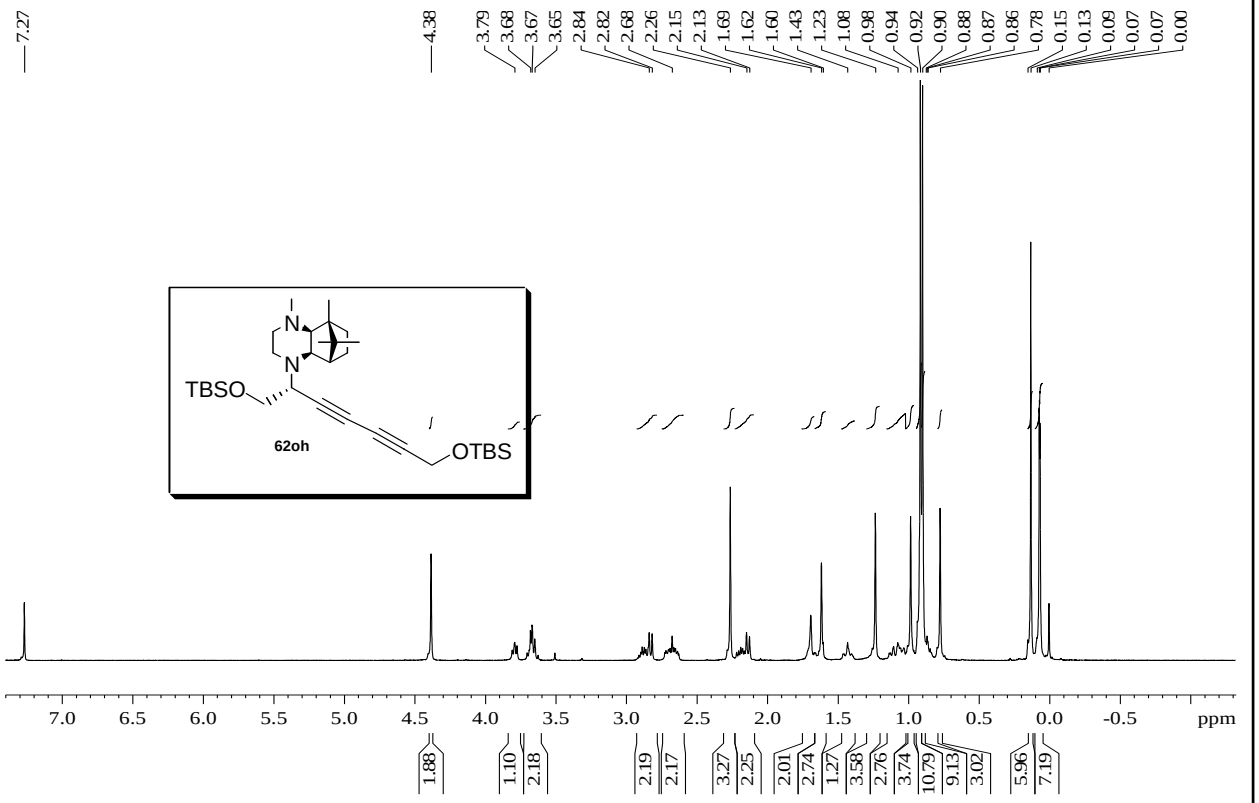
Spectrum No. 39 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



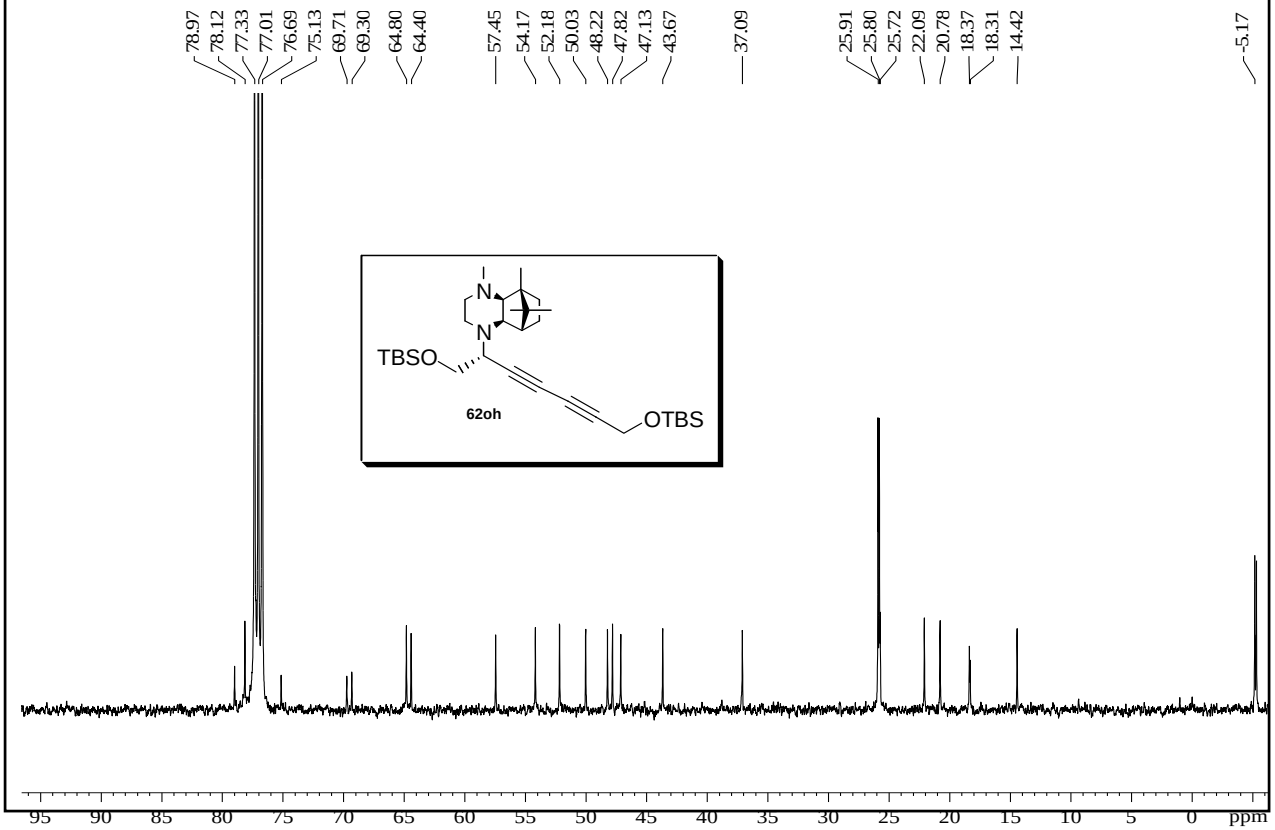
Spectrum No. 40 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



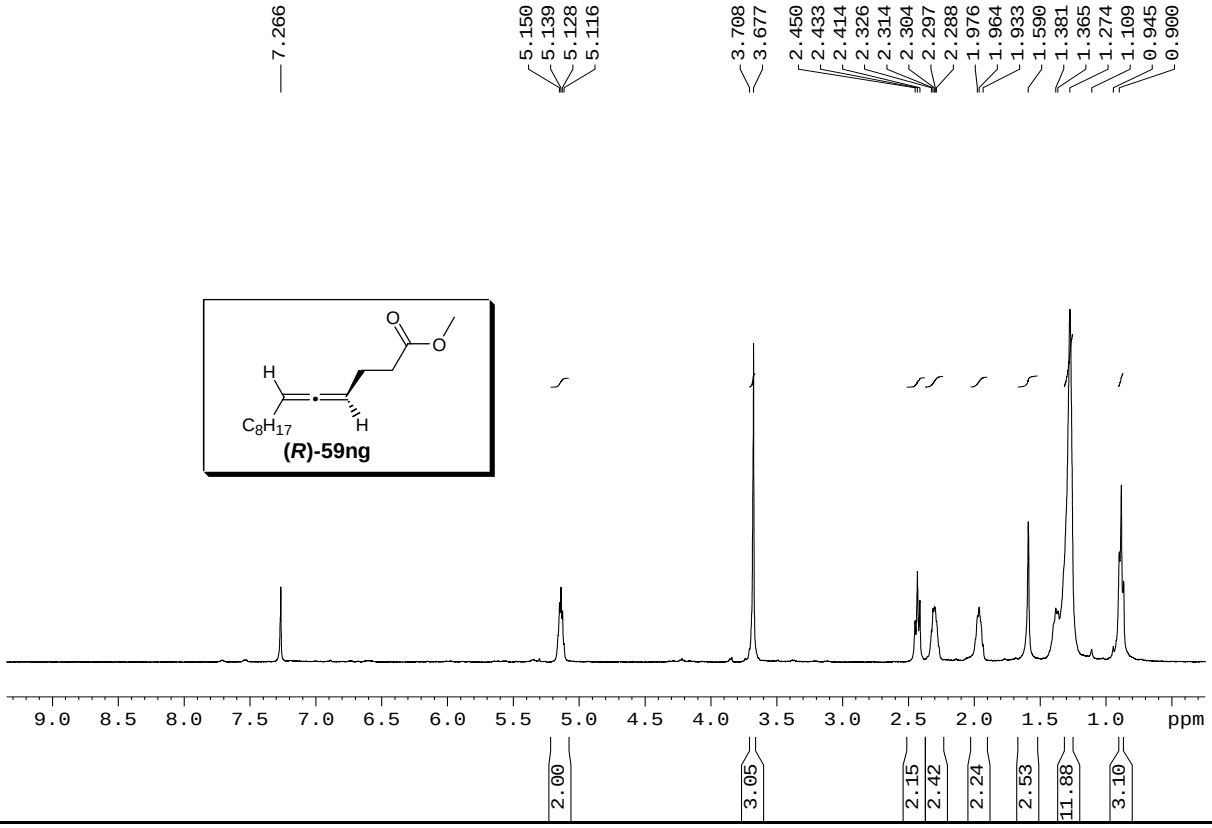
Spectrum No. 41 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



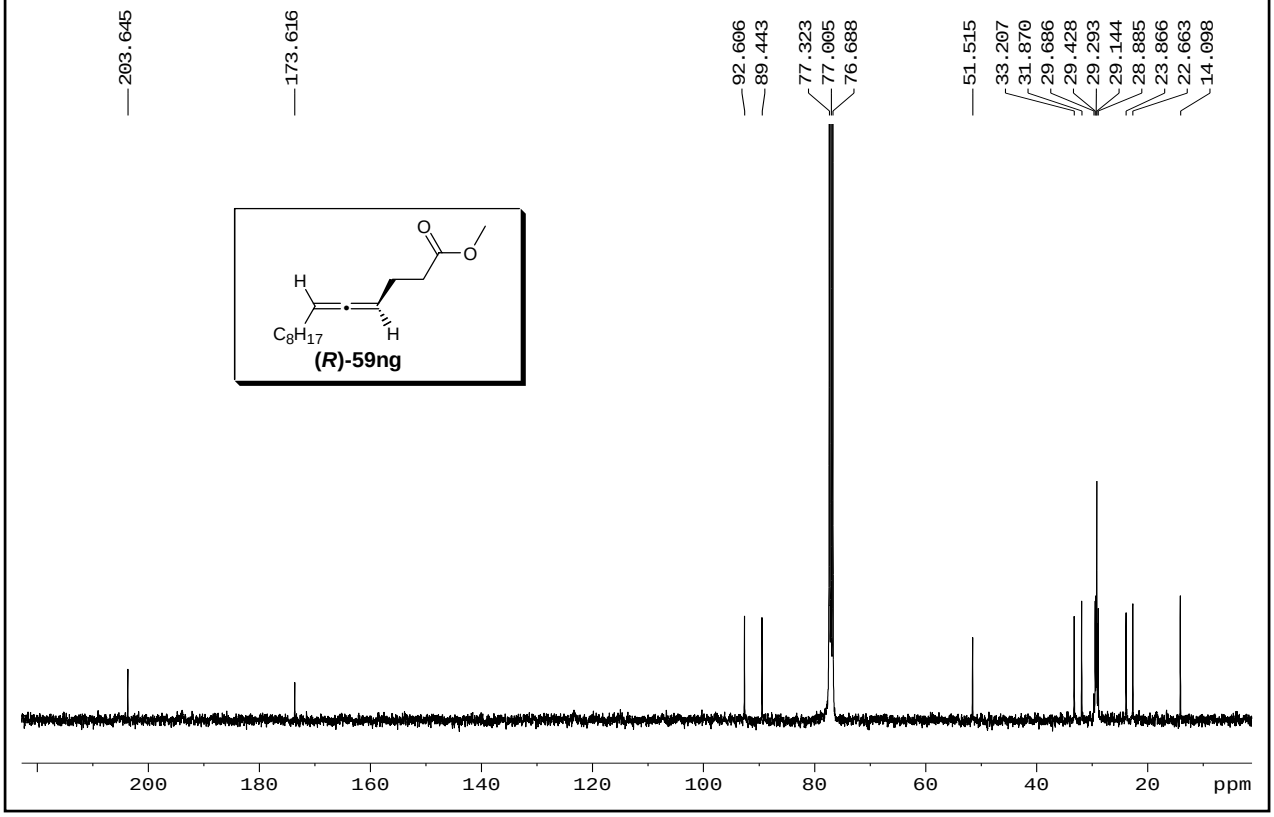
Spectrum No. 42 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



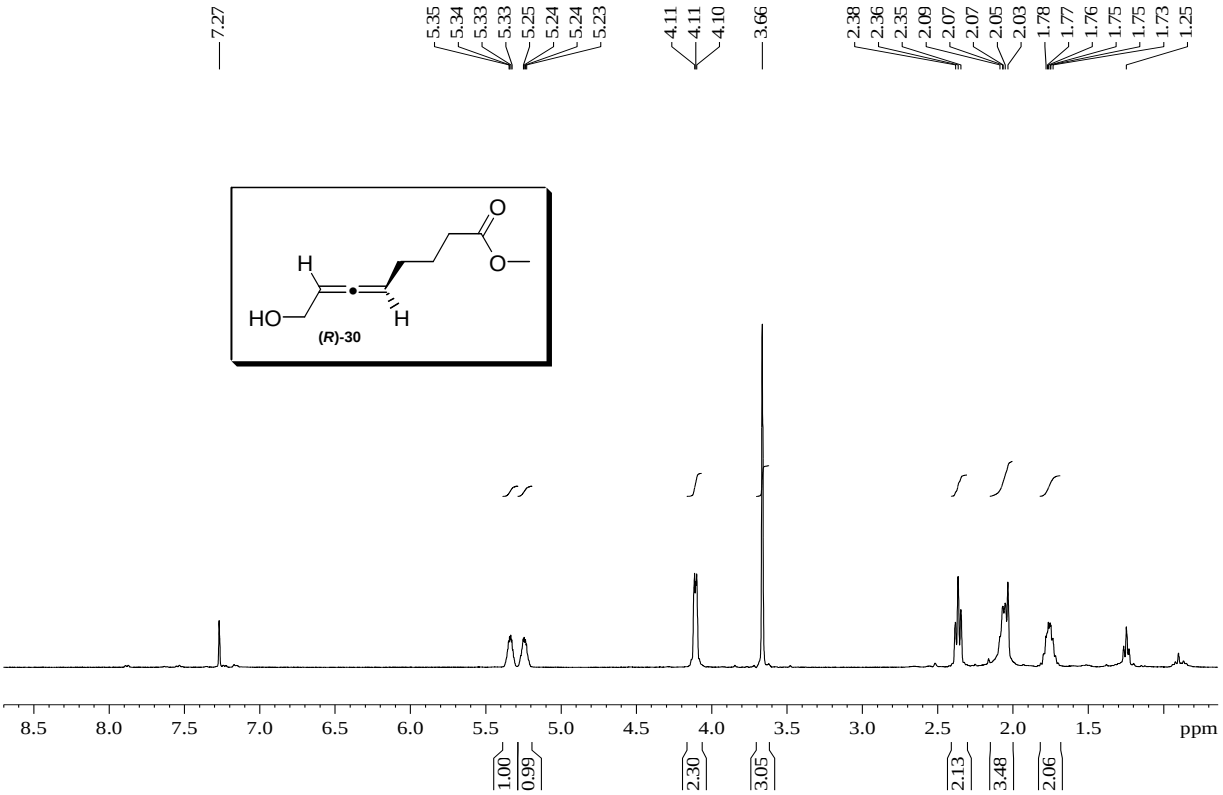
Spectrum No. 43 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



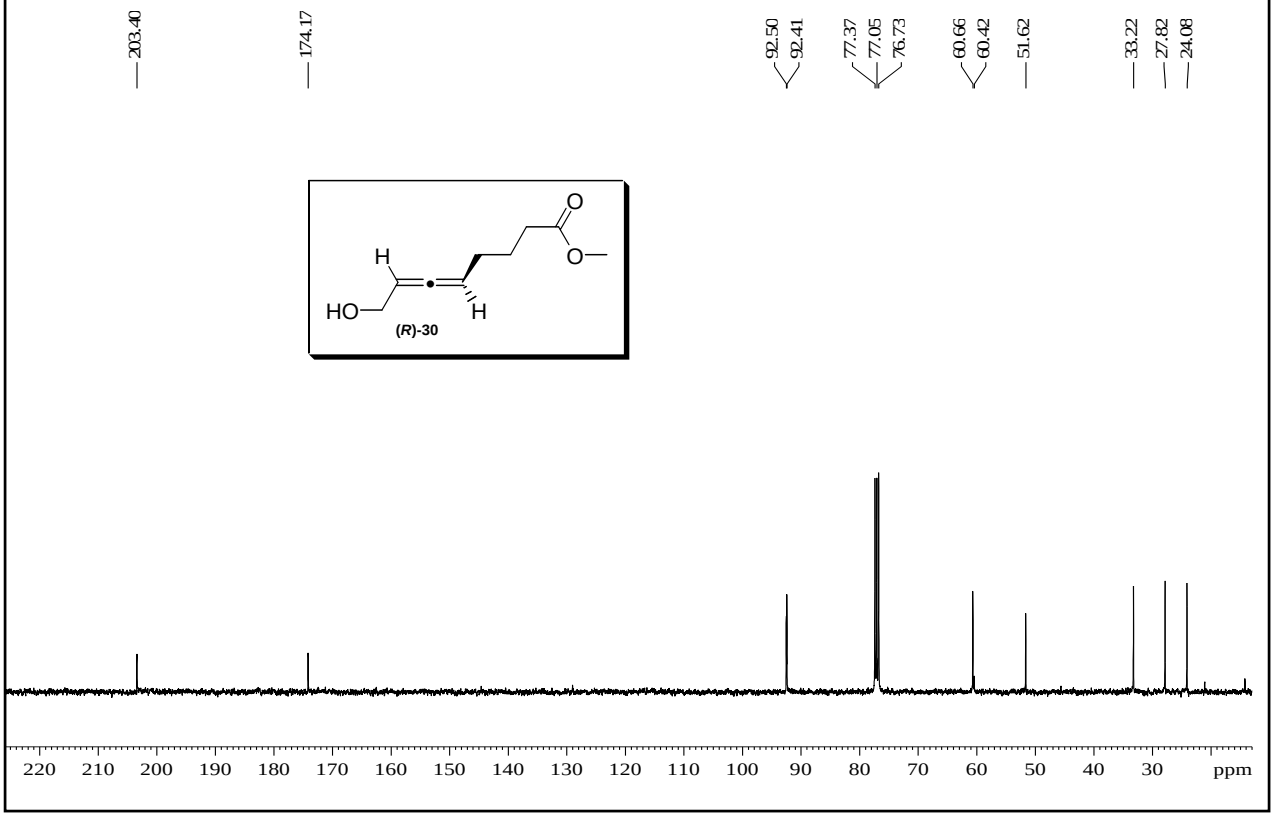
Spectrum No. 44 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



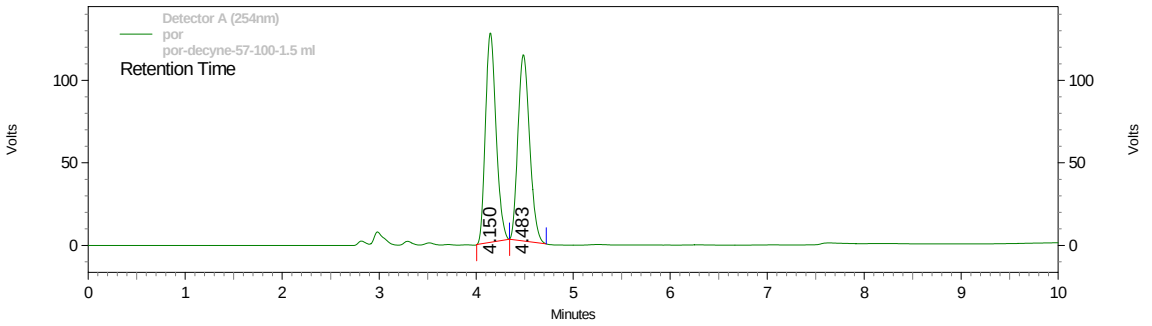
Spectrum No. 45 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



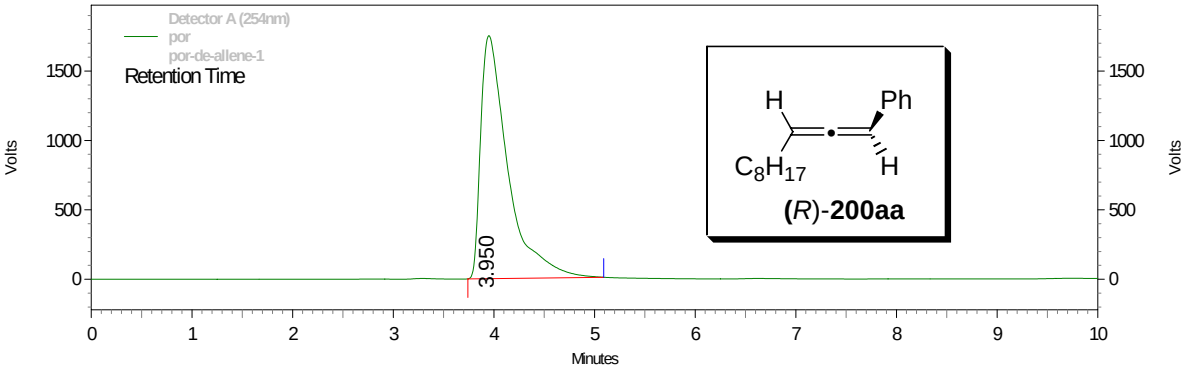
Spectrum No. 46 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



HPLC profile of 200aa: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.
Racemic 200aa:

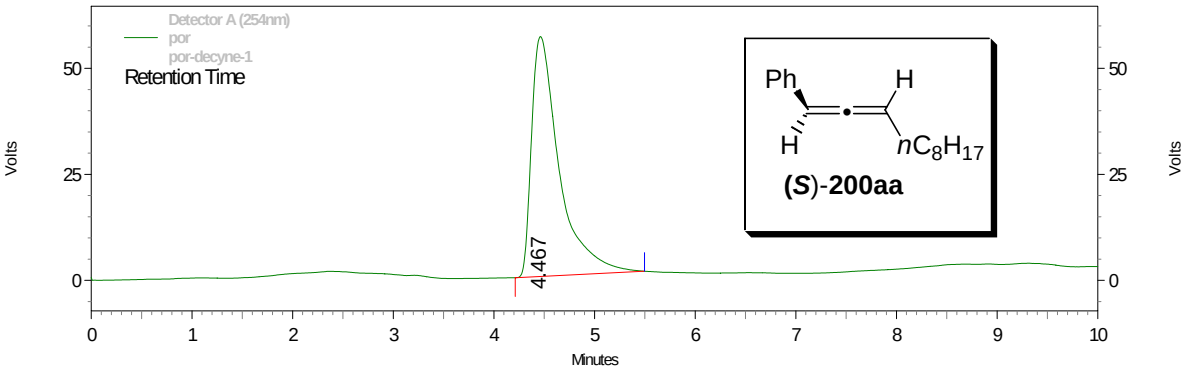


***(R)*-200aa: (Chapter 2, Table 3)**



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	3.950	32819923	100.000	1752092	100.000
Totals		32819923	100.000	1752092	100.000

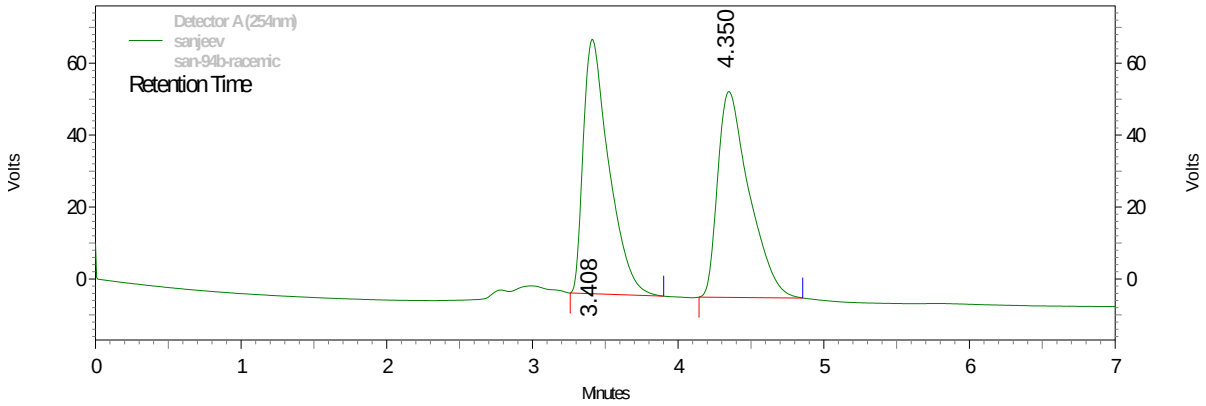
***(S)*-200aa: (Chapter 2, Table 4)**



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	4.467	1080884	100.000	56583	100.000
Totals		1080884	100.000	56583	100.000

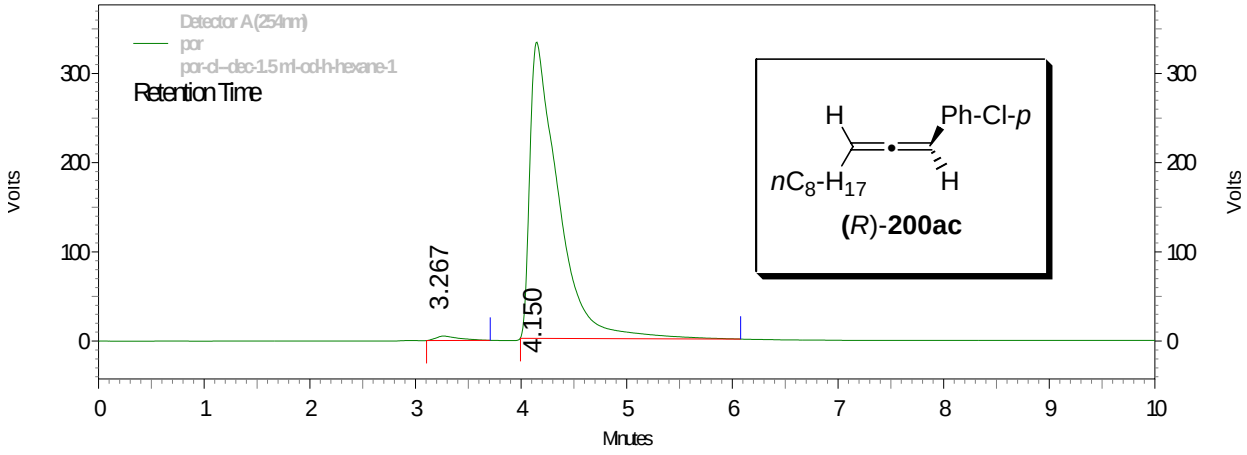
HPLC Profile of 200ac: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	3.408	864861	50.198	70751	55.256
2	4.350	858034	49.802	57292	44.744

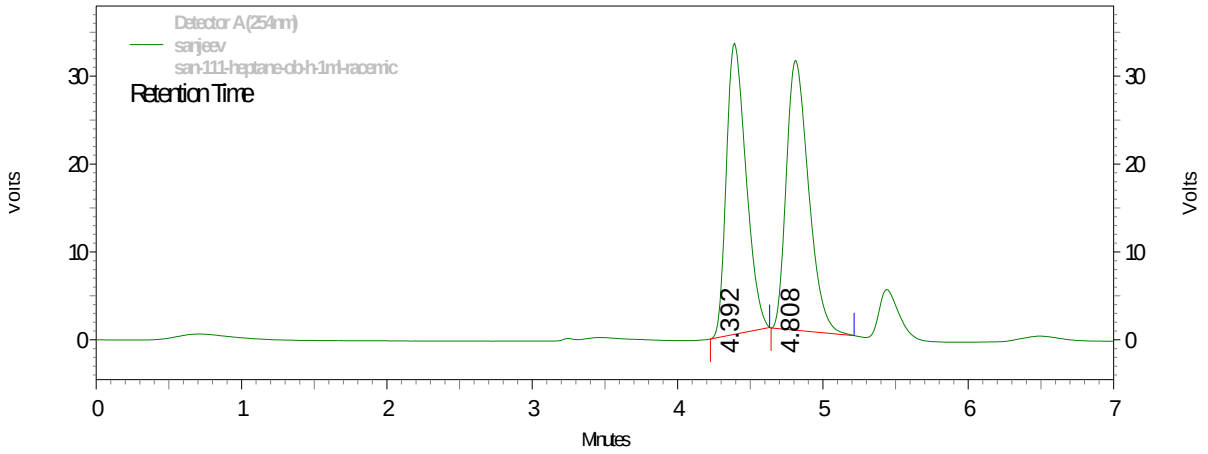
(*R*)-200ac: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	3.267	74703	1.183	4979	1.477
2	4.150	6240095	98.817	332099	98.523
Totals		6314798	100.000	337078	100.000

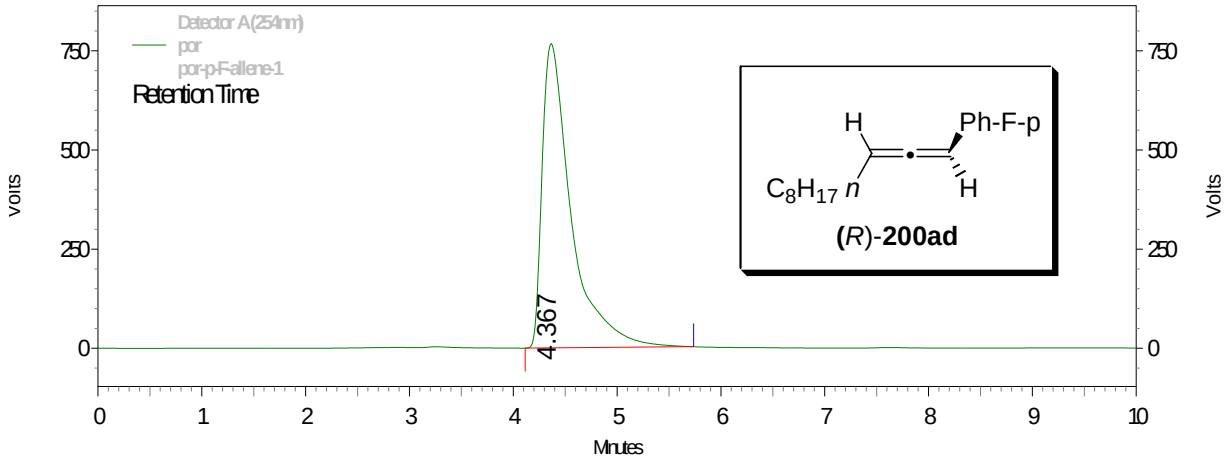
HPLC Profile of 200ad: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min.

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	4.392	311840	48.779	33107	51.898
2	4.808	327454	51.221	30685	48.102

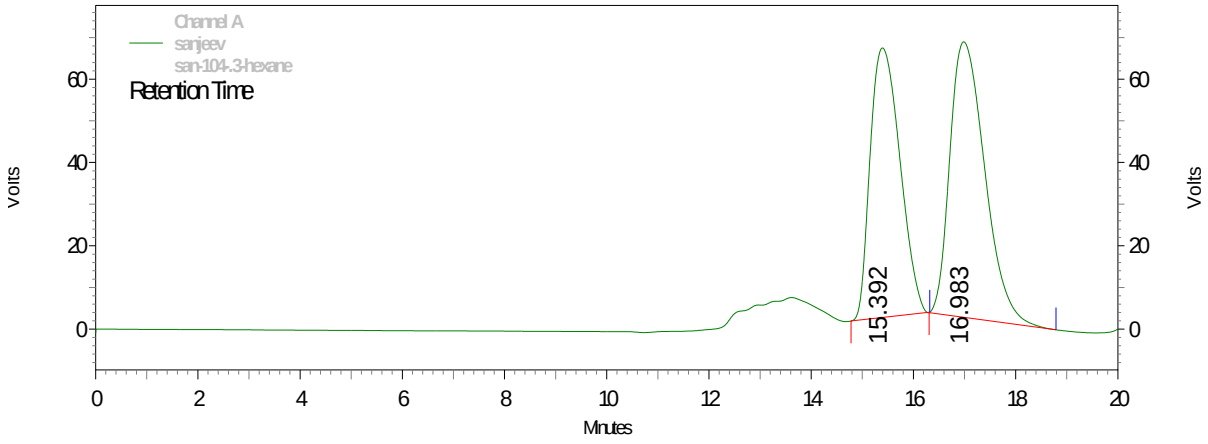
(*R*)-200ad: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	4.367	14863140	100.000	766992	100.000
Totals		14863140	100.000	766992	100.000

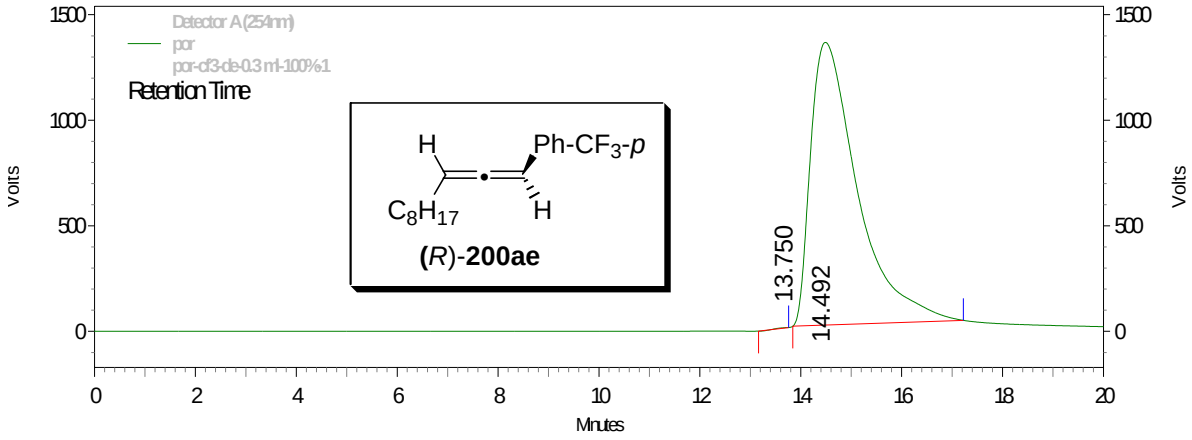
HPLC Profile of 200ae: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	15.392	2619110	45.424	64723	49.456
2	16.983	3146759	54.576	66146	50.544

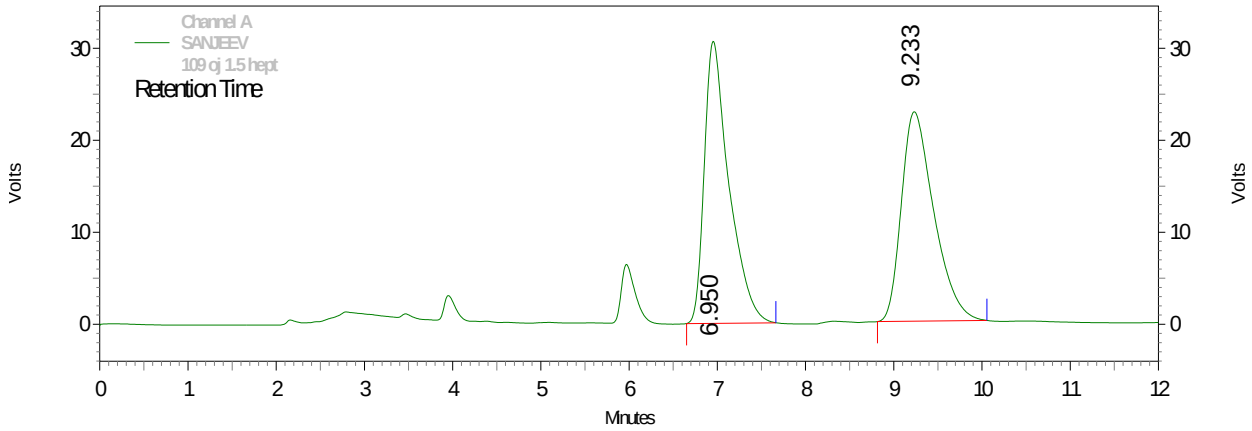
(*R*)-200ae: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	13.750	20802	0.024	99	0.007
2	14.492	86307969	99.976	1339279	99.993
Totals		86328771	100.000	1339378	100.000

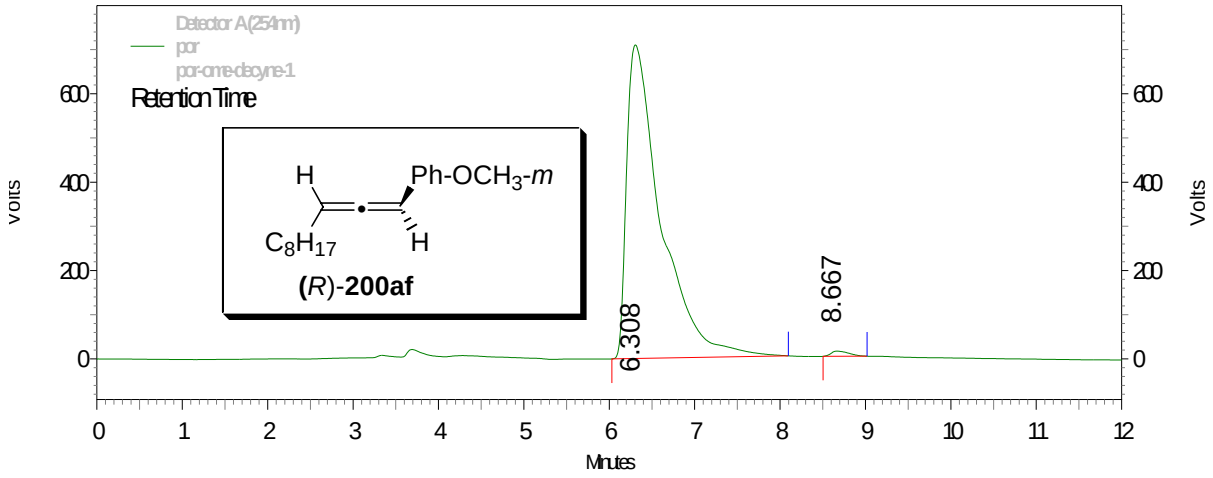
HPLC Profile of 200af: chiral column, chiralcel OJ-H, hexanes:i-PrOH/100:0; flow rate 1.0 mL/min.

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	6.950	594045	50.510	30647	57.376
2	9.233	582059	49.490	22767	42.624

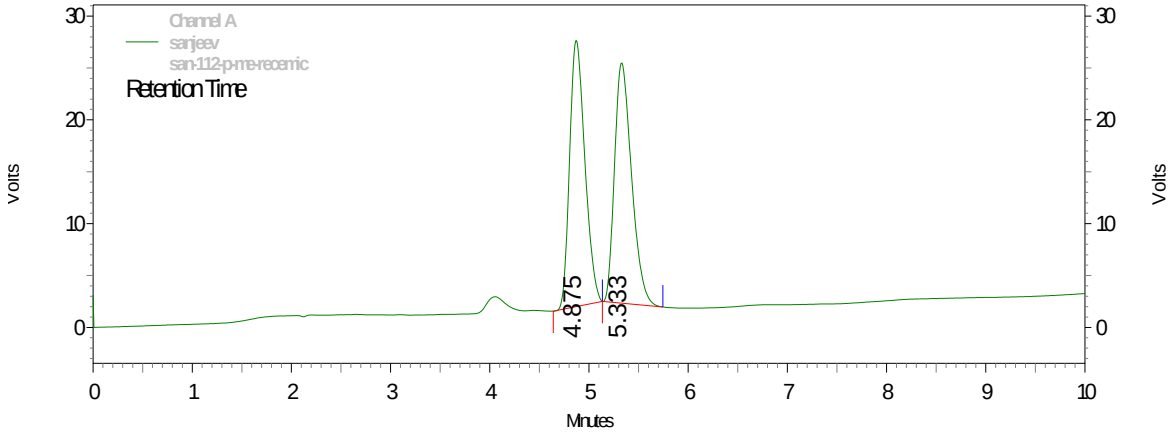
(*R*)-200af: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	6.308	19705312	99.161	709759	98.383
2	8.667	166709	0.839	11666	1.617
Totals		19872021	100.000	721425	100.000

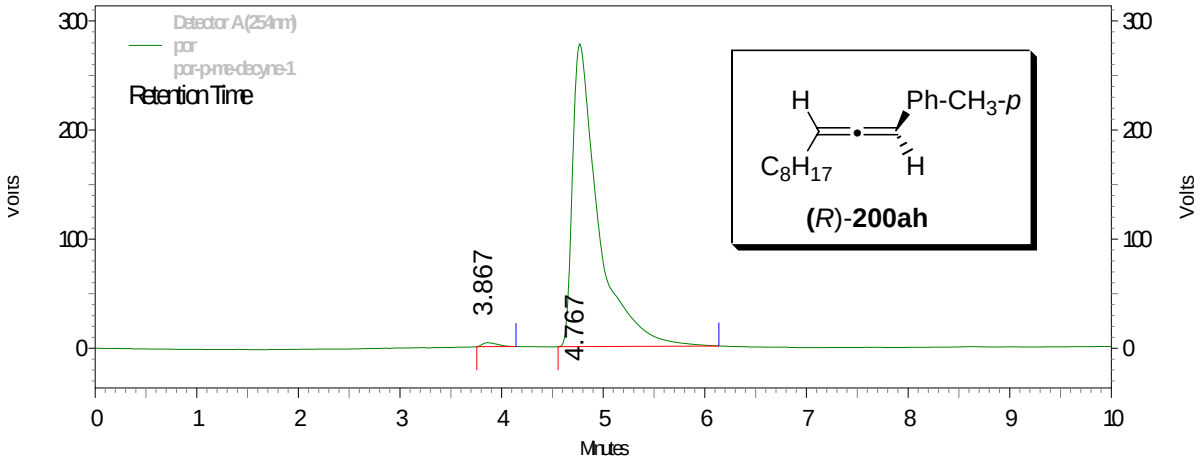
HPLC Profile of 200ah: chiralcel OJ-H, solvent system, heptane:i-PrOH/100:0; flow rate 1.5 mL/min

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	4.875	274117	49.760	25620	52.543
2	5.333	276757	50.240	23140	47.457

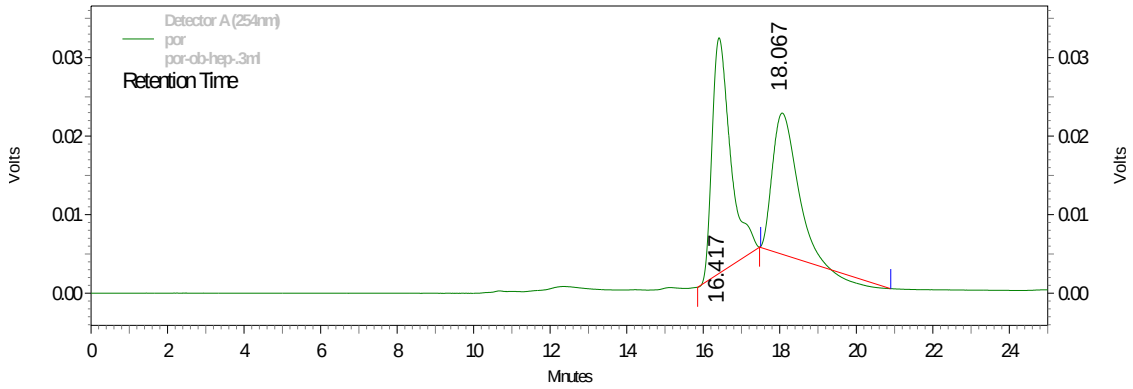
(*R*)-200ah: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	3.867	38466	0.780	3708	1.319
2	4.767	4895265	99.220	277382	98.681
Totals		4933731	100.000	281090	100.000

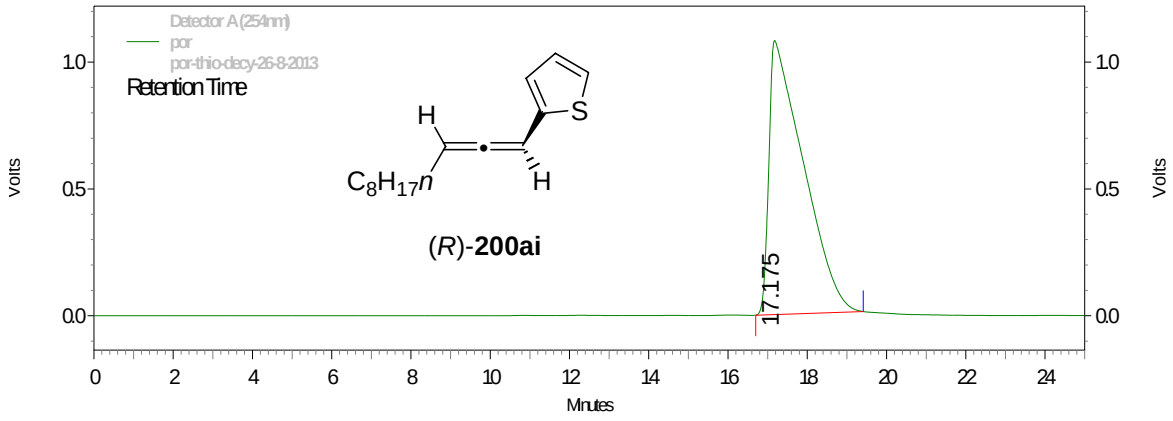
HPLC Profile of 200ai: chiralcel OB-H, heptane:i-PrOH/100:0; flow rate 0.3 ml/min

Racemic



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	16.417	1003397	56.247	29966	62.486
2	18.067	780525	43.753	17990	37.514

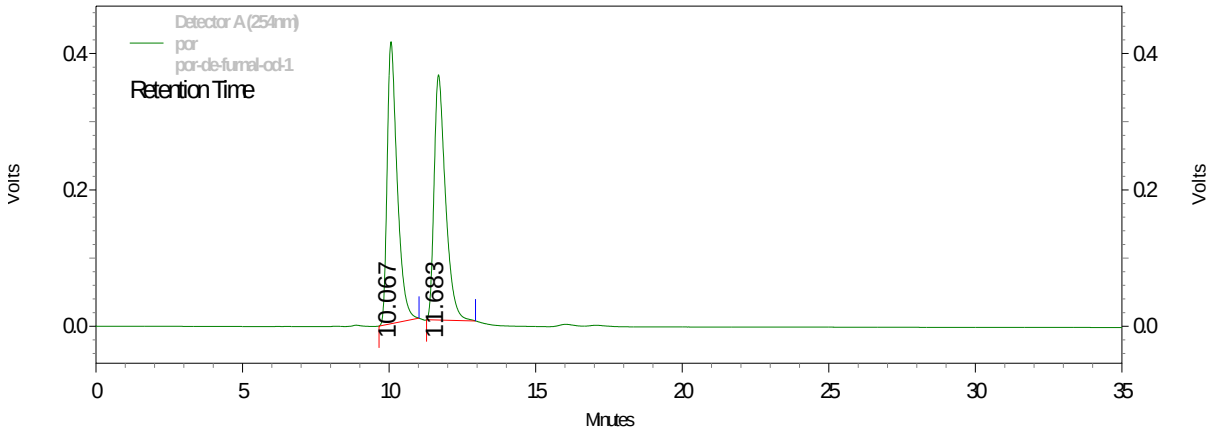
(*R*)-200ai: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	17.175	65095012	100.000	1080429	100.000
Totals		65095012	100.000	1080429	100.000

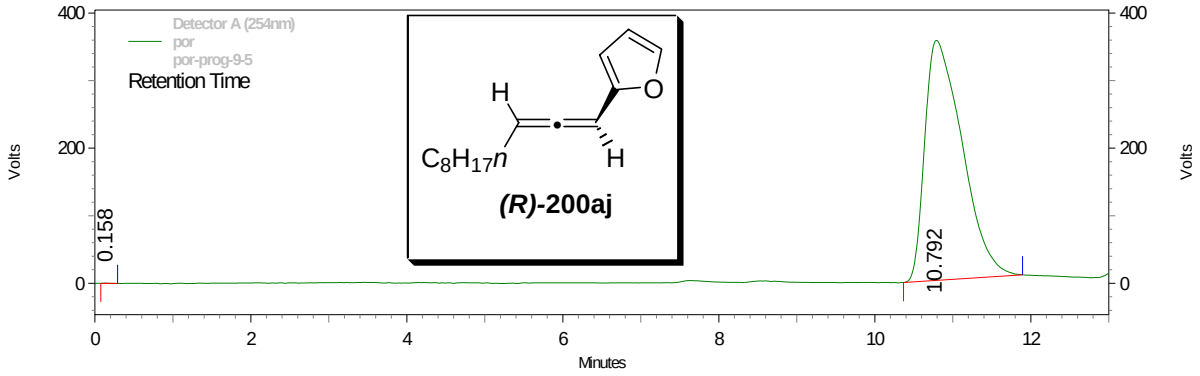
HPLC Profile of 200aj: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 0.5 mL/min.

Racemic:



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	10.067	9821790	50.328	413387	53.488
2	11.683	9693890	49.672	359474	46.512

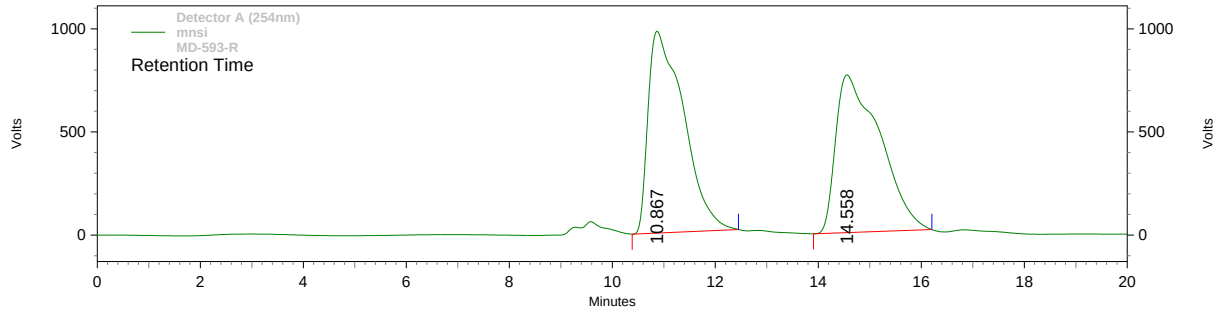
(*R*)-200aj: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	0.158	967	0.008	180	0.051
2	10.792	11821863	99.992	355267	99.949
Totals		11822830	100.000	355447	100.000

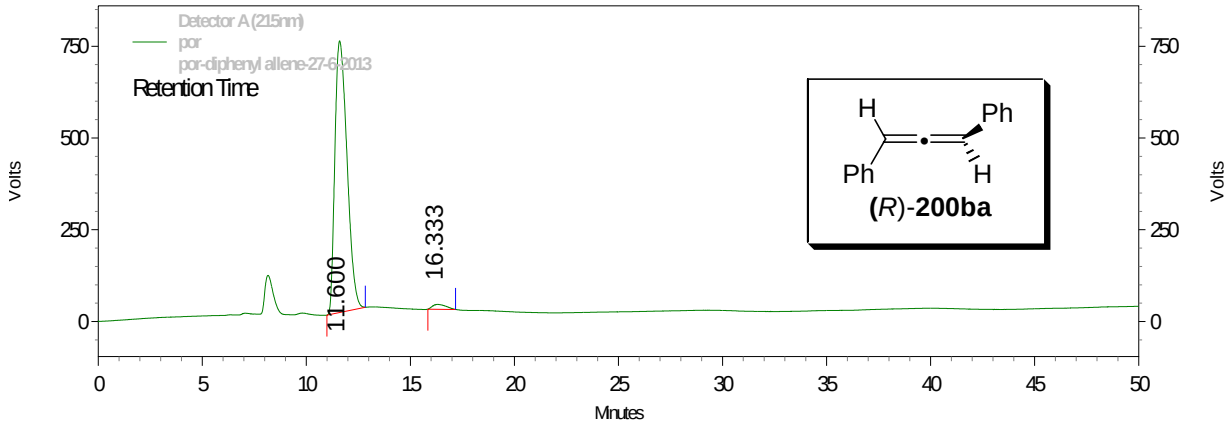
HPLC profile of 200ba: chiralcel OD-H column, 1% IPA in Hexane, 0.5 mL/min.

Racemic:



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	10.877	46818382	50.884	977805	57.630
2	14.558	45563244	49.116	764211	42.370

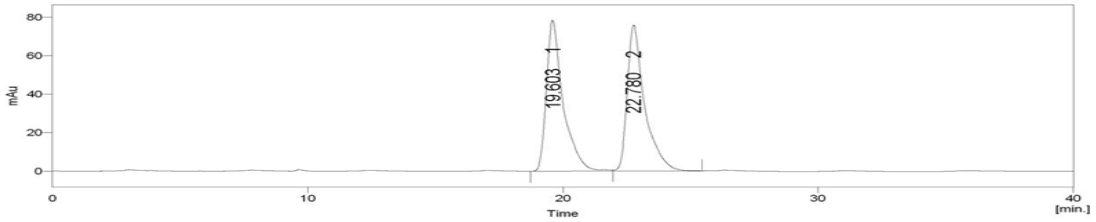
(*R*)-200ba: (Chapter 2, Table 3)



Detector A (215nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	11.600	29953679	98.052	740251	98.262
2	16.333	595080	1.948	13094	1.738
Totals		30548759	100.000	753345	100.000

HPLC Profile of 200ea: chiralcel OD-H, hexanes:i-PrOH/99:1; flow rate 1 mL/min.

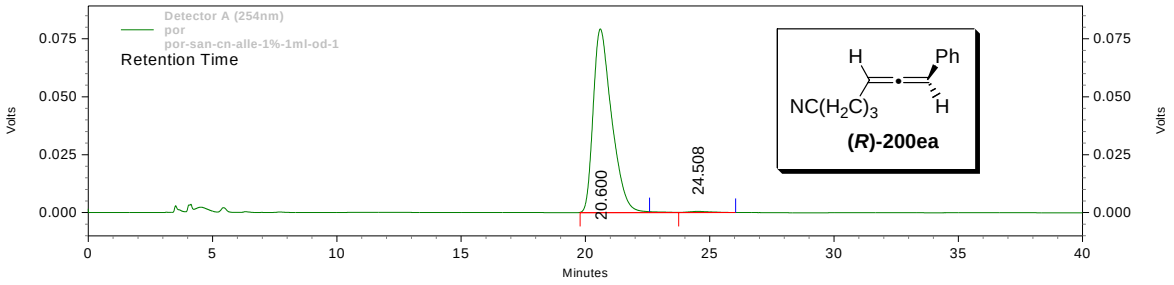
Racemic



Result Table (Uncal - D:\Prof.MP Lab\GBRAHMAM\777..RAC)

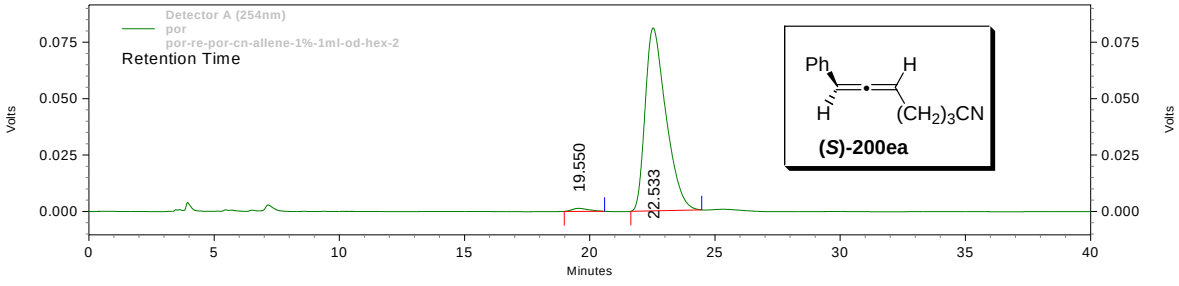
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.603	3577.986	78.514	49.9	50.8	0.62
2	22.780	3593.137	75.906	50.1	49.2	0.65
	Total	7171.122	154.420	100.0	100.0	

(*R*)-200ea: (Chapter 2, Table 3)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	20.600	4105983	99.233	79323	99.401
2	24.508	31751	0.767	478	0.599

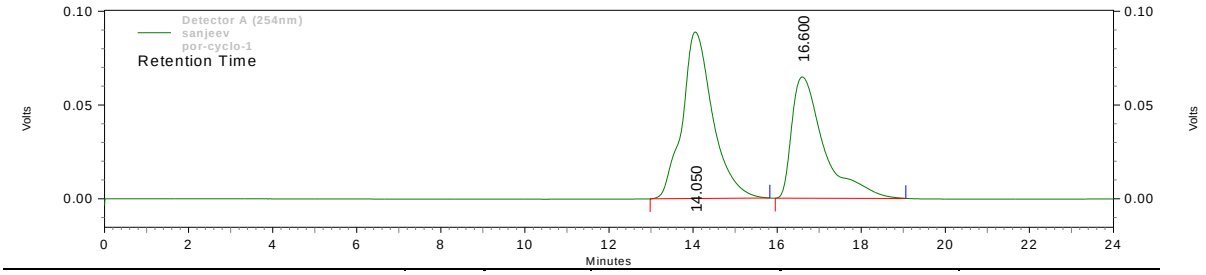
(*S*)-200ea: (Chapter 2, Table 4)



Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	19.550	61077	1.287	1339	1.623
2	22.533	4683972	98.713	81142	98.377

HPLC Profile of 200fa: chiralcel OD-H, hexanes:i-PrOH/99:1; flowrate 0.3 mL/min.

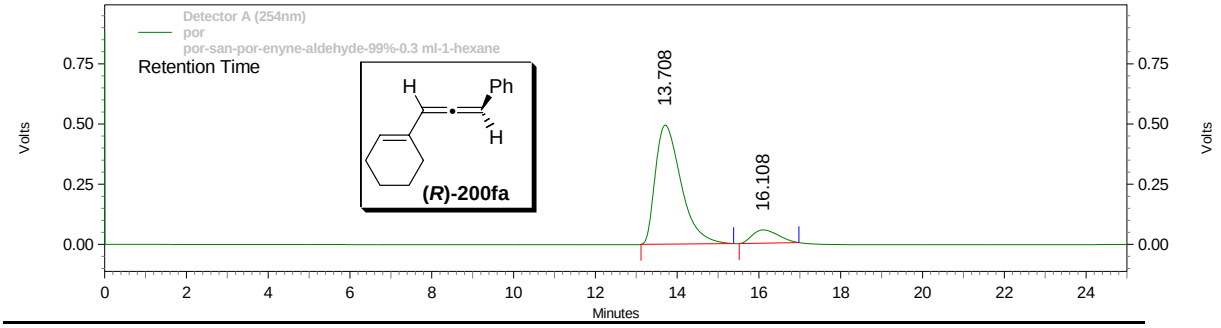
Racemic



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	14.050	4481972	56.574	88801	57.859
2	16.600	3440280	43.426	64677	42.141

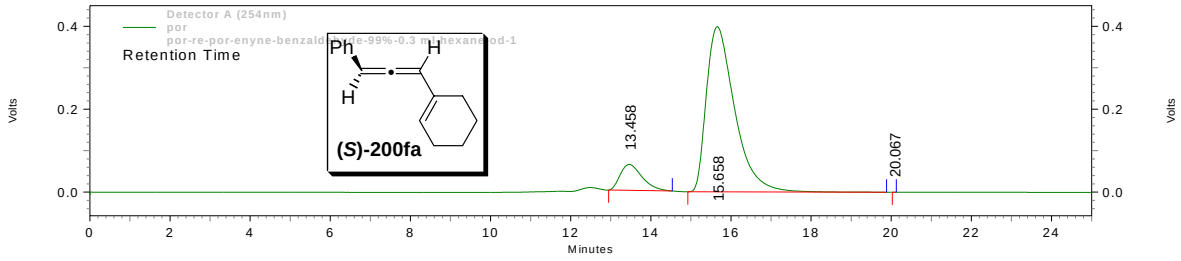
(*R*)-200fa: (Chapter 2, Table 3)



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	13.708	21609030	89.863	494679	89.948
2	16.108	2437519	10.137	55281	10.052

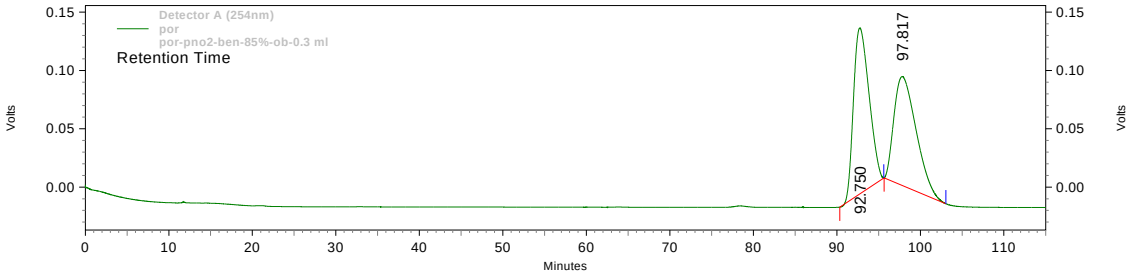
(*S*)-11fa: (Chapter 2, Table 3)



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	13.458	2375567	10.836	62507	13.559
2	15.658	19547105	89.164	398473	86.439

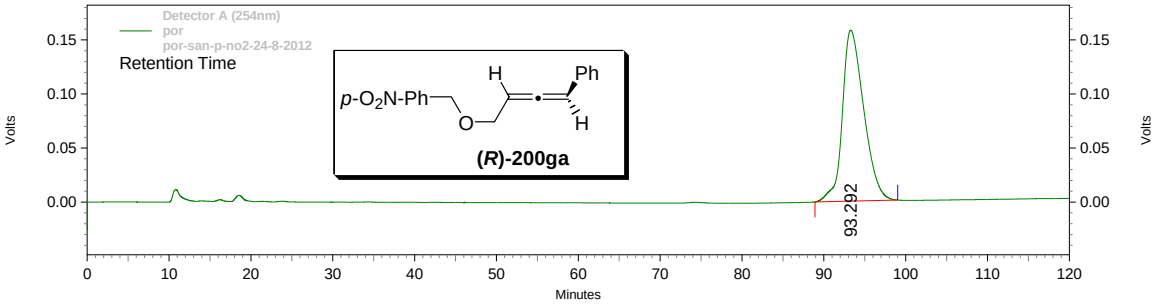
HPLC Profile of 200ga: chiralcel OB-H, hexanes:i-PrOH/ 85.15 flow rate 0.3 mL/min.
Racemic



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	92.750	18359911	51.451	142295	60.380
2	97.817	17324080	48.549	93369	39.620

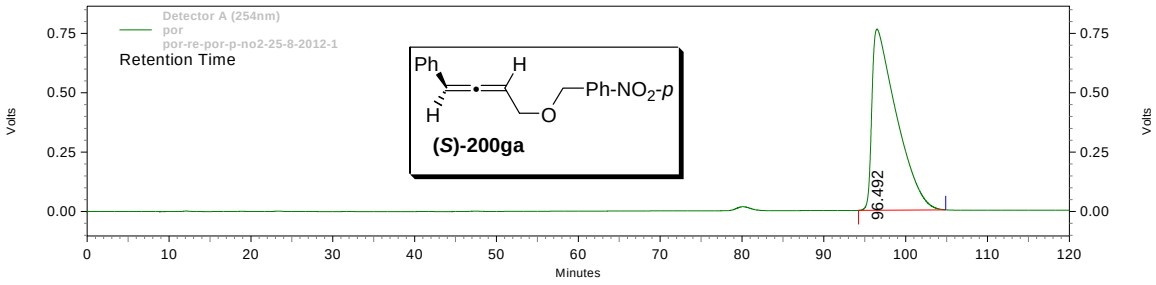
(*R*)-200ga: (Chapter 2, Table 3)



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	99.125	393251932	100.000	1081168	100.000

(*S*)-200ga, (Chapter 2, Table 4)

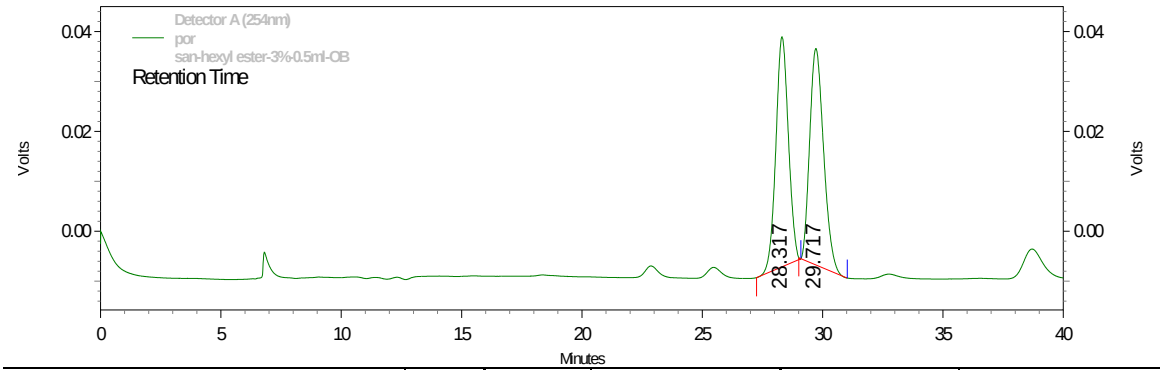


Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	96.492	159239813	100.000	762781	100.000

HPLC Profile of 59ba: chiralcel OB-H, hexanes:i-PrOH/97:3; flow rate 0.5 mL/min

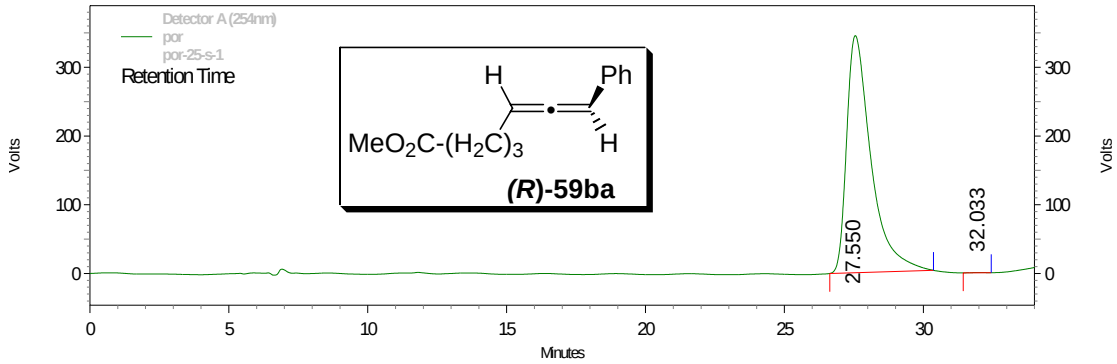
Racemic:



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	28.317	1665489	48.907	46055	51.513
2	29.717	1739950	51.093	43350	48.487
Totals		3405439	100.000	89405	100.000

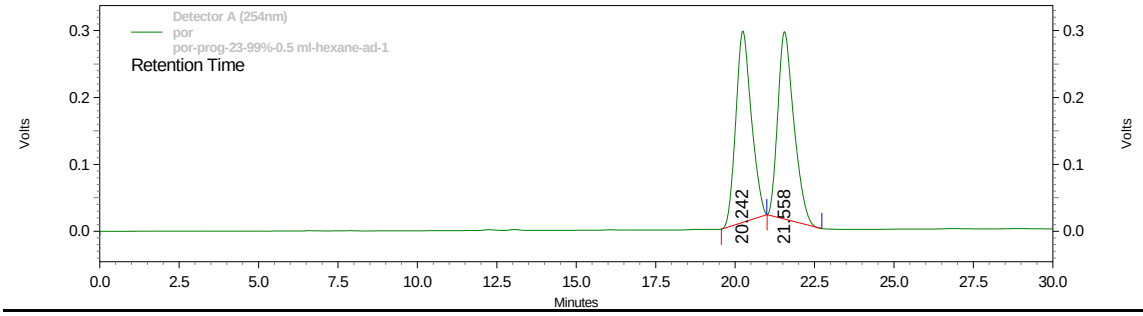
***(R)*-59ba:(Chapter 3, Table 1)**



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	27.550	21033550	99.959	344935	99.931
2	32.033	8698	0.041	238	0.069
Totals		21042248	100.000	345173	100.000

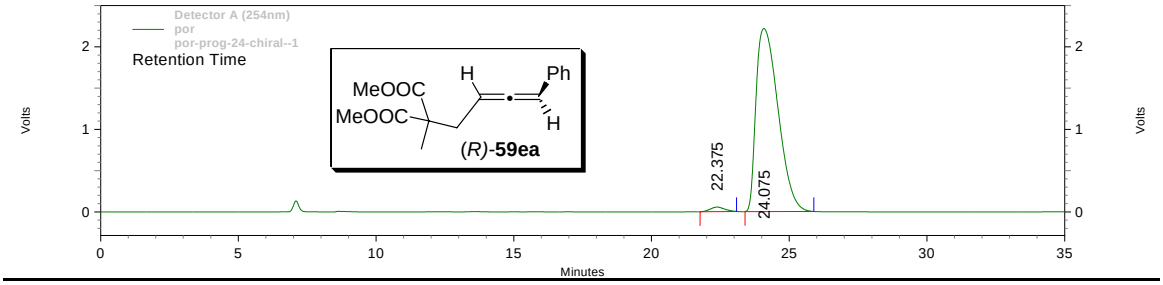
HPLC profile of 59ea: chiralcel AD-H, hexanes:i-PrOH/99:1; flow rate 0.5 mL/min.
Racemic 59ea:



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	20.242	9720898	49.624	285825	50.509
2	21.558	9868393	50.376	280059	49.491
Totals		19589291	100.000	565884	100.000

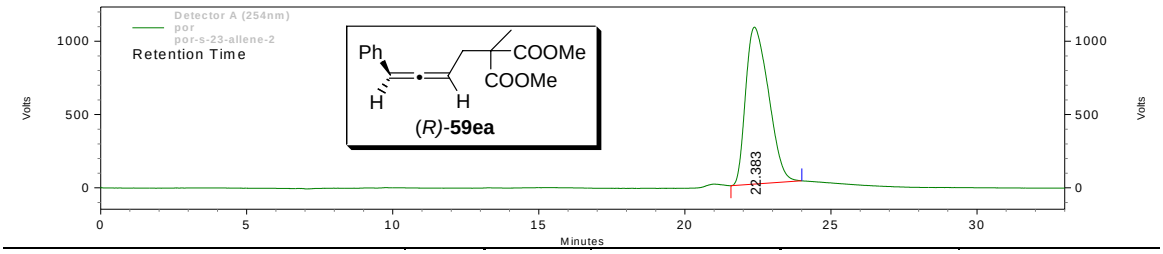
***(R)*-59ea: (Chapter 3, Table 3)**



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	22.375	1979910	1.580	55088	2.424
2	24.075	123330922	98.420	2217587	97.576
Totals		125310832	100.000	2272675	100.000

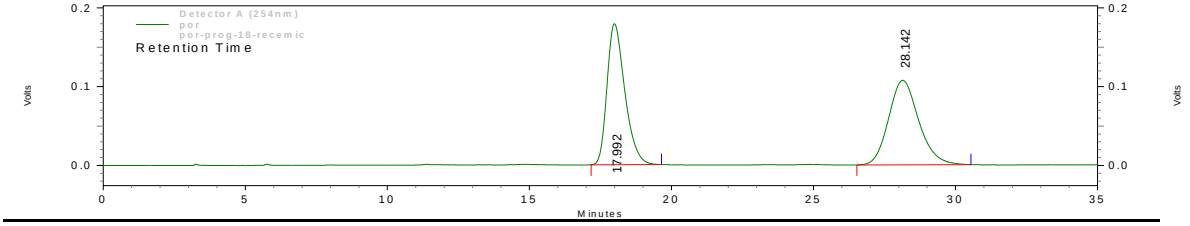
***(S)*-59ea: (Chapter 3, Table 3)**



Detector A (254nm)

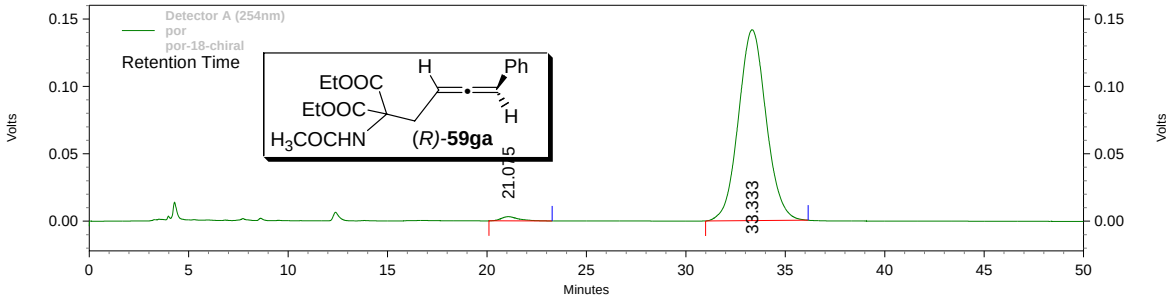
Pk #	Retention Time	Area	Area %	Height	Height %
1	22.383	58315413	100.000	1070660	100.000
Totals		58315413	100.000	1070660	100.000

HPLC profile of 59ga: chiralcel OD-H, hexanes:i-PrOH/100:0; flow rate 1.5 mL/min
Racemic 59ga:



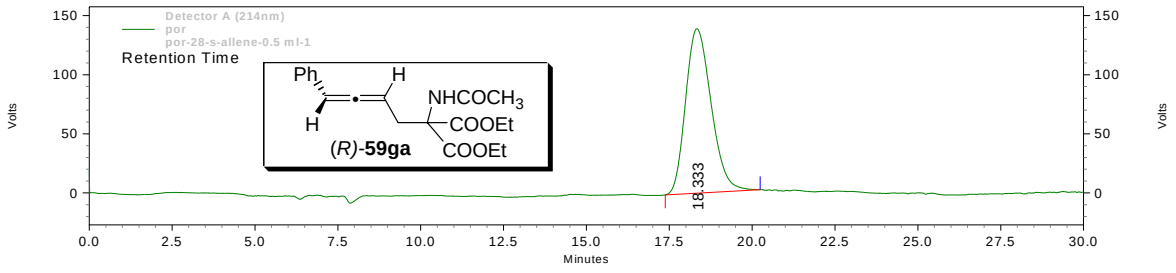
Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	17.992	7799148	49.690	178832	62.511
2	28.142	7896425	50.310	107248	37.489
Totals		15695573	100.000	286080	100.000

***(R)*-59ga: (Chapter 3, Table 3)**



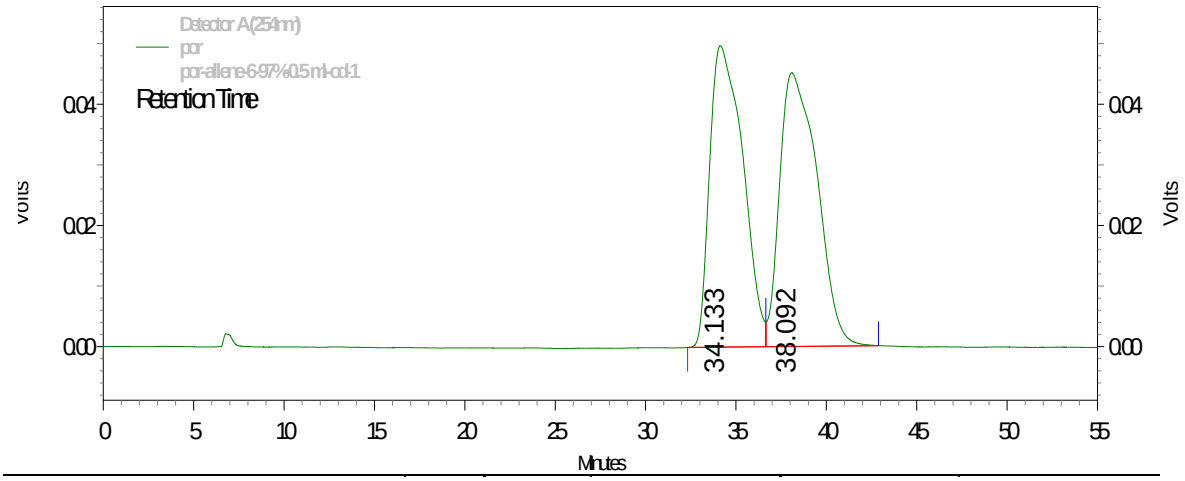
Detector A (254nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	21.075	190655	1.371	3129	2.161
2	33.333	13718071	98.629	141638	97.839
Totals		13908726	100.000	144767	100.000

***(S)*-59ga (Chapter 3, Table 3)**



Detector A (214nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	18.333	7453058	100.000	139157	100.000
Totals		7453058	100.000	139157	100.000

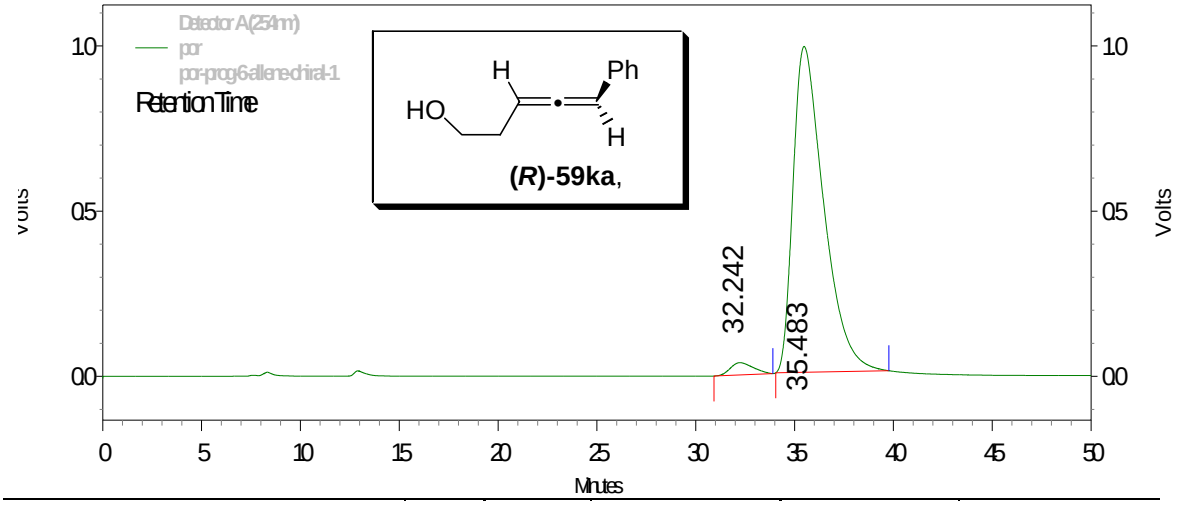
HPLC profile of 59ka: chiralcel OD-H, hexanes:i-PrOH/97:3; flow rate 0.5 mL/min
Racemic:



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	34.133	6335046	49.291	49761	52.413
2	38.092	6517175	50.709	45180	47.587
Totals		12852221	100.000	94941	100.000

***(R)*-59ka: (Chapter 3, Table 3)**

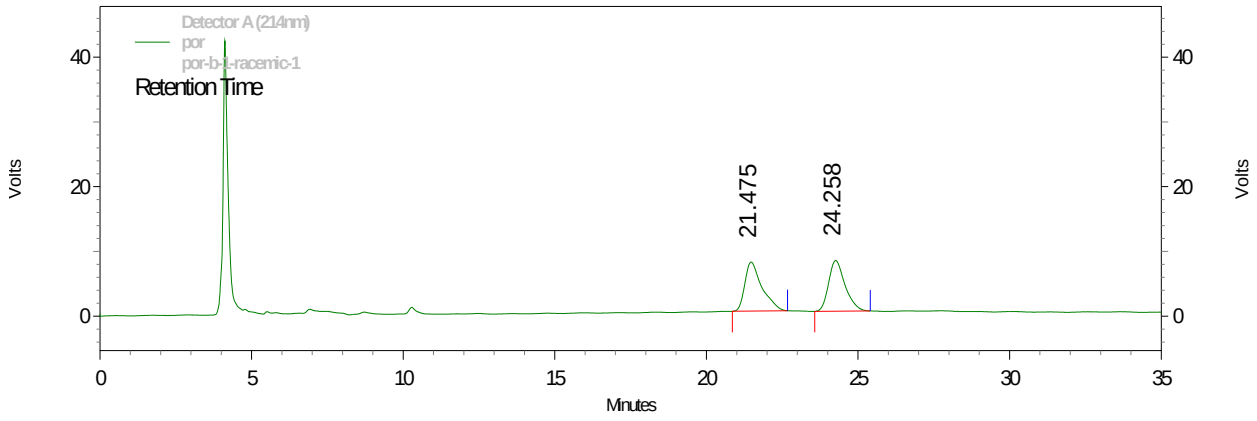


Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	32.242	2986908	2.731	37204	3.634
2	35.483	106364258	97.269	986439	96.366
Totals		109351166	100.000	1023643	100.000

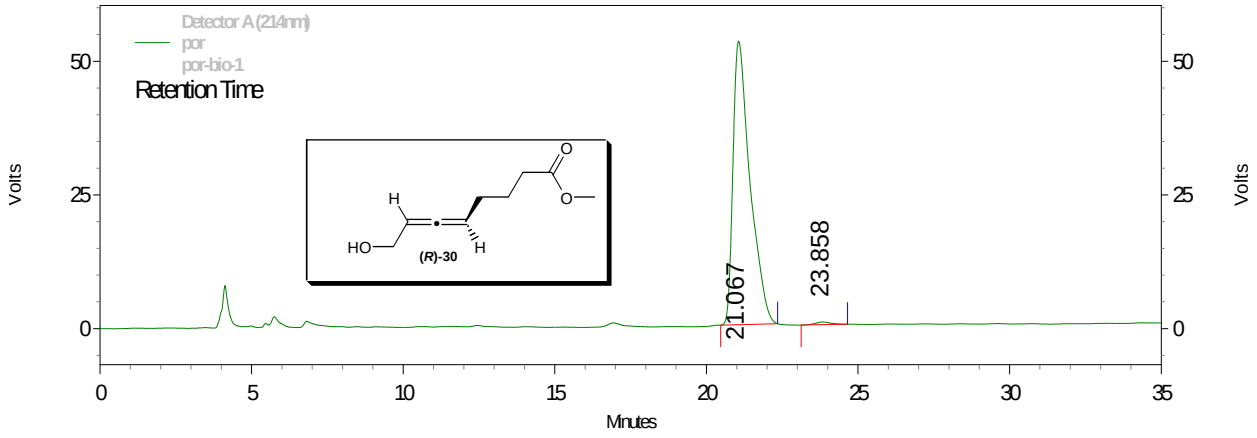
HPLC Profile of 30: chiral column, chiralcel AS-H, hexanes:i-PrOH/100:0; flow rate 0.8 mL/min.

Racemic



Detector A (214nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	21.475	296092	50.053	7567	49.156
2	24.258	295469	49.947	7827	50.844
Totals		591561	100.000	15394	100.000

***(R)*-30: (Chapter 3, Scheme 3.2.3)**



Detector A (214nm)					
Pk #	**Retention Time**	**Area**	**Area %**	**Height**	**Height %**
1	21.067	2066684	99.142	53000	99.078
2	23.858	17891	0.858	493	0.922
Totals		2084575	100.000	53493	100.000

Appendix II

X-Ray Crystallographic Data

Table A1. Crystal data and structure refinement for compound **67.**

Empirical formula	C_{20} H_{20} F_6 N_2 O_2	
Formula weight	434.38	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.7470(12) Å	a= 90°.
	b = 12.8835(14) Å	b= 90°.
	c = 14.0668(15) Å	g = 90°.
Volume	1947.7(4) $Å^3$	
Z	4	
Density (calculated)	1.481 Mg/m^3	
Absorption coefficient	0.135 mm^{-1}	
F(000)	896	
Crystal size	0.34 x 0.32 x 0.30 mm^3	
Theta range for data collection	2.14 to 26.03°.	
Index ranges	-13<=h<=13, -15<=k<=15, -17<=l<=17	
Reflections collected	20057	
Independent reflections	3840 [R(int) = 0.0275]	
Completeness to theta = 26.03°	99.7 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9607 and 0.9556	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3840 / 0 / 275	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0550, wR2 = 0.1526	
R indices (all data)	R1 = 0.0598, wR2 = 0.1579	
Absolute structure parameter	0.7(13)	
Extinction coefficient	0.034(3)	
Largest diff. peak and hole	0.308 and -0.308 e.$Å^{-3}$	

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

For U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	966(2)	1679(2)	1995(2)	39(1)
N(1)	2158(2)	1695(2)	3430(1)	43(1)
C(2)	973(2)	1633(2)	2979(2)	40(1)
N(2)	2146(2)	1781(2)	1538(1)	43(1)
C(3)	-124(3)	1477(2)	3477(2)	50(1)
C(4)	2435(3)	2496(2)	872(2)	59(1)
C(5)	-145(3)	1566(2)	1497(2)	49(1)
C(6)	-1229(3)	1395(2)	2982(2)	59(1)
C(7)	-1238(3)	1442(2)	1998(2)	55(1)
C(8)	3186(2)	1145(2)	1903(2)	44(1)
C(9)	3293(3)	-79(2)	3223(2)	49(1)
C(10)	3192(2)	1094(2)	3008(2)	42(1)
F(3)	2293(3)	4066(2)	4617(3)	147(1)
C(11)	3271(3)	3(2)	1611(2)	53(1)
F(1)	865(4)	3575(2)	3732(3)	157(2)
F(5)	869(3)	3690(2)	1386(3)	144(1)
C(12)	2054(3)	-563(2)	1839(2)	64(1)
O(1)	3391(3)	2489(3)	422(2)	109(1)
O(2)	3415(3)	2334(3)	4574(2)	107(1)
F(6)	2232(3)	4220(2)	463(2)	129(1)
C(13)	4158(2)	-416(2)	2385(2)	54(1)
C(14)	2065(3)	-605(2)	2935(2)	62(1)
F(4)	854(3)	3232(3)	-48(3)	156(1)
C(15)	1614(4)	3279(3)	4370(3)	79(1)
C(16)	4362(3)	-1598(2)	2324(3)	78(1)
C(17)	1564(3)	3418(3)	685(3)	74(1)
C(18)	5464(2)	83(3)	2379(3)	76(1)
C(19)	2466(3)	2367(3)	4137(2)	61(1)
F(2)	956(4)	3065(3)	5111(3)	172(2)
C(20)	3743(4)	-315(3)	4220(2)	81(1)

Table A3. Crystal data and structure refinement for compounds **68**.

Empirical formula	C_{29} H_{45} Cl N_2 O	
Formula weight	473.12	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 13.839(2) Å	a= 90°.
	b = 12.6381(18) Å	b= 101.777(2)°.
	c = 15.679(2) Å	g = 90°.
Volume	2684.5(7) $Å^3$	
Z	4	
Density (calculated)	1.171 Mg/m^3	
Absorption coefficient	0.166 mm^{-1}	
F(000)	1032	
Crystal size	0.36 x 0.24 x 0.12 mm^3	
Theta range for data collection	1.33 to 28.67°.	
Index ranges	-18<=h<=17, -16<=k<=16, -20<=l<=20	
Reflections collected	30710	
Independent reflections	12516 [R(int) = 0.0348]	
Completeness to theta = 28.67°	93.2 %	
Absorption correction	None	
Max. and min. transmission	0.9804 and 0.9428	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12516 / 1 / 611	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0507, wR2 = 0.1338	
R indices (all data)	R1 = 0.0591, wR2 = 0.1425	
Absolute structure parameter	0.00(4)	
Largest diff. peak and hole	0.800 and -0.739 e.$Å^{-3}$	

Table A4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

For **68**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

___	x	y	z	U(eq)
Cl(01)	9747(1)	2762(1)	3691(1)	23(1)
Cl(02)	6082(1)	3451(1)	8895(1)	20(1)
N(003)	5809(1)	1297(2)	1017(1)	17(1)
N(004)	7365(1)	1803(2)	1313(1)	16(1)
N(005)	7592(1)	2280(2)	6897(1)	16(1)
N(007)	8980(1)	2393(2)	6436(1)	16(1)
C(78)	6254(2)	772(2)	1783(2)	18(1)
C(71)	5701(2)	1989(2)	6435(2)	20(1)
C(69)	11120(2)	974(2)	6858(2)	18(1)
C(80)	9051(2)	1997(2)	21(2)	20(1)
C(67)	9791(2)	1022(2)	5608(2)	18(1)
C(72)	6670(2)	1871(2)	7141(2)	17(1)
C(65)	8713(2)	3427(2)	6607(1)	17(1)
C(75)	4743(2)	1171(2)	603(2)	16(1)
C(68)	10893(2)	2160(2)	6655(2)	17(1)
C(79)	9137(2)	1663(2)	989(2)	19(1)
C(77)	3978(2)	1803(2)	1010(2)	18(1)
C(66)	9143(2)	4406(2)	6497(2)	21(1)
C(76)	3740(2)	2798(2)	410(2)	21(1)
C(73)	5725(2)	258(2)	6818(2)	21(1)
C(74)	4498(2)	1492(2)	-370(2)	19(1)
C(70)	10516(2)	455(2)	7459(2)	21(1)
C(025)	7857(2)	3352(2)	6936(1)	17(1)
C(026)	8220(2)	3330(2)	703(2)	19(1)
C(027)	5895(2)	34(2)	2299(2)	20(1)
C(028)	6704(2)	668(2)	7348(2)	18(1)
C(029)	9081(2)	3194(2)	229(2)	21(1)
C(030)	7428(2)	4231(2)	7245(2)	21(1)
C(031)	10854(2)	632(2)	5893(2)	19(1)
C(032)	9841(2)	2138(2)	6037(2)	16(1)
C(033)	4902(2)	709(2)	7246(2)	29(1)
C(034)	3541(2)	2134(2)	-435(2)	22(1)
C(035)	10092(2)	2257(2)	1426(2)	25(1)
C(036)	8321(2)	2343(2)	1296(2)	16(1)
C(037)	12208(2)	763(2)	7276(2)	25(1)
C(038)	10047(2)	3309(2)	915(2)	28(1)
C(039)	5596(2)	888(2)	5959(2)	23(1)
C(040)	7238(2)	1122(2)	1986(2)	17(1)
C(041)	8295(2)	1748(2)	6600(1)	16(1)

C(042)	4235(2)	1999(2)	1978(2)	28(1)
C(043)	6531(2)	-283(2)	3048(2)	23(1)
C(044)	11508(2)	1351(2)	5458(2)	22(1)
C(045)	7870(2)	827(2)	2759(2)	20(1)
C(047)	9151(2)	485(2)	1176(2)	25(1)
C(048)	3015(2)	1147(2)	707(2)	23(1)
C(049)	5616(2)	2970(2)	5871(2)	29(1)
C(050)	7499(2)	134(2)	3284(2)	22(1)
C(051)	11036(2)	2898(2)	7429(2)	21(1)
C(052)	4890(2)	1904(2)	6983(2)	26(1)
C(053)	11567(2)	2395(2)	6003(2)	21(1)
C(055)	8710(2)	5277(2)	6778(2)	21(1)
C(056)	2830(2)	3417(2)	549(2)	31(1)
C(057)	6494(2)	1888(2)	759(2)	17(1)
C(058)	7882(2)	5192(2)	7162(2)	23(1)
C(059)	8125(2)	1611(2)	-607(2)	24(1)
C(060)	4579(2)	742(3)	5353(2)	36(1)
C(061)	2741(2)	1352(2)	-280(2)	28(1)
C(062)	9940(2)	1628(2)	-365(2)	29(1)
C(063)	6370(2)	650(2)	5405(2)	27(1)
C(064)	4578(2)	3607(2)	493(2)	29(1)
O(1)	7903(2)	2695(2)	4600(1)	38(1)
C(81)	7262(2)	3448(3)	4153(2)	40(1)
C(85)	2168(2)	3250(2)	3213(2)	27(1)
O(2)	2883(2)	2798(3)	3971(2)	68(1)
C(82)	6416(3)	2994(3)	3548(3)	57(1)
C	1583(1)	4089(2)	3451(2)	12(1)

Table A5. Crystal data and structure refinement for compound 7.

Identification code	compound 71	
Empirical formula	C_{20} H_{30} N_2	
Formula weight	298.46	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.0884(16) Å	a= 90°.
	b = 11.257(2) Å	b= 105.982(3)°.
	c = 8.9644(18) Å	g = 90°.
Volume	784.7(3) $Å^3$	
Z	2	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	328	
Crystal size	0.40 x 0.34 x 0.22 mm^3	
Theta range for data collection	2.36 to 25.08°.	
Index ranges	-9<=h<=9, -13<=k<=13, -10<=l<=10	
Reflections collected	7534	
Independent reflections	2772 [R(int) = 0.0191]	
Completeness to theta = 25.08°	99.5 %	
Absorption correction	Not measured	
Max. and min. transmission	1.00000 and 0.995	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2772 / 1 / 214	
Goodness-of-fit on F^2	1.149	
Final R indices [I>2sigma(I)]	R1 = 0.0724, wR2 = 0.2198	
R indices (all data)	R1 = 0.0737, wR2 = 0.2220	
Absolute structure parameter	2(5)	
Extinction coefficient	0.084(18)	
Largest diff. peak and hole	0.591 and -0.399 $e.Å^{-3}$	

Table A6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for mp119_m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(2)	5343(4)	7736(3)	8177(4)	40(1)
N(1)	2563(4)	7211(3)	9234(3)	42(1)
C(11)	4069(5)	8629(3)	8075(4)	41(1)
C(15)	1430(5)	9223(4)	8604(5)	48(1)
C(12)	4205(6)	9735(3)	7479(5)	50(1)
C(6)	3256(4)	6178(3)	8591(4)	41(1)
C(16)	2672(4)	8349(3)	8633(4)	39(1)
C(1)	2013(5)	5577(4)	7164(4)	46(1)
C(13)	3004(6)	10606(4)	7500(5)	58(1)
C(7)	3318(5)	4873(4)	6527(5)	51(1)
C(3)	2980(7)	6782(4)	5315(5)	59(1)
C(14)	1637(5)	10351(4)	8078(5)	56(1)
C(4)	4363(6)	5988(4)	6343(5)	50(1)
C(9)	2494(7)	4207(5)	5006(5)	66(1)
C(5)	4857(5)	6482(3)	8004(4)	41(1)
C(2)	1384(6)	6512(4)	5889(5)	60(1)
C(8)	4381(8)	3940(4)	7625(6)	70(1)
C(10)	569(7)	4892(5)	7561(7)	73(1)
C(18)	1961(4)	6090(3)	11149(4)	36(1)
C(20)	8192(4)	7325(4)	8688(5)	44(1)
C(17)	2016(5)	7032(4)	10530(5)	51(1)
C(19)	7035(6)	8032(4)	8571(5)	53(1)

Table A7. Crystal data and structure refinement for compound **219** .

Identification code	compound **219**	
Empirical formula	C_{42} H_{42} N_2	
Formula weight	574.78	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P_2(1)$	
Unit cell dimensions	a = 12.2203(10) Å	a= 90°.
	b = 11.9463(7) Å	b= 112.557(9)°.
	c = 12.8709(11) Å	g = 90°.
Volume	1735.2(2) $Å^3$	
Z	2	
Density (calculated)	1.100 Mg/m^3	
Absorption coefficient	0.063 mm^{-1}	
F(000)	616	
Crystal size	0.42 x 0.34 x 0.32 mm^3	
Theta range for data collection	3.20 to 26.37°.	
Index ranges	-8<=h<=15, -14<=k<=14, -16<=l<=10	
Reflections collected	6805	
Independent reflections	5427 [R(int) = 0.0199]	
Completeness to theta = 26.37°	99.7 %	
Max. and min. transmission	0.9801 and 0.9739	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5427 / 1 / 401	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0447, wR2 = 0.1004	
R indices (all data)	R1 = 0.0567, wR2 = 0.1079	
Absolute structure parameter	-3(3)	
Extinction coefficient	0.0255(19)	
Largest diff. peak and hole	0.126 and -0.139 $e.Å^{-3}$	

Table A8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for mp28. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

___	x	y	z	U(eq)
C(1)	9373(2)	3301(2)	5202(2)	43(1)
C(2)	8470(2)	2691(2)	4137(2)	38(1)
C(3)	7463(2)	2303(2)	4547(2)	39(1)
C(4)	7919(2)	2754(2)	5765(2)	51(1)
C(5)	8951(2)	1992(2)	6453(2)	65(1)
C(6)	9947(2)	2355(2)	6059(2)	54(1)
C(7)	8553(2)	3863(2)	5722(2)	51(1)
C(8)	7744(2)	4792(2)	5001(2)	63(1)
C(9)	9227(3)	4376(3)	6901(2)	80(1)
C(10)	10279(2)	4042(2)	4995(2)	60(1)
C(11)	6827(2)	3433(2)	2374(2)	45(1)
C(12)	6075(2)	2574(2)	2648(2)	46(1)
C(13)	8806(2)	3012(2)	2417(2)	47(1)
C(14)	8824(2)	3909(2)	1580(2)	53(1)
C(15)	8674(2)	5024(2)	1758(2)	66(1)
C(16)	8781(3)	5840(3)	1036(3)	94(1)
C(17)	9030(4)	5554(5)	129(3)	114(2)
C(18)	9192(3)	4448(5)	-65(3)	110(1)
C(19)	9087(2)	3609(3)	655(2)	76(1)
C(20)	8429(2)	1904(2)	1872(2)	56(1)
C(21)	8040(2)	1022(2)	1460(2)	59(1)
C(22)	7542(2)	-41(2)	985(2)	59(1)
C(23)	6932(4)	-678(3)	1482(3)	105(1)
C(24)	6443(4)	-1683(4)	1031(4)	119(1)
C(25)	6526(3)	-2076(3)	76(3)	90(1)
C(26)	7130(3)	-1469(3)	-414(3)	89(1)
C(27)	7643(3)	-456(3)	29(2)	73(1)
C(28)	5351(2)	2075(2)	4109(2)	43(1)
C(29)	4169(2)	2708(2)	3653(2)	41(1)

C(30)	4169(2)	3867(2)	3747(2)	52(1)
C(31)	3116(2)	4456(2)	3395(2)	60(1)
C(32)	2044(2)	3902(2)	2944(2)	60(1)
C(33)	2039(2)	2757(2)	2851(2)	59(1)
C(34)	3087(2)	2166(2)	3200(2)	49(1)
C(35)	5218(2)	884(2)	3745(2)	50(1)
C(36)	5091(2)	-64(2)	3423(2)	55(1)
C(37)	4905(2)	-1204(2)	3027(2)	58(1)
C(38)	3915(3)	-1500(3)	2084(3)	92(1)
C(39)	3738(3)	-2578(3)	1691(4)	108(1)
C(40)	4523(4)	-3397(3)	2233(4)	98(1)
C(41)	5489(4)	-3139(3)	3167(3)	90(1)
C(42)	5699(3)	-2044(2)	3571(2)	70(1)
N(1)	8107(1)	3347(2)	3079(1)	40(1)
N(2)	6266(1)	2684(1)	3838(1)	39(1)

Table A9. Crystal data and structure refinement for compound **224**.

Identification code	Compound **224**	
Empirical formula	C_{28} H_{33} N_2	
Formula weight	397.56	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)	
Unit cell dimensions	a = 11.2047(14) Å	a= 90°.
	b = 11.8881(13) Å	b= 90°.
	c = 17.991(3) Å	g = 90°.
Volume	2396.4(5) $Å^3$	
Z	4	
Density (calculated)	1.102 Mg/m^3	
Absorption coefficient	0.064 mm^{-1}	
F(000)	860	
Crystal size	0.42 x 0.30 x 0.28 mm^3	
Theta range for data collection	3.37 to 26.37°.	
Index ranges	-14<=h<=10, -14<=k<=14, -16<=l<=22	
Reflections collected	6682	
Independent reflections	4634 [R(int) = 0.0247]	
Completeness to theta = 26.37°	96.4 %	
Max. and min. transmission	0.9824 and 0.9737	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4634 / 0 / 276	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0635, wR2 = 0.1308	
R indices (all data)	R1 = 0.1233, wR2 = 0.1628	
Absolute structure parameter	-5(5)	
Extinction coefficient	0.0120(16)	
Largest diff. peak and hole	0.151 and -0.139 $e.Å^{-3}$	

Table A10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 224. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

_____	x	y	z	U(eq)
C(1)	9278(3)	409(3)	3259(2)	65(1)
C(2)	9152(3)	1009(3)	2493(2)	59(1)
C(3)	7861(3)	1528(2)	2527(2)	54(1)
C(4)	7464(3)	1194(3)	3308(2)	66(1)
C(5)	8176(4)	1919(3)	3853(2)	93(1)
C(6)	9433(3)	1376(4)	3818(2)	86(1)
C(7)	7992(3)	16(3)	3436(2)	69(1)
C(8)	7529(4)	-912(3)	2915(2)	87(1)
C(9)	7832(4)	-415(4)	4243(2)	115(2)
C(10)	10244(4)	-495(4)	3329(3)	100(1)
C(11)	8757(5)	635(7)	1177(3)	171(3)
C(12)	7645(3)	1183(3)	1207(2)	76(1)
C(13)	10663(4)	323(6)	1644(3)	161(3)
C(14)	5910(3)	1745(2)	1930(2)	52(1)
C(15)	5023(3)	1127(3)	1427(2)	56(1)
C(16)	4813(3)	-1(3)	1560(2)	78(1)
C(17)	4010(4)	-588(3)	1127(3)	95(1)
C(18)	3415(3)	-75(4)	566(3)	95(1)
C(19)	3611(4)	1033(4)	429(3)	95(1)
C(20)	4415(3)	1633(3)	863(2)	79(1)
C(21)	6022(3)	2954(3)	1737(2)	61(1)
C(22)	6104(3)	3915(3)	1569(2)	61(1)
C(23)	6131(3)	5073(2)	1329(2)	57(1)
C(24)	5631(3)	5382(3)	659(2)	75(1)
C(25)	5640(4)	6485(4)	428(3)	97(1)
C(26)	6165(5)	7276(4)	851(3)	107(2)
C(27)	6665(5)	7012(4)	1511(4)	114(2)
C(28)	6650(4)	5900(3)	1767(3)	88(1)
N(2)	7068(2)	1143(2)	1935(1)	49(1)
N(1)	9379(2)	325(3)	1828(2)	79(1)

Appendix-III

New Transformations Using Oxygen Doped Activated Charcoal

III. 1 Introduction

During our studies on the synthesis of camphanyl amines (Chapter **1**), we have used borohydride reagents in the presence of different additives like I_2 and benzyl chloride which produce more reactive diborane. It occurred to us that the borohydride reagents could be useful for assessment of extent of oxygen doping in carbon materials. Accordingly, we have carried out a series of experiments on studying the nature and extent of oxygen doping of activated charcoal by reaction with various reagents including borane and borohydride reagents. The details are described here.

III.1.1. Carbon materials

Carbon materials are useful for a wide variety of applications, such as medical implants, high-performance materials, electrochemical electrodes, electrochemical capacitors and fuel cells.[1] Carbon materials may be collectively called as a family of carbon obtained from carbonization of organic raw materials. Generally, heat treatment at inert atmosphere results increase in carbon contents and decrease in content of heteroatoms.[2, 3] The carbonization process is conversion of an organic macromolecular system (e.g. coal, wood, nutshell, etc.) to a "macro-atomic" network of carbon atoms via elimination of small molecules, such as water, methanol, carbon dioxide and carbon monoxide by progressive heating.[4] The resultant movement of atoms over short atomic distances creates a space network of porosity.

Recently, investigations were undertaken in this laboratory on the production of pyrolysis gas from woody biomass for use in electricity generation sets. The commercially important charcoal is a byproduct in this carbonization process from the woody biomass.

This charcoal byproduct can be further activated for high end applications by known industrial methods. Therefore, we became interested in the development of organic synthetic methods to increase the value of this readily accessible activated charcoal.

Activated charcoal is widely used in electrochemical double layer capacitors (supercapacitors) for storage of electricity, potential for use in electric vehicles. Activated charcoal act as a semiconductor with narrow band gap (34 meV) with potential for use in harvesting "IR" portion of the solar spectrum.[5] Our interest is to develop electron transfer reactions for use in energy harvesting cells as well as in organic transformations. Accordingly, a brief review on the nature and properties of activated charcoal for applications in organic transformations would facilitate the discussion.

III.1.2 Characterization and properties of activated carbons:

The characteristics of carbon materials and chemistry of their surface depends on the heteroatom presence which is in turn dependent on the nature of the materials and methods used for their preparation.[6] The surface chemistry of the carbon materials are also depend on the nature and presence of graphene edge sites. Further, it was suggested that the heteroatom (like oxygen) free graphene edge sites in carbon materials are neither H terminated nor free radicals. Instead, the edge sites are carbine-like zigzag sites with triplet ground state **3** or aryne-like (arm chair sites) with singlet ground state **1** (Figure **1**).[7a, 7b]

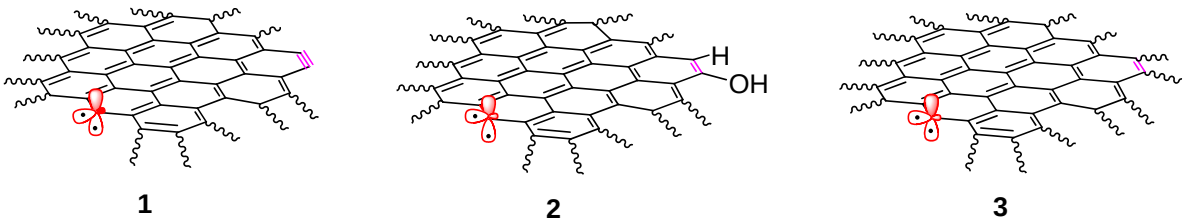
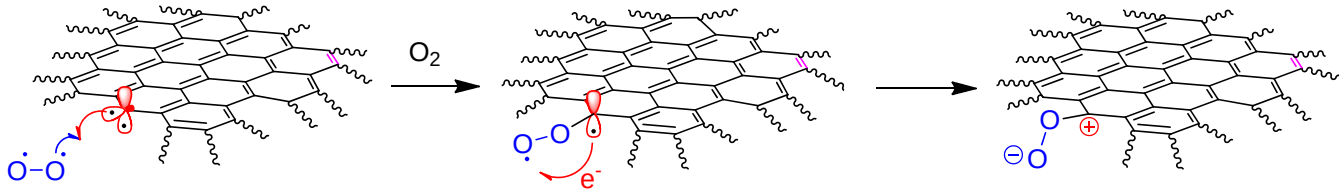


Figure 1. Surface characteristics of the carbon materials

The aryne-like sites are expected to give phenolic groups upon reaction with moisture resulting in phenolic sites like in **2** or could undergo trimerization to give benzenoid aggregates like **3** under ambient atmospheric conditions.[8] However, the magnetic properties and chemisorptions with molecular oxygen reported for the carbon materials are in accordance with the proposal that the graphene edge sites are carbene-like with triplet ground state.[7]

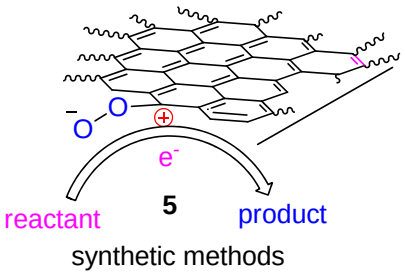
It has been reported that chemisorption of molecular oxygen by activated carbon fibre materials leads to formation of negatively charged oxygen (C-O-O$^{\delta-}$) species.[8,11]Accordingly, we envisaged the formation of such species **5** through electron transfer from the carbon radical site in **4** formed by reaction with molecular oxygen with activated carbon **3** (Scheme **1**).

Scheme 1



It is of our interest to design experiments for practical use of the reactive intermediate **5** in the oxygen doped activated charcoal in synthetic transformations (Scheme **2)**.

Scheme 2



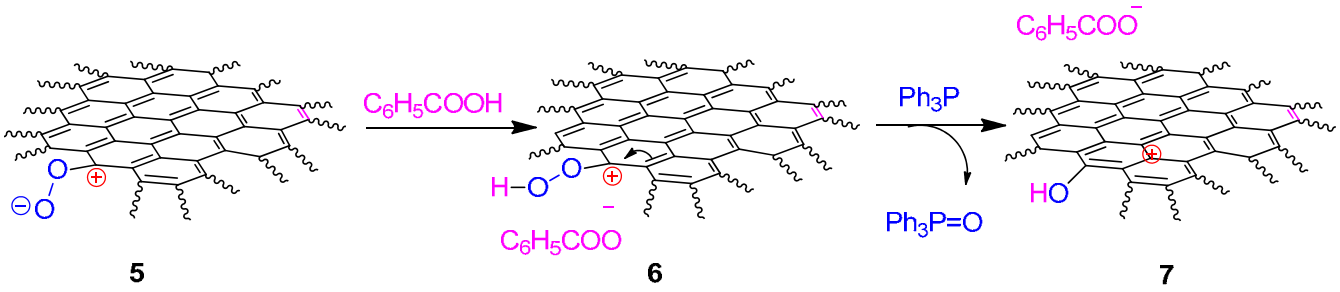
The results are discussed in the next section.

III.2 Results and Discussion

III.2.1 Reactions of molecular oxygen doped activated charcoal

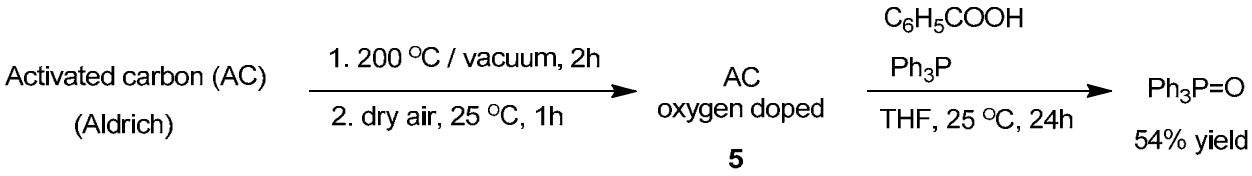
As outlined in the introduction section, the activated carbon would probably react with molecular oxygen to give the intermediate **5**. Such species are expected to react with proton containing compounds like benzoic acid to give the corresponding hydroperoxide intermediate **6** (Scheme **3**).[8]

Scheme 3



To examine this possibility, we have reacted the activated carbon **5** with Ph_3P and benzoic acid and isolated the triphenylphosphine oxide ($Ph_3P=O$) in 54% yield (Scheme **4**). When the reaction was carried out with water instead of benzoic acid, the $Ph_3P=O$ was obtained only in 7% yield.[12]

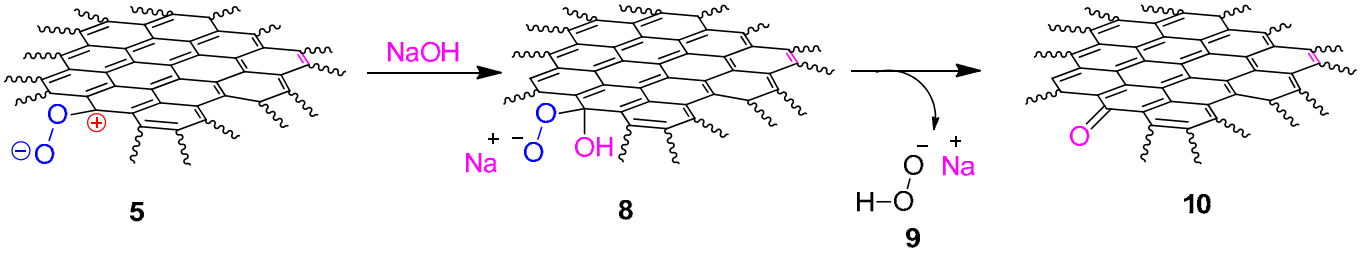
Scheme 4



III.2.2 Reactions of oxygen doped activated charcoal with alkylboranes

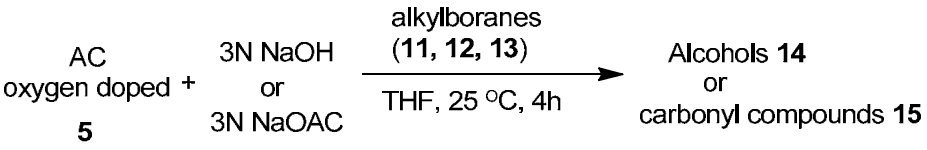
The oxygen chemisorption intermediate like **5** is expected to react with NaOH to give the species like **8** which could also decompose to give the HOO^-Na^+ species **9**. Accordingly, the intermediate **8** could function as a source of HOO^- or its equivalent (Scheme **5)**.

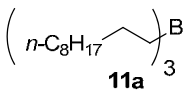
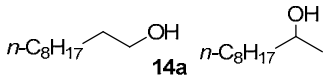
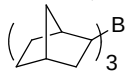
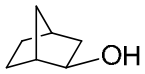
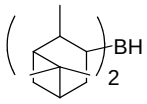
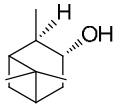
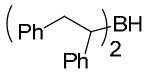
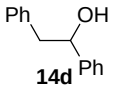
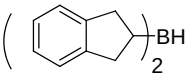
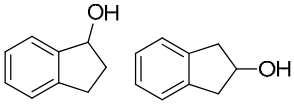
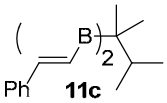
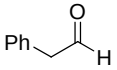
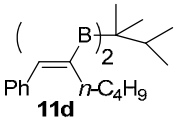
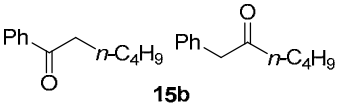
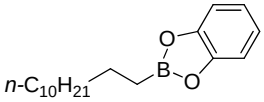
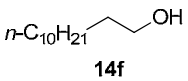
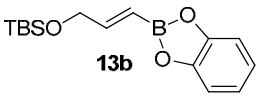
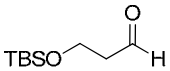
Scheme 5



In order to examine this, we have performed a series of experiments on the oxidation of alkylboranes. We have observed that trialkylboranes **11a** and **11b** prepared by using hydroboration of 1-decene and norbornene with the $NaBH_4$-I_2 in THF reagent system react with a mixture of oxygen doped charcoal **5** and 3N NaOH to give the corresponding alcohol **14a, 14b** in 72-93% yield (Table **1**, entry **1**,**2**). The reaction of dialkylboranes **12a-12c** prepared by using $NaBH_4$-I_2 in THF reagent system with a mixture of activated carbon and 3N NaOH, gives the corresponding alcohols **14c-14e** in 82-99% yield (Table **1**, entry **3-5**). Further, we have observed that the reaction of alkenylborane **11c** (prepared using the thexylborane, which in turn formed *in situ* by the reaction of tetramethyl ethylene with borane gas generated by the reaction of I_2 with Bu_4NBH_4) with oxygen doped activated carbon and 3N NaOAc gave the phenylacetaldehyde **15a** in 79% yield (Table **1,** entry **6**). Whereas, the reaction with the alkenylborane **11d** gave the corresponding regioisomeric mixture **15b** in 73% yield (Table **1,** entry **7**).

Table 1 Reaction of molecular oxygen doped activated carbon **5** with alkylboranes.



Entry	AC[a] (g m)	alkylboranes 11, 12, 13	Products 14, 15	Yield %[b]
1[b]	AC(5)	 **11a**	 **14a**	93
2[b]	AC(5)	 **11b**	 **14b**	72
3[c]	AC(5)	 **12a**	 **14c**	82
4[c]	AC(5)	 **12b**	 **14d**	94
5[c]	AC(5)	 **12c**	 **14e**	99
6[d,]	AC(5)	 **11c**	 **15a**	79
7[e,h, g]	AC(5)	 **11d**	 **15b**	73
8[d]	AC(5)	 **13a**	 **14f**	72
9[d,h]	AC(5)	 **13b**	 **15c**	68

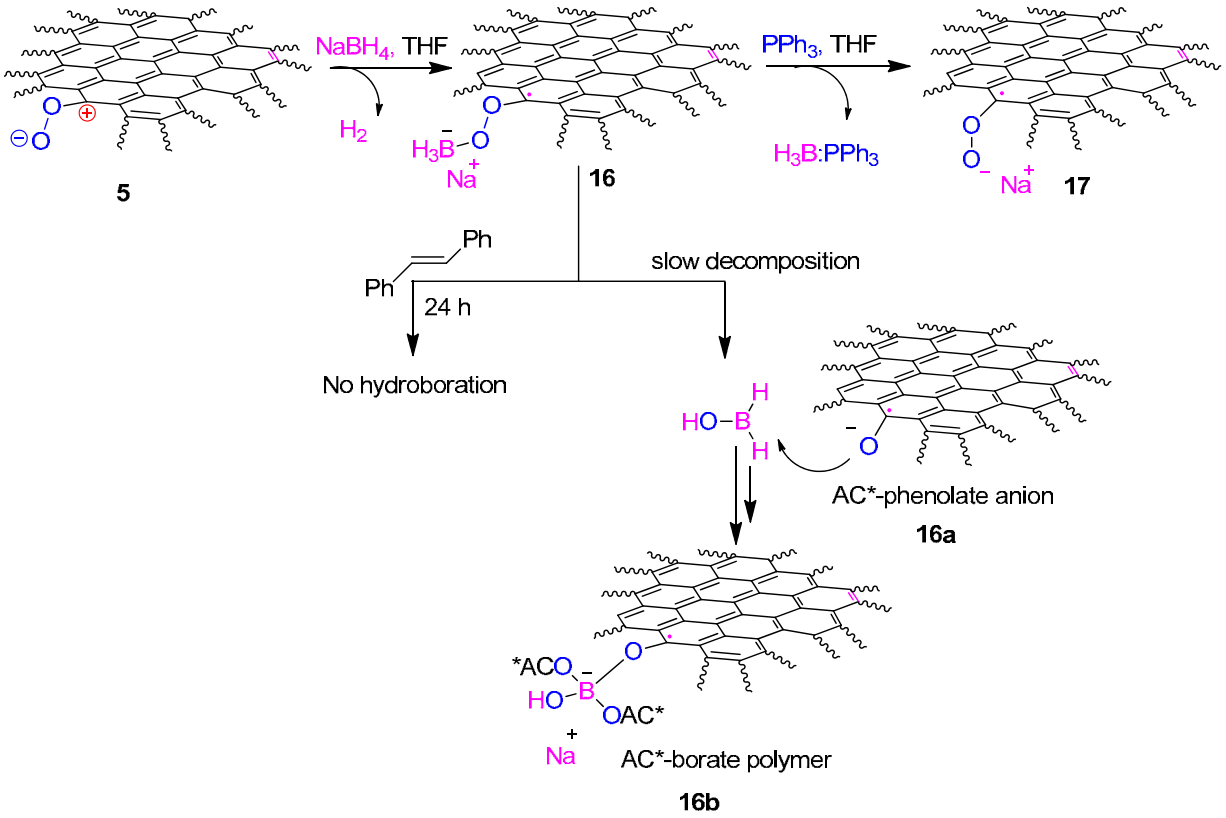
[a] The activated charcoal heated at 200 °C under high vacuum (0.001 Hg) for 2h, brought to 25 °C under nitrogen atmosphere and saturated with dry air for 1h. The oxidations of organoboranes were carried out after adding aq. NaOH. [b]The reactions were carried out with trialkylboranes (5 mmol). [c]The reactions were carried out with dialkylboranes (10 mmol) at 25 °C. [d]The reactions were carried out alkoxyboranes (10 mmol). · [e]The reactions were carried out with alkenylboranes (10 mmol). [f]Isolated yield. [g]Mixture of isomers conformed by C^{13}-NMR.[h b]The reactions were carried out using aq. NaOAc.

The oxidation of B-alkylcatecholborane **13a** (prepared by the catechol borane with dodecene) gave the dodecanol **14f** in 72% yield (Table **1,** entry **8**). Similarly, B-alkenylcatecholborane **13b** prepared using catecholborane reacts with the mixture of oxygen doped activated carbon and 3N NaOAc, to give the corresponding aldehyde **15c** in 68% yield (Table **1,** entry **9**).[13, 14]

III.2.3 Reaction of sodium borohydride with molecular oxygen doped activated charcoal and Lewis bases

We have also observed that the reaction of oxygen doped activated carbon with $NaBH_4$ in THF or diglyme lead to slow hydrogen gas evolution. Accordingly, we have envisaged the formation of the AC*-O-O-BH_3 intermediate **16** as shown in Scheme **6**.

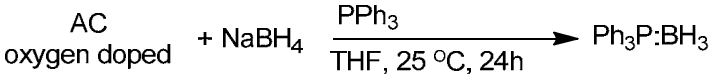
Scheme 6



To examine this, we have carried out a reaction of the intermediate **16** with stilbene in THF at 25 °C for 24 h. There was no hydroboration observed. Presumably, the intermediate **16** may not be stable and may further decomposed to AC* borate polymer.

However, when the reaction of the borane complex **16** was carried out with Ph_3P obtained the $Ph_3P:BH_3$ complex was obtained in 17% yield (Scheme **6)**.[15,16] The $Ph_3P:BH_3$ was obtained in up to 93% yield when the reaction was carried out with increased amount of oxygen doped activated charcoal. The results are summarized in Table **2**.

Table 2. Reaction of oxygen doped activated carbon (AC) **5** with Ph_3P.[a]

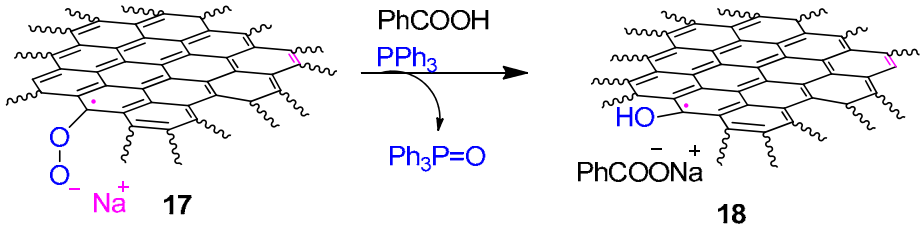


Entry	AC 5 (gm)	$NaBH_4$ (mmol)	Ph_3P (mmol)	THF (ml)	$Ph_3P:BH_3$[b]17 Yield %[b]
1	AC(1)	10	10	10	5
2	AC(2)	10	10	10	17
3	AC(3)	10	10	20	31
4	AC(5)	10	10	20	55
5	AC(10)	10	10	20	73
6	AC(12.5)	10	10	30	81
7	AC(15)	10	10	30	90
8	AC(17.5)	10	10	30	93

[a]The reactions were carried out by using $NaBH_4$ (10 mmol) and PPh_3 (10 mmol) at 25 °C. [b]Isolated yield.

We have also observed that the residual activated carbon remained after reaction with $NaBH_4$ and Ph_3P further reacts with benzoic acid and Ph_3P to give the $Ph_3P{=}O$ in 22% yield. This transformation can be rationalized as shown in Scheme **7**.

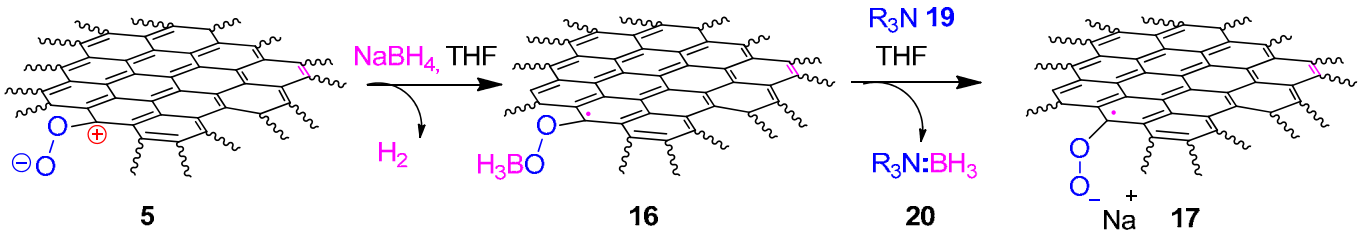
Scheme 7



III.2.4 Reaction of oxygen doped activated charcoal with $NaBH_4$ and R_3N 19

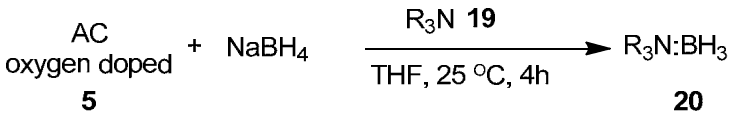
We then turned our attention towards the reaction of amines with the AC*-O-O-BH_3 intermediate **16** (Scheme **8).**[17]

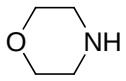
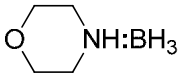
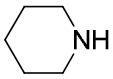
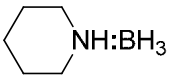
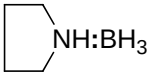
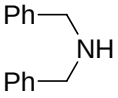
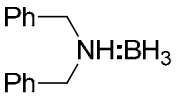
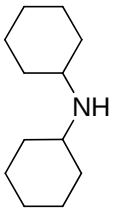
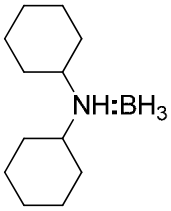
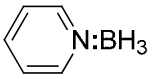
Scheme 8



We have found that the reaction of morpholine **19a** with $NaBH_4$ in presence of oxygen doped activated carbon in THF at 25°C for 24 h gives the morpholine:BH_3 **20a** in 42% yield (Table **3,** entry **1**). Following this method, different amine borane complexes were obtained in reactions using the corresponding amines **19b-19e** (Table **3**). The yields of amine boranes produced here are relatively low compared to the yield of Ph_3P (Table **2).** Presumably, the reaction of amines with AC*-BH_3 complex may be slow resulting in decomposition of the peroxy borane species **16** or the amine borane products may further react with the peroxy species present in the carbon byproduct **21** leading to reduction in yields.

Table 3. Reaction of molecular oxygen doped activated charcoal with R_3N. [a,b]



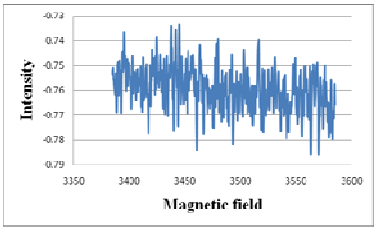
Entry	AC (gm)	R_3N 19	$R_3N:BH_3$ Complex 20	Yield(%)
1	AC(5)	 **19a**	 **20a**	42%
2	AC(5)	 **19b**	 **20b**	59%
3	AC(5)	 **19c**	 **20c**	19%
4	AC(5)	 **19d**	 **20d**	25%
5	AC(5)	 **19e**	 **20e**	38%
6	AC(5)	 **19f**	 **20f**	15%

[a]The reactions were carried out by using $NaBH_4$ (10 mmol) and R_3N (10 mmol) at 25 °C.[b]Isolated yield.

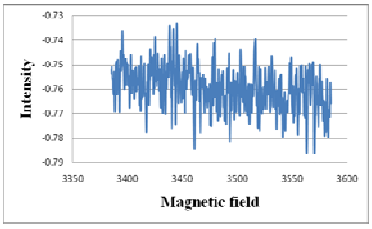
III.2.5 ESR spectra.

ESR spectra were recorded for the activated carbon samples at various stages and the spectras are presented below.

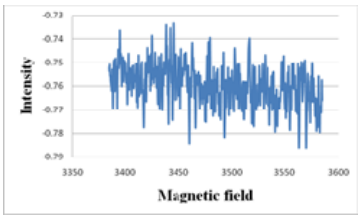
III.2.5.1. ESR spectrum of commercial activated carbon



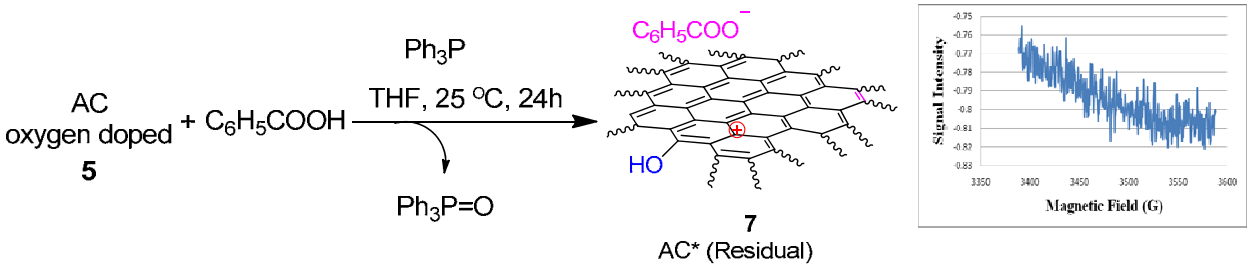
III.2.5.2. ESR spectrum of vacuum dried activated carbon (Scheme **4**)



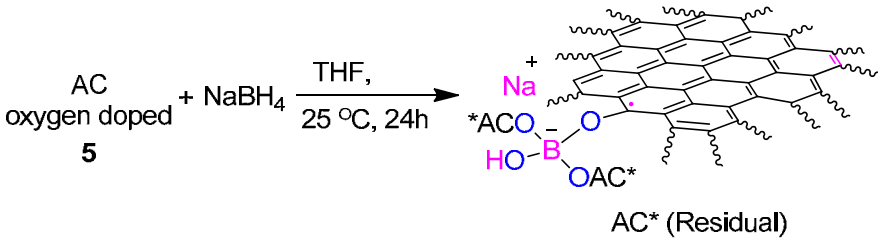
III.2.5.3. ESR spectrum of oxygen doped activated carbon (Scheme **4**)

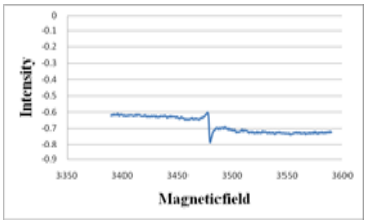


III.2.5.4. ESR spectrum of residual activated carbon (Scheme **3**)



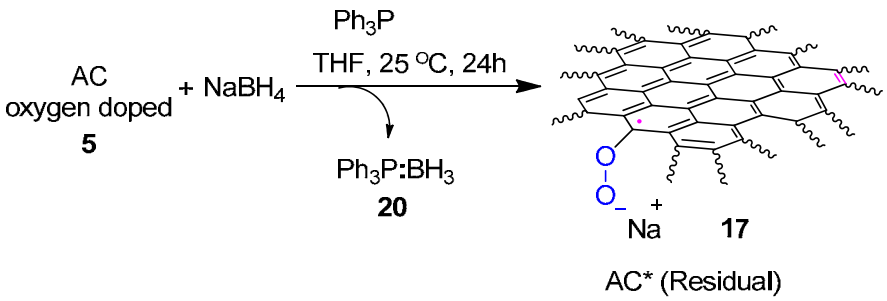
III.2.5.5. ESR spectrum of paramagnetic AC*borate polymer (Scheme **6**)

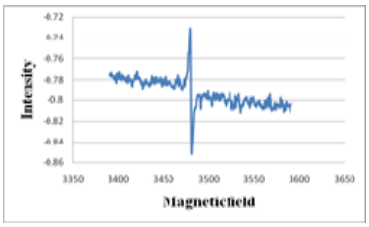




X = 3479.2 G, g = 2.00304

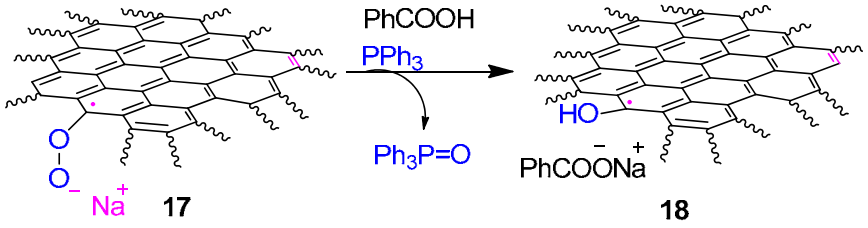
III.2.5.6. ESR spectrum of paramagnetic species **17** (Scheme **6**)

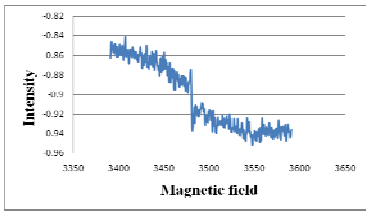




X = 3480.0 G, g = 2.00209

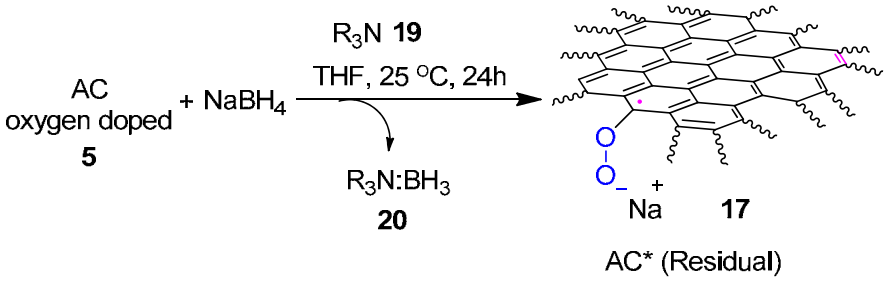
III.2.5.6. ESR spectrum of paramagnetic species **18** (Scheme **7**)

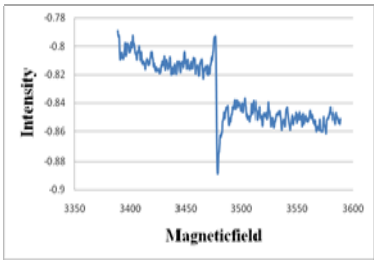




X = 3470.0 G, g = 2.00309

III.2.5.7. ESR spectrum of paramagnetic species **17** (Scheme **8**)



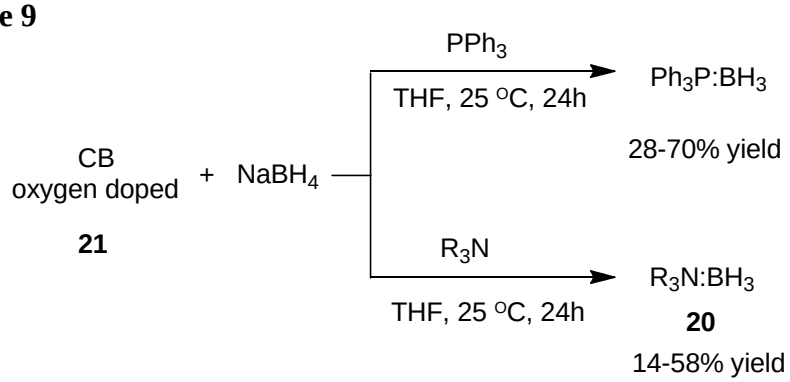


X = 3477.4 G, g = 2.00315

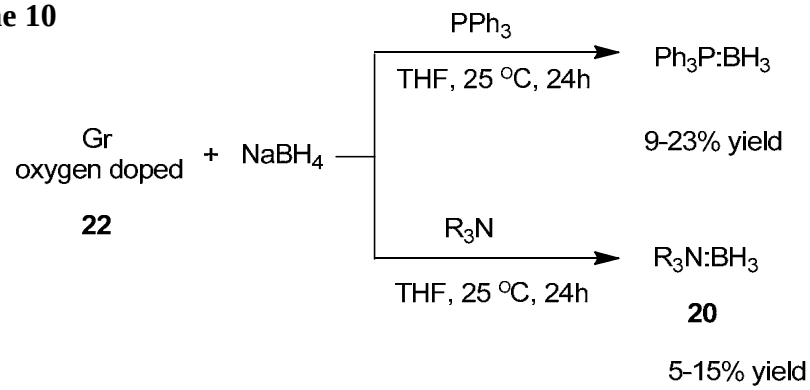
The obtained ESR signals are in accordance with that expected for the proposed paramagnetic species present in residual activated carbon samples (Scheme **6**, and Scheme **8**).

It has been observed in this laboratory that other oxygen doped carbon materials like carbon black (CB) **21** and graphite (Gr) **22** also react in a similar way with $NaBH_4$ and Lewis bases like Ph_3P and R_3N. In the case of carbon black (CB), the $Ph_3P{:}BH_3$ and $R_3N{:}\ BH_3$ are obtained in comparable yields. Whereas, the oxygen doped graphite (Gr) gives lower yields, indicating that the Gr is oxygen doped to lesser extent.[18]

Scheme 9

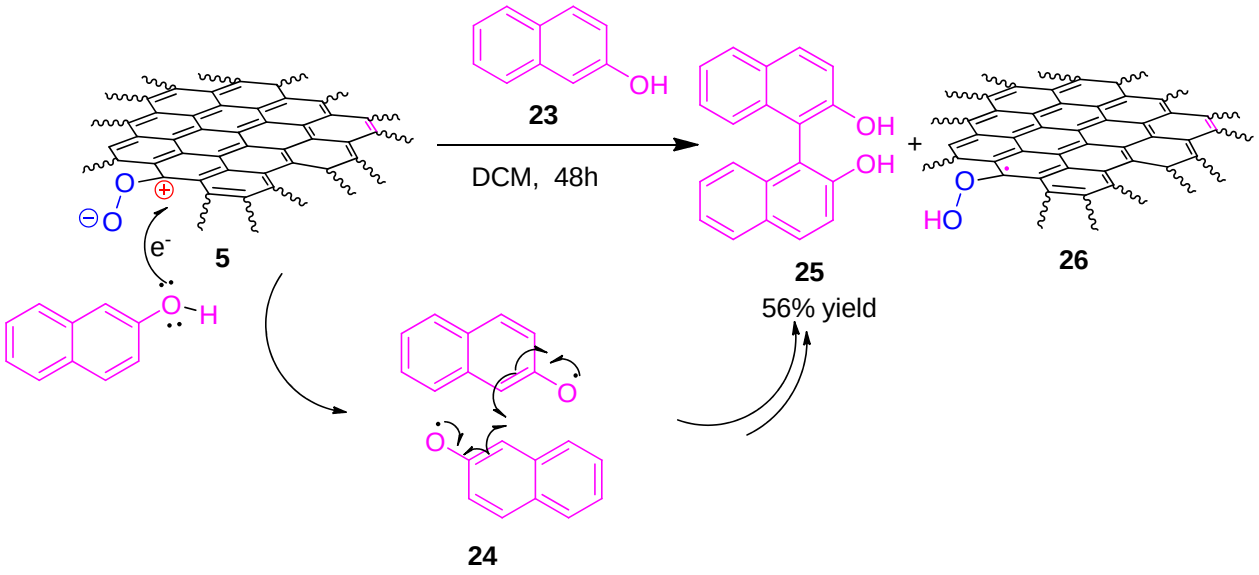


Scheme 10



Also, it was found that 2-naphthol **23** undergoes oxidative coupling reactions in the presence of oxygen doped activated charcoal **5** to give the bi-2-naphthol **25** (BINOL) in 56% yield (Scheme **11)**.[19]

Scheme 11



Very recently, it was found in this laboratory that reaction of molecular oxygen doped activated carbon with amines produces the corresponding amine radical cations. These reactive intermediates have potential for application in the development of new organic transformations involving electron transfer reactions. Therefore, further systematic studies on the reaction of oxygen doped activated carbon and other readily accessible carbon materials like carbon black (CB) and graphite (Gr) with electron donors are expected to give fruitful results.

III.3 Conclusions

Convenient methods have been developed for practical use of molecular oxygen doped activated carbon. Oxygen doped activated carbon reacts with benzoic acid and Ph_3P to give $Ph_3P{=}O$ in 54% yield. Similarly, the activated carbon **5** reacts with NaOH and alkylboranes to give the corresponing alcohols. The $Ph_3P{:}BH_3$ and $R_3N{:}BH_3$ complexes are prepared in moderate to good yields upon reaction of oxygen doped activated carbon with $NaBH_4/Ph_3P$ and $NaBH_4/R_3N$ reagent systems. Further systematic studies of the reaction of the oxygen doped activated carbon with electron donating organic compounds and reducing agents are expected to lead to the discovery of several new organic transformations.

III.4 Experimental Section

III.4.1 General procedure for reaction of molecular oxygen doped activated charcoal with Ph_3P in presence of benzoic acid:

In a 50 mL RB flask, activated charcoal (5g) heated at 200 °C under high vacuum (0.001 mm of Hg) for 2h. After the RB flask was brought to room tempature under nitrogen atmosphere, the contents were saturated with dry air for 1h. To this, Ph_3P (2.62 g 10 mmol) and benzoic acid (1.221 g, 10 mmol) in THF were added. The reaction mixture was further stirred for 24 h. The reaction mixture filtrated and the organic layer was separated. The solvent was evaporated under reduced pressure and the crude product $Ph_3P{=}O$ was purified by silica gel column chromatography using hexane as eluent.

Yield **:** 1.501 g, 54%

IR (neat) **:** 3073, 3046, 1599, 1489, 1435, 1308, 1188, 1117, 1002 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.67-7.62 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.40 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 133.0, 132.1, 132.0, 131.9, 128.5, 128.4.

^{31}P NMR : (162 MHz, $CDCl_3$ δppm) 29.3 (Reference: H_3PO_4 signal locked at 0.00 ppm)

III.4.2 Preparation of trialkylborane (11a-11b):

The $NaBH_4$ (0.450 g, 12 mmol) was taken in a two-necked RB flask and dry THF (20 ml) was added. The RB flask placed at -30 °C and iodine (1.2 g, 5 mmol) in THF (20 ml) was added slowly during 10 min. After evolution of hydrogen gas ceased, the reaction

mixture was further stirred for 1h at -30 °C. A solution of olefin (30 mmol) in THF (10 ml) was slowly added during 15 min under nitrogen atmosphere. The reaction mixture was brought to 25 °C and further stirred for 4h at the same temperature to give trialkylborane.

III.4.3 Preparation of dialkylborane, 12a-12c.

The procedure followed was as in earlier experiment but using only 20 mmol of olefin along with the $NaBH_4$ (0.45 g, 12 mmol) and iodine (1.2 g, 5 mmol).

III.4.4 Preparation of dialkenyl(thexyl)borane, 11c-11d.

The Bu_4NBH_4 (3 g, 12 mmol) was taken in a two-necked RB flask and dry toluene (10 ml) was added followed by iodine (1.55g, 7 mmol) in toluene (20 ml). The generated diborane was carried off through a side tube and bubbled through a solution of tetramethyl ethylene (10 mmol) for 15 min. The reaction mixture was brought to 25 °C and further stirred for 4h. In another two-necked RB flask the alkyne (20 mmol) in dry THF (20 ml) was taken and cooled to 0 °C under nitrogen atmosphere. The thexylborane in toluene prepared as above was added through a cannula under nitrogen atmosphere. The contents were further stirred for 4h at 0 °C.

III.4.5 Preparation of alkyl and alkenyl catecholborane, 13a-13b.[13c]

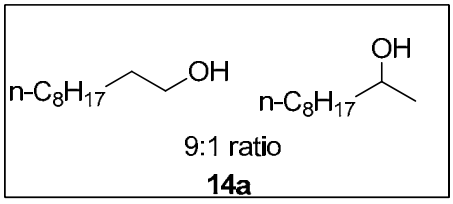
To a solution of Bu_4NBH_4 (3 g, 12 mmol) in toluene was taken in a two-necked RB flask and dry toluene (30 ml) and iodine (1.55g, 7 mmol) in toluene (20 ml) was added at 25 °C. The generated diborane was carried off through a side tube and bubbled through a solution of catechol (1.11 g 10 mmol) in benzene (40 ml) for 20 min at 0 °C. The reaction mixture was brought to 25 °C and a solution of olefin (10 mmol) or alkyne (10 mmol) in

THF (10 ml) was slowly added during 15 min under nitrogen atmosphere and further stirred for 12h at 80 °C.

III.4.6 General procedure for reaction of molecular oxygen doped activated charcoal with alkylboranes

In a 50 mL RB flask, activated charcoal (5g) and 3N NaOH (10 mL) in THF 15 ml were stirred for about 4h. To this reaction mixture, the alkylborane (5 mmol) was added dropwise for 20 min at 0 °C and further stirred for 4h. The reaction mixture was filtered and the organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The solvent was evaporated and the crude products were purified on silica gel column chromatography using hexane: ethyl acetate (95:5) as eluent. The spectral data of these products showed 1:1 correspondence with the reported data.

Decan-1-ol (14a):



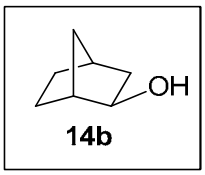
14a

Yield **:** 1.488 g, 93%, colorless liquid.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 4.01 (m, 1H), 1.42-1.39 (m, 14H), 0.94-0.86 (m, 4H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 70.5, 36.2, 32.4, 31.9, 29.6, 29.4, 29.4, 25.6, 25.6, 24.9, 24.0, 22.6, 14.1.

Bicyclo [2.2.1] heptan-2-ol (14b):



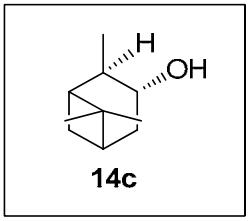
14b

Yield **:** 0.806 g, 72%, yellow liquid.

IR (neat) : 3430 (br), 3024, 2935, 2869, 1597, 1495, 1450, 1066, 1042, 755, 741, 702 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 4.23 (m, 3H), 2.50 (m, 1H), 2.17 (m, 1H), 1.99-1.84 (m, 2H), 1.62-1.52 (m, 1H), 1.42-1.27 (m, 5H), 0.84 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 73.1, 42.5, 39.6, 37.6, 37.2, 29.9, 19.9.



14c

2, 6, 6-Trimethyl-bicyclo [3.1.1] heptan-3-ol (14c):

Yield **:** 1.262 g, 82%, colorless liquid.

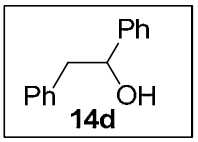
IR (neat) **:** 3327, 2905, 1147, 1055, 808, 692 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 2.35 (m, 1H), 1.94-1.50 (m, 8H), 1.22 (s, 3H), 1.14-1.02 (m, 3H), 0.92 (s, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 71.4, 47.8, 47.5, 41.7, 38.9, 38.1, 34.2, 27.6, 23.6, 20.7.

The spectral data of this compound showed 1:1 correspondence with the reported data

1, 2-Diphenyl-ethanol (14d):



14d

Yield **:** 1.861 g, 94%, soild.

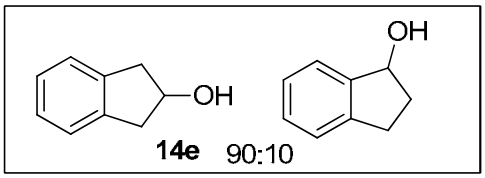
IR (KBr) **:** 3329, 3078, 3026, 2922, 1039, 696 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.36-7.26 (m, 10H), 4.91-4.88 (m, 1H), 3.03-2.96 (m, 2H), 1.95 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 143.9, 138.1, 129.5, 128.4, 127.6, 126.6, 125.9, 75.3, 46.1.

The spectral data of this compound showed 1:1 correspondence with the reported data

Indan-2-ol (14e):



Yield **:** 1.322 g, 99%

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

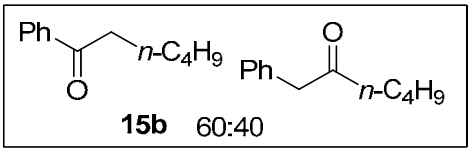
^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) mixture of isomers (α:β 1:9)

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 140.8, 126.6, 126.5, 73.1, 42.6 (major isomer)

III.4.7 General procedure for reaction of molecular oxygen doped activated charcoal with alkenylboranes (11c, 11d) or alkoxyboranes 13b

In a 50 mL RB flask, activated charcoal (5g) and 3N NaOAc (10 mL) in THF 15 ml stirred for about 4h. To this reaction mixture, alkenylborane (10 mmol) or alkoxyboranes (10 mmol) in benzene was added dropwise for 20 min at 0 °C and further stirred for 4h. The reaction mixture was filtered and organic layer was separated. The aqueous layer was extracted with ether (2 x 10 mL). The solvent was evaporated and the crude products were purified on silica gel column chromatography using hexane: ethyl acetate (98:2) as eluent. The spectral data of these products showed 1:1 correspondence with the reported data.

1-Phenyl-hexan-2-one; 1-phenyl-hexan-1-one (15b):



Yield **:** 1.343 g, 79%, colorless liquid.

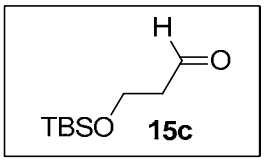
IR (neat) **:** 3060, 2960, 2940, 1675, 1600, 1450, 1350, 1220, 950, 760, 700 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) mixture of isomers (60:40).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 208.6, 200.6, 137.1, 134.4, 132.8, 128.8, 128.6, 128.5, 128.0, 126.9, 50.1, 41.7, 38.5, 31.5, 25.8, 24.7, 22.5, 22.2, 13.9, 13.8.

The spectral data of this compound showed 1:1 correspondence with the reported data.

3-(tert-Butyl-dimethyl-silanyloxy)-propionaldehyde (15c):



Yield **:** 1.278 g, 68%, colorless liquid.

IR (neat) **:** 2955, 2930, 2886, 2858, 1728, 1472, 1462, 1390, 1362, 1254, 1095, 970, 832, 775cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 9.80 (s, 1H), 4.01-3.91 (t, *J*=4.0Hz, 1H), 2.60-2.59 (m, 1H), 1.25 (s, 1H), 0.92-0.88 (m, 6H), 0.09-0.07 (s, 9H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 202.0, 57.4, 46.5, 29.7, 25.8, 18.2, 1.02, -5.44.

The spectral data of this compound showed 1:1 correspondence with the reported data

III.4.8 General procedure for reaction of activated carbon and $NaBH_4$ with PPh_3:

In a 50 mL RB flask, activated charcoal (5g), and $NaBH_4$ (0.38 g, 10 mmol) in THF (20 mL) were taken added under nitrogen atmosphere. To this reaction mixture PPh_3 (2.62 g, 10 mmol) was added and the contents were stirred for about 24 h. The reaction mixture was filtered and the organic layer was separated. The solvent was evaporated under reduced pressure and the crude product was purified on silica gel column chromatography using hexane as eluent to isolate pure $Ph_3P{:}BH_3$.

Yield **:** 1.501 g, 54%

IR (neat) **:** 3057, 2372, 2344, 1478, 1435, 1314, 1177, 1106, 1056, 733 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.63-7.60 (m, 1H), 7.53-7.50 (m, 1H), 7.46-7.43 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 133.2, 133.1, 131.1, 129.4, 128.8, 128.7.

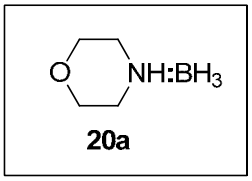
^{11}B NMR **:** (128.3 MHz, $CDCl_3$ δppm) -37.8 (Reference: $B(OMe)_3$ signal locked at 0.00 ppm).

^{31}P NMR : (162 MHz, $CDCl_3$ δppm) 21.5.

III.4.9 General procedure for reaction of activated carbon and $NaBH_4$ with R_3N:

In a 50 mL RB flask, activated charcoal (5g) and $NaBH_4$ (0.380g 10 mmol) were taken and THF (20 mL) was added under nitrogen atmosphere. To this, R_3N (10 mmol) was added and the contents were stirred for 24 h. The contents were filtered and the solvent was evaporated under reduced pressure to afford the crude product $H_3B{:}NR_3$ as white soild.

Morpholine borane complex (20a):



20a

Yield **:** 0.421 g, 42%, white soild.

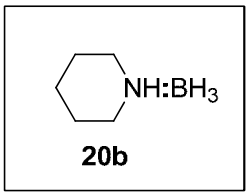
IR (KBr) **:** 3178, 2975, 2953, 2860, 2367, 2323, 2263, 1452, 1419, 1375, 1326, 1227, 1156 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 4.05-4.04 (d, *J*=4.0Hz, 1H), 3.68-3.64 (t, *J*=16.0Hz, 3H), 3.11-3.07 (d, *J*=16.0Hz, 1H), 2.80-2.74 (m, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 65.7, 52.1.

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -16.5

Piperidine borane complex (20b):



Yield **:** 0.578 g, 59%, white soild.

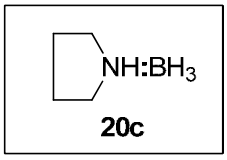
IR (KBr) **:** 3221, 2936, 2849, 2349, 2350, 2273, 1463, 1364, 1276, 1161, 1123, 1057 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 3.69 (b, 1H), 3.25-3.21 (d, *J*=16.0Hz, 2H), 2.54-2.44 (q, *J*=40.0Hz, 1H), 1.78-1.75 (m, 3H), 1.57-1.46 (m, 3H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 53.3, 25.3, 22.4.

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -15.3.

Pyrrolidine borane complex (20c):



Yield **:** 0.168 g, 19%, white soild.

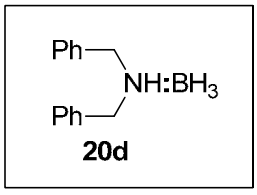
IR (KBr) **:** 3227, 2931, 2854, 2389, 2356, 2279, 1452, 1358, 1331, 1276, 1161, 1134, 1106 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 3.28-3.25 (m, 1H), 2.79-2.74 (m, 1H), 2.03-1.91 (m, 1H), 1.85-1.79 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 54.2, 24.6.

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -15.1

Dibenzyl amine borane complex (20d):



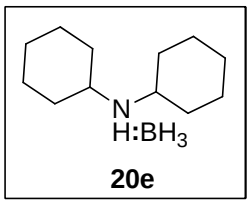
Yield **:** 0.527 g, 25%, white soild.

IR (KBr) **:** 3189, 2969, 2936, 2860, 2372, 2323, 2263, 1457, 1424, 1380, 1282, 1232, 1161 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 7.39 (m, 2H), 7.21-7.19 (s, 1H), 4.02-3.99 (d, *J*=12.0Hz, 1H), 3.82-3.77 (m, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 134.3, 128.9, 128.7, 128.2, 58.4

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -14.4



20e

Dicyclohexyl amine borane complex (20e):

Yield **:** 0.741 g, 38%, white soild.

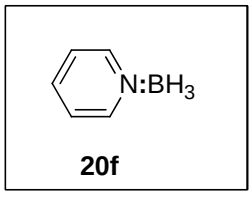
IR (KBr) **:** 3200, 3030, 2936, 2372, 2328, 2301, 2273, 1495, 1457, 1413, 1347, 1161 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 2.84-2.83 (m, 4H), 1.89-1.78 (m, 6H), 1.66-1.59 (m, 6H), 1.32-1.24 (m, 6H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 60.6, 30.8, 29.6, 25.6, 25.3, 25.2

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -.-19.4

Pyridine borane complex (20f):



20f

Yield **:** 0.135 g, 15%, colorless liquid.

IR (neat) **:** 2964, 2832, 2750, 2712, 2531, 2460, 2400, 2062, 1419, 1304, 1145 cm^{-1}.

^{1}H NMR **:** (400 MHz, $CDCl_3$, δppm) 8.52 (s, 1H), 7.91 (s, 1H), 7.50-7.48 (s, 1H).

^{13}C NMR **:** (100 MHz, $CDCl_3$, δppm) 147.3, 134.3, 125.4.

^{11}B NMR : (128.3 MHz, $CDCl_3$ δppm) -11.4

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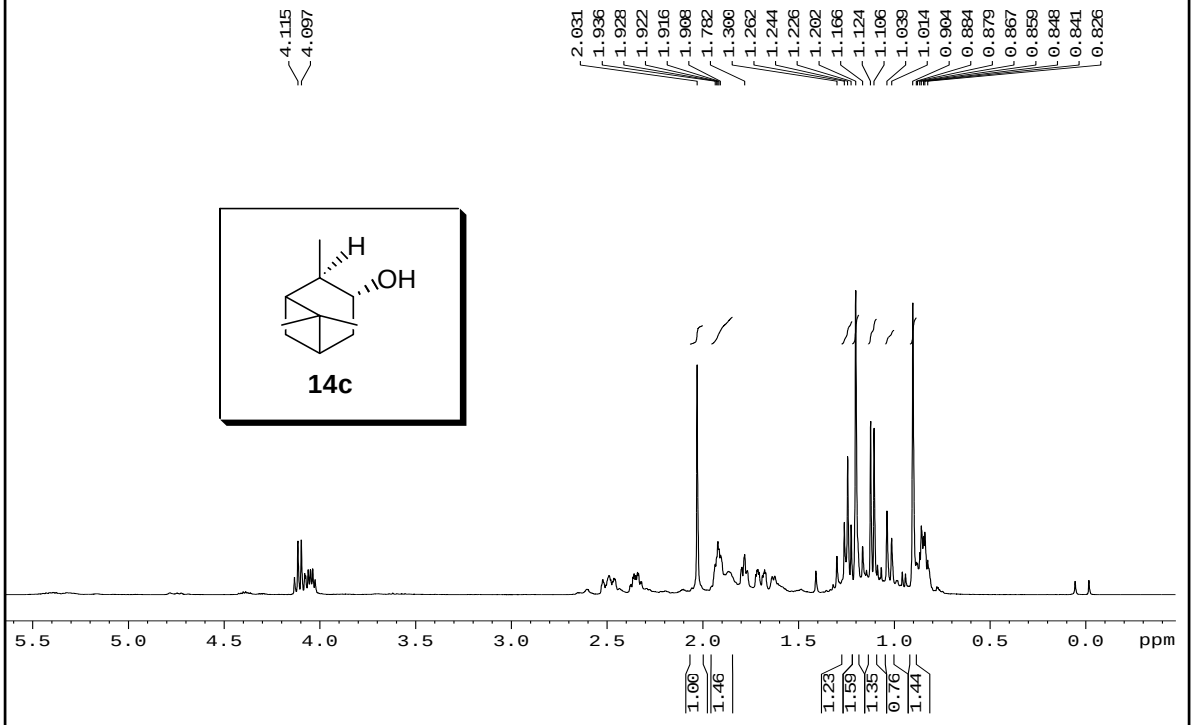
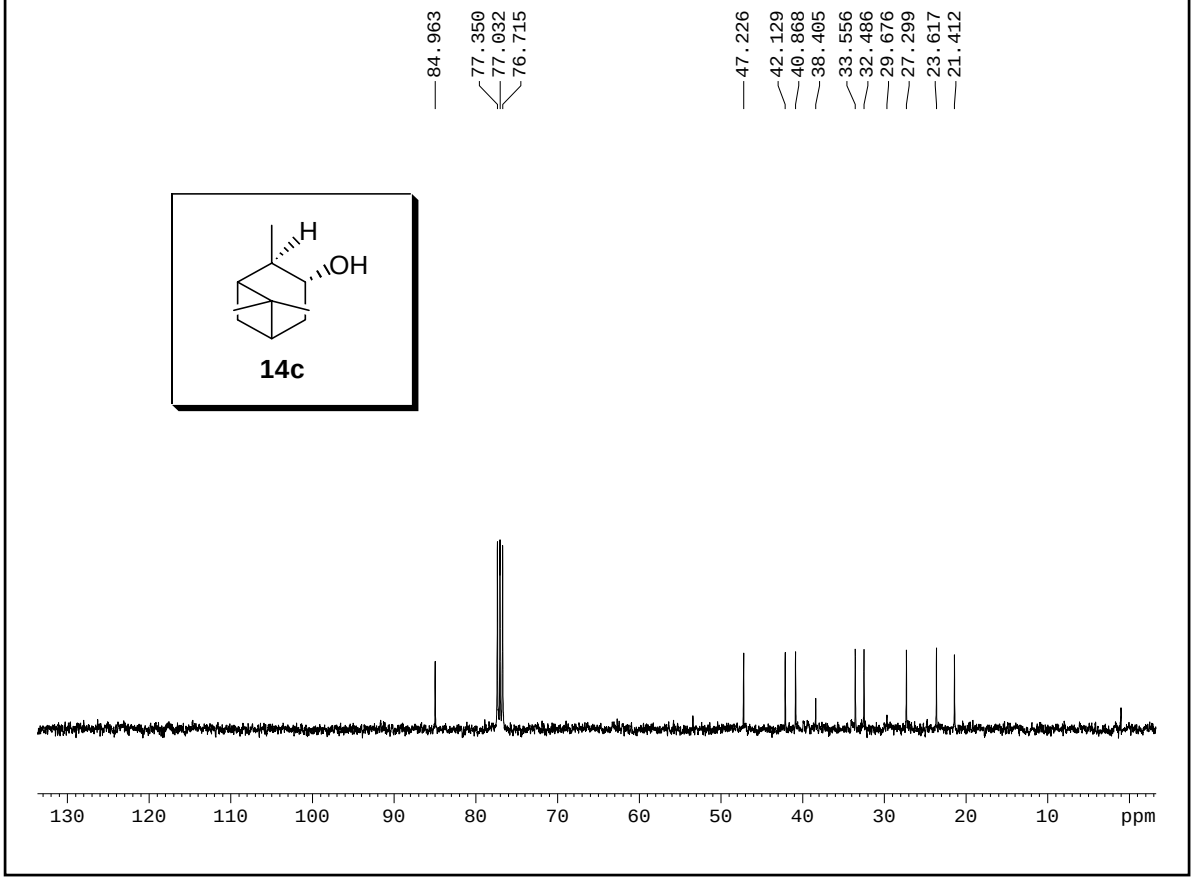
19. Ramusagar, M. unpublished results.

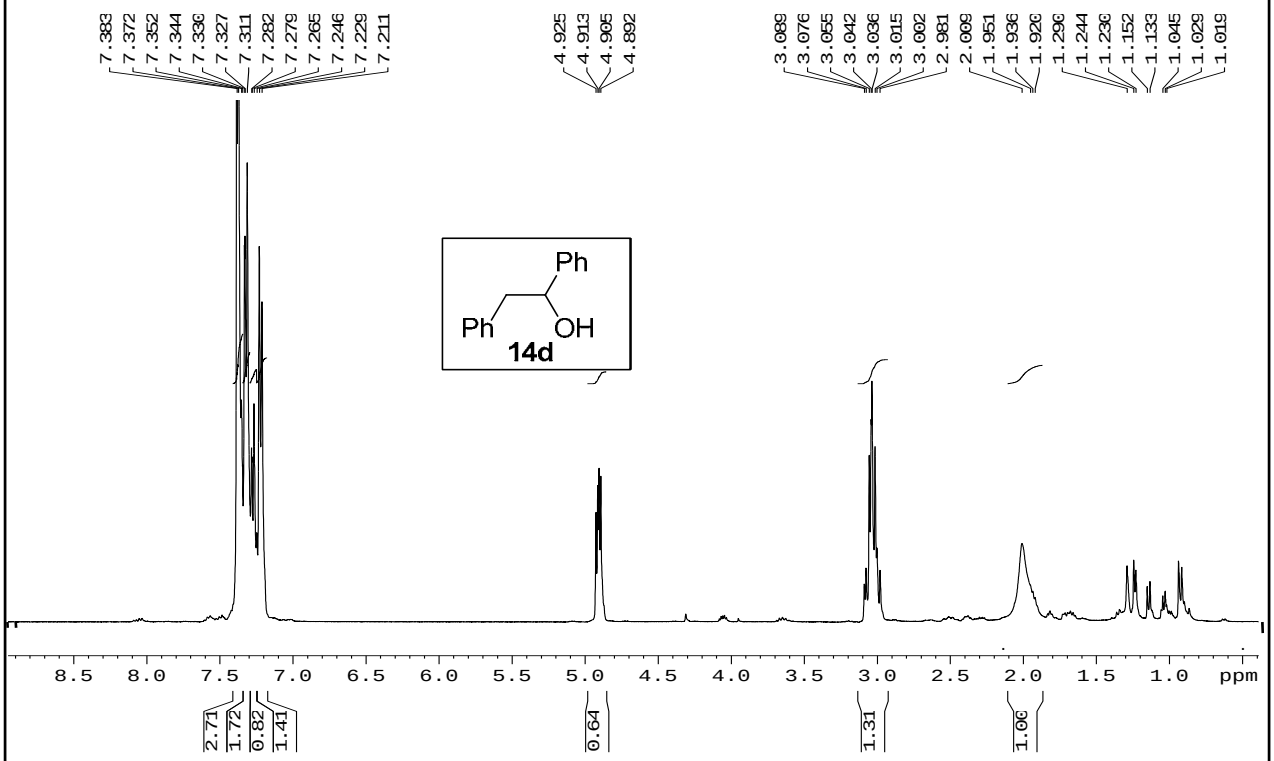
Spectrum No. 1 (Appendix-III, Section III.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



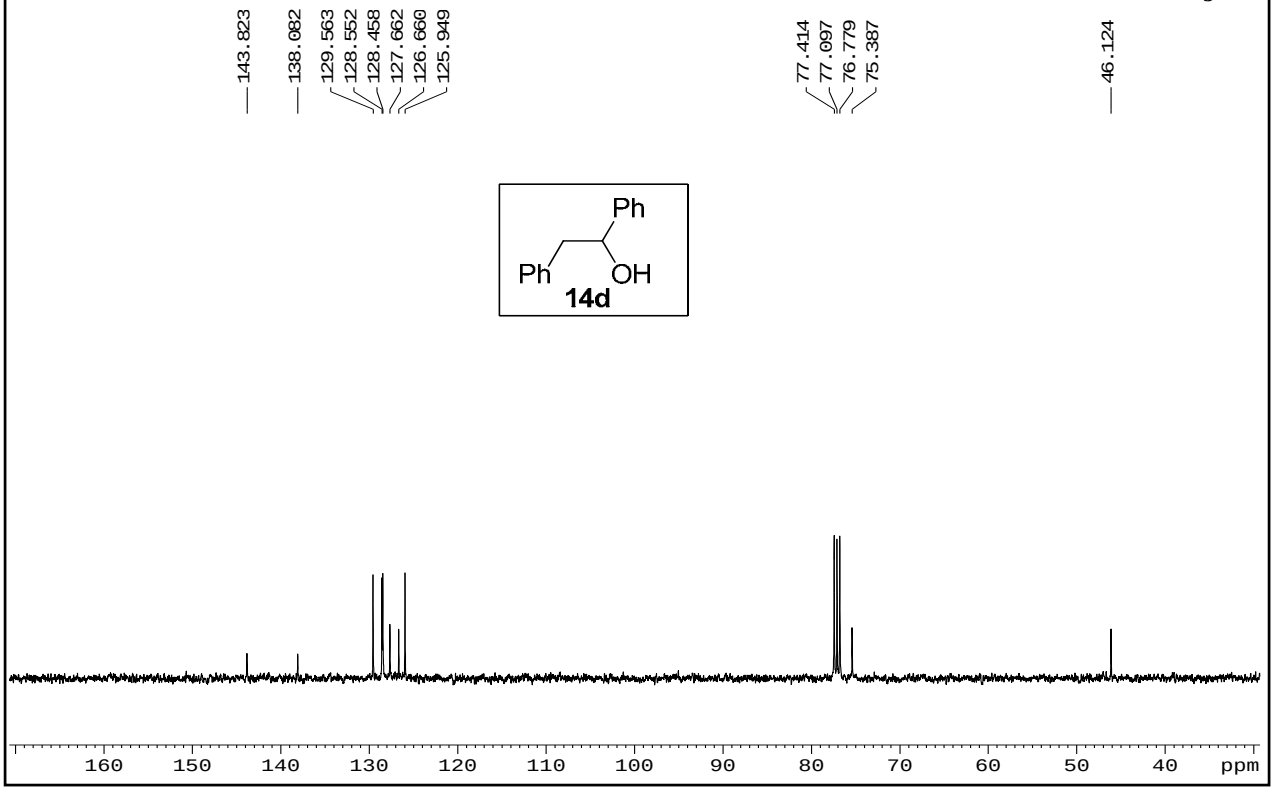
Spectrum No. 2 (Appendix-III, Section III.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



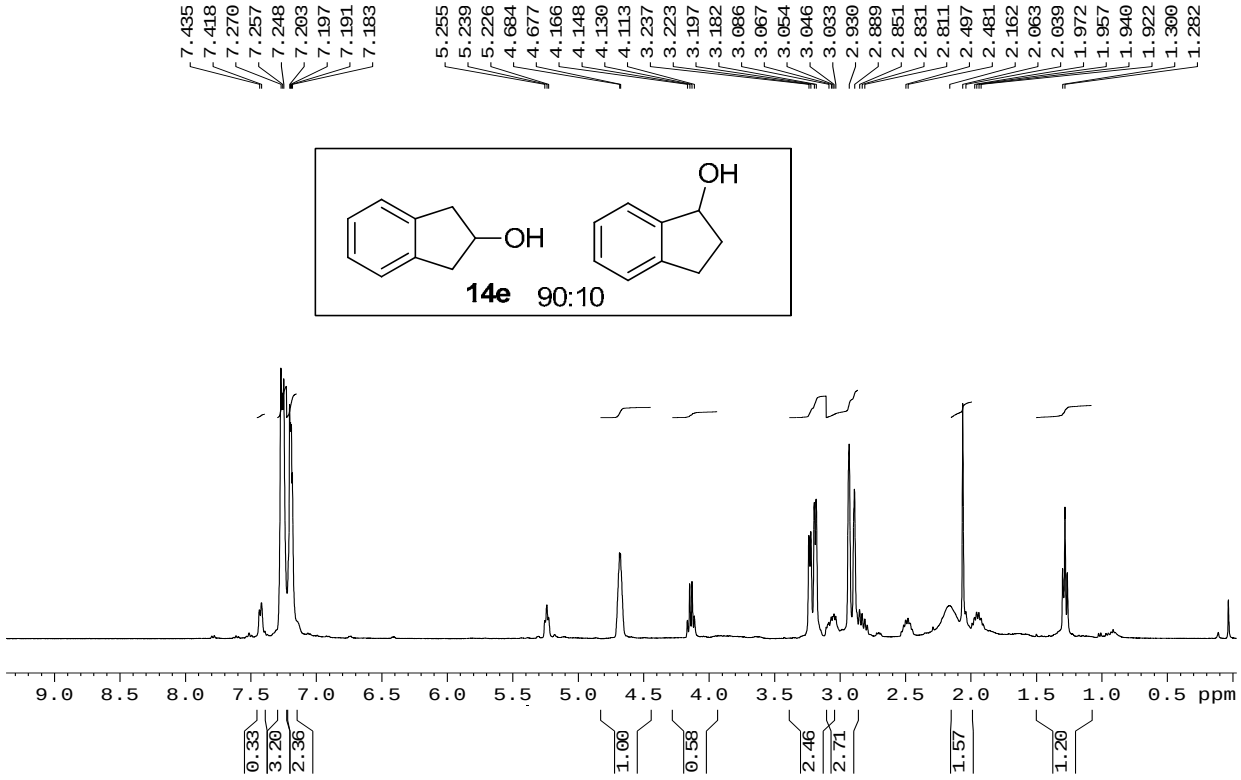
Spectrum No. 3 (Appendix-III, Section III.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



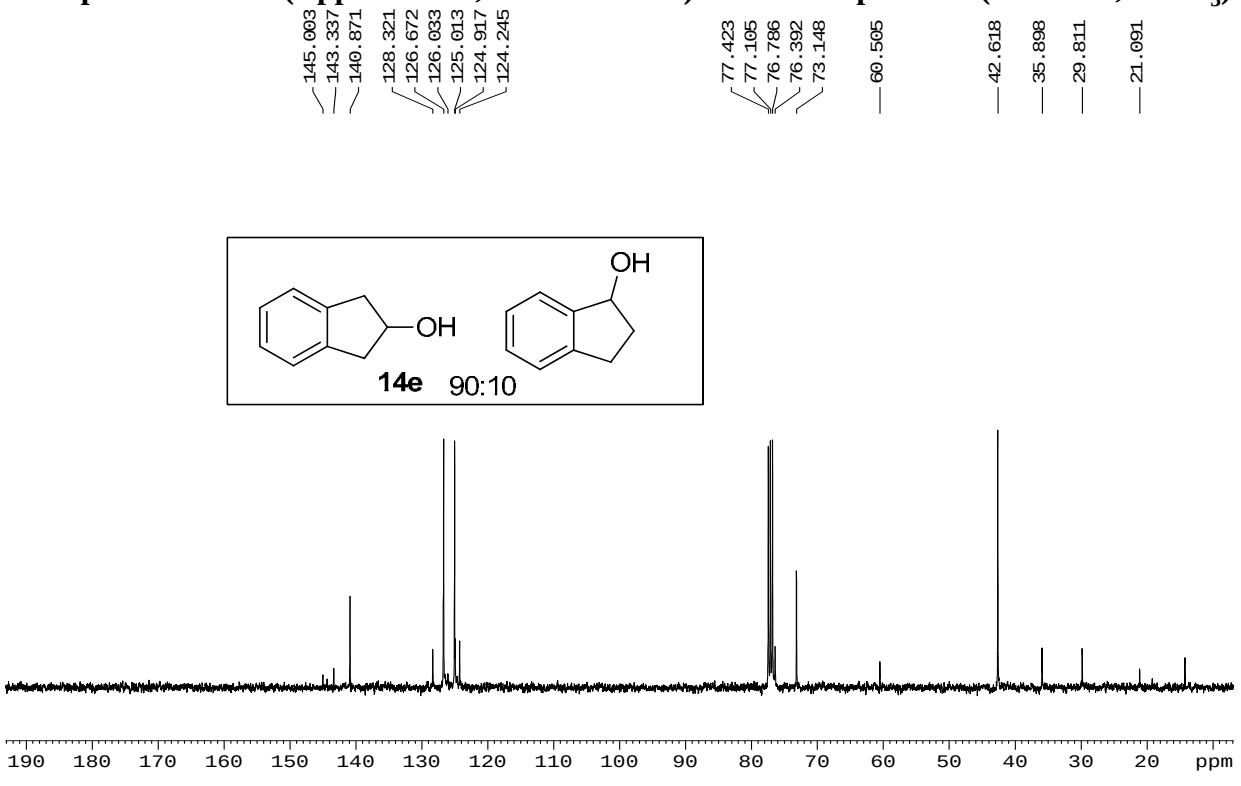
Spectrum No. 4 (Appendix-III, Section III.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



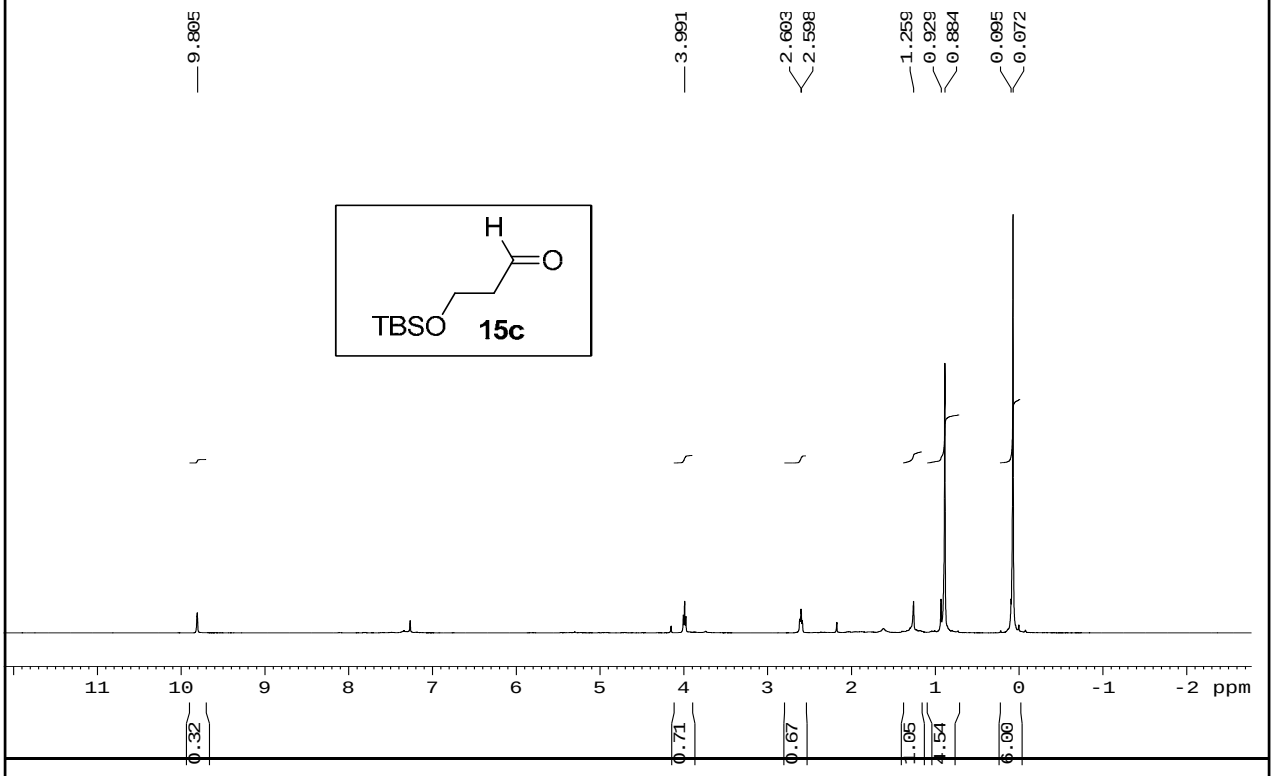
Spectrum No. 5 (Appendix-III, Section III.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



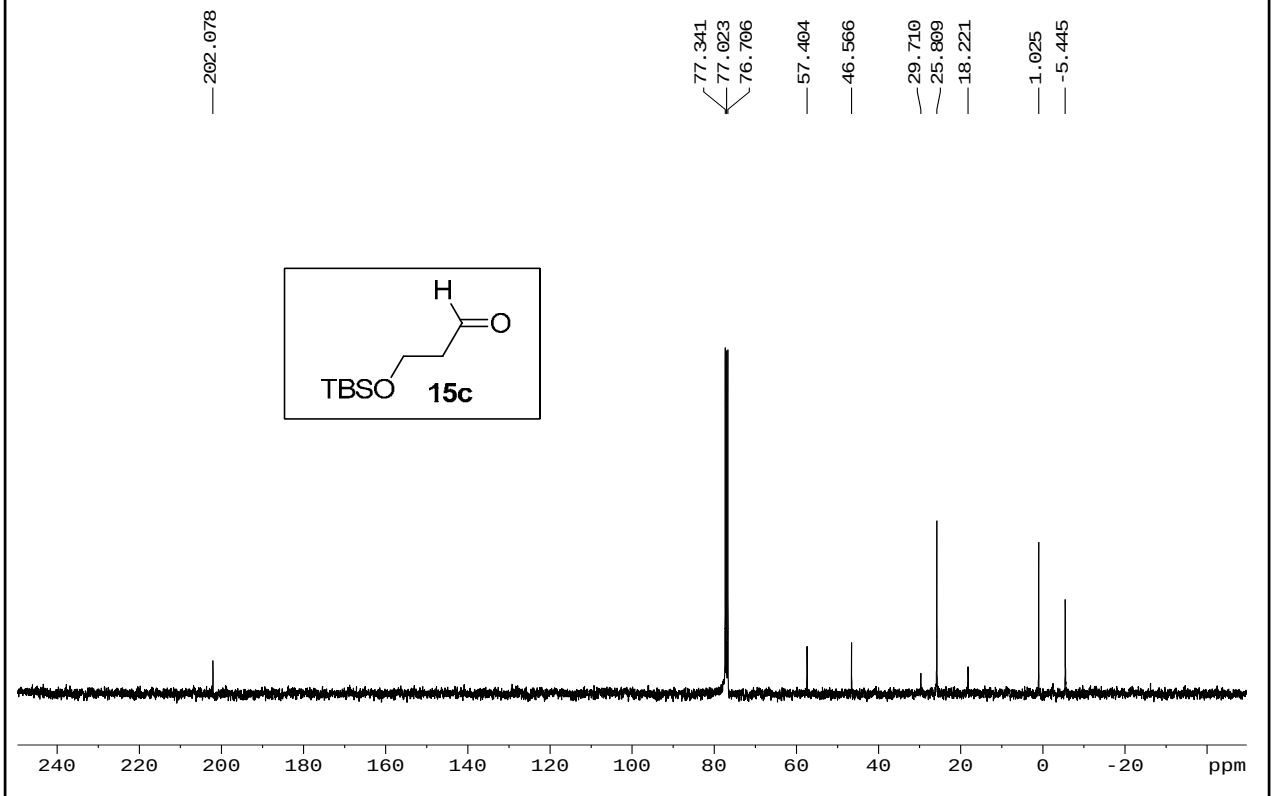
Spectrum No. 6 (Appendix-III, Section III.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



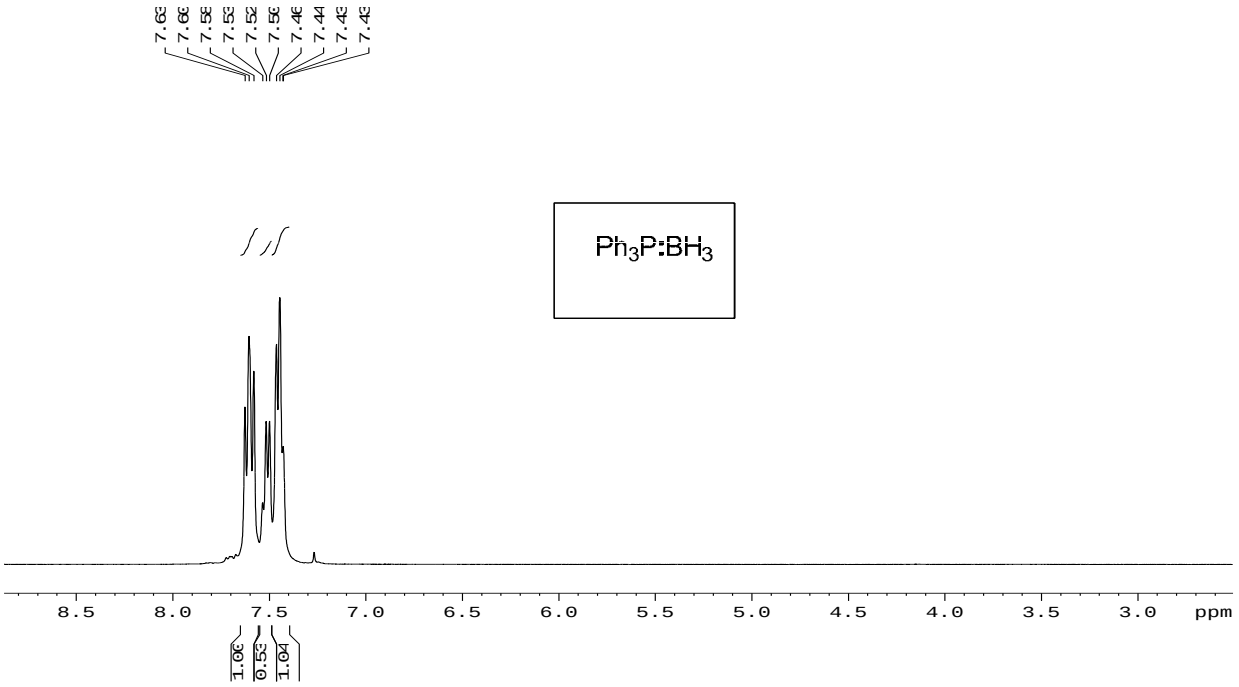
Spectrum No. 7 (Appendix-III, Section III.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



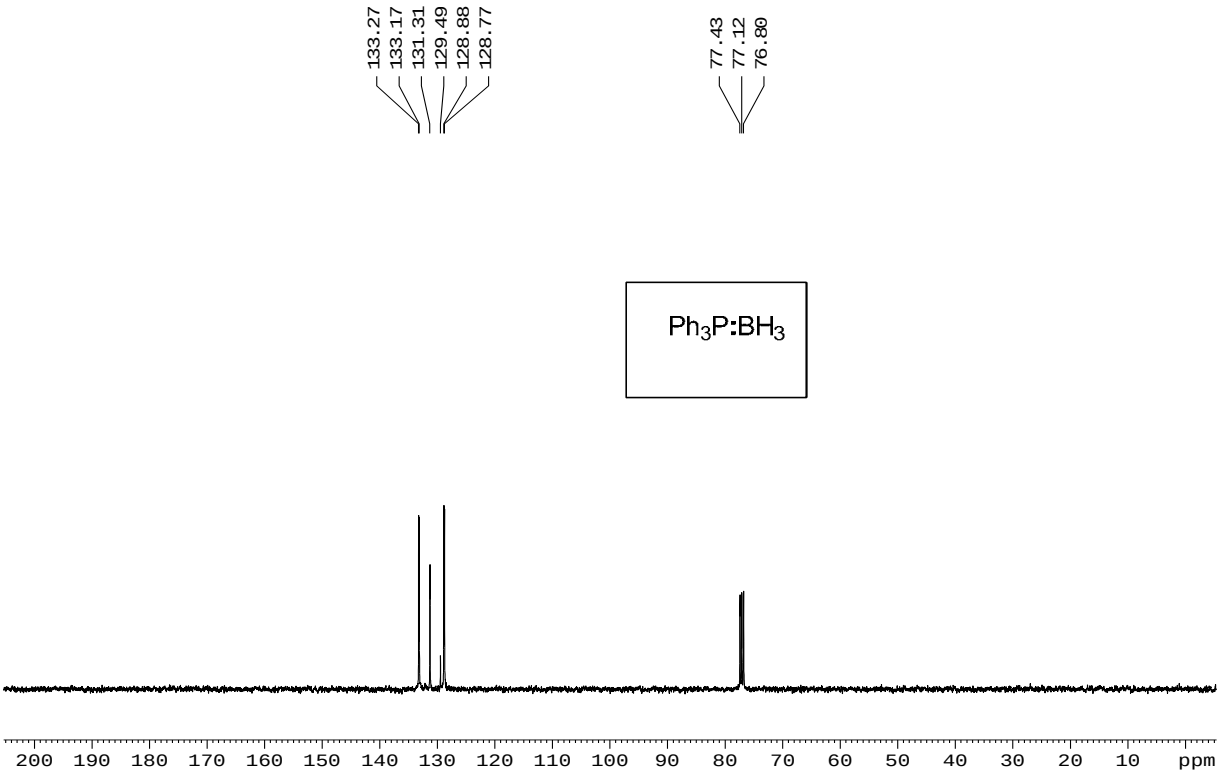
Spectrum No. 8 (Appendix-III, Section III.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



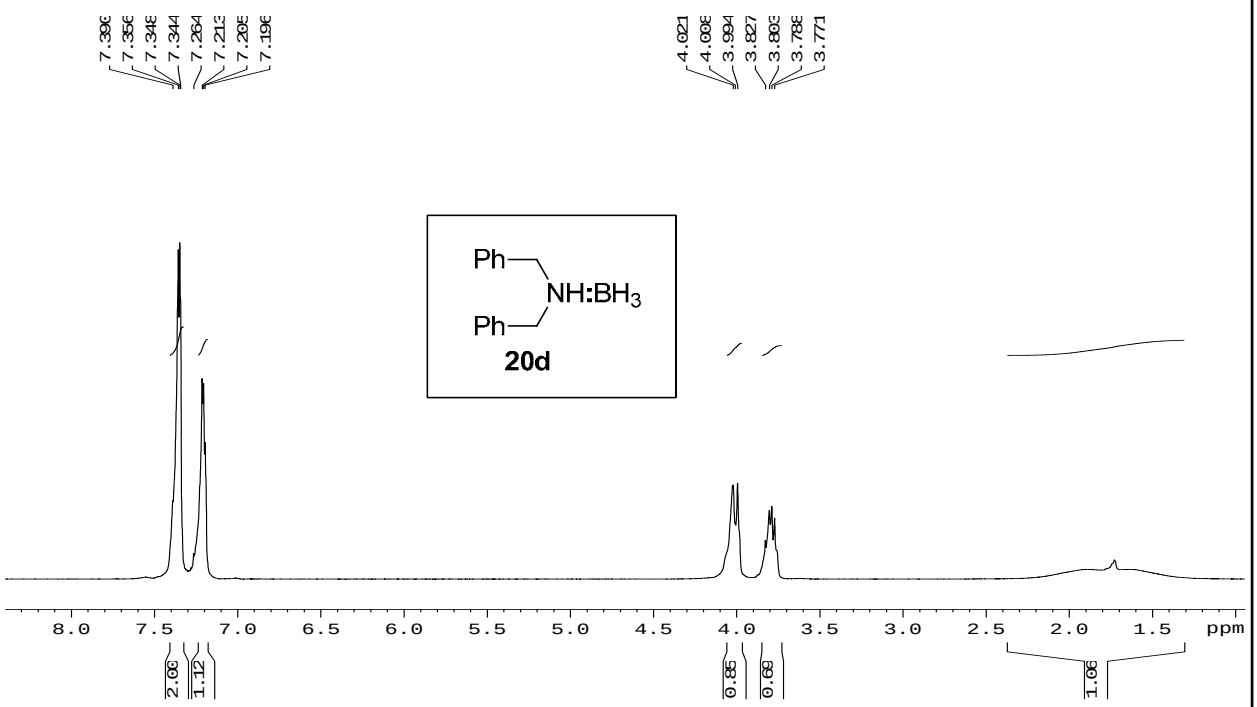
Spectrum No. 9 (Appendix-III, Section III.2.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



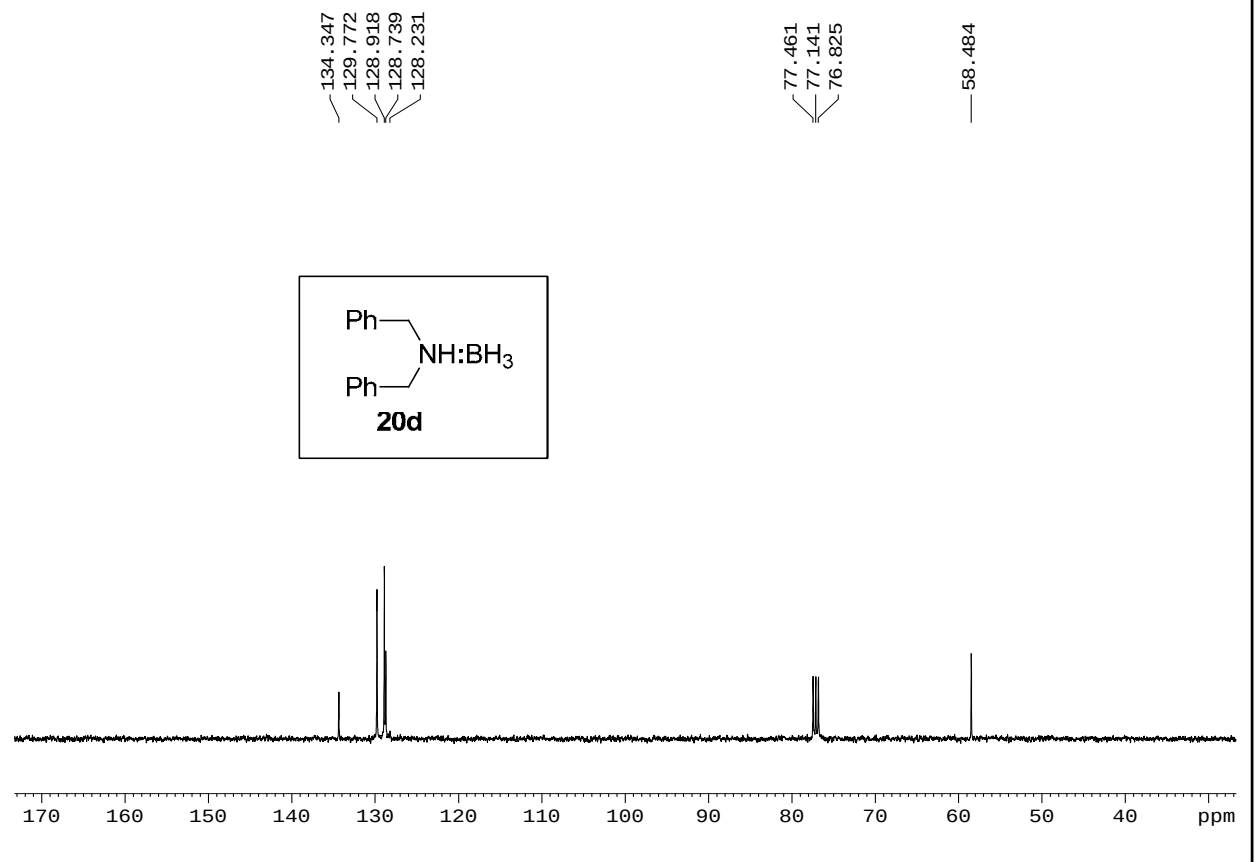
Spectrum No. 10 (Appendix-III, Section III.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



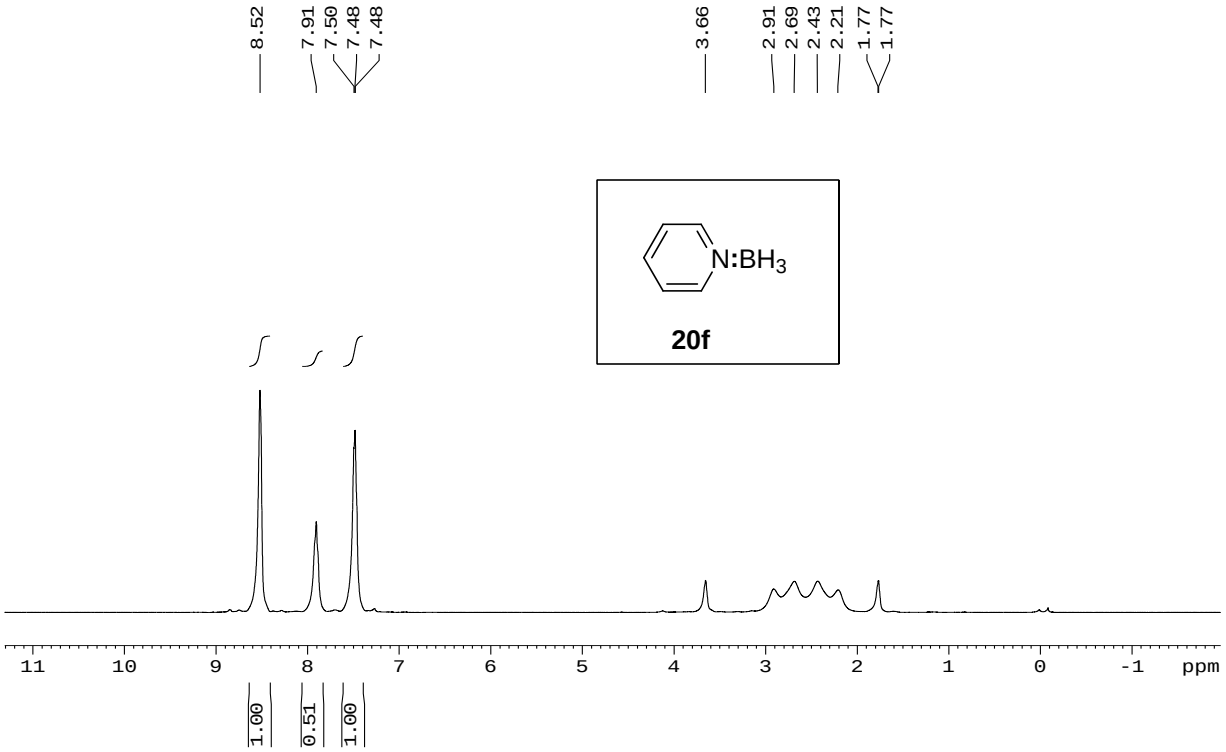
Spectrum No. 11 (Appendix-III, Section III.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



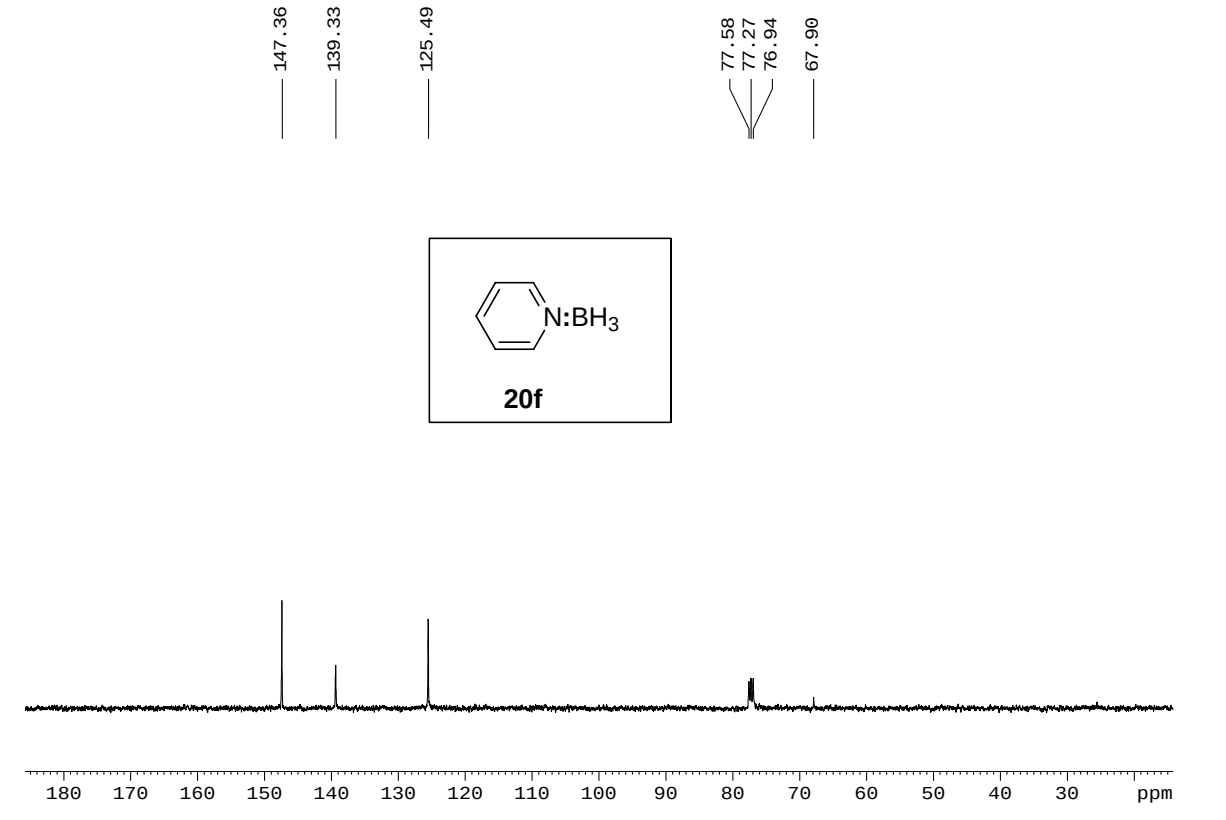
Spectrum No. 12 (Appendix-III, Section III.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



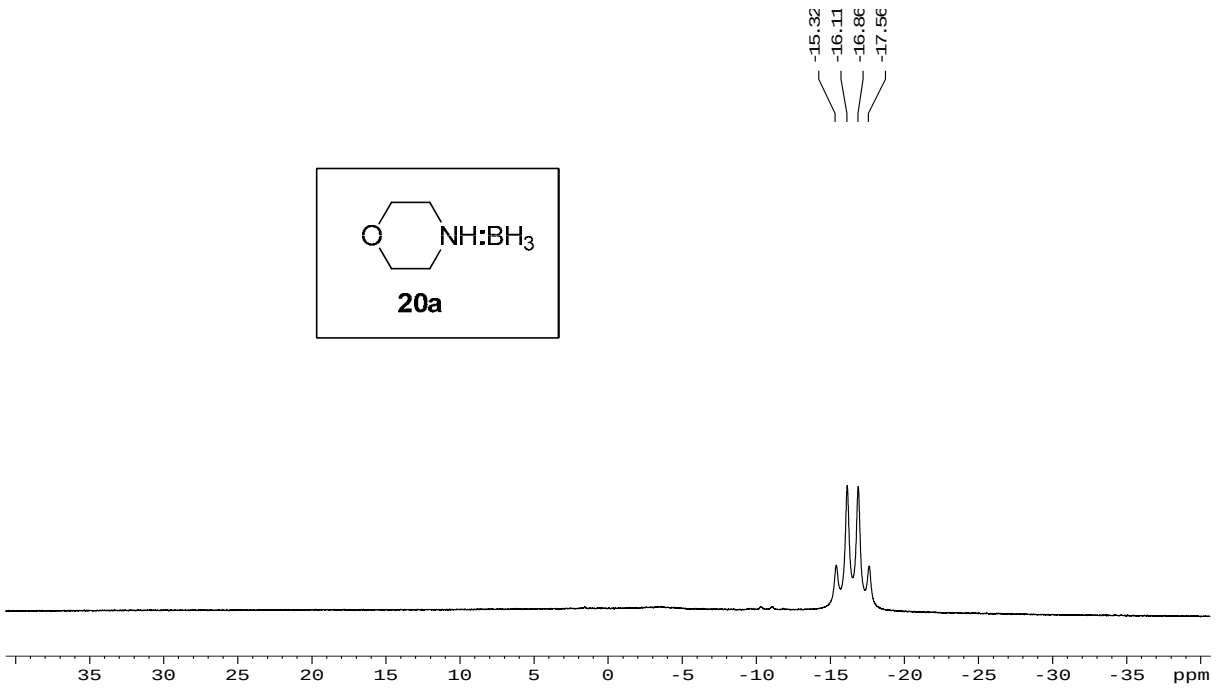
Spectrum No. 13 (Appendix-III, Section III.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



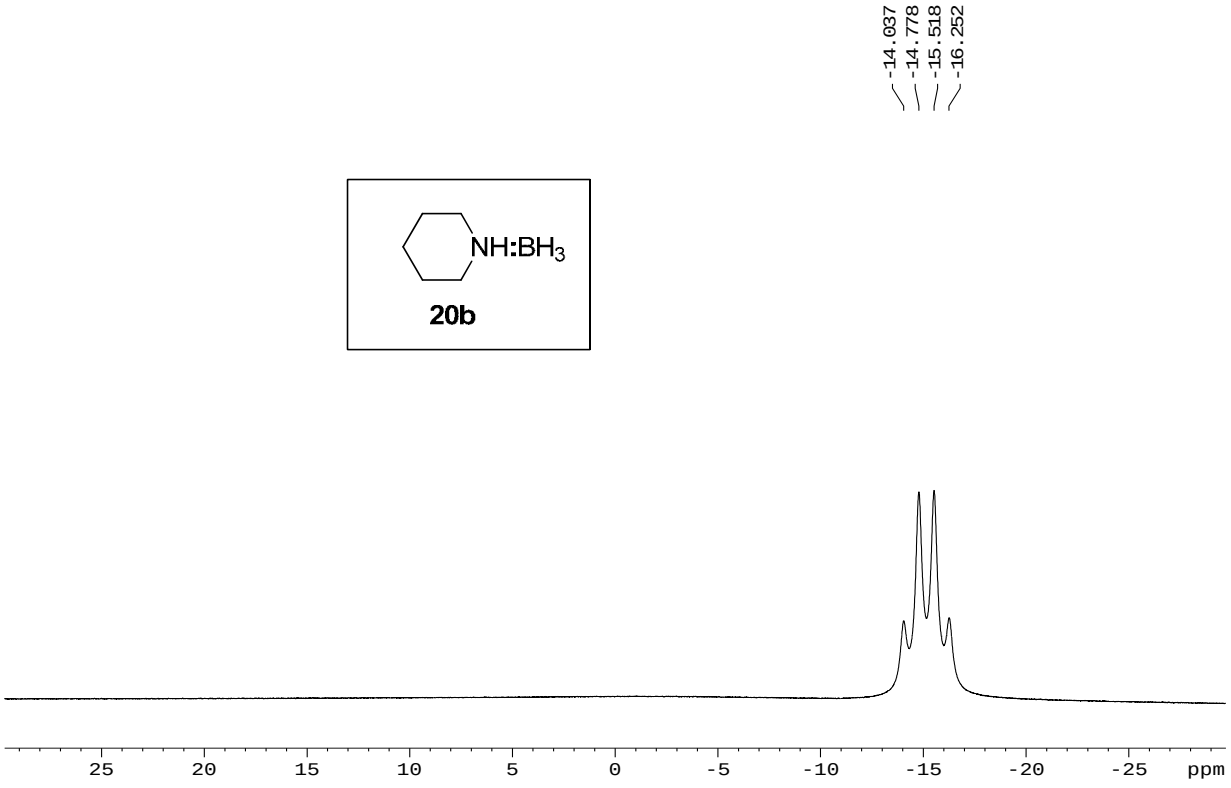
Spectrum No. 14 (Appendix-III, Section III.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



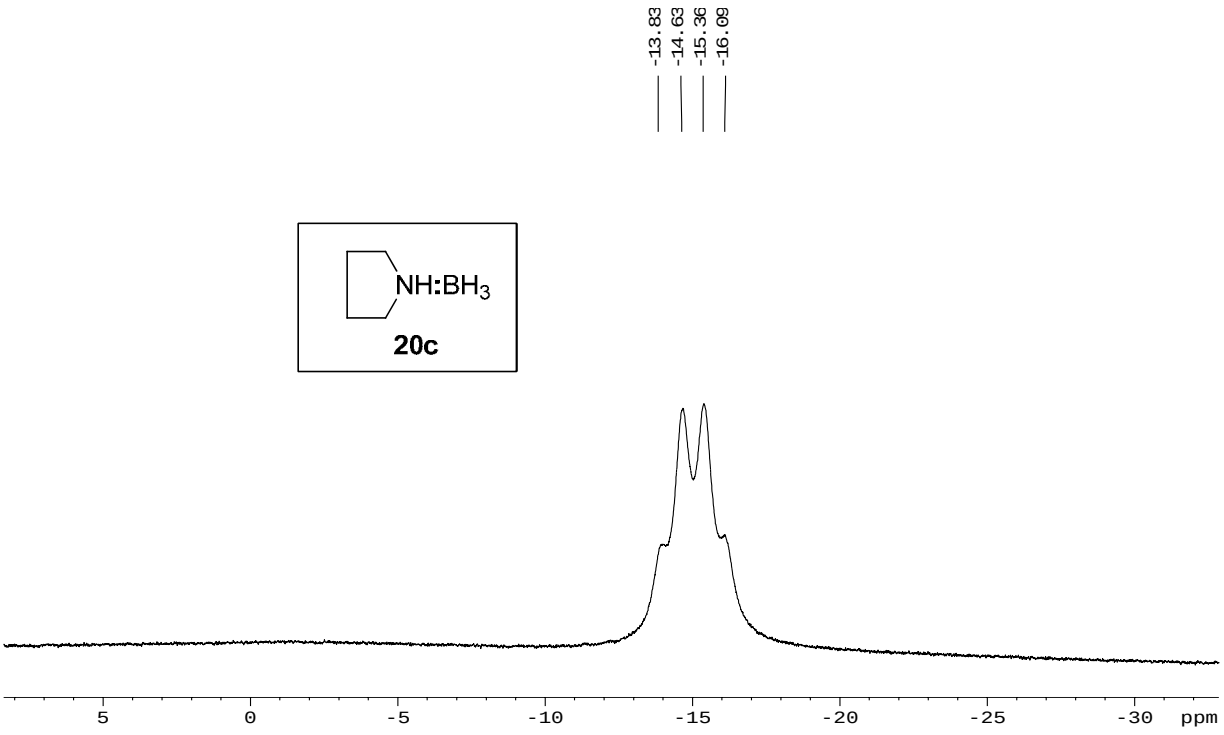
Spectrum No. 15 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



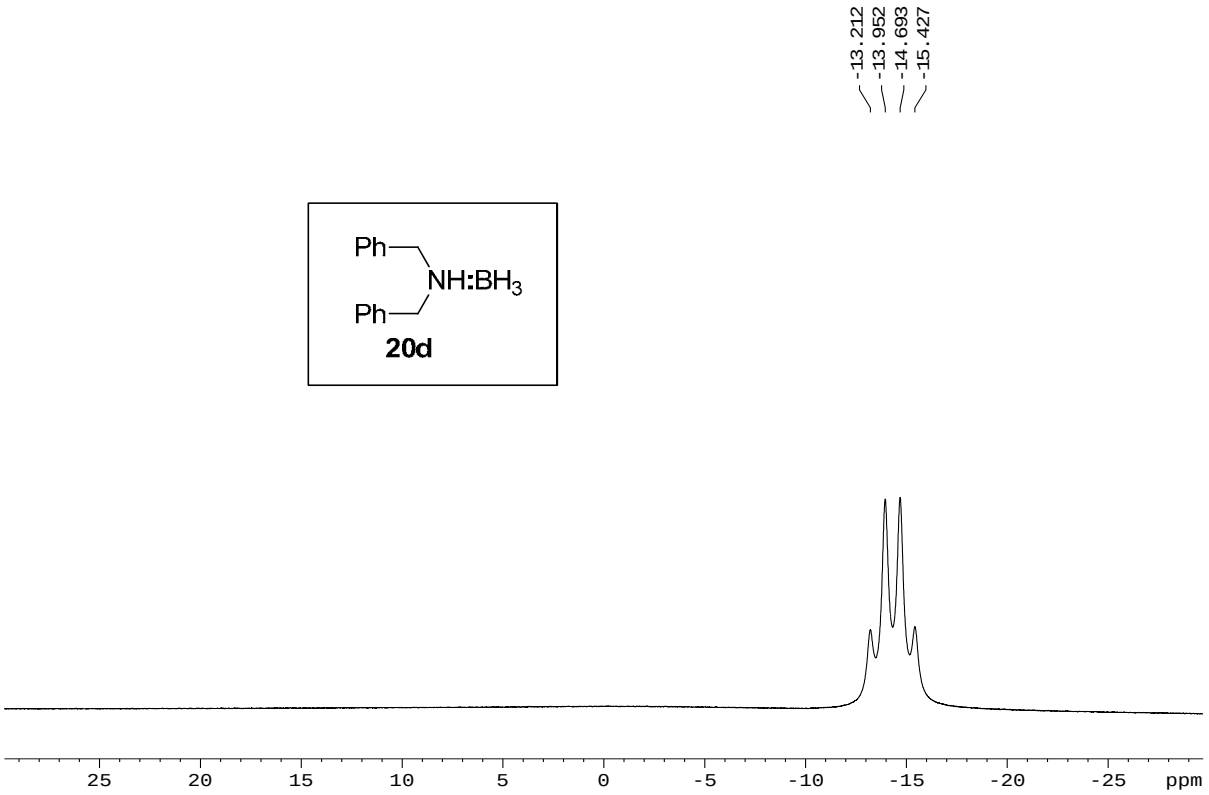
Spectrum No. 16 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



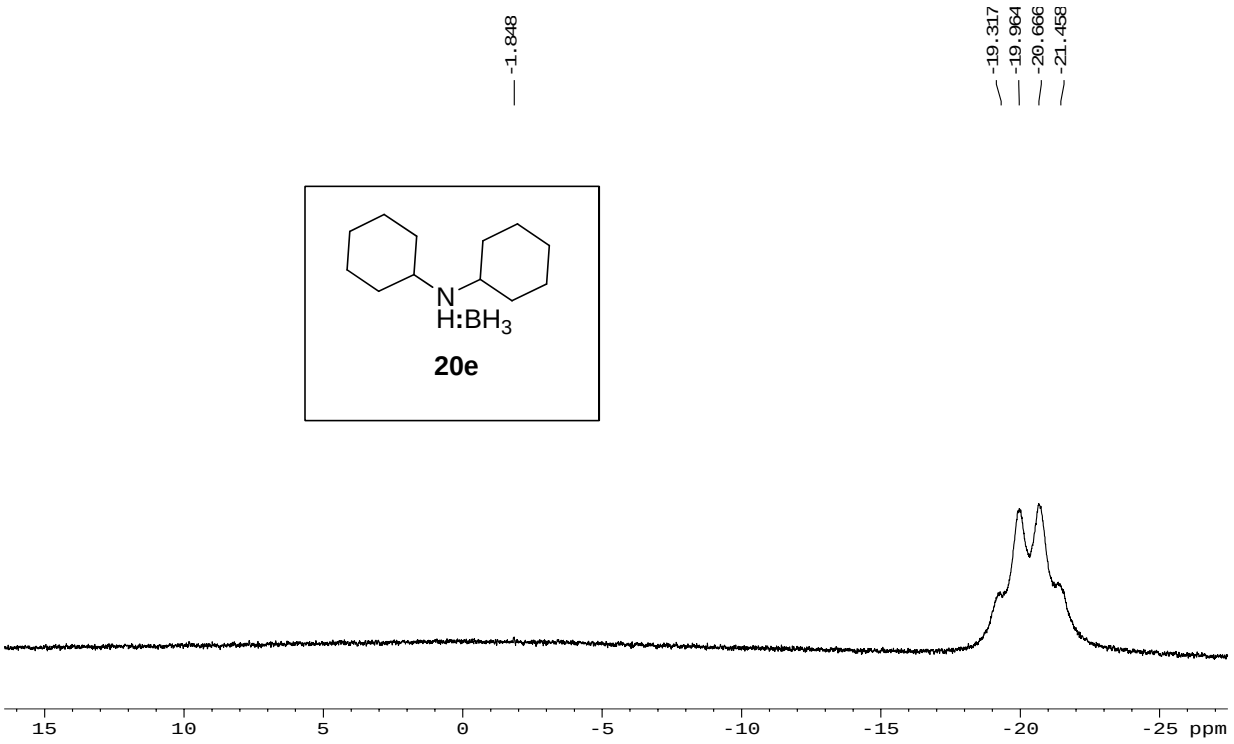
Spectrum No. 17 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 Hz, $CDCl_3$)



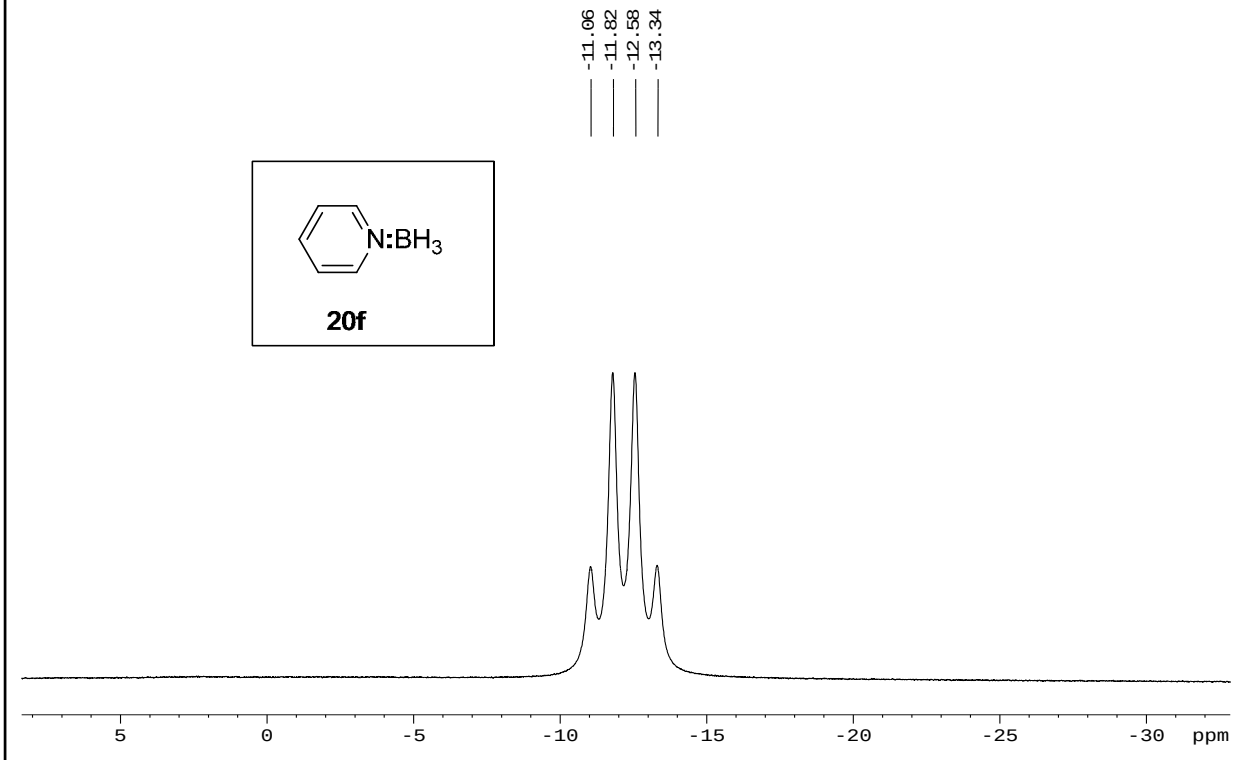
Spectrum No. 18 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



Spectrum No. 19 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



Spectrum No. 20 (Appendix-III, Section III.2.4) ^{11}B NMR Spectrum (128.3 MHz, $CDCl_3$)



LIST OF PUBLICATIONS

1. Highly enantioselective synthesis of chiral allenes by sequential asymmetric synthesis and chirality transfer in a single pot operation; Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; **Obula Reddy, P.** *Org. Lett.* **2012,** *14*, 2932.
2. Convenient methods for the synthesis of new chiral amines and amino alcohols using D-(+)-camphor and D-(-)-camphorquinone; Periasamy, M.; Sanjeevakumar, N.; **Obula Reddy, P**. *Synthesis* **2012,** *44*, 3185.
3. Highly enantioselective synthesis of both isomers of chiral allenes using a single chiral D-(+)-camphor based diamine; Periasamy, M.; **Obula reddy, P**.;Sanjeevakumar, N. *Eur. J. Org. Chem.* **2013**, *18*, 3866.
4. Convenient Methods for the Synthesis of Chiral Amino Alcohols and Amines; periasamy, M.; Gurubrahamam, Ramani.; Sanjeevakumar, Nalluri.; Dalai, Manasi.; Alakonda Laxhmaiah.; **Reddy, Polimera Obula**.; Suresh, Sundaram.; Satishkumar, Sakilam.; Padmaja, Meduri.; Reddy, Meda.; Suresh, Surisetti.; Anwar, Shaik.; Muthukumargopal, G.P.; Vairaprakash, Pothiappan.,Seenivasaperumal, Muthu. *Chimia* **2013,** *67*, 23.
5. Diastereoselective synthesis of chiral propargylamines using chiral piperazines and their enantioselective conversion to chiral allenes; Periasamy, M.; **Obula Reddy, P**. Edukondalu, A. Dalai, M. Alakonda, L. M. Udaykumar, B. .*communicated*.
6. Highly enantioselective synthesis of functionalized chiral allenes. Periasamy, M.; **Obulareddy, P.** Sanjeevakumar, N. *to be communicated.*
7. New synthetic methods using molecular oxygen doped carbon materials Periasamy, M.; **Obula Reddy, P**. Shanmugaraja, M. Ramusagar, M. *to be communicated.*

PRESENTATIONS:

- ► Oral presentation in the ***"Chemfest 2012"*** in house symposium held at University of Hyderabad, Hyderabad, February 13, 2012; Title: Synthesis of chiral amine derivatives using D-(+)-camphor and their application in asymmetric transformations.
- ► Presented a poster in the ***"Chemfest 2012"*** in house symposium held at University of Hyderabad, Hyderabad, February 13, 2012; Title: Synthesis of chiral amine derivatives using D-(+)-camphor and their application in asymmetric transformations.