Development of Organic Synthetic Methods for N-Arylation and for Synthesis of Chiral Propargylamines and Chiral Allenes

A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

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SEPTEMBER 2012

Dedicated to

My Parents and Mentors

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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 **“Studies on the Development of Organic Synthetic Methods for N-Arylation and for Synthesis of Chiral Propargylamines and Chiral Allenes”** has been carried out by **Mr. LAXHMAIAH. A** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

Acknowledgements

I wish to express my deep sense of gratitude and indebtedness with profound respect to my mentor ***Prof. M. Periasamy*** *for his inspiring teaching, guidance, constant encouragement and personal motivation throughout my tenure here. It is always a pleasure for me to be his student. I will always be indebted to him for this.*

I thank present and former deans of school of chemistry, Prof. M. V. Rajashekaran, Prof. D. Basavaiah, Prof. M. Periasamy and Prof. E.D. Jemmis 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. Saireddy, Mr. Sivanarayana, Dr. Rammohan Rao and Dr. Venkatakrishna who taught the basics of science in my school and college days.

I wish to extend my deep sense of gratitude to my colleague Dr. S. Selvaganesan for his timely help and cooperation for carrying out some of the experiments during my thesis work. I also thank my past and present labmates, Dr. P. Vairaprakash, Dr. D. Shyam Raj, Dr. S. Anwar, Dr. G. P. Muthukumaragopal, Dr. S. Satish Kumar, Mr. M. Nagaraju, Dr. B. Mallesh, Dr. N. Sanjeevakumar, Dr. M. Dalai, Mr. R. Gurubrahamam, Mr. P. Obula Reddy, Mr. S. Suresh, Mr. B. Venkanna, Mr. M. Shanmugaraja, Mr. Arif, Mr. M. Raju, Mr. A. Yedukondalu, Mr. Ramu Sagar, Mr. V. Harish, Mr. Ananda Rao, Mr. Sathyanarayana, Mr. Uday, Mr. Sathyamoorthy, Mr. V. Arun, Mr. Yesupadam and Mr. Srinivas for creating a pleasant working atmosphere.

I thank my friends Dr. M. Ramu, Dr. G. Vikram, Mr. K. Srinivas (Kops), Mr. T. Ganesh kumar, Dr. S. Ravikumar, Dr. vijayendar, Mr. Bharat, Mr. Swamy, for their help.

All the research scholars of the school of chemistry have been extremely helpful and I thank them all. Dr. T. K. Chaitanya, Dr. D. K. Srinivas, Mr. Viji, Mr. S. Ramesh, Dr. Ramesh Reddy, Dr. Shekar reddy, Mr. Satpal, Mr. Raghavaiah, Mr. Santosh, Mr. Sai, Mr. Chandu, Mr. Lings, Mr. Mallikarjun, Dr. Phanipavan, Mr. K. Ramesh, Mr. Anji, Mr. Venky, Mr. Sivaprasad, Mr. Madhavachary, Mr. Srinivasa reddy, Mr. Shashank, Mr. Murali, Mr. Ravindrababu, Mr. Ramana, Mr. Naveen, Mr. Manojveer, Mr. Sheshadri, Mr. Venukumar, Mr. Anesh, Mr. Praveen, Mr. B. Satish, Mr. Obaiah, Mr. Brijesh, Mr. Nandakishore, Mr. Kishore, Mr. Maddileti, Mr. Karunakar, Mr. Balaswamy, Mr. Hariprasad, Mr. Gupta, Mr. Thirupathireddy, Mr. Ashok 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. Dilip kumar, Mr. Naik, Mr. K. R. B. V. Prasad, Mr. Ramana, Mr. Joseph, Mr. Sambasiva Rao, Mr. Santosh, Mr. Anand, Mr. Sudhakar, Mr. Chittibabu, Mr. Subramanyam, and Mr. Durgesh are a few to mention.

It is beyond this book to acknowledge the contributions of my parents Mr. A. Buchaiah, Mrs. A. Susheela, my Brother Mr. Ramcharan, my sisters (Mrs. Laxmi and Mrs. Alivela), my brothers-in-law (Mr. P. Balaswamy and Mr. Narasimha) and their children (Shivaranjan, Sirisha, Prabhudeva and Pramod) at each and every stage of my life. I would like to express my special gratitude to my all-time friends Seenanna, Murthy, Prasad, Vengi, Satya, Rahul, Malli, Chicha, Ramarao, Sivareddy, Venkateswarlu, Madhu Sudhan Reddy, Venu Gopal, Pradeep Kumar, Adi, Ramesh are few to mention.

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 research grant of DST-J.C BOSE National fellowship of Prof. M. Periasamy is gratefully acknowledged.

Laxman

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
Aq.	aqueous
Ac	acetyl
BINAM	1,1’-binapthyl-2,2’-diamine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
Boc_2	di-*tert*-butyl dicarbonate
Bz	benzoyl
bp	boiling point
br s	broad singlet (spectral)
Bu	butyl
t-Bu	*ter*-butyl
^{o}C	degree Celsius
conc.	concentrated
Cat.	catalyst
Cbz	carboxybenzyl
Cg	carbon graphite
cm^{-1}	wavenumber(s)
δ	chemical shift in parts per million downfield from tetramethyl silane
DAB	diazabutadiene
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
dil.	diluted
DMA	dimethylacetamide

DMEDA	N,N'-dimethylethylenediamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-dis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
dt	doublet of triplet (spectral)
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol
equiv.	equivalent
g	gram (s)
gla.	glacial
h	hour (s)
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant (in NMR Spectrometry)
lit.	literature
LCMS	liquid chromatography-mass spectrometry
m	multiplet (spectral)
m	*meta*
Me	methyl
MeCN	acetonitrile
MW	molecular weight
MHz	megahertz
min.	minute(s)
mmol	millimolar
mp	melting point
MS	molecular sieves

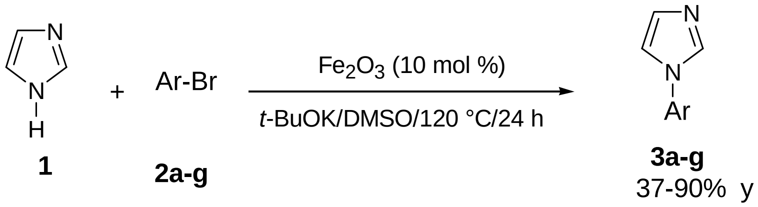
NMR	nuclear magnetic resonance
n-	primary
Nu	nucleophile
o	ortho
ORTEP	oak ridge thermal ellipsoid plot
OTf	trifluoromethanesulfonate
Ph	phenyl
p	*para*
PTSA	*p*-toluenesulfonic acid
Pybox	2,6-bis[(4R)-4-phenyl-2-oxazolinyl]pyridine
q	quartet (in spectroscopy)
RT	room temperature
Ruphos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
Sol.	solution
Temp	temperature
THF	tetrahydrofuran
TMS-Cl	trimethylsilyl chloride
TFA	trifluoroacetic acid
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMHD	2,2,6,6-tetramethyl-3,5-heptanedion
TfOH	triflic acid
uv	ultraviolet

Abstract

This thesis describes studies on the "**Development of Organic Synthetic Methods for N-Arylation and for Synthesis of Chiral Propargylamines and Chiral Allenes**". It 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.

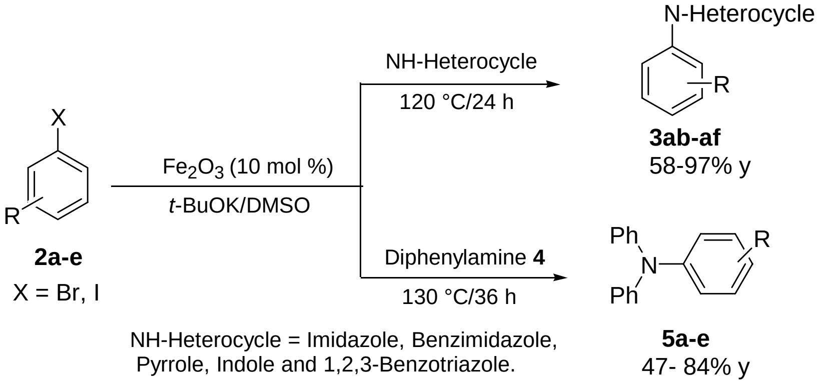
Studies on the synthesis of various N-aryl heterocyles **3a-g**, **3ab-af** and triarylamines **5a-e** using ligand free Fe_2O_3 promoted *t*-BuOK/DMSO reagent system are described in chapter 1. Reports on N-arylation methods are reviewed in the introductory section. We have observed that the reaction of imidazole **1** with substituted aryl halides using the ligand free Fe_2O_3 promoted *t*-BuOK/DMSO reagent system give the corresponding N-aryl imidazoles **3a-g** in moderate to very good yields (Scheme **1**).

Scheme 1



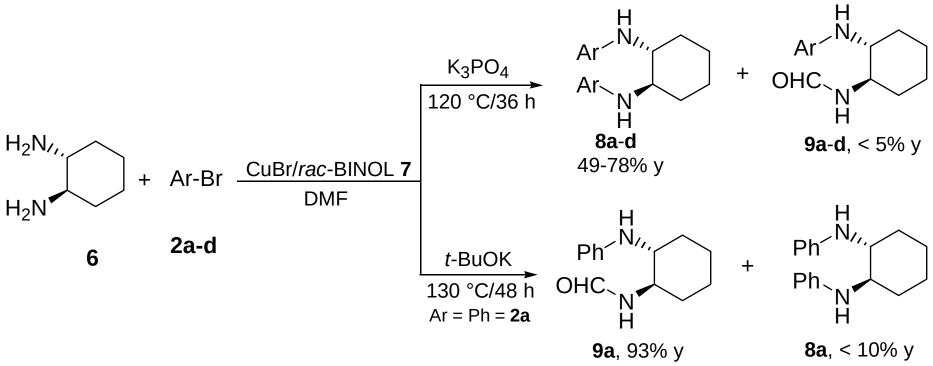
This method is also useful for the N-arylation of various NH-heterocyles like benzimidazole, triazole, pyrrole, indole and diphenylamine **4** (Scheme **2**).

Scheme 2



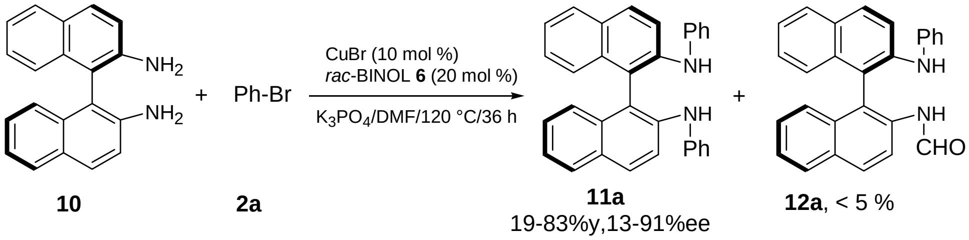
Investigations on the copper catalyzed N,N'-diarylation of C_2-symmetric chiral diamines are described in chapter 2. The CuBr/*rac*-BINOL **7** catalyst system is useful for the synthesis of N,N'-diaryl C_2-symmetric chiral diamines **8a-d**. The N-formyl,N'-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **9a** was also prepared in good yield by using *t*-BuOK along with the CuBr/*rac*-BINOL **7** catalyst system (Scheme **3**).

Scheme 3



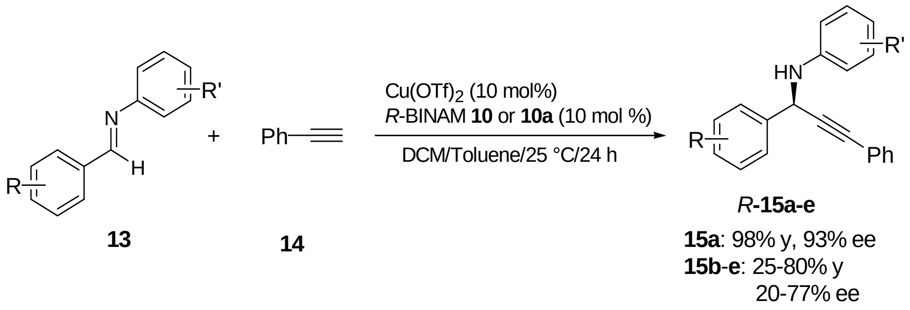
We have also carried out this transformation using the (*R*)-1,1'-binaphthyl-2,2'-diamine **10** and the corresponding (*R*)-N,N'-diphenyl-1,1'-binaphthyl-2,2'-diamine **11a** was obtained in 19 % to 83 % yield (Scheme **4**).

Scheme 4



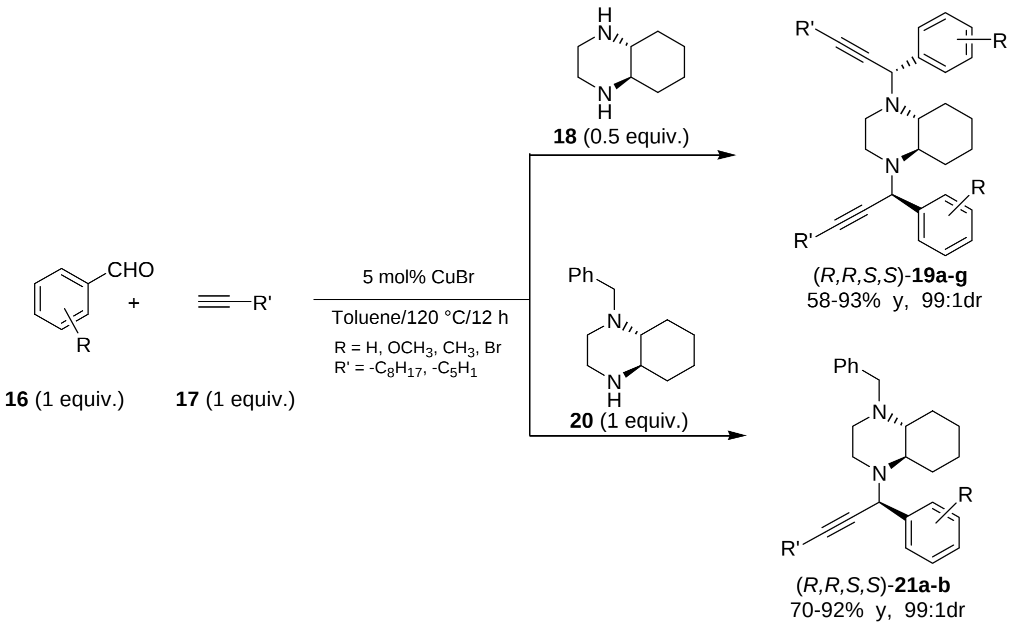
Studies undertaken for the synthesis of chiral propargylamines and allenes are described in chapter 3. Various methods reported for the synthesis of propargylamines and allenes are reviewed in the introductory section. A method for enantioselective synthesis of chiral propargyl amines **15a-e** from imines **13** and phenyl acetylene **14** using bi-2-naphthyl diamine (BINAM) **10** or N,N′-dibenzylidine-1,1′-binaphthyl-2,2′-diamine **10a** and Cu(OTf)$_2$ complex has been developed (Scheme **5**).

Scheme 5



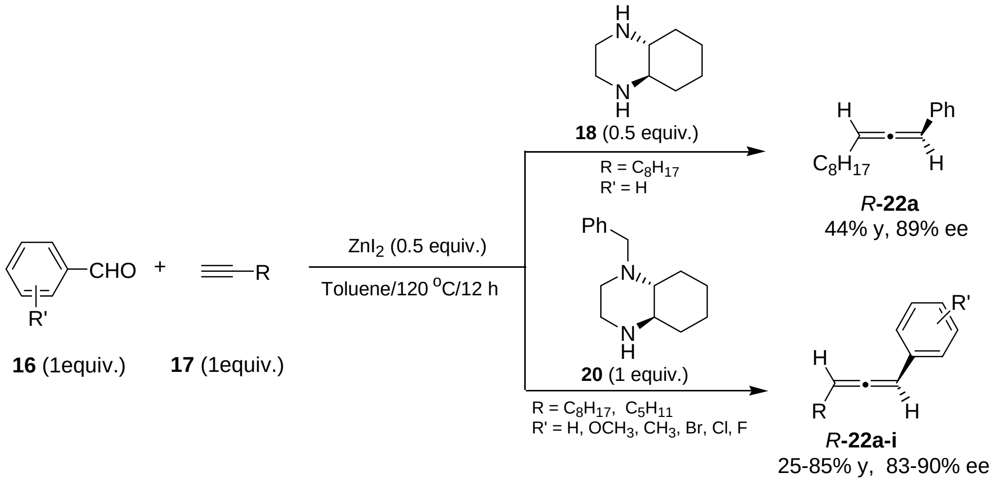
We have observed that the reaction of chiral diamines **18** and **20** with aryl aldehydes **16** and 1-alkynes **17** in the presence of CuBr catalyst in toluene gave the corresponding *bis*-propargylamines **19a-g** and propargylamines **21a-b** in good to excellent yields with excellent diastereoselectivity (Scheme **6**).

Scheme 6



The chiral propargylamines **19a** and **21a** are readily converted to chiral allenes **22** upon reaction with ZnI_2. We have also examined the efficacy of chiral diamines **18** and **20** for the enantioselective synthesis of axially chiral allenes from aldehydes **16**, 1-alkynes **17** promoted by ZnI_2 (Scheme **7**).

Scheme 7



The results are discussed by considering appropriate mechanisms and stereochemical models.

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

Chapter 1

Studies on N-Arylation of NH-Heterocycles and Diphenylamine

1.1 Introduction

In recent years, there has been sustained interest on the development of transition metal catalyzed coupling reactions. Well-known cross coupling reactions in the literature are Wurtz-Fittig,[1] Ullmann,[2] Goldberg,[3] Suziki,[4] Stille,[5] Sonogashira,[6] Heck,[7] Negishi,[8] Hiyama,[9] Kumada,[10] Buchwald-Hartwig,[11] and Chan-Lam[12] coupling reactions. Various cross coupling reactions C-C, C-N, C-O, C-S, and C-P have been reported. We have undertaken studies on the C-N cross coupling reaction. A brief review on this topic will be helpful for the discussion.

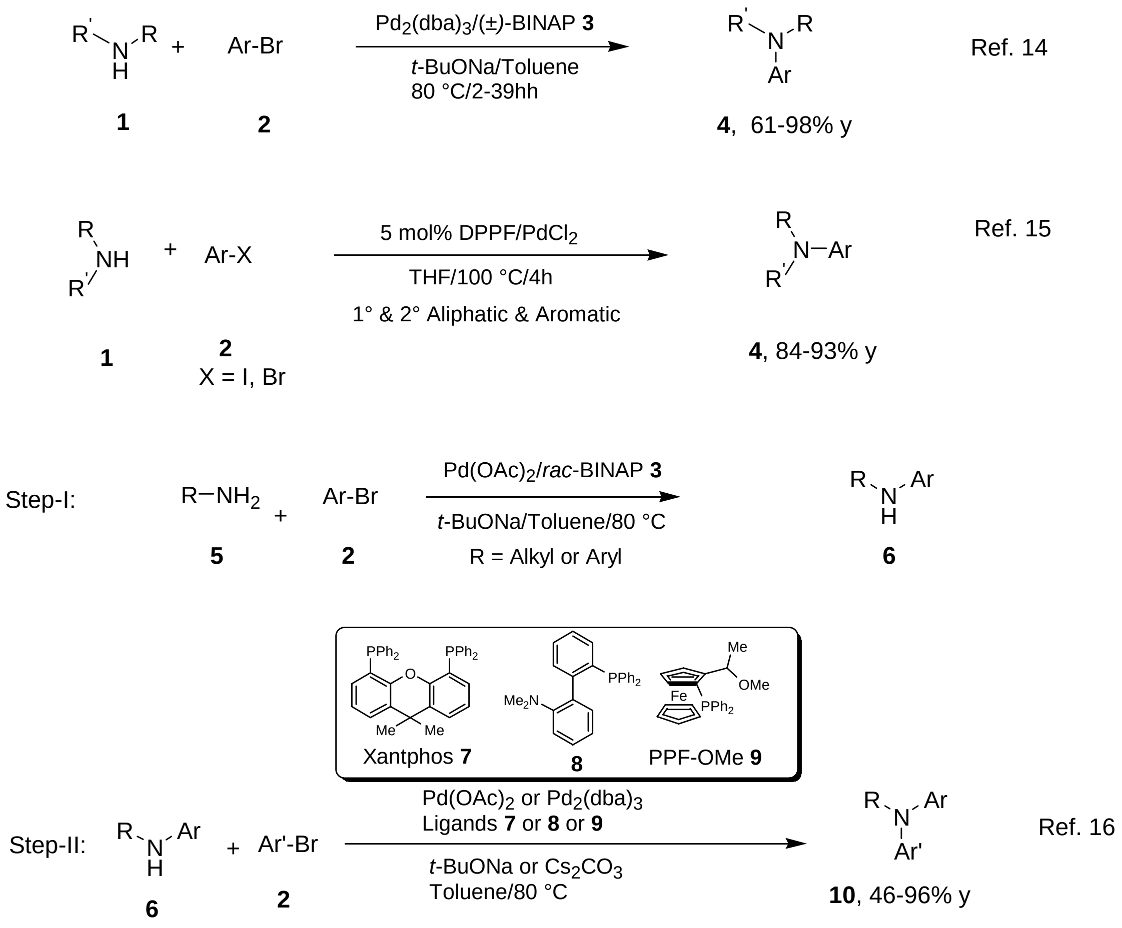
1.1.1 N-Arylation of amines

The C-N bond formation is one of the most important transformations useful for the synthesis of compounds of interest to pharmaceutical and material science applications. In recent years, transition-metal-mediated N-aryl bond formation has become a standard procedure for the introduction of amines into aromatic systems.[13] The reports on this topic are reviewed in this section.

1.1.1.1 Palladium catalyzed N-arylations of amines

Reports on the palladium complexes with various ligands like *rac*-BINAP **3** or xantpos **7** or PPF-OMe **9** are useful in N-arylation of both aliphatic and aromatic amines (chart **1**).[14-16]

Chart 1



In recent years, there have been immense interest on the development of robust methodology to obtain triarylamines.[17-25] Various triarylatnines **14**, **18** and **21** are readily prepared by palladium complexes catalyzed cross coupling reactions of arylhalides and diarylamines in excellent yields (Chart **2**).[26-30]

Chart 2

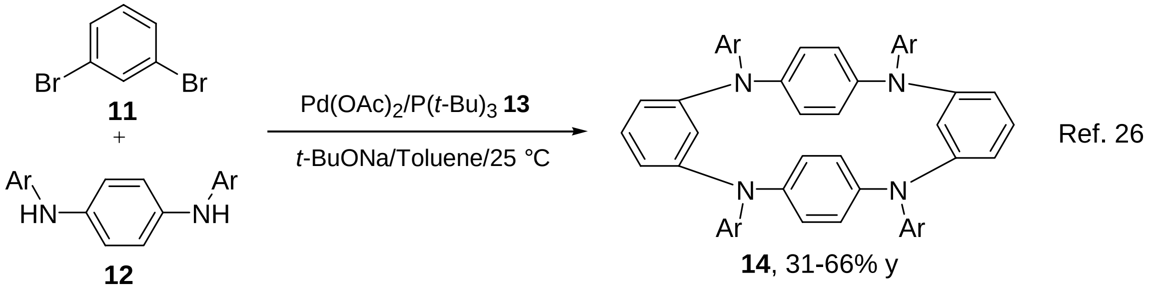
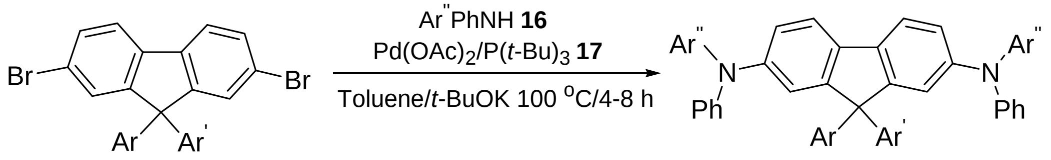


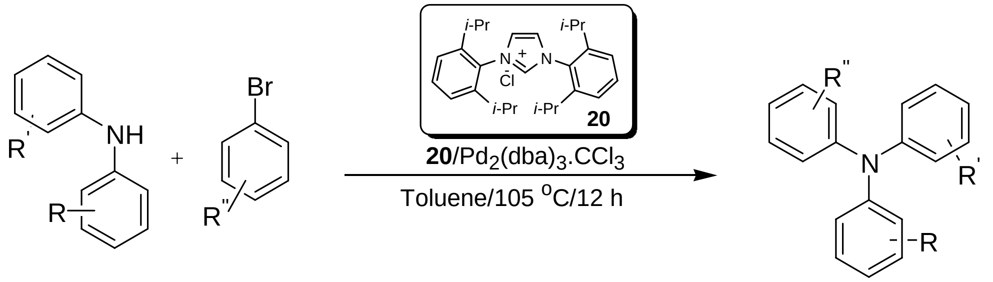
Chart 2 continued



Ref. 27

15

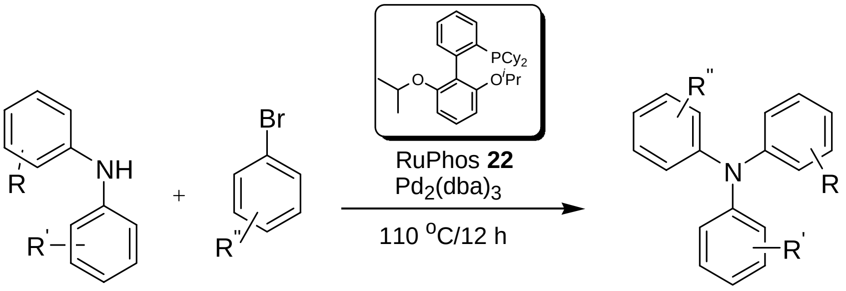
18, 69-96% y



Ref. 28

19 **2**

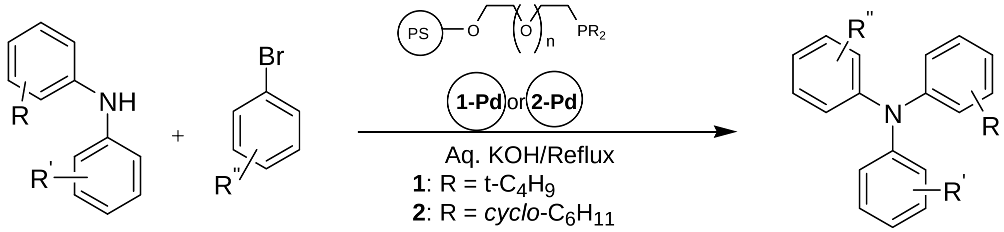
21, 71-98% y



Ref. 29

19 **2**

21, 89-90% y



1: R = t-C$_4$H$_9$
2: R = *cyclo*-C$_6$H$_{11}$

Ref. 30

19 **2**

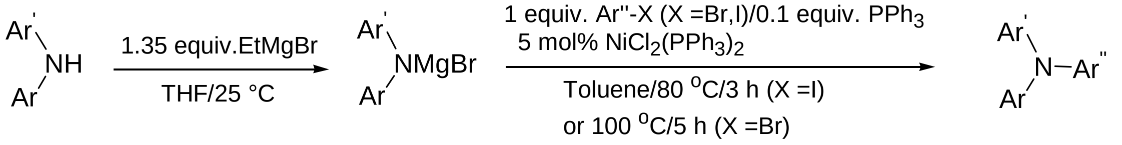
1-Pd: (5 mol% Pd): 92%y
1-Pd: After 5th reuses: 92%y
2-Pd: (5 mol% Pd): < 2% y
1(Without Pd): < 2%y
K$_2$PdCl$_4$(Without **1**): messy mixture
none (without Pd or **1**): < 2%y

21, 89-90% y

1.1.1.2 Nickel catalyzed N-arylation of amines

A methodology using the $NiCl_2(PPh_3)_2$-PPh_3 was reported for the synthesis of triarylamines from bromomagnesium intermediates, generated *in situ* from diarylamines (Scheme **1**).[31]

Scheme 1



23 **24** **25**, 13-96% y

1.1.1.3 Copper catalyzed N-arylations of amines

Recently, copper catalyzed N-arylation reactions have gained importance over palladium catalyzed N-arylations. Some of the important reports on N-arylation of amines with various copper catalyzed catalysts are outlined in the chart **3.**[32-36]

Chart 3

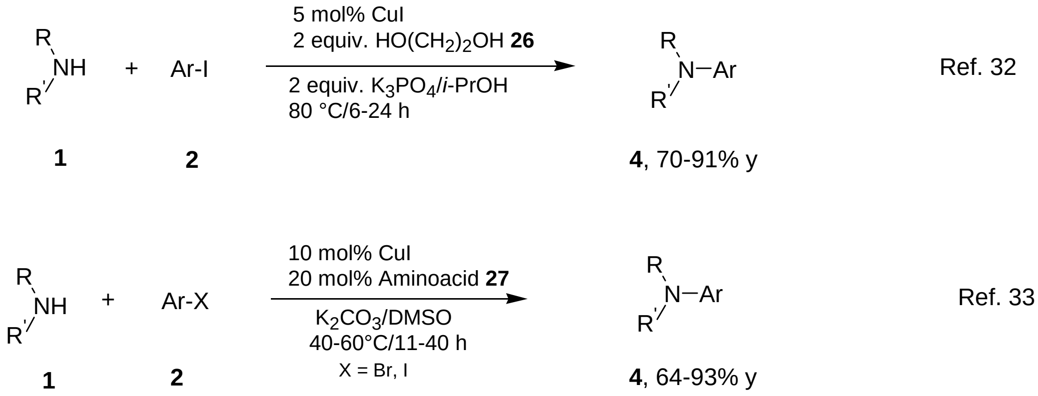
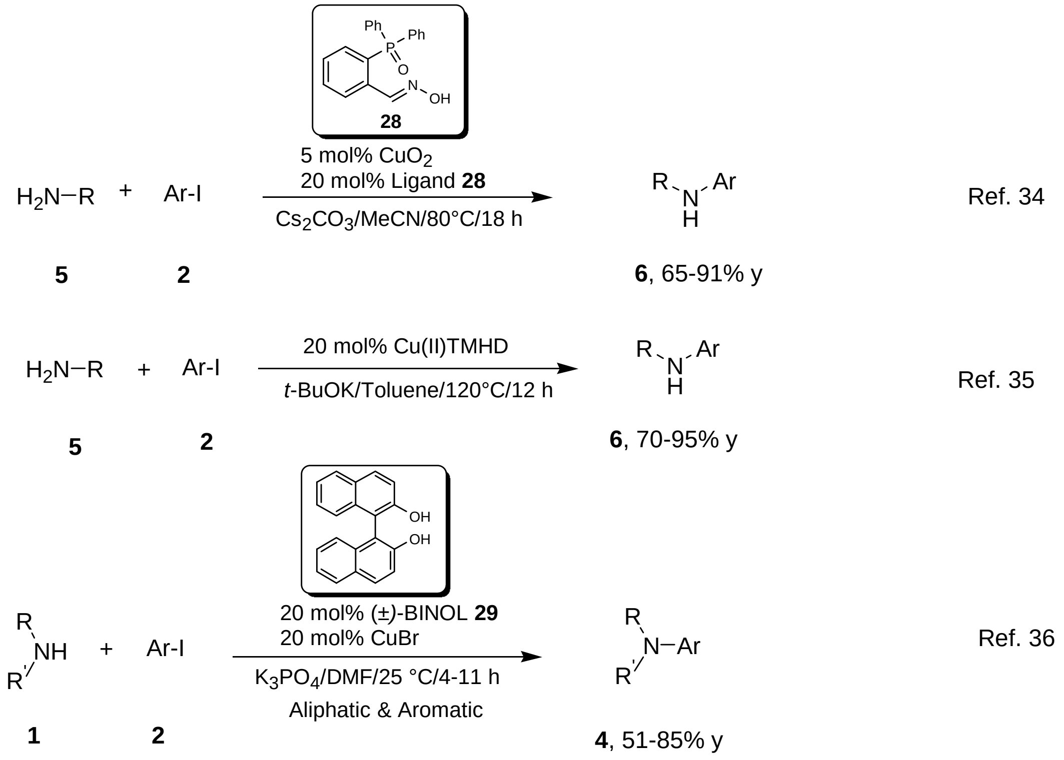
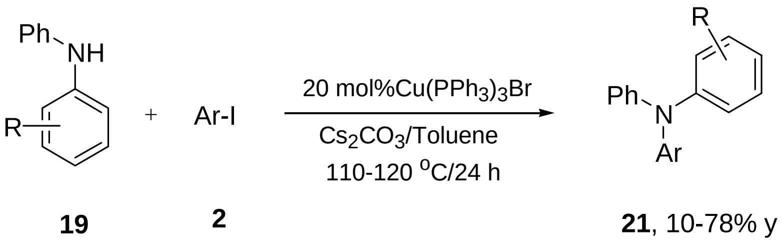


Chart 3 continued



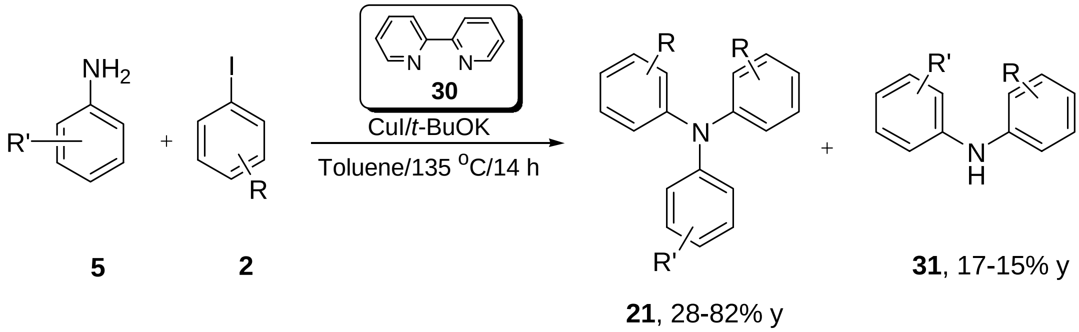
The air-stable and soluble Cu(PPh$_3$)$_3$Br catalyst system is useful for the synthesis of functionalized diaryl and triarylamines under mild conditions (Scheme **2**).[37]

Scheme 2



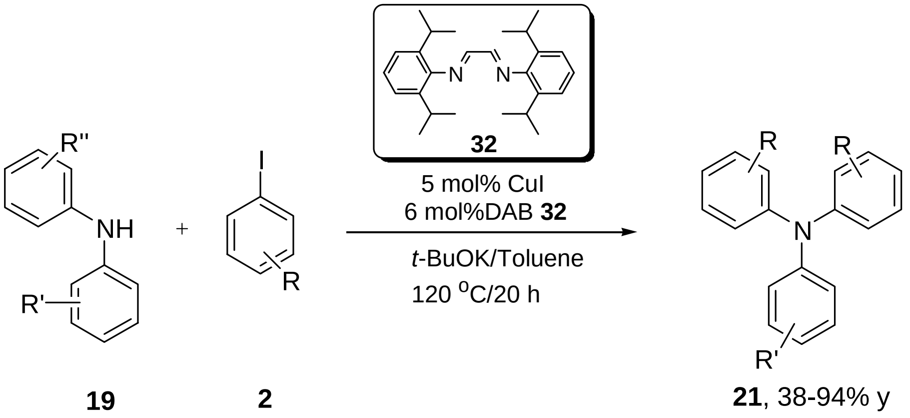
Synthesis of triarylamines in a single step has been demonstrated using a ligand-free CuI catalyst and *t*-BuOK.[38] Optimum results were obtained using 2,6-diphenylpyridine as a ligand (Scheme **3**).

Scheme 3



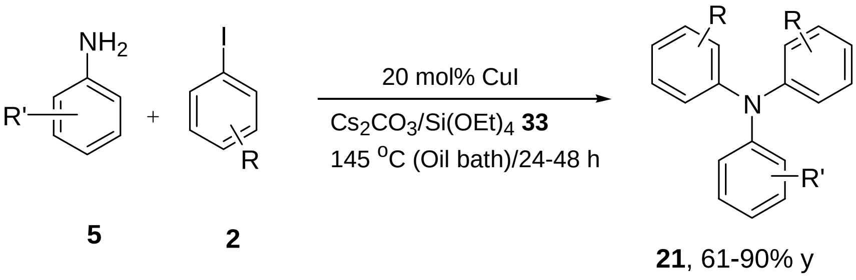
The CuI/diazabutadienes (DABs) catalyst system has been developed for the synthesis of triarylamines by N-arylation of diarylamines **19** and anilines with aryl iodides (Scheme **4**).[39]

Scheme 4



A ligand free CuI catalysed methodology for the synthesis of triarylamines using anilines and aryl iodides has been reported (Scheme **5**).[40]

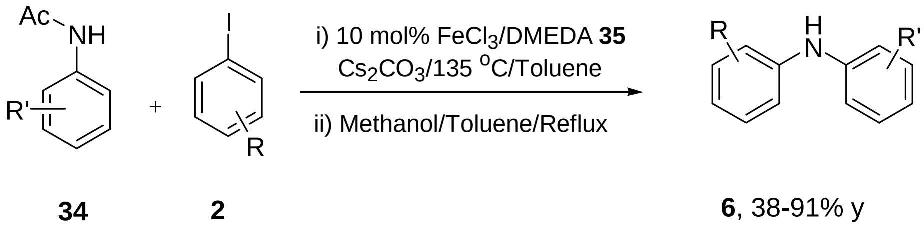
Scheme 5



1.1.1.4 Iron catalyzed method for the synthesis of diarylmaines

Diarylamines were synthesized from N-acylamides and aryl iodides using the $FeCl_3$ and DMEDA catalyst system (Scheme **6**).[41]

Scheme 6



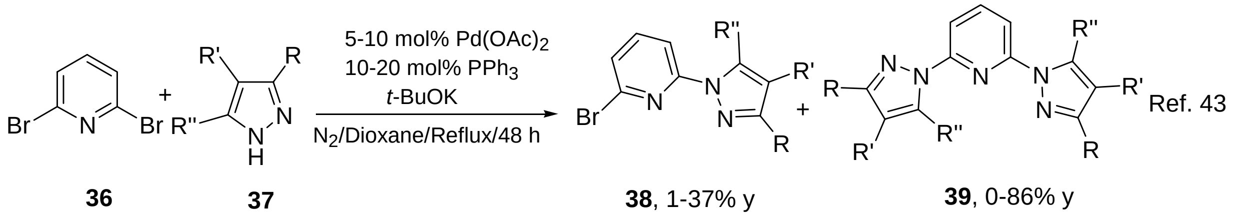
1.1.2 N-Arylation of NH-heterocycles

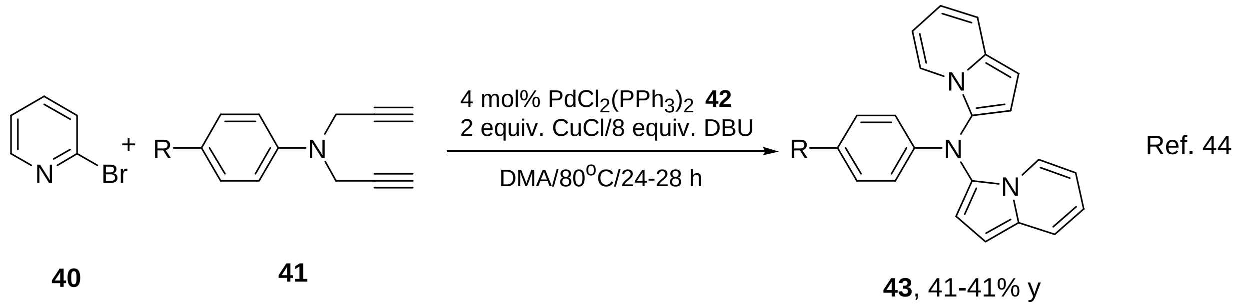
Heterocyclic skeletons are widely found in nature, particularly in nucleic acids, plant alkaloids, anthocyanins, flavones, haem, chlorophyll and some vitamins, proteins and hormones. Synthetically produced heterocycles are widely used as agrochemicals, pharmaceuticals and play an important role in biological processes. Heterocycles have enormous potential as promising molecules as lead structures for the design of new drugs.[42] A brief review of reports on the N-aryalation of heterocyclics will facilitate the discussion.

1.1.2.1 Palladium catalyzed N-arylations of NH-heterocyles

Reports on some typical palladium catalyzed N-arylation of NH-Heterocycles methods are outlined in chart **4**.[43-44]

Chart 4





1.1.2.2 Copper catalyzed N-arylations of NH-heterocyles

Reports on the inexpensive copper catalyzed N-arylation of NH-heterocycles (pyrroles, pyrazoles, indazoles, imidazoles, and triazoles) with various aryl halide coupling partners are outlined in chart **5**.[45-50]

Chart 5

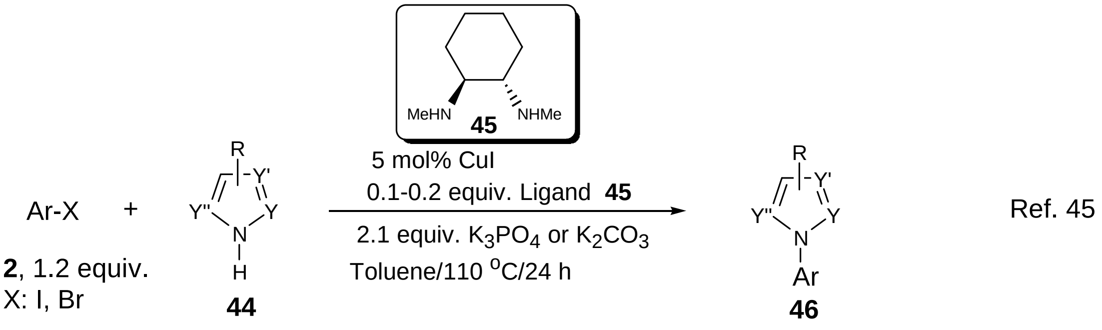


Chart 5 continued

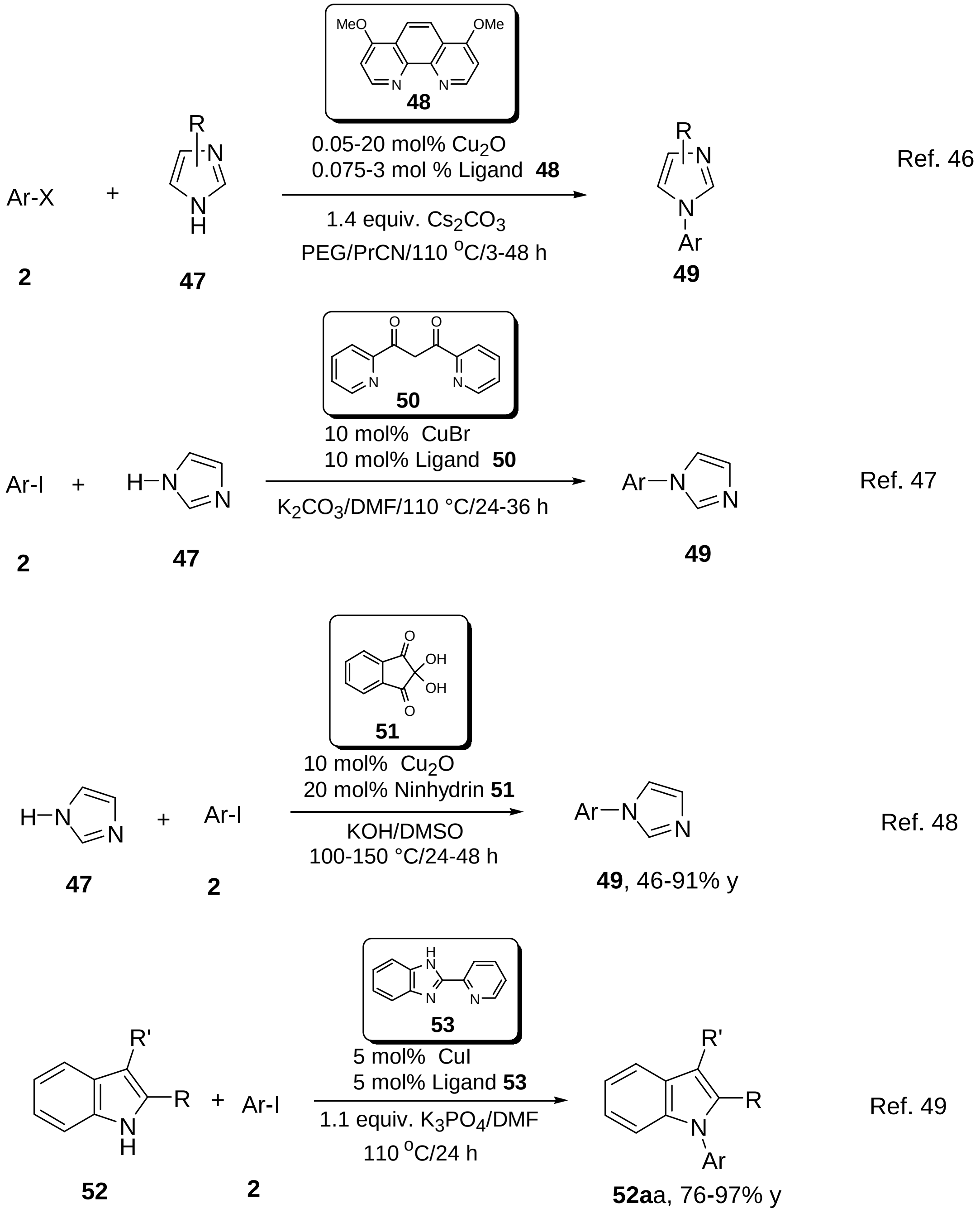
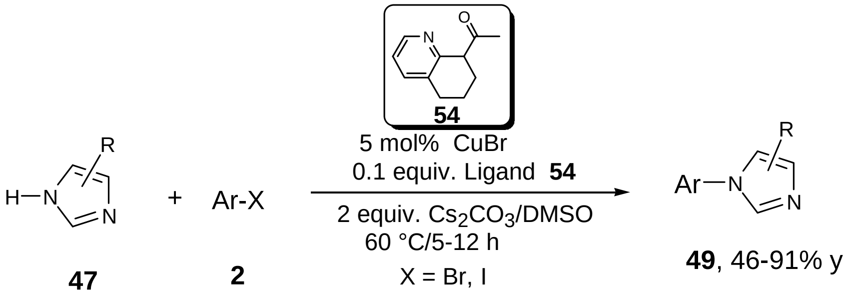


Chart 5 continued

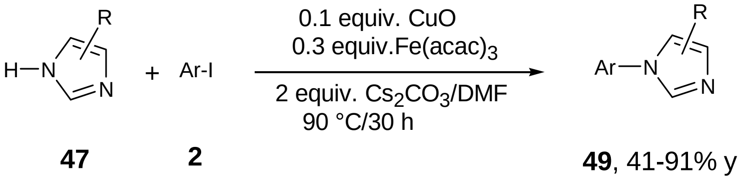


Ref. 50

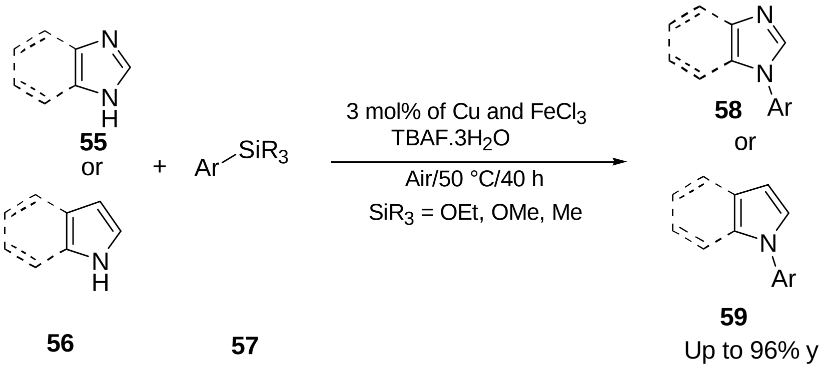
1.1.2.3 Iron/Copper catalyzed N-arylation of NH-heterocycles

Besides palladium,[51] nickel,[52] copper,[53] and iron complexes[54] have been also reported for the arylation of amines,[55-57] pyrroles,[58] imidazoles,[54b,56,59] benzimidazoles[59,60] triazoles, pyrazoles, indazoles, and indoles.[61] Iron, being an abundant, inexpensive, environmentally benign transition metal is widely used in various organic transformations. Some N-arylation methods using Cu/Fe reagents are described in chart **6**.

Chart 6



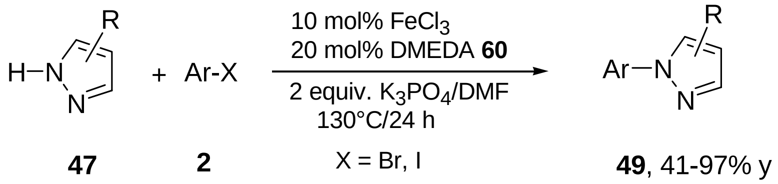
Ref. 62



Ref. 63

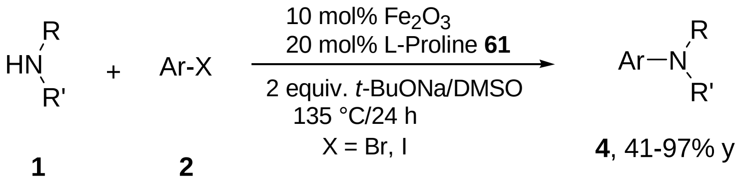
The $FeCl_3$/DMEDA catalyst system has been reported for the N-arylation of NH-heterocycles with different aryl halides to obtain N-aryl heterocycles (Scheme **7**).[64]

Scheme 7



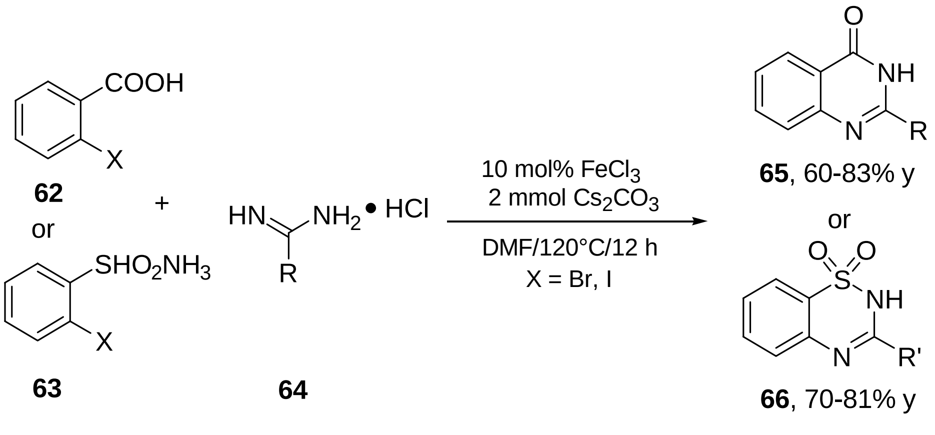
The Fe_2O_3/L-proline **32** catalyst system was useful for the N-arylation of NH-heterocycles with various aryl halides (Scheme **8**).[65]

Scheme 8



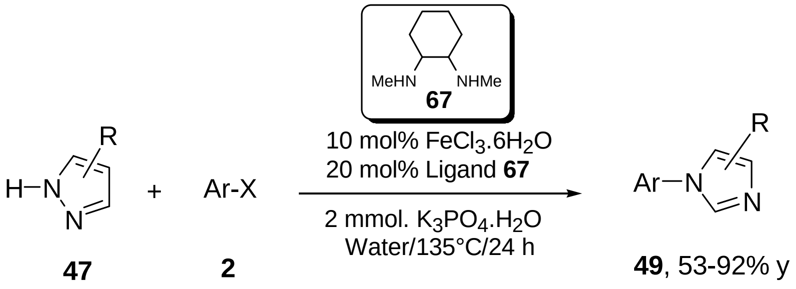
A ligand free environmentally benign iron catalyzed method for the cascade synthesis of 1,2,4-benzothiadiazine 1,1-dioxide **62** and quinazolinone **63** derivatives has been reported (Scheme **9**).[66]

Scheme 9



An alternative protocol to Cu- and Pd-catalyzed N-arylation reactions was reported using commercially available $FeCl_3.6H_2O$ with conformationally rigid diamine ligand **67** for N-arylation of NH-heterocycles using aryl and heteroaryl iodides in aqueous medium (Scheme **10**).[67]

Scheme 10



Recently, a ligand free Fe/Cg air sensitive catalyst system was reported for the N-aryaltion of NH-heterocycles with various aryl halides (Scheme **11**).[68]

Scheme 11

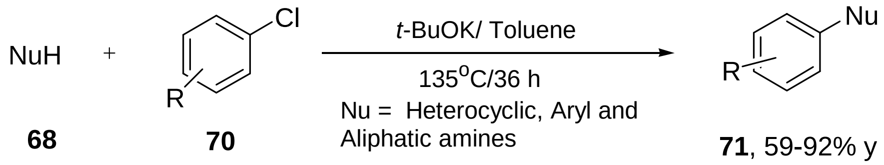
$$\underset{\mathbf{2}}{\text{Ar-X}} + \underset{\mathbf{68}}{\text{NuH}} \xrightarrow[\text{2.5 equiv. KOH/DMSO, } N_2\text{/120°C/24 h}]{\text{5 mol\% Fe/Cg}} \underset{\mathbf{69}\text{, 41-95\% y}}{\text{Ar-Nu}}$$

NuH = Pyrazole, Indole, Benamide, Marpholine, Imidazole, Benzimidazole, Thiobenzamide, Aniline, Benzylamine etc

1.1.3 Ligand and transition metal free N-arylation of NH-nucleophiles

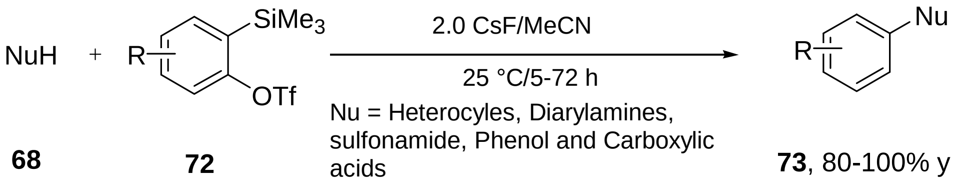
Aliphatic and aromatic amines react with chlorobenzenes in the presence of *t*-BuOK to give the N-aryl amines **71** (Scheme **12**).[69]

Scheme 12



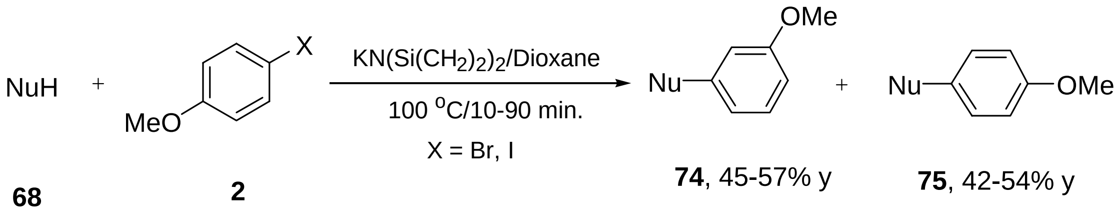
Transition metal free procedure for the N-arylation of amines, sulfonamides, and carbamates and O-arylation of phenols and carboxylic acids using a variety of O-silylaryl triflates in the presence of CsF has been reported (Scheme **13**).[70]

Scheme 13



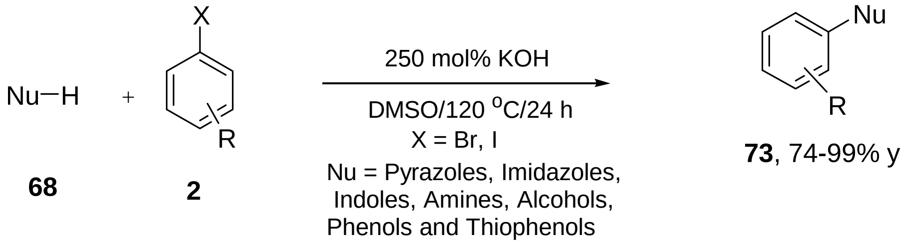
Transition metal free $KN(Si(CH_3)_3)_2$/dioxane methodology has been reported for the synthesis of various N-aryl amines (Scheme **14**).[71]

Scheme 14



Transition metal free KOH(excess)/DMSO promoted N-arylation has been reported (Scheme **15**).[71] The reaction involves, the corresponding aryne intermediates.

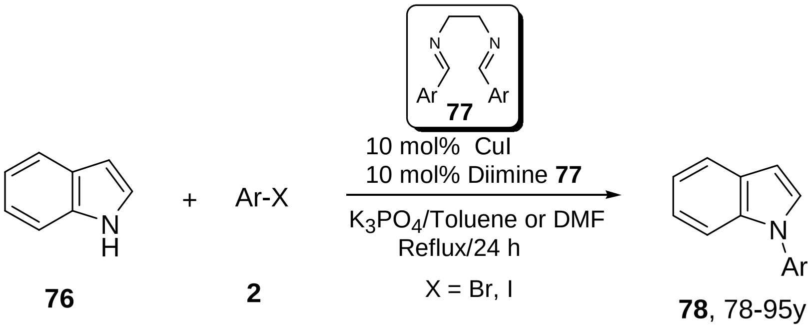
Scheme 15



1.1.4 Previous work from this laboratory

The copper iodide and diimine complexes are useful for the Buchwald N-arylation of heterocyles, particularly indoles that are very important structural moieties present in various biologically active molecules and natural products (Scheme **16**).[72]

Scheme 16



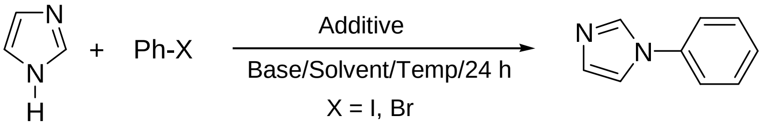
We have undertaken efforts on the development of new methodologies for the N-arylation of various NH-heterocyles and diphenylamine. The results are described in the next section.

1.2 Results and Discussion

1.2.1 N-Phenylation of imidazole

Pursue of literature reports indicates that the most simple and straightforward method for N-arylation involves the use of *t*-BuOK/DMSO under ligand free and transition metal

Scheme 17: Optimization condition for the N-phenylation of imidazole



47 **2a** **49a**

Table 1: Optimization of N-Phenylation of imidazole[a]

Entry	Additive	Base	Solvent	Temp(˚C)	Yield(%)[b]
1	**-**	***t*-BuOK**	**DMSO**	**120**	**76**
2	-	*t*-BuOK	DMSO	25	0[c]
3	-	*t*-BuOK	DMSO	80	50[c]
4	-	K_3PO_4	DMSO	120	Trace
5	-	KOH	DMSO	120	72
6	-	*t*-BuOK	DMF	120	Trace
7	-	*t*-BuOK	Toluene	120	Trace
8	-	*t*-BuOK	H_2O	120	5
9	**Fe_2O_3**	***t*-BuOK**	**DMSO**	**120**	**90**
10	$FeCl_3$	*t*-BuOK	DMSO	120	76
11	$FeSO_4$	*t*-BuOK	DMSO	120	37
12	$ZnCl_2$	*t*-BuOK	DMSO	120	19
13	$NiCl_2$	*t*-BuOK	DMSO	120	50
14	Fe_2O_3	-	DMSO	120	0
15	**Fe_2O_3**	***t*-BuOK**	**DMSO**	**120**	**81[d]**

[a] Unless noted otherwise, all the reactions were carried out with an additive (10 mol %), imidazole **47a** (1 mmol), iodobenzene **2a** (2 mmol), base (2 mmol) and solvent (3 mL) for 24 h. [b] Isolated yields and product was identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. [c] Reaction was carried out for 48 h. [d] Reaction was carried out using bromobenzene.

free conditions. Accordingly, we decided to examine the N-arylation of imidazole **47a** under these conditions. The reaction of imidazole **47a** with phenyl halide gave N-phenyl imidazole **49a** in 76% yield (Table **1**, Entry 1).[73] The reaction does not take place at 25 ˚C (Table **1**, Entry 2) and the N-phenyl product **49a** is obtained only in 50% yield at 80 °C (Table **1**, Entry 3). The use of *t*-BuOK and KOH bases gave better yields over K_3PO_4 (Table **1**, Entries 1, 4 and 5). Among the solvents screened, toluene, DMF and water were less effective compared to DMSO (Scheme **17**, Table **1**, Entries 1 and 6-8).

Experiments using various additives revealed that the products are obtained in higher yields when the transformation is carried out using Fe_2O_3 as an additive (Table **1**, Entries 9-13). There is no reaction without *t*-BuOK (Table **1**, Entry 14). As expected, iodobenzene is more reactive than bromobenzene and gave the N-phenyl imidazole **49a** in higher yields (Table **1**, Entries 9 and 15). The results revealed that the *t*-BuOK/DMSO reagent system is essential for this transformation (Table **1**, Entry 14). Whereas the recently reported Fe/graphite system requires dry N_2 atmosphere,[68] the present *t*-BuOK/DMSO/Fe_2O_3 reagent system does not require inert conditions.

1.2.2 N-Arylation of imidazoles

We have then examined the reaction using various substituted aryl halides with imidazole **47** (Scheme **18**, Compounds **49a-g**). This methodology is equally effective for both electron donating and withdrawing substituents containing aryl halides (Compounds **49d** and **49e**). In the case of 2-bromopyridine as coupling partner, the corresponding N-aryl product is obtained in 90% yield (Compound **49g**). Two regioisomers are obtained when 1-

bromonaphthalene and 4-bromoanisole are used as aryl halide coupling partners (Compounds **49b** and **49d**).

Scheme 18: N-Arylation of imidazole using various aryl halides.

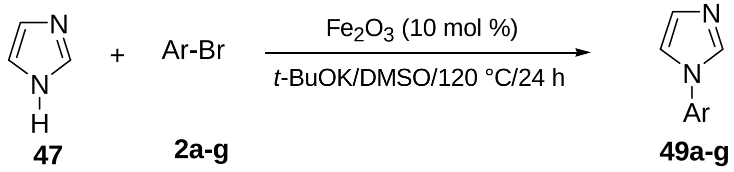
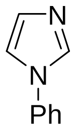
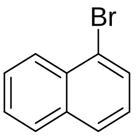
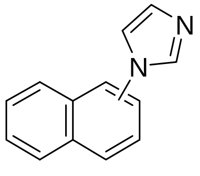
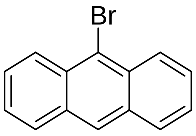
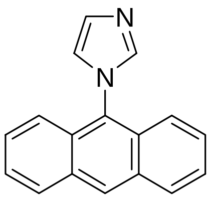
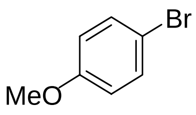
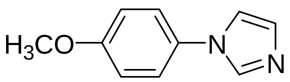
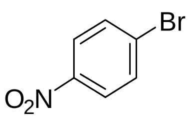
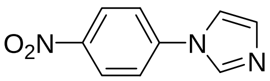
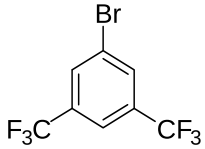
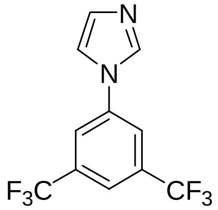
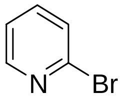
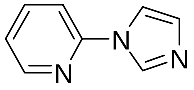


Table 2: Synthesis of various N-aryl heterocycles **49a-g**^{a}

Entry	Aryl bromide (Ar-Br)	Product		Yield (%)^{b}
1	Ph-Br		**49a**	81
2		 **1** and **2**%	**49b**	**1**-39 **2**-37
3			**49c**	70
4			**49d**	71
5			**49e**	76

6			**49f**	82
7			**49g**	90

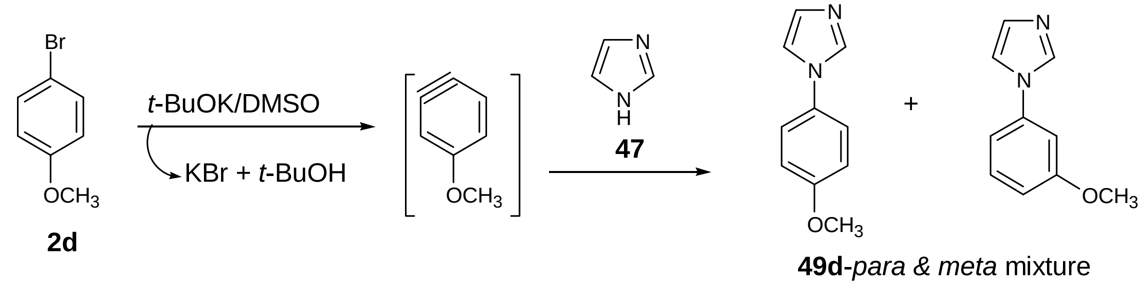
[a]All the reactions were carried out with Fe_2O_3 (10 mol %), imidazole **47** (1 mmol), aryl bromide **2a** (2 mmol), *t*-BuOK (2 mmol) and DMSO (3 mL) at 120 ˚C for 24 h. [b]Isolated yields and the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

1.2.3 Plausible mechanistic pathways for N-arylation of imidazole

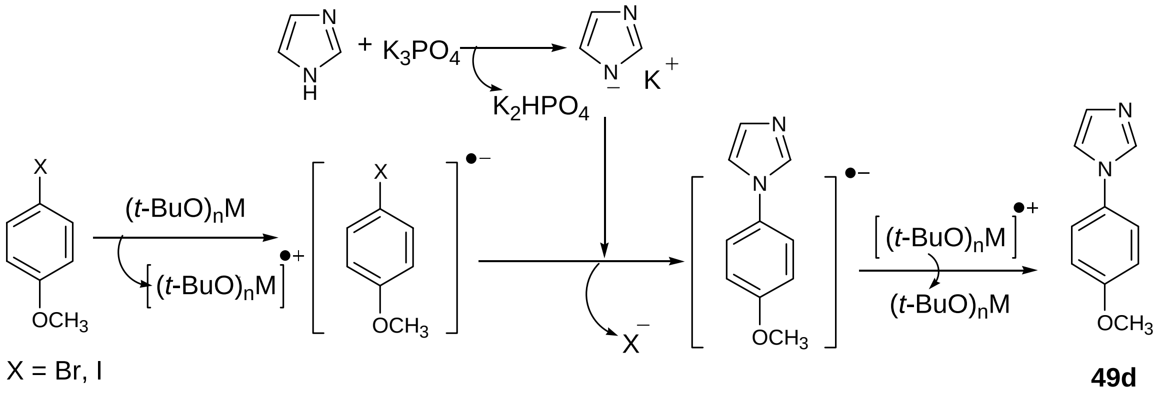
Formation of regioisomeric products **49b** suggests the involvement of aryne intermediates in this reaction (Scheme **20**).[65] The reaction of *para*-substituted arylbromide and *t*-BuOK would give the aryne intermediate which could in turn react with the deprotonated imidazole intermediate to give the mixture of regioisomers (Scheme **19**, Mechanism-1). However, the pathway involving electron transfer mechanism cannot be ruled out (Scheme **20**) considering some recent reports in this area, especially when mild bases are used.[74] In the electron transfer mechanism (Scheme **19**, Mechanism-**2**), the alkoxide would transfer an electron to the aryl halide to give the corresponding radical anion which could then react with the deprotonated imidazole followed by electron transfer to give the corresponding N-aryl product **49d** as a single regioisomer.

Scheme 19: Plausible mechanistic pathways for N-arylation of imidazole

Mechanism-1: Aryne intermediate:



Mechanism-2: Electron transfer mechanism:



In these transformations, the aryne intermediates are formed due to the highly basic nature of the *t*-BuOK/DMSO reagent system. In order to reduce the basic nature of *t*-BuOK, we have carried out a set of experiments using $FeCl_3$ and 3 equivalents of *t*-BuOK under the conditions in which iron alkoxides are expected to form (Scheme **20**, Table **3**).[75] In all these experiments, only one regioisomer **49b** was obtained albeit in low yields (Table **3**, Entries 1-3). The N-aryl products are obtained in slightly higher yields using 4-iodoanisole **2d** as coupling partner (Table **3**, Entries 4 and 5). Presumably, the reaction goes through the electron transfer mechanism under these conditions (Scheme **19**, Mechanism-**2**).

Scheme 20: N-Arylation using the $FeCl_3$/*t*-BuOK reagent system

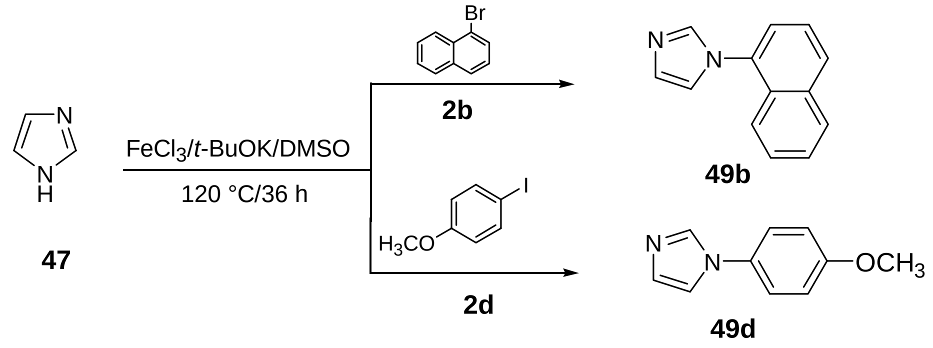


Table 3: Effect of $FeCl_3$/*t*-BuOK combination[a]

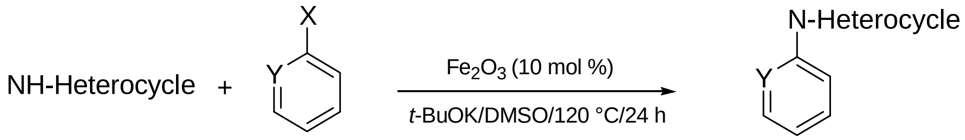
Entry	Ar-X	$FeCl_3$ (mmol)	*t*-BuOK (mmol)	K_3PO_4 (mmol)	Product	Yield(%)[b]
1	**2b**	1	3	-	**49b**	4
2	**2b**	0.1	0.3	1.5	**49b**	10
3	**2b**	1	3	1.5	**49b**	11
4	**2d**	0.1	0.3	1.5	**49d**	37
5	**2d**	1	3	1.5	**49d**	35

[a] Unless noted otherwise, all the reactions were carried out with imidazole **47a** (1 mmol), aryl halide **2** (2 mmol), K_3PO_4 (1.5 mmol) and DMSO (5 mL) at 120 ˚C for 36 h. [b] Isolated yields.

1.2.4 N-Arylation of NH-heterocycles

We have then examined this methodology (Scheme **18**) for the N-phenylation of various NH-heterocycles such as benzimidazole, pyrrole, indole and 1,2,3-benzotriazole. The corresponding N-phenyl products are obtained in moderate to excellent yields (Scheme **21**, Table **4**).

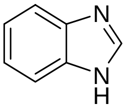
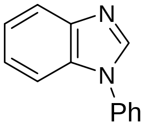
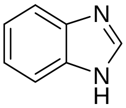
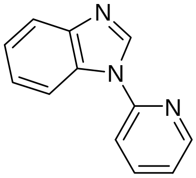
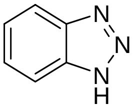
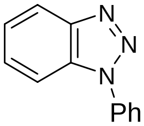
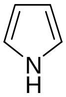
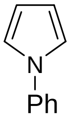
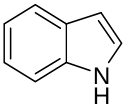
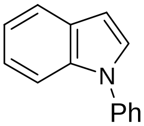
Scheme 21: N-Phenylation of various NH-heterocycles



2a X=I, Y=CH
2bc X=Br, Y=N

49ab-49ae Y=CH
49abc Y=N

Table 4: N-Arylation of various NH-heterocyles **49ab-ae**[a]

Entry	Aryl bromide	Product		Yield (%)[b]
1			**49ab**	71
2			**49abc**	97
3			**49ac**	79
4			**49ad**	58
5			**49ae**	64

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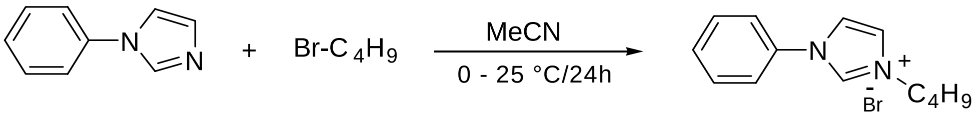
[a] All the reactions were carried out with Fe_2O_3 (10 mol %), NH-heterocycle (1 mmol), aryl halide **2** (2 mmol), ^{t}BuOK (2 mmol) and DMSO (3 mL) for 24 h at 120 ˚C. [b] Isolated yields and the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

1.2.5 Applications of N-aryl imidazoles 49

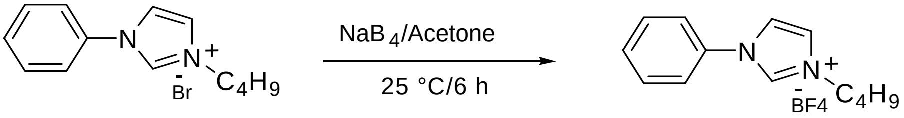
The N-phenyl imidazole **49a** is readily converted to the corresponding N-butyl,N'-phenyl ionic liquid **81** following a procedure reported for the preparation of ionic liquids containing N,N'-dialkyl moieties (Scheme **22**).[76] This observation illustrates the synthetic potential of the N-arylation methodology to access a series of ionic liquids that have proven applications in electrochemical devices.[76b]

Scheme 22: Synthesis of N-butyl,N'-phenyl imidazolium bromide salt **80**



49a **79** **80**, 70% y

Scheme 23: Synthesis of N-butyl,N'-phenyl imidazolium tetrafluoroborate **81**



80 **81**, 96% y

1.2.6 N-Arylation of diphenylamine

We have then turned our attention towards examining the use of the *t*-BuOK/DMSO/Fe_2O_3 reagent system for N-arylation of diphenylamine **82** to obtain the corresponding triarylamine derivatives **83a-e** since such a methodology has potential for use in the synthesis of optoelectronic materials. We have carried out the N-arylation of diphenylamine **82** with various aryl bromides **2a-e** at 130 °C (Scheme **24**). It was observed

Scheme 24: N-Arylation of diphenylamine with various aryl bromides[a]

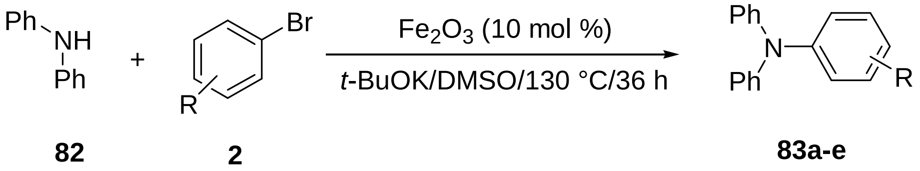
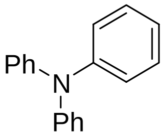
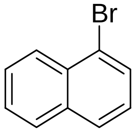
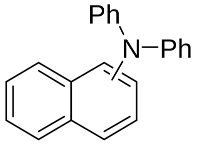
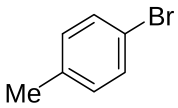
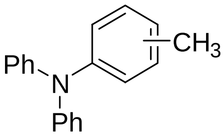
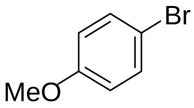
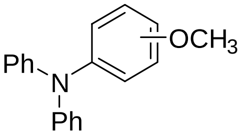
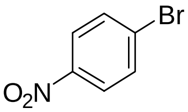
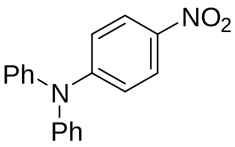


Table 5: Synthesis of various triarylamines **83a-e**[a]

Entry	Aryl bromide (**2**)	Triarylmine		Yield (%)[b]
1	Ph-Br		**83a**	83
2		 1&2 ratio:60:40	**83b**	76
3		 *p&m* ratio:56:44	**83c**	84
4		 *p&m* ratio:61:39	**83d**	72
5			**83e**	47

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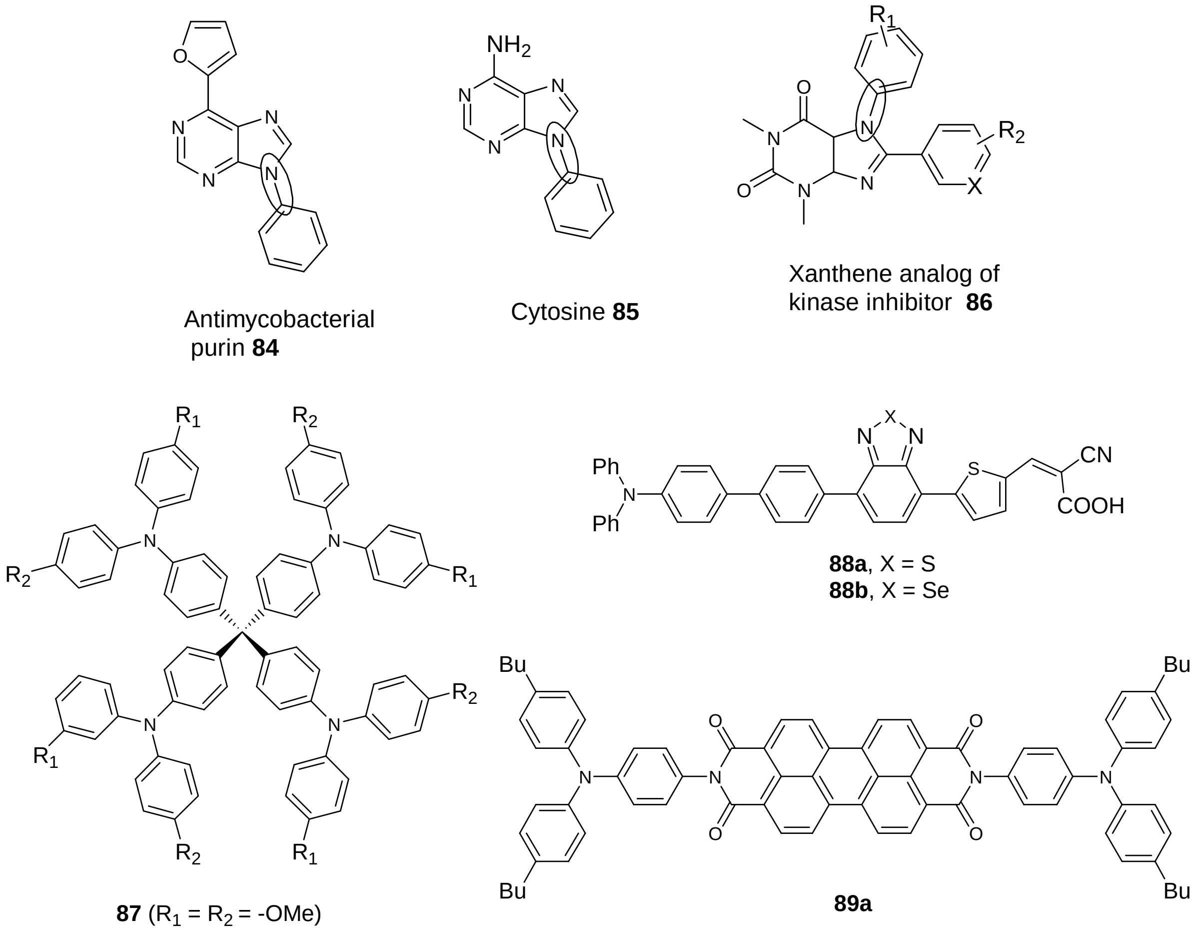
[a] All the reactions were carried out with Fe_2O_3 (10 mol %), diphenylamine **82** (1 mmol), aryl bromide **2** (2 mmol), *t*-BuOK (2 mmol) and DMSO (3 mL) at 130 ˚C for 36. [b] Isolated yields and all the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR.

that the aryl halides containing electron donating substituents gave the products in higher yields (Compounds **83c** and **83d**) compared to the derivatives containing electron withdrawing groups (Compound **83e**). Again, two regioisomers are obtained in reactions using some substituted aryl halides (Compounds **83b**, **83c** and **83d**) indicating the involvement of aryne intermediates in this transformation (Scheme **19**, Table **3**).

Previously, N-arylation methods using palladium[77] and copper[78] catalyst systems have been employed in the synthesis of bioactive and energy harvesting molecules (Fig. **1**).



Antimycobacterial purin **84**

Cytosine **85**

Xanthene analog of kinase inhibitor **86**

87 ($R_1 = R_2 = -OMe$)

88a, X = S
88b, X = Se

89a

Figure 1

The Fe_2O_3 promoted method for N-arylation described here involves a simple and inexpensive ligand free *t*-BuOK/DMSO reagent system which does not require dry N_2 atmosphere. Accordingly, the methods described here are expected to be useful in accessing compounds which have potential for applications in the synthesis of bioactive molecules, organic optoelectronics and electricity storage materials.

1.3 Conclusions

In summary, we have developed a simple and inexpensive ligand free *t*-BuOK/DMSO reagent system promoted by Fe_2O_3 for the successful synthesis of different N-aryl substituted imidazoles **49a-g** and various other N-aryl substituted NH-heterocyles **49ab-ae**. We have also synthesized various triarylamines **83a-e** starting from diphenyl amines using this reagent system. We have also demonstrated the synthesis of N-alkyl,N'-aryl ionic liquids **81** starting from N-phenyl imidazole.

The methods described here are expected to be useful in the synthesis of N-aryl heterocyclic derivatives, with potential applications for the synthesis of a variety of biologically active compounds and for the synthesis of organic optoelectronics and electrochemically active materials.

1.4 Experimental Section

1.4.1 General Information

The information given in the section 1.4 are also applicable for experiments outlined in this section. *t*-BuOK (Spectrum, India), all aryl halides and metal catalysts were supplied from Aldrch chemicals Ltd., used as purchased. Fe_2O_3 (J. T. Baker Chemicals Co. assay Fe_2O_3 by iodometry) 100% and all solvents (Merck) were used as such without any further purification. Melting points were determined using a Superfit capillary point apparatus and are uncorrected. IR (KBr) spectra were recorded on JASCO-FT-IR model 5300 spectrometer with polystyrene as reference. ^1H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance 400 spectrometer using TMS as internal standard (δ = 0 ppm). For TLC analysis, plates coated with silica gel were run in hexane/EtOAc mixture and spots were developed in an I_2 chamber.

Liquid Chromatography (LC) and mass analysis (LC-MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electro Spray Ionization (ESI) techniques. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250mμ acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's silica gel (100-200 or 230-400 mesh) and neutral alumina.

All the glassware were pre-dried at 140 °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.

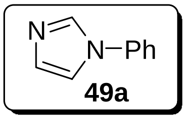
In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (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.

1.4.2 Representative procedure for the N-arylation of aryl halides with NH-heterocycles 49a-g and 49a-49ae

In a 25 mL, round-bottom (RB) flask with side arm, containing magnetic stirring bar equipped with an air condenser (condenser without water circulation), were placed Fe_2O_3 (0.016 g, 10 mol %), imidazole **47** (0.068 g, 1 mmol), *t*-BuOK (0.22 g, 2 mmol), DMSO (3 mL) and idobenzene **2a** (0.41 g, 2 mmol) in open atmosphere. The contents were stirred for

24 h at 120 °C and allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL) and the stirring was continued for another 10 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with water and brine solution and dried using anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel 100-200 mesh, 1:1 hexanes/ethyl acetate) to obtain the desired product **20a** as yellow solid.

1-Phenyl-1H-imidazole 49a



49a

Yield : 0.129 g (90%).

IR (neat) : (cm^{-1}) 3113, 1956, 1873, 1674, 1601, 1512, 1249.

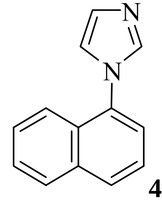
^{1}H NMR : (400MHz, $CDCl_3$) δ: 7.22 (s, 1H), 7.29-7.30 (m, 1H), 7.37-7.41 (m, 3H), 7.47-7.51 (m, 2H), 7.87 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 118.2, 121.5, 127.5, 129.9, 130.4, 135.6, 137.4

LCMS : (EI, m/z): 143 (M-1).

The same procedure was followed for N-arylation of several other NH-heterocycles. The physical constant and spectral data are listed below.

1-Naphthalen-1-yl-1*H*-imidazole 49b



49b

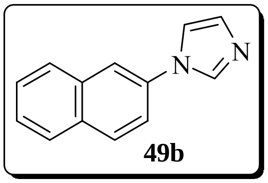
Yield : 0.076 g (39%), colorless solid.

mp : 58-60 °C (lit. 62 °C).[79]

IR (KBr) : (cm^{-1}) 3109, 3055, 1595, 1489, 1304, 802, 661.

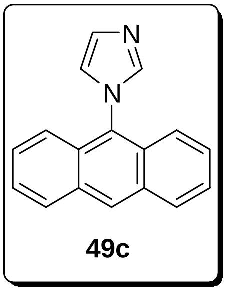
^{1}H NMR	**:**	(400MHz, $CDCl_3$) δ: 7.27-7.31 (m, 2H), 7.46-7.63 (m, 5H), 7.77 (s, 1H), 7.95-7.97 (m, 2H).
^{13}C NMR	**:**	(100 MHz, $CDCl_3$) δ: 121.7, 122.3, 123.7, 125.2, 126.9, 127.6, 128.3, 129.2, 129.5, 134.1, 138.4.
LCMS	**:**	(EI, m/z): 193 (M-1).

1-Paphthalen-2-yl-1*H*-imidazole 49b


49b

Yield	**:**	0.072 g (37%), yellow solid.
mp	**:**	122-124 °C (lit. 122-123 °C).[80]
IR (KBr)	**:**	(cm^{-1}) 3094, 1631, 1493, 1307, 1057, 814, 657.
^{1}H NMR	**:**	(400MHz, $CDCl_3$) δ: 7.27 (s, 1H), 7.41 (s, 1H), 7.53-7.60 (m, 3H), 7.83-7.98 (m, 5H).
^{13}C NMR	**:**	(100 MHz, $CDCl_3$) δ: 118.5, 119.1, 120.3, 126.5, 127.4, 127.9, 130.1, 130.6, 132.2, 133.5, 134.7, 135.8.
LCMS	**:**	(EI, m/z): 193 (M-1).

1-Anthracen-9-yl-1*H*-imidazole 49c

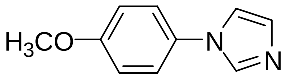

49c

Yield	**:**	0.086 g (70%), yellow solid.
mp	**:**	154-156 °C (lit. 154-156 °C).[81]
IR (KBr)	**:**	(cm^{-1}) 3094, 1626, 1493, 1307, 1059, 733, 659.
^{1}H NMR	**:**	(400MHz, $CDCl_3$) δ: 7.28 (s, 1H), 7.45-7.54 (m, 7H), 7.79 (s, 1H), 8.08-8.1 (m, 2H), 8.61 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 122.4, 122.7, 125.9, 127.6, 128.4, 128.5, 128.8, 129.7, 131.2, 139.6.

LCMS : (EI, m/z): 245 (M+1).

1-(4-Methoxy-phenyl)-1*H*-imidazole 49d



49d

Yield : 0.123 g (71%), yellow oil.

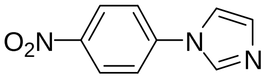
IR (neat) : (cm^{-1}) 3117, 2941, 2839, 1608, 15206, 1249, 831.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 3.86 (s, 3H), 6.97-7.03 (m, 2H), 7.20-7.21 (m, 2H), 7.23-7.35 (m, 2H), 7.82 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 55.6, 109.1, 112.4, 115.0, 123.3, 129.8, 130.6, 135.8, 158.9.

LCMS : (EI, m/z): 174 (M+1).

1-(4-Nitro-phenyl)-1*H*-imidazole 49e



49e

Yield : 0.143 g (76%), yellow solid.

mp : 202-204 °C (lit. mp 204.4–205.2 °C).[82]

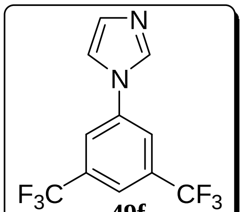
IR (KBr) : (cm^{-1}) 2926, 1599, 1510, 1338, 1051, 848, 648.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 7.27-7.28 (m, 1H), 7.38 (s, 1H), 7.58-7.60 (m, 2H), 7.99 (s, 1H), 8.37-8.40 (m, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 117.6, 121.1, 125.8, 131.7, 135.4, 142.0, 146.3

LCMS : (EI, m/z): 189 (M-1).

1-(3,5-*Bis*-trifluoromethyl-phenyl)-1*H*-imidazole 49f



49f

Yield : 0.229 g (82%), white solid.

mp : 92-94 °C (lit. 93-95 °C).[83]

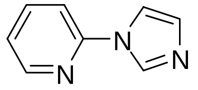
IR (KBr) : (cm^{-1}) 3113, 3049, 1626, 1508, 1248, 1124, 1060, 887.

^{1}H NMR : (400MHz, CDCl$_3$) δ: 7.30-7.31 (m, 1H), 7.38-7.39 (m, 1H), 7.88-7.97 (m, 3H), 8.23 (s, 1H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 117.9, 120.9-121.4 (quartet) 123.9, 126.6, 133.2-134.2 (quartet), 133.8, 134.2, 135.4, 138.

LCMS : (EI, m/z): 279 (M-1).

2-Imidazol-1-*yl*-pyridine 49g



49g

Yield : 0.130 g (90%), light yellow oil.

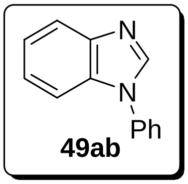
IR (neat) : (cm^{-1}) 3117, 2592, 1670, 1597, 1304, 1055, 904.

^{1}H NMR : (400 MHz, CDCl$_3$) δ: 7.21-7.29 (m, 2H), 7.36-7.38 (m, 1H), 7.65-7.66 (m, 1H), 7.81-7.86 (m, 1H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 112.3, 116.1, 121.9, 130.7, 134.9, 138.9, 149.1

LCMS : (EI, m/z): 290 (M+1).

1-Phenyl-1*H*-benzoimidazole 49ab



49ab

Yield : 0.137 g (71%), yellow solid.

mp : 94-96 °C (lit. 96-98 °C).[83]

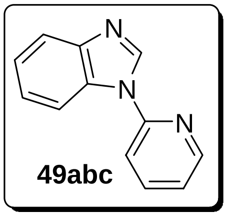
IR (KBr) : (cm^{-1}) 3117, 2592, 1670, 1597, 1304, 1055, 904.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 7.32-7.35 (m, 2H), 7.47-7.60 (m, 7H), 7.88-7.90 (m, 1H), 8.13 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 110.5, 120.6, 122.8, 123.7, 124.1, 127.8, 130.1, 133.7, 136.3, 142.3, 144.1.

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

1-Pyridin-2-yl-1*H*-benzoimidazole 49abc



49abc

Yield : 0.189 g (97%), yellow solid.

mp : 54-56 °C (lit. 59-60 °C).[84]

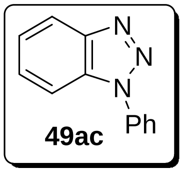
IR (neat) : (cm^{-1}) 1589, 1473, 1371, 1143, 887, 744.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 7.24-7.27 (m, 1H), 7.32-7.38 (m, 2H), 7.52-7.54 (m, 1H), 7.84-7.87 (m, 2H), 8.03-8.05 (m, 1H), 8.56-8.58(s, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 112.6, 114.3, 120.6, 121.8, 123.3, 124.2, 132.1, 138.9, 141.3, 144.6, 149.4, 149.8.

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

1-Phenyl-1*H*-benzotriazole 49ac


49ac

Yield : 0.155 g (79%), white solid.

mp : 84-86 °C (lit. 85-87 °C).[85]

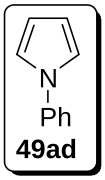
IR (KBr) : (cm^{-1}) 3055, 1595, 1500, 1275, 1057, 572.

^{1}H NMR : (400MHz, CDCl$_3$) δ: 7.29-7.47 (m, 1H), 7.48-7.57 (m, 2H), 7.59-7.62 (m, 2H), 776-7.88 (m, 3H), 8.16-8.18 (m, 1H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 110.4, 120.3, 122.9, 124.4, 128.3, 128.7, 129.9, 132.3, 137.0, 146.5.

LCMS : (EI, m/z): 196 (M+1).

1-Phenyl-1*H*-pyrrole 49ad


49ad

Yield : 0.082 g (58%), white solid.

mp : 58-60 °C (lit. 58-60 °C).[86]

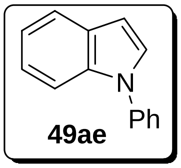
IR (KBr) : (cm^{-1}) 3138, 2928, 1510, 1253, 1022, 607.

^{1}H NMR : (400MHz, CDCl$_3$) δ: 6.38-6.39 (m, 2H), 7.12-7.13 (m, 2H), 7.25-7.31 (m, 1H), 7.36-7.47 (m, 4H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 110.4, 119.3, 120.5, 125.6, 129.5, 140.8

LCMS : (EI, m/z): 143 (M+1).

1-Phenyl-1*H*-indole 49ae


49ae

Yield : 0.124 g (64%), yellow oil.

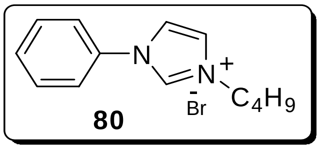
IR (neat) : (cm^{-1}) 3055, 1888, 1597, 1331, 1014, 740.

^{1}H NMR	:	(400MHz, $CDCl_3$) δ: 6.77 (d, 1H), 7.24-7.33 (m, 2H), 7.39-7.46 (m, 2H), 7.56-7.59 (m, 4H), 7.65-7.67 (m, 1H); 7.77-7.79 (m, 1H).
^{13}C NMR	:	(100 MHz, $CDCl_3$) δ: 103.6, 110.5, 120.4, 121.2, 122.4, 126.5, 128.0, 129.4, 129.7, 135.9, 139.9.
LCMS	:	(EI, m/z): 194 (M+1).

1.4.3 N-Butyl,N'-phenyl imidazolium bromide salt 80

A slightly modified reported procedure was followed.[76a] To a stirred solution of N-phenyl imidazole **49a** (0.14 g, 1 mmol) and acetonitrile (5 mL) in a 25 mL, round-bottom (RB) flask with side arm, was added n-butyl bromide **79** (0.41 g, 3 mmol) in drops at 0°C. The contents were slowly brought to 25 °C and stirring was continued for another 24 h. The solvent was evaporated under reduced pressure and washed with hexane and dried under high vacuum to obtain the desired product **80**.

Yield : 0.196 g (70%), brown color oil.

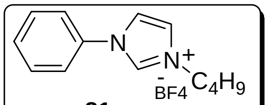


80

We proceeded to next step without further purification of the product.

N-Butyl,N'-phenyl imidazolium tetrafluoroborate 81[74a]

In a 25 mL RB flask, to a stirred solution of bromide salt **80** (0.28 g, 1 mmol) in acetone (10 mL) at 25 °C, was added $NaBF_4$ salt (0.13 g, 1.2 mmol). The contents were stirred for another 6 h. The reaction mixture was filtered through Buchner funnel and evaporated the solvent. The residue was diluted with dichloromethane (20 mL), followed by filtration and concentration of solvent. The residue was washed with hexane and dried under high vacuum to obtain the desired product **81** as brown oil.



81

Yield : 0.277 g (96%)

IR (neat) : (cm^{-1}) 3157, 2876, 1746, 1599, 1203, 763.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 0.90-0.94 (m, 3H), 1.34-1.39 (m, 2H), 1.85-1.93 (m, 2H), 4.32-4.36 (t, 2H), 7.36-7.52 (m, 4H), 7.60-7.69 (m, 3H), 9.36 (s, 1H).

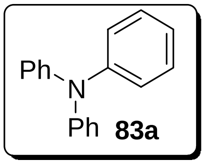
^{13}C NMR : (100 MHz, $CDCl_3$) δ: 13.3, 19.4, 32.0, 50.2, 121.3, 121.5, 123.4, 129.9, 130.3, 130.5, 134.3.

^{11}B NMR : (100 MHz, $CDCl_3$) δ: -0.90.

1.4.4 Representative procedure for synthesis of triarylamines 83a-e

In a 25 mL, round-bottom (RB) flask with side arm, containing magnetic stirring bar equipped with an air condenser (condenser without water circulation), Fe_2O_3 (0.016 g, 10 mol %), diphenylamine (0.17 g 1, mmol), *t*-BuOK (0.22 g, 2 mmol), DMSO (3 mL) and iodo benzene (0.41 g, 2 mmol) were placed. The contents were stirred for 36 h at 130 °C and allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL) and stirring was continued for another 10 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with water and brine solution and dried using anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel 100-200 mesh, pure hexanes) to obtain the desired product **83a** as colorless solid.

Triphenylamine 83a


83a

Yield : 0.202 g (83%) using bromobenzene and

0.220 g (90%) using iodobenzene.

mp : 124-126 °C (lit.126-128 °C).[73a]

IR (KBr) : (cm^{-1}) 1583, 1489, 1329, 1277, 748, 692.

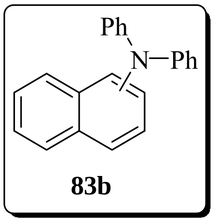
^{1}H NMR : (400MHz, $CDCl_3$) δ: 6.98-7.03 (m, 3H), 7.09-7.11 (m, 6H), 7.23-7.27 (m, 6H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 122.6, 124.2, 129.2, 147.8.

LCMS : (EI, m/z): 246 (M+1).

The same procedure was followed for the preparation of several other N-aryl diphenyl amines. The physical constant and spectral data are listed below.

Naphthalene-1 or 2-yl-diphenylamine 83b


83b

Yield : 0.224 g (76%), colorless solid; regeoisomeric ratio was calculated based on ^{1}H-NMR spectra. All spectral details are for a mixture of regioisomers in 60:40 ratio.

^{1}H-NMR : range of values 7.08-7.17 and 7.21-7.27.

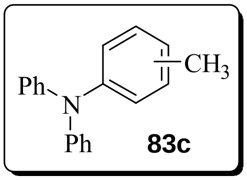
IR (KBr) : (cm^{-1}) 3057, 1626, 1589, 1493, 1273, 750, 696.

^{1}H NMR : (400MHz, $CDCl_3$) δ: of 6.95-7.75.

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 120.3, 120.5, 121.3, 121.7, 121.9, 122.9, 124.4, 126.3, 126.4, 126.9, 127.3, 127.6, 128.4, 128.9, 129.1, 129.2, 129.3, 130.1, 134.5, 145.5, 147.8, 148.5, 149.1.

LCMS : (EI, m/z): 296 (M+1).

Diphenyl-*p* or *m*-tollyl-amine 83c



83c

Yield : 0.217 g (84%), colorless solid; regeoisomeric ratio was calculated based on ^{1}H-NMR analysis of –CH_3 protons at 2.28 and 2.34. All spectral details are for a mixture of regioisomers in 56:44 ratio.

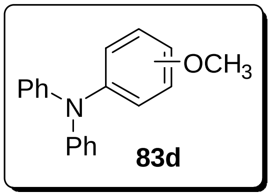
IR (KBr) : (cm^{-1}) 3028, 2916, 1593, 1504, 1284, 1024, 754, 694.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 2.28 (s, 3H), 2.34 (s, 3H), 6.85-7.04 (m, 9H), 7.09-7.18 (m, 11H), 7.22-7.28 (m, 8H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 20.8, 21.6, 121.6, 122.2, 122.5, 123.6, 124.1, 124.9, 132.7, 139.1, 145.3, 147.8, 147.9, 148.1.

LCMS : (EI, m/z): 260 (M+1).

Diphenyl-*p* or *m*-methoxy-amine 83d



83d

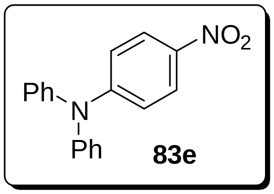
Yield : 0.20 g (72%), colorless solid; regeoisomeric ratio was calculated based on ^{1}H-NMR analysis of –OCH_3 protons 3.78-3.8 and 3.87-3.89. All spectral details are for a mixture of regioisomers in 61:39 ratio.

IR (KBr) : (cm^{-1}) 3036, 2951, 1593, 1587, 1485, 1242, 1035, 694.

^{1}H NMR : (400MHz, $CDCl_3$) δ: 3.78-3.8 (d, 3H), 3.87-3.89 (d, 3H), 6.63-7.34 (m, 28H).

^{13}C NMR **:** (100 MHz, CDCl$_3$) δ: 55.3, 55.6, 108.1, 109.8, 114.8, 116.5, 121.9, 122.9, 124.5, 127.4, 129.2, 129.3, 129.8, 140.8, 147.8, 148.3, 149.2, 156.2, 160.5.

(4-Nitrophenyl)-diphenylamine 83e



83e

Yield **:** 0.14 g (47%), yellow solid.

IR (KBr) **:** (cm^{-1}) 1581, 1491, 1313, 1109, 841, 694.

^{1}H NMR **:** (400MHz, CDCl$_3$) δ: 6.92-6.94 (m, 2H), 7.18-7.31 (m, 6H), 7.36-7.39 (m, 4H), 8.03-8.05 (m, 2H).

^{13}C NMR **:** (100 MHz, CDCl$_3$) δ: 118.1, 125.5, 125.7, 126.5, 129.9, 140.1, 145.6, 153.5.

LCMS **:** (EI, m/z): 291 (M+1).

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Chapter 2

Studies on N-Arylation of Chiral C_2-Symmetric Diamines

2.1 Introduction

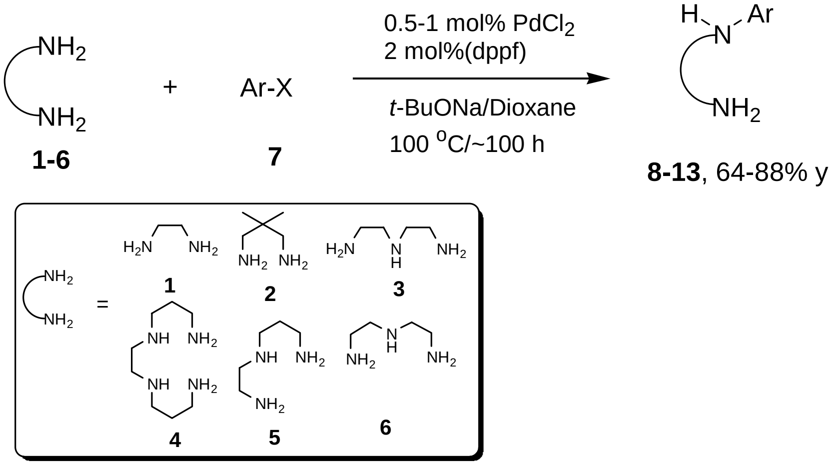
N,N'-Diaryl derivatives of *trans*-(1*R*,2*R*)-diaminocyclohexane **17** and *R*-bi-2-naphthyldiamine (*R*-BINAM) **22**, are useful as chiral ligands, scaffolds and building blocks for the synthesis of biologically active compounds.[1] A brief review of reports on the N-aryl derivatives of these amines would facilitate the discussion.

2.1.1 Palladium catalyzed N-arylation of diamines

2.1.1.1 N-Arylation of achiral diamines

A method for the preparation of aryl substituted achiral polyamine compounds has been reported using polyamine (1equiv) and aryl halide (1equiv) through the palladium catalyzed N-arylations at 100 °C (Scheme **1**).[2]

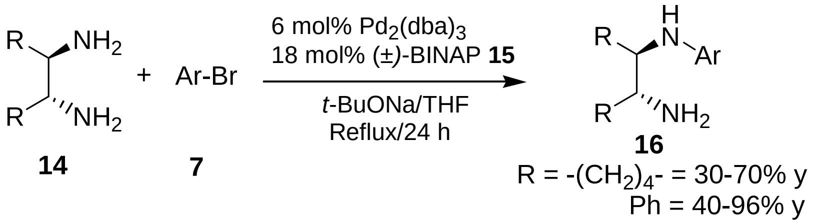
Scheme 1



2.1.1.2 N-Arylation of chiral 1,2-diphenyl-1,2-diamine

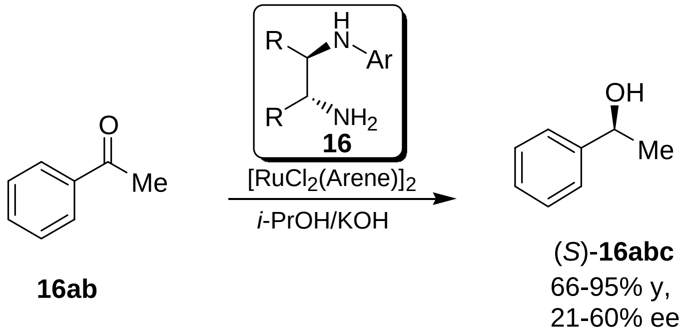
Mono aryl substituted chiral diamine derivatives have been prepared by using palladium/*rac*-BINAP **15** catalyzed N-arylation of chiral diamine derivatives at reflux conditions in THF. By employing this methodology, a variety of new mono-*N*-aryl enantiopure diamine ligands have been prepared for application in catalytic asymmetric transfer hydrogenation of acetophenone (Scheme **2**).[3]

Scheme 2



Enantiopure mono-N-aryl diamines **16** were used as ligands in the ruthenium catalysed asymmetric hydrogenation of acetophenone (Scheme **3**).[3]

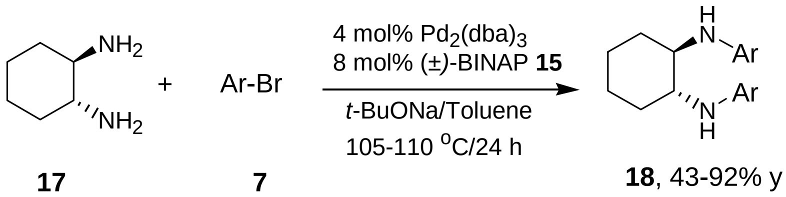
Scheme 3



2.1.1.3 N,N'-Diarylation of chiral diamines

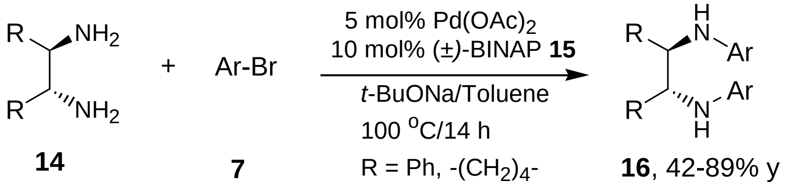
A method N,N'-diarylation of chiral diamines **17** has been reported by using pd(dba) and *rac*-BINAP **15** catalyst system (Scheme **4**).[4]

Scheme 4



An alternative method for the synthesis of N,N'-diaryl substituted compounds of chiral diamines **14** has been reported using Pd(OAc)/*rac*-BINAP **15** catalyst system (Scheme **5**).[5]

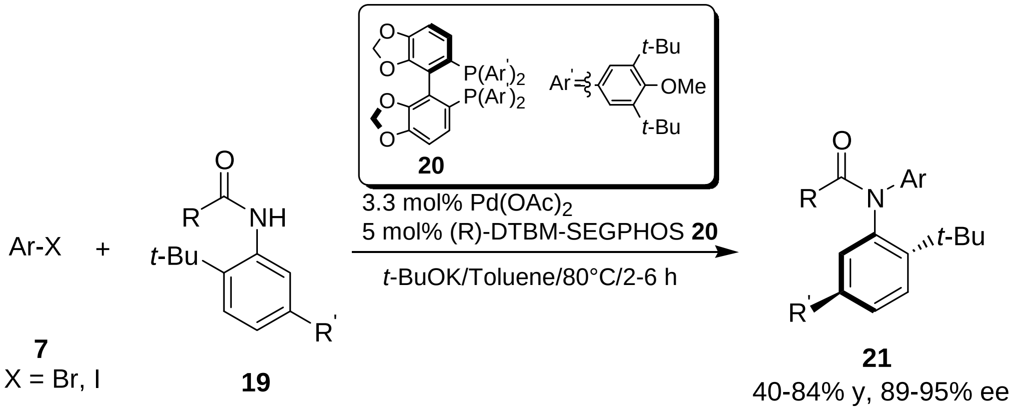
Scheme 5



2.1.1.4 N-Arylation of *o*-*t*-butylanilides

(*R*)-DTBM-SEGPHOS-Pd(OAc)$_2$ catalyzed N-arylation of various *o*-*t*-butylanilides with *p*-iodonitrobenzene has been reported to give atropisomeric *E*-rotamer N-(*p*-nitrophenyl) anilides in good yields with 88-96% ee (Scheme **6**).[6]

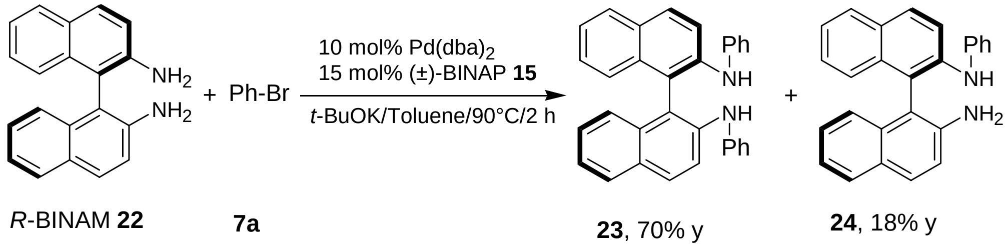
Scheme 6



2.1.1.5 N-Arylation of chiral 1,1′-binaphthyl-2,2′-diamine 22

The N-phenyl derivatives **23**, **24** were obtained using the Pd(dba)/rac-BINAP **15** catalyzed coupling of (*R*)-bi-2-naphthyldiamine **22** with bromobenzene (Scheme **7**)[7]

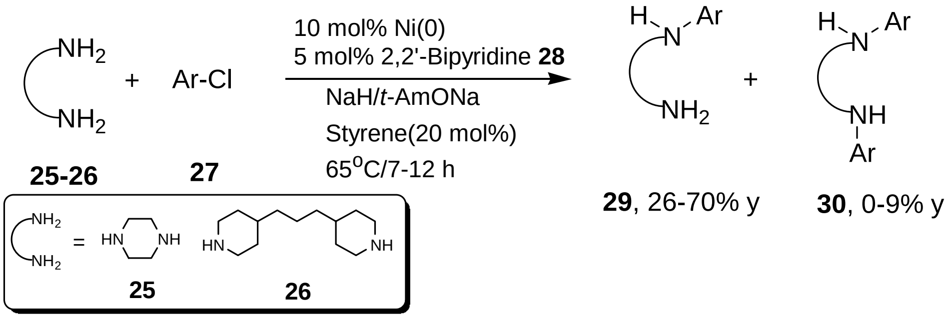
Scheme 7



2.1.2 Nickel catalyzed mono N-arylation of achiral diamines

Selective synthesis of N-aryl or N,N'-diaryl piperazines and trimethylene(bis)piperidines from the corresponding diamines and aryl chlorides using a Ni(0)/2,2'-bipyridine combination has reported.[8] The Ni/2,2'-bipyridine catalyst is also effective for the sequential arylation of piperazine (Scheme **8**).

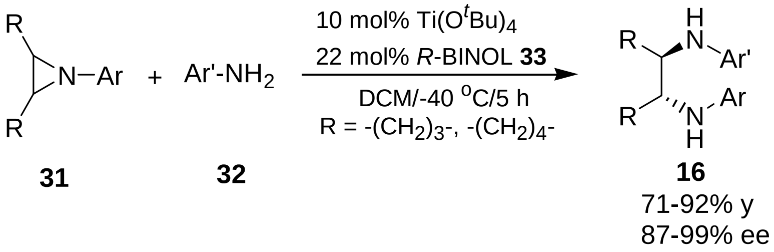
Scheme 8



2.1.3 Synthesis of N,N'-diaryl chiral diamines from aziridines

N,N'-Diaryl substituted C_2-symmetric chiral 1,2-diamine derivatives have been also obtained using Ti(OBu^t)$_4$/*R*-BINOL **33** catalysis *via* ring opening aminolysis of meso aziridines (Scheme **9**).[9]

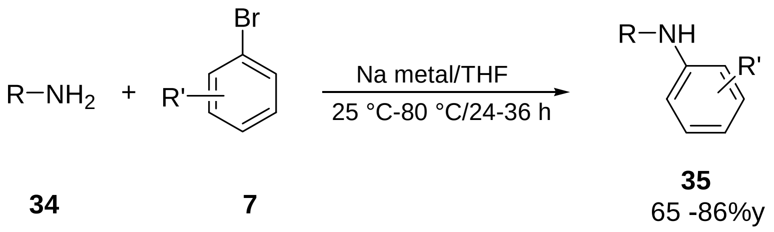
Scheme 9



2.1.4 Previous work from this laboratory

Earlier, a method for N-arylation of various primary and secondary amines has reported using halobenzene, alkali metal (Li or Na) in THF (Scheme **10**).[10]

Scheme 10



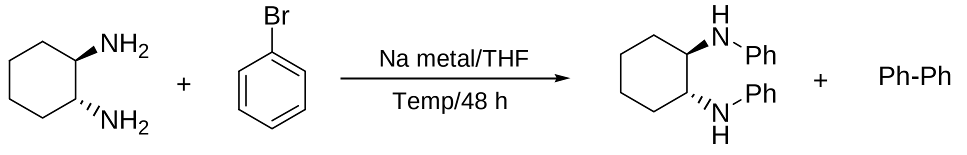
Ligands derived from certain C_2-symmetric enantiopure diamines have been widely employed in asymmetric transformations. Especially, the *trans*-(1*R*,2*R*)-diaminocyclohexane or *trans*-(1*R*,2*R*)-cyclohexyldiamine **17** and its derivatives were widely used as chiral reagents, scaffolds and as ligands in many organic transformations.[1] We have undertaken investigations towards development of N-arylation of C_2-symmetric trans-1,2-diaminocyclohexane **17** and (*R*)-(+)-1,1′-bi-2-naphthylamine (BINAM) other names are (*R*)-(+)-1,1′-binaphthalene-2,2′-diamine or (*R*)-(+)-2,2′-diamino-1,1′-binaphthalene or (*R*)-(+)-DABN **22**. The results are described in the next section.

2.2 Results and Discussion

2.2.1 N,N'-Diarylation of chiral *trans*-1,2-diaminocyclohexane

Initially, we have examined N,N'-diphenylation of C_2-symmetric diamine **17** using bromobenzene and sodium metal in THF. We have observed that the N,N'-diphenyl *trans*-(1*R*,2*R*)-diaminocyclohexane **18a** was obtained in poor yield (10 %) besides biphenyl **36** as a major product (Scheme **11**).

Scheme 11

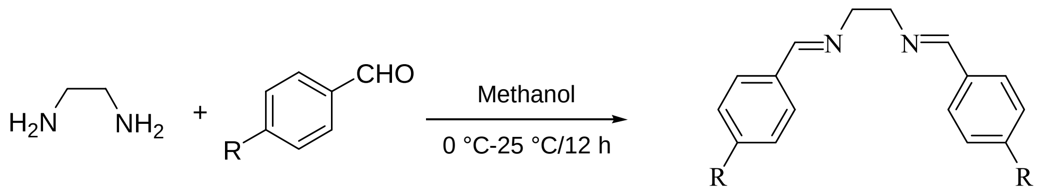


17 **7a** **18a** **36**, 73% y

25°C: 4 % y
70 °C: 10% y

Therefore, we were looking for a convenient alternative method for N-arylation of C_2-symmetric diamines. Though, the $C_{(aryl)}$-N bond forming reactions employing chiral C_2-symmetric diamines and aryl halides as coupling partners using palladium catalyst system has been reported,[11] there is no report in the literature with copper catalyst systems for the N-arylation of chiral C_2-symmetric diamines. Hence, still there is a scope for the development of a mild, inexpensive and efficient catalytic system for the N-arylation of chiral C_2-symmetric diamines. We have prepared the inexpensive bidentate ligands **39** and **40** from ethylene diamine **37** and arylaldehyde **38** and anisole respectively for application in N-arylation of chiral 1,2-diamines and (*R*)-(+)-1,1′-bi-2-naphthylamine (BINAM) (Scheme **12**).

Scheme 12



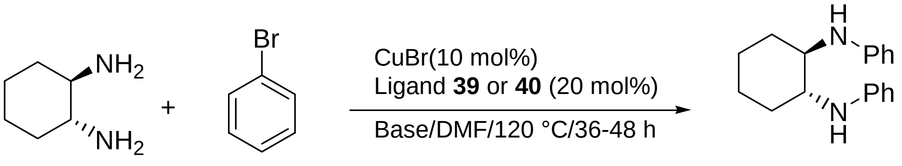
37, (1 equiv.) **38**, (2 equiv.)

39, R = H, N,N'-dibenzylidineethane-1,2-diamine

40, R = OMe, N,N′-bis(4-methoxybenzylidine) ethane-1,2-diamine

We have utilized the ligands **39** and **40** as bidentate ligands with copper bromide catalyst for the N-arylation of *trans*-(1*R*,2*R*)-diaminocyclohexane **17**. The product **18a** was obtained in 17 % and 34 % yields for bidentate ligands **39** and **40** respectively. Encouraged by these results, we have screened the reaction with various parameters like ligands, metal catalysts, bases, solvents, temperature and time (Scheme **13**, Table **1**).

Scheme 13



17 **7a** **18a**

for **39**: 17%y

for **40**: 34%y

Table 1: N-Phenylation of *trans*-(1*R*,2*R*)-diaminocyclohexane **17**[a]

Entry	Ligand	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	**39**	K_2CO_3	DMF	25	48	-
2	**39**	K_2CO_3	DMF	120	48	10
3	**39**	K_3PO_4	DMF	120	48	17
4	**39**	K_2CO_3	THF	120	48	8
5	**39**	K_2CO_3	Toluene	120	48	11
6	**39**	K_2CO_3	DMSO	120	48	10
7	**39**	K_2CO_3	MeCN	120	48	8
8	**40**	K_3PO_4	DMF	120	48	34

[a] All the reactions were carried out with each copper bromide (10 mol %), ligand **39** or **40** (20 mol %), *trans*-(1*R*,2*R*)-diaminocyclohexane **17** (1 mmol), bromobenzene (4 mmol) and solvent (5 mL) at mentioned temperature. [b] Product **18a** was identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Unfortunately, attempts to optimize the reaction conditions of bidentate ligands **39** and **40** were not successful. N-Arylation of some amines has been reported using *rac*-BINOL **33** as ligand.[12] We have therefore examined the reaction of CuBr with *rac*-BINOL **33** for the N-arylation of chiral 1,2-diaminocyclohexane **17** and bi-2-naphthylamine **22**. We have not observed the formation of desired product N,N′-diphenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **18a** at 25 °C. Fortunately, we have observed 50 % yield of N,N'-diphenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **18a** from *trans*-(1*R*,2*R*)-diaminocyclohexane **18** at slightly higher temperatures (Scheme **14**). We have also observed low yields for conditions not employing any ligand (Table **2**, Entry 5) and for the combination of CuO/NiBr (Table **2**, Entry 9). We have further screened the reaction with various parameters like metal catalysts, bases, and time (Scheme **14**). The results are summerised in Table **2**.

Scheme 14: Coupling of *trans*-(1*R*,2*R*)-diaminocyclohexane **17** and halobenzene in the presence of copper(I) catalyst.

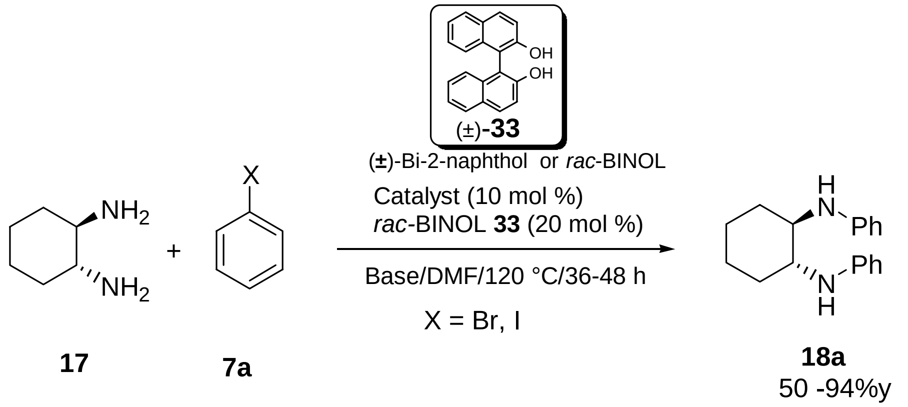
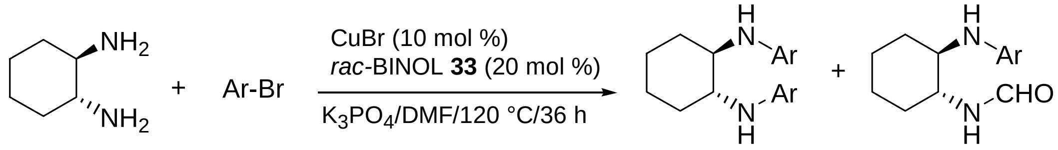


Table 2: N-Arylation of *trans*-(1*R*,2*R*)-diaminocyclohexane **17** under various conditions[a]

Entry	Catalyst	Halobenzenes	Ligand	Base	Solvent	Time(h)	Yield(%)[b]
1	CuBr	Ph-Br	**33**	K_2CO_3	DMF	48	50
2	**CuBr**	**Ph-Br**	**33**	**K_3PO_4**	DMF	**36**	**78**
3	**CuBr**	**Ph-I**	**33**	**K_3PO_4**	DMF	**36**	**94**
4	CuI	Ph-Br	**33**	K_3PO_4	DMF	36	56
5	CuBr	Ph-I	**-**	K_3PO_4	DMF	36	5[c]
6	CuBr/Fe_2O_3	Ph-I	**33**	K_3PO_4	DMF	36	84
7	CuBr/Fe_2O_3	Ph-Br	**33**	K_3PO_4	DMF	36	76
8	CuBr/ZnO	Ph-I	**33**	K_3PO_4	DMF	36	73
9	CuO/NiBr	Ph-I	**33**	K_3PO_4	DMF	48	15

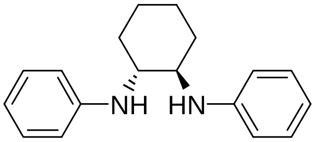
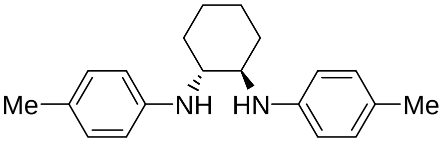
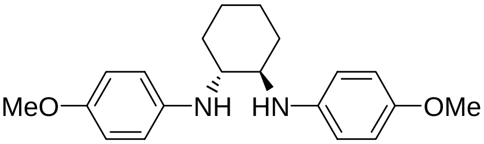
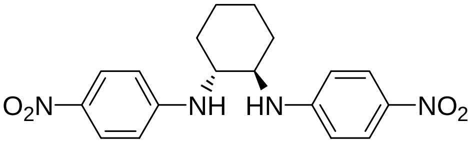
[a] All the reactions were carried out with each metal catalyst (10 mol %), ligand **33** (20 mol %), *trans*-(1*R*,2*R*)-diaminocyclohexane **17** (1 mmol), halobenzene (4 mmol) and DMF (5 mL) at 120 °C. [b] Product was identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. [c] Reaction was carried out without employing any ligand.

Scheme 15



17 **7a-d** **18a-d** 49-78%y **41a-d** < 5% y

Table 3: Synthesis of N,N'-diaryl-*trans*-(1*R*,2*R*)-diaminocyclohexane **18a-d**[a]

Entry	Aryl halide	Product	Time (h)	Yield (%)[b]	ee (%)
1	C_6H_5-Br	 **18a**	36	78	-
2	*p*-CH_3-C_6H_4-Br	 **18b**	36	61	-
3	*p*-OMe-C_6H_4-Br	 **18c**	36	71	-
4	*p*-NO_2-C_6H_4-Br	 **18d**	36	49	-

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[a] Unless noted otherwise, all the reactions were carried out with copper bromide (10 mol %), *rac*-BINOL **33** (20 mol %), *trans*-(1*R*,2*R*)-diaminocyclohexane **17** (1 mmol), aryl bromide (4 mmol), K_3PO_4 (3 mmol), DMF (5 mL) at 120 °C. [b] All the products **18a-d** were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

The CuBr/*rac*-BINOL **33** combination gave better results in the N,N'-diphenylation of *trans*-(1*R*,2*R*)-diaminocyclohexane **17** (Scheme **14**, Table **2**). With this optimized condition in hand, we have further examined the diarylation of *trans*-(1*R,*2*R*)-diaminocyclohexane **17** with various aryl bromides **7a-d** (Scheme **15**, Table **3**, Entries 1-4). The yields are better in reactions using aryl bromides containing electron donating substituents (Table **3** entries 2 and 3) compared to electron withdrawing substituents on aryl bromides (Table **3**, Entry 4).

2.2.2 N,N'-Diphenylation of 1,1'-binaphthyl-2,2'-diamine 22

N-Phenylation using CuBr/*rac*-BINOL/K_3PO_4 system was also examined with (*R*)-1,1'-binaphthyl-2,2'-diamine **22**. We have observed partial racemization of the (*R*)-N,N'-diphenyl-1,1'-binaphthyl-2,2'-diamine **23a** under the reaction conditions. The corresponding (*R*)-N,N'-diphenyl-1,1'-binaphthyl-2,2'-diamine **23a** was obtained in 83 % yield to 13 % ee in one condition (Table **4**, Entry 1) and in another condition we have observed 19 % yield across 91 % ee (Scheme **16**, Table **4**, Entry 3).

Scheme 16: Synthesis of (*R*)-N,N'-diphenyl-1,1'-binaphthyl-2,2'-diamine **23a**.

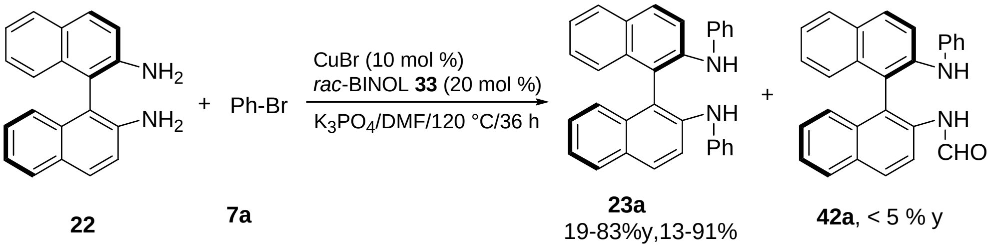
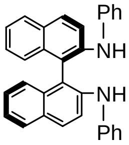


Table 4: (*R*)-N,N'-Diphenyl-1,1'-binaphthyl-2,2'-diamine **23a**.[a]

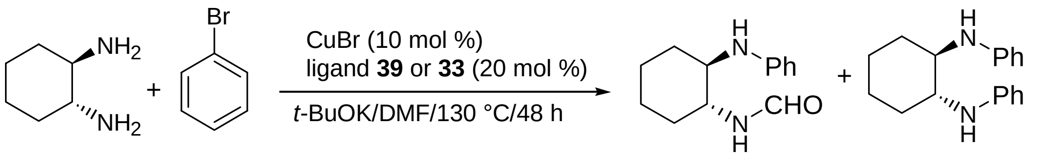
Entry	Aryl halide	Product	Time (h)	Yield (%)[b]	ee (%)[d]
1[c]	C_6H_5-I	 **23a**	36	83	13[c]
2	C_6H_5-I	**23a**	24	36	59
3	C_6H_5-I	**23a**	12	19	91
4[e]	C_6H_5-I	**23a**	48	39	58

[a] Unless noted otherwise, all the reactions were carried out with CuBr (10 mol %), *rac*-BINOL **33** (20 mol %), (*R*)-N,N'-diphenyl-1,1'-binaphthyl-2,2'-diamine **22** (1 mmol), iodobenzene (4 mmol), K_3PO_4 (3 mmol), DMF (5 mL) at mentioned temperature. [b]The product was identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data, [c]*Bis*-phenylation of *rac*-BINOL **33** was also observed (up to 20 %). [d]*ee* of the product **23a** was determined by using chiral HPLC on Daicel Chiral Pak AD-H (elution hexane-ethanol 19:1, flow rate:1 mL/min UV detection at 256 nm) showed 13-91 % ee (t_S = 4.3min, t_R = 5.8 min).[35] [e]Reaction was carried out at 100 ˚C.

2.2.3 N-Arylation,N'-formylation of *trans*-(1*R*,2*R*)-diaminocyclohexane 41

In all the above cases, the N-aryl,N'-formyl-*trans*-(1*R,*2*R*)-diaminocyclohexane **41** was obtained in trace amount (< 5%). Interestingly, when *t*-BuOK was used in combination with the CuBr/*rac*-BINOL **33** system, the formyl product **41a** was obtained in good to excellent yields (Scheme **17**, Table **5**, entries 1 and 2). This may be attributed to increased solubility and basicity of the *t*-BuOK. It may be of interest to note that formylation of certain amines has reported in reactions with CH_3ONa and DMF.[13]

Scheme 17: Synthesis of N-formyl,N'-phenyl-*trans*-(1*R,*2*R*)-diaminocyclohexane **41a**.



17 **7a** **41a**, 78-93%y **18a**, < 10%y

Table **5**: Synthesis of N-formyl,N'-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **41a**.[a]

Entry	Catalyst	Ligand	Base	Yield (%)[b]
1	CuBr	**39**	*t*-BuOK	78
2	CuBr	**33**	*t*-BuOK	93
3[c]	CuBr	-	*t*-BuOK	76
4	CuBr	**33**	K_3PO_4	trace

[a]Unless noted otherwise, all the reactions were carried out with CuBr (10 mol %), ligand **39** or **33** (20 mol %), *trans*-(1*R*,2*R*)-diaminocyclohexane **17** (1 mmol), bromobenzene **7a** (1.2 mmol), *t*-BuOK (2.5 mmol) and DMF (5 mL) at 130 ˚C for 48 h., [b]Product **41a** was identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data, X-ray crystal structure analysis, [c] Reaction was carried out without employing any ligand.

Interestingly, the compound **41a** was isolated in 76 % yield, even in the absence of ligand (Table **5**, Entry 3). We thought that the initially formed N-formyl,N'-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **41a** itself is acting as a ligand to give product **41a**. In order to examine this possibility, we have used the compound **41a** in the N,N'-diphenylation of *trans*-(1*R,*2*R*)-diaminocyclohexane **33**. In this run, the corresponding N,N'-diphenyl derivative **18a** was obtained in 40 % yield.

The structure of the N-formyl,N′-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **41a** was further confirmed by X-ray crystal structure analysis. The ORTEP diagram is shown in Fig. **1**.

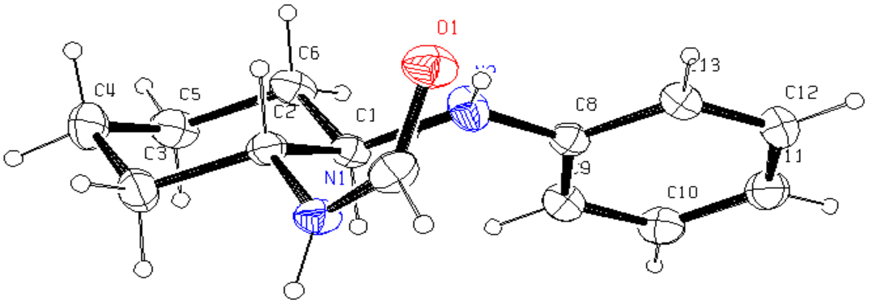


Fig. **1**: ORTEP diagram of N-formyl,N'-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **41a**.

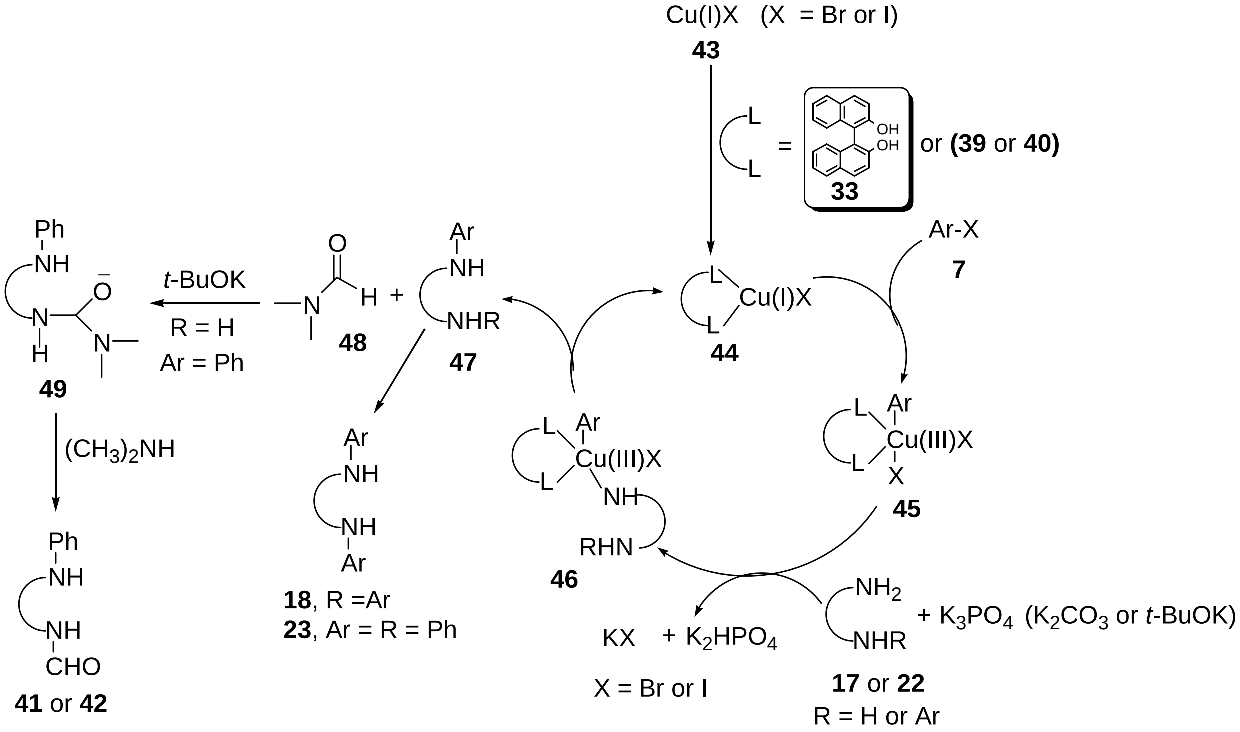
Crystal data for N-((1*R*,2*R*)-2-(phenylamino)cyclohexyl)formamide 41a

Molecular formula: C_{13} H_{18} N_2 O, *Mw* = 218.29, orthorhombic, space group: P2(1)2(1)2(1), a = 5.1335(4) Å,b = 7.7826(6) Å, c = 30.628(2) Å, α = 90.00, β = 90.00, γ = 90.00, V = 1223.66(16) Å, Z = 4, ρ_c = 1.185 mg m^{-3} , μ = 0.08 mm^{-1}, T = 298(2) K. Of the 12,650 reflections collected, 8389 were unique (R_{int} = 0.0311). Refinement on all data converged at R_1 = 0.0489, wR_2 = 0.1142 (CCDC Deposition Number: CCDC-728374).

2.2.4 Mechanistic aspects

The formation of N,N'-diarylation and N-aryl,N'-formylation results may be rationalized by the mechanism outlined in scheme **18** by considering related reports on copper(I) catalyzed N-arylation (Scheme **18**).[14]

Scheme 18



Initially, the copper(I) halide **43** coordinates with bidentate ligand **33** (**39** or **40**) to form the metal–ligand complex **44**. Subsequent, oxidative addition of aryl halide **7** would give the copper(III) complex **45**. Then, the deprotonated amine **17** or **22** would react with the diamine to form the complex **46**, which on reductive elimination would give the product **18** or **23** and the copper(I) that could participate in the catalytic cycle again. The product **47** could react with DMF **48** in the presence of *t*-BuOK to yield N'-formylated compound **41** or **42** through the intermediate **49**.

2.3 Conclusions

In summary, we have developed an inexpensive convenient *rac*-BINOL **33**/CuBr catalyzed methodology for the synthesis of N,N'-diarylation of *trans*-(1*R*,2*R*)-diaminocyclohexane **17** and (*R*)-1,1'-binaphthyl-2,2'-diamine **22** with various aryl bromides. The products are expected to be useful as ligands for developing new chiral catalyst systems for the application in various asymmetric transformations.

We have also synthesized N-formyl,N'-phenyl-*trans*-(1*R*,2*R*)-diaminocyclohexane **41a** in one pot operation. This protocol has potential for use in the synthesis of unsymmetrically substituted N-alky and N'-aryl chiral C_2-symmetric diamines.

2.4 Experimental Section

2.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr and neat) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 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_6 as solvent and TMS as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Liquid Chromatography (LC) and mass analysis (LC-MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electro Spray Ionization (ESI) techniques. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{\circ}$) and AUTOPOL-IV (readability $\pm 0.001^{\circ}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*R*)-(+)-α-methylbenzylamine $\{[\alpha]_D^{25} = +30.2$ (*c* 10, EtOH)$\}$ supplied by Fluka.

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

All the glassware were pre-dried at 140 °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.

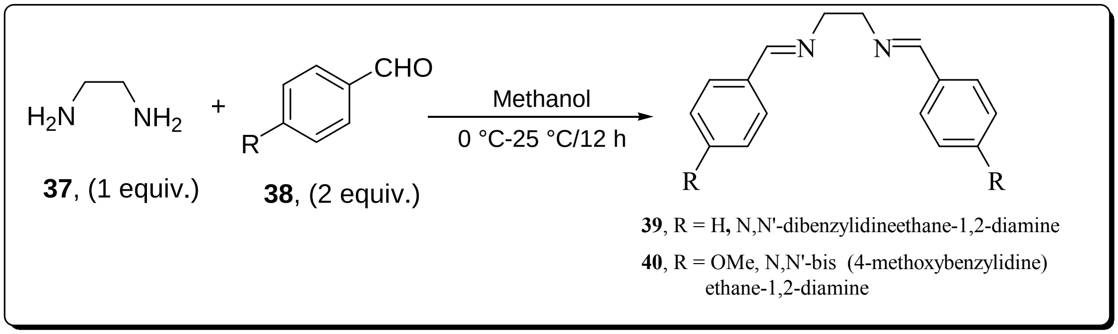
In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All solvents and reagents were used as purchased. 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.

All aryl halides, metal catalysts were supplied by Aldrich chemicals Ltd., were used as purchased. $NaBH_4$ and carbon disulfide were supplied by E-Merck (India). 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.

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).

The *cis*/*trans* mixture of 1,2-diaminocyclohexane was supplied by Across Organics Ltd. It was resolved following a reported procedure to obtain enantio pure *trans*-(1*R*,2*R*)-diaminocyclohexane.[15] (±)-*Bi*-2-naphthol (*rac*-BINOL) and (*R*)-(+)-1,1'-Binaphthyl-2 2'-diamine were supplied by Gerchem Laboratory (Pvt) Ltd., India.

2.4.2 General procedure for the preparation of ethylene diamine based ligands 39 and 40



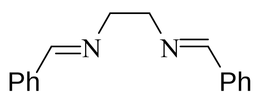
37, (1 equiv.) **38**, (2 equiv.)

39, R = H, N,N'-dibenzylidineethane-1,2-diamine

40, R = OMe, N,N'-bis (4-methoxybenzylidine) ethane-1,2-diamine

To a solution of aryl aldehyde (100 mmol) in methanol (80 mL) was added ethylenediamine (3.61 g, 4.0 mL, 60 mmol) at 0 ^{0}C slowly in drops. Then the contents were brought to room temperature and stirred for 12h. The solvent and excess diamine were evaporated and the crude reaction mixture was evacuated under vacuum. To the residue, CH_2Cl_2 (100 mL) was added, dried using anhydrous K_2CO_3. The solvent was evaporated under high vacuum. The diimines obtained in quantitative yields were pure enough and used in further reactions. The imines were recrystallized from methanol.

N,N'-Dibenzylidineethane-1,2-diamine 39



39

Yield : 10.5 g (89%), colorless solid.

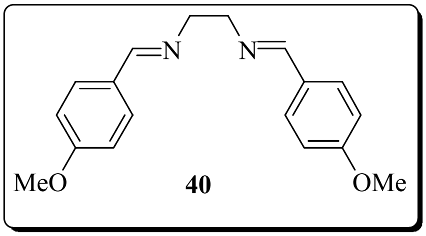
mp : 36-38 ^{0}C (lit. 37-39 ^{0}C).[16]

IR (KBr) : (cm^{-1}) 3024, 2916, 2848, 1653, 1593.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 3.94 (s, 4H), 7.36-7.40 (m, 6H), 7.66-7.3 (m, 4H), 8.16 (s, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$, δ ppm) 61.3, 127.9, 128.2, 130.2, 136.3, 162.4.

N,N'-*Bis* (4-methoxybenzylidine) ethane-1,2-diamine 40



40

Yield : 11.3 g (76%), colorless solid.

mp : 105-107 ^{0}C (lit. 110-111 ^{0}C).[17]

IR (KBr) : (cm^{-1}) 3036, 2919, 2853, 1647, 1602.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 3.81 (s, 6H), 3.93 (s, 4H), 6.89 (d, 4H, *J* = 8.8Hz), 7.63 (d, 4H, *J* = 8.8Hz), 8.23 (s, 2H).

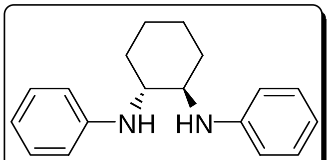
^{13}C NMR : (100 MHz, $CDCl_3$) δ: 55.1, 61.3, 114.2, 129.7, 129.9, 1 61.5, 161.8.

2.4.3 General procedure for the synthesis of N-arylated chiral C_2-symmetric diamines 18a-d and 23a

In a 25 mL two necked flask equipped with air condenser protected by a mercury trap, CuBr (0.014 g, 10 mol %), *rac*-BINOL **33** (0.57 g, 20 mol %), K_3PO_4 (0.64 g, 3 mmol) and DMF (5 mL) were placed under nitrogen. The contents were stirred for 20-30 min at 25 °C. To this, chiral diamine **17** or **22** (0.11 g, 1 mmol) and aryl halide **7a-d** (0.63 g, 4 mmol) were added and stirring was continued for 36 h at 120 °C. The reaction mixture was brought to 25 °C, diluted with 10 mL of ethyl acetate and 5 mL of water and stirred for 10 min at 25 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extract was washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel 100-200 mesh, hexanes/ethyl acetate) to yield the desired product as yellow oil.

trans-(1*R*,2*R*)-N,N'-Diphenylcyclohexane-1,2-diamine 18a

Synthesized following the above general procedure



18a

Yield : 0.21 g (78%).

$[\alpha]_D^{25}$: + 66.3° (*c* = 0.58, benzene), [lit. $[\alpha]_D^{25}$ = + 64.1° (*c* = 0.95, benzene)].[18]

IR (neat) : (cm^{-1}) 3391, 3051, 2930, 1601, 1500.

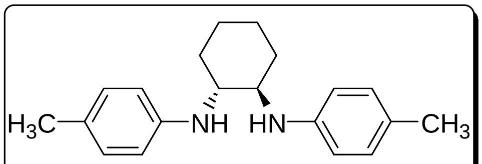
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 1.21–1.24 (m, 2H), 1.32–1.47 (m, 2H), 1.76–1.79 (m, 2H), 2.33–2.36 (m, 2H), 3.17–3.21 (m, 2H), 3.89 (brs, 2H, NH), 6.61–6.63 (m, 4H), 6.69–6.73 (m, 2H), 7.15–7.19 (m, 4H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 24.6, 32.6, 57.3, 113.5, 117.6, 129.3, 147.8

LCMS : (m/z): 267 (M+1).

***trans*-(1*R*,2*R*)-N,N'-Di-*p*-tolylcyclohexane-1,2-diamine 18b**

Synthesized following the above general procedure:



18b

Yield : 0.18 g (61%), colorless gummy liquid.

$[\alpha]_D^{20}$: + 85.7° (*c* = 0.58, benzene), [lit. $[\alpha]_D^{29}$ = + 101.5° (*c* = 0.98, benzene)].[18]

IR (neat) : (cm^{-1}) 3385, 3018, 2928, 1616, 1516, 1300, 808.

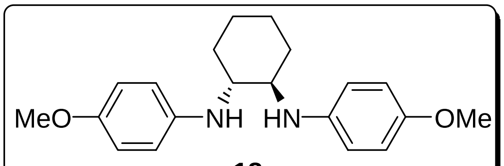
^{1}H NMR : (400 MHz, CDCl$_3$) δ: 1.19–1.21 (m, 2H), 1.37–1.40 (m, 2H), 1.75–1.77 (m, 2H), 2.22–2.24 (d, 6H), 2.31–2.34 (m, 2H), 3.13–3.15 (m, 2H), 3.75 (brs, 2H, NH), 6.53–6.56 (m, 4H), 6.96–7.00 (m, 4H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 20.4, 24.6, 32.6, 57.68, 113.9, 126.9, 129.8, 145.5.

LCMS : (m/z): 295 (M-1).

***trans*-(1*R*,2*R*)-N,N'-*Bis*-(4-methoxyphenyl)-cyclohexane-1,2-diamine 18c**

Synthesized following the above general procedure:



18c

Yield : 0.23 g (71%), colorless gummy liquid.

$[\alpha]_D^{20}$: + 29.2° (*c* = 0.24, CHCl$_3$).

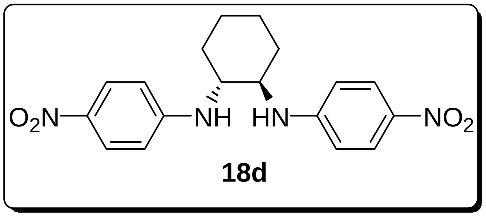
IR (neat) : (cm^{-1}) 3354, 3030, 2993, 1616, 1510, 1037, 819.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 1.4 (m, 2H), 1.76–1.78 (m, 2H), 2.30–2.33 (m, 2H), 3.07–3.09 (m, 2H), 3.68 (brs, 2H, NH), 3.75–3.76 (d, 6H), 6.61–6.64 (m, 4H), 6.78–6.81 (m, 4H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 24.7, 32.6, 55.8, 58.5, 114.9, 115.5.3, 141.9, 152.4.

LCMS : (m/z): 327 (M+1).

***trans*-(1*R*,2*R*)-N,N'-*Bis*-(4-nitrophenyl)-cyclohexane-1,2-diamine 18d**



18d

Synthesized following the above general procedure:

Yield : 0.17 g (49%), yellow solid.

mp : 200-202 °C (lit. 204-206 °C).[19]

$[\alpha]_D^{20}$: + 904. 5° (*c* = 0.34, methanol), [lit. $[\alpha]_D^{20}$ = + 875° (*c* = 0.192, methanol)].[19]

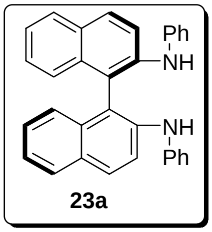
IR (KBr) : (cm^{-1}) 3356, 3084, 2930, 1595, 1527, 1298, 1111, 831.

^{1}H NMR : (400MHz, DMSO-D_6) δ: 1.26–1.33 (m, 2H), 1.36–1.45 (m, 2H), 1.84 (m, 2H), 2.25–2.28 (m, 2H), 3.42 (m, 2H), 5.63 (brs, 2H, NH), 6.53–6.55 (m, 4H), 7.93–7.95 (m, 4H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 24.4, 32.1, 56.3, 111.1, 126.4, 136.9, 153.3.

LCMS : (m/z): 357 (M+1).

(*R*)-N,N'-Diphenyl-1,1′-binaphthyl-2,2′-diamine 23a



23a

Synthesized following the above general procedure

Yield : 0. 36 g (83%), amorphous solid.

$[\alpha]_D^{20}$: + 54. 9° (*c* = 0.15, THF) for 91 % ee [lit. $[\alpha]_D$ = + 63. 4° (*c* = 0.4, THF) for 98 % ee].[7]

IR (KBr) : (cm^{-1}) 3395, 3051, 1936, 1732, 1612, 1591, 1494, 810, 738

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 5.60 (brs, 2H), 6.81–6.97 (m, 6H), 7.12–7.24 (m, 7H), 7.29–7.42 (m, 4H), 7.67–7.89 (m, 5H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 116.4, 117.9, 120.0, 122.2, 123.5, 124.5, 127.1, 128.3, 129.1, 129.3, 129.4, 134.0, 140.4, 142.5.

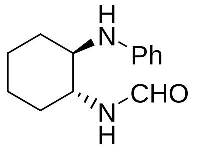
LCMS : (m/z): 267 (M+1); 437 (M+1).

HPLC : on Daicel Chiral Pak AD-H (elution hexane-ethanol 19:1, flow rate: 1 mL/min UV detection at 256 nm) showed 13-91 % ee (t_S = 4.3min, t_R = 5.8 min).[7]

2.4.4 Representative procedure for the synthesis of N-((1*R*,2*R*)-2-(phenylamino)cyclohexyl)formamide 41a

In a 25 mL two necked flask equipped with air condenser protected by a mercury trap, CuBr (0.014 g, 10 mol %), *rac*-BINOL **33** (0.57 g, 20 mol %), *t*-BuOK (0.34 g, 3 mmol) and DMF (5 mL) were placed under N_2. The contents were stirred for 20-30 min. at 25 °C. To this, *trans*-(1*R,*2*R*)-diaminocyclohexane **17** (0.11 g, 1 mmol) and bromobenezene **7a** (0.19 g, 1.2 mmol) were added and stirring was continued for 48 h at 130 °C. The reaction mixture was brought to 25 °C, diluted with 10 mL of ethyl acetate and 5 mL of water and stirred for 10 min at 25 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extract was washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate = 75/25) to yield the desired product.

Physical and spectral data for N-((1*R*,2*R*)-2-(phenylamino)cyclohexyl)formamide 41a



41a

Yield : 0.203 g (93%), colorless solid.

m.p : 106-108 °C.

$[\alpha]_D^{25}$: + 39.4° (*c* = 0.86, $CHCl_3$).

IR (KBr) : (cm^{-1}) 3400, 3333, 3022, 2924, 1635, 1604, 1523, 746, 690.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 1.12–1.27 (m, 2H), 1.30–1.43 (m, 2H), 1.66–1.76 (m, 2H), 2.07–2.10 (m, 1H), 2.24–2.28 (m, 1H), 3.07 (brs, 1H), 3.85-3 (m, 1H), 4.06 (brs, 1H), 5.56 (m, 2H, NH), 6.53–6.58 (m, 2H), 6.63–6.70 (m, 1H), 7.11–7.25 (m, 2H), 8.09 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 24.5, 24.8, 32.5, 32.7, 51.8, 58.0, 112.6, 117.0, 129.3, 147.5, 161.8.

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

Elemental analysis: calcd (%) for $C_{13}H_{18}N_2O$: C 71.53, H 8.31, N 12.83; found: C 71.46, H 8.35, N 12.91.

2.5 References

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Chapter 3

Synthetic Applications of Chiral C_2-Symmetric Diamines: Enantioselective Synthesis of Chiral Propargylamines and Chiral Allenes

3.1 Introduction

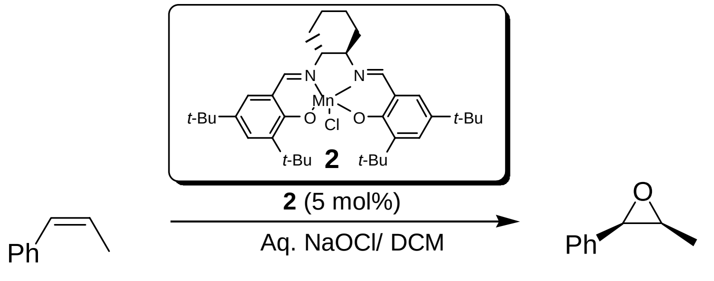
3.1.1 Synthetic applications of chiral 1,2-diamines

Ligands derived from certain C_2-symmetric enantiopure diamines have been widely employed in asymmetric transformations including epoxidation,[1] allylic substitution[2] and hydrogenation reactions.[3] Especially, the chiral *trans*-(1*R*,2*R*)-diaminocyclohexane and its derivatives were widely used in asymmetric synthesis as chiral reagents, scaffolds and as ligands in many organic transformations.[4] A brief review of reports on the use of chiral trans-(1*R*,2*R*)-diaminocylohexane and (*R*)-bi-2-naphthylamine derivatives will facilitate the discussion.

Salen complexes of chiral 1,2-diaminocyclohexane

The Mn(salen) complex **2** and Cr(salen) complex **5** have been used in the asymmestric epoxidation of a variety of olefins and asymmetric epoxide opening reactions respectively (chart **1**).[5-6]

Chart 1

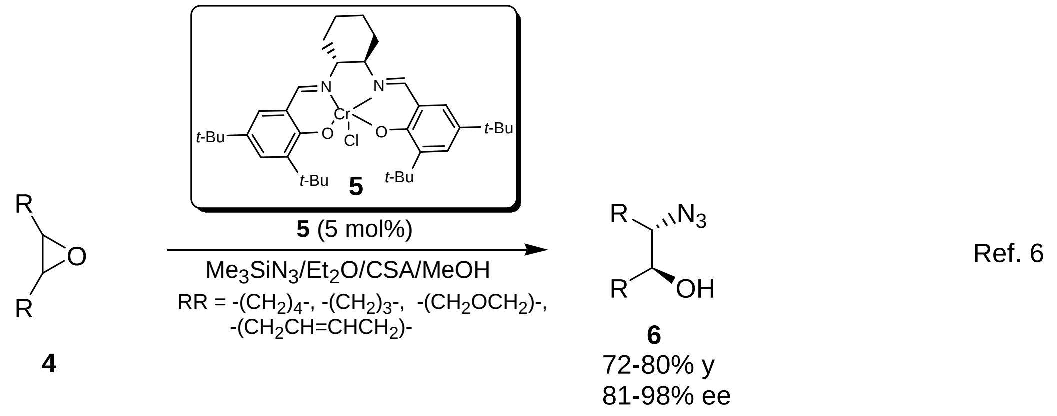


1

3, 81% y, 92-% ee

Ref. 5

Chart 1 continued



Chiral 1,2-diamides

Several C_2-symmetric chiral 1,2-diamide derivatives have been prepared and used as ligands in transition metal catalyzed asymmetric C-C and C-N bond forming reactions (Chart **2**).[7-10]

Chart 2

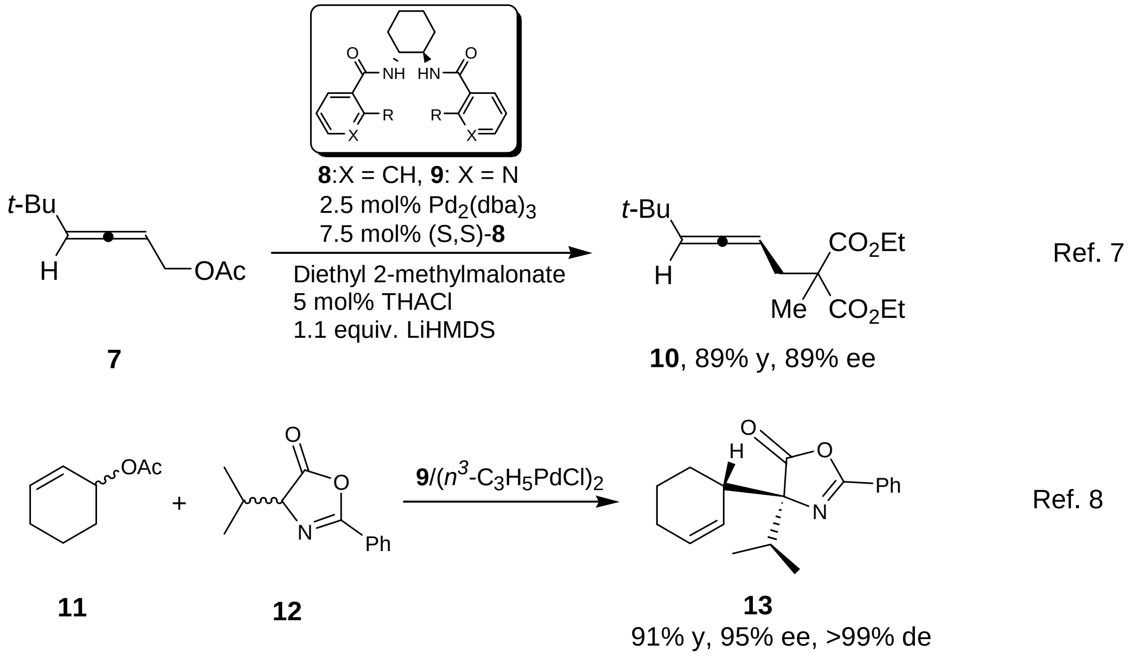
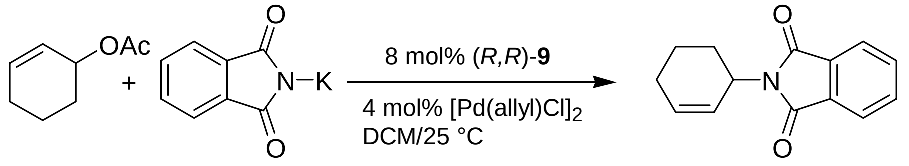
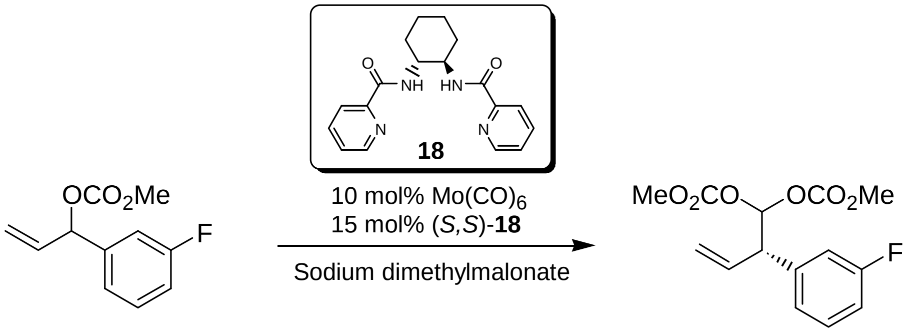


Chart 2 continued



Ref. 9

14 **15** **16**, 99% y, 94% ee



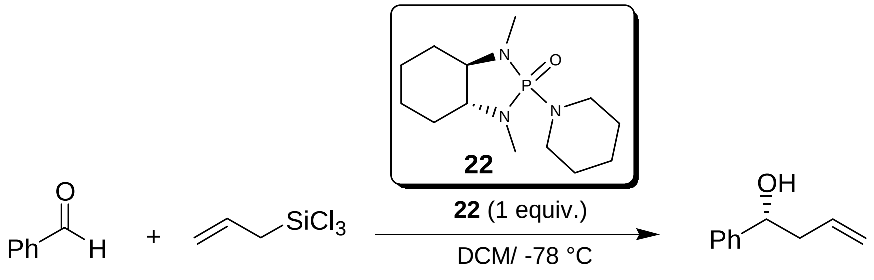
Ref. 10

17 **19**, 90% y, 96% ee

Chiral phosphoramides

Chiral phosphoramide derivatives of C_2-symmetric 1,2-diaminocyclohexane have been used as reagents and catalysts in allylation of aldehydes, diethylzinc addition, asymmetric olefination of ketones and trichlorisilyl enolate addition to aldehydes (chart **3**).[11-13]

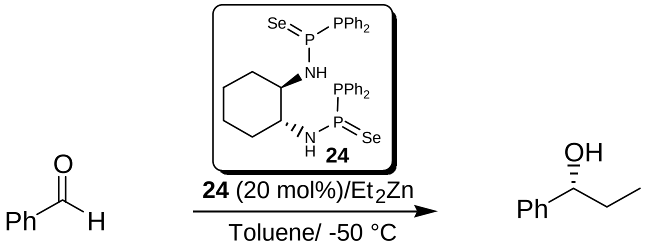
Chart 3



Ref. 11

20a **21** *R*-**23**
81% y, 60% ee

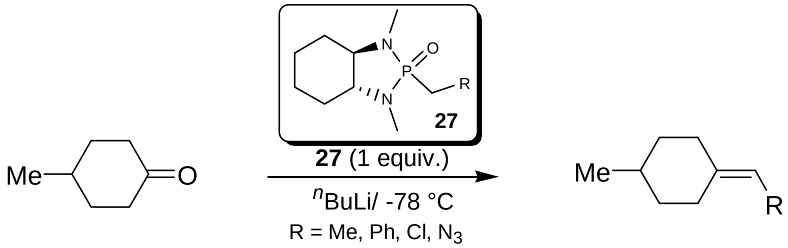
Chart 3 continued



Ref. 12

20a

R-**25**
93% y, 95% ee



Ref. 13

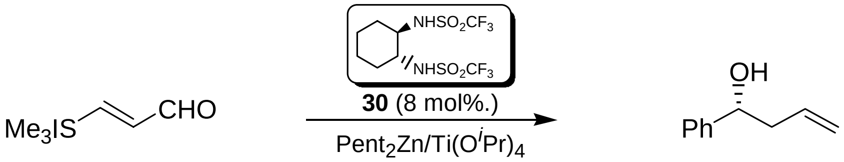
26

28
91% y, >98% ee

Chiral sulfonamides

Chiral bi-sulfonamides have been demonstrated for use as catalysts in various C-C bond forming reactions (chart **4**).[14-18]

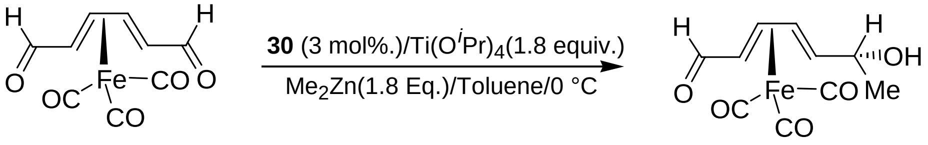
Chart 4



Ref. 14

29

R-**23**
70% y, 92% ee

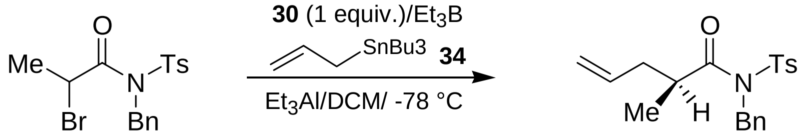


Ref. 15

31

32

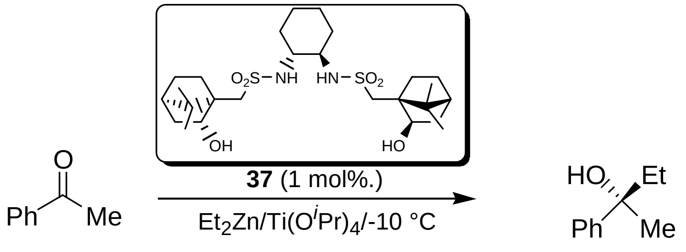
Chart 4 continued



33

S-35
72% y, 53% ee

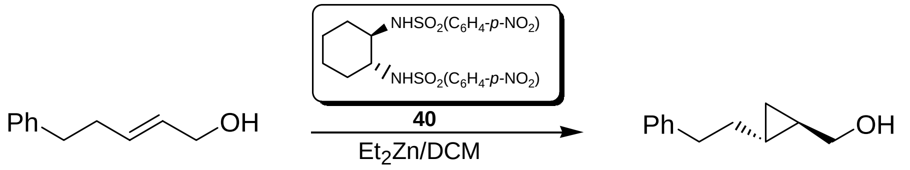
Ref. 16



36

38
71% y, 97% ee

Ref. 17



39

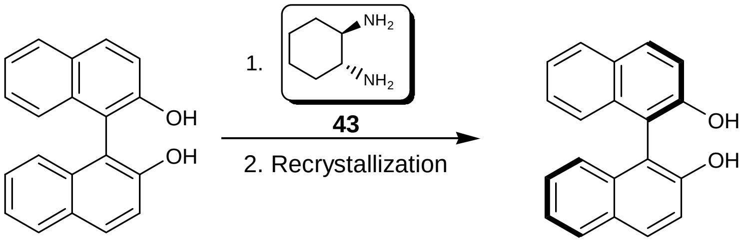
41
100% y, 82% ee

Ref. 18

Chiral 1,2-diamines

Chiral C_2-symmetrical 1,2-diamines containing *trans*-(1*R*,2*R*)-diaminocyclohexane **43** moiety were used in the resolutions of *rac*-BINOL **42**, in enantioselective aldol reactions, asymmetric pinacol coupling and dihydroxylation of alkenes (chart **5**).[19-23]

Chart 5

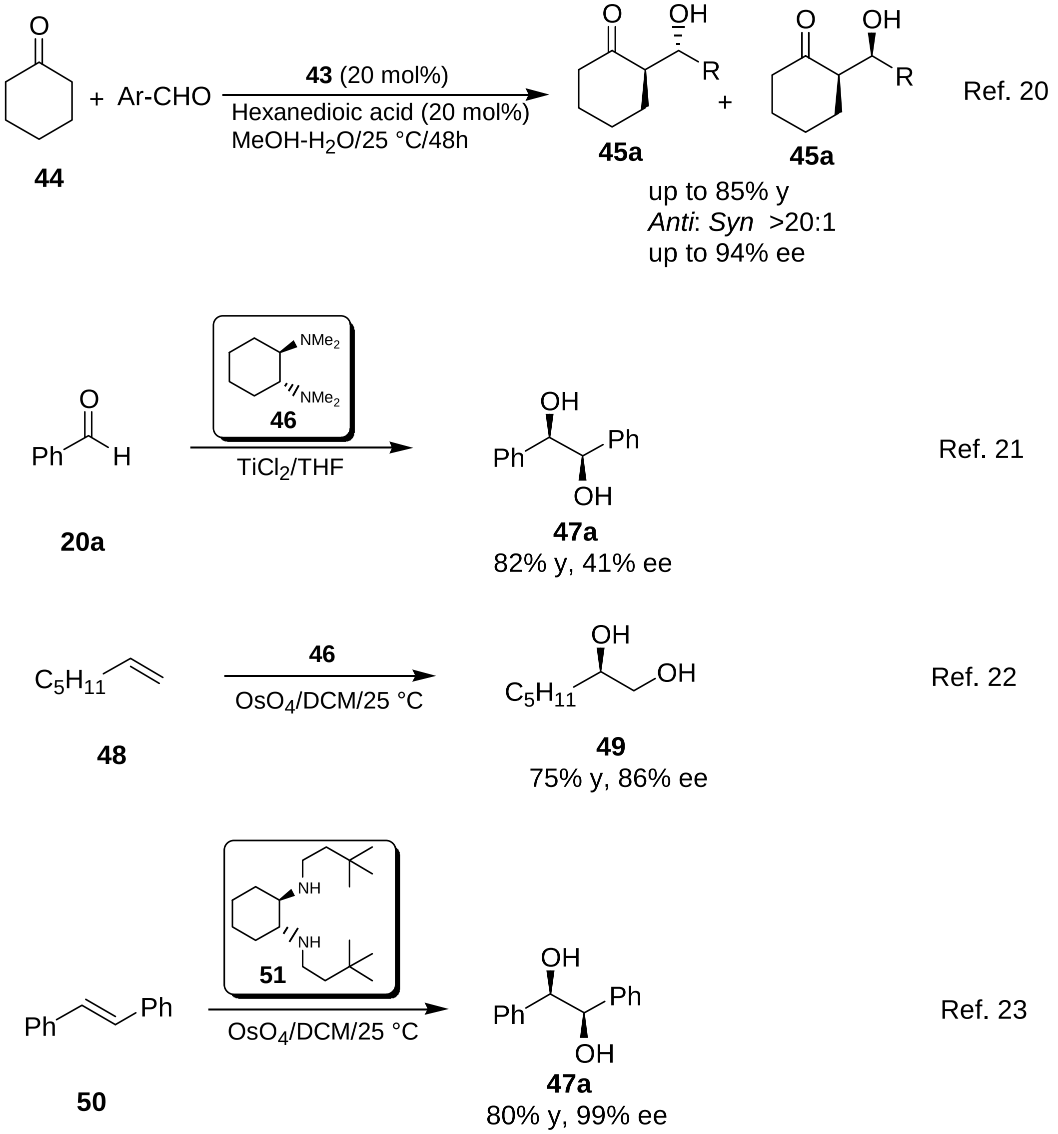


± BINOL **42**

R-BINOL **42**

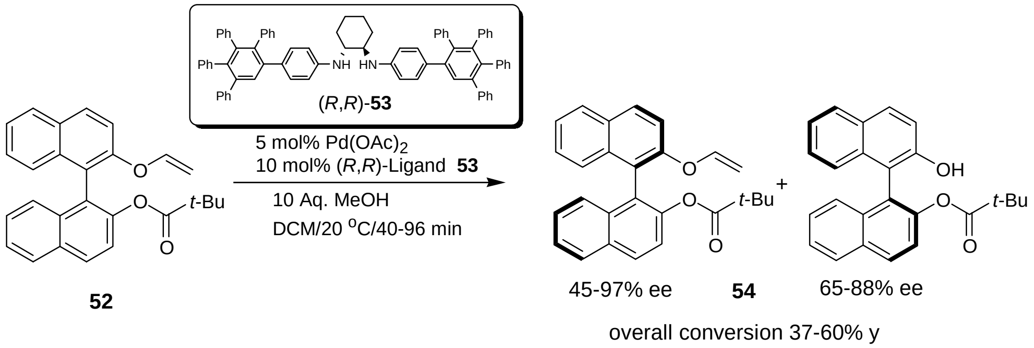
Ref. 19

Chart 5 continued



Kinetic resolution of axially chiral 2,2′-dihydroxy-1,1′-biaryl derivatives by palladium/N,N'-diaryl (1*R*,2*R*)-cyclohexane-1,2-diamine reagent system has been reported (Scheme **1**).[24]

Scheme 1



3.1.2 Synthetic applications of chiral 1,1'-binaphthyl-2,2′-diamine ligands

Configurationally stable 2,2′-substituted 1,1′-binaphthyl derivatives represent one of the most investigated class of chiral compounds.[25] A brief review on the synthetic applications of the 1,1′-binaphthyl-2,2′-diamine would facilitate the discussion (Chart **6**).[26-33]

Chart 6

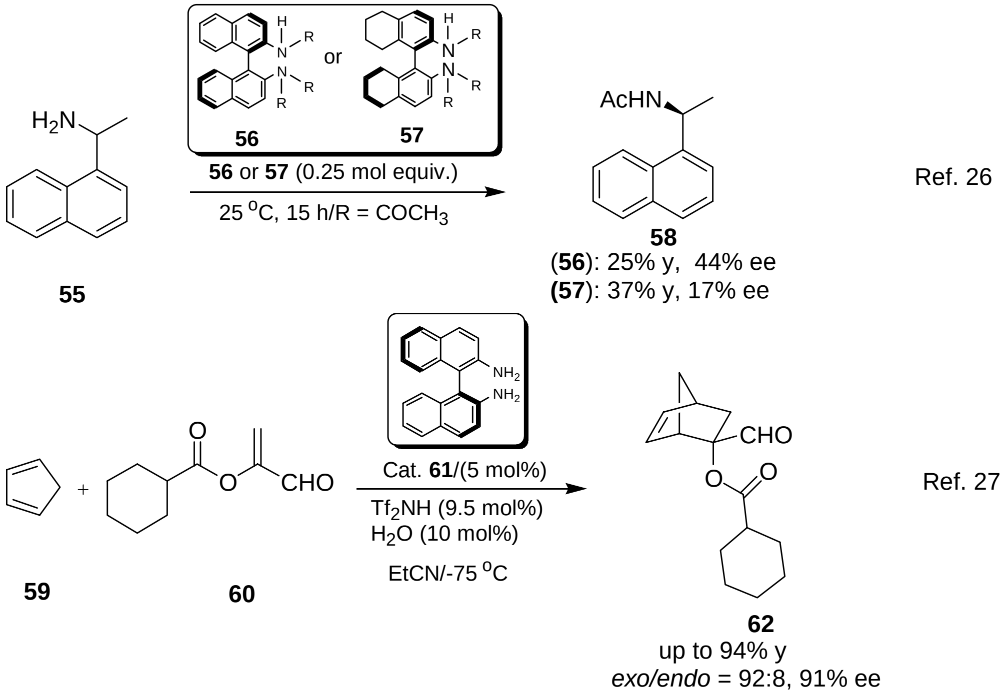


Chart 6 continued

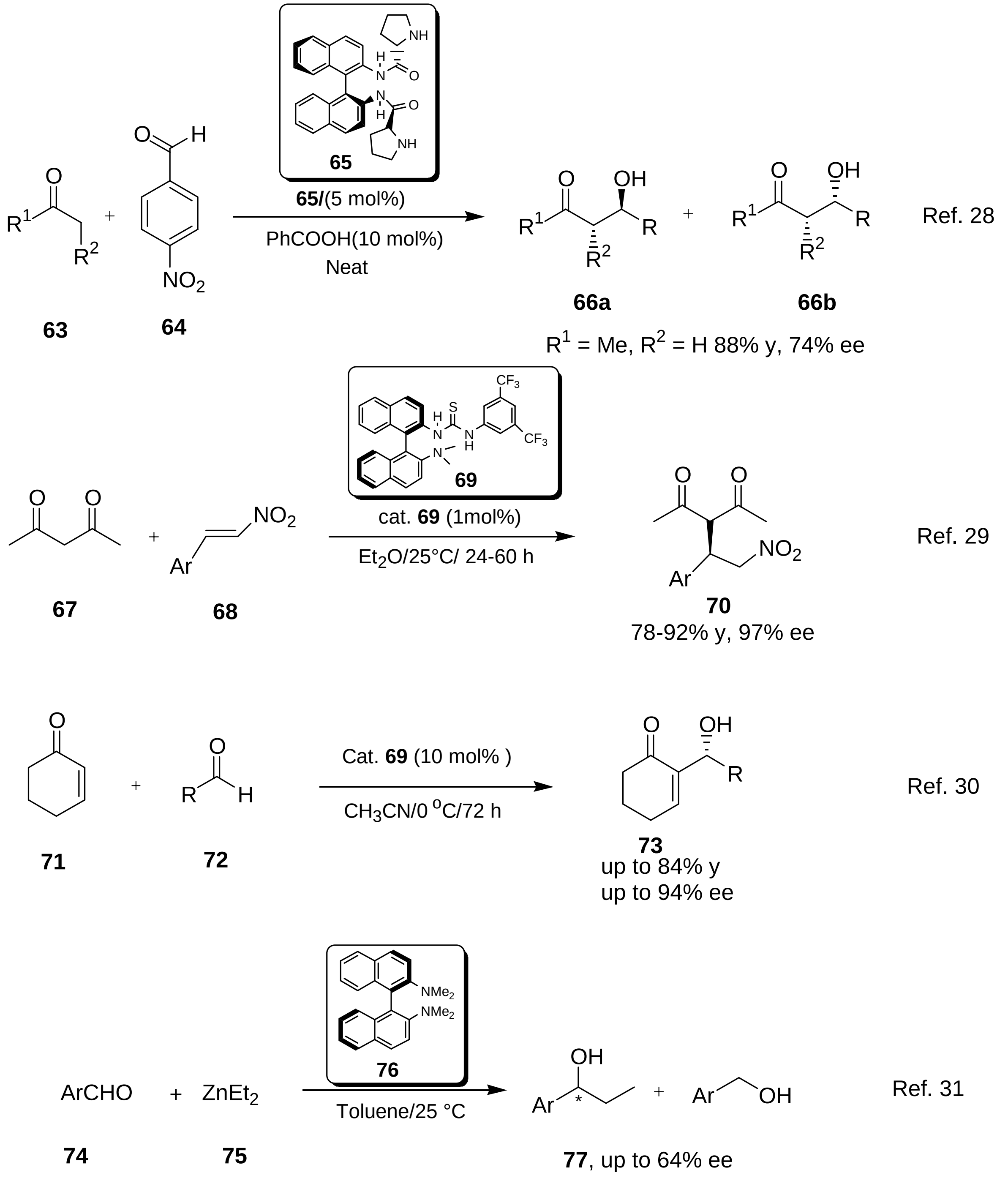
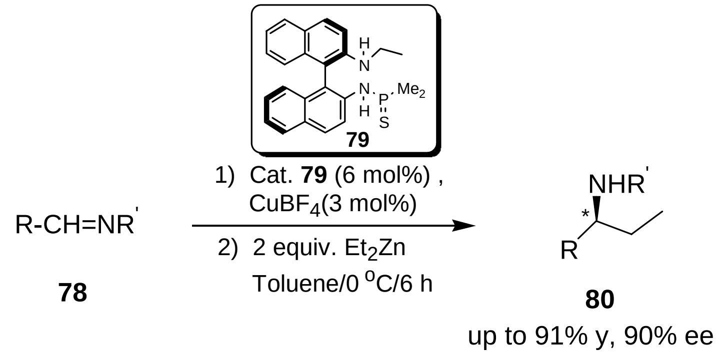
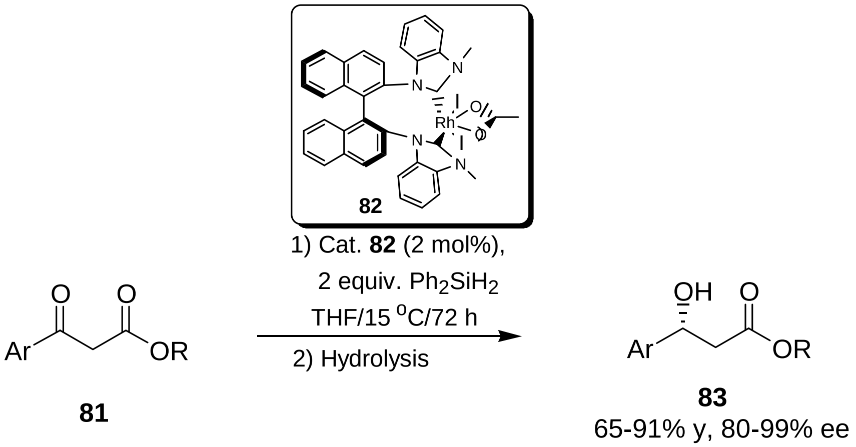


Chart 6 continued



Ref. 32



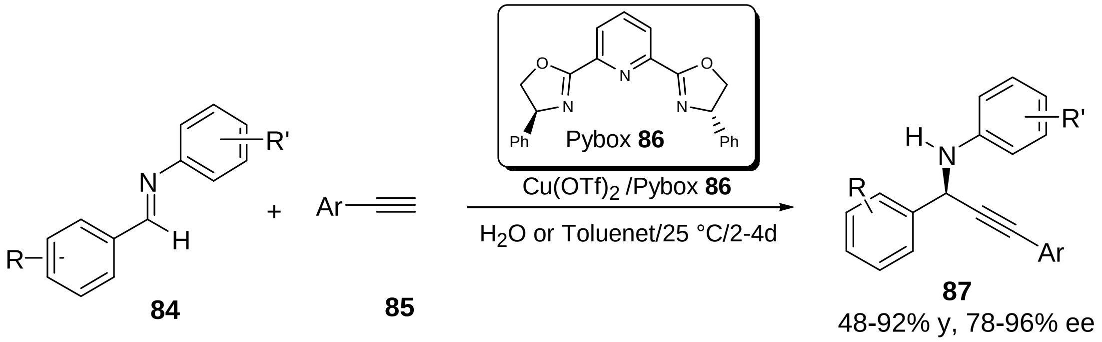
Ref. 33

3.1.3 Methods for the enantioselective synthesis of propargylamines

We describe the investigations undertaken on the methods of synthesis of chiral propargylamines in this chapter. Hence, a brief review of the reports on the methods of synthesis of optically active propargylamines would facilitate the discussion.

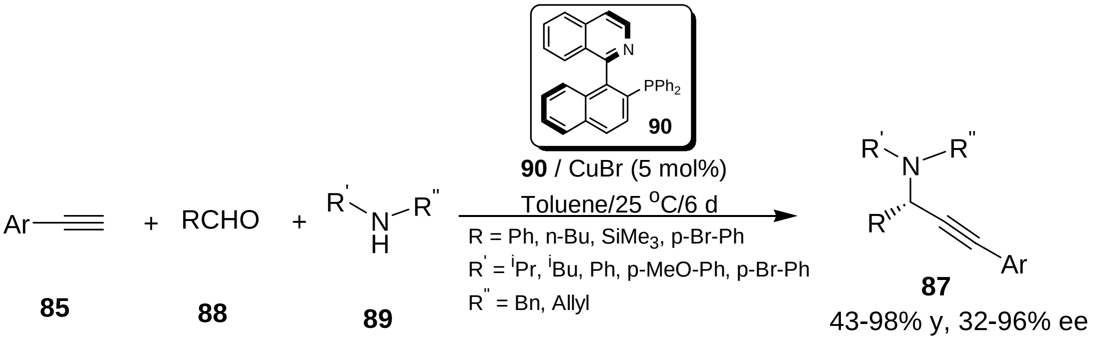
The copper(II) triflate/pybox ligand **86** system has been reported to be useful in catalytic enantioselective synthesis of chiral propargylamines (Scheme **2**).[34]

Scheme 2



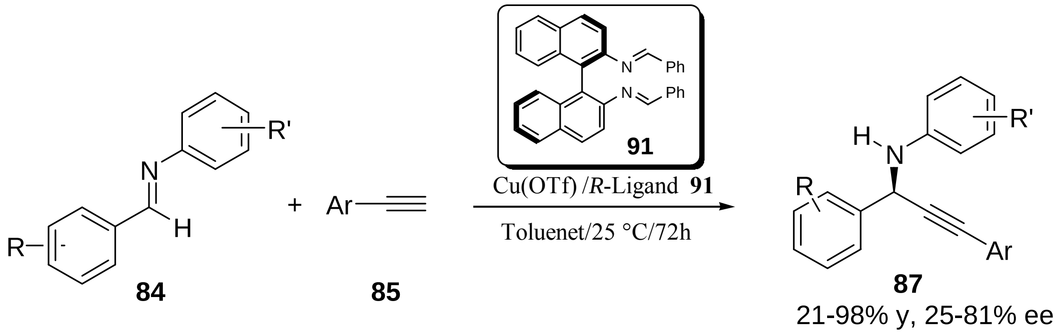
Recently, it has been reported that the reaction of 1-alkyne **85**, aldehyde **88** and secondary amines **89** using CuBr in the presence of the chiral ligand **90** gives the corresponding chiral propargylamine **87** derivatives (Scheme **3**).[35]

Scheme 3



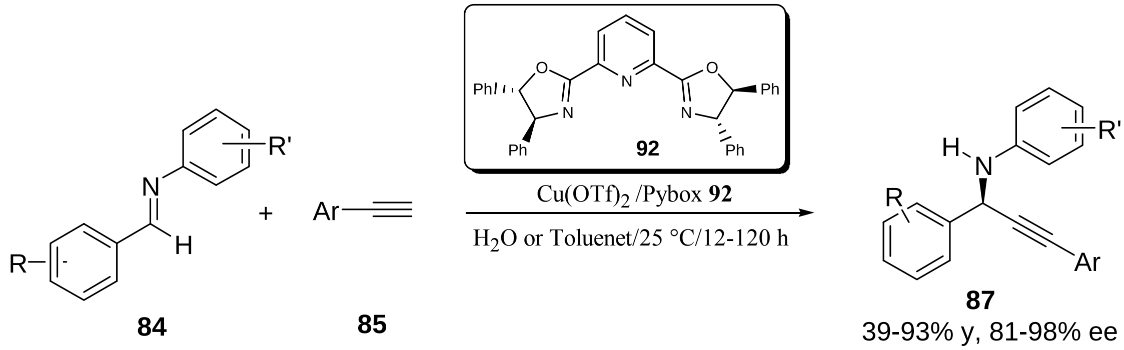
Copper(I) triflate/*R*-N2,N2'-Dibenzylidene-[1,1'-binaphthalene]-2,2'-diamine ligand **91** system is useful for enantioselective synthesis of chiral propargylamines (Scheme **4**).[36]

Scheme 4



Copper(II) triflate/pybox ligand **92** reagent system is also useful for enantioselective synthesis of chiral propargylamines (Scheme **5**).[37]

Scheme 5



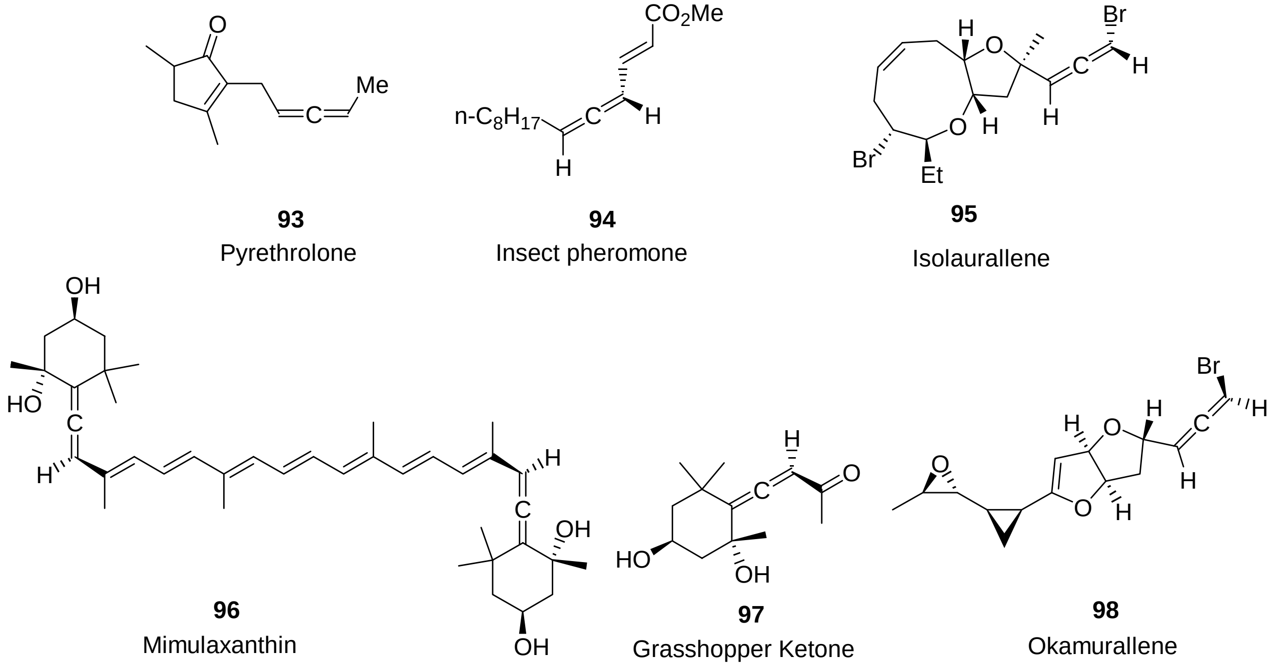
3.1.4 Chiral allenes

In 1875, Jacob van't Hoff predicted the existence of an asymmetrically substituted allene in two enantiomeric forms.[38] The first naturally occuring allene pyrethrolone **93** was characterized by H. Staudinger and L. Ruzicka.[39] Occurrence of allenic structures in a variety of natural products and pharmacologically active compounds have inspired ample interest on developing methods of synthesis of chiral allenes among organic and medicinal chemists.[40] Allenes are much more reactive than most other alkenes. For example, their reactivity with gaseous chlorine is more like the reactivity of alkynes than that of alkenes.

Since results of investigations on the synthesis of enantiomerically enriched allenes are described in this chapter, a brief review of literature reports on allene chemistry would facilitate the discussion.[40]

Chiral allenic natural products

In the last few years, many natural products containing chiral allene moiety were isolated (Fig. **1**).[42]



93
Pyrethrolone

94
Insect pheromone

95
Isolaurallene

96
Mimulaxanthin

97
Grasshopper Ketone

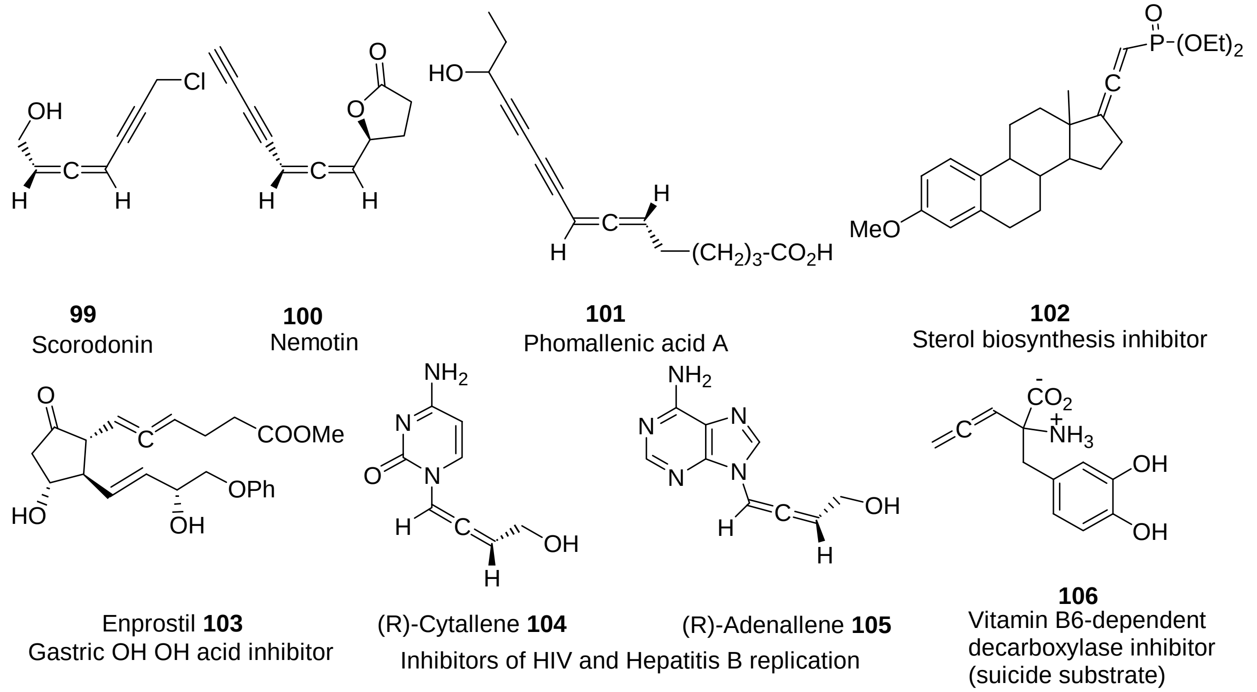
98
Okamurallene

Figure 1

Biologically active chiral allenes

Allenic derivatives not only occur in nature but also have considerable potential as pharmacologically active molecules. For example, the compounds scorodonin **99**, nemotin

100 and phomallenic acid **101** have inhibiting effects on the growth of bacteria, yeasts and filamentous fungi. Other allenic moieties with such inhibiting effects are sterol biosynthesis inhibitor **102**, gastric acid inhibitor **103**, HIV inhibitor **104**, hepatitis B replication inhibitor **105** and vitamin B_6-dependent decarboxylase inhibitor (suicide substrate) **106** (Fig. **2**).[42,43]



99 Scorodonin

100 Nemotin

101 Phomallenic acid A

102 Sterol biosynthesis inhibitor

Enprostil **103** Gastric OH OH acid inhibitor

(R)-Cytallene **104**

(R)-Adenallene **105**

Inhibitors of HIV and Hepatitis B replication

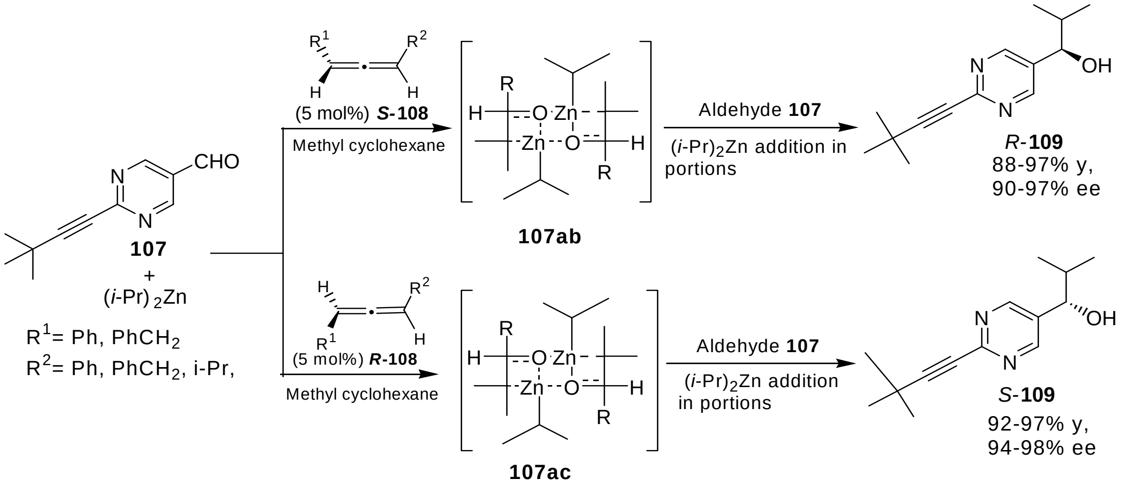
106 Vitamin B6-dependent decarboxylase inhibitor (suicide substrate)

Figure 2

3.1.5 Synthetic applications of axially chiral allenes

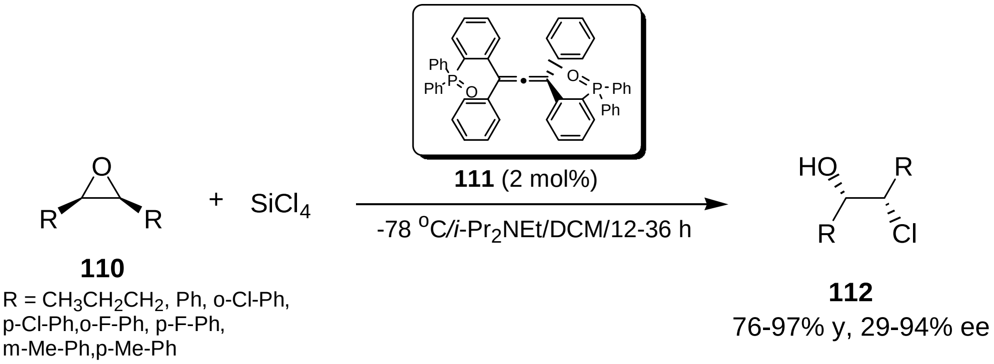
1,3-Disubstituted chiral allenes *R*-**108** and *S*-**108** act as chiral initiators in the addition of (*i*-Pr)$_2$Zn to pyrimidine-5-carbaldehyde **107** to afford the chiral pyrimidin-5-yl alkanols *R*-**109** and *S*-**109**. Subsequent autocatalysis by the resulting alkoxide intermediates **107ab** and **107ac** leads to the formation of chiral pyrimidin-5-yl alkanols after workup with up to 98% ee (Scheme **6**).[44]

Scheme 6



cis-Stilbene oxides **110** react with SiCl$_4$ and ^{i}Pr$_2$NEt in the presence of chiral allene containing *bis*-phosphine oxide moiety **111** to give the corresponding chlorohydrins **112** in 97% yield with up to 94% ee (Scheme **7**).[45]

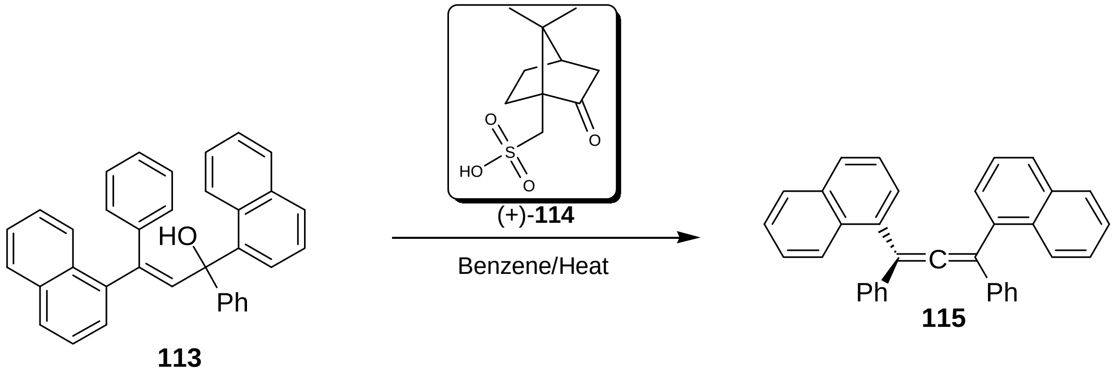
Scheme 7



3.1.6 Methods for the synthesis of axially chiral allenes

In 1935, P. Maitland and W. H. Mills proved the van't Hoff's prediction of allene chirality by synthesizing the chiral **115** by dehydration of the corresponding allylic alcohol **113** in the presence of (+)-camphor-10-sulfonic acid **114** (scheme **8**).[46]

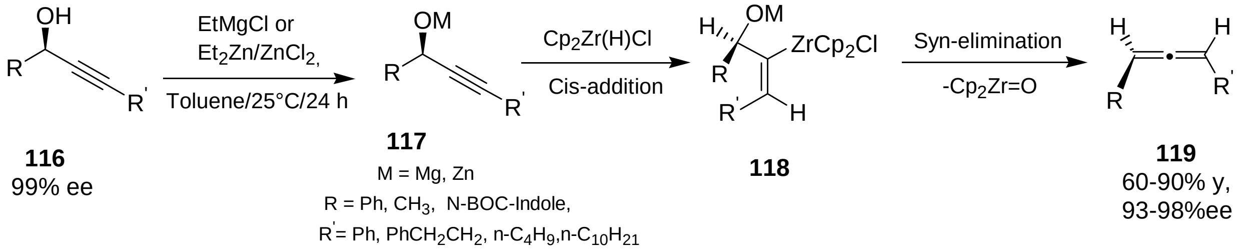
Scheme 8



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

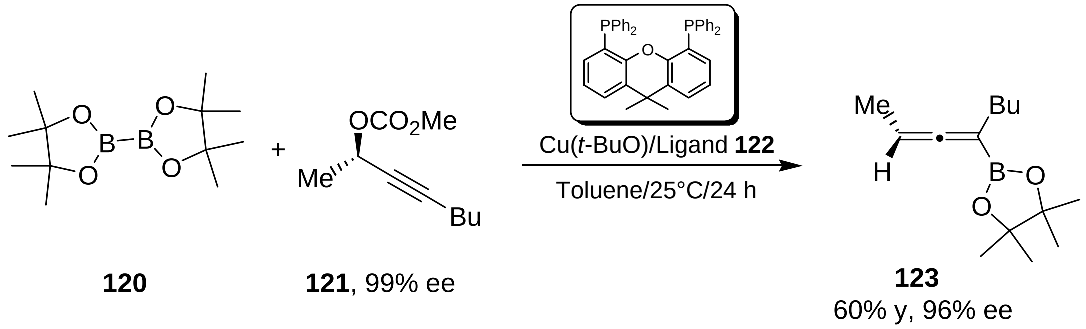
Hydrozirconation of propargylic derivative **117** generated *in situ* by the reaction of organomagnasium or organozinc with propargylic alcohols **116** by Cp$_2$Zr(H)Cl furnishes the allenes **119** in good yields with high optical purities (Scheme **9**).[47]

Scheme 9



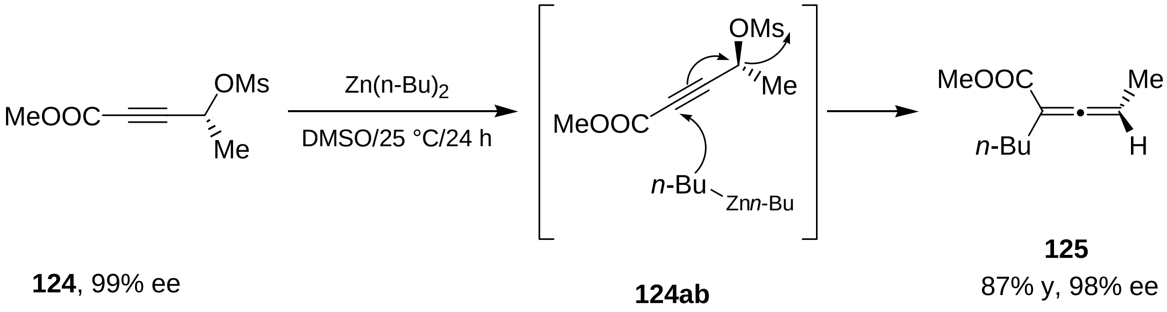
The Cu(*t*-BuO)/triarylphosphine reagent system is useful for the stereoselective substitution of propargylic carbonates **121** with bis(pinacolato)diboron **120** to give the boroallene **123** with 96% ee (Scheme **10**).[48]

Scheme 10



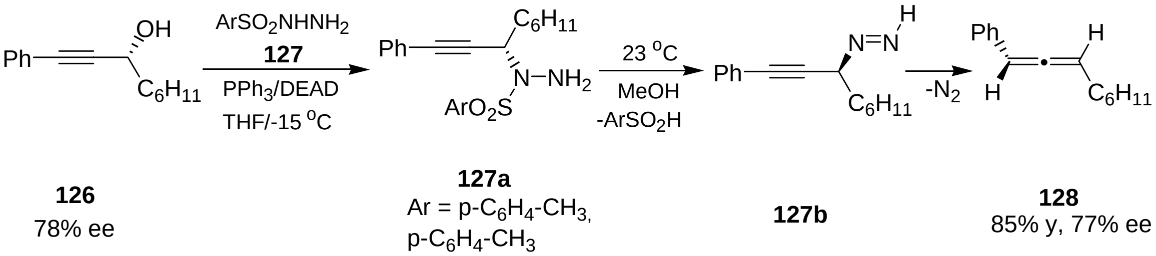
The S_N2' reaction of propragyl mesylates **124** with organozinc reagents gives the chiral allene **125** in 87% yield with up to 98% ee (Scheme **11**).[49]

Scheme 11



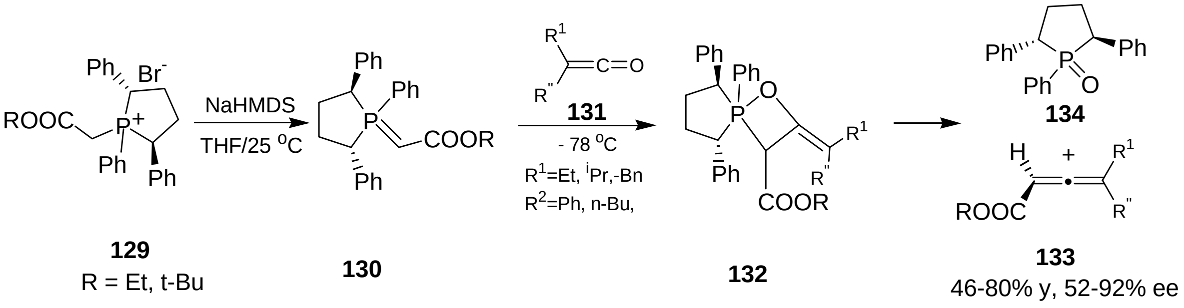
A method for the preparation of axially chiral allene **128** (77% ee) from the chiral propargylic alcohol **126** (78% ee) by using aryl sulphonamide **127** under Mistunubu reaction conditions has been reported (Scheme **12**).[50]

Scheme 12



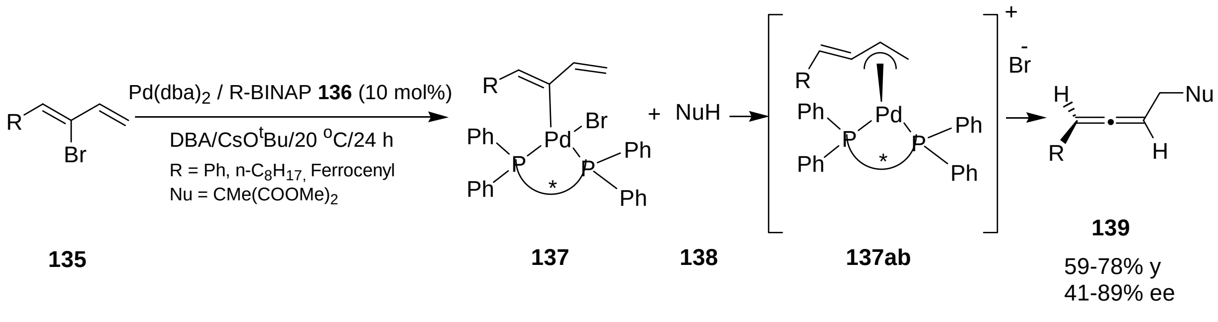
Highly enantioselective synthesis of allenic esters **133** by the condensation of pseudo *C*$_2$-symmetrical chiral phosphorus ylides **130** with various ketenes **131** using NaHMDS as base at -78 °C has been reported.[51] The chiral phosphine oxide **134** was recovered without loss in its optical purity (Scheme **13**).

Scheme 13



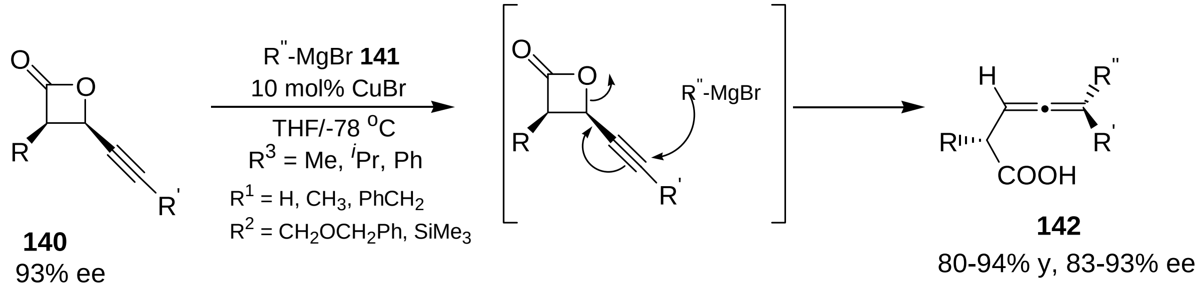
A novel route to enantiomerically enriched axially chiral allenes **139** was reported *via* the reaction of achiral conjugated dienes **137** with nuchleophiles catalyzed by a palladium-BINAP **136** complex (Scheme **14**).[52]

Scheme 14



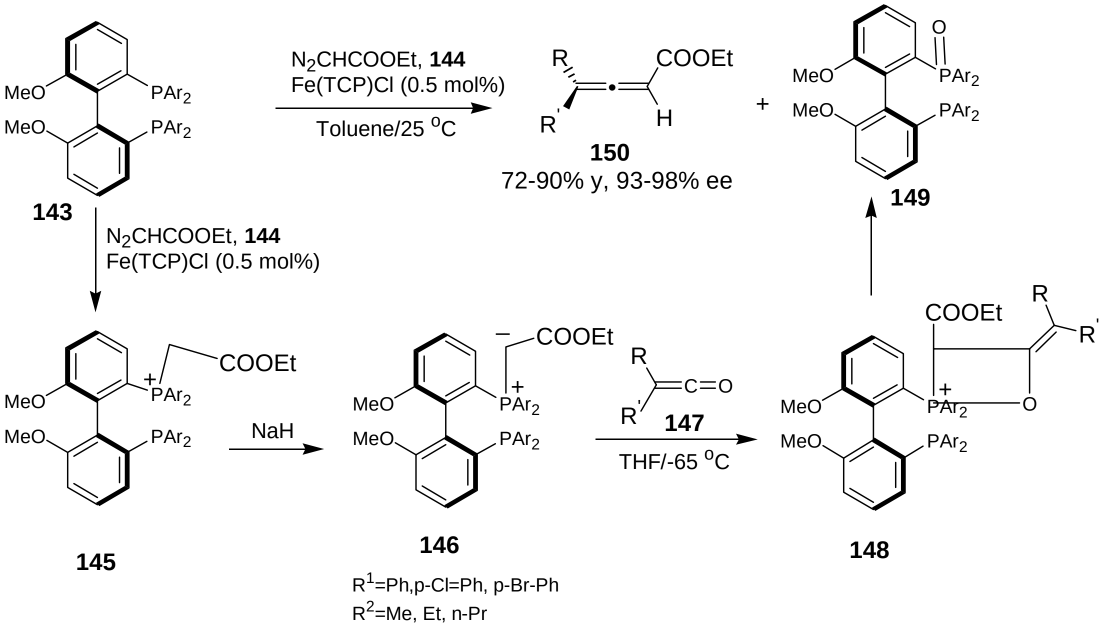
The S$_N$2' ring opening reaction of β-lactones **140** provides an efficient and operationally simple enantioselective synthesis of *di*- and *tri*-substituted allene derivatives **142** using various Grignard reagents **141** (Scheme **15**).[53]

Scheme 15



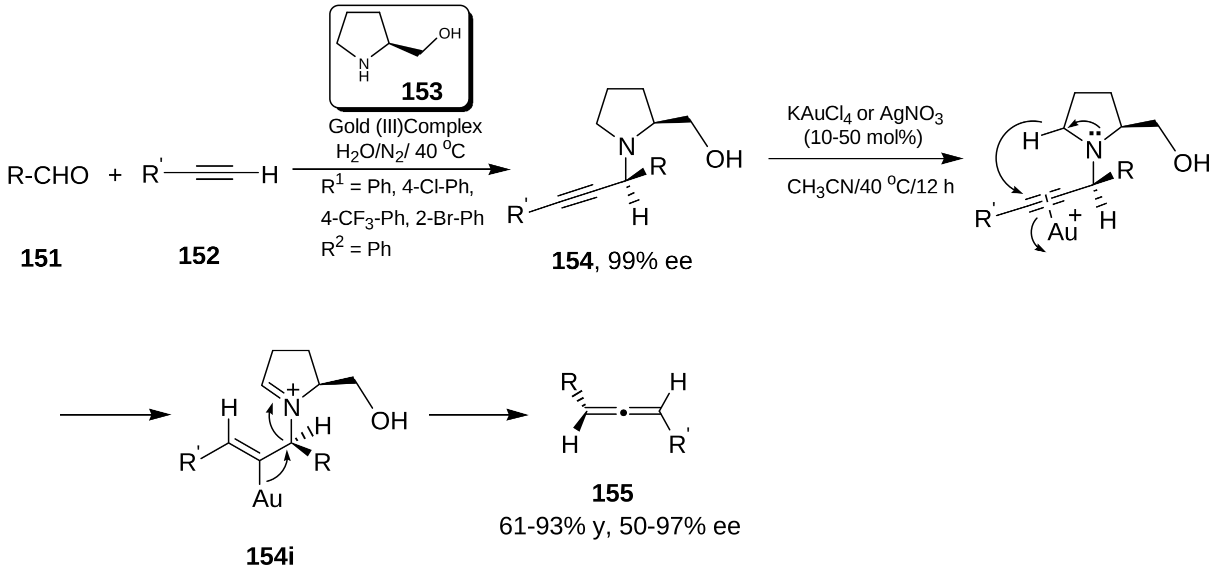
An efficient method for the synthesis of chiral allenes **150** by olefination of ketenes **147** with ethyl diazoacetate (EDA) **144** in the presence of chiral phosphine **145-**Fe(TCP)-Cl catalyst system has been reported (Scheme **16**).[54]

Scheme 16



Chiral propargyl amines **154**, prepared using various aldehydes **151**, 1-alkynes **152** and chiral amine **153** using a gold(III)-salen complex, have been reported to yield axially chiral allenes **155** (50-97% ee) under $KAuCl_4$ or $AgNO_3$ catalysis in CH_3CN at 40 °C (Scheme **17**).[55]

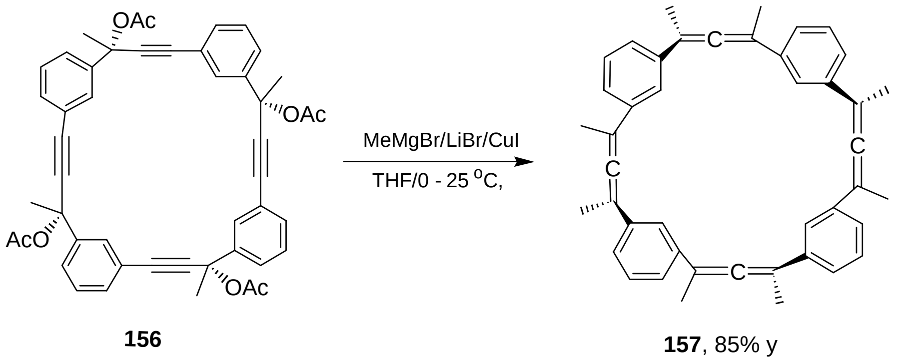
Scheme17



3.1.7 Synthesis of chiral allenophane macrocycles

Allenyl macrocycles are useful as chiral ligands and as hosts for metal ions and small guest molecules. The chiral allenophane **157** was prepared by organocuprate mediated S_N2' coupling reaction with optical active cyclic propargyl acetates **156** (Scheme **18**).[56]

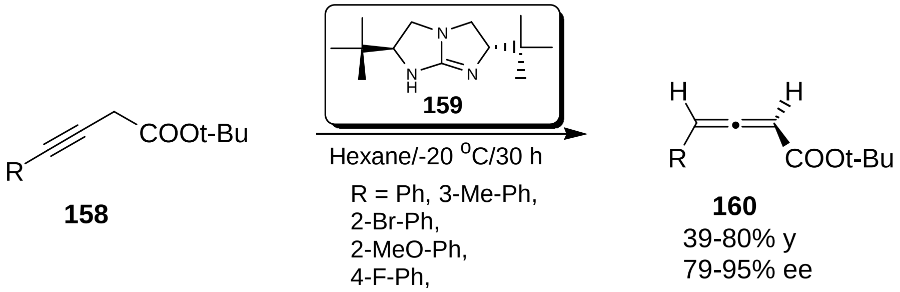
Scheme 18



3.1.8 Synthesis of chiral allenes using organo catalytic methods

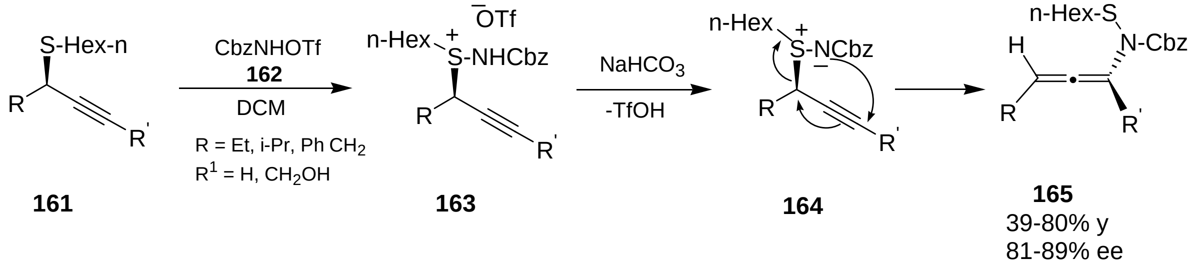
Chiral bicyclic guanidine **159** has been reported to catalyze the isomerization of highly reactive alkyne derivatives **158** to chiral allenoates **160** with 79-95% ee (Scheme **19**).[57]

Scheme 19



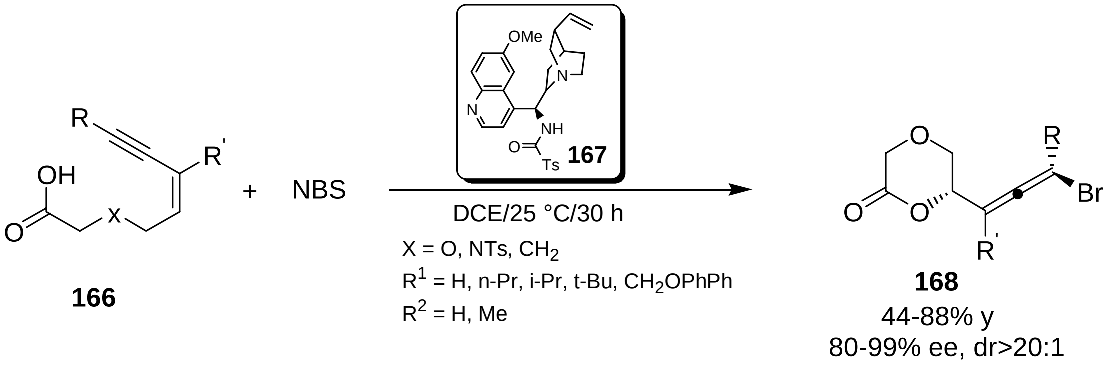
Chiral allenamides **165** were prepared with high levels of enantiomeric purity by [2,3]-sigmatropic rearrangement of propargylic sulfides **161** and the amide derivative **162** (Scheme **20**).[58]

Scheme 20



The bifunctional cinchonidine catalyst **167** promotes the highly enantioselective bromolactonization of conjugated (*Z*)-enynes **166** to give the versatile bromoallenes **168** containing lactone moiety with high optical purity (Scheme **21**).[59]

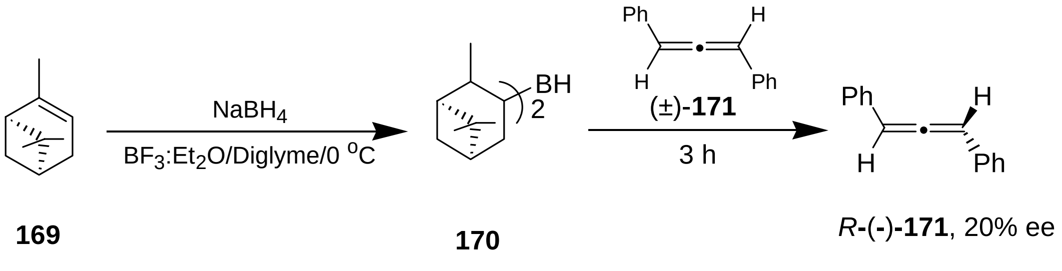
Scheme 21



3.1.9 Synthesis of enantiomerically enriched chiral allenes by kinetic resolution

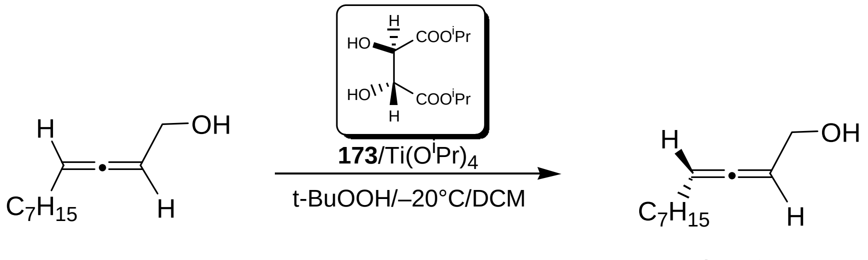
Kinetic resolutions of racemic allenes is an alternative method to access enantiomerically enriched allenes. Hydroboration of (-)-α-pinene **169** using $NaBH_4$ and $BF_3{:}Et_2O$ in diglyme leads to (+)-$(Ipc)_2BH$ **170**, a highly stereoselective hydroborating agent. The (+)-$(Ipc)_2BH$ reagent **170** hydroborates (±)-allenes **171** to give the *R*-(-)-allene **171** with low optical purity (Scheme **22**).[60]

Scheme 22



The titanium-catalyzed epoxidation of racemic allenic alcohol was reported in 1983.[61] Oxidation of racemic allene **172** under the widely used Sharpless epoxidation conditions, i.e with Ti(O^{i}Pr)$_4$, (+)-diisopropyl tartrate **173** [(+)-DIPT], and t-BuOOH, gives the (*S*)-(+)-allene **172** with 40% ee (Scheme **23**).

Scheme 23

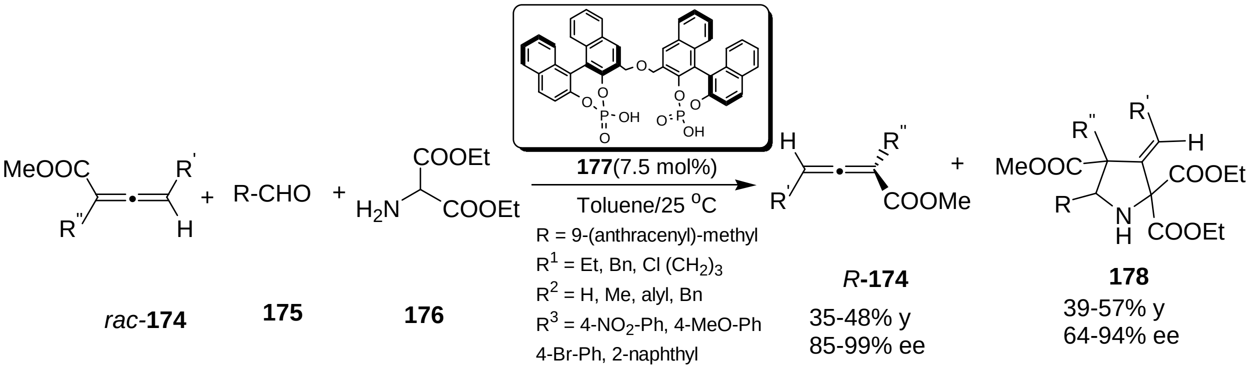


rac-**172**

S-**172**
60% y, 40% ee

Very recently, chiral bisphosphoric acid **177** catalyzed kinetic resolution of racemic 2,3-allenoates **174** via 1,3-dipolar cycloaddition has been reported. In this way, optically active 2,3-allenoates **174** with (*R*)-configuration are obtained in 35-48% yield with 85-99% ee, besides the 3-methylene pyrrolidine derivative **178** (Scheme **24**).[62]

Scheme 24



rac-**174** **175** **176**

R-**174**
35-48% y
85-99% ee

178
39-57% y
64-94% ee

We have undertaken research efforts on the development of methods for the synthesis of chiarl propargylamines and chiral allenes. The results are described in the next section.

3.2 Results and Discussion

3.2.1 Enatioselective synthesis of acyclic mono propargylamines

We have prepared a series of chiral ligands **179**, **180**, **181**, **76** and **91** based on the chiral cyclohexly diamine **43** and bi-2-naphthyl diamine **61** moieties. As outlined in the introductory section, some of these chiral skeletons were employed as chiral ligands for the enantioselective synthesis of propargylamines (Fig. **3**).

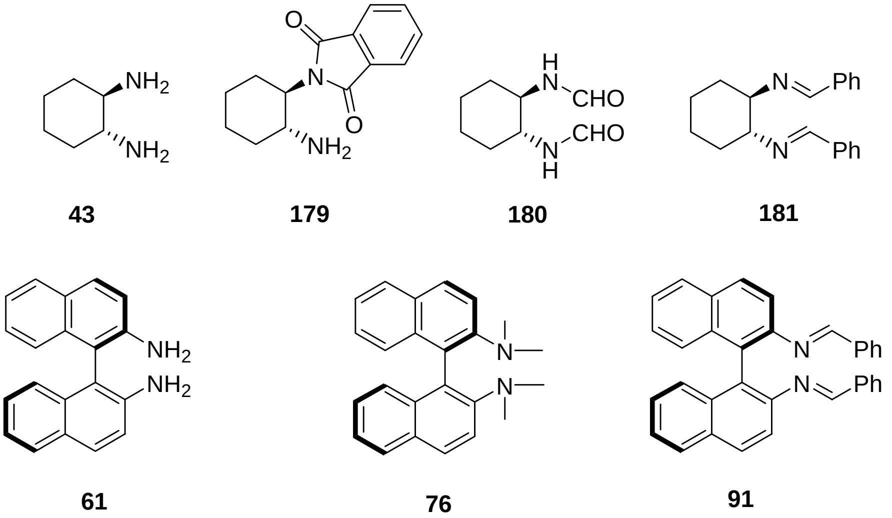


Figure 3

Initially, a set of experiments were carried out using copper complexes of these ligands with the (*E*)-N-benzylideneaniline **84a** and phenylacetylene **85a** as model substrates for the synthesis of propargylamine **87a** (Scheme **25**). The reaction was further optimized by using various reaction parameters like temperature, solvent, base, ligand and copper catalyst (Table **1**). Whereas the reaction does not took place in CCl_4, toluene/CCl_4, and toluene/MeCN solvent systems (Table **1**, Entries 5, 8 and 10). Among several solvents tested, toluene/DCM solvent system gave the optimum 92% ee with moderate yields 76%

Scheme 25: Synthesis of propargylamine **87a**

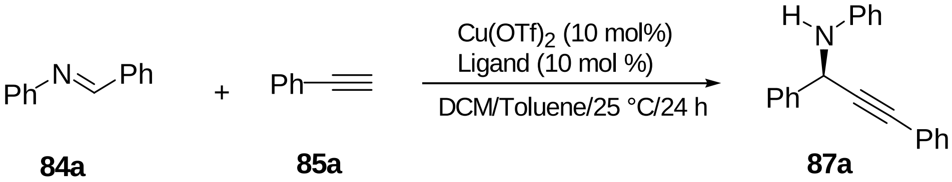


Table 1: Optimization of the condition for the synthesis of optically active propargylamine[a]

Entry	Copper source	Ligand	Solvent System	Yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	**61**	Toluene	65	61
2	$Cu(OTf)_2$	**61**	DCM	77	33
3	**$Cu(OTf)_2$**	**61**	**$CHCl_3$**	**76**	**92**
4	$Cu(OTf)_2$	**61**	DCE	50	63
5	$Cu(OTf)_2$	**61**	CCl_4	NR	NR
6	**$Cu(OTf)_2$**	**61**	**Toluene/DCM**	**78**	**92**
7	$Cu(OTf)_2$	**61**	Toluene/$CHCl_3$	64	87
8	$Cu(OTf)_2$	**61**	Toluene/CCl_4	NR	NR
9	$Cu(OTf)_2$	**61**	Toluene/DCE	95	66
10	$Cu(OTf)_2$	**61**	Toluene/CH_3NO_2	35	26
11	$Cu(OTf)_2$	**61**	Toluene/CH_3CN	NR	NR
12	$Cu(OTf)_2$	**61**	Toluene/THF	64	73
13	$Cu(OTf)_2$	**61**	Toluene/MeOH	23	11
14	$CuBr_2$	**61**	Toluene/DCM	76	0
15	CuO_2	**61**	Toluene/DCM	62	0
16	$Cu(OAc)_2$	**61**	Toluene/DCM	79	0
17	$Cu(OTf)_2$	**43**	Toluene/DCM	28	0
18	$Cu(OTf)_2$	**179**	Toluene/DCM	64	0
19	$Cu(OTf)_2$	**180**	Toluene/DCM	82	0
20	$Cu(OTf)_2$	**181**	Toluene/DCM	72	3
21	$Cu(OTf)_2$	**76**	Toluene/DCM	95	0
22	**$Cu(OTf)_2$**	**91**	**Toluene/DCM**	**98**	**93**

[a]Unless noted otherwise, all the reactions were carried out with Cu(II) source (10 mol %), Ligand (10 mol %) benzylidene-phenyl-amine **84a** (1 mmol), phenylacetylene **85a** (2 mmol), Toluene (3 mL) and DCM (2 mL) for 24 h at 25 °C. [b]All the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. [c]ee was confirmed by HPLC analysis (chiralcel OD-H column) using hexane and isopropanol as eluents and the compared with reported $[\alpha]_D^{25}$ value.

(Table **1**, Entry 3). Whereas, other solvents like dry DCM, $CHCl_3$ and DCE gave yields up to 95% but with low enantioselectivity. We have also tried the combination of toluene and DCM as solvent system for performing the reaction with ligand **91** and obtained the product in 95% yield and 92% ee. Likewise, we have also screened a mixture of toluene and other solvents DCM, $CHCl_3$, CCl_4, DCE, $MeNO_2$, MeCN, THF and MeOH. The propargylamine **87a** was obtained in moderate yield and ee in DCM, toluene/$MeNO_2$ and toluene/MeOH (Table **1**, Entries 2, 10 and 13). The toluene/DCM solvent system with the **61** and or **91**/$Cu(OTf)_2$ reagent system gave optimum results (Table **1**, Entries 6 and 22). Among metal sources, $Cu(OTf)_2$ gave optimum results. The chiral ligands **61** and **91** both were found to be good ligands for this transformation (Scheme **25** and Table **1**).

This reagent system is also useful for the conversion of other substituted aryl imines and phenyl acetylene to the corresponding propargylamines (Scheme **26**). *p*-Methoxy substituents on both aryl aldehydes and aryl amine moiety gave moderate results (Table **2**, Entries 3 & 5) compared to halide substituents (Table **2**, Entries 2 & 4). Unfortunately, use of imines prepared using aliphatic amines and aldehydes and alkyl substituted 1-alkynes did not give the desired products.

Scheme 26: Synthesis of various propargylamines **87a-e**

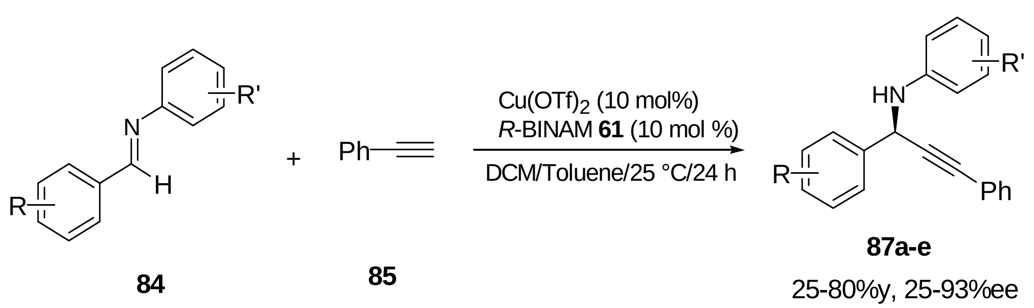
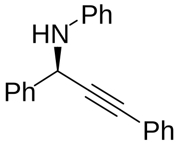
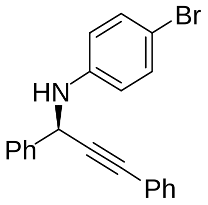
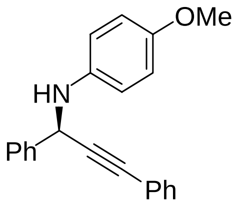
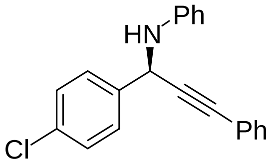
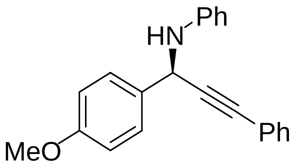


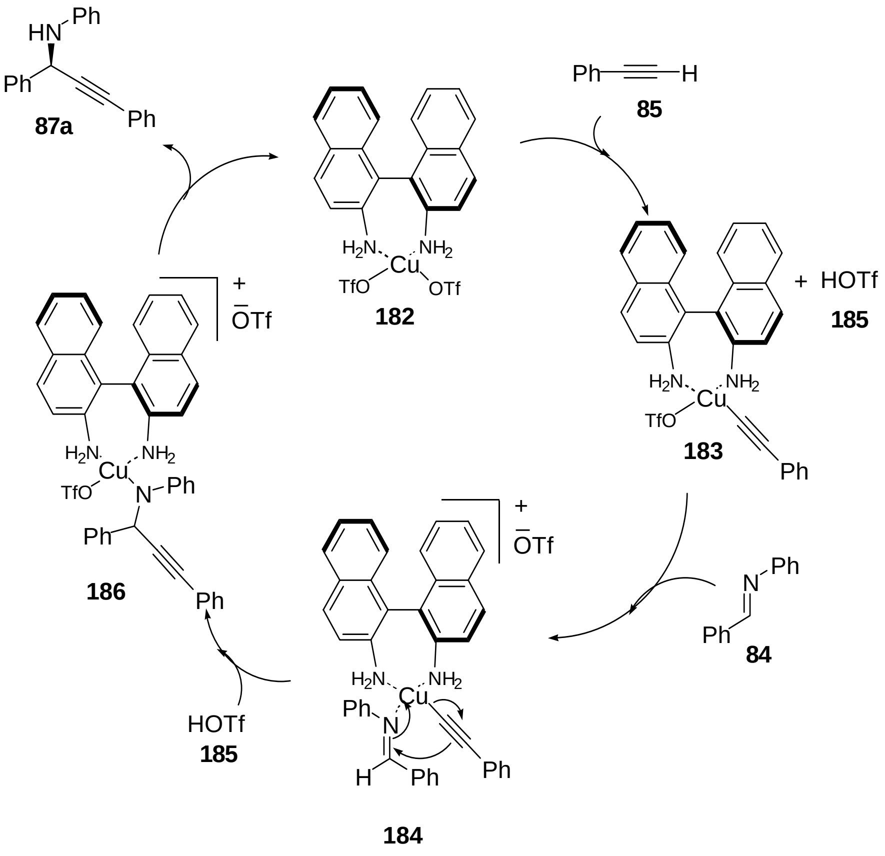
Table 2: Synthesis of various propargylamines **87a-e**[a]

Entry	Imine **84**	Product		Yield (%)[b]	ee (%)[c]
1	R' = H, R = H		**87a**	98	93
2	R' = *p*Br, R = H		**87b**	30	25
3	R' = *p*OMe, R = H		**87c**	95	60
4	R' = H, R = *p*Cl		**87d**	19	20
5	R' = H, R = *p*OMe		**87e**	25	77

[a] Unless noted otherwise, all the reactions were carried out with $(CuOTf)_2$ (10 mol %), R-BINAM **61** (10 mol %) imine **84** (1 mmol), alkyne **85** (2 mmol), Toluene (3 mL) and DCM (2 mL) for 24 h at 25 °C. [b] All the products **87a-e** were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. [c] ee was confirmed by HPLC analysis (chiralcel OD-H or AD-H columns) using hexane and isopropanol as eluents.

Based on the previous reports[63] on similar transformations, a tentative mechanism as outlined in Scheme **27** may be considered for this transformation. The chiral ligand would bind to the copper source to give the complex **182** which on further add to alkyne **85** to give the complex **183**. The polarization of copper with imine **84** gives the complex **184** which in turn would rearranges *in situ* to give the complex **186**, which on elimination will give the desired product **87a** and complex **182** and cycle continuous (Scheme **27**).

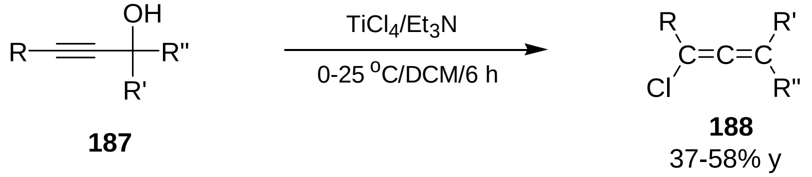
Scheme 27



3.2.2 Previous reports on chiral allene synthesis from this laboratory

Previously, efforts were undertaken in this laboratory towards the synthesis of allenes. It was found that the reaction of propargylic alcohol **187** with the $TiCl_4/Et_3N$ reagent system gave the corresponding racemic chloroallenes **188** (Scheme **28**).[64]

Scheme 28



Also, methods were reported on the enantioselective synthesis of chiral allenes via ZnX_2 promoted reaction of 1-alkyne **189** and arylaldehyde **190** using several chiral amine systems (Chart **7**).[65,66]

Chart 7

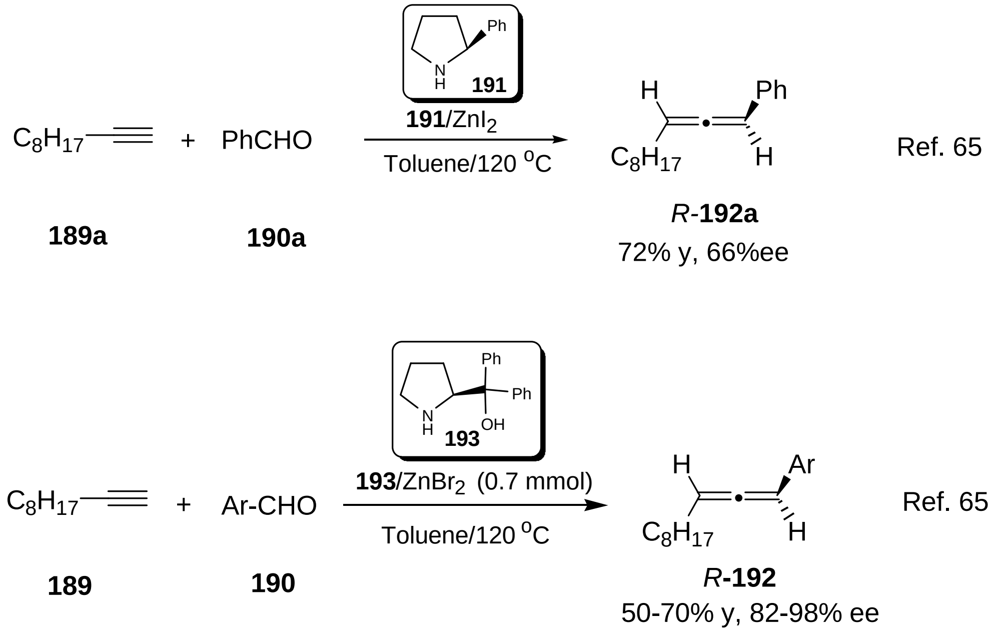
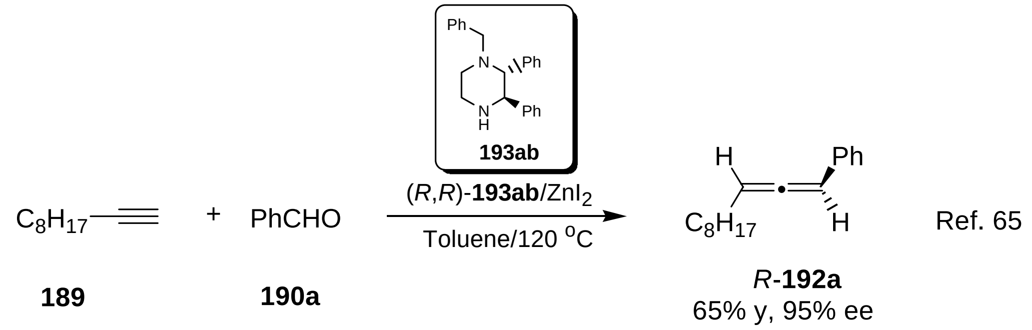
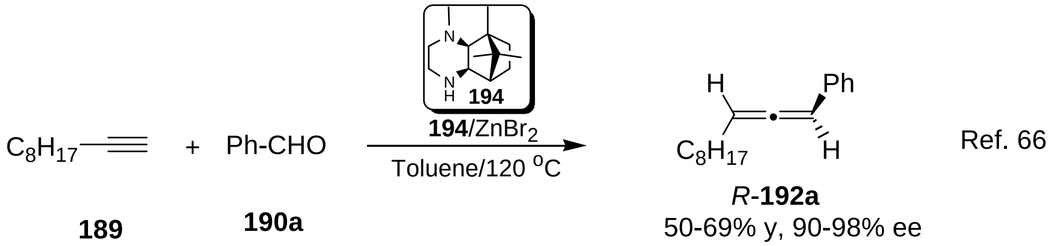
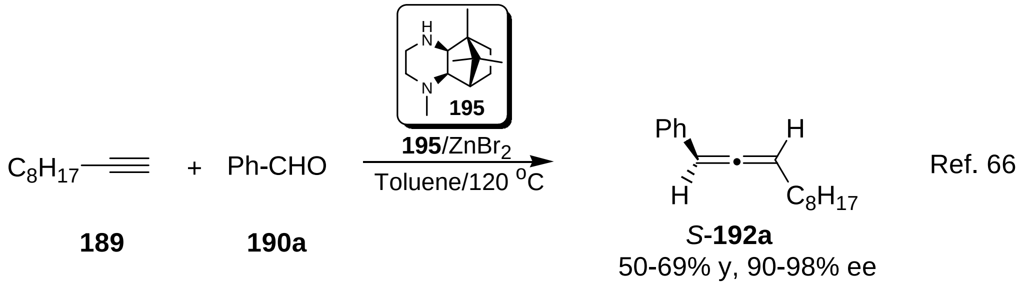


Chart 7 continued



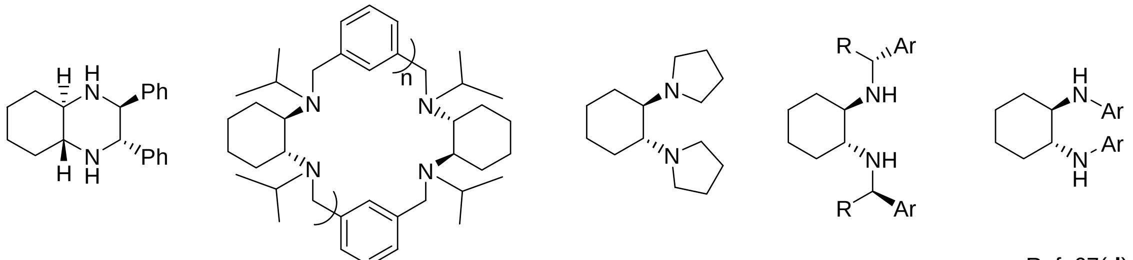




However, methods for accessing optically pure allenes are still very few and often involve expensive reagents. In the reported procedures, several steps are required to make various chiral amine derivatives. Therefore, the development of cost effective method for preparation of optically pure allenes by using easily accessible reagents is still a challenging research topic. We were looking for simple, convenient and one-pot methods for enantiopure allene synthesis using the readily accessible chiral 1,2-diamine derivatives. The results of these studies are discussed in the next section.

3.2.3 Synthesis of *trans*-(1*R*,2*R*)-diaminocyclohexane derivative 198

In recent years, methods were developed in this laboratory to access several chiral diaminocyclohexane derivatives (Fig. **4**).[67]

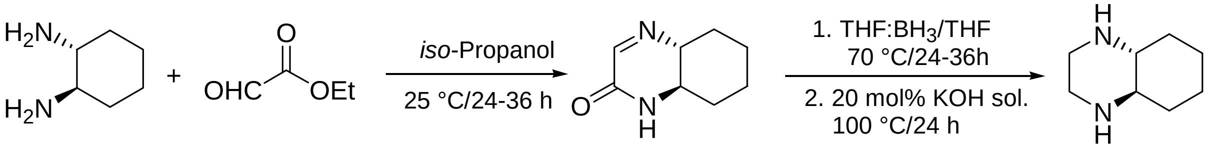


Ref. 67(**a**) Ref. 67(**b**) Ref. 67(**b**) Ref. 67(**c**) Ref. 67(**d**)

Figure 4

We have developed a method to access the chiral C_2-symmetric decahydroquinoxaline **198** containing *trans*-(1*R*,2*R*)-diaminocyclohexane **43** moiety following the synthetic methods outlined in Scheme **29**.[68]

Scheme 29



43 **196** **197,** 96% y **198**, 89% y

We have decided to examine the efficacy of the chiral C_2-symmetric secondary diamine **198** for the highly enantioselective synthesis of ***bis-propargylamines*** and ***allenes*** using aromatic aldehydes and 1-alkynes promoted by Lewis acids.

3.2.4 Highly enantioselective synthesis of axially chiral allenes

As outlined in the introductory section, axially chiral allenes can be readily accessed from 1-alkynes **189**, aldehydes **190**, certain secondary amines and ZnX_2 in toluene.[69] We have examined the efficacy of the chiral decahydroquinoxaline **198** in the preparation of axially chiral allenes from 1-alkynes **189**, aldehydes **190** and ZnI_2 in toluene (Scheme **30**).

Scheme 30

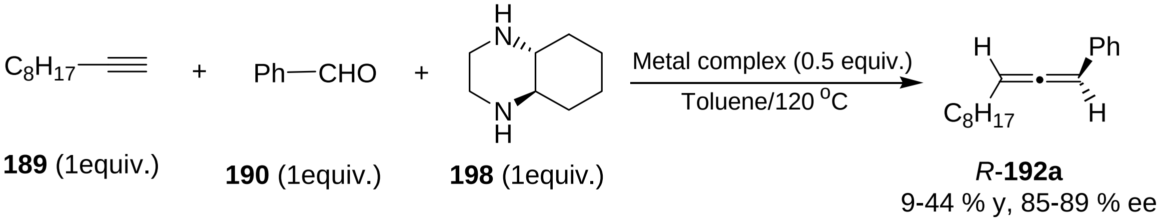


Table 3: Optimization of the reaction conditions[a]

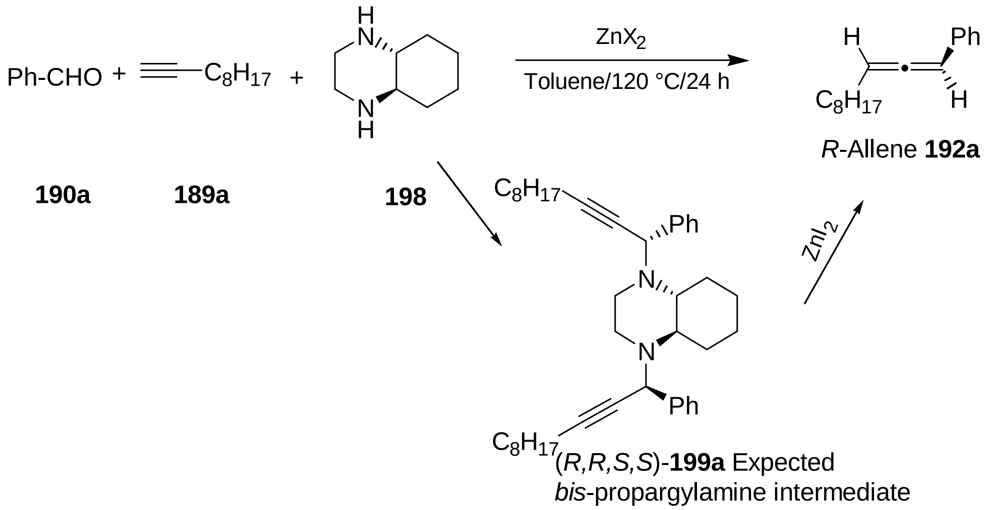
Entry	Metal complex	Ligand	mmol	Time (h)	Yield (%)[b]	ee (%)[c]
1	CuBr	**198**	0.5	24	9	88
2	$Cu(OTf)_2$	**198**	0.5	24	33	89
3	$ZnBr_2$	**198**	0.5	24	25	85
4	ZnI_2	**198**	0.5	24	44	89

[a] All the reactions were carried out with chiral diamine **198** (1 mmol), 1-Decyne **189** (2 mmol), Zinc halide at 110°C in toluene for 15min. followed by addition of benzaldehyde **190a** (2 mmol) at 130 °C. [b] Isolated yield of product **192a**. [c] ee was confirmed by HPLC analysis (chiralcel OD-H column) using hexane as eluent and the compared with reported $[\alpha]_D^{25}$ value.[70]

The corresponding chiral *R*-allene **192a** was obtained in 9% yield and 88% ee with chiral diamine **198** and CuBr (Table **3**, Entry 1). The allene **192a** was obtained using $Cu(OTf)_2$ in 33% yield and 89% ee with chiral diamine **198** (Table **3**, Entry 2), 25% yield and 85% ee with chiral diamine **198** and $ZnBr_2$ (Table **3**, Entry 3). The use of ZnI_2 with chiral diamine **198** gave the *R*-allene **192a** in 44% yield and 89% ee (Table **3**, Entry 4).

The allene product **192a** would be formed *via* formation of the corresponding chiral propargylamine intermediate **199a** as outlined in Scheme **31**. A probable reason for obtaining low yield may be due to the formation of *bis*-propargylamines **199** with chiral diamine **198** which could result in steric hindrance in the transition state for the formation of ligand and ZnI_2 complex leading to low conversion of the *bis*-propargylamine **199a** to allene **192a** .[71]

Scheme 31



Accordingly, we have undertaken systematic studies on the synthesis of the *bis*-propargylamines **199** for subsequent conversion to allenes **192**.

3.2.5 Synthesis of chiral cyclic *bis*-propargylamines 199

Synthesis of *bis*-propargylamines starting from 1-alkynes **189**, aldehydes **190** and decahydroquinoxaline **198** is promoted by zinc and copper salts. We have observed that the reaction using CuBr at 120 °C for 12 h in toluene gave the corresponding propargylamine in 93% yield with 99% dr (Scheme **32**, Table **4**, and Entry 6).

Scheme 32

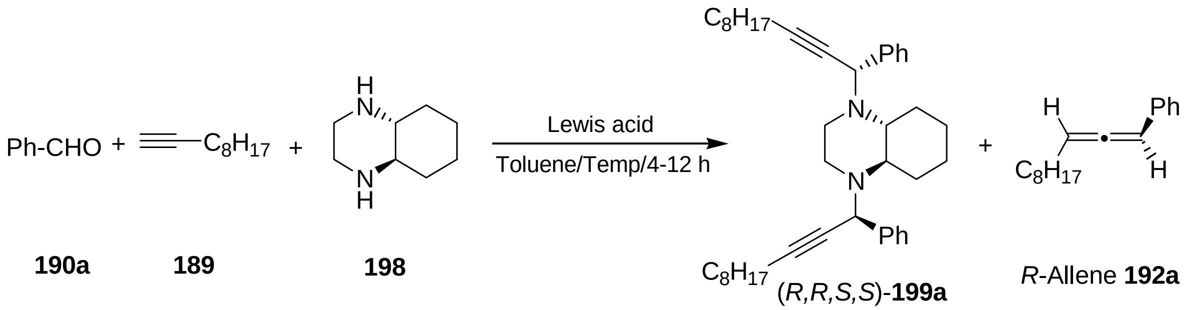


Table 4: Optimization table for the synthesis of *bis*-propargylamines **199a**[a]

Entry	Lewis acid	Mol %	Time (h)	Temp (°C)	Yield of **199a** (%)[b]	dr ratio of **199a**[c]	Yield of **192a** (%)[b]
1	$ZnBr_2$	5	12	110	54	99	15
2	ZnI_2	5	12	110	62	99	14
3	$Cu(OTf)_2$	5	12	110	69	99	14
4	CuBr	5	12	80	NR	-	-
5	CuBr	5	12	110	44	99	9
6	**CuBr**	**5**	**12**	**120**	**93**	**99**	**3**
7	CuBr	5	4	130	53	99	10
8	CuBr	5	12	130	45	99	9

[a] All the reactions were carried out with **198** (1 mmol), 1-decyne **189** (2 mmol), followed by addition of benzaldehyde **190a** (2 mmol) and 5mol% of Lewis acid. [b] Isolated yield of product **199a**. [c] The ratio of the dr was confirmed by ^{1}H-NMR spectral analysis. NR = No Reaction.

We have followed this optimized protocol (Scheme **32**, Table **4**, Entry 6) for the synthesis of various substituted *bis*-propargylamines (*R,R,S,S*)-**199a-g**. The configurations of the newly formed chiral centers in the propargylamines were assigned based on the previous reports.[71] The diasteriomeric ratio (dr) was determined by the proton NMR spectroscopy (Scheme **33**).

Scheme 33

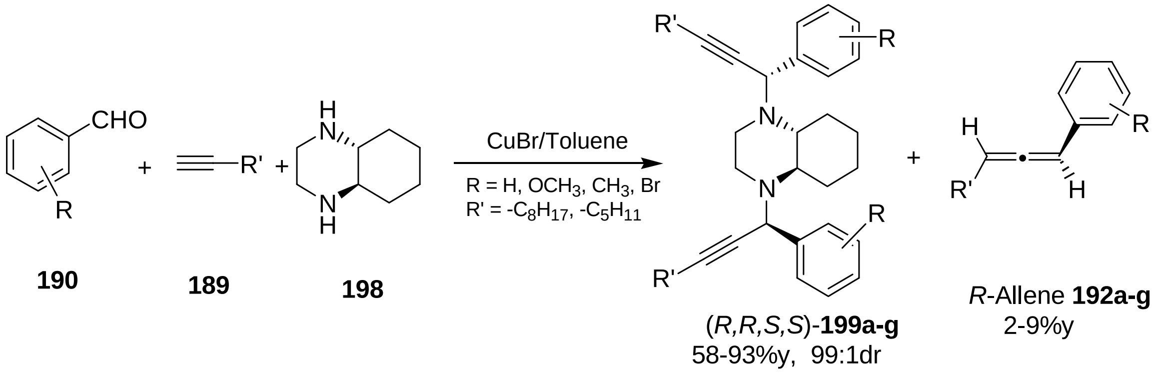
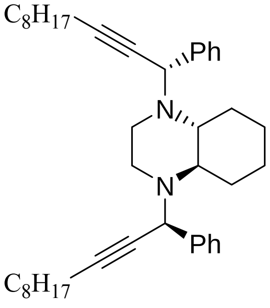
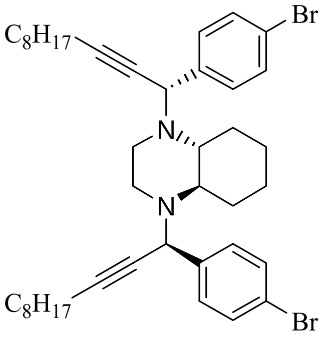
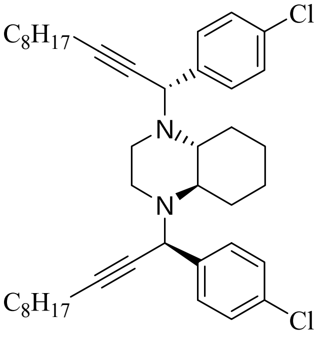
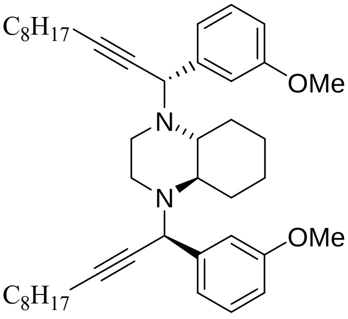
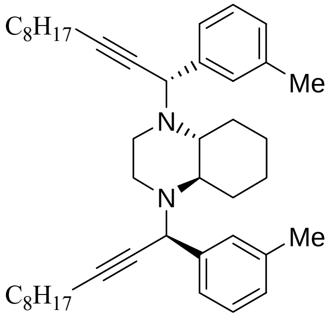
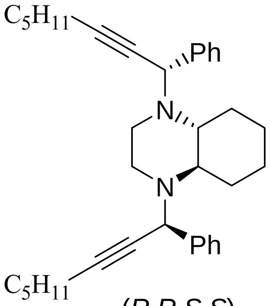
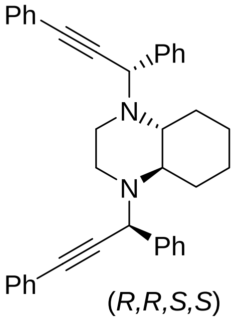


Table 5: Synthesis of *bis*-propargylamines **199a-g**[a]

Entry	Alkyne **189**/Aldehyde **190**	Product		Yield of **199** (%)[b]	dr ratio of **199**[c]	Yield of **192** (%)[b]
1	**189/190a** R' = nC_8H_{17}, R = Ph	 (*R,R,S,S*)	**199a**	93	99:1	2

2	**189/190b** R' = nC_8H_{17}, R = *p*BrPh	 (*R*,*R*,*S*,*S*)	**199b**	81	99:1	4
3	**189/190c** R' = nC_8H_{17}, R = *p*ClPh	 (*R*,*R*,*S*,*S*)	**199c**	58	99:1	7
4	**189/190d** R' = nC_8H_{17}, R = *m*OMePh	 (*R*,*R*,*S*,*S*)	**199d**	87	99:1	6

5	**189/190e** R' = $n\mathrm{C_8H_{17}}$, R = *m*MePh	 (*R*,*R*,*S*,*S*)	**199e**	88	99:1	4
6	**189/190f** R' = $n\mathrm{C_5H_{11}}$, R = Ph	 (*R*,*R*,*S*,*S*)	**199f**	78	99:1	9
7	**189/190g** R' = Ph, R = Ph	 (*R*,*R*,*S*,*S*)	**199g**	80	99:1	4

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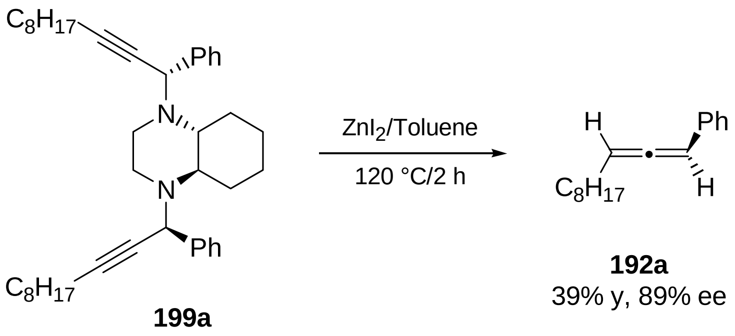
[a] All the reactions were carried out with **198** (1 mmol), 1-alkyne **189** (2 mmol), aromatic aldehydes **190a-g** (2 mmol) and CuBr (5 mol%) in toluene at 120 °C for 12h. [b] Isolated yield of bis-propargylamines **199a-g**. [c] The dr was confirmed by ^{1}H-NMR spectral analysis.

3.2.6 Conversion of *bis*-propargylmaine 199a to allene 192a

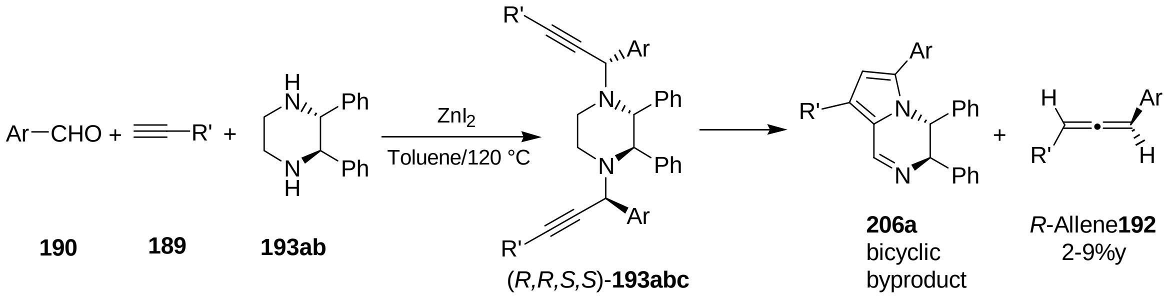
We have observed that the reaction of *bis*-propargylamine **199a** with $\mathrm{ZnI_2}$ at 120 °C gave the corresponding chiral *R*-allene **192a** in 39% yield and 89% ee (Scheme **34**).

Scheme 34



Though, the enantioselectivity of this transformation is high, the chemical yield is only moderate. Previously, it was reported that the *bis*-propargylamine **193abc** leads to formation of a bicyclic byproduct **206a** (Scheme **35**).

Scheme 35

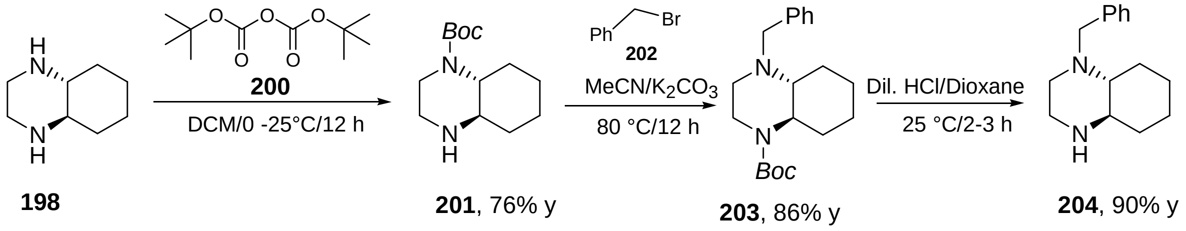


Though, we could not isolate such a bicyclic product in the reaction using the bis-propargylamine **199a**, we have decided to block one of the NH with benzyl group to avoid formation of such byproducts to improve the chemical yields.

3.2.7 Synthesis of chiral cyclic diamines 201 and 204

We have developed a convenient methodology for the synthesis of chiral diamine **201** from chiral diamine **198** by the reaction of *Boc*-anhydride **200** to obtain the one side NH protected chiral diamine **201**. The compound **201** was further N-benzylated using benzyl bromide **202** to give the corresponding tertiary chiral diamine **203**. It was deprotonated with 2N HCl in dioxane solvent to obtain the desired product **204** in 90% yield (Scheme **36**).

Scheme 36



3.2.8 Synthesis of chiral cyclic mono-propargylamines

We have prepared the chiral cyclic propargylamines **205a-b** 92% and 70% yields respectively using the chiral diamine **204** by following the above mentioned protocol. The configuration of the isomers **205a** and **205b** were also assigned based on the previous reports.[71] The diasteriomeric ratio (dr) was determined by the proton NMR spectroscopy (Scheme **37**).

Scheme 37

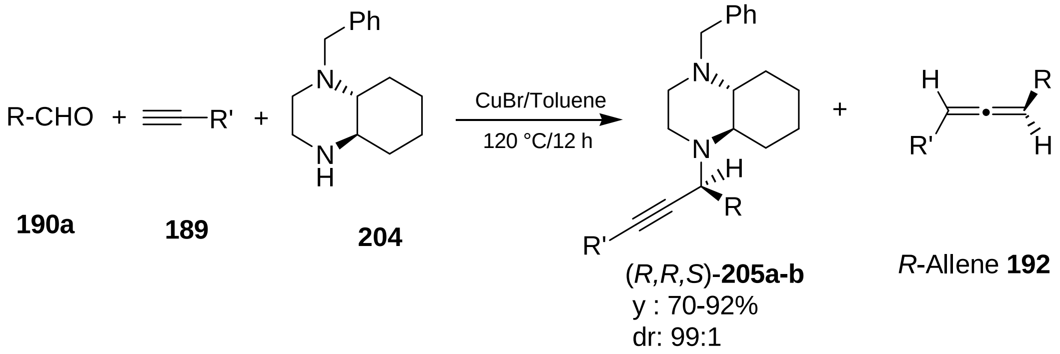
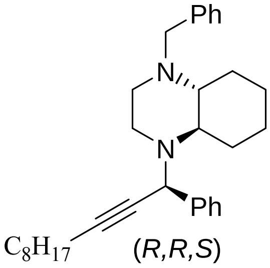
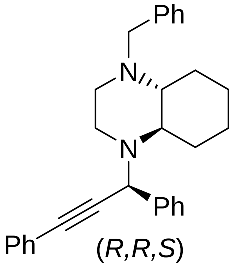


Table 6: Synthesis of chiral cyclic mono-propargylamines **205a-b**^{a}

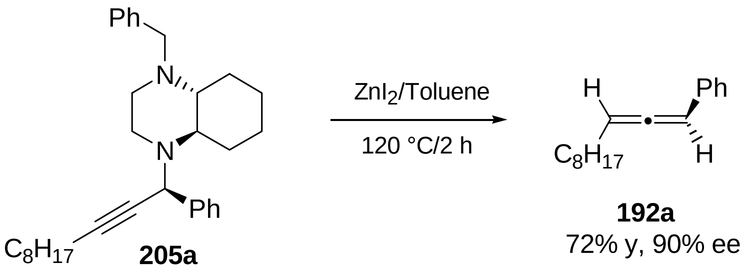
Entry	Alkyne **189**/Aldehyde **190**	Product		Yield of **205** (%)^{b}	dr ratio of **205**^{c}	Yield of **192** (%)^{b}
1	**189/190a** R' = $n\mathrm{C}_8\mathrm{H}_{17}$, R = Ph		**205a**	92	99:1	3
2	**189/190** R' = Ph, R = Ph		**205b**	70	99:1	9

[a] All the reactions were carried out with **204** (1 mmol), 1-alkyne **189** (1 mmol), aromatic aldehydes **190a-g** (1 mmol) and CuBr (5 mol%) in toluene at 120 °C for 12h. [b] Isolated yield of mono-propargylamines **205a-b**. [c] The dr was confirmed by ^{1}HNMR spectral analysis.

3.2.9 Conversion of cyclic propargylamine 205a to chiral allene 192a

We have observed that the propargylamine **205a** gives the corresponding axially chiral allene in 72% yield and 90% ee by the reaction with ZnI_2 in toluene at 120 °C (Scheme **38**).

Scheme 38



3.2.10 Highly enantioselective synthesis of axially chiral allenes 192

We have also examined the use of chiral diamines **201** and **204** in the ZnI_2 promoted enantioselective synthesis of axially chiral allenes in an one pot operation using 1-decyne

Scheme 39

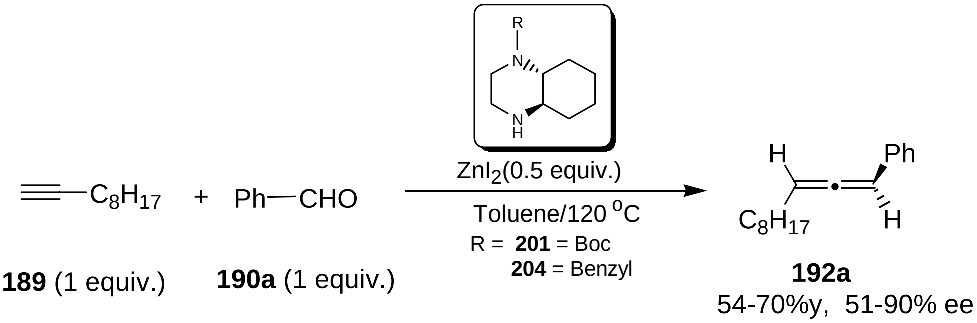


Table 7: Optimization of the reaction conditions[a]

Entry	Metal complex	Ligand	mmol	Time (h)	Yield (%)[b]	ee (%)[c]
1	ZnI_2	**201**	0.5	24	54	51
2	ZnI_2	**204**	0.5	24	62	83
3	**ZnI_2**	**204**	**0.5**	**12**	**70**	**90**

[a] All the reactions were carried out with chiral diamines **201** or **204** (1 mmol), 1-Decyne **189** (1 mmol), ZnI_2 at 110°C in toluene for 15min. followed by addition of benzaldehyde **190a** (1 mmol) at 130 °C. [b] Isolated yield of product **192a**. [c] ee was confirmed by HPLC analysis (chiralcel OD-H column) using hexane as eluent and the compared with reported $[\alpha]_D^{25}$ value.[70]

189 and benzaldehyde **190a**. Whereas the chiral diamine **201** gave 54% yield with 51% ee, the chiral diamine **204** gave the chiral allene in 70% yield and 90% ee (Scheme **39**, Table **7**, and Entry 3).

Clearly, the N-Boc substituted diamine **201** give poor results indicating the importance of coordination of the tertiary amine nitrogen in **204** with zinc halide moiety in the transition state (see discussion on mechanism later, Scheme **45**).

We have carried out this ZnI_2 promoted one pot operation using different 1-alkynes **189** and aryl aldehydes **190** 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 (Scheme **40**, Table **8**).

Scheme 40

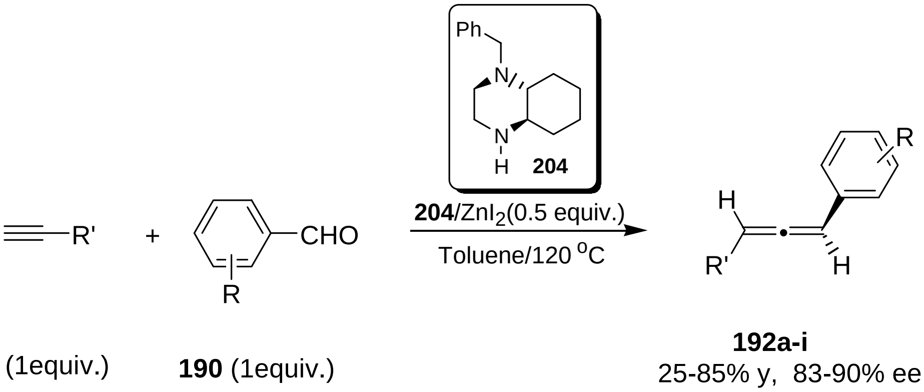
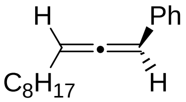
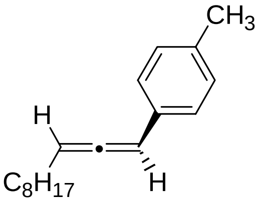
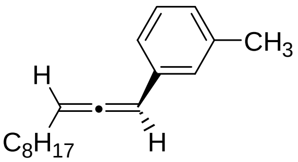
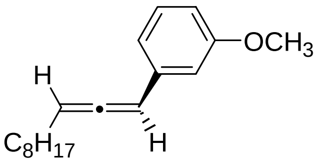
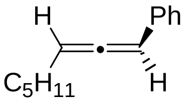
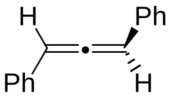
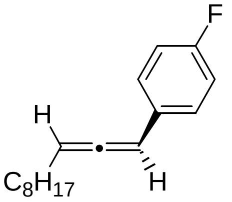
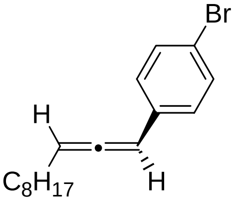
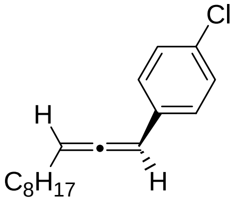


Table 8: Synthesis of various axially chiral allenes[a]

Entry	Alkyne **189**/Aldehyde **190**	*R*-Allene		Yield (%)[b]	ee (%)[c]
1	**189/190a** R' = nC_8H_{17}, R = Ph		**192a**	70	90
2	**189/190b** R' = nC_8H_{17}, R = *p*MePh		**192b**	57	83
3	**189/190c** R' = nC_8H_{17}, R = *m*MePh		**192c**	85	84
4	**189/190d** R' = nC_8H_{17}, R = *m*OMePh		**192d**	76	87
5	**189/190e** R' = nC_5H_{11}, R = Ph		**192e**	70	86
6	**189/190f** R' = Ph, R = Ph		**192f**	25	84

7	**189/190g** R' = $n\mathrm{C_8H_{17}}$, R = *p*FPh		**192g**	80	89
8	**189/190h** R' = $n\mathrm{C_8H_{17}}$, R = *p*BrPh		**192h**	67	90
9	**189/190i** R' = $n\mathrm{C_8H_{17}}$, R = *p*ClPh		**192i**	69	87

---

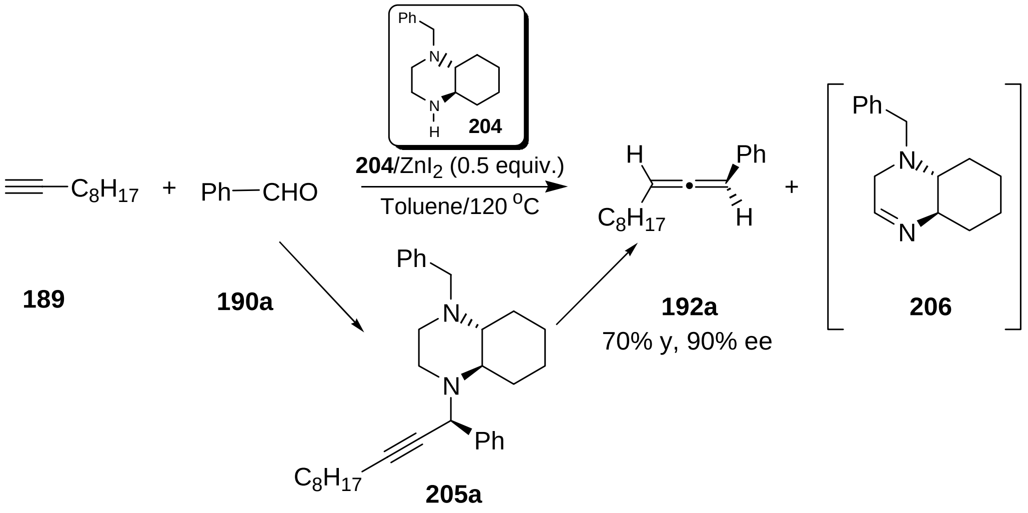
[a] All the reactions were carried out with **204** (1 mmol), 1-alkyne **189** (1 mmol), $\mathrm{ZnI_2}$ at 110 °C in toluene for 15min. followed by addition of aromatic aldehydes **190** (1 mmol) at 130 °C. [b] Isolated yield of R-allenes **192a-i**. [c] The % ee was confirmed by HPLC analysis (chiralcel OD-H, OJ-H, OB-H column) using hexane as eluent.

All the optically active allenes obtained by using chiral diamine **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.[72] Comparison of $[\alpha]_D^{25}$ values with reported values also confirms this stereochemical assignment.[70]

3.2.11 Efforts towards isolation of the imine intermediate 206

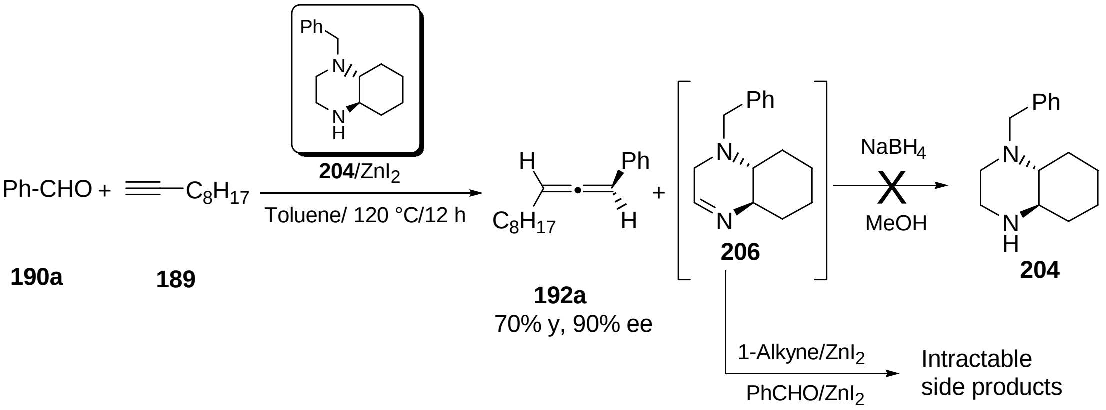
As discussed previously, this one pot transformation of 1-alkyne **189** and aldehydes **190** is expected to go through the intermediacy of the corresponding propargylamine intermediate. The corresponding imine byproduct **206** should have also formed in the conversion of propargylamine **205** to chiral allene **192** (Scheme **41**). Unfortunately, the expected imine **206** could not be isolated by silica gel column chromatography. Presumably, the imine byproduct **206** may be unstable.

Scheme 41



We have also attempted to recover the chiral diamine **204** back from the reaction mixture by *in situ* reduction of the expected imine byproduct using NaBH$_4$/MeOH (Scheme **42**).

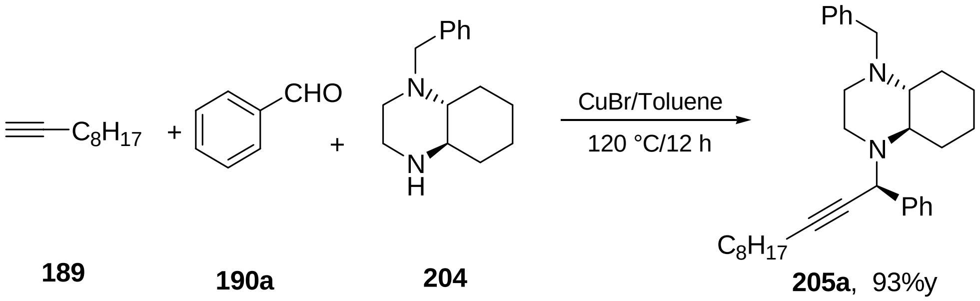
Scheme 42



Unfortunately, the starting chiral diamine **204** could not be isolated from the crude reaction mixture (Scheme **42**). Presumbly, the imine byproduct **206** is highly unstable under the reaction conditions and might lead to intractable side products through reaction with 1-decyne **189**/ZnI_2 or benzaldehyde **190**/ZnI_2.

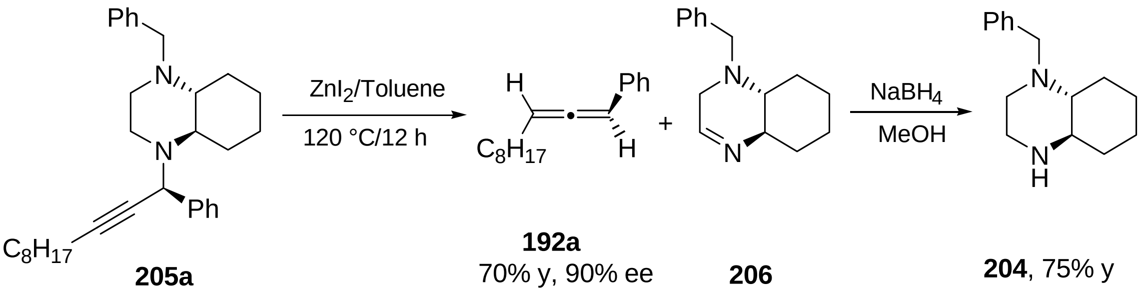
We have then turned our attention towards the synthesis of axially chiral allenes **192** in a two step synthetic operation (Scheme **43** and **44**). First, we have isolated the propargylamine **205a** in 93% yield using CuBr/toluene by column chromatography of the reaction mixture (Scheme **43**).

Scheme 43



The propargylamine **205a** was then converted to the *R*-allene **192a** by reaction with ZnI_2 in toluene at 120 °C for 2 h. Then, the reaction mixture was brought to room temperature under N_2 and reduced with $NaBH_4/CH_3OH$. In this run, the starting chiral diamine **204** was isolated in 75% yields without loss of its optical purity (Scheme **44**).

Scheme 44

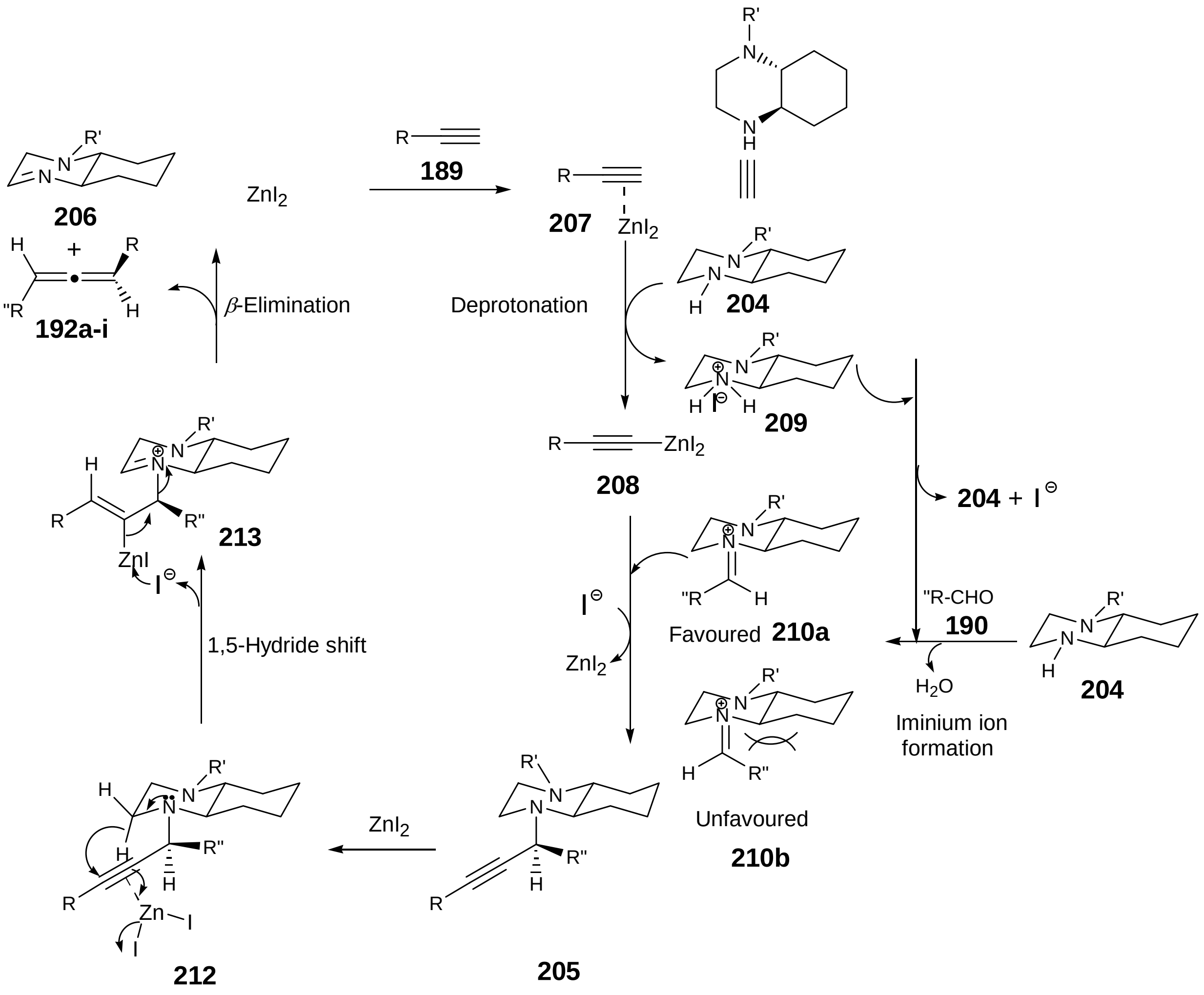


Clearly, in previous experiments (Scheme **41** and Scheme **42**), the imine byproduct **206** would have given intractable side products by reaction with ZnI_2 1-alkyne **189** and benzaldehyde **190a** present in the medium.

3.2.12 Tentative mechanistic pathway for the allene formation

The formation of chiral propargylamines and chiral allenes **192** in the ZnX_2 promoted reaction of 1-alkyne **189** and benzaldehyde **190a** can be explained by a tentative mechanism outlined in Scheme **45** considering previous reports on similar transformations.[73] The initially formed alkynyl zinc intermediate **207** would react with the favoured conformer **210a** of the iminium ion derived from various aromatic aldehydes and diamine **204** to give selectively the corresponding propargylamine intermediate **205** (Scheme **45**). Thus, the formation of the single propargylamine derivative **205** isomer is mainly due to the exclusive formation of the favoured conformer of the iminium ion **210a** compared to unfavoured conformer **210b**, because of steric repulsions with the bridged bicyclic system in the crucial step of the addition of the alkynl zinc reagent.[73] Subsequently, the zinc halide complexed with propargylamine intermediate **205** would give the complex **212** which would undergo an intramolecular hydride shift from the decahydroquinoxaline skeleton to the acetylinic moiety leading to the alkenyl zinc intermediate **213**. Finally, cleavage of C-N bond in intermediate **213** would result in the formation the allene **192** and the imine **206** (Scheme **45**).

Scheme 45



The creation of the stereogenic center in the propargylamine intermediate and subsequent chirality transfer *via* the hydride shift from the decahydroquinoxaline skeleton takes place with very high selectivity, even though the transformations are carried out at higher temperature. Also, the results indicate that the ZnX_2 promoted reaction of 1-alkynes and aryl aldehydes involving the creation of stereogenic center in the intermediate propargylamines and subsequent chirality transfer to the corresponding chiral allenes further are general transformations with various chiral cyclic secondary amines (Scheme **45**).

3.3 Conclusions

In summary, we have developed a general and efficient Cu(II)/*R*-BINAM **61** catalyst system for the enantioselective synthesis of propargylamines **87** with 20-93% ee and 19-98 % yields.

We have developed a convenient protocol for the synthesis of various chiral *bis*-propargylamines **199a-g**, in a CuBr promoted reaction using 1-alkynes **189**, aromatic aldehydes **190** and chiral diamine **198** with moderate to excellent 58-93% yields with 99:1 dr. The cyclic propargylamine **205a-b** were also synthesized using the chiral diamine **204**, 1-alkyne **189** and benzaldehyde **190a** promoted by CuBr at 120 ^{o}C for 12 h.

We have also synthesized the 1,2-diaminocyclehexane derivatives **198**, **201** and **204** for use in the highly enantioselective synthesis of *R*-allenes **192** using 1-alkyne **189** and aromatic aldehydes **190** promoted by ZnI_2 in toluene at 120 °C. The axially chiral allenes **192a-i** were obtained in 25-87% yield with 83-90% ee.

Since the chiral sources **198**, **204** and **61** are recoverable for reuse without loss in optical purity, the methods have considerable potential for wide utility in the synthesis of optically active propargylamines and allenes.

3.4 Experimental Section

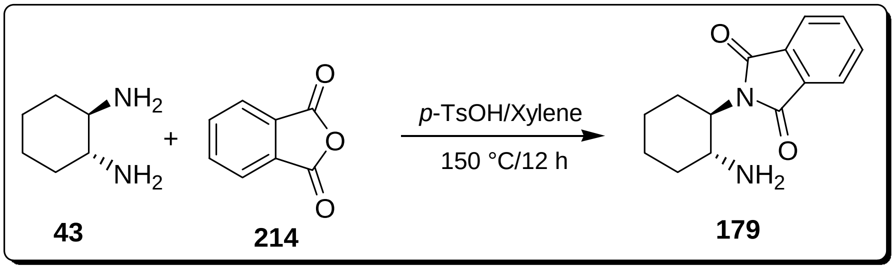
3.4.1 General information

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 ($\delta = 0$ 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.

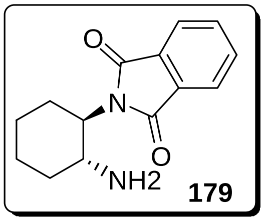
Analytical grade of CuBr, Cu(OTf) and ZnI_2 were purchased from Sigma-Aldrich. $ZnBr_2$ was purchased from E-Merck. Toluene supplied by E-Merck, India was freshly distilled over sodium-benzophenone ketyl before use. Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 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°) and AUTOPOL-IV (readability ±0.001°) 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.

3.4.2 Preparation of 2-{(1*R*,2*R*)-2-aminocyclohexyl}isoindoline-1,3-dione 179[74]



A solution of *p*-TsOH·H2O (1.92 g, 0.01 mol) in xylenes (50 mL) was dehydrated by azeotropic distillation. After, cooling to room temperature, to the solution was added diaminocyclohexane **43** (1.14 g, 0.01mol) followed by phthalic anhydride **214** (1.48 g, 0.01mol). The mixture was heated with stirring until homogeneous solution was obtained and the product begun to crystallize. The product **179** was collected by filtration, washed with xylene–hexane and air-dried.


179

Yield : 1.926 g (57%), colorless solid.

mp : 122–124°C (lit. mp 123–125°C).[74]

IR (KBr) : (cm^{-1}) 3052, 2942, 2858, 1714, 1646, 1553, 1373, 839, 836

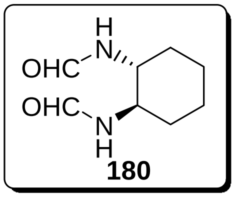
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 1.13–1.22 (m, 3H), 1.31–1.43 (m, 2H), 1.72–1.81 (t, 3H), 2.00–2.03 (m, 1H), 2.12-2.21 (m, 1H), 3.36-3.40 (m 1H), 3.74–3.79 (m, 1H), 7.67(s, 2H), 7.79 (s, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 168.7, 133.8, 131.9, 123.1, 58.5, 50.8, 36.7, 29.3, 25.6, 25.1.

LCMS : *m/z* 243(M-1).

N,N'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)diformamide 180[75]

A procedure reported by Betschart et al. was adapted with small modifications.[75] A solution of chiral *trans*-1,2-cyclohexanediamine **43** (10 mL, 0.041 mol) in ethyl formate (50 mL, 0.25 mmol) was heated at 50 ºC for 8 h. The resulting thick, white suspension was allowed to reach room temperature and filtered. After the filter cake was washed with ethyl acetate (80 mL), the solid was dried under vacuum to obtain the product *trans*-N,N'-diformyl-(1*R*,2*R*)-cyclohexanediamine **180** as a colorless solid.


180

Yield : 1.79 g (63%).

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

^{1}H NMR : (400 MHz, CDCl$_3$) δ: 1.29-1.31 (d, *J* = 8, 4H), 1.76 (s, 2H), 2.02-2.04 (d, *J* = 8, 2H), 3.78 (s, 2H), 6.41 (s, 2H).

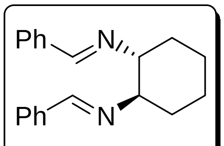
^{13}C NMR : (100 MHz, CDCl$_3$) δ: 161.7, 52.1, 32.2, 24.6.

(1*R*,2*R*,N1E,N2E)-N1,N2-Dibenzylidenecyclohexane-1,2-diamine 181

To an oven dried RB flask, was added silicagel (0.5 g) followed by ethanol (10-25 mL), amine **43** and aryl aldehydes **190a**. All the contents were subjected to sonication for about 10-20 min. at 25 °C. The progress of the reaction was monitored by the TLC and after completion of the reaction the reaction mixture was diluted with DCM (10 mL) and filtered off the silica gel. The solvent was evaporated and the residue was washed with hexane. The residue was recrystallized further to obtain the desired imine **181** as colorless solid.

Yield : 2.29 g (79%).

mp : 102-104 °C (lit. 102-104).[76]



181

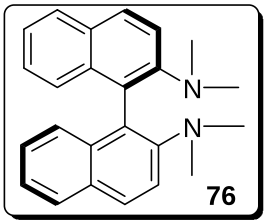
IR (KBr) : (cm^{-1}) 3059, 2926, 1641, 1530, 1356, 1064, 754, 692

^{1}H NMR : (400 MHz, CDCl$_3$) δ: 8.23-8.27 (d, 2H, *J* = 14 Hz), 7.6-7.64 (t, 4H), 7.32-7.35 (s, 4H), 3.45-3.46 (d, 2H, *J* = 4.0 Hz), 1.88 (s, 4H), 1.51-1.53 (d, 4H, *J* = 8 Hz).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 163.2, 136.4, 131.2, 128.4, 127.9.

N2,N2,N2',N2'-Tetramethyl-[1,1'-binaphthalene]-2,2'-diamine 76

To a stirred suspension of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine **61** (1.42 g, 5 mmol) in 20 mL of methanol, formaldehyde **215** (37% solution, 5.4 mL, 30 mmol) and formic acid (3 mL, 30 mmol) were slowly added at 25 °C under nitrogen atmosphere. The contents were heated to reflux for 8 h. The solvents were removed under reduced pressure and the residue was dispersed in 20 mL of water. The NaOH (3N) solution was slowly added to the mixture till it becomes slightly basic. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on silica gel (230-400 mesh) using hexanes/ethyl acetate (99/1) as eluent to obtain the desired amine **76** as a colorless solid.


76

Yield : 1.24 g (73%).

mp : 206-208 °C (Lit. 216-218).[77]

$[\alpha]_D^{25}$: -18.22 (*c* 0.5, $CHCl_3$).

IR (KBr) : (cm^{-1}) 3047, 2966, 2928, 1612, 1591, 1502

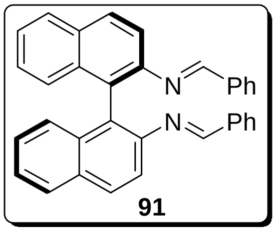
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 2.5 (s, 12H), 7.18-7.19 (m, 4H), 7.28-7.32 (m, 2H), 7.50 (d, 2H, *J* = 8.8 Hz), 7.83 (d, 2H, *J* = 8.3 Hz), 7.90 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 43.5, 120.7, 123.4, 125.9, 126.1, 126.3, 127.8, 128.5, 129.8, 134.7, 149.8.

LCMS : *m/z* 341 (M+1).

(N2Z,N2'Z)-N2,N2'-Dibenzylidene-[1,1'-binaphthalene]-2,2'-diamine 91

To an oven dried RB flask, was added silica gel (0.5 g) followed by ethanol (10-25 mL), amine and aryl aldehydes **190**. All the contents were subjected to sonication for about 10-20 min. at room temperature. The progress of the reaction was monitored by the TLC and after completion of the reaction the reaction mixture was diluted with DCM (10 mL) and filtered off the silica gel. The solvent was evaporated and the residue was washed with hexane and recrystallized to obtain the desired bimine-BINAM **91** as a colorless solid.



91

Yield : 1.73 g (79%).

mp : 118-120 °C; (lit. 119-124 °C).[36]

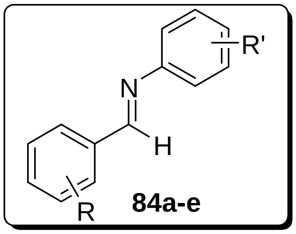
$[\alpha]_D^{25}$: +115.2 (*c* 0.56, DCM); (lit. +112.9 (*c* 0.23, CH2Cl2).[36]

IR (KBr) : (cm^{-1}) 3049, 2860, 1610, 1575, 1496, 1307, 970, 752, 690

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 8.34 (s, 2H), 7.92-7.98 (q, 4H), 7.25-7.48 (m, 18H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 160.6, 148.9, 136.4, 133.6, 131.6, 130.9, 129.1, 128.5, 128.4, 127.9, 126.8, 126.4, 126.2, 124.7, 119.3.

3.4.3 General procedure for the preparation of imines 84a-e



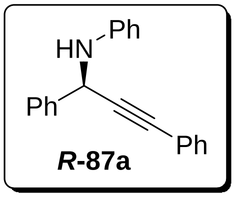
84a-e

To an oven dried RB flask, was added silica gel (0.5 g) followed by ethanol (10-25 mL), amine and aryl aldehydes. All the contents were subjected to sonication for about 10-20 min. at room temperature. The progress of the reaction was monitored by the TLC and after completion of the reaction the reaction mixture was diluted with DCM (10mL) and filtered off the silica gel. The solvent was evaporated and the residue was washed with hexane and recrystallized to obtain the desired imines **84a-e**.

3.4.4 General procedure for the enantioselective synthesis of propargylamines 87a-e

An oven dried reaction flask (25 mL) was cooled under N_2 and charged with $Cu(OTf)_2$ and (*R*)-BIANM **61** or (*R*)-bisimine-BINAM **91** followed by toluene (2 mL) and dry DCM (3 mL) and the mixture was stirred for 30 min at room temperature. Then was added imine **84a-e** followed by phenyl acetelyne **85** and the mixture was stirred for 24h at room temperature. After completion of the reaction, solvents were removed under high pressure and the residue was chromatographed on silica gel column to obtain **87a-e**.

(*R*)-N-(1,3-Diphenylprop-2-yn-1-yl)aniline 87a



R-87a

Yield : 0.28 g (98%), colorless solid.

$[\alpha]_D^{25}$: + 130.8 (*c* 0.24, $CHCl_3$ for 93% ee); [lit. + 114.3 (*C* 2.0, $CHCl_3$ for 96% ee].[36]

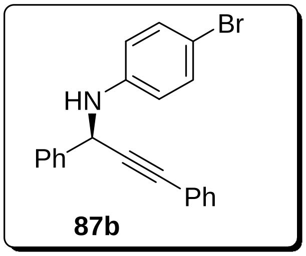
IR (KBr) : (cm^{-1}) 3337, 2974, 1684, 1413, 1167, 698

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.69-7.71 (d, *J* = 12, 2H), 7.43-7.47 (m, 4H), 7.36-7.40 (m, 1H), 7.31-7.33 (m, 3H), 7.24-7.28 (m, 2H), 6.81-6.85 (m, 3H), 5.54 (s, br, 1H), 4.19 (s, br, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 146.6, 139.8, 131.8, 129.2, 128.8, 128.4, 128.3, 128.2, 127.4, 122.8, 118.6, 114.1, 88.5, 85.1, 50.7.

Enantiomeric purity: 92% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/98:2; flow rate 1mL/min., λ = 254nm, retention times: 20.5 min. (*R*) and 24.5 min (*S*)].

(R)-4-Bromo-N-(1,3-diphenylprop-2-yn-1-yl)aniline 87b



87b

Yield : 0.11 g (30%), yellow oil.

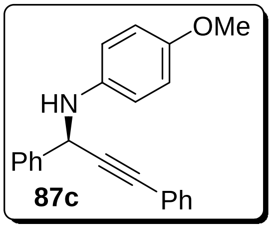
IR (neat) : (cm^{-1}) 3401, 2232, 1589, 1498, 1313, 1188.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 7.6Hz, 2H), 7.48-7.41 (m, 4H), 7.41-7.35 (m, 1H), 7.35-7.28 (m, 5H), 6.70-6.64 (m, 2H), 5.48 (s, 1H), 4.21 (s, 1H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 145.8, 139.5, 132.2, 132.1, 129.2, 128.8, 128.6, 127.7, 122.9, 115.9, 110.7, 88.2, 85.6, 50.9.

<u>Enantiomeric purity:</u> 25% ee [determined by HPLC using chiral column, Diacel chiralpak AD-H, solvent system, hexanes: *i*-PrOH/95:5; flow rate 1mL/min., λ = 254nm, retention times: Major isomer-21.4 min. (*R*) and minor isomer-25.3 min. (*S*)].

(R)-N-(1,3-Diphenylprop-2-yn-1-yl)-4-methoxyaniline 87c



Yield : 0.032 g (19%), yellow oil.

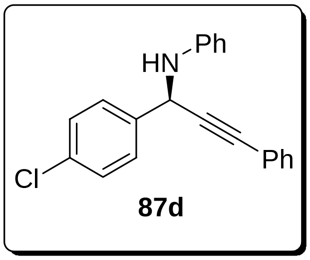
IR (neat) : (cm^{-1}) 3296, 2982, 1679, 1419, 1178, 706

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.70 (m, 2H), 7.45–7.60 (m, 8H), 6.85-6.75 (m, 4H), 5.50 (s, 1H), 3.8 (s, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 153.7, 143.1, 132.3, 129.2, 129.0, 127.4, 127.5, 127.8, 123.6, 114.3, 114.7, 109.8, 89.5, 85.7, 55.6, 52.3.

<u>Enantiomeric purity</u> 20% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.5 mL/min., λ = 254nm, retention times: Major isomer-32.7 min. (*R*) and minor isomer-37.3 min. (*S*)].

(R)-N-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)aniline 87d


87d

Yield : 0.15 g (95%), yellow oil.

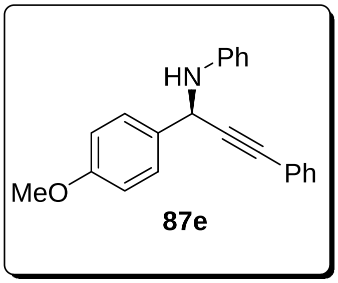
IR (neat) : (cm^{-1}) 3408, 2229, 1608, 1509, 1311, 1176.

^{1}H NMR : (400 MHz, CDCl$_3$) δ: 7.64-7.59 (m, 2H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 2H), 7.35-7.28 (m, 3H), 7.28-7.21 (m, 2H), 6.87-6.75 (m, 3H), 5.50 (s, 1H), 4.23 (br, 1H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 146.6, 138.6, 134.2, 132.1, 129.5, 129.2, 128.9, 128.8, 128.6, 122.8, 119.2, 114.5, 88.2, 85.7, 50.4.

<u>Enantiomeric purity:</u> 60% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/99:1; flow rate 1mL/min., 254nm, retention times: Major isomer-30.1 min. (*R*) and Minor isomer-36.3 min. (*S*)].

(R)-N-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)aniline 87e


87e

Yield : 0.080 g (25%), yellow oil.

IR (neat) : (cm^{-1}) 3328, 2969, 1682, 1416, 1166, 692

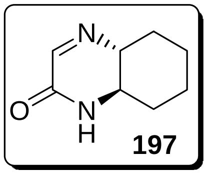
^{1}H NMR : (400 MHz, CDCl$_3$) δ: 7.56 (d, 3 *J* = 7.5 Hz, 2H), 7.38 (m, 2H), 7.18-7.28 (m, 5H), 6.91 (d, 3 *J* = 6.5 Hz, 2H), 6.77 (m, 3H), 5.46 (s, 1H,), 3.78 (s, 3H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 146.5, 130.8, 129.7, 128.8, 126.9, 127.4, 127.2, 124.4, 122.1, 120.1, 116.5, 111.4, 91.2, 87.7, 57.3, 45.9.

Enantiomeric purity: 77% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/98:2; flow rate 0.5 mL/min., λ = 254nm, retention times: Major isomer-19.1 min. (*R*) and Minor isomer-23.3 min. (*S*)].

3.4.5 (4a*R*,8a*R*)-4a,5,6,7,8,8a-Hexahydroquinoxalin-2(1H)-one 197[44]

To a solution of *trans*-1,2-diaminocyclohexane **43** (1.14 g, 10 mmol) in 2-PrOH (10 mL), a solution of ethyl glyoxylate **196** polymer form (45-50% in toluene, 2 mL, 10 mmol) in 2-PrOH (10 mL) was added drop wise over 30 min at 25 °C. The mixture was stirred for 12 h. The solvent was evaporated and the residue was purified by flash column chromatography (ethyl acetate as eluent) to afford **197**.


197

Yield : 1.46 g (96%), colorless solid.

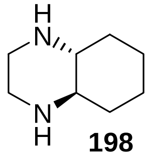
IR (KBr) : (cm^{-1}) 3184, 3107, 2935, 1712, 1666, 1413, 1359, 951, 773

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.64-7.67 (d, *J* = 12, 2H), 3.01-3.15 (m, 2H), 2.28-2.34 (m, 1H), 1.92-1.95 (d, *J* = 12, 1H), 1.85-1.87 (d, J = 8, 1H), 1.75-1.78 (d, J = 12, 1H), 1.23-1.42 (m, 4H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 158.1, 156.3, 62.8, 53.8, 31.4, 30.8, 25.2, 23.5.

(4a*R*,8a*R*)-Decahydroquinoxaline 198[76]

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 **197** (1.52 g, 10 mmol) was added to the generated diborane and refluxed for 24-36 h. The raection was brought to room temperature and quenched with methanol and the solvents were evoperated. The residue obtained after evoperation was refluxed with 10N KOH for 6h and resultant polyamine was extracted with DCM (2 X 30 mL). The combined organic extract was evoperated to obtain the decahydroquinazoline **198**. The crude amine **198** was chromatographed on a basic Al_2O_3 column using 50:50 hexane and ethylacetate as eluent to isolate the decahydroquinazoline **198**.



198

Yield : 1.25 g (89%), colorless solid.

IR (KBr) : (cm^{-1}) 3223, 2922, 1452, 1340, 1136, 833, 619

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 2.90-2.94 (t, 2H), 2.78-2.85 (q, 2H), 2.17-2.19 (q, 2H), 1.65-1.67 (d, *J* = 8, 2H), 1.59-1.62 (d, *J* = 12, 2H), 1.49 (s, 2H), 1.25-1.30 (t, 2H), 1.13-1.18 (t, 2H).

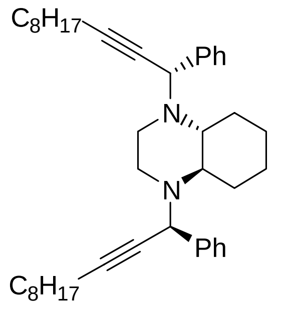
^{13}C NMR : (100 MHz, $CDCl_3$) δ: 61.6, 47.4, 32.2, 25.0.

LCMS : *m/z* 139 (M+1).

3.4.6 General procedure for the preparation of chiral *bis*-propargylamines 199a-i

To a 25 mL of reaction flask was added CuBr (0.07 g, 5 mol %), decahydroquinazoline **198** (0.5 g, 2 mmol), 1-alkyne **189** (0.30 g, 2.2 mmol) and aryl benzaldehydes **190** in toluene (3 mL) was heated to 120 °C for 12 h. The reaction mixture was brought to room temperature after the required time. After evaporation of the solvent toluene, the residue was column chromatographed on silica gel (100-200 mesh) using hexane and ethylacetae as eluent to obtain the chiral dipropargyl amines **199a-g**.

(4a*R*,8a*R*)-1,4-*Bis*-((S)-1-phenylundec-2-yn-1-yl)decahydroquinoxaline 199a



(*R,R,S,S*)-**199a**

Yield : 0.26 g (93%), yellow oil.

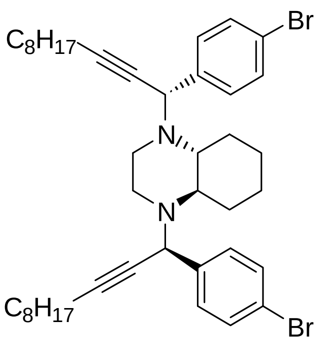
IR (neat) : (cm^{-1}) 2928, 2856, 1602, 11492, 1450, 1074, 700

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.57-7.59 (d, *J* = 8, 4H), 7.26-7.31 (m, 4H), 7.19-7.23 (t, 2H), 5.15 (s, 2H), 2.43-2.45 (m, 2H), 2.32-2.36 (dd, 6H), 2.25-2.27 (d, *J* = 8, 2H), 2.09-2.11 (d, *J* = 8, 2H), 1.85-1.87 (d, *J* = 8, 2H), 1.57-1.62 (m, 5H), 1.50-1.52 (m, 5H), 1.31-1.44 (m, 25H), 0.88-0.92 (m, 7H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.9, 128.6, 127.8, 126.9, 88.5, 74.4, 63.6, 54.3, 45.8, 46.8, 31.9, 29.3, 29.2, 28.9, 28.6, 25.2, 22.7, 18.8, 14.2.

HRMS : (ESI) $C_{42}H_{60}N_2$ $[M+H]^+$ calcd 593.4834 and found 593.5056.

((4a*R*,8a*R*)-1,4-*Bis*-((S)-1-(4-bromophenyl)undec-2-yn-1-yl) decahydroquinoxaline 199b



(*R*,*R*,*S*,*S*)-**199b**

Yield : 0.304 g (81%), yellow oil.

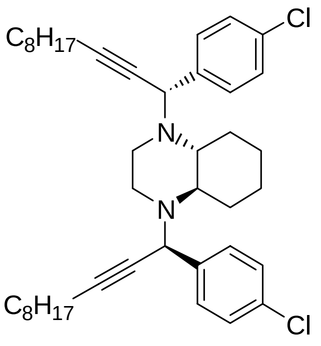
IR (neat) : (cm^{-1}) 2930, 2847, 1610, 1490, 1458, 1098, 709

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.41-7.45 (m, 8H), 5.06 (s, 2H), 2.22-2.28 (m, 10H), 2.04 (s, br, 2H), 1.85 (s, br, 2H), 1.59 (s, br, 5H), 1.48 (s, br, 4H), 2.09-2.11 (m, 21H), 0.89 (s, br, 6H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.1, 130.9, 130.2, 120.8, 88.9, 73.8, 63.6, 53.7, 45.7, 31.9, 29.3, 29.2, 29.1, 28.9, 28.5, 25.1, 22.7, 18.8, 14.2.

HRMS : (ESI) $C_{42}H_{58}Br_2N_2$ $[M+H]^+$ calcd 751.3122 found 751.3029.

(4a*R*,8a*R*)-1,4-*Bis*-((S)-1-(4-chlorophenyl)undec-2-yn-1-yl)decahydroquinoxaline 199c



(*R*,*R*,*S*,*S*)-**199c**

Yield : 0.18 g (58%), yellow oil.

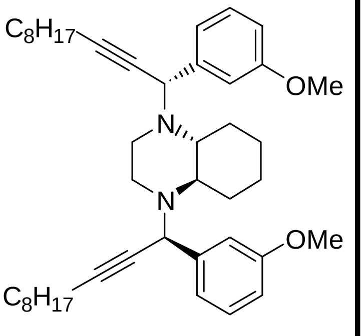
IR (neat) : (cm^{-1}) 2933, 2852, 1608, 1492, 1456, 1072, 711

^{1}H NMR **:** (400 MHz, $CDCl_3$) δ: 7.36-7.41 (s, br 4H), 7.02-7.06 (s, br 4H), 5.03-5.06 (s, br 2H), 2.11-2.19 (m, br 18H), 1.76 (s, br 2H), 1.26-1.47 (m, br 32H), 0.82 (s, br 8H).

^{13}C NMR **:** (100 MHz, $CDCl_3$) δ: 136.8, 136.4, 128.5, 88.3, 63.6, 54.0, 45.7, 31.9, 29.2, 28.9, 28.6, 25.2, 21.0, 18.8, 14.2.

HRMS **:** (ESI) $C_{42}H_{58}Cl_2N_2$ calcd 661.4076 found 661.4076.

(4aR,8aR)-1,4-*Bis*-((S)-1-(3-methoxyphenyl)undec-2-yn-1-yl) decahydroquinoxaline 199d



(*R*,*R*,*S*,*S*)-**199d**

Yield **:** 0.28 g (87%), yellow oil.

IR (neat) **:** (cm^{-1}) 2929, 2853, 1609, 1487, 1454, 1070, 703

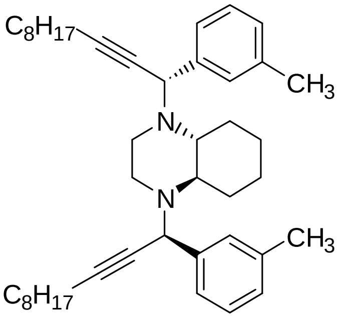
^{1}H NMR **:** (400 MHz, $CDCl_3$) δ: 7.19-7.20 (d, br, 6H), 6.75-6.77 (m, 2H), 5.11 (s, br 2H), 3.80 (m, br 6H), 2.41-2.43 (m, br 2H), 2.32-2.35 (m, br 5H), 2.26-2.27 (m, 3H), 2.12-2.14 (s, br 2H), 1.71 (m, 1H), 1.58-1.61 (m, 4H), 1.49-1.50 (s, br 4H), 1.30-1.40 (m, 20H), 0.87-0.90 (m, 6H)

^{13}C NMR **:** (100 MHz, $CDCl_3$) δ: 159.3, 141.7, 128.7, 120.9, 114.2, 112.3, 88.4, 74.4, 63.6, 55.2, 54.2, 45.9, 31.9, 29.3, 29.2, 28.9, 28.6, 25.2, 22.7, 18.8, 14.1.

HRMS : (ESI) $C_{44}H_{64}N_2O_2$ $[M+H]^+$ calcd 653.5045 found 653.5046.

(4aR,8aR)-1,4-*Bis*-((S)-1-(m-tolyl)undec-2-yn-1-yl)decahydroquinoxaline

199e



(*R,R,S,S*)-**199e**

Yield : 0.27 g (88%), yellow oil.

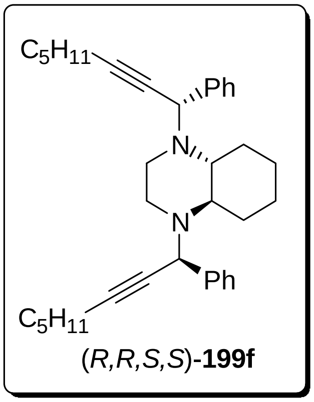
IR (neat) : (cm^{-1}) 2923, 2850, 1612, 1489, 1457, 1078, 715

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.35-7.37 (d, *J* = 8, 4H), 7.14-7.18 (m, 2H), 7.00-7.02 (d, br 2H), 5.10 (s, br, 2H) 2.41-2.44 (m, br 2H), 2.32-2.35 (m, br 5H), 2.26-2.27 (m, 3H), 2.12-2.14 (d, br 2H), 2.32 (m, 13H), 2.23-2.25 (d, br 2H), 2.11-2.13 (d, br 2H), 1.55-1.60 (m, 6H), 1.49-1.51 (m, 4H), 1.29-1.33 (m, 21H), 0.86-0.89 (m, 7H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.7, 137.3, 127.6, 125.7, 88.3, 74.6, 63.6, 54.3, 45.8, 31.8, 29.3, 29.2, 28.9, 28.6, 25.2, 22.7, 21.4, 18.8, 14.1.

HRMS : (ESI) $C_{44}H_{64}N_2$ $[M+H]^+$ calcd 621.5147 found 621.5148.

(4aR,8aR)-1,4-*Bis*-((S)-1-phenyloct-2-yn-1-yl)decahydroquinoxaline 199f


(*R*,*R*,*S*,*S*)-**199f**

Yield : 0.20 g (78%), yellow oil.

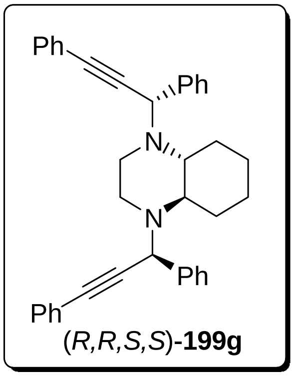
IR (neat) : (cm^{-1}) 2943, 2862, 1611, 1493, 1458, 1063, 733

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.57 (d, br, 4H), 7.27 (m, 4H), 7.22 (s, br, 2H), 5.14 (s, 2H), 2.26-2.43 (m, 12H), 2.10 (s, br, 2H), 1.77-1.85 (d, br, 5H), 1.27-1.60 (m, 23H), 0.94.0.96 (d, br, 9H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.9, 128.6, 127.8, 126.9, 88.5, 74.5, 63.6, 54.3, 45.8, 31.1, 28.8, 28.6, 25.2, 22.3, 18.8, 14.1.

HRMS : (ESI) $C_{36}H_{48}N_2$ $[M+H]^+$ calcd 509.3895 found 509.3896.

(4a*R*,8a*R*)-1,4-*Bis*-((S)-1,3-diphenylprop-2-yn-1-yl)decahydroquinoxaline 199g


(*R*,*R*,*S*,*S*)-**199g**

Yield : 0.22 g (80%), colorless solid.

IR (neat) : (cm^{-1}) 3065, 3028, 2922, 2812, 1489, 1446, 1072, 760, 964

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.67-7.69 (m, 4H), 7.57-

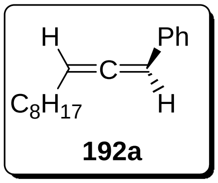
7.60 (m, 4H), 7.33-7.39 (m, 10H), 7.25-7.29 (m, 2H), 5.43 (s, br, 2H), 2.59-2.62 (m, 2H), 2.43-2.45 (m, 4H), 2.28-2.32 (d, br, 2H), 1.91-1.93 (m, 2H), 1.46-1.51 (m, 2H), 1.36-1.38 (m, 2H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.2, 132.0, 128.6, 128.3, 128.1, 128.0, 127.2, 123.5, 88.4, 84.6, 63.9, 54.7, 46.1, 28.7, 25.2.

HRMS : (ESI) $C_{38}H_{36}N_2$ $[M+H]^+$ calcd 521.2956 found 521.2956.

3.4.7 Conversion of cyclic *bis*-propargylamine 199a to allene 192a

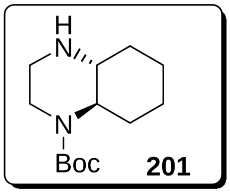
A flame–dried 25 mL reaction flask was charged with chiral propargylamine **199a** (0.59 g, 1 mmol) and ZnI_2 (0.16 g, 0.5 mmol) in toluene (3 mL) and stirring in pre heated oil bath at 120 °C for 2 h. The mixture was brought to 25 °C after evaporation of toluene, the residue was column chromatographed on silica gel (100-200 mesh) using hexane as eluent to afford the chiral allene **192a**.



192a

(4a*R*,8a*R*)-*t*-Butyl octahydroquinoxaline-1(2H)-carboxylate 201

To the (4a*R*,8a*R*)-decahydroquinoxaline **198** (1.40 g, 10.0 mmol) solution in DCM (10 mL), di-*t*-butyldicarbonate **200** (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 (4a*R*,8a*R*)-tert-butyl octahydroquinoxaline-1(2H)-carboxylate **201** as colorless viscous liquid.



201

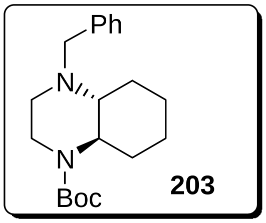
Yield : 1.82 g (76%), colorless liquid.

IR (neat) : (cm^{-1}) 3302, 2924, 1656, 1614, 1527, 749, 696

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 3.52-3.53 (d, *J* = 4, 1H), 3.02-3.14 (m, 2H), 2.97-2.3.02 (m, 1H), 2.68-2.69 (m, 1H), 2.21-2.24 (d, *J* = 12, 1H), 1.85-1.88 (d, *J* = 12, 1H), 1.70-1.72 (d, *J* = 8, 2H), 1.44 (s, 9H), 1.18-1.33 (m, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 155.5, 79.4, 63.7, 56.2, 44.9, 41.3, 33.2, 30.3, 28.5, 25.4, 25.2.

N-Benzylated mono protected (4a*R*,8a*R*)-decahydroquinoxaline 203



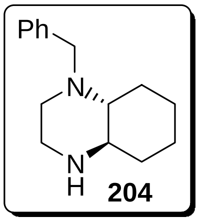
203

To a solution of (4a*R*,8a*R*)-*t*-butyl octahydroquinoxaline-1(2H)-carboxylate **201** (1.50 g, 6.25 mmol) in dry acetonitrile (30 mL) was added benzyl bromide **202** (0.83 mL, 7 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 under reduced pressure. The residue was extracted with DCM (2 X 40 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 on silica gel (100-200 mesh) using hexane/EtOAc (50:50) afforded (*R***,** *R*)-*t*-

butyl-4-benzyl-2, 3-diphenyl-1-piperazinecarboxylate **203** [0.28g (86%)] as colorless liquid. We have proceeded to next step without further purification of this product **203**.

(4aR,8aR)-1-Benzyldecahydroquinoxaline 204

To a solution of (*R*, *R*)-*tert*-butyl-4-benzyl-2, 3-diphenyl-1-piperazinecarboxylate **203** (1.831 g) 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 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 was column chromatographed on basic alumina (100-200 mesh) using hexane/EtOAc (50:50) as eluent to obtain the (4a*R*,8a*R*)-1-benzyldecahydroquinoxaline **204**.



204

Yield : 1.16 g (90%), colorless solid.

IR (KBr) : (cm^{-1}) 3000, 3026, 2926, 2854, 1641, 1452, 1067, 750, 700

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.21-7.23 (d, *J* = 8, 3H), 7.11-7.13 (d, *J* = 8, 2H), 6.14 (s, br, 1H), 3.98-4.02 (d, *J* = 16, 1H), 3.04-3.08 (d, *J* = 16, 1H), 2.76-2.78 (d, *J* = 8, 1H), 2.49-2.52 (d, *J* = 12, 2H), 2.18-2.21 (d, *J* = 12, 1H), 1.81-1.98 (m, 4H), 1.71-1.74 (d, *J* = 12, 2H), 1.26-1.35 (m, 4H).

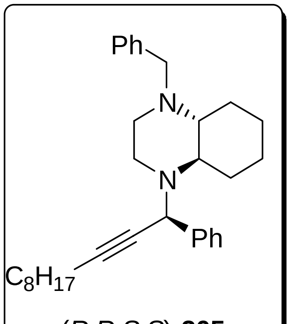
^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.2, 129.1, 128.1, 126.1, 67.1, 60.5, 57.4, 53.8, 46.1, 32.9, 29.0, 25.3, 24.9.

HRMS : (ESI) $C_{15}H_{22}N_2$ $[M+H]^+$ calcd 231.1861 found 231.1861.

3.4.8 General procedure for the preparation of cyclic mon-propargylamines 205a-b

To a 25 mL of reaction flask was added CuBr (0.07 g 0.5 mol %), decahydroquinazoline derivative **204** (0.23 g, 1 mmol), 1-alkyne **189** (0.15 g, 1.1 mmol) and aryl benzaldehydes **190** in toluene (3 mL) was heated to 120 °C for 12 h. The reaction mixture was brought to room temperature after the required time. After evaporation of the solvent toluene, the residue was column chromatographed on silica gel 100-200 (~95:5) using hexane/ethylacetae as eluent to obtain the chiral *bis*-propargylamines **205a-b**.

(1*S*,4*R*,4a*R*,8a*S*)-1-Benzyl-4-((*S*)-1-phenylundec-2-yn-1-yl) decahydronaphthalene 205a



(*R*,*R*,*S*,*S*)-**205a**

Yield : 0.19 g (92%), yellow oil.

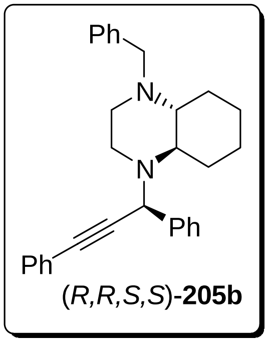
IR (neat) : (cm^{-1}) 3061, 3024, 2928, 2856, 1602, 1493, 1448, 1086, 733.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.57-7.59 (m, 2H), 7.28-7.32 (m, 6H), 7.21-7.25 (m, 2H), 5.14 (s, br, 1H), 4.07-4.11 (d, *J* = 16, 1H), 3.23-3.26 (d, *J* = 12, 1H), 2.58-2.61 (m, 1H), 2.42-2.48 (m, 2H), 2.31-2.36 (m, 4H), 2.06-2.18 (m, 3H), 1.81-1.86 (m, 2H), 1.57-1.64 (m, 2H), 1.47-1.53 (m, 3H), 1.19-1.39 (m, 14H), 0.89-0.92 (m, 4H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.8, 138.8, 129.3, 128.6, 128.0, 127.8, 126.9, 126.7, 88.7, 74.2, 65.9, 63.4, 57.4, 54.3, 55.6, 31.9, 29.6, 29.3, 29.2, 28.9, 28.6, 25.3, 25.0, 22.7, 18.8, 14.1.

HRMS : (ESI) $C_{32}H_{44}N_2$ $[M+H]^+$ calcd 457.3582 found 457.3581.

(1*S*,4*R*,4a*R*,8a*S*)-1-Benzyl-4-((S)-1,3-diphenylprop-2-yn-1-yl) decahydronaphthalene 205b



(*R*,*R*,*S*,*S*)-**205b**

Yield : 0.15 g (70%), colorless solid.

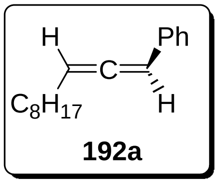
IR (neat) : (cm^{-1}) 2963, 2843, 1623, 1508, 1436, 1059, 742.

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.63-7.67 (m, 2H), 7.56-7.57 (m, 2H), 7.34-7.37 (m, 6H), 7.28-7.31 (m, 5H), 5.40 (s, br, 1H), 4.10-4.13 (d, *J* = 12, 1H), 3.34-3.37 (d, *J* = 12, 1H), 2.63-2.66 (d, *J* = 12, 1H), 2.53-2.58 (m, 2H), 2.29-2.43 (m, 4H), 2.09-2.17 (m, 3H), 1.84-1.90 (t, 2H), 1.40-1.51 (m, 2H), 1.25-1.37 (m, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 139.2, 138.8, 131.9, 129.3, 128.6, 128.3, 128.1, 127.8, 127.3, 126.7, 123.4, 88.6, 88.3, 66.1, 63.6, 57.5, 54.6, 52.9, 52.6, 45.7, 29.6, 28.7, 25.3, 25.0.

HRMS : (ESI) $C_{30}H_{32}N_2$ $[M+H]^+$ calcd 421.2643 found 421.2644.

3.4.9 Conversion of cyclic mono-propargylamine 205a to allene 192a

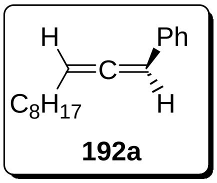


A flame–dried 25 mL reaction flask was charged with chiral cyclic mono-propargylamine **205a** (0.458 g, 1 mmol) and ZnI_2 (0.16 g, 0.5 mmol) in toluene (3 mL) and stirring in pre heated oil bath at 120 °C for 2 h. The mixture was brought to 25 °C after evaporation of toluene, the residue was column chromatographed on silica gel (100-200 mesh) using hexane as eluent to afford the chiral allene **192a**.

3.4.10 General procedure for synthesis of axially chiral allenes 192a-i

A flame–dried 25 mL reaction flask was charged with (4a*R*,8a*R*)-1-benzyldecahydroquinoxaline **204** (0.23 g, 1 mmol) in toluene (3 mL) and ZnI_2 (0.16 g, 0.5 mmol), alkyne **189** (0.138 g, 1.1 mmol) was added and stirring in pre heated oil bath at 110 °C for 10 min. After 10 minutes the reaction flask was lifted from oil bath and cooled to room temperature under nitrogen. Freshly distilled aromatic aldehydes **190** (0.11 g, 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 12 h. The mixture was brought to 25 °C after evaporation of toluene, the residue was column chromatographed on silica gel (100-200 mesh) using hexane as eluent to afford the chiral allenes **192a-i**.

(*R*)-Undeca-1,2-dien-1-ylbenzene 192a



Yield	:	0.17 g (70%), colorless liquid.

$[\alpha]_D^{25}$: -223.2 (*c* 0.52, $CHCl_3$, 90% ee), [lit. $[\alpha]_D^{20}$ = +298.8 (*c 0*.60, EtOH, 99% ee (*S*))].[61]

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

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

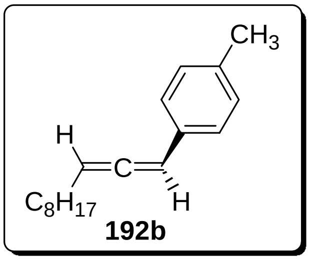
^{13}C NMR : (100 MHz, $CDCl_3$) δ: 205.1, 135.1, 128.5, 126.5, 95.5, 94.5, 31.8, 29.4, 29.3, 29.1, 28.7, 22.6, 14.1.

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

Enantiomeric purity 90% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.5 mL/min., 254nm, retention times: 4.4 min. (S) and 4.8 min. (*R*)].

The above procedure was followed for the preparation of other allenes **192b-i**.

(*R*)-1-Methyl-4-(undeca-1,2-dien-1-yl)benzene 192b



192b

Yield : 0.14 g (57%), colorless liquid.

$[\alpha]_D^{25}$: -136.3 (*c* 0.6.1, $CHCl_3$ for 83% ee)

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

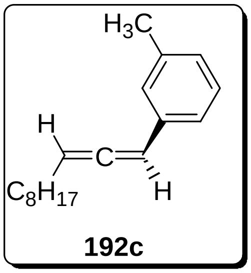
^{1}H NMR : (400 MHz, CDCl$_3$) δ: 7.20-7.18 (d, *J* = 8.0 Hz, 2H), 7.12-7.10 (d, *J* = 8.0 Hz, 2H), 6.12-6.09 (m, 1H), 5.55-5.54 (m, 1H), 2.36 (s, 3H), 2.15-2.10 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.27 (m, 10H), 0.94-0.90 (m, 3H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 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)

<u>Enantiomeric purity</u>: 83% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, heptane:*i*-PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times: 5.1 min. (*R*) and 5.7 min. (*S*)].

(*R*)-1-Methyl-3-(undeca-1,2-dien-1-yl)benzene 192c



192c

Yield : 0.206 g (85%), colorless liquid.

$[\alpha]_D^{25}$: -119.0 (*c* 0.6, CHCl$_3$ for 84% ee).

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

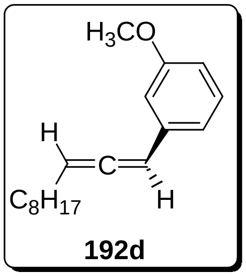
^{1}H NMR : (400 MHz, CDCl$_3$) δ: 7.28-7.22 (m, 1H), 7.16-7.14 (d, *J* = 8.0, Hz, 2H), 7.05-7.04 (d, *J* = 4 0 Hz, 1H), 6.16-6.13 (m, 1H), 5.62-5.57 (m, 1H), 2.38 (s, 3H), 2.20-2.15 (m, 2H), 1.56-1.52 (m, 2H) 1.43-1.32 (m, 10H), 0.94-0.92 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR : (100 MHz, CDCl$_3$) δ: 205.1, 138.1, 135.0, 128.4, 127.4, 127.2, 123.7, 94.9, 94.5, 31.9, 29.4, 29.3, 29.2, 28.8, 22.7, 21.4, 14.1.

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

<u>Enantiomeric purity</u>: 84% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.0 mL/min., 254 nm, retention times: 5.8 min. (*R*) and 8.3 min. (*S*)].

(*R*)-1-Methoxy-3-(undeca-1,2-dien-1-yl)benzene 192d



Yield : 0.20 g (76%), colorless liquid.

$[\alpha]_D^{25}$: -172.9 (*c* 0.57, $CHCl_3$ for 87% ee).

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

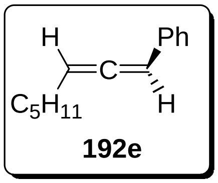
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.24-7.20 (m, 1H), 6.90-6.86 (m, 2H), 6.76-6.74 (m, 1H), 6.12-6.10 (m, 1H), 5.58-5.57 (m, 1H), 3.81 (s, 3H), 2.17-2.12 (m, 2H), 1.53-1.46 (m, 2H), 1.39-1.28 (m, 10H), 0.91-0.87 (t, *J* = 12.0 Hz, 3H).

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

Enantiomeric purity: 87% ee [determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.0 mL/min., 254 nm, retention times: 7.3 min. (*R*) and 9.5 min. (*S*)].

(*R*)-Octa-1,2-dien-1-ylbenzene 192e



192e

Yield : 0.065 g (70%), colorless liquid.

$[\alpha]_D^{25}$: -132.1 (*c* 0.51, $CHCl_3$ for 86% ee).

IR (neat) : (cm^{-1}) 3059, 2955, 2932, 2852, 1949, 1591, 1467, 779.

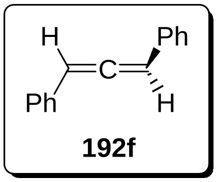
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.30-7.29 (m, 4H), 7.21-7.15 (m, 1H), 6.13-6.10 (m, 1H), 5.59-5.54 (m, 1H), 2.16-2.09 (m, 2H), 1.51-1.45 (m, 2H), 1.37-1.27 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR : (100 MHz, $CDCl_3$) δ: 205.2, 135.2, 128.5, 126.8, 126.6, 95.1, 94.5, 31.4, 28.9, 28.7, 22.4, 14.0.

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

Enantiomeric purity: 86%, HPLC analysis (Chiralcel OD-H column, 100% n-Hexane, and Flow rate: 0.5 mL/min, 254 nm, and Retention time: 10.4 min. (*R* isomer) and 11.7 min. (*S* isomer).

(***R***)-1,3-Diphenylpropa-1,2-diene 192f



192f

Yield : 0.048 g (25%), colorless solid.

mp : 48-50 °C 46% ee.

$[\alpha]_D^{25}$: -425.1 (*c* 0.31, $CHCl_3$ for 84% ee).

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

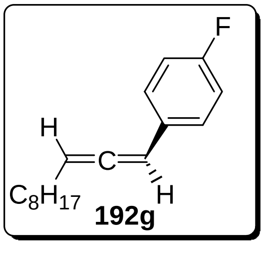
^{1}H NMR : (500 MHz, $CDCl_3$) δ: 7.36-7.30 (m, 8H), 7.25-7.21 (m, 2H), 6.60 (s, 2H).

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

LCMS : *m/z* 193 (M+1).

<u>Enantiomeric purity</u> 84%, HPLC analysis (Chiralcel OD-H column, n-Hexane: IPA = 99:1, Flow rate: 0.5 mL/min, 254 nm, Retention time: 11.3 min. (*R* isomer) and 26.9 min. (*S* isomer).

(***R***)-1-Fluoro-4-(undeca-1,2-dien-1-yl)benzene 192g



192g

Yield : 0.19 g (80%), colorless liquid.

$[\alpha]_D^{25}$: -141.8 (*c* 0.79, $CHCl_3$ for 89% ee).

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

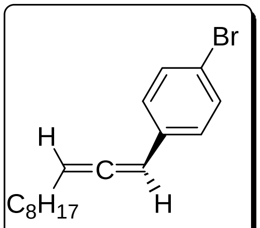
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.26-7.22 (m, 2H), 7.01-6.96 (m, 2H), 6.11-6.08 (m, 1H), 5.57-5.56 (m, 1H), 2.15-2.09 (m, 2H), 1.50-1.44 (m, 2H), 1.37-1.28 (m, 10H), 0.98-0.89 (m, 3H).

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

LCMS : m/z 247 (M+1)

<u>Enantiomeric purity</u> 89% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times: 4.4 min. (S) and 4.8 min. (*R*)].

(*R*)-1-Bromo-4-(undeca-1,2-dien-1-yl)benzene 192h



192h

Yield : 0.206 g (67%), colorless liquid.

$[\alpha]_D^{25}$: -138.1 (*c* 0.85, $CHCl_3$ for 90% ee).

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

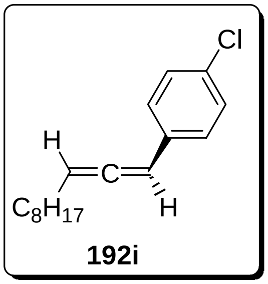
^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.44-7.41 (m, 2H), 7.18-7.15 (m, 2H), 6.10-6.07 (m, 1H), 5.61-5.56 (m, 1H), 2.17-2.11 (m, 2H), 1.51-1.46 (m, 2H), 1.39-1.28 (m, 10H), 0.92-0.89 (m, 3H).

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

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

Enantiomeric purity: 90% ee [determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/100:0; flow rate 1.5 mL/min., 254 nm, retention times: 3.5 min. (S) and 4.6 min. (*R*)].

(*R*)-1-Chloro-4-(undeca-1,2-dien-1-yl)benzene 192i



192i

Yield : 0.18 g (69%), colorless liquid.

$[\alpha]_D^{25}$: -159.4 (*c* 0.75, $CHCl_3$ for 87% ee).

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

^{1}H NMR : (400 MHz, $CDCl_3$) δ: 7.27-7.20 (m, 4H), 6.09-6.06 (m, 1H), 5.60-5.55 (m, 1H), 2.16-2.09 (m, 2H), 1.51-1.44 (m, 2H), 1.37- 1.26 (m, 10H), 0.92-0.87 (m, 3H).

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

LCMS : m/z 263 (M+1).

Enantiomeric purity: 87% 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 timess: 3.3 min. (*S*) and 4.2 min. (*R*)].

3.4.11 Recovery of the chiral diamine 204 by $NaBH_4$ reduction

Conversion of propargylamine 205a to allene 192a and chiral diamine 204

A flame dried 25 mL reaction flask was charged with chiral cyclic mono-propargylamine **205a** (0.46 g, 1 mmol) and ZnI_2 (0.16 g, 0.5 mmol) followed by toluene (3 mL). The reaction mixture was stirred on pre heated oil bath at 120 °C for 2 h. The reaction mixture was slowly brought to 25 °C under N_2. Then was added $NaBH_4$ and methanol to the mixture and stirred for 12 h at room temperature. The residue was column chromatographed on silica gel (100-200 mesh) using hexane as eluent to afford the *R*-allene **192a** in 70% yield and 90% ee. The chiral diamine **204** [0.37 g (75%)] was isolated by ethyl acetate as eluent.

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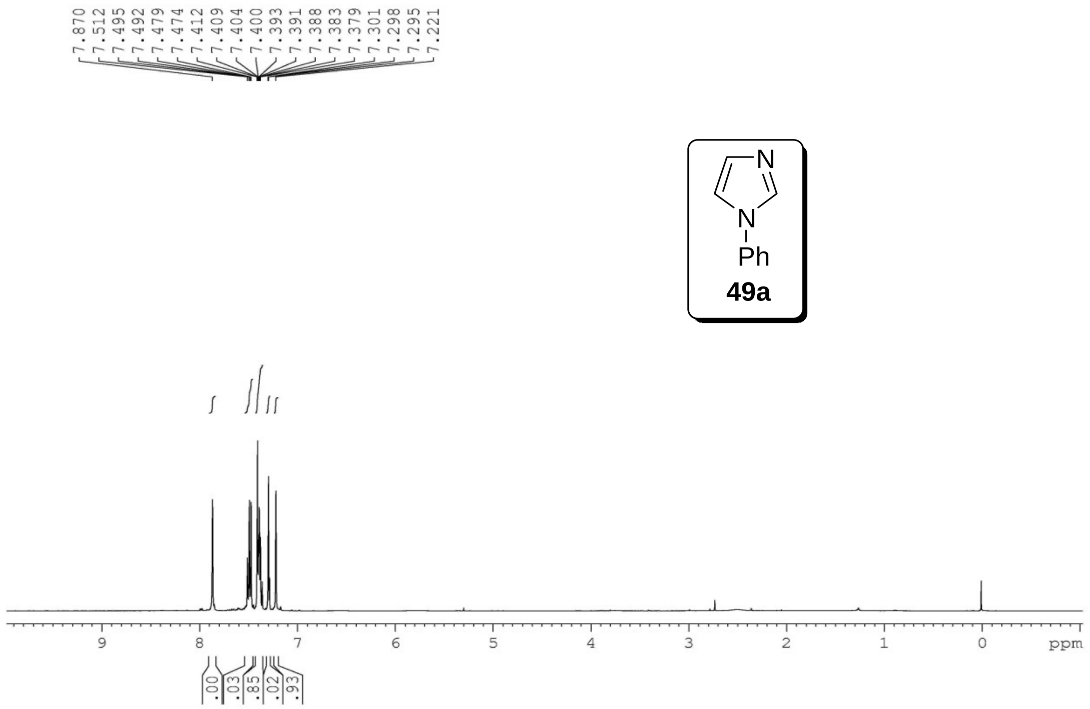
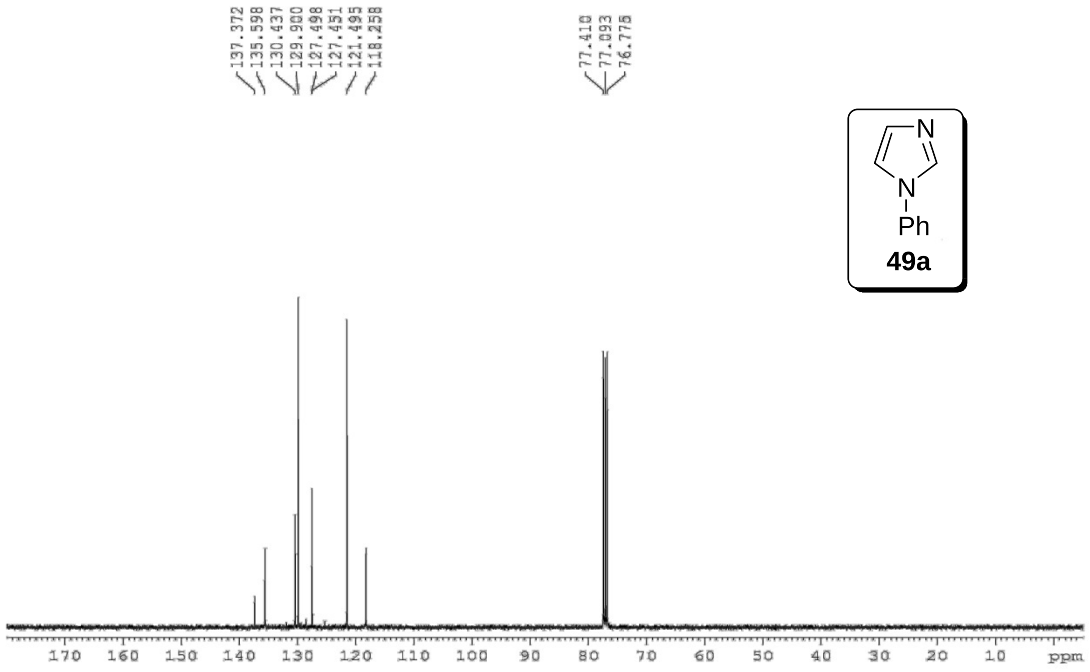
Appendix I

(Representative Spectra)

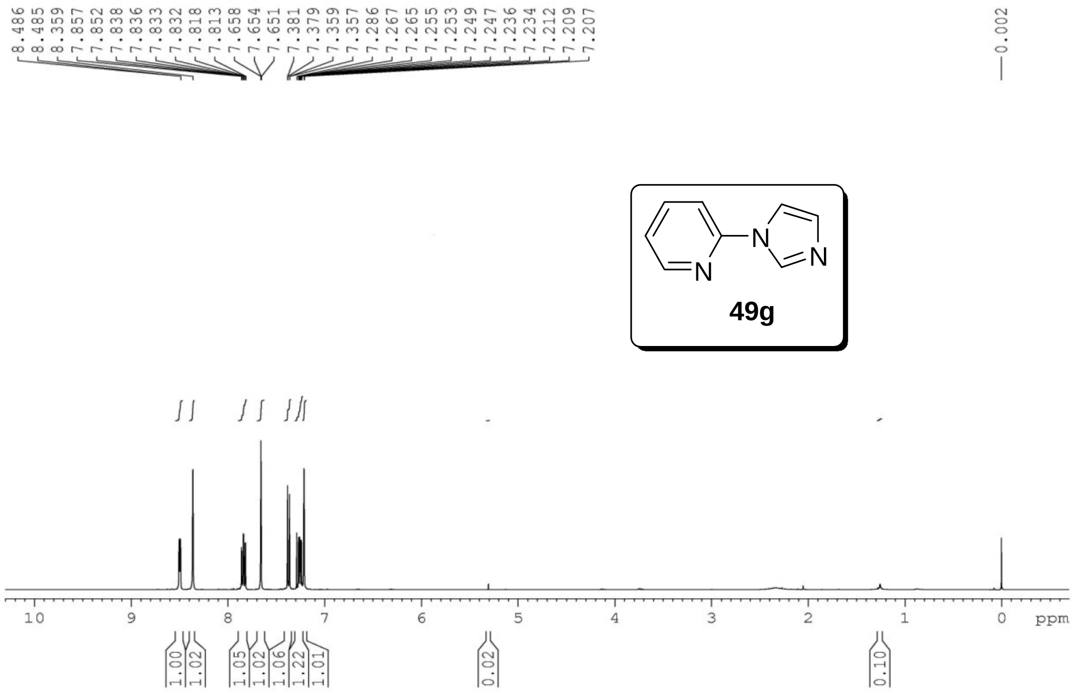
Spectrum No.1 (Chapter 1, Section 1.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



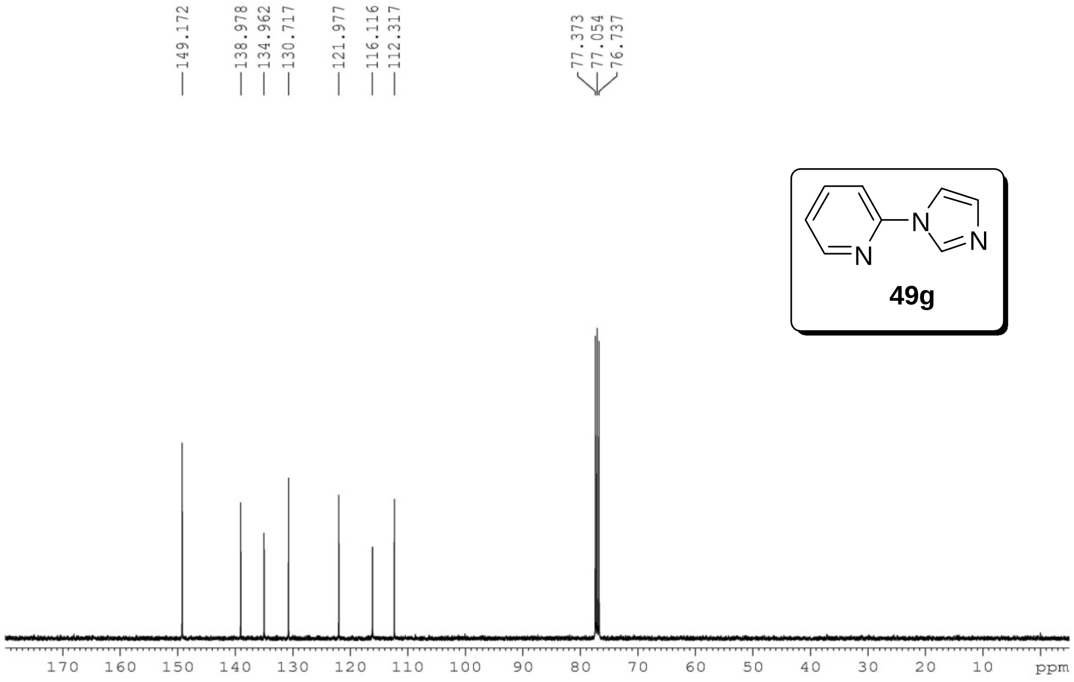
Spectrum No.2 (Chapter 1, Section 1.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



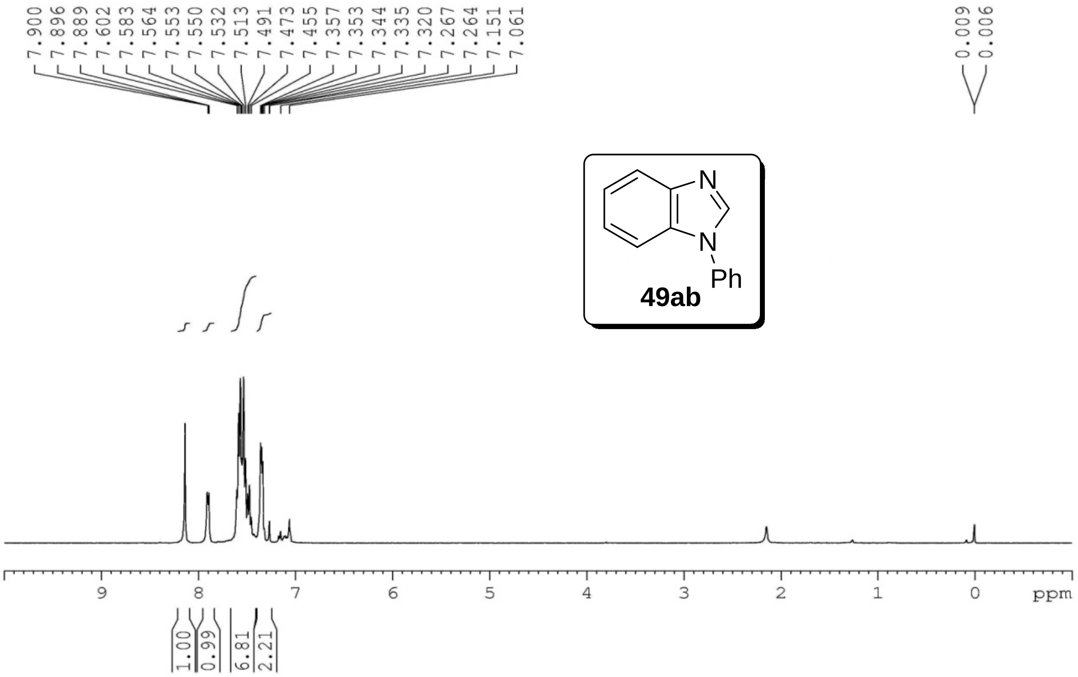
Spectrum No.3 (Chapter 1, Section 1.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



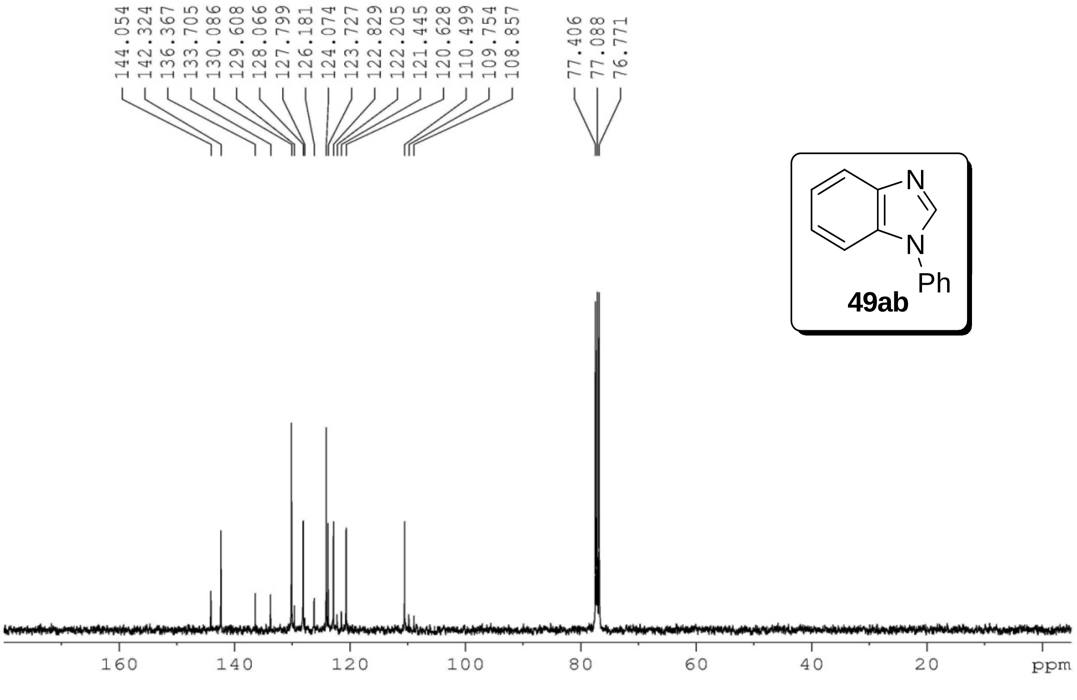
Spectrum No.4 (Chapter 1, Section 1.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



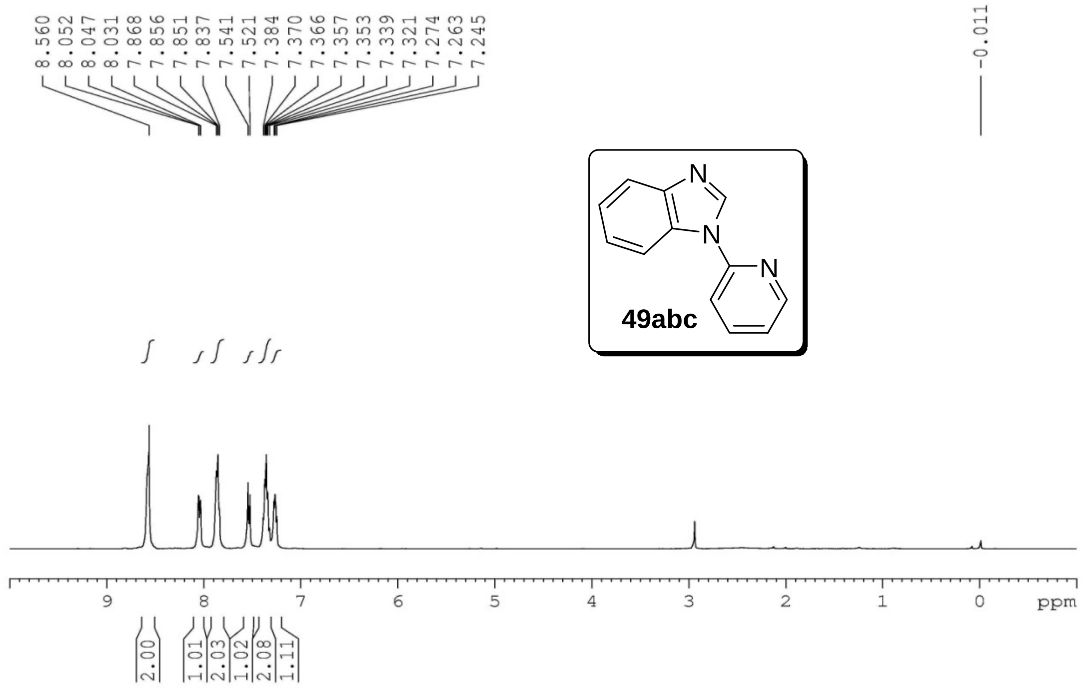
Spectrum No.5 (Chapter 1, Section 1.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



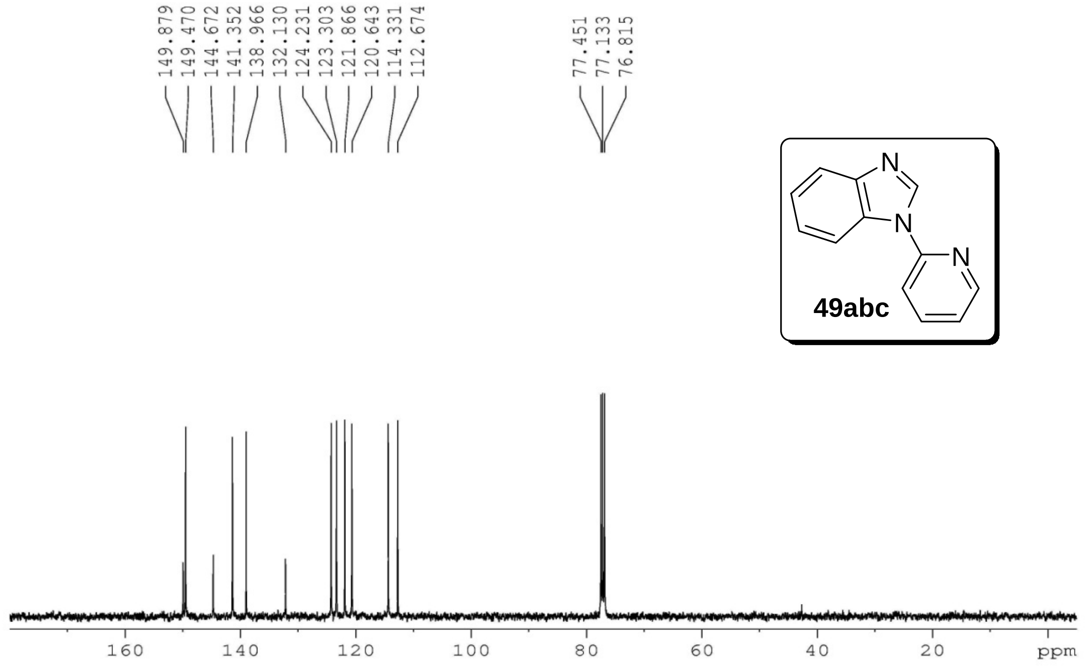
Spectrum No.6 (Chapter 1, Section 1.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



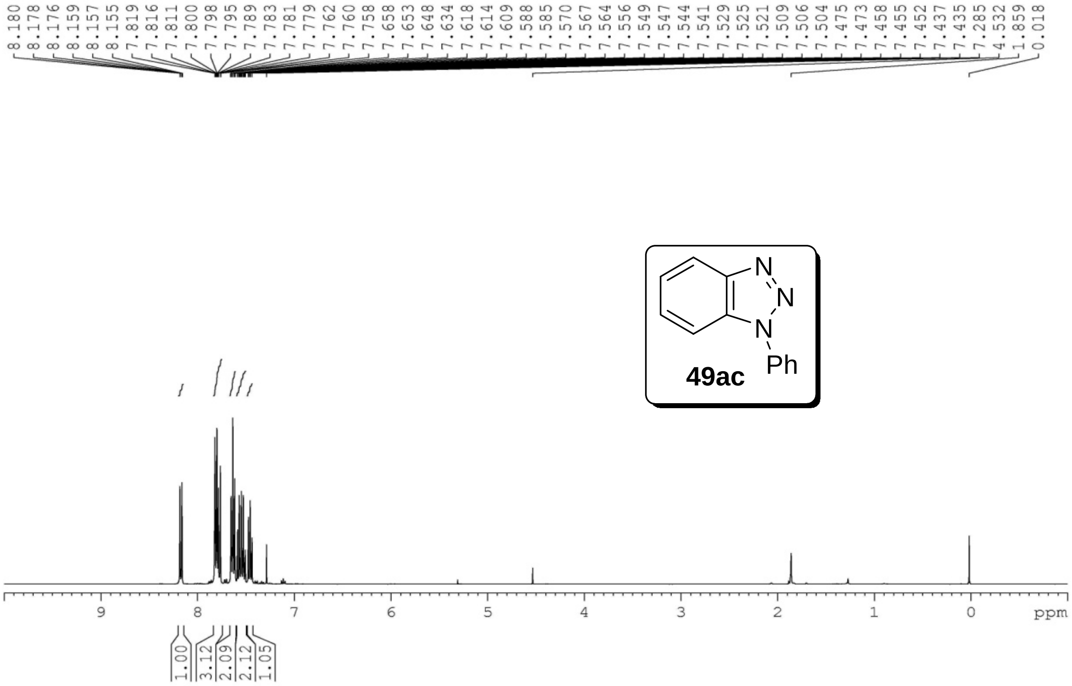
Spectrum No.7 (Chapter 1, Section 1.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



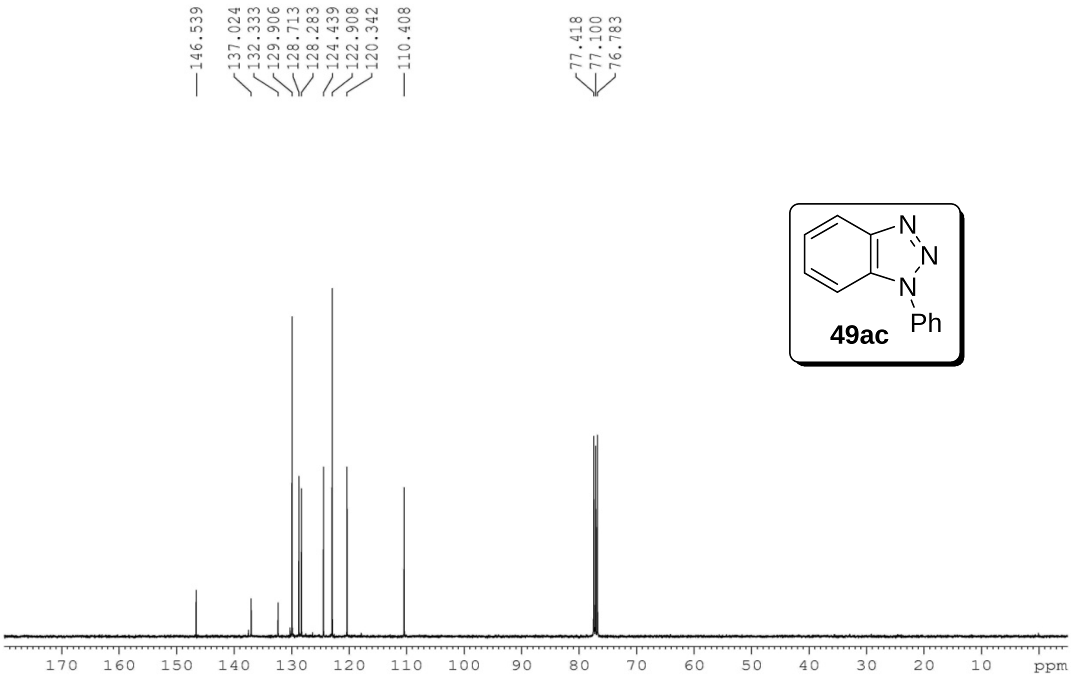
Spectrum No.8 (Chapter 1, Section 1.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



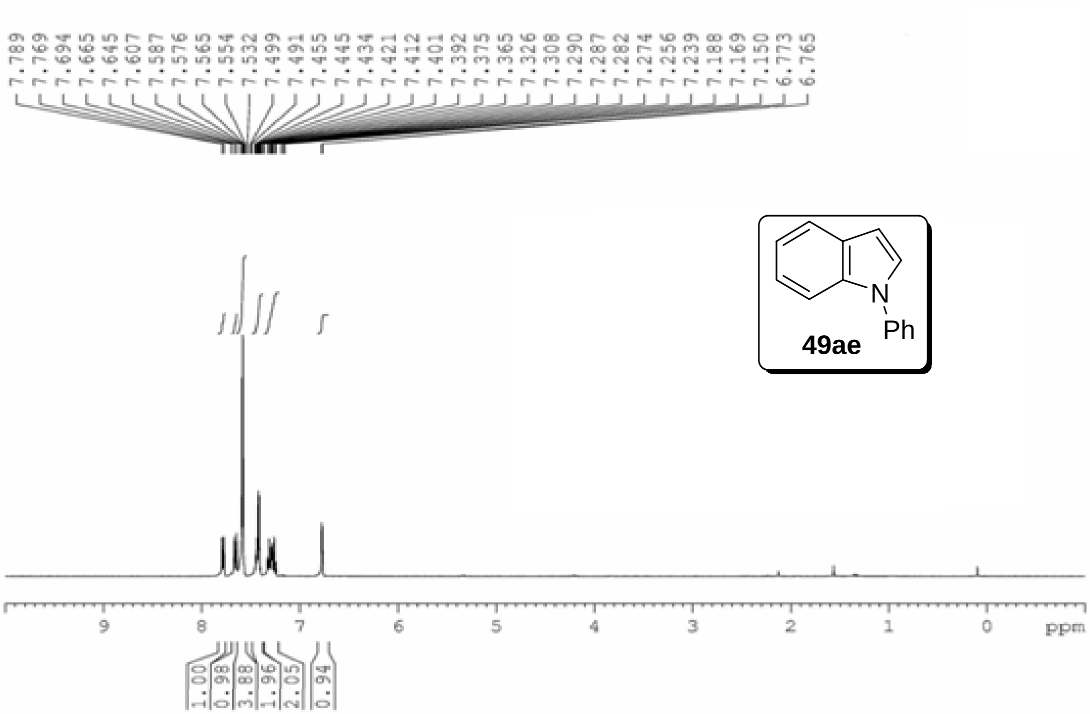
Spectrum No.9 (Chapter 1, Section 1.2.4) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



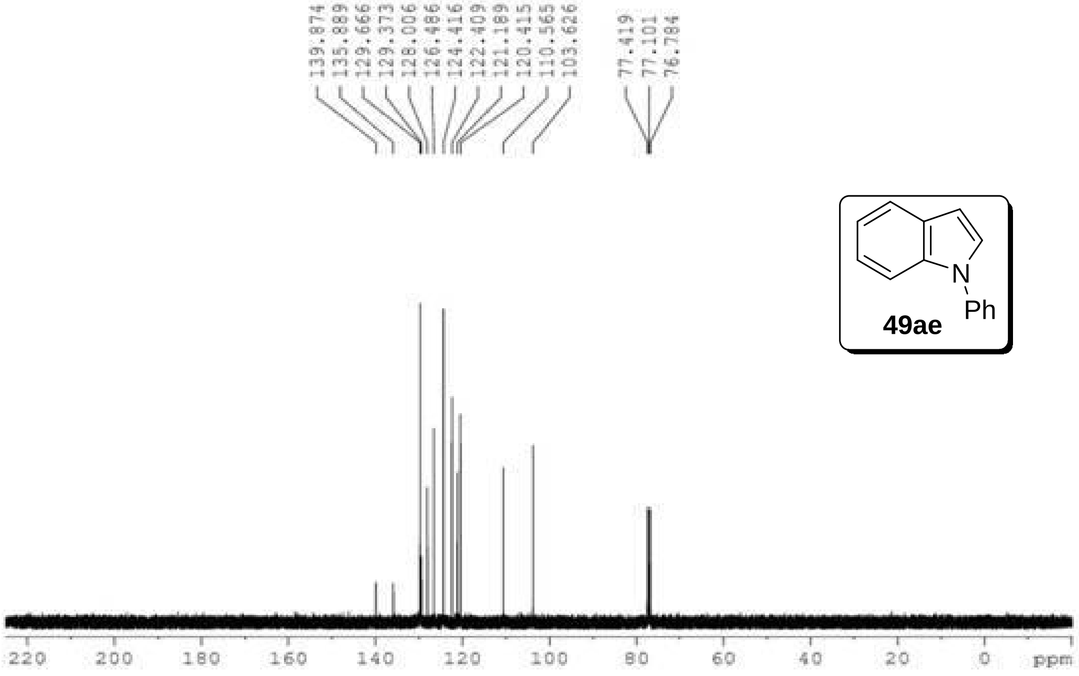
Spectrum No.10 (Chapter 1, Section 1.2.4) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



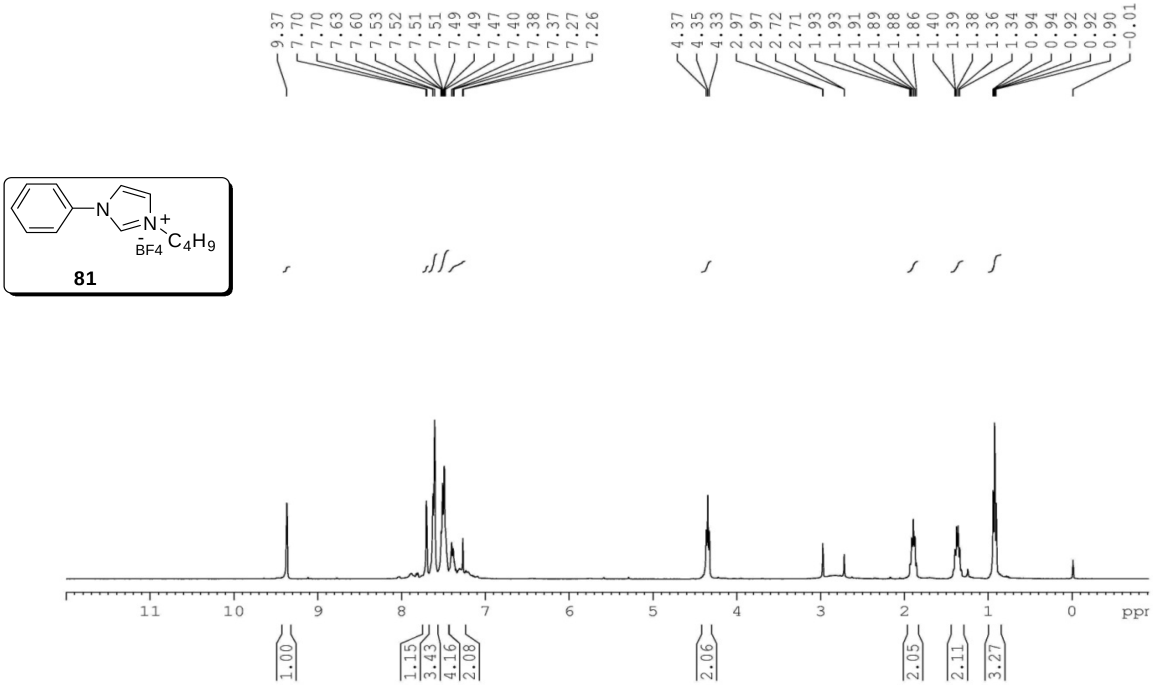
Spectrum No.11 (Chapter 1, Section 1.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No.12 (Chapter 1, Section 1.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

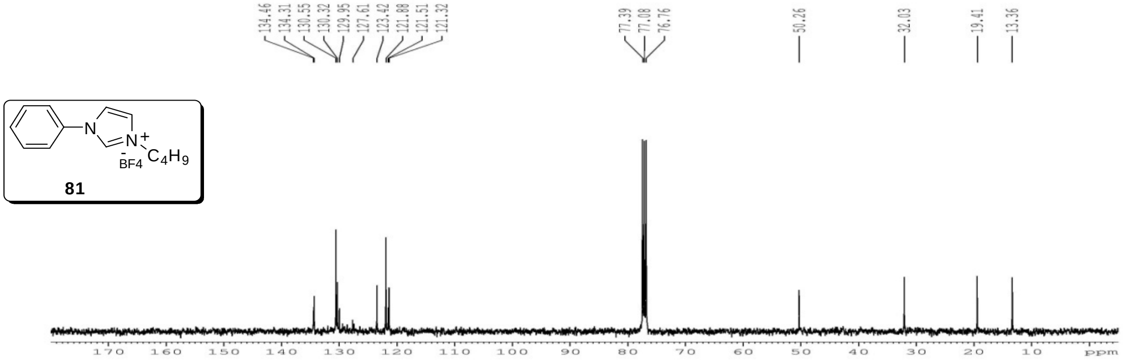


Spectrum No.13 (Chapter 1, Section 1.2.5) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



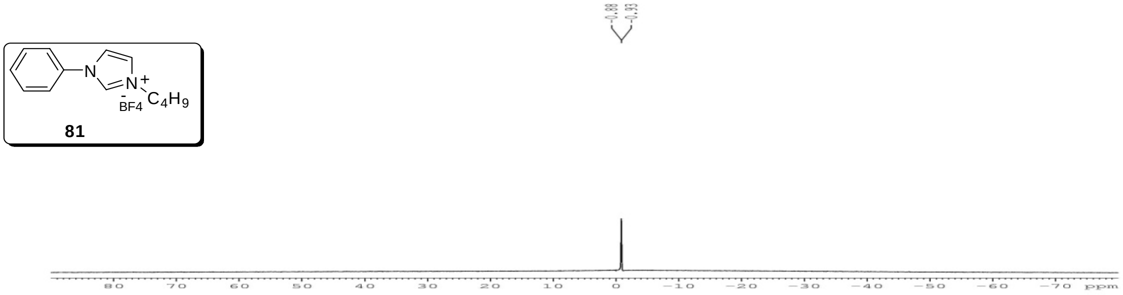
81

Spectrum No.14 (Chapter 1, Section 1.2.5) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



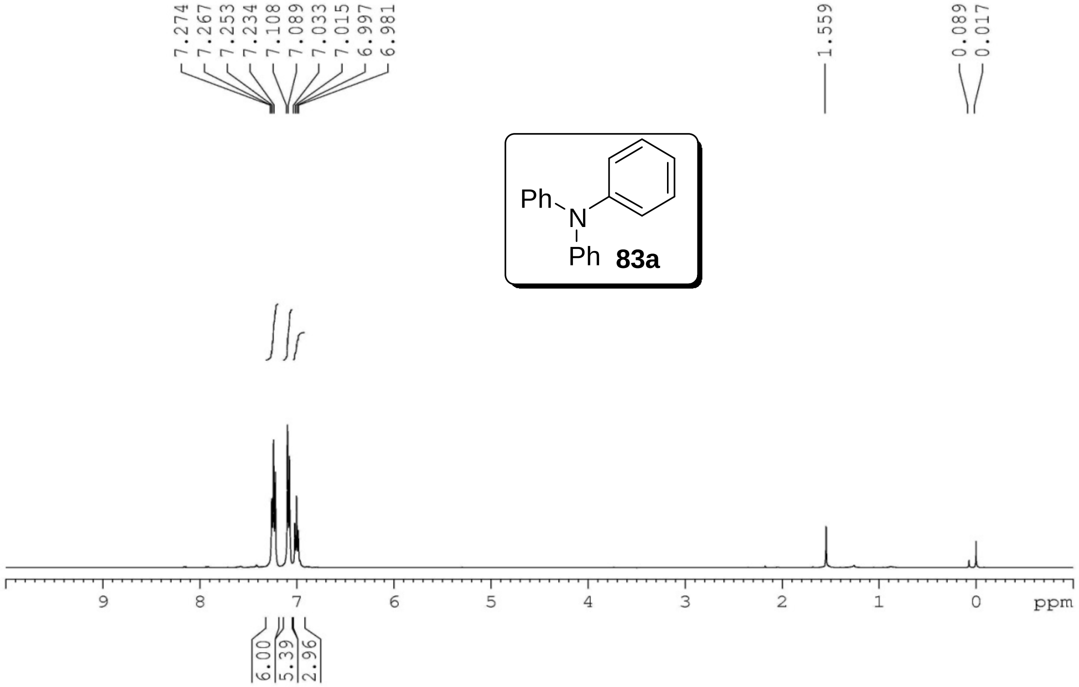
81

Spectrum No.15 (Chapter I, Section 1.2.5) ^{11}B NMR Spectrum (128.3 MHz, CDCl$_3$)

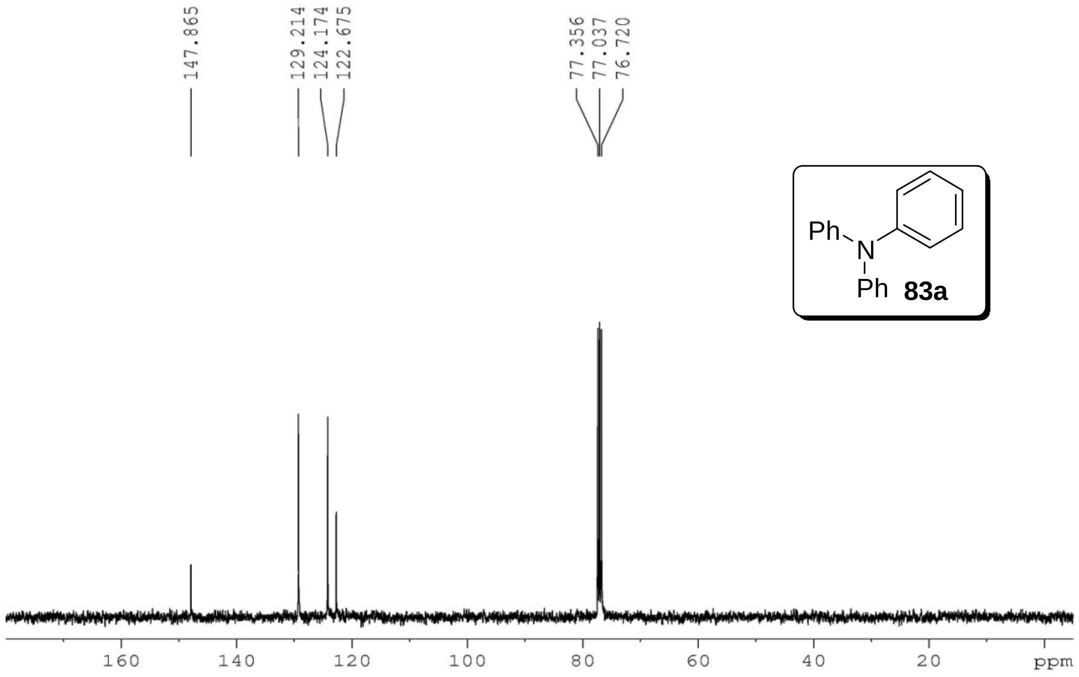


81

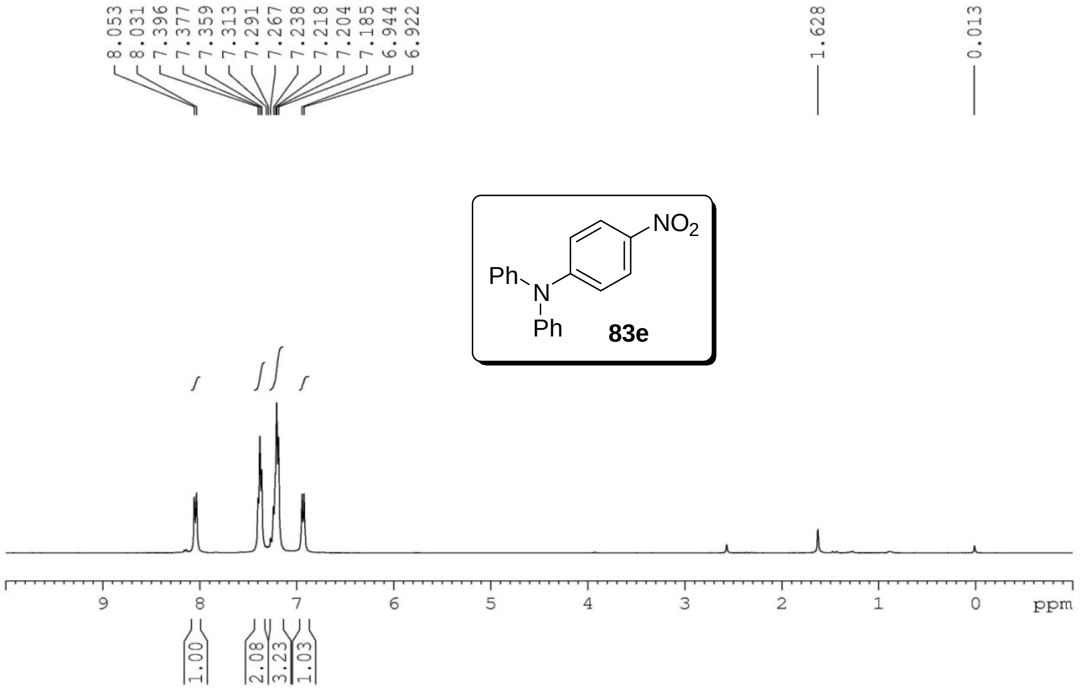
Spectrum No.16 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



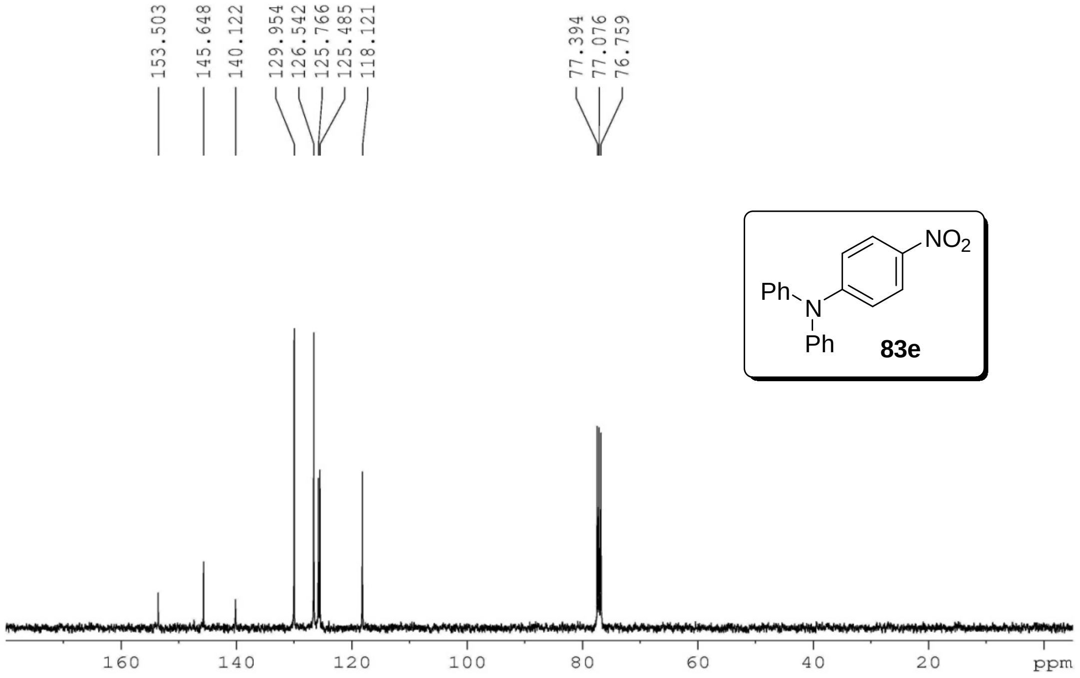
Spectrum No.17 (Chapter 1, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



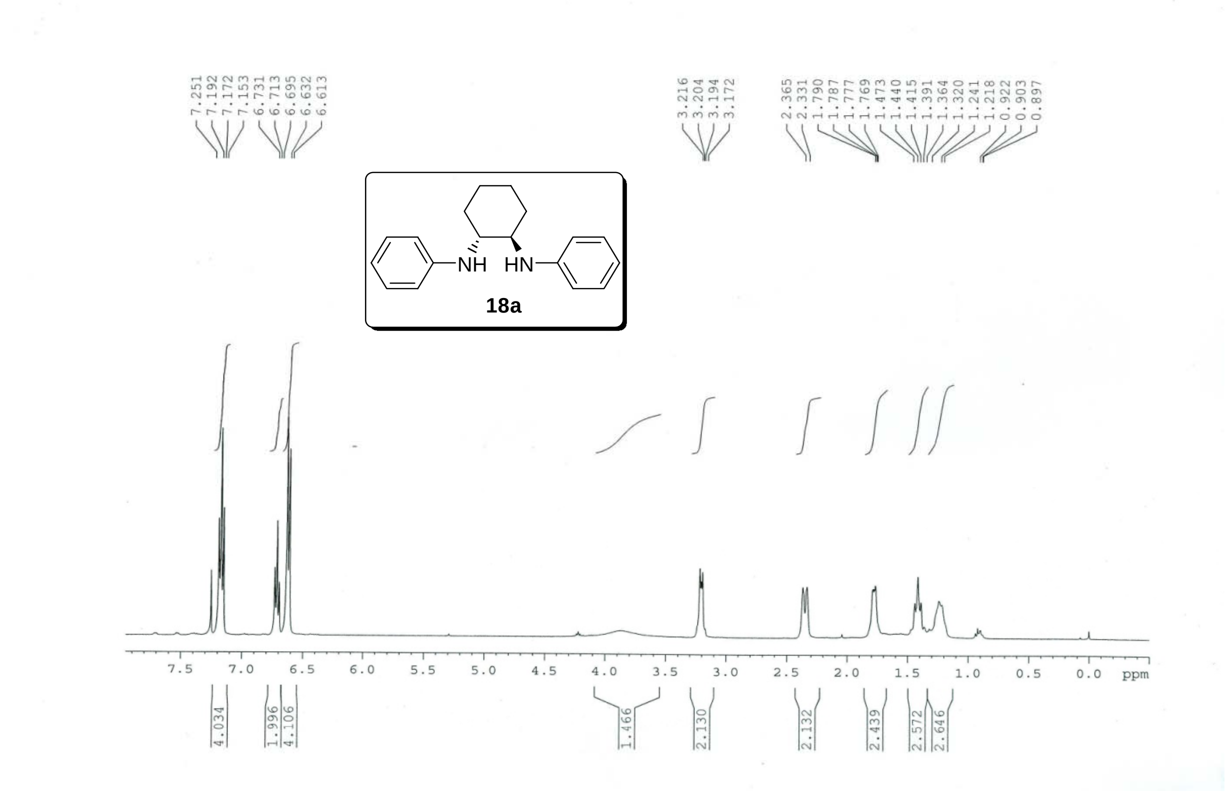
Spectrum No.18 (Chapter 1, Section 1.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



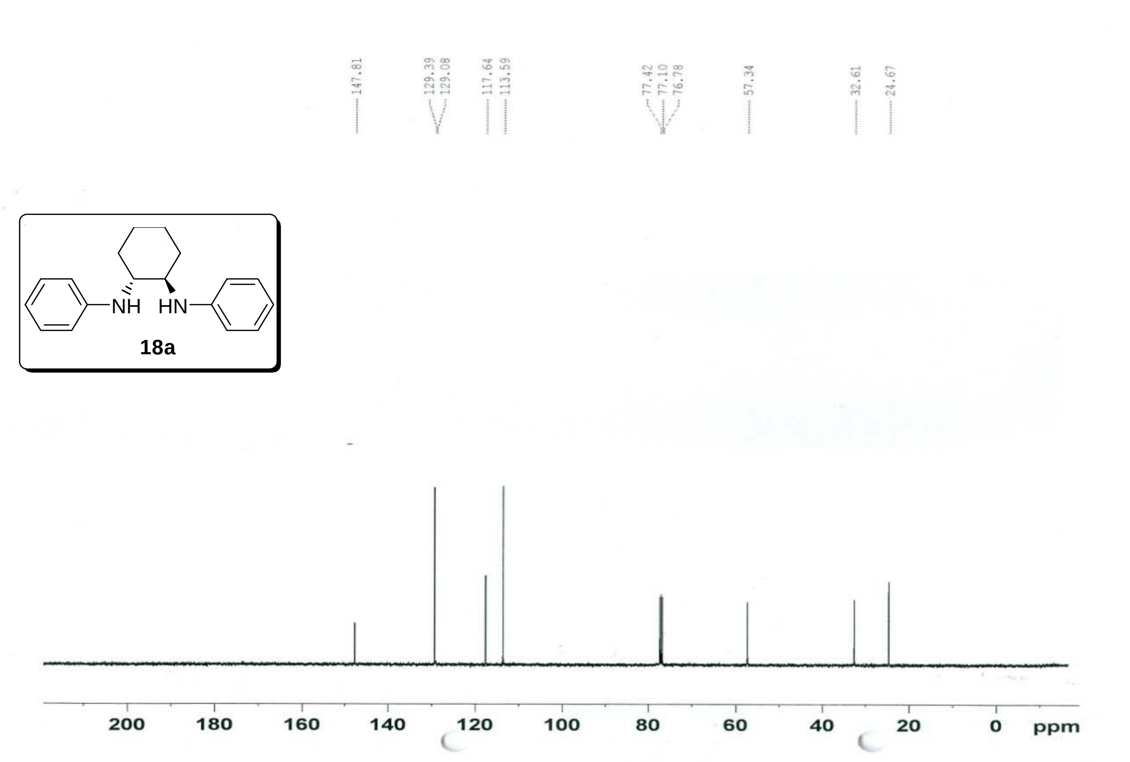
Spectrum No.19 (Chapter 1, Section 1.2.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



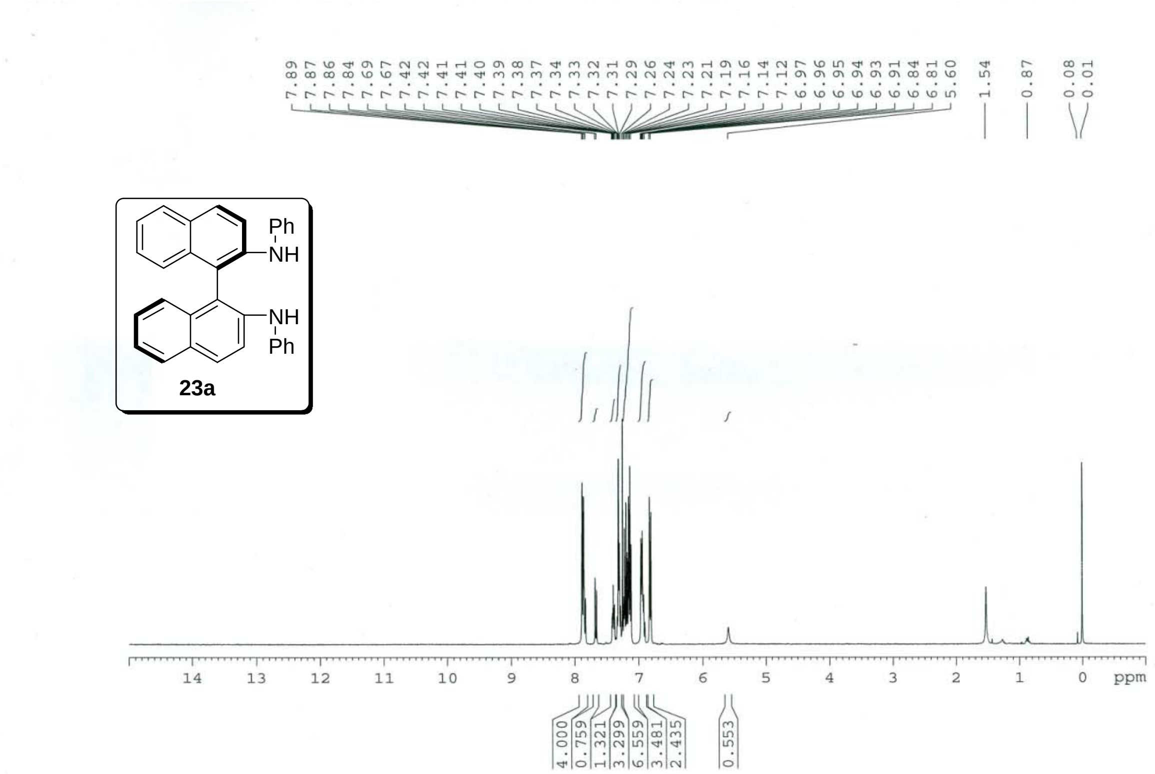
Spectrum No.20 (Chapter 2, Section 2.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



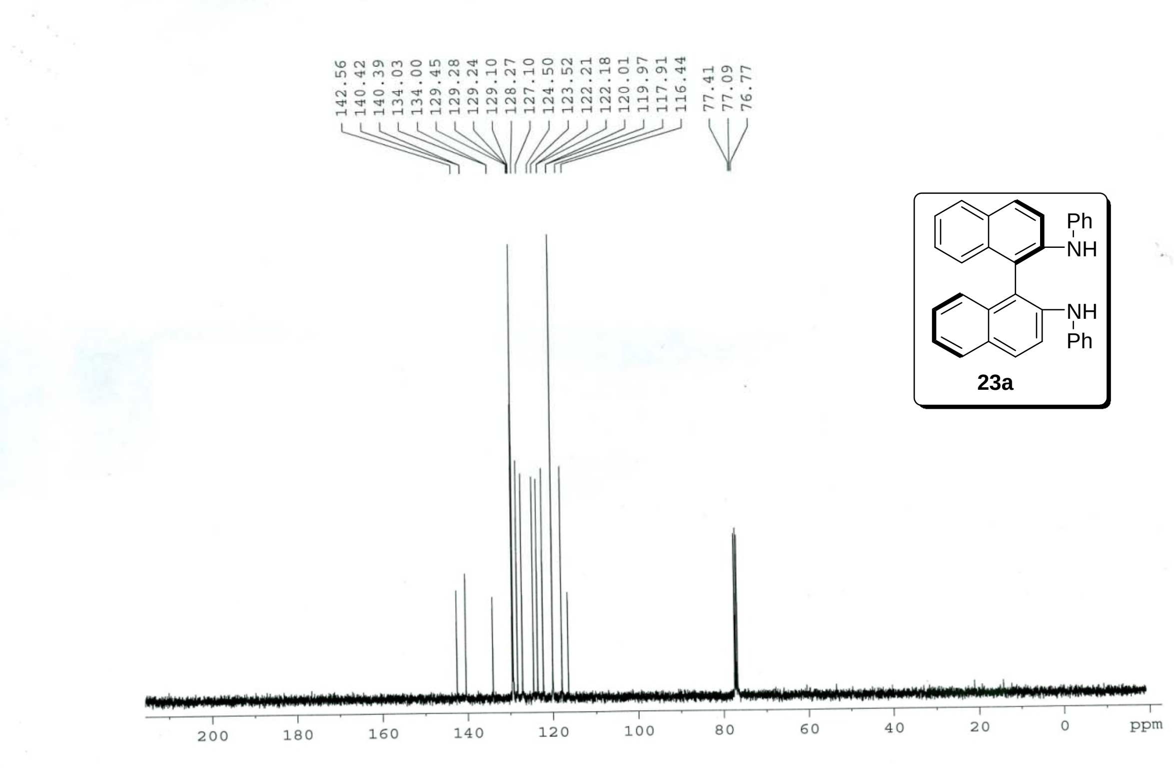
Spectrum No.21 (Chapter 2, Section 2.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



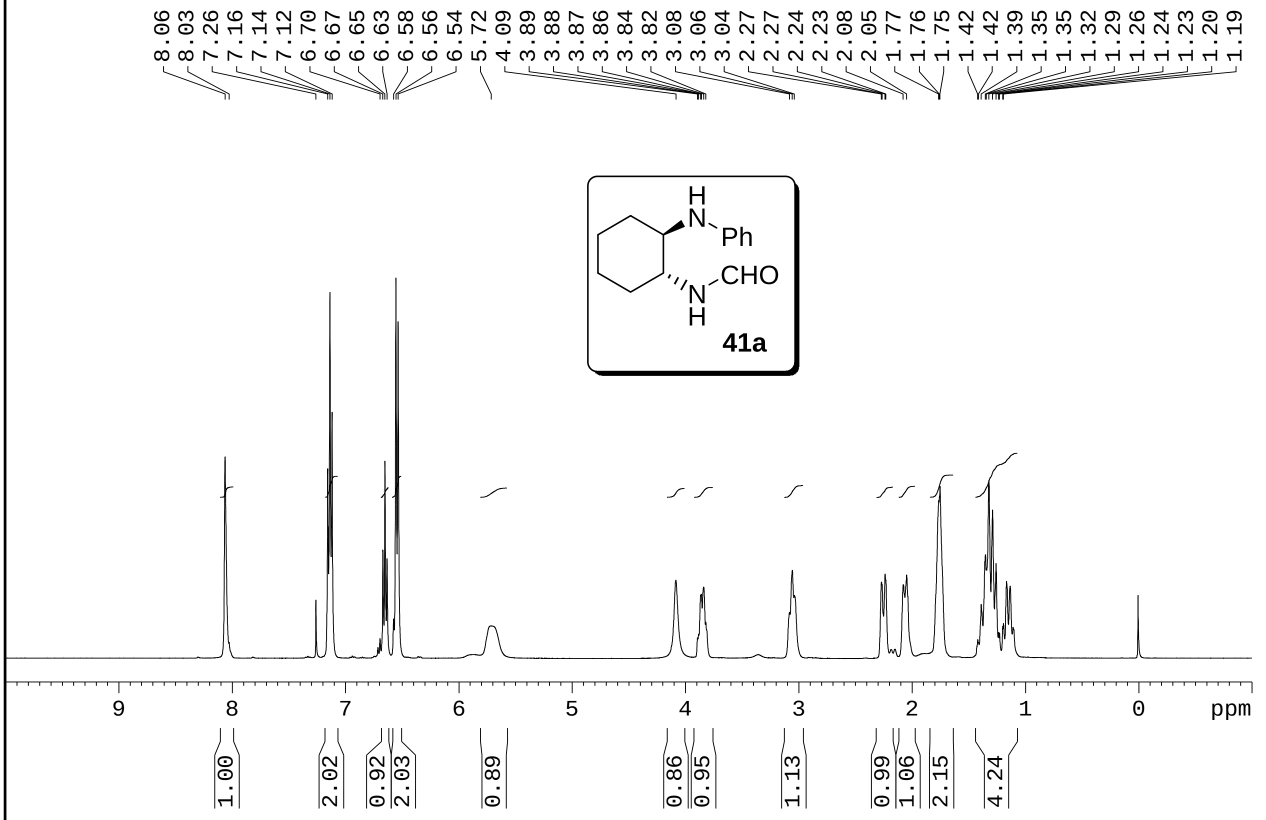
Spectrum No.22 (Chapter 2, Section 2.2.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No.23 (Chapter 2, Section 2.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No.24 (Chapter 2, Section 2.2.3) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



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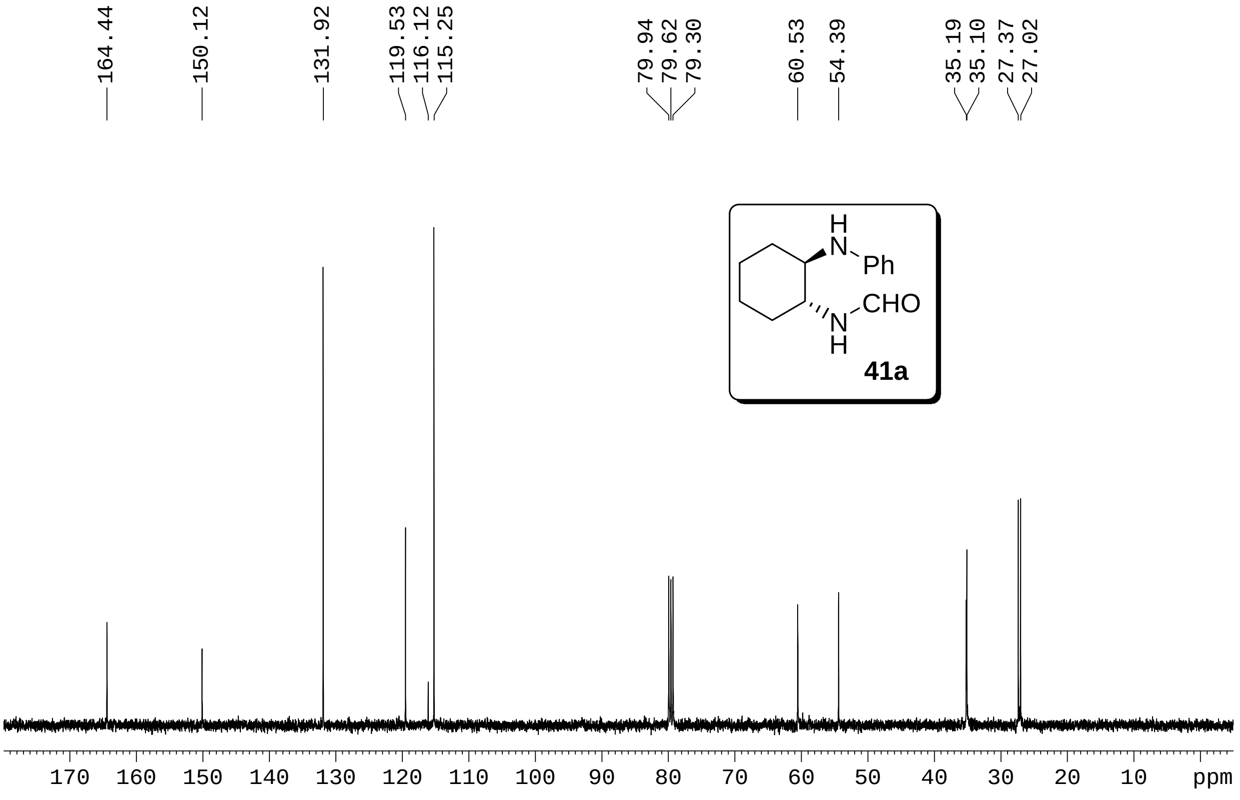
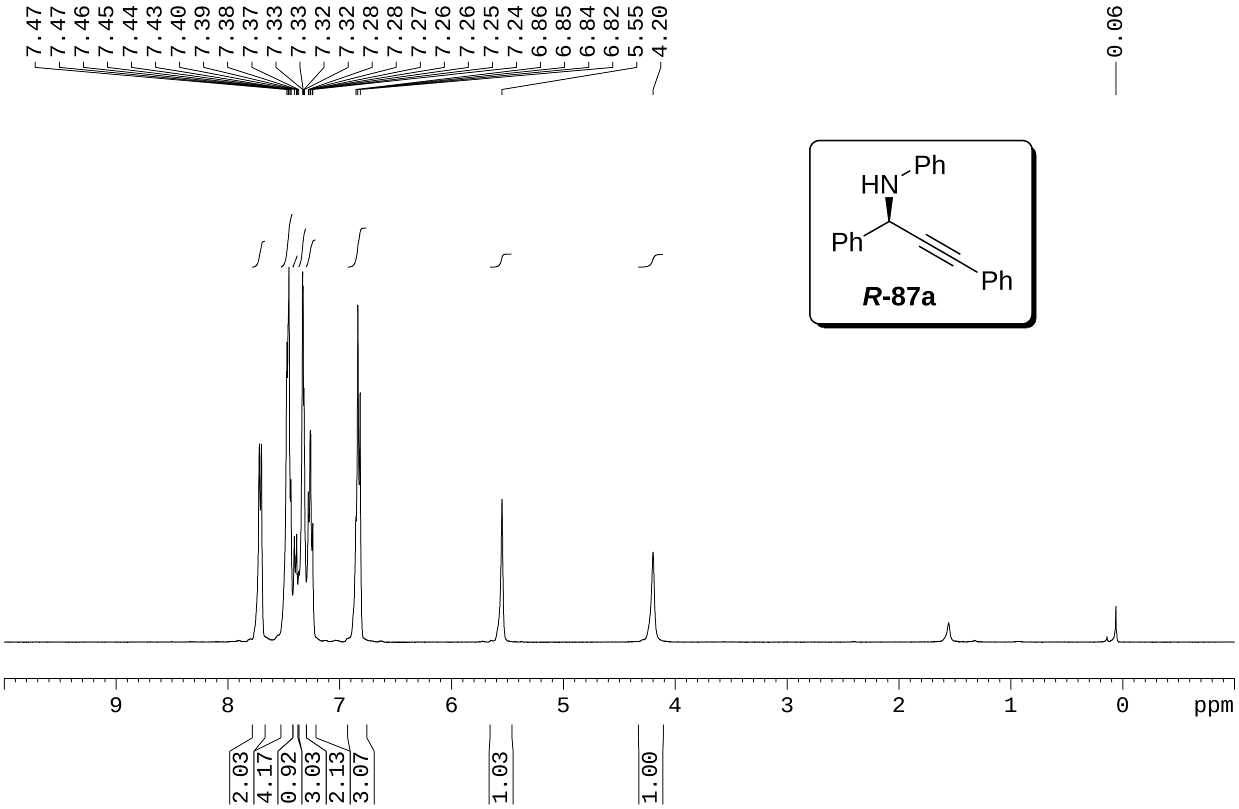
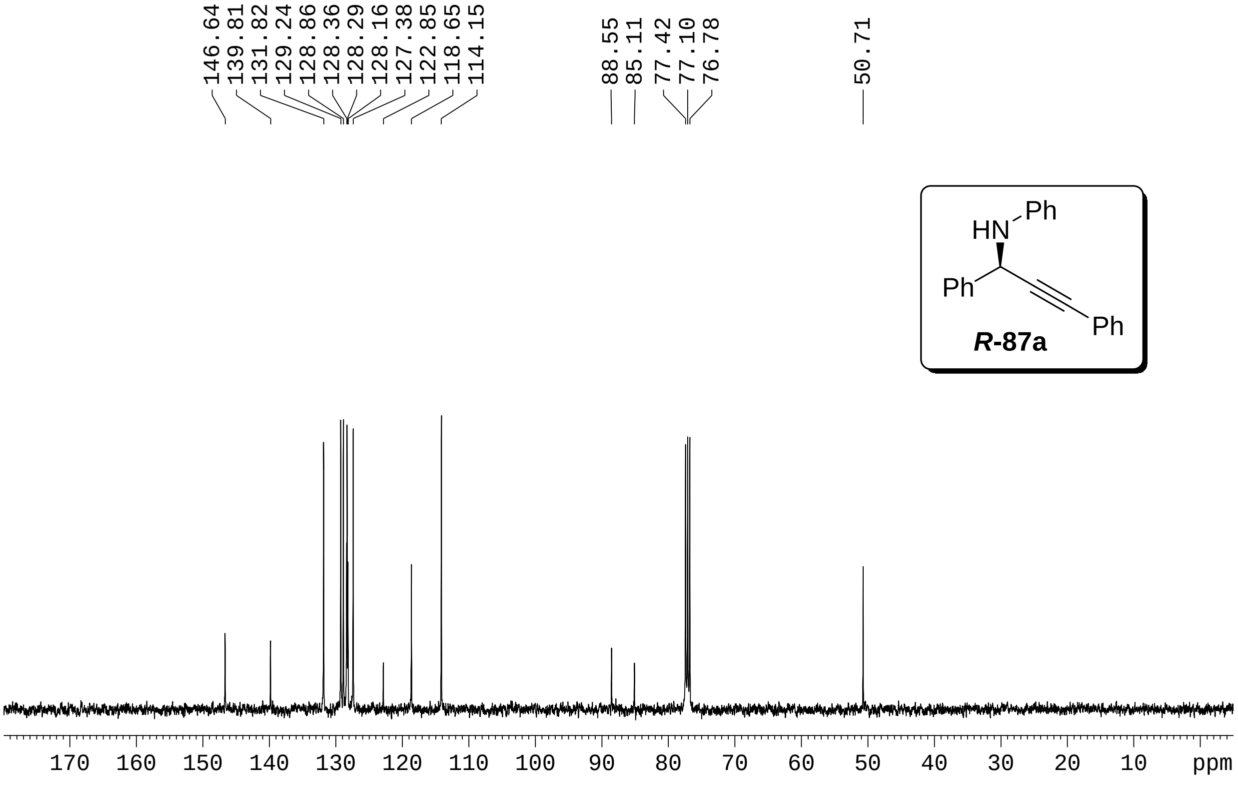


Spectrum No.26 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



Spectrum No.27 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



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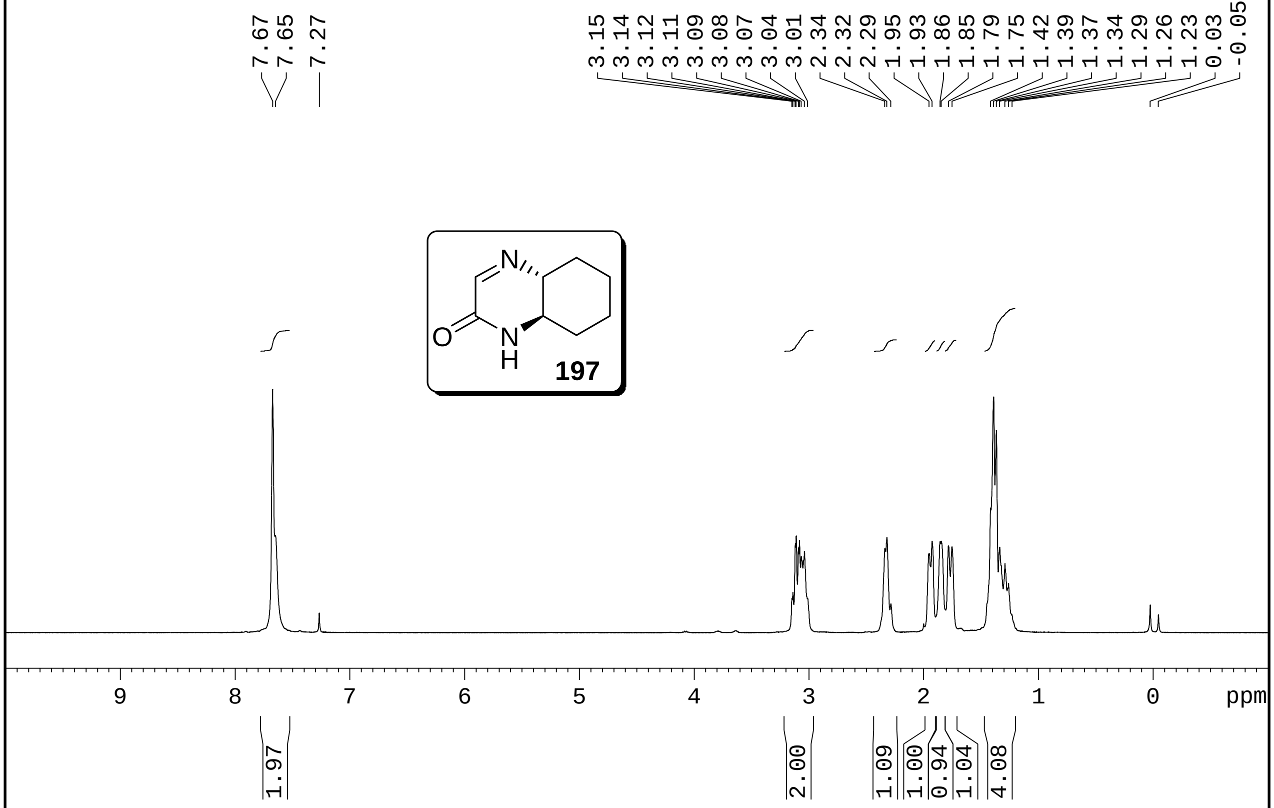
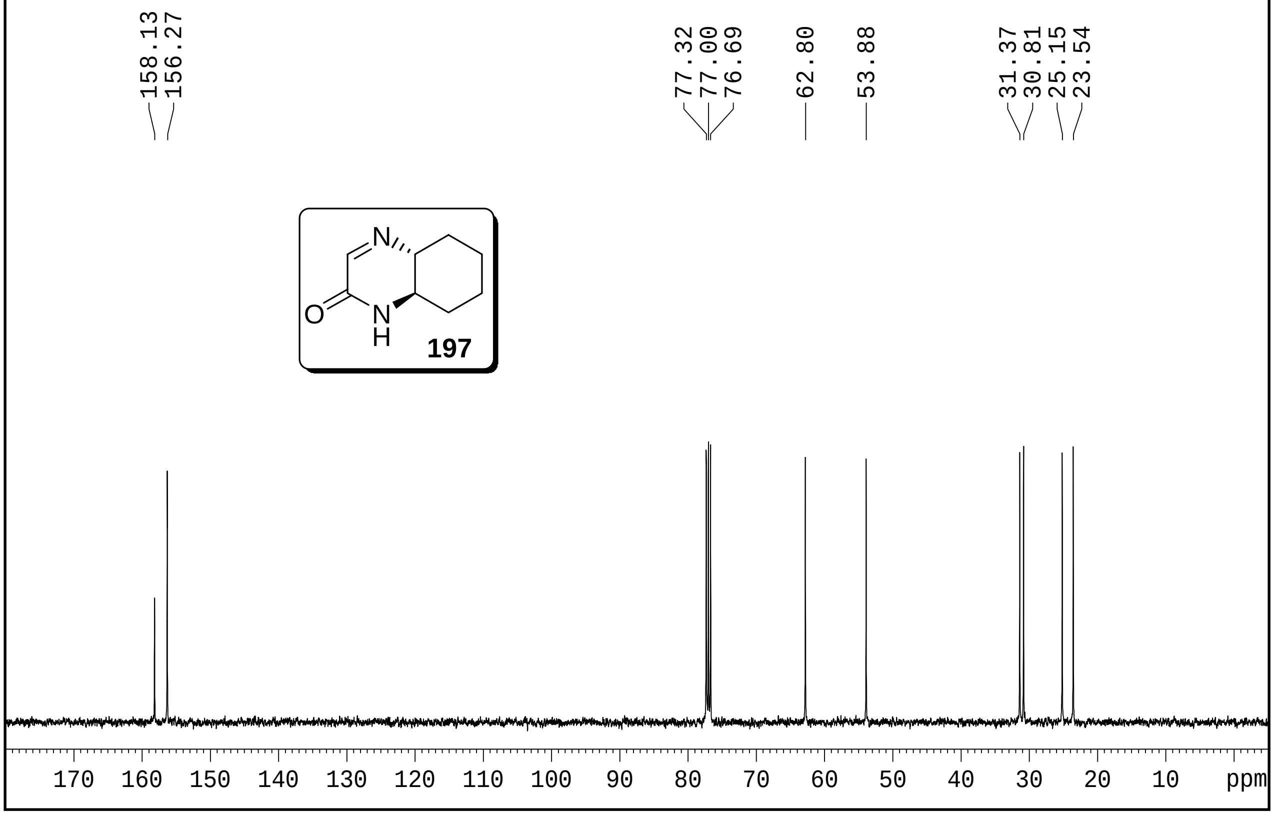


Spectrum No.29 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



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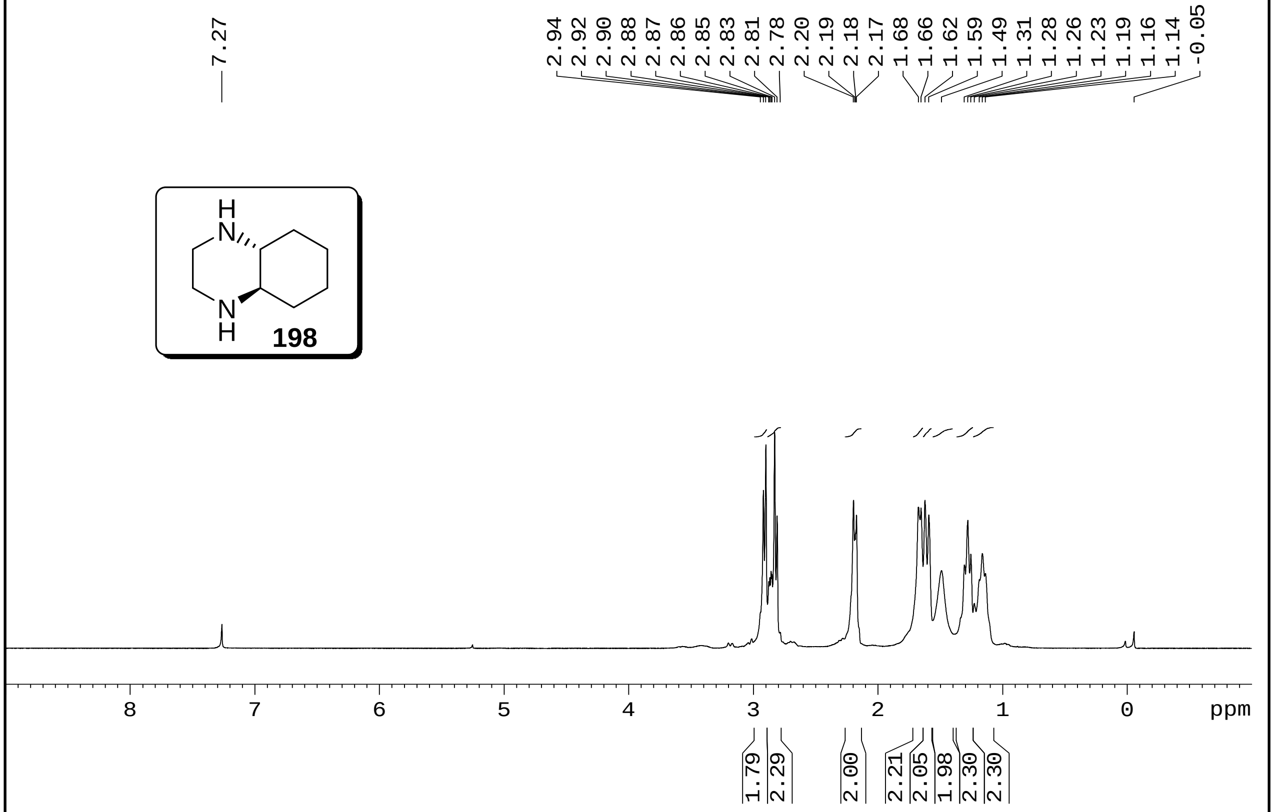

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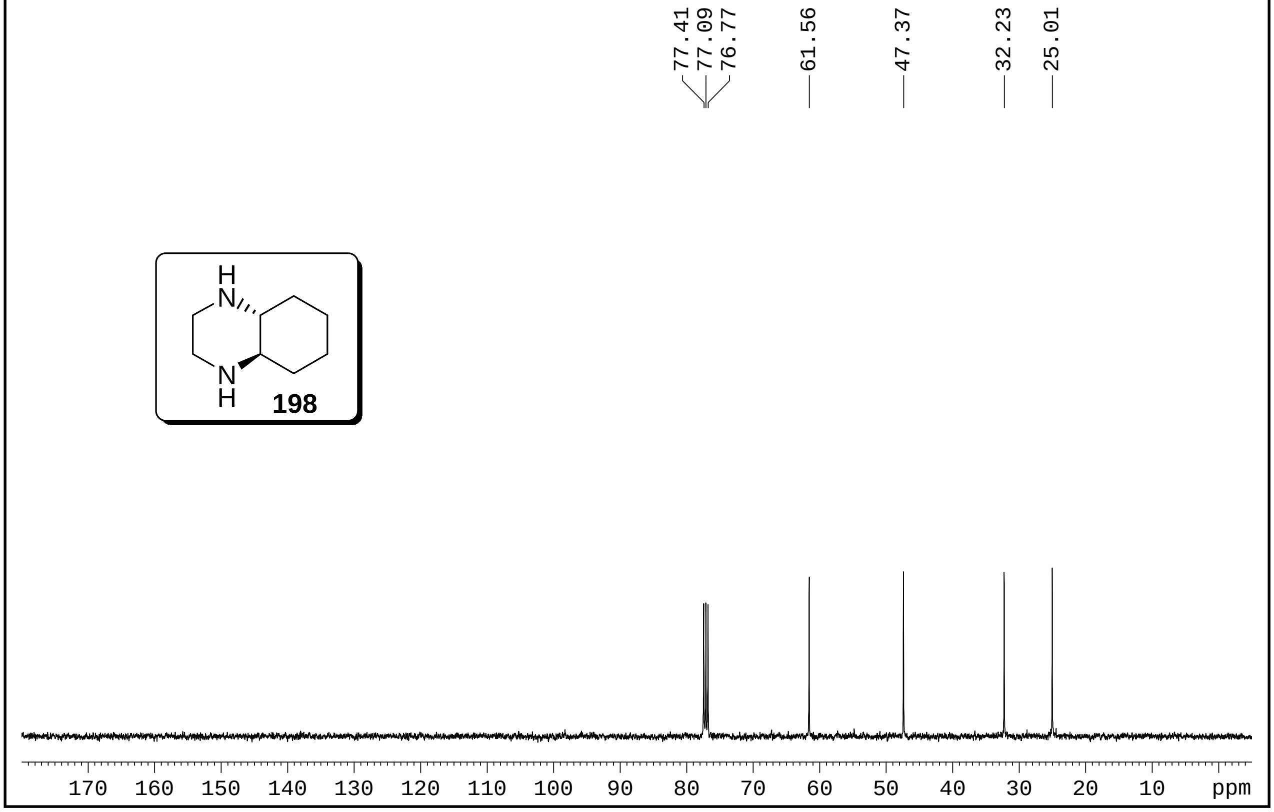
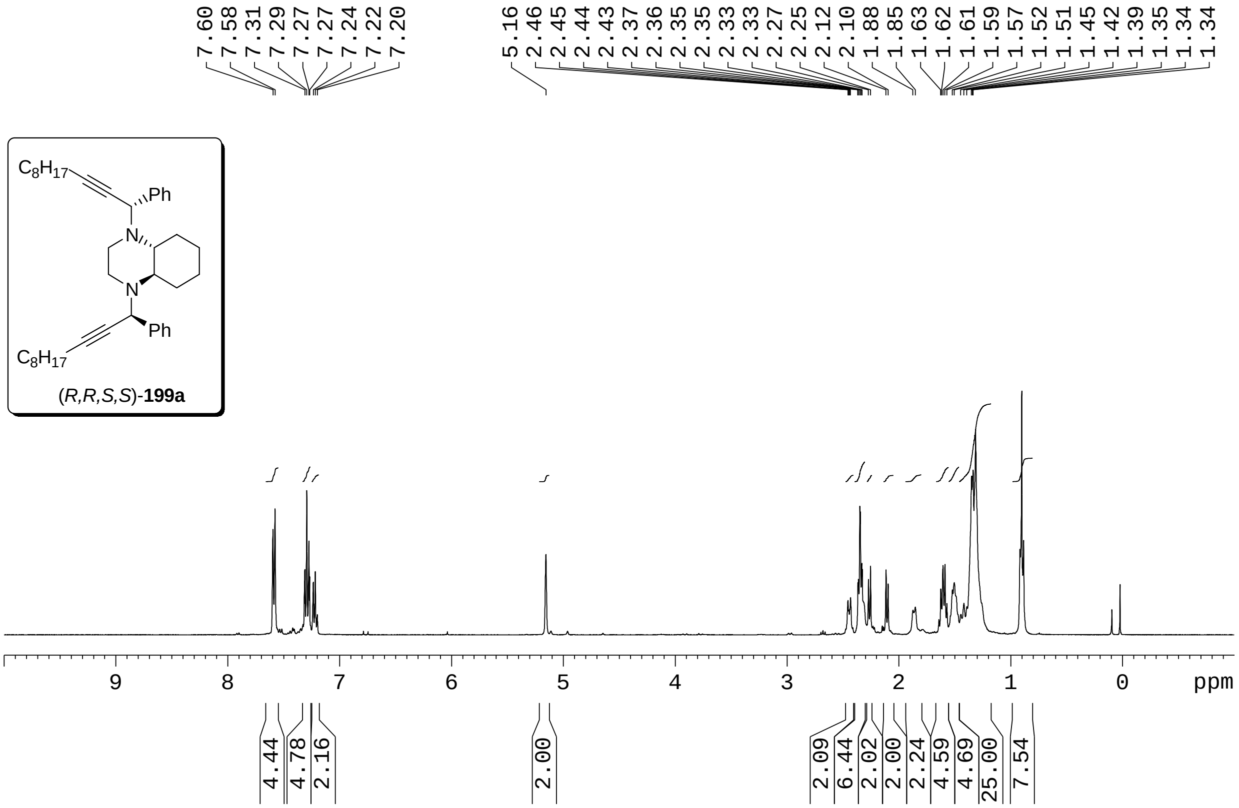
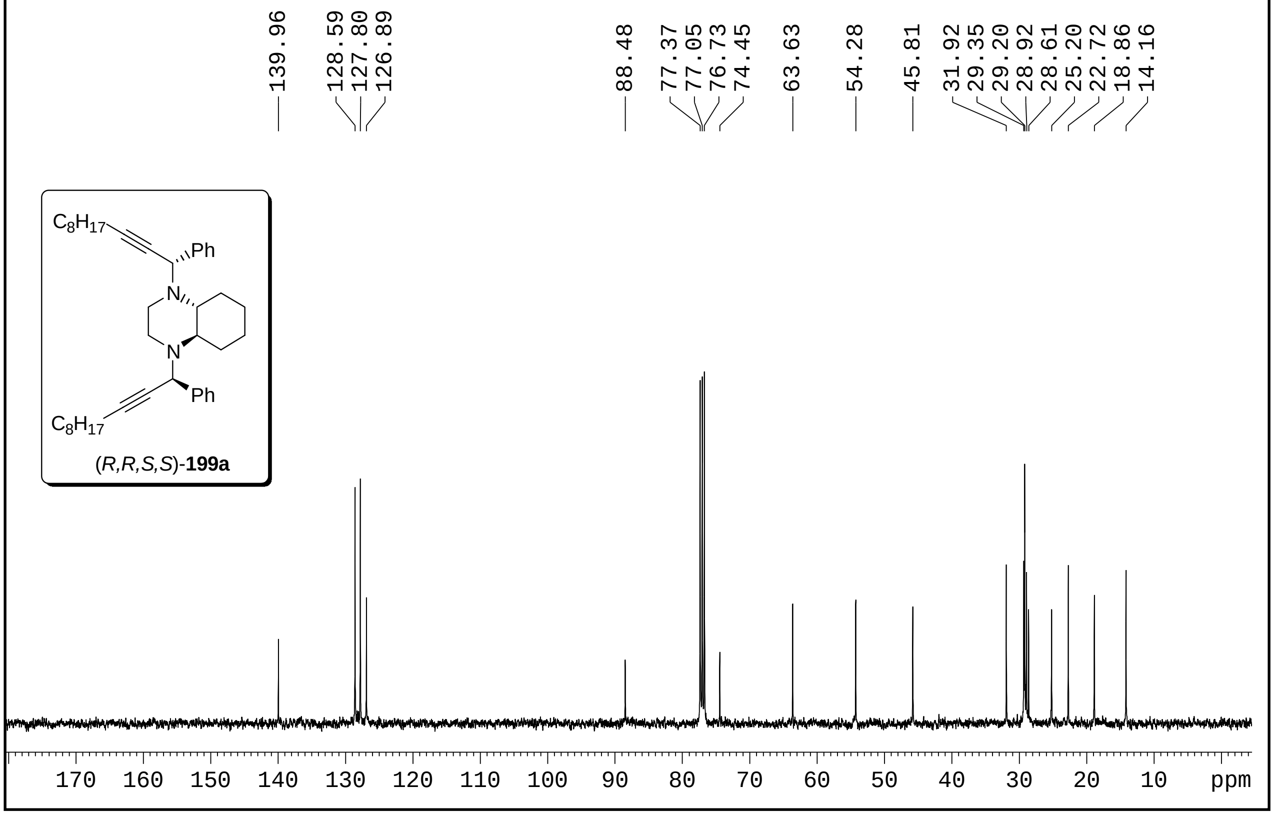


Spectrum No.32 (Chapter 3, Section 3.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No.33 (Chapter 3, Section 3.2.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



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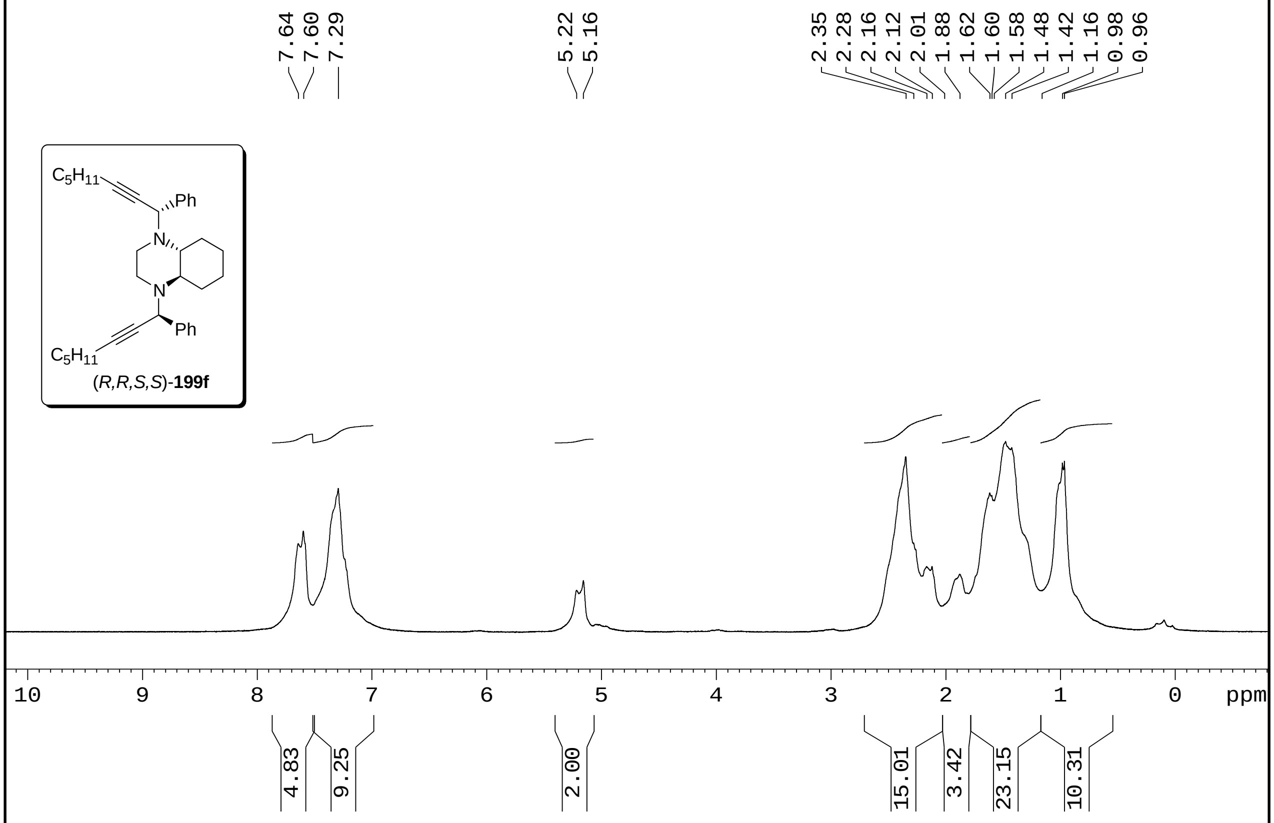
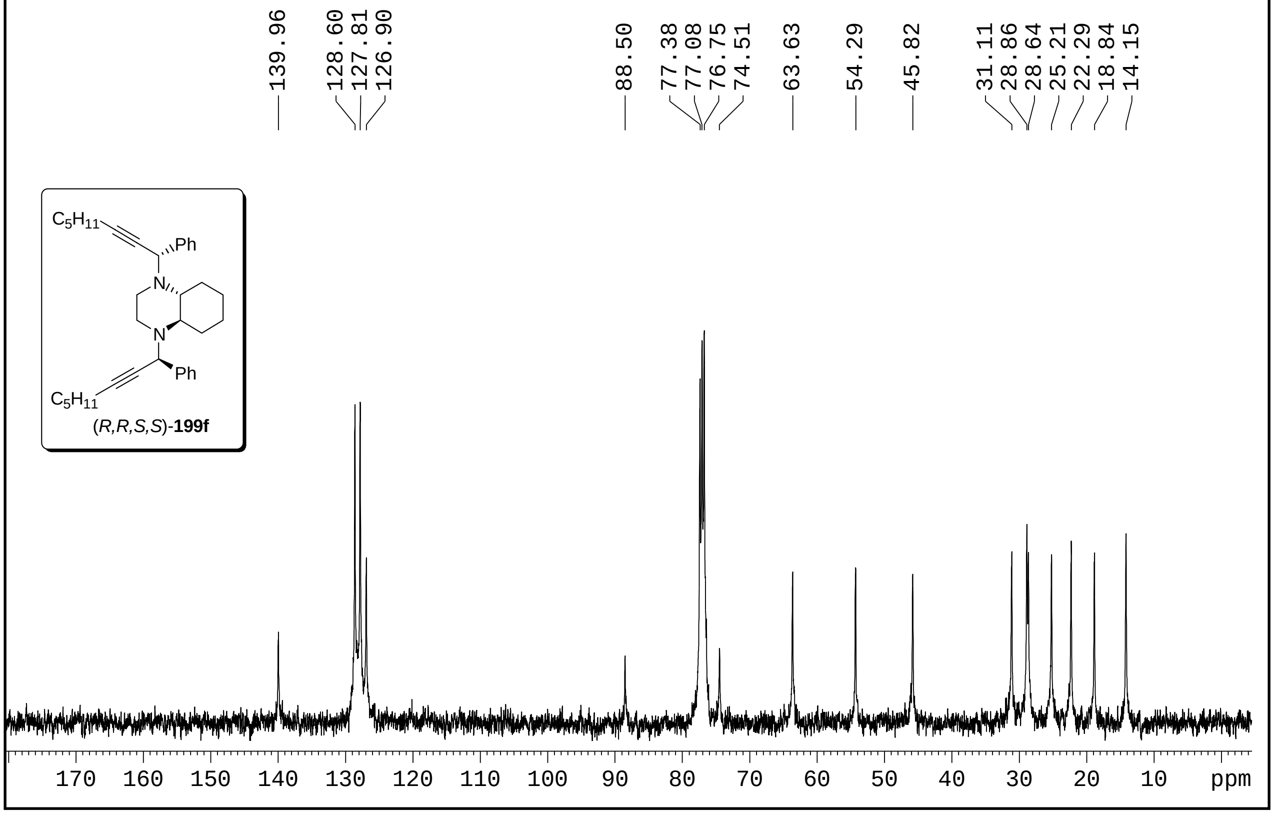
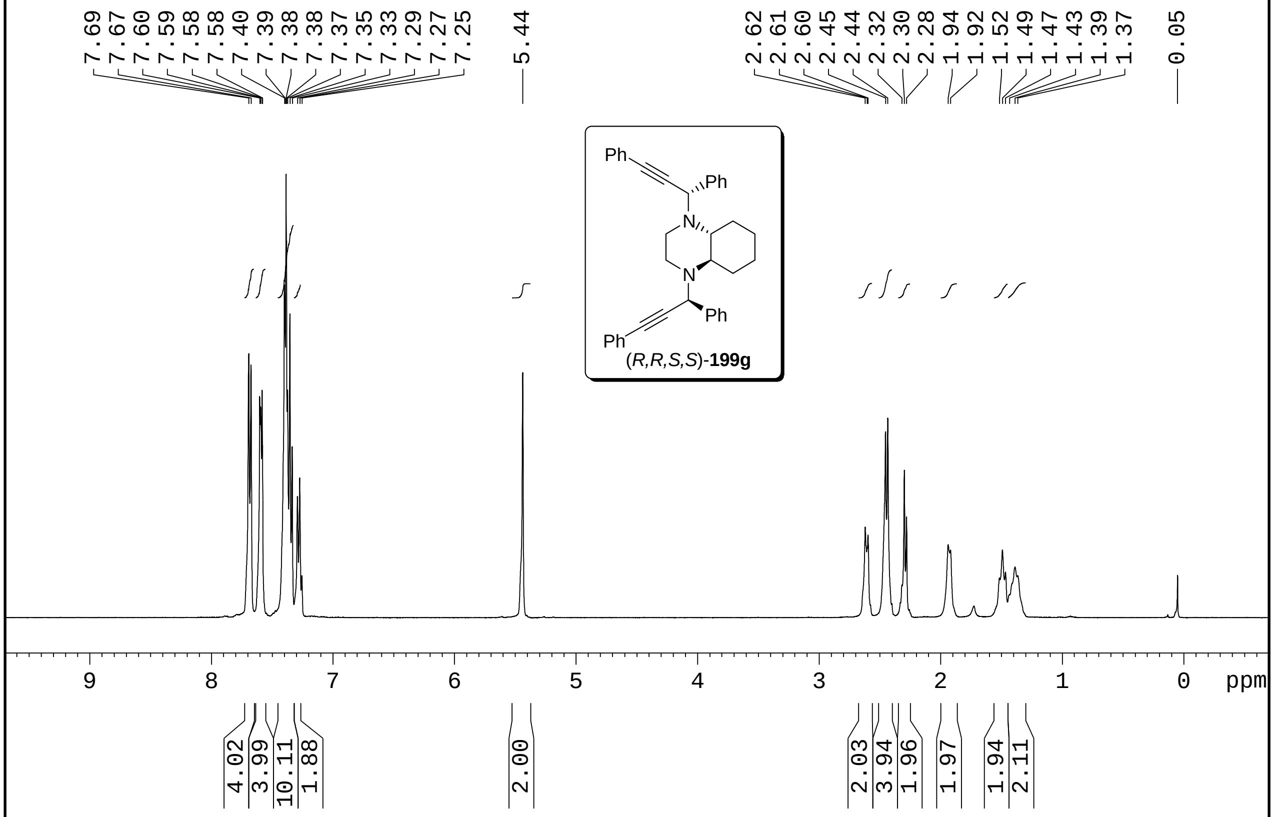


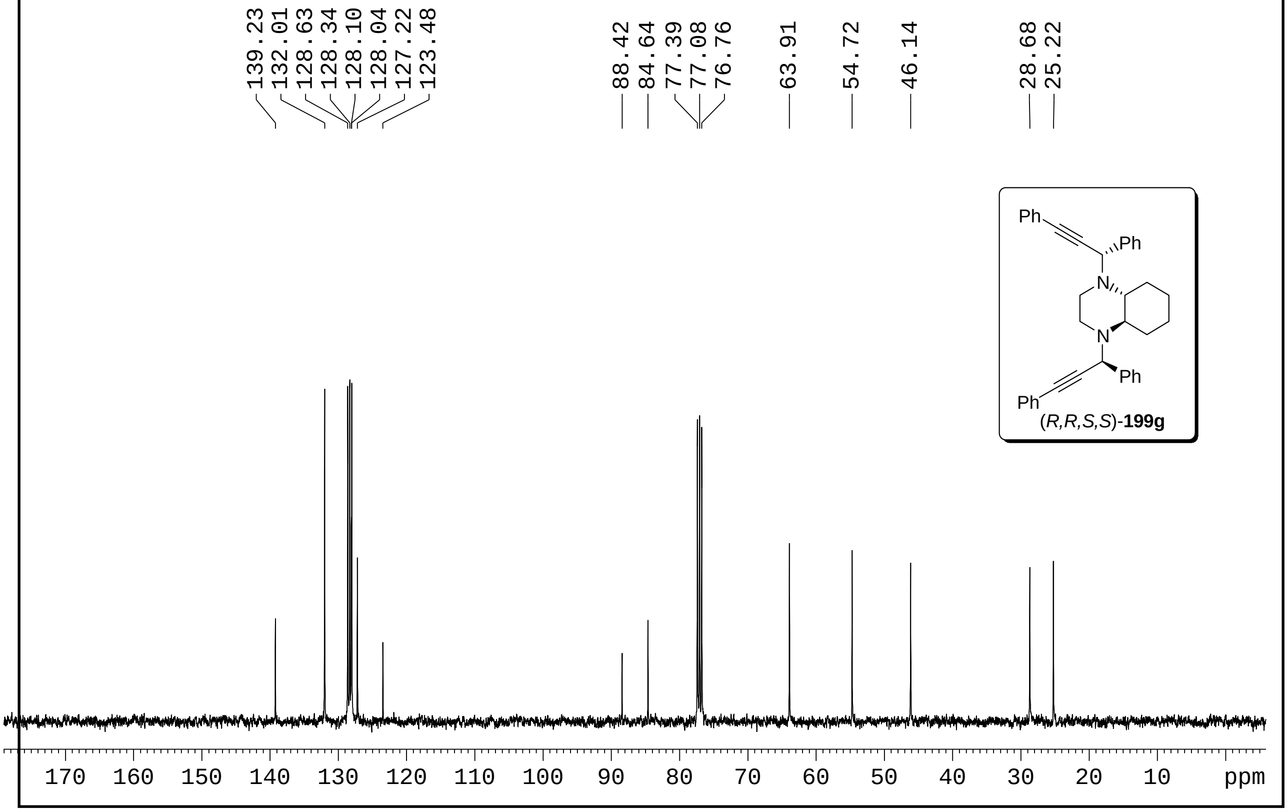
Spectrum No.35 (Chapter 3, Section 3.2.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



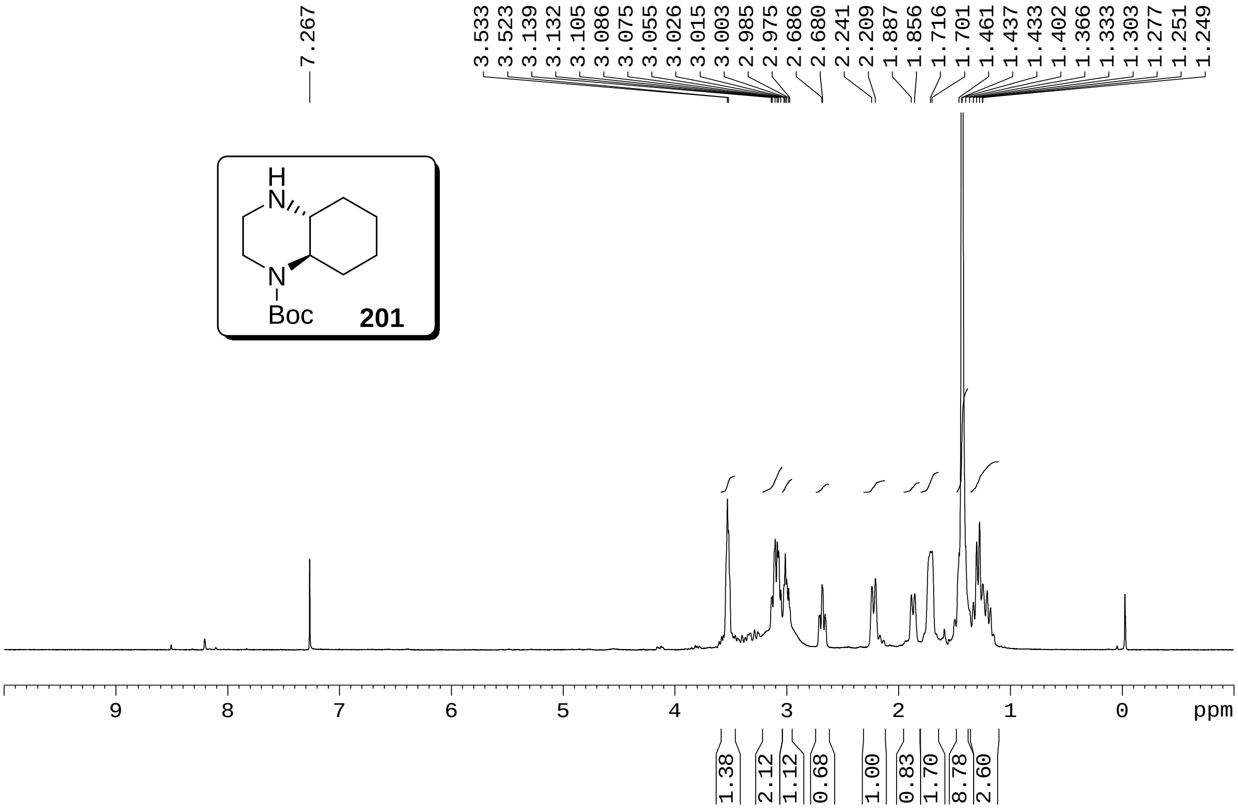
Spectrum No.36 (Chapter 3, Section 3.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



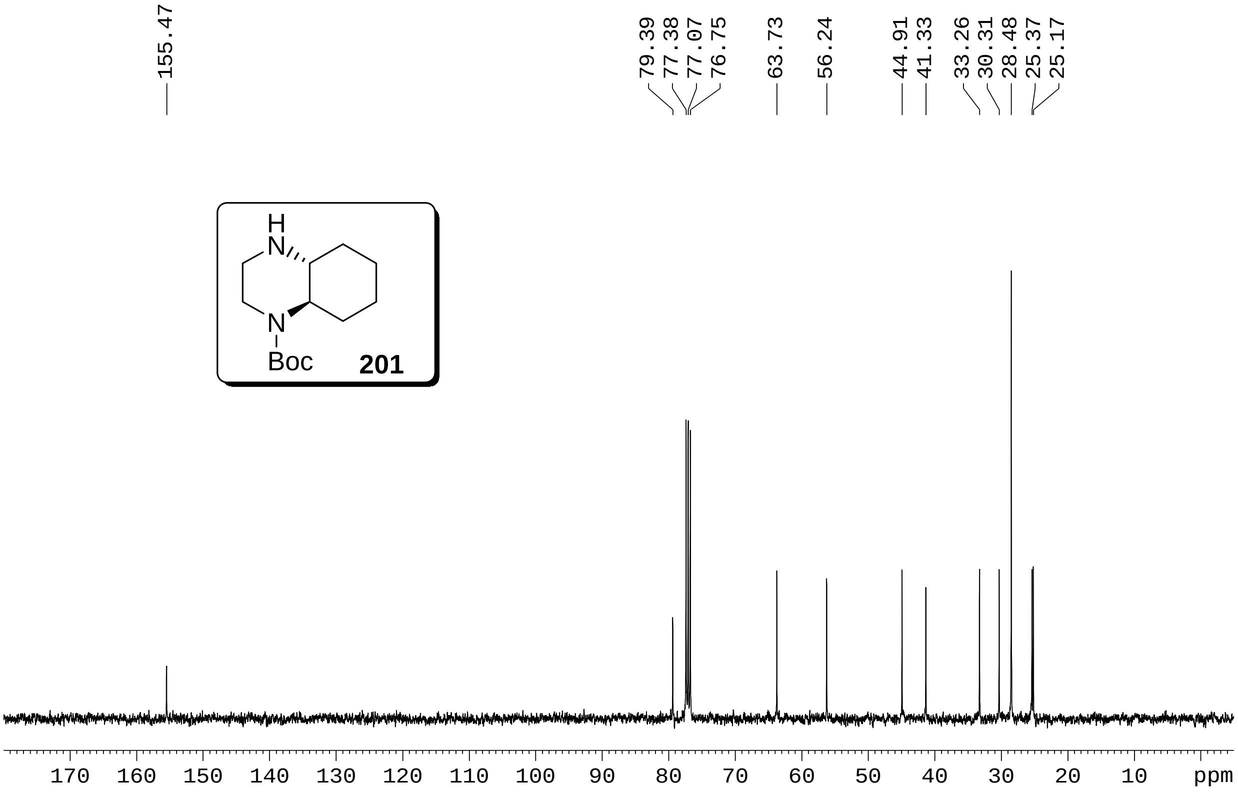
Spectrum No.37 (Chapter 3, Section 3.2.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



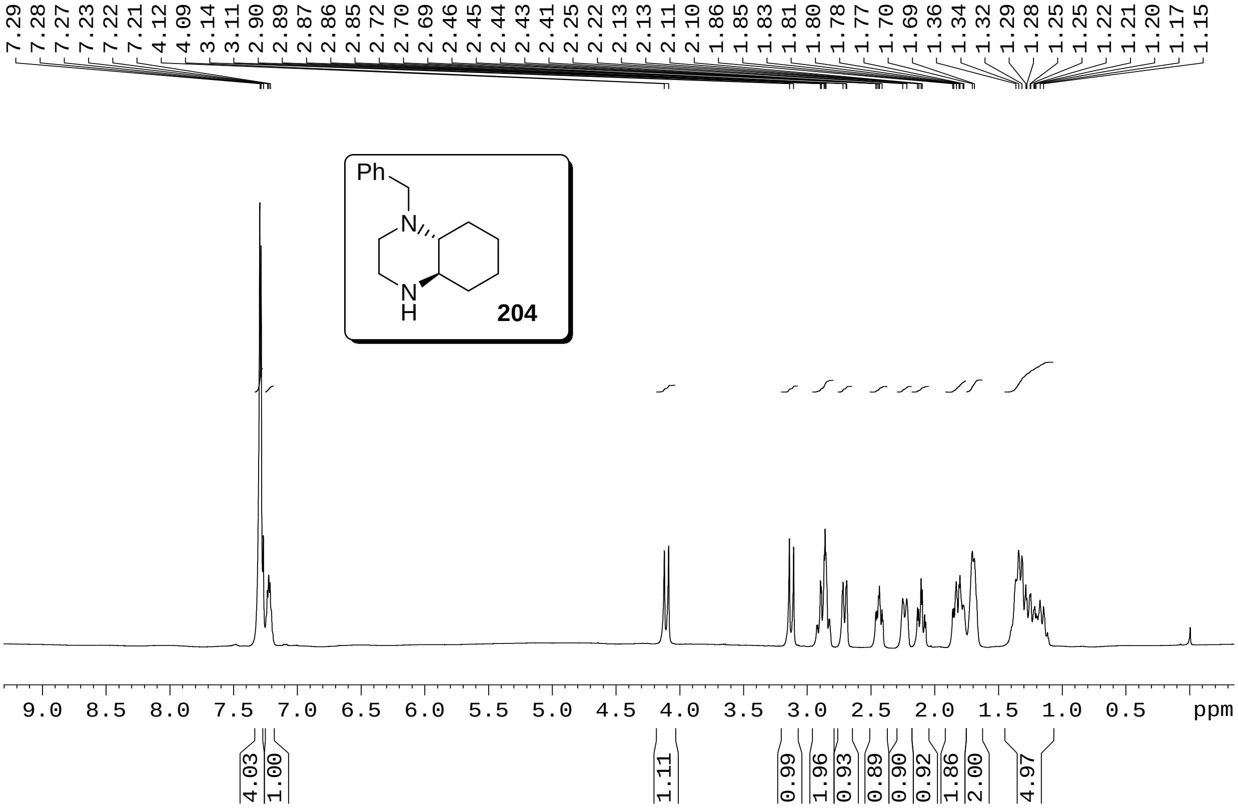
Spectrum No.38 (Chapter 3, Section 3.2.7) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



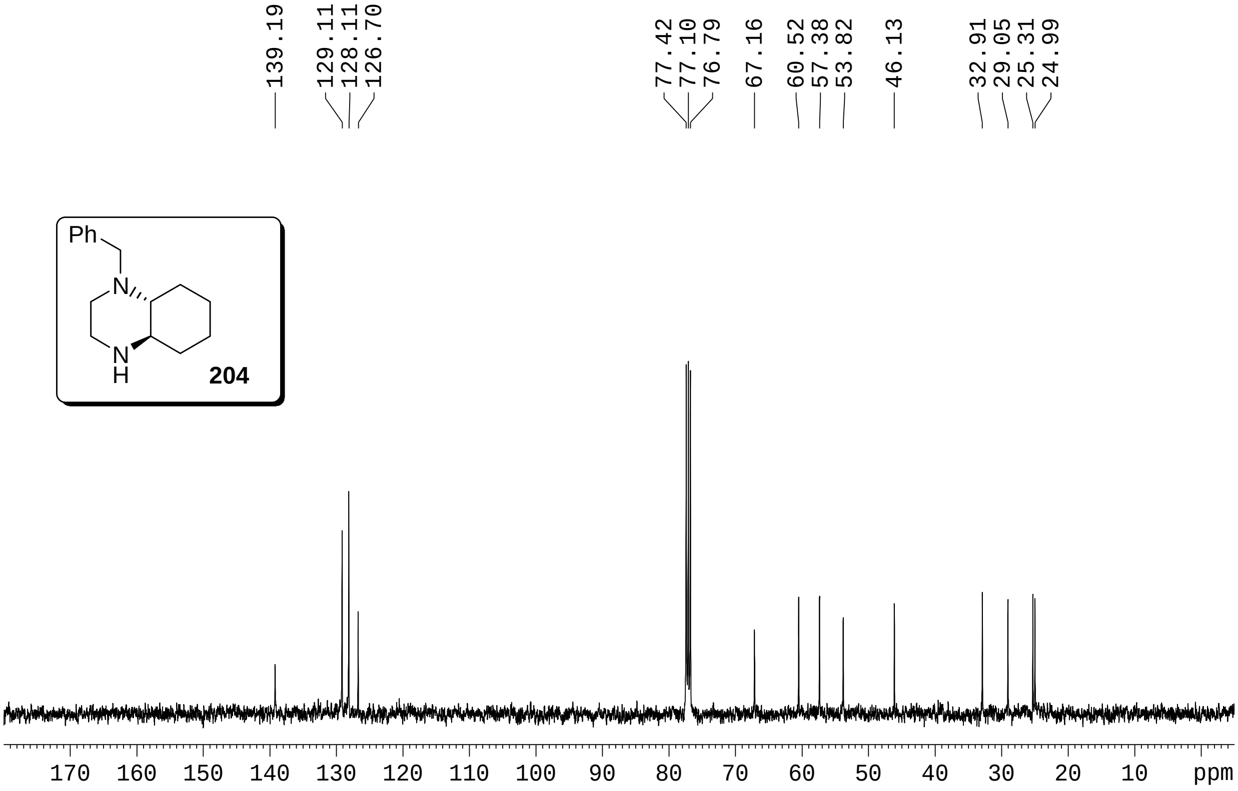
Spectrum No.39 (Chapter 3, Section 3.2.7) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



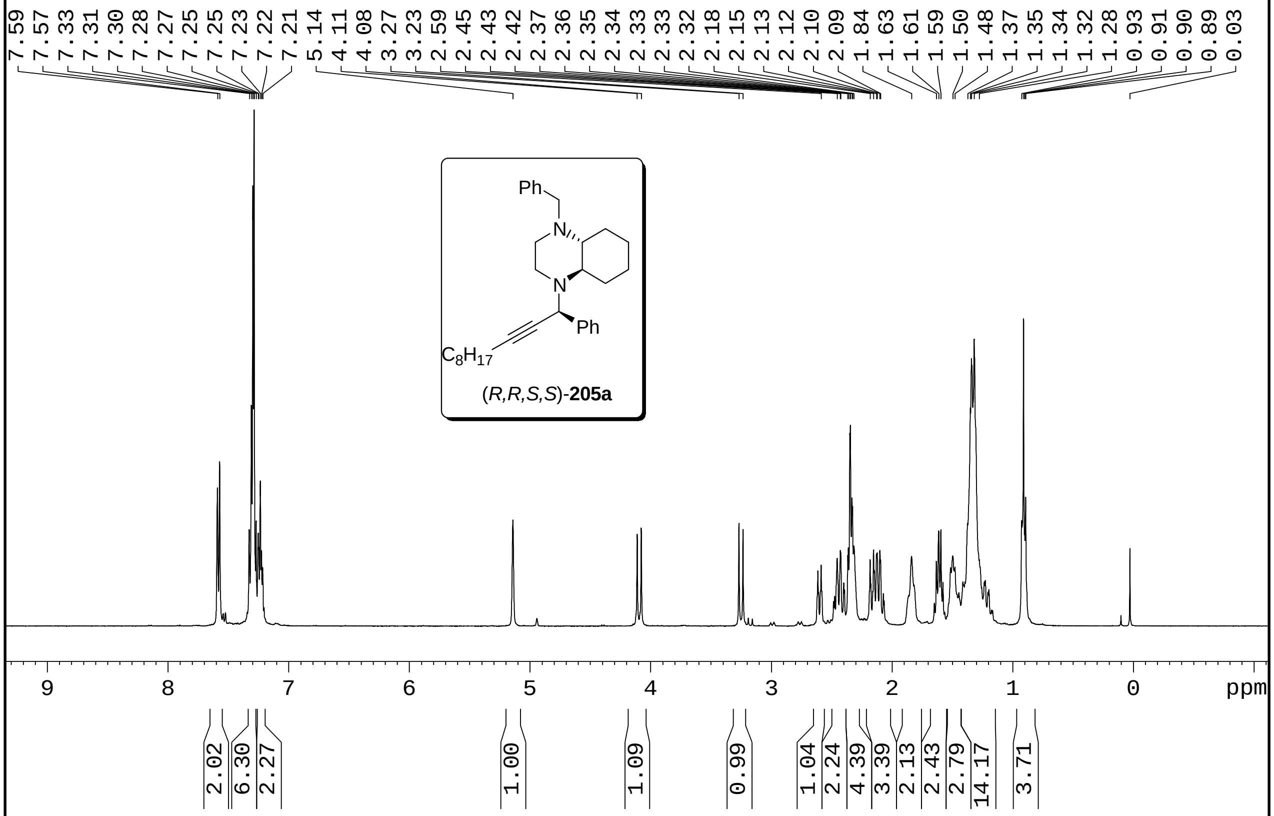
Spectrum No.40 (Chapter 3, Section 3.2.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



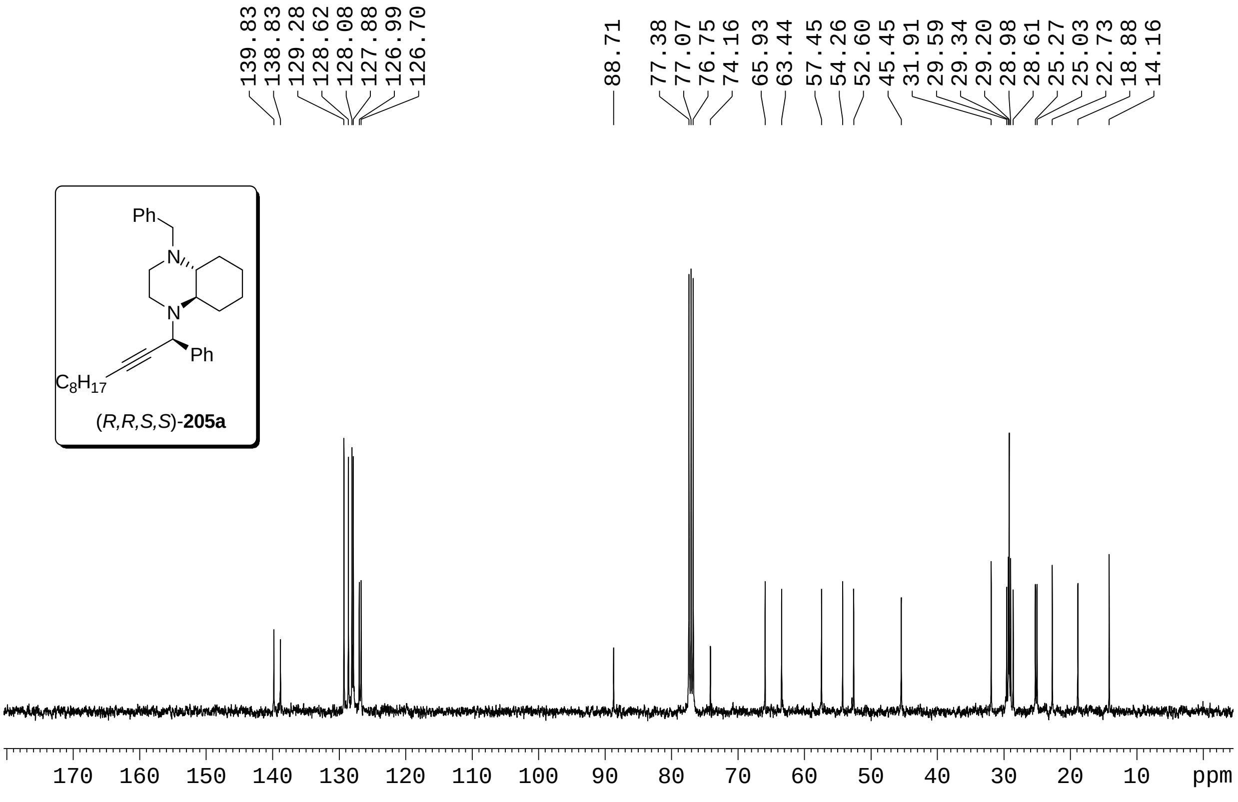
Spectrum No.41 (Chapter 3, Section 3.2.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



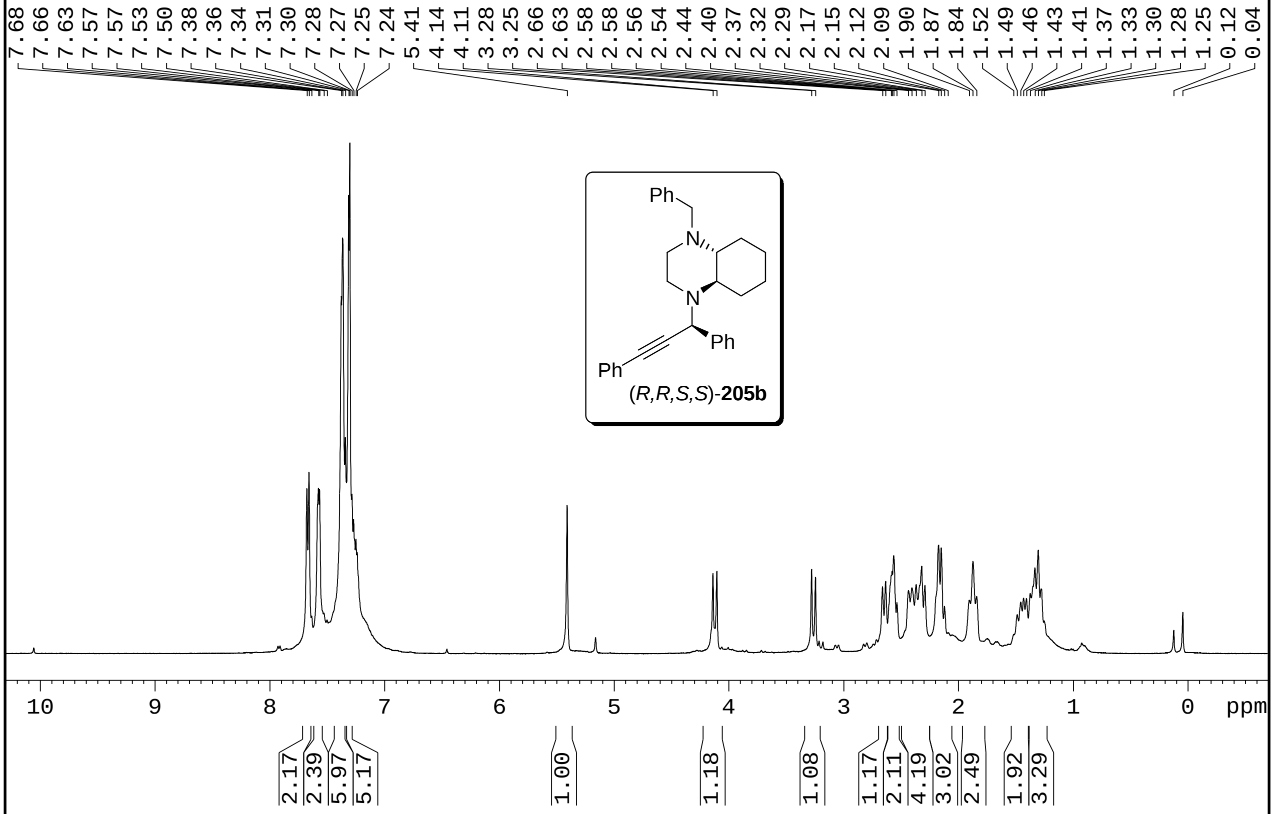
Spectrum No.42 (Chapter 3, Section 3.2.8) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



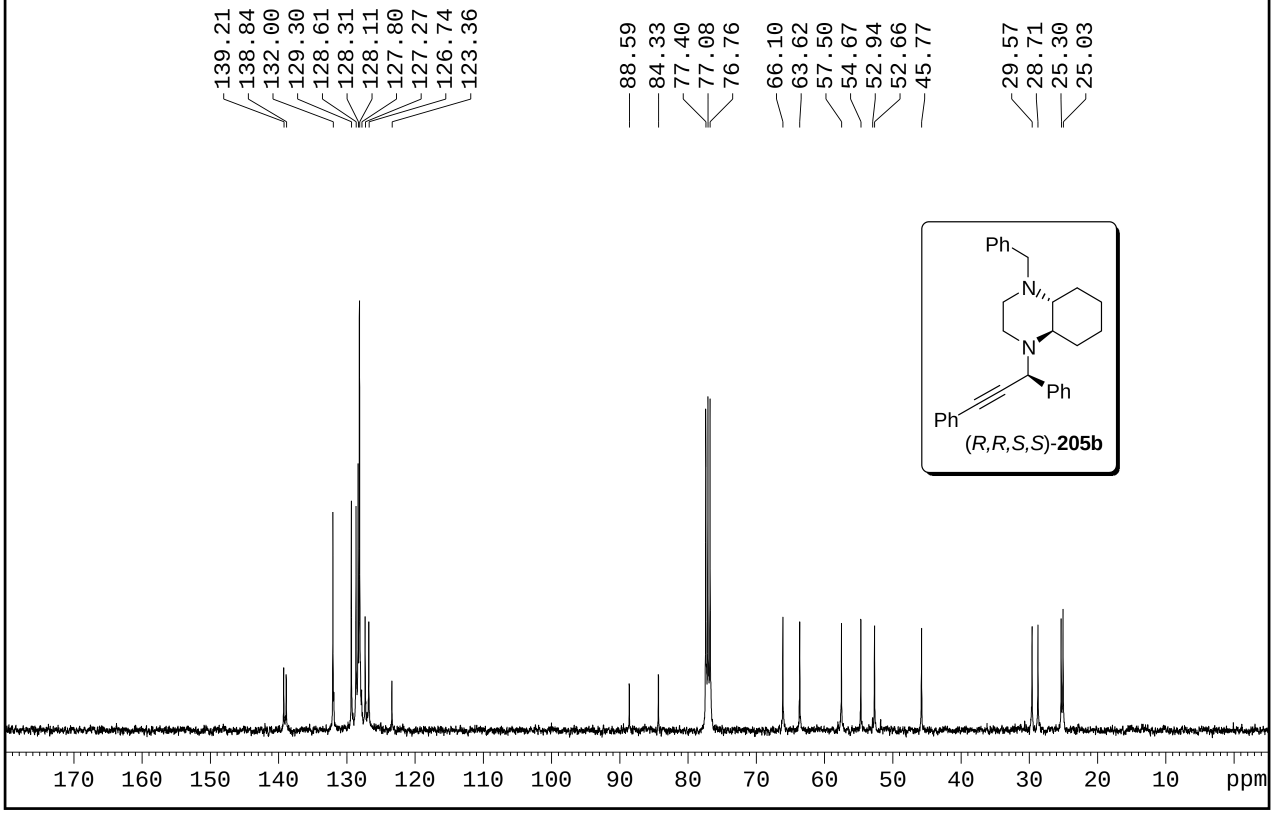
Spectrum No.43 (Chapter 3, Section 3.2.8) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



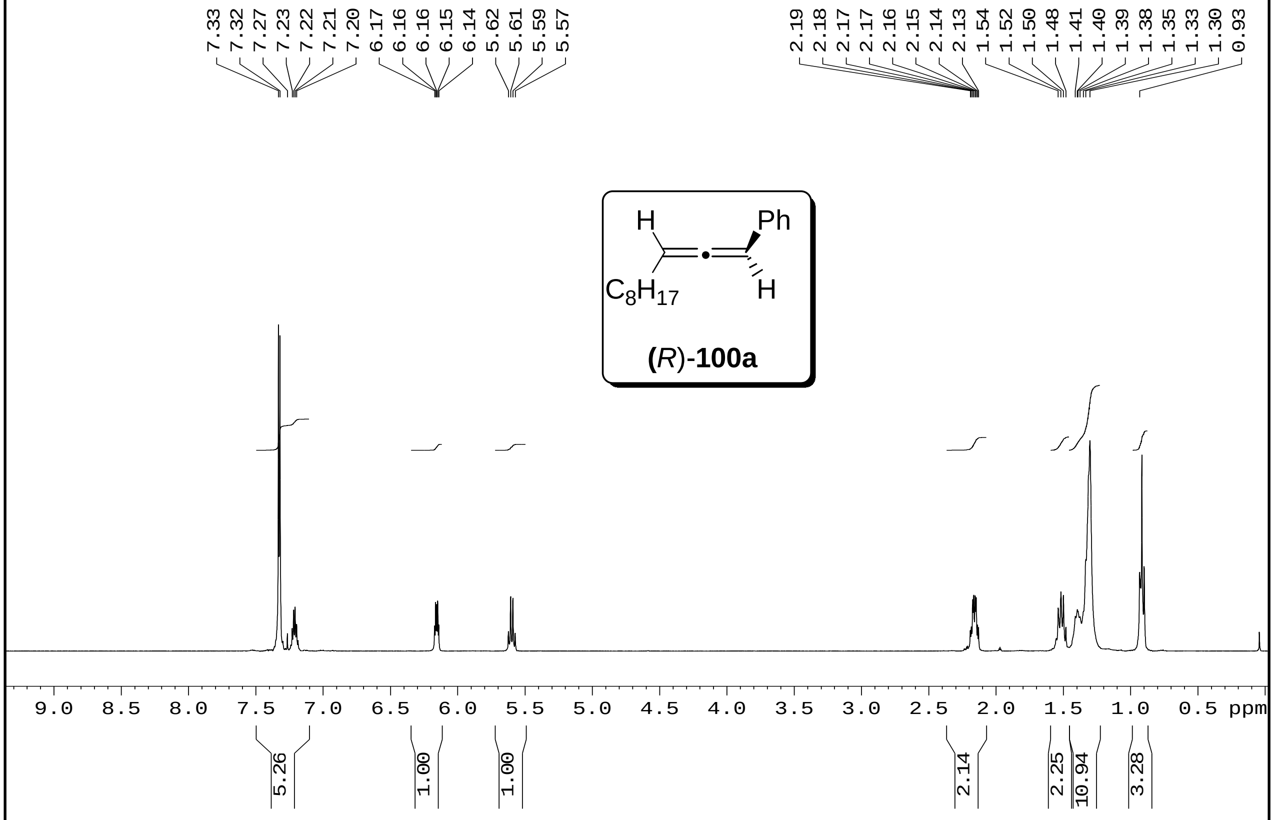
Spectrum No.44 (Chapter 3, Section 3.2.8) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



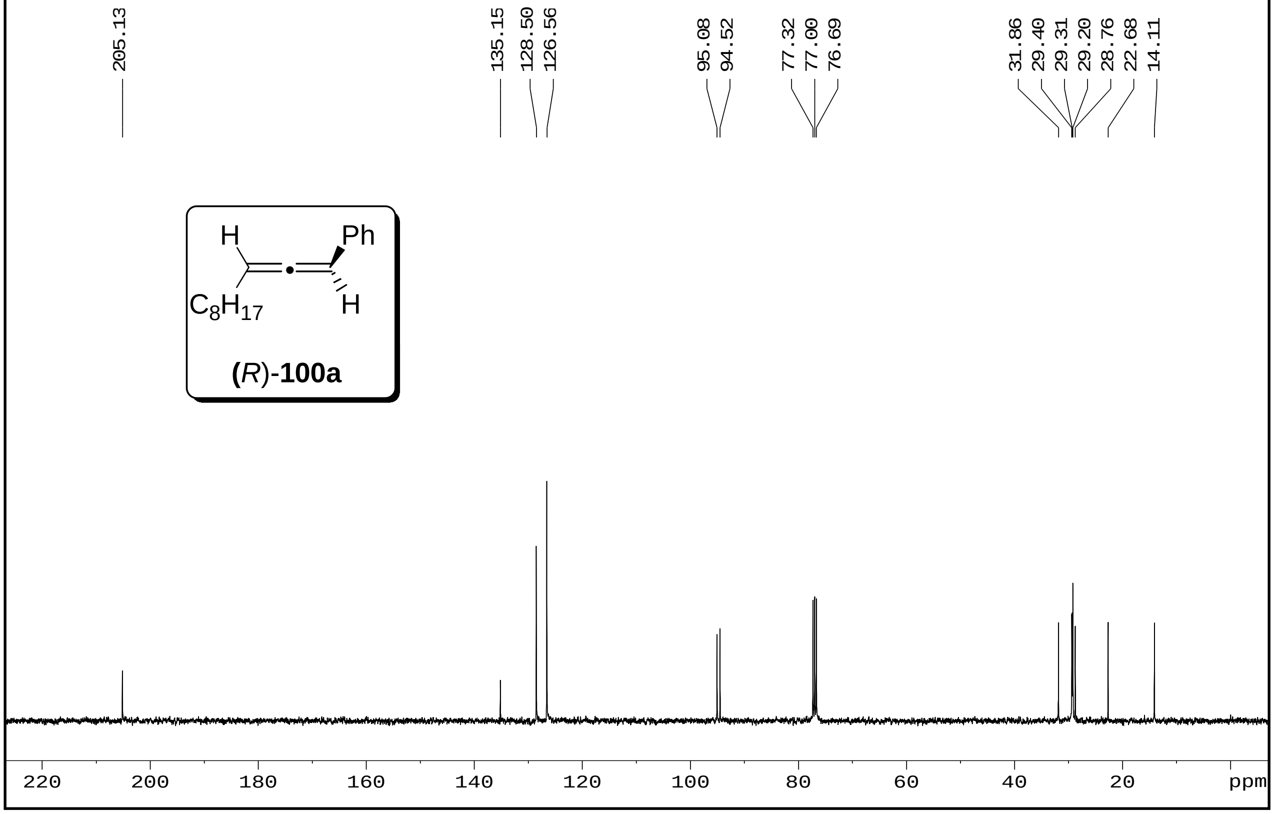
Spectrum No.45 (Chapter 3, Section 3.2.8) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



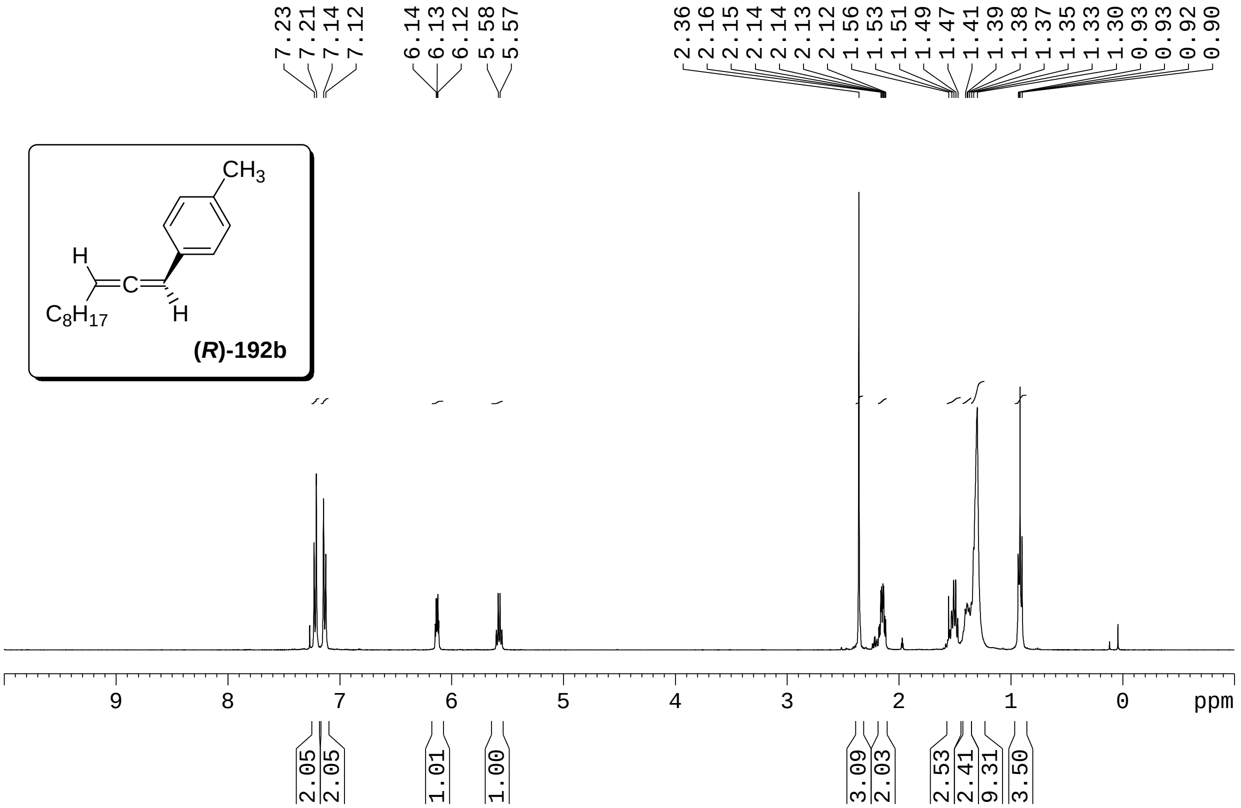
Spectrum No.46 (Chapter 3, Section 3.2.10) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



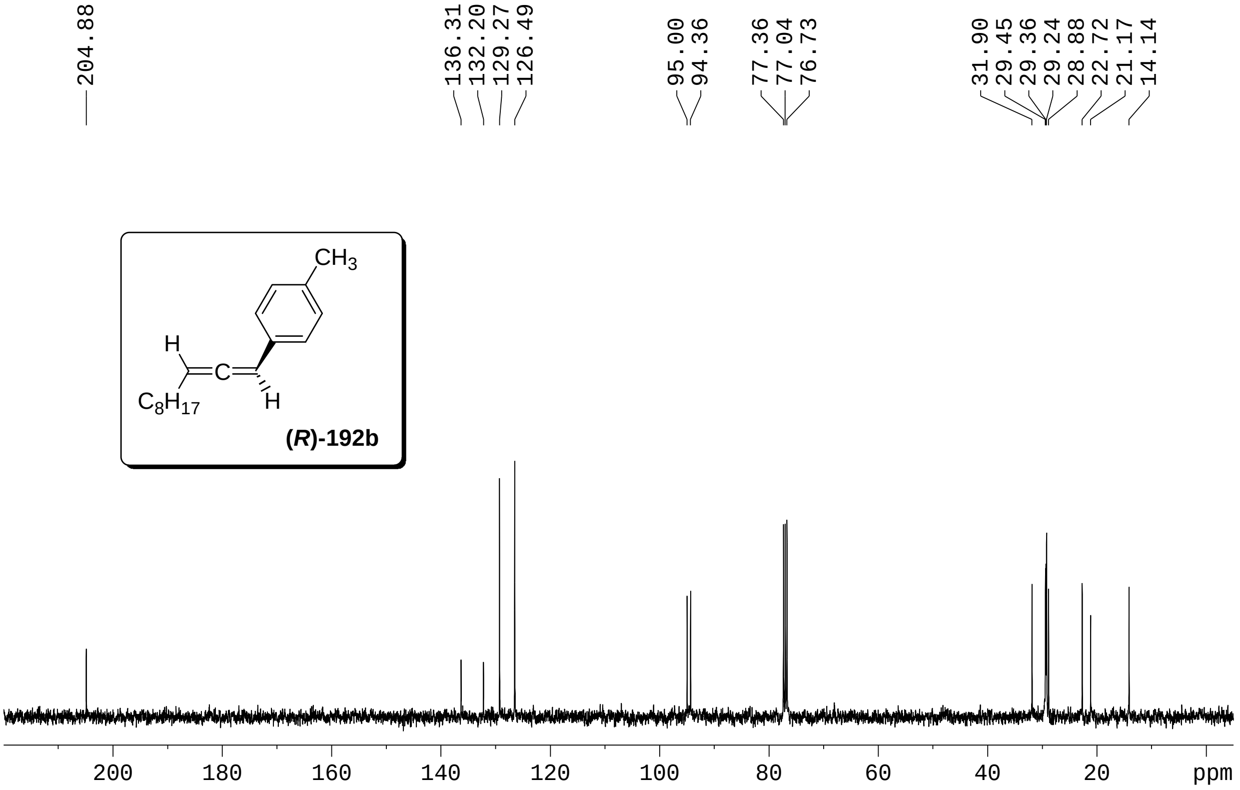
Spectrum No.47 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



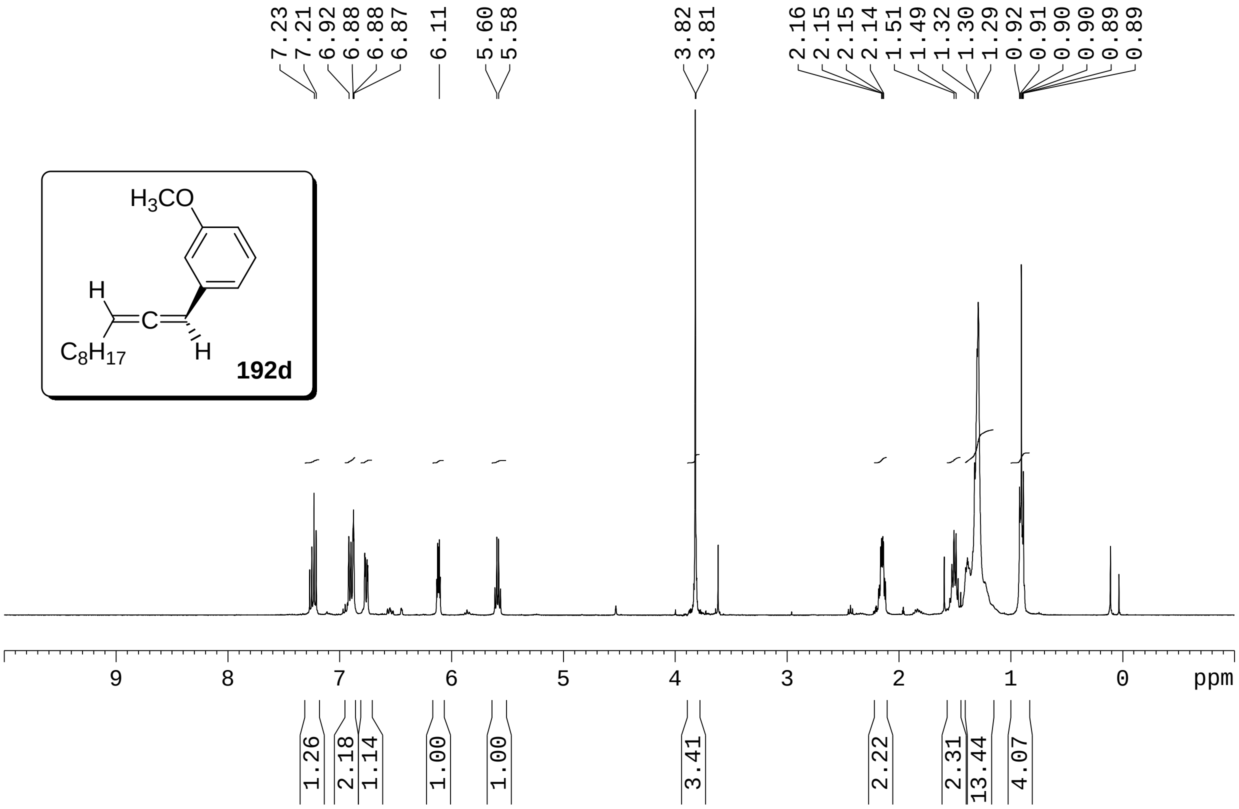
Spectrum No.48 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



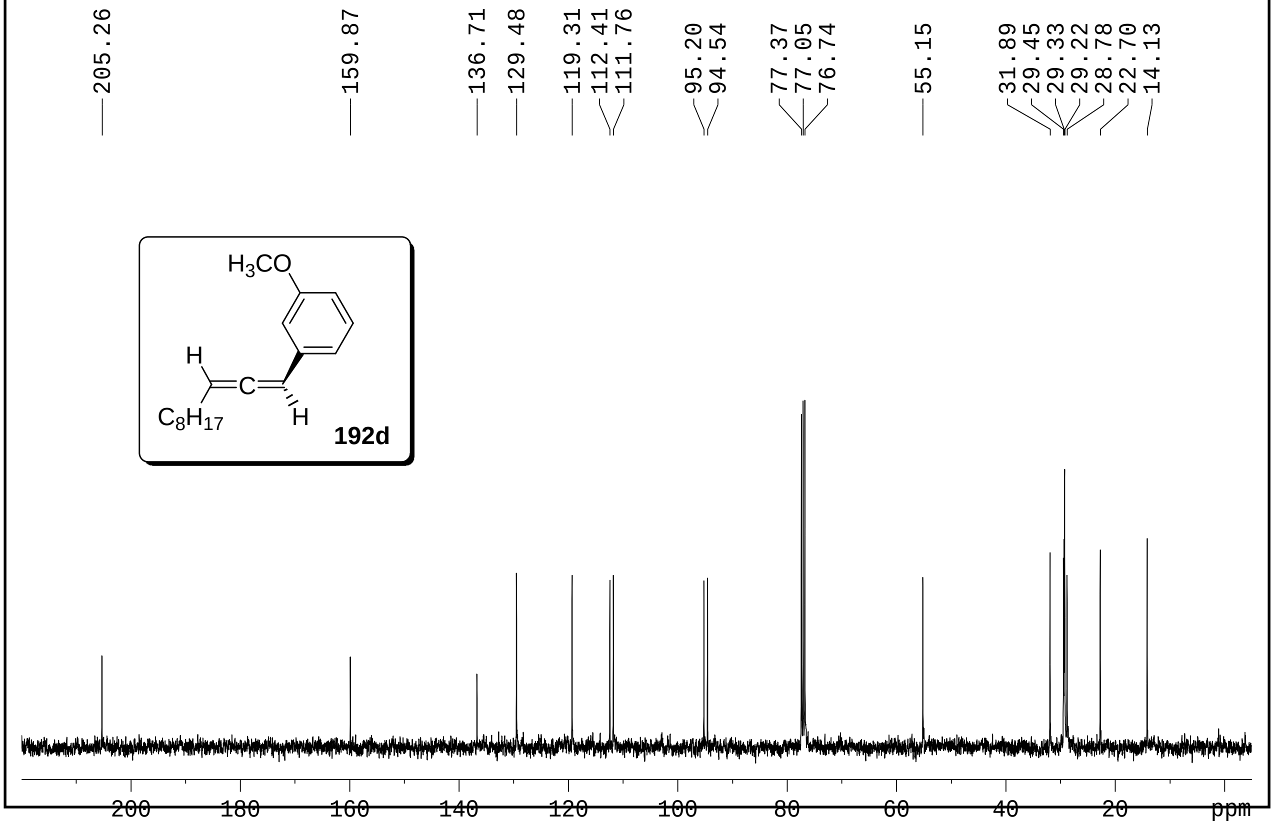
Spectrum No.49 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



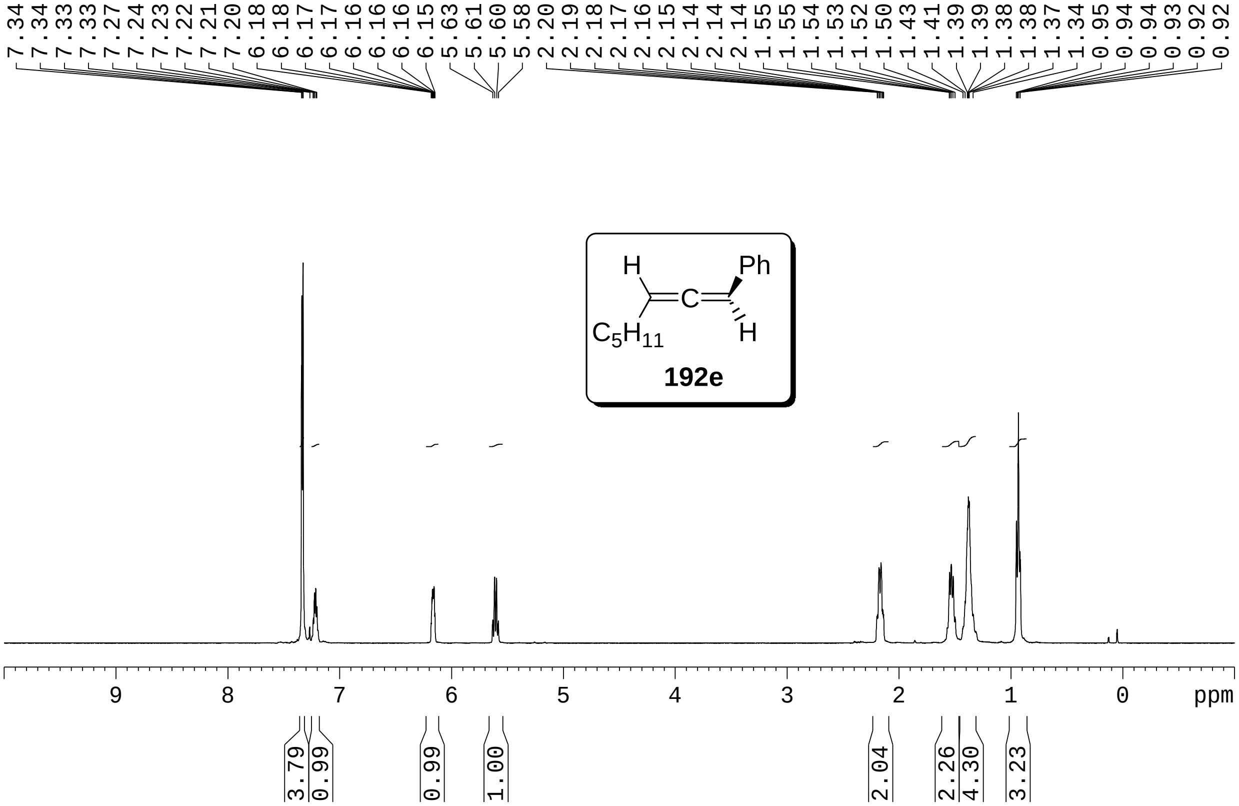
Spectrum No.50 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



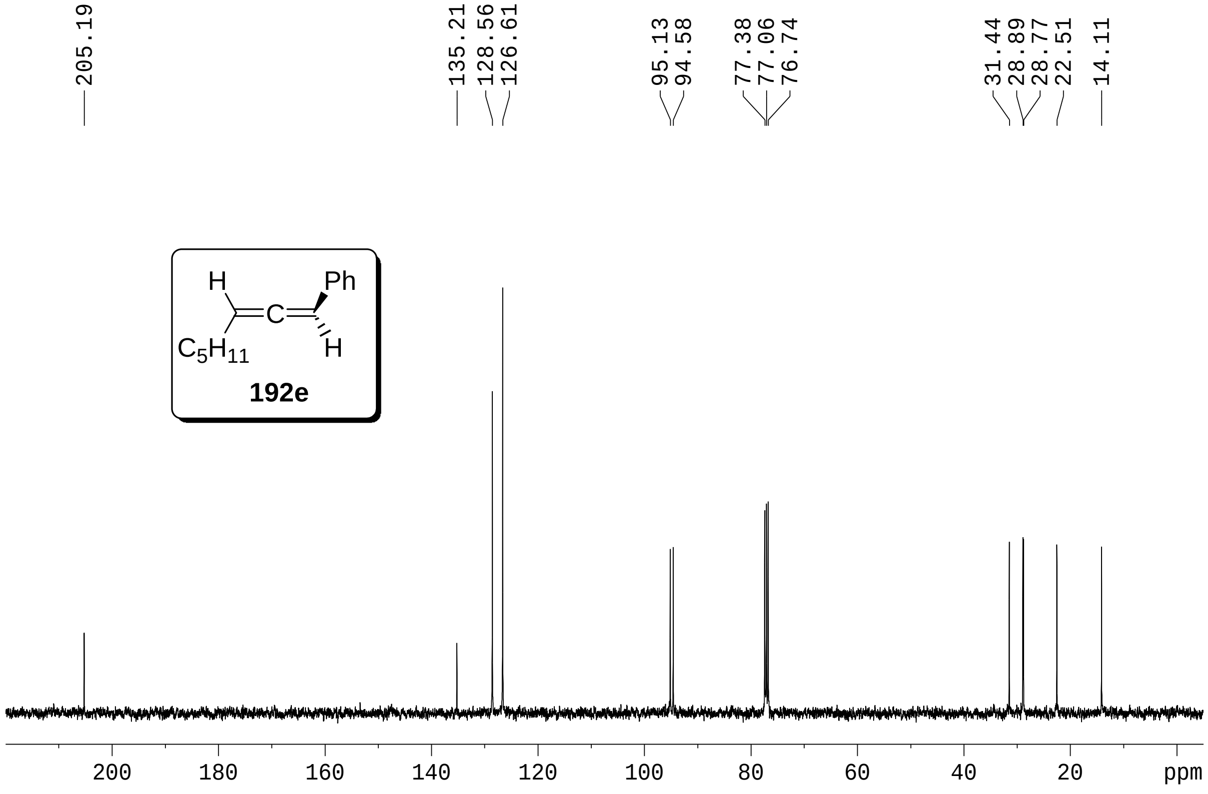
Spectrum No.51 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



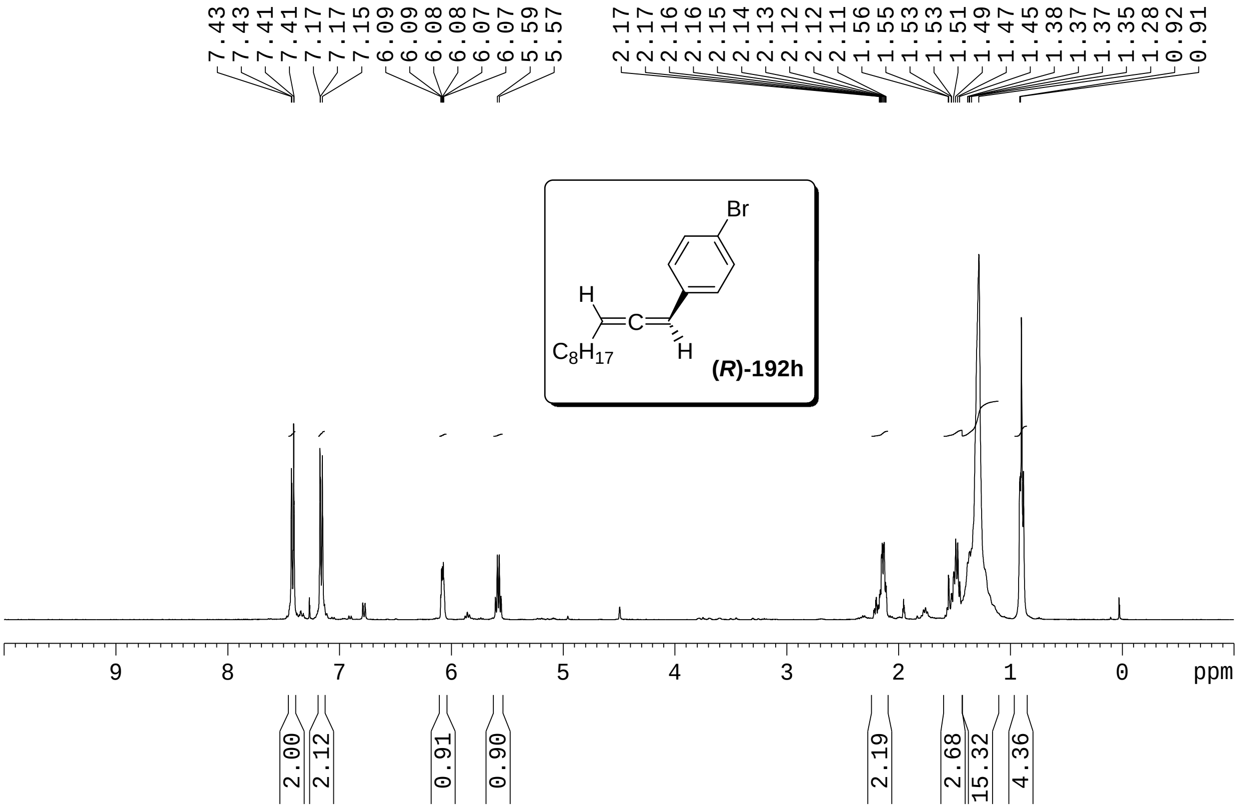
Spectrum No.52 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



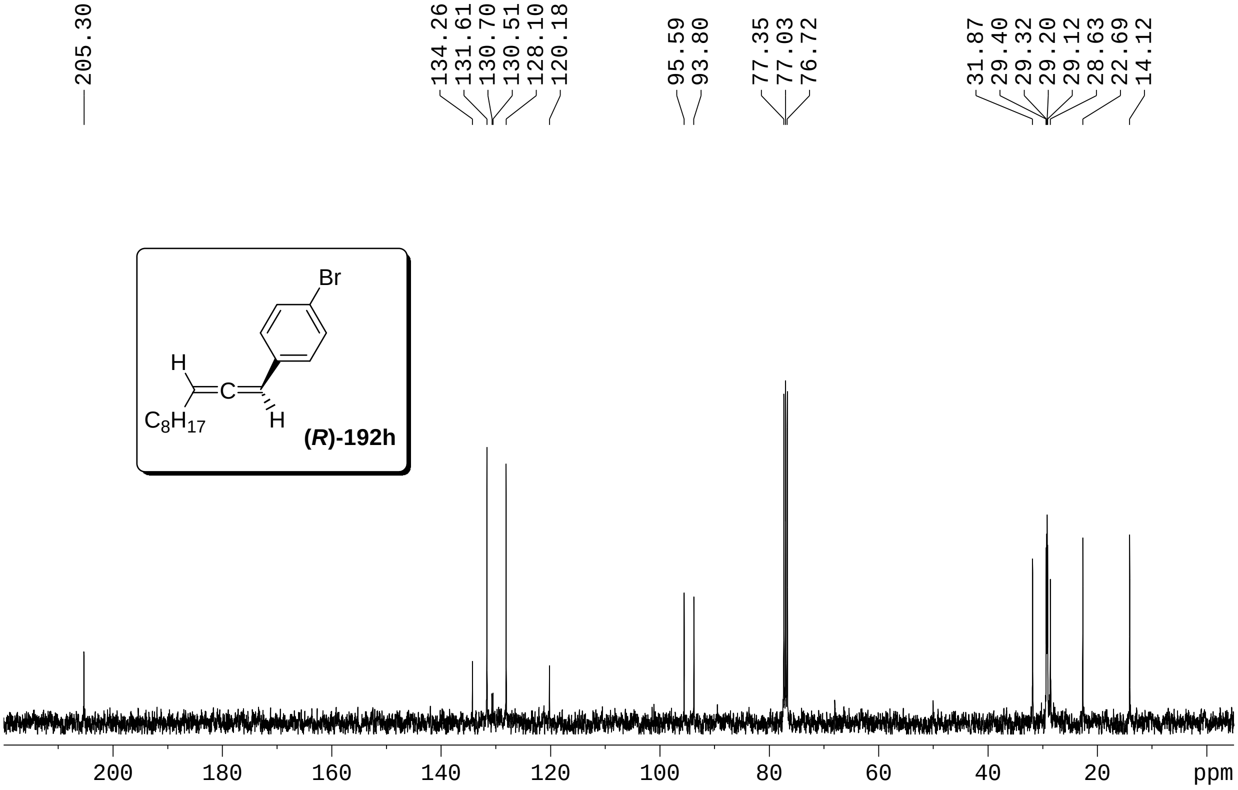
Spectrum No.53 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



Spectrum No.54 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 55 (Chapter 3, Section 3.2.10) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table 1. Crystal data and structure refinement for compound **41a** (**Chapter 2**, **Section 2.2.3**)

Empirical formula	C13 H18 N2 O	
Formula weight	218.29	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	'Orthorhombic'	
Space group	'P2(1)2(1)2(1)'	
Unit cell dimensions	a = 5.1335(4) Å	α= 90°.
	b = 7.7826(6) Å	β= 90°.
	c = 30.628(2) Å	γ = 90°.
Volume	1223.66(16) Å^3	
Z	4	
Density (calculated)	1.185 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	472	
Crystal size	0.40 x 0.36 x 0.30 mm^3	
Theta range for data collection	2.66 to 26.05°.	
Index ranges	-6<=h<=6, -9<=k<=9, -37<=l<=37	
Reflections collected	12650	
Independent reflections	2423 [R(int) = 0.0311]	
Completeness to theta = 26.05°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2423 / 0 / 154	
Goodness-of-fit on F^2	1.256	
Final R indices [I>2sigma(I)]	R1 = 0.0489, wR2 = 0.1135	
R indices (all data)	R1 = 0.0503, wR2 = 0.1141	
Absolute structure parameter	1(2)	
Largest diff. peak and hole	0.135 and -0.163 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound **41a** (**Chapter 2**, **Section 2.2.3**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	**x**	**y**	**z**	**U(eq)**
C(1)	8123(4)	8741(3)	1189(1)	46(1)
C(2)	8143(4)	8416(2)	699(1)	45(1)
C(3)	10091(5)	7011(3)	580(1)	63(1)
C(4)	9609(6)	5361(3)	832(1)	76(1)
C(5)	9573(5)	5685(3)	1318(1)	68(1)
C(6)	7605(4)	7063(3)	1432(1)	57(1)
C(7)	6875(5)	11012(3)	298(1)	55(1)
C(8)	6377(4)	11117(3)	1653(1)	45(1)
C(9)	8263(4)	10953(3)	1975(1)	55(1)
C(10)	8301(5)	12057(4)	2327(1)	63(1)
C(11)	6475(5)	13330(4)	2370(1)	69(1)
C(12)	4601(5)	13502(3)	2052(1)	66(1)
C(13)	4542(4)	12421(3)	1698(1)	54(1)
N(1)	8706(4)	9971(2)	450(1)	51(1)
N(2)	6210(4)	10036(3)	1295(1)	58(1)
O(1)	4531(3)	10836(2)	352(1)	64(1)

LIST OF PUBLICATIONS

1 Copper(I) catalysis: Synthesis of N,N'-diarylated and N-aryl,N'-formylated chiral C_2-symmetric diamines; **Alakonda**, **L**.; Periasamy, M. *J. Organomet. Chem*., **2009**, *694*, 3859.

2 Simple and Convenient Methods for N-Arylation of Heterocycles and Diphenylamine; **Alakonda**, **L**.; Periasamy, M. *Synthesis*, **2012**, *44*, 1063.

3 Enantioselective Synthesis of Chiral Allenes by Sequential Creation of Stereogenic Center and Chirality Transfer in a Single Pot Operation; Periasamy, M.; **Alakonda**, **L** (To be communicated).

4 CuBr Promoted Diastreoselective Synthesis of Chiral *bis*-Propargylamines in One Pot Operation; Periasamy, M.; **Alakonda**, **L** (Manuscript under preparation).

ORAL PRESENTATIONS/POSTERS

1 Oral presentation in the *"Chemfest 2012"* in house symposium held at University of Hyderabad, Hyderabad, February 24-25, **2012**; *Title*: Transition metal catalyzed C-N cross couplings and enantioselective synthesis chiral allenes; **Alakonda**, **L**.; Periasamy, M.

2 Poster presentation in the *"Chemfest 2012"* in house symposium held at University of Hyderabad, Hyderabad, February 24-25, **2012**; *Title*: Transition metal catalyzed C-N cross couplings and enantioselective synthesis chiral allenes; **Alakonda**, **L**.; Periasamy, M.