Synthesis and Applications of Chiral Diamines: Chiral 2,3-Diarylpiperazines

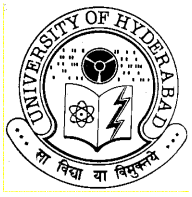
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

Pothiappan Vairaprakash



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November 2007

Dedicated to all my Shepherds

Contents

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled "**Synthesis and Applications of Chiral Diamines: Chiral 2,3-Diarylpiperazines"** has been carried out by **Mr. Pothiappan Vairaprakash** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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Acknowledgements

I take immense pleasure in expressing my deep sense of gratitude and indebtedness to my mentor **Prof. M. Periasamy** for his inspiring guidance and constant encouragement and support throughout my tenure here. I hold him in high regard.

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I would like to express my sincere gratitude to all my friends in UoH. All of them have been very kind, generous, affectionate, caring……..

I wish to extend my sincere thanks to the university authorities for providing all the necessary facilities for this work, CSIR, DST and NATCO Pharma for the financial support during my tenure here.

Finally, yet importantly, I would like to express my heartfelt thanks to my beloved parents for their blessings and other members of my family for their kindness and support, my friends and classmates for their help and good wishes for the successful completion of this project. I am grateful to all of those, who supported me right from my schooling days till this date.

Vairaprakash, P.

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
Ac	acetyl
anhyd.	anhydrous
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bmim	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	*tertiary*-butoxycarbonyl
br	broad (in spectroscopy)
BtOH	*N*-hydroxybenzotriazole
Bu	butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
conf	configuration
cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
d	doublet (in spectroscopy)
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
DBTA	*O*,*O*-dibenzoyltartaric acid
DCC	*N*,*N*'-dicyclohexylcarbodiimide
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

DPEPhos	bis[(2-diphenylphosphino)phenyl]ether
dr	diastereomeric ratio
EDCI	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact (in mass spectrometry)
equiv.	equivalent
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
i	iso
IPA	2-propanol
IR	infrared
J	coupling constant (in NMR spectroscopy)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature
LVT	low valent titanium
m	multiplet (in spectroscopy)
Me	methyl
min	minute(s)
mp	melting point
MS	mass spectrum
Ms	methanesulfonyl
M.S.	molecular sieves
MSA	methanesulfonic acid
NBD	norbornadiene
Nf	4-nitrobenzenesulfonyl
NMR	nuclear magnetic resonance
Np	naphthyl

Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Pent	pentyl
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet (in spectroscopy)
ref	reference number
rt	room temperature
s	singlet (in spectroscopy)
sat.	saturated
sec	secondary
soln	solution
T	temperature
t	tertiary
t	triplet (in spectroscopy)
TADDOL	α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxalan-4,5-dimethanol
TBDMS	*tertiary*-butyldimethylsilyl
TBHP	*tertiary*-butylhydroperoxide
TEAF	triethylammonium formate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THACl	tetrahexylammonium chloride
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-methylbenzenesulfonyl
Uv	ultraviolet

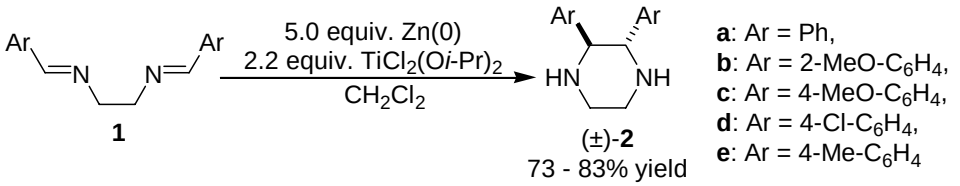
ABSTRACT

This thesis describes, "**Synthesis and Applications of Chiral diamines: Chiral 2,3-Diarylpiperazines**". It comprises of three chapters, 1) **Introduction**, 2) **Results and Discussion** and 3) **Experimental Section**. The work described in this thesis is exploratory in nature.

The first chapter describes a brief review on the applications of chiral 1,2-diamine derivatives in various organic transformations. Synthesis of different kinds of substituted piperazines, their applications and their biological importance are also discussed. The second chapter deals with the results and discussion on the synthesis of chiral 2,3-diarylpiperazines, their application as chiral catalysts in aldol reaction, application of chiral piperazines/CuCl reagent system for the oxidative coupling of 2-naphthol and the application of (±)-2,3-diarylpiperazines/CuX reagent system in the *N*-arylation of indole.

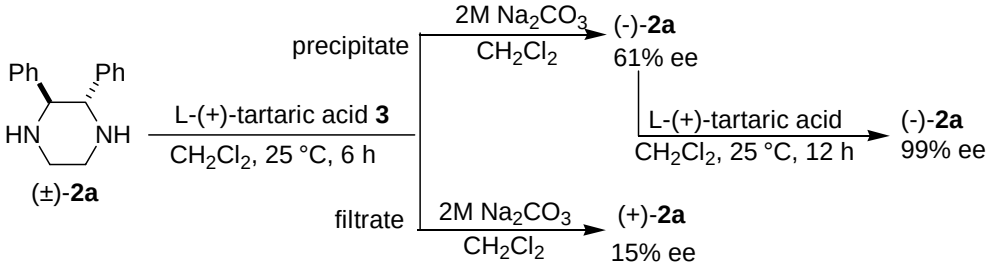
The (±)-2,3-diarylpiperazines were obtained in up to 83% yields in the intramolecular reductive coupling of diimines promoted by the $TiCl_2(O\textit{i}\text{-}Pr)_2$/Zn reagent system (Scheme **1**). The *dl*:*meso* ratio was determined to be >99% from ^{13}C NMR spectra of the corresponding piperazines and also by HPLC analysis of the trifluoroacetamide derivatives of corresponding piperazines.

Scheme 1.



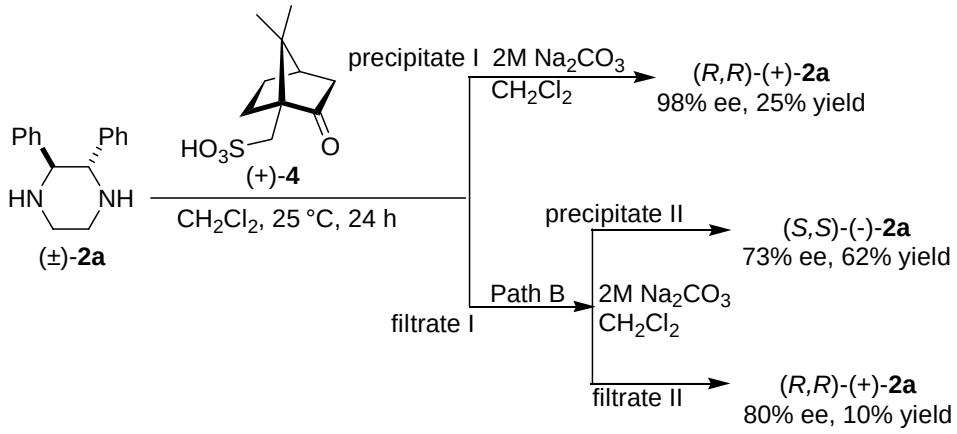
The racemic 2,3-diphenylpiperazine obtained in the intramolecular reductive coupling was resolved using L-(+)-tartaric acid (Scheme **2**). The configuration of the enantiomer (-)-**2a** was assigned (*S*,*S*) by single crystal X-ray analysis of the corresponding tartrate salt.

Scheme 2.



By using (1*S*)-(+)-10-camphorsulfonic acid in the resolution of racemic 2,3-diphenylpiperazine, enantiomerically pure 2,3-diphenylpiperazine was obtained with 98% ee in a single step (Scheme **3**).

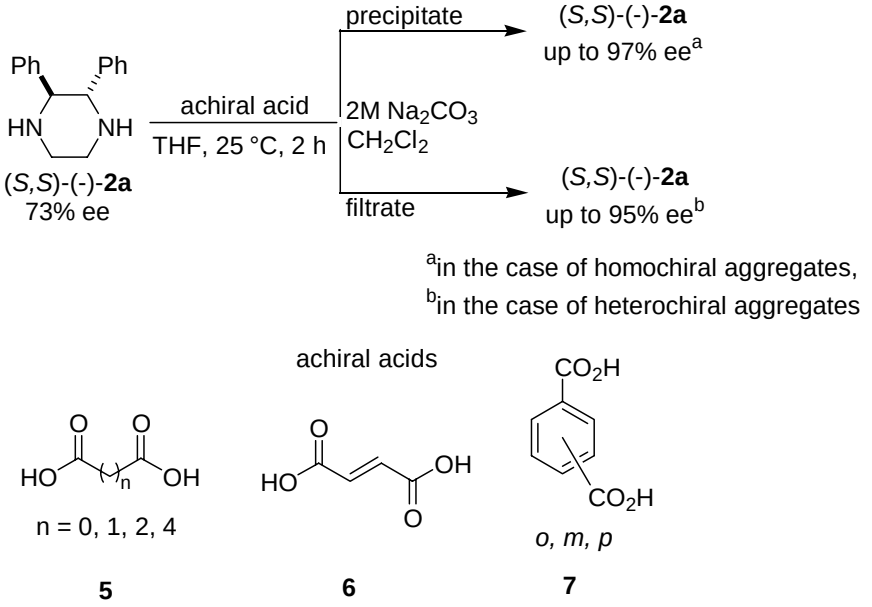
Scheme 3.



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

The partially resolved (non-racemic) samples were purified using different achiral dicarboxylic acids *via* preparation of homochiral or heterochiral aggregates (Scheme **4**).

Scheme 4.



Chiral titanium reagents derived from different chiral ligands (Figure **1**) were developed for the enantioselective intramolecular reductive cyclization of diimines **1a** and **1c.** Using the chiral titanium reagents derived from the hemisalen ligands **12**, the chiral 2,3-diarylpiperazines were obtained in up to 97% ee.

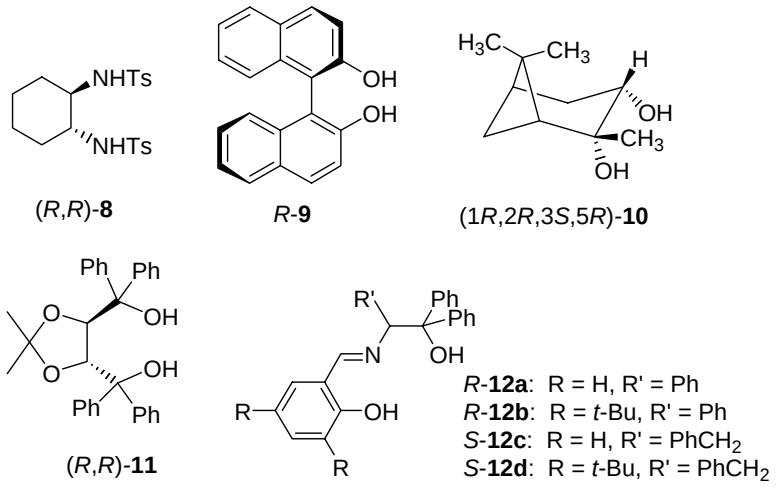
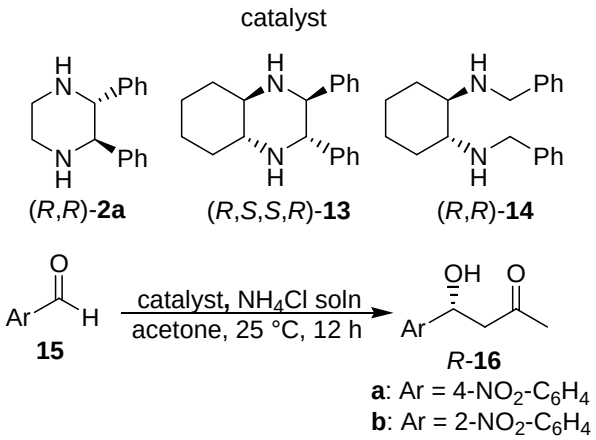


Figure 1.

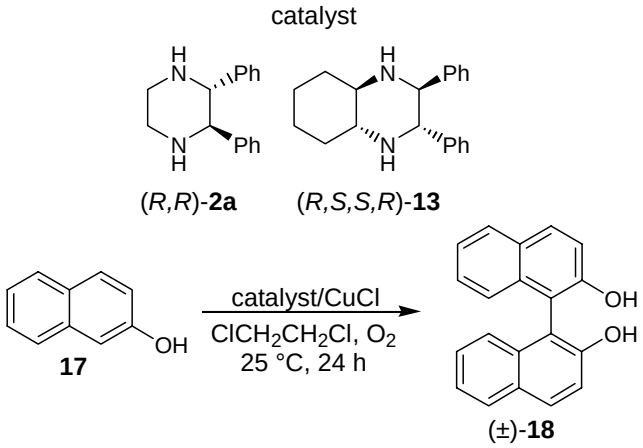
Chiral 2,3-disubstituted piperazines and chiral diamines derived from 1,2-diaminocyclohexane were examined for use in the aldol reaction of aryl aldehydes with acetone in saturated ammonium chloride solution (Scheme **5**). Enantioselectivity up to 31% ee was realized using the chiral diamine (*R,R*)-**14**.

Scheme 5.



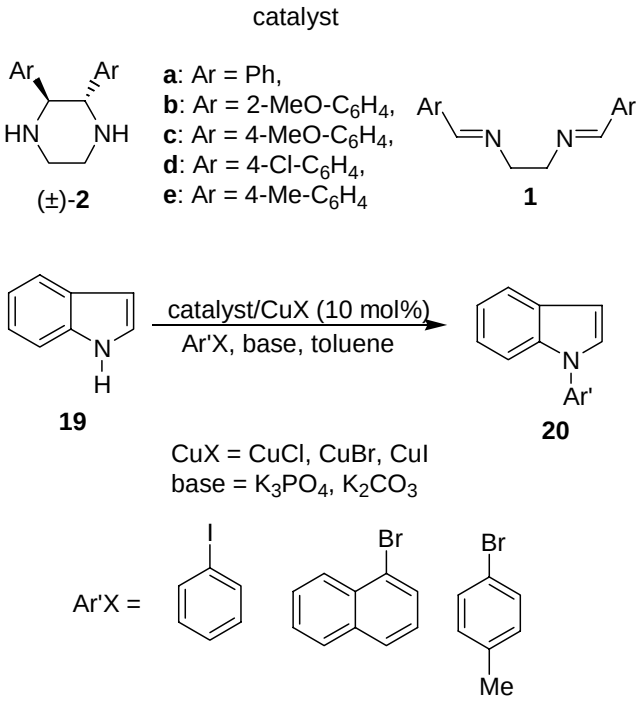
Application of CuCl/chiral piperazines as a catalyst in the dimerization of 2-naphthol in the presence of oxygen was examined, and the BINOL was obtained in moderate yield (up to 60%) with no enantioselectivity (Scheme **6**).

Scheme 6.



A simple catalyst system consisting of the easily accessible piperazine ligand and copper(I) halide was developed for the *N*-arylation of indole (Scheme **7**). The electronic control by the substituent of the phenyl ring over the reaction was studied. It was observed that the piperazine was oxidatively cleaved to diimine in presence of oxygen under this reaction condition. Based on this observation, a new convenient catalyst system using the diimine/CuI was also developed for the *N*-arylation of indole.

Scheme 7.



The experimental details are described in the third chapter. The IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, HPLC data and physical constant data (mp) are presented.

Portions of the results described in this thesis have been published:

1. A simple method of synthesis of (±)-2,3-diarylpiperazines and a novel method of resolution of (±)-2,3-diphenylpiperazine, Vairaprakash, P.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 3636-3638.

2. New chiral titanium complexes for enantioselective reductive cyclizations of diimines to *trans*-2,3-diarylpiperazines, Vairaprakash, P.; Periasamy, M. *Tetrahedron Lett.* **2007**, *48*, 0000.

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

1. Introduction

Both chiral and achiral amines play a central role in chemistry. Among the amine family, chiral 1,2-diamines and modified 1,2-diamino compounds have many useful applications in almost all branches of organic chemistry. Optically pure vicinal diamines are used as a basic skeleton in the synthesis of many biologically active compounds. They account for most of the chiral inducers and used as important chiral ligands or chiral auxiliaries for asymmetric synthesis. The amine synthons have been used as precursors in the synthesis of heterocyclic ring systems as well as chelating agents in medicinal chemistry and radiopharmaceuticals.[1-3] A brief review of literature related to the applications of 1,2-diamines/1,2-diamino compounds will be helpful for the discussion.

1.1 Applications of chiral 1,2-diamines and their derivatives in organic transformations

Enantiopure 1,2-diamines have been used as efficient chiral catalysts and reagents. The molecules with diamine skeletons listed in Figure **1** have been widely used in the asymmetric organic transformations such as oxidation,[4] reduction,[5] C-C bond forming reactions[6] and other functional group transformations.[7]

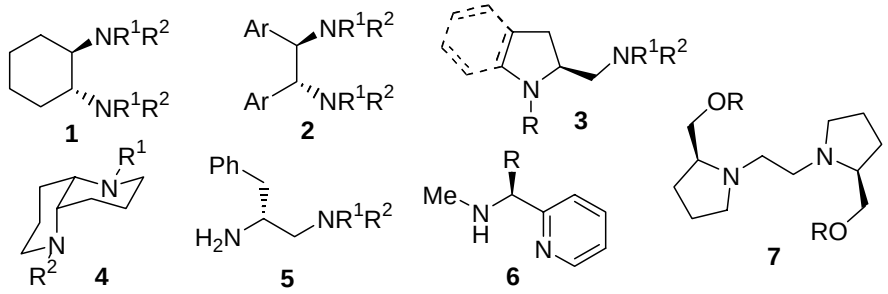


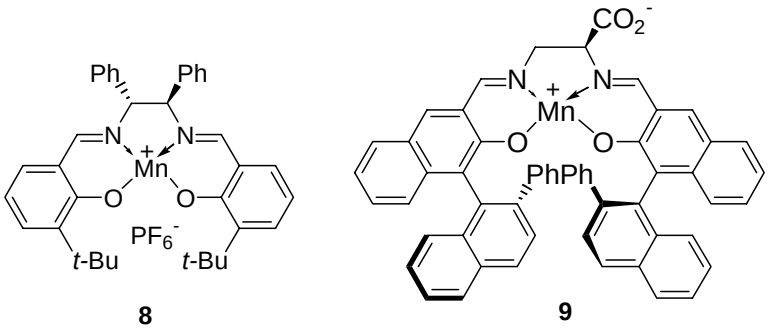
Figure 1.

Applications of these diamines and derivatives are summarized below.

1.1.1 Mn(salen) complexes

The Mn(salen) complexes have been widely utilized in the organic transformations. The Mn(salen) complexes **8-11** have been used in the asymmetric epoxidations of variety of unfunctionalized olefins and in the oxidation of sulfides (Chart **1**).

Chart 1.



8

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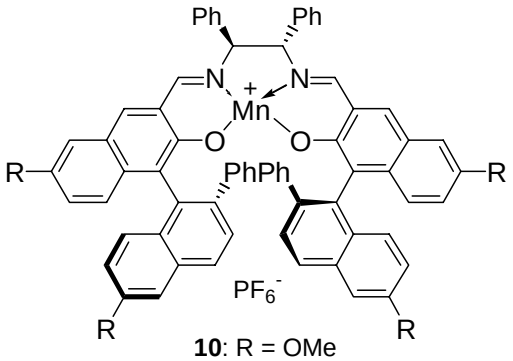
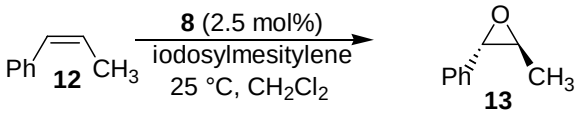
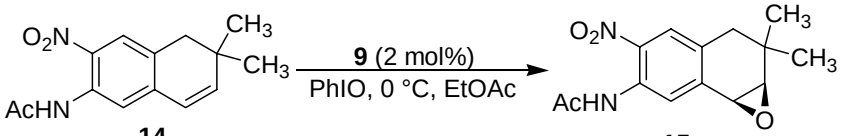


10: R = OMe
11: R = H

(ref)

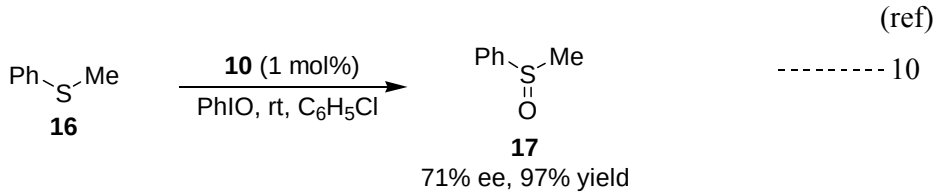


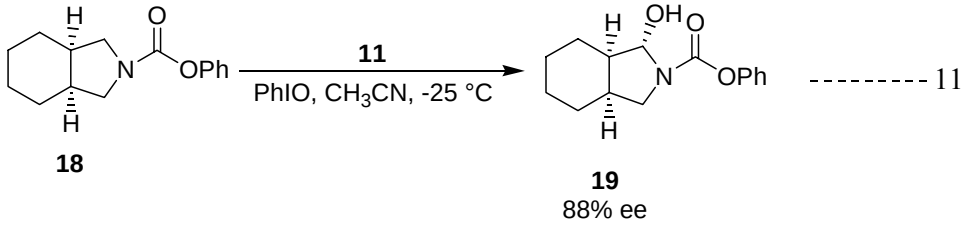
57% ee, 75% yield ---------8



94% ee, 94% yield ---------9

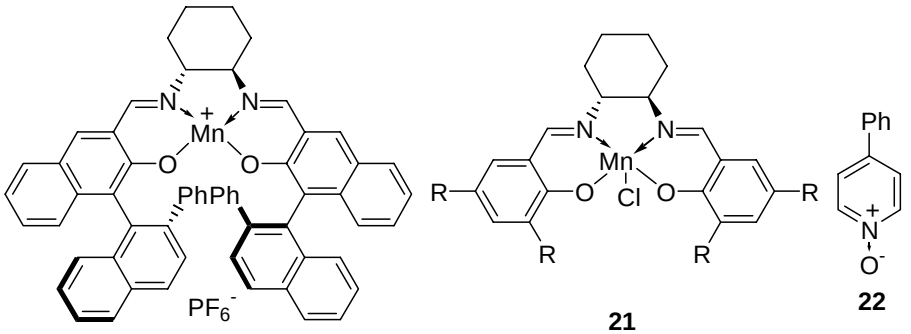
Chart 1. (continued)





The Mn(salen) complexes have also been used in the oxidation of C-H bonds (Chart **2**). For example, the complex **20** has been used in the benzylic oxidation of indane and the complex **21** in the desymmetrization of indane derivative.

Chart 2.



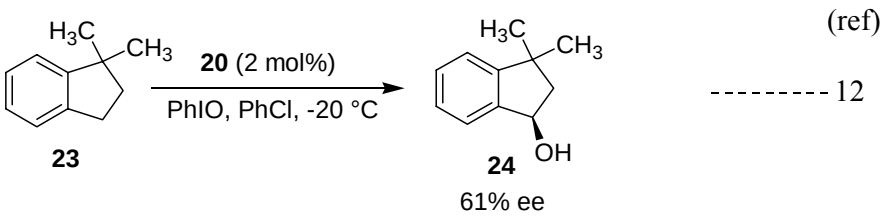
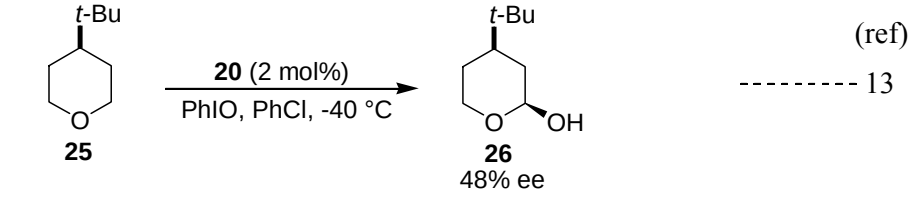
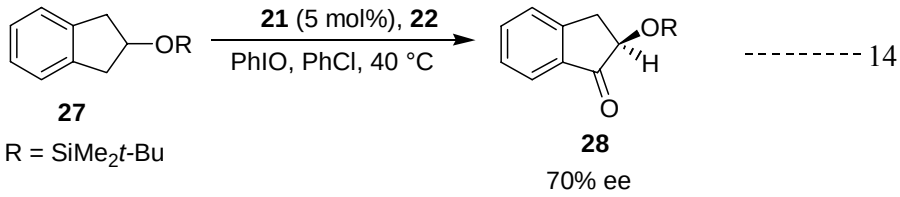


Chart 2. (continued)

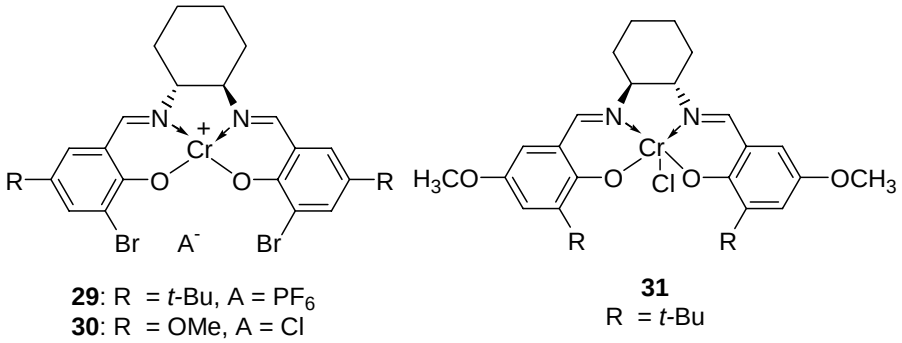




1.1.2 Cr(salen) complexes

Numerous Cr(salen) complexes have been prepared and used in the epoxidation of alkenes, asymmetric ring opening of epoxides with various nucleophiles and allylation of aldehydes (Chart **3**).

Chart 3.



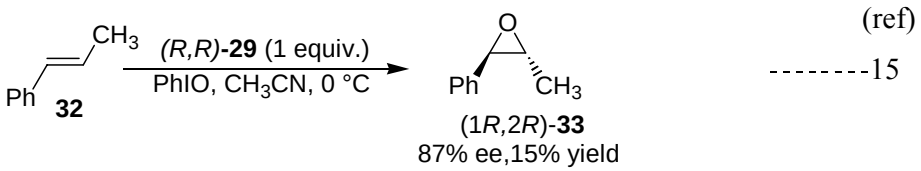
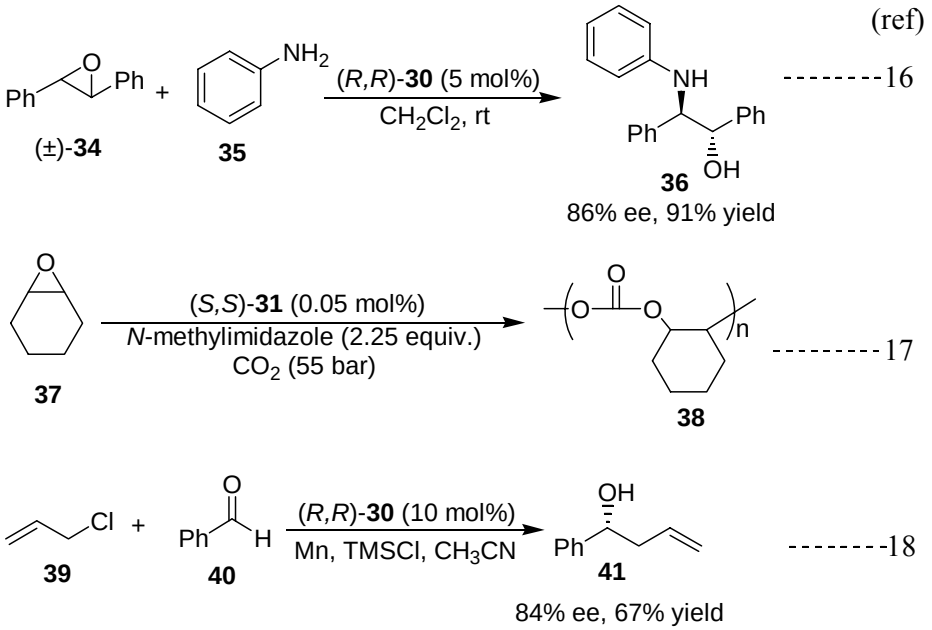


Chart 3. (continued)



1.1.3 Ru(salen) complexes

Chiral ruthenium-Schiff base complexes have been used in the oxidation of secondary alcohols, oxidative coupling of 2-naphthols and *cis*-dihydroxylation of alkenes (Chart **4**).

Chart 4.

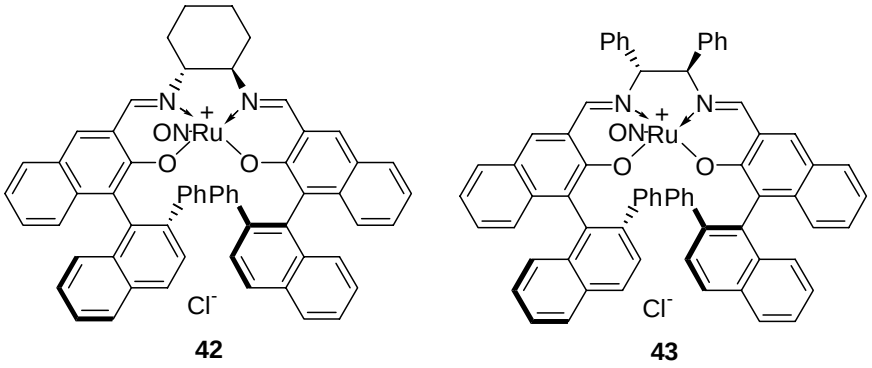
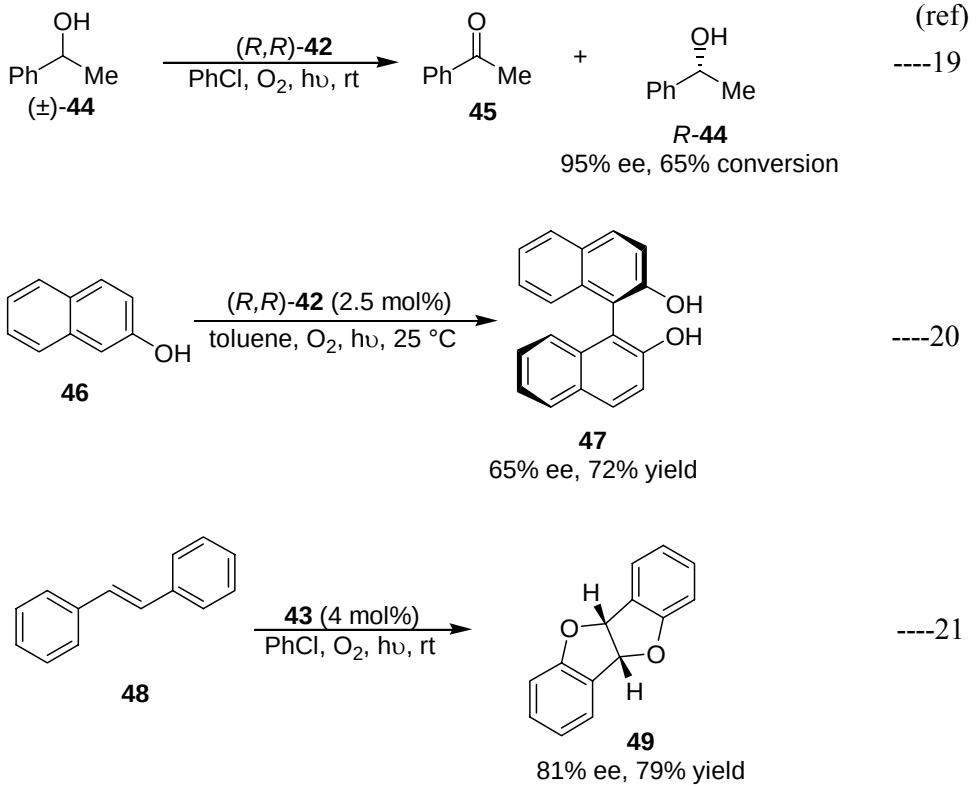


Chart 4. (continued**)**



1.1.4 Co(salen) complexes

A range of chiral Co(salen) complexes have been synthesized and utilized in the asymmetric ring opening of epoxides by water, CO_2 and amino nucleophiles (Chart **5**).

Chart 5.

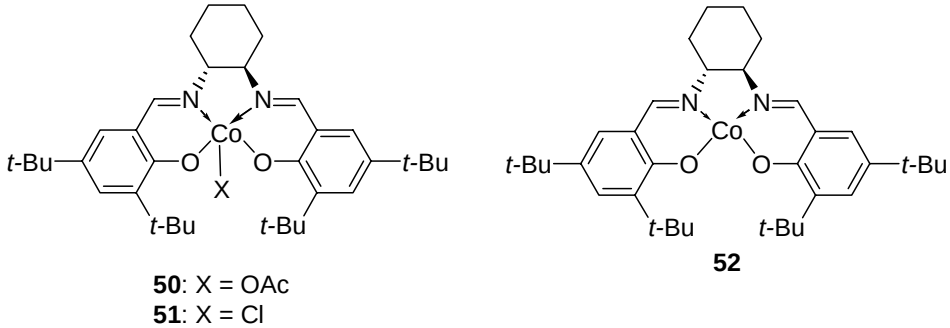


Chart 5. (continued**)**

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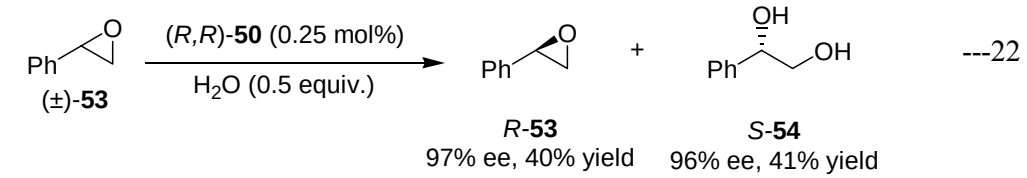

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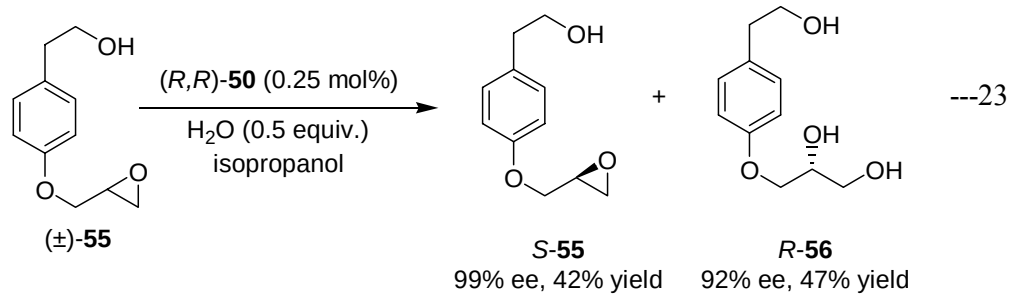

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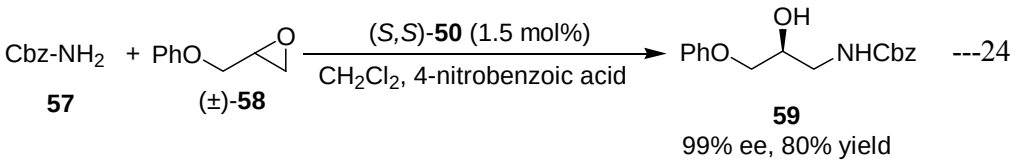

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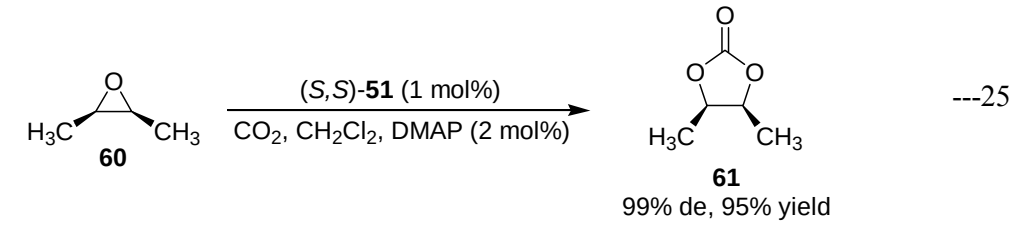

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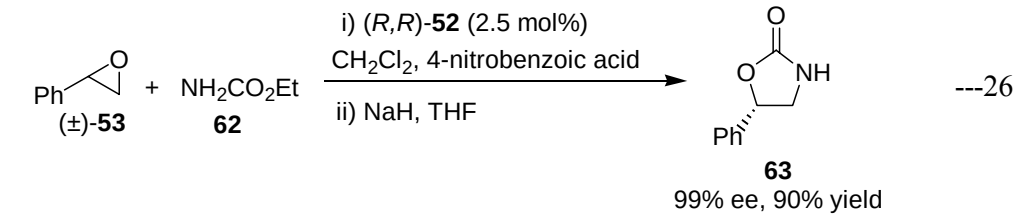
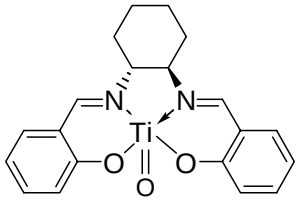


---26

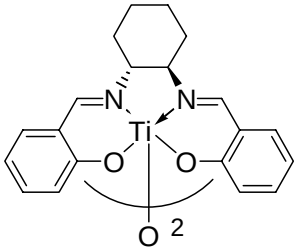
1.1.5 Ti(salen) complexes

Titanium complexes prepared from chiral 1,2-diaminocyclohexane derived salen ligands have been used in the oxidation of sulfides, asymmetric ring opening of epoxides and pinacol coupling of aromatic aldehydes (Chart **6**).

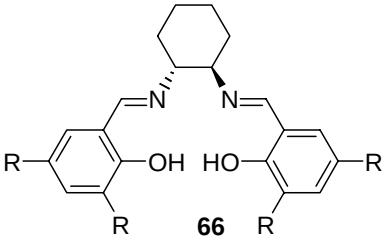
Chart 6.



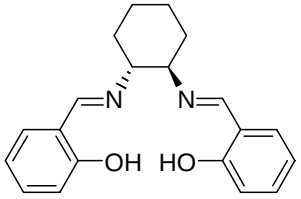
64



65

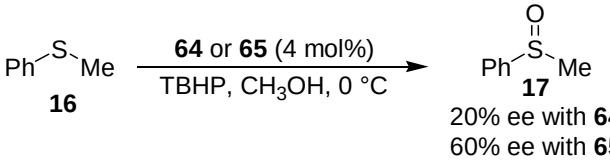


66
R = *t*-Bu



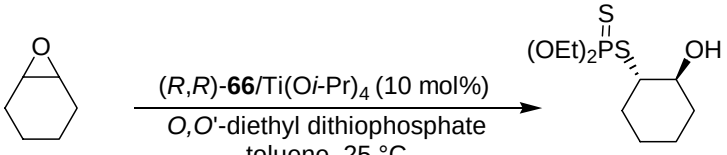
67

(ref)



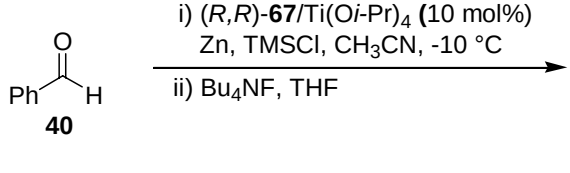
16 → **17**
64 or **65** (4 mol%), TBHP, CH_3OH, 0 °C
20% ee with **64**
60% ee with **65**

27



37 → **68**
(*R*,*R*)-**66**/Ti(O*i*-Pr)$_4$ (10 mol%), *O,O*'-diethyl dithiophosphate, toluene, 25 °C
73% ee, 90% yield

28



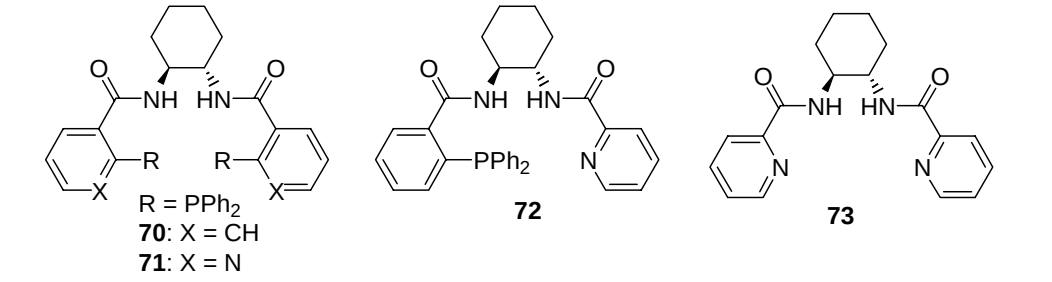
40 → **69**
i) (*R,R*)-**67**/Ti(O*i*-Pr)$_4$ (10 mol%), Zn, TMSCl, CH_3CN, -10 °C
ii) Bu_4NF, THF
95% ee, 94% yield

29

1.1.6 Chiral 1,2-diamides

Several diamide derivatives of chiral 1,2-diamines have been prepared and used as ligands for transition metal catalyzed C-C and C-N bond forming reactions (Chart **7**).

Chart 7.



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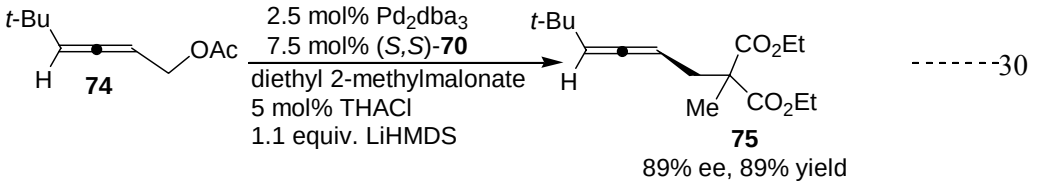

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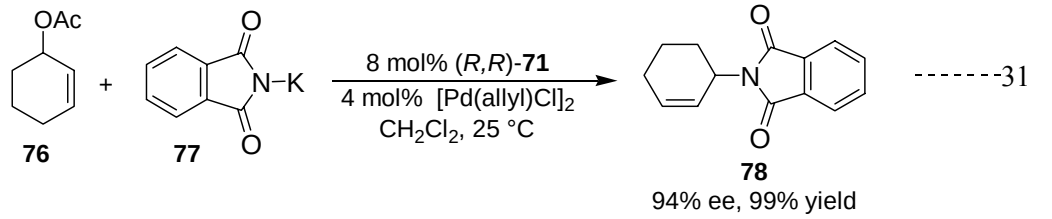

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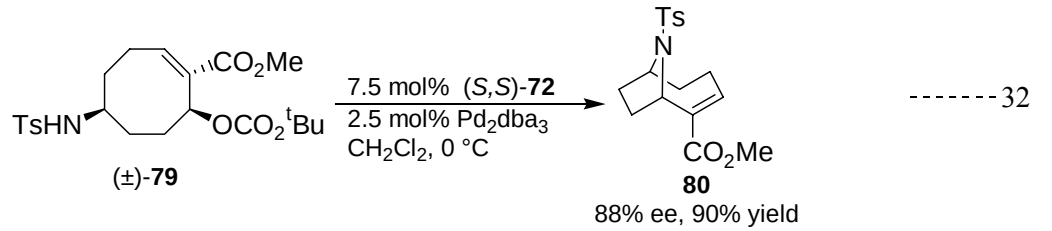

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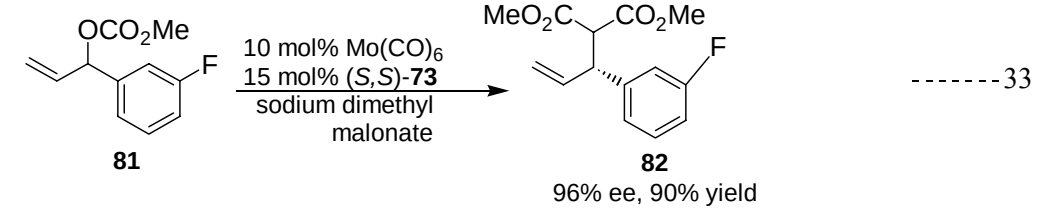

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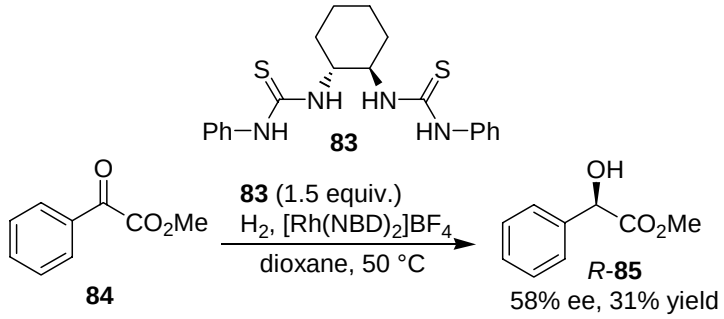
The rhodium complex of thiourea derivative **83** was used in the asymmetric reduction of phenylglyoxylate methyl ester **84** (Scheme **1**).[34]

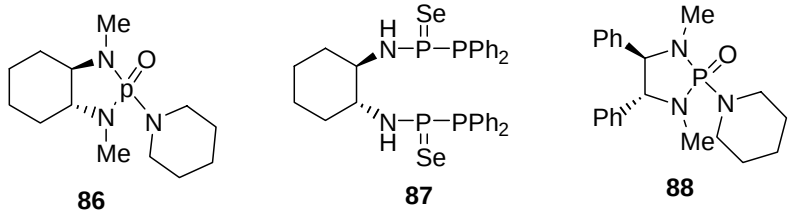
Scheme 1.



1.1.7 Chiral phosphoramides

Chiral phosphoramides have been used as catalysts in allylation of aldehydes, diethylzinc addition and trichlorosilyl enolates addition to aldehydes (Chart **8**).

Chart 8.



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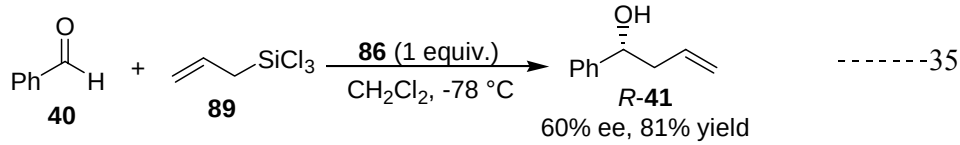

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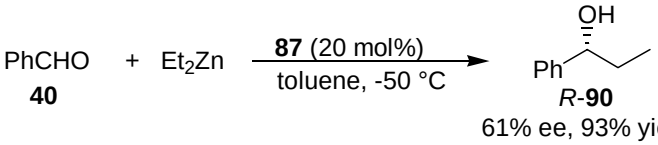

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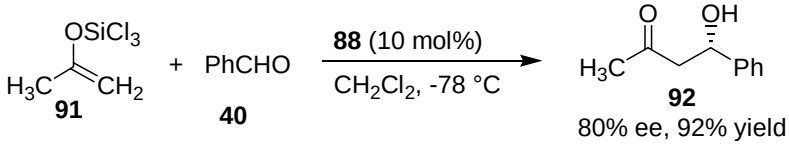

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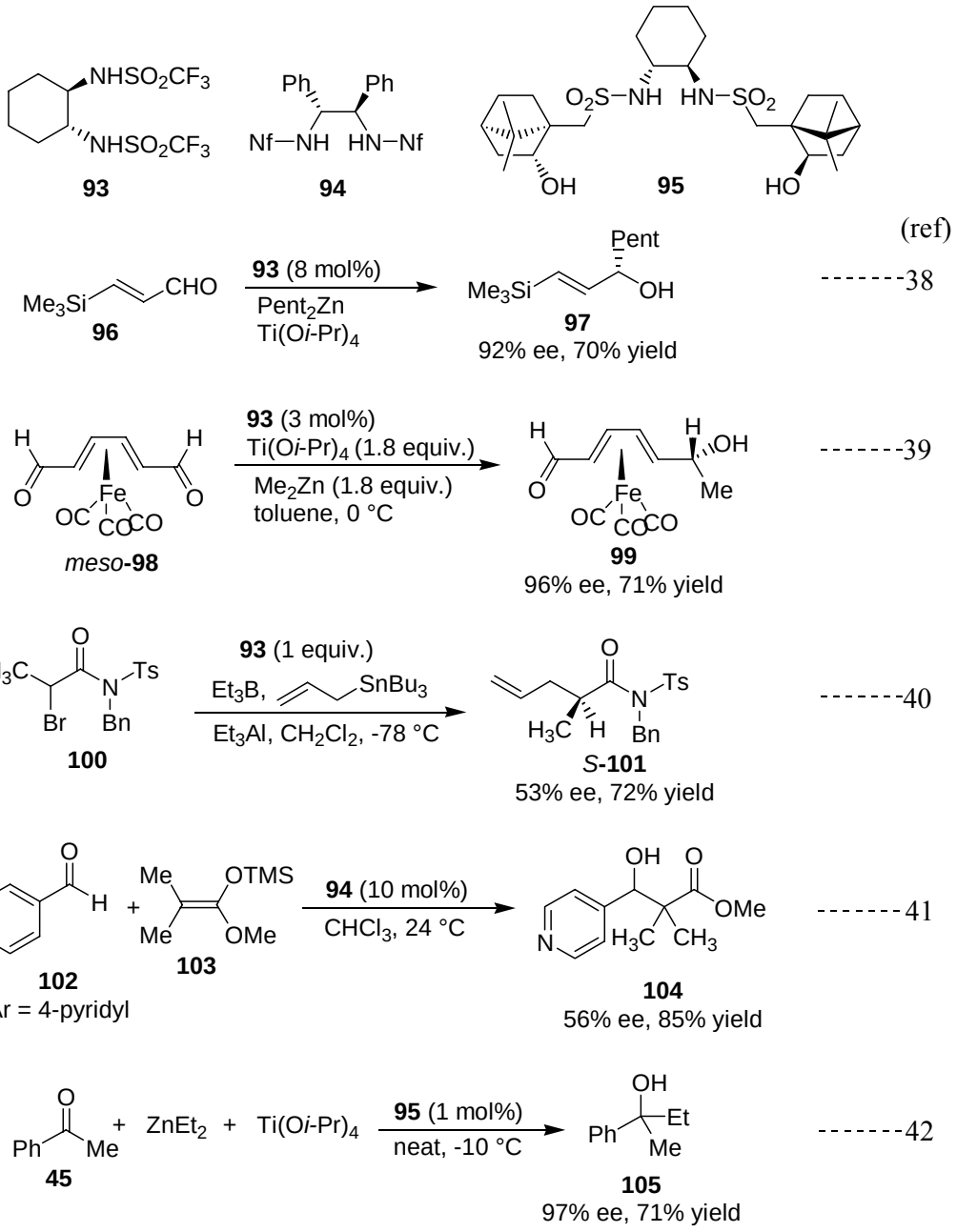
1.1.8 Chiral sulfonamides

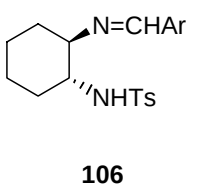
Bis(sulfonamides) have been demonstrated for use as catalysts in diethylzinc addition to various aldehydes and ketones and in the C-C bond forming reactions (Chart **9**).

Chart 9.

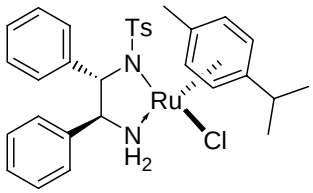


Unsymmetrical sulfonamides and their metal complexes have been used in the cyclopropanation reactions, aldol reactions and asymmetric transfer hydrogenation of various ketones (Chart **10**).

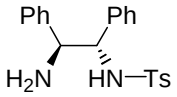
Chart 10.



106
Ar = 2-OH-C_6H_4



107



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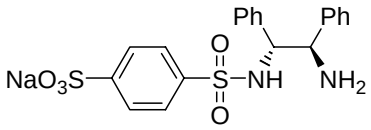

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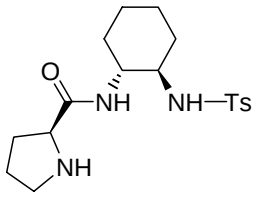

110

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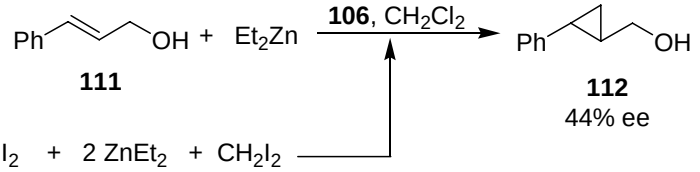
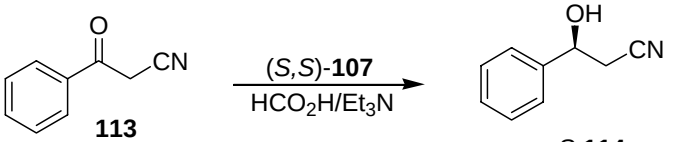


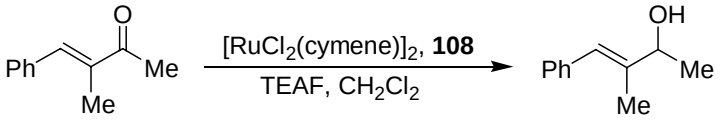
111 **112**
44% ee

-------43



113 *S*-**114**
98% ee, 100% yield

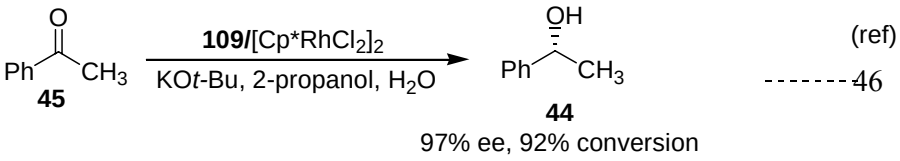
-------44

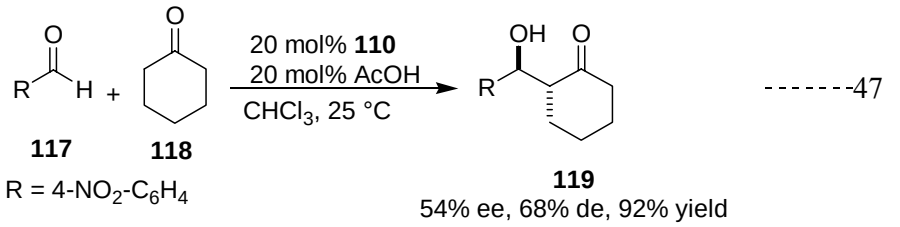


115 **116**
76% ee, 85% yield

-------45

Chart 10. (continued**)**

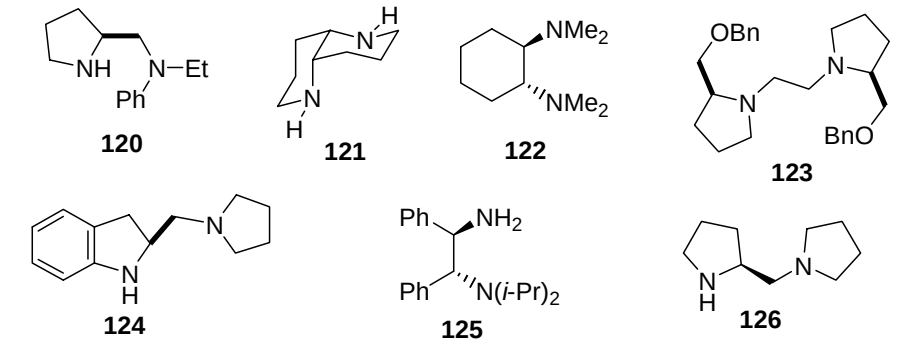




1.1.9 Chiral 1,2-diamines

Chiral 1,2-diamines of varied structural features have been used in the oxidative coupling of 2-naphthols, titanium catalyzed enantioselective pinacol coupling reactions, atom transfer reactions, diethylzinc additions and organocatalysis (Chart **11**).

Chart 11.



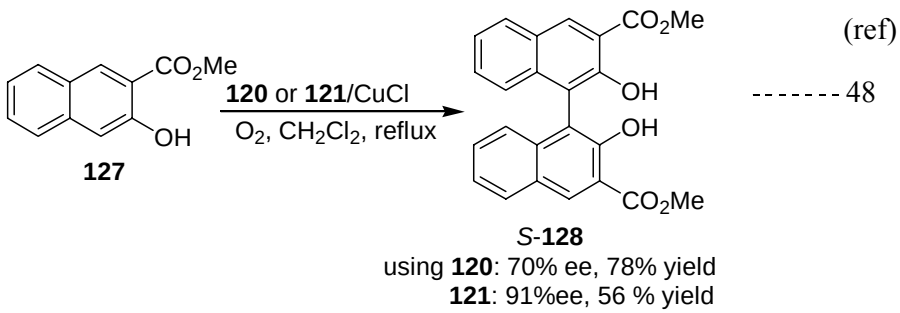
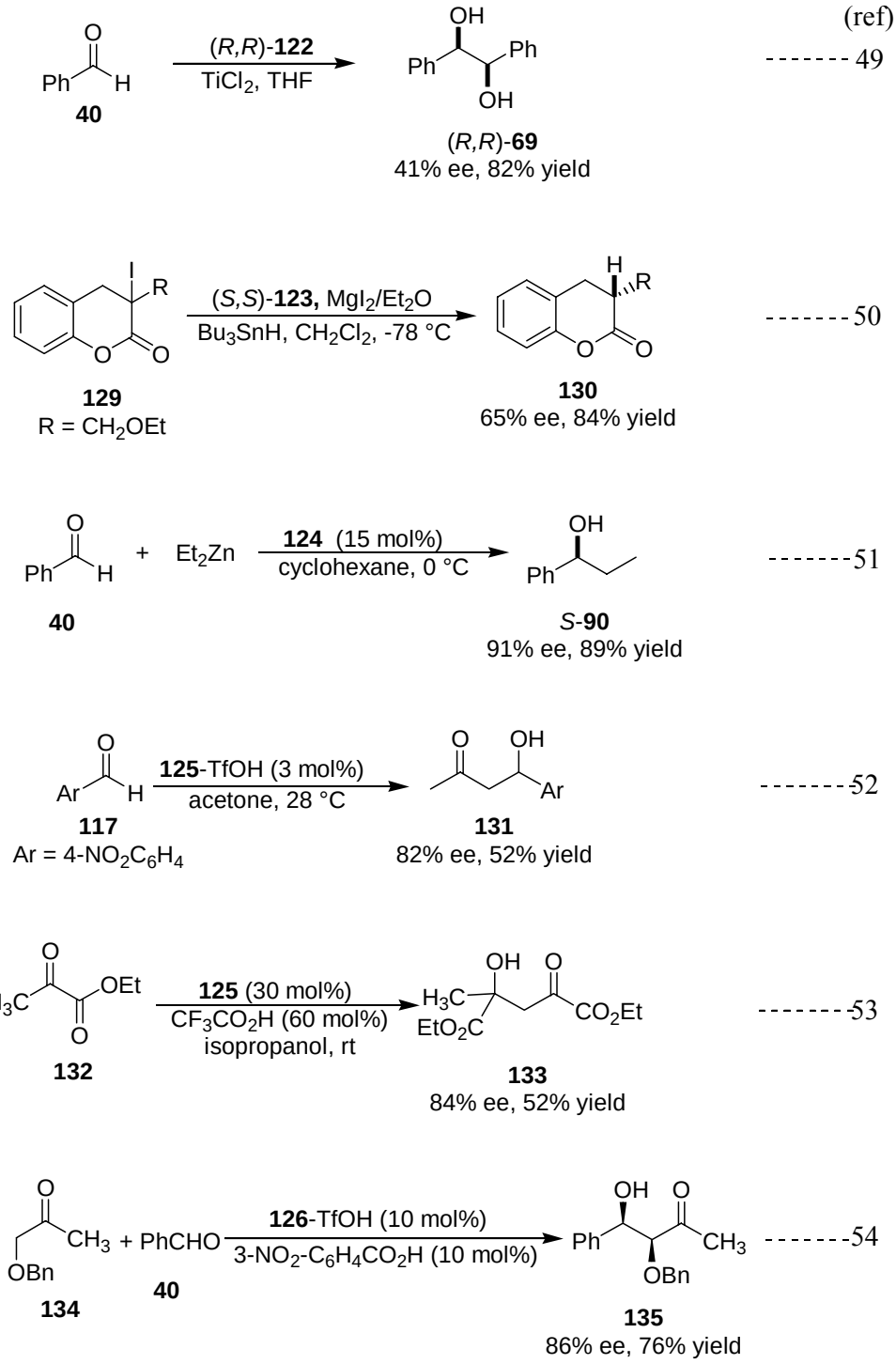


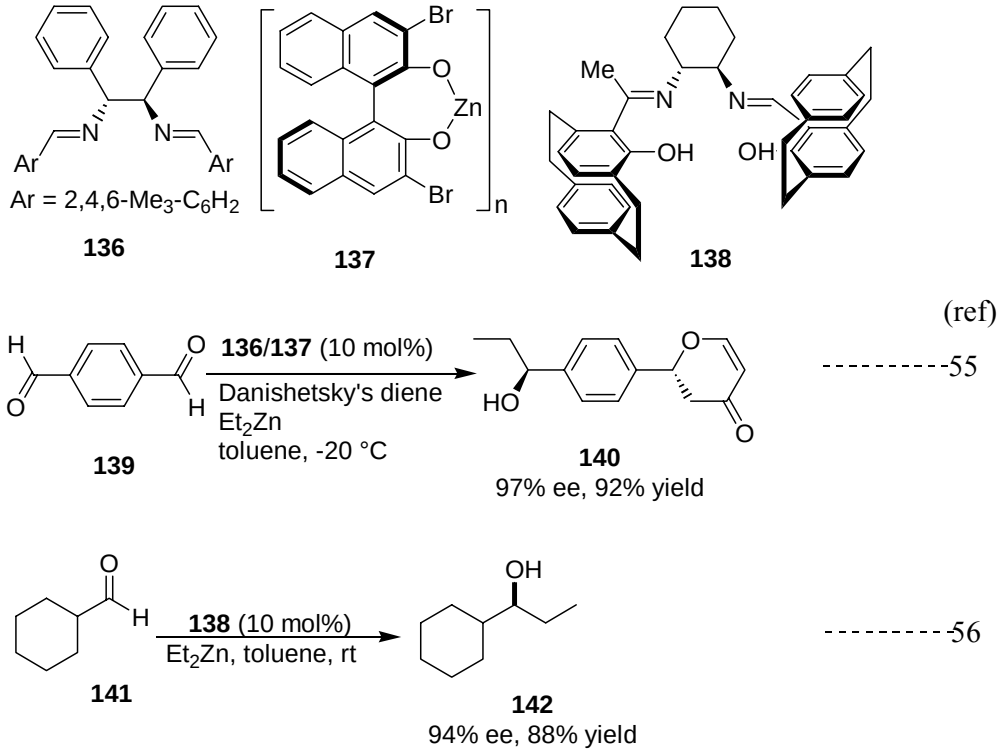
Chart 11. (continued**)**



1.1.10 Chiral diimines

Chiral diimines and multistereogenic salens based on a [2.2]paracyclophane skeleton have been used in the diethylzinc addition to aldehydes (Chart **12**).

Chart 12.



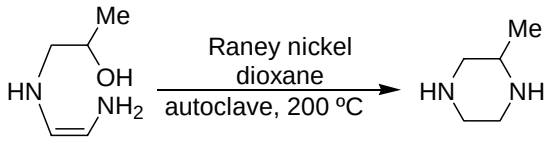
1.2 Synthesis and applications of chiral piperazines

We have studied the synthesis and applications of chiral 2,3-diarylpiperazines. Accordingly, it is of interest to briefly review the synthesis of piperazines. Piperazine was first introduced as an anthelmintic in 1953.[57] A large number of piperazine compounds have anthelmintic action. Piperazines are also used in the manufacture of plastics, resins, pesticides, brake fluid and other industrial materials.[58]

1.2.1 Synthesis of substituted piperazines

Kitchen *et al*[59] reported a method of preparation of piperazine and numerous of its *C*-substituted homologs by the catalytic cyclodehydration of *N*-(2-hydroxyethyl)–ethenediamine **143** and its *C*-substituted derivatives (Scheme **2**).

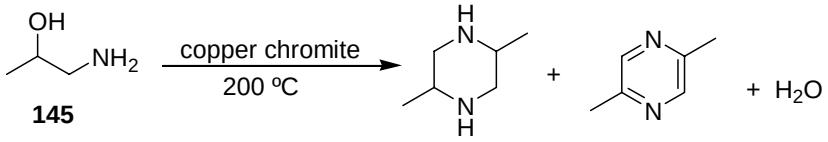
Scheme 2.



143 **144**
70% yield

Langdon *et al*[60] prepared piperazines in the bimolecular reaction of alkanolamines such as isopropanolamine (1-amino-2-propanol) in the presence of hydrogenation-dehydrogenation catalysts under either liquid-phase or vapor-phase conditions, and by batch or continuous processes (Scheme **3**).

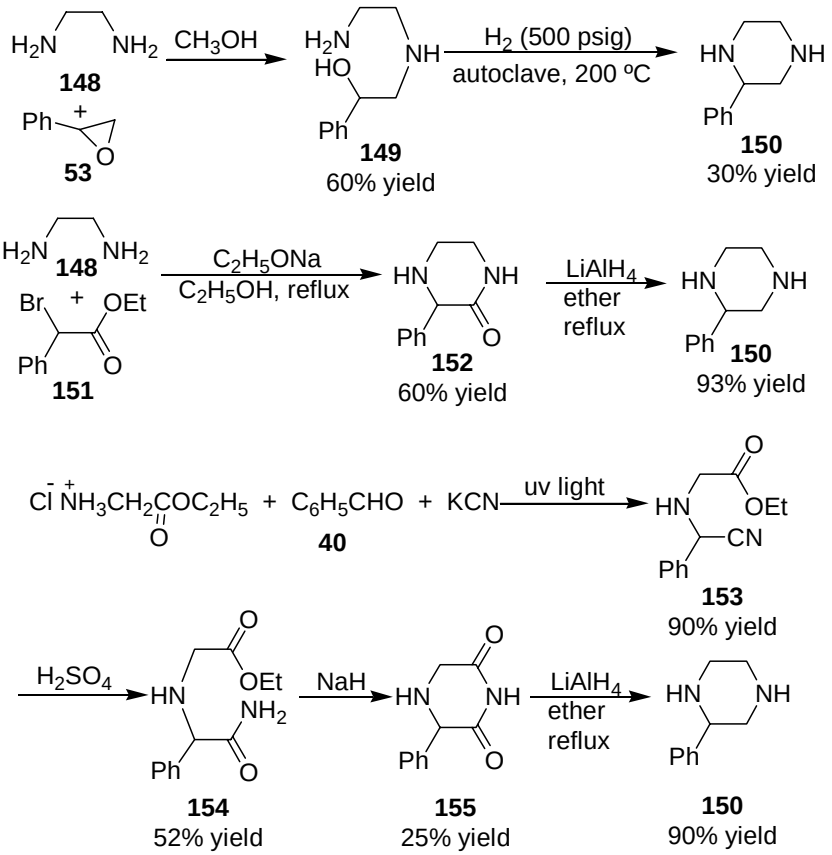
Scheme 3.



145 **146** **147**
23% yield 35% yield

Rodrick *et al*[61] reported three methods for the synthesis of 2-phenylpiperazine; i) by the opening of styrene epoxide by ethylenediamine followed by cyclization, ii) reaction of ethylenediamine with α-haloesters and reduction of 2-alkyl-3-oxopiperazines, and iii) by the reaction of β-amino esters, benzaldehyde and KCN (Scheme **4**).

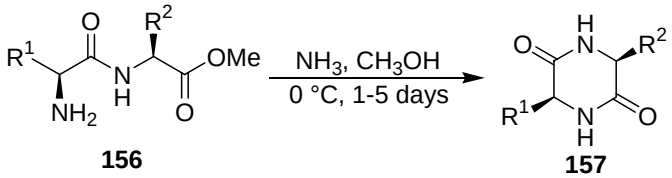
Scheme 4.



1.2.2 Synthesis of 2,5-diketopiperazines

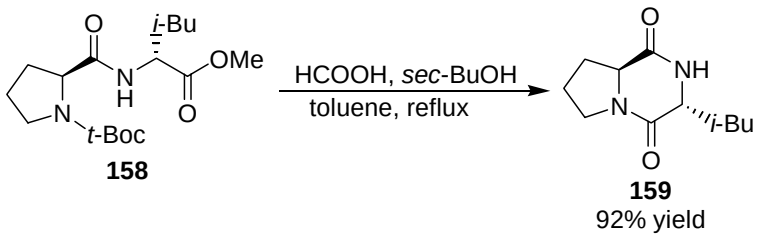
Piperazines can also be synthesized either by the reduction of 2,5-diketopiperazines or pyrazines. In 1906, Fischer[62] reported the synthesis of chiral diketopiperazines **157** by the cyclization of dipeptide methyl ester **156** in methanol solvent saturated with ammonia (Scheme **5**).

Scheme 5.



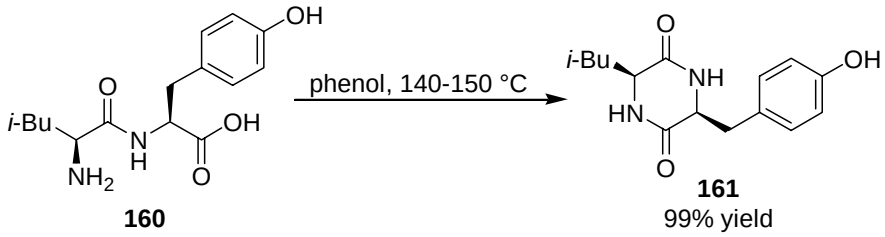
Later in 1968, Nitecki *et al*[63] reported the synthesis of diketopiperazines from dipeptides in 2-butanol-toluene solvent system (Scheme **6**).

Scheme 6.



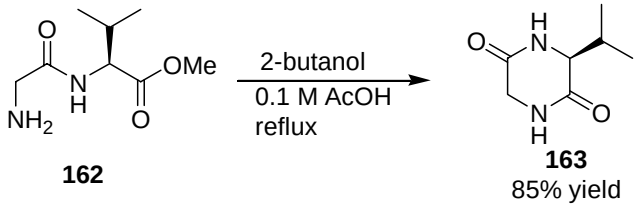
Kopple *et al*[64] reported the cyclization of unblocked dipeptides by heating the dipeptides in phenol below its boiling point (Scheme **7**).

Scheme 7.



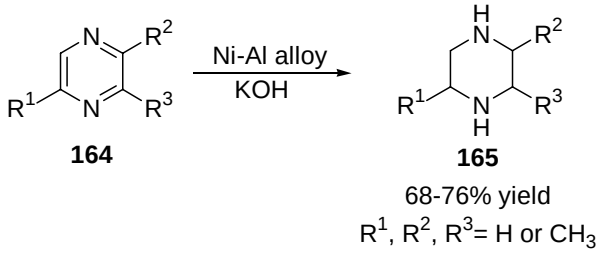
Suzuki *et al*[65] synthesized various diketopiperazines by the cyclization of corresponding dipeptide esters in refluxing 2-butanol (Scheme **8**). The 1,4-diketopiperazines were obtained in 74-97% yields.

Scheme 8.



In 1987, Lunn[66] reported the synthesis of different substituted piperazines **165** by the reduction of pyrazines **164** using Ni/Al alloy in KOH solution (Scheme **9**).

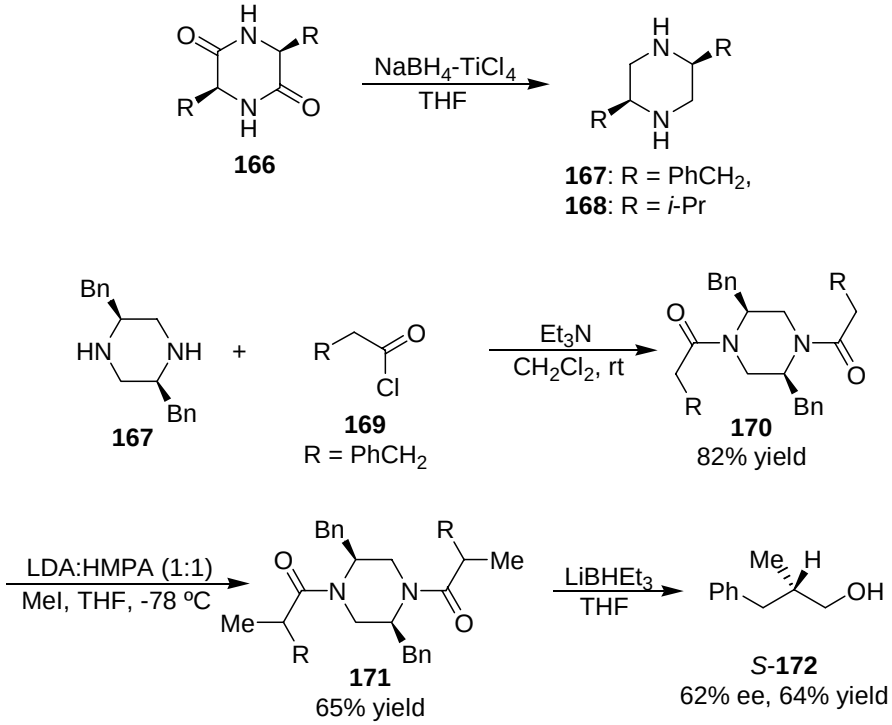
Scheme 9.



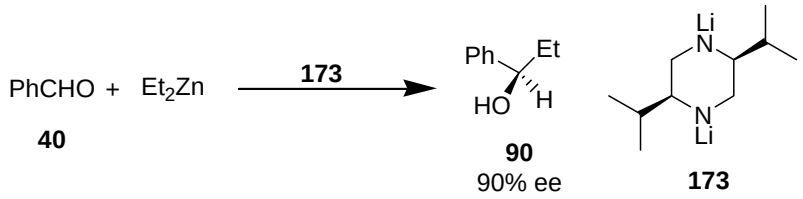
1.2.3 Applications of chiral piperazines

Chiral piperazines were prepared and used as chiral auxiliaries in the diastereoselective alkylation of chiral diamides.[67] The optically active alcohols were obtained with moderate ee's. In another study, lithium salt of chiral piperazine was used to promote the asymmetric addition of dialkylzincs to benzaldehyde (Scheme **10**).[68]

Scheme 10.

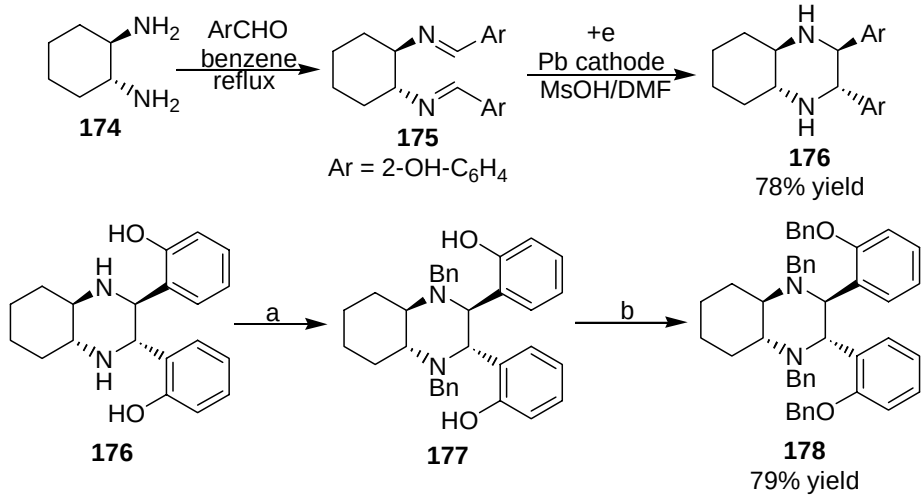


Scheme 10. (continued)

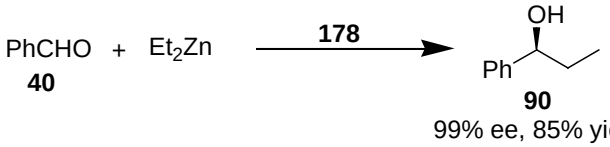


Chiral 2,3-diarylpiperazine derivatives **178** prepared from (*1R,2R*)-1,2-diaminocyclohexane were used as chiral ligands by Shono *et al*[69] in the asymmetric addition of diethylzinc to aryl aldehydes (Scheme **11**). The chiral secondary alcohols were obtained in very good yields up to 90% (up to 99% ee).

Scheme 11.



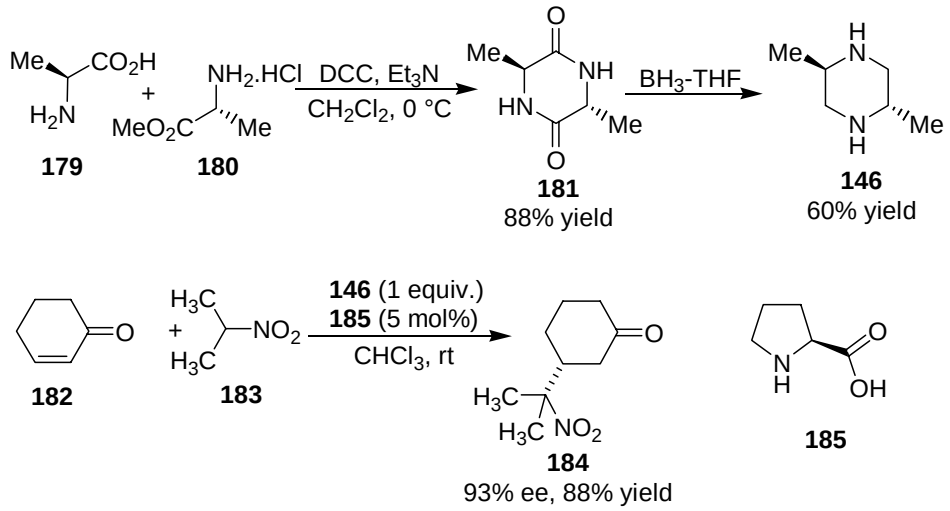
a): i) TMSCl, Et_3N, toluene, reflux; ii) BnBr, reflux.
b): NaH, BnBr, THF, reflux



Achiral piperazine **146** has been synthesized by the cyclization of corresponding amino acid and its methyl ester hydrochloride salt followed by reduction using BH_3/THF. It has been used as additives in the asymmetric conjugate addition of

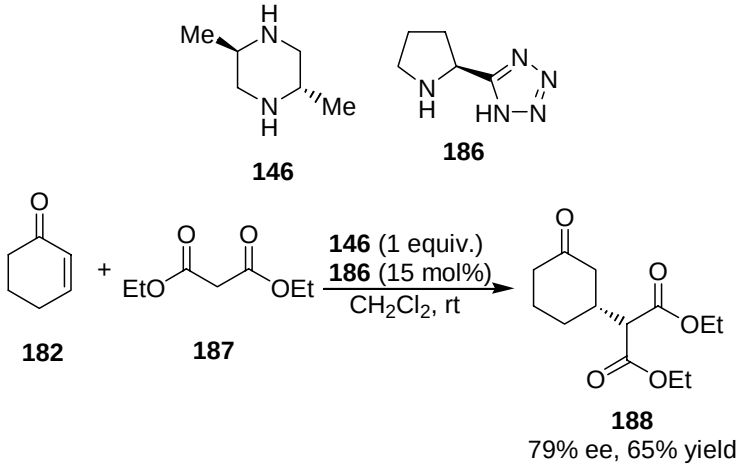
nitroalkanes **183** to enones **182** catalyzed by L-proline **185** to improve enantioselectivity (Scheme **12**).[70]

Scheme 12.

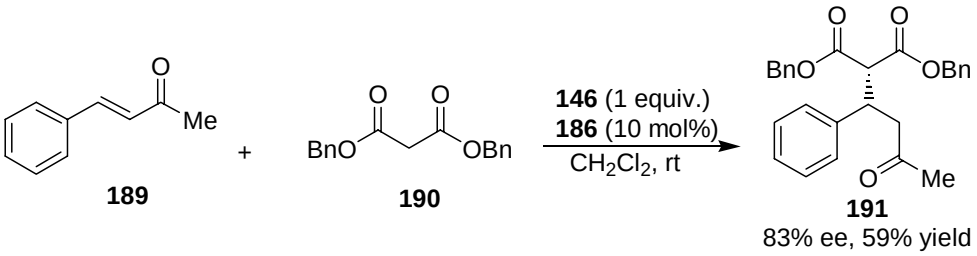


Ley *et al*[71] used the achiral *meso*-2,5-dimethylpiperazine **146** as a base in the asymmetric organocatalytic conjugate addition of malonates to enones catalyzed by proline tetrazole catalyst **186** (Scheme **13**).

Scheme 13.



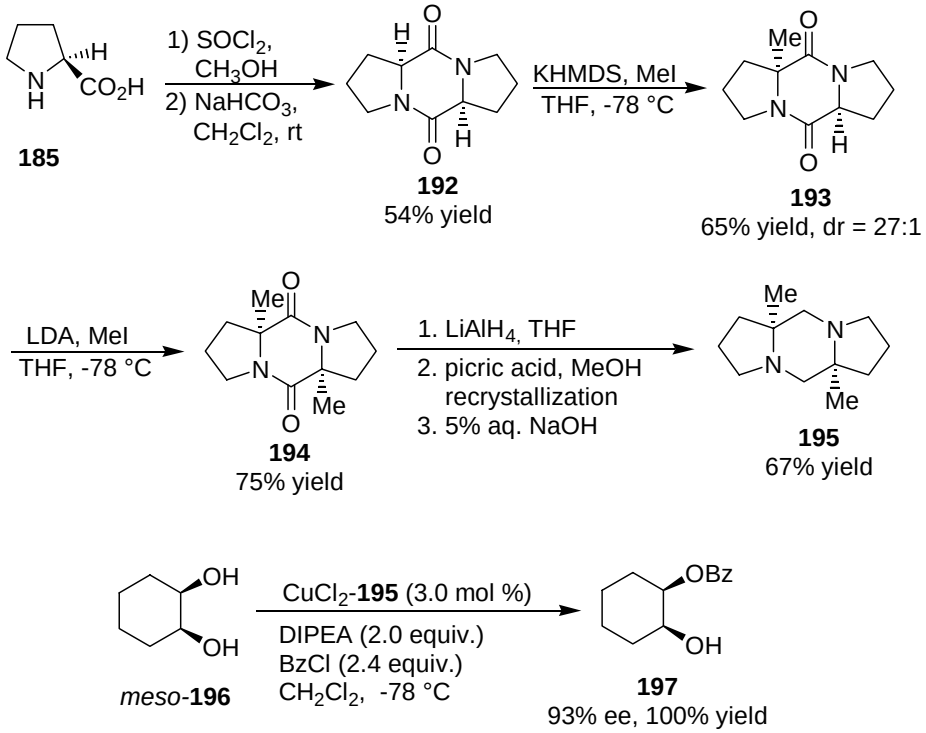
Scheme 13. (continued)



189 + **190** → **191**
83% ee, 59% yield

Shirai *et al*[72] used several alicyclic chiral C_2-symmetric diamines with $CuCl_2$ in the benzoylation of a series of cyclic and acyclic *meso*-1,2-diols to provide optically active monobenzoates with high enantioselectivity (Scheme **14**). It was concluded that the L-proline based C_2-symmetric alicyclic chiral piperazine (*S,S*)-**195** is an effective ligand for copper-catalyzed asymmetric acylation of *meso*-1,2-diols.

Scheme 14.



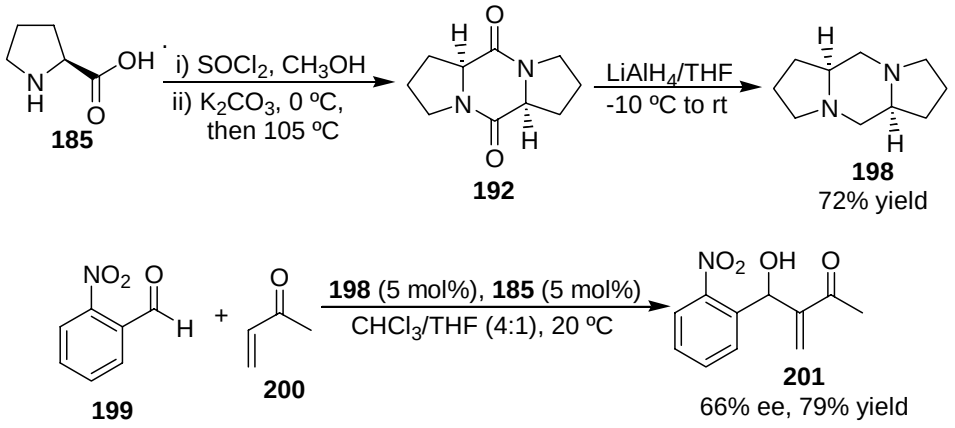
185 → **192** (54% yield) → **193** (65% yield, dr = 27:1)

194 (75% yield) → **195** (67% yield)

meso-**196** → **197** (93% ee, 100% yield)

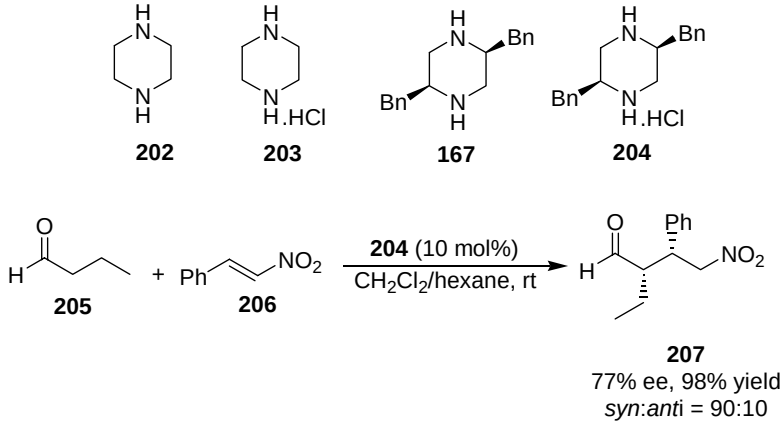
Zhao *et al*[73] synthesized tertiary piperazine from L-proline. The catalyst **198** along with L-proline was used as an efficient catalyst in the Baylis-Hillmann reaction between 2-nitrobenzaldehyde and methyl vinyl ketone (Scheme **15**).

Scheme 15.



Recently, Barros *et al*[74] reported the synthesis of achiral *γ*-nitroaldehydes catalyzed by piperazine **202** or its monohydrochloride **203** (Scheme **16**). In piperazine monohydrochloride catalyzed reactions, very good diastereoselectivity (up to 98:2) was obtained. In a chiral piperazine **167** or its monohydrochloride **204** catalyzed reaction, the products were obtained with up to 85% ee (Scheme 1**6**).

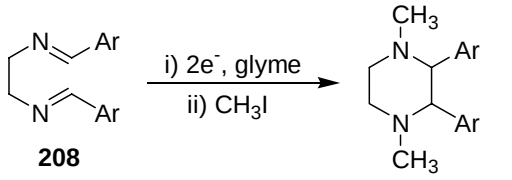
Scheme 16.



1.2.4 Synthesis of 2,3-disubstituted piperazines from diimines

2,3 Disubstituted piperazines can be easily accessed through the intramolecular reductive dimerization of diimines. Dessy *et al*[75] developed an electrochemical method for the synthesis of *N,N*'-dimethyl-2,3-diphenylpiperazine by the electrochemical reduction of diimine followed by the reaction with iodomethane (Scheme **17**).

Scheme 17.

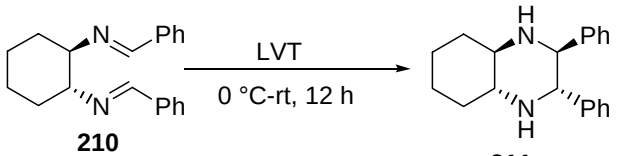


208 **209**

up to 42% yield

From our laboratory,[76] it has been reported that chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes **211** can be prepared from (1*R*,2*R*)-1,2-diaminocyclohexane derived diimines through the intramolecular reductive coupling using low valent titanium reagent systems (Scheme **18**).

Scheme 18.

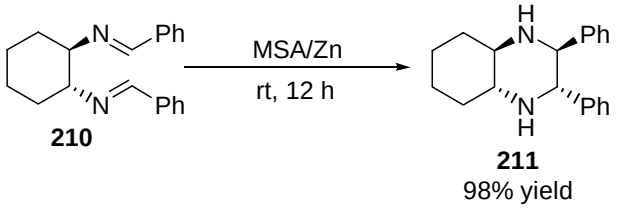


210 **211**

$TiCl_4/Et_3N$ 26%
$TiCl_4/Mg$ 54%
$TiCl_4/Zn$ 75%

Moreau *et al*[77] reported intramolecular reductive coupling of diimines derived from (1*R*,2*R*)-1,2-diaminocyclohexane for the synthesis of disubstituted-2,5-diazabicyclo[4.4.0]decanes by using zinc and trifluoroacetic acid or methanesulfonic acid (Scheme **19**).

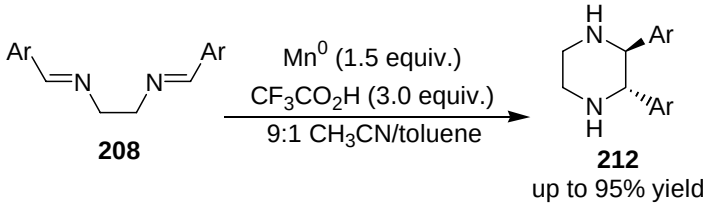
Scheme 19.



210 **211**
98% yield

In the same year, Sigman and Mercer reported the synthesis of *trans*-2,3-diaryl substituted piperazines from diimines derived from ethylenediamine using Bronsted acid and Mn^0 (Scheme **20**).[78]

Scheme 20.



208 **212**
up to 95% yield

1.2.5 Biological importance of piperazine moieties

The piperazine motif appears in many drugs encompassing a broad range of activities (e.g. Oxatomide, Almitrine, Hydroxyzine, Buclizine, Lomerizine (Figure **2**)). This motif is also found in drug candidates displaying anti-allergenic, antibacterial, anti-anxiety, anti-emetic, antimigraine, and platelet anti-aggregatory activity.[79,80] In addition, the piperazine motif is present in many cardiovascular drugs and drug candidates.[81] Benzhydryl piperazines are prevalent in many antihistamines.[82]

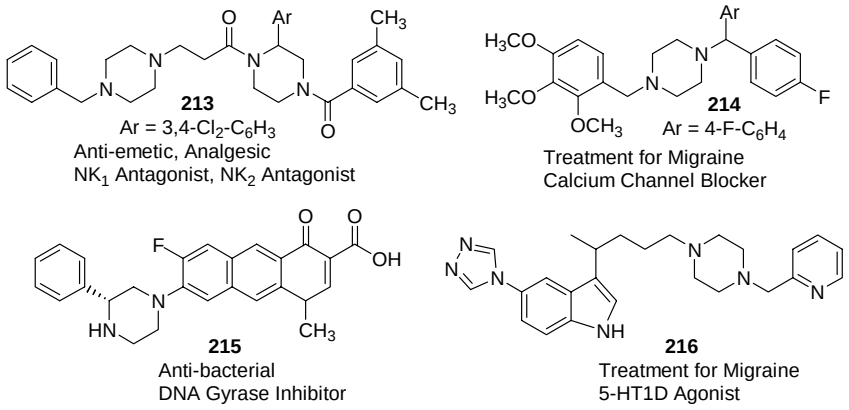
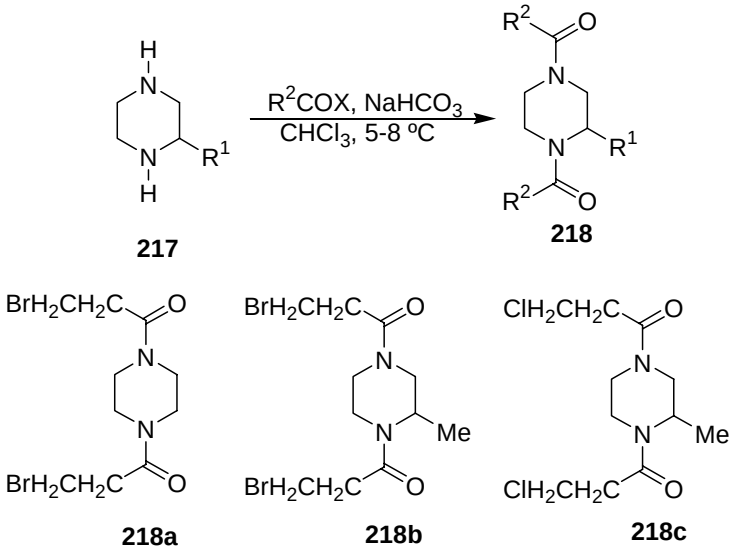


Figure 2.

Groszkowski *et al*[83] synthesized *N,N*'-bis(haloacyl)-2-methylpiperazines by condensation of appropriate haloacyl chloride with piperazine hexahydrate or 2-methylpiperazine and studied their cytostatic activity (Scheme **21**). The activity was found to be in the order **218a** < **218b** < **218c.**

Scheme 21.



Gootz *et al*[84] tested several substituted analogs of 7-(*cis*-3,5-dimethylpiperazinyl)-6,8-difluoro-5-amino-1-cyclopropylquinolone **219**-**221** in a DNA cleavage assay with calf thymus topoisomerase II. They have observed that positioning

of the methyl groups on the C-7 piperazine ring influenced potency against the mammalian enzyme.

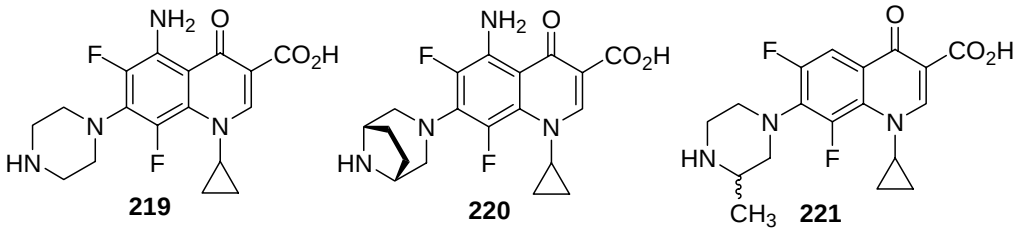
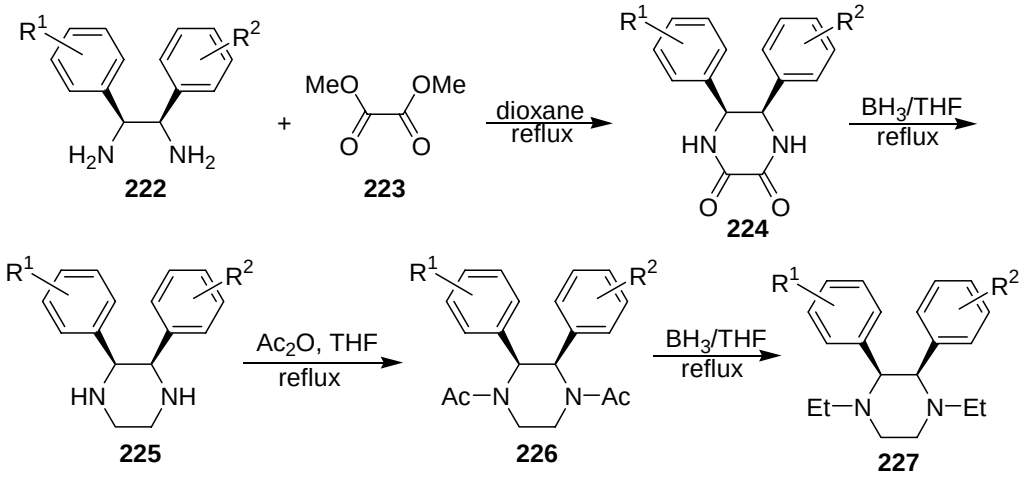


Figure 3.

Gust *et al*[85] synthesized various *meso*-2,3-diarylpiperazines and their *N*-ethyl derivatives from *meso*-1,2-diarylethylenediamines and studied their interaction with estrogen receptors (scheme **22**). *O*-Methylated diarylpiperazines are inactive showed the necessity of hydrogen bridges from the piperazines to the estrogen receptors for activating gene expression.

Scheme 22.



A molecular docking study of estrogenically active compounds with 1,2-diarylethene **228** and 1,2-diarylethene pharmacophores **229-232** by Knapp *et al*[86]

reveals that the 2,3-diarylpiperazines **230** are potentially active estrogen receptor modulators (Figure **4**).

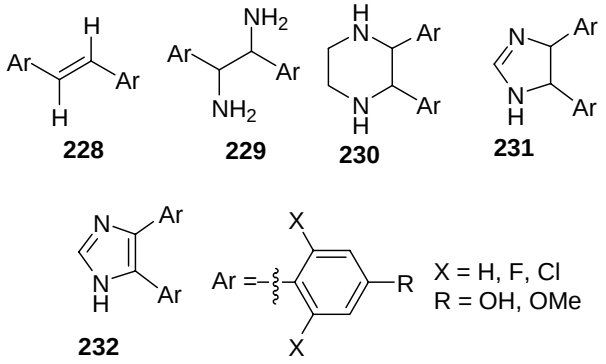


Figure 4.

Kim *et al*[87] isolated a novel bioactive alkaloid having alkylated piperazine skeleton from the leaves extract of *Arum palaestinum* Boiss. The alkaloid piperazirum (3,5-diisobutyl-6-isopropyl-piperazin-2-one) **233** (Figure **5**) showed a significant cytotoxicity against cultured tumor cell lines *in vitro*.

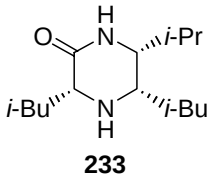
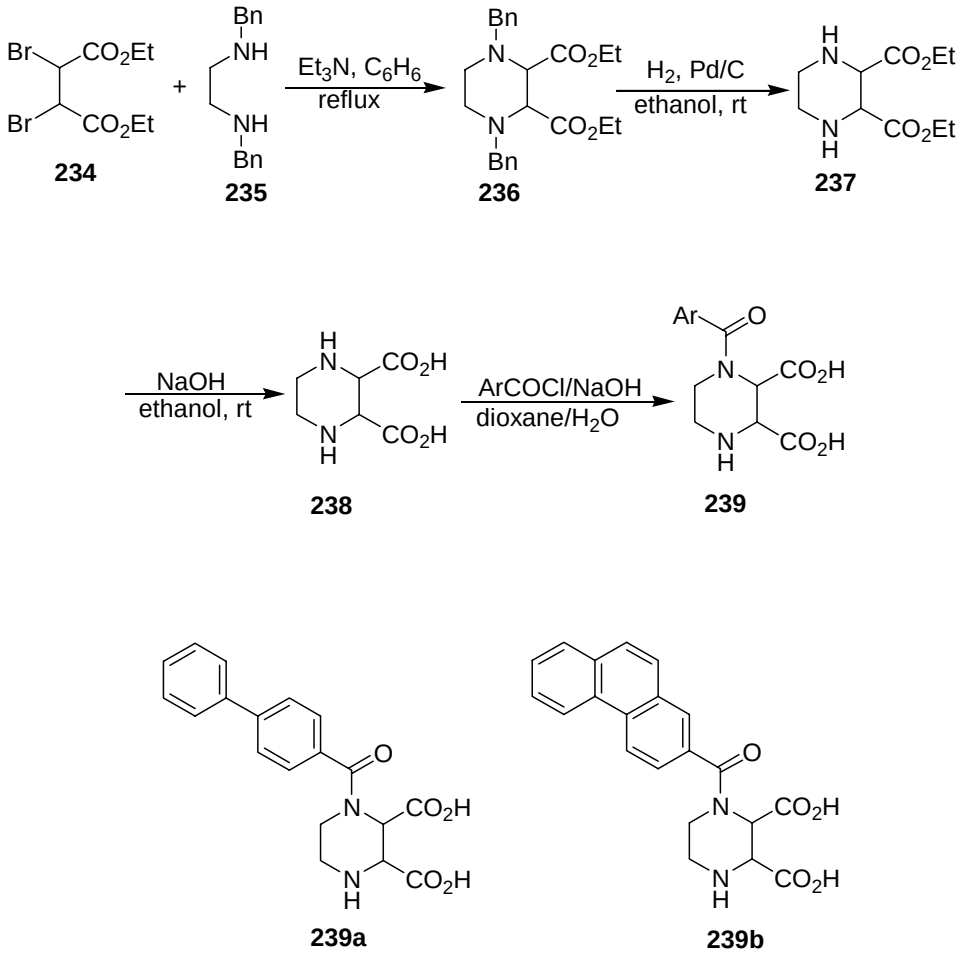


Figure 5.

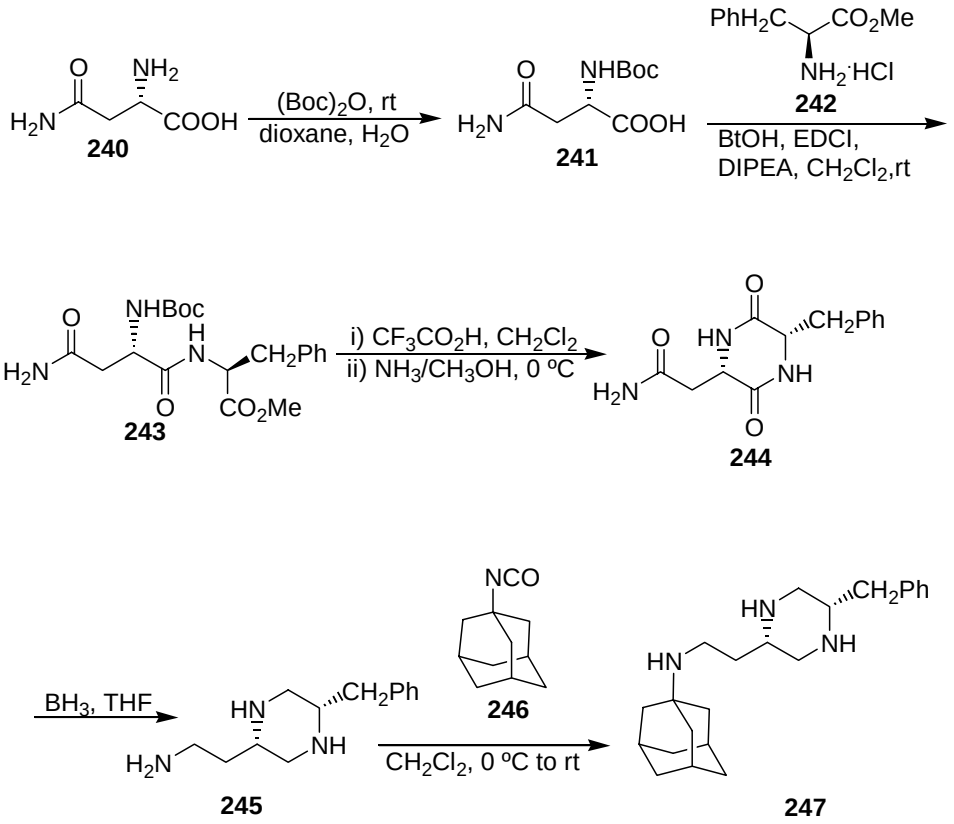
Jane *et al*[88] synthesized *N*-substituted piperazine-2,3-dicarboxylic acid derivatives (Scheme **23**). These derivatives are found to be active NMDA antagonists. The compound **239a** displays an unusual selectivity with improved relative affinity for NR2C and NR2D vs NR2A and NR2B. A phenanthrenyl-2-carbonyl analogue, **233b**, had >60-fold higher affinity for NR2C and NR2D and showed 3-5 fold selectivity for NR2C/NR2D vs NR2A/NR2B.

Scheme 23.



Long *et al*[89] designed and synthesized a new class of potent inhibitors of soluble epoxide hydrolase (sEH) by the introduction of a polar constrained piperazino group to the right side of adamantyl urea to increase the water solubility (Scheme **24**). A series of 1-adamantan-1-yl-3-(2-piperazin-2-yl-ethyl)-ureas with various 5-substitutions on the 2-piperazino ring was synthesized. The effect of the 5-substitution on the activity and the water solubility was examined. In these molecules, the 5-substituted piperazine skeleton serves as a favourable secondary pharmacophore and a water-solubility enhancing group.

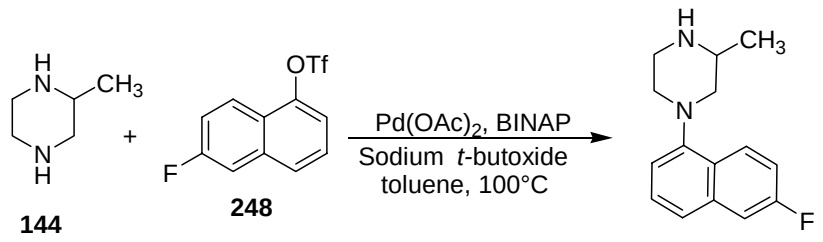
Scheme 24.



240 **241** **242** **243** **244** **245** **246** **247**

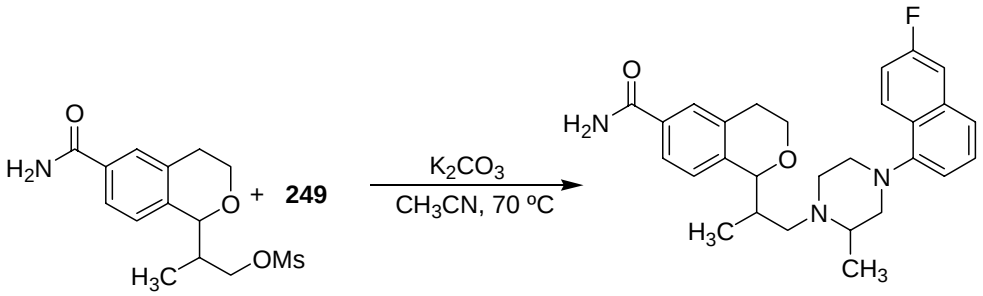
In a recent study by Bueno *et al*,[90] 1-naphthyl- and 2-naphthyl-piperazines have been shown to be good 5-HT1D/SRI pharmacophores, with the presence of a 3-methyl group in the piperazines improving the affinity for the transporter. The isomer with *S* configuration at the isochroman center shows a better profile (Scheme **25**).

Scheme 25.



144 **248** **249**

Scheme 25. (continued)



250 **251**

In this section, various applications of chiral diamines, their derivatives and their metal complexes have been outlined. The chemical and biological importance of chiral piperazines and their derivatives have been also described. Though chiral 2,5-disubstituted piperazines have been used as base, additives and also as organocatalysts in different organic transformations, the application of chiral 2,3-disubstituted piperazines are limited as they are not easily accessible. Hence, we have decided to develop simple, convenient methods for the synthesis of chiral 2,3-disubstituted piperazines for examining their applications.

2. Results and Discussion

In the introductory part, applications of chiral 1,2-diamine derivatives in organic transformations were discussed. However, a simple and easy access to chiral 2,3-disubstituted piperazines is yet to be developed. There has been sustained interest in this laboratory in the development of various organic transformations using the $TiCl_4$/amine reagent system (Chart **13**).

Chart 13.

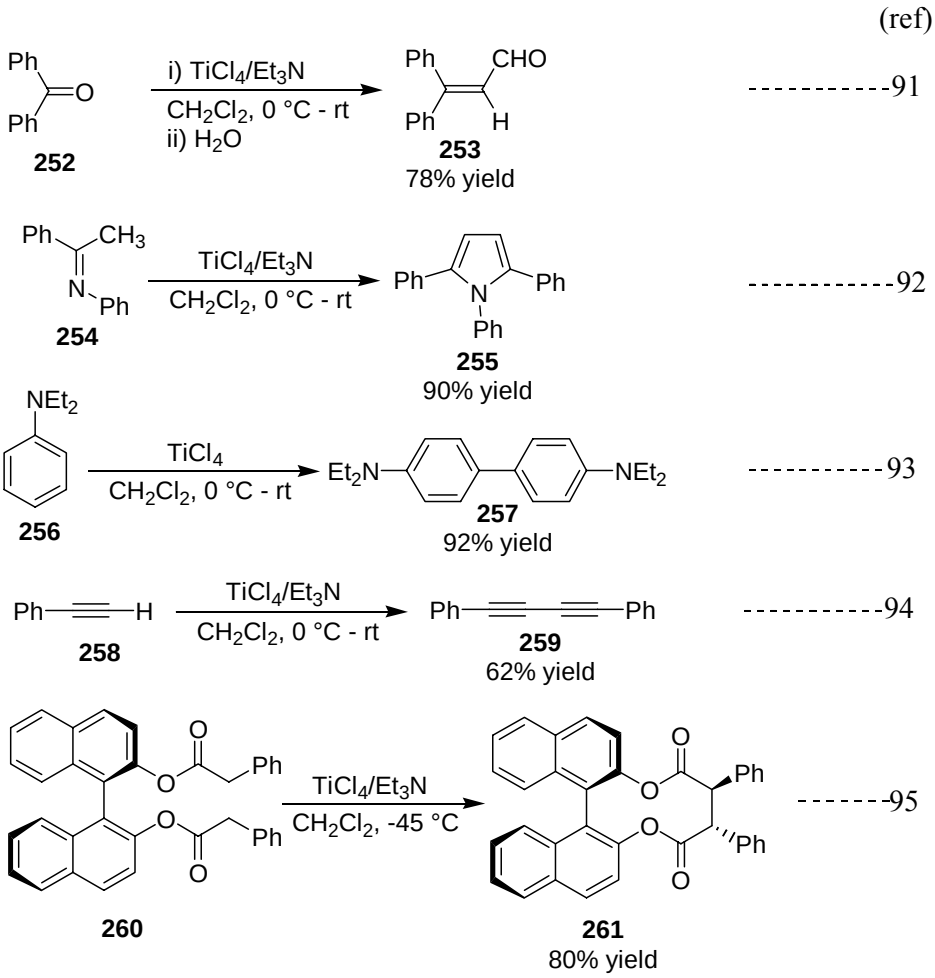
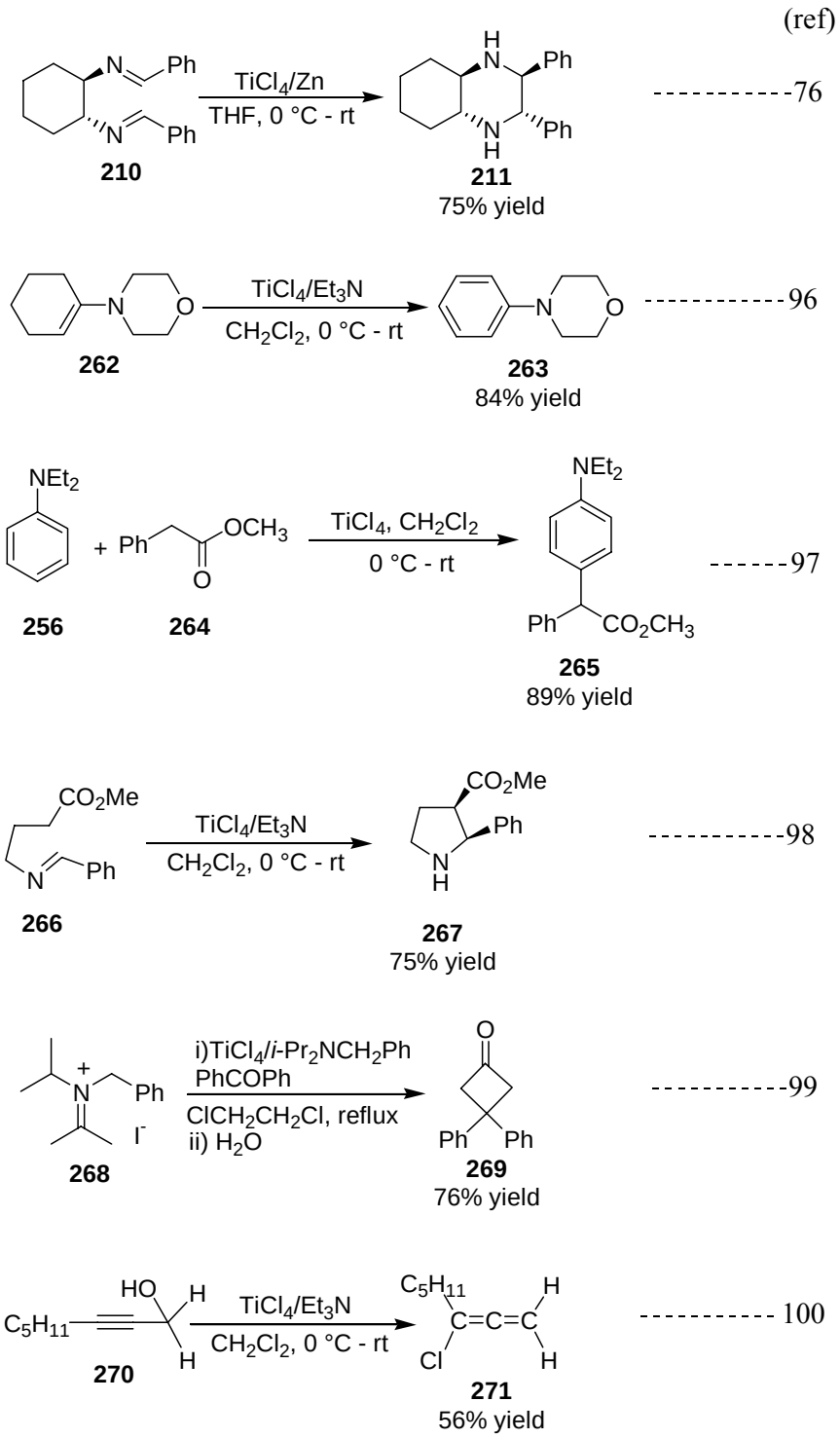


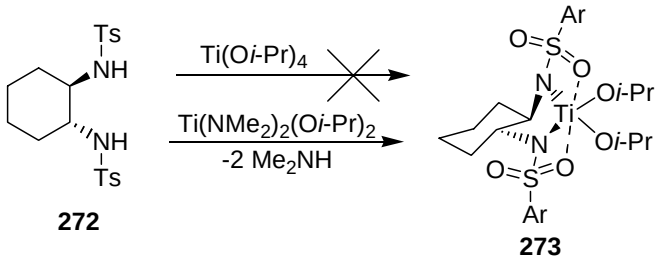
Chart 13. (continued)



2.1 Attempts toward enantioselective Kulinkovich reaction

In continuation of these studies, we have carried out an exploratory research work on the synthetic applications of (1*R*,2*R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane **272** and titanium reagents. Application of this ligand in the addition of diethylzinc to aldehydes is well studied.[101] In the titanium complexes of these ligands, the coordination of the titanium-sulfonyl oxygens maintains a rigid C_2-symmetric environment that may be an important factor in the transfer of chirality (Scheme **26**). We have initially examined the synthetic application of this catalyst system in the Kulinkovich cyclopropanol synthesis.

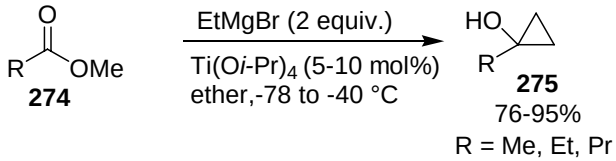
Scheme 26.



272 **273**

We were interested to examine the synthetic application of the ligand **(**1*R*,2*R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane **272** in Kulinkovich reaction. In 1989, Kulinkovich *et al*[102] reported the formation of cyclopropanol in the reaction of esters with a mixture of 1 equivalent of titanium(IV) isopropoxide and an excess of ethylmagnesium bromide at –78 to –40 ^{o}C (Scheme **27**).

Scheme 27.



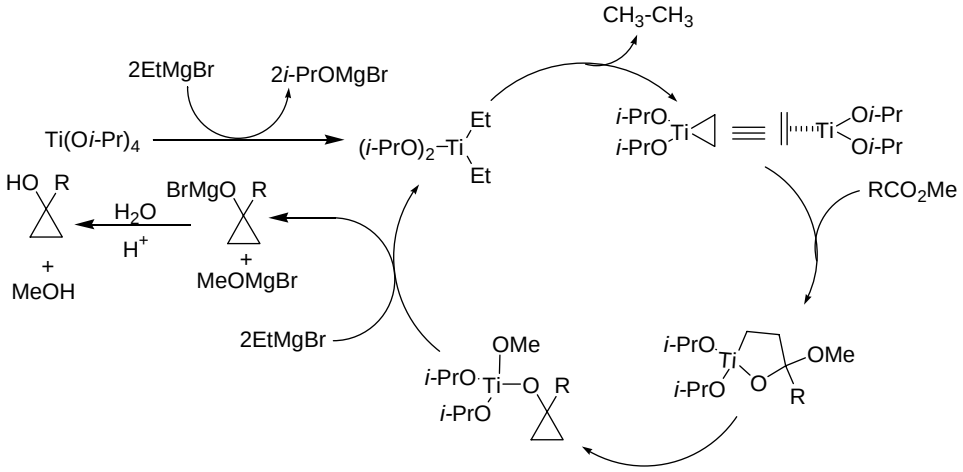
274 **275**

76-95%

R = Me, Et, Pr

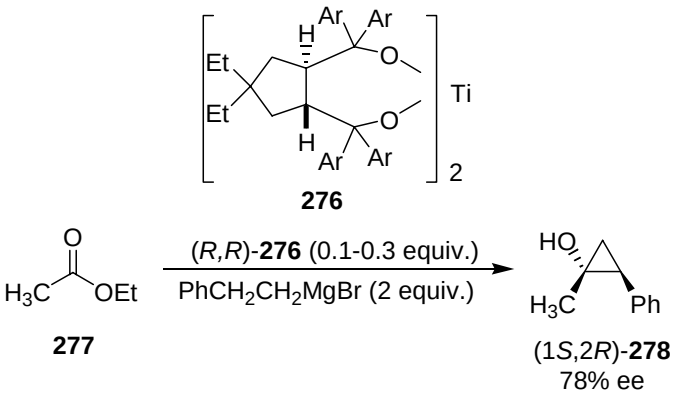
The reaction proceeds through the titanocyclopropane intermediate as in the mechanism given in the Scheme **28**. Using this reaction, 1,2-disubstituted cyclopropanols can be prepared by the reaction of esters with 2-substituted ethylmagnesium bromide. The products are formed with high diastereoselectivity even without any chelating substituents in the substrate. The two substituents on the 1,2-disubstituted cyclopropanol are *cis* to each other.[103]

Scheme 28.



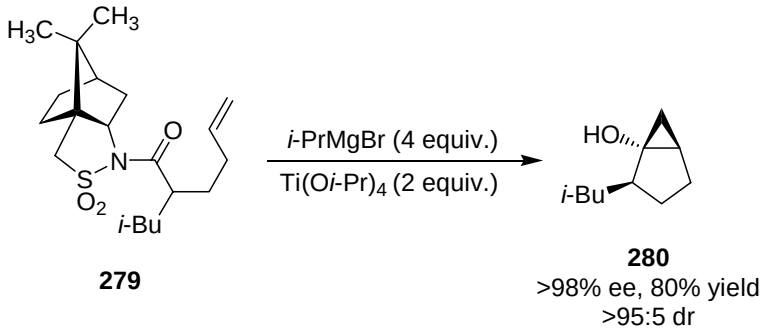
Only a very few reports appeared on the asymmetric version of this interesting reaction. Corey *et al*[104] reported an enantioselective (70-78% ee) synthesis of *cis*-1,2-disubstituted cyclopropanol using a TADDOL derived titanocyclopropane (Scheme **29**).

Scheme 29.



Sato *et al*[105a] obtained more than 98% ee's in the enantioselective synthesis of bicycliccyclopropanol from *N*-acylcamphorsultam derivatives (Scheme **30**).

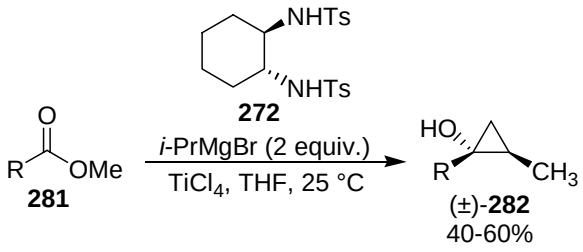
Scheme 30.



279 **280**
>98% ee, 80% yield
>95:5 dr

In our initial studies, we have decided to examine the synthetic application of the ligand **272** in the enantioselective cyclopropanation reactions. It has been reported[101d] that the **(**1*R*,2*R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane **272** does not complex with titanium(IV) isopropoxide. For this reason, we have used the chiral titanium complex derived from titanium(IV) chloride and bis-sulfonamide ligand **272** in the Kulinkovich reaction (scheme **31**).

Scheme 31.

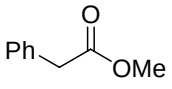
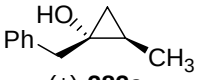
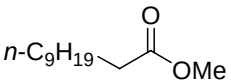
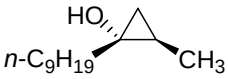
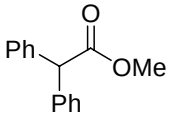
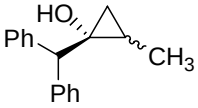
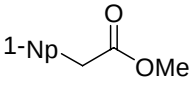
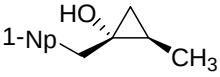


(±)-**282**
40-60%

The chiral titanium complex was prepared *in situ* by taking the ligand **272** (20 mol%) and isopropylmagnesium bromide (60 mol%) in THF followed by the addition of $TiCl_4$ (20 mol%). To the preformed titanium complex, magnesium turnings (2.0 equiv.), 2-bromopropane (2.2 equiv.) and ester (1.0 equiv.) were added and stirred for 1

hour at 25 °C. The corresponding *cis*-cyclopropanols **282** were isolated in 40-60% yields (Table 1).

Table 1. Kulinkovich reaction of *i*-PrMgBr with carboxylic esters mediated by chiral titanium complexes[a]

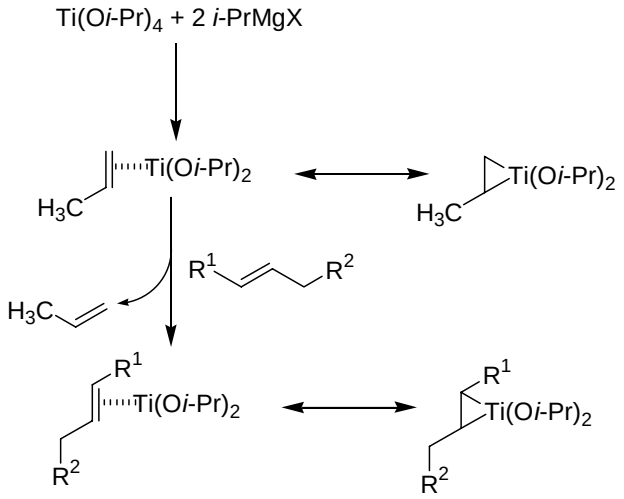
entry	ester	cyclopropanol[b]	yield (%)[c]
1		 (±)-**282a**	60
2		 (±)-**282b**	38
3		 (±)-**282c** *cis/trans*	60[d]
4		 (±)-**282d**	40

[a]All the reactions were carried out with sulfonamide ligand **272** (0.5 mmol), *i*-PrMgBr (1.5 mmol), $TiCl_4$ (0.5 mmol) and THF for 20 min, then *i*-PrMgBr (5.0 mmol) and ester (2.5 mmol). [b]The products were identified by IR, ^1H, ^{13}C-NMR and DEPT experiments. [c]The yields are based on the esters used. [d]*Cis*/*trans* mixture obtained in the ratio 0.6:0.4 (^1H NMR).

Though the cyclopropanols were obtained in the yields up to 60%, enantioselectivity was not observed in these reactions using the bis-sulfonamide ligand **272.**

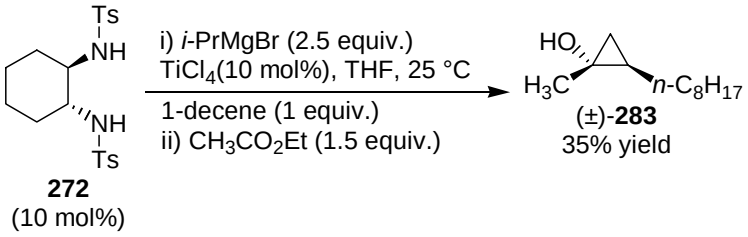
The titanocyclopropane intermediate formed in the Kulinkovich reaction is the π-complex of olefin and the titanium(II) (Scheme **28**). The olefin of the titanocyclopropane can be exchanged by some other external olefin. Sato *et al*[105] and Cha *et al*[106] have independently developed an intramolecular hydroxycyclopropanation. In these reactions, the coordinated alkene in the titanocyclopropane intermediate was replaced by external olefins (Scheme **32**).

Scheme 32.



We have examined the olefin exchange reaction by using 1-decene in the reaction of isopropylmagnesium bromide and chiral bis-sulfonamide/titanium(IV) chloride complex (Scheme **33**).

Scheme 33.

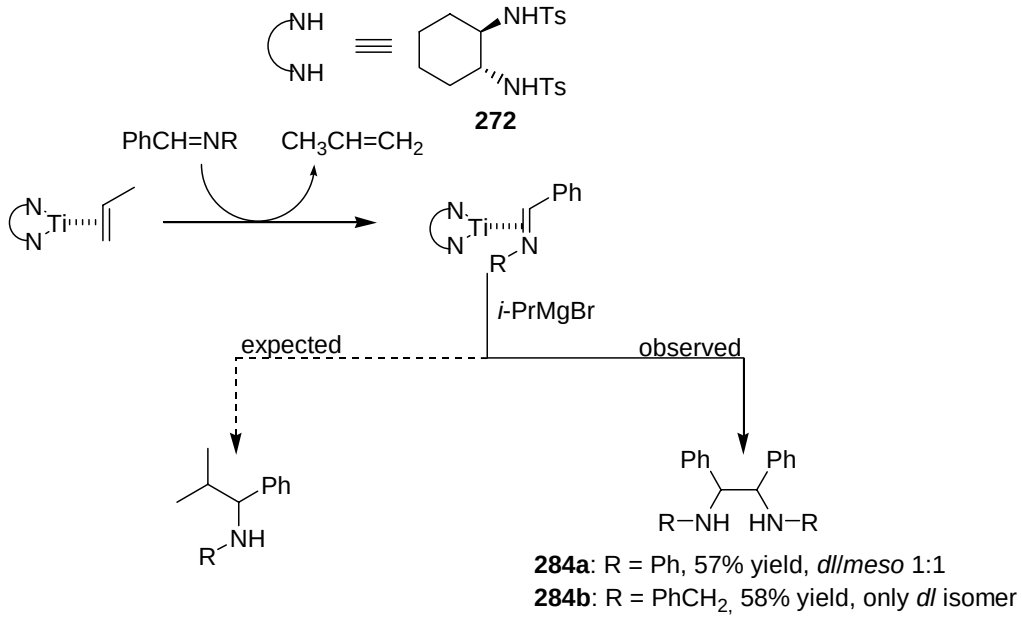


In this reaction, 1-methyl-2-octylcyclopropanol **283** was obtained in 35% yield. Since the enantioselectivities obtained in these reactions were negligible, we have not pursued these studies further.

Clearly, the alkene in the titanocyclopropane intermediate (Scheme **28**) can be exchanged by 1-decene and the corresponding cyclopropanol was obtained (Scheme **33**). It was of interest to study the exchange of simple alkene in the titanocyclopropane

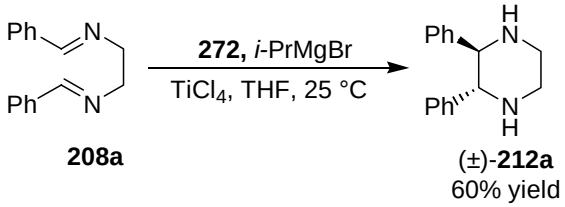
intermediate by imines so as to explore the possibility of the enantioselective alkylation of imines (Scheme **34**).

Scheme 34.



However, in this reaction only the reductively coupled 1,2-diamines **284** were obtained (Scheme **34**). Also, intramolecular reductive coupled product was obtained when the diimine **208a** was used in this reaction (Scheme **35**). Interestingly, only the *trans*-(±)-2,3-diphenylpiperazine **212a** was obtained.

Scheme 35.

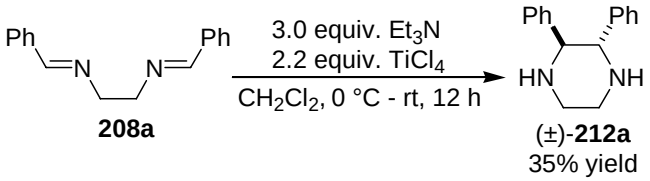


As discussed in the introduction, the molecules having piperazine moieties are biologically as well as synthetically important. Therefore, we have turned our attention towards developing methods for the synthesis of chiral 2,3-diarylpiperazines and exploring their applications in various organic transformations

2.2 Synthesis of 2,3-diarylpiperazines using $TiCl_4$/Zn reagent

The $TiCl_4/Et_3N$ and $TiCl_4$/Zn reagent systems have been used in the reductive coupling of aldehydes[29] and imines.[76] We have used these reagent systems in the intramolecular reductive coupling of diimines **208** derived from ethylenediamine. The reaction was not clean and yields were lower using the $TiCl_3$ formed in the reaction of the $TiCl_4$ with Et_3N,[76,100] since the imine was cleaved to some extent into aldehyde under the reaction conditions (Scheme **36**).

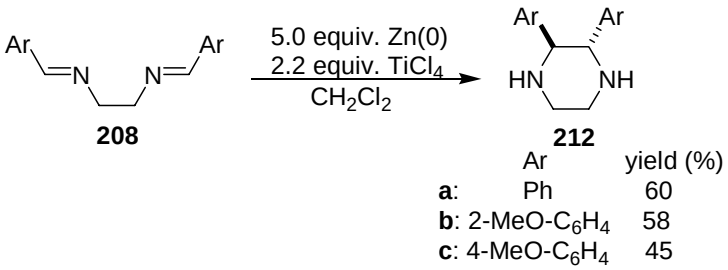
Scheme 36.



208a (±)-**212a** 35% yield

Then, we have studied the Lewis acid/Zn catalyzed synthesis of (±)-*trans*-2,3-disubstituted piperazines. In our initial studies, we have observed that diastereomerically pure (±)-2,3-diarylpiperazines **212** can be readily prepared in 45-60% yield by the intramolecular reductive coupling of diimines in the presence of $TiCl_4$/Zn (Scheme **37,** Table **2**).

Scheme 37.



2.3 Synthesis of 2,3-diarylpiperazines using $TiCl_2(O$*i*$-Pr)_2$/Zn reagent

The (±)-2,3-diarylpiperazines **212** were obtained in the yields up to 60% in the reductive coupling promoted by the $TiCl_4$/Zn reagent system. The lower yields may be due to the strong Lewis acidity of the $TiCl_4$ causing the cleavage of the imine. The Lewis acidity of $TiCl_4$ can be reduced by exchanging two chloro ligands with isopropoxy ligands for use in the reductive coupling of diimines. As anticipated, the $Ti(O$*i*$-Pr)_2Cl_2$/Zn system gave better yields up to 83% (Scheme **38,** Table **2**). Optimum yields were obtained by using five molar equivalent of zinc powder. The yields were lower when two molar equivalent of zinc powder was used.

Scheme 38.

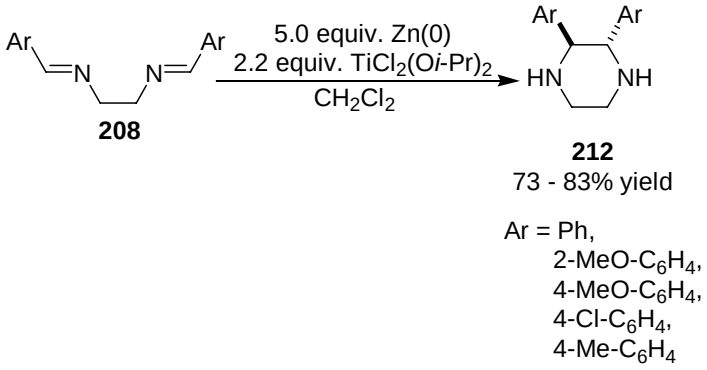


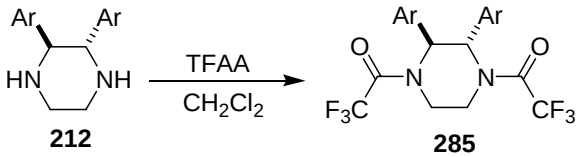
Table 2. Intramolecular reductive coupling of diimines with $Zn/TiCl_2X_2$

entry	Ar	X	product[a]	yield (%)[b]	de[c] (%)
1	Ar = phenyl	O*i*-Pr	**212a**	83	>99
2	Ar = phenyl	Cl	**212a**	60	>99
3	Ar = 2-methoxyphenyl	O*i*-Pr	**212b**	73	>99
4	Ar = 2-methoxyphenyl	Cl	**212b**	58	>99
5	Ar = 4-methoxyphenyl	O*i*-Pr	**212c**	75	>99
6	Ar = 4-methoxyphenyl	Cl	**212c**	45	>99
7	Ar = 4-chlorophenyl	O*i*-Pr	**212d**	80	>99
8	Ar = 4-methylphenyl	O*i*-Pr	**212e**	76	>99

[a]The products were identified using physical constant and spectroscopic data (IR, ^1H, ^{13}C-NMR and mass spectral data) and comparison with reported data.[69,78] [b]Yields are of the isolated products. [c]The de values are based on HPLC analysis and ^{13}C NMR spectra.

The *dl*:*meso* ratio was determined to be >99% from ^{13}C NMR spectra of the corresponding piperazines and also by HPLC analysis of the trifluoroacetamide derivatives **285** (Scheme **39**). The stereochemistry of the product was confirmed to be *trans* by single crystal X-ray analysis of the trifluoroacetamide derivative **285a** (Figure **6**, Table **3**). The ORTEP diagram of the trifluoroacetamide derivative **285a** is shown in Figure **6**.

Scheme 39.



212 **285**

a: Ar = Ph,
b: Ar = 2-MeO-C_6H_4,
c: Ar = 4-MeO-C_6H_4,
d: Ar = 4-Me-C_6H_4

Table 3. Crystal data and structure refinement for compound 285a	
Identification code	**285a**
Empirical formula	$C_{20}H_{16}F_6N_2O_2$
Formula weight	430.35
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P2(1)/c
Unit cell dimensions	a = 22.3786(10) Å, b = 16.5405(7) Å, β = 103.3050(10)° c = 11.1443(5) Å,
Volume	4014.4(3) $Å^3$
Z, Calculated density	8, 1.424 Mg M^{-3}
Absorption coefficient	0.130 mm^{-1}
F(000)	1760
Crystal size	0.40 x 0.38 x 0.23 mm
Theta range for data collection	1.55 to 28.29 °
Limiting indices	-29≤h≤29, -22≤k≤21, -14≤l≤14
Reflections collected / unique	45980 / 9632 [R(int) = 0.0378]
Completeness 2θ = 28.29	96.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9632 / 0 / 541
Goodness-of-fit on F^2	1.020
Final R indices [I>2σ (I)]	R1 = 0.0799, wR2 = 0.2291
R indices (all data)	R1 = 0.1580, wR2 = 0.2847
Largest diff. peak and hole	0.422 and -0.236 e. $Å^{-3}$

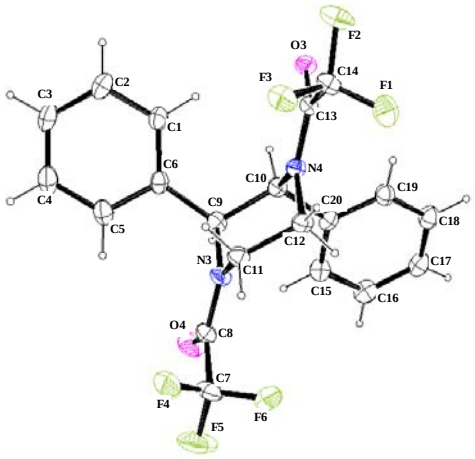
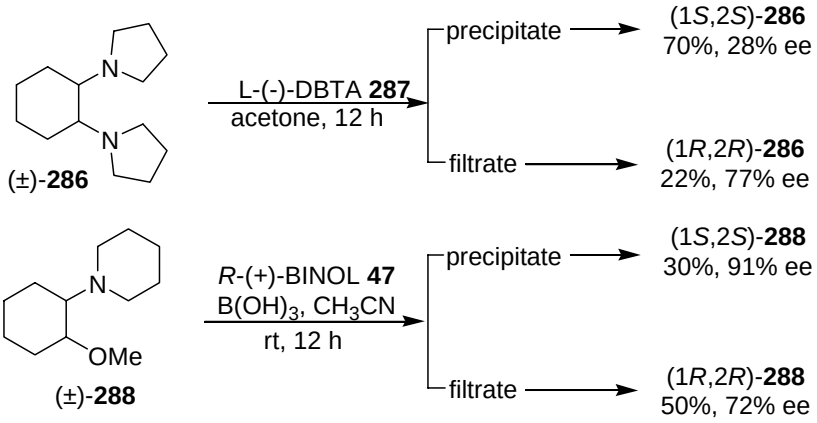


Figure 6. ORTEP diagram of the racemic **285a** (one enantiomer is shown; thermal ellipsoids are drawn at 20% probability).

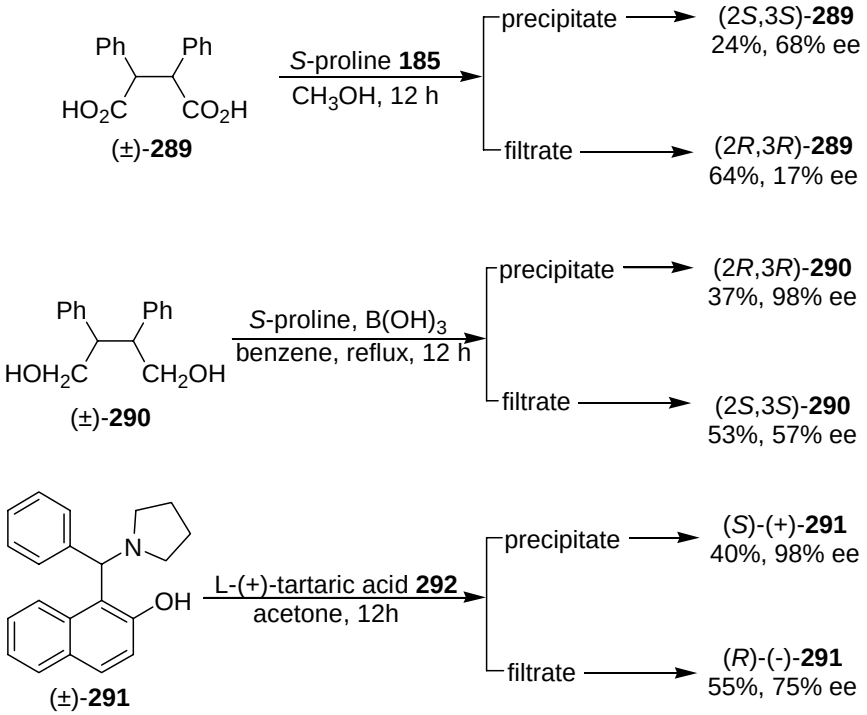
2.4 Resolution of (±)-2,3-diphenylpiperazine

New procedures of resolution of variety of diamines,[107] amino alcohols[108] (Scheme **40**), diols,[109] diacids[110] (Scheme **41**) and BINOL[111] (Scheme **42**, **43**) have been developed in this laboratory using a range of commercially available and less expensive chiral resolving agents such as L-(+)-tartaric acid, *O*,*O*-dibenzoyltartaric acid, BINOL/boric acid, L-proline and chiral amine/boric acid etc.

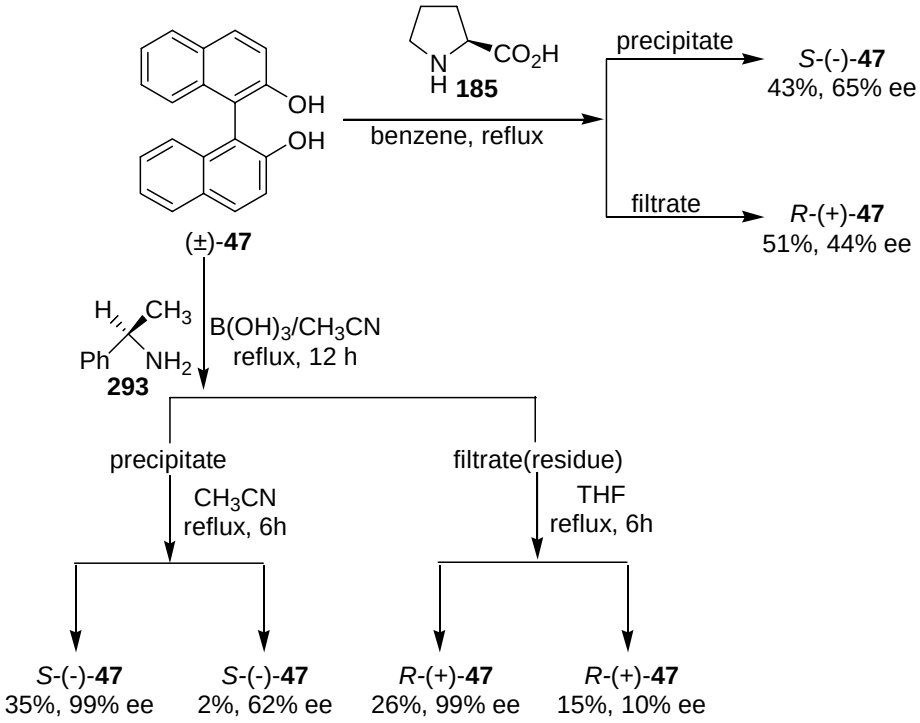
Scheme 40.



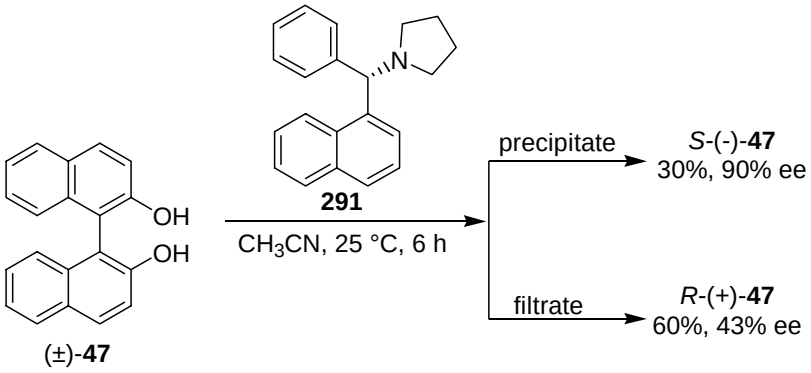
Scheme 41.



Scheme 42.



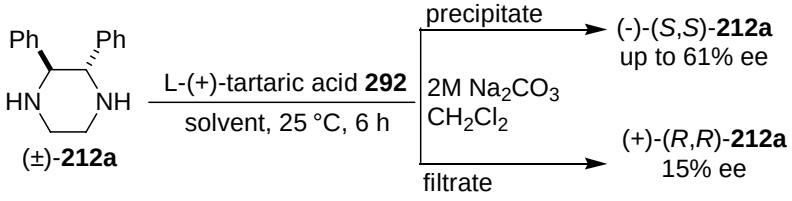
Scheme 43.



2.4.1 Resolution of (±)-2,3-diphenylpiperazine using L-(+)-tartaric acid

The resolution of the (±)-2,3-diphenylpiperazine **212a** was examined using the commercially available L-(+)-tartaric acid. We have carried out the resolution of (±)-2,3-diphenylpiperazine **212a** in various solvents using L-(+)-tartaric acid (Scheme **44**, Table **4**). We have also examined the effect of the amount of THF (Table **4**) and the amount of chiral resolving agent on the resolution process. When (±)-2,3-diphenylpiperazine **212a** and L-(+)-tartaric acid were used in 1:1 ratio, precipitation occurred, but no resolution was observed. Reasonable results were realized using the components in 1:0.5 ratio (Table **4**, entries **1,2 and 4-8**). Use of tartaric acid in 0.25 mole ratio, gave samples with only 20% ee in the precipitate fraction and samples of 12% ee in the filtrate fraction (Table **4**, entry **3**). Results were better when 50 mL THF was used per one mmol of amine (Table **4**, entry **5**). There was no appreciable change in ee, when acetone was used as solvent (Table **4**, entry **6**).

Scheme 44.



In CH_2Cl_2 solvent, sample with 61% ee was obtained from precipitate fraction by using the (±)-2,3-diphenylpiperazine **212a** and L-(+)-tartaric acid in 1:1 ratio (Table **4**, entry **8**). The partially resolved sample (61% ee) could be readily purified to obtain samples of >99% ee by repeating the operation (Scheme **45**). The configuration of the enantiomer (-)-**212a** was assigned (*S,S*) by single crystal X-ray analysis of the corresponding tartrate salt **294**. The ORTEP diagram of the tartrate salt **294** is shown in Figure **7**.

Scheme 45.

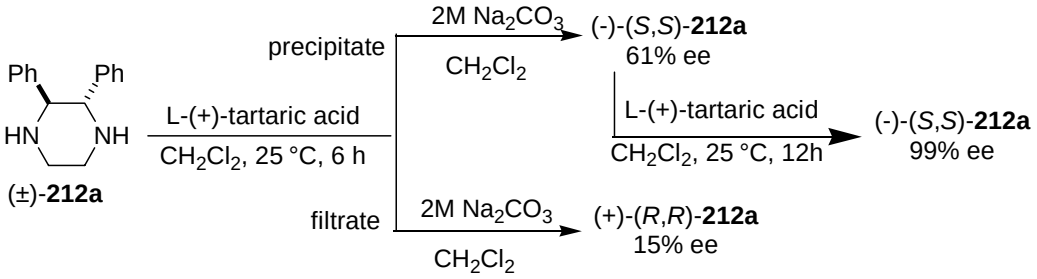


Table 4. Resolution of (±)-2,3-diphenylpiperazine **212a** using L-(+)-tartaric acid[a]

entry	solvent (mL)	piperazine **212a** obtained from			
		precipitate fraction		filtrate fraction	
		% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	THF (50)	16 (*S,S*)	56	8 (*R,R*)	39
2	THF (100)	20 (*S,S*)	62	25 (*R,R*)	38
3[d]	THF (100)	20 (*S,S*)	38	12 (*R,R*)	52
4	THF (250)	31 (*S,S*)	38	16 (*R,R*)	54
5	THF (500)	48 (*S,S*)	42	22 (*R,R*)	57
6	acetone (50)	15 (*S,S*)	43	12 (*R,R*)	51
7	CH_2Cl_2 (200)	45 (*S,S*)	32	27 (*R,R*)	67
8	CH_2Cl_2(250)	61 (*S,S*)	33	15 (*R,R*)	63

[a]All experiments were carried out using 10.0 mmmol of (±)-2,3-diphenylpiperazine **212a** and 5.0 mmol of L-(+)-tartaric acid **292**, [b]All ee values reported here are based on HPLC analysis and the maximum $[\alpha]_D^{25}$ = -104.6 (*c* 1.0, $CHCl_3$) for (*S,S*)-**212a**, [c]The yields are of the isolated products, based on the total amount of the piperazine **212a** used. [d]2.5 mmol of L-(+)-tartaric acid was used.

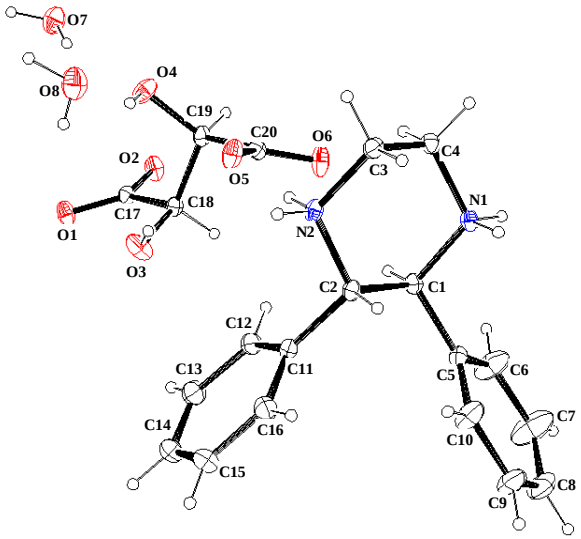


Figure 7. ORTEP diagram of the tartrate salt **294** (thermal ellipsoids are drawn at 20% probability)

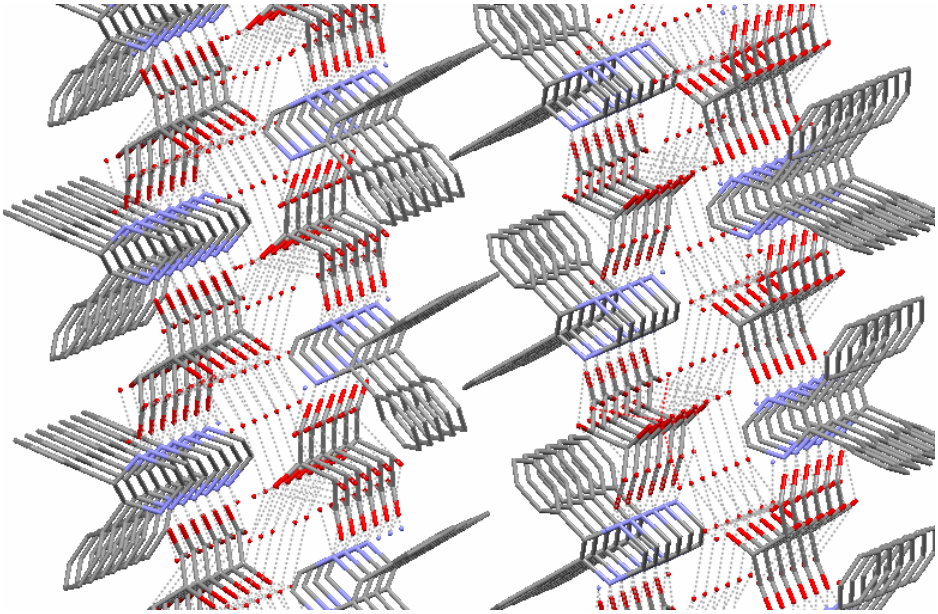
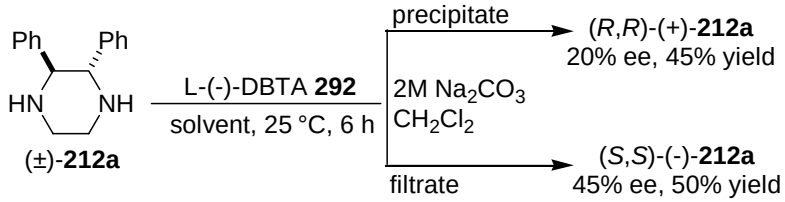


Figure 8. Packing diagram of the tartarate salt **294**. (The hydrogen bondings are denoted in dotted lines)

Table 5. Crystal data and structure refinement for compound 294	
Identification code	**294**
Empirical formula	$C_{20}H_{28}N_2O_8$
Formula weight	424.44
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2
Unit cell dimensions	a = 9.2088(10) Å, b = 35.387(4) Å, c = 6.2519(7) Å,
Volume	2037.3(4) $Å^3$
Z, Calculated density	8, 1.424 Mg M^{-3}
Absorption coefficient	0.107mm^{-1}
F(000)	904
Crystal size	0.42 x 0.26 x 0.20 mm
Theta range for data collection	2.29 to 28.24 °
Limiting indices	$-12\leq h\leq 12$, $-46\leq k\leq 46$, $-8\leq l\leq 8$
Reflections collected / unique	23736 / 4860 [R(int) = 0.0451]
Completeness 2θ = 28.24	97.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4860 / 0 / 289
Goodness-of-fit on F^2	1.069
Final R indices [I>2σ (I)]	R1 = 0.0483, wR2 = 0.1071
R indices (all data)	R1 = 0.0562, wR2 = 0.1108
Absolute structure parameter	0.0(9)
Largest diff. peak and hole	0. 242 and -0.204 e. $Å^{-3}$

By using dibenzoyl-L-(-)-tartaric acid **287** for the resolution of (±)-2,3-diphenylpiperazine **212a** in the solvent THF, (*R,R*)-**212a** was obtained in the precipitate fraction in yield up to 45% with 20% ee (Scheme **46**). The filtrate fraction gave the (*S,S*) isomer in 50% yield with an enantiomeric excess of 45%.

Scheme 46.



2.4.2 Resolution of (±)-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid

In the resolution of (±)-2,3-diphenylpiperazine **212a** using L-(+)-tartaric acid, enantiomerically pure (*S,S*)-2,3-diphenylpiperazine was obtained in two successive operations from racemic piperazine using L-(+)-tartaric acid. It was of our interest to design a single step resolution process to get the enantiomerically pure compound. In this context, we have examined the resolution of (±)-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid **295**. Enantiomerically pure 2,3-diphenylpiperazine was obtained with 98% ee in a single step resolution using this acid (Scheme **47,** Table **6,** entry **4**).

In our initial studies, the effect of the quantity of solvent and chiral resolving agent was examined (Table **6**). When the resolution was carried out in THF solvent using 2.25 mmol of (1*S*)-(+)-10-camphorsulfonic acid (for 1.5 mmol of (±)-2,3-diphenylpiperazine), up to 58% ee was obtained from filtrate fraction (Table **6,** entry **1**).

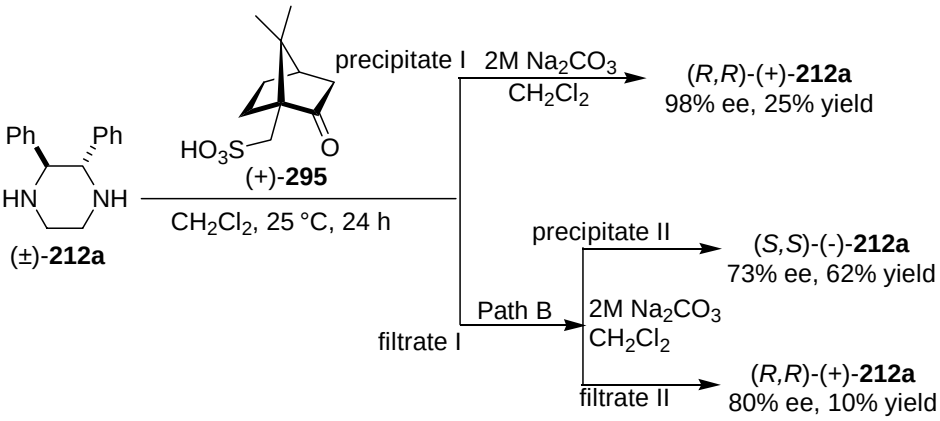
By using 3.0 mmol of (1*S*)-(+)-10-camphorsulfonic acid, the enantiopurity was increased up to 80% ee, but the yield in the filtrate fraction was reduced to 20% (Table **6,** entry **2**). When CH_2Cl_2 was used as solvent, a sample with 90% ee was obtained from precipitate fraction and a sample of 60 % ee was obtained from filtrate fraction (Table **6,** entry **3**).

Table 6. Resolution of (±)-2,3-diphenylpiperazine **212a** using (1*S*)-(+)-10-camphorsulfonic acid[a]

entry	piperazine **212a** (mmol)	CSA **(+)-295** (mmol)	piperazine **212a** obtained from			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1[d]	1.5	2.25	50(*R,R*)	42	58(*S,S*)	52
2[d]	1.5	3.0	3(*R,R*)	75	80(*S,S*)	20
3[e]	1.5	3.0	90(*R,R*)	32	60(*S,S*)	59
4[e,f]	**10.0**	**20.0**	**98(*R,R*)**	**25**	**73(*S,S*)**	**62**

[a]All the reactions were carried out using racemic piperazine **212a** and CSA **(+)-295** in solvent (10 mL per mmol of piperazine) for 12 hours. [b]All ee values reported here are based on HPLC analysis. [c]The yields are of the isolated products, based on the total amount of the piperazine **212a** used. [d]THF was used as solvent. [e]CH_2Cl_2 was used as solvent. [f]The resolution was done as in Scheme **47**.

Scheme 47.



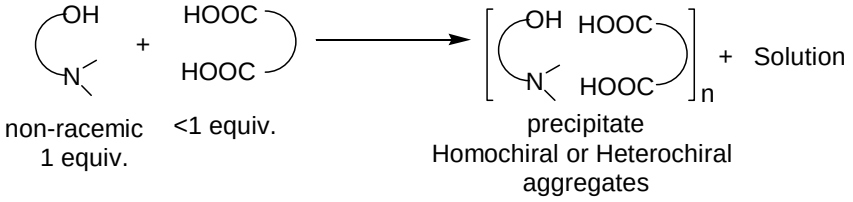
Path B: the volume of the solvent was reduced to half and then stirred at 25 °C, 12 h

When the resolution was carried out in 10 mmol scale in CH_2Cl_2 solvent, a sample with 98% ee was obtained from precipitate fraction. In this process, 10 mmol of (±)-2,3-diphenylpiperazine and 20 mmol of (1*S*)-(+)-10-camphorsulfonic acid were taken in CH_2Cl_2 (100 mL) and stirred for 24 hours. (*R,R*)-(+)-2,3-Diphenylpiperazine with 98% ee was obtained from precipitate fraction I (Table **6,** entry **4**). The filtrate was reduced to approximately 50 mL in volume, stirred for another 12 hours. The precipitate was separated. From the precipitate fraction II, (*S,S*)-(-)-2,3-diphenylpiperazine with 73% ee was obtained in 62% yield. The (*R,R*)-(+)-2,3-diphenylpiperazine with 80% ee was obtained from filtrate fraction in 10% yield.

2.5 Enrichment of enantiomeric purity of non-racemic-2,3-diphenylpiperazine using achiral acids

A method of achieving homogeneity of chirality via purification of non-racemic materials of lower enantiomeric purities has good synthetic potential, in addition to serving as a model for the evolution of homochirality in nature under prebiotic conditions.[112] Accordingly, a novel method of achieving homogeneity of chirality by purification of partially resolved amino alcohols and a C_2-symmetric chiral diamine via preparation of the corresponding hydrogen bonded homochiral or heterochiral aggregates was reported from this laboratory (Scheme **48**).[113] It was described that this method may serve as a model for developing a new way of purification of non-racemic samples.

Scheme 48.



We have followed this methodology to enhance the optical purity of the partially resolved piperazine **212a** using oxalic acid. Enantiomerically enriched samples with 99% ee can be readily obtained following this method (Scheme **49**, Table **7**).

Scheme 49.

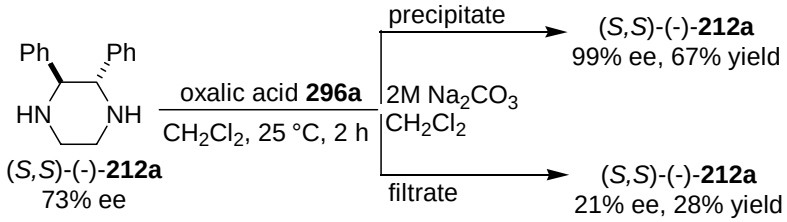


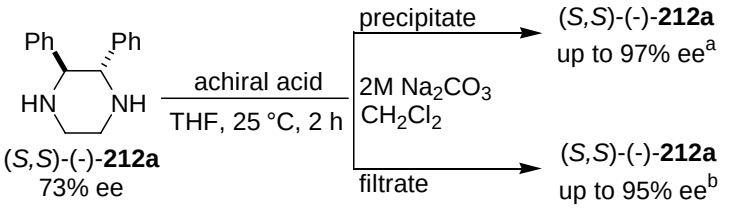
Table 7. Purification of non-racemic 2,3-diphenylpiperazine **212a** using oxalic acid[a]

entry	substrate % ee[b]/(mmol) conf	oxalic acid (mmol)	piperazine **212a** obtained from precipitate fraction		piperazine **212a** obtained from filtrate fraction	
			% ee[b]/ conf	yield[c] (%)	% ee[b]/ conf	yield[c] (%)
1	39 (2.00) (*S*,*S*)	0.60	71 (*S*,*S*)	30	22 (*S*,*S*)	65
2	45 (2.00) (*S*,*S*)	0.75	73 (*S*,*S*)	51	18 (*S*,*S*)	37
3	73 (2.00) (*S*,*S*)	1.30	99 (*S*,*S*)	62	21 (*S*,*S*)	33
4	53 (2.00) (*S*,*S*)	1.00	84 (*S*,*S*)	21	28 (*S*,*S*)	77
5	84 (0.75) (*S*,*S*)	0.55	99 (*S*,*S*)	67	20 (*S*,*S*)	28
6	48 (2.00) (*R*,*R*)	0.80	77 (*R*,*R*)	36	19 (*R*,*R*)	60

[a] All the reactions were carried out using non-racemic piperazine **212a** and oxalic acid in THF(10mL per mmol). [b]All ee values reported here are based on HPLC analysis and the maximum $[\alpha]_D^{25}$ = -104.6 (*c* 1.0, $CHCl_3$) for (*S*,*S*)-**212a**. [c]The yields are of the isolated products, based on the total amount of the starting non-racemic mixture used.

The concept of preparation of homochiral/heterochiral aggregates for the purification of non-racemic samples was further applied using different achiral dicarboxylic acids for the enrichment of partially resolved non-racemic 2,3-diphenylpiperazine (Scheme **50,** Table **8**). Among the achiral acids used, oxalic acid and malonic acid gave enantiomerically enriched products in the precipitate fraction; in accordance with the predominant formation of homochiral salt aggregates in the precipitate fraction (Table **8**, entries **1**,**2**). By using other dicarboxylic acids like fumaric acid, succinic acid, adipic acid, phthalic acid, isophthalic acid and terephthalic acid, enantiomerically enriched product was obtained in the filtrate fraction. In these cases, presumably, heterochiral aggregates are formed predominantly in the precipitate fraction, leaving the enantiomerically enriched product in the filtrate fraction (Table **8**, entries **3**-**8**).

Scheme 50.



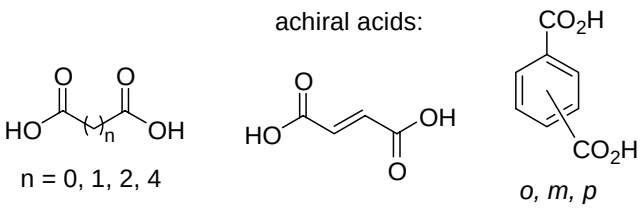


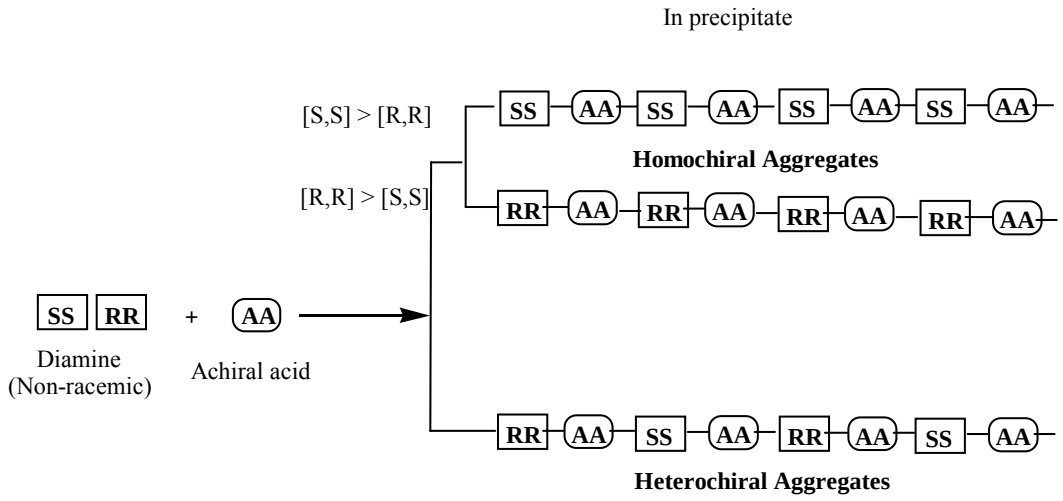
Table 8. Purification of non-racemic 2,3-diphenylpiperazine (*S*,S)-**212a** using achiral acids[a]

entry	achiral acid	piperazine **212a** obtained from			
		precipitate fraction		filtrate fraction	
		% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	oxalic acid	97(*S,S*)	62	21(*S,S*)	31
2	malonic acid	94(*S,S*)	65	35(*S,S*)	33
3	succinic acid	58(*S,S*)	50	95(*S,S*)	35
4	adipic acid	46(*S,S*)	51	90(*S,S*)	42
5	fumaric acid	48(*S,S*)	58	94(*S,S*)	34
6	phthalic acid	61(*S,S*)	60	82(*S,S*)	35
7	isophthalic acid	57(*S,S*)	58	80(*S,S*)	38
8	terephthalic acid	63(*S,S*)	51	81(*S,S*)	40

[a] All the reactions were carried out using non-racemic piperazine (*S*,S)-**212a** (73% ee, 0.5 mmol) and achiral acid (0.3 mmol) in THF (5 mL) for 2 hours. [b]All ee values reported here are based on HPLC analysis. [c]The yields are of the isolated products, based on the total amount of the starting non-racemic piperazine used.

The formation of homochiral and heterochiral aggregates can be visualized from the Scheme **51**.

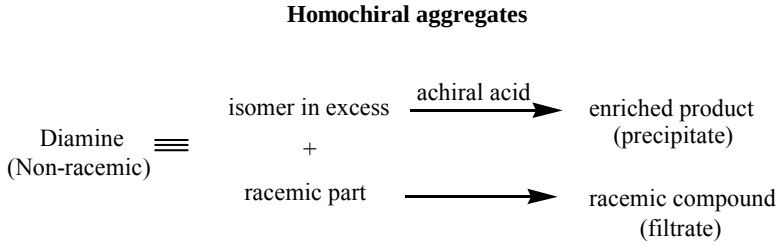
Scheme 51.



Under suitable conditions (solvent, achiral acids and their amount), particular non-racemic diamine predominantly gives either homochiral or heterochiral aggregates. The formation of either type of the aggregates depends on the above said conditions. Samples with >99% ee could be achieved from non-racemic sample following this strategy under ideal conditions. This will be the case, when non-racemic sample with high ee was enriched enantiomerically using this technique (Table **7**, entries **3,5)**.

The non-racemic sample can be considered as a combination of racemic sample and single isomer present in excess. In homochiral aggregates/salt aggregates, the isomer present in excess in the non-racemic diamine forms aggregates with achiral acid and precipitates out, leaving the racemic part in the filtrate fraction (Scheme **52**). To get maximum enrichment, the amount of achiral acid to be taken is equivalent to the amount of one isomer present in excess excluding the racemic compound, or less than that.

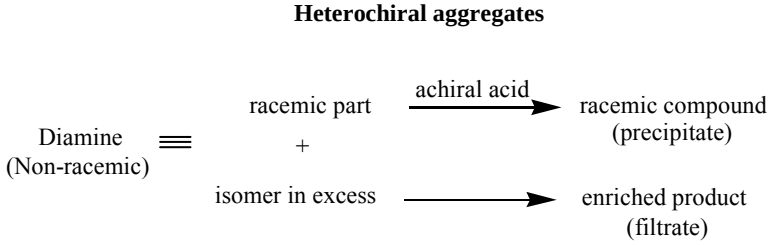
Scheme 52.



In the formation of heterochiral aggregates/salt aggregates, the racemic part in the non-racemic sample forms aggregates with achiral acid and precipitates out. The isomer present in excess will be left out in the filtrate fraction, giving enantiomerically enriched product in the filtrate fraction (Scheme **53,** Table **8,** entries **3-8**). The amount

of achiral acid to be taken is equivalent to the racemic part present in the non-racemic sample or little more than that.

Scheme 53.



If the amount of achiral acid taken is less than the required quantity, the racemic part also will be left out in the filtrate fraction, leading to lower enantiomeric purity in the filtrate fraction.

2.6 Development of chiral titanium reagent for the reductive cyclization of diimine

In the previous sections, synthesis of (±)-2,3-diphenylpiperazine **212a**, resolution using chiral acids and enrichment of enantiomeric purity using achiral acids have been described. A more interesting way to access chiral piperazine is asymmetric imino-pinacol type coupling. Since the chiral titanium reagents can be employed in the reductive cyclization of diimines, we explored the enantioselective intramolecular reductive coupling of diimines to obtain enantiomerically pure piperazines using various chiral titanium complexes.

Titanium is the most successful among all the metals in producing optically active pinacols from aldehydes. A preformed chiral titanium complex or titanium reagent in combination with a chiral ligand is used as the most reliable tool to perform enantioselective pinacol coupling reactions.[29,114]

Many reports are available in literature for the enantioselective pinacol coupling of aldehydes using chiral titanium complexes. However, asymmetric reductive cyclization of diimines using chiral titanium reagents is yet to be realized. In this section, we describe the development of chiral titanium reagents derived from different chiral ligands (Figure **9**) for the enantioselective intramolecular reductive cyclizations of diimines **208a** and **208c.**

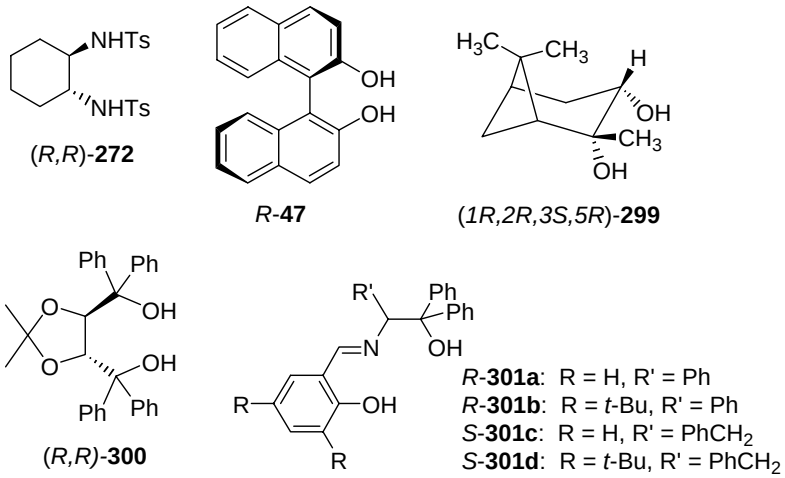
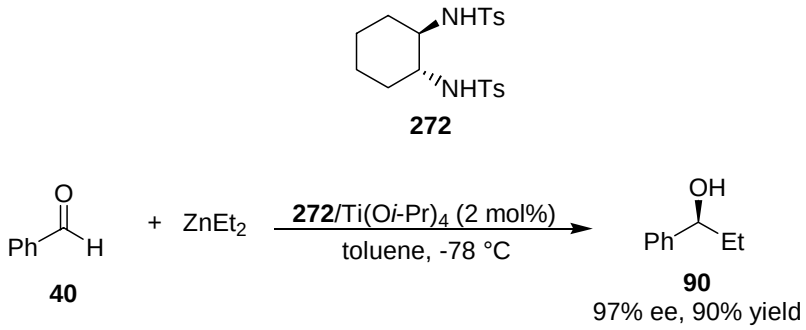


Figure 9.

2.6.1 Chiral titanium reagent derived from bis(sulfonamide) ligand

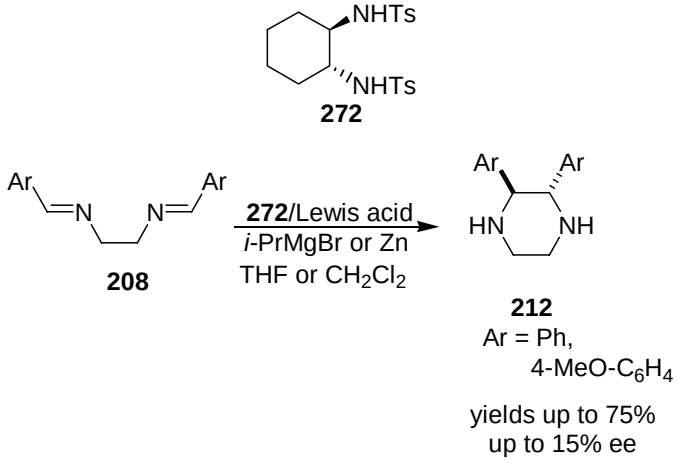
The titanium complexes of chiral diol or bis(sulfonamide) based ligand systems were used in the addition of dialkylzinc to aldehydes.[38,39,42,101] The products were obtained with excellent enantioselectivities. For example, the ligand **272** and the ligands with the same skeleton having different sulfonyl groups were used by Walsh *et al*[101d] in the enantioselective alkylation of benzaldehyde using dialkylzinc reagents in the presence of Ti(O*i*-Pr)$_4$ (Scheme **54**).

Scheme 54.



In our initial studies on the enantioselective alkylation of imines, reductively coupled 1,2-diamines were obtained (Scheme **34**) and intramolecular reductive coupling was observed with diimine **208a** (Scheme **35**). This reagent system was further studied by varying the temperature and the titanium reagents to get better enantioselectivity (Scheme **55**, Table **9**).

Scheme 55.



When the reaction was carried out at room temperature, the piperazine **212a** was obtained in moderate yields up to 60%. However, the enantioselectivity obtained was very poor (<5%) (Table **9**, entry **1**). Decrease in the reaction temperature also gave same enantioselectivity (Table **9**, entry **2**). The reaction of the diimine **208c** in the

reaction temperature -40 °C, gave the product (*S,S*)-**212c** in 50% yield with enantioselectivity up to 10% (Table **9**, entry **3**). Similar results were obtained using zinc as reducing agent in CH_2Cl_2 solvent. Use of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ as Lewis acid enhances the yield as well as the enantioselectivity (Table **9**, entries **4** and **5**). The piperazine (***S,S***)-**212c** was obtained in 72% yield and the enantioselectivity obtained was up to 18%. Addition of activated molecular sieves did not enhance the enantioselectivity further.

Table 9. Enantioselective reductive coupling of diimines **208** with $TiCl_2X_2$/(*R,R*)-**272**

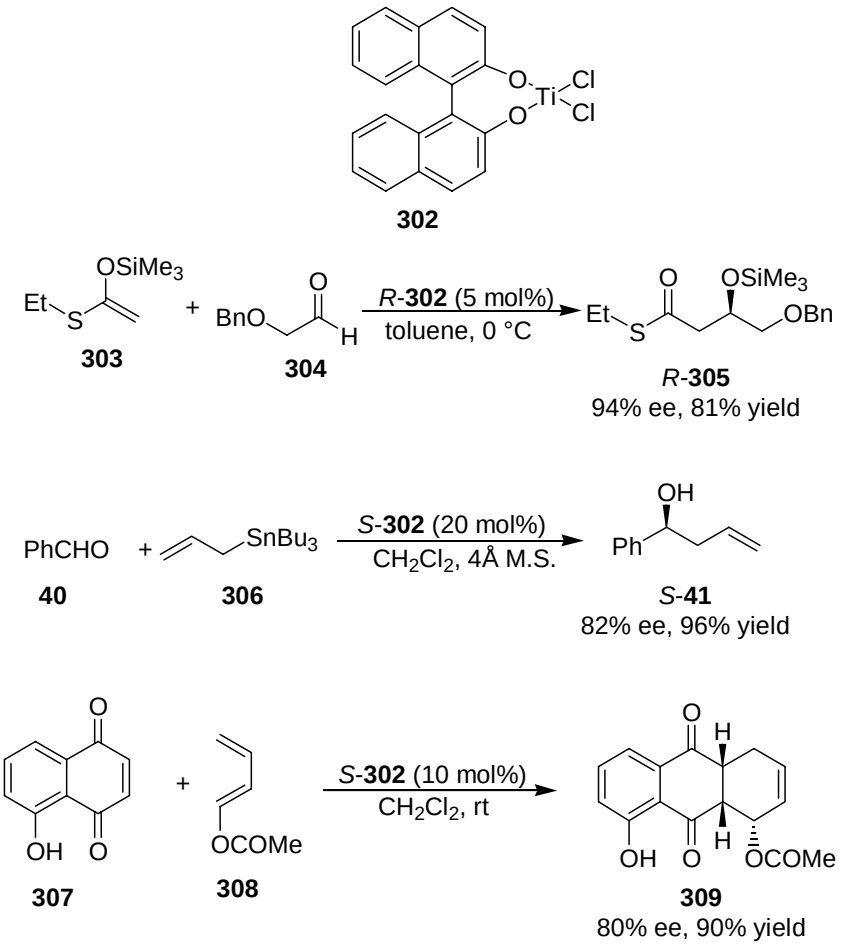
entry	diimine **208**	X	T (°C)	yield (%)[b]	% ee[c]/conf
1	Ar = phenyl	Cl	25	60	--
2	Ar = phenyl	Cl	-40	40	--
3	Ar = 4-methoxyphenyl	Cl	-40	45	10 (*S,S*)
4	Ar = phenyl	O*i*-Pr	25	75	15 (*S,S*)
5	Ar = 4-methoxyphenyl	O*i*-Pr	25	72	18 (*S,S*)

[a]The products **212** were identified using physical constant and spectroscopic data (IR, ^1H, ^{13}C-NMR and mass spectral data). [b]Yields are of the isolated products. [c]The ee values are based on HPLC analysis.

2.6.2 Chiral titanium reagent derived from chiral BINOL

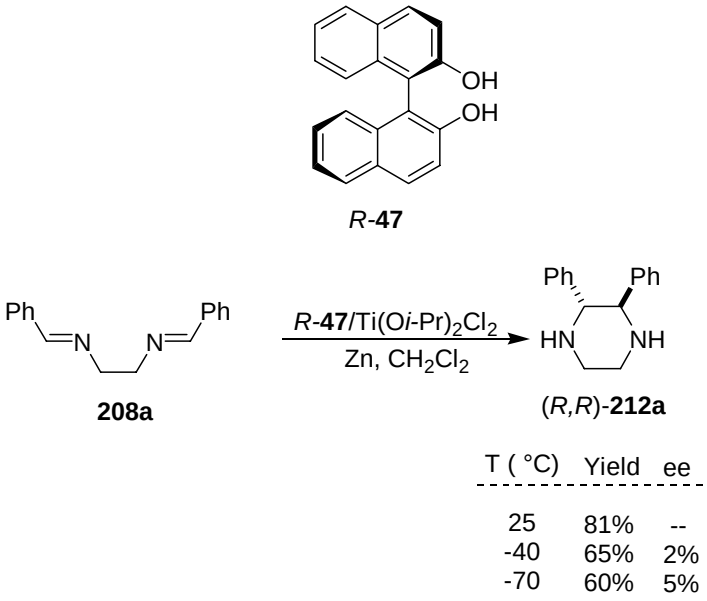
The enantiomerically pure BINOL-titanium complex (1,1'-bi-2,2'-naphthotitanium(IV) dichloride) **302** has been well exploited as a chiral Lewis acid in the asymmetric reactions. It has been employed in asymmetric aldol reaction of aldehydes with ketene silyl acetals,[115] catalytic asymmetric synthesis of homoallylic alcohols [116] and Diels-Alder cycloadditions[117] (Scheme **56**).

Scheme 56.



We have studied the application of the BINOL-titanium complex *R*-**302** in the enantioselective intramolecular reductive coupling of the diimine **208a** (Scheme **57**). The titanium complex *R*-**302** was prepared *in situ* by the reaction of chiral BINOL with $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ in the presence of activated molecular sieves following a literature procedure.[116] The complex was reduced with zinc and used for reductive coupling. When the reaction was carried out in 25 °C, only racemic piperazine **212a** was obtained in 81% yield (Scheme **57**). Even at low temperatures (-40 to -70 °C), the enantioselectivities obtained were very poor (Scheme **57**).

Scheme 57.



2.6.3 Pinane diol/TADDOL derived chiral titanium reagents

The reductive coupling was further studied with pinane diol and TADDOL as a chiral ligand in separate runs. In these cases also enantioselectivities obtained were up to 10% with the product yields up to 75% (scheme **58**).

Scheme 58.

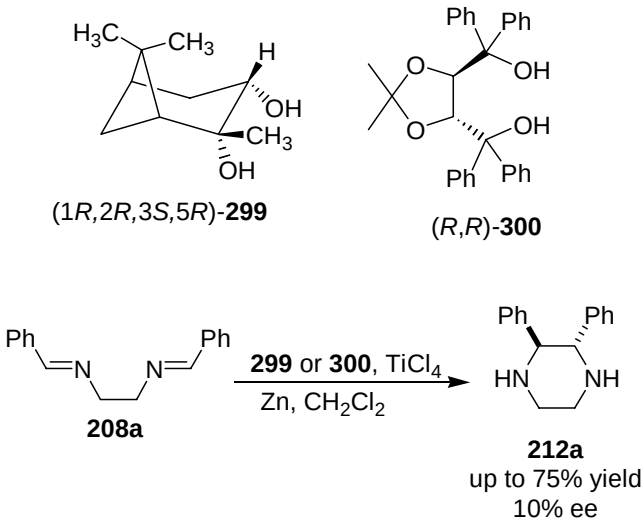


Table 10. Reductive coupling of diimine **208a** in the presence of chiral ligands and Lewis acid.[a]

entry	ligand	Lewis acid	T (°C)	yield (%)[b]	% ee[c]/conf
1[d]	(*R*,*R*)-**272**	$TiCl_4$	25	60	--
2[d]	(*R*,*R*)-**272**	$TiCl_4$	-40	40	--
3[d]	(*R*,*R*)-**272**	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	25	75	12(*S,S*)
4	*R*-**47**	$Ti(O\textit{i}\text{-}Pr)_4$	25	65	--
5	*R*-**47**	$Ti(O\textit{i}\text{-}Pr)_4$	-70	60	5(*R,R*)
6	*R*-**47**	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	25	82	--
7[e]	**299**	$TiCl_4$	25	75	--
8[e]	**299**	$TiCl_4$	-70	70	10(*R,R*)
9	(*R*,*R*)-**300**	$TiCl_4$	25	40	10(*S,S*)

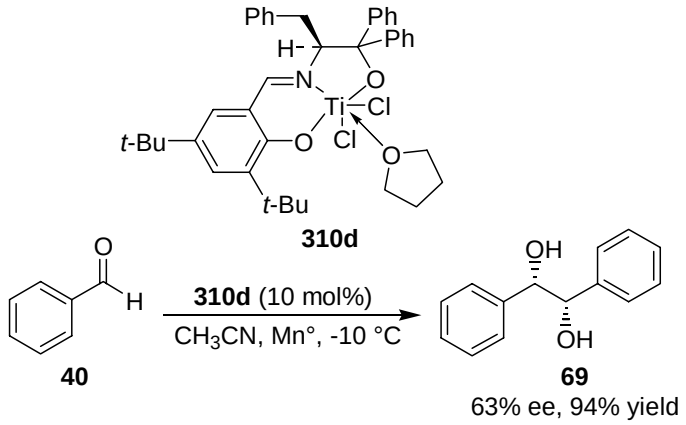
[a]Unless noted otherwise, all the reactions were carried out with 1.0 mmol of diimine **208a**, 2.5 mmol of chiral ligands, 2.2 mmol of Lewis acid and 5 mmol of Zn dust in CH_2Cl_2. [b]Yields are of the isolated product after flash column chromatography on silica. [c]All ee values reported here are based on HPLC analysis on a Chiralcel OD-H column. [d]THF was used as solvent and *i*-PrMgBr was used as reductant. [e]4.0 mmol of diimine **208a**, 11.0 mmol of chiral ligand **299**, 10.0 mmol of $TiCl_4$ and 25 mmol of Zn.

In brief (Table **10**), in the case of diamide (*R*,*R*)-**272,** only racemic 2,3-diphenylpiperazine was obtained when the $TiCl_4$/*i*-PrMgBr reagent system was used (Table **10,** entry **1**). Lowering of temperature to -40 °C did not give any enantioselectivity. Instead, the chemical yield of the product decreased (Table **10, e**ntry **2**). Slight enhancement in enantioselectivity was observed by the use of the $Ti(O\textit{i}\text{-}Pr)_2Cl_2$/Zn reagent system (Table **10, e**ntry **3**). Though, 2,3-diphenylpiperazine was obtained in higher yields in the presence of chiral BINOL *R*-**47,** the enantioselectivity was poor (Table **10,** entries **4-6**). Use of pinanediol **299** and (*R*,*R*)-*trans*-*α,α'*-(2,2-dimethyl-1,3dioxalone-4,5-diyl)bis(diphenylmethanol) TADDOL **300** also gave only poor enantioselectivity, up to 10% ee (Table **10,** entries **7-9**).

2.6.4 Chiral titanium-hemisalen reagent

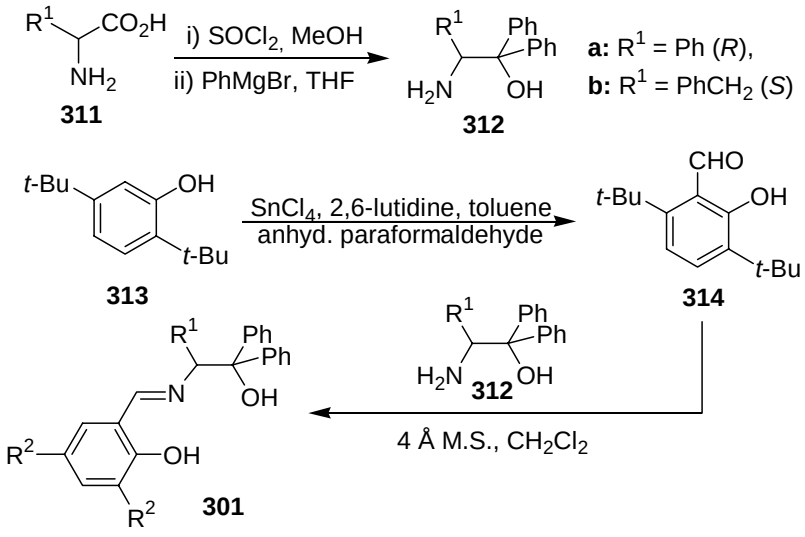
Riant *et al*[114b] prepared the tridentate hemi-salen ligand *S*-**301d**. The titanium complex of the ligand *S*-**310d** was used in the pinacol coupling of aryl aldehydes (Scheme **59**). The diol **69** was obtained with 63% ee.

Scheme 59.

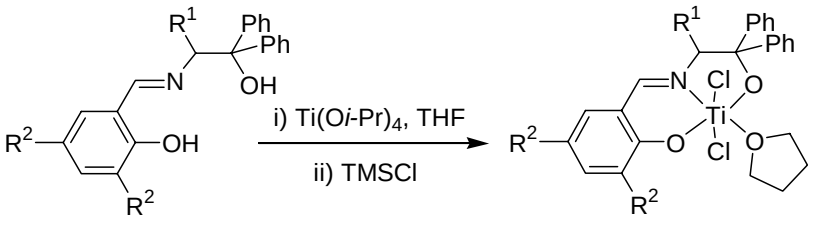


We have prepared a similar ligand system **310a-d** (Scheme **60**) and explored its application in the intramolecular reductive coupling of diimines **208a** and **208c**.

Scheme 60.



Scheme 60. (continued)

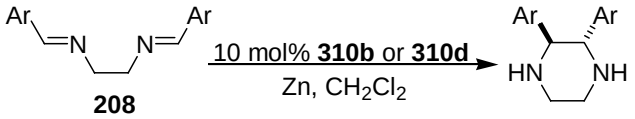


301 **310**

a: R^1 = Ph, R^2 = H (*R*);
b: R^1 = Ph, R^2 = *t*-Bu (*R*);
c: R^1 = $PhCH_2$, R^2 = H (*S*);
d: R^1 = $PhCH_2$, R^2 = *t*-Bu (*S*)

The chiral titanium complexes **310a-d** were prepared *in situ* and used for the reductive coupling of diimines (Scheme **61**). Initially, the reaction was carried out with catalytic amount (10 mol%) of the chiral titanium complexes **310b** and **310d** and the results are listed in the Table **11**. The reductive coupling was done at 25 °C using zinc as reductant.

Scheme 61.



208 **212**

Ar = Ph, 4-MeO-C_6H_4
yield up to 77%
ee up to 28%

By using the complex *R*-**310b**, the chiral piperazine (*R,R)*-**212a** was obtained in 77% yield and 15% ee (Table **11**, entry **1**). In the reaction using *S*-**310d,** the chiral piperazine **212c** was obtained in moderate enantioselectivity up to 28% ee (Table **11,** entry **4**). Encouraged by this result, we carried out the reductive coupling in different conditions and also with chiral titanium complexes with different substitutions **310b-d** (Table **12**).

Table 11. Asymmetric synthesis of 2,3-diarylpiperazine **212** using catalytic amount of chiral titanium complexes **310b** and **310d**[a]

entry	chiral titanium complex	Ar	yield (%)[b]	% ee[c]/conf
1	*R*-**310b**	phenyl	77	15(*R,R*)
2	*R*-**310b**	4-methoxyphenyl	60	18(*R,R*)
3	*S*-**310d**	phenyl	54	15(*S,S*)
4	*S*-**310d**	4-methoxyphenyl	48	28(*S,S*)[d]

[a]Unless noted otherwise, all the reactions were carried out with 2.5 mmol of diimine **208**, 0.5 mmol of chiral titanium complex **310b** or **310d** (prepared *in situ*), 10.0 mmol of Zn dust in CH_2Cl_2 (20 mL) CH_3CN (2mL) and TMSCl (5.0 mmol) at 25 °C. [b]Yields are of the isolated product after flash column chromatography on silica. [c]All ee values reported here are based on HPLC analysis on a Chiralcel OD-H column. [d]Absolute configuration was assigned (*S,S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt prepared from the >99% ee sample.

In catalytic versions, piperazines **212** were obtained in moderate to good yields with ee's up to 28% (Table **11**). The reaction was then repeated with stoichiometric amount of chiral titanium complexes (Table **12**). When the reaction was carried out using the chiral titanium complex *R*-**310a,** chiral piperazine (*R,R*)-**212a** was obtained with 60% ee. Under the same conditions, the reaction was examined with titanium complexes **310a-d** and the results are tabulated in Table **12**. We have observed that the bulky group like *t*-butyl group in the phenyl ring has a significant role in enhancing the enantioselectivity as well as the chemical yield. The chiral titanium complexes **310b** and **310d** gave the product 2,3-diphenylpiperazine **212a** in 76-88 % ee (Table **12,** entries **2,5**). Decreasing the reaction temperature (-10 °C) did not lead to improvement in enantioselectivity (Table **12,** entry **4**). By using the chiral titanium complex **310d,** the 2,3-bis(4-methoxyphenyl)piperazine **212c** was obtained with very good enantioselectivity, up to 97% ee (Table **12,** entry **6**).

Table 12. Asymmetric synthesis of 2,3-diarylpiperazine **212** using stoichiometric amount of chiral titanium complexes **310**[a]

entry	chiral titanium complex	Ar	yield (%)[b]	% ee[c]/conf
1	*R*-**310a**	phenyl	45	60(*R,R*)
2	*R*-**310b**	phenyl	72	76(*R,R*)
3	*S*-**310c**	phenyl	55	50(*S,S*)
4[d]	*S*-**310c**	phenyl	40	55(*S,S*)
5	*S*-**297d**	phenyl	75	88(*S,S*)
6	*S*-**310d**	p-methoxyphenyl	55	97(*S,S*)[e]

[a]Unless noted otherwise, all the reactions were carried out with 0.5 mmol of diimine **208**, 1.25 mmol of chiral titanium complex **310a-d** (prepared *in situ*), and 2.5 mmol of Zn dust in CH_2Cl_2 (10 mL), CH_3CN (2mL) at 25 °C. [b]Yields are of the isolated product after flash column chromatography on silica. [c]All ee values reported here are based on HPLC analysis. [d]The reaction was carried out at -10 °C. [e]Absolute configuration was assigned (*S,S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt **315**.

To get the absolute configuration of the newly formed chiral centres, the compound **212c** with 97% ee was stirred with (1*S*)-(+)-10-camphorsulfonic acid in THF. The precipitate was filtered and from the residue, the single crystals suitable for XRD studies were obtained by crystallization from water. The absolute configuration of the newly formed chiral centres in 2,3-bis(4-methoxyphenyl)piperazine **212c** was assigned (*S,S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt **315** (Figure **10**).

Riant *et al*[114b] reported that the ligand **301d** forms a hexacoordinated complex **310d**, which is monomeric in nature. Presumably, the compounds **301a, 301b** and **301c** could also form hexacoordinate complexes that are monomeric in nature resulting in high enantioselectivities.

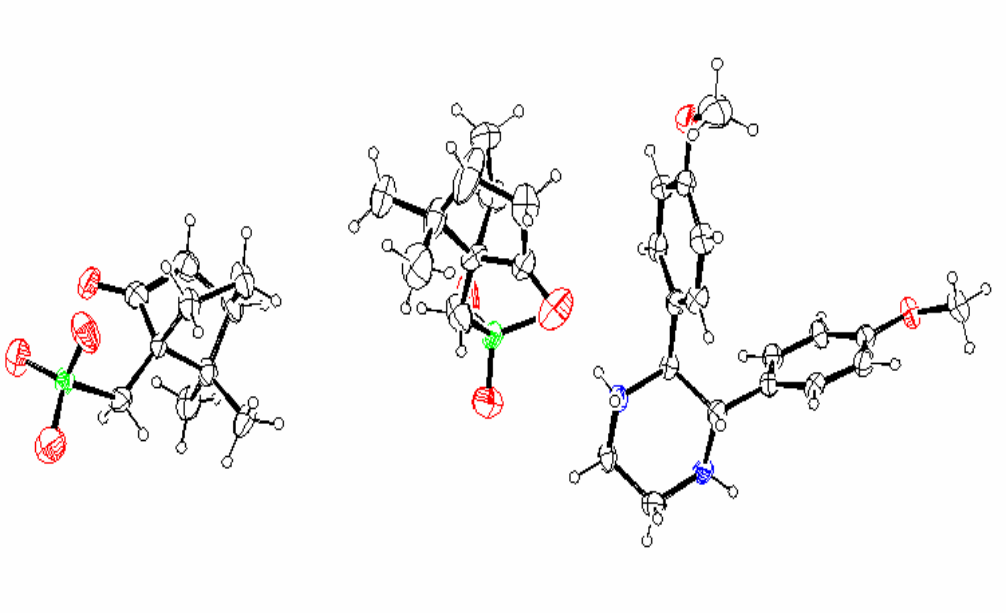


Figure 10. ORTEP diagram of the (*S*)-camphorsulfonate salt **315** (thermal ellipsoids are drawn at 20% probability)

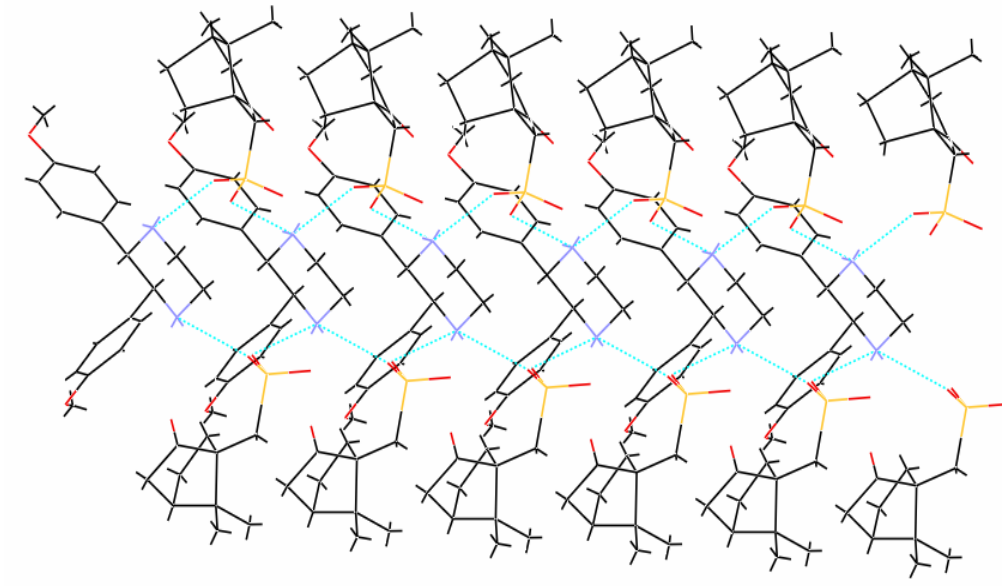


Figure 11. Packing diagram of the (*S*)-camphorsulfonate salt **315** (The H-bondings are shown in blue colour)

Table 13. Crystal data and structure refinement for compound 315	
Identification code	**315**
Empirical formula	$C_{38}H_{54}N_2O_{10}S_2$
Formula weight	762.95
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 6.7095(10) Å, b = 17.741(3) Å, β = 99.641(2) c = 16.365(3) Å,
Volume	1920.5(5) $Å^3$
Z, Calculated density	2, 1.319 Mg M^{-3}
Absorption coefficient	0.198mm^{-1}
F(000)	816
Crystal size	0.42 x 0.22 x 0.20 mm
Theta range for data collection	1.71 to 25.00 °
Limiting indices	-7≤h≤7, -21≤k≤21, -16≤l≤19
Reflections collected / unique	13082 / 6705 [R(int) = 0.0317]
Completeness 2θ = 25.00	100%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6705 / 8 / 493
Goodness-of-fit on F^2	1.045
Final R indices [I>2σ (I)]	R1 = 0.0781, wR2 = 0.2063
R indices (all data)	R1 = 0.0870, wR2 = 0.2162
Absolute structure parameter	-0.01(2)
Largest diff. peak and hole	0. 948 and -0.346 e. $Å^{-3}$

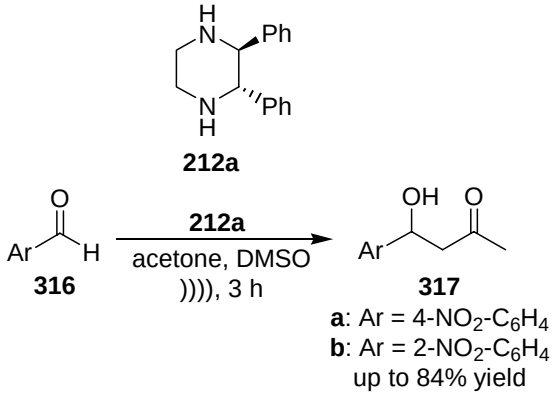
2.7 Applications of chiral piperazines

The piperazine skeleton is containing 1,2-diamine moiety. As outlined in the introductory part, the diamines and diamine derived compounds have been used in large number of organic transformations. However, only a few reports are known in literature for the applications of chiral piperazines in organic reactions.

2.7.1 Applications of chiral piperazines in aldol reaction

As described in the introductory section, various chiral amines, amino acids and their derivatives have been used as organocatalysts in the aldol, nitroaldol and Mannich reactions. We have examined the chiral 2,3-disubstituted piperazines in the aldol reaction of aromatic aldehydes with acetone (Scheme **62**).

Scheme 62.



When the aldol reaction of 4-nitrobenzaldehyde was carried out in room temperature with chiral piperazine (*R,R*)-**212a,** no product was obtained even after 24 hours. When the reaction was carried out under ultrasonication at room temperature, the product was obtained in yields up to 84% with poor enantioselectivity (Table **14,** entries **2-5**).

Table **14.** Aldol reaction of aryl aldehyde with acetone catalyzed by chiral piperazine[a]

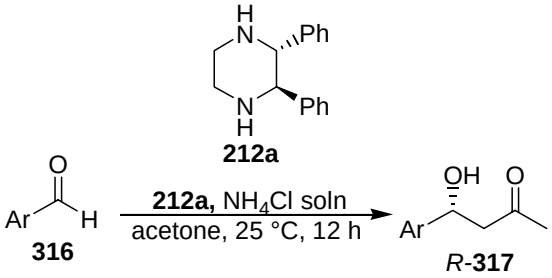
entry	chiral catalyst/(mol%)	condition	product	yield (%)	% ee/conf[b]
1	(*R,R*)-**212a**/20 mol%	rt, 24 h	**317a**	--	--
2	(*R,R*)-**212a**/20 mol%	))))), 3h	**317a**	70	--
3	(*R,R*)-**212a**/50 mol%	))))), 3h	**317a**	80	5 (*R*)
4	(*R,R*)-**212a**/20 mol%	))))), 3h	**317b**	84	5 (*R*)
5	(*S,S*)-**212a**/20 mol%	))))), 3h	**317b**	82	7 (*S*)

[a]All the reactions were carried out with acetone (2 mL), DMSO (0.5 mL), aldehyde (0.5 mmol) and piperazine. [b]The ee values and configuration reported here are based on the HPLC study on Chiralpak AS-H column.

To increase the enantioselectivity, the reaction was carried out in low temperature under ultrasonication condition. Under this condition, the aldol product was not obtained when the reaction mixture was quenched by adding saturated ammonium chloride solution and worked up immediately. However, when the mixture was stirred for 2 hours after quenching, a considerable conversion of starting material to product was observed. This gave us an idea that the reaction could be catalyzed by piperazine at room temperature in saturated ammonium chloride solution. Accordingly, we have studied the aldol reaction in saturated ammonium chloride solution using the chiral piperazines and chiral amines (Table **15**).

The aldol reaction of aryl aldeheydes with acetone was carried out in saturated ammonium chloride solution in the presence of chiral 2,3-diphenylpiperazine **212a** (Scheme **63**). The aldol products were obtained in 90% yields with enantioselectivities up to 10% ee .

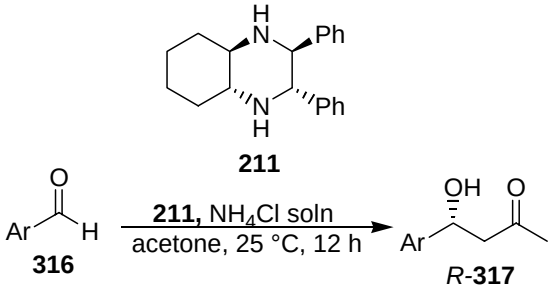
Scheme 63.



a: Ar = 4-NO_2-C_6H_4 (90%, 8% ee)
b: Ar = 2-NO_2-C_6H_4 (88%, 10% ee)

When the aldol reaction was carried out using chiral piperazine **211** derived from 1,2-diaminocyclohexane, the yield of the aldol product was slightly reduced and similar enantioselectivity was obtained (Scheme **64**).

Scheme 64.



a: Ar = 4-NO_2-C_6H_4 (80%, 8% ee)
b: Ar = 2-NO_2-C_6H_4 (75%, 12% ee)

In the chiral diamine **318** catalyzed aldol reaction of 4-nitrobenzaldehyde with acetone in sat. NH_4Cl solution, the corresponding aldol product was obtained in 82% yield with 10% ee. When 2-nitrobenzaldehyde was used as substrate, the aldol product was obtained with significant increase in ee (up to 31%) (Scheme **65**).

Scheme 65.

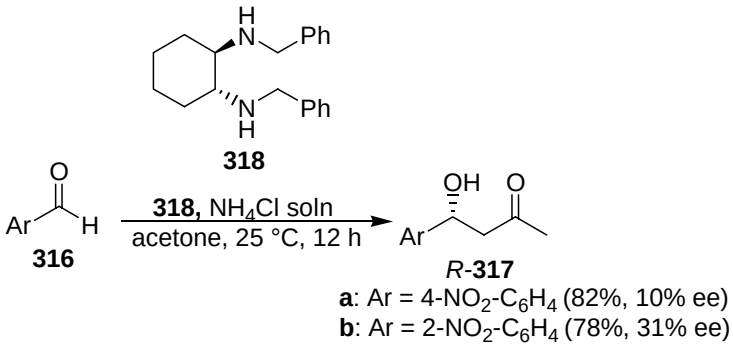


Table **15.** Aldol reaction of aryl aldehydes with acetone catalyzed by chiral piperazine and chiral diamine in sat. NH_4Cl solution [a]

entry	chiral catalyst	product	yield (%)	% ee/conf[b]
1	(*R,R*)-**212a**	**317a**	90	8 (*R*)
2	(*R,R*)-**212a**	**317b**	88	10 (*R*)
3	(*R,S,S,R*)-**211**	**317a**	80	8 (*R*)
4	(*R,S,S,R*)-**211**	**317b**	75	12 (*R*)
5	(*R,R*)-**318**	**317a**	82	10 (*R*)
6	(*R,R*)-**318**	**317b**	78	31 (*R*)

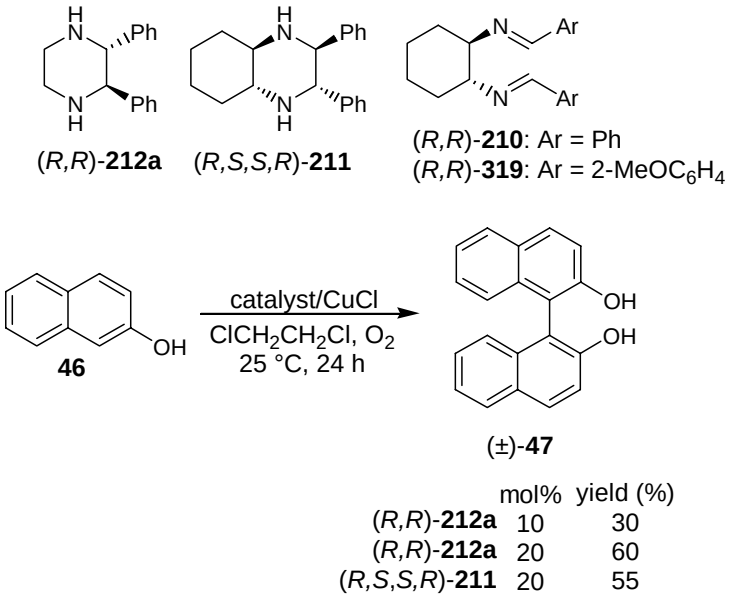
[a]All the reactions were carried out with acetone (1.0 mL), sat. NH_4Cl solution (1.0 mL), aldehyde (0.5 mmol) and catalyst (0.10 mmol) at rt for 12 h. [b]The ee values and configauration reported here are based on the HPLC study on Chiralpak AS-H column.

In the chiral piperazine/diamine catalyzed aldol reactions, the aldol products were obtained in good yields with enantioselectivity up to 31% ee. Further modifications in the reaction conditions or by adding other additives, it should be possible to realize better enantioselectivity in this reaction

2.7.2 Oxidative dimerization of 2-naphthol using chiral piperazine/CuCl

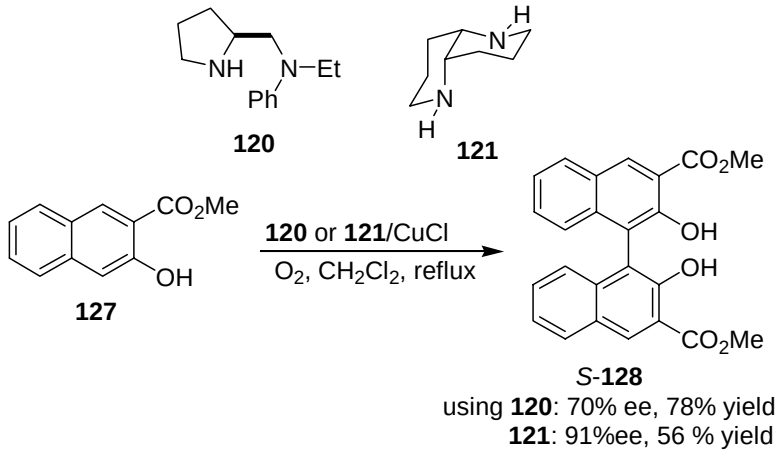
The oxidative dimerization of 2-naphthol is a well-established reaction, which can be promoted stoichiometrically by $FeCl_3 \cdot 6H_2O$,[118] and $TiCl_4$[119] and catalytically by a Cu(II)-amine complex.[48] We have examined the applications of Cu(I)/chiral piperazine catalyst in the oxidative dimerization of 2-naphthol in the presence of oxygen. The BINOL **47** was obtained in moderate yield (up to 60%) without enantioselectivity (Scheme **66**). When the chiral piperazine (*R*,*R*)-**212a** was used in 10 mol% quantity, the racemic BINOL was obtained in 30% yield. The yield was increased to 60% by using 20 mol% of chiral piperazine (*R,R*)-**212a,** but the enantioselectivity could not be achieved. Similar result was obtained in the reaction catalyzed by the piperazine **211**. When the chiral imines **210** and **319** were used as catalysts, the self coupled product was not obtained and only the 2-naphthol was recovered.

Scheme 66.



It should be pointed out that in the oxidative coupling of 2-naphthols with ester group at C3, very good enantioselectivity (70% to 91% ee) was realized and with the parent compound 2-naphthol, the BINOL was obtained with only low enantioselectivity up to 10% ee (Scheme **67**).[48]

Scheme 67.



The oxidative coupling reaction of 2-naphthol using our catalyst system did not give any enantioselectivity but the product was obtained in moderate to good yields (Scheme **66**). It may be worthwhile to use substituted 2-naphthols so as to examine whether our catalyst system could be used for such applications.

2.8 Applications of (±)-2,3-diarylpiperazine/CuX catalyst system

The *N*-aryl nitrogen heterocycle motif is present in a multitude of important bioactive natural products and pharmaceutically interesting compounds.[120] Various strategies have been developed for the *N*-arylation of heterocycles using arylboronic acids and aryl halides in the presence of palladium salts and copper salts. The copper catalyzed Ullmann reaction is very old reaction used for the *N*-arylation of amines and nitrogen containing heterocycles. This reaction has seen a gradual expansion in the past

few years, by the correct choice of copper sources, bases, ligands and other additives.[121] We have developed a simple reagent system consisting of the easily accessible (±)-2,3-diarylpiperazines **212** and copper(I) halides, which catalyzes the *N*-arylation of indole.

2.8.1 *N*-Phenylation of indole using iodobenzene/2,3-diarylpiperazines/CuI

We have developed a simple catalyst system consisting the easily accessible piperazine ligands for the *N*-arylation of indole **320**. In this study, the effect of substitution in the phenyl ring of piperazine on the reactivity has also been examined (Scheme **68**, Table **16**).

Scheme 68.

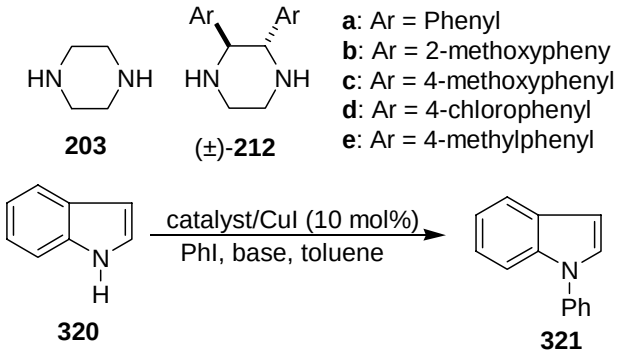


Table 16. 2,3-Diarylpiperazine/CuI catalyzed *N*-phenylation of indoles using PhI.[a]

entry	ligand	condition	yield (%)[b]	
			K_2CO_3[c]	K_3PO_4[d]
1	**203**	reflux, 24 h	70	75
2	(±)-**212a**	reflux, 24h	44	52
3	(±)-**212b**	reflux, 24h	90	94
4	(±)-**212c**	reflux, 24h	93	96
5	(±)-**212d**	reflux, 24h	39	45
6	(±)-**212e**	reflux, 24h	63	85
7	(±)-**212c**	rt, 48h	<5%	<5%

[a]Unless noted otherwise, all the reactions were carried out with 0.1 mmol of piperazine, 0.1 mmol of CuI, 1.0 mmol of indole and 1.5 mmol of PhI in toluene (2 mL).[b]Yields are of the isolated product and the product was identified using spectroscopic data (IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[122] [c]Using 5.0 mmol of K_2CO_3. [d]Using 2.0 mmol of K_3PO_4.

Simple piperazine **203** gave the product *N*-phenylindole **321** in 75% yield. When the *N*-phenylation of indole was carried out using (±)-2,3-diphenylpiperazine/CuI in the presence of PhI and K_2CO_3, the product was obtained in 44% yield (Table **16**, entry **2**). The yield was improved up to 52% by using K_3PO_4 as a base (Table **16**, entry **2**). Piperazines with methoxy substitution in aryl group gave the *N*-phenylindole in very good yields (Table **16**, entries **3** and **4**). The yields were very low when (±)-2,3-bis(4-chlorophenyl)piperazine/CuI was used (Table **16**, entry **5**). When the reaction was carried out at 25 °C, only a trace amount of product (<5%) was obtained (Table **16**, entry **7**). Ultrasonication of the reaction mixture for 1 hour in an ultrasonication bath did not give the product and the starting materials were recovered.

As expected, there is electronic control by the substituent of the phenyl ring over the reaction. The enhanced reactivity of the complex by using the ligand **212b** and **212c** may be due to the presence of the methoxy group in the phenyl ring. Presumably, the aryl group in the piperazine moiety electronically control the reactivity of the copper complex formed during the reaction in the present case.

Though the substituent in the phenyl ring is far away from the reaction centre, it still has electronic control over the reactivity through the aryl group. Such systems and their effect/control in reactivity as well as stereoselectivity have also been noted by others. For example, in a recent study using sulfonylated diarylethylenediamines-ruthenium complex in asymmetric transfer hydrogenation of α-tetralone, greater reactivity was observed for methoxyphenyl derivatives compared to phenyl substituted diamine complex, even though enantioselectivities were the same.[123]

2.8.2 *N*-Phenylation of indole using iodobenzene/piperazine/CuX

The *N*-phenylation was further studied using other copper halides (Scheme **69**, Table **17**) using the ligands **212b** and **212c**. In the presence of CuCl or CuBr, *N*-phenylindole was obtained in moderate yields (up to 67%) using the ligand **212b** or **212c,** and it needed 48 hours reflux.

Scheme 69.

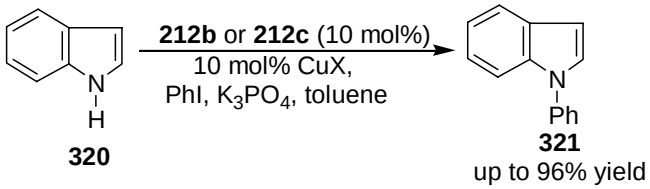


Table 17. 2,3-Diarylpiperazine/CuX catalyzed *N*-phenylation of indole using PhI and K_3PO_4[a]

entry	ligand	CuX	condition	yield (%)[b]
1	(±)-**212b**	CuI	reflux, 24h	94
2	(±)-**212b**	CuBr	reflux, 48h	62
3	(±)-**212b**	CuCl	reflux, 48h	58
4	(±)-**212c**	CuI	reflux, 24h	96
5	(±)-**212c**	CuBr	reflux, 48h	67
6	(±)-**212c**	CuCl	reflux, 48h	55

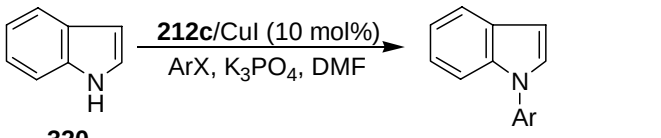
[a]Unless noted otherwise, all the reactions were carried out with 0.1 mmol of piperazine, 0.1 mmol of CuX, 1.0 mmol of indole, K_3PO_4 (2.0 mmol), and 1.5 mmol of PhI in toluene (2 mL).[b]Yields are of the isolated product and the product was identified using spectroscopic data (IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[122]

2.8.3 *N*-Arylation of indole using ArX/piperazine/CuI

The reaction was also studied using other aryl halides with the ligand **212c** (scheme **70,** Table **18**). In the arylation using 1-bromonaphthalene, the product **322** was obtained by using toluene as a solvent in <5% yield (Table **18**, entry **1**). When toluene DMF solvent mixture (1:1) was used, the *N*-arylated product was obtained, but only in

lower yield, up to 20% (Table **18**, entry **2**). By using DMF alone as solvent, the product was obtained in better yield, up to 82% (Table **18**, entry **3**). In the reaction of 4-bromotoluene, an electron rich aryl bromide, the product was obtained in 95% yield (Table **18**, entry **4**). Only a trace amount of product was obtained in the reaction of 4-chloroanisole in the presence of (±)-2,3-bis(4-methoxyphenyl)piperazine/CuI/K_3PO_4 (Table **18**, entry **5**). The reason for the need of DMF as a solvent for ArBr could be explained from the polarizing nature of the solvent. Whereas the reaction using highly polarized C-I bond takes place in toluene, the solvent DMF is needed in the case of ArBr.

Scheme 70.



320

322: Ar = 1-naphthyl,
323: Ar = 4-methylphenyl

Table 18. 2,3-Bis(4-methoxyphenyl)piperazine **212c** catalyzed *N*-arylation of indoles using ArX and K_3PO_4[a]

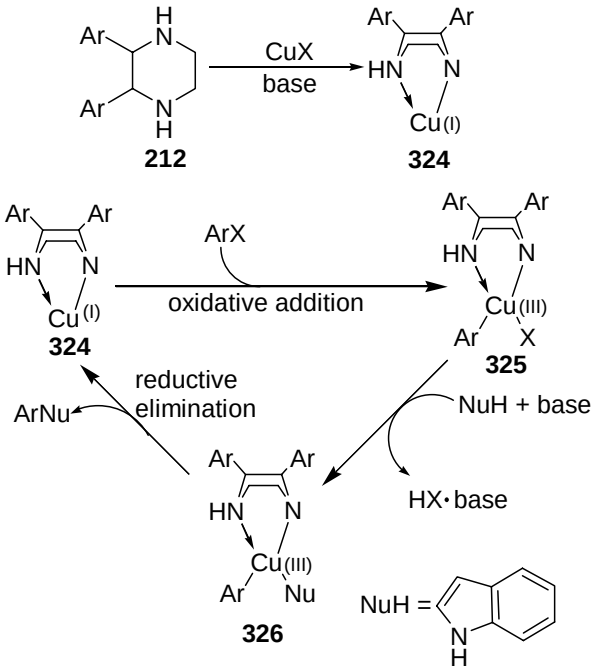
entry	ArX	solvent	condition	yield (%)[b]
1	1-bromonaphthalene	toluene	reflux, 24h	--
2	1-bromonaphthalene	toluene/DMF (1:1)	reflux, 24h	20
3	1-bromonaphthalene	DMF	reflux, 24h	82
4	4-bromotoluene	DMF	reflux, 24h	95
5	4-chloroanisole	DMF	reflux, 24h	<5

[a]Unless noted otherwise, all the reactions were carried out with 0.05 mmol of piperazine **212c**, 0.05 mmol of CuI, 0.5 mmol of indole and 1.0 mmol of ArX in solvent (2 mL).[b]Yields are of the isolated product and the products were identified using physical constant and spectroscopic data (mp, IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[122]

The *N*-arylation reaction can proceed through oxidative addition/reductive elimination mechanism proposed by Cohen[124a] in 1974 or π-complex mechanism

proposed by Paine[124b] in 1987. In our study, we have considered a mechanism based on the oxidative addition/reductive elimination mechanism (Scheme **71**). When the piperazine **212** and CuI are heated under reflux in the presence of base, the complex **324** or a similar derivative could be formed. Then, the ArX oxidatively adds to the complex **324** across the C-X bond to form the complex **325**. The replacement of X with nucleophile followed by reductive elimination affords the *N*-arylated product and the piperazine/Cu complex **324** enters into the catalyst cycle again.

Scheme 71.



To further understand the nature of the complex formed during the reaction, CuI, (±)-2,3-bis(4-methoxyphenyl)piperazine **212c,** and K_3PO_4 were heated under reflux for 12 hours in toluene solvent. We could not isolate piperazine/copper complex but instead observed that there is C-C bond cleavage and the (±)-2,3-bis(4-methoxyphenyl)piperazine was completely converted to *N,N*'-bis-(4-

methoxybenzylidene)-ethane-1,2-diamine (Scheme **72**). The C-C bond cleaving and the conversion to diimine was observed with other piperazines also (Table **19**). In the case of (±)-2,3-bis(4-methoxyphenyl)piperazine, complete conversion was observed (Table **19**, entry **2**). For (±)-2,3-bis(4-chlorophenyl)piperazine, the conversion to diimine is 25% (Table **19**, entry **3**) and for (±)-2,3-diphenylpiperazine, the conversion is 85% (Table **19**, entry **4**). In the reaction of (±)-2,3-bis(4-methylphenyl)piperazine with 10 mol% of CuI, 85% conversion to diimine was observed (Table **19**, entry **6**).

Scheme 72.

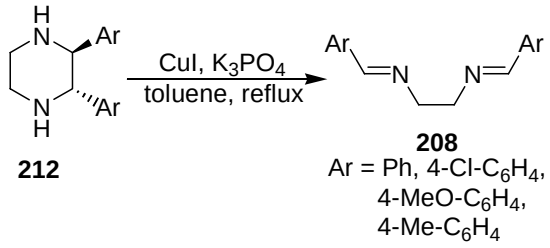


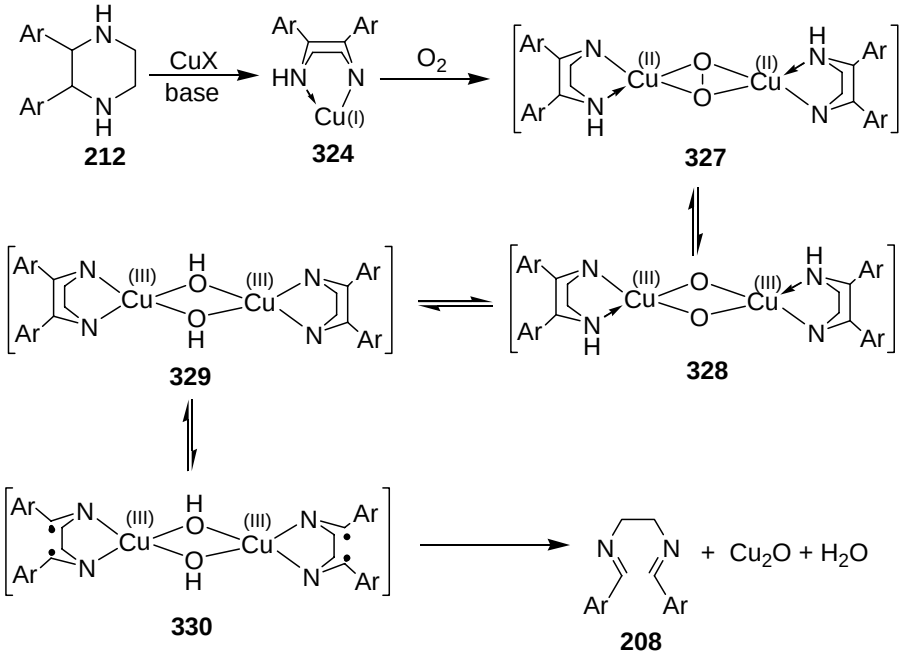
Table 19. Conversion of piperazine to diimine[a]

entry	2,3-diarylpiperazine	diimine	conversion (%)[b]
1	**212a**	**208a**	85
2	**212c**	**208c**	>99
3	**212d**	**208d**	25
4	**212e**	**208e**	87
5[c]	**212e**	**208e**	<20
6[d]	**212e**	**208e**	85

[a]All the experiments were carried out with 2,3-diarylpiperazine (0.5 mmol), CuI (0.5 mmol), K_3PO_4 (1.0 mmol) and toluene (5 mL). [b]The % of conversion was obtained by comparing the integration values of the corresponding ^{1}H NMR peaks. [c]The experiment was carried out under nitrogen. [d]10 mol% of CuI with respect to piperazine was used.

The oxidative cleaving of the C-C bond can be explained by considering the mechanism shown in Scheme **73**. The reactivity of Cu(I) complexes with O_2 and the subsequent oxidative reactivity of the formed Cu–O_2 species has been well studied[125] and the formation of diamine-Cu-O_2 complexes of the structures **327-329** with other amines have been reported. Accordingly, we have postulated the mechanism (Scheme **73**). We have observed that when the reaction was carried out in the absence of O_2, the conversion of piperazine to diimine is very low (Table **19,** entry **5**). Presumably, the cleavage of piperazine is mediated by O_2 as outlined in Scheme **73**. Formation of the complex **324** would be less favoured with chloro substituents in the phenyl ring. Consequently, the conversion to the imine is less favoured. Hence, the yield of oxidative C-C bond cleavage reaction with piperazine **212d** is very less (Table **19,** entry **3**) compared to that of the piperazine **212c**.

Scheme 73.



2.8.4 *N*-Phenylation of indole using iodobenzene/diimines/CuI

As outlined above, in the piperazine catalyzed *N*-arylation of indole, the 2,3-diarylpiperazines are converted to the corresponding diimines. To give further support to this fact, *N*-arylation of indole was carried out using the diimine and CuI. Using this system, the *N*-phenylindole was obtained in similar yields or even higher yields in some cases (Scheme **74**, Table **20**).

Scheme 74.

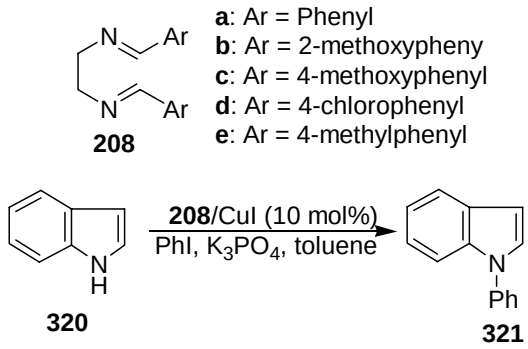


Table 20. Diimine/CuI catalyzed *N*-phenylation of indole using PhI and K_3PO_4[a]

entry	ligand	condition	Yield (%)
1	**208a**	reflux, 24 h	85
2	**208a**	rt, 48h	--
3	**208b**	reflux, 24h	93
4	**208c**	reflux, 24h	95
5	**208d**	reflux, 24h	78
6	**208e**	reflux, 24h	90

[a]Unless noted otherwise, all the reactions were carried out with 0.05 mmol of diimine **208**, 0.05 mmol of CuI, 0.5 mmol of indole and 0.75 mmol of PhI in toluene (2 mL).[b]Yields are of the isolated product and the product was identified using spectroscopic data (IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[122]

The *N*-arylation using diimine/copper complex was studied using different aryl halides and the diimine **208c** (Scheme **75,** Table **21**). The yields of the product obtained

were almost similar to the yields obtained by using (±)-2,3-bis(4-methoxyphenyl)piperazine **212c** (Table **18**). The *N*-arylindoles were obtained in very good yields by using the solvent DMF. Using this catalyst also, 4-chloroanisole did not react. No product was obtained when the reaction was carried out at room temperature and also in ultrasonication (Table **21**).

Scheme 75.

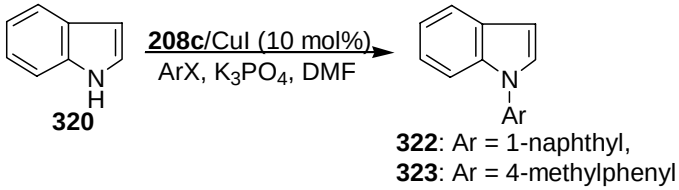


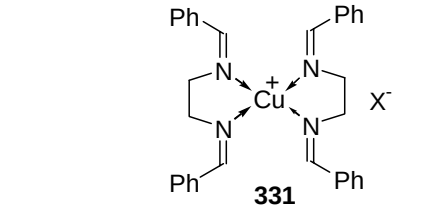
Table 21. *N,N*'-Bis-(4-methoxybenzylidene)-ethane-1,2-diamine **208c** catalyzed *N*-arylation of indole using ArX and K_3PO_4[a]

entry	ArX	solvent	condition	yield (%)[b]
1	1-bromonaphthalene	DMF	reflux, 24 h	82
2	4-bromotoluene	DMF	reflux, 24 h	95
3	4-bromotoluene	DMF	rt, 48 h	--
4	4-bromotoluene	DMF	))))), 1 h	--
5	4-chloroanisole	DMF	reflux, 24 h	<5

[a]Unless noted otherwise, all the reactions were carried out with 0.05 mmol of piperazine **208c**, 0.05 mmol of CuI, 0.5 mmol of indole and 1.0 mmol of ArX in DMF (2 mL).[b]Yields are of the isolated product and the products were identified using physical constant and spectroscopic data (mp, IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[122]

A plausible mechanism for the diimine/CuI catalyzed *N*-arylation of indole is given in Scheme **76.** Formation of the diimine-copper(I) complexes **331** was reported

with other anions (Figure **12**).[126] Accordingly, the formation of a similar complex **330** is not entirely unexpected.



331

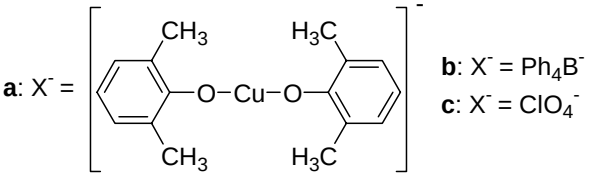
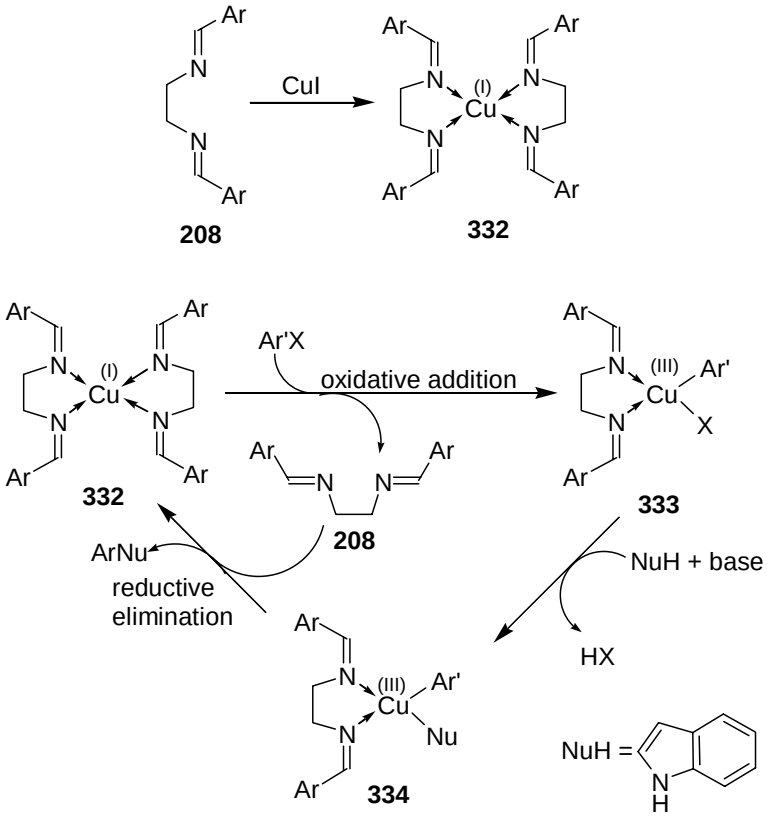


Figure 12.

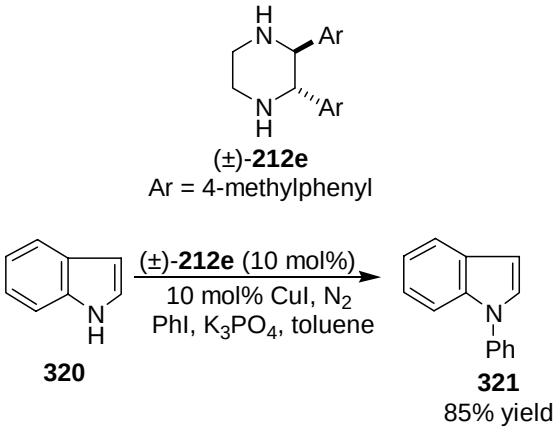
Scheme 76.



2.8.5 *N*-Phenylation of indole under N_2

The *N*-phenylation of indole using 2,3-bis(4-methylphenyl)piperazine also takeplaces under N_2 and the *N*-phenyl product was obtained in 85% yield (Scheme **77**). Also, in this case, it was found that piperazine was not cleaved to diimine. Accordingly, it is concluded that both piperazine/copper complex and diimine/copper complex are active catalysts in the *N*-arylation reaction.

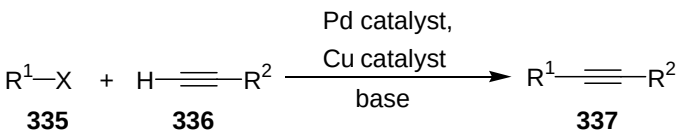
Scheme 77.



2.8.6 Homocoupling of phenylacetylene using the piperazine/CuI system

We have anticipated that this reagent system would be useful for the arylation of terminal alkynes. Such arylations have been achieved earlier under the Sonogashira reaction conditions[126] (Scheme **78**).

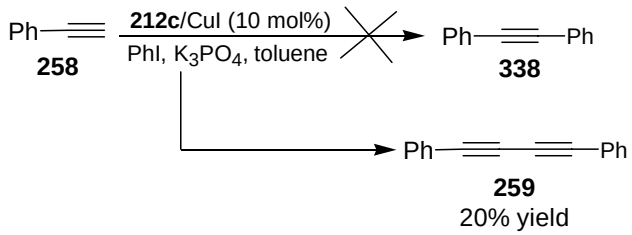
Scheme 78.



R^1 = aryl, heteroaryl, vinyl
R^2 = aryl, heteroaryl, alkenyl, alkyl, SIR_3,
X = I, Br, Cl, OTf

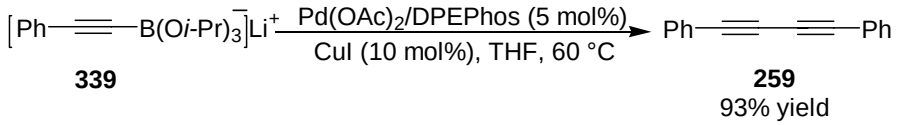
To examine this possibility, we carried out the reaction of phenylacetylene with iodobenzene in the presence of (±)-2,3-bis(4-methoxyphenyl)piperazine/CuI (Scheme **79**). The expected product diphenylacetylene **332** was not isolated and the corresponding homocoupled product 1,3-diyne **259** was obtained in 20 % yield.

Scheme 79.



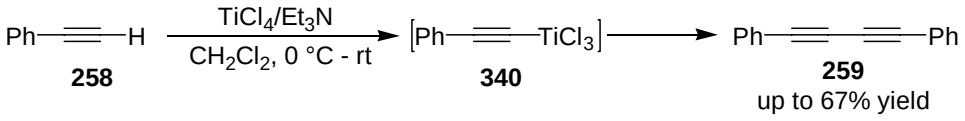
Dimerization reaction of terminal alkynes to 1,3-diynes is well studied and catalyzed by palladium salts, titanium reagents and amine-copper reagent systems. Oh *et al*[128] reported a method of synthesis of 1,3-diynes by the homocoupling of lithium alkynyltriisopropoxyborates in the presence of palladium catalyst and catalytic amount of CuI (Scheme **80**).

Scheme 80.



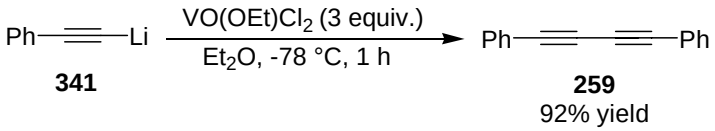
It has been reported from our laboratory that terminal alkynes on reaction with $TiCl_4/Et_3N$ give the homocoupled products in yields up to 67% (Scheme **81**).[94] In this reaction, alkynyltitanium reagents are formed *in situ* and homocoupled.

Scheme 81.



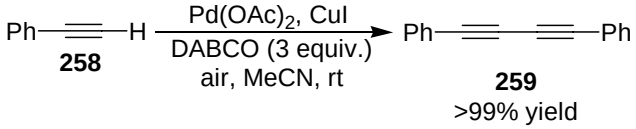
Hirao *et al*[129] homocoupled various alkynyllithium compounds by oxidation with oxovanadium(V) compounds under mild conditions to obtain the 1,3-diynes in the yields up to 92% (Scheme **82**).

Scheme 82.



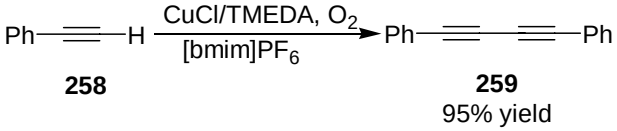
Li *et al*[130] reported a method for palladium catalyzed homocoupling reaction terminal alkynes to symmetrical 1,3-diynes in the presence of 3 equivalent of DABCO (Scheme **83**).

Scheme 83.



Yadav *et al*[131a] observed enhanced reactivity and selectivity in the CuCl/TMEDA catalyzed oxidative homocoupling of terminal alkynes by using ionic liquids (Scheme **84**).

Scheme 84.



In our studies, the product 1,4-diphenyl-1,3-butadiyne **259** was obtained in 20% yield in the initial studies. After this preliminary result, we have standardized the reaction conditions (Table **22**). We have observed that the diyne could be obtained in 95% yield by using 10 mol% CuI, 10 mol% (±)-2,3-bis(4-methoxyphenyl)piperazine in the presence of 4Å molecular sieves and O_2 atmosphere (Table **22**, entry **3**).

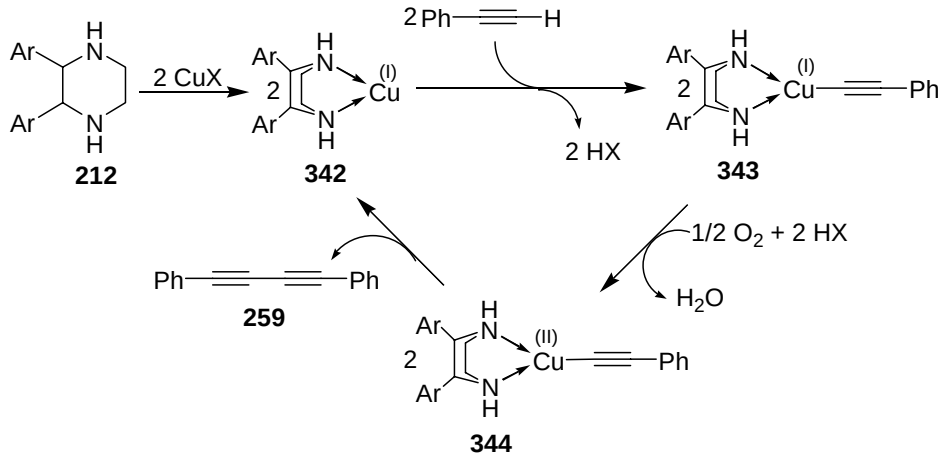
Table 22. Homocoupling of phenylacetylene catalyzed by (±)-2,3-bis(4-methoxyphenyl)piperazine **212c**/CuI[a]

entry	catalyst	condition	yield (%)[b]
1[c]	CuI/piperazine **212c**/K_3PO_4	reflux, 24 h	20
2	CuI/piperazine **212c**/O_2	rt, 48 h	50
3	CuI/piperazine **212c**/4 Å M.S./O_2	rt, 48 h	95

[a]All the reactions were carried out with phenylacetylene **258** (2.5 mmol), piperazine **212c** (0.25 mmol), CuI (0.25 mmol) and dichloroethane (10 mL). [b]isolated yield, the products were confirmed by physical data and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) and comparison with reported data.[94] [c]5.0 mmol of K_3PO_4 was used.

The piperazine/CuI catalyzed dimerization of phenylacetylene can be explained by considering the mechanism given in Scheme **85**.[131b]

Scheme 85.



Though the homocoupling of terminal alkynes are well studied and various catalyst systems have been developed for this reaction, the piperazine/CuX catalyst system has some advantages. An interesting possibility is trapping of the piperazine-copper-alkynyl intermediate by electrophiles so as to achieve chirality transfer. It may be worthwhile to direct future studies towards these objectives.

2. 9 Conclusions

Preliminary studies on the synthetic applications of the **(**1*R*,2*R*)-1,2-di(4-methylphenylsulfonamido)cyclohexane ligand in enantioselective Kulinkovich reaction, lead to the observation that the 2,3-diarylpiperazines could be obtained by the reductive coupling of diimines. The *trans*-(±)-2,3-diarylpiperazines were obtained in the yields up to 83% in the intramolecular reductive coupling of diimines catalyzed by $TiCl_2$(O*i*-Pr)$_2$/Zn reagent system.

The racemic 2,3-diphenylpiperazine obtained in this way was resolved using L-(+)-tartaric acid. In two successive resolution operations, samples with >99% ee were obtained. The configuration of the (-)-enantiomer was assigned (*S*,*S*) by single crystal X-ray analysis of the corresponding tartrate salt. When the resolution of racemic 2,3-diphenylpiperazine was carried out by using (1*S*)-(+)-10-camphorsulfonic acid, enantiomerically pure (*R*,*R*)-2,3-diphenylpiperazine was obtained with 98% ee in a single step. Based on the concept of homochiral/heterochiral aggregates, the partially resolved non-racemic sample of 2,3-diphenylpiperazine was enantiomerically enriched to obtain samples with higher ee's using different achiral dicarboxylic acids.

Chiral titanium reagents derived from different chiral ligands such as bis-sulfonamide, BINOL, pinane-diol, TADDOL and hemisalen ligands were developed for the enantioselective intramolecular reductive cyclizations of diimines. Using the chiral titanium reagents derived from the hemisalen ligands, the chiral 2,3-diarylpiperazines were obtained in up to 97% ee.

Chiral 2,3-disubstituted piperazines and Chiral diamines derived from 1,2-diaminocyclohexane were examined in the aldol reaction of arylaldehydes with acetone. The enantioselectivity up to 31% ee was achieved in this reaction.

The applications of CuCl/chiral piperazines as catalysts in the dimerization of 2-naphthol in the presence of oxygen was tested. In this reaction, the BINOL was obtained in moderate yield (up to 60%) without any enantioselectivity.

A simple catalyst system consisting of the easily accessible piperazine systems was developed for the *N*-arylation of indole. The electronic control by the substituent of the phenyl ring over the reaction was studied. It was observed that the piperazines are oxidatively cleaved to diimines in the presence of oxygen under these reaction conditions. Based on this observation, a new catalyst system diimine/CuI was also developed for the *N*-arylation of indole.

In the homocoupling reaction of phenylacetylene catalyzed by 2,3-diphenylpiperazine/CuI reagent system, 1,4-diphenyl-1,3-butadiyne was obtained in up to 95% yield in presence of oxygen and molecular sieves.

3. Experimental Section

3.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra and the neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz)) and ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and tetramethylsilane as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal tetramethylsilane. Mass spectral analyses for the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{o}$) and AUTOPOL-IV (readability $\pm 0.001^{o}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*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 mesh and 230-400 mesh), and neutral alumina.

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

all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive 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 was used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ or Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy. Ultrasonication was carried out in a sonorex washing bath (BANDELIN electronic, type RK31H, 120W, 35 kHz).

Dichloromethane, 1,2-dichloroethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Titanium(IV) chloride was supplied by E-Merck, India. Triethylamine was distilled over CaH_2 and stored over KOH pellets. (*S*)-Phenylalanine and (*R*)-phenylglycine were supplied by Aldrich, USA. Iodine, thionyl chloride, 2-bromopropane and bromoethane were supplied by E-Merck (India). All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents before use.

The X-ray diffraction measurements for the respective compounds were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. The data were reduced using SAINT program,[132] without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).[133]

3.2 Resolution of 1,2-diaminocyclohexane

A reported procedure was followed.[134] A 250 mL beaker was charged with L(+)-tartaric acid (37.5 g, 250 mmol) and distilled water (100 mL). The mixture was stirred at room temperature until complete dissolution occurred. At this point, a mixture of *cis/trans*-1,2-diaminocyclohexane (60 mL, 500 mmol) was added at a rate such that the reaction temperature is below 70 ˚C. To the resulting solution, glacial acetic acid (25 mL) was added at a rate such that the reaction temperature is below 90 ˚C. The precipitate formed immediately upon the addition of glacial acetic acid and the slurry was vigorously stirred. It was cooled to 25 ˚C over a period of 2 hours. The mixture was cooled to 5 ˚C for 2 hours and the precipitate was collected by suction filtration. The wet cake was washed with cooled water (25 mL) followed by cold methanol till the cake turned to white solid. The product was dried to obtain (*R,R*)-*trans*-1,2-diammoniumcyclohexane mono-(+)-tartrate salt.

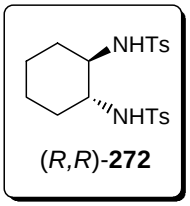
Yield: 111 g (85%).

The (*R,R*)-*trans*-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (42 g, 159 mmol) was taken in a separatory funnel. Approximately, 30 g of KOH dissolved in

water (20 mL) was added. It was shaken well and the amine layer was separated. The (*R,R*)-*trans*-1,2-diaminocyclohexane was distilled under reduced pressure.

3.3 Synthesis of (*1R,2R*)- 1,2-di(4-methylbenzene-sulfonamido)cyclohexane

To a cooled (-40 °C) solution of (*R,R*)-1,2-diaminocyclohexane (2.28 g, 20 mmol) in CH_2Cl_2 (50 mL) was added *N,N*-diisopropylethylamine (11.6 g, 15.5 mL, 90 mmol). After 10 minutes, a solution of *p*-toluenesulfonyl chloride (7.7 g, 40 mmol) in CH_2Cl_2 (100 mL) was added in drops at -40 °C. The mixture was allowed to warm to room temperature. After being stirred for 30 minutes, the mixture was poured in to 1N HCl (150 mL), and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was recrystallized from CH_2Cl_2–hexanes mixture to give (*R,R*)-**272** as colourless crystals.



(*R,R*)-**272**

Yield 7.0 g (83%).

mp 170-172 °C (lit.[101b] 172-174 °C).

IR (KBr) (cm^{-1}) 3288, 3060, 2930, 2872, 1597, 1327, 1153.

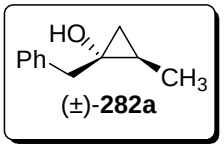
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.01-1.18 (m 4H), 1.51-1.59 (m, 2H), 1.82-1.90 (m, 2H), 2.44 (s, 6H), 2.67-2.78 (m, 2H), 4.77 (d, *J* = 5.6 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 4H), 7.76 (d, *J* = 8.4 Hz, 4H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.5, 24.1, 33.0, 56.6, 127.2, 129.8, 137.2, 143.5.

3.4 General procedure for the enantioselective Kulinkovich reaction

(*R,R*)-Bis(sulfonamide) **272** (0.25 g, 0.6 mmol), magnesium turnings (0.4 g, 16 mmol) and 2-bromopropane (0.25 g, 0.2 mL, 2 mmol) were taken in 20 mL of dry THF under N_2 atmosphere at 25 °C. It was stirred for 20 minutes at 25 °C. Then, $TiCl_4$ (95 mg, 0.055 mL, 0.5 mmol) was added at 25 °C. Then, the ester (3 mmol) and 2-bromopropane (1.25 g, 1 mL, 10 mmol) were taken in 20 mL dry THF and added dropwise to the reaction mixture for 2 h at 25 °C. The reaction mixture was stirred for 1 h at 25 °C. The reaction was quenched with 30 mL of 10% H_2SO_4 at 0 °C and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extract was washed with water, brine solution (10 mL) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ester was eluted using 1:99 EtOAc/hexane mixture. The corresponding cyclopropanol was eluted using 2:98 EtOAc/hexane mixture.

1-Benzyl-2-methyl-cyclopropanol



(±)-**282a**

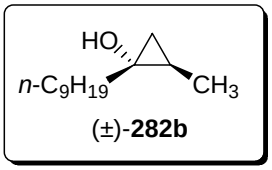
Yield 0.38 g (60%).

IR (neat) (cm^{-1}) 3361, 3064, 3028, 2954, 2929, 1600, 1494, 1454, 1238, 709.

^1H NMR (200 MHz, $CDCl_3$, δ ppm): 0.27-0.35 (m, 1H), 0.86-1.01 (m, 2H), 1.18 (s, 3H), 1.94 (s, 1H), 2.92 (dd, *J* = 13.67 Hz, 20.50 Hz, 14.65 Hz, 2H) , 7.23-7.38 (m, 5H) **(Spectrum No 1)**.

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 14.9, 19.5, 20.6, 39.6, 58.9, 126.4, 128.5, 129.5, 138.9 **(Spectrum No 2)**.

2-Methyl-1-nonyl-cyclopropanol



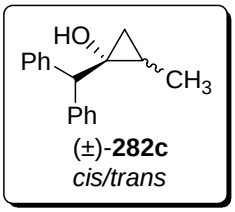
Yield 0.14 g (38%).

IR (neat) (cm^{-1}) 3325, 3068, 2925, 2854, 1461.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): -0.05-0.06 (m, 1H), 0.74-0.93 (m, 4H), 0.99 (s, 3H), 1.25 (br s, 13H), 1.51 (br s, 4H) **(Spectrum No 3)**.

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 14.0, 14.1, 19.5, 20.6, 22.6, 25.9, 29.3, 29.6, 29.7, 29.9, 31.9, 33.9, 58.8 **(Spectrum No 4)**.

1-Benzhydryl-2-methyl-cyclopropanol



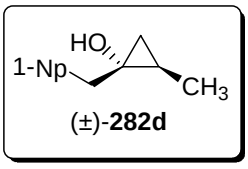
Yield 0.42 g (60%).

IR (neat) (cm^{-1}) 3527, 3440, 3026, 2954, 2927, 1598, 1492, 1450, 1197.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.47-0.61 (m, 1H), 0.89-1.17 (m, 2H), 1.23, 1.39 (2d, J = 6.84 Hz, 5.86 Hz, 3H), 2.24, 2.14 (br s, 1H), 3.96 (s, 1H), 7.33-7.64 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 12.6, 15.1, 18.5, 19.5, 20.1, 21.7, 53.8, 58.9, 60.7, 61.3, 126.5, 126.7, 128.5, 129.5, 129.6, 129.8, 142.2, 142.3, 143.0.

2-Methyl-1-naphthalen-1-ylmethyl-cyclopropanol



Yield 0.28 g (40%).

IR (neat) (cm^{-1}) 3340, 3036, 2952 2930, 1594, 1497, 1459.

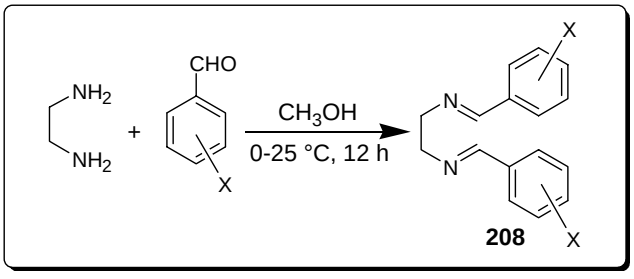
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.41 (m, 1H), 0.83-1.01 (m, 2H), 1.24 (s, 3H), 1.56 (br s, 1H), 3.42 (dd, *J* = 14.65 Hz, 17.58 Hz, 16.60 Hz 2H), 7.40-8.18 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 14.9, 19.8, 21.2, 35.7, 58.5, 124.3, 125.7, 125.9, 126.8, 127.1, 127.8, 128.9, 133.0, 134.1, 135.1.

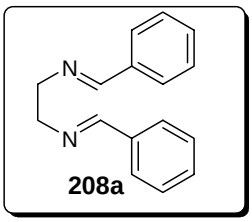
(The spectral data of the cyclopropanols **282a-d** are compared with the spectral data of similar compounds reported in the literature.[104])

3.5 General procedure for the preparation of diimines derived from ethylenediamine and aryl aldehydes

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 ^{o}C slowly in drops. Then the contents were brought to room temperature and stirred for 12 h. The solvent and the 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. For measuring the melting point, the imines were recrystallized from methanol.



_N,N'_-Dibenzylidineethane-1,2-diamine



208a

mp 38-40 °C (lit.[135] 37-39 °C).

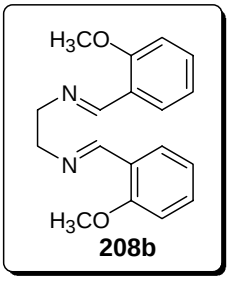
Yield 11.3 g (95%).

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

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

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

_N,N'_-Bis(2-methoxybenzylidine)ethane-1,2-diamine



208b

Yield 13.2 g (90%).

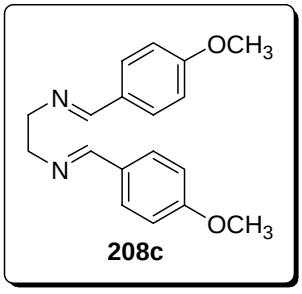
mp 112-114 °C (lit.[136] 116-118 °C).

IR (KBr) (cm^{-1}) 3031, 2914, 2843, 1633, 1601.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 3.81 (s, 6H), 3.96 (s, 4H), 6.85-6.99 (m, 4H), 7.33-7.47 (m, 2H), 7.91 (d, 2H, J = 5.8 Hz), 8.71 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 55.4, 61.9, 111.0, 120.7, 124.9, 127.4, 131.7, 158.2, 158.7.

_N,N'_-Bis(4-methoxybenzylidine)ethane-1,2-diamine



208c

Yield 13.5 g (93%).

mp 106-108 °C (lit.[137] 110-111 °C).

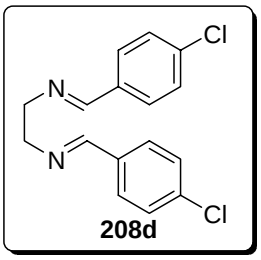
IR (KBr) (cm^{-1}) 3033, 2917, 2851, 1643, 1604.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 3.83 (s, 6H),

3.91 (s, 4H), 6.89 (d, 4H, *J* = 8.8 Hz), 7.63 (d, 4H, *J* = 8.8 Hz), 8.21 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 55.3, 61.7, 114.0, 129.3, 129.6, 161.5, 161.8.

_N,N'_-Bis(4-chlorobenzylidine)ethane-1,2-diamine



208d

Yield 14.2 g (93%).

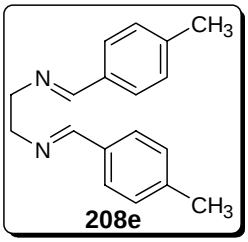
mp 140-142 °C (lit.[136] 144-145 °C).

IR (KBr) (cm^{-1}) 3031, 2916, 2855, 1645, 1593.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 3.95 (s, 4H), 7.35 (d, 4H, *J* = 8.8 Hz), 7.62 (d, 4H, *J* = 8.8 Hz), 8.23 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 61.5, 128.9, 129.3, 134.6, 136.7, 161.3.

_N,N'_-Bis(4-methylbenzylidine)ethane-1,2-diamine



208e

Yield 11.5 g (90%).

mp 152-154 °C (lit.[138] 156-157 °C).

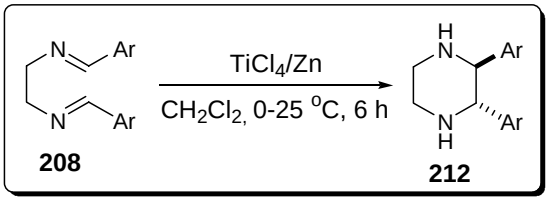
IR (KBr) (cm^{-1}) 3029, 2914, 2849, 1633, 1601.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 2.36 (s, 6H), 3.94 (s, 4H), 7.18 (d, 4H, *J* = 8.8 Hz), 7.58 (d, 4H, *J* = 8.8 Hz), 8.24 (s, 2H).

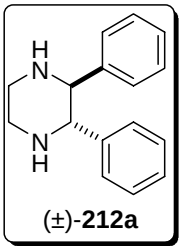
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 21.5, 61.7, 128.1, 129.3, 133.7, 140.8, 162.5.

3.6 General procedure for the intramolecular reductive coupling of diimines using Zn and $TiCl_4$

To the $TiCl_4$ (2.08 g, 1.21 mL, 11.0 mmol) solution in CH_2Cl_2 (40 mL), activated zinc powder (1.65 g, 25.0 mmol) was added in three portions under nitrogen and the stirring was continued for one hour. Then, diimine (5.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added in drops through dropping funnel at 0 °C. After the addition was completed, the reaction mixture was stirred at 25 °C for 5-6 hours. The reaction mixture was poured into saturated aqueous K_2CO_3 solution at 0 °C and filtered. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with water, brine solution and dried using anhydrous K_2CO_3. The solvent was evaporated and the product was purified by flash column chromatography (Silica gel, $CHCl_3$ and then $CHCl_3/CH_3OH$ = 9/1).



(±)-2,3-Diphenylpiperazine



Yield 0.72 g (60%).

mp 94-96 °C (lit.[69] 96-98 °C).

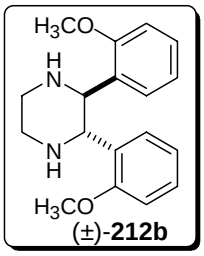
IR (KBr) (cm^{-1}) 3318, 3280, 3030, 2949, 2820, 1603.

^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.00 (br s, 2H), 3.15 (s, 4H), 3.72 (s, 2H), 7.02-7.12 (m, 10H) **(Spectrum No 5)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.9, 67.7, 128.1, 129.3, 133.0, 139.7 **(Spectrum No 6)**.

MS (EI) *m/z* 238 (M^+) **(Spectrum No 7)**.

(±)-2,3-Bis(2-methoxyphenyl)piperazine



(±)-**212b**

Yield 0.86 g (58%).

mp 106-108 °C.

IR (KBr) (cm^{-1}) 3314, 3032, 3006, 2955, 1605.

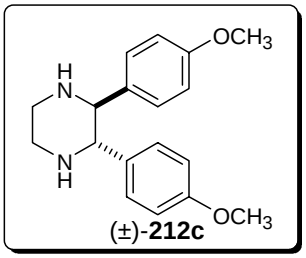
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.96 (br s, 2H), 3.10 (s, 4H), 3.56 (s, 6H), 4.30 (s, 2H), 6.61 (d, 2H, *J* = 8.8 Hz), 6.76 (t, 2H, *J* = 6.8 Hz), 7.04 (t, 2H, *J* = 6.8 Hz), 7.28 (d, 2H, *J* = 8.8 Hz) **(Spectrum No 8)**.

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 46.9, 55.1, 59.9, 110.2, 120.1, 127.9, 128.9, 129.2, 157.0 **(Spectrum No 9)**.

MS (EI) *m/z* 298 (M^+) **(Spectrum No 10)**.

(The spectral data of the compound **212b** are compared with the spectral data of similar compounds reported in the literature.[69])

(±)-2,3-Bis(4-methoxyphenyl)piperazine



(±)-**212c**

Yield 0.67 g (45%).

mp 96-98 °C (lit.[69] 96-98 °C).

IR (KBr) (cm^{-1}) 3271, 3040, 3003, 2957, 1612.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.27 (br s, 2H), 3.10

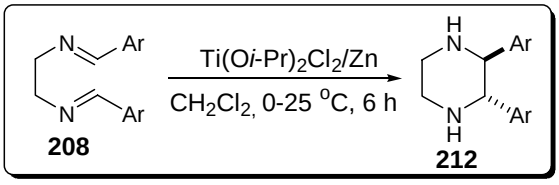
(s, 4H), 3.63 (s, 2H), 3.70 (s, 6H), 6.65 (d, 4H, *J* = 8.0 Hz), 7.00 (d, 4H, *J* = 8.0 Hz) **(Spectrum No 11)**.

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 45.4, 54.0, 65.8, 112.3, 128.0, 131.8, 157.7 **(Spectrum No 12)**.

MS (EI) *m/z* 298 (M^+) **(Spectrum No 13)**.

3.7 General procedure for the intramolecular reductive coupling of diimines using Zn and Ti(*i*-OPr)$_2$Cl$_2$

To the $TiCl_4$ (1.04 g, 0.60 mL, 5.5 mmol) solution in CH_2Cl_2 (40 mL), Ti(O*i*-Pr)$_4$ (1.56 g, 5.5 mmol) was added under nitrogen and stirred for 10-15 min. To this, activated zinc powder (1.65 g, 25.0 mmol) was added in three portions and the stirring was continued for another one hour. Then, diimine (5.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added in drops through dropping funnel at 0 °C. After the addition was completed, the reaction mixture was stirred at 25 °C for 5-6 hours. The reaction mixture was poured into saturated aqueous K_2CO_3 solution at 0 °C and filtered. The procedure outlined in experiment **3.3** was followed.



208 **212**

(±)-2,3-Diphenylpiperazine

Yield 83% (0.99 g).

mp 94-96 °C.

(±)-2,3-Bis(2-methoxyphenyl)piperazine

Yield 73% (1.08 g).

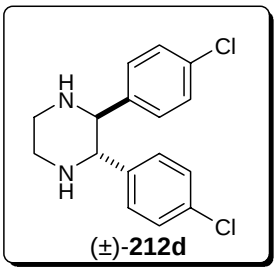
mp 106-108 °C.

(±)-2,3-Bis(4-methoxyphenyl)piperazine

Yield 75% (1.12 g).

mp 96-98 °C.

(±)-2,3-Bis(4-chlorophenyl)piperazine



(±)-**212d**

Yield 80% (1.23 g).

mp 119-120 °C.

IR (KBr) (cm^{-1}) 3317, 3047, 3003, 2947, 2893, 1593.

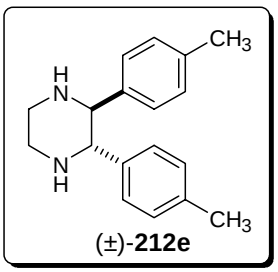
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.91 (br s, 2H), 3.11 (s, 4H), 3.60 (s, 2H), 6.99 (d, 4H, *J* = 8.4 Hz), 7.10 (d, 4H, *J* = 8.4 Hz) **(Spectrum No 14)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.9, 67.7, 128.1, 129.3, 133.0, 139.7 **(Spectrum No 15)**.

MS (EI) *m/z* 306 (M^+) **(Spectrum No 16)**.

(The spectral data of the compound showed 1:1 correspondence with the reported data.[78])

(±)-2,3-Bis(4-methylphenyl)piperazine



(±)-**212e**

Yield 76% (1.01 g).

mp 128-130 °C (lit.[69] 96-98 °C).

IR (KBr) (cm^{-1}) 3321, 3024, 3003, 2953, 2814, 1598.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.88 (br s, 2H),

2.23 (s, 6H), 3.13 (s, 4H), 3.68 (s, 2H), 6.93 (d, 4H, *J* = 7.6 Hz), 6.98 (d, 4H, *J* = 7.6 Hz) **(Spectrum No 17)**.

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.1, 47.2, 67.8, 128.0, 128.5, 136.6, 138.7 **(Spectrum No 18)**.

MS (EI) *m/z* 266 (M^+) **(Spectrum No 19)**.

3.8 HPLC analysis of the trifluoroacetamide derivatives of (±)-2,3-diarylpiperazines

The piperazine **212** (0.5 mmol) in CH_2Cl_2 (10 mL) was stirred overnight with excess trifluoroacetic anhydride (TFAA). The solution was concentrated under reduced pressure to remove the solvent and excess TFAA. The residue recrystalised from hexane/CH_2Cl_2 (99:1) mixture. The trifluoroacetamide derivatives **285** obtained in this way were dissolved in isopropanol (~10 mg/mL) and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd. with a binary gradient method using hexanes:isopropanol (98:2) in the flow rate of 0.5 mL/min. Retention time for the trifluoroacetamide derivatives of 2,3-diphenylpiperazine **285a** is 10.5 minutes for the (*R*,*R*) and 12.3 minutes for the (*S*,*S*).

3.9 HPLC analysis of (±)-2,3-diphenylpiperazine

The (±)-2,3-diphenylpiperazine **212a** was dissolved in isopropanol (~10 mg/mL) and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd. with a binary gradient method using hexanes:isopropanol

(90:10) in the flow rate of 0.5 mL/min. Retention time for the enantiomers of (±)-2,3-diphenylpiperazine is 11.8 minutes (*S,S*) and 14.7 minutes (*R,R*).

3.10 Resolution of (±)-2,3-diphenylpiperazine

3.10.1 Resolution of (±)-2,3- diphenylpiperazine using L-(+)-tartaric acid

The L-(+)-tartaric acid (1.50 g, 10.0 mmol) and (±)-*trans*-2,3-diphenylpiperazine **212a** (2.40 g, 10.0 mmol) were taken in CH_2Cl_2 (250 mL) and the contents were stirred at 25 °C for 6 hours and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enriched (*S,S*)-(-)-**212a**. The filtrate was digested with aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enriched (*R,R*)-(+)-**212a**.

After decomposition

From precipitate

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

Yield	0.79 g (33%).
Enantiomeric purity	61% ee from HPLC.

From filtrate

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

Yield 1.51 g (63%).

Enantiomeric purity 15% ee from HPLC.

3.10.2 Purification of nonracemic 2,3-diphenylpiperazine using L-(+)-tartaric acid

To a solution of nonracemic 2,3-diphenylpiperazine (*S*,*S*)-**212a** (61% ee, 0.60 g, 2.5 mmol) in CH_2Cl_2 (60 mL), L-(+)-tartaric acid (0.38 g, 2.5 mmol)) was added and the contents were stirred at room temperature for 12 hours and filtered. The procedure outlined in experiment 1.4.5.1 was followed The enriched (*S*,*S*)-(-)-**212a** was obtained from the precipitate and the (*S*,*S*)-(-)- **212a** with lower ee was obtained from the filtrate.

After decomposition

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

From precipitate

Yield 0.21 g (35%).

Enantiomeric purity >99% ee from HPLC.

From filtrate

Yield 0.36 g (61%).

Enantiomeric purity 38% ee from HPLC.

3.10.3 Resolution of (±)-*trans*-2,3-diphenylpiperazine 212a using dibenzoyl-L-(-)-tartaric acid

The dibenzoyl-L-(-)-tartaric acid (4.48 g, 12.5 mmol) and (±)-*trans*-2,3-diphenylpiperazine **212a** (6.00 g, 25 mmol) were taken in THF (125 mL) and the contents were stirred at 25 °C for 2 hours and filtered. The procedure outlined in experiment 1.4.5.1 was followed. The enriched (*R*,*R*)-(+)- **212a** enantiomer was obtained from the precipitate and the enriched (*S*,*S*)-(-)-**212a** enantiomer was obtained from the filtrate.

After decomposition

From precipitate

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

Yield 2.64 g (44%).

Enantiomeric purity 20% ee from HPLC.

From filtrate

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

Yield 3.02 g (50%).

Enantiomeric purity 45% ee from HPLC.

3.10.4 Resolution of (±)-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid

The (1*S*)-(+)-10-camphorsulfonic acid (4.64 g, 20 mmol) and (±)--2,3-diphenylpiperazine **212a** (2.4 g, 10 mmol) were taken in CH_2Cl_2 (100 mL) and the contents were stirred at 25 °C for 24 hours and filtered. The precipitate(I) was

suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enriched (*R*,*R*)-**212a**. The filtrate was concentrated to reduce its volume by 50 mL and stirred for another 12 hours and filtered. The precipitate(II) was suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enriched (*S*,*S*)-**212a**. The filtrate was stirred with aq. Na_2CO_3 (2M) for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain the enriched (*R*,*R*)-**212a**.

After decomposition

From precipitate (I)

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

Yield 0.60 g (25%).

Enantiomeric purity 98% ee from HPLC.

From precipitate (II)

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

Yield 1.50 g (63%).

Enantiomeric purity 73% ee from HPLC.

From filtrate

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

Yield 0.24 g (10%).

Enantiomeric purity 80% ee from HPLC.

3.11 Enhancement of enantiomeric purity of nonracemic 2,3-diphenylpiperazine 212a using achiral dicarboxylic acids

The partially resolved (*S*,*S*)-(-)-2,3-diphenylpiperazine **212a** (73% ee, 120 mg, 0.50 mmol) was taken in THF (5 mL). To this, achiral dicarboxylic acid (0.30 mmol) was added and the contents were stirred at 25 ^{o}C for 2 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (10 mL) and 2M Na_2CO_3 (5 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 5 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched sample of (*S*,*S*)-(-)-**212a**. The filtrate was evaporated and the residue was taken in CH_2Cl_2 (10 mL) and digested with 2M Na_2CO_3 (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 5 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain the sample of (*S*,*S*)-(-)-**212a** with lower ee.

After decomposition

Using oxalic acid dehydrate (37 mg)

From precipitate

Yield	75 mg (62%).
Enantiomeric purity	97% ee from HPLC.

From filtrate

Yield	38 mg (31%).
Enantiomeric purity	21% ee from HPLC.

Using malonic acid (31 mg)

From precipitate

Yield	78 mg (65%).
Enantiomeric purity	94% ee from HPLC.

From filtrate

Yield	40 mg (33%).
Enantiomeric purity	35% ee from HPLC.

Using succinic acid (36 mg)

From precipitate

Yield	60 mg (50%).
Enantiomeric purity	58% ee from HPLC.

From filtrate

Yield	42 mg (35%).
Enantiomeric purity	95% ee from HPLC.

Using adipic acid (44 mg)

From precipitate

Yield	61 mg (51%).
Enantiomeric purity	46% ee from HPLC.

From filtrate

Yield	50 mg (42%).
Enantiomeric purity	90% ee from HPLC.

Using fumaric acid (35 mg)

From precipitate

Yield	70 mg (58%).
Enantiomeric purity	48% ee from HPLC.

From filtrate

Yield	40 mg (34%).
Enantiomeric purity	94% ee from HPLC.

Using phthalic acid (50 mg)

From precipitate

Yield	72 mg (60%).
Enantiomeric purity	61% ee from HPLC.

From filtrate

Yield	42 mg (35%).
Enantiomeric purity	82% ee from HPLC.

Using isophthalic acid (50 mg)

From precipitate

Yield 70 mg (58%).

Enantiomeric purity 57% ee from HPLC.

From filtrate

Yield 46 mg (38%).

Enantiomeric purity 80% ee from HPLC.

Using terephthalic acid (50 mg)

From precipitate

Yield 61 mg (51%).

Enantiomeric purity 63% ee from HPLC.

From filtrate

Yield 48 mg (40%).

Enantiomeric purity 81% ee from HPLC.

3.12 Reductive coupling of diimine 208a using (*1R,2R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane, Lewis acid and *i*-PrMgBr

In a 50 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed THF (20 mL), activated magnesium (300 mg, 12 mmol), and (*1R,2R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane (*R,R*)-**272** (1.1 g, 2.5 mmol) under nitrogen. To this, 2-bromopropane (1.5 g, 1.2 mL, 12 mmol) in THF (5 mL) was added in drops

through dropping funnel and stirred at 25 °C for 30 min and then cooled to 0 °C. Then, Lewis acid (2.5 mmol, 2M solution in toluene, 1.25 mL) was added slowly and stirred at 0 °C for another 30 min and then brought to the required temperature. To this, *N*,*N*'-dibenzylidene-ethane-1,2-diamine **208a** (240 mg, 1.0 mmol) dissolved in THF (5 mL) was added and the stirring was continued at the same temperature for 24 hours. The reaction mixture was poured into saturated aqueous K_2CO_3 solution at 0 °C and filtered. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic extract was washed with water, brine solution and dried using anhydrous K_2CO_3. The solvent was evaporated and the product was purified by flash column chromatography (Silica, $CHCl_3$ and then $CHCl_3/CH_3OH$ = 9:1). Identical spectral data were obtained for the product as given in the section **3.3** for **206a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.13 Procedure for the reductive coupling of diimine 208a using (*1R,2R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane, Lewis acid and Zn

In a 50 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (20 mL), and Lewis acid (5.0 mmol, 2M solution in toluene, 2.5 mL) under nitrogen. To this (*1R,2R*)-1,2-di(4-methylbenzene-sulfonamido)cyclohexane (*R,R*)-**272** (2.4 g, 5.5 mmol) in CH_2Cl_2 (10 mL) was added in drops stirred at 25 °C for 30 min and then cooled to 0 °C. Then, activated zinc powder (1.65 g, 25 mmol) was added in one portion and stirred at 0 °C for another 30 min and then brought to the required temperature. To this, *N*,*N*'-dibenzylidene-ethane-1,2-diamine **208a** (600 mg, 2.5 mmol)

dissolved in CH_2Cl_2 (10 mL) was added and the stirring was continued at the same temperature for 24 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.14 Procedure for the reductive coupling of diimine 208a using *R*-BINOL, Lewis acid and Zn:

In a 50 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (15 mL), and *R*-BINOL (720 mg, 2.5 mmol) and activated powder molecular sieves (500 mg) under nitrogen. To this, Lewis acid (2.5 mmol, 2M solution in toluene, 1.25 mL) was added and stirred at 25 °C. After 6 hours, activated zinc powder (650 mg, 10 mmol) was added and the stirring was continued for another two hours at 25 °C and then brought to the required temperature. Then, *N*,*N*'-dibenzylidene-ethane-1,2-diamine **208a** (240 mg, 1.0 mmol) dissolved in CH_2Cl_2 (5 mL) was added in drops through dropping funnel. The stirring was continued at the same temperature for 24 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.15 Procedure for the reductive coupling of diimine 208a using (1*R*,2*R*,3*S*,5*R*)-pinanediol,$TiCl_4$ and Zn

In a 25 mL RB flask, containing a magnetic stirring bar protected by mercury trap, were placed CH_2Cl_2 (15 mL), and (1*R*,2*R*,3*S*,5*R*)-pinanediol (1.9 g, 11.0 mmol) under nitrogen. To this, $TiCl_4$ (950 mg, 0.55 mL, 5.0 mmol) was added and stirred for 2 hours. The solvent was removed under vacuum. The solid obtained was dissolved in CH_2Cl_2 (15 mL) under nitrogen, $TiCl_4$ (850 mg 4.5 mmol) was added and stirred for 1 hour. To this, activated zinc powder (1.7 g, 25 mmol) was added and the stirring was continued for another one hour at 25 °C and then brought to the required temperature. Then, *N*,*N*'-dibenzylidene-ethane-1,2-diamine **208a** (960 mg, 4.0 mmol) dissolved in CH_2Cl_2 (5 mL) was added in drops through dropping funnel. After the addition was completed, the reaction mixture was stirred at the same temperature for 24 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.16 Procedure for the reductive coupling of diimines 208a using TADDOL, $TiCl_4$ and Zn

In a 50 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (15 mL), powdered dry K_2CO_3 (1.4 g, 10 mmol) and TADDOL (1.2 g, 2.5 mmol) under nitrogen. To this, $TiCl_4$ (425 mg, 0.30 mL, 2.5 mmol) was added and stirred at 25 °C for 1 hour. Activated zinc powder (325 mg, 5 mmol) was added and the

stirring was continued for another one hour. Then, *N,N*'-dibenzylidene-ethane-1,2-diamine **208a** (240 mg, 1.0 mmol) dissolved in CH_2Cl_2 (5 mL) was added in drops through dropping funnel. After the addition was completed, the reaction mixture was stirred for 36 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.17 Preparation of *R*-2-amino-1,1,2-triphenylethanol *R*-312a

3.17.1 Preparation of *R*-phenylglycine methyl ester hydrochloride

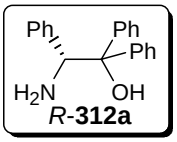
In a 100 ml RB flask, containing a magnetic stirring bar equipped with a reflux condenser, were placed CH_3OH (30 mL), *R*-phenylglycine (1.5 g, 10 mmol). To this, excess of thionyl chloride was added slowly at 0 °C. Then, the contents were refluxed for 2-3 hrs. The solvent was completely removed under vacuum. The solid obtained was dried fully and used as such in the next step.

3.17.2 Reaction of phenylmagnesium bromide with *R*-phenylglycine methyl ester hydrochloride

In a 250 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed THF (100 mL), activated magnesium (2.0 g, 80 mmol) under nitrogen. To this, 2-bromopropane (10.0 g, 8.0 mL, 80 mmol) in THF (40 mL) was added at 0 °C in drops through dropping funnel. After the addition was over, it was slowly warmed to 25 °C and stirred for 2h. To this, *R*-phenylglycine methyl ester hydrochloride (1.87 g, 10

mmol) was added and the stirring was continued for another 24 hours. The reaction was quenched by adding saturated aqueous NH_4Cl slowly at 0 °C. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic extract was washed with water, brine solution and dried using anhydrous K_2CO_3. The solvent was evaporated and the product was purified by flash column chromatography.

***R*-2-Amino-1,1,2-triphenylethanol**



R-**312a**

Yield 1.88 g (65%).

mp 112–114°C (lit.[139] 114-116 °C).

IR (KBr) (cm^{-1}) 3371, 3311, 3061, 3031, 2928, 2888.

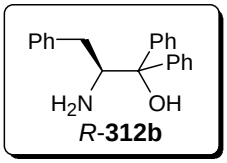
^1H NMR (200 MHz, $CDCl_3$, δ ppm) 1.58 (br s, 2H), 4.68 (br s, 1H), 5.02 (s, 1H), 7.01–7.13 (m, 9H), 7.17–7.41 (m, 4H), 7.76 (d, 2H, J = 6.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 61.9, 79.7, 126.2, 126.3, 126.6, 127.1, 127.3, 127.4, 127.5, 128.6, 128.8, 140.2, 144.0, 146.6.

3.18 Preparation of *S*-2-amino-1,1,3-triphenylpropan-1-ol *S*-312b

Amino alcohol *S*-**312b** was synthesized from L-phenylalanine according to the procedure given in section **3.17**. L-Phenylalnine methyl ester hydrochloride reacted with an 8-fold excess of phenylmagnesium bromide in THF at room temperature for 24 hrs.

***S*-2-Amino-1,1,3-triphenylpropan-1-ol**



R-**312b**

Yield 70%.

mp 132-136 ºC (lit.[139] 134-136 °C) .

IR (KBr) 3503, 3392, 3337, 3025, 2985, 2923 1599, 1491, 1447.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.20 (s, 2H), 2.47 (dd, 1H, *J* = 10.8 Hz, *J* = 14.0 Hz), 2.68 (d, 1H, *J* = 14.0 Hz), 4.20 (dd, 1H, *J* = 2.4 Hz, *J* = 10.0 Hz), 4.52 (br s, 1H), 7.36–7.19 (m, 11H), 7.63 (d, 2H, *J* = 7.6 Hz), 7.68 (d, 2H, *J* = 7.6 Hz).

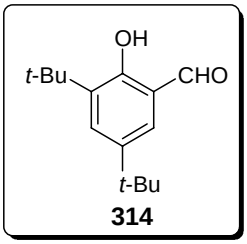
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 36.9, 58.3, 78.7, 125.5, 125.9, 126.5, 126.6, 126.9, 127.2, 127.9, 128.3, 128.6, 128.8, 129.2, 139.8, 144.5, 147.0.

3.19 Preparation of 3,5-di-*t*-butyl-2-hydroxybenzaldehyde 314 (Di-*t*-butylsalicylaldehyde)

In a 200 mL three-necked RB flask containing a magnetic stirring bar and a reflux condenser protected by mercury trap was charged with 2,6-lutidine (2.57 g, 2.80 mL, 24 mmol), 2,4-di-*t*-butylphenol(12.40 g, 60 mmol) and dry toluene (15 mL). To this, $SnCl_4$ (1.56 g, 0.70 mL, 6 mmol) was added drop wise to the solution. The heterogeneous yellow mixture was stirred at room temperature under nitrogen for 1 h. Then anhydrous paraformaldehyde (6.0 g, 200 mmol) was added and the mixture was heated to 100 °C. After 3 h, the mixture was allowed to cool to room temperature, and stirring was continued while 100 mL of water was added to the flask. The thick mixture was transferred to a separatory funnel, and the flask was rinsed with an additional 100-mL portion of water. The aqueous layer was acidified to approximately pH 2 with 2N HC1 and shaken with 150 mL of ether. The resulting emulsion was filtered through Buchner flask to facilitate subsequent phase separation. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 X 50 mL). The combined organic extract was washed with water, brine and dried over sodium sulfate.

The solvent was evaporated and the product was purified by flash column chromatography to obtain 3,5-di-*t*-butylsalicylaldehyde as fine, pale yellow solid in 70 % yield.

3,5-Di-*t*-butylsalicylaldehyde



314

Yield 9.80 g (70%).

mp 56-58 °C (lit.[140] 54-56 °C).

IR (KBr) (cm^{-1}) 3420, 2959, 2868, 2743, 1651, 1610, 1481.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.37 (s, 9H), 1.47 (s, 9H), 7.39 (d, 1H, *J* = 2.4 Hz), 7.64 (d, 1H, *J* = 2.4 Hz), 9.91 (s, 1H), 11.69 (s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 29.3, 31.3, 34.3, 35.0, 120.0, 127.9, 131.9, 137.6, 141.6, 159.1, 197.3.

3.20 Representative procedure for the enantioselective intramolecular reductive coupling of diimines 208 (using *in situ* prepared 10 mol% chiral titanium complex 310b, 310d and Zn)

In a 50 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (10 mL), 2-hydroxy-3,5-di(tertiarybutyl)benzaldehyde (180 mg, 0.6 mmol), *R*-2-amino-1,1,2-triphenylethanol (175 mg, 0.6 mmol), and 4 Å molecular sieves (500 mg) under nitrogen and stirred for 6-8 hours. To this, Ti(O*i*-Pr)$_4$ (142 mg, 0.15 mL, 0.5 mmol) and THF (1 mL) were added and the stirring was continued for another one hour. Then the chiral titanium complex was formed by the addition of TMSCl (110 mg, 0.13 mL, 1.0 mmol) in CH_3CN (5 mL), followed by stirring for 15 min. To this, activated

zinc powder (653 mg, 10.0 mmol) was added and the stirring was continued for another one hour and then brought to the required temperature. Then, diimine (2.5 mmol) dissolved in CH_2Cl_2 (10 mL) was added in drops through dropping funnel. After stirring for 20-30 min, TMSCl (550 mg, 0.65 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) was added in drops through dropping funnel for 3-4 hours. After the addition was completed, the reaction mixture was stirred at the same temperature for 24 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

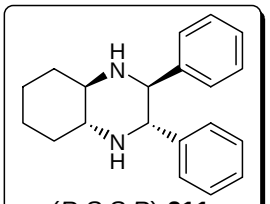
3.21 Representative procedure for the enantioselective intramolecular reductive coupling of diimines 208 (using stoichiometric amount of chiral titanium complex 310a-310d and Zn)

In a 25 mL two necked RB flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (5 mL), 2-hydroxy-3,5-di(tertiarybutyl)benzaldehyde (340 mg, 1.1 mmol), *R*-2-amino-1,1,2-triphenylethanol (320 mg 1.1 mmol) and 4 Å molecular sieves (1.0 g) under nitrogen and stirred for 6-8 hours. To this, Ti(O*i*-Pr)$_4$ (284 mg, 0.30 mL, 1.0 mmol) and THF (1 mL) were added and the stirring was continued for another 1 hour. Then the chiral titanium complex **310b** was formed by the addition of TMSCl (220 mg, 0.26 mL, 2.0 mmol) in CH_3CN (5 mL), followed by stirring for 15 min. To this, activated zinc powder (325 mg, 5.0 mmol) was added and the stirring was continued for another one hour and then brought to the required temperature. Then, diimine (0.5

mmol) dissolved in CH_3CN (5 mL) was added in drops through dropping funnel. After the addition was completed, the reaction mixture was stirred at the same temperature for 24 hours. The procedure outlined in experiment **3.12** was followed. Identical spectral data were obtained for the product as given in the section **3.6** for **212a**. The ee of the product was calculated from HPLC analysis on a Chiralcel OD-H column.

3.22 Procedure for the synthesis of 3,4-diphenyl-2,5-diazabicyclo-[4.4.0]decane using diimines and low-valent titanium reagents

In dry CH_2Cl_2 (100 mL), THF (2 mL) and $TiCl_4$ (3.8 g, 2.2 mL, 20 mmol) were added under N_2 atmosphere at 0 ^oC. Zn dust (2.6 g, 40 mmol) was added with a solid addition flask for 10 min. The reaction mixture was stirred for 0.5 h at 0 ^oC and the imine (5 mmol) in 50 mL of CH_2Cl_2 was added for 15 min. The reaction mixture was stirred for 0.5 h at 0 ^oC and for 12 h at 25 ^oC. It was quenched with saturated K_2CO_3 (30 mL) and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extract was washed with brine solution (20 mL) and dried over anhydrous K_2CO_3. The solvent was removed and the residue was chromatographed on basic alumina column using EtOAc/hexanes mixture as eluent.



(*R*,*S*,*S*,*R*)-**211**

Yield 1.03 g (72%).

mp 60-62 ^oC (lit.[76] 60-62 °C).

IR (KBr) (cm^{-1}) 3220, 3060, 2955.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.32-1.48 (m, 4H), 1.69-1.75 (m, 4H), 1.77 (br s, 2H), 2.58-2.70 (m, 2H), 3.83 (s, 2H), 7.05-7.20 (m, 10H).

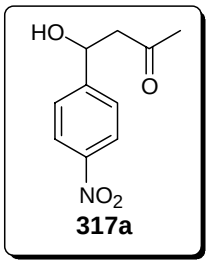
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 24.9, 31.9, 61.6, 68.6, 127.0, 127.6, 128.1, 142.6.

$[\alpha]_D^{25}$ -77.6 (*c* 1, $CHCl_3$).

3.23 Aldol reaction of benzaldehydes with acetone catalyzed by (*S*,*S*)-2,3-diphenylpiperazine under ultrasonication

In a 5 mL sample vial with screw cap containing acetone (2 mL) and DMF (0.5 mL) was taken (*S*,*S*)-2,3-diphenylpiperazine (25 mg, 0.1 mmol) and sonicated for 15 min. The aldehyde (0.5 mmol) was added and sonicated for another 3 hours. After the reaction was over, 2 mL water was added and extracted with diethyl ether (2 x 10 mL). The combined organic extract was washed with brine solution (5 mL), dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the product was purified by flash column chromatography (Silica, Hexanes/EtOAc = 80:20).

(±)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one



317a

Yield 75 mg (70%).

mp 54-56 °C (lit.[141] 53-55 °C).

IR (KBr) (cm^{-1}) 3442, 3083, 2908, 1711, 1605, 1531, 1346.

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 2.18 (s, 3H), 2.82 (d, 2H, *J* = 6.7 Hz) 3.53 (br s, 1H), 5.23 (s, 1H), 7.50 (d, 2H, *J* = 6.7 Hz), 8.13 (d, 2H, *J* = 6.7 Hz).

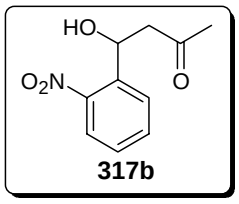
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 30.8, 51.6, 69.0, 123.8, 126.5, 147.5, 150.1, 208.5 **(Spectrum No 20)**.

ee racemic product, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 13.0 (*R* isomer) and 16.3 (*S* isomer)).

(*S*)-4-Hydroxy-4-(2-nitrophenyl)butan-2-one

Yield 88 mg (84%).

IR (neat) (cm^{-1}) 3431, 3075, 2922, 2857, 1711, 1608, 1525, 1348.



317b

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 2.24 (s, 3H), 2.65-3.18 (m, 2H) 3.72 (br s, 1H), 5.68 (d, 1H, *J* = 9.8 Hz), 7.44 (t, 1H, *J* = 7.8 Hz), 7.66 (t, 1H, *J* = 7.8 Hz), 7.89 (d, 1H, *J* = 7.8 Hz), 7.96 (d, 1H, *J* = 7.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 30.4, 51.2, 65.6, 124.4, 128.2, 128.3, 133.8, 138.6, 147.2, 208.5 **(Spectrum No 21)**.

ee 5%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 10.6 (*S* isomer) and 13.4 (*R* isomer)).

(The spectral data of the compound showed 1:1 correspondence with the reported data.[141])

3.24 Aldol reaction of 2-nitrobenzaldehyde with acetone catalyzed by (*R,R*)-2,3-diphenylpiperazine in saturated NH_4Cl solution

In a 5mL RB flask containing acetone (1 mL) and saturated NH_4Cl solution (1 mL) was taken (*R,R*)-2,3-diphenylpiperazine (24 mg, 0.10 mmol). After stirring for 15

min, 2-nitrobenzaldehyde (75 mg, 0.5 mmol) was added and further stirred for 12 hours. After the reaction was over, 5 mL of water was added, extracted with diethyl ether (2 x 10 mL) and the procedure outlined in experiment **3.23** was followed.

(*R*)-4-Hydroxy-4-(2-nitrophenyl)butan-2-one

Yield 100 mg (90%).

ee 10%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 10.6 (*S* isomer) and 13.4 (*R* isomer)).

3.25 Aldol reaction of aryl aldehydes with acetone catalyzed by (*R,S,S,R*)-3,4-diphenyl-2,5-diazabicyclo-[4.4.0]decane in saturated NH_4Cl solution

In a 5mL RB flask containing acetone (1 mL) and saturated NH_4Cl solution (1 mL) was taken (*R,S,S,R*)-3,4-diphenyl-2,5-diazabicyclo-[4.4.0]decane (30 mg, 0.10 mmol). After stirring for 15 min, aldehyde (0.5 mmol) was added and further stirred for 12 hours. After the reaction was over, 5 mL of water was added, extracted with diethyl ether (2 x 10 mL) and the procedure outlined in experiment **3.23** was followed.

***R*-4-Hydroxy-4-(4-nitrophenyl)butan-2-one**

Yield 90 mg (80%).

ee 10%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 13.0 (*R* isomer) and 16.3 (*S* isomer)).

***R*-4-Hydroxy-4-(2-nitrophenyl)butan-2-one**

Yield 85 mg (78%).

ee 12%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 10.6 (*S* isomer) and 13.4 (*R* isomer)).

3.26 Aldol reaction of benzaldehydes with acetone catalyzed by (*R,R*)- *N,N*'-dibenzylcyclohexane-1,2-diamine in saturated NH_4Cl solution:

In a 5mL RB flask containing acetone (1 mL) and saturated NH_4Cl solution (1 mL) was taken (*R,R*)-*N,N*'-dibenzylcyclohexane-1,2-diamine (30 mg, 0.10 mmol). After stirring for 15 min, aldehyde (0.5 mmol) was added and further stirred for 12 hours. After the reaction was over, 5 mL of water was added, extracted with diethyl ether (2 x 10 mL) and the procedure outlined in experiment **3.23** was followed.

***R*-4-Hydroxy-4-(4-nitrophenyl)butan-2-one**

Yield 95 mg (82%).

ee 10%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 13.0 (*R* isomer) and 16.3 (*S* isomer)).

***R*-4-Hydroxy-4-(2-nitrophenyl)butan-2-one**

Yield 85 mg (78%).

ee 31%, HPLC (Chiralpak AS-H, Hexane-IPA = 70:30, Flow rate: 1mL/min, Retention time: 10.6 (*S* isomer) and 13.4 (*R* isomer).

3.27 (*R,R*)-2,3-Diphenylpiperazine/CuCl/O_2 catalyzed oxidative coupling of 2-naphthol

In dry dichloroethane (10 mL), (*R,R*)-2,3-diphenylpiperazine (100 mg, 0.40 mmol), CuCl (40 mg, 0.40 mmol) and 2-naphthol (290 mg, 2.0 mmol) were taken and stirred under oxygen atmosphere using oxygen balloon. After 24 hours stirring, the reaction mixtured was poured in to aqueous ammonia solution and then filtered through

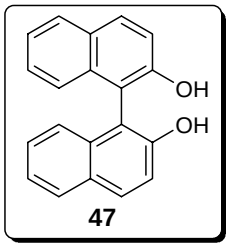
small silica column. The filtrate was evaporated and the product was purified by flash column chromatography (Silica, Hexanes/EtOAc = 95:5).

1,1'-Bi-2,2'-naphthol

Yield 170 mg (60%).

mp 214-216 ^{o}C (lit.[118a] 216-218 °C).

IR (KBr) (cm^{-1}) 3487, 3404, 3049, 1618, 1595, 1510, 1462, 1381, 1321.



47

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 3.89 (s, 2H), 7.03-7.24 (m, 8H), 7.68 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 113.1, 118.0, 123.4, 124.6, 126.8, 128.1, 129.1, 130.3, 134.0, 152.7.

3.28 *N*-Phenylation of indole using (±)-2,3-diarylpiperazine, CuX, PhI and K_3PO_4

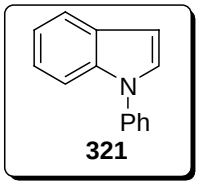
In a 5 mL RB flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, were placed (±)-2,3-diarylpiperazine (0.1 mmol), CuX (0.1 mmol), K_3PO_4 (430 mg, 2.0 mmol), indole (117 mg, 1 mmol) and toluene (2 mL) under nitrogen and stirred for 10-15 min. To this, PhI (310 mg, 1.5 mmol) was added and heated under reflux for 24 hours. The reaction mixture was cooled and filtered through small silica gel column and washed with EtOAc. The filtrate was

evaporated and the product was purified by column chromatography (Silica, Hexane/EtOAc = 99.5/0.5). The product was obtained as colourless oil.

***N*-Phenylindole**

Yield 146 mg (75%).

IR (neat) (cm^{-1}) 3055, 1597, 1498.



321

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 6.70 (d, 1H, *J* = 4.0 Hz), 7.21-7.69 (m, 10H) **(Spectrum No 22)**.

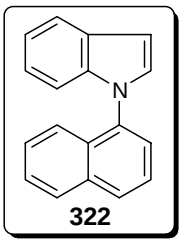
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 103.8, 110.7, 120.6, 121.4, 122.6, 124.6, 126.6, 128.1, 129.6, 130.4, 136.1,140.0 **(Spectrum No 23)**.

(The spectral data of the compound showed 1:1 correspondence with the reported data.[122])

3.29 *N*-Arylation of indole using (±)-2,3-bis(4-methoxyphenyl)piperazine, CuI, ArBr and K_3PO_4

In a 5 mL RB flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, were placed (±)-2,3-bis(4-methoxyphenyl)piperazine (15 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (215 mg, 1.0 mmol), indole (60 mg, 0.5 mmol) and DMF (2 mL) under nitrogen and stirred for 10-15 min. To this, ArBr (0.75 mmol) was added and heated under reflux for 24 hours. The reaction mixture was cooled and filtered through small silica gel column and washed with EtOAc. The filtrate was evaporated and the product was purified by column chromatography (Silica, Hexane/EtOAc = 99.5/0.5).

***N*-(1-Naphthalenyl)indole**



322

1-Bromonaphthalene (155 mg, 0.75 mmol) was used.

Yield 100 mg (82%).

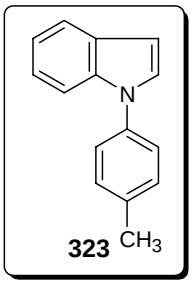
mp 74-76 °C (lit.[122] 76-78 °C).

IR (KBr) (cm^{-1}) 3048, 1593, 1578, 1508.

^1H NMR (200 MHz, $CDCl_3$, δ ppm): 6.78 (d, 1H, *J* = 2.8 Hz), 7.03-7.78 (m, 9H), 7.76 (d, 1H, *J* = 6.8 Hz) 7.96 (br s, 1H), 8.00 (d, 1H, *J* = 2.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 103.0, 110.9, 120.2, 121.0, 122.2, 123.5, 125.2, 125.6, 126.7, 127.0, 128.3, 128.5, 129.8, 130.7, 134.6, 136.2, 138.1 **(Spectrum No 24)**.

***N*-(4-Methylphenyl)indole**



323

4-Bromotoluene (130 mg, 0.75 mmol) was used.

Yield 98 mg (95%).

IR (neat) (cm^{-1}) 3032, 2922, 2860, 1608, 1520, 1456.

^1H NMR (200 MHz, $CDCl_3$, δ ppm): 2.44 (s, 3H), 6.67 (d, 1H, *J* = 4.0 Hz), 7.19-7.71 (m, 9H) **(Spectrum No 25)**.

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.1, 103.3, 110.6, 120.3, 121.1, 122.3, 124.4, 128.1, 129.3, 130.2, 136.1, 136.4, 137.4 **(Spectrum No 26)**.

(The spectral data of the compound showed 1:1 correspondence with the reported data.[122])

3.30 Procedure for the oxidative cleavage of 2,3-diarypiperazine

In a 5 mL RB flask containing toluene (2 mL), CuI (100 mg, 0.5 mmol), K_3PO_4 (210 mg, 1.0 mmol) was taken 2,3-diarylpiperazine **212** (0.5 mmol) and heated under reflux for 12 hours. After cooling the reaction mixture, the inorganic solid was filtered through small silica gel column and the filtrate was concentrated under reduced pressure. The % of conversion of piperazine to diimine was calculated from the integration value of ^{1}H NMR signals.

3.31 *N*-Phenylation of indole using diimine/CuI/ K_3PO_4 reagent system

In a 5 mL RB flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, were placed *N*,*N*'-dibenzylidene-ethane-1,2-diamine (12 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (215 mg, 1.0 mmol), indole (60 mg, 0.5 mmol) and toluene (2 mL) for 10-15 min. To this, PhI (310 mg, 1.5 mmol) was added and heated under reflux for 24 hours. The procedure outlined in experiment **3.28** was followed. Identical spectral data were obtained for the product as given in the section **3.28** for **321**.

***N*-Phenylindole**

Yield 185 mg (96%).

3.32 *N*-Arylation of indole using *N*,*N*'-bis-(4-methoxybenzylidene)-ethane-1,2-diamine, CuI, ArX and K_3PO_4

In a 5 mL RB flask, containing a magnetic stirring bar equipped with a reflux condenser protected by mercury trap, were placed *N*,*N*'-bis-(4-methoxybenzylidene)-

ethane-1,2-diamine (15 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (220 mg, 1.0 mmol), indole (60 mg, 0.5 mmol) and DMF (2 mL) under nitrogen and stirred for 10-15 min. To this, ArX (0.75 mmol) was added and heated under reflux for 24 hours. The procedure outlined in experiment **3.29** was followed.

***N*-(1-Naphthalenyl)indole**

1-Bromonaphthalene (155 mg, 0.75 mmol) was used.

Yield 100 mg (82%).

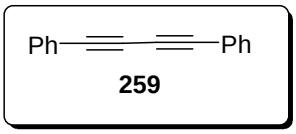
***N*-(4-Methylphenyl)indole**

4-Bromotoluene (130 mg, 0.75 mmol) was used.

Yield 98 mg (95%).

3.33 Synthesis of 1,3-diynes using (±)-2,3-diarylpiperazine/CuI

In dry dichloroethane (10 mL), 4 Å molecular sieves (1.0 g), (±)-2,3-bis(4-methoxyphenyl)piperazine (75 mg, 0.25 mmol) and CuCl (25 mg, 0.25 mmol) were taken and sonicated for 5 min. Phenylacetylene (255 mg, 0.27 mL, 2.5 mmol) was added and stirred at 25 °C under O_2 atmosphere using oxygen balloon for 48 hours and then filtered. The filtrate was evaporated and the product was purified by column chromatography (Silica, Hexanes). The product was obtained as a white solid.



259

Yield 94% (240 mg).

mp 84-86 °C (lit.[94] 88 °C).

IR (KBr) (cm^{-1}) 3053, 748, 693.

^1H NMR (200 MHz, $CDCl_3$, δ ppm): 7.3-7.4 (m, 6H), 7.5-7.6 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 74.0, 81.7, 121.9, 128.5, 129.2, 132.6.

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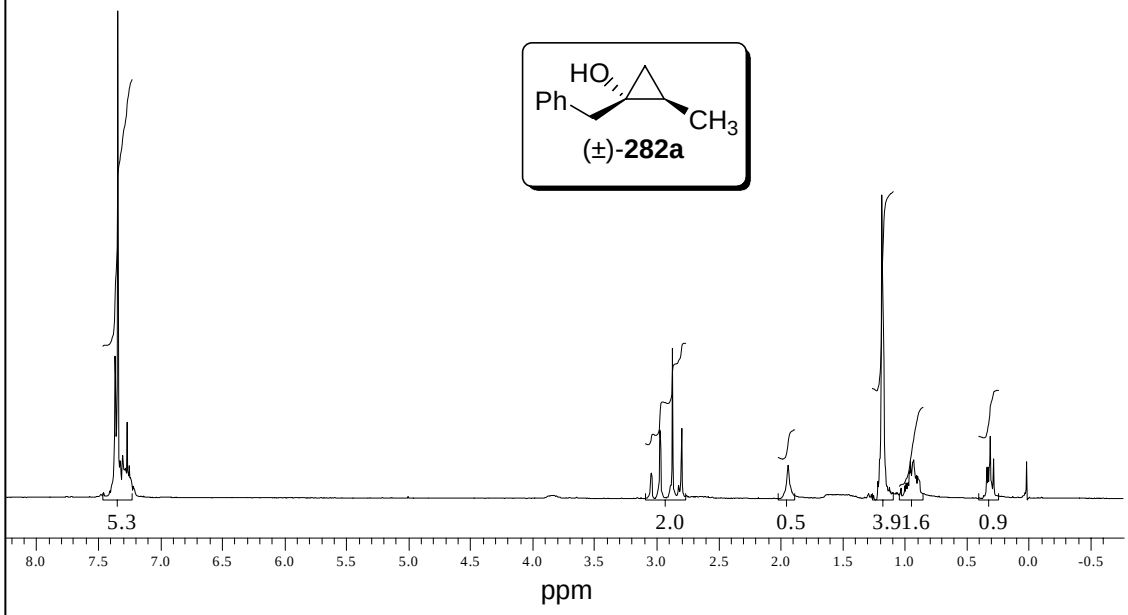
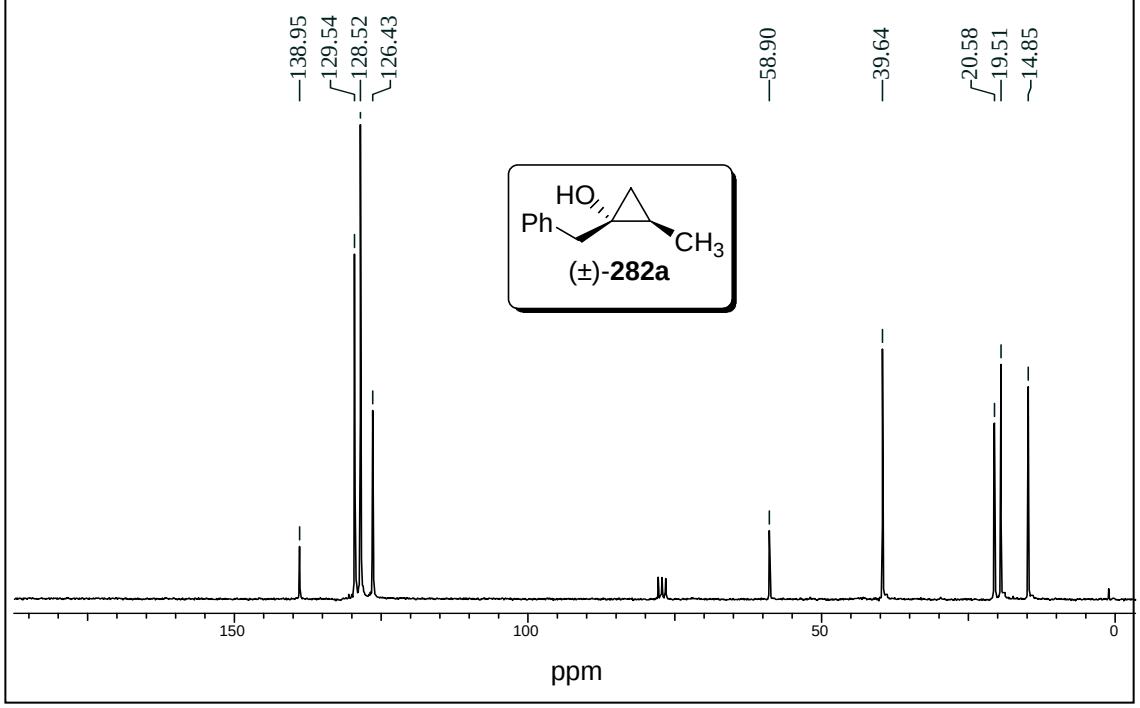
Appendix I

(Representative Spectra)

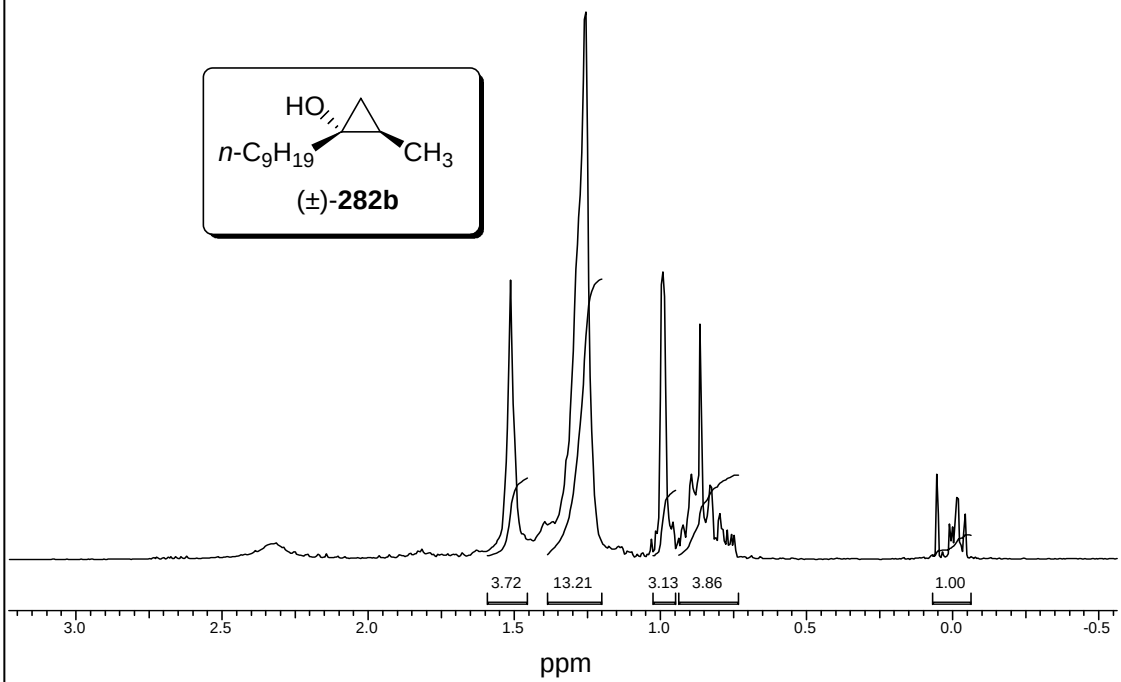
Spectrum No: 1 (Chapter 3, Section 3.4), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



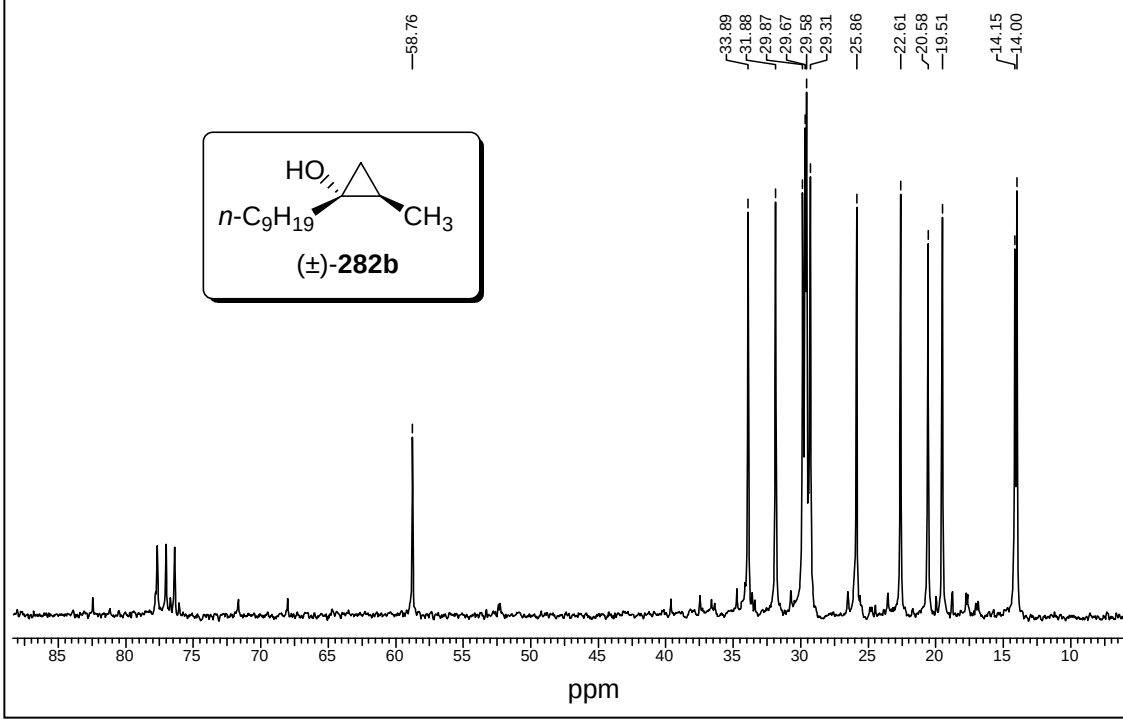
Spectrum No: 2 (Chapter 3, Section 3.4), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



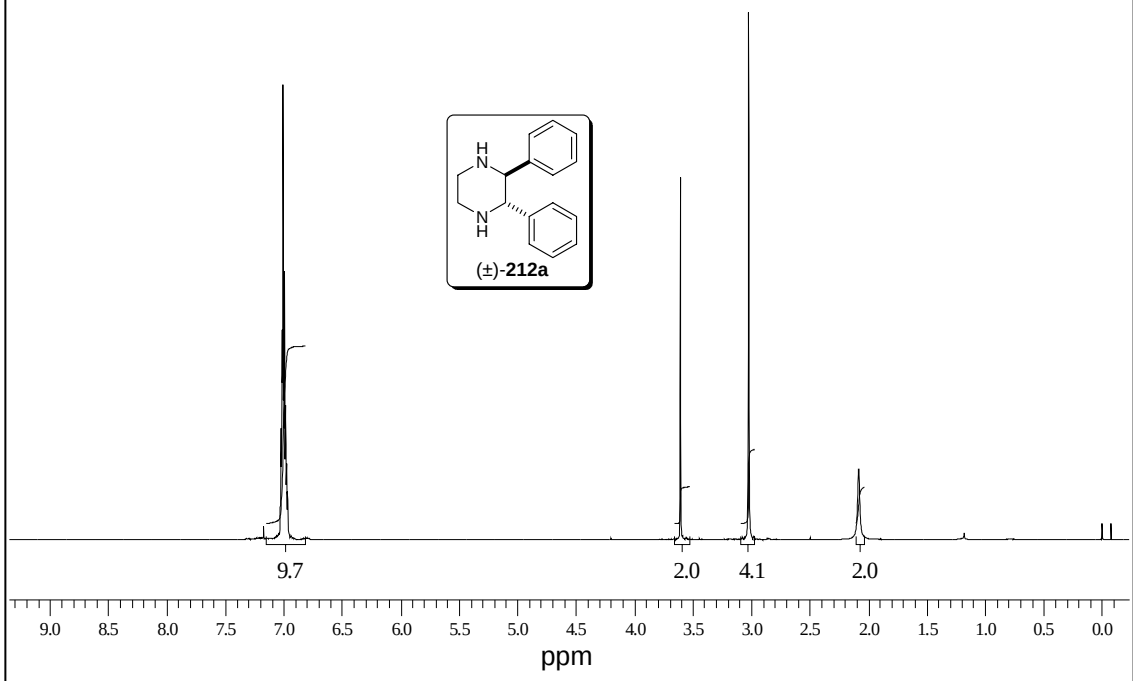
Spectrum No: 3 (Chapter 3, Section 3.4), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



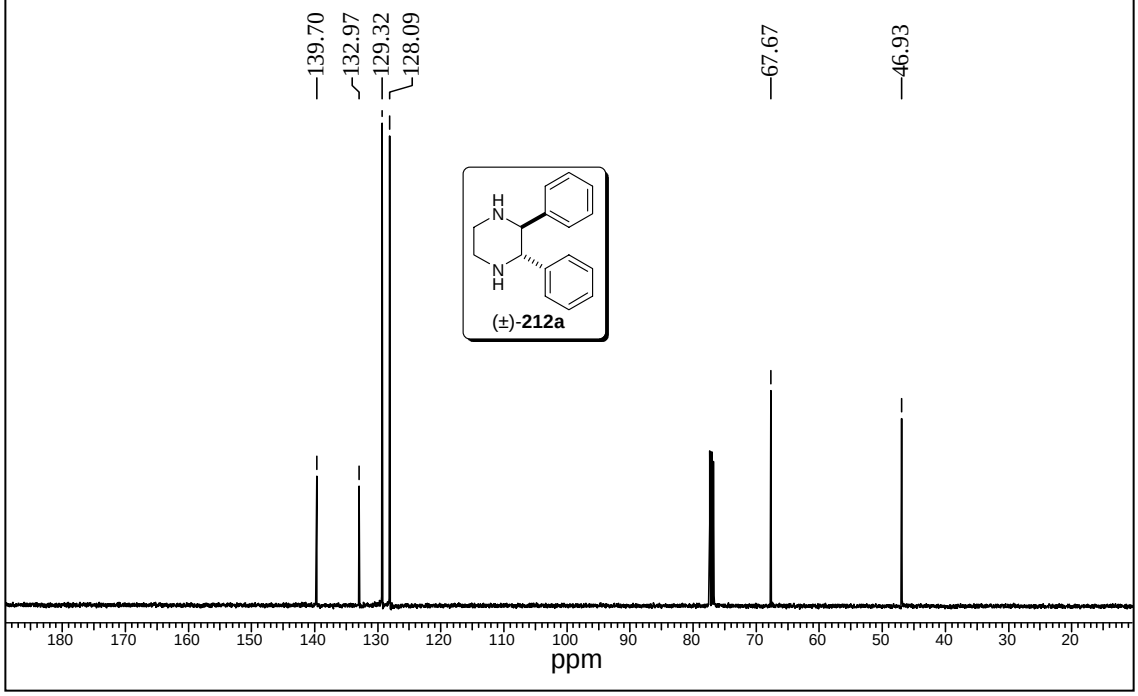
Spectrum No: 4 (Chapter 3, Section 3.4), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



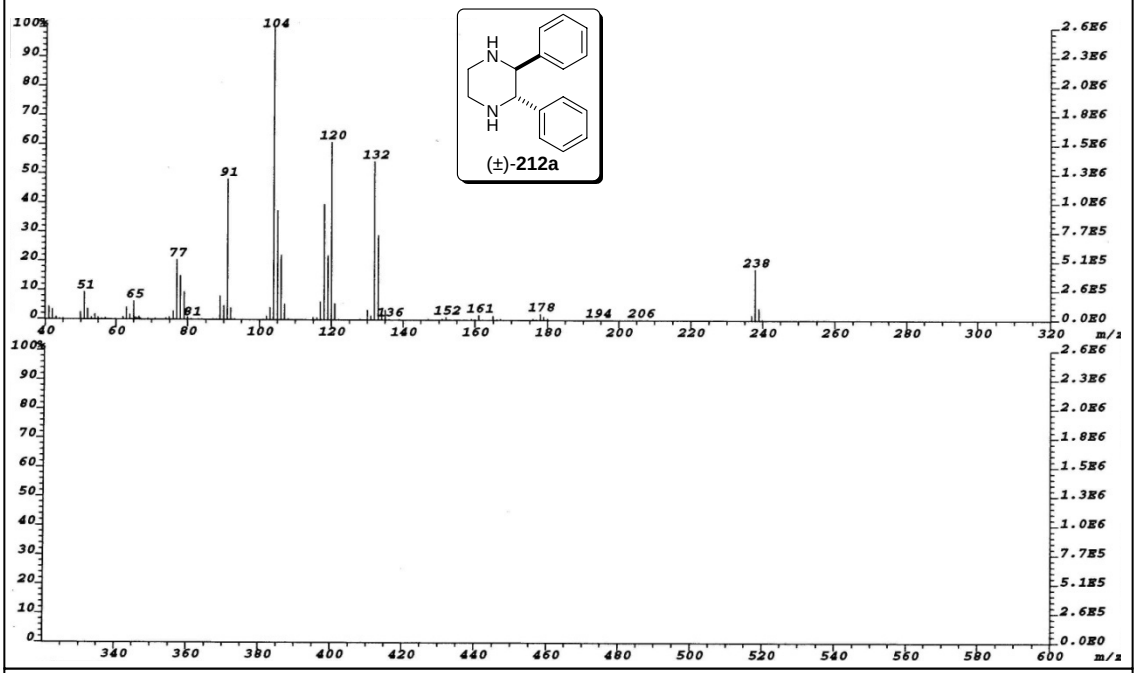
Spectrum No: 5 (Chapter 3, Section 3.6), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



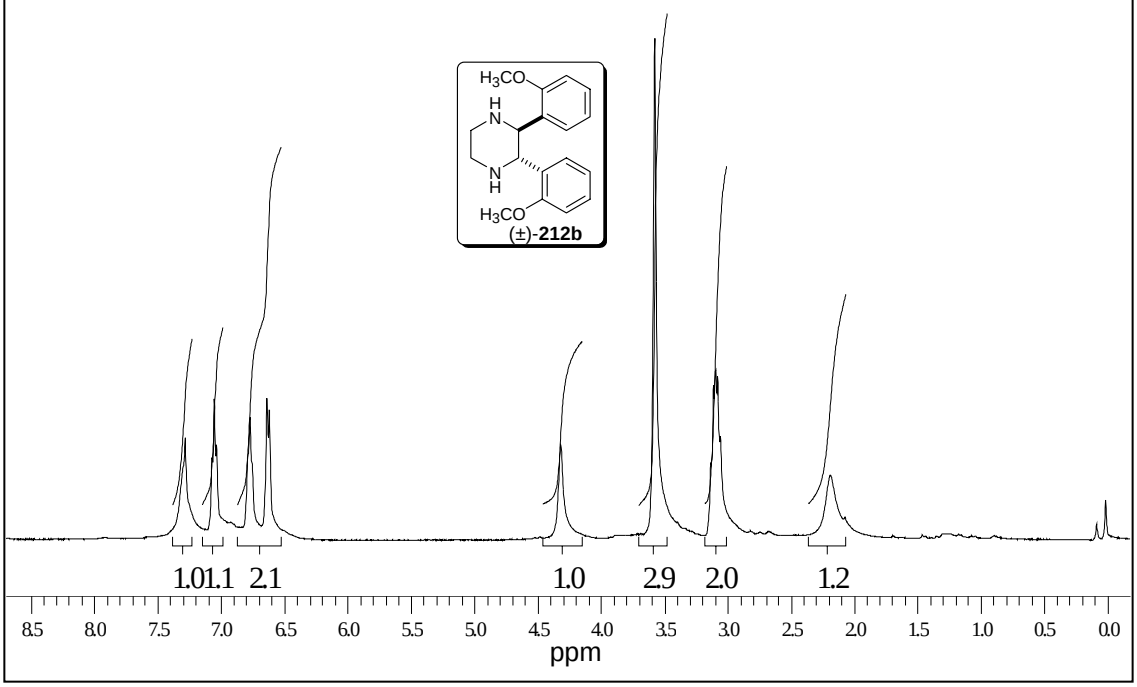
Spectrum No: 6 (Chapter 3, Section 3.6), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



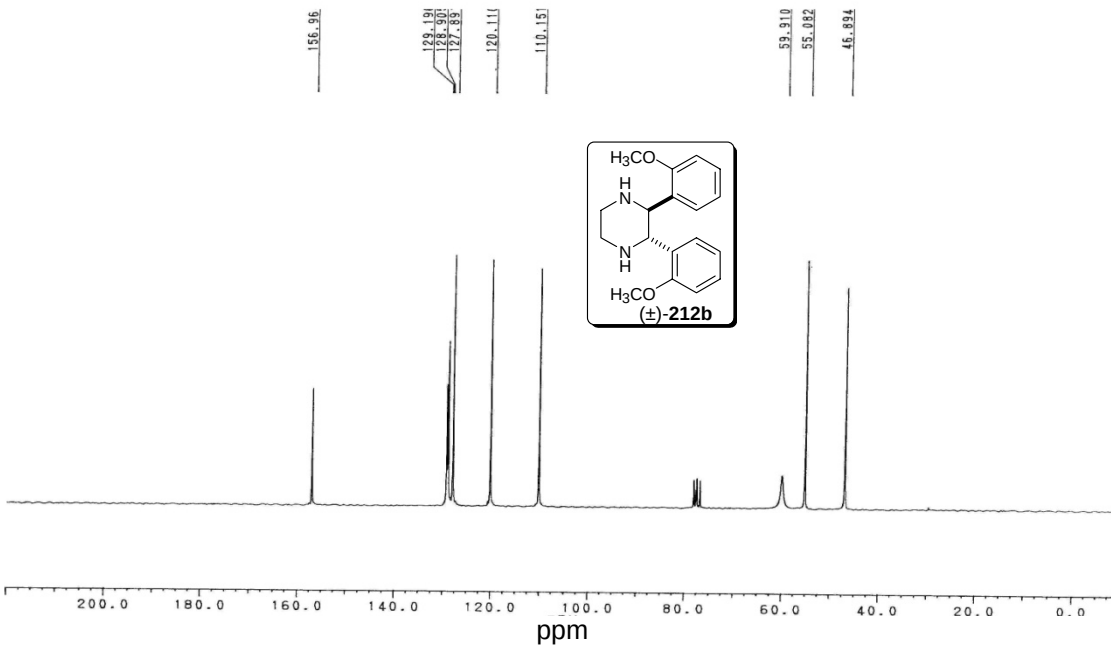
Spectrum No: 7 (Chapter 3, Section 3.6), Mass spectrum (EI))



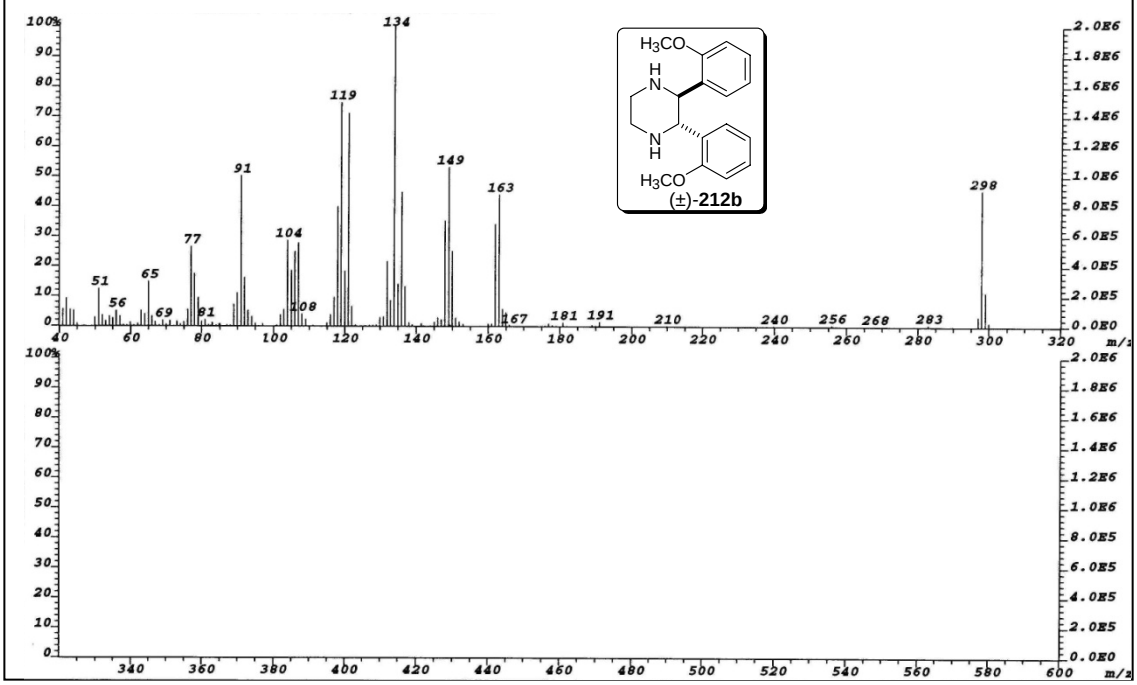
Spectrum No: 8 (Chapter 3, Section 3.6), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



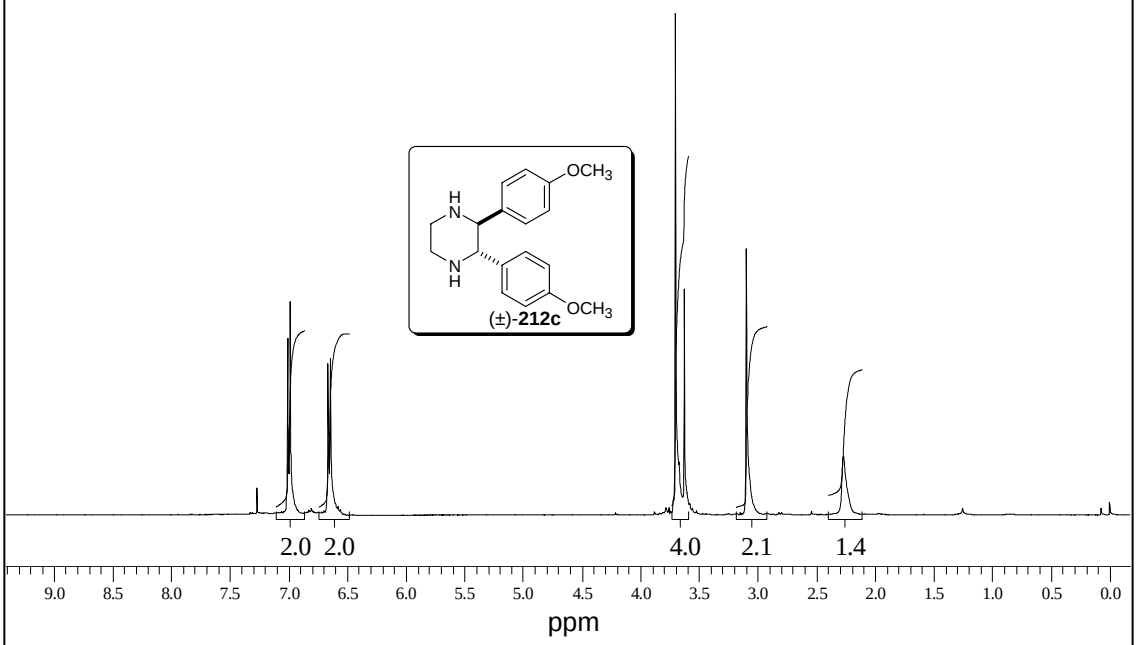
Spectrum No: 9 (Chapter 3, Section 3.6), ^{13}C NMR Spectrum (50 MHz, CDCl3)



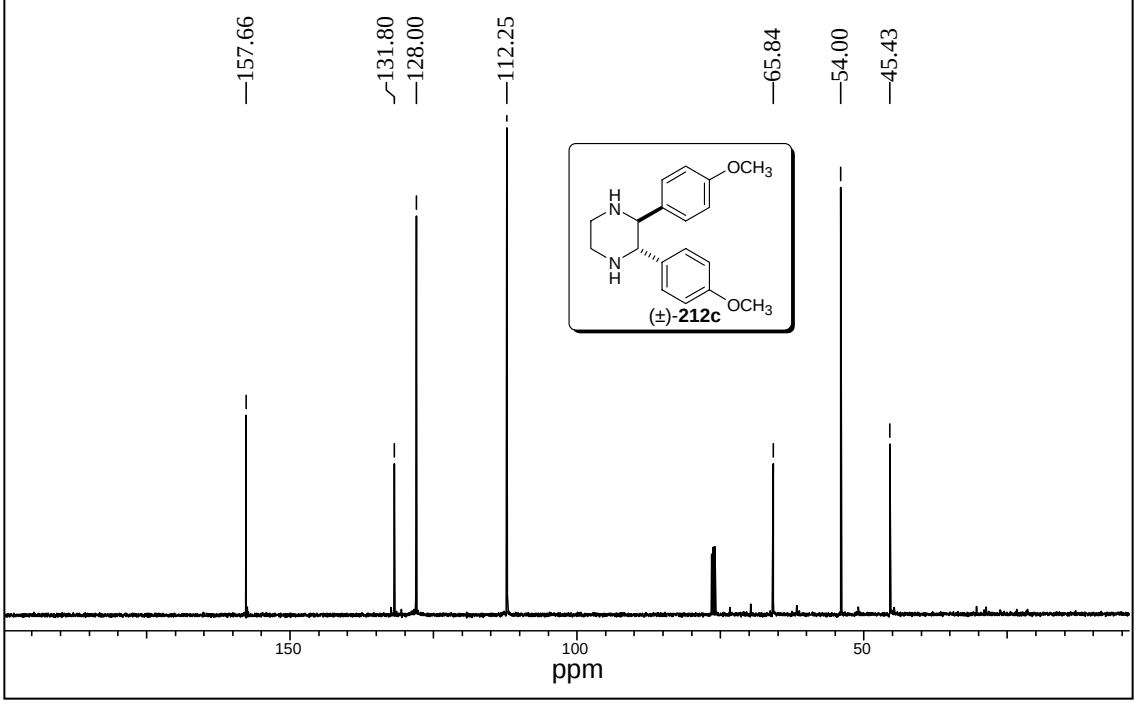
Spectrum No: 10 (Chapter 3, Section 3.6), Mass spectrum (EI))



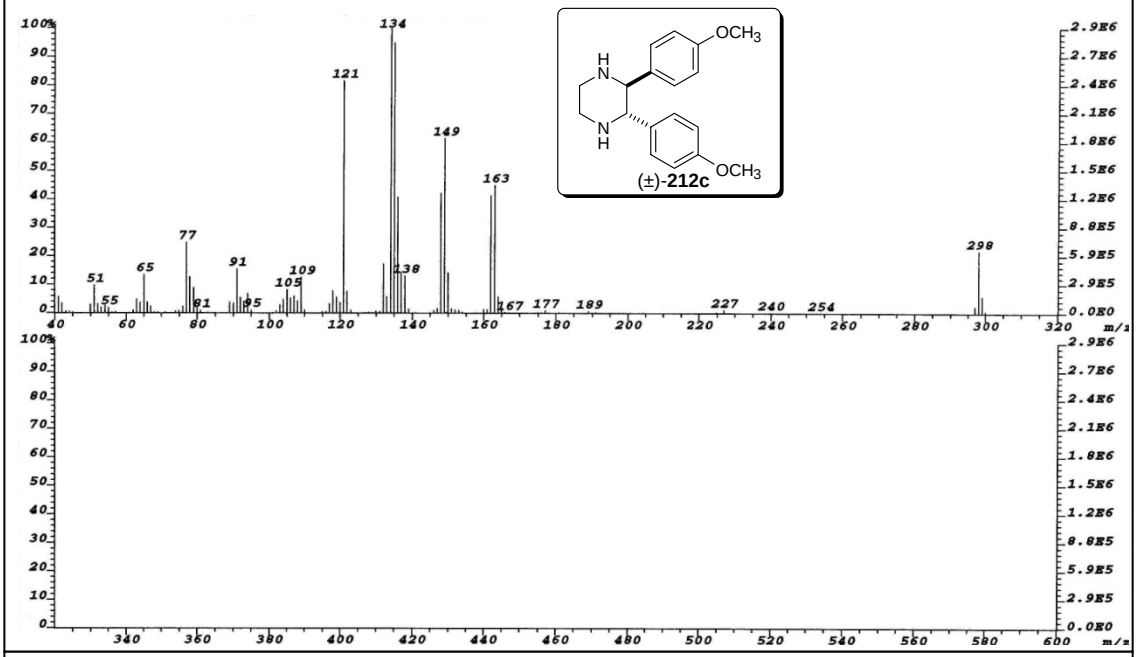
Spectrum No: 11 (Chapter 3, Section 3.6), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



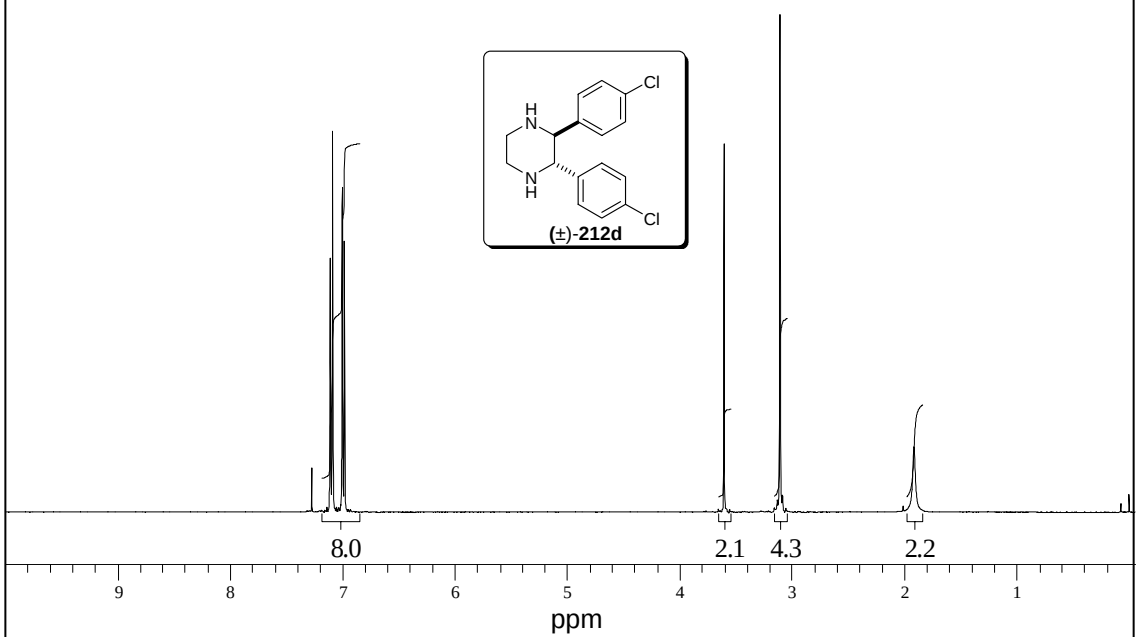
Spectrum No: 12 (Chapter 3, Section 3.6), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



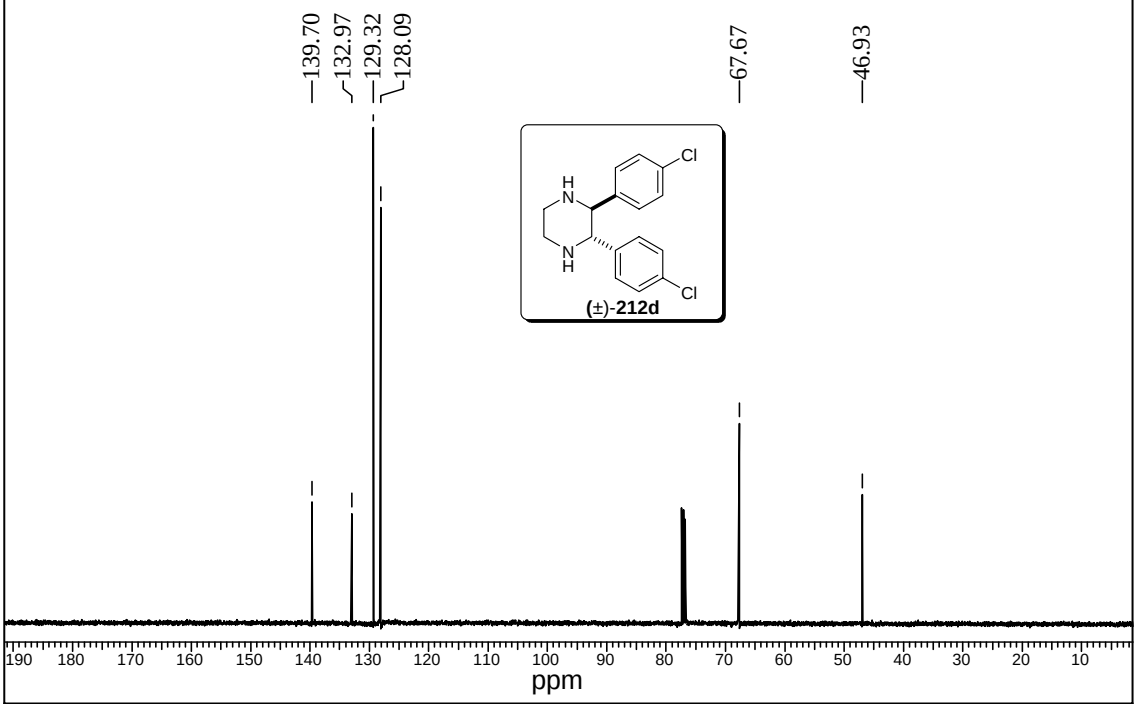
Spectrum No: 13 (Chapter 3, Section 3.6), Mass spectrum (EI))



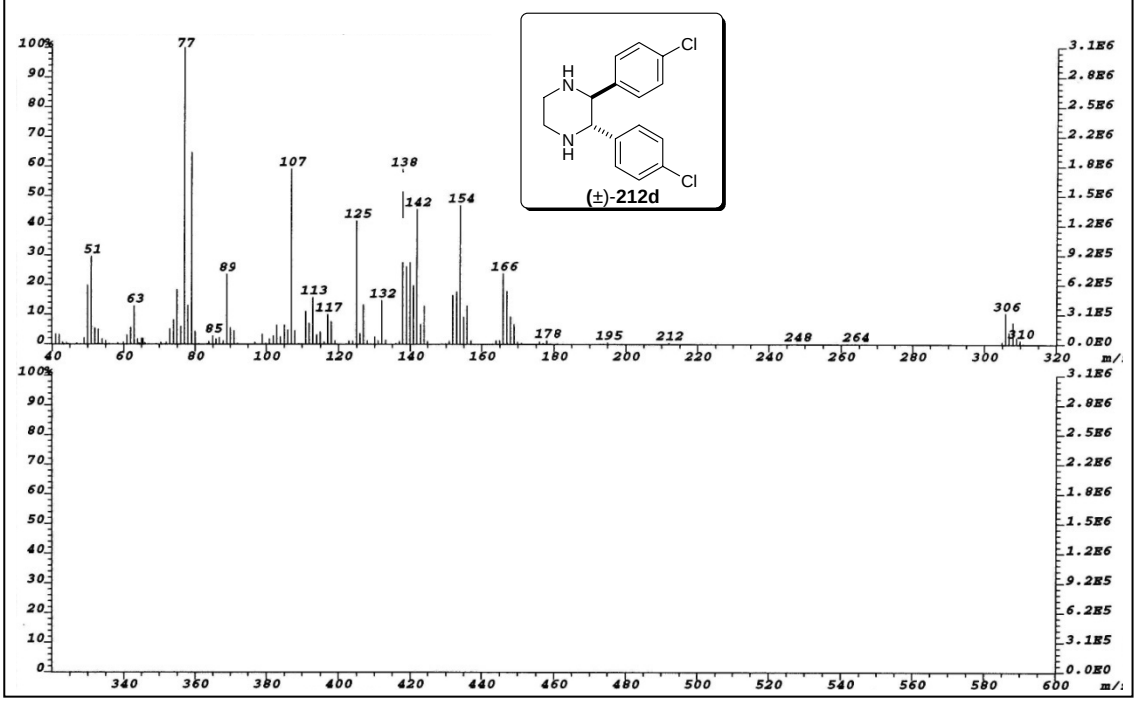
Spectrum No: 14 (Chapter 3, Section 3.7), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



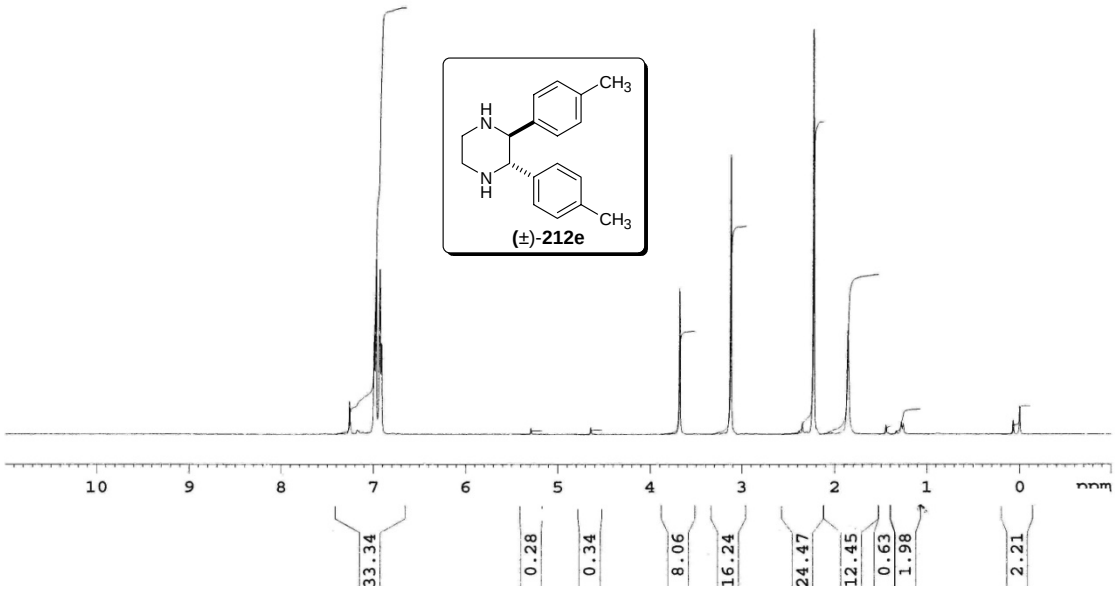
Spectrum No: 15 (Chapter 3, Section 3.7), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No: 16 (Chapter 3, Section 3.7), Mass spectrum (EI))

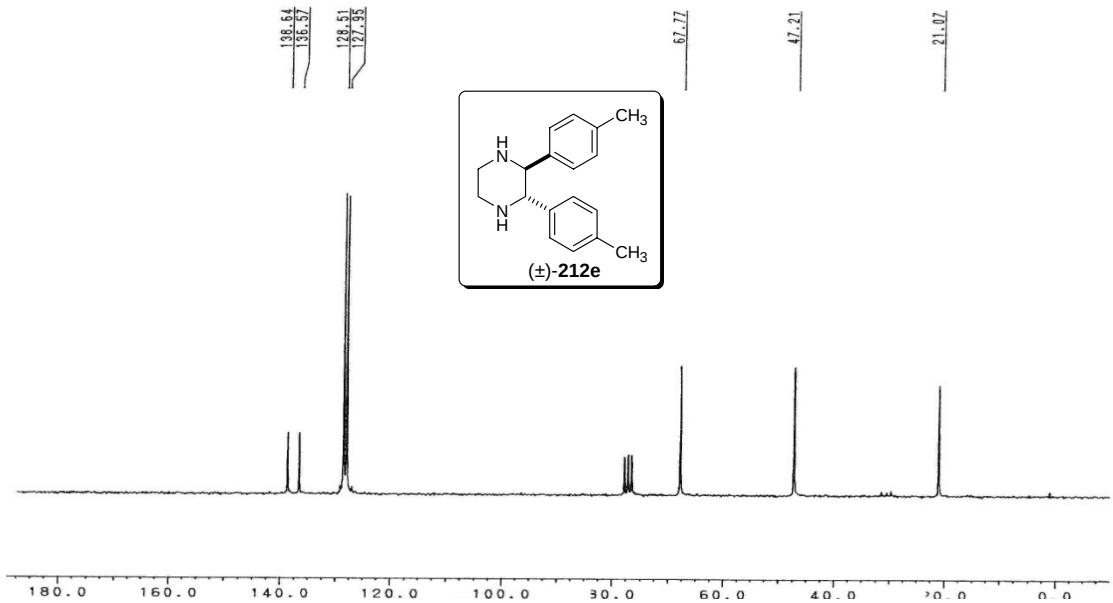


Spectrum No: 17 (Chapter 3, Section 3.7), ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



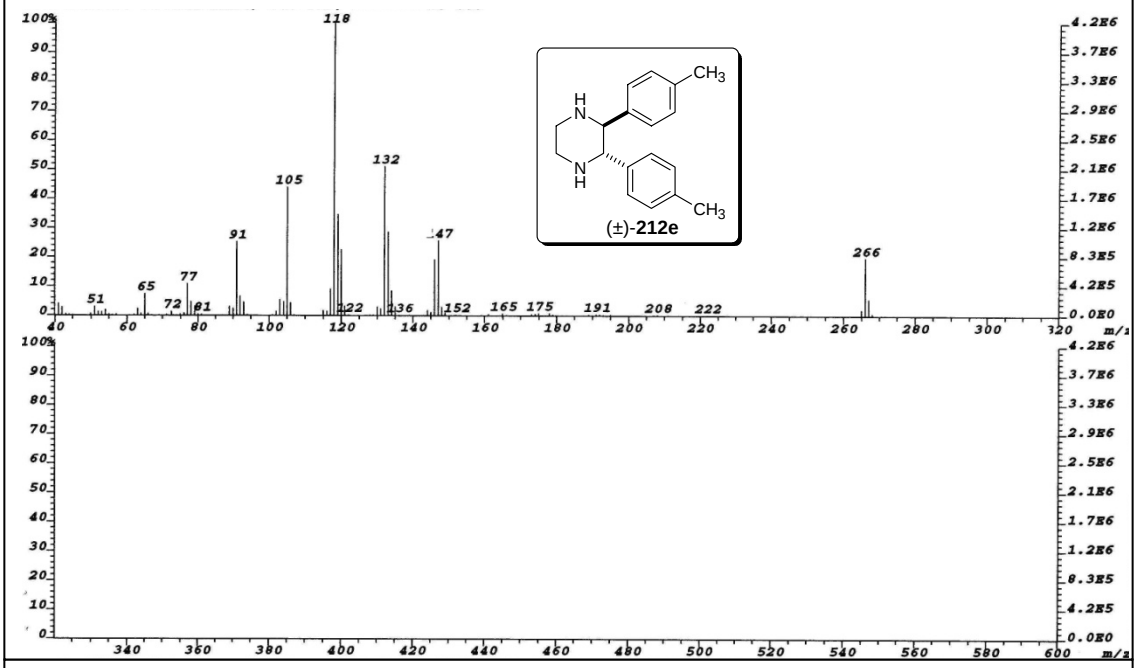
ppm

Spectrum No: 18 (Chapter 3, Section 3.7), ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

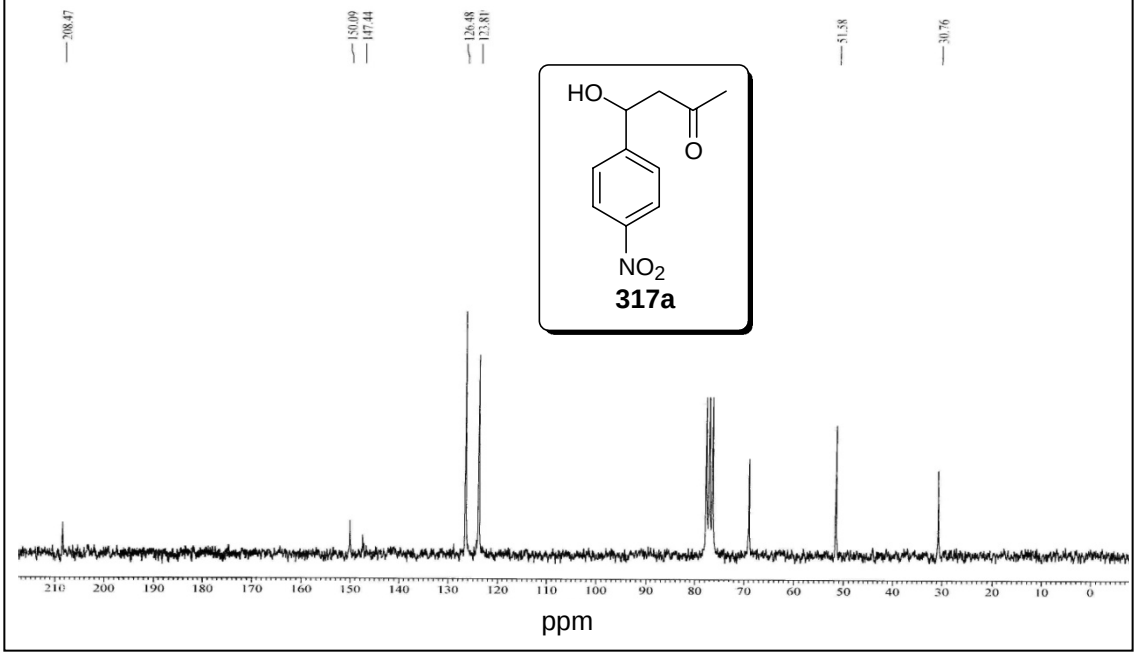


ppm

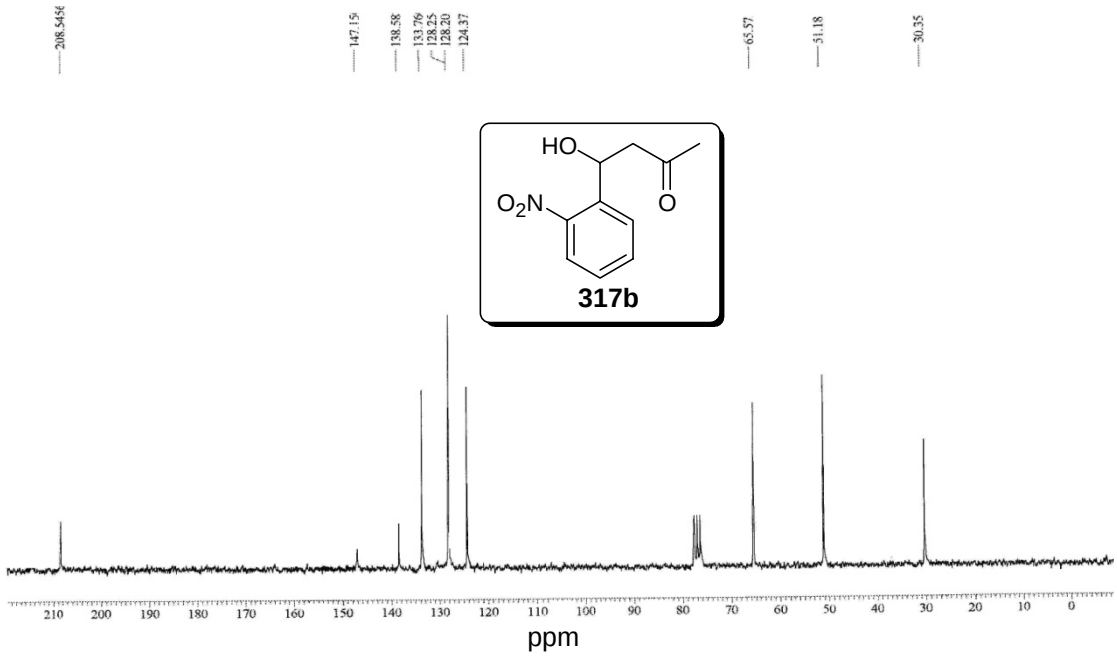
Spectrum No: 19 (Chapter 3, Section 3.7), Mass spectrum (EI))



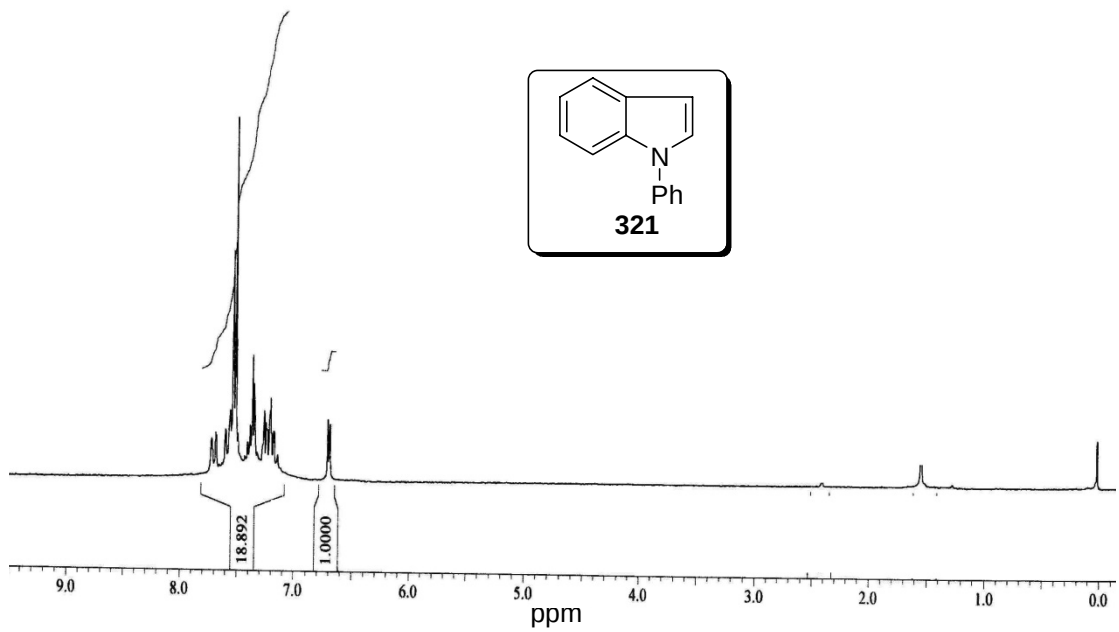
Spectrum No: 20 (Chapter 3, Section 3.23), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



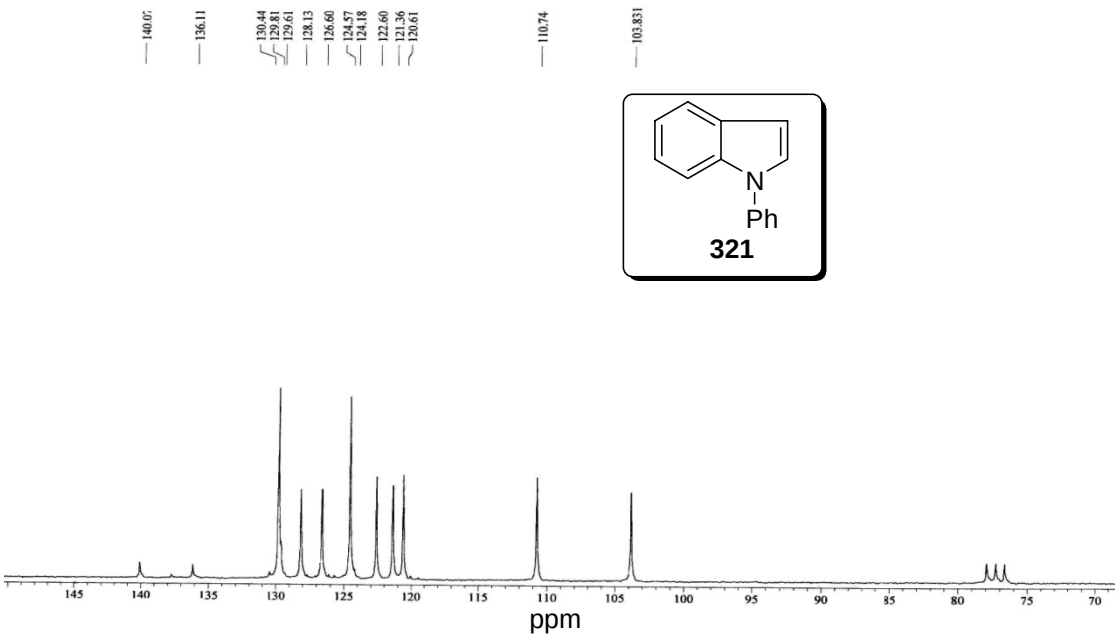
Spectrum No: 21 (Chapter 3, Section 3.23), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



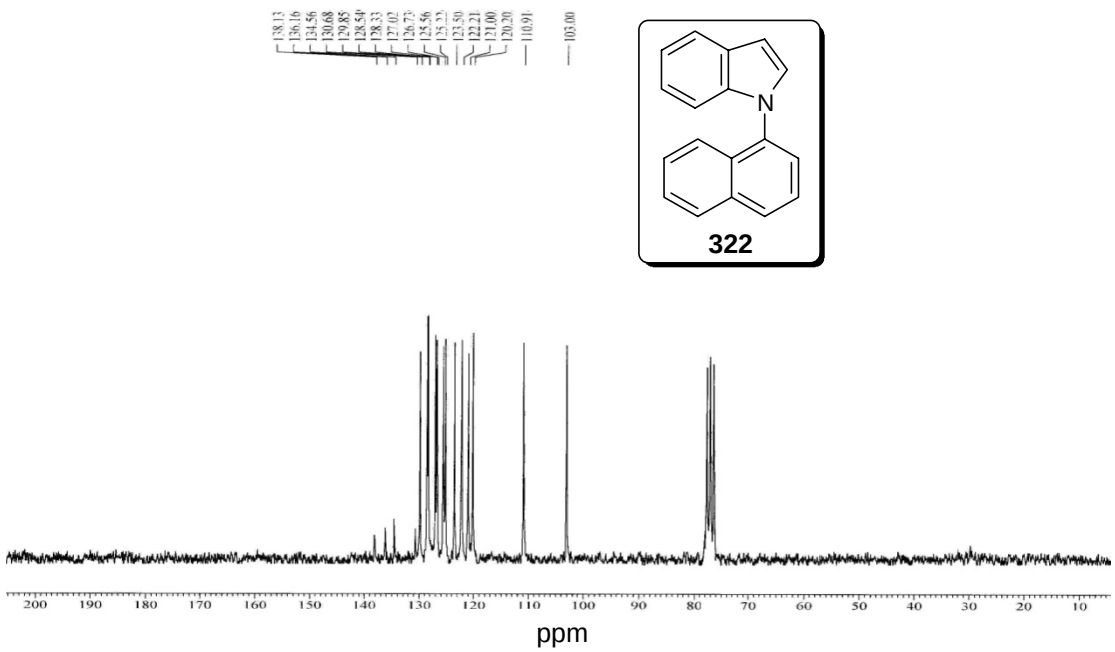
Spectrum No: 22 (Chapter 3, Section 3.28), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



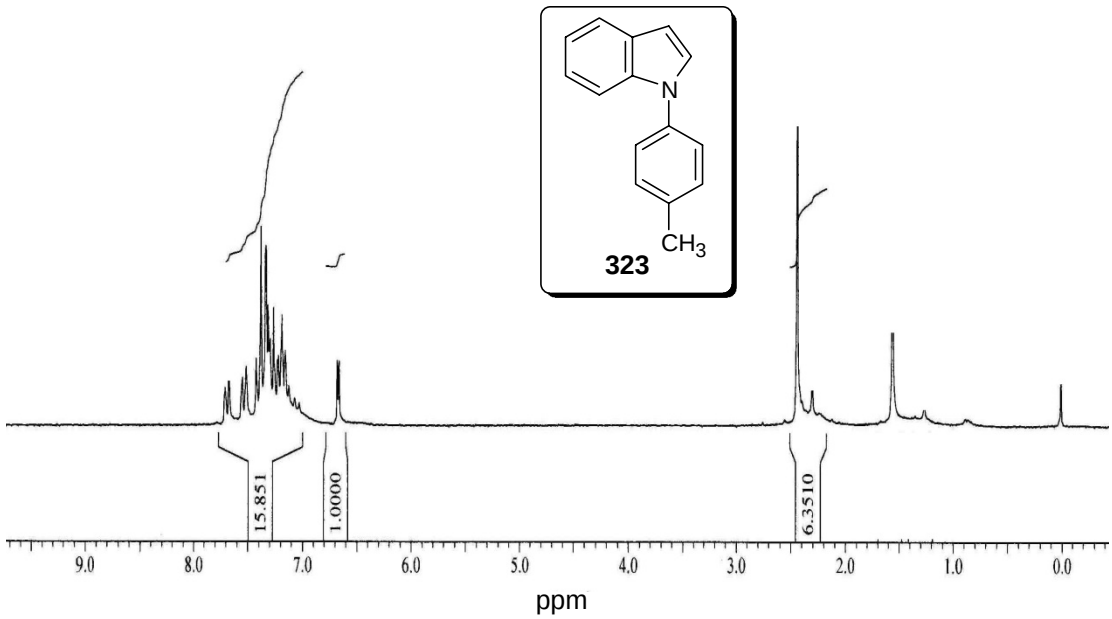
Spectrum No: 23 (Chapter 3, Section 3.28), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



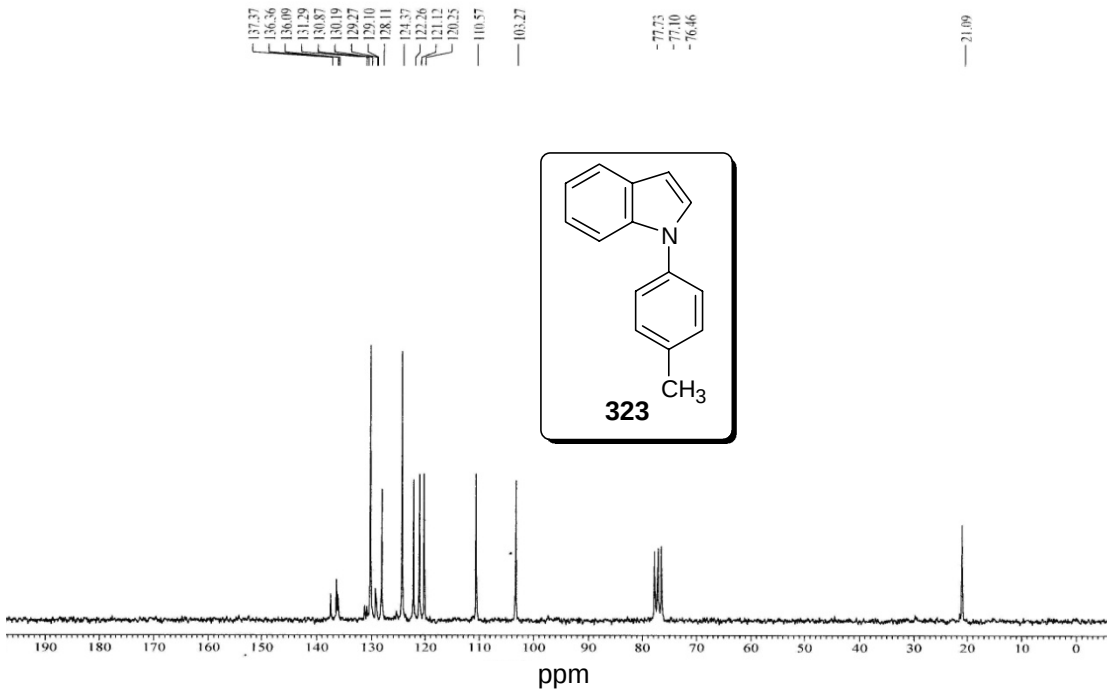
Spectrum No: 24 (Chapter 3, Section 3.29), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Spectrum No: 25 (Chapter 3, Section 3.29), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



Spectrum No: 26 (Chapter 3, Section 3.29), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (±)-*trans*-2,3-diphenylpiperazine *N*,*N'*-bis(trifluoroacetyl) **285a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U (eq)
C(1)	3543(2)	4949(3)	3172(3)	102(1)
C(2)	3606(3)	4404(3)	2268(4)	127(2)
C(3)	3963(3)	4577(4)	1485(4)	118(2)
C(4)	4277(2)	5276(4)	1604(4)	120(2)
C(5)	4226(2)	5817(3)	2513(4)	101(1)
C(6)	3850(2)	5669(2)	3300(3)	77(1)
C(7)	5268(3)	7551(3)	5463(6)	128(2)
C(8)	4631(2)	7309(2)	4669(4)	92(1)
C(9)	4668(2)	6026(2)	5881(3)	78(1)
C(10)	4255(2)	5886(2)	6719(3)	76(1)
C(11)	3780(2)	6349(2)	4190(3)	76(1)
C(12)	3355(2)	6162(2)	5036(3)	72(1)
C(13)	3379(2)	4900(2)	6162(3)	67(1)
C(14)	3720(2)	4320(2)	7138(4)	92(1)
C(15)	3151(2)	7695(3)	5210(4)	94(1)
C(16)	2863(2)	8326(3)	5694(4)	106(1)
C(17)	2526(2)	8160(3)	6548(4)	100(1)
C(18)	2496(2)	7387(3)	6939(4)	100(1)
C(19)	2782(2)	6772(3)	6480(4)	89(1)
C(20)	3107(2)	6907(2)	5603(3)	74(1)
C(21)	1400(2)	5948(3)	3875(5)	115(2)
C(22)	1103(2)	5766(5)	2704(5)	128(2)
C(23)	867(3)	5038(5)	2447(4)	138(2)
C(24)	933(2)	4447(3)	3326(4)	109(1)
C(25)	1249(2)	4605(3)	4528(3)	78(1)
C(26)	1477(2)	5363(3)	4800(4)	91(1)
C(27)	2304(2)	3474(3)	8664(4)	104(1)
C(28)	1972(2)	3322(2)	7490(3)	80(1)
C(29)	1921(2)	2549(3)	7095(4)	102(1)
C(30)	2203(3)	1901(3)	7875(7)	124(2)
C(31)	2528(3)	2093(4)	9020(6)	125(2)
C(32)	2583(2)	2862(4)	9411(5)	127(2)
C(33)	1558(2)	5241(2)	7905(3)	82(1)
C(34)	1128(3)	5743(3)	8525(5)	116(2)
C(35)	745(2)	4172(2)	7415(3)	82(1)
C(36)	382(2)	4017(3)	6165(3)	85(1)
C(37)	1702(2)	4065(2)	6697(3)	74(1)
C(38)	1336(2)	3872(2)	5424(3)	80(1)

C(39)	572(2)	2803(3)	4930(4)	97(1)
C(40)	27(3)	2422(4)	5057(6)	131(2)
N(1)	738(1)	3499(2)	5500(3)	81(1)
N(2)	1322(1)	4561(2)	7346(2)	72(1)
N(3)	3661(1)	5592(2)	5991(2)	68(1)
N(4)	4389(1)	6615(2)	4939(2)	76(1)
O(1)	866(2)	2440(2)	4303(3)	134(1)
O(2)	2068(1)	5492(2)	7942(3)	104(1)
O(3)	4400(2)	7761(2)	3866(3)	132(1)
O(4)	2872(1)	4700(1)	5574(2)	82(1)
F(1)	3827(2)	4621(2)	8257(2)	137(1)
F(2)	3395(1)	3653(2)	7141(3)	142(1)
F(3)	4257(1)	4095(1)	6943(3)	113(1)
F(4)	5689(2)	7005(3)	5345(3)	158(1)
F(5)	5423(2)	8246(2)	5124(4)	225(2)
F(6)	5275(2)	7598(2)	6651(3)	151(1)
F(7)	1002(2)	5400(3)	9461(3)	176(2)
F(8)	1409(2)	6446(2)	8911(4)	189(2)
F(9)	613(2)	5937(2)	7751(3)	137(1)
F(10)	-508(2)	2867(3)	4555(3)	170(1)
F(11)	-95(2)	1711(2)	4551(5)	215(2)
F(12)	-53(2)	2328(2)	6231(4)	162(1)

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (*S*,*S*)-2,3-diphenylpiperazinium tartrate salt **294**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	135(2)	8810(1)	6281(3)	27(1)
C(2)	991(2)	8736(1)	8343(3)	27(1)
C(3)	363(2)	8057(1)	8103(3)	33(1)
C(4)	-391(2)	8123(1)	5999(3)	33(1)
C(5)	-601(2)	9195(1)	6220(3)	31(1)
C(6)	-969(4)	9346(1)	4280(4)	72(1)
C(7)	-1658(5)	9692(1)	4143(5)	102(1)
C(8)	-1974(3)	9892(1)	5931(5)	64(1)
C(9)	-1652(3)	9743(1)	7859(4)	59(1)
C(10)	-976(3)	9394(1)	8019(4)	54(1)
C(11)	2260(2)	9006(1)	8653(3)	31(1)
C(12)	3308(2)	9055(1)	7097(4)	40(1)
C(13)	4497(2)	9284(1)	7471(5)	53(1)
C(14)	4626(2)	9472(1)	9390(5)	57(1)

C(15)	3596(3)	9429(1)	10931(5)	57(1)
C(16)	2422(2)	9196(1)	10581(4)	45(1)
C(17)	7075(2)	8507(1)	845(3)	28(1)
C(18)	5706(2)	8528(1)	2231(3)	30(1)
C(19)	4926(2)	8149(1)	2272(3)	30(1)
C(20)	3518(2)	8194(1)	3540(3)	29(1)
N(1)	-1002(2)	8512(1)	5980(2)	29(1)
N(2)	1550(2)	8337(1)	8376(2)	28(1)
O(1)	8281(1)	8563(1)	1678(2)	41(1)
O(2)	6861(1)	8434(1)	-1097(2)	40(1)
O(3)	6068(2)	8657(1)	4290(2)	51(1)
O(4)	5839(2)	7866(1)	3149(3)	47(1)
O(5)	3620(1)	8143(1)	5504(2)	44(1)
O(6)	2411(2)	8303(1)	2584(2)	49(1)
O(7)	8201(2)	7512(1)	942(3)	54(1)
O(8)	6144(2)	7679(1)	7569(3)	61(1)

Table A3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (*S*,*S*)-2,3-bis(4-methoxyphenyl)piperazinium (*S*)-camphorsulfonate salt **315** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U (eq)**
C(1)	8152(7)	3944(3)	2857(3)	40(1)
C(2)	9733(8)	3690(3)	2342(3)	41(1)
C(3)	9524(10)	2387(3)	2907(4)	55(1)
C(4)	7967(9)	2655(3)	3416(3)	51(1)
C(5)	8299(8)	4768(3)	3111(3)	44(1)
C(6)	6588(8)	5188(4)	3116(3)	50(1)
C(7)	6688(9)	5934(3)	3361(4)	57(2)
C(8)	8549(10)	6269(3)	3609(3)	54(1)
C(9)	10371(14)	7379(5)	4059(6)	91(3)
C(10)	10271(10)	5848(4)	3634(4)	58(2)
C(11)	10156(9)	5108(3)	3396(4)	50(1)
C(12)	9723(7)	4137(3)	1568(3)	39(1)
C(13)	11443(8)	4455(3)	1375(4)	50(1)
C(14)	11458(9)	4842(3)	642(4)	56(1)
C(15)	9709(9)	4923(3)	90(3)	47(1)
C(16)	11249(13)	5704(4)	-833(6)	85(2)
C(17)	7940(9)	4616(3)	273(3)	49(1)
C(18)	7935(8)	4225(3)	995(4)	48(1)
C(19)	2699(8)	2453(3)	9737(3)	39(1)
C(20)	572(9)	2714(3)	9736(4)	53(1)

C(21)	-105(10)	3077(4)	8890(4)	68(2)
C(22)	1671(12)	2945(4)	8467(4)	71(2)
C(23)	3368(13)	3502(4)	8840(4)	72(2)
C(24)	3948(9)	3195(3)	9736(4)	56(2)
C(25)	2520(9)	2187(3)	8820(3)	49(1)
C(26)	1044(11)	1529(4)	8616(4)	69(2)
C(27)	4540(11)	1977(5)	8573(4)	75(2)
C(28)	3579(9)	1869(3)	10353(4)	52(1)
C(29)	5445(8)	4527(4)	5793(4)	55(1)
C(30)	7321(9)	4792(4)	5522(4)	61(2)
C(31)	7845(11)	5560(5)	5915(5)	85(2)
C(32)	6230(20)	5591(8)	6472(9)	182(9)
C(33)	070(12)	825(4)	722(5)	0(2)
C(34)	813(13)	094(5)	263(6)	5(2)
C(35)	505(13)	922(5)	612(5)	8(3)
C(36)	367(16)	71(7)	240(5)	11(3)
C(37)	672(14)	840(6)	022(6)	6(3)
C(38)	964(17)	735(5)	642(5)	6(3)
N(1)	236(7)	459(3)	609(3)	7(1)
N(2)	350(7)	864(3)	145(3)	7(1)
O(1)	502(8)	014(3)	814(4)	8(1)
O(2)	530(7)	294(3)	655(3)	8(1)
O(3)	476(7)	035(3)	1799(3)	8(1)
O(4)	743(9)	556(4)	1775(3)	0(2)
O(5)	117(10)	856(3)	1490(3)	9(2)
O(6)	477(7)	625(3)	0269(3)	6(1)
O(7)	517(7)	843(3)	020(3)	5(1)
O(8)	803(8)	401(7)	600(4)	50(4)
O(9)	676(19)	634(5)	683(6)	64(4)
O(10)	539(9)	486(5)	175(4)	11(2)
S(1)	274(2)	111(1)	1437(1)	3(1)
S(2)	920(2)	374(1)	668(1)	49(1)

List of publications

1. A simple method of synthesis of (±)-2,3-diarylpiperazines and a novel method of resolution of (±)-2,3-diphenylpiperazine; **Vairaprakash, P.**; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 3636-3638.
2. New chiral titanium complexes for enantioselective reductive cyclizations of diimines to *trans*-2,3-diarylpiperazines; **Vairaprakash, P.**; Periasamy, M. *Tetrahedron Lett.* **2007**, *48*, 0000.
3. Efficient resolution of (±)-*trans*-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid and enrichment of enantiomeric purity of nonracemic (*S,S*)-2,3-diphenylpiperazine using different achiral acids; **Vairaprakash, P.;** Periasamy, M. **(**communicated**)**.
4. New diimine-copper complexes, an efficient and simple catalyst system for Buchwald *N*-arylation of indole; Periasamy, M.; **Vairaprakash, P.**; Dalai, M. (to be communicated).

PRESENTATIONS

1. Oral presentation in the *"Chemfest 2006"* in house symposium held at University of Hyderabad, Hyderabad, March 4, **2006**; Title: Synthesis of (±)-2,3-diarylpiperazines and resolution of (±)-2,3-diphenylpiperazine.

2. Presented a poster in the *"Chemfest 2006"* in house symposium held at University of Hyderabad, Hyderabad, March 4, **2006**; Title: Synthesis of (±)-2,3-diarylpiperazines and resolution of (±)-2,3-diphenylpiperazine.
3. Oral presentation in the "Second NOST Symposium for Research Scholars" held at International College for Girls, Jaipur, India. (11th to 14th October **2006**); Title: Synthesis and resolution of (±)-2,3-diarylpiperazines.