Studies on Chiral Amines, Sulphides and Borane reagents prepared using Tetraalkyl Ammonium Borohydride

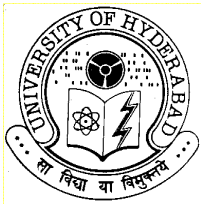
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

G. P. Muthukumaragopal



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Contents

Chapter 2

Synthesis of C_2-symmetric diphenyl substituted pyrrolidines, piperidines and sulfur heterocycles

Chapter 3

Generation of diborane using Bu_4NBH_4 for synthetic applications

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled **"Studies on Chiral Amines, Sulphides and Borane reagents prepared using Tetraalkyl Ammonium Borohydride"** has been carried out by **Mr. G. P. Muthukumaragopal** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN

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G. P. Muthukumaragopal

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	α,α'-azobisisobutyronitrile
anhyd.	anhydrous
aq.	aqueous
Ar	aryl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tertiary*-butoxycarbonyl
br	broad (in spectroscopy)
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
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
DBTA	*O*,*O*-dibenzoyltartaric acid
DCE	dichloroethane
de	diastereomeric excess
DPPM	α,α'-diphenylpyrrolidine methanol
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact (in mass spectrometry)
equiv	equivalent
Et	ethyl
Fc	Ferrocenyl
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
i	iso
IPA	2-propanol
Ipc	isophinocampheyl
IR	infrared
J	coupling constant (in NMR spectroscopy)
LDA	lithium diisopropylamide
LiDBB	lithium 4,4'-di-*tert*-butylbiphenyl
lit.	literature
m	multiplet (in spectroscopy)
Me	methyl
min	minute(s)
Mp	melting point
MS	mass spectrum
Ms	methanesulfonyl
M.S.	molecular sieves
MSA	methanesulfonic acid
NBS	*N*-bromosuccinamide
NCS	*N*-chlorosuccinamide
NMR	nuclear magnetic resonance
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot

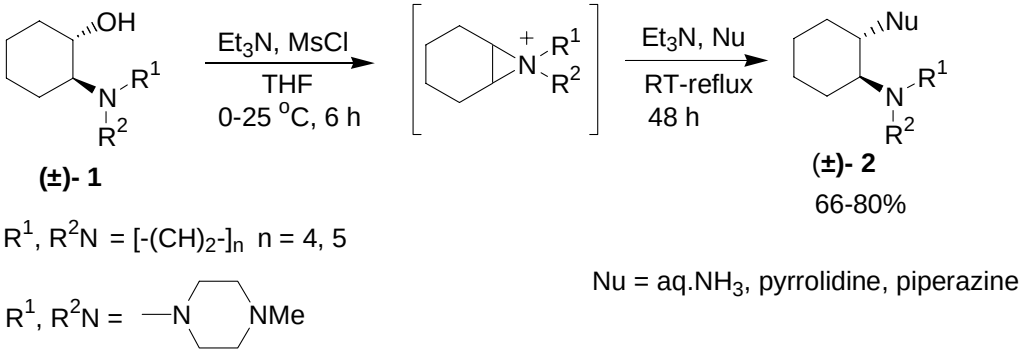
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet (in spectroscopy)
ref	reference number
RT	room temperature
s	singlet (in spectroscopy)
sat.	saturated
sec	secondary
soln	solution
T	temperature
t or *tert*	tertiary
t	triplet (in spectroscopy)
TBDMSCl	*tertiary*-butyldimethylsilylchloride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-methylbenzenesulfonyl
Uv	ultraviolet
Y	yield

Abstract

This thesis deals with **Studies on Chiral Amines, Sulphides and Borane reagents prepared using Tetraalkyl Ammonium Borohydride**. It comprises of three chapters. Each chapter is subdivided into four parts, **1) Introduction, 2) Results and Discussion 3) Conclusions and 4) Experimental Section** along with **References**. The work described in thesis is explorative in nature.

The first chapter deals with synthesis of racemic *trans*-1,2-diamines and their derivatives. A brief review on the synthesis of 1,2-diamines by various methods is presented in the introductory section. The (±)-*trans*-1,2-diamines were readily prepared from the corresponding (±)-*trans*-1,2-amino alcohols via formation of aziridinium ions and the subsequent ring opening with nitrogen nucleophiles such as aqueous NH_3, pyrrolidine, and piperazine in good yields (Scheme 1).

Scheme 1

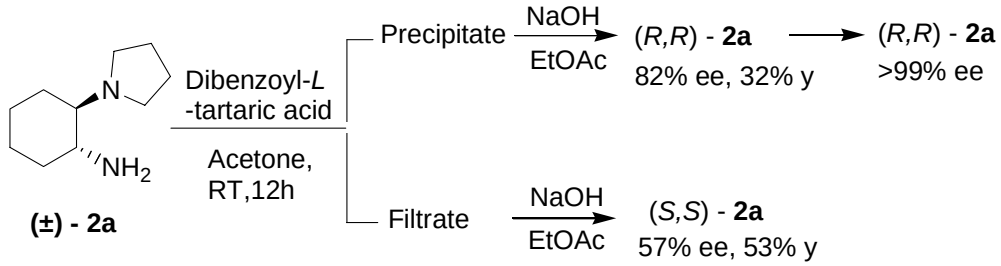


The (±)-*trans*-1,2-diamines prepared in this way were resolved using commercially available resolving agents such as dibenzoyl-*L*-tartaric acid and (*R*)-(-)-bi-2-napthyl-phosphoric acid to obtain optically pure *trans*-1,2-diamines. Also, the bi-2-napthol boric

acid complex prepared *in situ* using bi-2-napthol and $B(OMe)_3$ was used as a resolving agent in the resolution of racemic *trans*-1,2-diamines and its derivatives.

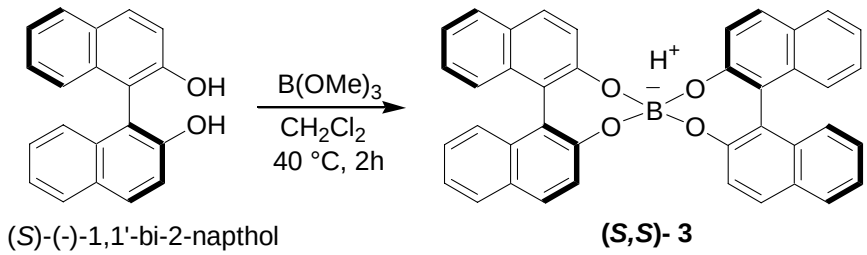
The racemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine **2a** was resolved by formation of diastereomeric salt with dibenzoyl-*L*-tartaric acid in acetone at 25 ^{o}C. Partially resolved sample of **2a** was obtained in 82% ee under these conditions which upon further enrichment gave samples with >99% ee (Scheme 2).

Scheme 2



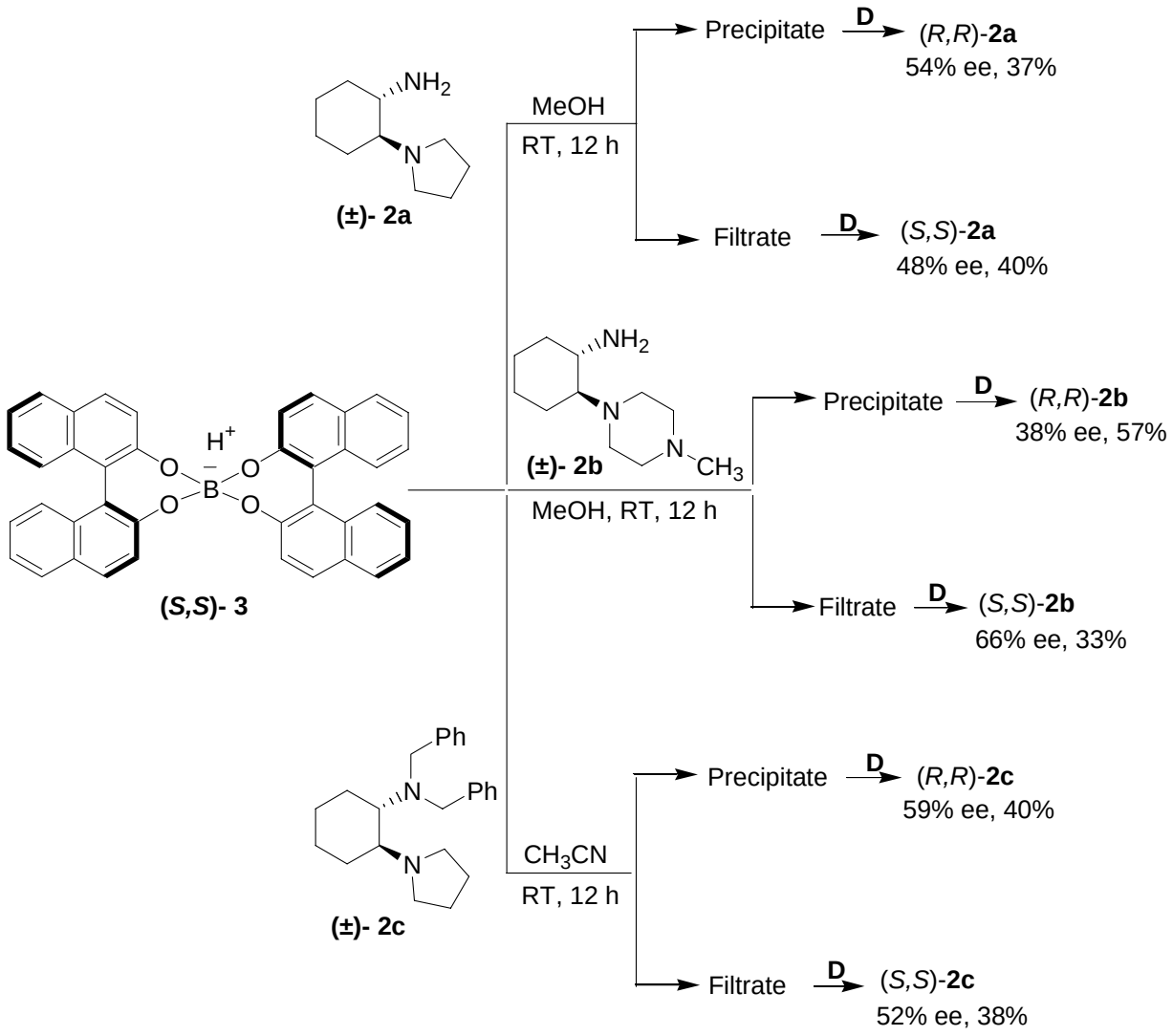
The chiral complex **3** was readily prepared using optically pure (*S*)-1,1`-bi-2-napthol and trimethyl borate in dichloromethane under mild conditions (Scheme 3).

Scheme 3



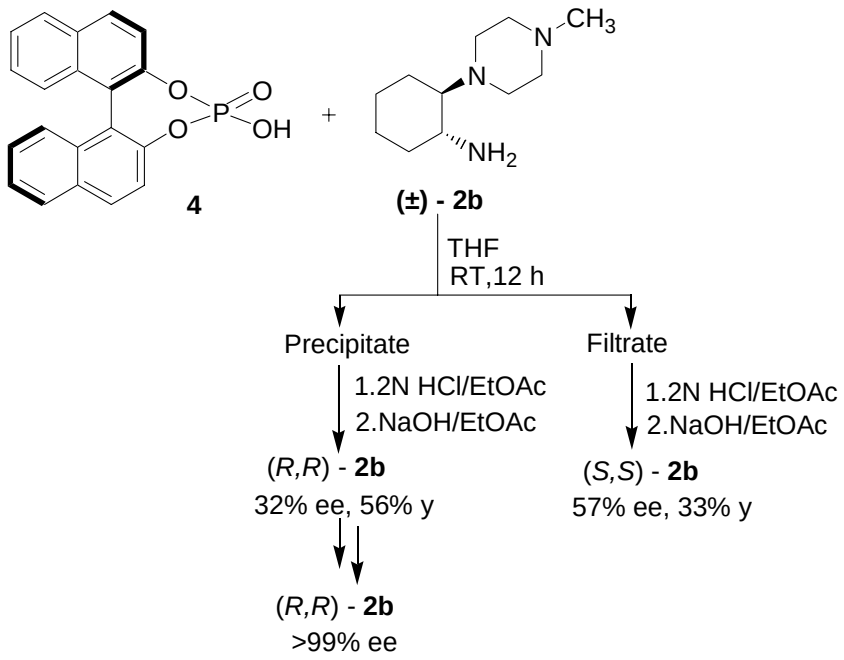
The bi-2-naptholborate complex **3** has been used for the resolution of series of (±)-*trans*-1,2-diamines successfully under ambient conditions as shown in the Scheme 4.

Scheme 4



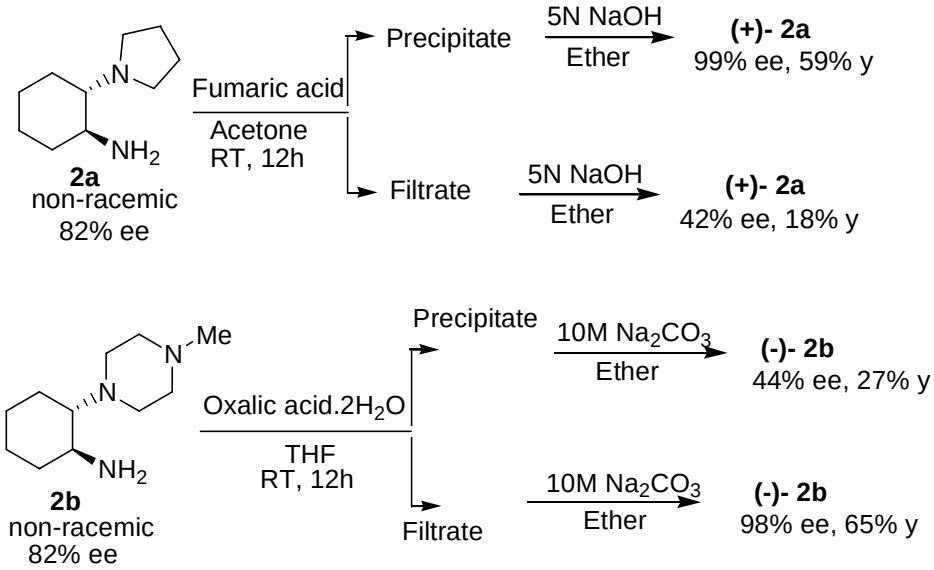
We have developed an improved method for the resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine **2b** using (*R*)-(-)-bi-2-napthylphosphoric acid in THF at 25 ^{o}C (Scheme 5).

Scheme 5



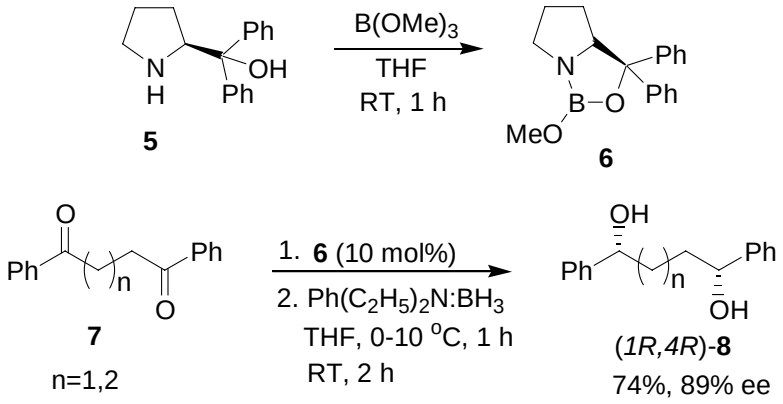
The non-racemic 1,2-diamines **2a** and **2b** were purified by following a method developed in this laboratory using achiral acids such as fumaric acid and oxalic acid respectively to obtain enantiomerically enriched samples (Scheme 6).

Scheme 6



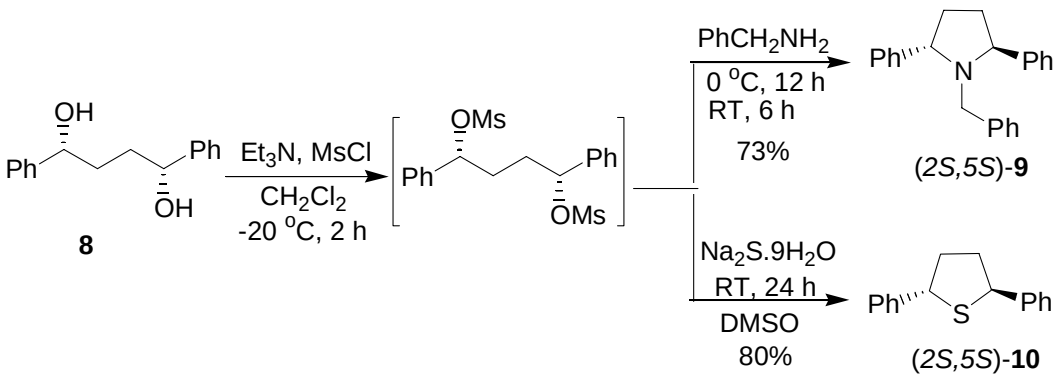
Development of methods for the synthesis of diphenyl substituted pyrrolidines, piperidines and thiolanes is described in Chapter 2. A brief overview on the synthesis of C_2-symmetric pyrrolidine, piperidine and thiolane derivatives is presented in the introductory section. The chiral *N*-benzyl-2,5-diphenylpyrrolidine and 2,5-diphenylthiolane were prepared from optically pure 1,4-diphenylbutane-1,4-diol. The chiral diols were obtained from asymmetric reduction of 1,4-diphenylbutane-1,4-dione and 1,5-diphenylpentane-1,5-dione using B-methoxyoxazaborolidine (10 mol%) prepared *in situ* using (*S*)-α,α'-diphenylpyrrolidinemethanol, $B(OMe)_3$ and *N,N*-diethylaniline-BH_3 (1 equiv) (Scheme 7).

Scheme 7



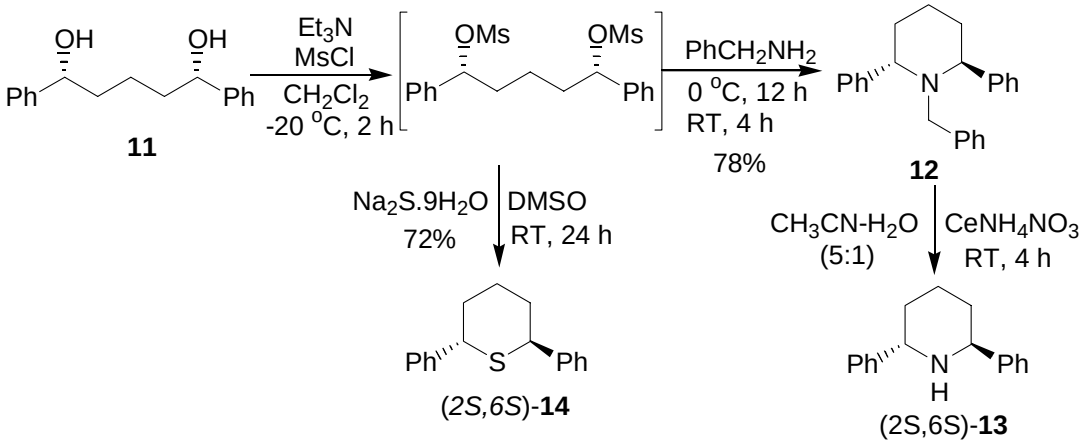
The C_2-symmetric *N*-benzyl-2,5-diphenylpyrrolidine **9** and 2,5-diphenylthiolane **10** were prepared from the diol **8** via the cyclization of the corresponding dimesylates with benzyl amine and sodium sulfide respectively (Scheme 8). The configuration of the 2,5-diphenylthiolane **10** was confirmed (*2S,5S*) from X-ray crystal structure analysis.

Scheme 8



The (*2S,6S*)-2,6-diphenylpiperidine **13** and (*2S,6S*)-2,6-diphenyltetrahydrothiopyran **14** were readily prepared from (*1R,5R*)-1,5-diphenylpentane-1,5-diol. The 1,5-diol **11** was mesylated using Et_3N/MsCl in anhydrous dichloromethane (CH_2Cl_2) and the corresponding dimesylate was treated with benzyl amine and sodium sulfide ($Na_2S.9H_2O$) to obtain the products (*2S,6S*)-*N*-benzyl-2,6-diphenylpiperidine **12** and its sulfur analogue (Scheme 9).

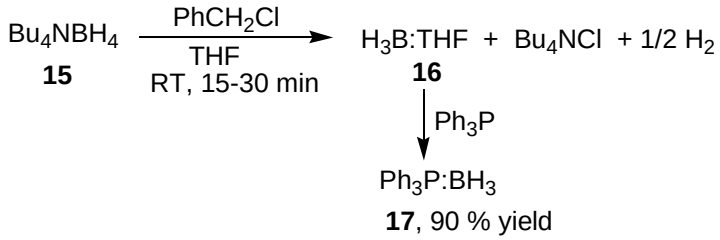
Scheme 9



Studies on the use of tetrabutylammonium borohydride (Bu_4NBH_4) and additives like benzyl chloride and iodine to prepare borane for the reduction of carbonyl compounds are described in chapter 3. A brief review on the modified borohydride reagents presented in the

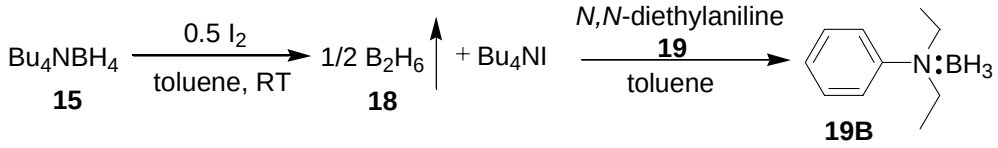
introductory section. A convenient procedure has been developed for the generation of diborane (B_2H_6) *in situ* using Bu_4NBH_4 using benzyl chloride in toluene (Scheme 10).

Scheme 10



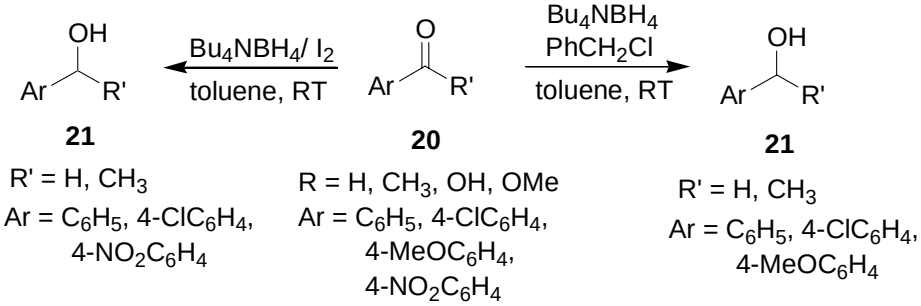
The Bu_4NBH_4/I_2 reagent system provides a convenient source for the *ex situ* generation of diborane (B_2H_6) which could be used for the preparation Lewis base-BH_3 complexes (Scheme 11).

Scheme 11



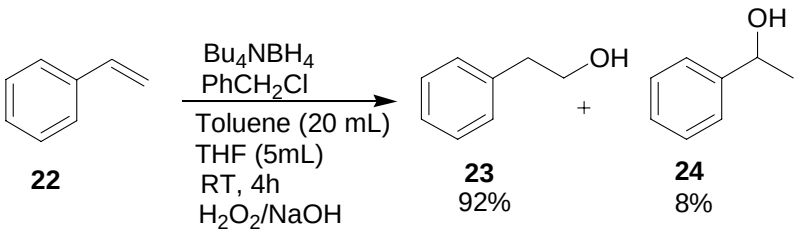
The diborane (*in situ*) generated using $Bu_4NBH_4/PhCH_2Cl$ and Bu_4NBH_4/I_2 effectively reduces various functional groups like aldehydes, ketones, carboxylic acids, acid chlorides and esters at 25 ^oC in toluene (Scheme 12)

Scheme 12



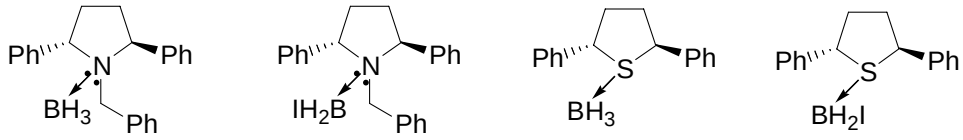
Also, the $Bu_4NBH_4/PhCH_2Cl$ reagent system is useful for the hydroboration of olefins under ambient conditions in toluene/THF mixture. The corresponding alcohols were obtained in good yields after H_2O_2/OH^- oxidation (Scheme 13).

Scheme 13



The hydroboration reactions of prochiral olefins were carried out using chiral Lewis base-BH_3 and BH_2I complexes prepared using Bu_4NBH_4/I_2 in toluene to examine the recently introduced concept of iodine activation of the borane complexes (Figure 1).

Figure 1



25 **26** **27** **28**

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

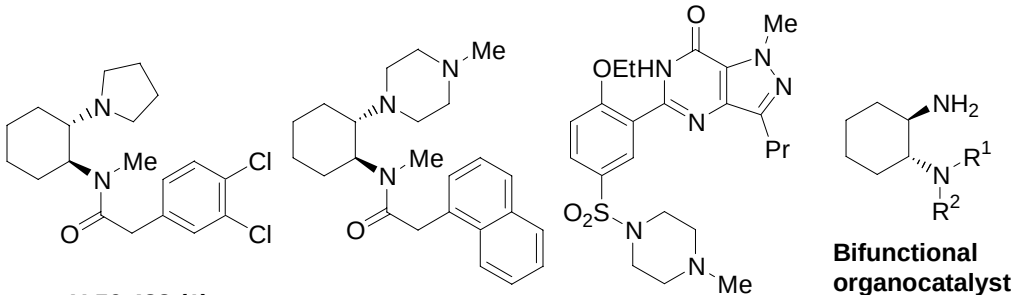
Chapter 1

Synthesis and Resolution of (±)-1,2-diamines

1.1 Introduction

A vast majority of biologically important molecules such as drugs and natural products contains nitrogen in their framework. Enantiomerically pure 1,2-diamines and their derivatives are also widely used as chiral auxiliaries[1] in a variety of asymmetric transformations involving chiral phosphonamides Lewis acids or electrophiles, metal enolates, dienophiles and transition metal reagents.[2] Also, the compounds containing 1,2-diamine moieties are valuable intermediates in the synthesis of biologically active molecules. For example, the diamine derivative **U 50,488** (**1**) a potent κ-opioid agonist is reported to have analgesics activity[3] and the compound **WO9902159** (**2**) (Figure 1) containing a N-alkyl piperazino moiety is reported to have potential for treating sexual disorders.[4]

Figure 1

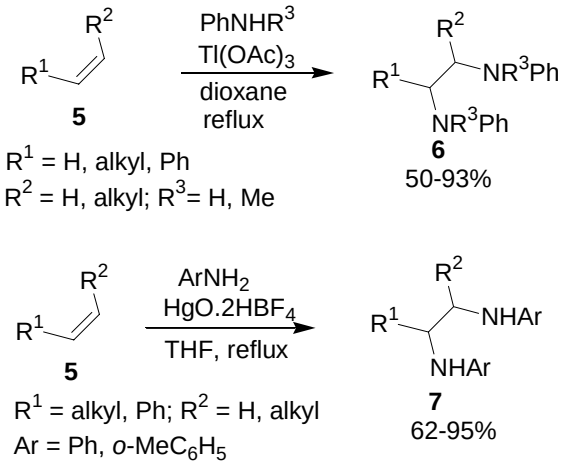


Accordingly, there have been several efforts towards the syntheses of these compounds in recent years.[5] We describe here a new approach to the synthesis and separation of enantiopure 1,2-diamines that are useful as precursors of the biologically active molecules **1** and **2**. A brief overview on the synthesis of 1,2-diamines by various methods would facilitate further discussion.

Synthesis of Vicinal diamines

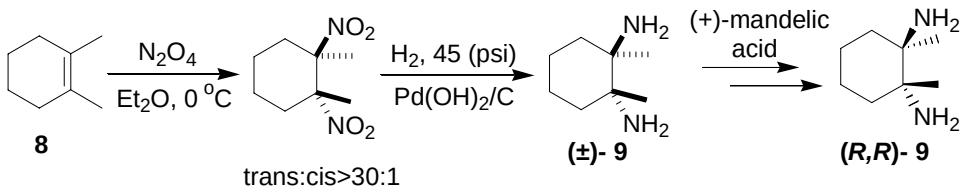
Barluenga *et al*[6] reported the preparation of aromatic vicinal diamines from olefins. The reaction of alkenes with thallium or mercury salts in the presence of primary or secondary amines leads to 1,2-diamines in good yields (50-95%). This procedure is limited to aromatic vicinal diamines (Scheme 1).

Scheme 1



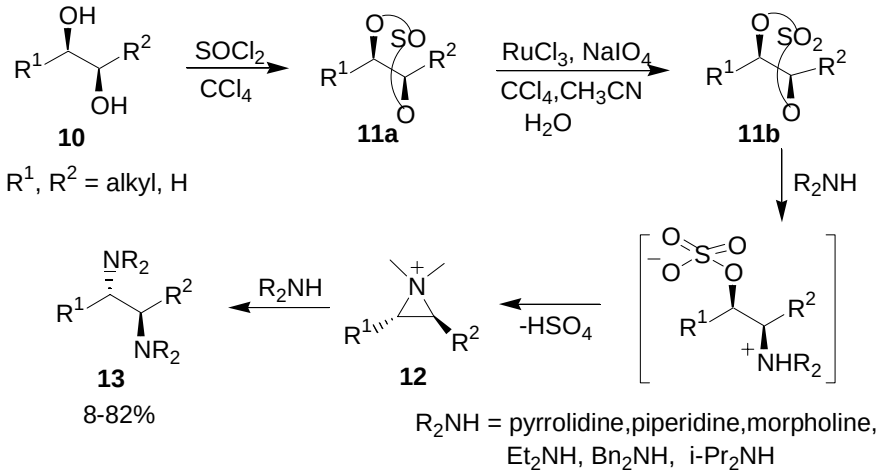
Jacobsen and Zhang[7] reported the preparation of *trans*-1,2-diamino-1,2-dimethylcyclohexane **9** by reaction of olefin **8** by dinitrogen tetraoxide with very good diastereoselectivity. Subsequent resolution with (+)-mandelic acid gave the enantiopure diamines (Scheme 2). This methodology is applicable only for vicinal diamines adjacent to tertiary centers because primary and secondary dinitro intermediates would be prone to epimerization.

Scheme 2



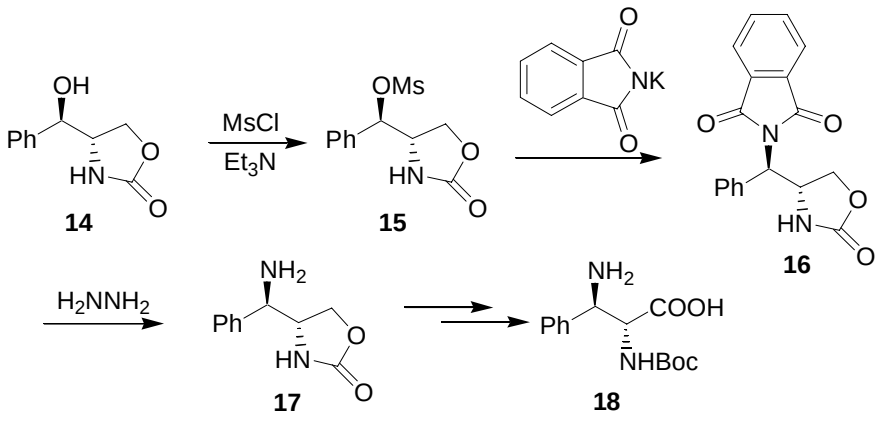
Sharpless *et al*[8] developed a method to convert 1,2-diols **10** into vicinal diamines. The conversion of optically pure 1,2-diols into cyclic sulfites **11a**, sulfates **11b** and subsequent reaction with various nitrogen nucleophiles affords the vicinal 1,2-diamines **13** in good yields (Scheme 3).

Scheme 3



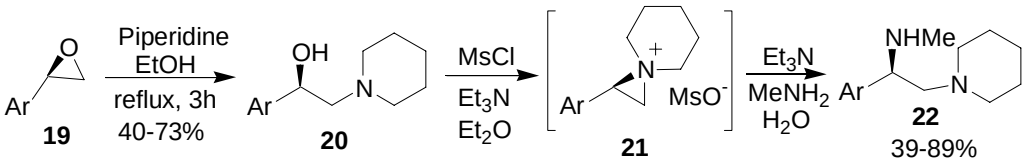
Rosi *et al*[9] synthesized 1,2-diamine precursors of taxol side chain analogue with retention in configuration via the reaction of potassium phthalimide with the mesylate of **14** as a consequence of the participation of the oxazolidinone nitrogen atom in the displacement mechanism (Scheme 4).

Scheme 4



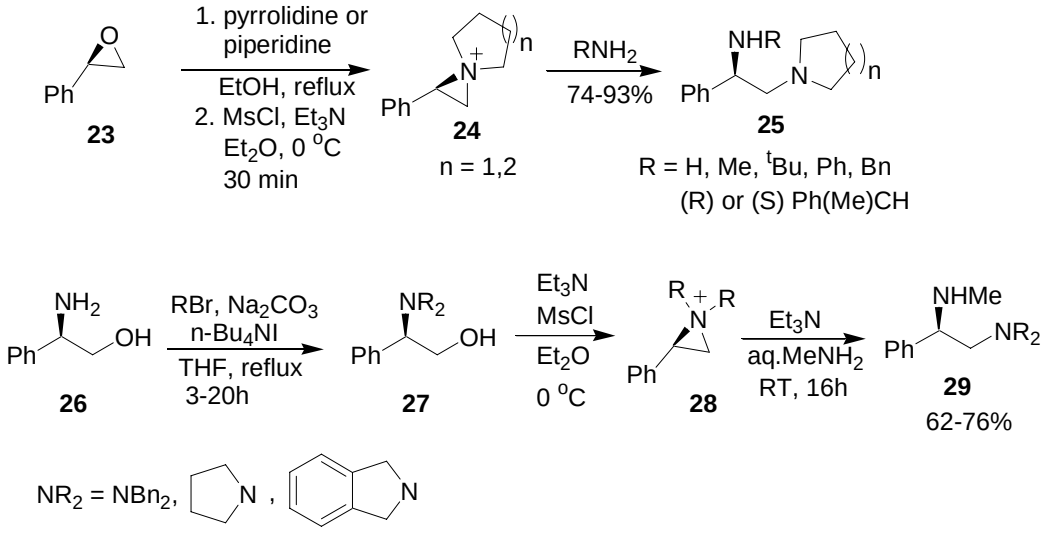
Rossiter and Miao[10] synthesized 1,2-diamines from 1,2-amino alcohols by nucleophilic opening of aziridinium ions **21** with methylamine (Scheme 5). The diamines were used as ligands for chiral amidocuprates in enantioselective conjugate addition to cyclic enones.

Scheme 5



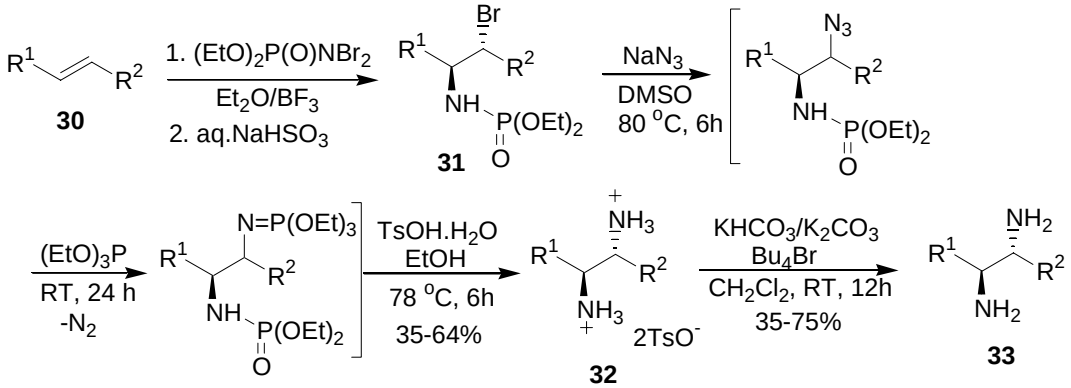
O`Brien *et al*[11] developed a one pot synthesis of 1,2-diamines from (*R*)-styrene oxide **23**. Mesylation of vicinal tertiary amino alcohols produced aziridinium ions which on treatment with primary amines affords diamines in good yields (Scheme 6).

Scheme 6



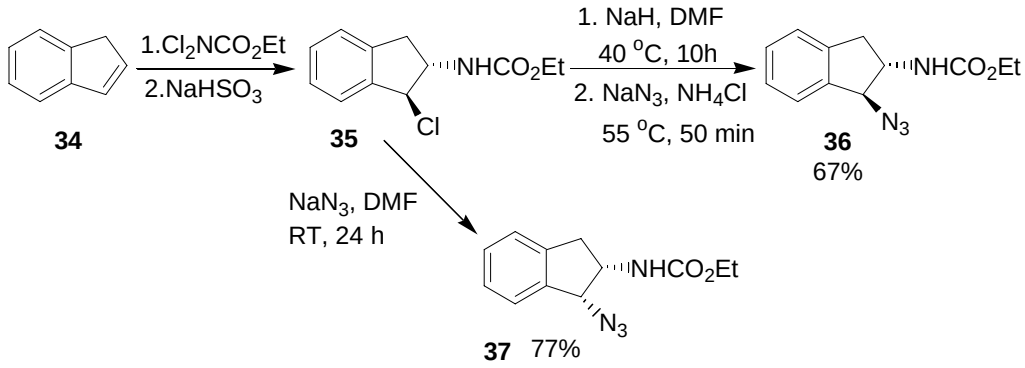
Zwierzak and Pacewicka[12] reported the synthesis of vicinal diamines from the bromophosphoramidates **31**, using a procedure involving the displacement of bromide ion by sodium azide and reduction of the azide in a Staudinger reaction (Scheme 7).

Scheme 7



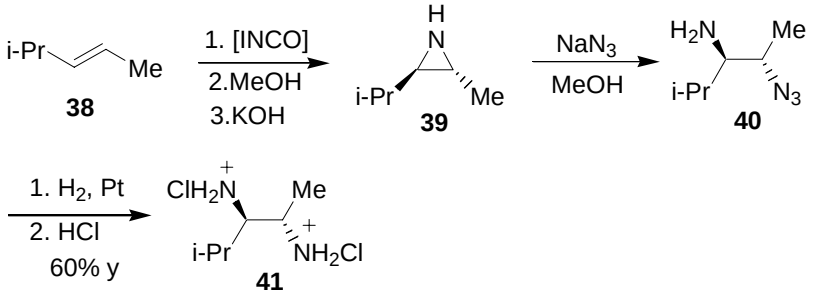
Orlek and Stemp[13] reported the synthesis of *trans*-1,2-diamine derivatives from β-halogenoalkylamines. The reaction of the intermediate N-chlorourethane **35** with nitrogen nucleophiles led to either *trans*-adducts **36** or *cis*-adducts **37** depending upon the conditions used (Scheme 8).

Scheme 8



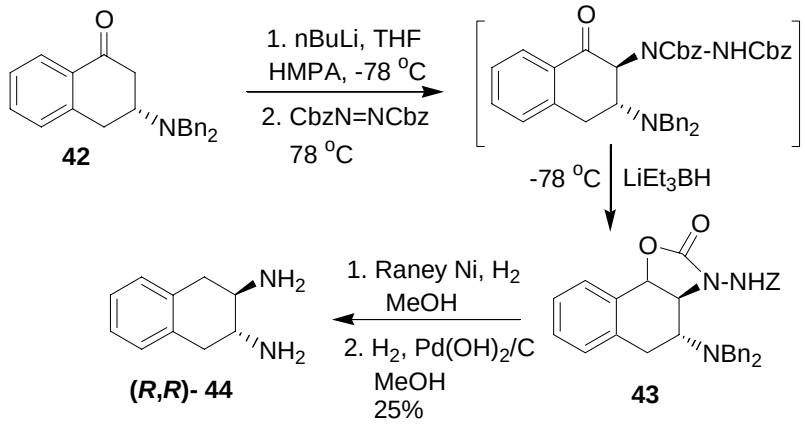
Swern and Swift[14] developed a strategy to synthesize either *syn* or *anti*-1,2-diamines from olefins. The aziridine intermediates were opened by the azide ion in the presence of isocyanate, and catalytic hydrogenation of resulting azide afforded diamines in moderate yields (Scheme 9).

Scheme 9



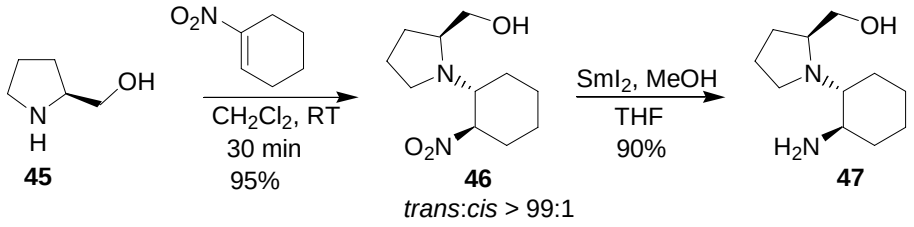
Hummel and Gmeiner[15] prepared chiral vicinal diamines from electrophilic amination of a chiral β-amino ketone **42** with dibenzylazodicaboxylate and obtained the *trans*-adduct **44** exclusively after the reduction (Scheme 10).

Scheme 10



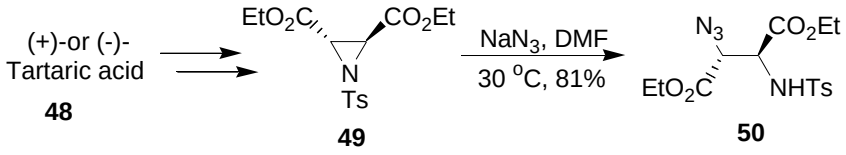
Strugess and Yarberry[16] prepared the diamine **47** by treating (*S*)-2-pyrrolidinylmethanol **45** with 1-nitrocyclohexene followed by reduction with samarium diiodide in methanol to obtain a single adduct in excellent stereoselectivity (Scheme 11).

Scheme 11



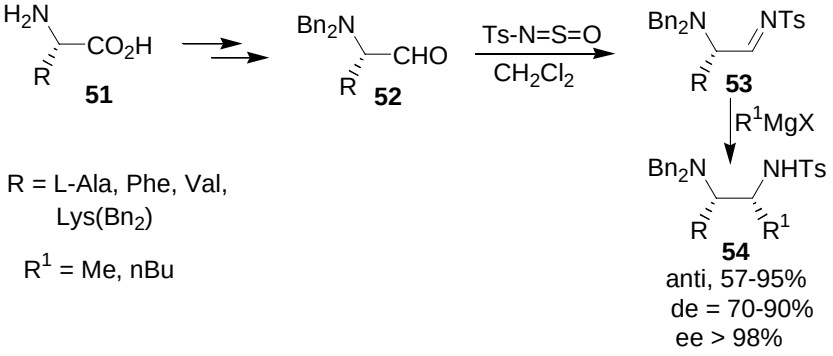
Tanner *et al*[17] synthesized C_2-symmetric aziridines **49** from easily available (+)- and (-)-tartaric acid **48**. Subsequent nucleophilic attack gave enantiopure amines **50** in good yields (Scheme 12).

Scheme 12



Reetz *et al*[18] synthesized vicinal diamines **54** based on stereoselective alkylation of imines **53** derived from *N*,*N*-dibenzylamino aldehydes **52** which were in turn obtained from α-amino acids **51** (Scheme 13).

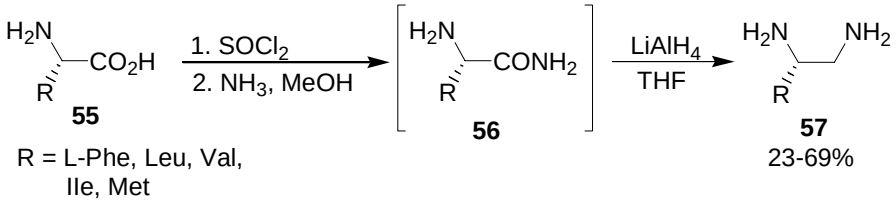
Scheme 13



Brunner *et al*[19] synthesized mono substituted vicinal diamines by reduction of amides **56** derived from natural α-amino acids with high enantiomeric purity (Scheme

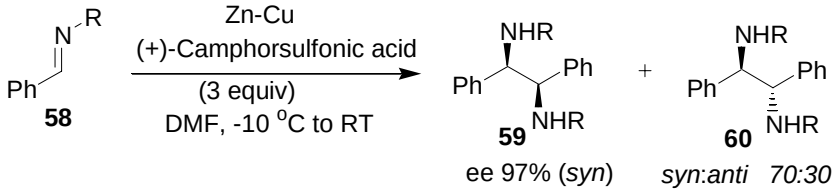
14). The derivatives are useful as ligands in platinum complexes that cause inhibition of DNA synthesis in tumor cells.

Scheme 14



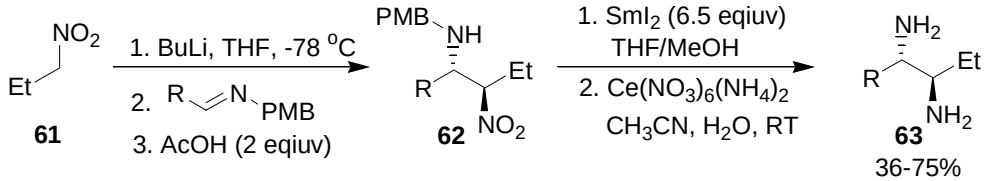
Fujisawa *et al*[20] reported the enantioselective pinacol coupling of benzaldimine **58** promoted by zinc-copper couple in the presence of excess (+)-camphorsulphonic acid (Scheme 15).

Scheme 15



Anderson *et al*[21] developed a method based on nitro-Mannich reaction by coupling of alkyl nitro compounds and aldimines in the presence of a Bronsted acid. The corresponding β-nitro-amines **62** were reduced with samarium diiodide to obtain 1,2-diamines in moderate to good yields (Scheme 16).

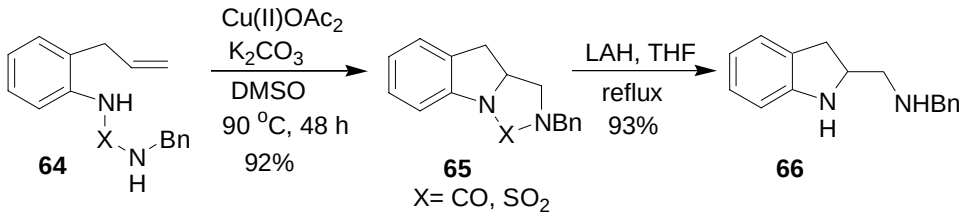
Scheme 16



R	*anti*:*syn*
Ph	10:1
$(CH_2)_4CH_3$	9:1
$(CH_3)_3Ph$	7:1

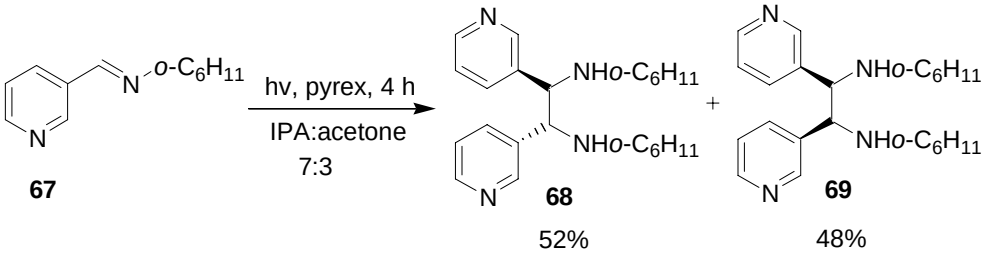
Chemler *et al*[22] developed a copper catalyzed intramolecular diamination, in which the two nitrogen groups are tethered by SO_2 or CO groups and the copper (II) salt mediated addition to the terminal double bond takes place to give a bicyclic diamine **66** products as shown in Scheme 17.

Scheme 17



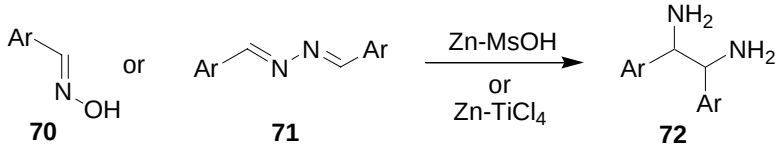
Symmetric vicinal diamines were prepared through photo-reductive coupling of pyridine, arene and alkylcarboxaldimines in good yields. This procedure tolerates bulky groups such as *tert*-butyl and diphenylmethyl on nitrogen atom (Scheme 18).[23]

Scheme 18



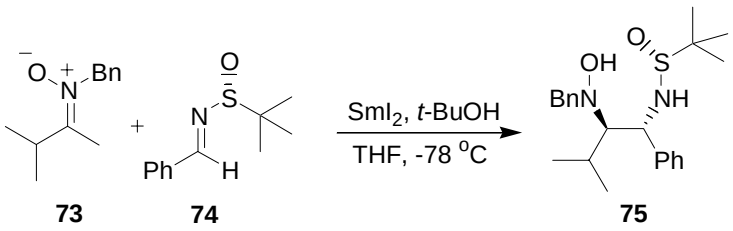
Kise and Veda[24] prepared vicinal diamines from reductive coupling reactions of oximes **70** and azines **71** in the presence of excess zinc at room temperature. Addition of MsOH selectively affords meso-1,2-diamines, while that of $TiCl_4$ led to dl-1,2-diamines (Scheme 19).

Scheme 19



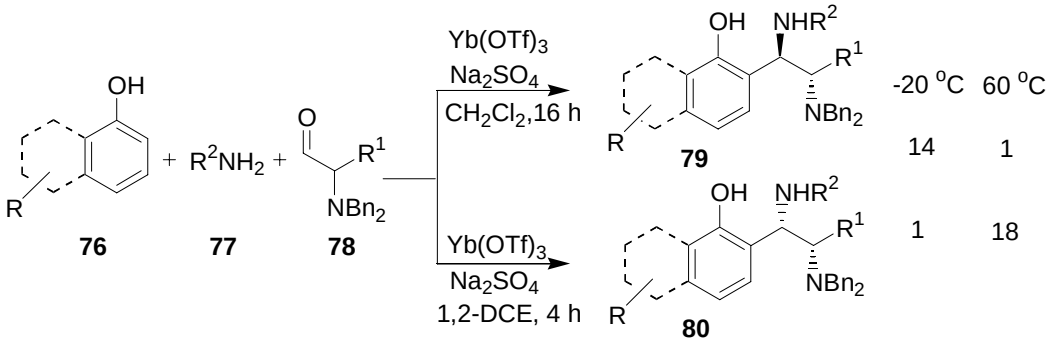
Xu *et al*[25] developed SmI_2 mediated heteronuclear reductive cross coupling of nitrones **73** with *N*-*tert*-butanesulfinyl imines **74** at -78 ^oC in tertiary butanol (Scheme 20). The sulfinyl group can be removed using copper acetate and zinc in acetic acid.

Scheme 20



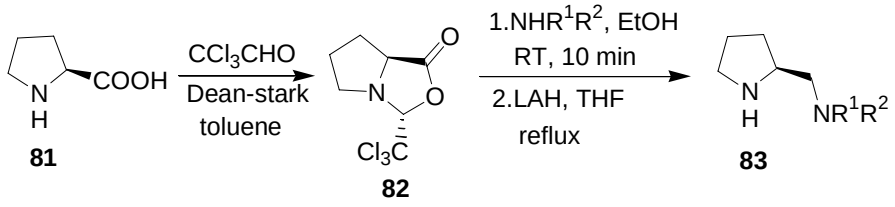
Zhu and Rondot[26] reported three component synthesis of chiral *O*-1,2-diaminoalkyl phenol from electron rich phenol **76**, an amine **77** and a chiral α-*N*,*N*-dibenzyaminoaldehyde **78**. By controlling reaction conditions, either *anti* **79** or *syn* **80** diastereomer can be prepared (Scheme 21).

Scheme 21



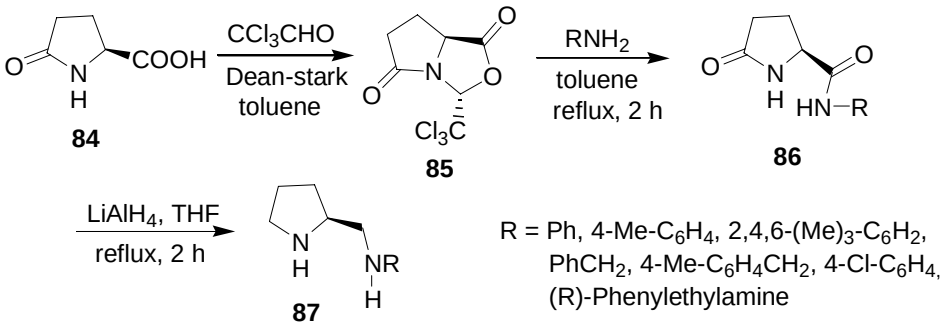
Amedjouk and Ahlberg[27] developed a strategy to transform (*S*)-proline **81** in to 1,2-diamines via reaction with chloral followed by introduction secondary amine group. The amide **82** is reduced to diamine **83** by $LiAlH_4$ with no loss of stereoselectivity (Scheme 22).

Scheme 22



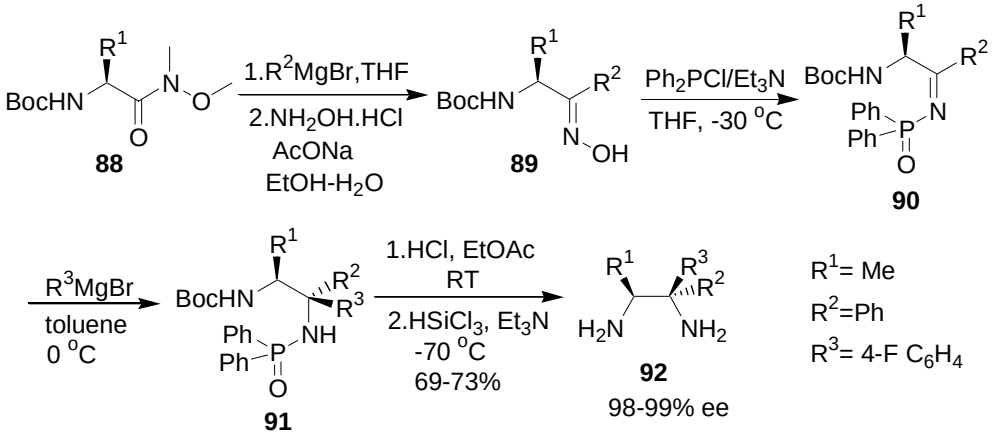
Anders *et al*[28] developed a modified procedure for the synthesis of unsymmetrical chiral secondary vicinal diamines **87** via primary amine mediated ring opening reaction of diastereomeric oxazolidinone **85** derivative (Scheme 23).

Scheme 23



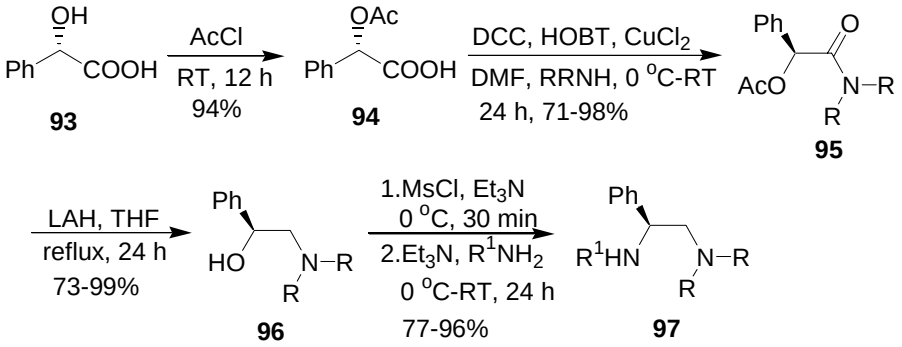
Optically active diamines were synthesized from amino acid derived N-diphenylphosphinoyl ketimines and Grignard reagents in excellent selectivity (up to 99% ee) (Scheme 24).[29]

Scheme 24



Singh *et al*[30] reported the synthesis of various chiral non-racemic 1,2-diamines (**97**) from readily available (*S*)-*O*-acetylmandelic acid **94** as shown in Scheme 25.

Scheme 25



In recent years, significant progress has been made towards the synthesis of enantiopure chiral compounds by enantioselective chemical and enzymatic synthesis, enantioselective chromatography and selective transformation of compounds from natural chiral pool. However, not all of these methods are practical for execution on large scale synthesis. On the other hand, methods for the synthesis of racemic compounds are much simpler and can be extended to large scale synthesis.[31] Stereospecific syntheses of (±)-*trans*-*N,N*-cyclohexane-1,2-diamines were carried out from the corresponding (±)-*trans*-*N,N*-dialkylaminocyclohexanols. The ring opening of intermediate aziridinium ions by nitrogen nucleophiles affords the corresponding 1,2-diamines.[32] We have undertaken research efforts on the use of this route for the synthesis of chiral 1,2-diamines. The results are described in the next section.

1.2. Results and discussion

1.2.1 Preparation of (±)-*trans*-*N*,*N*-dialkylaminocyclohexanols

The racemic 1,2-amino alcohols are readily prepared using cyclohexene oxide by refluxing with the corresponding secondary amines such as pyrrolidine, piperidine, and 4-methylpiperazine in high yields following a reported procedure (Scheme 26, Table 1).[32]

Scheme 26

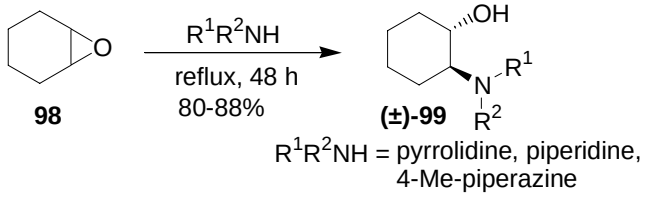
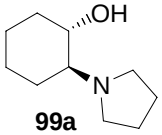
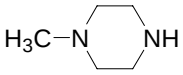
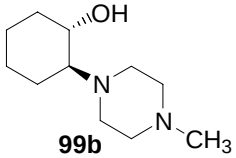
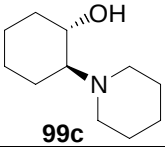


Table 1 Preparation of (±)-*trans*-*N*,*N*-dialkylaminocyclohexanols[a]

entry	R^1R^2NH	(±)-*trans*-1,2-amino alcohol[b]	yield (%)[c]
1		 **99a**	88
2		 **99b**	80
3		 **99c**	87

[a]All the reactions were carried out with 280 mmol of secondary amine and 300 mmol of cyclohexene oxide. [b]The products were identified using spectral data (IR, ^{1}H, ^{13}C-NMR) and comparison with reported data.[32] [c]Yields are of isolated products.

1.2.2 Preparation of (±)-*trans*-*N*,*N*-cyclohexane-1,2-diamines

Syntheses of the (±)-*trans*-1,2-diamines were carried out using the corresponding (±)-*trans*-1,2-amino alcohols **99** by successive treatment with mesyl chloride in the presence of Et_3N and subsequent reaction of aziridinium ion **100**

intermediate prepared *in situ* with nitrogen nucleophiles such as aqueous ammonia, pyrrolidine and piperazine to afford the corresponding (±)-*trans*-1,2-diamines **101** in good yields (66-80%) (Scheme 27, Table 2).

Scheme 27

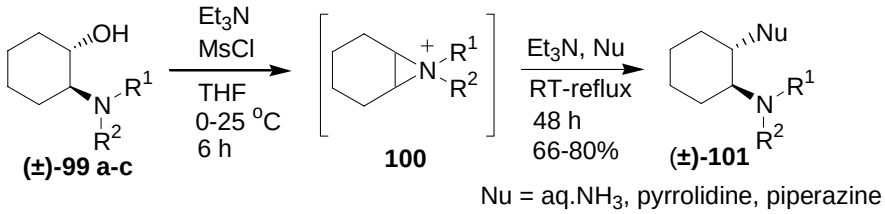
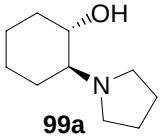
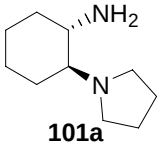
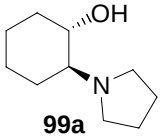
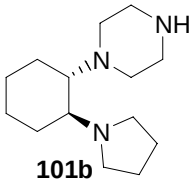
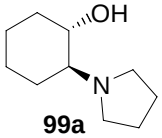
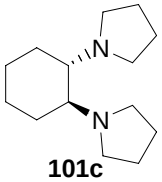
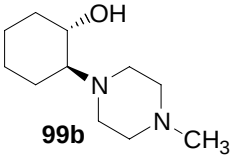
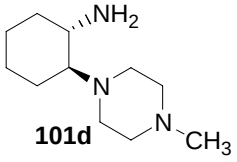
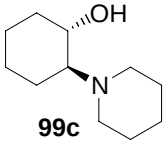
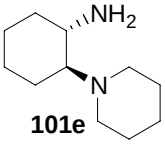


Table 2 Synthesis of (±)-*trans*-*N,N*-cyclohexane-1,2-diamines[a]

entry	(±)-*trans*-1,2-amino alcohols	nucleophiles	(±)-*trans*-1,2-diamine[b]	yield (%)[c]
1	 **99a**	$aq.NH_3$	 **101a**	80
2	 **99a**	Piperazine	 **101b**	66
2	 **99a**	Pyrrolidine	 **101c**	70
3	 **99b**	$aq.NH_3$	 **101d**	70
4	 **99c**	$aq.NH_3$	 **101e**	76

[a]All the reactions were carried out in 25 mmol of amino alcohol. [b]The products were identified using spectral data (IR, ^1H, ^{13}C-NMR). [c]Yields are of isolated products.

1.2.3 Resolution of (±)-*trans*-*N*,*N*-cyclohexane-1,2-diamines

Synthesis of enantiomerically pure compounds is an important area of research relevant to pharmaceutical industries. Although the chemical and physical properties of both enantiomers (*R* and *S*) are same in the achiral environment, they are readily distinguished by biological systems. Therefore, enantiomers often have different pharmacokinetic properties such as absorbtion and distribution rate and may also have different toxicological effects.[33] Despite the tremendous progress made in enantioselective processes, resolution of racemates via diastereoisomeric salt formation remains the most inexpensive and operationally simplest method for producing pure enantiomers on a larger scale. Also, it has been estimated that more than half of the chiral drugs on the pharmaceutical market are produced by the diastereomeric salt formation method using enantiomerically pure resolving agents.[34]

In recent years, we have developed convenient methods to resolve several synthetically useful optically pure compounds from racemic amines,[32b,35] amino alcohols,[36] diols,[37] diacids,[38] and BINOL[39] using commercially available resolving agents and also reagents prepared *in situ* using bi-2-napthol and $B(OMe)_3$ **111** (Chart 1).

Chart 1

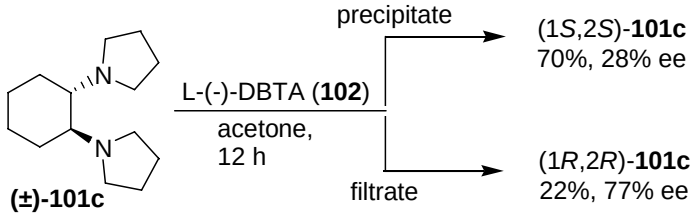
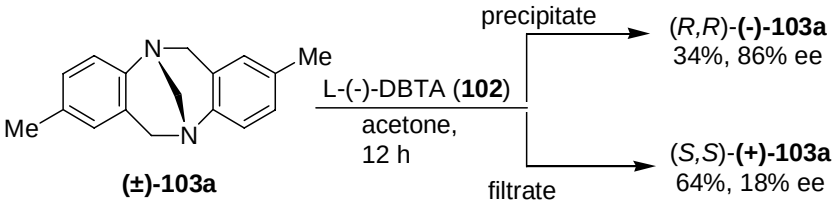
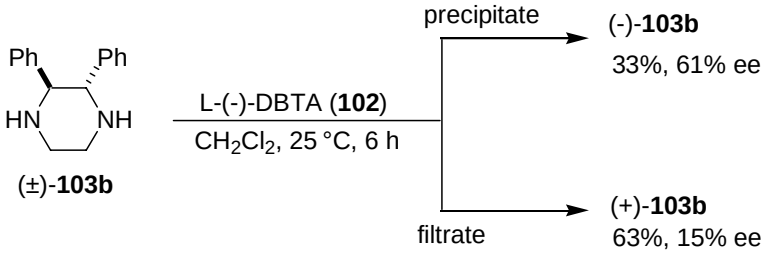


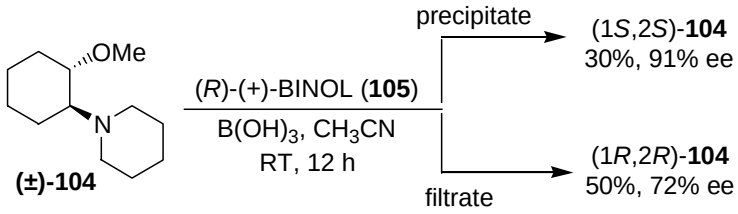
Chart 1 (continued)

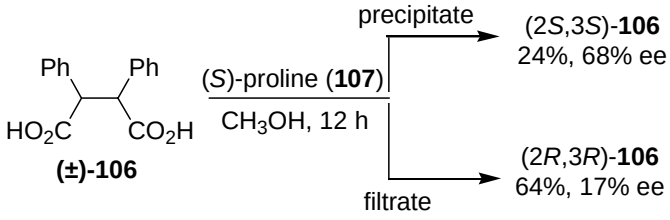


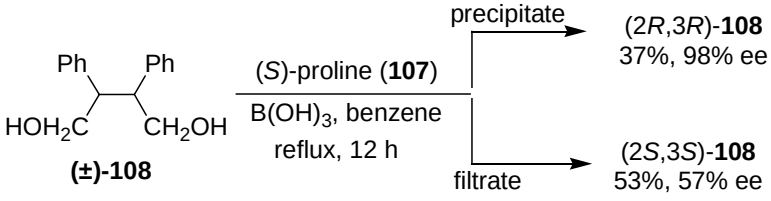
DBTA = *O,O'*-dibenzoyl-L-tartaric acid

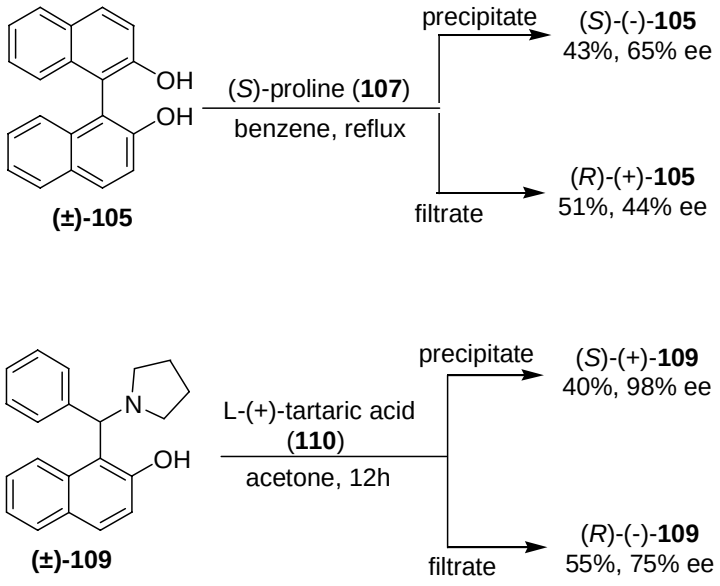


DBTA = *O,O'*-dibenzoyl-L-tartaric acid









As outlined in the introductory section, the optically pure diamines **101a** and **101d** are potentially useful precursors for the synthesis of biologically active target molecules of **1** and **2** are of our interest. Also, these chiral 1,2-diamines can be used as a chiral auxiliaries in organic synthesis.[40]

Recently, an enzyme catalyzed kinetic resolution[41] of (±)-*trans*-cyclohexane-1,2-diamines were reported using lipase B, *canadida antartica* with ethyl acetate as a solvent and acyl donor. Enzymes required careful handling, and tend to lose activity or decompose at higher temperatures. Resolution of racemates via diastereomeric salt formation, however, usually requires relatively cheap reagents and simple reaction conditions.

1.2.4 Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using Dibenzoyl-*L*-tartaric acid

The racemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a** was resolved[42] by formation diastereomeric salt with dibenzoyl-*L*-tartaric acid **102** in acetone at 25 ^{o}C. Optimum results were obtained using the (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine

and the resolving agent in 2:1 ratio. Partially resolved sample of **101a** was obtained in 82% ee under these conditions which upon further enrichment gave samples with >99% ee (Scheme 28, Table 3).

Scheme 28

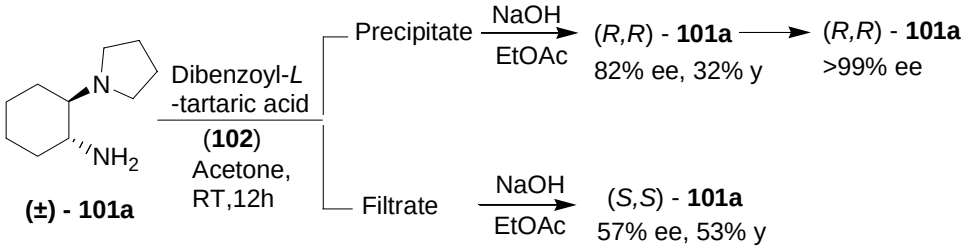


Table 3 Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using *O,O'*-dibenzoyl-*L*-tartaric acid[a]

entry	**101a** mmol solvent (mL)	% ee[b]/ (conf)	*trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a**			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	10 (60)	00	82 (*R,R*)	32	57 (*S,S*)	53
2	2.5 (25)	82 (*R,R*)	>99[d] (*R,R*)	31	68 (*R,R*)	42

[a]All the reactions were carried out in acetone at RT. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 68 (c 0.73, $CHCl_3$) for (*R,R*)-**101a**[41]. [c]The yields are of the isolated products, based on the total amount of the diamine **101a** used. [d]Maximum ee value reported here is based on HPLC analysis of amide derivative **118** of the diamine **101a.**

We have also observed that the partial resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a** can be carried out via the preparation of the borate complex **111**[43] using optically pure (*S*)-1,1`-bi-2-napthol and trimethyl borate (Scheme 29, Table 4).

Scheme 29

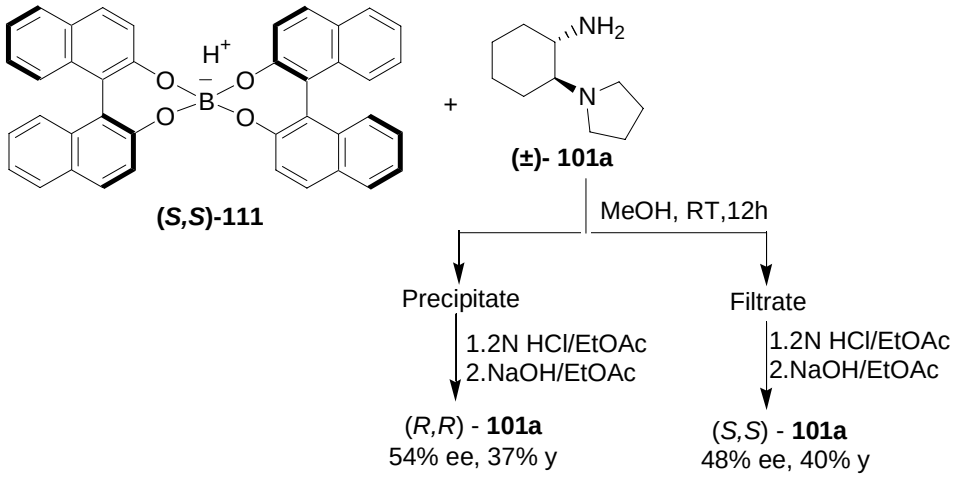


Table 4 Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using the chiral complex 111[a]

entry	**101a** mmol solvent (mL)	% ee[b]/ (conf)	*trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a**			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	10 (150)	00	54 (*R*,*R*)	37	48 (*S*,*S*)	40
2	2.5 (30)	54	98[d] (*R*,*R*)	30	83 (*R*,*R*)	20

[a]All the reactions were carried out in MeOH at 25 °C. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 68 (c 0.73, $CHCl_3$) for (*R*,*R*)-**101a**.[41] [c]The yields are of the isolated products, based on the total amount of the diamine **101a** used. [d]Maximum ee value reported here is based on HPLC analysis of amide derivative of the diamine **101a**.

Among the solvents used, methanol gave optimum results (Table 5).

Table 5 Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using the chiral complex 111[a]

entry	solvent	*trans*-(±)-2-(1-pyrrolidinyl)cyclohexylamine **101a**			
		precipitate fraction		filtrate fraction	
		% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	CH_3CN	15 (*R*,*R*)	72	67 (*S*,*S*)	11
2	THF	30 (*R*,*R*)	24	21 (*S*,*S*)	66
3	**MeOH**	**54** (*R*,*R*)	37	**48** (*S*,*S*)	40

[a]All the reactions were carried out with 5 mmol of diamine in 60 mL of the solvent. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 68 (c 0.73, $CHCl_3$) for (R,R)-**101a**. [c]The yields are of the isolated products, based on the total amount of the diamine **101a** used.

1.2.5 Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using the chiral complex 111 in methanol

We have then undertaken efforts to resolve the (±)-*trans*-2-(4-methyl-piperazinyl)cyclohexylamine **101d** using commercially available *L*-(+)-tartaric acid, dibenzoyl-*L*-tartaric acid, mandelic acid and 10-camphorsulfonic acid in individual runs. Unfortunately, there was no resolution observed in several solvents using these chiral acids. However, we have observed that the racemic diamine **101d** can be partially resolved by using the complex **111** prepared using (*S*)-(-)-bi-2-napthol and $B(OMe)_3$ in methanol to obtain the chiral diamine **101d** in 66% ee under these reaction conditions (Scheme 30, Table 6).

Scheme 30

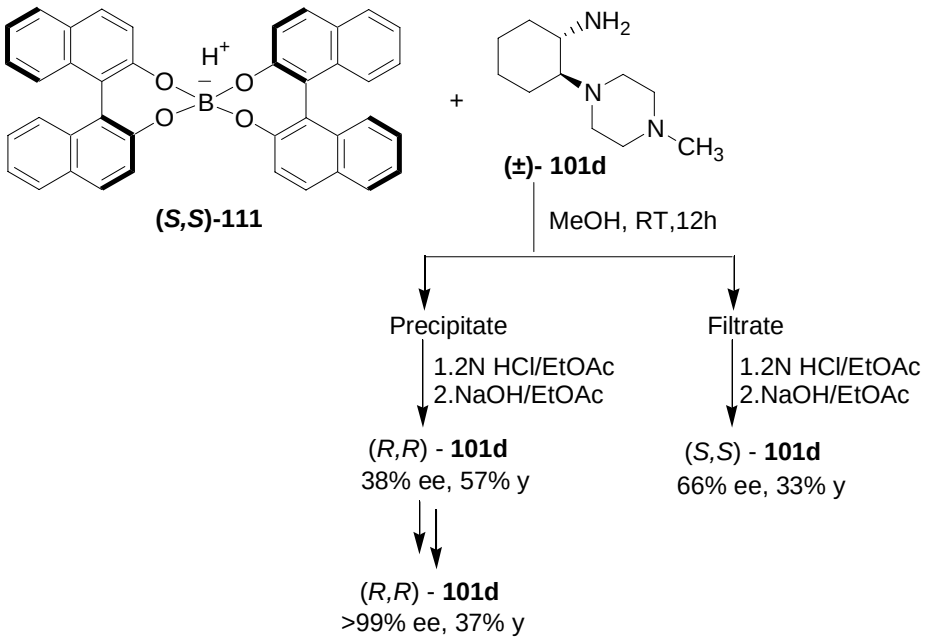


Table 6 Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using the chiral complex 111[a]

entry	**101d** mmol, solvent (mL)	% ee[b] (conf)	*trans*-2-(4-methylpiperazinyl)cyclohexylamine **101d**			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	10 (180)	00	38 (*R*,*R*)	57	66 (*S*,*S*)	33
2	5 (120)	38 (*R*,*R*)	80 (*R*,*R*)	44	22 (*S*,*S*)	35
3	2.5 (50)	80 (*R*,*R*)	>99[d] (*R*,*R*)	37	34 (*R*,*R*)	26

[a]All the reactions were carried out MeOH at 25 °C. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 43 (c 0.92, $CHCl_3$) for (*R*,*R*)-**101d**. [c]The yields are of the isolated products, based on the total amount of the diamine **101d** used. [d]Maximum ee value reported here is based on HPLC analysis of amide derivative of diamine **101d.**

1.2.6 Preparation of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine 112a

Optically active cyclohexane-1,2-diamine derivatives are widely used in chemistry.[44] However, their use is mainly limited to those ligands easily prepared from commercially available optically active *trans*-cyclohexane-1,2-diamine.[45] This may be due to complications involved in the preparation of optically active nonsymmetric ligands from this diamine, involving additional steps of protection and subsequent reactions leading to lower yields.[46]

The (±)-*trans*-*N*,*N*-cyclohexane-1,2-diamines **101a, 101d** and **101e** can be readily used for preparing nonsymmetric ligands by treating with appropriate reagents. We have prepared tetrasubstituted (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexyl-amine **112** by treating (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine with benzyl bromide in the presence base (Scheme 31). Also, the 1,2-diamines **112b** and **112d** can be further derivatized (Table 7).

Scheme 31

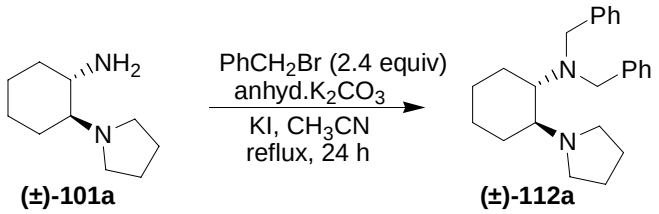
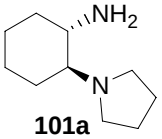
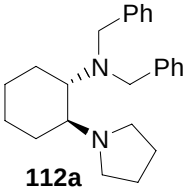
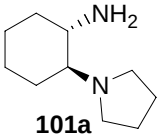
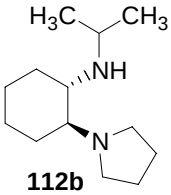
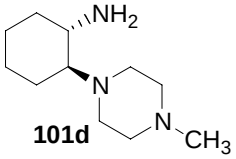
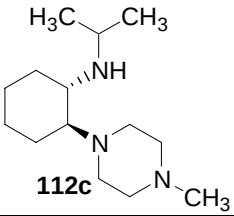


Table 7 Preparation of (±)-*trans*-*N*,*N*-cyclohexane-1,2-diamine derivatives

entry	(±)-*trans*-1,2-diamines	RX (equiv.)	product[c]	yield (%)[d]
1[a]	 **101a**	$C_6H_5CH_2Br$ (2.4)	 **112a**	92
2[b]	 **101a**	$(CH_3)_2CHBr$ (1.2)	 **112b**	76
3[b]	 **101d**	$(CH_3)_2CHBr$ (1.2)	 **112c**	70

[a]Reaction was carried out in 20 mmol of 1,2-diamine **101a**. [b]Reactions were carried out in 10 mmol of 1,2-diamine **101a** and **101d**. [c]The products were identified using spectral data (IR, ^1H, ^{13}C-NMR). [d]Yields are of isolated products.

1.2.7 Resolution of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine 112a using the chiral complex 111 in acetonitrile

We have carried out the resolution of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)-cyclohexylamine **112a** using commercially available *L*-(+)-tartaric acid, dibenzoyl-L-tartaric acid, mandelic acid, 10-camphorsulfonic acid and (*S*)-(-)-1,1'-bi-2-napthol/$B(OH)_3$, in various solvents in individual runs. Though in the case of (*S*)-(-)-1,1'-bi-2-napthol/$B(OH)_3$ a precipitate was formed after the addition of substrate to the

resolving agent, no resolution was observed. Fortunately, we have observed that the pre-formed complex **111** prepared using (*S*)-(-)-1,1'-bi-2-napthol and $B(OMe)_3$ in acetonitrile resolved the *trans*-(±)-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine at 25 °C. The partial resolution was achieved to obtain a sample with 59% ee. Subsequently, the non-racemic sample can be enriched to >99% ee (Scheme 32, Table 8).

Scheme 32

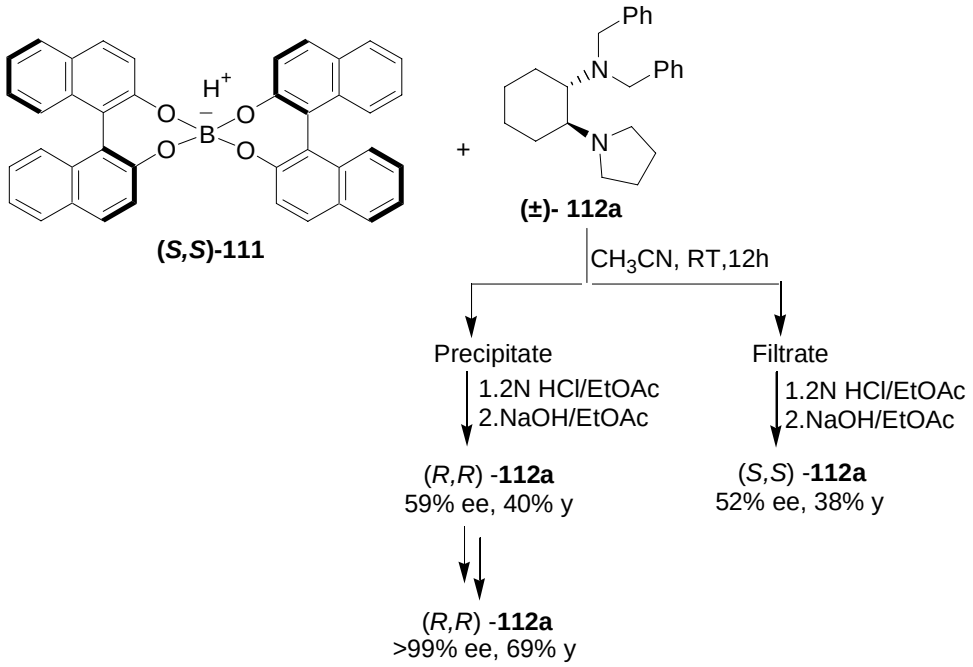


Table 8 Resolution of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine 112a using the chiral complex 111[a]

entry	**112a** mmol solvent (mL)	% ee[b]/ conf	*trans*-1,2-diamine **112a**			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	10 (150)	00	59 (*R*,*R*)	40	52 (*S*,*S*)	38
2	5 (80)	59 (*R*,*R*)	86 (*R*,*R*)	68	12 (*S*,*S*)	15
3	2.5 (50)	86 (*R*,*R*)	>99 (*R*,*R*)	69	44 (*R*,*R*)	5

[a]All the reactions were carried out in acetonitrile at 25 °C. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 37 (c 0.81, $CHCl_3$) for (R,R)-**112a.**[47] [c]The yields are of the isolated products, based on the total amount of the diamine **112a** used.

1.2.8 Partial resolution of (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine 101b

In order to further examine the applicability and the scope of this resolving system with other amines, we carried out the resolution of the (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine **101b** with the chiral complex **111**. Indeed, the partial resolution was achieved in methanol at 25 °C. Comparable results were obtained using the solvents methanol and acetonitrile (Scheme 33, Table 9).

Scheme 33

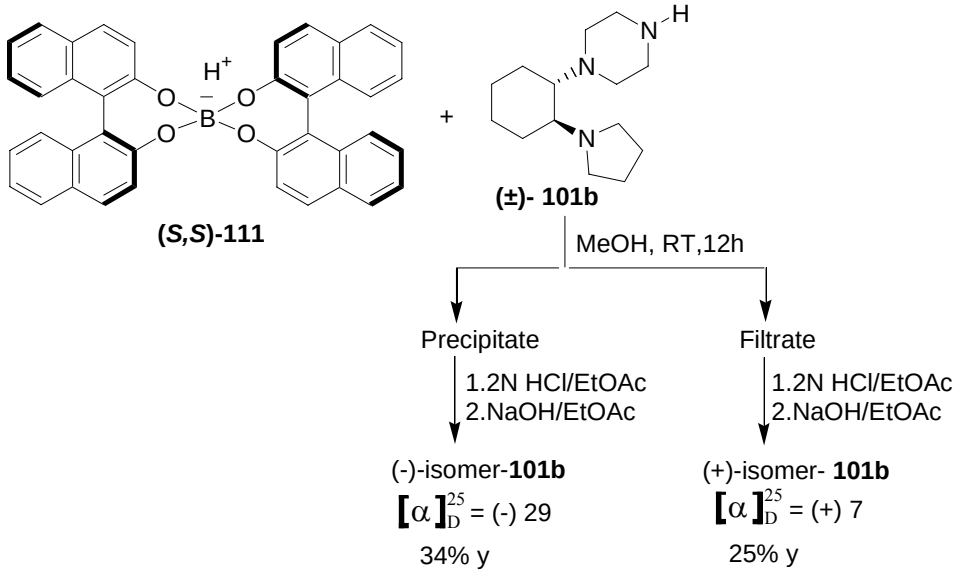


Table 9 Partial resolution of (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine 101b using the chiral complex 111[a]

entry	solvent	*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine **101b**			
		precipitate fraction		filtrate fraction	
		$[\alpha]_D^{25}$	yield (%)[b]	$[\alpha]_D^{25}$	yield (%)[b]
1	CH_3CN	(-) 24	22	(+) 5	6
2	MeOH	(-) 29	34	(+) 7	25

[a]All the reactions were carried out at 25 °C. [b]The yields are of the isolated products, based on the total amount of the diamine **101b** used.

1.2.9 Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine (101d) using (*R*)-(-)-binapthylphosphoric acid (113)

We have successfully resolved a series of (±)-*trans*-1,2-diamines **101a**, **101b** (partial resolution), **101d**, and **112a** using the bi-2-napthol complex **111** prepared *in situ* under ambient conditions. However, as the preparation of the bi-2-napthol complex **111**, is somewhat tedious, we were looking for a much simpler resolving agent. Fortunately, we have found that the optically active binapthylphosphoric acid[48] (BNP) **113**, which can be easily accessed from optically pure 1,1'-bi-2-napthol, is useful for the resolution of the (±)-*trans*-1,2-diamine **101d** in THF. With this resolving agent, partial resolution of the diamine **101d** occurs to afford samples with 57 % ee under these conditions (Scheme 34, Table 10). Further enrichment of this sample in two successive operations gives >99% ee. We have also observed that the binapthylphosphoric acid **113** can be easily recovered and reused without losing any activity.

Scheme 34

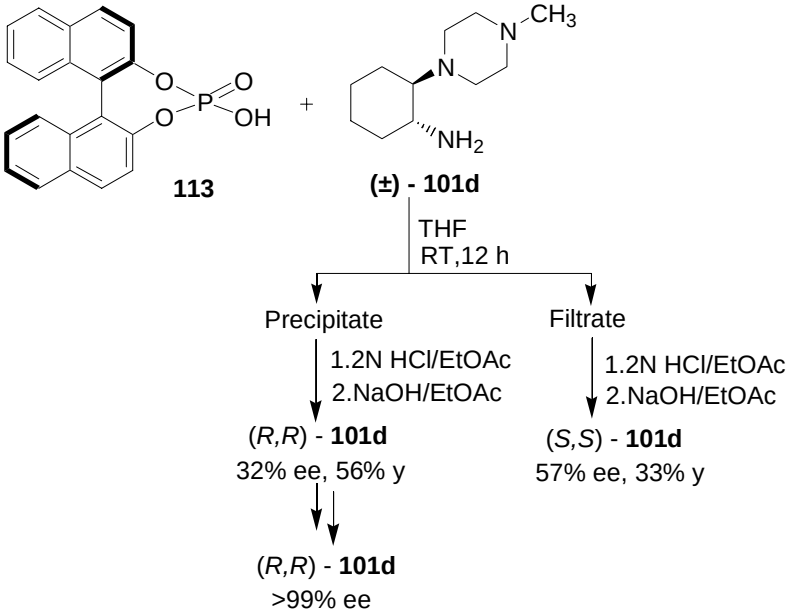


Table 10 Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using (*R*)-(-)-binapthylphosphoric acid 113[a]

entry	**101d** mmol solvent (mL)	% ee[b] (conf)	*trans*-1,2-diamine **101d**			
			precipitate fraction		filtrate fraction	
			% ee[b]/conf	yield (%)[c]	% ee[b]/conf	yield (%)[c]
1	10 (180)	00	32 (*R*,*R*)	56	57 (*S*,*S*)	33
2	5 (150)	32 (*R*,*R*)	80 (*R*,*R*)	45	21 (*S*,*S*)	35
3	2.5 (60)	80 (*R*,*R*)	>99[d] (*R*,*R*)	37	34 (*R*,*R*)	26

[a]All the reactions were carried out in THF at 25 °C. [b]The ee values reported here are based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 43 (c 0.92, $CHCl_3$) for (*R*,*R*)-**101d**. [c]The yields are of the isolated products, based on the total amount of the diamine **101d** used. [d]Maximum ee value reported here is based on HPLC analysis of amide derivative of the diamine **101d**.

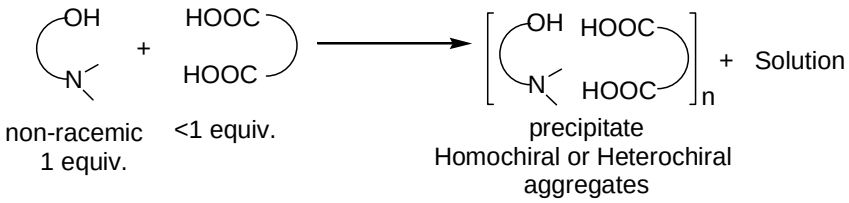
1.2.10 Enrichment of enantiomeric purity of non-racemic diamines using achiral acids

In 1973, Horeau[49] reported that the chemical duplication of a non-racemic substrate through formation of two diastereomeric carbonate diesters from an scalemic (partially resolved) alcohol and subsequent separation and hydrolysis of the homochiral (*RR*,*SS*) esters gave the alcohol with increased enanatiomeric excess. Later, Fleming and Gosh[50] applied the same method to enrich partially resolved alcohol from 92% ee to 99.6% ee by using oxalyl chloride.

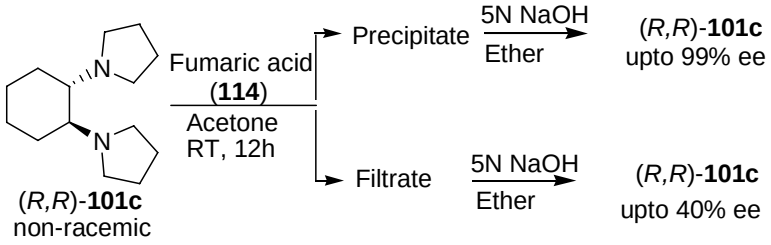
Enanatiomeric enrichment based on manipulation of non-racemic substrates with achiral reagent like Horeau`s method involves chemical reaction and its limitations have been discussed in detail in a review.[51] Horeau method can be used for microscale determinations provided a highly sensitive method (GC, HPLC, MS or CD) is available to determine the composition of the diastereomeric esters formed.

Recently, a novel method for the purification of partially resolved amino alcohols (Scheme 35) and a C_2-symmetric *trans*-1,2-bis(pyrrolidino)cyclohexane (Scheme 36) was developed in this laboratory via preparation of the corresponding hydrogen bonded homochiral or heterochiral aggregates.[52]

Scheme 35

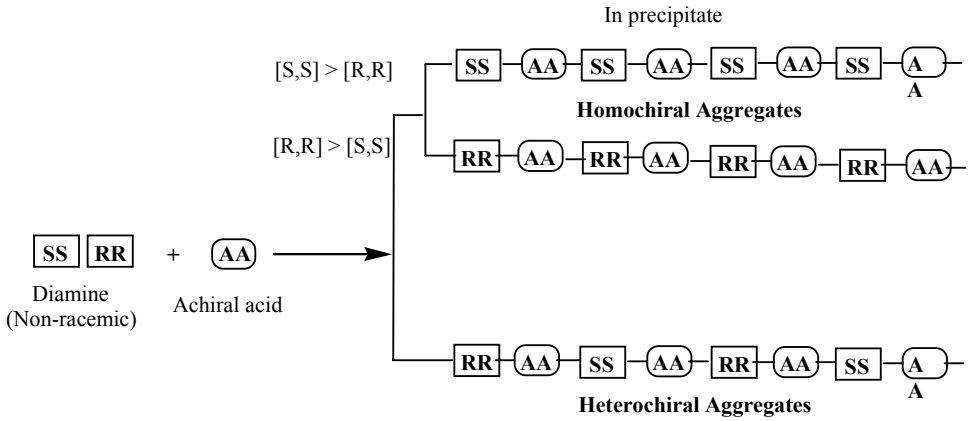


Scheme 36



"Homochiral interactions" are defined as intermolecular nonbonded interactions (such as Van der Walls and electrostatic interactions, hydrogen bonding and π-complex formation) between homochiral molecules present in assemblies of molecules having like chirality sense. Homochiral and heterochiral interactions among molecules of like constitution leads to two types of aggregates, which is anisometric (diastereomeric).[53] The difference ($\Delta G_{homo} \neq \Delta G_{hetero}$) between homochiral and heterochiral interactions is responsible for measurable differences in physical properties exhibited by racemates and the corresponding enantiomerically pure compounds (Scheme 37).

Scheme 37 Pictorial representation of homochiral/heterochiral aggregates formation[52c]



A method, where a non-racemic sample could be enriched using a cheap and commercially available achiral substrates, would serve as an important synthetic tool for chemistry in general. We have exploited this idea to enrich our non-racemic diamines **101a** and **101d** using achiral acids such as fumaric acid and oxalic acid.

1.2.11 Purification of non-racemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using fumaric acid 114

We have followed the above mentioned method to enhance the optical purity of the partially resolved *trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a** using fumaric acid in acetone.[52] Enantiomerically enriched samples with upto 99% ee were readily obtained following this method (Scheme **38**, Table 11).

Scheme 38

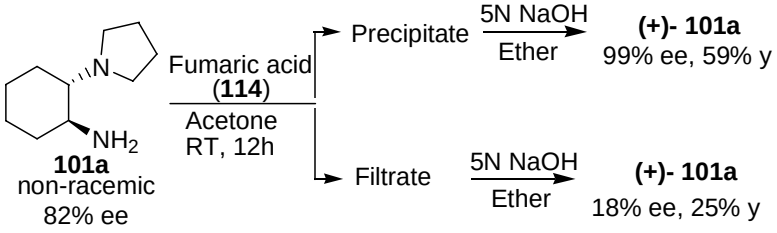


Table 11 Purification of non-racemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using fumaric acid 114[a]

entry	substrate (% ee)	fumaric acid **114** (mmol)	diamine **101a** obtained from			
			precipitate		filtrate	
			% ee[b]/conf.	yield (%)[c]	% ee[b]/conf.	yield (%)[c]
1[d]	(*R*,*R*) 58	2.9	87 (*R*,*R*)	63	22 (*R*,*R*)	28
2[e]	(*R*,*R*) 87	2.18	98 (*R*,*R*)	62	30 (*R*,*R*)	30
3[d]	(*S*,*S*) 54	2.7	72 (*S*,*S*)	45	26 (*S*,*S*)	32
4[e]	(*S*,*S*) 82	2.1	99 (*S*,*S*)	59	18 (*S*,*S*)	25

[a]All the reactions were carried out in acetone at 25 °C. [b]The ee values based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 68 (*c* 0.73, $CHCl_3$) for (*R*,*R*)-**101a.** [c]The yields are of the isolated products, based on the total amount of the starting diamine used. [d]The reactions were carried out using non-racemic **101a** (5 mmol) and fumaric acid in acetone (30 mL). [e]The reactions were carried out using non-racemic **101a** (2.5 mmol) and fumaric acid in acetone (15 mL).

1.2.12 Purification of non-racemic *trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using oxalic acid 115

The partially resolved diamine **101d** was further enriched using oxalic acid.$2H_2O$ **115** in quantities equal to the amount of racemic-**101d** present in the non-racemic sample **101d** in THF (Scheme 39). Enantiomerically enriched samples with 98% ee were readily obtained following this method. These results are summarized in Table 12.

Scheme 39

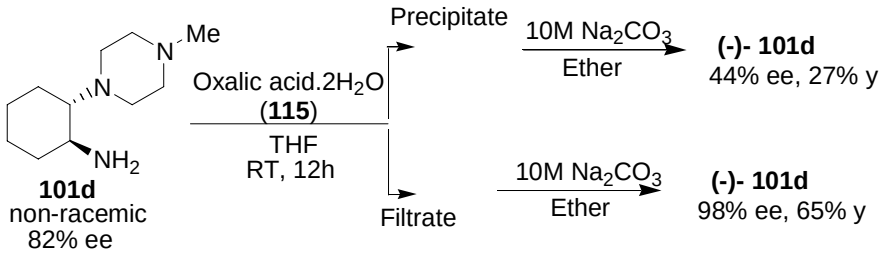


Table 12 Purification of non-racemic *trans*-2-(4-methylpiperazinyl)cyclohexyl-amine 101d using oxalic acid 115[a]

entry	substrate (% ee)	oxalic acid **115** (mmol)	diamine **101d** obtained from			
			precipitate		filtrate	
			% ee[b]/conf.	yield (%)[c]	% ee[b]/conf.	yield (%)[c]
1[d]	(*R*,*R*) 45	2.75	10 (*R*,*R*)	40	72 (*R*,*R*)	43
2[e]	(*R*,*R*) 63	0.93	34 (*R*,*R*)	38	82 (*R*,*R*)	48
3[e]	(*R*,*R*) 82	0.45	44 (*R*,*R*)	27	98 (*R*,*R*)	65
4[d]	(*S*,*S*) 47	2.65	32 (*S*,*S*)	47	80 (*S*,*S*)	30
5[e]	(*S*,*S*) 79	0.53	38 (*S*,*S*)	25	97 (*S*,*S*)	44

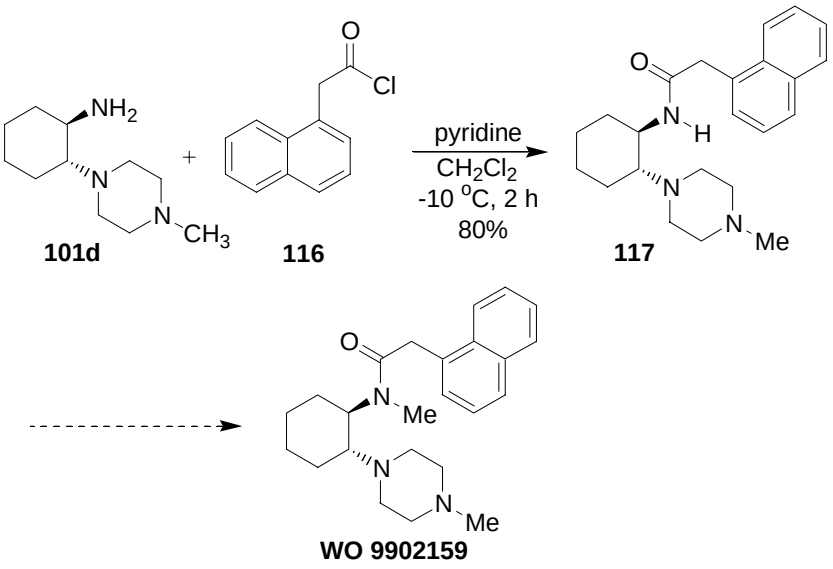
[a]All the reactions were carried out in THF at 25 °C. [b]The ee values based on optical rotation and the maximum $[\alpha]_D^{25}$ = (-) 43 (*c* 0.92, $CHCl_3$) for (*R*,*R*)-**101d.** [c]The yields are of the isolated products, based on the total amount of the starting diamine used. [d]The reactions were carried out using non-racemic **101d** (5 mmol) and oxalic acid in acetone (30 mL). [e]The reactions were carried out using non-racemic **101d** (2.5 mmol) and oxalic acid in acetone (20 mL).

Interestingly, anhydrous oxalic acid did not give the precipitate under these reaction conditions. Presumably, the presence of H_2O perhaps assists in the formation hydrogen bonded aggregates. Unfortunately, however, crystals suitable for X-ray analysis could not be obtained to ascertain the nature of aggregates in this case.

1.2.13 Preparation of *N*-[2-(4-methylpiperazinyl)cyclohexyl]-2-napthalenyl-acetamide

We have undertaken efforts, to prepare the biologically active compound **WO9902159** (**2**) by treating the optically pure *trans*-2-(4-methylpiperazinyl)-cyclohexylamine **101d** with 1-napthylacetyl chloride (Scheme 40). The amide **117** was obtained in 80% yield.

Scheme 40



The enantiomeric purity of the amide derivative **117** is easily determined by chiral HPLC analysis (chiralcel OD-H analytical column, hexane:2-propanol (95:5) with flow rate 1.0 mL/min.).

1.3. Conclusion

The *trans*-1,2-diamines **101a-101e** and **112a-112c** with cyclohexyl moiety as a structural backbone are readily synthesized via opening of aziridinium ions with nitrogen nucleophiles. The racemic *trans*-1,2-diamines **101a, 101d, 112a** were resolved to obtain enantiopure compounds using commercially available dibenzoyl-*L*-tartaric acid, binol-borate complex prepared *in situ* using (*S*)-1,1'-bi-2-napthol and $B(OMe)_3$ and (*R*)-binapthylphosphoric acid under ambient reaction conditions. The (*S*)-1,1'-bi-2-napthol boric acid complex is also useful as a resolving system for the partial resolution of the diamine **101b**. The non racemic samples of **101a** and **101d** were enriched using achiral dicarboxylic acids like fumaric acid and oxalic acid to obtain samples with increased enantiomeric purity (upto 99%).

Considering the biological importance of molecules **1** and **2** and the overall synthetic importance of 1,2-diamines with cyclohexyl backbone in organic synthesis, the simple and convenient methods described here to prepare optically pure compounds have potential for further synthetic exploitations.

1.4. Experimental section

1.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra 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. Elemental analyses were carried out using a Perkin-Elmer elemental analyser model-240C and Thermo Finnigan analyser series Flash EA 1112. 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 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.

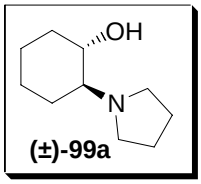
In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler was used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (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 Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy. Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Triethylamine was distilled over CaH_2 and stored over KOH pellets. Pyrrolidine, piperidine, piperazine and methanesulfonyl chloride supplied by Loba were used as purchased. N-methyl piperazine, was supplied by Aldrich, USA. Ammonia solution (30%), Iodine, fumaric acid, thionyl chloride, and benzyl chloride were supplied by E-Merck (India). Dibenzoyl-L-tartaric acid was supplied by Fluka, Switzerland. Cyclohexene oxide was purchased from Lancaster Synthesis Ltd., UK. All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents

before use. (*R*)-(+)-1,1'-bi-2-napthol and (*S*)-(-)-1,1'-bi-2-napthol were supplied by Gerchem Labs (Pvt) Ltd., India.

1.4.2 General procedure for the preparation of (±)-*trans*-1,2-amino alcohol.

A mixture of cyclohexene oxide (33mL, 300 mmol) and pyrrolidine (30.8mL, 280 mmol) was refluxed for 48 h. The product was distilled under reduced pressure to obtain (±)-*trans*-2-(1-pyrrolidinyl)cyclohexanol.

1.4.2a (±)-*trans*-2-(1-pyrrolidinyl)cyclohexanol 99a



(±)-99a

Yield 41.9g (88%)

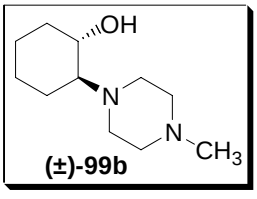
B.p 142 ^{o}C/20mm Hg

IR (neat) (cm^{-1}) 3450, 2932, 2857, 1450, 1078

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.08-1.39 (m, 4H), 1.55-1.90 (m, 7H), 2.00-2.19 (m, 1H), 2.32-2.77 (m, 5H), 3.20-3.39 (m, 1H), 4.12 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 21.2, 23.6, 24.2, 25.4, 33.3, 47.2, 64.9, 70.7

1.4.2b *trans*-(±)-2-(4-methylpiperazinyl)cyclohexanol 99b



(±)-99b

Yield 44.3 g (80%)

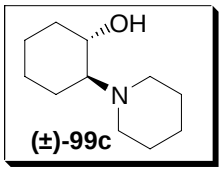
B.p 150 ^{o}C/20 mm Hg

IR (neat) (cm^{-1}) 3451, 2935, 2850, 1452, 1348

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.15-1.24 (m, 4H), 1.71-1.89 (m, 4H), 2.12-2.24 (m, 3H), 2.29 (s, 3H), 2.45 (m, 4H), 2.76 (s, br, 2H), 3.36-3.38 (t, 1H), 3.97 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 22.1, 24.0, 25.4, 33.1, 46.0, 47.9, 55.6, 68.4, 69.9.

1.4.2c (±)-*trans*-2-(1-piperidinyl)cyclohexanol (99c)



Yield 44.6 g (87%)

B.p 145 ^{o}C/20mm Hg

IR (neat) (cm^{-1}) 3454, 2934, 2856, 1452, 1082

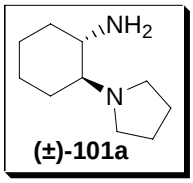
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.00-1.29 (m, 4H), 1.32-1.82 (m, 9H), 2.03-2.17 (m, 2H), 2.23-2.40 (m, 2H), 2.58-2.72 (m, 2H), 3.26-3.43 (m, 1H), 4.1 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.9, 23.9, 24.6, 25.4, 26.5, 33.1, 49.5, 68.2, 70.8

1.4.3 Synthesis of (±)-*trans*-1,2-diamines by aziridinium ion opening with nitrogen nucleophiles

1.4.3a Synthesis of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexanol (4.2 g, 25 mmol) in dry THF (70 mL) was added Et_3N (9.9 mL, 75 mmol) and MsCl (2.4 mL, 30 mmol) at 0 ^{o}C. The contents were warmed to 25 ^{o}C and stirred for 6 h. Et_3N (6.6 mL, 50 mmol) was added. After stirring for 2 h, excess aqueous ammonia (70 mL) was added and stirred for 48 h. The organic layer was separated and aqueous layer was extracted with ether (2×25 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the product (±)-**101a** was isolated by distillation under reduced pressure.



Yield 3.36 g (80%)

B.p 148 ^{o}C/10mm Hg

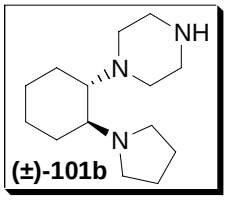
IR (neat) (cm^{-1}) 3356, 2961, 2928, 1448, 1246, 1024, 941

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.82-1.18 (m, 4H), 1.44-1.62 (m, 6H), 1.70-1.83 (m, 1H), 2.01-2.25 (m, 1H) 2.31-2.65 (m, 6H), 3.10 (br, s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.5, 23.6, 24.9, 25.3, 34.6, 47.0, 52.6, 64.9.

1.4.3b Synthesis of (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine 101b

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexanol (4.2 g, 25 mmol) in dry THF (70 mL) was added Et_3N (9.9 mL, 75 mmol) and MsCl (2.4 mL, 30 mmol) at 0 ^{o}C. The contents were warmed to 25 ^{o}C and stirred for 6 h. Et_3N (6.6 mL, 50 mmol) was added. After stirring for 2 h, excess piperazine (4.3 g, 50 mmol) dissolved in THF-H_2O was added and refluxed for 48 h. The organic layer was separated and aqueous layer was extracted with ether (2×25 mL). The combined organic extracts were washed with water (10mL), brine (10mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the crude product was purified by column chromatography on neutral alumina using EtOAc/hexane (2:98) as an eluent to obtain (±)-**101b**.



(±)-101b

Yield 4.15 g (70%)

IR (neat) (cm^{-1}) 3468, 2937, 2860, 2797, 1448

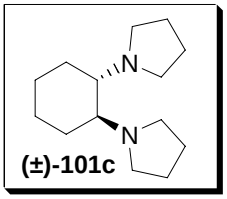
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.26-1.30 (m, 4H), 1.58-1.76 (m, 10H), 1.85-1.91 (m, 2H), 2.10-2.25 (m, 2H), 2.46-2.59 (m, 8H), 4.08 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 22.2, 22.8, 23.6, 24.7, 32.7, 49.6, 61.6, 65.0

1.4.3c Synthesis of (±)-*trans*-1,2-bis(pyrrolidino)cyclohexane 101c

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexanol (4.2 g, 25 mmol) in dry THF (70 mL) was added Et_3N (9.9 mL, 75 mmol) and MsCl (2.4 mL, 30 mmol) at 0

^{o}C. The contents were warmed to 25 ^{o}C and stirred for 6 h. Et_3N (6.6 mL, 50 mmol) was added. After stirring for 2 h, excess pyrroline (3.6 g, 50 mmol) was added and refluxed for 48 h. The organic layer was separated and aqueous layer was extracted with ether (2×25 mL). The combined organic extracts were washed with water (10mL), brine (10mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane as an eluent to afford (±)-*trans*-1,2-bis(pyrrolidino)cyclohexane.



(±)-101c

Yield 3.88 g (70%)

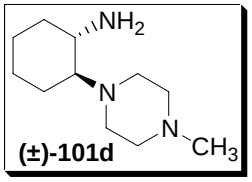
IR (neat) (cm^{-1}) 2935, 2872, 2777, 1446

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.26-1.27 (m, 2H), 1.42-1.46 (m, 2H), 1.56-1.68 (m, 10H), 1.78-1.84 (m, 2H), 2.25 (br, 2H), 2.48 (d, 8H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.2, 23.3, 25.1, 51.4, 63.1

1.4.3d Synthesis of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d

To the solution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexanol (4.95 g, 25 mmol) in dry THF (70 mL) was added Et_3N (9.9 ml 75 mmol) and MsCl (2.4 mL, 30 mmol) at 0 ^{o}C. The contents were warmed to 25 ^{o}C and stirred for 6 h. Et_3N (6.6 mL, 50 mmol) was added. After stirring for 2 h, excess aqueous ammonia (70 mL) was added and stirring continued for 48 h. The organic layer was separated and aqueous layer was extracted with ether (2×25 mL). The combined organic extracts were washed with water (10mL), brine (10mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the product (±)-**101d** was isolated by distillation under reduced pressure.



(±)-101d

Yield 3.45 g (70%)

B.p 150 ^{o}C/10mm Hg

IR (neat) (cm^{-1}) 3356, 3285, 2930, 2852, 2852, 1452

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.11-1.18 (m, 4H), 1.64-2.06 (m, 9H), 2.27-1.83 (t, 3H), 2.43 (s, 2H) 2.59-2.65 (m, 1H), 2.71 (s, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 22.3, 24.6, 25.5, 34.7, 45.7, 47.7, 50.3, 55.5, 69.9

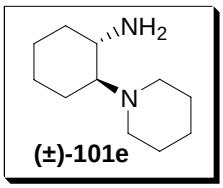
Anal. calcd

for $C_{11}H_{23}N_3$ C, 66.96; H, 11.75; N, 21.29. Found: C, 67.05; H, 11.76; N, 21.18

LCMS (m/z) 198.3 (M+1)

1.4.3e Synthesis of (±)-*trans*-2-(1-piperidinyl)cyclohexylamine 101e

To the solution of (±)-*trans*-2-(1-piperidinyl)cyclohexanol (1.8 g, 10 mmol) in dry THF (30 mL) was added Et_3N (4 mL, 30 mmol) and MsCl (2.4 mL, 30 mmol) at 0 ^{o}C. The contents were warmed to 25 ^{o}C and stirred for 6 h. Et_3N (2.6 mL, 20 mmol) was added. After stirring for 2 h, excess aqueous ammonia (35 mL, 50 mmol) was added and stirred for 48 h. The organic layer was separated and aqueous layer was extracted with ether (2×10 mL). The combined organic extracts were washed with water (10mL), brine (10mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the residue was distilled under reduced pressure to obtain (±)-**101e**.



(±)-101e

Yield 1.28 g (70%)

B.p 145 ^{o}C/20mm Hg

IR (neat) (cm^{-1}) 3354, 2928, 1450

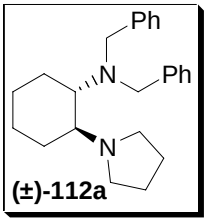
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.77-1.18 (m, 4H), 1.08-1.42 (m, 9H), 1.62 (br, s, 2H), 1.97 (br, s, 2H), 2.28 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 22.6, 24.7, 24.8, 25.6, 26.6, 34.9, 49.4, 50.3, 70.9

1.4.3f Synthesis of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine 112a

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine (3.36 g, 20 mmol) in dry CH_3CN (50 mL) was added oven dried K_2CO_3 (6.9 g, 50 mmol), KI (0.17 g, 1 mmol) and benzyl bromide (5.6 mL, 48 mmol). The contents were refluxed for 24 h and filtered. The acetonitrile was removed under vacuum and the crude was dissolved in diethyl ether-H_2O (3:1). The organic layer was separated and aqueous layer was extracted with ether (2×25 mL). The combined organic extracts were washed with water (10mL), brine (10mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane:EtOAc (98:2) as an eluent to afford (±)-**112a**.

Yield 6.41 g (92%)



(±)-112a

IR (neat) (cm^{-1}) 3061, 3026, 2928, 2854, 1602, 1493, 744, 698

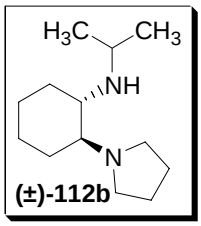
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.38-1.46 (m, 4H), 1.63-1.68 (m, 1H), 2.02-2.16 (m, 8H), 2.38-2.41 (d, 1H), 2.83 (m, 3H), 2.86-2.88 (d, 2H), 3.17 (m, 1H), 3.95 (d, 2H), 4.2 (d, 2H), 7.50-7.83 (m, 10H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.5, 23.6, 24.9, 25.3, 34.6, 47.0, 52.6, 64.9.

LCMS (m/z) 349.35 (M+1)

1.4.3g Synthesis of (±)-*trans*-2-isopropyl-(1-pyrrolidinyl)cyclohexylamine 112b

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine (1.68 g, 10 mmol) in dry CH_3CN (20 mL) was added oven dried K_2CO_3 (3.4 g, 50 mmol), KI (0.08 g, 0.5 mmol) and isopropyl bromide (1.2 mL, 12 mmol). The contents were refluxed for 24 h and filtered. The acetonitrile was removed under vacuum and the crude was dissolved in diethyl ether-H_2O (3:1). The organic layer was separated and aqueous layer was extracted with ether (2×10 mL). The combined organic extracts were washed with water (5mL), brine (5mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the crude product was purified by column chromatography on neutral alumina using hexane as an eluent to afford (±)-**112b**.



Yield 1.6 g (76%)

IR (neat) (cm^{-1}) 3288, 2961, 2928, 2856, 1448

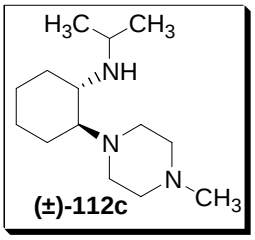
^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.00-1.02 (d, 2H), 1.07-1.09 (d, 2H), 1.21-1.25 (m, 4H), 1.64-1.75 (m, 8H), 2.1 (d, 1H), 2.39-2.41 (2H, m), 2.41-2.58 (m, 4H), 2.80 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.6, 22.4, 23.8, 24.6, 25.0, 25.3, 32.6, 45.6, 46.8, 56.8, 62.1.

1.4.3h Synthesis of (±)-*trans*-2-isopropyl-(4-methylpiperazinyl)cyclohexylamine

To the solution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexanol (1.98 g, 10 mmol) in dry CH_3CN (20 mL) was added oven dried K_2CO_3 (3.4 g, 50 mmol), KI (0.08 g, 0.5 mmol) and isopropyl bromide (1.2 mL, 12 mmol). The contents were refluxed for 24 h and filtered. The acetonitrile was removed under vacuum and the crude was dissolved in diethyl ether-H_2O (3:1). The organic layer was separated and the aqueous

layer was extracted with ether (2×10 mL). The combined organic extracts were washed with water (5mL), brine (5mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the residue was purified by column chromatography on neutral alumina using hexane:EtOAc (99:1) as an eluent to afford (±)-**112c**.



(±)-112c

Yield 1.56 g (65%)

IR (neat) (cm^{-1}) 3287, 2932, 2858, 2791, 1454

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.82-1.18 (m, 4 H), 1.44-1.62 (m, 6H), 1.70-1.83 (m, 1H), 2.01-2.25 (m, 1H) 2.31-2.65 (m, 6H), 3.10 (br, s, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 21.5, 23.6, 24.9, 25.3, 34.6, 47.0, 52.6, 64.9

1.4.4 Resolution of (±)-*trans*-1,2-diamines with chiral resolving reagents

1.4.4a Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using *O,O'*-dibenzoyl-*L*-tartaric acid

To the solution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine **101a** (1.68g, 10 mmol) in acetone (60 mL) was added *O,O'*-dibenzoyl-*L*-tartaric acid (1.79g, 5mmol) and the contents were stirred at 25 ^oC for 20 h and filtered. The precipitate was suspended in a mixture of ethyl acetate and 5N NaOH and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous K_2CO_3. The solvent was removed to obtain **101a** enriched in (*R*,*R*) isomer. The filtrate was concentrated and residue was digested as outlined above to obtain the product **101a** enriched in (*S*,*S*) isomer.

After decomposition

From precipitate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.55 g (32%)

Enantiomeric purity $[\alpha]_D^{25}$ = (-) 56.5 (c 0.83, $CHCl_3$)

82% ee from optical rotation

From filtrate

(*S*,*S*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.89 g (53%)

Enantiomeric purity $[\alpha]_D^{25}$ = (+) 39 (c 0.92, $CHCl_3$)

57% ee from optical rotation

1.4.4b Purification of nonracemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using *O,O'*-dibenzoyl-*L*-tartaric acid

To the solution of non-racemic **101a** (0.42g, 2.5mmol) in acetone (25 mL), was added DBTA (0.45g, 1.25 mmol) and the contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of ethyl acetate and 5N NaOH and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. The solvent was removed to obtain **101a** enriched in (*R*,*R*) isomer (>99% ee). The filtrate was concentrated and residue was digested as outlined above to obtain the product **101a** enriched in (*R*,*R*) isomer.

From precipitate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.13 g (31%)

Enantiomeric purity $[\alpha]_D^{25}$ = (-) 68.6 (c 0.73, $CHCl_3$)

>99% ee from HPLC analysis

From filtrate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.164 g (42%)

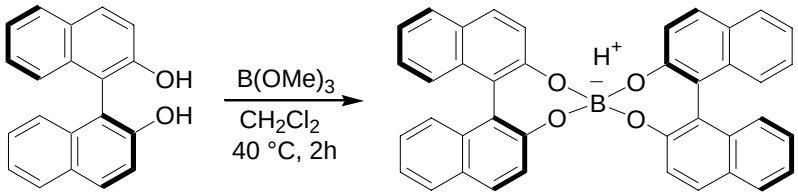
Enantiomeric purity $[\alpha]_D^{25}$ = (-) 46.01 (c 0.85, $CHCl_3$)

68% ee from optical rotation

1.4.5 Preparation of (*S*)-(-)-1,1'-bi-2-napthol and $B(OMe)_3$ complex 111

A mixture of (*S*)-(-)-1,1'-bi-2-napthol (2.86g, 10 mmol), $B(OMe)_3$ (0.61mL) was refluxed in dichloromethane(20 mL) for 2 h. The dichloromethane was distilled out to obtain the air stable complex **111** in quantitative yield (Scheme 41).

Scheme 41



(*S*)-(-)-1,1'-bi-2-napthol **(*S*,*S*)-111**

1.4.5a Resolution of (±)-*trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using chiral complex 111

To the solution of (*S*)-(-)-1,1'-bi-2-napthol-$B(OMe)_3$ complex **111** (10 mmol) in methanol (150 mL) was added (±)-**101a** (1.68 g, 10 mmol) and stirred for 12 h at 25 ^oC

and filtered. The precipitate was suspended in a mixture of ethyl acetate (25 mL) and 2N HCl (10 mL), stirred until complete dissolution occurs. The (*S*)-(-)-1,1'-bi-2-napthol (90%) was recovered from the organic layer. The aqueous layer was treated with NaOH/EtOAc and the free diamine was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain **(-)-101a** enriched in (*R*,*R*) isomer. The filtrate was concentrated and the residue was digested as outlined above, to obtain the **(+)-101a** enriched in (*S*,*S*) isomer.

After decomposition

From precipitate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield	0.62 g (37%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (-) 36.7 (c 1.01, $CHCl_3$)
	54% ee from optical rotation

From filtrate

(*S*,*S*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield	0.68 g (40%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (+) 32.6 (c 0.75, $CHCl_3$)
	48% ee from optical rotation

1.4.5b Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using chiral complex 111

To the solution of (*S*)-(-)-1,1'-bi-2-napthol-$B(OMe)_3$ complex **111** (10 mmol) in methanol (180 mL) was added (±)-**101d** (1.96 g, 10 mmol) and stirred for 12 h at 25 ^oC

and filtered. The precipitate was suspended in a mixture of ethyl acetate (25 mL) and 2N HCl (10 mL), stirred until complete dissolution occurs. The (*S*)-(-)-1,1'-bi-2-napthol (90%) was recovered from the organic layer. The aqueous layer was treated with NaOH/EtOAc and the free diamine was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain **(-)-101d** in enriched in (*R*,*R*) isomer. The filtrate was concentrated and the residue was digested as outlined above, to obtain the **(+)-101d** enriched in (*S*,*S*) isomer.

After decomposition

From precipitate

(*R*,*R*)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine

Yield	1.12 g (57%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (-) 16 (c 0.91, $CHCl_3$)
	38% ee from optical rotation

From filtrate

(*S*,*S*)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine

Yield	0.64 g (33%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (+) 28 (c 0.75, $CHCl_3$)
	66% ee from optical rotation

1.4.5c Resolution of (±)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine 112a using chiral complex 111

To the solution of (*S*)-(-)-1,1'-bi-2-napthol-$B(OMe)_3$ complex **111** (10 mmol) in acetonitrile (150 mL) was added (±)-**112a** (3.48 g, 10 mmol) and stirred for 12 h at 25

^{o}C and filtered. The precipitate was suspended in a mixture of EtOAc (25 mL) and 2N HCl (10 mL), stirred until complete dissolution occurs. The (*S*)-(-)-1,1'-bi-2-napthol (90%) was recovered from the organic layer. The aqueous layer was treated with NaOH/EtOAc and the free diamine was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain **(-)-112a** enriched in (*R*,*R*) isomer. The filtrate was concentrated and the residue was digested as outlined above, to obtain the **(+)-112a** enriched in (*S*,*S*) isomer.

After decomposition

From precipitate

(*R*,*R*)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine

Yield	1.38 g (40%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (-) 22 (c 0.94, $CHCl_3$)
	59% ee from optical rotation

From filtrate

(*S*,*S*)-*trans*-2-dibenzyl-(1-pyrrolidinyl)cyclohexylamine

Yield	1.32 g (38%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (+) 19 (c 0.87, $CHCl_3$)
	52% ee from optical rotation

1.4.5d Resolution of (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine 101b using chiral complex 111

To the solution of (*S*)-(-)-1,1'-bi-2-napthol-$B(OMe)_3$ complex **111** (5 mmol) in methanol (60 mL) was added (±)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine **101b**

(1.18 g, 5 mmol) and stirred for 12 h at 25 ^{o}C. The precipitate was filtered and suspended in a mixture of ethyl acetate (25 mL) and 2N HCl (10 mL), stirred until complete dissolution occurs. The S-(-)-1,1'-bi-2-napthol (90%) was recovered from the organic layer. The aqueous layer was treated with NaOH/EtOAc and the free diamine was extracted with ether (2×25 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain **(-)-101b.** The filtrate was concentrated and the residue was digested as outlined above to isolate the **(+)-101b**.

After decomposition

From precipitate

(-)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine

Yield 0.41 g (34%)

Optical rotation $[\alpha]_D^{25}$ = (-) 29 (c 1.12, $CHCl_3$)

From filtrate

(+)-*trans*-1-(2-pyrrolidinyl)cyclohexylpiperazine

Yield 0.3 g (25%)

Optical rotation $[\alpha]_D^{25}$ = (+) 7 (c 1.2, $CHCl_3$)

1.4.5e Resolution of (±)-*trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using (*R*)-(-)-binapthylphosphoric acid (BNP)

To the solution of racemic**-101d** (1.96g, 10 mmol) in THF (180 mL) was added (*R*)-BNP (3.48g, 10 mmol) and stirred for 12 h at 25 ^{o}C. The precipitate was filtered and suspended in a mixture of EtOAc (25 mL) and 2N HCl (10 mL), stirred until complete dissolution occurs. The (*R*)-BNP was recovered from the EtOAc layer. The

aqueous layer was treated with NaOH/ EtOAc and the free diamine was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain **(-)-101d** enriched in (*R*,*R*) isomer. The filtrate was concentrated and the residue was digested as outlined above and the **(+)-101d** enriched in (*S*,*S*) isomer was isolated.

After decomposition

From precipitate

(*R*,*R*) *trans*-2-(4-methylpiperazinyl)cyclohexylamine

Yield 1.08 g (56%)

Enantiomeric purity $[\alpha]_D^{25}$ = (-) 14 (c 0.93, $CHCl_3$)

32% ee from optical rotation

From filtrate

(*S*,*S*) *trans*-2-(4-methylpiperazinyl)cyclohexylamine

Yield 0.64 g (33%).

Enantiomeric purity $[\alpha]_D^{25}$ = (+) 24 (c 0.88, $CHCl_3$)

57% ee from optical rotation

1.4.6 Purification of non-racemic diamines using achiral acids

1.4.6a Purification of non-racemic *trans*-2-(1-pyrrolidinyl)cyclohexylamine 101a using fumaric acid.

To the solution of partially resolved **101a** (0.84g, 5 mmol, 58% ee) in acetone (30mL) was added fumaric acid (0.33g, 2.9 mmol) and the contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of ether and 5N NaOH and stirred until the dissolution occurred. The organic layer was separated and

the aqueous layer was extracted with ether (2×10 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous K_2CO_3. The solvent was evaporated to obtain the (*R*,*R*)-**(-)-101a** isomer (87% ee, 63% yield). The filtrate was concentrated and the residue was digested as outlined above to obtain the product enriched in (*R*,*R*) isomer (22% ee, 28% yield).

After decomposition

From precipitate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.53 g (63%)

Enantiomeric purity $[\alpha]_D^{25}$ = (-) 59 (c 1.21, $CHCl_3$)

87% ee from optical rotation

From filtrate

(*R*,*R*) *trans*-2-(1-pyrrolidinyl)cyclohexylamine

Yield 0.23 g (28%)

Enantiomeric purity $[\alpha]_D^{25}$ = (-) 15 (c 0.75, $CHCl_3$)

22% ee from optical rotation

1.4.6b Purification of non-racemic *trans*-2-(4-methylpiperazinyl)cyclohexylamine 101d using oxalic acid.

To the solution of non-racemic **(+)-101d** (0.49g, 2.5 mmol, 79% ee) in THF (30mL) was added oxalic acid (0.05g, 0.53 mmol). The contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of ether and 10M Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with ether (2×10 mL). The combined organic extracts

were washed with brine (20mL), dried over anhydrous K_2CO_3. The solvent was evaporated to obtain the (*S*,*S*) **(+)-101d** isomer (38% ee, 25% yield). The filtrate was concentrated and the residue was digested as outlined above to obtain the product enriched in (*S*,*S*) **(+)-101d** isomer (97% ee, 44% yield).

After decomposition

From precipitate

(*S*,*S*) *trans*-2-(4-methylpiperazinyl)cyclohexylamine

Yield	0.12 g (25%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (+) 16 (c 0.97, $CHCl_3$)
	38% ee from optical rotation

From filtrate

(*S*,*S*) *trans*-2-(4-methylpiperazinyl)cyclohexylamine

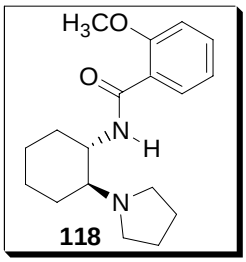
Yield	0.22 g (44%)
Enantiomeric purity	$[\alpha]_D^{25}$ = (+) 41.5 (c 1.02, $CHCl_3$)
	97% ee from optical rotation

1.4.7 HPLC analysis of the diastereomeric amide derivatives of 101a and 101d

1.4.7a Preparation of 2-methoxy-*N*-(2-pyrrolidinyl)cyclohexylbenzamide 118

To the solution of **101a** (0.168 g, 1 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.24 mL, 3 mmol), 2-methoxy benzoylchloride (0.15 mL, 1 mmol) at 0 ^oC. The contents were warmed to 25 ^oC and stirred for 2 h. The reaction was quenched with 2 mL water. The organic layer was separated, washed with water (2×5 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on a silica gel using $CHCl_3$/MeOH

(97:3) as eluent. The diastereomeric amide was analyzed by HPLC using chiralcel OD-H analytical column, hexane:2-propanol (90:10) with flow rate 0.5 mL/min.



118

Yield 0.26 g (87%)

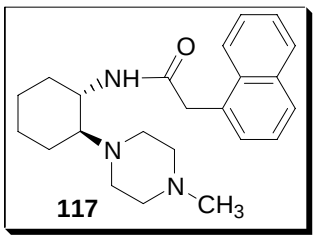
IR (neat) (cm^{-1}) 3380, 2934, 1701, 1651, 752

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.19-1.82 (m, 12H), 2.56-2.69 (m, 6H), 3.93 (s, 3H), 6.94 (d, 1H), 7.06 (t, 1H), 7.39 (m, 1H), 8.16-8.18 (m, 1H), 8.4 (br, s, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 23.3, 23.7, 23.9, 23.9, 23.97, 30.8, 48.1, 51.6, 55.8, 62.2, 111.3, 121.0, 122.3, 131.8, 132.2, 157.4, 165.0

1.4.7b Preparation of N-[2-(4-methylpiperazinyl)cyclohexyl]-2-napthalenyl-acetamide 117

To the solution of **101d** (0.197 g, 1 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.24 mL, 3 mmol), 1-acetyl napthylchloride (0.21 g, 1 mmol) at 0 ^oC. The contents were warmed to 25 ^oC and stirred for 2 h. The reaction was quenched with 2 mL water. The organic layer was separated, washed with water (2×5 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on a neutral alumina using hexane/EtOAc (98:2) as eluent. The diastereomeric amide was analyzed by HPLC using chiralcel OD-H analytical column, hexane:2-propanol (95:5) with flow rate 1.0 mL/min.



117

Yield 0.29 g (80%)

IR (neat) (cm^{-1}) 3294, 3047, 2930, 2854, 1653, 787

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.85-0.87

	(m, 1H), 0.98-1.07 (m, 3H), 1.22-1.25 (m, 2H), 1.63-2.43 (m, 15H), 3.40 (br, 1H), 3.74-4.09 (m, 2H), 7.46-7.56 (m, 4H), 7.82-7.84 (m, 2H), 8.09-8.11 (m, 1H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm): 23.0, 24.4, 25.2, 32.2, 42.0, 42.2, 45.8, 50.1, 53.6, 54.3, 66.6, 124.2, 125.3, 125.6, 126.9, 127.6, 128.4, 128.7, 132.3, 170.9
LCMS (m/z)	366.3 (M+1)

1.5. References

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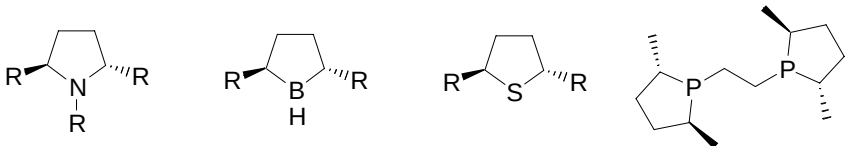
Chapter 2

Synthesis of chiral diphenyl pyrrolidine, diphenyl piperidine and diphenyl thiolane and diphenyl tetrahydrothiopyran derivatives

2.1 Introduction

C_2-symmetric compounds are widely used as chiral auxiliaries and ligands in asymmetric tranformations.[1] Among these a few notable C_2-symmetric derivatives such as 2,5-disubstituted pyrrolidines[2], borolanes[3], thiolanes[4], and phospholanes[5] have been used extensively (Figure 1). Of these chiral compounds, 2,5-disubstituted pyrrolidines constitute an important class of chiral auxiliaries used in a variety of transformations including alkylation, radical cyclizations, Michael addition, enantioselective deprotonation, Claisen rearrangements and addition to arene- manganese complexes.[6]

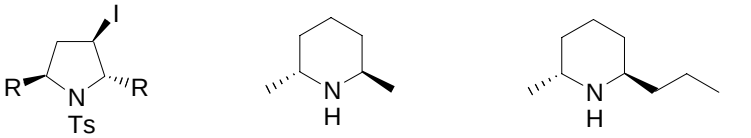
Figure 1



1 R= alkyl, aryl **2** **3** **4**

Also, saturated nitrogen heterocycles, including pyrrolidines and piperidines, occur in a wide variety of natural products, alkaloids and biologically active compounds (Figure 2).[7]

Figure 2



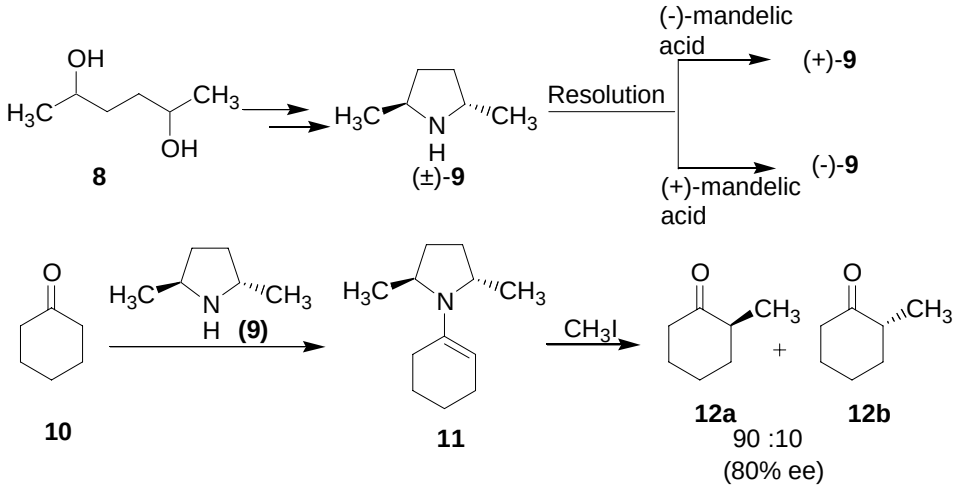
5 Pyrrolidine (-)- 197 B **6** (-)-2,6-Lubetidine **7** (+)-Epidihydropinidine

There have been numerous syntheses of substituted pyrrolidines and other heterocycles reported in the literature.[8] A brief review on the preparation of compounds

with C_2-symmetric chiral auxiliary and their application in organic synthesis would facilitate discussion.

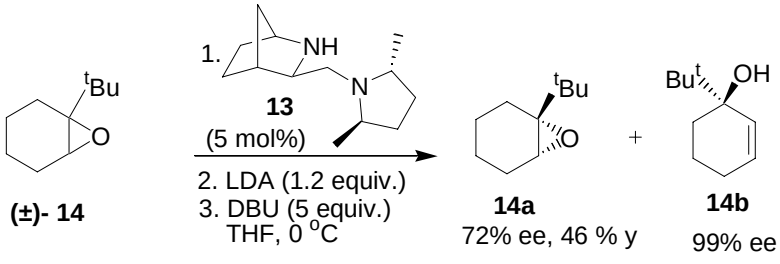
In 1977, Whitesell and Felman[9] first introduced chiral 2,5-dimethylpyrrolidine. This derivative can be accessed as outlined in Scheme 1. The C_2-symmetric chiral ligand has been used as amine component in enamine alkylation with good enantioselectivity.

Scheme 1



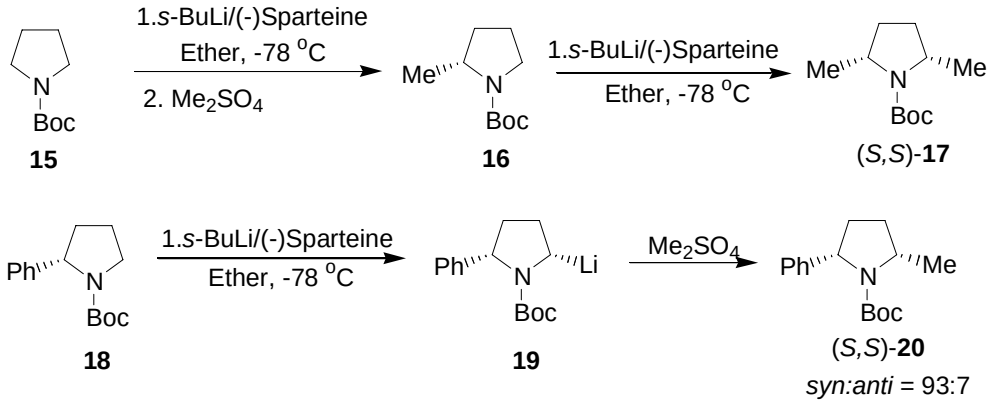
Later, Anderson and Gayet[10] used the dimethylpyrrolidine diamine **13** in combination with LDA as a stoichiometric base as a very selective catalyst (5 mol%) for the kinetic resolution of racemic epoxides with enantioselectivity upto 99% ee (Scheme 2).

Scheme 2



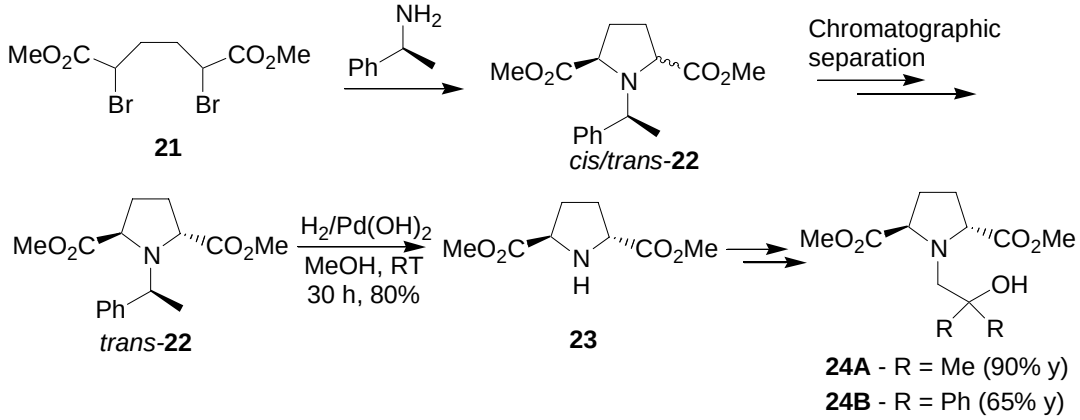
Beak *et al*[11] synthesized 2,5-disubstituted pyrrolidines **17** and **20** by asymmetric deprotonation of *N*-Boc pyrrolidines using BuLi/(-)Sparteine and dimethylsulfate with high enantioselectivity (Scheme 3).

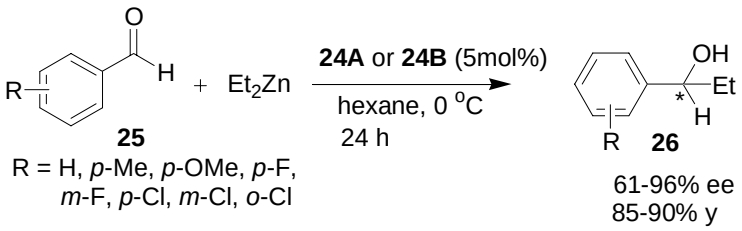
Scheme 3



Yamamoto *et al*[12] synthesized C_2-symmetric 2,5-disubstituted pyrrolidines **22** by the reaction of dimethyl-2,5-dibromoadipate with (*S*)-(-)-1-phenylethylamine and chromatographic separation. Asymmetric addition reaction of diethylzinc with arylaldehyde using C_2-symmetric 2,5-disubstituted pyrrolidine derivatives **24A** and **24B** affords products **26** with very good enantioselectivity (Scheme 4).

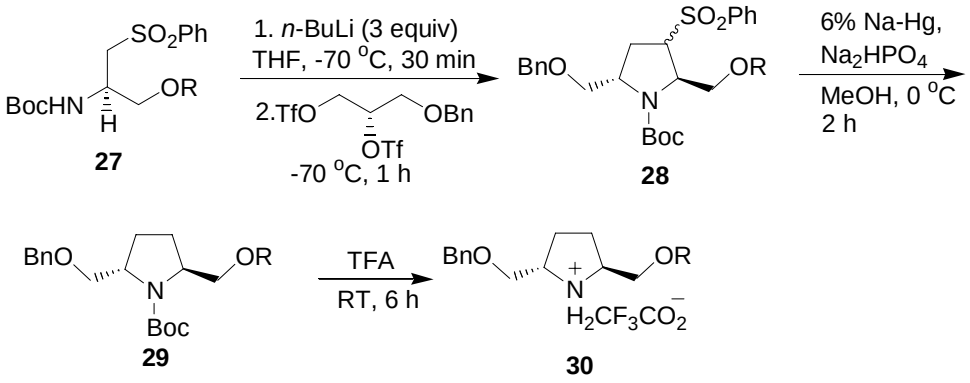
Scheme 4





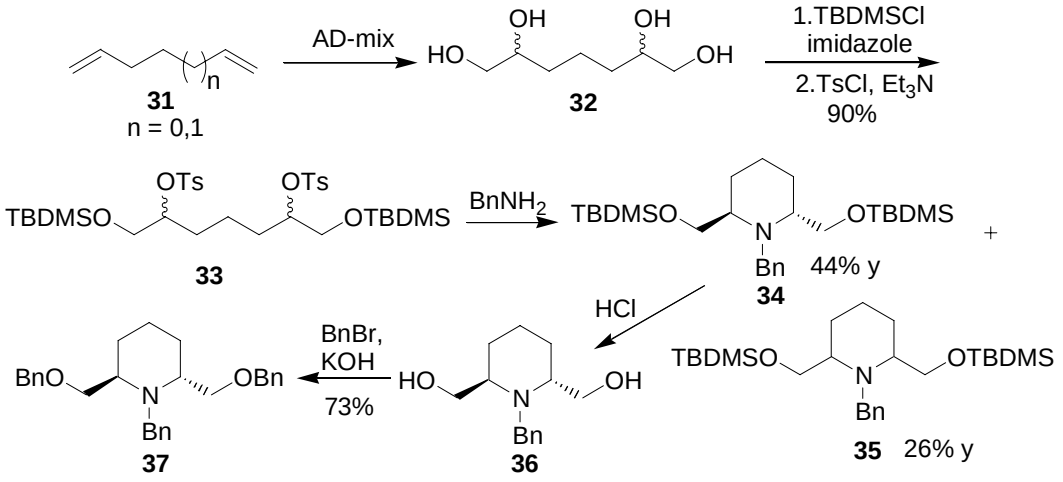
In 1999, Sasaki *et al*[13] prepared enantiopure *trans* and *cis*-2,5-disubstituted pyrrolidines from bistriflate of (*R*)-1-*O*-benzylglycerol. The bistriflate was treated with trilithiated chiral builing blocks to provide 2,3,5-trisubstituted pyrrolidines **28** which gives 2,5-disubstituted pyrrolidine **30** on subsequent reductive desulfonylation (Scheme 5).

Scheme 5



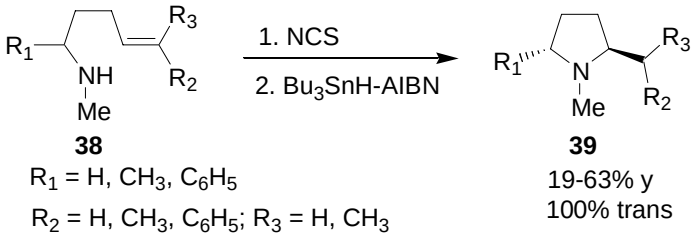
In 1998, Takahata *et al*[14] synthesized C_2-symmetric *trans* α, α'-bis-(hydroxymethyl)pyrrolidine and piperidine derivatives starting from symmetric α,ω-terminal dienes by double asymmetric dihydroxylation (AD) reaction as shown in Scheme 6.

Scheme 6



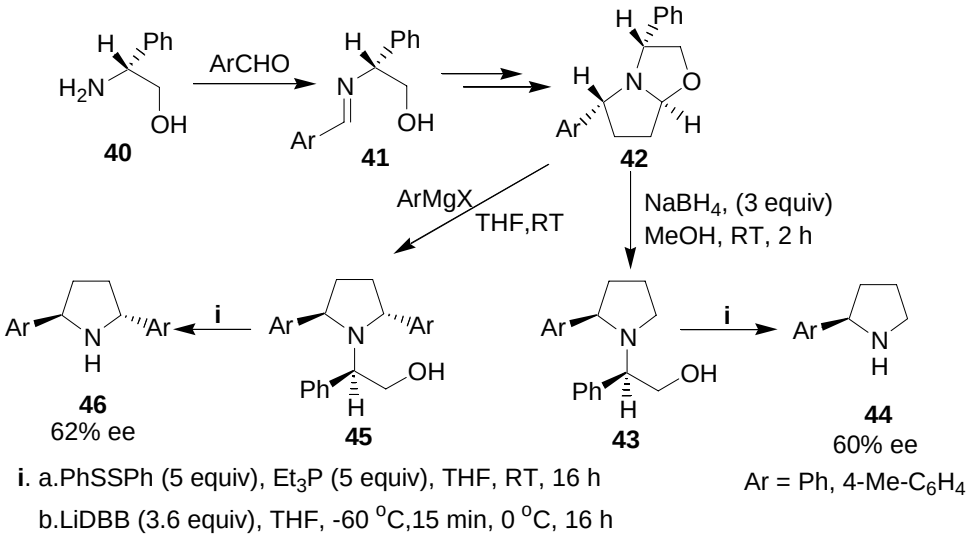
Tokuda *et al*[15] prepared *trans*-2,5-disubstituted pyrrolidines **39** following intramolecular cyclization of *N*-chloroalkenylamine in the presence of tributyltin hydride and azoisobutyronitrile with moderate yields (Scheme 7).

Scheme 7



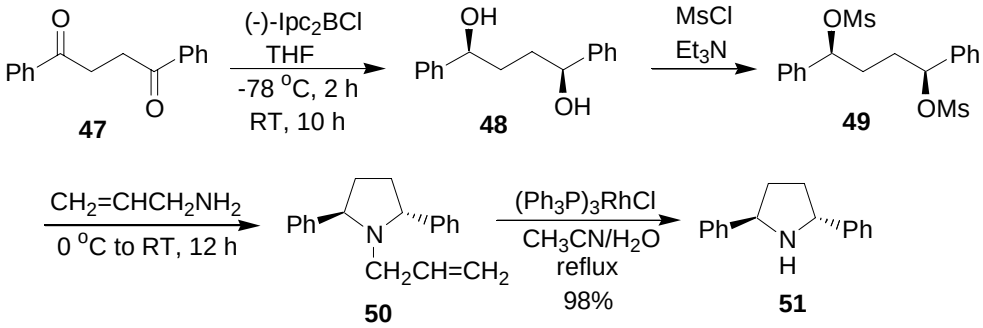
In 1994, Higahiyama *et al*[16] reported the synthesis of substituted pyrrolidines from chiral aromatic imines derived from (*R*)-phenylglycinol. Diastereoselective addition of Grignard reagent to the chiral imines and 1,3-oxazolines gave substituted pyrrolidines **44** and **46** in moderate yields (Scheme 8).

Scheme 8



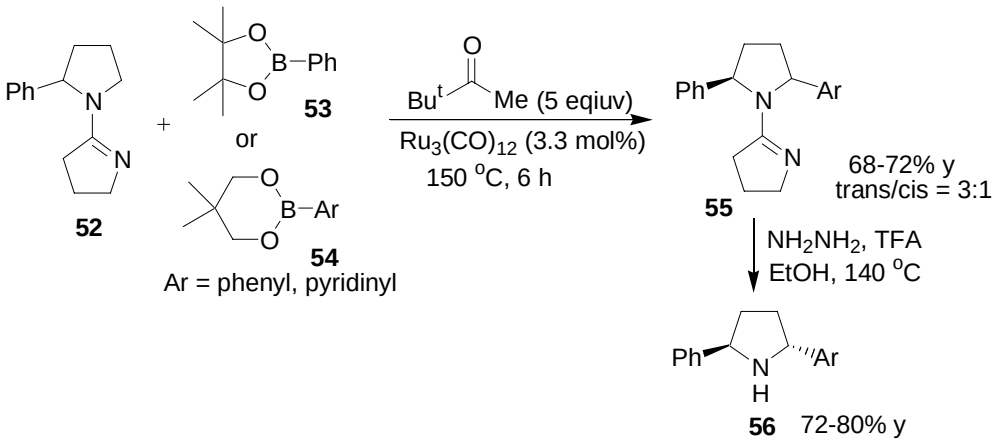
Chong *et al*[17] prepared (2*R*,5*R*)-2,5-diphenylpyrrolidine **51** from 1,4-diphenyl-1,4-butanedione **47** in four steps with high enantiomeric purity (>98% ee) (Scheme 9).

Scheme 9



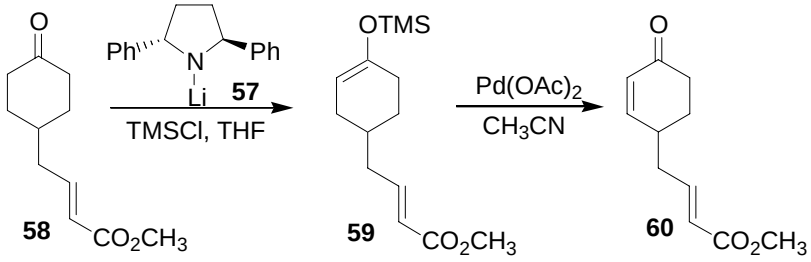
In 2006, Sames *et al*[18] synthesized pyrrolidines **56** and piperidines by direct arylation of sp^3 C-H bonds directed by Amidine protecting group **52** (Scheme 10).

Scheme 10



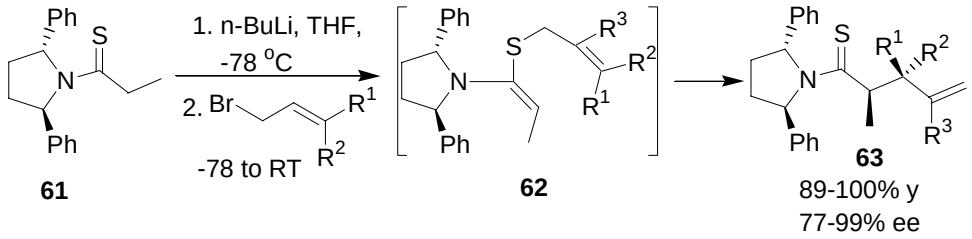
Takasu *et al*[19] reported that the enantioselective deprotonation of ketone **58** using chiral lithium amide base **57**, prepared using (*2S,5S*)-2,5-diphenylpyrrolidine in the presence of TMSCl gave the product enone in 29% ee after rearrangement (Scheme 11).

Scheme 11



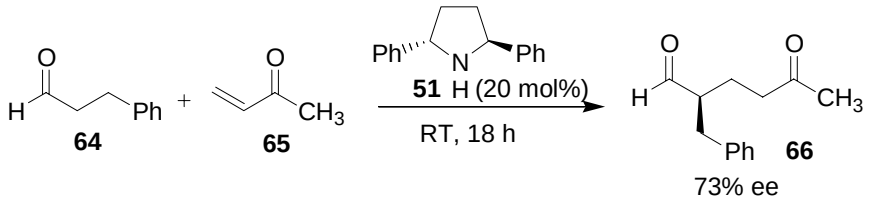
Rawel *et al*[20] investigated asymmetric thio-Claisen rearrangements using C_2-symmetric pyrrolidine as the removable chiral auxiliary. The rearrangements proceed with high *syn:anti* selectivities with excellent asymmetric induction (Scheme 12).

Scheme 12



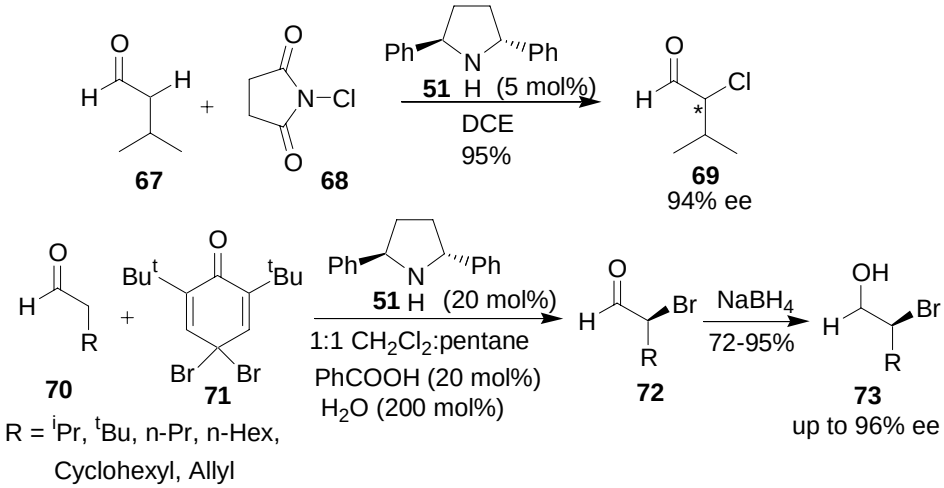
Jorgenson *et al*[21] reported the Michael addition of aldehydes to the methyl vinyl ketone catalyzed by (*2S,5S*)-2,5-diphenylpyrrolidine **51** under organocatalytic conditions with good enantioselectivity (Scheme 13).

Scheme 13



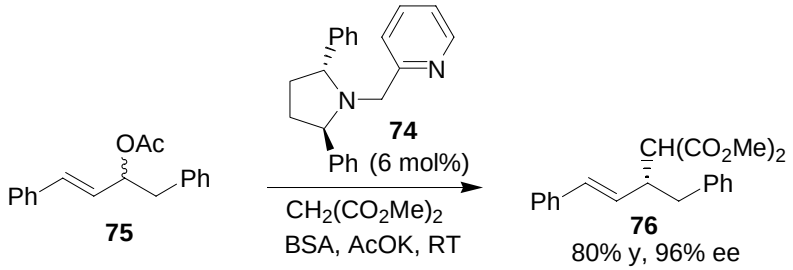
Recently, the same authors reported organocatalytic asymmetric α-chlorination and α-bromination of aldehydes **67** and ketones **70** respectively using the corresponding halogenating agents **68** and **71** in the presence of *trans*-2,5-diphenylpyrrolidine **51** with high enantioselectivity (Scheme 14).[22, 23]

Scheme 14



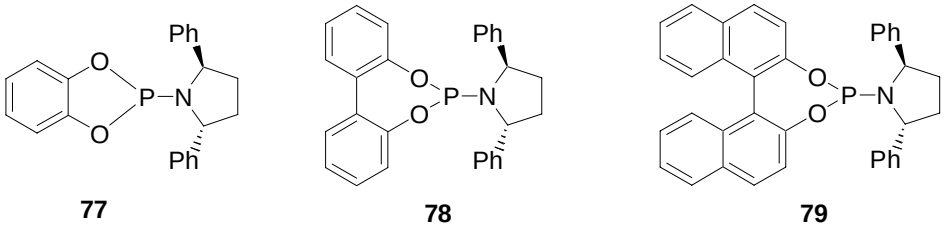
Koga[24] and Sweet[25] prepared C_2-symmetric 2,5-diphenylpyrrolidine derivative **74** and demonstrated enantioselective palladium catalyzed alkylations in enantioselectivity up to 96% ee (Scheme 15).

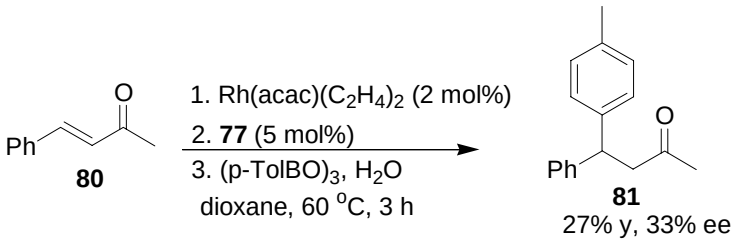
Scheme 15

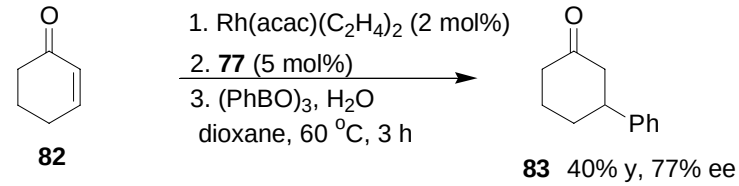


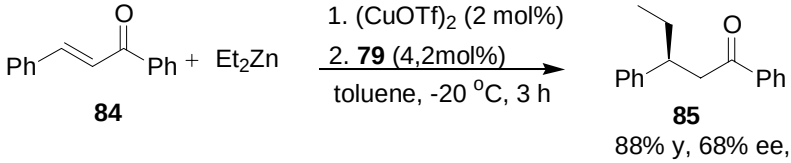
In recent years, phosphoramidites **77**[26], **78**[27], and **79**[28] containing chiral 2,5-diphenylpyrrolidine moiety were used as catalysts in the copper, rhodium catalyzed enantioselective conjugate addition of organometallic reagents to enones with moderate to very good enantioselectivity (Chart 1).

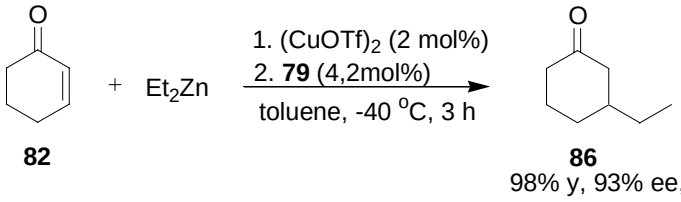
Chart 1





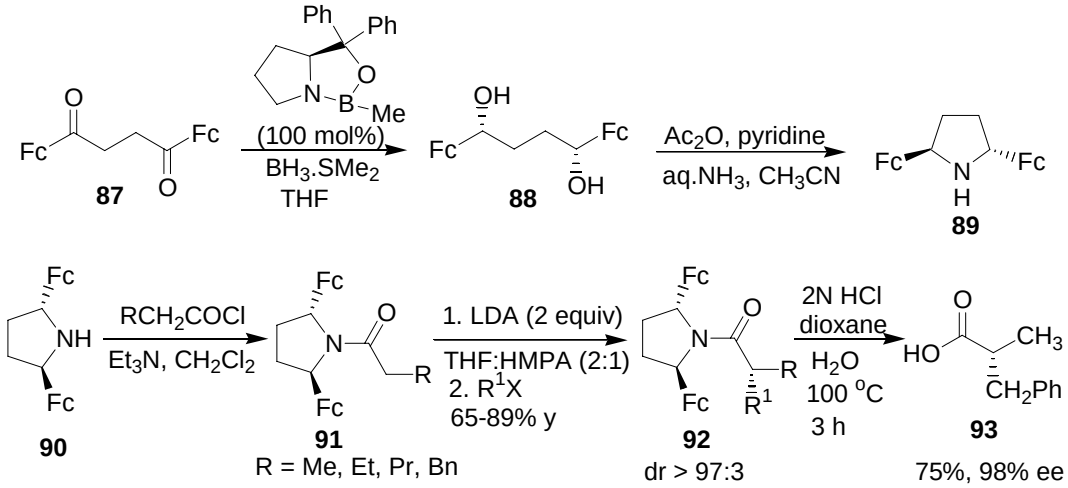






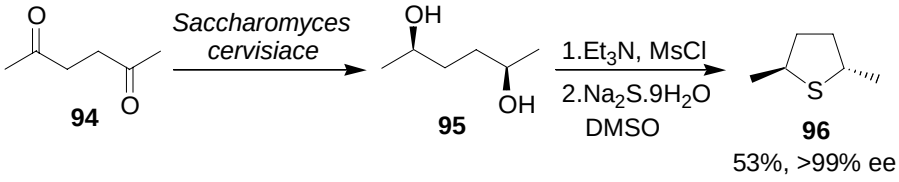
Knochel and Schwink[29] prepared C_2-symmetrical ferrocenyl amines **90** from the diferrocenyl-1,4-diketone via the diol **88** and utilized in the diastereoselective alkylations of the amide **91** (Scheme 16).

Scheme 16



Otten *et al*[30] synthesized (*2R,5R*)-*trans*-2,5-dimethylthiolane **96** from (*2S,5S*)-2,5-hexanediol **95** as shown in Scheme 17 with >99% diastereoselectivity and >99% ee.

Scheme 17



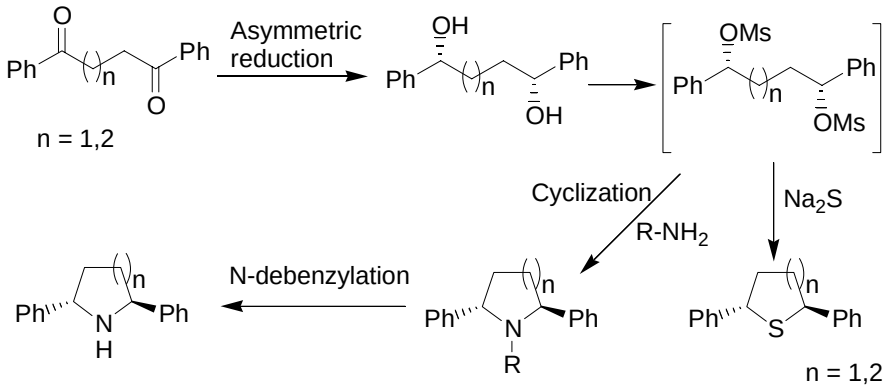
We have undertaken studies on the synthesis of of 2,5-diphenyl and 2,6-diphenyl substituted nitrogen and sulfur heterocycles. The results are discussed in the next section.

2.2 Results and discussion

2.2.1 Synthesis of disubstitued pyrrolidine, piperidine and thiolanes

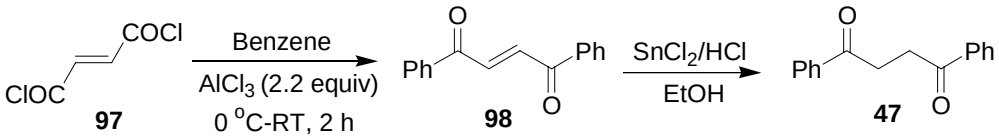
The chiral auxiliaries with C_2 symmetry elements generally give a greater stereochemical control compared to those totally lacking symmetry. Accordingly, synthesis and methods which allow construction of these C_2 symmetry heterocycles with stereoselectivity are valuable for synthetic chemists. As a part of our research program, we have envisaged a convenient route to synthesize C_2-symmetric chiral compounds using methods developed from this laboratory. The synthetic strategies and the reactions involved are outlined in Scheme 18.

Scheme 18



The 1,4-diphenylbutane-1,4-dione was readily prepared following a reported procedure.[31] Friedel-Crafts acylation of benzene with fumaroyl chloride in the presence of Lewis acid catalyst $AlCl_3$ affords 1,4-diphenylbut-2-ene-1,4-dione. Subsequent reduction of the olefinic moiety using $SnCl_2$/HCl reagent system yielded 1,4-diphenylbutane-1,4-dione (Scheme 19). After work up, the resideue was recrystallized from methanol to obtain the product in good yields (76%).

Scheme 19

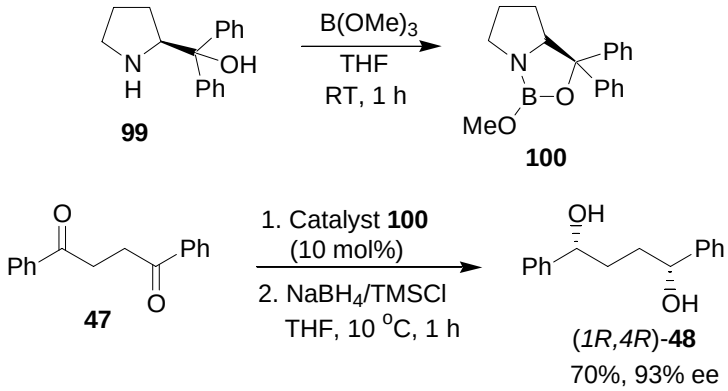


In 1995, Chong *et al*[17] reported the asymmetric reduction of 1,4-diphenylbutane-1,4-dione using stoichiometric reagent (-)-diisopinocampheylchloro-borane Ipc_2BCl derived from (+)-pinene. However, the disadvantage of this method is the removal of the chiral auxiliary which is tedious and requires considerable time. Later, Quallich[32] and Aldous[33] have developed methods to reduce 1,4-diketones with oxazaborolidine catalyst with BH_3-THF and BH_3-$S(CH_3)_2$. Although these methods gave good enantioselectivity, they involve handling of highly moisture sensitive reagents like BH_3-THF. Also, the BH_3-THF is thermally unstable reagent, needs storing below 4 ^oC. With this background, we have developed convenient route to synthesize chiral diols using *N,N*-diethylaniline-borane which is relatively stable, less moisture sensitive and easier to prepare and store without loss of hydride.[34] We have decided to use these convenient and easy to handle reagent systems for the reduction of the ketone **47**.

2.2.2 Asymmetric reduction 1,4-diphenylbutane-1,4-dione, 47

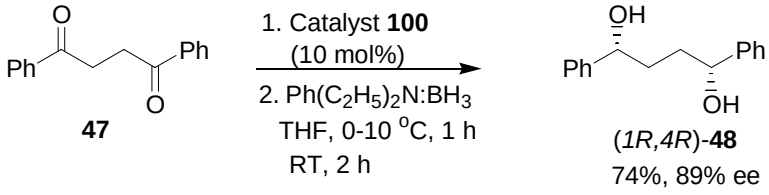
Recently, it was reported from this laboratory that asymmetric reduction of 1,4-diphenylbutane-1,4-dione **47** using B-methoxyoxazaborolidine (10 mol%) prepared *in situ* using (*S*)-α,α'-diphenylpyrrolidinemethanol, $B(OMe)_3$ and $NaBH_4$/TMSCl (Scheme 20). The (*1R,4R*)-diol **48** was obtained in good diastreoselectivity (93%).[35]

Scheme 20



We have also developed a method for the preparation of the (*1R,4R*)- 1,4-diphenylbutane-1,4-diol through the preparation of the oxazaborolidine *in situ* using α,α'-diphenylpyrrolidinemethanol and $B(OMe)_3$ and *N,N*-diethylaniline-BH_3 as a borane reagent. The 1,4-diketone **47** was added to a solution of B-methoxy oxazaborolidine (10 mol %) prepared *in situ* using (*S*)-α,α'-diphenylpyrrolidine-methanol and $B(OMe)_3$ and *N,N*-diethylaniline-BH_3 (1 equiv.) to obtain the (*1R,4R*)-1,4-diphenylbutane-1,4-diol **48** in good yield (74%) and diastereomeric ratio (92:8) (Scheme 21).

Scheme 21

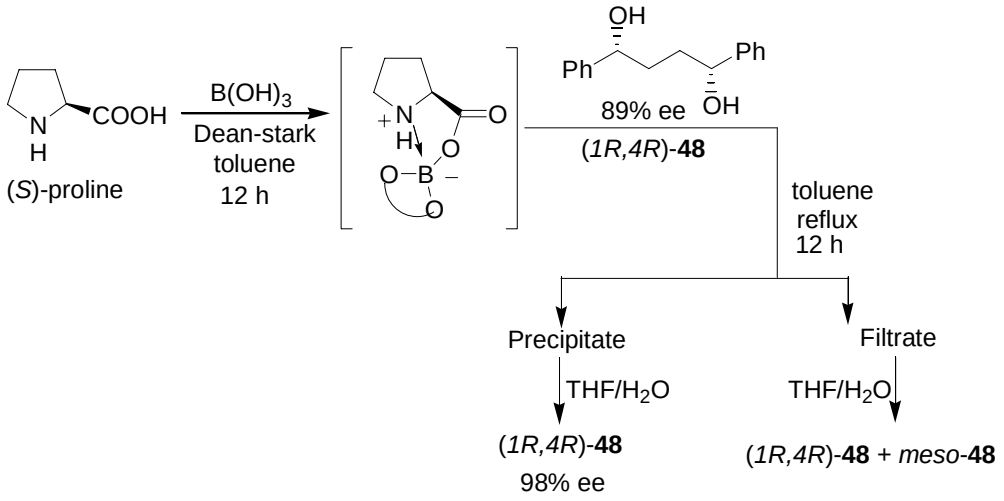


2.2.3 Enrichment of (*1R,4R*)-1,4-diphenylbutane-1,4-diol using (*S*)-proline/-$B(OMe)_3$

The chiral diol prepared in this way contains small amounts of (8-10%) of the corresponding meso diol. However, the mixtures of (*1R,4R*)-diol and *meso*-diol can be

readily purified using (*S*)-proline/$B(OH)_3$ to obtain the samples of higher optical purity, up to 98% ee (Scheme 22).[36]

Scheme 22

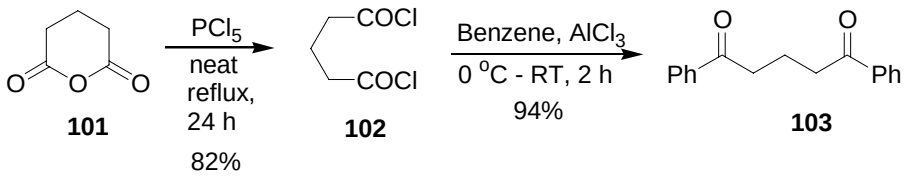


The chiral 1,4-diol was purified following the above procedure to obtain optically pure samples for the preparation of 2,5-diphenyl substituted pyrrolidines and thiolanes.

2.2.4 Preparation of 1,5-diphenylpentane-1,5-dione

The 1,5-diphenylpentane-1,5-dione was readily prepared from the commercially available glutaric anhydride. The reaction of glutaric anhydride **101** with PCl_5 at reflux condition gave pentanedioyl dichloride **102** in 82% yield. The subsequent Friedel-Crafts acylation of **102** with benzene afforded 1,5-diphenylpentane-1,5-dione **103** in very good yield (94%). The 1,5-diketone was recrystallized from hexane to afford the product in crystalline form (Scheme 23).

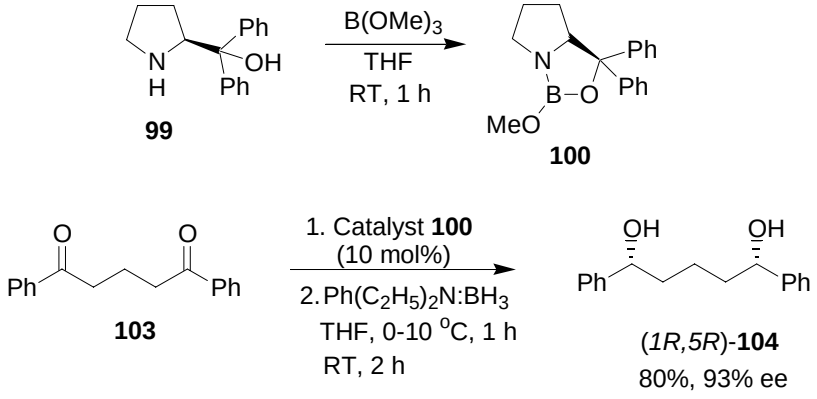
Scheme 23



2.2.5 Asymmetric reduction 1,5-diphenylpentane-1,5-dione

We extended the same methodology, described earlier for the reduction of 1,4-diketone to 1,5-diketone as well. The 1,5-diphenylpentane-1,5-dione **103** was reduced using *in situ* prepared B-methoxy oxazaborolidine (10 mol %) and *N,N*-diethylaniline-BH_3 (1 equiv.) afforded (*1R,5R*)-1,5-diphenylpentane-1,5-diol **104** in very good yield (80%) and with good diastereomeric ratio (93:7) (Scheme 24). The asymmetric induction observed for 1,5-diketone was comparable with the 1,4-diketone. The longer carbon chain length has little effect on the diastereoselectivity.

Scheme 24



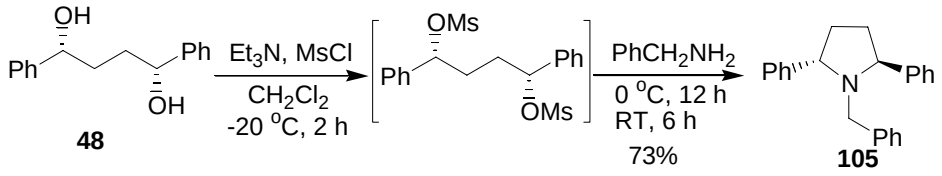
The 1,5-diol **104** obtained from this method was recrystallized from methanol to obtain optically pure sample (>98% ee) with overall 68%yield. The diols **48** and **104** obtained using above mentioned methods were utilized for the synthesis of nitrogen heterocycles and their sulfur analogues.

2.2.6 Synthesis of (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine

Previously, the 2,5-diphenylpyrrolidine derivatives were prepared from the diol via the cyclization of the corresponding dimesylates with allyl amine.[17] The (*1R,4R*)-1,4-diphenylbutane-1,4-diol **48** was mesylated using $MsCl/Et_3N$ in CH_2Cl_2 and then

subjected to reaction with benzyl amine (excess) to obtain the corresponding (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine in 73% yield (Scheme 25). We have observed that addition of benzyl amine to the dimesylate, without isolation and purification of the dimesylate has not affected the reaction outcome.

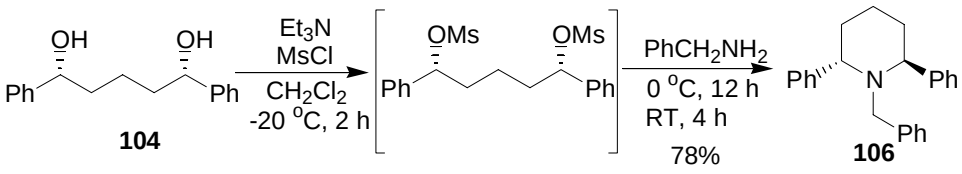
Scheme 25



2.2.7 Synthesis of (*2S,6S*)-2,6-diphenylpiperidine

The reactions were carried out in an identical fashion as described for the preparation of *N*-benzyl-2,5-diphenylpyrrolidine as shown in the Scheme 25. The (*1R,5R*)-1,5-diphenylpentane-1,5-diol was mesylated using MsCl/Et_3N in CH_2Cl_2 and then subjected to reaction with benzyl amine (excess) to obtain the corresponding (*2S,6S*)-*N*-benzyl-2,6-diphenylpiperidine in 78% yield (Scheme 26).

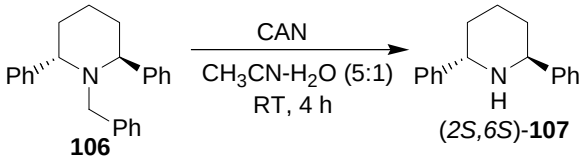
Scheme 26



It is noteworthy to mention that, the commonly employed methods for the debenzylation include hydrogenolysis with catalytic Pd/C, and acid hydrolysis in refluxing trifluroacetic acid, $FeCl_3$, lithium napthalemide. Although, these methods give very good yields, they lack the experimental simplicity.[37]

Recently, Davies *et al*[38] reported the oxidative debenzylation of tertiary *N*-benzylamines with ceric ammonium nitrate (CAN). We have followed this procedure for deprotection of *N*-benzyl-2,6-diphenylpiperidine using ceric ammonium nitrate in CH_3CN-H_2O (5:1) mixture at 25 ^oC. It was expected that the deprotection would be problematic since the amine is tribenzylic. However, the reaction proceeds readily to afford the 2,6-diphenylpiperidine in 65% yield along with starting material (15%) and some unidentified products (Scheme 27).

Scheme 27



2.2.8 Synthesis of sulfur analogs of nitrogen heterocycles

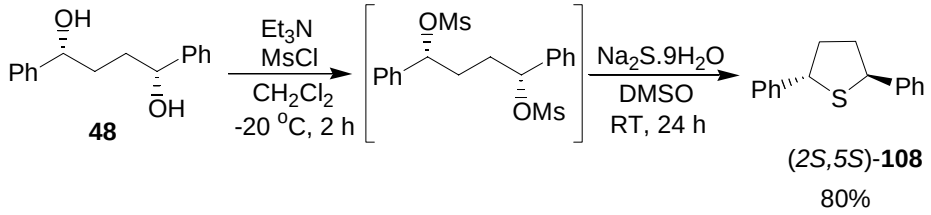
Enantiopure thioethers (**3**) have been used as chiral auxiliaries in asymmetric and stereoselective syntheses such as the non-racemic preparation of epoxides via sulfur ylides[39,40] or the electrophilic sulfenylation of unsaturated carbon-carbon bonds.[41] Metzner *et al*[39a] and Otten *et al*[19] have reported the synthesis of chiral 2,5-dialkyl substituted thiolane derivatives. We envisaged that compounds with bulky substituent like phenyl group would provide better facial discrimination with prochiral substrates. Accordingly, we have extended our work to the preparation of sulfur analogues of nitrogen heterocycles.

2.2.9 Synthesis of (*2S,5S*)-2,5-diphenylthiolane

The reported procedure for the synthesis of 2,5-dimethylthiolane involves either harsh conditions (DMSO, 15 h, reflux) or long reaction periods (EtOH, RT, 15 days).[39,19] Therefore, we have slightly modified the reaction with optimized conditions for the synthesis of (*2S,5S*)-2,5-diphenylthiolane. Indeed, we have obtained satisfactory results under milder reaction conditions.

The (*2S,5S*)-2,5-diphenylthiolane was readily prepared from the 1,4-diol **48**. The (*1R,4R*)-1,4-diphenylbutane-1,4-diol was mesylated using Et_3N/MsCl in anhydrous dichloromethane (CH_2Cl_2) and the corresponding dimesylate was treated with sodium sulfide ($Na_2S.9H_2O$) dissolved in dimethylsulfoxide (DMSO) to afford the product in 80% yield (Scheme 28).

Scheme 28



The (*2S,5S*)-2,5-diphenylthiolane **106** was crystallized from hexane to obtain crystals suitable for X-ray analysis. The configuration of the 2,5-diphenylthiolane was confirmed (*2S,5S*). The crystal structure data of the compound are summarized in Table 1 and Table 2 (Appendix II and III). The ORTEP diagram of the (*2S,5S*)-2,5-diphenylthiolane is shown in figure 3.

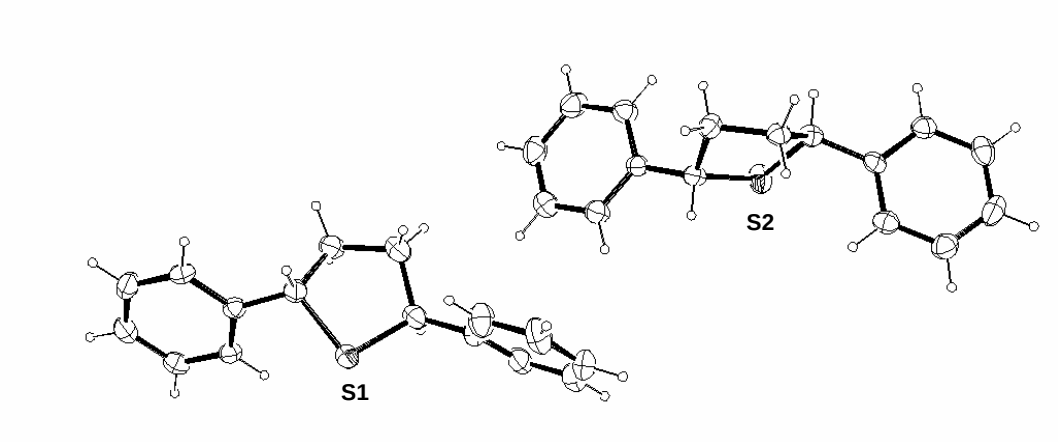
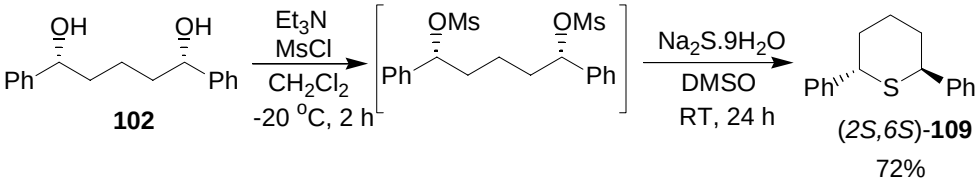


Figure 3 ORTEP diagram of the (*2S,5S*)-2,5-diphenylthiolane **108** (thermal ellipsoids are drawn at 20% probablity)

2.2.10 Synthesis of (*2S,6S*)-2,6-diphenyltetrahydrothiopyran

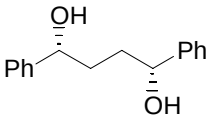
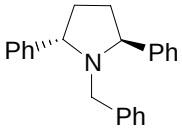
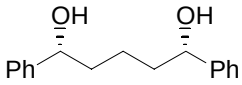
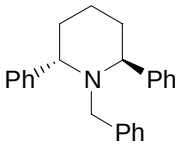
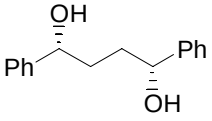
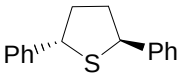
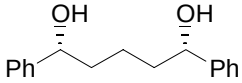
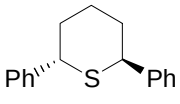
The dimesylate of (*1R,5R*)-1,5-diphenylpentane-1,5-diol was reacted with $Na_2S.9H_2O$ in dimethylsulfoxide yielded the condensed product (*2S,6S*)-2,6-diphenyltetrahydrothiopyran (Scheme 29).

Scheme 29



Synthesis of 2,5-and 2,6-diphenyl substituted nitrogen and sulfur heterocycles are summarized in table 1.

Table 1 Preparation of nitrogen and sulfur heterocycles[a]

entry	diol[b]	reagent[c]	product[d]	yield (%)[e]
1		$PhCH_2NH_2$	 (*2S,5S*)- **105**	73
2		$PhCH_2NH_2$	 (*2S,6S*)- **106**	78
3		$Na_2S.9\ H_2O$	 (*2S,5S*)- **108**	80
4		$Na_2S.9\ H_2O$	 (*2S,6S*)-**109**	72

[a]All the reactions were carried out in 10 mmol scale. [b]The optical purity diols were 98% ee, based on optical rotation.[42] [c]Benzylamine was freshly distilled before use, and sodium sulfide used without further purification (recrystallisation). [d]Products were identified using spectral data (IR, ^1H, ^{13}C-NMR and LCMS). [e]Yields are of isolated products.

2.3 Conclusion

Convenient methods were developed for the synthesis of (*2S,6S*)-*trans*-2,6-diphenylpiperidine, (*2S,5S*)-*trans*-2,5-diphenylthiolane and (*2S,6S*)-*trans*-2,6-diphenyl-tetrahydrothiopyran using readily accessible 1,4-diphenylbutane-1,4-dione and 1,5-diphenylpentane-1,5-dione. The C_2-symmetric ligands are expected to be useful in asymmetric transformations.

2.4 Experimental section

2.4.1 General information

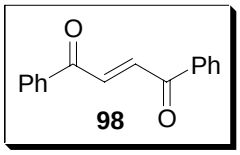
Most of the information in the experimental section of chapter 1 are also applicable to the experiments described in this chapter. The 1,4-diphenylbutane-1,4-dione was prepared following a reported procedure. The α,α'-diphenylpyrrolidine-methanol (DPPM) was purchased from Gerchem laboratory (Pvt) Ltd., India. The *N*,*N*-diethylaniline:borane was prepared following the procedure developed in this laboratory. Sodium borohydride, $AlCl_3$ and acetophenone were supplied by E.Merck India was used. (*S*)-proline supplied by Lancaster Synthesis Ltd., UK and boric acid from Sisco-Chemical (P) Ltd., were used.

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[42] without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).[43]

2.4.2 Preparation of *trans*-1,2-dibenzoylethylene 98

To a mixture of finely powdered aluminium chloride (30 g, 225 mmol) in benzene (200 mL), fumaryl chloride (11.5 g, 106 mmol) was added drop wise at 0 ^oC during 30 min. The stirring was continued for 2 h at 25 ^oC and the mixture was decomposed by pouring it upon ice. The benzene layer was separated and the aqueous layer was extracted with ether (2x50 mL). The combined organic extract was washed with aqueous sodium bicarbonate solution (2x25 mL), dried over anhydrous Na_2SO_4

and evaporated to obtain the product as a reddish brown solid. The crude product was recrystallized from ethyl alcohol to obtain **98**.



98

Yield 20.2 g (80%)

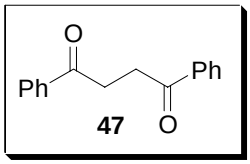
Mp 110-112 ^{o}C (lit[30] 111 ^{o}C)

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

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 7.51-7.83 (m, 6H), 8.02-8.30 (m, 6H)

2.4.3 Selective reduction of *trans*-1,2-dibenzoylethylene

To a hot suspension of stannous chloride (8.7 g, 39 mmol) in 8N HCl (12 mL) and ethyl alcohol (6 mL), a hot solution of trans-1,2-dibenzoylethylene **98** (8.7 g, 37 mmol) in ethyl alcohol (12 mL) was added carefully with stirring. The reaction was quenched with H_2O (5 mL), cooled and filtered. The filterate was washed with H_2O (20 mL) and the resulting solid was recrystallized from methanol to obtain **47**.



47

Yield 6.7 g (76%)

Mp 145 ^{o}C (lit[30] 145-147 ^{o}C)

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

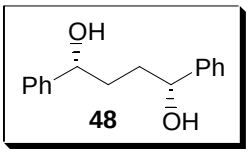
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 3.60 (s, 4H), 7.42-7.64 (m, 6H), 8.06 (d, *J*=6 Hz, 4H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 32.6, 128.1, 128.6, 133.1, 136.9, 198.6

2.4.4 Reduction of 1,2-dibenzoylethane with *N,N*-diethylaniline-BH_3 complex/B-methoxy oxazaborolidine (10 mol %) system

To a solution of (S)- α,α'-diphenylpyrrolidinemethanol (0.25g, 1 mmol) in THF (10 mL) at 25 ^{o}C, trimethylborate (0.15 mL, 1.25 mmol) was added and stirred for 1 h. *N,N*-diethylaniline-BH_3 (1M, 10 mL, 10 mmol) was added. 1,2-dibenzoylethane (1.19

g, 5 mmol) dissolved in THF (25 mL) was added to this suspension at 0 ^{o}C during 1 h, warmed to 25 ^{o}C and stirred further for 1 h. The reaction was carefully quenched with 2N HCl (5 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2x25 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane:ethyl acetate (75:25) as eluent to obtain the 1,4-diol **48**.



48

Yield 0.89 g (74%)

Mp 62-64 ^{o}C

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

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.82-2.05 (m, 4H), 2.68 (s, 2H), 4.73 (m, 2H), 7.21-7.38 (m, 10H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 35.0, 35.9, 74.0, 74.4, 125.9, 127.4, 128.4, 144.7

$[\alpha]_D^{25}$ (+)54.2 (c 1.01, $CHCl_3$) [lit[6] $[\alpha]_D^{25}$ = (-)58.5 (c 1.01, $CHCl_3$) >98% ee for (*1S,4S*)-**48**]

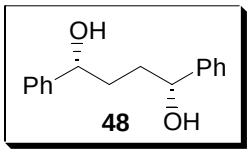
2.4.5 Purification of non-racemic diol 48 using (*S*)-proline and boric acid

(*S*)-Proline (0.26 g, 2.2 mmol) and boric acid (0.13 g, 2.2 mmol) were taken in dry toluene (16 mL) and refluxed for 12 h and the water produced was removed using a Dean-Stark apparatus. The non-racemic diol **48** (0.048 g, 2 mmol, 86% ee) dissolved in dry toluene (16 mL) was added to the reaction mixture under nitrogen atmosphere through cannula. The slurry becomes homogeneous and precipitation starts after 3 h. The contents were further refluxed for 9 h and brought to room temperature. The

precipitate was filtered in hot condition and was decomposed using a 1:1 mixture of THF and water (20 mL). 3N HCl (10 mL) was added and stirred at 25 ^{o}C for 5 h. The mixture was extracted with ethyl acetate (2x25 mL). The combined organic extract was washed successively with water (3x10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under pressure and the crude was purified by column chromatography on a silica gel (100-200 mesh) using hexane:ethyl acetate (75:25) as eluent to obtain the (*1R,4R*)-diphenylbutane-1,4-diol **48** in 98% ee.

After decomposition:

From precipitate after decomposition:



48

Yield 0.4 g (84%)

Mp 68-70 ^{o}C

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

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.67-2.05 (m, 4H), 3.52 (br, s, 2H), 4.65 (br, s, 2H), 7.04-7.51 (m, 10H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 35.9, 74.2, 125.9, 127.3, 128.4, 144.7

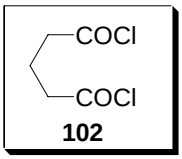
$[\alpha]_D^{25}$ (+) 58 (c 0.11, $CHCl_3$) [lit[6] $[\alpha]_D^{25}$ = (-) 58.5 (c 1.01, $CHCl_3$) >98% ee for (*1S,4S*)-**48**]

Absence of meso isomer was confirmed from the ^{13}C-NMR spectrum of the sample. The filtrate obtained was evaporated and decomposed using THF-water mixture. After work up as described above, the diol sample was isolated. It was essentially meso isomer.

2.4.6 Preparation of (*1R,5R*)-diphenylpentane-1,5-diol, 104

2.4 6a Preparation of pentanedioyl dichloride, 102

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



102

Yield 28 g (82%)

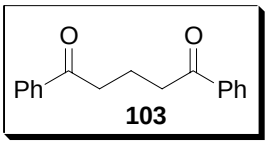
IR (neat) (cm^{-1}) 1799, 1298

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

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

2.4.6b Preparation of 1,5-diphenylpentane-1,5-dione, 103

To a mixture of finely powdered aluminium chloride (16 g, 120 mmol) in benzene (150 mL), was added pentanedioyl dicholride **102** (7 mL, 54 mmol) in benzene (50 mL) dropwise during 30 min. The stirring was continued for 2 h at 25 ^oC and the mixture was decomposed by pouring it upon ice. The benzene layer was separated and the aqueous layer was extracted with ether (2x50 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution (2x25 mL), water (25 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain the product as a pale white solid. It was recrystallized from pure hexane.



103

Yield 12.8 g (94%)

Mp 59-61 ^oC

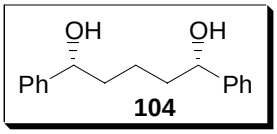
IR (KBr) (cm^{-1}) 3065, 2970, 2889, 1680, 1597, 731, 688

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 2.21 (m, 2H), 3.12 (m, 4H), 7.26-7.56 (m, 7H), 7.95-7.96 (m, 4H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 18.7, 37.6, 128.0, 133.0, 136.9, 199.7

2.4.6c Reduction of 1,5-diphenylpentane-1,5-dione with *N*,*N*-diethylaniline-BH_3 complex/B-methoxy oxazaborolidine (10 mol %) system

To a stirred solution of (S)- α,α'-diphenylpyrrolidinemethanol (0.25g, 1 mmol) in THF (10 mL) at 25 ^{o}C, $B(OMe)_3$ (0.15 mL, 1.25 mmol) was added and stirred for 1 h. *N*,*N*-Diethylaniline-BH_3 (1M, 10 mL, 10 mmol) was added. 1,5-diphenylpentane-1,5-dione **103** (1.26 g, 5 mmol) dissolved in THF (25 mL) was added to this suspension at 0 ^{o}C during 1 h and the reaction mixture was brought to 25 ^{o}C, stirred further for 1 h. The reaction was carefully quenched with 2N HCl (5 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2x25 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, the crude was purified by column chromatography on a silica gel (100-200 mesh) using hexane:ethyl acetate (70:30) as eluent to obtain the1,5-diol **104**.



104

Yield 0.99 g (80%)

M.p 89-91 ^{o}C

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

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.47-1.95 (m, 6H), 4.63 (t, 2H), 7.31 (m, 6H)

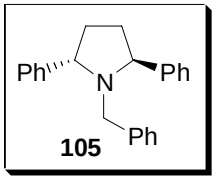
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 22.0, 38.6, 73.9, 74.1, 125.8, 127.2, 128.2, 144.8

$[\alpha]_D^{25}$ (+) 18.5 (c 1.03, MeOH) [lit[41] $[\alpha]_D^{25}$ = (-) 19.7 (c 1.01, $CHCl_3$) >99% ee for (*1S,5S*)-**104**]

2.4.7 Synthesis of *N*-substituted Pyrrolidines, Piperidines and Sulfur heterocycles

2.4.7a Preparation of (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine (105)

To a solution of (*1R,4R*)-1,4-diphenylbutane-1,4-diol **48** (2.42 g, 10 mmol) and Et_3N (4.2 mL, 30 mmol) in dry CH_2Cl_2 (50 mL) was added methanesulfonyl chloride (1.7 mL, 22 mmol) at -20 ^oC. The mixture was stirred for 2 h at -20 ^oC, and then brought to 0 ^oC. To this (dimesylate was not isolated), benzylamine (40 mL) excess was added and the resultant mixture was stirred at 0 ^oC for 12 h. After warming to 25 ^oC, stirring continued further for 4 h. The excess benzylamine was removed under vacuum and the residue was dissolved in ether (50 mL). The contents were washed with saturated $NaHCO_3$ solution (3x20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane as an eluent to obtain the *N*-benzyl-2,5-diphenylpyrrolidine **105**.



105

Yield 2.28 g (73%)

IR (neat) (cm^{-1}) 3061, 1602

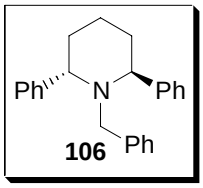
^1H NMR (200 MHz, $CDCl_3$, δ ppm): 1.98-2.22 (m, 2H), 2.43-2.81 (m, 2H), 3.15 (d, *J*=14 Hz, 1H), 3.65 (d, *J*=14 Hz, 1H), 4.28 (m, 2H), 7.11-7.35 (m, 15H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 32.8, 51.0, 65.2, 126.4, 126.9, 127.9, 128.1, 128.2, 128.3, 140.1, 143.9

$[\alpha]_D^{25}$ (-)126.4 (c 0.44, $CHCl_3$)

2.4.7b Preparation of (*2S,6S*)-*N*-benzyl-2,6-diphenylpiperidine, 106

To a solution of (*1R,5R*)-1,5-diphenylpentane-1,5-diol **104** (2.56 g, 10 mmol) and Et_3N (4.2 mL, 30 mmol) in dry CH_2Cl_2 (50 mL) was added methanesulfonyl chloride (1.7 mL, 22 mmol) at -20 ^oC. The mixture was stirred for 2 h at -20 ^oC, and then brought to 0 ^oC. To this (dimesylate was not isolated), benzylamine (40 mL) excess was added and the resultant solution was stirred at 0 ^oC for 12 h. After warming to 25 ^oC, stirring continued further for 4 h. The excess benzylamine was removed under reduced pressure and the residue was dissolved in ether (50 mL). The contents were washed with saturated $NaHCO_3$ solution (2x20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane as an eluent to obtain the *N*-benzyl-2,6-diphenylpiperidine **106**.



106

Yield 2.5 g (78%)

IR (neat) (cm^{-1}) 3065, 2931, 1602, 754

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.79-1.84 (m, 2H), 1.90-1.98 (m, 2H), 2.01-2.08 (m, 2H) 3.39-3.68 (m, 2H), 7-7.31 (m, 15H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 20.2, 27.21, 51.7, 58.4, 126.6, 128.2, 128.24, 128.3, 128.6, 128.69, 140.6, 144.2

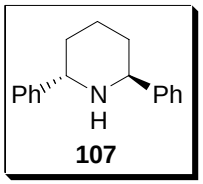
$[\alpha]_D^{25}$ (-) 113.7 (c 0.94, $CHCl_3$)

Anal. calcd for $C_{24}H_{25}N$ C, 88.03; H, 7.70; N, 4.28. Found: C, 88.12; H, 7.67; N, 4.29

LCMS (m/z) 327.65 (M+1)

2.4.7c Preparation of (*2S,6S*)-*trans*-2,6-diphenylpiperidine, 107

The (*2S,6S*)-*trans*-N-benzyl-2,6-diphenylpiperidine **106** (0.33 g, 1 mmol) was dissolved in CH_3CN-H_2O (5:1) mixture (5 mL). To this solution ceric ammonium nitrite (CAN) (1.2 g, 2.1 mmol) was added in portion and stirred for 2 h. The acetonitrile was removed and the contents were dissolved in ether (25 mL). The contents were washed thoroughly with saturated $NaCO_3$ solution (2x10 mL), water (5 mL), brine (5 mL) and dried over dry K_2CO_3. The solvent was evaporated and the crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane:ethyl acetate (80:20) as an eluent to afford (*2S,6S*)-*trans*-2,6-diphenylpiperidine **107**.



107

Yield 0.15 g (65%)

IR (neat) (cm^{-1}) 3321, 3061, 3028, 2926, 1601, 758, 698

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.71-1.75 (m, 2H), 1.93-2.05 (m, 4H), 2.4 (br, 1H), 4.15 (t, 2H), 7.25-7.46 (m, 10H)

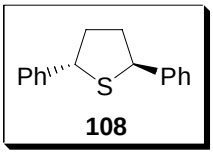
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 20.8, 31.4, 54.8, 126.6, 126.7, 128.5, 144.2

$[\alpha]_D^{25}$ -68.4 (c 0.94, $CHCl_3$) [lit[32] $[\alpha]_D^{25}$ = (+) 70.1 (c 4.63, EtOH) (*2R,6R*)-**107**]

2.4.8 Preparation of (*2S,5S*)-*trans*-2,5-diphenylthiolane, 108

To a solution of (*1R,4R*)-1,4-diphenylbutane-1,4-diol **48** (1.21 g, 5 mmol) and Et_3N (2.1 mL, 15 mmol) in dry CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (0.8 mL, 11.5 mmol) at -20 ^oC. The mixture was stirred for 2 h at -20 ^oC, and then brought to 0 ^oC. To this (dimesylate was not isolated), was added Sodium sulfide ($Na_2S.9H_2O$) (2.4 g, 10 mmol) dissolved in DMSO (10 mL). The reaction temperature brought to 25 ^oC and stirring continued for 36 h. The solvents were removed under

pressure and the crude was dissolved in ether (50 mL), washed several times with H_2O to remove any trace of DMSO. The organic layer was treated with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product was purified by column chromatography on a silica gel (100-200 mesh) using hexane as an eluent to obtain the *trans*-2,5-diphenylthiolane **108**.



108

Yield 0.96 g (80%)

IR (KBr) (cm^{-1}) 3054, 2932, 1601, 754, 698

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.12-2.19 (m, 2H), 2.55-2.62 (m, 2H), 4.83-4.89 (m, 2H), 7.23-7.51 (m, 10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 41.5, 54.8, 127.6, 128.1, 129.0, 142.9

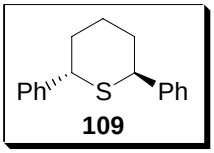
$[\alpha]_D^{25}$ (+)15.4 (c 1.0, $CHCl_3$)

LCMS (m/z) 241 (M+1)

2.4.9 Preparation of (*2S,6S*)-*trans*-2,6-diphenyltetrahydrothiopyran, 109

To a solution of (*1R,5R*)-1,5-diphenylpentane-1,5-diol **104** (1.28 g, 5 mmol) and Et_3N (2.2 mL, 15 mmol) in dry CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (0.8 mL, 11.5 mmol) at -20 ^oC. The mixture was stirred for 2 h at -20 ^oC, and then brought to 0 ^oC. To this (dimesylate was not isolated), was added Sodium sulfide ($Na_2S.9H_2O$) (2.4 g, 10 mmol) dissolved in DMSO (10 mL). The reaction temperature brought to 25 ^oC and stirring continued for 36 h. The solvents were removed under reduced pressure and the crude was dissolved in ether (50 mL), washed several times with H_2O to remove any trace of DMSO. The organic layer was treated with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product

was purified by column chromatography on a silica gel (100-200 mesh) using hexane as an eluent to obtain the *trans*-2,6-diphenyltetrahydrothiopyran **109**.



109

Yield 0.91 g (72%)

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

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.70-1.76 (m, 2H), 2.18-2.35 (m, 4H), 4.06-4.09 (m, 2H), 2.24-7.54 (m, 10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 21.6, 32.9, 43.6, 126.7, 127.7, 128.4, 142.1

$[\alpha]_D^{25}$ -12.1 (c 0.98, $CHCl_3$)

LCMS (m/z) 255.1 (M+1)

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Chapter 3

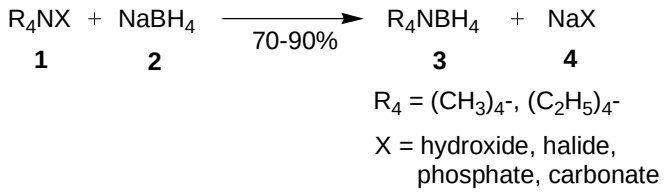
Generation of diborane using Bu_4NBH_4 for synthetic applications

3.1 Introduction

Diborane (B_2H_6) is a useful reagent in organic and inorganic syntheses such as hydroboration of carbon-carbon double and triple bonds, and reduction of various functional groups.[1,2] Diborane, a pyrophoric gas is not stable at room temperature and hence it is normally generated *in situ* in the glycol ethers and most commonly used as borane-Lewis base complexes [BH_3-THF, BH_3-$S(CH_3)_2$], as they are safer and convenient to handle. However, these commercially available reagents are expensive and hazardous to store. On the other hand, sodium borohydride and other modified borohydrides such as $LiBH_4$, lithium aminoborohydride, and $NaBH_3CN$ require solvents like THF, dioxane and diglyme. However, each system has their advantages and some limitations.

A brief literature is survey presented here on modified borohydride reagents to facilitate the discussion. The first preparation of quaternary ammonium borohydride **3** by metathesis reaction of alkali metal hydrides **2** with ammonium salts **1** was reported in 1952 (Scheme 1).[3]

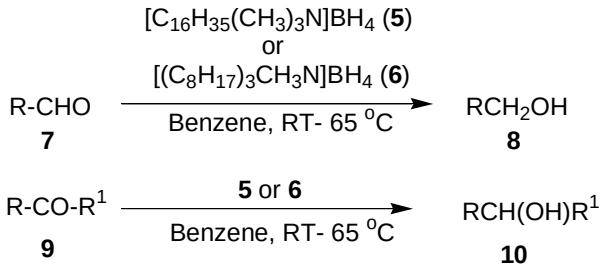
Scheme 1



Sullivan and Hinckley[4] reported the synthesis of cetyl trimethyl ammonium borohydride **5** and tricaprylmethyl ammonium borohydride **6** containing longer chain hydrocarbon groups for increased hydrocarbon solubility. Reduction of representative

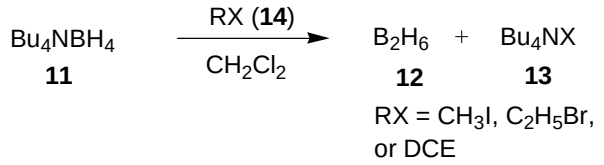
organic compounds **7** and **9** were carried out with 50 to 100% excess borohydride in benzene (Scheme 2).

Scheme 2



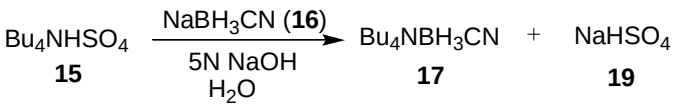
In 1972, Lamm *et al*[5] reported that the generation diborane by addition of alkyl halide like methyl iodide, ethyl bromide to an anhydrous solution of tetraalkyl ammonium borohydride in dichloromethane (Scheme 3).

Scheme 3



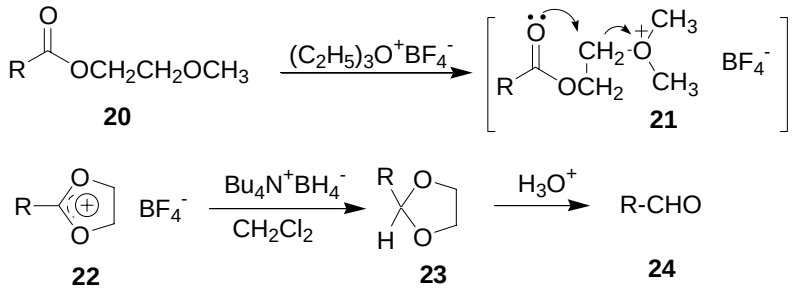
The synthesis of exceptionally mild reagent tetrabutylammonium cyanoborohydride (Bu_4NBH_3CN) was reported by Hutchins and Kandasamy[6] (Scheme 4). This reagent reduces only primary iodides and to lesser extent bromides to the corresponding hydrocarbons in hexamethylphophoramide (HMPA) solvent at 25 °C.

Scheme 4



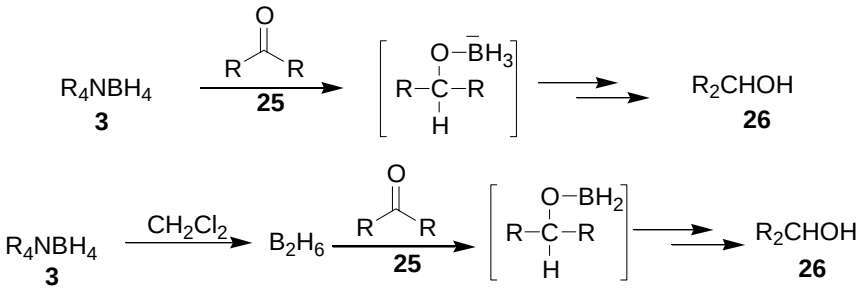
Raber and Guida[7] used Bu_4NBH_4 in dichloromethane for the reduction of oxonium ions **22** to avoid the difficulties resulting from insolubility of the dioxaolanium salts in ethereal solvents and from Lewis acidity of various reducing agents in the synthesis of acetals **23** (Scheme 5).

Scheme 5



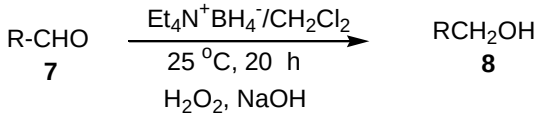
Later, the same authors reported that the reduction of aldehydes and ketones with Bu_4NBH_4 in dichloromethane. In order to achieve convenient rate of reduction of ketones four equivalents of excess hydride was used (Scheme 6).[8]

Scheme 6



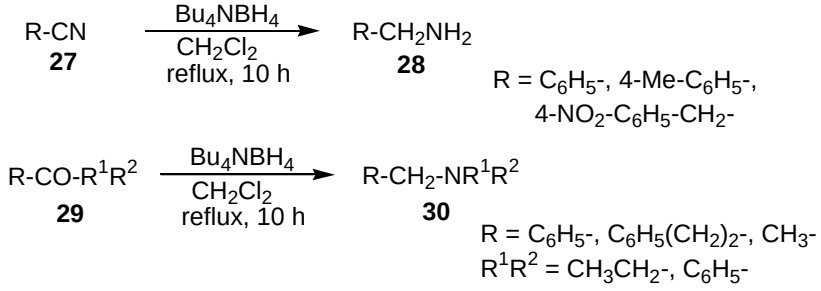
Sorrell and Pearlman[9] reported the selective reduction of aldehydes to the corresponding alcohols in dichloromethane at 25 ^oC within 20h (Scheme 7).

Scheme 7



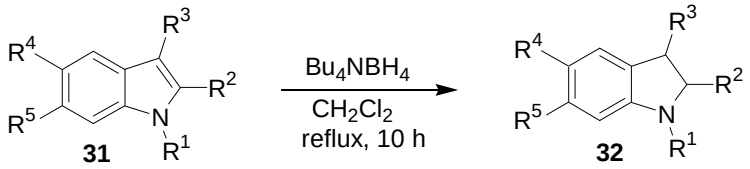
Wakamatsu *et al*[10] reported the reduction of nitriles and amides to the corresponding amines with tetrabutylammonium borohydride (Bu_4NBH_4) in dichloromethane at refluxing conditions (Scheme 8).

Scheme 8



Indole derivatives **31** were reduced with tetrabutylammonium borohydride **11** in dichloromethane to the corresponding indulines **32** under reflux conditions (Scheme 9).[11]

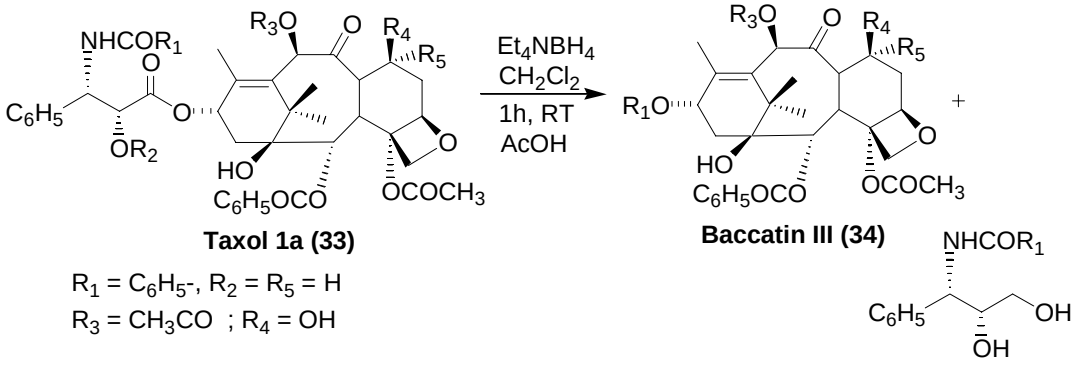
Scheme 9



R^1 = H, CH_3- ; R^2 = H, CH_3-, -$(CH_2)_4$-
R^3 = H, CH_3-, ; R^4 = H, CH_3O-
R^5 = H, CH_3O-

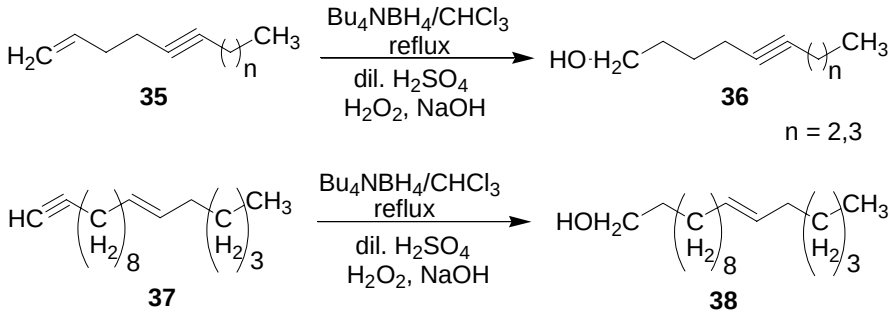
Preparation of Baccatin III **34**, a key component in studies on structure-activity relationship in the Taxol, was achieved by reduction of Taxol 1a with tetrabutylammonium borohydride in dichloromethane in 97% yield (Scheme 10).[12]

Scheme 10



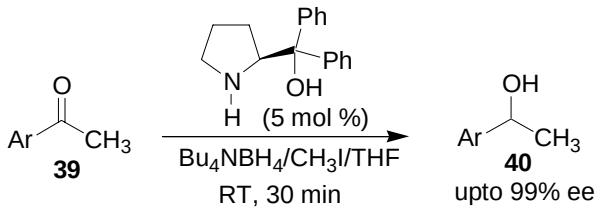
In 1998, hydroboration of alkenes and alkynes with tetrabutylammonium borohydride in chloroform at refluxing temperature were reported by Narasimhan *et al*[13] (Scheme 10). There was no selectivity observed in the hydroboration of dienes. However, with enynes the reagent selectively reacts towards terminal double bonds and triple bonds.

Scheme 10



More recently, oxazaborolidine catalyzed asymmetric reduction of prochiral ketones with good enantioselectivity, upto 99% ee using Bu_4NBH_4/CH_3I in THF was reported from this laboratory (Scheme 11).[14]

Scheme 11



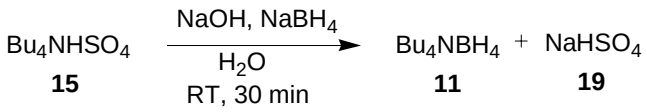
It was of interest to examine the preparation of reactive borane species from tetrabutylammonium borohydride using other alkyl halides as additives since the methyl iodide is carcinogenic. The results are described in the next section.

3.2 Results and discussion

3.2.1 Preparation of tetrabutylammonium borohydride (Bu_4NBH_4)

The tetraalkylammonium borohydrides are readily soluble in organic solvents and they have low reactivity as reducing agents. It is considerably easier to handle these reagents compared to other metal borohydrides (eg., $NaBH_4$, $LiAlH_4$). For instance, they can be recrystallized from the ethyl acetate. The tetrabutylammonium borohydride was readily prepared following a reported procedure (Scheme 12).[5]

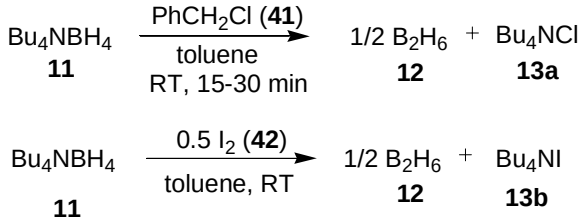
Scheme 12



3.2.2 Generation of diborane (B_2H_6) from Bu_4NBH_4 using additives

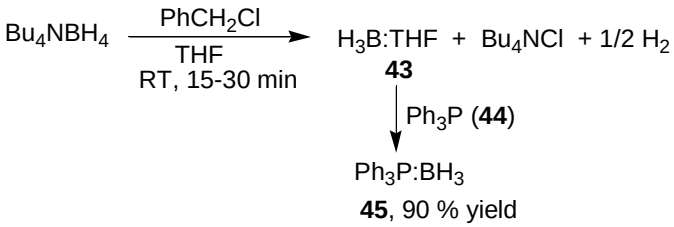
As noted earlier, addition of alkyl halide to a solution of Bu_4NBH_4 generates diborane in THF. However, ether solvents have a high tendency to form peroxides. Also, it is difficult to recover these solvents after aqueous work-up. Accordingly, we carried out the reaction of tetrabutylammonium borohydride **11** with additives like benzyl chloride **41** and iodine **42** in toluene. Indeed, the diborane was readily generated in >90% yield in this way (Scheme 13).

Scheme 13



We have observed that the addition of benzyl chloride to tetrabutylammonium borohydride in THF at 25 ^{o}C for 30 min. followed by the addition of Ph_3P **44** gives the $Ph_3P:BH_3$ (^{11}B NMR: -37.6 ppm) in 90% yield (*in situ*). This indicates the formation of borane in the reaction of Bu_4NBH_4 with $PhCH_2Cl$ (Scheme 14).

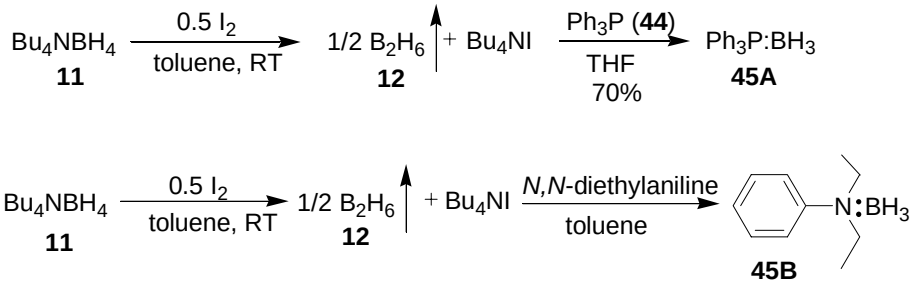
Scheme 14



3.2.3 Preparation of Lewis base-BH_3 complexes using the Bu_4NBH_4/I_2 system

The Bu_4NBH_4/I_2 system provides a convenient source of diborane gas. This reagent can be used for preparing various Lewis base-BH_3 complexes. For example, the $Ph_3P:BH_3$ can be prepared (*ex situ*) in 70% yield by passing B_2H_6, generated by Bu_4NBH_4/I_2 in toluene, through a solution of Ph_3P in THF. Also, Bu_4NBH_4/I_2 can be utilized to prepare the stock solution of *N,N*-diethylaniline-borane in toluene (Scheme 15).

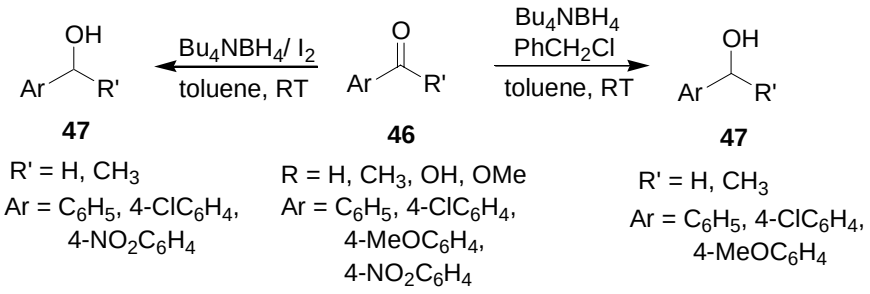
Scheme 15



3.2.4 Reduction of carbonyl compounds with $Bu_4NBH_4/PhCH_2Cl$ and Bu_4NBH_4/I_2 reagent systems

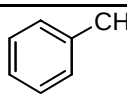
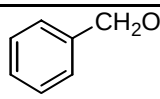
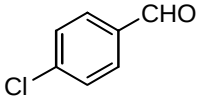
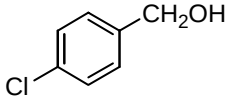
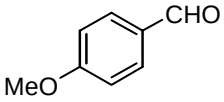
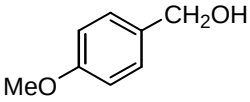
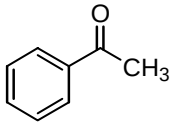
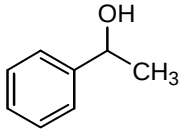
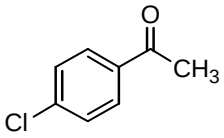
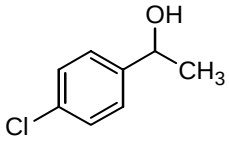
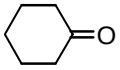
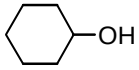
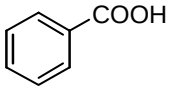
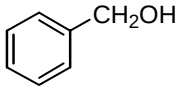
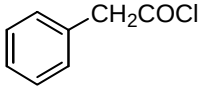
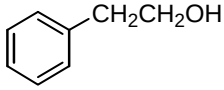
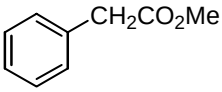
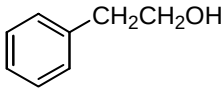
We have observed that the diborane (*in situ*) generated in this way effectively reduces various functional groups like aldehydes, ketones, carboxylic acids, and acid chlorides readily at 25 ^oC (Scheme 16, Table 1 and 2). However, esters took 12 h for the completion of the reaction. The general reactivity pattern of $Bu_4NBH_4/PhCH_2Cl$ towards various carbonyl compounds is in the order aldehyde > ketone > acid chloride > carboxylic acids >> esters. The process is simple and amenable to scale up.

Scheme 16



It is important to note that the $Bu_4NBH_4/PhCH_2Cl$ reagent system does not reduce the carbonyl compounds at 0 ^oC in toluene even at prolonged reaction time (48 h). However, the reaction readily takes place at 25 ^oC.

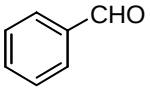
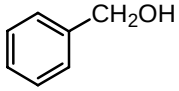
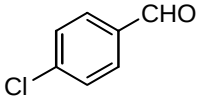
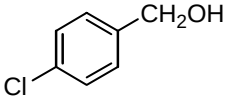
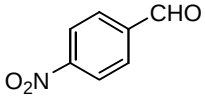
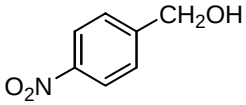
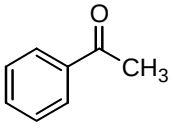
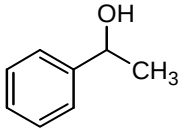
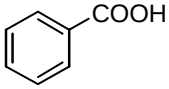
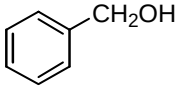
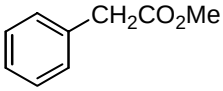
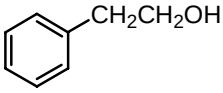
Table 1 Reduction of representative carbonyl compounds with Bu_4NBH_4/-$PhCH_2Cl$

entry	substrate[a]		time (min)	product[b]		yield (%)[c]
1		**47**	15		**56**	86
2		**48**	15		**57**	92
3		**49**	30		**58**	91
4		**50**	15		**59**	91
5		**51**	15		**60**	94
6		**52**	90		**61**	82
7		**53**	120		**56**	89
8		**54**	15		**62**	90
9		**55**	720		**62**	82

[a]All the reactions were carried out using 5 mmol substrate with 7 mmol of the $Bu_4NBH_4/PhCH_2Cl$ reagent. [b]Products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and by comparison with reported data.[15] [c]Yields of isolated products.

It is desirable to add the iodine at 0 ^oC to the solution of the Bu_4NBH_4 (*in situ*) and the carbonyl compound in toluene and then warm to room temperature in order to avoid the borane loss during the reduction with Bu_4NBH_4/I_2 reagent system.

Table 2 Reduction of representative carbonyl compounds with Bu_4NBH_4/I_2

entry	substrate[a]		time (min)	product		yield (%)[c]
1		**47**	15		**56**	90
2		**48**	15		**57**	94
3		**63**	15		**64**	89
4		**50**	15		**59**	91
5		**53**	30		**56**	89
6		**55**	720		**62**	86

[a]All the reactions were carried out using 5 mmol substrate with 6 mmol of the Bu_4NBH_4/I_2 reagent. [b]Products were characterized by IR, ^1H NMR, ^{13}C NMR and by comparison with reported data.[15] [c]Yields of isolated products.

3.2.5 Hydroboration of alkenes using $Bu_4NBH_4/PhCH_2Cl$ reagent system

Hydroboration is one of the most important methods for the synthesis of organoboranes from unsaturated compounds. Diverse hydroborating agents such as BH_3:THF, BH_3:$S(CH_3)_2$, 9-BBN and thexylborane are commercially available. However, each of these reagents has limitations and all are air sensitive. Previously, hydroboration of olefins has been reported using tetrabutylammonium borohydride in chloroform under refluxing conditions.[13] The $R_4N^+BH_4^-/Me_3SiCl$ system has been used for the conversion of olefins to alcohols without any oxidizing agent.[16]

In order to extend the scope and applicability of the $Bu_4NBH_4/PhCH_2Cl$ reagent system, we have carried out hydroboration reactions with olefins. We have observed

that the $Bu_4NBH_4/PhCH_2Cl$ reagent system hydroborates olefins under ambient conditions in toluene/THF mixture and the corresponding alcohols were obtained in good yields after H_2O_2/OH^- oxidation (Scheme 17, Table 3). The regioselectivity of the hydroboration is 92:8 (^{1}H-NMR), favoring the terminal position of unhindered olefin like phenylstyrene.

Scheme 17

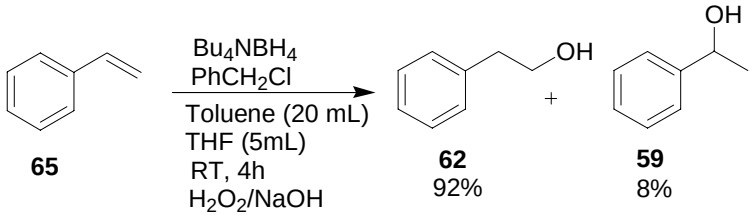
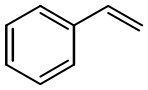
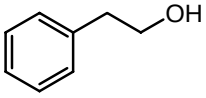
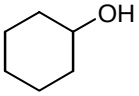
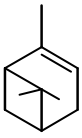
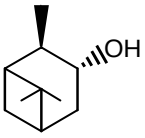


Table 3 Hydroboration of alkenes using $Bu_4NBH_4/PhCH_2Cl$

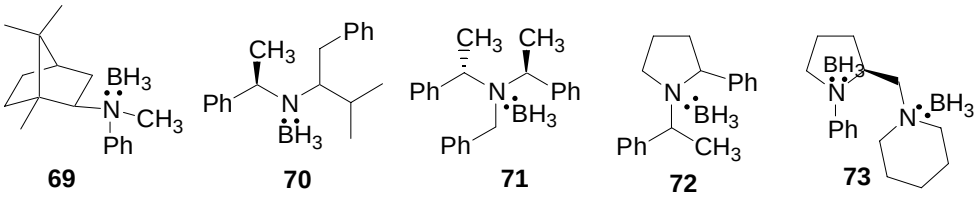
entry	substrate[a]		time (h)	product[b]		yield (%)[c]
1		**65**	3		**62**	86
2		**66**	4		**61**	82
3		**67**	4		**68**	80

[a]All the reactions were carried out using 7.5 mmol substrate with 9 mmol of the $Bu_4NBH_4/PhCH_2Cl$ reagent. [b]Products were characterized by IR, ^{1}H NMR, ^{13}C NMR and by comparison with reported data.[15] [c]Yields of isolated products.

3.2.6 Hydroboration of prochiral olefins with chiral amine-borane complexes

Borane reagents continue to attract much interest owing to its versatile chemistry. Previously, it was reported from this laboratory[17] that chiral amine-borane complexes (**69-73**) hydroborate the prochiral olefins to the corresponding alcohols up to 19% ee after alkaline oxidation.

Figure 1



The results obtained previously in hydroboration using chiral amine-borane complexes with prochiral olefins (**69-73**) are summarized in Table 4 (Scheme 18).

Scheme 18

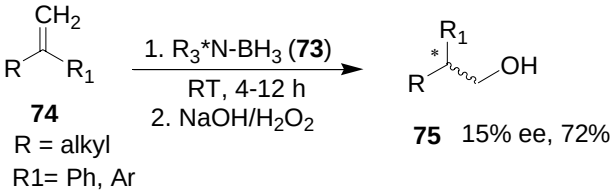
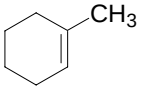
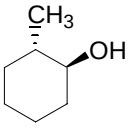
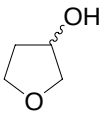
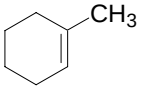
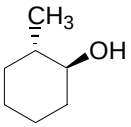
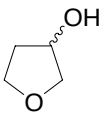
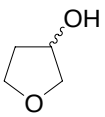
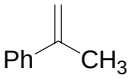
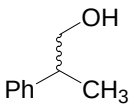
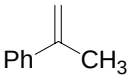
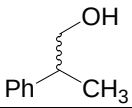


Table 4 Hydroboration of prochiral olefins with chiral amine-borane complexes

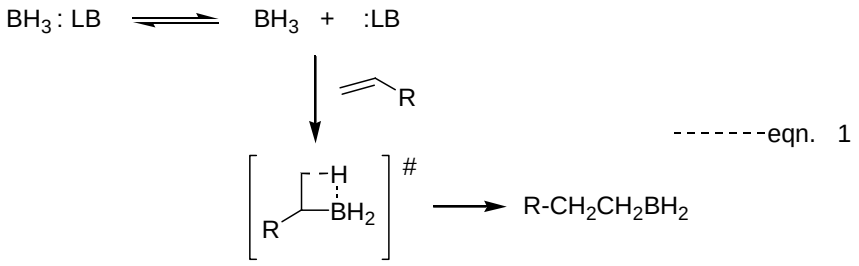
entry	R_3*N:BH_3	substrate	product	% ee[a]	yield (%)[b]	Ref.
1	**69**			4	70	17a
2	**69**			19	76	17a
3	**70**			3	68	17a
4	**70**			12	69	17a
5	**71**			14	72	17b
6	**72**			10	72	17b
7	**73**			15	72	17c

[a]All the ee values are based on optical rotation. [b]Yields are of the isolated products.

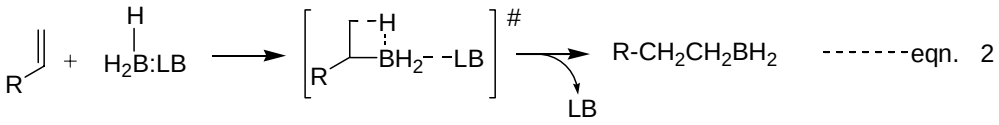
These results indicates that the hydroboration reaction may proceed via S_N1 (eqn.1), S_N2 (eqn.2) or S_N2-type with π-complex (eqn.3) mechanistic pathway depending on the nature of the olefin and the amine borane complex (Scheme 19).[17,18]

Scheme 19

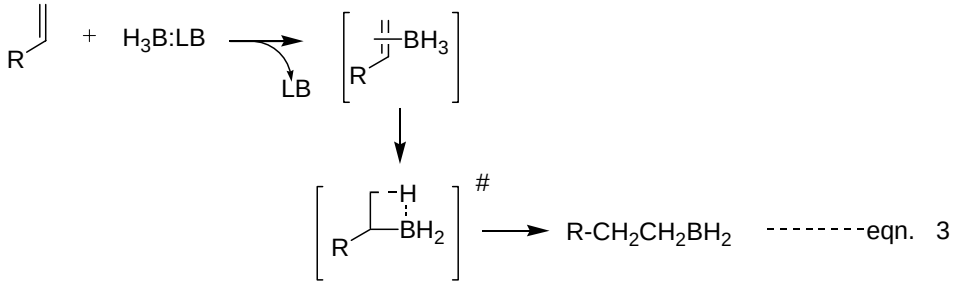
S_N1-type mechanism



S_N2-type mechanism



S_N2-type mechanism with π-complex intermediate

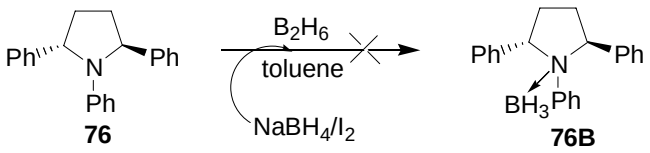


The racemic product would result if the dissociation of borane from the chiral amine-borane complex (R_3*N:BH_3) takes place before the hydroboration reaction in an '**S_N1** like' mechanism or **S_N2** reaction with π-complex intermediate.

We have investigated the hydroboration reaction using the borane complexes of chiral amines prepared earlier (Chapter 2). Previously, it was observed that *N*-phenyl-

2,5-diphenylpyrrolidine **76** does not form the amine-borane complex due to steric hindrance around the nitrogen atom (Scheme 20).

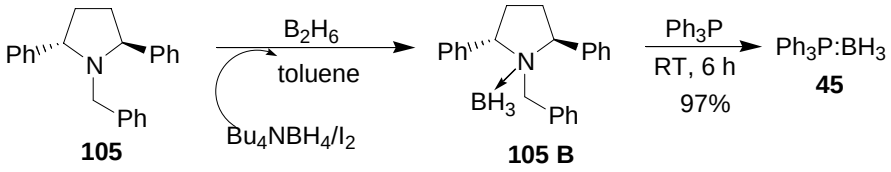
Scheme 20



With this background, we thought that the (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine-BH_3 complex would be structurally similar to that of (*S,S*)-(-)-*N*-benzyl-α,α'-dimethyl-dibenzylamine-BH_3 **71** (Figure 1) but has C_2-symmetry and hence would lead to improved facial discrimination resulting in better enantioselectivity. Accordingly, we prepared (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine-BH_3 complex *ex situ* for the hydroboration studies towards prochiral olefins like α-methylstyrene and *trans*-stilbene.

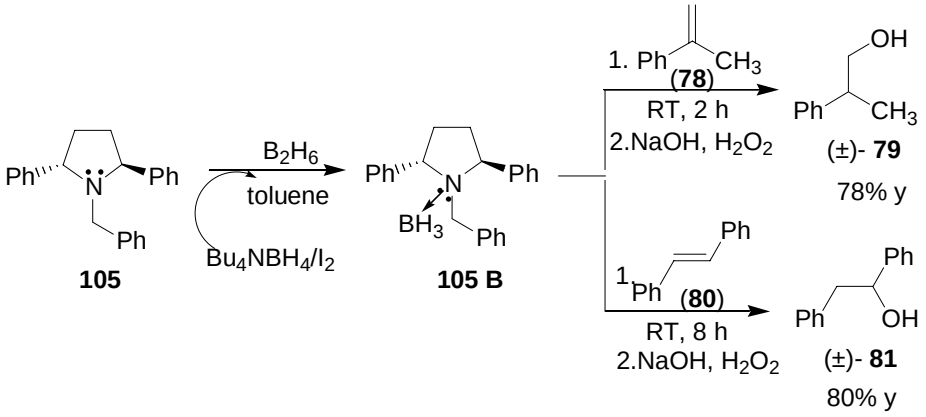
The chiral amine-borane complex, **105B** was readily prepared using Bu_4NBH_4/I_2 in toluene (*ex situ*). The diborane gas was bubbled through an anhydrous toluene solution of chiral amine **105**. In order to examine the stoichiometry of the amine borane in the solution, triphenyl phosphine (1 equiv) was added and $Ph_3P:BH_3$ was obtained in 97% yield (Scheme 21).

Scheme 21



It was found that the (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine-BH_3 **105B** hydroborates the prochiral olefins such as α-methylstyrene and *trans*-stilbene at 25 ^oC to the corresponding alcohol after alkaline oxidation in 80% yield, but the product was found to be racemic (Scheme 22).

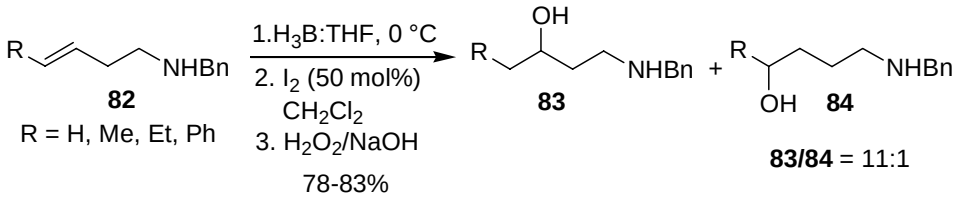
Scheme 22



Presumably, in the hydroborations using amine-borane complex **105B**, no ee was obtained because of the reaction taking the S_N1 or S_N2 pathway with π-complex intermediate (Scheme 19) in which the crowded chiral amine moiety leaves from the borane moiety before the hydroboration reaction.

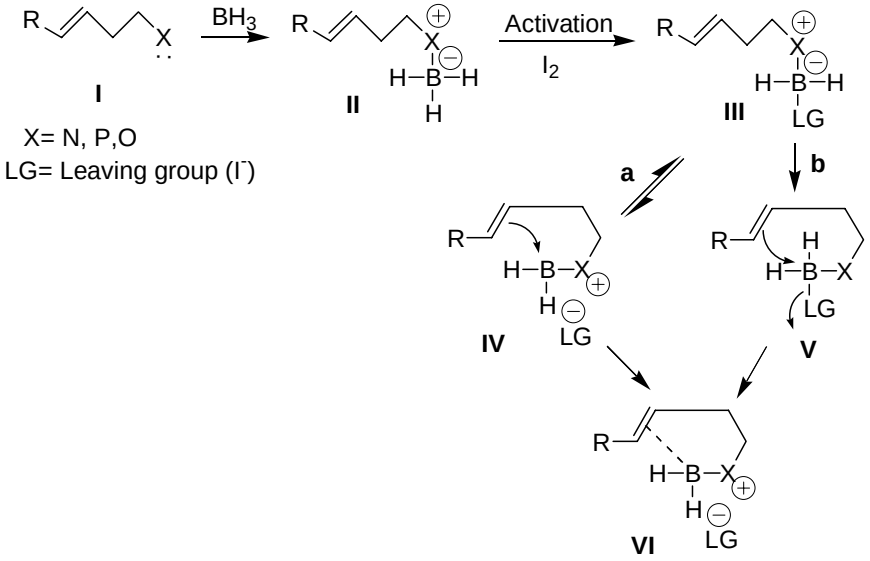
Recently, Vedejs *et al*[19] reported the intramolecular hydroboration of homoallylic amines and phosphine borane complexes using activating agents such as I_2, Br_2 and TfOH (Scheme 23).

Scheme 23



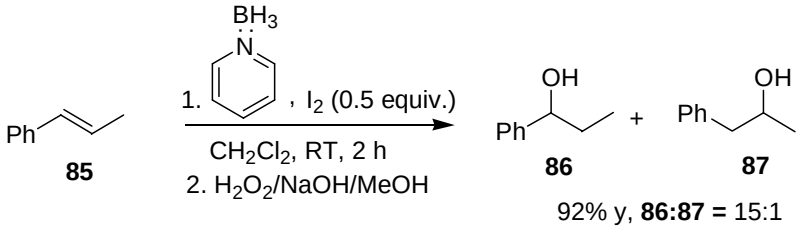
The proposed mechanistic pathway indicates that the intramolecular hydroboration may take place via S_N1 like mechanistic path way through intermediate **IV** or S_N2 like mechanistic pathway through intermediate **V** in the transition state where the iodide (I^-) act as a leaving group (Scheme 24).

Scheme 24



Also, Vedejs *et al*[20] reported intermolecular hydroboration of β-methylstyrene using pyridine-BH_3 complex and 50 mol% I_2 at 25 ^oC (Scheme 25).

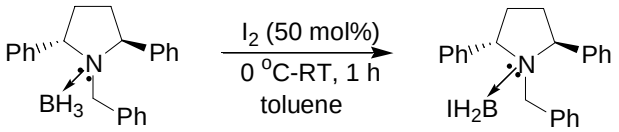
Scheme 25



It was of interest to examine whether the chiral amine **105** can be anchored to the boron moiety and the iodide could serve as a leaving group in the case of chiral amine borane **105B**. In order to examine this possibility, we examined the hydroboration of prochiral olefins after making the amine-BH_2I complex.

The amine-BH_2I complex **110** was prepared by addition of 0.5 equivalents I_2 to the amine-BH_3 **105B** at 0 ^oC and warmed to room temperature till the solution became colourless (scheme 26).

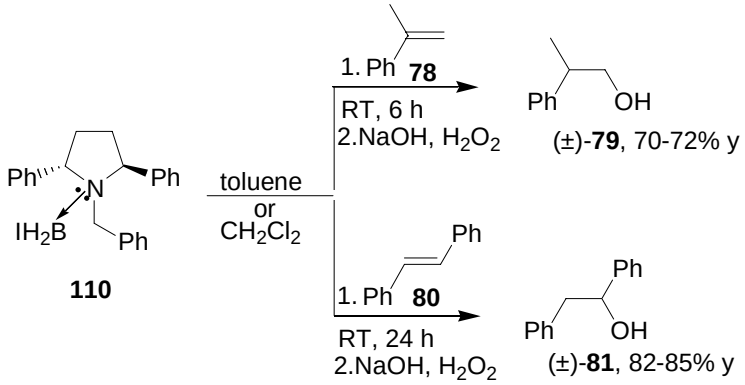
Scheme 26



105B **110**

We have carried out the hydroboration of prochiral olefins such as α-methyl-styrene and *trans*-stilbene using the amine-BH_2I complex **110** in toluene or CH_2Cl_2 at 25 ^oC. However, the corresponding alcohols obtained after oxidation were found to be racemic (Scheme 27). We have also observed that no hydroboration takes place at 0 ^oC.

Scheme 27

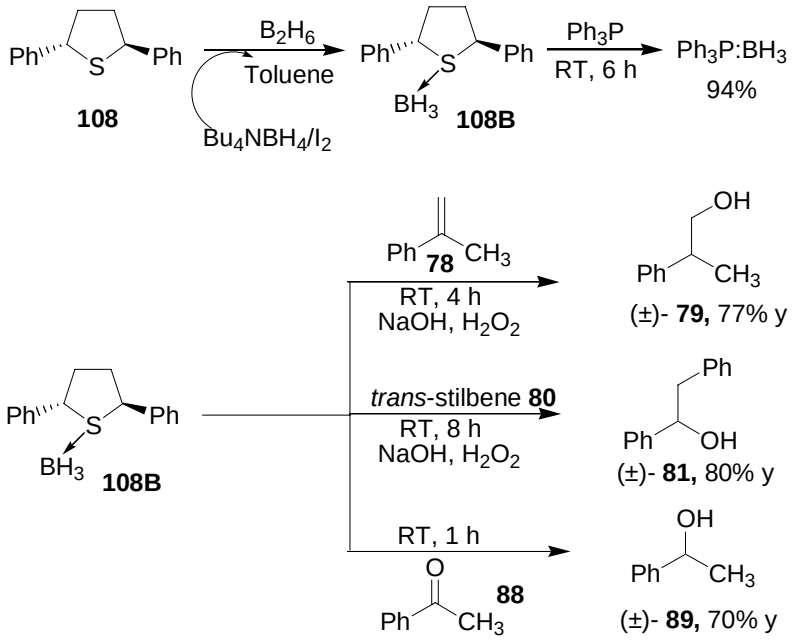


110

It was thought that addition of I_2 to the amine-borane complex would increase the Lewis acidity of the boron which in turn would increase the strength of the N-B coordination bond. Thus, the chiral amine would bind to the BH_2I moiety strongly and could lead to assosiative S_N2-like mechanistic pathway. Perhaps, along with stereo electronic factors, the steric hindrance around the amino nitrogen atom weakened the nucleophilicity of the amine. This could lead to displacing the crowded chiral amine

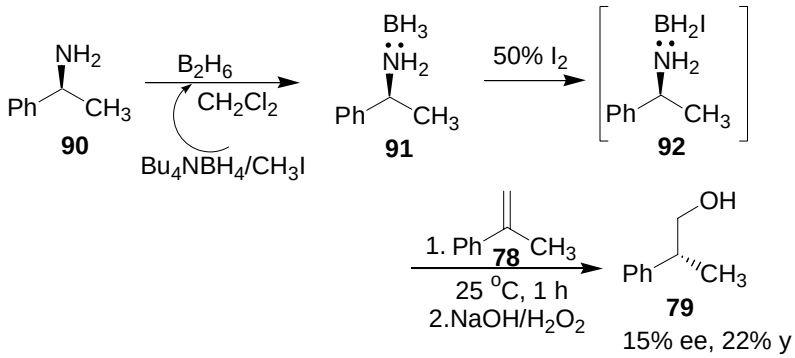
instead of the iodide (I^-) resulting in the S_N1 like mechanism or S_N2 like mechanism with π-complex intermediate leading to racemic product. We have also examined the (*2S,5S*)-*trans*-2,5-diphenylthiolane as a chiral source for carrying the borane. Accordingly, the (*2S,5S*)-*trans*-2,5-diphenylthiolane-BH_3 complex **108B** in toluene was prepared by bubbling the diborane into the solution of *trans*-2,5-diphenylthiolane in toluene. However, the hydroboration of α-methylstyrene with **108B** at 25 ^oC gave the racemic product after alkaline oxidation (Scheme 28).

Scheme 28



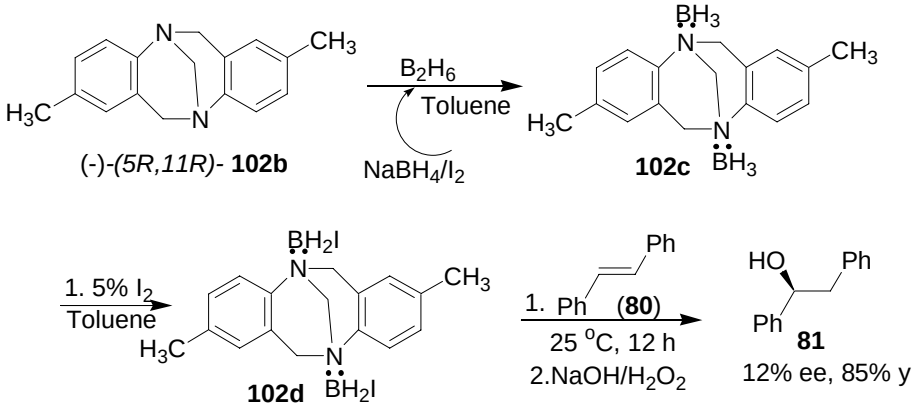
Clearly, even here the chiral diphenyl thiolane seems to leave the borane moiety before the hydroboration takes place (Scheme 18). Recently, it was observed in this laboratory that optically pure α-methylbenzylamine-BH_3, hydroborates the prochiral olefins to the corresponding alcohols upon activation using 50 mol% iodine with up to 15% ee (Scheme 29).[21a]

Scheme 29



Also, hydroboration of *trans*-stilbene using the relatively less hindered chiral Trogers base:BH_3 with catalytic amount of iodine (5 mol%) gave the corresponding alcohol **81** with enantioselectivity up to 12% ee (Scheme 30).[21b]

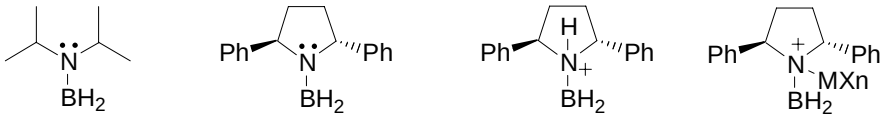
Scheme 30



Recently, it has been reported that the diisopropylborane derivative **93** does not hydroborate olefins under ambient conditions. Presumably, due to the mesomeric effect of the nitrogen lone pair.[22]

Systematic studies on preparation of the covalent borane derivative like **94** followed by activation by Bronsted acid **95** and Lewis acid **96** (Figure 2) may be helpful in achieving higher selectivities in the asymmetric hydroboration reaction using these chiral borane reagents.

Figure 2



93 **94** **95** **96**

3.3 Conclusion

We have demonstrated the general applicability and successful utilization of $Bu_4NBH_4/PhCH_2Cl$ as a borane source in the reduction of various carbonyl compounds such as aldehydes, ketones, carboxlic acids, acid chlorides and esters. The $Bu_4NBH_4/PhCH_2Cl$ reagent system is useful for the hydroboration reactions of olefins as well. The yields of the products obtained with $Bu_4NBH_4/PhCH_2Cl$ reagent system are as high as the literature reports using other borane reagents. The Bu_4NBH_4/I_2 reagent system is used effectively for the reduction of various carbonyl compounds, also, it was used for generating diborane *ex situ* to prepare stable Lewis base-BH_3 complexes in toluene.

We have carried out hydroboration reactions using chiral C_2-symmetric 2,5-diphenylpyrrolidine-BH_3, and 2,5-diphenylpyrrolidine-BH_2I complexes and 2,5-diphenylthiolane-BH_3 complex prepared *ex situ* using Bu_4NBH_4/I_2 with prochiral olefins under various conditions. Though, these studies are somewhat inconclusive, it is hoped that the results obtained here would help in developing more appropriate reagents for asymmetric hydroboration of olefins.

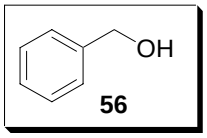
3.4 Experimental section

3.4.1 General information

Most of the information in the experimental section of chapter 1 are also applicable to the experiments described in this chapter. Aldehydes, ketones and olefins were obtained from commercial source were used without further purification.

3.4.2a Reduction of carbonyl compounds utilizing the $Bu_4NBH_4/PhCH_2Cl$ reagent system

The procedure for the reduction of benzaldehyde is representative: To a solution of Bu_4NBH_4 (1.54 g, 6 mmol) in toluene (25 mL) was added benzyl chloride (0.84 mL, 7 mmol) at 25 ^oC. The substrate, benzaldehyde (0.5 mL, 5 mmol) was added slowly and the reaction mixture was stirred until the starting material had disappeared (15 minutes, TLC analysis). The reaction mixture was carefully quenched with 2N HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 25 ml). The combined organic extracts was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (98:2) as eluent to obtain the benzylalcohol **56**.



56

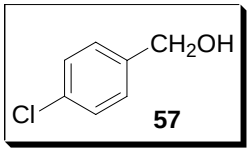
Yield 0.46 g (86%)

IR (neat) (cm^{-1}) 3331, 3030, 2932, 1606, 1018, 734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.41-7.28 (m, 5H), 4.70 (s, 2H), 1.95 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 140.8, 128.3, 127.3, 126.9, 64.7

3.4.2b Reduction of 4-chloro benzaldehyde with $Bu_4NBH_4/PhCH_2Cl$ reagent system



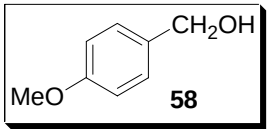
Yield 0.66 g (92%)

IR (KBr) (cm^{-1}) 3312, 2922, 1597, 1012, 644

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.36-7.26 (m, 4H), 4.67 (d, 6 Hz, 2H), 1.76 (t, 6 Hz, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 139.1, 133.2, 128.5, 128.2, 64.1

3.4.2c Reduction of 4-methoxybenzaldehyde with $Bu_4NBH_4/PhCH_2Cl$ reagent system



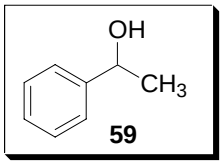
Yield 0.63 g (91%)

IR (neat) (cm^{-1}) 3387, 3003, 1612, 1033, 817

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.28 (d, 2 Hz, 2H), 6.89 (d, 2 Hz, 2H), 4.59 (d, 4.8 Hz, 2H), 3.79 (s, 3H), 1.87 (t, 4.8 Hz, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 159.0, 133.2, 128.5, 113.8, 64.5, 55.1

3.4.2d Reduction of Acetophenone with $Bu_4NBH_4/PhCH_2Cl$ reagent system



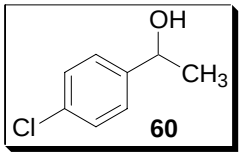
Yield 0.56 g (91%)

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

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

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 145.8, 128.3, 127.2, 125.3, 70.0, 25.0

3.4.2e Reduction of 4-chloroacetophenone with $Bu_4NBH_4/PhCH_2Cl$ reagent system



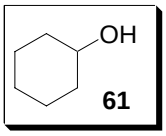
Yield 0.73 g (94%)

IR (neat) (cm^{-1}) 3328, 3031, 1608, 754

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.22-7.16 (m, 4H), 4.76 (q, 6.3 Hz, 1H), 2.27 (br, 1H), 1.36 (d, 6.3 Hz, 3H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 144.3, 133.0, 128.6, 126.8, 126.8, 69.7, 25.2

3.4.2f Reduction of Cyclohexanone with $Bu_4NBH_4/PhCH_2Cl$ reagent system



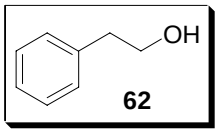
Yield 0.41 g (82%)

IR (neat) (cm^{-1}) 3342, 2932, 1068

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.65-3.59 (m, 1H), 1.91 (t, 5.2 Hz, 2H), 1.76-1.70 (m, 3H), 1.57 (t, 4 Hz, 1H), 1.31-1.16 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 70.1, 35.4, 25.5, 24.1

3.4.2g Reduction of Benzoyl chloride with $Bu_4NBH_4/PhCH_2Cl$ reagent system



Yield 0.55 g (90%)

IR (neat) (cm^{-1}) 3339, 3028, 2943, 1602, 1045, 746

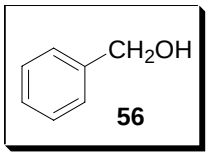
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.37-7.21 (m, 5H), 3.88(q, 6.4 Hz, 2H), 2.88 (t, 6.4 Hz 2H), 1.50-1.1.45 (m, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 138.5, 128.9, 128.3, 126.2, 63.3, 39.0

3.4.3 Reduction of benzoic acid with the $Bu_4NBH_4/PhCH_2Cl$ reagent system

To a solution of Bu_4NBH_4 (1.54 g, 6 mmol) in toluene (25 mL) was slowly added benzoic acid (0.61 g, 5 mmol) at 10 ^oC. The mixture was stirred until the evolution of gas ceases. Benzyl chloride (0.72 mL, 6 mmol) was added and the contents

were further stirred for 2 h at 25 ^{o}C. The mixture was carefully quenched with 2N HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined organic extracts was washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (98:2) as eluent to obtain the benzyl alcohol **56**.



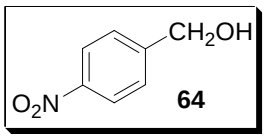
Yield 0.46 g (86%)

IR (neat) (cm^{-1}) 3331, 3030, 1606, 734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.41-7.28 (m, 5H), 4.70 (s, 2H), 1.95 (s, 1H)

3.4.4 Reduction of carbonyl compounds utilizing the Bu_4NBH_4/I_2 reagent system

The procedure for the reduction of 4-nitrobenzaldehyde is representative. To a solution of Bu_4NBH_4 (1.54 g, 6 mmol) in toluene (15 mL) and THF (5 mL) in a two-neck RB flask was added iodine (I_2) (0.76 g, 3 mmol) dissolved in toluene (10 mL) over 10 min at 0 ^{o}C. The substrate, 4-nitrobenzaldehyde (0.75 g, 5 mmol) was added and the reaction mixture was warmed to 25 ^{o}C and stirred until the starting material had disappeared (15 minutes, TLC analysis). The mixture was carefully quenched with 2N HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined organic extracts was washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (96:4) as eluent to obtain the 4-nitro benzyl alcohol **64**.



Yield 0.68 g (89%)

IR (KBr) (cm^{-1}) 3306, 2952, 1601, 754

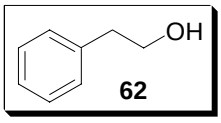
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 8.19(d, 8.4 Hz, 2H), 7.53 (d, 8.4 Hz, 2H), 4.83(d, 5.2 Hz, 2H), 2.53 (t, 5.2 Hz, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 148.3, 147.3, 127.0, 123.7, 63.9

3.4.5a Hydroboration-oxidation of olefins with the $Bu_4NBH_4/PhCH_2Cl$ reagent system

The procedure for the hydroboration-oxidation of styrene is representative. To a solution of Bu_4NBH_4 (2.31 g, 9 mmol) in toluene (20 mL) and THF (5 mL) was added benzyl chloride (1.1 mL, 9 mmol) and the mixture stirred for 5 min at 25 ^{o}C. Styrene (0.9 mL, 7.5 mmol) was added and the reaction mixture was further stirred for 4 h at room temperature. The excess hydride was carefully destroyed by the dropwise addition of H_2O (2 mL) while cooling the reaction flask with ice-cold H_2O. The oxidation was carried out by the addition of 3N NaOH (5 mL) followed by dropwise addition of H_2O_2 (5 mL, 30%). The contents were further stirred at room temperature for 4 h. The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (97:3) as eluent to obtain **62** and **59**.

Yield 0.78 g (86%)



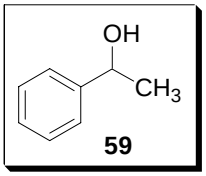
62

IR (neat) (cm^{-1}) 3339, 3028, 2943, 1602, 1045, 746

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.37-7.21 (m, 5H), 3.88(q, 6.4 Hz, 2H), 2.88 (t, 6.4 Hz 2H), 1.50-1.1.45 (m, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 138.5, 128.9, 128.3, 126.2, 63.3, 39.0

1-phenylethanol

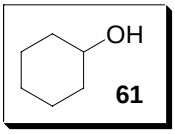


Yield 0.06 g (7%)

IR (neat) (cm^{-1}) 3351, 3029, 2974, 1601, 1078, 748

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

3.4.5b Hydroboration-oxidation of cyclohexene with the $Bu_4NBH_4/PhCH_2Cl$ reagent system



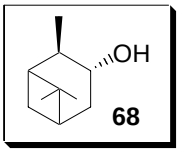
Yield 0.62 g (82%)

IR (neat) (cm^{-1}) 3342, 2932, 1068

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.65-3.59 (m, 1H), 1.91 (t, 5.2 Hz, 2H), 1.76-1.70 (m, 3H), 1.57 (t, 4 Hz, 1H), 1.31-1.16 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 70.1, 35.4, 25.5, 24.1

3.4.5c Hydroboration-oxidation of α-pinene with the $Bu_4NBH_4/PhCH_2Cl$ reagent system



Yield 0.92 g (80%)

IR (KBr) (cm^{-1}) 3327, 2905, 1043

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.35 (br, 1H), 1.94-1.50 (m, 8H), 1.22 (s, 3H), 1.14-1.02 (m, 3H), 0.92 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 71.4, 47.8, 47.5, 41.7, 38.9, 38.1, 34.2, 27.6, 23.6, 20.7

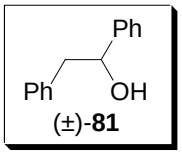
3.4.6 Preparation (*ex situ*) of chiral amine-BH_3 and thiolane-BH_3 complexes

The procedure is representative: The *trans* (*2S,5S*)-*N*-benzyl-2,5-diphenyl-pyrrolidine-BH_3 complex **105B** (2 mmol) was prepared *in situ* by bubbling diborane gas [generated by dropwise addition of I_2 (0.77 g, 3 mmol) in toluene (10 mL) to Bu_4NBH_4 (1.54 g, 6 mmol) in toluene (5 mL) at 25 ^oC] into the solution of (*2S,5S*)-*N*-benzyl-2,5-diphenyl-pyrrolidine (0.63 g, 2 mmol) in dry toluene (5 mL) for 15 min. at 0 ^oC.

3.4.7 Hydroboration reaction using chiral amine-BH_3 and thiolane-BH_3 complex

3.4.7a Hydroboration of *trans*-stilbene using (*2S,5S*)-*N*-benzyl-2,5-diphenyl-pyrrolidine-BH_3 105B complex

To the amine-BH_3 complex **105B** (2 mmol) prepared (*ex situ*) in toluene was added *trans*-stilbene (0.36 g, 2 mmol) in toluene (3 mL) at 0 ^oC and the reaction warmed to 25 ^oC, stirred further for 8 h. The reaction was quenched with methanol (2 mL), cooled with ice water, 5N NaOH (3 mL) was added followed by H_2O_2 (5 mL) 30% solution. The stirring continued for 2h at room temperature. The organic layer was separated, and the aqueous layer was extracted with ether (2x10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane:EtOAc (95:5) as eluent to obtain **81**.



(±)-**81**

Yield 0.32 g (80%)

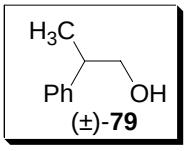
IR (KBr) (cm^{-1}) 3380, 3061, 2962, 1601, 748, 700

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.03 (br, 1H), 2.97-3.08 (m, 2H), 4.90 (t, 1H), 7.20-7.56 (m, 10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 46.1, 75.3, 126.0, 126.6, 127.6, 128.2, 128.4, 128.5, 129.4, 129.6, 138.2, 143.9

3.4.7b Hydroboration of α-methylstyrene using (*2S,5S*)-*N*-benzyl-2,5-diphenyl-pyrrolidine-BH_3 105B complex

To the amine-BH_3 complex **105B** (2 mmol) prepared (*ex situ*) in anhydrous toluene was added α-methyl styrene (0.24 g, 2 mmol) at 0 ^oC and the reaction warmed to 25 ^oC, stirred further for 4 h. The reaction quenched with methanol (2 mL), cooled with ice water, 5N NaOH (3 mL) was added followed by H_2O_2 (5 mL) 30% solution. The stirring continued for 2h at room temperature. The organic layer was separated, and the aqueous layer was extracted with ether (2x10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was column purified on a silica gel (100-200 mesh) using hexane:EtOAc (98:2) as eluent to obtain **79**.



(±)-**79**

Yield 0.32 g (80%)

IR (neat) (cm^{-1}) 3379, 3061, 3028, 2962, 2879, 1602, 760

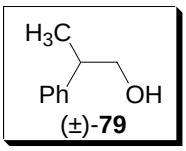
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.28 (d, 3H), 1.83 (S, 1H), 2.92-2.98 (m, 1H), 3.67 (d, 2H), 7.24-7.36 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 17.6, 42.4, 68.6, 126.6, 127.5, 128.6, 143.8

3.4.7c Hydroboration of α-methylstyrene using (*2S,5S*)-*N*-benzyl-2,5-diphenyl-pyrrolidine-BH_2I (110) complex

The procedure is representative: To the amine-BH_3 complex **105B** (2 mmol) prepared (*ex situ*) was added I_2 (0.254 g, 1 mmol) via solid addition funnel at 0 ^oC and the reaction warmed to 25 ^oC, stirred until it became colourless (1 h). To this amine-

BH_2I complex **110** was added α-methylstyrene (0.24 g, 2 mmol) at 25 ^oC and stirred for 6 h. The reaction quenched with methanol (2 mL), cooled with ice water, 5N NaOH (3 mL) was added followed by H_2O_2 (5 mL) 30% solution. The stirring continued for 2h at 25 ^oC. The organic layer was separated, and the aqueous layer was extracted with ether (2x10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was column purified on a silica gel (100-200 mesh) using hexane:EtOAc (98:2) as eluent to obtain **79**.



(±)-**79**

Yield 0.32 g (80%)

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.28 (d, 3H), 1.83 (S, 1H), 2.92-2.98 (m, 1H), 3.67 (d, 2H), 7.24-7.36 (m, 5H)

3.4.7d Preparation of $Ph_3P:BH_3$ from amine borane complex 105B

The *trans*-(*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine-BH_3 complex **105B** (2 mmol) was prepared *in situ* by bubbling diborane gas [generated by dropwise addition of I_2 (0.77 g, 3 mmol) in toluene (10 mL) to Bu_4NBH_4 (1.54 g, 6 mmol) in toluene (5 mL) at 25 ^oC] into the solution of (*2S,5S*)-*N*-benzyl-2,5-diphenylpyrrolidine (0.63 g, 2 mmol) in dry toluene (5 mL) for 15 min. at 0 ^oC. To this solution triphenyl phosphine (0.53 g, 2 mmol) was added and stirred for 6 h at 25 ^oC. The solvent was removed under vaccum and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexane as eluent to obtain **45** ($Ph_3P:BH_3$).

Yield 0.54 g (97%)

IR (KBr) (cm^{-1}) 3055, 2961, 2378, 2337, 2253

^{11}B NMR -37.6 ppm

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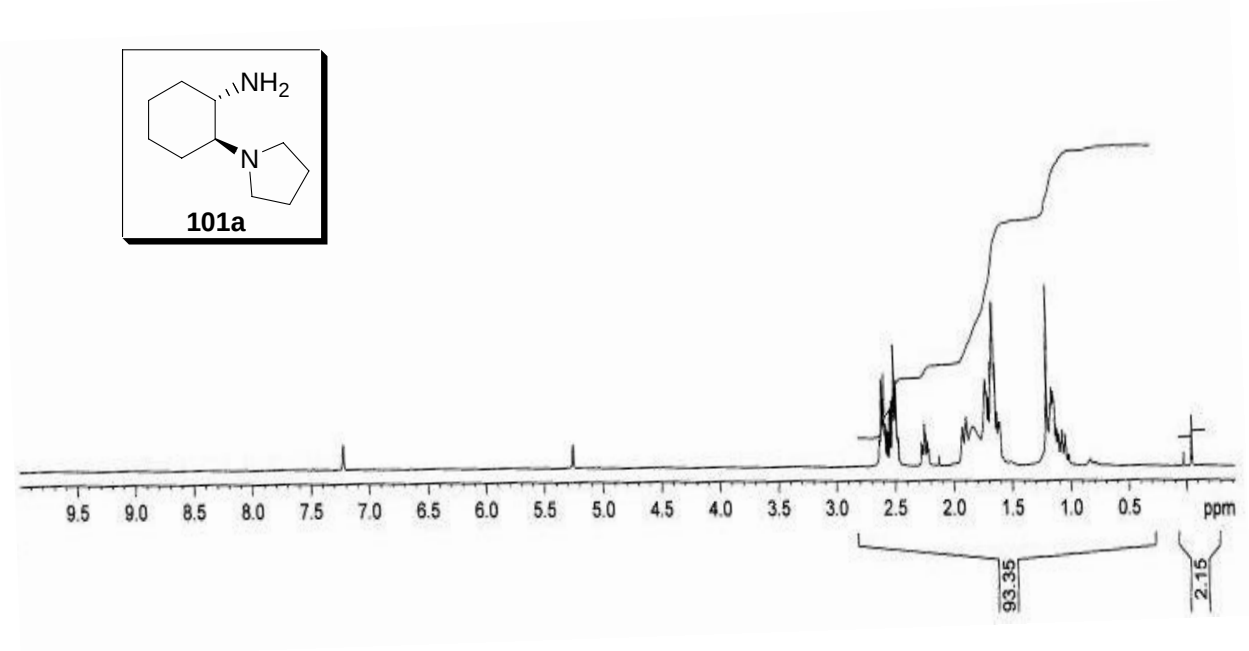
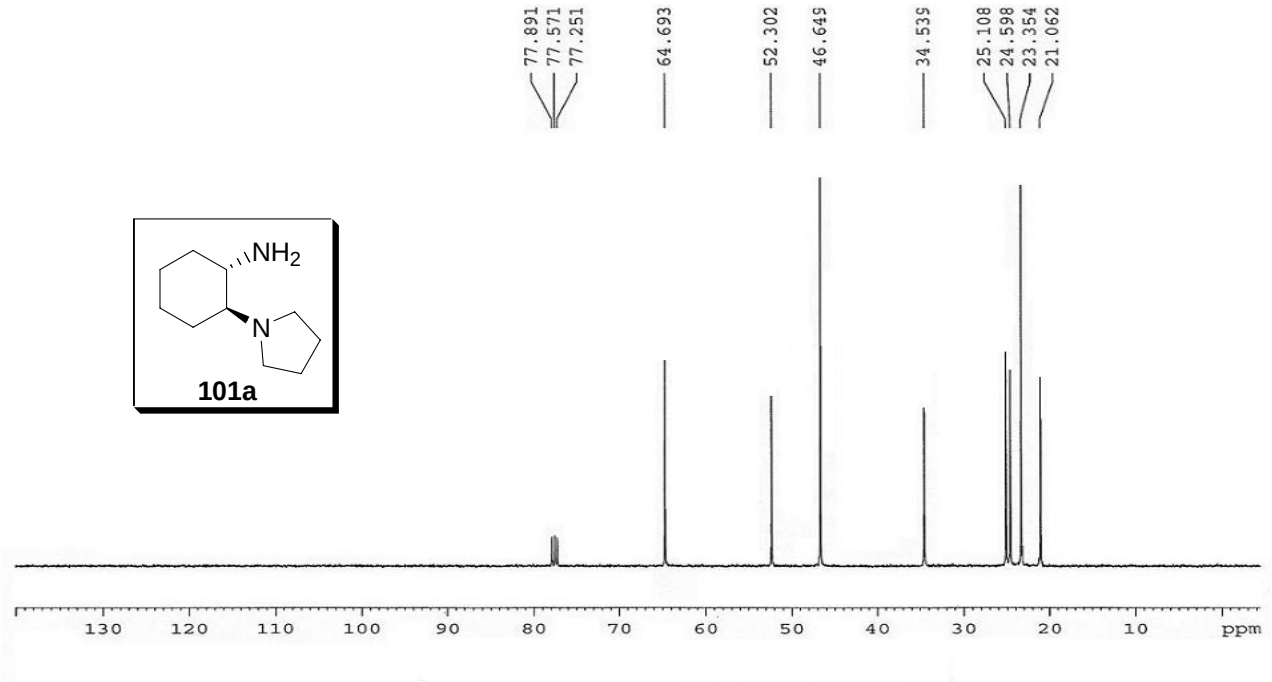
21 (a) Anwar, S., Periasamy, M. Unpublished results. (b) Satishkumar, S. Periasamy, M. Unpublished results

22 Paumansky, L.; Haddenham, D.; Clary, J. W.; Fisher, G. B.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2008**, *73*, 1898-1905.

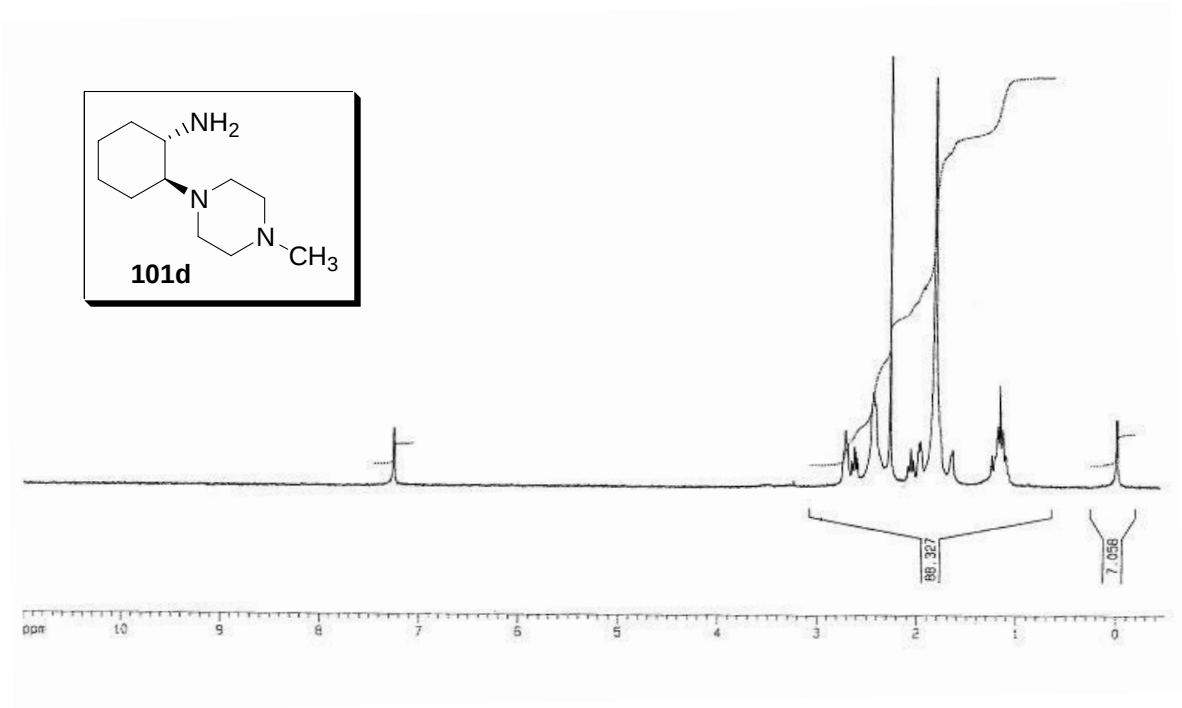
Spectrum No 1 (Chapter 1, Section 1.4.3a) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



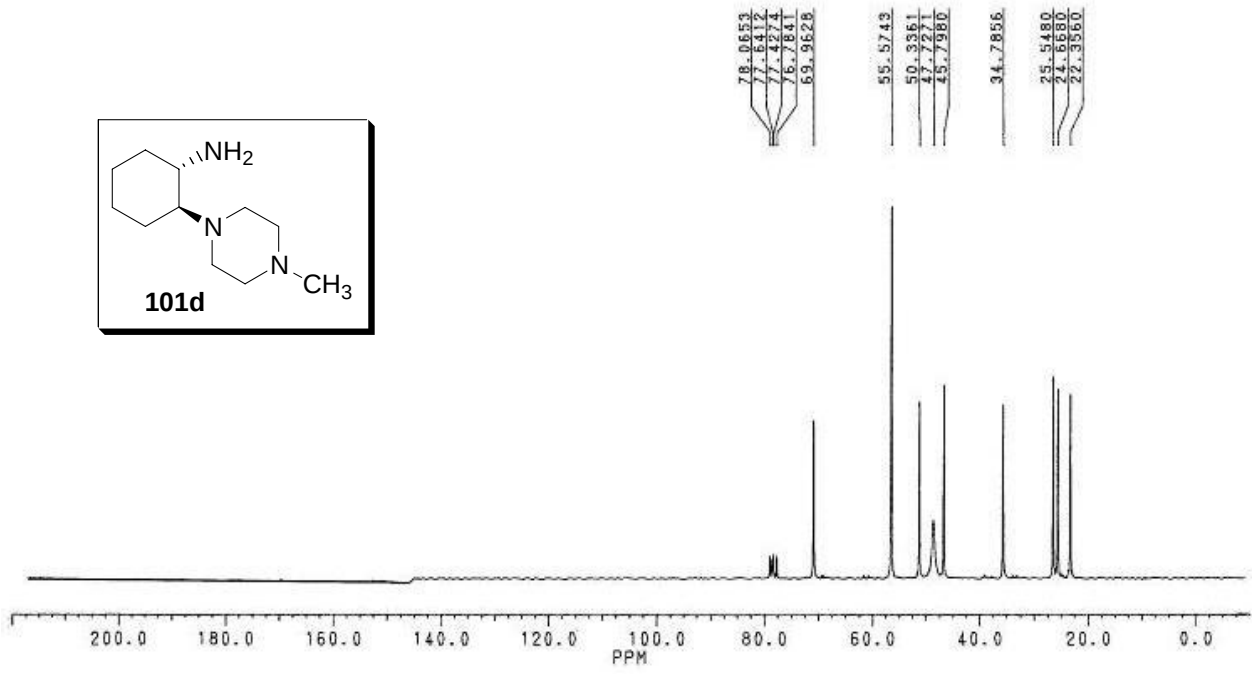
Spectrum No 2 (Chapter 1, Section 1.4.3a) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



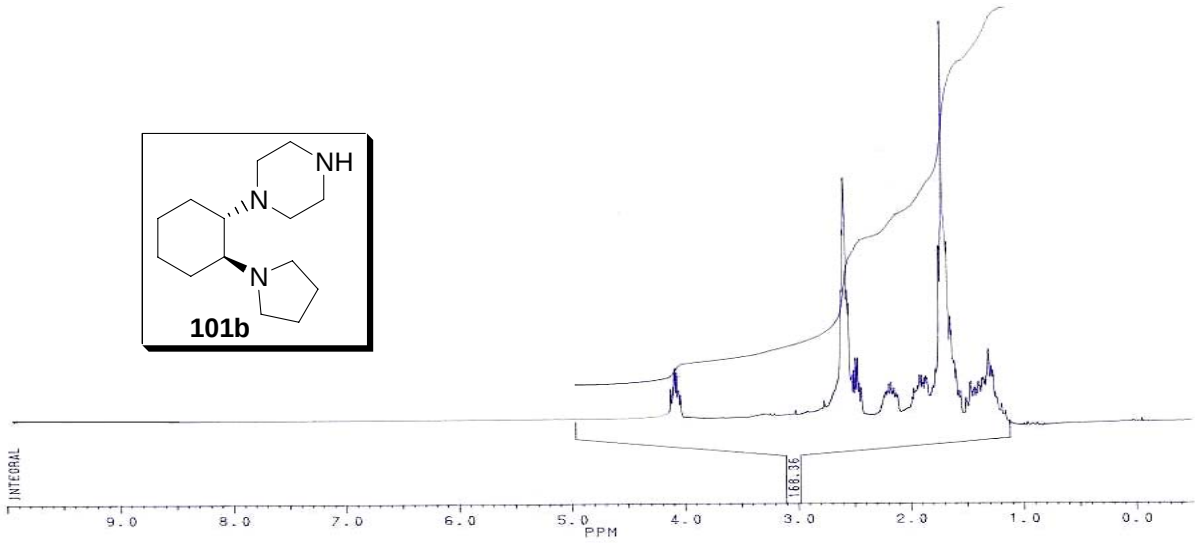
Spectrum No 3 (Chapter 1, Section 1.4.3d) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



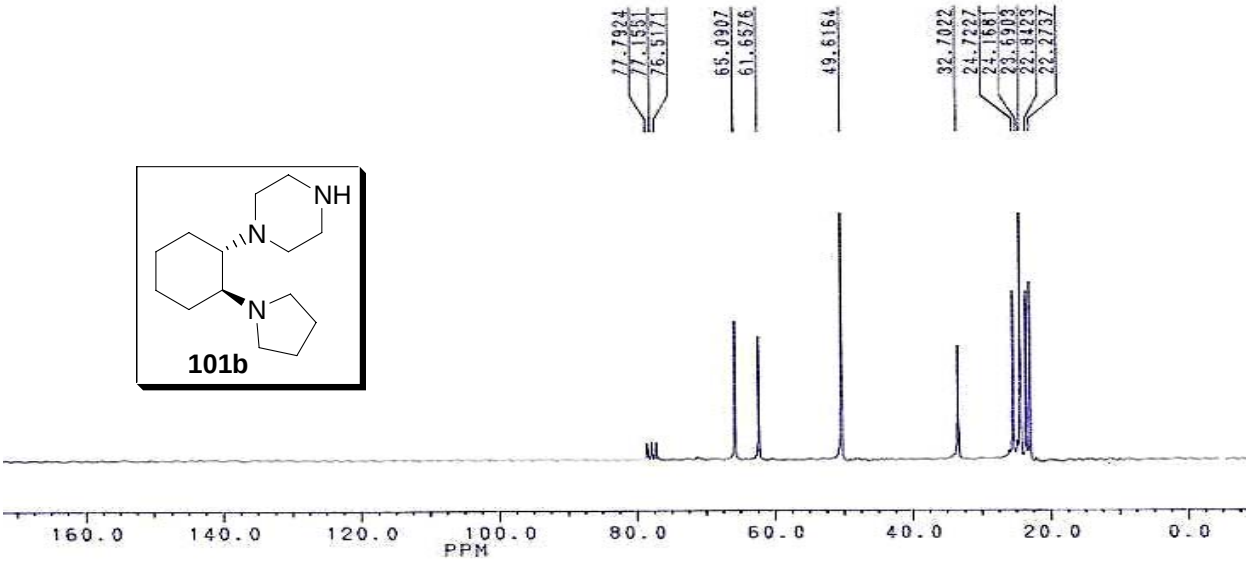
Spectrum No 4 (Chapter 1, Section 1.4.3d) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



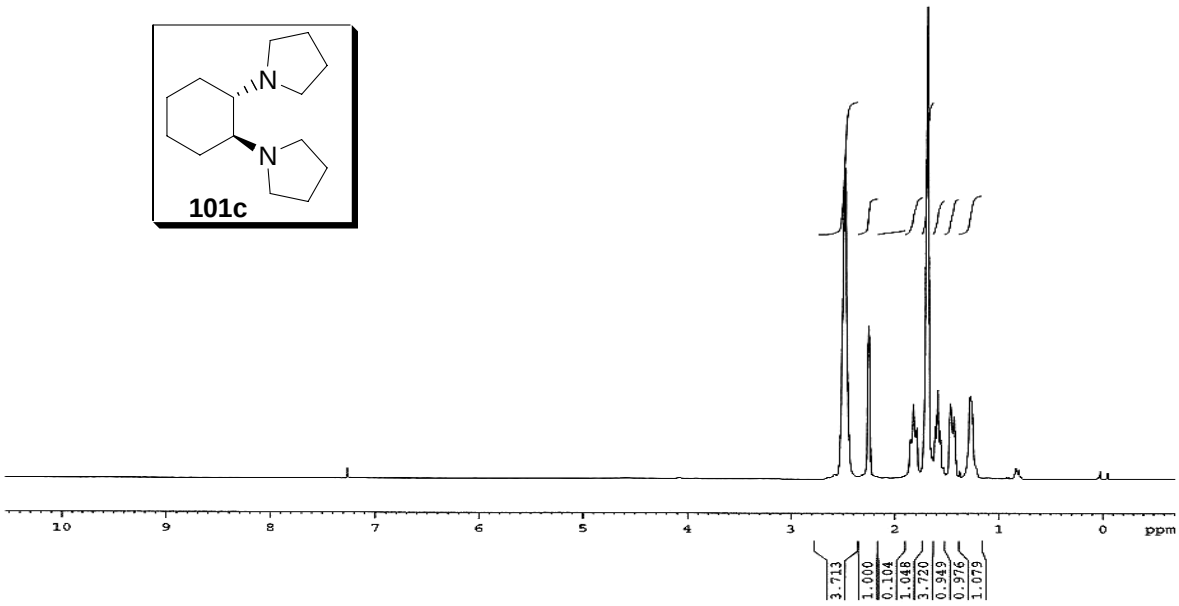
Spectrum No 5 (Chapter 1, Section 1.4.3b) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



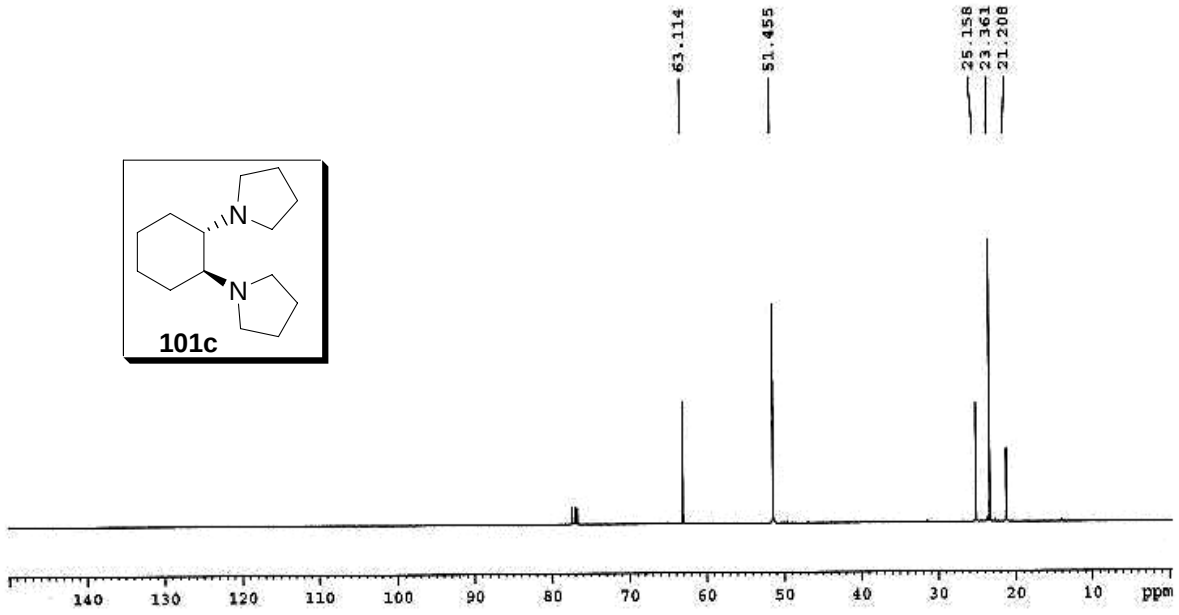
Spectrum No 6 (Chapter 1, Section 1.4.3a) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



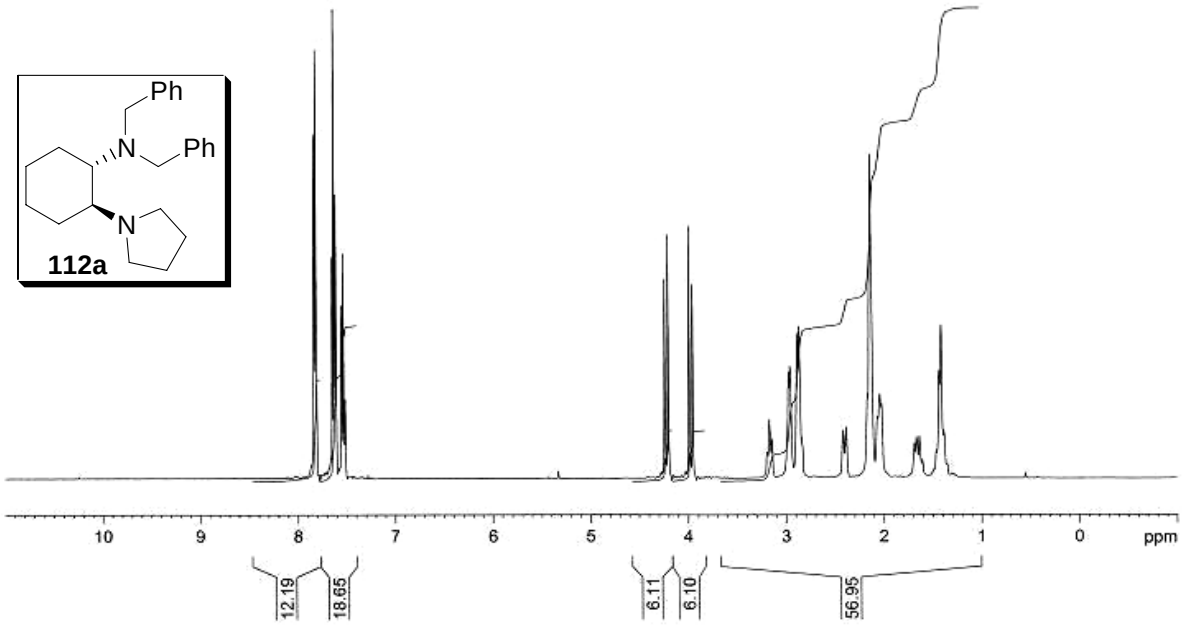
Spectrum No 7 (Chapter 1, Section 1.4.3c) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



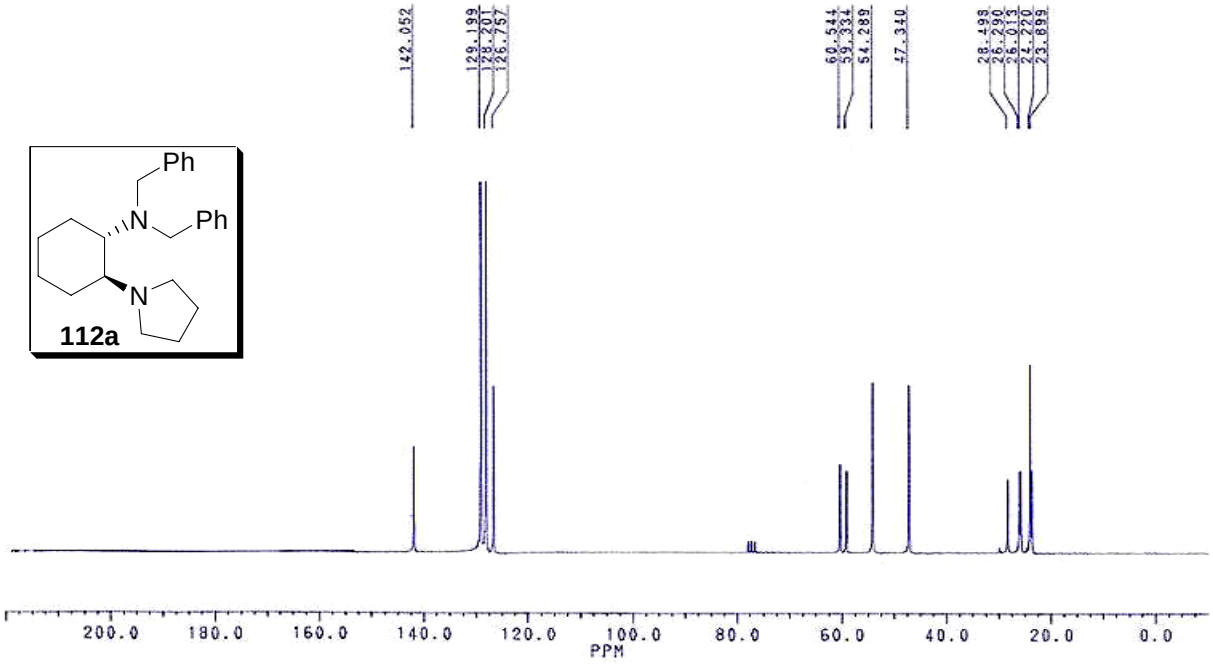
Spectrum No 8 (Chapter 1, Section 1.4.3c) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



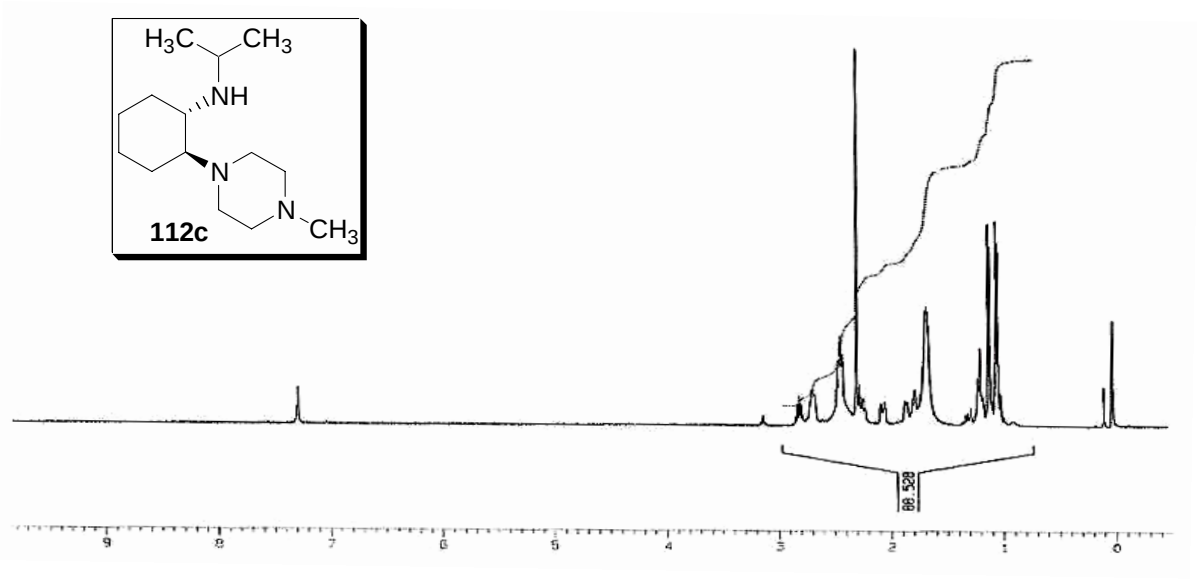
Spectrum No 9 (Chapter 1, Section 1.4.3f) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



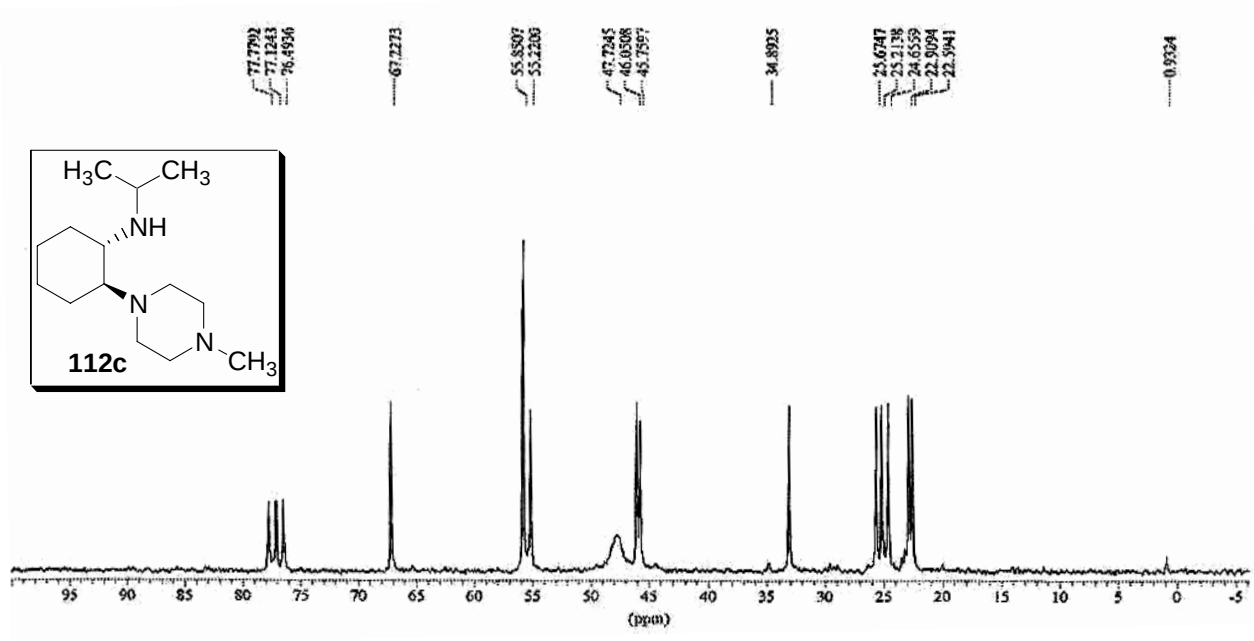
Spectrum No 10 (Chapter 1, Section 1.4.3f) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



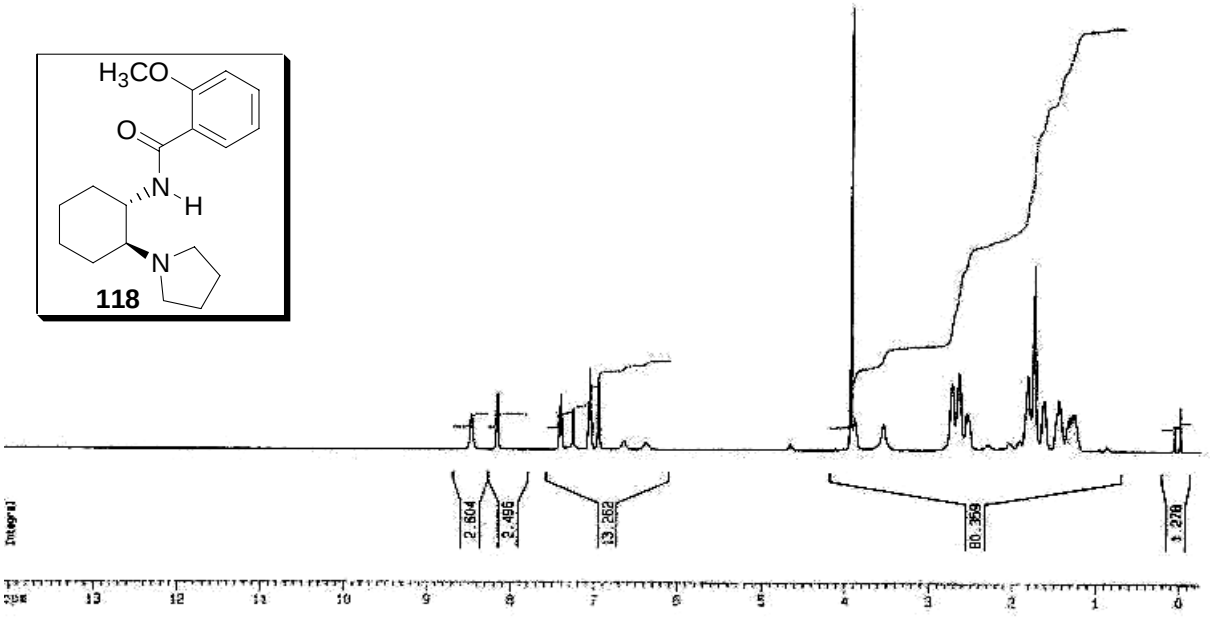
Spectrum No 11 (Chapter 1, Section 1.4.3h) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



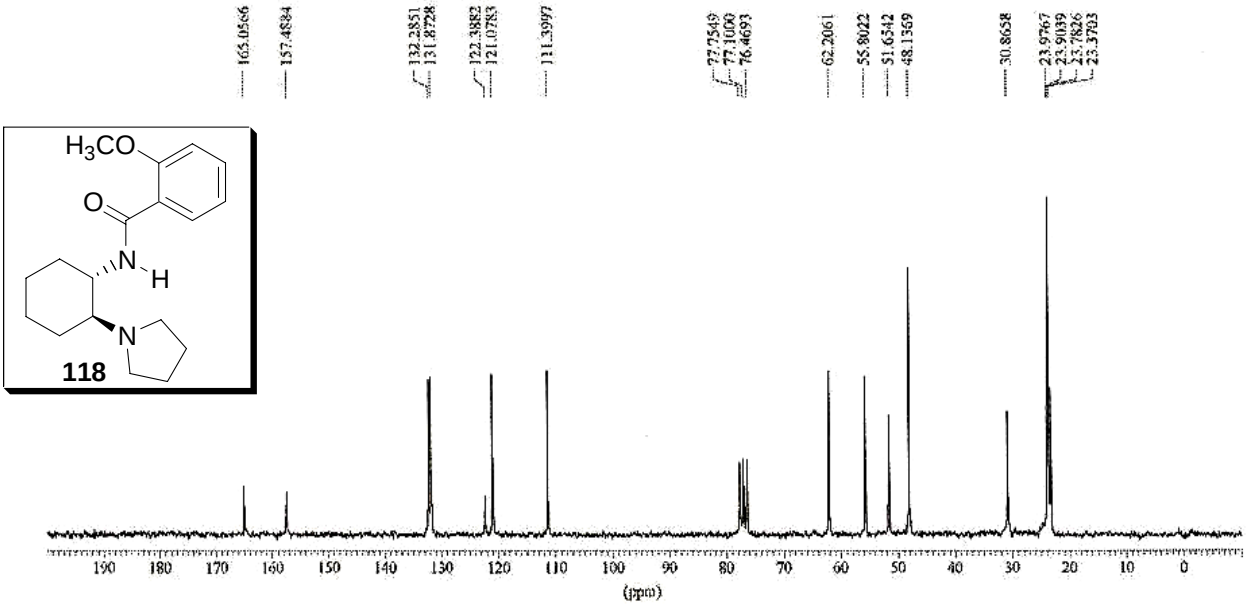
Spectrum No 12 (Chapter 1, Section 1.4.3h) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



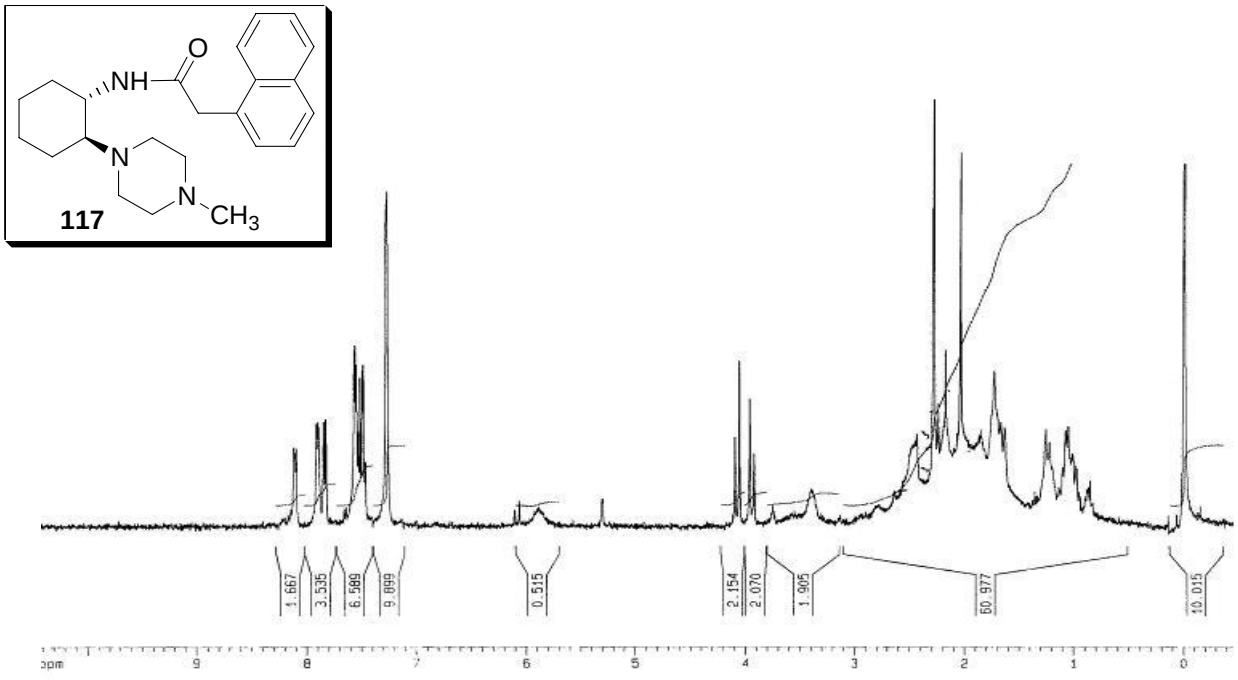
Spectrum No 13 (Chapter 1, Section 1.4.7a) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



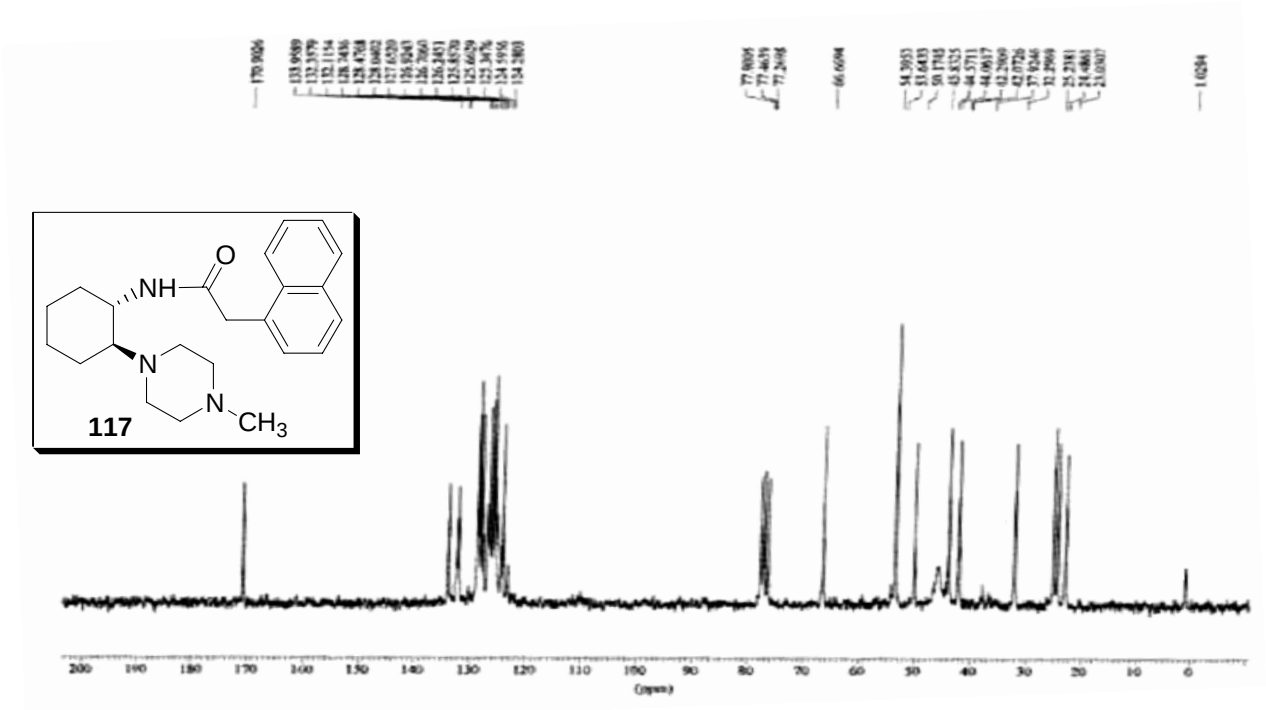
Spectrum No 14 (Chapter 1, Section 1.4.7a) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



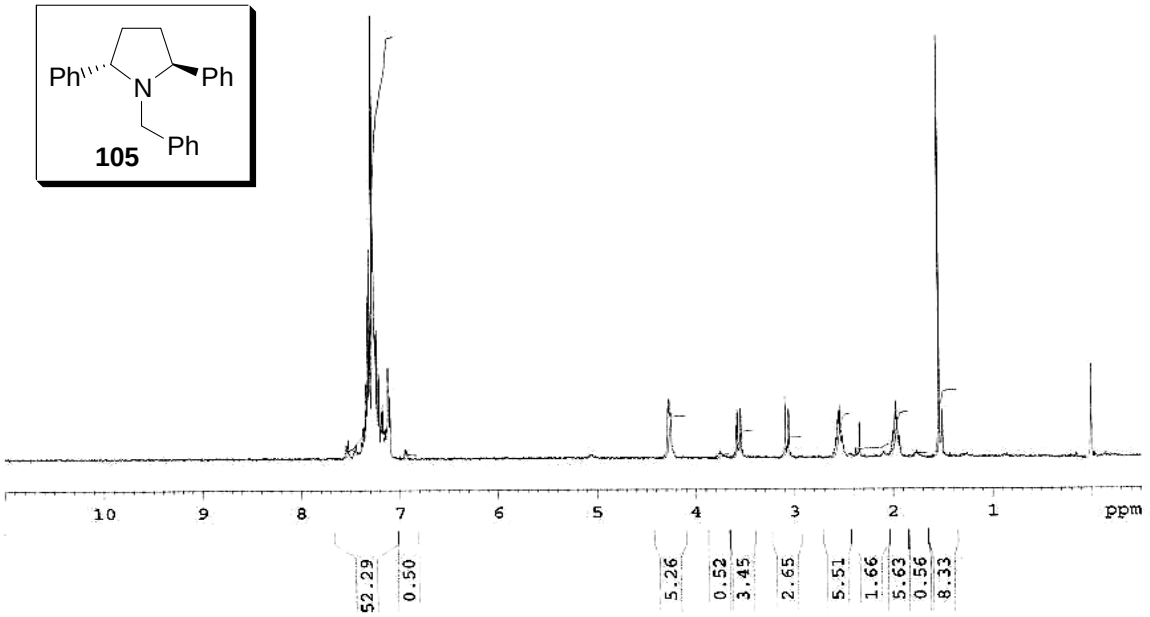
Spectrum No 15 (Chapter 1, Section 1.4.7b) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



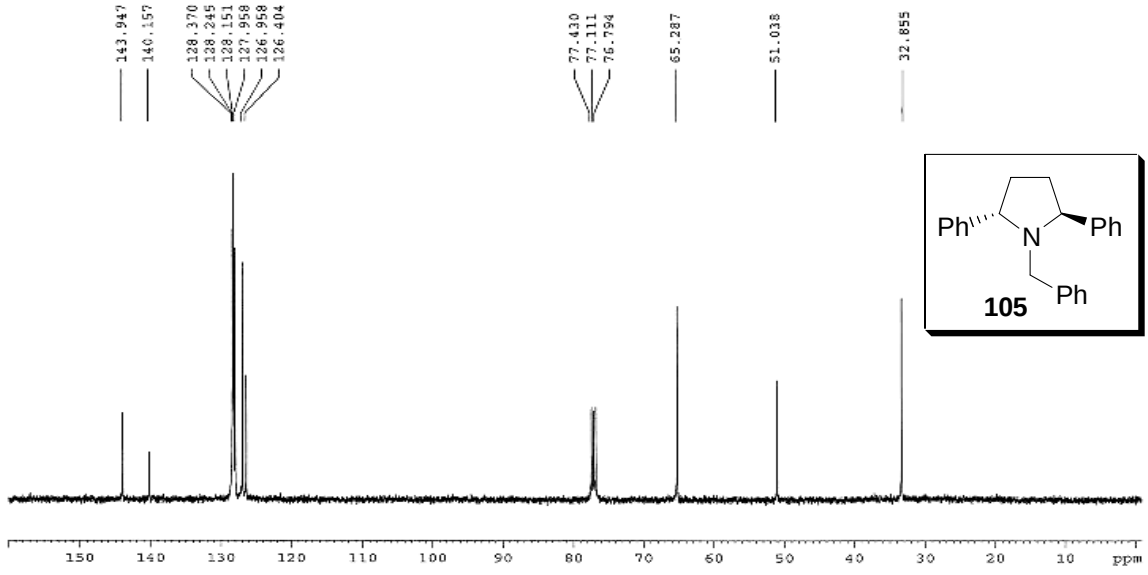
Spectrum No 16 (Chapter 1, Section 1.4.7b) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



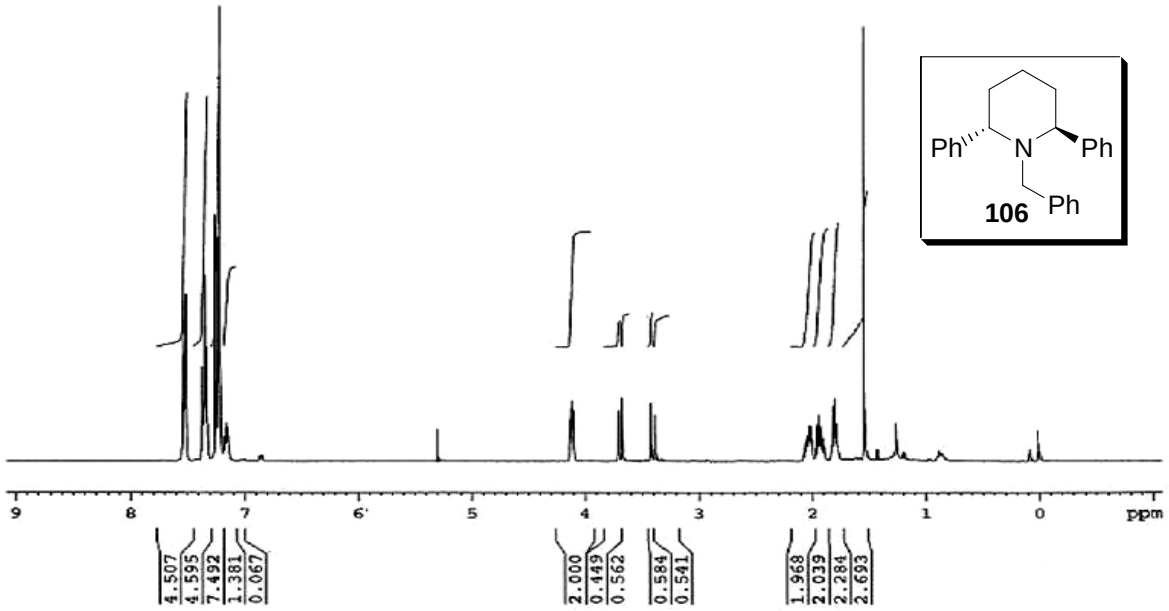
Spectrum No 17 (Chapter 2, Section 2.4.7a) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



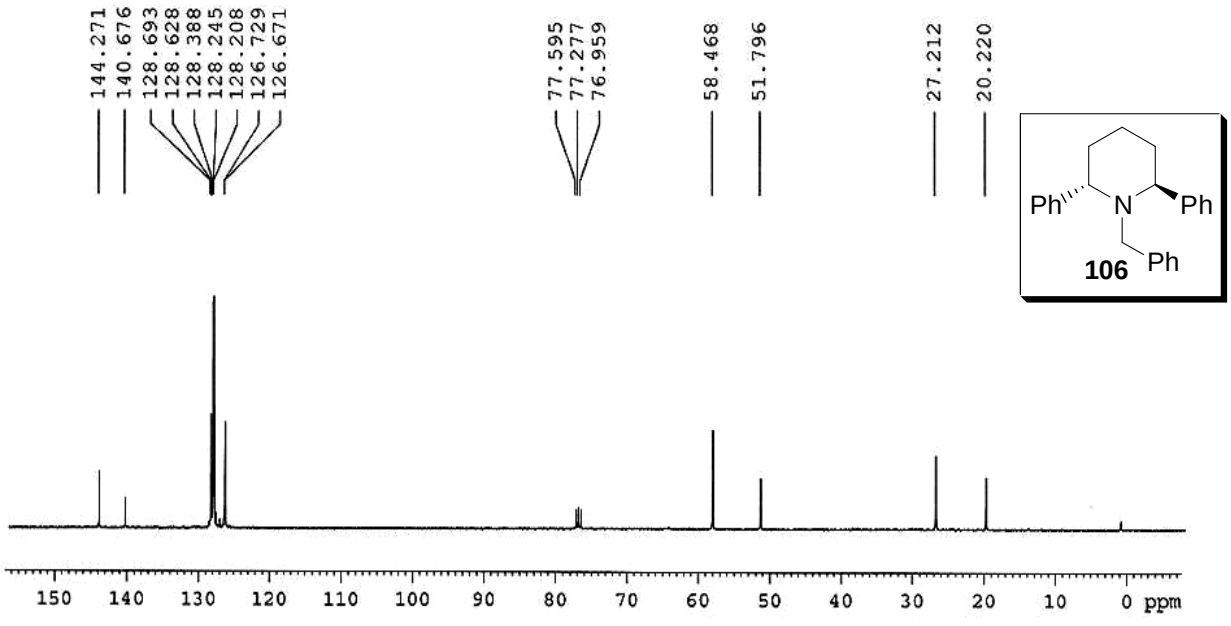
Spectrum No 18 (Chapter 2, Section 2.4.7a) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



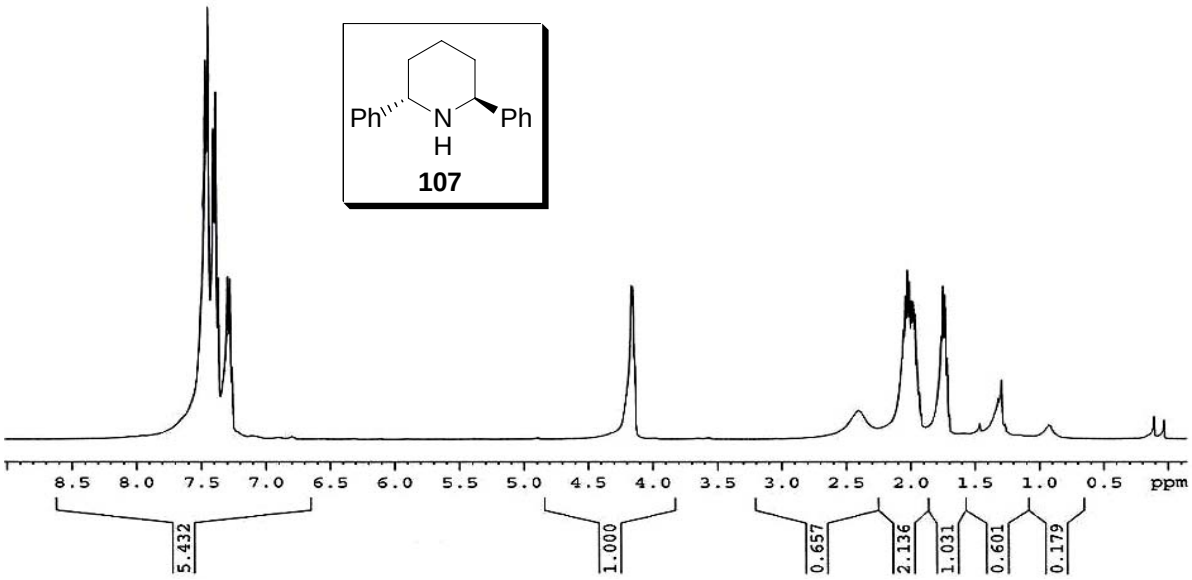
Spectrum No 19 (Chapter 2, Section 2.4.7b) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



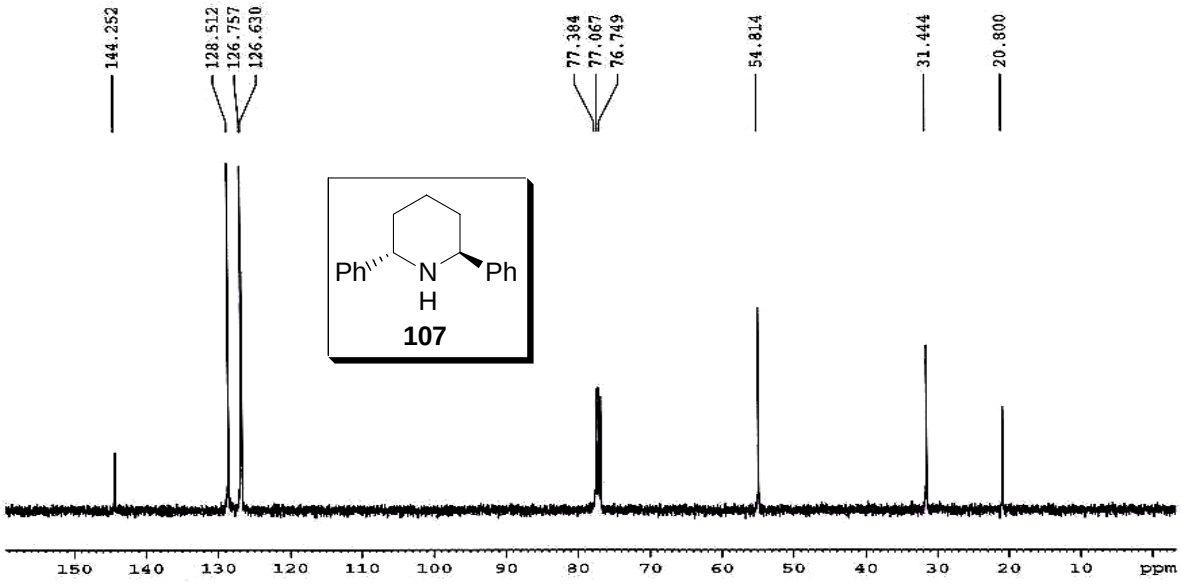
Spectrum No 20 (Chapter 2, Section 2.4.7b) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



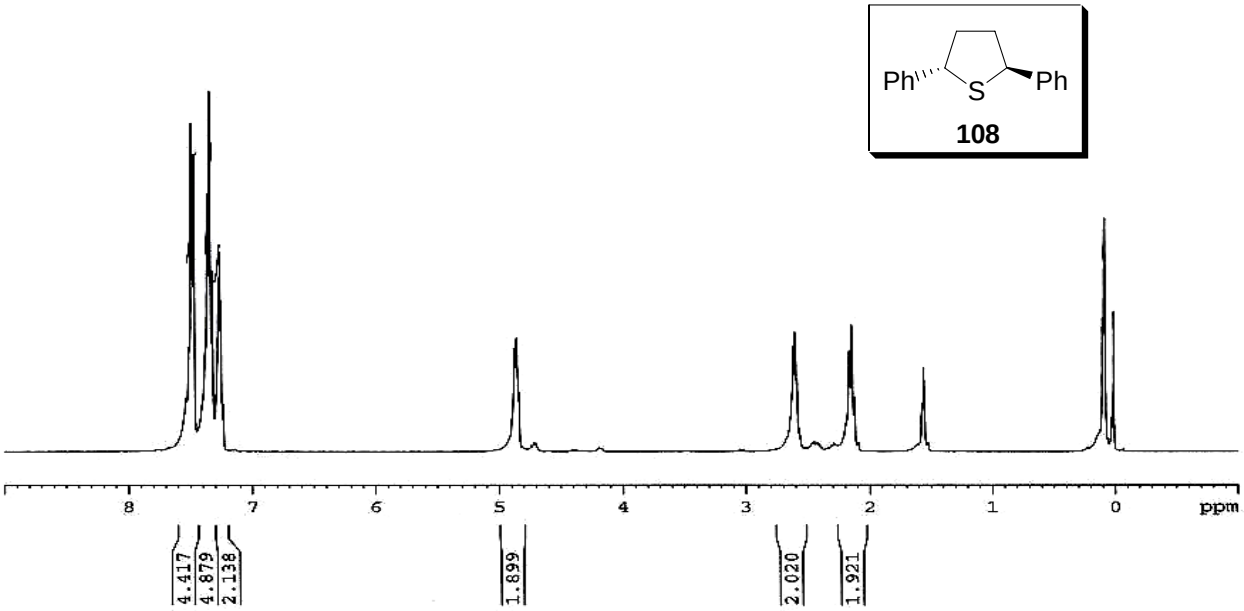
Spectrum No 21 (Chapter 2, Section 2.4.7c) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



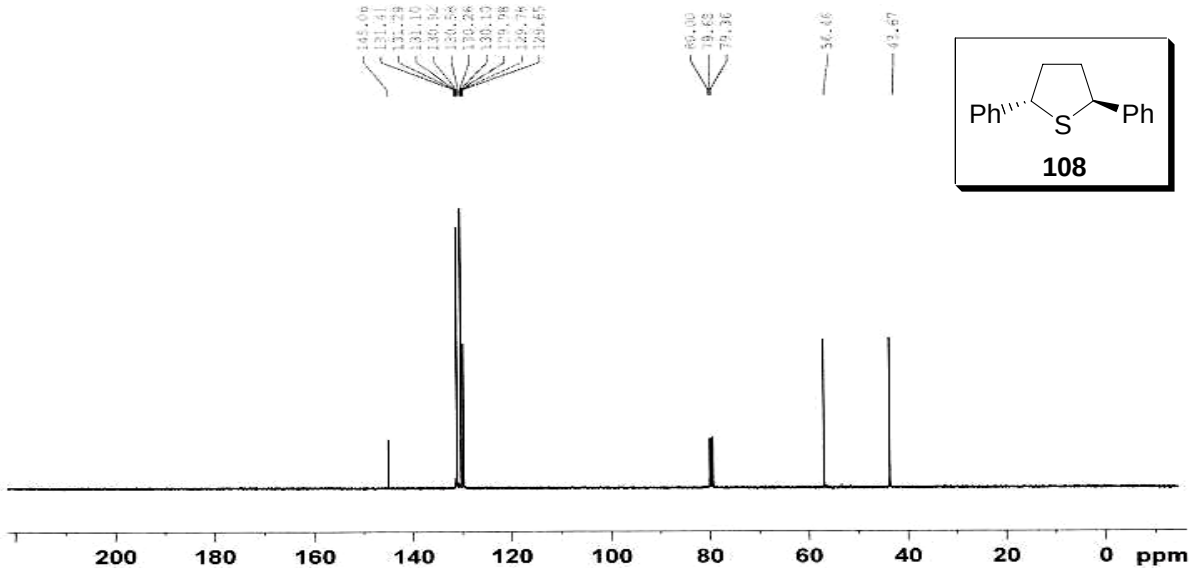
Spectrum No 22 (Chapter 2, Section 2.4.7c) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



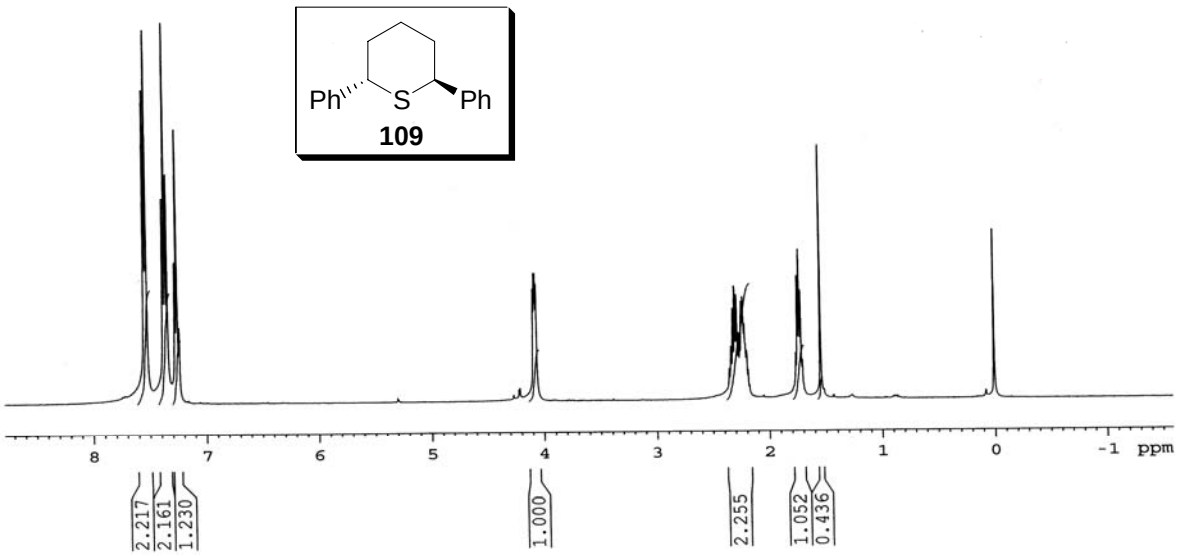
Spectrum No 23 (Chapter 2, Section 2.4.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



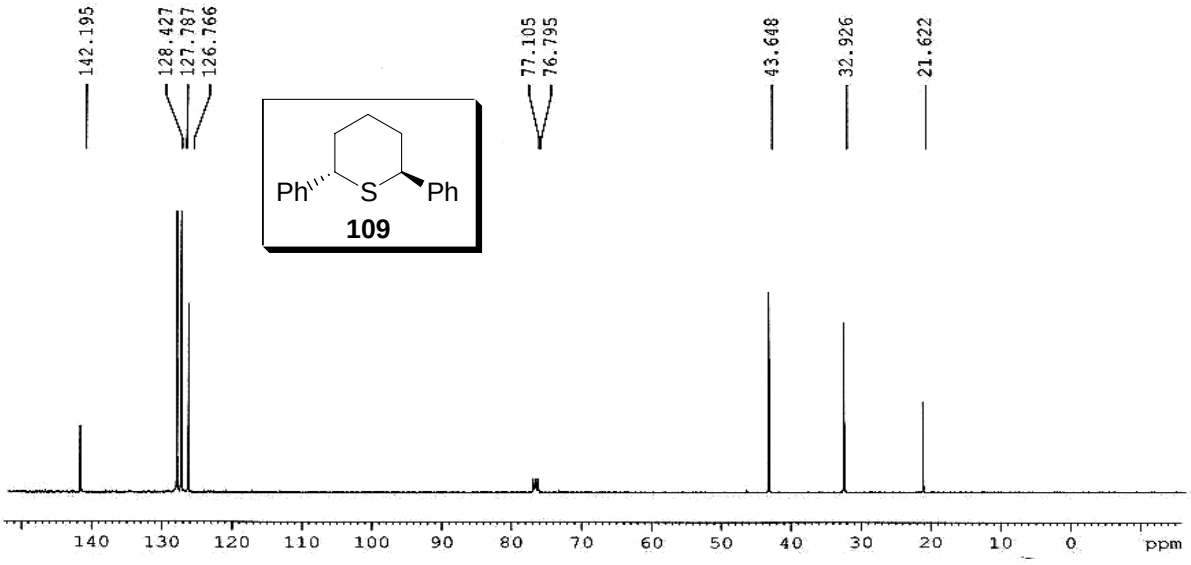
Spectrum No 24 (Chapter 2, Section 2.4.8) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No 25 (Chapter 2, Section 2.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No 26 (Chapter 3, Section 2.4.9) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II Crystal data and structure refinement for compound **108**

Identification code	**108**
Empirical formula	C16 H16 S
Formula weight	240.36
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P2(1)
Unit cell dimensions	a = 13.484(4) Å, α = 90 b = 5.7240 Å, β = 99.658 c = 17.464 (5) Å, γ =90
Volume	1328.8 (6) $Å^3$
Z, Calculated density	29, 1.634 Mg M^{-3}
Absorption coefficient	1.187 mm^{-1}
F(000)	667
Crystal size	0.24 x 0.06 x 0.05 mm
Theta range for data collection	1.18 to 24.96 °
Limiting indices	-16≤h≤15, -6≤k≤6, -20≤l≤20
Reflections collected / unique	12767 / 4627 [R(int) = 0.0889]
Completeness 2θ = 24.96	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4627 / 1 / 307
Goodness-of-fit on F^2	0.968
Final R indices [I>2σ (I)]	R1 = 0.0659, wR2 = 0.0990
R indices (all data)	R1 = 0.1553, wR2 = 0.1236
Largest diff. peak and hole	0.195 and -0.124 e. $Å^{-3}$

Appendix III

X-ray crystallographic data of compound (*2S,5S*)-*trans*-2,5-diphenylthiolane **108**

	x	y	z	U(eq)
C(1)	-12(4)	4289(9)	8636(3)	61(1)
C(2)	-1032(4)	4163(11)	8625(3)	74(2)
C(3)	-1543(4)	5941(13)	8916(3)	74(2)
C(4)	-1018(5)	7851(11)	9233(3)	77(2)
C(5)	8(4)	8017(9)	9251(3)	63(1)
C(6)	526(3)	6217(10)	8958(3)	57(1)
C(7)	1633(3)	6537(9)	8941(3)	65(1)
C(8)	1840(4)	7549(9)	8185(3)	74(2)
C(9)	2938(4)	7055(9)	8136(3)	83(2)
C(10)	3101(4)	4465(10)	8305(3)	73(2)
C(11)	4193(4)	3670(11)	8521(4)	75(2)
C(12)	4822(5)	4580(12)	9150(4)	97(2)
C(13)	5814(5)	3811(16)	9309(4)	111(2)
C(14)	6147(6)	2159(15)	8860(6)	121(3)
C(15)	5527(7)	1276(14)	8243(5)	121(3)
C(16)	4550(5)	2050(11)	8070(4)	90(2)
C(17)	5411(4)	6439(11)	6593(3)	74(2)
C(18)	4395(5)	6901(13)	6351(4)	94(2)
C(19)	4115(4)	8856(15)	5920(4)	96(2)
C(20)	4828(5)	10332(11)	5715(3)	89(2)
C(21)	5839(4)	9853(10)	5947(3)	75(2)
C(22)	6134(4)	7897(10)	6391(3)	58(1)
C(23)	7232(4)	7314(8)	6667(3)	60(1)
C(24)	7880(3)	9317(9)	7048(3)	68(1)
C(25)	8959(3)	8608(9)	7044(3)	60(1)
C(26)	9028(3)	7920(9)	6215(3)	59(1)
C(27)	9943(3)	6474(10)	6129(3)	55(1)
C(28)	10630(4)	7289(9)	5693(3)	65(2)
C(29)	11490(4)	6002(13)	5640(3)	81(2)
C(30)	11666(4)	3909(13)	6032(4)	87(2)
C(31)	10984(5)	3092(11)	6460(3)	82(2)
C(32)	10130(4)	4359(10)	6504(3)	67(2)
S(1)	2378(1)	3848(3)	9080(1)	78(1)
S(2)	7855(1)	6357(3)	5864(1)	79(1)

List of publications

1 A one-dimensional assembly of a square planar copper (II) complex with alternate short and long Cu…Cu distances. Metal ion spin-exchange with π-π interactions; Das, S, **Muthukumaragopal, G. P**, Pal, S. N, Pal, S. *New.J.Chem*. **2003**, *27*, 1102-1107.

2 A simple and convenient method for the preparation of diborane from tetrabutylammonium borohydride and benzyl chloride for application in organic synthesis; Periasamy, M, **Muthukumaragopal, G. P**, Sanjeevakumar, N. *Tetrahedron Lett.,* **2007**, *48*, 6966-6969.

3 Convenient methods for synthesis of C_2-symmetric diphenyltetrahydrothiophenes; Periasamy, M, Ramani, G, **Muthukumaragopal, G. P.** *Synthesis.* **2009**, 1739-1743.

4 Synthesis and Resolution of *trans*-(±)-1,2-diaminocyclohexane derivatives via opening of cyclohexene oxide and aziridinium ion intermediates; Periasamy, M.; **Muthukumaragopal, G. P**.; Seenivasaperumal, M. (to be communicated).