Synthesis and Applications of Chiral Aminonaphthols, Amino Alcohols and Amines

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY

By
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Dedicated to

My
Beloved Parents

Contents

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled “**Synthesis and Applications of Chiral Aminonaphthols, Amino Alcohols and Amines”** has been carried out by **Mr. Shaik Anwar** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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Shaik Anwar

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g. dm, are understood]
aq.	aqueous
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*ter*-butoxycarbonyl
bp	boiling point
br	broad (spectral)
Bu	butyl
t-Bu	*ter*-butyl
^{o}C	degree celsius
cat.	catalytic
cm^{-1}	wavenumber(s)
δ	chemical shift in parts per million downfield from tetramethyl silane
dr	diastereomeric ratio
DPP	α,α-diphenylpyrrolidinemethanol
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol
equiv.	equivalent
eqn.	equation
g	gram (s)
h	hour (s)
HPLC	high-performance liquid chromatography
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	Coupling constant (in NMR Spectrometry)

lit.	literature
m	multiplet (spectral)
Me	methyl
MHz	megahertz
mmol	millimolar
mp	melting point
n-	primary
Nu	nucleophile
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
rt	room temperature
THF	tetrahydrofuran
TMS-Cl	trimethylsilyl chloride
Bz	Benzoyl
Ac	Acetyl
TFA	trifluoroacetic acid
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
q	quartlet (in spectroscopy)
min.	minute(s)
NMR	nuclear magnetic resonance
M.S.	molecular sieves
BtH	1H-benzotriazole
$BtCH_2OH$	1-hydroxymethylbenztriazole
dppp	1,3-bis(diphenylphosphino)propane
TfOH	Triflic acid
))))))	Ultra sound

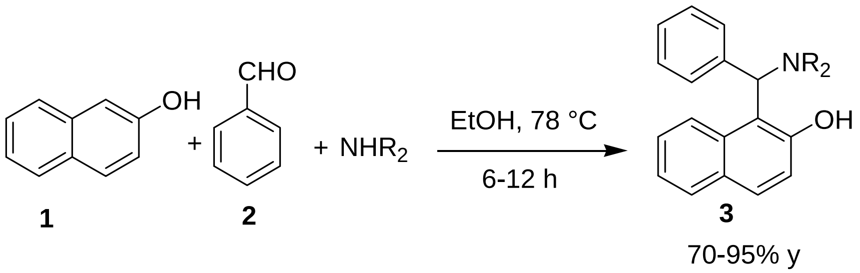
Abstract

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

The first chapter describes a brief review on the preparation as well as applications of chiral aminonaphthols, amino alcohols and amine derivatives in various organic transformations. The second chapter deals with the results and discussion on the synthesis of aminonaphthols, amino alcohols and amines for application in resolution, reductions, and hydroboration studies.

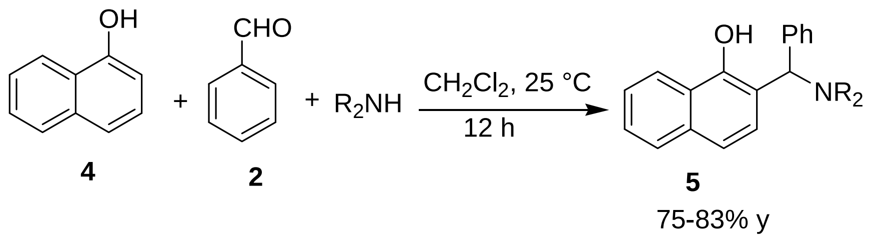
A convenient method was developed for the synthesis of aminonaphthols **3** by straightforward condensation of β-naphthol **1**, benzaldehyde **2** and 1^o or 2^o amines in ethanol at 78 ^{o}C for 6-12 h (Scheme 1).

Scheme 1



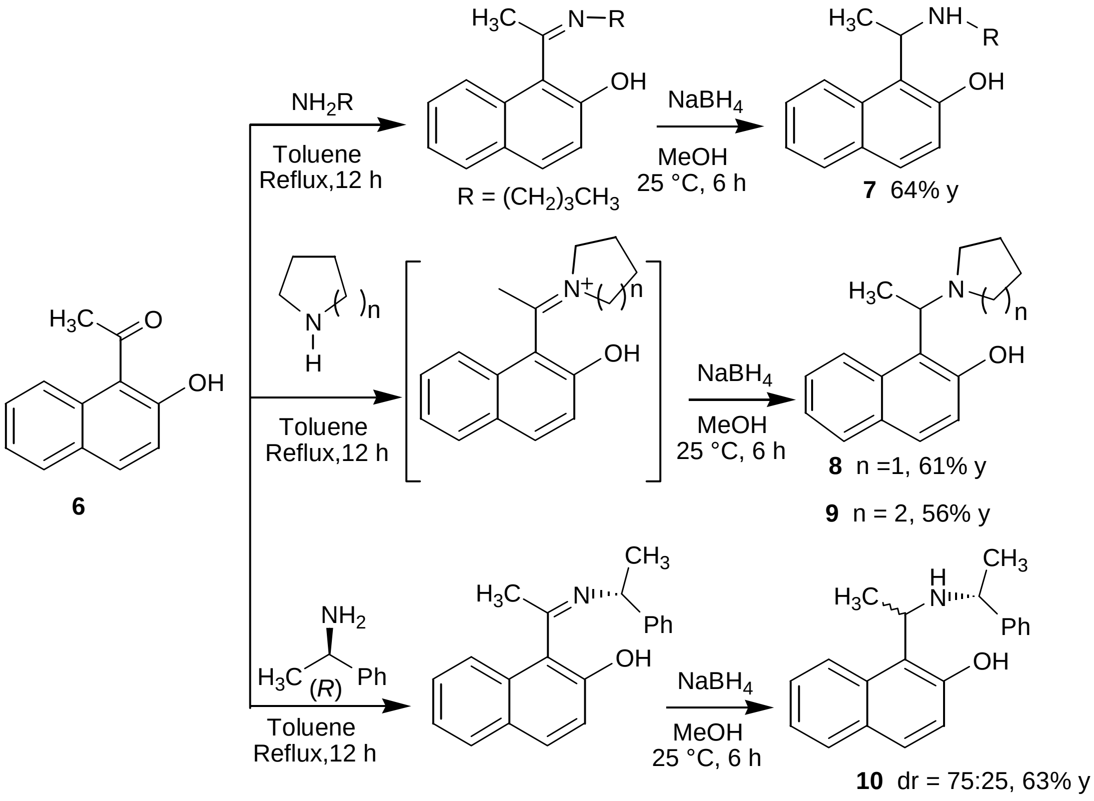
Similarly, aminonaphthols **5** were prepared from α–naphthol **4**, benzaldehyde **2** and 2^o amines (Scheme 2).

Scheme 2



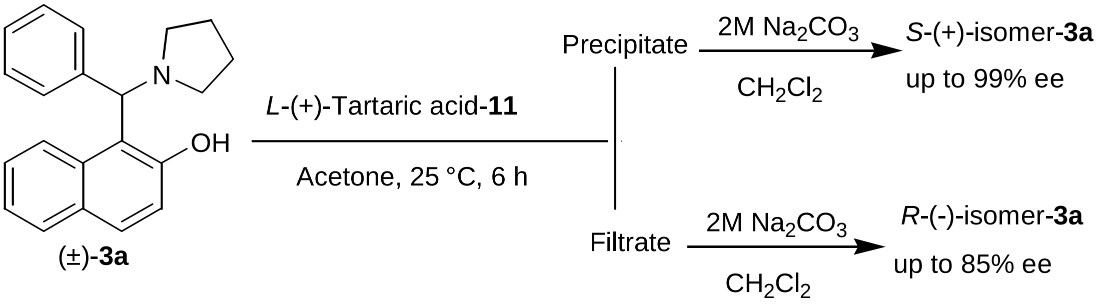
A simple and convenient methodology for the synthesis of aliphatic aminonaphthols using the readily accessible 1-acetyl-2-naphthol **6** as precursor was developed (Scheme 3).

Scheme 3



Racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol **3a** was resolved using inexpensive *L*-(+)-tartaric acid **11** in acetone through formation of diastereomeric complexes (Scheme 4).

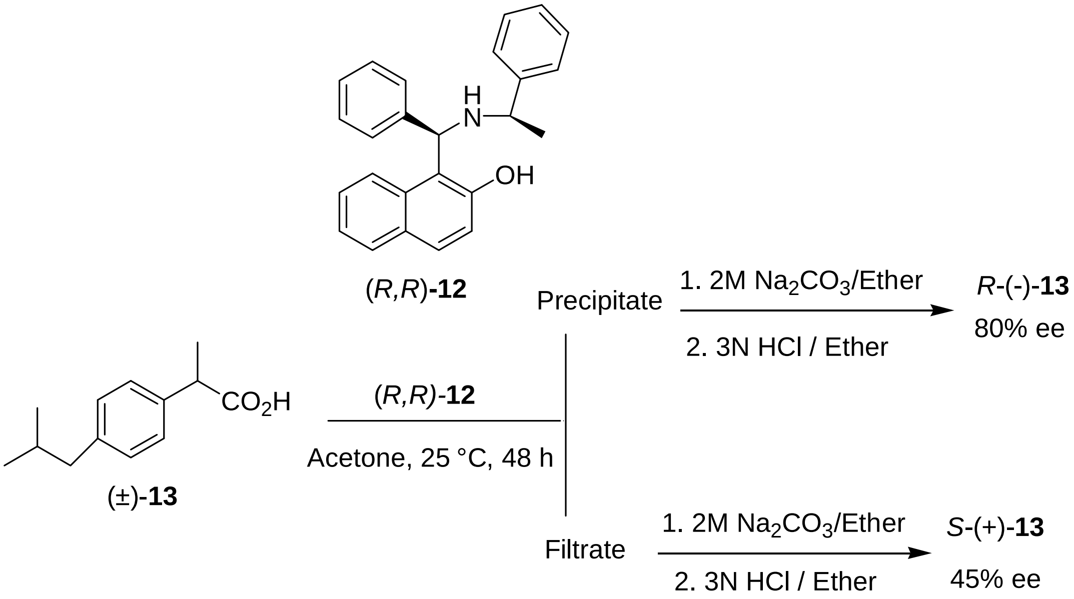
Scheme 4



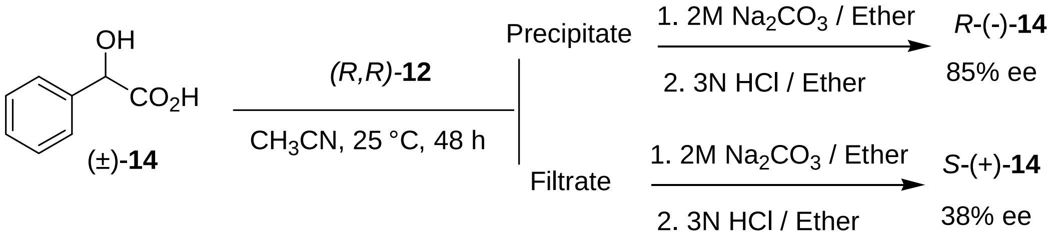
The chiral aminonaphthol *S*-(+)-**3a** was used for the resolution of racemic 1,1′-bi-2-naphthol.

We have observed that the readily accessible aminonaphthol **12** is useful for the resolution of racemic ibuprofen **13** and mandelic acid **14**. Racemic ibuprofen **13** was resolved in acetone, whereas mandelic acid **14** gave good results in CH_3CN solvent (Scheme 5 and 6).

Scheme 5



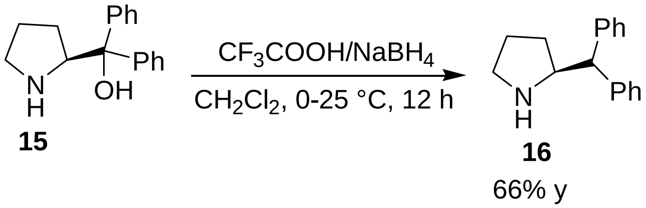
Scheme 6



These partially resolved samples were further enriched to obtain samples with 97% ee.

Preparation of (*S*)-2-diphenylpyrrolidinemethane **16** was carried out in a single step by the reduction of (*S*)-2-diphenylpyrrolidinemethanol **15** with trifluroacetic acid and sodium borohydride (Scheme 7).

Scheme 7



Various chiral C_2 and C_3-symmetrical ligands were synthesized using (*S*)-2-diphenylpyrrolidinemethanol **15** and (*S*)-2-diphenylpyrrolidinemethane **16** as starting materials (Chart 1 and 2).

Chart 1

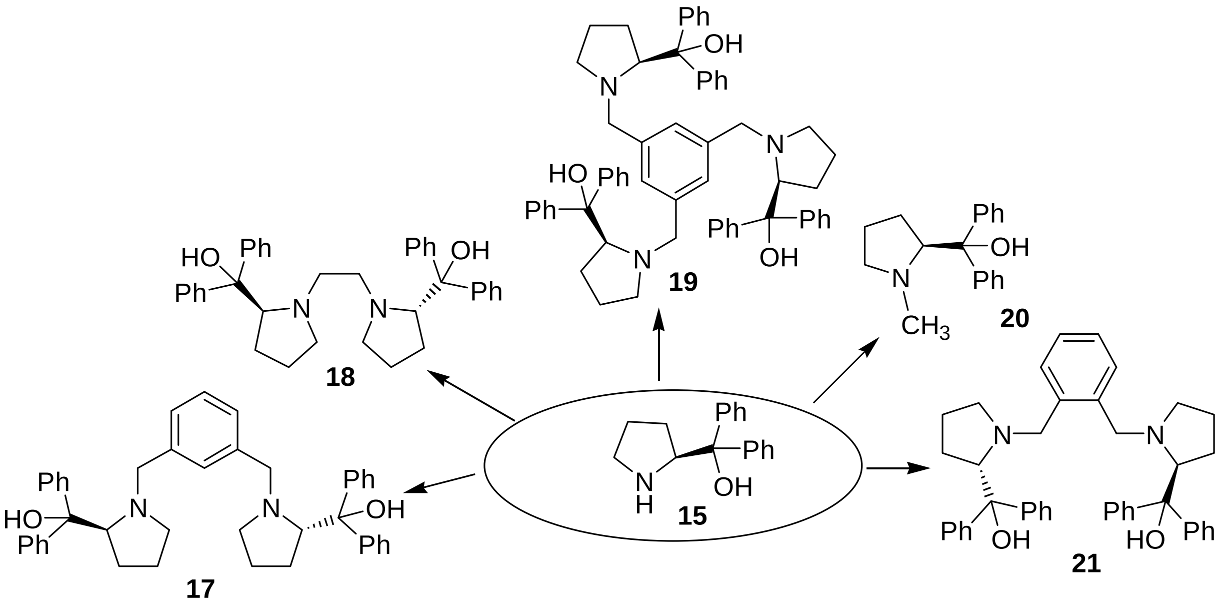
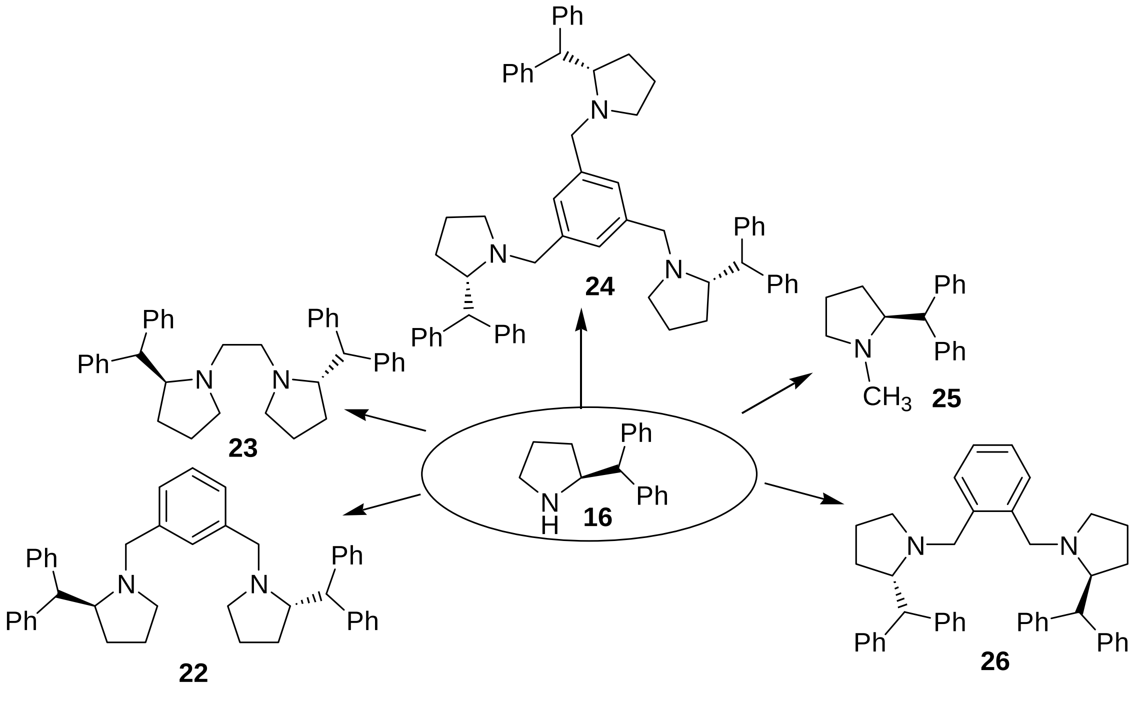
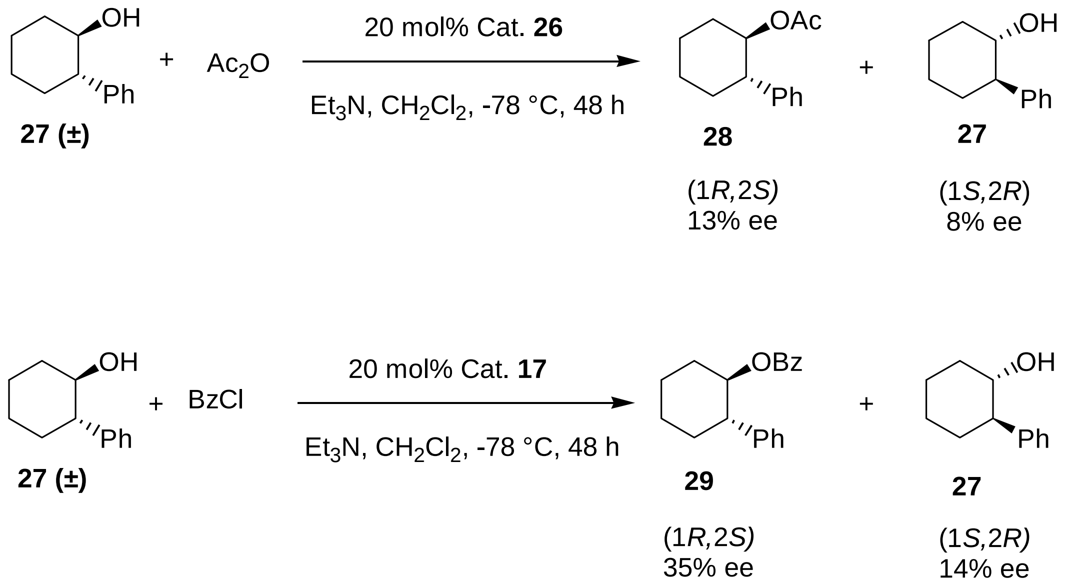


Chart 2



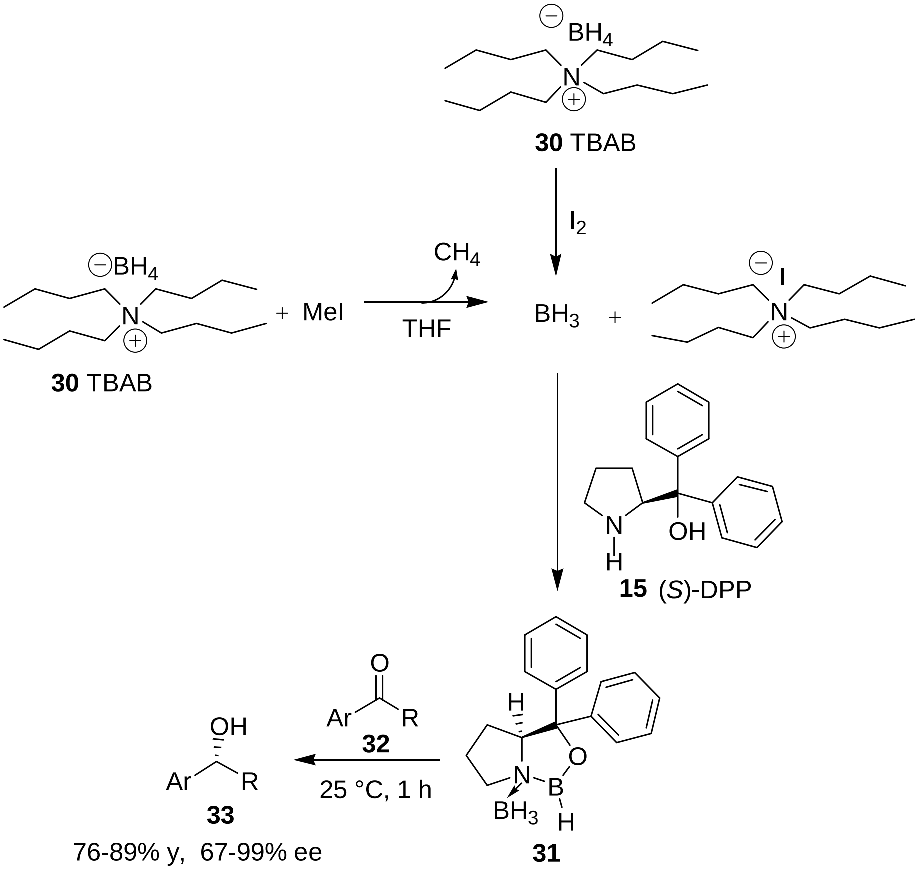
Enantioselective acylation of racemic *trans*-2-phenylcyclohexanol **27** was examined using some of these chiral ligands (Scheme 8).

Scheme 8



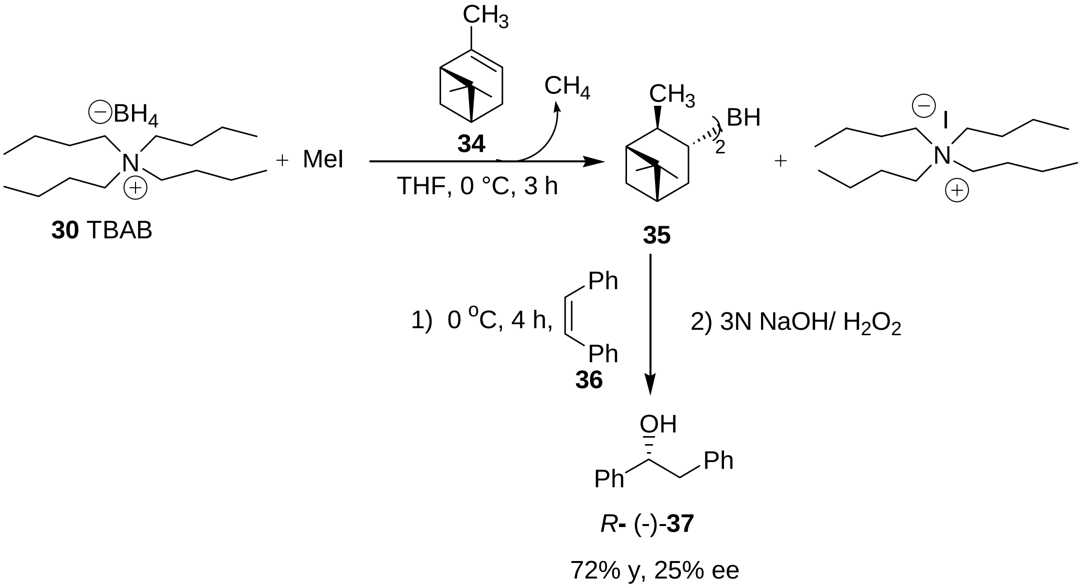
The chiral oxazaborolidine catalyst **31** was readily prepared *in situ* at 25 °C in THF using (*S*)-2-diphenylpyrrolidinemethanol **15** and borane generated from tetrabutylammonium borohydride **30**/CH_3I or I_2 reagent system. The oxazaborolidine **31**/BH_3 prepared in this way is useful for the reduction of prochiral ketones **32** to the corresponding alcohols **33** in up to 99% ee (Scheme 9).

Scheme 9

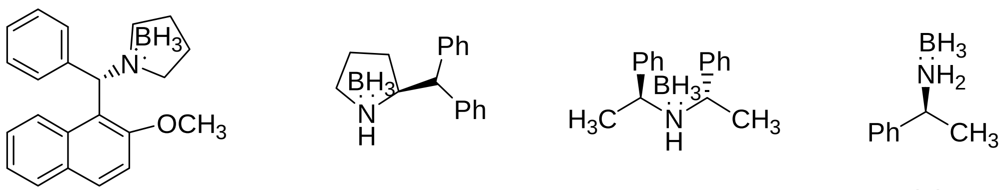


A simple *in situ* preparation of (-)-Ipc$_2$BH **35** was carried using readily accessible tetrabutylammonium borohydride **30**/MeI reagent system in combination with (1*R*,5*R*)-(+)-α-pinene **34**. The use of Ipc$_2$BH **35** prepared in this way was studied for the hydroboration of *cis*-stilbene **36**. Optimum results were obtained when excess (15%) of α-pinene **34** was used to prepare (-)-Ipc$_2$BH **35** (Scheme 10).

Scheme 10



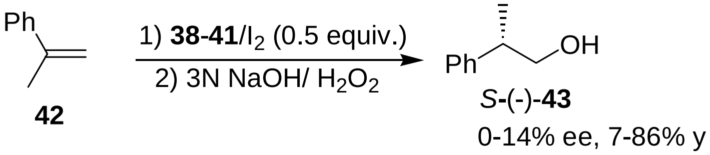
Hydroboration of α-methylstyrene **42** was studied by activating various chiral amine borane complexes **38-41** (Figure 1) using 0.5 equiv. of iodine (Scheme 11).



(*S*)-**38** (*S*)-**39** (*S,S*)-**40** (*S*)-**41**

Figure 1

Scheme 11

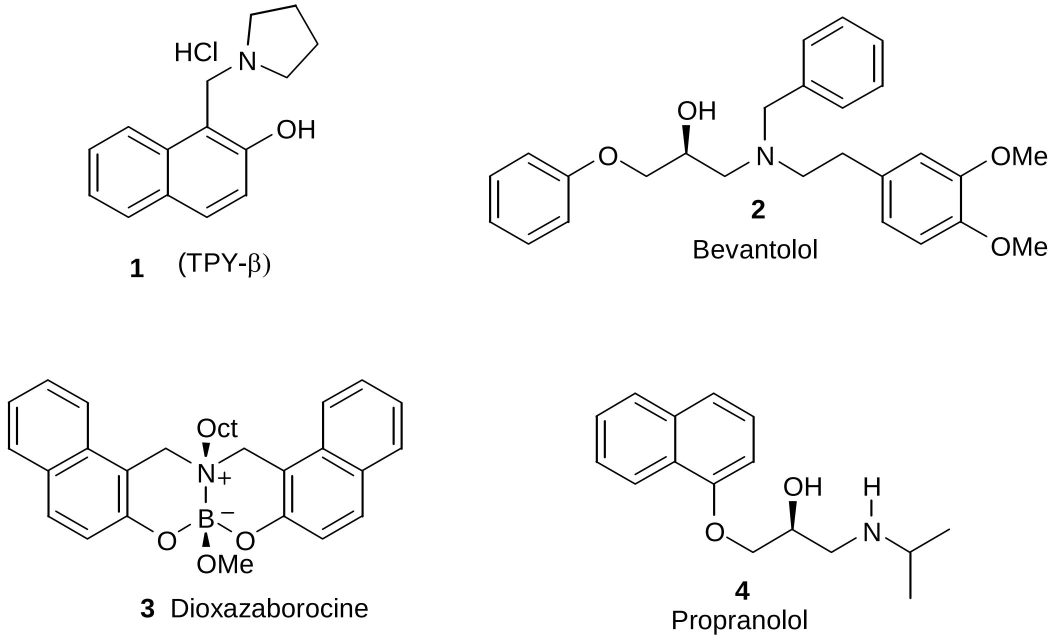


The experimental details are described in the third chapter. The IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, HPLC data and physical constant data (mp) are presented.

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

1. Introduction

The search for new chiral ligands, useful in asymmetric transformations, is of great interest in modern organic chemistry research.[1-7] In this context, aminonaphthols, amino alcohols and amines have proved to be useful ligands in a variety of asymmetric transformations. We have undertaken efforts towards the synthesis and application of chiral aminonaphthols, amino alcohols and amines. Aminonaphthol and amino alcohol moieties are also present in therapeutic agents and biological active compounds (Figure 1).



1 (TPY-β)

2 Bevantolol

3 Dioxazaborocine

4 Propranolol

Figure 1

For example, 1-pyrrolidinylmethyl-2-naphthol hydrochloride (TPY-β) **1** an aminonaphthol derivative, reduces blood pressure (BP) and heart rate (HR) in anesthetized rats.[8] Dioxazaborocine **3**, a derivative of aminonaphthol is capable of releasing borate ions and can be used as insecticides and timber preservatives.[9] 1,2-Amino alcohols such as the β-adrenergic blockers bevantolol **2** and propranolol **4** are effective therapeutic agents in the treatment of heart diseases.[10]

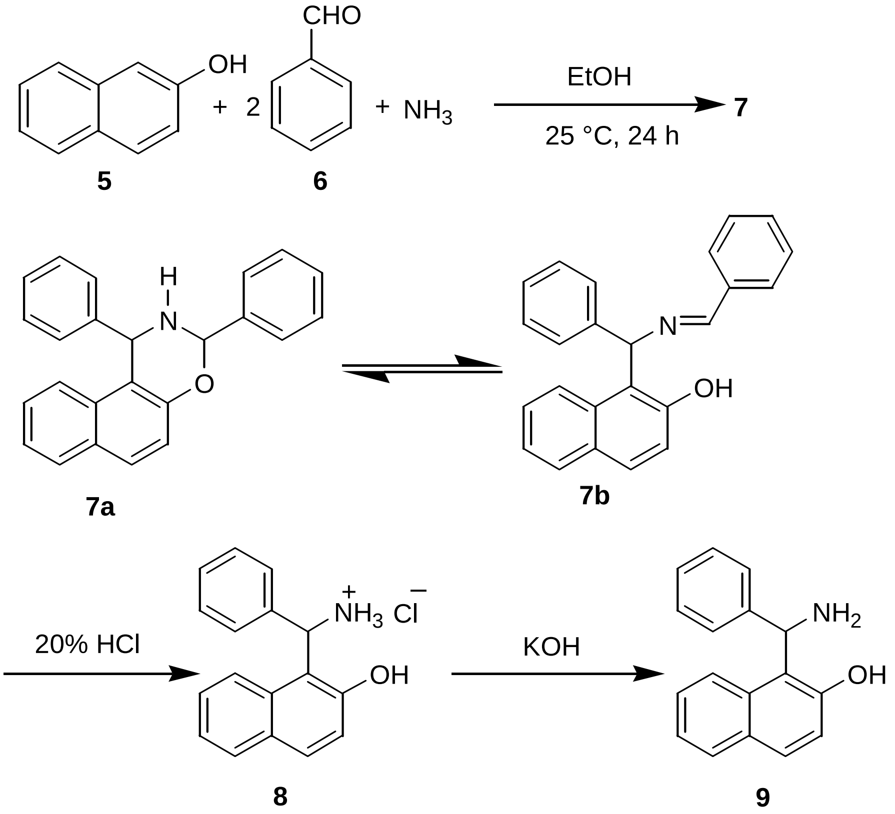
A brief review on each topic regarding synthesis and applications of aminonaphthols, amino alcohols and amines will be helpful for the discussion.

1.1 Synthesis of racemic aminonaphthols

In 1900, Betti, reported a simple straightforward condensation of β-naphthol, ammonia and 2 equivalents of benzaldehyde.[11-13] A mixture of products **7a** and **7b** was obtained, which on treatment with acid followed by the addition of KOH yielded the aminonaphthol **9** (Scheme 1).

The crystalline product **7** was first assigned as the 1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine structure **7a**[14-15] based on the reaction of **7** with nitrous acid in Et_2O which gives the *N*-nitroso-1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine derivative of **7a**.[16] Later, on the basis of its reaction with ethereal ferric chloride leading to an intense reddish-violet colour, the Schiff base structure, *N*-benzylidine-1-(α-aminobenzyl)-2-naphthol **7b** was proposed.[17]

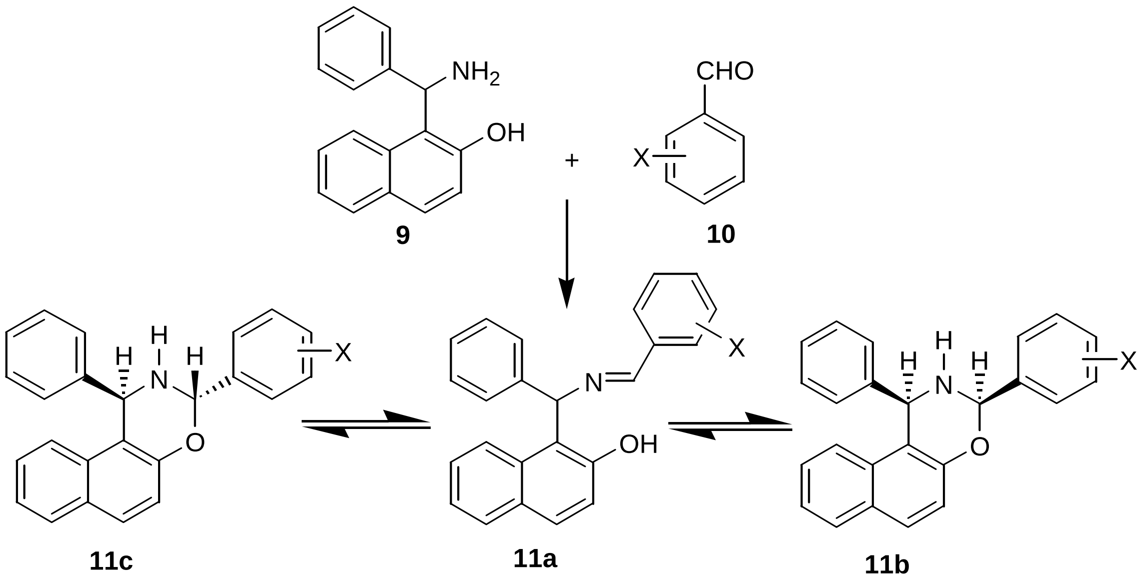
Scheme 1



Further, on the basis of IR data, it was confirmed that the structure **7a** is valid for the solid material, whereas a tautomeric equilibrium between **7a** and **7b** exists in solution.[18] The free Betti base **9** condenses with aliphatic aldehydes to give oxazines **7a,** whereas with aromatic aldehydes and aliphatic ketones Schiff bases **7b** were obtained.[19]

Later, *Smith* and *Cooper*[18] studied the reaction of Betti base **9** with substituted benzaldehydes **10**. The IR spectra of these condensation products indicated that in the crystalline state the product has the oxazine structure, whereas in solution an equilibrium mixture of *cis*- and *trans*-naphthoxazine (ring) and the corresponding Schiff base (chain) exists through a ring chain tautomerism (Scheme 2).

Scheme 2



The ratio of ring/chain tautomers depends on the substituent in the benzaldehyde moiety. The greater the electron-withdrawing power of the substituents, the larger is the ring/chain isomeric ratio. Various derivatives and different modes for the preparation of racemic aminonaphthols have been reported in literature, few of them are shown in Chart 1.

Chart 1

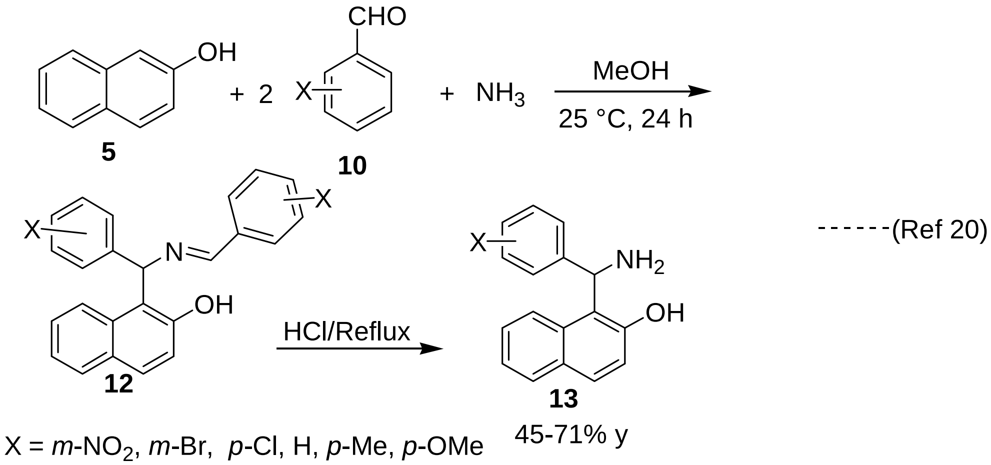


Chart 1 (continued)

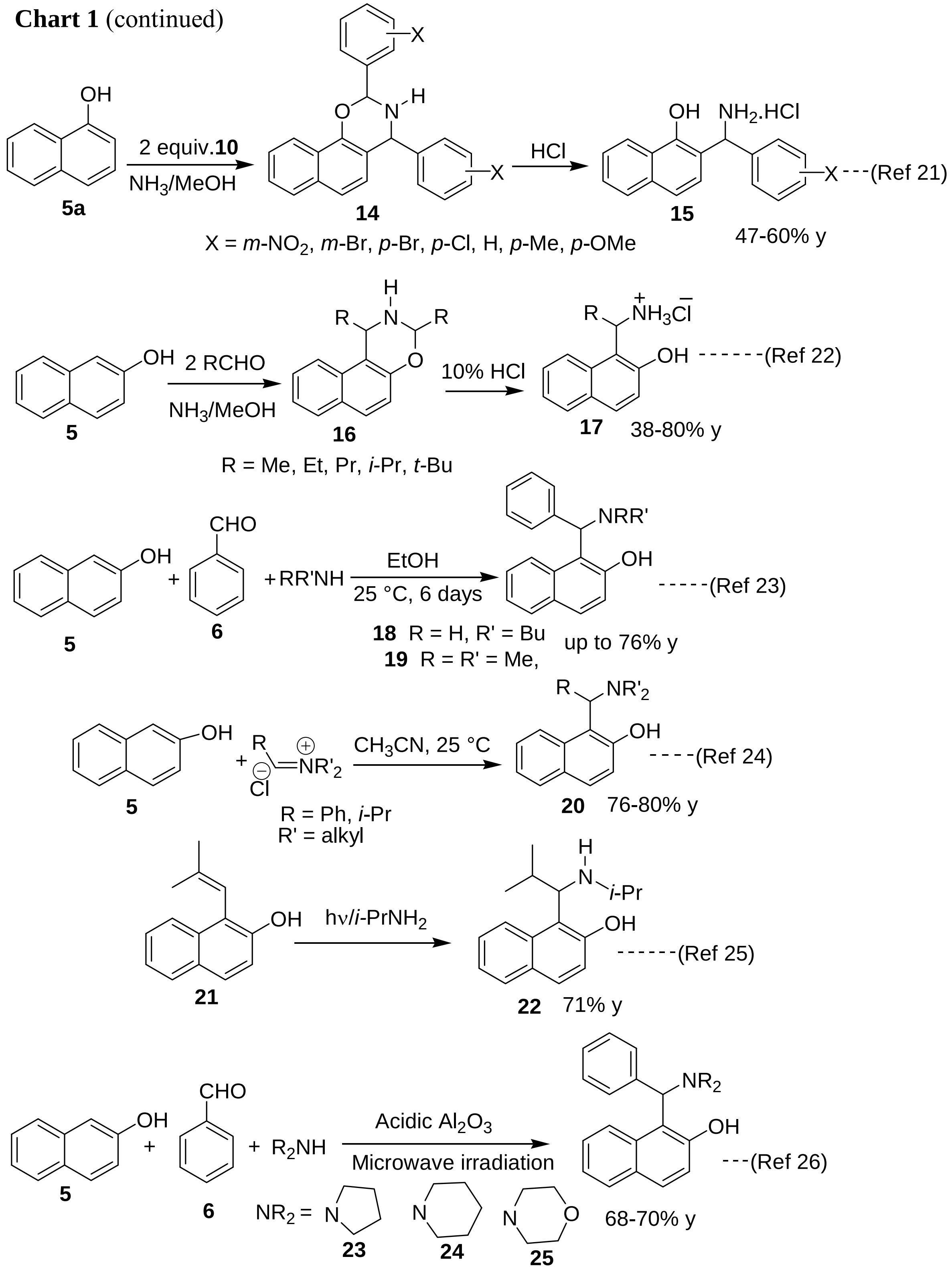
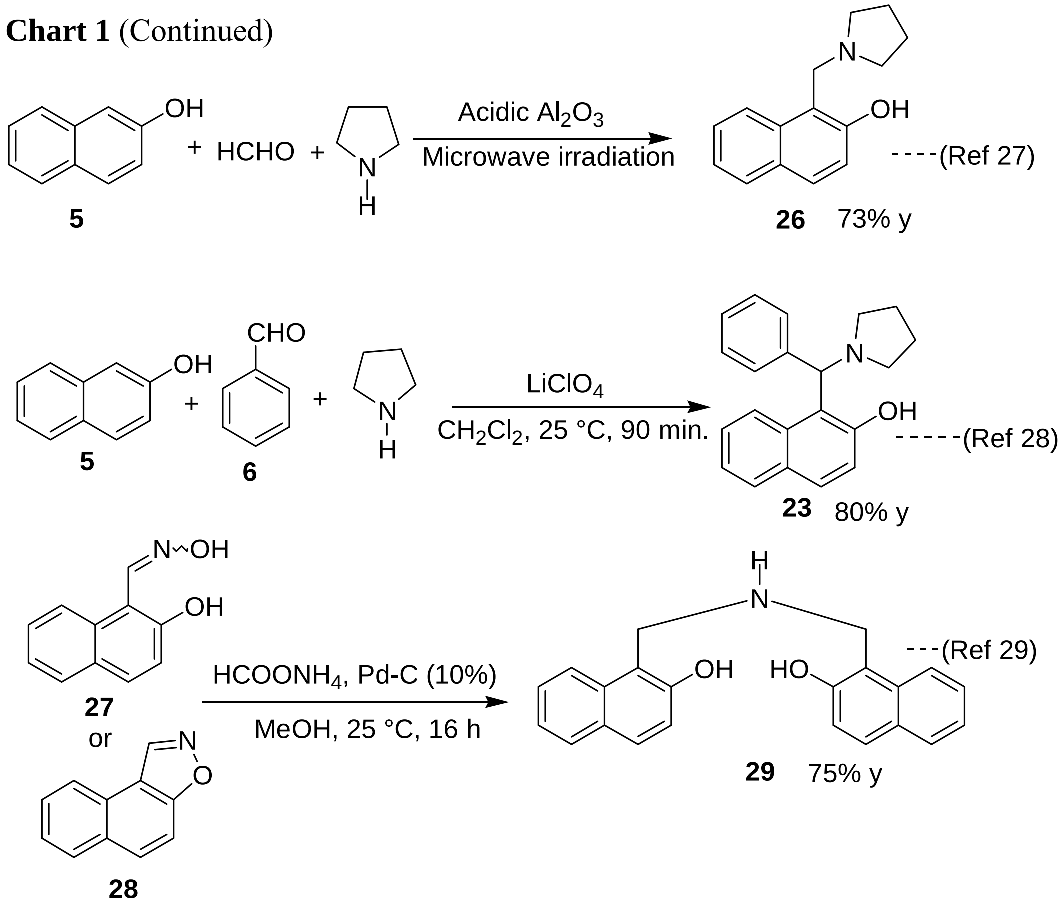


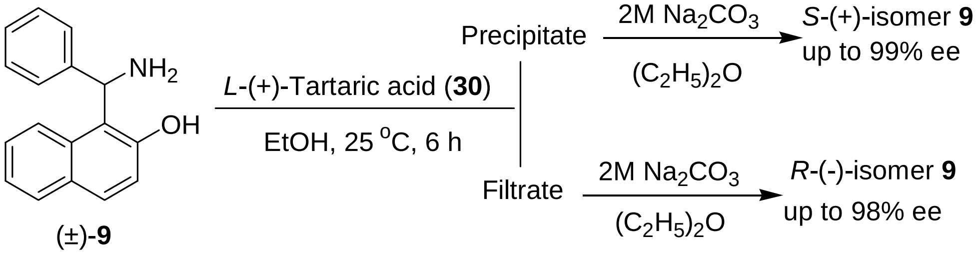
Chart 1 (Continued)



1. 2 Synthesis of enantiopure aminonaphthols

Enantiopure aminonaphthols are normally prepared by the resolution of racemic aminonaphthols using chiral resolving agents. For example, the Betti base **9** is easily resolved into pure enantiomers using inexpensive *L*-(+)-tartaric acid (Scheme 3).[30]

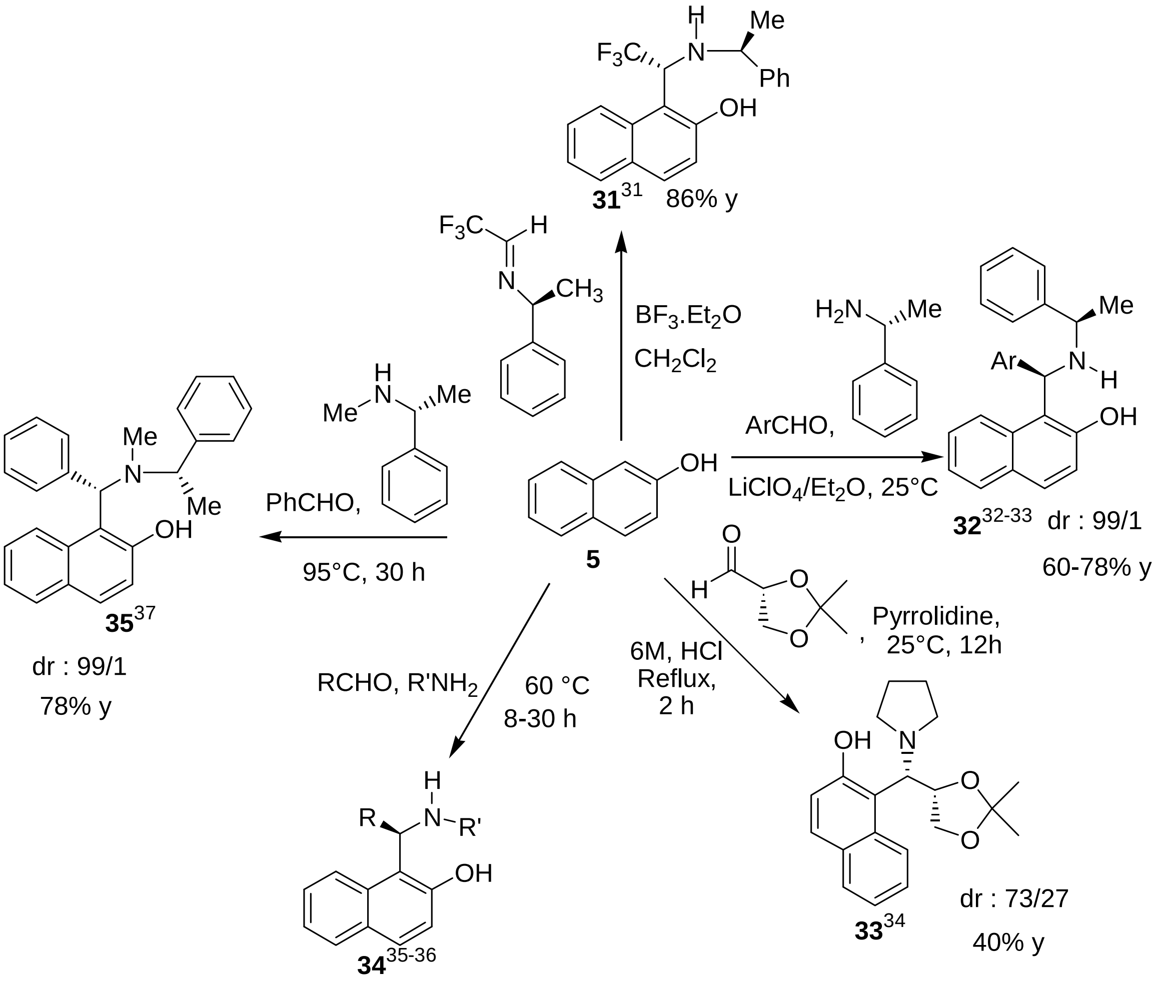
Scheme 3



1.2.1 Asymmetric synthesis

Chiral aminonaphthols **31-35** were prepared starting from β-naphthol **5** with various substituted aldehydes and chiral amines under various conditions (Chart 2).

Chart 2

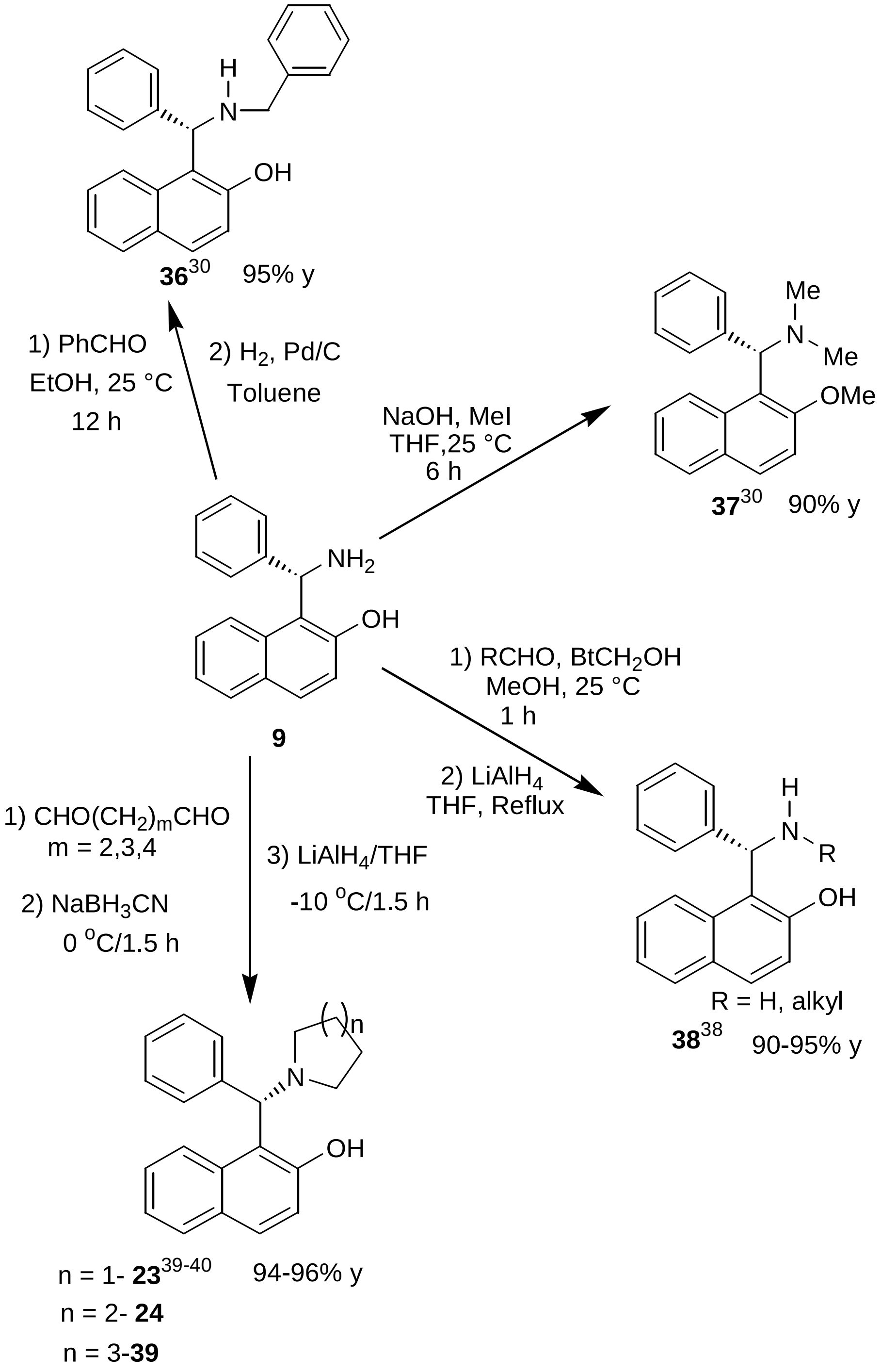


R = C_6H_5, C_6F_5, *i*-Pr, Cyclohexyl, 2-Pyridyl, 2-Furyl, 2-Thienyl

R' = (*R*)-PhCHMe, (*R*)-PhCHCH$_2$OH, (*R*)-(1-Naphthyl)CHMe

Various *N*-substituted derivatives of chiral aminonaphthols have been prepared starting from chiral betti base **9** as shown in Chart 3.

Chart 3

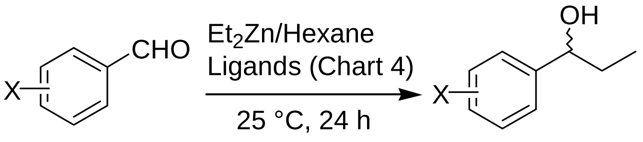

1) PhCHO
EtOH, 25 °C
12 h
2) H2, Pd/C
Toluene
36[30] 95% y
NaOH, MeI
THF,25 °C
6 h
37[30] 90% y
Me
N
Me
OMe
H
N
OH
NH2
OH
9
1) RCHO, BtCH2OH
MeOH, 25 °C
1 h
2) LiAlH4
THF, Reflux
H
N
R
OH
R = H, alkyl
38[38] 90-95% y
1) CHO(CH2)mCHO
m = 2,3,4
2) NaBH3CN
0 °C/1.5 h
3) LiAlH4/THF
-10 °C/1.5 h
n
N
OH
n = 1- 23[39-40] 94-96% y
n = 2- 24
n = 3-39

1.3 Applications of chiral aminonaphthols

1.3.1 Enantioselective diethylzinc addition reactions to aldehydes

The major application of aminonaphthols, till now is the addition of diethylzinc to the aldehydes (Scheme 4). Various derivatives of aminonaphthols have been used for this reaction. These results are summarized in Chart 4.

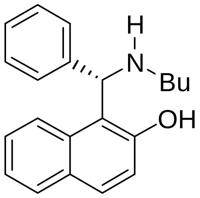
Scheme 4



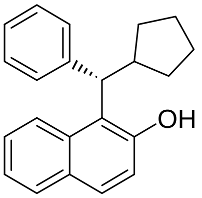
10 **40**

75-99% ee, 90-98% y

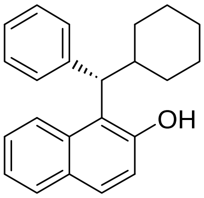
Chart 4



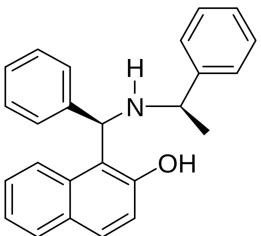
(*S*)-**18**[23]



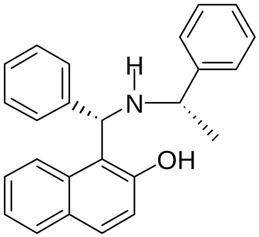
(*S*)-**23**[40]



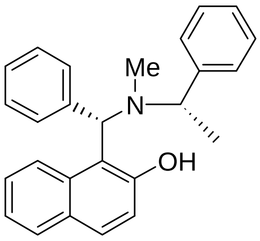
(*S*)-**24**[40]



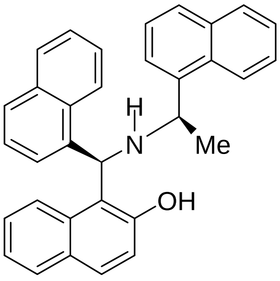
(*R*,*R*)-**41**[95]



(*S*,*S*)-**41**[41]



(*S*,*S*)-**35**[37]

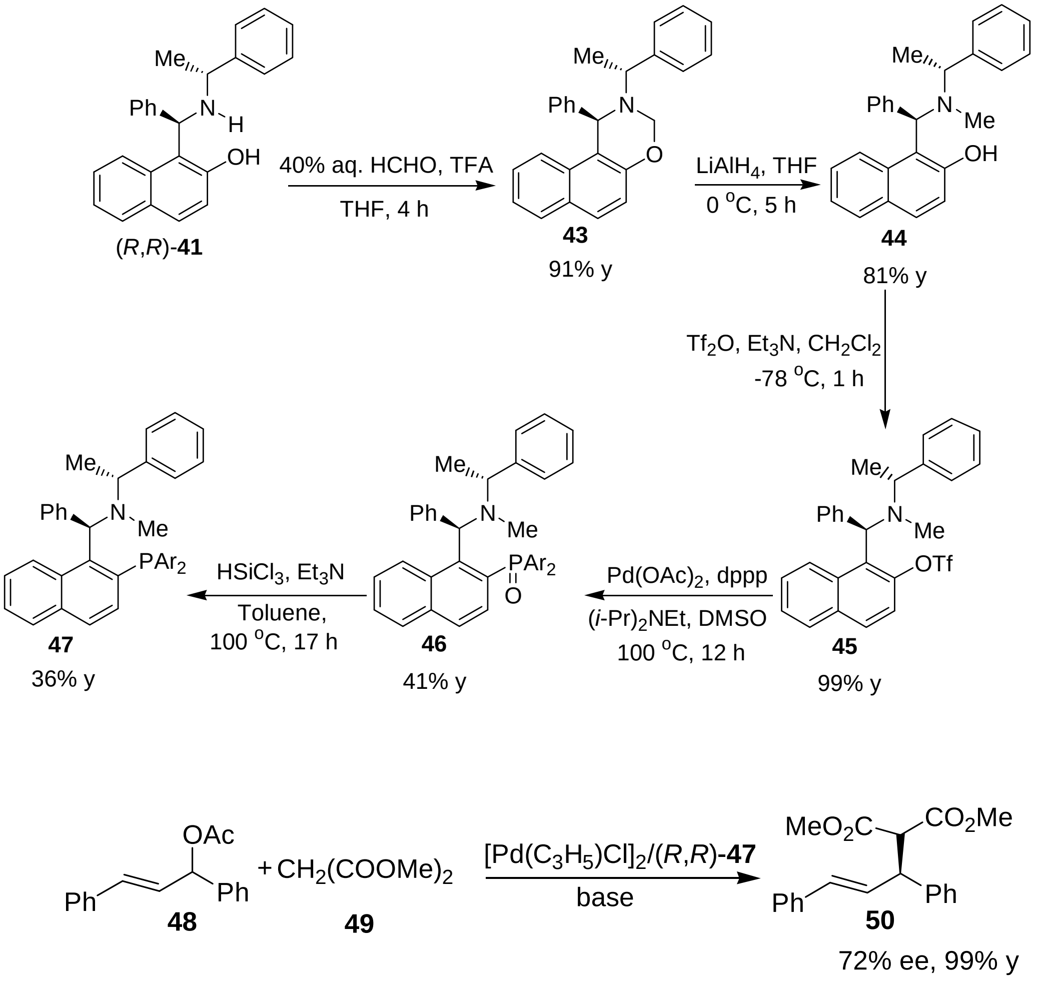


(*R*,*R*)-**42**[42]

1.3.2 Synthesis and application of chiral amino phosphine ligands

Chiral amino phosphine ligands have been prepared starting from chiral aminonaphthol **41**. This ligand has been used in the Pd-catalyzed asymmetric allylation of **48** using dimethyl malonate **49** to obtain the product **50** in 72% ee and in quantitative yield (Scheme 5).[43]

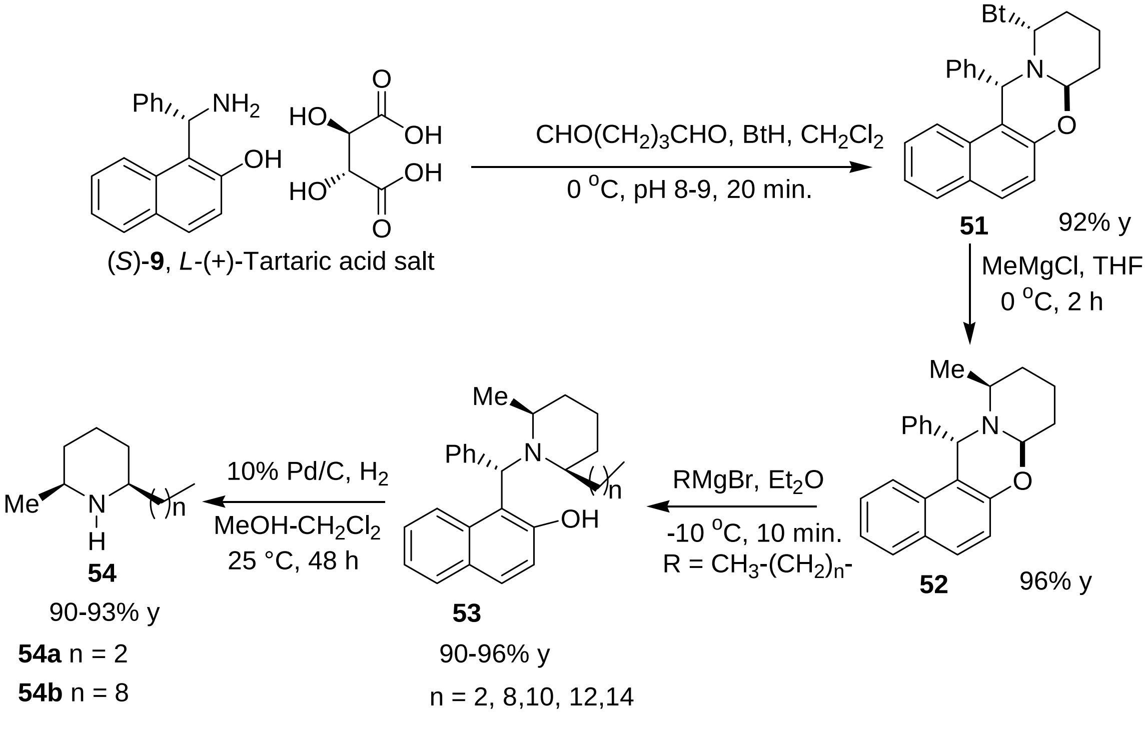
Scheme 5



1.3.3 Total synthesis of enantiopure (2*S*,6*R*)-dihydropinidine and (2*S*,6*R*)-isosolenopsins

Total synthesis of enantiopure alkaloid natural products (2*S*,6*R*)-dihydropinidine **54a** (as hydrochloride) and (2*S*,6*R*)-isosolenopsin **54b** (as hydrochloride) have been achieved in four steps and in 80-82% total yields by following a synthetic strategy of formation and cleavage of the corresponding 1,3-oxazine from (*S*)-Betti base **9,** followed by Pd/C catalyzed *N*-debenzylation (Scheme 6).[44]

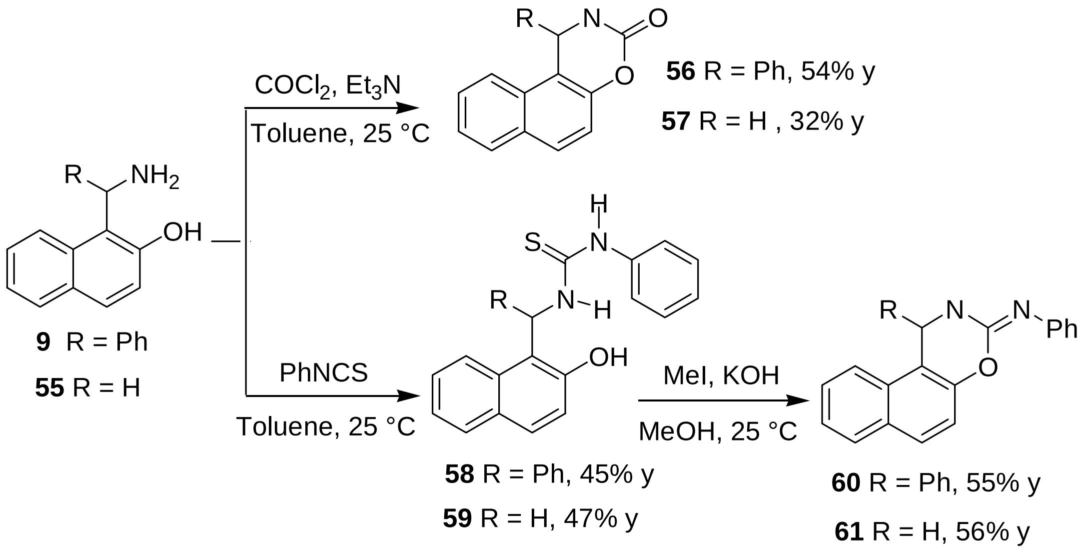
Scheme 6



1.3.4 Synthesis of new heterocyclic compounds

Betti base **9** and 1-aminomethyl-2-naphthol **55** were used in the preparation of a variety of heterocyclic compounds. They react with phosgene and phenyl isothiocyanate to give the corresponding 1,3-oxazine-2-ones as well as thiourea derivatives **56-59** (Scheme 7).[45]

Scheme 7



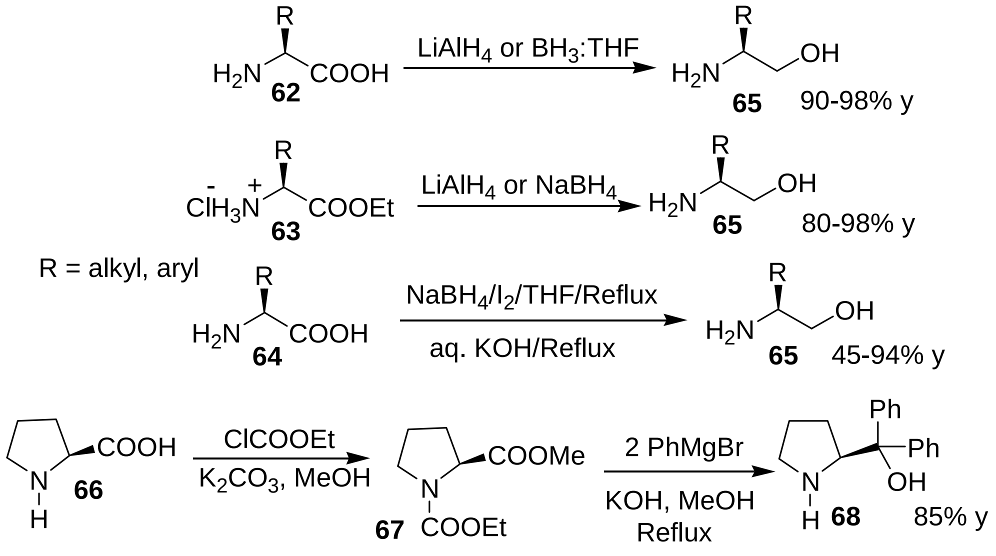
These thiourea derivatives **58** and **59** can be easily converted to isothiourea derivatives using MeI, and subsequent treatment with methanolic KOH gives the corresponding 2-arylimino-susbstituted 1,3-oxazines **60** and **61** *via* elimination of methyl mercaptan.

1.4 Synthesis of amino alcohols

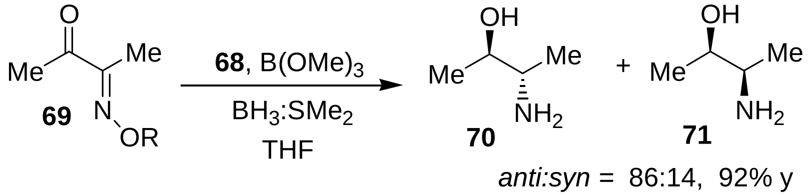
Several enantiomerically pure amino alcohols are used as chiral auxiliaries and chiral catalysts in asymmetric organic transformations.[7] A large number of enantiomerically pure amino alcohols derived chiral auxiliaries and chiral catalysts have been synthesized and used for the past 20 years. Reports on the synthesis of chiral amino alcohols are summarized in Chart 5.

Chart 5

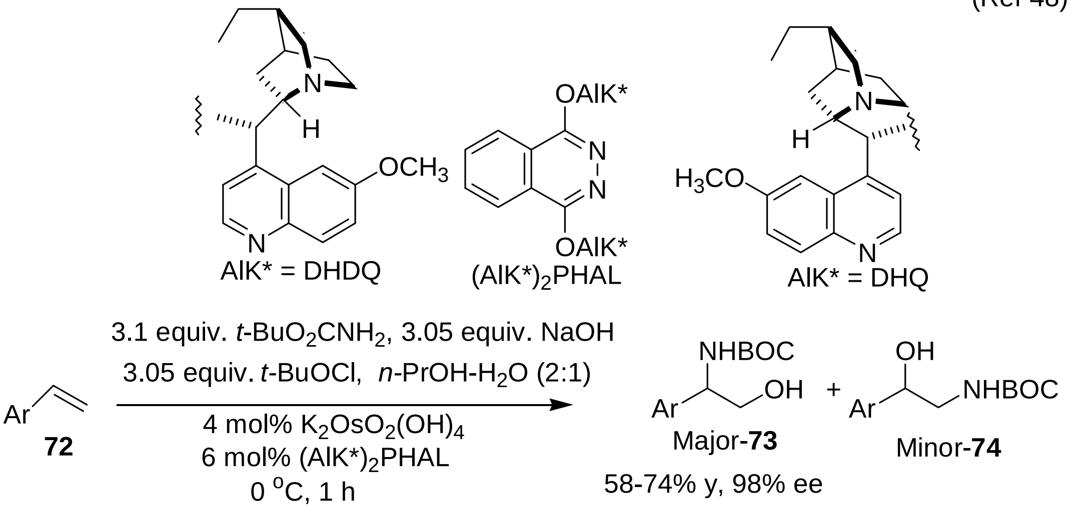
From Amino acids and their derivatives ------(Ref 46)



From α-oxoketoxime ethers -----(Ref 47)



From Amino hydroxylation of olefins -----(Ref 48)

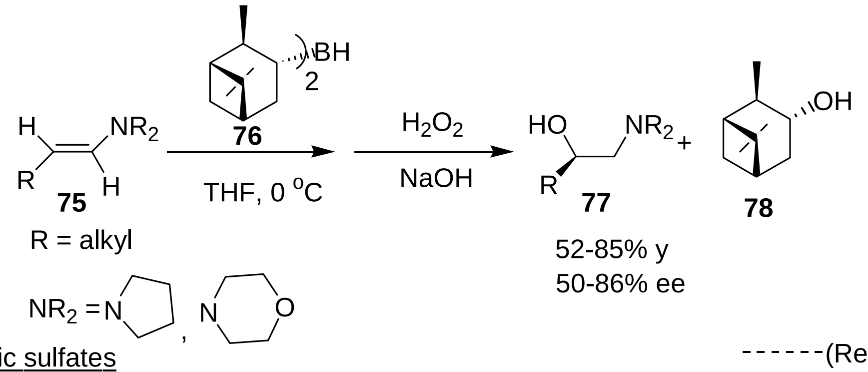


Ar = Ph, 2-ClC$_6$H$_4$,2-MeOC$_6$H$_4$,
4-MeOC$_6$H$_4$, Naphthyl

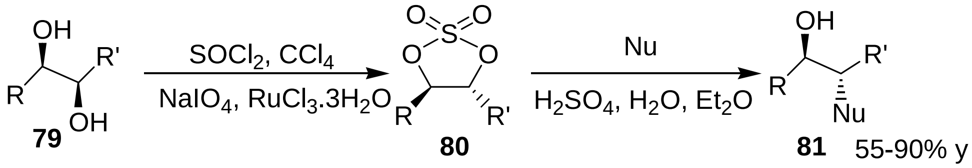
73:74 = 55:45 - 83:17

Chart 5 (continued)

From Hydroboration of enamines ------(Ref 49)

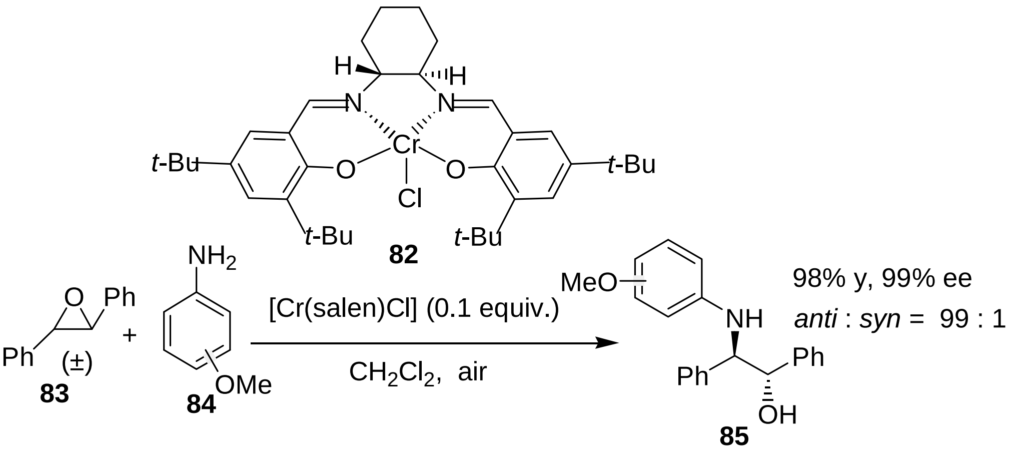


From Cyclic sulfates ------(Ref 50)



Nu = H^-,F^-,SCN^-,NO_3^-

From Epoxides ---(Ref 51)



1.5 Synthesis of amines

The amine synthons have been used as precursors in the synthesis of heterocyclic ring systems as well as chelating agents.[52] Reports on the synthesis of amines/1,2-diamines are outlined in Chart 6.

Chart 6

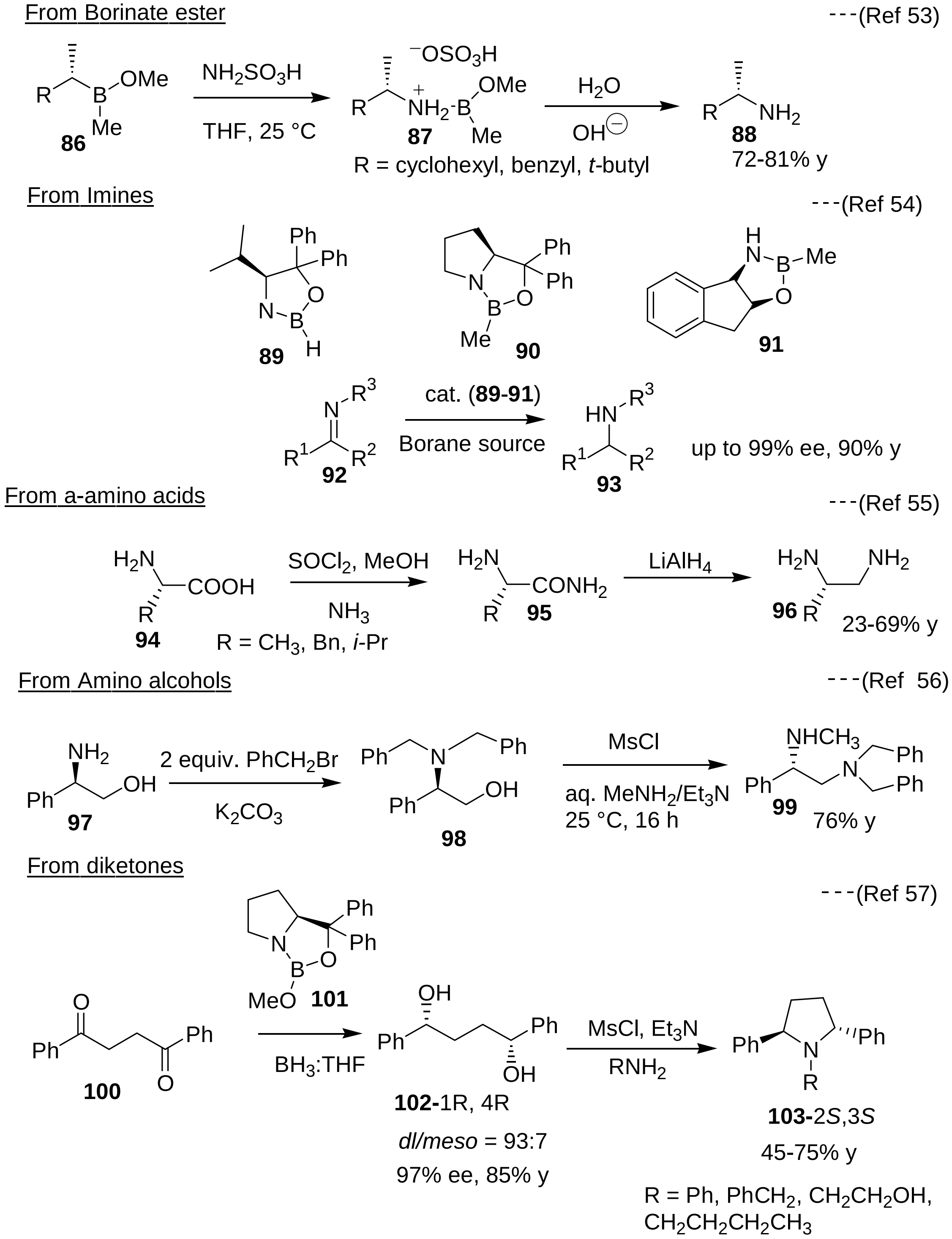
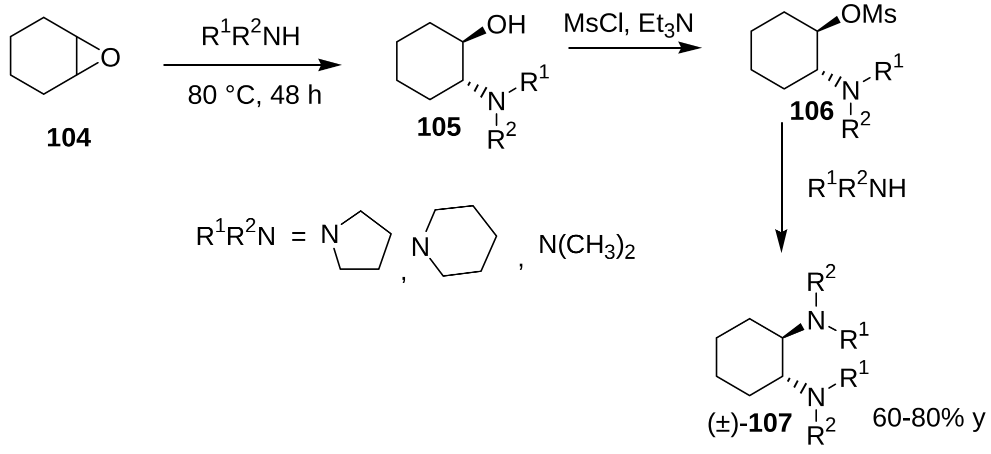

From Borinate ester
---(Ref 53)
86
NH2SO3H
THF, 25 °C
87
H2O
OH⊖
88
72-81% y
R = cyclohexyl, benzyl, t-butyl
From Imines
---(Ref 54)
89
90
91
cat. (89-91)
Borane source
92
93
up to 99% ee, 90% y
From a-amino acids
---(Ref 55)
94
SOCl2, MeOH
NH3
R = CH3, Bn, i-Pr
95
LiAlH4
96
23-69% y
From Amino alcohols
---(Ref 56)
97
2 equiv. PhCH2Br
K2CO3
98
MsCl
aq. MeNH2/Et3N
25 °C, 16 h
99
76% y
From diketones
---(Ref 57)
101
100
BH3:THF
102-1R, 4R
dl/meso = 93:7
97% ee, 85% y
MsCl, Et3N
RNH2
103-2S,3S
45-75% y
R = Ph, PhCH2, CH2CH2OH, CH2CH2CH2CH3

Chart 6 (continued)

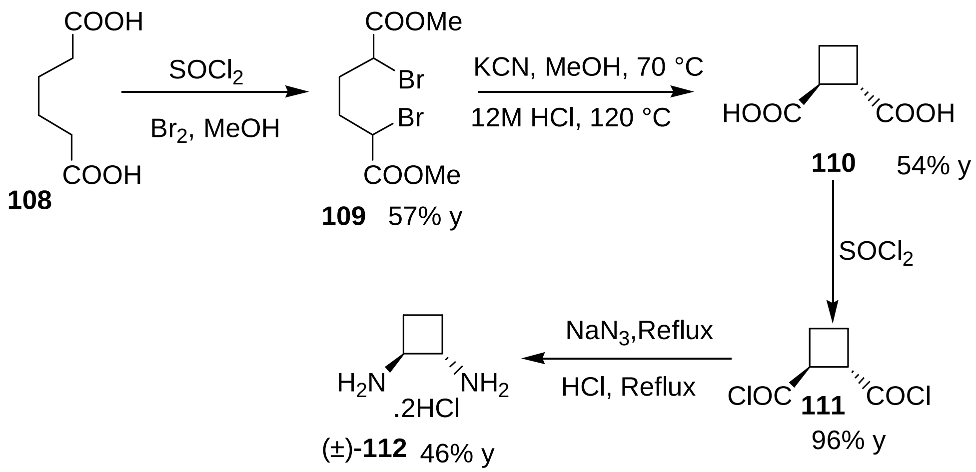
From Epoxides

---(Ref 58)



From Carborcylic acids

---(Ref 59)



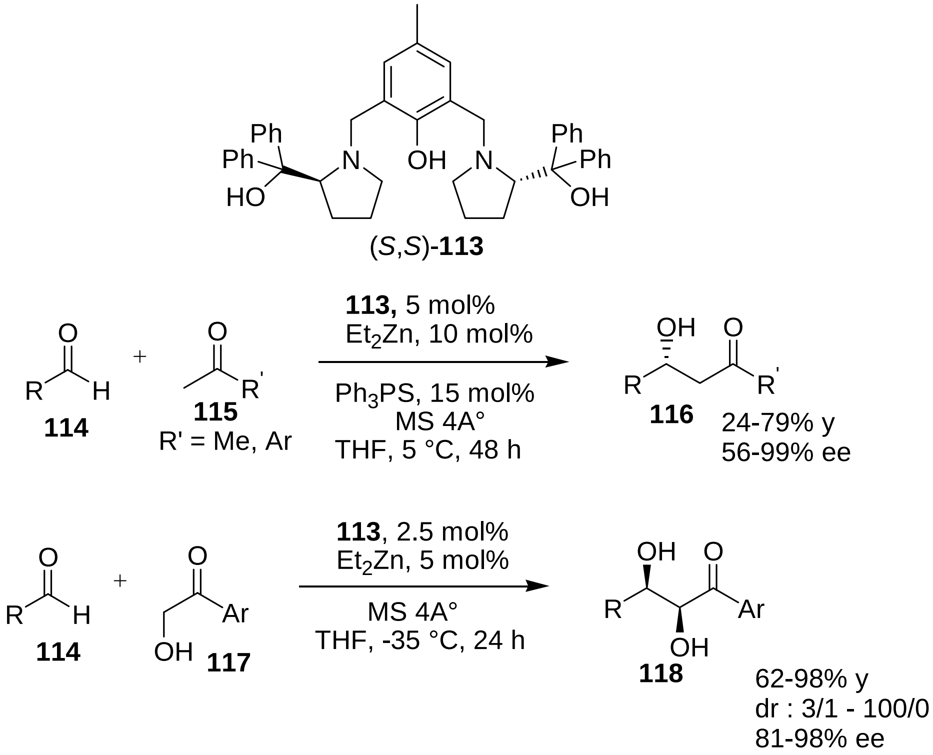
1.6 Application of amino alcohols and amines

As we have made efforts on the synthesis and application of amino alcohols and amines derivatives containing chiral α,α-diphenylpyrrolidinyl (DPP) moiety, it is of interest to briefly review literature for application in some asymmetric methods.

1.6.1 Application in aldol reactions

Trost *et al.*[60-64] designed semi-crown **58** for their molecular recognition properties to perform the direct catalytic enantioselective aldol reaction (DCEAR). Good yields and a high level of induction were recorded with various aryl methyl ketones, methyl ynones, methylvinyl ketone and acetone upon reaction with various aldehydes (Scheme 8).

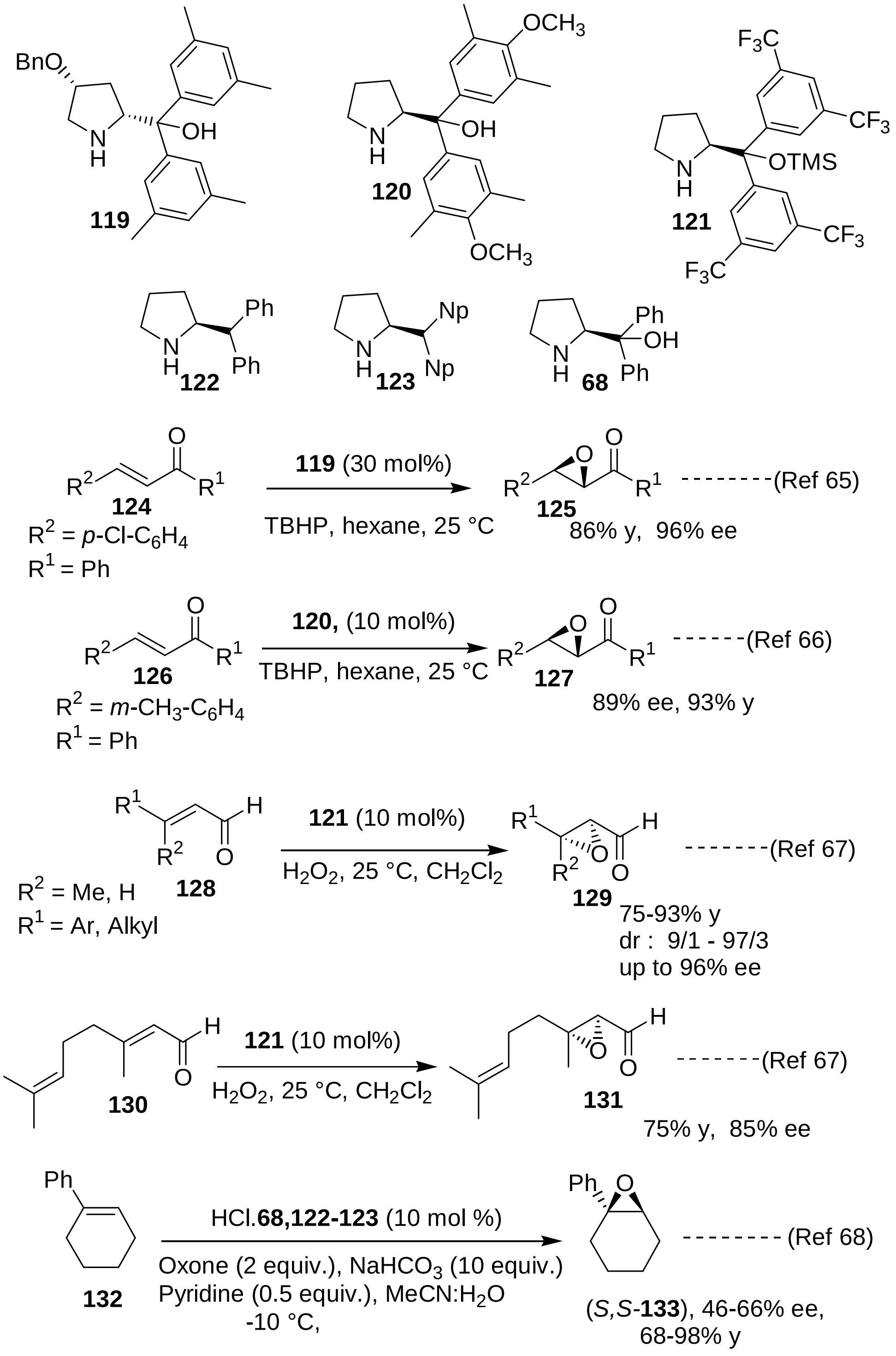
Scheme 8



1.6.2 Application in asymmetric epoxidation

Highly enantioselective asymmetric epoxidation for α,β-enones, α,β-unsaturated aldehydes and alkenes were carried out using easily obtained DPP based moieties as organocatalyst and TBHP as an oxidant. Corresponding chiral epoxides in good yields and high enantioselectivities under mild reaction conditions have been obtained (Chart 7).

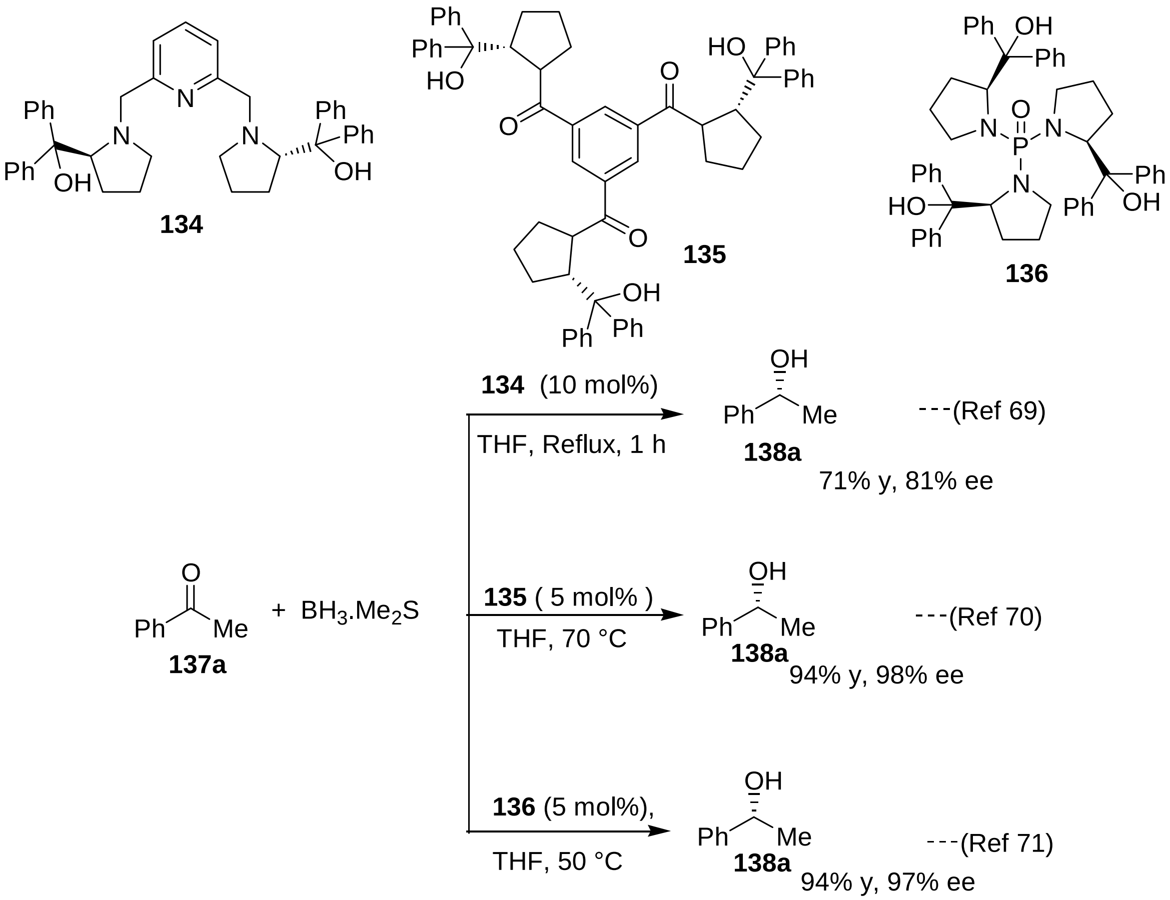
Chart 7


BnO
OH
N
H
119
OCH3
OH
N
H
120
OCH3
F3C
CF3
OTMS
N
H
121
CF3
F3C
Ph
N
H
122
Ph
Np
N
H
123
Np
Ph
OH
N
H
68
Ph
O
R2
R1
124
R2 = p-Cl-C6H4
R1 = Ph
119 (30 mol%)
TBHP, hexane, 25 °C
O
O
R2
R1
125
86% y, 96% ee
(Ref 65)
O
R2
R1
126
R2 = m-CH3-C6H4
R1 = Ph
120, (10 mol%)
TBHP, hexane, 25 °C
O
O
R2
R1
127
89% ee, 93% y
(Ref 66)
R1
H
R2
O
128
R2 = Me, H
R1 = Ar, Alkyl
121 (10 mol%)
H2O2, 25 °C, CH2Cl2
R1
H
O
R2
O
129
75-93% y
dr : 9/1 - 97/3
up to 96% ee
(Ref 67)
H
O
130
121 (10 mol%)
H2O2, 25 °C, CH2Cl2
H
O
O
131
75% y, 85% ee
(Ref 67)
Ph
132
HCl.68,122-123 (10 mol %)
Oxone (2 equiv.), NaHCO3 (10 equiv.)
Pyridine (0.5 equiv.), MeCN:H2O
-10 °C,
Ph
O
(S,S-133), 46-66% ee,
68-98% y
(Ref 68)

1.6.3 Application in asymmetric reductions

Various *C*$_2$ as well as *C*$_3$-symmetric chiral ligands possessing diphenylpyrrolidinol unit have been used for asymmetric borane reduction of ketones with good level of enantioselectivity (Scheme 9).

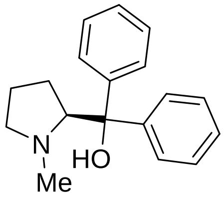
Scheme 9



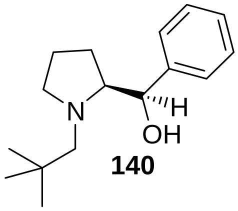
1.6.4 Application in dialkyl zinc addition

Various chiral diphenylpyrrolidinylmethanol derivatives prepared were used in catalytic asymmetric additions of organozinc reagents like Et_2Zn and Ph_2Zn to aldehydes (Chart 8).

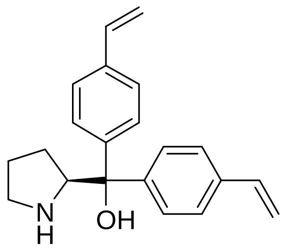
Chart 8



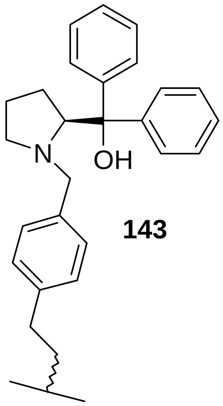
139



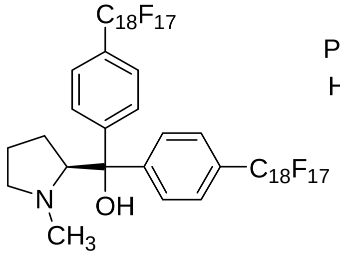
140



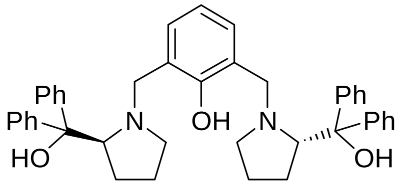
141



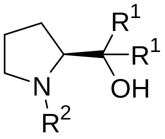
143



142

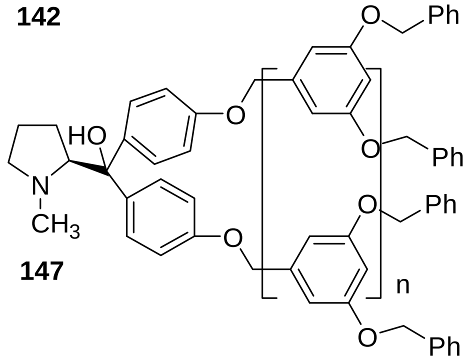


(*S*,*S*)-**144**

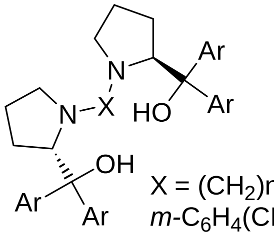


145 R^1 = Me, R^2 =Bn

146 R^1 = Ph, R^2 =SO_2 -Ph



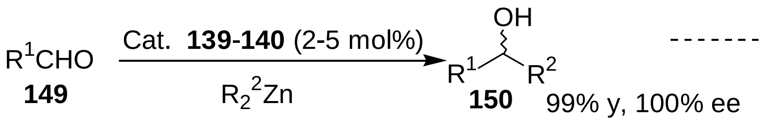
147



148

X = $(CH_2)n$, *p*-$C_6H_4(CH_2)_2$, *m*-$C_6H_4(CH_2)_2$, *o*-$C_6H_4(CH_2)_2$

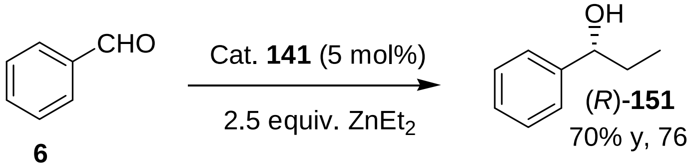
n = 2, 4, 6



99% y, 100% ee

--------- (Ref 72)

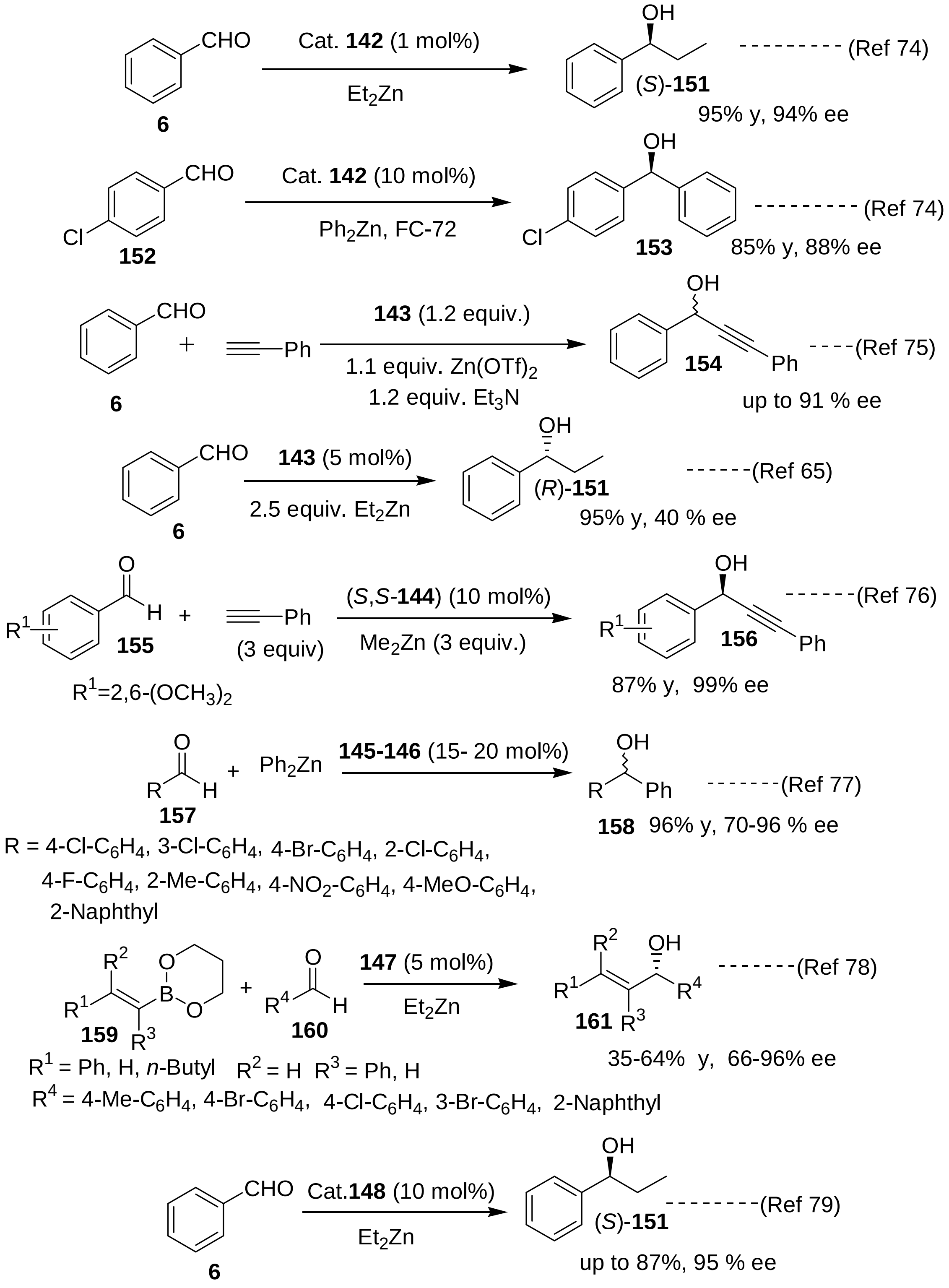
R^1= Ph, *p*-Cl-C_6H_4, *p*-MeO-C_6H_4 R^2 = Et, Me



70% y, 76 % ee

----------- (Ref 73)

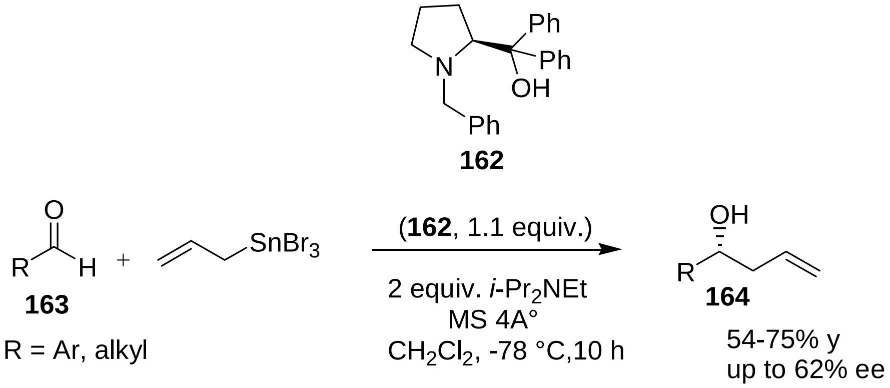
Chart 8 (continued)



1.6.5 Application in allylation

Asymmetric allylation of aldehydes with the allyltin tribromide was achieved using catalyst **162** in dichloromethane in the presence of Lewis base. Various optically active homoallylic alcohols were obtained in high yields with moderate enatioselectivities of up to 62% ee (Scheme 10).[80]

Scheme 10



We have examined the applications of aminonaphthols, amines and amino alcohols for various synthetic applications (Figure 2). Synthesis and applications of these derivatives are discussed in detail under the results and discussion (Chapter 2).

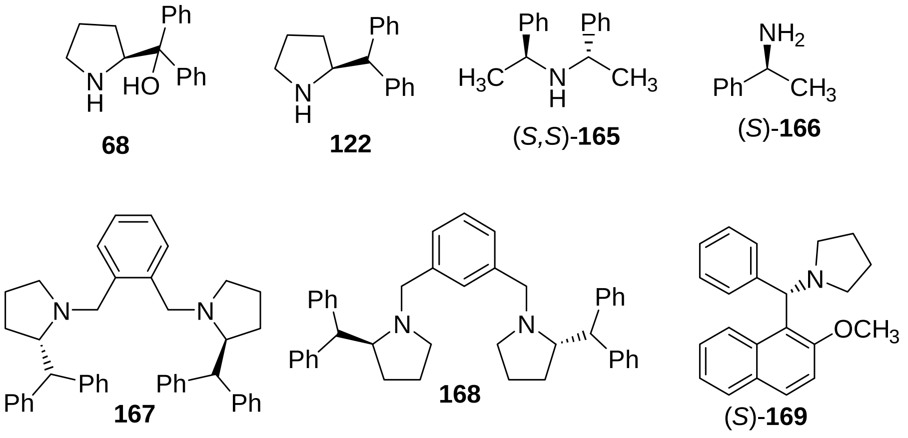


Figure 2

2. Results and Discussion

2.1 Synthesis and application of aminonaphthols

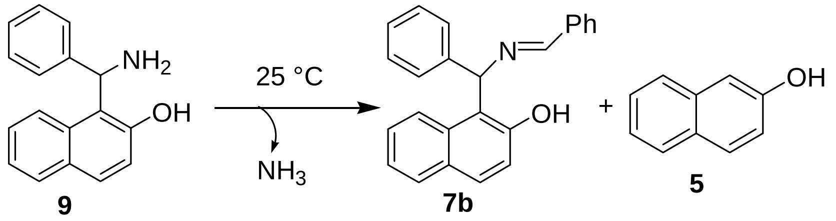
2.1.1 Synthesis of 1-(α-aminobenzyl)-2-naphthol

The Betti synthesis of aminonaphthols is a type of Mannich condensation, using an aromatic aldehyde in place of formaldehyde, secondary amine instead of ammonia and an electron-rich aromatic compound i.e. 2-naphthol in place of enolizable carbonyl compound.[13] Recently, the Betti reaction (Scheme 1) has received renewed interest, since the chiral aminonaphthol products are readily accessible through this reaction.[39-40] These aminonaphthols are useful as catalysts in asymmetric carbon-carbon bond forming reactions.[30, 38] Thus, we have undertaken efforts towards the synthesis and resolution of aminonaphthols. The Betti aminonaphthol **9** was prepared by the condensation of 2-naphthol, benzaldehyde and ammonia in the ratio of 1:2:1 following a reported procedure.[13] The product **7** (Scheme 1) was obtained as intermediate, which on treatment with 20% hydrochloric acid followed by the addition of 2M Na_2CO_3 to the ammonium salt yielded the aminonaphthol **9** (Scheme 1, Chapter 1).

2.1.2 Synthesis of aminonaphthols derived from β-naphthol and α-naphthol

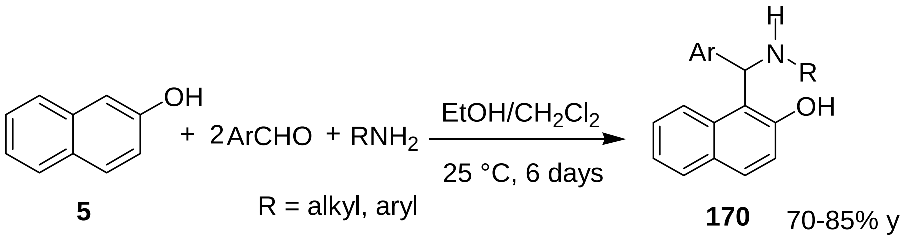
The Betti aminonaphthol **9** is thermally unstable and decomposes easily to give **7b** and β-naphthol **5** (Scheme 11).[39-40]

Scheme 11



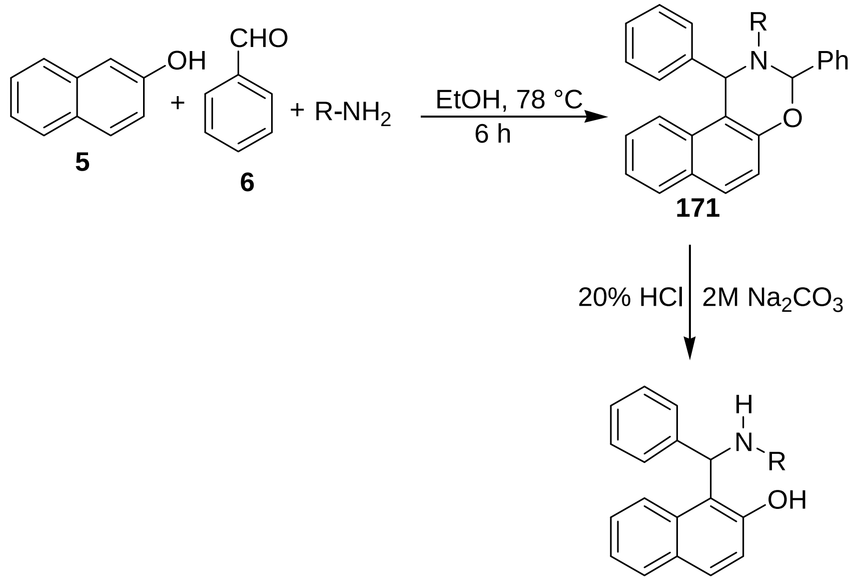
Generally, the derivatives of the Betti aminonaphthols are prepared by condensing the β-naphthol, benzaldehyde and amines in the ratio of 1:2:1 in ethanol or dichloromethane for 6 days (Scheme 12).[30, 81]

Scheme 12



These reactions suffer from the requirement of a long reaction time. In our laboratory the above procedure was modified and reactions were carried out using ethanol as solvent under reflux conditions. The reactions were completed within 6-12 h under these conditions. Thus, the derivatives of the aminonaphthol **9** are readily prepared in good yields by condensation of β-naphthol **5**, benzaldehyde **6** and 1^o or 2^o amines in ethanol at 78 ^oC for 6-12 h (Schemes 13 and 14).[82]

Scheme 13

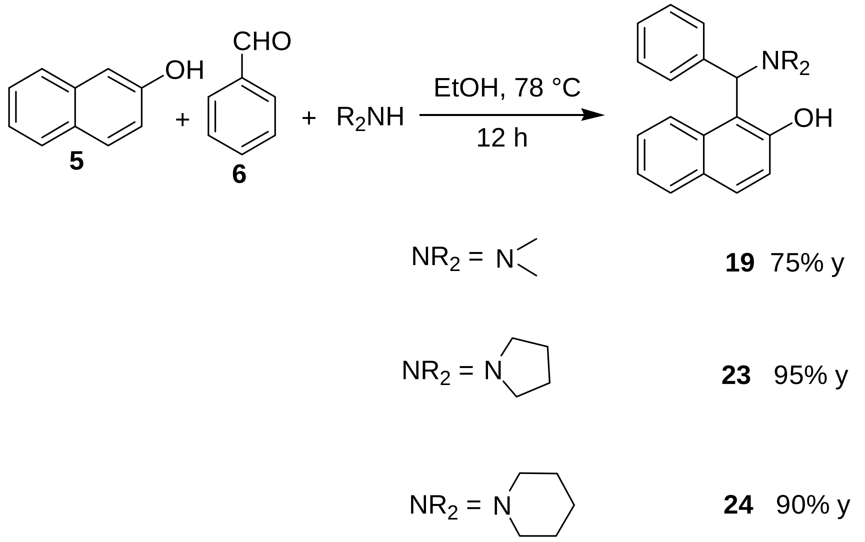


R = C_4H_9- **18** 70% y

R = Ph-CH_2- **36** 70% y

R = Ph- **172** 75% y

Scheme 14



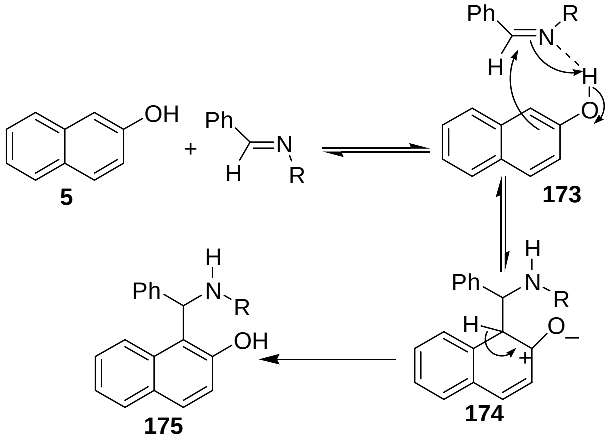
19 75% y

23 95% y

24 90% y

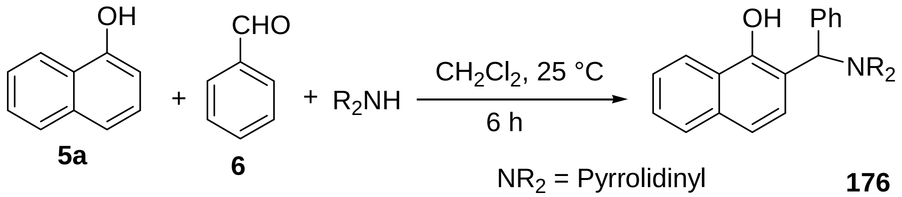
In the preparation of aminonaphthols **18**, **36** and **172** using 1^o amines, the yields were moderate to good as the aminonaphthols could react further with benzaldehyde to give the oxazine compounds as outlined in the introductory section (Scheme 1). However, use of 2^o amines gives the products **19, 23** and **24** in excellent yields. We have observed that the reaction did not take place using β-methoxynaphthalene, α-bromo-β-naphthol and phenol. The mechanism of this transformation involves the intermediacy of an imine, followed by the addition of β-naphthol. The OH group of naphthol protonates the C=N nitrogen through a 'double' activation pathway. This activation consists of increasing of the elecrtophilicity of the imine and the enhancement of the electron density at the α-position of the naphthalene ring. The unreactivity of the β-methoxynaphthalene can be readily explained by this mechanism (Scheme 15).

Scheme 15. Possible mechanism for the synthesis of aminonaphthols



We have applied this methodology for the synthesis of 1-naphthol derivatives as well (Scheme 16).

Scheme 16. Synthesis of aminonaphthols *via* the reactions of α–naphthol, benzaldehyde and 2^{o} amines



NR_2 = Pyrrolidinyl	**176**	83% y
NR_2 = Piperidinyl	**177**	75% y
NR_2 = *N*-methylpiperizinyl	**178**	78% y

The structure of the compound **176** was confirmed by single crystal X-ray analysis (Figure 3.

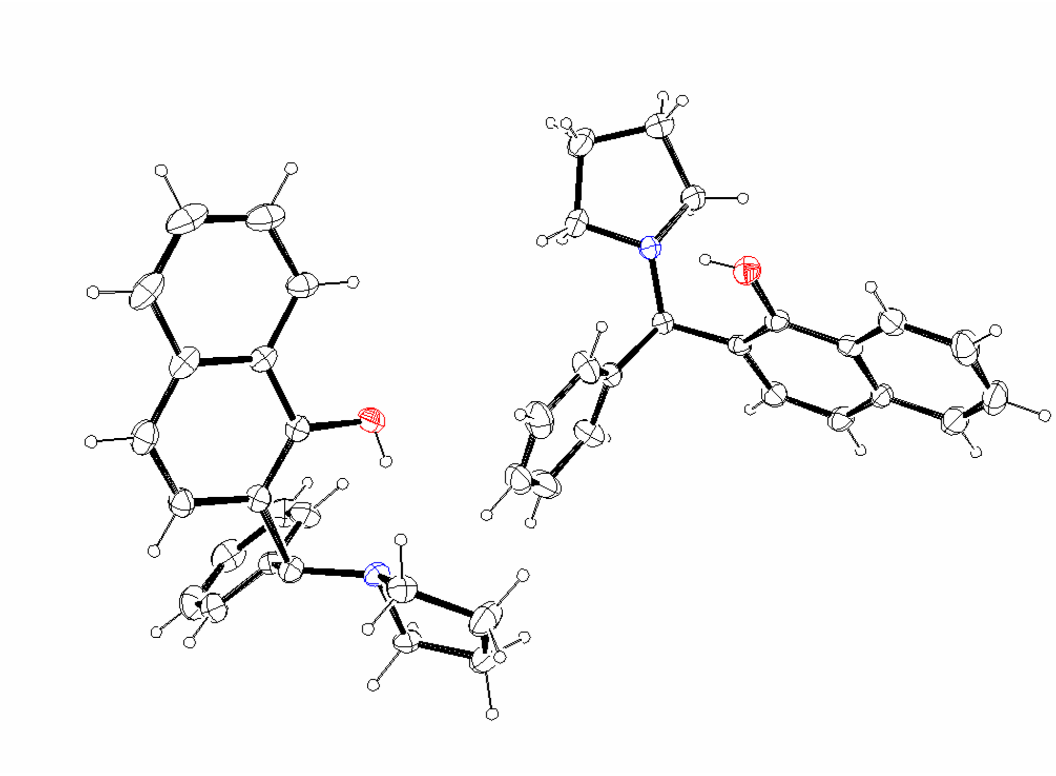


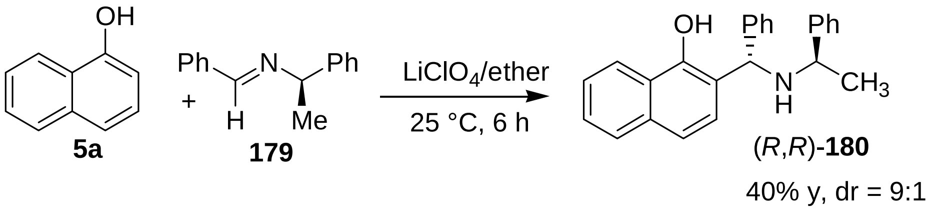
Figure 3 ORTEP diagram of the aminonaphthol **176** (thermal ellipsoids are drawn at 20% probability)

Table 1. Crystal data and structure refinement of racemic aminonaphthol 176

Empirical formula	$C_{84} H_{80} N_4 O_4$
Formula weight	1209.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 14.510 Å, α = 90°
	b = 15.210 Å, β = 98.57 (3)°
	c = 15.210 Å, γ = 90°
Volume	3299.7 $Å^3$
Z	2
Calculated density	1.217 mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	1288
θ Range for data collection	1.81 to 25.01°
Limiting indices	$0 \leq h \leq 17$, $0 \leq k \leq 18$, $-17 \leq l \leq 17$
Reflections collected/unique	5801 / 5801 [R(int) = 0.0000]
Completeness $2\theta = 25.01$	99.9 %
Refinement method	full-matrix least-square on F^2
Data / restraints / parameters	5801 / 0 / 415
Goodness-of-fit on F^2	1.003
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0704$, $wR_2 = 0.1337$
R indices (all data)	$R_1 = 0.1861$, $wR_2 = 0.1816$
Largest diff. peak and hole	0.443 and -0.180 $eÅ^{-3}$

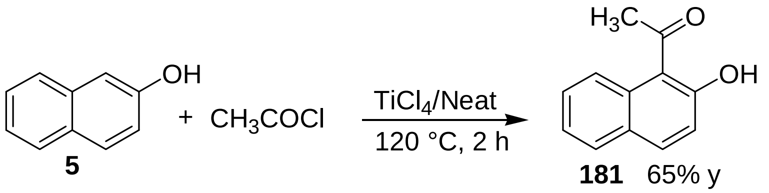
Attempts to resolve aminonaphthols **176-178** using resolving agents like *L*-(+)-tartaric acid, dibenzoyl-*L*-tartaric acid and BINOL-boric acid were unsuccessfull. Further studies for the preparation of chiral compounds using α-naphthol was not pursued, as a paper appeared on the synthesis of chiral aminonaphthol **180** using imine derived from chiral (*R*)-α-methylbenzylamine **179** during the course of our studies (Scheme 17).[33]

Scheme 17



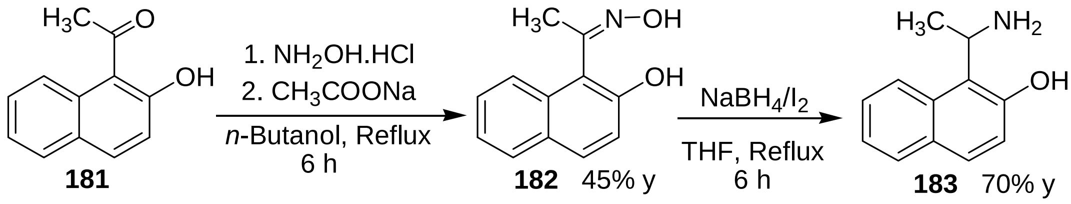
Reactions using these substituted napthols are applicable only to aromatic aldehydes and use of aliphatic aldehydes did not give the corresponding aminonaphthols. Hence, we developed a simple and convenient methodology for the synthesis of aliphatic aminonaphthols using 1-acetyl-2-naphthol **181** as precursor. This precursor was easily prepared by the Fries rearrangement of the intermediate prepared *in situ* from β-naphthol and acetyl chloride using $TiCl_4$ as catalyst (Scheme 18).

Scheme 18



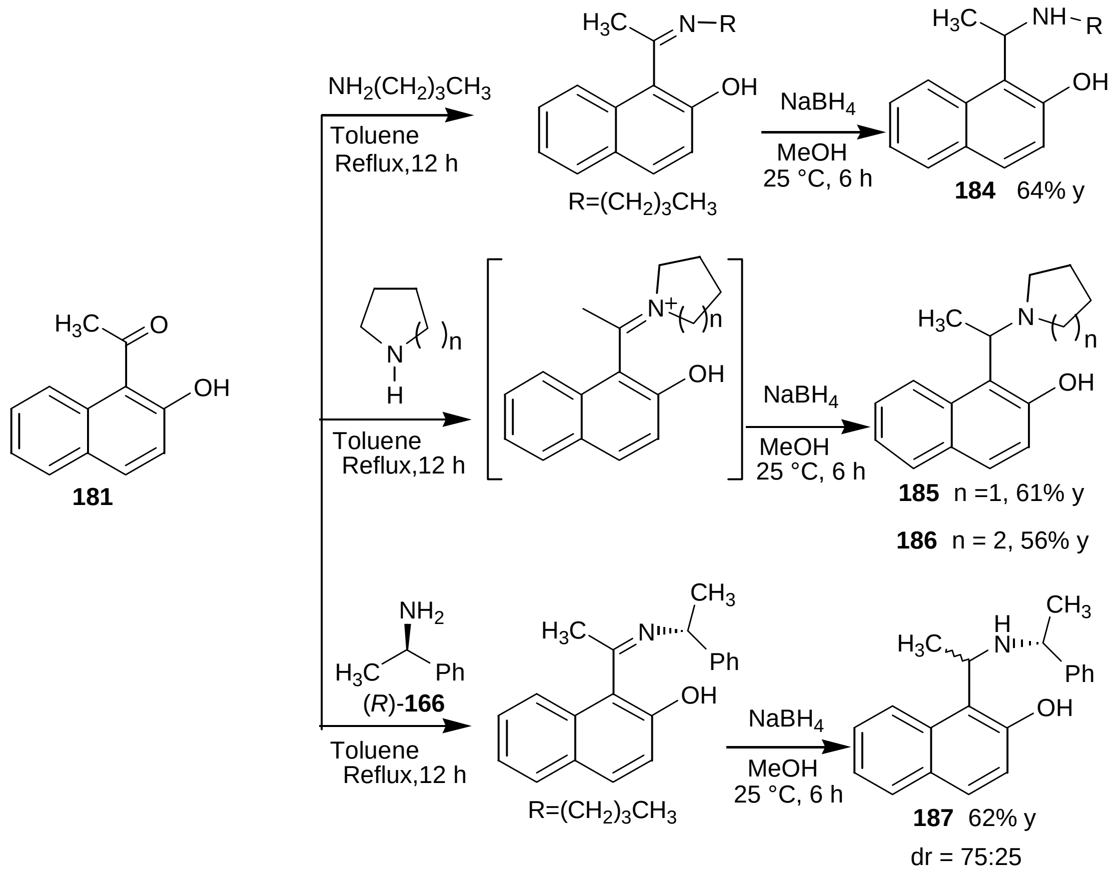
The corresponding oximes were prepared by following a reported procedure.[83] Reduction of oximes to the corresponding aminonaphthols was readily carried out by using the simple and easy to handle $NaBH_4/I_2$ reagent system (Scheme 19).[82]

Scheme 19



The aminonaphthol **183** is known to be highly unstable.[84] Hence, we have synthesized the corresponding secondary amine derivatives as outlined in Scheme 20.

Scheme 20



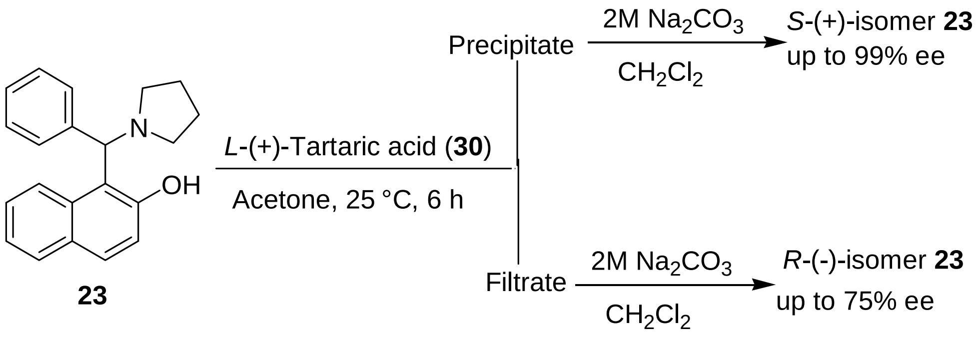
Synthesis of chiral aminonaphthol **187** was carried out using chiral (*R*)-α-methylbenzylamine. The ^{1}H as well as ^{13}C NMR spectra of compound **187** indicates the presence of two diastereomers (*R*,*R* and *R*,*S*) with a diastereomric ratio of 75:25.

2.1.3 Resolution of aminonaphthols

In recent years, there has been an immense research efforts in asymmetric synthesis to obtain enantiopure organic compounds compared to development of new methods of resolutions. However, still resolution methods are widely used in large-scale preparations, especially if both the enantiomers are required.[85] In continuation of development of new methods of resolution to obtain important chiral reagents,[86-93] we have undertaken studies on the resolution of aminonaphthols through formation of diastereomeric complexes using readily available, inexpensive chiral resolving agent like *L*-(+)-tartaric acid. It was observed that *L*-(+)-tartaric acid **30** formed diastereomeric complex with aminonaphthol **23** (Scheme 21). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically.[94]

2.1.3.1 Resolution of racemic aminonaphthol 23 using the inexpensive *L*-(+)-tartaric acid 30

Scheme 21



To optimize the reaction conditions, we have initially examined the resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol **23** using various solvents like acetone, THF, CH_2Cl_2, CH_3CN, ethanol and methanol. In all these solvents, aminonaphthol **23** gave precipitate within 30 minutes leading to partial resolutions. The results are summarized in Table 2.

Table 2. Effect of various solvents on the resolution of aminonaphthol 23[a]

S.No	Time	Solvent	Chiral aminonaphthol **23** obtained from			
			Precipitate		Filtrate	
			% ee[b]/Conf.	Yield(%)[c]	% ee[b]/Conf.	Yield(%)[c]
1[a]	1 h	Acetone	35 (*S*)	45	30 (*R*)	50
2[a]	6 h	Acetone	98 (*S*)	40	75 (*R*)	55
3[a]	12 h	Acetone	95 (*S*)	40	68 (*R*)	50
4[a]	24 h	Acetone	94 (*S*)	38	60 (*R*)	53
5	6 h	CH_2Cl_2	20 (*S*)	35	18 (*R*)	54
6	6 h	CH_3CN	15 (*S*)	40	10 (*R*)	50
7	6 h	THF	35 (*S*)	25	15 (*R*)	65
8	6 h	EtOH	60 (*S*)	30	30 (*R*)	60
9	6 h	MeOH	10 (*S*)	60	15 (*R*)	35

a. Unless otherwise mentioned all the reactions were performed using racemic aminonaphthol **23** (5 mmol) and *L*-(+)-tartaric acid **30** (5 mmol) in 70 mL of the solvent and stirred at 25 °C.

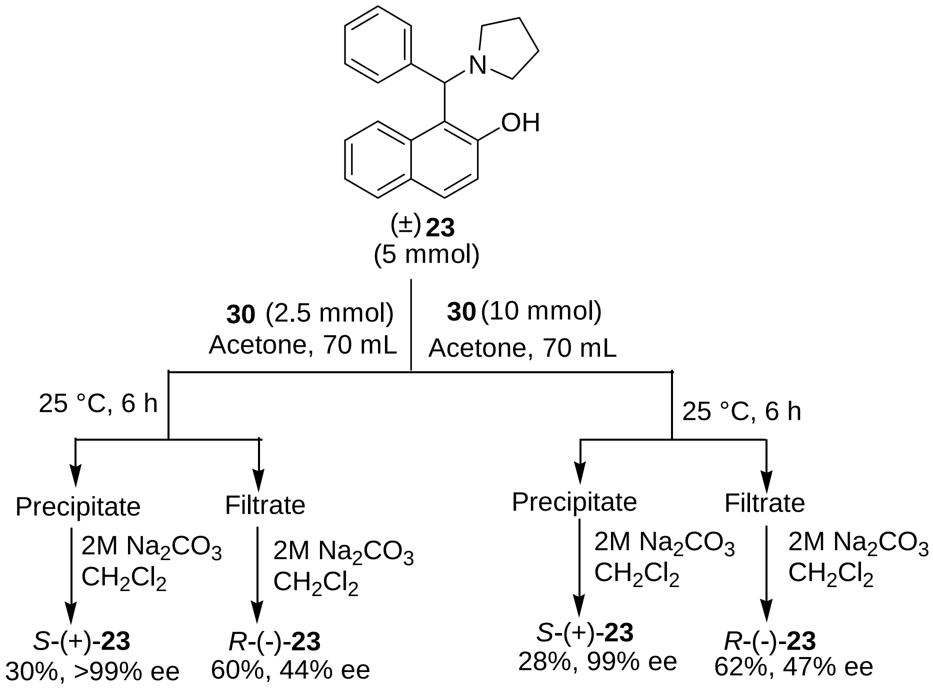
b. All ee values reported here are based on reported maximum[15] $[\alpha]_D^{25}$ = +179.1 (*c* 1.30, $CHCl_3$) for (*S*)-**23** and $[\alpha]_D^{25}$ = -179.0 (*c* 1.30, $CHCl_3$) for (*R*)-**23**. These maximum ee's were further confirmed by using $Eu(tfc)_3$ as chiral shift reagent and HPLC using chiralcel OD-H using 10 % isopropanol in hexane.

c. The yields are of the isolated products, based on the total amount of the starting racemic aminonaphthol **23** used.

Comparisons of these results indicate that acetone is the best solvent for the resolution of the aminonaphthol **23**. Ethanol gave moderate ee and other solvents gave poor results. It was also observed that increasing the reaction time from 1-6 h gave better results (Table 2, entries 1-2) and there was no significant effect on the ees of the samples obtained when the reaction was carried out for more than 6 h (Table 2, entries 2-4).

To determine the optimum amount of the chiral resolving agent required for the resolution process, we have studied the effect of concentration of *L*-(+)-tartaric acid **30** (Scheme 22).

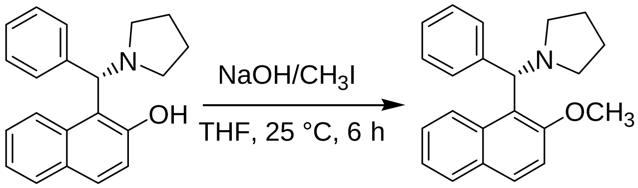
Scheme 22



It is clear that irrespective of the ratio of aminonaphthol **23** and *L*-(+)-tartaric acid **30** (1:2 or 2:1), always enantiomerically pure sample of *S*-(+)-**23** obtained from precipitate fraction and the *R*-(-)-**23** samples were obtained in 44-47% ee from the filtrate fraction.

The aminonaphthol (*S*)-(+)-**169** was prepared starting from chiral aminonaphthol (*S*)-**23** by simple *O*-methylation (Scheme 23).

Scheme 23



(*S*)-**23**

(*S*)-**169**
94% y

The borane complex of aminonaphthylether (*S*)**-169** was prepared to carry out asymmetric hydroboration reaction of *trans*-stilbene using TBAB (**216**)/MeI reagent system. Details regarding the application of the reagent system for use in asymmetric reductions and hydroboration studies will be discussed in section 2.2 and 2.3

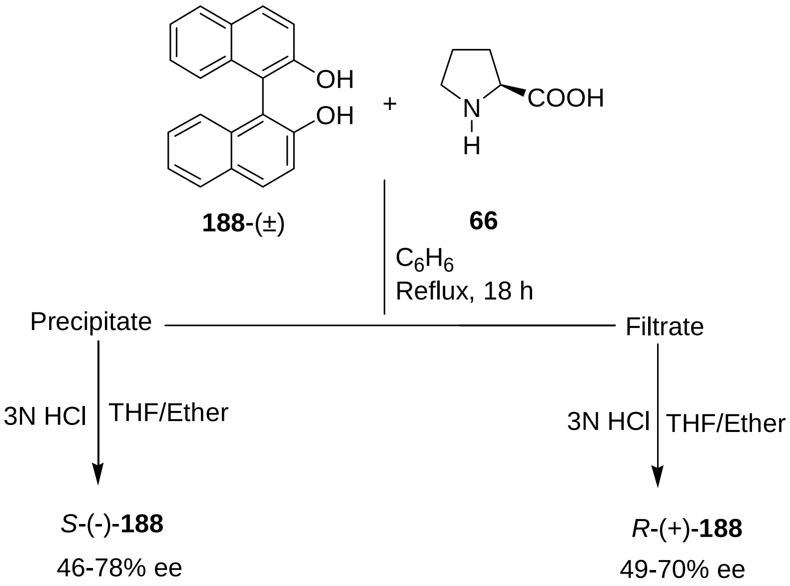
2.1.4 Applications of chiral aminonaphthols

As outlined in the introductory section, there are only a very few reports available on the applications of the readily accessible chiral aminonaphthols. So, we have undertaken to examine the synthetic applications of some of these readily accessible chiral aminonaphthols.

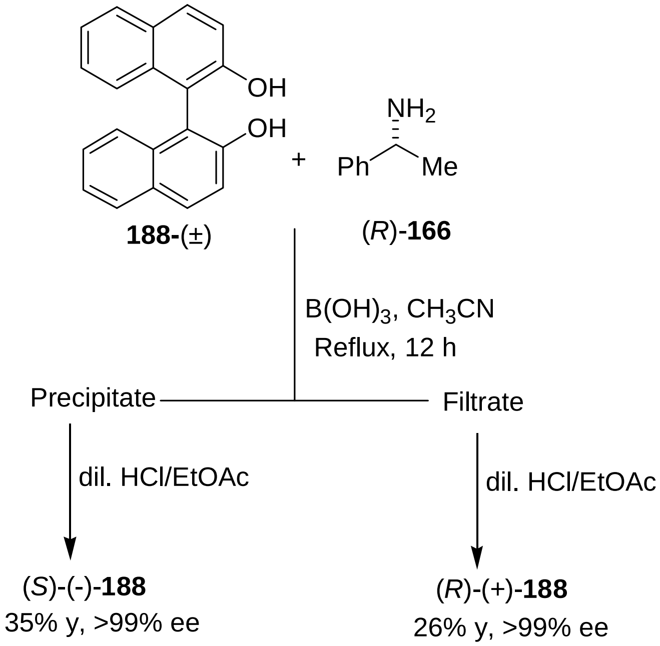
2.1.4.1 Resolution of 1,1'-bi-2-naphthol using chiral aminonaphthol 23 and boric acid

Previously, it was observed in this laboratory that 1,1′-bi-2-naphthol (BINOL) **188** can be readily prepared in enantiomerically pure form by preparation of diasteriomeric complexes using *S*-proline **66** (Scheme 24) or borate complexes using chiral α-methylbenzylamine (*R*)-**166** and boric acid (Scheme 25).[86-92]

Scheme 24

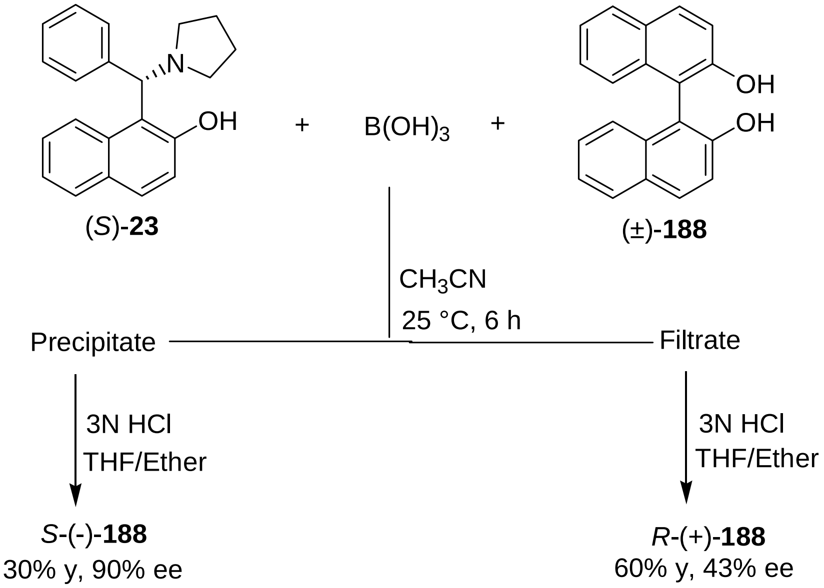


Scheme 25



Accordingly, we have examined the resolution of racemic 1,1'-bi-2-naphthol (BINOL) **188** using the readily accessible aminonaphthol **23** and boric acid through formation of the corresponding diastereomeric borate complexes (Scheme 26).[94]

Scheme 26



It was observed that optimum results were obtained when aminonaphthol, boric acid and BINOL were taken in ratio of 1:1:1. For example, the racemic BINOL **188** reacts with aminonaphthol (*S*)-**23** and boric acid in CH_3CN solvent to give precipitate and filtrate fractions. After digestion of the precipitate fraction, BINOL **188** enriched in (*S*)-isomer (90 % ee) was obtained. After work up, (*R*) isomer of **188** (43% ee) was obtained from the filtrate fraction. These results are summarized in Table 3.

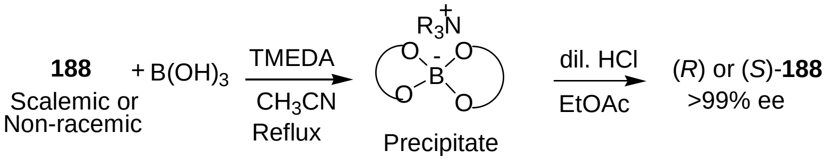
Table 3. Resolution of BINOL 188 using aminonaphthol 23 and boric acid [a]

S. No.	BINOL **188**	**23**	BINOL **188** obtained from			
			Precipitate		Filtrate	
	%ee	*S* or *R*	%ee[b]/Conf.	Yield(%)[c]	%ee[b]/Conf.	Yield(%)[c]
1[a]	0	(*S*)	90 (*S*)	30	43 (*R*)	60
2[d]	0	(*S*)	82 (*S*)	35	45 (*R*)	50
3[e]	0	(*S*)	30 (*S*)	30	20 (*R*)	62
4[f]	90 (*S*)	(*S*)	99 (*S*)	80	10 (*S*)	10
5[f]	43 (*R*)	(*R*)	75 (*R*)	45	20 (*R*)	38
6[f]	75 (*R*)	(*R*)	99 (*R*)	65	15 (*R*)	20
7[a]	0	(*R*)	88 (*R*)	32	45 (*S*)	57
8[d]	0	(*R*)	78 (*R*)	30	40 (*S*)	55
9[e]	0	(*R*)	32 (*R*)	29	18 (*S*)	60

a. Unless otherwise mentioned all the reactions were performed using racemic **188** (5 mmol), boric acid (5 mmol) and aminonaphthol **23** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.
b. All ee values reported here are based on reported maximum[72] $[\alpha]_D^{25}$ = +35 (*C* 1, THF) for (*R*)-**188**.
c. The yields are of the isolated products, based on the total amount of the starting non-racemic mixture.
d. Racemic **188** (5 mmol), boric acid (2.5 mmol) and aminonaphthol **23** (5 mmol) in 50 mL of the acetonitrile solvent and stirred at 25 °C for 6 h.
e. Racemic **188** (10 mmol), boric acid (5 mmol) and aminonaphthol **23** (5 mmol) in 50 mL of the acetonitrile solvent and stirred at 25 °C for 6 h.
f. Non-racemic **188** (5 mmol), boric acid (5 mmol) and aminonaphthol **23** (5 mmol) in 50 mL of the CH_3CN solvent and stirred at 25 °C for 6 h.

The non-racemic 1,1'-bi-2-naphthol **188** could be purified to obtain samples of 99% ee using $B(OH)_3$ and TMEDA following a procedure reported from this laboratory (Scheme 27).[88]

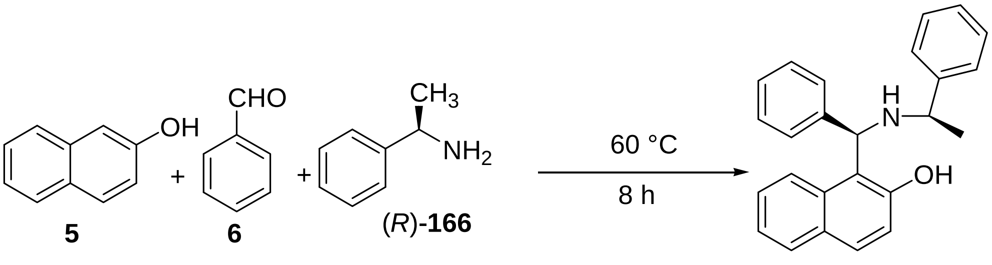
Scheme 27



2.1.4.2 Resolution of ibuprofen 189 and mandelic acid 190.

One of the widely used chiral resolving agents in industry is chiral α-methylbenzylamine. However, this low molecular weight liquid amine pose problems during recovery. The corresponding chiral aminonaphthol **41** can be readily accessed using chiral (*R*)-α-methylbenzylamine **166** (Scheme 28).[95]

Scheme 28



(*R,R*)-**41**, 83% y, >99% ee

We have observed that this readily accessible aminonaphthol **41** is useful for the resolution of ibuprofen **189** and mandelic acid **190.** The ibuprofen **189** forms a salt with aminonaphthol **41** in acetone to give precipitate and filtrate fractions which upon further work up gives partially resolved enriched samples of **189** (Scheme 29, Table 4).

Scheme 29

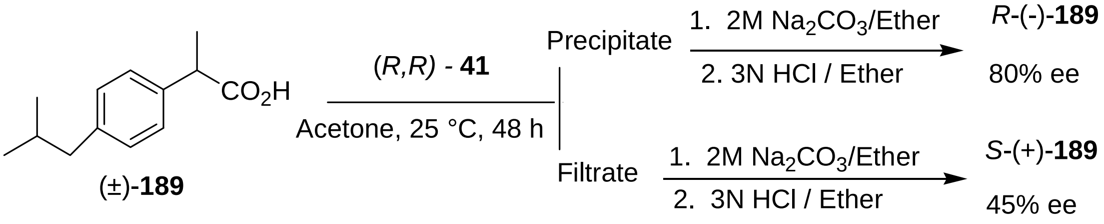


Table 4. Resolution of racemic ibuprofen 189 using aminonaphthol 41[a]

Entry	(*R,R*)-**41** (equiv.)	Solvent (mL)	Precipitate			Filtrate		
			% ee[b]	Conf.[c]	Yield[d](%)	% ee[b]	Conf.[c]	Yield[d](%)
1	0.5	Acetone (2.5)	83	*R* (-)	19	24	*S* (+)	59
2	1	Acetone (2.5)	73	*R* (-)	31	38	*S* (+)	66
3	2	Acetone (6)	75	*R* (-)	28	31	*S* (+)	65
4	3	Acetone (10)	81	*R* (-)	24	33	*S* (+)	69
5[e]	1	Acetone (13)	80	*R* (-)	34	45	*S* (+)	60
6[f]	1	Acetone (5)	97	*R* (-)	44	57	*R* (-)	42
7[g]	1	Acetone (13)	78	*S* (+)	32	42	*R* (-)	67
8[h]	1	Acetone (5)	98	*S* (+)	35	64	*S* (+)	59
9	1	CH_3CN (5)	83	*R* (-)	12	14	*S* (+)	71
10[i]	(*S*)-**166**	Acetone (7)	42	*R* (-)	52	56	*S* (+)	35

a. Unless otherwise mentioned all reactions were carried out using (2 mmol) of (*R,R*) aminonaphthol **41**, (2 mmol) of racemic ibuprofen **189** stirred at 25 °C for 48 h.

b. Determined by HPLC analysis using the chiral column, Chiralcel OD-H, 980:20:2.5, hex:*i*-PrOH:TFA, 0.5 mL/min.

c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.

d. The yields are of the isolated products.

e. Reaction carried out using (10 mmol) of (*R,R*) aminonaphthol **41**, (10 mmol) of ibuprofen **189** stirred at 25 °C for 48 h.

f. Non-racemic ibuprofen **189** (4 mmol) and aminonaphthol **41** (4 mmol) were stirred at 25 °C for 48 h.

g. Reaction carried out using (10 mmol) of (*S,S*) aminonaphthol **41**, (10 mmol) of ibuprofen **189** stirred at 25 °C for 48 h.

h. Non-racemic ibuprofen **189** (3 mmol) and (*S,S*) aminonaphthol **41** (3 mmol) were stirred at 25 °C for 48 h.

i. Reaction carried out using (2 mmol) of (*R*)-α-phenylethylamine **166**, (2 mmol) of ibuprofen **189** stirred at 25 °C for 48 h.

Increasing the quantity of aminonaphthol did not lead to a significant change in the ee of sample obtained from the precipitate fraction (Table 4, entries 2-4). The partially resolved *R*-(-)-**189** sample can be further enriched to essentially pure enantiomer by repeating the procedure (entries 6 and 8). Also, *S*-(+)-**189**-ibuprofen is obtained from the precipitate fraction by using (*S,S*) aminonaphthol **41** (entry 7). Use of other solvents like CH_3CN did not provide the desired yields (entry 9). We have also carried out the resolution using (*R*)-α-phenylethylamine **166** (entry 10) under similar reaction conditions and found that the results are better using the aminonaphthol **41**.

The CH_3CN proved to be ideal solvent for mandelic acid **190**. It was found that the racemic mandelic acid reacts with aminonaphthol **41** in CH_3CN to give the precipitate and filtrate fractions (Scheme 30, Table 5). After digestion of the precipitate fraction with 2M Na_2CO_3/Ether mixture, followed by acidification of the aq. layer with 3N HCl, mandelic acid **190** enriched in (*R)*-(-) enantiomer (85% ee) was obtained. After workup, (*S*)-(+)-**190** isomer (38% ee) was obtained from the filtrate fraction. Similarly (*S*)-(+)-**190** mandelic acid can be obtained from the precipitate fraction by using readily accessible (*S,S*) aminonaphthol **41** as done earlier for ibuprofen(entry 5). These partially resolved samples were further enriched to enantiopure samples of up to 97% ee (entries 4 and 6).

Scheme 30

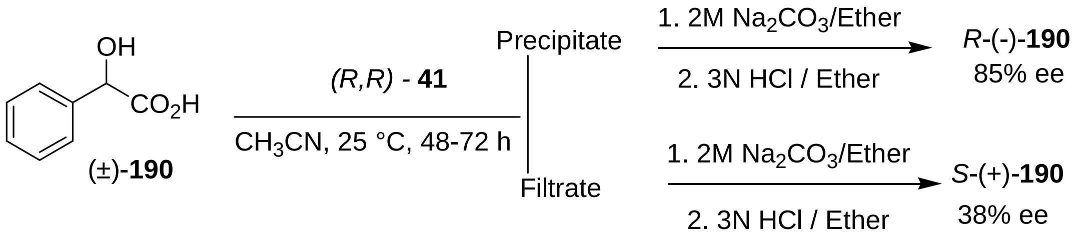


Table 5. Resolution of racemic mandelic acid 190 using aminonaphthol 41[a]

Entry	Solvent (mL)	Precipitate			Filtrate		
		% ee[b]	Conf.[c]	Yield[d]	% ee[b]	Conf.[c]	Yield[d]
1[e]	CH_3CN (2)	82	*R* (-)	20	21	*S* (+)	76
2	CH_3CN (2)	85	*R* (-)	29	38	*S* (+)	64
3[f]	CH_3CN (5)	82	*R* (-)	24	20	*S* (+)	71
4[g]	CH_3CN (2)	97	*R* (-)	61	26	*R* (-)	27
5[h]	CH_3CN (5)	79	*S* (+)	24	23	*R* (-)	70
6[i]	CH_3CN (1)	97	*S* (+)	56	24	*S* (+)	41
7	THF(3)	81	*R* (-)	16	17	*S* (+)	66
8	Acetone (2.5)	46	*R* (-)	27	61	*S* (+)	62

a. Unless otherwise mentioned all reactions were carried out using (2 mmol) of aminonaphthol (*R,R*)-**41**, (2 mmol) of racemic mandelic acid **190** stirred at 25 °C for 48 h.

b. Determined by HPLC analysis using the chiral column, Chiralcel OD-H, 875:125:2.5, hex:*i*-PrOH:TFA, 0.5 mL/min.

c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.

d. The yields are of the isolated products.

e. Racemic mandelic acid **190** (2 mmol) and aminonaphthol (*R,R*)-**41** (2 mmol) stirred at 25 °C for 24 h.

f. Racemic mandelic acid **190** (5 mmol) and aminonaphthol (*R,R*)-**41** (5 mmol) stirred at 25 °C for 72 h.

g. Non-racemic mandelic acid **190** (1 mmol) and aminonaphthol (*R,R*)-**41** (1 mmol) stirred at 25 °C for 24 h.

h. Racemic mandelic acid **190** (5 mmol) and aminonaphthol (*S,S*)-**41** (5 mmol) were stirred at 25 °C for 72 h.

i. Non-racemic mandelic acid **190** (1 mmol) and aminonaphthol (*S,S*)-**41** (1 mmol) stirred at 25 °C for 24 h.

2.2 Synthesis and applications of amines and diamines

2.2.1 Synthesis of chiral ligands containing α,α-2-diphenylpyrrolidinemethane 122 and α,α-2-diphenylpyrrolidinemethanol 68 moiety

We have undertaken studies on the synthesis of chiral ligands with amines **68** and **122** using bromocompounds **196, 197** and **206** (Figure 4).

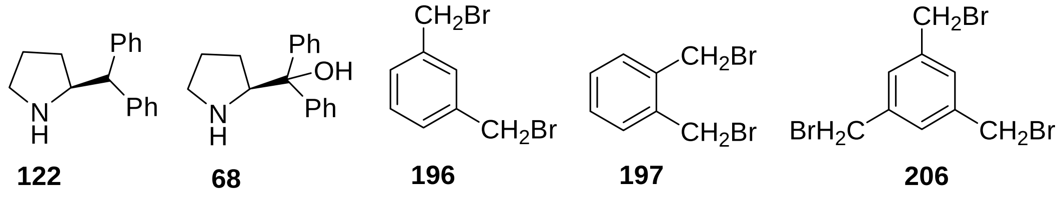
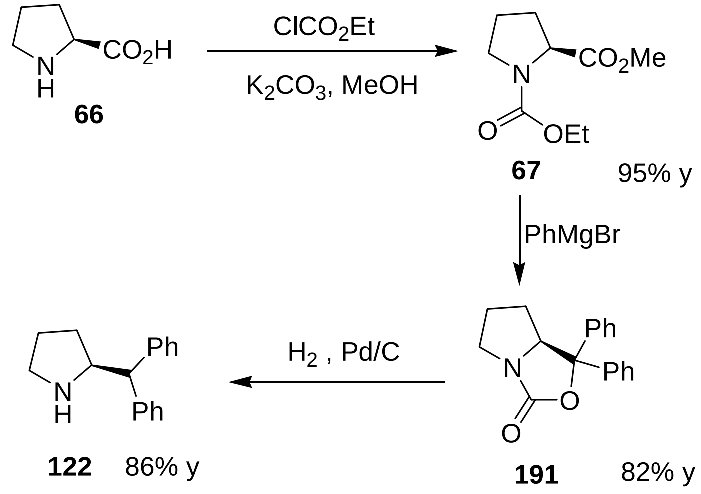


Figure 4

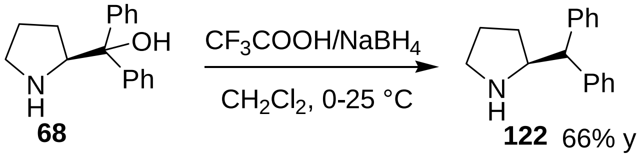
Preparation of (*S*)-2-diphenylmethylpyrrolidine **122** was reported by Hagan *et. al.* using (*S*)-L-proline in a three step sequence of reactions. This pyrrolidine was assessed as a chiral solvating agent for carboxylic acids and some secondary alcohols (Scheme 31).[96]

Scheme 31



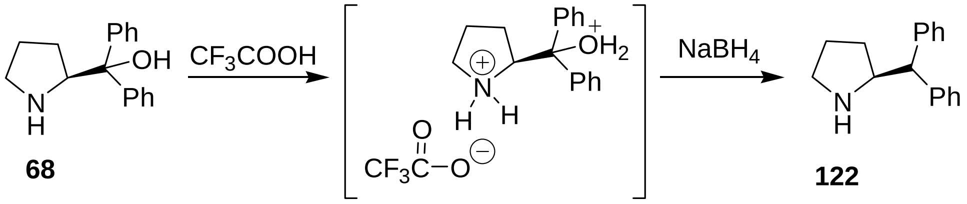
We have developed a simple method for synthesis of (*S*)-2-diphenylpyrrolidinemethane **122** starting from the commercially available (*S*)-diphenylpyrrolidinemethanol **68** by the reaction with trifluroacetic acid and sodium borohydride with retention of configuration (Scheme 32).

Scheme 32



A tentative mechanism for the conversion involving protonation by trifluroacetic acid at the nitrogen as well at the oxygen atom may be considered. The sodium borohydride could then reduce the develping diphenyl carbocation produced *in situ* (Scheme 33).

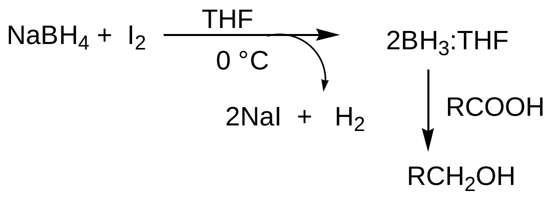
Scheme 33



The $NaBH_4/CF_3COOH$ reagent system was earlier used for reduction of diarylmethanols as well as triarylmethanols to the corresponding hydrocarbons.[97a] Under the same conditions, the reduction of diarylketones to diarylmethanes was also reported.[97b]

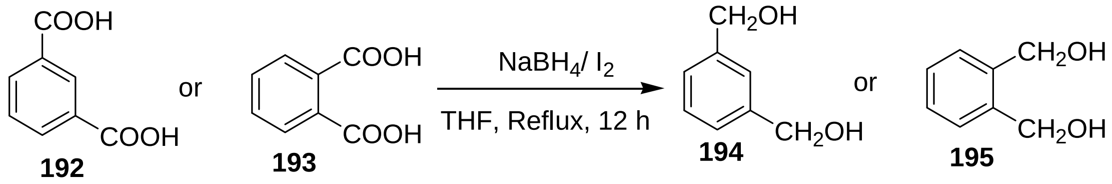
It was also previously reported from this laboratory that carboxylic acids and esters could be readily reduced to the corresponding alcohol by BH_3:THF generated *in situ* from $NaBH_4$ and I_2 (Scheme 34).[98]

Scheme 34



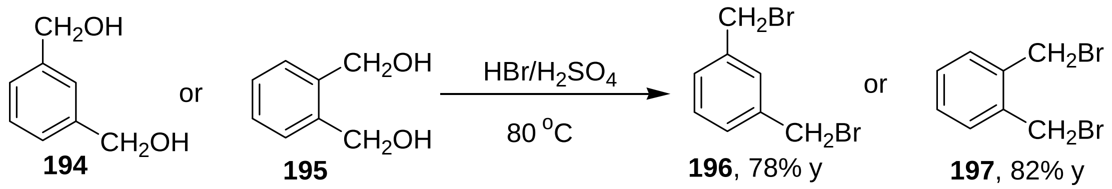
Thus, the reduction of isophthalic **192** and phthalic acid **193** was achieved easily using $NaBH_4$ and I_2 to obtain the corresponding diols **194** and **195** (Scheme 35).

Scheme 35



These diols obtained were as such converted to their respective dibromides **196** and **197** upon reacion with hydrobromic acid and sulphuric acid (Scheme 36).

Scheme 36



Preparation of various chiral diamines and triamines was then carried out using (*S*)-diphenylpyrrolidinemethanol **68** and (*S*)-diphenylpyrrolidinemethane **122** as starting material (Chart 9 and 10).

Chart 9

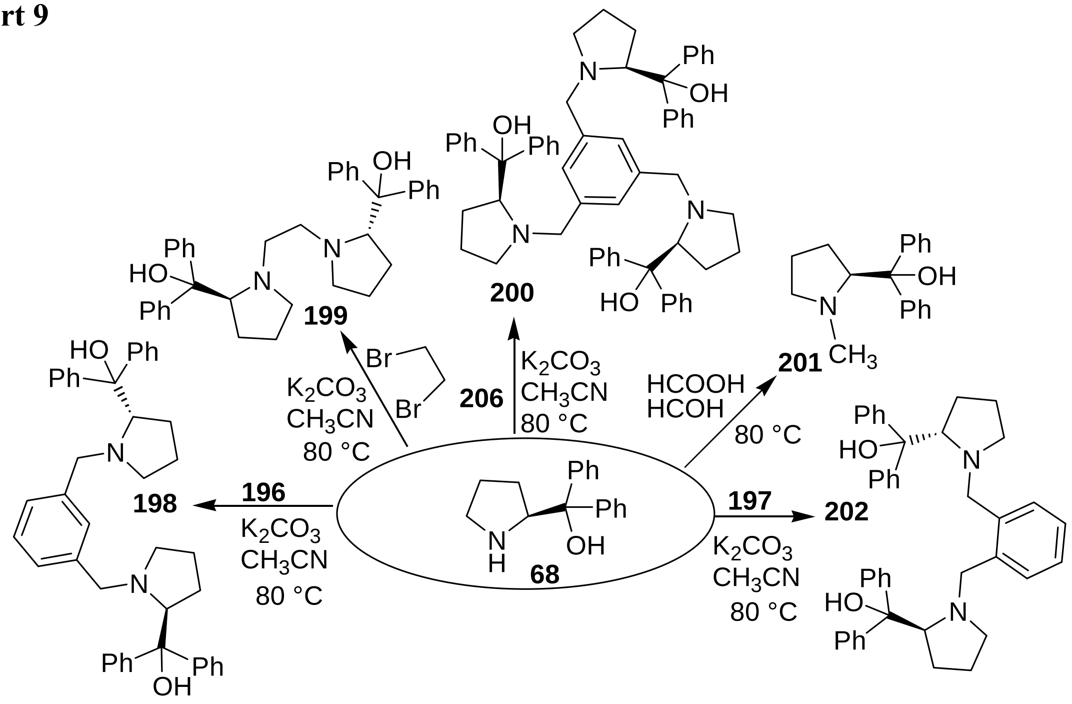
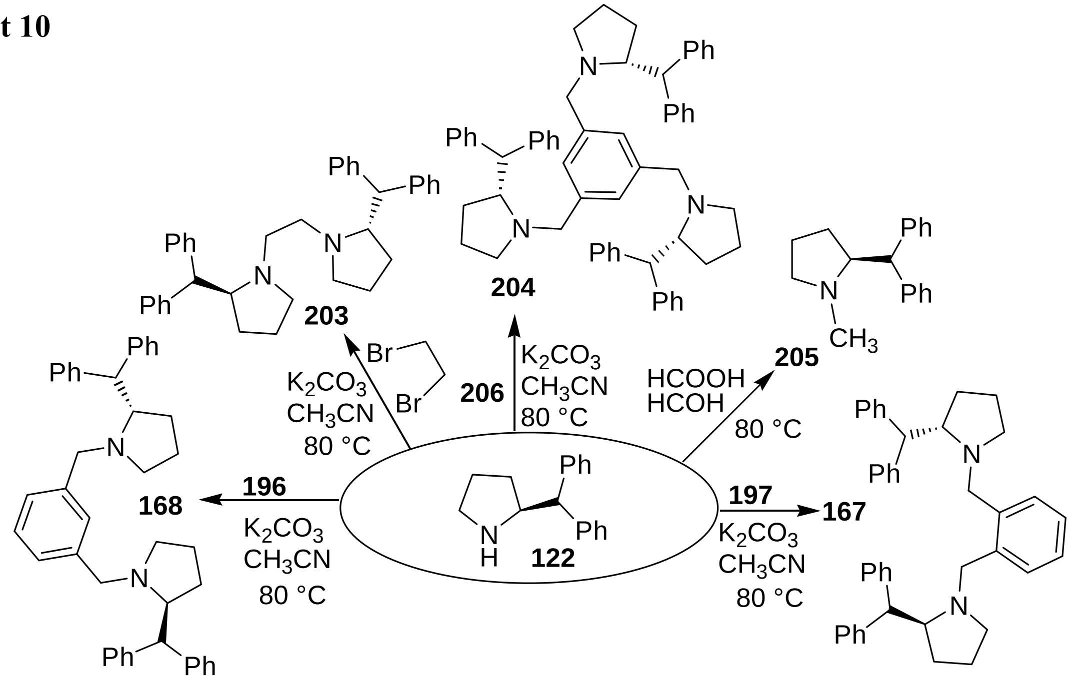


Chart 10



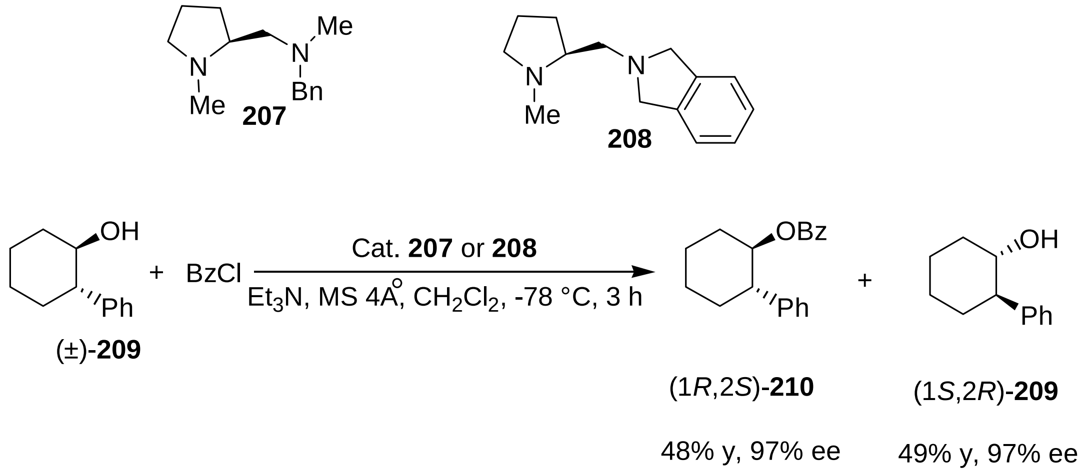
The triamines **200** and **204** were prepared using 1,3,5-tris(bromomethyl)benzene **206**. Studies on the utility of the derivatives for molecular recognition studies and other synthetic applications would lead to fruitful results.

2.2.2 Application in kinetic acylation studies

Kinetic resolution is a promising method to obtain optically active compounds. It has been widely used for the synthesis of complex natural products and their derivatives.[99] Despite the development of some effective methods for enzymatic kinetic resolution,[100] racemate resolution through nonenzymatic, enantioselective acylation pathway has become the focus of research attention over the past few years. It remains as a valuable alternative method for the preparation of optically active compounds.[101]

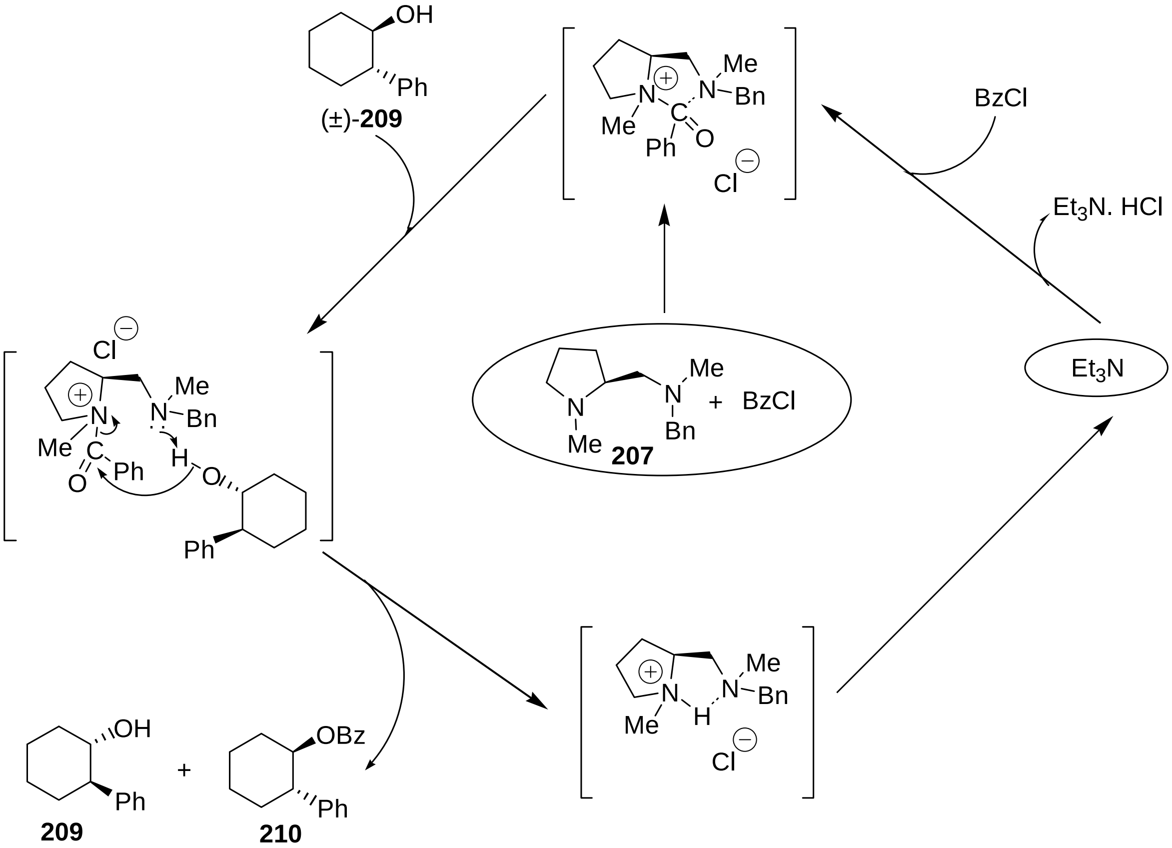
Diamines **207** and **208** prepared from (*S*)-proline were used by *Oriyama et al.*[102] for kinetic resolution of racemic secondary alcohol **209** to obtain both alcohol and ester **210** in enantiopure form (Scheme 37).

Scheme 37



The authors did not clarify the details of the reaction mechanism, but a tentative catalytic cycle can be anticipated for the following process. The two nitrogen atoms of the chiral diamine presumably coordinate to the carbonyl carbon of benzoyl chloride in a rigid and bidentate manner and play a important role in enantioselection (Scheme 38).

Scheme 38



We have examined the use of some of the C_2-symmetric chiral diamines for enantioselective acylation of racemic 1-phenylethanol **138a** and racemic *trans*-2-phenylcyclohexanol **209**. The catalyst **198** and **168** were screened at various conditions using racemic 1-phenylethanol **138a.** It was observed that enantioselective induction was not observed by varying the catalyst, temperature as well as acylating agents (Scheme 39, Table 6).

Scheme 39

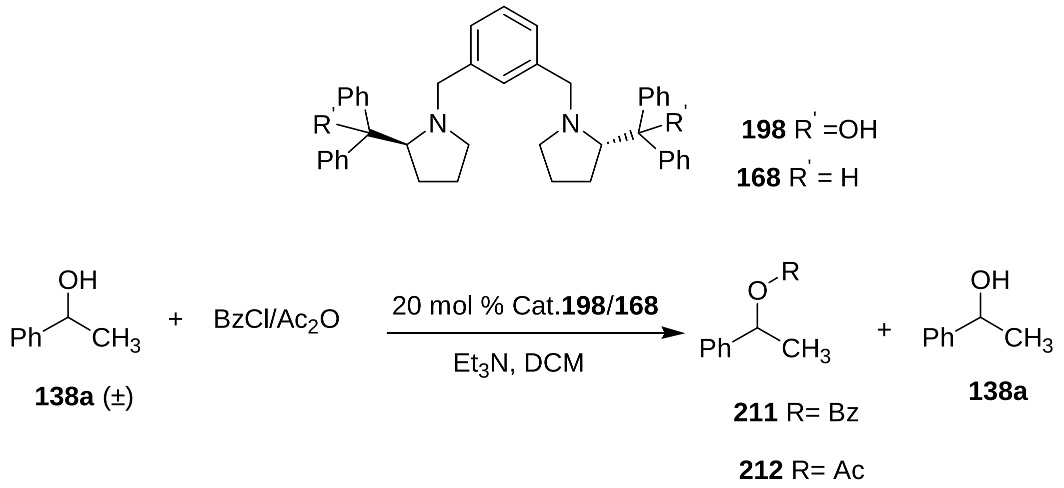


Table 6 Kinetic resolution of (±)1-phenylethanol 138a using catalyst 198/168[a]

S.No	Cat.	Acylating agent	Temp.	Time	Ester (**211/212**) Yield[b](%)	Alcohol **138a** Yield[b] (%)
1	**198**	PhCOCl	25 °C	24 h	**211**, 44	46
2	**198**	PhCOCl	-30 °C	24 h	**211**, 39	48
3	**168**	PhCOCl	-30 °C	24 h	**211**, 38	48
4	**168**	PhCOCl	-78 °C	48 h	**211**, 29	61
5	**198**	$(CH_3CO)_2O$	-30 °C	24 h	**212**, 38	47
6	**168**	$(CH_3CO)_2O$	-30 °C	24 h	**212**, 40	43

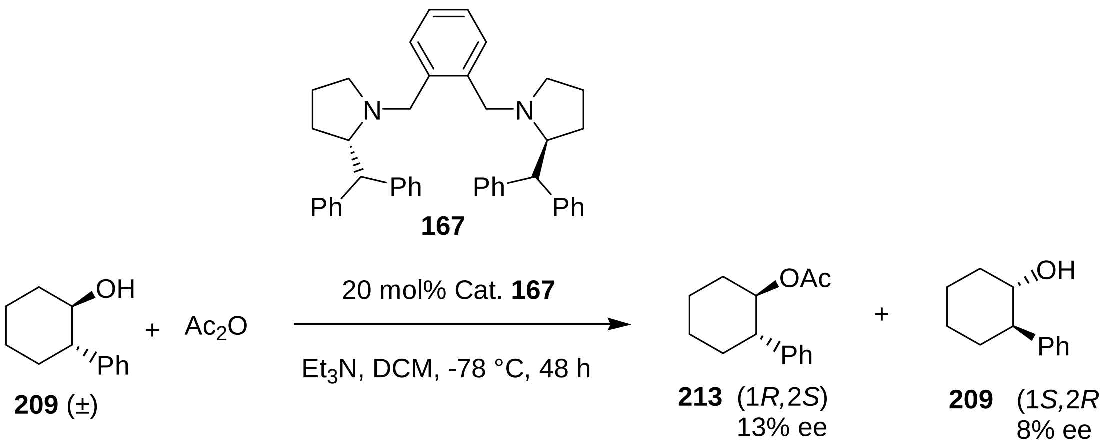
a. The reactions were carried out using **138a** (5 mmol), acylating agent (3.75 mmol) and triethyl amine (3.75 mmol) in CH_2Cl_2 10 mL.

b. The yields are of isolated products.

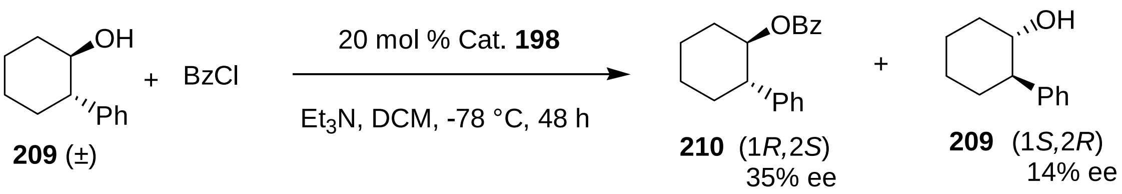
Presumably, the reaction may not follow through the envisaged transition state (Scheme 38) using 1-phenylethanol **138a** as substrate. Use of racemic *trans*-2-phenylcyclohexanol **209** as substrate for kinetic resolution studies provided better results.

We have examined the use of benzoyl chloride and acetic anhydride as acylating agents with C_2-symmetrical ligands **167** and **198** as catalyst. The results are better using benzoyl chloride with diamine **198** (Scheme 40 and 41, Table 7).

Scheme 40



Scheme 41



When reaction using diamine **167** was carried at -25°C, the ester **213** and alcohol **209** were obtained with very low enantioselectivity using acetic anhydride (Table 7, entry 1). Decreasing the temperature led to improvement in enantioselectivity of ester as well as alcohol (Entry 2). Results using benzoyl chloride was found to be better, and the ester product **210** was obtained with moderate selectivity when diamine **198** was used as catalyst (20 mol%) for kinetic resolution of racemic *trans*-2-phenylcyclohexanol **209** (entry 3 and 4).

Table 7 Kinetic resolution of (±) *trans*-2-phenylcyclohexanol 209[a]

S.No	Cat.	Temp.	Time	Ester **213/210** %ee/config.[c]	Ester **213/210** Yield[b](%)	Alcohol **209** %ee/config.[c]	Alcohol **209** Yield[b](%)
1	**167**	-25 °C	48h	**213**, 6 (1*R*,2*S*)[d]	34	2 (1*S*,2*R*)[e]	53
2	**167**	-78 °C	48 h	**213**, 13 (1*R*,2*S*)[d]	27	8 (1*S*,2*R*)[e]	64
3	**198**	-25 °C	48 h	**210**, 14 (1*R*,2*S*)[f]	36	4 (1*S*,2*R*)[e]	55
4	**198**	-78 °C	48 h	**210**, 35 (1*R*,2*S*)[f]	24	14 (1*S*,2*R*)[e]	68

a. The reactions were carried out using **209** (2.5 mmol), acylating agent (1.87 mmol) and triethyl amine (1.25 mmol) in CH_2Cl_2 10 mL.
b. The yields are of isolated products.
c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.
d. Determined by HPLC using the chiral column, Chiralcel AS-H, 99:1, hex:*i*-PrOH, 1.0 mL/min.
e. Determined by HPLC using the chiral column, Chiralcel OD-H, 95:5, hex:*i*-PrOH, 1.0 mL/min.
f. Determined by HPLC using the chiral column, Chiralcel AD-H, 99:1, hex:*i*-PrOH, 1.0 mL/min.

Presumably, under the present set of conditions, the difference in the reactivity of two enantiomers of racemic *trans*-2-phenylcyclohexanol **209** may not be very large enough to get complete selectivity. Careful further investigation of the structural effects of the ligand on the enantioselectivity of the reaction should lead to more fruitful results.

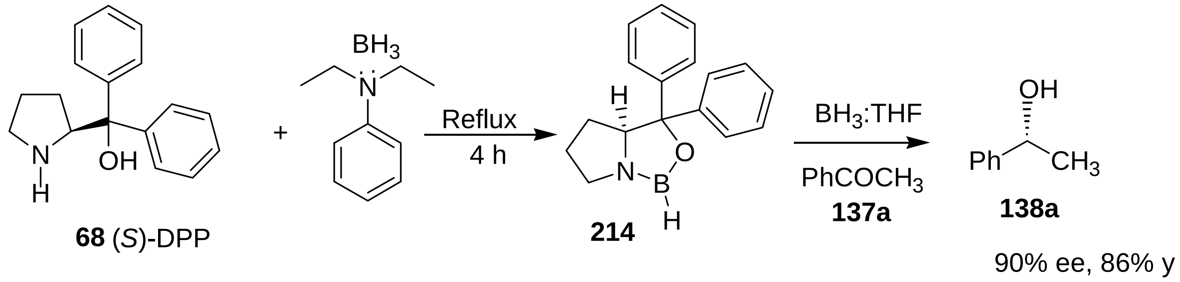
2.3 Efforts towards development of simple methods for asymmetric reductions and hydroborations.

2.3.1 Asymmetric oxazaborolidine reductions

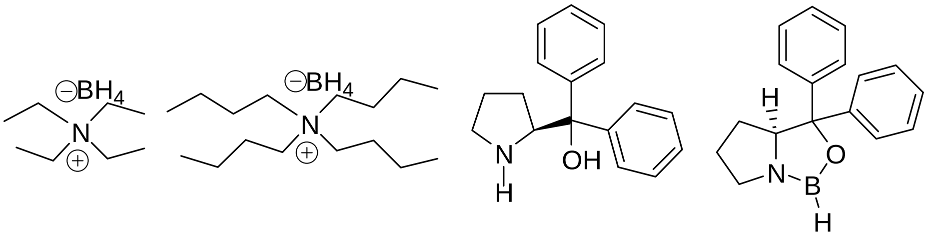
Asymmetric reduction of prochiral ketones is an important methodology for the synthesis of chiral secondary alcohols. The oxazaborolidine (CBS reagent)-catalyzed asymmetric reduction methodology has been extensively used for this purpose.[103-105] Even though the parent catalyst H-CBS **214** prepared *in situ* using α,α-diphenylpyrrolidinemethanol and BH_3:THF has been found to give good results in asymmetric reductions, the corresponding B-methyl derivative **90** is preferred. However, this reduction method has not been entirely satisfactory, particularly for large-scale productions, owing to the requirement of trimethyl boroxine[106a] or methyl boronic acid[106b] and the requirement of complete removal of water from such condensations to avoid undesired effects.[107] The other difficulty is the requirement of the highly reactive reagents such as BH_3:THF,[108,109] borane-SMe_2,[110] borane-1,4-thioxane,[111] catecholborane,[112] and *N*,*N*-diethylaniline-borane[113] (DEANB) complexes for the oxazaborolidine catalyzed asymmetric reduction of ketones.

Although several of these borane complexes are commercially available, these borane carriers suffer from drawbacks to commercial application because of the difficulties in handling and transporting these reagents, especially for large scale applications. We have reported from this laboratory that the BH_3:THF prepared *in situ* using $NaBH_4$ and I_2 in THF is useful for several synthetic applications that require BH_3:THF.[98, 108] Unfortunately, the α,α-diphenylpyrrolidinemethanol **68** and $NaBH_4/I_2$ combination gave poor results in the asymmetric reduction of acetophenone.[109] However good results are obtained using BH_3:THF prepared by passing B_2H_6 generated using $NaBH_4/I_2$ through THF (Scheme 42).

Scheme 42



A major problem in using $NaBH_4$ is that it is only sparingly soluble in THF. Accordingly, we have undertaken studies to examine the use of the readily accessible $R_4N^+BH_4^-$ reagent for this purpose. We found that the $R_4N^+BH_4^-$, CH_3I and (*S*)-α,α-diphenylpyrrolidinemethanol **68** combination is useful for the asymmetric reduction of aryl alkyl ketones to obtain the corresponding alcohols in up to 99% ee (Figure 5).[119a]

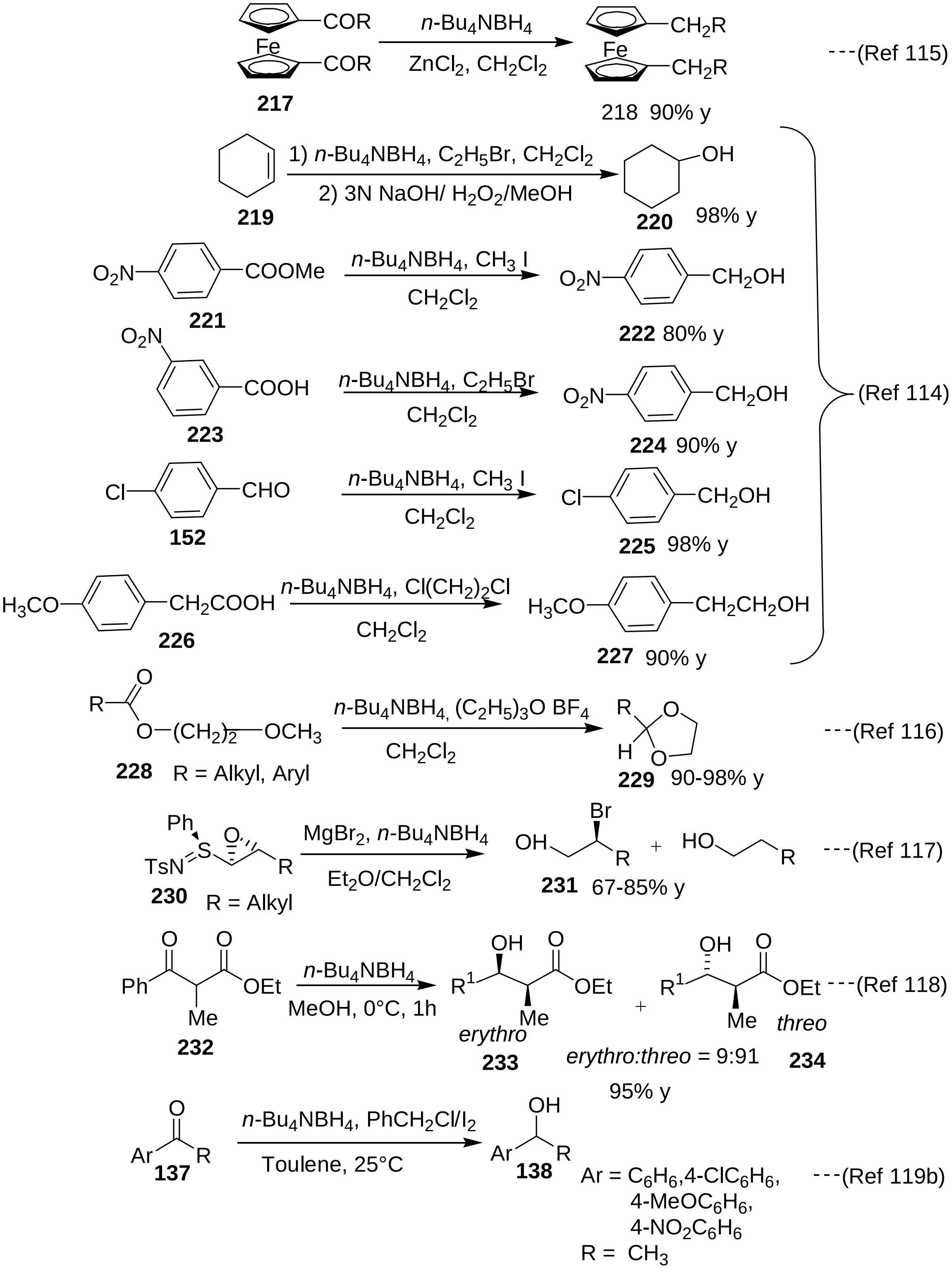


215 TEAB **216** TBAB **68** (*S*)-DPP **214**

Figure 5

Preparation of tetraalkylammonium borohydride ($R_4N^+BH_4^-$) is carried out by means of the ion displacement reaction of sodium borohydride with tetraalkylammonium hydrogen sulphate.[114] The borohydride can be used to prepare solutions of diborane in dichloromethane by reaction with various alkyl halides. The $R_4N^+BH_4^-$ undergoes slow decomposition in chlorinated solvents at room temperature and reflux temperature, presumably due to the reduction of C-Cl bond by the reagent in the order $CH_2Cl_2 < CHCl_3 < CCl_4 < CH_2Cl\text{-}CH_2Cl$. Analysis of the chloroform solution by ^{11}B NMR showed a peak around -27.4 ppm corresponding to $B_2H_7^-$ species, indicating the availability of electrophilic borane (BH_3) species along with the BH_4^- species. It is a mild reducing agent having more solubility in common organic solvents, i.e. polar as well as non-polar. It is considerably easier to handle these reagents compared to other metal borohydrides. Being a solid reagent, it can be stored for longer periods of time without loss of activity and can be handled safely unlike borane which is available as BMS or BH_3-THF which requires careful handling. The $R_4N^+BH_4^-$ species has been reported to have a low reactivity as reducing agent.[114] This is easily realized by the fact that it can be recrystallized from ethyl acetate or even acetone if the operation is rapidly performed. This reagent had been known for some time and it has been used for reduction of a number of representative carbonyl functionalities. Reactions using this borohydride in combination with various alkyl halides/additives are presented in Chart 11.

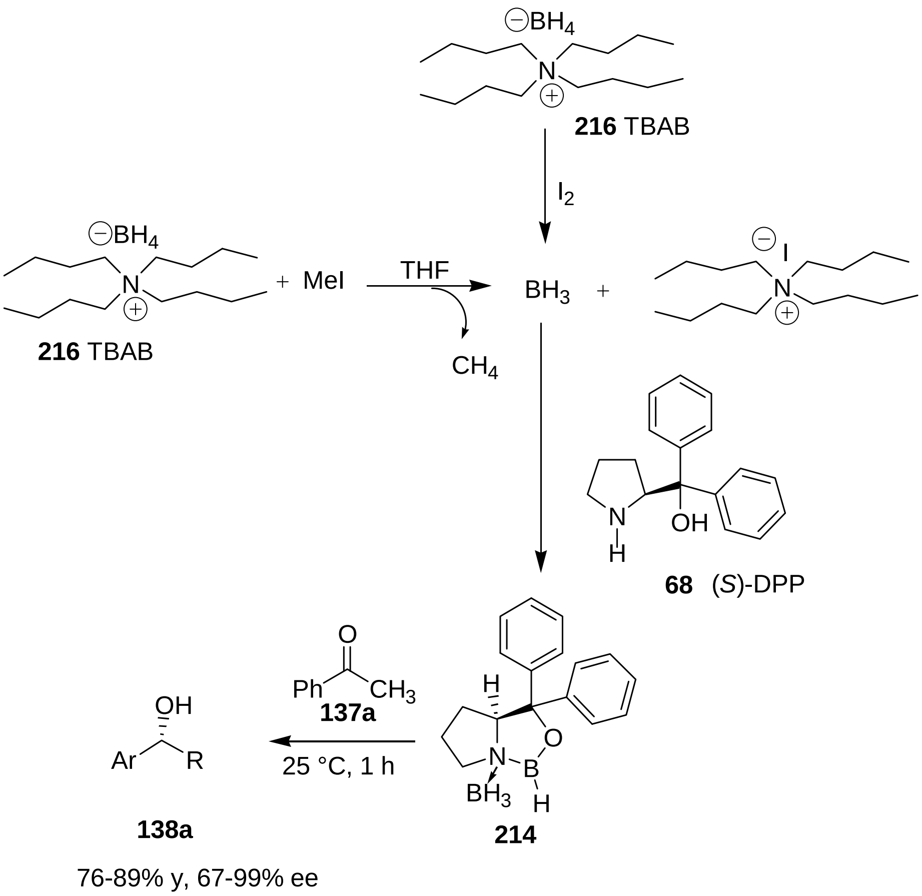
Chart 11



COR
Fe
COR
217
n-Bu4NBH4
ZnCl2, CH2Cl2
CH2R
Fe
CH2R
218 90% y
---(Ref 115)
219
1) n-Bu4NBH4, C2H5Br, CH2Cl2
2) 3N NaOH/ H2O2/MeOH
OH
220 98% y
O2N
COOMe
221
n-Bu4NBH4, CH3 I
CH2Cl2
O2N
CH2OH
222 80% y
O2N
COOH
223
n-Bu4NBH4, C2H5Br
CH2Cl2
O2N
CH2OH
224 90% y
(Ref 114)
Cl
CHO
152
n-Bu4NBH4, CH3 I
CH2Cl2
Cl
CH2OH
225 98% y
H3CO
CH2COOH
226
n-Bu4NBH4, Cl(CH2)2Cl
CH2Cl2
H3CO
CH2CH2OH
227 90% y
R
O
O—(CH2)2—OCH3
228 R = Alkyl, Aryl
n-Bu4NBH4, (C2H5)3O BF4
CH2Cl2
R
H
O
O
229 90-98% y
---(Ref 116)
Ph
TsN
S
O
R
230 R = Alkyl
MgBr2, n-Bu4NBH4
Et2O/CH2Cl2
OH
Br
R
+
HO
R
231 67-85% y
---(Ref 117)
Ph
O
O
OEt
Me
232
n-Bu4NBH4
MeOH, 0°C, 1h
R1
OH
O
OEt
Me
erythro
233
+
R1
OH
O
OEt
Me
threo
234
erythro:threo = 9:91
95% y
---(Ref 118)
Ar
O
R
137
n-Bu4NBH4, PhCH2Cl/I2
Toulene, 25°C
Ar
OH
R
138
Ar = C6H6,4-ClC6H6,
4-MeOC6H6,
4-NO2C6H6
R = CH3
---(Ref 119b)

Previously, this reagent system has not been employed for asymmetric reduction of prochiral ketones. We have examined that the tetrabutylammonium borohydride (TBAB **216**) in combination with CH_3I or iodine reagent system in the presence of (*S*)-α,α-diphenylpyrrolidinemethanol **68** (5 mol%) affords a very easy and simple preparation of the oxazaborolidine catalyst **214** as well as the BH_3 species which effectively reduces acetophenone within about 30 min at 25 °C (Scheme 43).

Scheme 43



Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-$NO_2C_6H_4$

R = CH_3, C_2H_5, C_3H_7, CH_2Cl, CH_2Br, $C(Ph)_2OH$

To examine the effect of solvent, temperature and reagent system enantioselective reduction of acetophenone was carried out using 20 mol% of catalyst **68** loading (Table 8).

Table 8 Enantioselective reduction of acetophenone 137a using different solvent and reagentsystems[a]

S. No	Reagent (equiv.)	Additive (equiv.)	Solvent	Temp.	Yield (%)[b]	Conf.[c]	e.e (%)[d]
1	TEAB **215** (1)	CH_3I (1)	CH_2Cl_2	0 ^{0}C	76	*R*	63
2	TBAB **216** (1)	CH_3I (1)	THF	25 ^{0}C	86	*R*	97
3[e]	TBAB **216** (1)	I_2 (0.5)	THF	25 ^{0}C	78	*R*	89
4	TBAB **216** (1)	CH_3I (1)	Toluene	25 ^{0}C	68	*R*	47

a. All reactions were carried out at 25°C using 5 mmol of TEAB **215** or TBAB **216**, 5 mmol of CH_3I, 5 mmol of ketone in 25 mL of solvent.
b. The yields are of the isolated products after purification by column chromatography. Products were identified by spectral data (IR, ^{1}H NMR and ^{13}C NMR) and physical constant data.
c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.
d. Determined by HPLC using the chiral column, Chiralcel OD-H, 95:5, hex:*i*-PrOH, 1.0 mL/min.
e. Reaction carried out using (5 mmol) TBAB **130/ (**2.5 mmol) I_2.

Initially, we have examined the reduction of acetophenone using tetraethylammonium borohydride (TEAB **215**)/CH_3I combination under the influence of (*S*)-α,α-diphenylpyrrolidinemethanol **68** (20 mol%) in CH_2Cl_2 at 0 °C. In this case, the desired alcohol was obtained in moderate yields with 63% ee (Table 8, entry 1). The ketone remained unreacted when reaction was carried out in THF solvent, as the TEAB **215** is insoluble in THF at room temperature. Fortunately, the more soluble TBAB **216** gave better results. We have observed that the TBAB **216**/CH_3I reagent system in presence of catalyst **68** (20 mol%) yielded the desired alcohol in 97% ee (Table 8, entry 2). These results suggest that sovent and temperature have profound effect on the enantioselectivity of the product, with THF better than toluene and dichloromethane.

Use of I_2 in place of CH_3I or change of solvent led to decreased ee (Table 8, entries 3 and 4). Omitting CH_3I or I_2 additives to the reaction mixture yielded back-unreacted acetophenone. Clearly, addition of CH_3I or I_2 is necessary in liberating BH_3 from tetraalkylammonium borohydride.

With a view to obtain optimum enantioselectivity with low catalyst loading and minimal use of reagent system, reduction of acetophenone **137a** was carried out at 25 °C in THF solvent (Table 9).

Table 9 Enantioselective reduction of acetophenone 137a at various conditions[a]

Entry	Reagent (equiv.)	Additive (equiv.)	Cat **68** (mol%)	Yield (%)[b]	Conf.[c]	ee (%)[d]
1	TBAB **216** (1)	CH_3I (1)	5	87	*R*	97
2	TBAB **216** (1)	CH_3I (1)	1	85	*R*	84
3	TBAB **216** (0.8)	CH_3I (0.8)	1	86	*R*	87
4	TBAB **216** (0.8)	CH_3I (0.8)	5	89	*R*	>99

a. All reactions were carried out at 25°C using (5 mmol) of TBAB **216**, (5 mmol) of CH_3I, (5 mmol) of ketone in 25 mL of solvent except for entries (3-4) where 4 mmol of TBAB **216**, (4 mmol) of CH_3I, and (5 mmol) of ketone was used.

b. The yields are of the isolated products after purification by column chromatography. Products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR) and physical constant data.

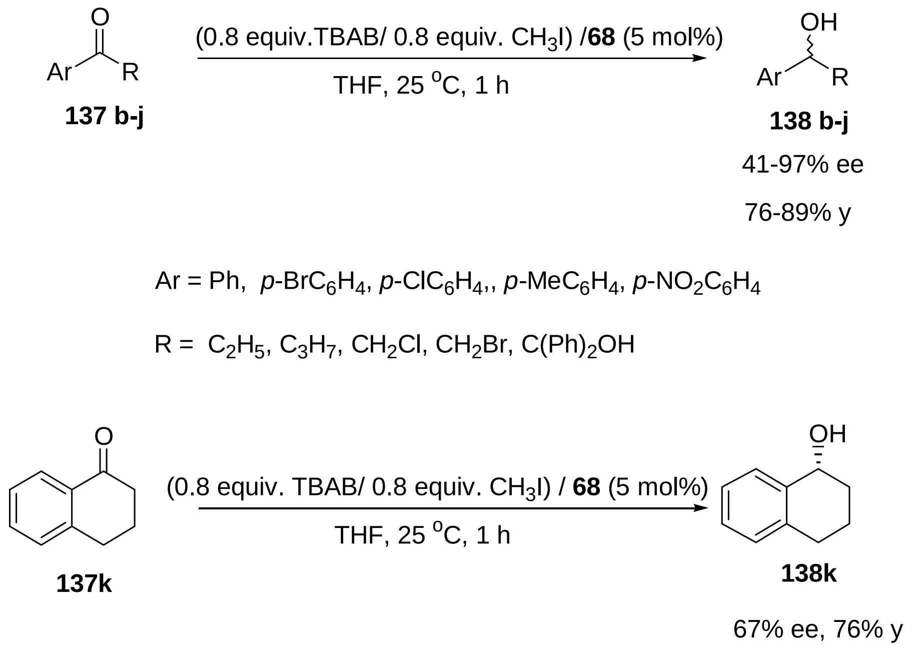
c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.

d. Determined by HPLC using the chiral column, Chiralcel OD-H, 95:5, hexanes:*i*-PrOH, 1.0 mL/min.

Decreasing the catalyst loading to 5 mol% in THF maintained the selectivity as well as yield (Table 9, entry 1). Further decrease in catalyst loading (i.e. 1 mol%) drastically decresed the e.e of the product (Table 9, entry 2). Reducing the reagent system to 0.8 equiv. gave fruitful results using 5 mol% of the catalyst (Table 9, entries 3 and 4).

With a view to extend the scope and to understand the applicability of this reagent system, we have examined the reduction of representative class of aryl alkyl ketones using 5 mol% catalyst **68** to obtain the corresponding secondary alcohols **138b-138k** in 41-96% ee (Scheme 44, Table 10).

Scheme 44



Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4,, *p*-MeC_6H_4, *p*-$NO_2C_6H_4$

R = C_2H_5, C_3H_7, CH_2Cl, CH_2Br, $C(Ph)_2OH$

Table 10. Asymmetric reduction of representative ketones[a]

Substrate	Ar	R	Product	Yield (%)[b]	Conf.[c]	ee (%)
137b	4-Methylphenyl	CH_3	**138b**	88	*R*	96[d]
137c	4-Nitrophenyl	CH_3	**138c**	82	*R*	93[e]
137d	4-Bromophenyl	CH_3	**138d**	89	*R*	97[d]
137e	4-Chlorophenyl	CH_3	**138e**	89	*R*	96[d]
137f	Phenyl	C_2H_5	**138f**	87	*R*	91[f]
137g	Phenyl	C_3H_7	**138g**	89	*R*	94[g]
137h	Phenyl	CH_2Cl	**138h**	79	*S*	82[f]
137i	Phenyl	CH_2Br	**138i**	76	*S*	76[f]
137j	Phenyl	$C(Ph)_2OH$	**138j**	78	*R*	41[h]
137k	α-Tetralone		**138k**	76	*R*	67[f]

a. All reactions were carried out using (4 mmol) of TBAB **216**, (4 mmol) of CH_3I, and (5 mmol) of ketone in the presence of **68** (5 mol%) in THF (25 mL) for 30 min and stirred at 25 °C.

b. The yields are of the isolated products after purification by column chromatography. Products were identified by spectral data (IR, ^{1}H NMR and ^{13}C NMR) and physical constant data.

c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.

d. Determined by HPLC using the chiral column, Chiralcel OJ-H, 95:5 hexanes/i-PrOH, 0.5-0.8 ml/min.

e. Based on reported maximum[120] $[\alpha]_D^{25}$ = +31.0 (*c* 1.2, MeOH) for (*R*) isomer.

f. Determined by HPLC using the chiral column, Chiralcel OD-H, 95:5 hexanes/i-PrOH, 1.0-0.4 ml/min

g. Based on reported maximum[121] $[\alpha]_D^{25}$ = +45.2 (*c* 3.0, Benzene) for (*R*) isomer.

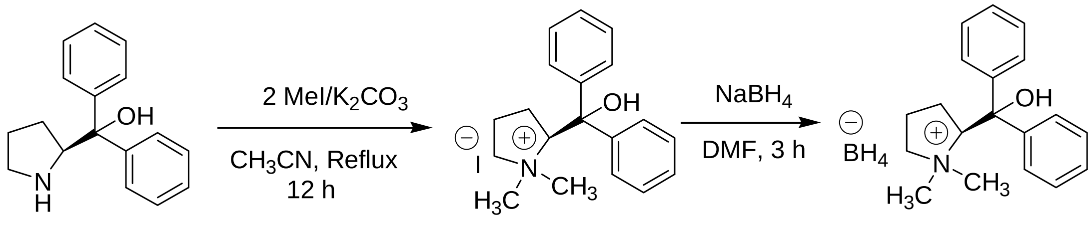
h. Based on reported maximum[122] $[\alpha]_D^{25}$ = +223.6 (*c* 1.3, $CHCl_3$) for (*R*) isomer.

The *para* substituted acetophenones are reduced to give 93-96% ee as observed in the reductions using the B-methyl CBS catalyst system **90**.[107] The ee's are not affected significantly by alkyl groups of the aryl alkyl ketones. The electron donating or withdrawing nature of the aromatic substituent also did not gave significant effect (Table 10, ketones **137b-g**). α-Haloketones are reduced with moderate to good enantioselectivities (Table 10, ketones **137h** and **137i**). However, α-tetralone **137k** gave poor results. Presumably, this may be due to competing uncatalyzed reduction. The ketone **137j** also gave poor results as such derivatives may find it difficult to anchor onto the oxazaborolidine catalyst.[54, 104]

2.3.1.1 Preparation of (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium borohydride 218

After successfully carrying out asymmetric borane reductions using tetraalkylammonium borohydride species, next we have attempted the preparation of chiral borohydride **218** starting from α,α-diphenylpyrrolidinemethanol **68** for asymmetric reductions of prochiral ketones. Treatment of chiral α,α-diphenylpyrrolidine methanol **68** with excess of methyl iodide in acetonitrile at reflux conditions yielded the chiral pyrrolidinium iodide salt **217**.[123] Reaction of chiral *N*,*N*′-dimethyl-2-hydroxy-diphenylmethylpyrrolidiniumiodide **217** with $NaBH_4$ following a closely related procedure produced the chiral borohydride **218** (Scheme 45).[124]

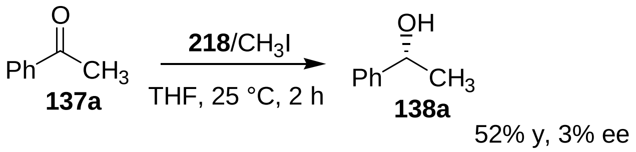
Scheme 45



68 **217** **218** 79% y

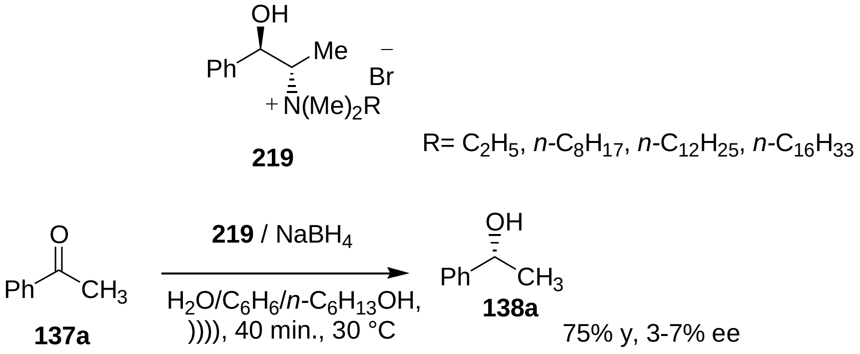
The reduction of acetophenone using (*S*)-*N*,*N*-dimethyl-2-hydroxydiphenylmethylpyrrolidinium borohydride **218** in combination with methyl iodide gave the (*S*)-1-phenylethanol **138a** in 52% yield but only with 3% ee (Scheme 46).

Scheme 46



Previously, *Zhang et. al.* [125] prepared such quartenary ammonium salts from (-)-(1*S*, 2*R*)-ephedrine **219**. These quartenary ammonium salts in combination with $NaBH_4$ give only poor asymmetric induction in reductions of prochiral ketones (Scheme 47).

Scheme 47



Accordingly, we did not pursue the investigation on the use of chiral borohydride reagent **218**.

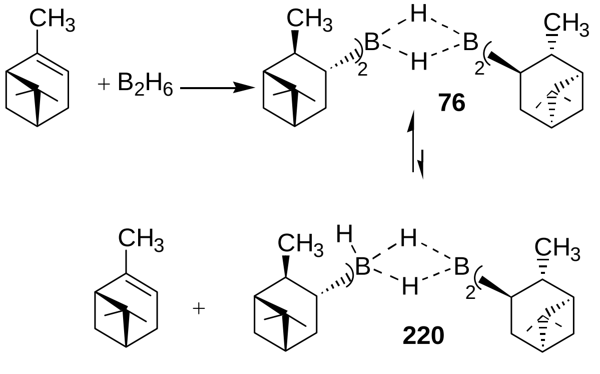
2.3.2 Efforts towards asymmetric hydroborations through preparation of Ipc_2BH *in situ* from TBAB 216/MeI reagent system

Diisopinocamphenylborane (Ipc_2BH) **76** is perhaps one of the most versatile chiral reagents readily available for laboratory use.[136] It has been used for the synthesis of many chiral products, such as alcohols, halides, amines, ketones, hydrocarbons and amino-acids.[126] It has also been used for reduction of prochiral ketones to chiral alcohols.[160] The kinetic resolution of alkenes,[127] dienes[128] and allenes[129] with this valuable reagent has also been extensively studied. A major advantage of Ipc_2BH **76** is the ready availability of both enantiomers of α-pinene. Consquently, chiral centres of opposite configuration can be generated using Ipc_2BH **76** derived from the appropriate antipode of α-pinene. The reagent Ipc_2BH is conventionally prepared by treating the calculated quantity of α-pinene and sodium borohydride in diglyme at 0 °C with the theoretical quantity of boron trifluoride etherate over a period of 15 min (eqn. 1).[126] The reaction mixture is then maintained for an additional 4 hr prior to use, in order to ensure completion of hydroboration reaction.

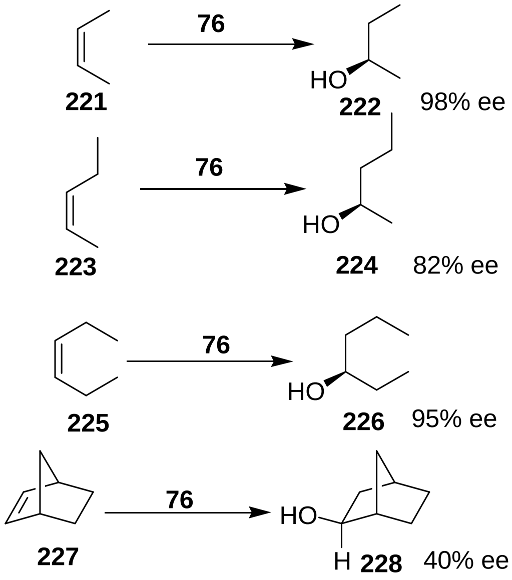
$$8\ \text{a-pinene} + 3\ NaBH_4 + 4\ BF_3 : O(C_2H_5)_2 \longrightarrow 4\ Ipc_2BH + 3\ NaBF_4 + 4\ (C_2H_5)_2O \longrightarrow \text{eqn. } \mathbf{1}$$

α-Pinene readily undergoes hydroboration at 0° C to form *sym*-tetraisopinocampheyldiborane **76** (dimeric form of Ipc_2BH). Even in the presence of excess α-pinene, the reaction does not proceed further. Indeed, in the absence of excess α-pinene, there is evidence for a significant dissociation of **76** into α-pinene and triisopinocampheyldiborane **220** (Scheme 48).

Scheme 48



The product Ipc$_2$BH **76** is less soluble in diglyme than it is in tetrahydrofuran. The product evidently exists in the solid state and in ether solvents as the dimeric diborane derivative, but it is usually referred by its monomeric name i.e. diisopinocampheyl borane (Ipc$_2$BH) for the sake of convenience. It has been reported that Ipc$_2$BH **76** is a highly selective hydroborating agent and exhibits a remarkable asymmetric induction when applied to the hydroboration of *cis*-olefins (eqns. 2-5).[127, 130]



--eqn. **2**

--- eqn. **3**

--- eqn. **4**

--eqn. **5**

We have examined the preparation of *in situ* (-)-Ipc$_2$BH **76** using readily accessible tetrabutylammonium borohydride (**216**)/methyl iodide reaget system in combination with (+)-(*1R,* 5*R*)-α-pinene. The Ipc$_2$BH **76** prepared was then used for hydroboration of *cis*-stilbene **229**. Optimum results were obtained when excess of α-pinene (2.3 equiv.) was used to prepare (-)-Ipc$_2$BH (Scheme 49, Table 11).

Scheme 49

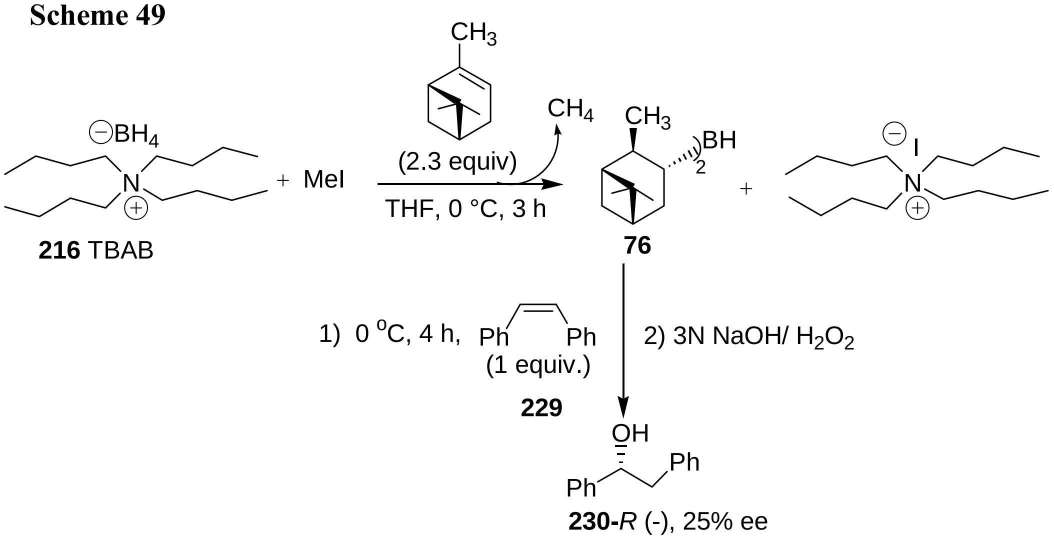


Table 11 Hydroboration of *cis*-stilbene using TBAB/MeI reagent system

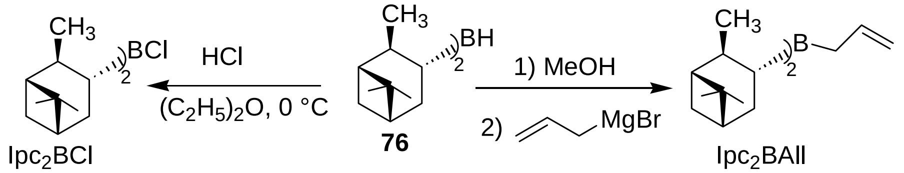
Entry	α-pinene (equiv.)	Temp	Solvent	Yield (%)[a]	e.e(%)[b]
1	2	25 °C	THF	54	9
2	2	25 °C	Toulene	48	10
3	2.3	0 °C	THF	72	25
4	2.3	-25 °C	THF	<15	23

a. The yields are of the isolated products after purification by column chromatography.
b. Determined by HPLC using chiral column, Chiralcel OD-H, 97.5:2.5, hexanes:*i*-PrOH, 1.0 mL/min.

An excess of α-pinene (2.3 equiv.) was used to minimize the dissociation to triisopinocampheyldiborane **220** (entries 1-2 vs 3-4). Hydroboration of *cis*-stilbene **229** at 0 °C gave alcohol product **230** in 25% ee after oxidation. Further decrease in temperature to -25 °C led to decrease in yield as well as ee (entry 3 and 4). In the reaction with *trans*-stilbene **231**, only the starting material was recovered at 0-25 °C. This is not unexpected as the reactions of *trans* olefins and highly hindered olefins with diisopinocampheylborane (Ipc_2BH) are reported to be very slow.[130]

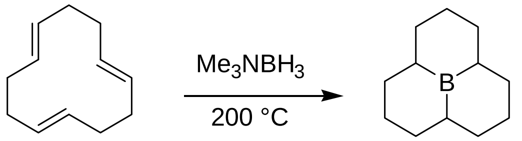
The Ipc$_2$BH is also useful for the preparation of Ipc$_2$BCl and Ipc$_2$BAll which have proven applications in various asymmetric transformations (Scheme 50).[141] A systematic investigationson the applications of Ipc$_2$BH prepared following the method described here may lead to more fruitful results.

Scheme 50

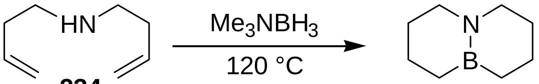


2.3.3 Efforts towards asymmetric hydroborations using amine boranes

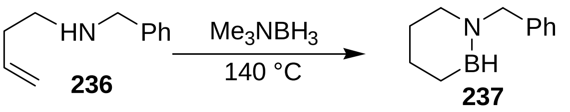
Hydroboration of olefins readily takes place at room temperature using weak complexes of boranes (eg. BH_3:THF, BH_3:SMe_2, BH_3:$N(C_2H_5)_2Ph$).[98, 108, 131] Since alkyl amine borane complexes are relatively stable and are easily handled carriers of borane, it is not surprising that the use of such complexes as hydroborating agents has attracted attention.[132] Most amine boranes hydroborate olefins only at elevated temperatures. For example pyridine borane in diglyme hydroborates alkenes at 100 °C.[133] The reactions were carried out overnight in pressure bottles on the steam bath using stoichiometric quantities of reactants. Similar is the case with trimethyl amine borane complex[134] (eqns. 6-9).



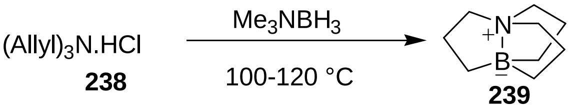
232 **233** --eqn. **6**



234 **235** --eqn. **7**



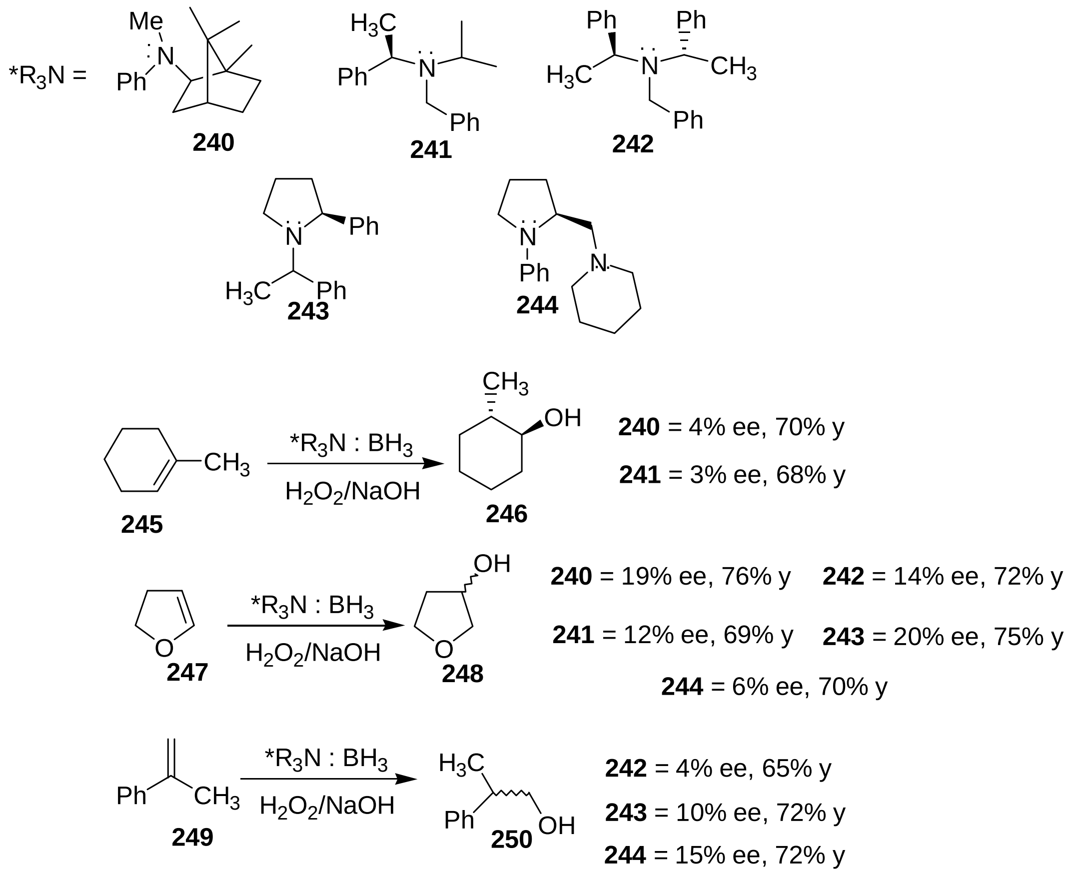
--eqn. **8**



--eqn. **9**

Previously, hydroboration of representative prochiral olefins **245**, **247** and **249** were carried out using chiral tertiary amine borane complexes of amines **240-244** to produce alcohols with up to 20% ee (Scheme 51).[135]

Scheme 51



240 = 4% ee, 70% y
241 = 3% ee, 68% y

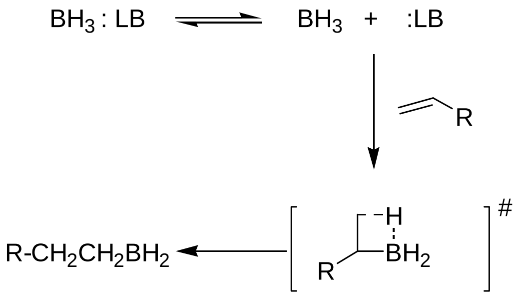
240 = 19% ee, 76% y **242** = 14% ee, 72% y
241 = 12% ee, 69% y **243** = 20% ee, 75% y
244 = 6% ee, 70% y

242 = 4% ee, 65% y
243 = 10% ee, 72% y
244 = 15% ee, 72% y

These results indicate that the hydroboration reaction may go through a spectrum of mechanisms SN^1 or SN^2 depending on the nature of the olefin and amine borane complex.[135b-c]

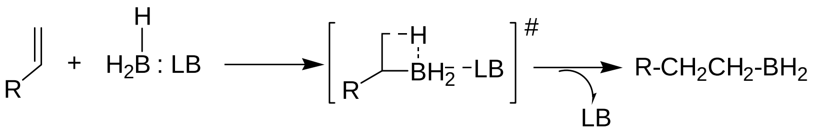
Whereas the reaction with electron rich olefins may take the SN^2 mechanistic pathway, the reaction involving sterically crowded borane or olefin may go through SN^2 reaction with a π-complex intermediate or the SN^1 reaction in which the borane complex dissociates in to free BH_3 species before hydroboration (eqns. 10-12).

SN^1-Type mechanism



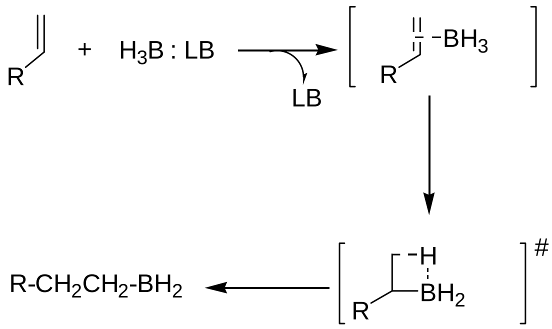
---eqn. **10**

SN^2-Type mechanism



---eqn. **11**

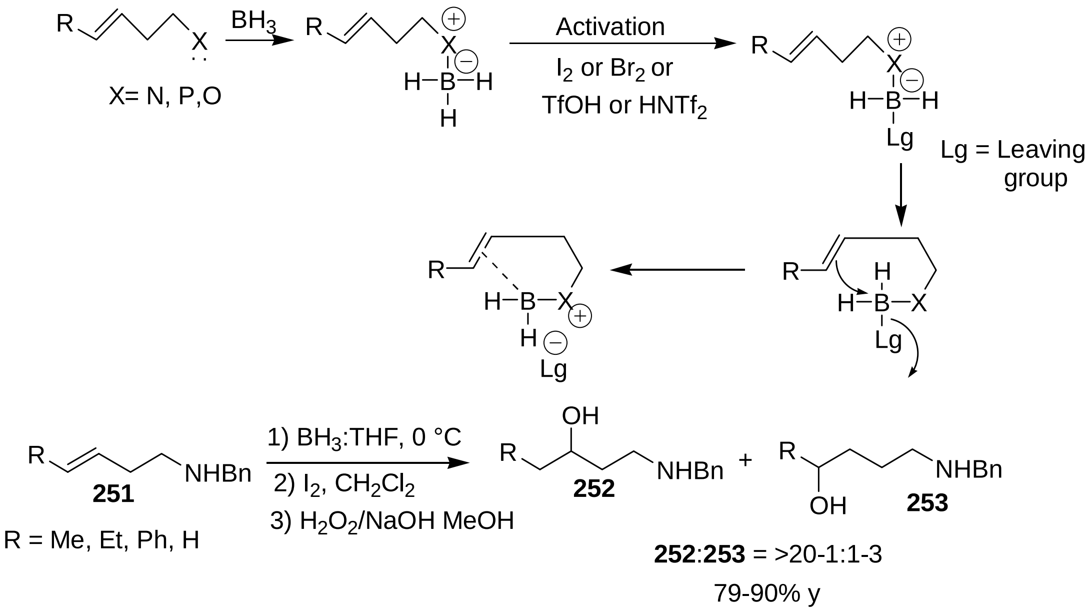
SN^2-Type mechanism with π-complex intermediate



---eqn. **12**

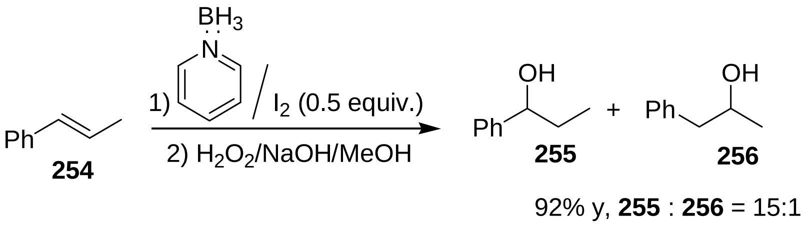
Recently, *Vedejs* and co-workers reported that the intramolecular hydroboration of homoallylic amine boranes and phosphine boranes takes place at room temperature through activation by agents like I_2, Br_2, TfOH, $HNTf_2$.[137] This process involves activation *via* incorporation of leaving group at the boron by replacing one of the hydrides, leading to a new mechanistic pathway for internal hydroboration (Scheme 52).

Scheme 52



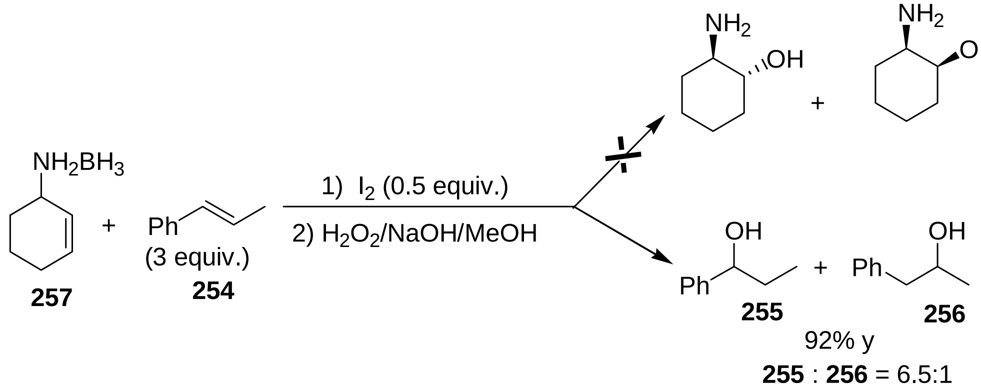
Intermolecular hydroboration of β-methylstyrene **254** using pyridine borane complex (Py:BH_3) at room temperature has been also reported (Scheme 53).[138]

Scheme 53

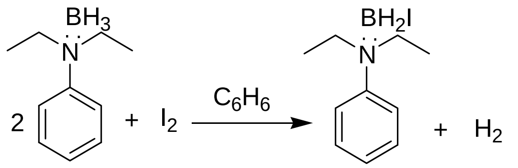


In some cases intramolecular hydroboration can be effectively suppressed using β-methylstyrene **254** (Scheme 54).

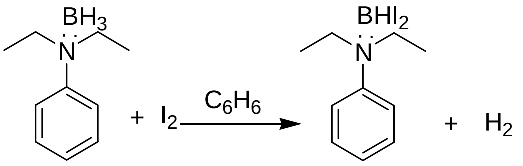
Scheme 54



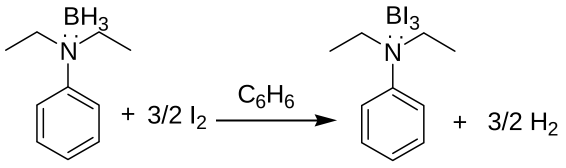
Previously, hydroboration studies using *N*,*N*-diethylaniline iodoborane complexes have been reported from this laboratory.[139] It was found that appropriate amounts of I_2 give the corresponding BH_2I, BHI_2 and BI_3 complexes (eqns. 13-15).



---eqn. **13**



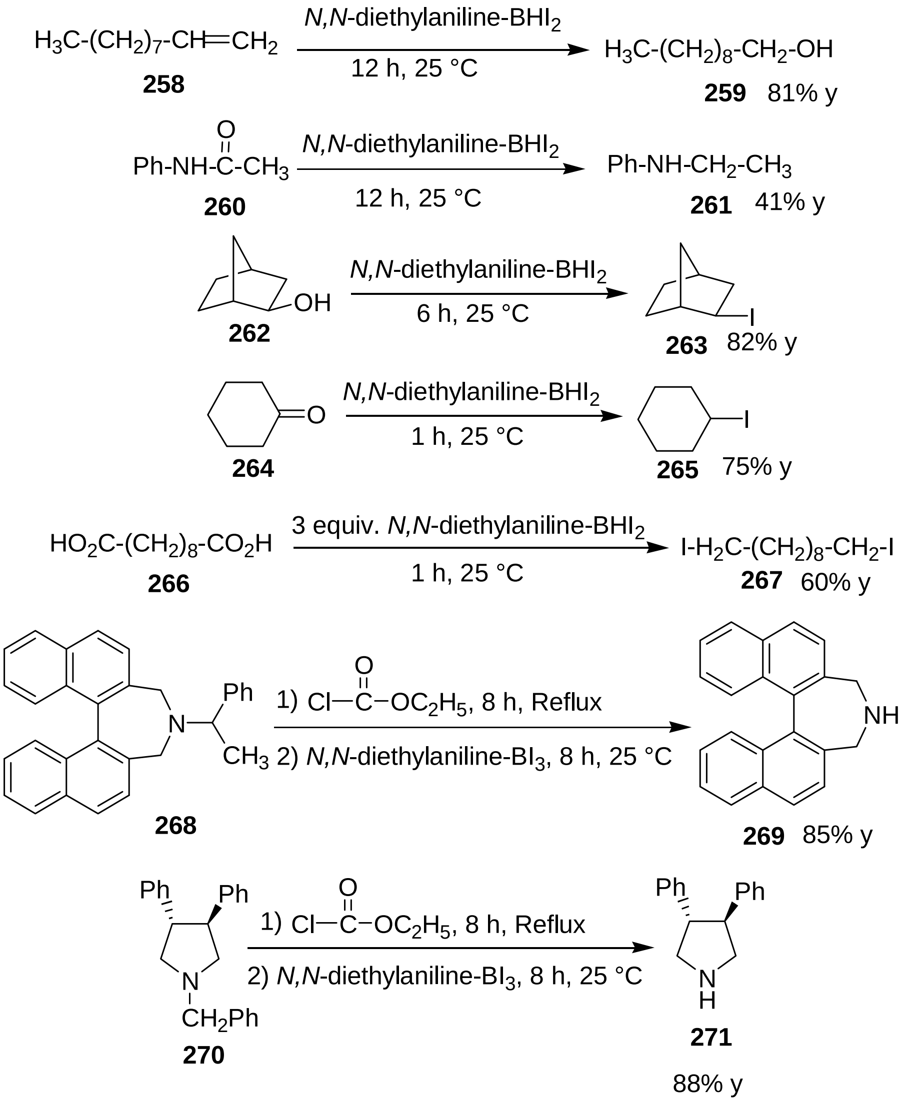
---eqn. **14**



---eqn. **15**

These complexes have been used for hydroborations of alkenes, reduction of amides, iodination of alcohols, reductive iodination of carbonyl compounds and *N*-debenzylation of tertiary amines (Chart 12).[139]

Chart 12

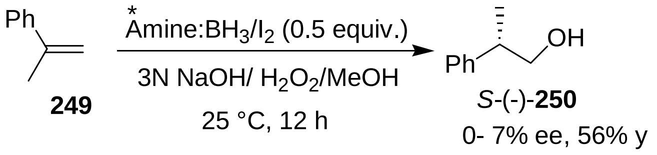


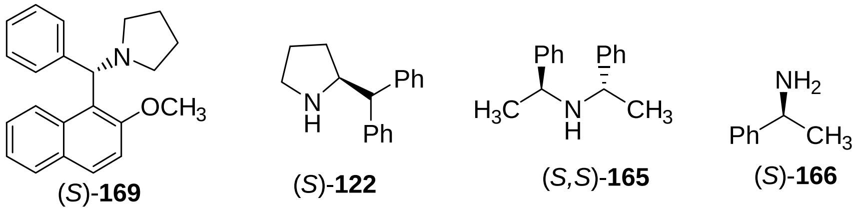
In the past, haloboranes, XBH_2, X_2BH were reported to be useful reagents, especially in selective hydroboration.[140] These haloboranes have an advantage over monoalkyl and dialkyl boranes since oxidation of organoboranes obtained using the alkylboranes agents give products derived from the alkyl moieties which might pose problems during work up.

In continuation of our efforts on achieving asymmetric hydroboration as discussed in the previous section, we have examined the the hydroboration of prochiral olefins using chiral amine borane complexes activated with iodine. The amine-borane complexes in turn were prepared from the corresponding amines by passing diborane gas generated from tetrabutylammonium borohydride in combination with methyl iodide or molecular iodine.[119]

We have examined the hydroboration of simple prochiral olefins i.e. α-methyl styrene **249** and *trans*-stilbene **231** in dichloromethane using borane complexes of various amines (Figure 6) activated with 0.5 equiv. of iodine (Scheme 55, Table 12).

Scheme 55

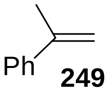
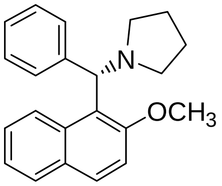
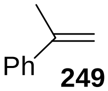
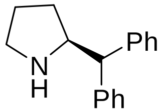
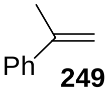
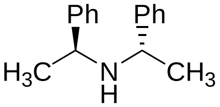
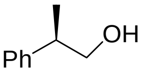
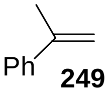
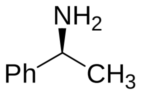
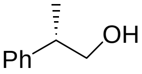
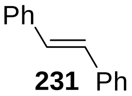
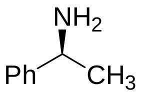
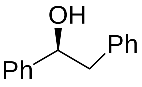




(*S*)-**169** (*S*)-**122** (*S*,*S*)-**165** (*S*)-**166**

Figure 6

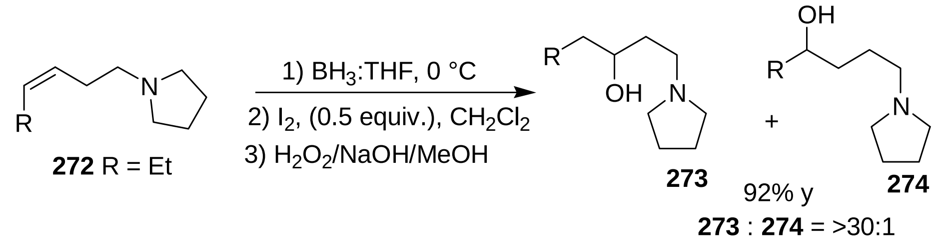
Table 12. Hydroboration of prochiral olefins using various chiral amines

S.No	Substrate	Amine	Product (config)[c]	Time (h)	% ee[a]	Yield(%)[b]
1	 **249**	 (*S*)-**169**	-	12	0	10
2	 **249**	 (*S*)-**122**	-	12	0	23
3	 **249**	 (*S*,*S*)-**165**	 (*R*)-**250**	12	3	7
4	 **249**	 (*S*)-**166**	 (*S*)-**250**	10	7	56
5[d]	 **231**	 (*S*)-**166**	 (*S*)-**230**	12	8	<5

a. Determined by HPLC analysis using the chiral column, Chiralcel OB-H; 95:5, hexanes:*i*-PrOH, 0.3 mL/min.
b. Yields are of isolated products.
c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.
d. Determined by HPLC analysis using the chiral column, Chiralcel OD-H; 97.5:2.5, hexanes:*i*-PrOH, 1.0 mL/min.

Vedejs et. al.[137c] reported intramolecular hydroboration of tertiary amine borane are slow even after activation with 0.5 equiv. I_2, but the reaction involving the olefinic amine **272** containing pyrrolidine moiety gave better results (Scheme 56). They reported the reactivity order: $RNH_2{:}BH_3 > R_2NH{:}BH_3 > R_3N{:}BH_3$ under iodine activated hydroboration.[137c]

Scheme 56



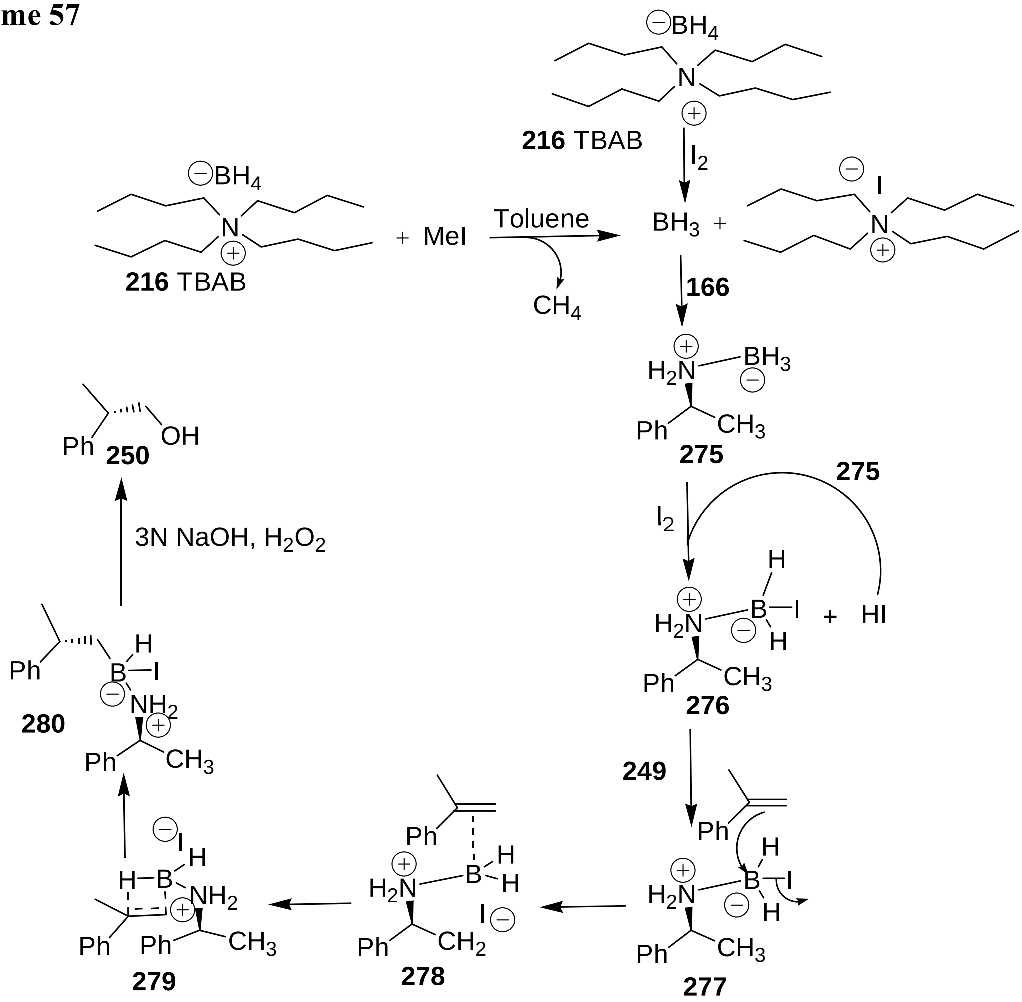
Accordingly, we have chosen the readily accessible tertiary amine (*S*)-**169**:BH_3 complex for hydroboration studies. Hydroboration of α-methylstyrene **249** with amine borane complex of (*S*)-**169**, activated with 0.5 equiv. of I_2 yielded only <10% of alcohol product **250** after 12 h (Table 12, entry 1). Reaction of (*S*)-**169**:BH_3 complex with *trans*-stilbene **231** did not yield any alcoholic product **230**, which clearly indicates that, the reactivity of tertiary amine (*S*)-**169**:BH_3 complex is sluggish towards prochiral olefins.

The secondary amine (*S*)-**122**:BH_3 complex also gave poor yields (23%) and only racemic product **250** was obtained (Table 12, entry 2). This amine (*S*)-**122**:BH_3 complex was unreactive towards *trans*-stilbene **231**.

Next, we pursued hydroboration studies using the acyclic secondary amine (*S*,*S*)-**165**:BH_3 complex. The amine (*S*,*S*)-**165** was prepared by reductive amination of acetophenone using (*S*)-α-methylbenzylamine.[157] Reaction of amine (*S*,*S*)-**165**:BH_3/I_2 (0.5 equiv.) with α-methylstyrene **249** gave poor chemical (7%) and optical (3%) yields (Table 12, entry 3).

Finally, we examined borane complex of the simple commercially available α-methylbenzylamine (*S*)-**166**. The reaction with α-methylstyrene **249** gave an asymmetric induction of 7% with 56% yield (Table 12, entry 4). On the other hand, the reaction with *trans*-stilbene **231** gave very poor chemical yield (<5%) with 8% ee (Table 12, entry 5). Thus, among the amines screened only the chiral (*S*)-α-methylbenzylamine (*S*)-**166** gave reasonable yields, though asymmetric induction is still poor. This activation of chiral (*S*)-α-methylbenzylamine borane complex may be rationalized by the mechanism and intermediates outlined in Scheme 57.

Scheme 57



By introducing iodine on to the boron atom of chiral amine borane complex a more facile version of the SN^2 pathway is possible in which the N-B bond remains intact thus maintaining the chiral environment throughout the course of the hydroboration reaction. With a view to get the higher enantioselectivity conditions and yields, we carried out the hydroboration of α-methylstyrene **249** under various conditions using chiral α-methylbenzylamine **166**:BH_3 complex (Scheme 58, Table 13).

Scheme 58

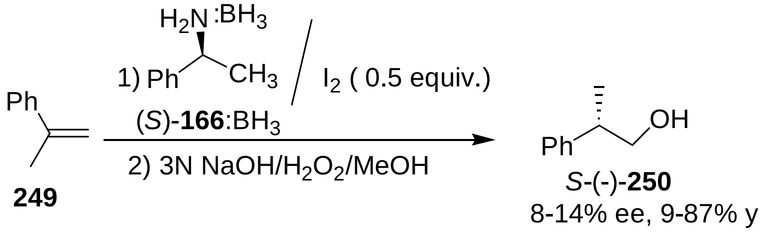


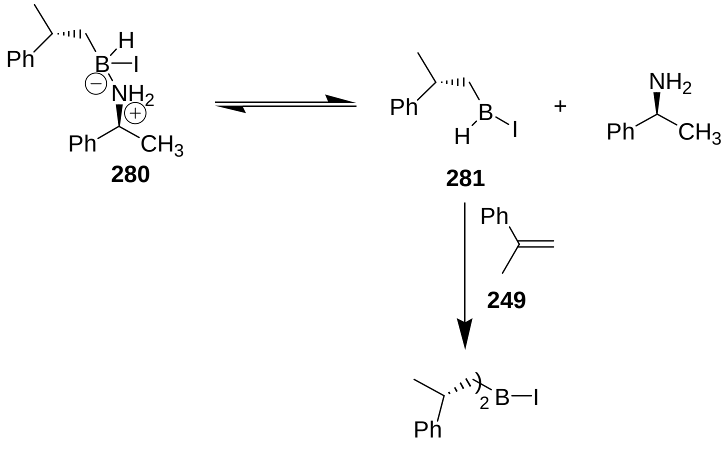
Table 13. Hydroboration of α-methyl styrene using chiral α-methylbenzylamine borane complex

S.No	Activating agent (equiv.)	Amine	Product (config)[c]	Temp.	Time (h)	Solvent	% ee[a]	Yield (%)[b]
1[d]	TfOH (1.0)	(*S*)-**166**	**250** (*S*)	25 °C	12	CH_2Cl_2	11	35
2	I_2 (0.5)	(*S*)-**166**	**250** (*S*)	0 °C	2	CH_2Cl_2	8	9
3	I_2 (0.5)	(*S*)-**166**	**250** (*S*)	25 °C	1	CH_2Cl_2	14	22
4	I_2 (0.5)	(*S*)-**166**	**250** (*S*)	25 °C	1	Toulene	12	19
5[e]	I_2 (0.5)	(*R*)-**166**	**250** (*R*)	25 °C	1	Toulene	13	87

a. Determined by HPLC analysis with chiral column, Chiralcel OB-H; 95:5, hexanes:*i*-PrOH, 0.3 mL/min.
b. Yields are of isolated products.
c. Absolute configuration was assigned by comparison of the sign of the specific rotation with that of literature value.
d. Amine borane activated using 1.0 equiv of Triflic acid.
e. Reaction carried out by using 4.0 equiv. of amine (*R*)-**166**:BH_3.

Activation by use of triflic acid, yielded product **250** with 35% yield with an e.e of 11% (Table 13, entry 1). Experiment conducted at 0 °C led to drop in the yield as well as ee (Table 13, entry 2). Decreasing the time of the reaction to 1 h gave better ee (14%) but a drop in yield was observed (Table 13, entry 3). A change in the solvent to toluene did not lead to considerable variation in the optical yield (Table, entry 4). This may be due to the possibility that, the monoalkylborane species **280** formed after intial hydroboration with α-methylstyrene **249** could be more crowded and hence could decompose to RBHI species **281** which may hydroborate α-methylstyrene with different characteristics (Scheme 59).

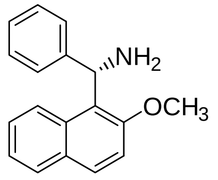
Scheme 59



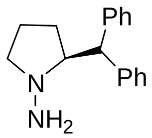
To circumvent this possibility, we have examined the reaction using 4.0 equiv. of the chiral amine borane complex (*R*)-**166**:BH_3 so as to facilitate predominant formation of the monohydroboration product. However, in this case, the chemical yield increased to 87% but the optical yield is only 13% (Table 13, entry 5).

Presumably, the poor asymmetric induction realized may be due to poor chiral discriminating ability of this primary amine system. Further experiments using various chiral primary amines **283-285** may lead to more fruitful results (Figure 7).

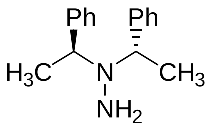
Figure 7



(*S*)-**283**



(*S*)-**284**



(*S*,*S*)-**285**

We have also attempted to probe the sequence of events using ^{11}B-NMR experiments for understanding the nature of boron species during the course of the reaction. The amine borane complex **275** shows a signal with a ^{11}B value at δ = -20.1 ppm as expected for such amine boranes.[138] Activation of the amine borane **275** with iodine (0.5 equiv.) shows an appearance of a new peak at -10.5 ppm in addition to the peak at δ = -20.1 ppm, presumably due to the BH_2I complex **276**. Also, we have made attempts to quench the intermediate **276** as a stable phosphine complex by treating the reaction mixture with triphenyl phosphine. The NMR spectral analysis of the isolated product exhibited signals corresponding to only the $PPh_3{:}BH_3$ complex. Since the haloborane species are known to readily undergo disproportionation reactions in solution, it may be difficult to obtain conclusive evidence for the presence of such species in the reaction mixture.

2.4 Conclusions

Racemic aminonaphthols have been synthesized by condensation of β-naphthol, benzaldehyde with 1°and 2° amines using ethanol as solvent under reflux condition. The racemic aminonaphthol 1-(α-pyrrolidinylbenzyl)-2-naphthol was resolved conveniently using *L*(+)-tartaric acid. Similarly, α-naphthol substituted aminonaphthols have been synthesized by straight forward condensation of α-naphthol, benzaldehyde and 2^o amines. Efforts were taken for the resolution of these aminonaphthols. A simple and convenient methodology for the synthesis of aminoalkyl 2-naphthols using 1-acyl-2-naphthol as precursor was developed.

The racemic bi-2-naphthol was resolved using the chiral 1-(α-pyrrolidinylbenzyl)-2-naphthol and boric acid to obtain samples of >98% ee. The readily accessible 1-((*R*)-phenyl{[(1'*R*)-1'-phenylethyl]amino}methyl)-2-naphthol prepared using chiral (*R*)-(+)-α-methylbenzylamine, β-naphthol and benzaldehyde has been used for the resolution of important carboxylic acids like ibuprofen and mandelic acid.

The chiral (*S*)-2-diphenylpyrrolidinemethane was prepared by the reaction of (*S*)-2-diphenylpyrrolidinemethanol with trifluroacetic acid and sodium borohydride. Preparation of various chiral diamines and triamines was then carried out using (*S*)-2-diphenylpyrrolidinemethane and (*S*)-2-diphenylpyrrolidinemethanol as starting materials. Studies on the application of some of these chiral diamines in kinetic resolution of *trans*-2-

phenylcyclohexanol were carried out. Samples of benzoyl ester with 35% ee and alcohol with 14% ee were obtained.

The oxazaborolidine catalyst was readily prepared *in situ* at 25 ^{o}C in THF using (*S*)-2-diphenylpyrrolidinemethanol and borane generated from tetrabutylammonium borohydride/CH_3I reagent system. The oxazaborolidine/BH_3 prepared in this way is useful for the reduction of prochiral ketones to obtain the corresponding alcohols with up to 99% ee. Hydroboration of *cis*-stilbene in presence of diisopinocampheylborane (Ipc_2BH) using tetrabutylammonium borohydride/CH_3I reagent system as borane source gave the corresponding alcohol with 25% ee and 72% yield. Hydroboration of α-methylstyrene was carried out at room temperature by activating various chiral amine borane complexes using iodine to obtain the corresponding 2-phenylpropanol with up to 14% ee.

3. Experimental Section

3.1 General information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra and the neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz)) and ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and tetramethylsilane as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal tetramethylsilane. Mass spectral analyses for the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{\circ}$) and AUTOPOL-IV (readability $\pm 0.001^{\circ}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*R*)-(+)-α-methylbenzylamine $\{[\alpha]_D^{25} = +30.2$ (*c* 10, EtOH)$\}$ supplied by Fluka.

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

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless otherwise mentioned, all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive reagents and organometallic compounds. Reagents prepared *in situ* in solvents were transferred using a double-ended stainless steel (Aldrich) needle under a pressure of nitrogen whenever required.

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

Dichloromethane, 1,2-dichloroethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Triethylamine was distilled over CaH_2 and stored over KOH pellets. β-Naphthol, α-Naphthol, pyrrolidine, N-methylpiperizine, piperidine, acetyl chloride, supplied by Loba chemie (P) Ltd, India were used as purchased. Benzaldehyde, ammonia solution, aniline, benzylamine, *n*-butylamine were supplied by E-Merck (India). Preparation of tetrabutylammonium borohydride was carried out according to reported procedure.[114] Tetrabutylammonium hydrogen sulfate was supplied by Sisco Research Laboratories (P) Ltd. Tetraethylammonium chloride was purchased from by E-Merck (India). (*S*)-(-)-α,α-diphenylpyrrolidinemethanol (*S*-DPP) was supplied by Gerchem Labs. (P) Ltd. $NaBH_4$, trifluroacetic acid and Iodine were used as such supplied by E. Merk (India).

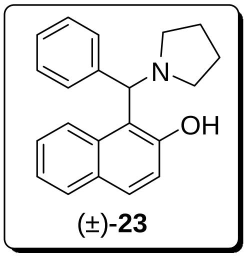
Isophthalic and phthalic acid supplied by Loba chemie (P) Ltd. Racemic *trans*-2-phenyl cyclohexanol was synthesized following a reported procedure.[142] The racemic 1-phenylethanol was synthesized by the reduction of acetophenone using NaBH4 in methanol under refluxing conditions.[143] Bromobenzene supplied by E-merck, India used was freshly distilled. Magnesium turnings were purchased from Rankem, India (P), Ltd. Cyclohexene oxide used was obtained from Lancaster, India (P), Ltd. CuCl was supplied by Aldrich, USA.

X-ray diffraction measurements for the compound **176** carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system.

3.2 Synthesis of aminonaphthols by condensation of β-naphthol, benzaldehyde and amines

3.2.1 Synthesis of 1-(α-pyrrolidinylbenzyl)-2-naphthol (23)

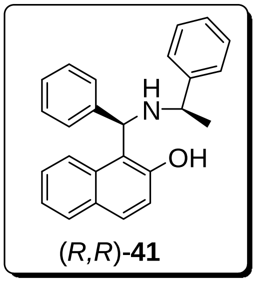
Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this pyrrolidine (8.4 mL, 100 mmol) was added. The reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and washed with 95% ethanol (2 x 20 mL) to isolate the 1-(α-pyrrolidinylbenzyl)-2-naphthol **23** as a white solid.


(±)-**23**

Yield	25.6 g (86%)
mp	172-173 ^{o}C (lit.[26] mp 173 ^{o}C)
IR (KBr)	(cm^{-1}) 3120, 3057, 2970, 2845, 1620, 1452, 1238, 750
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.86 (br s, 4H), 2.63 (br s, 3H), 3.27 (br s, 1H), 5.14 (s, 1H), 7.15-7.28 (m, 5H), 7.38 (t, *J* = 8 Hz, 1H), 7.60-7.71 (m, 4H), 7.88 (d, *J* = 8 Hz, 1H), 13.88 (br s, 1H) **(Spectrum No. 1)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 23.4, 53.5, 70.9, 116.7, 119.9, 121.1, 122.3, 126.3, 127.8, 128.5, 128.7, 128.9, 129.4, 132.0, 141.3, 155.6 **(Spectrum No. 2)**

3.2.2 Synthesis of 1-(*R*)-phenyl{[(1′*R*)-1′-phenylethyl]amino}methyl)-2-naphthol (41)

A mixture of benzaldehyde (17.80 g, 17.05 mL, 168 mmol), 2-naphthol (20.0 g, 140 mmol) and (*R*)-(+)-1-phenylethylamine (17.81 g, 18.71 mL, 147 mmol) were taken in a two neck RB flask. The contents were stirred at 60 ^{o}C for 8 h under N_2 atmosphere and brought to room temperature. The precipitate was filtered and washed with 95% ethanol (3 x 30 mL) to isolate the corresponding 1-(*R*)-phenyl{[(1′*R*)-1′-phenylethyl]amino}methyl)-2-naphthol **41** as white solid. It was recrystallized from ethyl acetate/hexane mixture to obtain colourless crystals.


(*R,R*)-**41**

Yield	41.24 g (84 %)
mp	154-156 ^{o}C (lit.[95] mp 155-156 ^{o}C)
$[\alpha]^{25}_{D}$	-223.5 (*c* 1, $CHCl_3$) lit.[95] $[\alpha]^{25}_{D}$ = -220.7 (*c* 2.1, $CHCl_3$)

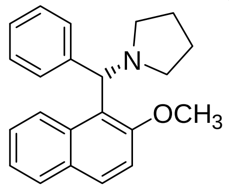
IR (KBr) (cm^{-1}) 3271, 1621, 1238, 1077, 743, 693

^{1}H NMR (400 MHZ, $CDCl_3$) δ 1.52 (d, *J* = 6.8 Hz, 3H,), 2.35 (br s, 1H), 3.92 (q, 1H, *J* = 6.8 Hz), 5.47 (s, 1H), 7.20-7.28 (m, 10H), 7.38-7.43 (m, 4H), 7.75-7.77 (m, 2H), 13.71 (br s, 1H) **(Spectrum No. 3)**

^{13}C NMR (100 MHZ, $CDCl_3$) δ 23.0, 56.7, 60.3, 113.1, 120.1, 121.1, 122.4, 126.4, 126.7, 127.7, 127.9, 128.0, 128.7, 128.8, 129.0, 129.1, 129.7, 132.6, 141.5, 143.1, 157.3 **(Spectrum No. 4)**

3.2.3 Synthesis of [(2-methoxynaphth-1-yl)benzyl]pyrrolidine (169)

Powdered NaOH (0.45 g, 11.3 mmol) was added to a solution of *S*-(+)-**23** (0.75 g, 2.5 mmol) in THF (30 mL). After 10 min CH_3I (1.50 mL, 25 mmol) was injected into the slurry. The mixture was stirred for 6 h and then a solution of saturated NH_4Cl (5 mL) was added. After extraction with diethyl ether, the organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to chromatography on silica gel column using hexane:ethyl acetate (98:2) as eluent to obtain the product *R*-(-)-**169**.


R-(-)-**169**

Yield 0.74 g (94%)

mp 120-122 °C

$[\alpha]_D^{25}$ -37.5 (*c* 1, $CHCl_3$)

IR (KBr) (cm^{-1}) 3047, 2962, 2872, 1622, 1450, 1248, 804

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.78 (s, 4H), 2.40 (d, *J* = 8 Hz, 2H), 2.66 (d, *J* = 8 Hz, 2H), 4.01 (s, 3H), 5.57 (s, 1H), 7.07 (t, *J* = 8 Hz, 1H), 7.17-7.29 (m, 4H), 7.41 (t, *J* = 8 Hz, 1H), 7.63-7.70 (m, 4H), 9.33 (d, *J* = 8 Hz, 1H) **(Spectrum No. 5)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 23.8, 53.8, 56.8, 66.2, 113.9, 123.4, 125.3, 125.8, 126.0, 126.5, 127.8, 127.9, 128.1, 129.1, 129.6, 132.9, 144.1, 154.3 **(Spectrum No. 6)**

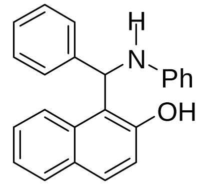
Analysis Calculated for $C_{22}H_{23}NO$: C, 83.24 %; H, 7.30 %; N, 4.41 %; O, 5.04 %

Found : C, 83.28 %; H, 7.32 %; N, 4.33 %; O, 5.05 %

LCMS m/z 318 (M+1)

3.2.4 Synthesis of 1-(α-*N*-phenylaminobenzyl)-2-naphthol (172)

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this distilled aniline (9.1 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl followed by 2M Na_2CO_3 to isolate the 1-(α-*N*-phenylaminobenzyl)-2-naphthol **172** as a white solid.



(±)-**172**

Yield 24.4 g (75%)

mp 128-130 °C (lit.[81] mp 131-132 °C)

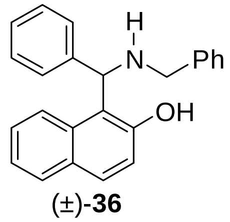
IR (KBr) (cm^{-1}) 3350, 1600, 1450, 1230, 770

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 4.15 (s, 1H), 6.18 (s, 1H), 6.78 (d, *J* = 8 Hz, 2H), 6.94 (t, *J* = 8 Hz, 1H), 7.16 (m, 3H), 7.28-7.41 (m, 5H), 7.48 (d, *J* = 8 Hz, 2H), 7.78 (q, *J* = 8 Hz, 3H), 11.48 (br s, 1H) **(Spectrum No. 7)**

^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 62.6, 116.1, 119.8, 121.2, 121.6, 122.6, 126.5, 127.7, 128.3, 128.8, 128.9, 129.1, 129.2, 129.7, 130.9, 131.4, 140.9, 146.6, 156.0 **(Spectrum No. 8)**

3.2.5 Synthesis of 1-(α-*N*-benzylaminobenzyl)-2-naphthol (36)

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this distilled benzylamine (10.9 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl followed by 2M Na$_2$CO$_3$ to isolate the 1-(α-*N*-benzylaminobenzyl)-2-naphthol **36** as a white solid.

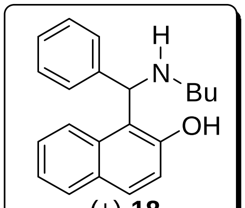


(±)-**36**

Yield	23.6 g (70%)
mp	140-142 °C (lit.[30] mp 143 °C)
IR (KBr)	(cm^{-1}) 3340, 3050, 1652, 1270, 780
^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) 2.29 (br s, 1H), 3.83 (dd, *J* = 8, 4 Hz, 1H), 4.05 (dd, *J* = 8, 4 Hz, 1H), 5.77 (s, 1H), 7.21-7.40 (m, 13H), 7.68-7.76 (m, 3H), 13.6 (br s, 1H) **(Spectrum No. 9)**
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 52.9, 62.9, 113.1, 120.2, 121.2, 122.5, 126.5, 127.8, 128.1, 128.6, 128.8, 129.1, 129.9, 132.8, 138.1, 141.4, 156.9 **(Spectrum No. 10)**

3.2.6 Synthesis of 1-(α-*N*-butylaminobenzyl)-2-naphthol (18)

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this distilled *n*-butylamine (10.0 mL, 100 mmol) was added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered, treated with 20% HCl followed by 2M Na_2CO_3 as above to isolate the 1-(α-*N*-butylaminobenzyl)-2-naphthol **18** as a white solid.


(±)-**18**

Yield	21.3 g (70%)
mp	130-132 °C (lit.[23] mp 131-132 °C)
IR (KBr)	(cm^{-1}) 3314, 3058, 2958, 1621, 1601, 1456, 1241, 1090
^1H NMR	(400 MHz, $CDCl_3$, δ ppm) 0.91 (t, *J* = 8 Hz, 3H), 1.38-141 (m, 2H), 1.56-1.61 (m, 3H), 2.83 (t, *J* = 8 Hz, 2H), 5.67 (s, 1H), 7.18 (d, *J* = 12 Hz, 1H), 7.21-7.36 (m, 5H), 7.46 (d, *J* = 8 Hz, 3H) 7.72 (t, *J* = 8 Hz, 2H) 13.6 (br s, 1H) **(Spectrum No. 11)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 13.9, 20.4, 31.7, 49.0, 64.5, 113.4, 120.2, 121.2, 122.4, 126.5, 127.8, 128.1, 128.7, 128.1, 128.9, 129.7, 132.8, 141.8, 157.0 **(Spectrum No. 12)**

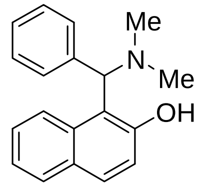
3.2.7 Synthesis of 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol (19)

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this 40% aqueous solution of *N*,*N*-dimethylamine (12.6 mL, 100 mmol) was added. The reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and washed with 95% ethanol (2 x 20 mL) to isolate the 1-(α-*N*,*N*-dimethylaminobenzyl)-2-naphthol **19** as a white solid.

Yield	20.8 g (75%)
mp	161-162 °C (lit.[159] mp. 164-164.5 °C)

IR (KBr) (cm^{-1}) 3058, 2958, 1620, 1454, 1238, 1006

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm) 2.36 (br s, 6H), 5.01 (s, 1H), 7.20-7.45 (m, 6H), 7.61-7.75 (m, 4H), 7.91 (d, *J* = 8 Hz, 1H), 13.69 (br s, 1H) **(Spectrum No. 13)**



(±)-**19**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 44.2, 73.1, 116.3, 112.0, 121.1, 122.4, 126.4, 128.0, 128.8, 128.9, 129.5, 132.3, 140.5, 155.5 **(Spectrum No. 14)**

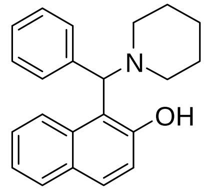
3.2.8 Synthesis of 1-(α-piperidylbenzyl)-2-naphthol (24)

Freshly distilled benzaldehyde (13.3 mL, 130 mmol) was added to a solution of 2-naphthol (14.4 g, 100 mmol) in 50 mL of 95% ethanol. To this piperidine (10.0 mL, 100 mmol) was added and the reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered and washed with 95% ethanol (2 x 20 mL) to isolate the 1-(α-piperidylbenzyl)-2-naphthol **24** as a white solid.

Yield 28.4 g (90%)

mp 195-196 °C (lit.[159] mp 198-198.5 °C)

IR (KBr) (cm^{-1}) 3214, 3058, 2958, 1621, 1601, 1456, 1241, 109



(±)-**24**

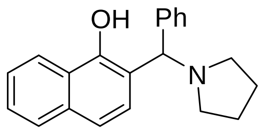
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.31 (br s, 1H), 1.78 (br s, 5H), 2.00 (br s, 1H), 2.18 (br s, 1H), 2.70 (br s, 1H), 3.30 (br s, 1H), 5.12 (s, 1H), 7.18-7.30 (m, 6H), 7.39 (t, *J* = 8 Hz, 1H), 7.57-7.72 (m, 3H), 7.85 (d, *J* = 8 Hz, 1H), 13.92 (br s, 1H) **(Spectrum No. 15)**

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 24.2, 26.1, 53.5, 72.4, 116.2, 120.0, 121.1, 122.4, 126.4, 127.9, 128.9, 129.1, 129.4, 132.5, 139.7, 155.6 **(Spectrum No. 16)**

3.3 Synthesis of aminonaphthols by condensation of α-naphthol, benzaldehyde and 2° amines

3.3.1 Synthesis of 2-(β-pyrrolidinylbenzyl)-1-naphthol (176)

Freshly distilled benzaldehyde (1.33 mL, 13 mmol) was added to a solution of 1-naphthol (1.44 g, 10 mmol) in 5 mL of CH_2Cl_2. To this pyrrolidine (0.84 mL, 10 mmol) was added. The reaction mixture was stirred for 6 h at room temperature. The precipitate was filtered to isolate the 2-(β-pyrrolidinylbenzyl)-1-naphthol **176** as a white solid.

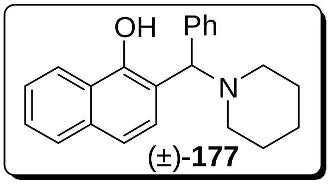


(±)-**176**

Yield	2.52 g (83%)
mp	72-73 °C (lit.[32] mp 72-74 °C)
IR (KBr)	(cm^{-1}) 2972, 2795, 1574, 1452, 1388, 891, 738
^1H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.88 (br s, 4H), 2.55-2.72 (m, 4H), 4.50 (s, 1H), 7.04-7.06 (d, *J* = 8 Hz, 1H), 7.20-7.28 (m, 4H), 7.42-7.51 (m, 4H), 7.60 (d, *J* = 8Hz, 1H), 8.31 (d, *J* = 8Hz, 1H), 13.25 (br s, 1H) **(Spectrum No. 17)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 23.5, 53.3, 75.9, 118.4, 119.3, 122.4, 124.7, 125.4, 125.9, 126.3, 127.2, 127.6, 127.8, 128.6, 133.5, 142.12, 152.1 **(Spectrum No. 18)**

3.3.2 Synthesis of 2-(β-piperidylbenzyl)-1-naphthol (177)

Freshly distilled benzaldehyde (1.33 mL, 13 mmol) was added to a solution of 1-naphthol (1.44 g, 10 mmol) in 5 mL CH_2Cl_2. To this piperidine (1.0 mL, 10 mmol) was added and the reaction mixture was refluxed for 6 h and brought to room temperature. The precipitate was filtered to isolate the 2-(β-piperidylbenzyl)-1-naphthol **177** as a pale yellow solid.

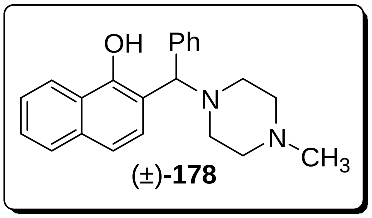


(±)-**177**

Yield	2.38 g (75%)
mp	108-109 °C (lit.[144] mp 110 °C)
IR (KBr)	(cm^{-1}) 2937, 2843, 1620, 1456, 1236, 742
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.59 (s, 2H), 1.68 (s, 6H), 2.47 (br s, 2H), 5.09 (s, 1H), 7.19-7.45 (m, 6H), 7.50-7.75 (m, 4H), 7.86 (d, J = 8.6 Hz, 1H), 13.9 (br s, 1H)
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 24.2, 26.1, 53.5, 72.2, 116.2, 120.0, 121.1, 122.3, 126.3, 127.9, 128.7, 128.9, 129.1, 129.4, 132.5, 139.7, 155.6
LCMS	*m/z* 318 (M+1)

3.3.3 Synthesis of 2-(β-N-methypiperizylbenzyl)-1-naphthol (178)

Freshly distilled benzaldehyde (1.1 mL, 11 mmol) was added to a solution of 1-naphthol (1.44 g, 10 mmol) in 50 mL CH_2Cl_2. To this *N*-methylpiperizine (1.22 mL, 11 mmol) was added and the reaction mixture was allowed to stirr at room temperature for 6 h. The precipitate was filtered to isolate the 2-(β-*N*-methylpiperizylbenzyl)-1-naphthol **178** as a pale yellow solid.



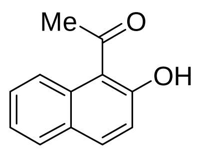
(±)-**178**

Yield	2.58 g (78 %)
mp	70-72 °C
IR (KBr)	(cm^{-1}) 3055, 2934, 2793, 1452, 1388, 1290, 1138, 744

^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.25 (s, 1H), 1.63 (br s, 3H), 2.31 (s, 3H), 2.54 (br s, 4H), 4.53 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.18-7.30 (m, 4H), 7.43-7.48 (m, 4H), 7.60 (d, *J* = 7.6 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 12.7 (br s, 1H) **(Spectrum No. 19)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 45.8, 51.8, 55.2, 76.5, 118.0, 118.8, 122.5, 124.9, 125.5, 126.1, 127.1, 127.3, 128.0, 128.7, 128.9, 129.7, 133.7, 139.8, 139.8, 152.0 **(Spectrum No. 20)**
Analysis	Calculated for $C_{22}H_{24}N_2O$: C, 79.48 %; H, 7.28 %; N, 8.43 %; O, 4.81 % Found:C, 79.52 %; H, 7.25 %; N, 8.50 %; O, 4.71 %
LCMS	*m/z* 333 (M+1)

3.4 Preparation of 1-acetyl-2-naphthol (181)

$TiCl_4$ (2.4 mL, 22 mmol) was added to β-naphthol under N_2 atmosphere (2.88 g, 20 mmol) using a syringe. The resulting dark cherrey-coloured mixture was stirred at 25°C until the evolution of HCl gas had ceased. Then acid chloride (30 mmol) was added to the reaction mixture and the resulting thick solution was stirred at 25°C for 15 min, then heated to 120 ^{o}C and stirring was continued at this temperature for 1 h. The reaction mixture was cooled to 25 °C and quenched with water (30 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed to obtain the crude product as reddish brown solid. It was purified by silica gel column chromatography using hexane: ethyl acetate (99:1) as eluent.



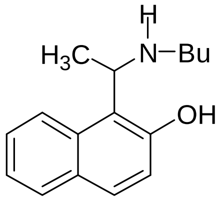
181

Yield	2.4 g (65%)
mp	116-118 °C (lit.[83] mp 120-121 °C)
IR (KBr)	(cm^{-1}) 3352, 3055, 2927, 1624, 1575, 1465, 1245, 1024
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 2.89 (s, 3H), 7.15 (d, *J* = 12 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.59 (t, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 8.11 (d, *J* = 8 Hz, 1H) 13.45 (br s, 1H) **(Spectrum No. 21)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 32.0, 114.4, 119.9, 123.0, 123.9, 127.5, 128.2, 128.7, 129.1, 131.8, 136.5, 164.0, 202.7 **(Spectrum No. 22)**

Representative procedure for preparation of α-aminoalkyl-2-naphthols (184-187)

Amine (10 mmol) was added through syringe to a stirred solution of 1-acetyl -2-naphthol **181** (1.86 g, 10 mmol) in MeOH (20 mL). The reaction mixture was refluxed for 12 h and brought to room temperature. It was concentrated to obtain a dark brown viscous liquid. This ketimine was as such used for reduction by using excess of $NaBH_4$ (0.76 g, 20 mmol) and adding gradually through a solid addition funnel to the stirred solution of ketimine in MeOH (10 mL) at 0 °C for about 0.5 h. After the addition was complete, the contents were stirred at room temperature for 12 h. The reaction mixture was cooled to 0 °C and then quenched carefully with H_2O (10 mL). The reaction mixture was then evaporated and then extracted with CH_2Cl_2 (2 x 20 mL). The organic and aqueous layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulphate. The solvent was concentrated under reduced pressure to obtain the product.

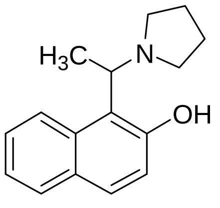
3.4.1 *N*-^{n}Butyl-1-(α-aminoethyl)-2-naphthol (184)



(±)-**184**

Yield	1.55 g (64%)
mp	63-64 °C
IR (KBr)	(cm^{-1}) 3310, 2964, 2928, 1618, 1460, 1236, 823, 754
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 0.89 (t, *J* = 8 Hz 3H), 1.32-1.54 (m, 9H), 2.66 (t, 2H), 4.78 (q, *J* =7 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 7.45-7.41 (m, 2H), 7.66-7.63 (m, 2H), 7.74-7.84 (m, 1H) **(Spectrum No. 23)**
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 13.9, 20.3, 21.2, 31.8, 47.8, 54.3, 116.1, 119.9, 120.6, 122.0, 122.2, 126.3, 128.5, 128.9, 132.3, 155.9 **(Spectrum No. 24)**
Analysis	Calculated for $C_{16}H_{21}NO$: C, 78.97%; H, 8.7%; N, 5.76%; O, 6.57% Found : C, 78.84%; H, 8.78%; N, 5.78%; O, 6.58%
LCMS	244 (M+1)

3.4.2 1-(α-Pyrrolidinylethyl)-2-naphthol (185)

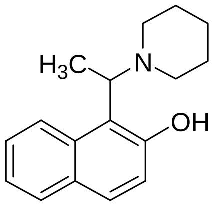


(±)-**185**

Yield	1.84 g (61%)
mp	58-60 °C
IR (KBr)	(cm^{-1}) 3369, 3061, 2974, 2928, 1622, 1599, 1242, 817, 746
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.52 (d, *J* = 8 Hz, 3H), 1.89 (br s, 5H), 2.09 (br s, 1H), 2.38 (br s, 1H), 3.06 (br s, 1H), 3.40 (br s, 1H), 4.28 (q, *J* =8 Hz, 1H),

	7.08 -7.16 (m, 1H), 7.25-7.33 (m, 1H), 7.39-7.45 (m, 1H), 7.64-7.67 (m, 1H), 7.72-7.76 (m, 1H), 7.81-7.83 (d, *J* = 8 Hz, 1H) **(Spectrum No. 25)**
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 19.5, 23.5, 52.7, 60.2, 109.4, 118.2, 119.5, 120.6, 122.2, 123.2, 126.3, 127.7, 128.5, 128.9, 129.6, 131.5, 134.8, 154.3, 155.2 **(Spectrum No. 26)**
Analysis	Calculated for $C_{16}H_{19}NO$: C, 79.63%; H, 7.94%; N, 5.8%; O, 6.63%
	Found : C, 79.62%; H, 7.88%; N, 5.55%; O, 6.94%
LCMS	*m/z* 242 (M+1)

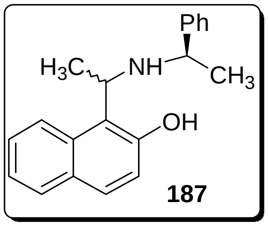
3.4.3 1-(α-Piperidinylethyl)-2-naphthol (186)



(±)-**186**

Yield	2.02 g (56%)
mp	68-69 °C (lit.[161] mp 68 °C)
IR (KBr)	(cm^{-1}) 3369, 3061, 2974, 2928, 1622, 1599, 1242, 817, 746
^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) 1.44-1.53 (m, 8H), 1.68 (br s, 3H), 2.21-2.23 (m, 2H), 5.37-5.39 (m, 1H), 7.08 -7.16 (m, 1H), 7.25-7.33 (m, 1H), 7.39-7.45 (m, 1H) 7.64-7.67 (m, 1H), 7.72-7.76 (m, 1H), 7.81-7.83 (d, *J* = 8 Hz, 1H) **(Spectrum No. 27)**
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 26.0, 28.8, 41.7, 61.4, 74.3, 109.4, 113.8, 117.9, 119.7, 122.7, 123.3, 126.3, 126.9, 127.7, 128.5, 129.1, 129.6, 130.4, 132.7, 134.6, 151.4, 153.7 **(Spectrum No. 28)**

3.4.4 1-{1-[(1*R*)-1-Phenylethylamino]ethyl}-2-naphthol (187)



187

Yield	0.91 g (63%)
dr	75:25
$[\alpha]_D^{25}$	+4.9 (*c* 0.5, CHCl$_3$)
IR (KBr)	(cm^{-1}) 3362, 3064, 2972, 2926, 1620, 1590, 1241, 807, 742
^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) for major diastereomer: 1.39 (d, *J* = 8 Hz, 3H), 1.45 (d, *J* = 8 Hz, 3H), 3.73 (q, *J* = 8 Hz, 1H), 4.52 (q, *J* = 7 Hz, 1H), 7.08-7.13 (m, 3H), 7.23 -7.33 (m, 5H), 7.41-7.44 (m, 1H), 7.67 (d, *J* = 8 Hz, 1H) 7.74 (d, *J* = 8 Hz, 1H), 13.07 (s, 1H) Additional peaks for minor diastereomer: 1.49 (d, *J* = 8 Hz, 3H), 3.92 (q, *J* = 8 Hz, 1H), 4.95 (q, *J* = 8 Hz, 1H) **(Spectrum No. 29)**
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) for major diastereomer: 21.2, 23.0, 50.6, 55.5, 116.1, 119.8, 119.9, 120.4, 120.6, 122.2, 126.2, 126.4, 127.3, 127.5, 128.6, 128.7, 128.8, 128.9, 132.0, 132.2, 143.3, 156.2. Additional peaks for minor diastereomer: 20.3, 50.0, 54.3, 155.8 **(Spectrum No. 30)**
Analysis	Calculated for C$_{16}$H$_{19}$NO : C, 82.44%; H, 7.26%; N, 4.81%; O, 5.49% Found: C, 82.40%; H, 7.29%; N, 5.07%; O, 5.21%
LCMS	*m/z* 292 (M+1)

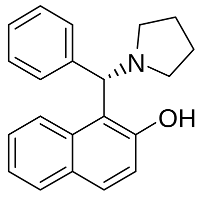
3.5 Resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol (23)

The *L*-(+)-tartaric acid **30** (0.75 g, 5 mmol) and the racemic 1-(α-pyrrolidinylbenzyl)-2-naphthol **23** (1.5 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and evaporated to dryness to obtain the *S*-(+)-**23**. The filtrate was concentrated and the residue taken in CH_2Cl_2 (20 mL) and was digested using 1N KOH (10 mL) to obtain the *R*-(-)-**23**.

After decomposition

From precipitate

Yield	0.60 g (40%)
$[\alpha]_D^{25}$	+176 (*c* 1, $CHCl_3$), {lit.[40] for 100% ee, $[\alpha]_D^{25}$ = +179.1 (*c* 1.30, $CHCl_3$)}

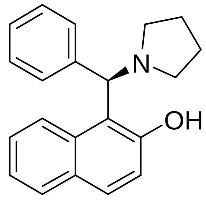


S-(+)-**23**

Enantiomeric purity 99% ee (determined by HPLC using chiral column, ciralcel OD-H)

From filtrate

Yield	0.82 g (55%)
$[\alpha]_D^{25}$	-134 (*c* 1, $CHCl_3$), {lit.[40] for 100% ee, $[\alpha]_D^{25}$ = 179.1(*c* 1.3, $CHCl_3$)



R-(-)-**23**

Enantiomeric purity >75% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH = 90:10; flow rate 0.9 mL/min., retention times 5.19 min. (*S*) and 5.63 (*R*). The spectral data were identical to the data obtained from the racemic samples.

Purification of partially resolved 1-(α-pyrrolidinylbenzyl)-2-naphthol (23) using *L*-(+)-tartaric acid (30)

The partially resolved 1-(α-pyrrolidinylbenzyl)-2-naphthol *R*-(-)-**23** (75% ee, 1.5 g, 5 mmol) and the *L*-(+)-tartaric acid **30** (0.75 g, 5 mmol) were taken in acetone (70 mL) and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (20 mL) and 2M Na_2CO_3 (10 mL) and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO4 and evaporated to dryness to obtain the product enriched in *R*-(-)-**23** (≥ 99% ee).

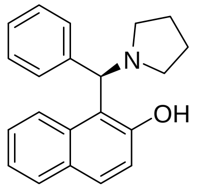
After decomposition

From precipitate

Yield 1.00 g (70%)

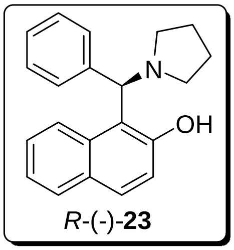
$[\alpha]_D^{25}$ -179 (*c* 1, $CHCl_3$), {lit.[40] for 100% ee,

$[\alpha]_D^{25}$ = -179.1 (*c* 1.30, $CHCl_3$)}



R-(-)-**23**

From filtrate


R-(-)-**23**

Yield 0.30 g (20%)

$[\alpha]_D^{25}$ -32 (*c* 1, $CHCl_3$), {lit.[43] for 100% ee,

$[\alpha]_D^{25}$ = -179.1 (*c* 1.30, $CHCl_3$)}

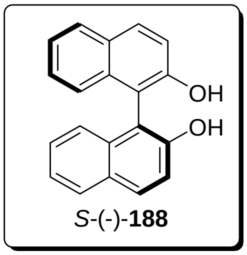
3.6 Synthetic applications of aminonaphthols

3.6.1 Resolution of BINOL using aminonaphthol (23) and boric acid

S-(+)-Aminonaphthol **23** (1.5 g, 5 mmol), $B(OH)_3$ (0.31 g, 5 mmol) and racemic BINOL **188** (1.46 g, 5 mmol) were taken in CH_3CN (50 mL) and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of THF (50 mL) and 2N HCl (20 mL) and stirred until complete dissolution occurs. The organic and aqueous layers were separated. The aqueous layer was extracted with ether (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO4 and evaporated to obtain the *S*-(-)-**188** (90% ee, 30% yield). The filtrate was concentrated and the residue was treated as outlined above to obtain **188** enriched in *R*-(+)-**188** (43% ee, 60% yield).

After decomposition

From precipitate

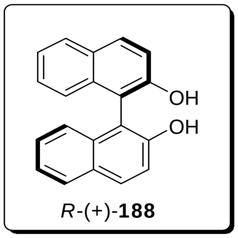

S-(-)-**188**

Yield 0.42 g (30%)

$[\alpha]_D^{25}$ -31.5 (*c* 1, THF), {lit.[145] for 100% ee,

$[\alpha]_D^{25}$ = -35.0 (*c* 1, THF)}

From filtrate



R-(+)-**188**

Yield 0.86 g (60%)

$[\alpha]_D^{25}$ +15.0 (*c* 1, THF), {lit.[145] for 100% ee,

$[\alpha]_D^{25}$ = +35 (*c* 1 THF)}

The partially resolved *R*-(+)-**188** (43% ee) sample was enriched by following the same procedure as mentioned above.

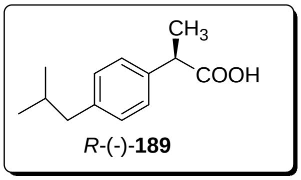
3.6.2 Resolution of racemic ibuprofen (189)

The (*R*,*R*)-(-)-aminonaphthol **41** (3.53 g, 10 mmol) and racemic ibuprofen **189** (2.06 g, 10 mmol) were taken in acetone (13 mL) and the contents were stirred at 25 °C for 48 h and filtered. The precipitate was suspended in a mixture of ether and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The aq. layer was treated with 3N HCl/ether and the free acid was extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain (*R*)-(-)-**189** enantiomer (0.70 g, 34% yield, 80% ee). The filtrate was concentrated and the residue was treated as outlined above to obtain (*S*)-(+)-**189** enantiomer (1.23 g, 60% yield, 45% ee). The samples were also analyzed using HPLC (chiralcel OD-H, eluent: hexanes: 2-propanol: trifluoroacetic acid=980:20:2.5, v/v).[146]

After decomposition

From precipitate

Yield 0.70 g (34%)



R-(-)-**189**

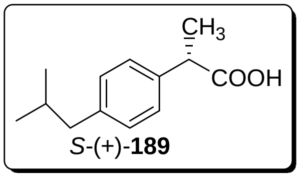
$[\alpha]_D^{25}$ -45 (c 1, C_2H_5OH {lit.[146] for 100% ee,

$[\alpha]_D^{25}$ = -58 (c 2, C_2H_5OH)}

Enantiomeric purity 80% ee (determined by HPLC using chiral column, chiralcel OD-H)

From filtrate

Yield 1.23 g (60%)



S-(+)-**189**

$[\alpha]_D^{25}$ +27 (c 1, C_2H_5OH), {lit.[146] for 100% ee,

$[\alpha]_D^{25}$ = +59 (c 2, C_2H_5OH)}

Enantiomeric purity 45% ee (determined by HPLC using chiral column, chiralcel OD-H), solvent system, hexanes:*i*-PrOH:trifluoroacetic acid/980:20:2.5, flow rate 0.5 mL/min., retention times of racemic ibuprofen **189** showed two peaks at 18.39 min. (*R*) and 20.54 min. (*S*) in 1:1 ratio on chiral column, chiralcel OD-H.[146] Similar HPLC analysis of the chiral ibuprofen (*R*)-**189** showed two peaks at (major) 18.39 min. (*R*) and (minor) 20.54 min. (*S*) in the ratio of 90:10 indicating that its enantiomeic purity is 80% ee (for precipitate fraction). In the similar way HPLC analysis of the chiral ibuprofen (*S*)-**189** showed two peaks at 18.39 min. (*R*) and 20.53 min. (*S*) in the ratio of 27:73 indicating that its enatiomeric purity is 45% ee for filtrate fraction.

Purification of partially resolved ibuprofen (189)

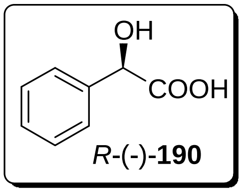
The partially resolved (*R*)-(-)-**189** sample with 80% ee was enriched following the repetitive resolution procedure gave (*R*)-(-)-**189** enantiomer (0.30 g, 44% yield, 97% ee) from the precipitate fraction, $[\alpha]_D^{25}$ = -56 (*C* 1, C_2H_5OH) lit.[146] $[\alpha]_D^{25}$ =-58 (*C* 2, C_2H_5OH). The filtrate part after workup gave the (*R*)-(-)-**189** enantiomer (0.29 g, 42% yield, 57% ee).

3.6.3 Resolution of racemic mandelic acid (190)

The (*R,R*)-(-)-aminonaphthol **41** (1.76 g, 5 mmol) and racemic mandelic acid **190** (0.76 g, 5 mmol) were taken in CH_3CN (5 mL)and the contents were stirred at 25 °C for 72 h and filtered. The precipitate was suspended in a mixture of ether and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The aq. layer was treated with 3N HCl/ether and the acid was extracted with ether (3 X 25 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain (*R*)-(-)-**190** enantiomer (0.18 g, 24% yield, 82% ee). The filtrate part was concentrated and the residue was treated as outlined above to obtain (*S*)-(+)-**190** enantiomer (0.53 g, 71% yield, 20% ee).

After decomposition:

From precipitate:



R-(-)-**190**

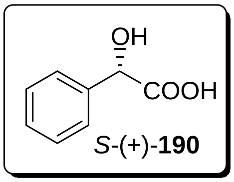
Yield 0.18 g (24%)

$[\alpha]_D^{25}$ -126 (*c* 1, H_2O), {lit.[147] for 100% ee,

$[\alpha]_D^{25}$ = -153 (*c* 2.5, H_2O)}

Enantiomeric purity 82% ee (determined by HPLC using chiral column, chiralcel OD-H).[146]

From filtrate:



S-(+)-**190**

Yield 0.53 g (71%)

$[\alpha]_D^{25}$ +31 (*c* 1, H_2O), {lit.[147] for 100% ee

$[\alpha]_D^{25}$ = +154 (*c* 2.8, H_2O)}

Enantiomeric purity 20% ee (determined by HPLC using chiral column, chiralcel OD-H), solvent system, hexanes:*i*-PrOH:trifluoroacetic acid=875:125:2.5, flow rate 0.5 mL/min., retention time of racemic mandelic acid **190** showed two peaks at 16.33 min. (*R*) and 18.14 min. (*S*) in 1:1 ratio on chiral column, chiralcel-OD-H.[146] Similar HPLC analysis of the chiral mandelic acid (*R*)-**190** showed two peaks at (minor) 16.33 min. (*S*) and (major) 18.14 min. (*R*) in the ratio of 9:91 indicating that its enantiomeic purity indicating that its enantiomeic purity is 82% ee (for precipitate fraction). In the similar way HPLC analysis of the chiral mandelic acid (*S*)-**190** showed two peaks at 16.33 min. (*S*) and 18.14 (*R*) in the ratio of 60:40 indicating that its enatiomeric purity is 20% ee for filtrate fraction.

Purification of partially resolved mandelic acid (190)

Further enrichment of (*R*)-(-)-**190** sample with 82% ee following the repetitive resolution procedure gave (*R*)-(-)-**190** enantiomer (0.11 g, 61% yield, 97% ee) from the precipitate fraction. $[\alpha]_D^{25}$ = -151 (*C* 1, H_2O) lit.[147] $[\alpha]_D^{25}$ =-153 (*C* 2.5, H_2O). The filtrate part after workup gave the (*R*)-(-)-**190** enantiomer (49 mg, 27% yield, 26% ee). The samples were also analyzed using HPLC (chiralcel OD-H, eluent: hexanes: 2-propanol: trifluoroacetic acid=875:125:2.5, v/v).[146]

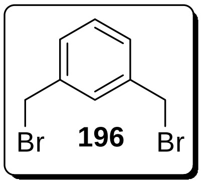
3.7 Synthesis of di(bromomethyl) benzene derivatives

3.7.1 Preparation of 1,3-di(bromomethyl)benzene (196)

$NaBH_4$ (4.56 g, 120 mmol) in THF (20 mL) was taken in a two neck RB flask. I_2 (12.69 g, 50 mmol) in THF (20 mL) was added slowly for about 1.5 h through a pressure equalizer at 0 ^{o}C under N_2 atmosphere. Isophthalic acid (8.30 g, 50 mmol) was added slowly using a solid addition flask. The mixture was refluxed for 12 hrs. It was brought to 25 ^{o}C and was carefully quenched with 3N HCl (20 mL). The organic layer was extracted with ether (3 x 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get the crude diol. It was used as such in the next step.

Hydrobromic acid (48%, 21 mL, 125 mmol) was taken in a two neck 50 mL RB flask. The reaction flask was cooled to 0 °C and conc. H_2SO_4 (3 mL) was added in portions with shaking. The diol (5.74 g, 41.57 mmol) was added followed by conc. H_2SO_4 (2.2 mL) in several portions with shaking. The reaction mixture was refluxed gently at 80 °C for 12 h. The product was separated by adding CH_2Cl_2 (10 mL) and water (10 mL). The organic layer was washed with 10% $NaHCO_3$ (20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a silica gel column to obtain the dibromo compound **196** using hexanes as eluent.

Yield	0.84 g (90%)
mp	76 °C {Lit.[148] mp 77 °C}
IR (KBr)	(cm^{-1}) 2968, 696



196

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 4.39 (s, 4H), 7.28 (m, 4H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 32.5, 129.4, 138.0

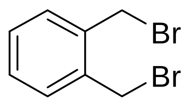
3.7.2 Preparation of 1,2-di(bromomethyl)benzene (197)

$NaBH_4$ (4.56 g, 120 mmol) in THF (20 mL) was taken in a two neck RB flask. I_2 (12.69 g, 50 mmol) in THF (20 mL) was added slowly for about 1.5 h through a pressure equalizer at 0 °C under N_2 atmosphere. Phthalic acid (8.3 g, 50 mmol) was added slowly using a solid addition flask. The mixture was refluxed for 12 h. It was brought to 25 °C and was carefully quenched with 3N HCl (20 mL). The organic layer was extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get the crude diol. It was used as such in the next step.

Hydrobromic acid (48%, 21 mL, 125 mmol) was taken in a two neck 50 mL RB flask. The reaction flask was cooled to 0 °C and conc.H_2SO_4 (3 mL) was added in portions with shaking. The diol (5.74 g, 41.57 mmol) was added followed by conc. H_2SO_4 (2.2 mL) in several portions with shaking. The reaction mixture was refluxed gently at about 80 °C for 12 h. The product was separated by adding CH_2Cl_2 (10 mL) and water (10 mL). The organic layer was washed with 10% $NaHCO_3$ (20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a silica gel column to obtain the dibromo compound **197** using hexanes as eluent.

Yield 0.76 g (86%)

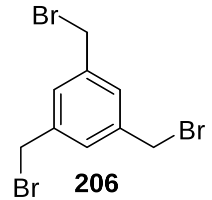
mp	88 °C{Lit.[148]mp 95 °C}
IR (KBr)	(cm^{-1}) 2968, 696
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 4.67 (s, 4H), 7.31 (m, 4H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 29.9, 129.4, 138.0


197

3.7.3 Preparation of 1,3,5-tri(bromomethyl)benzene (206)

Freshly distilled mesitylene (13.9 mL, 100 mmol) and freshly recrystallised *N*-bromosuccinamide (53.4 g, 300 mmol) were taken in dry CCl_4 (250 mL) in a 500 mL single neck RB flask containing a side septum under N_2 atmosphere. The reaction mixture was allowed to reflux for 24 h. The reaction mixture was filtered off to remove succinamide and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane to elute the tribromo product **206**.

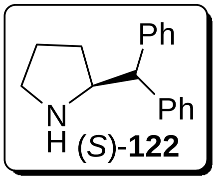
Yield	18.6g (52%)
m.p	93-94 °C {Lit.[149] 94 °C}
IR (KBr)	(cm^{-1}) 2968, 702
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 4.47 (s, 6H), 7.37 (s, 3H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm 32.4, 129.6, 139.0


206

3.8 Preparation of chiral amines

3.8.1 Preparation of (*S*)-α,α-diphenyl–2-pyrrolidinemethane (122)

(*S*)-(-)-α,α-Diphenylpyrrolidinemethanol **68** (0.25 g, 1 mmol) in CH_2Cl_2 (25 mL) was taken in a two necked 50ml RB flask under N_2 atmosphere. Trifluoroacetic acid (7.67 g, 5 mL, 67.3 mmol) was added at 0 °C for about 10 min. through pressure equalizer followed by $NaBH_4$ (1.10 g, 29.3 mmol) addition through a solid addition flask for about 30 min and stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aq. NaOH (20 mL). CH_2Cl_2 (20 mL) was added and the contents were stirred for 15 min. The CH_2Cl_2 layer was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was subjected to chromatography on silica gel column to obtain the (*S*)-α,α-diphenyl-2-pyrolidinemethane **122** using $CHCl_3/CH_3OH$ (99:1) as eluent.


(*S*)-**122**

Yield	0.162 g (66%)
$[\alpha]_D^{25}$	-7.8 (*c* 2.0, $CHCl_3$), {lit.[96] $[\alpha]_D^{25}$ 7.8 (*c* 2.1, $CHCl_3$)}
IR (neat)	(cm^{-1}) 3405, 2962
^1H-NMR	(400 MHz, $CDCl_3$, δ ppm) 7.28 (m, 10H), 3.89 (m, 2H), 2.93-2.85 (m, 2H), 1.69 (m, 3H), 1.37 (m, 1H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 24.3, 30.5, 45.6, 57.2, 62.1, 126.4, 127.9, 128.4, 128.6, 142.8, 142.9

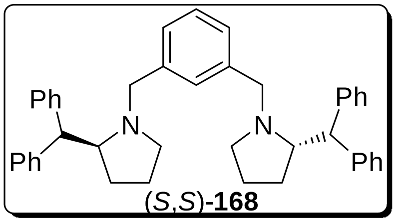
Enantiomeric purity >99% ee (determined by HPLC using chiral column, chiralcel OD H).

HPLC analysis of the acetamide derivative of (*S*)-α,α-diphenyl–2-pyrrolidinemethane

(*S*)-α,α-diphenyl-2-pyrolidinemethane **122** (0.11 g, 0.46 mmol) in CH_2Cl_2 (10 mL) was taken in a single necked 50 mL RB flask under N_2 atmosphere. Acetyl chloride (0.05 mL, 0.7 mmol) was added, followed by pyridine (0.05 mL, 0.7 mmol) at 0 °C and allowed to stirr at 0 °C-25 °C for about 12 h. The reaction mixture was quenched with water (5 mL). CH_2Cl_2 (20 mL) was added and the contents were stirred for 15 min. The CH_2Cl_2 layer was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was subjected to chromatography on silica gel column to obtain the corresponding acetamide using hexane/ethyl acetate (60:40) as eluent. The acetamide obtained in this way was subjected to HPLC analyses using chiralcel OD-H supplied by Diacel Chemical Industries, Ltd. With a binary gradient method using hexanes:*i*-PrOH (90:10) in the flow rate of 1.0 mL/min. with retention time at 10.3 min. for (*S*) and 13.7 min. for (*R*) isomer.

3.8.2 Preparation of (2*S*)-2-benzhydryl-1-{3-[(2*S*)-2-benzhydryl tetrahydryl terahydro-1H-1-pyrrolyl methyl]benzyl}terahydro-1H-pyrrole (168)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethane **122** (0.46 g, 2 mmol) and 1,3-bis(bromomethyl)benzene **196** (0.27 g, 1 mmol) were taken in 20 mL dry CH_3CN in a 50 mL single-neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (10 mg) was added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (97:3) to elute the product **168**.



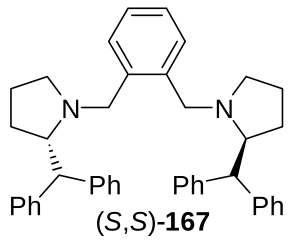
(*S*,*S*)-**168**

Yield	0.22 g (39%)
$[\alpha]_D^{25}$	+7.0 (*c* 1.7, $CHCl_3$)
IR (neat)	(cm^{-1}) 3024, 2934, 1599, 752
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.43-1.65 (m, 6H), 1.88-1.98 (m, 2H), 2.15-2.22 (m, 2H), 2.81-2.87 (m, 2H), 3.04-3.09 (m, 2H), 3.40-3.45(m, 2H), 3.56 (d, *J* = 12 Hz, 2H), 4.06 (d, *J* = 12 Hz, 2H), 6.93-6.95 (m, 2H), 7.17 (m, 22H) **(Spectrum No. 31)**
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 23.6, 30.1, 54.5, 57.0, 60.5, 67.4, 126.0, 126.2, 127.1, 128.1, 129.1, 139.9, 143.8, 144.0 **(Spectrum No. 32)**
Analysis	Calculated for $C_{42}H_{44}N_2$: C, 87.45 %; H, 7.69 %; N, 4.86 %
	Found : C, 87.42 %; H, 7.69 %; N, 4.90 %
LCMS	*m/z* 577 (M+1)

3.8.3 Preparation of (2*S*)-2-benzhydryl-1-{2-[(2*S*)-2-benzhydryl tetrahydryl terahydro-1H-1-pyrrolyl methyl]benzyl}terahydro-1H-pyrrole (167)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethane **122** (0.46 g, 2 mmol) and 1,2-bis(bromomethyl)benzene **197** (0.27 g, 1 mmol) were taken in 20 mL dry CH_3CN in a 50 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (10 mg) was added and the reaction mixture was refluxed for 24 h.

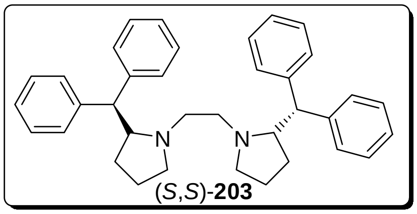
The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (97:3) to elute the product **167**.


(*S*,*S*)-**167**

Yield	0.19 g (34%)
$[\alpha]_D^{25}$	+14.8 (*c* 0.5, $CHCl_3$)
IR (neat)	(cm^{-1}) 3024, 2825, 1590, 753
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.92-2.27 (m, 4H), 3.80 (t, *J* = 8 Hz, 2H), 4.14 (d, *J* = 11 Hz, 2H,), 4.38-4.40 (m, 2H), 4.65-4.76 (m, 4H), 4.89 (d, *J* = 12 Hz, 2H), 5.20 (d, *J* = 12 Hz, 2H), 5.76 (q, *J* = 10 Hz, 2H), 6.64 (d, *J* = 8 Hz, 2H), 7.18 (m, 22H) **(Spectrum No. 33)**
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 18.9, 28.9, 53.1, 61.4, 67.6, 76.3, 122.2, 122.8, 127.0, 127.2, 127.8, 128.51, 128.6, 128.7, 128.8, 129.0, 129.1, 129.9, 132.3, 133.1, 139.1, 141.7 **(Spectrum No. 34)**
Analysis	Calculated for $C_{42}H_{44}N_2$: C, 87.45 %; H, 7.69 %; N, 4.86 %
	Found : C, 87.45 %; H, 7.69 %; N, 4.87 %
LCMS	*m/z* 577 (M+1)

3.8.4 Preparation of (2*S*)-2-benzhydryl-1-{2-[(2*S*)-2-benzhydryltetrahydro-1H-1-pyrrolyl]ethyl}tetrahydro-1H-pyrrole (203)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethane **122** (0.47 g, 2 mmol) and 1,2-dibromoethane (0.1 mL, 1.1 mmol) were taken in 20 mL dry CH_3CN in a 50 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (1.0 g) and KI (10 mg) were added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (30:70) to elute the product **203**.



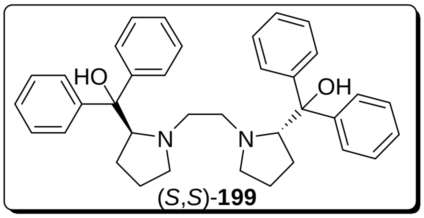
(*S*,*S*)-**203**

Yield	0.37 g (74%)
mp	102-103 °C (lit.[96] mp 103-104°C)
$[\alpha]_D^{25}$	-49.1 (*c* 1.3, $CHCl_3$) {lit.[96] $[\alpha]_D^{25}$ -49.5 (*c* 1.0, $CHCl_3$)}
IR (KBr)	(cm^{-1}) 3026, 2825, 1493, 703
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.36-1.58 (m, 6H), 1.76-1.86 (m, 2H), 2.06-2.14 (m, 4H), 2.38-2.43 (m, 2H), 2.92-2.96 (m, 2H), 3.17-3.23 (m, 2H), 3.89 (d, *J* = 7.3 Hz, 2H), 7.15-7.33 (m, 20H) **(Spectrum No. 35)**
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 23.7, 29.8, 54.5, 54.6, 56.7, 67.8, 126.0, 126.2, 128.0, 128.3, 128.9, 129.1, 143.6, 144.1 **(Spectrum No. 36)**

LCMS *m/z* 501 (M+1)

3.8.5 Preparation of (2*S*)-1-{2-[(2*S*)-2-hydroxy(diphenyl)methyltetrahydro-1H-1-pyrrolyl]ethyl}tetrahydro-1H-2-pyrrolyl-diphenylmethanol (199)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol **68** (0.50 g, 2 mmol) and 1,2-dibromoethane (0.1 mL, 1.1 mmol) were taken in 20 mL dry CH_3CN in a 50 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (1.0 g) and KI (10 mg) were added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (93:7) to elute the product **199**.



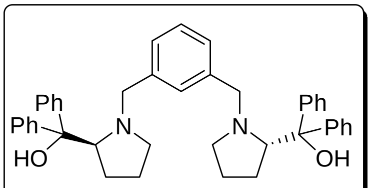
(*S*,*S*)-**199**

Yield	0.54 g (74%)
mp	173-175 °C (lit.[79] mp 174-175°C)
$[\alpha]_D^{25}$	-5.3 (*c* 1.0, CH_2Cl_2), {lit.[79] $[\alpha]_D^{25}$ -5.6 (*c* 1.0, CH_2Cl_2)}
IR (KBr)	(cm^{-1}) 3349, 3026, 2825, 1493, 1180, 703
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.38-1.62 (m, 6H), 1.65-1.70 (m, 2H), 1.72-1.97 (m, 4H,), 2.16-2.22 (m, 2H), 2.32-2.39 (m, 2H), 3.69-3.75 (m, 2H,), 4.75 (br s,1H), 7.08-7.32 (m, 12H),7.48-7.53 (m, 4H), 7.64-7.68 (m, 4H)

^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 24.1, 29.6, 53.9, 54.8, 70.0, 77.3, 125.4, 125.7, 126.0, 126.1, 127.9, 128.1, 147.0, 148.5

3.8.6 Preparation of (2*S*)-1-(3-((2*S*)-2-hydroxy(diphenyl)methyltetrahydro-1H-1-pyrrolylmethyl)benzyl)tetrahydro-1H-2-pyrrolyl-diphenylmethanol (198)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol **68** (0.50 g, 2 mmol) and 1,3-bis(bromomethyl)benzene **196** (0.27 g, 1 mmol) were taken in 20 mL dry CH_3CN in a 50 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (10 mg) were added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (95:5) to elute the product **198**.



(*S*,*S*)-**198**

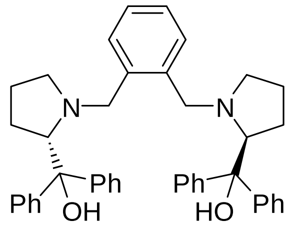
Yield	0.22 g (39%)
mp	170-172 °C (lit.[179] mp 170-171 °C)
$[\alpha]_D^{25}$	+18.4 (*c* 1.0, CH_2Cl_2) {lit.[79]$[\alpha]_D^{25}$ +18.8 (*c* 0.50, CH_2Cl_2)}
IR (KBr)	(cm^{-1}) 3345, 3023, 2825, 1492, 11790, 703
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.61-1.66 (m, 4H), 1.74-1.81 (m, 2H), 1.94-1.99 (m, 2H), 2.30-2.36 (m, 2H), 2.84-2.98 (m, 2H), 2.97 (d, *J* = 12 Hz, 2H), 3.19 (d, *J* = 12 Hz, 2H), 3.95-3.99 (m, 2H), 4.95 (s, 2H), 6.83-6.85 (d, *J* = 7.7 Hz,

	2H), 7.06-7.11 (m, 4H), 7.15-7.18 (m, 2H), 7.26-7.32 (m, 8H), 7.59 (d, *J* = 7.7 Hz, 4H), 7.74 (d, *J* = 7.7 Hz, 4H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 24.2, 29.7, 55.5, 60.4, 70.6, 77.9, 125.6, 125.7, 126.2, 126.4, 127.1, 127.8, 128.1, 128.2, 128.7, 139.5, 146.7, 148.1

3.8.7 Preparation of (2*S*)-1-(2-((2*S*)-2-hydroxy(diphenyl)methyltetrahydro-1H-1-pyrrolylmethyl)benzyl)tetrahydro-1H-2-pyrrolyl-diphenylmethanol (202)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol **68** (0.50 g, 2 mmol) and 1,2-bis(bromomethyl)benzene **197** (0.27 g, 1 mmol) were taken in 15-20 mL dry CH_3CN in a 50 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (5-10 mg) were added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (93:7) to elute the product **202**.

Yield	0.19 g (34%)
mp	110-111 °C (lit.[79] mp 110-112 °C)
$[\alpha]_D^{25}$	+4.8 (*c* 0.4, $CHCl_3$) {lit.[79] $[\alpha]_D^{25}$ = +4.5 (*c* 0.53, CH_2Cl_2)}
IR (KBr)	(cm^{-1}) 3349, 3028, 2825, 1497, 1180, 703



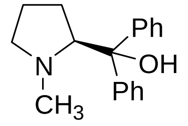
(*S*,*S*)-**202**

^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.52-1.65 (m, 4H), 1.70-1.77 (m, 2H), 1.93-2.03 (m, 2H), 2.19-2.26 (m, 2H), 2.71-2.76 (m, 2H), 2.93 (d, *J* = 12 Hz, 2H), 3.07 (d, *J* = 12 Hz, 2H), 3.95-3.99 (m, 2H), 4.84 (s, 2H), 7.05-7.33 (m, 16H), 7.58 (d, *J* =8 Hz, 4H), 7.67 (d, *J* =8 Hz, 4H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 24.2, 29.8, 55.5, 57.1, 71.3, 78.0, 125.5, 125.7, 126.3, 126.6, 128.1, 128.8, 137.2, 146.7, 147.9

3.8.8 Synthesis of *N*-methyl diphenylpyrrolidine methanol (201)

Synthesis of *N*-methyl diphenylpyrrolidine methanol **201** was carried out by the reaction of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol **68** with formic acid and formaldehyde mixture.[131]

To a solution of (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol **68** (1.26 g, 5.0 mmol) in formic acid (2.4 mL) was added formaldehyde at 100 °C (37 % aqueous solution, 1.8 mL) and stirring was continued for 20 h. The mixture was cooled and made alkaline with 2N NaOH followed by extraction with ethyl acetate (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel column using hexane/ethyl acetate (98:2) to elute the product **201**.


(*S*)-**201**

Yield	0.88 g (66%)
mp	68-69 °C (lit.[72] mp 68.5-68.9 °C)
$[\alpha]_D^{25}$	+57.2 (*c* 0.4, $CHCl_3$) {lit.[72] $[\alpha]_D^{25}$ = +57.5 (*c* 1.0, $CHCl_3$)}
IR (KBr)	(cm^{-1}) 3024, 2934, 1599, 752

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.58-1.71 (m, 4H), 1.18(s, 3H), 2.45-2.47 (m, 1H), 3.11-3.14 (m, 1H), 3.61-3.65 (m, 1H), 4.81 (s, 1H), 7.14-7.15 (m, 2H), 7.26-7.30 (m, 4H), 7.55(d, *J* = 7.6 Hz, 2H), 7.65(d, *J* = 7.6 Hz, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 24.0, 29.9, 43.0, 59.1, 72.0, 125.5, 126.1, 128.0, 146.8, 148.3

3.8.9 Synthesis of *N*-methyl diphenylpyrrolidine methane (205)

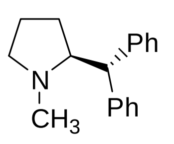
Preparation was carried as above by treating (*S*)-α,α-diphenyl-2-pyrrolidinemethane **62** using formic acid and formaldehyde mixture.[131]

To a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethane **122** (1.18 g, 5.0 mmol) in formic acid (2.4 mL) was added formaldehyde at 100 °C (37 % aqueous solution, 1.8 mL) and stirring was continued for 20 h. The mixture was cooled and made alkaline with 2N NaOH followed by extraction with ethyl acetate (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel column using hexane/ethyl acetate (8:2) to elute the product **205**.

Yield 0.8 g (64%)

$[\alpha]_D^{25}$ +10.7 (*c* 1.0, $CHCl_3$)

IR (KBr) (cm^{-1}) 3024, 2934, 1599, 752



(*S*)-**205**

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.58-1.66 (m, 3H), 1.82-1.92 (m, 1H), 1.96 (s, 3H), 2.25-2.31 (m, 1H), 3.04-3.13 (m, 2H), 3.91 (d, *J* = 4 Hz, 1H), 7.12-7.18 (m, 2H), 7.22-7.29 (m, 6H), 7.35-7.37(m, 2H) **(Spectrum No. 37)**

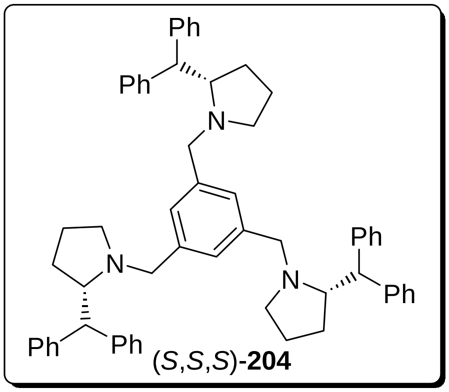
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 22.8, 31.1, 42.8, 57.8, 58.5, 69.0, 126.0, 126.2, 128.2, 128.4, 128.6, 144.2 **(Spectrum No. 38)**

3. 9 Synthesis of tripodal compounds

3.9.1 Synthesis of (2*S*)-1-{3,5-di[(2*S*)-2-benzhydryltetrahydro-1H-1-pyrrolylmethyl]-benzyl}tetrahydro-1H-2-pyrrolyl(diphenyl)methane (204)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethane **122** (0.71 g, 3.0 mmol) and tri bromide **206** **(**0.53 g, 1.5 mmol) were taken in 40 mL dry CH_3CN in a 100 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (10 mg) were added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (93:7) to elute the product **204**.

Yield	0.26 g (32%)
$[\alpha]_D^{25}$	-10.0 (*c* 0.4, $CHCl_3$)
IR (neat)	(cm^{-1}) 3024, 2934, 1599, 752
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.48-1.75 (m, 3H), 1.88-2.24 (m, 2H), 2.72-3.10 (m, 2H), 3.45 (d, 2H, *J*=12 Hz), 4.08 (s, 1H), 7.17 (m, 33H) **(Spectrum No. 39)**



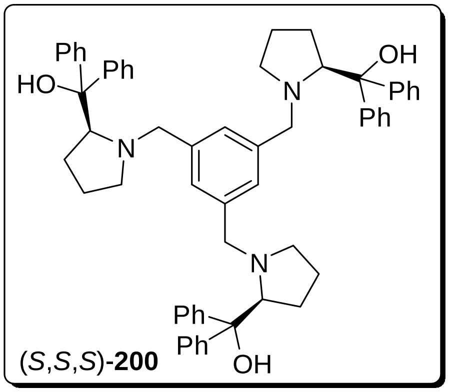
(*S*,*S*,*S*)-**204**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 23.6, 30.3, 54.6, 56.8, 60.5, 67.6, 126.0, 126.2, 128.1, 128.3, 129.1, 139.3, 144.0 **(Spectrum No. 40)**

3.9.2 Synthesis of (2*S*)-1-{3,5-di[(2*S*)-2-hydroxy(diphenyl)methyltetrahydro-1H-1-pyrrolylmethyl]-benzyl}tetrahydro-1H-2-pyrrolyl(diphenyl)methanol (200)

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol **68** (0.76 g, 3.0 mmol) and tri bromide **206** **(**0.53 g, 1.5 mmol) were taken in 40 mL dry CH_3CN in a 100 mL single neck RB flask containing a side septum under N_2 atmosphere. Oven dried K_2CO_3 (2.0 g) and KI (10 mg) was added and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered off to remove K_2CO_3 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (20 mL) and water (10 mL) were added and stirred for 15 min. The organic extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel column using hexane/ethyl acetate (93:7) to elute the product **200**.

Yield 0.25 g (30%)



(*S*,*S*,*S*)-**200**

m.p 114-115 °C (lit.[71] mp 114-116 °C)

$[\alpha]_D^{25}$ +111.0 (*c* 0.4, CH_2Cl_2) {lit.[71] $[\alpha]_D^{25}$ +110.0 (*c* 1.1, CH_2Cl_2)}

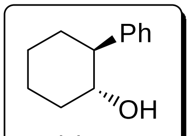
IR (KBr) (cm^{-1}) 3024, 2934, 1599, 752

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.9-2.1 (m, 4H), 2.2-2.4 (m,1H), 2.70-2.83 (m, 1H), 2.92 (d, *J* = 12 Hz, 1H), 3.14 (d, *J* = 12 Hz, 1H), 3.97-4.00 (m, 1H), 4.92 (s,1H), 7.10-7.34 (m, 27H), 7.63 (d, *J* = 7.58 Hz, 3H), 7.79 (d, *J* = 7.60 Hz, 3H)

^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 24.2, 29.8, 55.4, 60.3, 70.6, 77.9, 125.6, 125.7, 126.3, 126.4, 127.3, 128.1, 128.2, 139.9, 146.7, 148.1

3.10 Synthesis of (±) *trans*-2-phenylcyclohexanol (209)

To a 250 mL three-neck reaction flask was taken magnesium turnings (3.57 g, 147 mmol) in N_2 atmosphere. To it, 40 mL of dry THF was added and bromobenzene (15.5 mL, 147 mmol) dissolved in 100mL dry THF was added dropwise at 0 °C for about 30 min. Then the reaction mixture was cooled to -30 °C and CuCl (0.65 g, 6.6 mmol) was added gradually through solid addition funnel. The resulting mixture was allowed to stir at this temperature for about 15 min. and then a solution of cyclohexene oxide (10.1 mL, 100 mmol) in dry THF (10 mL) was added dropwise slowly for a period of about 40 min. Upon completion of the addition, the reaction mixture was warmed to 0 °C and stirred for 2 h, then quenched by saturated ammonium sulfate solution (15-25 mL). The layers were separated and the organic layer was washed with saturated ammonium sulfate solution (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel column using hexane/ethyl acetate (97:3) to elute the product **209**.



(±)-**209**

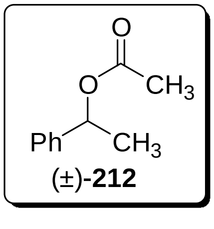
Yield	14.2 g (80%)
mp	56-57 °C (lit.[142] mp 57-58 °C)
IR (KBr)	(cm^{-1}) 3461, 2941, 2863, 1604, 1497

^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.34-1.60 (m, 5H), 1.75-1.88 (m, 3H), 2.11-2.17 (m, 1H), 2.40-2.46 (m, 1H), 3.65-3.69 (m, 1H), 7.22-7.26 (m, 3H), 7.32-7.36 (m, 2H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.1, 26.0, 33.3, 34.4, 53.2, 74.3, 126.7, 127.9, 128.7, 143.4

3.11 Representative procedure for the kinetic resolution of racemic 1-phenylethanol 138a

To a stirred solution of racemic 1-phenylethanol **119** (0.6 mL, 5 mmol) in CH_2Cl_2 (5 mL), the chiral diamine (5 mol%) and triethylamine (0.52 mL, 3.75 mmol) were added at -30 °C and stirred for about 45 min. Acetic anhydride (0.35 mL, 3.75 mmol) was then added to the reaction mixture and continued to stir for another 48 h. The reaction was quenched with water (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed on a silica gel column using hexanes:ethyl acetate (99:1) as eluent to isolate 1-phenylethyl acetate **212** and hexanes:ethyl acetate (97:3) as eluent to isolate 1-phenylethanol **138a**.

1-Phenylethyl acetate (212)

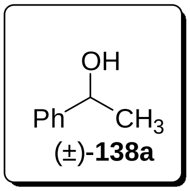


(±)-**212**

Yield	0.32g (38%)
IR (neat)	(cm^{-1}) 3034, 2982, 2934, 1747, 1244, 761
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.56 (d, *J* = 6.4 Hz, 3H), 2.10 (s, 3H), 5.91 (q, *J* = 6.4 Hz, 1H), 7.31-7.39 (m, 5H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 21.2, 22.1, 72.2, 126.0, 127.8, 128.4, 141.7, 170.1

Enantiomeric purity Racemic product {determined by HPLC using chiral column, chiralcel OB-H, hexanes:*i*-PrOH/99:1; flow rate 0.5 mL/min, Retention time: 15.4 min and 17.9 min.}.

1-Phenylethanol (138a)



(±)-**138a**

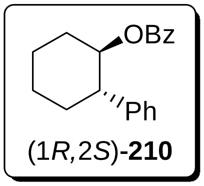
Yield	0.28g (47%)
IR (neat)	(cm^{-1}) 3352, 3063, 3030, 2973, 761
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.52 (d, *J* = 6.4 Hz, 3H), 4.91 (q, *J* = 6.4 Hz, 1H), 7.30-7.39 (m, 5H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.0, 70.2, 125.3, 127.3, 128.4, 145.8

Enantiomeric purity Racemic product {determined by HPLC using chiral column, chiralcel OD-H, hexanes: *i*-PrOH/95:5; flow rate: 1.0 mL/min, retention time: 8.0 and 8.8 min.}.

3.12 Representative procedure for the kinetic resolution of racemic (±) *trans*-2-phenylcyclohexanol 209 using ligand 198

To a stirred solution of racemic *trans*-2-phenylcyclohexanol **209** (0.44 g, 2.5 mmol) in CH_2Cl_2 (5 mL), the chiral catalyst **198** (0.3 g, 0.5 mmol, 20 mol%) and triethylamine (0.17 mL, 1.25 mmol) were added at -78 °C and stirred for about 15 min. Benzoyl chloride (0.21 mL, 1.87 mmol) was then added to the reaction mixture and continued to stir for another 48 h. The reaction was quenched with water (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on a silica gel column using hexanes as eluent to isolate ester **210** and hexanes:ethyl acetate (97:3) as eluent to isolate phenylcyclohexanol **209**.

1*R*,2*S*-Cyclohexanol, 2-phenyl-1-benzoate (210)



(1*R*,2*S*)-**210**

Yield 0.16g (24%)

$[\alpha]_D^{25}$ + 3.5 (*c* 0.5, $CHCl_3$)

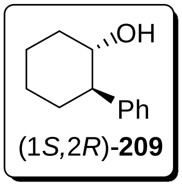
IR (neat) (cm^{-1}) 3034, 2982, 2934, 1788, 1214, 761

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.41-1.73 (m, 4H), 1.84-2.05 (m, 3H), 2.30-2.33 (m, 1H), 2.84-2.91 (m, 1H), 5.17-5.23 (m, 1H), 7.12-7.15 (m, 1H), 7.23-7.26 (m, 4H), 7.4-7.52 (m, 2H), 7.82 (d, *J* = 4 Hz, 2H), 8.08-8.15 (m,1H) **(Spectrum No. 41)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 24.8, 25.9, 32.4, 33.9, 49.9, 76.9, 126.4, 127.4, 128.1, 128.3, 128.4, 128.5, 129.3, 129.7, 130.2, 130.7, 132.5, 133.0, 133.7, 143.1, 165.9 **(Spectrum No. 42)**

<u>**Enantiomeric purity**</u> 35% ee {determined by HPLC using chiral column, chiralpak AD-H, hexanes:*i*-PrOH = 99:1, Flow rate: 0.5 mL/min, Retention time: 19.7 (1*R*,2*S* major isomer) and 46.1 (1*S*,2*R* minor isomer)}.[150]

1*S*,2*R*-Phenylcyclohexanol (209)



(1*S*,2*R*)-**209**

Yield 0.30g (68%)

mp 59-61 °C (lit.[142] mp 60-62 °C)

$[\alpha]_D^{25}$ +6.1 (*c* 1.0, MeOH) {lit.[142] $[\alpha]_D^{25}$ = +52.8 (*c* 5.4, MeOH)}

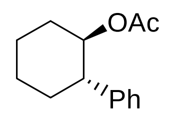
IR (KBr)	(cm^{-1}) 3461, 2941, 2863, 1604, 1497
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.34-1.60 (m, 5H), 1.75-1.88 (m, 3H), 2.11-2.17 (m, 1H), 2.40-2.46 (m, 1H), 3.65-3.69 (m, 1H), 7.22-7.26 (m, 3H), 7.32-7.36 (m, 2H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.1, 26.0, 33.3, 34.4, 53.2, 74.3, 126.7, 127.9, 128.7, 143.4

Enantiomeric purity 14% ee {determined by HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH = 99.5:0.5, Flow rate: 0.5mL/min, Retention time: 39.0 (1*R*,2*S* minor isomer) and 46.1 (1*S*, 2*R* major isomer)}.

3.13 Representative procedure for the kinetic resolution of racemic (±) *trans*-2-phenylcyclohexanol 209 using ligand 167

To a stirred solution of racemic *trans*-2-phenylcyclohexanol **209** (0.44 g, 2.5 mmol) in dichloromethane (5 mL), the chiral ligand **167** (0.3 g, 0.5 mmol, 20 mol %) and triethylamine (0.17 mL, 1.25 mmol) were added at -78°C and stirred for about 15 min. Acetic anhydride (0.177 mL, 1.87 mmol) was then added to the reaction mixture and continued to stir for another 48 h. The reaction was quenched with water (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on a silica gel column using hexanes as eluent to isolate ester **213** and hexanes:ethyl acetate (97:3) as eluent to isolate phenylcyclohexanol **209**.

1*R*,2*S*-Cyclohexanol,-2-phenyl-1-acetate (213)



(1*R*,2*S*)-**213**

Yield 0.15g (27%)

$[\alpha]_D^{25}$ -1.1(*c* 0.8, EtOH) {lit.[151] $[\alpha]_D^{25}$ = -6.5(*c* 0.32, EtOH)}

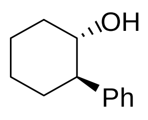
IR (neat) (cm^{-1}) 3034, 2982, 2934, 1736, 1242, 1037

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.36-1.64 (m, 4H), 1.79 (s, 3H), 1.82-1.98 (m, 3H), 2.11-2.17 (m, 1H), 2.64-2.71 (m, 1H), 4.96-5.03 (m, 1H), 7.19-7.22 (m, 3H), 7.28-7.31 (m, 2H) **(Spectrum No. 43)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 20.9, 24.7, 25.8, 32.3, 33.8, 49.7, 75.9, 126.3, 127.5, 128.2, 148.1, 170.3 **(Spectrum No. 44)**

<u>**Enantiomeric purity**</u> 13% ee {determined by HPLC using chiral column, chiralpak AS-H, hexanes: *i*-PrOH = 99:1, Flow rate: 0.5 mL/min, Retention time: 9.7 (minor 1*S*,2*R* isomer) and 10.9 (1*R*,2*S* major isomer)}.

1*S*,2*R*-Phenylcyclohexanol (209)



(1*S*,2*R*)- **209**

Yield 0.28 g (64%)

mp 59-61 °C (lit.[142] mp 60-62 °C)

$[\alpha]_D^{25}$ +4.2 (*c* 1.0, MeOH) {lit.[142] $[\alpha]_D^{25}$ = +52.8 (c 5.4, MeOH)}

IR (KBr) (cm^{-1}) 3461, 2941, 2863, 1604, 1497

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.34-1.60 (m, 5H), 1.75-1.88 (m, 3H), 2.11-2.17 (m, 1H), 2.40-2.46 (m, 1H), 3.65-3.69 (m, 1H), 7.22-7.26 (m, 3H), 7.32-7.36 (m, 2H)

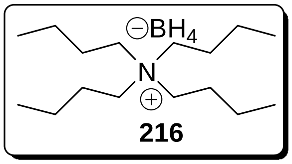
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.1, 26.0, 33.3, 34.4, 53.2, 74.3, 126.7, 127.9, 128.7, 143.4

Enantiomeric purity 8% ee {determined by HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH = 99.5:0.5, flow rate: 0.5 mL/min, retention time: 39.0 (1*R*, 2*S* minor isomer) and 46.1 (1*S*,2*R,* major isomer)}.

3.14 Preparation of tetraalkylammonium boronate species

3.14.1 Preparation of tetrabutylammonium borohydride (216)[114]

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



216

Yield 25.32 g (98%)

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

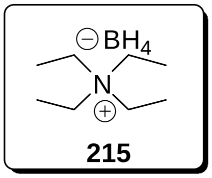
^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -39.93 {δ = 0, BF_3:Et_2O}

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.99 (t, *J* = 8 Hz, 3H), 1.46 (m, 2H), 1.62 (m, 2H), 3.29 (t, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 13.5, 19.5, 24.0, 58.8

3.14.2 Preparation of tetraethylammonium borohydride (215)[124]

To a single neck 100 mL reaction flask with side septum tetraethylammonium chloride (5.51 g, 30 mmol) was dissolved in DMF (70 mL) under N_2 atmosphere. To it solution of $NaBH_4$ (1.14 g, 30 mmol) in DMF (5 mL) was added and the reaction mixture was allowed to stir for 30 min. The reaction mixture was then filtered off and the filtrate was diluted with ether (150 mL) to obtain white turbid solution. The solution was cooled at 0 °C for about 10 min. and filtered off. To remove the traces of DMF present, the precipitate was dried under reduced pressure to obtain tetraethylammonium borohydride as white solid.


215

Yield 4.14 g (95%)

IR (neat) (cm^{-1}) 2982, 2291, 2208, 2137, 1070

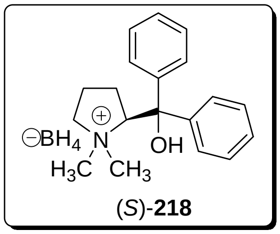
^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -40.23 {δ = 0, BF_3:Et_2O}

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.37 (t, *J* = 8 Hz, 3H), 3.41 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 7.7, 52.8

3.15 Preparation of (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium borohydride (218)

A mixture of (*S*)-(-)-α,α-diphenylpyrrolidinemethanol **68** (1.26 g, 5 mmol), methyl iodide (0.62 mL, 10 mmol) and oven dried K_2CO_3 (0.70 g, 5mmol) in dry CH_3CN (25 mL) was refluxed under N_2 atmosphere for 24 h. The reaction mixture was then filtered off to remove K_2CO_3 and the filterate was concentrated under reduced pressure to obtain (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium iodide **217** as white solid.[123] This iodide salt **217** was used as such in the next step. To a single neck 10 mL reaction flask with side septum (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium iodide **217** (2.04 g, 5 mmol) was dissolved in DMF (5 mL) under N_2 atmosphere. To it, solution of $NaBH_4$ (0.19g, 5 mmol) in DMF (3 mL) was then added and the reaction mixture was allowed to stir for 30 min. The precipitated NaI was filtered off and the filtrate was diluted with ether (50 mL). The solution was cooled at 0 °C for about 10 min and the product that precipitated was collected by filtration and washed with ether (2 x 25 mL). Additional amount of ether (50 mL) was added to the filtrate to precipitate out final traces of product which was then collected by filtration and washed with ether (2 x 25 mL). To remove the traces of DMF present, the combined precipitate products was dried under reduced pressure to obtain (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium borohydride **218** as white solid.



(*S*)-**218**

Yield	1.2 g (79%)
$[\alpha]_D^{25}$	-18.5 (*c* 0.4, DMSO)
IR (neat)	(cm^{-1}) 3489, 2376, 2287, 2222, 1630
^{11}B NMR	(128.3 MHz, DMSO-d_6, δ ppm) -40.97 {δ = 0, BF_3:Et_2O}
^{1}H NMR	(400 MHz, D_2O, δ ppm) 1.97-2.25 (m, 3H), 2.37-2.56 (m, 4H), 2.88-2.98 (m, 3H), 3.52-3.58 (m, 2H), 5.00 (t, 1H, *J* = 8 Hz), 7.24-7.40 (m, 6H), 7.54 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8 Hz, 2H) **(Spectrum No. 45)**
^{13}C NMR	(50 MHz, , D_2O- DMSO-d_6, δ ppm) 19.0, 24.9, 48.5, 53.9, 69.4, 77.9, 78.7, 125.59, 126.0, 127.6, 127.8, 128.8, 129.0, 144.1, 147.2 **(Spectrum No. 46)**

3.16 Typical experimental procedure to prove BH_3 species formation by preparation of PPh_3:BH_3 *in situ* from TBAB 216/CH_3I reagent system

Tetrabutylammonium borohydride **216** (1.02 g, 4 mmol) and triphenylphosphine (1.04 g, 4.0 mmol) in THF (25 mL) were taken in a two-neck RB flask. The contents were stirred at 25 °C for 5 min under N_2 atmosphere. Methyl iodide (0.56 g, 0.25 mL, 4 mmol) was added using a syringe and the reaction mixture was stirred for about 12 h. at room temperature. The solvent was evaporated and residue was subjected to column chromatography using silica gel to obtain triphenylphosphene borane complex using hexane/ethyl acetate (97:5) as eluent.

Yield	1.04 g (94%)
mp	187 °C (lit.[152] mp 188 °C)
IR (KBr)	(cm^{-1}) 2378, 2343, 2253, 740, 710
^{11}B NMR	(128.3 MHz, $CDCl_3$, δ ppm) -37.78 {$\delta = 0$, BF_3:Et_2O}
^{31}P NMR	(162 MHz, $CDCl_3$, δ ppm) 20.98 {$\delta = 0$, H_3PO_4}

The reaction was carried out in various solvents. The yields and melting point values are summarized below.

Solvent	**Yield (%)**	**mp (°C)**
CH_2Cl_2	84	188
Toluene	81	187

3.17 Typical experimental procedure to prove formation of BH_3 species via PPh_3:BH_3 by bubbling diborane generated from TBAB 216/CH_3I reagent system

In a two-neck reaction flask, tetrabutylammonium borohydride **216** (1.02 g, 4 mmol) dissolved in dry toluene (5 mL) and methyl iodide (0.56 g, 0.25 mL, 4 mmol) dissolved in dry toluene (25 mL) was added dropwise for 1 h. Thus generated diborane gas was bubbled through a side arm using a bubbler into another reaction flask containing triphenylphosphine (1.04 g, 4.0 mmol) in dry THF (25 mL) cooled at 0 °C. The reaction mixture was then stirred at 0-25 °C for about 12 h. The solvent was evaporated and residue was subjected to column chromatography using silica gel column to obtain triphenylphosphene borane complex using hexane/ethyl acetate (97:3) as eluent.

Yield	0.46 g (42%)
mp	187 °C (lit.[152] mp 188 °C)
IR (neat)	(cm^{-1}) 2378, 2343, 2253, 740, 710
^{11}B NMR	(128.3 MHz, $CDCl_3$, δ ppm) -37.81 {δ = 0, BF_3:Et_2O}
^{31}P NMR	(162 MHz, $CDCl_3$, δ ppm) 20.96 {δ = 0, H_3PO_4}

3.18 Typical experimental procedure to prove formation of BH_3 species via PPh_3:BH_3 by bubbling diborane generated from TBAB 216/I_2 reagent system

In a two-neck reaction flask, tetrabutylammonium borohydride **216** (1.02 g, 4 mmol) dissolved in dry toluene (5 mL) and iodine (0.50 g, 2 mmol) dissolved in dry toluene (35 mL) was added dropwise for about 4 h. Diborane generated was bubbled through a side tube using a bubbler into another reaction flask containing triphenylphosphine (1.04 g, 4.0 mmol) in dry THF (45 mL) cooled at 0 °C. The reaction mixture was then allowed to stir at 25 °C for about 12 h. The solvent was evaporated and residue was subjected to column chromatography using silica gel (i.e. 100-200 mesh) column to obtain triphenylphosphene borane complex using hexane/ethyl acetate (97:3) as eluent.

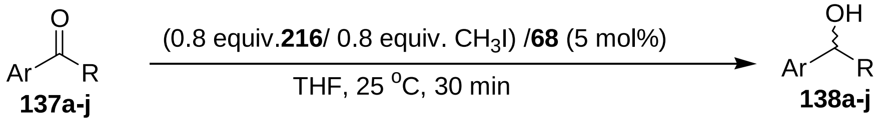
Yield	0.31 g (28%)
mp	187 °C (lit.[152] mp 188 °C)
IR (KBr)	(cm^{-1}) 2378, 2343, 2253, 740, 710
^{11}B NMR	(128.3 MHz, $CDCl_3$, δ ppm) -38.02 {δ = 0, BF_3:Et_2O}
^{31}P NMR	(162 MHz, $CDCl_3$, δ ppm) 20.56 {δ = 0, H_3PO_4}

3.19 General procedure for asymmetric reduction of acetophenone utilizing BH_3 generated *in situ* using TBAB 216/CH_3I reagent system

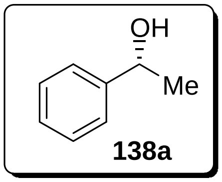
Tetrabutylammonium borohydride 216 (1.02 g, 4 mmol) and (*S*)-α,α-diphenylpyrrolidinemethanol 68 (0.06 g, 0.25 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 15 min under N_2 atmosphere. Methyl iodide (0.25 mL, 4 mmol) was added using a syringe and the reaction mixture was stirred for about 30 min. Acetophenone (0.58 mL, 5 mmol) in THF (12 mL) was added dropwise through a pressure equalizer for about 30 min. under N_2 atmosphere. The reaction mixture was stirred until the ketone disappeared. The mixture was carefully quenched with 3N HCl (10 mL). The organic layer was extracted with $(C_2H_5)_2O$ (3 x 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get yellow residue. The residue was purified on a silica gel column to obtain the (*R*)-1-phenylethanol using hexane/ethyl acetate (97:3) as eluent.

3.20 Procedure utilizing TBAB 216/I_2 reagent system

Tetrabutylammonium borohydride **216** (1.02 g, 4 mmol) and (*S*)-α,α-diphenylpyrrolidinemethanol **68** (0.06 g, 0.25 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 5 min. under N_2 atmosphere. I_2 (0.50 g, 2 mmol) dissolved in THF (12 mL) was added slowly for about 15-20 min through a pressure equalizer at 0 °C under N_2 atmosphere and the reaction mixture was allowed to stir at 0 °C for about 30 min. The reaction mixture was then slowly brought to 25 °C and was stirred for about 10 min. under N_2 atmosphere. Acetophenone **137a** (0.60 g, 0.58 mL, 5 mmol) in THF (15 mL) was added dropwise through a pressure equalizer for about 30 min. The reaction mixture was stirred until the ketone disappeared. The mixture was carefully quenched with 3N HCl (10 mL). The organic layer was extracted with ether (3 x 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get yellow residue. The residue was purified on a silica gel column chromatography to obtain the (*R*)-1-phenylethanol using hexane/ethyl acetate (97:3) as eluent.



(*R*)-1-Phenylethanol (138a)



Yield	0.54 g (89%)
IR (neat)	(cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900

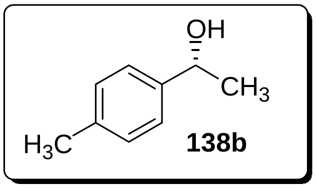
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.46 (d, *J* = 7 Hz, 3H), 2.65 (br s, 1H), 4.74 (q, *J* = 7 Hz, 1H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 25.1, 70.3, 125.5, 127.4, 128.5, 146.0

$[\alpha]_D^{25}$ +45 (*c* 1, MeOH), {lit.[121] for 100% ee, $[\alpha]_D^{25}$ = +45 (*c* 1.0, MeOH)}

Enantiomeric purity 99% (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 1.0 mL/min., 254 nm, retention times: 8.0 min. (*R*) and 8.82 min. (*S*).

(*R*)-1-(4-Methylphenyl)ethanol (138b)



138b

Yield 0.60 g (88%)

IR (neat) (cm^{-1}) 3408, 1435, 744

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.50 (d, *J* = 6.5 Hz, 3H), 2.0 (br s, 1H), 2.37 (s, 3H), 4.89 (q, *J* = 6.5 Hz, 1H,), 7.18 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.7 Hz 2H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 21.1, 25.0, 70.17, 125.4, 129.1, 137.0, 142.9

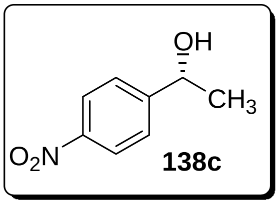
$[\alpha]_D^{25}$ +42.0 (*c* 1.0, MeOH), {lit.[103c] for 100% ee, $[\alpha]_D^{25}$ = +43.8 (*c* 0.9, MeOH)

Enantiomeric purity 95% ee (determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.8 mL/min., 254 nm, retention times: 14.28 min. (*S*) and 15.56 min. (*R*).

(*R*)-1-(4-Nitrophenyl)ethanol (138c)

Yield 0.68 g (82%)

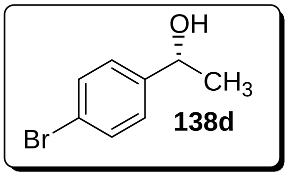
IR (neat) (cm^{-1}) 3395, 1604, 1520, 856



138c

^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) 1.52 (d, *J* = 6.7 Hz, 3H), 2.16 (br s, 1H), 5.02 (q, *J* = 6.7 Hz, 1H), 7.54-7.56 (m, 2H), 8.19-8.21(m, 2H)
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 25.4, 69.4, 123.7, 126.1, 147.0, 153.2
$[\alpha]_D^{25}$	+30 (*c* 1.0, MeOH), {lit.[120] for 100% ee, $[\alpha]_D^{25}$ = +31 (*c* 1.2, MeOH)}

(*R*)-1-(4-Bromophenyl)ethanol (138d)

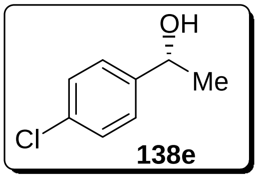


138d

Yield	0.89 g (82%)
IR (neat)	(cm^{-1}) 3377, 1086
^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) 1.47 (d, *J* = 6.5 Hz, 3H), 1.94 (br s, 1H), 4.87 (q, *J* = 6.5 Hz, 1H), 7.25-7.28 (m, 2H), 7.47-7.49 (m, 2H)
^{13}C NMR	(50 MHz, CDCl$_3$, δ ppm) 25.1, 69.6, 121.0, 127.1, 131.5, 144.7
$[\alpha]_D^{25}$	+32 (*c* 1.0, MeOH), {lit.[103c] for 100% ee, $[\alpha]_D^{25}$ = +32.9 (*c* 1.0, MeOH)}

Enantiomeric purity 97% ee (determined by HPLC using chiral column OJ-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.5 mL/min., 254 nm, retention times: 22.38 min. (*S*) and 23.04 min. (*R*).

(*R*)-1-(4-Chlorophenyl)ethanol (138e)



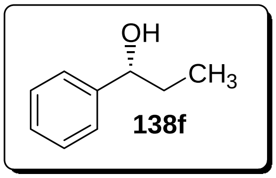
138e

Yield	0.69 g (89%)
IR (neat)	(cm^{-1}) 3366, 1493, 1089
^{1}H NMR	(400 MHz, CDCl$_3$, δ ppm) 1.48 (d, *J* = 6.5 Hz, 3H), 2.00 (s, 1H), 4.89 (q, *J* = 6.5 Hz, 1H), 7.28-7.34 (m, 4H)
^{13}C NMR	50 MHz, CDCl$_3$, δ ppm) 25.1, 69.6, 126.8, 128.5, 132.9, 144.2

$[\alpha]_D^{25}$ +39 (c 1.0, MeOH), {lit.[103c] for 100% ee, $[\alpha]_D^{25}$ = +39.8 (c 1.0, MeOH)}

Enantiomeric purity 96% ee (determined by HPLC using chiral column, chiralcel OJ-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.5 mL/min., 254 nm, retention times: 20.51 min. (*S*) and 21.0 min. (*R*).

(*R*)-1- Phenylpropanol (138f)



138f

Yield 0.59 g (87%)

IR (neat) (cm^{-1}) 3363, 3063, 1454, 1076

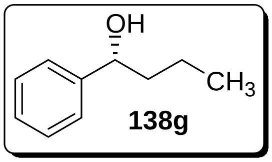
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.94 (t, J = 7.0 Hz, 3H), 1.74-1.88 (m, 2H), 1.99 (s, 1H), 4.61 (t, J = 7 Hz, 1H), 7.78-7.39 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 10.1, 31.8, 75.9, 126.0, 127.4, 128.3, 144.6

$[\alpha]_D^{25}$ +40.0 (c 1.3, $CHCl_3$), {lit.[153] for 96% ee, $[\alpha]_D^{25}$ = +43.0 (c 2.1, $CHCl_3$) for (*R*)-configuration}

Enantiomeric purity 91% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH = 95:5; flow rate 1.0 mL/min., 254 nm, retention times 20.0 min (*R*) and 25.8 min (*S*).

(*R*)-1-Phenylbutan-1-ol (138g)



138g

Yield 0.66 g (89%)

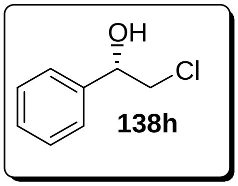
IR (neat) (cm^{-1}) 3300, 2955, 1454

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.94 (d, J = 7.0 Hz, 3H), 1.34-1.82 (m, 4H), 2.12 (s, 1H), 4.67 (t, J = 7 Hz, 1H), 7.28-7.39 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 13.9, 19.0, 41.2, 74.4, 125.9, 127.4, 128.4, 144.9

$[\alpha]_D^{25}$	+42.7 (*c* 0.6, Benzene), {lit.[121, 154] for 100% ee, $[\alpha]_D^{25}$ = -45.2 (*c* 4.8, Benzene) for (*S*)-configuration}

(*S*)-2-chloro-1-Phenylethanol (138h)

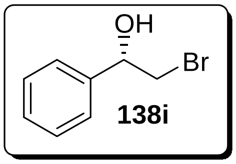


138h

Yield	0.61 g (79%)
IR (neat)	(cm^{-1}) 3429, 1064, 700
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 2.71(m, 1H), 3.65-3.79 (m, 2H), 4.90-4.94 (m, 1H), 7.28-7.41(m, 5H)
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 50.8, 74.0, 125.8, 126.1, 128.3, 128.5, 140.0
$[\alpha]_D^{25}$	+39 (*c* 1.2, Cyclohexane), {lit.[155] for 100% ee, $[\alpha]_D^{25}$ = -48.1 (*C* 1.73, Cyclohexane) for(*R*)-configuration}

<u>Enantiomeric purity</u> 82% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH /95:5; flow rate 1.0 mL/min., 254 nm, retention times: 10.6 min (*S*) and 13.1 min (*R*).

(*S*)-2-bromo-1-Phenylethanol (138i)

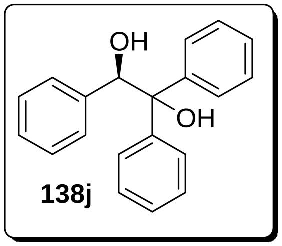


138i

Yield	0.76 g (76%)
IR (neat)	(cm^{-1}) 3418, 1059, 763
^{1}H NMR	(400 MHz, $CDCl_{3,}$ δ ppm) 2.50 (br s 1H), 3.38 (m, 2H), 4.81-4.84 (m, 1H), 7.18-7.5 (m, 5H)
^{13}C NMR	(50 MHz, $CDCl_{3,}$ δ ppm) 40.1, 73.8, 125.8, 126.0, 128.4, 128.7, 141.2
$[\alpha]_D^{25}$	+28 (*c* 1.0, $CHCl_3$), {lit.[155] for 93% ee, $[\alpha]_D^{25}$ = -39 (*c* 8.0, $CHCl_3$) for (*R*)-configuration}

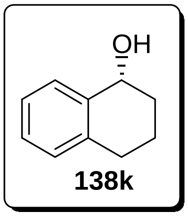
Enantiomeric purity 76% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH /95:5; flow rate 1.0 mL/min., 254 nm, retention times 10.8 min. for (*R*) and 12.1 min. for (*S*) isomer.

(*R*)-1,1,2-Triphenyl-1,2-ethanediol (138j)


138j

Yield	1.13 g (78%)
IR (neat)	(cm^{-1}) 3560, 1435, 744
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 2.43 (d, *J* = 3.0, 1H), 3.15 (s, 1H), 5.67 (d, *J* = 3.0, 1H), 7.07-7.73 (m, 15H)
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 78.0, 80.7, 126.2, 126.7, 127.0, 127.4, 127.6, 127.7, 128.0, 128.4, 138.8, 143.3, 145.1
$[\alpha]_D^{25}$	+91 (*c* 1.0, $CHCl_3$), {lit.[122] for 100% ee, $[\alpha]_D^{25}$ = +223.6 (*c* 1.3, $CHCl_3$)}

(*R*)-1,2,3,4-Tetrahydro-1-naphthol (138k)

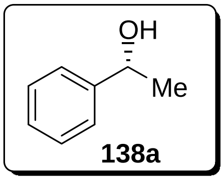

138k

Yield	0.56 g (76%)
IR (neat)	(cm^{-1}) 3406, 1454, 738
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.68-2.03 (m, 5H), 2.75-2.88 (m, 2H), 4.80 (s, 1H), 7.12-7.47 (m, 4H)
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 18.8, 29.2, 32.2, 68.1, 126.1, 127.5, 128.6, 129.0, 137.1, 138.8
$[\alpha]_D^{25}$	-14.7 (*c* 1.2, MeOH), {lit.[121] for 100% ee, $[\alpha]_D^{25}$ = -23.14 (*c* 1.3, MeOH)}

Enantiomeric purity 67% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/99:1; flow rate 0.4 mL/min., 254 nm, retention times: 59.0 min (S) and 68.13 min (R).

3.21 General procedure for asymmetric reduction of acetophenone utilizing the (*S*)-*N*,*N*-dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium borohydride 218/CH_3I reagent system

(*S*)-*N*,*N*-Dimethyl-2-(hydroxydiphenylmethyl)pyrrolidinium borohydride **218** (0.59 g, 2 mmol) in THF (12 mL) were taken in a two neck RB flask. It was allowed to stir at 25 ^{o}C for 5 min. under N_2 atmosphere. Methyl iodide (0.12 mL, 2 mmol) was added using a syringe and the reaction mixture was stirred for about 30 min. Acetophenone (0.23 mL, 2 mmol) in THF (12 mL) was added dropwise through a pressure equalizer for about 30 min. under N_2 atmosphere. The reaction mixture was stirred until the ketone disappeared. The mixture was carefully quenched with 3N HCl (10 mL). The organic layer was extracted with ether (3 x 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get yellow residue. The residue was purified on a silica gel column to obtain the (*R)*-1-phenylethanol **138a** using hexane/ethyl acetate (97:3) as eluent.



138a

Yield	0.12 g (51%)
IR (neat)	(cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900
^1H NMR	(400 MHz, $CDCl_3$, δ ppm) 1.46 (d, *J* = 6.5 Hz, 3H), 2.65 (br s, 1H), 4.74 (q, *J* = 6.5 Hz, 1H), 7.34 (m, 5H)
^{13}C NMR	(50 MHz, $CDCl_3$, δ ppm) 25.1, 70.3, 125.5, 127.4, 128.5, 146.0

$[\alpha]_D^{25}$ +2 (*c* 1, MeOH), {lit.[121] for 100% ee, $[\alpha]_D^{25}$ = +45 (*c* 1.0, MeOH)

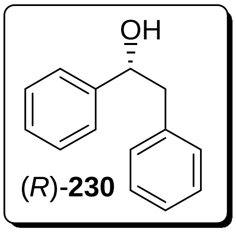
Enantiomeric purity 3% ee (determined by HPLC using chiral column, chiralcel OD-H), solvent system, hexanes:*i*-PrOH/95:5; flow rate 1.0 mL/min., 254 nm, retention times: 8.0 min. for (*R*) and 8.82 min. for (*S*) isomer.

3.22 General procedure for hydroboration/oxidation of *cis*-stilbene 229 with diisopinocamphenylborane (Ipc_2BH) 76 utilizing the TBAB 216/CH_3I reagent system

Tetrabutylammonium borohydride **216** (0.51 g, 2.0 mmol) in THF (40 mL) was taken in a two neck RB flask. The contents were stirred at 25 °C for 5 min under N_2 atmosphere. The reaction mixture was cooled to 0 °C under N_2 atmosphere. Methyl iodide (0.125 mL, 2.0 mmol) was added using a syringe and the reaction mixture was stirred for about 45 min. at the same temperature. α-(-)-Pinene (0.73 mL, 4.6 mmol) was then added to the reaction mixture directly using a syringe and continued to stir at 0 ° C for about 3 h. To it *cis*-stilbene (0.35 mL, 2.0 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 4 h. Water (10 mL) was then added to the reaction mixture to decompose the residual hydride. The organoborane was oxidized by adding 3N NaOH (10 mL) followed by H_2O_2 (10 mL) and stirred for about 1 h. The organic layer was extracted with ether (3 x 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to get yellow residue. The residue was purified on silica gel column (230-400) using hexane/ethyl acetate (97:3) to obtain the product (*R*)-**230**.

Yield 0.28 g (72%)

mp	63-64 °C (lit.[156] mp 63-64 °C)
$[\alpha]^{25}_{D}$	-13.8 (*c* 1, C_2H_5OH), {lit.[156] for 65% ee $[\alpha]^{25}_{D}$ -36.7 (*c* 1, C_2H_5OH)}
IR (KBr)	(cm^{-1}) 3319, 3084, 2922, 1039, 696
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.96 (s, 1H), 2.96-3.03 (m, 2H), 4.88-4.91 (m, 1H), 7.19-7.36 (m, 10H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 46.1, 75.3, 125.9, 126.6, 127.6, 128.4, 128.5, 129.5, 138.1, 143.8

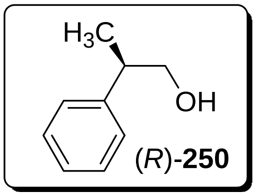

(*R*)-**230**

Enantiomeric purity 25% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/97.5:2.5; flow rate 1.0 mL/min., 254 nm, retention times: 18.0 min (*R*) and 22.4 min (*S*).

3.23 Hydroboration/oxidation of α-methylstyrene 249 using chiral amine 166:BH_2I complex system activated by iodine

Diborane gas (12 mmol) generated by the addition of MeI (0.77 mL,12 mmol) in toluene(30 mL) to tetrabutylammonium borohydride **216** (3.21 g, 12 mmol) in toluene (5 mL) at room temperature was passed through the toulene solution (35 mL) of chiral α-methylbenzylamine (*R*)-**166** (0.63 mL, 5 mmol) slowly during 2 h at 0 °C. The bubbler was replaced by an addition funnel under the flush of nitrogen gas. Iodine (0.5 g, 2 mmol) dissolved in toluene (9 mL) was added drop wise at 0 °C for a period of 15 min. After gas evolution has ceased the reaction mixture was slowly allowed to warm at room temperature followed by addition of α-methylstyrene (0.65 mL, 5 mmol) using a syringe. It was then allowed to stir at room temperature for about 1 h and then quenched with MeOH (5 mL).

The organoborane was oxidized using 3N NaOH (10 mL), H_2O_2 (30 %, 10 mL) and stirred for about 4 h. The organic layer was separated and the aq. layer was extracted with ether (2 x 20 mL). The combined organic layer was concentrated under reduced pressure and the residue was purified on silica gel column (230-400) using hexane/ethyl acetate (95:5) to obtain the product (*R*)-**250**.



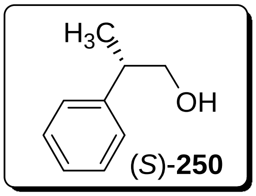
(*R*)-**250**

Yield	0.59 g (87%)
$[\alpha]_D^{25}$	-2.1 (*c* 0.6, $CHCl_3$), {lit.[158] $[\alpha]_D^{25}$ -13.9 (*c* 1.25, $CHCl_3$)}
IR (neat)	(cm^{-1}) 3375, 3050, 2950, 1603, 1057
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.12-1.32 (d, 3H), 1.88 (s, 1H), 2.76-3.12 (m, 1H), 3.52-3.72 (d, 2H), 7.20-7.46 (m, 5H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 17.4, 42.1, 68.1, 126.3, 127.3, 128.3, 143.9

Enantiomeric puruty 13% ee (determined by HPLC using chiral column, chiralcel OB-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.3 mL/min., 254 nm, retention times: 24.9 min. for (*S*) and 26.8 min. for (*R*) isomer.

3.24 Hydroboration/oxidation of α-methylstyrene 249 using chiral amine 166:BH_3 activated by triflic acid

Diborane gas (12 mmol) generated by the addition of MeI (0.77 mL, 12 mmol) in toluene (30 mL) to tetrabutylammonium borohydride (3.21 g, 12 mmol) in toluene (5 mL) at room temperature was passed through the CH_2Cl_2 solution (35 mL) of chiral α-methylbenzylamine (*S*)-**166** (0.63 mL, 5 mmol) slowly during 2 h at 0 °C. The bubbler was replaced by a stopper under the flush of nitrogen gas. Triflic acid (0.44 mL, 5.0 mmol) was then added directly to the reaction mixture at 0 °C. After gas evolution has ceased the reaction mixture was slowly allowed to warm at room temperature followed by addition of α-methylstyrene (0.65 mL, 5 mmol) in CH_2Cl_2 (10 mL) drop wise for a period of about 10 min. It was then allowed to stir at room temperature for about 1 h and then quenched with MeOH (5 mL). The organoborane was oxidized using 3N NaOH (10 mL), H_2O_2 (30 %, 10 mL) and stirred for about 4 h. The organic layer was separated and the aq. layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was concentrated under reduced pressure and residue was purified on silica gel column (230-400) using hexane/ethyl acetate (95:5) to obtain product (*S*)-**250**.



(*S*)-**250**

Yield	0.24 g (35%)
$[\alpha]^{25}_{D}$	-1.6 (*c* 0.5, $CHCl_3$), {lit.[158] $[\alpha]^{25}_{D}$ -13.9 (*c* 1.25, $CHCl_3$)}
IR (KBr)	(cm^{-1}) 3375, 3050, 2950, 1603, 1057
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.12-1.32 (d, 3H), 1.88 (s, 1H), 2.76-3.12 (m, 1H), 3.52-3.72 (d, 2H), 7.20-7.46 (m, 5H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm) 17.4, 42.1, 68.1, 126.3, 127.3, 128.3, 143.9.

Enantiomeric purity 11% determined by HPLC using chiral column chiralcel OB-H, solvent system, hexanes:*i*-PrOH/95:5; flow rate 0.3 mL/min., 254 nm, retention times: 24.9 min. for (*S*) and 26.8 min. for (*R*) isomer.

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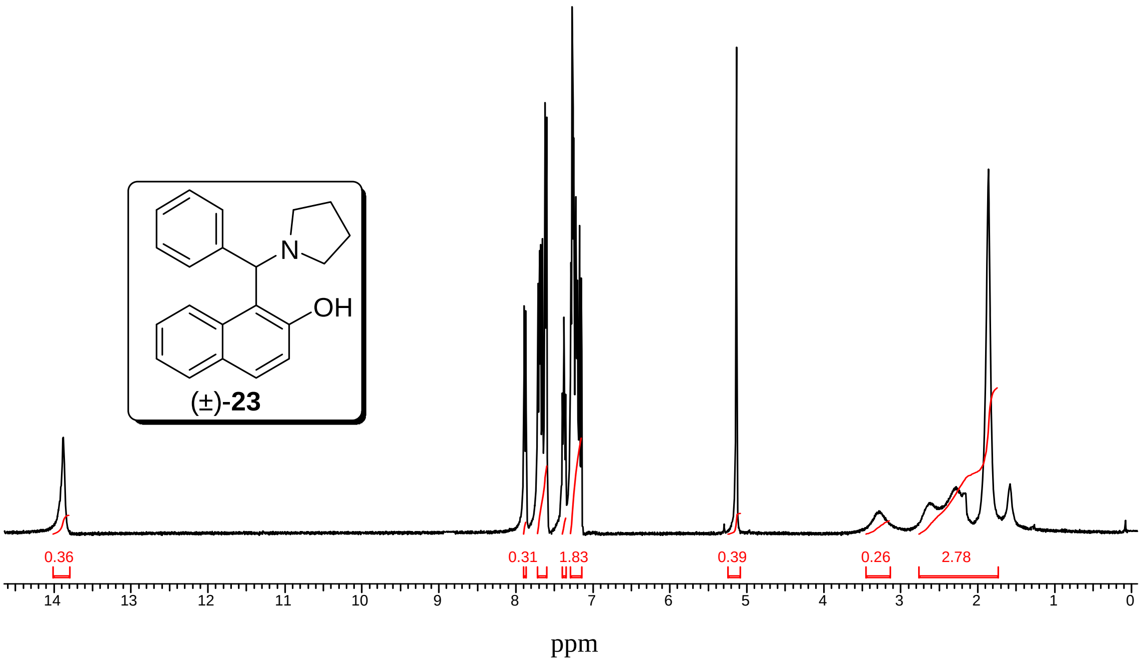
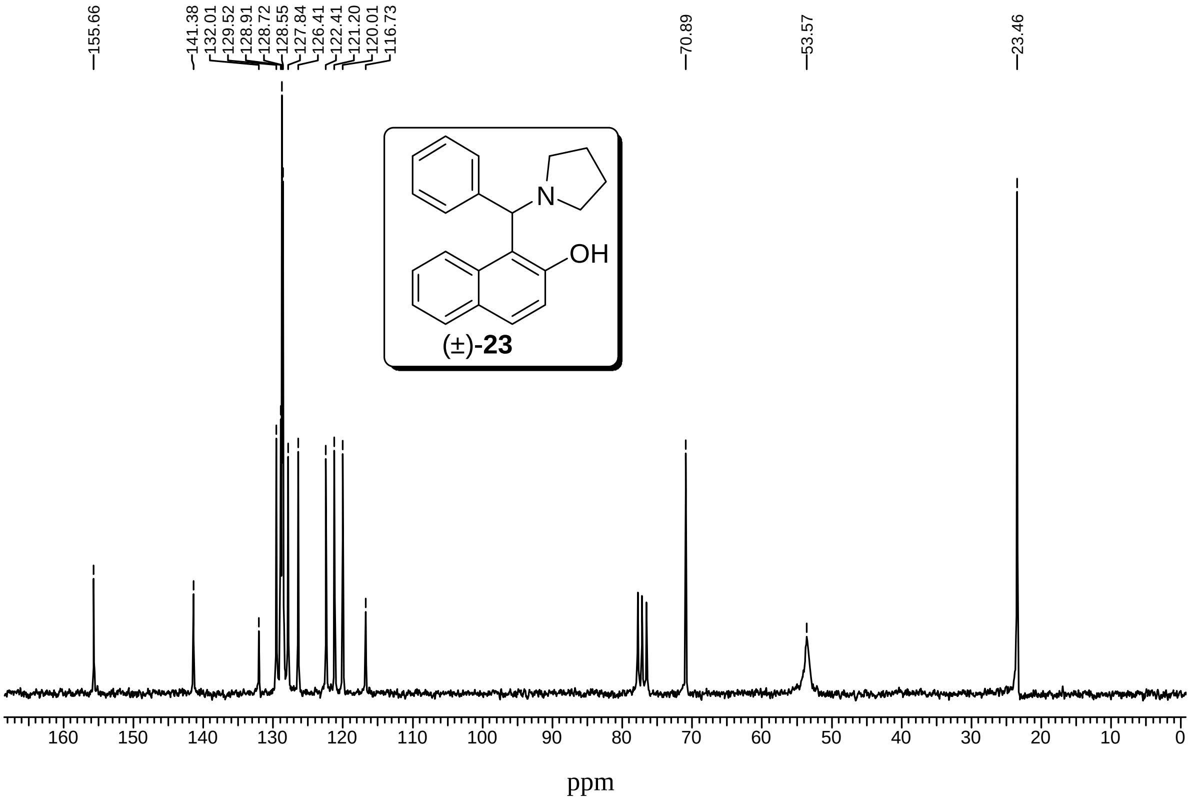
Appendix I

(Representative Spectra)

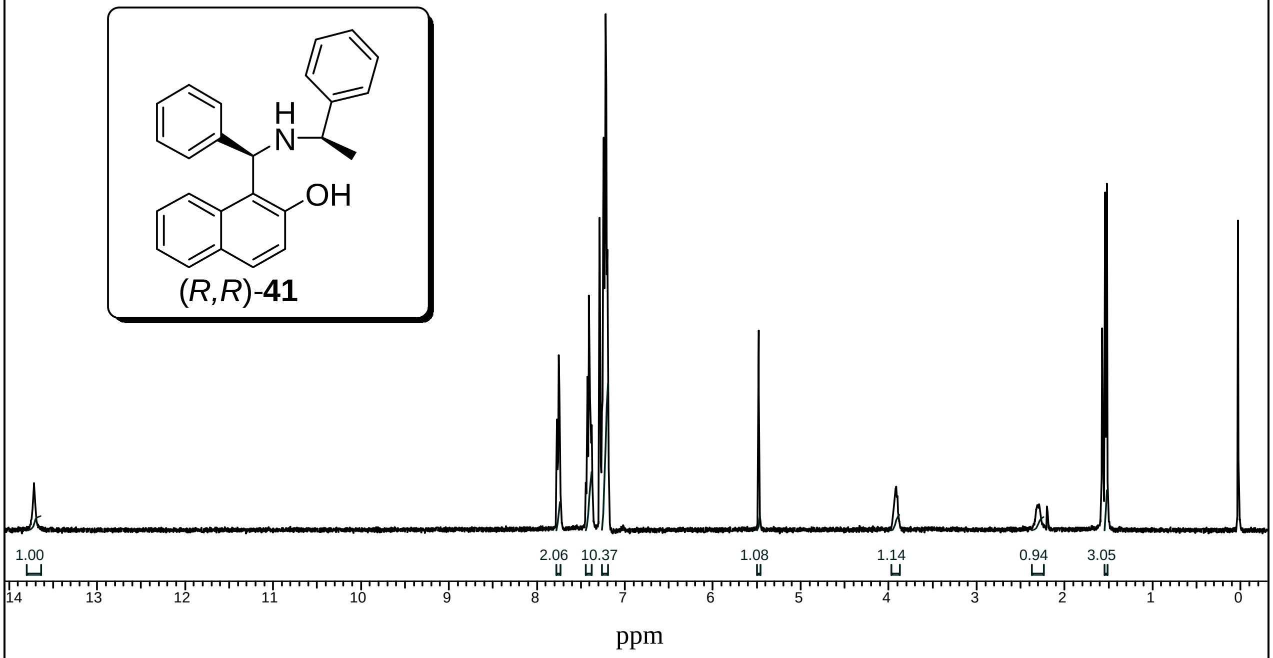
Spectrum No. 1 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



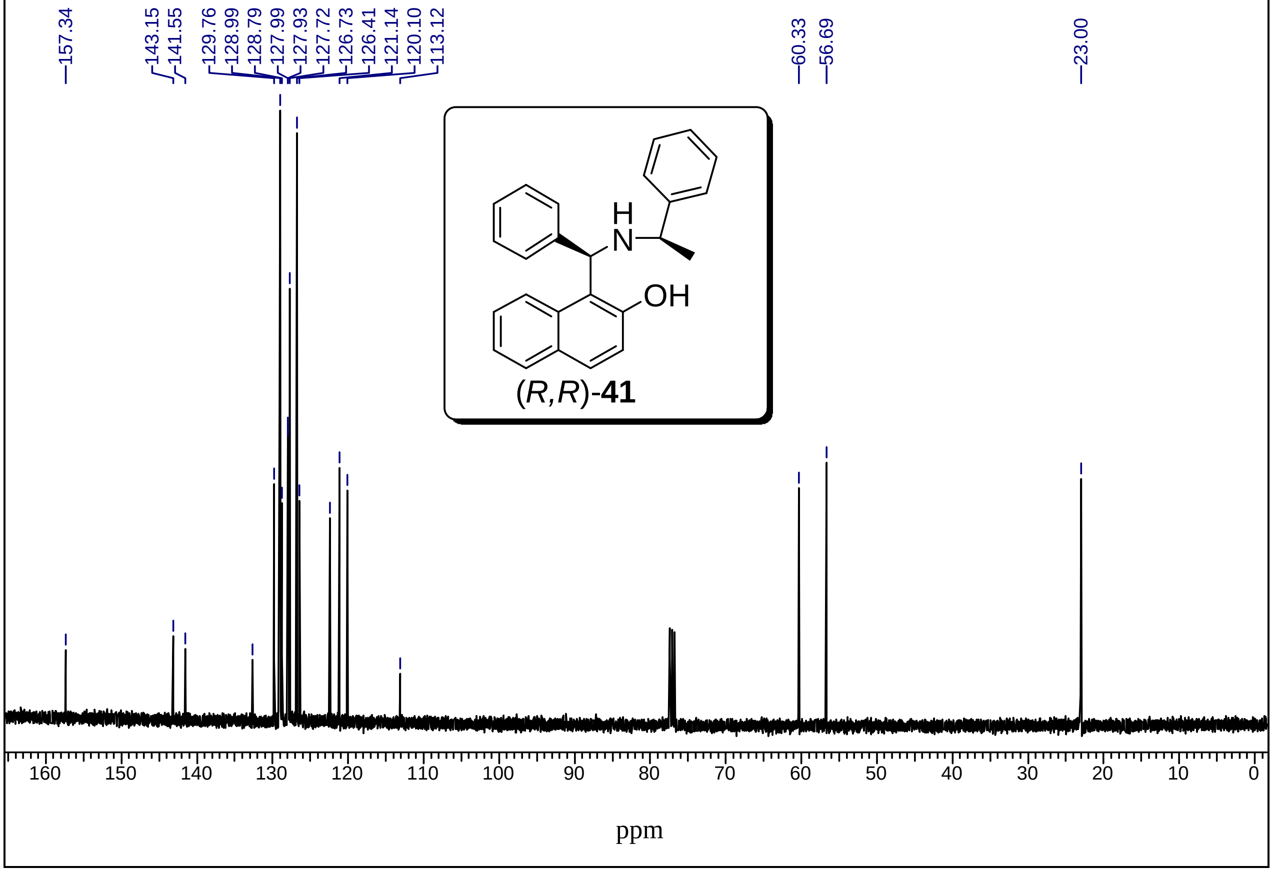
Spectrum No. 2 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (50 MHz, CDCl$_3$)



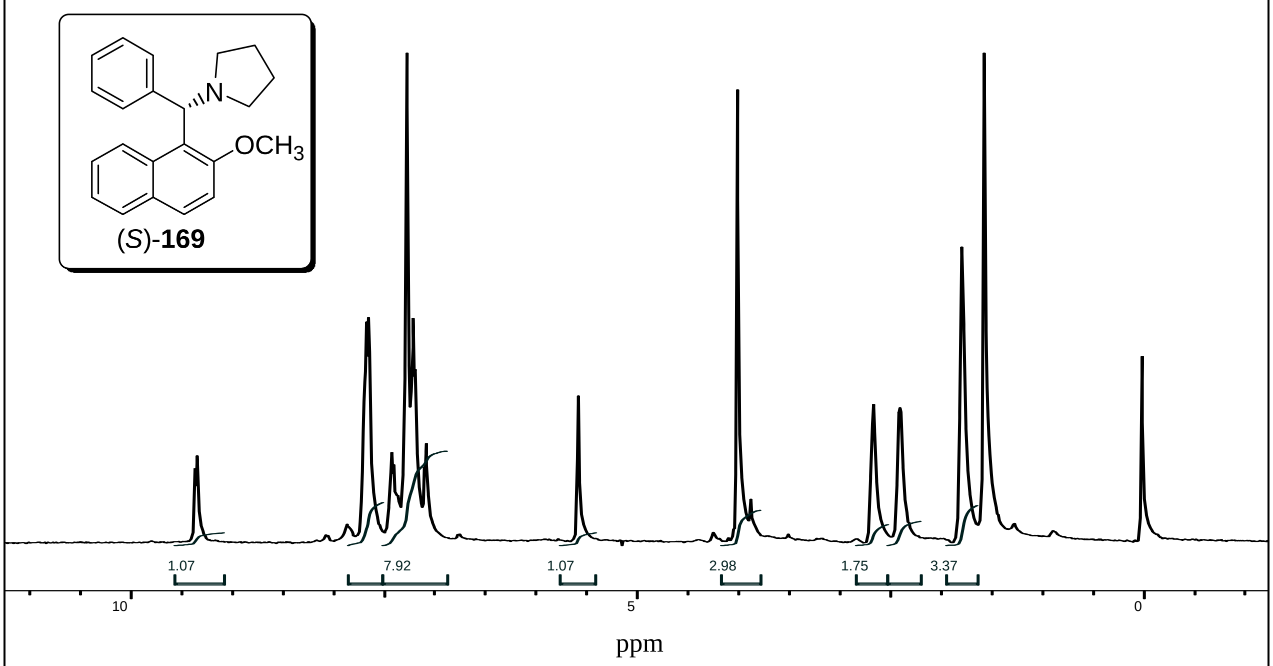
Spectrum No. 3 (Chapter 3, Section 3.2.2) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



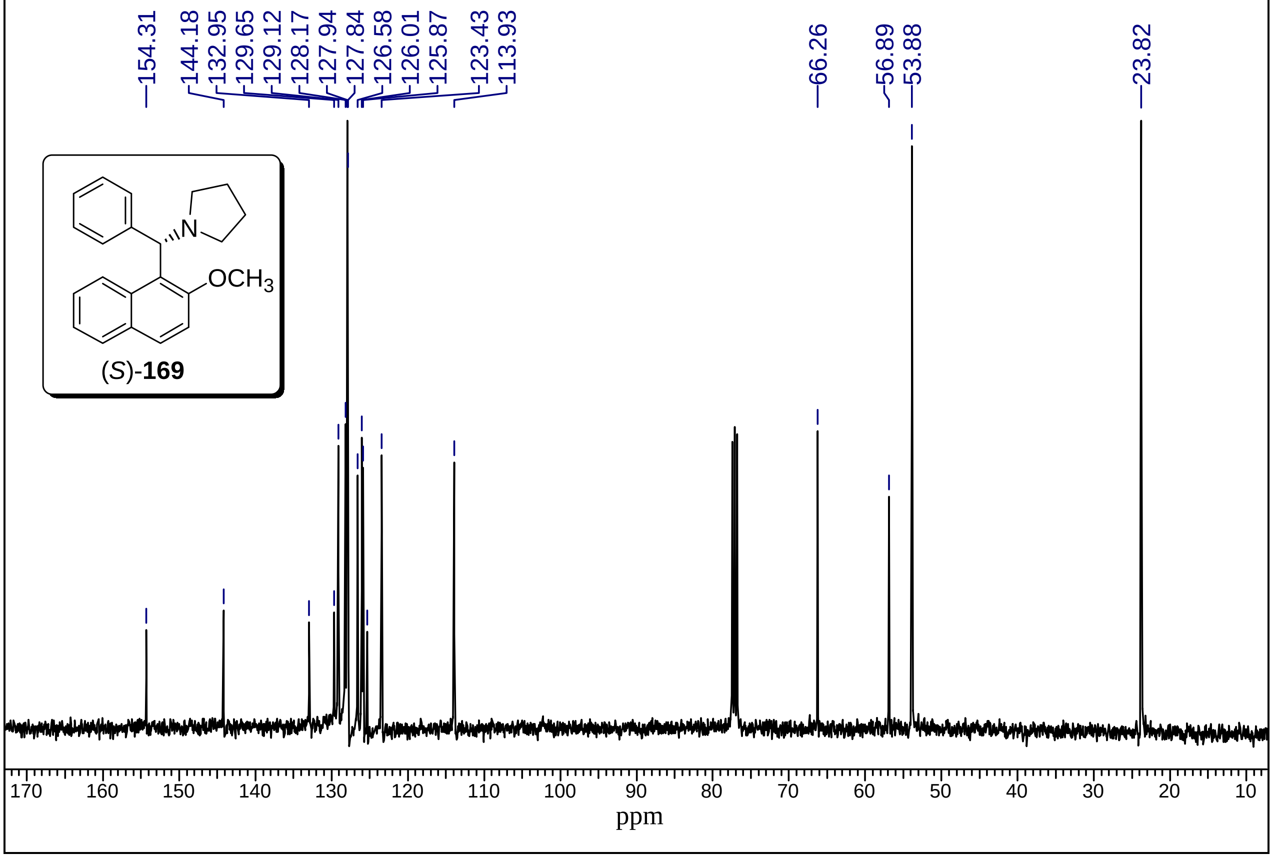
Spectrum No. 4 (Chapter 3, Section 3.2.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



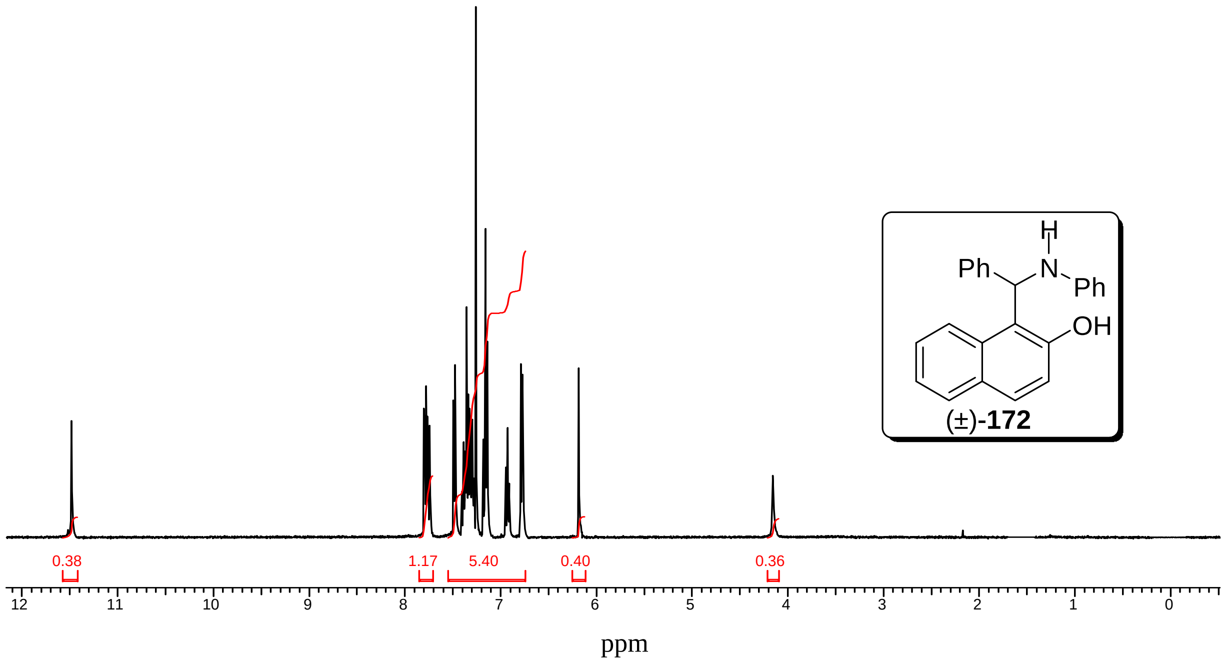
Spectrum No. 5 (Chapter 3, Section 3.2.3) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



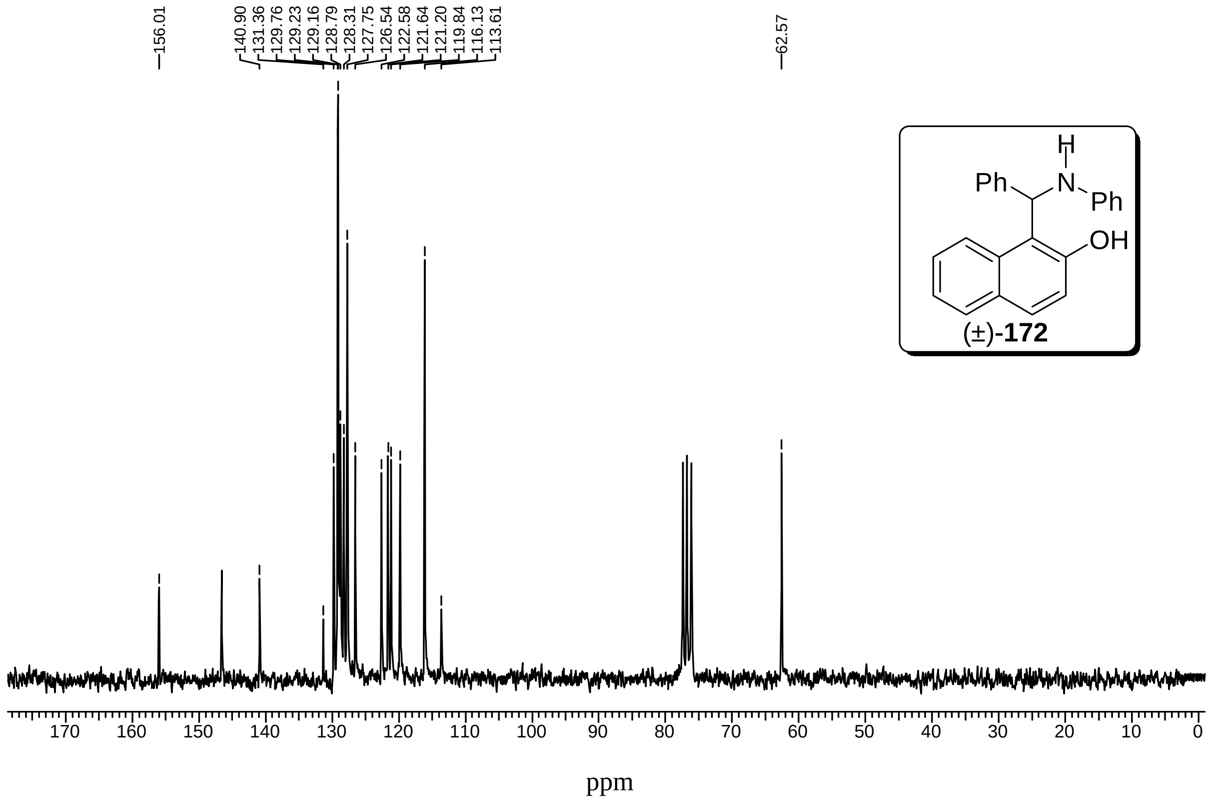
Spectrum No. 6 (Chapter 3, Section 3.2.3) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



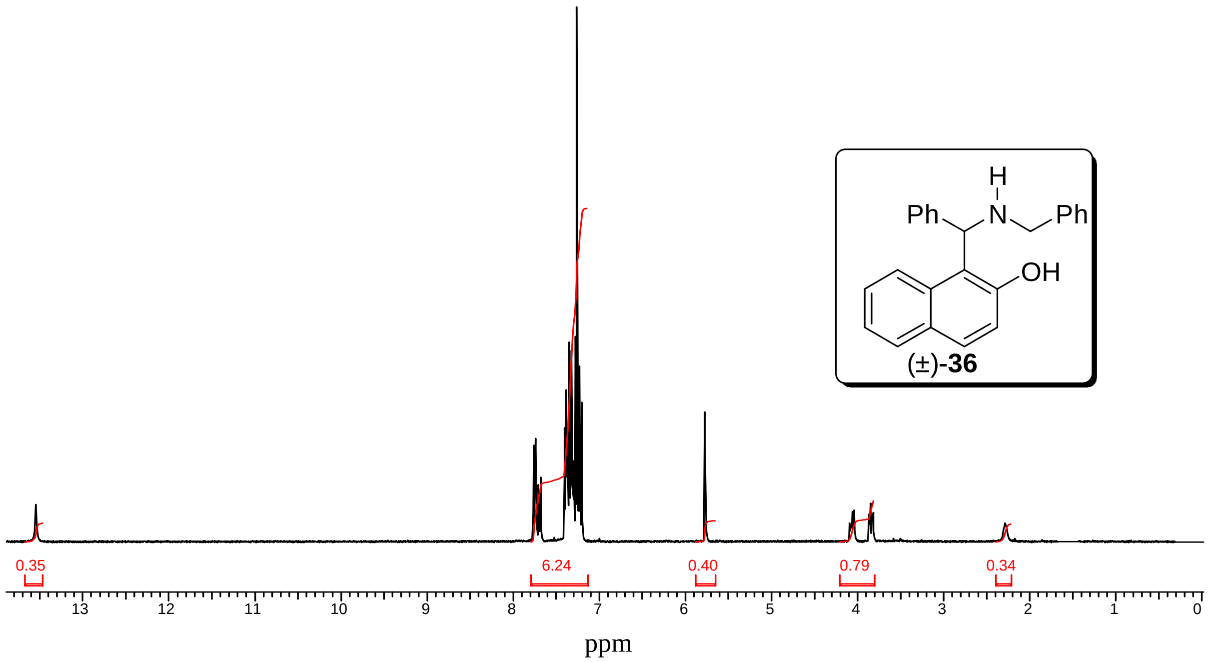
Spectrum No. 7 (Chapter 3, Section 3.2.4) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



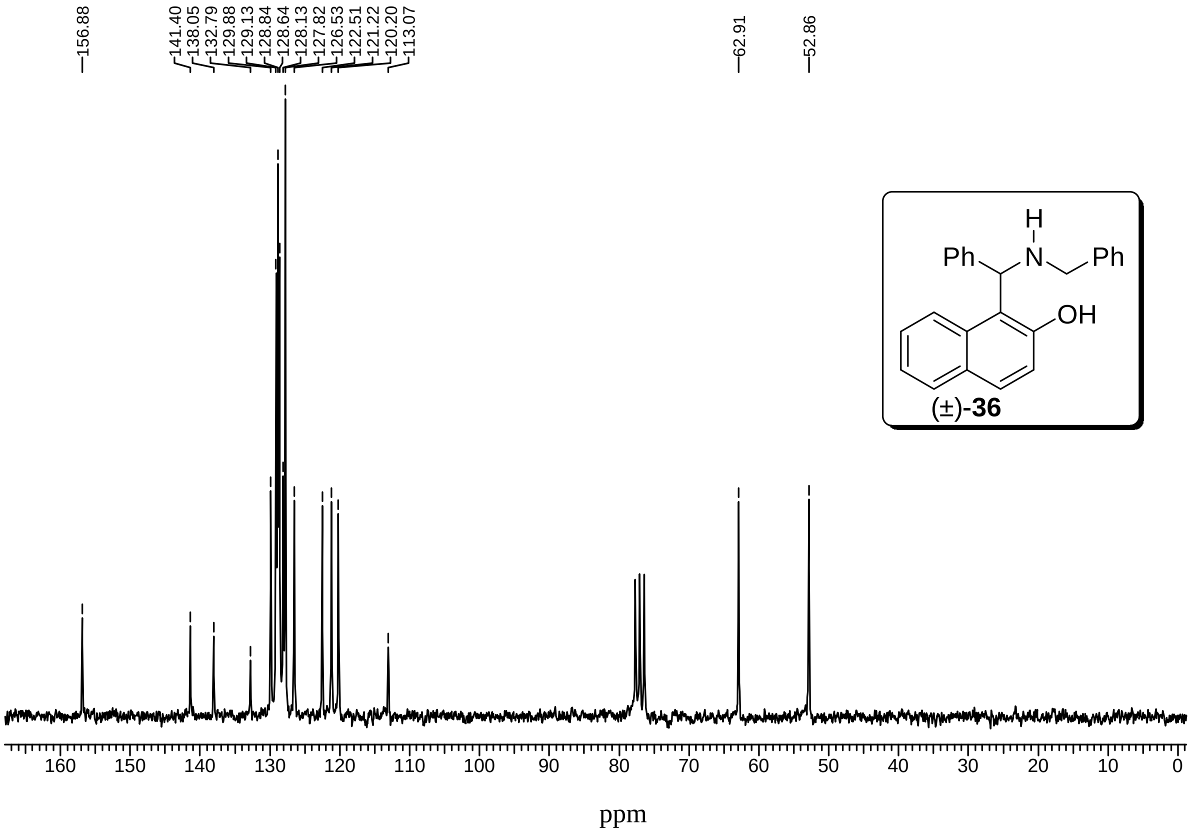
Spectrum No. 8 (Chapter 3, Section 3.2.4) ^{13}C NMR Spectrum (50 MHz, CDCl$_3$)



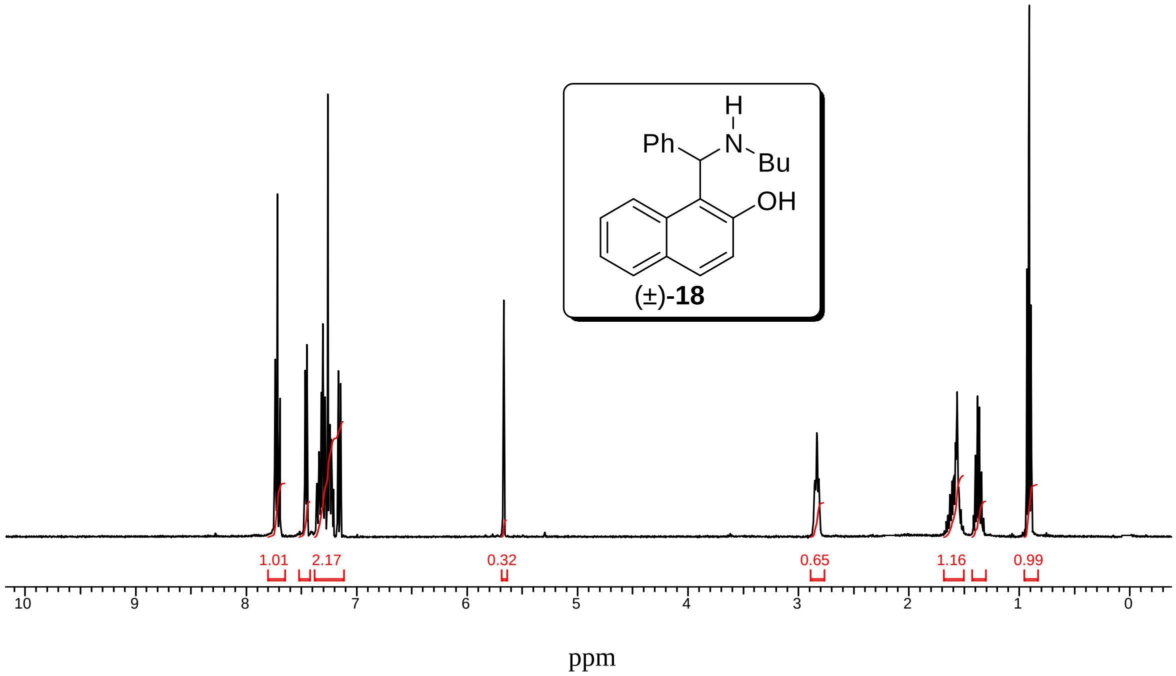
Spectrum No. 9 (Chapter 3, Section 3.2.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



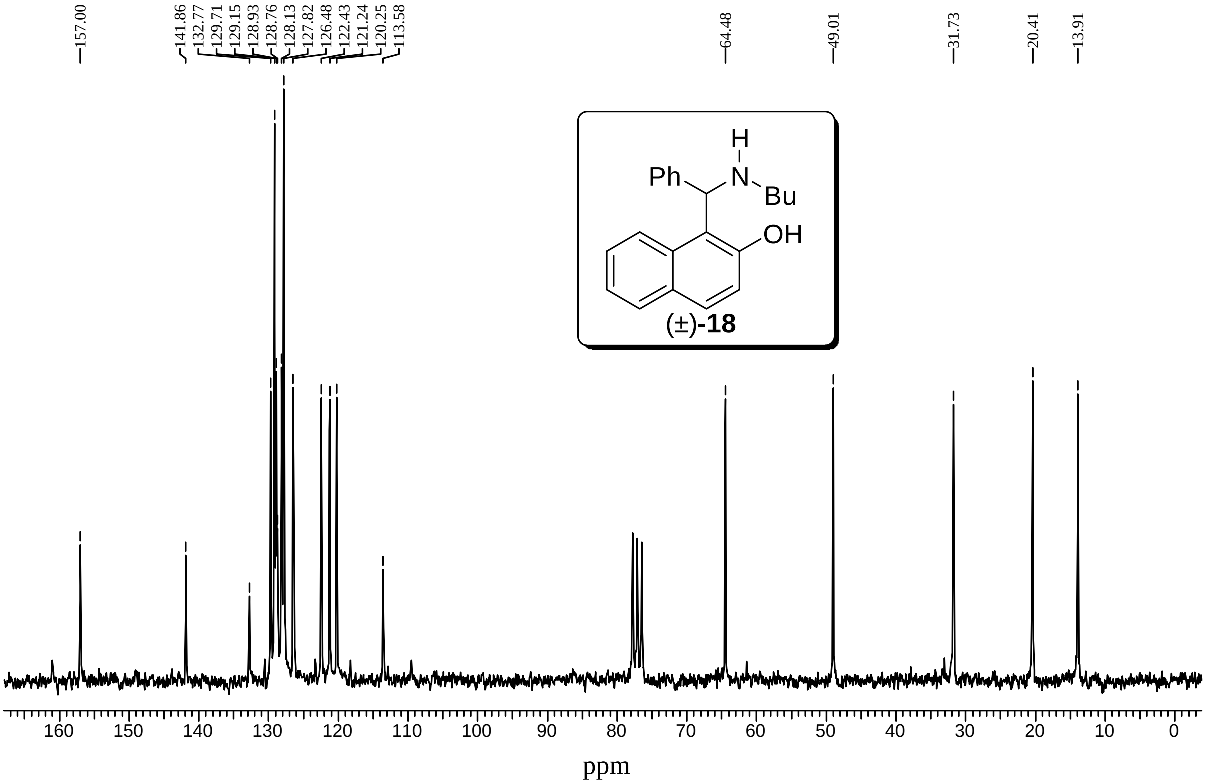
Spectrum No. 10 (Chapter 3, Section 3.2.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



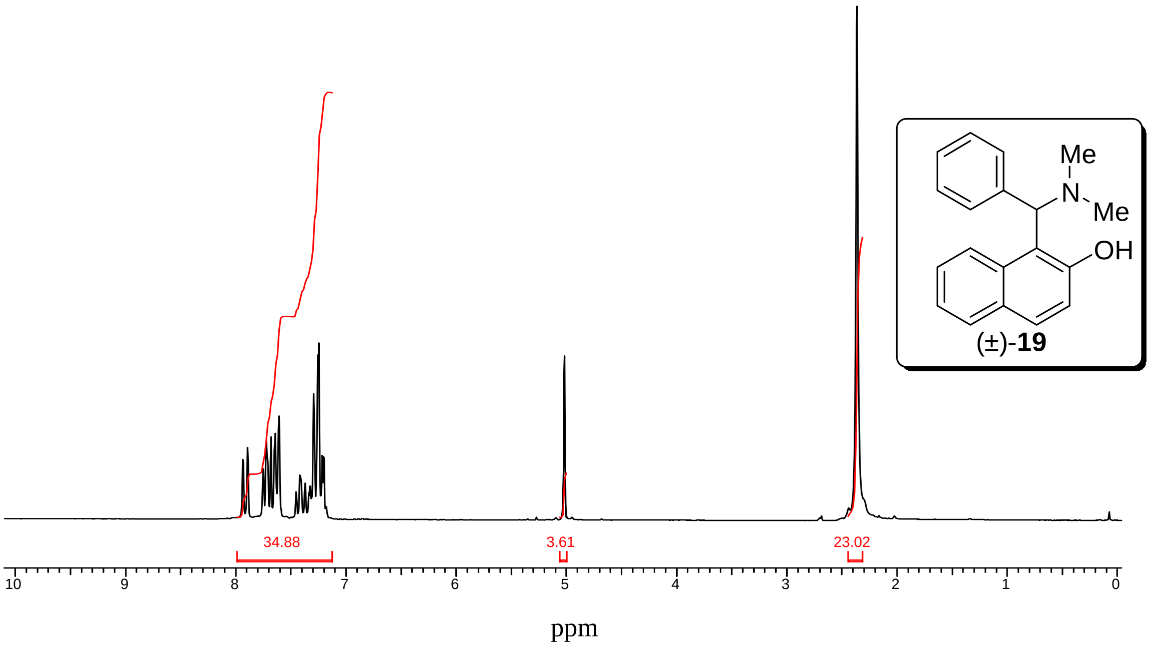
Spectrum No. 11 (Chapter 3, Section 3.2.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



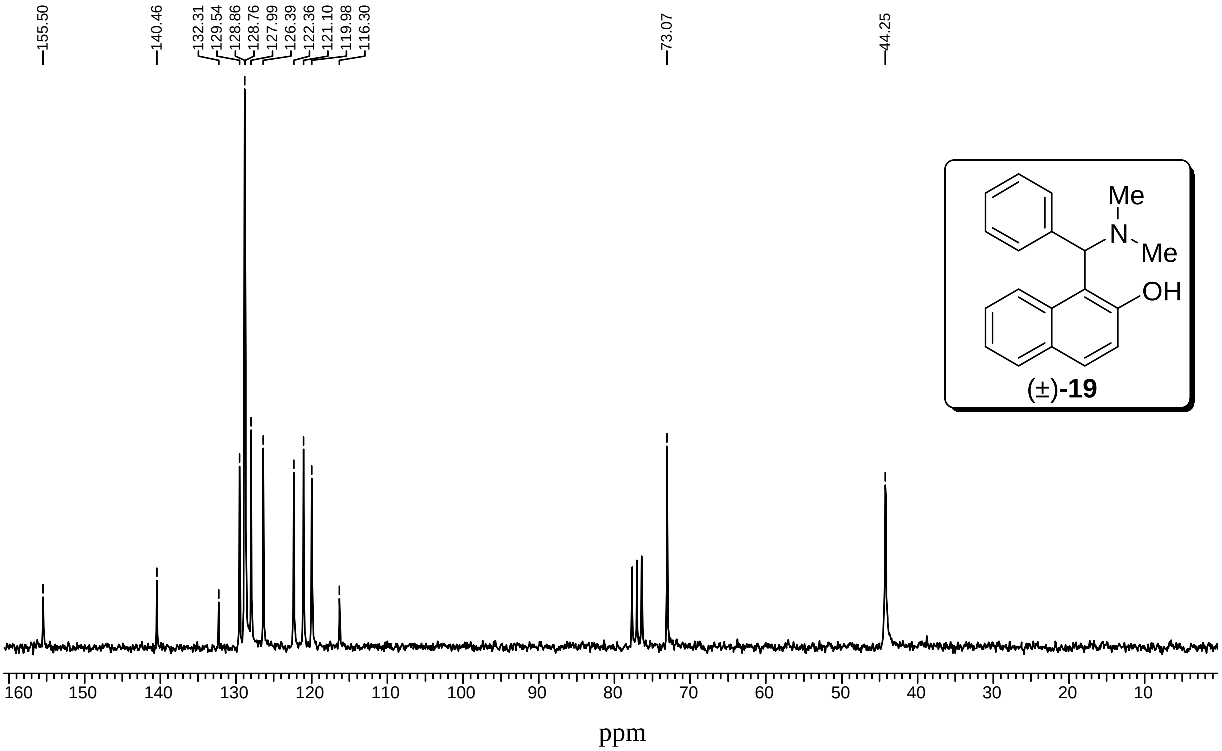
Spectrum No. 12 (Chapter 3, Section 3.2.6) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



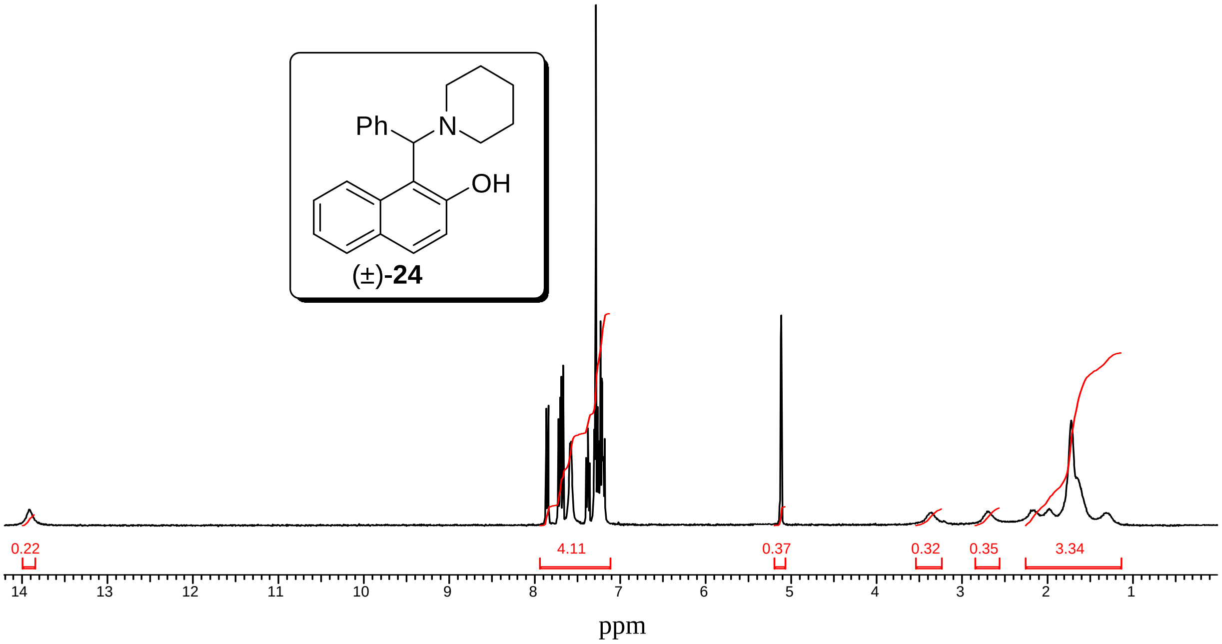
Spectrum No. 13 (Chapter 3, Section 3.2.7) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



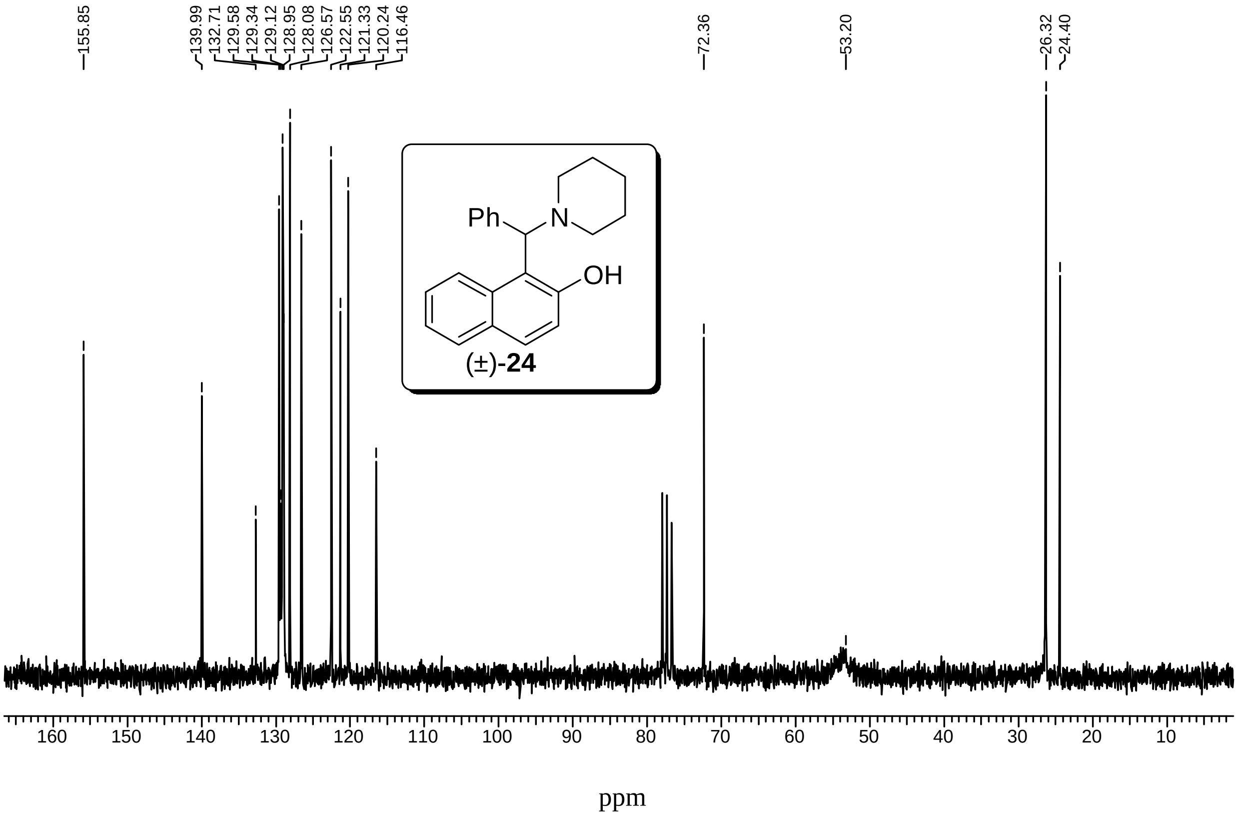
Spectrum No. 14 (Chapter 3, Section 3.2.7) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



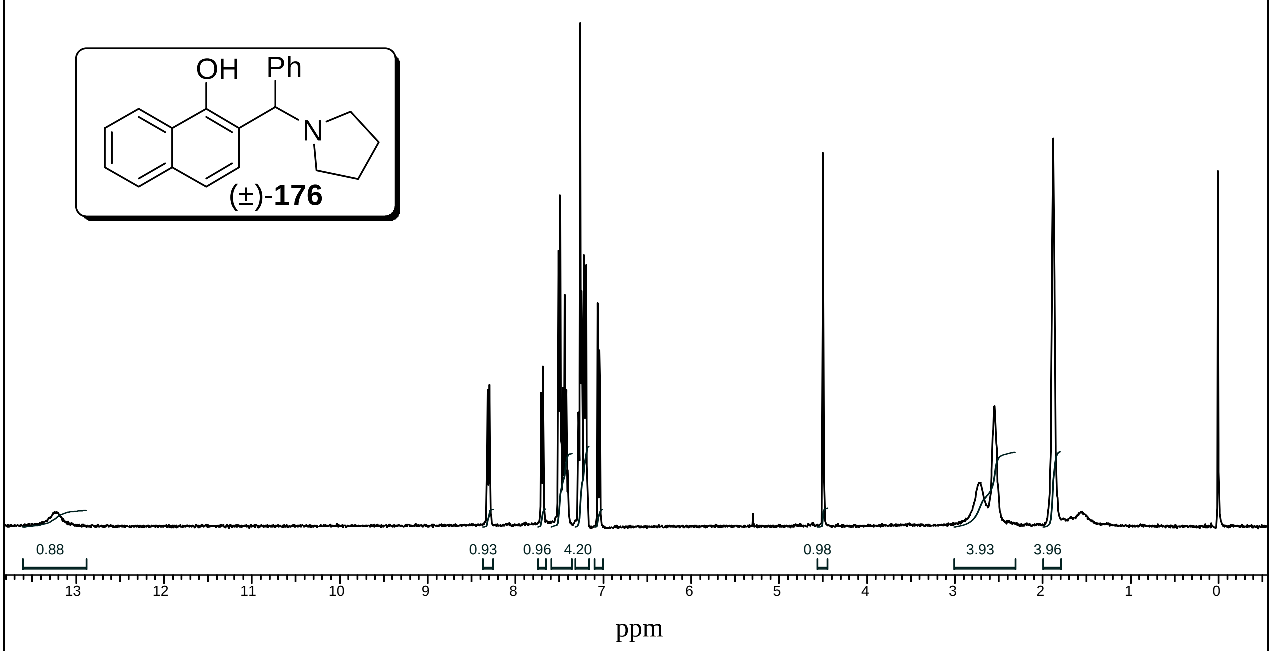
Spectrum No. 15 (Chapter 3, Section 3.2.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



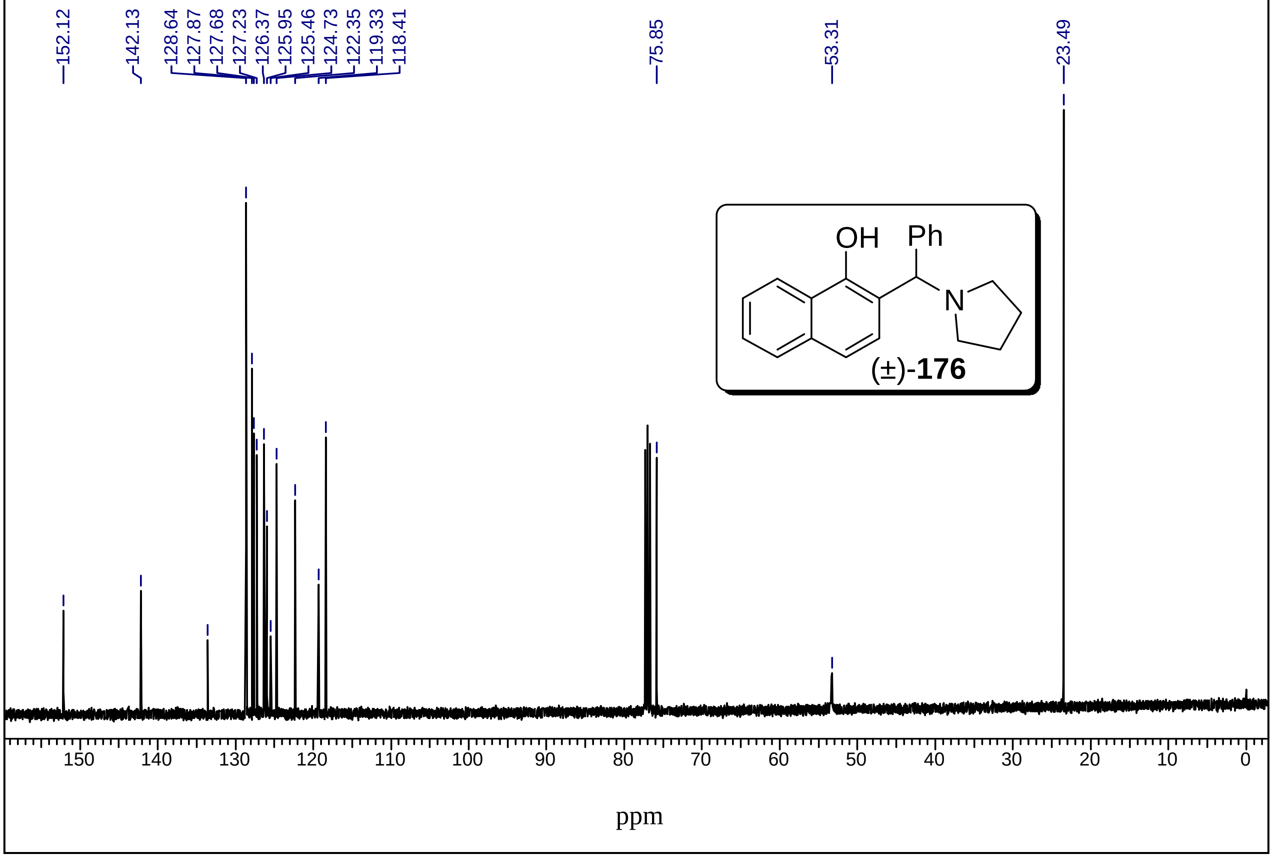
Spectrum No. 16 (Chapter 3, Section 3.2.8) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



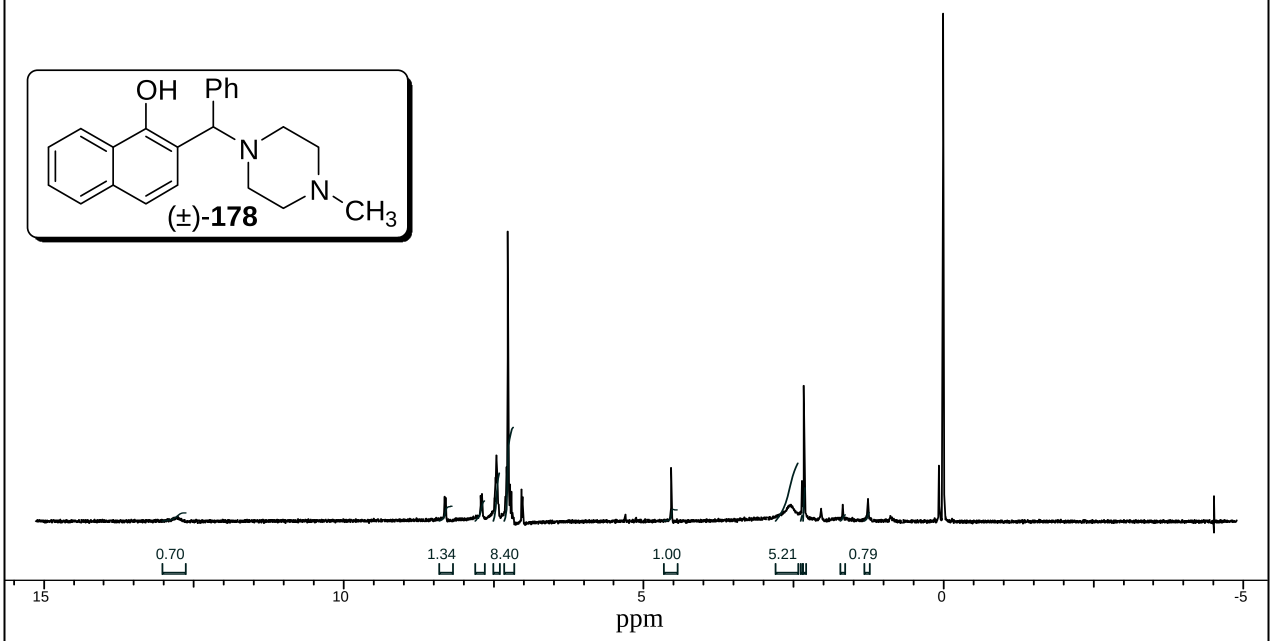
Spectrum No. 17 (Chapter 3, Section 3.3.1) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



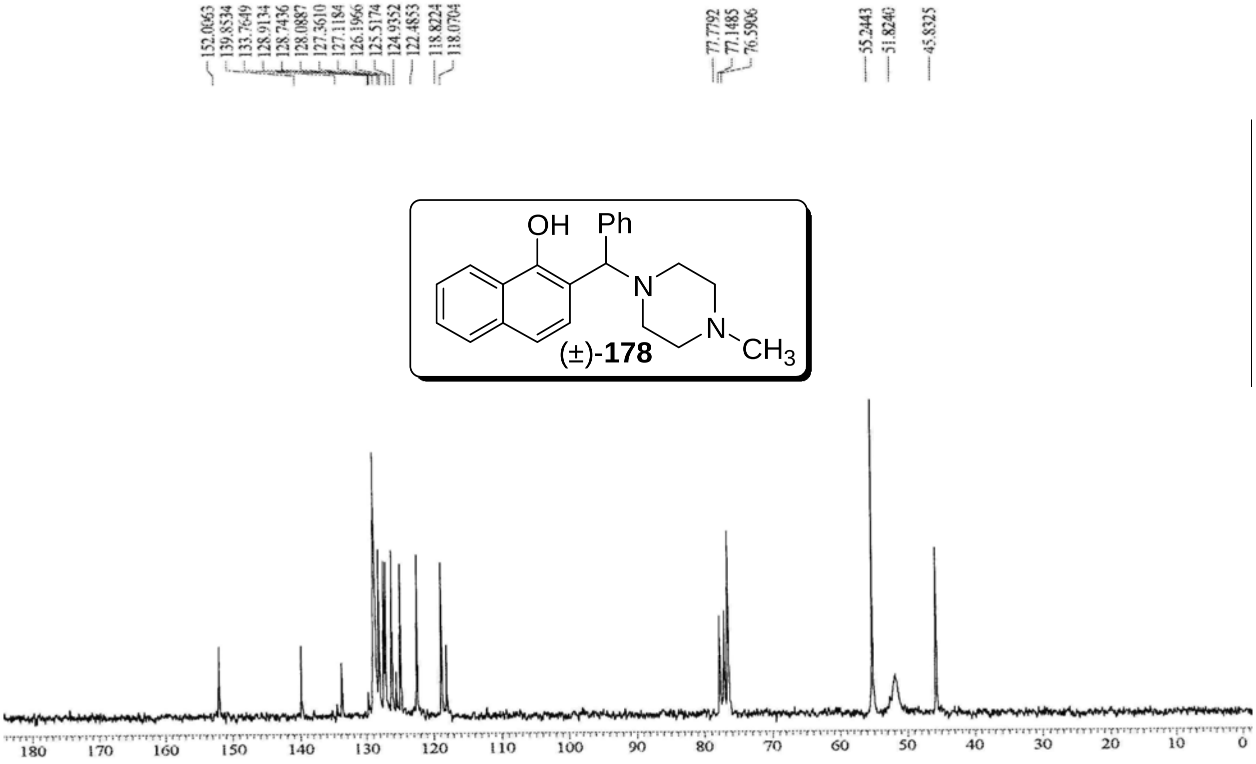
Spectrum No. 18 (Chapter 3, Section 3.3.1) ^{13}C NMR Spectrum (50 MHz, CDCl$_3$)



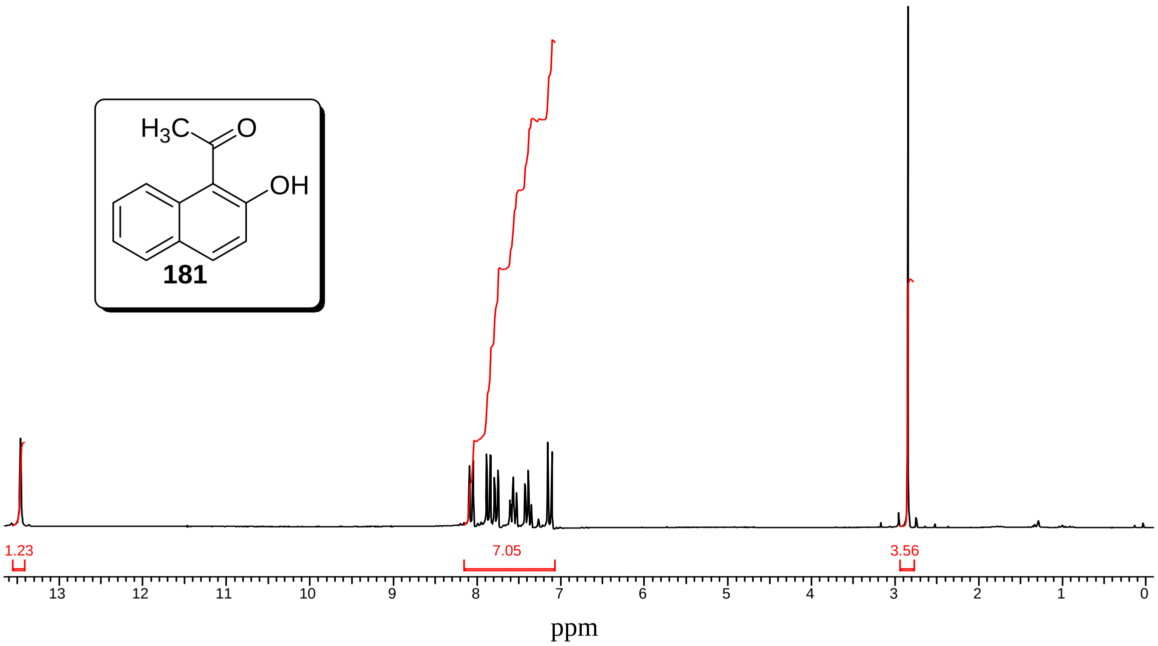
Spectrum No. 19 (Chapter 3, Section 3.3.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



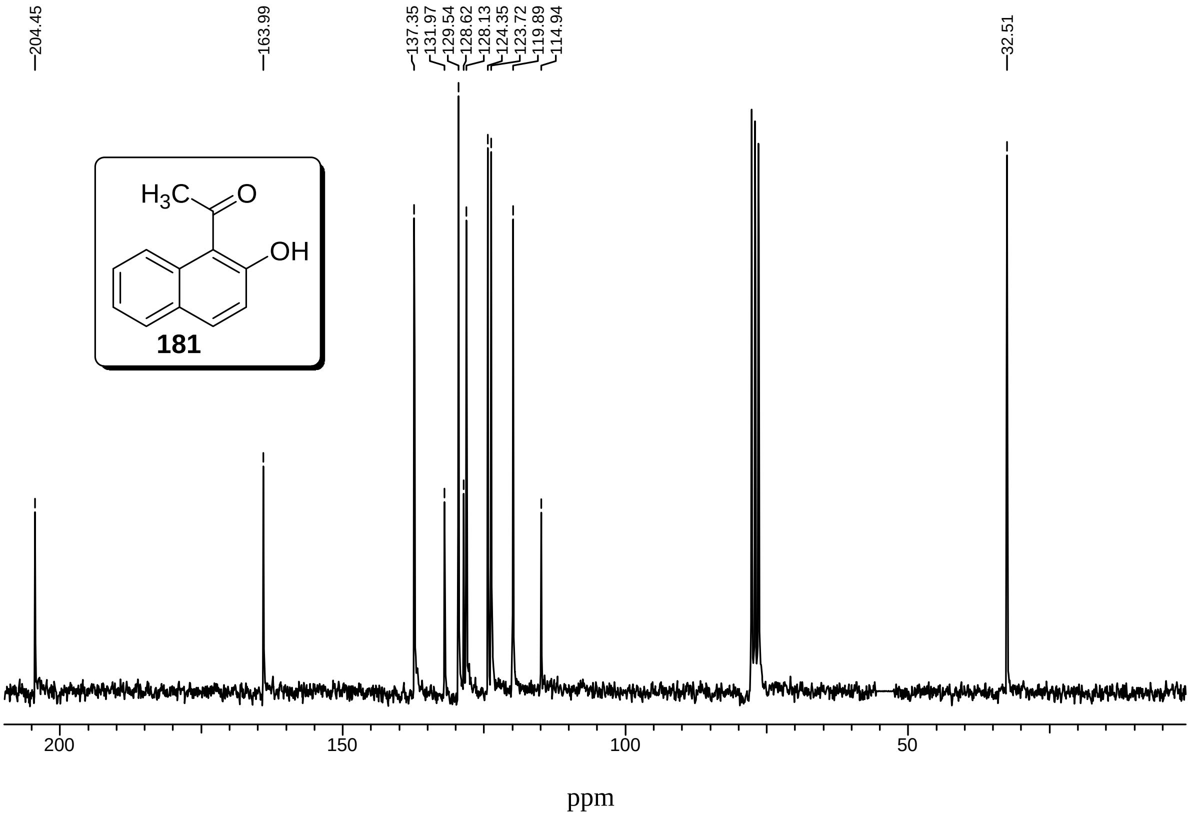
Spectrum No. 20 (Chapter 3, Section 3.3.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



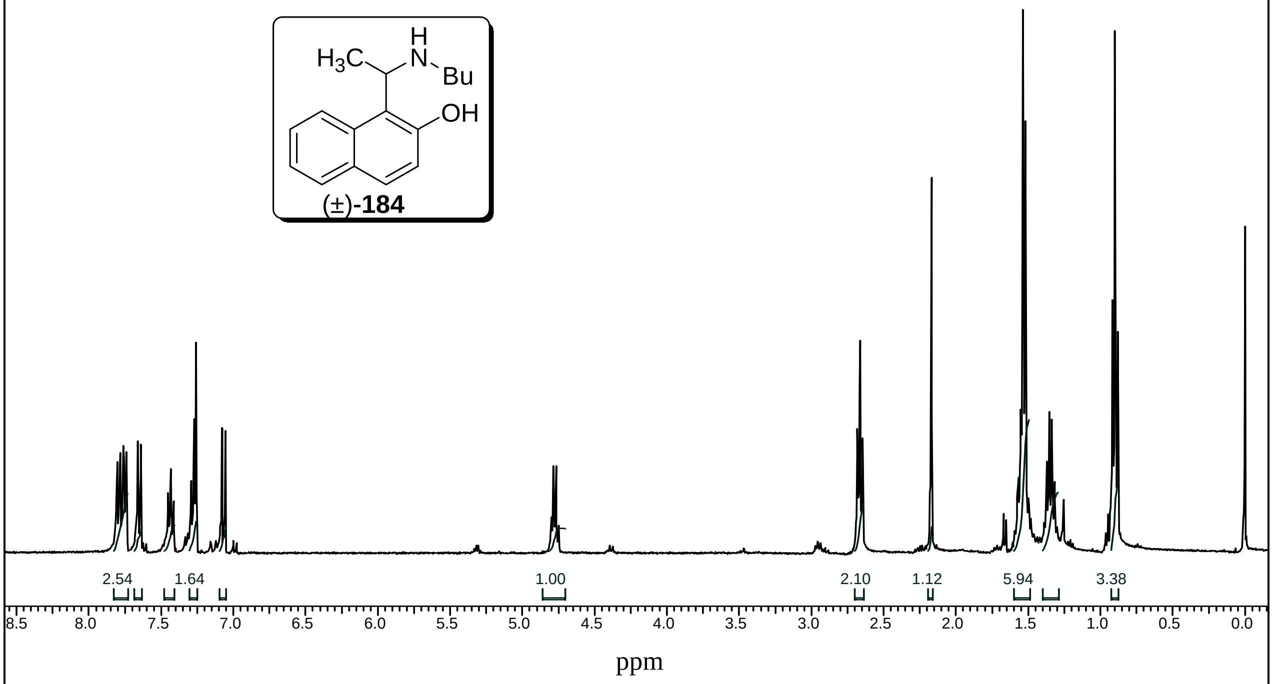
Spectrum No. 21 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



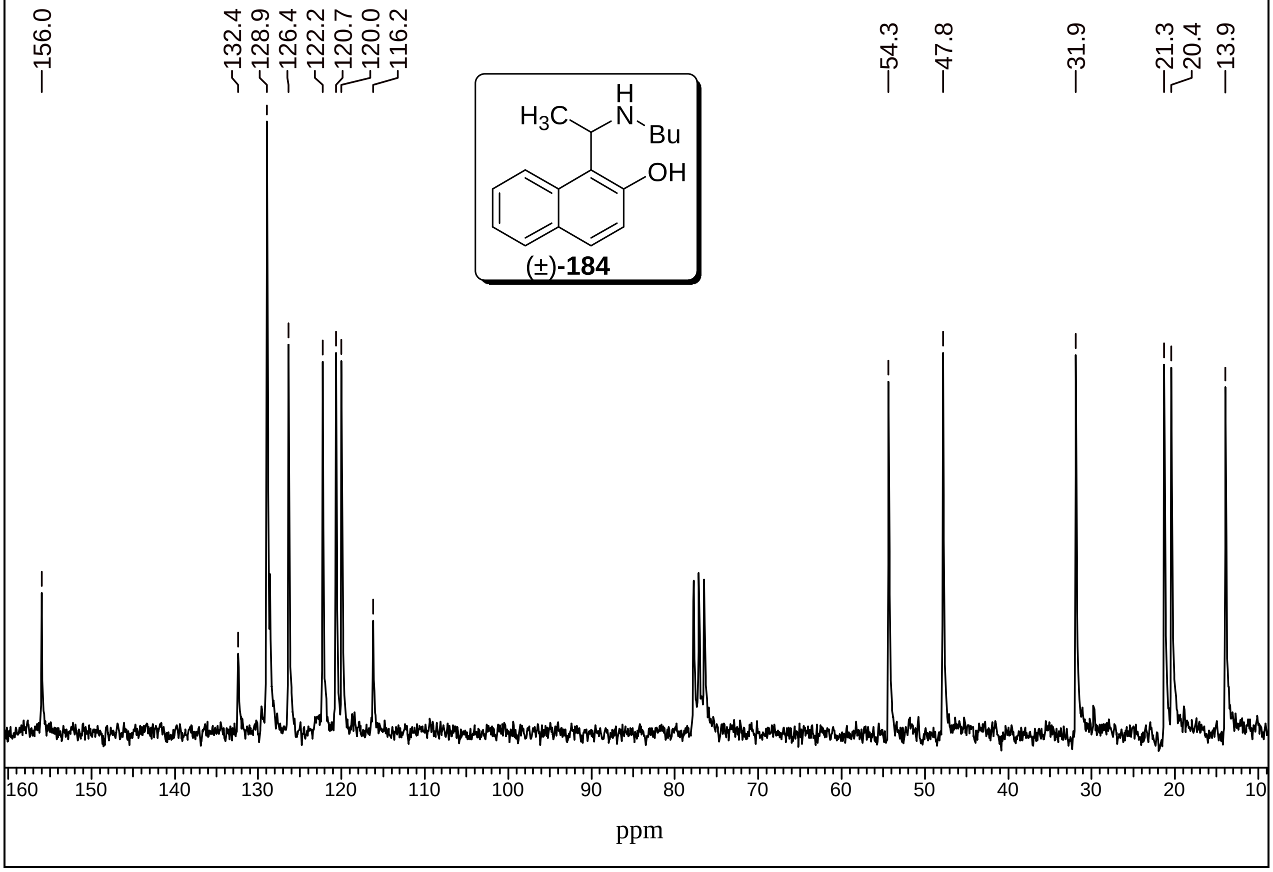
Spectrum No. 22 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



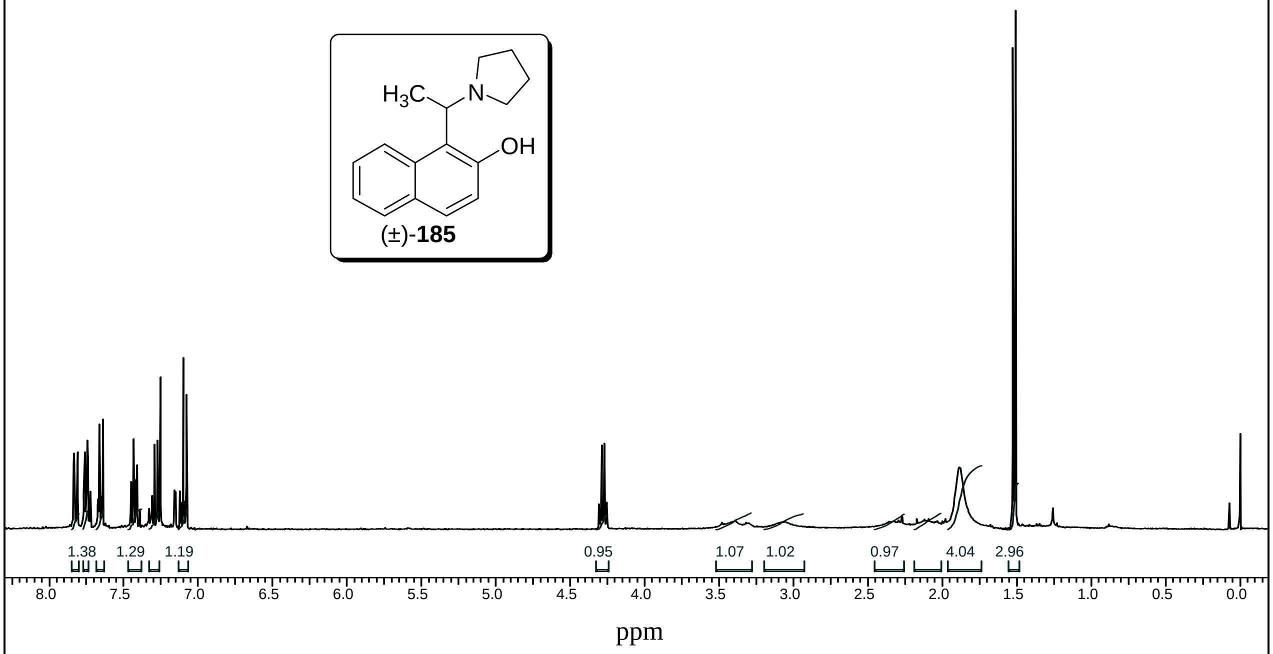
Spectrum No. 23 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



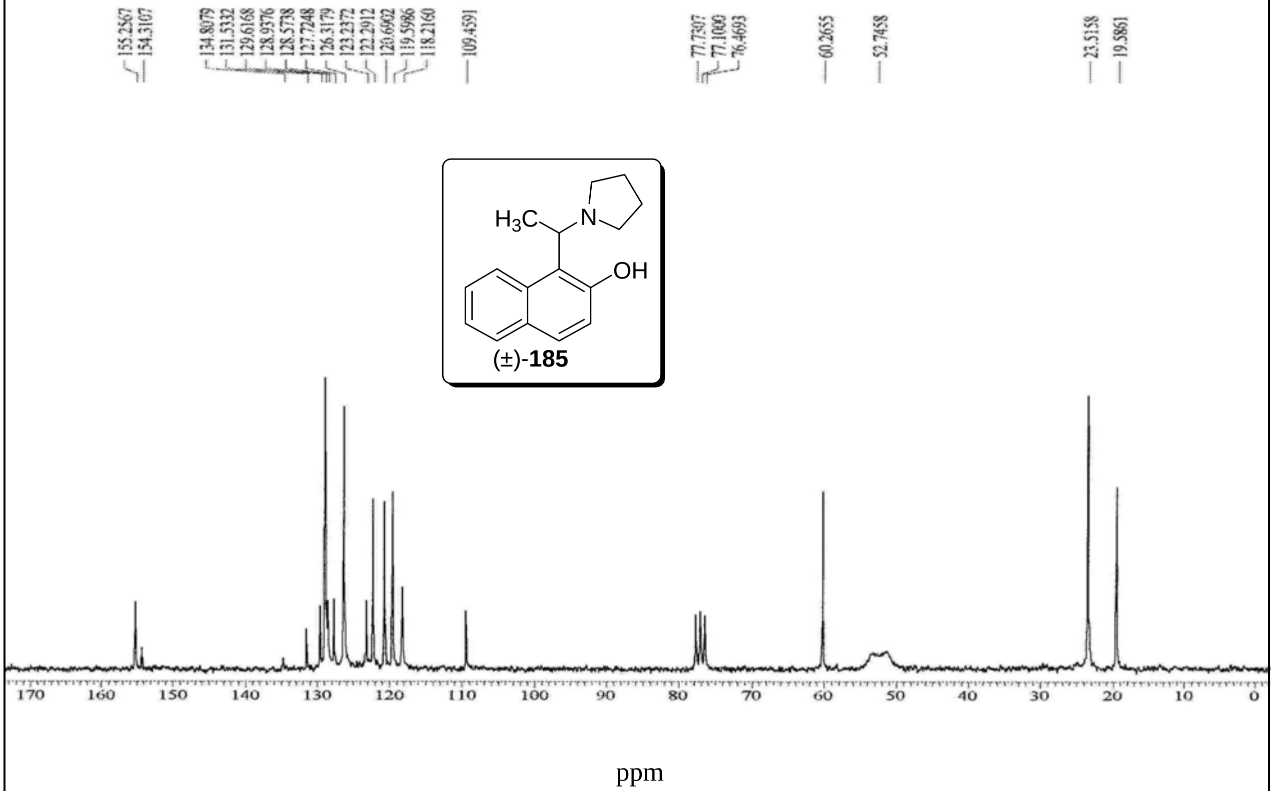
Spectrum No. 24 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



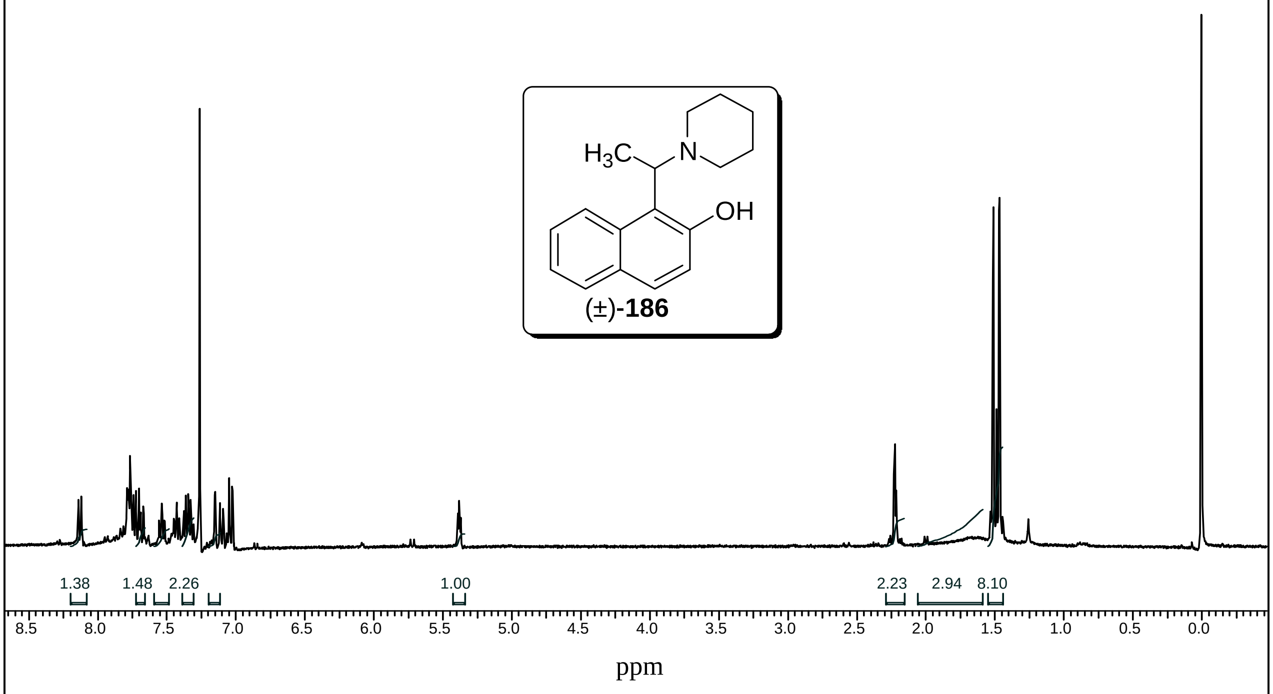
Spectrum No. 25 (Chapter 3, Section 3.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



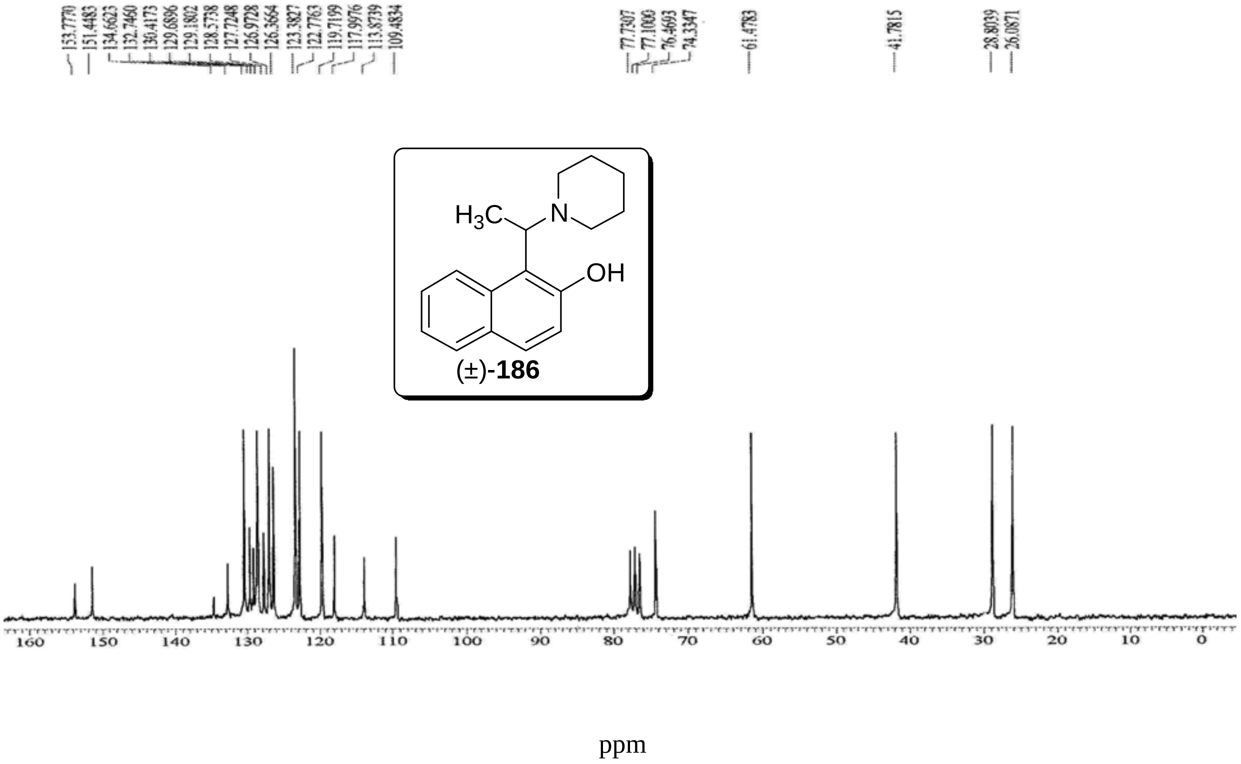
Spectrum No. 26 (Chapter 3, Section 3.4.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



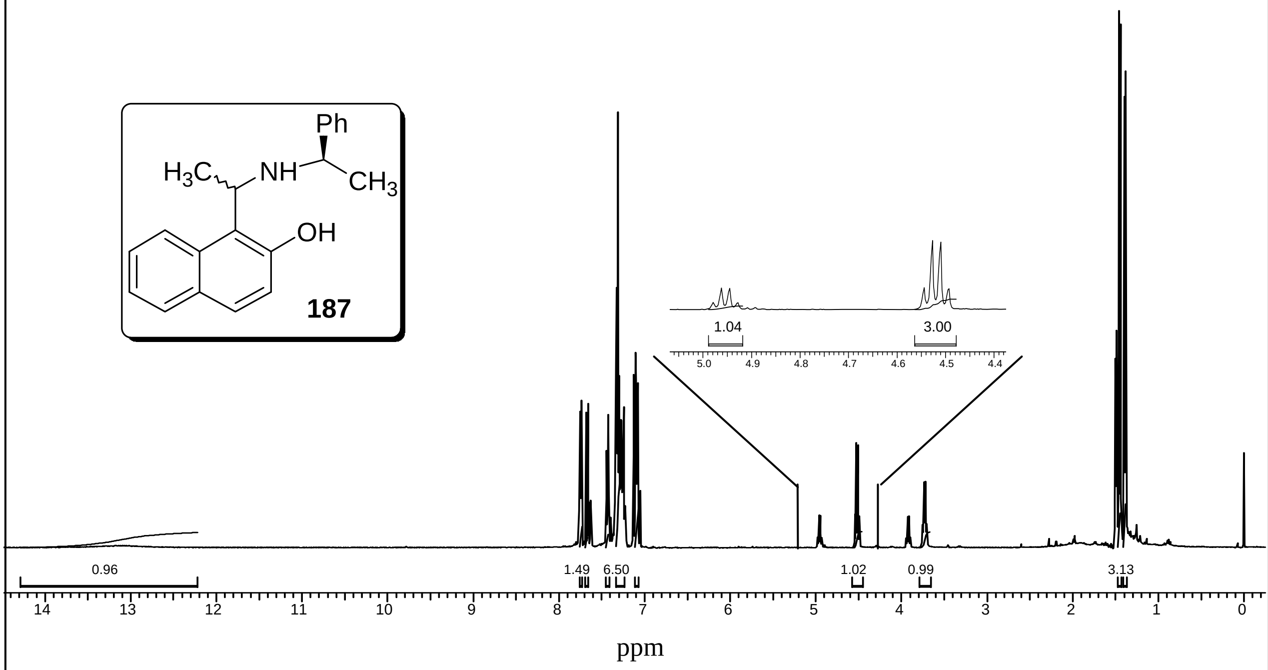
Spectrum No. 27 (Chapter 3, Section 3.4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



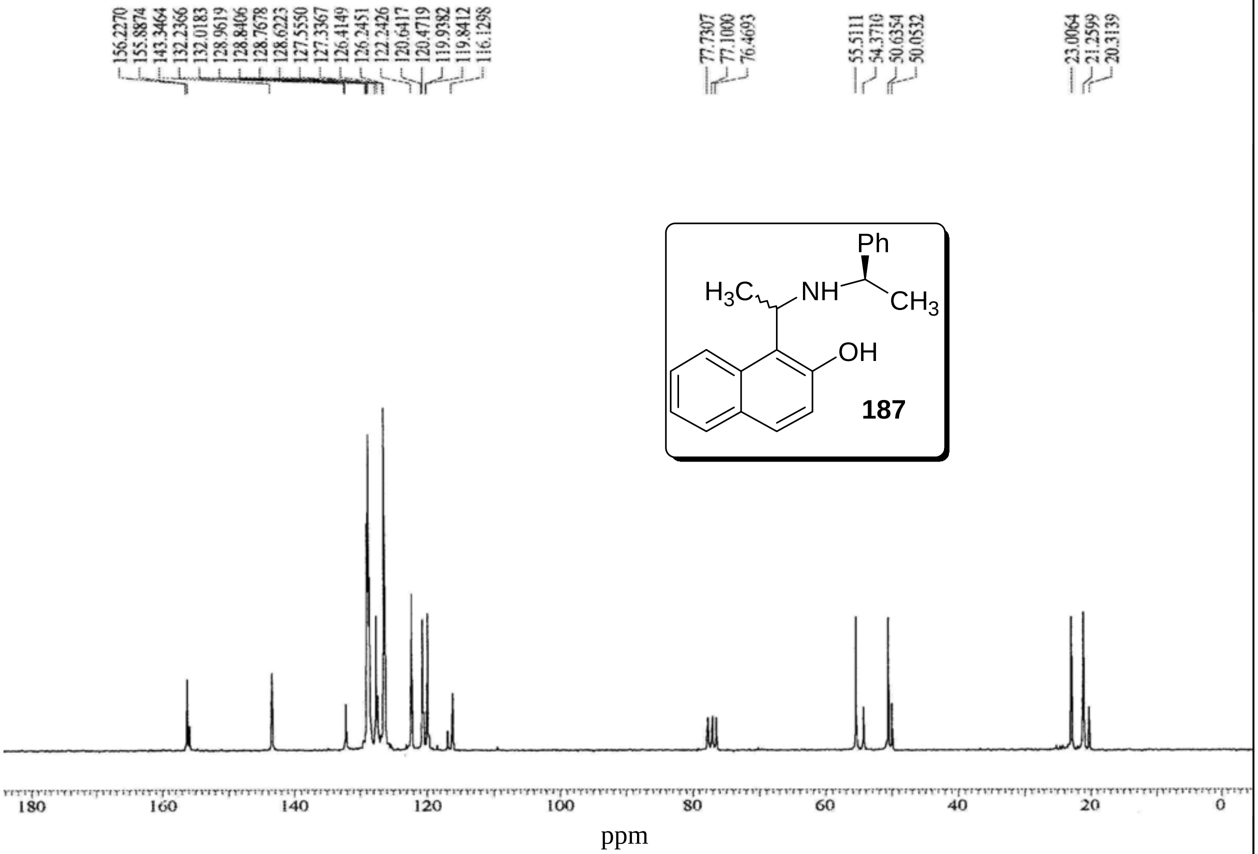
Spectrum No. 28 (Chapter 3, Section 3.4.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



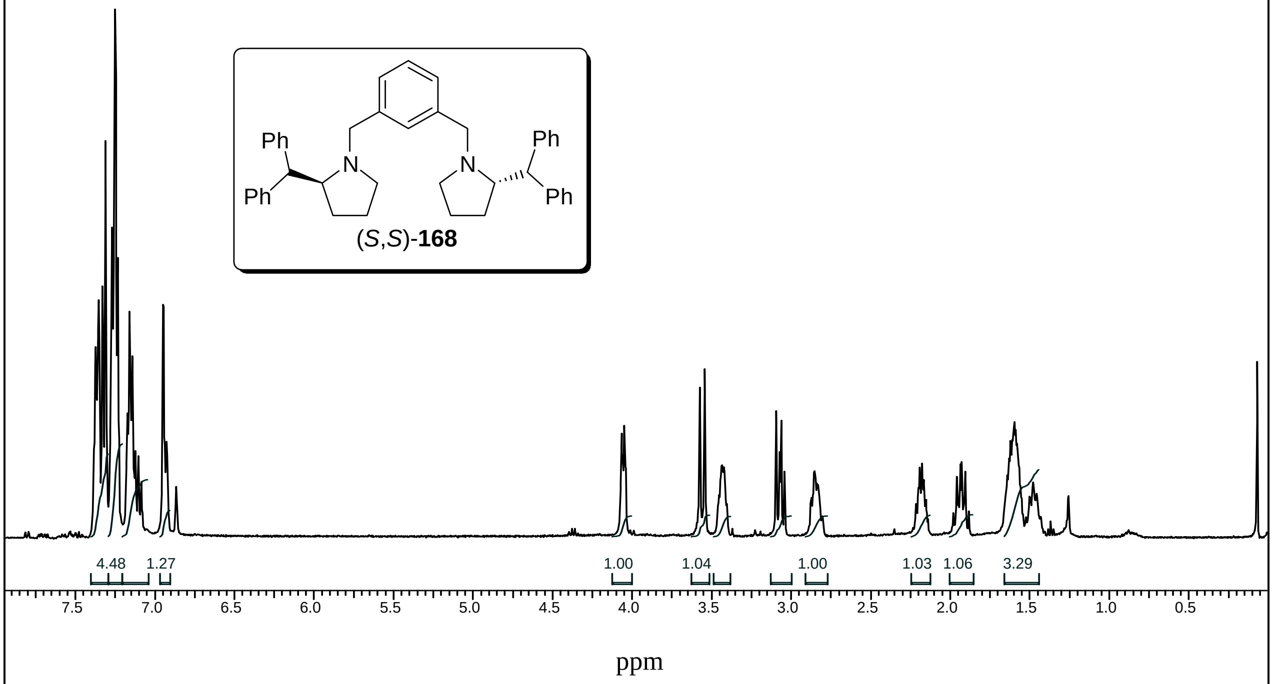
Spectrum No. 29 (Chapter 3, Section 3.4.4) ^{1}H NMR Spectrum (400 Hz, $CDCl_3$)



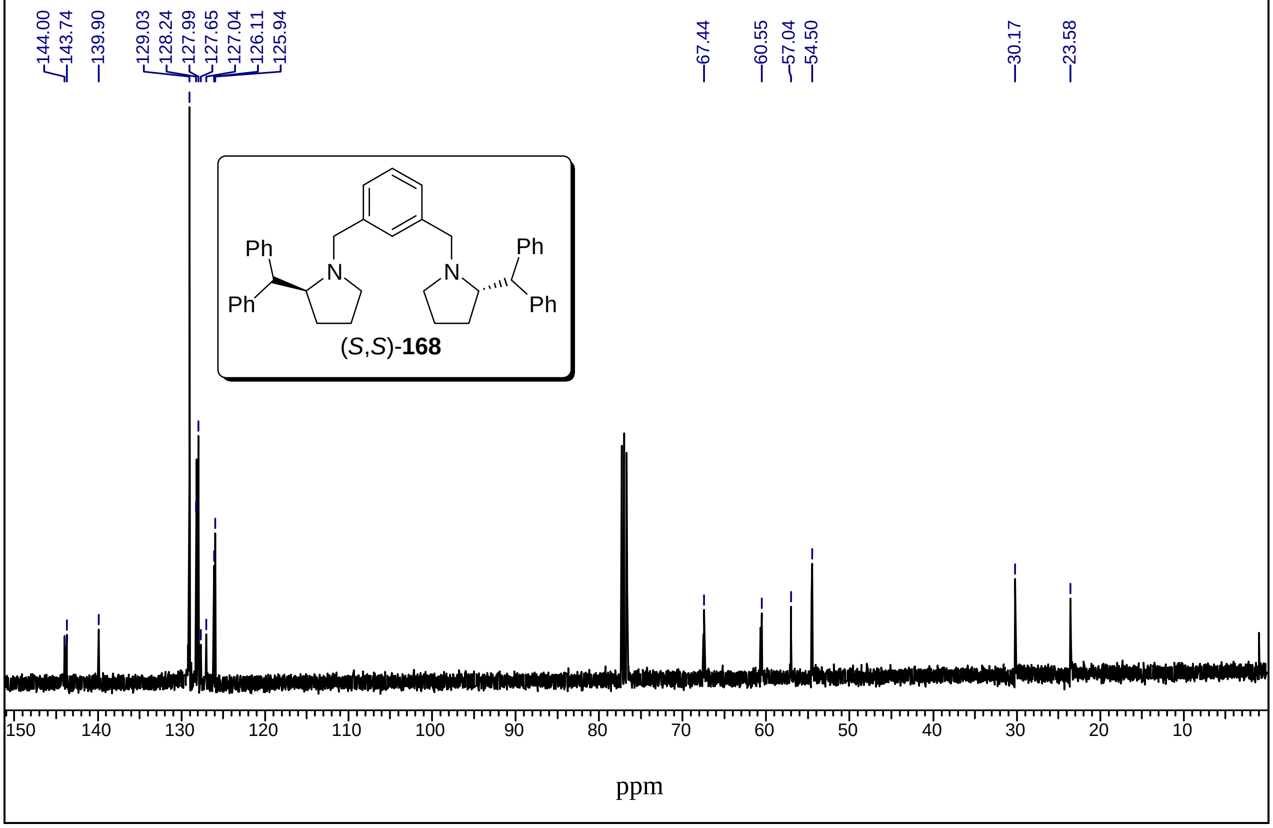
Spectrum No. 30 (Chapter 3, Section 3.4.4) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



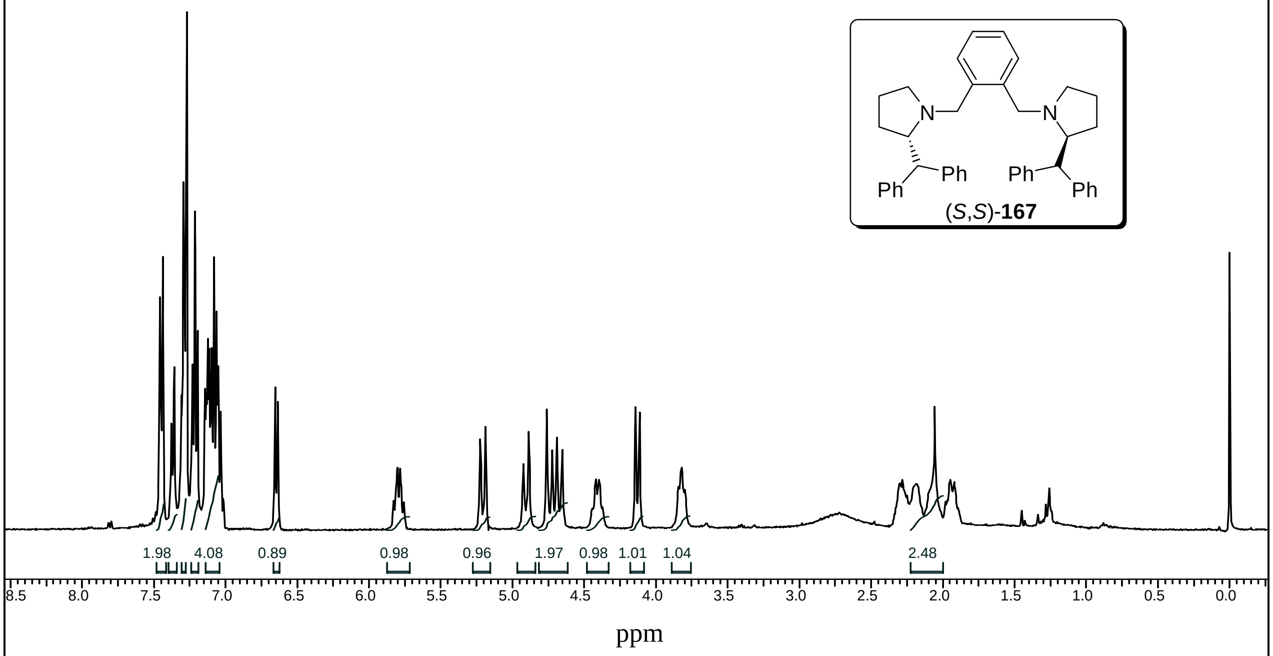
Spectrum No. 31 (Chapter 3, Section 3.8.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



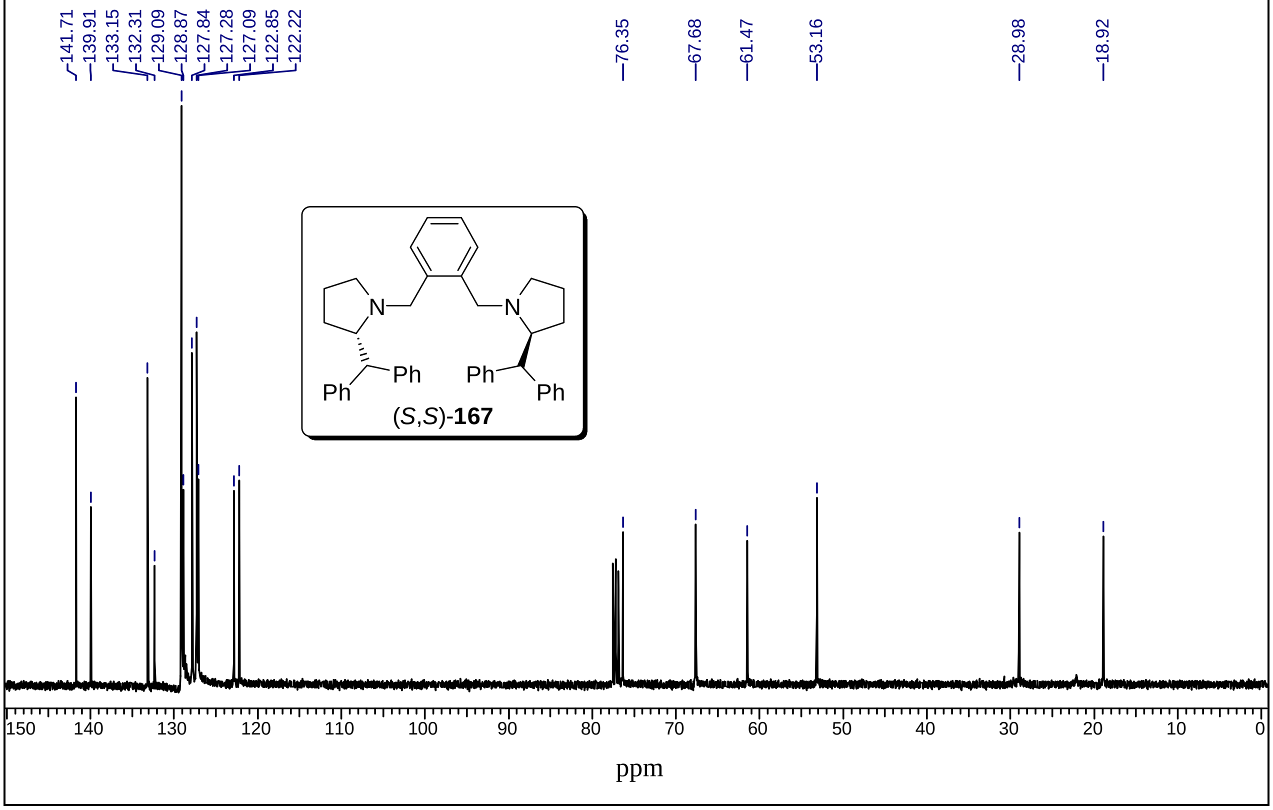
Spectrum No. 32 (Chapter 3, Section 3.8.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



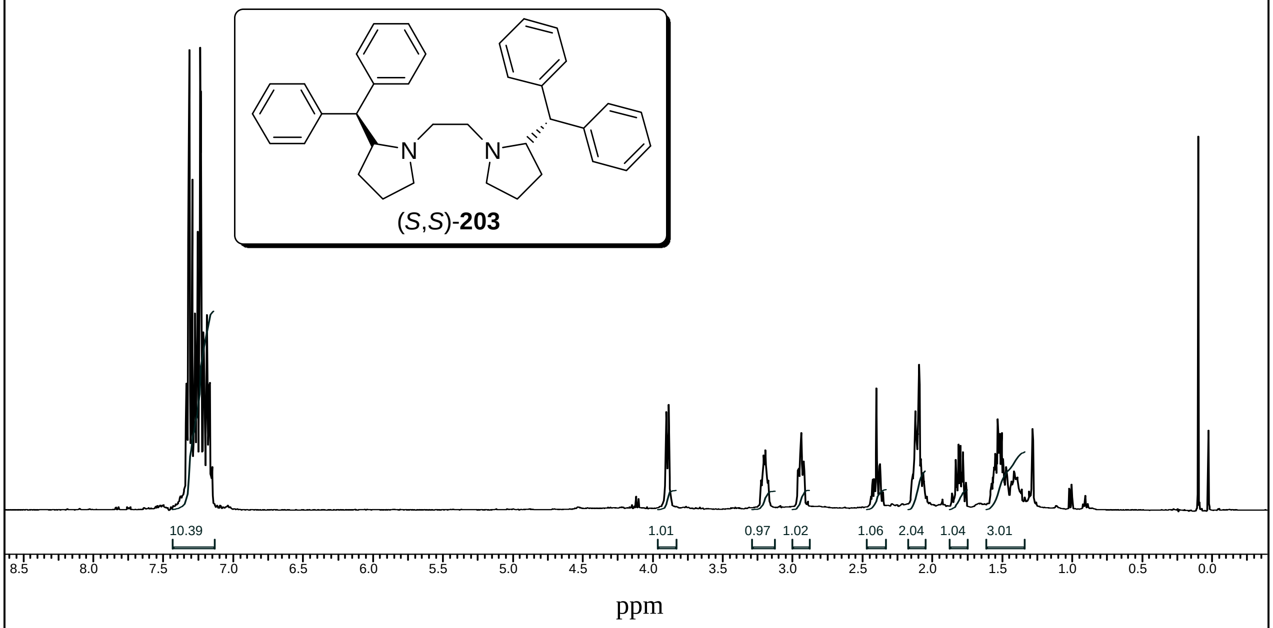
Spectrum No. 33 (Chapter 3, Section 3.8.3) ^{1} H NMR Spectrum (400 MHz, CDCl$_3$)



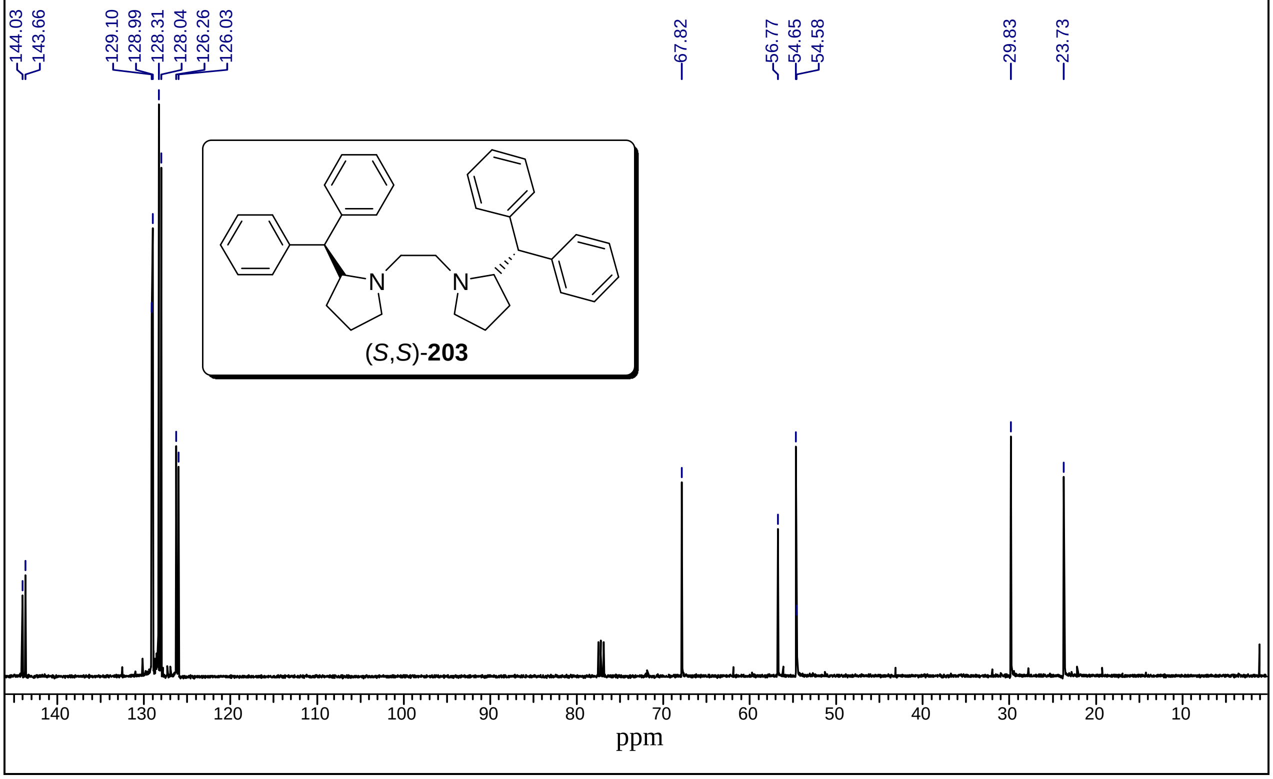
Spectrum No. 34 (Chapter 3, Section 3.8.3) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



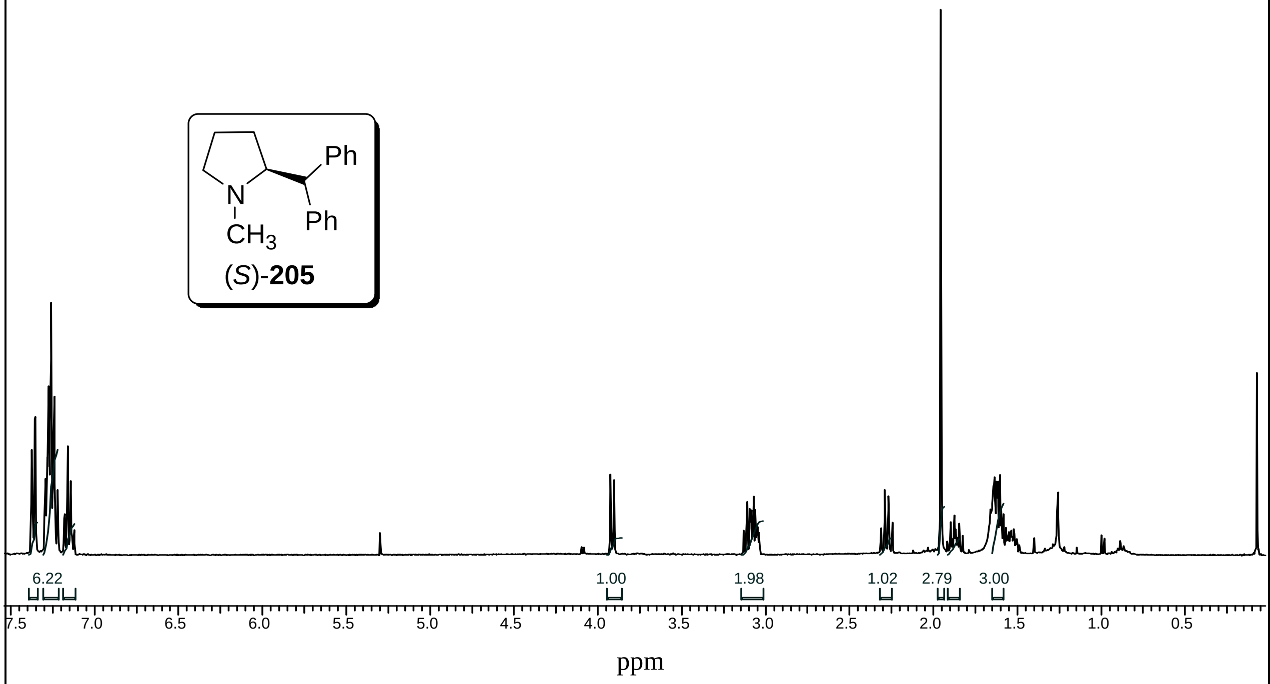
Spectrum No. 35 (Chapter 3, Section 3.8.4) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



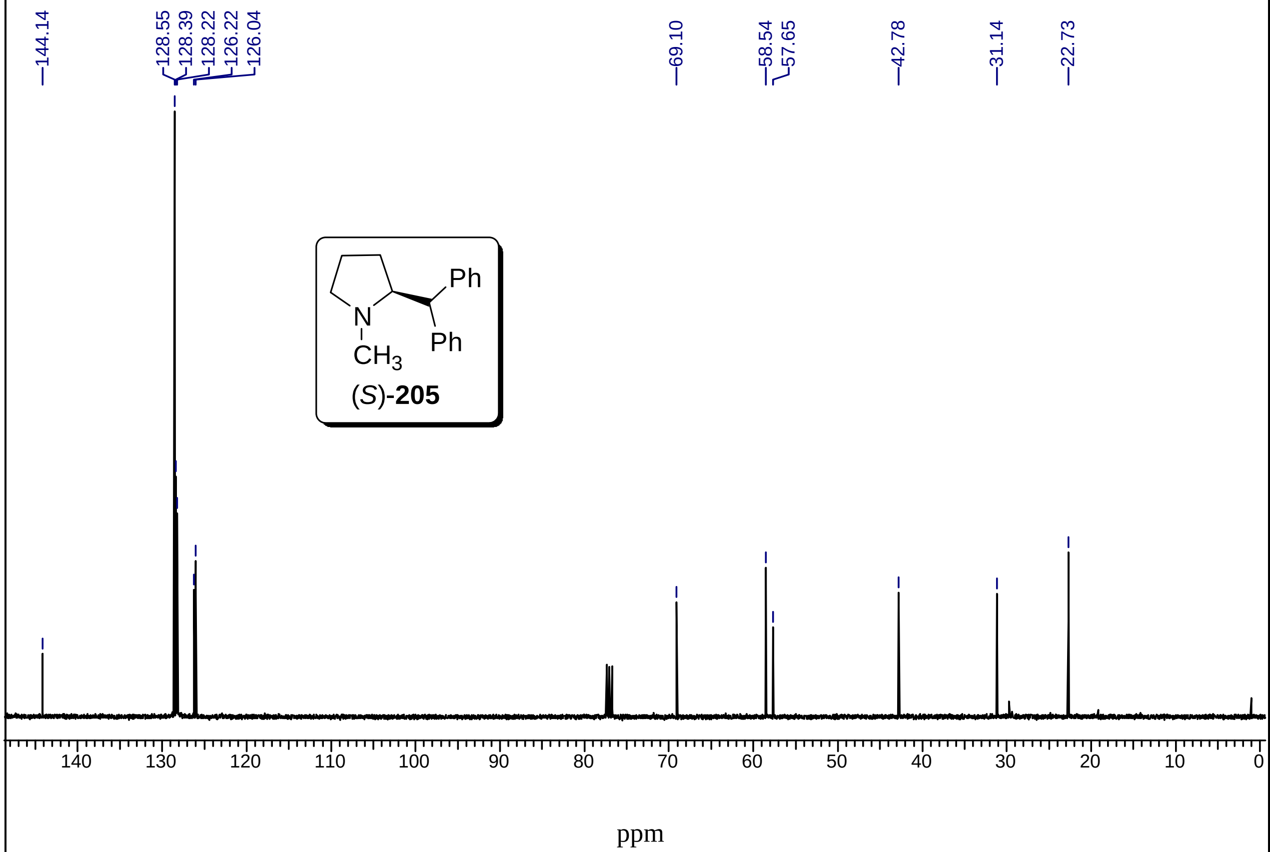
Spectrum No. 36 (Chapter 3, Section 3.8.4) ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)



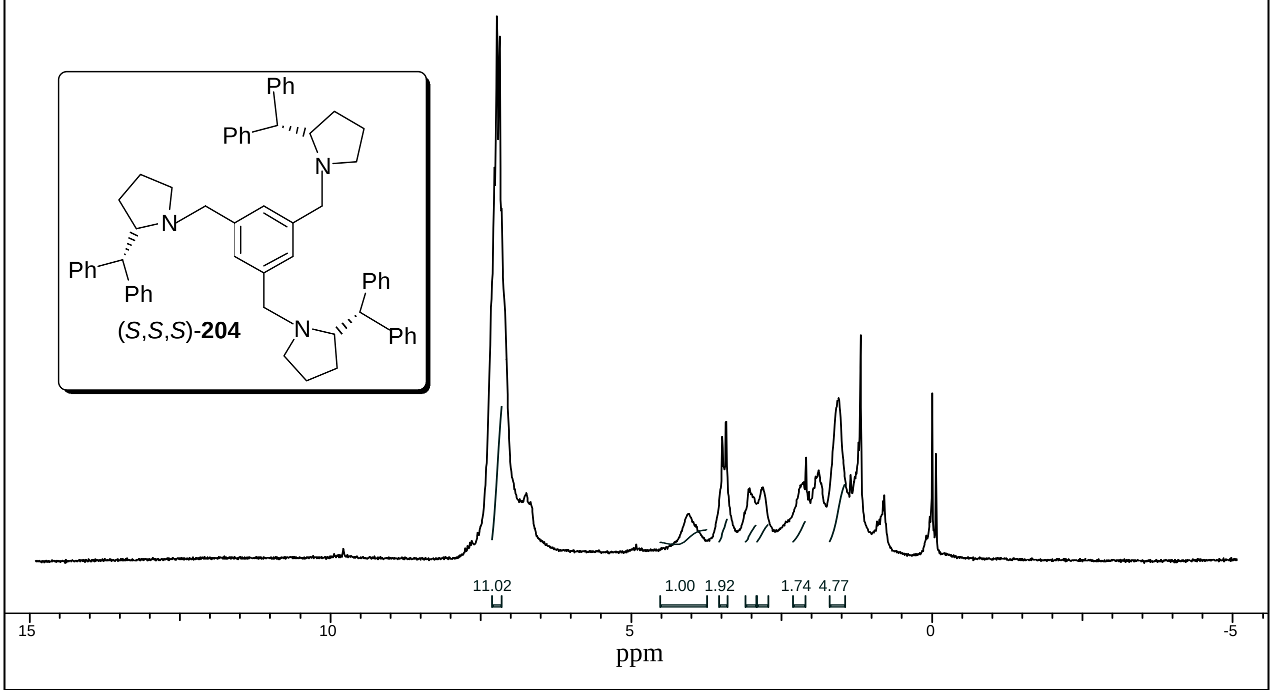
Spectrum No. 37 (Chapter 3, Section 3.8.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



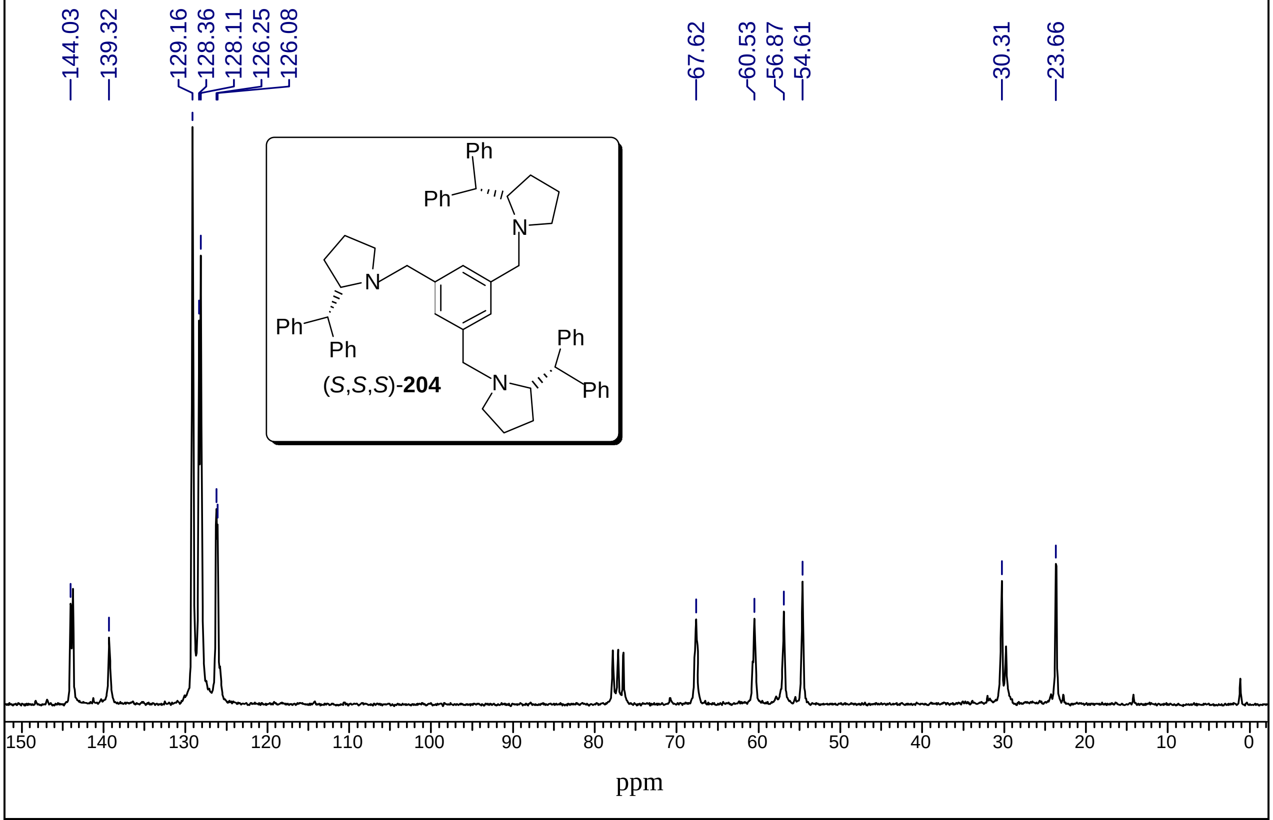
Spectrum No. 38 (Chapter 3, Section 3.8.9) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



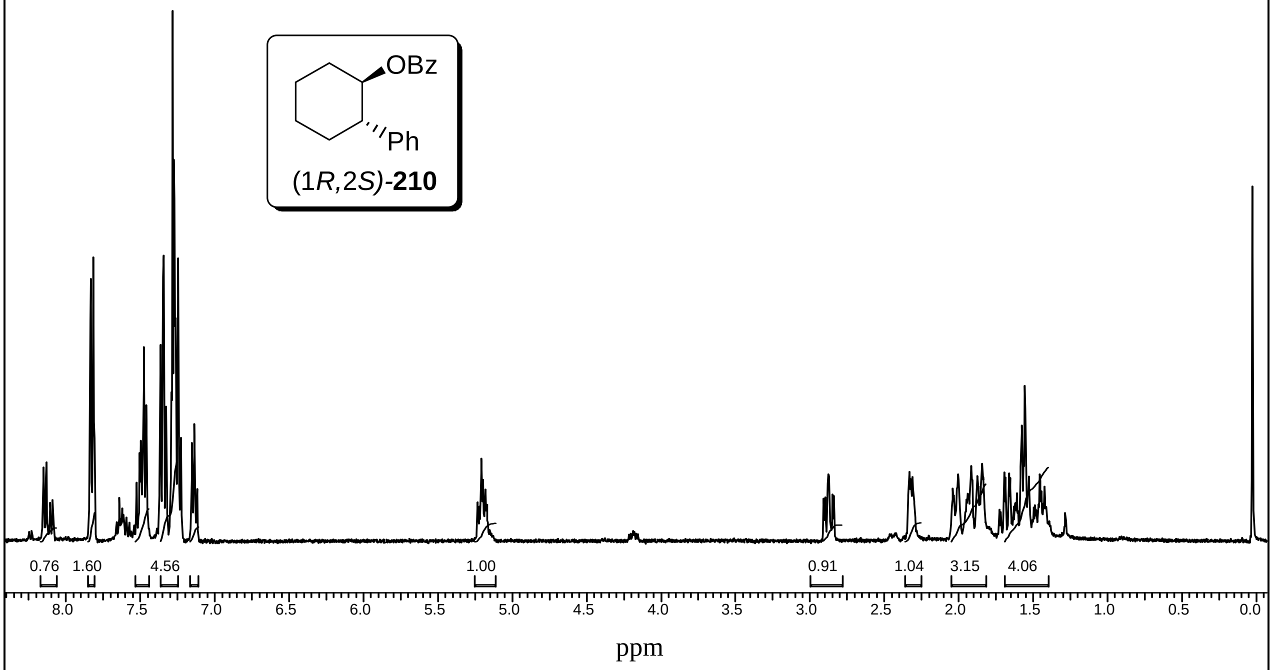
Spectrum No. 39 (Chapter 3, Section 3.9.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



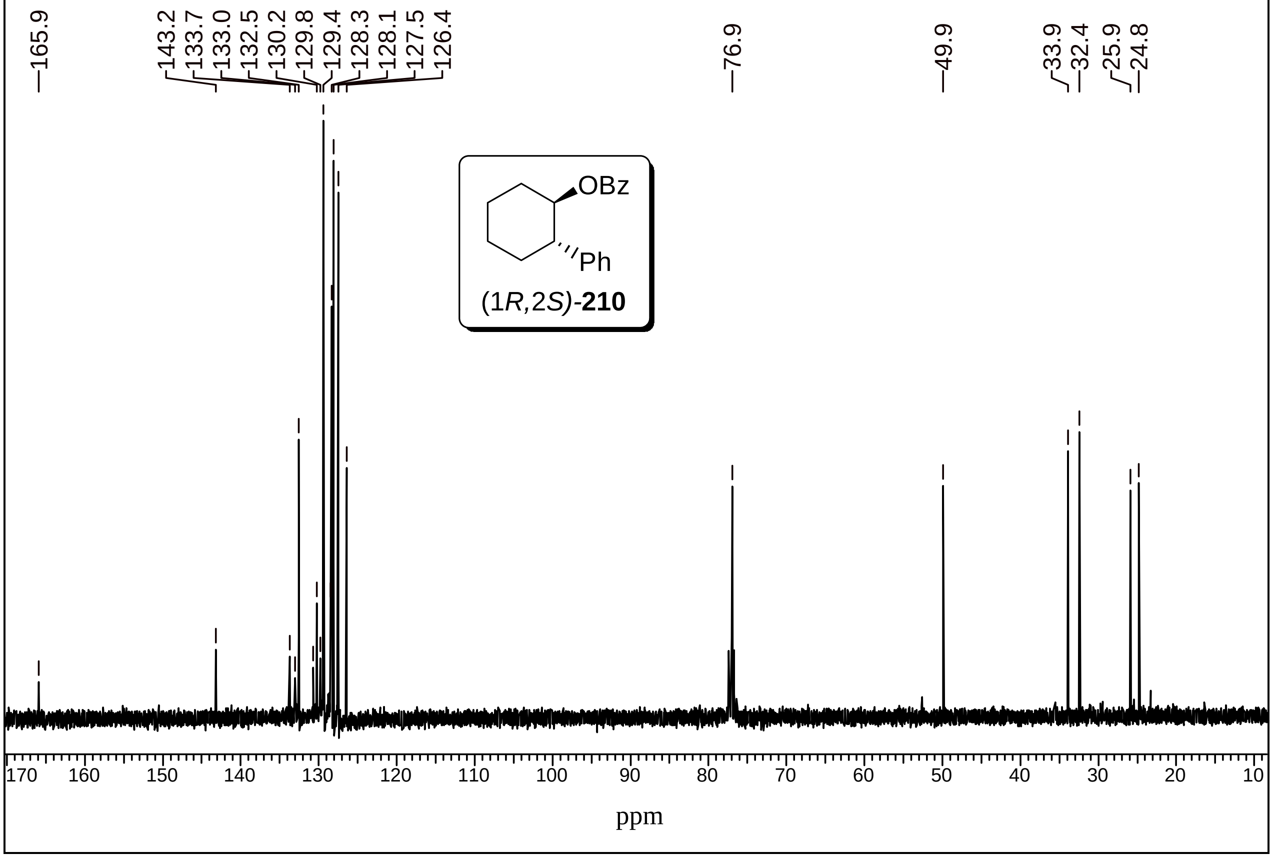
Spectrum No. 40 (Chapter 3, Section 3.9.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



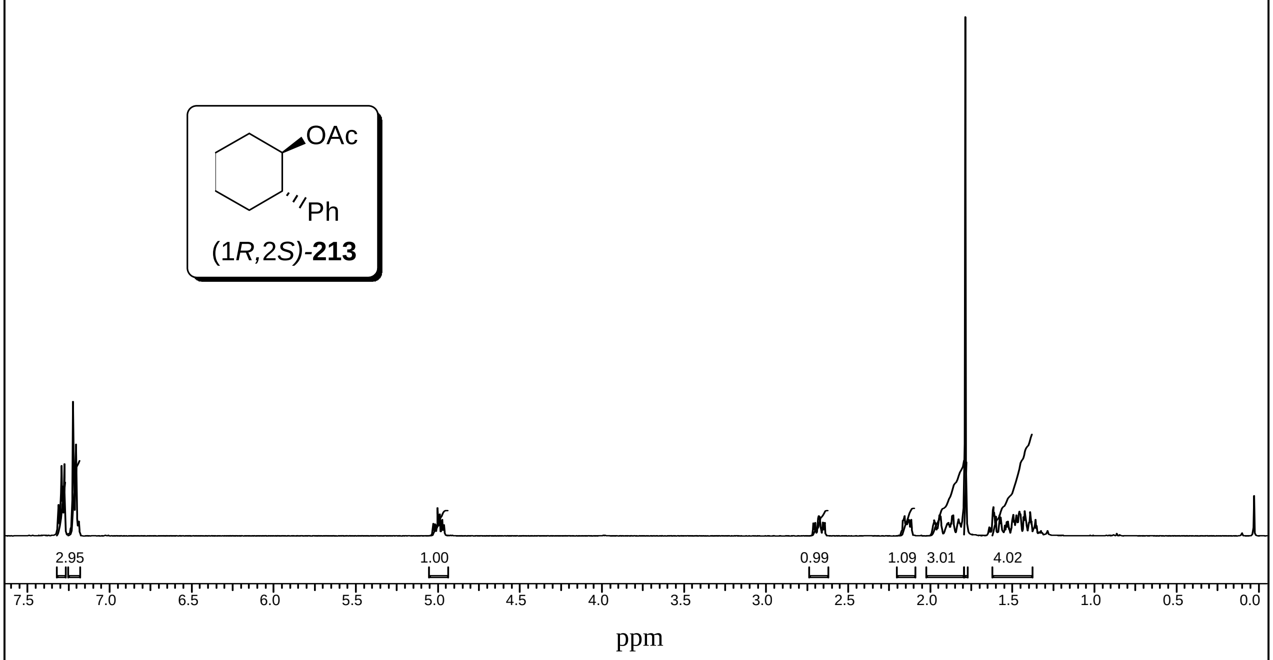
Spectrum No. 41 (Chapter 3, Section 3.12) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



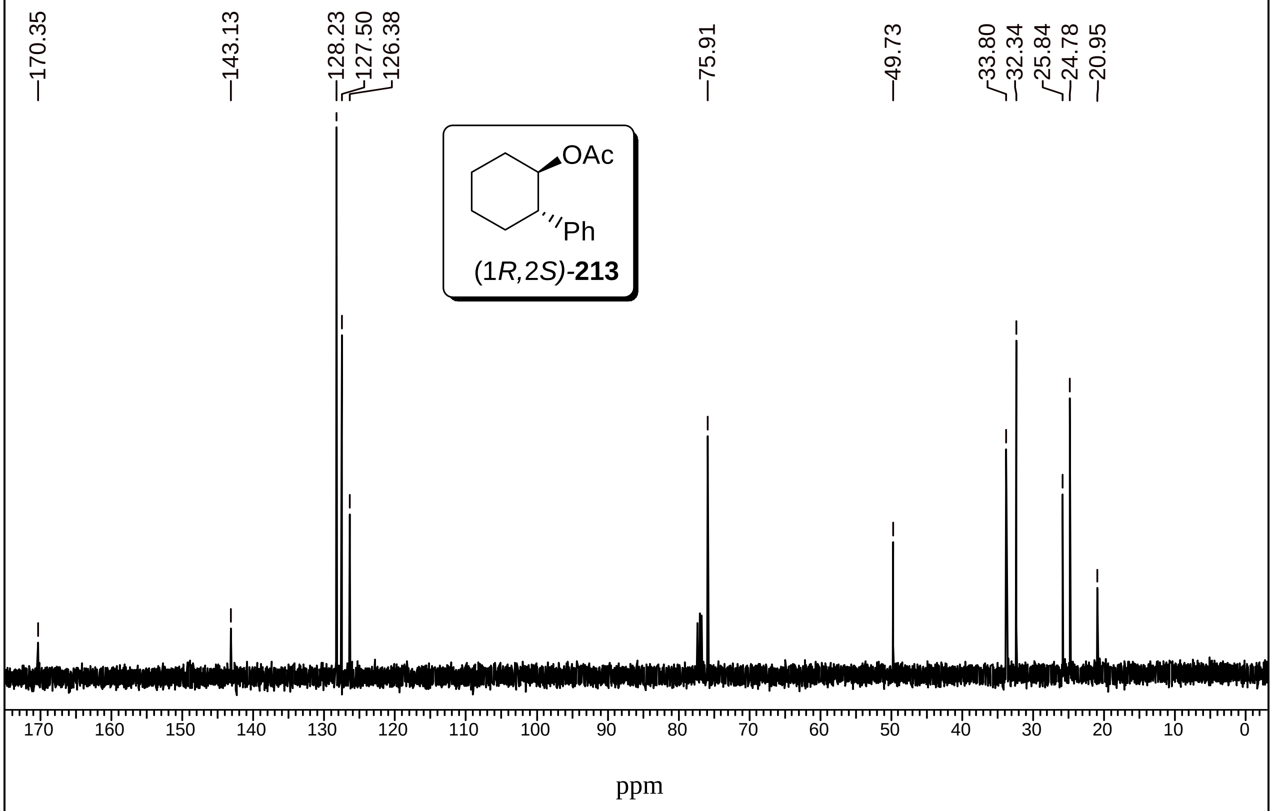
Spectrum No. 42 (Chapter 3, Section 3.12) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



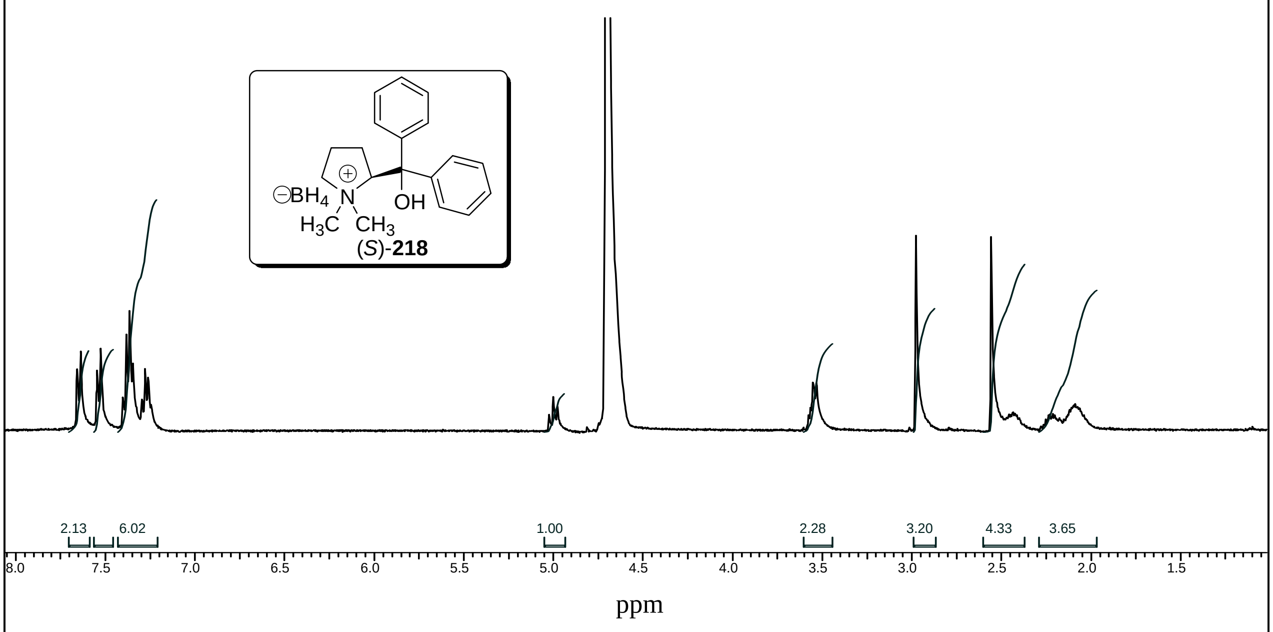
Spectrum No. 43 (Chapter 3, Section 3.13) ^{1}H NMR Spectrum (200 MHz, CDCl$_3$)



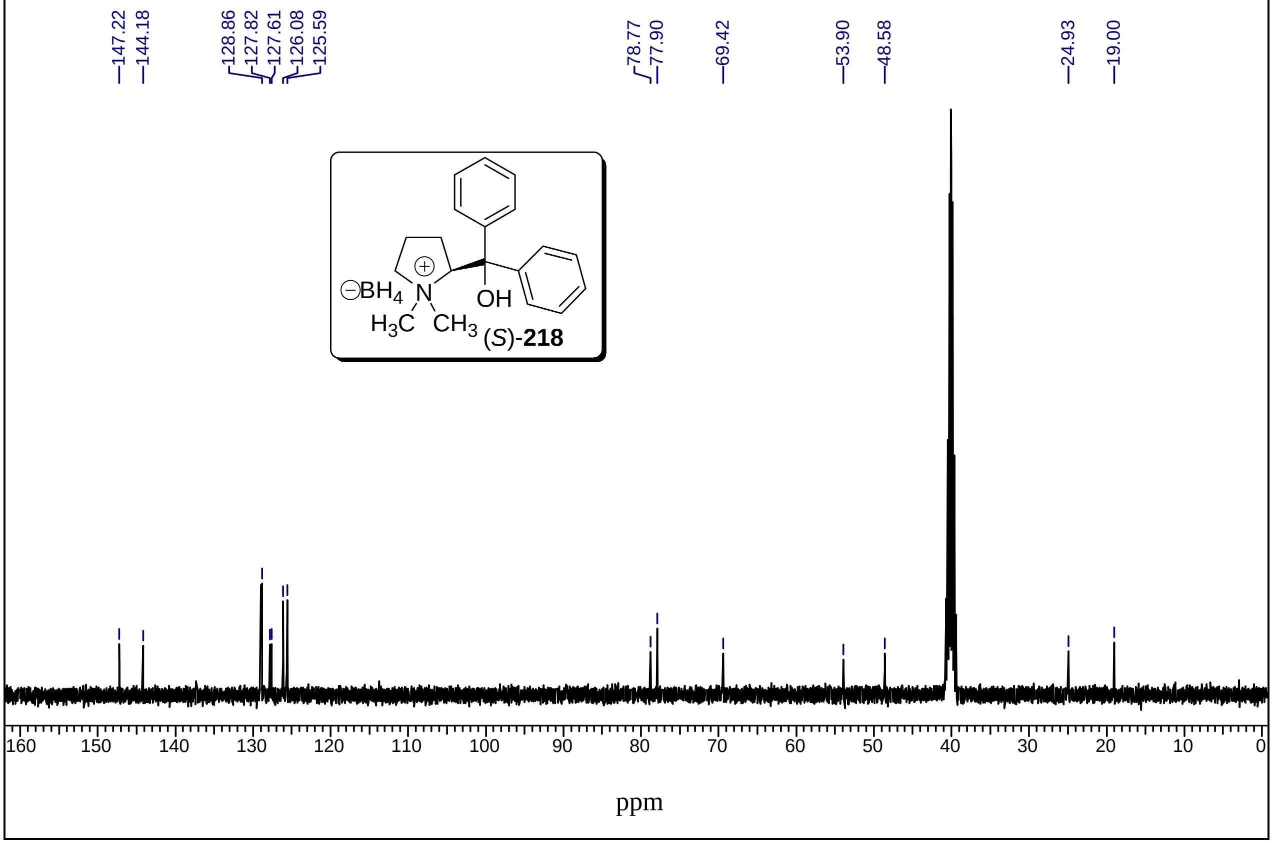
Spectrum No. 44 (Chapter 3, Section 3.13) ^{13}C NMR Spectrum (50 MHz, CDCl$_3$)



Spectrum No. 45 (Chapter 3, Section 3.15) ^{1}H NMR Spectrum (400 MHz, CDCl$_3$)



Spectrum No. 46 (Chapter 3, Section 3.15) ^{13}C NMR Spectrum (50 MHz, CDCl$_3$)



Appendix II

(X-Ray Crystallographic Data)

Table A_1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **176** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
C(1)	7215(3)	3763(3)	6300(3)	44(1)
C(2)	8034(3)	3320(3)	6541(3)	46(1)
C(3)	8838(3)	3646(3)	6255(3)	54(1)
C(4)	8831(3)	4397(3)	5766(3)	64(1)
C(5)	8002(4)	4872(3)	5527(3)	58(1)
C(6)	7972(4)	5666(3)	5037(3)	75(2)
C(7)	7163(5)	6120(3)	4850(3)	82(2)
C(8)	6353(4)	5805(3)	5118(3)	76(2)
C(9)	6346(3)	5037(3)	5573(3)	59(1)
C(10)	7174(3)	4555(3)	5797(2)	46(1)
C(11)	8108(3)	2513(3)	7150(3)	47(1)
C(12)	8271(3)	2815(3)	8118(3)	46(1)
C(13)	7594(3)	3180(3)	8550(3)	61(1)
C(14)	7787(4)	3451(3)	9425(3)	74(2)
C(15)	8683(5)	3380(3)	9876(3)	79(2)
C(16)	9365(4)	3022(4)	9458(3)	78(2)
C(17)	9157(3)	2738(3)	8585(3)	63(1)
C(18)	7120(3)	1592(3)	6060(3)	57(1)
C(19)	6446(4)	850(3)	6111(3)	87(2)
C(20)	6634(3)	541(3)	7071(3)	70(1)
C(21)	7318(3)	1185(3)	7547(3)	52(1)
C(22)	1218(3)	2295(3)	7188(3)	44(1)
C(23)	1625(3)	2364(3)	8068(3)	41(1)
C(24)	1450(3)	1687(3)	8654(3)	56(1)
C(25)	901(3)	990(3)	8385(3)	60(1)
C(26)	479(3)	919(3)	7496(3)	53(1)
C(27)	-103(3)	203(3)	7179(4)	74(2)
C(28)	-478(4)	152(4)	6314(5)	86(2)
C(29)	-322(4)	790(4)	5707(4)	82(2)
C(30)	232(3)	1490(3)	5978(3)	63(1)
C(31)	645(3)	1570(3)	6877(3)	49(1)
C(32)	2284(3)	3106(3)	8414(3)	48(1)
C(33)	3273(3)	2842(3)	8289(3)	49(1)
C(34)	3619(3)	2954(3)	7502(3)	72(1)
C(35)	4506(4)	2672(4)	7403(4)	87(2)
C(36)	5036(4)	2257(4)	8102(5)	89(2)
C(37)	4698(4)	2134(4)	8883(5)	96(2)
C(38)	3820(3)	2425(3)	8978(3)	72(1)

C(39)	1101(3)	4254(3)	8143(3)	62(1)
C(40)	1056(4)	5187(3)	7788(4)	81(2)
C(41)	2072(3)	5469(3)	7862(4)	96(2)
C(42)	2623(3)	4679(3)	8202(4)	77(2)
N(1)	7254(2)	1968(2)	6967(2)	43(1)
N(2)	1999(2)	3929(2)	7938(2)	49(1)
O(1)	6388(2)	3485(2)	6527(2)	57(1)
O(2)	1348(2)	2915(2)	6565(2)	59(1)

List of publications

1. Synthesis and resolution of 1-(α-pyrrolidinylbenzyl)-2-naphthol and its application in the resolution of 2,2'-dihydroxy-1,1′-binaphthyl, Periasamy, M.; Reddy, M. N.; **Anwar**, **S**. *Tetrahedron: Asymmetry*, **2004**, *15*, 1809.
2. A convenient method for the preparation of oxazaborolidine catalyst in situ using (S)-α,α-diphenylpyrrolidinemethanol, tetrabutylammonium borohydride and methyl iodide for the asymmetric reduction of prochiral ketones, **Anwar, S**.; Periasamy, M. *Tetrahedron: Asymmetry*, **2006**, *17*, 3244.
3. A Simple and Convenient Method of Synthesis, Resolution and Application of aminonaphthols, Periasamy, M.; **Anwar**, **S**.; Reddy, M. N. (Manuscript communicated).

PRESENTATIONS

1. Oral presentation in the *"Chemfest 2007"* in house symposium held at University of Hyderabad, Hyderabad, March, **2007**; Title: Synthesis and Application of Chiral Amino Alcohols, Aminonaphthols and Amines in Asymmetic Reductions and Resolutions.
2. Presented a poster in the *"Chemfest 2007"* in house symposium held at University of Hyderabad, Hyderabad, March, **2007**; Title: Synthesis and Application of Chiral Amino Alcohols, Aminonaphthols and Amines in Asymmetic Reductions and Resolutions.