Studies on the Reactive Organotitanium Intermediates and Chiral 1,1′-Binaphthyl-2,2′-Diamine Derivatives

A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

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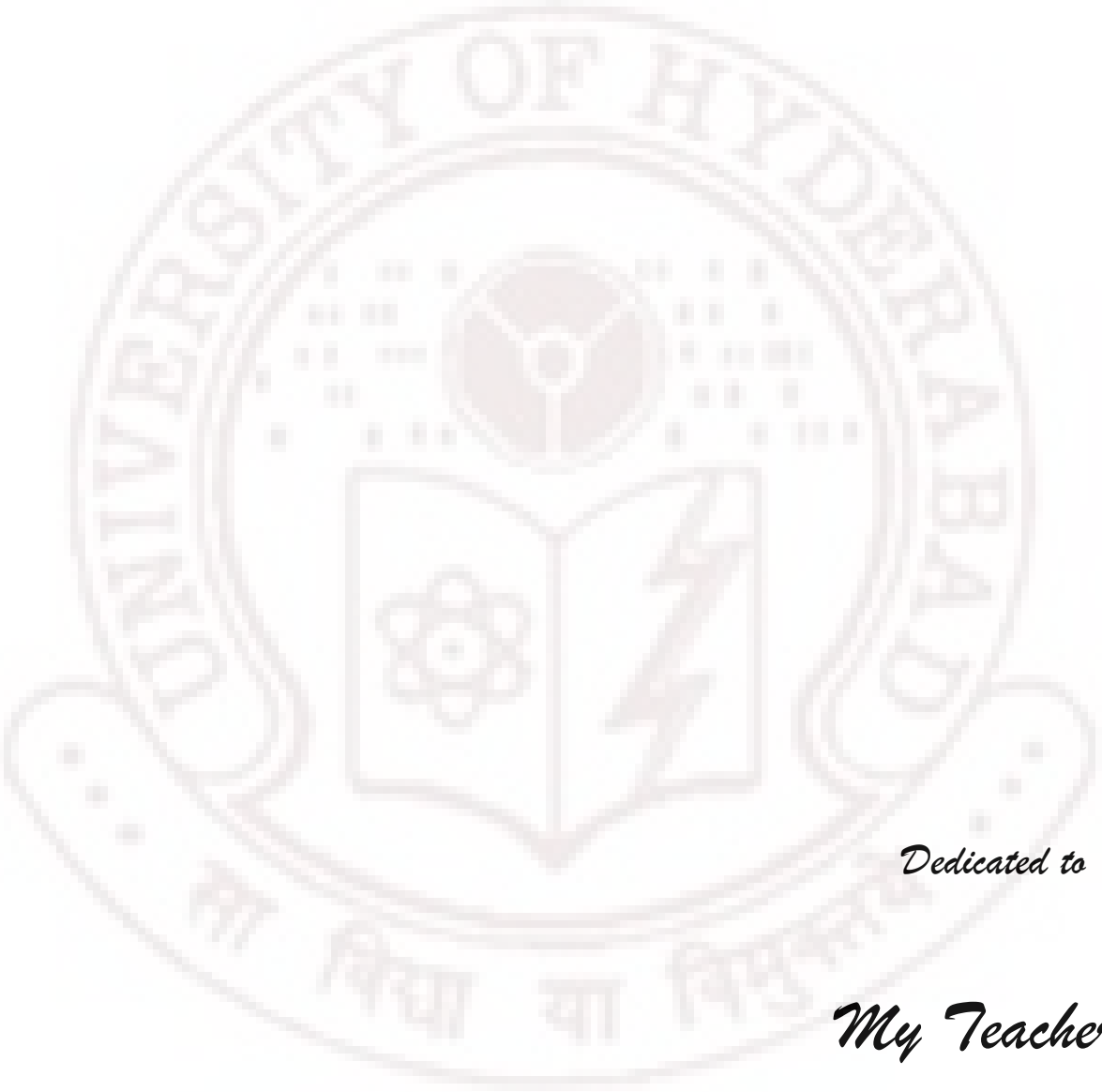

Dedicated to

My Teachers

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Statement

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

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

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Certificate

Certified that the work embodied in this thesis entitled **"Studies on the Reactive Organotitanium Intermediates and Chiral 1,1′-Binaphthyl-2,2′-Diamine Derivatives"** has been carried out by **Mr. S. Selva Ganesan** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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Selva Ganesan

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g. dm, are understood]
aq.	Aqueous
Ac	Acetyl
BINOL	1,1'-bi-2-naphthol
BINAM	1,1'-binapthyl-2,2'-diamine
Bn	benzyl
Bz	Benzoyl
bp	boiling point
br s	broad singlet (spectral)
Bu	butyl
^{t}Bu	*ter*-butyl
^{o}C	degree Celsius
conc.	Concentrated
Cat.	Catalytic
Cbz	Carboxybenzyl
cm^{-1}	wavenumber(s)
δ	chemical shift in parts per million downfield from tetramethyl silane
dr	diastereomeric ratio
dt	doublet of triplet (spectral)
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol
equiv.	equivalent
eqn.	equation
g	gram (s)
h	hour (s)
HPLC	high-performance liquid chromatography

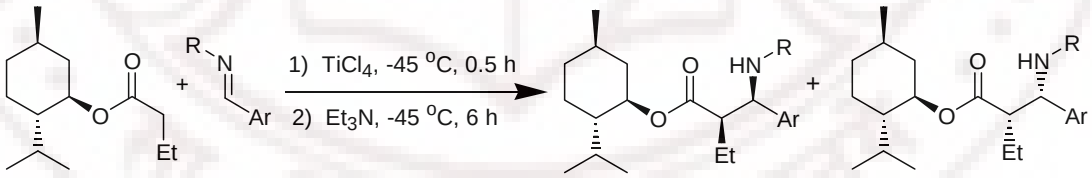
Hz	hertz
^{i}Pr	isopropyl
IR	infrared
J	Coupling constant (in NMR Spectrometry)
lit.	literature
m	multiplet (spectral)
MALDI-TOF	Matrix Assisted Laser Desorption/Ionisation-Time of Flight
Me	methyl
MW	molecular weight
M_W	weight average molecular weight
MHz	megahertz
min.	minute(s)
mmol	millimolar
mp	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
n-	primary
Nu	nucleophile
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
PMP	*p*- methoxyphenyl
PMB	*p*- methoxybenzyl
q	quartet (in spectroscopy)
RT	room temperature
TBAB	tetrabutylammonium borohydride
THF	tetrahydrofuran
TMS-Cl	trimethylsilyl chloride
TFA	trifluoroacetic acid
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TfOH	Triflic acid

Abstract

This thesis entitled "**Studies on the Reactive Organotitanium Intermediates and Chiral 1,1′-Binaphthyl-2,2′-Diamine Derivatives**" comprises of two parts. Each part is subdivided into two chapters under four sections namely **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**. The work described in this thesis is exploratory in nature and the chapters are arranged in the order the investigations were executed.

In Part **I**, investigations on the titanium reagents are described. Results of studies on the use of the $TiCl_4/Et_3N$ reagent system for the preparation of chiral enolates for use in Mannich-type reaction are described in Chapter **1**. The reaction of *L*-(-)-menthyl butyrate **1** and imines **2a-g** with the $TiCl_4/Et_3N$ reagent system gave the corresponding *syn*-β-amino esters **3-9** in moderate to good yields with good selectivity (Scheme **1**).

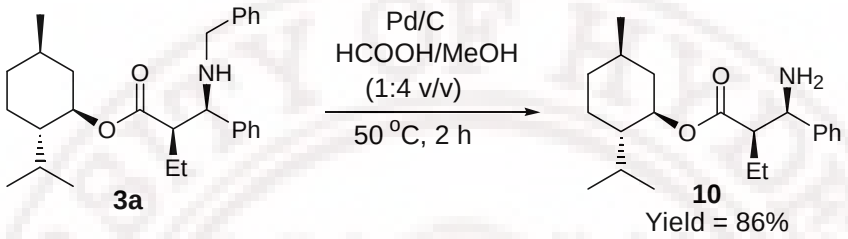
Scheme 1



The major amino ester products **3a** and **9a** were characterized by the single crystal X-ray analysis of the corresponding mandelic acid salt. The compound **3a** has been found to be useful for the resolution of the racemic mandelic acid to >99% ee in a single step.

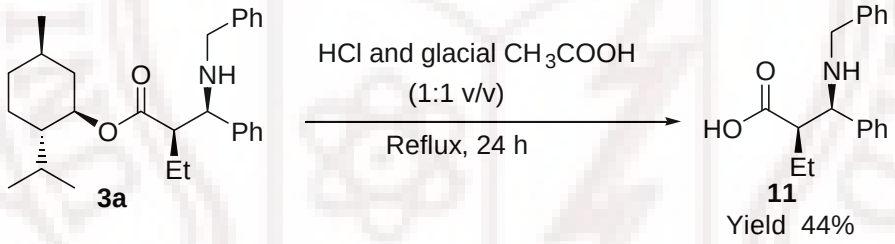
The *syn*-β-amino ester **3a** was debenzylated using Pd/C in formic acid/methanol mixture under ambient condition (Scheme **2)**.

Scheme 2



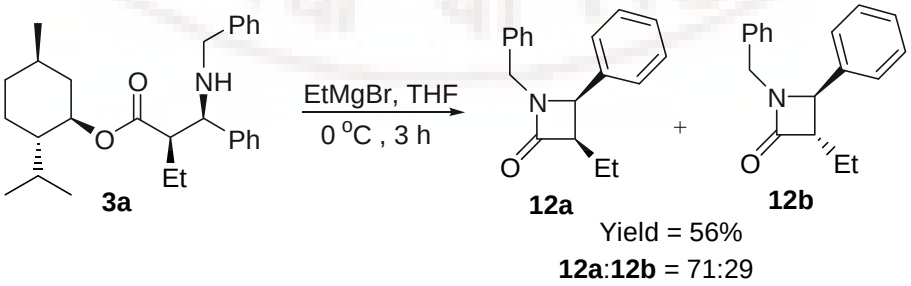
The corresponding β-amino acid **11** was obtained in 44% yield by acid hydrolysis of the *syn*-β-amino ester **3a** (Scheme **3**).

Scheme 3



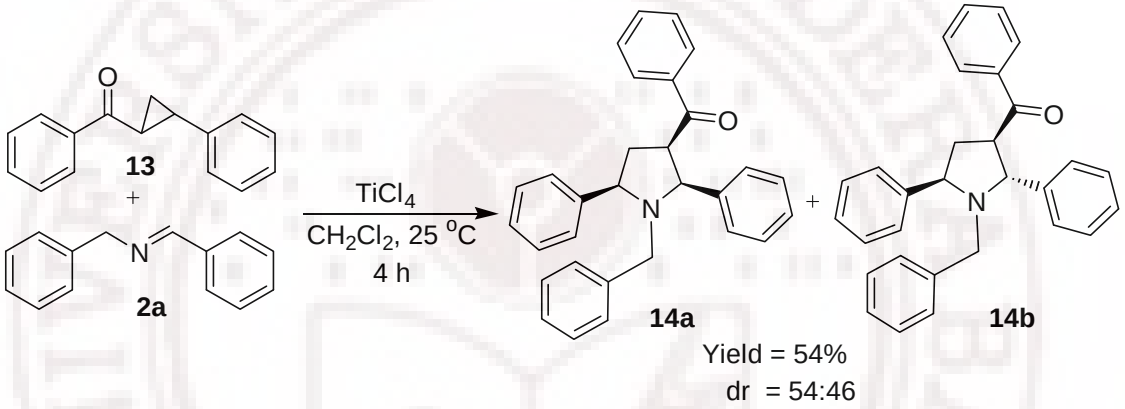
The β-lactam **12** was prepared by the reaction of *syn*-β-amino ester **3a** with ethylmagnesium bromide. Partial racemization of the β-lactam product **12** was observed (Scheme **4**).

Scheme 4



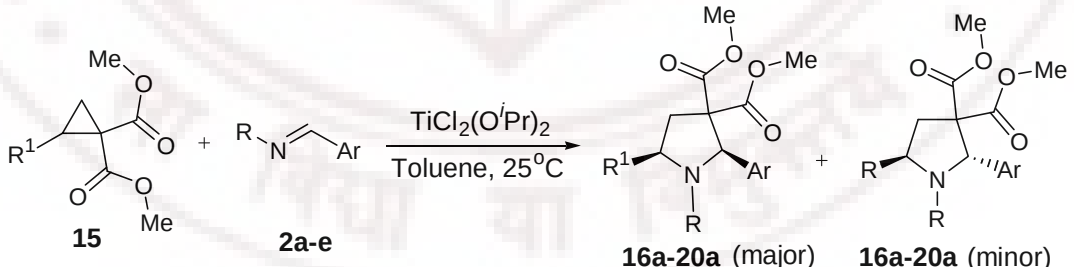
Studies on the titanium complex promoted reactions of donor-acceptor cyclopropanes **13** and **15** are described in Chapter **2**. The cycloaddition reaction of cyclopropyl ketone **13** and imine **2a** in the presence of $TiCl_4$ gave the corresponding pyrrolidine ketone **14** in 54% yield (Scheme **5**).

Scheme 5



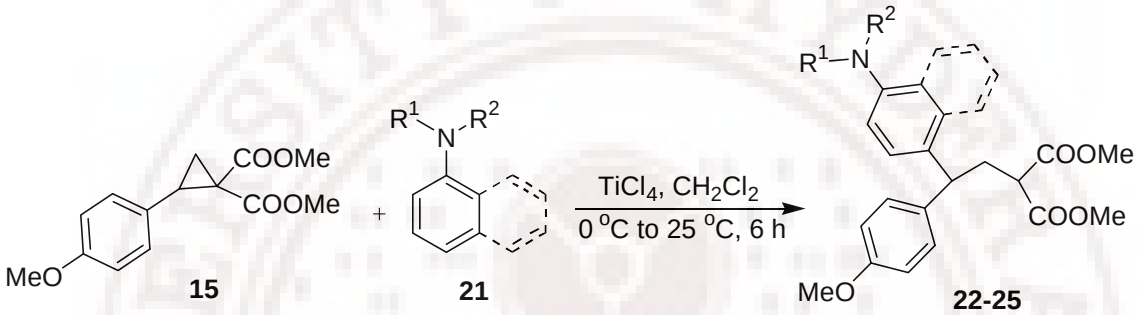
The intermediate prepared using cyclopropyl diester **15** and $TiCl_2(O^iPr)_2$ on reaction with imines **2a-e** gave the corresponding pyrrolidines **16** - **20** (Scheme **6**).

Scheme 6



Whereas, the reaction of cyclopropyl diester **15** with $TiCl_4$ and tertiary aryl amine **21** gave the corresponding ring opened addition products **22-25** in 74-84% yields (Scheme **7**).

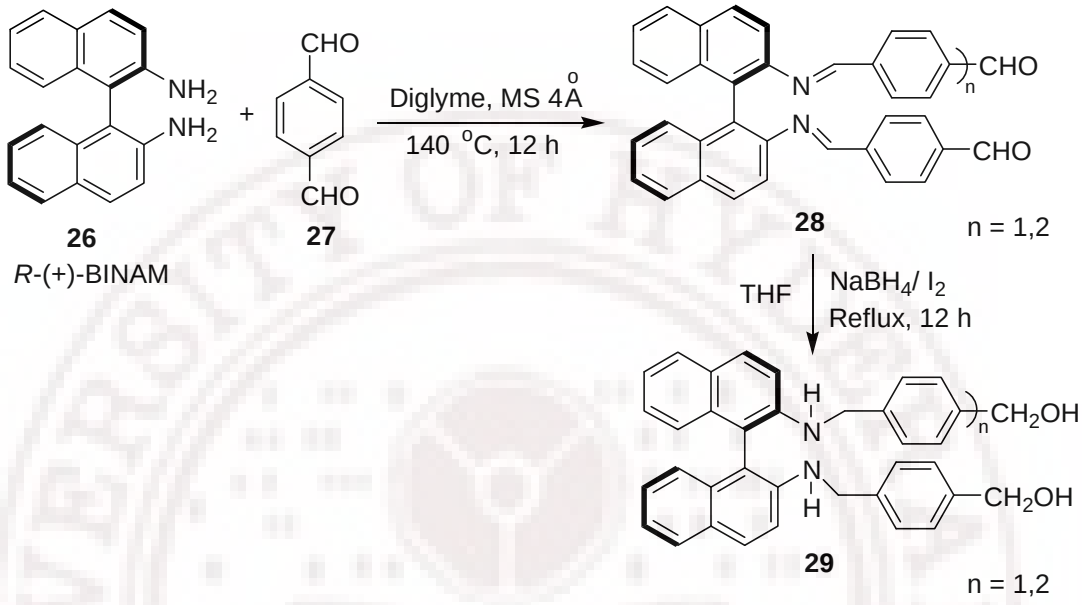
Scheme 7



Investigations undertaken on the synthesis and application of chiral 1,1′-binaphthyl-2,2′-diamine (BINAM) derivatives are described in Part **II** under Chapters **3** and **4**. Efforts toward the synthesis of oligomeric amine and amide derivatives of BINAM **26** are described in Chapter **3**.

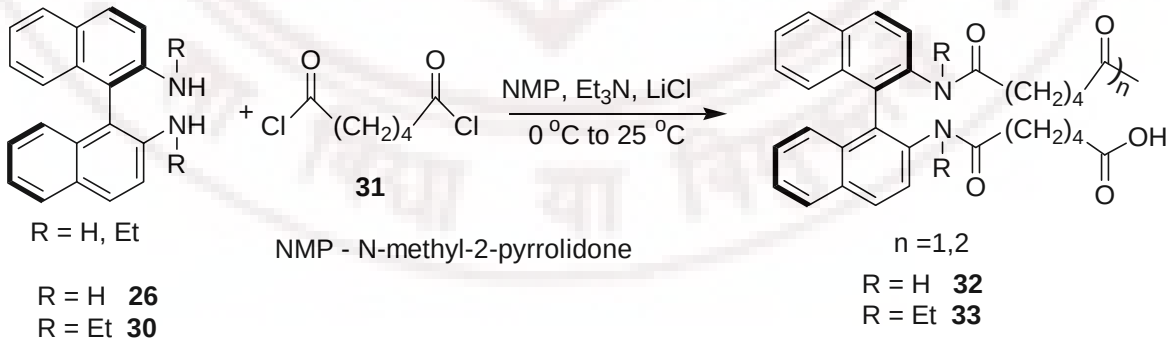
The reductive coupling of *N,N*′-dibenzylidine-1,1′-binaphthyl-2,2′-diamine by $TiCl_4$/Zn system to obtain macrocycles and polymers was not successful. However, monomeric and dimeric amine derivatives **29** were readily prepared through the $NaBH_4/I_2$ reduction of the corresponding imine **28** (Scheme **8**). Mass spectral analysis of the products revealed that the imine **28** and amine **29** products are mostly of [1+1] and [2+2] adducts.

Scheme 8



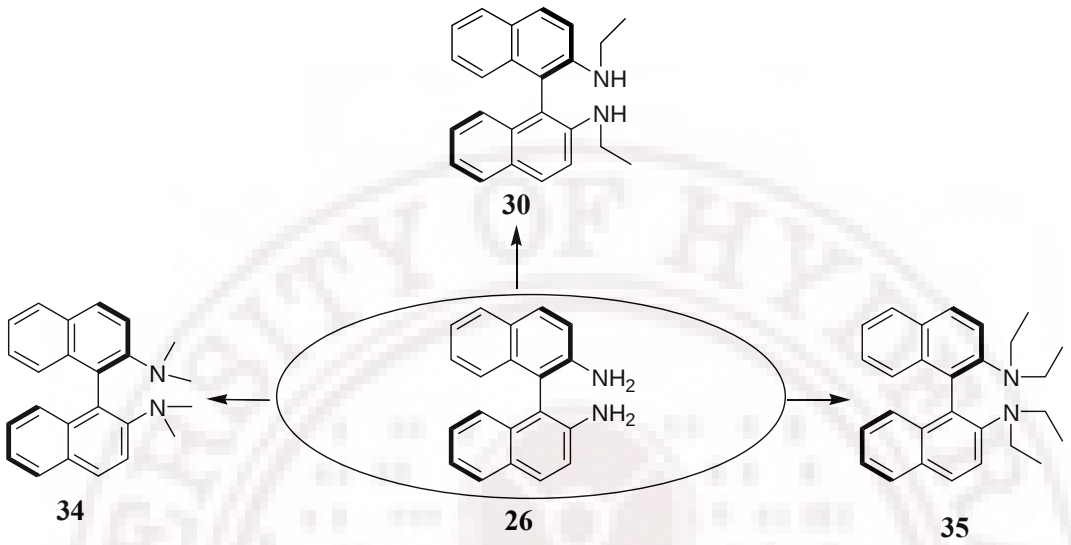
The reaction of BINAM **26** with terephthaloyl chloride gave the sparingly soluble amide. The soluble monomeric and dimeric amides **32** and **33** were readily prepared by the reaction of BINAM **26** and *N,N′*-diethyl BINAM **30** with adipoyl chloride **31** (Scheme **9**).

Scheme 9



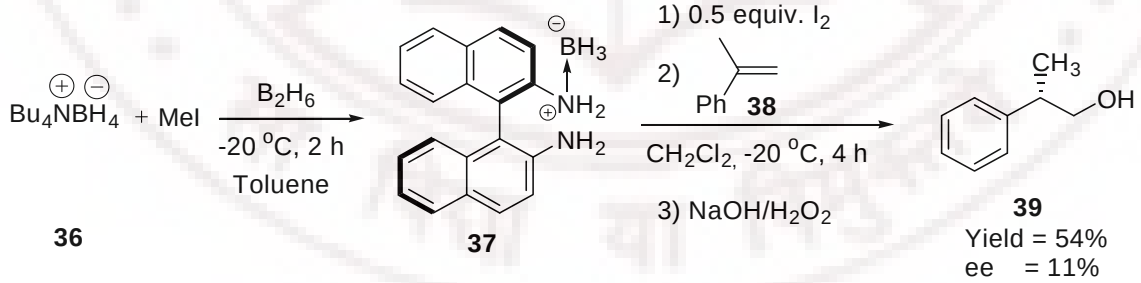
Studies on the hydroboration reaction using borane complexes of the chiral BINAM **26** and its derivatives **30**, **34** and **35** are described in Chapter **4** (Figure **1**).

Figure 1



The borane complexes obtained from BINAM derivatives **30**, **34** and **35** gave only racemic products upon hydroboration-oxidation reaction with α-methylstyrene **38**. However, the borane complex **37** of the primary amine **26** upon activation by iodine, hydroborated the α-methylstyrene **38** and the alcohol product **39** was obtained with up to 11% ee (Scheme **10**).

Scheme 10



Salient features of these results are discussed considering the mechanistic aspects of the hydroboration reaction.

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

Part I

Studies on the Reactive Organotitanium Intermediates

Chapter 1

$TiCl_4/Et_3N$ Mediated Synthesis of β-Amino Esters

1.1 Introduction

β-Amino acids and esters are useful building blocks for the synthesis of β-lactam and β-peptide moieties that are present in several potent drugs.[1] Also, the β-amino acid moiety is an integral part in numerous biologically and pharmacologically important compounds. For example, one of the best-known molecules that contain β-amino acid moiety is taxol **1**, which is composed of a polyoxygenated diterpene and (2*R*,3*S*)-phenylisoserine.[2] Bestatin **3**,[3] another β-amino acid moiety containing molecule, is an immunological response modifier (Figure **1**). Also, numerous biologically active molecules such as dolastins, astins, onchidin, jasplakinolide, motuporin, kynostatins, scytonemyn A and microginin contain β-amino acid moieties.[1]

β-Lactam antibiotics are readily accessible from β-amino acid derivatives and they gained significance in clinical practice.[4] Ezetimibe **4**, is the first example among the drugs which inhibit cholesterol absorption in the small intestine.[5] The β-lactam functionality is essential for the activity of the molecule and substitution on the phenolic oxygen increases the activity.

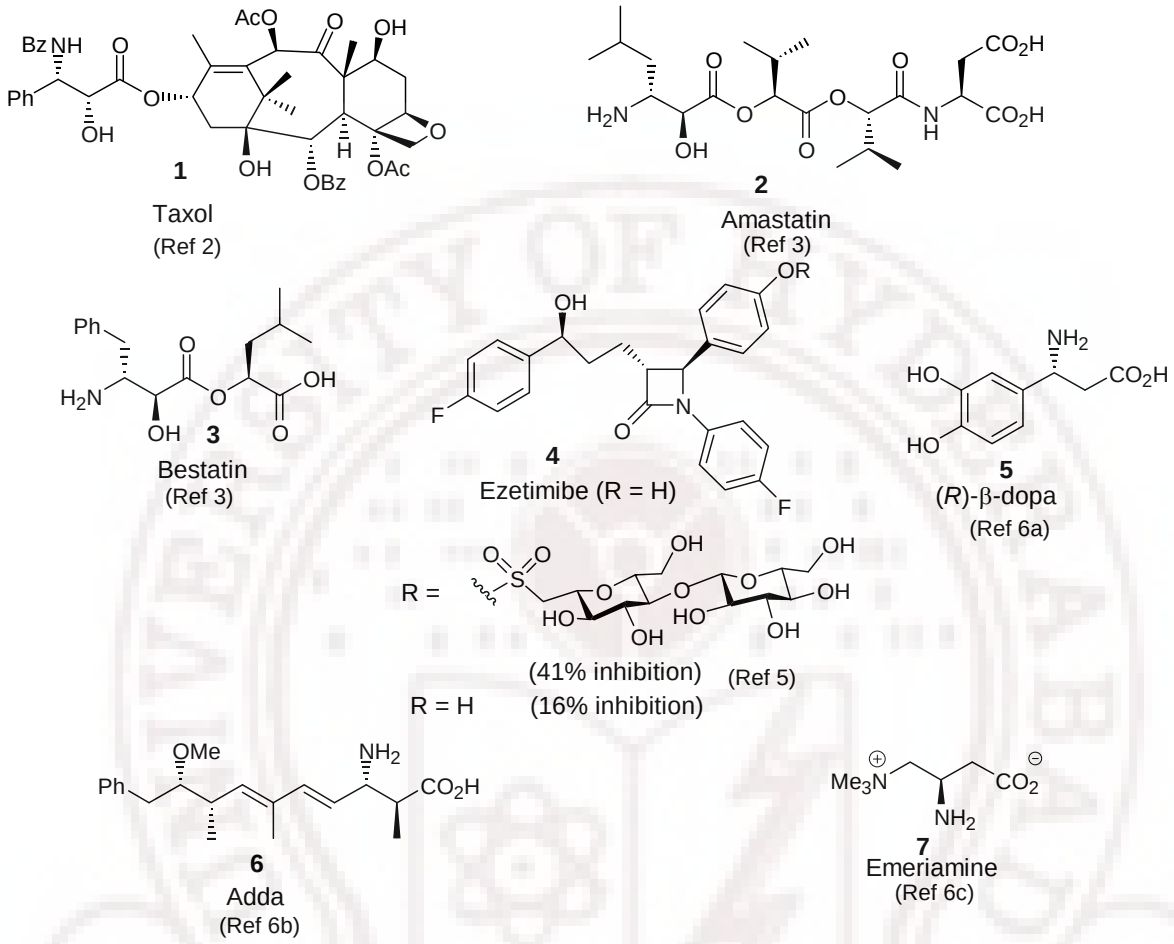


Figure 1

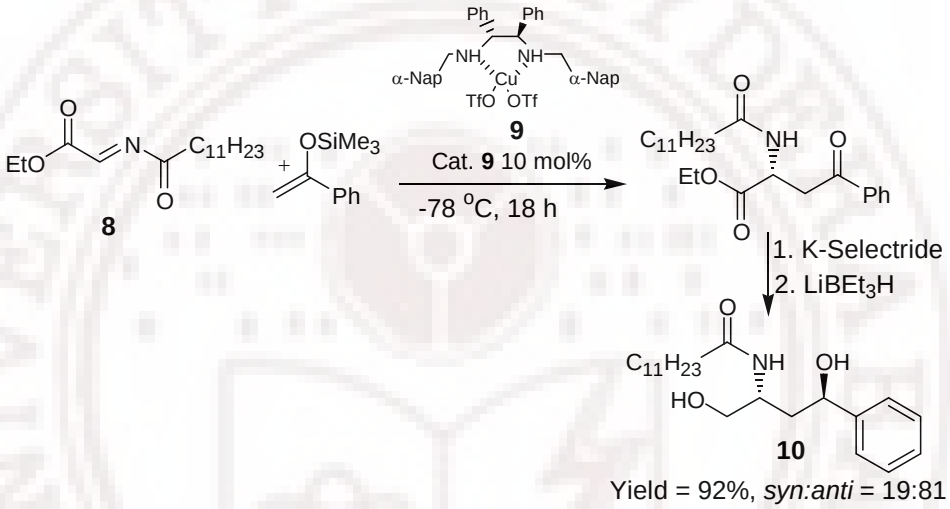
Several methods are available for the preparation of β -amino acid derivatives.[7] The β-peptides formed from β-amino acids display stability towards enzymatic degradation.[8]

1.1.1 Bioactive moieties *via* Mannich-type reaction

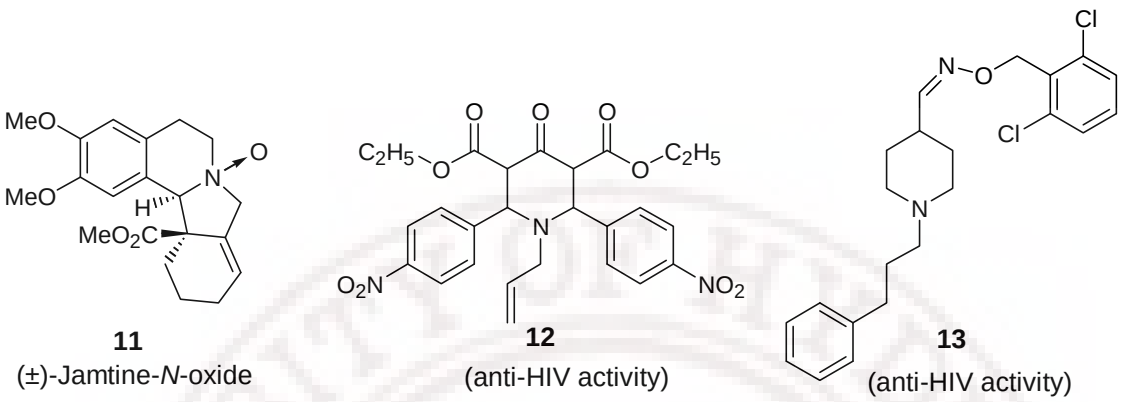
Mannich-type reaction and its variants provide convenient route for the synthesis of amino carbonyl derivatives.[9] Syntheses of several bioactive molecules and natural products have been achieved *via* Mannich-type reaction in crucial steps.[10] For instance, asymmetric

Mannich-type reaction of *N*-acylimino esters is useful in the direct formation of *N*-acylated amino acid derivatives. This methodology has been adopted in the synthesis of the novel inhibitor of ceramide trafficking agent **10** (Scheme **1**).[11]

Scheme 1



The tandem Pummerer/Mannich cyclization sequence is useful for the synthesis of novel putative alkaloid jamtine **11**.[12] Mannich-type reaction has been also used in a crucial step in the synthesis of molecules with anti-HIV activity **12** and **13**,[13] anti malarial activity **14**[14] and for the synthesis of molecule **15** with human purine nucleoside inhibitory activity (Figure **2**).[15]



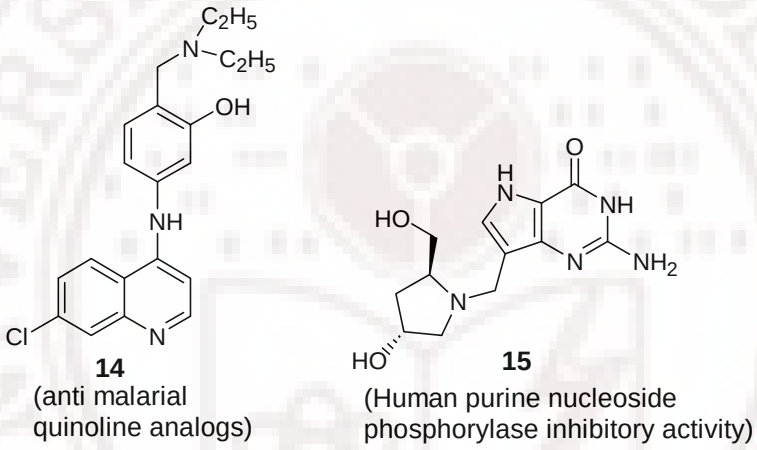


Figure 2

The coumarine derived Mannich-base **16** acts as an anti-inflamatory agent.[16] The phenolic Mannich bases exhibit anti-malarial activity **17** (Figure **3**).[17]

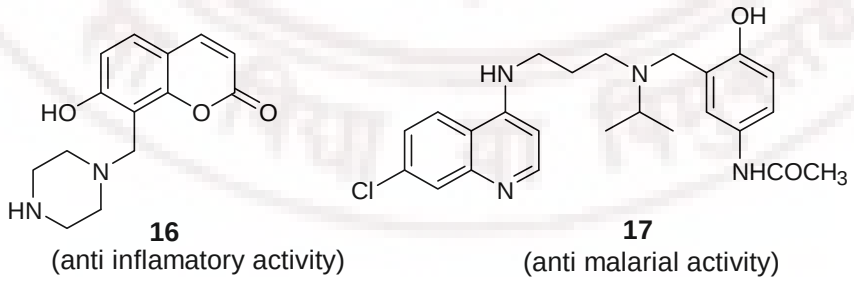
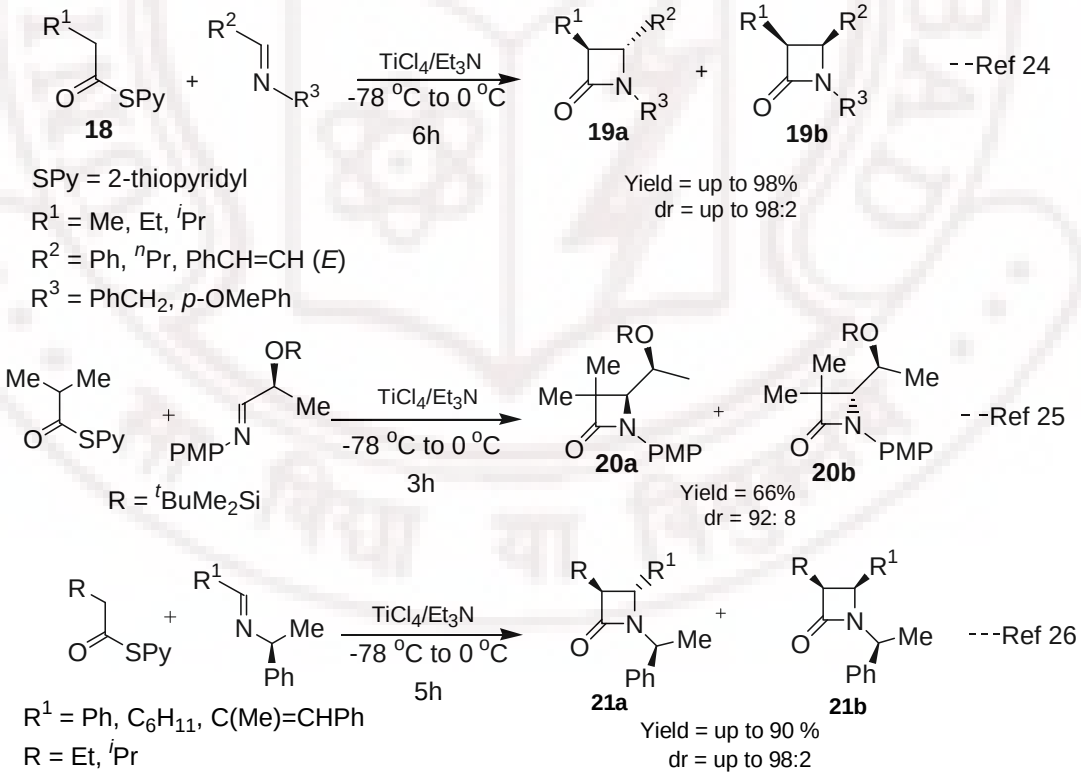


Figure 3

1.1.2 Titanium reagents in Mannich-type reaction

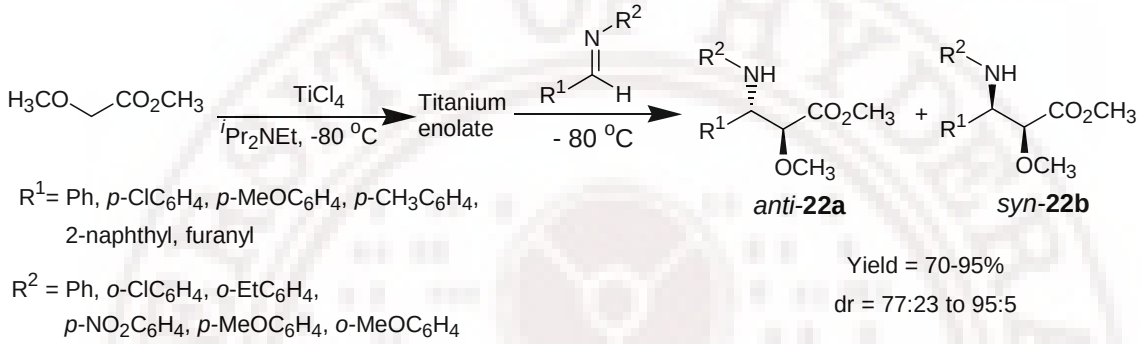
Titanium reagents have been extensively used in various organic transformations. The Ziegler-Natta catalysis using $TiL_n/AlEt_3$, is an important polymerization process.[18] Also, $TiCl_4$/R(Li)MgX, Cp_2TiCl_2/R(Li)MgX or $LiAlH_4$,[19] $TiCl_4/KO^tBu$/Na/naphthalene,[20] $TiCl_4$/Li/TMSCl[21] and several titanium compounds in combination with other reagents are useful in fixing molecular nitrogen.[22] The Kulinkovich hydroxycyclopropanation reaction allows esters ($RCOOR^1$) to react with the $RMgX/Ti(O^iPr)_3X$ (X = O^iPr, Cl and Me) reagent system to yield cyclopropanols.[23] The use of titanium enolates in Mannich-type reaction gives high level of selectivity with interesting reactivity pattern (**Chart 1**).

Chart 1



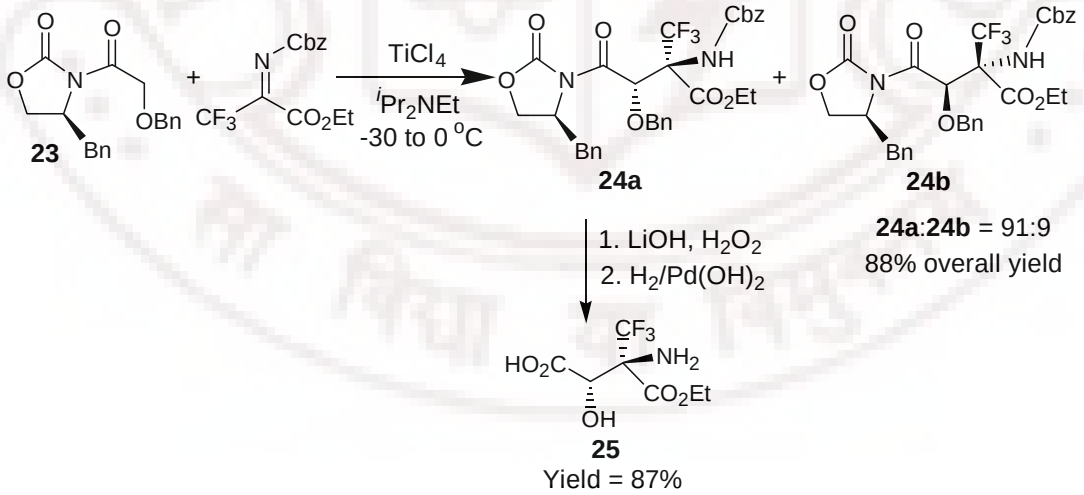
Andrian *et al.*[27] reported an *anti* selective synthesis of α-methoxy-β-substituted-β-amino esters **22** by the reaction of the titanium enolate of methyl methoxyacetate with imines (Scheme **2**).

Scheme 2



Mannich-type reaction of a ketimine with the titanium enolate of *N*-acyloxazolidinone **23** was exploited for the synthesis of densely functionalized (2*R*,3*S*)-α-trifluoromethyl-β-hydroxy-aspartic unit **25** (Scheme **3**).[28]

Scheme 3

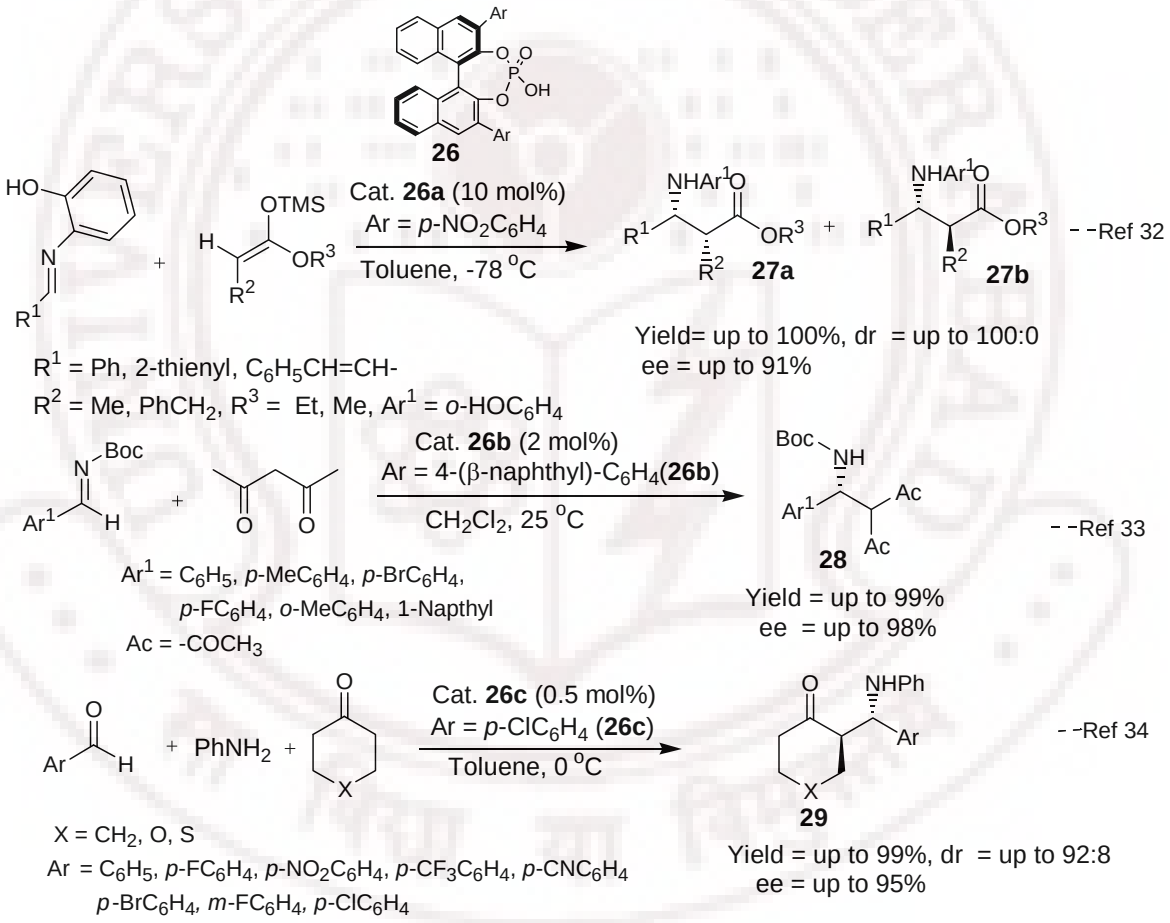


It has been reported that the use of titanium enolate instead of lithium enolate or enol silane gave the corresponding products with different selectivity.[29,30]

1.1.3 Catalytic asymmetric Mannich-type reaction

The catalytic asymmetric Mannich-type reaction is useful for the synthesis of versatile chiral building blocks.[31] The chiral Brönsted acid, derived from axially chiral BINOL, was used as an effective catalyst for the enantioselective Mannich-type reaction (Chart **2**).

Chart 2

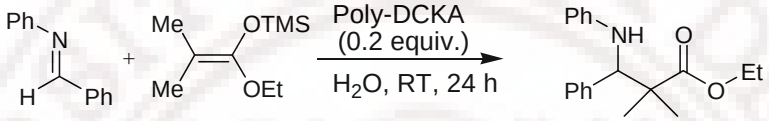


The catalytic asymmetric Mannich-type reaction of unmodified carbonyl compounds with *in situ* prepared imines generated considerable interest in recent years.[35]

The optically pure α- and β-amino acid derivatives, β-lactams, and 1,2-and-γ-amino alcohol derivatives were prepared by this method.

Mannich-type reactions also proceed smoothly in water in the presence of poly-DCKA as catalyst (Scheme **4**).[36]

Scheme 4



Poly-DCKA = Poly dicyanoketene acetal

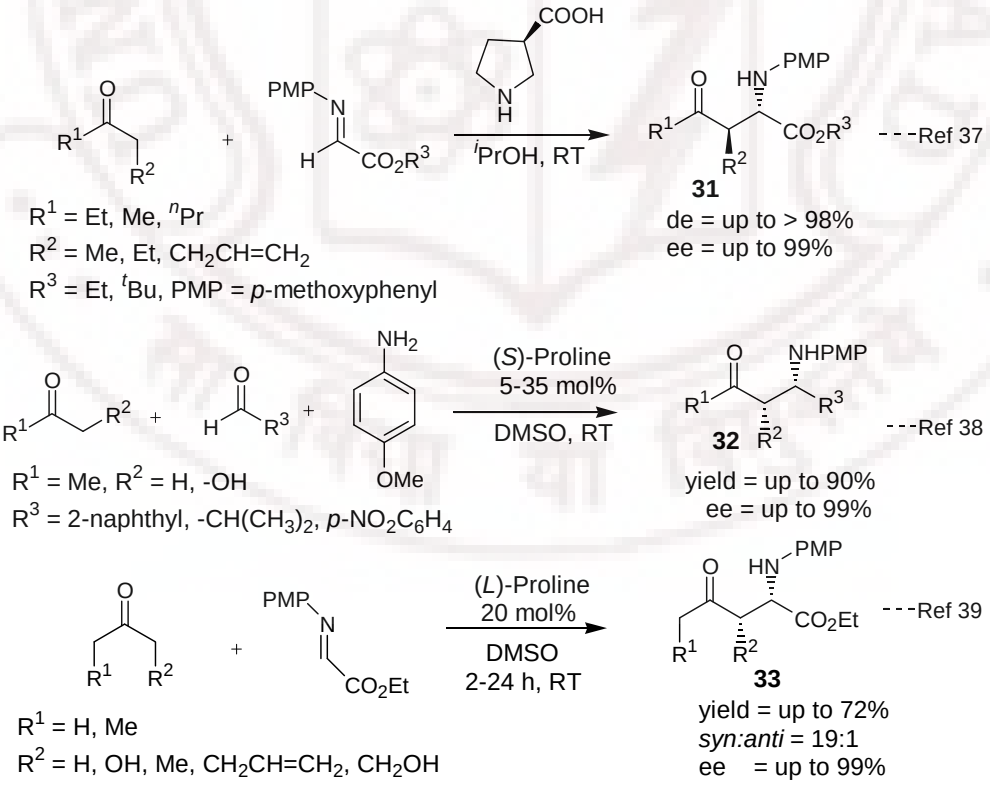
30

Yield = 84%

1.1.4 Organocatalyzed Mannich-type reactions

In recent years, organocatalyzed Mannich-type reaction has been exploited for the synthesis of β- amino carbonyl compounds (Chart **3**).

Chart 3



31

R^1 = Et, Me, ^{n}Pr

R^2 = Me, Et, $CH_2CH{=}CH_2$

R^3 = Et, ^{t}Bu, PMP = *p*-methoxyphenyl

de = up to > 98%

ee = up to 99%

32

R^1 = Me, R^2 = H, -OH

R^3 = 2-naphthyl, $-CH(CH_3)_2$, *p*-$NO_2C_6H_4$

yield = up to 90%

ee = up to 99%

33

R^1 = H, Me

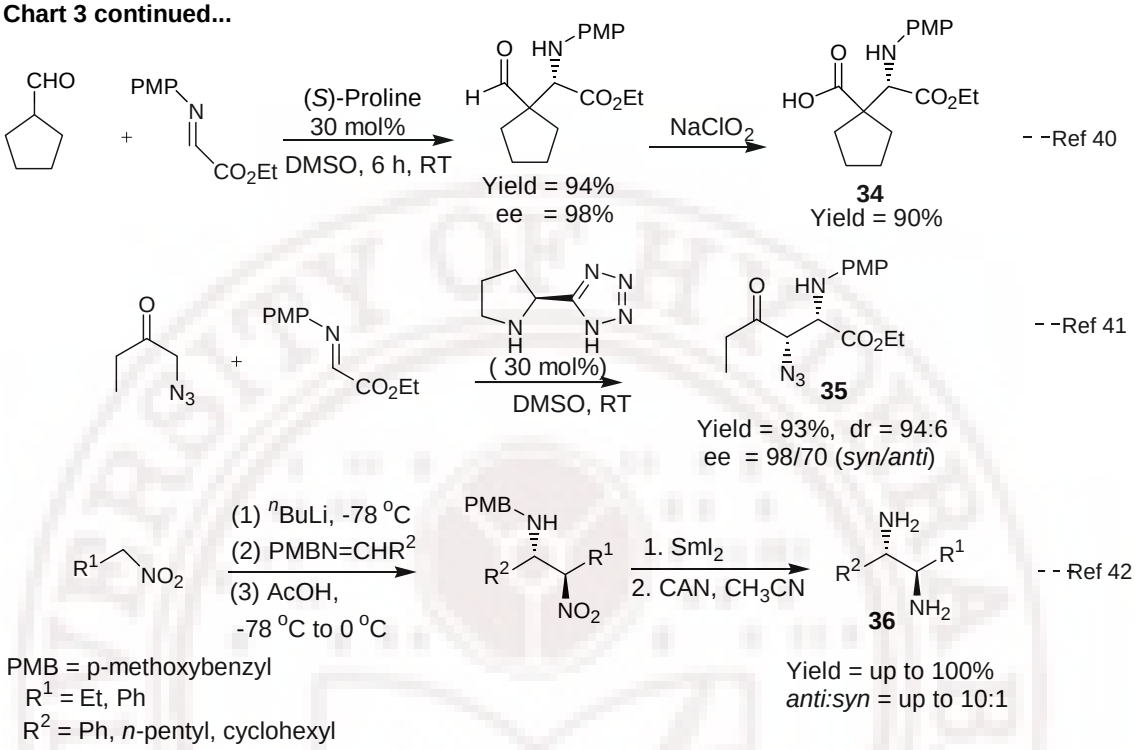
R^2 = H, OH, Me, $CH_2CH{=}CH_2$, CH_2OH

yield = up to 72%

syn:anti = 19:1

ee = up to 99%

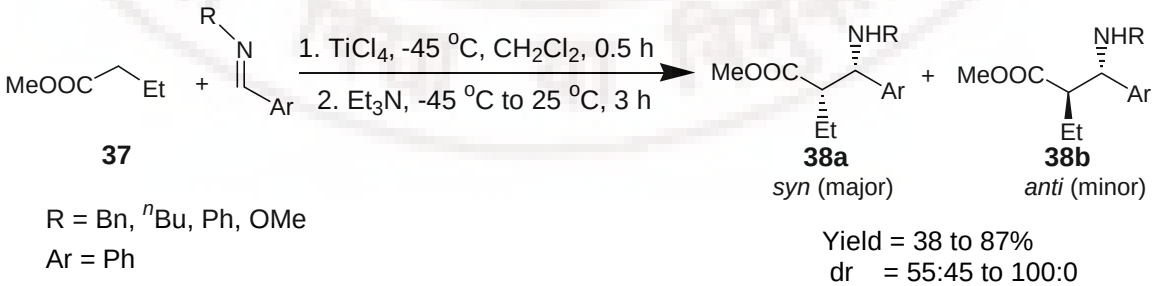
Chart 3 continued...



1.1.5 Previous work from this laboratory

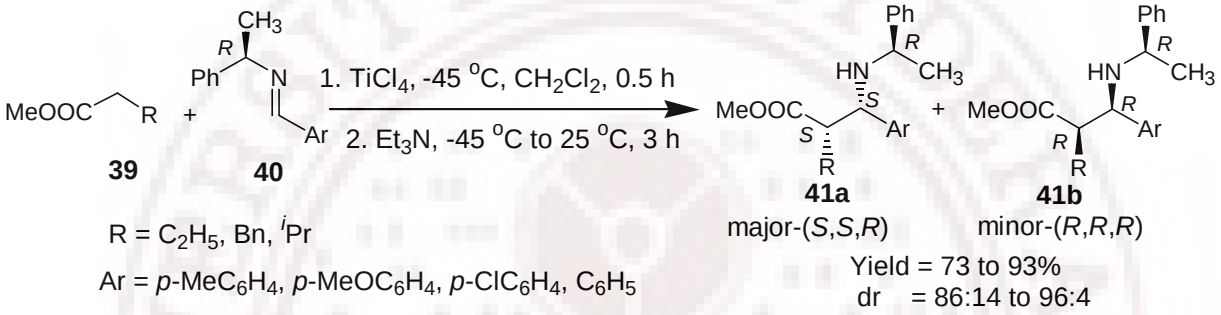
It was observed in this laboratory that the titanium enolate of prochiral ester **37** on addition with imine gave the corresponding β-amino ester **38** in good yield with *syn* selectivity (Scheme **5**).[43]

Scheme 5



Asymmetric Mannich-type reaction of chiral imine **40** and prochiral esters **39** with the $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino esters **41** in good yield with *syn* selectivity (Scheme **6**).[44a]

Scheme 6



However, it is somewhat difficult to remove and reuse the α-methylbenzyl group present in the *syn*-β-amino ester products. Attempted removal of the chiral auxiliary from the *syn*-β-amino ester **41** by Pd/C, resulted in loss of chirality of the chiral auxiliary.[44b] Accordingly, we have undertaken efforts to utilize chiral ester moieties which can be easily removed and reused. Moreover, it is of interest to study the stereochemical outcome of the reaction of chiral titanium ester enolates with prochiral imines. The results are discussed in the next section.

1.2 Results and Discussion

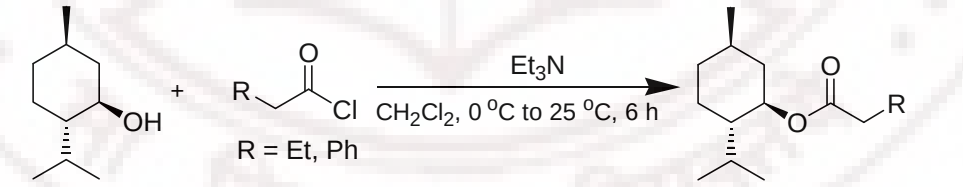
1.2.1 Asymmetric Mannich-type reaction of menthyl esters and imines

Chiral auxiliaries are powerful molecular elements for creating optically active compounds. Menthol and its derivatives have been widely used as chiral handles in various asymmetric transformations[45] and the $TiCl_4/R_3N$ reagent system facilitates the formation of ester enolate. We have chosen the readily available naturally occurring *L*-(-)-menthol **42** as chiral auxiliary for the asymmetric Mannich-type reaction of chiral esters with imine in presence of $TiCl_4/Et_3N$ reagent system.

1.2.1.1 Synthesis of *L*-(-)-menthyl esters

The *L*-(-)-menthyl esters **43** and **44** were prepared by the reaction of *L*-(-)-menthol **42** with butyryl chloride and phenylacetyl chloride as shown in Scheme **7**.

Scheme 7



42
L-(-) menthol

(1*R*,2*S*,5*R*)- **43** (R=Et), Y = 89%
44 (R=Ph), Y = 82%

1.2.2 Synthesis of *syn*-β-amino esters

Initially, the reaction between *L*-(-)-menthyl butyrate **43** with *N*-benzylidenebenzyl amine **45a** was screened with $TiCl_4$ in combination with different tertiary amines. The $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino ester **46** in good yield with high

selectivity (Scheme **8**). We have observed that lowering of the temperature further below -45 ^{o}C did not increase the yield and selectivity. The results are summarized in Table **1**.

Scheme 8

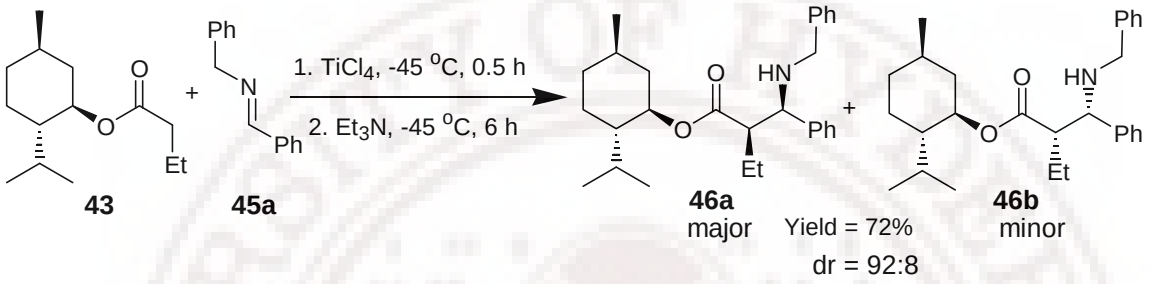


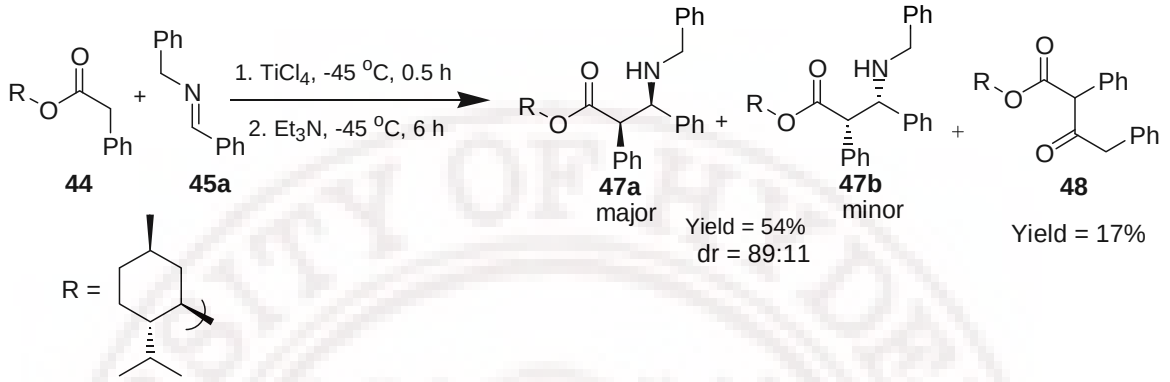
Table 1. Reaction of menthyl ester 43 and imine 45a with $TiCl_4/R_3N$ reagent system[a]

Entry	R_3N	$TiCl_4$(equiv.)	Temp. (ºC)	Yield(%)[b]
1	$^{i}Pr_2NEt$	2	-45	0
2	$^{i}Pr_2NCH_2Ph$	2	-45	<10
3	$^{n}Bu_3N$	2	-45	44
4	Et_3N	2	-45	72
5	Et_3N	1	-45	36
6[c]	Et_3N	2	-65	70[d]

[a]All the reactions were carried out using 2.2 mmol of menthyl butyrate **43** and 2 mmol of *N*-benzylidenebenzyl amine **45a** and 1.1 mmol of R_3N in 20 mL of CH_2Cl_2.
[b]Yields are for the isolated product.
[c]The reaction was carried for 12 h.
[d]Diastereomeric ratio of the entry 6 was similar to entry 4.

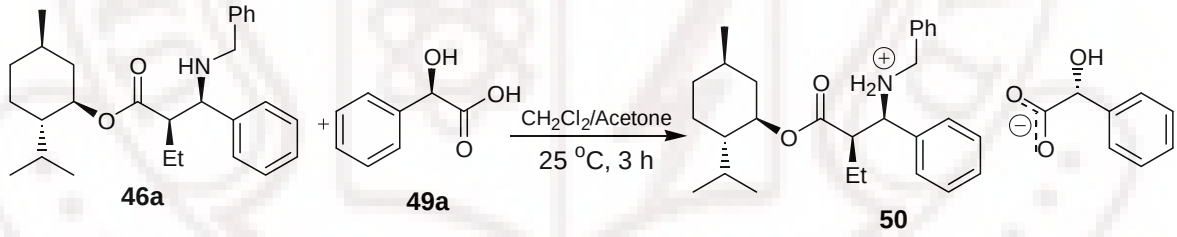
The reaction of *L*-(-)-menthyl phenylacetate **44** and imine **45a** with the $TiCl_4/Et_3N$ reagent system gave the expected amino ester besides the Claisen condensation product **48** in 17% yield (Scheme **9**). The reaction was then carried out at -65 ^{o}C with an objective to avoid the formation of Claisen condensation product. However, the reaction was slow at -65 ^{o}C and the β-amino ester product **47** was formed only in 46% yield.

Scheme 9



The major product **46a** isolated in the Mannich-type reaction (Scheme **8**) readily forms salt **50** with *R*-(-)-mandelic acid **49a** in CH_2Cl_2-acetone mixture at 25 ^oC (Scheme **10**).

Scheme 10



Crystals suitable for single crystal X-ray diffraction analysis were obtained by crystallizing the complex **50** from toluene-isopropanol mixture. The X-ray analysis of the complex **50** revealed that the product has the absolute configuration (*R*,*R*) at the newly formed chiral centers. The crystal structure of the compound **50** is given in Figure **4**.

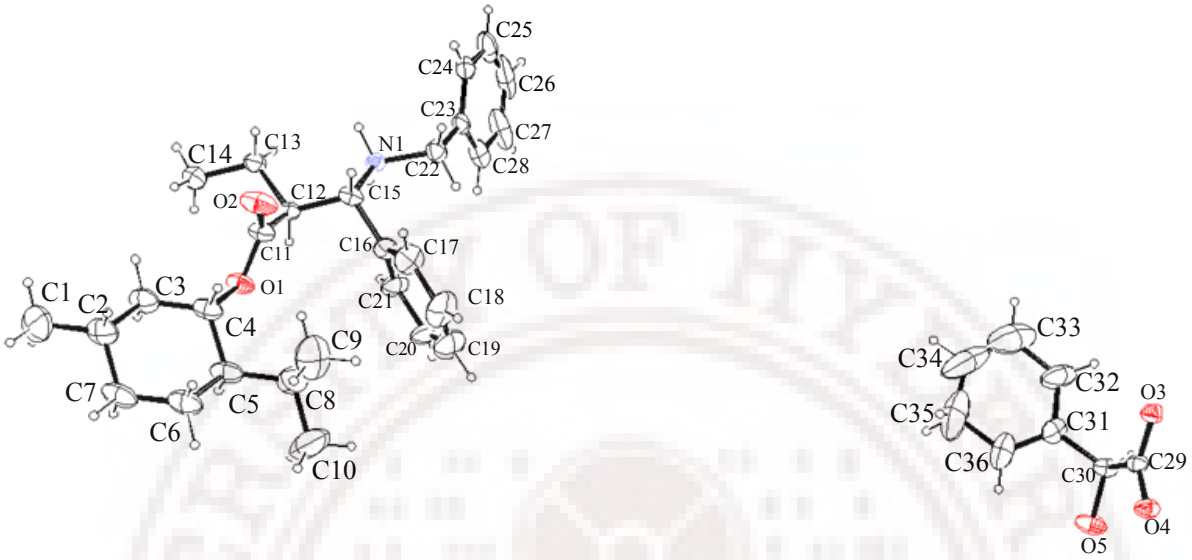
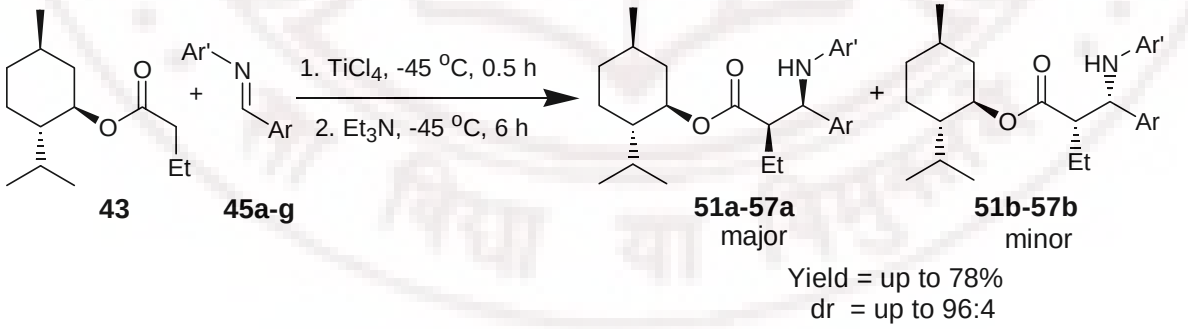


Figure 4 ORTEP representation of the crystal structure of complex **50** (Thermal ellipsoids are drawn at 20% probability)

The reaction of *L*-(-)-menthyl butyrate **43** with various imines **45a-g** in presence of the $TiCl_4/Et_3N$ reagent system gave the corresponding *syn*-β-amino esters **51-57** in moderate to good yields with good selectivity (Scheme **11**).

Scheme 11



The diastereomeric ratios of the β-amino esters **51-57** were estimated from the ^{1}H-NMR signals of the product mixture. The results are summarized in Table **2**.

Table 2. Mannich-type reaction of menthyl ester 44 with imines

Entry	Ar′ (amine)	Ar (aldehyde)	Product[a]	Yield (%)[b]	dr[c]
1	-CH_2Ph(**45b**)	*p*-MeC_6H_4	**51**	69	82:18
2	-CH_2Ph(**45c**)	*p*-$OMeC_6H_4$	**52**	64	83:17
3	-CH_2Ph(**45d**)	*m*-MeC_6H_4	**53**	71	96:4
4	-^{n}Bu(**45e**)	-Ph	**54**	78	81:19
5	-CH_2Ph(**45f**)	*p*-ClC_6H_4	**55**	54	79:21
6[d]	-CH_2Ph(**45a**)	-Ph	**56**[e]	76	7:93
7[f]	-Ph(**45g**)	-Ph	**57**	45	72:28

[a]The products were identified by the spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass).
[b]Yields are for the isolated product.
[c]The diastereomeric ratios (dr's) were determined by the ^{1}H-NMR (400 MHz) analysis of the product mixture.
[d]The reaction was carried out with *D*-(+)-menthyl butyrate.
[e]The absolute configuration of the major product **56** was assigned as (*S*,*S*) from the crystal structure of its complex **58** with *S*-(+)-mandelic acid.
[f]After the addition of Et_3N, the reaction mixture was warmed from -45 ^{o}C to 0 ^{o}C and then stirred at the same temperature for further 12 h.

The reactions were carried out at -45 ^{o}C to get better diastereoselectivity and to minimize the formation of the Claisen condensation product of the ester. The imines derived from aliphatic amines **45a-f** gave better yield and selectivity compared to the aniline derived imine **45g** (Table **2**, entry **7**). The stereochemistry of the major isomer of the products **51-55** and **57** was assigned *syn* by comparison of ^{1}H-NMR data of the products with **46**.

The origin of asymmetric induction in the asymmetric Mannich-type reaction and the formation of major isomer can be rationalized as outlined in Figure **5**. It has been

reported in the literature that the presence of chelating atom or group in the substrate favors the preferential formation of *Z*-titanium ester enolate over *E*-enolate.[27,46] In other cases, the equilibrium favour towards *E*-enolate (alkyl group and O-Ti are *trans* to each other).[43,44,47] Based on the stereochemistry of the products formed and the absence of chelating atom or group in the menthyl butyrate, the geometry of the titanium menthyl ester enolate participating in the reaction was assigned as *E*.

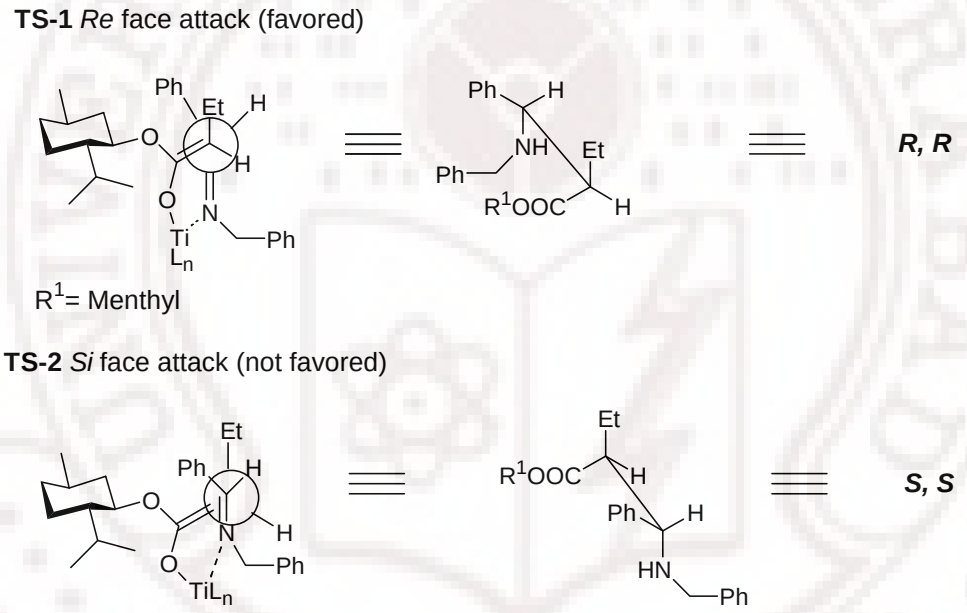


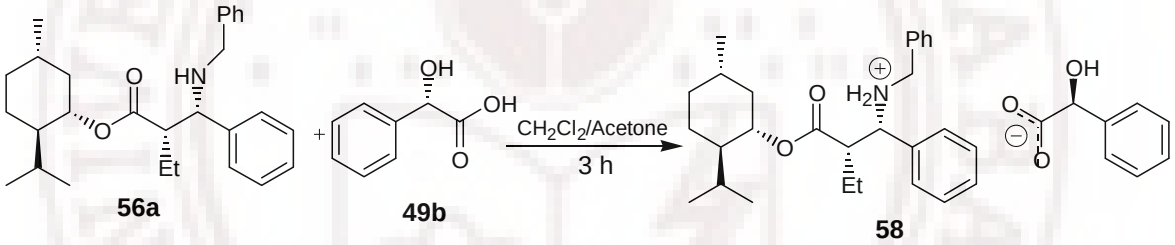
Figure 5 Stereochemical models

The *re*-face attack of the chiral ester enolate onto the imine in **TS-1** is more favourable because the bulky isopropyl group of the ester enolate is positioned far away from the **C-C** bond forming side. Hence, the low-energy transition state **TS-1** would give the major isomer with (*R,R*) absolute configuration. Whereas the *si*-face attack of the chiral ester enolate would experience greater repulsion from the bulky isopropyl group which is

positioned on the **C-C** bond forming side. This would lead to the high energy transition state **TS-2** and hence the formation of the isomer (*S*,*S*) is not favourable.

The amino ester **56** obtained by the reaction of *D*-(+)-menthyl butyrate with *N*-benzylidenebenzyl amine **45a** has the specific rotation equal in magnitude but opposite in direction to that of **46**. The configuration at the newly formed chiral centers were assigned as (*S*,*S*) by X-ray crystal structural analysis of the *S*-(+)-mandelic acid salt **58** of the major isomer **56a** crystallized from benzene-isopropanol mixture (Scheme **12**).

Scheme 12



The crystal structure of the complex **58** is given in Figure **6**.

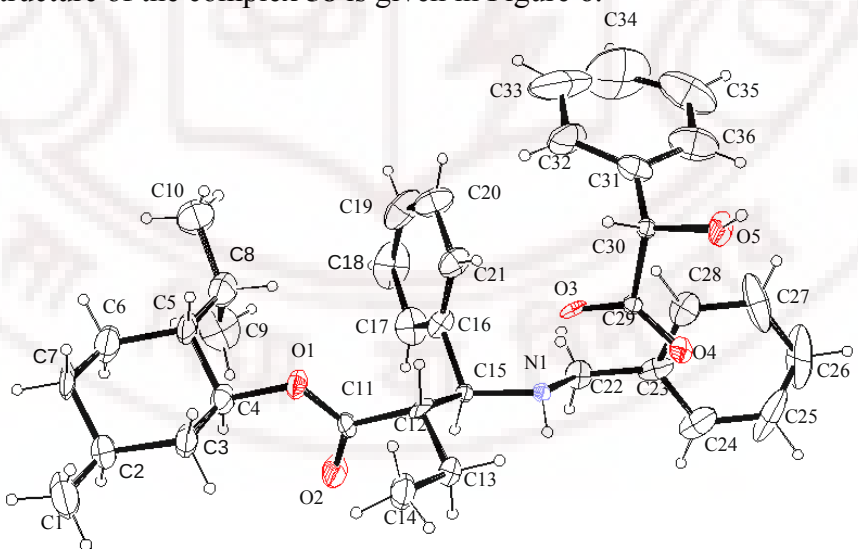
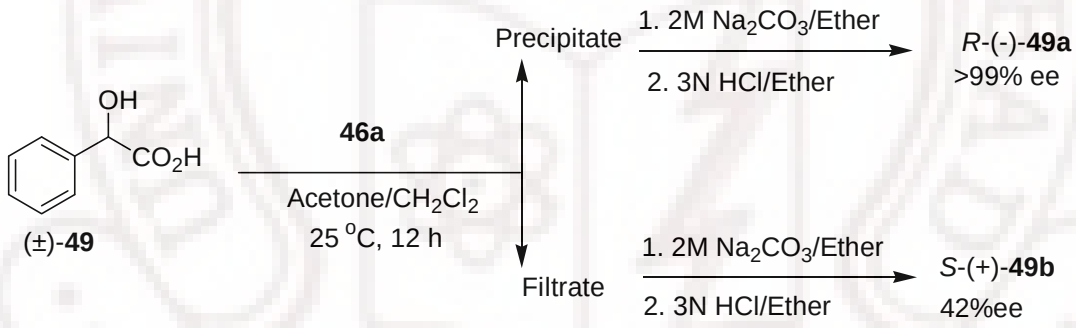


Figure 6 ORTEP representation of the crystal structure of complex **58** (Thermal ellipsoids are drawn at 20% probability)

1.2.3 Resolution of racemic mandelic acid 49

The anticipated salt formed between the *R*-(-)-mandelic acid **49a** and the compound **56a** does not precipitate out from the CH_2Cl_2/acetone solvent mixture even after stirring for 3 days. Whereas, the compound **46a** readily forms salt with *R*-(-)-mandelic acid **49a** that precipitates out from the solution. This difference in solubility of the diastereomeric salts prompted us to examine the resolution of racemic mandelic acid **49** using the chiral amino ester **46a**. Indeed, the major *syn*-β-amino ester **46a** isolated from the diastereomeric mixture is useful for the resolution of the racemic mandelic acid **49** (Scheme **13**).

Scheme 13



As expected, the salt **50** of *syn*-β-amino ester **46a** and (*R*)-(-)-mandelic acid **49a** precipitated out leaving the (*S*)-(+) mandelic acid **49b** in the filtrate fraction. The conditions were standardized as outlined in Table **3**. Optimum results were obtained when the resolution of racemic mandelic acid **49** was carried out with amino ester **46a** in acetone-CH_2Cl_2 solvent system.

Table 3. Resolution of racemic mandelic acid 49 using menthyl aminoester 46a[a]

Entry	Solvent (mL)	Precipitate			Filtrate		
		ee(%)[b]	Conf.[c]	Yield(%)[d]	ee(%)[b]	Conf.[c]	Yield(%)[d]
1[e]	Acetone/CH_2Cl_2(3) (1.5:1.5 v/v)	90	*R* (-)	21	20	*S* (+)	65
2[f]	Acetone/CH_2Cl_2(3) (1.5:1.5 v/v)	98	*R* (-)	35	33	*S* (+)	54
3[g]	CH_2Cl_2 (3)	8	*R* (-)	11	6	*S* (+)	78
4[g]	Acetone(8)	88	*R* (-)	13	14	*S* (+)	75
5[h]	Acetone/CH_2Cl_2(16) (11:5 v/v)	94	*R* (-)	29	36	*S* (+)	51
6[i]	Acetone/CH_2Cl_2(16) (11:5 v/v)	>99	*R* (-)	28	42	*S* (+)	61

[a]Unless otherwise mentioned, all the reactions were carried out using 1 mmol of *syn*-β-amino ester **46a**, 1 mmol of racemic mandelic acid **49** and stirred at 25 °C.
[b]Determined by HPLC analysis using the chiral column, Chiralcel OD-H; Hex:^{i}PrOH:trifluoroacetic acid (9:1:0.025 v/v); 0.5 mL per 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 **49** (2 mmol) and *syn*-β-amino ester **46a** (1 mmol) stirred at 25 °C for 6 h.
[f]Racemic mandelic acid **49** (1 mmol) and *syn*-β-amino ester **46a** (1 mmol) stirred at 25 °C for 0.5 h.
[g]Racemic mandelic acid **49** (1 mmol) and *syn*-β-amino ester **46a** (1 mmol) stirred at 25 °C for 48 h.
[h]Racemic mandelic acid **49** (5 mmol) and *syn*-β-amino ester **46a** (5 mmol) stirred at 25 °C for 0.5 h.
[i]Racemic mandelic acid **49** (5 mmol) and *syn*-β-amino ester **46a** (5 mmol) stirred at 25 °C for 12 h.

When the resolution was carried out with CH_2Cl_2 or acetone alone, the precipitate was formed in low yield resulting in poor enantioselectivity. In THF solvent, the precipitate did not form. We have observed that the *syn*-β-amino ester **46a** is partially soluble in acetone and completely soluble in CH_2Cl_2. Presumably, the efficient resolution

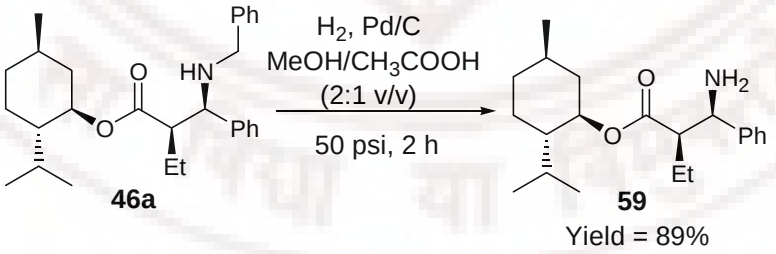
of mandelic acid **49** in the acetone-CH_2Cl_2 solvent mixture is due to this solubility difference.

The amino ester **46a** can be easily recovered from the reaction mixture and reused without any loss in optical activity. The crystalline nature and its high resistance to air and moisture would make the amino ester **46a** an efficient reagent for the resolution of racemic carboxylic acids. Hence, it has good potential for use in the resolution of various racemic carboxylic acids.[48]

1.2.4 *N*- and *O*-Deprotection of *syn*-β-amino esters 46a

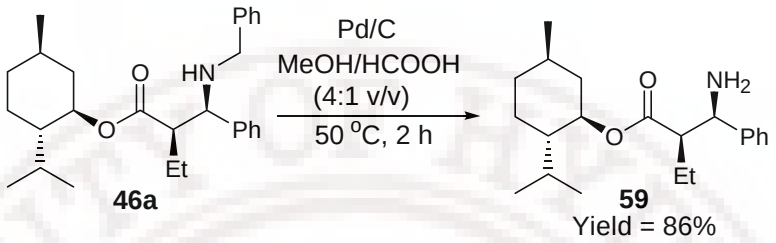
We have examined the debenzylation of the *syn*-β-amino ester **46a** by hydrogenation using Pd/C. The β-amino ester **46a** was partially soluble in methanol. Hence, the reaction was carried out in methanol/glacial acetic acid mixture (2:1 v/v). The reaction proceeds smoothly and the debenzylated product **59** was obtained in 89% yield (Scheme **14**).

Scheme 14



Later, it was found that the dispersion of Pd/C in formic acid and methanol (1:4 v/v) is also useful for the debenzylation of the amino ester **46a** at 50 ^oC (Scheme **15**).

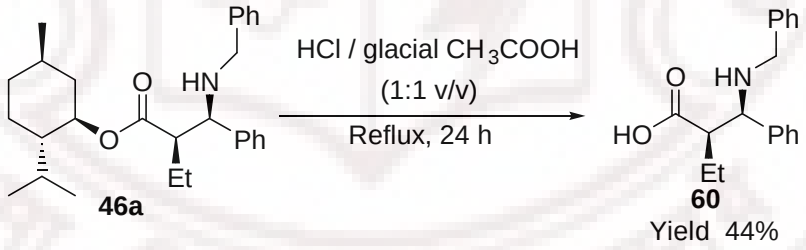
Scheme 15



1.2.4.1 Synthesis of β-amino acids

We have also carried out experiments to prepare the corresponding β-amino acids by the hydrolysis of the menthyl amino esters. We have observed that the hydrolysis of the menthyl amino ester **46a** in conc. HCl under reflux condition gave the amino acid **60** in 11% yields. However, the β-amino acid **60** was obtained in 44% yield by refluxing with a mixture of glacial acetic acid and conc. HCl mixture (1:1 v/v) (Scheme **16**). [49]

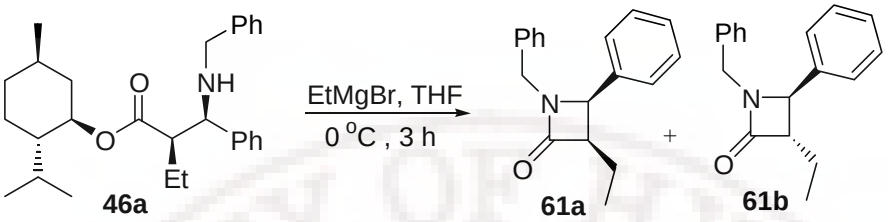
Scheme 16



1.2.5 Synthesis of β-lactam

We have also examined the conversion of the representative *syn*-β-amino ester **46a** to the corresponding β-lactam. We have observed that the reaction of *syn*-β-amino ester **46a** with the ethyl Grignard reagent gave the β-lactam product **61** in 56% yield with partial racemization even at 0 °C (Scheme **17**). Unfortunately, β-lactam was not formed at -30 °C.

Scheme 17



46a **61a** **61b**

Yield = 56%

61a:61b = 71:29

These studies illustrate that the chiral β-amino esters prepared in this way has considerable potential for further synthetic exploitations.

1.3 Conclusions

The *syn* β-amino esters **46**, **51**-**57** were obtained in moderate to good yields with good selectivity by the reaction of (*L*)-(-)-menthyl butyrate **43** and imine **45a-g** with $TiCl_4/Et_3N$ reagent system. The configuration of the newly formed chiral centre of the *syn* β-amino esters was determined by single crystal X-ray analysis. The *syn*-β-amino ester **46a** was useful in the resolution of racemic mandelic acid **49** to obtain samples with >99% ee in a single step. A method for the debenzylation of *syn*-β-amino ester **46a** using Pd/C in HCOOH/MeOH was developed. The *syn*-β-amino acid **60** was obtained in 44% yield by the acid hydrolysis of *syn*-β-amino ester **46a**. The β-lactam **61** was obtained by the reaction of *syn*-β-amino ester **46a** with C_2H_5MgBr.

1.4. Experimental Section

1.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. The neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (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 TMS as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Liquid Chromatography (LC) and mass analysis (LC-MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electro spray Ionization (ESI) techniques. MALDI-TOF mass spectral analysis was carried out using Brucker Daltonics-Autoflex III-smart beam instrument using dihydroxybenzoic acid/α-cyano-4-hydroxycinnamic acid as matrixes. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II

(readability ±0.01°) and AUTOPOL-IV (readability ±0.001°) 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.

(*R*)-(+)-1,1'-Binaphthyl-2 2'-diamine was supplied by Gerchem Laboratory (Pvt) Ltd., India. Adipoyl chloride was prepared by the reaction of thionyl chloride with adipic acid, supplied by Sisco Chem. Pvt. Ltd., India.

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

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

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

a long tube. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ or Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy.

Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Titanium tetrachloride was supplied by E-Merck, India. Triethylamine was distilled over CaH_2 and stored over KOH pellets. Aniline, benzylamine, *n*-butylamine, *N,N*-diisopropylethylamine, *n*-tributylamine, *N,N,N',N'*-tetramethylethylenediamine and pyridine, supplied by Lancaster Synthesis, Ltd., England were used as purchased. The racemic-α-methylbenzylamine, (*L*)-(-)-menthol was supplied by Aldrich, USA. Iodine was supplied by Spectrochem, India. Thionyl chloride, butyryl chloride, methyl butyrate and ethyl bromide were supplied by E-Merck (India) and were distilled before use. All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents before use. $NaBH_4$ and carbon disulfide were supplied by E-Merck (India). The Pd/C catalyst was supplied by Aldrich, USA. Hydrogenation was carried out on Parr hydrogenation apparatus. HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. The ee values were determined using CHIRALCEL OD-H column (4.6 x 250 mm) with eluents: hexane, 2-

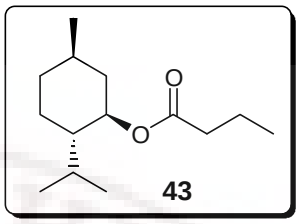
propanol, trifluoroacetic acid at a rate 0.5 mL/min, with the monitoring wave length 254 nm.

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

1.4.2 General procedure for the synthesis of *L*-(-)-menthyl esters

To a stirred solution of *L*-(-)-menthol (1.56 g, 10 mmol) in CH_2Cl_2 (30 mL), acid chloride (11 mmol) was added at 0 ^oC under N_2 atmosphere, followed by slow addition of triethylamine (1.31 g, 1.81 mL, 13 mmol) in CH_2Cl_2 (10 mL) using a dropping funnel over a period of 10 minutes. The reaction mixture was stirred at 0 ^oC for 15 minutes. It was slowly warmed to 25 ^oC and stirred at the same temperature for further 6 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed successively with 5% $NaHCO_3$ (20 mL), water (20 mL) and brine solution (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash slica gel column (230-400 mesh) to isolate pure *L*-(-)-menthyl butyrate using hexane/EtOAc (99/1) as eluent.

1.4.2.1 (*L*)-(-)-menthyl butyrate (43)



Yield 2.01 g (89%)

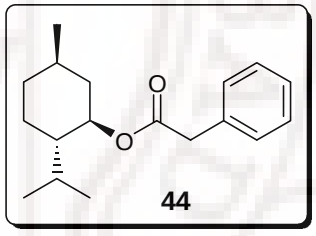
IR (Neat) (cm^{-1}) 2961, 2872, 1726

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.76 (d, 3H, *J* = 6.8 Hz), 0.88-1.08 (m, 12H), 1.34-1.50 (m, 2H), 1.62-1.68 (m, 4H), 1.85-2.10 (m, 2H), 2.26 (t, 2H, *J* = 7.3), 4.68 (dt, 1H, *J* = 10.8 Hz, *J* = 4.4 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 13.7, 16.3, 18.7, 20.8, 22.1, 23.5, 26.3, 31.4, 34.4, 36.7, 41.0, 47.1, 73.9, 173.3

$[\alpha]_D^{25}$ -74.72 (*c* 1.1, C_2H_5OH). {Lit.[50] $[\alpha]_D^{25}$= -75.8 (*c* 1, C_2H_5OH)}

1.4.2.2 (*L*)-(-)-menthylphenyl acetate (44)



Yield 2.25 g (82%)

IR (Neat) (cm^{-1}) 3065, 3032, 2955, 1730, 1454

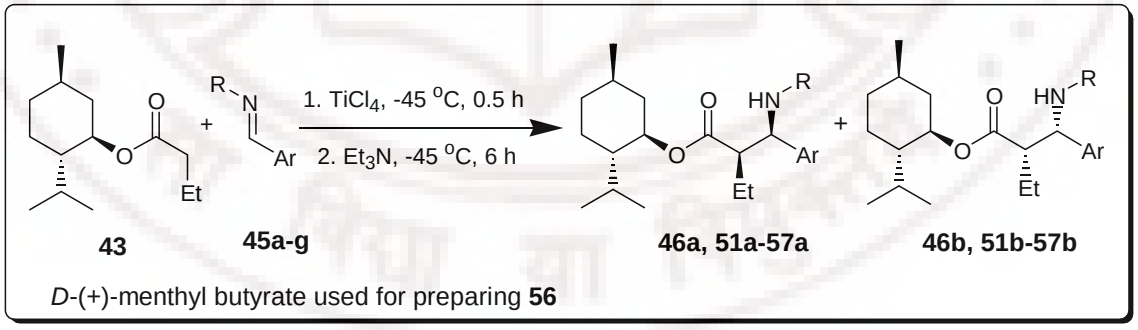
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.70 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 7.1 Hz), 0.90-0.93 (m, 4H), 0.96-1.10 (m, 2H), 1.33-1.50 (m, 2H), 1.64-1.79 (m, 3H), 1.98-2.0 (m, 1H), 3.61 (s, 2H), 4.69 (dt, 1H, *J* = 10.9 Hz, *J* = 4.4 Hz), 7.26-7.34 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 16.3, 20.7, 22.0, 23.5, 26.2, 31.4, 34.3, 40.8, 41.9, 47.1, 74.7, 126.9, 128.5, 129.2, 134.4, 171.2

$[\alpha]_D^{25}$ -71.79 (*c* 0.62, $CHCl_3$) {Lit.[51] $[\alpha]_D^{25}$= -58.0 (*c* 0.5, DMF)}

1.4.3 General procedure for the synthesis of *syn* β-amino esters derived from menthyl butyrate and imines

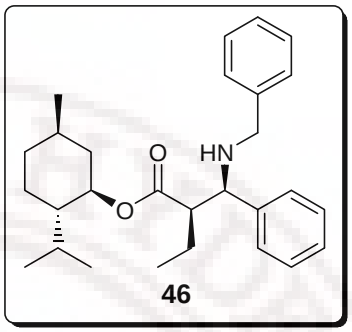
To a stirred solution of menthyl butyrate **43** (1.18 g, 5.2 mmol) and imine (5 mmol) in CH_2Cl_2 (40 mL) at -45 ^oC, a solution of $TiCl_4$ (12 mmol, 2.28 g, 1.3 mL) in 15 mL of CH_2Cl_2 was slowly added through addition funnel over a period of 10 minutes under N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.70 mL, 5 mmol) was added and the reaction mixture was stirred at -45 ^oC for further 6 h. The reaction mixture was quenched with saturated aq. K_2CO_3 (15 mL) solution, brought to room temperature and filtered through a Buckner funnel. The organic layer was separated and the aqueous layer was counter extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230-400 mesh) column using hexane/EtOAc (98/2) as eluent.



43 **45a-g** **46a, 51a-57a** **46b, 51b-57b**

D-(+)-menthyl butyrate used for preparing **56**

1.4.3.1 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-benzylamino-1-phenylmethyl]butanoate (46)



46

Yield 1.51 g (72%)

mp 124-126 ^{o}C

dr 92:8

IR (KBr) (cm^{-1}) 3321, 3061, 2962, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.44 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.8 Hz), 0.76-0.92 (m, 9H), 1.18-1.27 (m, 2H), 1.32-1.42 (m, 1H), 1.54-1.80 (m, 5H), 1.90-2.0 (m, 1H), 2.56-2.62 (m, 1H), 3.44 (d, 1H, *J* = 13.2 Hz), 3.59 (d, 1H, *J* = 13.2 Hz), 3.80 (d, 1H, *J* = 8.3 Hz), 4.49 (dt, 1H, *J* = 11.0 Hz, *J* = 4.6 Hz), 7.21-7.30 (m, 10H) **(Spectrum No. 1)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.3, 41.0, 46.8, 51.5, 55.1, 63.7, 74.0, 126.9, 127.3, 128.0, 128.2, 128.4, 140.6, 141.9, 174.0 **(Spectrum No. 2)**

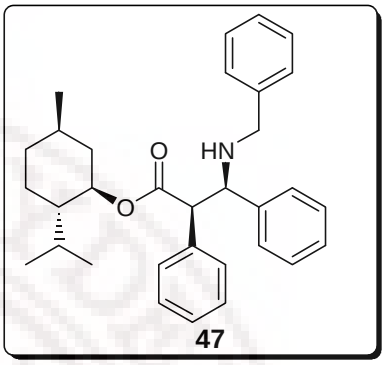
LCMS m/z 422 (M+1)

$[\alpha]_D^{25}$ -11.2 (*c* 1, $CHCl_3$)

Analysis Calculated for $C_{28}H_{39}NO_2$: C, 79.76%; H, 9.32%; N, 3.32%; O, 7.59%

Found : C, 79.45%; H, 9.32%, N, 3.49%; O, 7.74%

1.4.3.2 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*,3*R*)-3-benzylamino-2,3-diphenylpropanoate (47)



47

Yield 1.26 g (54%)

mp 136-138 ^oC

dr 89:11

IR (KBr) (cm^{-1}) 3323, 3061, 3028, 2953, 1711

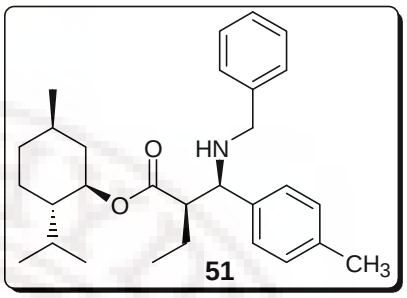
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.29 (d, 3H, *J* = 6.8 Hz), 0.60 (d, 3H, *J* = 6.8 Hz), 0.75 (m, 4H, *J* = 6.4 Hz), 0.83-0.90 (m, 3H), 1.06-1.13 (m, 1H), 1.26 (br s, 1H), 1.47-1.56 (m, 3H), 1.81 (br s, 1H), 3.28 (d, 1H, *J* = 13.9 Hz), 3.52 (d, 1H, *J* = 13.7 Hz), 3.82 (d, 1H, *J* = 10.5 Hz), 4.23 (d, 1H, *J* = 10.5 Hz), 4.32-4.39 (m, 1H), 6.96 (d, 2H, *J* = 6.4 Hz), 7.19-7.22 (m, 3H), 7.26-7.35 (m, 6H), 7.45 (d, 2H, *J* = 6.8 Hz), 7.48 (d, 2H, *J* = 7.3 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 15.9, 20.8, 21.9, 23.0, 25.2, 31.3, 34.2, 40.3, 46.7, 50.8, 60.2, 63.6, 74.0, 126.8, 127.7, 127.9, 128.0, 128.2, 128.3, 128.6, 128.7, 128.8, 136.3, 140.1, 141.1, 171.3.

LCMS m/z 470 (M+1)

$[\alpha]_D^{25}$ -12.83 (*c* 0.25, $CHCl_3$)

1.4.3.3 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-benzylamino-1-(4-methylphenyl)methyl]butanoate (51)



51

Yield 1.5 g (69%)

mp 126-128 ^{o}C

dr 82:18

IR(KBr) (cm^{-1}) 3348, 2947, 2922, 2866, 1718

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.43 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.8 Hz), 0.75-0.91 (m, 9H), 1.17-1.19 (m, 2H), 1.33-1.38 (m, 1H), 1.54-1.78 (m, 5H), 1.93-2.0 (m, 1H), 2.33(s, 3H), 2.54-2.59 (m, 1H), 3.43 (d, 1H, *J* = 13.1 Hz), 3.59 (d, 1H, *J* = 13.1 Hz), 3.75 (d, 1H, *J* = 8.8 Hz), 4.48 (dt, *J* = 10.8, *J* = 4.4, 1H), 7.10-7.28 (m, 9H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 15.8, 20.9, 21.2, 22.0, 22.8, 23.0, 25.4, 31.3, 34.2, 41.0, 46.8, 51.4, 55.2, 63.4, 73.9, 126.8, 127.9, 128.2, 128.3, 129.0, 136.7, 138.9, 140.6, 174.0

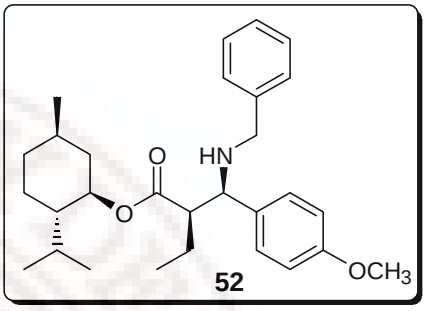
LCMS m/z 436 (M+1)

$[\alpha]_D^{25}$ -8.01(*c* 1, $CHCl_3$)

Analysis : Calculated for $C_{29}H_{41}NO_2$: C,79.95%; H, 9.49%; N, 3.22%; O, 7.35

Found : C, 80.07%, H, 9.47%, N, 3.28%; O, 7.18

1.4.3.4 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-benzylamino-1-(4-methoxyphenyl)methyl]butanoate (52)



52

Yield 1.44 g (64%)

mp 150-152 ^oC

dr 83:17

IR (KBr) (cm^{-1}) 3346, 3026, 2951, 2860, 1718

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.44 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.8 Hz), 0.77-0.91 (m, 9H), 1.17-1.23 (m, 2H), 1.36-1.41 (m, 1H), 1.54-1.79 (m, 5H), 1.92-1.98 (m, 1H), 2.52-2.58 (m, 1H), 3.43 (d, 1H, *J* = 13.4 Hz), 3.59 (d, 1H, *J* = 13.9 Hz), 3.74 (d, 1H, *J* = 8.8 Hz), 3.80 (s, 3H), 4.48 (dt, 1H, *J* = 11.0 Hz, *J* = 4.4 Hz), 6.84 (d, 2H, *J* = 8.3), 7.20-7.29 (m, 7H) **(Spectrum No. 3)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 11.9, 15.8, 20.8, 22.0, 22.9, 25.4, 31.3, 34.2, 41.0, 46.8, 51.3, 55.1, 55.3, 63.0, 73.9, 113.6, 126.8, 128.2, 128.3, 129.0, 133.9, 140.6, 158.8, 174.0 **(Spectrum No. 4)**

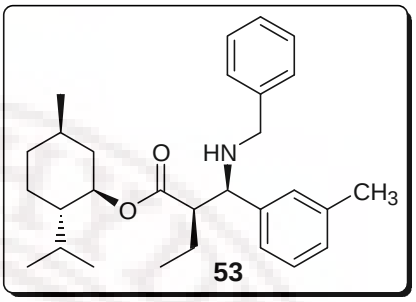
LCMS m/z 452 (M+1)

$[\alpha]_D^{25}$ -5.80 (*c* 1,$CHCl_3$)

Analysis : Calculated for $C_{29}H_{41}NO_3$: C, 77.12%; H, 9.15%; N, 3.10%; O, 10.63

Found : C, 77.16%; H, 9.17%; N, 3.29%; O, 10.38

1.4.3.5 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-benzylamino-1-(3-methylphenyl)methyl]butanoate (53)



53

Yield 1.55 g (71%)

mp 112-114 ^{o}C

dr 96:4

IR (KBr) (cm^{-1}) 3319, 3024, 2957, 2868, 1718

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.43 (d, 3H, *J* = 6.85 Hz), 0.72 (d, 3H, *J* = 6.85 Hz), 0.76-0.92 (m, 9H), 1.18-1.24 (m, 2H), 1.34-1.41 (br, 1H), 1.55-1.78 (m, 5H), 1.95-1.20 (m, 1H), 2.34 (s, 3H), 2.55-2.60 (m, 1H), 3.44 (d, 1H, *J* = 13.2 Hz), 3.59 (d, 1H, *J* = 13.2 Hz), 3.74 (d, 1H, *J* = 8.6 Hz), 4.48 (dt, 1H, *J* = 10.3 Hz, *J* = 3.9 Hz), 7.04-7.10 (m, 3H), 7.17-7.31 (m, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) for major diastereomer: 12.0, 15.8, 20.9, 21.5, 22.1, 22.8, 23.0, 25.4, 31.3, 34.2, 41.0, 46.8, 51.4, 55.1, 63.7, 73.9, 125.1, 126.9, 128.1, 128.2, 128.3, 128.6, 137.7, 140.5, 141.8, 173.9

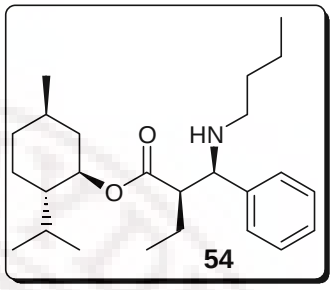
LCMS m/z (M+1) 436

$[\alpha]_D^{25}$ -7.41 (*c* 1, $CHCl_3$)

Analysis : Calculated for $C_{29}H_{41}NO_2$: C, 79.95%; H, 9.49%; N, 3.22%; O, 7.35%

Found : C, 79.99%; H, 9.46%; N, 3.42%; O, 7.13%

1.4.3.6 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-butylamino-1-phenylmethyl]butanoate (54)



54

Yield 1.51 g (78%)

mp 78-80 ^oC

dr 81:19

IR (KBr) (cm^{-1}) 3323, 2959, 2868, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.48 (d, 3H, *J* = 6.85 Hz), 0.74 (d, 3H, *J* = 6.85 Hz), 0.78-0.92 (m, 12H), 1.21-1.41 (m, 8H), 1.55-1.87 (m, 5H), 2.33-2.39 (m, 2H), 2.54 (br, 1H), 3.75-3.77 (m, 1H), 4.51 (dt, 1H, *J* = 11.0 Hz, *J* = 4.2 Hz), 7.2-7.28 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 14.0, 15.8, 20.4, 20.9, 22.0, 22.4, 23.0, 25.4, 31.3, 32.3, 34.2, 40.9, 46.8, 47.3, 55.0, 64.4, 73.9, 127.1, 127.8, 128.1, 142.3, 174.0

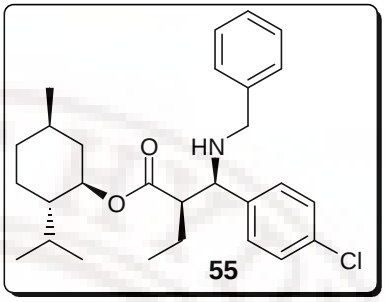
LCMS m/z 389 (M+1)

$[\alpha]_D^{25}$ -27.33 (*c* 1, $CHCl_3$)

Analysis : Calculated for $C_{25}H_{41}NO_2$: C, 77.47%; H, 10.66%; N, 3.61%; O, 8.26

Found : C, 77.47%; H, 10.63%; N, 3.52%; O, 8.38

1.4.3.7 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-benzylamino-1-(4-chlorophenyl)methyl]butanoate (55)



55

Yield 1.23 g (54%)

mp 128-130 ^{o}C

dr 79:21

IR (KBr) (cm^{-1}) 3061, 2962, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.45 (d, 3H, *J* = 6.8 Hz), 0.70-0.92 (m, 12H), 1.10-1.23 (m, 2H), 1.34-1.42 (m, 1H), 1.55-1.80 (m, 5H), 1.89-1.97 (m, 1H), 2.56-2.59 (m, 1H), 3.36-3.46 (m, 1H), 3.52-3.61 (m, 1H), 3.72-3.81 (m, 1H), 4.48 (dt, 1H, *J* = 11 Hz, *J* = 4.4 Hz), 7.22-7.31 (m, 9H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.2, 40.9, 46.7, 51.4, 55.0, 63.6, 73.9, 126.9, 127.3, 128.0, 128.2, 128.3, 140.5, 141.9, 173.9

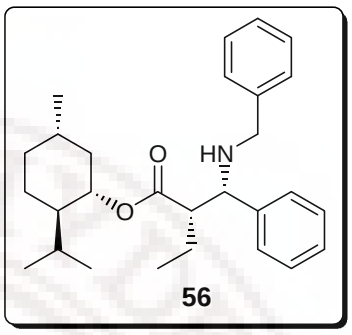
LCMS m/z 422 (M+1)

$[\alpha]_D^{25}$ -3.20 (*c* 1, $CHCl_3$)

Analysis : Calculated for $C_{28}H_{38}ClNO_2$: C, 73.74%; H, 8.4%; N, 3.07%; Cl, 7.77%; O, 7.02

Found : C, 73.7%; H, 8.47%; N, 3.19%

1.4.3.8 (1*S*,2*R*,5*S*)-2-Isoproyl-5-methylcyclohexyl(2*S*)-2-[(*S*)-1-benzylamino-1-phenylmethyl]butanoate (56)



56

Yield 1.6 g (76%)

mp 124-126 ^oC

dr 7:93

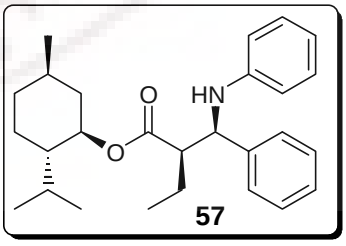
IR (KBr) (cm^{-1}) 3321, 3061, 2962, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.44 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.8 Hz), 0.76-0.91 (m, 9H), 1.18-1.23 (m, 2H), 1.33-1.38 (m, 1H), 1.54-1.79 (m, 5H), 1.92-1.98 (m, 1H), 2.56-2.61 (m, 1H), 3.44 (d, 1H, *J* = 13.0 Hz), 3.59 (d, 1H, *J* = 13.2 Hz), 3.79 (d, 1H, *J* = 8.5 Hz), 4.49 (dt, 1H, *J* = 10.8 Hz, *J* = 4.2 Hz), 7.21-7.31 (m, 10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.3, 41.0, 46.8, 51.5, 55.1, 63.7, 74.0, 126.9, 127.3, 128.0, 128.2, 128.3, 140.6, 141.9, 173.9

$[\alpha]_D^{25}$ +11.4 (*c* 1, $CHCl_3$)

1.4.3.9 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-anilino-1-phenyl methyl]butanoate (57)



57

Yield 0.91 (45%)

mp 174-176 ^oC

dr 72:28

IR(KBr) (cm^{-1}) 3389, 3051, 2953, 1703

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): for major diastereomer: 0.42 (d, 3H, *J* = 6.8 Hz), 0.66 (d, 3H, *J* = 6.8 Hz), 0.83-0.92 (m, 9H), 1.25-1.42 (m, 3H), 1.56-1.65 (m, 3H), 1.75-1.89 (m, 2H), 2.69-2.75 (m, 1H), 4.31 (br s, 1H), 4.60-4.66 (m, 2H), 6.48 (d, 2H, *J*= 8Hz), 6.62 (t, 1H, *J* = 7.4), 7.05 (t, 2H, *J* = 7.8Hz), 7.18-7.34 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.4, 15.6, 20.8, 20.9, 22.1, 23.0, 25.7, 31.5, 34.3, 41.1, 47.0, 54.8, 59.5, 74.6, 113.5, 117.6, 127.2, 127.3, 128.5, 129.1, 141.2, 147.2, 173.3

LCMS m/z 408 (M+1)

$[\alpha]_D^{25}$ -21.42 (*c* 0.5, $CHCl_3$)

Analysis : Calculated for $C_{27}H_{37}NO_2$; C, 79.56%; H, 9.15%; N, 3.44%; O, 7.85

Found : C, 79.58%; H, 9.17%; N, 3.48%; O, 7.77

1.4.4 Procedure for the preparation of mandelic acid salt of β-amino esters 46 and 56

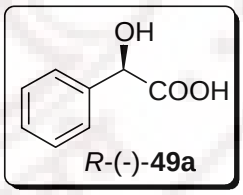
The *syn*-β-amino ester **46** (0.42 g, 1 mmol) was taken in CH_2Cl_2/acetone mixture (3 mL, 1:1 v/v ratio) and stirred for 10 minutes at 25 ^{o}C till complete dissolution occurs. To the solution, (*R*)-(-)-mandelic acid **49a** (0.15 g, 1 mmol) was added and the contents were stirred at 25 ^{o}C for 3 hours. The precipitate formed was filtered and crystallized from benzene-isopropanol mixture to obtain the crystals suitable for X-ray structure analysis. The salt **58** of *syn*-β-amino ester **56** with (*S*)-(+)-mandelic acid **49b** was obtained following the similar procedure. The salt **58** was crystallized from benzene-isopropanol mixture to obtain crystals suitable for X-ray structure analysis.

1.4.4.1 Procedure for the resolution of racemic mandelic acid 49 using β-amino esters

The *syn*-β-amino ester **46a** (2.1 g, 5 mmol) was taken in acetone- CH_2Cl_2 mixture (16mL, 11:5 v/v ratio) and stirred for 10 minutes till complete dissolution occurs. Racemic mandelic acid **49** (0.77 g, 5mmol) was added in a single lot and the contents were stirred at 25 ^oC for 12 h. The precipitate formed was filtered and was suspended in a mixture of ether and 2M Na_2CO_3 solution, stirred until complete dissolution occurred. The aqueous layer was treated with dil HCl (3N)/ether and the mandelic acid was extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain (*R*)-(-)-**49a** mandelic acid enantiomer (>99% ee, 28% yield). The filtrate part was concentrated under reduced pressure and the residue was treated as outlined above to obtain (+)-(*S*)-**49b** enantiomer (42% ee, 61% yield). The samples were analyzed using HPLC (CHIRALCEL OD-H, eluent: hexane: 2-propanol: trifluoroacetic acid=900:100:2.5, v/v).[52]

After decomposition:

From precipitate:

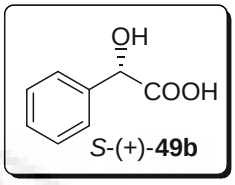


Yield 0.215 g (28%)

$[\alpha]_D^{25}$ -147.0 (*c* 0.5, ethanol), {Lit.[53] $[\alpha]_D^{25}$= -153.0 (*c* 5, H_2O)}

Enantiomeric purity >99% ee (Determined by HPLC using chiral column, chiralcel OD-H solvent system; Hexane: 2-propanol: trifluoroacetic acid=900:100:2.5, v/v flow rate 0.5 mL/min., 254 nm, retention times: 14.6 min. for minor (*S*) and 16.4 min. for major (*R*) isomer).

From filtrate:



Yield 0.470 g (61%)

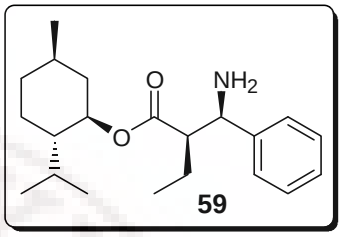
$[\alpha]_D^{25}$ +60.4 (*c* 1, ethanol)

Enantiomeric purity 42% ee (Determined by HPLC using chiral column, chiralcel OD-H solvent system, Eluent: hexane: 2-propanol: trifluoroacetic acid=900:100:2.5, v/v ; flow rate 0.5 mL/min., 254 nm, retention times: 14.6 min. for major (*S*) isomer and 16.5 min. for minor (*R*) isomer.

1.4.5 Procedure for the debenzylation of menthyl aminoester

To a stirred solution of menthyl amino ester **46a** (0.42 g, 1 mmol) in a mixture of methanol and formic acid (100%) (20 mL, 4:1 v/v), Pd/C (50 mg, 5% by weight) was added. The reaction mixture was heated to 50 ^oC for 2 h. The reaction mixture was brought to room temperature, filtered and neutralized slowly by adding 3N NaOH solution till the solution becomes slightly basic. The reaction mixture was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with water (20 mL), brine (15 mL), dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230-400 mesh) column using hexane/EtOAc (95/5) as eluent.

1.4.5.1 (1*R*,2*S*,5*R*)-2-Isoproyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-amino-1-phenyl methyl]butanoate (59)



59

Yield 0.28 g (86%)

mp 96-98 ^oC

IR (KBr) (cm^{-1}) 3371, 3308, 3061, 2955, 1714

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.43 (d, 3H, *J* = 6.8 Hz), 0.69-0.96 (m, 12H), 1.16-1.37 (m, 3H), 1.57-1.85 (m, 7H), 2.54-2.60 (m, 1H), 4.07 (d, 1H, *J* = 8.6 Hz), 4.50 (dt, 1H, *J* = 10.8 Hz, *J* = 4.2 Hz), 7.21-7.32 (m, 5H) **(Spectrum No. 5)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 11.9, 15.8, 20.8, 22.0, 22.6, 23.0, 25.3, 31.3, 34.2, 40.9, 46.7, 55.9, 57.6, 73.9, 127.0, 127.3, 128.4, 144.1, 173.9 **(Spectrum No. 6)**

LCMS m/z 332 (M+1)

Analysis Calculated for $C_{21}H_{33}NO_2$: C, 76.09%; H, 10.03%; N, 4.23%; O, 9.65%

Found C, 76.20%; H, 10.02%; N, 4.29%; O, 9.48%

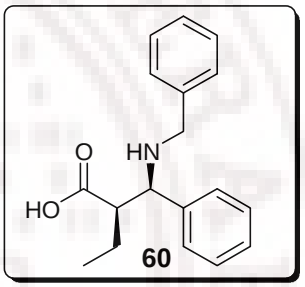
$[\alpha]_D^{25}$ -61.67 (*c* 0.5, $CHCl_3$)

1.4.6 Procedure for the hydrolysis of menthyl aminoester

The menthyl amino ester **46a** (0.421 g, 1 mmol) was taken in a mixture of gla. acetic acid and hydrochloric acid (10 mL, 1:1 v/v) and refluxed for 24 h. The solvents were distilled off and the residue was taken in 5 mL of distilled water. A saturated sodium

bicarbonate solution was added dropwise to the mixture till it becomes slightly basic. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (230-400 mesh) column using hexane/EtOAc (90/10) as eluent.

1.4.6.1 (2*R*,3*R*)-2-ethyl-3-benzylamino-3-phenylpropionic acid (60)



60

Yield 0.12 g (44%)

mp 80-82 ^{o}C

IR (KBr) (cm^{-1}) 3400, 3034, 2964, 1684, 1624, 1583

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.74 (t, 3H, *J* = 7.2 Hz), 1.26-1.31 (m, 1H), 1.65-1.72 (m, 1H), 2.77 (br s, 1H), 3.80 (d, 1H, *J* = 13.2 Hz), 4.11-4.21 (m, 2H), 7.26-7.40 (m, 10H), 8.75 (br s, 2H) **(Spectrum No. 7)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 12.3, 20.7, 49.0, 50.0, 61.5, 128.6, 128.9, 129.1, 129.3, 129.5, 129.8, 132.0, 133.4, 177.3 **(Spectrum No. 8)**

LCMS m/z 284 (M+1)

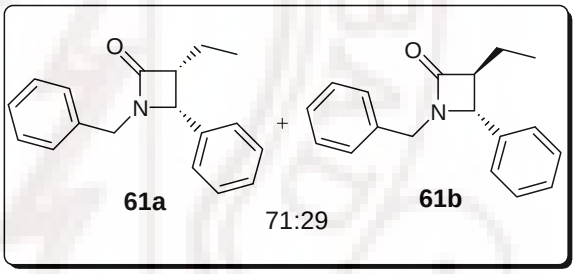
Analysis Calculated for $C_{18}H_{21}NO_2$: C, 76.29%; H, 7.47%; N, 4.94%; O, 11.29%

Found : C, 76.35%; H, 7.48%; N, 5.0%; O, 11.16%

$[\alpha]_D^{25}$ +43.38 (*c* 0.15, $CHCl_3$)

1.4.7 Procedure for the preparation of β-lactam (61)

To a stirred solution of *syn* β-amino ester **46a** (0.42 g, 1 mmol) in dry THF (10 mL), a solution of ethylmagnesium bromide (0.13 g, 1 mmol) in 5 mL of dry THF was added slowly at 0 ^oC under N_2 atmosphere over 10 min. The reaction mixture was stirred at 0 ^oC for 3 h and then quenched with saturated NH_4Cl solution. The reaction mixture was diluted with ether (20 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2 x 15 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (230-400 mesh) using hexane/EtOAc (95/5) as eluent.



Yield 0.23 g (56%)

dr 71:29

IR (Neat) (cm^{-1}) 3030, 2926, 1738

^1H-NMR (400 MHz, $CDCl_3$, δ ppm): for the diastereomeric mixture: 0.69 (t, 3H, *J* = 7.3 Hz), 0.99-1.10 (m, 1H), 1.37-1.48 (m, 1H), 3.19-3.24 (m, 1H), 3.78 (d, 1H, *J* = 14.9 Hz), 4.51 (d, 1H, *J* = 5.4 Hz), 4.80 (d, 1H, *J* = 14.6 Hz), 7.06-7.30 (m, 12H). Additional signals for the minor isomer: 0.90 (t, 3H, *J* = 7.3 Hz), 1.60-1.67 (m, 1H), 1.71-1.80 (m, 1H), 2.89-2.92 (m, 1), 3.64 (d, 1H, *J* = 14.9 Hz), 3.97 (s, 1H), 4.79-4.80 (m, 1H) **(Spectrum No. 9)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for the diastereomeric mixture: 11.4, 11.7, 18.7, 21.7, 44.1, 44.2, 57.1, 57.7, 59.9, 62.0, 126.4, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.4, 135.7, 170.2, 170.7 **(Spectrum No. 10)**

Mass m/z 266 (M+1).

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Chapter 2

$TiCl_4$ Promoted Reactions of Donor-Acceptor Cyclopropane Derivatives

2.1 Introduction

The donor-acceptor cyclopropanes play an important role in the organic synthesis.[1] These cyclopropanes act as 1,3-dipolar synthons in cycloaddition reactions.[2] The asymmetric versions of cycloaddition reactions are useful in the construction of valuable synthetic intermediates.[3] A brief review on the Lewis acid mediated cycloaddition reactions of the cyclopropanes will facilitate the discussion.

2.1.1 Lewis acid promoted reactions of cyclopropyl ketones

Lewis acid mediated ring opening of cyclopropyl ketones have been widely studied.[4] Various Lewis acid promoted reactions of cyclopropyl ketones with diffenent substrates are listed in Chart **1**.

Chart 1

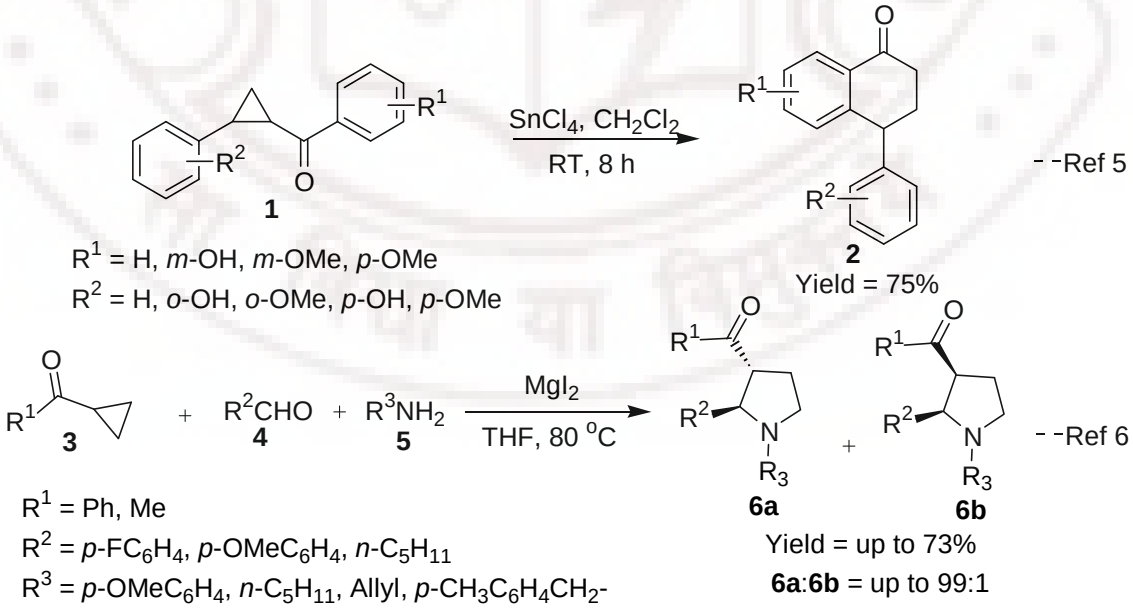
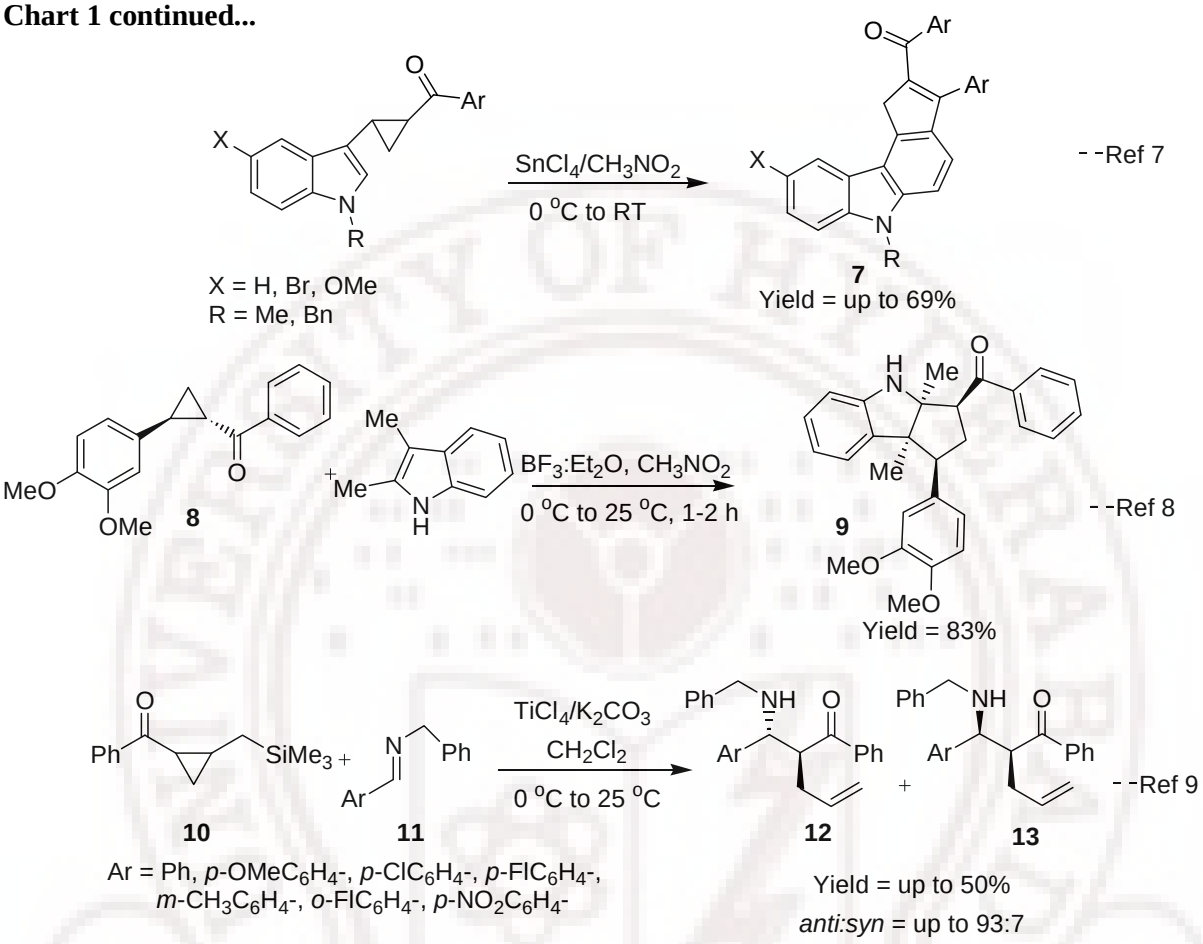


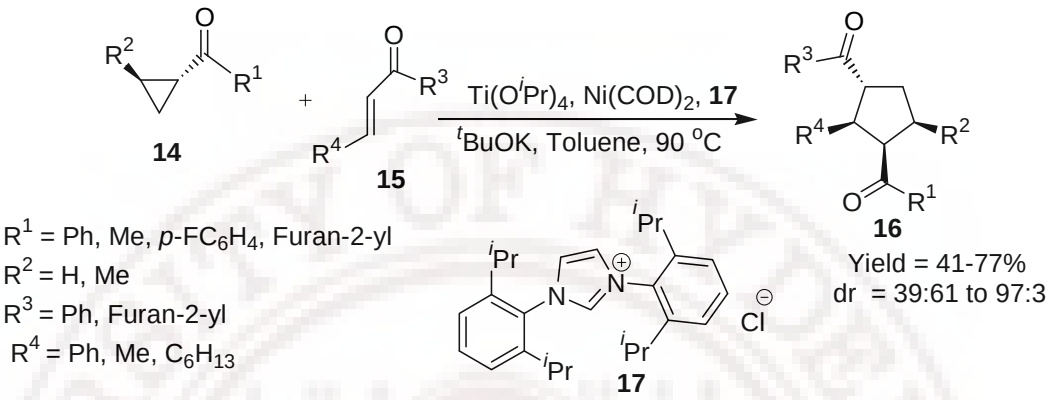
Chart 1 continued...



2.1.2 Titanium reagents mediated cycloaddition reactions

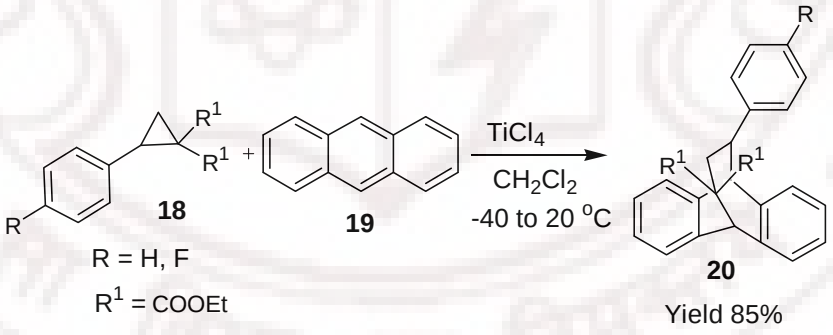
Titanium mediated cycloaddition reactions are useful for the synthesis of five member carbocyclic and heterocyclic ring systems.[10] Montgomery *et al.*[11] reported the cycloaddition reaction of cyclopropyl ketones **14** and enones **15** with $Ni(COD)_2$ in presence of $Ti(O^iPr)_4$ or $Ti(O^iBu)_4$. The substituted cyclopentane **16** was obtained in moderate to good yields with good selectivity (Scheme **1**).

Scheme 1



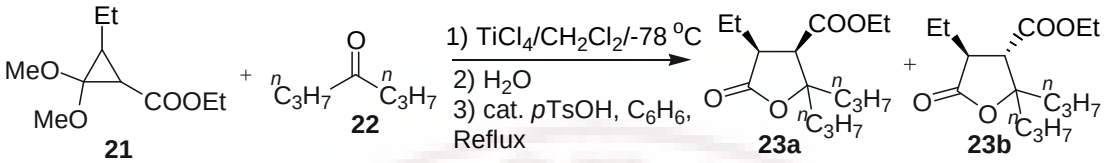
Substituted pyrrolidines were prepared by the cycloaddition reaction of cyclopropyl diesters with imines.[12] Ivanova *et al.*[13] reported the reaction of donor-acceptor cyclopropanes **18** and anthracene **19** with $TiCl_4$ in CH_2Cl_2 solvent. The [4+3] cycloaddition product **20** was obtained in 85% yield (Scheme **2**).

Scheme 2



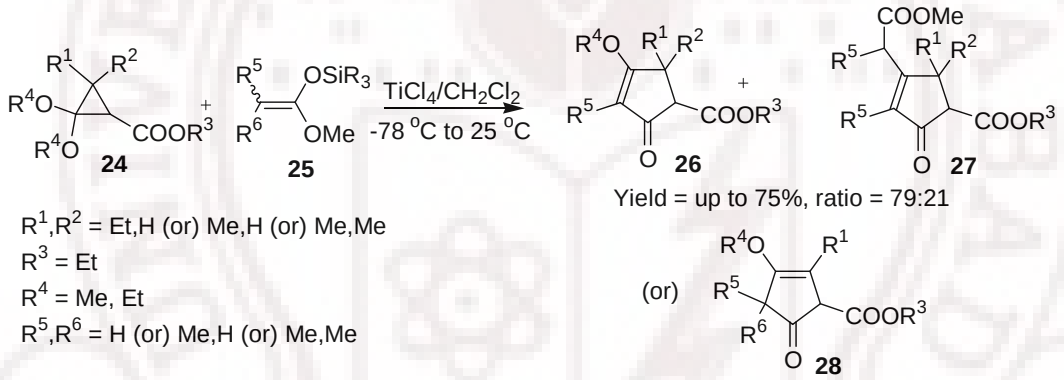
The $TiCl_4$ mediated cycloaddition reaction of donor-acceptor cyclopropanes **21** and the ketone **22** was reported by Saigo *et al.*[14] The γ-lactone **23** was obtained in good yield with excellent selectivity (Scheme **3**).

Scheme 3



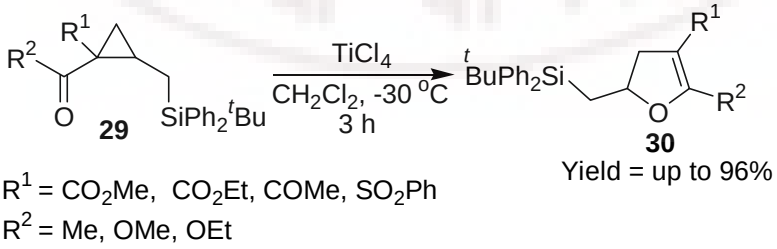
Highly substituted cyclopentenones **26-28** were prepared by the $TiCl_4$ mediated reaction of dialkoxycyclopropanecarboxylic ester **24** and ketene silyl acetals **25** (Scheme **4**).[15]

Scheme 4



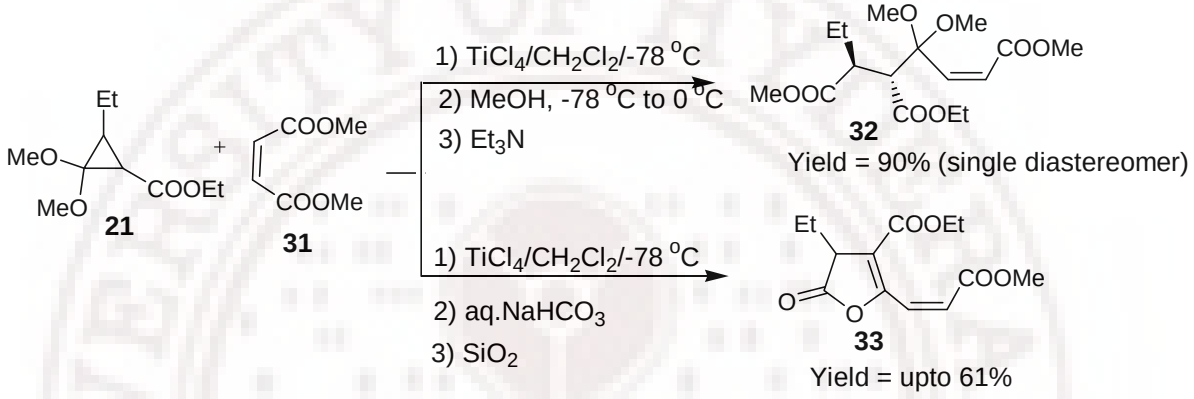
The $TiCl_4$ mediated intramolecular cycloaddition reaction of cyclopropyl ketone **29** was reported by Yadav *et al.*[16] The substituted dihydrofuran products **30** were obtained in good yields (Scheme **5**).

Scheme 5



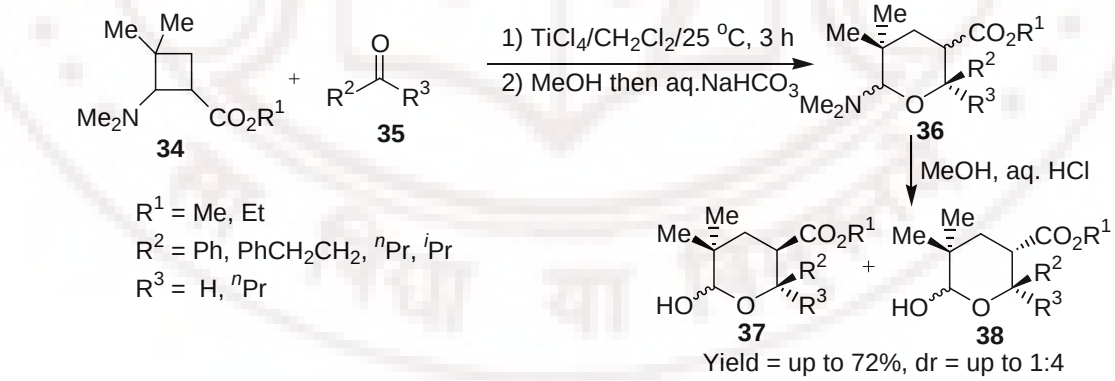
Saigo *et al.*[17] also reported the $TiCl_4$ mediated reaction of cyclopropyl ester **21** with α,β-unsaturated ester **31**. Claisen condensation-type product **32** was obtained in good yields with high diastereoselectivity (Scheme **6**).

Scheme 6



Shimada *et al.*[18] reported the $TiCl_4$ mediated [4+2] cycloaddition reaction of cyclobutane carboxylic esters **34** and carbonyl compounds **35**. The dihydropyrans were obtained in up to 72% yield (Scheme **7**).

Scheme 7

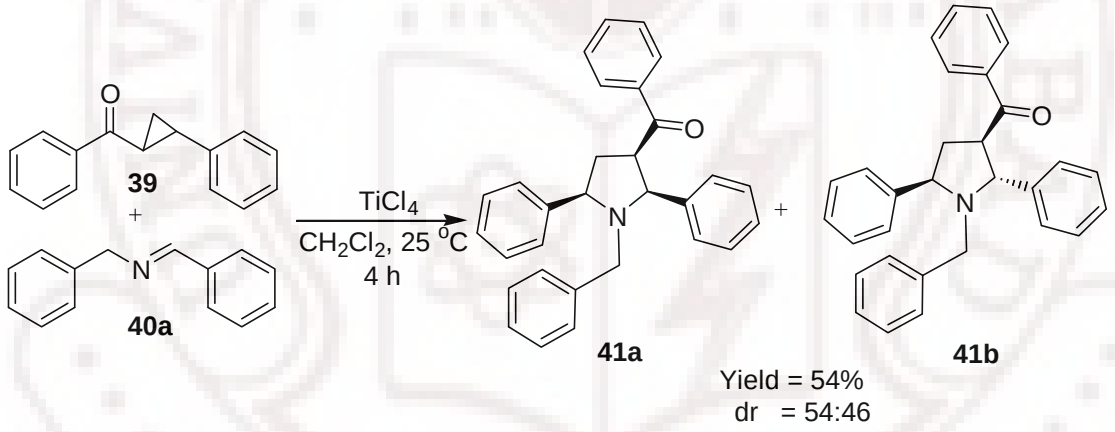


We have examined the titanium(IV) reagent mediated [3+2] cycloaddition reaction of imines with the readily accessible cyclopropyl ketone **39** and cyclopropyl diester **45**. The results are discussed in the next section.

2.2 Results and Discussion

We have explored the titanium mediated cycloaddition reaction of the readily accessible cyclopropyl ketone **39** with imines. The cyclopropyl ketone **39** was prepared following a reported procedure using the Corey-Chaykovsky reagent.[5,19] The cycloaddition reaction of cyclopropyl ketone **39** was carried out with *N*-benzylidenebenzylamine **40a** and $TiCl_4$ at 25 ^oC (Scheme **8**).

Scheme 8

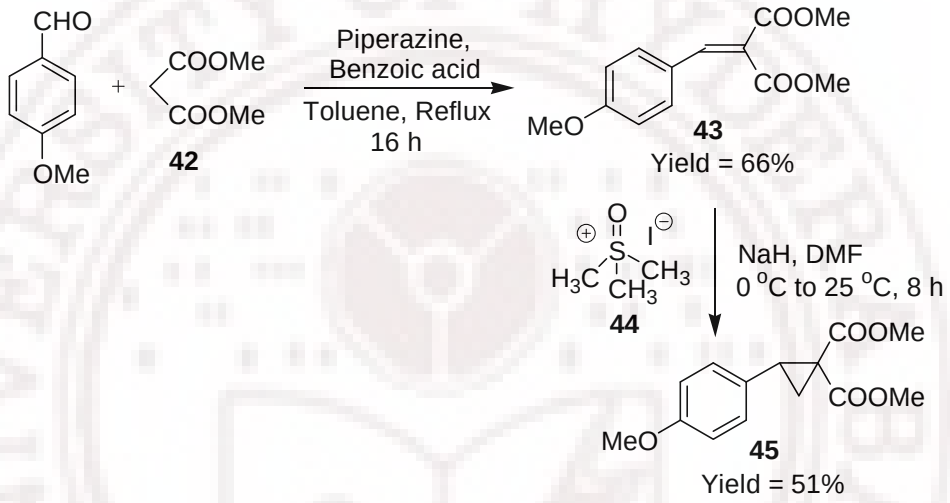


The expected pyrrolidine product **41** was formed in moderate yield with low diastereoselectivity. The cycloaddition reaction carried out at 0 ^oC for 4 h did not yield the pyrrolidine product **41**. The reaction in nitromethane solvent with $TiCl_4$ also did not yield the pyrrolidine product. Hence, we have undertaken research efforts towards the preparation of malonic acid ester moiety containing electron rich *p*-methoxyphenyl group to make the cyclopropyl moiety more reactive towards the [3+2] cycloaddition reaction. The results are described in the next section.

2.2.1 Titanium mediated [3+2] cycloaddition reaction of cyclopropyl diester 45

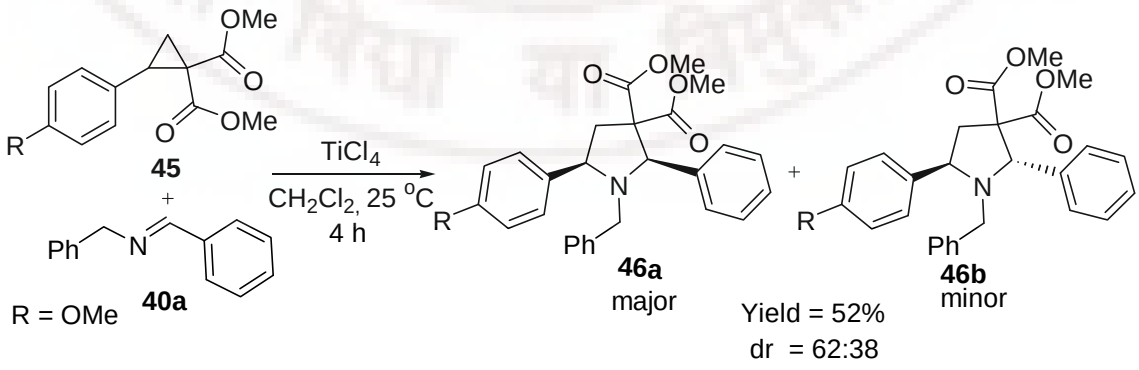
The donor-acceptor cyclopropyl diester **45** was prepared by a previously reported method (Scheme **9**).[20,21] The cyclopropyl diester **45** was obtained in 51% yield.

Scheme 9



We have carried out the cycloaddition reaction of cyclopropyl diester **45** and imine **40a** using $TiCl_4$ in CH_2Cl_2 solvent. The reaction proceeds smoothly and the expected pyrrolidine **46** formed in 52% yield (Scheme **10**). The diastereoselectivity of the product formed was poor.

Scheme 10



Several Lewis acids were screened for further optimization of the reaction. The results are summarized in Table **1**.

Table 1. Reaction of cyclopropyl diester 45 and imine 40a with various Lewis acids[a]

Entry	Lewis acid	Solvent	Temp. (^oC)	Yield[b] (%)	dr[c]
1	$TiCl_2(O^iPr)_2$[d]	CH_2Cl_2	25	61	56:44
2	$TiCl_4$	CH_2Cl_2	25	52	62:38
3	$SnCl_4$	CH_2Cl_2	25	Traces	ND
4	$AlCl_3$	Toluene	25	<10%	ND
5[e]	$Ti(O^iPr)_4$	CH_2Cl_2	25	---	---
6	$TiCl_4$	Toluene	25	67%	88:12
7	$TiCl_4$	Toluene	-30	55	31:69
8[f]	$TiCl_4$	Toluene	50	55	93:7
9[f]	$TiCl_2(O^iPr)_2$	Toluene	25	73	93:7

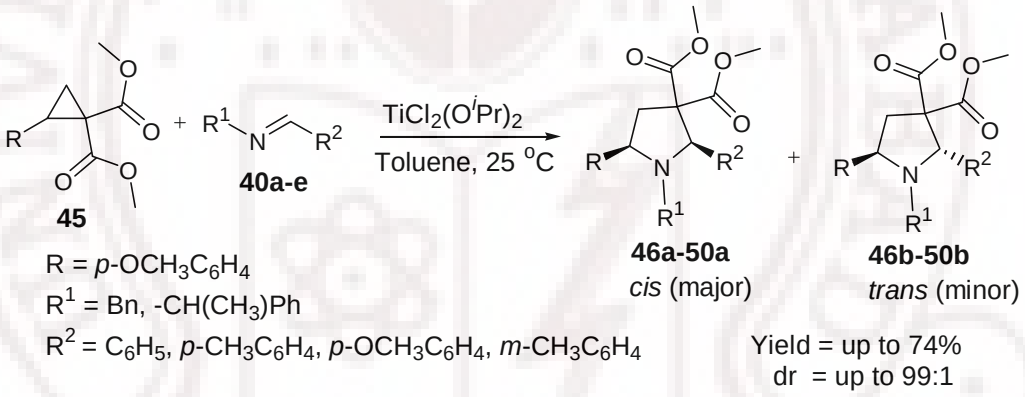
[a] Unless otherwise mentioned all the reactions were carried out with 1 mmol of cyclopropyl diester **45**, 1.2 mmol of imine **40a** and 2 mmol of Lewis acid and stirred for 4 h.
[b]Yields are for the isolated products.
[c]Diastereomeric ratio was calculated from the ^{1}H-NMR analysis of the product mixture.[12]
[d]$TiCl_2(O^iPr)_2$ was prepared *insitu* by mixing 1 equiv. of $TiCl_4$ and 1 equiv. of $Ti(O^iPr)_4$ in 4 mL of CH_2Cl_2 or toluene at 25 ^oC and stirred at the same temperature for 10 minutes.
[e]Formation of product was not observed in the similar reaction carried out in toluene solvent at 80 ^oC for 12 h.
[f]Increase of temperature to 80 ^oC and above make the reaction unclean.

The $TiCl_4$ and $TiCl_2(O^iPr)_2$ gave the pyrrolidine product in good yields but the diastereoselectivity observed was still poor (Table **1**, entry 1, 2). The diastereoselectivity and chemical yield decreased when the temperature of the reaction mixture was lowered to -30 ^oC (Table **1**, entry 7). The yield of the product also decreased upon increasing the temperature to 50 ^oC (Table **1**, entry 8). Fortunately, the reactions carried out with titanium

reagents in toluene solvent gave good yield with good diastereoselectivity (Table **1**, entry 8,9). The reaction gave insoluble black mass at 80 ^oC (Table **1**, Footnote f). It was previously reported that in the $TiCl_4$ mediated cycloaddition reaction of cyclopropyl diesters with anthracene, considerable polymerization of cyclopropanes was observed at higher temperatures.[13]

The [3+2] cycloaddition reaction of cyclopropyl diester **45** was examined with several imines (Scheme **11**, Table **2**).

Scheme 11



The substitution on the imine moiety did not affect the diastereoselectivity to significant extent (Table **2**, entries 2-4). In the cycloaddition reaction of imine **40e** prepared from racemic α-methylbenzylamine, four diastereomeric product pairs are possible. Surprisingly, only two diastereomers are formed as major product. (Table **2**, entry 5). Presumably, the steric effect of the α-methylbenzyl group of the imine **40e** plays a major role in the selectivity. This indicates that the environment around the nitrogen atom affects the stereochemical outcome of the reaction to a greater extent.

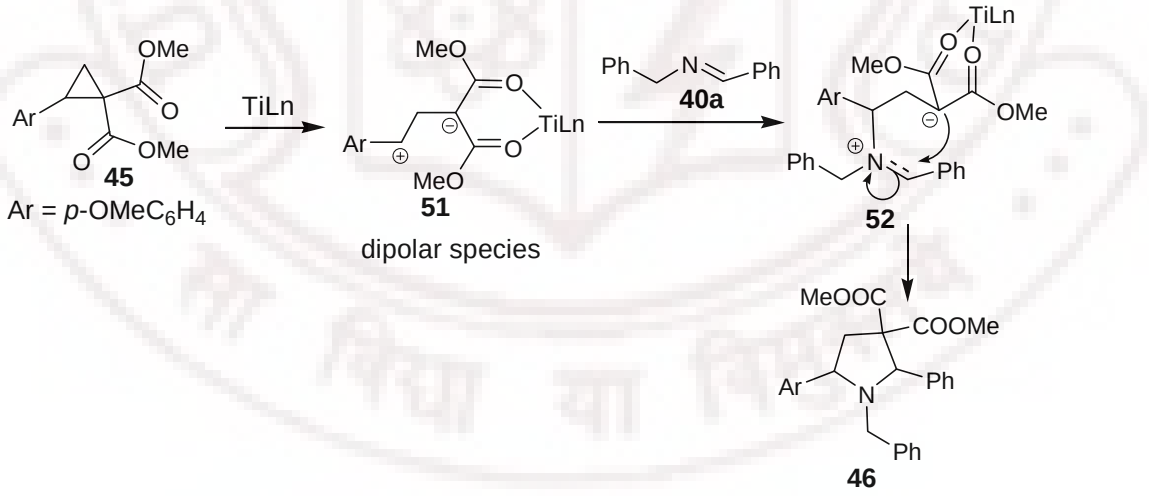
Table 2. Reaction of cyclopropyl diester 45 and imines with $TiCl_2(O^iPr)_2$[a]

Entry	R^1(amine)	R^2(Aldehyde)	Product	Yield(%)[d]	dr[e]
1[b]	-$CH_2C_6H_5$(**40a**)	C_6H_5-	**46**	74	93:7
2[c]	-$CH_2C_6H_5$(**40b**)	4-MeC_6H_4-	**47**	72	86:14
3[b]	-$CH_2C_6H_5$(**40c**)	4-$MeOC_6H_4$-	**48**	64	85:15
4[b]	-$CH_2C_6H_5$(**40d**)	3-MeC_6H_4-	**49**	74	83:17
5[b]	-$CH(CH_3)C_6H_5$(**40e**)	C_6H_5-	**50**	53	99:1

[a]Unless otherwise noted all the reactions are carried out with 1mmol of cyclopropyl diester **45** and 1.3mmol of imine with 2 mmol of $TiCl_2(O^iPr)_2$ at 25 ^oC for 4 h.
[b]The reaction was carried out with $TiCl_2(O^iPr)_2$.
[c]The reaction was carried out with $TiCl_4$.
[d]Yields are for the isolated products.
[e]Diastereomeric ratios were calculated from ^1H NMR analysis of the product mixture.

Additives like lithium chloride did not increase the diastereoselectivity. In the case of $TiCl_4$-TMEDA complex, the formation of pyrrolidines was not observed. The transformation may be rationalized considering the mechanism outlined in Scheme **12**.

Scheme 12



The addition of titanium reagents to the cyclopropyl diester **45** may result in the possible formation of a dipolar intermediate **51**.[13,22a] The nucleophilic attack of the imine

40a nitrogen on to the dipolar species **51** and subsequent cyclization may result in the formation of pyrrolidine **46**. The formation of major pyrrolidine product can be rationalized by considering the following stereochemical model (Figure **1**).[22b] In **TS-I**, the phenyl groups are positioned away from each other. Hence, the low energy transition state **TS-I** lead to the formation of the major *cis* isomer. The steric repulsion between the phenyl group and R^1 may lead to the high energy transition state **TS-II**. Hence, the *trans* isomer was formed as minor product.

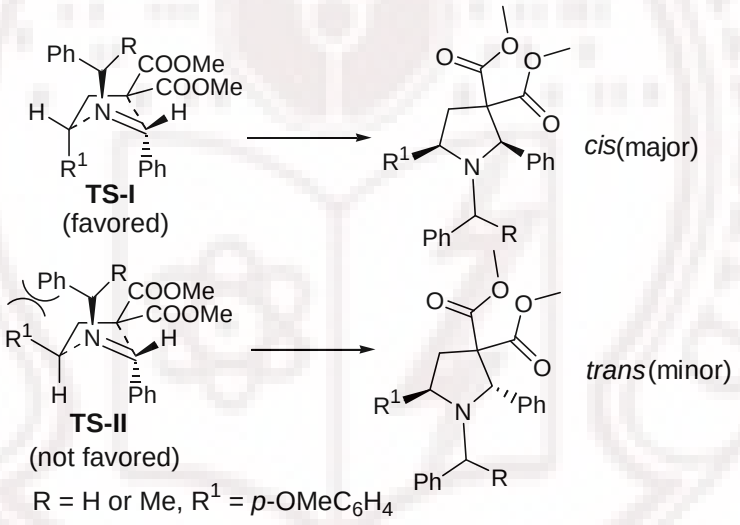


Figure 1. Stereochemical models

The substituted pyrrolidines moieties are found in several natural products and in biologically active skeleton.[23] Some of the important pyrrolidine moieties are given in Figure **2**. The *N*-methyl pyrrolidine derivative **53** was found to be active in the brine shrimp assay. The structurally related pyrrolidines **56** and **57** were isolated from the leaves of bluebells. The pyrrolidine derivative **58** (BIRZ-227) acts as LTB_4 inhibitor.

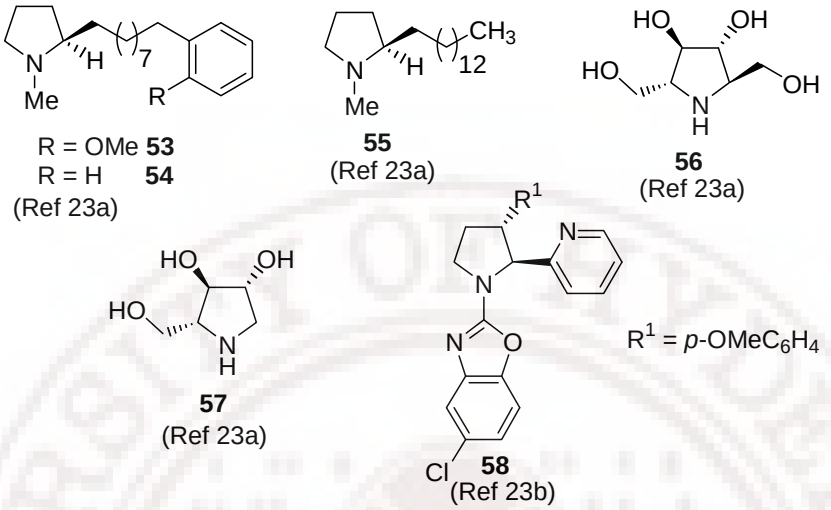


Figure 2

The chiral pyrrolidine reagents, especially the C_2 symmetric 3,4 and 2,5-substituted pyrrolidines **59**-**64** have been widely used in asymmetric transformations (Figure **3**).[24]

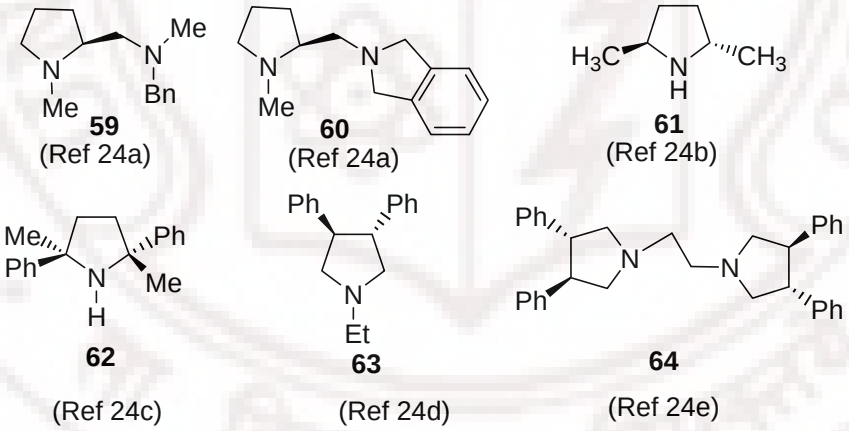
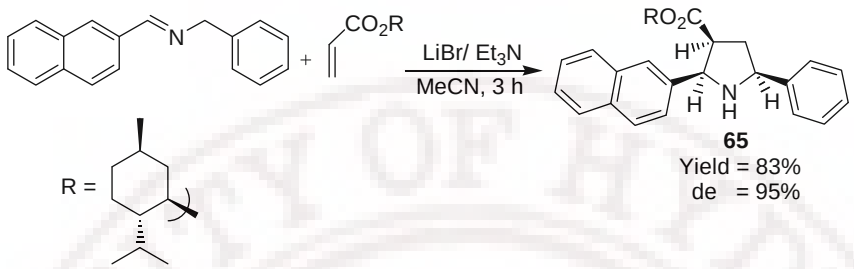


Figure 3

A few reported methods for the synthesis of pyrrolidine moieties are given in Chart **2**.[25-30]

Chart 2

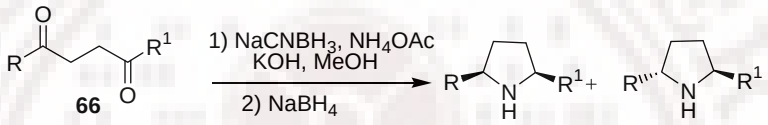
(a) Cycloaddition reaction



65
Yield = 83%
de = 95%

Ref 25

(b) Reductive amination of 1,4-diketones



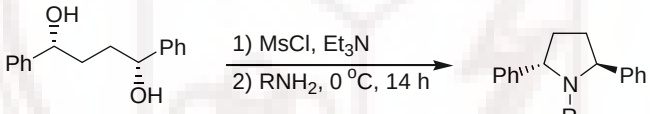
66 **67a** **67b**

Ref 26

R, R^1 = CH_3 (or) $^nC_5H_{11}$, $^nC_6H_{13}$ (or) C_2H_5, $^nC_5H_{11}$ (or) $^nC_5H_{11}$, $(CH_2)_4CH{=}CH_2$

Yield = up to 70%
cis:trans = 1;1

(c) Intermolecular cyclization of 1,4-diols



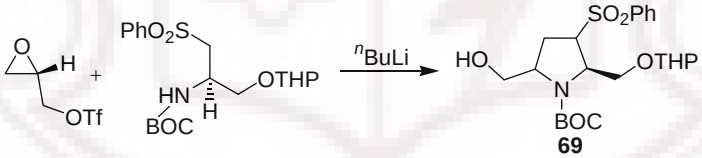
68

Ref 27

R = Ph, CH_2Ph, *o*-OMePh, ^nBu

Yield = 75%

(d) From chiral epoxides

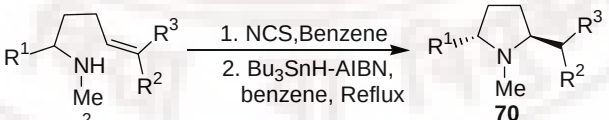


69

Ref 28

Yield = 90%

(e) Intramolecular cyclization of alkenyl amines



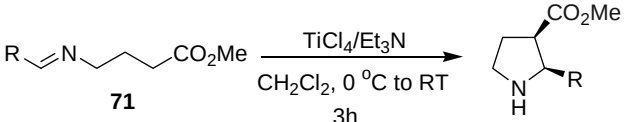
70

Ref 29

R^1 = H, Me, C_6H_5, R^2 = H, Me, C_6H_5
R^3 = H, Me

Yield = up to 63%
trans:*cis* = >99:1

(f) Intramolecular cyclization of imino esters



71 **72**

Ref 30

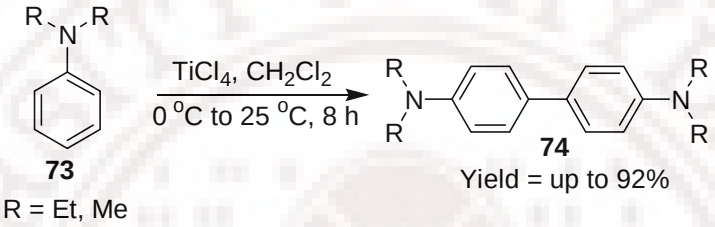
R = Ph, *p*-$CH_3C_6H_4$, *p*-$OCH_3C_6H_4$ p-ClC_6H_4, p-$NO_2C_6H_4$

Yield = up to 75%

2.2.2 Addition of tertiary aromatic amines to activated cyclopropanes

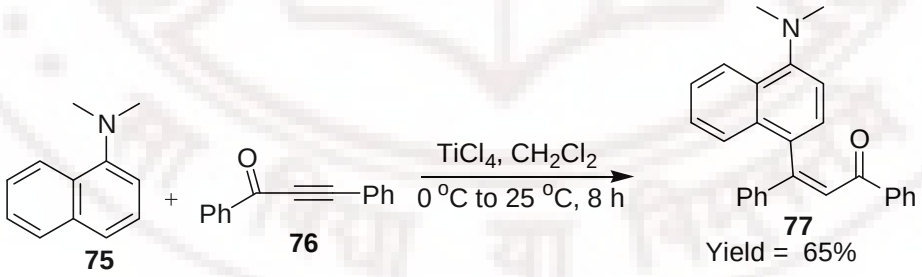
It was reported from this laboratory that the reaction of tertiary aryl amines **73** with $TiCl_4$ gave the corresponding benzidines **74** in good yields (Scheme **13**).[31]

Scheme 13



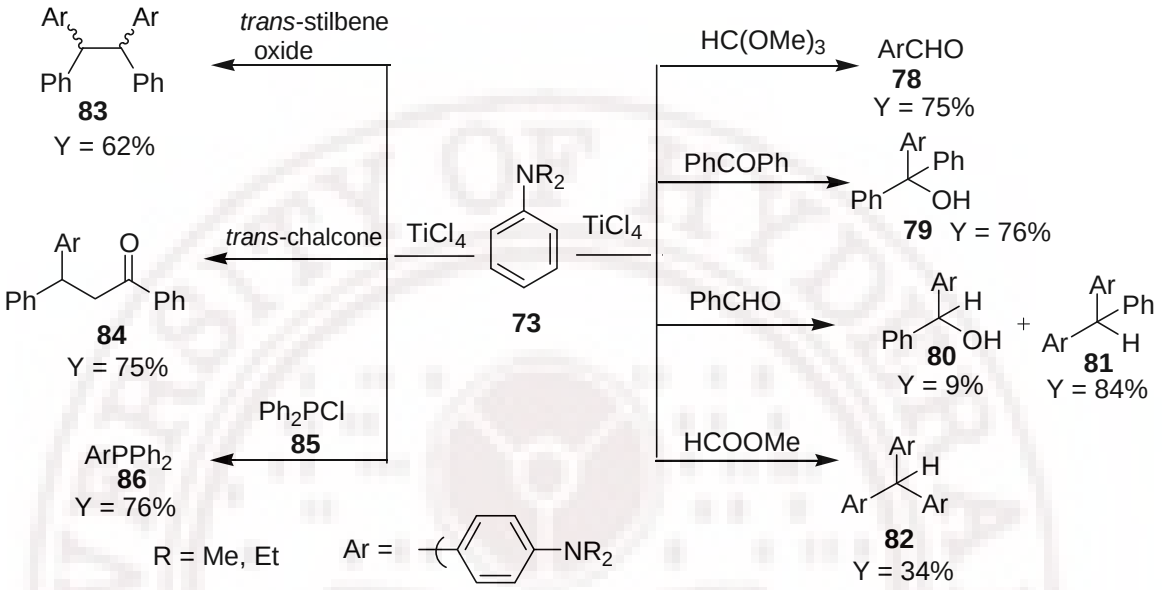
It was also reported from this laboratory that the $TiCl_4$ mediated reaction of tertiary aryl amines with arylacetic acid esters gave the corresponding α-arylated product in good yields.[32] The reaction of *N,N*-dimethyl-1-naphthylamine **75** and alkynyl ketone **76** in presence of $TiCl_4$ gave the corresponding 1,4-addition product **77** in 65% yield (Scheme **14**).[33]

Scheme 14



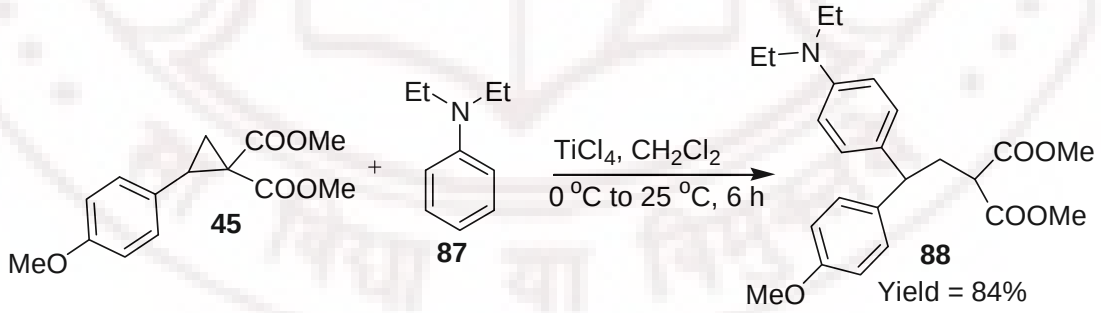
The addition of tertiary aryl amine **73** to a variety of organic substrates in the presence of $TiCl_4$ gave different products ranging from alcohols to aldehydes (Chart **3**).[31,34]

Chart 3



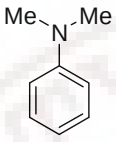
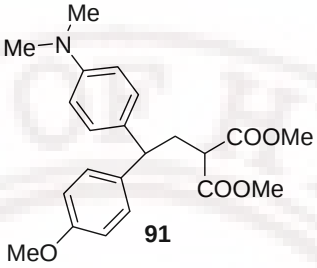
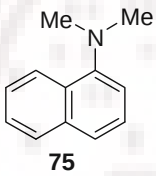
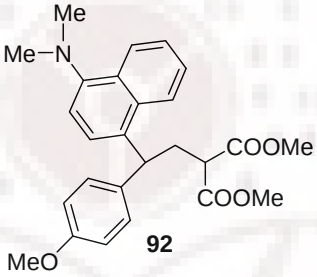
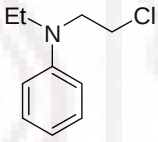
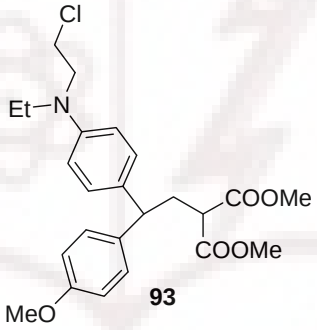
We have examined the reaction of cyclopropyl diester **45** with *N,N*-diethylaniline **87** in the presence of $TiCl_4$. The corresponding addition product **88** was obtained in 84% yield (Scheme **15**).

Scheme 15



The reaction was also generalized with other *N,N*-dialkylaniline derivatives (Table 3). The substituent on the alkyl group of the amine does not have any effect on the transformation (Table **3**, entry 1-3).

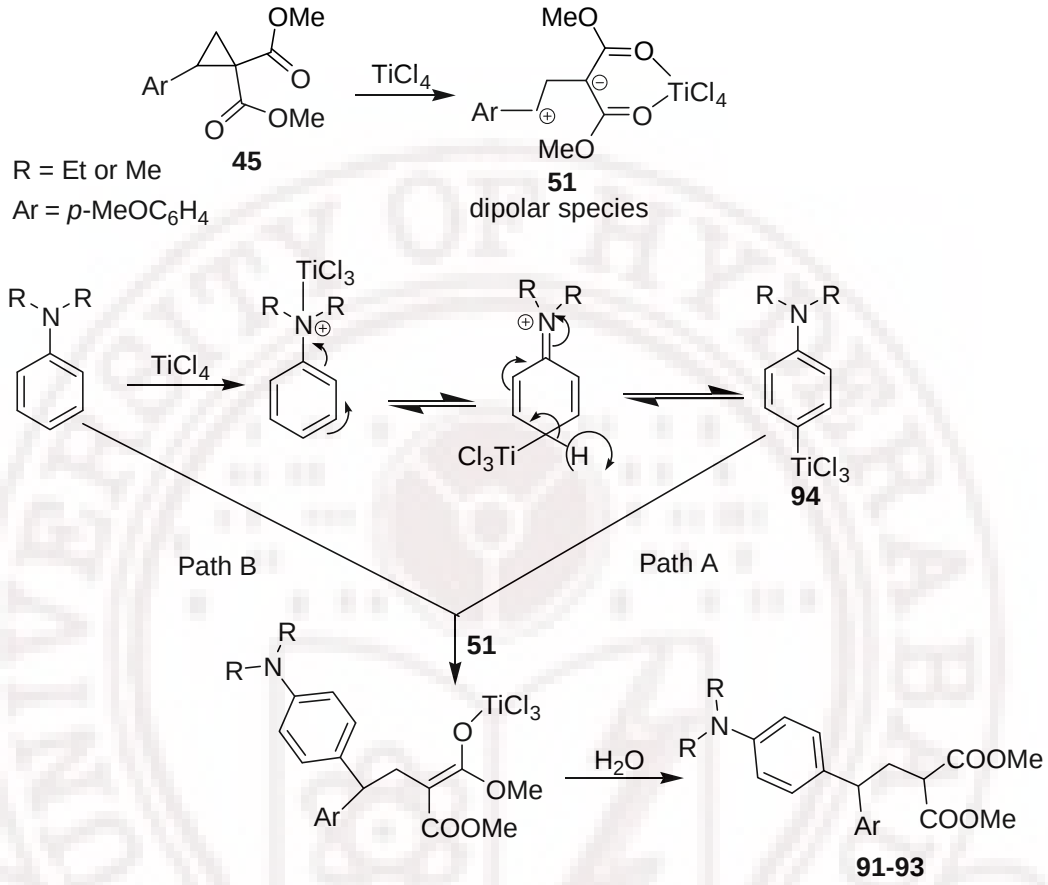
Table 3 Reaction of aryl tertiary amines with cyclopropyl diester 45[a]

Entry	Aryl amine	Product[b]	Yield(%)[c]
1	 **89**	 **91**	74
2	 **75**	 **92**	76
3	 **90**	 **93**	82

[a]All the reactions were carried out with 1 mmol of cyclopropyl diester **45**, 1.5 mmol of aryl amine and 2 mmol of $TiCl_4$ in CH_2Cl_2 solvent. The addition of $TiCl_4$ was at 0 ^oC and the reaction mixture was slowly warmed to 25 ^oC for 6 h.
[b]The products were confirmed by IR, ^1H and ^{13}C-NMR and mass spectroscopy.
[c]Yields are for the isolated products.

The titanium mediated addition of tertiary aryl amines on to the cyclopropyl diester **31** may be rationalized by considering the mechanism outlined in Scheme **16**.

Scheme 16



The reaction of tertiary aryl amines with $TiCl_4$ would result in the possible formation of the aryl titanium intermediate **94**.[31] The $TiCl_4$ also could activate the cyclopropyl diester **45** to give the dipolar species **51**.[13,22a] Addition of the aryl titanium intermediate **94** to the dipolar species **51** could lead to the corresponding addition product (Path A). Alternatively, the tertiary aryl amines could directly react with the dipolar species to give the product (Path B).

The studies described here illustrate the titanium mediated reaction of activated cyclopropyl diester **45** has considerable potential for further synthetic exploitations.

2.3 Conclusions

The donor-acceptor cyclopropyl ketone **39** and cyclopropyl diester **45** were prepared using the Corey-Chaykovsky reagent. The [3+2] cycloaddition reaction of cyclopropyl ketone with *N*-benzylidenebenzylamine **40a** gave the corresponding pyrrolidine ketone **41** in moderate yield. The [3+2] cycloaddition reaction of cyclopropyl diester **45** with various imines in the presence of $TiCl_4$ gave the corresponding pyrrolidine diester derivatives **46**-**50** in moderate to good yields with good selectivity. The solvent plays a major role in the selectivity of [3+2] cycloaddition reaction. The reaction of *N*,*N*-dialkylaniline with the cyclopropyl diester **45** in the presence of $TiCl_4$ gave the corresponding ring opened addition products **88**, **91**-**93** in good yields.

2.4 Experimental Section

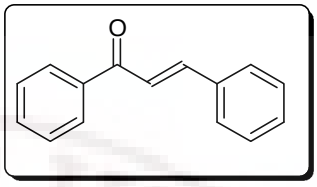
General Information

The informations given in the section **1.4.1** are also applicable for the experiments outlined in this section. Trimethylsulfoxonium iodide was purchased from Avra chemicals (P) Ltd., Hyderabad. Sodium hydride (50% by weight dispersion in mineral oil) was purchased from Loba chemie (P) Ltd.

2.4.1 Procedure for the preparation of donor-acceptor cyclopropanes

2.4.1.1 Synthesis of chalcone

The preparation of chalcone was carried out following a reported procedure.[19] To a solution of sodium hydroxide (2.6 g, 6.5 mmol) in distilled water and ethanol mixture (50 mL, 2:1 v/v) at 0 ^{o}C, acetophenone (6 g, 5.8 mL, 50 mmol) was added and the mixture was stirred well and kept at 0 ^{o}C. To the mixture, benzaldehyde (5.3 g, 5.1 mL, 50 mmol) was slowly added with vigorous stirring for 10 minutes. After completion of the addition, the reaction mixture was brought to room temperature and further stirred for 3 h. The reaction mixture was tightly closed and kept at 0 ^{o}C for 12 h. The reaction mixture was filtered in a Buckner funnel and the precipitate was washed repeatedly with cold water until the washings are neutral to litmus, and then with 10 mL of ice-cold ethanol. The residue was air dried and recrystallized from ethanol. The product was obtained as a pale yellow solid.



Yield 8.5 g (82%)

mp 52-54 ^{o}C {Lit.[35] mp 55-56 ^{o}C}

IR (KBr) (cm^{-1}) 1664, 1606, 1446, 750

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.41-7.46 (m, 3H), 7.49-7.54 (m, 2H), 7.56 (d, 1H, *J* = 15.8 Hz), 7.58-7.63 (m, 1H), 7.65-7.70 (m, 2H), 7.83 (d, 1H, *J* = 15.8 Hz), 8.0-8.07 (m, 2H)

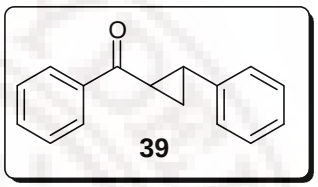
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 122.3, 128.5, 128.6, 129.0, 130.5, 132.8, 135.0, 138.3, 144.8, 190.5

LCMS m/z 209 (M+1)

2.4.1.2 Synthesis of cyclopropyl ketone (39)

The preparation of **39** was carried out by closely following a reported procedure.[5] To a solution of trimethylsulfoxonium iodide (23.1 g, 105 mmol) in 60 mL of dry DMF at 0 ^{o}C under N_2 atmosphere, sodium hydride (5.04 g, 105 mmol,) was added portion wise through solid addition funnel. During the addition of sodium hydride, vigorous evolution of hydrogen was observed. After the complete addition, the reaction mixture was slowly warmed to room temperature and stirred for 30 minutes till the hydrogen evolution ceases. The chalcone (20.8 g, 100 mmol) was taken in 20 mL of dry DMF and slowly added drop wise to the reaction mixture through addition funnel. Heating of the reaction mixture was observed during the addition of chalcone. After completion of the addition, the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with cold water (30 mL) and

extracted with ether (3 x 30 mL). The organic layer was washed with 3N HCl (2 x 20 mL), water (4 x 20 mL), brine and dried over anhydrous Na_2SO_4. The solvents were removed under vacuum and the residue was chromatographed with silica gel (230-400 mesh) column using hexanes/EtOAc (98/2) as eluent.



39

Yield 15.9 g (72%)

mp 42-44 ^oC {Lit.[36] mp 44^oC}

IR (KBr) (cm^{-1}) 3084, 3028, 1660, 1597, 1494

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.54-1.58 (m, 1H), 1.91-1.95 (m, 1H), 2.68-2.73 (m, 1H), 2.88-2.93 (m, 1H), 7.17-7.33 (m, 5H), 7.44-7.48 (m, 2H), 7.54-7.58 (m, 1H), 7.98-8.0 (m, 2H) **(Spectrum No. 11)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 19.2, 29.3, 30.0, 126.2, 126.6, 128.1, 128.5, 132.9, 137.7, 140.5, 198.5 **(Spectrum No. 12)**

Mass m/z 223 (M+1)

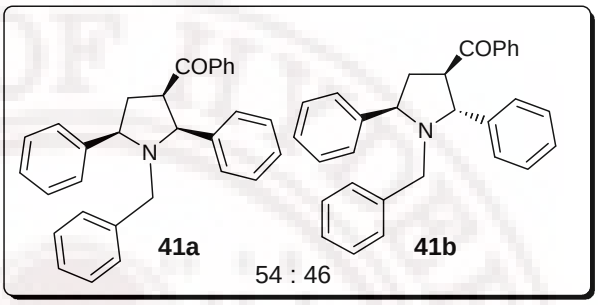
2.4.2 Reaction of imine and cyclopropyl ketone with $TiCl_4$

To a solution of cyclopropyl ketone (0.22 g, 1 mmol) and *N*-benzylidenebenzyl amine (0.23 g, 1.2 mmol) in 5 mL of dry CH_2Cl_2 under N_2 atmosphere, a solution of $TiCl_4$ (0.38 g, 0.22 mL, 2 mmol) was added at 25 ^oC. Immediately after the addition of $TiCl_4$, the colour of the solution turned to dark red. The reaction mixture was further stirred at 25 ^oC for 4 h. The reaction mixture was quenched with saturated potassium carbonate solution (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was washed with brine (1 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude residue was purified by flash column chromatography on silica gel (230-400 mesh) column using hexanes/EtOAc (98/2) as eluent.

Yield 0.23 g (54%)

dr 54:46 (based on ^{1}H NMR)



IR (Neat) (cm^{-1}) 3061, 3028, 2924, 2851, 1682

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : For the diastereomeric mixture: 2.05-2.13 (m, 1H), 2.18-2.25 (m, 1H), 2.35-2.42 (m, 1H), 2.71-2.77 (m, 1H), 2.78 (d, 1H, *J* = 14.4 Hz), 3.42 (d, 1H, *J* = 14.4 Hz), 3.52 (s, 2H), 3.75-3.82 (m, 2H), 3.98-4.04 (m, 1H), 4.17 (d, 1H, *J* = 7.6 Hz), 4.26 (t, 1H, *J* = 7.1 Hz), 4.59 (d, 1H, *J* = 4.8 Hz), 6.80-6.82 (m, 2H), 7.01-7.21 (m, 24 H), 7.24-7.30 (m, 6H), 7.42-7.45 (m, 4H), 7.55 (d, 2H, *J* = 7.6 Hz), 7.70 (d, 2H, *J* = 7.6 Hz) **(Spectrum No. 13)**

^{13}C-NMR` (100 MHz, $CDCl_3$, δ ppm): For the diastereomeric mixture: 37.7, 39.5, 50.7, 52.7, 53.3, 54.0, 65.2, 65.6, 67.4, 68.2, 126.5, 126.9, 127.3, 127.4, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 129.8, 130.4, 133.0, 133.1, 134.5, 135.5, 136.5, 139.6, 141.0, 142.8, 142.9, 143.5, 192.4, 199.9, 200.5 **(Spectrum No. 14)**

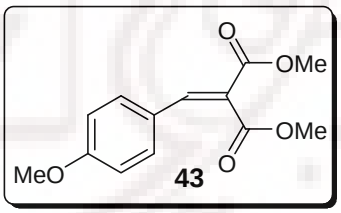
LCMS m/z 418 (M+1)

Analysis Calculated for $C_{30}H_{27}NO$: C, 86.30%; H, 6.52%; N, 3.35%; O, 3.83%

Found C, 86.45 %; H, 6.48%; N, 3.41%; O, 3.66%

2.4.3 Preparation of dimethyl-2-(4-methoxyphenylmethylene)malonate (43)

The preparation of **43** was carried out following a reported procedure.[20] To a solution of *p*-anisaldehde (6.8 g, 6.1 mL, 50 mmol) and dimethyl malonate (6.6 g, 5.7 mL, 50 mmol) in 50 mL of toluene at room temperature under nitrogen atmosphere, piperidine (0.43 g, 0.5 mL, 5 mmol) and benzoic acid (0.61 g, 5 mmol) were added. The reaction vessel was fitted with Deans-Stark apparatus and refluxed for 16 h. The reaction mixture was diluted with 30 mL of ethyl acetate and was washed with 3N HCl (1 x 20 mL), saturated $NaHCO_3$ (1 x 10 mL), water (2 x 20 mL), brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The unreacted starting materials were distilled off from the reaction mixture under reduced pressure and the crude residue was chromatographed with silica gel (230-400 mesh) column using hexanes/EtOAc (98/2) as eluent.



43

Yield 8.2 g (66%)

IR (Neat) (cm^{-1}) 3061, 2984, 1726, 1631

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.89 (d, 2H, *J* = 8.6 Hz), 7.38 (d, 2H, *J* = 8.6 Hz), 7.70 (s, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 52.5, 52.6, 55.3, 114.4, 122.8, 125.2, 131.5, 142.6, 161.7, 164.8, 167.6

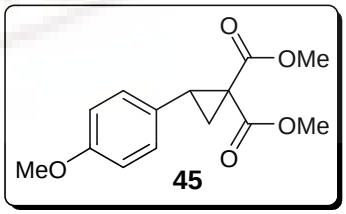
2.4.3.1 General procedure for the preparation of dimethyl 2-(4-methoxyphenyl)-1,1'-cyclopropanedicarboxylate(45)

The preparation of **45** was carried out by closely following a reported procedure.[21] To a solution of trimethylsulfoxonium iodide (23.1 g, 105 mmol) in 60 mL of dry DMF at 0 ^{o}C under nitrogen atmosphere, sodium hydride (5.04 g, 105 mmol) was added portion wise through solid addition funnel. During the addition of sodium hydride, vigorous evolution of hydrogen was observed. After the complete addition, the reaction mixture was slowly warmed to room temperature and stirred for 30 minutes till the hydrogen evolution ceases. The α, β-unsaturated diester **43** (22.0 g, 100 mmol) was taken in 20 mL of dry DMF and slowly added drop wise to the reaction mixture through addition funnel. Heating of the reaction mixture was observed during the addition of chalcone. After completion of the addition, the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with cold water (1 x 30 mL) and extracted with ether (3 x 30 mL). The organic layer was washed with 3N HCl (2 x 20 mL), water (4 x 20 mL), brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was chromatographed on silica gel (230-400 mesh) column using hexanes/EtOAc (98/2) as eluent.

Yield 6.8 g (51 %)

IR (Neat) (cm^{-1}) 3001, 2955, 2839, 1730, 1612

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.72 (dd, 1H, *J*



45

= 9.3 Hz, *J* = 5.1 Hz), 2.15 (dd, 1H, *J* = 8.0 Hz, *J* = 5.3 Hz), 3.18 (t, 1H, *J* = 8.4 Hz), 3.38 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 6.80 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 2H, *J* = 8.7 Hz) **(Spectrum No. 15)**

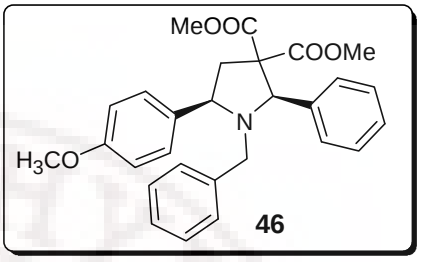
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 19.3, 32.2, 37.1, 52.2, 52.7, 55.2, 113.6, 126.5, 129.6, 158.9, 167.2, 170.3 **(Spectrum No. 16)**

LCMS m/z 265 (M+1)

2.4.4 General Procedure for the reaction of cyclopropyl diester and imine in the presence of $TiCl_4$

To a stirred solution of cyclopropyl diester **45** (0.26 g, 1 mmol) and imine (1.2 mmol) in 5 mL of dry toluene under nitrogen atmosphere at 25 ^oC, a freshly prepared solution of $TiCl_2(O^iPr)_2$ (2 mmol in 2 mL of toluene) was added. Immediately after the addition of $TiCl_2(O^iPr)_2$, the colour of the reaction mixture turned red. The reaction mixture was further stirred at 25 ^oC for 4 h. The reaction mixture was quenched with saturated K_2CO_3 solution (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were washed with brine (1 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (230-400 mesh) column using hexanes/EtOAc (98/2) as eluent.

2.4.4.1 Dimethyl-1-benzyl-5-(4-methoxyphenyl)-2-phenyl-3,3-pyrrolidine dicarboxylate (46)



Yield 0.34 g (74%)

dr 93:7

IR (Neat) (cm^{-1}) 3030, 2951, 2837, 1734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.36 (dd, 1H, *J* = 13.4 Hz, *J* = 6.6 Hz), 2.83 (t, 1H, *J* = 11 Hz), 3.04 (s, 3H), 3.25-3.65 (m, 3H), 3.68 (s, 3H), 3.85 (s, 3H), 4.71 (s, 1H), 6.88-6.90 (m, 2H), 6.95-6.96 (m, 2H), 7.14-7.17 (m, 2H), 7.22-7.32 (m, 4H), 7.49-7.54 (m, 4H)

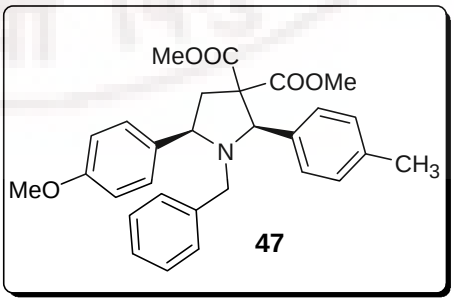
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 42.2, 52.0, 52.1, 52.7, 55.3, 63.4, 63.8, 69.3, 114.1, 126.9, 127.6, 127.7, 127.9, 129.1, 129.2, 130.3, 133.6, 134.9, 139.3, 159.1, 169.6, 172.0

LCMS m/z 460 (M+1)

Analysis Calculated for $C_{28}H_{29}NO_5$: C, 73.18%; H, 6.36%; N, 3.05%; O, 17.41%

Found : C, 73.09%; H, 6.41%; N, 3.11%; O, 17.39%

2.4.4.2 Dimethyl-1-benzyl-5-(4-methoxyphenyl)-2-(4-methylphenyl)-3,3-pyrrolidine dicarboxylate (47)



Yield 0.34 g (72%)

dr 86:14

IR (Neat) (cm^{-1}) 3026, 2939, 2841, 1726

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.23 (s, 3H), 2.23-2.29 (m, 1H), 2.70 (t, 1H, *J* = 11 Hz), 2.98 (s, 3H), 3.48 (d, 2H, *J* = 7.1 Hz), 3.49-3.54(m, 1H), 3.56 (s, 3H), 3.72 (s, 3H), 4.58 (s, 1H), 6.78-6.86 (m, 4H), 7.02-7.07 (m, 5H), 7.32 (d, 2H, *J* = 7.6 Hz), 7.42 (d, 2H, *J* = 8.3 Hz) **(Spectrum No. 17)**

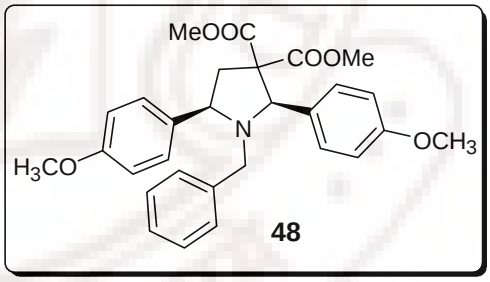
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 21.2, 42.1, 51.6, 52.0, 52.6, 55.3, 63.1, 63.7, 69.0, 114.0, 126.8, 127.7, 128.6, 129.0, 129.1, 130.3, 133.7, 134.7, 136.0, 137.1, 159.1, 170.0, 172.1 **(Spectrum No. 18)**

LCMS m/z 474 (M+1)

Analysis Calculated for $C_{29}H_{31}NO_5$: C, 73.55%; H, 6.60%; N, 2.96%; O, 16.89%

Found : C, 73.44%; H, 6.65%; N, 3.01%; O, 16.9%

2.4.4.3 Dimethyl-1-benzyl-2,5-di(4-methoxyphenyl)-3,3-pyrrolidinedicarboxylate (48)



48

Yield 0.31 g (64%)

dr 85:15

IR (Neat) (cm^{-1}) 2953, 2835, 1734, 1612

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.36 (dd, 1H, *J* = 13.5 Hz, 6.6 Hz), 2.81 (t, 1H, *J* = 10.7 Hz), 3.11 (s, 3H), 3.55-3.66 (m, 3H), 3.65 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.66 (s, 1H), 6.84-6.95 (m, 6H), 7.14-7.16 (m, 3H), 7.44 (d, 2H, *J* = 8.3 Hz), 7.52 (d, 2H, *J* = 8.6 Hz)

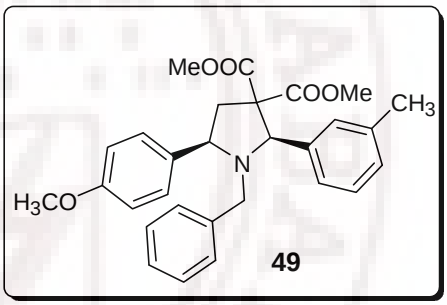
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 42.1, 51.9, 52.0, 52.7, 55.2, 55.3, 63.3, 63.7, 68.9, 113.3, 114.1, 126.9, 127.7, 129.1, 130.1, 130.3, 131.1, 133.7, 134.9, 159.1, 170.0, 172.0

LCMS m/z 490 (M+1)

Analysis Calculated for $C_{29}H_{31}NO_6$: C, 71.15%; H, 6.38%; N, 2.86%; O, 19.61%

Found :C, 71.30%; H, 6.47%; N, 2.80%; O, 19.43%

2.4.4.4 Dimethyl-1-benzyl-5-(4-methoxyphenyl)-2-(3-methylphenyl)-3,3-pyrrolidine dicarboxylate (49)



49

Yield 0.35 g (74%)

dr 83:17

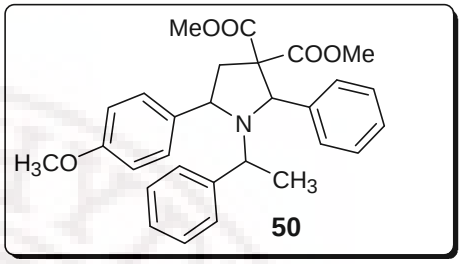
IR (Neat) (cm^{-1}) 3034, 2920, 2840, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.26 (s, 3H), 2.23-2.28 (m, 1H), 2.74 (dd, 1H, *J* = 10.7 Hz, *J* = 2.4 Hz), 2.95 (s, 3H), 3.42-3.53 (m, 2H), 3.55 (s, 3H), 3.66 (d, 1H, *J* = 2.9 Hz), 3.71 (s, 3H), 4.59 (s, 1H), 6.79-6.81 (m, 2H), 6.85 (d, 2H, *J* = 8.5 Hz), 6.93 (d, 1H, *J* = 7.3 Hz), 7.04-7.11 (m, 4H), 7.19 (s, 1H), 7.24 (d, 1H, *J* = 7.3 Hz), 7.43 (d, 2H, *J* = 8.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 21.5, 42.2, 51.8, 52.0, 52.6, 55.2, 63.3, 63.7, 69.4, 114.0, 126.2, 126.8, 127.6, 127.7, 128.2, 129.1, 129.6, 130.2, 133.6, 134.9, 137.2, 139.1, 159.0, 169.8, 172.0

LCMS m/z 474 (M+1)

2.4.4.5 Dimethyl-5-(4-methoxyphenyl)-2-phenyl-1-(1-phenylethyl)-3,3-pyrrolidine dicarboxylate (50)



50

Yield 0.25 g (53%)

dr 99:1

IR (Neat) (cm^{-1}) 2953, 2835, 1734, 1510, 1456

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : For the diastereomeric mixture: 1.02 (d, 3H, *J* = 7.1 Hz), 1.16 (d, 3H, *J* = 7.1 Hz), 2.33-2.40 (m, 2H), 2.77-2.84 (m, 2H), 3.03 (s, 3H), 3.04 (s, 3H), 3.59 (s, 3H), 3.72 (s, 3H), 3.73-3.77 (m, 2H), 3.83 (s, 6H), 3.94 (t, 2H, *J* = 6.8 Hz) 4.94 (s, 1H), 4.97 (s, 1H), 6.91-7.27 (m, 20H), 7.40-7.54 (m, 8H) **(Spectrum No. 19)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) : For the diastereomeric mixture: 16.2, 20.5, 42.3, 42.6, 51.8, 51.9, 52.8, 52.9, 55.3, 56.8, 58.8, 62.3, 63.7, 64.1, 65.1, 67.1, 68.1, 113.8, 114.0, 126.7, 126.8, 127.1, 127.3, 127.4, 127.5, 127.6, 127.7, 128.4, 128.5, 128.8, 129.1, 134.8, 135.3, 140.1, 140.7, 141.1, 143.3, 159.0, 159.1, 168.8, 169.5, 171.7 **(Spectrum No. 20)**

LCMS m/z 474 (M+1)

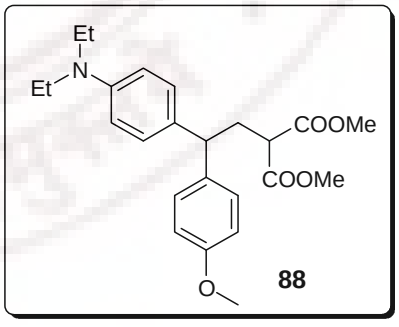
Analysis Calculated for $C_{29}H_{31}NO_5$: C, 73.55%; H, 6.60%; N, 2.96%; O, 16.89%

Found :C, 73.61%; H, 6.57%; N, 3.06%; O, 17.39%

2.4.5 General procedure for the reaction of *N,N*-dialkylaniline with cyclopropyl diester in the presence of $TiCl_4$

To a stirred solution of cyclopropyl diester (0.26 g, 1 mmol) and *N,N*-dialkylaniline (1.5 mmol) in 10 mL of dry CH_2Cl_2 at 0 ^oC under nitrogen atmosphere, a 1:1 solution of $TiCl_4$ in CH_2Cl_2 (2 mmol) was added slowly through syringe. Immediately after the addition of $TiCl_4$, the reaction mixture turned dark red in colour. The solution was slowly warmed to room temperature and stirred at the same temperature for 6 h. The reaction mixture was quenched with saturated potassium carbonate solution and was extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was washed with washed with water (2 x 10 mL), brine (1 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230-400 mesh) using hexanes/ethyl acetate (98/2) as eluent.

2.4.5.1 Dimethyl-2-[2-(4-diethylaminophenyl)-2-(4-methoxyphenyl)ethyl]malonate (88)



88

Yield 0.35 g (84%)

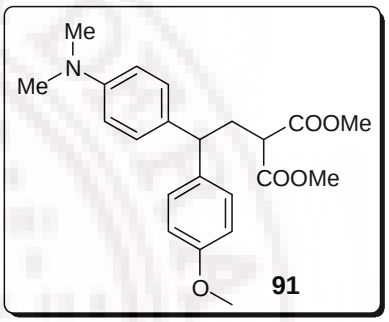
IR (Neat) (cm^{-1}) 3061, 1738, 1608, 1500

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.13 (t, 6H, *J* = 7.1 Hz), 2.59 (t, 2H, *J* = 7.8 Hz), 3.27-3.30 (m, 5H), 3.70 (s, 6H), 3.77 (s, 3H), 3.77-3.78 (m, 1H), 6.60 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 7.03 (d, 2H, *J* = 8.6 Hz), 7.14 (d, 2H, *J* = 8.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 12.7, 35.1, 44.4, 46.9, 50.2, 52.5, 55.3, 112.0, 113.9, 128.6, 128.8, 130.4, 136.6, 146.5, 158.1, 170.0

LCMS m/z 414 (M+1)

2.4.5.2 Dimethyl-2-[2-(4-dimethylaminophenyl)-2-(4-methoxyphenyl)ethyl]malonate (91)



Yield 0.28 g (74%)

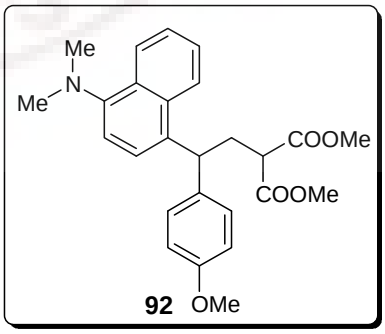
IR (Neat) (cm^{-1}) 3462, 2957, 2058, 1734, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.49 (t, 2H, *J* = 7.6 Hz), 2.75 (s, 6H), 3.20 (t, 1H, *J* = 7.3 Hz), 3.56 (s, 6H), 3.60 (s, 3H), 3.70 (t, 1H, *J* = 7.9 Hz), 6.55 (d, 2H, *J* = 8.8 Hz), 6.69 (d, 2H, *J* = 8.8 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz) **(Spectrum No. 21)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 34.8, 40.5, 46.8, 50.0, 52.3, 55.0, 112.7, 113.8, 128.2, 128.6, 131.4, 136.2, 149.2, 157.9, 169.7 **(Spectrum No. 22)**

LCMS m/z 386 (M+1)

2.4.5.3 Dimethyl-2-[2-(4-dimethylamino-1-napthyl)-2-(4-methoxyphenyl)ethyl] malonate (92)



Yield 0.33 g (76%)

IR (Neat) (cm^{-1}) 2951, 2833, 1732, 1583

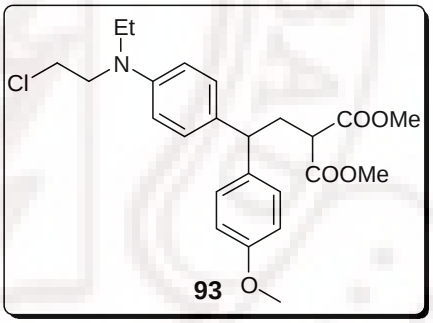
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.60-2.67 (m,

2H), 2.72 (s, 6H), 3.34 (t, 1H, *J* = 7.5 Hz), 3.51 (s, 3H), 3.57 (s, 3H), 3.60 (s, 3H), 4.58 (t, 1H, *J* = 7.6 Hz), 6.68 (d, 2H, *J* = 8.3 Hz), 6.92 (d, 1H, *J* = 7.8 Hz), 7.09 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 7.30-7.32 (m, 2H), 7.97-8.0 (m, 1H), 8.14-8.17 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 35.0, 42.7, 45.2, 50.0, 52.4, 55.0, 113.5, 113.9, 123.9, 124.0, 124.7, 124.8, 125.9, 129.1, 129.3, 132.9, 133.6, 135.4, 149.9, 158.1, 169.8

LCMS m/z 436 (M+1)

2.4.5.4 Dimethyl-2-[2-{4[2-chloroethyl(ethyl)amino]phenyl}-2-(4-methoxyphenyl) ethyl]malonate (93)



93

Yield 0.37 g (82%)

IR (Neat) (cm^{-1}) 2955, 2837, 1732, 1612

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.03 (t, 3H, *J* = 7 Hz), 2.50 (t, 2H, *J* = 7.6 Hz), 3.19-3.28 (m, 3H), 3.46 (s, 4H), 3.59 (s, 6H), 3.64 (s, 3H), 3.69 (t, 1H, *J* = 8.1 Hz), 6.50 (d, 2H, *J* = 8.3 Hz), 6.72 (d, 2H, *J* = 8.5 Hz), 6.97 (d, 2H, *J* = 8.5 Hz), 7.04 (d, 2H, *J* = 8.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm).12.6, 35.0, 40.6, 45.4, 46.9, 50.2, 52.4, 52.5, 55.2, 112.0, 113.9, 128.7, 128.8, 131.6, 136.2, 145.6, 158.1, 169.9

LCMS m/z 447 (M^+)

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Part II

Efforts Toward the Synthesis of Chiral Oligomeric Amines, Amides and Investigations on the Hydroboration Reaction Using Chiral 1,1'-Binaphthyl-2,2'-Diamine-Borane complexes

Chapter 3

Efforts Toward the Synthesis of Chiral Oligomeric Amines and Amides

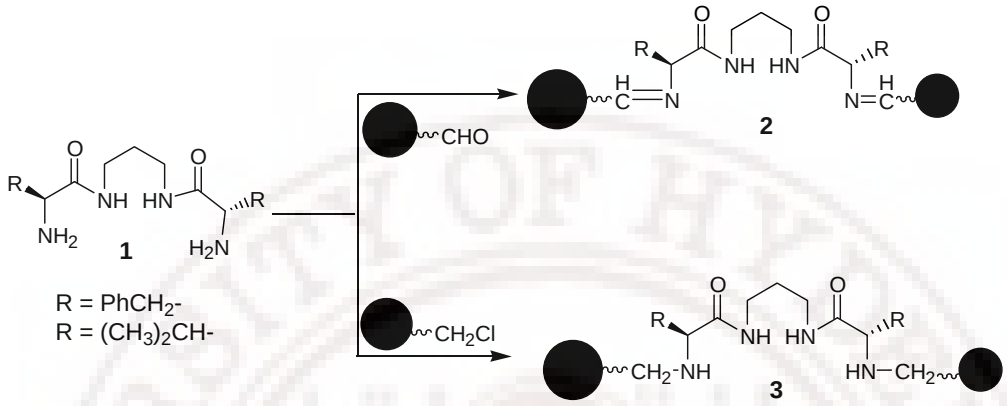
3. 1 Introduction

3.1.1 Chiral macrocycles and polymeric amines

Chiral macrocycles attracted considerable attention since the initial studies by Pederson on the synthesis and molecular recognition studies of cyclic ethers.[1] Macrocycles have found applications in diverse areas like medicinal[2], analytical[3,4] and supramolecular chemistry.[5] In recent years, the chiral polymeric amines and their derivatives were also reported to have several material science applications.[6] Composite materials prepared using dielectric materials and certain chiral polymers were reported to enhance microwave absorption properties.[7a-e] Though, the theory behind such properties of chiral composite materials is not clearly understood,[7f] it was of interest to synthesize chiral amides and amine derivatives for such studies. A brief review of the literature on the synthesis of chiral polymeric amides and amines will facilitate the discussion.

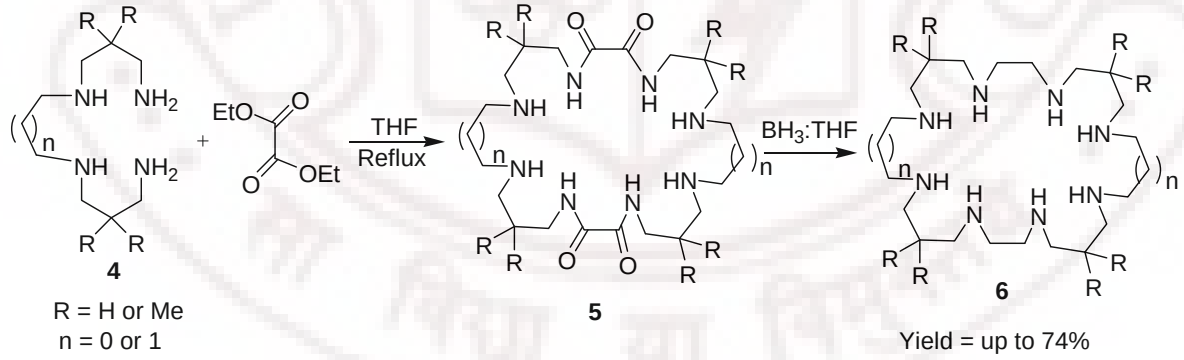
Burguete *et al.*[8] synthesized polymeric amine embedded with polymer chain **2** and **3** by coupling the polyamine **1** with polystyrene having halogen or aldehyde end group (Scheme **1**). Such polymers having polyamine moieties bind with copper ions.

Scheme 1



Guilard *et al.*[9] synthesized cyclic polyamide **5** by the condensation reaction of the amine **4** with diethyl oxalate (Scheme **2**). The polyamide on reduction with BH_3:THF gave the corresponding amine **6**. Such macrocyclic amines form stable complexes with transition metals as well as with lanthanides and actinides.

Scheme 2



The open chain chiral oligomeric amines **7** and **8** prepared from 1,2-diaminocyclohexane were used as DNA binding agents (Figure **1**).[10] Similar derivatives were reported to stabilize DNA duplex in very low concentrations.[11] The polymeric amine conjugates with cytotoxic drugs are useful in treating certain tumor cells.[12]

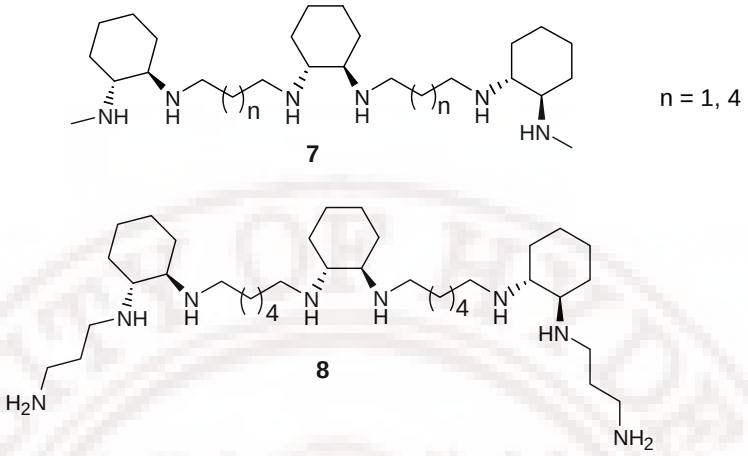
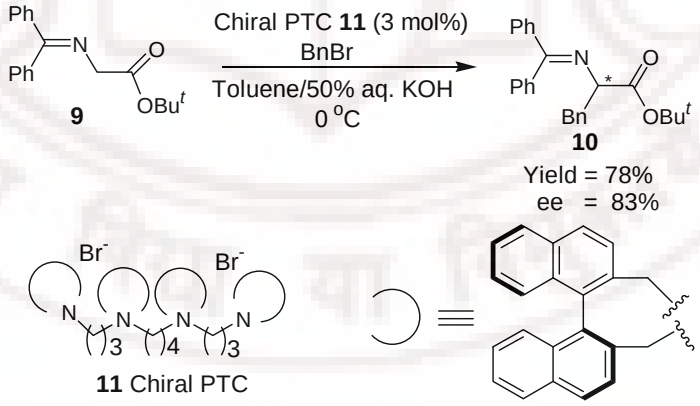


Figure 1

Maruoka *et al.*[13] reported the preparation of polymeric amine-based chiral phase-transfer catalysts **11**, through the reaction of polymeric amines with dibromides. The catalyst **11** has been employed in the enantioselective synthesis of phenylalanine derivatives. The benzylated product **10** was obtained up to 83% ee (Scheme **3**).

Scheme 3



In recent years, several non-symmetrically substituted binaphthyl derivatives were prepared and found to be useful in various asymmetric transformation reactions.[14] The

optically active BINOL was used to build a class of chiral conjugated polymers for material science applications.[15]

Liu *et al.*[16] reported the oligomeric amine coupled β-cyclodextrine moieties **12** and **13** which act as hosts for selective binding to some steroid molecules. The aminated bridged bis-β-CD's exhibit enhanced molecular binding abilities through the cooperative electrostatic and van der Waals interaction (Figure **2**).

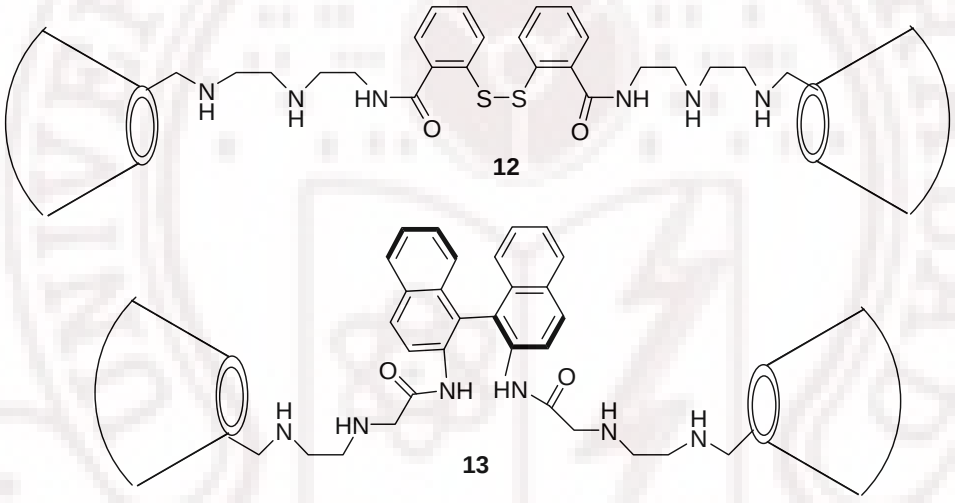
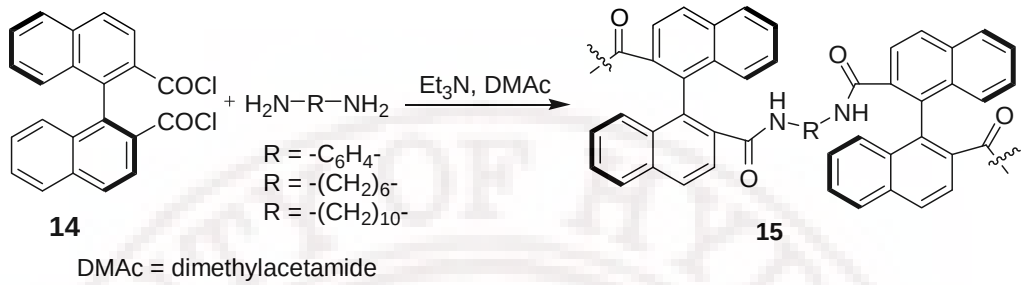


Figure 2

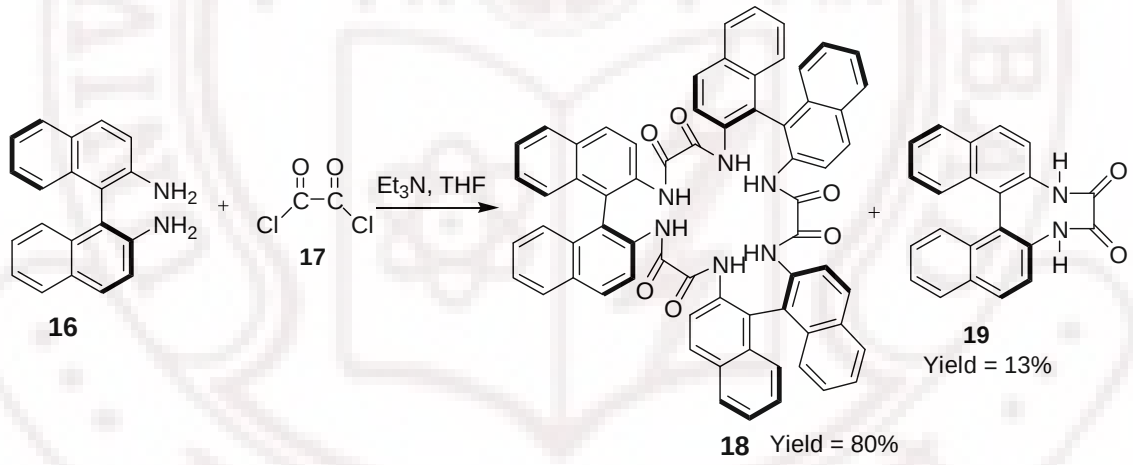
Miyano and co-workers reported the preparation of binaphthyl-based polyamides **15** by the condensation of diacid chloride **14** with diamines.[17] The polymers **15** obtained were soluble in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide (DMAc), and DMSO, but insoluble in THF, chloroform, and other common nonpolar solvents. The molecular weights of polymers obtained were in the range of 20,000-27,000. Formation of cyclic oligomers was observed in polymerization with aliphatic diamines (Scheme **4**).

Scheme 4



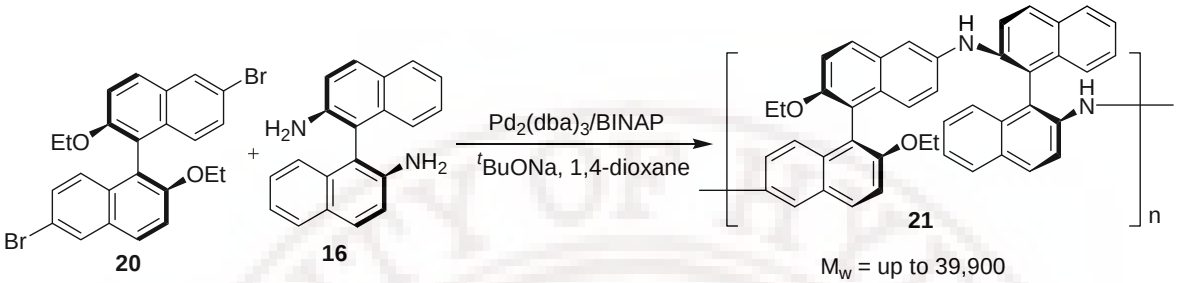
The reaction of chiral 1,1′-binaphthyl-2,2′-diamine **16** with oxallyl chloride **17** gave the [3+3] coupled adduct **18** as major product along with [1+1] adduct **19** as minor product (Scheme **5**).[18]

Scheme 5



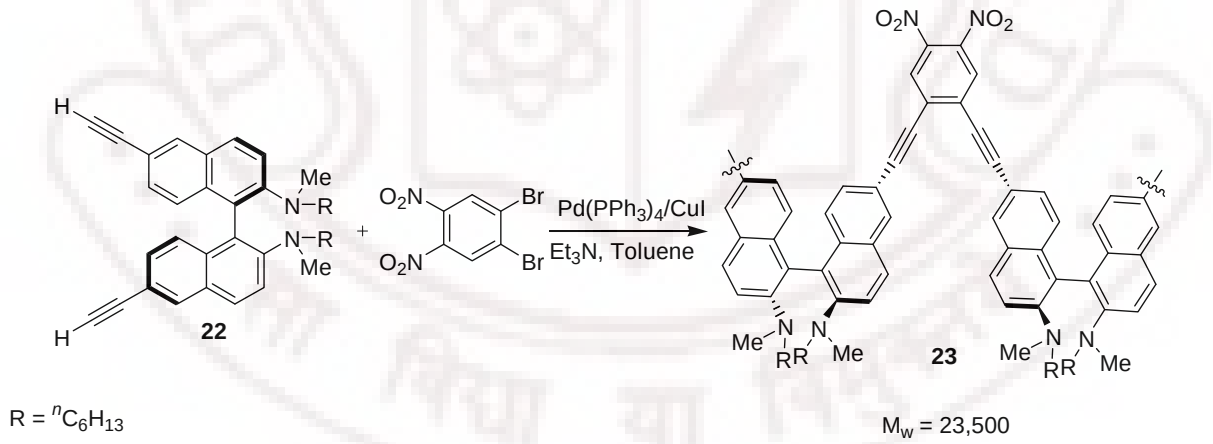
The chiral BINAM derived conjugated polymers were prepared by the palladium mediated coupling reaction of diamine with dibromides. Kobayashi *et al.*[19] reported the palladium catalyzed condensation of (*R*)-2,2′-diethoxy-6,6′-dibromo-1,1′-binaphthyl **20** with (*R*)-1,1′-binaphthyl-2,2′-diamine **16.** The high molecular weight helical polymeric amines **21** were obtained in good yields (Scheme **6**).

Scheme 6



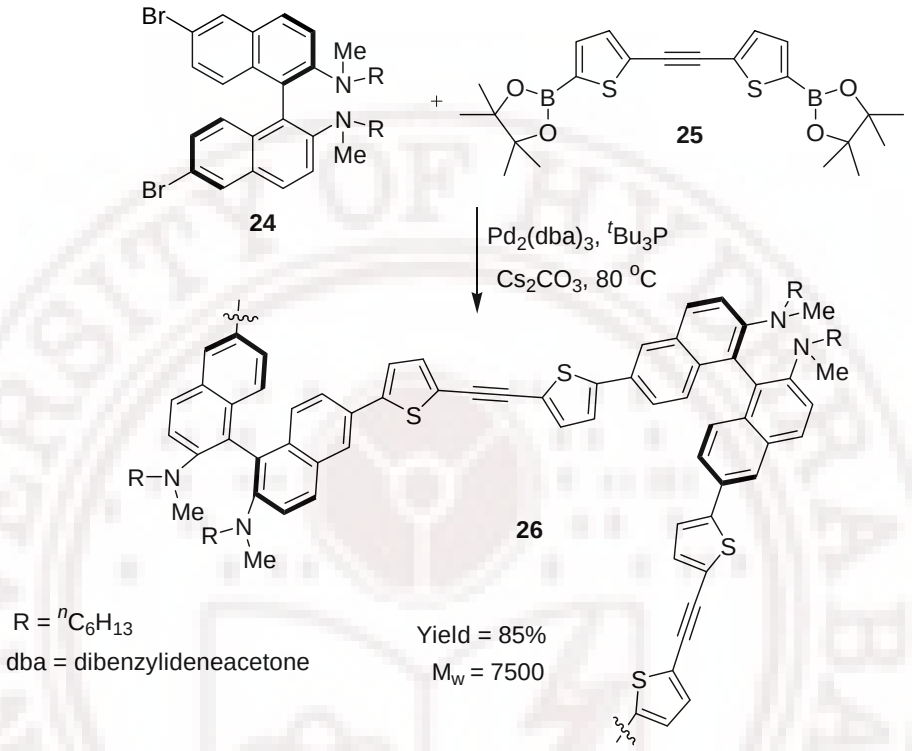
Pu *et al.*[20] reported the synthesis of propeller like polymers **23** by the transition metal catalyzed cross coupling reaction of aryl halides with terminal alkynes or alkenes. The polymer **23** obtained from chiral 1,1′-binaphthyl-2,2′-diamine has been reported to show significantly different UV and CD features compared to their BINOL counterpart (Scheme **7**).

Scheme 7



Pu *et al.*[21] also reported the synthesis of chromophore embedded chiral polymers by Suzuki coupling of the chiral diamine **24** with diboronic ester **25** to obtain the chiral conjugated polymer **26** in 85% yield (Scheme **8**).

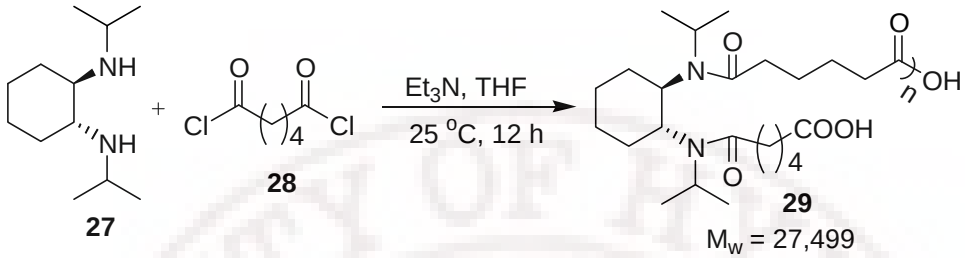
Scheme 8



3.1.2 Previous work from this laboratory

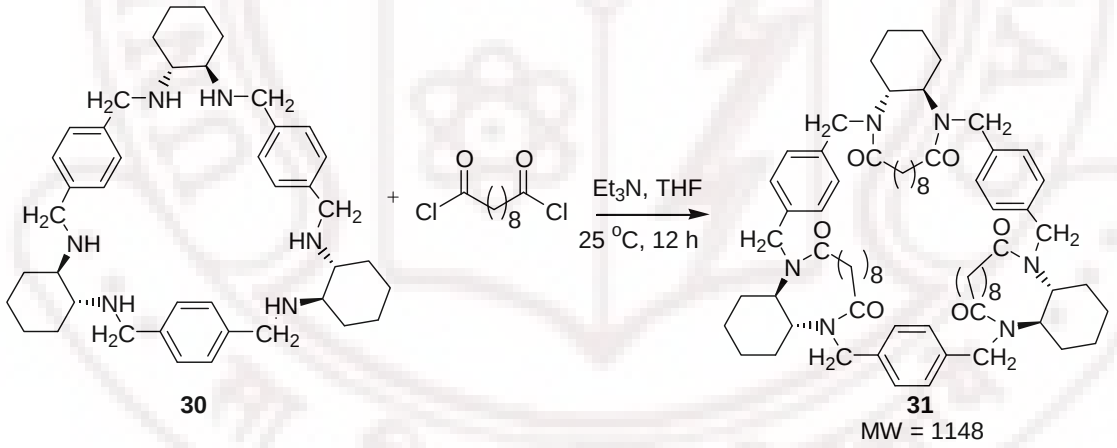
Previously, efforts were undertaken in this laboratory towards the synthesis of macrocycles and polymers based on chiral 1,2-diaminocyclohexane. It was found that the reaction of *N,N′*-diisopropylcyclohexyldiamine **27** with adipoyl chloride **28** gave the corresponding polymeric amide **29** with carboxylic acid end group. The molecular weight of the polymer obtained was found to be 27,499 by GPC analysis (Scheme **9**).[22]

Scheme 9



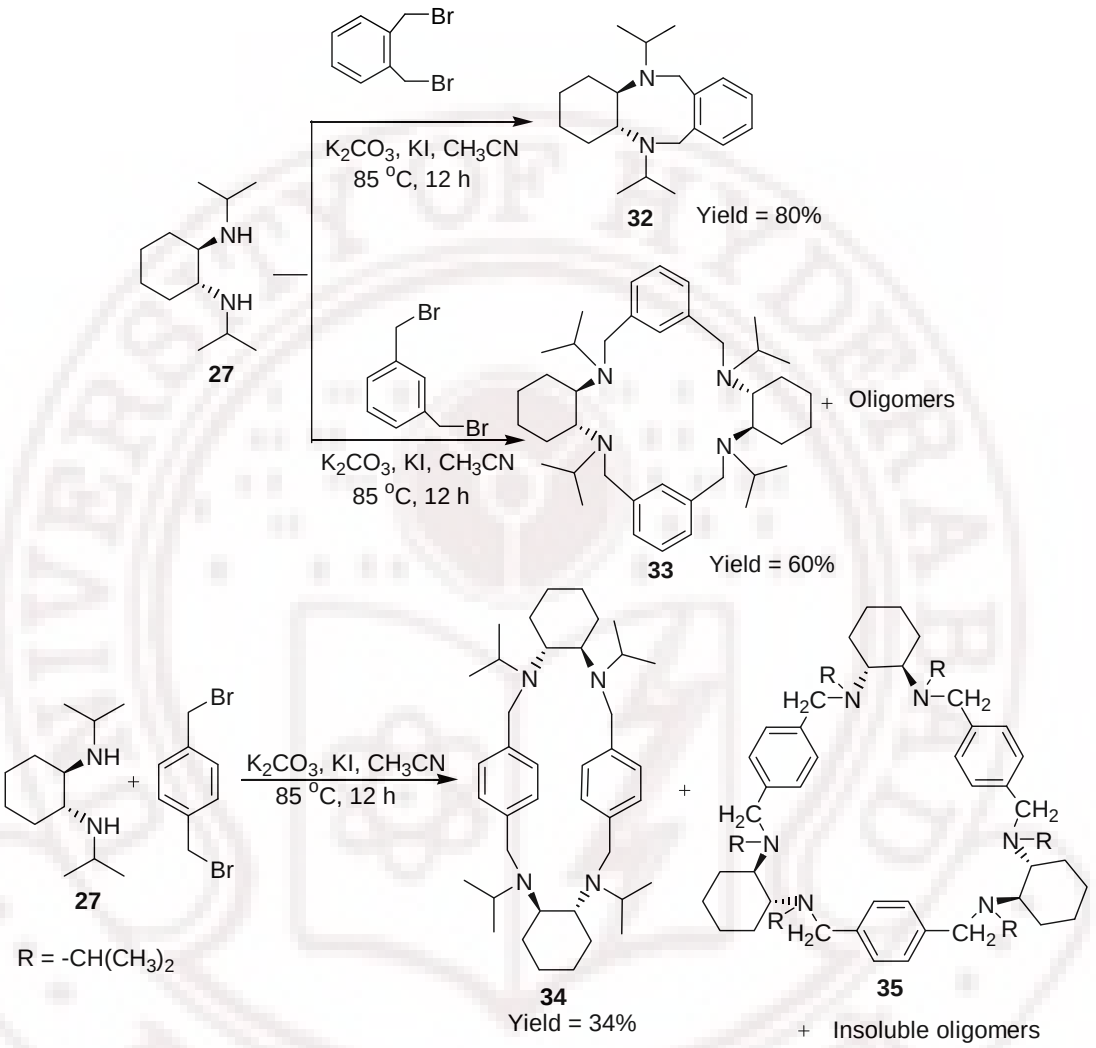
The reaction of macrocyclic amine **30** with sebacoyl chloride gave the soluble polymeric amides. The MALDI-TOF (Matrix Assisted Laser Desorption and Ionisation-Time of Flight) mass spec analysis of the product revealed the formation of a mixture of oligomers along with the [3+3] condensation product **31** (Scheme **10**).[23]

Scheme 10



The reaction of *N,N′*-diisopropylcyclohexyldiamine **27** with *ortho, meta* and *para*-xylyl bromides gave the corresponding macrocycles **32-35** (Chart **1**).[22]

Chart 1



The reaction of *o*-xylyl bromide with diamine **27** gave the [1+1] condensation product **32**. The reaction of *m*-xylyl bromide with diamine **27** gave the [2+2] product **33** along with oligomers. The reaction of *p*-xylyl bromide with diamine **27** gave both [2+2] **34** and [3+3] **35** products along with some insoluble oligomers.

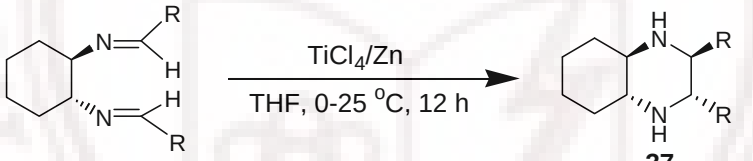
We have initiated studies on the synthesis of polymeric derivatives using chiral 1,1′-binaphthyl-2,2′-diamine. The results are discussed in the next section.

3.2 Results and Discussion

3.2.1 Efforts toward the synthesis of oligomeric amines from BINAM *via* imine derivatives

It has been reported from this laboratory that the reaction of low-valent titanium species prepared using the $TiCl_4$/Zn reagent system with chiral diimines **36** derived from (1*R*,2*R*)-1,2-diaminocyclohexane, gave the intramolecular coupled product **37** in good yields (Scheme **11**).[24]

Scheme 11



(1*R*,2*R*)-**36**

37

75-86%

R = C_6H_5, *o*-$OMeC_6H_4$, *o*-MeC_6H_4, *o*-OHC_6H_4, *o*-ClC_6H_4, -naphthyl

In the atropisomeric 1,1′-binaphthyl-2,2′-diamine derived ligand, the dihedral angle of the napthyl rings are expected to be 90° to each other (Figure **3**).[25]

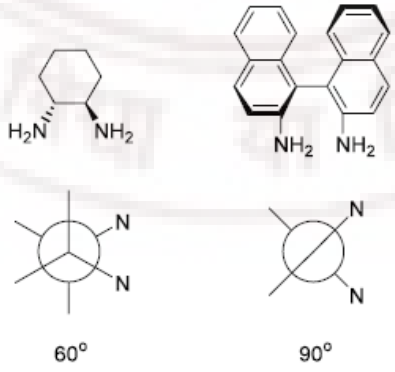
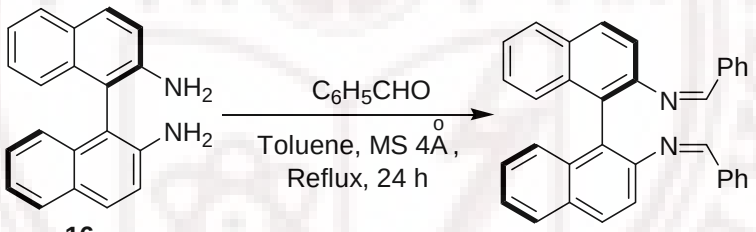


Figure 3

Hence, the low valent titanium mediated reductive coupling of the diimines derived from 1,1'-binaphthyl-2,2'-diamine may lead to the intermolecular coupling of the diimines resulting in the formation of the polymeric amines.

The (*R*)-(+)-*N*,*N*′-dibenzylidene-1,1′-binaphthyl-2,2′-diamine **38** was readily obtained by the condensation reaction of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine **16** and benzaldehyde in presence of molecular sieves (4Å) in refluxing toluene for 24 h (Scheme **12**).[26]

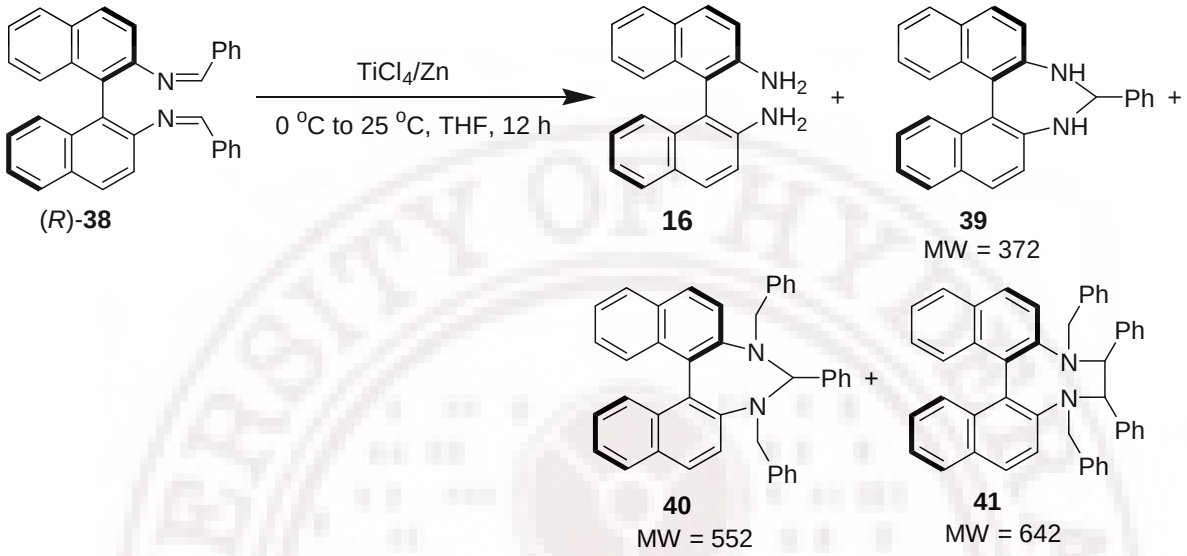
Scheme 12



16 **38**
Yield 82%

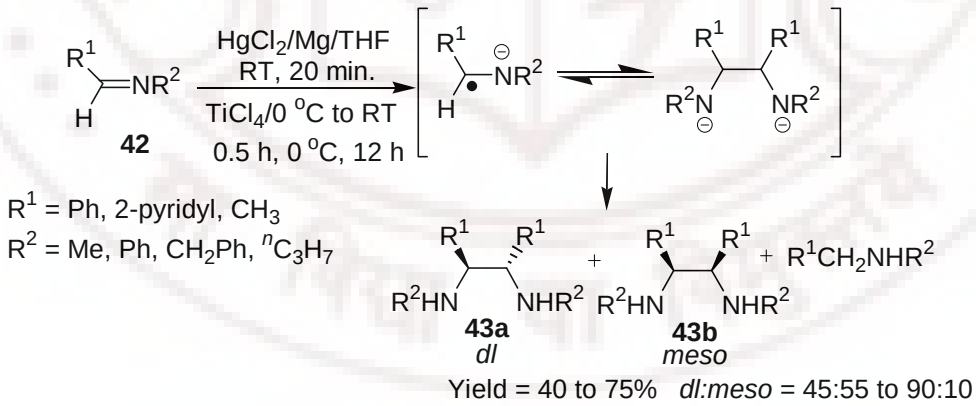
The reductive coupling of dibenzylidene-1,1′-binaphthyl-2,2′-diamine **38** was examined by the low valent titanium species prepared *in situ* from $TiCl_4$/Zn reagent system in THF solvent (Scheme **13**). The product mixture was found to contain the intramolecular coupled products **39-41** and the oligomeric and polymeric products are not formed (MALDI-TOF mass spectral analysis). The formation products **39-41** in the reductive coupling BINAM diimine **38** suggest that the reaction may go through intramolecular pathway (Scheme **13**).

Scheme 13



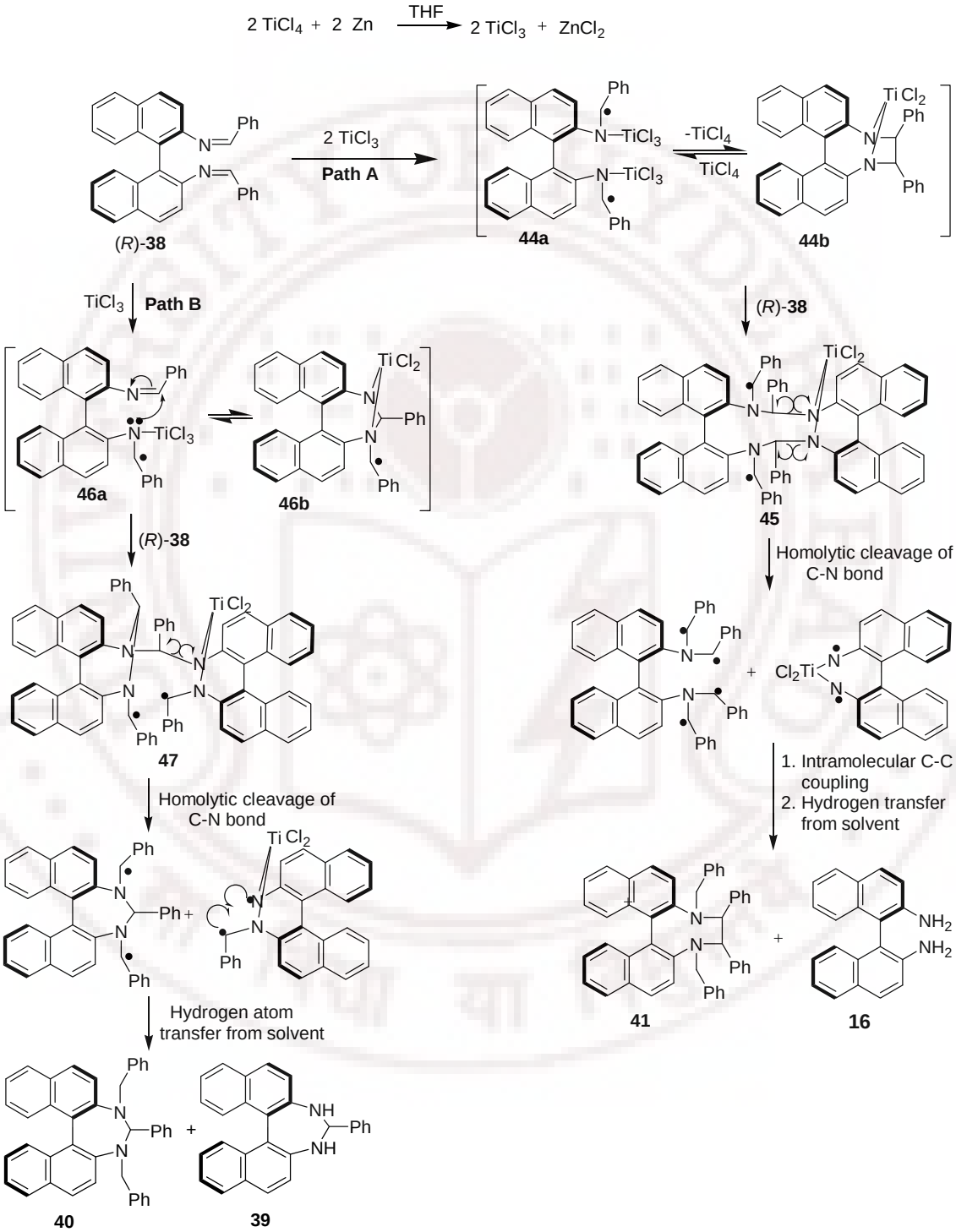
The reaction of $TiCl_4$ and Zn result in the formation of low valent titanium species.[27,28a] It has been reported that the low valent titanium mediated reductive coupling of imine gave the major *dl* -isomer through the radical anion intermediate (Scheme **14**).[28b]

Scheme 14



The formation of the products **39**, **40** and **41** can be rationalized by considering the mechanism outlined in Scheme **15**.

Scheme 15

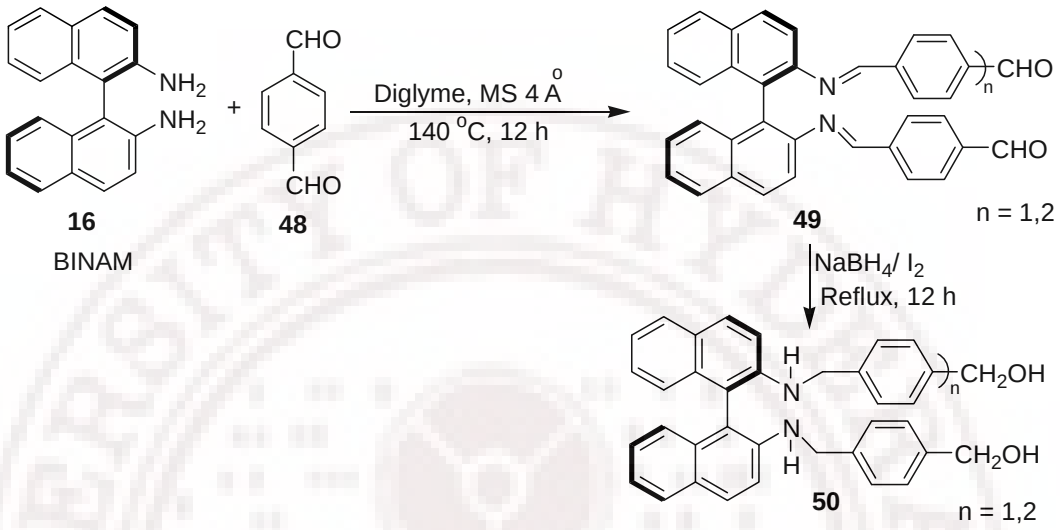

2 TiCl4 + 2 Zn
THF
2 TiCl3 + ZnCl2
(R)-38
2 TiCl3
Path A
44a
-TiCl4
TiCl4
44b
TiCl3
Path B
(R)-38
46a
46b
45
(R)-38
47
Homolytic cleavage of C-N bond
Homolytic cleavage of C-N bond
1. Intramolecular C-C coupling
2. Hydrogen transfer from solvent
Hydrogen atom transfer from solvent
41
16
40
39

The low valent titanium mediated reductive coupling of imines may involve $TiCl_3$ species leading to the radical intermediate **44a** (Scheme **15**).[29] The addition of intermediate **44** on to the imine **38** may result in the formation of intermediate **45**. The homolytic cleavage followed by the facile proton or hydrogen atom transfer from the THF solvent could quench the intermediate **45** (Path A, Scheme **15**). The intramolecular coupling of imine may lead to the intermediate **46** (Path B, Scheme **14**). Addition of intermediate **46** on to the imine **38** followed by homolytic cleavage and hydrogen atom abstraction from the solvent could give the products **39** and **40**. It is of interest to note that the low valent titanium mediated reductive coupling of imines gave the corresponding imidazolidines in 74% yield by the transfer of CH_3CH- group from the THF solvent.[30]

We have then turned our attention towards the use of Schiff base[31] derivatives of the BINAM **16** in the synthesis of polymeric/oligomeric derivatives. The Schiff base is readily prepared by the condensation reaction of 1,1′-binaphthyl-2,2′-diamine **16** and terephthalaldehyde **48** in CH_2Cl_2 solvent at 25 ^oC. The LCMS analysis of the imine product showed the formation of only low molecular weight condensation products.

To obtain high molecular weight imines, the reaction was carried out at elevated temperature in diglyme solvent in presence of molecular sieves (4Å). The imine **49** thus obtained was reduced to the corresponding amines **50** with $NaBH_4/I_2$ reagent system (Scheme **16**).

Scheme 16



The LCMS analysis of the mixture of products indicated the formation of [1+1] and [2+2] products **51**-**61** (Chart **2)**.

Chart 2

Monomeric and dimeric imines

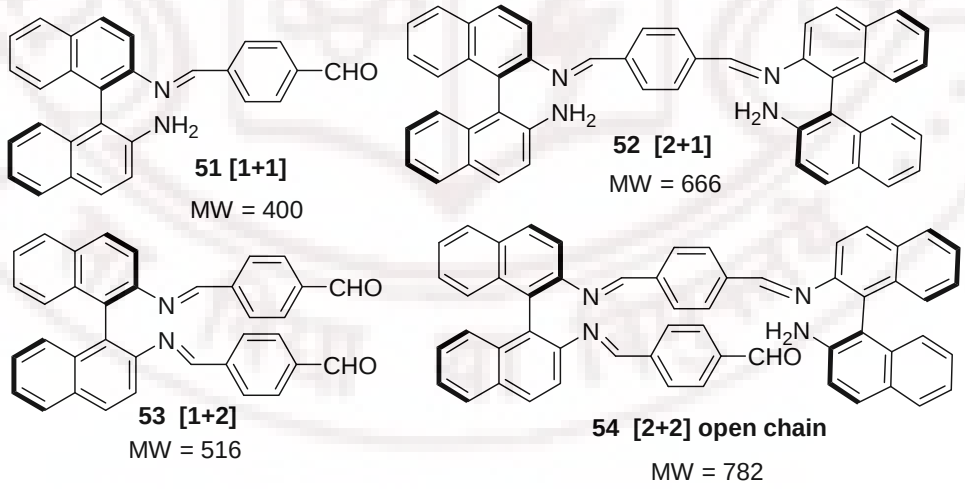
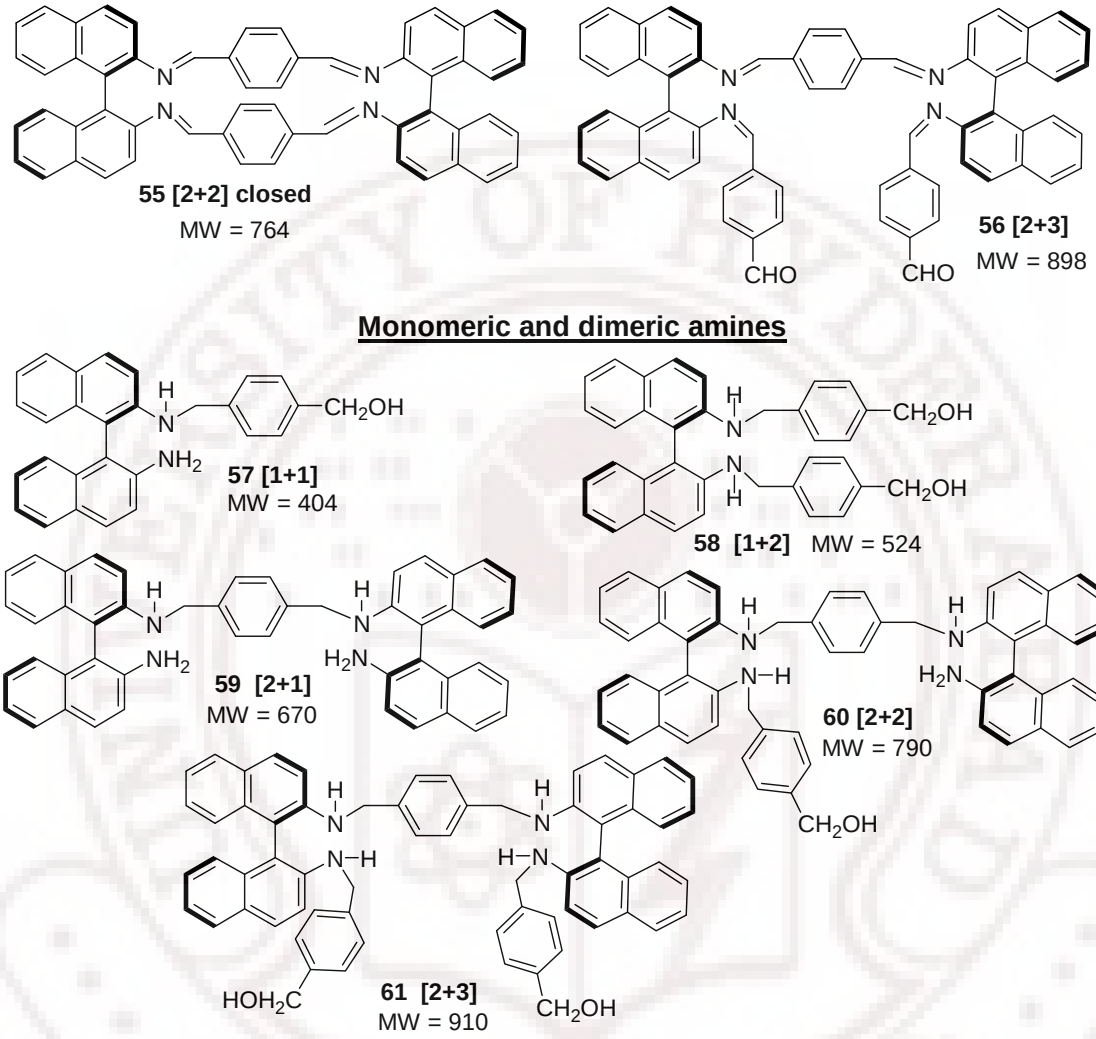
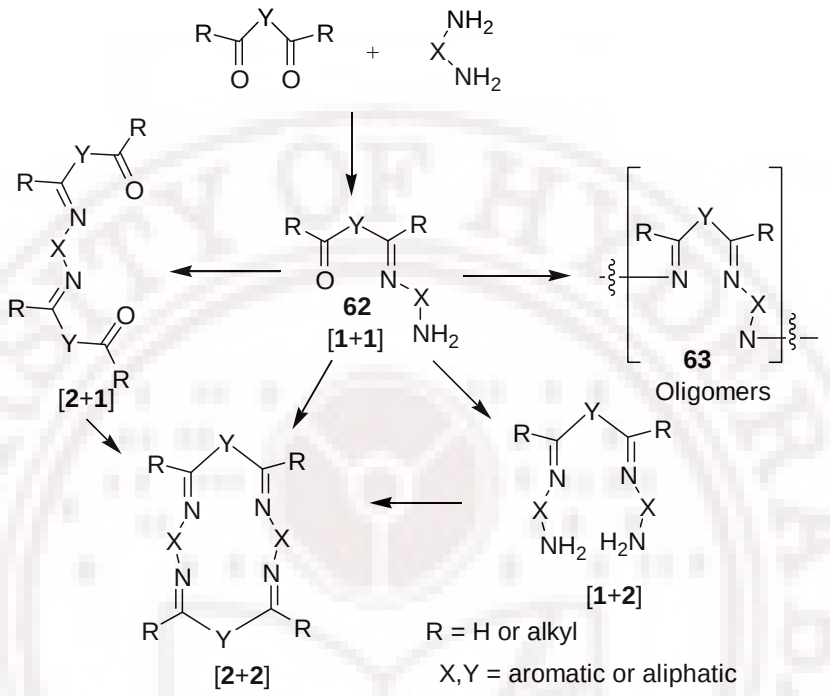


Chart 2 continued...



The condensation products obtained in the reaction of BINAM with dialdehyde were in accordance with the previous reports that the reaction of dicarbonyl compounds with diamines can produce a spectrum of products ranging from [1+1] adduct **62** to linear oligomer **63** (Scheme **17**).[32]

Scheme 17

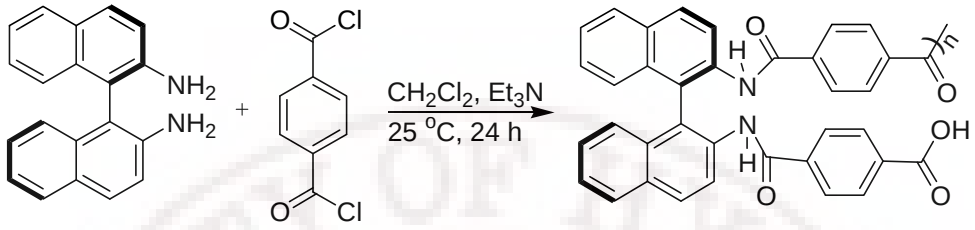


The formation of lower molecular weight products **51**-**61** in the condensation reaction between diamine **16** and terephthalaldehyde **48** may be due to the poor nucleophilicity of the aromatic amine nitrogen of **16** in the nucleophilic addition reaction.

3.2.2 Efforts toward the synthesis of chiral oligomers *via* amide derivatives

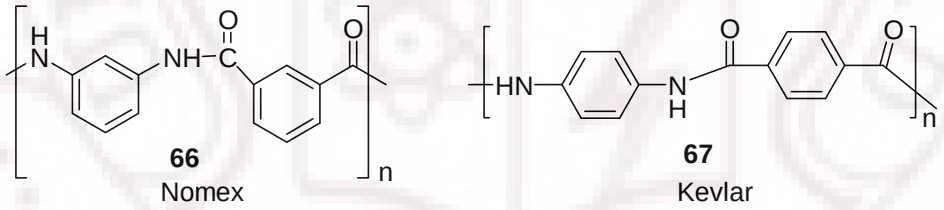
We have then examined the condensation polymerization of the diamine with aromatic diacid chloride. Initially, the reaction of terephthaloyl chloride **64** with BINAM **16** in CH_2Cl_2 solvent was examined at 25 ^oC (Scheme **18**).

Scheme 18



16 **64** **65**

The amide **65** thus obtained was sparingly soluble in common organic solvents. Hence, it was difficult to convert these amides to the corresponding amines by conventional reduction methods. Earlier, it was reported that the aryl amide polymers give exceptional heat, solvent resistance and have very high melting point.[33] Nomex **66** and Kevlar **67** are the examples of the aryl amide polymers having potential applications in industry (Figure **4**).



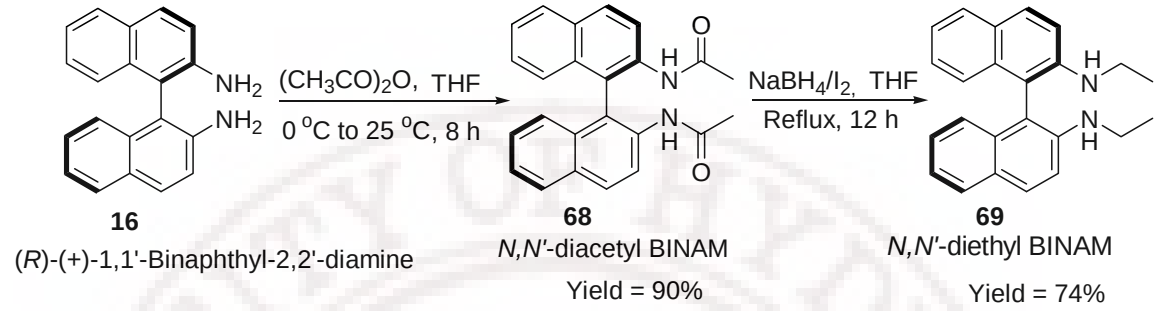
66
Nomex

67
Kevlar

Figure 4

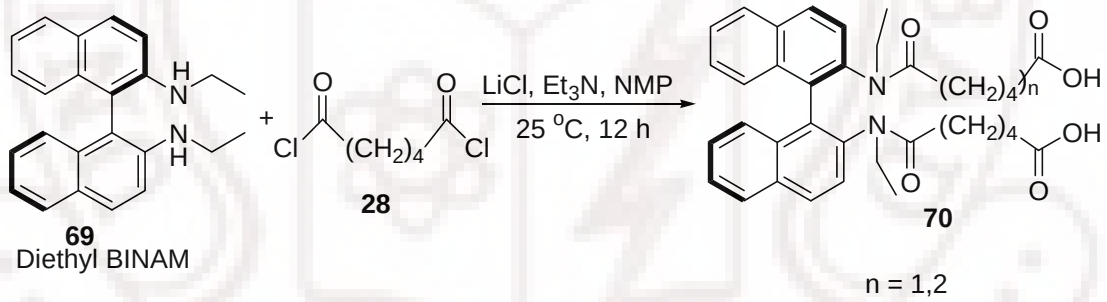
To obtain soluble polymeric amides, aliphatic diacid chlorides may have to be used. It was reported that the presence of alkyl or aryl substituent on the nitrogen atom and the presence of flexible alkyl chain between the rigid aromatic moieties can increase the solubility of polymeric amides in common organic solvents.[34] Accordingly, *N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine **69** was prepared by the diacetylation followed by the $NaBH_4/I_2$ mediated reduction (Scheme **19**).

Scheme 19



The amide **70** was prepared by the reaction of *N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine **69**, adipoyl chloride **28** and triethylamine in *N*-methylpyrrolidone (NMP) as solvent (Scheme **20**).

Scheme 20



Previous reports indicate that the use of highly polar solvents such as NMP, dimethylacetamide, tetramethylurea prevents the premature precipitation of the growing polymer chains.[33] The presence of salts like LiCl or $CaCl_2$ in the reaction medium increases the solubility of the growing polymer chain by coordinating with the amide carbonyl group of the growing polymer chain and thus reduces the hydrogen bonding interactions of the amide groups.[35]

The aliphatic spacer groups in the amide **70** decrease the rigidity of the polymer backbone chain. Hence, the amide **70** obtained was soluble in $CHCl_3$, CH_2Cl_2, THF, DMSO and in acetonitrile. The products formed were analyzed by MALDI mass spectral analysis (Figure **5**).

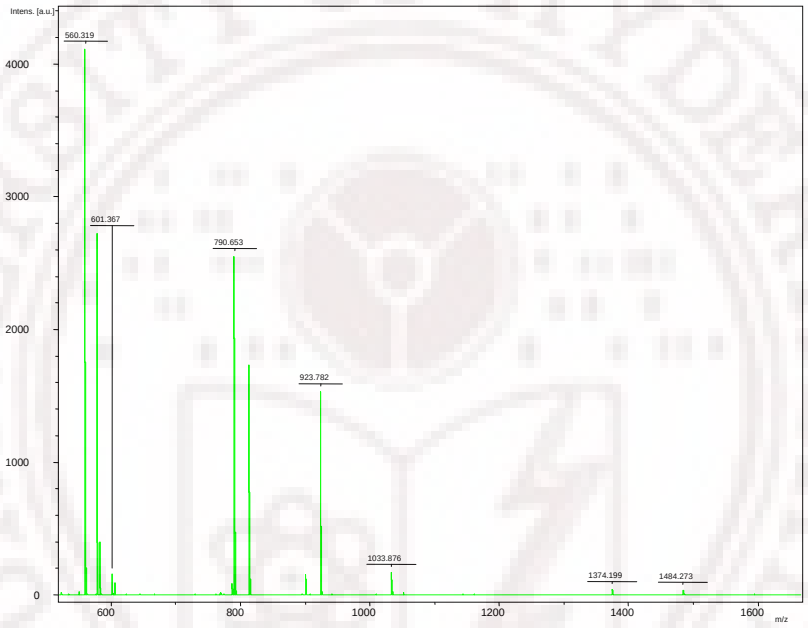
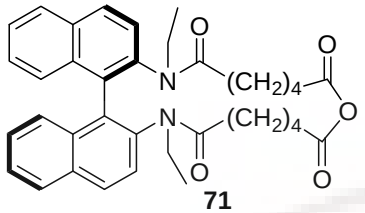
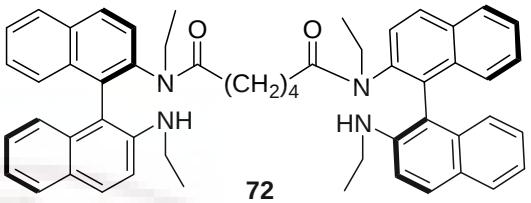


Figure 5 MALDI mass spec. analysis of compound 70

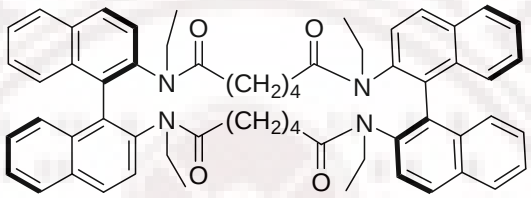
Presumably, the peaks with m/z values 601, 813 and 923 are due to the sodium salts of the compounds **71**, **72** and **73**.[36] The MALDI mass spec analysis indicates the formation of [1+2] **71**, [2+1] **72** and [2+2] **73** adducts (Figure **6**).



71
MW = 578 **[1+2]**



72
MW = 790 **[2+1]**



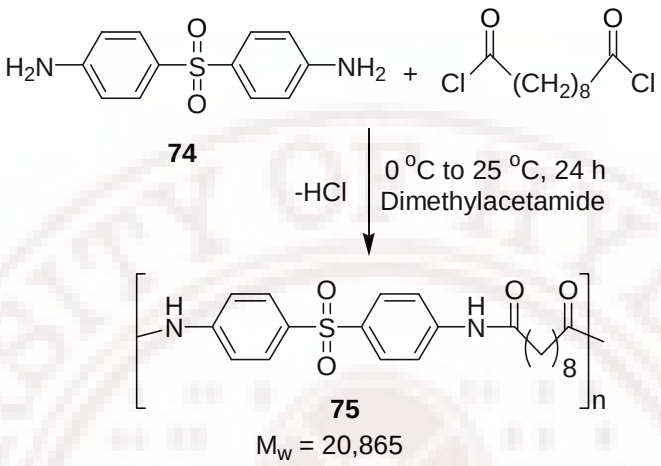
73
MW = 900 **[2+2]**

Figure 6

The condensation polymerization reaction of diisopropylcyclohexyl diamine with adipoyl chloride gave the corresponding polymeric amide with high molecular weight (Scheme **9**).[22] Presumably, the lower nucleophilicity of the aromatic amines compared to their aliphatic counterparts may result in the formation of low molecular weight amides (Scheme **20**).

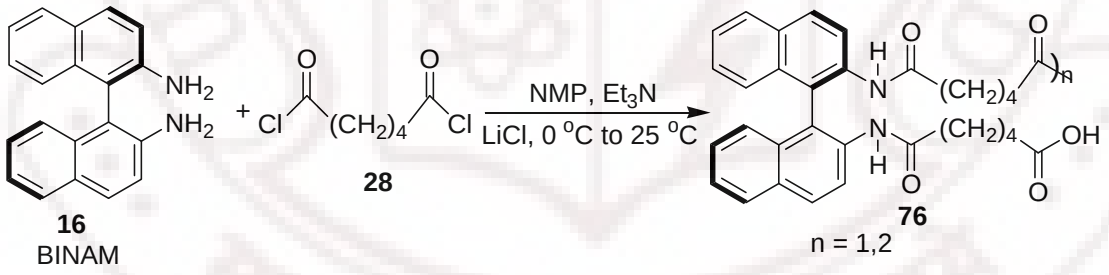
Previously, the aromatic-aliphatic polymeric amide **75** was prepared in good yields by the condensation reaction of aromatic diamines **74** with sebacoyl chloride in dimethylacetamide solvent (Scheme **21**).[37a] The polymeric amides **75** thus obtained were useful in the preparation of polymeric amide-silicate hybrid films.

Scheme 21



Hence, we have turned our attention towards the condensation polymerization reaction of BINAM with adipoyl chloride in NMP solvent (Scheme **22**).

Scheme 22



The [1+1] **77** and [2+2] **78** addition products were formed along with [2+1] adduct **79** (Figure **7**). The amide products thus obtained were in accordance with the literature report.[37b]

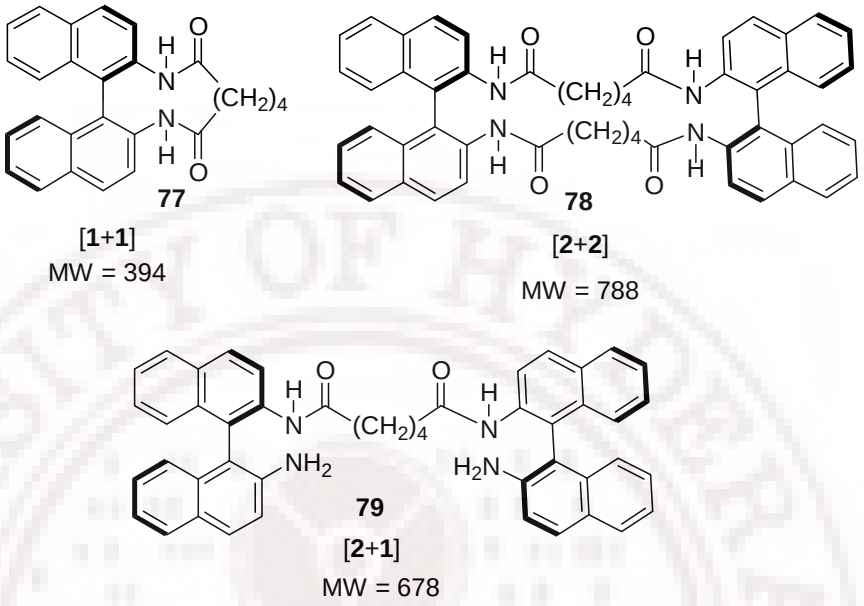
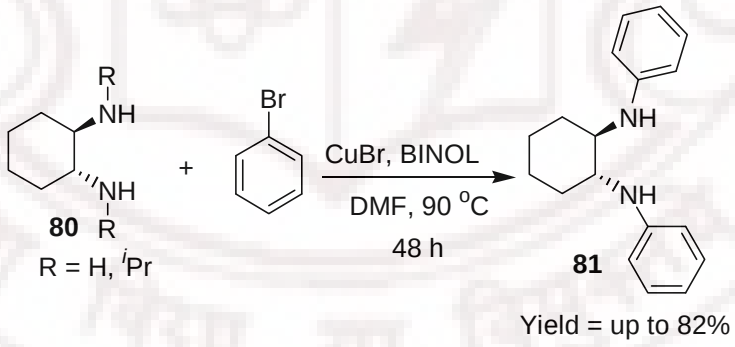


Figure 7

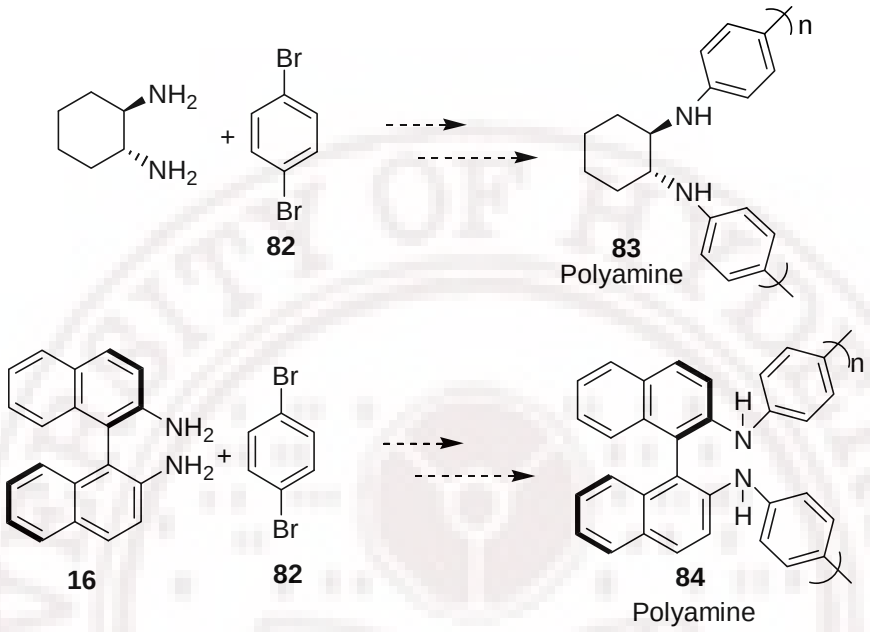
Recently, a method for the *N*-arylation of (1*R*,2*R*)-1,2-diaminocyclohexane **80** was reported from this laboratory (Scheme **23**).[38]

Scheme 23



Application of such copper (I) halide catalyzed coupling reaction of BINAM **16** or cyclohexyldiamine with 1,4-dibromo compound **82** should yield more fruitful results (Scheme **24**).

Scheme 24



Investigations are being undertaken in this direction.

3.3 Conclusions

The reductive coupling of dibenzylidene-1,1′-binaphthyl-2,2′-diamine **38** with $TiCl_4$/Zn reagent system yield intramolecular coupled products. The condensation reaction of BINAM and terephthalaldehyde gave the chiral monomeric and dimeric imines **49**. The imine **49** on $NaBH_4/I_2$ reduction gave the corresponding chiral amine **50** in good yields. The amides prepared by the condensation reaction of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine **16** and terephthaloyl chloride gave sparingly soluble amide product **65**. The soluble chiral monomeric and dimeric amides **70**, **76** were prepared from diethyl BINAM **69** and BINAM **16** using adipoyl chloride spacers.

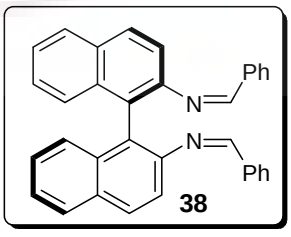
3.4 Experimental Section

3.4.1 General Information

Several informations given in the section **1.4.1** are also applicable for the experiments outlined in this section. The *R*-(+)-1,1′-binaphthyl-2,2′-diamine was purchased from Gerchem Labs (P) Ltd. Hyderabad. Analytical grade *N*-methylpyrrolidinone was purchased from E-Merck and stored over 4Å molecular sieves. Lithium chloride was dried in a vacuum oven at 200 ^{o}C for 24 h.

3.4.2 Procedure for the synthesis of (1*R*)-*N,N*′-dibenzylidene-1,1′-binaphthyl-2,2′-diamine (38)

To a stirred suspension of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (5 mmol, 1.42 g) in 25 mL of toluene, freshly distilled solution of benzaldehyde (12 mmol, 1.27 g, 1.22 mL) and 0.5 g of molecular sieves (4Å) were added under nitrogen atmosphere. The reaction mixture was fitted with Deans-stark apparatus and was refluxed for 24 h. The reaction mixture was brought to room temperature, filtered and the excess toluene was distilled off under reduced pressure. The crude reaction product was washed with hexane (2 x 5 mL) and recrystallized from THF-hexane mixture.



38

Yield 1.88 g (82%)

mp 124-126 ^{o}C (Lit[39] 119-124 ^{o}C)

IR (KBr) (cm^{-1}) 3057, 2866, 1701, 1610

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.25-7.31 (m, 8H), 7.34-7.42 (m, 10H), 7.90 (d, 2H, *J* = 8.0 Hz,), 7.95 (d, 2H, *J* = 8.0 Hz), 8.24 (s, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 119.3, 124.7, 126.4, 126.8, 127.9, 128.2, 128.4, 128.5, 129.1, 131.0, 131.6, 133.6, 136.3, 148.8, 160.7

LCMS m/z 461 (M+1)

$[\alpha]_D^{25}$ +176.8 (*c* 0.22, CH_2Cl_2) {Lit.[26] $[\alpha]_D^{25}$ = +161.8 (*c* 0.5, CH_2Cl_2)}

3.4.3 Reaction of (*R*)-*N,N′*-dibenzylidene-1,1′-binaphthyl-2,2′-diamine with the $TiCl_4$/Zn reagent system

In dry THF (100 mL), $TiCl_4$ (3.8 g, 2.2 mL, 20 mmol) was added under N_2 atmosphere at 0 °C. Zn dust (2.6 g, 40 mmol) was added with a solid addition flask for 10 min. The reaction mixture was stirred for 0.5 h at 0 °C and the imine (5 mmol, 2.3 g) in 50 mL of THF was added for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and for 12 h at 25 °C. It was quenched with saturated K_2CO_3 soln. (30 mL) and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic extracts were washed with brine solution (20 mL) and dried over anhydrous K_2CO_3. The solvent was removed and the residue was chromatographed on basic alumina column using EtOAc/hexanes mixture as eluent.

(Analysis for product mixture obtained in Scheme **13**)

Yield 0.38 g

mp 226-230 °C

IR (KBr) (cm^{-1}) 3393, 3060, 3026, 1618

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.22-1.24 (m, 5H), 1.97 (s, 4H), 2.3 (br s, 5H), 3.69-4.07 (m, 2H), 6.63-7.59 (m, 49H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 59.4, 59.6, 60.6, 77.3, 77.4, 111.6, 114.7, 122.1, 122.9, 122.3, 124.2, 126.8, 126.9, 127.1, 127.3, 127.4, 127.5, 127.9, 128.3, 129.3, 129.5, 129.6, 133.4, 142.6, 142.7

MALDI-TOF (m/z) 284, 373, 461, 552, 642

$[\alpha]_D^{25}$ +94.6 (*c* 1, $CHCl_3$)

3.4.4 Procedure for the condensation reaction of BINAM with terephthalaldehyde

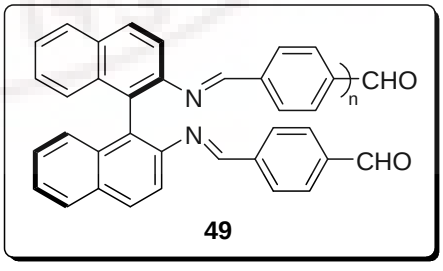
To a solution of *R*-(+)-1,1'-binaphthyl-2,2'-diamine (1.42 g, 5 mmol) and terephthalaldehyde (0.67 g, 5mmol) in 15 mL of dry diglyme solvent, 0.5 g of molecular sieves (4Å) was added under nitrogen atmosphere. The reaction mixture and was heated to 140 ^oC for 12 h. The reaction mixture was filtered off and the solvents were evaporated under reduced pressure. The residue was washed with hexane: diethyl ether mixture (9:1 v/v) to remove the low molecular weight compounds. The crude residue was taken as such to the next stage without further purification.

Yield 1.42 g (71%)

mp 214-219 ^oC

IR (KBr) (cm^{-1}) 3379, 3057, 2862, 1697, 1612

^{1}H-NMR (400MHz, $CDCl_3$, δ ppm) 3.49 (br s, 3H), 6.49-7.99 (m, 45H), 9.1-9.3 (m, 1H)



49

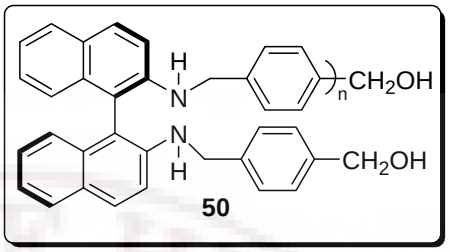
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm):112.5, 114.4, 117.9, 118.3, 118.7, 118.9, 119.8, 120.3, 120.4, 122.0, 122.4, 123.7, 123.9, 124.0, 124.4, 124.9, 125.3, 125.4, 126.2, 126.4, 126.8, 127.0, 127.9, 128.1, 128.4, 129.2, 129.4, 129.9, 130.2, 130.5, 130.9, 131.7, 132.1, 133.5, 133.7, 134.3, 134.5, 136.3, 136.4, 137.1, 142.1, 142.7, 148.7, 148.9, 160.0, 160.2, 191.6 **(Spectrum No. 23)**

LCMS (m/z) 401, 517, 666, 782, 898 **(Spectrum No. 24)**

$[\alpha]_D^{25}$ +239.27 (*c* 0.2, $CHCl_3$)

3.4.4.1 General procedure for the reduction of chiral imines 49 to amines 50 using $NaBH_4/I_2$ reagent system

To a stirred suspension of $NaBH_4$ (1.89 g, 50 mmol) in THF (30 mL), a solution of iodine (5.58 g, 22 mmol) in THF (50 mL) of was added slowly over a period of 1 h at 0 ^oC under N_2 atmosphere. The chiral oligomeric imines (1 g) in 15 mL of THF were slowly added to the reaction mixture for 10 minutes. The reaction mixture was brought to 25 ^oC and stirred for 0.5 h and then refluxed for 12 h. The reaction mixture was brought to room temperature and quenched carefully with 3N HCl (15 mL). The organic layer was separated and the aqueous layer was neutralized with 3N NaOH solution till it became slightly basic. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic extracts were washed with brine (1 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated.



50

Yield 0.7 g (63%)

mp 103-108 ^{o}C

IR (KBr) (cm^{-1}) 3418, 3385, 3051, 2964, 1616

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.55-1.80 (m, 3H), 4.1-4.5 (m, 4H) 6.99-7.47 (m, 14H) 7.77-8.01 (m, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 13.9, 18.9, 25.6, 29.7, 29.9, 33.3, 34.8, 47.6, 62.6, 64.6, 67.9, 114.5, 118.6, 122.4, 122.6, 122.8, 123.9, 124.0, 126.9, 127.0, 127.2, 127.3, 128.2, 129.6, 129.8, 133.4, 133.5, 133.7, 143.4

LCMS (m/z) 910, 789, 670, 524, 404 **(Spectrum No. 25)**

$[\alpha]_D^{25}$ +74.9 (*c* 0.5, $CHCl_3$).

3.4.5 Procedure for the synthesis of monomeric and dimeric amides derived from BINAM

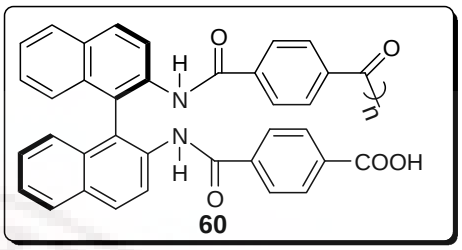
3.4.5.1 Preparation of polymeric amide derived from BINAM and terephthaloyl chloride

To a stirred solution of (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine (0.284 g, 1mmol) and triethyl amine (0.20 g, 0.28 ml, 2 mmol) in 5 mL of CH_2Cl_2, terephthaloyl chloride (0.20 g, 1 mmol) was added at 0 ^{o}C and then the reaction mixture was slowly warmed to 25 ^{o}C and stirred at the same temperature for 24 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with 10 mL of water. The solvent was removed under reduced pressure.

Yield 0.38 g (66%)

mp > 240 °C

IR (KBr) (cm^{-1}) 3370, 2959, 1655, 1498, 1259



60

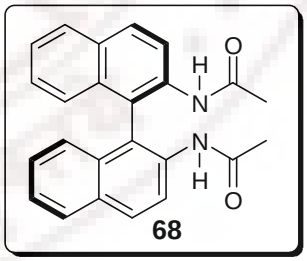
3.4.5.2 Preparation of (*R*)-*N*,*N*′-diacetyl-1,1′-binaphthyl-2,2′-diamine (68)

To a solution of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (1.42 g, 5 mmol) in dry THF (20 mL), freshly distilled acetic anhydride (1.23 g, 1.1 mL, 12 mmol) in 5mL of dry THF was added drop wise at 0 °C under nitrogen atmosphere over a period of 5 minutes. After 30 minutes stirring at 0 °C, the reaction mixture was warmed to 25 °C and stirred at the same temperature for 8 h. The reaction mixture was quenched with water and extracted with ether (3 x 20 mL). The combined organic extracts were washed with 10% $NaHCO_3$ (2 x 10 mL) solution, water (20 mL), brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was purified by silica gel (100-200 mesh) column using hexane/ethyl acetate (90:10) as eluent.

Yield 1.65 g (90%)

mp 118-120 °C

IR (KBr) (cm^{-1}) 3252, 3055, 1668, 1597, 1502, 1278



68

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.83 (s, 6H), 6.95 (br s, 2H), 7.05 (d, 2H, *J* = 8.6 Hz), 7.25-7.29 (m, 2H) 7.44-7.47 (m, 2H), 7.95 (d, 2H, *J* = 8.3 Hz), 8.05 (d, 2H, *J* = 8.8 Hz), 8.33 (d, 2H, *J* = 9.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 23.9, 122.8, 125.3, 125.7, 127.2, 128.3, 129.8, 131.5, 132.5, 134.9, 169.5

LCMS m/z 369 (M+1)

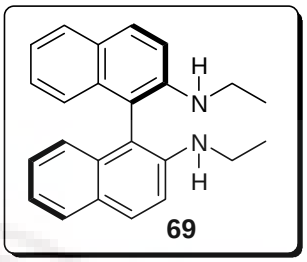
$[\alpha]_D^{25}$ +92.74 (*c* 0.12, $CHCl_3$)

Analysis Calculated for $C_{24}H_{20}N_2O_2$: C, 78.24%; H, 5.47%; N, 7.60%; O, 8.69%

Found : C, 78.32%; H, 5.49%; N, 7.68%; O, 8.51%

3.4.5.3 Preparation of (*R*)-*N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine (69)

To a dispersion of $NaBH_4$ (1.14 g, 30 mmol) in dry THF (30 mL), iodine (3.17 g, 12.5 mmol) in dry THF (20 mL) was added drop wise at 0 ^oC under nitrogen atmosphere over a period of 30 minutes. After the colour of the iodine was completely disappeared, (*R*)-*N,N′*-diacetyl-1,1′-binaphthyl-2,2′-diamine (1.84 g, 5 mmol) in dry THF (10 mL) was added slowly through addition funnel for 10 minutes. The reaction mixture was brought to room temperature and refluxed for 12 h. The reaction mixture was quenched with 5N HCl. The organic layer was separated and the aqueous layer was neutralized with 5N NaOH till the solution becomes slightly basic and extracted with ether (20 mL x 3). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4.The solvent was evaporated under reduced pressure and the residue was purified by neutral alumina column using hexane: ethylacetate (97:3) as eluent. The product obtained as yellow gummy solid.



69

Yield 1.25 g (74%)

IR (KBr) (cm^{-1}) 3400, 3053, 2968, 2930, 1738, 1616, 1597

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.01 (t, 6H, *J* = 7.0 Hz), 3.21 (q, 4H, *J* = 7.1 Hz), 3.76 (br s, NH, 2H), 6.96 (d, 2H, *J* = 8.3 Hz), 7.13-7.22 (m, 4H), 7.29 (d, 2H, *J* = 9 Hz), 7.78 (d, 2H, *J* = 8.1 Hz), 7.89 (d, 2H, *J* = 8.8 Hz)

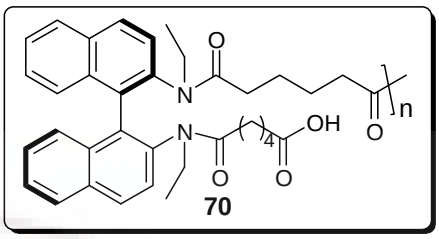
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 15.3, 38.7, 112.3, 114.3, 121.9, 123.9, 126.7, 127.8, 128.1, 129.6, 133.9, 144.6

LCMS m/z 341 (M+1)

$[\alpha]_D^{25}$ +163.71 (*c* 0.12, $CHCl_3$) (Lit.[40] $[\alpha]_D^{25}$ = +165° in benzene, *c* 0.98).

3.4.5.4 Preparation of monomeric and dimeric amide derived from *N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine

To a stirred solution of diethyl BINAM (1.70 g, 5mmol), triethyl amine (2.02 g, 2.8 ml, 20 mmol) and anhydrous lithium chloride (0.5 g) in dry NMP, adipoyl chloride (0.92 g, 0.73 ml, 5mmol) was added at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred at the same temperature for 12 h. The reaction mixture was quenched with 10 mL of water and extracted with ether (3 x 20mL). The combined organic extracts were washed with 3N NaOH solution, brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure.



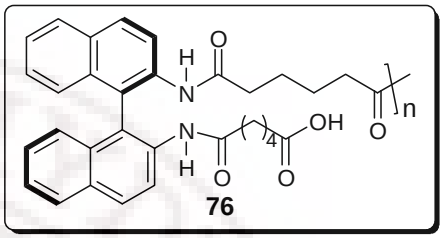
70

Yield	1.8 g (70%)
mp	68-74 ^{o}C
IR(KBr)	(cm^{-1}) 3498, 3051, 2964, 2922, 1732, 1616, 1597
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm): 0.91-1.06 (m, 21H), 1.27-2.50 (m, 17H), 2.80 -3.32 (m, 13H), 6.96-8.01 (m, 38H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm): 8.6, 12.7, 13.0, 14.4, 15.2, 23.9, 24.9, 25.5, 25.8, 29.3, 33.3, 35.0, 38.3, 38.7, 42.1, 42.5, 42.8, 44.0, 113.6, 113.9, 120.9, 121.6, 121.9, 123.5, 126.3, 128.3, 129.3, 132.3, 133.2, 134.0, 140.3, 143.6, 145.5, 172.9, 173.9 **(Spectrum No. 26)**
MS	(MALDI-TOF) 1033, 923, 790, 560
$[\alpha]_D^{25}$	+10.6 (*c* 0.5, $CHCl_3$)

3.4.5.5 Procedure for the reaction of BINAM with adipoyl chloride (66)

To a solution of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (1.42 g, 5 mmol), triethylamine (2.02 g, 2.8 ml, 20 mmol) and anhydrous lithium chloride (0.5 g) in 25 mL of dry *N*-methyl-2-pyrrolidinone solvent (NMP), adipoyl chloride (0.95 g, 0.76 mL, 5.2 mmol) was added slowly through syringe over a period of 5 minutes under nitrogen atmosphere at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h and at 25 ^{o}C for a further 12 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with

water (4 x 10 mL) repeatedly. The organic layer was washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated.



76

Yield	1.3 g (62%)
mp	127-132 ^{o}C
IR (KBr)	(cm^{-1}) 3061, 2962, 2932, 1745, 1651
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm): 0.75-0.88 (m, 3H), 1.10-1.23 (m, 6H), 1.61-1.63 (m, 2H), 1.81-1.97 (m, 5H), 4.2 (br s, 11H), 6.67-6.77 (m, 1H), 6.87-7.25 (m, 28H), 7.50-7.84 (m, 15H), 8.40-8.45 (m, 2H)
^{13}C-NMR	(100 MHz, $CDCl_3$, δ ppm): 23.8, 24.3, 24.5, 24.8, 29.7, 33.6, 36.3, 37.1, 110.3, 112.6, 118.2, 118.3, 121.3, 122.4, 122.6, 123.5, 123.9, 125.2, 125.4, 126.8, 127.3, 128.1, 128.2, 128.4, 129.1, 129.4, 130.3, 131.3, 132.4, 133.6, 133.7, 134.7, 136.9, 142.7, 142.9, 171.5, 172.3, 176.8
LCMS	m/z 394, 678, 787
$[\alpha]_D^{25}$	+65.56 (*c* 0.3 , $CHCl_3$)

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Chapter 4

Hydroboration Studies Using Chiral 1,1'-Binaphthyl-2,2'-Diamine-Borane Complexes

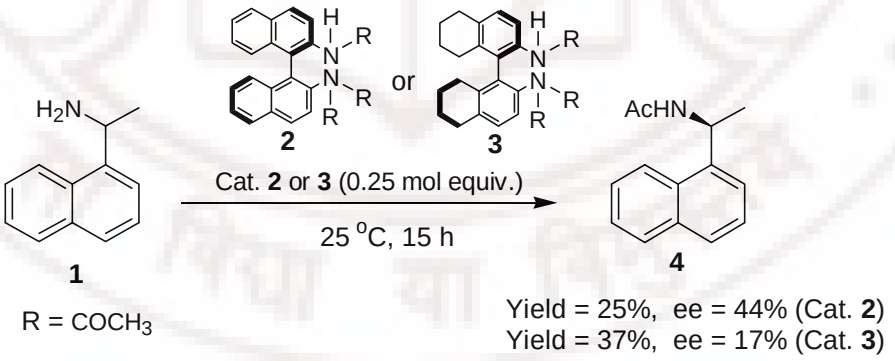
4.1 Introduction

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

Configurationally stable 2,2′-substituted 1,1′-binaphthyl derivatives represent one of the most investigated class of chiral compounds.[1] A brief review on the synthetic application of the 1,1′-binaphthyl-2,2′-diamine would facilitate the discussion.

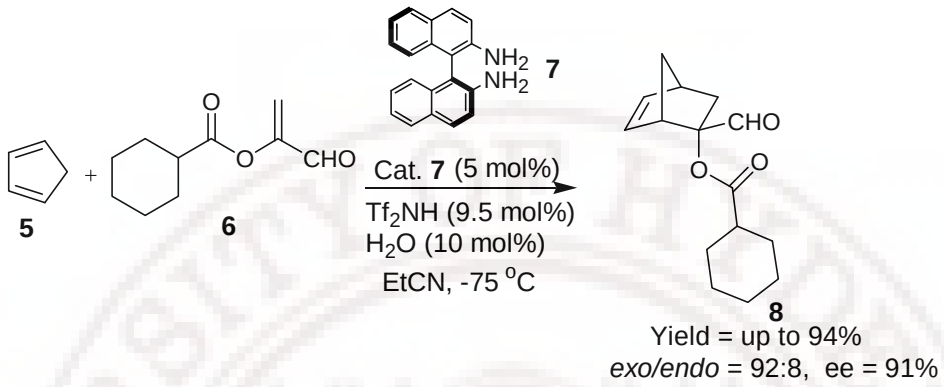
Murakami *et al.*[2] reported the enantioselective *N*-acetylation of racemic alkyl amines **1** with chiral 2-acetylamino-2′-diacetylamino-1,1′-binaphthyl **2**. The *N*-acetylation was effective for 1-arylethylamine and phenylalanine benzyl ester to obtain the corresponding *N*-acetylamine **4** with up to 44% ee (Scheme **1**).

Scheme 1



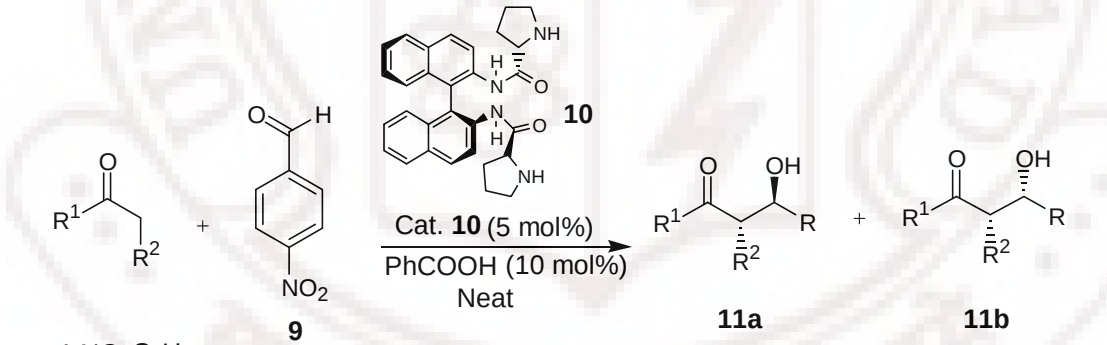
Ishihara *et al.*[3] reported that the chiral 1,1′-binaphthyl-2,2′-diamine complex catalyzes Diels-Alder reaction of cyclic dienes **5** with α-acyloxyacroleins **6** (Scheme **2**). The cyclic adduct **8** was obtained in good yield with excellent selectivity.

Scheme 2



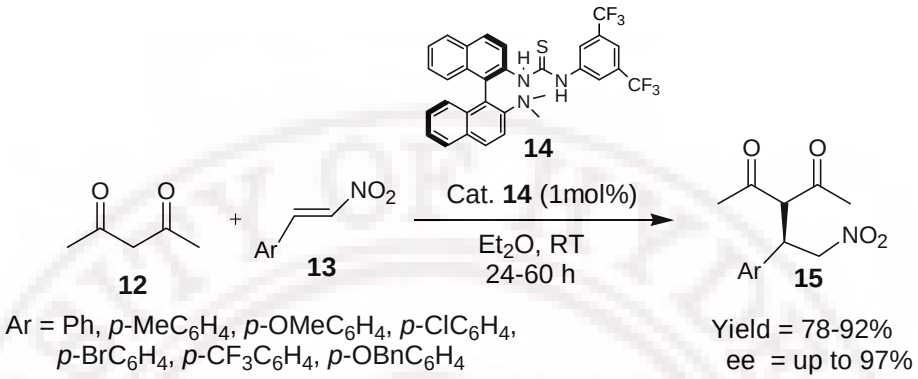
The BINAM-*L*-prolinamide **10** catalyzed solvent free asymmetric direct aldol reaction.[4] The alcohols **11** were obtained in good yield with excellent enantioselectivity (Scheme **3**).

Scheme 3



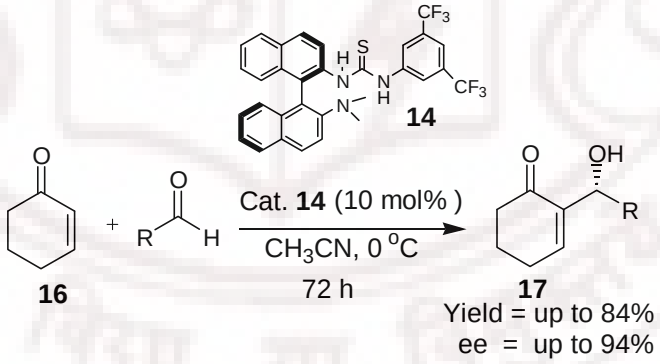
Wang *et al.*[5] reported the binaphthyl diamine-thiourea organocatalyst **14** mediated Michael addition reaction of diketone **12** and nitroalkene **13**. The product **15** was obtained in good yield with excellent selectivity (Scheme **4**).

Scheme 4



Wang *et al.*[6] also reported the bifunctional binaphthyl diamine-thiourea organocatalyst **14** mediated enantioselective Morita-Baylis-Hillman reaction of cyclohexenone **16** and aldehydes. The synthetically valuable chiral allylic alcohol building blocks were obtained in good yields with high enantioselectivity (Scheme **5**).

Scheme 5

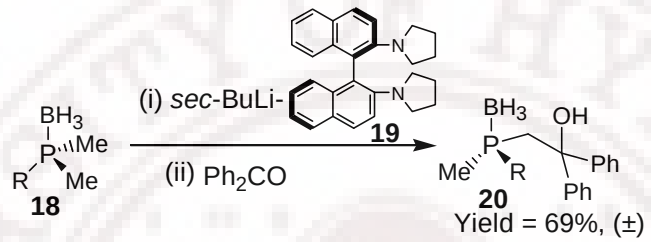


R = $C_6H_5CH_2CH_2$-, $(CH_3)_2CHCH_2$-, $^nC_4H_9$, $^nC_5H_{11}$, $^nC_6H_{13}$, $^nC_7H_{15}$

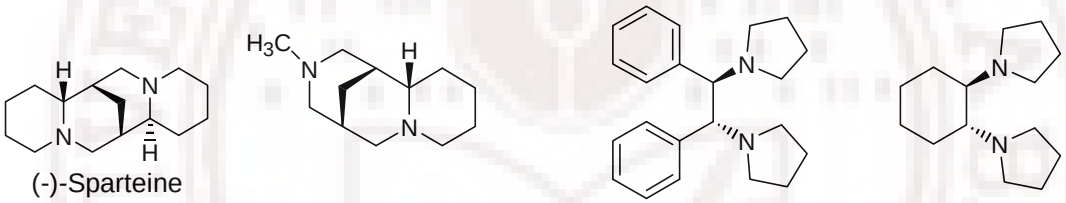
Desymmetrization of prochiral phosphine borane substrates **18** with chiral amine-alkyllithium complexes **19** has been reported by Kann *et al.*[7] The chiral BINAM derived tertiary amine catalyst **19** gave the racemic alcohol product in 69% yield. The lithium salt

of (-)-cytisine derivative **22** gave the dimethyl phosphine boranes **20** up to 92% ee (Scheme **6**).

Scheme 6

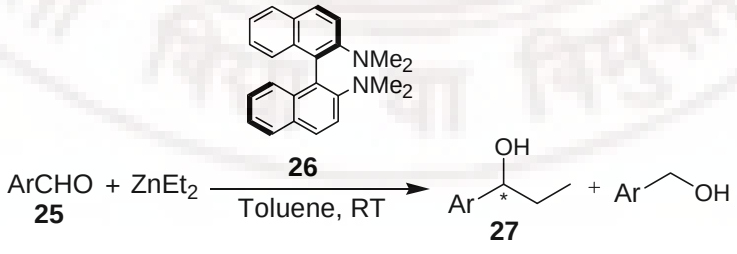


The other chiral amines employed



Salvadori *et al.*[8] reported the *N,N,N′,N′*-tetramethyl-2,2′-diamino-1,1′-binaphthyl **26** mediated asymmetric alkylation of aromatic aldehydes with diethylzinc. The substituted alcohols were obtained up to 64% ee (Scheme **7**).

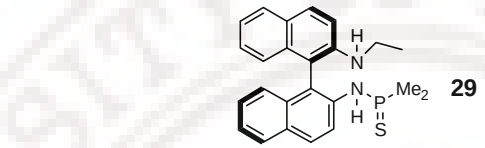
Scheme 7



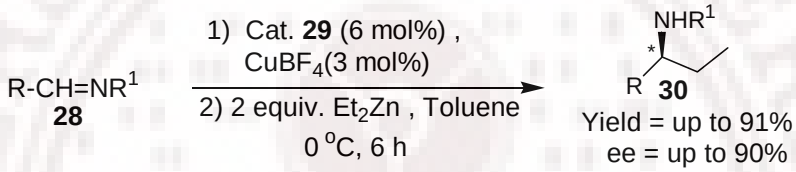
Ar = 2-napthyl, phenyl, *p*-methoxyphenyl, *o*-methoxyphenyl, biphenyl, *p*-chlorophenyl

A binaphthylthio phosphoramide **29** catalyzed asymmetric addition of diethylzinc to *N*-sulfonylimines was reported by Shi *et al.*[9] The substituted amines were obtained in good yields with moderate to high enantioselectivity (Scheme **8**).

Scheme 8



29

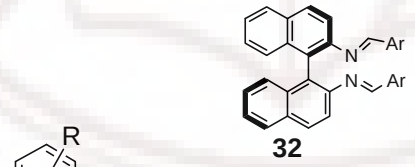


R^1= Tosyl, Ms

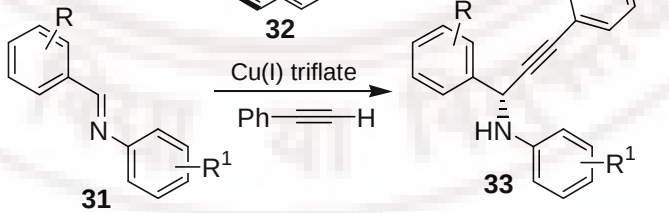
R = C_6H_5, *p*-MeC_6H_4, *m*-MeC_6H_4, *p*-$OMeC_6H_4$, *m*-MeC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4

Benaglia *et al.*[10] reported the chiral bisimine **32** mediated aryl and alkylacetylene addition to prochiral imines. The optically active propargyl amines **33** were obtained in excellent yields with good enantioselectivity (Scheme **9**).

Scheme 9



32



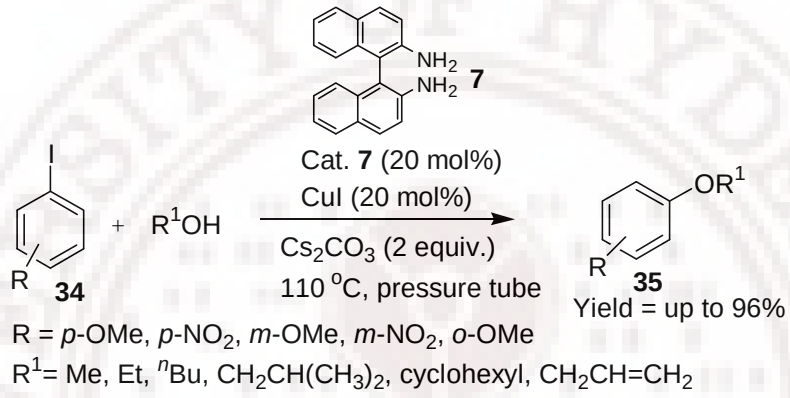
R = 4-OMe, 2-OMe, 2-Cl, 2,6-dichloro, 4-F, 4-Cl, 4-Br, 4-NO_2

R^1 = 4-OMe, 2-OMe, 4-Cl, 4-F, 3,5-dichloro

Ar = pentafluorophenyl, 2-thienyl, 2-methoxyphenyl, 2,4,6-trimethylphenyl, 2,6-dichlorophenyl

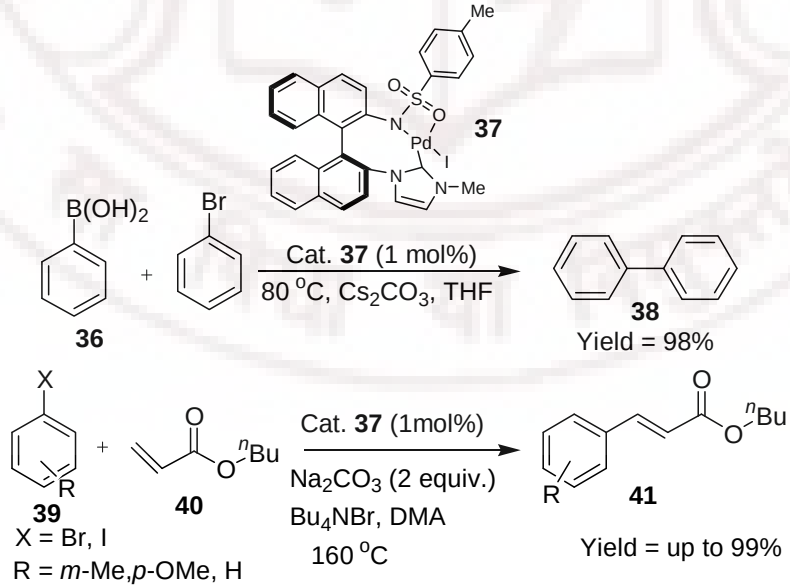
A BINAM–CuI complex mediated Ullmann-type intermolecular coupling reactions of aryl iodides **34** and aliphatic alcohols was reported by Sekar *et al.*[11] The alkyl aryl ethers **35** were obtained in good yields (Scheme **10**).

Scheme 10



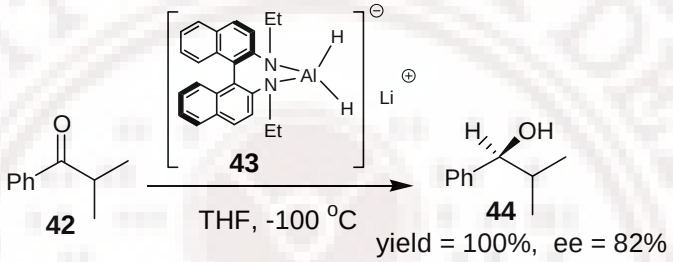
Shi *et al.*[12] reported the BINAM derived NHC–Pd(II) complex **37** mediated Suzuki and Heck-type cross coupling reactions. The products **38** and **41** were obtained in good to excellent yields (Scheme **11**).

Scheme 11



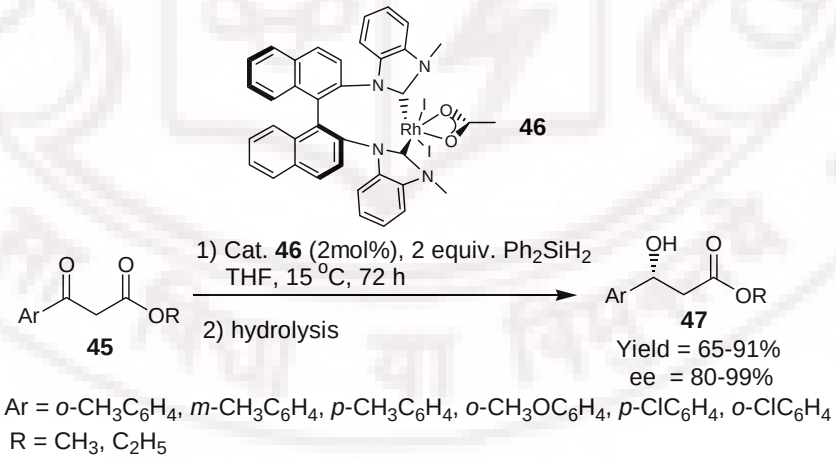
Enantioselective reduction of ketones catalyzed by the $LiAlH_4$ complex of the 2,2′-diamino-1,1′-binaphthyl derivatives **43** was reported by Hashimoto *et al.*[13] The introduction of alkyl group on to the chiral amine catalyst reverses the stereochemical outcome of the product (Scheme **12**).

Scheme 12



Shi *et al.*[14] reported the BINAM-Rhodium complex **46** mediated enantioselective hydrosilylation of arylpropionic acid esters **45**. The reduction products **47** were obtained in good yields with excellent selectivity (Scheme **13**).

Scheme 13



As a part of an ongoing studies in this laboratory, we have decided to examine the synthesis and applications of borane complexes of 1,1′-binaphthyl-2,2′-diamine derivatives.

4.2 Results and Discussion

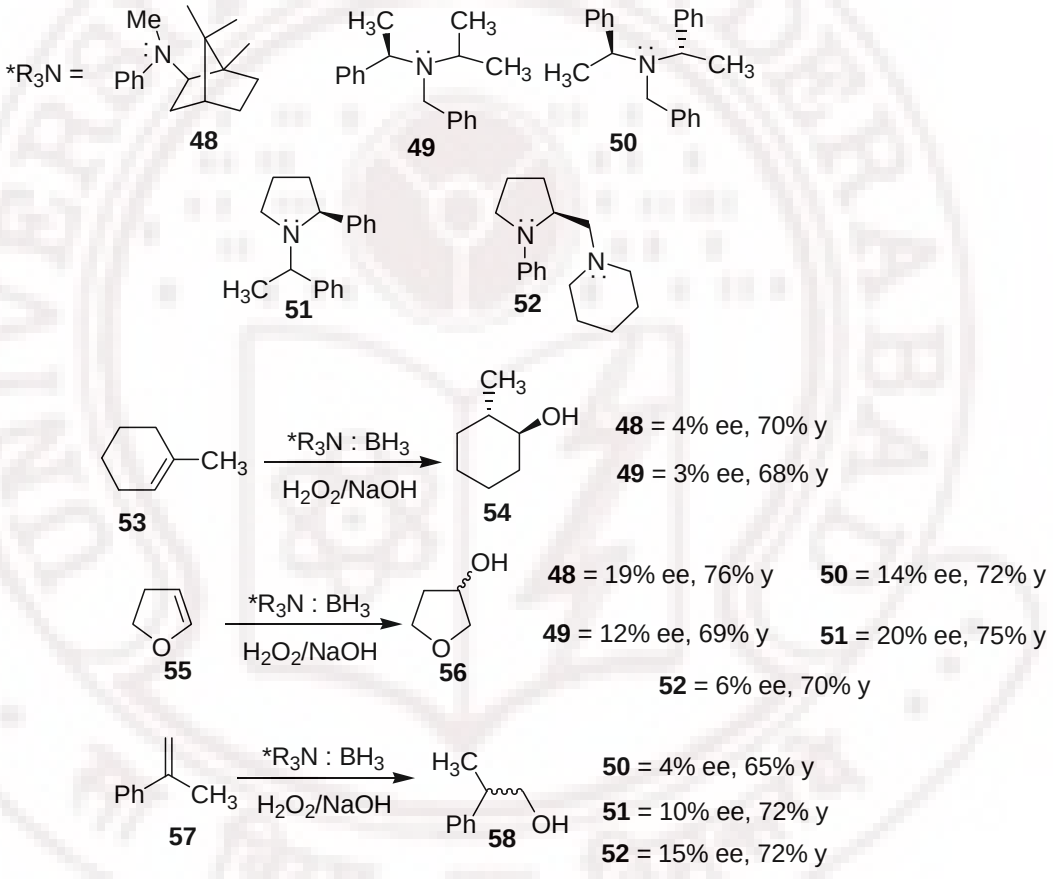
4.2.1 Efforts toward asymmetric hydroboration of prochiral olefins

Asymmetric hydroboration and reductions are important organic transformations leading to the formation of chiral alcohols from prochiral olefins and ketones.[15] The alkyl amines form relatively stable amine borane complexes.[16] The hydroboration reaction with amine borane adducts is rather limited due to strong complexation which makes their reactivity much lower as compared to the adducts with ethers and sulfides.[16,17] Hence, amine borane complexes are relatively less sensitive to moisture, air and they have high borane concentration compared to the other borane sources. The amine boranes and related derivatives also have a wide range of biological activities.[18]

The pyridine-borane and trimethyl amine-borane complexes hydroborate olefins at elevated temperatures.[19] The *N*-alkyl substituted anilines form more reactive amine borane complexes.[20] The order of reactivity among the amine borane complexes is closely related to its stability. The less basic aniline derivatives form weaker and hence more reactive adducts with borane. The aryl amine borane adducts were used for hydroboration and other reactions such as reduction of functional groups such as aldehydes, ketones, carboxylic acids, tertiary amides, lactams, and Schiff bases as well as for the oxazaborolidine-catalyzed enantioselective reduction of prochiral ketones.[21]

It has been reported from this laboratory that the hydroboration of representative prochiral olefins **53**, **55** and **57** using chiral tertiary amine borane complexes of amines **48-52** gave the alcohols with up to 20% ee (Chart **1**).[22]

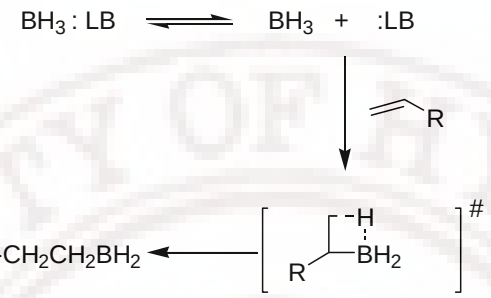
Chart 1



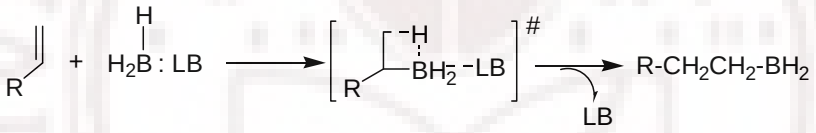
The hydroboration reaction may go through a spectrum of mechanisms outlined in Chart **2** depending on the nature of the olefin and amine borane complex employed.

Chart 2

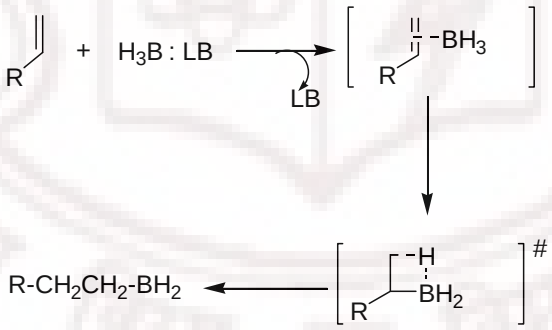
S_N^1-Type mechanism



S_N^2-Type mechanism



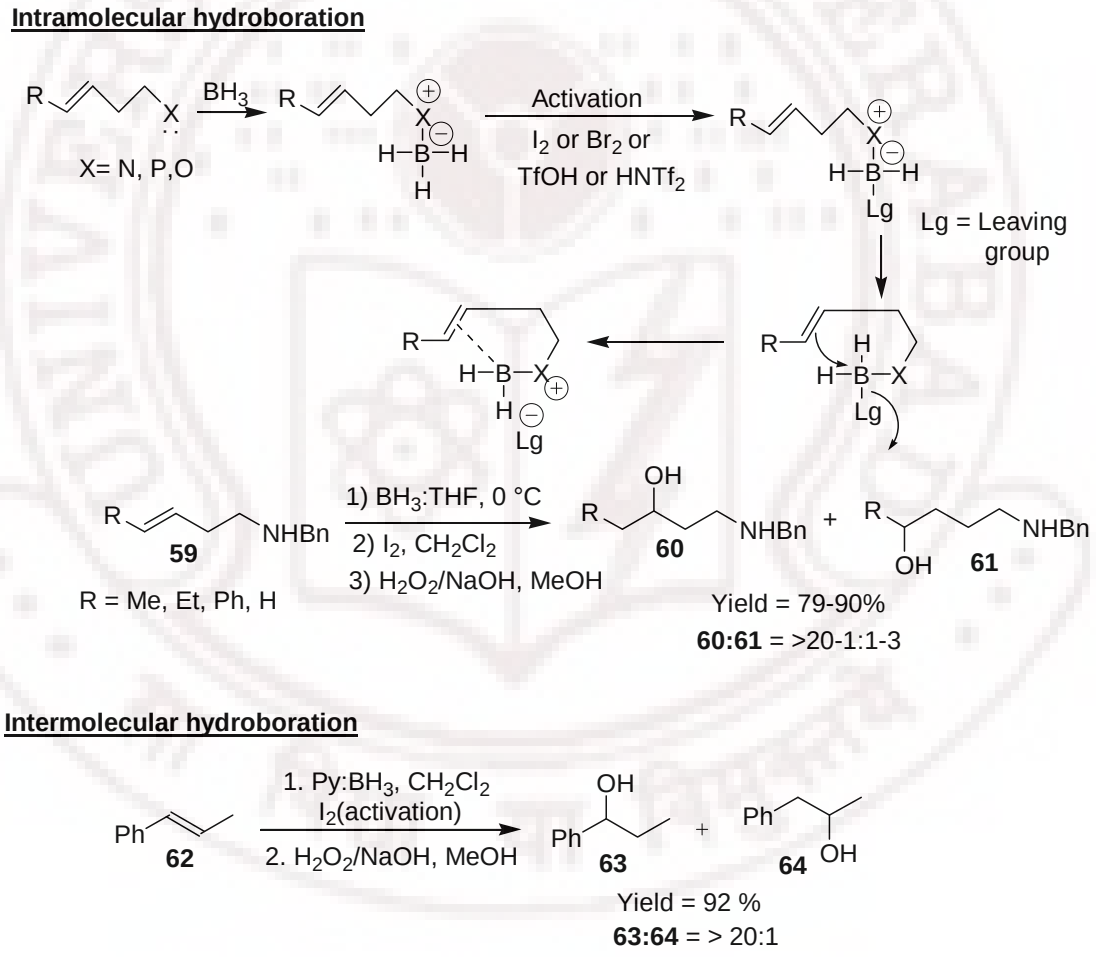
S_N^2-Type mechanism with π-complex intermediate



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

Recently, Vedejs *et al.*[23a-c] reported the iodine activation of amine boranes and phosphine boranes towards the intramolecular hydroboration reaction. Presumably, the iodine in the amine-BH_2I complex acts as a better leaving group and thus increases the rate of hydroboration to several folds (Chart **3**).

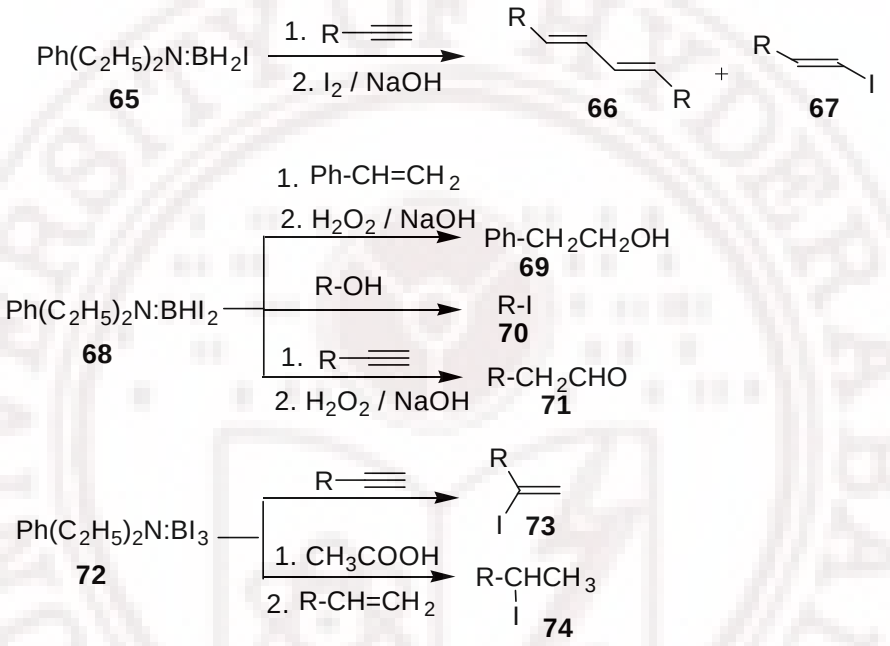
Chart 3



The iodine activation has been also reported for intermolecular hydroboration reaction.[23d] Previously, preparation and application of amine-BH_2I, BHI_2, BI_3 complexes

65, **68** and **72** were reported from this laboratory.[24] The *N,N*-diethylaniline was used for the preparation of iodoborane complexes (Chart **4**).

Chart 4



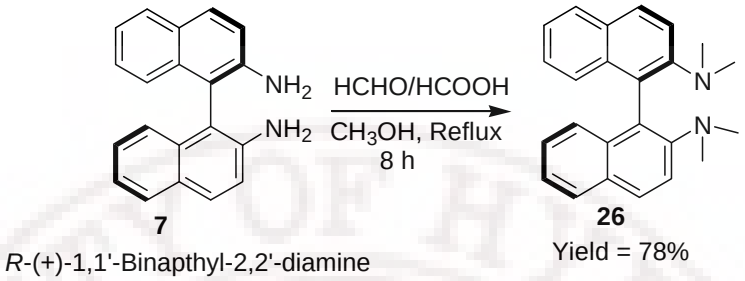
We became interested in examining the stereochemical outcome of the hydroboration reaction of prochiral olefins with chiral amine boranes derived from axially chiral C_2 symmetric 1,1′-binaphthyl-2,2′-diamine **7** derivatives.

4.2.2 Synthesis of tertiary amines derivatives of BINAM

4.2.2.1 Synthesis of *N,N,N′,N′*-tetramethyl BINAM

The *N,N,N′,N′*-tetramethyl BINAM **26** was prepared by refluxing the mixture of BINAM, formaldehyde and formic acid in methanol for 8 h.[8,25] The reaction proceeds smoothly and the tertiary amine was obtained in 78% yield (Scheme **14**).

Scheme 14



The product was crystallized from toluene to obtain the crystals suitable for single crystal X-ray diffraction analysis. The ORTEP diagram of the compound **26** is shown in Figure **1**.

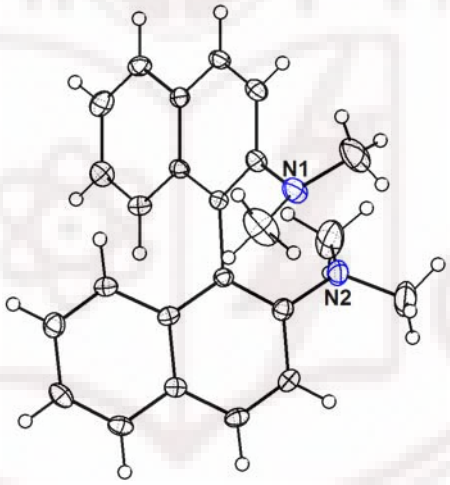


Figure 1 ORTEP diagram of the compound 26 (Thermal ellipsoids are drawn at 20% probability)

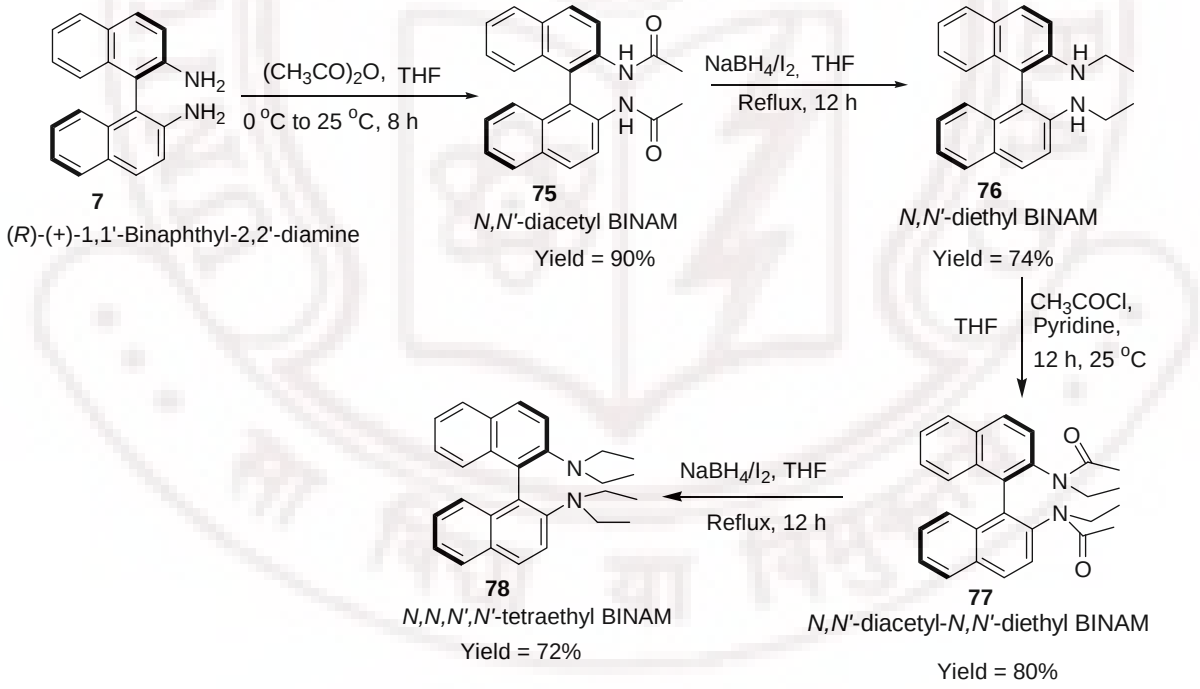
4.2.2.2 Synthesis of *N,N,N′,N′*-tetraethyl BINAM

The preparation of *N,N,N′,N′*-tetraethyl BINAM **78** was initially attempted by refluxing a mixture of BINAM **7**, ethyl bromide and K_2CO_3 in acetonitrile solvent for 48 h. The reaction gave a mixture of *N*-ethyl substituted products. The reaction of BINAM with

excess acetyl chloride in presence of pyridine as base under reflux condition gave the diacetylated product **75** besides unidentified polar products. Hence, the stepwise acetylation-reduction method was followed for the preparation of the tetraethyl BINAM **78**.

The reaction of acetic anhydride with BINAM **7** in dry THF solvent at room temperature gave diacetyl BINAM **75** in quantitative yield. The product was reduced to diethyl BINAM **76** by using the $NaBH_4/I_2$ reagent system developed in this laboratory.[26] Repetition of the acetylation/reduction using the diethyl BINAM **76** gave the tetraethyl BINAM **78** (Scheme **15**).

Scheme 15



The *N,N,N′,N′*-tetraethyl BINAM **78** was crystallized from toluene to obtain the crystals suitable for single crystal X-ray diffraction analysis. The ORTEP diagram of the compound **78** is shown in Figure **2**.

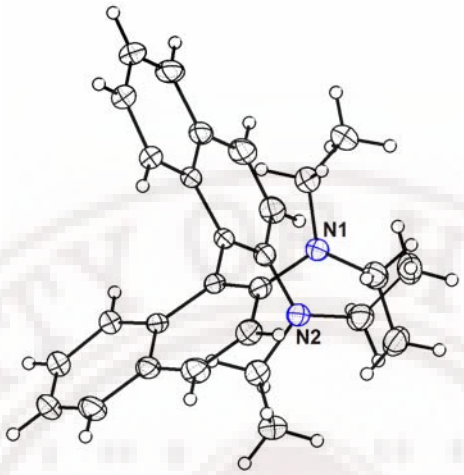
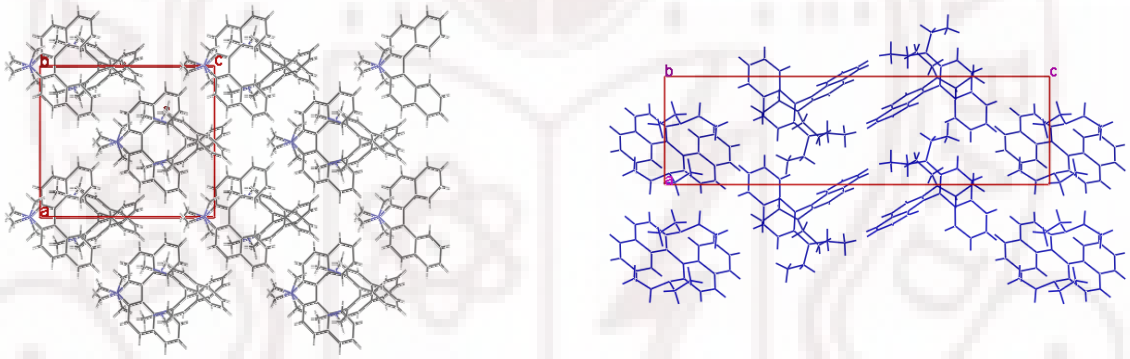


Figure 2 ORTEP diagram of the compound 78 (Thermal ellipsoids are drawn at 20% probability)



(a) **(b)**

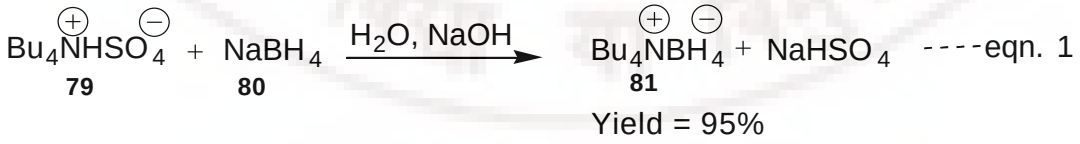
Figure 3. (a) The packing diagram for tetramethyl BINAM **26** viewed along the crystallographic *b*-axis. (b) The packing diagram for tetraethyl BINAM **78** as viewed along the crystallographic *b*-axis.

Due to the presence of methyl and ethyl groups on the nitrogen atom of compounds **26** and **78**, the π-π interactions between the aromatic rings are not observed (Figure **3**). In tetramethyl BINAM **26** a weak supramolecular C–H···π interaction was observed between aromatic C–H and naphthyl ring. The distance between the C–H proton and napthyl ring is 2.62 Å to 2.99 Å. Because of the steric repulsion of the bulky ethyl groups on the nitrogen,

the C–H···π interaction was not observed in tetraethyl BINAM **78**. The N---N intramolecular bond distance in tetramethyl BINAM **26** is 3.263 Å and in tetraethyl BINAM it is 3.504 Å.

4.2.3 Asymmetric hydroboration reaction of BINAM and its derivatives

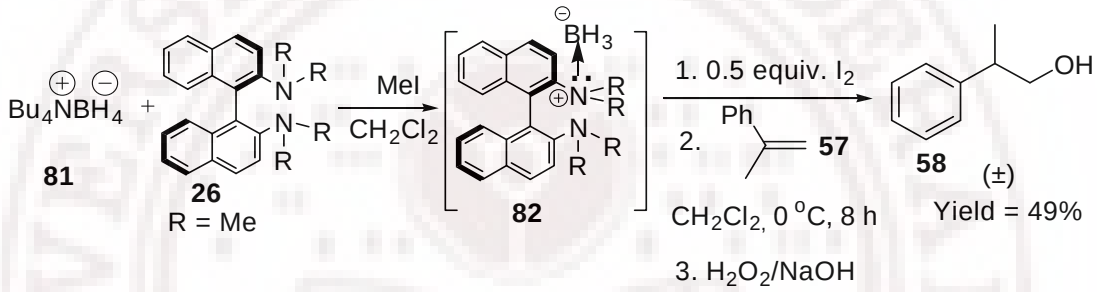
The tetrabutylammonium borohydride **81** in combination with methyl iodide or I_2 or $PhCH_2Cl$ reagent is useful for the generation of diborane gas which facilitates several organic and asymmetric transformations.[27] Earlier, sodium borohydride was used for the generation of diborane gas.[28] As sodium borohydride exhibits poor solubility in common organic solvents, diglyme is the preferred solvent for the generation of diborane. Due to the presence of lengthy alkyl chains, the solubility of tetrabutylammonium borohydride **81** in toluene and other common organic solvents is much higher than that of sodium borohydride. Moreover, the tetrabutylammonium borohydride **81** is less moisture sensitive compared to sodium borohydride. It can be conveniently prepared in quantitative yields by the reaction of sodium borohydride **80** and tetrabutylammonium hydrogen sulphate **79** (Eqn **1**).[29]



We have undertaken studies towards the hydroboration reaction of α-methylstyrene with chiral amine borane complexes prepared from axially chiral tertiary diamine ligands

26 and **78** using tetrabutylammonium borohydride and methyl iodide reagent system. Initially, the amine borane was prepared *in situ* the reaction of tetrabutylammonium borohydride **81** with methyl iodide. The reaction proceeds smoothly but the alcohol product **58** formed was found to be only racemic (Scheme **16**).

Scheme 16



To avoid the possible interference of the tetrabutylammonium iodide formed during the generation of diborane gas in the *in situ* experiments, we have carried out the borane complex formation generating diborane gas *ex situ* using tetrabutylammonium borohydride and methyl iodide reagent system. The results are given in Table **1**. The less basic more sterically hindered tetramethyl and tetraethyl binaphthyl diamines **26** and **78** form weaker complex with borane. The hydroboration takes place at 0 ^{o}C even without the activation of amine borane with iodine (Table **1**, entry 1). Addition of iodine to the amine borane also gave only racemic products in the hydroboration-oxidation of α-methylstyrene (Table **1**, entry 2-4).

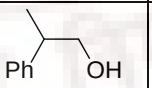
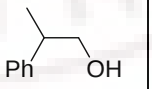
Table 1 Hydroboration reaction of α-methylstyrene using tertiary amine borane complexes of 26 and 78[a]

Entry	Ligand	Solvent	Activating agent	Temp. (^oC)	Time h	Yield[b] %
1	**78**	Toluene	---	0	12	58
2[c]	**78**	CH_2Cl_2	I_2	25	12	66
3[d]	**78**	Toluene	I_2	0	3	52
4[e]	**26**	Toluene	I_2	0	8	62

[a]Unless otherwise noted all the reactions were carried out by purging excess diborane gas through a solution of amine **26** or **78** (2 mmol) in toluene or CH_2Cl_2 for 2 h. The amine borane complexes were activated with 1 mmol of I_2. The α-methylstyrene (2 mmol) was added after the activation of amine borane with iodine
[b]Yields are for the isolated products.
[c]Similar reaction carried out using *in situ* generated amine borane, the racemic alcohol was obtained in 49% yield.
[d]In the reaction carried out with 1 mmol of iodine and 1 mmol of amine borane, the alcohol was obtained in <10% yield and was racemic.
[e]The lowering of temperature to -20 ^oC did not give asymmetric induction of the alcohol product formed.

Similar results were also obtained using secondary amine (**76**) borane complex. (Table **2**).

Table 2 Hydroboration of α-methylstyrene using diethyl BINAM borane complex[a]

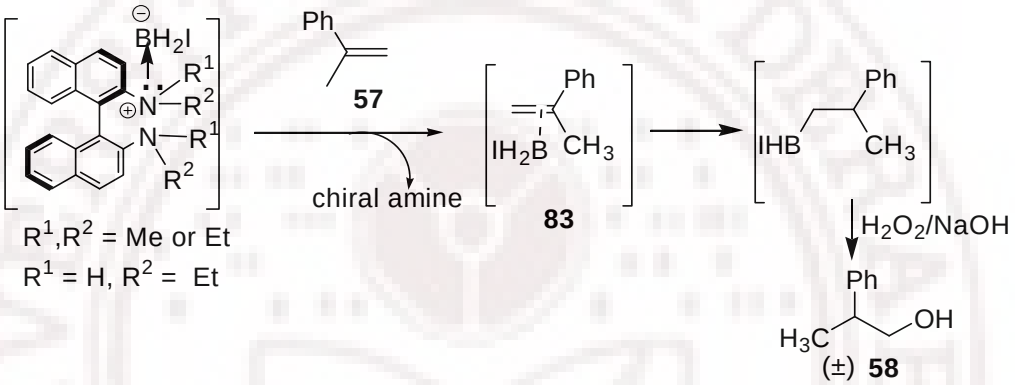
Entry	Activating Agent	Temp. ^oC	Time h	Product[b]	Yield (%)[c]
1	I_2	0	6		78
2	I_2	-20	6		49

[a]All the reactions were carried out by purging excess B_2H_6 through a solution of *N,N'*-diethyl BINAM **76** (2 mmol) in toluene at above mentioned temperature. The amine borane was activated with 1 mmol of I_2. α-methylstyrene (2 mmol) was added after the activation of amine borane with iodine.
[b]Product was analyzed by IR, ^1H and ^{13}C-NMR.
[c]Yields are of isolated products.

The alcohol **58** obtained in the hydroboration-oxidation reaction of α-methylstyrene using amine **76** borane complex was also found to be racemic.

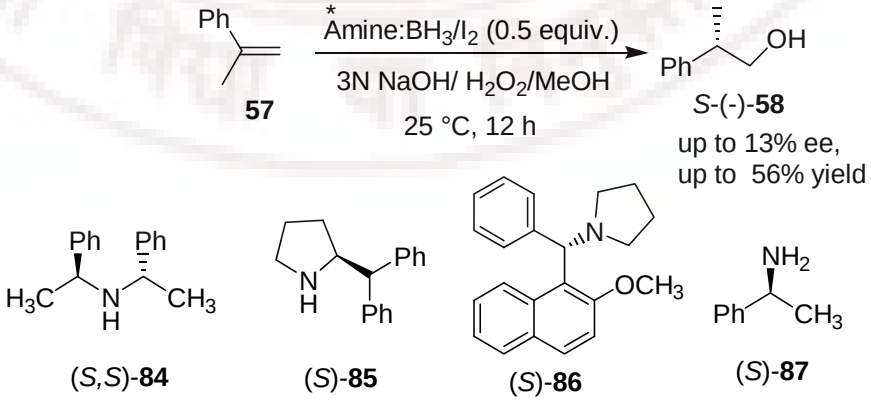
Presumably, in all these cases the chiral amine leaves the borane complex before the hydroboration step (Scheme **17**).

Scheme 17



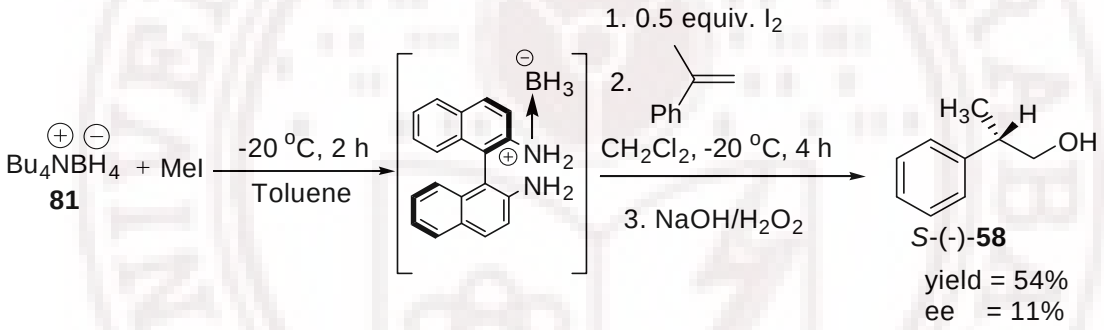
Recent hydroboration studies from this laboratory reported the selectivity order: $RNH_2:BH_3 > R_2NH:BH_3 > R_3N:BH_3$ under iodine activated hydroboration reactions (Scheme **18**).[30] The results indicated that the α-methylbenzylamine **87** gave better results (up to 13%ee) compared to the corresponding borane complexes of secondary and tertiary amine derivatives **84**, **85** and **86**.

Scheme 18



Accordingly, we have examined the hydroboration reaction of the prochiral olefins with *R*-(+)-1,1′-binaphthyl-2,2′-diamine (BINAM) **7**. The amine borane complex was prepared by purging borane gas generated using tetrabutylammonium borohydride in combination with methyl iodide or iodine reagent system in toluene or CH_2Cl_2. The chiral amine borane formed was activated with iodine and the asymmetric hydroboration reaction was carried out at different conditions (Scheme **19**, Table **3**).

Scheme 19



The hydroboration reaction of α-methylstyrene carried out without activating agent in toluene solvent gave the racemic alcohol with poor yield (Table **3**, entry 1). The 1,1′-binaphthyl-2,2′-diamine **7** forms stable complex with borane compared to the corresponding tertiary amine and hence the rate of hydroboration of BINAM:BH_3 without activation was very slow. The formation of racemic alcohol in the hydroboration reaction of unactivated amine borane indicates that the chiral amine did not participate in the hydroboration step of the olefin (Table **3**, entry 1). The high yield of the alcohol product obtained in the hydroboration reaction in CH_2Cl_2 solvent probably due to the possible hydroboration of the olefin by the CH_2Cl_2:BH_3 complex (Table **3**, Footnote e).[31a] Increase in the enantioselectivity of the product was observed by carrying out the reaction at -20 °C

(Table **3**, entry 4). Further decrease in the reaction temperature drastically affects the yield and enantioselectivity of the product formed in the reaction (Table **5**, entry 5). The decrease in the mol% of I_2 from 50 to 20 affects the yield and enantioselectivity of the alcohol product formed in the reaction (Table **3**, entry 6).

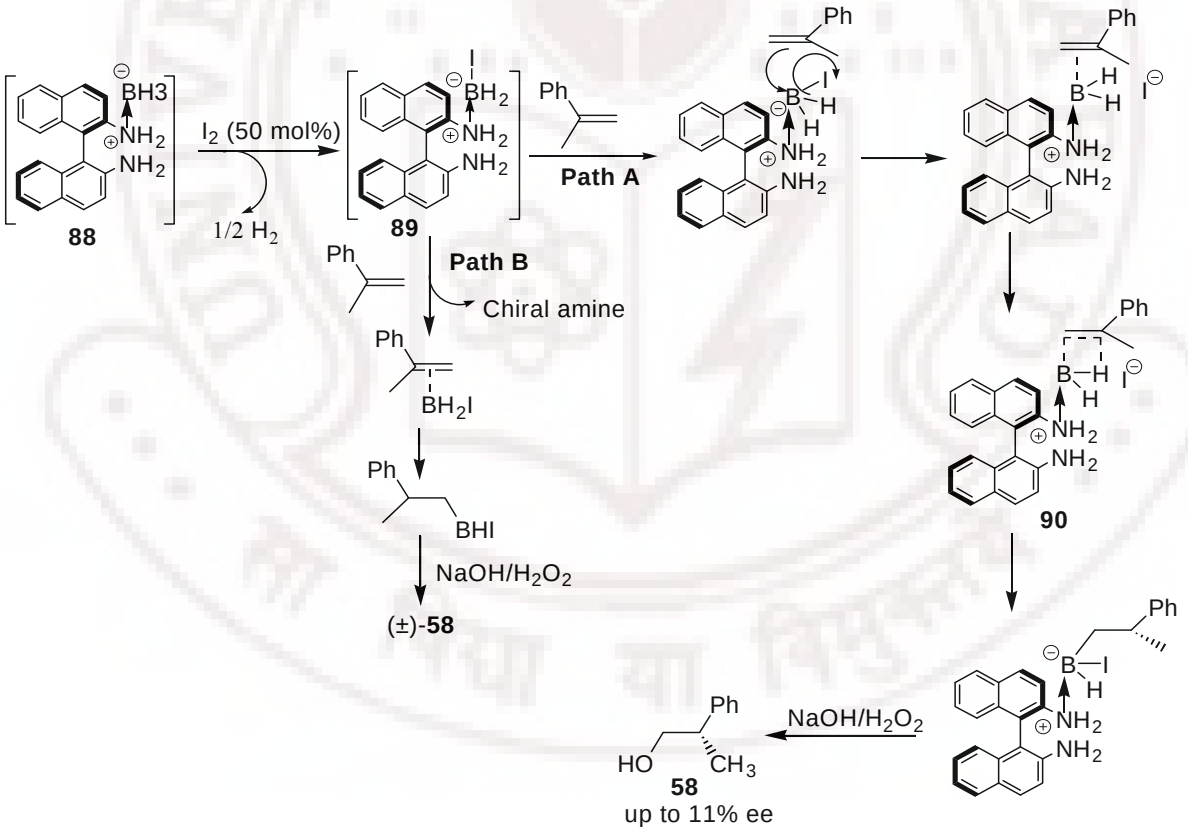
Table 3 Hydroboration reaction of α-methylstyrene with BINAM-borane complex[a]

Entry	Activating agent[d]	Temp. (^oC)	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1[e]	---	0	Toluene	12	13	(±)
2[f]	I_2[g]	25	Toluene	1	38	(*S*)-7
3	I_2[g]	0	CH_2Cl_2	12	49	(*S*)-5
4[h]	I_2[g]	-20	CH_2Cl_2	4	54	(*S*)-11
5	I_2[g]	-40	CH_2Cl_2	8	<5	(±)
6	I_2[i]	-20	CH_2Cl_2	6	<5	(±)
7	TfOH[j]	0	CH_2Cl_2	6	---	---

[a]Unless otherwise noted all the reactions were carried out by purging excess B_2H_6 to a solution of BINAM **7** (2 mmol) in CH_2Cl_2 or toluene for 2 h. The amine borane was activated with 1 mmol of I_2 and α-methylstyrene (2 mmol) was added after the activation of amine borane.
[b]Yields are for the isolated products.
[c]Determined by HPLC analysis using the chiral column OB-H; Hex:^{i}PrOH:97:3, 0.3 mL/min. The chiral alcohol obtained in all the cases having *S*-absolute configuration.
[d]Unless otherwise mentioned activating agent was added prior to the addition of substrate.
[e]The same reaction in CH_2Cl_2 solvent at 25 ^oC gave 77% yield of the product. The product obtained was racemic.
[f]Similar reaction carried out in diglyme solvent with 50 mol% of I_2 yield 28% of racemic alcohol product.
[g]50 mol% of I_2 was used.
[h]Similar reaction quenched after 1 h, the formation of product was not observed.
[i]20 mol% of I_2 was used.
[j]100 mol% of triflic acid was used.

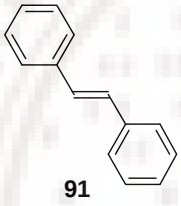
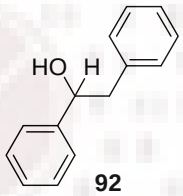
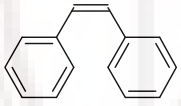
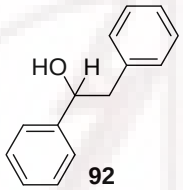
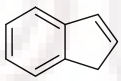
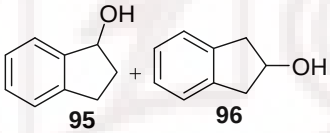
A plausible mechanism for the asymmetric induction (Table **3**, entry 4) can be considered as outlined in Scheme **20**. The reaction of iodine with amine-borane would give the amine- BH_2I complex **89** and hydrogen. In reaction with olefin, if iodine serves as a leaving group in the transition state, the chiral amine would be still attached to the boron leading to the optically active product (Path A, Scheme **20**). However, if the chiral amine leaves before the hydroboration of olefin, only the racemic product would result (Path B, Scheme **20**).

Scheme 20



The hydroboration reaction of 1,2-substituted prochiral olefins **91**,**93** and **94** were also carried out using the BINAM-borane complex. The yield of the alcohol formed after the hydroboration-oxidation reaction of *trans* and *cis* stilbene **91** and **93** were high.

Table 4 Hydroboration of prochiral olefins with BINAM-borane complex[a]

Entry	Substrate	Temp. (°C)	Product	Yield (%)[d]	ee (%)
1[b]	 **91**	25	 **92**	82	(*S*)-2[e]
2[c]	 **93**	25	 **92**	86	(*S*)-2[e]
3[g]	 **94**	25	 **95** : **96** 1 : 9	49	(±)[f]

[a]All the reactions were carried out by purging excess B_2H_6 through a solution of BINAM (2 mmol) in toluene at 0 °C. The amine borane was activated with 1 mmol of I_2. Substrate (2 mmol) was added after the activation of iodine and the reaction mixture was warmed to room temperature and stirred for further 8 h.

[b]The reaction was carried out in CH_2Cl_2 solvent yield the racemic alcohol.

[c]Similar reaction at 0 °C for 4 h, the formation of product was not observed. The olefin remains unreacted.

[d]Yields are of isolated products.

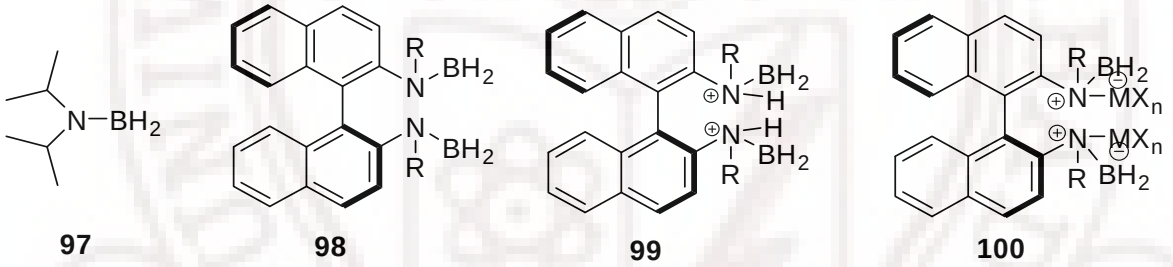
[e]Determined by HPLC analysis using the chiral column, Chiralcel OD-H; 90:10, hexanes:*i*-PrOH, 0.3 mL/min. The alcohol obtained are having *S*-absolute configuration.

[f]Determined by HPLC analysis using the chiral column, Chiralcel OB-H; 98:2, hexanes:*i*-PrOH, 0.5 mL/min.

[g]Similar reaction carried out at -20 °C, the olefin remains unreacted.

Unfortunately, the enantioselectivity of the alcohol **92** obtained was very poor (Table **4**, entry 1 and 2). In the case of indene **94**, the achiral β-indanol **96** was formed as major product. Presumably, in the case of 1,2-disubstituted olefins, the crowded transition state in the S_N^2-pathway would be crowded leading to departure of the amine instead of the iodide (Path B, Scheme **20**).

Recently, the aminoborane **97** has been prepared as a stable compound (Figure **4**).[31b] It was reported that the compound **97** does not hydroborate olefins under ambient conditions.



97 **98** **99** **100**

Figure 4

Systematic studies using such aminoborane derivatives derived from the corresponding chiral 1,1′-binaphthyl-2,2′-diamine **98** and studies on the activation of such derivatives towards hydroboration by Bronsted or Lewis acids, through preparation of intermediates of **99** or **100**, would give more fruitful results.

4.3 Conclusions

The axially chiral ligands *N,N,N′,N′*-tetramethyl BINAM **26** and *N,N,N′,N′*-tetraethyl BINAM **78** were prepared from (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine **7**. The asymmetric hydroboration reaction of prochiral olefins such as α-methyl styrene, *trans*-stilbene, *cis*-stilbene and indene were carried out using the borane complexes of the chiral amines **7**, **26**, **76** and **78**. Only in the case of BINAM-borane, the alcohol **58** was obtained in 11% ee, indicating that the reaction is highly sensitive to steric effects.

4.4 Experimental Section

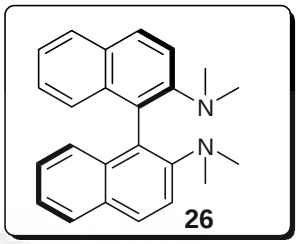
4.4.1 General Information

Several informations given in the section **1.4.1** are also applicable for the experiments outlined in this section. The *R*-(+)-1,1′-binaphthyl-2,2′-diamine was purchased from Gerchem Labs (P) Ltd., Hyderabad. The tetrabutylammonium hydrogen sulphate was purchased from Loba Chemie (P), Ltd., India. The sodium borohydride was purchased from E-Merck, India.

4.4.2 Procedure for the synthesis of BINAM derivatives

4.4.2.1 Preparation of (*R*)-*N,N,N′,N′*-tetramethyl-1,1′-binaphthyl-2,2′-diamine (26)

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



26

Yield 1.33 g (78%)

mp 205-207 ^{o}C (Lit.[32] 216-218)

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

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.5 (s, 12H), 7.18-7.19 (m, 4H), 7.28-7.32 (m, 2H), 7.50 (d, 2H, *J* = 8.8 Hz), 7.83 (d, 2H, *J* = 8.3 Hz), 7.90 (d, 2H, *J* = 8.8 Hz) **(Spectrum No. 27)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 43.5, 120.7, 123.4, 125.9, 126.1, 126.3, 127.8, 128.5, 129.8, 134.7, 149.8 **(Spectrum No. 28)**

LCMS m/z 341 (M+1)

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

Analysis Calculated for $C_{24}H_{24}N_2$: C, 84.67 %; H, 7.11%; N, 8.23%

Found : C, 84.69%; H, 7.16 %; N, 8.12%

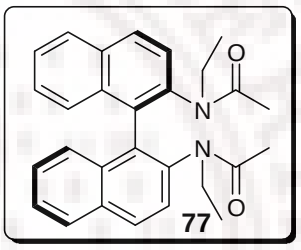
4.4.2.2 Preparation of (*R*)-*N,N′*-diacetyl-1,1′-binaphthyl-2,2′-diamine (75) and (*R*)-*N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine (76)

The products **75** and **76** were prepared by following the procedure reported in Chapter **3**, Section **3.4.5.2** and **3.4.5.3**.

4.4.2.3 Preparation of (*R*)-*N,N′*-diacetyl-*N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine (77)

To a solution of (*R*)-*N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine (1.70 g, 5 mmol) and pyridine (1.19 g, 1.2 mL, 15 mmol) in dry THF (20 mL), acetyl chloride (0.94 g, 0.85 mL, 12 mmol) in 2 mL dry THF was slowly added through syringe over a period of 5 min at 0 ^{o}C under nitrogen atmosphere. The reaction mixture was slowly warmed to 25 ^{o}C and

stirred at the same temperature for 12 h. The reaction mixture was quenched with water (20 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with 3N HCl (20 mL), saturated $NaHCO_3$ solution (2 x 10 mL), water (2 x 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by silica gel (100-200 mesh) column using hexane: ethyl acetate (95:5) as eluent.



77

Yield 1.69 g (80%)

mp 216-218 ^{o}C

IR (KBr) (cm^{-1}) 2964, 1956, 1655, 1589, 1502

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.80 (t, 6H, *J* = 6.8 Hz), 1.97 (s, 6H), 2.44-2.50 (m, 2H), 3.72-3.78 (m, 2H), 6.91 (d, 2H, *J* = 8.4 Hz), 7.28-7.36 (m, 4H), 7.52-7.56 (m, 2H), 8.0 (d, 2H, *J* = 8.3 Hz), 8.05 (d, 2H, *J* = 8.7 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 12.4, 23.4, 41.51, 126.1, 126.6, 127.4, 128.4, 129, 129.7, 130.5, 132.3, 133.9, 139, 171.3

LCMS m/z 425 (M+1)

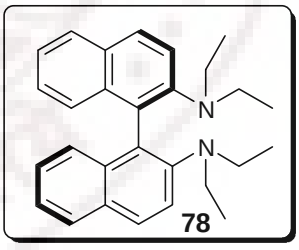
$[\alpha]_D^{25}$ +419.3 (*c* 1, $CHCl_3$)

Analysis Calculated for $C_{28}H_{28}N_2O_2$: C, 79.22%; H, 6.65%; N, 6.60%; O, 7.54%

Found : C, 79.18%; H, 6.68%; N, 6.72%; O, 7.42%

4.4.2.4 Procedure for the preparation of (*R*)-*N,N,N′,N′*-tetraethyl-1,1′-binaphthyl-2,2′-diamine (78)

To a stirred suspension of $NaBH_4$ (1.14 g, 30 mmol) in dry THF (30 mL), iodine (3.17 g, 12.5 mmol) in dry THF (20 mL) was added drop wise through an addition funnel at 0 ^oC under nitrogen atmosphere over a period of 30 minutes. After the disappearance of iodine colour, (*R*)-*N,N′*-diacetyl-*N,N′*-diethyl-1,1′-binaphthyl-2,2′-diamine (2.12 g, 5 mmol) in dry THF (15 mL) was added slowly over a period of 10 minutes. The reaction mixture was brought to room temperature and then refluxed for 12 h. The reaction mixture was quenched with 5N HCl (20 mL). The organic layer was separated and the aqueous layer was neutralized with 5N NaOH till the solution becomes slightly basic and extracted with ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by silica gel (230-400 mesh) column using hexanes: ethyl acetate (98:2) as eluent.



78

Yield 1.43 g (72%)

mp 76-78 ^oC

IR (KBr) (cm^{-1}) 3057, 2968, 1954, 1612, 1593, 817, 750

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.68 (t, 12H, *J* = 7.0 Hz), 2.78-2.88 (m, 8H), 7.04 (d, 2H, *J* = 8.3 Hz), 7.09-7.13 (m, 2H), 7.24-7.28 (m, 2H), 7.46 (d, 2H, *J* = 8.8 Hz), 7.80 (d, 2H, *J* = 8.1 Hz), 7.85 (d, 2H, *J* = 9 Hz) **(Spectrum No. 29)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 11.2, 49.4, 120.6, 125.8, 126.5, 127.8, 128.6, 131.4, 131.7, 133.8, 161.9 **(Spectrum No. 30)**

LCMS m/z 397 (M+1)

Analysis Calculated for $C_{28}H_{32}N_2$: C, 84.80%; H, 8.13%; N, 7.06%

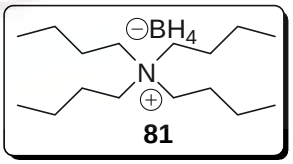
Found : C, 84.87%; H, 8.08%; N, 6.98%

$[\alpha]_D^{25}$ -64.68 (*c* 0.13, $CHCl_3$)

4.4.3 Asymmetric hydroboration of prochiral olefins with BINAM ligands

4.4.3.1 Preparation of tetrabutylammonium borohydride (81)

To a single neck round bottom flask tetrabutylammonium hydrogen sulphate (33.95 g, 100 mmol) was dissolved in distilled water (20 mL). A 5M NaOH (25 mL) was added to it and the mixture was cooled to room temperature. A solution of $NaBH_4$ (4.18 g, 110 mmol) dissolved in distilled 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 again 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.



81

Yield 24.5 g (95%)

IR (KBr) (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), 1.46-1.48 (m, 2H), 1.62-1.65 (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

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

To a stirred solution of tetrabutylammonium borohydride **81** (1.02 g, 4 mmol) in dry toluene (5 mL), iodine (0.50 g, 2 mmol) dissolved in dry toluene (35 mL) was added drop wise over a period of 4 h. The generated diborane 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 ^{o}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 triphenylphosphine borane complex using hexane/ethyl acetate (97:3) as eluent.

Yield 0.31 g (28%)

mp 187 ^{o}C (lit.[33] mp 188 ^{o}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}

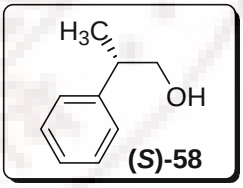
4.4.3.3 General procedure for the hydroboration reaction of olefins using the diborane gas generated *in situ*

To a stirred solution of tetrabutylammonium borohydride (1.28 g, 5 mmol) in toluene/CH_2Cl_2 (15 mL) at 0 ^oC under nitrogen atmosphere, (*R*)-(+)-binaphthyl diamine (0.57 g, 2 mmol) was added and the reaction mixture was stirred at the same temperature for 10 minutes. To the reaction mixture, methyl iodide (0.7 g, 0.31 mL, 5 mmol) in 20 mL of toluene/CH_2Cl_2 was slowly added through a pressure equalizing addition funnel over a period of 30 minutes. After the completion of the addition, iodine (1 mmol) or triflic acid (2 mmol) in CH_2Cl_2/toluene (2 mL) was added drop wise to the reaction mixture at the above mentioned temperature through syringe. The reaction mixture was further stirred at the same temperature for 15 minutes and the olefin (2 mmol) in 5 mL of toluene/CH_2Cl_2 was slowly added to the reaction mixture through a syringe for 5 minutes. After stirred for the required time, the reaction mixture was quenched with methanol (10 mL) and the oxidation was carried out by adding 3N NaOH (10 mL) and H_2O_2 solution (30% solution, 5 mL) to the reaction mixture. The reaction mixture was stirred at room temperature for further 6 h. The reaction mixture was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with water (1 x 20 mL), brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (230-400 mesh) using hexanes/ethyl acetate (99/1) as eluent.

4.4.3.4 General procedure for the hydroboration reaction of olefins using the diborane gas generated *ex situ*

The diborane gas was generated *ex situ* by the slow addition of methyl iodide (2.8 g, 1.21 mL, 20 mmol) in 20 mL of dry toluene to a dispersion of tetrabutylammonium borohydride (20 mmol, 5.12 g) in 5 mL of dry toluene at 25 ^{o}C under nitrogen atmosphere. The diborane gas generated was purged to a solution of (*R*)-(+)-binaphthyl diamine (2 mmol) in CH_2Cl_2/toluene (10 mL) at 0 ^{o}C for 2 h. After completion, the bubbler was replaced with a stopper and the iodine (1 mmol) or triflic acid (2 mmol) in CH_2Cl_2/toluene was added drop wise at the aforementioned temperature through a syringe over a period of 5 minutes. The reaction mixture was stirred at the same temperature for further 15 minutes. The olefin (2 mmol) in 5 mL of CH_2Cl_2/toluene was then slowly added through a syringe over a period of 5 minutes. The quenching, oxidation and the purification of the products were carried out similar to the *in situ* method.

(*S*)-2-Phenylpropan-1-ol (58)



Yield 0.37 g (54%)

$[\alpha]_D^{25}$ -2.0 (*c* 1, $CHCl_3$), {Lit.[34] $[\alpha]_D^{25}$ -16.1 (*c* 0.51, $CHCl_3$)}

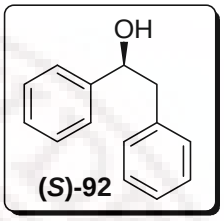
IR (neat) (cm^{-1}) 3375, 3050, 2950, 1603, 1057

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.22 (d, 3H, *J* = 6.8), 1.88 (br s, 1H), 2.86-3.12 (m, 1H), 3.62 (d, 2H, *J* = 6.5), 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% 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: 25.5 min. for major (*S*) and 27.6 min. for minor (*R*) isomer.

(*S*)-1,2-diphenylethan-1-ol (92)



Yield 0.72 g (72%)

mp 61-63 °C (Lit[35] 63-64 °C)

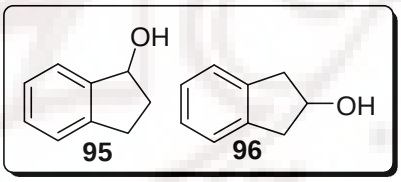
IR (KBr) (cm^{-1}) 3319, 3084, 2922, 1039, 696

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.02 (br s, 1H), 2.94-3.04 (m, 2H), 4.84-4.87 (m, 1H), 7.16-7.33 (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

Enantiomeric purity: 2% ee (determined by HPLC using chiral column, chiralcel OD-H, solvent system, hexanes:*i*-PrOH/90:10; flow rate 0.3 mL/min., 254 nm, retention times: 26.66 min (*R*) and 30.27 min (*S*).

Indanol



Yield 0.13 g (49%)

IR (KBr) (cm^{-1}) 3319, 3084, 2922, 1039, 696

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) (For β-indanol) 42.6, 73.1, 125.0, 126.7, 140.8

Additional signals for minor α-indanol: 29.8, 35.9, 124.2

Enantiomeric purity:[36] Racemic (determined by HPLC using chiral column, chiralcel OB-H, solvent system, hexanes:*i*-PrOH/98:2; flow rate 0.5 mL/min., 254 nm, retention times: 32.71 min (*R*) and 55.15 min (*S*). The β-alcohol comes at 38.1 retention time).

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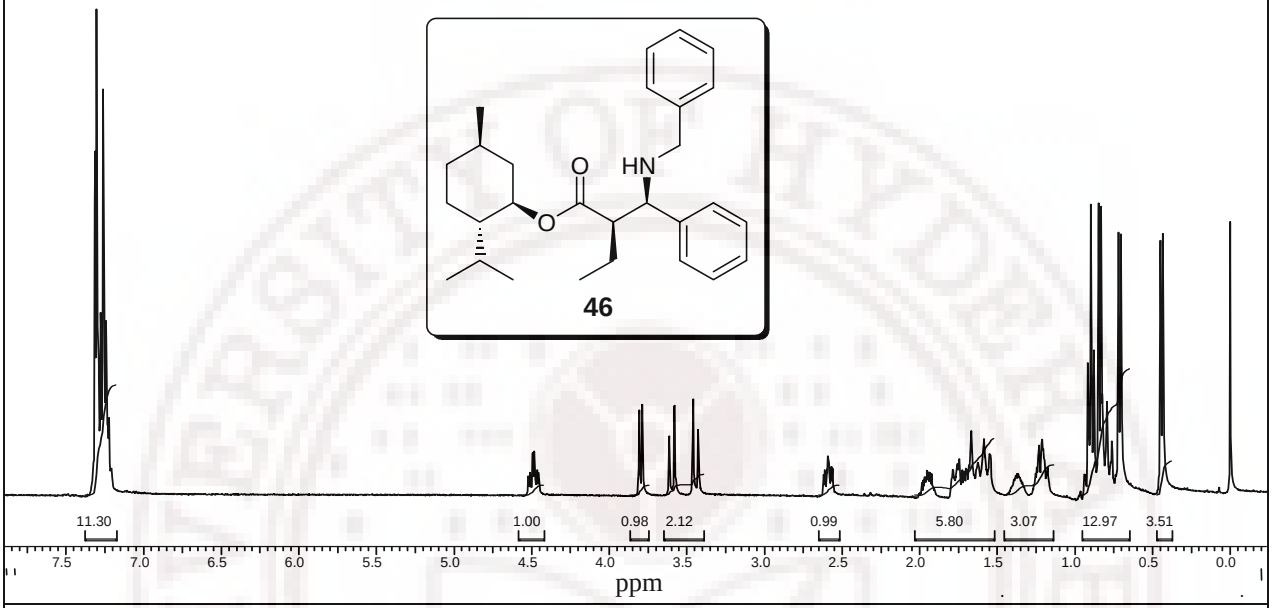
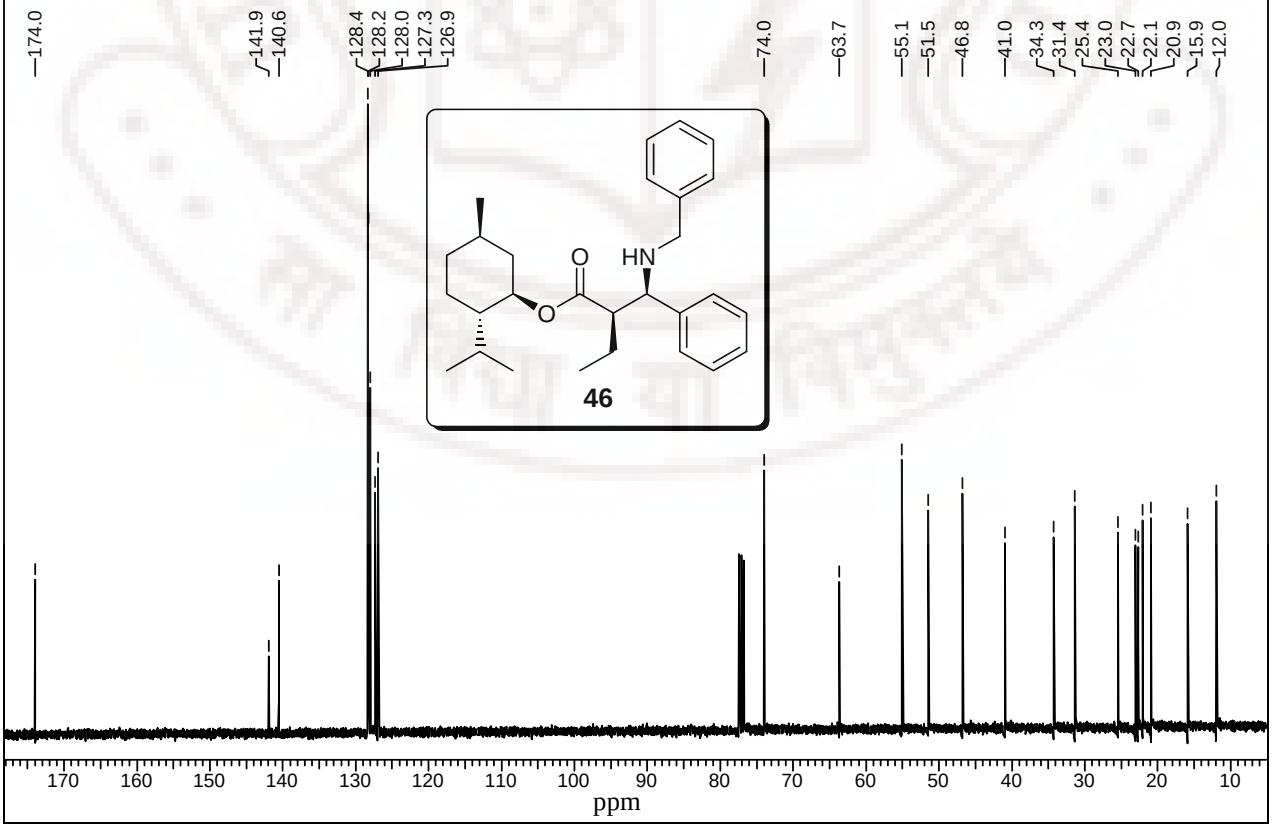
Appendix I

(Representative Spectra)

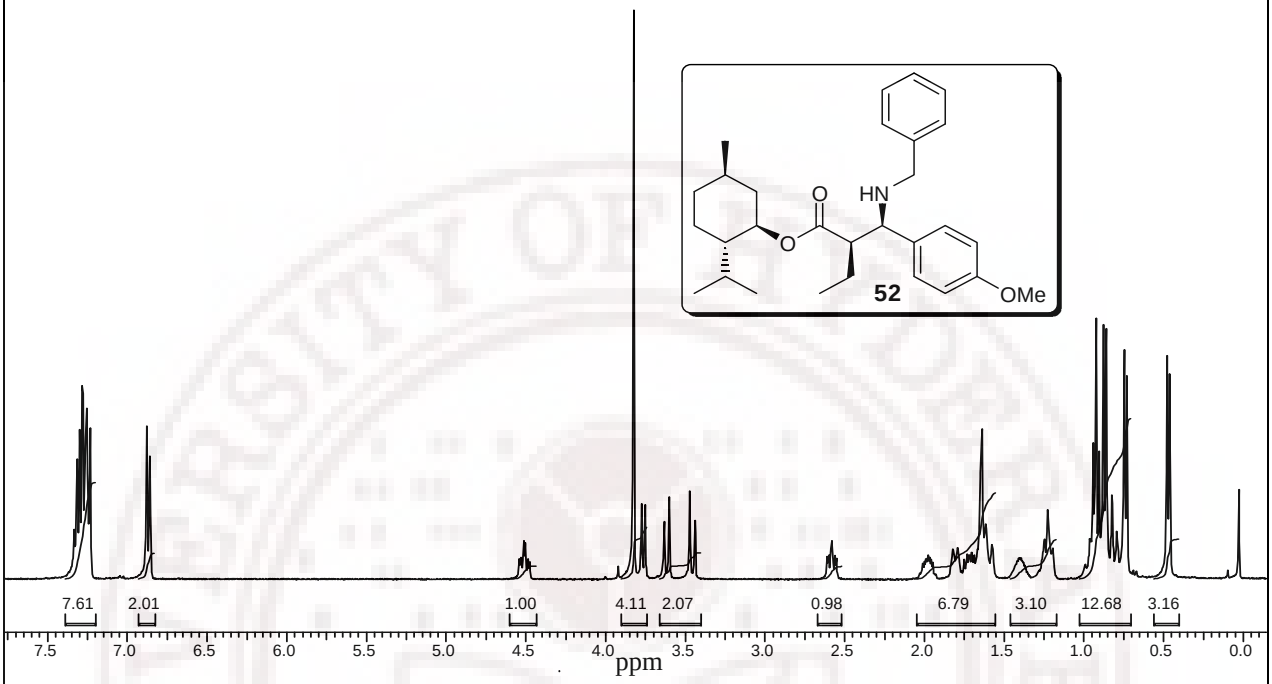
Spectrum No. 1 (Chapter 1, Section 1.4.3.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



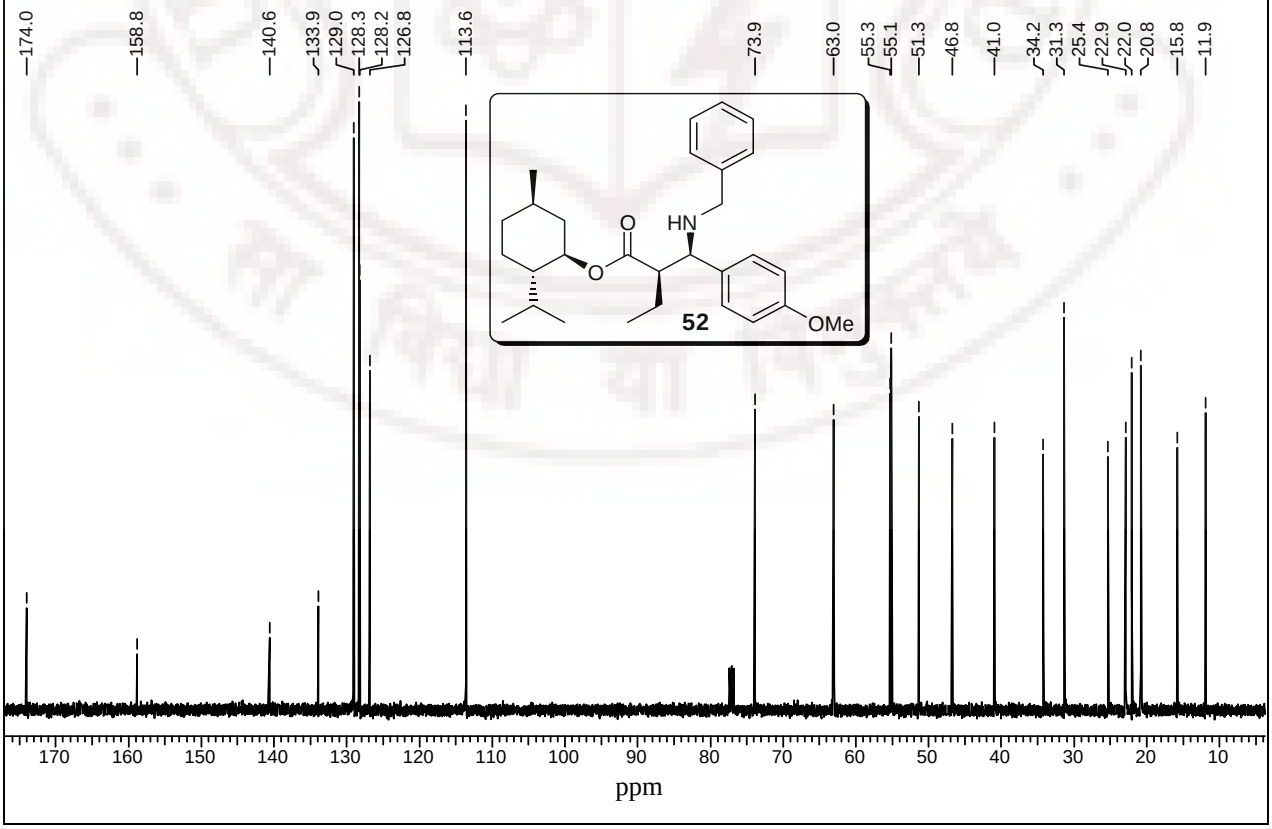
Spectrum No. 2 (Chapter 1, Section 1.4.3.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



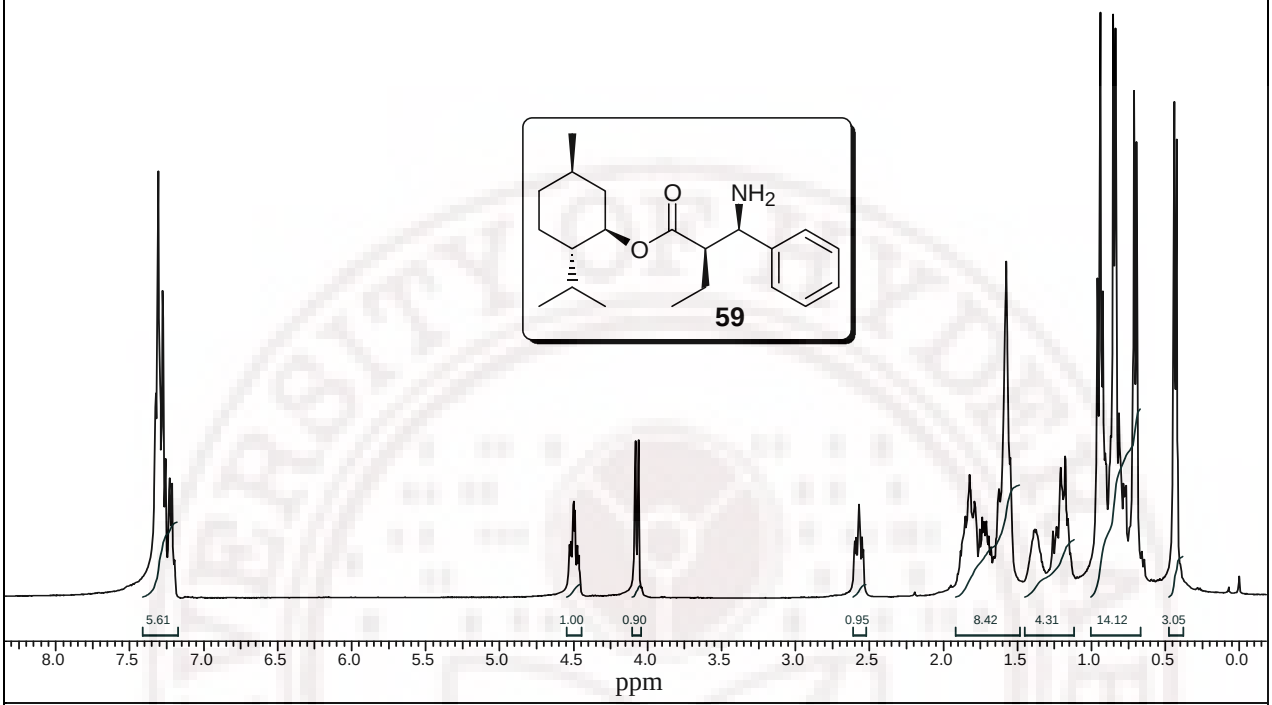
Spectrum No. 3 (Chapter 1, Section 1.4.3.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



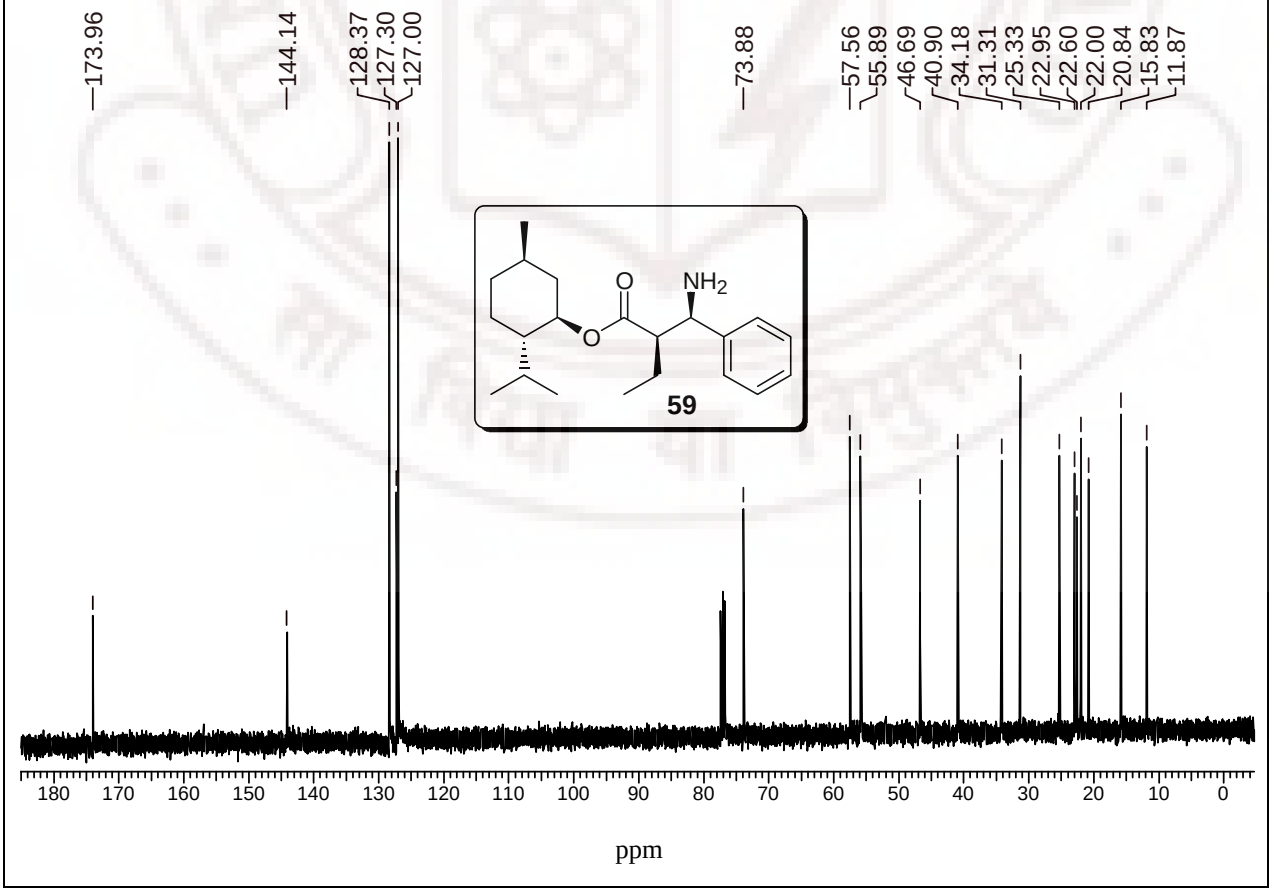
Spectrum No. 4 (Chapter 1, Section 1.4.3.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



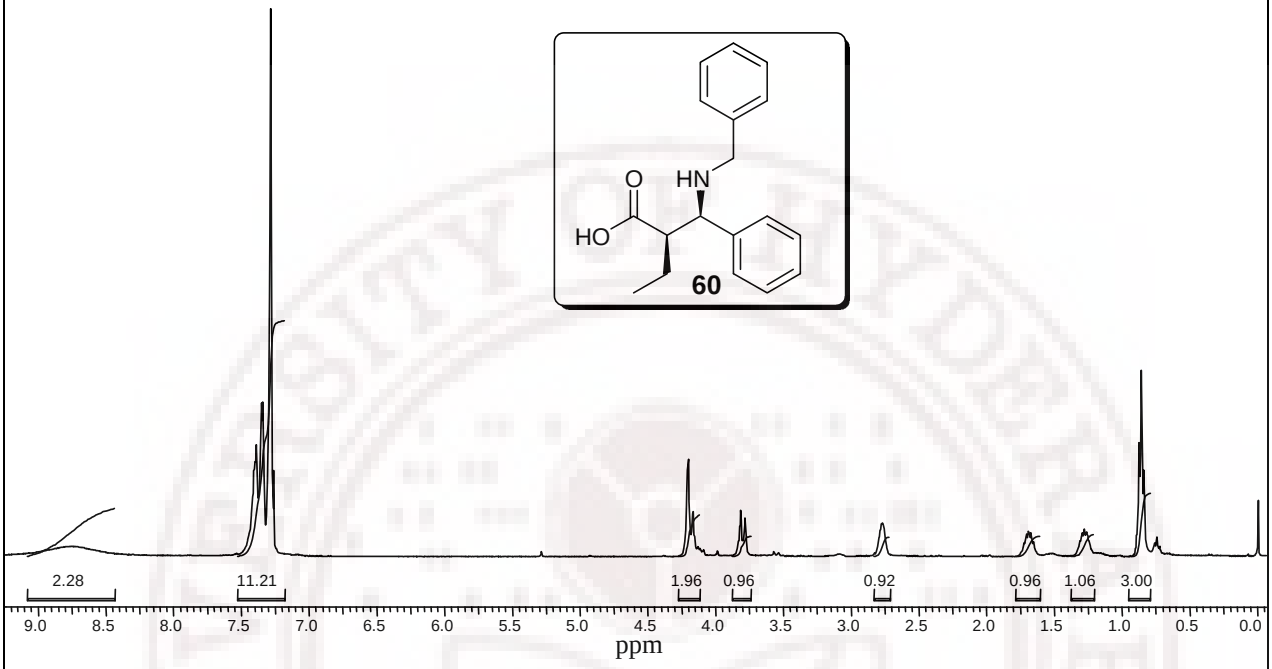
Spectrum No. 5 (Chapter 1, Section 1.4.5.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



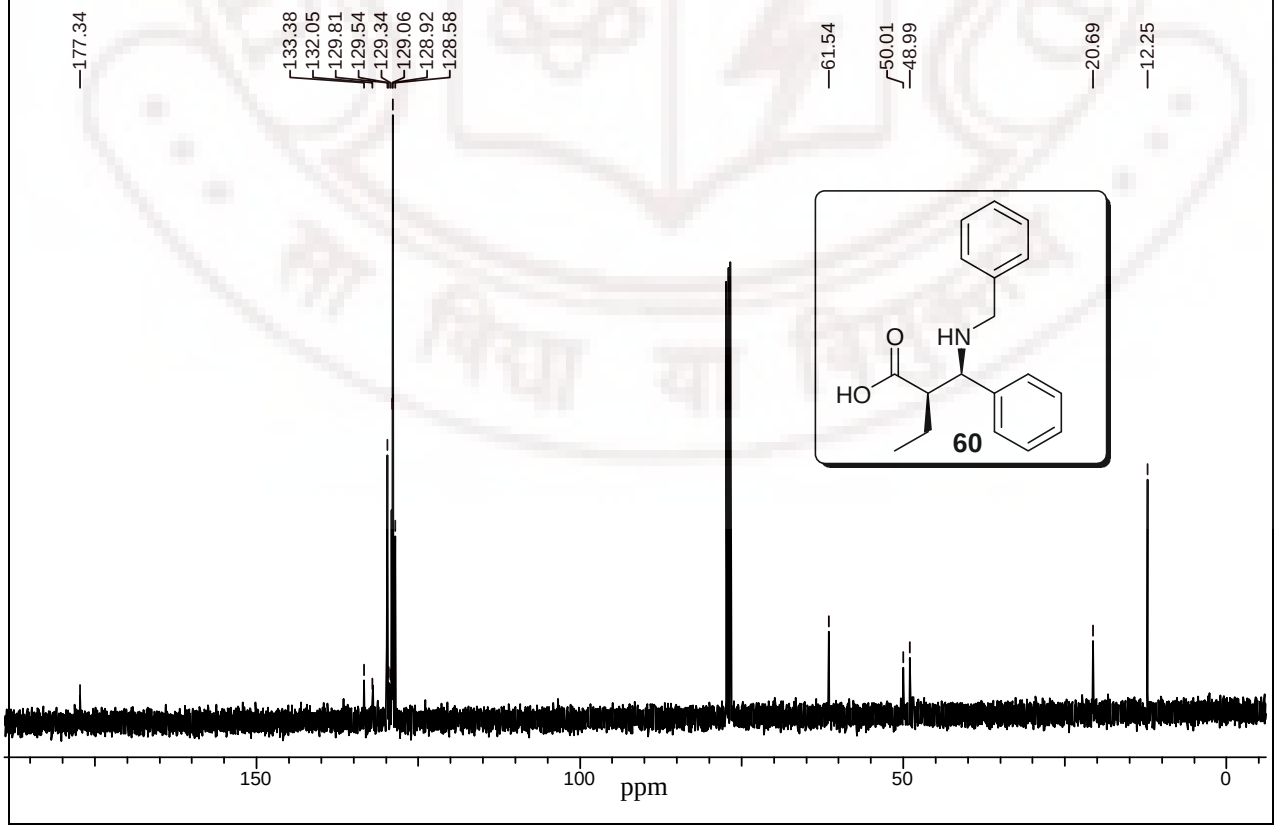
Spectrum No. 6 (Chapter 1, Section 1.4.5.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



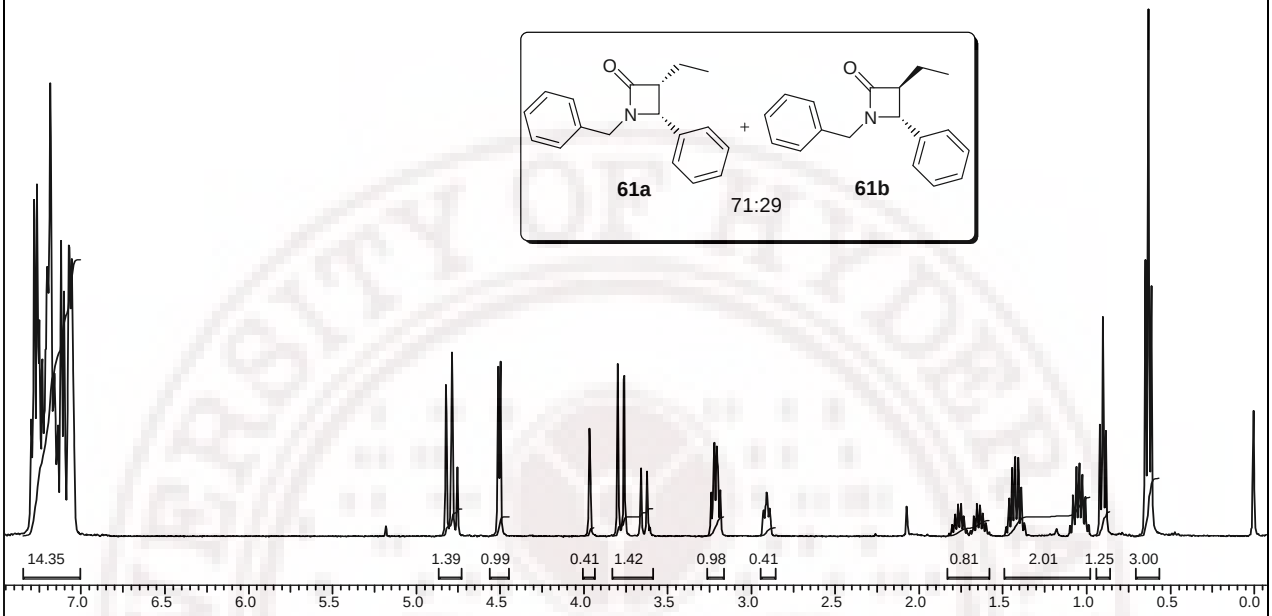
Spectrum No. 7 (Chapter 1, Section 1.4.6.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



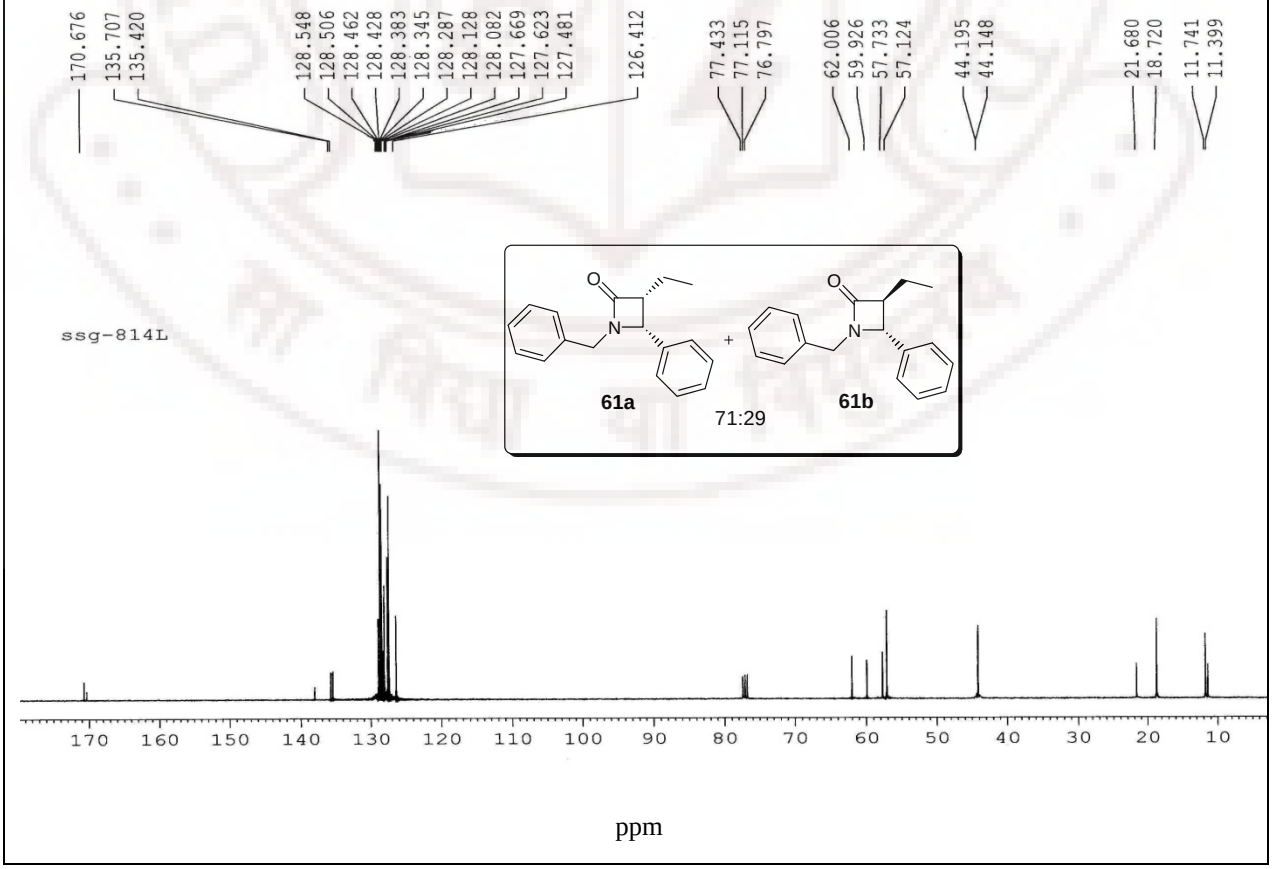
Spectrum No. 8 (Chapter 1, Section 1.4.6.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



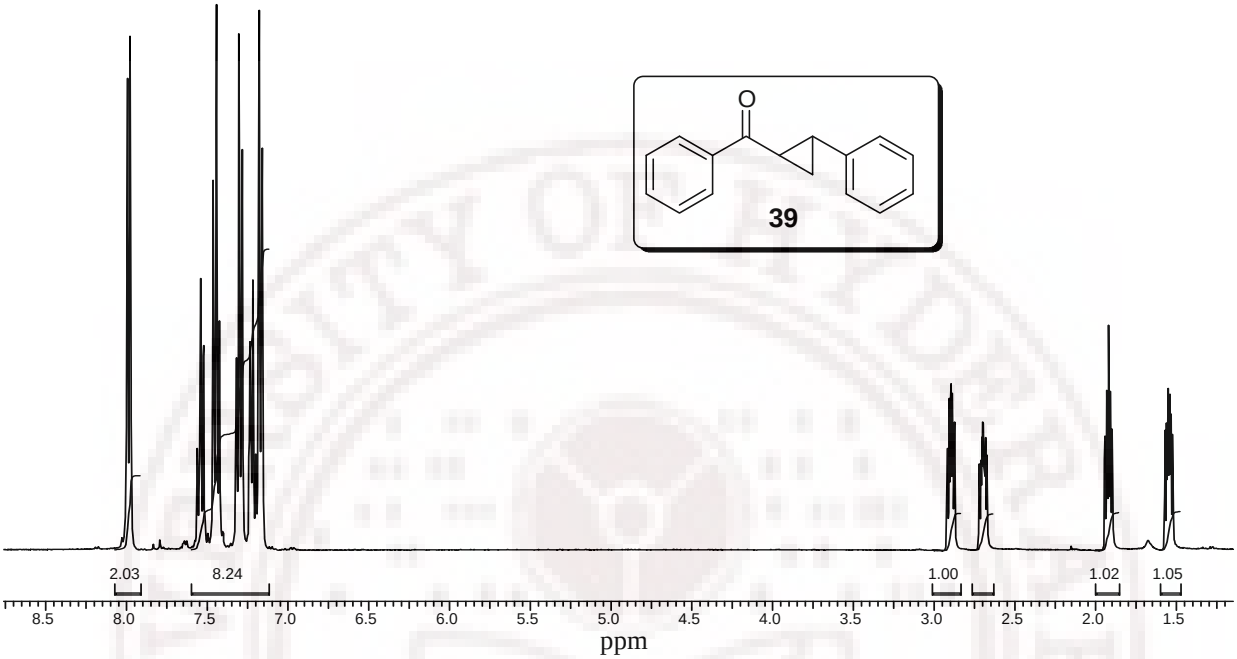
Spectrum No. 9 (Chapter 1, Section 1.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



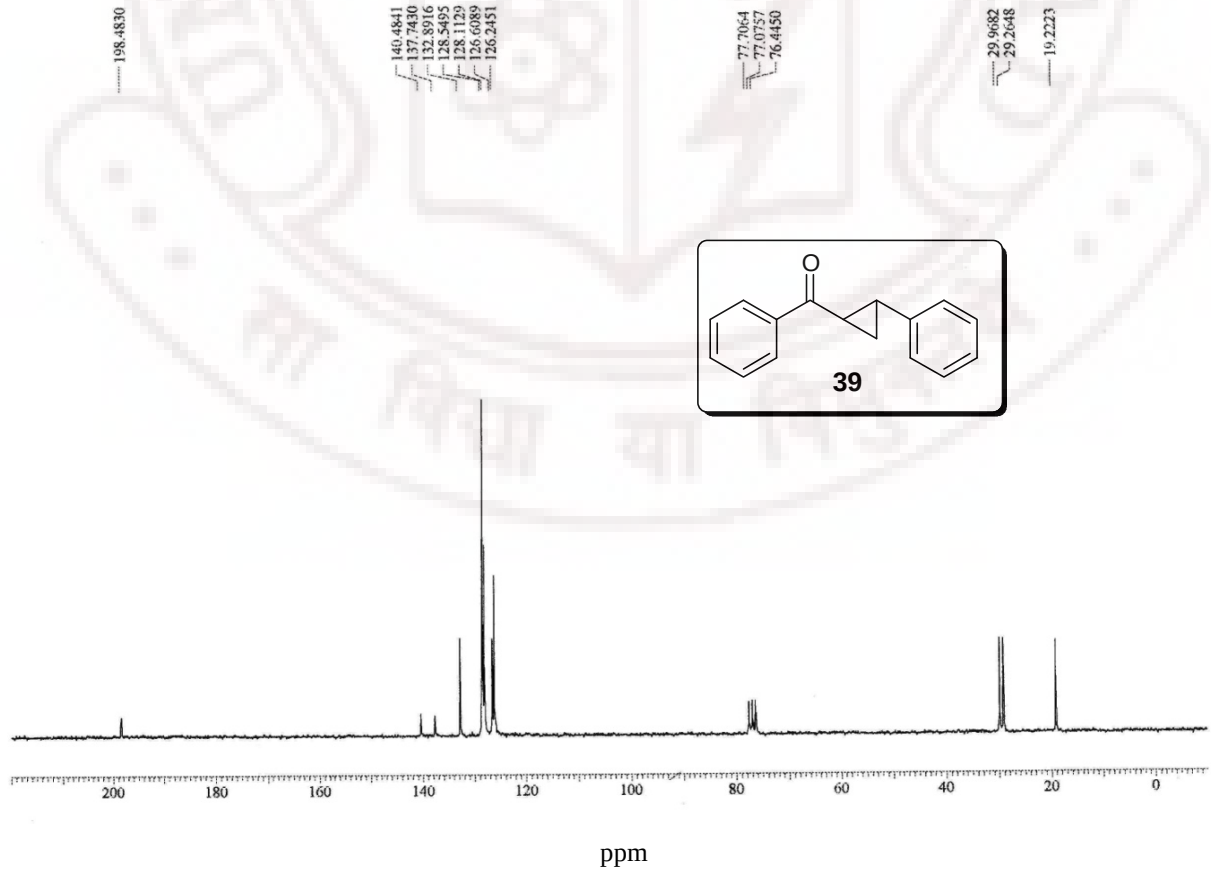
Spectrum No. 10 (Chapter 1, Section 1.4.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



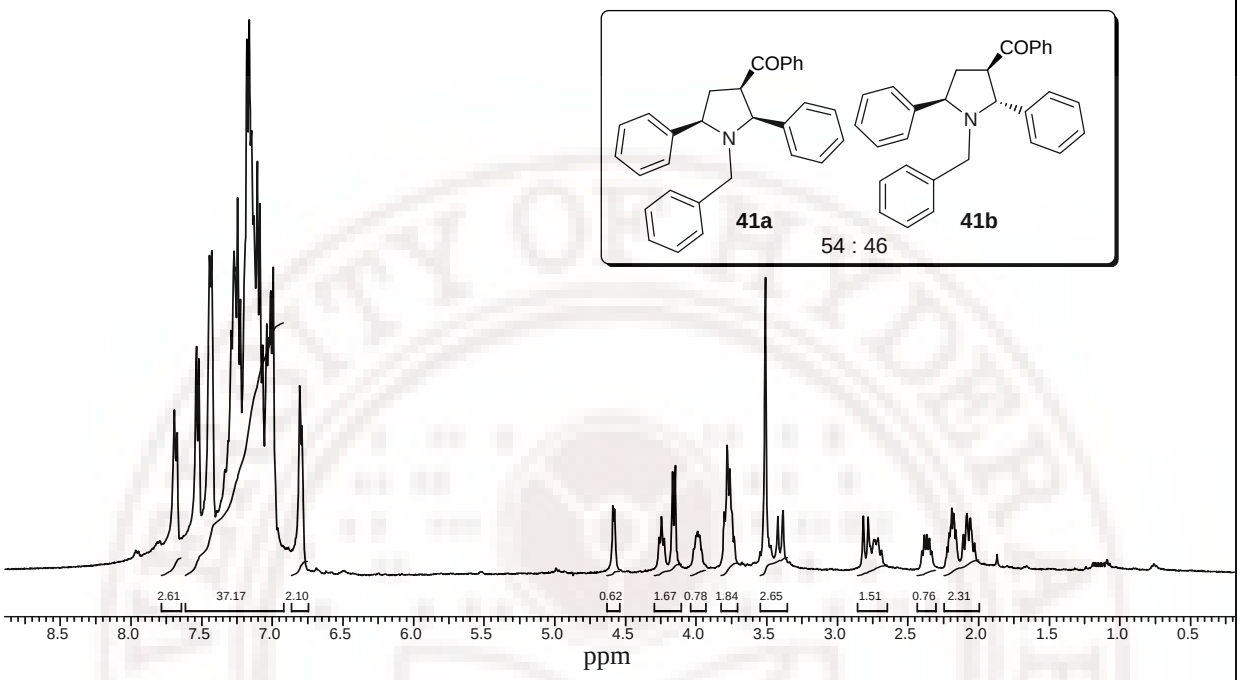
Spectrum No. 11 (Chapter 2, Section 2.4.1.2) ^{1}H NMR Spectrum (400 Hz, $CDCl_3$)



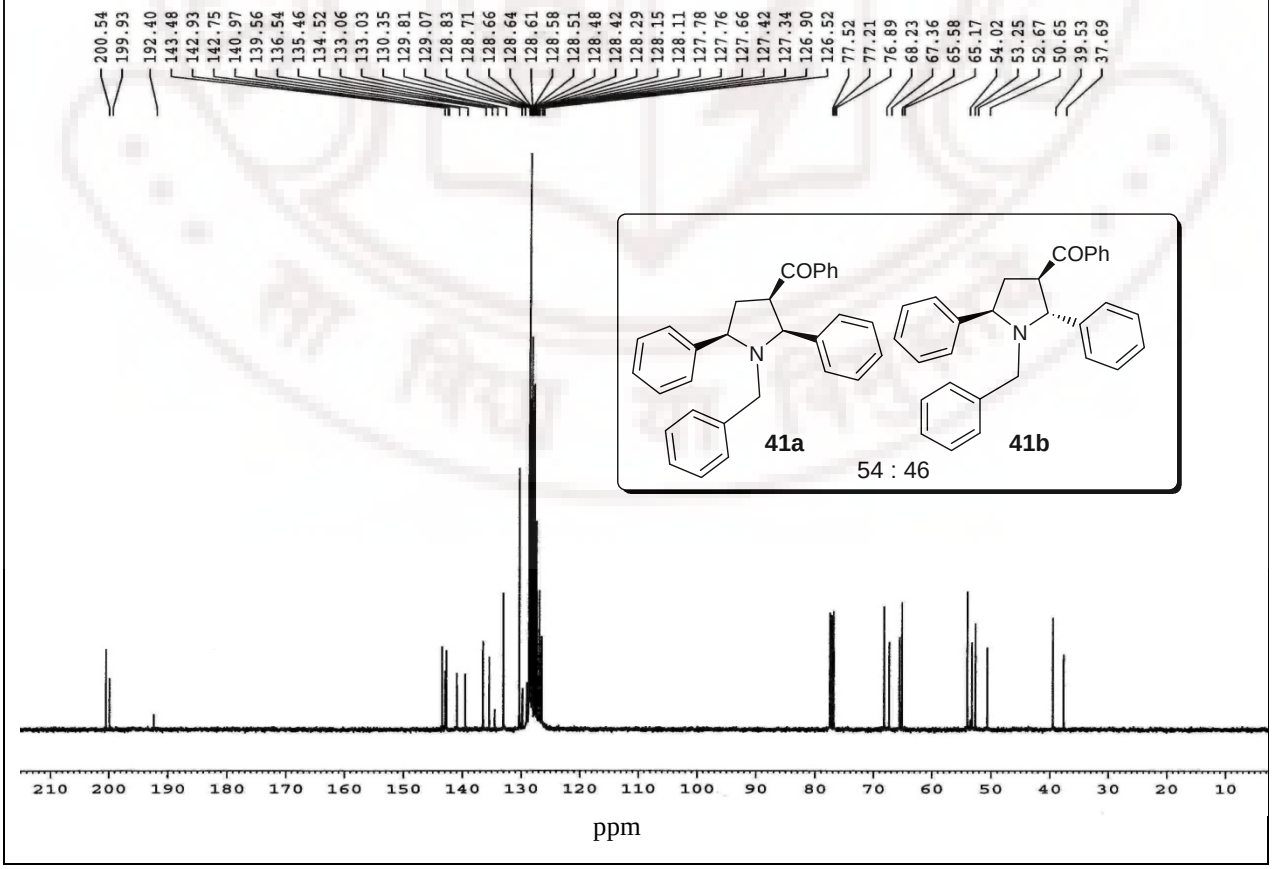
Spectrum No. 12 (Chapter 2, Section 2.4.1.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



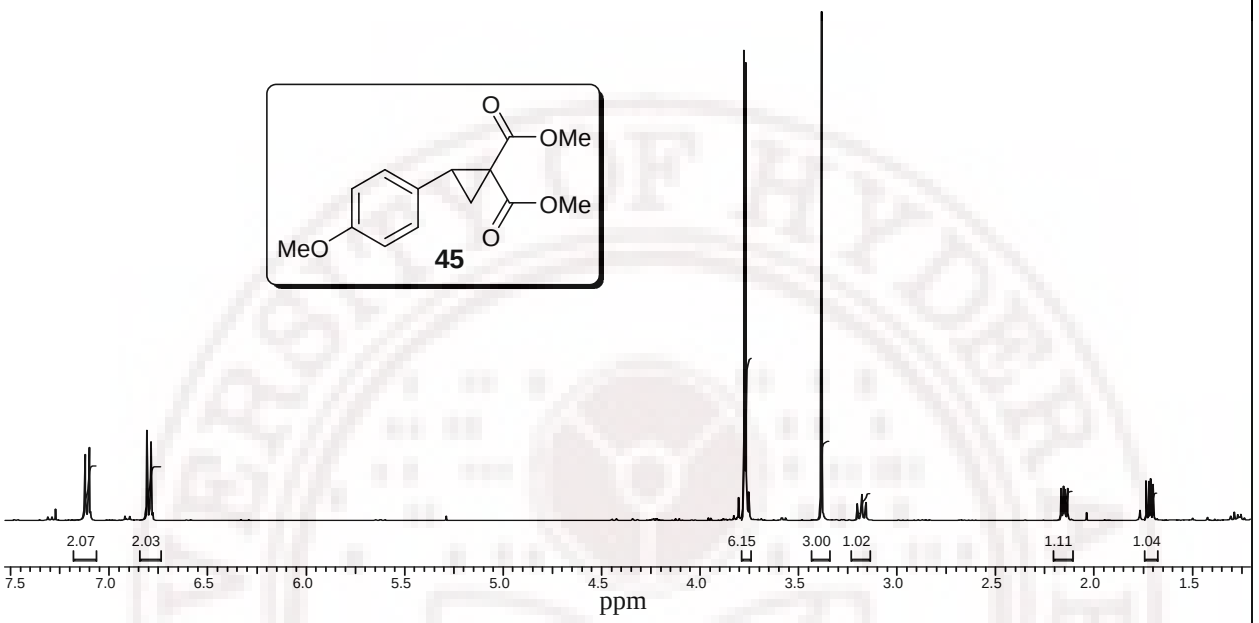
Spectrum No. 13 (Chapter 2, Section 2.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



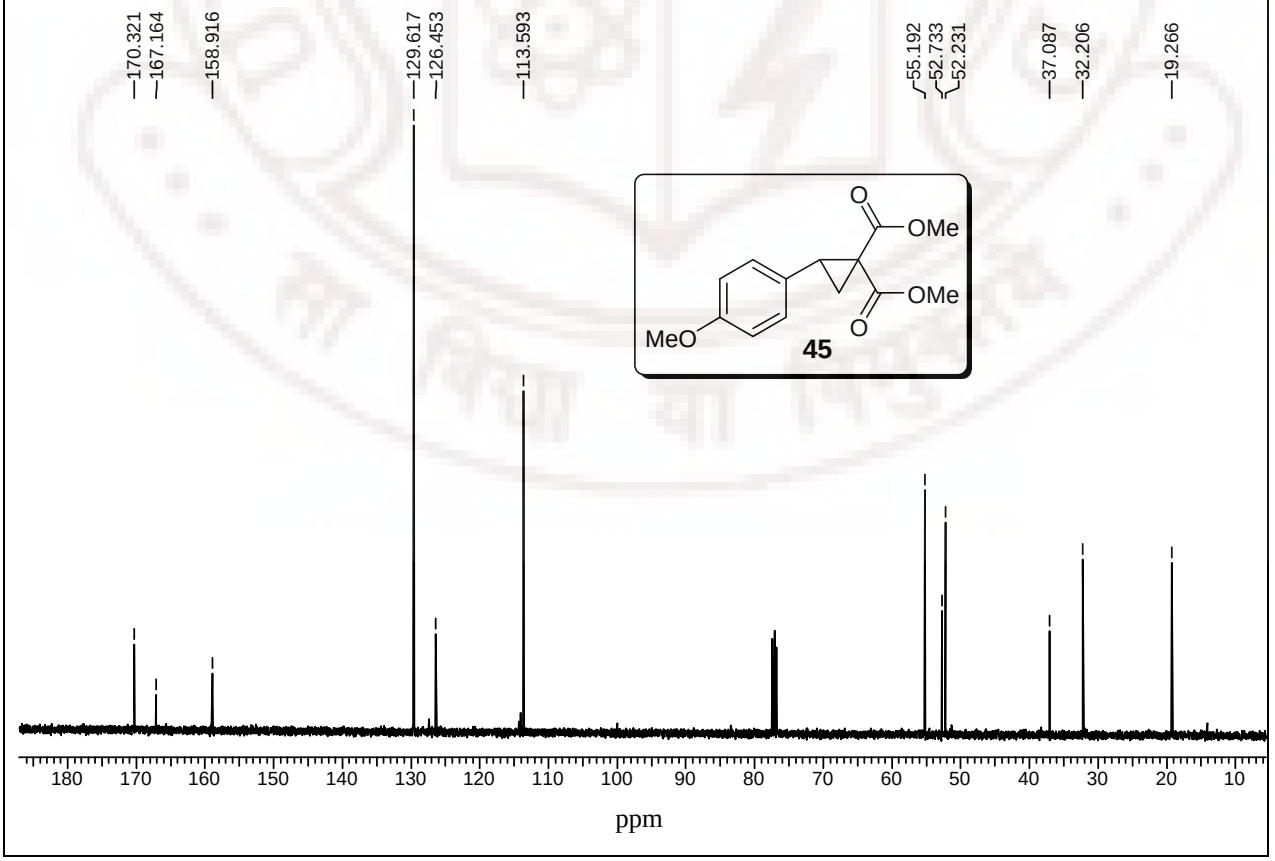
Spectrum No. 14 (Chapter 2, Section 2.4.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



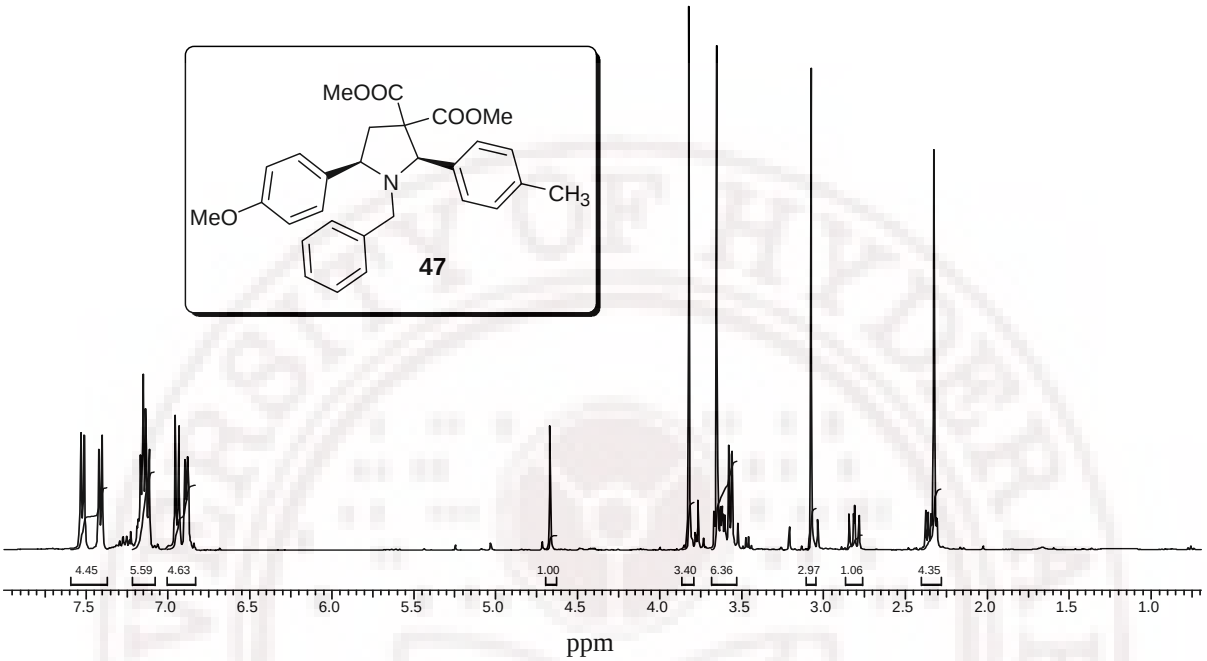
Spectrum No. 15 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



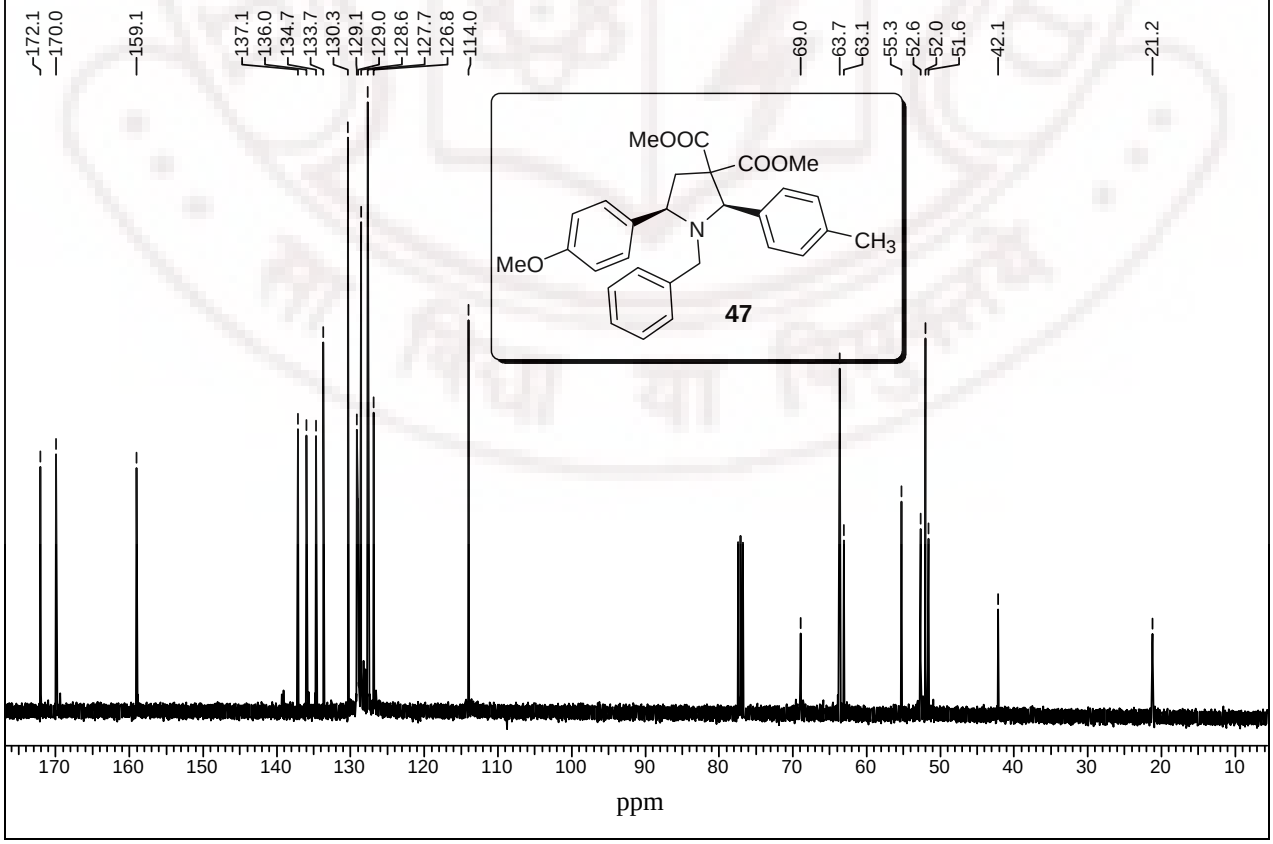
Spectrum No. 16 (Chapter 2, Section 2.4.3.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



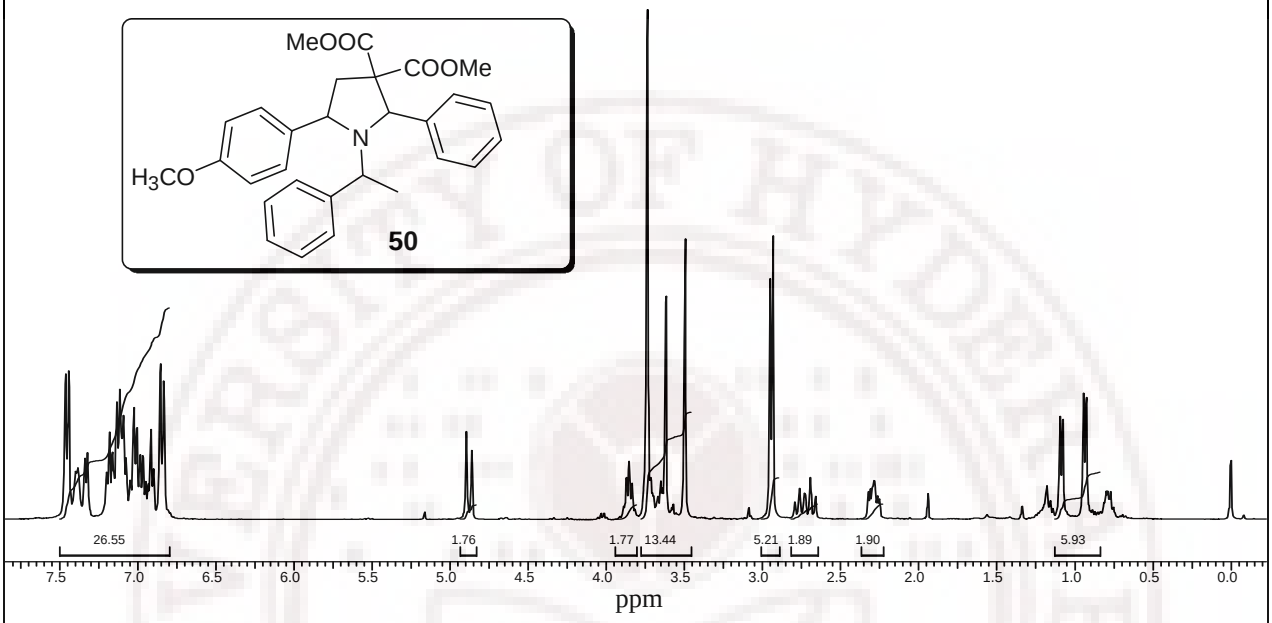
Spectrum No. 17 (Chapter 2, Section 2.4.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



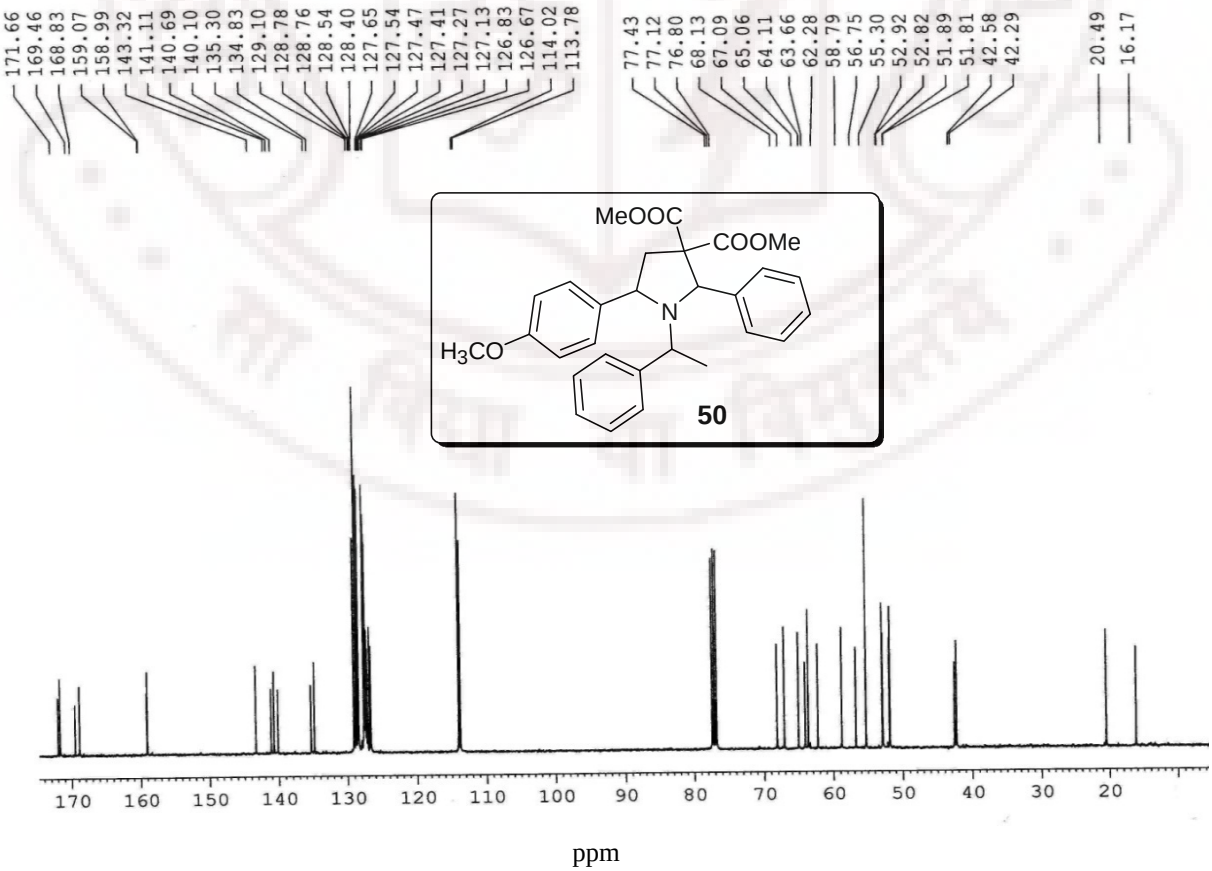
Spectrum No. 18 (Chapter 2, Section 2.4.4.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



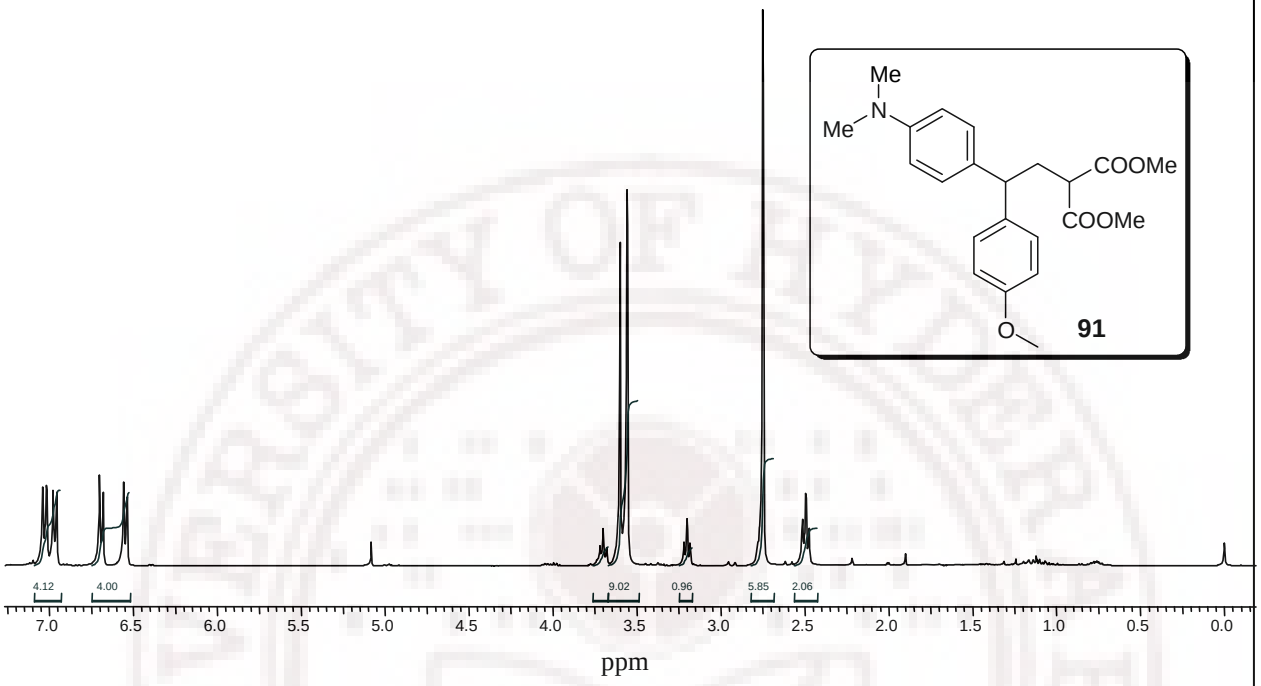
Spectrum No. 19 (Chapter 2, Section 2.4.4.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



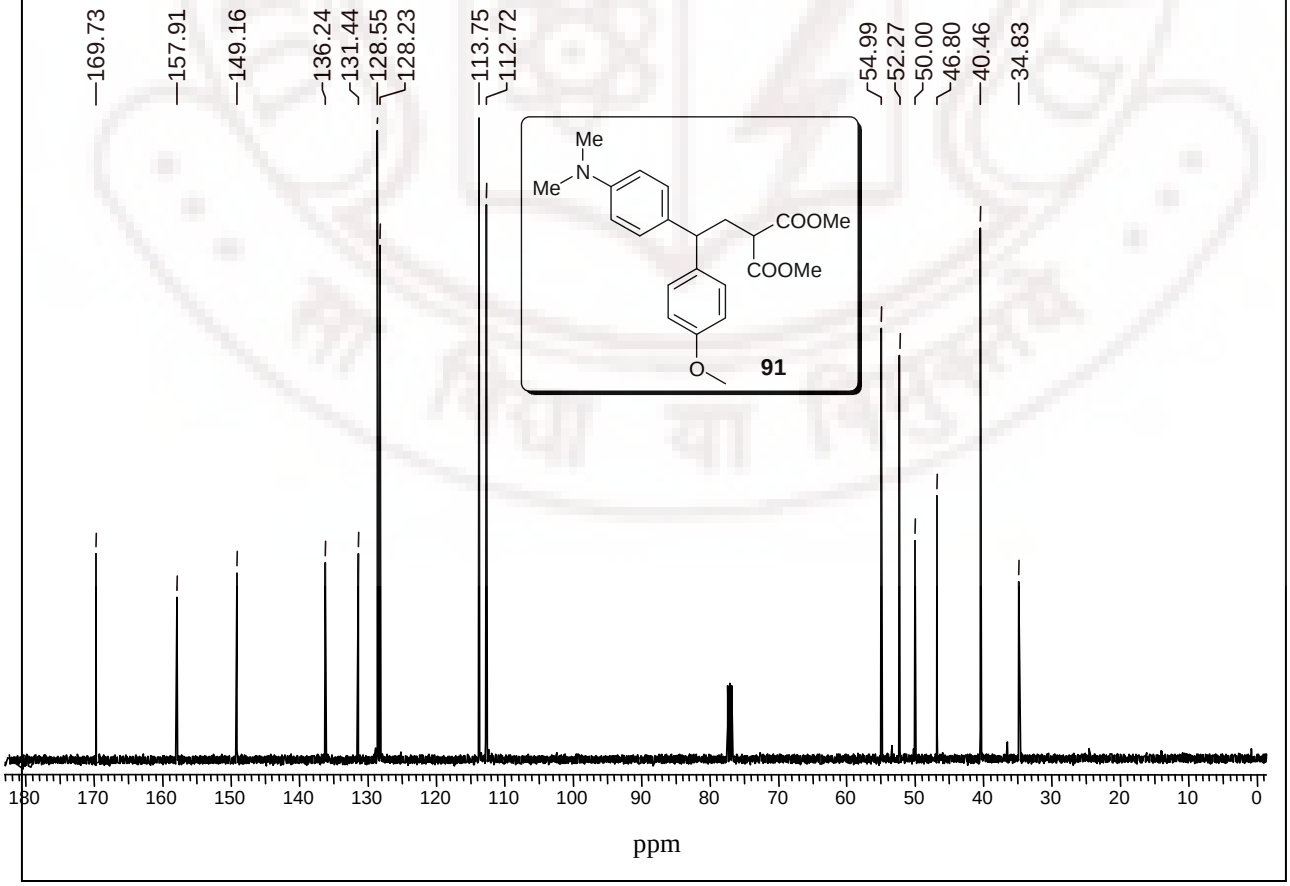
Spectrum No. 20 (Chapter 2, Section 2.4.4.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



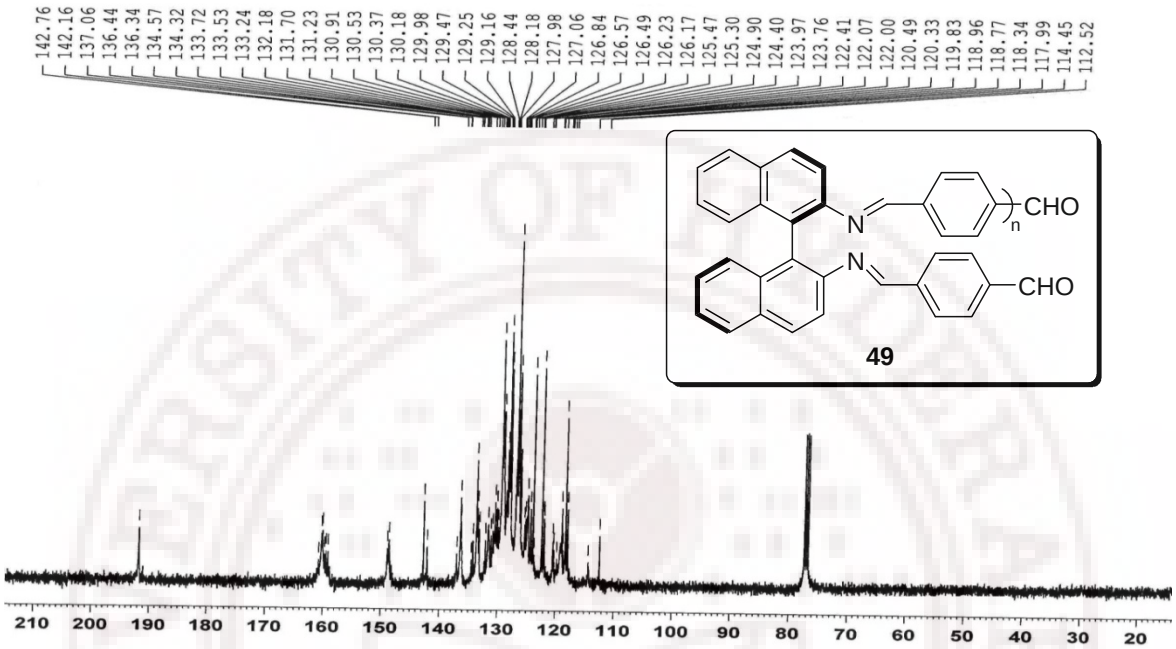
Spectrum No. 21 (Chapter 2, Section 2.4.5.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



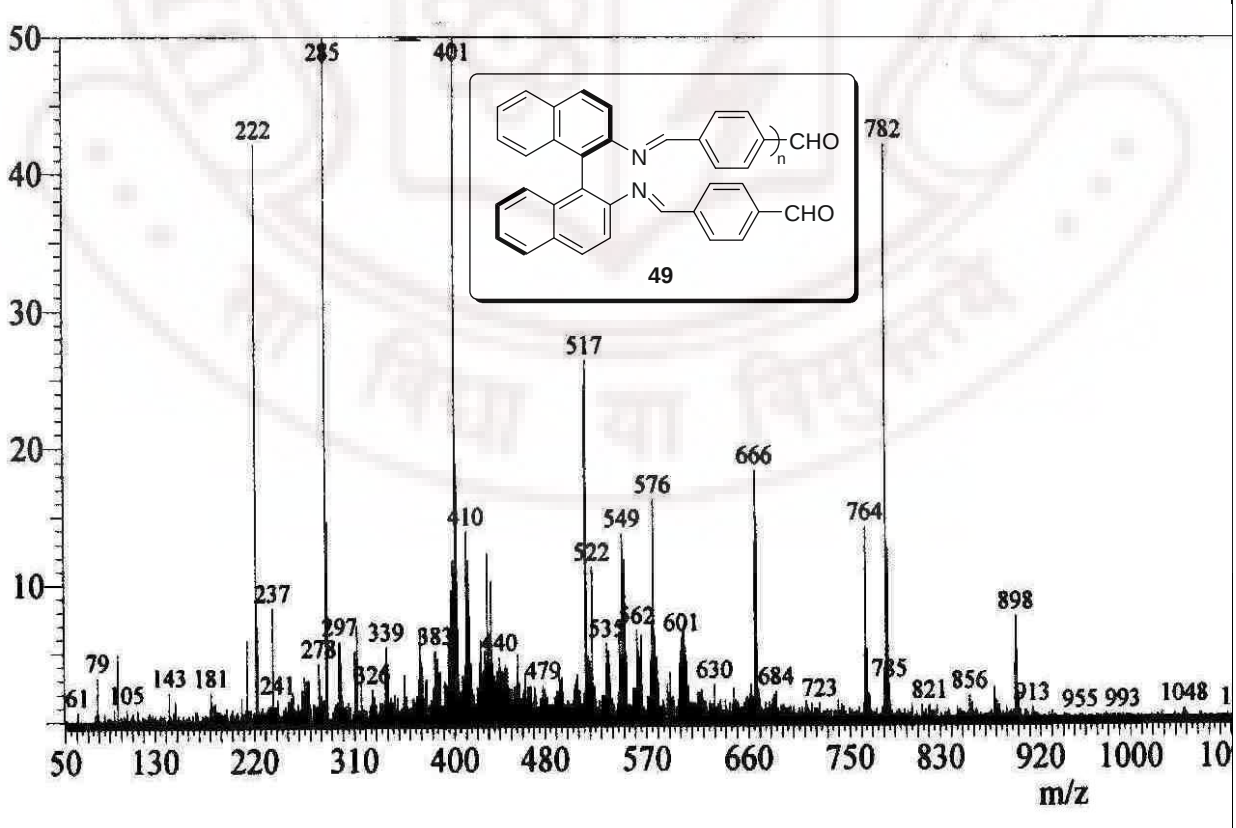
Spectrum No. 22 (Chapter 2, Section 2.4.5.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



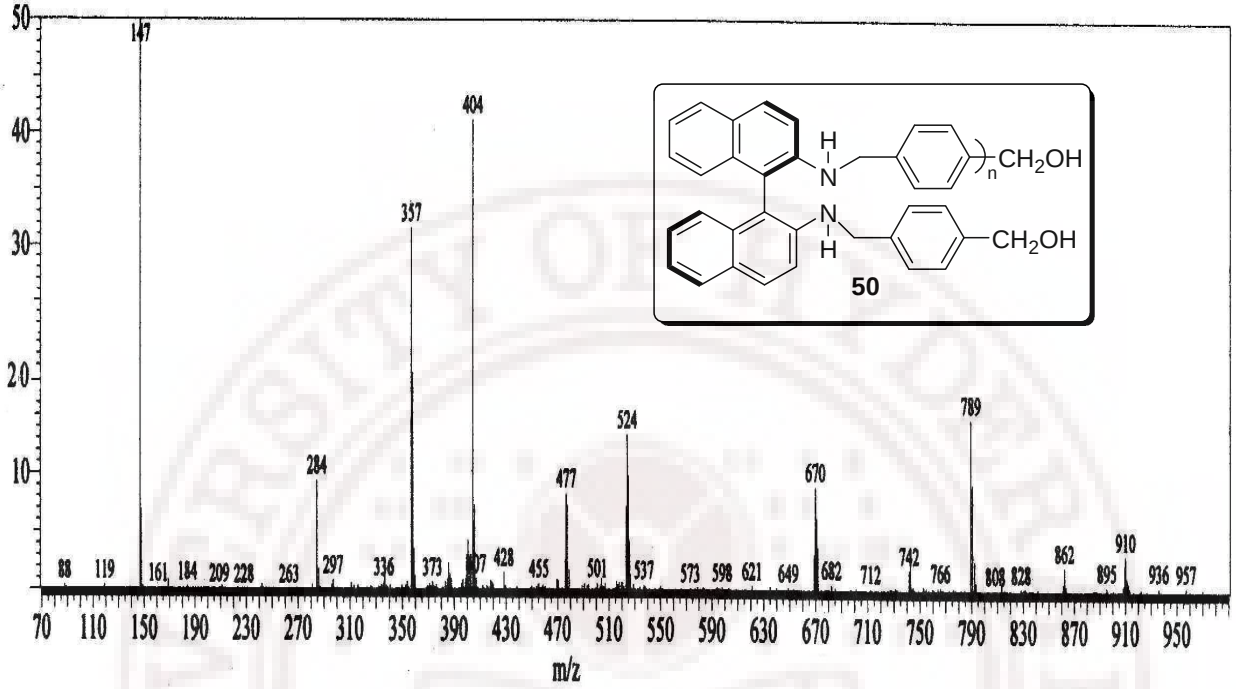
Spectrum No. 23 (Chapter 3, Section 3.4.4) ^{13}C NMR Spectrum of imine 49 (100 MHz, $CDCl_3$)



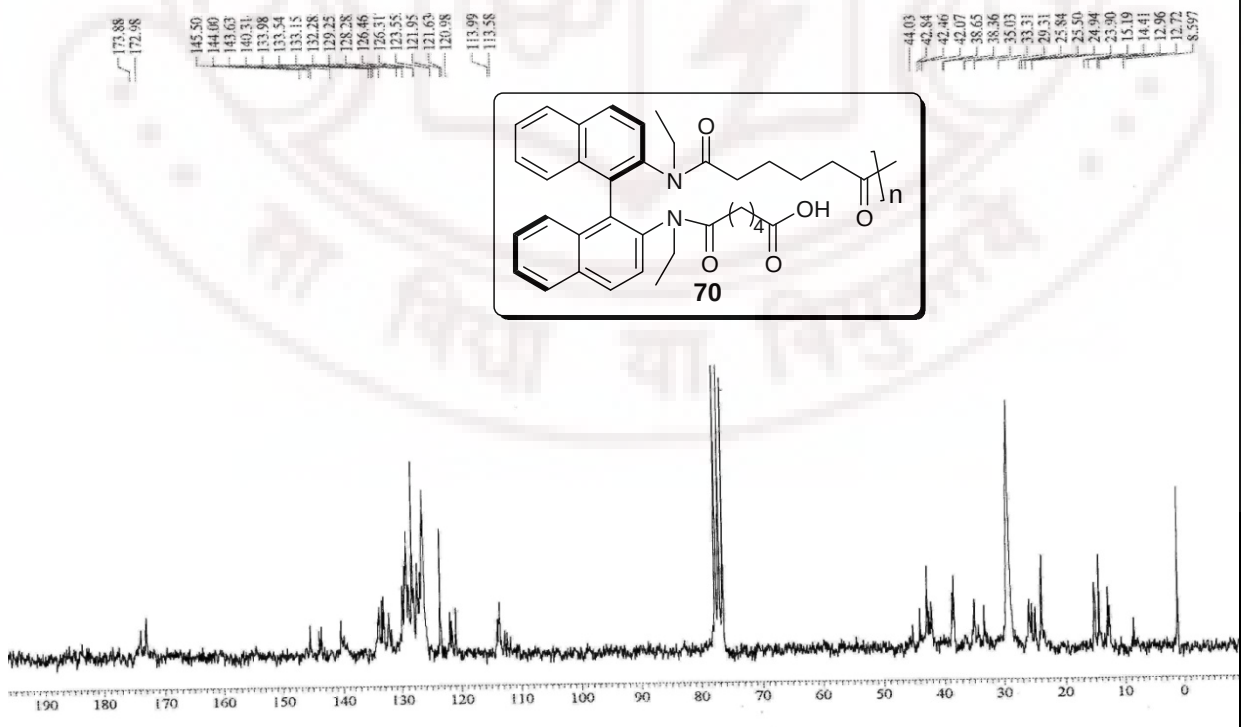
Spectrum No. 24 (Chapter 3, Section 3.4.4) Mass Spectrum of imine 49



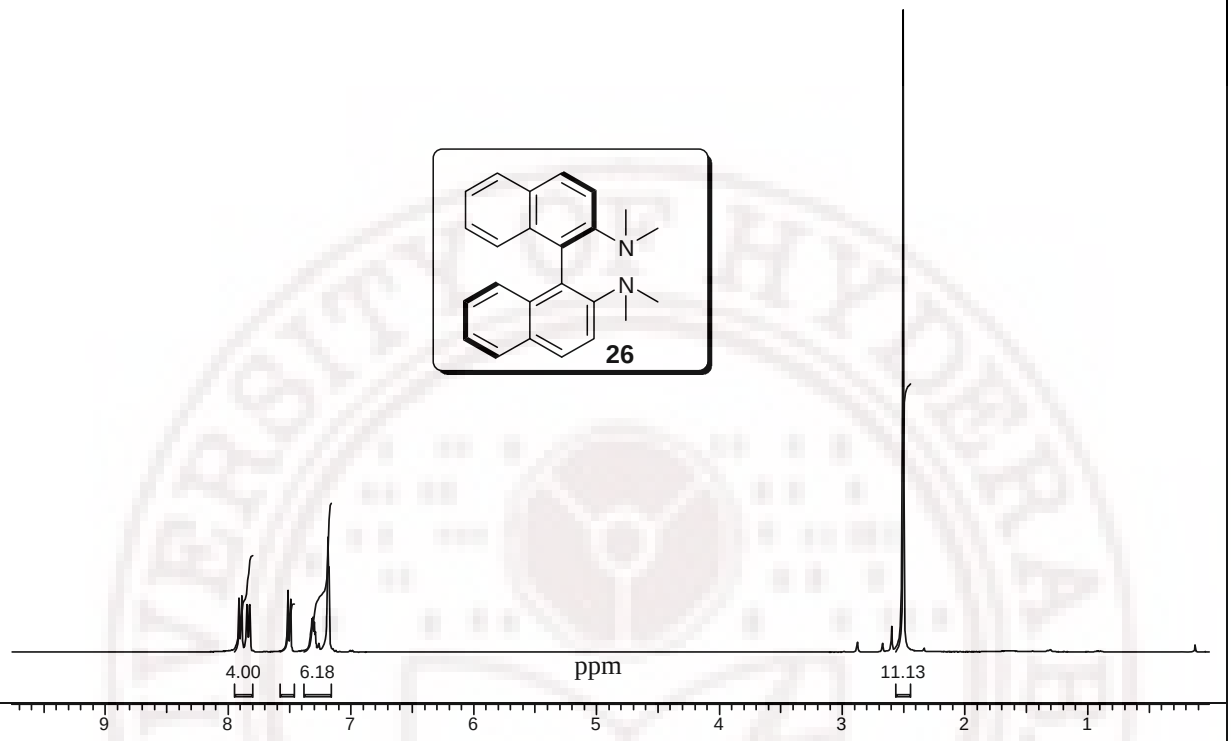
Spectrum No. 25 (Chapter 3, Section 3.4.4.1) Mass Spectrum of amine 50



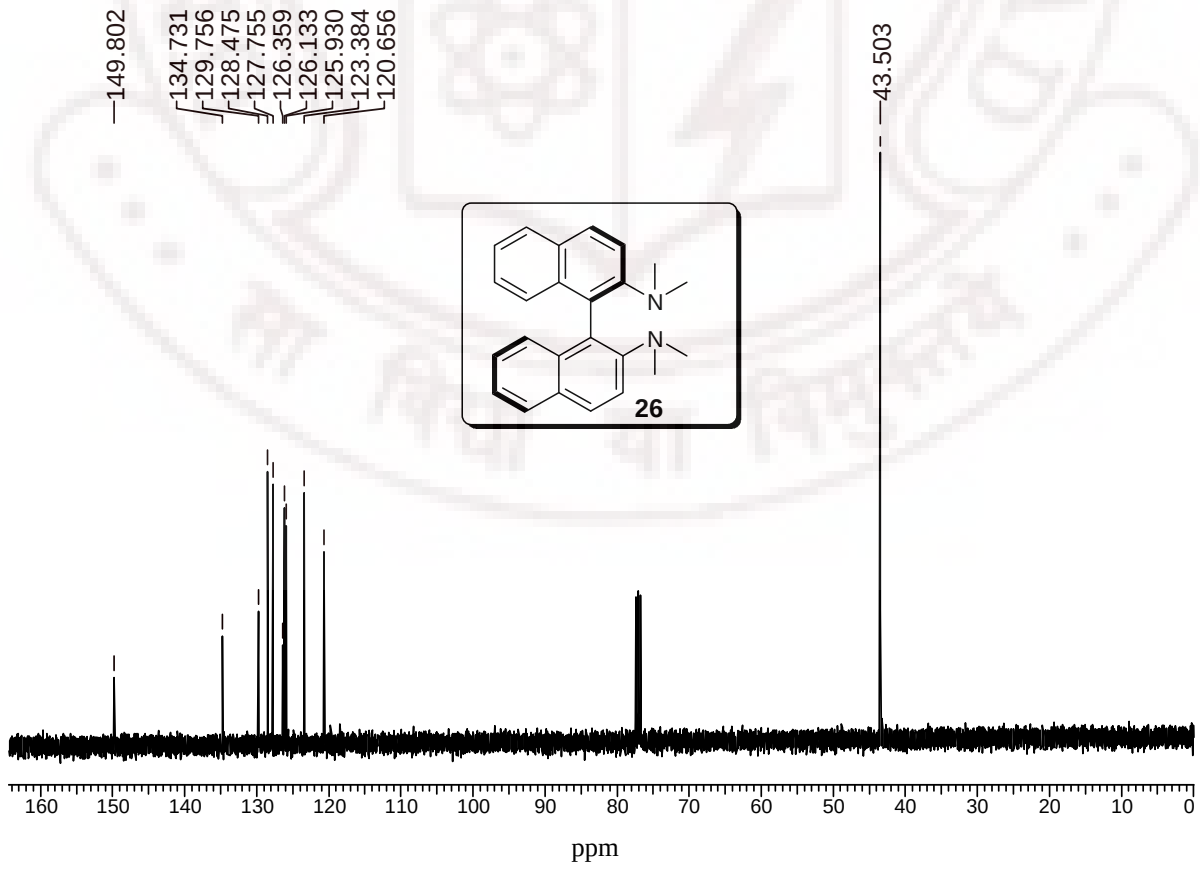
Spectrum No. 26 (Chapter 3, Section 3.4.5.4) ^{13}C NMR Spectrum of amide 70 (100 MHz, $CDCl_3$)



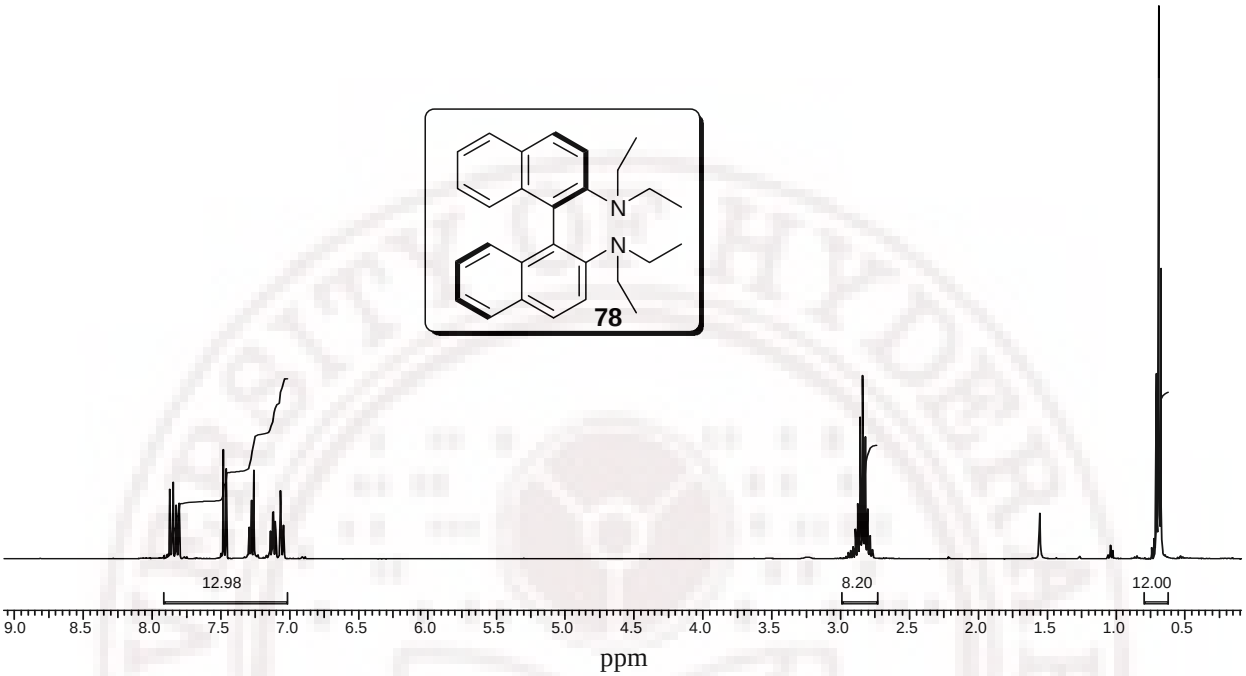
Spectrum No. 27 (Chapter 4, Section 4.4.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



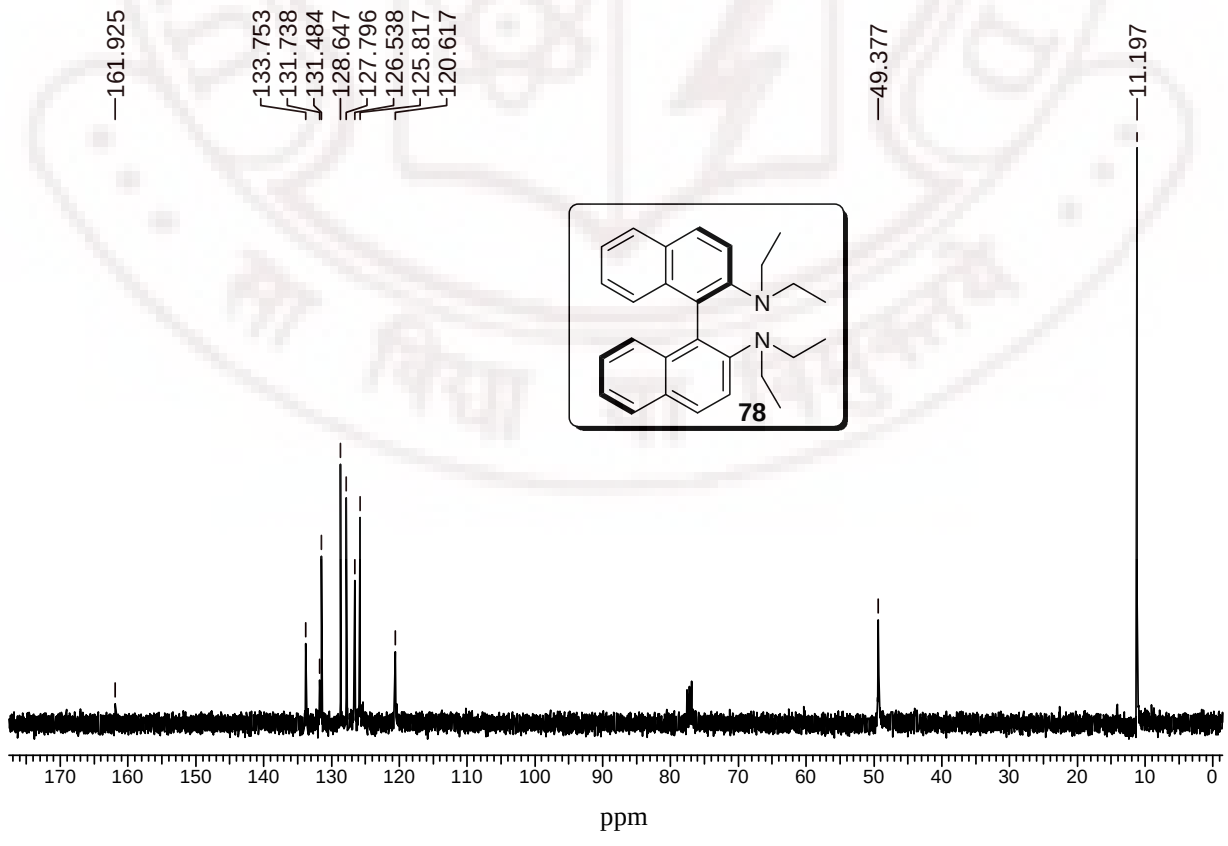
Spectrum No. 28 (Chapter 4, Section 4.4.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 29 (Chapter 4, Section 4.4.2.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 30 (Chapter 4, Section 4.4.2.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table 1 X-ray data collection and structure refinement for the complex 50 (Chapter 1, Section 1.2.2)

Empirical Formula	$C_{36}\ H_{47}\ N\ O_5$
Formula weight F_w	573.75
Temperature T (K)	298(2)
Wavelength λ (Å)	0.71073
Crystal system, Space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	
a (Å), α (°)	9.694 (3), 90
b (Å), β (°)	16.116 (6), 90
c (Å), γ (°)	21.580 (12), 90
Volume V (Å^3)	3371 (3)
Z	4
Calculated density ρ_{calcd} mg/M^3	1.130
Absorption coefficient μ (mm^{-1})	0.074
F (000)	1240
Crystal Size (mm)	0.38 x 0.14 x 0.08 mm
θ for data collection range/deg	1.58 to 28.32 deg
Limiting indices	-12<=h<=11, -20<=k<=3, -27<=l<=26
Reflections collected/unique	9909 / 5934 [R(int) = 0.0520]
Completeness to θ	28.32, 88.2 %
Max. and min. transmission	0.994 and 0.988
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5934 / 0 / 392
Goodness-of-fit on GOF (F^2)	0.859
Final R indices *R1, wR2 [I>2σ(I)]*	*R1* = 0.0552, *wR2* = 0.0990
R indices (all data) *R1, wR2*	*R1* = 0.1519, *wR2* = 0.1278
Largest diff. Peak and hole (e·Å^{-3})	0.147 and -0.189

Table A1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the complex **50** (**Chapter 1, Section 1.2.2**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
C(1)	4418(8)	8584(3)	-1137(3)	176(3)
C(2)	4135(6)	8255(3)	-488(3)	109(2)
C(3)	4639(5)	8826(3)	3(3)	106(2)
C(4)	4358(6)	8485(3)	645(3)	111(2)
C(5)	5066(5)	7641(2)	754(3)	90(2)
C(6)	4573(4)	7071(2)	242(2)	78(1)
C(7)	4802(5)	7398(2)	-397(2)	92(2)
C(8)	4849(7)	7288(3)	1403(3)	119(2)
C(9)	3323(8)	7190(4)	1572(3)	171(3)
C(10)	5637(9)	7811(4)	1878(3)	208(4)
C(11)	4686(5)	5593(3)	221(2)	69(1)
C(12)	5639(4)	4844(2)	232(2)	54(1)
C(13)	5663(4)	4436(2)	-406(2)	66(1)
C(14)	6146(5)	5015(2)	-920(2)	97(2)
C(15)	5109(4)	4278(2)	757(2)	57(1)
C(16)	5395(6)	4661(2)	1384(2)	66(1)
C(17)	4299(6)	4912(3)	1751(3)	106(2)
C(18)	4553(9)	5269(4)	2326(3)	133(3)
C(19)	5875(10)	5343(4)	2523(3)	143(3)
C(20)	6954(7)	5093(3)	2172(3)	117(2)
C(21)	6713(6)	4754(3)	1597(2)	86(2)
C(22)	5270(4)	2896(2)	1249(2)	70(1)
C(23)	5971(6)	2069(3)	1240(2)	66(1)
C(24)	7238(6)	1973(3)	1506(3)	92(2)
C(25)	7881(7)	1214(5)	1499(4)	144(3)
C(26)	7279(12)	551(6)	1244(4)	181(6)
C(27)	6088(12)	645(5)	968(3)	167(5)
C(28)	5347(7)	1402(3)	972(2)	110(2)
C(29)	4319(4)	1968(2)	9577(2)	51(1)
C(30)	5805(4)	1811(2)	9377(2)	57(1)
C(31)	5864(4)	1682(4)	8702(2)	79(1)
C(32)	5639(6)	924(4)	8456(3)	149(3)
C(33)	5617(13)	784(11)	7800(6)	249(9)
C(34)	5869(15)	1449(12)	7479(7)	250(10)
C(35)	6041(12)	2235(8)	7679(5)	232(5)
C(36)	6067(7)	2337(5)	8310(3)	139(2)
N(1)	5710(4)	3424(2)	712(2)	49(1)
O(1)	5366(3)	6297(2)	286(1)	72(1)
O(2)	3474(3)	5541(2)	141(2)	108(1)
O(3)	3471(3)	1407(2)	9435(1)	61(1)
O(4)	4029(3)	2615(2)	9859(1)	64(1)
O(5)	6638(3)	2491(2)	9559(2)	83(1)

Table 2 X-ray data collection and structure refinement for the complex 58 (Chapter 1, Section 1.2.2)

Empirical Formula	$C_{36}\ H_{47}\ N\ O_5$
Formula weight F_w	573.75
Temperature T (K)	298(2)
Wavelength λ (Å)	0.71073
Crystal system, Space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	
a (Å), α (^{o})	9.695 (2), 90
b (Å), β (^{o})	16.159 (4), 90
c (Å), γ (^{o})	21.623 (5), 90
Volume V (Å^3)	3387.5 (14)
Z	4
Calculated density ρ_{calcd} mg/M^3	1.125
Absorption coefficient μ (mm^{-1})	0.074
F (000)	1240
Crystal Size (mm)	0.36 x 0.12 x 0.08 mm
θ for data collection range/deg	1.57 to 25.50 deg
Limiting indices	-11<=h<=11, -19<=k<=14, -23<=l<=25
Reflections collected/unique	18455 / 6241 [R(int) = 0.0642]
Completeness to θ	25.50, 99.6 %
Max. and min. transmission	0.994 and 0.989
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6241 / 0 / 384
Goodness-of-fit on GOF (F^2)	1.107
Final R indices $R1$, $wR2$ $[I>2\sigma(I)]$	$R1$ = 0.0933, $wR2$ = 0.1560
R indices (all data) $R1$, $wR2$	$R1$ = 0.1649, $wR2$ = 0.1790
Largest diff. Peak and hole (e·Å^{-3})	0.182 and -0.144

Table A2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the complex **58 (Chapter 1, Section 1.2.2)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	Z	U(eq)
C(1)	4404(10)	1422(4)	-1129(3)	165(3)
C(2)	4145(7)	1741(3)	-484(3)	103(2)
C(3)	4804(6)	2600(3)	-389(3)	91(2)
C(4)	4580(4)	2933(3)	241(3)	73(2)
C(5)	5062(5)	2355(3)	749(3)	86(2)
C(6)	4367(6)	1518(3)	640(3)	107(2)
C(7)	4637(6)	1171(3)	8(3)	100(2)
C(8)	4846(8)	2709(4)	1396(4)	118(2)
C(9)	5625(12)	2189(5)	1875(4)	210(5)
C(10)	3325(10)	2821(5)	1571(4)	166(3)
C(11)	4696(4)	4410(3)	219(2)	61(1)
C(12)	5638(4)	5157(2)	232(2)	48(1)
C(13)	5663(5)	5559(3)	-404(2)	64(1)
C(14)	6145(6)	4981(3)	-919(2)	88(2)
C(15)	5108(4)	5721(2)	753(2)	53(1)
C(16)	5388(5)	5340(3)	1386(2)	62(1)
C(17)	6707(6)	5241(3)	1598(2)	81(2)
C(18)	6957(7)	4911(4)	2172(3)	114(2)
C(19)	5905(11)	4659(5)	2521(3)	133(3)
C(20)	4577(9)	4732(5)	2328(3)	128(3)
C(21)	4304(6)	5088(3)	1756(3)	101(2)
C(22)	5266(5)	7112(3)	1244(2)	65(1)
C(23)	5969(6)	7935(3)	1240(2)	63(1)
C(24)	5354(8)	8603(4)	975(2)	107(2)
C(25)	6057(16)	9356(5)	959(4)	165(5)
C(26)	7268(14)	9442(7)	1242(5)	167(6)
C(27)	7883(8)	8791(6)	1499(4)	139(3)
C(28)	7234(6)	8031(4)	1506(3)	87(2)
C(29)	862(4)	6681(4)	1295(3)	76(2)
C(30)	655(7)	5919(5)	1542(4)	149(3)
C(31)	649(17)	5756(12)	2211(9)	255(12)
C(32)	822(19)	6445(15)	2492(9)	267(14)
C(33)	1061(12)	7228(10)	2328(6)	226(6)
C(34)	1072(8)	7328(5)	1686(4)	134(3)
C(35)	806(4)	6811(2)	620(2)	50(1)
C(36)	-681(4)	6964(3)	423(2)	44(1)
N(1)	5707(3)	6575(2)	715(1)	48(1)
O(1)	5358(3)	3705(2)	286(1)	68(1)
O(2)	3486(3)	4457(2)	145(2)	105(1)
O(3)	1636(3)	7490(2)	443(2)	79(1)
O(4)	-963(3)	7617(2)	140(1)	59(1)
O(5)	-1523(3)	6412(2)	565(1)	57(1)

Table 3 X-ray data collection and structure refinement for tetramethyl BINAM 26 (Chapter 4, Section 4.2.2.1)

Empirical Formula	$C_{24}\ H_{24}\ N_2$
Formula weight F_w	340
Temperature T (K)	298(2)
Wavelength λ (Å)	0.71073
Crystal system, Space group	Tetragonal, I4(1)
Unit cell dimensions	
a (Å), α (^{o})	11.847(3), 90
b (Å), β (^{o})	11.847 (3), 90
c (Å), γ (^{o})	13.732(8), 90
Volume V (Å^3)	1927.2(13)
Z	4
Calculated density ρ_{calcd} mg/M^3	1.173
Absorption coefficient μ (mm^{-1})	0.069
F (000)	728
Crystal Size (mm)	0.2 x 0.14 x 0.12
θ for data collection range/deg	2.27 to 28.31
Limiting indices	-15 =< h =< 15, -15 =< k =< 15, -18 =< l =< 18
Reflections collected/unique	11128 / 2307 [R(int) = 0.0748]
Completeness to θ	28.31, 98.6 %
Max. and min. transmission	0.9918 and 0.9864
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2307 / 1 / 120
Goodness-of-fit on GOF (F^2)	1.123
Final R indices *R1*, *wR2 [I>2σ(I)]*	*R1* = 0.0789 *wR2* = 0.1450
R indices (all data) *R1*, *wR2*	*R1* = 0.1109 *wR2* = 0.1572
Largest diff. Peak and hole (e·Å^{-3})	0.183 and -0.197

Table A3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for tetramethyl BINAM **26** (**Chapter 4, Section 4.2.2.1**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	X	y	Z	U(eq)
C(1)	562(2)	9697(2)	841(2)	36(1)
C(2)	808(2)	8931(3)	114(2)	42(1)
C(3)	1902(3)	8451(3)	68(2)	46(1)
C(4)	2707(3)	8715(3)	733(2)	43(1)
C(5)	3309(2)	9733(3)	2202(3)	46(1)
C(6)	3085(3)	10477(3)	2929(3)	54(1)
C(7)	2027(3)	10999(3)	2980(2)	51(1)
C(8)	1214(2)	10764(2)	2311(2)	43(1)
C(9)	1397(2)	9975(2)	1548(2)	35(1)
C(10)	2487(2)	9473(2)	1494(2)	36(1)
C(11)	-998(4)	8061(5)	-272(4)	105(2)
C(12)	386(4)	8276(6)	-1534(3)	110(2)
N(1)	-7(2)	8623(3)	-584(2)	60(1)

Table A4 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for tetraethyl BINAM **78** (**Chapter 4, Section 4.2.2.2**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	Z	U(eq)
C(1)	4798(2)	4147(3)	215(1)	50(1)
C(2)	4436(3)	2397(3)	240(1)	55(1)
C(3)	5059(3)	1850(3)	660(1)	67(1)
C(4)	5967(3)	2995(4)	1038(1)	75(1)
C(5)	7275(4)	5992(4)	1426(1)	85(1)
C(6)	7550(4)	7690(4)	1417(1)	89(1)
C(7)	6961(3)	8268(3)	1010(1)	80(1)
C(8)	6132(3)	7162(3)	613(1)	66(1)
C(9)	6357(3)	4785(3)	1028(1)	65(1)
C(10)	5782(3)	5377(3)	610(1)	56(1)
C(11)	4419(4)	1429(3)	-625(1)	79(1)
C(12)	3284(4)	1278(4)	-1067(1)	113(1)
C(13)	2403(3)	-741(3)	-7(1)	74(1)
C(14)	1076(4)	-1127(4)	406(1)	87(1)
N(1)	3445(2)	1159(2)	-145(1)	58(1)

Table 4 X-ray data collection and structure refinement for tetraethyl BINAM 78 (Chapter 4, Section 4.2.2.2)

Empirical Formula	$C_{28}\ H_{32}\ N_2$
Formula weight F_w	396.56
Temperature T (K)	293(2)
Wavelength λ (Å)	0.71073
Crystal system, Space group	Trigonal, P3121
Unit cell dimensions	
a (Å), α (°)	8.6244(4), 90
b (Å), β (°)	8.6244(4), 90
c (Å), γ (°)	26.665(3), 120
Volume V ($Å^3$)	1717.7 (2)
Z	3
Calculated density ρ_{calcd} mg/M^3	1.150
Absorption coefficient μ (mm^{-1})	0.067
F (000)	642
Crystal Size (mm)	0.46 x 0.40 x 0.38
θ for data collection range/deg	2.29 to 25.97
Limiting indices	-10 =< h =< 10, -10 =< k =< 10, -32 =< l =< 31
Reflections collected/unique	6348 / 2260 [R(int) = 0.0219]
Completeness to θ	25.97, 99.9 %
Max. and min. transmission	0.9751 and 0.9700
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2260 / 0 / 138
Goodness-of-fit on GOF (F^2)	1.039
Final R indices *R1*, *wR2 [I>2σ(I)]*	*R1* = 0.0518 *wR2* = 0.1308
R indices (all data) *R1*, *wR2*	*R1* = 0.0699 *wR2* = 0.1450
Largest diff. Peak and hole ($e \cdot Å^{-3}$)	0.171 and -0.196

LIST OF PUBLICATIONS

1. Stereoselective synthesis of *syn*-β-amino esters using the $TiCl_4/R_3N$ reagent system; Periasamy, M.; Suresh, S.; **Selva Ganesan**, **S**. *Tetrahedron Lett.* **2005**, *46*, 5521.
2. Addition of titanium ester enolates to aldimines containing a chiral α-methylbenzylamine moiety: synthesis of chiral syn-β-amino esters; Periasamy, M.; Suresh, S.; **Selva Ganesan, S**. *Tetrahedron: Asymmetry* **2006**, 17, 1323.
3. Diastereoselective synthesis of chiral *syn*-β-amino esters via addition of chiral titanium menthyl ester enolate to imines; Periasamy, M.; **Selva Ganesan, S**.; Suresh, S.; (communicated).
4. Titanium mediated diastereoselective [3+2] cycloaddition of donor-acceptor cyclopropanes and imines: Synthesis of substituted pyrrolidines; Periasamy, M.; **Selva Ganesan, S**. (manuscript under preparation).

POSTERS/PAPERS PRESENTED IN SYMPOSIA

1. Oral presentation in the *"Chemfest 2008"* in house symposium held at University of Hyderabad, Hyderabad, March 1-2, **2008**; Title: Synthesis and application of *syn*-β-amino esters and chiral polyamines.
2. Poster presented in the *"Chemfest 2008"* in house symposium held at University of Hyderabad, Hyderabad, March 1-2, **2008**; Title: Synthesis and application of *syn*-β-amino esters and chiral polyamines.