CONTENTS

ACKNOWLEDGMENTS

I take this opportunity to express my heartfelt gratitude towards my research supervisor Dr. A. Sudalai, whose timely help during the crucial phase of my career has made possible to achieve this target. His suggestions, criticisms and constant encouragement helped me immensely to grow as a chemist. His true scientific spirit has helped me a lot during my research work. My everlasting gratitude goes towards him.

I am equally indebted to Dr. A. R. A. S. Deshmukh for preliminary training, expert guidance and valuable suggestions during the course of this investigation.

I owe a word of gratitude to Dr. S. Devotta, Deputy Director and Head, PD division, for his help and support. I wish to thank Dr. B. M. Bhawal, Dr. A. Sarkar and S. A. R. Mulla, for useful training in the initial phase of my career.

I am also grateful to Dr. Md. Qudrathullah Head, Chemistry Department, Poona College, Dr. G. M. Nazeruddin, Dr. Rafique Sarkhwas, Dr. Ejazuddin Khan, Dr. Alamgir Shaikh, Dr. Mrs. Mulla, Aziz Mohinuddin, Dr. M. S. Wadia and Dr. H. R. Sonawane for inspiring me towards research. I am equally thankful to Mr. H. S. Jagtap and Mr. A. P. Pendse for their keen interest and moral support during my research work.

I wish to thank Drs. K. N. Ganesh, D. G. Panse, N. P. Argade, V. K. Gumaste, P. P. Wadgaonkar, Vinay V. Thakur, Milind D. Nikalje, Sushil Jha, Dilip Maji, Suresh, Godwin C. G. Pais, K. Sarvanan, Anil Deshpande, S. S. Surange, R. P. Jain, T. T. Upadhya, Prodeep Phukan, Gurunath, Rodney, Jakkam, Kotwal, Kapoor, Vallabh Desai for their help, cooperation, encouragement and motivation during my research at NCL.

My special thank goes to all my lab mates Gajanan, Abhimanyu, Ramesh, Siva, Shriram, Srinu, Pandurang, Victor, Arun and Tanveer for the cheerful atmosphere in lab and help in every aspect through out this research.

I thank all my friends in particular Moballigh Ahmed, Anis, Khalil, Zubair, Naveed, Rashid, Farid Shaikh, Rajesh, Shinde, Kobal, Hasmat, Mandar, Sandesh, Sumbhaji, Zahid, Anmitra, Rani Jha, M. Sharbani, Indu, Shafi, Shabir, Iqbal, Hamid, Haroon, Rafique, Sharif, Asif, Nagprasad, Ekambram, Siddharth, Sachin, Ramesh Kale, Sivappa, Rahul, Shishir, Shams-ul Haq, Palaskar, Girish, Shabib, Riyaz Patel, Amin Dange, Irfan, Santosh, Eshwar, Asif, Mangal, Krishnaswamy, Kailas, Bennur, Mustafa, Isaque, Senthil, Vivek and Avinash for their encouragement and cooperation.

I wish to thank Mrs. Kale (for IR), Mrs. Shantakumari (for mass), Mrs. Bhalerao (for allowing to use polarimeter), and elemental analysis group, NMR group, especially to Mr. Samuel, Dr. Rajmohan, Mr. Sathe, and Mrs. Deshpande (for mass) for their cooperation in obtaining the analytical data. I thank library staff, chemical stores, purchase staff, glass blowing section and other supporting staff of NCL for their cooperation.

I thank PD office staff Mr. Bhosale, Mrs. Puranik Mr. Kakade and Chawan for their cooperation. I also thank PG section of Pune University for their cooperation and help.

It's my privilege to thank the Director, NCL for giving me this opportunity and providing all necessary infrastructure and facilities. Financial assistance from CSIR, New Delhi is greatly acknowledged.

I wish to thank great scientific community of this world whose achievements are constant source of inspiration for me.

Finally, no wards can express the feelings towards my bellowed parents, sister Julekha Shaikh, brother Vazir Shaikh, Jabbar bhai, Siraj and my relatives for their timely assistance, constant love, care and overwhelming support during my entire course of research work. They always remain a sole sourse of inspiration in my life.

Iliyas Sayyed Ali

ABBREVATIONS

AD	Asymmetric Dihydroxylation
AH	Asymmetric Hydrogenation
AIBN	2,2'-Azobisisobutyronitrile
Ac	Acetyl
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi(2-naphthol)
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DIPT	Diisopropyltartarate
DKR	Dynamic kinetic resolution
DME	1,2-Dimethoxyethane
DMAC	*N,N*-Dimethylacetamide
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
HMPA	Hexamethylphosphoramide
M^+	Molecular ion
Me	Methyl
ml	Milliliter
mp	Melting point
MS	Mass spectrum
MW	Molecular weight
NMP	*N*-Methyl-2-pyrolidinone
NMR	Nuclear Magnetic Resonance
NMP	*N*-Methylpyrrolidone
Pet. ether	Petroleum ether
Ph	Phenyl
TLC	Thin layer chromatography

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80^{o}C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 mesh).
5. TLC analyses were performed over glass plates coated with silica gel (5-25 μ) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C-NMR spectra were recorded on Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25^{o}C using sodium D light.
10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
11. Elemental analysis was done on Carlo ERBA EA 110B instrument.
12. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.
13. The ligands DHQD, $(DHQ)_2$-PHAL, $(DHQD)_2$-PYR, $(DHQ)_2$-PYR were purchased from Aldrich

ABSTRACT

The thesis entitled **"Asymmetric Synthesis of Bioactive Molecules using Asymmetric Hydroxylation, Aziridination of Olefins and Kinetic Resolution of Alcohols"** is divided, into four chapters.

The title of the thesis clearly indicates the objective that is to synthesize enantiomerically pure drugs and to interface synthetic organic chemistry for the development of new methodologies.

Chapter 1 presents an enantioselective synthesis of (*R*)-tomoxetine (**7**) and (*S*)-fluoxetine (**8**) hydrochlorides, important antidepressants *via* Pd-catalyzed oxidative kinetic resolution of benzylic alcohols. This chapter also deals with the oxidative kinetic resolution of *β*-azido benzyl alcohols. **Chapter 2** describes the asymmetric synthesis of three *β*-blockers *i.e* (*S*)-bunitrolol (**20**), (*S*)-practolol (**21**) and (*S*)-lifibrol (**22**). The stereogenic center in all three cases is introduced *via* OsO_4-catalysed asymmetric dihydroxylation (AD) as a key reaction. This chapter also deals with a simple methodology for the direct conversion of aromatic aldehydes to the corresponding nitriles in a single step. **Chapter 3** describes the enantioselective synthesis of L-DOPA [3-(3,4-dihydroxyphenyl)-L-alanine (**39**)] and (*R*)-seligiline (**46**). Chiral aziridines, the key intermediates in this reaction are synthesized using asymmetric dihydroxylation in a sequence of steps. This chapter also deals with, Pd-catalyzed regiospecific reductive ring opening of a variety of aziridines *via* transfer hydrogenation to afford the corresponding optically active amines. **Chapter 4** deals with novel methodologies involving the use of pyridinium hydrobromide perbromide ($PyHBr_3$) as a catalyst for aziridination of olefins, esterification of carboxylic acids and protection of alcohols.

CHAPTER 1

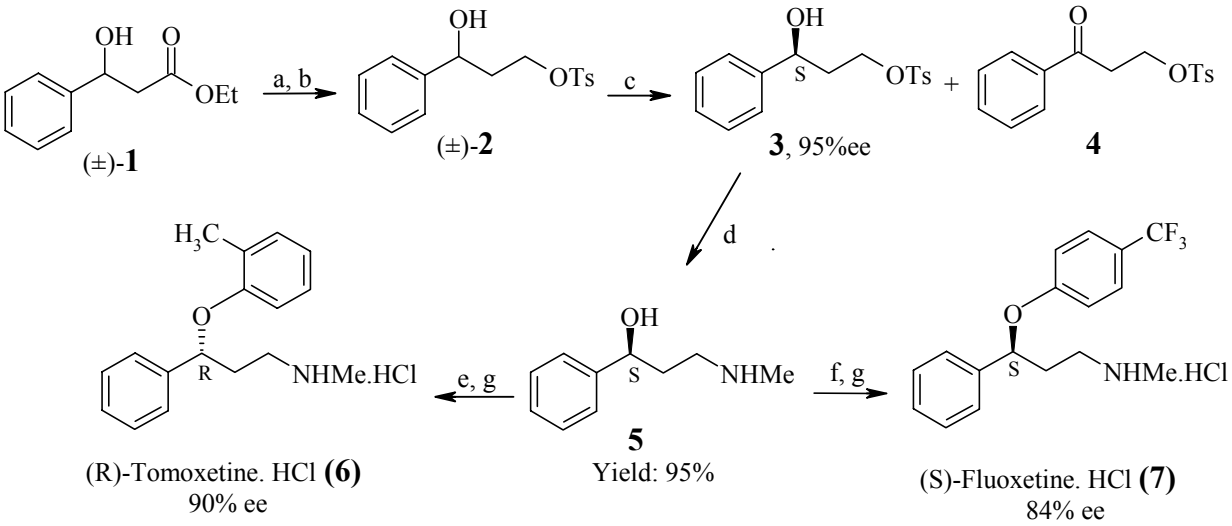
Pd-Catalyzed Oxidative Kinetic Resolution of Benzylic Alcohols using (–)-Sparteine as Chiral Auxiliary

This chapter is divided into two sections. Section I deals with Pd-catalyzed oxidative kinetic resolution of benzylic alcohol for the enantioselective synthesis of hydrochlorides of (*R*)-tomoxetine (**7**) and (*S*)-fluoxetine (**8**) while section II deals with Pd-catalyzed oxidative kinetic resolution of 2-azido 1-arylethanols.

SECTION I:

Pd-Catalyzed Oxidative Kinetic Resolution of Benzylic Alcohols: A Practical Synthesis of (*R*)-Tomoxetine and (*S*)-Fluoxetine Hydrochlorides

Tomoxetine hydrochloride (**6**) and fluoxetine hydrochloride (**7**) are among the most important drugs for treatment of psychiatric disorders and also metabolic problems.[1] Kinetic Resolution (KR)[2] of benzylic alcohols has emerged as an effective synthetic method for the preparation of optically pure alcohols, particularly if the corresponding racemates are readily available. The use of molecular oxygen as a stoichiometric reoxidant in combination with a metal catalyst has practical advantages for application in organic synthesis.[3] This section describes a convenient enantioselective synthesis of (*R*)-tomoxetine (**6**) and (*S*)-fluoxetine (**7**) hydrochlorides by applying the methodology of kinetic resolution of racemic alcohol **2** mediated by Pd(II) and (–)-sparteine as chiral diamine complex. Thus, Pd-catalyzed oxidative kinetic resolution of benzyic alcohol **2**, in presence of (–)-sparteine as a chiral ligand gave enantiomerically pure alcohol **3**, in 95% ee and 47% yield along with the corresponding oxidized product.[4] Subsequent displacement of tosylate **3** with $MeNH_2$ gave the common intermediate **5** in 95% yield. Finally, amino alcohol **5** was transformed to (*R*)-tomoxetine (**6**) and (*S*)-fluoxetine (**7**) hydrochlorides in excellent optical purity (90% ee and 84% ee) respectively (**Scheme 1**).[5]



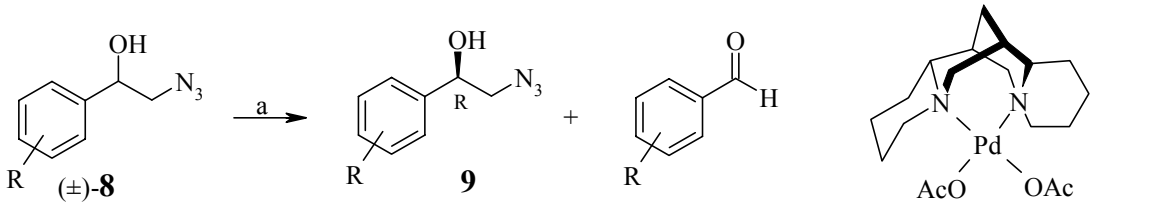
Scheme 1: a) $LiAlH_4$, ether, 2 h, 85%; b) TsCl, Et_3N, CH_2Cl_2, –10-0°C, 95%; c) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, O_2 (1 atm), 3Å MS, toluene, 80°C, 36 h, $[\alpha]_D$ – 15.1 (c 1.0, $CHCl_3$), 95% ee, 47%; d) 40% *aq*. $MeNH_2$, THF, 65°C, $[\alpha]_D$ – 49.1 (c 1.0, $CHCl_3$), 95%; e) *o*-cresol, PPh_3, DEAD, ether, –10-0°C, $[\alpha]_D$ – 36.3 (c 1.0, EtOH), 90% ee; g) HCl (gas), ether; f) NaH, DMAC, 90°C, *p*-chlorobenzotrifluoride, 105°C, $[\alpha]_D$ – 9.1 (c 1.0, H_2O), 84% ee.

SECTION II:

Pd-Catalyzed Oxidative Kinetic Resolution of 2-Azido-1-arylethanols

The value of enantiopure azido alcohols such as **10** lies in their utility as direct precursors of aziridines,[6] vicinal amino alcohols[7] and chiral ligands for asymmetric catalysis.[8]

This section describes a new synthetic procedure involving Pd-catalyzed oxidative kinetic resolution of racemic *β*-azido benzylic alcohols **8** using (–)-sparteine as a chiral ligand to afford (*R*)-*β*-azido benzylic alcohols **9** in moderate optical purity along with the formation benzaldehydes as side products (**Scheme 2**).



Scheme 2: a) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, O_2 (1 atm), toluene, 80°C, 36 h.

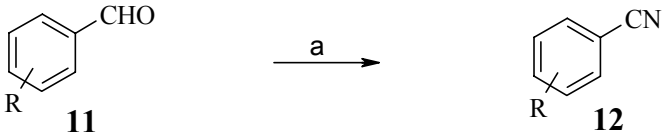
CHAPTER -2

Asymmetric Synthesis of *β*-Adrenergic Blockers via OsO_4 Catalyzed Asymmetric Dihydroxylation

SECTION I:

Formamide Assisted Direct Conversion of Aromatic Aldehydes to the corresponding Nitriles and its Application to Enantioselective Synthesis of (*S*)-Bunitrolol

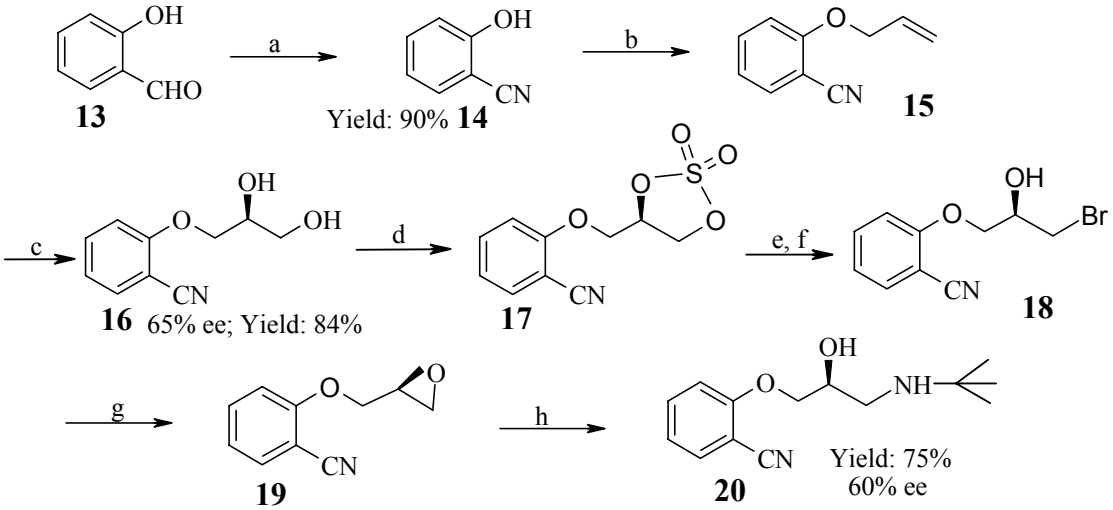
Nitriles are of particular interest in preparative organic chemistry due to their conversion into carboxylic acids, aldehydes, amides, amines and ketones.[9] This section describes a single step conversion of aromatic aldehydes **11** into the corresponding nitriles **12** in high yields when stoichiometric amounts of aldehydes, hydroxylamine hydrochloride, pyridine and formamide are refluxed (**Scheme 3**).[10]



Scheme 3: a) $NH_2OH.HCl$, $HCONH_2$, pyridine, xylene, reflux, 6 h.

The catalytic asymmetric dihydroxylation (AD) of olefins using dihydroquinidine or dihydroquinine derivatives as ligand has became a useful and most reliable transformation in organic synthesis.[11]

β-Adrenergic blocking agents are important drugs widely used for treatment of hypertension and angina pectoris.[12] Blocking of *β*-receptor system reduces the overall activity of the sympathetic nervous system. *β*-Blockers are thus used to increase life expectancy after the occurrence of the heart attack. Most of the *β*-blockers are still prepared and commercialized as racemates. However, in numerous cases, the adrenolytic activity was found to be strongly dependent on the (*S*) configuration.[13]



Scheme 4: a) $NH_2OH.HCl$, $HCONH_2$, pyridine, xylene, reflux, 90%; b) K_2CO_3, allyl bromide, acetone, reflux, 12 h, 97%; c) cat. OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 25°C, 12 h, $[\alpha]_D$ + 21.8 (c 0.5, EtOH); 84% d) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min, 96%; cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min, $[\alpha]_D$ + 8.6 (c 2.0, EtOH), 86%; e) anhyd. LiBr, THF, 60°C, 45 min, $[\alpha]_D$ – 6.8 (c 1.2, EtOH); f) 20% H_2SO_4, Et_2O, 4 h; $[\alpha]_D$ + 2.3 (c 2.3, $CHCl_3$) 85%, g) K_2CO_3, MeOH, –10-15°C, 2 h, 90%; h) ^{t}Bu-NH_2, reflux 4 h, $[\alpha]_D$ +10.0 (c 1.4, H_2O), 75%.

This section describes the enantioselective synthesis of (*S*)-bunitrolol (**20**), starting from readily available salicyaldehyde (**13**) in a sequence of steps. Salicyaldehyde was transformed to o-cyano phenol by employing the above methodology. The phenol **14** was O-allylated followed by its ADH in presence of $(DHQD)_2$-PYR [hydroquinidine 2,5-diphenyl-2,6-pyrimidinediyl diether] as a chiral ligand afforded chiral diol **16**. The chiral diol **16** was converted to cyclic sulphate **17** in a two-step procedure. Opening of cyclic sulphate **17** with *tert*-butylamine gave low yield. Hence, cyclic sulphate **17** was transformed to epoxide **19** in

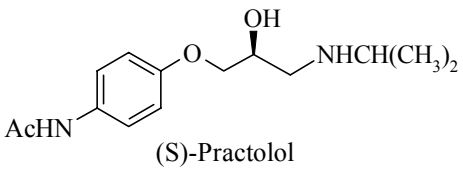
three steps. Epoxide **19** was opened with *tert*-butylamine in regiospecific manner to afford (*S*)-bunitrolol (**20**), in excellent yield and optical purity (**Scheme 4**).

SECTION II:

Asymmetric Synthesis of (*S*)-Practolol and (*S*)-Lifibrol

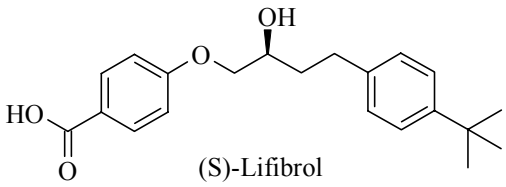
Coronary artery disease, commonly known as heart disease is the leading cause of death in human beings. The effect of cholesterol on the brain is complex. High cholesterol has been linked to Alzheimers disease and a greater risk of getting its stroke. Lifibrol (**22**) [4-(4'-ter-butylphenyl)-1-(4'-carboxyphenoxy)-2-butanol] is a new hypocholesterolemic compound.[14] It effectively lowers total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotien B.

This section describes enantioselective synthesis of two *β*-blockers, (*S*)-practolol (**21**) and (*S*)-lifibrol (**22**) (**Fig. 1**) using ADH as a key reaction.



(S)-Practolol

21

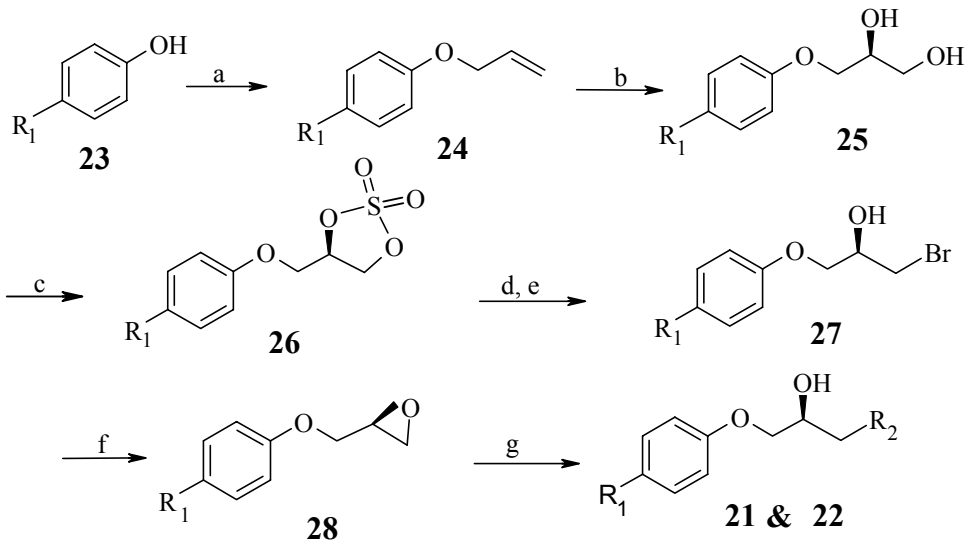


(S)-Lifibrol

22

Fig. 1

O-Allylation of phenols gave O-allyl ethers **24**, which were subjected to AD in presence of $(DHQD)_2$-PHAL as a chiral ligand to afford chiral diols **25**. The chiral diols were converted to cyclic sulphates **26** in a two-step procedure. Opening of cyclic sulphates **26** with the corresponding nucleophiles gave the products in low yield. Hence, cyclic sulphates were transformed to epoxides **28** in three steps. Epoxides **28** were subjected to opening with the corresponding nucleophiles in a highly regiospecific way to afford (*S*)-practolol (82% ee) and (*S*)-lifibrol (75% ee), in good yield and optical purity (**Scheme 5**).



	R_1	R_2	% ee
(*S*)-Practolol (**30**)	-NHAc	-NHiPr	75 %
(*S*)-Lifibrol (**31**)	$-CO_2CH_3$		

Scheme 5: a) K_2CO_3, allyl bromide, acetone, 56°C, 12 h, 95-97%; b) cat.OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 25°C, 12 h, 85-90%; c) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min, 90-96%; cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min, 86-88%; d) anhyd. LiBr, THF, 60°C, 45 min; e) 20% H_2SO_4, Et_2O, 4 h, 58%; f) K_2CO_3, MeOH, – 10-15 °C, 2 h, 80-85%; g) ^{i}Pr-NH_2, reflux, 5 h, $[\alpha]_D$ – 2.6 (c 2.5, EtOH), 70%

CHAPTER-3

Chiral Aziridines Versatile Synthons for the Asymmetric Synthesis of Neurotransmitter Drugs

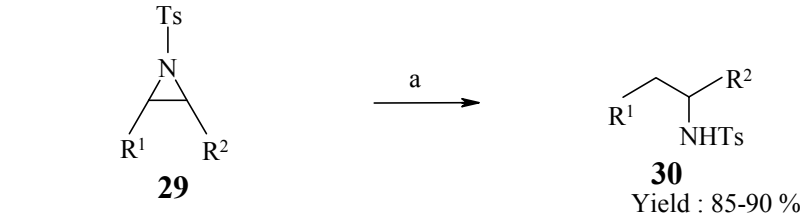
Due to the strained nature of aziridines, ring-opening reactions are a dominant feature of this class of compounds. Section I presents a convenient method for the regiospecific reductive ring opening of tosylaziridines to give the corresponding tosyl amines. This chapter also deals with asymmetric synthesis of two neurotransmitter drugs, *i.e.* L-DOPA (**39**) and (*R*)-seligiline (**46**). L-DOPA (**39**) is used for the treatment of Parkinson's diseases.[15]

SECTION I:

Pd-Catalyzed Reductive Ring Opening of Aziridines to Amines *via.* Transfer Hydrogenation

Transfer hydrogenation appears to be preferable to catalytic hydrogenation due to its simplicity while catalytic hydrogenation at high pressures using hydrogen causes potential hazards due to its diffusibility and flammability.[16]

This section presents the regiospecific reductive ring opening of a variety of protected aziridines **29** (see chapter 4 for their synthesis) with ammonium formate as hydrogen source and Pd-C as catalyst to produce protected amines **30** in excellent yields (**Scheme 6**).



29 **30**

Yield : 85-90 %

R^1 = Ar, alkyl, vinyl, etc.

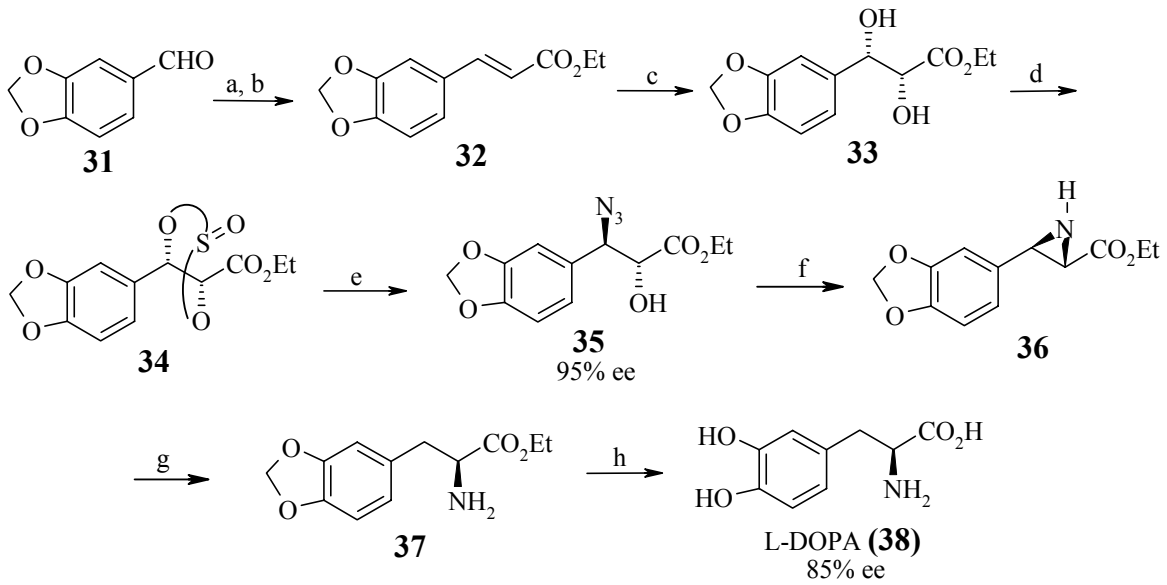
R^2 = H, CO_2R, Ar, COPh, etc.

Scheme 6: a) HCO_2NH_4 (1.5 equiv), 10% Pd-C (5 wt %), MeOH, reflux, 3-4 h.

SECTION II:

Asymmetric Synthesis of L-DOPA *via,* OsO_4-Catalyzed Asymmetric Dihydroxylation

This section presents the enantioselective synthesis of L-DOPA (**39**), using ADH as the key reaction. α,β-Unsaturated ester **32,** readily prepared by Reformatsky reaction of



Scheme 7: a) $BrCH_2CO_2Et$, Zn, benzene, reflux, 92%; b) *p*-TSA, benzene, 90%; c) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0°C, $[\alpha]_D$ +4.0 (c 0.6, $CHCl_3$), 85%; d) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, $[\alpha]_D$ – 100.0 (c 2.3, EtOH), 88%; e) NaN_3, acetone: H_2O, 80°C, $[\alpha]_D$ – 65.0 (c 0.8, EtOH), 95% ee, 82%; f) PPh_3, CH_3CN, $[\alpha]_D$ +176.2 (c 1.0, $CHCl_3$), 90%; g) 10% Pd/C, HCO_2NH_4, MeOH, reflux, $[\alpha]_D$ +7.5 (c 0.6, $CHCl_3$), 92%; h) 6 N HCl, PhOH, AcOH, 130-135°C, 24 h, $[\alpha]_D$ – 11.0 (c 1.0, 1N HCl), 85% ee, 70%.

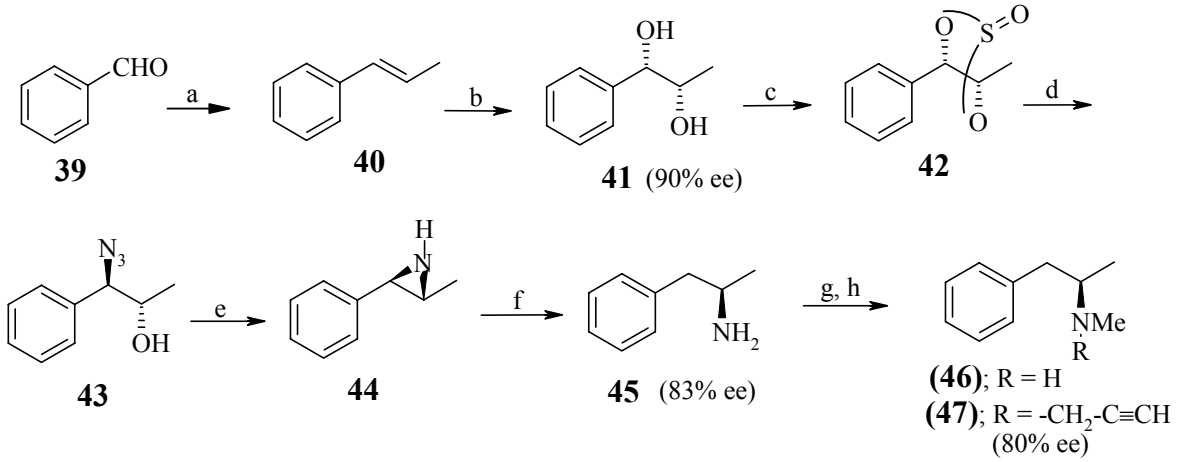
piperonal (**31**) was subjected to AD reaction to afford the diol **33**, which was further transformed to cyclic sulphite **34**. Cyclic sulphite **34** on reaction with NaN_3 gave azidoalcohol **35**. Azido alcohol **35** on reaction with triphenylphosphine and subsequent heating of the initially formed oxazaphospholidines gave aziridine **36** (the Staudinger reaction).[17] Aziridine **36** underwent hydrogenolysis to give α-amino ester **37**, which was converted, to L-DOPA (**38**) in two steps of hydrolysis and deprotection (**Scheme 7**).

SECTION III:

Asymmetric Synthesis of (*R*)-Seligiline *via,* OsO_4-Catalyzed Asymmetric Dihydroxylation

Seligiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred in the clinical and pharmacological literature as L-deprenyl and used for the treatment of Alzheimer's disease.[18]

Alzheimer's disease is believed to affect 5 to 10% of people over the age of 65 years and up to 47% of people over the age of 85 years of age. In Australia, Alzheimer's disease is the most common cause of dementia accounting for 50 to 60% of cases. This section presents the successful synthesis of (*R*)-seligiline (**47**) using asymmetric dihydroxylation as the key reaction (**Scheme 8**). Diol **41** on reaction with thionyl chloride gave cyclic sulphite **42**, which was subjected to regioselective opening with azide



Scheme 8: a) cat.OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0°C, $[\alpha]_D$ + 58.2 (c 1.06, $CHCl_3$), 90% ee, 82%; b) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, $[\alpha]_D$ – 17.1 (c 1.04, $CHCl_3$), 85%; c) NaN_3, acetone:H_2O, 80°C, $[\alpha]_D$ – 228.1 (c 1.2, $CHCl_3$), 82%; d) PPh_3, CH_3CN, $[\alpha]_D$ + 58.5 (c 0.8, $CHCl_3$), 90%; e) Pd-C (10%), HCO_2NH_4, MeOH, reflux, $[\alpha]_D$ – 25.6 (c 2.0, MeOH), 83% ee, 88%; f) (i) $ClCO_2CH_3$, CH_2Cl_2, *aq* K_2CO_3, 45 min, 90% (ii) $LiAlH_4$, dry THF, 65°C, 4 h, $[\alpha]_D$ – 8.1 (c 0.8, EtOH), 83% ee, 65%; g) propargyl bromide, toluene, 80 °C, $[\alpha]_D$ – 9.0 (c 6.5, EtOH), 80% ee, 72%.

nucleophile at benzylic position to give azido alcohol **43**. Azido alcohol was converted to aziridine **44** using PPh_3. Aziridine **44** underwent hydrogenolysis at benzylic position to give amine **45**. Subsequently amine **45** was transformed to (*R*)-seligiline (**47**) in two steps.

CHAPTER –4

Pyridinium Hydrobromide Perbromide ($PyHBr_3$) as Catalyst in Organic Synthesis

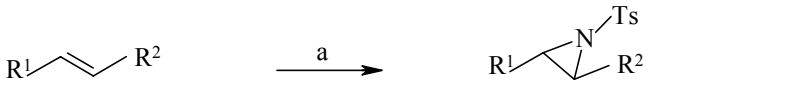
This chapter describes the use of pyridinium hydrobromide perbromide as a catalyst in organic synthesis and is divided into three sections.

SECTION I:

Pyridinium Hydrobromide Perbromide Catalyzed Aziridination of Olefins using Chloramine-T

The aziridine ring is a versatile building block for organic synthesis, not only because the ring opening of aziridines provides a convenient entry to the stereoselective preparation of functionalized amino compounds but also because the exocyclic N–substituent modulates the properties and reactivity of the three membered ring.[19] Many biologically active compounds such as amino acids, β-lactam antibiotics and alkaloids have been derived from aziridines.

This section describes aziridination of a variety of alkenes **48** using anhydrous chloramine–T as nitrogen source and pyridinium hydrobromide perbromide[20] as a new catalyst to yield the corresponding aziridines **49** in excellent yields. Both electron rich and electron-deficient olefins underwent aziridination in moderate to good yields (**Scheme 9**).



48 **49**

Yield: 20-70 %

R^1 =alkyl, aryl,vinyl
R^2 =H, CHO, COR, CH_2X (X = O, Br, OR)

Scheme 9: a) $PyHBr_3$ (10 mol%), Chloramine-T, CH_3CN, 25°C, 4-16 h.

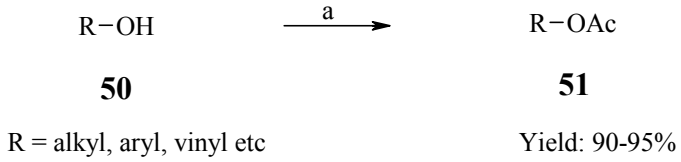
SECTION II:

Pyridinium Hydrobromide Perbromide Catalyzed Protection of Alcohols

The acetylation of alcohols is one of the most basic transformations in organic synthesis.[21] It is generally carried out by using acetic anhydride or acetyl chloride in the

presence of tertiary amines or protic or Lewis acids. DMAP is known to increase the rate of acetylation when used as a co-catalyst.

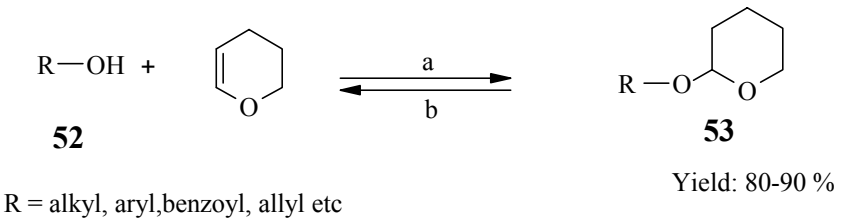
This section describes acetylation of alcohols **50** with Ac_2O using $PyHBr_3$ as a catalyst in CH_2Cl_2 at room temperature to obtain the corresponding acetyl derivatives **51** in excellent yields (**Scheme 10**).



Scheme 10: a) $PyHBr_3$ (10 mol%), acetic anhydride (1.1 equiv.), CH_2Cl_2, 25°C

The protection of alcohols as their tetrahydropyranyl ethers is a useful method in modern synthetic chemistry due to their stability towards basic media, Grignards reagents, alkylating and acylating reagents and reactions involving oxidation and reduction by inorganic hydrides. Deprotection of these ethers to their corresponding alcohols is also of practical importance.

This section also describes the use of $PyHBr_3$ as a catalyst for the DHP protection of alcohols **52**. Deprotection is effected merely by heating in methanol in presence of $PyHBr_3$. In this way, variety of alcohols underwent protection and deprotection in excellent yields (**Scheme 11**).

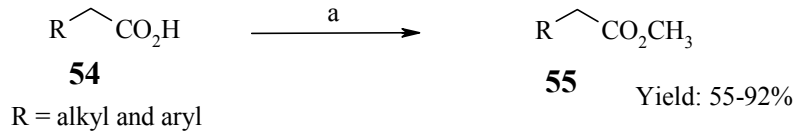


Scheme 11: a) $PyHBr_3$ (10 mol%), CH_2Cl_2, 25°C; b) $PyHBr_3$ (10 mol%), MeOH, reflux.

SECTION III:

Pyridinium hydrobromide perbromide catalyzed esterification of aliphatic carboxylic acids.

Esterification is a well-established tactic for the protection of acid functionality. Selective esterification of non-conjugated carboxyl group in presence of conjugated or aromatic carboxyl group is an important reaction for the manipulation of functional groups in multi-step organic synthesis.[22]



Scheme 12: a) $PyHBr_3$ (10 mol%), MeOH, 25°C.

This section describes $PyHBr_3$ catalyzed mild, practical and efficient method for the preparation of methyl esters from the corresponding carboxylic acids at room temperature. A wide spectrum of aliphatic non-conjugated acids **54** were readily transformed to the corresponding esters **55** in good to excellent yields using catalytic amount of $PyHBr_3$ in methanol at room temperature (**Scheme 12**).

References:

1. Schneider, M.P., Goergens, U. *Tetrahedron: Asymmetry* **1992**, *3*, 525.
2. Kagan, H. B., Fiard, J. C. ***"In Topics in Stereochemistry"***; Eliel, E. L., Wilen, S. H. Eds, Wiley New York, **1987**, *14*, 249.
3. Barton, D. H. R., Martell, A. E., Sawyer, D. T. *The Activation of Dioxygen and Homogenous Catalytic Oxidation*; Plenum Press, New York, **1993**.
4. a) Jensen, D. R., Pugsley, J. S., Sigman, M. S. *J. Am. Chem. Soc*. **2001**, *123*, 7475; b) Ferreira, E. M., Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.
5. Sayyed, I. A., Sudalai, A. *Tetrahedran Lett*. **2002**, 43, 5435.
6. Leffler, J. E., Temple.R. D. *J. Am. Chem. Soc*. **1967**, *89*, 5235.
7. Besse, P., Veschambre, H., Chenevert, R., Dickman, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1727.
8. a) Blasser, H. U. *Chem*. *Rev*. **1992**, *92*, 935. b) Kolb, H.C., Van Nieeuwenhze, M. S., Sharpeless, K. B. *Chem*. *Rev*. **1994**, *94*, 2483.
9. Mowry, D. T. *Chem. Rev*. **1948**, *42*, 189.
10. Sayyed, I. A., Nikalje, M. D., Dewkar, G. K., Paraskar, A. S., Jagtap, H. S., Sudalai, A. *J. Chem. Research (S)*, **2000**, 32.
11. Kolb, H. C., Wenhze, V. Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
12. a) Barret, C., *Brit. J. Pharmacol.* **1968**, *34*, 43. b) Hansteen, V., *Brit. Med. J.* **1982**, *284*, 155. c) Fitzgerald, J. D., in *"Pharmacology of Antihypertensive Drugs"* A. Acriabine, Ed., Raven Press, NY, **1980**, p 195.
13. a) Leftheris, K., Goodman, M. J., *J. Med. Chem.* **1990**, *33*, 216. b) Shiratsuchi, M.,

Kawamura, K., Akashi, T., Ishihama, H., Nakamura, M., Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.

14. *Drugs of the Future*. **2002**, 27(1), 83.
15. a) Yamada, S., Yamamotto, M., Chibata, I. *J. Org. Chem.* **1975**, *40*, 3360; b) Klibanov, A. M., Berman, Z., Alberti, B. N. *J. Am. Chem. Soc.* **1981**, *103*, 6263; c) Tyagi, O. D., Boll, P. M., Parmar, V. S., Taneja, O., Singh, S. K. *Indian*. *J. Chem. Sec*. *B*. **1992**, *31*, 851; d) Jung, M. E., Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553; e) Antilla, J. C., Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518.
16. a) Noyori, R., Hishigushi, S. *Acc. Chem. Res*. **1997**, *30*, 97; b) Zassinovich, G., Mestroni, Gladiali, S. *Chem. Rev*. **1992**, *92*, 1051.
17. Gololobov, Y. G., Zhmurova, I. N., Kasukhin, L.F. *Tetrahedron* **1981**, *37*, 437-472.
18. Merck Index 13th Edn.
19. a) Tanner, D. *Angew*. *Chem*. *Int*. *Ed*. *Eng*. **1994**, *33*, 599; b) Pearson, W. H., Lian, B. W., Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*, *Vol. 1A* (Ed.: A. Padwa), Pergamon, Oxford, **1996**, p. 1; (c) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.
20. Sayyed, I. S., Nikalje, M. D., Sudalai, A. *Org. Lett*. **1999**, *1*, 705.
21. a) Greene, T. W., Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, 150; b) Larock, R. C. *Comprehensive Organic Transformation*, 2nded., Wiley-VCH: New York , **1999**, 1995.
22. a) Ogliaruso, M. A., Wolfe, J.F. Synthesis of Carboxylic Acids, Esters And Their Derivatives; Patai, S., Rappoport, Z. Eds., John Wiley & Sons, Inc.: New York, 1991, 145; b) Greene, T. W., Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 2rd ed.; John Wiley & Sons, Inc., **1991**, 224.

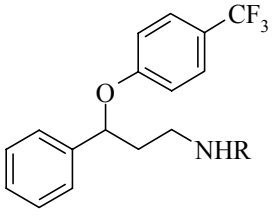
SECTION-I

Pd-Catalyzed Oxidative Kinetic Resolution of Benzylic Alcohols: A Practical Synthesis of (*R*)-Tomoxetine and (*S*)-Fluoxetine Hydrochlorides

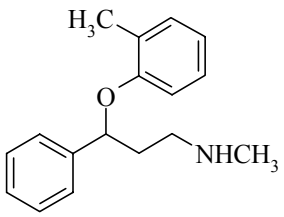
1.0.1 Introduction

Chiral drugs continue to be a significant force in the pharmaceutical market. Most of the new drugs reaching the market today are single enantiomers, rather than the racemic mixtures that dominated till ten years ago.[1] The issue of drug chirality is now a major theme in the design, discovery and development of new drugs, underpinned by a new understanding of the role of molecular recognition in many pharmacological relevant events.[2] Drugs that modulate the physiological and pathophysiological actions of serotonin are potentially useful in treating a variety of major psychiatric and metabolic problems.[3] One can manipulate actions of serotonin by using drugs that interfere with its biosynthesis, stimulate its release from presynaptic storage vesides, occupy one or more of the serotonin receptor subtypes and antagonize enzymes responsible for catabolism of serotonin.[4]

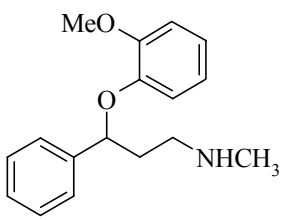
1.0.2 The Pharmacology of Tomoxetine and Fluoxetine



R = CH_3 (±)-Fluoxetine **(1a)**
R = H (±)-Norfluoxetine **(1b)**



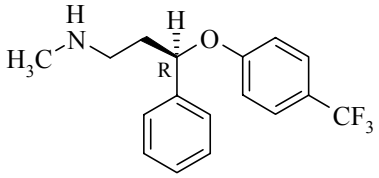
(±)-Tomoxetine **(1c)**



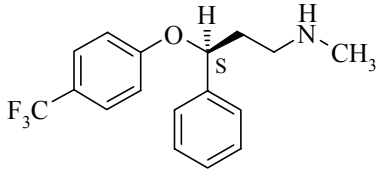
(±)-Nisoxetine **(1d)**

Fig. 1

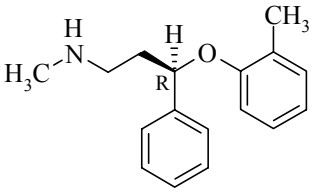
Fluoxetine (**1a**), norfluoxetine (**1b**), tomoxetine (**1c**), and nisoxetine (**1d**) have received growing interest due to the important biological activity associated with them. These compounds are regarded as potent antidepressants **(Fig. 1)**.[5] Fluoxetine (**1a**) marketed as Prozac is a bicyclic derivative of phenylpropyl amine, a drug which enhances serotonergic neurotransmission through potent and selective inhibition of the neuronal reuptake of serotonin. It is prescribed for a variety of psychopathological conditions including mood and eating disorders, obsessive-compulsive disorders, depression in the elderly and dysthymia. Fluoxetine (**1a**) is among the most important drug for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity, bulimia).[6] It is well absorbed from the gastrointestinal track after oral administration, highly protein bound, and has a large volume of distribution. Tomoxetine (**1c**) is the first norepinephrine reuptake antidepressant, which does not possess strong affinity for either α or β-adrenergic



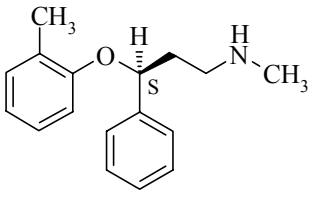
(R)-(-)-Fluoxetine.HCl **(2a)**
(R)-(-)-Fluoxetine **(2c)**



(S)-(+)-Fluoxetine.HCl **(2b)**
(S)-(+)-Fluoxetine **(2d)**



(R)-(-)-Tomoxetine.HCl **(3a)**
(R)-(-)-Tomoxetine **(3c)**



(S)-(+)-Tomoxetine.HCl **(3b)**
(S)-(+)-Tomoxetine **(3d)**

Fig. 2

receptors.[7] In recent years, use of enantiomerically pure drugs in chemotheraphy has became mandatory not only to realize enhanced specificity of the drug action but also to avoid the possible toxicity and undesired load on the metabolism by the another enantiomer.

At the time of discovery, the biological and pharmacological activities of both the enantiomers of fluoxetine and tomoxetine were found to be essentially the same.[5] However, many differences have been reported in the literature with regard to the pharmacological potencies of the isomers of the fluoxetine (**1a**). Wong and coworkers reported that the enantiomers of fluoxetine (**1a**) had different biological activity and (*S*)-fluoxetine (**2b**) is found to be more potent than (*R*)-fluoxetine (**2a**).[8] Also (*R*)-tomoxetine (**3a**) is about nine times more active than its (*S*)-isomer (**3b**) **(Fig 2)**. Therefore it is essential to provide enantioselective synthesis of these drugs in the highest optical purity possible.

1.0.3 Kinetic Resolution

Resolution strategies have always played a central role in the preparation of optically active compounds.[9] Resolutions fall broadly into three classes: (i) *Classical resolutions* involve the use of stoichiometric amount of chiral resolving agent.[10] (ii) *Chiral chromatography* generally relies on the use of chiral stationary phases to resolve enantiomers contained in a mobile phase, and in principal it can be carried out on analytical or preparative scale. (iii) *Kinetic resolution* involves use of a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantioenriched starting material and product, the desired component is then isolated **(Fig. 3)**.[11]

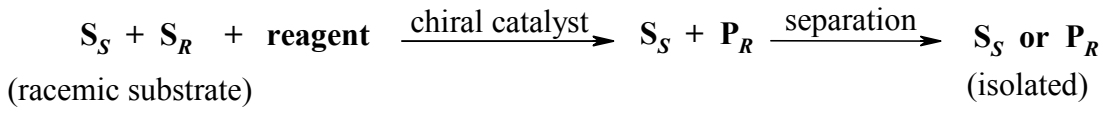


Fig. 3: Catalytic kinetic resolution

If the undesired resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality of the resolution process. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to covert essentially 100% of the racemate to the desired product. Such process constitutes a very special subclass of kinetic resolution known as dynamic kinetic resolutions. Catalytic kinetic resolutions are particularly attractive, because of the need for only small amounts of chiral "resolving agent".

1.0.4 Theoretical Considerations

Standard Kinetic Resolutions

In kinetic resolutions, enantiomers of a racemic substrate (**S**) react at different rates to form a product (**P**) that may or may not be a chiral. In a catalytic kinetic resolution, the relative rates of reaction for the substrate enantiomers, typically expressed as s or $k_{rel} = k_{fast}/ k_{slow}$, are dictated by the magnitude of $\Delta\Delta G^{\#}$ thus corresponds to the difference in energies

$$k_{rel} = s = k_{fast}/ k_{slow} = e^{\Delta\Delta G\#/ RT} \qquad \textbf{---Eq. 1}$$

between the diastereomeric transition states in the selectivity determining step of the catalytic reaction (**Eq. 1**). Thus, k_{rel} in a kinetic resolution is related to $\Delta\Delta G^{\#}$ in the same manner as it is in an enantioselective reaction of a prochiral substrate.

Although the selectivities observed for both kinetic resolution and enantioselective reactions of prochiral substrates reflect the magnitude of $\Delta\Delta G^{\#}$, there is also an important practical difference between the two. While under normal conditions, enantioselective reactions of prochiral substrates yield product of constant ee, the ee obtained in a kinetic resolution changes as a function of conversion **(Fig. 4)**.

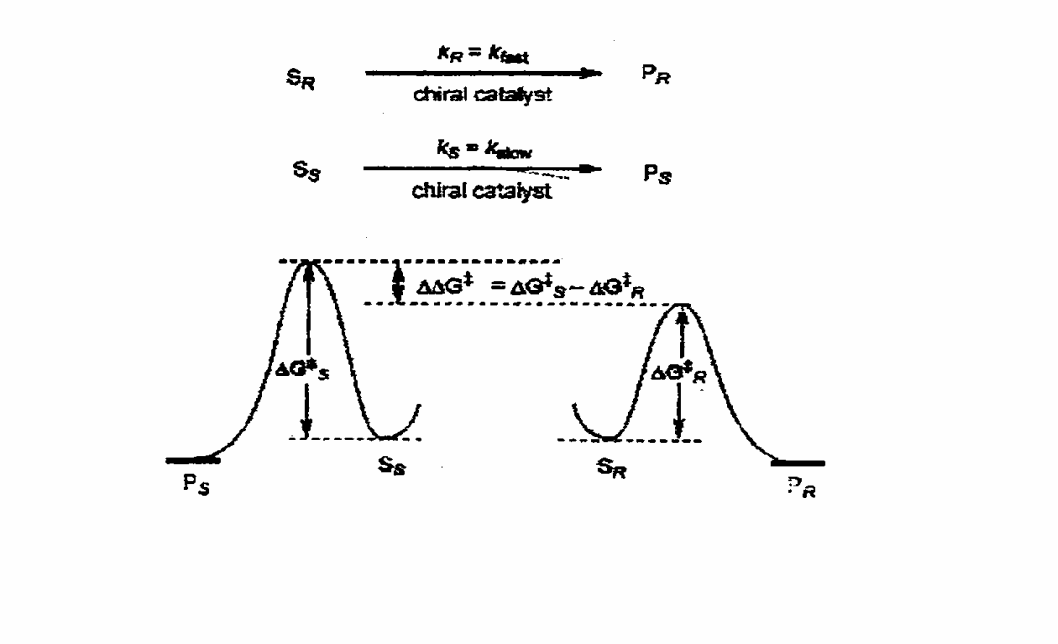


Fig. 4: Relative rate constants in kinetic resolutions

1.0.5 Dynamic and Parallel Kinetic Resolutions

Dynamic and parallel kinetic resolutions really on differential reactivity of substrate enantiomers toward a chiral catalyst, however they are also quite different from standard kinetic resolutions because in principle the catalyst is always encountering a racemic or nearly racemic substrate. In dynamic kinetic resolution, the substrate undergoes racemization at a rate greater than that of its transformation to the product **(Fig. 5)**.[12] Under such circumstances, the product of the resolution reaction can theoretically be isolated in 100% yield with an ee determined by the magnitude of k_{rel}.

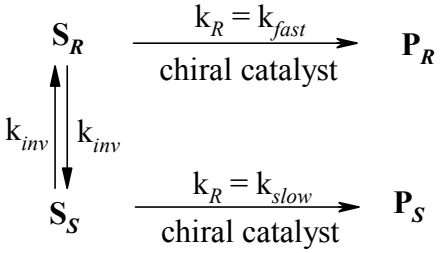


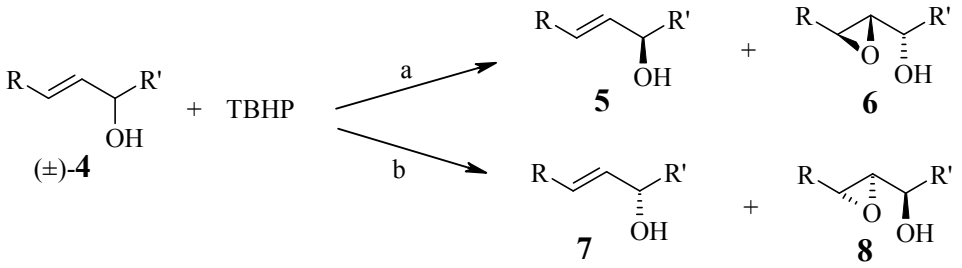
Fig. 5: Dynamic kinetic resolution

In a parallel kinetic resolution, both enantiomers undergo reaction at comparable rates to give different products.[13] In this case, as with standard kinetic resolutions, the maximum yield is 50% for each product. However, the ee of the products is much less depending on the degree of conversion.

1.0.6 Oxidative Kinetic Resolution of alcohols

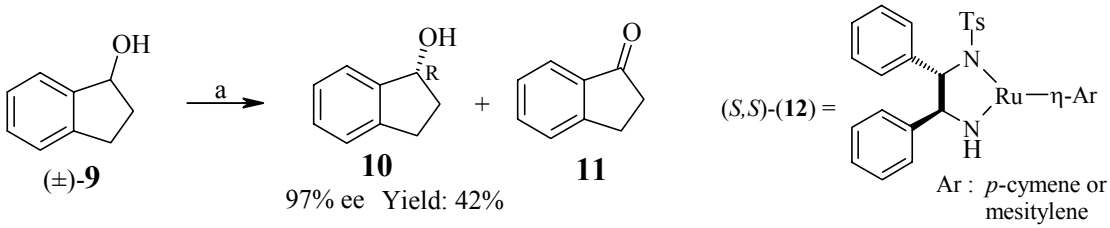
Although excellent catalytic enantioselective methods exist for a variety of oxidation processes such as epoxidation,[14] dihydroxylation,[15] and aziridination,[16] there are relatively few catalytic enantioselective examples of ubiquitous alcohol oxidation.[17]

In 1981, Sharpless reported asymmetric epoxidation of allylic alcohols **4**. The same catalytic system (Ti(O-^{i}Pr)$_4$/diisopropyl tartarate) was used for the kinetic resolution of secondary allylic alcohols **4** to afford corresponding optically pure alcohol (**5** or **7**) and epoxide (**6** or **8**) depending on the ligand used (**Scheme 1**).[18]



Scheme 1: a) (+)-tartarate ester, Ti(O-*i*Pr)$_4$, molecular sieves; b) (–)-tartarate ester, Ti(O-*i*Pr)$_4$, molecular sieves.

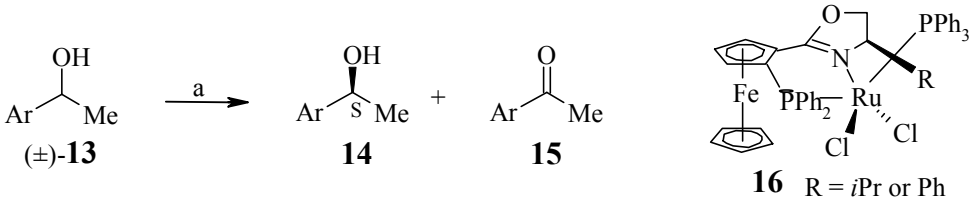
Subsequently, Noyori's Ru-catalyzed oxidative kinetic resolution of racemic benzylic



Scheme 2: a) 0.2 mol%, (*S*,*S*)-**12**, acetone.

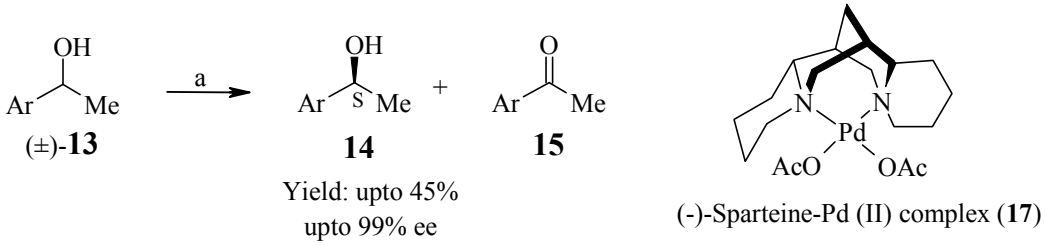
and allylic alcohols **9** to afford the optically pure alcohol **10** and the corresponding ketone **11** also merits special consideration from a practical perspective (**Scheme 2**).[19] Acetone was used as hydrogen acceptor in the oxidative reaction.

More recently, Uemura and Hidai reported the successful kinetic resolution of benzylic alcohols **13** catalyzed by (oxazolinylferrocenylphosphine)Ru complex (**16**) to yield optically pure alcohol **14** and the corresponding ketone **15** (**Scheme 3**).[20]



Scheme 3: a) 0.5 mol % catalyst (**16**), NaOiPr, *i*-PrOH, acetone.

A recent advance in this regard is the catalytic oxidative kinetic resolution of secondary alcohols using molecular oxygen as the terminal stoichiometric reoxidant.[21] The use of molecular oxygen in combination with a catalytic metal complex has exceptional advantages for applications in organic synthesis.[22] This is partly due to the favorable economy associated with molecular oxygen and the formation of environmentally benign byproducts in the oxidation manifold (water and H_2O_2). In this connection, Pd-catalyzed kinetic resolution of secondary alcohols that uses molecular oxygen as the terminal oxidant and naturally occurring (–)-sparteine as a chiral ligand has been reported affording chiral alcohols **14** (ee upto 99%) and the corresponding ketones **15** (**Scheme 4**).[23]



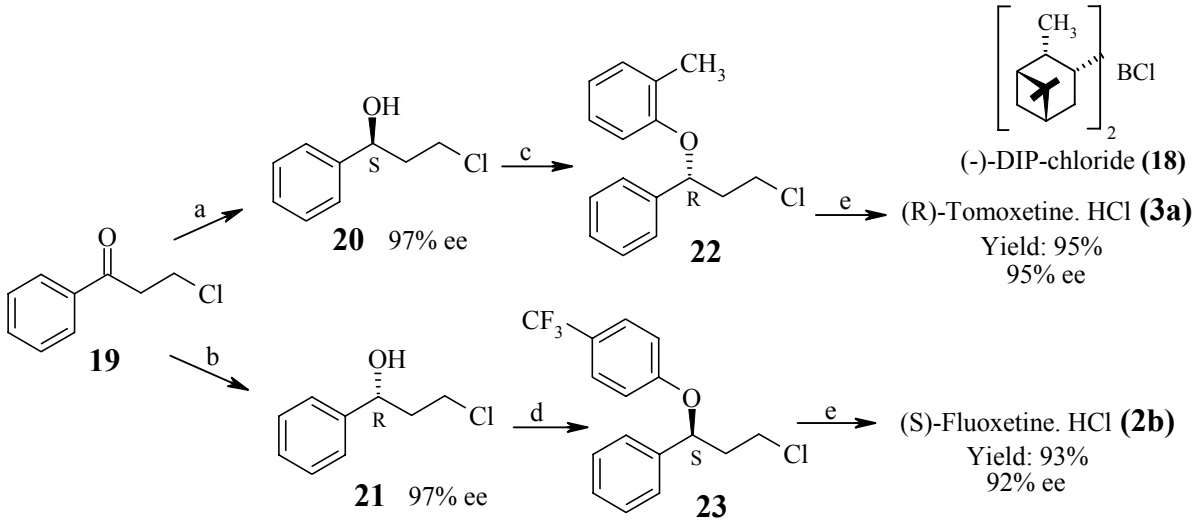
Scheme 4: a) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, MS 3Å, O_2 (1 atm.), toluene, 80^0C.

1.0.7 Review of literature

Literature search reveals that there are various methods available for the enantioselective synthesis of (*R*)-fluoxetine (**2a**), (*S*)-fluoxetine (**2b**), (*R*)-tomoxetine (**3a**) and (*S*)-tomoxetine (**3b**), which are presented below.

Brown's approach (1988)[24]

Brown *et al.* have employed diisopinocampheylchloroborane (Ipc_2BCl) (**18**) for the reduction of halo alkylketones **19** to afford corresponding chiral alcohols **20** or **21** in excellent enantiomeric excess (97% ee). These chiral alcohols were converted to corresponding chiral ethers **22** or **23** using Mitsunobu reaction. Treatment of these ethers (**22** or **23**) with aq. $MeNH_2$ afforded (*R*)-tomoxetine (**3a**) and (*S*)-fluoxetine (**2b**) respectively (**Scheme 5**).

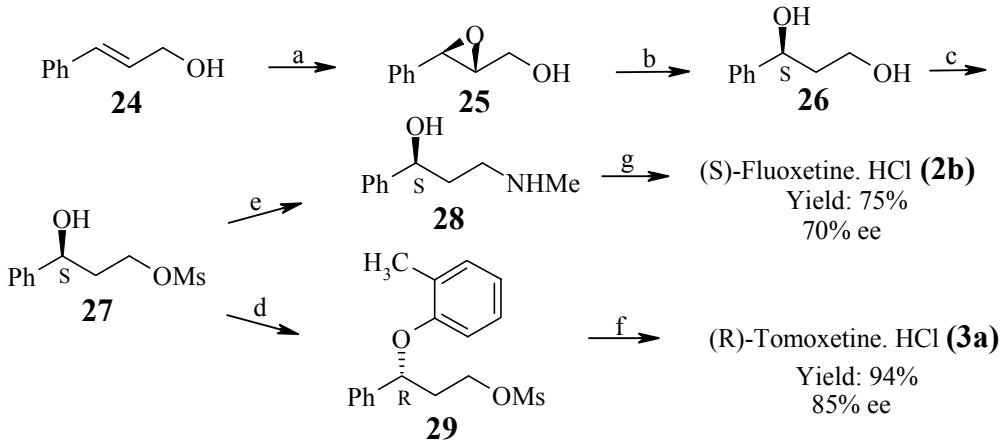


Scheme 5: a) (+)-Ipc_2BCl , recrystallization; b) (-)-Ipc_2BCl, recrystallization; c) *o*-cresol, DEAD, PPh_3; d) *p*-(trifluoromethyl) cresol, DEAD, PPh_3; e) *aq*. $MeNH_2$, EtOH, HCl. (ether).

Sharpless' approach (1988)[25]

(*R*)-Tomoxetine (**3a**) and (*S*)-fluoxetine (**2b**) hydrochlorides were synthesized by using Ti-catalyzed asymmetric epoxidation of cinnamyl alcohol (**24**) as a key reaction. Thus,

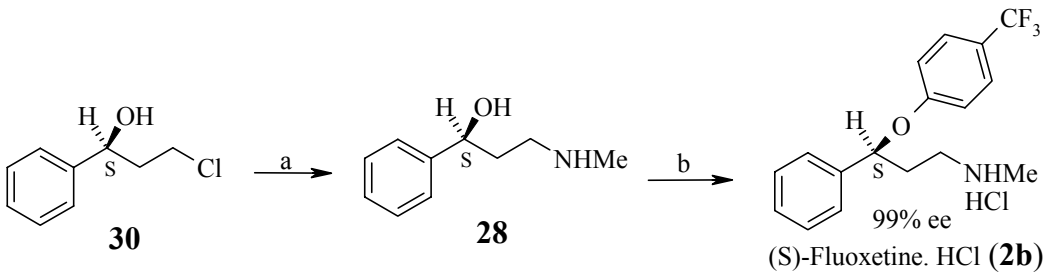
epoxidation of cinnamyl alcohol (**24**) using L-(+)-diisopropyl tartarate (DIPT) gave (–)-(2*S*,3*S*)-2,3-epoxycinnamyl alcohol (**25**). Regioselective reduction of epoxide **25** with Red-Al gave (*R*)-3-phenyl-1,3-dihydroxypropane (**26**) in 90% yield. Subsequently, selective mono mesylation, inversion using Mitsunobu reaction and displacement with methylamine gave (*R*)-tomoxetine hydrochloride (**3a**) in 85% yield. Similarly, (*S*)-isomer of tomoxetine (**3b**) hydrochloride was obtained from the corresponding (2*R*,3*R*)-epoxycinnamyl alcohol (**Scheme 6**).



Scheme 6: a) $Ti(O^iPr)_4$, DIPT, TBHP, CH_2Cl_2; b) Red-Al, DME, 0-25°C; c) MsCl, Et_3N, ether, –10-0°C; d) *o*-cresol, Ph_3P, DEAD, ether, –10°C; e) 40% *aq*.$MeNH_2$, THF, 65°C; f) (i) 40% *aq*. $MeNH_2$, THF, 65°C; (ii) HCl (gas), ether; g) NaH, DMAC, 90°C, *p*-chlorobenzotrifluoride, 100-105°C; (ii) HCl (gas).

Robertson's approach (1988)[5]

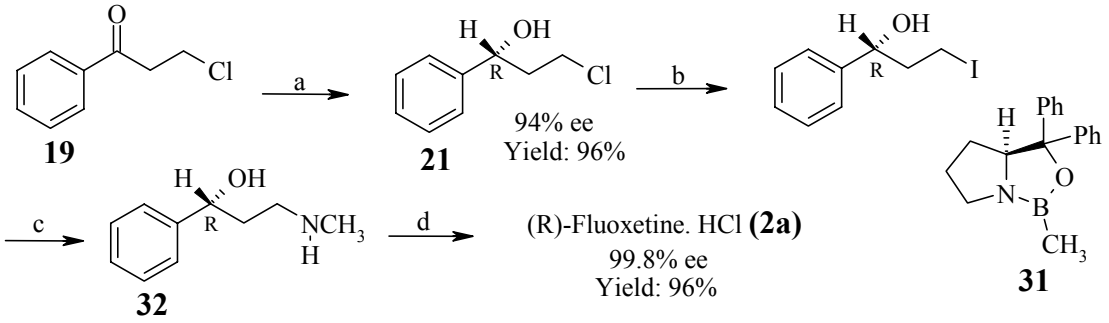
In this approach, commercially available (*S*)-(–)-3-chloro-1-phenylpropanol (**30**) on sequential reaction with sodium iodide and methylamine gave aminoalcohol **28**, which on treatment with *p*-fluorobenzotrifluoride gave (*S*)-fluoxetine (**2b**) in 99% ee (**Scheme 7**).



Scheme 7: a) NaI, then *aq*. $MeNH_2$, reflux; b) NaH, *N,N*-dimethylacetamide (DMAC), *p*-fluorobenzotrifluoride, HCl.

Corey's approach (1989)[26]

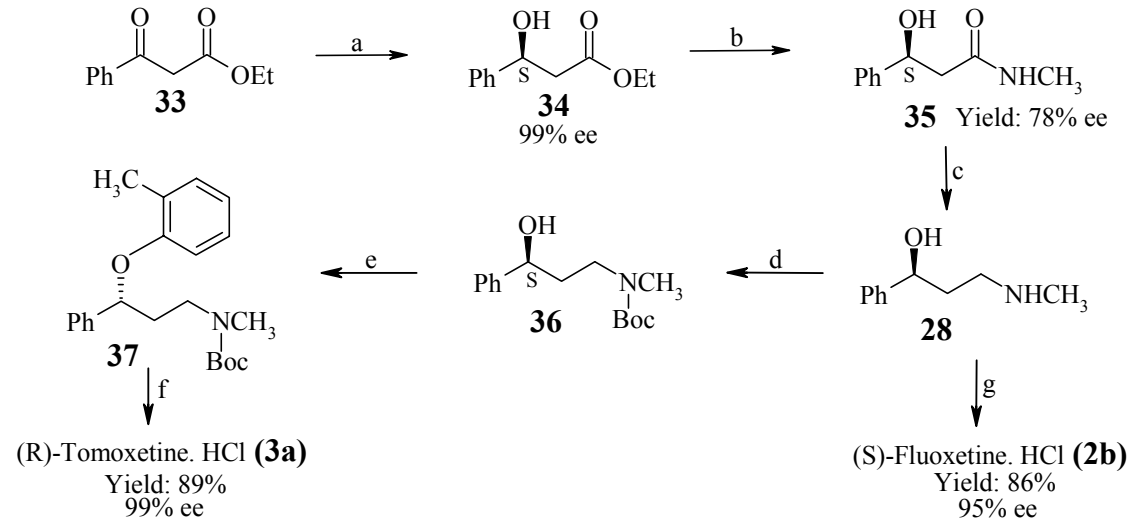
Corey *et al.* has developed a four step synthesis of (*R*)-fluoxetine (**2a**) hydrochloride from commercially available *β*-chloropropiophenone **19** in 77% overall yield. The key step of the synthesis involves enantioselective catalytic reduction of *β*-chloropropiophenone **19** using CBS catalyst **31**. Borane was used as a reducing agent in presence of (*S*)-oxazaborolidine **31** as catalyst to afford secondary alcohol **21** in 94% ee. The resulting alcohol **21** was then transformed to amino alcohol **32** in two steps. Finally, the amino alcohol **32** was transformed to (*R*)-fluoxetine hydrochloride (**2a**) in 96% yield and 99.8% ee by following the literature procedures (**Scheme 8**).



Scheme 8: a) 0.6 eq. BH_3, 0.1 eq (*S*)-oxazaborolidine (**31**), 0°C, THF, 99%, 94% ee; b) NaI, acetone, reflux, 16 h, 99%; c) 40% *aq*. $MeNH_2$, THF, 23°C, 2 h, 99%; d) (i) NaH, DMAC, 0-70°C, *p*-chlorobenzotrifluoride 100°C, 2.5 h; (ii) HCl (gas), ether, 96%, 99.8% ee.

Kumar's approach (1991)[27]

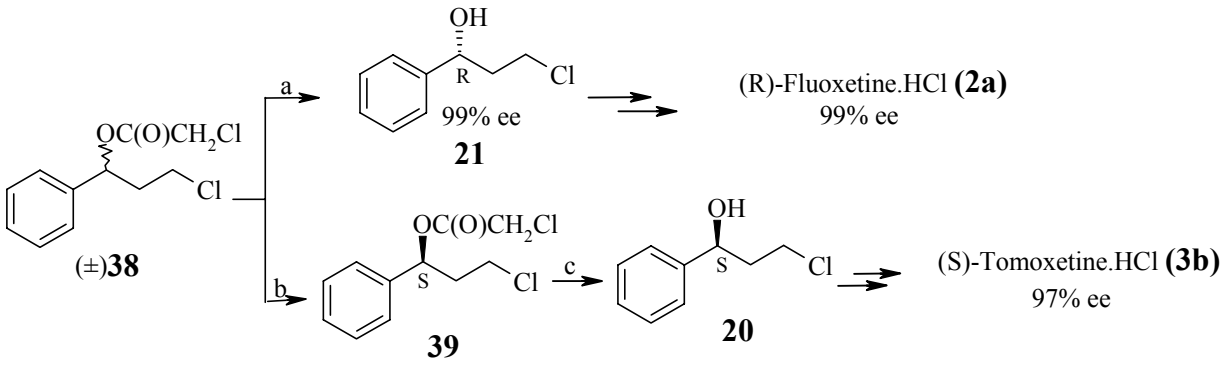
This strategy involves enzymatic reduction of *β*-keto ester **33** as a key step for the synthesis of (*R*)-tomoxetine (**3a**) and (*S*)-fluoxetine (**2b**) hydrochlorides. (*S*)-Ethyl-3-hydroxy-3-phenyl propionate (**34**) was obtained *via* baker's yeast reduction of commercially available *β*-keto ester **33** in 99% ee. Subsequently, amide formation and reduction of amide **35**, yielded *N*-methyl-3-phenyl-3-hydroxypropylamine (**28**), from which (*R*)-tomoxetine (**3a**) and (*S*)-fluoxetine (**2b**) hydrochlorides were obtained by known sequence of reactions (**Scheme 9**).



Scheme 9: a) Baker's yeast, glucose, H_2O, 99% ee; b) *aq*. $MeNH_2$, 78%; c) $LiAlH_4$, ether, 98%; d) di-*t*-butylcarbamate, 95%; e) *o*-cresol, PPh_3, DEAD; f) HCl, ether, 89%; g) NaH, DMAC, *p*-chlorobenzotrifluoride, then HCl, ether, 86%.

Schneider's approach (1992)[28]

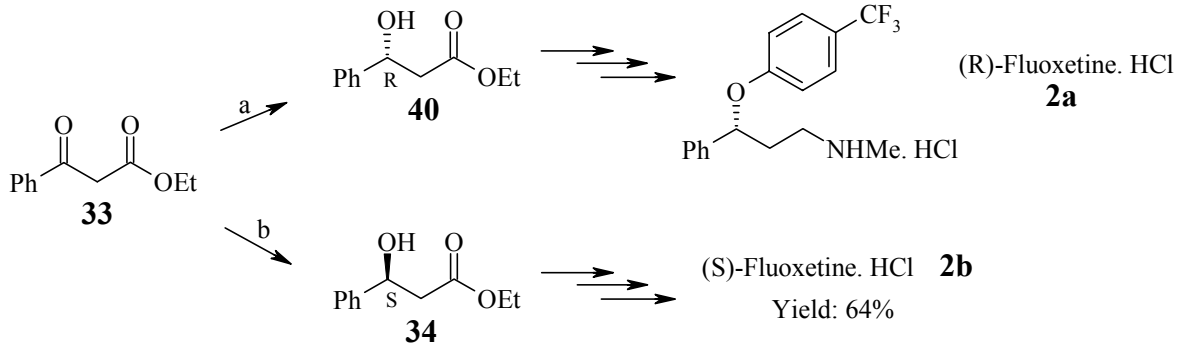
Schneider *et al.* have reported *lipase*-catalyzed enzymatic resolution of ester **38** as a key reaction to synthesize enantiomerically pure (*R*)-fluoxetine (**2a**) and (*S*)-tomoxetine (**3b**) hydrochlorides. The enantiomers (*R*) and (*S*)-3-chloro-1-phenyl-1-propanol (**21** and **20**) thus obtained were converted to the (*S*)-tomoxetine (**3b**) and (*R*)-fluoxetine (**2a**) hydrochlorides by known sequence of reactions (**Scheme 10**).



Scheme 10: a) *lipase SAM-2*, buffer pH-7; b) *lipase SAM-2*, buffer pH-7; c) hydrolysis.

Gu Jian-Xin's approach (1993)[29]

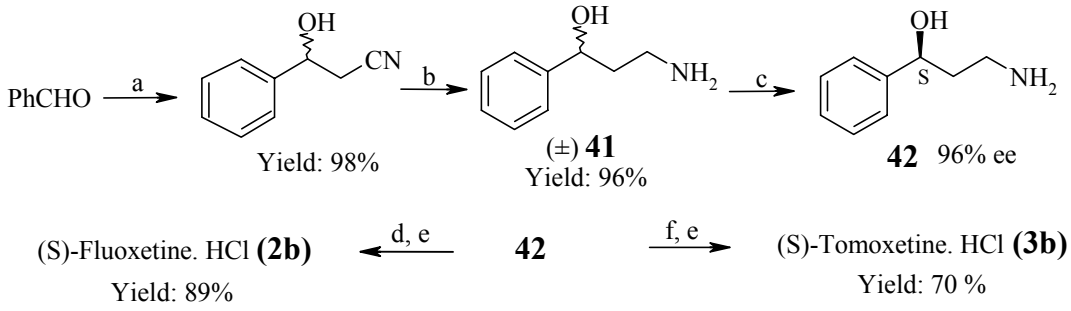
In this approach, microbial reduction of *β*-keto ester **33** was used as a key reaction to generate the chiral alcohols **40** or **34** by using G-38 and baker's yeast respectively. (*R*)-Fluoxetine (**2a**) and (*S*)-fluoxetine (**2b**) hydrochlorides were prepared in 5-steps in overall yield of 64% (**Scheme 11**).



Scheme 11: a) G-38, 28°C; b) bakers yeast reduction.

Koenig's approach (1994)[30]

A novel synthesis of (*S*)-fluoxetine (**2b**) and (*S*)-tomoxetine (**3b**) hydrochlorides *via* resolution approach has been described. Condensation of acetonitrile with benzaldehyde afforded hydroxynitrile, which on reduction gave amino alcohol **41**. Optically pure amino alcohol **42** was obtained by kinetic resolution of **41** with (*S*)-mandelic acid in 96% ee.

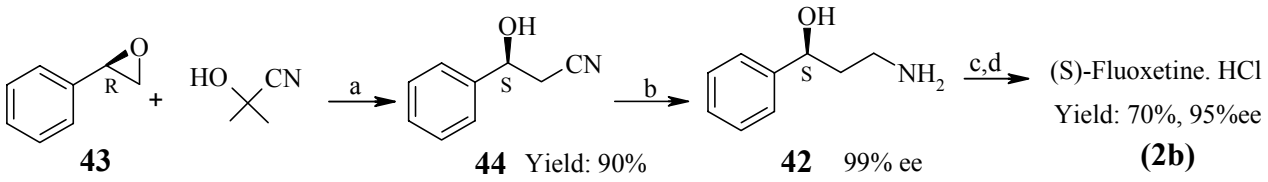


Scheme 12: a) CH_3CN, KO^tBu, THF, –50-0°C, 3 h, 98%; b) $BH_3.SMe_2$, THF, 65°C, 3 h, 96%; c) (*S*)-mandelic acid, ethanol, crystallization, 1-5 days, 24%, 96% ee; d) NaH, DMSO, 4-chlorobenzotrifluoride, HCl; e) THF, $ClCO_2CH_3$, $NaHCO_3$, LAH; f) NaH, DMSO, 2-fluorotoluene, HCl.

Subsequently alcohol **42**, was transformed to (*S*)-fluoxetine (**2b**) and (*S*)-tomoxetine (**3b**) hydrochlorides (**Scheme 12**).

Mitchell's approach (1995)[31]

Mitchell and co-workers utilized (*R*)-styrene oxide (**43**) as a starting material. Epoxide **43** was subjected to regioselective opening with acetone cyanohydrin to produce hydroxy compound **44**, which was reduced with borane to afford amino alcohol **42**. Amino alcohol **42** was converted to (*S*)-fluoxetine hydrochloride (**2b**) by known sequence of reactions (**Scheme 13**).

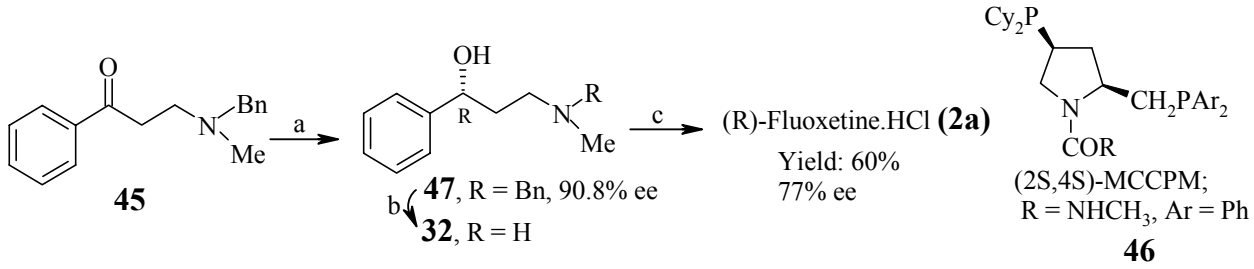


Scheme 13: a) Et_3N, THF; b) $BH_3.Me_2$, THF, 90%; c) NaH, DMSO, 4-$ClC_6H_4CF_3$, HCl; d) $ClCO_2Me$, LAH, then, NaH, DMSO, 4-$ClC_6H_4CF_3$, HCl.

Achiwa's approach (1995)[32]

Achiwa *et al.* have reported a simple practical synthesis of (*R*)-fluoxetine hydrochloride (**2a**) by Rh-catalyzed asymmetric hydrogenation of *β*-amino ketone **45** using

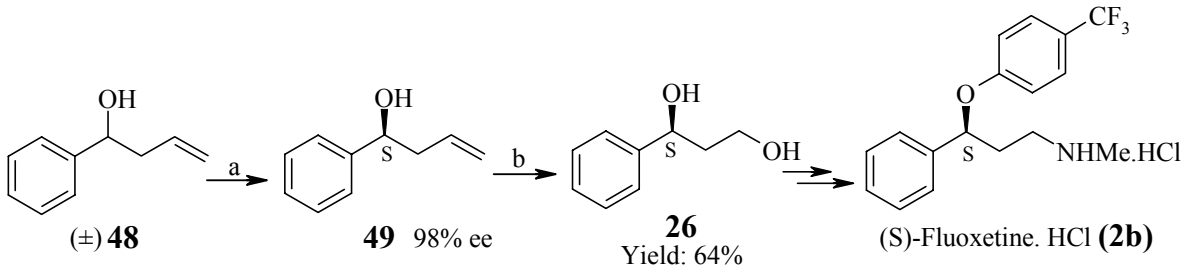
chiral phosphine ligands **46** to yield amino alcohol **47** in 90.8% ee which was converted to (*R*)-fluoxetine hydrochloride (**2a**) by known sequence of reactions (**Scheme 14**).



Scheme 14: a) H_2, (30 atm), $[Rh(COD)Cl]_2$/diphosphine ligand (**46**); b) H_2, Pd-C; c) NaH, *p*-chlorobenzotrifluoride, HCl gas.

Master's approach (1996)[33]

An enzymatic resolution of homoallyl alcohols and its utility in the synthesis of (*S*)-fluoxetine hydrochloride (**2b**) is described. Alcohol **48** on kinetic resolution with *lipase* gave chiral alcohol **49** in 98% ee along with its antipode acetate. Subsequently, ozonolysis of alcohol **49** followed by $NaBH_4$ reduction of the aldehyde gave (*S*)-3-phenyl-1,3-propanediol (**26**) in 64% yield. Further, the diol **26** was transformed to (*S*)-fluoxetine hydrochloride (**2b**) by known sequence of reactions (**Scheme 15**).

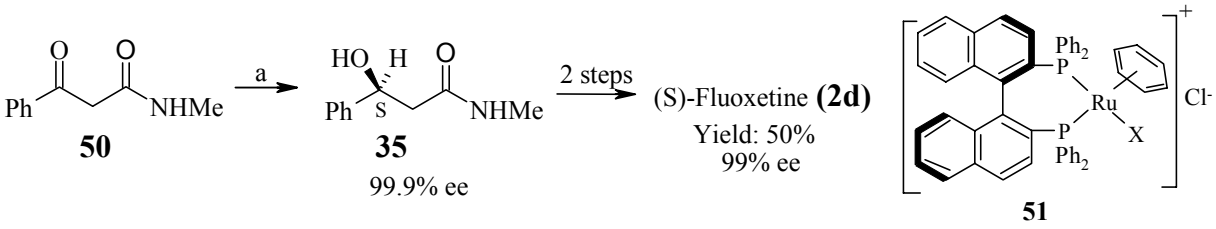


Scheme 15: a) vinyl acetate, *lipase* PS, 0°C-RT, 98% ee; b) O_3, –78°C, then $NaBH_4$, MeOH, 64%.

Haungs's approach (1998)[34]

Asymmetric hydrogenation of *β*-keto amide **50** with H_2 (200 *psi*) in presence of (*R*)-BINAP-ruthenium(II) complex (**51**) afforded (*S*)-3-hydroxy propanoic acid *N*-methyl amide (**35**) as a single enantiomer (99.9% ee). Using (*R*) and (*S*)-BINAP both (*R*) and (*S*)-

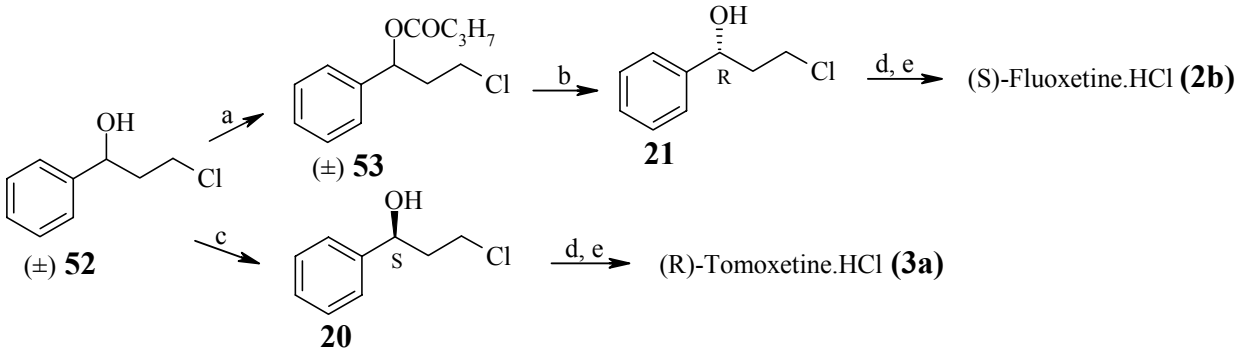
enantiomers of amide can be obtained. Further amide **35** was converted to (*S*)-fluoxetine (**2d**) by known sequence of reactions (**Scheme 16**).



Scheme 16: a) (*R*)-BINAP-$RuCl_2$ (**51**), MeOH, H_2 (200) *psi,* 100°C, 18 h, 50%.

Liu's approach (2000)[35]

3-Chloro-1-phenolpropan-1-ol (**52**) and the corresponding butanoate **53** were kinetically resolved using *lipase-B* from *Candida antartica* by transesteifiaction and hydrolysis respectively. The resulting chiral building blocks **20** and **21** were converted into (*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a)** by known sequence of reactions (**Scheme 17**).

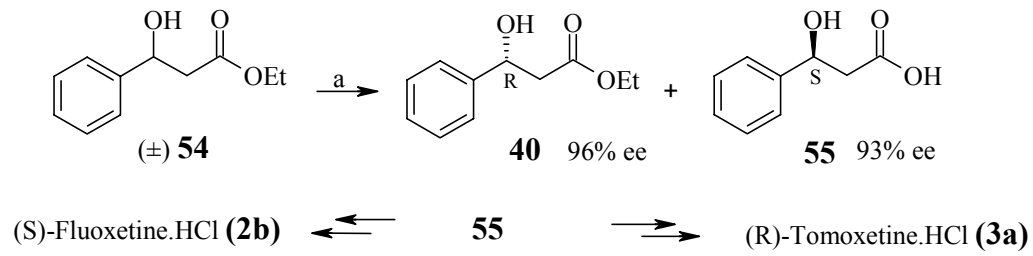


Scheme 17: a) butanoic anhydride, pyridine, CH_2Cl_2, 93%; b) buffer pH: 7, CALB, 30°C, 50%; c) vinyl butanoate, hexane, CALB, 80°C, 50%; d) PPh_3, DEAD, *o*-cresol or 4-$CF_3C_6H_4OH$; e) $MeNH_2$, EtOH, reflux, HCl.

Riberio's approach (2001)[36]

This approach is based upon the enzymatic hydrolysis of *β*-hydroxyester **54** as a key reaction. Ethyl 3-hydroxy-3-phenylpropanoate (**54**) on treatment with *PCL* enzyme gave (*R*)-hydroxyester **40** in 98% ee along with the acid (*S*)-**55** in 93% ee. Acid **55** was converted to

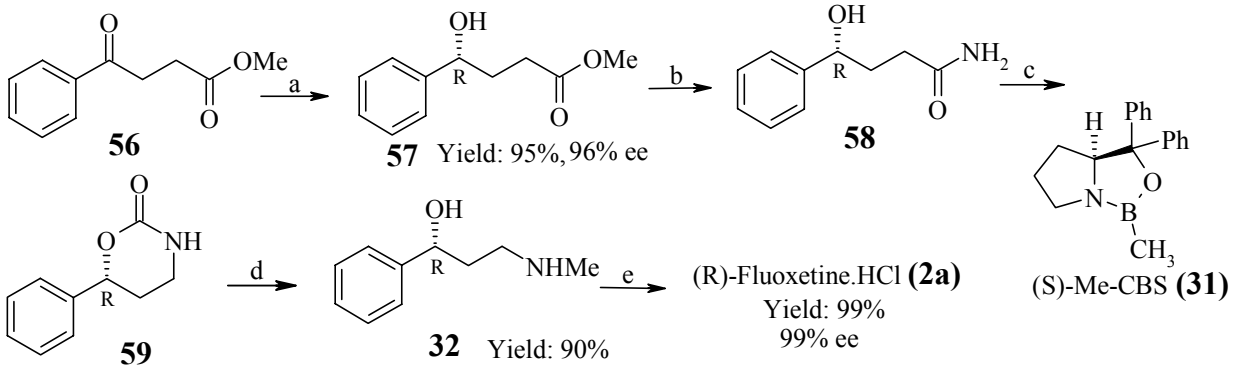
(*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a**) hydrochlorides by known sequence of steps (**Scheme 18**).



Scheme 18: a) PCL, pH: 7, 30 min.

Hilborn's approach (2001)[37]

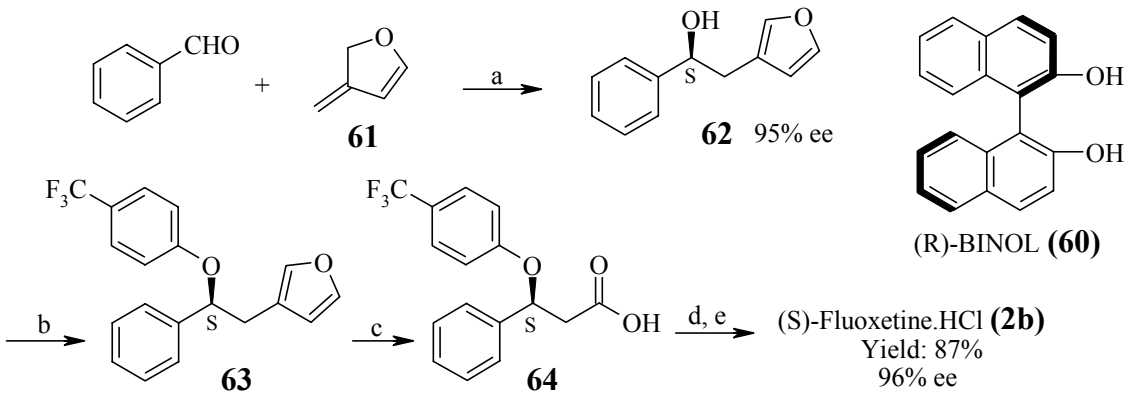
Hilborn's approach is based on the use of CBS reduction of γ-keto ester **56** followed by Hofman rearrangement as the key steps. The first step involves asymmetric reduction of γ-keto ester **56** using (*S*)-Me-CBS **31** to afford γ-hydroxy ester **57** in 96% ee, which was converted to cyclic carbamate **59** *via* amide **58**. Reduction of optically pure carbamate **59**, afforded *N*-methyl aminoalcohol **32**, which was converted into (*R*)-fluoxetine hydrochloride (**2a)** by known sequence of steps (**Scheme 19**).



Scheme 19: a) Me-CBS, BH_3.THF, THF, 0°C, 95%; b) $NH_3.H_2O$, MeOH, 40°C, 3 h, 80%; c) $PhI(OAc)_2$, CH_3CN, 40°C, 5 h, 83%, 99% ee; d) $LiAlH_4$, THF, reflux, 90%; e) NaH, DMAC, 4-chlorobenzotrifluoride, 90°C, HCl.

Mile's approach (2001)[38]

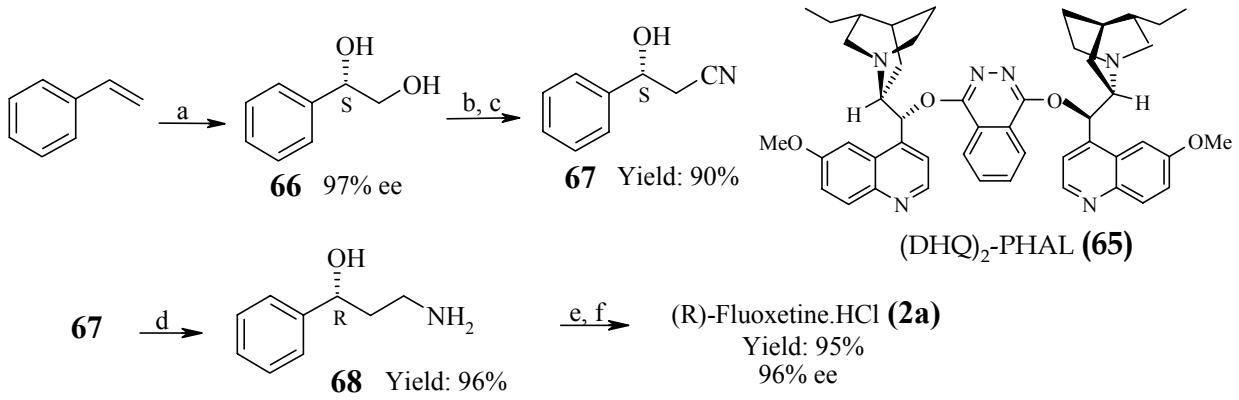
This approach involves asymmetric carbonyl-ene reaction as a key step to introduce chirality. Ti(^{i}OPr)$_4$/(*R*)-BINOL (**60**) catalyzed reaction of benzaldehyde with 3-methylene-2,3-dihydrofuran (**61**) gave (*S*)-2-(3-furyl)-1-phenyl-1-ethanol (**62**) in 95% ee. The alcohol **62**, was converted in four steps to (*S*)-fluoxetine hydrochloride (**2b**) in 96% ee. Similarly, (*R*)-fluoxetine hydrochloride (**2a**) was obtained by using (*S*)-BINOL (**Scheme 20**).



Scheme 20: a) Ti(*i*-Pr)$_4$, (*R*)-BINOL (**60**); b) NaH, DME, *p*-fluoro$C_6H_4CF_3$; c) $RuCl_3.xH_2O$, $NaIO_4$, EtOAc, H_2O; d) hydroxybenzotriazole hydrate, *N*-methylmorpholine, CH_3NH_2, 1-[3-(dimethylamino) propcarbodiimide hydrochloride; e) BH_3, THF, 6 M HCl, HCl in Et_2O.

Pandey's approach (2002)[39]

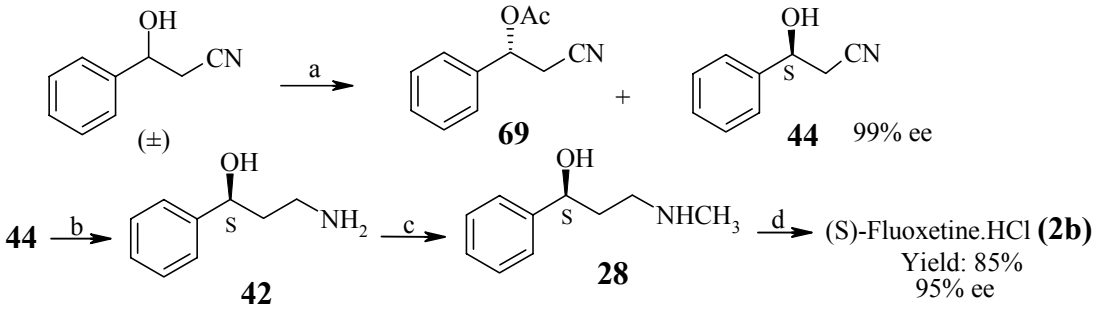
This strategy involves the use of Sharpless asymmetric dihydroxylation as a key reaction. Styrene on ADH reaction in presence of (DHQ)$_2$-PHAL (**65**) gave diol **66** in 97% ee. Diol **66** was selectively monotosylated at –15^{o}C and subsequent displacement with cyanide gave cyanohydrin **67**. Reduction of cyano group with borane reagent gave amino alcohol **68**, which was converted to (*R*)-fluoxetine hydrochloride (**2a**) (**Scheme 21**).



Scheme 21: a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2$-PHAL, OsO_4 (cat), *t*-BuOH:H_2O, 0°C, 24 h, 100%; b) *p*-TsCl, pyridine, CH_2Cl_2, –15°C, 24 h, 78%; c) NaCN, MeOH:H_2O, 24 h, 90%; d) $BH_3.SMe_2$, THF, reflux, 2 h, 96%; e) NaH, DMSO, 55°C, 0.5 h, 4-chlorobenzotrifluoride, 90°C, 1 h, 90%; f) (i) $ClCO_2Me$, CH_2Cl_2, *aq*. K_2CO_3, 30 min; (ii) $LiAlH_4$, THF, 65°C, 2 h, 90%, HCl gas, 95%.

Kamal's approach (2002)[40]

Kamal's strategy involves chemoenzymatic approach to the synthesis of (*S*)-fluoxetine hydrochloride (**2b**). Racemic *β*-hydroxy nitrile underwent kinetic resolution with vinyl acetate catalyzed by *lipase* to give (*S*)-cyanohydrin **44** and (*R*)-acetate **69** in high optical purity. Further, cyanohydrin **44** was converted to (*S*)-fluoxetine hydrochloride (**2b**) by following known sequence of reactions (**Scheme 22**).

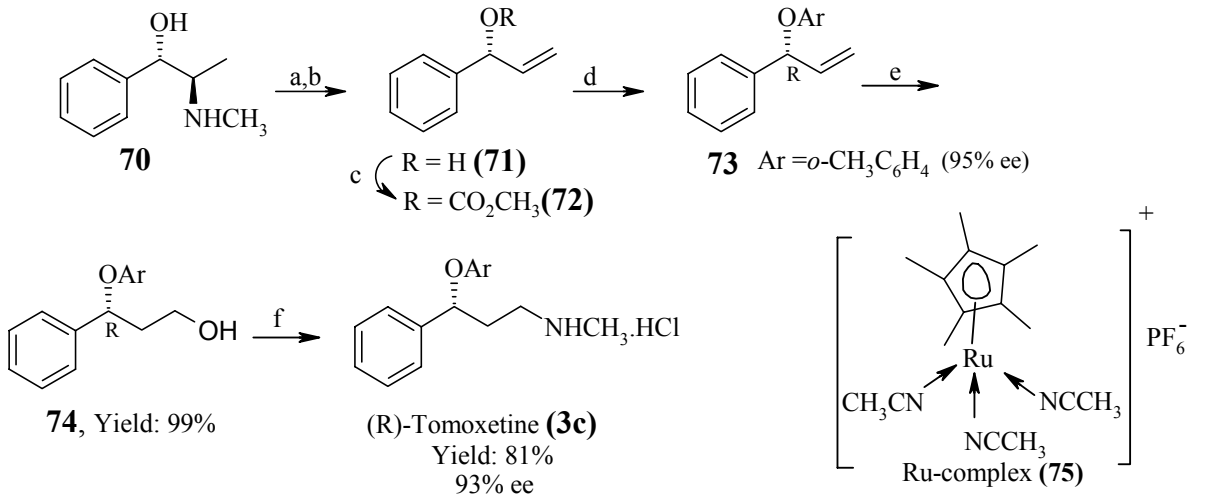


Scheme 22: a) *lipase*, vinylacetate, 40°C, 99% ee; b) BH_3-Me_2S, THF; c) Ethylchloroformate, K_2CO_3, CH_2Cl_2; d) LAH, THF; e) 4-chlorobenzotrifluoride, NaH, dry DMSO, HCl .

Trost's approach (2002)[41]

(*R*)-Tomoxetine (**3c**) was synthesized from (*S*)-ephedrine (**70**). The starting allyl alcohol **71** was obtained by Hoffmann elimination from (*S*)-ephedrine (**70**). The silyl ether of

o-cresol in the presence of catalytic amount of desilylating agent TBAC and 1 mol% of [Cp* $Ru(NCCH_3)_3]PF_6$ (Cp*=η-C_5Me_5) gave corresponding ether **73**. Subsequently hydroboration, oxidation, and substitution provided (*R*)-tomoxetine (**3c**) in 81% yield (**Scheme 23**).



Scheme 23: a) CH_3I, K_2CO_3, CH_3OH, RT; b) LDA, THF, HMPA, –50-0°C; c) *n*-C_4H_9Li, $ClCO_2CH_3$, THF, –78-0°C; d) 1 mol% [Cp* $Ru(NCCH_3)_3]PF_6$,(**75**), *o*-$CH_3C_6H_4OTMS$, 5 mol% (*n*-$C_4H_9)_4NCl$, 10 mol% Et_3N, neat 35°C; e) 9-BBN-H, THF, 35°C, then KOH, H_2O_2, 0°C; f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C, $MeNH_2$, MeOH, 70°C.

1.0.8 Present Work

1.0.8.1 Objective

Although a variety of methods are reported in the literature for enantioselective synthesis of (*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a**) hydrochlorides, they suffer from disadvantages such as the use of costly catalysts, chiral starting materials, large number of steps, cumbersome experimental procedures, *etc*.

Recently, a catalytic method of the oxidative kinetic resolution of benzylic alcohols was discovered using a (–)-sparteine/Pd(II) catalyst[23] (see introduction for details). The objective of this Chapter is to explore the usefulness of the Pd-catalyzed oxidative kinetic resolution of benzylic alcohols for application to the enantioselective synthesis of (*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a**) hydrochlorides. Accordingly, the retro-synthetic

analysis for (*S*)-3-methylamino-1-phenylpropan-1-ol (**28**), a key precursor both for (*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a**) hydrochlorides, is shown in **(Fig. 6)**.

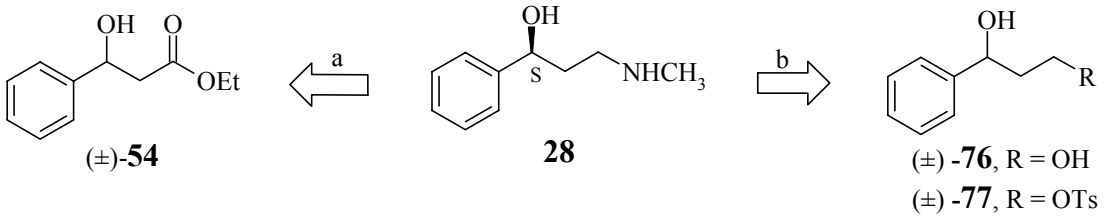
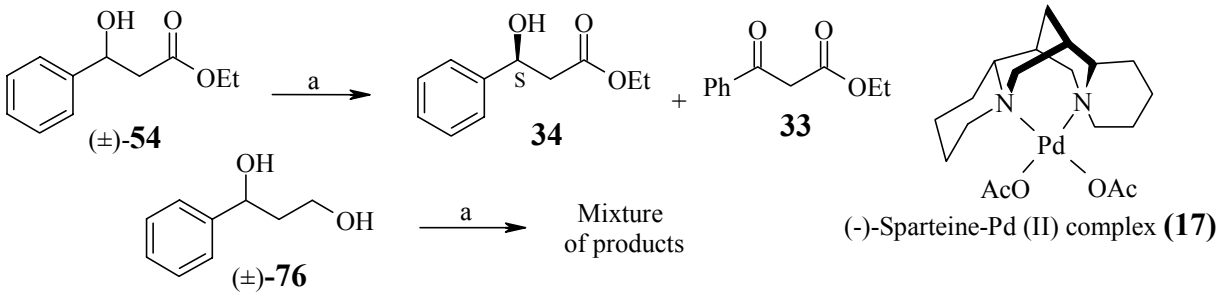


Fig. 6: Retro-synthetic analysis for (*S*)-3-methylamino-1-phenylpropan-1-ol (**28**)

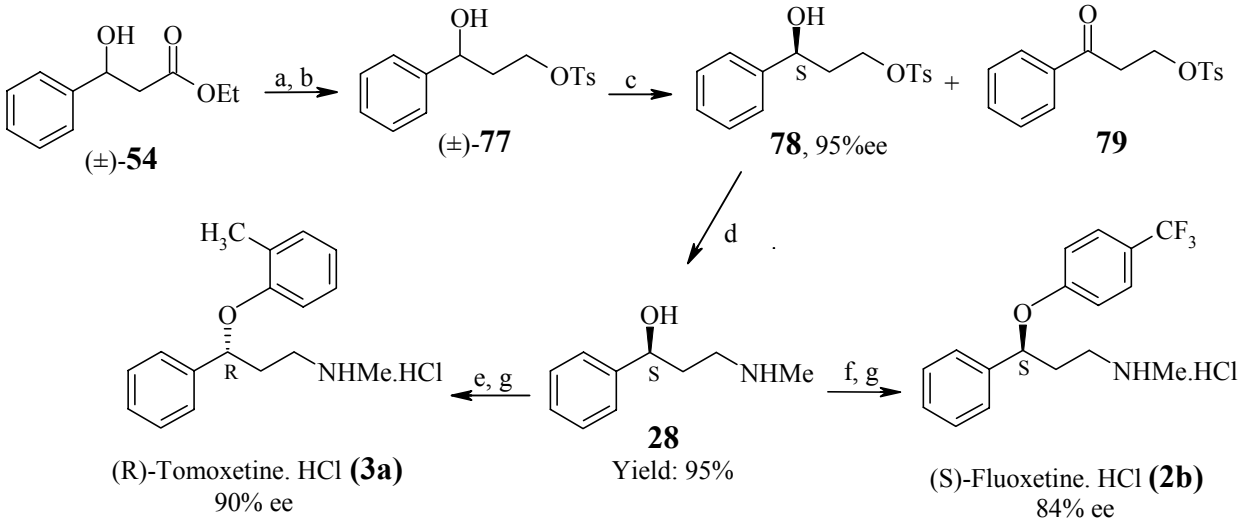
Either the racemic *β*-hydroxy ester **54** (route a), 1,3-diol **76** or the monotosyl compound **77** (route b) can be visualized as starting material to obtain optically pure amino alcohol **28**. Thus, when racemic *β*-hydroxy ester **54** was subjected to oxidative kinetic resolution with the catalytic system such as 5 mol% $Pd(OAc)_2$/ 20 mol% (–)-sparteine/ O_2 (1 atm), the chiral (*S*)-*β*-hydroxy ester **34** was indeed obtained although in low ee (12% ee) along with its oxidized product, *β*-keto ester **33** in 15% yield. However, when the diol **76** was subjected to the same oxidative kinetic resolution, it gave the mixtures of products, which were difficult to separate (**Scheme 24**). Hence, primary hydroxyl group of 1,3-diol **76** was protected and subjected to oxidative kinetic resolution using $Pd(OAc)_2$/(-)-sparteine/ O_2 catalytic system (**Scheme 25**).



Scheme 24: a) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine (**17**), O_2 (1 atm), 3Å MS, toluene, 80°C, 36 h.

1.0.9 Results and Discussion

The overall synthetic sequence for the preparation of (*S*)-fluoxetine (**2b**) and (*R*)-tomoxetine (**3a**) hydrochlorides is depicted in (**Scheme 25**).[42] As can be seen, palladium catalyzed oxidative kinetic resolution of racemic secondary benzylic alcohol **77** constitutes the key step of introducing stereogenecity into the target molecule.

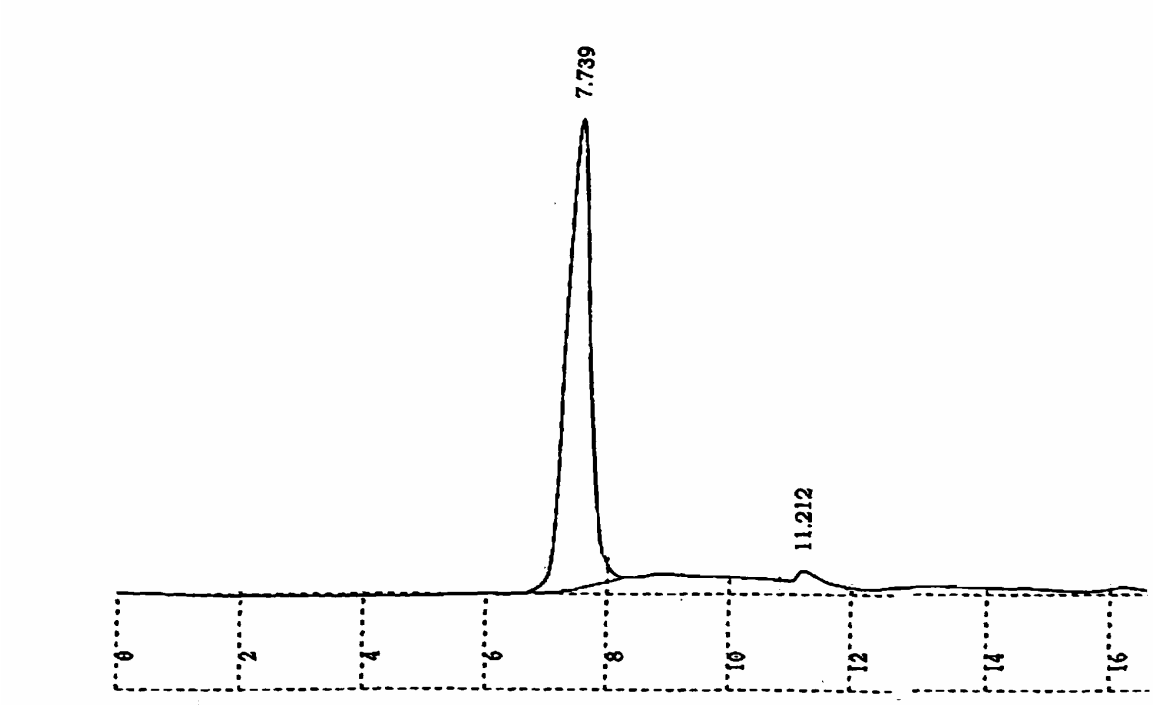


Scheme 25: a) $LiAlH_4$, ether, 2 h, 85%; b) TsCl, Et_3N, CH_2Cl_2, –10-0°C, 95%; c) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, O_2 (1 atm), 3Å MS, toluene, 80°C, 36 h, $[\alpha]_D$ – 15.1 (c 1.0, $CHCl_3$), 95% ee, 47%; d) 40% *aq*. $MeNH_2$, THF, 65°C, $[\alpha]_D$ – 49.1 (c 1.0, $CHCl_3$), 95%; e) *o*-cresol, PPh_3, DEAD, ether, –10-0°C, $[\alpha]_D$ – 36.3 (c 1.0, EtOH), 90% ee; g) HCl (gas), ether; f) NaH, DMAC, 90°C, *p*-chlorobenzotrifluoride, 105°C, $[\alpha]_D$ – 9.1 (c 1.0, H_2O), 84% ee.

The first step involves the Reformatsky reaction of benzaldehyde with ethylbromoacetate in the presence of zinc-wool to give racemic β-hydroxy ester **54** in 90% yield. Its ^{1}H-NMR spectrum showed a triplet at δ 1.25 and a quartet at δ 4.05-4.25 indicating the presence of ethyl group and a doublet of doublet at δ 5.05-5.20 corresponding to benzylic proton. β-Hydroxy ester **54** was reduced with lithium aluminum hydride to give 1,3-diol **76** in 85% yield. Its IR spectrum showed the disappearance of carbonyl group. Selective protection of primary hydroxyl group of the diol **76** was carried out by treatment with *p*-toluenesulfonyl

chloride in presence of Et_3N in CH_2Cl_2 at -10^oC to give racemic mono tosylate **77** in 95% yield.

When racemic mono tosylate **77** was subjected to oxidative kinetic resolution [5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine/ O_2 (1 atm), 3Å MS, $PhCH_3$, 80^oC, 36 h], it smoothly afforded (*S*)-3-phenyl-3-hydroxypropyl-*p*-toluenesulfonate (**78**) in 47% yield along with its



** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	7.739	13971	507			97.2897	
	2	11.212	389	21			2.7103	
		TOTAL	14360	528			100	

Fig. 7: HPLC chromatogram of chiral monotosylate 78

oxidized product **79**. The optical purity of alcohol **78** as determined by HPLC analysis using chiralcel OD-H column was found to be 95% ee **(Fig. 7)**. Chiral alcohol **78** was readily separated from its oxidized product by simple column chromatographic purification and thoroughly characterized. Its ^{1}H-NMR spectrum showed a singlet at δ 2.46 corresponding to methyl protons of tosyl group and multiplets in the range of δ 4.00-4.40 corresponding to

methylene protons adjacent to tosyl group. Its ^{13}C-NMR spectrum also showed characteristic signal at δ 21.46 corresponding to methyl carbon of tosyl group, while its benzylic carbon appeared at δ 69.98 **(Fig. 8)**.

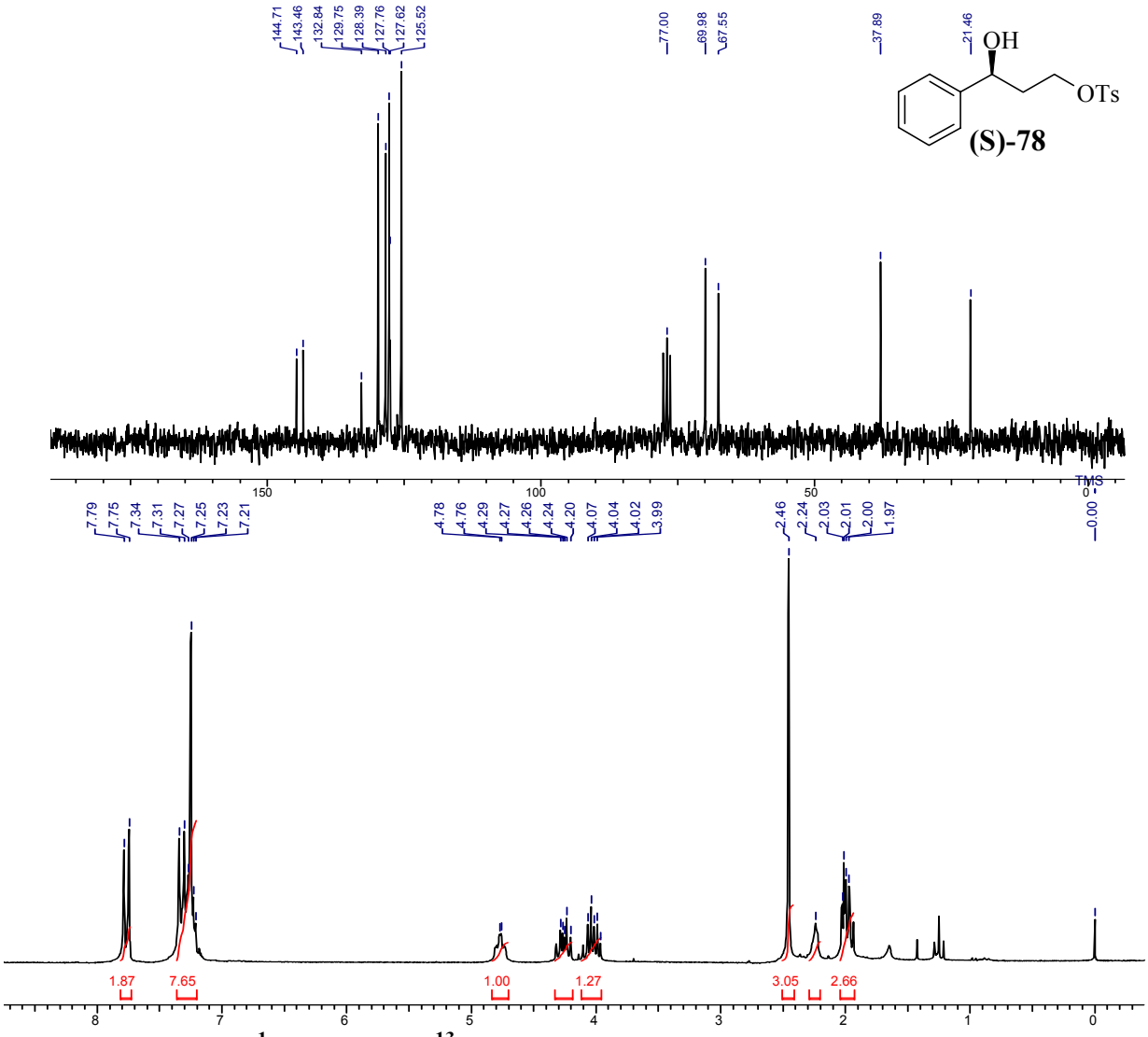


Fig. 8: ^{1}H-NMR and ^{13}C-NMR spectra of chiral monotosylate 78

The mechanism of oxidative kinetic resolution of alcohol **77** is believed to involve *in situ* formation of a chiral Pd(II)-(–)-sparteine complex **A** assisted by the presence of 10 mol% excess of (–)-sparteine.[43] The first step probably involves the coordination of alcohol **77** with Pd-complex **A** to produce species **B**. Subsequently, species **B** undergoes *β*-hydride elimination

so that the simultaneous oxidation of alcohol take place resulting in the formation of kinetically resolved product **78** along with Pd(0) species **C**. Species **C** undergoes further oxidation with molecular O_2 in the presence of AcOH to regenerate the active species **A** thus completing the catalytic cycle **(Fig. 9)**.

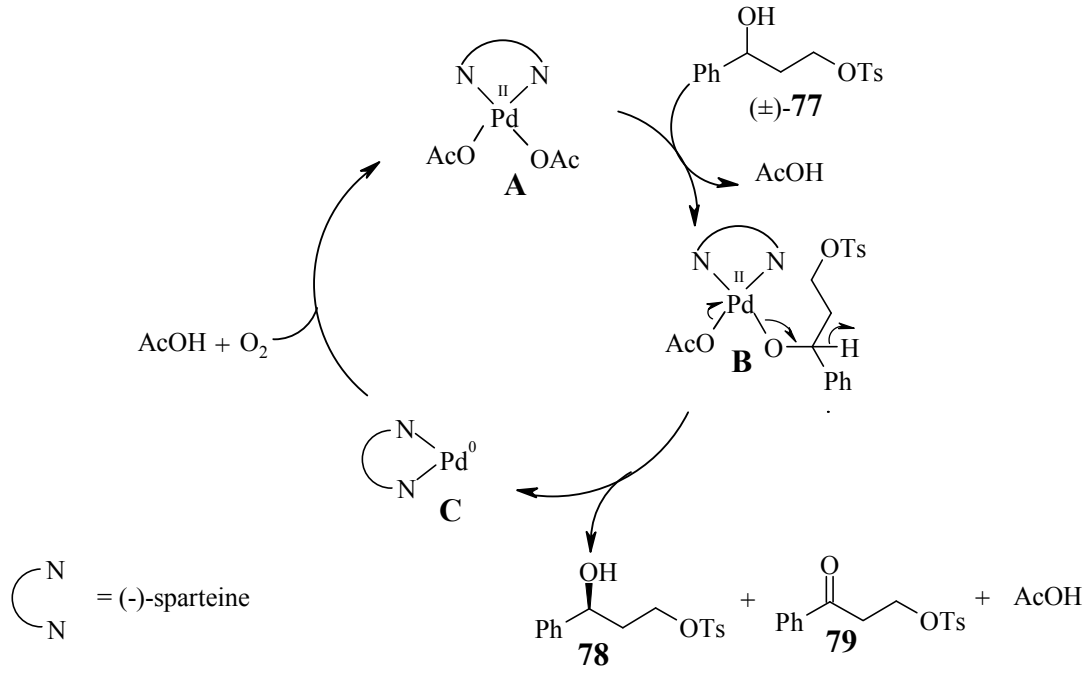


Fig. 9: Probable mechanism for oxidative kinetic resolution of alcohol 77

Reaction of (*S*)-3-phenyl-3-hydroxypropyl-*p*-toluenesulfonate (**78)** with excess of *aq*. $MeNH_2$ afforded the common intermediate, (*S*)-methyl-3-phenyl-3-hydroxypropylamine (**28**), in 95% yield and high enantiomeric excess. {$[\alpha]_D$ – 49.18 (c 1.0, $CHCl_3$); maximum $[\alpha]_D$ reported in the literature[26] being $[\alpha]_D$ – 37.37 (c 1.0, $CHCl_3$)}. The ^{1}H-NMR spectrum of amino alcohol **28** showed a sharp singlet at δ 2.45 corresponding to N-CH_3 group.

Mitsunobu inversion of (*S*)-methyl-3-phenyl-3-hydroxypropylamine (**28**) with *o*-cresol was achieved by employing standard reaction conditions {PPh_3, diethyl azodicarboxylate (DEAD)}, followed by its treatment with conc. HCl gave (*R*)-tomoxetine hydrochloride (**3a**)

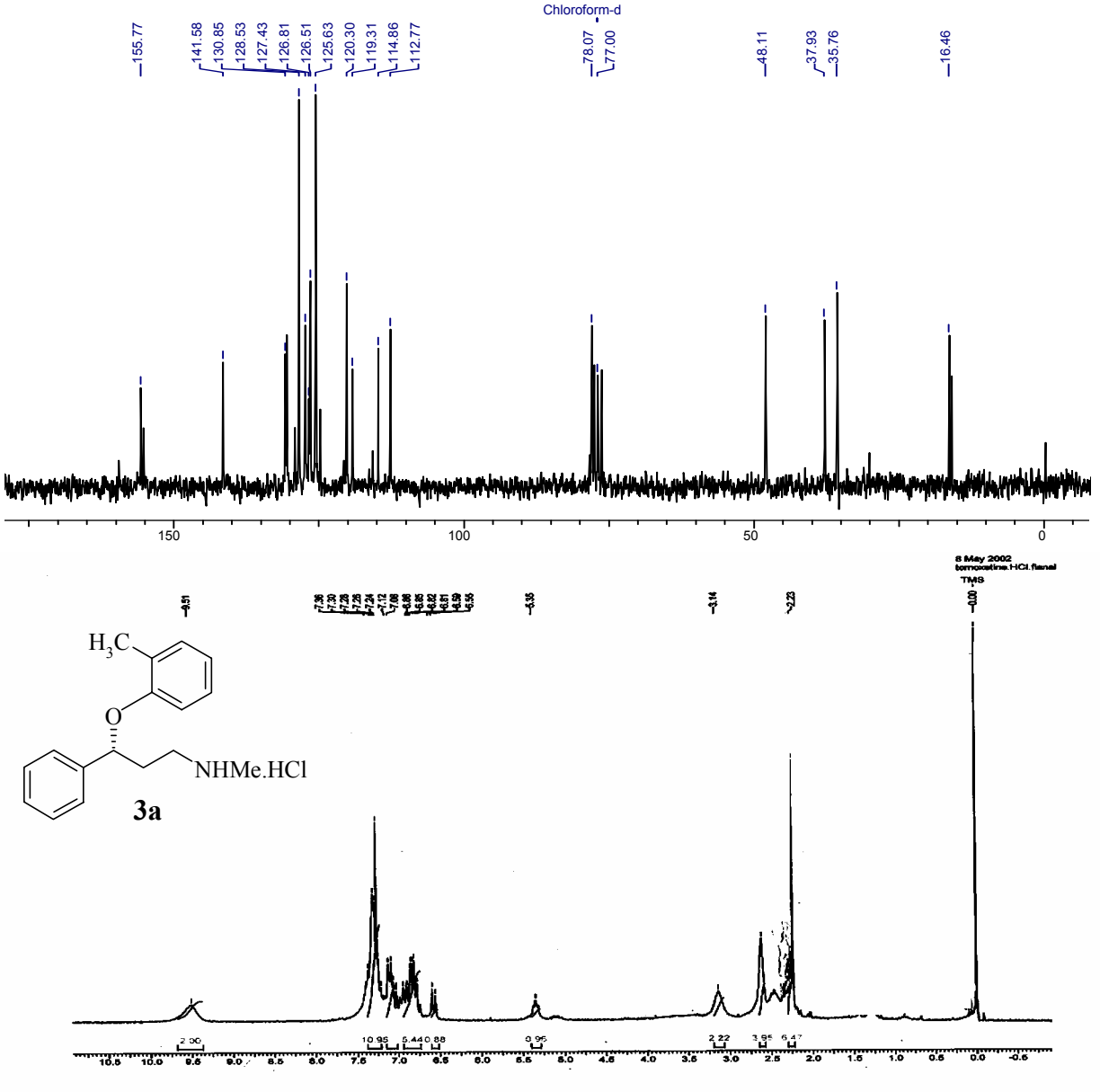


Fig. 10: ^{1}H-NMR and ^{13}C-NMR spectra of (*R*)-Tomoxetine hydrochloride (3a)

in 90% ee {$[\alpha]_D$ – 36.3 (c 1.0, EtOH); lit.[25] $[\alpha]_D$ – 40.03 (c 0.94, EtOH)} and 72% yield. Its ^{1}H-NMR spectrum showed a downfield shift for benzylic proton at δ 5.35 compared to the corresponding alcohol **78**. Its ^{13}C-NMR spectrum showed typical carbon signals at δ 16.46, 35.76, 48.11 and 78.07 **(Fig.10)**.

In order to achieve the synthesis of (*S*)-fluoxetine hydrochloride (**2b**), arylation of amino alcohol **28** was carried out by treatment with *p*-chlorobenzotrifluoride in the presence of sodium hydride in DMSO at 105°C. It was then subjected to treatment with conc. HCl to give (*S*)-fluoxetine hydrochloride (**2b**) in 80% yield and its optical purity was found to be 84% ee {$[\alpha]_D$ – 9.18 (c 1.0, H_20); lit.[25] $[\alpha]_D$ – 10.85 (c 1.0, H_2O)}. Its ^{1}H-NMR spectrum showed a multiplet at δ 5.56 corresponding to benzylic proton. The methylene group α to nitrogen appeared at δ 3.11 as broad singlet **(Fig. 11)**. Its ^{13}C-NMR showed a characteristic signal at δ 159.7 corresponding to the carbon attached to CF_3 group and the benzylic carbon signal is observed at δ 76.9.

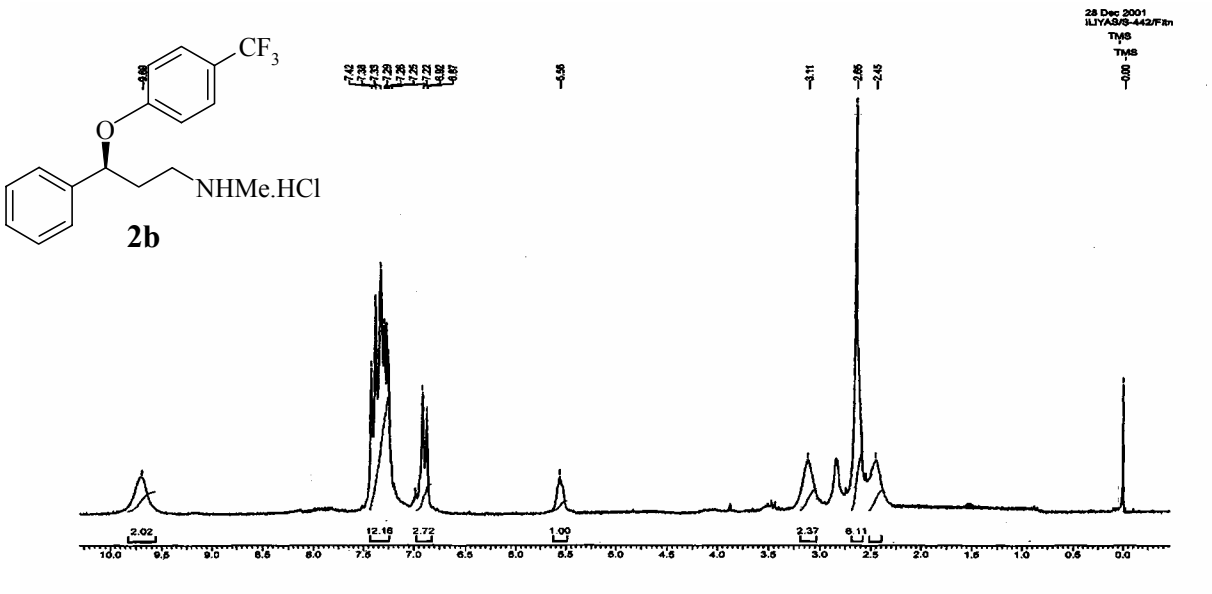


Fig. 11: ^{1}H-NMR spectra of (*S*)-Fluoxetine hydrochloride (2b)

1.0.10 Conclusion

In conclusion, a convenient synthetic route to enantioselective synthesis of (*R*)-tomoxetine hydrochloride (**3a**) (90% ee) and (*S*)-fluoxetine hydrochloride (**2b**) (84% ee) is described in this chapter. The strategy involves (*S*)-3-phenyl-3-hydroxypropyl-*p*-toluenesulfonate (**78**), as the key intermediate which is obtained by the oxidative kinetic resolution of the corresponding racemic 3-phenyl-3-hydroxypropyl *p*-toluenesulfonate (**77**)

using (–)-sparteine/ Pd(II)/ O_2 (1 atm) catalytic system. All the steps are high yielding and easy to handle.

1.0.11 Experimental Section

Preparation of ethyl 3-hydroxy-3-phenylpropanoate (54)

A 100 ml two-necked flask equipped with water condenser and septum was charged with activated zinc (3.67 g, 0.056 mol), and kept under N_2 atmosphere. Dry benzene (25ml) was introduced in the flask and the reaction flask was heated up to 80^{o}C (oil bath temp). A solution of ethyl bromoacetate (8.63 g, 0.051 mol) and benzaldehyde (5 g, 0.047 mol) in dry benzene was added dropwise to the reaction mixture. After completion of addition, the reaction flask was refluxed for 5 h, cooled to RT and then quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether. After evaporation of the solvent under reduced pressure the crude hydroxyester was purified by column chromatography packed with silica gel, eluting with pet. ether : EtOAc (9:1) to give 8.12 g of ethyl 3-hydroxy–3-phenylpropanoate (**54**).

Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3488, 3150, 2983, 1728, 1494, 1454, 1390, 1373, 1270, 1195, 1035, 757; **^{1}H-NMR:** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 6.0 Hz, 3H), 2.65-2.75 (m, 2H), 3.5-3.75 (brs, 1H), 4.05-4.25 (q, *J* = 8.0 Hz, 2H), 5.05-5.20 (dd, *J* = 4.0 and 6.0 Hz, 1H), 7.25-7.45 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.78, 43.29, 60.46, 70.02, 125.45, 127.36, 128.17, 142.61, 171.87; **MS** (m/z, % RI): 194 (M^+, 28), 176 (4), 165 (5), 147 (8), 131 (6), 120 (16), 107 (98), 106 (28), 105 (74), 92 (10), 88 (20), 79 (100), 78 (26), 77 (90), 70 (8), 60 (24); **Analysis**: $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.25; found C, 68.05; H, 7.29%.

Preparation of (±) - 3-phenyl-1,3-dihydroxypropane (76)

A 100 ml two-necked flask equipped with water condenser and septum was charged with lithium aluminium hydride (0.430 g, 0.01mol), and kept under N_2 atmosphere. Dry diethyl ether (30 ml) was introduced in the flask and it was cooled to 0^{o}C. A solution of ethyl 3-hydroxy-3-phenylpropanoate (**54**) (2 g, 0.01 mol) in diethyl ether was introduced dropwise over a period of 30 min. Then, reaction mixture was heated up to reflux for 2 h. After cooling to RT reaction was quenched with ethyl acetate and water. The crude 1,3-diol was extracted with ethyl acetate (3 x 60 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulphate. After evaporation of the solvent under reduced pressure the crude

1,3-diol was purified by column chromatography packed with silica gel, eluting with pet. ether : EtOAc (1:1) to give 1.32 g of 3-phenyl-1,3-dihydroxypropane (**76**).

Yield: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3944, 3596, 3415, 3055, 2985, 2304, 1421, 1265, 1053, 896, 738, 703; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.90-2.00 (m, 2H), 2.04 (s, 1H), 3.40-3.60 (br s, 1H), 3.78-3.84 (t, *J* = 6.0 Hz, 2H), 4.89-4.95 (dd, *J* = 2.0 Hz, 1H), 7.25-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 40.32, 60.31, 72.96, 125.52, 127.21, 128.20, 144.19; **MS** (m/z, % RI) 152 (M^+, 9), 134 (6), 133 (7), 115 (3), 108 (8), 107 (70), 104 (11), 91 (10), 79 (89), 77 (74), 65 (6), 63 (7); **Analysis:** $C_9H_{12}O_2$ requires C, 71.03; H, 7.94; found C, 71.05, H, 7.89%.

Preparation of (±) - 3-phenyl-3-hydroxypropyl *p*-toluenesulfonate (77)

To a solution of 3-phenyl-1,3-dihydroxypropane (**76**) (0.8 g, 5.26 mmol) and triethylamine (0.583 g, 5.78 mmol) in CH_2Cl_2 (90 ml) at –10°C was added TsCl (1.1 g, 5.78 mmol) portion wise using solid addition funnel. After stirring at –10 - 0°C for 6 h, the mixture was poured into ice water (30 ml), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous sodium sulphite. The crude product was purified by column chromatography on silica gel eluting with 35% ethyl acetate in pet. ether to give 1.53 g 3-phenyl-3-hydroxypropyl *p*-toluenesulphonate (**77**) in 95% yield.

Preparation of (*S*)-3-phenyl-3-hydroxypropyl *p*-toluenesulphonate (78)

To a 50 ml side arm flask (0.020 mg, 0.089 mmol) of $Pd(OAc)_2$ was added followed by 20 ml of dry toluene and 100 mg of 3Å sieves and (84 mg, 0.35 mmol) of (–)-sparteine. A condenser with balloon filled with O_2 was then attached to flask. The whole system was evacuated and refilled with O_2 from the balloon three to four times. The flask was warmed to 80°C in an oil bath. After 30 min, (±)-3-phenyl-3-hydroxypropyl *p*-toluenesulfonate (**77**) (0.550 g, 1.8 mmol) in toluene was added dropwise. After 36 h of reflux temperature, the reaction was cooled to RT and 15 ml of 2% TFA/ methanol was added to quench the reaction. The solvent was removed under reduced pressure and the residue was taken up in minimal amount of dichloromethane. The crude residue was then purified by column chromatography eluting with 25% ethyl acetate: pet. ether to get 0.258 g of (*S*)-3-phenyl-3-hydroxypropyl *p*-toluenesulphonate (**78**) in 95% ee and 47% yield.

Yield: 47%; **gum**; **$[\alpha]^{25}_D$** – 15.15 (c 1.0, $CHCl_3$); **HPLC**: 95% ee, Chiralcel OD-H, λ = 254 nm, 5% 2-propanol/hexane, 0.5 ml/min., Retention time: (S) 7.739 min. (R) 11.212 min.; **IR**

($CHCl_3$, cm^{-1}): 3541, 3056, 2985, 2962, 2925, 2306, 1920, 1731, 1598,1494, 1454, 1357, 1265, 1188, 1097, 968, 910, 815; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.96-2.05 (m, 2H), 2.26 (brs, 1H), 2.48 (s, 3H), 4.01-4.09 (m, 1H), 4.23 -4.31 (m, 1H), 4.70-4.85 (m, 1H), 7.23-7.37 (m, 7H), 7.77-7.81 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.46, 37.89, 67.55, 69.98, 125.52, 127.75, 127.76, 128.39, 129.75, 132.84, 143.46, 144.71; **MS** (m/z, % RI): 306 (M^+, 13), 305 (16), 278 (3), 200 (7), 173 (45), 155 (17), 134 (85), 118 (18), 107 (80), 92 (90), 91 (100), 77 (60), 65 (45); **Analysis:** $C_{16}H_{18}SO_4$ requires C, 62.72; H, 5.91; found C, 62.65; H, 5.88%.

Preparation of (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine (28)

In a 50 ml flask equipped with condenser was charged with (*S*)-3-phenyl-3-hydroxypropyl *p*-toluenesulphonate (**78**) (0.250 g, 0.816 mmol), 40% methylamine (15 ml) and of THF (15 ml). The reaction flask was then heated at 65^{o}C for 3 h. After cooling, the solution was diluted with ether, washed with saturated aqueous solution of $NaHCO_3$, brine, and then dried over anhydrous K_2CO_3. Removal of solvent under reduced pressure gave (*S*)-*N*-methyl-3- phenyl-3-hydroxypropylamine (**28**) (0.127 g, 95% yield).

Yield: 95%; **gum**; **$[\alpha]^{25}_D$** – 49.18 (c 1.0, $CHCl_3$); lit.[26] **$[\alpha]^{25}_D$** – 37.37 (c 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3341, 3018, 2935, 1215, 1205, 960, 760; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.68-2.00 (m, 3H), 2.45 (s, 3H), 2.82-2.92 (m, 2H), 3.74 (brs, 1H), 4.94 (dd, *J* = 3.8 Hz, 7.2 Hz, 1H), 7.20-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 35.17, 36.79, 48.30, 72.74, 125.85, 127.43, 128.35, 143.90; **MS** (m/z, % RI): 165 (M^+, 8), 150 (3), 118 (13), 107 (26), 105 (70), 91 (32), 79 (60), 77 (100), 72 (30), 58 (55); **Analysis**: $C_{10}H_{15}NO$ requires C, 72.63, H, 9.14, N, 8.47; found C, 72.64, H, 9.10, N, 8.40%.

Preparation of (*R*)-tomoxetine hydrochloride (3a)

To a stirred solution of (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine (**28**) (0.120 g, 0.727 mmol), *o*-cresol (0.157 g, 1.45 mmol) and triphenylphosphine (0.285 g, 1.09 mmol) in ether (20 ml) was added dropwise diethyl azodicarboxylate (0.266 g, 1.09 mmol) at –10^{o}C under nitrogen atmosphere. After stirring at –10^{o}C for 4 h, the mixture was concentrated to get crude residue as oil. The oil was dissolved in ether and hydrogen chloride gas was bubbled through the solution until a white precipitate of (*R*)-tomoxetine (**3a**) hydrochloride was formed (0.152 g, 72%).

Yield: 72%; **mp**: 162-164^{0}C (hexane/EtOAc) (lit.[25] 166-168^{0}C); **[α]$^{25}_D$** –36.3 (c 1.0, $CHCl_3$) 90% ee; {lit.[25] **[α]$^{25}_D$** – 40.03 (c 0.94, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 2945, 2625, 1590, 1495, 1220, 1280, 1120, 1050; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.40-2.55 (m, 2H), 2.62 (brs, 3H), 3.14 (brs, 2H), 5.35 (m, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.75-7.00 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.25-7.50 (m, 5H), 9.51 (brs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 16.46, 35.76, 48.11, 78.07, 112.77, 120.30, 125.63, 126.51, 126.81, 128.53, 129.23, 130.85, 141.58, 155.77; **MS** (m/z, % RI): 177 (18), 176 (16), 161 (4), 117 (10), 108 (28), 107 (34), 91 (35), 79 (54), 78 (60), 77 (100), 65 (38), 62 (27); **Analysis**: $C_{17}H_{22}ClNO$ requires C, 69.97; H, 7.59; N, 4.80; found C, 69.90; H, 7.57; N, 4.81%.

Preparation of (*S*)-fluoxetine hydrochloride (2b)

To a solution of (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine (**28**) (0.120 g, 0.727 mmol) in dimethylacetamide (4 ml) was added 60% sodium hydride (0.033 g, 1.37 mmol) with cooling. The reaction mixture was then heated at 90^{o}C for 1.5 h. Then 4-chlorobenzotrifluoride (0.314 g, 1.74 mmol), was added to the reaction mixture, the reaction flask was heated at 100-105^{o}C, for 3 h. The reaction mixture was cooled and diluted with toluene, the mixture was washed with water, and the aqueous layer was extracted with toluene. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulphate. After concentration provided crude fluoxetine as oil. The oil was dissolved in ether; it was acidified with dry hydrogen chloride gas. The resulting white solid was filtered and was washed with ether to give (*S*)-fluoxetine (**2b**) hydrochloride (0.200 g, 80% yield).

Yield: 80%; **mp**: 140^{0}C (hexane/EtOAc), lit.[25] **mp**: 140-142^{0}C; **[α]$^{25}_D$** – 9.1(c 1.0, H_2O) 84% ee; {lit.[25] **[α]$^{25}_D$** – 10.85 (c 1.0, H_2O)} ; **IR** ($CHCl_3$, cm^{-1}): 3394, 3018, 2975, 2775, 2447, 2401, 1614, 1515, 1467, 1423, 1326, 1215, 1164, 1122, 1068, 780; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.40-2.50 (m, 2H), 2.65 (s, 3H), 3.11 (brs, 2H), 5.56 (brs, 1H), 6.87-6.92 (d, *J* = 8.0 Hz, 2H), 7.10-7.50 (m, 7H), 9.69 (brs, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 33.5, 37.5, 45.0, 76.5, 115.7, 124.8, 125.3, 127.1, 127.5, 127.8, 139.3, 159.7; **MS** (m/z, % RI): 309 (M^+, 15), 164 (6), 162 (8), 133 (8), 117 (12), 115 (30), 104 (50), 91 (42), 77 (80), 57 (100), 55 (70); **Analysis**: $C_{17}H_{19}ClF_3NO$ requires C, 59.05; H, 5.53, N, 4.05; found C, 59.10; H, 5.55, N, 4.04%.

SECTION II:

Pd-Catalyzed Oxidative Kinetic Resolution of 2-Azido-1-arylethanols

1.1.1 Introduction

Traditionally, oxidations of alcohols are performed with stoichiometric amounts of inorganic oxidations, notably Cr(VI) reagents. These are relatively expensive reagents that generate copious amounts of heavy metal wastes in environmentally undesirable solvents, typically chlorinated solvents. Hence, there is a need for catalytic oxidations that use dioxygen (O_2) or hydrogen peroxide as the stoichiometric oxidant. These oxidants are atom efficient and produce water as the only by-product.[44]

Pd (II)-catalyzed aerobic oxidations are a powerful class of transformations for organic synthesis.[45] The palladium-catalyzed Wacker process (**Eq. 2**) was developed more than forty years ago and remains one of the most successful aerobic oxidation reactions in the chemical industry. Also simple oxidation of alcohols, which provides a practical alternative to high oxidation state metal-mediated oxidations.[46] Nishimura reported a novel combination of $Pd(OAc)_2$/ pyridine catalyzed aerobic oxidation of various benzylic alcohols to aldehydes and ketones.

$$CH_2{=}CH_2 + {}^1/_2O_2 \xrightarrow{Pd/Cu\ cat.} CH_3CHO \qquad \textbf{--Eq. 2}$$

1.1.2 Biological Importance

Optically active β-azido alcohols are of great significance as they are direct precursors of chiral aziridines[47] and vicinal amino alcohols.[48] During recent years, there has been a growing interest in chiral aziridines due to the increasing importance of functionalized

aziridines in organic synthesis and their presence in bioactive molecules. Moreover, chiral β-amino alcohols are important structural elements in chiral ligands for asymmetric catalysis as well as in biologically active compounds e.g., β-adrenergic receptor blockers and agonists in the treatment of cardiovascular disease, cardiac failure, asthma and glaucoma.[49]

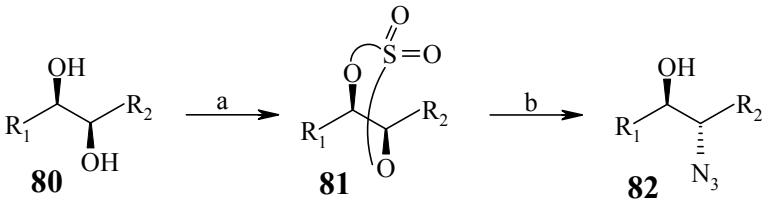
The proper choice of bridging ligands is also important, since they influence the magnetic strength and behavior of the molecules. The azido ligand has been widely utilized because of its diverse binding modes leading to variations in the magnetic properties that depend on its orientation with respect to the magnetic centers. In contrast to chiral 2-amino-1-ols, which are readily available by reduction of α-amino acids,[50] the corresponding regioisomeric chiral 1-amino-2-ols are not as easy to access.

1.1.3 Review of Literature

Literature search reveals that there are some reports for the enantioselective synthesis of azido alcohols, which are described below. They are based on either classical resolution method, which makes use of either costly chiral auxiliary, use of enzymes or formation of the products in low optical purity.

Lohray's approach[51]

This method provides the synthesis of chiral azido alcohols **82** starting with chiral diols **80**, obtained from asymmetric dihydroxylation of the corresponding olefins. Diol **80** is



80 **81** **82**

R_1= cyclohexyl, benzyl, phenyl. etc
R_2= H, *n*-butyl, phenyl. etc

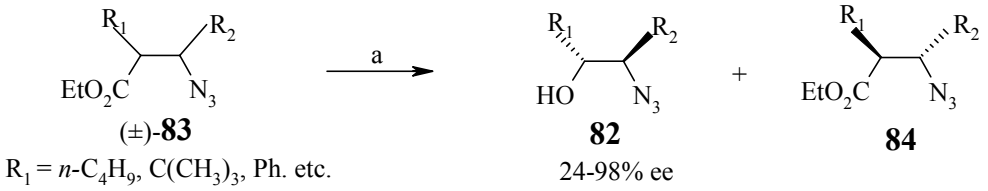
60-96% ee

Scheme 26: a) $SOCl_2$, Et_3N, CH_2Cl_2, then $RuCl_3$, $NaIO_4$; b) LiN_3, THF, reflux.

then converted to cyclic sulphates **81** in a two-step sequence of reactions. Treatment of cyclic sulphates **81** with LiN_3 in THF gives azido sulphates, *in situ* which are subsequently converted to azido alcohols **82** after acidic hydrolysis (**Scheme 26**).

Foelsche's approach[52]

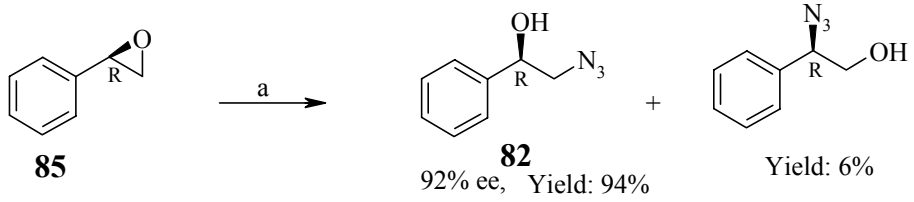
Foelsche *et al.* have reported lipase catalyzed kinetic resolution, of azido esters **83** using commercially available lipases such as *Candida cylindracea* and *pseudomonas*. Azido alcohols **82** have obtained with enantiomeric excess ranging from 24 - 98% (**Scheme 27**).



Scheme 27: a) Enzyme, *Candida cylindracea*

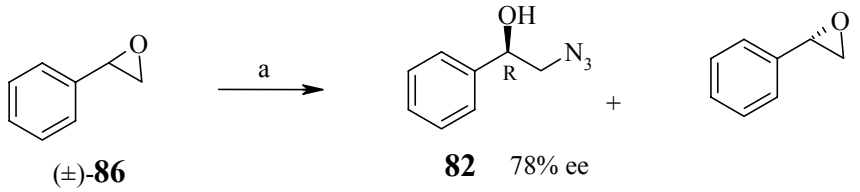
Guy's approach[53]

Guy *et al.* have reported regio and stereoselective ring opening of styrene oxide **85** at the non-benzylic position with lithium azide in HMPA. The optically pure (*R*)-2-azido-1-phenyl ethanol (**82**) was obtained with complete retention of configuration (**Scheme 28**).



Scheme 28: a) LiN_3, HMPA.

These authors have further established that regioselective ring opening of racemic styrene oxide **86** with lithium azide in the presence of *β*-cyclodextrin was carried out which resulted in the kinetic resolution of racemic epoxide **86** and 1-phenyl-2-azido ethanol (**82**) in 78% ee. The reaction occurs at room temperature in aqueous medium (**Scheme 29**).

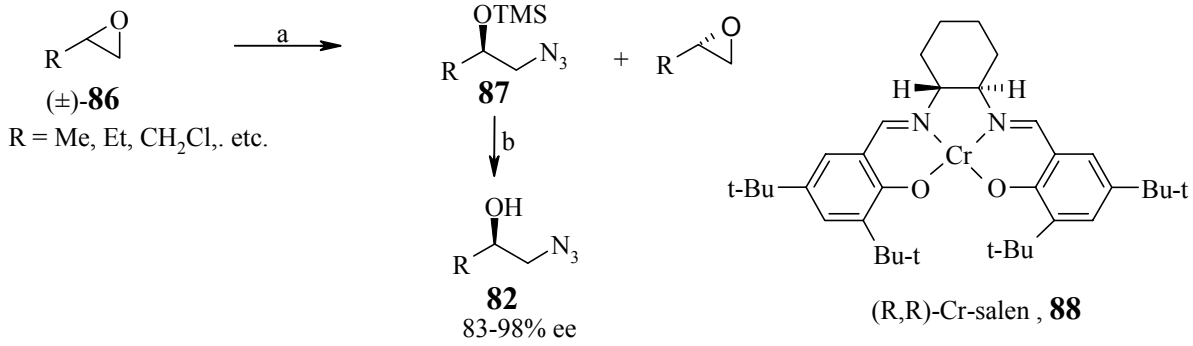


(±)-**86** **82** 78% ee

Scheme 29: a) β-cyclodextrin, LiN_3, H_2O.

Hansen's approach[54]

Hansen *et.al.* have reported the application of Cr-salen **88** catalyzed epoxide ring opening reaction as a key step. This method allows recovery of epoxides with high enantiomeric excess and also a clean production of 1-azido-2-trimethylsiloxyalkanes (**87**) in very high optical purity, which on hydrolysis gives azido alcohols **82** (**Scheme 30**).



(±)-**86**
R = Me, Et, CH_2Cl,. etc.

87

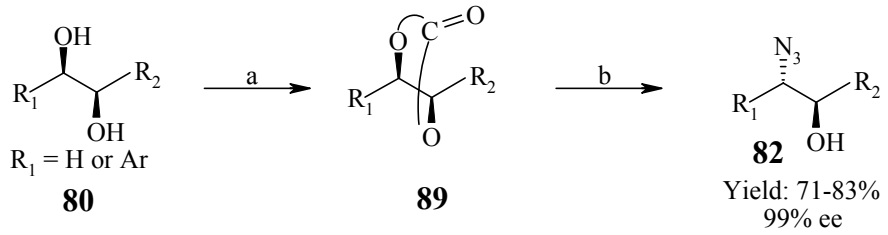
82
83-98% ee

(R,R)-Cr-salen , **88**

Scheme 30: a) 2 mol% (R,R) Cr-salen (**88**), Me_3SiN_3, Et_2O; b) CSA, MeOH.

Chang's approach[55]

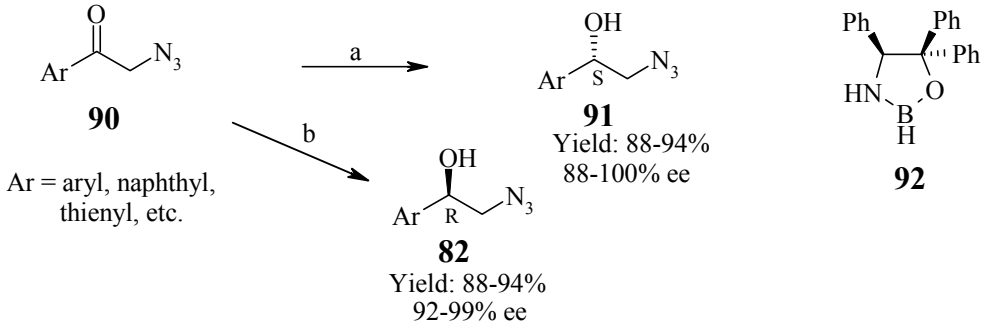
The asymmetric dihydroxylation of olefins leading to chiral diols **80** is a key step for the synthesis of enantiopure 1,2-azido alcohols **82**. The chiral diols **80** were first activated by converting to their cyclic carbonates **89**, which were subjected to stereospecific opening with sodium azide to give enantiopure azido alcohols **82** in 99% ee (**Scheme 31**).



Scheme 31: a) $(CH_3CO)_2CO$, NaH; b) NaN_3, H_2O, DMF.

Yadav's approach[56]

This approach reports the synthesis of optically active (*S*)-2-azido-1-phenyl ethanols **91** by following the asymmetric reduction of 2-azidophenone **90** with oxazaborolidine-borane complex **92**.

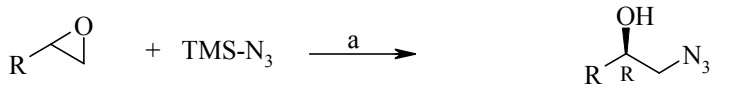


Scheme 32: a) 10 mol% catalyst (**92**); $BH_3.SMe_2$, toluene-THF, 40°C; b) baker's yeast/sucrose, phosphate buffer, pH: 6.5, RT, 18-24 hrs.

Yadav *et al*. have further described a novel, efficient and environmentally friendly stereoselective reduction of 2-azido-1-aryl ketones **90** to give (*R*)-2-azido-1-arylethanols **82** by making use of fermented bakers yeast in aqueous medium (**Scheme 32**).

Kamal's approach[57]

Kamal and co-workers have demonstrated that the ring opening of epoxides **86** with $TMSN_3$ was achieved in a stereoselective manner in presence of *β*-cyclodextrin under extremely mild conditions to yield optically pure azido alcohols **82** (**Scheme 33**).



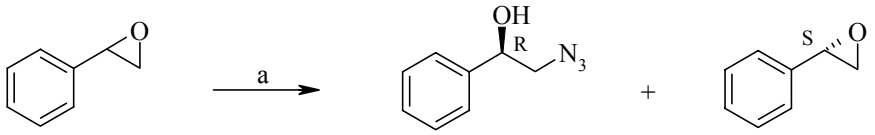
(±)-**86**
R = CH_3, *p*-C_6H_4, 1-naphthyl, etc.

82
56-99% ee
Yield: 38-48%

Scheme 33: a) *β*-Cyclodextrin, H_2O, 5-6 hrs.

Spelburg's approach[58]

This presents an enantioselective azidolysis of styrene oxides, carried out by using halohydrin *dehalogenase* from *Agrobacterium radiobacter* AD1. Racemic styrene oxide **86** yields the corresponding azido alcohol **82** with high regio and enantioselectivity under very mild conditions (**Scheme 34**).

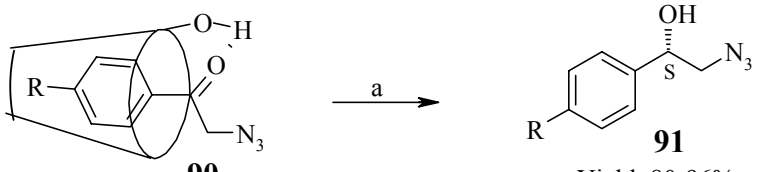


(±)-**86** **82** 96% ee 99% ee

Scheme 34: a) *halohydrin dehalogenase*, NaN_3

Reddy's approach[59]

β-Cyclodextrin catalyses the asymmetric reduction of *α*-azido aryl ketones **90** using sodium borohydride in water. Electron donating substituents on the aromatic ring show higher enantioselectivity as compared with the electron withdrawing substituents (**Scheme 35**).



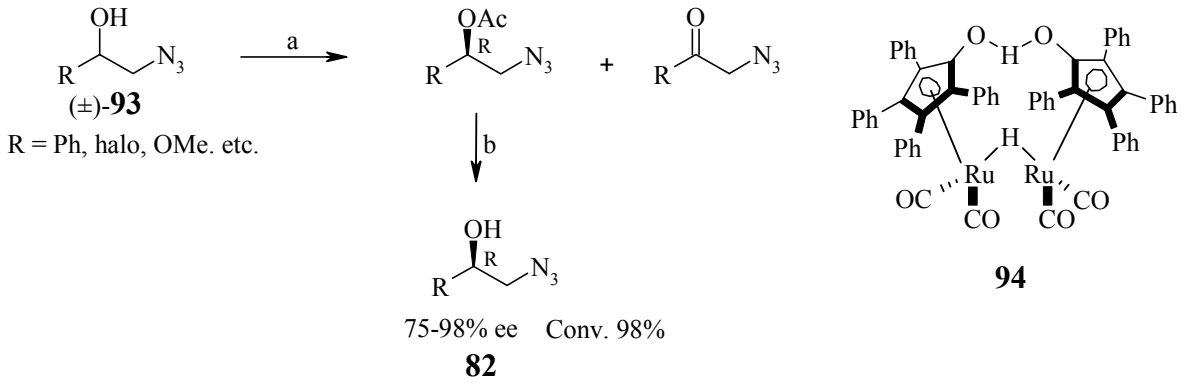
90
R = H, Cl, Br, OEt, OH. etc.

91
Yield: 80-96%
4 -80% ee

Scheme 35: a) $NaBH_4$, H_2O, RT - 60°C.

Pamies's approach[60]

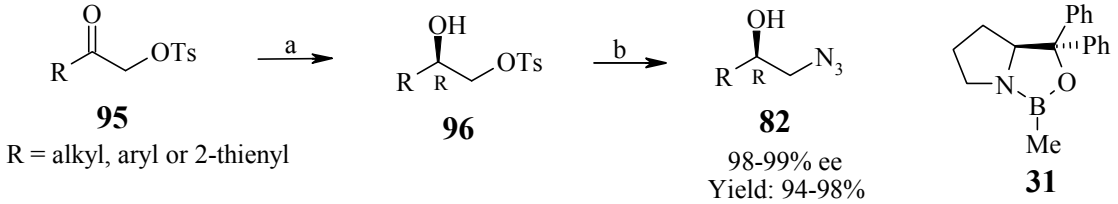
This presents a chemoenzymatic *Dynamic Kinetic Resolution* (DKR) of racemic *β*-azido alcohols **93** to give optically pure *β*-azido alcohols **82** in 75-98% ee. *p*-Chlorophenyl acetate is used as an acyl donor with a ruthenium-catalyzed racemization *via* hydrogen transfer in presence of Ru-catalyst **94** (**Scheme 36**).



Scheme 36: a) 4 mol% catalyst (**94**), *p*Cl-C_6H_4OAc.

Cho's approach[61]

Cho and co-workers have reported (*S*)-CBS-oxazoborolidine **31** catalyzed asymmetric borane reduction of 1-substituted-2-(*p*-tosyloxy)ethanones **95**, using *N*-ethyl-*N*-isopropylaniline-borane complex as the hydride source. Thus, reduction of **95** gave optically active monotosylate **96** with high ee. Monotosylate **96** on treatment with NaN_3 resulted in formation of (*R*)-2-azido ethanols (**82**) in 98-99% ee (**Scheme 37**).



Scheme 37: a) (*S*)-CBS-oxazaborolidine (**31**) (0.1 equiv.), THF, 25°C; b) NaN_3, (2 equiv.), DMSO, 80°C.

1.1.4 Present Work

1.1.4.1 Objective

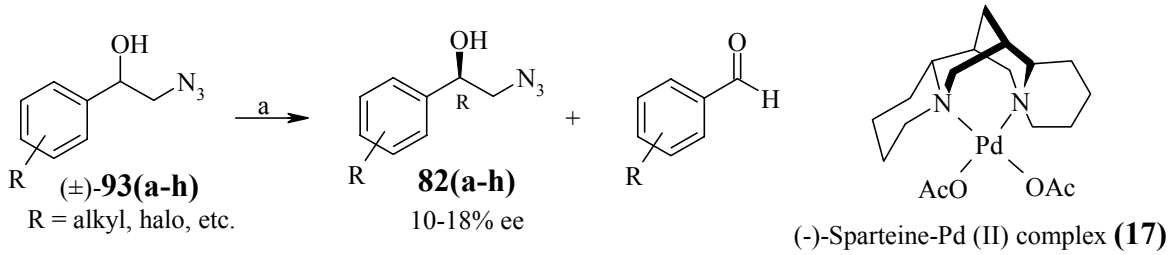
Although there are many methods reported in the literature for regio and enantioselective synthesis of enantiopure 2-azido-1-arylethanols (**82**), they suffer from the following drawbacks; (i) the azidolysis of aryloxiranes is commonly accompanied by the formation of undesired regio isomers having the azido group at the benzylic position; (ii) other methods involve multi-step synthesis using optically active cyanohydrins as starting materials; (iii) enzymatic methods involve the use of costly enzymes; (iv) there are few other reports on kinetic resolution but they too involve the use of costly reagents. In order to overcome these difficulties, there is a definite need to develop a convenient method for the synthesis of enantiopure 2-azido-1-arylethanols (**82**).

Recently, Sigmann and Ferreira have independently discovered that a combination of Pd(II) salts with (–)-sparteine effectively catalyses the aerobic oxidative kinetic resolution of secondary benzylic alcohols[23] (See **Section I** of this chapter for details). Inspired by the above result, we became interested to apply this methodology for the synthesis of chiral 2-azido-1-arylethanols (**82**) from the corresponding racemic 2-azido-1-arylethanols (**93**) (**Scheme 38**), the results of which are presented in this Chapter.

1.1.5 Results and Discussion

Racemic 2-azido-1-arylethanols (**93**) were readily obtained from the corresponding styrenes in two steps by following the known literature procedures. Thus, styrene on treatment with NBS in presence of acetonitrile: water mixture at room temperature gave 2-bromo-1-phenylethanol in almost quantitative yield followed by displacement of bromide with azide was achieved in DMF at 100^{o}C to produce the racemic 2-azido-1-phenylethanol (**93**).

When the racemic 2-azido-1-arylethanols (**93a-h**) were subjected to oxidative kinetic resolution with $Pd(OAc)_2$ as catalyst and (–)-sparteine as chiral auxiliary at 80°C, (*R*)-2-azido-1-arylethanols (**82a-h**) were obtained in only 10-18% ee along with its over oxidized product aldehydes in 10-18% yield (**Scheme 38**).

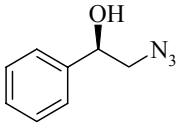
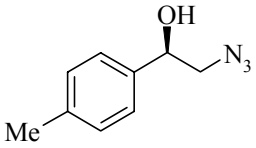
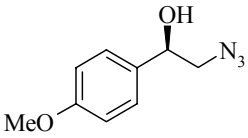
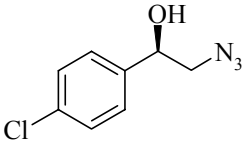
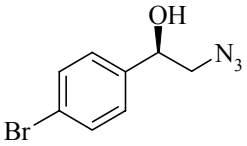
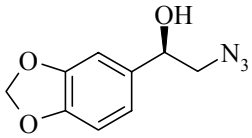
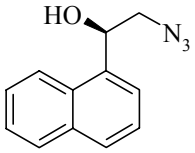
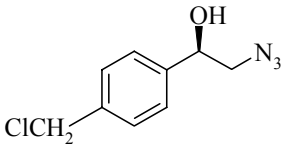


Scheme 38: a) 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, O_2 (1 atm), toluene, 80°C, 36 h.

The results of the oxidative kinetic resolution of various substituted 2-azido-1-arylethanols (**93a-h**) are presented in **Table 1**. As can be seen from the **Table 1**, a variety of racemic aromatic azido alcohols underwent oxidative kinetic resolution to afford the corresponding enantiopure (*R*)-2-azido-1-arylethanols (**82a-h**) although in low enantiomeric excess.

In order to improve the enantioselectivity of the process, various parameters were evaluated. First, we increased the time of the reaction upto 72 hrs, but this did not show any appreciable increase in enantioselectivity. Secondly, increase of concentration of (–)-sparteine also did not improve the enantioselectivity. Variety of solvents like benzene, acetonitrile, methanol, acetone and THF were tested for this reaction, but toluene proved to be the best among all other solvents used. Other Pd-catalysts like $PdCl_2$, $Pd(acac)_2$ and $(C_6H_5CN)_2PdCl_2$ were also screened for the above reaction, but this also did not show any appreciable increase in enantioselectivity. One more reason for low enantioselectivity may be due to the presence of azido alcohol moiety which may prohibit the (–)-sparteine-$Pd(OAc)_2$ complex formation.

Table 1: Pd-catalyzed oxidative kinetic resolution of racemic 2-azido-1-arylethanols[a] (**93**) using (–)-sparteine as chiral auxiliary.

Entry	Product[b] (82a-h)	Yield (%)[c]	$[\alpha]_D$ in $CHCl_3$	ee (%)[d]
a		80	– 8.5 (c 0.8, $CHCl_3$)	10.6
b		72	– 4.5 (c 1.2, $CHCl_3$)	17.8
c		75	– 8.1 (c 0.9, $CHCl_3$)	16.0
d		85	– 9.1 (c 1.2, $CHCl_3$)	11.5
e		75	– 6.5 (c 0.9, $CHCl_3$)	18.0
f		82	– 3.5 (c 2.6, $CHCl_3$)	e
g		76	– 7.2 (c 2.0, $CHCl_3$)	e
h		73	– 4.7 (c 2.0, $CHCl_3$)	e

a: reaction conditions: azido alcohol **93(a-h)** (3 mmol), 5 mol% $Pd(OAc)_2$, 20 mol% (–)-sparteine, O_2 (1 atm), toluene, 80°C, 36 h; b: absolute configuration is (*R*) as determined by sign of $[\alpha]_D$ reported in literature; c: yields refer to isolated product after column chromatography; d: ee based on comparison of $[\alpha]_D$ values reported in literature; e: $[\alpha]_D$ not known in the literature.

To investigate this we prepared an orange colored complex of (–)-sparteine and $Pd(OAc)_2$ separately and used for this reaction. We observed that the isolated Pd[(–)-sparteine]OAc_2 complex was also incompetent to increase the enantioselectivity of the above reaction. Further, when the azido alcohols, prepared from disubstituted olefins like stilbene and *β*-methylstyrene, were subjected to oxidative kinetic resolution, they gave the mixtures of products. The azido alcohol formation was confirmed by ^{1}H and ^{13}C-NMR, IR and mass spectroscopy. The IR spectrum of all azido alcohols showed characteristic strong absorption peak for azide functionality at 2095-2110 cm^{-1}. Mass spectrum showed molecular ion peaks and fragmented ion peaks due to loss of azide group as the prominent ions in all cases studied.

As an example, ^{1}H-NMR spectrum of **82f** showed doublet of doublet at δ 4.70-4.87 corresponding to benzylic proton. Further, a doublet of doublet at δ 3.35-3.45 was observed corresponding to the methylene protons attached to azide group slightly upfield as compared to the corresponding bromo alcohol. Its ^{13}C-NMR spectrum showed signals at δ 57.70 and 72.92 due to homo benzylic and benzylic carbons respectively **(Fig. 12)**. Its IR spectrum showed strong absorptions at 2104 cm^{-1} due to azide functionality. Its mass spectrum showed molecular ion peak at m/z 207 and also fragmented ion peak at 165, due to loss of azide group.

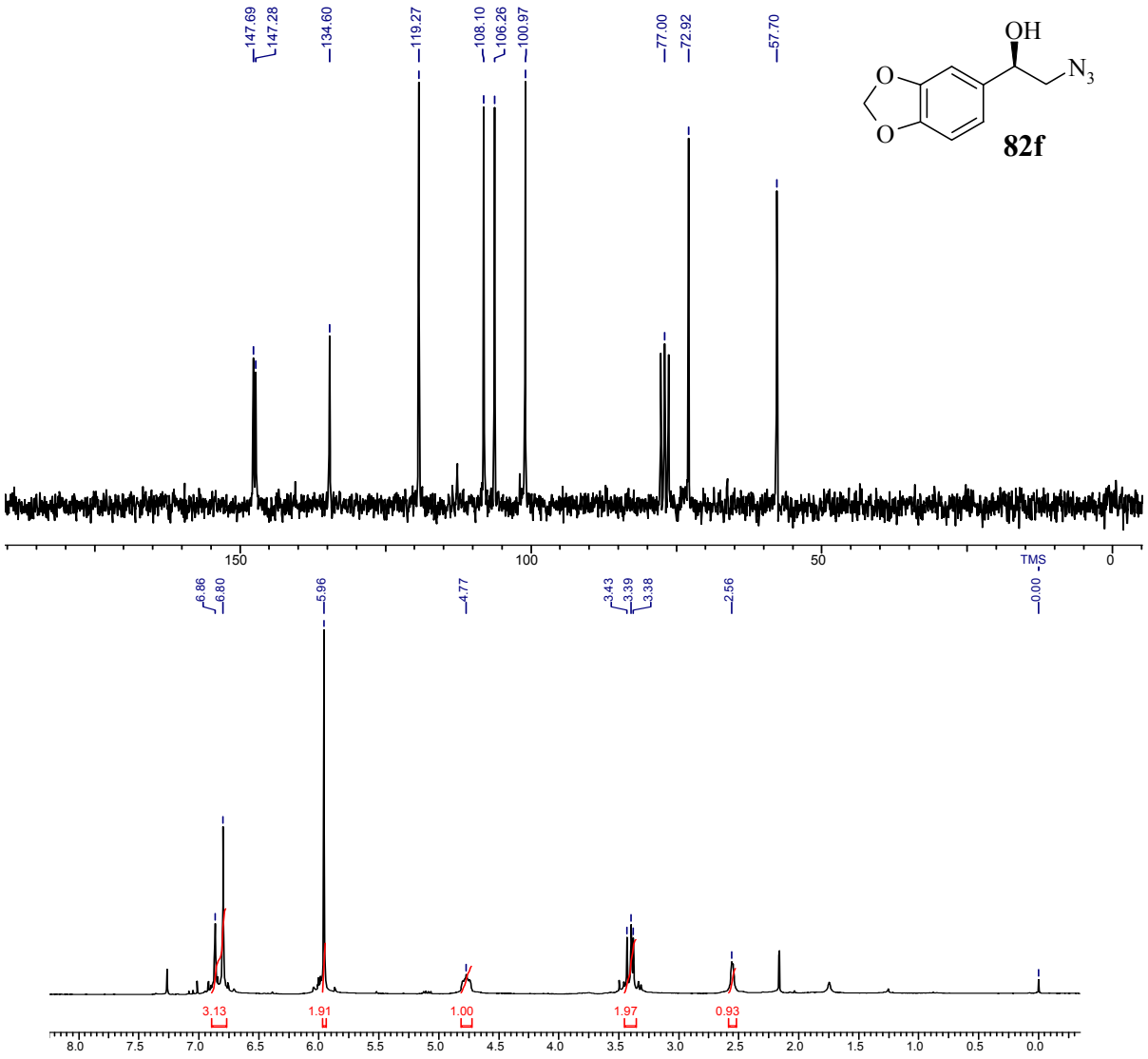


Fig. 12: ^{1}H and ^{13}C-NMR spectra of 82f

1.1.6 Conclusion

We have developed a new method for the synthesis of chiral 2-azido-1-arylethanols (**82**) by following the oxidative kinetic resolution of racemic 2-azido-1-arylethanols (**93**) with (–)-sparteine/Pd(II) catalyst system. The reaction makes use of easily available and cheap chiral reagents. Molecular oxygen is used as terminal oxidant. The present method provides a new route to optically active (*R*)-2-azido-1-arylethanols (**82**), however enantioselectivity observed is not very high (10-18% ee).

1.1.7 Experimental Section

General procedure for kinetic resolution of racemic azido alcohols

To a 50 ml side arm flask, $Pd(OAc)_2$ (0.140 mg, 0.59 mmol) was added followed by dry toluene (20 ml), 3Å MS (50 mg) and (–)-sparteine (0.033 g, 0.14 mmol). A condenser and balloon filled with O_2 were then attached to the flask. The whole system was evacuated and refilled with O_2 from the balloon three to four times. The flask was warmed to 80°C in an oil bath. After 30 min. of reflux azido alcohol (**93a-h**) (3 mmol) in toluene (10 ml) was added dropwise and refluxed for 36 h, then it was cooled to RT. The reaction was quenched with 2% TFA/ methanol (15 ml). The solvent was removed under reduced pressure and the residue was taken up in minimal amount of dichloromethane. The crude residue was then purified by column chromatography to give (*R*)-azido alcohol (**82a-h**).

(*R*)-2-Azido-1-phenylethanol (82a): **Yield**: 80%; **gum**; **$[\alpha]^{25}_D$** – 8.5 (c 0.8, $CHCl_3$); [lit. **$[\alpha]^{25}_D$** – 80.1 (c 0.78, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 3421, 3015, 2107, 1493, 1216, 761, 701; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.42 (brs, 1H), 3.35-3.55 (dd, *J* = 4.0 and 6.0 Hz, 2H), 4.82-4.90 (m, 1H), 7.25-7.45 (m 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 57.81, 73.18, 125.81, 128.17, 128.53, 140.55; **MS** (m/z, % RI): 164 (M^{+1}, 2), 146 (3), 135 (4), 107 (100), 91 (6), 79 (70), 77 (68), 63 (10), 51 (50); **Analysis**: $C_8H_9N_3O$ requires C, 58.88; H, 5.55; N, 25.75; found C, 58.82; H, 5.56; N, 25.79 %.

(*R*)-2-Azido-1-(4-methylphenyl)ethanol (82b): Yield: 72%; **gum**; **$[\alpha]^{25}_D$** – 4.5 (c 1.2, $CHCl_3$); [lit. **$[\alpha]^{25}_D$** – 28.2 (c 1.0, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 3449, 3020, 2950, 2095, 1710, 1495, 1363, 1222, 750; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.25 (brs, 1H), 2.35 (s, 3H), 3.43 (t, *J* = 4.0 and 6.0 Hz, 2H), 4.80-4.86 (dd, *J* = 4.0 Hz, 1H), 7.10-7.30 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.87, 57.59, 72.92, 125.70, 129.09, 137.58, 137.80; **MS** (m/z, % RI): 177 (M^+, 5), 122 (55), 120 (15), 105 (100), 92 (15), 65 (50), 64 (20); **Analysis:** $C_9H_{11}N_3O$ requires C, 61.00; H, 6.25; N, 23.7; found C, 61.09; H, 6.32; N, 23.7 %.

(*R*)-2-Azido-1-(4-methoxyphenyl)ethanol (82c): Yield: 75%; **gum**; **$[\alpha]^{25}_D$** – 8.1 (c 0.9, $CHCl_3$); [lit. **$[\alpha]^{25}_D$** – 39.0 (c 1.0, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 3256, 3019, 2676, 2107, 1215, 750, 669; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.20 (brs, 1H), 3.42 (m, 2H), 3.79 (s, 3H), 4.80 (dd, *J* = 7.5 and 4.0 Hz, 1H), 6.90 (d, *J* = 6.5 Hz, 1H), 7.29 (d, *J* = 6.5 Hz, 1H); **^{13}C-NMR** (50

MHz, $CDCl_3$): δ 55.5, 58.3, 73.2, 114.3, 127.4, 132.5, 159.8; **Analysis**: $C_9H_{11}N_3O$ requires C, 55.95; H, 5.73; N, 21.75; found C, 55.86; H, 5.77; N, 21.79 %.

(*R*)-2-Azido-1-(4-chlorophenyl)ethanol (82d): Yield: 85%; **mp**: 46-48^{0}C; **[α]$^{25}_D$** – 9.1 (c 1.2, $CHCl_3$); [lit. **[α]$^{25}_D$** – 79.1 (c 1.2, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 3418, 3017, 2923, 2106, 1493, 1215, 1091, 1014, 754; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.81 (brs, 1H), 3.37 (d, *J* = 6.0 Hz, 2H), 4.78 (t, *J* = 2.0 and 6.0 Hz, 1H), 7.25-7.35 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 57.70, 72.52, 127.17, 128.68, 133.90, 138.94; **Analysis**: $C_8H_8N_3ClO$ requires C, 48.62; H, 4.07; N, 21.26, Cl, 17.94; found C, 48.55; H, 4.16; N, 21.21, Cl, 17.93 %.

(*R*)-2-Azido-1-(4-bromophenyl)ethanol (82e): Yield: 75%; **mp**: 65-66^{0}C; **[α]$^{25}_D$** – 6.5 (c 0.9, $CHCl_3$); [lit. **[α]$^{25}_D$** – 36.4 (c 0.95, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 3430, 3153, 3018, 2724, 2108, 1215, 1012, 980, 761; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.55 (d, *J* = 2.5 Hz, 1H), 3.50 (m, 2H), 4.82 (m, 1H), 7.24 (d, *J* = 6.5 Hz, 2H), 7.50 (d, *J* = 6.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39.5, 73.3, 122.4, 127.5, 131.5, 139.8; **MS** (m/z, % RI): 275 (M^+, 10), 273 (10), 223 (25), 221 (25), 144 (65), 143 (10), 128 (18), 65 (100); **Analysis**: $C_8H_8BrN_3O_3$ requires C, 39.69; H, 3.32; N, 17.35; Br, 33.00; found C, 39.69; H, 3.33; N, 17.42; Br, 33.10 %.

(*R*)-2-Azido-1-(3,4-methylenedioxyphenyl)ethanol (82f): Yield: 82%; **gum**; **[α]$^{25}_D$** – 3.5 (c 2.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3437, 3015, 2899, 2359, 2104, 1489, 1444, 1249, 1039, 658; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.70 (brs, 1H), 3.35-3.45 (dd, *J* = 2.0 and 6.0 Hz, 2H), 4.70-4.80 (dd, *J* = 2.5 Hz, 1H), 5.96 (s, 2H), 6.75-6.90 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 57.70, 72.92, 100.97, 106.26, 108.10, 119.27, 134.60, 147.28, 147.69; **MS** (m/z, % RI): 207 (M^+, 8), 151 (80), 150 (24), 123 (20), 122 (12), 93 (100), 75 (8), 65 (68), 64 (28); **Analysis**: $C_9H_9N_3O_3$ requires C, 52.17; H, 4.37; N, 23.16; found C, 52.19; H, 4.33; N, 23.19 %.

(*R*)-2-Azido-1-(1-naphthyl)ethanol (82g): Yield: 76%; **gum**; **[α]$^{25}_D$** – 7.2 (c 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3460, 3018, 2926, 2105, 1215, 756, 669; **^{1}H-NMR** (200 MHz, $CDCl_3$): 2.80 (brs, 1H), 3.50 (m, 2H), 5.50 m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 57.22, 70.24, 122.25, 123.43, 125.30, 125.59, 126.33, 128.57, 128.94, 129.97, 133.61, 136.00; **MS** (m/z, % RI): 233 (M^+, 5), 171 (10), 165 (3), 149 (100), 121 (30), 91 (10), 65 (15); **Analysis**: $C_{12}H_{11}N_3O$ requires C, 67.59; H, 5.19; N, 19.70; found C, 67.63; H, 5.21; N, 19.78 %.

(*R*)-3-Azido-1-(4-chloromethylphenyl)ethanol (82h): Yield: 73%; **gum**; **[α]$^{25}_D$** – 4.7 (c 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3500, 3019, 2400, 2104, 1215, 756; **^{1}H-NMR** (200 MHz, $CDCl_3$):

δ 2.53 (d, *J* = 4.0 Hz, 1H), 3.35-4.46 (dd, *J* = 4.0 and 6.0 Hz, 2H), 4.32 (s, 2H), 4.85 (brs, 1H), 7.25-7.45 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 54.17, 57.70, 72.81, 126.26, 128.31, 135.26, 140.70; **MS** (m/z, % RI): 175 (4), 161 (15), 132 (100), 119 (55), 104 (20), 91 (25), 77 (80), 63 (10), 51 (5); **Analysis**: $C_9H_{10}ClN_3O$ requires C, 51.07; H, 4.75; N, 19.85; Cl, 16.75; found C, 51.16; H, 4.75; N, 19.81; Cl, 16.79 %.

1.1.8 References

1. Agranat, I.; Canner, H.; Cadwell, J. *Nature Reviews* **2002**, *1*, 753.
2. a) Eichelbaum, M.; Gross, A. S. *Adv. Drug. Res*. **1996**, *28*, 1-64. b) Crossley, R. *Chirality and the Biological Activity of Drugs* (CRC Press, Boca Raton, Florida, **1995**). c) Aboul-Enein, H. Y.; Wainer, I. W. *The impact of Stereochemistry on Drug Development and use* (Chemical Analysis Vol. *142*) (Wiley New York, **1997**). d) Rriggle, D. *J. Stereoselectivity of drug action, Drug Discov. Today* **1997**, *2*, 138-147. e) Cadwell, J. Through the looking glass in chiral drug development. *Modern Drug Discov*. **1999**, *2*, 51-60. f) Challencer, C. A.(*eds*) *Chiral Drugs* (Ashgate, Burlington, Vermont, **2001**).
3. Murphy, D. L.; Mueller, E. A.; Garrick, N. A.; Aulakh, C. S. *J. Clin. Psychiatry* **1986**, *47*, 9.
4. Fuller, R. W. *J. Clin. Psychiatry* **1986**, *47*, 4.
5. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem*. **1988**, *31*, 1412.
6. a) Foster, B. J.; Lavagnino, E. R. *Drugs Future* **1986**, *11*, 134. b) Ankier, S. I. *Prog. Med. Chem*. **1986**, *23*, 121.
7. Murphy, D. L.; Mueller, E. A.; Garrick, N. A.; Aulakh, C. S. *J. Clin. Psychiatry* **1986**, *47*, (4, Suppl.) 9; DE 2 500 110
8. Wong, D. T.; Threlkeld.; Robertson, D. W. *Neuropsychopharmacology* **1991**, *5*, 43.
9. a) Wistuba, D.; Schurig, V. *J. Chromatogr*. **A 2000**, *75*, 255. b) Collect, A. *Enantiomer* **1999**, *4*, 157.
10. Jacques, J.; Collect, A.; Wilen, S. H. *Enantiomers*, *Racemates and Resolutions*, Krieger, Malabar, FL, **1991**.
11. Kagan, H. B.; Fiaud, J. C *In Topics in Stereochemistry*, Wiley, New York, **1988**, *18*,

249.

12. a) Noyori, R.; Tokunaga, M.; Kitamuru, M. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36. b) Strauss, U. T.; Felfer, U, *Tetrahedron: Asymmetry* **1999**, *10*, 107.
13. a) Kagan, H.; *Croat. Chem. Acta* **1996**, *69*, 669. b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc*. **1997**, *119*, 2584. c) Eames, J, *Angew. Chem. Int. Ed*. **2000**, *39*, 885.
14. Johnson, R. A.; Sharpless, K. B.; in "*Catalytic Asymmetric Synthesis"* Ojima, I.; (Ed.); Wiley and Sons, New York, **2000**, pp. 227-270.
15. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
16. Muller, P.; in "*Advances in Catalytic Processes"* JAI Press Inc. Greenwich, CT, **1997**, *2*, 113.
17. a) Ohkubo, K.; Hirata, K.; Yoshinaga, K.; Okada, M. *Chem. Lett*. **1976**, 183. b) Ma, Z.; Huang, Q.; Bobbitt, J. M. J. *Org. Chem.* **1993**, *58*, 4837. c) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. J. *Org. Chem.* **1996**, *61*, 1194. d) Berti, C.; Perkins, M. J. *Angew Chem. Int. Ed. Engl.* **1979**, *18*, 864.
18. a) Katsuki, T.; Sharpless, K. B, *J. Am. Chem. Soc.* **1980**, *102*, 5971. b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M. Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
19. a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T. Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. b) Hashiguchi, S.; Fujii, A.; Haack, J. K.; Matsumura, K.; Ikariya, T. Noyori, R. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 288.
20. Nishibayashi, S.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.
21. a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. b) Kagan, H. B.; Fiaud, J. C.; in *"Topics in Stereochemistry"* Eliel, E. L.; (Ed.); Wiley and Sons: New York, **1988**, *18,* 249. c) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. d) Wong, C. H.; Whitesides, G. M. "*Enzymes in Synthetic Organic Chemistry"* Pergamon, Oxford, UK, **1994**.
22. Barton, D. H. R.; Martell, A. E.; Sawyer, D. T.; in "*The Activation of Dioxygen and Homogenous Catalytic Oxidation"* Plenum Press, New York, **1993**.
23. a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7425. b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

24. Srebnik, N.; Ramachandan, P. V.; Brown, H. C. *J. Org. Chem*. **1988**, *53*, 2916.
25. Gao, Y.; Sharpless, K. B. *J. Org. Chem*. **1988**, *53*, 4081.
26. Corey,E. J.; and Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.
27. Kumar, A.; Ner, D. H.; Dike, S.Y. *Tetrahedron Lett.* **1991**, *32*, 1901.
28. Schneider, M. P.; Goergens, U. *Tetrahedron: Asymmetry* **1992**, *3*, 525.
29. Xin, G. J.; Yi, L.Z.; Qiang, L. G. *Tetrahedron* **1993**, *49*, 5805.
30. Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
31. Mitchell, D.; Koenig, T. M. *Synthetic Commun.* **1995**, *25*, 1231.
32. Sakuraba, S.; Achiwa, K. *Chem. Phar. Bull.* **1995**, *43*, 748.
33. a) Master, H. E.; Newadkar, R. V.; R. A. Rane.; Kumar, A. *Tetrahedron Lett.* **1996**, *37*, 9253. b) Bracher, F.; Litz, T. *Bioorganic and Medicinal Chemistry* **1996**, *4*, 877.
34. Huang H.L.; Liu, L.T.; Chen, S. F.; Ku, H. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1637.
35. Liu, H. L.; Hoff, B. H.; Anthonsen, T. *J. Chem. Soc. Perkin Trans*. **2000**, *1*, 1767.
36. Riberio, C. M. R.; Rassaroto, E. N.; Brenelli, E. C. S. *J. Braz. Chem. Soc*. **2001**, *12*, 742.
37. Hilborn, J. W.; Lu, H. L.; Jurgens, A. R.; Fang, K, Q.; Byers, P.; Wald, S. A.; Senanayakee, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919.
38. Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S. *Tetrahedron* **2001**, *57*, 9925.
39. Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2002**, *43*, 4425.
40. Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039.
41. Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem. Int. Ed*. **2002**, *41*, 1059.
42. Ali, I. S.; Sudalai, A. *Tetrahedron Lett*. **2002**, *43***,** 5435.
43. Mueller, J. A.; Jensen, D. R.; Sigmann, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.
44. Brink, G. J.; Arends, I, W.; Sheldon, R. A. *Science* **2000**, *287*, 1636.
45. a) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed*. **2002**, *41*, 164. b) Nishimura, T.; Ohe, K.; Uemura, S. J. *J. Org. Chem.* **2001**, *66*, 1455.
46. a) Sheldon, R. A.; Arends, I, W.; Dijksmann, A. *Catal. Today* **2000**, *57*, 157. b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. c) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.
47. a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. c) Tanner, D. *Angew. Chem. Int. Ed.*

Engl. **1994**, *33*, 599.

48. a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
49. Crosseley, R. *Chirality and the Biological Activity of Drugs;* CRC Press: New York, **1995**.
50. Blasser, H-U. *Chem. Rev*. **1992**, *92*, 935.
51. Lohray, B.B.; Gao, Y.; Sharpless, K. B. *Tetrahedron. Lett.* **1989**, *30*, 2623.
52. Foelsche, E.; Hickel, A.; Honig, H.; Seufer-Wasserthal, P. *J. Org. Chem.* **1990**, *55*, 1749.
53. a) Guy, A.; Dubuffet, T.; Doussot, J.; Godefroy-Falguieres, A. *Synlett.* **1991**, 403. b) Guy, A.; Doussot, J.; Ferroud, C.; Garreau, A.; Godefroy-Falguieres, A. *Synlett.* **1991**, 403.
54. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.
55. Chang, H. T.; Sharpless, K. B. *Tetrahedron. Lett.* **1996**, 37, 3219.
56. a) Yadav, J. S.; Reddy, P. T.; Hashim, S. R. *Synlett.* **2000**, 1049. b) Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 63.
57. Kamal, A.; Arifuddin, M.; Rao, M. V. *Tetrahedron: Asymmetry* **1999**, *10*, 4261.
58. Lutje. Spelburg, J. H.; Van Hylckama Vleig, J. E. T.; Tang, L.; Janseen, D. B.; Kellogg, R. M. *Org. Lett*. **2001**, 41.
59. Reddy, M. A.; Bhanumathi, N.; Rao, K, R. *J. Chem. Soc. Chem. Commun.* **2001**, 1974.
60. Pamies, O.; Backvasll, J. E. *J. Org. Chem*. **2001**, *66*, 4022.
61. Cho, B. T.; Kang, S. K.; Shin, S. H. *Tetrahedron: Asymmetry* **2002**, *13*, 1209.

SECTION I:

Formamide Assisted Direct Conversion of Aromatic Aldehydes to the corresponding Nitriles and its Application to Enantioselective Synthesis of (*S*)-Bunitrolol

2.0.1 Introduction

The conversion of aldehydes to the corresponding nitriles is an important functional group transformation, especially in the fine chemicals industry.[1] Particularly, nitriles are important reagents in organic synthesis as these could be readily converted into carboxylic acids, aldehydes, amides, amines, and ketones.[2] In recent reports nitriles were converted to thiazole derivatives as inhibitors of superoxide. Nitrile when condensed with *β*-amino alcohols affords chiral 2-oxazolines. Nitriles can be transformed to 1,2-diarylimidazoles, which are potent anti-inflammatory agents as a starting material for synthesizing triazolo [1, 5c] pyrimidines and benzamidines, with potential anti-asthma and fibrinogen antagonists activity.[3] Vanillylamine is an important synthon of capsaicinoide[4] that could be obtained by reduction of vanillylonitrile.

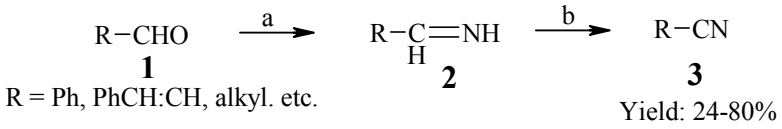
The most widely applicable and convenient method for carbon-nitrogen triple bond formation involves elimination processes. They are usually prepared by nucleophilic substitution with CN^- or by regenerating the cyanide group *via* oxidation, rearrangement or elimination.[5] The direct preparation of nitriles from aldehydes is generally achieved by dehydration of the corresponding aldoximes using classical reagents or other new reagent

2.0.2 Review of literature

Literature search revealed that there are various methods available for the conversion of aldehydes to nitriles, which are described below. Several one-pot conversions of aldehydes to nitriles have also been reported.

Erman *et al.*[7]

This method reports the reaction of aldehydes with ammonia and H_2O_2 in the presence of copper salts under mild conditions to yield nitriles (**Scheme 1**).



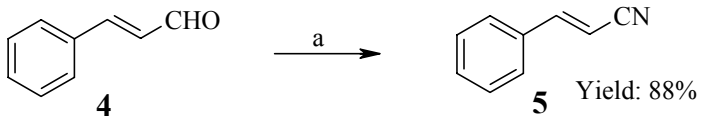
Scheme 1: a) ammonia; b) H_2O_2, Cu-catalyst.

Parameshwaran *et al.*[8]

The reaction of aliphatic and aromatic aldehydes with ammonia and $Pb(OAc)_4$ gave the corresponding nitriles in excellent yields.

Pomeroy *et al.*[9]

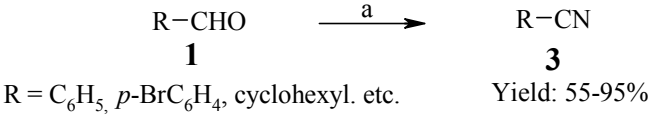
In this approach *O,N*-bis(trifluoroacetyl)hydroxylamine reacts with aldehyde **4** in the presence of pyridine to yield the corresponding nitrile **5** (**Scheme 2**).



Scheme 2: a) $(CF_3CO)_2NOH$, pyridine, benzene, reflux, 1-2 h.

Talukdar *et al.*[10]

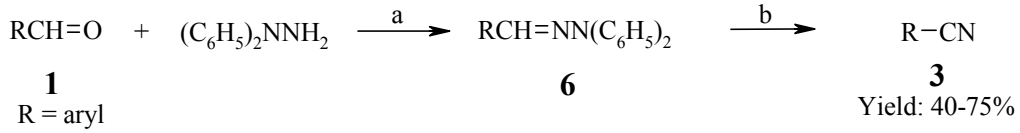
Treatment of various aldehydes with iodine in ammonia water at room temperature for a short period gave the corresponding nitriles in high yields (**Scheme 3**).



Scheme 3: a) I_2, *aq*. NH_3, RT.

Binkley *et al.*[11]

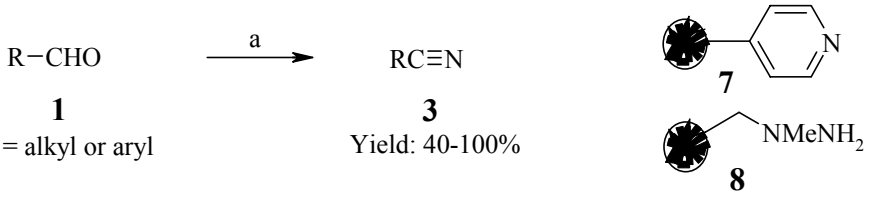
Binkley *et al*. have reported photochemical approach for the synthesis of nitriles. Aldehydes react with diphenylhydrazine to give diphenylhydrazone **6**, which on photochemical decomposition in the presence of oxygen gave the corresponding nitriles (**Scheme 4**).



Scheme 4: a) RT stirring; b) hv, O_2, 40-75%.

Protic acids such as hydroxylamine-*o*-sulphonic acid,[12] ***p***-toluene sulphonic acid,[13] formic acid[14] as well as Lewis acid like $AlCl_3$ along with sodium azide[15] have been reported for the direct conversion of aldehydes to nitriles.

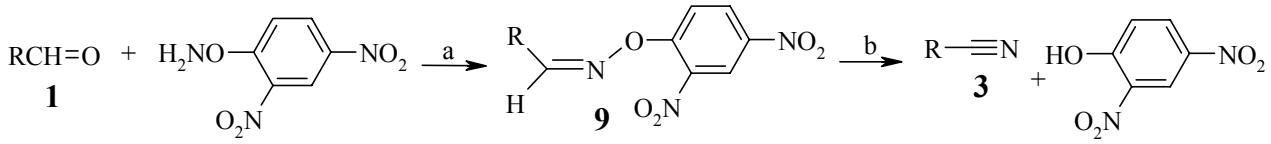
Recently, Baxendale *et al.*[16] have reported that immobilized hydrazine on reaction with various aldehydes give hydrazones, which on treatment *m*-CPBA gives the corresponding nitriles in excellent yields. Polymer-supported hydrazine reagents **7** and **8** have also been used (**Scheme 6**).



Scheme 6: a) **7** or **8**, *m*-CPBA.

Miller *et al.*[17]

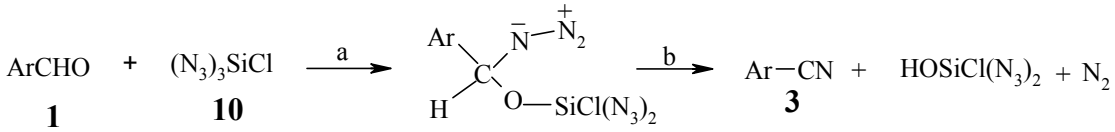
This presents reaction between aldehydes and 2,4-dinitrophenylhydroxylamine to form the corresponding oxime **9**, which after elimination yields nitriles (**Scheme 7**).



Scheme 7: a) EtOH, conc HCl; b) EtOH, KOH, reflux, 3 h.

Elmorsy *et al.*[18]

Elmorsy *et al.* have reported one pot synthesis of nitriles using triazidochlorosilane (TACS) **10** (**Scheme 8**).

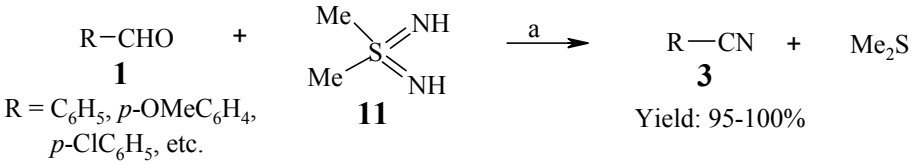


Scheme 8: a) NaN_3, CH_3CN, 0-25°C, 30 min; b) heat.

Various metal salts such as SeO_2,[19] magnesium monoperoxyphthalate hexahydrate (MMPP)[20], NH_4Cl/ copper powder/ O_2 system,[21] and $NiCl_2$ have also been used for the conversion of aldehydes to the nitriles.

Georg *et al.*[23]

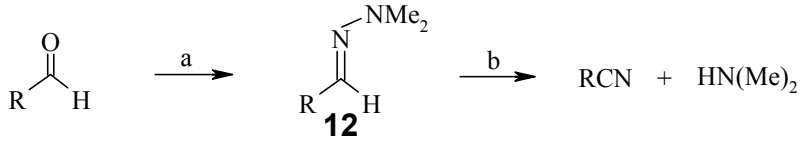
Dimethylsulfurdiimide **11** was used as a reagent for the direct conversion of aromatic aldehydes to the nitriles (**Scheme 9**).



Scheme 9: a) acetonitrile, reflux, 7-15 h.

Kamal *et al.*[24]

N,N-Dimethylhydrazones **12** of aldehydes undergo oxidative cleavage to the corresponding nitriles on treatment with dimethyl sulphate and K_2CO_3 in quantitative yields (**Scheme 10**).



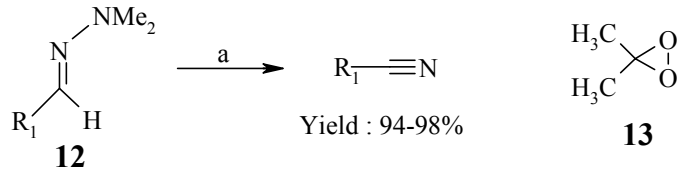
Scheme 10: a) $H_2NN(CH_3)_2$, MeOH, RT, 5-15 min; b) dimethyl sulphate, K_2CO_3, reflux, 8-10 hrs.

Wang *et al.*[25]

Alkyl and aryl aldehydes were readily converted to their corresponding nitriles in good yields using hydroxylamine hydrochloride and phthalic anhydride as reagents (**Scheme 11**).

Altamura *et al.*[26]

The transformation of *N,N*-dimethylhydrazones **12** of aldehydes into the corresponding nitriles was achieved under mild conditions using dimethyldioxirane (**13**) (**Scheme 12**).



Scheme 12: a) dimethyldioxirane, acetone, 0°C, 2-3 min, 94-98%.

Chakraborti *et al.*[27]

This presents use of *N*-methyl-2-pyrrolidinone (NMP) under microwave irradiation. Similarly, one pot conversion of aldehydes to the corresponding nitriles was also reported[28] by reaction with $NH_2OH.HCl$ under microwave irradiation in the (**Scheme 13**).

2.0.3 Present Work

2.0.3.1 Objective

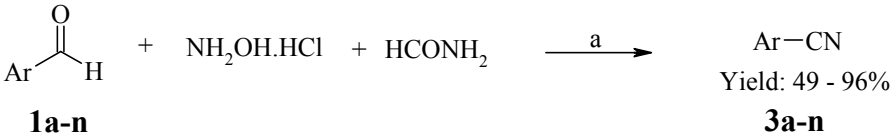
Several procedures for the direct conversion of aldehydes into nitriles without isolation of the nitrogen containing intermediate have been reported. However, these procedures are deficient in some respects. For example, the preparation of Et_3N-SO_2 and sulfuryl chloride is inconvenient (–70°C), dehydration with KSF and zeolites requires high temperature (350°C).

Further, the reagents like phosgene, diphosgene and triphosgene are hazardous to handle. Other reports involve use of costly reagents. In order to overcome these difficulties, there is still a need for a convenient and generally applicable method for the direct conversion of aldehydes into nitriles in a single step.

The objective of the present investigation is to make use of easily available formamide as a dehydrating source in conversion of aldehydes into the corresponding nitriles.

2.0.4 Results and Discussion

When *o*-anisaldehyde was reacted with hydroxylamine hydrochloride, in presence of pyridine and formamide in refluxing xylene, the corresponding nitrile was obtained in 96% yield. Among various solvents studied, xylene is the choice as the best results were obtained.

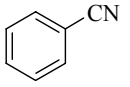
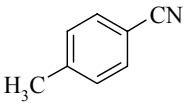
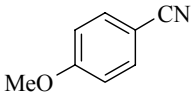
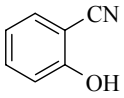
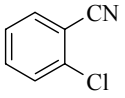
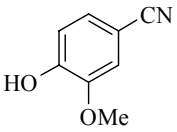
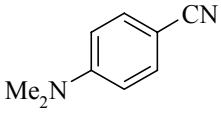
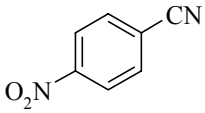
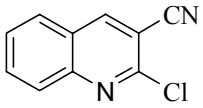


1a-n **3a-n**

Scheme 14: a) pyridine, xylene, reflux, 5-6 hrs.

Also, when this reaction was conducted in $CHCl_3$ and MeOH, the conversion was only marginal even after longer time. Variety of aromatic aldehydes **1a-n** were successfully converted to their corresponding nitriles **3a-n** in moderate to good yields (**Scheme 14**).[29] The results of the reaction are summarized in **Table 1**. Various aryl aldoximes also underwent dehydration to give the corresponding nitriles when reacted with formamide in xylene at reflux temperature. As seen from the **Table 1**, aldehydes possessing both, electron donating as well as electron withdrawing groups underwent to afford the corresponding nitriles. However, the reaction failed to proceed in case of aliphatic aldehydes. The nitrile formation was

Table 1: Formamide assisted direct conversion of aryl aldehydes into aryl nitriles (**Scheme 14**)[a]

Entry	Product (3a-n)[b]	Time (h)	Yield[c] (%)	M.p (^{o}C)
a		6	50	gum
b		6	51	gum
c		5	96	58
d		5	60	95-97
e	4-Hydroxybenzonitrile	5	65	112-114
f		6	70	42-44
g		6	51	83-85
h	3,4-Dimethoxybenzonitrile	6	75	67-69
i	3,4,5-Timethoxybenzonitrile	6	65	142-144
j		5	80	71-73
k	3-Nitrobenzonitrile	5	61	117-118
l		5	76	148-150
m	1-Naphthylbenzonitrile	5	70	34-35
n		6	49	183-185

reaction conditions: a: aldehyde (5 mmol); hydroxylamine hydrochloride (5 mmol); pyridine (5 mmol); formamide (5 mmol); 140^{o}C, 5-6 hrs; b: all the products were characterized by m.p, CH-analysis, IR, ^{1}H and ^{13}C-NMR spectroscopy; c: Isolated yield after chromatographic purification.

confirmed by ^{1}H- NMR and IR spectroscopy. The IR spectrum of all nitriles showed a characteristic strong absorption peak for nitrile functionality at 2200-2220 cm^{-1}.

The ^{1}H-NMR spectra of *o*-cyanophenol **3d** showed the presence of aromatic protons in the region δ 6.80-7.25. Its ^{13}C-NMR spectra showed presence of nitrile carbon at δ 160 **(Fig. 1)**.

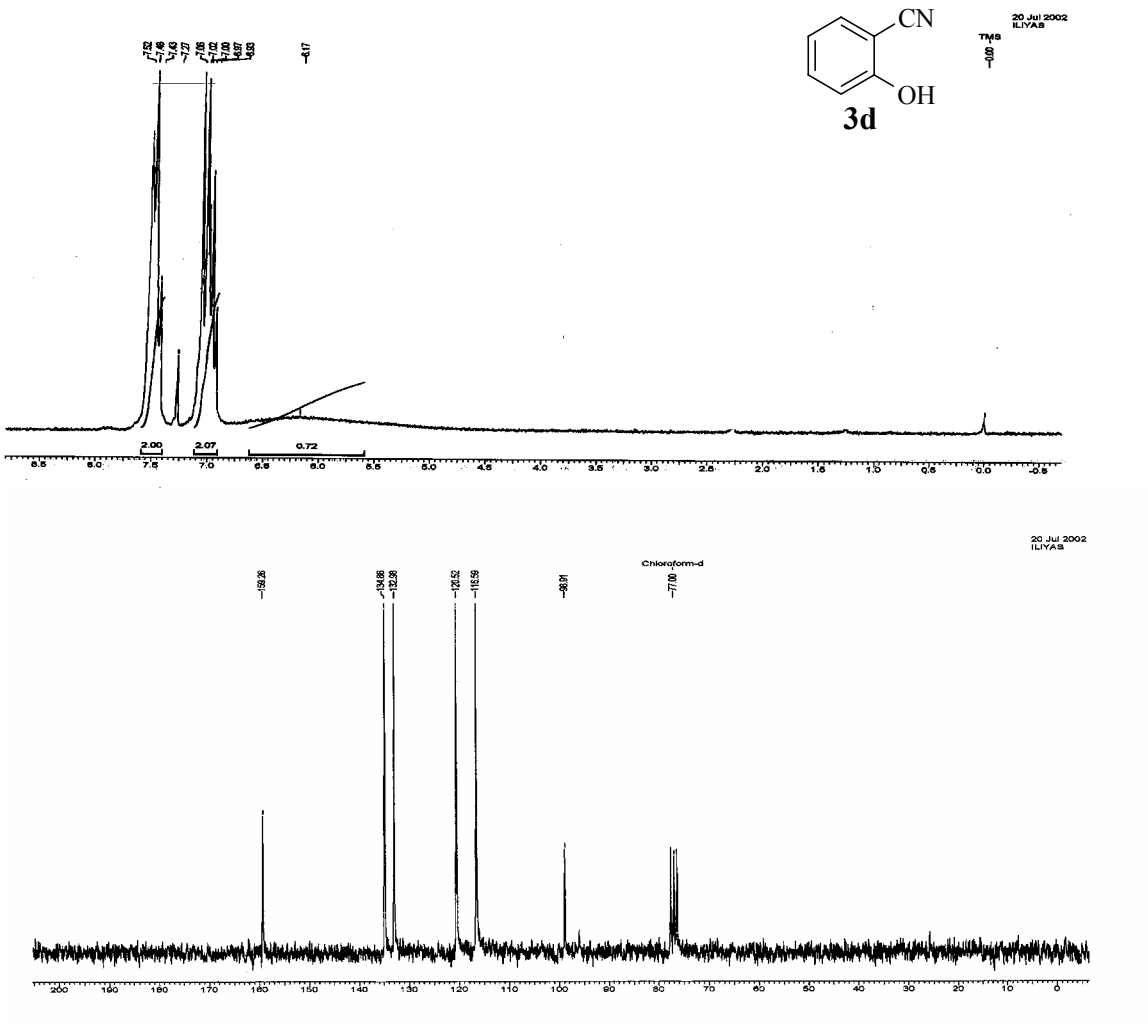


Fig. 1: ^{1}H and ^{13}C-NMR spectra of *o*-cyanophenol 3d

Mechanism

The proposed mechanism of the reaction is shown in **Fig. 3**. The first step probably involves reaction between aldehyde **1** and hydroxylamine hydrochloride to form aldoxime **14**.

Aldoxime **14** reacts with formamide to generate aldoxime formate **15**, the key intermediate that subsequently undergoes elimination thermally to produce the nitrile **28**, with the liberation of formic acid.

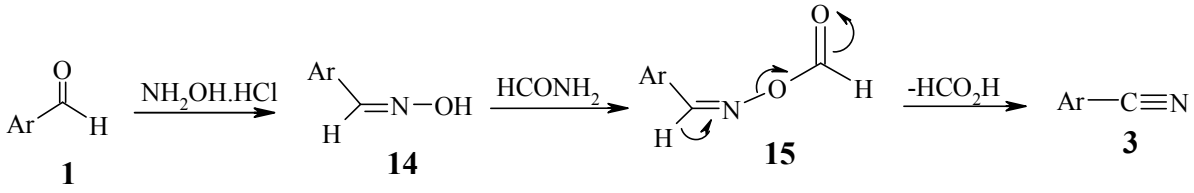


Fig. 3: Possible mechanistic pathway.

2.0.5 Conclusion

In conclusion, we have developed a new reagent system ($NH_2OH.HCl$-Py-$HCONH_4$), which can directly convert aromatic aldehydes into the corresponding nitriles in high yields.

2.0.6 Experimental Section

General procedure for conversion of aldehyde to nitriles

A 50 ml RB flask equipped with water condenser was charged with a mixture of aldehyde **1a-n** (5 mmol), hydroxylamine hydrochloride (5 mmol), pyridine (5 mmol) and formamide (5 mmol) in xylene (10 ml). The reaction flask was subjected to reflux for 5-6 hrs. After completion of the reaction, as monitored by TLC, xylene was distilled under reduced pressure. Water (20 ml) was added to the reaction mixture followed by neutralization with 2N HCl. It was then extracted with ethyl acetate (3 x 20 ml), washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, to get the crude product, which was purified by column chromatography to give the corresponding nitriles **3a-n**.

Benzonitrile (3a): Yield: 50%; **gum**; **IR** (nujol, cm^{-1}): 3410, 2900, 2825, 2220, 1560, 1360, 1220, 825; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.40-7.50 (m, 3H), 7.55-7.70 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 112.2, 118.4, 129.0, 132.1, 134.5; **Analysis**: C_7H_5N requires C, 81.53; H, 4.88; N, 13.58; found C, 81.55; H, 4.85; N, 13.57 %.

4-Methylbenzonitrile (3b): Yield: 51%; **gum**; **IR** (nujol, cm^{-1}): 3445, 2200, 1570, 1430, 1360, 1165, 1040, 760; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 7.10 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 112.2, 119.5, 129.3, 132.4, 133.6,

139.4; **Analysis**: C_8H_7N requires C, 82.02; H, 6.01; N, 11.96; found C, 82.09; H, 6.08; N, 11.90%.

4-Methoxybenzonitrile (3c): Yield: 96%; **mp**: 58°C; **IR** (nujol, cm^{-1}): 2900, 2200, 1590, 1440, 1250, 950, 840; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.8 (s, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.2, 104.1, 114.4, 119.3, 134.0, 162.4; **Analysis**: C_8H_7NO requires C, 72.16; H, 5.29; N, 10.52; found C, 72.09; H, 5.29; N, 10.52%.

2-Hydroxybenzonitrile (3d): Yield: 60%; **mp**: 95-97°C; **IR** (nujol, cm^{-1}): 2860, 2200, 1580, 1440, 1350, 840, 730; **^{1}H-NMR** (200 MHz, $CDCl_3$ + DMSO-D_6): δ 4.40 (brs, 1H), 7.00 (m, 2H), 7.40-7.60 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 99.0, 116.1, 116.4, 119.0, 132.2, 134.1, 160.0**; Mass** (m/z, % RI): 119 (M^+, 50), 91 (100), 77 (10), 64 (38); **Analysis**: C_7H_5NO requires C, 70.58; H, 4.22; N, 11.75; found C, 70.50; H, 4.25; N, 11.76%.

4-Hydroxybenzonitrile (3e): Yield: 65%; **mp**: 112-114°C; **IR** (nujol, cm^{-1}): 3400, 2900, 2820, 2220, 1560, 1440, 1360, 1220, 820; **^{1}H-NMR** (200 MHz, $CDCl_3$+DMSO-D_6): δ 2.10 (brs, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 102.0, 116.2, 119.8, 134.0, 162.1; **Analysis**: C_7H_5NO requires C, 70.58; H, 4.22; N, 11.75; found C, 70.52; H, 4.27; N, 11.73%.

2-Chlorobenzonitrile (3f): Yield: 70%; **mp**: 42-44°C; **IR** (nujol, cm^{-1}): 2200, 1570, 1430, 1360, 1165, 1040; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.70 (m, 1H), 7.50-7.70 (m, 2H); **Analysis**: C_7H_4NCl requires C, 61.09; H, 2.92; N, 10.18; Cl, 25.78; found C, 61.11; H, 2.89; N, 10.12; Cl, 25.76%.

4-Hydroxy 3-methoxybenzonitrile (3g): Yield: 51%; **mp**: 83-85°C; **IR** (nujol, cm^{-1}): 3445, 2200, 1570, 1430, 1360, 1165, 1040, 760; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.45 (brs, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.2, 102.5, 114.1, 114.5, 119.4, 126.4, 146.2, 150.1; **Analysis**: $C_8H_7NO_2$ requires C, 64.42; H, 4.72; N, 9.39; found C, 64.38; H, 4.75; N, 9.41%.

3,4-Dimethoxybenzonitrile (3h): Yield: 75%; **mp**: 67-69°C; **IR** (nujol, cm^{-1}): 2900, 2800, 2200, 1580, 1440, 1360, 1240, 810; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.95 (s, 3H), 6.90 (d, *J* = 8.0 Hz, 1H) 7.10 (s, 1H), 7.30 (d, *J* = 3.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ

56.0, 103.9, 110.6, 114.0, 119.4, 148.7, 152.3; **Analysis**: $C_9H_9NO_2$ requires C, 66.25; H, 5.55; N, 8.58; found C, 66.20; H, 5.58; N, 8.50%.

3,4,5-Trimethoxybenzonitrile (3i): Yield: 65%; **mp**: 142-144^oC; **IR** (nujol, cm^{-1}): 2900, 2800, 2200, 1580, 1500, 1350, 1245, 960, 830; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.95 (s, 6H), 3.97 (s, 3H), 6.95 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.2, 60.5, 106.2, 109.1, 119.1, 142.2, 153.1; **Analysis**: $C_{10}H_{11}NO_3$ requires C, 62.19; H, 5.73; N, 7.25; found C, 62.22; H, 5.80; N, 7.22%.

4-*N*,*N*-Dimethylbenzonitrile (3j): Yield: 80%; **mp**: 71-73^oC; **IR** (nujol, cm^{-1}): 2900, 2800, 2210, 1600, 1130, 800; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.05 (s, 6H), 6.60 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 40.0, 97.2, 111.1, 120.4, 120.4, 133.2, 152.1; **Analysis**: $C_9H_{10}N_2$ requires C, 73.94; H, 6.88; N, 19.16; found C, 73.94; H, 6.90; N, 19.10%.

3-Nitrobenzonitrile (3k): Yield: 61%; **mp**: 117-118^oC; **IR** (nujol, cm^{-1}): 2800, 2200, 1580, 1500, 1350, 960, 830; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.50-8.50 (m, 2H), 8.30-8.50 (m, 2H); **Analysis**: $C_7H_4N_2O_2$ requires C, 56.76; H, 2.71; N, 18.91; found C, 56.73; H, 2.77; N, 18.88%.

4-Nitrobenzonitrile (3l): Yield: 76%; **mp**: 148-150^oC; **IR** (nujol, cm^{-1}): 2800, 2205, 1585, 1490, 1350, 960, 830, 720; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 2H), 8.40 (d, J = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 116.4, 118.2, 124.3, 133.2; **Analysis**: $C_7H_4N_2O_2$ requires C, 56.76; H, 2.71; N, 18.91; found C, 56.77; H, 2.72; N, 18.89 %.

1-Naphthylbenzonitrile (3m): Yield: 70%; **mp**: 34-35^oC; **IR** (nujol, cm^{-1}): 3445, 2800, 2205, 1570, 1430, 1360, 1165, 1040, 760; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.45-7.70 (m, 3H), 7.80-7.90 (m, 2H), 8.05 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 110.0, 117.8, 124.6, 124.9, 127.1, 128.4, 128.6, 132.0, 132.2, 133.0, 133.2; **Analysis**: $C_{11}H_7N$ C, 86.25; H, 4.60; N, 9.14; found C, 86.20; H, 4.66; N, 9.10 %.

2-Chloro 3-quinolinecarbonitrile (3n): Yield: 49%; **mp**: 183-185^oC; **IR** (nujol, cm^{-1}): 2180, 1580, 1430, 1360, 960; **^{1}H-NMR** (200 MHz, $CDCl_3$+DMSO-D_6): δ 8.10-8.40 (m, 1H), 7.50-7.60 (m, 1H), 7.0-7.20 (m, 1H); **Analysis**: $C_{10}H_5N_2Cl$ requires C, 63.66; H, 2.67; N, 14.86; Cl, 18.80; found C, 63.63; H, 2.60; N, 14.79; Cl, 18.77%.

Application to Enantioselective Synthesis of (*S*)-Bunitrolol

2.0.7 Introduction

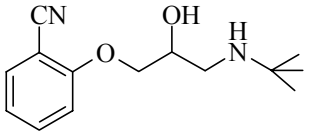
The members of a pair of enantiomers often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[30] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic.

There are several methods to obtain enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution and asymmetric synthesis. OsO_4-catalyzed asymmetric dihydroxylation (AD), developed by Sharpless *et al*.[31] is a simple, efficient and the most reliable method for asymmetric synthesis of chiral vicinal diols.

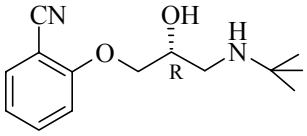
2.0.8 Pharmacology of Bunitrolol

The mechanism of the vasodilator action of bunitrolol was investigated in pentbarbital-anesthetized dogs. When injected intraarterially, bunitrolol increased blood flow through the femoral arterial bed more effectively than that through the vascular bed of the left anterior descending coronary artery (LAD). The former is rich in alpha adrenoceptors and tonically controlled by the sympathetic nerves, whereas the later is not. Intraarterial prazosin increased femoral flow but not the LAD flows. These effects of bunitrolol were similar to that prazosin and dissimilar to those of yohimbine. In similarly treated dogs, bunitrolol suppressed more

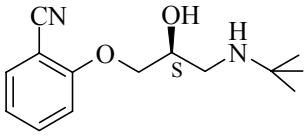
effectively increases in mean systemic arterial pressure in response to methoxamine than those to B-HT 920 from these results, it was concluded that an alpha 1-adrenoceptor blocking action is mainly involved in the acute vasodilator effect of bunitrolol. These actions may also contribute to the decrease in total peripheral resistance seen in hypertensive patients treated chronically with bunitrolol.



(±)-Bunitrolol (**16**)



(R)-Bunitrolol (**17**)



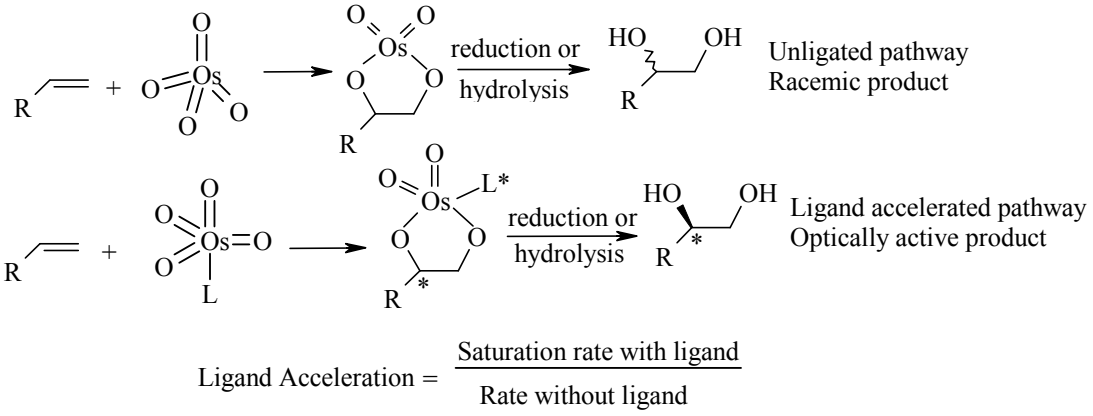
(S)-Bunitrolol (**18**)

2.0.9 Asymmetric Dihydroxylation (AD)

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomers, enzymatic resolution and asymmetric synthesis.[32] It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[33] Among all these reactions, Sharpless's Catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-cis*-diols from activated as well as inactivated olefins.[34]

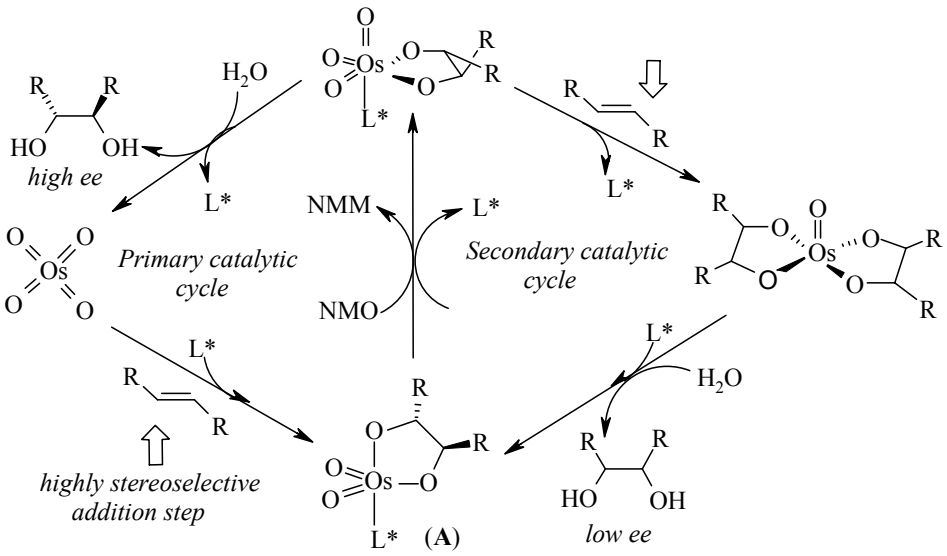
In 1936, Criegee *et al.*[35] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al.*[34b]

demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[36] A number of recent methods employ chiral diamine ligands for the asymmetric osmylation of olefins. The simplified mechanism of achiral and chiral dihydroxylation is given in **Scheme 15**.



Scheme 15: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[37] hydrogen peroxide,[38] *tert*-butyl hydroperoxide[39] and *N*-methylmorpholine *N*-oxide (NMO)[40] were introduced. The idea to use these co-oxidants was to minimize the amount of toxic and costly osmium so as to make the process more economical.



Scheme 16: Catalytic cycle for AD using NMO as co-oxidant.

Sharpless *et al.*[41] have established that the most practical and suitable catalytic method is with NMO as co-oxidant but the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle, **Scheme 16**). The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle, **Scheme 16**), which results in low or no ee at all. To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 4)**.[32,42] These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Scheme 16**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) gets reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly.[32] Addition of methyl

sulfonamide also allowed carrying out the reactions of 1,2-di, tri and tetra substituted olefins at 0^0C, which improved the selectivity as well as %ee.

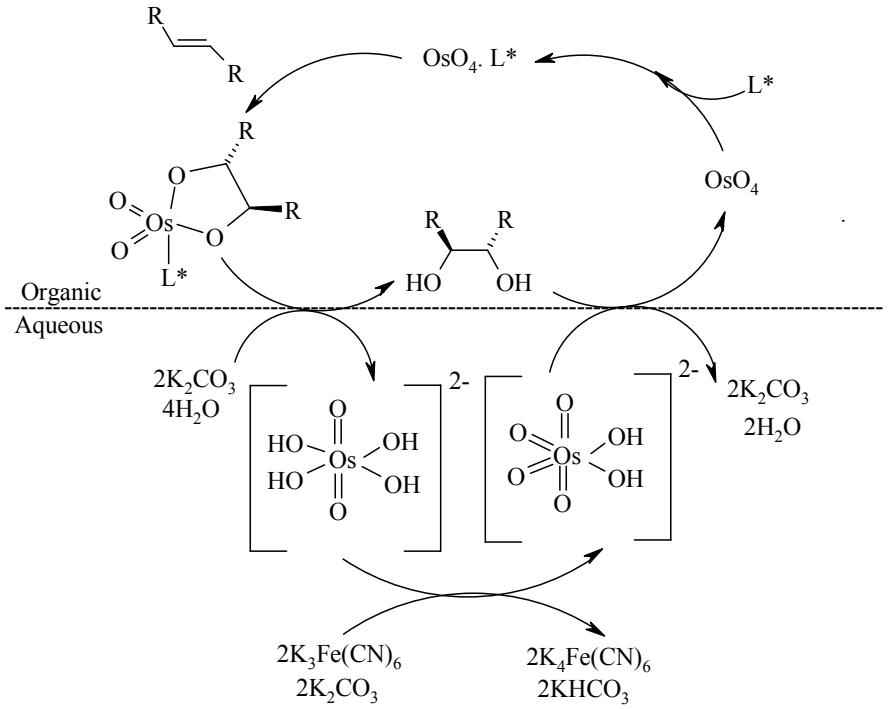
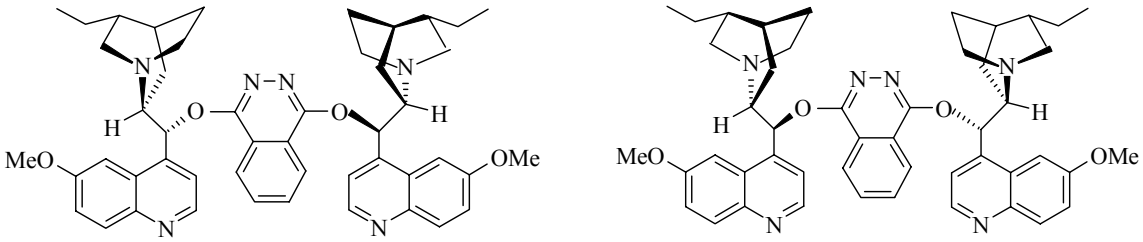


Fig. 4: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant.

In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ **19** or DHQD **20** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols[43] **(Fig. 5)**.



$(DHQ)_2$-PHAL (19) **$(DHQD)_2$-PHAL (20)**

Fig. 5: Ligands for asymmetric dihydroxylation reaction

The recent studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[43] [44] Sharpless *et al*.[34] have shown that the facial selectivity for both ligands **19** and **20** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 6)** in which olefin with the constraints will be attacked either from the top (i. e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

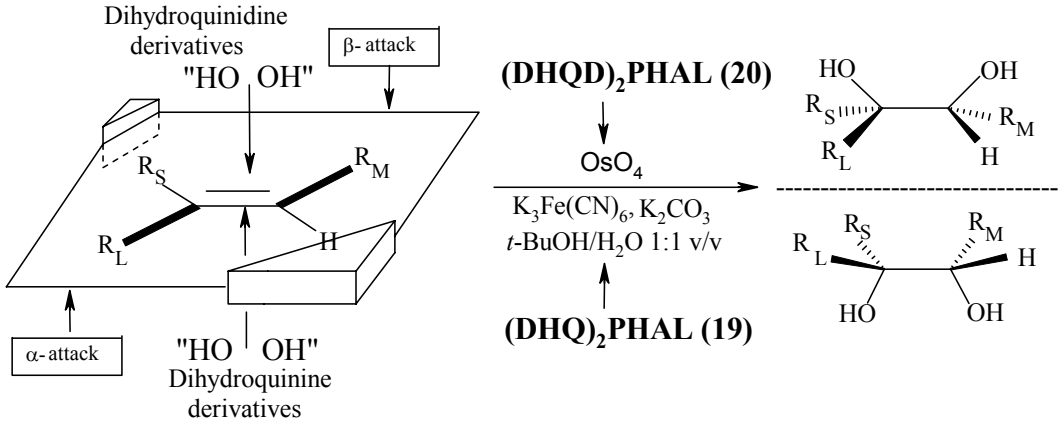


Fig. 6: Enantioselectivity mnemonic scheme

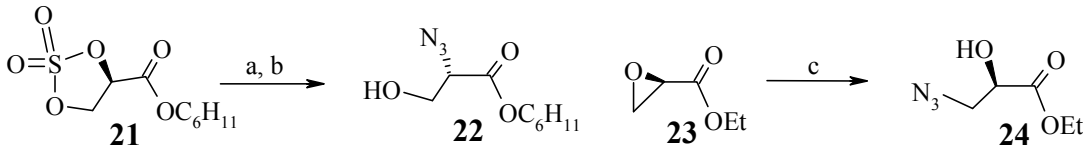
2.0.10 Chemistry of Cyclic Sulfites and Sulfates

The chemistry of cyclic sulfites and sulfates is very old.[45] These are esters of 1,2; 1,3 or 1,4 diols and possess properties similar to epoxides. Unlike epoxide, chemistry of cyclic sulfites and sulfates is less explored in organic synthesis due to lack of an efficient method for their preparation. The significant role of cyclic sulfates in organic synthesis is realized due to their unique properties such as (i) high reactivity towards nucleophiles which is comparable to epoxides (ii) attack of nucleophile is regiospecific and thereby serving as a protecting group at a second position (iii) nucleophilic opening of five-membered cyclic sulfates generates two contiguous stereocenters.[46] The recent developments in Ru-catalyzed oxidation of the cyclic sulfites with sodium periodate extend the scope of cyclic sulfates in organic synthesis.[47]

Cyclic sulfates are important intermediates in obtaining bioactive molecules containing hydroxyl functionality.[46] Chiral cyclic sulfates are easily prepared from the corresponding chiral glycols, which could be obtained from a variety of olefins by OsO_4-catalyzed asymmetric dihydroxylation.

2.0.11 Reactivity of Cyclic Sulfates

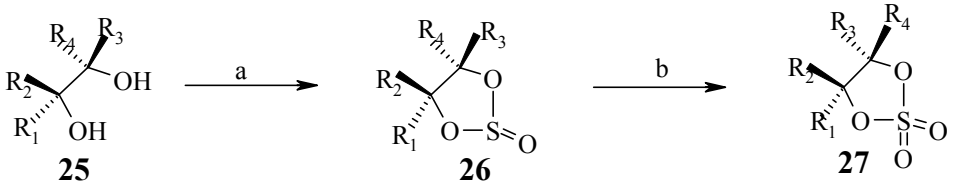
The cyclic sulfates (1,3,2-dioxathiolane-2,2-dioxde) are more reactive than their immediate cyclic sulfites (1,3,2-dioxathiolane-2-oxide). The high reactivity of the cyclic sulfate has been attributed to the ring strain and partial double bond character between ring oxygen and sulfur and also due to 2p(O)-3d(S) orbital interaction[48] The good leaving ability of the $ROSO_3^-$ moiety also enhances the reactivity of cyclic sulfates towards various nucleophilic reagents. The reactivity of cyclic sulfates and epoxides are similar in nature towards nucleophiles but vary in regioselective approach (**Scheme 17**). For example, the reactions of cyclic sulfate **21** with sodium azide in acetone: water system preferentially gave α-azido-product **2**, whereas epoxyester **23**, under similar reaction conditions gave β-azido-product **24**.[49]



Scheme 17: Reactivity pattern of cyclic sulfate *vs* epoxide a) NaN_3; b) H_2SO_4; c) NaN_3, H_2O.

2.0.12 Preparation of Cyclic Sulfites and Sulfates

Cyclic sulfites **26** are conveniently prepared by condensation of 1,2-, 1,3- and 1,4-diols **25** with thionyl chloride (**Scheme 18**).[47,50] In case of acid sensitive substrates, triethyl amine or pyridine is required to scavenge the hydrogen chloride generated in the reaction. It is then transformed to cyclic sulfates **27** by Ru-catalyzed oxidation with $NaIO_4$.[46,47]



Scheme 18: a) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C; b) cat. $RuCl_3.3H_2O$, $NaIO_4$, $CH_3CN:H_2O$.

2.0.13 *β*-Adrenergic Blockers

β-Adrenergic blocking agents (*β*-blockers) are important drugs used for the treatment of hypertension and angina pectoris.[51] Most of the *β*-blockers possess a general structure Ar-O-$CH_2CH(OH)CH_2NHCH(CH_3)_2$ **(Fig. 7)** and have been used in the form of racemic mixtures.[52]

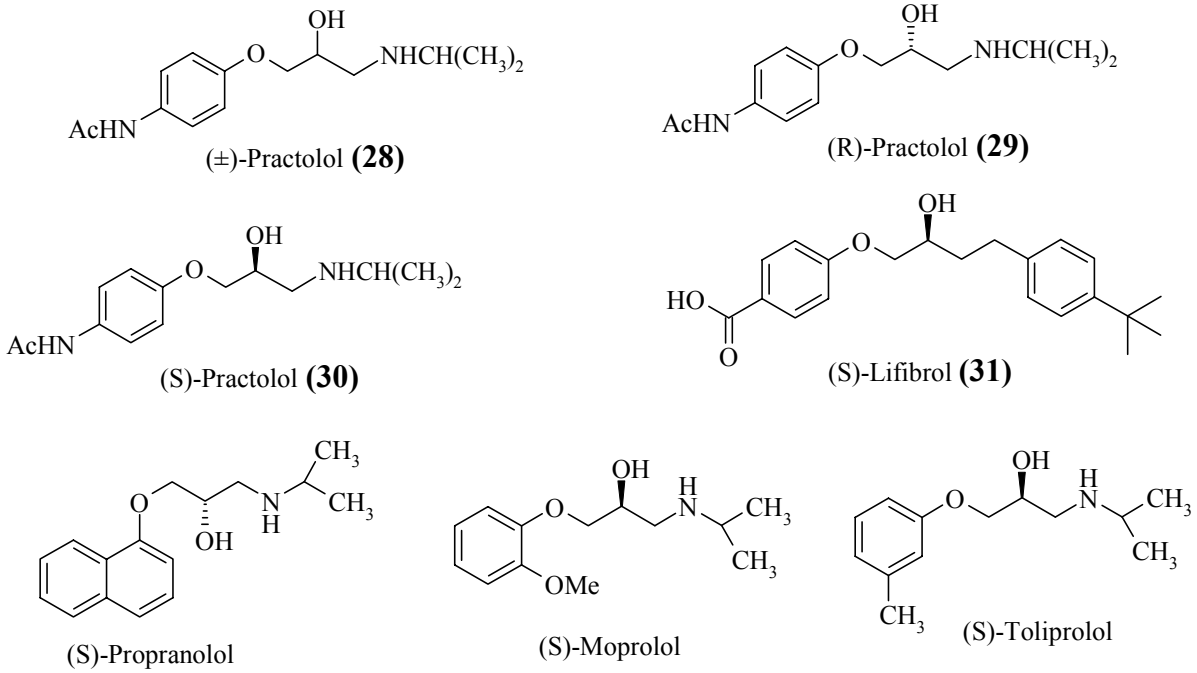


Fig. 7

Three fundamental goals of cardiovascular drugs are; the lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[53] Biochemically, the mechanism of

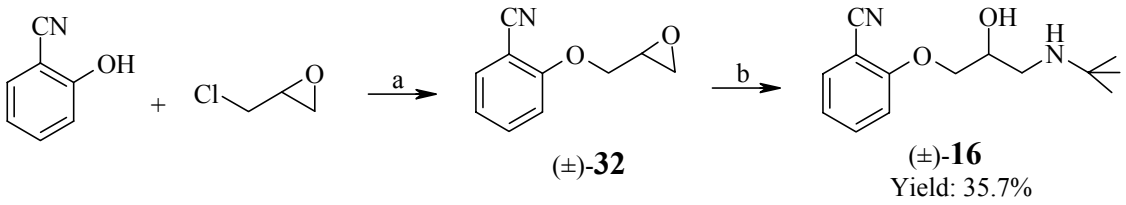
action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[54] Some of the representative β-blockers are shown in **(Fig. 7)**. There are four types of receptors for these molecules α_1, α_2, β_1 and β_2. Blocking of β-receptor system reduces the overall activity of the sympathetic nervous system. Agents, which are β-blockers, are thus used to increase life expectancy after the heart attack. Although (*S*)-isomers are known to be much more effective (100-500 fold) than the (*R*)-isomer,[55] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some case toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is desirable. (*S*)-Bunitrolol (**18**), (*S*)-Practolol (**30**) and (*S*)-Lifibrol (**31**) are among the most widely used β-blockers, which possesses antihypertensive, antianginal and sympatholytic properties.

2.0.14 Review of Literature

Literature search revealed that there are some reports available on the synthesis of β-blockers bunitrolol, practolol and lifibrol, which are described below.

Zhenya's approach (1987)[56]

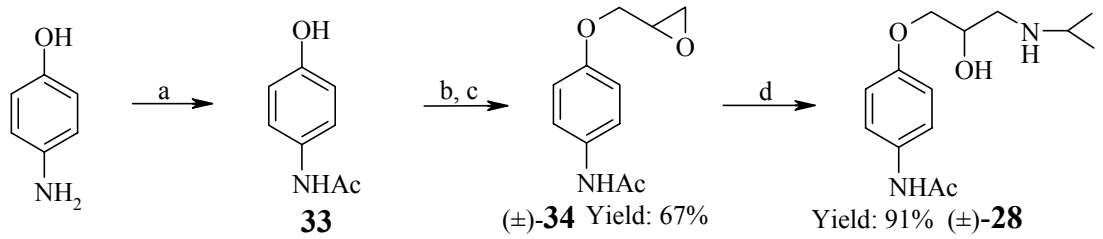
Zhenya *et al.* have reported the synthesis of racemic Bunitrolol (**16**) by etherification of salicylnitrile with racemic epichlorohydrin to give epoxide 32. Thus, epoxide 32 on treatment with *t*-butylamine afforded racemic Bunitrolol (**16**) in 35.7% overall yield (**Scheme 19**).



Scheme 19: a) NaOH; b) *t*-$BuNH_2$, 35%.

Apparu's approach (2000)[57]

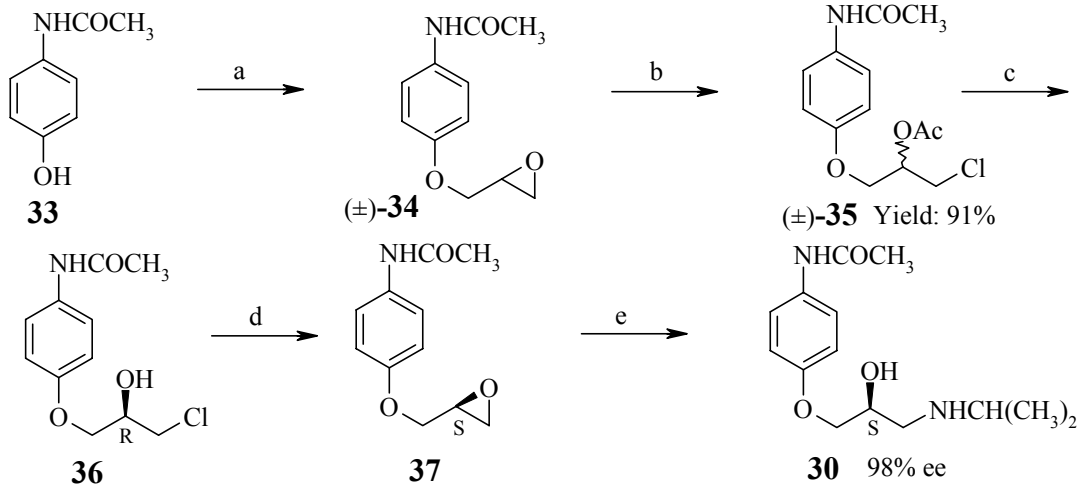
Apparu *et al.* have reported the synthesis of racemic Practolol (**28**). *N*-Acetyl 4-amino phenol (**33**) on treatment with base generated the corresponding phenoxide ion, which on subsequent reaction with glycidyl tosylate gave epoxide **34** in 67% yield. The epoxide **34** on treatment with isopropylamine gave the racemic Practolol (**28**) in 91% yield (**Scheme 20**).



Scheme 20: a) AcCl, THF, CH_3CN, RT, 93%; b) NaH, DMF; c) glycidyl tosylate, 67%; d) *i*$PrNH_2$, 2-propanol, reflux, 91%.

Thakkar's approach (1995)[58]

This reports an efficient synthesis of (*S*)-Practolol (**30**) using *Lipase Amno P. S* (LAPS) mediated acetylation as a key step. Thus, *N*-acetyl-4-aminophenol (**33**) on treatment with epichlorohydrin was converted to epoxide **34** which was subsequently acetylated to give

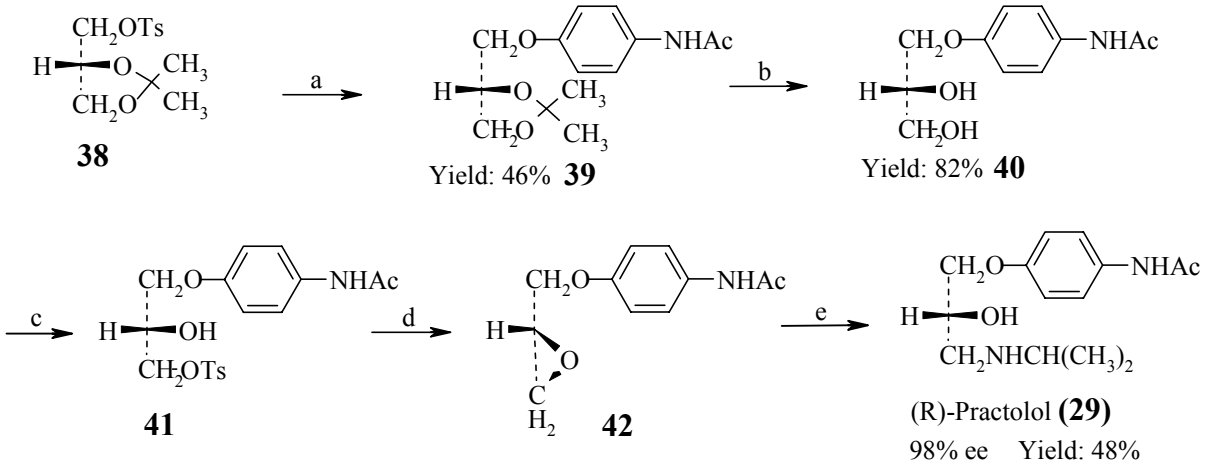


Scheme 21: a) NaOH, epichlorohydrin; b) CH_3COCl, $CHCl_3$, RT; c) LAPS, *n*-BuOH; d) K_2CO_3, MeOH; e) *i*$PrNH_2$, 98%ee.

chloroacetate **35**. Chloroacetate **35** was subjected to enzymatic hydrolysis with LAPS to give optically pure chloroalcohol **36** along with unreacted acetate **35**. Chloroalcohol **36** was then converted to (*S*)-Practolol (**30**) by known sequence of reactions in 98% ee (**Scheme 21**).

Danilewicz's approach (1973)[59]

Danilewicz *et al.* have reported preparation of (*R*)-Practolol (**29**) starting from mannitol as a chiral starting material. Thus, (*R*)-α-(4-toluenesulfonyl)acetone glycerol (**38**) was converted to the corresponding 4-acetamidophenoxy derivative **39** on treatment with 4-acetamidophenoxide. Hydrolysis afforded the diol **40**, which was then converted to (*R*)-1-(4-acetamidophenoxy)-2,3-epoxypropane (**42**). Finally, epoxide **42** gave (*R*)-Practolol (**29**) on reaction with isopropylamine in 98% ee (**Scheme 22**).

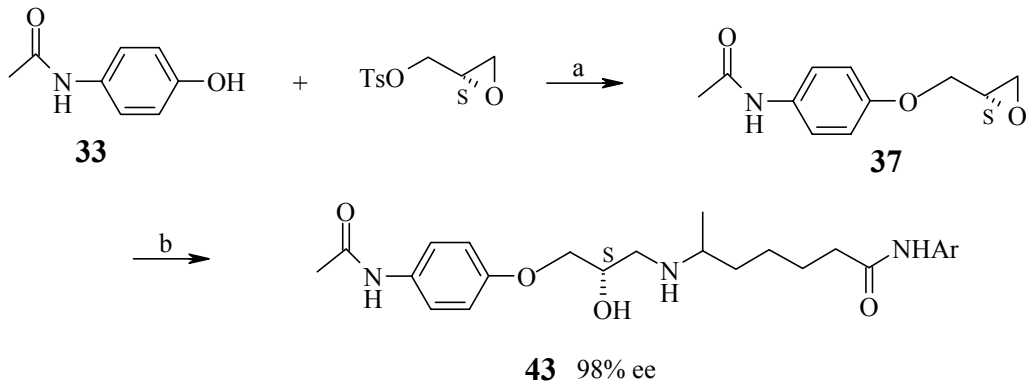


Scheme 22: a) Na, 4-acetamidophenol, $CH_3OCH_2CH_2OH$, reflux, 1.5 h, 46%; b) 80% AcOH, 50-75°C, 82%; c) TsCl-pyridine, –10-5°C, 53%; d) 20% NaOH, DMSO, RT, 55%; e) *i*-$PrNH_2$, 3 days, 48%.

Leftheris approach (1990)[60]

Leftheris *et al.* have reported synthesis of a derivative of (*S*)-Practolol (**43**) by using Ti-catalyzed asymmetric epoxidation as a key step to prepare (*S*)-glycidyl tosylate. Further, glycidyl tosylate on treatment with 4-acetamidophenol (**33**) gave the (*S*)-epoxide **37**. Reaction

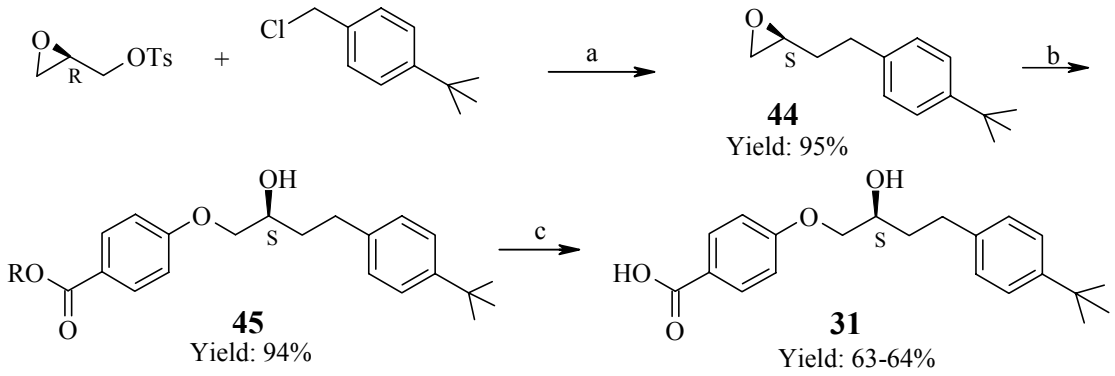
of epoxide **37** with appropriate amide afforded the desired product **43** in >98% optical purity (**Scheme 23**).



Scheme 23: a) NaOH; b) $H_2NCHCH_3(CH_2)_4CONHAr$, reflux, 98%ee.

Rieter's approach (1992)[61]

This approach reports preparation of (*S*)-Lifibrol (**31**) by using optically active (*R*)-glycidyl tosylate. Thus, Grignard reaction of (*R*)-glycidyl tosylate with 4-tert-butyl benzyl chloride gave (*S*)-4-(4'-tert-butylphenyl)-1,2-epoxybutane (**44**) in 95% yield. Epoxide **44** was then treated with 4-$NaOC_6H_4CO_2Me$ to give hydroxy ester **45** in 94% yield, which on subsequent mild hydrolysis afforded (*S*)-Lifibrol (**31**) in 64% yield (**Scheme 24**).



Scheme 24: a) Mg, ether, 95%; b) 4-$NaOC_6H_4CO_2Me$, DMF, 125°C; c) KOH in *aq* MeOH, 64%.

2.0.15 Present Work

2.0.15.1 Objective

Although racemic β-blockers have been administered over the last two decades, there is now a great demand for enantiomerically pure isomers, which show higher affinity to β-receptors. All the reported methods described above for the synthesis of (*S*)-Bunitrolol, (*S*)-Practolol and (*S*)-Lifibrol suffer from drawbacks such as the use of expensive enzymes and resolving agents, low overall yields, low optical purity, *etc*. To develop a new general route for the asymmetric synthesis of β-adrenergic blockers with good optical purity and yield, we have decided to make use of Sharpless Asymmetric Dihydroxylation (AD) of aryl allyl ethers followed by employing the chemistry of chiral cyclic sulfates.

Retro-synthetic analysis of these homochiral β-adrenergic blocking agents (**A**) is presented in **(Fig. 8)**. Evidently, there are three possible disconnections of bonds as shown at a, b and c positions of **A**. However most of the synthetic routes are based on the disconnection of bonds at either a or b.

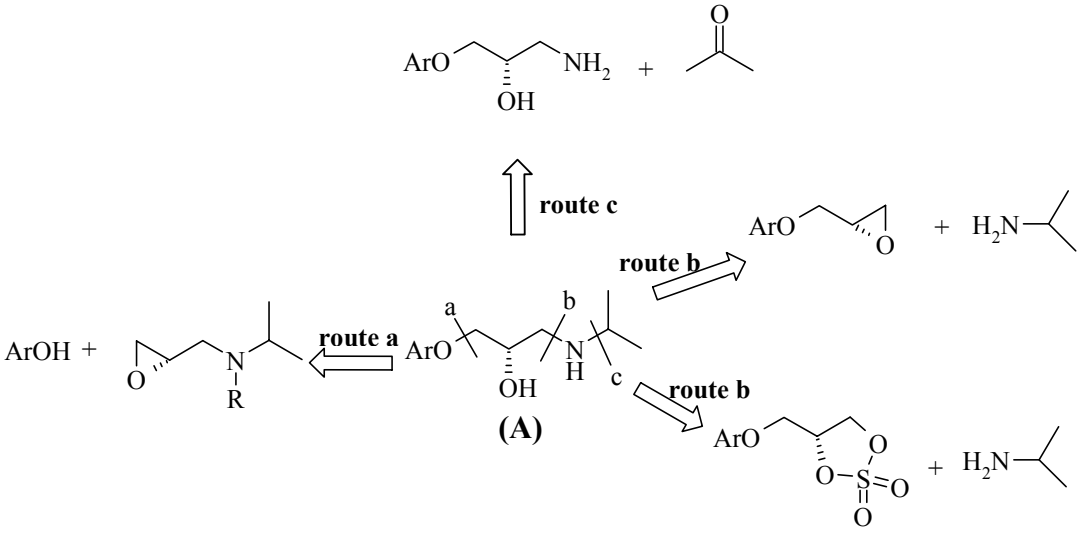
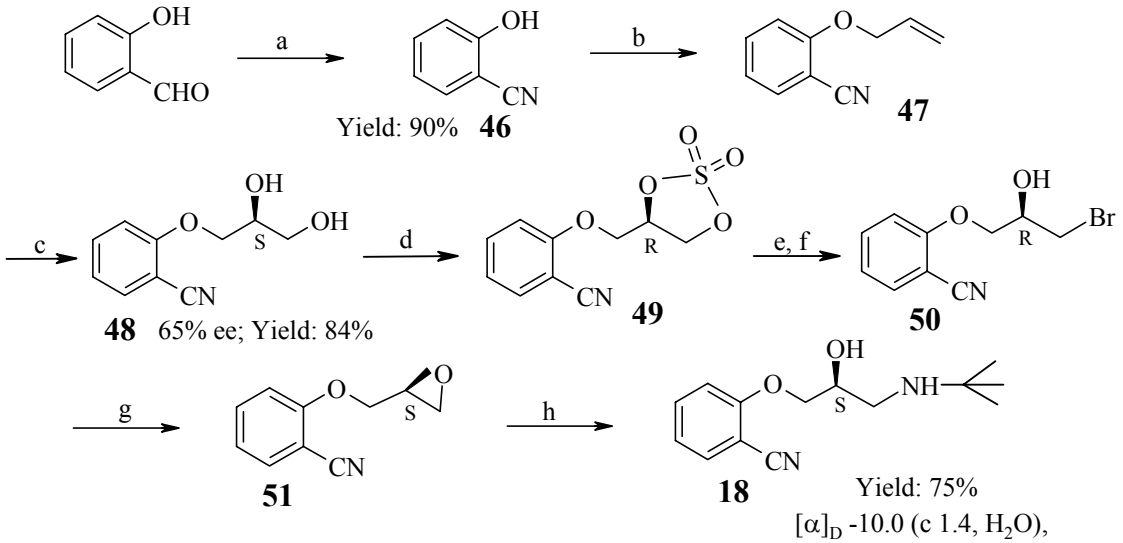


Fig. 8: Retro-synthetic analysis of β-blockers (A)

2.0.16 Results and Discussion

Our approach for the synthesis of (*S*)-Bunitrolol (**18**) is based on the disconnection route b, which results in two chiral synthons (cyclic sulfate **49** and epoxide **51**), both of which are accessible using AD method. The overall synthetic sequence for the synthesis of (*S*)-Bunitrolol (**18**) is presented in **Scheme 25**.



Scheme 25: a) $NH_2OH.HCl$, $HCONH_2$, pyridine, xylene, reflux, 90%; b) K_2CO_3, allyl bromide, acetone, reflux, 12 h, 97%; c) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 25°C, 12 h, $[\alpha]_D$ +21.8 (c 0.5, EtOH); 84% d) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min, 96%; cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min, $[\alpha]_D$ +8.6 (c 2.0, EtOH), 86%; e) anhyd. LiBr, THF, 60°C, 45 min, $[\alpha]_D$ – 6.8 (c 1.2, EtOH); f) 20% H_2SO_4, Et_2O, 4 h; $[\alpha]_D$ +2.3 (c 2.3, $CHCl_3$) 85%, g) K_2CO_3, MeOH, –10-15°C, 2 h, 90%; h) *t*$BuNH_2$, reflux 4 h, $[\alpha]_D$ –10.0 (c 1.4, H_2O), 75%.

The first step involves the preparation of 2-cyanophenol **46**, which was obtained from *o*-salicylaldehyde by utilizing formamide as a dehydrating agent. Thus, *o*-salicylaldehyde on treatment with a reagent comprising $NH_2OH.HCl$-Py-$HCONH_4$ gave 2-cyanophenol **46** in 90% yield. Its ^{1}H-NMR spectrum showed disappearance of aldehyde signal while the IR spectrum showed a strong nitrile absorption at 2225 cm^{-1}.

Allylation of phenol **46** with allyl bromide gave allyl ether **47** in 97% yield. Its ^{1}H-NMR spectrum showed a pattern typical of allyl functionality in the region δ 4.50-6.25. Its

^{13}C-NMR spectrum showed the characteristic signals in the region of δ 69-118 due to carbons of the allylic functionality

The allylic ether **47** was then subjected to Os-catalyzed Sharpless Asymmetric Dihydroxylation (AD) using $(DHQD)_2$-PYR [hydroquinidine 2,5-diphenyl-2,6-pyrimidinediyl diether] as chiral ligand in the presence of $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant to yield optically active diol **48** in 65% ee.[62] Its ^{1}H-NMR spectrum showed disappearance of signals for allylic moiety and appearance of new signals in the region δ 3.50-4.50. The ^{13}C-NMR spectrum shows signals at δ 63.22, 69.83 and 70.02 for carbons bearing oxo-functionality **(Fig. 9)**.

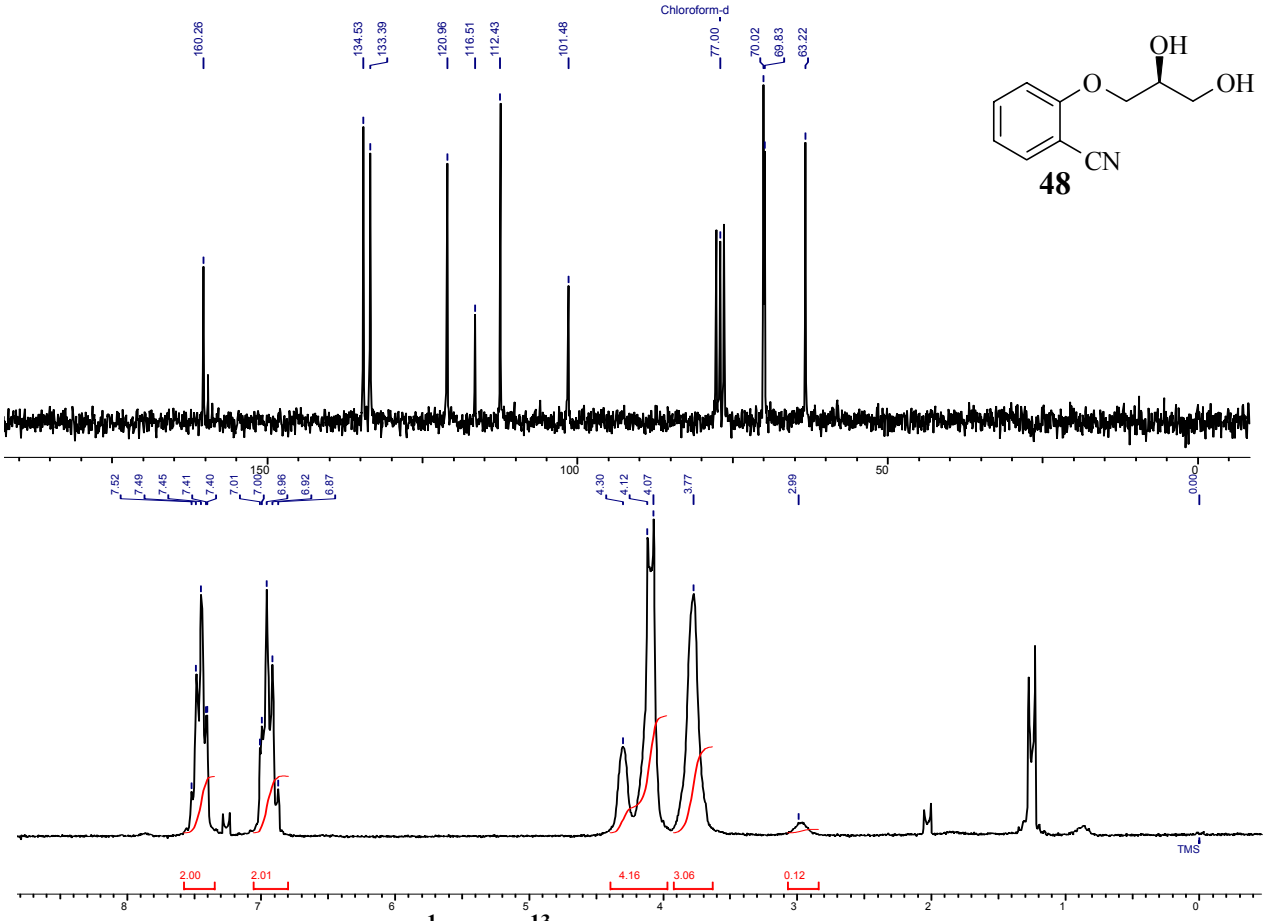


Fig. 9: ^{1}H and ^{13}C-NMR spectra of the diol 48

The diol **48** was then treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0^0C to afford cyclic sulfite in 96% yield. The formation of cyclic sulfite was clearly evident from the appearance of multiplets in ^{1}H-NMR spectrum in the region δ 4.00-5.50 due to the presence of diastereomeric mixtures. The cyclic sulfite was then oxidized to cyclic sulfate **49** in 86% yield using catalytic amount of $RuCl_3$ and $NaIO_4$ as oxidant. The formation of cyclic sulphate **49** was evidenced by its ^{1}H-NMR spectrum which showed disappearance of signals due diastereomeric mixture, formation of multiplet at δ 4.35-4.55 corresponding to -CH_2 of the ether linkage, while the other two signals appearing as multiplets at δ 4.75-5.00 and δ 5.25-5.55 correspond to -CH_2 and -CH protons of the five membered cyclic sulphate moiety. Its

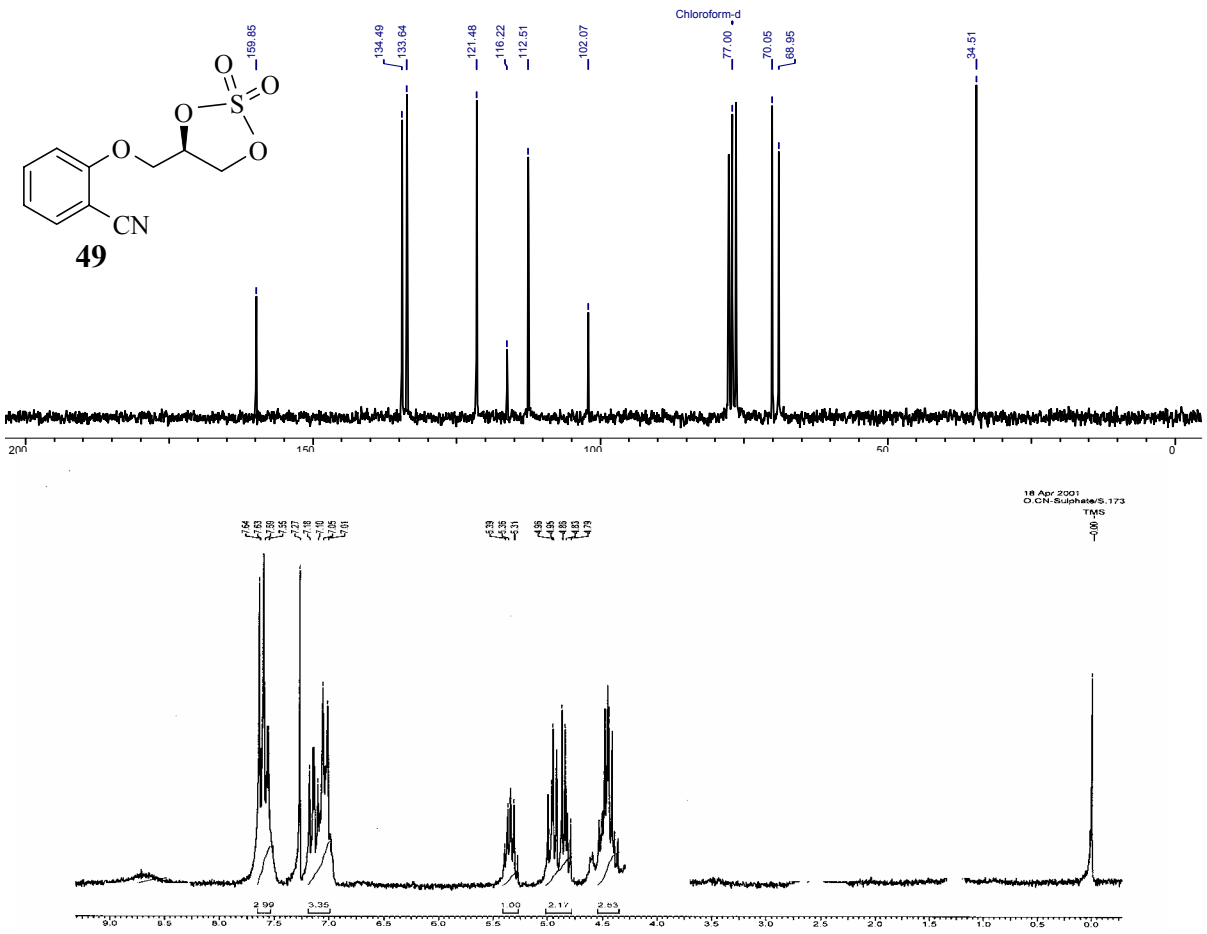


Fig. 10: ^{1}H and ^{13}C-NMR spectra of cyclic sulphate 49

^{13}C-NMR spectrum also showed simplified pattern because of the absence of diastereomeric mixtures. Thus, it showed characteristic signals at δ 68.95, 70.05 and 78.84 corresponding to O-CH_2, CH_2 and CH carbons respectively **(Fig. 10)**. Finally, the cyclic sulfate **49** was subjected to nucleophilic displacement with *t*-butylamine followed by hydrolysis of the resulting salt in order to afford (*S*)-Bunitrolol (**18**). However, the opening and hydrolysis of the cyclic sulfate **49** resulted in very low yield of (*S*)-Bunitrolol (**18**). (Yields were <30%). Various other reaction conditions for hydrolysis such as 20% and 50% H_2SO_4 in ether, 20% HCl, conc. HCl, 20% and 50% *aq*. NaOH were tried but all of them failed to provide the improvement in the yield of the final product.

Hence, we converted the cyclic sulfate **49** into the corresponding epoxide **51** using a three-step procedure. Thus, cyclic sulfate **49** was first treated with anhydrous LiBr, then with 20% aqueous H_2SO_4 in ether to give bromoalcohol **50**. The opening of cyclic sulphate **49** was found to be regiospecific, wherein bromide attacks the cyclic sulphate at the less substituted carbon atom, giving rise to secondary alcohol. Its ^{1}H-NMR spectrum showed OH peak at δ 2.73, multiplets at δ 3.60-3.80 and 4.15-4.40 corresponding to two and three protons respectively.

The bromo alcohol **50** was then treated with anhydrous K_2CO_3 in MeOH at 0^{o}C to give epoxide **51** in 90% yield. Its ^{1}H-NMR spectrum showed an overall upfield shift of the protons as compared to bromoalcohol **50**. The –CH_2 protons of of Ph-O-CH_2- moiety became diastereotopic giving rise to ABX pattern in the region δ 2.84-4.42 **(Fig. 11)**. Further its mass spectrum showed molecular ion peak at m/z: 175.

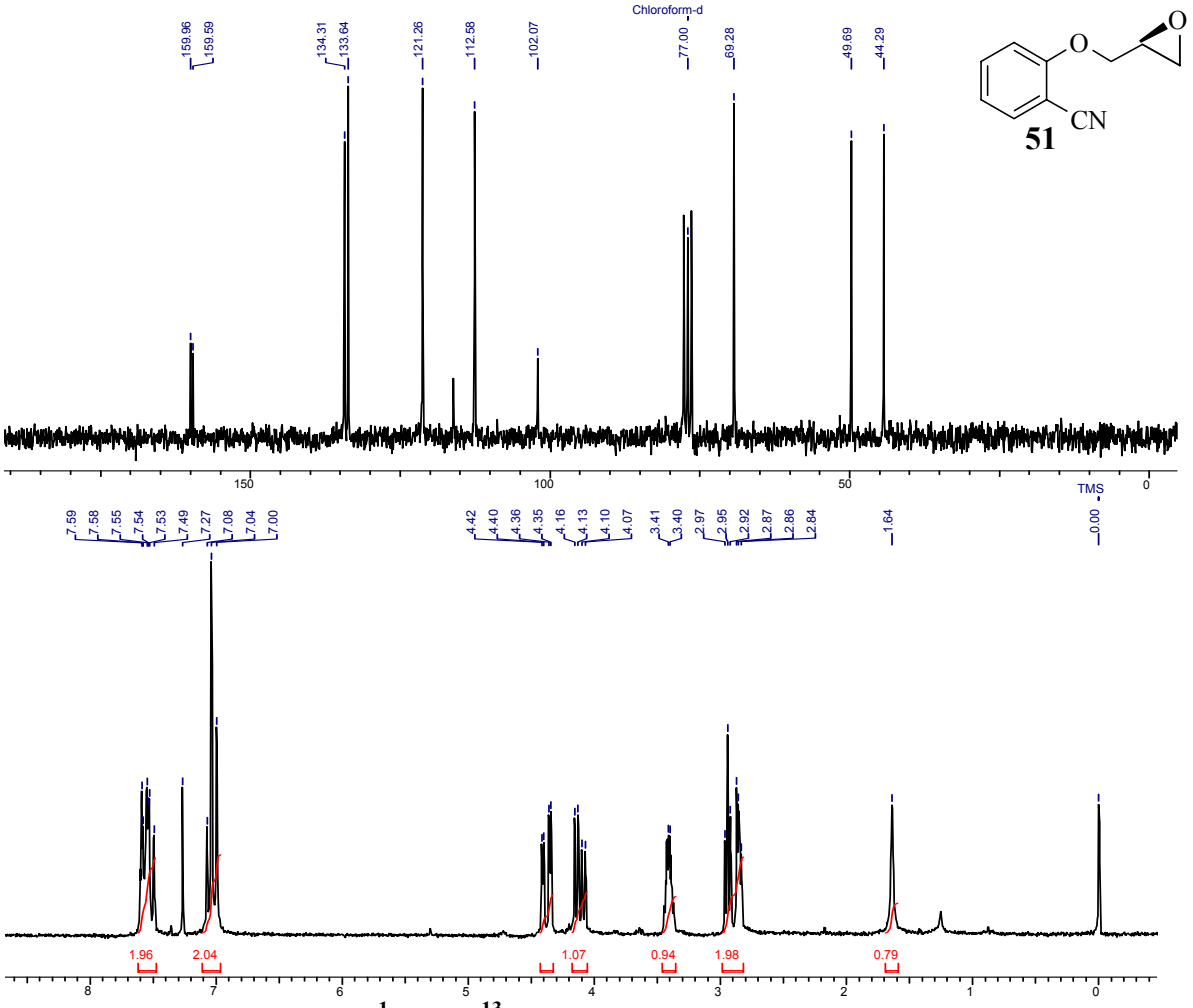


Fig. 11: ^{1}H and ^{13}C-NMR spectra of epoxide 51

Finally, the chiral epoxide **51** was then subjected to regiospecific ring opening with *t*-butylamine to afford the optically active (*S*)-Bunitrolol (**18**) in 75% yield. The presence of tertiary butyl group of amine has influenced its attack from the less hindered side of the epoxide **51**. Its ^{1}H-NMR spectrum showed sharp singlet at δ 1.14 corresponding to *t*-butyl group. Its ^{13}C-NMR spectrum showed peaks at δ 28.66 and 50.64 corresponding to methyl and quaternary carbons of tertiary group respectively; other peaks at δ 44.40, 67.74 and 71.60 correspond to methylene carbon attached to nitrogen and methine carbons bearing OH group

and methylene carbon of ether linkage respectively; thus confirming the formation of (*S*)-Bunitrolol (**18**) **(Fig. 12)**.

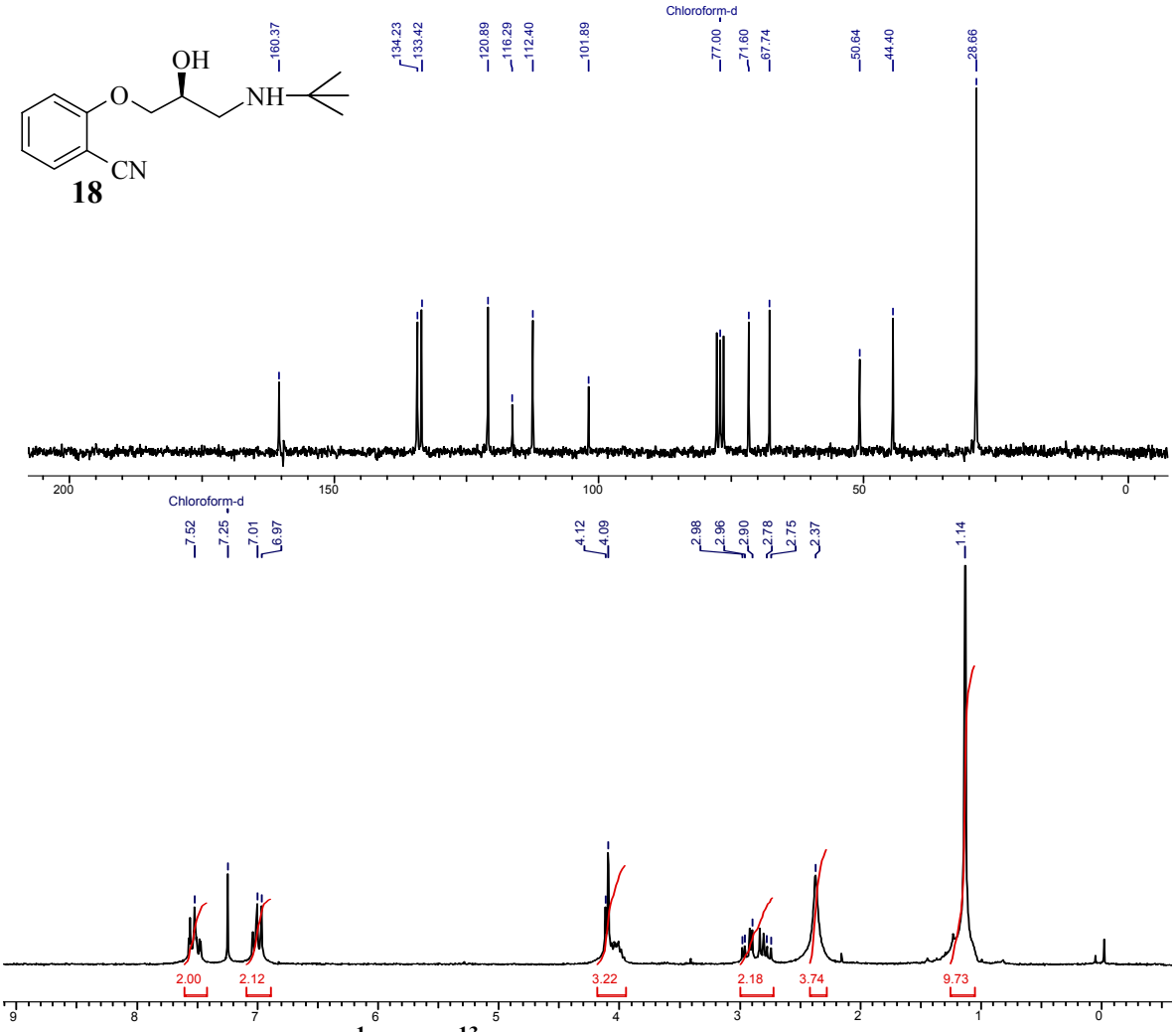


Fig. 12: ^{1}H and ^{13}C-NMR spectra of (*S*)-Bunitrolol 18

2.0.17 Conclusion

In conclusion, we have developed a simple and efficient method for the asymmetric synthesis (*S*)-Bunitrolol (**18**) [34.73% overall yield] in eight steps starting from commercially available starting materials. The Sharpless asymmetric dihydroxylation has been employed for the induction of chirality into the molecule. The activation of the chiral diol was attempted by transforming it into a reactive intermediate, cyclic sulphate. However, this cyclic sulphate

after opening with amine had the problem of hydrolyzing its salt. Therefore, cyclic sulphate was transformed into optically active epoxide, which underwent opening smoothly with *t*-butylamine to afford (*S*)-Bunitrolol (**18**).

2.0.18 Experimental Section

All solvents were distilled and dried before use. Chromatography was performed over silica gel (60-120 mesh). IR spectra were recorded on a Perkin-Elmer 137 E spectrometer. ^{1}H- and ^{13}C-NMR were recorded on Brucker FT 200 MHz instruments using TMS as an internal standard. The mass spectra (MS) were recorded on an automated 1020C mass spectrometer using ionization energy of 70 eV. The optical rotations were carried out on JASCO-181 digital polarimeter at 25^{o}C using sodium D light.

Preparation of 2-cyanophenol (46)

A 50 ml RB flask was charged with a mixture of *o*-anisaldehyde (5.0 g, 40.9 mmol), hydroxylamine hydrochloride (2.82 g, 40.9 mmol), pyridine (3.23 g, 40.9 mmol) and formamide (1.84 g, 40.9 mmol) in xylene (10 ml). The resulting reaction mixture was subjected to reflux for 5-6 hr (monitored by TLC). After completion of the reaction, xylene was distilled under reduced pressure. Water 20 ml was added to the reaction mixture followed by neutralization of pyridine with 2N HCl. It was then extracted with ethyl acetate (3 x 20 ml) washed with brine and dried over anhyd. Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography to give 4.30 g of 2-cyanophenol (**46**).

Yield: 90%; **mp**: 95-97^{o}C (benzene); **IR** (nujol, cm^{-1}): 2860, 2200, 1580, 1440, 1350, 840, 730; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 6.17 (brs, 1H), 6.85-7.15 (m, 2H), 7.40-7.60 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 98.91, 116.59, 120.52, 132.98, 134.86, 159.26; **MS** (m/z, RI): M^{+}(119, 70), 193 (12), 91 (100), 88 (3), 75 (4), 65 (30), 63 (35), 61 (20), 52 (12); **Analysis**: C_7H_5NO requires C, 70.59; H, 4.22; N, 11.75; found C, 70.69; H, 4.22; N, 11.79 %.

Preparation of allyl 2-cyanophenyl ether (47)

A 50 ml RB flask was charged with 2-cyanophenol (2 g, 16.8 mmol), allyl bromide (2.43 g, 20.16 mmol), anhydrous K_2CO_3 (3.47 g, 25.2 mmol) in dry acetone (30 ml). The resulting reaction mixture was then refluxed under N_2 for 18h (monitored by TLC). The reaction mixture was then filtered through sintered funnel and the filtrate was evaporated up to

dryness. The residue was then purified by column chromatography using pet. ether: EtOAc (9:1) to give 2.58 g of pure allyl ether **47**.

Yield: 97%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3082, 2925, 2227, 1598, 1579, 1490, 1450, 1425, 1290, 1259, 1234, 1166, 1110, 995, 933, 788, 756, 732; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 4.66 (d, *J* = 2.0 Hz, 2H), 5.31-5.36 (m, 1H), 5.44 -5.53 (m, 1H), 5.90-6.20 (m, 1H), 6.90-7.10 (m, 2H), 7.45-7.65 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 69.16, 101.87, 112.56, 116.07, 117.77, 120.67, 131.66, 133.37, 134.04, 159.92; **MS** (m/z, RI): 159 (M^+, 100), 158 (98), 143 (5), 130 (14), 119 (20), 118 (18), 104 (7), 92 (21), 90 (22), 82 (6), 76 (12), 69 (7), 64 (16), 58 (8); **Analysis**: $C_{10}H_9NO$ requires C, 75.45; H, 5.69; N, 8.79; found C, 75.41; H, 5.79; N, 8.78 %.

Preparation of (2*S*)-1-(2-cyanophenoxy)-2,3-propanediol (48)

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (6.198 g, 18.84 mmol), K_2CO_3 (2.59 g, 18.84 mmol), $(DHQD)_2$-PYR (54 mg, 0.062 mmol) and *t*-BuOH : H_2O (1:1, 60 ml) and the resulting mixture was stirred for 10 minutes at 25^0C. It was then cooled to 0^0C and a solution of OsO_4 (256 µl, 0.124 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^0C for 5 minutes and then allyl ether **47** (1.0 g, 6.28 mmol) was added. The reaction mixture was stirred at 0^0C for 20-22 h (monitored by TLC). It was quenched with sodium sulfite (4.0 g) and extracted with ethyl acetate (4 x 25 ml). Combined organic extracts were washed with brine (20 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in pet. ether as eluent to yield 1.01 g of pure diol **48** as white solid in 84% yield.

Yield: 84%; **mp**: 140-142°C (hexane and EtOAc); **$[\alpha]^{25}_D$**: + 21.8 (c 0.5, EtOH); 65% ee, {lit.[62] **$[\alpha]^{25}_D$** + 9.4 (c 0.49, EtOH) for 28% ee}; **IR** ($CHCl_3$, cm^{-1}): 3421, 3018, 2229, 1598, 1492, 1450, 1290, 1215; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 3.50-3.90 (m, 4H), 4.10-4.25 (m, 3H), 7.90-7.05 (m, 2H), 7.45-7.55 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.22, 69.83, 70.02, 101.48, 112.43, 116.51, 120.96, 133.39, 134.53, 160.26; **MS** (m/z, RI): 193 (M^+, 10), 162 (12), 149 (4), 133 (38), 119 (100), 104 (42), 91 (80), 85 (4), 75 (16), 64 (22), 57 (12); **Analysis**: $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.73; N, 7.25; found C, 62.10; H, 5.75; N, 7.30 %.

Preparation of (2*R*)-1-(2-cyanophenoxy)-1,3,2-dioxathiolane-2,2-dioxide (49)

[A] To a solution of diol **48** (1.0 g, 5.18 mmol) and triethylamine (2.88 ml, 20.72 mmol) in CH_2Cl_2 (10 ml) at 0^0C was added freshly distilled thionyl chloride (0.56 ml, 7.77

mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0^0C for 30-45 minutes (monitored by TLC). The reaction mixture was quenched by the addition of cold water (10 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 25 ml). The combined organic extract was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure yielded pale yellow colored liquid, which was purified by the column chromatography using 10% EtOAc in pet. ether as a eluent to afford 1.18 g of the cyclic sulfite as viscous yellow liquid in 96% yield.

[B] To a solution of the above cyclic sulfite (0.800 g, 3.34 mmol) in CH_3CN: H_2O mixture (9: 1, 10 ml) at 0^0C was added solid $NaIO_4$ (1.072 g, 5.01 mmol) and $RuCl_3.3H_2O$ (0.012 g, 0.06 mmol). The reaction mixture was stirred for 30-40 minutes at 0^0C (monitored by TLC). After the reaction was complete, it was filtered through a pad of celite. Solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to afford 0.733 g of cyclic sulfate **49**. **Yield**: 86%; **gum**; $\mathbf{[\alpha]^{25}_D}$ + 8.6 (c 2.0, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3082, 2873, 2227, 1649, 1598, 1579, 1492, 1450, 1425, 1411, 1365, 1290, 1259, 1234, 1166, 1110, 1043, 995, 933, 839, 756, 590, 497; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.35-4.55 (m, 1H), 4.90-5.05 (dd, J = 2.0 and J = 6.0 Hz, 2H), 5.25-5.45 (m, 1H), 6.95-7.20 (m, 2H), 7.50-7.70 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 96.95, 70.05, 78.84, 102.07, 112.62, 115.63, 122.18, 133.64, 134.53, 158.75; **MS** (m/z, RI): 255 (M^+, 6), 232 (3), 218 (4), 204 (4), 193 (11), 176 (4), 162 (15), 146 (6), 134 (15), 133 (56), 119 (100), 104 (45), 102 (15), 91 (72), 80 (27), 75 (24), 64 (45), 57 (26); **Analysis**: $C_{10}H_9NSO_5$ requires C, 47.05; H, 3.55; N, 5.48; found C, 47.01; H, 3.66; N, 5.49%.

Preparation of (2*R*)-1-(2-cyanophenoxy)-3-bromo-2-propanol (50)

To a solution of cyclic sulfate **49** (0.700 g, 2.74 mmol) in dry THF (15 ml) was added anhydrous LiBr (1.413 g, 16.44 mmol) and the resulting reaction mixture was stirred for 40-50 minutes (monitored by TLC for the disappearance of cyclic sulfate) at 25^0C. After completion of the reaction, solvent was removed under reduced pressure. In the resulting residue diethyl ether (25 ml) and 20% H_2SO_4 (25 ml) were added and stirred at 25^0C for 4-5 h (monitored by TLC). After completion of the reaction, the two layers were separated. The aqueous layer was extracted with diethyl ether (3 x 25 ml), combined organic extracts were then washed with saturated $NaHCO_3$, water and brine, dried over anhydrous sodium sulfate and the solvent

evaporated under reduced pressure to give the crude bromoalcohol. It was purified by column chromatography eluting with pet. ether and EtOAc (4:1) to yield 0.595 g of bromoalcohol (**50**) in 85% yield.

Yield: 85%; **gum**; $[\alpha]^{25}_{D}$ − 6.8 (c 1.2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 4214, 3652, 3020, 2399, 2229, 1730, 1600, 1492, 1450, 1375, 1215, 1045, 769, 699; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 2.73 (brs, 1H), 3.65-3.85 (m, 2H), 4.10-4.40 (m, 3H), 6.95-7.15 (dd, *J* = 8.0 Hz, 2H), 7.50-7.70 (t, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.33, 68.78, 69.88, 101.90, 112.33, 116.05, 121.30, 133.47, 134.32, 159.68; **Analysis**: $C_{10}H_{10}NBrO_2$ requires C, 46.90; H, 3.93; N, 5.46; Br, 31.20; found C, 46.84; H, 3.83; N, 5.42; Br, 31.30 %.

Preparation of (2*S*)-1-(2-cyanophenoxy)-1,2-epoxypropane (51)

The bromoalcohol (**50**) (0.540 g, 2.11mmol) was dissolved in MeOH (20 ml) and treated with anhydrous K_2CO_3 (1.173 g, 8.5 mmol) at 0^0C. The resulting reaction mixture was stirred at 0^0C for 2 h (monitored by TLC). After completion the reaction was quenched with the addition of saturated NH_4Cl solution (10 ml) and extracted with CH_2Cl_2 (4 x 15 ml), washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give crude product. It was then purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to afford 0.333 g of pure epoxide **51**, in 90 % yield.

Yield: 90%; **gum**; $[\alpha]^{25}_{D}$ + 2.3 (c 2.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 4217, 3614, 3020, 2399, 2231, 1600, 1514, 1505, 1450, 1290, 1261, 1210, 1045, 1026, 908, 760, 669; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 2.80-2.95 (m, 2H), 3.35-3.45 (m, 1H), 4.05-4.20 (dd, *J* = 6.0 Hz each, 1H), 4.30-4.45 (dd, *J* = 4.0 and 8.0 Hz, 1H), 6.95-7.10 (dd, *J* = 8.0 Hz, 2H), 7.45-7. 65 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 44.29, 49.69, 69.28, 102.07, 112.58, 116.11, 121.26, 133.64, 134.31, 159.96; **MS** (m/z, RI): 175 (M^+, 8), 162 (10), 149 (10), 133 (28), 119 (45), 104 (36), 102 (32), 91 (80), 90 (32), 77 (20), 76 (18), 75 (28), 64 (52), 63 (45), 57 (100), 77 (72); **Analysis**: $C_{10}H_9NO_2$ requires C, 68.56; H, 5.17; N, 7.99; found C, 68.59; H, 5.17; N, 7.98 %.

Preparation of (S)-Bunitrolol (18)

The epoxide **51** (0.310 g, mmol) was dissolved in *t*-butylamine (6 ml) and was refluxed in presence of water (1 drop) for 45 min (monitored by TLC). Excess of *t*-butylamine was removed under reduced pressure and the resulting solid product was purified by column chromatography to give pure 0.310 g of (*S*)-Bunitrolol (**18**) in 75% yield.

Yield: 75%; **mp**: 162°C (EtOH) (lit. 163-165°C)[62]; **[α]$^{25}_{D}$** – 10.0 (c 1.4, H_2O); **HPLC**: 60% ee, ChiraSpher NT, λ = 254 nm, {n-hexane/EtOH/MeOH (60:20:20)/ 0.05% NH_3 (25%)}, 0.5 ml/min., Retention time: (S) 9.359 min. (R) 12.354 min.; **IR** ($CHCl_3$, cm^{-1}): 3400, 3019, 2995, 1485, 1410, 2227, 1554, 1490, 1215, 756; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.14 (s, 9H), 2.37 (brs, 1H), 2.70-2.84 (dd, *J* = 4.0 and 6.0 Hz, 1H), 2.86-3.05 (dd, *J* = 4.0 and 6.0 Hz, 1H), 3.80-4.15 (m, 3H), 6.90-7.05 (d, *J* = 8.0 Hz, 2H), 7.45-7.60 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.66, 44.40, 50.64, 67.74, 71.60, 101.89, 112.40, 116.29, 120.89, 133.42, 134.23, 160.37; **Analysis**: $C_{14}H_{20}NO_2$ requires C, 71.76; H, 4.29; N, 5.97; found C, 71.79; H, 4.31; N, 5.98 %.

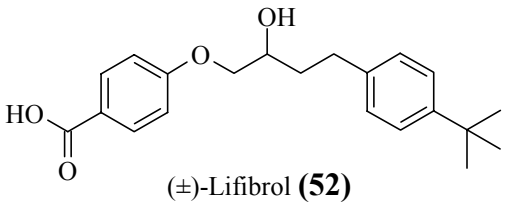
SECTION II:

Asymmetric Synthesis of (*S*)-Practolol and studies towards synthesis of (*S*)-Lifibrol

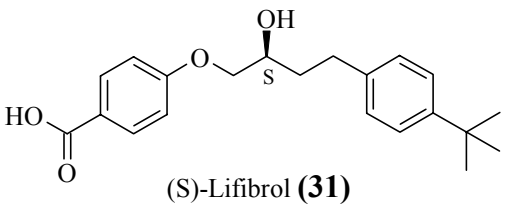
2.1.1 Pharmacology of Practolol and Lifibrol

Practolol (**28**), the β-adrenoceptor blocking drug, was introduced in the market in 1970. Due to its cardio selectivity, it was found to be good for patients who manifested bronchospasm to propanolol.[63] Practolol (**28**) is still available for intravenous administration to treat cardiac arrhythmias.[64] Many doctors obtained confidence in β-adrenergic blockade by using practolol (**52**).

Lifibrol (**52**) is a new hypocholesterolemic compound. It effectively lowers total cholesterol, low-density lipoprotein (LDL) cholesterol.[65a] In addition, it reduces lipoprotein, serum triglycerides, and fibrinogen.[65b] It is a novel lipid-lowering agent. Thus, lifibrol appears to be a multivalent anti-atherosclerotic agent.[65c] Similar to lovastrain, lifibrol had no effect on



(±)-Lifibrol **(52)**



(S)-Lifibrol **(31)**

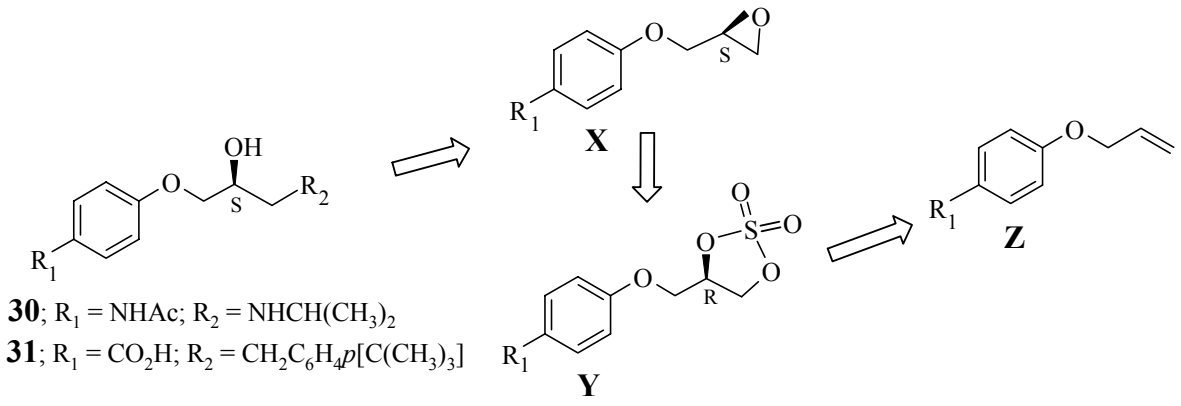
Fig. 13

the synthesis of sterols from [14C]-mevalonic acid. Instead, cholesterol synthesis inhibition by lifibrol was entirely accounted for by competitive inhibition of HGA-CoA synthase. The stimulation of LDL receptors was significantly stronger than expected from the effect of Lifibrol on sterol synthesis. In parallel to the receptor-mediated endocytosis of LDL, Lifibrol increased the amounts of LDL receptor *m*RNA and have immunologically detectable receptor protein **(Fig. 13)**.

2.1.2 Present Work:

2.1.2.1 Objective

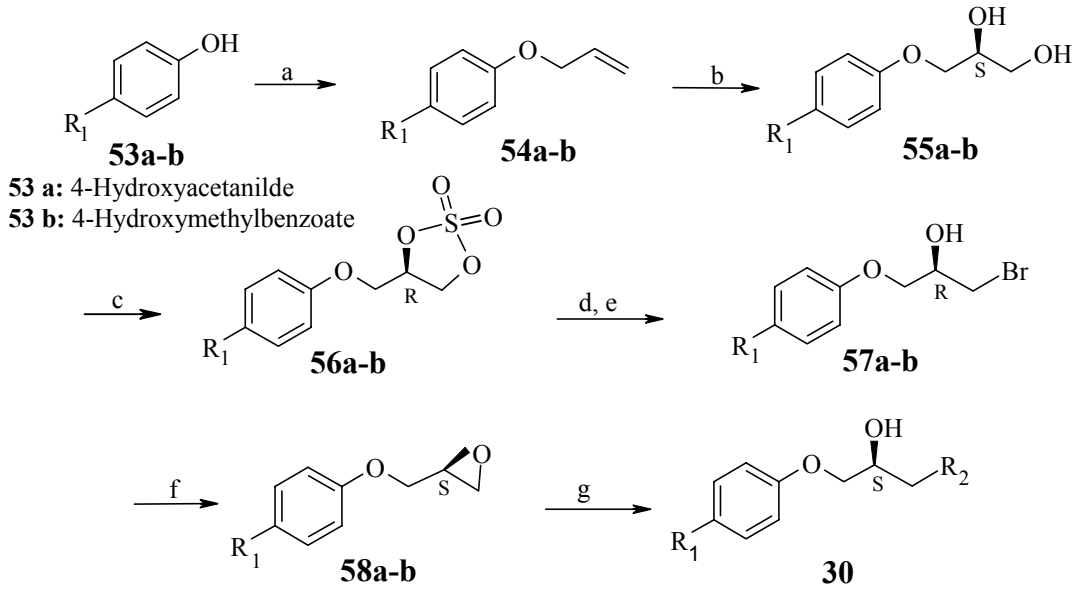
Due to the lack of suitable methods for the asymmetric synthesis of Practolol (**28**) and Lifibrol (**52**) and also in view of their high biological activity associated with one of the isomers, their asymmetric synthesis is highly desirable. Consequently, the objective of the present investigation is to synthesize (*S*)-Practolol (**30**) and (*S*)-Lifibrol (**31**) using Sharpless Asymmetric Dihydroxylation (AD) as a key step. The retro-synthetic analysis of (*S*)-Practolol (**30**) and (*S*)-Lifibrol (**31**) is given in **Scheme 26**.



Scheme 26: Retro-synthetic analysis of (*S*)-Practolol and (*S*)-Lifibrol.

2.1.3 Results and Discussion

The present strategy for the asymmetric synthesis of (*S*)-Practolol (**30**) and (*S*)-Lifibrol (**31**) is depicted in **Scheme 27**. Our approach for the synthesis of (*S*)-Practolol (**30**) and (*S*)-Lifibrol (**31**) is based on the disconnection route b, which results in two chiral synthons (**X** and **Y**) (epoxide **58a-b** and cyclic sulfate **56a-b**), both of which are accessible using AD method. As can be seen, Os-catalyzed Asymmetric Dihydroxylation of olefins constitutes the key step for introducing stereogenecity into the target molecules.



	R_1	R_2	% ee
(*S*)-Practolol (**30**)	-NHAc	-NHiPr	75 %
(*S*)-Lifibrol (**31**)	$-CO_2CH_3$		

Scheme 27: a) K_2CO_3, allyl bromide, acetone, 56°C, 12 h, 95-97%; b) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 25°C, 12 h, 85-90%; c) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min, 90-96%; cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min, 86-88%; d) anhyd. LiBr, THF, 60°C, 45 min; e) 20% H_2SO_4, Et_2O, 4 h; f) K_2CO_3, MeOH, – 10 -15°C, 2 h, 80-85%; g) ^{i}Pr-NH_2, reflux, 5 h, $[\alpha]_D$ – 2.6 (c 1.0, EtOH), 70%.

The first step involves the allylation of phenols **53a-b** with allylbromide to give allyl ethers **54a-b** in >95% yield. Its ^{1}H-NMR spectrum showed pattern typical for the allylic functionality in the region of δ 4.00-6.00. Its ^{13}C-NMR spectrum showed the signals for the carbons of the allylic functionality in the region of δ 68-118.

These allylic ethers **54a-b** were then subjected to the Os-catalyzed Sharpless Asymmetric Dihydroxylation (AD) using $(DHQD)_2$-PHAL [hydroquinidine 1,4-phthalazinediyl diether] as chiral ligand in the presence of $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant to give optically active diols **55a-b**. The ^{1}H-NMR spectrum of the diols showed disappearance of signals for allylic protons in the region of δ 4.0-6.0. Multiplets in the region of δ 3.65-3.80 and δ 4.00-4.15 accounting for 5 protons confirmed the formation of the diols. The IR

spectrum of these diols, showed a broad band in the region of 3400-3500 cm^{-1} indicating the presence of hydroxyl functionality in the molecules. The ^{13}C-NMR spectrum for **55a** showed signals at δ 62.72, 69.80 and 69.86 for the three aliphatic carbons bearing oxo-functionality. Also ^{13}C-NMR spectrum for **55 b** showed signals at δ 63.11, 68.94, 70.07 for the three

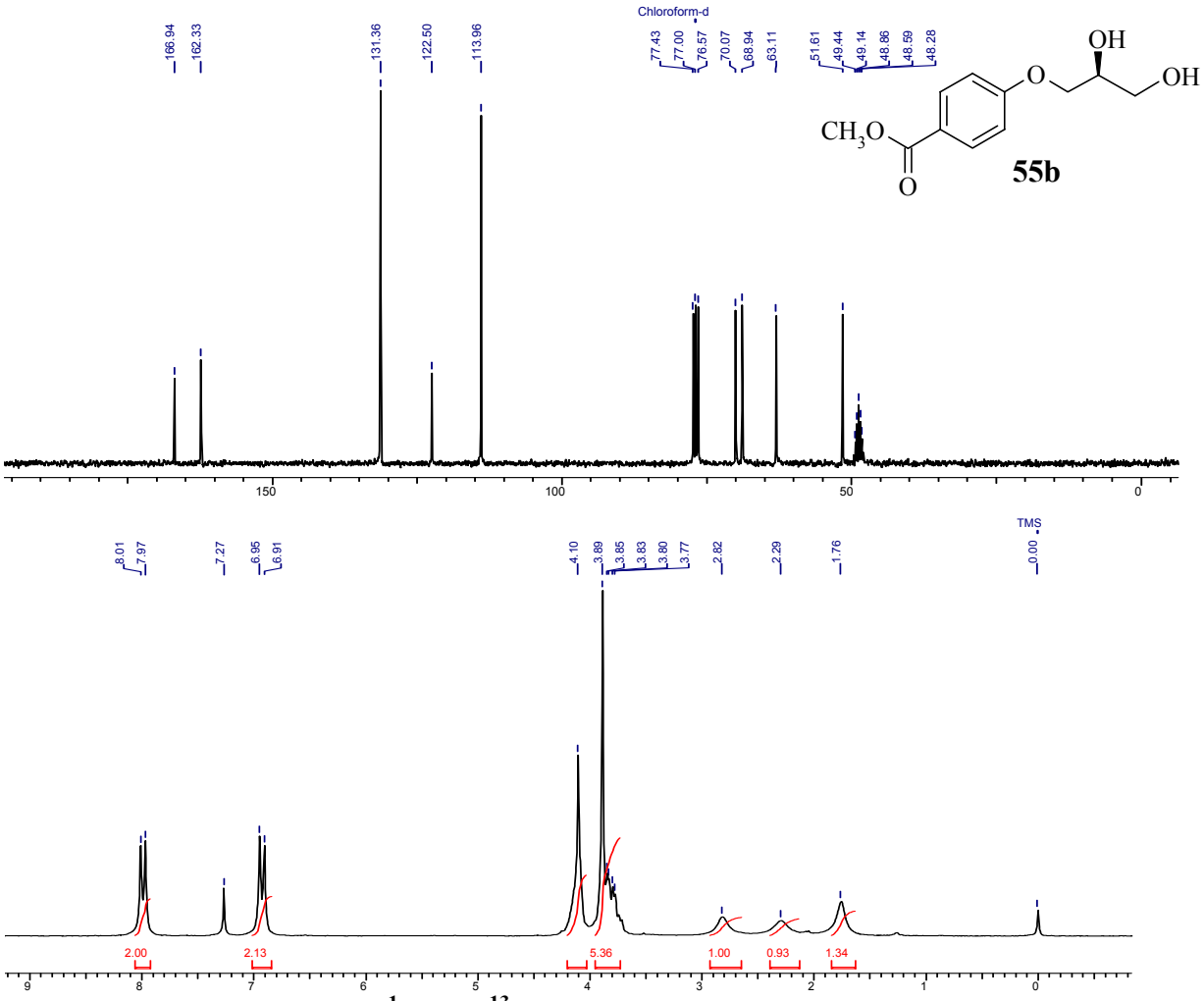


Fig. 14: ^{1}H and ^{13}C-NMR spectra of the diol 55b

aliphatic carbons bearing oxo-functionality **(Fig. 14)**. The optical purity (80% ee) of diol **55a**, was confirmed by HPLC analysis using chiralcel OD-H column **(Fig. 15)**. The optical purity of diol **55b** was found to be 80%, as determined by ^{1}H-NMR spectrum of its Mosher's ester.

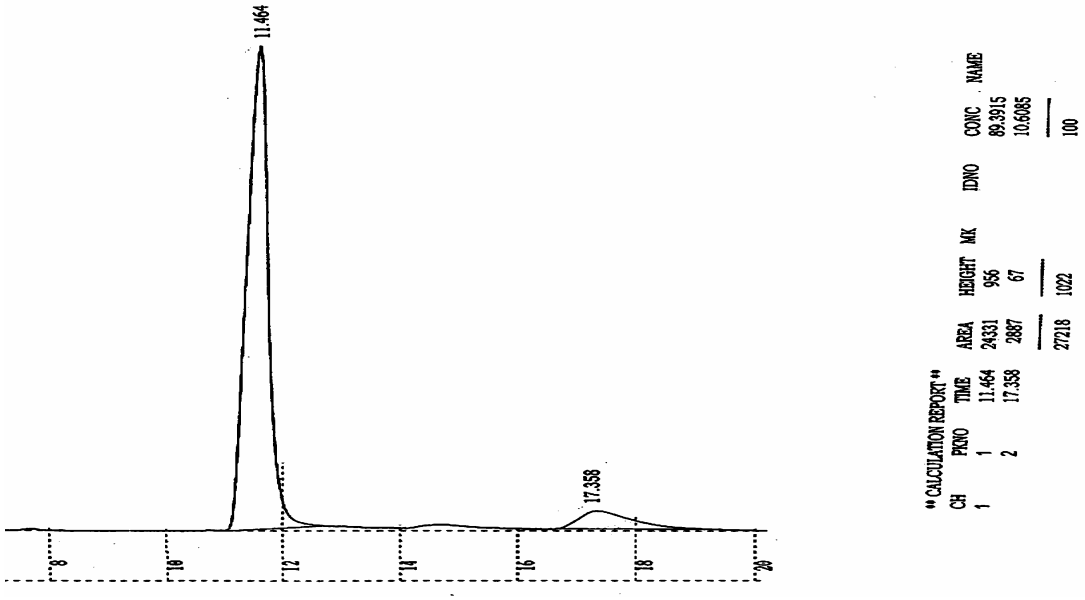


Fig. 15: HPLC chromatogram of the diol 55a

The diols **55a-b** were treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0^0C to afford the corresponding cyclic sulfites in 90-96% yield. The formation of cyclic sulfite was clearly evident from the appearance of multiplets in ^{1}H-NMR spectra in the region δ 4.00-5.50 due to the presence of diastereomeric mixtures. The cyclic sulfites of the corresponding diols were then converted into cyclic sulfates **56a-b** in 86-88% yield using $RuCl_3$ and $NaIO_4$. The ^{1}H-NMR spectrum of cyclic sulfates **56a-b** confirmed the disappearance of multiplets in the region δ 4.25-4.32, 4.72-4.86 and at 5.22-5.26 due to diastereomeric mixtures **(Fig 16)**. The ^{13}C-NMR spectrum of cyclic sulfates **56a-b** also showed simplified patterns because of the absence of diastereomeric mixtures.

Finally, the cyclic sulfate **56a** was subjected to nucleophilic displacement with isopropylamine followed by hydrolysis of the resulting salt afforded the *β*-blocker (**30**) although in low yield (<30%). Hydrolysis of sulphate using various reaction conditions such as 20% H_2SO_4 in ether, 50%

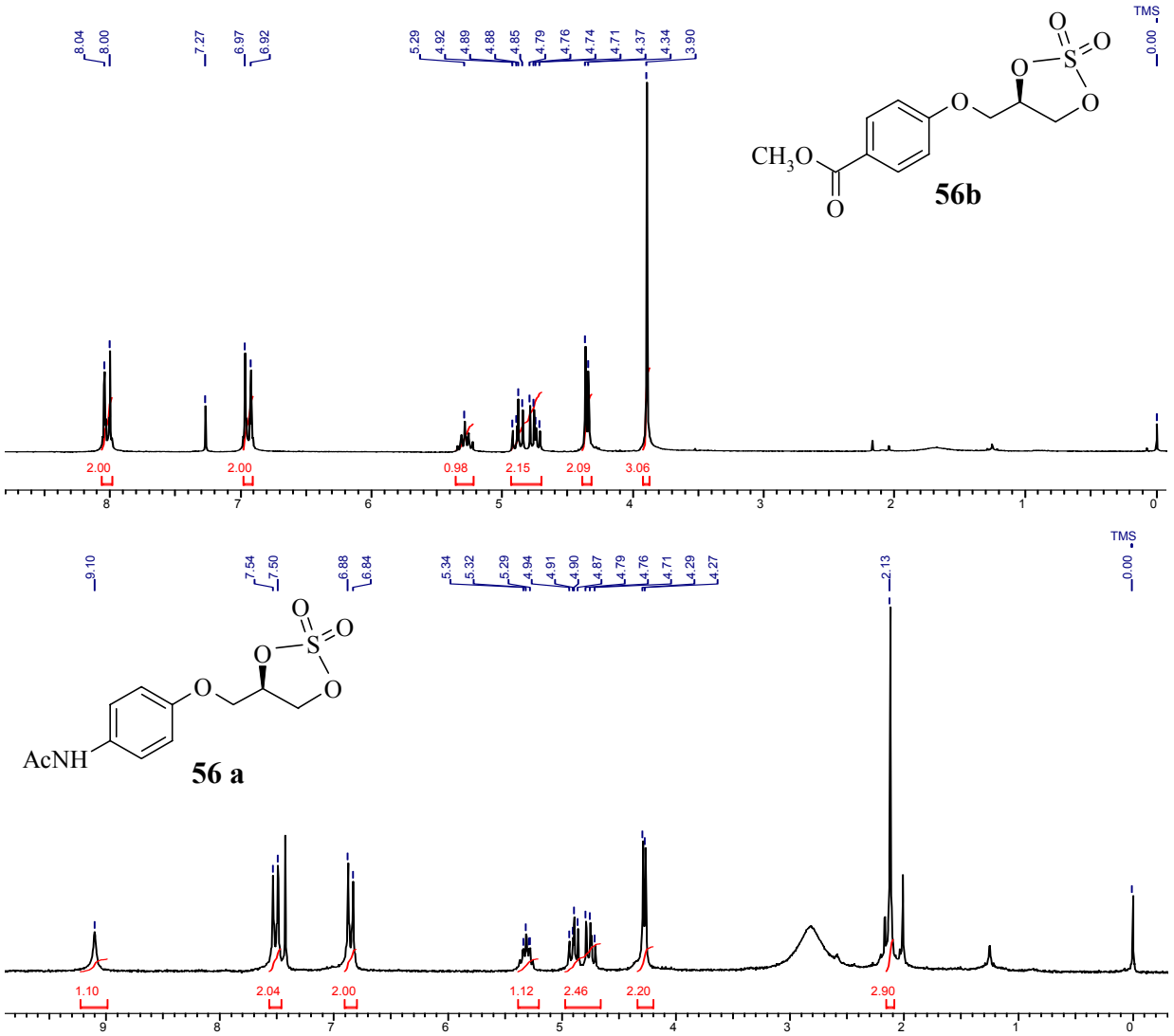


Fig. 16: ^{1}H-NMR spectra of the sulphate 56a-b

H_2SO_4 in ether, 20% HCl, concentrated HCl, 20% aqueous NaOH and 50% *aq*. NaOH were attempted but all of them failed to improve the yield of the final product.

Hence, we decided to convert these cyclic sulfates **56a-b** into the corresponding epoxides **58a-b** using a three-step procedure in high overall yields (80-85% in three steps). Thus, cyclic sulfates **56a-b** were first treated with anhydrous LiBr, then with 20% aqueous H_2SO_4 in ether to give bromoalcohol **57a-b**. It was then treated with K_2CO_3 in MeOH at 0^0C to afford the corresponding epoxides **58a-b**. The ^{1}H-NMR of **58b** showed two doublet of doublet at δ 3.95-4.05 and δ 4.25-4.35 which indicates the presence of

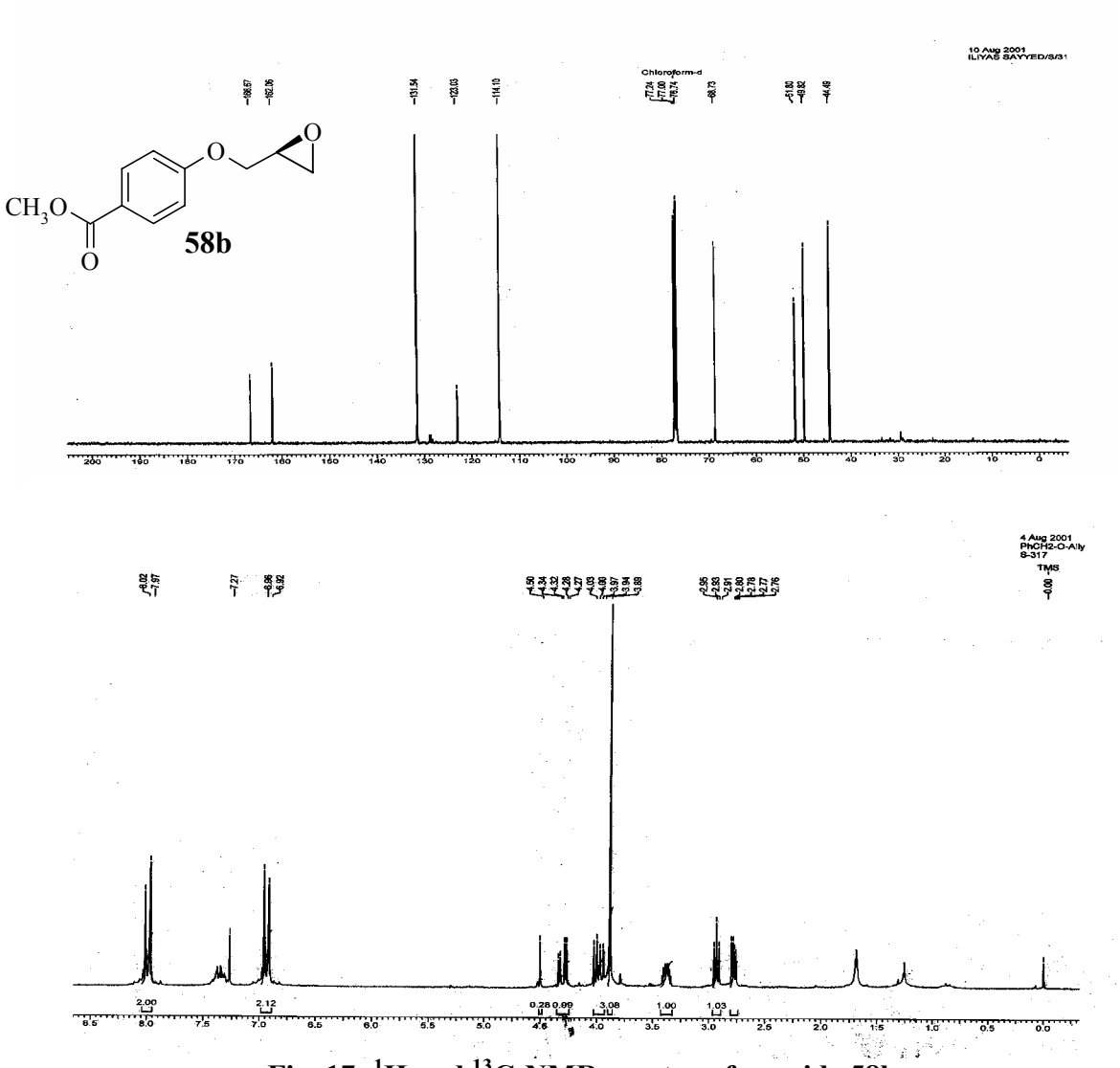


Fig. 17: ^{1}H and ^{13}C-NMR spectra of epoxide 58b

the epoxide functionality. The ^{13}C-NMR spectrum showed the typical signals at δ 44.49, 49.82 and 68.73 **(Fig. 17)**. By following the similar procedure, the (*S*)-epoxide **58a** was obtained in 76% optical purity, [{$[\alpha]_D$ +14.0 (c 2.0, EtOH); lit.[59] $[\alpha]^{25}_{D}$ – 18.5 (c 2.0, EtOH)} for (*R*)-epoxide].

The epoxide **58a** was then subjected to regiospecific nucleophilic attack with isopropyl amine to furnish the (*S*)-Practolol (**30**) in 75% ee {$[\alpha]_D$ – 2.6 (c 1, EtOH); lit.[59] $[\alpha]^{25}_{D}$ + 3.5 (c 1.0, EtOH) for (*R*)-Practolol} and 70% yield. Its ^{1}H-NMR spectrum showed a doublet at δ

0.95 for two methyl of isopropyl group and multiplets in the region δ 3.50-3.70 and δ 3.80-4.15 confirming the formation of (*S*)-practolol (**30**) **(Fig 18)**.

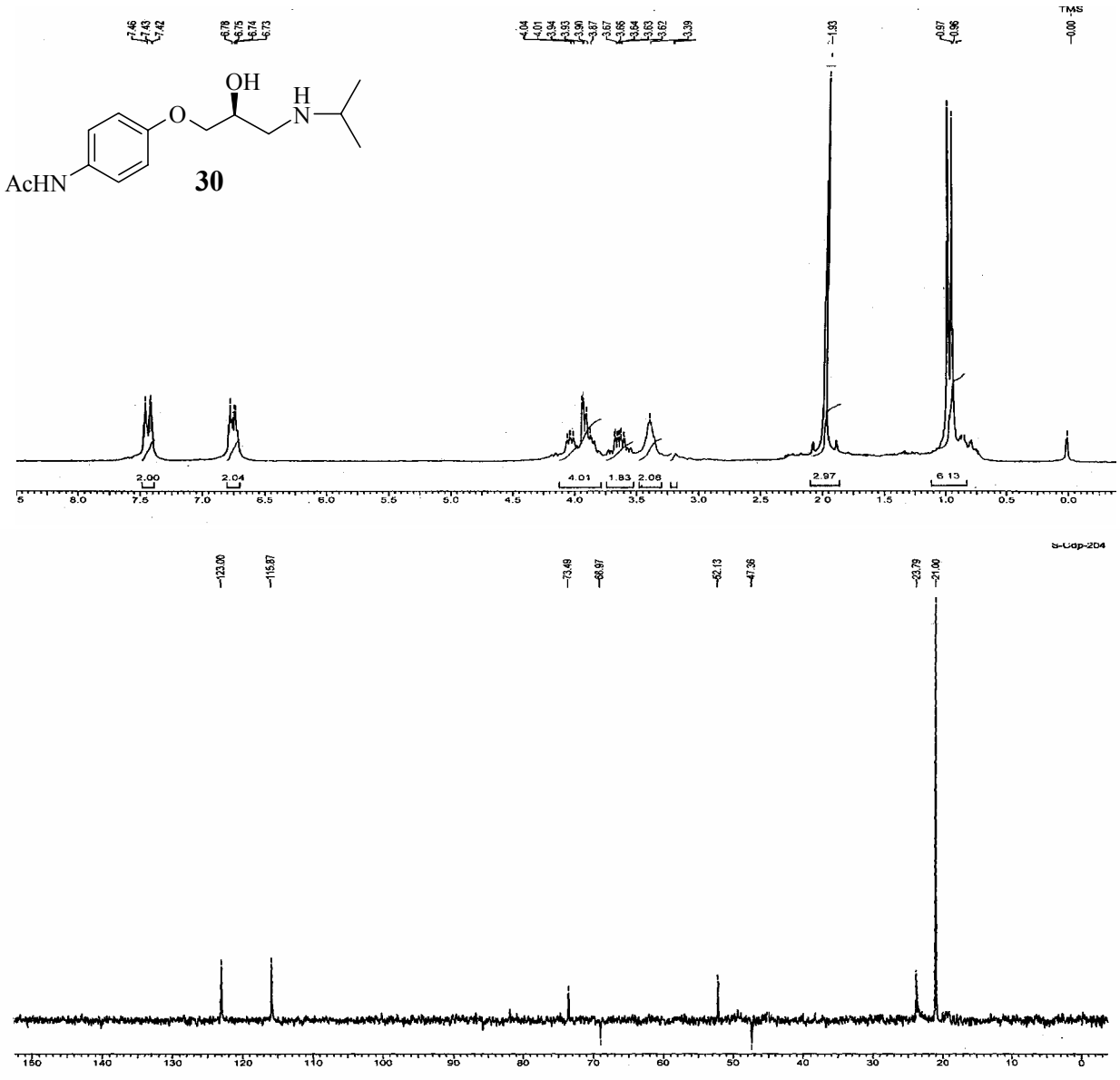


Fig. 18: ^{1}H and ^{13}C-NMR (DEPT) spectra of (S)-Practolol 30

However, various attempts to open the epoxide **58b** with Grignard's reagent prepared from 4-tert-butylbenzyl bromide and magnesium in the presence of CuCN as catalyst failed to afford (*S*)-Lifibrol (**31**).

2.1.4 Conclusion

In conclusion, we have developed a simple and efficient method for the asymmetric synthesis of *β*-blocker namely (*S*)-practolol (**30)** [31.11% overall yield, 82% ee], and intermediate for (*S*)-lifibrol (**31**) in eight steps starting from the corresponding phenols **53a-b**. We have also demonstrated a simple and efficient method for the conversion of cyclic sulfates **56a-b** to the corresponding epoxides **58a-b** in high yields using a three-step procedure.

2.1.5 Experimental Section

Preparation of allyl phenyl ethers 54a-b

A mixture of phenols **53a-b** (10 mmol), allylbromide (1.45 g, 12 mmol) and anhydrous K_2CO_3 (2.07 g, 15 mmol) in dry acetone (20 ml) was refluxed under N_2 for 20 h (reactions monitored by TLC). The reaction mixture then cooled to room temperature, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to get pure allyl phenyl ethers **54 a-c** in 95-97% yield.

Allyl-(4-acetamidophenoxy) ether (54a): Yield: 95%; **mp:** 100-102^{o}C (EtOAc and hexane); **IR** ($CHCl_3$, cm^{-1}): 3298, 3020, 2962, 1685, 1605, 1589, 1514, 1435, 1280, 1217, 1118, 850; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.14 (s, 3H), 4.51 (d, *J* = 6.0 Hz, 2H), 5.20-5.50 (dd, *J* = 12.0 and 16.0 Hz, 2H), 5.95- 6.20 (two dd, *J* = 4.0 and 6.0 Hz, 1H), 6.80-6.95 (d, *J* = 8.0 Hz, 2H), 7.30-7.45 (d, *J* = 8.0 Hz, 2H), 7.50-7.65 (brs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 33.09, 72.34, 79.17, 79.48, 123.79, 130.23, 141.80, 164.14, 177.26; **Mass** (m/z, RI): 191 (M^+, 18), 190 (6), 150 (12), 149 (5), 109 (11), 108 (100), 95 (3), 80 (12), 65 (4), 57 (5); **Analysis**: $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.84; N, 7.32; found 69.13; H, 6.87; N, 7.32%.

Allyl-(4-methylcarboxyphenoxy) ether (54b): Yield: 97%; **gum; IR** (neat, cm^{-1}): 3410, 3082, 2994, 2953, 1718, 1606, 1580, 1511, 1435, 1376, 1281, 1251, 1170, 1112, 1014; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.57 (d, *J* = 6.0 Hz, 2H), 5.20-5.50 (dd, *J* = 10 .0 and 16.0 Hz, 2H), 5.90-6.15 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.56, 68.62, 114,13, 117.76, 122.54, 131.36, 132.43, 162.17, 166.34; **Mass** (m/z, RI): 192 (M^+, 6), 161 (4), 133 (8), 132(5), 120 (15), 105 (16), 104 (18), 92 (32),

76 (25), 65 (56), 64 (80), 62 (100); **Analysis**: $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.28; found C, 68.75; H, 6.21%.

Preparation of diols 55a-b

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (5.92 g, 18.0 mmol), K_2CO_3 (2.48 g, 18.0 mmol), $(DHQD)_2$-PHAL (0.192 g, 0.24 mmol) and *t*-BuOH : H_2O (1:1, 60 ml) and the resulting mixture was stirred for 10 minutes at 25^0C. It was then cooled to 0^0C and a solution of OsO_4 (256 µl, 0.124 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^0C for 5 minutes and then one of the olefins **54a-b** (6 mmol) was added. The reaction mixture was stirred at 0^0C for 20-22 h (monitored by TLC). It was quenched with sodium sulfite (4.0 g) and extracted with ethyl acetate (4 x 25 ml). Combined organic extracts were washed with brine (20 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in pet. ether as eluent to yield pure diols **55a-b** as white solids in 85-90% yield.

(2*S*)-1-(4-Acetamidophenoxy)-2,3-propanediol (55a): Yield: 85%; **mp**: 142-144°C (EtOAc); **$[\alpha]^{25}_D$** + 7.0 (c 1.0, EtOH); **HPLC**; 80% ee, Chiralcel OD-H, λ = 254 nm, 10% 2-propanol/hexane, 1 ml/min, Retention time: (S) 11.464. (R) 17.358 min.; **IR** ($CHCl_3$, cm^{-1}): 3321, 3240, 3138, 3077, 2941, 2882, 1663, 1604, 1554, 1514, 1414, 1284, 1254, 1113, 1050; **^{1}H-NMR** (200 MHz, DMSO-D_6): δ 2.10 (s, 3H), 3.60-3.75 (m, 2H), 3.90-4.05 (m, 3H), 4.24 (brs, 1H), 4.45 (brs, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 9.35 (brs, 1H); **^{13}C-NMR** (50 MHz,): δ 23.47, 62.72, 69.80, 69.86, 114.17, 120.61, 132.18, 154.52; **Mass** (m/z, RI): 225 (M^+, 10), 183 (4), 151 (16), 135 (4), 117 (5), 110 (8), 109 (100), 108 (15), 93 (7), 74 (4), 65 (8), 60 (6), 57 (15); **Analysis**: $C_{11}H_{15}NO_4$ requires C, 58.66; H, 6.70; N, 6.21; found C, 58.63; H, 6.79; N, 6.26%.

(2*S*)-1-(4-Methylcarboxyphenoxy)-2,3-propanediol (55b): Yield: 90%; **mp:** 80-84°C (EtOAc); **$[\alpha]^{25}_D$** + 10.38 (c 1.3, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3453, 3020, 1713, 1607, 1511, 1437, 1397, 1286, 1252, 1172, 1114, 985, 816, 668; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.30 (brs, 1H), 2.83 (brs, 1H), 3.70-3.85 (m, 2H), 3.90 (s, 3H), 4.05-4.25 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.61, 63.11, 68.94, 70.07, 113.96, 122.50, 131.36, 162.33, 166.94; **Mass** (m/z, RI): 226 (M^+, 12), 195 (7), 165 (7), 152

(35), 135 (8), 121 (100), 105 (6), 93 (20), 77 (12), 65 (30), 57 (15); **Analysis**: $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.23; found C, 58.43; H, 6.22%.

Preparation of Mosher ester of diol 55b

A two-neck 25 ml flask with septum was charged with (22 mg, 0.103 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (5 ml) under argon atmosphere. The flask was allowed to cool at 0^oC for 10 min and a solution of diol **55b** (12 mg, 0.089 mmol) in CH_2Cl_2 (5 ml) was introduced through syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (23 mg, 0.098 mmol) in CH_2Cl_2 was done. This reaction mixture was then stirred at 0^oC for additional one hour and then at room temperature for overnight. The solvent was evaporated under reduced pressure to get crude material, which was then purified by column chromatography eluting with 5% ethyl acetate in pet. ether to get Mosher ester of the diol (14 mg).

Yield: 70%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.47 (s, 0.6H), 3.56 (s, 2.4H), 3.90 (s, 3H), 4.01 (d, *J* = 6.0 Hz, 2H), 4.25-4.40 (m, 1H), 4.50-4.60 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 7.25-7.60 (m, 5H), 8.00 (d, *J* = 8.0 Hz, 2H).

Preparation of cyclic sulfates 56a-b

[A] To a solution of one of the diols **55a-b** (4 mmol) and triethylamine (2.21 ml, 16 mmol) in CH_2Cl_2 (10 ml) at 0^0C was added freshly distilled thionyl chloride (ml, 6 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0^0C for 30-45 minutes (monitored by TLC). The reaction mixture was quenched by the addition of cold water (10 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 25 ml). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure yielded pale yellow colored liquid, which was purified by the column chromatography using 10% EtOAc in pet. ether as an eluent to afford the corresponding cyclic sulfite as viscous yellow liquid in 90-96% yield.

[B] To a solution of one of the cyclic sulfites (3 mmol) in CH_3CN: H_2O mixture (9: 1, 8 ml) at 0^0C was added solid $NaIO_4$ (0.963 g, 4.5 mmol) and $RuCl_3.3H_2O$ (0.012 g, 0.06 mmol). The reaction mixture was stirred for 30-40 minutes at 0^0C (monitored by TLC). After

the reaction was completed, it was filtered through a pad of celite. Solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to afford cyclic sulfates **56a-b** in 86-88% yield.

(4*R*)-4-(4-Acetamidophenoxy)-1,3,2-dioxathiolane-2,2-dioxide (56a): Yield: 86%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3409, 3018, 1652, 1627, 1419, 1215, 1053, 1029, 757; **^{1}H-NMR** (200 MHz, DMSO-D_6): δ 2.13 (s, 3H), 4.28 (d, *J* = 4 .0 Hz, 2H), 4.70-4.80 (dd, *J* = 2.0 and 6.0 Hz, 1H), 4.86-4.95 (dd, *J* = 2.0 Hz and 6.0 Hz) 5.20-5.40 (m, 1H), 6.84-6.88 (d, *J* = 8.0 Hz, 1H), 7.50-7.54 (d, *J* = 8.0 Hz, 2H), 9.10 (s, 1H); **^{13}C-NMR** (50 MHz,): δ 23.61, 67.80, 70.99, 81.99, 116.10, 123.08, 156.16, 158.70, 171.56; **Analysis**: $C_{11}H_{13}NSO_6$ requires C, 45.99; H, 4.55; N, 4.87; S, 11.16; found C, 51.93; H, 4.47; N, 4.82; S, 11.13%.

(4*R*)-1-(4-Methylcarboxyphenoxy)-1,3,2-dioxathiolane-2,2-dioxide (56b): Yield: 88%; **mp**: 120-122^{o}C (benzene); **$[\alpha]^{25}_D$** + 19.35 (c 1.1, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3443, 3019, 1710, 1605, 1287, 1254, 1216, 1171, 760, 669; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.36 (d, *J* = 6.0 Hz, 2H), 4.70-4.80 (dd, *J* = 6.0 Hz each, 1H), 4.85-4.92 (dd, *J* = 6.0 Hz each, 1H), 5.29 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.75, 65.61, 69.32, 78.98, 114.09, 123.68, 131.51, 160.99, 166.62; **Mass** (m/z, RI): 288 (M^+, 44), 257 (100), 165 (15), 152 (6), 137 (7), 135 (12), 121 (30), 104 (10), 92 (15), 76 (18), 57 (20); **Analysis**: $C_{11}H_{12}SO_7$ requires C, 45.83, H, 4.19; S, 11.12; found C, 45.76, H, 4.22; S, 11.19%.

Preparation of bromo alcohols 57a-b

To a solution of the cyclic sulfates **56a-b** (2.5 mmol) in dry THF (15 ml) was added anhydrous LiBr (1.04 g, 12 mmol) and the resulting reaction mixture was stirred for 40-50 minutes (monitored by TLC for the disappearance of cyclic sulfate) at 25^{0}C. After completion of the reaction the solvent was removed under reduced pressure. In the resulting residue diethyl ether (25 ml) and 20% H_2SO_4 (25 ml) were added and stirred at 25^{0}C for 4-5 h (monitored by TLC). After completion of the reaction the two layers were separated, the aqueous layer extracted with diethyl ether (3 x 15 ml), combined organic extracts were washed with saturated $NaHCO_3$, water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the corresponding bromoalcohols.

(2*R*)-3-(4-Acetamidophenoxy)-3-bromo-2-propanol (57a): Yield: 80%; **gum; $[\alpha]^{25}_{D}$** + 3.1 (c 2.8, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3382, 3018, 1652, 1419, 1215, 1022, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.07 (s, 3H), 3.54 (t, *J* = 2.0 and 4.0 Hz, 2H), 3.97 (d, *J* = 4.0 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.52 (brs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.61, 35.38, 70.70, 71.21, 115.88, 123.11, 133.37, 156.93, 171.49; **Mass** (m/z, RI): 290 (M^{+1}, 6), 289 (5), 287 (M^+, 12), 286 (10), 245 (9), 208 (3), 207 (4), 166 (4),165 (4), 151 (8), 150 (8), 123 (5), 121 (5), 109 (90), 108 (100), 92 (10), 91 (10), 80 (22), 64 (20); **Analysis**: $C_{11}H_{14}NBrO_3$ requires C, 45.85; H, 4.89; N, 4.86; Br, 27.73; found C, 45.88; H, 4.81; N, 4.86; Br, 27.74%.

(2*R*)-3-(4-Methylcarboxyphenoxy)-3-bromo-2-propanol (57b): Yield: 85%; **gum**: **$[\alpha]^{25}_{D}$** + 2.7 (c 1.6, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3448, 3014, 2950, 1710, 1605, 1512, 1436, 1286, 1255, 1170, 1112, 1035, 484; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.69 (brs, 1H), 3.64 (t, *J* = 4.0 and 2.0 Hz, 2H), 3.89 (s, 3H), 4.10-4.30 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.54, 51.75, 69.21, 69.39, 114.09, 123.06, 131.48, 161.91, 166.73; **Mass** (m/z, RI): 290 (M^+, 15), 289 (15), 259 (5), 257 (5), 195 (4), 177 (6), 165 (28), 153 (21), 152 (38), 135 (20), 121 (100), 104 (12), 93 (21), 76 (21), 65 (20), 57 (18); **Analysis**: $C_{11}H_{13}BrO_4$ requires C, 45.69; H, 4.52; Br, 27.63; found C, 45.61; H, 4.52; Br, 27.64%.

Preparation of epoxides 58a-b

The crude bromoalcohols (2 mmol) were dissolved in MeOH (20 ml) and treated with anhydrous K_2CO_3 (1.10g, 8 mmol) at 0^0C. The resulting reaction mixture was stirred at 0^0C for 2 h (monitored by TLC). After completion of the reaction, it was quenched by the addition of saturated NH_4Cl solution (10 ml) and extracted with CH_2Cl_2 (4 x 15 ml), washed with water and brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give crude product. It was then purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to give pure epoxides **58 a-b** as oil in 80-85% yield.

(2*S*)-3-(4-Acetamidophenoxy)-1,2-epoxypropane (58a): Yield: 80%; **mp**: 104^{o}C (EtOAc and hexane); **$[\alpha]^{25}_{D}$** + 14.0 (c 2.0, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3299, 2931, 1664, 1604, 1540, 1510, 1411, 1240, 1038, 828; **^{1}H-NMR** (200 MHz, $CDCl_3$)): δ 2.15 (s, 3H), 2.76-2.78 (dd, *J* = 5.0 and 3.0 Hz, 1H), 2.89-2.94 (dd, *J* = 5.0 and 3.0 Hz, 1H), 3.25-3.45 (m, 1H), 3.85-4.10 (dd, *J* = 8.0 and 5.0 Hz, 1H), 4.15-4.40 (dd, *J* = 8.0 and 5.0 Hz, 1H), 6.85-6.95 (d, *J* = 8.0 Hz, 2H),

7.40-7.55 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 24.03, 44.58, 50.13, 68.91, 114.82, 121.92, 131.51, 154.78, 168.75; **Analysis**: $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.31; N, 6.75; found C, 63.77; H, 6.35; N, 6.66%.

(2*S*)-3-(4-Methylcarboxyphenoxy)-1,2-epoxypropane (58b): Yield: 85%; **gum**; **$[\alpha]^{25}_D$** + 4.85 (c 2.1, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3019, 2931, 2400, 1713, 1606, 1511, 1436, 1285, 1215, 1171, 1036, 755; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.75-2.82 (dd, *J* = 4.0 Hz each, 1H), 2.94 (t, *J* = 4.0 and 6.0 Hz, 1H), 3.33-3.43 (m, 1H), 3.89 (s, 3H), 3.95-4.03 (dd, *J* = 6.0 Hz each, 1H), 4.26-4.35 (dd, *J* = 4.0 Hz each, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 44.49, 49.82, 51.80, 68.73, 114.10, 123.03, 131.54, 162.06, 166.67; **Analysis**: $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.80; found C, 63.44; H, 5.83%.

Preparation of (*S*)-Practolol (30)

The epoxide **58 a** (0.208 g, 2 mmol) was dissolved in isopropylamine (10 ml) and kept for reflux for 4 -5 hrs till all starting material disappeared. Evaporation of isopropylamine gave crude oil, which was purified by column chromatography to give a white solid which on crystallization from dioxane yielded pure (*S*)-Practolol (**30**) (0.186 g), in 70% yield.

(*S*)-1-(4-Acetamidophenoxy)-3-(isopropylamino)propan-2-ol: Yield: 70%; **mp:** 125°C (dioxane); lit: 128-129°C; {**$[\alpha]^{25}_D$** – 2.6 (c 1.0, EtOH); lit.[59] **$[\alpha]^{25}_D$** + 3.5 (c 1.0, EtOH) for (*R*)-Practolol}; **IR** ($CHCl_3$, cm^{-1}): 3314, 3284, 2975, 2359, 1715, 1665, 1511, 1398, 1220, 1040, 769; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.0 Hz, 6H), 1.93 (s, 3H), 3.30-3.50 (m, 2H), 3.55-3.70 (m, 1H), 3.80-4.10 (m, 4H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.76, 45.04, 49.90, 52.14, 69.08, 73.53, 115.95, 123.08, 133.76, 156.35, 171.49; **Mass** (m/z, RI): 248 (4), 222)3), 178 (5), 151 (40), 136 (20), 109 (100), 98 (15), 91 (10), 80 (32), 64 (60); **Analysis**: $C_{14}H_{22}NO_3$ requires C, 63.14; H, 8.31; N, 10.51; found C, 63.10; H, 8.25; N, 11.02%.

2.1.6 References

1. Friedrich, K.; Wallensfels, K, *In The Chemistry of Cyano Group*; Rappoport, Z, Ed.; Wiley-Interscience: New York, **1970**.
2. Mowry, D.T. *Chem. Rev*. **1948**, *42*, 250.
3. Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. *Synth*. *Commun*. **1996**, *26*, 4351.

4. March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, **1992**, 918.
5. a) Fatiadi, A. J, *The Chemistry of triple bonded functional group* Part 2, Ed by S. Patai and Rappoport, John Wiley and Sons, New York, **1983**, 1057. b) T, E. Stevens, *J. Org. Chem.* **1961**, *26*, 2531.
6. a) Harrison, I. T, Harrison, S, *In Compendum of Organic Synthetic Methods*, Interscience Publishers, New York, **1971**, 1, 457, **1972**, 2, 185. b) Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1980**, 659. c) Saednya, A. *Synthesis* **1983**, 748.
7. Erman, M. B.; Snow, J. W. *Tetrahedron Lett.* **2000**, *35*, 6749.
8. Parameswaran, K. N.; Friedman, O. M. *Chem. Ind.* **1965**, 988.
9. Pomeroy, J. H.; Craig, C. A, 1959. *J. Am. Chem. Soc.* **1959**, *81*, 6340.
10. Talukdar, S.; Hsu, J. L.; Chou, T, C.; Fang, J. M. *Tetrahedron Lett.* **2001**, *42*, 1103.
11. Binkley, R. W. *Tetrahedron Lett.* **1970**, *11*, 2085.
12. Fizet, C.; Streigh. *Tetrahedron Lett.* **1974**, *15*, 3187.
13. Glass, R. S.; Hoy, R. C. *Tetrahedron Lett.* **1976**, *17*, 1781.
14. Olah, G. A.; Keumi, T. *Synthesis* **1979**, 112.
15. Suzuki, H.; Nakaya, C. *Synthesis* **1992**, 641.
16. Baxendale, I. R.; Steven, L. V.; Sheddon, H. F. *Synlett*. **2002**,
17. Miller, M.; Loudon, G. S. *J. Org. Chem*. **1975**, *40*, 126.
18. Elmorsy, S. S.; El-Ahl, A. A. S.; Soliman, H.; Amir, F, A. *Tetrahedron Lett.* **1995**, *36*, 2639.
19. Sasnovsky, G.; Krogh, J. A.; Umhoeter, G. S. *Synthesis* **1979**, 722.
20. Fernandez, R.;Gasch, C.; Lassdetta, J. M.;Liera, J. M.; Yazqwez, J. *Tetrahedron Lett.* **1993**, *34*, 141.
21. Capdevielle, P.; Lavigne, A.; Mavmy, M. *Synthesis* **1989**, 451.
22. Imran, M. B.; Snow, J. S.; Williams, M. J. *Tetrahedron Lett.* **2000**, *35*, 6749.
23. George, G. I.; Pfeifer, S. A. *Tetrahedron Lett.* **1985**, *26*, 2739.
24. Kamal, A.; Arifuddin, M.; Venugopal Rao, N. *Synth. Commun*. **1998**, *28*, 4577.
25. Wang, E. C.; Lin, G-J. *Tetrahedron Lett.* **1998**, *39*, 4047.
26. Atamura, A.; D'Accothi, L.; Defomass, A.; Dinoi, A.; Fioretino, M.; Fusco, C.; Curki, R. *Tetrahedron Lett.* **1988**, *38*, 2009.
27. Chakrobarthi, A. K.; Kaur, K. G. *Tetrahedron* **1999**, 13266.

28. Das, B. *Synlett*. **2000**, *11*, 1599.
29. Ali, I. S.; Nikalje, M. D.; Dewkar, G. K.; Paraskar, A. S.; Jagtap, H. S. Sudalai, A.; *J. Chem. Res.(S)*. **2000**, 30.
30. Stinson, S.C. *C and EN*, **1998**, *77* (*September 21*), 83.
31. a) Kolb H. C.; VanNieuwenhze, M, S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. b) Johnson, R. A. Sharpless K. B. In "*Catalytic Asymmetric Synthesis*" Ojima I. (Ed.); VCH Publishers (New York), **1993,** Chap. 4, pp. 227-270.
32. Johnson, R. A.; Sharpless K. B. In "*Catalytic Asymmetric Synthesis*" Ojima I.; (Ed.); VCH Publishers (New York), **1993,** Chap. 4, pp. 227-270.
33. a) Jacobsen E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737. b) Kolb, H. C.; Anderson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K. S.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.
34. a) Kolb H. C.; Van-Nieuwenhze, M, S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
35. a) Criegee, R.; *Justus Liebigs Ann. Chem.* **1996**, *522*, 75. b) Criegee, R. *Angew. Chem. Int. Ed. Engl.* **1937,** *50*, 153. c) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liegs*. *Ann. Chem.* **1942**, *550*, 99. d) Sharpless, K. B.; Teranishi, A. Y.; Backwall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120. e) Jorgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483.
36. Gawley, R. A.; Aube, J. In "*Principles of Asymmetric Synthesis*" Elesevier Science (Oxford), **1996**, Vol. 14, (Chap. 8), pp 314-350.
37. Hoffman, K. A. *Chem. Ber.* **1912**, *45*, 3329.
38. a) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 1302. b) Milas, N. A.; Trepagnier, J. H.; Nolan, J. T.; Jr. Iliopulos, M. I. *J. Am. Chem. Soc.* **1959**, *81*, 4730.
39. Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986.
40. a) VanRheenen, V.; Kelly, R. C.; Cha. D. Y. *Tetrahedron Lett*. **1976**, *17*, 1973. b) Schneider, W. P.; Mclntosh, A. V.; US 2769284, Nov. 6, **1956**.
41. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
42. Minato, M.; Yamamota, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
43. Sharpless K. B.; Amerg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu. D.; Zhang, X.-L. *J. Org. Chem.* **1992**,

57, 2768.

44. Amerg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless K. B. *J. Org. Chem.* **1993**, *58***,** 844.
45. a) Baker, W.; Field, F. B. *J. Chem. Soc.* **1932**, 86. b) Carlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1952.
46. a) Byun, H. -S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051. b) Lohary, B. B. *Synthesis* **1992**, 1035.
47. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
48. Tellett, J. G. *Phosphorous Sulfur* **1976,** 1341.
49. Poorker, C. S.; Kagan, J. *Tetrahedron Lett.* **1985**, *26*, 6405.
50. Breslow, D. S.; Skolnik, H. In "*Heterocyclic Compounds"* Wiley Interscience, **1966**, p 1, and references cited therein.
51. a) Barret, C. *Brit. J. Pharmacol.* **1968**, *34*, 43. b) Hansteen, V. *Brit. Med. J.* **1982**, *284*, 155. c) Fitzgerald, J. D. In *"Pharmacology of Antihypertensive Drugs"* Acriabine, A.; (Ed.), Raven Press, NY, **1980**, p 195.
52. a) Howe, S. *Nature* **1966**, *210*, 1336. b) Leftheris, K.; Goodman, M. J. *J. Med. Chem.* **1990**, *33*, 216. c) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.
53. Hanson, R. M. *Chem*. *Rev*. **1991**, *119*, 437.
54. Taylor, S. M.; Grimm, R. H. *J. Am. Heart*. J. **1990**, *119*, 655.
55. a) Leftheris, K. Goodmann, M. J. *J. Med. Chem*. **1990**, *33*, 216. b) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem*. *Pharm. Bull*. **1987**, *35*, 3691.
56. Zhenya, H.; *Gongye, Y*. **1987**, *18*, 339 (Chinese).
57. Apparu, M.; Tiba, Y. B.; Leo, P. M.; Fagret, D. *Eur. J. Org. Chem*. **2000**, *6*, 1007.
58. Thakkar, N. V.; Banerji, A. A.; Berinakatti.; Hanumanthsa, S. *Biotechnology Lett*. **1995**, *17*, 217.
59. Danilewicz, J. C.; Kemp, J. E. G. *J. Med. Che*m. **1973**, *16*, 168.
60. Leftheris, K.; Goodmann, M. *J. Med. Chem*. **1990**, *33*, 216.
61. Rieter, F.; Henschel, H. H. *Eur. Pat. Appl*. EP 518110 A2 16 Dec **1992**. *CA 118: 168821*
62. The Merck Index, 13th Ed. Merck and Co.; Inc. Whitehouse Station NJ.

63. a) Wiseman, R. *Postgrad Med. J*. **1971**, *47*, 68. b) Arcy, P. D. *Iatrogenic Dieseases*, 3rd Ed. (ed. D Arcy and Griffin) **1986**, Oxford Medical Publications.

64. Shanks, R.; *The discovery of beta adrenceptor blocking drugs, in Discoveries in Pharmacology*, **1984**. (ed Parnharm and Bruinvels) Elsevier.

65. a) Winkler, K.; Schaefer, J. R.; Klima, B.; Nuber, C.; Friedrich, I.; Koster, W.; Gierens, H.; Scharnagl, H.; Soufi, M.; Wieland, H.; Marz, W. *Arherosclerosis* **2000**, *150*, 113. b) *Drugs of Future*. **2002**, *27*, 83. c) Scharnagl, H.; Maerz, W.; Winfried, H. *Expert*. *Opin*. *Invest*. *Drugs*, **1997**, *6*, 583.

SECTION I:

Pd-Catalyzed Reductive Ring Opening of Aziridines to Amines *via* Transfer Hydrogenation

3.0.1 Introduction

Aziridines are saturated three membered heterocycles containing one nitrogen atom. This class of compounds dates back to 1888 when Gabriel synthesized the parent member. Like other three membered rings such as cyclopropanes and epoxides, aziridines are highly strained. Ring strain renders aziridines susceptible to ring opening reactions that dominate their chemistry resulting in useful synthetic intermediates that fully deserve a prominent place in the arsenal of the organic chemist.[1] It is well known that the reactivity of NH aziridines **1b** towards nucleophiles is relatively low. Hence, activation by the introduction of the electron-withdrawing group on the nitrogen atom is required. Arenesulfonyl groups such as *p*-toluenesulfonyl (Ts) or methanesulfonyl (Mts) serve as the effective activating groups that can withstand wide range of chemical manipulations.

According to the nature of substituent on nitrogen two types of ring opening reactions occur. First, the non-activated aziridines **1a** contain a basic nitrogen atom and ring-opening reactions usually occur only after protonation, quaternization or formation of Lewis acid adduct **(Fig. 1)**. Second, the activated aziridines **1c** contain a substituent,

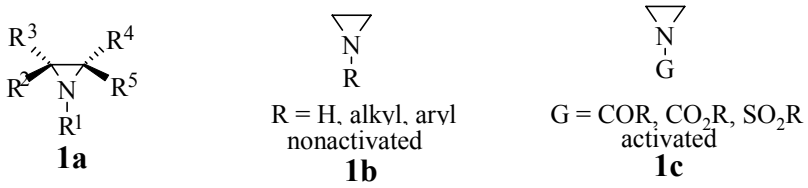


Fig.1

which can conjugatively stabilize the negative charge that develops on the nitrogen atom in the transition state resulting in opening by a nucleophile. If aziridines, whether activated or not are to be used in synthesis, it is of prime importance to control the stereochemistry and regio-chemistry of the ring opening process.[2]

The chemistry and the preparation of enantiomerically pure aziridine-2-carboxylates has been the target of many synthetic efforts for the synthesis of both α or β-amino acids, which are building blocks for biologically important compounds.[3,4] The control of both the stereochemistry as well as the regio-chemistry in the ring opening reactions became very important to make those reactions synthetically useful. The β-amino acids, which are not as common as α-amino acids are present in natural product such as peptides, and exhibit important biological properties.[5,2] β-Amino acids also serve as valuable building blocks for the asymmetric construction of β-lactam antibiotics, which are increasingly employed as chiral building blocks. Moreover, novel β-amino acids are frequently incorporated into biologically active molecules, both to enhance bioactivity and to probe mechanisms of action. The regio and stereoselective ring-opening reactions of aziridine 2-carboxylate esters serve as valuable sources of structurally diverse α and β-amino acids.[6]

The discovery of the aminohydroxylation reaction[7] by Sharpless *et.al*. has allowed easy entry into chiral as well as non chiral aziridines by simple Mitsunobu reaction[8] of the resultant amino alcohol. Due to the strained nature of aziridines, ring-opening reactions are a dominant feature of this class of compounds.[1]

3.0.2 Transfer Hydrogenation

Transfer hydrogenation is one of the most widely studied reduction process due to its potential over conventional hydrogenation process.[9] In comparison with the catalytic hydrogenation using molecular hydrogen, the transfer hydrogenation is potentially advantageous due to its simplicity. Use of molecular hydrogen needs high-pressure reactors and causes potential hazards due to its high diffusibility and flammability.

This process entails hydrogen abstraction from the reagent (hydrogen donor) by means of a catalyst, followed by hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor). This is represented in **(Fig. 2)**.

$$DH_2 + A \xrightleftharpoons{\text{cat.}} D + AH_2$$

DH_2 = hydrogen donor
A = hydrgen acceptor

Fig. 2

Effect of temperature and solvent on catalytic transfer hydrogenation

Generally increase in temperature leads to increase in rates of reduction for most of the cases. However, the other factors such as catalyst and hydrogen donor also need to be taken into account to achieve the optimal conditions. Increase of temperature may lead to unwanted side reactions.

Proper choice of solvent is an important factor governing the activity of catalyst in transfer hydrogenation. Some metal catalysts are active in solutions only after dissociation of one or more ligands from the central metal atom with less than its maximum coordination number, thereby facilitating oxidative addition. The coordinate link between the solvent and catalyst should not be stronger than the binding of donor or acceptor.

From the mechanistic point of view, two general reactions can be taken into consideration for hydrogen transfer[10] a stepwise process called hydridic route and a concerted process called direct hydrogen transfer.

Hydrogen donors

Hydrogen donor can, in principle, be any organic compound whose oxidation potential is sufficiently low so that the hydrogen transfer can occur under mild conditions. The choice of hydrogen donor is generally determined by the ease of reaction and availability. The most popular hydrogen donors are alcohols and formic acid. Others include[9a] cyclohexene, cyclohexadiene, indene, tetraline, tetrahydroquinoline, dihydrofuran, dioxane, ethanol, 2-methoxyethanol, benzyl alcohol, polyvinyl alcohol, ascorbic acid, hydrazine. etc. Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process.[9a] The use of such H-donors is recommended in reactions where unfavorable energetic balances are expected. Secondary alcohols are better H-donors than primary alcohols.[11]

Promoters

Strong bases like KOH or NaOH or sodium alkoxides are commonly used promoters in H-transfer reactions since they often exert a beneficial effect on reaction rates. In the reduction of ketones with propan-2-ol, the base is essential for their activity.

Base is believed to be effective by removing a proton from the reacting complex **Fig. 3** indicates how base promotes the transfer of hydride ion from an alkoxy radical onto an adjoining coordinated ketone.

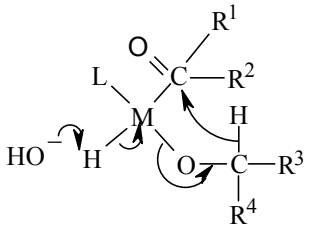


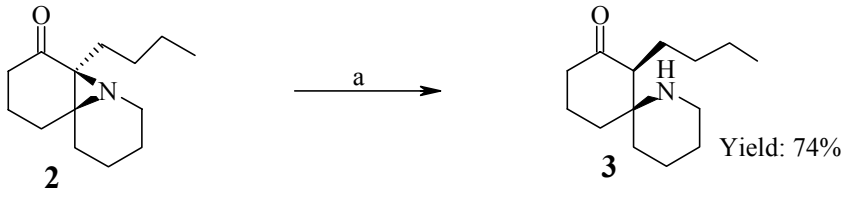
Fig. 3

3.0.3 Review of Literature

Literature search reveals that there are only few reports known in literature for reductive ring opening of aziridines in regiospecific manner, which are described below.

Ska *et al.*[12]

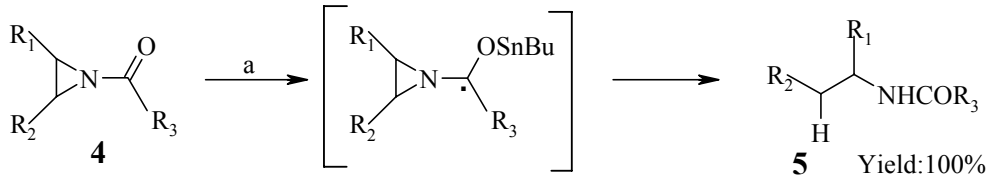
Ska *et al*. have reported the reductive cleavage of aziridine ring **2** by using chromium (II) chloride in 74% yield. This step is utilized in the formal synthesis of perhydrohistroionicotoxin (**Scheme 1**).



Scheme 1: a) $CrCl_2$, acetone, RT, 5 min, 74%.

Werry *et al.*[13]

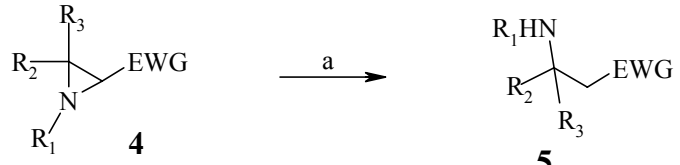
This approach for the reduction of aziridines makes use of tributyltin hydride (Bu_3SnH) as a reducing agent (**Scheme 2**).



Scheme 2: a) Bu_3SnH, AIBN (cat), benzene, 24 h.

Molander *et al.*[14]

Molander *et.al*. have reported a convenient method for the reduction of 2-substituted aziridines **4**. Samarium (II) iodide (SmI_2) is used as a reducing agent along with a proton source. The reduction was extremely rapid and highly regioselective, giving rise to β-amino carbonyl compounds **5** (**Scheme 3**).

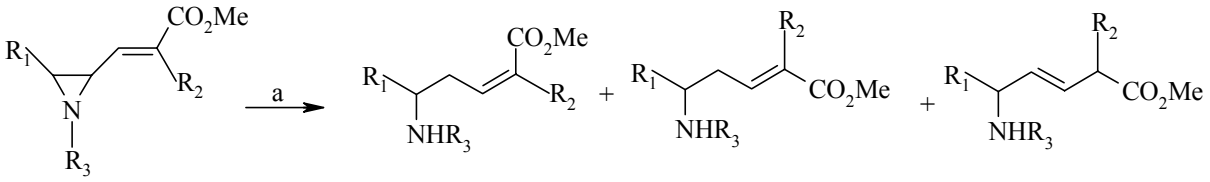


R_2, R_3 = alkyl, aryl EWG = Ac, CO_2Et
R_1 = Ts, Boc, CO_2Et, etc.
Yield : 79 -88%

Scheme 3: a) SmI_2, MeOH, THF, 0°C.

Satake *et al.*[15]

This reports Pd-catalyzed reduction of various *N*-arenesulfonylaziridines bearing α,β-unsaturated ester groups with formic acid to yield mixture of products (**Scheme 4**).

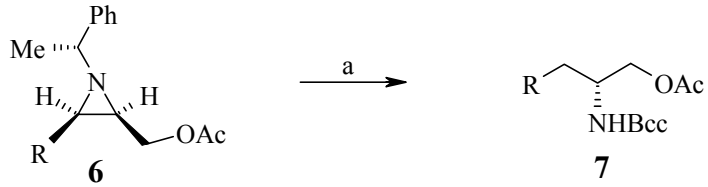


R_1 = H, $PhCH_2$, etc. R_3 = Ts, Ns. etc
R_2 = H, Me, $C_6H_4SO_2$,etc.

Scheme 4: a) Pd, HCO_2H, heat.

Chang *et al.*[16]

Chang and co-workers have reported regioselective reduction of *cis*-2,3-disubstituted aziridines to give (D)-phenylalanine derivatives with catalytic hydrogenation. Various disubstituted aziridines **6** were reduced at the ring C(3)-N bond in the presence of $(Boc)_2O$ to provide (D)-phenylalaninol **7** analogues in good yields (**Scheme 5**).



R = phenyl, naphthyl, Me, etc.
Yield : 67-85%

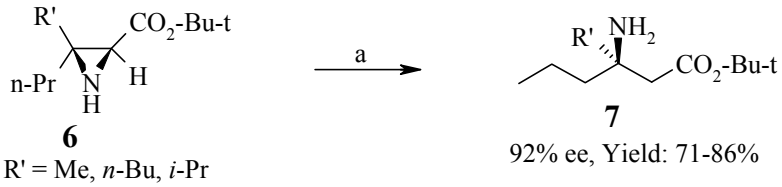
Scheme 5: a) $Pd(OH)_2$, H_2, $(Boc)_2O$, MeOH, RT.

Chwang *et al.*[17]

In this approach for the reduction of aziridines, Mg in methanol is used as the electron-transfer reagent.

Davis *et al.*[18, 19]

This reports, regioselective hydrogenation of enantiopure aziridine 2-carboxylate esters **6**, with Raney-Ni to afford *β*-amino acids **7** in good yield (**Scheme 6**).

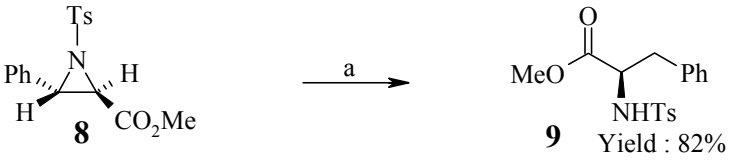


6
R' = Me, *n*-Bu, *i*-Pr

7
92% ee, Yield: 71-86%

Scheme 6: a) Ra-Ni, EtOH, H_2.

Davis *et al.* have also reported only one example of the use of transfer hydrogenation for the reduction of aziridines. Thus, Pd-catalyzed reductive ring opening of aziridine **8** in the presence of formic acid as a hydrogen donor afforded the corresponding 2-(*R*)-phenylalanine derivative **9** in 82% yield (**Scheme 7**).

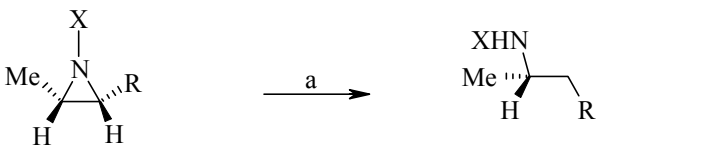


8 **9** Yield : 82%

Scheme 7: a) HCO_2H, Pd (0), MeOH, 82%.

Lim *et al.*[20]

Regiospecific reductive ring cleavage of aziridines **8** was accomplished under



8
R = CO_2Me, CH_2OH
X = trityl, *p*-toluenesolfonyl, benzyl.

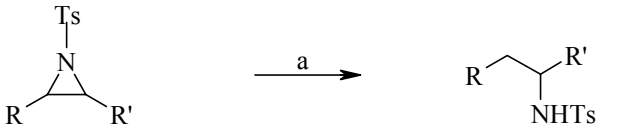
9 Yield: 80-95%

Scheme 8: a) $Pd(OH)_2$, AcOH, H_2.

under catalytic hydrogenation conditions in 80-95% yield (**Scheme 8**).

Chandrasekhar *et al.*[21]

Chandrasekhar *et al.* have described regioselective ring opening of tosyl aziridines **8**, using catalytic amount of Pd/carbon and polymethylhydrosiloxane as a soluble hydrogen source. Electron deficient aziridines as well as aliphatic aziridines **8** underwent reduction to give the corresponding amines **9** in 60-97% yield (**Scheme 9**).



8

R = Ph, *p*-OMe-C_6H_4, $C_6H_5CH_2$, etc.
R' = H, C_6H_5, CO_2Et., etc.

9

Yield: 60 - 97%

Scheme 9: a) Pd-C, polymethylhydrosiloxane, EtOH, RT, 6 h.

3.0.4 Present work

3.0.4.1 Objective

There are few methods reported in the literature, which deal with the opening of aziridines with hydride sources leading to regioselective C-N bond cleavages. Examples include the reductive cleavage reactions by conventional catalytic hydrogenations (Pd/ H_2, EtOH) catalytic transfer hydrogenations (Pd/ HCO_2H), Mg in methanol, SmI_2, Bu_3SnH etc. However these methods suffer from the disadvantages such as use of costly reagents, low yields, poor regioselectivity and formation of undesired side products.

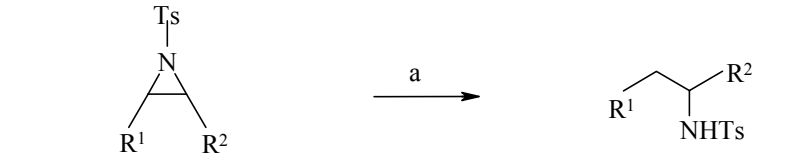
Consequently, we thought it would be worthwhile to develop an alternative catalytic method for this reaction. Our approach for the reductive cleavage of tosyl aziridines makes use of transfer hydrogenation approach. Ammonium formate has advantages of being cheap, readily available, stable, non-toxic and can be used in conjunction with either palladium on carbon or Ranney-Ni as catalyst.[22] Moreover, it can be added to the reaction mixture in a

single portion. Although ammonium formate has been used as a source of hydrogen for the reduction of variety of functional groups,[22,23] its use in reduction of aziridines has not been reported. This prompted us to make use of ammonium formate as a transfer hydrogenation source for the reduction of aziridines.

3.0.5 Results and Discussion

A variety of aziridines (**8a-j**) were prepared by reacting olefins with Chloramine-T in the presence of catalytic amount of pyridinium hydrobromide perbromide ($Py.HBr_3$) at room temperature.[24]

When 2-phenyl-*N*-tosylaziridine **8a**, was treated with ammonium formate in presence of catalytic amount of Pd-C in methanol at reflux temperature yielded 2-phenyl-*N*-tosyl ethylamine **9a** in 90% yield. Encouraged by this finding, a variety of aziridine substrates were subjected to transfer hydrogenation under similar conditions.



8a-j

R^1 = Ar, alkyl, vinyl, etc.

R^2 = H, CO_2R, Ar, COPh, etc.

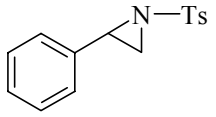
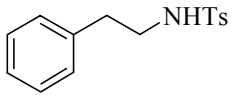
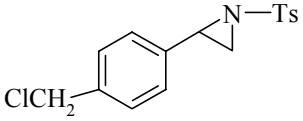
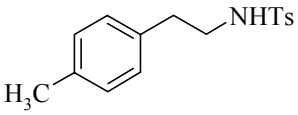
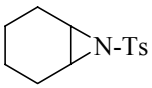
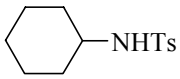
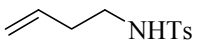
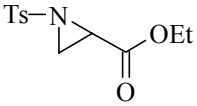
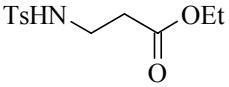
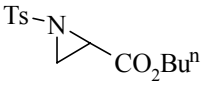
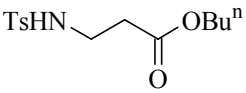
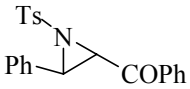
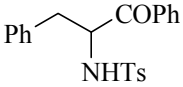
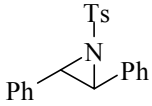
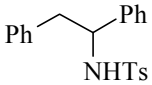
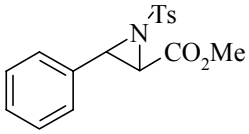
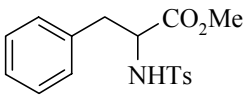
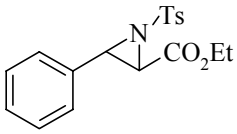
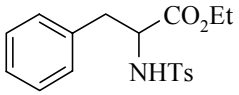
9a-j

Yield : 85-90 %

Scheme 10: a) HCO_2NH_4 (1.5 equiv), 10% Pd-C (5 wt %), MeOH, reflux, 3-4 h.

A variety of aziridines **8a-j** were reduced to the corresponding amines **9a-j** in good to excellent yields (**Scheme 10**). The results of reduction are summarized in **Table 1**. However, when the reaction was performed at room temperature, all the starting material was recovered back. As can be seen from the **Table 1**, corresponding amines were formed in good to excellent yields (85-90%) using ammonium formate as hydrogen donor. The reduction takeplace generally at the benzylic/ allylic positions giving the

Table 1: Pd-catalyzed reductive ring opening of aziridines with ammonium formate [a].

Entry	Substrate (8a-j)	Product (9 a-j)	Yield [b] (%)	M.p. (°C)
a			90	gum
b			90	68-70
c			85	132-134
d			85	gum
e			86	gum
f			85	gum
g			85	118-120
h			90	92
i			90	150-152
j			88	115-118

a) Reaction conditions: ammonium formate (1.5 equiv), aziridine (1.0 equiv), 10% Pd/C (5 wt %), MeOH, reflux; b) yields refer to isolated after column chromatographic purification.

corresponding amino compounds. It is remarkable to note that in the case of aziridines with electron withdrawing group (entries e and f), the reduction takes place at the α-position regioselectively to produce the corresponding amines in high yields. Also it may be noted that in case of vinyl aziridines, the double bond is not affected during reduction (entry d). The catalyst was recovered by simple filtration and the product was isolated by distillation of the solvent.

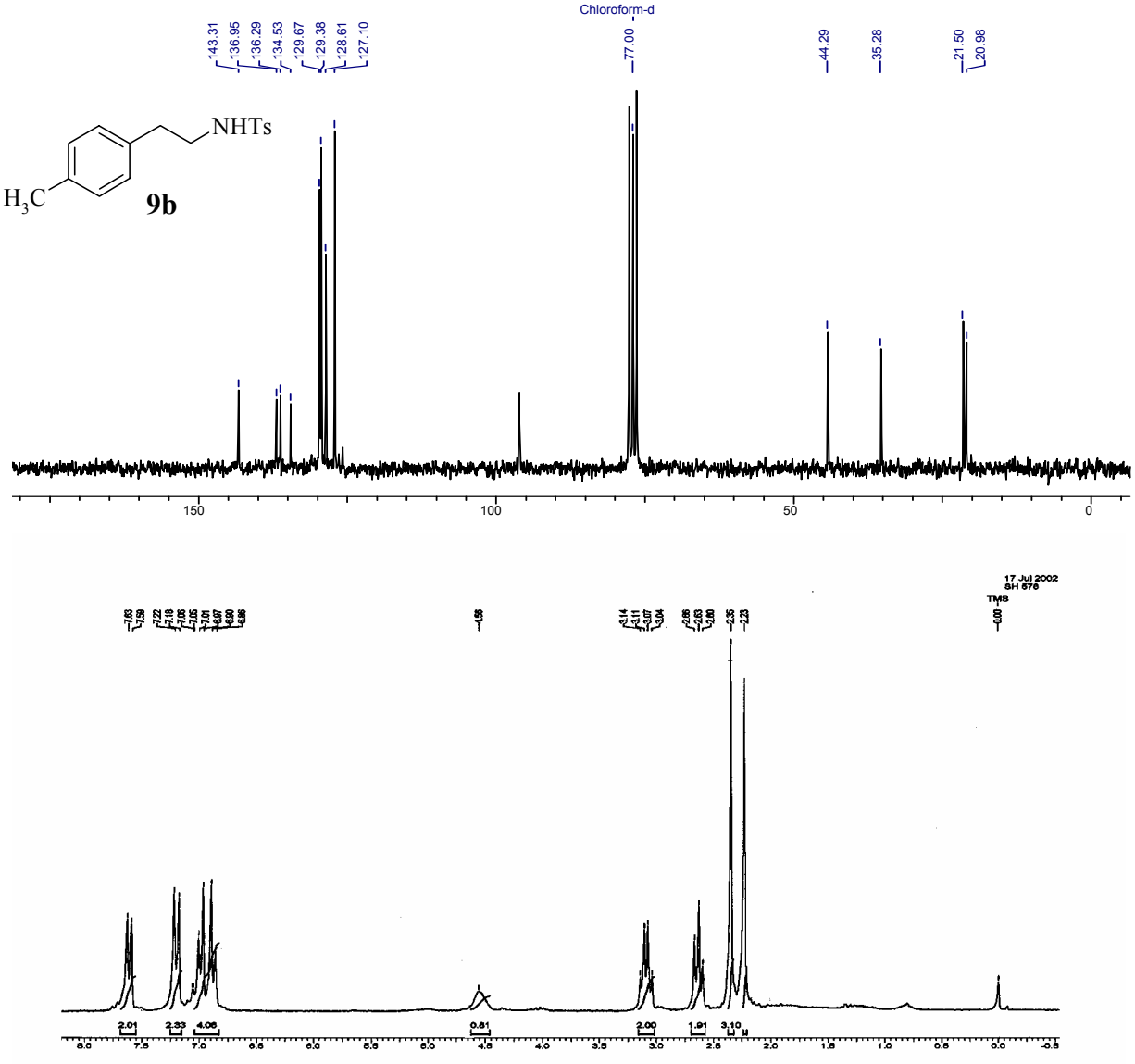


Fig. 4: ^{1}H and ^{13}C-NMR spectra of amine 9b

The structures of **9a-j** were confirmed by ^{1}H, ^{13}C-NMR and mass spectroscopy. As an example, compound **9b** showed triplet at δ 2.63 for benzylic protons and quartet at δ 3.09 for homobenzylic proton in its ^{1}H-NMR spectrum. Further, a broad singlet at δ 4.56 is due to N-H proton, which is exchangeable with D_2O. Singlet at δ 2.23 indicates the loss of chlorine atom during hydrogenation. Its ^{13}C-NMR spectrum showed typical peaks at δ 35.28 and 44.29 corresponding to two methylene carbon atoms **(Fig. 4)**.

The ^{1}H-NMR spectrum of compound **9d**, shows the presence of olefinic protons in the region δ 5.00-6.00, indicating that double bond is intact under the reaction conditions **(Fig 5)**.

Similarly, ^{1}H-NMR spectrum of compound **9h**, showed a doublet at δ 2.90 corresponding to protons β to amine, a quartet observed at δ 4.41 and a doublet at δ 5.19 due to NH proton, which is exchangeable with D_2O. Further, its ^{13}C-NMR spectrum showed typical peaks at δ 44.18 and 59.28 corresponding to two methylene carbons.

Entry **8i** and **8j**, which has an ester moiety on the aziridine ring, underwent regioselective opening to furnish a phenylalanine derivative in 90 and 88% yield respectively. The stilbene derivative entry **8h**, also furnished the 1,2 diphenyl-*N*-tosyl ethylamine in 90% yield. The aziridines obtained from acrylic acid derivatives entry **8d** and **8e**, also underwent smooth reductive aziridine opening.

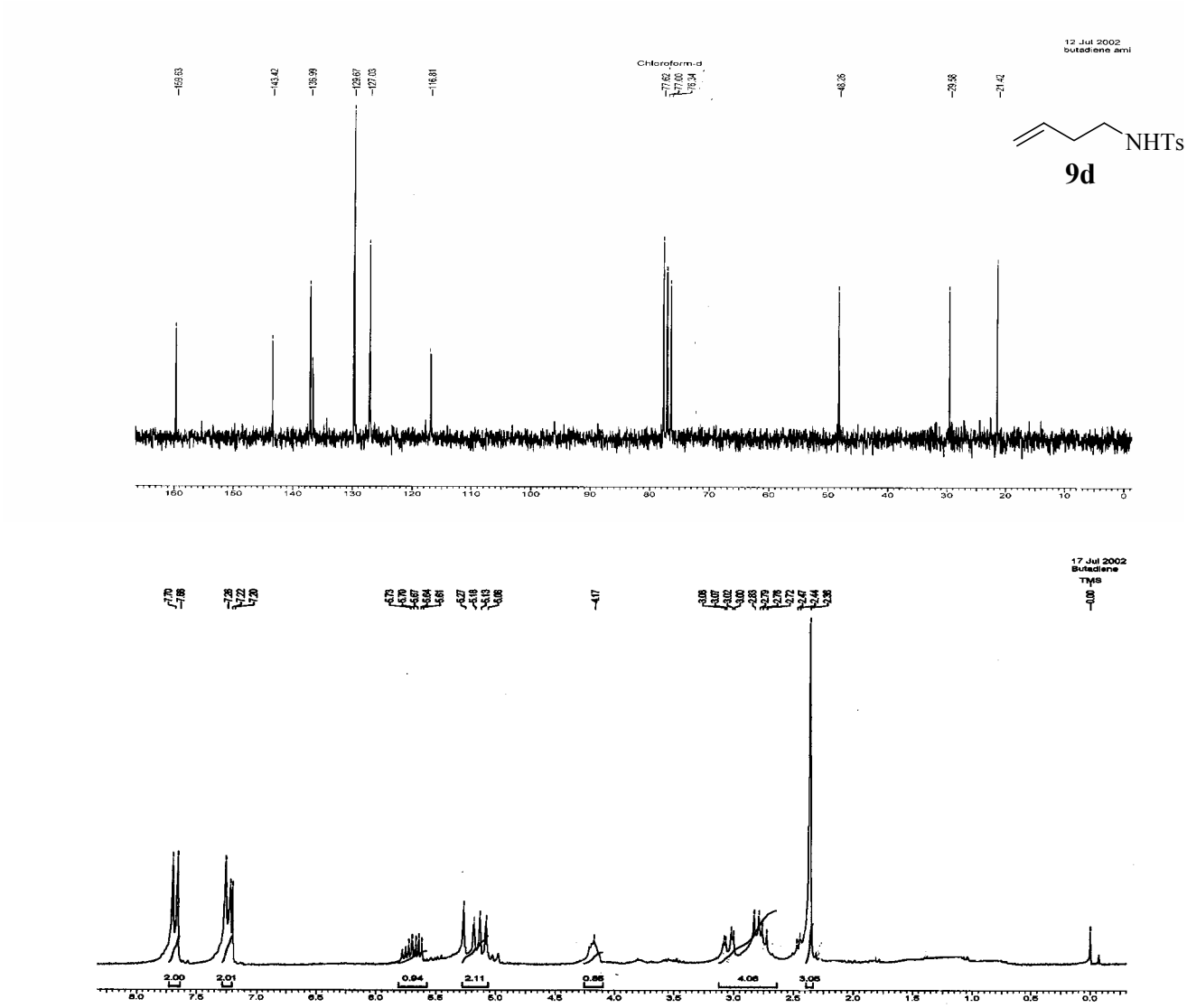


Fig. 5: ^{1}H and ^{13}C-NMR spectra of amine 9d

3.0.6 Conclusion

In conclusion, an efficient procedure for the regio- and chemo-selective reductive ring opening of aziridines is described by using ammonium formate in presence of catalytic amount of Pd-C. The products formed, especially the α-aminoesters finds wide application as unusual amino acids in peptide chemistry. The reduction of the *N*-tosylaziridine-2-carboxylates examined was highly regioselective, giving rise to β-amino carbonyl compounds.

Further it tolerates a variety of reducible functional groups like olefin, ketone and ester moiety.

3.0.7 Experimental Section

General procedure for reductive ring opening of aziridines

A 25 ml RB flask was charged with aziridine **8a-j** (3 mmol), ammonium formate (0.283 g, 4.5 mmol), 10% Pd-C (5% wt) in methanol (10 ml), under nitrogen atmosphere. The reaction mixture was then heated to reflux. After completion of the reaction as monitored by TLC, the catalyst was removed by filtration and the solvent was removed under reduced pressure. The reaction mixture was then diluted with water (8 ml) and it was extracted with ethyl acetate (3x30 ml) and washed with brine. The organic layer was then dried over anhydrous sodium sulphate, concentrated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to afford the corresponding amines **9a-j**.

2-Phenyl-*N*-(*p*-tosyl ethyl amine (9a): Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3370, 3278, 3020, 2400, 2329, 1495, 1410, 1305, 1215, 1160, 1079, 804; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.77 (t, *J* = 6.5 Hz, 2H), 3.15-3.30 (m, 2H), 4.60 (t, *J* = 8.0 Hz, 1H, NH), 7.10 (d, *J* = 8.0 Hz, 2H), 7.15-7.35 (m, 5H), 7.65-7.75 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.24, 35.61, 44.14, 126.37, 126.84, 128.35, 128.50, 129.45, 136.73, 137.76, 143.05; **MS** (m/z, % RI): 275 (M^+, 5), 184 (23), 155 (35), 39 (25), 118 (40), 104 (75), 91 (100), 77 (35), 65 (30); **Analysis**: $C_{15}H_{17}NO_2S$ requires C, 65.43; H, 6.21; N, 5.08; S, 11.64; found C, 65.49; H, 6.25; N, 5.18; S, 11.66%.

2-(4-Methylphenyl-*N*-*p*-tosyl ethylamine (9b): Yield: 90%; **mp**: 68-70^{o}C; **IR** ($CHCl_3$, cm^{-1}): 3375, 3012, 2964, 2514, 1450, 1325, 1215, 1161, 912; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.35 (s, 3H), 2.63 (t, *J* = 6.0 Hz, 2H), 3.09 (q, *J* = 6.0 Hz, 2H), 4.56 (brs, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.98, 21.50, 35.28, 44.29, 127.10, 128.61, 129.38, 129.67, 134.53, 136.29, 136.95, 143.31; **MS** (m/z, % RI): 110 (4), 98 (80), 95 (10), 83 (72), 79 (5), 55 (100), 43 (85); **Analysis**: $C_{16}H_{19}NO_2S$ requires C, 66.40; H, 6.61; N, 4.84; S, 11.05; found C, 66.42; H, 6.69; N, 4.90; S, 11.10%.

***N*-(*p*-Tosyl cyclohexyl amine (9c): Yield**: 85%; **mp**: 132-134^{o}C; **IR** ($CHCl_3$, cm^{-1}): 3019, 2939, 2350, 2329, 1510, 1330, 1210, 1135, 1081, 884; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.05-1.35 (m, 4H), 1.50-1.80 (m, 3H), 1.95-2.10 (m, 1H), 1.15-2.40 (m, 1H), 2.44 (s, 3H), 2.75-2.95 (m, 1H), 3.20-3.40 (m, 1H), 5.03 (brs, 1H, NH), 7.32 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.50, 23.77, 24.58, 31.64, 33.33, 127.1, 129.71, 137.58, 143.42, 159.67; **MS** (m/z, % RI): 253 (M^+), **Analysis**: $C_{13}H_{19}NO_2S$ requires C, 61.63; H, 7.55; N, 5.52; S, 12.65; found C, 61.53; H, 7.65; N, 5.52; S, 12.66%.

***N*-(*p*-Tosylamino 3-butene (9d): Yield**: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3374, 3090, 3023, 2957, 2925, 1597, 1447, 1404, 1325,1220, 1159, 1092, 984, 933, 841; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.78 (q, *J* = 6.0 and 8.0 Hz, 2H), 3.04 (q, *J* = 2.0 and 4.0 Hz, 2H), 4.17 (brs, 1H), 5.08-5.27 (dd, *J* = 10.0 and 18.0 Hz, 2H), 5.60-5.75 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.42, 29.58, 48.26, 116.81, 127.03, 129.67, 136.99, 143.42, 159.63; **MS** (m/z, % RI): 225 (M^+), **Analysis**: $C_{11}H_{15}NO_2S$ requires C, 58.64; H, 6.70; N, 6.21; S, 14.23; found C, 58.72; H, 6.70; N, 6.25; S, 14.24%.

Ethyl 3-(*p*-tosylamino)propaneoate (9e):Yield: 86%; gum; **IR** ($CHCl_3$, cm^{-1}): 3330, 3010, 2965, 2942, 1722, 1215, 1161, 756; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.65 (t, *J* = 7.5 Hz, 3H), 2.35 (s, 3H), 2.48 (t, *J* = 6.0 Hz, 1H), 3.25 (q, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 7.5 Hz, 1H), 5.27 (brs, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); **Analysis**: $C_{12}H_{17}NO_4S$ requires C, 53.12; H, 6.30; N, 5.16; S, 11.81; found C, 53.13; H, 6.38; N, 5.16; S, 11.88%.

Butyl 3-(*p*-tosylamino)propaneoate (9f): Yield: 85%; gum; IR ($CHCl_3$, cm^{-1}): 3333, 3020, 2962, 2942, 1726, 1215, 1161, 756; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 8.0 Hz, 3H), 1.20-1.35 (m, 2H), 1.45-1.55 (m, 1H), 2.36 (s, 3H), 2.45 (t, *J* = 6.0 Hz, 2H), 3.11 (q, *J* = 6.0 Hz, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 5.26 (brs, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.63, 19.03, 21.53, 30.46, 33.92, 38.74, 64.83, 126.99, 129.71, 136.95, 143.38, 172.13; Analysis: $C_{14}H_{21}NO_4S$ requires C, 56.16; H, 7.06; N, 4.67; S, 10.71; found C, 56.09; H, 7.10; N, 4.71; S, 10.72%.

***N*-(*p*-tosylamino)-2-benzoyl phenyl ethyl amine (9g): Yield**: 85%; **mp**: 118-120^{o}C; IR ($CHCl_3$, cm^{-1}): **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.36-2.42 (m, 1H), 4.38-4.48 (dd, *J* = 10.0 and 12.0 Hz, 1H), 5.05-5.15 (m, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 7.10-7.90 (m, 14 H);

Analysis: $C_{22}H_{21}NO_3S$ requires C, 69.63; H, 5.57; N, 3.69; S, 8.45; found C, 69.65; H, 5.57; N, 3.75; S, 8.54%.

1, 2-Diphenyl-*N*-(*p*-tosyl ethyl amine (9h): Yield: 90%; **mp**: 92^{o}C; IR ($CHCl_3$, cm^{-1}): 3031, 1595, 1496, 1454, 1340, 1153, 1085, 900, 756, 588; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.90 (d, *J* = 6.0 Hz), 4.41(q, *J* = 8.0 Hz, 1H), 5.19 (d, *J* = 8.0 Hz, 1H), 6.80-6.84 (m, 2H), 6.86-7.15 (m, 10H), 7.35 (d, *J* = 8.0 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.35, 44.18, 59.28, 126.77, 127.10, 127.30, 128.31, 129.34, 136.51, 137.58, 140.55, 142.87, 159.63, 159.74, 169.15; **MS** (m/z, % RI): 351 (M^+), **Analysis**: $C_{21}H_{21}NO_2S$ requires C, 71.76; H, 6.01; N, 3.98; S, 9.12; found C, 71.76; H, 6.11; N, 3.92; S, 9.12%.

Methyl 2-*N*-(*p*-tosylamino)-3-phenylpropanoate (9i): Yield: 90%; **mp**: 150-152^{o}C; IR ($CHCl_3$, cm^{-1}): 3356, 3293, 3019, 2552, 2334, 2942, 1725, 1215, 1160, 850, 585; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.65 (brs, 1H), 3.42 (s, 3H), 4.20-4.30 (dd, *J* = 4.0 Hz each, 1H), 5.07 (d, *J* = 4.0 Hz, 1H), 5.55 (d, *J* = 8.0 Hz, 1H), 7.15-7.40 (m, 7H), 7.68 (d, *J* = 8.0 Hz, 2H); **MS** (m/z, % RI): 253 (7), 210 (5), 155 (15), 114 (100), 96 (8), 91 (82), 79 (20), 65 (45); **Analysis**: $C_{17}H_{19}NO_4S$ requires C, 61.24; H, 5.73; N, 4.20; S, 9.61; found C, 61.25; H, 5.75; N, 4.14; S, 9.66%.

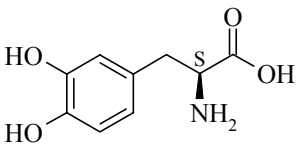
Ethyl 2-*N*-(*p*-tosylamino)-3-phenylpropanoate (9j): Yield: 88%; **mp**: 115-118^{o}C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.0 Hz, 3H), 2.45 (s, 3H), 2.60 (brs, 1H), 4.15 (t, *J* = 7.0 Hz, 2H), 4.22-4.33(dd, *J* = 4.0 Hz each, 1H), 5.08 (d, *J* = 4.0 Hz, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 7.15-7.45 (m, 7H), 7.68 (d, *J* = 8.0 Hz, 2H); **Analysis**: $C_{18}H_{21}NO_4S$ requires C, 62.23; H, 6.08; N, 4.03; S, 9.22; found C, 62.15; H, 6.09; N, 4.08; S, 9.30%.

SECTION-II

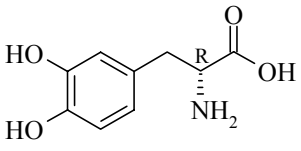
Asymmetric Synthesis of L-DOPA *via,* OsO_4-Catalyzed Asymmetric Dihydroxylation

3.1.1 Introduction

L-DOPA [(*S*)-3,4-dihydroxyphenylalanine] (**10**), and its antipode **11** have been known since 1913. It is a naturally occurring, unusual amino acid derived from post-translational modification of tyrosine.[25] It is one of the principal agents administered to patients with Parkinson's disease since 1967.[26] Although rarely found in proteins, L-DOPA (**10**) was detected in high yield (ca. 10%) in marine mussel adhesive proteins as well as eggshell precursor proteins of Fasciola hepatica and Schistosoma mansoni. It has been postulated that the presence of L-DOPA residues in these proteins could contribute to bioadhesion in seawater and sclerotization during eggshell formation, respectively. The ubiquitous nature of (*S*)-3,4-dihydroxyphenylalanine, L-DOPA (**10**) touches biological fields ranging from medicine to engineering. Most commonly known for pharmacological value, L-DOPA (**10**) has been the treatment of choice to alleviate Parkinson's disease symptom **(Fig. 6)**.[27]



L-DOPA **(10)**



D-DOPA **(11)**

Fig. 6

Parkinsonism is a chronic neurological disorder characterized by tremor, rigidity of the limbs and poverty of movement (hypokenesia). In most patients, initial symptoms develop in the fifth or sixth decade of life and gradually progress, death usually occurring about ten years after onset. Known causes of Parkinsonism include viral infection (encephalitis lethargica),

toxins (manganese, carbon monoxide), vascular disease (atherosclerosis) and drugs (phenothiazines, haloperidol, reserpine). In most cases, however, no cause can be identified. Pathological examination of the brain reveals widespread degenerative changes in the basal ganglia, particularly the substantia nigra and corpus striatum.

3.1.2 Pharmacology of L-DOPA

Parkinson's disease is caused by a shortage of a particular chemical that is produced in the brain. This chemical is called dopamine. Without this chemical messenger the signals from the brain do not get through to the spinal cord then to the various muscles of the body and muscular function is impaired. Dopamine is synthesized within nerve cells. Chemically, L-tyrosine is converted to (*S*)-dihydroxyphenylalanaine [L-DOPA (**10**)] and then to dopamine in a two-step process.[28a]

The symptoms appear when there is not enough dopamine in the brain. Dopamine is a naturally occurring chemical (neurotransmitter) that allows nerve cells to transmit messages between each other and then to muscles to allow normal movement to take place. In Parkinson's disease, many of these cells are died. The remaining cells cannot produce enough dopamine. Most drug therapy replaces dopamine in the brain. Parkinson's disease is believed to be related to low levels of dopamine in certain parts of the brain. When L-DOPA is taken orally, it crosses through the "blood-brain barrier." Once it crosses, it is converted to dopamine. The resulting increase in brain dopamine concentrations is believed to improve nerve conduction and assist the movement disorders in Parkinson's disease. Carbidopa does not cross the blood-brain barrier. Carbidopa is added to the L-DOPA (**10**) to prevent the breakdown of L-DOPA before it crosses into the brain. The addition of carbidopa allows lower doses of L-DOPA to be used. This reduces the risk of side effects from L-DOPA such as nausea and vomiting.

Metabolic path way of L-DOPA

L-DOPA is avidly decarboxylated in most species by the relatively non-specific decarboxylase,[28b] which is now known to consist of several isoenzymes. Direct O-methylation of L-DOPA is one of many other possible routes, which may be important during therapy. [28c]

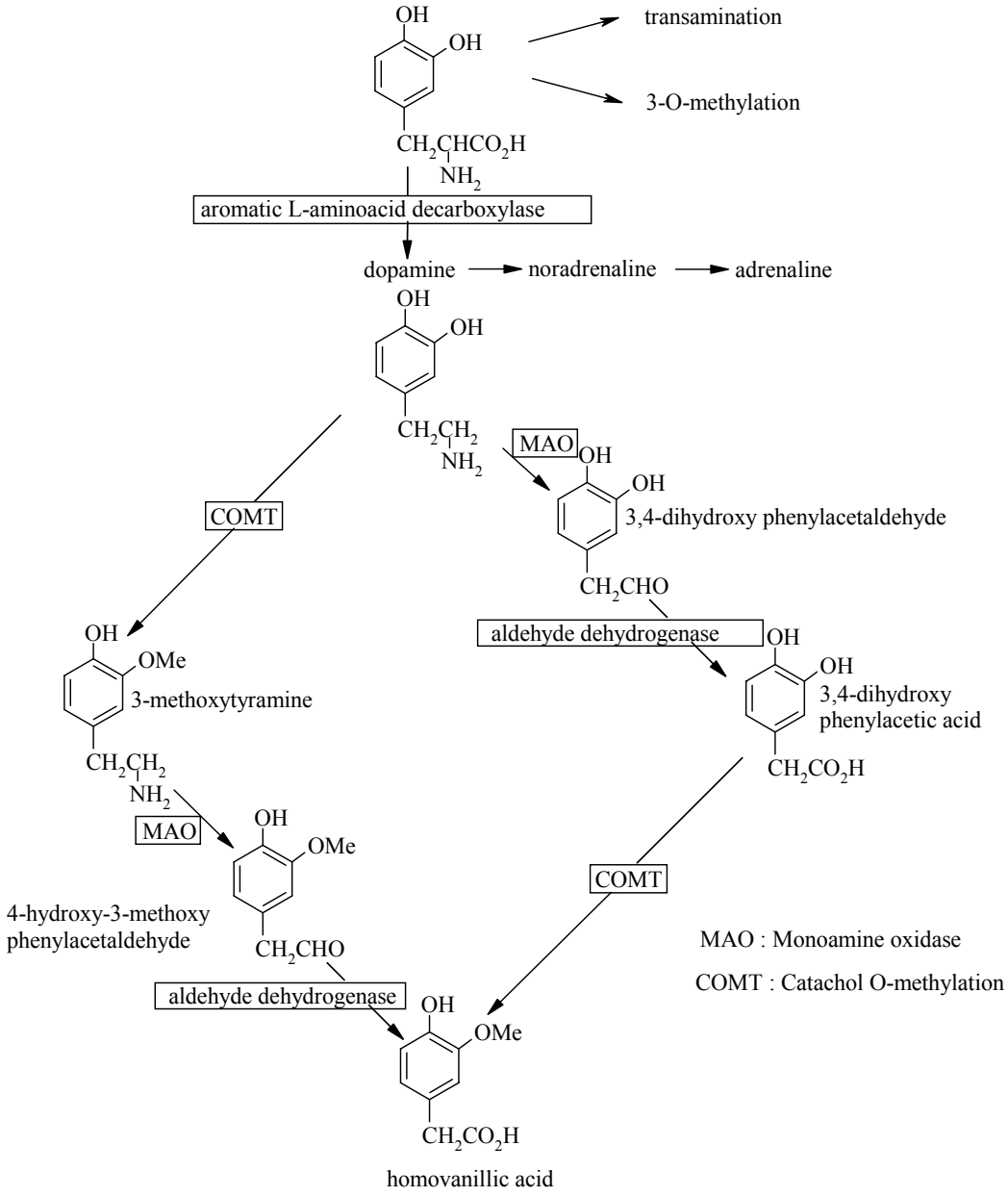


Fig. 7: Metabolic pathways of L-DOPA.

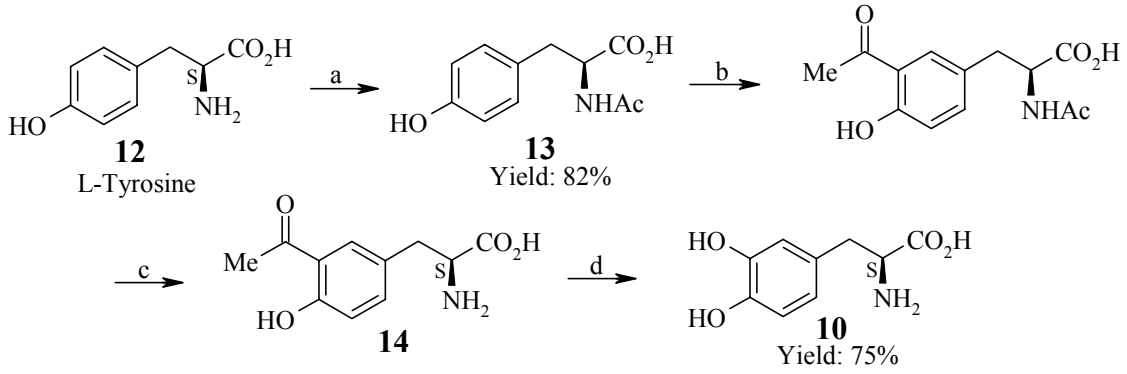
A portion of dopamine produced in the body is converted to noradrenaline by dopamine β-hydroxylase. Apart from its conversion to noradrenaline, dopamine may be degraded by O-methylation or oxidative deamination **(Fig. 7)**. The intermediate aldehyde formed by oxidative deamination of dopamine is largely oxidized to the corresponding acid, although the small amount is reduced to the alcohol. The acid, dihydroxyphenylacetic acid, may be 3-O-methylated to homovanillic acid.

3.1.3 Review of Literature

Literature search reveals that there are various methods available for the enantioselective synthesis of L-DOPA (**10**), which is presented below. Most of these methods make use of classical kinetic resolution of diastereomeric derivatives of L-DOPA, others on oxidation of L-tyrosine and probably the dominating industrial procedure is based upon catalytic asymmetric hydrogenation.

Breschneider's approach (1973)[29]

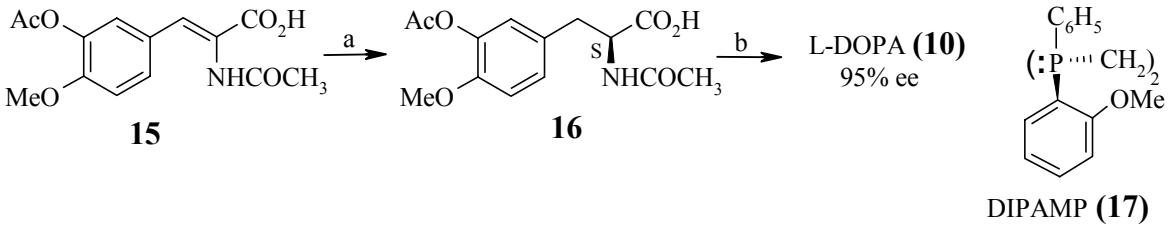
Breschneider *et al*. have reported use of Baeyer-Villiger oxidation as a key step for the synthesis of L-DOPA (**10**). The Friedel-Craft's reaction of *N*-acetylated tyrosine **13** followed by hydrolysis gave amine **14** in good yield. Amine **14** on Baeyer-Villiger oxidation with H_2O_2-NaOH gave L-DOPA (**10**) in 75% yield (**Scheme 11**).



Scheme 11: a) Ac_2O; b) CH_3COCl, $AlCl_3$, 100°C; c) 2N HCl; d) H_2O_2, NaOH, 75%.

Knowles' approach (1975) [30]

Knowles' *et al.* have demonstrated a short synthesis of L-DOPA (**10**) by Rh-catalyzed asymmetric hydrogenation of α-acylamido acrylic acid **15** using chiral phosphine ligand **17** to yield amino acid **16**. Amino acid **16** was converted to L-DOPA (**10**) by known sequence of reactions (**Scheme 12**).

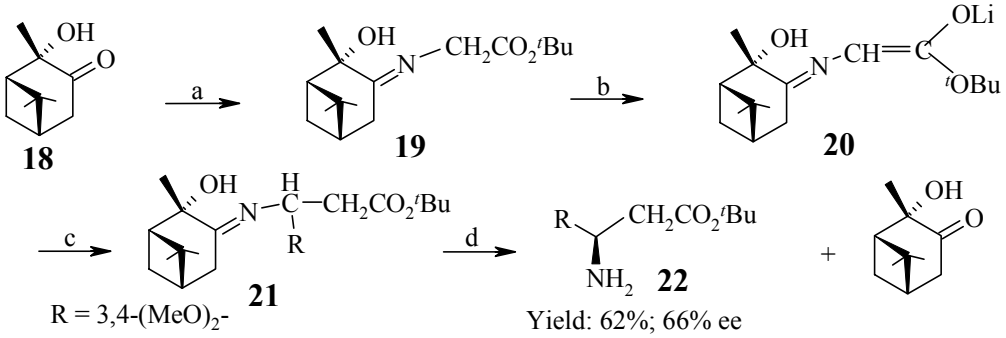


15 **16** DIPAMP **(17)**

Scheme 12: a) [Rh(COD) (DIPAMP)$^{+}BF_4^{-}$, ^{i}PrOH, 50^{o}C, H_2 (3.5 atm), 0.75 h; b) hydrolysis.

Yamada's approach (1976)[31]

Yamada *et al*. have described an asymmetric synthesis of α-amino acid derivatives by alkylation of Schiff base **19** as a key step. Condensation of glycidic *t*-butylester with ketone **18** furnished the required chiral Schiff base **19**. Schiff base **19** on lithiation with LDA followed by treatment with the corresponding alkyl halide gave mono alkylated Schiff base **21**, which on subsequent hydrolysis yielded compound **22** in 66% ee (**Scheme 13**).

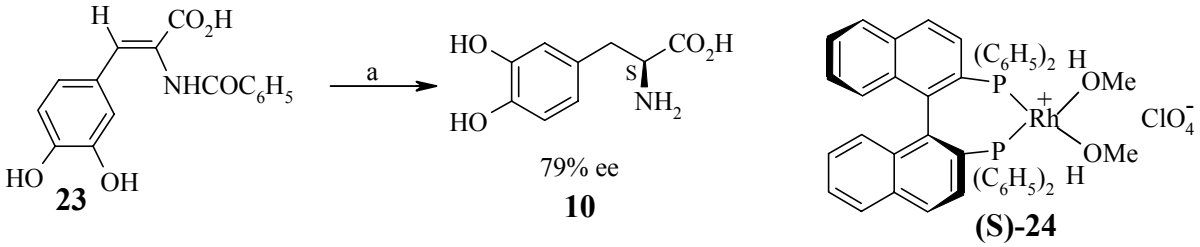


18 **19** **20** **21** **22**

Scheme 13: a) $NH_2CH_2CO_2{}^{t}Bu$; b) LDA; c) RX; d) hydrolysis.

Miyashita's approach (1980)[32]

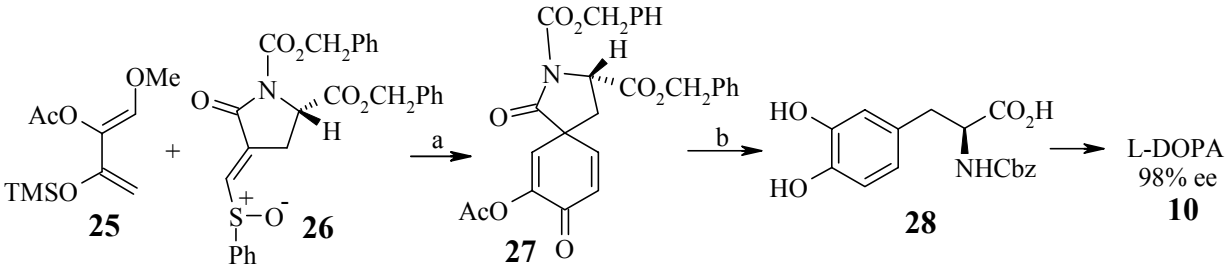
This approach is based upon Rh-catalyzed asymmetric hydrogenation of α-(acylamino) acrylic acid **23** by using [Rh-(*S*)-BINAP) (norbornadiene]ClO_4 (**24**) complex to yield L-DOPA (**10**) in 79% ee. Since both (*R*) and (*S*)-BINAP ligands are accessible, one can obtain both the enantiomers of amino acid (**Scheme 14**).



Scheme 14: a) Rh-catalyst (**24**), H_2, (3-4 atm), RT, 48 h.

Danishefski's approach (1981)[33]

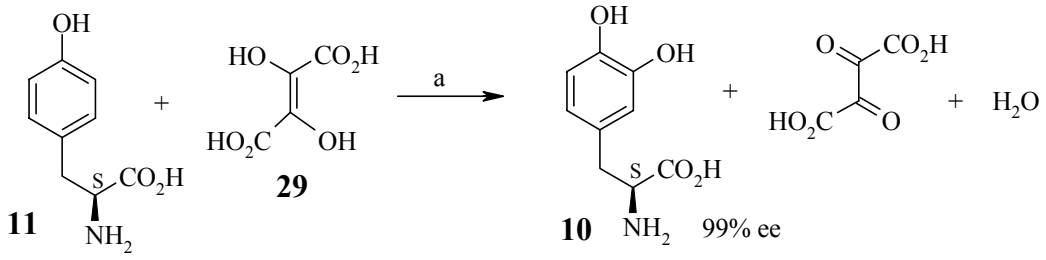
Danishefski *et al.* have reported the preparation of L-DOPA (**10**) *via* Diels-Alder reaction as a key step. Thus, cycloaddition of the diene **25** with dienophile **26**, gave compound **27** which was transformed to L-DOPA (**10**) in 98% ee (**Scheme 15**).



Scheme 15: a) xylene, 120°C, 7 h, 48%; b) NaOH, THF, 0°C, 58 %.

Klibnav's approach (1981)[34]

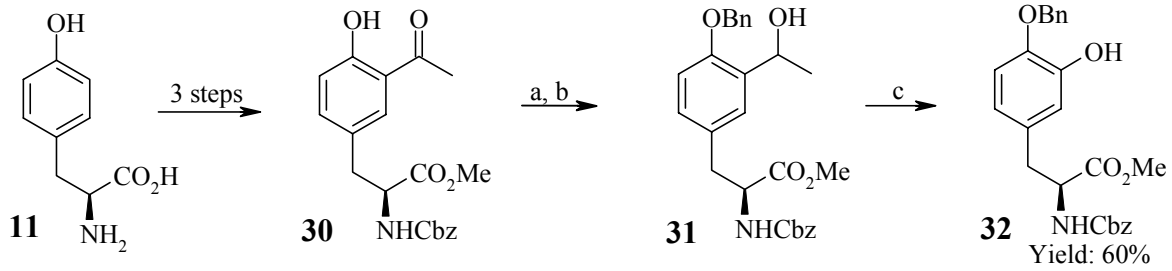
Klibnav *et al***.** have reported peroxidase-catalyzed hydroxylation of L-tyrosine (**11**) as a key step for the synthesis of L-DOPA (**10**). Dihydroxyfumaric acid (**29**) acts as a hydrogen donor in presence of oxygen (**Scheme 16**).



Scheme 16: a) acetate buffer (pH: 5.0), 0°C, horse radish peroxidase, O_2.

Boger's approach (1987)[35]

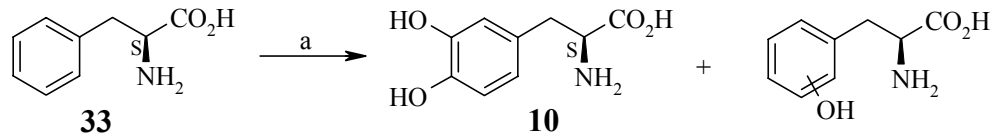
Boger *et al.* have prepared 4-*O*-benzyl-*N*-Cbz-L-Dopa methyl ester **32** starting from L-tyrosine (**11**) in six steps. The key step of this approach involves the acid promoted oxidative rearrangement of a benzylic hydroperoxide prepared by treatment of secondary benzylic alcohol **31** with 30% H_2O_2 and tosic acid (**Scheme 17**).



Scheme 17: a) BnBr, K_2CO_3, cat. (^{n}Bu)$_4$NI, DMF, 25°C, 6 h, 93%; b) $NaBH_4$, MeOH, 25°C, 1 h, 99%; c) 10 equiv. of 30% *aq*. H_2O_2, *p*-TsOH-$H_2$0, THF, 23°C, 24 h, 60%.

Blanchard's approach (1988)[36]

Blanchard *et. al*. have reported the results obtained by oxidation of L-phenylalanine (**33**). Thus, L-phenylalanine (**33**) was hydroxylated to 3,4-dihydroxyphen ylalanine (**10**) with

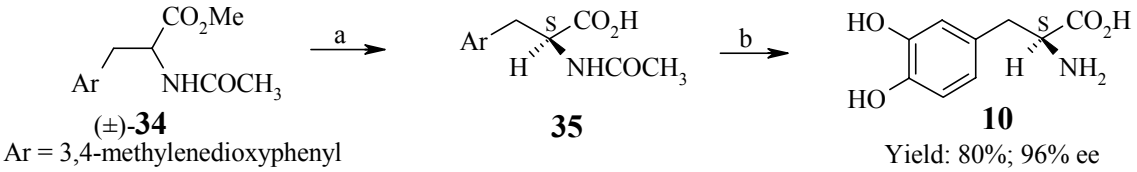


Scheme 18: a) O_2, Fe^{2+}, e^-, 40°C.

Fe^{2+} EDTA catalytic system in presence of oxygen. L-DOPA (**10**) was released from the reaction at 40°C (**Scheme 18**).

Tyagi's approach (1992)[37]

This paper describes the synthesis of L-DOPA (**10**) utilizing enzymatic resolution as a key step. Thus, racemic *N*-acetyl 3,4-methylenedioxyphenylalanine methyl ester **34** on enzymatic hydrolysis by *alcalase* provided (*S*)-*N*-acetyl-3,4-methylenedioxyphenylalinine (**35**), which was converted to L-DOPA (**10**) in high optical purity by known sequence of reactions (**Scheme 19**).



(±)-**34**
Ar = 3,4-methylenedioxyphenyl

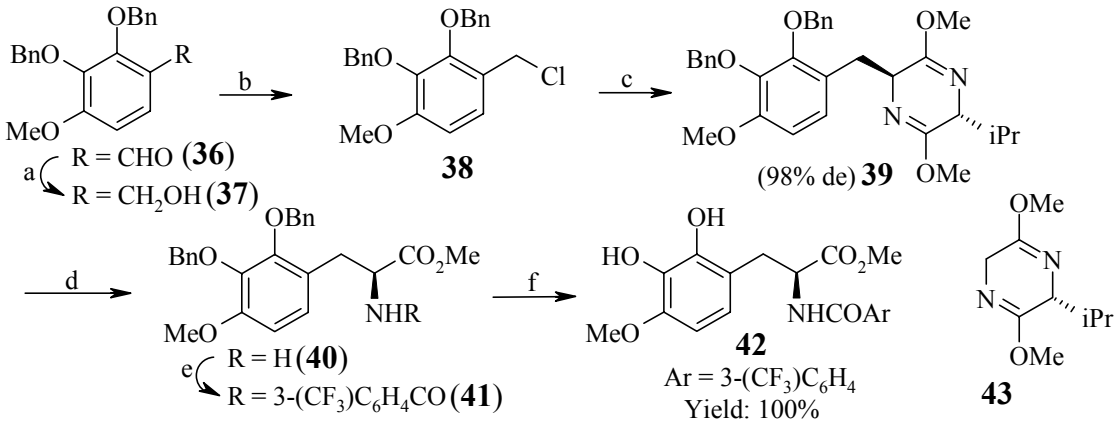
35

10
Yield: 80%; 96% ee

Scheme 19: a) *alcalase*, pH: 7.5; b) PhOH, HCl, reflux.

Baldwin's approach (1997)[38]

Baldwin *et al*. have utilized Scholkopf's *bis*-lactim ether methodology as a key step for the synthesis of L-DOPA analogue **42**. The benzyl chloride derivative **38** was obtained from the aldehyde **36** in two steps. Chirality was introduced using Scholkopf's *bis*-lactim

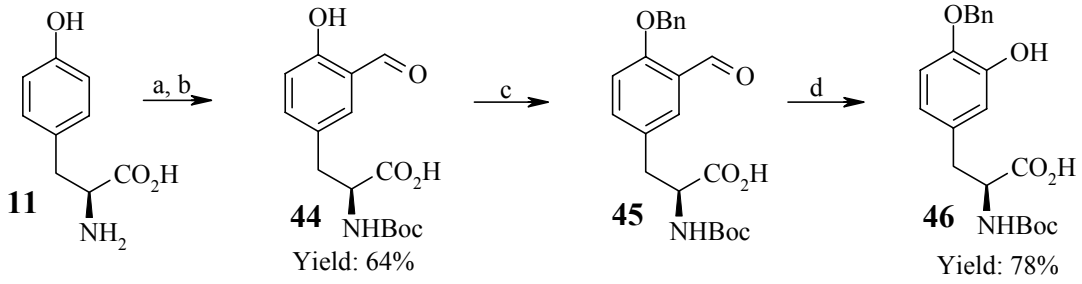


Scheme 20: a) $NaBH_4$, MeOH, 99%; b) $SOCl_2$, DMF, RT, 100%; c) (**43**), *n*-BuLi, – 78°C, 92%; d) 0.25 M HCl, CH_3CN, RT, 95%; e) 3-$(CF_3)C_6H_4COCl$, Et_3N, CH_2Cl_2, DMAP, RT, 89%; f) 10% Pd/C, MeOH, H_2, RT, 100%.

ether methodology to produce compound **39** in 98% de. Hydrolysis of compound **39** gave the free amine **40**, which was converted into derivative **41**. Hydrogenolysis of the benzyl groups gave amine **42** in quantitative yield (**Scheme 20**).

Jung's approach (1997)[39]

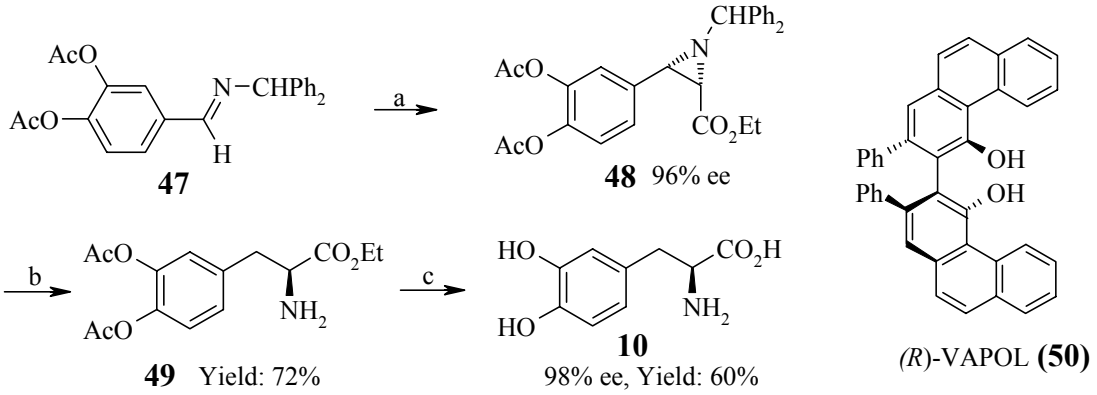
Synthesis of *N*-Boc-L-3-[3hydroxy-4-(phenylmethoxy)phenyl]alanine (**46**) was achieved by using a simple Reimer-Tiemann formylation and Dakin reaction as a key steps. Thus, L-tyrosine (**11**) on *N*-Boc protection and then subsequent formylation provided 2-formyl derivative **44**. Further, benzylation followed by reaction with 30% H_2O_2 in the presence of diphenyl diselenide gave the aryl formate which on subsequent treatment with methanolic ammonia afforded the desired phenol **46** in 78% yield (**Scheme 21**).



Scheme 21: a) $(BOC)_2O$, Et_3N, dioxane, H_2O, 92%; b) $CHCl_3$, NaOH, H_2O, heat, 4 h, 64%; c) K_2CO_3, BnBr, $CHCl_3$, MeOH; d) 30% H_2O_2, 4% $(PhSe)_2$, CH_2Cl_2, NH_3, 1 h, 78%.

Antilla's approach (2000)[40]

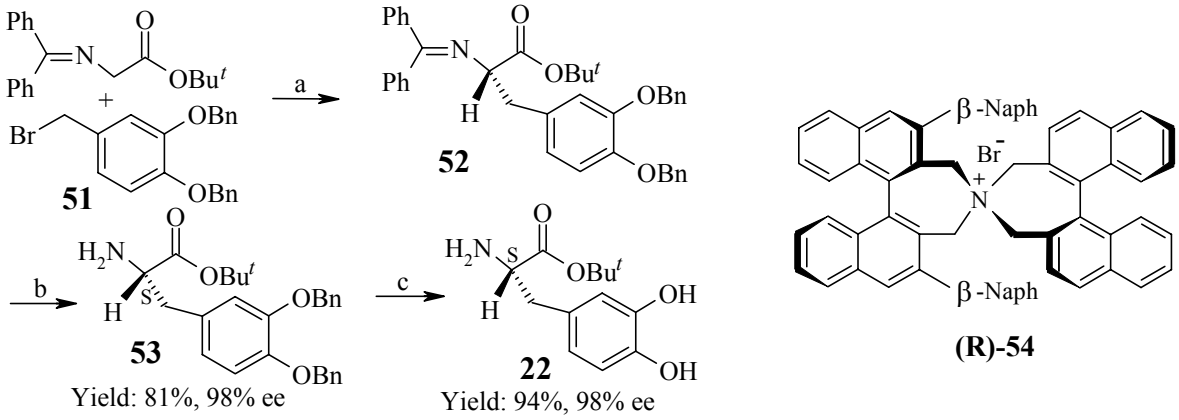
Antilla and co-workers have synthesized L-DOPA (**10**) by using asymmetric aziridination approach. Thus, reaction of imine **47** with ethyl diazoacetate (EDA) in the presence of catalytic amount of (*R*)-VAPOL (**50**) and triphenylborate afforded the chiral aziridines **48** in 96% ee. Hydrogenation of aziridine **48** at the *N*-benzylic bond occurred with cleavage of the benzhydral group to give the amino ester **49** in 72% yield. After hydrolysis L-DOPA (**10**) was obtained in 98% ee and 60% yield (**Scheme 22**).



Scheme 22: a) 1.1 equiv. EDA. (*R*)-VAPOL (**50**)/ $B(OPh)_3$, 8 h (2.5 mol%), 0°C, 6 h, 22°C, 14 h; b) Pd black, HCO_2H/ MeOH, 25°C; c) 3N HCl, acetone, 90°C, 20 h.

Takashi's approach (2000)[41]

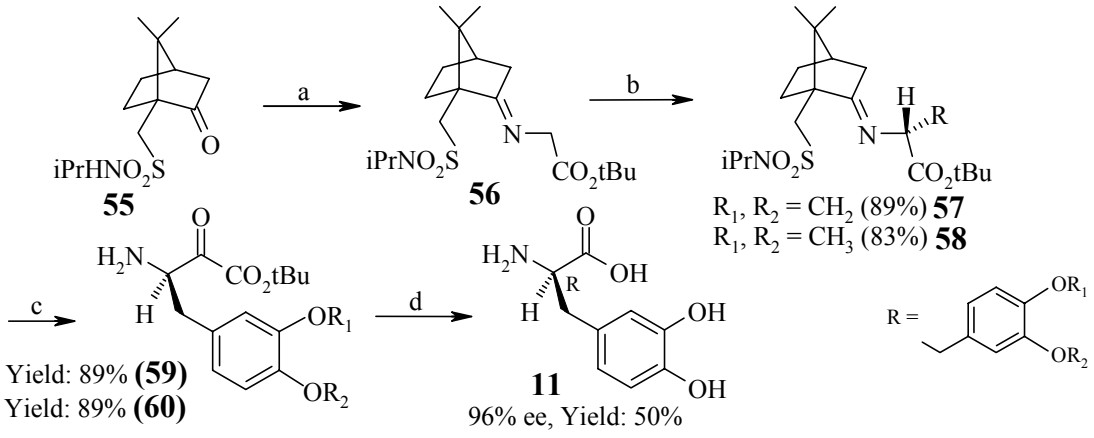
Takashi *et al.* have described synthesis of L-DOPA ester **22** by using chiral quaternary ammonium salt **54** as a phase-transfer catalyst. Thus, alkylation of imine with compound **51** in the presence of catalyst (*R*)-**54** gave *tert*-butyl ester **52**, which was subsequently treated with 1M citric acid to afford the corresponding amino ester **53** in 81% yield. Debenzylation of amine **53** afforded the desired *tert*-butyl ester of L-DOPA **22** in 98% ee (**Scheme 23**).



Scheme 23: a) (*R*)-**54** (1 mol%), toluene, 50% *aq*. KOH, 0°C; b) 1M citric acid, THF, RT, 10 h; c) 10% Pd-C, H_2, THF, RT, 5 h.

Chen's approach (2001)[42]

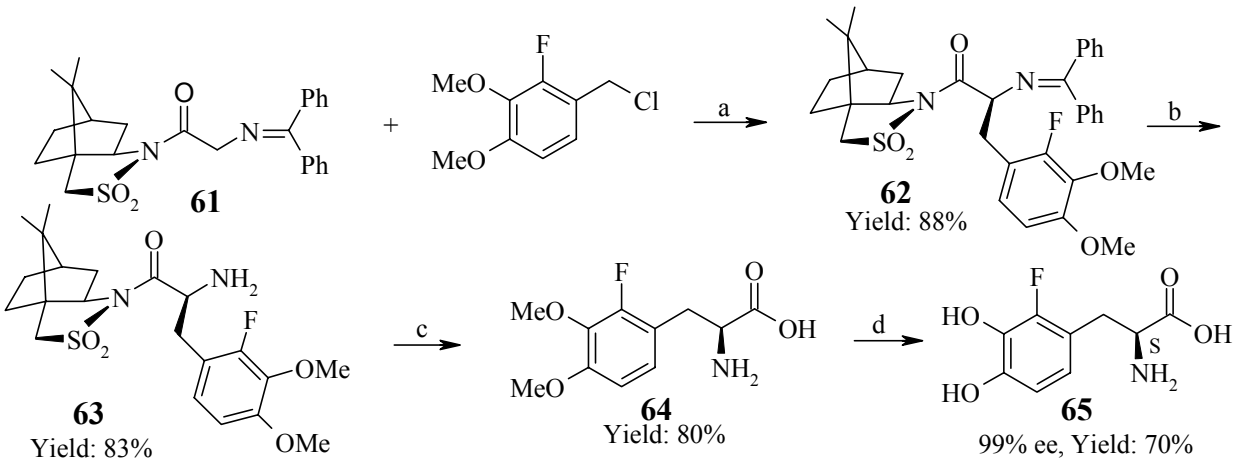
In this approach, D-DOPA (**11**) was prepared by using (1*S*)-*N*,*N*-diisopropyl-10-camphorsulfonamide (**55**) as a chiral auxiliary. Condensation of ketone **55** with excess of *tert*-butyl glycinate gave Schiff base **56**. Treatment of Schiff base **56** with LDA followed by HMPA and 3,4-*O*,*O*-methylenedihydroxybenzyl bromide or 3,4-dimethoxybenzyl bromide provided a single alkylated product **59** or **60** respectively. Hydrolysis of Schiff base and removal of the protecting group gave D-DOPA (**11**) in 96% ee (**Scheme 24**).



Scheme 24: a) *t*-butyl glycinate, toluene, reflux, 48 h, 71%; b) LDA, R-Br, HMPA; c) NaOH, MeOH, AcOH, NH_2OH-HCl; d) (i) 6N HCl, PhOH, AcOH, 130-135^oC; (ii) 47% HBr, PhOH, 120^oC, 13 h.

Deng's approach (2002)[43]

Deng and co-workers have reported alkylation under phase transfer condition as a key step for the synthesis of L-DOPA analogue Thus, chiral glycine synthon **61** on treatment with 2-fluoro-3,4-dimethoxybenzyl chloride gave Schiff base **62**. Subsequent, hydrolysis of the Schiff base **62**, removal of the chiral auxiliary and demethylation produced 2-fluoro L-DOPA (**65**) in 99% ee (**Scheme 25**).



Scheme 25: a) K_2CO_3, cat. Bu_4NBr, CH_3CN, 50°C; b) 1 M HCl, CH_2Cl_2, RT; c) 2.5 M LiOH, H_2O, THF, 0°C; d) 48% HBr, 145°C, 1 h.

3.1.4 Present Work

3.1.4.1 Objective

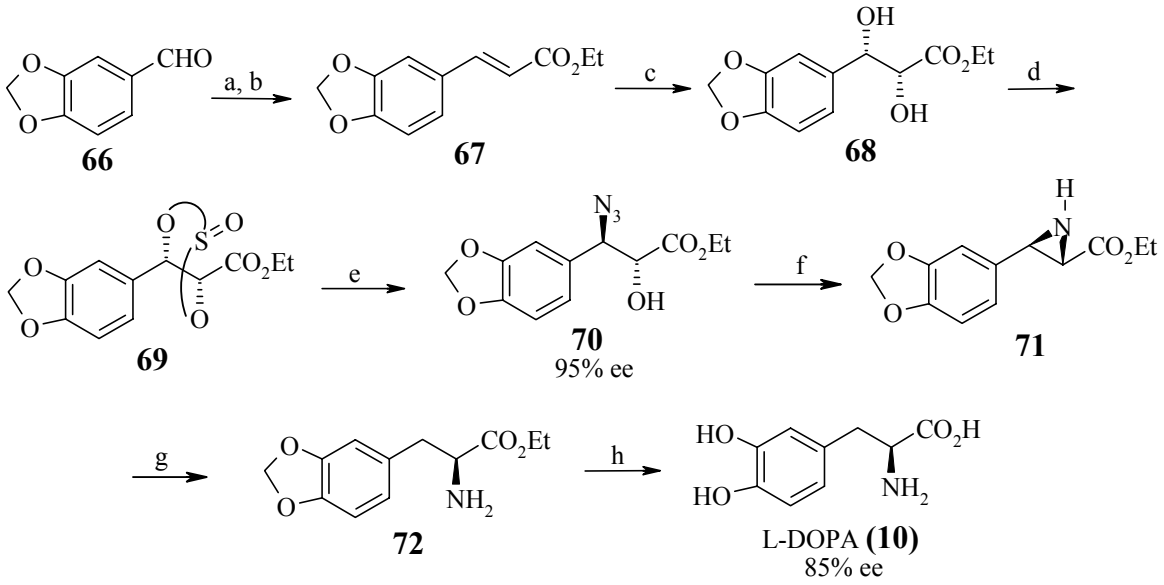
After the discovery of L-DOPA (**10**) for the treatment of Parkinson's disease, the preparation of this specific compound has attracted considerable synthetic attention. However, the literature methods suffer from the disadvantages such as low overall yields, the need for separation of diastereomers and the use of expensive reagents. In this context, more practical approach for the synthesis of L-DOPA (**10**) is highly desirable.

The ring opening of chiral aziridines is a potent method for the synthesis of optically active amines. Since no general methods for catalytic aziridination exist, chiral aziridines have been made from the materials in which the chiral centers already exist.

The catalytic asymmetric dihydroxylation (AD) of olefins using dihydroquinidine or dihydroquinine derivatives as ligands has become a useful and reliable transformation in organic synthesis. The objective of the present investigation is to synthesize L-DOPA (**10**). The key intermediate, 3-phenylaziridine-2-carboxylic ester **71**, was prepared from α,β-unsaturated ester **67** by employing Sharpless Asymmetric Dihydroxylation.

3.1.5 Results and Discussion

The synthetic strategy for the enantioselective synthesis of L-DOPA (**10**) is depicted in **Scheme 26**. In this strategy, Os-catalyzed asymmetric dihydroxylation (AD) constitutes a key reaction in introducing chirality into the molecule.



Scheme 26: a) $BrCH_2CO_2Et$, Zn, benzene, reflux, 92%; b) *p*-TSA, benzene, 90%; c) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0°C, $[\alpha]_D$ +4.0 (c 0.6, $CHCl_3$), 85%; d) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, $[\alpha]_D$ – 100.0 (c 2.3, EtOH), 88%; e) NaN_3, acetone: H_2O, 80°C, $[\alpha]_D$ – 65.0 (c 0.8, EtOH), 95% ee, 82%; f) PPh_3, CH_3CN, $[\alpha]_D$ +176.2 (c 1.0, $CHCl_3$), 90%; g) 10% Pd/C, HCO_2NH_4, MeOH, reflux, $[\alpha]_D$ +7.5 (c 0.6, $CHCl_3$), 92%; h) 6 N HCl, PhOH, AcOH, 130-135°C, 24 h, $[\alpha]_D$ – 11.0 (c 1.0, 1N HCl), 85% ee, 70%.

The *trans* olefin **67** was prepared by employing the Reformatsky reaction of 3,4-methylenedioxybenzaldehyde (**66**) with ethyl bromoacetate followed by *p*-TSA catalyzed dehydration of the corresponding *β*-hydroxy ester. The *trans* geometry of the olefin **67** was confirmed from ^{1}H-NMR spectrum, which showed two doublets at δ 6.26 and 7.59 respectively with a coupling constant of 16.0 Hz. The olefinic ester **67** was then subjected to Sharpless Asymmetric Dihydroxylation (AD) in the presence of catalytic amount of (DHQ)-PHAL (hydroquinine1,4-phthalazinediyl diether) as a chiral ligand to give (2*R*,3*S*)-diol **68** in 85% yield and excellent optical purity. Its ^{1}H-NMR spectrum showed the absence of olefinic

signals and the appearance of new proton signals in the range δ 4.00-5.00 for methine protons. Its ^{13}C-NMR spectrum showed signals at δ 74.35 and 74.87 due to the two carbons bearing the hydroxyl groups **(Fig. 8)**.

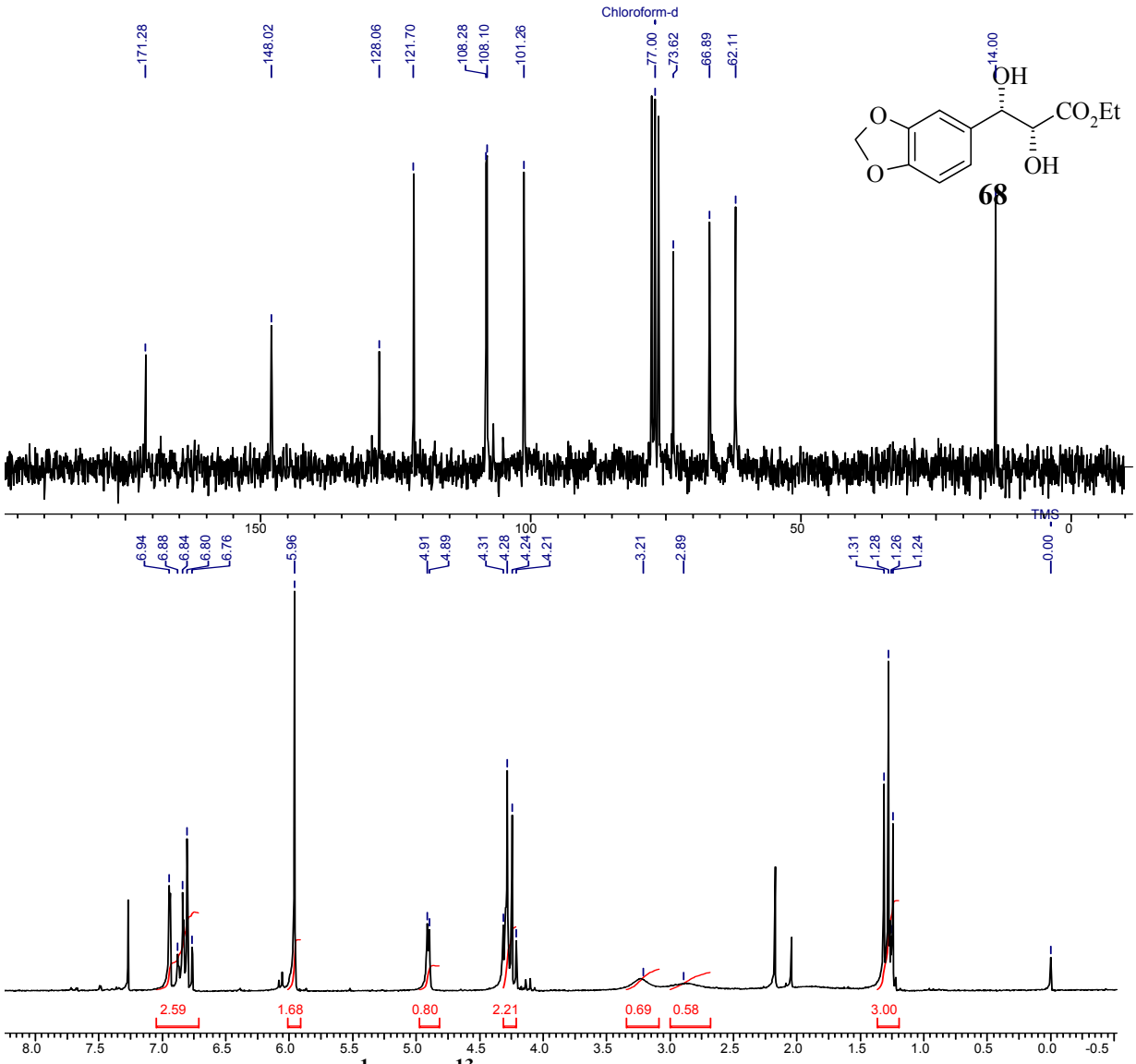


Fig. 8: ^{1}H and ^{13}C-NMR spectra of the diol 68

The vicinal diol **68** was then treated with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0^{o}C to yield the corresponding cyclic sulphite **69** in 88% yield. Its ^{1}H-NMR spectrum showed the presence of mixture of diastereomers in a 1:1 ratio, as evidenced by a set of four doublets in

the region δ 4.50-5.50. The methylenedioxy protons also showed two singlets at δ 5.97 and 6.00 in 1:1 ratio **(Fig. 9)**.

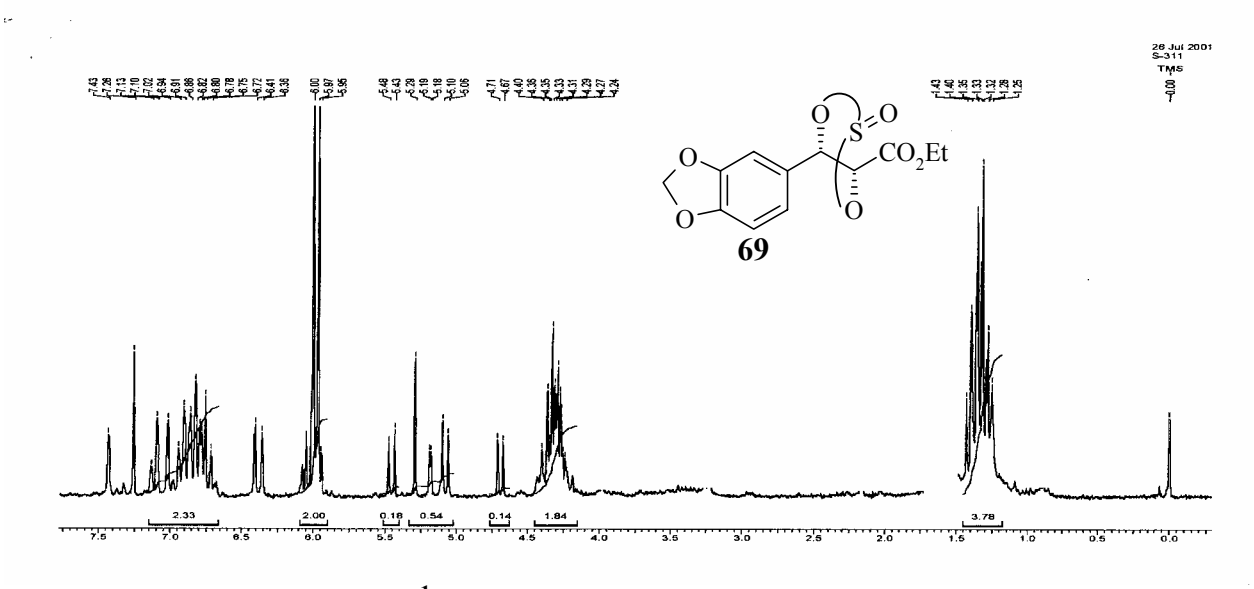


Fig. 9: ^{1}H-NMR spectra of cyclic sulphite 69

Cyclic sulphite **69** was further subjected to oxidation with catalytic amount of $RuCl_3.3H_2O$ employing $NaIO_4$ as stoichiometric oxidant in acetonitrile-water system at 0^oC, but all attempts to isolate the corresponding cyclic sulphate failed. Since the cyclic sulphates of cinnamate derivatives are known to be extremely unstable, isolation gave only decomposed by-products.

However, we solved this problem by carrying out the ring opening of cyclic sulphite **69**, in DMF at higher temperature (80^oC) with sodium azide to give azido alcohol **70** in 95% ee. The formation of azido alcohol **70**, was confirmed by its ^{1}H-NMR spectrum, which showed disappearance of the diastereotopic peaks of cyclic sulphite **69** and the appearance of doublets at δ 4.48 and 4.80 due to C_2 carbon bearing OH and C_3 carbon bearing N_3 functionalities respectively **(Fig. 10)**. Its IR spectrum showed strong absorbances at 2106 and 3480 cm^{-1} assigned to N_3 and OH groups respectively. Further its mass spectrum showed the

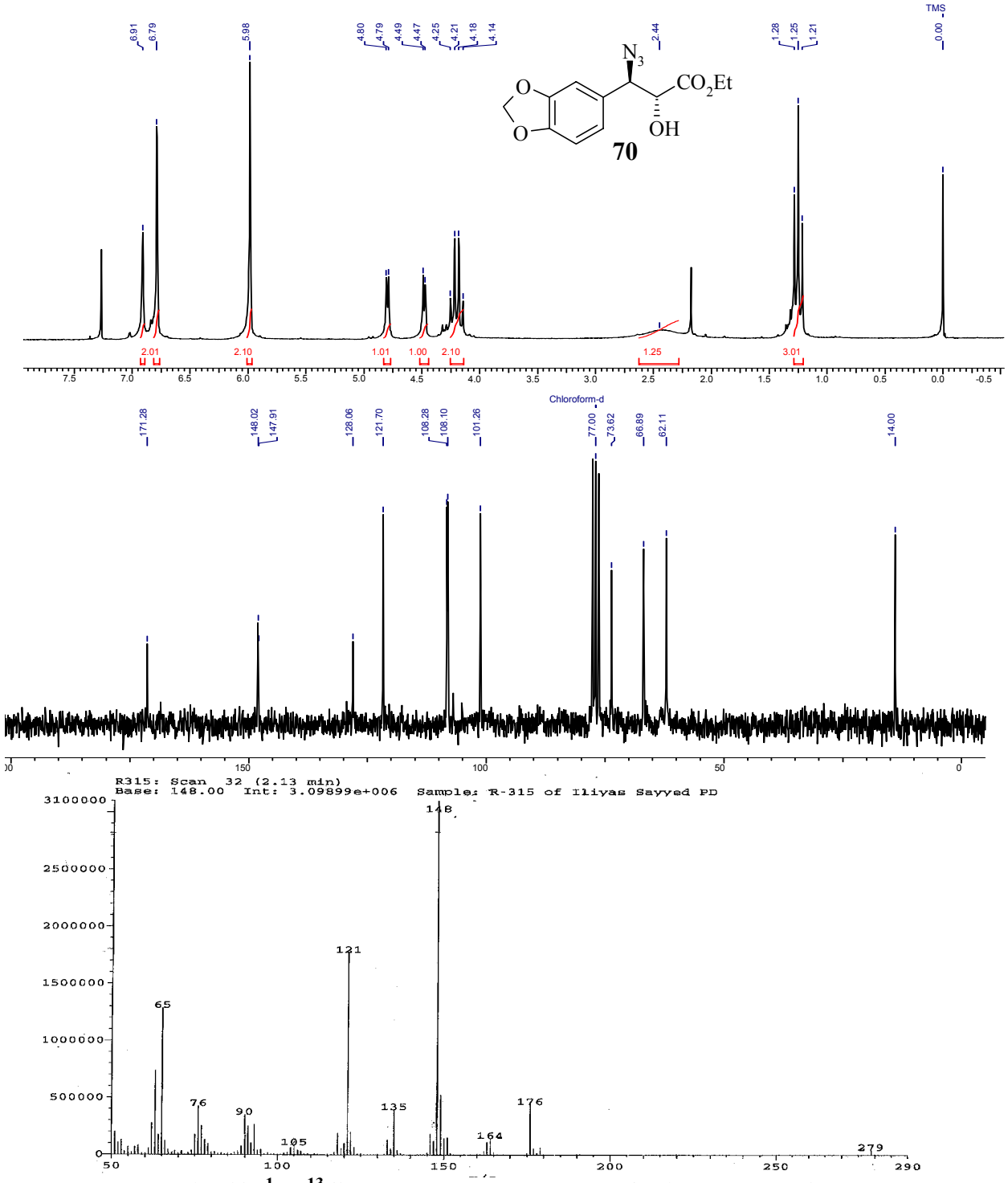


Fig. 10: ^{1}H, ^{13}C-NMR and mass spectra of azido alcohol 70

molecular ion peak at m/e 279. The other regio isomeric product of azido alcohol was not detected (^{1}H-NMR spectrum and GC).

The optical purity of azido alcohol **70** was determined by converting it into the corresponding Mosher ester. Thus, azido alcohol **70** was esterified with (*R*)-α-methoxy-α-trif-

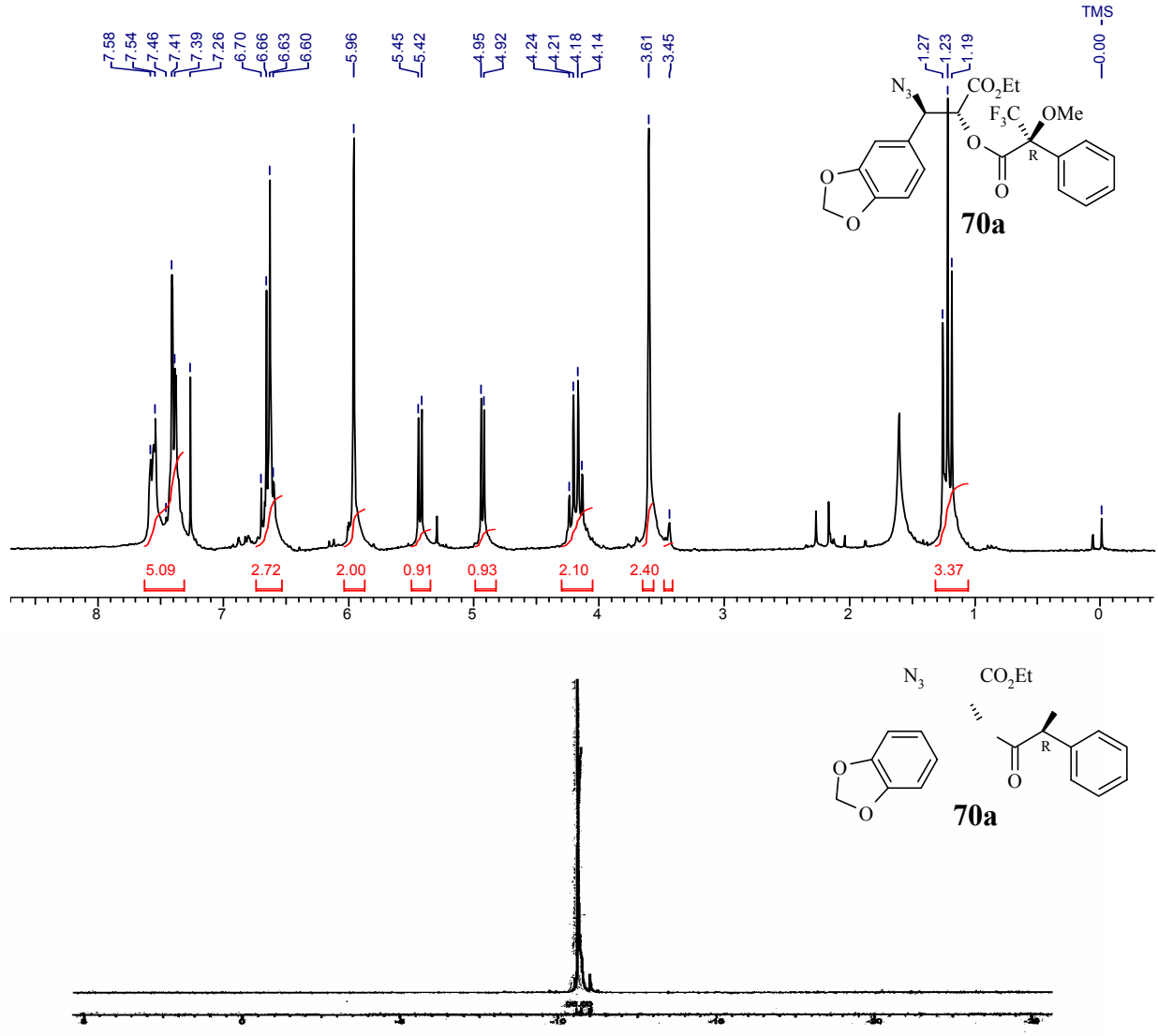


Fig. 11: ^{1}H and ^{19}F-NMR spectra of Mosher ester of azido alcohol 70a

fluoromethylphenyl acetic acid (Mosher's acid). Measurements of the diastereomeric methyl singlets at δ 3.45 and 3.61 in proton NMR spectrum in $CDCl_3$ demonstrated the ester to be of 95% diastereomeric excess. Also its ^{19}F spectrum showed two signals in the ratio 97.5: 2.5 further confirming the diastereomeric excess of 95% **(Fig. 11)**.

The azido alcohol **70** was then treated with triphenylphosphine in acetonitrile (Staudinger reaction). It involved the reduction of the azide functionality *via* imino phosphorane and then an oxazaphospholine intermediate to afford aziridine **71** in 90% yield. The ring closure took place with inversion of configuration at the carbon bearing the leaving group. Therefore, from the cyclic sulphite, to aziridine, the stereochemical configurations at both atoms have been inverted. Its ^{1}H-NMR spectrum showed broad signals at δ 2.51 and 3.18 indicating the formation of aziridine moiety. Its ^{13}C-NMR spectrum showed two new carbon

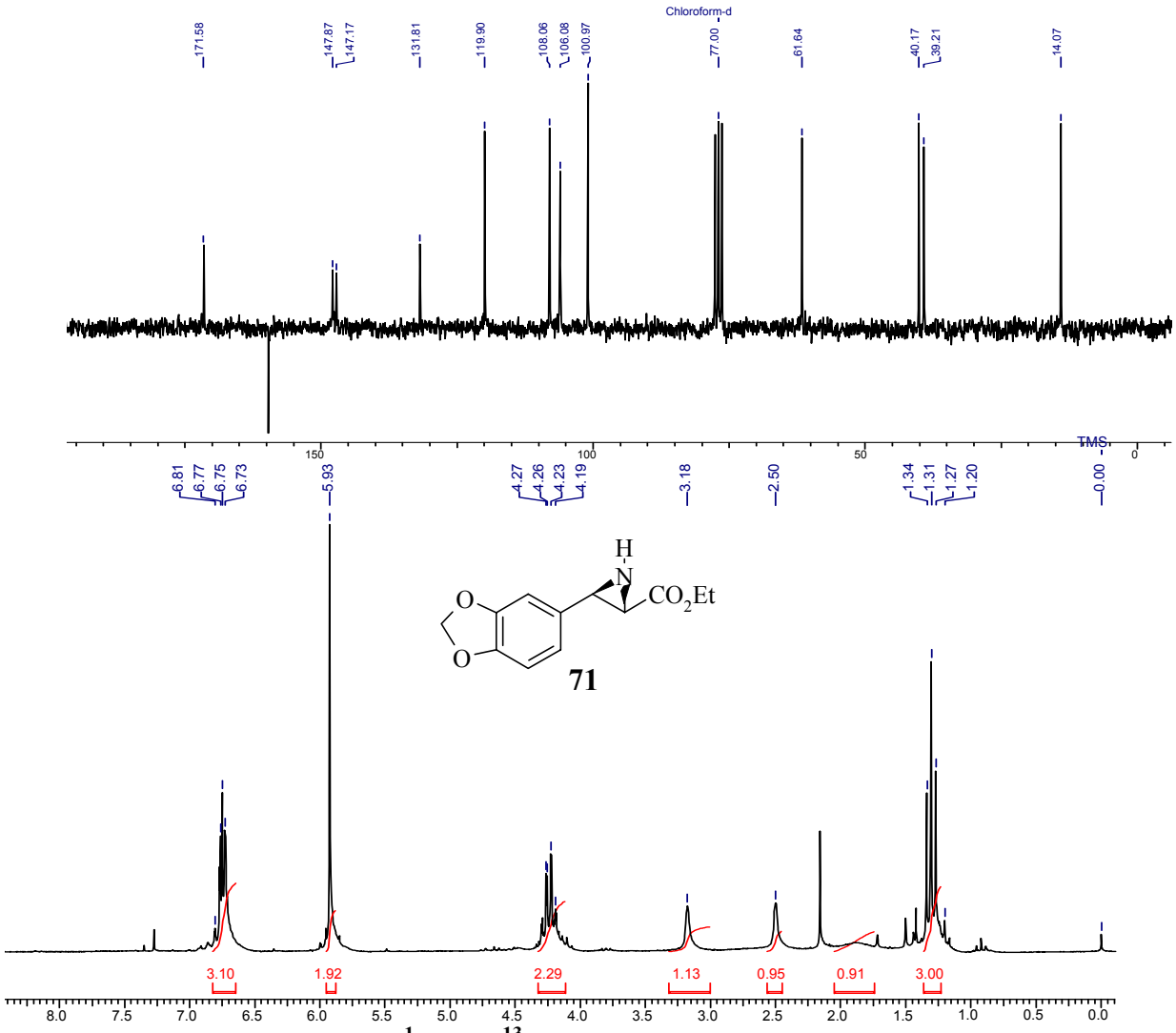


Fig. 12: ^{1}H and ^{13}C-NMR spectra of aziridine 71

signals at 39.21 and 40.17 **(Fig. 12)**. Mass spectrum of aziridine **71** showed the molecular ion peak at m/e 235. Further, base peak observed at m/e 161 is a fragmented ion arising due to the loss of ester functionality **(Fig. 13)**.

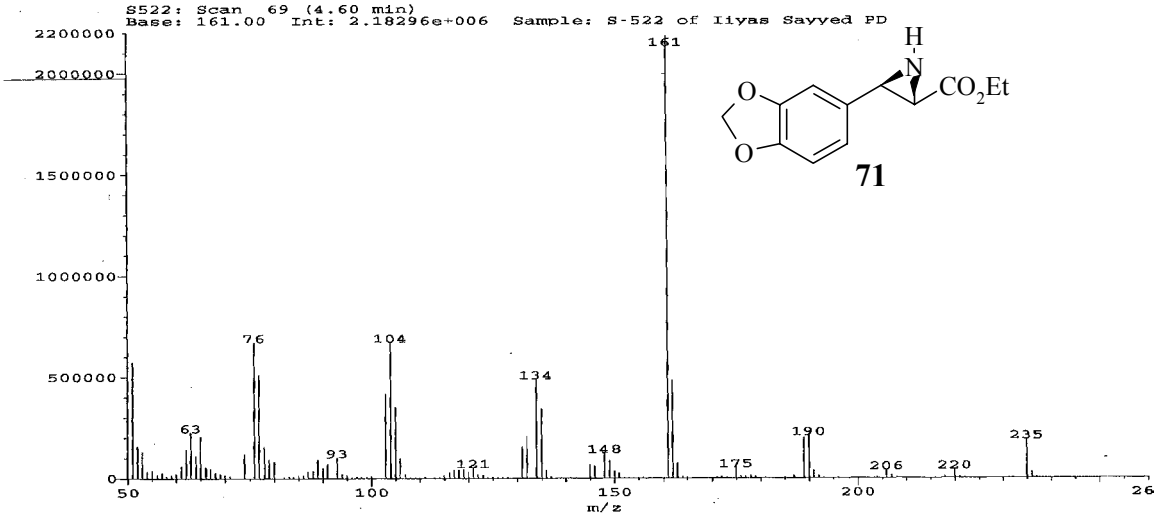


Fig. 13: Mass spectra of aziridine 71

Aziridine **71**, was then subjected to Pd-catalyzed reductive ring opening with ammonium formate as hydrogen source to produce amine **72** in 92% yield. Aziridine **71** underwent stereospecific and regioselective ring opening at the benzylic position. Its ^{1}H-NMR spectrum showed disappearance of broad signals of aziridine moiety and appearance of two doublet of doublet in the region δ 2.70-3.10 due to the diastereotopic benzylic protons. Broad signal due to NH_2 was observed at δ 2.50. Its ^{13}C-NMR spectrum showed signal at δ 40.46 due to C_3 methylene carbon and signal at δ 174.30 due to ester carbonyl.

Finally, aminoester **72** was treated with 6N HCl, PhOH, AcOH at 130-135^{o}C, to cleave 3,4-methylenedioxy group and followed by hydrolysis of the ester group gave L-DOPA (**10**), in 85% ee {$[\alpha]_D$ – 11.0 (c 1.0, 1N HCl); lit.[30] $[\alpha]_D$ – 12.3 (c 1.0, 1N HCl)} and 70% yield. Its ^{1}H-NMR spectrum showed absence of signals due to 3,4-methylenedioxy and ester

functionality. The benzylic methylene protons appeared as two doublet of doublet in the region δ 3.00-3.50 also methine proton α to carbonyl appeared as multiplet at δ 4.45 **(Fig. 14)**.

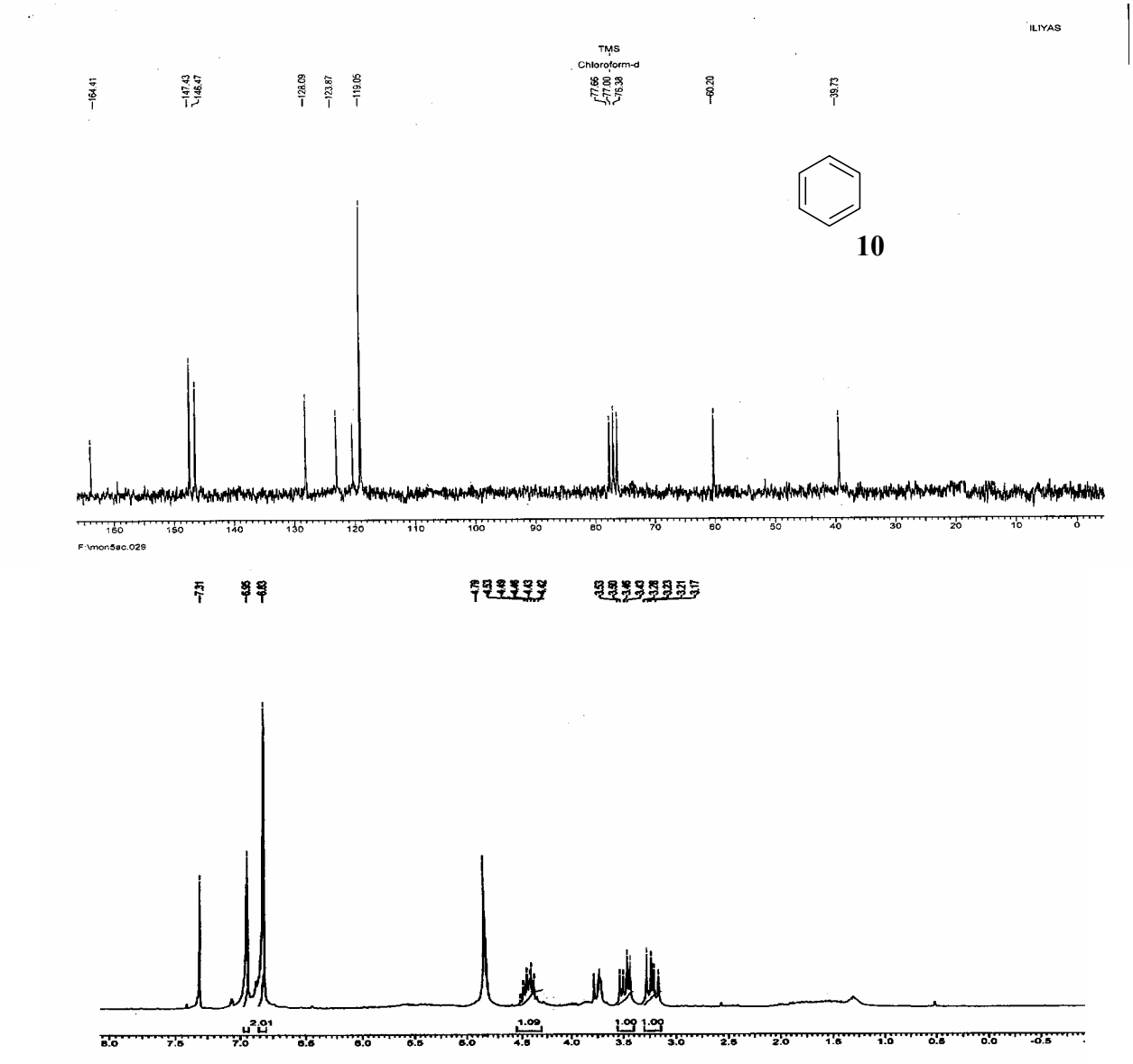


Fig. 14: ^{1}H and ^{13}C-NMR spectra of L-DOPA 10

3.1.6 Conclusion

In conclusion, an enantioselective synthesis of L-DOPA (**10**) was successfully developed. In this approach, the key intermediate, chiral aziridine **71** was prepared from α,β-unsaturated ester **67** by employing the Sharpless Asymmetric Dihydroxylation. L-DOPA (**10**)

was obtained in excellent yield and good optical purity [29.4% overall yield, 85% ee], in seven steps.

3.1.7 Experimental Section

Preparation of ethyl 3-(3,4-methylenedioxylphenyl)-2-propeonate (67)

A 100 ml two-necked RB equipped with water condenser and septum was charged with activated zinc (2.38 g, 36.6 mmol), and kept under N_2 atmosphere. Dry benzene (25ml) was introduced in the reaction flask and heated upto 80^oC (oil bath temp). A solution of ethyl bromoacetate (6.12 g, 36.6 mmol) and 3,4-methylenedioxybenzaldehyde (**66**) (5.00 g, 33.3 mmol) in dry benzene was added drop wise to the reaction flask. After completion of addition the reaction flask was refluxed for 5 h, cooled to RT and then quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether. After evaporation of the solvent under reduced pressure afforded the crude hydroxyester and then it was subjected to dehydration with *p*-toluenesulphonic acid (0.7 g, 3.6 mmol) in toluene at reflux temperature. Water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester **67** was purified by column chromatography packed with silica gel, eluting with pet. ether to give 6.59 g of **67**.

Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3010, 2898, 2400, 1701, 1632, 1495, 1410, 1350, 1300, 1250, 1200, 1100, 1020, 960, 750; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 8.0 Hz, 3H), 4.20-4.30 (q, *J* = 8.0 Hz, 2H), 6.01 (s, 2H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.81 ((d, *J* = 16.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 16.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.14, 60.09, 101.37, 106.48, 108.35, 116.33, 124.01, 128.98, 144.01, 148.27, 149.45, 166.84; **MS** m/z (% RI): 220 (M^+, 45), 192 (13), 175 (52), 148 (42), 145 (45), 117 (35), 89 (100), 73 (13), 65 (23), 63 (85), 62 (35); **Analysis:** $C_{12}H_{12}O_4$ requires C, 65.45; H, 4.87; found C, 65.40; H, 4.82%.

Preparation of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-(3,4-methylenedioxylphenyl) propionate (68)

A double-walled 250 ml RB flask was charged with K_3FeCN_6 (8.94 g, 27.2 mmol), K_2CO_3 (3.75 g, 27.2 mmol), $(DHQ)_2$-PHAL (140 mg, 0.18 mmol), $MeSO_2NH_2$ (0.855 g, 9.0 mmol) and *t*-BuOH: H_2O (1:1, v/v, 90 ml) and stirred for five minutes at 25^0C. Then cooled to 0^0C and a solution of OsO_4 (184 μl, 0.09 mmol, 0.5M solution in toluene) was added followed

by cinnamate **67** (2.0 g, 9.0 mmol). The reaction mixture was stirred for 24 h at 25^0C. (monitored by TLC). The reaction was then quenched with sodium sulfite (10 g) and extracted with ethyl acetate (3 x 60 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using EtOAc: pet. ether (1:1) as eluent to yield 1.95 g of **68**.

Yield: 85%; **gum**; $[\alpha]^{25}_{D}$ + 4.0 (c 0.6, $CHCl_3$), **IR** ($CHCl_3$, cm^{-1}): 3552, 2400, 1731, 1530, 1444, 1215, 1041, 930, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 8.0 Hz, 3H), 3.90 (brs, 1H), 3.75 (brs, 1H), 4.21-4.33 (m, 4H), 4.90 (d, *J* = 4.0 Hz, 1H), 5.96 (s, 2H), 6.75-7.00 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.00, 62.00, 74.35, 74.87, 101.00, 106.99, 107.99, 119.79, 133.94, 147.69, 155.48, 155.55, 172.53; **MS** m/z (% RI): 254 (M^+, 5), 220 (4), 175 (4), 166 (10), 165 (12), 151 (100), 150 (25), 135 (6), 123 (11), 121 (10), 104 (4), 93 (45), 67 (10), 65 (28), 63 (14); **Analysis:** $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.54; found C, 56.71; H, 5.50%.

Preparation of ethyl (4*R*,5*S*)-4-carbethoxy-5(3,4-methylenedioxylphenyl)1,3 ,2-dioxathiolane-2-oxide (69)

The diol **68** (1.90 g, 7.48 mmol) was dissolved in triethylamine (20 ml) and cooled to 0^0C in an ice bath under argon atmosphere. Freshly distilled thionyl chloride (1.33 g, 0.81 ml, 11.2 mmol) was added drop-wise and the reaction mixture was stirred at 0^0C for 45 minutes (monitored by TLC). After completion of reaction, ice-cold water (25 ml) was added and extracted with ether (3 x 25 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether : EtOAc (9:1) as eluent to furnish sulphite **69** as light yellow oil (1.97 g).

Yield: 88%; **brown liquid**; $[\alpha]^{25}_{D}$ – 100.0 (c 2.3, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3448, 3020, 2900, 1735, 1488, 1446, 1251, 1215, 1041, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.20-1.45 (m, 3H), 4.20-4.45 (m, 2H), 4.69 (d, *J* = 8.0 Hz), 5.08 (d, *J* = 8.0 Hz), 5.18 (d, *J* = 10.0 Hz), 5.40 (d, *J* = 10 Hz) 5.97 (s), 6.00 (s), 6.38 (d, *J* = 10.0 Hz, 1H), 6.75-7.25 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 13.85, 62.74, 81.30, 82.44, 83.21, 88.81, 101.26, 102.55, 165.77, 128.09, 128.90,

129.12, 132.43, 132. 96, 135.52, 135.70, 166.62; **MS** m/z (% RI): 292 (5), 236 (14), 208 (4), 179 (12), 162 (100), 149 (12), 135 (85), 134 (62), 121 (5), 93 (12), 92 (10), 77 (40), 76 (35), 63 (13); **Analysis:** $C_{12}H_{12}SO_7$ requires C, 48.00; H, 4.02; found C, 48.05; H, 4.08%.

Preparation of ethyl (2*R*,3*R*)-3-azido-2-hydroxy-3-(3,4-methylenedioxylphenyl)propionate (70)

To a stirred solution of cyclic sulphite **69** (1.85 g, 6.16 mmol) in DMF (5 ml) was added sodium azide (0.16 g, 24.6 mmol). The reaction flask was then heated to 80^{o}C for 6 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured in water (25 ml), and then it was extracted with ether (3 x 25 ml). The combined organic phases were washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude azidoalcohol was then purified with silica gel chromatography eluted with pet. ether : EtOAc (9:1) to give azido alcohol **70** (1.63 g).

Yield: 95%; **gum**; $[\alpha]^{25}_{D}$ – 65.0 (c 0.8, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3415, 3020, 2108, 1735, 1504, 1488, 1444, 1225, 1215, 1041, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 6.0 Hz, 3H), 2.45 (brs, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.80 (d, *J* = 4.0 Hz, 1H), 5.99 (s, 2H), 6.79 (s, 2H), 6.91 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.00, 62.11, 66.89, 73.62, 101.26, 108.10, 108.28, 121.70, 128.60, 148.01, 171.28; **MS** m/z (% RI): 279 (M^+, 4), 176 (15), 164 (6), 149 (20), 148 (100), 135 (13), 121 (60), 105 (3), 92 (7), 90 (12), 76 (14), 65 (43), 63 (24); **Analysis:** $C_{12}H_{13}N_3O_5$ requires C, 51.61; H, 4.68; N, 15.04; found C, 51.66; H, 4.65; N, 15.10%.

Preparation of Mosher ester of azido alcohol (70a)

A two-neck 25 ml flask with septum was charged with (44 mg, 0.206 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (5 ml) under argon atmosphere. The flask was allowed to cool at 0^{o}C for 10 min and a solution of azido alcohol **70** (50 mg, 0.179 mmol) in CH_2Cl_2 (5 ml) was introduced through syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 was done. This reaction mixture was then stirred at 0^{o}C for additional one hour and then at room temperature for overnight. The solvent was evaporated under reduced pressure to get crude material, which

was then purified by column chromatography eluting with 5% ethyl acetate in pet. ether to get Mosher ester of azido alcohol (85 mg).

Yield: 89%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 8.0 Hz, 3H), 3.45 (s, 0.15H), 3.61 (s, 2.85H), 4.18 (q, *J* = 8.0 Hz, 2H), 4.93 (s, 1H), 5.42 (s, 1H), 5.96 (s, 2H), 6.55-6.70 (m, 3H), 7.15-7.60 (m, 5H).

Preparation of ethyl (2*S*,3*R*)-3-(3,4-methylenedioxylphenyl) aziridine-2-carboxylate (71)

To a stirred solution of azido alcohol **70** (1.0 g, 3.58 mmol) in acetonitrile (30 ml) was added PPh_3 (0.937 g, 3.58 mmol). The reaction mixture was then stirred at 25^{o}C for 1 h and then it was refluxed for 6 h. After completion of reaction (monitored by TLC) the solvent was removed under reduced pressure to get crude aziridine. The pure product was isolated by silica gel chromatography eluted with pet. ether : EtOAc (9:1) to give aziridine **71** (0.757 g).

Yield: 90%; **gum**; **$[\alpha]^{25}_D$** + 176.2 (c 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3288, 3020, 2896, 2770, 2401, 1722, 1608, 1504, 1500, 1448, 1365, 1320, 1215, 1120, 1041, 939, 757, 680; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 6.0 Hz, 3H), 2.16 (s, 1H), 2.50 (brs, 1H), 3.18 (brs, 1H), 4.15-4.35 (q, *J* = 6.0 Hz, 2H), 5.93 (s, 3H), 6.65-6.85 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.07, 39.21, 40.17, 61.64, 100.97, 106.08, 108.06, 119.90, 131.81, 147.17, 147.87, 171.58; **MS** m/z (% RI): 235 (M^+, 30), 206 (11), 163 (6), 162 (40), 149 (8), 148 (10), 135 (48), 133 (12), 104 (20), 80 (12), 77 (15), 63 (4), 60 (5), 51 (18), 32 (100); **Analysis:** $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.56; N, 5.95; found C, 61.22; H, 5.52; N, 5.98%.

Preparation of ethyl (*S*)-2-amino-3-(3,4-methylenedioxylphenyl) propionate (72)

To a stirred solution of aziridine **71** (0.700 g, 2.97 mmol) in methanol (10 ml) was added 10% Pd/C (5 wt%) and ammonium formate (0.281 g, 4.46 mmol). The reaction flask was then heated to reflux for 4 h. After completion of the reaction, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give a residue. The residue was then purified by silica gel chromatography eluted with EtOAc to give amine **72** (0.634 g).

Yield: 90%; **gum**; **$[\alpha]^{25}_D$** + 7.5 (c 0.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3381, 3019, 1735, 1684, 1503, 1489, 1035, 910, 759; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 6.0 Hz), 2.35-2.70 (brs, 1H), 2.70-2.85 (dd, *J* = 8.0 and 14.0 Hz, 1H), 2.95-3.10 (dd, *J* = 16.0 and 14.0 Hz, 1H),

3.60-3.75 (brs, 1H), 4.10-4.25 (q, J = 6.0 Hz, 2H), 5.92 (s, 2H), 6.60-6.80 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.14, 40.50, 55.79, 60.94, 100.86, 108.21, 109.53, 122.36, 130.78, 146.47, 147.72, 174.30; **MS** m/z (% RI): 237 (M^+, 17), 220 (12), 206 (5), 165 (40), 164 (30), 149 (12), 136 (38), 135 (100), 121 (5), 106 (15), 102 (14), 91 (4), 77 (24), 69 (12); **Analysis:** $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.36; N, 5.90; found C, 60.70; H, 6.36; N, 5.92%.

Preparation of (*S*)-2-Amino-3(3,4-dihydroxyphenyl)propanoic acid (10)

To a 50 ml flask was added amine **72** (0.200 g, 0.84 mmol), phenol (0.236 g, 2.52 mmol), glacial acetic acid (0.151 g, 2.52 mmol), and 6N HCl (10 ml). The reaction mixture was heated to reflux for 36 h and then it was concentrated to give a residue. The residue was dissolved in EtOAc and extracted with water. The aqueous layer was adjusted to pH 5 with 28% ammonia water and a trace amount of sodium bisulphate and then cooled in crushed ice to give L-DOPA (**10**) as white crystals (0.116 g).

Yield: 70%; **mp:** 298^{0}C; lit. **mp:** 295^{0}C; **$[\alpha]^{25}_D$** – 11.0 (c 1.0, 1N HCl); {lit.[30] **$[\alpha]_D$** – 12.3 (c 1.0, 1N HCl)}; **IR** (KBr, cm^{-1}): 3500, 3203, 2925, 2854, 1696, 2599, 1654, 1610, 1591, 1514, 1454, 1245, 985, 840; **^{1}H-NMR** (200 MHz, D_2O, DCl): δ: 3.20 (dd, J = 6.0 Hz, 1H), 3.50 (dd, J = 6.0, 1H), 4.45 (m, 1H), 6.80-7.05 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39.73, 60.20, 119.05, 120.20, 123.87, 128.09, 146.47, 147.43, 164.41 **Analysis:** $C_9H_{11}NO_4$ requires C, 54.82; H, 5.61; N, 7.10; found C, 54.80; H, 5.66; N, 7.15%.

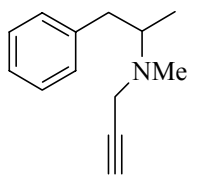
SECTION-III

Asymmetric Synthesis of (*R*)-Seligiline *via,* OsO_4-Catalyzed Asymmetric Dihydroxylation

3.2.1 Introduction

In recent years, the treatment of Parkinson's disease has undergone an immense amount of research, resulting in the development of new medications. Indeed, levodopa remains the most effective therapeutic agent for the treatment of Parkinson's disease (PD). Initially, levodopa provides a stable therapeutic response but during long-term treatment its beneficial effect declines and a gradually increasing number of patients experience fluctuations in motor response. Therefore, in the management of PD it is important to minimize the risk for the development of motor fluctuations. In this context, it appears advisable to initiate dopaminergic treatment in early PD. Another alternative would be to start with selegiline alone, then depending on the disability of the patient, add a dopamine agonist and finally levodopa.

L-Deprenyl (Selegiline) (**73**), a selective inhibitor of MAO (monoamineoxidase)-B, is effective in treating Parkinson's disease in combination with L-dopa and possibly Alzheimer's disease (AD).[44] Selegiline hydrochloride is a laevorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as L-deprenyl **(Fig. 15)**.



(±)-Selegiline **(73)**

Fig. 15

Alzheimer's disease (AD)[45]

Alzheimer's disease (AD) is named after Dr. Alois Alzheimer, a German doctor. Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. Alzheimer's disease (AD) is the most common form of dementia among older people. It involves the parts of the brain that control thought, memory, and language. The disease usually begins after age 60, and risk goes up with age. There is a loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. There are lower levels of chemicals in the brain that carry complex messages back and forth between nerve cells. AD may disrupt normal thinking and memory by blocking these messages between nerve cells. While the cause of Alzheimer's remains largely unknown it has been definitely linked to oxidative damage to brain cells. This damage accumulates over a period of time. There is overwhelming clinical evidence that antioxidants, those free radical fighters, are effective in preventing and beating back the symptoms of both dementia and Alzheimer's.

Symptoms of Alzheimer's disease

Alzheimer's disease (AD) begins slowly. At first, the only symptom may be mild forgetfulness. People with AD may have trouble in remembering recent events, activities, or the names of familiar people or things. Simple math problems may become hard to solve. However, as the disease goes on, symptoms are more easily noticed and become serious enough. They begin to have problems speaking, understanding, reading, or writing. Later on, people with AD may become anxious or aggressive, or wander away from home.

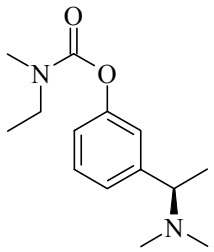
What Causes AD?

Scientists do not yet fully understand what causes AD. There probably is not one single cause, but several factors that affect each person differently. Apart from ageing and family history genetics play an important a role in many AD cases. One risk factor for AD is a

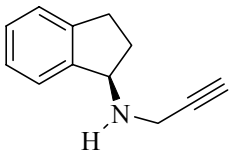
protein called apolipoprotein-E (apo-E). Everyone has apo-E, which helps carry cholesterol in the blood.

Therapy for Alzheimer's disease (AD)

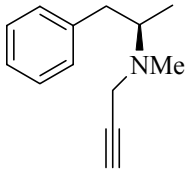
Currently**,** the only therapy for AD is based on a reduction of the cognitive defects by enhancing cholinergic transmission through inhibition of acetyl cholinesterase (AchE). These anti-AchE agents include tacrine, galanthamine, donepezine, and rivastigmine (**74**), which have been shown to induce a modest improvement in memory and cognitive function,[46] On the other hand, selegiline (**73**), a selective MAO-B inhibitor, has been reported to retard the further deterioration of cognitive functions to more advanced milestones in AD.[47] The propargylamine pharmacophore of resagiline (**75**), selegiline (**73**), and related compounds also appears to have neuroprotective activity independent of MAO inhibition.[48] (*R*)-Selegiline (**76**) was found to be more active than racemic selegiline (**73**) **(Fig. 16)**.



(*R*)-Rivastigmine **(74)**



(*R*)-Resagiline **(75)**



(*R*)-Selegiline **(76)**
(*R*)-Selegiline. HCl **(77)**

Fig: 16

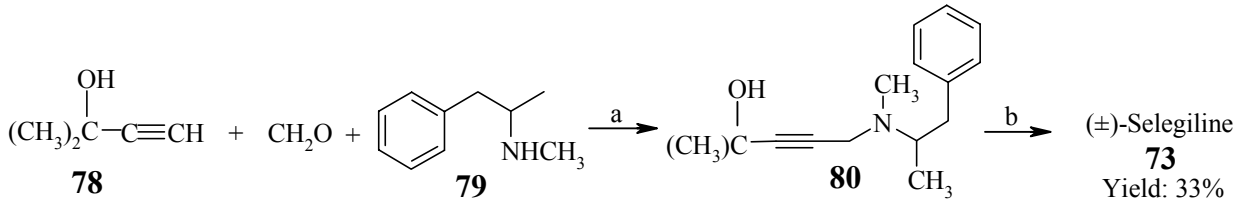
Selegiline and alpha-tocopherol (Vitamin-E) may slow important functional signs and symptoms of Alzheimer's disease. Taking selegiline, vitamin E, or a combination of the two drugs delayed by about 7 months the time it took for patients to reach one of four milestones: death, institutionalization (moving to a nursing home), loss of the ability to perform activities of daily living, or progression to severe dementia.

3.2.2 Review of Literature

Literature search reveals that there are some reports available for the synthesis of selegiline, which are described below.

Flower's approach (1977)[49]

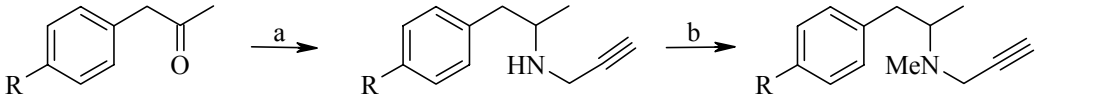
Flower *et al.* have reported the synthesis of racemic selegiline (**73**) involving the Mannich reaction as a key step. Thus, reaction of 2-methyl-butyn-ol (**78**) and formaldehyde with deoxyephedrine (**79**) gave compound **80**, which on subsequent base-catalyzed elimination of acetone gave racemic selegiline (**73**) in 33% yield (**Scheme 27**).



Scheme 27: a) CuCl, 110°C, 4 h, 60 %; b) KOH, 150°C, 33%.

Gyogy's approach (1988)[50]

Gyogy *et al.* have reported a method for the preparation of racemic selegiline (**73**) and 4-fluoroselegiline (**85**). Thus, phenylacetone (**81**) and propargylamine on treatment with $HgCl_2$-activated Al at 60°C gave amine (**83**), which on methylation yielded racemic selegiline (**73**). Similarly, (4-fluorophenyl)acetone (**82**) gave 4-fluoroselegiline (**85**) (**Scheme 28**).



R = H **(81)**
R = F **(82)**

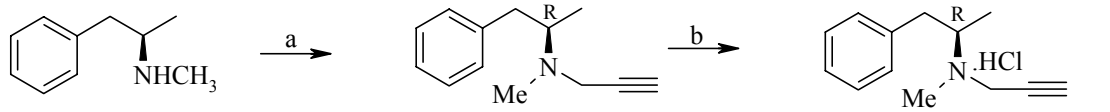
R = H **(83)**
R = F **(84)**

R = H, (±) Selegiline **(73)**
R = F, (±) 4-Fluoro selegiline **(85)**

Scheme 28: a) propargylamine, EtOH, 60°C, $HgCl_2$-Al; b) MeI, K_2CO_3, acetone.

Hajicek's approach (1988)[51]

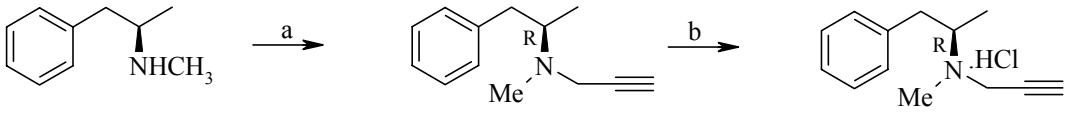
The title compound (**77**) was prepared by propargylation of deoxyephedrine (**86**) with propargyl bromide, K_2CO_3 in an inert solvent. Subsequent, treatment with HCl afforded (*R*)-selegiline hydrochloride (**77**) (**Scheme 29**).



(*R*)-Deoxyephedrine **(86)** **76** (*R*)-Selegiline. HCl **(77)**

Scheme 29: a) propargyl bromide, K_2CO_3, 5°C; b) HCl (gas).

Same group have prepared (*R*)-selegiline hydrochloride (**77**) by reaction of (*R*)-deoxyephedrine (**86**) with $HC{\equiv}CCH_2OP^+Ph_3Cl^-$, followed by HCl (**Scheme 30**).

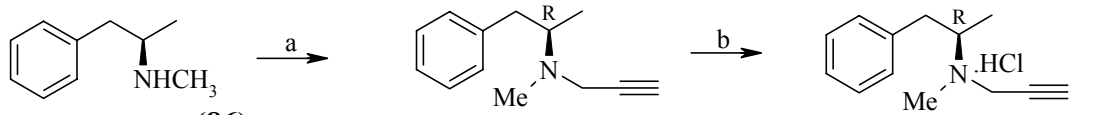


(*R*)-Deoxyephedrine **(86)** **76** (*R*)-Selegiline. HCl **(77)**
Yield: 36%

Scheme 30: a) $HC{\equiv}CCH_2OP^+Ph_3Cl$, Et_3N, CH_3CN 25°C, 10 h; b) HCl (gas), *i*PrOH, 36%.

Ott-Dombrowski's approach (1996)[52]

This process for the synthesis of (*R*)-selegiline (**77**) hydrochloride involves *N*-alkylation of deoxyephedrine (**86**) with propargyl bromide in two-phase system comprising



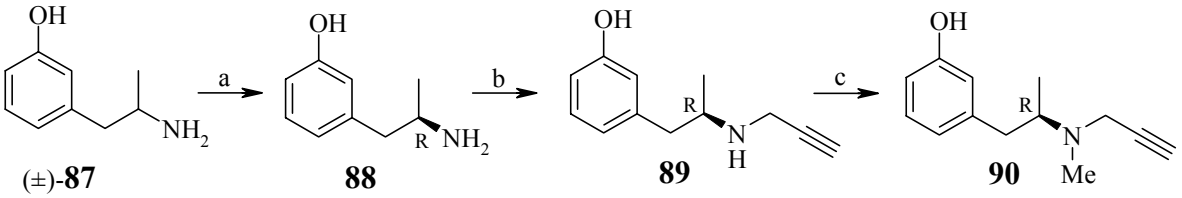
(*R*)-Deoxyephedrine **(86)** **76** (*R*)-Selegiline. HCl **(77)**

Scheme 31: a) propargyl bromide, H_2O and aromatic hydrocarbon; b) HCl (gas).

water and organic hydrocarbon without a catalyst followed by conversion to the (*R*)-selegiline hydrochloride (**77**) (**Scheme 31**).

Sterling's approach (2002)[53]

Sterling *et al.* have reported the synthesis of (*R*)-3-hydroxy selegiline (**90**), involving classical resolution of amine **87** with D-tartaric acid to give optically pure amine **88**. Subsequent, propargylation and reaction with ethyl formate gave formate derivative, which on reduction yielded (*R*)-3-hydroxy selegiline (**90**) (**Scheme 32**).

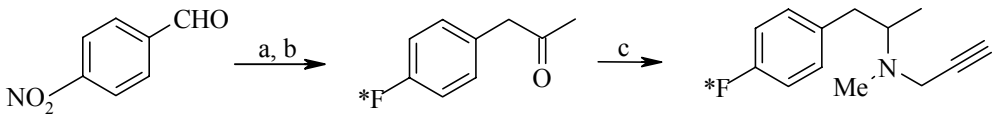


(±)-**87** **88** **89** **90**

Scheme 32: a) D-tartaric acid, MeOH, reflux; then 25% NH_4OH, RT; b) propargyl bromide, K_2CO_3, RT; c) HCO_2Et, reflux; then $LiAlH_4$, THF, 5 ^oC- RT.

Plenevaux's approach (2002)[54]

Racemic 4-[^{18}F]fluoroselegiline (**85**) was prepared *via* the three step procedure. First substitution by [^{18}F]fluoride on 4-nitrobenzaldehyde (**91**) followed by reaction with (1-chloro-1(trimethylsilyl)ethyl)lithium and hydrolysis gave 4-[^{18}F]flurophenylacetone (**82**) in 50% yield. Reductive alkylation of ketone **82** with *N*-methylpropnylamine in presence of $NaBH_3CN$ gave 4-[^{18}F]fluorodeprenyl (**85**) in 35% yield (**Scheme 33**).



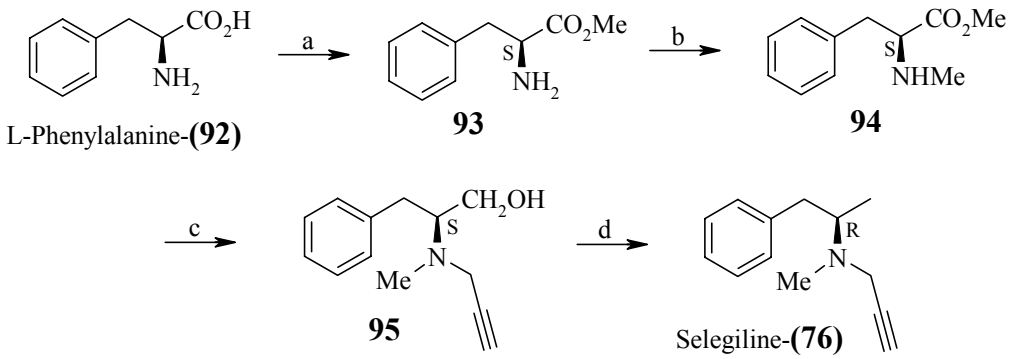
91 **82** (±)-**85** Yield: 35%

Scheme 33: a) KF, 65%; b) 1-chloro-1(trimethylsilyl)ethyl lithium, hydrolysis, 50%; c) *N*-methyl-propynylamine, $NaBH_3CN$, 35%.

www.selegiline.com[55]

In this method for the preparation of (*R*)-Selegiline (**76**), L-phenyl alanine (**92**) is used as starting material. Methyl ester of phenyl alanine (**93**) on condensation with formic acid gave *N*-formyl derivative, which on subsequent reduction gave *N*-methyl derivative **94**.

Further, propargylation and lithium aluminium hydride reduction of ester yielded alcohol **95**, which on subsequent reaction with thionyl chloride followed by reduction, gave (*R*)-Selegiline (**76**) (**Scheme 34**).



Scheme 34: a) MeOH, 95%; b) HCO_2H then $NaBH_4$ reduction, 85%; c) propargyl bromide, then $LiAlH_4$; d) $SOCl_2$, reduction.

3.2.3 Present work

3.2.3.1 Objective

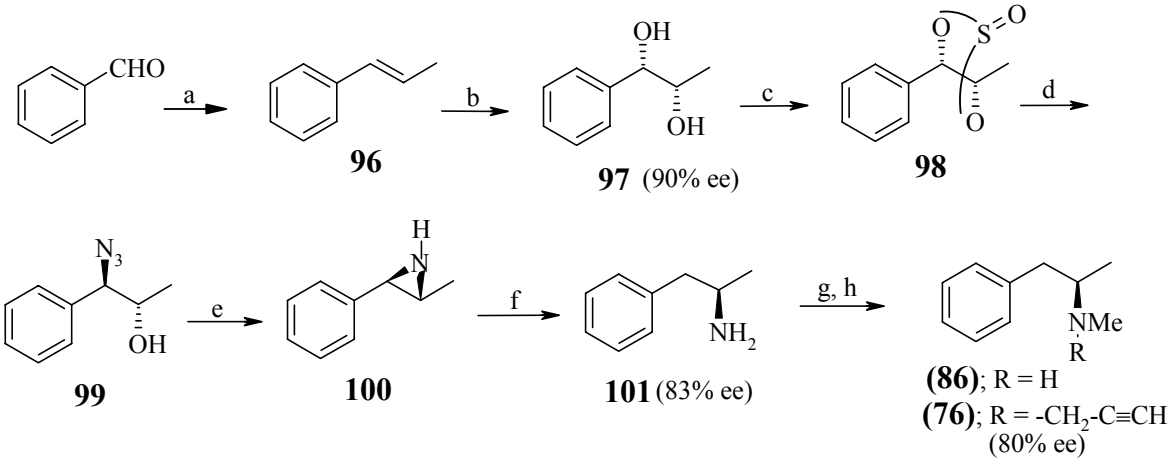
The high biological activity of selegiline is associated with (*R*)-enantiomer of selegiline (**76**). However, there are limited reports available in the literature for its synthesis. Most of them are either patented, involve resolution of racemic selegiline or involve use of chiral natural products like deoxyephedrine. In this context, a process for its direct production of the pure enantiomer from a prochiral substrate is highly desirable.

The objective of the present investigation is to synthesize (*R*)-enantiomer of selegiline (**76**) using Sharpless Asymmetric Dihydroxylation of olefins as a key step. Characteristic features of this method include products in high chemical and optical yield, clean reactions and easy isolation of products.

3.2.4 Results and Discussion

The overall sequence for the preparation of (*R*)-Selegiline (**76**) is depicted in **Scheme 35**. As can be seen, Os-catalyzed asymmetric dihydroxylation (AD) constitutes the key step for introducing chirality into the target molecule.

The first step involves the Grignard reaction of benzaldehyde with ethyl bromide in the presence of Mg-turnings followed by dehydration of the alcohol to give *trans* β-methyl styrene (**96**) in 92% yield. Its ^{1}H-NMR spectrum showed coupling constant values (J = 18.0 Hz) for the trans olefinic protons. β-methyl styrene (**96**) was then subjected to AD reaction using $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether] as a chiral ligand to give diol **97** in 92% ee {$[\alpha]_D$ + 58.2 (c 4.3, $CHCl_3$); lit.[56] $[\alpha]_D$ – 61.5 (c 4.3, $CHCl_3$) for (1*R*,2*R*) isomer of 95% optical purity} and 82% yield. Its ^{1}H-NMR spectrum indicated disappearance of olefinic signals and appearance of multiplet in the range δ 3.75-3.95 for homobenzylic proton.



Scheme 35: a) Mg, CH_3CH_2Br, ether, RT, overnight, 92%; b) cat.OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0°C, $[\alpha]_D$ +58.2 (c 4.3, $CHCl_3$), 90% ee, 82%; c) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, $[\alpha]_D$ – 17.1 (c 1.0, $CHCl_3$), 85%; d) NaN_3, acetone:H_2O, 80°C, $[\alpha]_D$ –228.1 (c 1.2, $CHCl_3$), 82%; e) PPh_3, CH_3CN, $[\alpha]_D$ +58.5 (c 0.8, $CHCl_3$), 90%; f) Pd-C (10%), HCO_2NH_4, MeOH, reflux, $[\alpha]_D$ – 25.6 (c 2.0, MeOH), 83% ee, 88%; g) (i) $ClCO_2CH_3$, CH_2Cl_2, *aq* K_2CO_3, 45 min, 90% (ii) $LiAlH_4$, dry THF, 65 °C, 4 h, $[\alpha]_D$ – 8.1 (c 0.8, EtOH), 83% ee, 65%; g) propargyl bromide, K_2CO_3, CH_3CN, RT, 80 , $[\alpha]_D$ – 9.0 (c 6.5, EtOH), 80% ee, 72%.

Benzylic proton doublet is seen at δ 4.34. Its ^{13}C-NMR spectrum showed signals at δ 72.05 and 79.35 due to benzylic and homobenzylic carbon atoms respectively.

The diol **97** was then converted to cyclic sulphite **98** by treatment with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0°C for 30 min in 85% yield. Its ^{1}H-NMR spectrum showed the presence of the diastereomeric mixture. Thus, two doublets are observed in the region δ 1.40-1.65 for methyl protons. Its ^{13}C-NMR spectrum also showed two sets of signals for every carbon atom i.e. at δ 14.88, 17.27, 80.82, 85.34, 85.71, 90.78 etc **(Fig. 17)**. Its mass spectrum showed molecular ion peak at m/z 198.

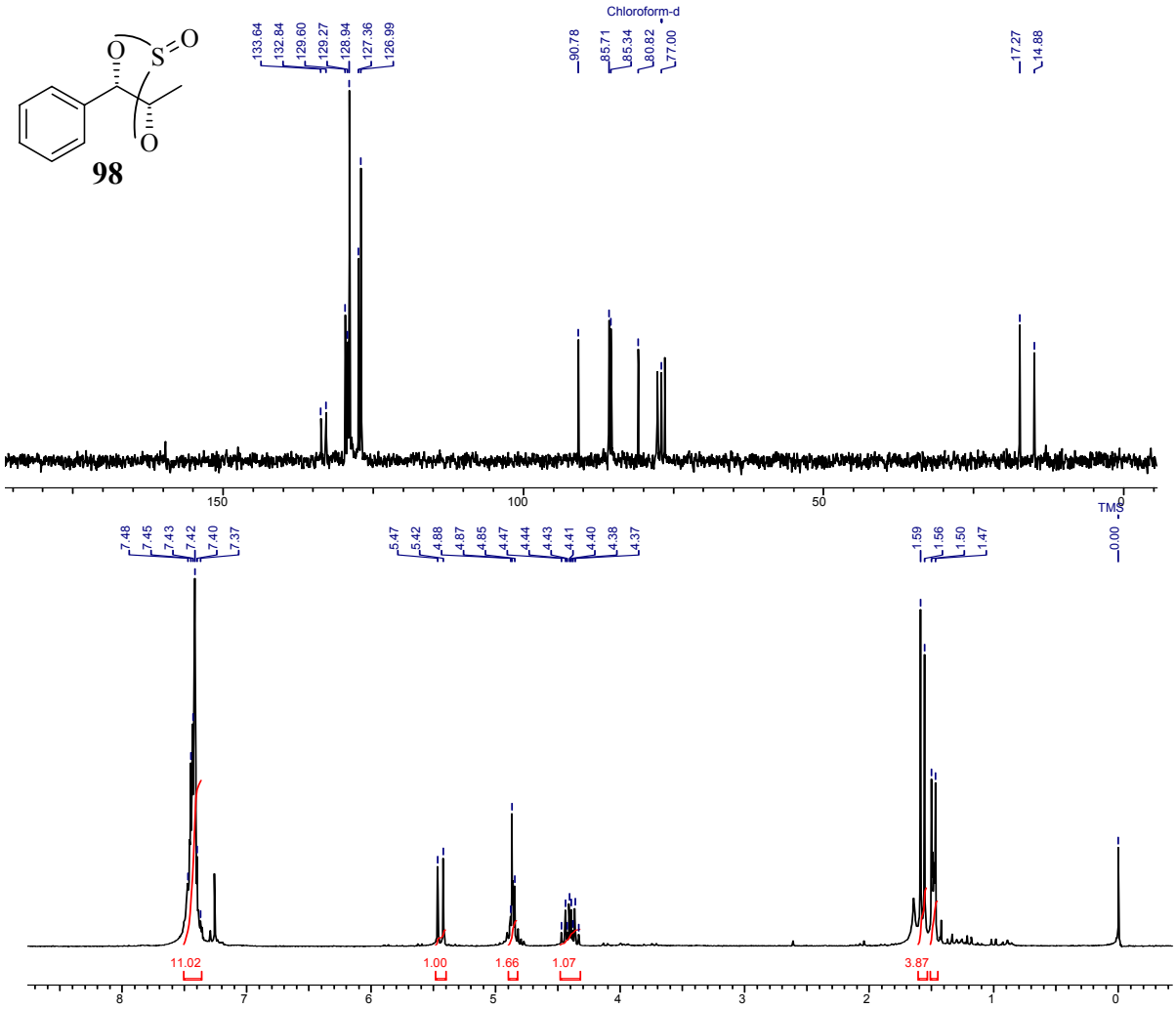


Fig. 17: ^{1}H and ^{13}C-NMR spectra of cyclic sulphite 98

Cyclic sulphite **98** was then subjected to oxidation with catalytic amount of $RuCl_3.3H_2O$ in presence of $NaIO_4$ as oxidant in acetonitrile-water system at 0^oC, but all attempts to isolate its cyclic sulphate in pure form failed. Since the cyclic sulphates of styrene

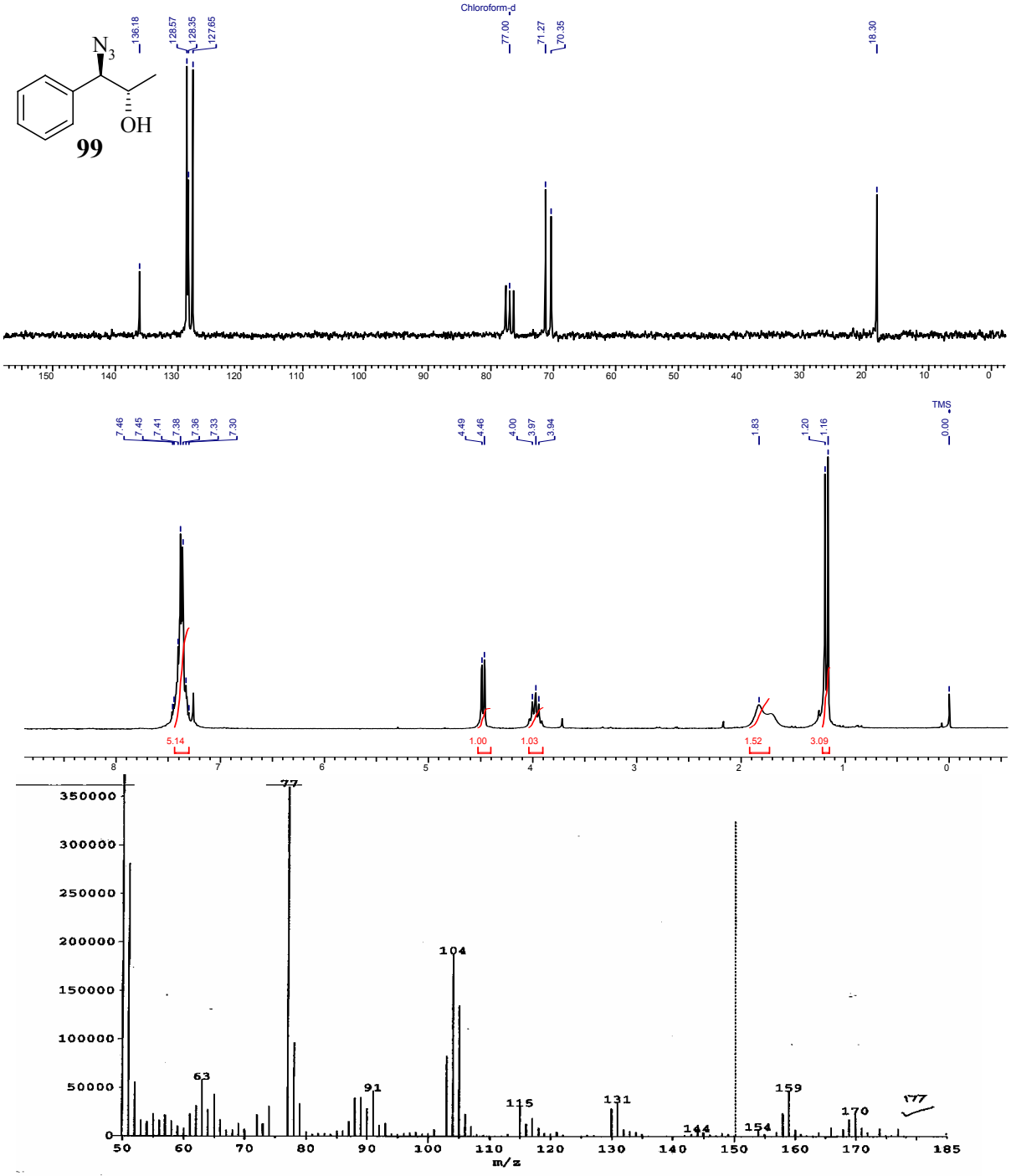


Fig. 18: ^1H, ^{13}C-NMR and Mass spectra of azido alcohol 99

derivatives are known to be extremely unstable, isolation gave only decomposed by-products. However, we solved this problem by carrying out ring opening of cyclic sulphite **98** in regioselective fashion at benzylic position with NaN_3 in DMF to give azido alcohol **99** in 82% yield. Its ^{1}H-NMR spectrum showed disappearance of signals due to cyclic sulphite and appearance of new signals at δ 3.90-4.05 as multiplet due to homo benzylic proton, and doublet at δ 4.47 due to benzylic proton. Its ^{13}C-NMR spectrum showed characteristic signals at δ 70.35 and 71.27 due to methine carbon atoms. Its mass spectrum shows molecular ion

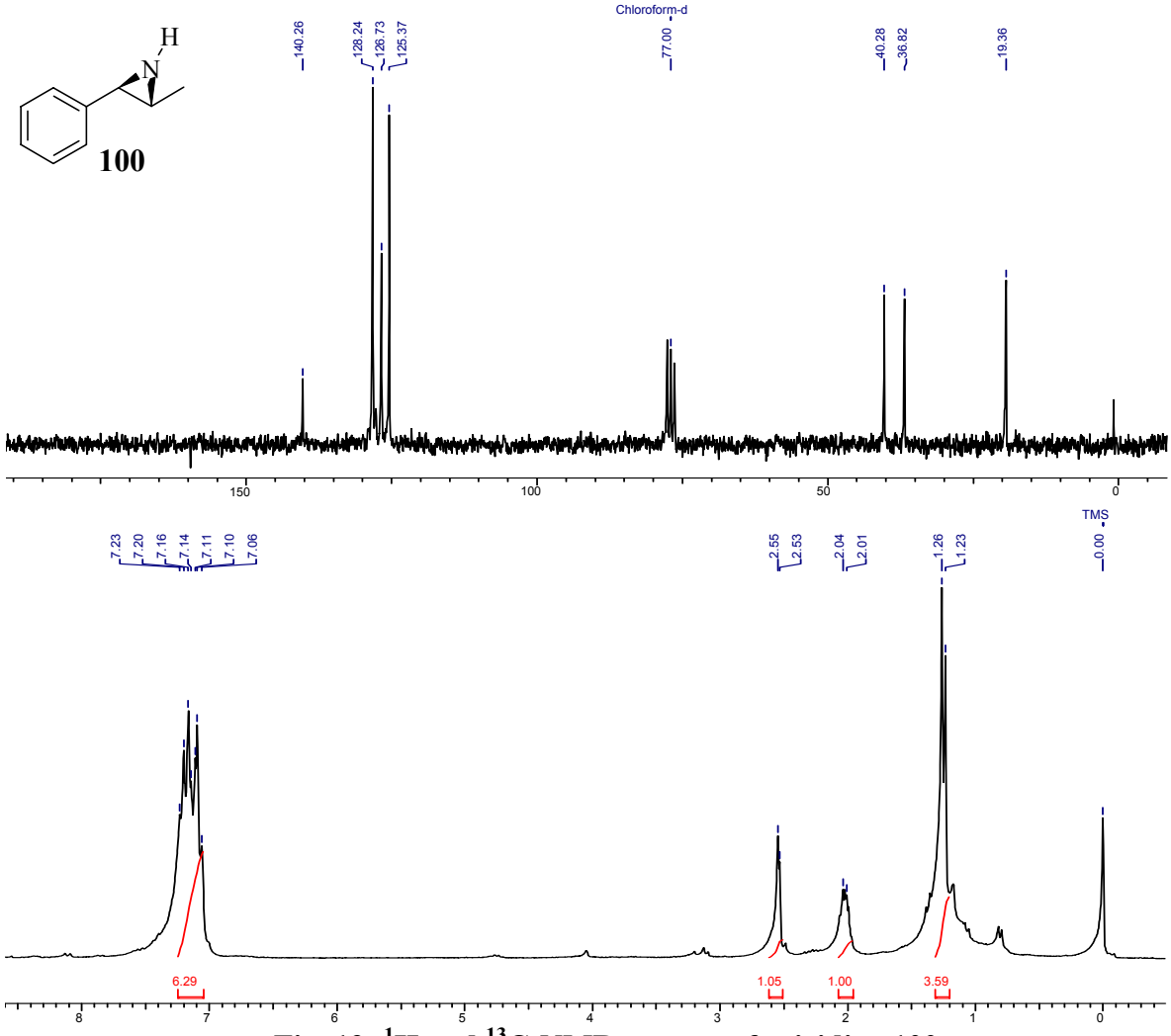


Fig. 19: ^{1}H and ^{13}C-NMR spectra of aziridine 100

peak at m/z 177. Fragmented ion peak at m/z 159 is due to loss of OH group while its IR spectrum showed absorption at 2106 cm^{-1} for the azide group **(Fig. 18)**.

The azido alcohol **99** smoothly reacted with triphenylphosphine in acetonitrile with evolution of nitrogen to afford aziridine **100**. It involved the reduction of the azide function to form first an imino phosphorane and then an oxazaphospholine intermediate, which was thermally induced to yield aziridine **100** in 90% yield. Its ^{1}H-NMR spectrum showed upfield shift for benzylic and homobenzylic protons compared to azido alcohol. Benzylic proton showed a doublet at δ 2.54 whereas homobenzylic proton appeared as a multiplet at δ 1.90-2.15. Its ^{13}C-NMR spectrum also showed signals upfield for methine carbons at δ 36.82 and 40.28 **(Fig. 19)**.

Aziridine **100** was subjected to Pd-catalyzed reductive ring opening with ammonium formate as hydrogen source to produce amine **101** in 83% ee {$[\alpha]_D$ – 25.6 (c 2.0, MeOH); lit.[57] $[\alpha]_D$ – 30.2 (c 2.55, MeOH)} and 88% yield. Aziridine underwent stereospecific and regioselective ring opening at the benzylic position. Its ^{1}H-NMR spectrum showed two doubl-

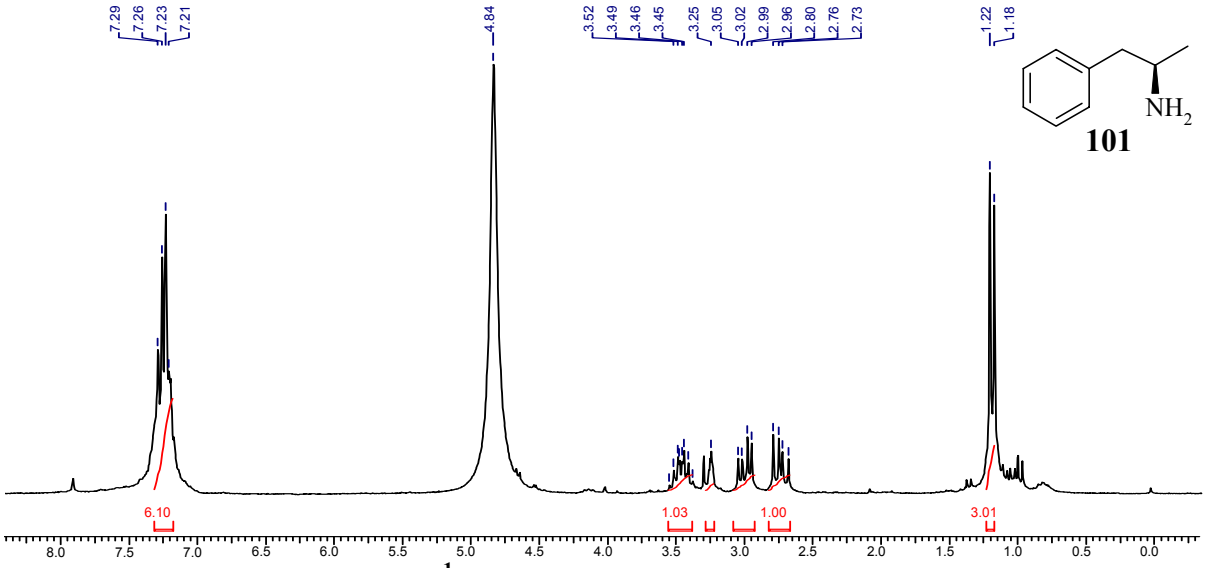


Fig. 20: ^{1}H -NMR spectrum of amine 101

et of doublet in the region δ 2.65-2.80 and 2.90-3.05 for the benzylic diastereotopic protons and a multiplet at δ 3.40-3.50 due to homobenzylic proton which clearly indicates the opening of aziridine ring occurring at the benzylic position **(Fig. 20)**. Its ^{13}C-NMR spectrum showed signals at δ 41.74 for methine and δ 50.37 for benzylic carbon atoms respectively.

The amine **101** was monomethylated by first forming the carbamate followed by its reduction with lithium aluminium hydride to obtain *N*-methylamine in 90% yield. Its ^{1}H-NMR

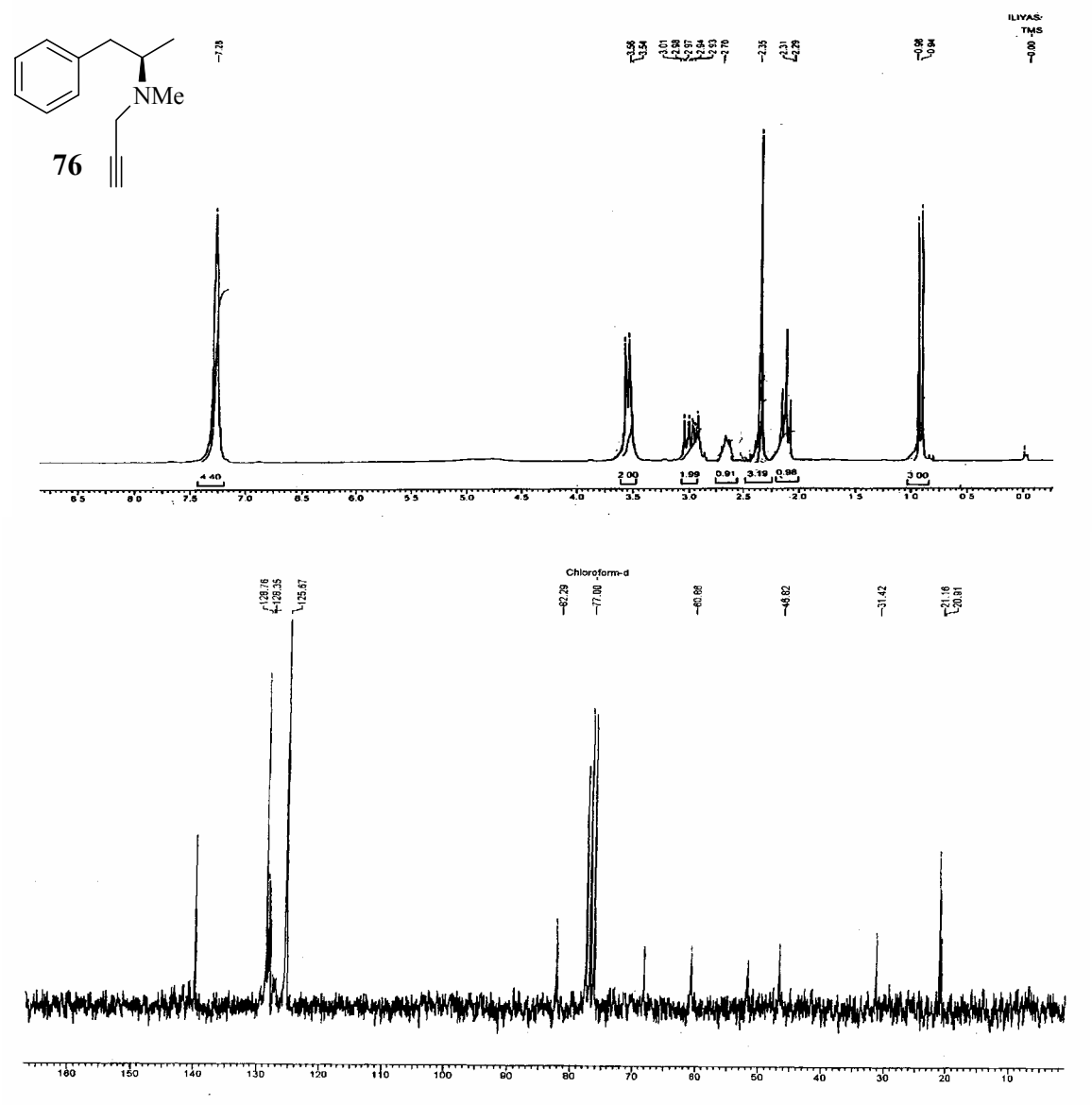


Fig. 21: ^{1}H and ^{13}C-NMR spectra of (*R*)-Selegiline 76

spectrum showed sharp singlet at δ 2.74 for N-CH_3. Finally, *N*-methylamine (**86**) on treatment with propargyl bromide at room temperature in presence of K_2CO_3 gave (*R*)-selegiline (**76**), in 80% ee {$[\alpha]_D$ – 9.0 (c 6.5, EtOH); lit.[58] $[\alpha]_D$ – 10.8 (c 6.4, EtOH)} and 72% yield. Its ^{1}H-NMR spectrum showed a doublet at δ 3.55 corresponding to N-CH_2 group and triplet at δ 2.30 corresponding to acetylenic proton. Its ^{13}C-NMR spectra showed typical peak for quaternary alkyne carbon at δ 82.29 **(Fig. 21)**.

3.2.5 Conclusion

We have achieved the enantioselective synthesis of (*R*)-Selegiline (**76**) in six steps with 17.54% overall yield and 80% ee *via* the Os-catalyzed asymmetric dihydroxylation (AD) as a key step. The key intermediate, chiral aziridine **100** is prepared *via* opening of cyclic sulphite **98**.

3.2.6 Experimental Section

Preparation of trans-*β*-methylstyrene (96)

A dry, argon flushed 100 ml round-bottom flask, equipped with a magnetic stirring bar, reflux water condenser and dropping funnel, was charged with 2-3 crystals of iodine, and magnesium turnings (1.35 g, 0.056 mol), which was covered with dry diethyl ether (20 ml) at 25^{o}C. Then ethyl bromide (6.16 g, 4.25 ml, 0.056 mol) was added dropwise at r.t. in diethyl ethers. After stirring for 3-4 hours, the dropping funnel was replaced by a rubber septum. The reaction flask was cooled in crushed ice water, followed by slow addition of benzaldehyde (5.0 g, 0.047 mol) in ether over a period of 10 minutes. Then it was allowed to stir over night. The reaction mixture was quenched with saturated solution of NH_4Cl, poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic fractions were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure to afford crude alcohol. This was subjected to dehydration with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux temperature. Water generated during the dehydration was azeotropically removed and toluene was distilled off. The crude *β*-methyl styrene was purified by column chromatography packed with silica gel, eluting with pet ether gave 5.28g of (**96**).

Yield: 92%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3055, 3015, 2985, 1650, 1500, 1425, 1300, 1075, 980; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.85 (d, *J* = 18.0 Hz, 3H), 6.15-6.30 (m, 1H), 6.40 (d, *J* = 18.0 Hz, 1H), 7.10-7.35 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.2, 125.8, 126.0, 124.4, 128.2, 131.0, 138.0.

Preparation of (1*S*,2*S*)-1-phenyl-1,2-propanediol (97)

A double-walled 250 ml RB flask was charged with K_3FeCN_6 (1.83 g, 55.8 mmol), K_2CO_3 (7.70 g, 55.8 mmol), $(DHQ)_2PHAL$ (280 mg, 0.36 mmol), $MeSO_2NH_2$ (1.767g, 18.6 mmol) and *t*-BuOH: H_2O (1:1, v/v, 90 ml) and stirred for five minutes at 25^0C. Then cooled to 0^0C and a solution of OsO_4 (376 µl, 0.18 mmol, 0.5M solution in toluene) was added followed by olefin **96** (2.2 g, 18.6 mmol). The reaction mixture was stirred for 24 h at 25^0C (monitored by TLC). The reaction was then quenched with sodium sulfite (10 g) and extracted with ethyl acetate (3 x 60 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using EtOAc: pet. ether (1:1) as eluent to yield 2.3 g of diol **97** as a white solid.

Yield: 82%; **gum**; **$[\alpha]_D$** + 58.2 (c 4.3, $CHCl_3$); {lit.[56] **$[\alpha]_D$** – 61.5 (c 4.3, $CHCl_3$) for (1*R*,2*R*) isomer of 95% optical purity}**IR** ($CHCl_3$, cm^{-1}): 3416, 3017, 2896, 1430, 1220, 1135, 1005, 1023, 890, 710, 680; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.03 (d, *J* = 6.4 Hz, 3H), 2.65-2.80 (brs, 2H), 3.75-3.95 (m, 1H), 4.34 (d, *J* = 7.4 Hz, 1H), 7.20-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.63, 72.07, 79.35, 126.84, 127.91, 128.31, 141.03; **Mass** (m/z, % RI): 152 (M^+, 8), 151 (5), 135 (4), 115 (5), 108 (13), 107 (20), 104 (19), 105 (28), 91 (33), 90 (17), 79 (93), 78 (54), 77 (100), 65 (2), 63 (15), 57 (14); **Analysis:** $C_9H_{12}O_2$ requires C, 71.03; H, 7.94; found C, 71.11; H, 7.96%.

Preparation of (1*S*,2*S*)-4-Methyl-5-phenyl 1,3,2-dioxathiolane-2-oxide (98)

The diol **97** (1.0 g, 6.57 mmol) was dissolved in triethylamine (20 ml) and cooled to 0^0C in an ice bath under argon atmosphere. Freshly distilled thionyl chloride (0.938 g, ml, 7.88 mmol) was added drop-wise and the reaction mixture was stirred at 0^0C for 45 minutes (monitored by TLC). After completion, was added ice-cold water (50 ml) and extracted with ether (3 x 25 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium

sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether : EtOAc (9:1) as eluent to furnish compound **98** as light yellow oil (1.1 g).

Yield: 85%; **gum**; **$[\alpha]_D$** – 17.1 (c 1.04, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3384, 3024, 2983, 2935, 1612, 1456, 1382, 1215, 1049, 962, 860, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.48 (d, *J* = 5.8 Hz, 1H), 1.57 (d, *J* = 6.3 Hz, 1H), 4.30-4.50 (two dd *J* = 6.4 Hz and *J* = 9.2 Hz, 1H), 4.80-4.90 (m, 1H), 5.44 (d, *J* = 9.3 Hz, 1H), 7.35-7.55 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.88, 17.27, 80.82, 85.34, 85.71, 90.78, 126.99, 127.36, 128.94, 129.27, 129.60, 132.84, 133.64, 159.52; **Mass** (m/z, % RI): 198 (M^+, 4), 154 (45), 133 (4), 126 (30), 117 (8), 106 (16), 105 (95), 91 (35), 90 (26), 90 (24), 78 (70), 77 (100), 65 (14), 63 (17), 57 (5); **Analysis:** $C_9H_{10}SO_3$ requires C, 54.53; H, 5.07; S, 16.18; found C, 54.55; H, 5.11; S, 16.13%.

Preparation of (1*R*,2*S*)-1-azido-1-phenyl-propane-2-ol (99)

To a stirred solution of cyclic sulphite **98** (0.9 g, 4.54 mmol) in DMF (5 ml) was added sodium azide (1.18 g, 18.18 mmol). The reaction flask was then heated to 80^{o}C for 6 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured in 25 ml of water, and then it was extracted with ether (3 x 25 ml). The combined organic phases was washed with brine, dried over anhydrous sodium sulphate, and concentrated. The crude azidoalcohol was the purified with silica gel chromatography eluted with pet. ether : EtOAc (9:1) to give azido alcohol **99** (0.680 g).

Yield: 82%; **gum**; **$[\alpha]_D$** – 228.16 (c 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3019, 2855, 2106, 1600, 1525, 1430, 1215, 1120, 1065, 930, 669; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.4 Hz, 3H), 1.65-1.90 (brs, 1H), 3.90-4.05 (m, 1H), 4.47 (d, *J* = 5.4 Hz, 1H), 7.30-7.50 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.30, 70.35, 71.27, 127.65, 128.35, 128.57, 136.18; **Mass** (m/z, % RI): 177 (M^+, 4), 159 (15), 131 (13), 115 (10), 105 (56), 104 (58), 103 (24), 91 (14), 77 (100), 63 (17); **Analysis:** $C_9H_{11}N_3O$ requires C, 61.00; H, 6.83; N, 23.71; found C, 61.05; H, 6.85; N, 23.68%.

Preparation of (2*R*,3*R*)-2-Methyl 3-phenyl aziridine (100)

To a stirred solution of azido alcohol **99** (0.650 g, 3.67 mmol) in 25 ml of acetonitrile was added PPh_3 (0.962 g, 3.67mmol). The reaction mixture was then stirred at room temp. for 1 h and then it was refluxed for 6 h. After completion of reaction as monitored by TLC, the

solvent was removed under deduced pressure to get crude aziridine. The pure product was then isolated by silica gel chromatography eluted with pet. ether : EtOAc (9:1) to give aziridine **100** (0.440 g).

Yield: 90%; **gum**; **$[\alpha]_D$** + 58.5 (c 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3285, 2890, 2395, 1608, 1504, 1500, 1470, 1380, 1320, 1215, 1120, 1041, 939, 790, 680; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.24 (d, *J* = 5.4 Hz, 3H), 1.90-2.15 (m, 1H), 2.54 (d, *J* = 2.9 Hz, 1H), 7.00-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.36, 36.82, 40.28, 125.37, 126.73, 128.24, 140.26; **Analysis:** $C_9H_{11}N$ requires C, 81.16; H, 8.31; N, 10.51; found C, 81.20; H, 8.35; N, 10.51%.

Preparation of (*R*)-2-amino-1-phenylpropane (101)

To a stirred solution of aziridine **100**, (0.400g, 3.0 mmol) in 10 ml of methanol was added Pd-C (10%), ammonium formate (0.378 g, 6.00 mmol). The reaction flask was then heated to reflux for 4 h. After completion of the reaction, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give a residue. The residue was then purified by silica gel chromatography eluted with EtOAc to give amine **101** (0.336 g).

Yield: 88%; **mp:** gum; **$[\alpha]_D$** – 25.6 (c 2.0, MeOH); lit.[57] **$[\alpha]_D$** – 30.2 (c 2.5, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3415, 3055, 3010, 2995, 1650, 1505, 1435, 1400, 1195, 1100, 1090, 870, 810, 750, 700; **^{1}H-NMR** (200 MHz, $CDCl_3$+CD_3OD): δ 1.20 (d, *J* = 6.40 Hz, 3H), 2.65-2.80 (dd, *J* = 8.30 and 8.80 Hz, 1H), 2.90-3.05 (dd, *J* = 5.80 Hz each, Hz, 1H), 3.40-3.50 (m, 1H), 7.10-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, CD_3OD): 18.28, 41.74, 50.37, 128.34, 129.96, 130.43, 137.20; **Analysis:** $C_9H_{13}N$ requires C, 79.95; H, 9.68; N, 10.36; found C, 79.91; H, 9.78; N, 10.39 %.

Preparation of (*R*)-2-(methylamino)-1-phenylpropane (86)

A 25 ml dry flask was charged with amine **101** (0.300g, 2.22 mmol) in dry CH_2Cl_2 (8 ml), to this was added methylchloroformate (0.263 g, 0.21 ml, 2.77 mmol), then the reaction flask was stirred vigorously. Then to this vigorously stirred mixture was added K_2CO_3 (1.531g, 11.10 mmol) in H_2O (8 ml) over a period of 5 minutes and then stirring was continued After completion of the reaction as indicated by the TLC, the reaction mixture was extracted with CH_2Cl_2, the solvent was evaporated under reduced pressure to give crude carbamate.

To a solution of lithium aluminum hydride (0.126 g, 3.33 mmol) in dry THF (15 ml) under nitrogen atmosphere at room temperature was added dropwise a solution of carbamate in dry THF. The reaction flask was then heated under reflux for 2 hours. After completion of the reaction the reaction mixture was cooled to room temperature and ethyl acetate was added slowly. The reaction mixture was then filtered; the filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography to yield 0.215 g of amine **86**.

Yield: 65%; **mp:** 38-40^{o}C; **[α]$_D$** – 8.1 (c 0.8, EtOH); lit.[53] **[α]$_D$** – 10.9 (c 0.8, EtOH); **IR** ($CHCl_3$, cm^{-1}): **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (d, *J* = 8.0 Hz, 3H), 1.50 (s, 1H), 2.25 (s, 3H), 2.65-2.95 (m, 3H), 7.20-7.60 (m, 5H); **Mass** (m/z, % RI): 149 (M^+, 4), 134 (10), 119 (5), 117 (5), 91 (45), 65 (16), 58 (100); **Analysis:** requires $C_{10}H_{15}N$ requires C, 80.49; H, 10.12; N, 9.38; found C, 80.41; H, 10.12; N, 9.45 %.

Preparation of (*R*)-Selegiline (76)

To a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane (**86**), (0.200 g, 1.34 mmol) in acetonitrile (10 ml) was K_2CO_3 (0.277 g, 2.01 mmol) and propargyl bromide (0.478 g, 0.36 ml, 4.02 mmol). The reaction mixture was then allowed to stir at RT for over night till all the starting material disappeared. The reaction mixture was then extracted with 5 % HCl (5 x 10 ml), made alkaline to get the oil, to give 0.215 g of (*R*)-selegiline (**76**) in 72 % yield.

Yield: 72%; **gum**; **[α]$_D$** – 9.0 (c 6.5, EtOH); lit.[58] **[α]$_D$** – 10.8 (c 6.48, EtOH); **IR** ($CHCl_3$, cm^{-1}): **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.0 Hz, 3H), 2.25 (t, *J* = 2.0 Hz, 1H), 2.35 (s, 1H), 2.40-2.55 (m, 1H), 2.80-3.10 (m, 2H), 3.40 (d, *J* = 2.0 Hz, 2H), 7.00-7.50 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 21.1, 31.4, 46.8, 51.90, 60.8, 68.1, 82.2, 125.6, 128.3, 128.6, 140.2; **Mass** (m/z, % RI): **Analysis:** requires $C_{13}H_{17}N$ requires C, 83.37; H, 9.14; N, 7.47; found C, 83.34; H, 9.11; N, 7.53 %.

3.2.7 References

1. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
2. Lim, Y.; Kee, W. K. *Tetrahedron Lett*. **1995**, *36*, 8431.
3. a) Williams, R.M. Synthesis of Optically Active *α*-Amino Acids, Pergamon Press, Oxoford, 1989. b) Kasai, M.; Kono, M. *Synlett*. **1992**, 778. c) Coleman, R. S.;

Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813.

4. a) Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett*. **1991**, *32*, 3807. b) Moran, E. J.; Armstrong, R. W. *J. Am. Chem. Soc.* **1992**, *114*, 371.
5. Ambrosi, H. D.; Duczek, W.; Ramm, M.; Jachnisch, K. *Tetrahedron Lett*. **1994**, *35*, 7613.
6. a) Arai, H.; Kanda, Y.; Ashizawa, T.; Morimoto, M.; Gomi, K.; Kono, M.; Kasai, M. *J. Med. Chem*. **1994**, *37*, 1805. b) Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett*. **1991**, *32*, 3807.
7. a) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177. b) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544.
8. a) Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett*. **1990**, *31*, 1903. b) Henry, J. R.; Markin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett*. **1989**, *30*, 5709.
9. a) Sheldon, R. A.; Arends, E. W. C. E.; Lempers, H. E. B. *Catal*. *Today* **1998**, *41*, 387. b) Cornelis, A.; Laszlo, P. *Synlett*. **1994**, 155.
10. Huckel, W.; Liegel, W. *Chem*. *Ber*. **1938**, *71*, 1442.
11. a) Porter, C. C.; Hellerman, L. *J. Am. Chem. Soc.* **1944**, *6*6, 1652. b) Wieland, K.; Kogl, F. *Chem*. *Ber*. **1922**, *55*, 1798.
12. Ska, C, K.; Ouyang, S. L.; Hsieh, D. Y.; Chang, R. C.; Chang, S. C. *J. Org. Chem*. **1986**. *51*, 1490.
13. Werrya, J.; Stamm, H. *Tetrahedron Lett*. **1989**, *16*, 5015.
14. Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660.
15. Satake, A.; Shimizu.; Yamamoto, A. *Synlett*. **1995**, *1*, 64.
16. Chang, J. W.; Bae, J. H.; Sin, S. H.; Park, S. C.; Choi, D.; Lee, W. K. *Tetrahedron Lett*. **1998**, *39*, 9193.
17. Chawang, S. P. *J. Org. Chem.* **1998**, *63*, 10006.
18. Davis, F. A. *Tetrahedron Lett*. **2002**, *58*, 7135.
19. Davis, F. A.; Faul, M. M.; Bilodeav, M. T.; Anderson, B. A.; Barnes, D, M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
20. Lim, Y.; Lee, W. K. *Tetrahedron Lett*. **1995**, *36*, 8431.
21. Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett*. **1999**, *40*, 9325.

22. Ram, S.; Ehrenkaufer. *Synthesis* **1988**, 91.
23. Moore, M. L. *Org*. *React*. **1941**, *5*, 301.
24. Ali, I. S.; Nikalje, M. D.; Sudalai, A. *Org*. *Lett*. **1999**, *1*, 705.
25. Longo, R.; Castellani, R.; Tibolla, M. *Phytochemistry* **1974**, *13*, 167.
26. Tolosa, E.; Marti, M. J.; Valldeoriola, F.; Molihuevo, J. L. *Neurology* **1995**, 50.
27. Mendis, T.; Suchowerski, O.; Lang, T.; Gauthier, S. *Can. J. Neur*. *Science* **1999**, *26*, 89.
28. a) Calne, D. B.; Sandler, M. *Nature* **1970**, *226*, 21. b) Sourkes, T. L. *Pharmacol*. *Rev*. **1966**, *18*, 53. c) Tissort, R.; Bartholini, G.; Pletscher, A. *Arch*. *Neurol*. **1969**, *20*, 187.
29. Breschneider, H.; Hohenlohe-Oehringer, K.; Kaiser, A.; Wolsche, U. *Helv. Chim. Acta* **1973**, *56*, 2857.
30. Knowles, W. S.; Sabaky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
31. Yamada, S. I.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136.
32. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
33. Danishefsky, S.; Craig, T. A. *Tetrahedron* **1981,** *37,* 4081.
34. Klibanov, A. M.; Berman, Z.; Alberti, B. N. *J*. *Am*. *Chem*. *Soc*. **1981**, *103*, 6263.
35. Boger, D, L.; Yohannes, D. *J. Org. Chem*. **1987**, *52*, 5283.
36. Blanchard, M.; Bouchoule, C.; Djaneye-Boundjou, G. and Canesson, P. *Tetrahedron Lett*. **1988**, *29*, 2177.
37. Tyagi, O. D.; Boll, P. M.; Parmar, V. S.; Taneja, O.; Singh, S. K. *Indian J. Chem., Sec-B.* **1992**, *31*, 851.
38. Baldwin, J. E.; Spyvee, M. R.; Whitehead, R. C. *Tetrahedron Lett*. **1997**, *38*, 2771.
39. Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553.
40. Antilla, J. C.; Wulff, W. D. *Angew*. *Chem*., *Int*. *Ed*. **2000**, *39*, 4518.
41. Takashi, O. *Tetrahedron Lett*. **2000**, *41*, 8339.
42. Chen, C.; Zhu, Y.-F.; Wilcoxen, K. *J. Org. Chem.* **2000**, *65*, 2574.
43. Wei-Ping Deng, W. P.; Kelli A. Wong, K. A.; Kirk, K. L. *Tetrahedron: Asymmetry* **2002***,13,*1135.
44. a) Mizutta, I.; Ohta, M.; Ohta, K.; Nishimura, M.; Mizutta, E.; Hayashi, K.; Kuna, S. *Biochemical and Biophysics Research Communication* **2000**, *279*, 751. b) Vagilini, F.;

Pardini, C.; Cavalletti, M.; Maggio, R.; Corsini, G. U. *Brain Research* **1996**, 7*4*1, 68.

45. http://www.alzheimers.org/pubs
46. Weinstock, S. Selectivity of Cholinesterase Inhibition: Clinical Implications for the Treatment of Alzheimer's Disease. *CNS Drugs* **1999**, *12*, 307.
47. Sano, M.; Ernesto, C.; Thomas, R. C.; Klauber, M. R. A controlled Trial of Selegiline, Alpha Tocopherol, or both as Treatment of Alzheimers Disease, *N. Eng. J. Med*. **1997**, *336*, 1216.
48. a) Abu-Raya, S.; Blaugrund, S.; Tremblower, V.; Shilderman, E.; Shohami, E. A Monoamine Oxidase-B Inhibitor, Protects NGF-Differentiated PC12 Cells Against Oxygen Glucose Deprivation. *J. Neurosci. Res*. **1999**, *58*, 456. b) Paterson, I. A.; Tatton, W. G. Antiapoptotic Actions of Monoamine Oxidase B Inhibitors, *Adv. Pharmacol.* **1998**, *42*, 312.
49. Flower, J. S. *J. Org. Chem*. **1977**, *42*, 2637.
50. Gyogy, B.; Jozsef, K. CA 110: 44960g.
51. a) Josef, H. CA 113: 590e. b) Josef, H. CA 117: 150680.
52. Ott-Dombrowski, S.; Richard, C.; Jeorge, S.; Hans, W. CA 124: 288969x.
53. Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein.; Lerner, D.; Goldenberg, W.; Miskolezi, I.; Molnar.; Rantal, F. *J. Med. Chem.* **2002**, *45*, 5260.
54. Plenevaux, A.; Flower, S. F.; Dewey, S. L.; Wolf, A. P.; Guillaume, M. *Int. J. Radiation Applications and Instrumentation Part A, Applied Radiation and Isotopes* **1991**, *42*, 121.
55. www.selegiline.com
56. a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. b) Dictionary of Organic Compounds. 6th Edn, Vol. 2. Chapman and Hall.
57. Dictionary of Organic Compounds. 6th Edn, Vol. 2. Chapman and Hall.
58. The Merck Index, *An Encyclopedia of Chemicals, Drugs and Biologicals*, 13th Edn. Merck and Co. Inc. Whitehouse Station, NJ **2001**.

SECTION-I

Pyridinium Hydrobromide Perbromide Catalyzed Aziridination of Olefins using Chloramine-T

4.0.1 Introduction

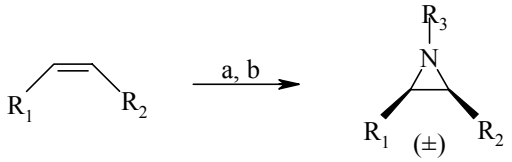
Aziridines and azirines can be regarded as representatives of the first and most simple of all heterocyclic systems, which are characterized by the presence of two carbon atoms and one nitrogen atom in a three-membered ring. Interest in these nitrogen containing small rings is due to the general influence of ring strain upon chemical reactivity. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression but also to the presence of the electron rich nitrogen atom.[1] The chemistry of aziridines has been a very active area of research. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines and the reactions of aziridines have received particular attention. The aziridine ring is a versatile building block for organic synthesis, not only because the ring opening of aziridines provides a convenient entry to the stereoselective preparation of functionalized amino compounds but also because the exocyclic *N*-substituent controls the properties and reactivity of the three membered ring. Many biologically active compounds such as amino acids, β-lactam antibiotics and alkaloids have been derived from aziridines.[2]

4.0.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic approaches available for the synthesis of aziridines. Important catalytic methods for the synthesis of aziridines are discussed below.

Baeckvall *et al.*[3]

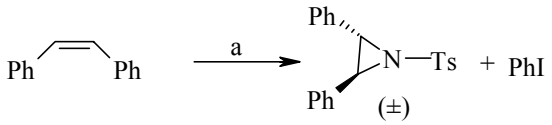
Aminopalladation of alkenes followed by oxidation by bromine gave *N*-substituted aziridines (**Scheme 1**).



Scheme 1: a) $PdCl_2(PhCN)_2$, R_3NH_2, -50^0C; b) Br_2.

Mahy *et al.*[4]

N-Substituted aziridines are formed by $Fe^{(III)}$- or $Mn^{(III)}$-porphyrin catalyzed reactions of PhI=NR compounds (R = tosyl or $COCF_3$) with alkenes (**Scheme 2**).

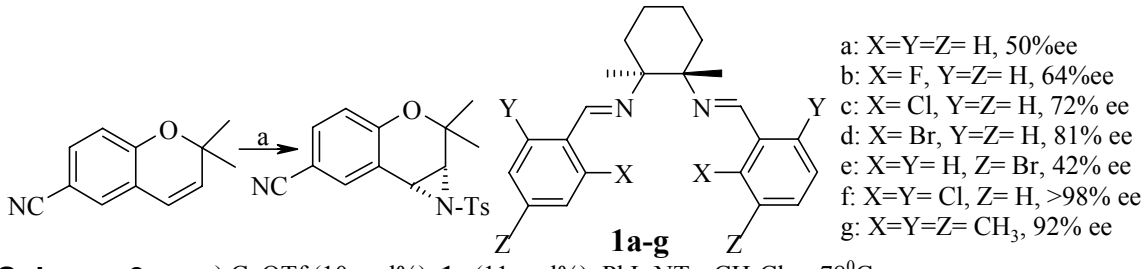


Catalyst: $Fe^{(III)}$(TPP) = 21-63% yield
$Mn^{(III)}$(TPP) = 20-80% yield

Scheme 2: a) catalyst, PhI=NTs, CH_2Cl_2.

Jacobsen *et al.*[5]

A new class of chiral bisbenzylidenediaminocyclohexane ligands **1 a-g** has been developed which, in association with CuOTf catalyze aziridination of alkenes by PhI=NTs (**Scheme 3**).



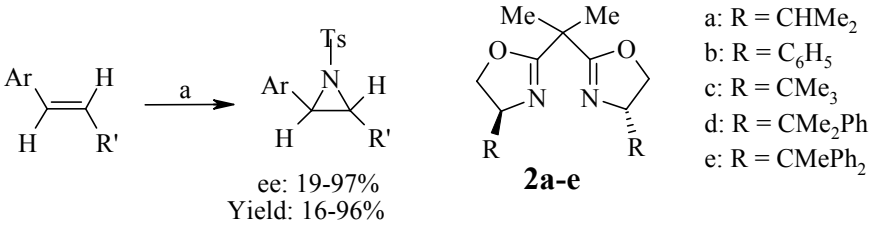
a: X=Y=Z= H, 50%ee
b: X= F, Y=Z= H, 64%ee
c: X= Cl, Y=Z= H, 72% ee
d: X= Br, Y=Z= H, 81% ee
e: X=Y= H, Z= Br, 42% ee
f: X=Y= Cl, Z= H, >98% ee
g: X=Y=Z= CH_3, 92% ee

Scheme 3: a) CuOTf (10 mol%), **1g** (11 mol%), PhI=NTs, CH_2Cl_2, -78^0C.

Evans *et al.*[6]

Copper (I) and (II) salts such as CuOTf, $Cu(OTf)_2$, *etc*. were found to be superior catalysts compared to other metal complexes for the aziridination of olefins employing

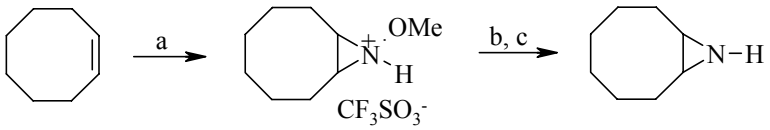
PhI=NTs as a nitrene source. Asymmetric version of this reaction was also developed using *bis*(oxazolines) **2 a-e** with CuOTf ; ee up to 97% was achieved (**Scheme 4**).



Scheme 4: a) PhI=NTs, CuOTf (10 mol%), **2a-e**.

Vedejs *et al.*[7]

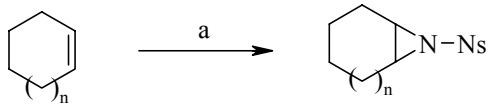
Electron rich alkenes are converted into *N*-methoxyaziridines by treatment with $HN(OMe)_2$ and trimethylsilyl triflate. Reduction afforded the aziridines (**Scheme 5**).



Scheme 5: a) $HN(OMe)_2$, TMSOTf; b) NaOH; c) Li/NH_3.

Muller *et al.*[8]

The $Rh_2(OAc)_4$ catalyzed decomposition of PhI=NNs (Ns: *p*-nitrobenzenesulfonyl) in the presence of olefins afforded aziridines in 18-85% yield. With chiral catalysts asymmetric induction up to 73% ee was obtained (**Scheme 6**).



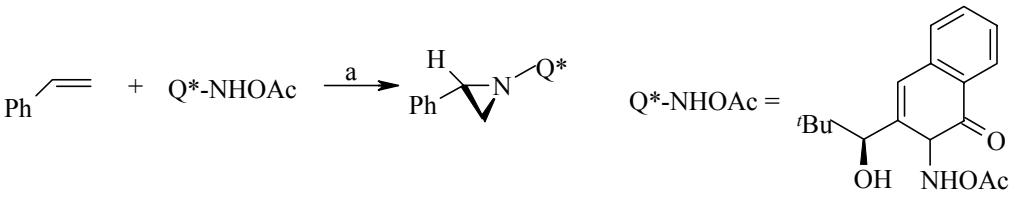
Scheme 6: a) $Rh_2(OAc)_4$, PhI=NNs, CH_2Cl_2.

Perez *et al.*[9]

The copper (I) complex $TpCu(C_2H_4)$ [Tp = hydrotris(3,5-dimethyl-1-pyrazolyl)borate] catalyzes nitrene transfer from PhI=NTs to olefins to produce aziridines in 40-90% yields.

Atkinson *et al.*[10]

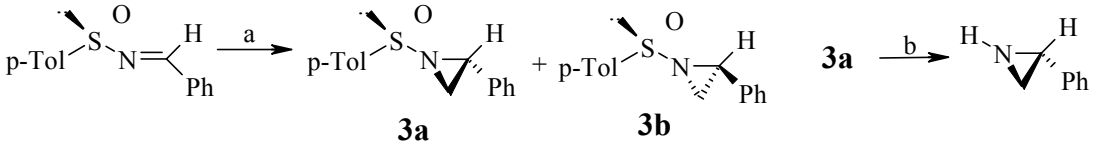
3-Acetoxyaminoquinazoline in the presence of $Ti(O^tBu)_4$, aziridinates olefins such as styrene, butadiene and indene in a stereoselective manner (**Scheme 7**).



Scheme 7: a) $Ti(O^tBu)_4$, CH_2Cl_2.

Ruano *et al.*[11]

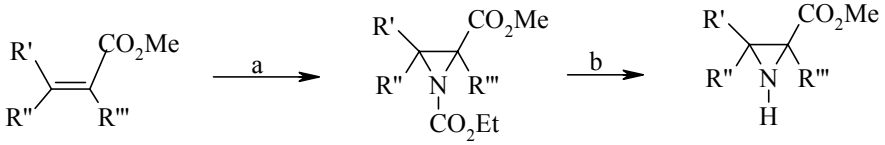
The reaction of optically pure *N*-sulfinyl phenylamine with dimethyloxosulfonium methylide afforded a mixture of *N*-sulfinylaziridines **3a-b**. The sulfinyl group can be eliminated under mild conditions to give optically pure phenylaziridines (**Scheme 8**).



Scheme 8: a) Me_2SOI, base, THF; b) MeLi, THF, -78^0C.

Pellacani *et al.*[12]

α,β-Unsaturated esters were aziridinated (**Scheme 9**) using CaO and ethyl *N*-[(4-nitrobenzenesulfonyl)oxy]carbamate ($NsONHCO_2Et$) in good yields (57-72%).

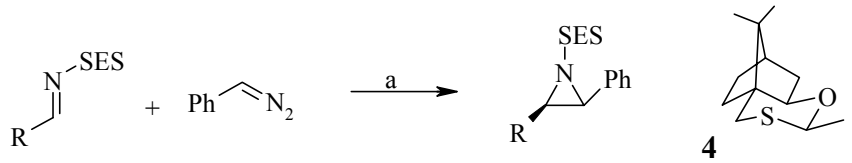


Scheme 9: a) $NsONHCO_2Et$, CaO, CH_2Cl_2; b) MeONa, MeOH.

Aggarwal *et al.*[13]

A new method for the preparation of aziridines from SES {*N*-[*β*-(trimethylsilyl)ethanesulfonyl]} protected imines and diazo compounds using Rh-catalyst in

presence of sulfide as co-catalyst was developed. The use of chiral sulfide **4** derived from (+)-camphor sulfonyl chloride gave the required aziridine (55% yield, 97% ee) (**Scheme 10**).

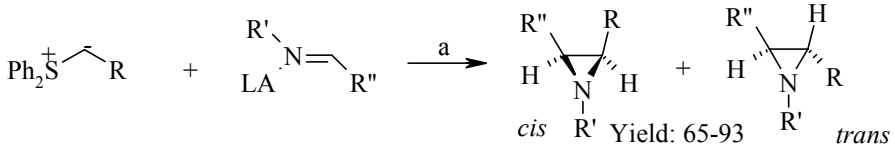


4

Scheme 10: a) $Rh_2(OAc)_4$ or $Cu(acac)_2$ (1 mol%), **4** (20 mol%).

Wang *et al.*[14]

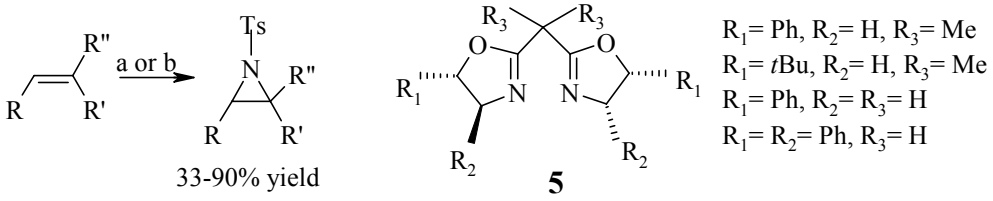
Aziridines were prepared in high yields and stereoselectivity by aziridination of *N*-aryl or *N*-alkyl imines with *S*-ylides in the presence of Lewis acids (**Scheme 11**).



Scheme 11: a) -78^0C- RT, Me_3SiCl or $BF_3.OEt_2$, THF.

Langham *et al.*[15]

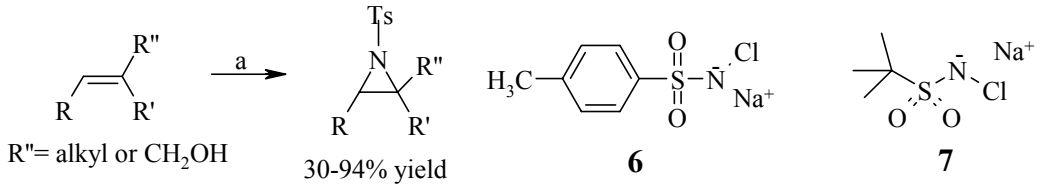
Copper-exchanged zeolite Y was used as a catalyst for the aziridination of olefins. Modification of the catalyst with chiral *bis*(oxazolines) **5** induced upto 61% ee (**Scheme 12**).



Scheme 12: a) CuHY, PhI=NTs, CH_3CN, 25^0C or b) CuHY, **5**, PhI=NTs, CH_3CN, 25^0C.

Sharpless *et al.*[16]

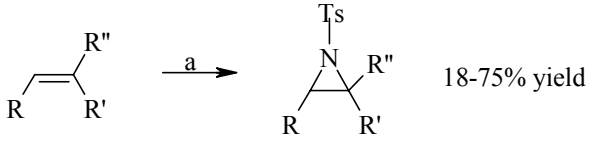
Aziridination of olefins and allylic alcohols by Chloramine-T (**6**) or *N*-chloramine salt of *tert*-butylsulfonamide **7** was carried out using PTAB (phenyltrimethylammonium tribromide, $PhNMe_3^+Br_3^-$) as catalyst (**Scheme 13**).



Scheme 13: a) PTAB (10 mol%), anhydrous **6** or **7**, CH_3CN, RT.

Minakata *et al.*[17]

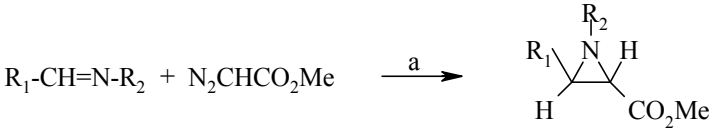
Various Cu(I) and Cu(II) salts were used as catalysts for aziridination of olefins with Chloramine-T as the nitrogen source (**Scheme 14**). Catalytic amount of iodine was also used for the same reaction.



Scheme 14: a) CuCl (5 mol%) or catalytic I_2, Chloramine-T, MS 5 Å, CH_3CN, 25^0C.

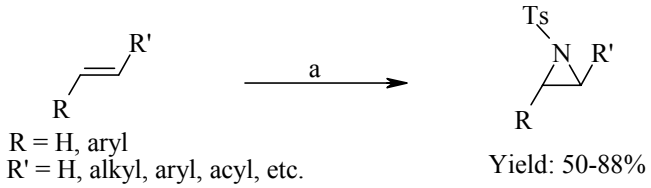
Sudalai *et al.*[18]

A heterogeneous catalytic method for the preparation of *trans*-aziridines from imines and methyl diazoacetate was developed using Rh^{III} and Mn^{III}-exchanged montmoritinolite K 10 clays as catalysts (**Scheme 15**).



Scheme 15: a) Rh-clay (10% m/m), benzene, reflux.

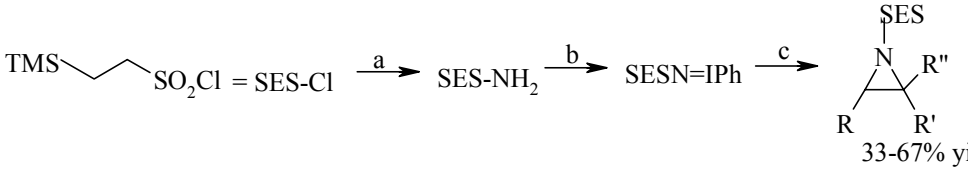
Same group has reported *N*-bromoamides as an effective catalyst for electron-deficient as well as electron-rich olefins using chloramine-T as a nitrogen source under ambient conditions to afford the corresponding aziridines in good to excellent yields (**Scheme 16**).



Scheme 16: a) *N*-Bromoamide (20 mol %), chloramine-T, CH_3CN, 25°C.

Dauban *et al.*[19]

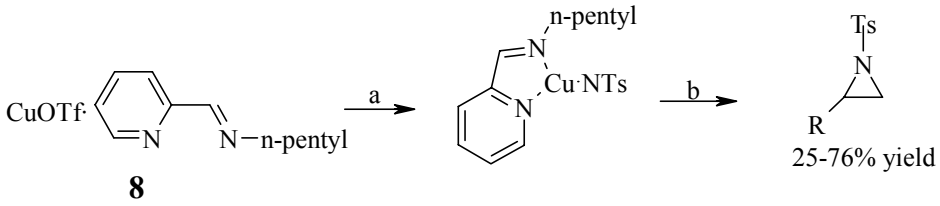
PhI=N-SES (SES=$Me_3SiCH_2CH_2SO_2$) reacted with olefins in presence of catalytic amount of CuOTf to give the corresponding *N*-SES aziridines (**Scheme 17**).



Scheme 17: a) NH_3, CH_2Cl_2; b) $PhI(OAc)_2$, KOH, MeOH, 95-100%; c) olefin, CuOTf, MS 4Å, CH_3CN.

Taylor *et al.*[20]

Cu-catalyst **8** was used for aziridination of olefins using Chloramine-T. $3H_2O$ as a nitrogen source (**Scheme 18**).

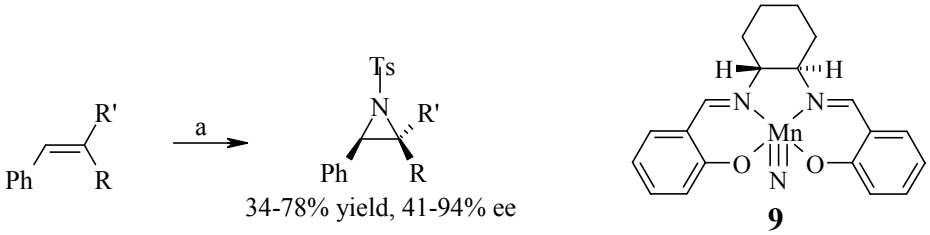


8

Scheme 18: a) Chloramine-T, $3H_2O$ (**8**); b) olefin, CH_3CN, 3 days.

Komatsu *et al.*[21]

The chiral nitridomanganese complex **9** was used to carry out aziridination of styrenes to afford *N*-tosylaziridines in good to excellent ee. Additive like Ts_2O (*p*-toluenesulfonic



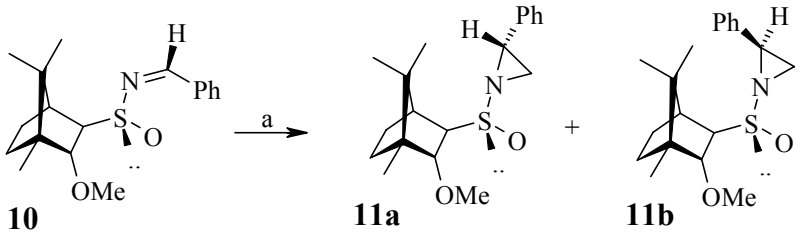
9

Scheme 19: a) **9**, pyridine, Ts_2O, pyridine *N*-oxide, CH_2Cl_2, 0^0C, 3 h.

anhydride) was found to be effective for the activation of the complex **9** (**Scheme 19**).

Zhu *et al.*[22]

Addition of dimethyloxosulfonium methylide, Me_2SOI, to chiral non-racemic pure (+)-camphor derived sulfinimine **10**, afforded sulfinyl aziridines **11a-b** (**Scheme 20**).

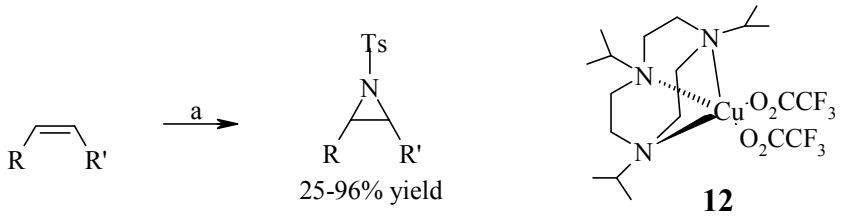


10 **11a** **11b**

Scheme 20: a) base, Me_2SOI, THF.

Halfen *et al.*[23]

Copper complex **12** was used as a catalyst for aziridination of olefins using PhI=NTs as nitrogen source (**Scheme 21**).

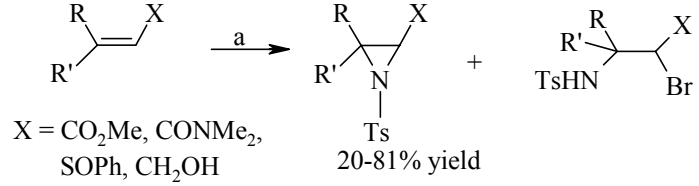


12

Scheme 21: a) Copper catalyst **12**, PhI=NTs, CH_3CN.

Antunes *et al.*[24]

Pd-Catalyzed preparation of *N*-tosyl aziridines was using Bromamine-T as nitrogen source (**Scheme 22**).



Scheme 22: a) $PdCl_2$ (20 mol%), Bromamine-T (1.2 equiv.), CH_3CN, RT.

Bedekar *et al.*[25]

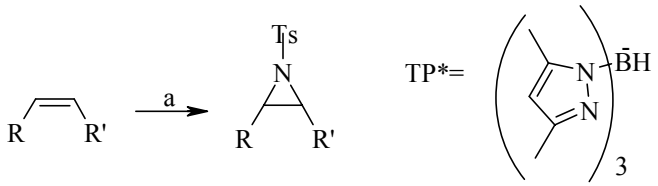
Variety of transition metal salts such as $CuCl_2$, $NiCl_2$, $CoCl_2$, $FeCl_3$, $MnCl_2$, $MgCl_2$, $SrCl_2$, $CuBr_2$, *etc*. were used as catalysts for aziridination of olefins using Bromamine-T as nitrogen source.

Nguyen *et al.*[26]

Methyltrioxorhenium (MTO) was found to catalyze the transfer of nitrene unit of PhI=NTs to a number of olefins providing aziridines in moderate to good yields (28-70%).

Handy *et al.*[27]

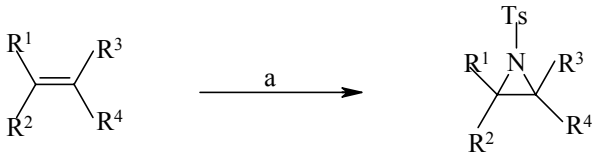
Copper-poly(pyrazolyl)borate complex generated in situ from copper chloride and a sodium poly(pyrazolyl)borate salt was found to be effective catalyst for the aziridination of variety of olefins (**Scheme 23**).



Scheme 23: a) TP*Na (10 mol%), CuCl (10 mol%), PhI=NTs, CH_3CN, RT.

Jain *et al.*[28]

N-Iodo-*N*-potassio-*p*-toluenesulphonamide was found to be a convenient nitrene precursor for the aziridination of alkenes in the presence of copper catalysts (**Scheme 24**).



Scheme 24: a) TsN.KI, CH_3CN, MS-3A, Cu-catalyst, RT.

4.0.3 Present work

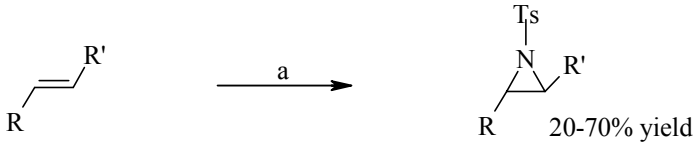
4.0.3.1 Objective

Although there are many methods available in the literature for aziridination of olefins they suffer from certain drawbacks such as use of metal salts, PhI=NTs as nitrogen source, limited substrate scope, *etc*. Catalytic aziridination has not yet entered the realm of practical organic synthesis, mainly due to expense and inconvenience of PhI=NTs as a reagent. Our objective is to look for nonmetallic source as catalyst for aziridination of variety of olefins including α, β-unsaturated carbonyl compounds.

$Py.HBr_3$ is one such nonmetallic solid complex of pyridine with bromine.[29] It is convenient to measure small amounts of active bromine with this stable reagent than bromine itself. Its mild reactivity makes it ideal for selective bromination and dehydrogenations of sensitive molecules. It has earlier been used as a selective brominating reagent for ketones, acetals, alkenes, etc. [30]

4.0.4 Results and Discussion

When styrene was reacted with anhydrous Chloramine-T (**6**) in the presence of catalytic amount of pyridinium hydrobromide perbromide at room temperature, the corresponding aziridinated product was obtained in 60% yield. Among various solvents such



15a-n **16a-n**

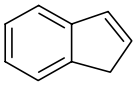
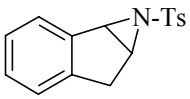
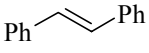
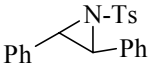
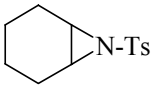
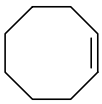
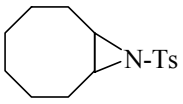
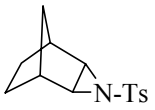
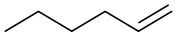
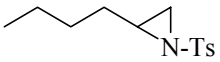
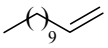
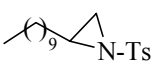
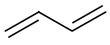
R = alkyl, aryl, vinyl, *etc*.
R' = H, CHO, COR, CH_2X (X = OH, Br, OR), *etc*.

Scheme 25: a) Pyridinium hydrobromide perbromide (20 mol%), Chloramine-T (1.1 equiv.), CH_3CN, 25^0C.

as THF, CH_2Cl_2, $CHCl_3$, acetone, CH_3CN and dioxane, only CH_3CN gave the aziridinated product in reasonably good yield.

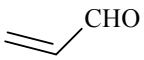
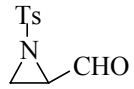
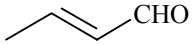
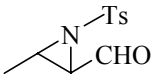
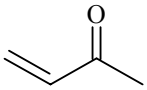
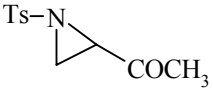
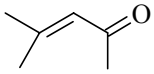
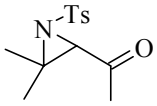
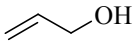
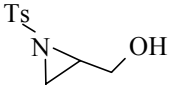
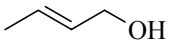
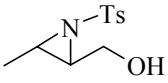
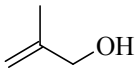
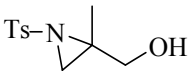
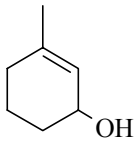
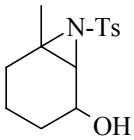
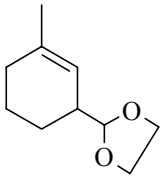
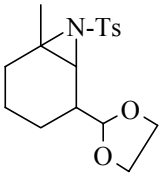
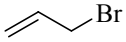
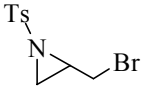
Variety of olefins **15a-t** were successfully aziridinated to afford the corresponding aziridines **16a-t** in moderate to good yields (**Scheme 25**). The results of aziridinations are summarized in **Table 1** and **2**.

Table 1: Py.HBr_3-catalyzed aziridination of olefins using anhydrous TsNClNa: [a]

No.	Olefins (15a-j)	Time (h)	Product (16a-j)	Yield (%)[b]	M.p (^oC)
a		4		60	94-96
b		10		50	165
c		8		40[c]	140
d		12		70	55
e		6		65	123
f		16		50	gum
g		12		40	gum
h		12		42	gum
i		12		65	gum

a: Olefin (5 mmol), anhydrous Chloramine-T, (1.1 equiv), Py.HBr_3 (10 mol%), CH_3CN, (25 ml), 25^oC; b: Isolated yields after column chromatographic purification; c: cis/trans isomers obtained in the ration 2:3.

Table 2: Py.HBr_3-catalyzed aziridination of α,β-unsaturated carbonyl compounds and allylic alcohols using anhydrous TsNClNa: [a]

No.	Olefins (15k-t)	Time (h)	Product (16k-t)	Yield (%)[b]	M.p (^oC)
j		12		20	gum
k		12		65	106
l		12		60	gum
m		14		60	gum
n		8		40	131
o		8		30	gum
p		14		35	gum
q		12		40	gum
r		12		50	gum
s		5		65	76-77

a: Olefin (5 mmol), anhydrous chloramine-T, (1.1 equiv), Py.HBr_3 (10 mol%), CH_3CN, (25 ml), 25^oC; b: Isolated yields after column chromatographic purification.

As can be seen from **Table 1** and **2**, tosyl aziridines were formed in good to excellent yields (20-70%) using Chloramine-T as a nitrogen source. Commercially available form of Chloramine-T that is a trihydrate (TsNClNa. $3H_2O$) also afforded the *N-p*-tolylsulfonyl-2-phenylaziridine from styrene in reasonable yield (50%). Variety of aromatic and non-aromatic olefins afforded the corresponding aziridines in good yields. As depicted in **Table 1**, 1,2-disubstituted olefins (entries b-f) provided the corresponding aziridines stereospecifically and in excellent yield. The three monosubstituted olefins (entries a, g and h) gave modest yields, albeit still in the useful range. Allylic alcohols and allyl bromide also reacted very well under these reaction conditions to afford the corresponding aziridines in excellent yields (entries o, q, r and t). α, β-Unsaturated carbonyl compounds are of great interest for the aziridination reactions because they can act as a synthon for the synthesis of biologically active compounds. It may be noted that previously reported catalytic systems such as PTAB[16] and I_2[17] were not effective against these systems. A novel feature of the Py.HBr_3-catalytic system is the unexpected reactivity shown by a variety of electron-deficient olefins affording good yields of aziridinated products. However, cinnamates such as methyl cinnamate and α, β-unsaturated amides such as acrylamide failed to aziridinate under these conditions. Further 1,2 disubstituted olefins also underwent the aziridination successfully. The stereochemistry of 1-2 disubstituted aziridines was found to be *trans* confirmed by its ^{1}H-NMR spectrum (J = 4.5 Hz).

The influence of the amount of the amount of Py.HBr_3 as catalyst was evaluated using styrene as a representative case. It is observed that no aziridinated product was formed when 1 mol% of Py.HBr_3 was employed. Increasing the catalyst to either 5 or 10-mol% has resulted in the formation of aziridines in 60% yield. However, further increase of catalyst (50 mol% to

stoichiometric amount) had a deleterious effect on improving the yield of aziridine. Also, when PPh_3Br_2 was used as a catalyst, aziridination of styrene still proceeded although in lower yield (30%).

The aziridine formation was confirmed by ^1H, ^{13}C-NMR, IR and mass spectroscopy. The mass spectra of aziridines showed a typical α-cleavage with ejection of the alkyl group attached to the carbon atom. In case of α,β-unsaturated aziridines fission of both CO-NH and CO-aziridine bonds occur, leading to isocyanate and aziridinium type ions respectively. The IR spectrum of all the aziridines showed typical absorption around 1310, 1150 (SO_2) cm^{-1} region. For example, ^1H-NMR spectrum of aziridine **16c** showed a sharp singlet at δ 4.22 corresponding to methine protons of aziridine ring. Further, a singlet observed at δ 2.44

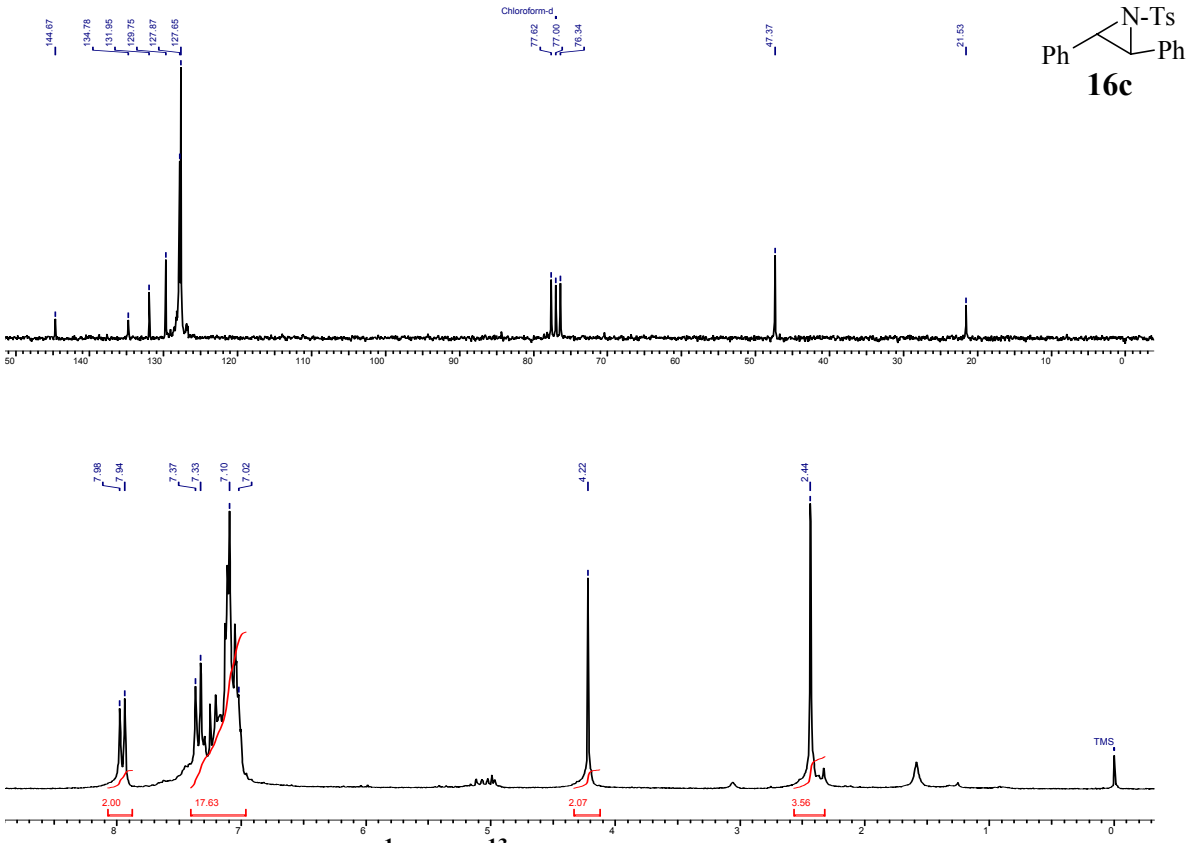


Fig. 1: ^1H and ^{13}C-NMR spectra of aziridine16c

corresponds to methyl of *N*-tosyl group. Its ^{13}C-NMR spectrum showed typical peaks at δ 21.53 and 47.37 for the tosyl methyl and benzylic carbon respectively **(Fig. 1)**. Its mass spectrum showed the molecular ion peak at m/z 349. The ^{1}H-NMR spectrum of aziridine **16m** shows singlet at δ 2.44 corresponding to methine proton of aziridine ring **(Fig. 2)**.

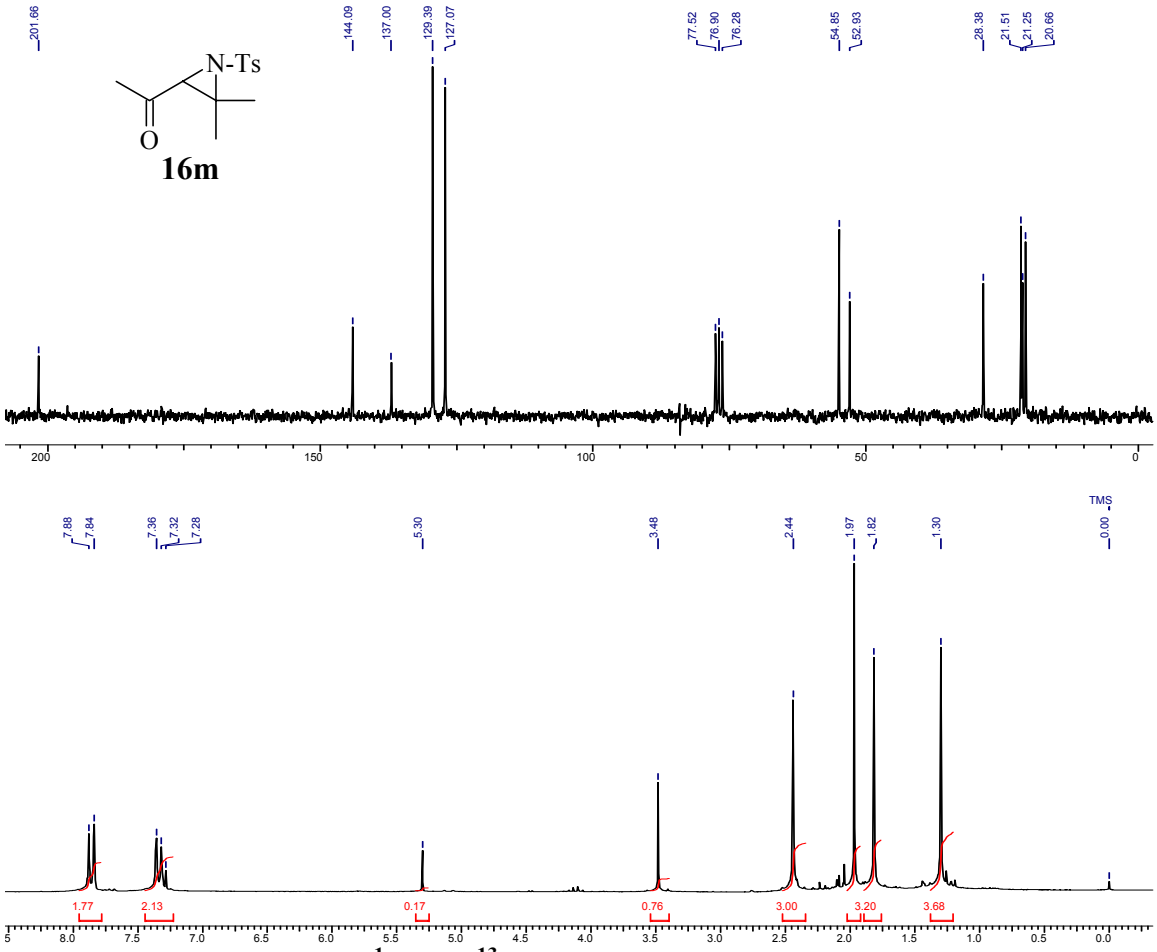


Fig. 2: ^{1}H and ^{13}C-NMR spectra of aziridine 16m

It is remarkable to note that when a conjugated diene such as 1,3-butadiene was subjected to aziridination, one of the double bonds was selectively aziridinated in high yields. Its ^{1}H-NMR spectrum showed a multiplet at δ 3.25 corresponding to allylic proton of aziridine ring. Further, doublets observed at δ 2.25 and 2.80 correspond to two ring protons. Other signals in the region δ 5.25-5.45 indicates the presence of one olefinic bond **(Fig. 3)**.

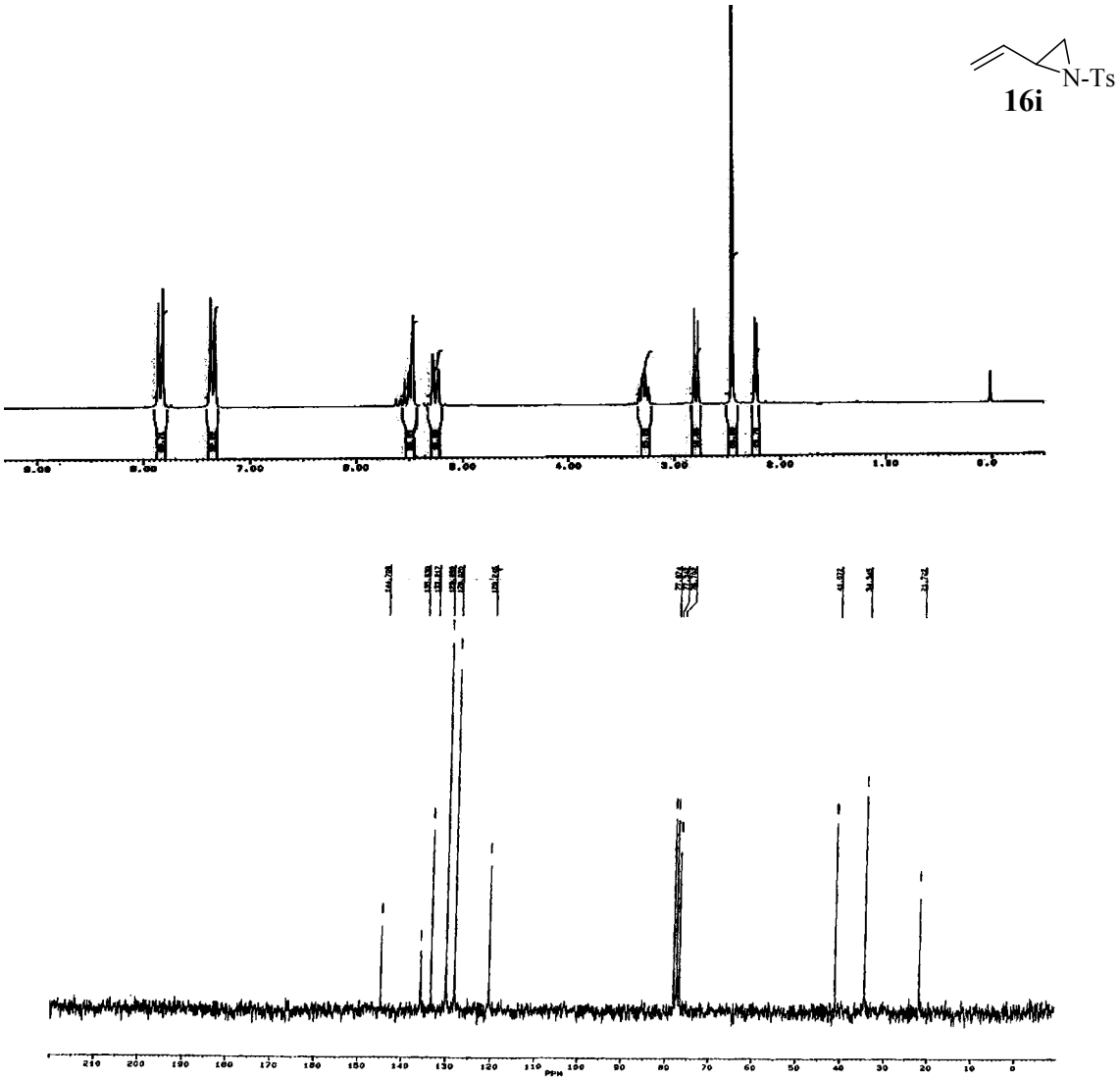


Fig. 3: ^{1}H and ^{13}C-NMR spectra of aziridine 16i

Mechanism

Although the mechanistic aspect of aziridination is not yet clear, we believe that Py.HBr_3 acts as the source for the generation of Br^+ species. The proposed catalytic pathway is shown in **Fig. 4**. Initially, Py.HBr_3 reacts with Chloramine-T to give the species **A**, which then reacts with the corresponding olefin to afford the bromonium ion **B**. The bromonium ion **B** then undergoes regiospecific opening by $TsNCl^-$ species to give *β*-bromo-*N*-chloro-*N*-toluenesulfonamide (**C**). Attack of Br- (or $TsNCl^-$) on the N-Cl group in putative intermediate

C generates the anion **D** and Br-X species. Cyclization of **D** leads to the formation of aziridine and the regeneration of species Br-X is ready to initiate another run of the catalytic cycle. The reaction between Chloramine-T and Br-Cl regenerates species A, thus completing the catalytic cycle. It has been observed that there was very slow reaction of olefin with stoichiometric amount of $Py.HBr_3$ in the absence of Chloramine-T to yield the corresponding dibromo compounds, indicating that $Py.HBr_3$ is not directly reacting with olefin. It is quite possible that species A is formed first which subsequently reacts with olefin.

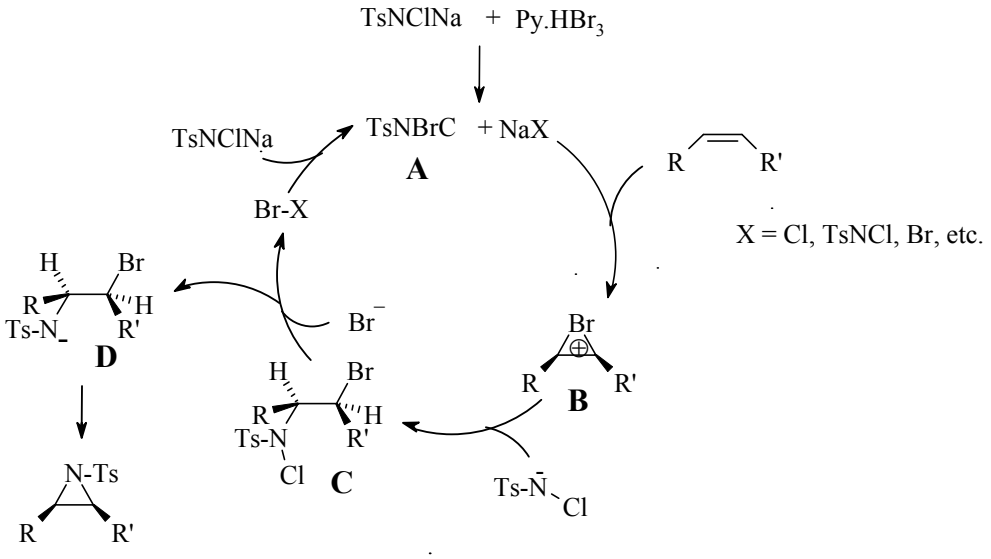


Fig. 4: Catalytic cycle for $Py.HBr_3$ -catalyzed aziridination of olefins

4.0.5 Conclusion

In conclusion, we have successfully demonstrated the use of pyridinium hydrobromide perbromide as a simple, safe and cheap catalyst for aziridination of olefins to afford the corresponding aziridines in good to excellent yields. Under these reaction conditions α, β-unsaturated compounds also reacted efficiently to give the corresponding aziridines in 20-60% yield.

4.0.6 Experimental Section

General procedure for aziridination of olefins

A 25 ml RB flask was charged with olefin **15a-t** [3 mmol (1 mmol in case of α, β-unsaturated systems)], anhydrous Chloramine-T (0.228 g, 1 mmol) $PyH.Br_3$ or Pyridinium hydrobromide perbromide (10 mol%) and acetonitrile (5 ml). The resulting reaction mixture was stirred at 25^0C (monitored by TLC). After completion, the reaction mixture was diluted with EtOAc (15 ml) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford crude product, which was purified by column chromatography on silica gel using pet. ether and EtOAc as eluent to afford pure aziridines **16a-t**.

***N*-(*p*-Toluenesulfonyl)-2-phenylaziridine (16a): Yield:** 60%; **mp:** 94-96ºC (hexane/ EtOAc), lit.[33] **mp**: 88-89^{0}C; **IR** (nujol, cm^{-1}): 3933, 3321, 3130, 3025, 2956, 2926, 1696, 1528, 1455, 1399, 1324, 1219, 1187, 1160, 1092, 911; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.40 (d, *J* = 4.6 Hz, 1H), 2.45 (s, 3H), 3.00 (d, *J* = 7.3 Hz, 1H), 3.80 (dd, *J* = 7.3 and 4.6 Hz, 1H), 7.15-7.45 (m, 7H),7.90 (d, *J* = 8.26 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.5, 37, 42.5, 127, 128, 128.5, 129, 130, 135.5; **MS**: m/z (% rel. intensity): 273 (M^+, 2), 155 (2), 139 (2), 119 (10), 118 (100), 117 (18), 107 (5), 91 (93), 65 (7); **Analysis:** $C_{15}H_{15}NS0_2$ requires C, 65.91; H, 5.52; N, 5.12; S, 11.73 %; Found: C, 65.89; H, 5.52; N, 5.11; S, 11.70 %.

***N*-(*p*-Toluenesulfonyl)-indeneaziridine (16b): Yield:** 50%; **mp:** 165ºC, (hexane/ EtOAc); **IR** (nujol, cm^{-1}): 3280, 2910-2980, 2880, 1480, 1400, 1355-1370, 1323, 1250, 1158, 1130, 1090, 915, 840, 770, 750, 675; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.40 (d, *J* = 6.48 Hz, 1H), 2.45 (s, 3H), 3.15-3.35 (dd, *J* = 8.1 and 7.0 Hz, 1H), 3.60 (dd,, *J* = 8.1 and 7.02 Hz, 1H), 4.2-4.40 (m, 1H), 7.15-7.50 (m, 6H), 7.85 (d, *J* = 8.26 Hz, 2H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.43, 41.02, 51.62, 67.09, 124.60, 127.26, 127.66, 129.07, 129.64, 137.42, 139.25, 140.07, 143.62; **MS**: m/z (% rel. intensity): 214 (14), 212 (15), 134 (10), 133 (100), 132 (18), 115 (32), 105 (23), 103 (18), 91(6), 79 (11), 77 (27), 55 (16), 51(16); **Analysis**: $C_{16}H_{15}NSO_2$ requires C, 67.34; H, 5.29; N, 4.90; S, 11.23 %; Found: C, 67.0; H, 5.27; N, 4.91; S, 11.21%.

***trans*-*N*-(*p*-Toluenesulfonyl)-2-3-biphenylaziridine (16c): Yield:** 40%; **mp:** 140ºC, (hexane/ EtOAc), lit.[33] **mp**: 139^{0}C; **IR** (nujol, cm^{-1}): 3000, 2800, 2650, 1450, 1380, 1240, 1180, 1020, 980; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 4.25 (s, 2H), 7.05-7.70 (m, 12H), 7.85 (d, *J*

= 8.26 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.53, 47.37, 127.65, 127.87, 129.75, 131.95, 134.78, 144.67; **MS**: m/z (% rel. intensity): 349 (M^+,7), 261 (3), 260 (3), 195 (12), 194 (100), 180 (8), 179 (6), 178 (6), 167 (15), 165 (21), 152 (7), 116 (12), 105 (9), 91 (20), 89 (12), 77 (7), 65 (13); **Analysis:** $C_{21}H_{19}NSO_2$ requires C, 72.18; H, 5.47; N, 4.00; S, 9.17%; Found: C, 72.20; H, 5.41; N, 3.98; S, 9.12 %.

7-[Methyl-7-(phenylsulfonyl) 7-azabicyclo[4.1.0] heptane (16d): Yield: 70%; **mp:** 55ºC, (hexane/ EtOAc), lit.[6b] **mp**: 55.3-55.9^{0}C;; **IR** (neat, cm^{-1}): 2937, 2862, 1597, 1439, 1400, 1320, 1238, 1184, 1156, 1091, 964, 920; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.05-1.45 (m, 4H), 1.65-1.80 (m, 4H), 2.45 (s, 3H), 2.95 (t, *J* = 1.3 Hz, 2H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 19.5, 21.5, 22.9, 40, 127.23, 129.49, 137.3, 144.1; **MS**: m/z (% rel. intensity): 252 (M^+ 17), 96 (100), 55 (8), 65 (22), 69 (45), 91 (50), 96 (100), 97 (8), 133 (2), 155 (18), 172 (6), 200 (2), 210 (15), 252 (6); **Analysis:** $C_{13}H_{17}NSO_2$ requires C, 62.12; H, 6.81; N, 5.57; S, 12.75; Found : C, 62.08; H, 6.81; N, 5.52; S, 12.74 %.

9-[Methyl-7-(phenylsulfonyl) 9-azabicyclo[6.1.0]nonane (16e): Yield: 65%; **mp**: 123ºC; **IR** (nujol, cm^{-1}): 2940, 2860, 1597, 1442, 1403, 1320, 1237, 1184, 1159, 1091, 964; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30-1.70 (m, 10H), 2.05 (m, 2H), 2.45 (m, 3H), 2.80 (m, 2H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 21.42, 25.10, 26.02, 26.24, 43.73, 127.39, 129.45, 135.80, 143.90; **MS**: m/z (% rel. intensity): 279 (M^+, 2), 250 (1), 210 (10), 155 (5), 125 (10), 124 (100), 97, 98 (15), 91 (23), 90 (15), 79 (6), 65 (12), 55 (21), 28 (1); **Analysis:** $C_{15}H_{21}NSO_2$ requires C, 64.48; H, 7.56; N, 5.01; S, 11.47; Found: C, 64.52; H, 7.59; N, 5.01; S, 11.50 %.

***N*-(*p*-Toluenesulfonyl)-3-azatricyclo[3.2.1.0.^{2,4exo}]octane (16f): Yield:** 50%; **gum**; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.3 (2H, m), 1.40-1.60 (m, 2H), 1.70-1.95 (m, 2H), 2.0-2.2 (m, 2H), 2.45 (s, 3H), 3.8-4.0 (m, 2H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (% rel. intensity): 264 (M^+, 83), 198(100), 155(65), 139(7), 133(18), 106(7), 91(73), 81(10), 78(8), 67(56), 65(23), 53(5). **Analysis**: $C_{14}H_{17}NSO_2$ requires C, 63.85; H, 6.50; N, 5.31; S, 12.17; Found: C, 63.80; H, 6.50; N, 5.27; S, 12.14 %.

***N*-(*p*-Toluenesulfonyl)-2-butylaziridine (16g): Yield:** 40%; **gum**; **IR** (neat, cm^{-1}): 3300, 3000, 2255, 1600, 1518, 1405, 1355, 1330, 1250, 1146; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.6-0.9 (m, 4H), 1.10-1.50 (m, 5H), 1.90 (d, *J* = 5.2 Hz, 1H), 2.20 (d, *J* = 7.3 Hz, 1H), 2.45 (s,

3H), 2.70 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **Analysis**: $C_{13}H_{19}NSO_2$ requires C, 61.63; H, 7.55; N, 5.52; S, 12.65; Found: C, 61.67; H, 7.56; N, 5.52; S, 12.69 %.

***N*-(*p*-Toluenesulfonyl)-2-decaneaziridine (16h): Yield:** 42%; **gum**; **IR** (neat, cm^{-1}): 3300, 3000, 2250, 1600, 1520, 1400, 1355, 1330, 1250, 1140, 1090; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 6.3 Hz, 3H), 1.05-1.50 (m, 18H), 2.10 (d, *J* = 7.4 Hz, 1H), 2.20 (d, 1H), 2.45 (s, 3H), 2.70 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H), **Analysis**: $C_{19}H_{31}NSO_2$ requires C, 61.63; H, 9.24; N, 4.14; S, 9.50; Found: C, 61.59; H, 9.24; N, 4.12; S, 9.48 %.

***N*-(*p*-Toluenesulfonyl)-2-vinylaziridine (16i): Yield:** 65%; **gum**; **IR** (neat, cm^{-1}): 3134, 3090, 3023, 2996, 2957, 2925, 1597, 1447, 1404, 1325,1220, 1159, 1092, 984, 933, 841; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.25 (d, *J* = 4.51 Hz, 1H), 2.45 (s, 3H), 2.80 (d, *J* = 7.16 Hz, 1H), 3.25 (m, 1H), 5.25 (dd, *J* = 5.21 and 2.79 Hz, 1H), 5.45 (m, 2H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 21.72, 34.34, 41.07, 120.24, 128.02, 129.89, 133.21, 135.63, 144.70; **MS**: m/z (% rel. intensity): 223 (M^+, 31), 222 (12), 155 (47), 92 (17), 91 (68), 68 (100), 65 (30), 41 (59), 49 (42); **Analysis**: $C_{11}H_{13}NSO_2$ requires C, 59.17; H, 5.90; N, 6.27; S, 14.36; Found: C, 59.14; H, 5.91; N, 6.26; S, 14.31 %.

***N*-(*p*-Toluenesulfonyl)-2-formylaziridine (16j): Yield:** 20%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3022, 2955, 2928, 1596, 1540, 1435, 1400, 1336, 1277, 1215, 1153, 1037, 755; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.25-3.35 (dd, *J* = 4.4 and 2.9 Hz, 1H), 4.15-4.20 (m, 1H), 4.25-4.40 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H), 9.10 (s, 1H); **Analysis**: $C_{10}H_{11}NSO_3$ requires C, 53.32; H, 4.91; N, 6.21; S, 14.23; Found C, 53.39; H, 4.91; N, 6.18; S, 14.21 %.

***N*-(*p*-Toluenesulfonyl)-3-methyl-2-formylaziridine (16k): Yield:** 65%, **mp**: 106ºC (hexane: EtOAc); **IR** ($CHCl_3$, cm^{-1}): 3025, 2955, 2928, 1540, 1437, 1403, 1336, 1277, 1215, 1153, 1082, 1055, 755; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.49 (d, 3H), 1.60 (s, 1H), 2.45 (s, 3H), 3.67 (q, *J* = 6.25 Hz, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H), 9.19 (s, 1H); **Analysis**: $C_{11}H_{13}NSO_3$ requires C, 55.21; H, 5.47; N, 5.85; S, 13.40; Found: C, 55.19; H, 5.47; N, 5.85; S, 13.37 %.

***N*-(*p*-Toluenesulfonyl)-2-acetylaziridine (16l): Yield**: 60%; **gum**; **IR** (nujol, cm^{-1}): 3120, 3056, 2986, 2926, 1717, 1407, 1333, 1264, 1163, 1092, 902, 739; **^{1}H-NMR** (200 MHz,

$CDCl_3$): δ 2.08 (s, 3H), 2.47 (s, 3H), 2.50 (d, *J* = 2.9 Hz, 1H), 2.81 (d, *J* = 7.8 Hz, 1H), 3.29 (dd, *J* = 4.4 and 2.9 Hz, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **Analysis**: $C_{11}H_{13}NSO_3$ requires C, 55.21; H, 5.47; N, 5.85; S, 13.40; Found: C, 55.17; H, 5.48; N, 5.83; S, 13.37 %.

***N*-(*p*-Toluenesulfonyl)-2-acetyl-3,3' dimethylaziridine (16m): Yield:** 60%; **gum**; **IR** (neat, cm^{-1}): 3398, 3139, 3023, 2964, 2927, 1717, 1699, 1451, 1401, 1325, 1217, 1157, 1091, 1048; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.80 (s, 3H), 1.95 (s, 3H), 2.45 (s, 3H), 3.50 (s, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H), **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.85, 21.37, 21.71, 28.39, 53.08, 55.03, 127.23, 129.49, 137.33, 144.13, 201.63; **MS**: m/z (% rel. intensity) : 224 (6), 155 (14), 139 (6), 113 (15), 112 (100), 91 (73), 84 (21), 71 (32), 70 (87), 65 (47), 55 (9); **Analysis**: $C_{13}H_{17}NSO_3$ requires C, 58.40; H, 6.40; N, 5.23; S, 11.99; Found: C, 58.41; H, 6.42; N, 5.25; S, 11.99 %.

***N*-(*p*-Toluenesulfonyl)-2-hydroxymethylaziridine (16n): Yield**: 40%; **mp**: 131ºC; **IR** ($CHCl_3$, cm^{-1}): 3524, 3300, 3175, 2922, 2854, 1456, 1376, 1317, 1154, 1081; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.90-3.10 (m, 2H), 3.50-3.75 (m, 2H), 5.50-5.80 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (rel. intensity): 227 (M^+, 3), 225 (4), 215 (10), 214 (100), 197 (7), 184 (19), 155 (80), 139 (15), 133 (7), 92 (13), 91 (97), 77(5), 65(23); **Analysis**: $C_{10}H_{13}NSO_3$ requires C, 52.84; H, 5.76; N, 6.16; S, 14.10; Found: C, 52.80; H, 5.74; N, 6.15; S, 14.11 %.

***N*-(*p*-Toluenesulfonyl)-2-methyl-3-hydroxymethylaziridine (16o): Yield:** 30%; **gum**; **IR** (nujol, cm^{-1}): 3500, 3250, 3000, 2860, 2840, 1775, 1700, 1575, 1455; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.45 (d, *J* = 5.9 Hz, 3H), 2.45 (s, 3H), 3.00 (m, 2H), 3.80 (m, 1H), 4.00 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (% rel. intensity): 241 (M^+, 1), 223 (1), 210 (4), 198 (9), 171(8), 155(36), 139(6), 107(6), 91(95), 86(97), 77(5), 65(37), 58(100); **Analysis**: $C_{11}H_{15}NSO_3$ requires C, 54.75; H, 6.25; N, 5.80; S, 13.28; Found: C, 54.75; H,6.27; N, 5.83; S, 13.29 %.

***N*-(*p*-Toluenesulfonyl)-2-methyl-2'-hydroxymethylaziridine (16p): Yield**: 35%; **gum**; IR (nujol, cm^{-1}): 2925, 2883, 1598, 1452, 1326, 1232, 1160, 1001, 813, 756, 700, 655; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (s, 3H), 2.35 (s, 2H), 3.00 (d, *J* = 6.5 Hz, 2H), 3.50 (d, *J* = 6.5 Hz, 2H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ

19.13, 21.63, 48.87, 59.64, 66.88, 127.05, 129.88, 136.83, 143.59; **MS**: m/z (% rel. intensity): 230 (4), 229 (7), 228 (42), 184 (5), 155 (40), 139 (8), 92 (22), 91 (100), 72 (21), 71 (27), 65 (66), 56 (23); **Analysis**: $C_{11}H_{15}NSO_3$ requires C, 54.75; H, 6.25; N, 5.80; S, 13.28; Found: C, 54.70; H, 6.23; N, 5.81; S, 13.26 %.

7-[Methyl-7-(phenylsulfonyl) 7-azabicyclo[4.1.0] heptane 3-Methyl-2-cyclohexen-1-ol (16q): Yield: 40%, **gum**; **IR** (nujol, cm^{-1}): 3540, 3400, 3300, 3040, 2950, 1620, 1460, 1425, 1345, 1230, 1180, 1105, 780, 685; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.20-1.55 (m ,4H), 1.75 (s, 3H), 1.85 (brs, 1H), 1.95-2.10 (m, 2H), 2.45 (s, 3H), 3.35 (d, *J* = 4.94 Hz, 1H), 3.90-4.10 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (rel. intensity): 281(M^+, 4), 263 (2), 253 (4), 237 (10), 224 (10), 210 (5), 171 (28), 155 (38), 139 (5), 126 (71); **Analysis**: $C_{14}H_{19}NSO_3$ requires C, 59.76; H, 6.80; N,4.97; S, 11.39; Found: C, 59.75; H, 6.78; N, 4.97; S, 11.35%.

2-(1',3'-Dioxalane)-6-methyl-7-[4-methyl-7-(phenylsulphonyl)-7-azabicyclo[4.1.0] heptane (16r): Yield: 50%; **gum**; **IR** (nujol, cm^{-1}): 2890-2990, 1620, 1470, 1420, 1300-1335, 1230, 1170, 1105, 1045, 1010, 960, 900; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.70 (m, 3H), 1.75-2.30 (m, 2H), 2.45 (s, 3H), 3.20 (dd, *J* = 7.3 and 4.6 Hz, 1H), 3.45-3.8 0 (m, 4 H), 4.40 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (rel. intensity): 337 (M^+, 12), 275 (14), 264 (16), 244 (10), 224 (10), 207 (8), 200 (2), 182 (100), 167 (10), 155 (10), 138 (10), 120 (27), 110 (22), 99 (17), 91 (40), 73 (70), 65 (15), 55 (7); **Analysis**: $C_{17}H_{23}NSO_4$ requires C, 60.51; H, 6.86; N,4.15; S, 18.96; Found: C, 60.53; H, 6.87; N, 4.19; S, 18.97 %.

***N*-(p-Toluenesulfonyl)-2-bromomethylaziridine (16s): Yield**: 65%; **mp**: 76-77ºC (benzene: EtOAc); **IR** (nujol, cm^{-1}): 3277, 3200, 3175, 3164, 3150, 3132, 3029, 2981, 2957, 2926, 1597, 1403, 1328, 1292, 1160, 1119, 1093; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.50-3.65 (m, 1H), 3.75-3.80 (m, 1H), 4.10-4.30 (m, 1H), 5.0-5.25 (m, 1H), 7.35 (d, *J* = 8.26 Hz, 2H), 7.85 (d, *J* = 8.26 Hz, 2H); **MS**: m/z (rel. intensity): 290 (M^+, 13), 210 (4), 184 (47), 155 (43), 91 (100, 89 (14), 65 (44), 56 (32), 134 (5), 105 (6), 79 (6); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 21.36, 32.82, 47.20, 49.92, 126.99, 129.77, 136.69, 143.77; **Analysis:** $C_{10}H_{12}NSO_2$ requires C, 41.39; H, 4.16; N, 4.82; S, 11.05; Br, 27.53; Found: C, 41.37; H, 4.17; N, 4.81; S, 11.05; Br, 27.50 %.

SECTION-II

Pyridinium Hydrobromide Perbromide Catalyzed Protection of Alcohols

4.1.1 Introduction

The protection of alcoholic hydroxyl functions has found widespread application especially in the chemistry steroids, sugars, glycerids and synthesis of natural products. Proper use of protecting groups is a prerequisite for the successful achievements of goals in any area of preparative organic chemistry. The major criteria that must be fulfilled by a protecting group are that: i) it must protect a specific functional group in a multifunctional molecule; ii) it must exclude the protected functional group from participating in the reaction to be carried out; iii) it must ensure that the functional group is not damaged during the protected synthetic transformation; iv) it must itself be stable during the projected reaction, but at the same time must be removable after the reaction, which should cause no damage to the newly synthesized structure and v) it should not exhibit a destabilizing, but rather a stabilizing influence on the compound to be protected.

The acetylation and tetrahydropyranylation are the methods of choice to protect a hydroxyl function in a multi-step organic synthesis. The widespread use of these protecting groups is due solubility in non-polar solvents and their reactivity towards attacking reagents.

The acetylation of alcohols is one of the most widely used process for the protection of hydroxy groups.[31] It is generally carried out by using acetic anhydride or acetyl chloride in presence of tertiary amines and 4-(dimethylamino)pyridine (DMAP) as a co-catalyst.[32] Tributylphosphine have been reported as a less basic catalyst for the acetylation of alcohols.[33] In addition to the above catalysts, protic or Lewis acids or sometimes solid acid catalysts are

also known to catalyze the acylation of alcohols. Recently, $Sc(OTf)_3$ has been used as a catalyst for the acetylation of alcohols.[34] More recently, the use of bismuth trifluoromethanesulfonate as a milder catalyst than $Sc(OTf)_3$ has been reported.[35] There are also reports of solid reagents or reagent supported on solid phase for easier work-ups. In this regard, montmorillonite K-10 and KSF,[36] silica supported $NaHSO_4$ and $TaCl_5$[37] have been reported.

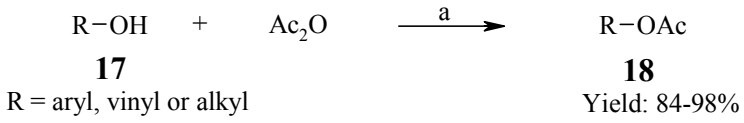
Tetrahydropyran is synthetically useful hydroxyl group protecting agent and also important building block for the synthesis of primary alcohols,[38] allylic alcohols[39] and alkyl halides,[40] due to outstanding stability of tetrahydropyranyl ethers under a variety of reaction conditions,[41] such as basic media, reduction with hydride, oxidations and reactions involving Grignard reagents, lithium alkyls, alkylating and acylating agents. Dihydropyran is still the reagent of choice for the hydroxyl group protection in peptide, nucleotide, carbohydrate and steroid chemistry.[42]

4.1.2 Review of Literature

Various methods of preparation of acetylation and tetrahydropyranylation of alcohols are available in the literature and new routes for their synthesis continue to be devised. Some of the important methods so far known are described below.

Methods of Acetylation

Protic acids such as sulphamic acid[43] and Nafion-H[44] catalyze the acetylation alcohols in excellent yields. Recently Karimi *et al.*[45] have reported a protocol were in a variety of alcohols **17** were acetylated in good to excellent yields with acetic anhydride in the presence of a catalytic amount of *N*-bromosuccinimide (NBS) in CH_2Cl_2 at RT (**Scheme 26**).



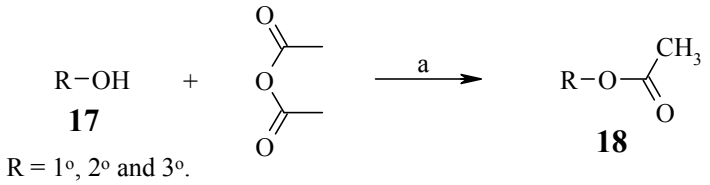
Scheme 26: a) Ac_2O (1.5-5 mmol), NBS (5-10 mol%), CH_2Cl_2, RT.

The combination of PPh_3/CBr_4 in ethyl acetate, at RT has also been reported for the acetylation of alcohols.[46]

Lewis acids such as $In(OTf)_3$, $Bi(OTf)_3$, $CoCl_2$, $Cu(OTf)_3$, $FeCl_3$, $MgBr_2$, $TaCl_5$ etc have shown good catalytic activity towards acetylation of alcohols.[47]

Borah *et al.*[48]

Variety of alcohols alcohol undergoes acylation when treated with acetic anhydride in the presence of catalytic amount of iodine at ambient temperature (**Scheme 27**).

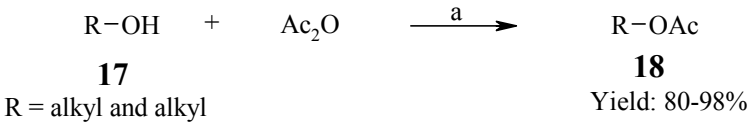


Scheme 27: a) Ac_2O-I_2.

The acetylation reaction is also been reported in heterogeneous fashion. Posner *et al.* have reported the use of commercially available Woelm-200-neutral chromatographic alumina for the effective acetylation of primary alcohols. Rare earth chlorides have also been used for acetylation of alcohols.[49]

Chandrasekhar *et al.*[37]

This method for acylation makes use of $TaCl_5$ and $TaCl_5$-silica gel as a Lewis acid catalyst. Variety of alcohols were acetylated in excellent yields (**Scheme 28**).

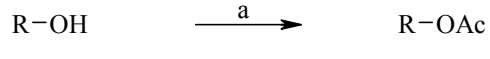


17
R = alkyl and alkyl

18
Yield: 80-98%

Scheme 28: a) $TaCl_5$-SiO_2, CH_2Cl_2, RT.

Curuni *et al.* have reported the use of inorganic-organic layered solids belonging to the class of zirconium phosphates to be an efficient heterogeneous catalyst for the acetylation of alcohols and phenols (**Scheme 29**).[50]

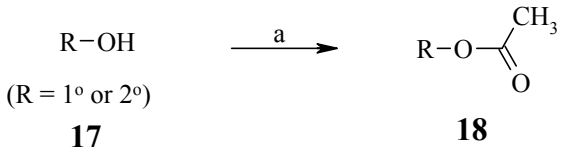


17 **18**

Scheme 29: a) zirconium sulfophenyl phosphonate, CH_2Cl_2, Ac_2O, RT.

Iranpoor *et al.*[51]

The efficient etherification of primary and secondary alcohols in acetic acid was achieved in the presence of $Cu(NO_3)_2.3H_2O$ in high yields (**Scheme 30**).

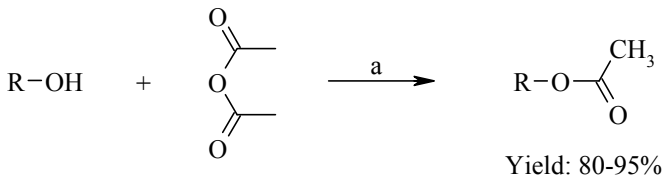


(R = 1° or 2°)
17

18

Scheme 30: a) $Cu(NO_3)_2.3H_2O$, AcOH, reflux.

Lithium chloride and $LiClO_4$ were found to be efficient catalyst for the acetylation of alcohols with acetic anhydride in excellent yields (**Scheme 31**).[52]



R = alkyl or aryl

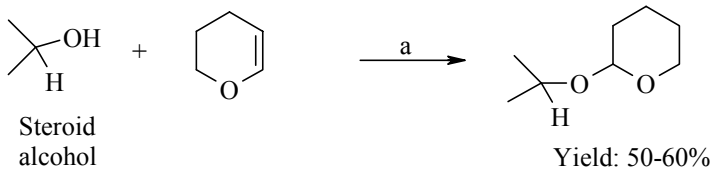
Yield: 80-95%

Scheme 31: a) LiCl, 3-5 h, RT.

Methods of tetrahydropyranylation/ depyranylation

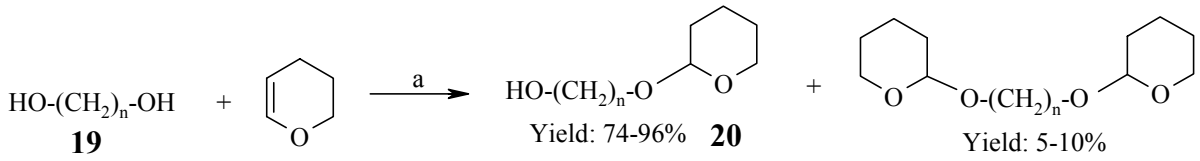
Various methods of tetrahydropyranylation/ depyranylation of hydroxyl compounds are available in the literature and new routes for their synthesis continue to be devised. Some of the important methods are discussed below.

Protic acids such as hydrochloric acid[53] and *p*-toluenesulphonic acid (PTSA),[54] heteropoly acids catalyze the protection and deprotection of hydroxyl group. In 1952 Ott *et al.* (**Scheme 32**) reported that mixing of steroids with excess of DHP in the presence of catalytic amount of PTSA gave the corresponding tetrahydropyranylation ethers in moderate yield.



Scheme 32: a) PTSA ether, RT, 3 days.

Lewis acids such as $BF_3.OEt$,[55] $Al_2(SO_4)_3$-SiO_2,[56] $Al_2O_3/ZnCl_2$,[57] $In(OTf)_3$,[58] LiOTf, [59] $TaCl_5$[60] etc. also catalyze the tetrahydropyranylation of alcohols. Recently, Kawamine *et al.* (**Scheme 33**) reported that the selective protection of 1,2-diols could be achieved by stirring the diol and $Al_2(SO_4)_3$-SiO_2 in DHP-hexane system.



Scheme 33: a) $Al_2(SO_4)_3$-SiO_2, (cat), hexane, RT.

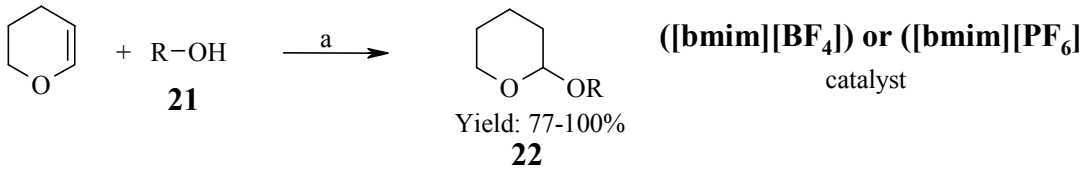
Ion-exchange resins such as Nafion-H,[61] Amberlyst H-15,[62] Reillex-HCl[63] etc. have shown good catalytic activity towards the tetrahydropyranylation of alcohols. Here reactions

are carried out in the presence of excess of DHP without the formation of troublesome oligomeric pyrans. High yields of ethers are obtained even in reactions with alcohols having steric restrictions or acid sensitive amine functionalities.

Synthetically exploitable catalytic activity was also observed from pyridinium *p*-toluenesulphonate (PPTS)[54] which can be easily prepared from pyridine and PTSA monohydrate. Recently, it has been found that heterogeneous catalysts such as sulphonated charcoal,[64] RhO-zeolite,[65] H-Y zeolites,[66] K-10 clay,[67] successfully catalyzed tetrahydropyranylation of alcohols and phenols in good yields.

Branco *et al.*[68]

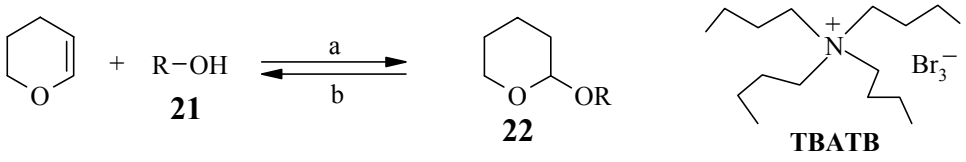
This study describes the tetrahydropyranylation of 1-phenylethanol in ionic liquids in the presence of *p*-toluenesulphonic acid, as a catalyst (**Scheme 34**).



Scheme 34: a) Ionic liquid, PPTS (cat).

Naik *et al.*[69]

Phase transfer catalyst like tetrabutyl ammonium tribromide (TBATB) also act as a catalyst for tetrahydropyranylation and depyranylation of alcohols (**Scheme 35**).



Scheme 35: a) TBATB (0.1 equiv), CH_2Cl_2; b) TBATB (0.1 equiv), MeOH.

Ma *et al.*[70]

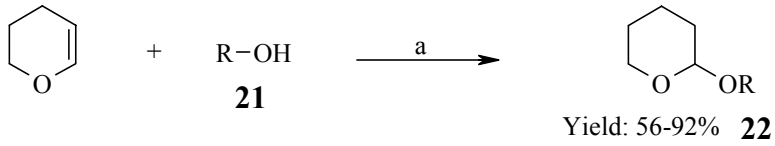
The tetrahydropyranyl derivatives of alcohols and phenols are prepared in the presence of catalytic amount of $[Ru(CH_3CN)_3(triphos)(OTf)_2$ under mild reaction conditions.

Bolitt *et al.*[71]

This method reports use of PPh_3.HBr as a catalyst for the tetrahydropyranylation of tertiary alcohols with DHP in CH_2Cl_2 at ambenient temperature.

Babu *et al.*[72]

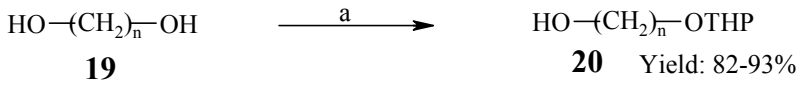
In this approach tetrahydropyranylation of alcohols is achieved by using catalytic amount of lithium perchlorate in neutral medium (**Scheme 36**).



Scheme 36: a) 5M lithium perchlorate, RT, 8-17 h.

Ravinranath *et al.*[73]

This process for tetrahydropyranylation of alcohols using silica chloride is highly selective for mono-protection of the hydroxyl groups of symmetrical diols (**Scheme 37**).



Scheme 37: a) DHP, Silica chloride, RT, 30-40 min.

4.1.3 Present Work

4.1.3.1 Objective

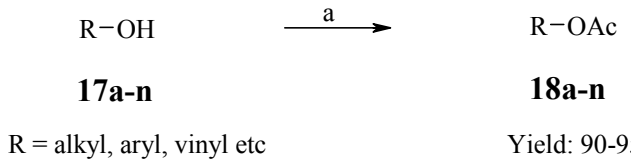
Most of the methods reported in the literature for acetylation and tetrahydropyranylation of alcohols have disadvantages such as tedious work up, corrosive nature of the reagent, strongly acidic media, high temperature etc. Hence there is still a

demand to develop a new mild method in presence of inexpensive catalysts. In our search for new methods for functional group transformations, we were especially interested in exploring the potential use of pyridinium hydrobromide perbromide ($Py.HBr_3$) as an acidic catalyst in organic synthesis. We therefore investigated the possibility of developing new catalytic system for the acetylation and tetrahydropyranylation of alcohols using catalytic amount of $Py.HBr_3$.

4.1.4 Results and discussions

a) $Py.HBr_3$ catalyzed acetylation of alcohols

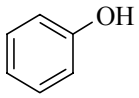
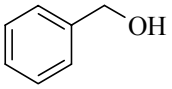
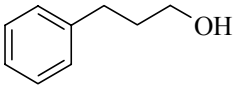
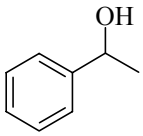
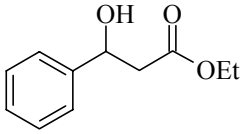
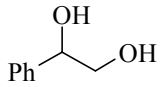
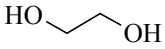
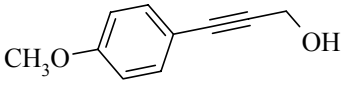
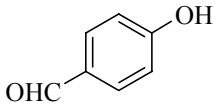
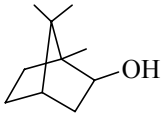
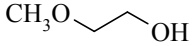
We have discovered an efficient protocol for the acetylation of a variety of alcohols using Ac_2O (1.1 equiv.) and catalytic amount of $Py.HBr_3$ (10 mol%) to the corresponding acetates at room temperature under mild reaction conditions (**Scheme 38**). Thus, benzyl alcohol was treated with Ac_2O in presence of catalytic amount of ($Py.HBr_3$) at RT, the corresponding acetylated product was obtained in 95% yield.



Scheme 38: a) $Py.HBr_3$ (10 mol%), acetic anhydride (1.1 equiv.), CH_2Cl_2, 25°C

Variety of alcohols **17a-n** were successfully acetylated to afford the corresponding acetylated products **18a-n** in excellent yields. As depicted in **Table 3**, primary alcohols (entries b and c) provided the corresponding acetylated products in excellent yields. Secondary alcohols (entries d, e, k and l) also gave acetylated products in good yields. Compounds having propargylic hydroxyl group (entry i) underwent smooth acetylation. Interestingly, sterically hindered alcohols such as campherol were also acetylated in excellent

Table 3: Acetylation of Alcohols using Ac_2O in the presence of $Py.HBr_3$.[a]

Entry	Alcohol	Time (h)	Yield (%)[b]
a		4	95
b		1.5	98
c		2	95
d		8	95
e		8	90
f		12	85[c]
g		3	92[c]
h		3.5	90[c]
i		6	95
j		4.5	90
k		10	92
l	Menthol	10	95
m	Geraniol	12	90
n		14	91

a: reaction conditions: alcohol **17**(**a-n**) (2 mmol), Ac_2O (2.2 mmol), $Py.HBr_3$ (10 mol%), CH_2Cl_2, RT; b: yields refer to isolated product after column chromatography; c: diacetate product was obtained.

yields. Diols underwent acetylation to yield the corresponding diacetate (entries g and h). Styrene diol having both primary and secondary hydroxyl group when subjected to acetylation with 1 equiv. of acetic anhydride failed to show selectivity in acetylation.

When tertiary alcohols were subjected to acetylation under various conditions failed to give acetylated product and the starting alcohol was recovered back. First, increasing the cata-

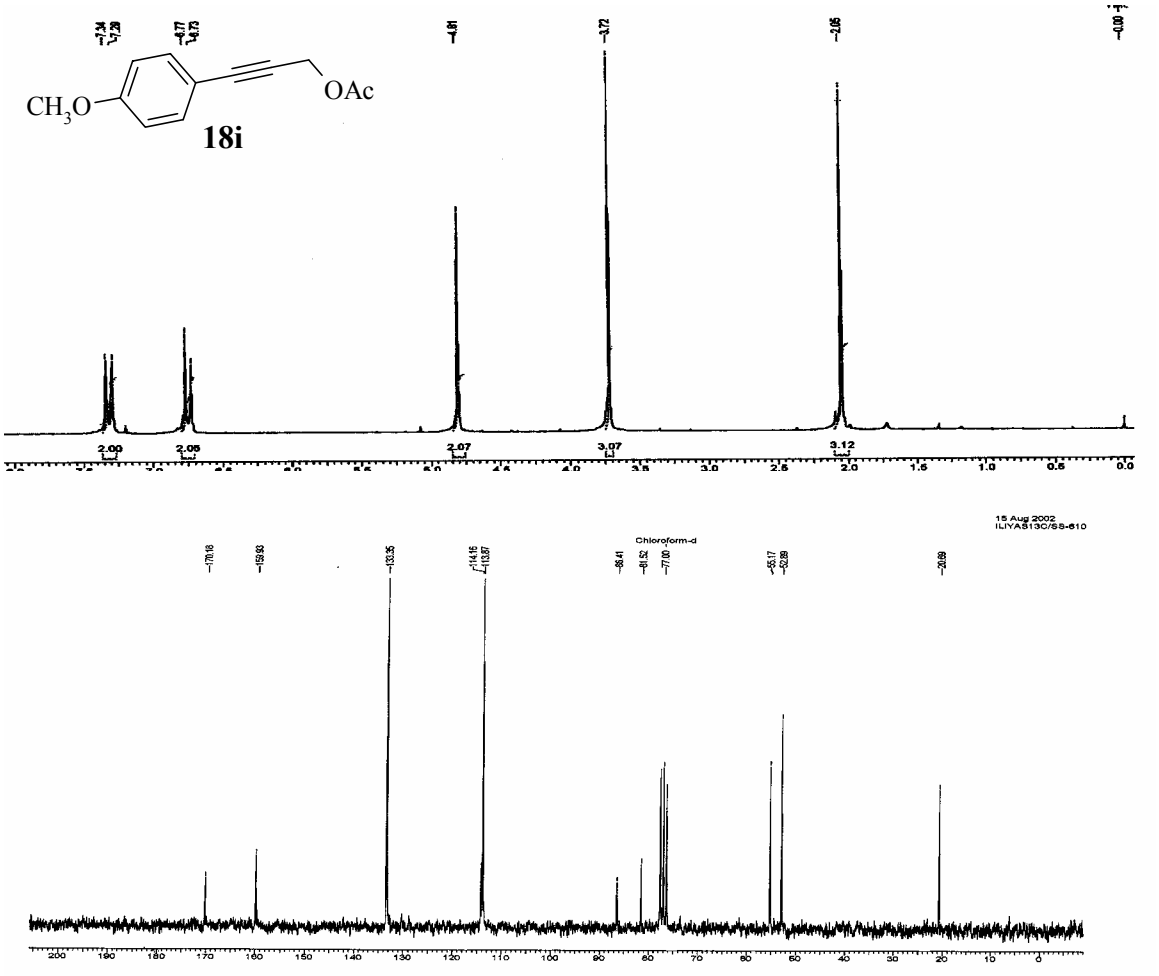


Fig. 5: ^{1}H and ^{13}C-NMR spectrum of 18i

lyst to either 20 or 50 mol%, also did not result in the product formation. Even at higher temperature reaction does not proceed. Advantages of this method is that acetylation works at milder temperature, reactions are clean and no other detectable side products are observed during the course of reactions. The reaction procedure is easy and product yields are excellent.

The formation of acetate was confirmed by ^{1}H, ^{13}C-NMR and IR spectroscopy. The IR spectrum of all acetates showed characteristic strong absorption peak for ester carbonyl. An example, the ^{1}H-NMR spectrum of compound **18i** showed singlet at δ 2.05 corresponding to methyl protons of acetate group. Its ^{13}C-NMR spectrum showed signal at δ 20.69 typical of acetate methyl group **(Fig. 5)**.

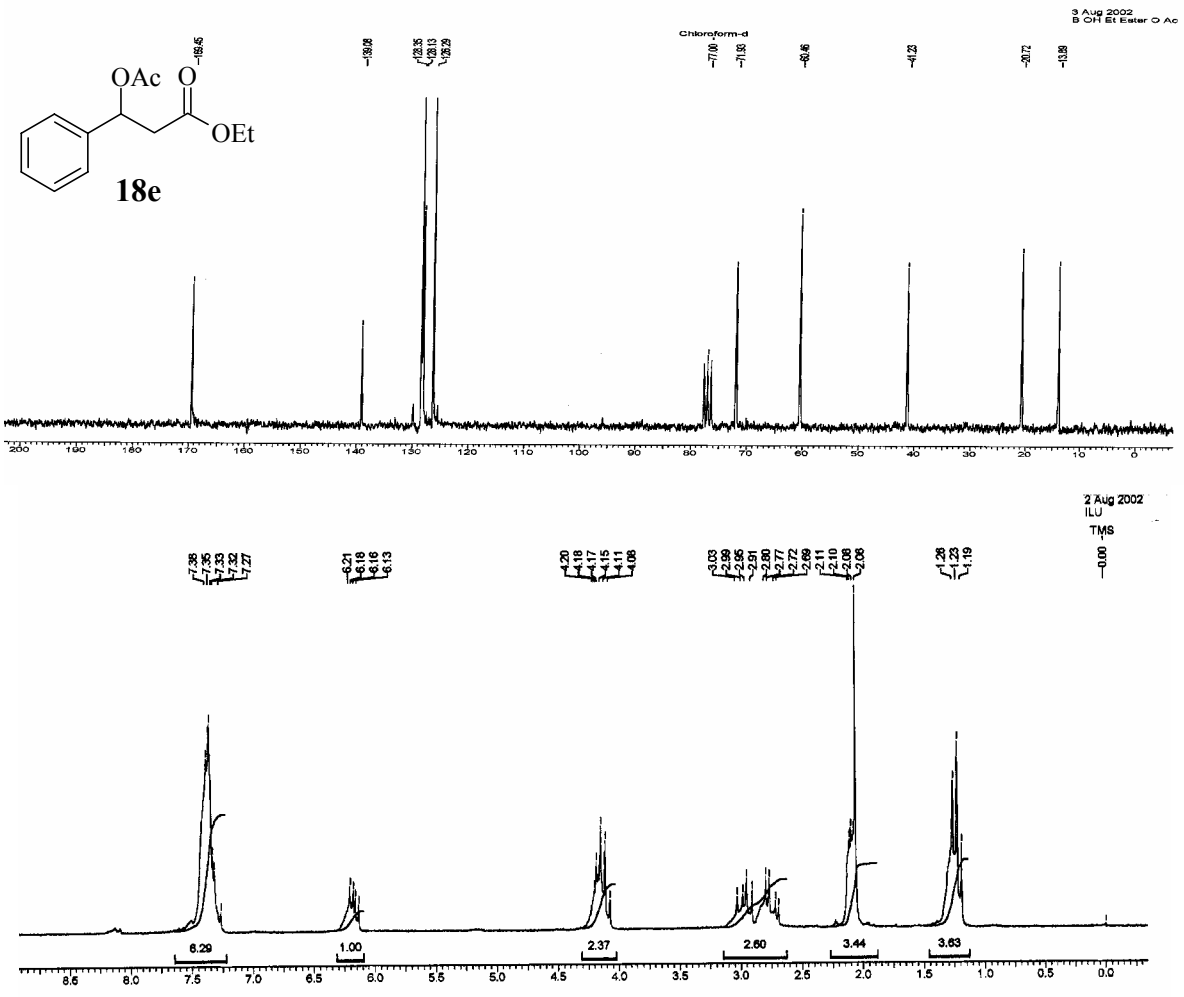


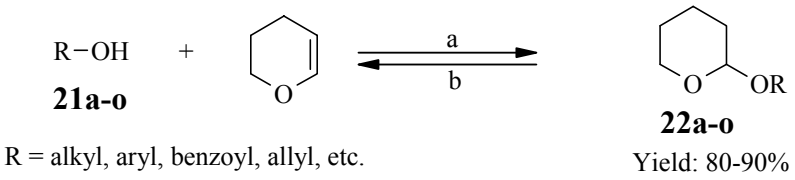
Fig. 6: ^{1}H and ^{13}C-NMR spectrum of 18e

The ^{1}H-NMR spectrum of compound **18e** showed sharp singlet at δ 2.06 corresponding to methyl protons of acetate group and a doublet of doublet at δ 6.13-6.21 for

the benzylic proton. Its ^{13}C-NMR spectrum showed signal at δ 20.72 typical of acetate methyl group **(Fig. 6)**.

b) $Py.HBr_3$ catalyzed Tetrahydropyranylation/Depyranylation of alcohols

A new method to protect the hydroxyl groups as THP ethers and deprotection of these THP ethers has been developed as shown in **Scheme 39**. In the present method, alcohol or phenol, 3,4-dihydro-2H-pyran (DHP) and $Py.HBr_3$ as catalyst are mixed together to yield the corresponding THP ether. A wide variety of hydroxyl compounds are converted to the corresponding THP ethers *via* this procedure and the results are shown in **Table 4**.



21a-o

R = alkyl, aryl, benzoyl, allyl, etc.

22a-o

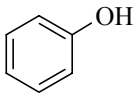
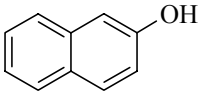
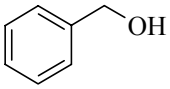
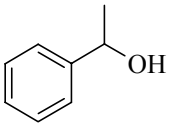
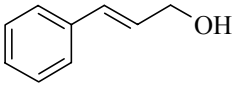
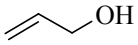
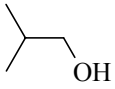
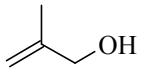
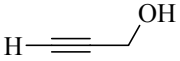
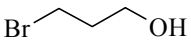
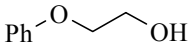
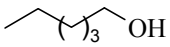
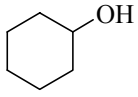
Yield: 80-90%

Scheme 39: a) $Py.HBr_3$ (1 mol%), CH_2Cl_2, RT; b) $Py.HBr_3$ (1 mol%), MeOH, reflux.

As depicted in **Table 4**, phenolic compounds (entries a and b) provided the corresponding THP ethers in excellent yields. Primary as well as secondary alcohols gave the corresponding THP ethers in good yields. Compounds having allylic, propargylic hydroxyl group (entry e, f, h and i) reacted smoothly to afford the corresponding THP ethers. Several other functionalities like halogen, benzyl and double bond were intact during the course of reaction.

The capability of $Py.HBr_3$ to cleave the THP protective group is also investigated to establish the regenerative potential of the catalyst. Thus, THP ethers **(22a-o)** on treatment with

Table 4: $Py.HBr_3$-catalyzed Tetrahydropyranylation[a]/ Depyranylation[b] of alcohols and phenols.

Entry	Alcohol (21a-o)	Protection (THP ether)		Deprotection (Alcohol)	
		Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
a		2.5	85	5	78
b		2.5	85	5	75
c		2	90	3.5	80
d		3	90	5	82
e		2.5	80	4	75
f		1.5	82	4	75
g		2	88	4	85
h		1.5	80	6	75
i		2	90	4	80
j		2	86	4	75
k		2	92	4	85
l		2	88	4	75
m		2	86	4	75
n		1.5	82	3	75
o	Menthol	1.5	85	3.5	80

a: reaction conditions: alcohol **21(a-o)** (5 mmol), DHP (5 mmol), $Py.HBr_3$ (1 mol%), CH_2Cl_2, RT; b: THP ether **22(a-o)** (5 mmol), $Py.HBr_3$ (1 mol%), MeOH, reflux; c) yields refer to isolated product after column chromatography.

$Py.HBr_3$ (1 mol%) at reflux temperature in methanol afforded the corresponding alcohols **(21a-o)** in excellent yields (**Table 4**).

The formation of THP ethers was confirmed by ^1H, ^{13}C-NMR and IR spectroscopy. For example, ^1H-NMR spectrum of compound **22b** showed a characteristic triplet at δ 5.30 corresponding to methine proton of THP ring. Further, the triplet and doublet observed at δ

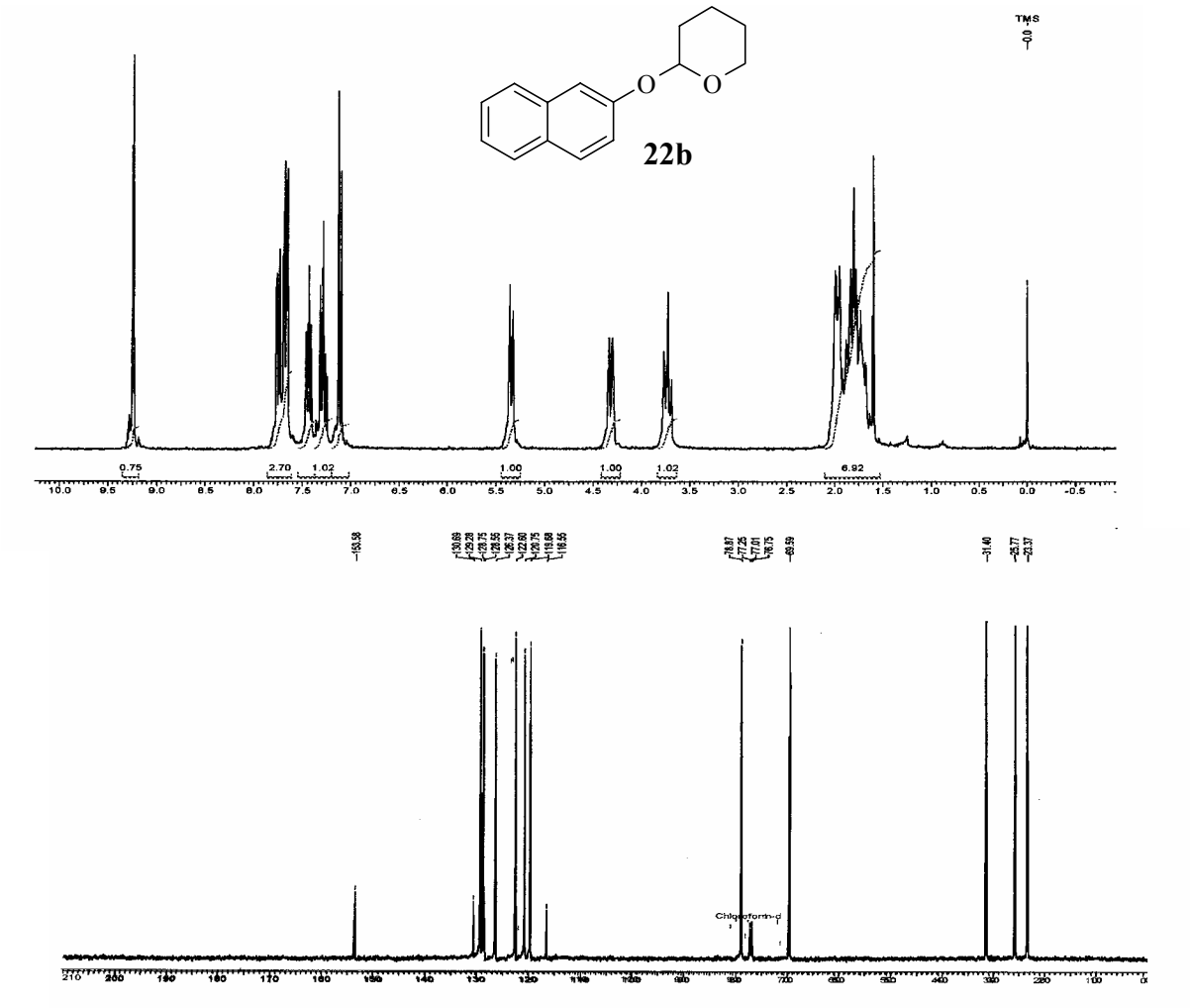


Fig. 7: ^1H and ^{13}C-NMR spectrum of 22b

3.60 and 4.30 corresponds to methylene proton of THP ring attached to oxygen atom. Its ^{13}C-NMR spectrum showed characteristic signals of THP ether at δ 23.37, 25.77, 31.40, 69.59 and 78.87 **(Fig. 7)**.

Mechanism

The probable mechanism of acetylation is shown in **Fig. 8**.

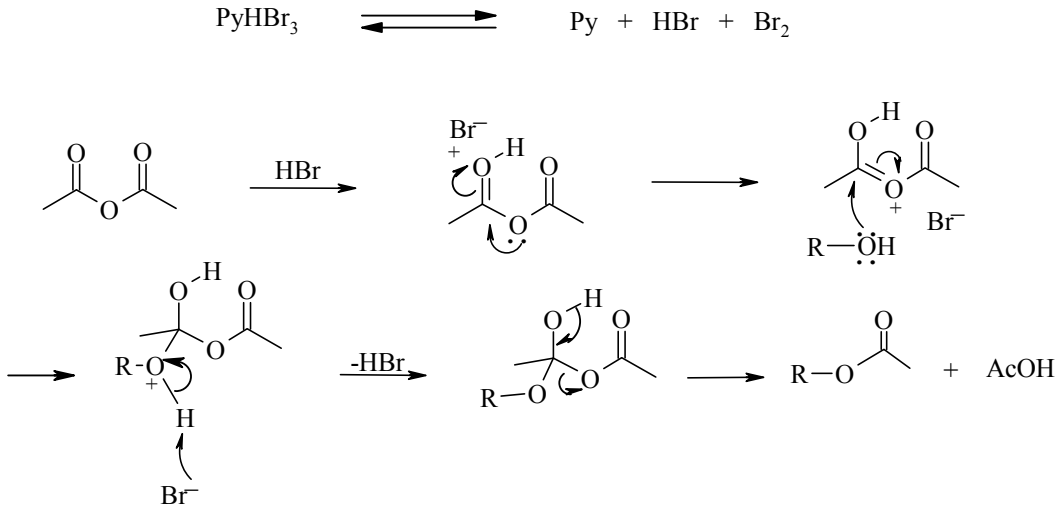


Fig. 8: Probable mechanism of acetylation

4.1.5 Conclusion

In conclusion we have successfully demonstrated that $Py.HBr_3$ as a good catalyst for acetylation and Tetrahydropyranylation/ Depyranylation of a variety of alcohols with acetic anhydride under mild reaction conditions. Reactions are clean and no other detectable side products are observed during the course of reactions. The reaction procedure is easy and product yields are excellent.

4.1.6 Experimental Section

General procedure for acetylation of alcohols

To a solution of alcohol **17a-n** (2.0 mmol) and acetic anhydride (2.2 mmol) in dichloromethane, $Py.HBr_3$ (10 mol%) was added at room temperature. The reaction flask was then stirred until complete disappearance of starting material (as monitored by TLC). After completion the reaction was quenched with water (10 ml), and the mixture was extracted with CH_2Cl_2 (2 x 25 ml). The organic layer was separated and washed with saturated $NaHCO_3$ (2 x 15 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure

to give almost pure acetate. Further purification of products was done by column chromatography to give pure acetates **18a-n**.

Phenyl acetate (18a): Yield: 98%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2939, 2862, 1745, 1454, 1255, 1217, 1037, 775; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.29 (s, 3H), 7.00-7.55 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 16.9, 68.5, 121.6, 125.0, 128.9, 153.1; **MS**: m/z (% rel. intensity): 136 (M^+, 10), 96 (4), 95 (100), 66 (15), 64 (10), 60 (4), 45 (8), 43 (28); **Analysis**: $C_8H_8O_2$ requires C, 71.10; H, 5.96; found C, 71.05; H, 5.87 %.

Benzyl acetate (18b): Yield: 98%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3020, 2935, 2865, 1730, 1454, 1249, 1232, 1217, 1176, 1037, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 5.10 (s, 2H), 7.35 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.3, 72.2, 127.1, 127.5, 128.7, 128.9, 140.9, 171.2; **MS**: m/z (% rel. intensity): 151 (M^{+1}, 4), 150 (30), 192 (5), 191 (100), 65 (10), 59 (6); **Analysis**: $C_9H_{10}O_2$ requires C, 71.98; H, 6.66; found C, 72.01; H, 6.56 %.

3-Phenylpropyl acetate (18c): Yield: 95%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3020, 2939, 2862, 1731, 1454, 1249, 1217, 1037, 757; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.90-2.00 (m, 2H), 2.04 (s, 3H), 2.68 (t, J = 8.0 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 7.05-7.35 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.69, 30.09, 32.08, 63.57, 96.04, 125.86, 128.21, 140.97, 170.54; **Analysis**: $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.91; found C, 74.12; H, 7.85 %.

1-Phenylethyl acetate (18d): Yield: 95%; **gum**; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.68 (d, J = 7.5 Hz, 3H), 2.03 (s, 3H), 5.35-5.45 (m, 1H), 7.10-7.25 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.4, 21.8, 75.5, 127.2, 127.7, 127.9, 140.9, 171.2; **MS**: m/z (% rel. intensity): 165 (M^{+1}, 5), 105 (10), 104 (100), 91 (18), 78 (4), 77 (4), 65 (5), 51 (3), 43 (60), 39 (3); **Analysis**: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.35; found C, 73.25; H, 7.29 %.

3-Acetyl-3-phenyl-propionate (18e): Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3022, 2983, 1737, 1715, 1456, 1373, 1232, 1176, 1026, 756; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, J = 3.50 Hz, 3H), 2.06 (s, 3H), 2.69-2.80 (m, 1H), 2.91-3.03 (m, 1H), 4.15 (q, J = 8.0 Hz, 2H), 6.13-6.22 (dd, J = 4.0 and 6.0 Hz, 1H), 7.25-7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.89, 20.72, 41.23, 60.46, 71.93, 126.29, 128.13, 128.35, 139.08, 169.45; **MS**: m/z (% rel. intensity): 236 (M^+, 5), 193 (75), 176 (55), 162 (10), 147 (80), 131 (50), 120 (35), 105 (35), 91 (60), 77 (65), 43 (100); **Analysis**: $C_{13}H_{16}O_4$ requires C, 66.09; H, 6.81; found C, 66.15; H, 6.85 %.

1-Phenyl-1,2-ethane diacetate (18f): Yield: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3020, 2254, 1730, 1566, 1436, 1373, 1217, 1037; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 6H), 4.60-4.65 (m, 2H), 5.85 (m, 1H), 7.10-7.20 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.5, 72.8, 78.5, 127.3, 127.6, 128.9, 141.0, 171.6; **Analysis**: $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.70; found C, 66.64; H, 6.77 %.

1,2-Ethane diacetate (18g): Yield: 92%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2960, 1741, 1440, 1377, 1236, 1051; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.06 (s, 6H), 4.25 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.5, 66.3, 172.0; **MS**: m/z (% rel. intensity): 147 (M^{+1}, 5), 116 (10), 103 (5), 86 (10), 73 (15), 61 (4), 43 (100); **Analysis**: $C_6H_{10}O_4$ requires C, 49.31; H, 6.89; found C, 49.33; H, 6.87 %.

1,8-Octane diacetate (18h): Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2938, 2632, 1746, 1400, 1072, 771; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25-1.45 (m, 8H), 1.55-1.70 (m, 4H), 2.05 (s, 6H), 4.05 (t, J = 7.5 Hz, 4H); **MS**: m/z (% rel. intensity): 130 (M^+, 2), 110 (15), 82 (40), 81 (22), 64 (40), 44 (30), 43 (100), 28 (5); **Analysis**: $C_{12}H_{22}O_4$ requires C, 62.58; H, 9.62; found C, 62.55; H, 9.62 %.

3-(4-Methoxyphenyl)-2-propyn-1-yl acetate (18i): Yield: 95%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3020, 2937, 2839, 2233, 1741, 1606, 1510, 1379, 1217, 1033; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.72 (s, 3H), 4.81 (s, 2H), 6.75 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.69, 52.89, 55.17, 81.52, 86.51, 113.87, 114.16, 133.35, 159.93, 170.18; **MS**: m/z (% rel. intensity): 204 (M^+, 15), 189 (26), 176 (10), 161 (15), 144 (100), 133 (50), 115 (40), 102 (65); (**Analysis**: $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.91; found C, 70.55; H, 5.95 %.

4-Acetatebenzaldehyde (18j): Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3020, 2399, 1735, 1687, 1604, 1514, 1421, 1215, 1159; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 7.27 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 9.88 (s, 1H); **MS**: m/z (% rel. intensity): 164 (M^+, 10), 122 (80), 121 (92), 93 (10), 65 (18), 43 (100), 39 (15); **Analysis**: $C_9H_8O_3$ requires C, 65.85; H, 4.90; found C, 65.88; H, 4.99 %.

endo-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-acetate (18k): Yield: 92%; **gum**; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.04 (s, 3H), 1.18 (s, 3H), 1.50-2.00 (m, 5H), 2.02 (s, 3H), 2.15-2.55 (m, 2H), 4.97 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.14, 20.91, 23.37,

27.16, 33.07, 35.57, 37.93, 40.94, 43.37, 47.26, 73.51, 170.14; **Analysis**: $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.26; found C, 73.45; H, 10.29 %.

(+)-2-Isopropyl-5-methylcyclohexylacetate (18l): Yield: 95%; **gum**; $[\alpha]_D$: – 80 (c 8, C_6H_6); **IR** ($CHCl_3$, cm^{-1}): 3018, 2871, 1725, 1454, 1375, 1245, 1215, 1033, 1025; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.70-1.25 (m, 9H), 1.25-1.95 (m, 8H), 2.05 (s, 3H), 4.70 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 16.24, 20.54, 21.05, 21.83, 23.44, 26.20, 31.24, 34.14, 40.83, 46.90, 73.95, 170.33; **MS**: m/z (% rel. intensity): 138 (40), 123 (28), 196 (20), 195 (100), 82 (25), 81 (58), 170 (18), 55 (20), 43 (65); **Analysis**: $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.17; found C, 72.68; H, 11.19 %.

(E)-3,7-Dimethyl-2,6-octadien-1-O-acetate (18m): Yield: 90%; **IR** ($CHCl_3$, cm^{-1}): 3446, 2949, 2875, 1752, 1467, 1393, 1277, 1140, 771; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30-1.50 (m, 4H), 1.60 (s, 3H), 1.68 (s, 3H), 1.71 (s, 3H), 2.05 (s, 3H), 4.00-4.10 (m, 3H), 5.05 (m, 1H); **MS**: m/z (% rel. intensity): 198 (M^+, 2), 140 (33), 123 (60), 109 (30), 195 (75), 82 (64), 163 (66), 69 (100), 68 (40), 67 (44), 43 (80), 41 (67); **Analysis**: $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.17; found C, 72.61; H, 11.25 %.

2-Methoxy-ethyl acetate (18n): Yield: 91%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2940, 2875, 2632, 1745, 1400, 1245, 1072, 771; **^{1}H-NMR** (200 MHz, $CDCl_3$): 2.10 (s, 3H), 3.35 (s, 3H), 3.55 (t, J = 7.5 Hz, 2H), 4.20 (t, J = 7.5 Hz, 2H); **Analysis**: $C_5H_{10}O_3$ requires C, 50.84; H, 8.52; found C, 51.00; H, 8.55 %.

General procedure for the tetrahydropyranylation of alcohols

The mixture of alcohol **21a-o** (5 mmol), 2,3-dihydro-4H-pyran (0.420g, 5 mmol) and pyridinium hydrobromide perbromide (0.016 g, 1 mol%) in dry CH_2Cl_2 (10 ml) was stirred at room temperature. After the reaction was complete (TLC), the solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (10 ml) and was extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with 10% sodium thiosulphate solution, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was purified by column chromatography to afford the THP ether **22a-o**.

Dehydropyranylation of THP ethers

The mixture of THP ether **22a-o** (5 mmol), and pyridinium hydrobromide perbromide (0.016 g, 1 mol%) in methanol (10 ml) was heated under reflux. After the reaction was

complete (TLC), solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (10 ml) and was extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with 10% sodium thiosulphate solution, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was then purified by column chromatography to afford the alcohol **21a-o**.

Tetrahydro-2-phenyloxy-2H-pyran (22a): Yield: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 1615, 1400, 1350, 1205, 1220, 1135, 1030, 822, 740, 710; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 3.55 (t, *J* = 3.5 Hz, 2H), 5.80 (t, *J* = 3.5 Hz, 1H), 6.65-7.20 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.5, 28.0, 35.5, 67.2, 72.2, 115.5, 122.0, 113.0, 156.5; **Analysis:** $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.91; found C, 74.19; H, 7.86%.

Tetrahydro-2-naphthyloxy-2H-pyran (22b): Yield: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2358, 1623, 1610, 1523, 1400, 1350, 1205, 1220, 1135, 1030, 822, 740, 710; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 3.60 (t, *J* = 4.0 Hz, 1H), 4.30 (m, 1H), 5.50 (t, *J* = 4.0 Hz, 1H), 7.1-7.4 (m, 3H), 7.60-7.80 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.37, 25.77, 31.40, 69.59, 78.87, 116.55, 119.68, 120.75, 122.60, 128.55, 128.75, 129.75,28, 130.69, 153.58; **Analysis:** $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.05; found C, 79.05; H, 7.11%.

Tetrahydro-2-benzyloxy-2H-pyran (22c): Yield: 90%; **gum**; **IR** (neat, cm^{-1}): 1615, 1405, 1355, 1205, 1135, 1030, 910, 822, 740, 710; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30-1.85 (m, 6H), 3.30-3.50 (m, 1H), 3.55-3.804.60 (m, 1H), 4.30 (s, 2H), 4.65 (brs, 1H), 7.00-7.20 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.5, 25.6, 30.6, 62.0, 68.8, 97.7, 127.5, 127.8, 128.3, 138.4; **Analysis:** $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.38; found C, 74.89; H, 8.40%.

Tetrahydro-2-(2-phenylethyloxy)-2H-pyran (22d): Yield: 90%; **IR** ($CHCl_3$, cm^{-1}): 1670, 1445, 1160, 1210, 1130, 880, 820; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.50 (d, *J* = 5.5 Hz, 3H), 1.60-2.00 (m, 6H), 3.62 (t, *J* = 3.0 Hz, 2H), 4.30 (m, 1H), 4.95 (t, *J* = 3.0 Hz, 1H), 5.55 (t, *J* = 3.5 Hz, 1H), 7.05-7.55 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.5, 23.2, 28.0, 33.5, 63.5, 70.5, 99.0, 127.0, 127.5, 128.9, 137.0; **Analysis:** $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.78; found C, 75.77; H, 8.90%.

Tetrahydro-2-(3-phenyl-2-propenyloxy)-2H-pyran (22e): Yield: 80%; **gum**; **IR** (neat, cm^{-1}): 1445, 1460, 1155, 1210, 1130, 1020, 755, 700; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 3.65 (t, *J* = 4.0 Hz, 2H), 4.20 (d, *J* = 3.5 Hz, 2H), 5.10 (m, 1H), 6.25 (m, 1H), 6.60

(d, J = 14.0 Hz, 1H), 7.00-7.50 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 25.4, 30.5, 62.0, 67.4, 97.6, 125.3, 126.3, 127.4, 128.3, 132.0, 136.0; **MS**: m/z (% rel. intensity): 218 (M^+, 6), 131 (4), 116 (15), 117 (45), 115 (20), 91 (12), 85 (100), 77 (10), 67 (15), 57 (10); **Analysis:** $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.30; found C, 77.10; H, 8.40%.

Tetrahydro-2-(2-propenyloxy)-2H-pyran (22f): Yield: 82%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 1655, 1445, 1200, 1270, 1130, 1020, 930, 830; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.40-1.85 (m, 6H), 3.40-3.60 (m, 1H), 3.80-4.05 (m, 2H), 4.25-4.35 (m, 1H), 4.65 (brs, 1H), 5.15-5.35 (m, 2H), 5.85-6.00 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.0, 28.0, 32.7, 63.5, 94.9, 103.0, 114.9, 115.5, 117.6, 148.2, 153.2; **Analysis:** $C_8H_{14}O_2$ requires C, 67.58; H, 9.91; found C, 67.66; H, 9.86%.

Tetrahydro-2-(2-methylpropyloxy)-2H-pyran (22g): Yield: 88%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 1720, 1670, 1440, 1165, 1205, 1130, 880, 820, 540; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 3.65 (t, J = 3.5 Hz, 2H), 4.00-4.10 (m, 1H), 4.20-4.25 (m, 1H), 5.60 (m, 1H), 6.50-6.65 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.0, 28.2, 34.5, 63.5, 83.1, 101.5, 151.5; **Analysis:** $C_9H_{18}O_2$ requires C, 69.20; H, 11.60; found C, 69.35; H, 11.55%.

Tetrahydro-2-(methyl-2-propeneloxy)-2H-pyran (22h): Yield: 80%; **gum**; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.60-2.00 (m, 6H), 2.05-2.20 (m, 1H), 3.35 (d, J = 3.5 Hz, 2H), 3.60 (t, J = 4.0 Hz, 2H), 5.00 (d, J = 8.5 Hz, 1H), 5.60 (d, J = 8.5 Hz, 1H); **Analysis:** $C_9H_{16}O_2$ requires C, 69.20; H, 10.30; found C, 69.35; H, 10.15%.

Tetrahydro-2-(2-propynyloxy)-2H-pyran (22i): Yield: 90%; **IR** ($CHCl_3$, cm^{-1}): 1455, 1365, 1270, 1205, 1120, 1030, 900, 820, 630, 520; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.45-1.80 (m, 6H), 2.40 (t, J = 3.5 Hz, 1H), 3.45-3.60 (m, 1H), 3.75-3.85 (m, 1H), 4.20 (t, J = 4.0 Hz, 2H), 4.70 (brs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.5, 19.0, 29.7, 53.3, 61.2, 73.8, 79.4, 96.2; **MS**: m/z (% rel. intensity): 139 (M^+, 6), 101 (20), 85 (100), 83 (13), 67 (18), 57 (22), 55 (43), 53 (18); **Analysis:** $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.78; found C, 75.77; H, 8.90%.

Tetrahydro-2-(3-bromopropanyloxy)-2H-pyran (22j): Yield: 86%; **IR** ($CHCl_3$, cm^{-1}): 1450, 1350, 1250, 1220, 1150, 1080, 1050, 880, 770, 550; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 2.52 (s, 1H), 3.70 (t, J = 4.0 Hz, 2H), 4.10 (s, 2H), 5.00 (m, 2H); **Analysis:** $C_8H_{15}BrO_2$ requires C, 43.07; H, 6.77; Br, 35.81; found C, 43.01; H, 6.65; Br, 35.88%.

Tetrahydro-2-(2-phenoxyethanloxy)-2H-pyran (22k): Yield: 92%; **IR** ($CHCl_3$, cm^{-1}): 1460, 1220, 1370, 1270, 1155, 1050, 925, 885, 530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60-2.00 (m, 6H), 3.65 (t, *J* = 4.0 Hz, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 4.10 (t, *J* = 3.5 Hz, 2H), 5.00 (t, *J* = 6.0 Hz, 1H), 6.00-7.50 (m, 5H); **Analysis:** $C_{13}H_{18}O_3$ requires C, 71.11; H, 8.25; found C, 71.20; H, 8.22%.

Tetrahydro-2-(hexanoloxy)-2H-pyran (22l): Yield: 88%; **IR** ($CHCl_3$, cm^{-1}): 1465, 1365, 1270, 1155, 1050, 920, 885, 530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 6.5 Hz, 3H), 1.30-1.45 (m, 8H), 1.60-2.00 (m, 6H), 3.35 (t, *J* = 4.0 Hz, 2H), 3.65 (m, 2H), 4.95 (m, 1H); **Analysis:** $C_{11}H_{22}O_2$ requires C, 62.82; H, 10.53; found C, 62.88; H, 10.53%.

Tetrahydro-2-(5-benzylpentyloxy)-2H-pyran (22m): Yield: 86%; **gum**; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.50-1.60 (m, 8H), 1.60-1.75 (m, 6H), 2.80 (m, 1H), 3.60 (t, *J* = 4.5 Hz, 2H), 5.05 (t, *J* = 4.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.0,19.5, 28.0, 31.3, 33.5, 63.5, 70.0, 98.2; **Analysis:** $C_{17}H_{29}O_3$ requires C, 72.56; H, 10.37; found C, 72.56; H, 10.35%.

Tetrahydro-2-cyclohexyloxy-2H-pyran (22n): Yield: 82%; **gum**; **IR** (neat, cm^{-1}): 1460, 1370, 1270, 1210, 1130, 1040, 1010, 970, 920, 830, 530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.10-1.90 (m, 16H), 3.45 (t, *J* = 5.0 Hz, 2H), 3.80-3.90 (m, 1H), 4.75 (brs, 1H); **Analysis:** $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.93; found C, 71.77; H, 10.98%.

Tetrahydro-2-menthyloxy-2H-pyran (22o): Yield: 85%; **gum**; **IR** (neat, cm^{-1}): 1450, 1385, 1210, 1140, 1050, 920, 880, 535; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.70-0.85 (m, 9H), 1.25-1.60 (m, 14H), 1.95-2.10 (m, 1H), 3.40 (t, *J* = 5.0 Hz, 2H), 3.80-3.90 (m, 1H), 4.70 (brs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.0, 24.5, 27.5, 28.0, 33.5, 63.5, 67.2, 70.5, 80.3, 102.2; **MS**: m/z (% rel. intensity): 240 (M^+, 6), 160 (5), 139 (20), 138 (10), 132 (5), 95 (12), 85 (100), 83 (43), 69 (15), 67 (25), 55 (20); **Analysis:** $C_{15}H_{28}O_2$ requires C, 74.95; H, 11.73; found C, 74.88; H, 11.80%.

SECTION-III

Pyridinium hydrobromide perbromide catalyzed esterification of aliphatic carboxylic acids.

4.2.1 Introduction

Esterifications of carboxylic acids with alcohols have been recognized, as one of the most important unit reactions due to the wide utility of esters in organic, bioorganic, and related fine chemical synthesis.[74] Esterification is a well-established tactic for the protection of acid functionality.[75] Of a number of well-known methods available for esterification of carboxylic acids, those using catalytic amounts of promoter and/or dehydrating reagents under mild conditions are limited.

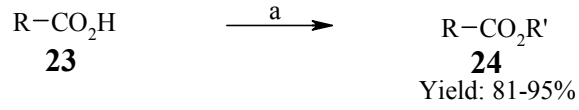
Particularly, variety of methods are available for the introduction of methyl esters, few are inexpensive, convenient, and use commercially reagents. Recent work by Spur and coworkers[76] reported a methodology which work at room temperature utilizes costly reagents like 2,2-Dimethoxypropane and chlorosilanes. Other reported catalysts like $NiCl_2$. $6H_2O$[77] and $Fe_2(SO_4)_3.xH_2O$[78] works at reflux temp. Other methods, $P_2O_5/CuSO_4/Na_2SO_4$, I_2[79] plus H_2O, strong acid exchange resign, DCC[80] and polymer supported-$AlCl_3$[81] utilizes either moisture sensitive or costly reagents and are incompatible with additional functionality in the molecule.

4.2.2 Review of Literature

Literature search revealed that there are large numbers of methods known in literature for esterification of carboxylic acids, which are described below.

Raber *et al.*[82]

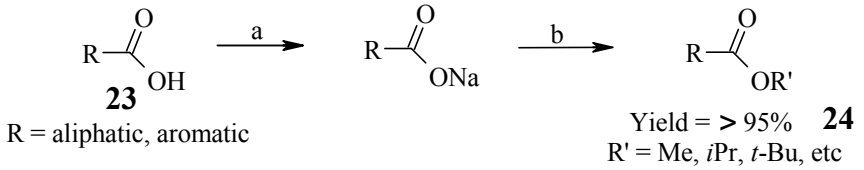
This paper presents esterification of sterically hindered carboxylic acids with triethyloxonium fluoroborate/ diisopropylethylamine leading to good yields of the corresponding esters (**Scheme 40**).



Scheme 40: a) triethyloxonium fluoroborate, CH_2Cl_2, diisopropylethyl amine, RT, 24h.

Shaw *et al.*[83]

In this approach carboxylic acids are quantitatively converted to their esters by reaction of their sodium salts with alkyl halides at room temperature (**Scheme 41**).



Scheme 41: a) NaOH, HMPA; b) R'-X, HMPA.

Blossey *et al.*[81]

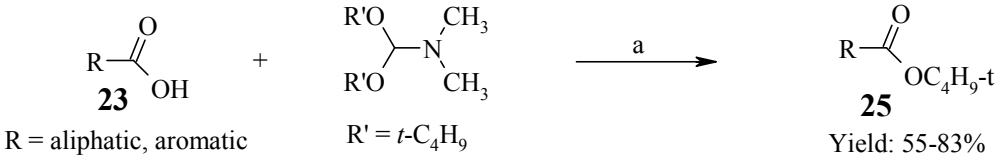
Blossey *et al.* have reported a polymer supported $AlCl_3$ as a mild catalyst for esterification reaction.

Hassner *et al.*[80]

This method reports reaction of carboxylic acid with DCC in presence of catalytic amount of DMAP to yield corresponding esters in high yields.

Widmer *et al.*[84]

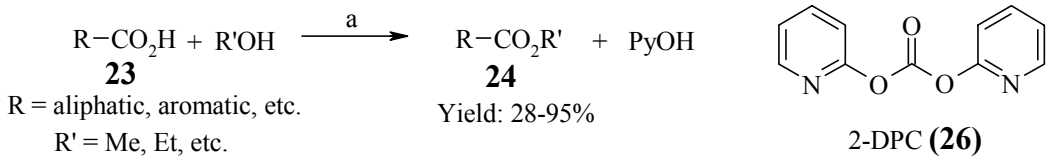
Various carboxylic acids react readily with *N*,*N*-dimethylformamide di-*t*-butylacetal to yield the corresponding *t*-butyl esters (**Scheme 42**).



Scheme 42: a) benzene or toluene 80°C.

Kim *et al.*[85]

Kim and co-workers have reported DMAP catalyzed esterification of carboxylic acids by using di-2-pyridyl carbonate (2-DPC) as a coupling reagent (**Scheme 43**).



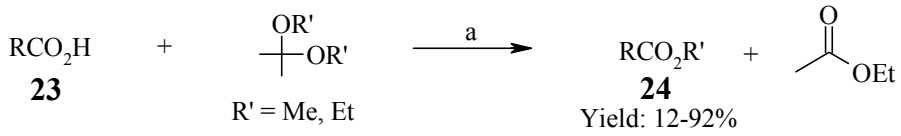
Scheme 43: a) 2-DPC, DMAP (cat)

Kumar *et al.*[86]

Kumar *et al.* have reported diphenyl tin chloride catalyzed esterification of various carboxylic acids in excellent yields under mild conditions.

Trujillo *et al.*[87]

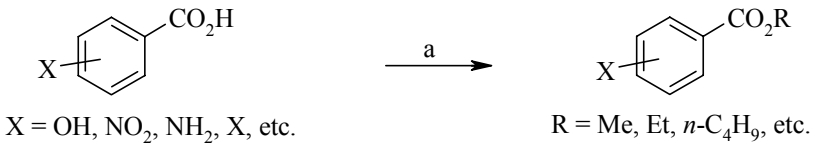
This reports use of trimethyl orthoacetate as a reagent for esterification of carboxylic acids (**Scheme 44**).



Scheme 44: a) TMEA (3.0 equiv), toluene, 110°C, 24h.

Hosangadi *et al.*[88]

A wide variety of carboxylic acid reacts with alcohols in the presence of thionyl chloride to afford the corresponding esters in excellent yields. Phenolic hydroxy, amino groups and double bonds are unaffected under these conditions (**Scheme 45**).



Scheme 45: a) $SOCl_2$, ROH, 0°C-RT.

Ram *et al.*[77]

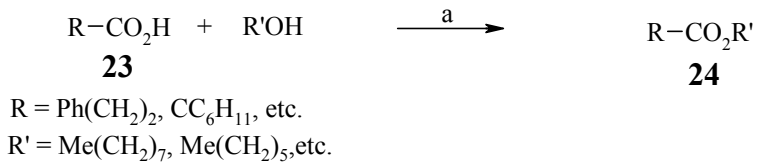
Unhindered aliphatic non-conjugated carboxylic acids were esterified selectively in the presence of aromatic or conjugated acids with catalytic amount of $NiCl_2$-$6H_2O$.

Zang *et al.*[78]

Treatment of various alcohols with aliphatic carboxylic acids with catalytic amount of $Fe_2(SO_4)_3$ x H_2O gives the corresponding esters in excellent yields.

Wakasui *et al.*[89]

Wakasui *et al.* have reported, diphenyl ammonium triflate (DPAT) as a catalyst for esterification of carboxylic acids under mild reaction conditions (**Scheme 46**).



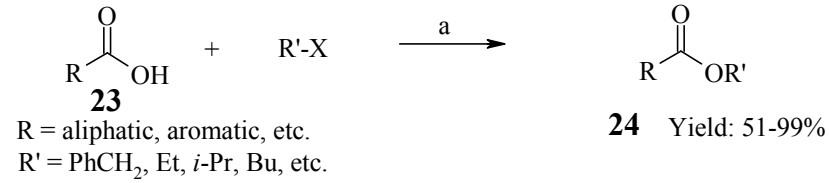
Scheme 46: a) DPAT (cat), TMSCl, toluene.

Yamamotto *et al.*[90]

Yamamotto *et al.* have reported environmentally friendly, the direct condensation of carboxylic acids and alcohols catalyzed by hafnium salts in excellent yields.

Ooi *et al.*[91]

This method reports, esterification of carboxylic acids with alkyl halides catalyzed by tetrabutylammonium fluoride, generated in *situ* from tetrabutylammonium hydrogensulphate ($TBAHSO_4$) and $KF.2H_2O$ at room temperature (**Scheme 47**).



Scheme 47: a) $TBAHSO_4$ (5 Mol%), $KF.2H_2O$ (5.0 EQ), THF, RT, 3-24 h.

Lee *et al.*[92]

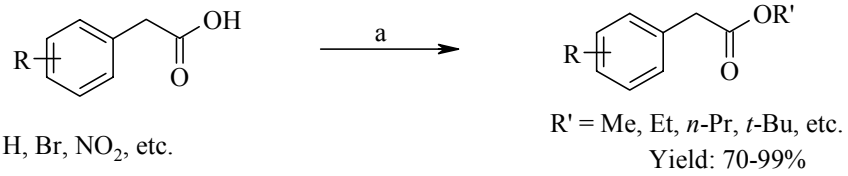
Lee *et al.* have reported a photochemical approach for esterification of carboxylic acids under CBr_4/ MeOH reaction condition in excellent yields.

Ramalinga *et al.*[79]

In this approach for the esterification of carboxylic acids, iodine is used as a Lewis acid catalyst. The method is applicable to aliphatic, unsaturated, hydroxy and dicarboxlic acids only, aromatic acids fail to undergo esterification.

Pan *et al.*[93]

This reports reaction between carboxylic acids and alcohols using cerium ammonium nitrate (CAN) at room temperature to give the corresponding esters (**Scheme 48**).



R = H, Br, NO_2, etc.

R' = Me, Et, *n*-Pr, *t*-Bu, etc.
Yield: 70-99%

Scheme 48: a) CAN, CH_3OH, RT.

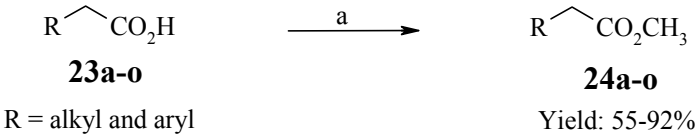
4.2.3 Present work

4.2.3.1 Objective

Although many effective and reliable methods for the preparation of methyl esters have been reported in the literature there is still a great need for a simple, mild and selective process. Some methods require moisture sensitive reagents or are incompatible with additional functionality in the molecule. During our search of new methods for functional group transformations, we were especially interested in exploring the potential use of pyridinium hydrobromide perbromide ($Py.HBr_3$) as an acidic catalyst in organic synthesis. We observed that pyridinium hydrobromide perbromide ($Py.HBr_3$) could accomplish esterification reaction in a highly efficient manner.

4.2.4 Results and discussions

Pyridinium hydrobromide perbromide ($Py.HBr_3$) is widely used as a mild and efficient reagent for selective brominations and dehydrogenations of sensitive molecules. To extend this methodology toward the carboxylic ester synthesis, we examined $Py.HBr_3$ as a suitable catalyst. Thus, a novel operationally simple procedure for the preparation of methyl esters of aliphatic carboxylic acids using catalytic amount of pyridinium hydrobromide perbromide ($Py.HBr_3$) at room temperature has been established (**Scheme 49**).



23a-o → **24a-o**

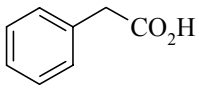
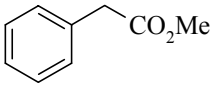
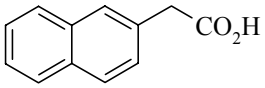
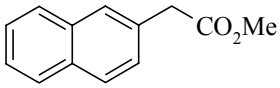
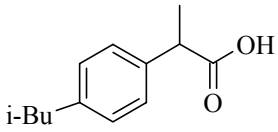
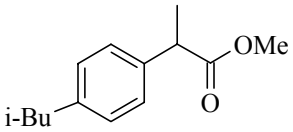
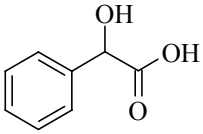
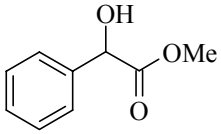
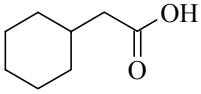
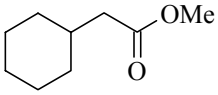
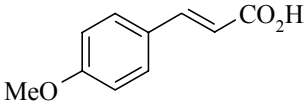
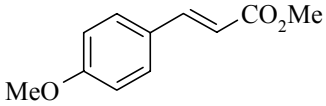
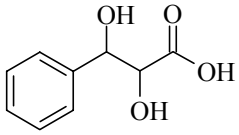
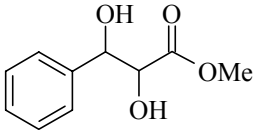
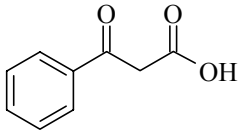
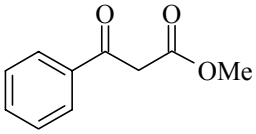
R = alkyl and aryl; Yield: 55-92%

Scheme 49: a) $Py.HBr_3$ (10 mol%), MeOH, 25 ^oC.

Variety of aliphatic carboxylic acids **23a-o** were successfully converted to their corresponding methyl esters **24a-o** in excellent yields at room temperature. The results are summarized in **Table 5**. Several functionalities present in the carboxylic acids such as such a double bond, a halogen, a methoxy, a ketone, a hydroxy group and a nitro group were tolerated. This method did not necessitate special use of the dehydrating reagent and or the technique of azeotropic removal of water. In all the cases methyl esters were obtained in good to excellent yields. The α,β-unsaturated acid such as 4-methoxy cinnamic acid afforded the corresponding methyl ester in low yield. In cases where a carboxylic acid group is directly attached to an aromatic ring such as benzoic acid, there was no reaction. No esterification product was obtained even by heating benzoic acid, methanol in the presence of catalyst.

To explore the generality and scope of the above $Py.HBr_3$ catalyzed esterification, we examined the reaction with various other alcohols like ethanol, propanol etc. However the

Table 5: Esterification of aliphatic carboxylic acids with pyridinium hydrobromide perbromide at room temperature.[a]

Entry	Carboxylic acid (23)	Time (h)	Methyl esters (24)	Yield (%)[b]
a		22		90
b		22		88
c	4-Nitrophenylacetic acid	18	Methyl 2-(4-nitrophenyl)acetate	85
d	4-Bromophenylacetic acid	20	Methyl 2-(4-bromophenyl)acetate	80
e		24		92
f		24		90
g	Octanoic acid	24	Methyl octaneoate	80
h	Propionic acid	24	Methyl propionate	82
i	Isobutyric acid	28	Methyl isopropionate	75
j	Malic acid	28	Diethyl maleate	80
k		18		82
l	Tartaric acid	20	Dimethyltartarate	78
m		32		55
n		24		78
o		22		82

a: Acid (5 mmol), $Py.HBr_3$ (10 mol %), MeOH (10 ml), 25°C.

b: Isolated yield after chromatographic purification.

esterification proceeded to afford the corresponding esters in very low yield. Increasing the catalyst to either 20 to 50 mol% did not increase the yields.

The ester formation was confirmed by ^{1}H, ^{13}C-NMR and IR spectroscopy. For example, ^{1}H-NMR spectrum of ester **24f** showed singlet at δ 3.75 corresponding to methyl ester group. Its ^{13}C-NMR spectra showed typical methyl ester signal at δ 52.5 **(Fig. 9)**.

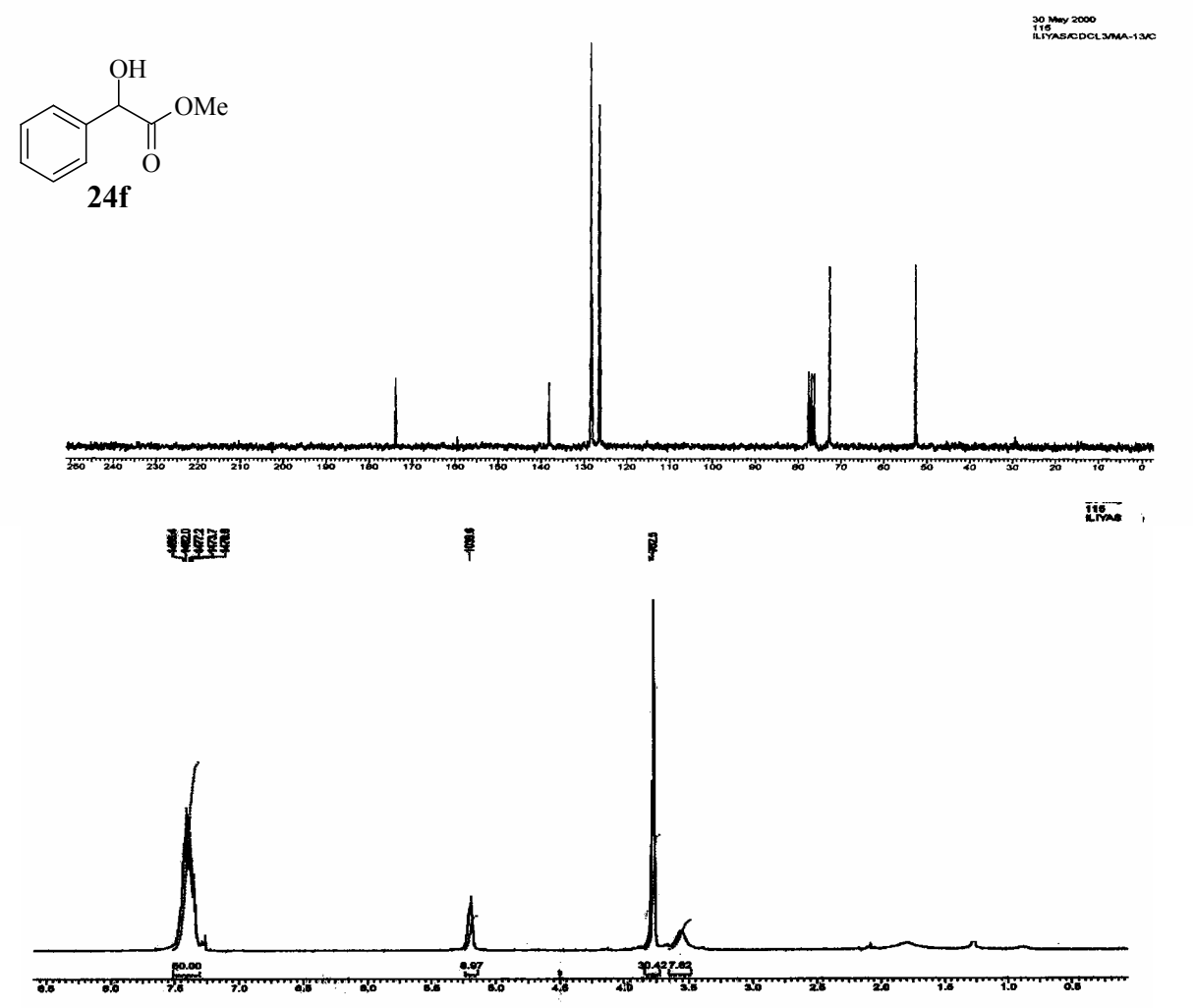


Fig. 9: ^{1}H-NMR spectra of ester 24f

The ^{1}H-NMR spectrum of ester **24e** shows sharp singlet at δ 3.67 corresponding to methyl group of ester. Its ^{13}C-NMR spectra showed typical methyl ester signal at δ 51.71.

Further, its mass spectra confirm the molecular ion peak at m/e 220, base peak observed at m/e is due to loss of $–CO_2CH_3$ group.

Mechanism

The probable mechanism of acetylation is shown in **Fig. 10**.

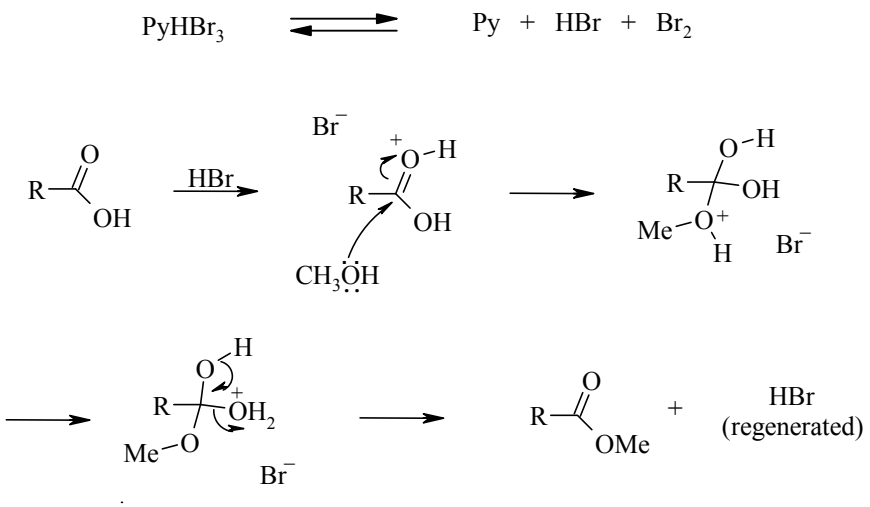


Fig. 10: Probable mechanism of esterification

4.2.5 Conclusion

In conclusion, we have explored an efficient route for the esterification reaction between aliphatic carboxylic acids and methanol using catalytic amount of $Py.HBr_3$. Evidently, the present procedure appears attractive for its operational simplicity, and generally high yields of products.

4.2.6 Experimental Section

General procedure for the esterification of carboxylic acids

A 25 ml RB flask was charged with carboxylic acid **23a-o** (5 mmol), methanol (10 ml) and $Py.HBr_3$ (10 mol%) were stirred at room temperature for the specified time. The progress of the reaction was monitored by TLC. After the reaction, excess methanol was removed under reduced pressure and the residue was extracted with diethyl ether. The ether extract were washed with a solution of sodium thiosulphate and subsequently with brine, dried over

anhydrous sodium sulphate and concentrated in vacuum to yield the crude product, which was purified by column chromatography on silica gel using pet. ether and EtOAc as eluent to afford pure corresponding methyl esters **24a-o**.

Methyl 2-phenylacetate (24a): Yield: 90%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2954, 1738, 1510, 1460, 1335, 1250, 1213, 1167, 1069, 849, 758; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 3.67 (s, 3H), 7.00-7.55(m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.8, 50.4, 127.3, 128.9, 129.9; **Analysis:** $C_9H_{10}O_2$ requires C, 71.98; H, 6.70; found C, 72.05; H, 6.66%.

Methyl 2-naphthylacetate (24b): Yield: 88%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2970, 1947, 1735, 1609, 1530, 1400, 1261, 1066, 928, 771; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.62 (s, 2H), 3.65 (s, 3H), 7.15-7.50 (m, 7H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39.2, 50.4, 125.2, 126.1, 127.2, 127.5, 127.7, 127.9, 128.9, 131.1, 133.5, 135.9, 173.2; **MS**: m/z (% rel. intensity): 201 (M^{+1}, 8), 200 (40), 142 (10), 141 (100), 139 (4), 115 (12); **Analysis:** $C_{13}H_{112}O_2$ requires C, 77.98; H, 6.03; found C, 77.88; H, 6.10%.

Methyl 2-(4-nitrophenyl)acetate (24c): Yield: 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 1950, 1735, 1534, 1405, 1255, 1066, 928, 775; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.45 (s, 2H), 3.70 (s, 3H), 7.35-8.00 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.0, 50.4, 130.1, 124.0, 141.9, 147.0, 173.0; **Analysis:** $C_9H_9NO_4$ requires C, 55.38; H, 4.64; N, 7.17; found C, 55.40; H, 4.60; N, 7.20%.

Methyl 2-(4-bromophenyl)acetate (24d): Yield: 80%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 295, 2954, 1735, 1522, 1460, 1245, 1213, 1167, 1069, 849, 755; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 3.70 (s, 3H), 6.90 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H); **Analysis:** $C_9H_7BrO_2$ requires C, 47.61; H, 3.10; Br, 35.19; found C, 47.55; H, 3.15; Br, 35.10%.

Methyl 2-(4-isobutylphenyl)acetate (24e): Yield: 92%; **IR** ($CHCl_3$, cm^{-1}): 3047, 2959, 1738, 1511, 1511, 1435, 1140; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.92 (d, J = 6.0 Hz, 6H), 1.50 (d, J = 6.0 Hz, 3H), 1.75-2.00 (m, 1H), 2.46 (d, J = 8.0 Hz, 2H), 3.67 (s, 3H), 7.10 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.4, 22.2, 30.0, 44.8, 51.7, 125.6, 126.9, 127.4, 129.1, 137.5, 140.3, 175.0, **Analysis:** $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.14; found C, 76.33; H, 9.20%.

Methyl mandelate (24f): Yield: 90%; **mp**: 50-52^{o}C; **IR** ($CHCl_3$, cm^{-1}): 3020, 1738, 1496, 1455, 1438, 1383, 1220, 1188, 1093, 1067, 732; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.50 (brs,

1H), 3.65 (s, 3H), 5.35 (d, J = 6.5 Hz, 1H), 7.00-7.15 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.5, 72.5, 126.3, 128.9, 138.5, 173.5; **MS**: m/z (% rel. intensity): 166 (M^+, 10), 108 (8), 107 (100), 74 (50), 72 (30), 51 (10); **Analysis:** $C_9H_{10}O_3$ requires C, 65.05; H, 6.06; found C, 65.10; H, 6.10%.

Methyl octaneoate (24g): Yield: 80%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 3019, 2951, 1739, 1598, 1511, 1434, 1267, 1067, 780; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, J = 7.5 Hz, 3H), 1.30-1.70 (m, 10 H), 2.25 (t, J = 6.0 Hz, 2H), 3.65 (s, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 23.1, 25.6, 29.5, 29.8, 30.1, 34.5, 50.5, 172.5; **MS**: m/z (% rel. intensity): 158 (M^+, 3), 127 (10), 115 (8), 101 (4), 87 (40), 75 (6), 74 (100), 59 (10), 57 (15), 55 (18), 44 (20), 41 (30); **Analysis:** $C_9H_{18}O_2$ requires C, 68.32; H, 11.45; found C, 68.33; H, 6.55%.

Methyl propionate (24h): Yield: 82%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2970, 1730, 1679, 1555, 1493, 1460, 1320, 1270, 1233, 1176, 995, 840; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, J = 7.5 Hz, 3H), 1.30-1.70 (m, 4H), 2.25 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.5, 22.5, 27.9, 33.5, 50.0, 173.0; **Analysis:** $C_6H_{12}O_2$ requires C, 62.04; H, 10.40; found C, 62.15; H, 10.45%.

Methyl isopropionate (24i): Yield: 75%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2935, 1745, 1550, 1465, 1410, 1326, 1255, 1190, 1178, 1022, 950; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.20 (d, J = 4.5 Hz, 6H, 2.65 (m, 1H), 3.65 (s, 3H); **Analysis:** $C_5H_{10}O_2$ requires C, 58.80; H, 4.93; found C, 58.77; H, 4.85%.

Dimethyl malate (24j): Yield: 80%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2956, 2929, 2858, 1745, 1458, 1436, 1357, 1276, 1214, 1153, 855; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.80 (d, J = Hz, 2H), 3.65 (s, 6H), 4.75 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 36.5, 51.6, 54.0 74.3, 173.5, 177.4; **MS**: m/z (% rel. intensity): 162 (M^+, 2), 130 (4), 123 (5), 102 (100), 74 (10), 71 (85), 60 (40), 58 (20), 42 (70); **Analysis:** $C_6H_{10}O_5$ requires C, 44.44; H, 6.21; found C, 44.42; H, 6.15%.

Methyl 2-cyclohexylacetate (24k): Yield: 82%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2964, 2931, 2875, 1761, 1465, 1400, 1376, 1326, 1245, 1210, 1193, 1178, 1022, 946; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.10-1.40 (m, 6H), 1.55-1.85 (m, 4H), 2.20 (m, 2H), 3.70 (s, 3H); **MS**: m/z (% rel. intensity): 156 (M^+, 2), 125 (6), 97 (3), 80 (7), 75 (30), 74 (100), 55 (15), 43 (25); **Analysis:** $C_9H_{16}O_2$ requires C, 69.20; H, 10.31; found C, 69.22; H, 10.18%.

Dimethyl tartrate (24l): Yield: 78%; **mp**: 58-60^{o}C; **IR** ($CHCl_3$, cm^{-1}): 2929, 2858, 1735, 1460, 1436, 1355, 1276, 1214, 1153, 955; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.50 (brs, 2H), 3.70 (s, 6H), 4.65 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 49.5, 80.0, 172.3; **MS**: m/z (% rel. intensity): 178 (M^+, 15), 119 (20), 186 (12), 185 (100), 75 (4), 73 (10), 64 (10), 160 (12), 45 (10); **Analysis:** $C_6H_{10}O_6$ requires C, 40.45; H, 5.65; found C, 44.52; H, 5.64%.

Methyl 4-methoxycinnamate (24m): Yield: 55%; **mp**: 115-117^{o}C; **IR** ($CHCl_3$, cm^{-1}): 2960, 2874, 1720, 1640, 1578, 1450, 1312, 1202, 1174, 1065, 998, 712, 685; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.65, 3.75 (s, 3H), (s, 3H), 6.35 (d, J = 14.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 14.0 Hz, 1H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.5, 55.3, 114.5, 120.2, 127.2, 127.2, 141.3, 161.2, 166.5, **MS**: m/z (% rel. intensity): 192 (M^+, 10), 191 (80), 162 (100), 128 (25), 123 (4); **Analysis:** $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.28; found C, 68.87; H, 6.55%.

Methyl 2,3-dihydroxy-phenyl propionate (24n): Yield: 78%; **mp**: 110^{o}C; **IR** ($CHCl_3$, cm^{-1}): 3445, 2980, 2978, 1715, 1660, 1560, 1455, 1288, 1220, 1121, 1018, 715; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.97 (brs, 1H), 3.25 (brs, 1H), 3.79 (s, 3H), 4.32 (brs, 1H), 4.96 (brs, 1H), 7.10-7.50 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.5, 74.5, 86.3, 127.2, 127.5, 128.6, 141.0, 172.3; **Analysis:** $C_{10}H_{12}O_4$ requires C, 61.22; H, 6.15; found C, 61.23; H, 6.05%.

Methyl 3-oxo phenyl propionate (24o): Yield: 82%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 2981, 2927, 1740, 1690, 1623, 1590, 1489, 1423, 1325, 1265, 1201, 1091, 1012, 840, 819; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.50 (s, 2H), 3.65 (s, 3H), 7.35-7.80 (m, 5H); **Analysis:** $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.65; found C, 67.45; H, 5.50%.

4.2.7 References

1. Pearson, W. H.; Lian, B. W.; Bergmeier, S. C.; in "*Comprehensive heterocyclic Chemistry II*" Padwa, A.; (Ed.), Pergamon Press, NY, **1996**, vol. 1A, pp 1.60.
2. Tanner, D.; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599.
3. Baeckwall, J. E. *J. Chem. Soc. Chem. Commun.* **1977**, 413.
4. a) Mansuy, D,; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161. b) Mahy, J. P.; Battioni, P.; Mansuy, D. *J. Am. Chem. Soc*. **1986**, *108*, 1079. c) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2*, **1988**, 1517.

5. Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
6. a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. b) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744.
7. Vedejs, E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261.
8. a) Mueller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. b) Mueller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Naegeli, I. *J. Phys. Org. Chem.* **1996**, *9*, 341.
9. Perez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1993**, *12*, 261.
10. Atkinson, R. S.; Gattrell, W.; Ayscough, A. P.; Raynham, T. M. *Chem. Commun.* **1996**, 1935.
11. Ruano, J. L. G.; Fernandez, I.; Hamdouchi, C. *Tetrahedron Lett.* **1995**, *36*, 295.
12. Carducci, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1996**, *37*, 3777.
13. Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368.
14. Wang, D. -K.; Dai, L. -X.; Hou, X. -L. *Chem. Commun.* **1997**, 1231.
15. Langham, C.; Piaggio, P.; McMorn, P.; Willock, D. J.; Hutchings, G. J.; Langham, C.; Bethell, D.; Lee, D. F.; Hutchings, G. J.; Bulman P.; Philip C.; Sly, C.; Hancock, F. E.; King, F. *Chem. Commun.* **1998**, 1601.
16. a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. b) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783.
17. a) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309. b) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485.
18. a) Mohan, J. M.; Uphade, B. S.; Choudhary, V. R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* **1997**, 1429. b) Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* 1999, *1*, 705.
19. Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304.
20. Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569.
21. Minakata, S.; Ando, T.; Nishimura, M.; Ryu, I.; Komatsu, M. *Angew. Chem., Int. Ed.*

1998, *37*, 3392.

22. Zhu, W.; Li, Y.; Chen, Z.; Li, D.; Yang, G. *Synth. Commun.* **2000**, *30*, 1075.
23. Halfen, J. A.; Hallman, J. K.; Schultz, J. A.; Emerson, J. P. *Organometallics* **1999**, *18*, 5435.
24. Antunes, A. M. M.; Marto, S. J. L.; Branco, P. S.; Prabhakar, S.; Lobo, A. M. *Chem. Commun.* **2001**, 405.
25. a) Vyas, R.; Chanda, B. M.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 4715. b) Vyas, R.; Chanda, B. M.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30.
26. Jeon, H. -J.; Nguyen, S. T. *Chem. Commun.* **2001**, 235.
27. Handy, S. C.; Czopp, M. *Org. Lett.* **2001**, *3*, 1423.
28. Jain, L. S.; Sain, B. *Tetrahedron Lett*. **2003**, 575.
29. a) Fieser; Fieser, L. F. *Experiments in Organic Chemistry*, 3 rd ed.; D. C. Health and Compony: Boston, **1957**, 65. b) Leo. Paquettee. *Encyclopedia of Organic Reagents.*
30. a) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc*. **1948**, *70*, 417. b) Fieser, L. F. *Org. Synth*. **1973**, *5*, 604.
31. a) Reese, C. B. *Protective Groups in Organic Chemistry*; McOmie, J. F. W., Ed.; Plenum: London, **1973**, 109. b) Kocienski, P. J. *Protective Groups*; Thieme: New York, **1994**, 22. c) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, 150. d) Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed.; Wiley-VCH: New York, **1999**, 1955.
32. a) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569. b) Scrieve, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.
33. a) Vedejs, E.; Diver, S, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. b) Vedejs, E.; E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286.
34. Zhao, H.; Pendri, A.; Greenwald.; R. B. *J. Org. Chem*. **1998**, *63*, 7559.
35. Orita, A.; Tanahashi, C.; Kakuda, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877.
36. Li, A. X.; Li, T. S.; Ding. T. H. *Chem*. *Commun*. **1997**, *15*, 1389.
37. Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett*. **1998**, *39*, 3263.
38. Debal, A.; Cunigyn, T.; Larcheveque, M. *Synthesis* **1976**, *83*, 1166.
39. Corey, E. J.; Wollemberg, R. H. *J. Org. Chem*. 1975, *40*, 2265.

40. Sonnet, P. E. *Synth. Commun*. **1976**, *6*, 21.
41. Hauptmann, H.; Moura, C. M. *J. Am. Chem. Soc.* **1950**, *72*, 1405.
42. Hoyer, S.; Lasalo, P. *Synthesis* **1986**, 655.
43. Jin, T. S.; Ma, Y-R.; Zang, Z. H.; Li, T. S. *Synth*. *Commun*. **1998**, *17*, 3173.
44. Kumareswaran, R.; Pachamutha, K.; Vankar, Y. D. *Synlett*. **2000**, 1652.
45. Karimi, B.; Seradji, H. *Synlett*. **2001**, 519.
46. Hagiwara, H.; Morohashi, K.; Sakai, H.; Suzuki, T.; Masayoshi. A. *Tetrahedron* **1998**, *54*, 5845.
47. a) Chauhan, K. K.; Frost, C, G.; Love, I.; Waite, D. *Synlett*. **1999**, *11*, 1743. b) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. c) Iqbal, J.; Srivastav, R. R. *J. Org. Chem.* **1992**, *57*, 2001. d) Sharma, G. V. S. M.; Mahalingam, A. K.; Nagarajan, M.; Radhakrishnan, P. *Synlett*. **1999**, *8*, 1200. e) Pansare, S. V.; Malusare, M. G.; Rai, A. N. *Synth. Commun*. **2000**, *30*, 2587.
48. Borah, R.; Deka, N.; Sarma, J. C. *J. Chem. Res. (S)* **1997**, 110.
49. Bianco, A.; Brufani, M.; Melchioni, C.; Romagnoli, P. *Tetrahedron* **1997**, *38*, 651.
50. Curini, M.; Epifano, F.; Marcotullio, M. C.; Ornelio, R.; Rossi, M. *Synth*. *Commun*. **2000**, *30*, 1319.
51. Iranpoor, N.; Firouzabadi, H.; Zolfigol, M. A. *Synth. Commun*. **1998**, *28*, 1923.
52. a) Sabita, G.; Reddy, B. V. S.; Srividya, R.; Yadhav, J. S. *Synth. Commun*. **1999**, *19*, 2311. b) Nakae, Y.; Kusaki, I.; Sato, T. *Synlett*. **2001**, 1584.
53. Jones, R. G.; Mann, M. S. *J. Am. Chem. Soc*. **1953**, *75*, 4043.
54. Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.
55. Alper, H.; Dinkes, L. *Synthesis* **1972**, 81.
56. Nishiguchi, T.; Kawamine, K. *J. Chem. Soc. Chem. Commun*. **1990**, 1766.
57. Ranu, B. S.; Saha, M. *J. Org. Chem*. **1994**, *59*, 8269.
58. Mineno, T. *Tetrahedron Lett*. **2002**, *43*, 7975.
59. Karimi, B.; Maleki, J. *Tetrahedron Lett*. 2002, 43, 533.
60. Chandrasekhar, S.; Takhi, M.; Reddy, Y. R.; Mohapatra, S.; Rao, C. R.; Reddy, K. V. *Tetrahedron* **1997**, *53*, 14997.
61. Olah, G. A.; Husain, A.; Singh, B. P. *Synthesis* **1983**, 892.
62. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.

63. Johnston, R. D.; Marston, C. R.; Krieger, P. E.; Goe, G. L. *Synthesis* **1988**, 393.
64. Patney, H. K. *Synth*. *Commun*. **1991**, *21*, 2329.
65. Sabde, D. P.; Naik, B. G.; Hegde, V. R.; Hegde, S. G. *J. Chem. Res (S)* **1996**, 494.
66. Kumar, P.; Dinesh, C. U.; Reddy, R. S.; Pandey, B. *Synthesis* **1993**, 1069.
67. Klebe, J. E.; Finkbeiner, H.; White, D. M. *J. Am. Chem. Soc*. **1966**, *88*, 3390.
68. Branco, L. C.; Afanso, C. A. M. *Tetrahedron* **2001**, *57*, 4405.
69. Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett*. **2001**, *42*, 7679.
70. Ma, S.; Venanzi, M. L. *Tetrahedron Lett*. **1993**, *34*, 5269.
71. Bolitt, V.; Mioskowski, C.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett*. **1988**, *29*, 4583.
72. Babu, B. S.; Balsubramanian, K. K. *Tetrahedron Lett*. **1998**, *39*, 9287.
73. Ravindranath, N.; Ramesh, C.; Biswanath, D. *Synlett*. **2001**, *11*, 1777.
74. a) Beaz, G. *In Comprehensive Organic Synthesis*; Trost, B. M.; Fleaming, I., Eds.; Pergamon: Oxoford, **1991**, *6*, 323. b) Franklin, A. S. *J. Chem. Soc., Perkin Trans*. 1, **1998**, 2451 and **1999**, 3537. c) Otera, J. *Chem. Rev*. **1993**, *93*, 1449. d) Greene, T. W.; Wuts, P. G. *In Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, **1999**, p. 372.
75. Ogliaruso, M. A.; Wolfe, J. F. *In Synthesis of Carboxylic Acids, Esters, and Their Derivatives;* Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: New York, **1991**.
76. Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett*. **1998**, *39*, 8563.
77. Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 145.
78. Zang, G. S.; Synth. *Commun*. **1998**, *28*, 1159.
79. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett*. **2002**, *43*, 789.
80. Hassner, A.; Alexanian. *Tetrahedron Lett*. **1978**, *19*, 1978.
81. Blossey, E. C.; Turner, L, M.; Neckers, D. C. *Tetrahedron Lett*. **1973**, *14*, 1823.
82. Raber, D. J.; Gariano, P. *Tetrahedron Lett*. **1971**, *12*, 4741.
83. Shaw, J. E.; Kunerth, D. C.; Sherry, J. J. *Tetrahedron Lett*. **1973**, *14*, 689.
84. Widmer, U.; *Synthesis*, **1983**, 135.
85. Kim, S.; Lee, J. I.; Ko, Y. K. *Tetrahedron Lett*. **1984**, *25*, 4943.
86. Kumar, A. K.; Chattopadhayay. *Tetrahedron Lett*. **1987**, *28*, 3713.
87. Trujillo, J. I.; Gopalan, A. S. *Tetrahedron Lett*. **1993**, *34*, 7355.

88. Hasangadi, D. B.; Dave, R. H. *Tetrahedron Lett*. **1996**, *37*, 6375.
89. Wakasugi, K.; Misaki, T.; Yamada, K.; Yanabe, Y. *Tetrahedron Lett*. **2000**, *41*, 5249.
90. Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140.
91. Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett*. **2001**, *42*, 9245.
92. Lee, A. S.; Yang, H. C.; Su, F. Y. *Tetrahedron Lett*. **2001**, *42*, 301.
93. Pan, W. B.; Chang, F. R.; Wie, M. L.; Wu, M. J.; Wu, Y. C. *Tetrahedron Lett*. **2003**, *44*, 331.