Asymmetric Synthesis of Bioactive Molecules and Synthetic Methodologies involving Arylation using Novel Palladacycles, Cyanation and Esterification of Aldehydes

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

To

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By

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UNDER THE GUIDANCE OF

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November 2007

DEDICATED TO MY BELOVED PARENTS

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Synthetic Methodologies involving Arylation using Novel Palladacycles, Cyanation and Esterification of Aldehydes**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

November 2007 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Synthetic Methodologies involving Arylation using Novel Palladacycles, Cyanation and Esterification of Aldehydes"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

November 2007
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I. Victor Paul Raj

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
KHMDS	potassium hexamethyl disilazide
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyl disilazide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide

NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
Red-Al	Bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

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 °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 aluminum plates coated with silica gel (5-25 m) 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, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of 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 °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. TMSCN, DBU, DABCO and acetonecyanohydrin were purchased from Aldrich.

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Synthetic Methodologies involving Arylation using Novel Palladacycles, Cyanation and Esterification of Aldehydes**" is divides into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and drugs, and also to develop useful synthetic methodologies. **Chapter 1** deals with enantioselective synthesis of (*S,S*)-ethambutol, a tuberculostatic antibiotic and synthesis of enalaprilat, angiotension converting enzyme inhibitor using hydrolytic kinetic resolution (HKR) approach. **Chapter 2** describes the synthesis of (*S*)-dihydrokavain and (*S*)-vigabatrin®, anticonvulsive drug based on stereoselective opening of chiral epoxides using dimethylsulfonium methylide and HKR. **Chapter 3** describes a new synthetic methodology involving hydrocyanation of aldehydes and imines catalyzed by ammonium salts as new organocatalysts and esterification of aldehydes mediated by acetone cyanohydrin. **Chapter 4** deals with the synthesis of several new phenyl hydrazine-based palladacycles, their applications in the arylation reactions including H- β zeolite-mediated synthesis of isatins.

CHAPTER 1

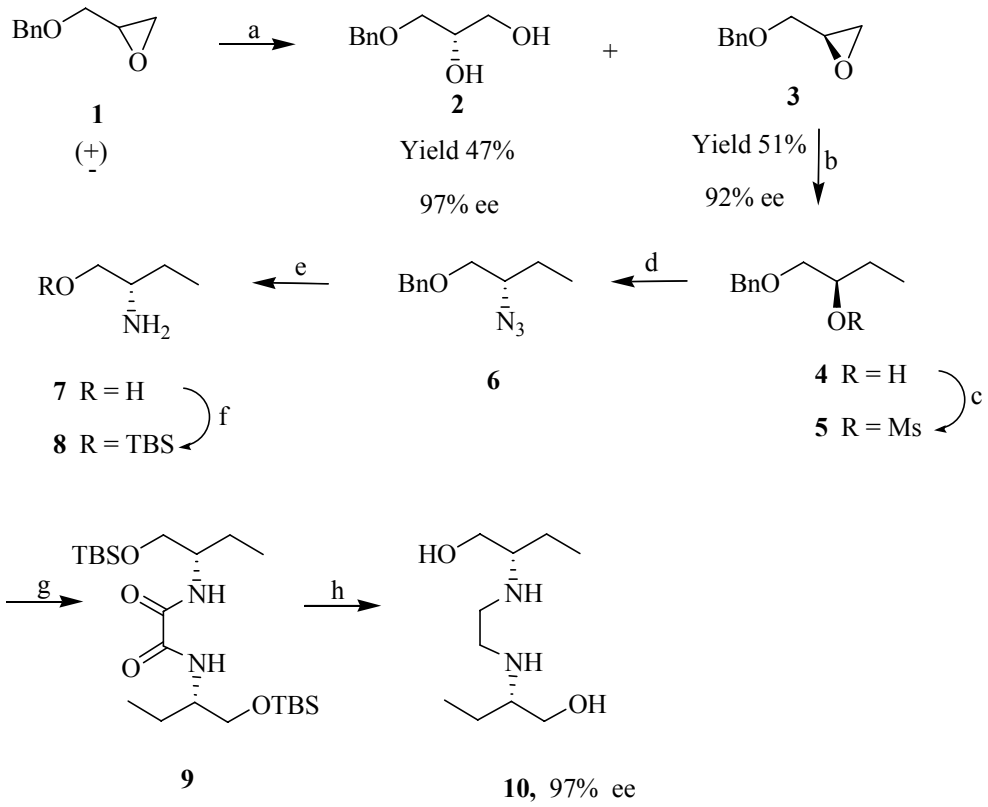
Asymmetric Synthesis of Ethambutol and Enalaprilat using Hydrolytic Kinetic Resolution of Terminal Epoxides

Jacobsen's Hydrolytic Kinetic Resolution (HKR) has emerged as an effective method for obtaining chiral epoxides and 1,2-diols in a highly enantioenriched forms.[1] In view of easy availability of chiral ligands and the simplicity of the reaction conditions with water being used as the nucleophile, HKR is being used extensively for providing several chiral building blocks in the synthesis of biologically active compounds. This chapter describes yet another application of this HKR strategy for the asymmetric synthesis of ethambutol and enalaprilat. This chapter is divided into two sections.

Section 1: Enantioselective Synthesis of (*S,S*)-Ethambutol

Ethambutol, [(*S,S*)-2,2'-(ethylenediimino)-di-butanol, **10**] is a long-known frontline anti-mycobacterial agent used against tuberculosis.[2] We envisaged *O*-protected (*S*)-2-amino-1-butanol (**8**) as the key intermediate for the synthesis of (*S,S*)-ethambutol, which was achieved by hydrolytic kinetic resolution of racemic

benzyl glycidyl ether (**1**) as the key reaction (**Scheme** 1). Thus, kinetic resolution of racemic benzyl glycidyl ether **1** in presence of (*R,R*)-Co(III)-salen.OAc gave enantiomerically enriched epoxide, **3**, in 47% yield and 97% ee and chiral diol **2** in 51% yield and 92% ee. Regioselective opening of epoxide **3** with methyl magnesium iodide in the presence CuI (0.2 mol%) provided the alcohol **4** in 78% yield. Mesylation of **4 (**MsCl, Et_3N) followed by nucleophilic displacement of the mesyl group with N_3^- (NaN_3, DMF) gave azido product **6** in 72 % yield with complete inversion of stereochemistry. Simultaneous deprotection of benzyl



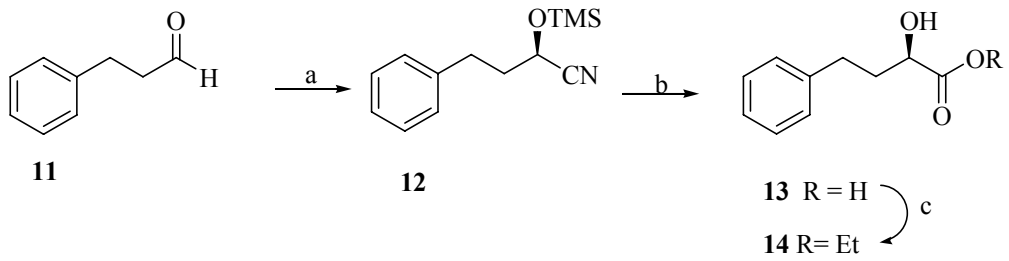
Scheme 1 Reagents and conditions: (a) (*R,R*)-Co(II)-salen, AcOH (0.01 eq), H_2O (0.55 eq), 25 °C; (b) MeMgI, CuI, THF, -40 °C, 78%; (c) MsCl, Et_3N, 24 h, 95%; (d) NaN_3, DMF, 60 °C, 30 h, 72%; (e) 10% Pd/C, H_2 (1atm.), MeOH, 76 h, 65%; (f) TBSCl, imidazole, CH_2Cl_2, 6 h, 92%; (g) $(COCl)_2$, pyridine, CH_2Cl_2 , 12 h, 93%; (h) $LiAlH_4$, THF, reflux, 24 h, 71%.

group and reduction of azide function was accomplished (in a single step) with 10% Pd/C H_2 (1 atm.) as catalyst, giving amine **7** in 65% yield. Selective protection of the hydroxyl group in amino alcohol **7** with TBSCl provided silyl ether **8** in 92% yield. Finally, amino alcohol **8** was transformed to (*S,S*)-ethambutol (**10**) in two steps: (i) treatment of amine **8** with 0.5 equiv. of oxalyl chloride and pyridine furnished oxalyl diamide **9** in 93% yield; (ii) reduction of

diamide function with simultaneous deprotection of TBS group in **9** was achieved in one-pot reaction using $LiAlH_4$ as the reducing agent to afford (*S,S*)-ethambutol (**10**) in 71% yield and 97% ee.

Section 2: Asymmetric Synthesis of Enalaprilat, an Angiotensin Converting Enzyme Inhibitor

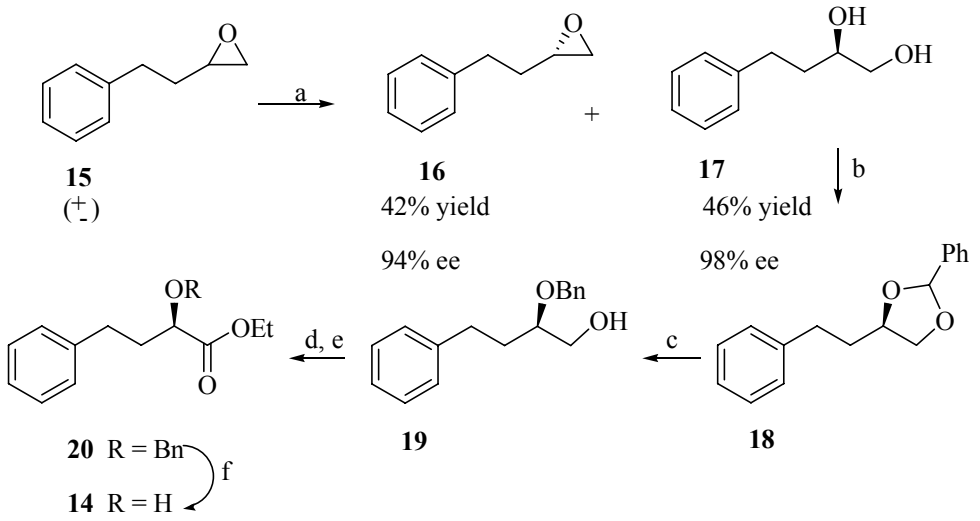
Enalaprilat **23,** the first dicarboxylate containing ACE inhibitor, used in the treatment of high blood pressure, works by blocking an enzyme in the body called angiotensin-converting enzyme (ACE), which produces a chemical that narrows the blood vessels raising blood pressure. The synthesis of (*R*)-ethyl 2-hydroxy-4-phenylbutanoate,[3] a key intermediate in the synthesis of enalaprilat, is achieved by employing two routes (**Schemes 2** and **3).** In the first approach, asymmetric hydrocyanation of aldehyde **11** was carried out using TMSCN as the cyanide source and (*S*)-BINOL as the chiral ligand catalyzed by *n*-BuLi to obtain silylated cyanohydrin **12** in 89% yield.[4] Hydrolysis of nitrile group and subsequent deprotection of silyl group in **12** with conc. HCl gave the hydroxy acid **13** in 71% yield. Selective esterification of hydroxy acid **13** catalysed by boric acid[5] (2.0 mol %) gave the hydroxy ester **14** in 68 % yield and 75% ee (**Scheme 2**).



Scheme 2: Reagents and conditions: (a) TMSCN, (*S*)-BINOL (1 mol%), *n*-BuLi (1 mol%), H_2O (10 mol%), toluene, -78 °C, 1 h, 89%; (b) conc. HCl, 25 °C 12 h, 71%; (c) boric acid (2 mol%), C_2H_5OH, 25 °C, 12 h, 68%.

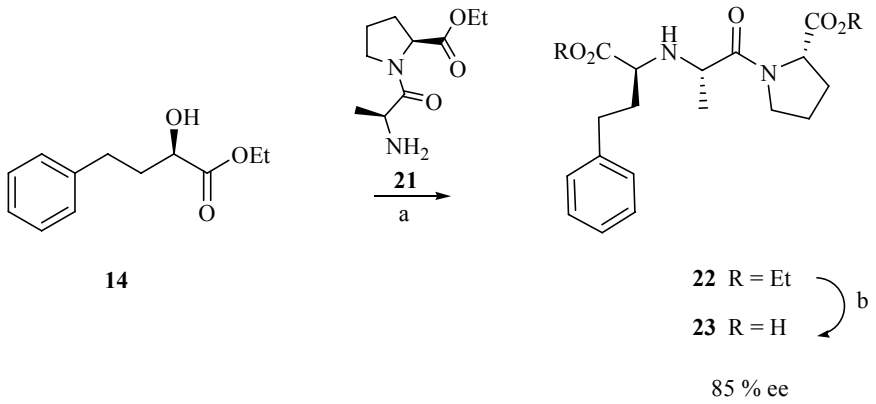
As we obtained a moderate enantiomeric excess of 75% for asymmetric hydrocyanation route, we turned our attention to hydrolytic kinetic resolution of epoxide. Thus, racemic epoxide **15** was subjected to hydrolytic kinetic resolution using (*S,S*)-Co(III)-salen.OAc complex, which led to isolation of both chiral compounds namely epoxide **16** in 42% yield and 94% ee and diol **17** in 46% yield and 98% ee. Diol **17** was then protected as benzylidine acetal **18** followed by reductive cleavage of acetal moiety using DIBAL-H gave the primary alcohol **19** in 62% yield. Oxidation of alcohol **19** using IBX produced aldehyde, which was

esterified to provide hydroxy ester **20** in 84% yield.[6] The deprotection of benzyl group [10% Pd/C, H_2(1 atm.)] afforded hydroxy ester **14** in 92% yield and 98 % ee (**Scheme 3**).



Scheme 3: Reagents and conditions: (a) (*S,S*)-Co(II)-salen, AcOH (0.01 eq), H_2O (0.5 eq), 25 °C; (b) $C_6H_5CH(OMe)_2$, PPTS (0.5 mol%), CH_2Cl_2 25 °C; (c) DIBAL-H, CH_2Cl_2, -78°C, 62%; (d) IBX, DMSO, 87%; (e) oxone, C_2H_5OH, 25 °C, 84%; (f) H_2 (1 atm), 10% Pd/C 92%.

The hydroxy ester **14** was subjected to amination under Mitsunobu condition with amine **21** to give diester **22** in 56% yield, which finally underwent mild hydrolysis using LiOH to afford enalaprilat **23** in 54% yield and 85% ee (**Scheme 4**).



Scheme 4: Reagents and conditions: (a) DEAD, Ph_3P, THF, 25 °C, 56%; (b) LiOH, THF:H_2O (1:1), 25 °C, 4 h, 54% .

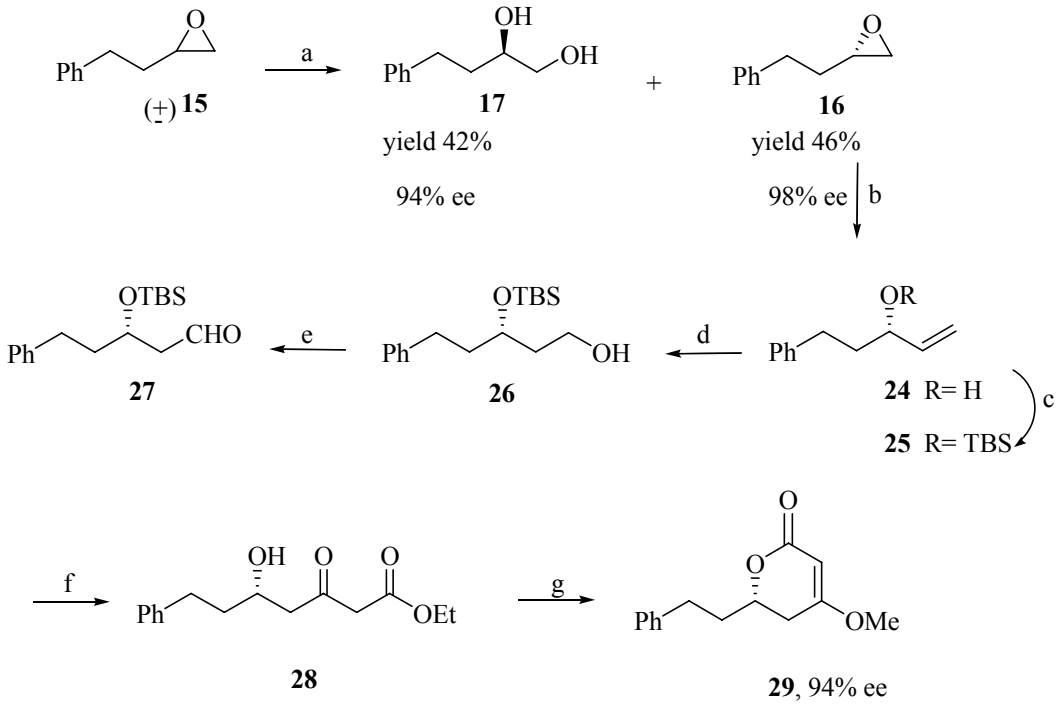
CHAPTER 2

Asymmetric Synthesis of (*S*)-Dihydrokavain and (*S*)-Vigabatrin® via Stereoselective Opening of Epoxide with Dimethylsulfonium Methylide

Sulfur ylides contain a negatively charged carbon atom directly bound to a positively charged sulfur atom and act as nucleophiles with complete stereo-and often regio-control when reacted with chiral epoxides giving allylic alcohols with excellent selectivity.[7] In this chapter, we have employed sulfur ylides derived from $(CH_3)_3S^+I^-$ and *n*-BuLi, for the stereoselective opening of terminal epoxides leading to the synthesis of (*S*)-dihydrokavain **29** and (*S*)-vigabatrin® **37**.

Section 1: Enantioselective Synthesis of (*S*)-Dihydrokavain

(*S*)-Dihydrokavain (**29),** isolated from the kava plant, *Piper methysticum*, has been found to be responsible for many biological activities including analgesic, anticonvulsive, antithrobotic and central muscular relaxing property.[8] Our approach to the synthesis of (*S*)-dihydrokavain starts with the hydrolytic kinetic resolution of racemic epoxide **15** using (*S,S*)-Co(III)-salen.OAc complex, which resulted in epoxide **16** in 42% yield and 94% ee and chiral diol **17** in 46% yield and 98% ee. Regioselective opening of epoxide **16** to the corresponding allyl alcohol **24** was readily achieved by using dimethylsulfonium methylide in 82% yield. The secondary alcohol group in **24** was protected with TBSCl to afford **25,** which on hydroboration-oxidation ($Me_2S.BH_3$, 3N NaOH and 30% H_2O_2) gave the primary alcohol **26** in 73% yield. The primary alcohol was oxidized to the corresponding aldehyde **27** followed by its reaction with ethyl diazoacetate in the presence of $BF_3.Et_2O$ gave *β*-keto ester **28**. The silyl group in **27** was also deprotected during the reaction to afford *δ*-hydroxy *β*-keto ester **28** in 77% yield. Lactonisation of **28** was smoothly accomplished under basic conditions (K_2CO_3, MeOH) followed by the methylation of its enol with dimethyl sulfate afforded dihydrokavain **29** in 81% yield and 94% ee (**Scheme 5**).



Scheme 5: Reagents and conditions: (a) (*S,S*)-Co(III)-salen.OAc (0.1mol %), H_2O, 25 °C; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, -10 °C 82%; (c) TBSCl, Imd, CH_2Cl_2, 97%; (d) i.$Me_2S.BH_3$, THF ii. 3N NaOH, 30% H_2O_2, 73%; (e) $(COCl)_2$, DMSO, Et_3N -78 °C, 96%; (f) $BF_3.OEt_2$, N_2CHCO_2Et, CH_2Cl_2, -10 °C, 77%; (g) i. K_2CO_3, MeOH; ii. $(CH_3)_2SO_4$, acetone, 81%.

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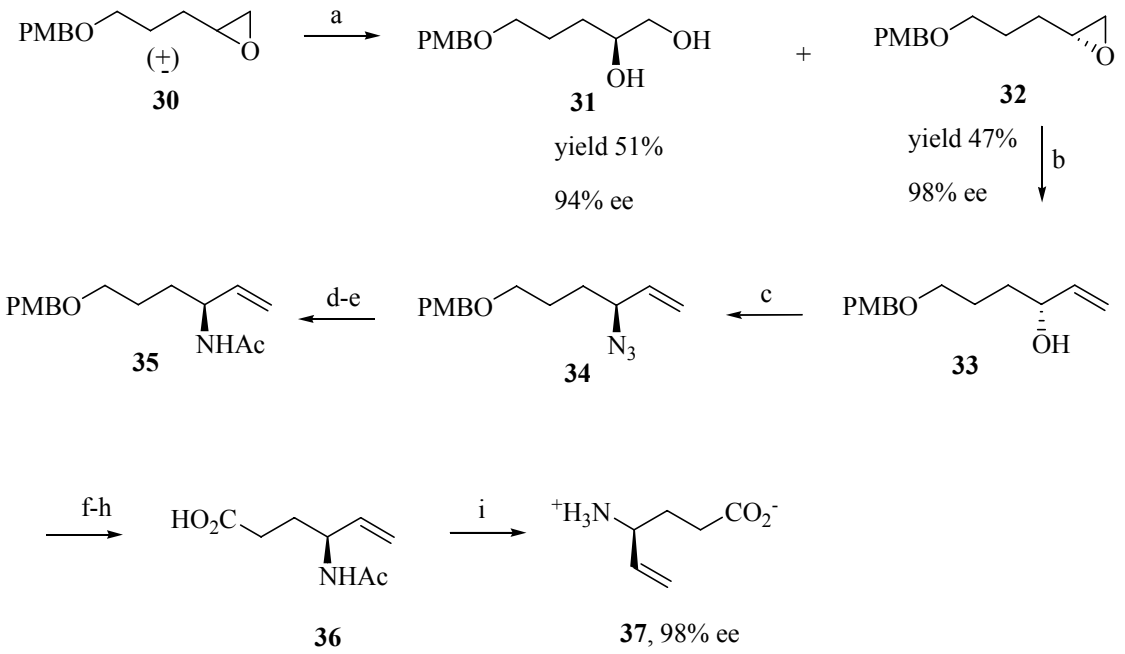
Section 2: Enantioselective Synthesis of (*S*)-Vigabatrin

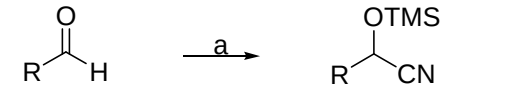
Vigabatrin (**37)** has been used in the treatment of disorders associated with depletion of GABA levels in the central nervous system (e.g. dyskinesia, schizophrenia and epilepsy). Our approach to the synthesis of (*S*)-vigabatrin (**37)** starts with the hydrolytic kinetic resolution of racemic epoxide **30** using (*R,R*)-Co(III)-salen.OAc, which furnished enantiomerically enriched epoxide **32** in 47% yield and 98% ee along with chiral diol **31** in 51% yield and 94% ee. Regioselective opening of epoxide **32** to the corresponding allyl alcohol **33** was readily achieved by using dimethylsulfonium methylide in 89% yield. Nucleophilic displacement of alcoholic group in **33** with N_3 anion gave the azide **34,** which was subsequently reduced to amine (Ph_3P, THF, H_2O), followed by its protection (Ac_2O, pyridine) as *N*-acetate **35** in 97% yield. At this stage, the PMB group was deprotected using DDQ to give the corresponding alcohol, *in situ* which underwent oxidation in two steps to give the carboxylic acid **36** in 77% yield. Finally, the *N*-acetyl moiety was deprotected using N_2H_4 to provide (*S*)-vigabatrin (**37)** in 87% yield and 98% ee (**Scheme 6**).



Scheme 6: Reagents and conditions: (a) (*R,R*)-Co(III)-salen.OAc, H_2O, 25 °C; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, -10 °C, 89%; (c) NaN_3, PPh_3, DMF, CCl_4, 60 °C 79%; (d) PPh_3, THF, H_2O, 89%; (e) Ac_2O, CH_2Cl_2, pyridine, 97%; (f) DDQ, CH_2Cl_2, 25 °C, 93%; (g) IBX, DMSO, 25 °C; (h) $NaClO_2$, NaH_2PO_4, DMSO, 77%; (i) N_2H_4, THF, MeOH, 87%.

CHAPTER 3

Section 1: Organocatalytic Activation of TMSCN by Ammonium Salts for Efficient Cyanation of Aldehydes and Imines



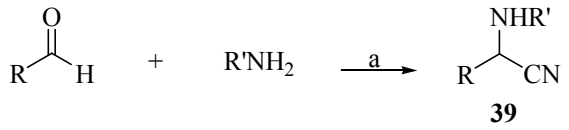
38

R= Aromatic, aliphatic yield 52 - 92 %

Scheme 7: Reagents and conditions: (a) TMSCN, cat 41 (0.5 mol%), CH_2Cl_2, 25 °C, 12 h.

Cyanation of aldehydes and imines are important C-C bond-forming reactions, as they provide versatile intermediates such as cyanohydrins and α-aminonitriles respectively, useful in the synthesis of several biologically active compounds. [9] This section describes a new high-yielding procedure for the synthesis of trimethylsilyl cyanides, **38** and α-aminonitriles **39** using catalytic amount of ammonium salts **40**, **41** and **42**, prepared readily for the first time (**Fig. 1**). Several such organocatalysts have been prepared, thoroughly characterized and their

catalytic activities for cyanation reactions have been evaluated systematically (**Scheme 7**).



R, R' = aromatic, aliphatic yield 75-90%

Scheme 8: Reagents and conditions: (a) TMSCN, cat **41** (0.5 mol%), amine, CH_2Cl_2, 25 ^{o}C, 12 h.

Among many ammonium salts screened, **42** and **43** were found to be are very efficient Lewis base catalysts for cyanation of aldehydes and imines giving high yields of trimethylsilyl cyanides **38** and aminonitriles **39** under ambient conditions (**Scheme 8).**

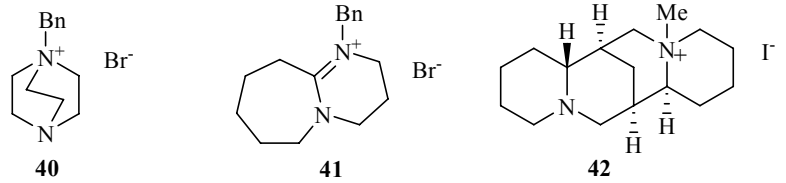
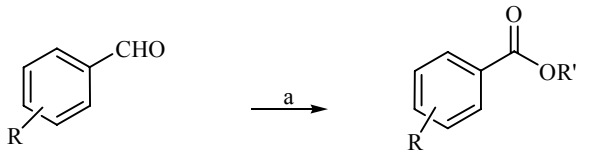


Fig. 1: Organocatalysts for TMSCN addition on to aldehydes and imines

Section 2: Direct Conversion of Aldehydes into Esters and Amides Mediated by Acetone Cyanohydrin and Base

The direct transformation of aldehydes into the corresponding esters **43** under mild conditions is often required in organic synthesis especially in the synthesis of natural products.[10] This section provides a simple procedure for the single-step conversion of electron-deficient aldehydes to the corresponding esters **43** and amides **44** on reaction with either an alcohol or a secondary amine in excellent yields mediated by acetone cyanohydrin and base (**Schemes 9 and 10**).



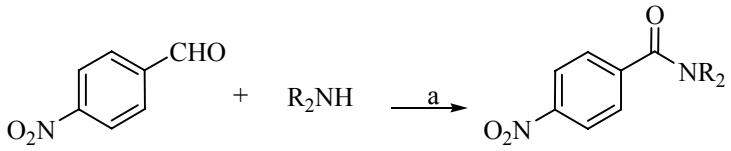
R = NO_2, Cl, Br, CF_3,

R' = Me, allyl, propargyl

yield 58 - 98%

Scheme 9: Reagents and conditions: (a) acetone cyanohydrin, base, alcohol 25 °C, 12 h.

Surprisingly, we found that α,β-unsaturated aldehydes **45** gave the corresponding saturated esters **46** when treated with acetone cyanohydrin in the presence of Et_3N the results of which are also presented in this section (**Scheme 11**).



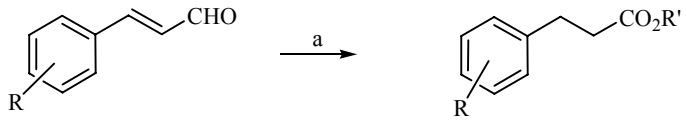
44

R_2N = morpholine, pyrrolidine piperidine

yield 50 -55%

Scheme 10: Reagents and conditions: (a) acetone cyanohydrin, KOH, amine, CH_3CN, 25 °C, 12 h.

This section also describes a short synthesis of nabumetone, **50**, a non-steroidal anti-inflammatory drug.[11] Thus, alcohol **47** on Vilsmeier-Haack reaction, gave the unsaturated aldehyde **48**, which was subjected to the cyanide-mediated ester formation–reduction



45 **46**

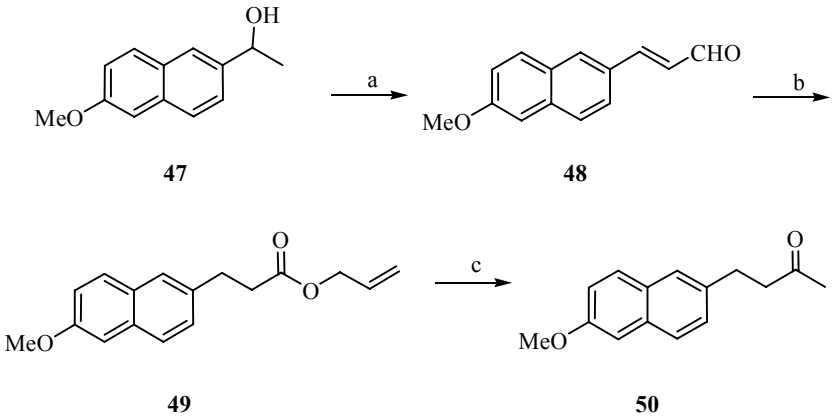
R = Me. CF_3, OMe

R' = Me, allyl, propargyl

yield 60 - 92%

Scheme 11: Reagents and conditions: (a) acetone cyanohydrin, base, alcohol, 25 °C, 12 h.

protocol to afford the saturated ester **49** in 61% yield. Treatment of ester with one mole of Grignard reagent afforded nabumetone **50** in 51% yield (**Scheme 12**).

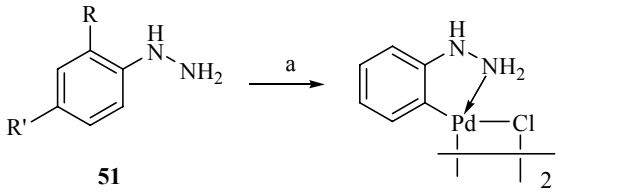


Scheme 12: Reagents and conditions: (a) $POCl_3$, DMF, 100 °C, 47 %; (b) acetone cyanohydrin, Et_3N, CH_2Cl_2, allyl alcohol, 25 °C, 2h, 61 %; (c) MeMgI, THF, -55 °C, 51%.

CHAPTER 4

Section 1: Synthesis of Novel Phenyl Hydrazine based Palladacycles: Its Application in Arylation Reactions in Aqueous Medium

Palladacycles have recently emerged as one of the most promising classes of catalysts or catalyst precursors in the Pd- catalyzed C–C bond forming arylation reactions. Aqueous-

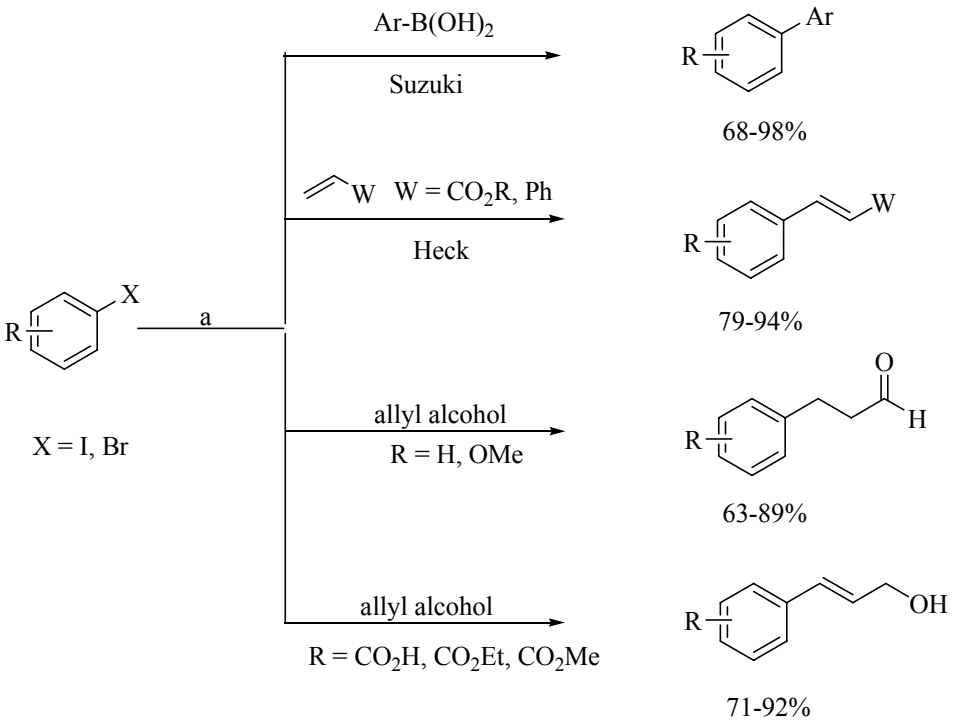


52 R= C_2H_5 R'= H; 67%, yield
53 R= H; R' = OMe; 68%, yield
54 R= H; R'= Cl; 66%, yield
55 R= H; R' = Me 64%, yield

Scheme 13: (a) Li_2PdCl_4, MeOH, 70 °C, 24 h.

phase palladium catalyzed reactions are of much interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify the catalyst recovery. This section presents a novel synthetic method for the preparation of several phenyl hydrazine-based palladacycles **52-55**, *via* carbopalladation reaction and its application in the arylation reactions like Heck and Suzuki coupling (**Scheme 13**). These novel Pd-catalysts are air, moisture-stable and very efficient catalysts for making several C-C bond forming cross-coupling reactions. High turn over number (TON) often reaching upto 3,72,000,

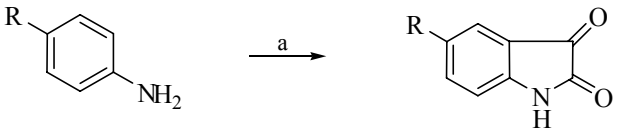
totally phosphine-free conditions and reactions in aqueous media are some of the salient features of these catalysts (**Scheme 14**).



Scheme 14: Reaction conditions: (a) K_2CO_3, palladacycle **52** ($5x10^{-6}$ mmol), tetrabutylammonium bromide, water, 90 ^oC 12 h.

Section 2: H- β Zeolite Mediated Synthesis of Isatins

Zeolites are aluminosilicates with general formula $Mx/n[(AlO_2)x(SiO_2)y]H_2O$ They possess Lewis acid sites predominatly at the inner surface. Particularly, H- β zeolites have been widely used as acid catalysts in organic chemical transformations such as alkylations and acylations.[12] Isatins (1H-indole-2,3-dione) are versatile unit and some of their derivatives show a wide range of biological and pharmacological activities.[13] This section describes a new, general method for the synthesis of isatins starting from the respective anilines using oxalyl chloride as the acylating agent and H-β zeolite as a reusable catalyst, under truly heterogenous conditions (**Scheme 15**).



R = OMe, Me, I, F, NO_2 yield 69 - 87%

Scheme 15: Reagents and conditions: (a) $(COCl)_2$, H-β zeolite (10% w/w), EDC, 90 °C, 12h.

It is remarkable that H-β zeolite-mediated synthesis of isatins provides a very simple and efficient procedure for the preparation of functionalized isatins from a variety of substituted anilines, which offer considerable synthetic advantages over previously described methods.

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CHAPTER 1

Asymmetric Synthesis of Ethambutol and Enalaprilat using Hydrolytic Kinetic Resolution of Terminal Epoxides

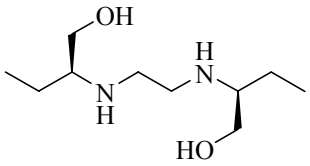
Section I:

Enantioselective Synthesis of (*S,S*)-Ethambutol

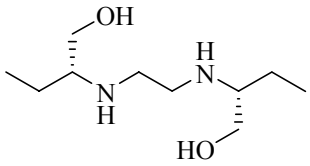
1.1.1 Introduction

Tuberculosis (TB)**,** a human disease caused by *Mycobacterium tuberculosis* is the cause of largest number of human deaths, nearly 3 million people infected with the tuberculosis perish every year.[1] Treatment of tuberculosis is often unsuccessful, and it continues to spread and cause immense mortality; moreover, there is an expanding epidemic of drug resistance that threatens TB control programs worldwide.[2-4] The mode of action of several major anti-tuberculosis drugs is even now not properly established, so there is still no basis for rational new-drug design.

Ethambutol, [(*S,S*)-2,2'-(ethylenediimino)-di-butanol, **1**], was developed by Lederle Laboratories in the 1950s from the simple lead molecule, *N,N*-diisopropylethylenediamine.[5-8] Ethambutol was a useful addition to tuberculosis chemotherapy, because of very low toxicity and relatively few side-effects and shows great activity against all strains of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* as well as a number of strains of *Mycobacterium avium*.[9]



1, (*S,S*)-Ethambutol



2, (*R,R*)-Ethambutol

1.1.2 Pharmacology of Ethambutol

Ethambutol (**1**) arrests multiplication of Mycobacterium sigmatic cells and eventually affects their death. It has no effect on the survival of non-proliferating cells. It has little or no effect on the metabolism of non-proliferating cells, but

cells from cultures whose growth has been inhibited by ethambutol shows evidence of impaired metabolism. Ethambutol exerts its antibacterial effect by interfering with the synthesis of a metabolite (s) needed for multiplication. Depletion of the metabolite (s) results in arrest of multiplication, impairment of metabolism, and loss of viability. Resistance to ethambutol cannot be explained by the failure of the cells to take up the drug, since the drug was equally bound by resistant and sensitive cells. In conclusion, biological activity of ethambutol has been attributed to its inhibition of mycobacterial arabinosyl transferases involved in bacterial cell wall biosynthesis.[10] From a structure–activity relationship (SAR) viewpoint, the (*S,S*)-absolute configuration as present in ethambutol was found to be essential for optimum activity. For example, compared to the parent (*S,S*)-stereoisomer, (**1**) the corresponding (*R,R*)-enantiomer (**2**) and the optically inactive meso-isomer were found to exhibit only 0.2 and 8.3% antibacterial activity, respectively.[11, 12]

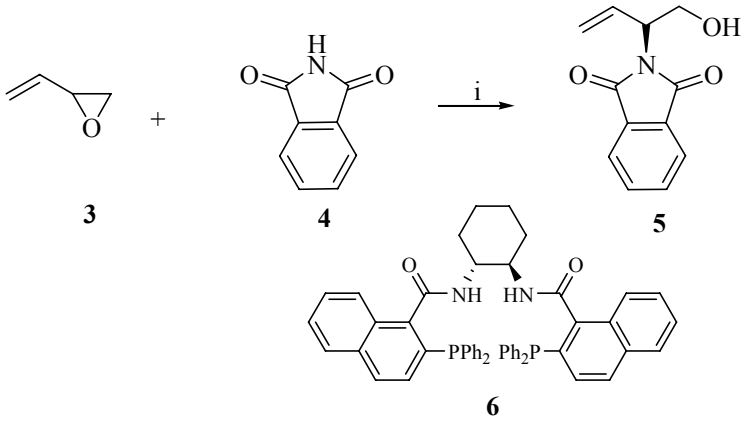
1.1.3 Review of Literature

Literature search reveals that there are only three reports available for the asymmetric syntheses of ethambutol (**1**), which are described below.

Trost's approach (2000)[13]

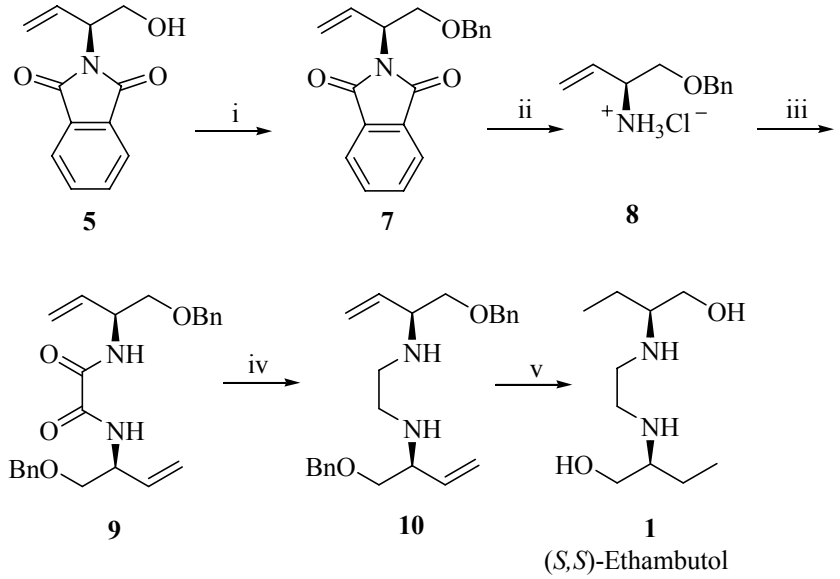
This approach employs dynamic kinetic asymmetric transformation (DYKAT) of butadiene monoepoxide with phthalimide using palladium-catalyzed asymmetric allylic alkylation (AAA) for the synthesis of (*S,S*)-ethambutol (**1**). Accordingly, exposing a mixture of butadiene monoepoxide and phthalimide to a catalyst formed *in situ* from π-allylpalladium chloride dimer and ligand **6** led to smooth formation of the corresponding alcohol **5** in 99% ee (**Scheme 1**). Benzyl protection of alcohol **5** followed by removal of phthalimide moiety with

ethylenediamine in refluxing ethanol gave protected amino alcohol **8** in 94% yield.



Scheme 1: (i) $[\eta^3\text{-}C_3H_5PdCl]_2$, Ligand **6**, rt, 14 h, 98%, 99% ee (after recrysatllization).

Condensation of amine **8** with oxalyl chloride afforded amide **9** in 97% yield. Further reduction with Red-Al furnished diamine **10** in 78% yield. Hydrogenolysis of **10**

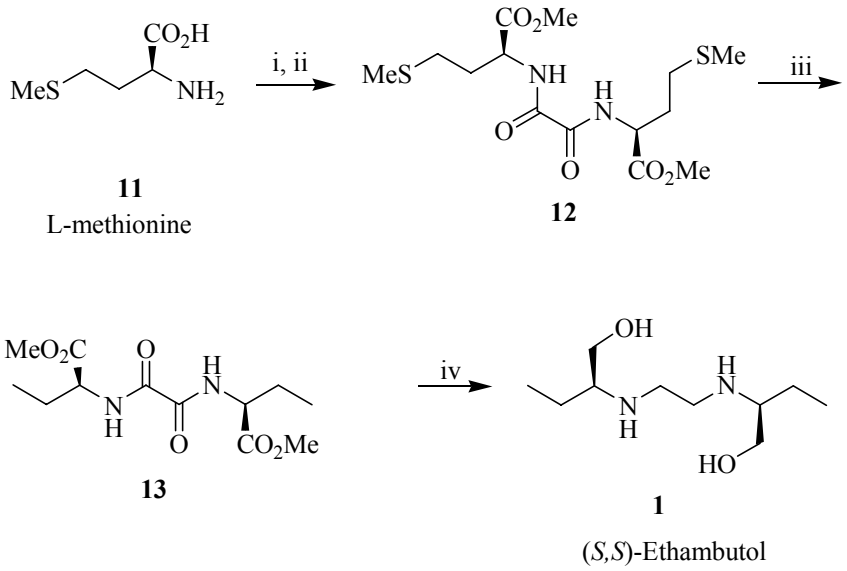


Scheme 2: (i) $PhCH_2Br$, NaH, DMF, 0 °C, 82%; (ii) Ethylenediamine, C_2H_5OH, reflux, then 6 N aqueous HCl, 94%; (iii) $(COCl)_2$, C_5H_5N, CH_2Cl_2, 0 °C, 97%; (iv) Red-Al, $PhCH_3$, 45 °C, 78%; (v) Pd/C, H_2 (1 atm.), CH_3OH, 25 °C; add 1.2 N HCl; ion-exchange resin, 74%.

with Pd/C, H_2 (1 atm.) followed by purification utilizing ion-exchange resin gave (*S,S*)-ethambutol (**1**) in 74% yield and 99% ee.

Datta's approach (2002)[14]

This approach describes the synthesis of (*S,S*)-ethambutol (**1**) starting from amino acid L-methionine. Esterification of L-methionine under standard reaction conditions (methanol, acetyl chloride) followed by the treatment of the free amine with 0.5 equiv. of oxalyl chloride produced the desired oxalyl diamide derivative **12** in 77% yield over two steps. Raney nickel desulfurization of the terminal thiomethyl groups provided penultimate intermediate **13** in 64% yield.



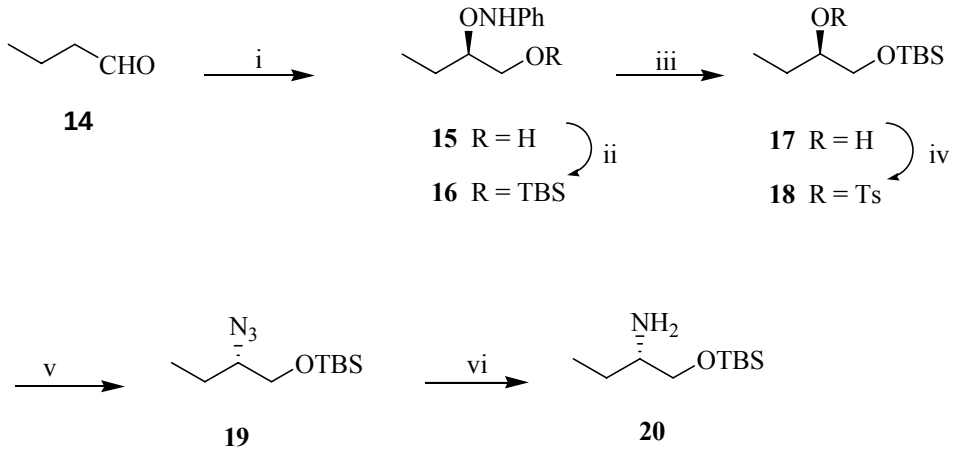
Scheme 3: (i) MeOH, AcCl ; (ii). $(COCl)_2$ (0.5 equiv.), pyridine, CH_2Cl_2, 77% (over two steps); (iii) Raney Ni (W-4), MeOH–H_2O (9:1), Δ, 64%; (iv) $LiAlH_4$, THF, Δ, 75%.

Finally, one-pot exhaustive reduction of the diamide and the diester functional groups of **13** with lithium aluminium hydride completed the synthesis of (*S,S*)-ethambutol (**1**).

Sudalai's approach[15]

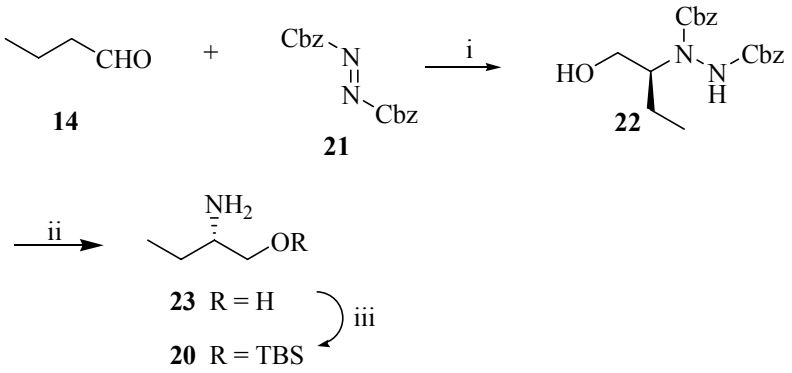
This approach describes the synthesis of (*S,S*)-ethambutol, using proline-catalyzed asymmetric α-aminooxylation and α-amination of *n*-butyraldehyde.

α-aminooxylation of *n*-butyraldehyde was carried out using nitrosobenzene and L-proline (25 mol%) followed by *in situ* reduction with sodium borohydride afforded the α-aminooxy alcohol **15.** The alcohol **15** was protected with TBSCl and subjected to hydrogenation over Pd/C furnished the monoprotected diol **17** in 88% yield. Tosylation of **17** followed by displacement of tosyl group with NaN_3 gave the azido product **19** in 75% yield. Subsequent catalytic hydrogenation of azide with 10% Pd/C-H_2 (1 atm.) afforded the protected amine **20** in 95% yield (**Scheme 4**).



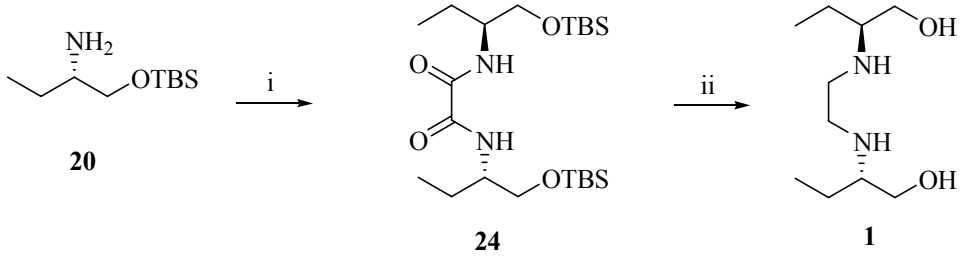
Scheme 4: Reagents and conditions: (i) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$, 85%. (ii) TBSCl, imidazole, CH_2Cl_2, 3 h, 90%. (iii) H_2 (1atm.), 10% Pd/C, Et_3N, MeOH, 12 h, 88%. (iv) *p*-TsCl, Py, 24 h, 95%. (v) NaN_3, DMF, 60 ºC, 30 h, 75%; (vi) H_2 (1atm.), 10% Pd-C, Et_3N, MeOH, 6 h, 95%.

In the second approach α-amination of *n*-butyraldehyde was carried with dibenzyl azodicarboxylate (DBAD) in the presence of D-proline (10 mol%) followed by *in situ* reduction with sodium borohydride afforded the protected amino alcohol **22** in 92% yield. The amino alcohol **22** was then hydrogenated over Raney nickel (H_2) to give (*S*)-2-amino-1-butanol **23** in 70% yield. Protection of the hydroxyl group in the amino alcohol **23** with TBSCl afforded the silyl ether **20** in 85% yield (**Scheme 5**).



Scheme 5: Reagents and conditions: (i) dibenzyl azodicarboxylate , D-Proline (10 mol%), 0-20 ºC, 3h then $NaBH_4$, EtOH, 92%; (ii) H_2 (12 bar), Raney-nickel, MeOH, AcOH, 70%;(iii) TBSCl, imidazole, CH_2Cl_2, 0-20 ºC, 3 h, 85%.

Finally amine **20** on treatment with 0.5 equiv. of oxalyl chloride and pyridine furnished oxalyldiamide **24** in 98% yield. The reduction of diamide and TBS deprotection were carried out in one-pot reaction using lithium aluminium hydride at reflux conditions to give (*S,S*)-ethambutol (**1**) in 80% yield and 99% ee (**Scheme 6**).



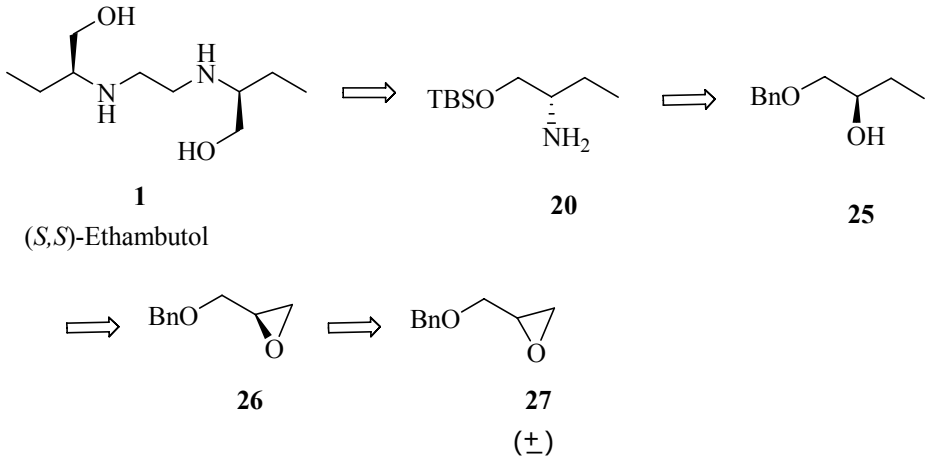
Scheme 6: Reagents and conditions: (i) oxalyl chloride (0.5 equiv.), Py, CH_2Cl_2, 12 h, 98%; (ii) $LiAlH_4$, THF, reflux, 24 h, 80%.

1.1.4 Present Work

1.1.4.1 Objective

As can be seen from the above descriptions, the literature methods for the synthesis of ethambutol (**1**), employ either chiral starting materials or expensive reagents. Hence, the synthesis of ethambutol (**1**), using catalytic enantioselective

reactions with less expensive catalyst, is desirable. Hence, we have decided to synthesize (*S,S*)-ethambutol (**1**) using Jacobsen's Hydrolytic Kinetic Resolution (HKR).[16] The retrosynthetic analysis for the synthesis of (*S,S*)-ethambutol (**1**) is shown in **Scheme 7**.



1
(*S,S*)-Ethambutol

20

25

26

27
(±)

Scheme 7 : **Retrosynthetic analysis for (*S,S*)-ethambutol (1)**

Retrosynthetic analysis for the (*S,S*)-ethambutol reveals that *O*-protected (*S*)-2-amino-1-butanol **20** could be visualized as the key intermediate for the synthesis of (*S,S*)-ethambutol, can be readily accessible from the chiral alcohol **25** by simple functional group transformations**.** We further envisioned that the chiral alcohol could be obtained by regioselective opening of chiral epoxide **26** with methyl magnesium iodide. The chiral epoxide **26** could be readily obtained from the hydrolytic kinetic resolution of racemic benzyl glycidyl ether **27**.

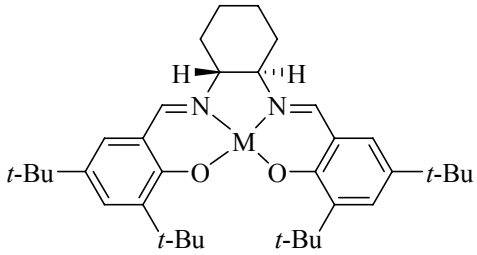
1.1.4.2 Hydrolytic Kinetic Resolution (HKR)

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[9] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been

well documented and utilized in synthesis.[17] Thus epoxides are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[18] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment.

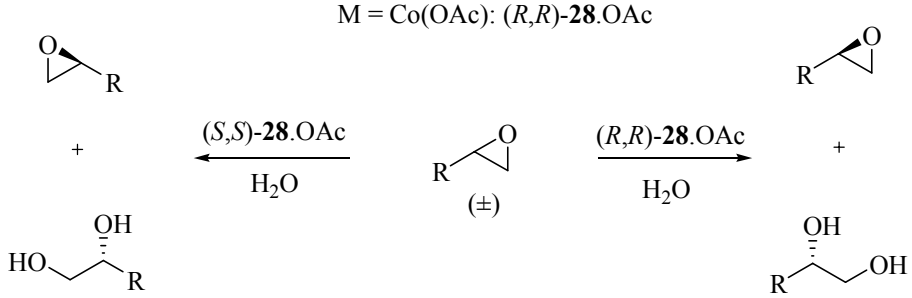
One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[19] (1) The racemic epoxides must be inexpensive

or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.



M = Co: (*R*,*R*)-**28**

M = Co(OAc): (*R*,*R*)-**28**.OAc

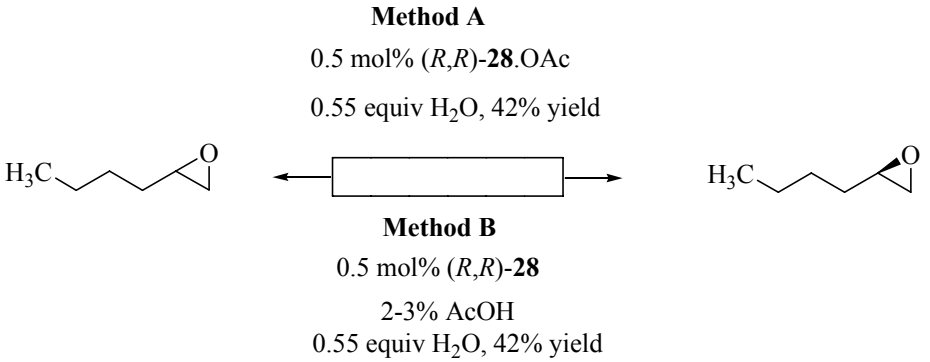


Scheme 8: Hydrolytic Kinetic Resolution (HKR) Reaction

The (salen)Co complex **28** catalyzed the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 8**).[20] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive

olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **28** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[21]

The cobalt analogues (*R*,*R*)-**28** and (*S*,*S*)-**28** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[22] Two useful methods for the generation of complex **28.**OAc have been developed (**Scheme 8**). Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. The Co(II) complex **28** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv.) is added.

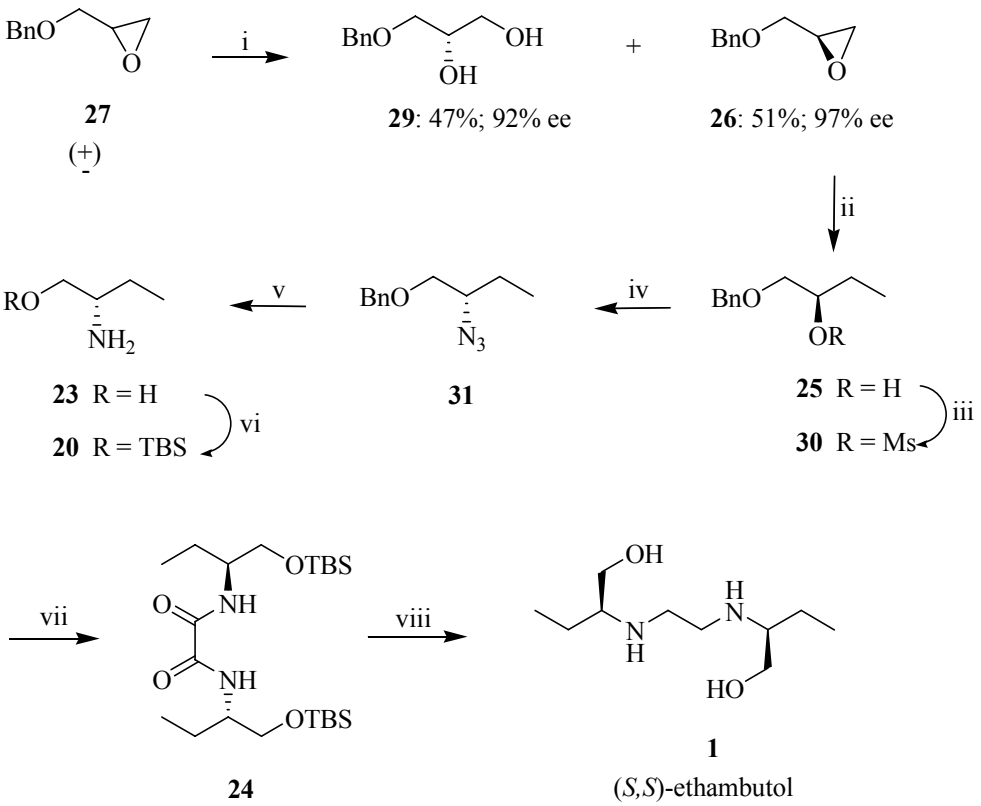


Scheme 9: Preparation of catalyst

The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed *in vacuo*, affording **28.**OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **28.**OAc under HKR conditions by suspension of the Co(II) complex **28** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

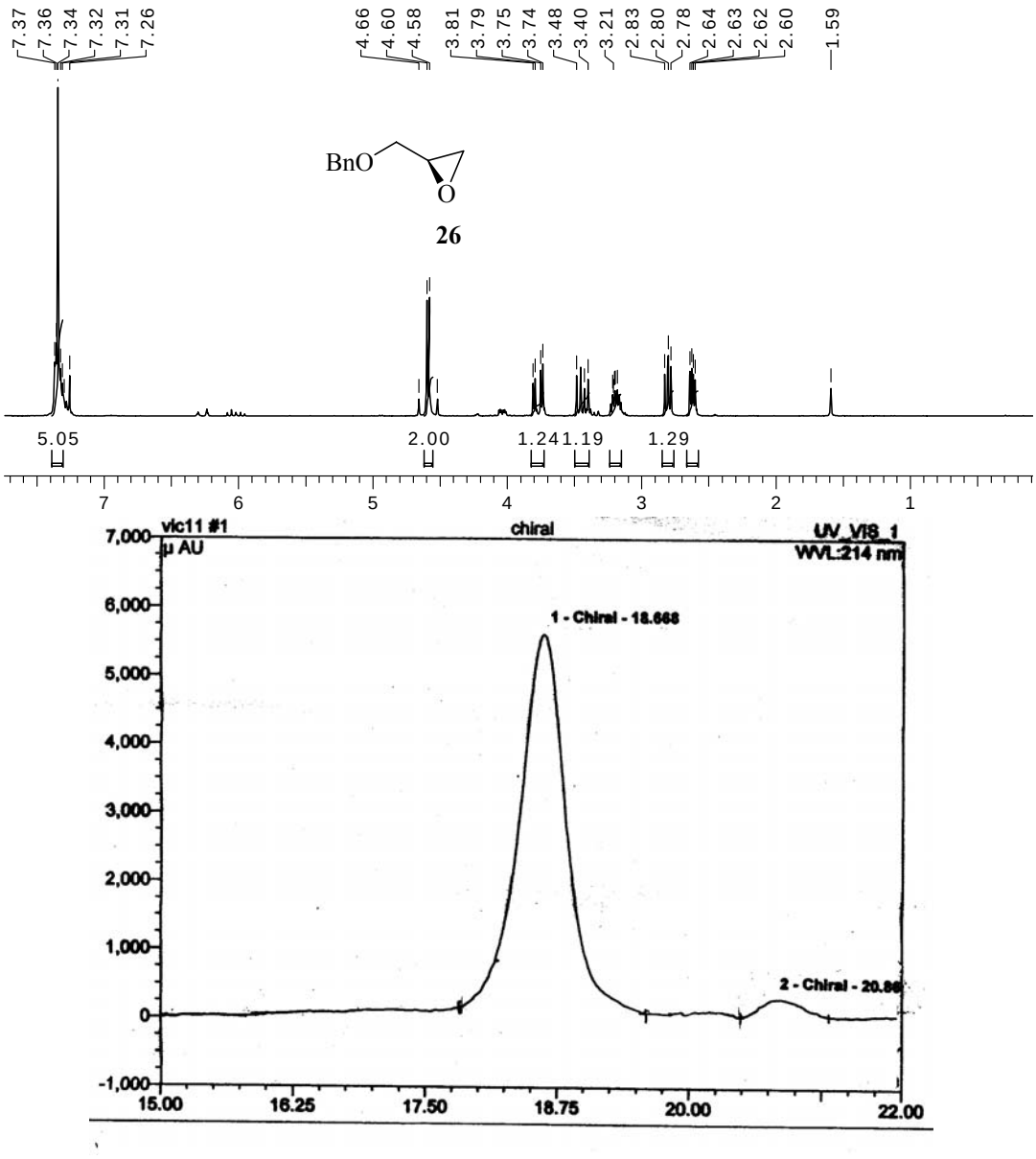
1.1.5 Results and Discussions:

The *O*-protected (*S*)-2-amino-1-butanol **(20),** the precursor for the synthesis of (*S,S)*-ethambutol (**1**), was prepared by employing Jacobsen's Hydrolytic Kinetic Resolution of epoxide recemic epoxide (±)-**27** as the key step (**Scheme 10)**.



Scheme 10: Reagents and conditions: (i) (*R,R*)-Co(II)-salen (**28**), AcOH (0.01 eq), H_2O (0.55 eq), 25 °C; (ii) MeMgI, CuI, THF, -40 °C, 78%; (iii) MsCl, Et_3N, 24 h, 95%; (iv) NaN_3, DMF, 60 °C, 30 h, 72%; (v) 10% Pd/C, H_2 (1atm.), MeOH, 76 h, 64%; (vi) TBSCl, imidazole, CH_2Cl_2, 6 h, 92%; (vii) oxalyl chloride (0.5 equiv.), Py, CH_2Cl_2, 12 h, 93%; (viii) $LiAlH_4$, THF, reflux, 24 h, 71%.

Thus, recemic epoxide (±)-**27** was subjected to HKR reaction using catalytic amount of (*R,R*)-salen-Co(III)OAc complex to give the corresponding enantiomerically enriched epoxide, **26** in 51% yield and 97% ee (% ee was determined by chiral HPLC analysis; Chiracel OD-H; **Fig. 1**) and chiral diol **29** in 47% yield.



Peak No.	R.T (min)	Area (mAU*s)	Area %
1	18.67	6109.336	98.62
2	20.86	85.48	1.38

Fig. 1: HPLC chromatogram,^{1}H and ^{13}C NMR spectra of epoxide 26

The ee of the chiral diol was found to be 92% based on comparison of its optical rotation$[\alpha]^{25}_{D}$ -1.31º (*c* 3.3, EtOH) with the reported value {lit.[16] $[\alpha]^{25}_{D}$ +1.4 (*c*

3.3, EtOH).[16] The formation of epoxide **26** was confirmed by the appearance of multiplets at δ 2.78 and 3.21 for methylene and methine protons respectively in its ^{1}H NMR spectrum (**Fig. 1**). Further, its ^{13}C NMR spectrum showed signals at δ 44.2 and 50.8 due to the two carbons of epoxy ring. Regioselective opening of epoxide **26** with methyl magnesium iodide in the presence CuI (0.2 mol%) provided the alcohol **25** in 78% yield. The appearance of signals at δ 0.95 (t) and 3.71 (m) in the ^{1}H NMR spectrum of the alcohol **25** confirms the presence of methyl and methine (C**H**OH) protons respectively. The ^{13}C NMR spectrum of **25** displayed characteristic carbon signal at δ 9.6 and 71.5 due to the methyl and methine carbons respectively. Alcohol **25** was treated with methanesulfonyl chloride and triethylamine at 25 ^{o}C in CH_2Cl_2 to give mesylate **30** in 95% yield. The display of signal at δ 2.97 (s) (C**H$_3$**SO$_2$) in the ^{1}H NMR spectrum of **30** confirms the presence of mesyl group. Its ^{13}C NMR spectrum displayed characteristic carbon signal at δ 38.3 and 83.05 due to the methyl carbon of the mesyl group (**C**H$_3$SO$_2$) and methine carbon (**CH**OMs) respectively (**Fig. 2**). Displacement of mesyl group in **30** with NaN_3 in DMF gave the azido product **31** in 72% yield with complete inversion of configuration. Its IR spectrum exhibited a characteristic strong band at 2109 cm^{-1} indicating the presence of azide moiety. The characteristic carbon signal at δ 65.6 (-**C**-N$_3$) in the ^{13}C NMR spectrum of the azide **31** confirmed the presence of the azide group (**Fig. 3**). Subsequent reduction of the azide function and deprotection of benzyl group in **31** was achieved in a single step using catalytic hydrogenation [10% Pd/C-H_2 (1 atm.)] to give (*S*)-2-amino-1-butanol (**23**) in 64% yield. The ^{1}H NMR spectrum of amino alcohol **23** showed multiplet at δ 2.89 corresponding to the methine (C**H**NH$_2$) proton. A

broad signal at δ 4.38 corresponds to NH_2 and OH protons respectively. Its ^{13}C NMR spectrum

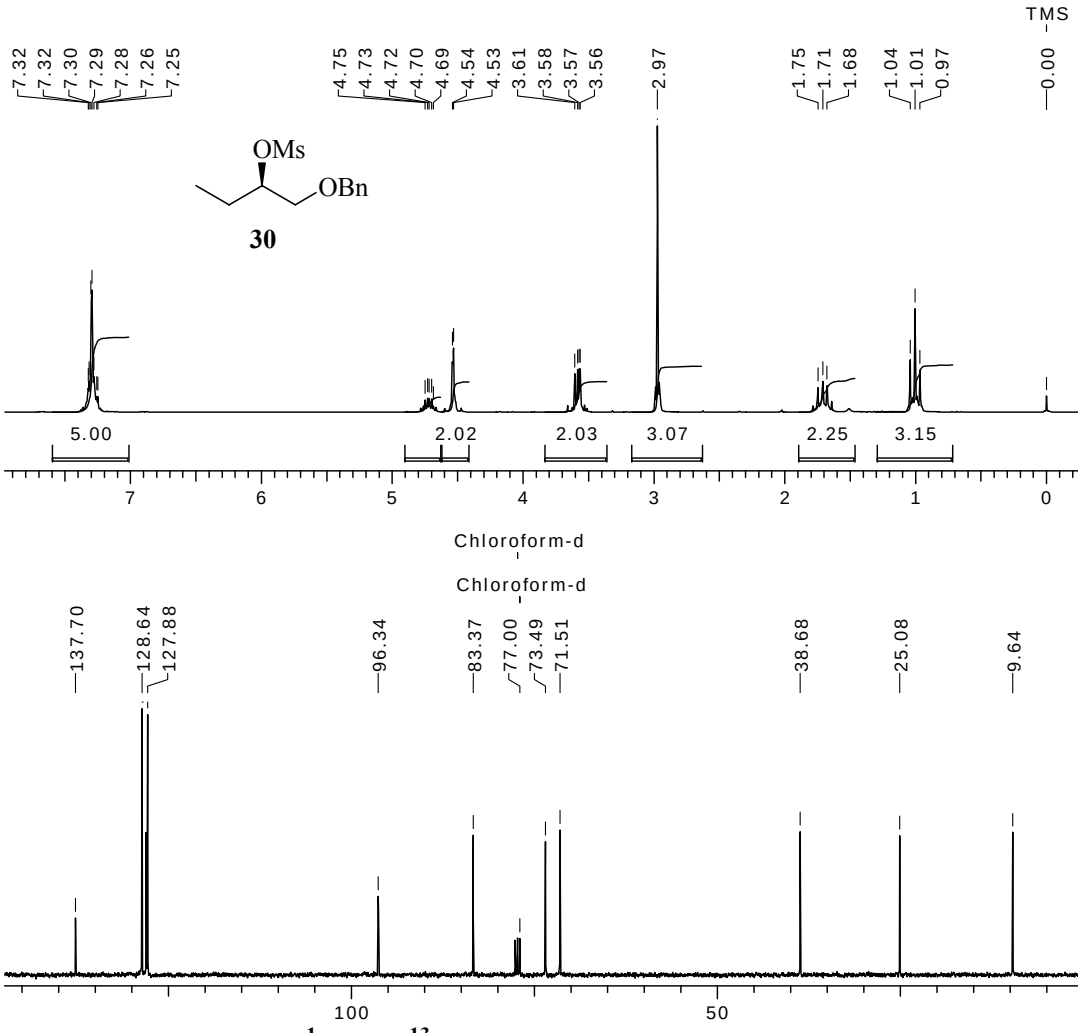


Fig 2: ^{1}H and ^{13}C NMR spectra of mesylate 30

showed carbon signals at δ 66.1 and 54.0 corresponding to the methylene and methine carbons (**CH**NH_2) respectively (**Fig. 4**). Selective protection of the hydroxyl group in amino alcohol **23** was achieved with TBSCl, imidazole in CH_2Cl_2 to give the silyl ether **20** in 92% yield. The appearance of signals at δ 0.03 (s) and 0.87 (s) in the ^{1}H NMR spectrum of **20** confirms the TBS protection. Its ^{13}C NMR spectrum showed carbon signals at δ -5.4 and 18.2 corresponding to the methyl and quaternary carbons in the silyl protecting group respectively. Finally,

protected amino alcohol **25** was transformed to (*S,S*)-ethambutol (**1**) in two steps: Thus, amine **20** on treatment with 0.5 equiv. of oxalyl chloride and pyridine furnished oxalyldiamide **24** in 93% yield. The ^{1}H NMR spectrum of amino oxalyldiamide **24** showed two multiplets at δ 3.61 and 3.63 corresponding to methine (**CH**NHCO) and methylene protons (**CH$_2$**OH) respectively.

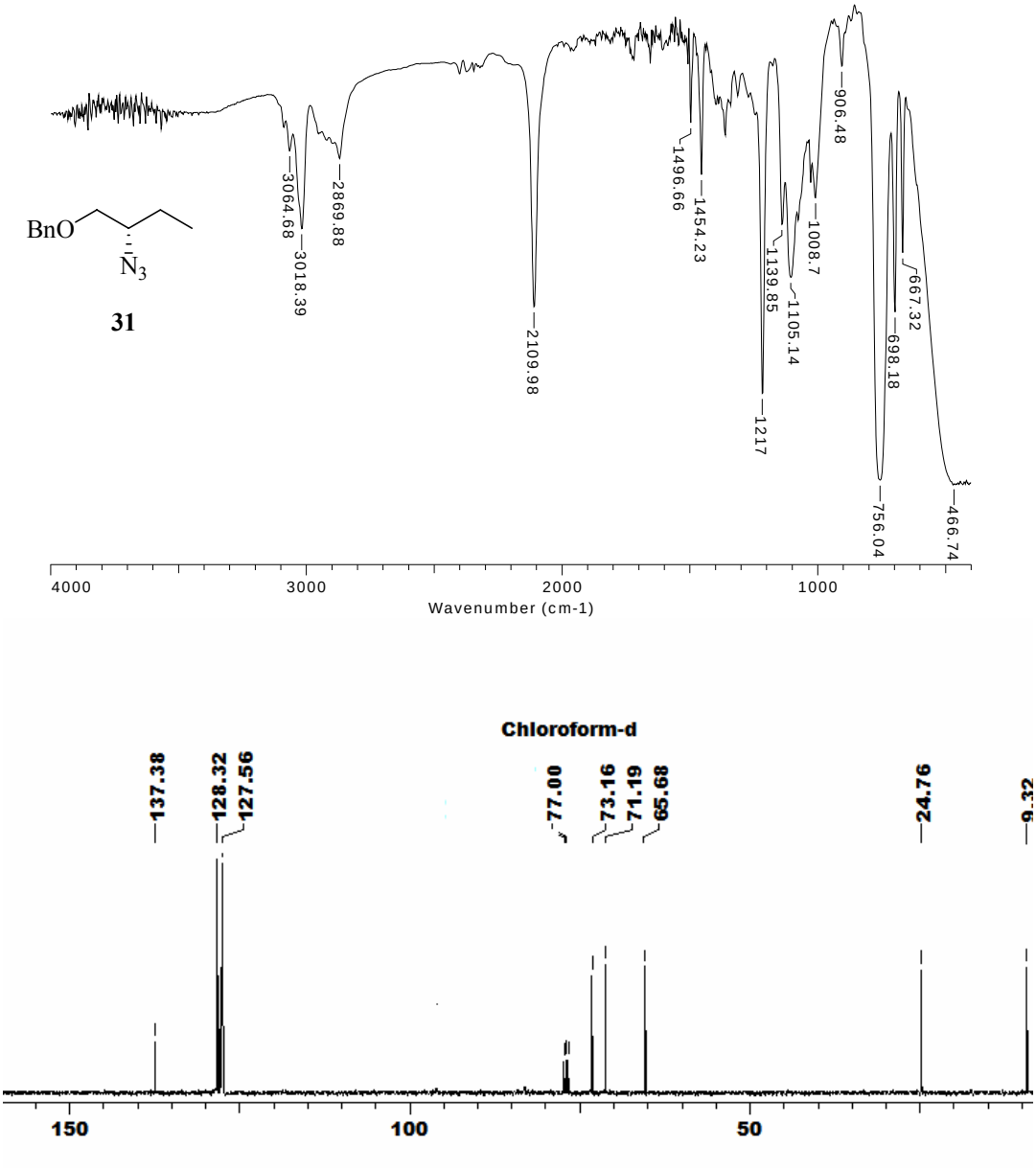


Fig 3: IR and ^{13}C NMR spectra of azide 31

Its ^{13}C NMR spectrum showed carbon signals at δ 52.7 and 63.7 corresponding to methylene and methine carbons (**CH**NHCO) respectively. Its IR spectrum

exhibited a characteristic strong band at 1739 cm^{-1} indicating the presence of amide group.

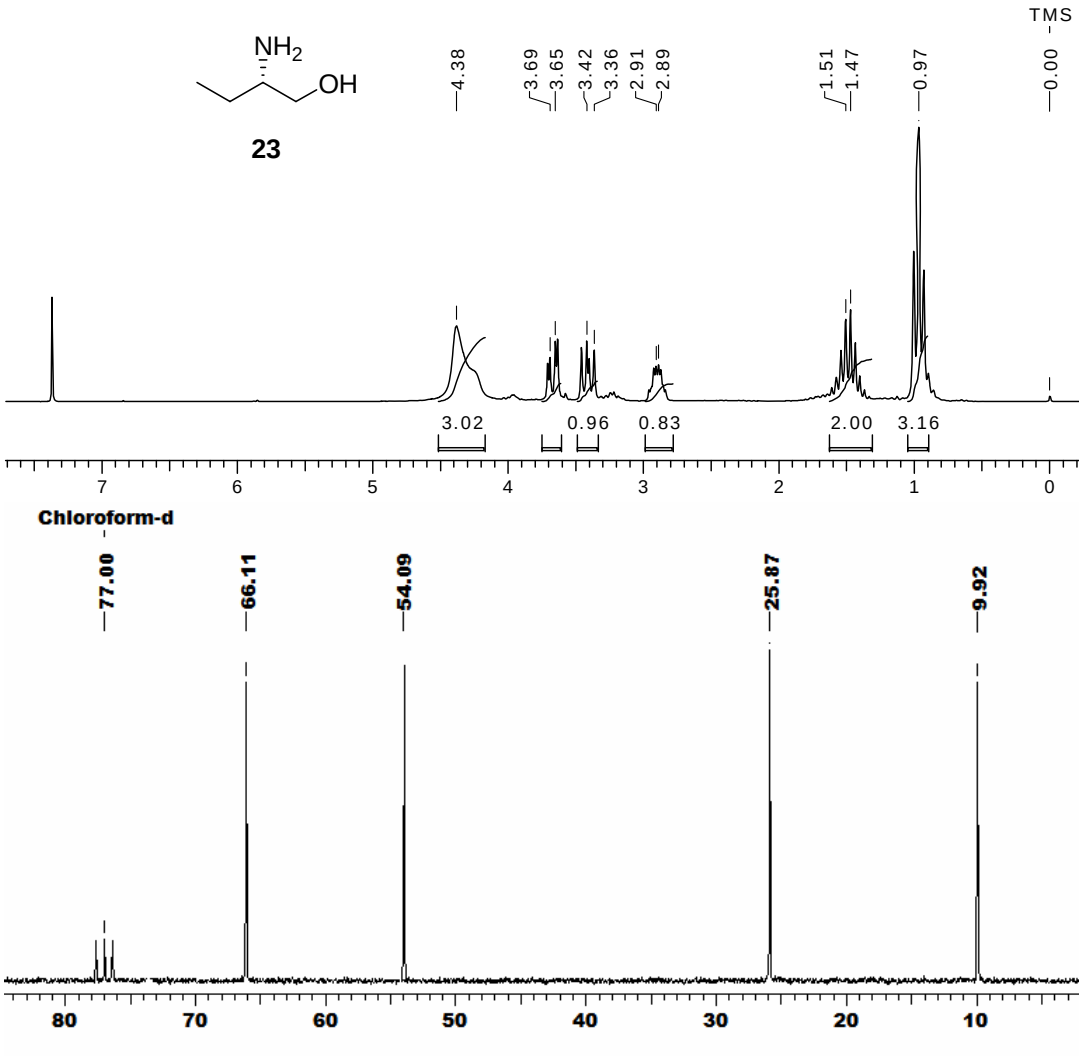


Fig 4: ^{1}H and ^{13}C NMR spectra of amino alcohol 23

The reduction of diamide and deprotection of TBS group in **24** was achieved in a one-pot reaction using $LiAlH_4$ at reflux conditions to give (*S,S*)-ethambutol (**1**) in 71% yield and 97% ee; $[\alpha]_D^{25}$ +13.4 (*c* 2, H_2O) (97% ee) { lit.[15] $[\alpha]^{25}_D$ +13.7 (c 2, H_2O). The ^{1}H NMR spectrum of (*S,S*)-ethambutol (**1**) showed signals at δ 2.52 (m), 2.71 (m) and 2.82 (m) and 2.86 (brs) corresponding to the methylene (**CH_2**NH), methine (**CH**NH), **NH** and **OH** protons respectively ((**Fig. 5**). Its ^{13}C NMR showed typical peaks at δ 46.5 and 60.4 corresponding to the methylene

(**CH_2**NH) and methine carbons (**CH**NH) respectively. The physical and spectroscopic data were thus in full agreement with the literature values.[15]

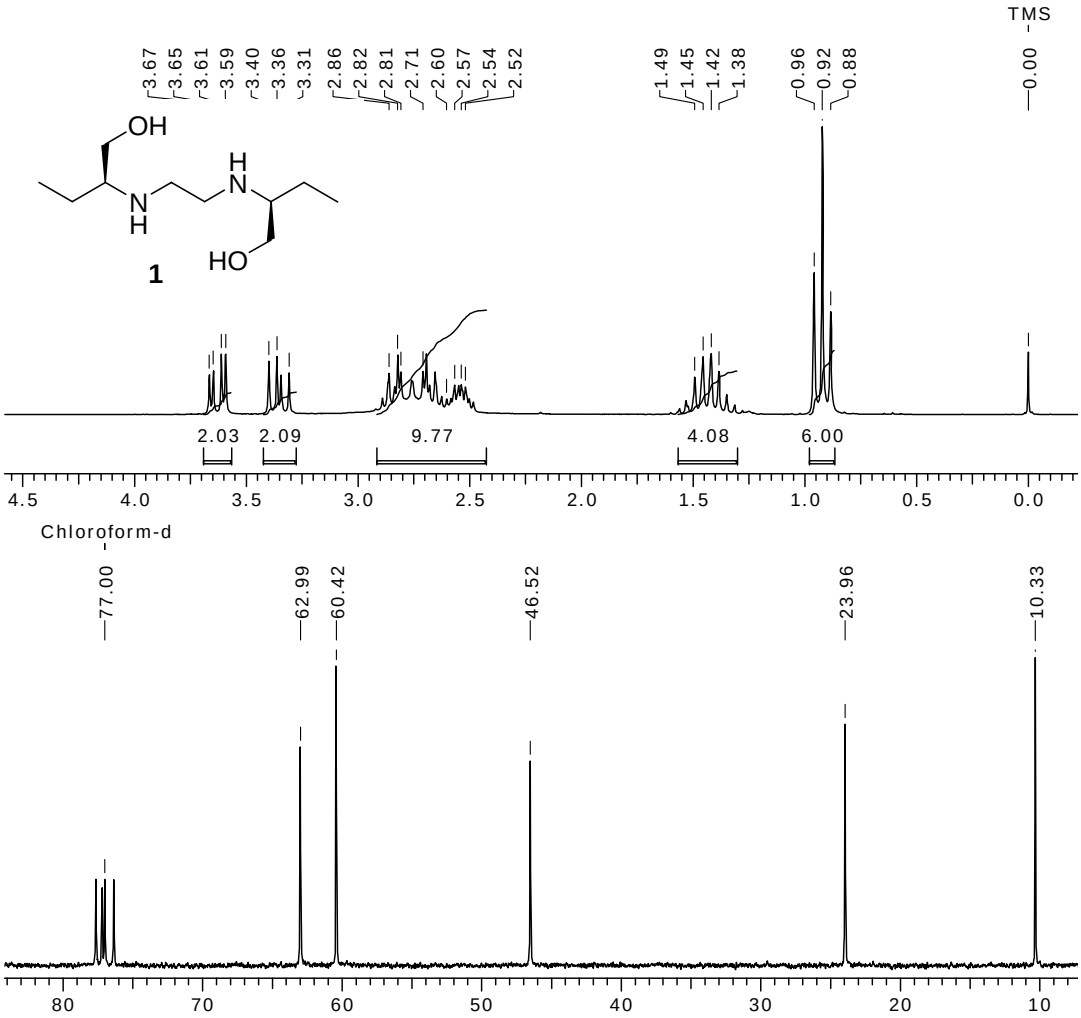


Fig. 5: ^{1}H and ^{13}C NMR spectra of ethambutol (1)

1.1.6 Conclusion:

In conclusion, we have successfully applied Hydrolytic Kinetic Resolution strategy for the synthesis of (*S,S*)-ethambutol (**1**), which was obtained in 97% ee and 9.7% overall yield. It requires a relatively low amount of an inexpensive and non-toxic catalyst (*R,R*)- cobalt-salen that is available in both enantiomeric forms. The overall yield and less-number of steps render our approach a good alternative to the known methods.

1.1.7 Experimental Section:

Hydrolytic kinetic resolution of Benzyl glycidyl ether (27):

To a solution of (*R,R*)- cobalt-salen (332 mg, 0.55 mmol) in toluene (10 ml) was added glacial AcOH (280 μL, 5.0 mmol). The solution was allowed to stir at 25 ºC (open to air) for 30 min. The solution was concentrated *in vacuo* to leave a crude-brown solid. The resulting residue was dissolved in benzyl glycidyl ether (45.15 g, 275 mmol), the reaction flask was cooled to 0 ºC and water (2.72 mL, 151 mmol, 0.55 eq) was added dropwise over 5 min. The reaction mixture was allowed to warm to 25 ºC and stirred for another 14 h. After completion of reaction (monitored by TLC), solvents were removed *in vaccuo*. The residue was extracted with EtOAc (3 × 100 mL), the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to give (*R*)-benzyl glycidyl ether, **26** (solvent system; pet ether: EtOAc = 98:2) and chiral diol **29** (solvent system; pet ether: EtOAc = 70:30).

(i) **(*R*)-Benzyl glycidyl ether (26)**

Yield: 23.02 g, 51%, colorless oil; **$[\alpha]_D^{25}$** + 9.8 (c 5.1, MeOH) {lit[16] $[\alpha]_D^{25}$ + 10 (c 5.2, MeOH)}; **IR** ($CHCl_3$): 877, 985, 1216, 1387, 1452, 1476, 3018, 3435 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.60-2.64 (m, 1H), 2.78-2.83 (m, 1H), 3.17-3.22 (m, 1H), 3.40-3.48 (m, 1H), 3.74-3.81 (dd, *J* = 3.0, 5.3 Hz, 1H), 4.58-4.60 (d, *J* = 3.9 Hz, 2H), 7.26-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.2, 50.8, 70.7, 73.2, 127.7, 127.9, 128.4, 137.8; **Analysis: $C_{10}H_{12}O_2$** requires C, 73.13; H, 7.37; found C, 73.17; H, 7.36%.

(ii) **(*S*)-Benzyloxy-1,2-propandiol (29)**

Yield: 23.55 g, 47%, Colorless oil; **$[\alpha]_D^{25}$** -1.31º (*c* 3, EtOH) {lit.[16] $[\alpha]^{25}_D$ -1.4 (*c* 3.3, EtOH)}; **IR** ($CHCl_3$): 700, 1039, 1216, 1494, 3024, 3391 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 2H), 3.47-3.74 (m, 4H), 3.88-3.90 (m, 1H), 4.54 (s, 2H), 7.32-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 63.5, 70.6, 71.2, 73.0, 127.4, 127.8, 128.1, 137.5; **Analysis: $C_{10}H_{14}O_3$** requires C, 65.89; H, 7.74; found C, 65.93; H, 7.71%.

(*R*)-1-(Benzyloxy)butan-2-ol (25)

To a stirred solution of epoxide **26 (**22.98 g, 140 mmol**)** in THF (100 mL) was added CuI (38.0 mg, 0.2 mol,) followed by slow addition of MeMgI (34.9 g, 210 mmol) at -78 ºC. The reaction mixture was then stirred at -40 ºC for 48 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl and was extracted with EtOAc (3 × 100 mL), the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (pet ether: EtOAc = 90:10) to give alcohol **25.**

Yield: 19.68 g, 78 %, colorless oil; **$[\alpha]_D^{25}$** -10.31º (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 1097 1452, 2873, 2962, 3442 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95-0.99 (t, *J* = 7.4 Hz, 3H), 1.46-1.49 (m, 2H), 2.46 (brs, 1H), 3.33-3.37 (dd, *J* = 7.7, 9.36 Hz, 1H), 3.47-3.54 (dd, *J* = 3.0, 9.4 Hz, 1H), 3.71 (m, 1H), 4.55 (s, 2H), 7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 25.9, 71.5, 73.0, 74.1, 127.5, 127.8, 128.2, 137.8: **Analysis: $C_{11}H_{16}O_2$** requires C, 73.30; H, 8.95; found C, 73.29; H, 8.99%.

(*R*)-1-(Benzyloxy)butan-2-yl methanesulfonate (30)

To a stirred solution of alcohol **25** (18.92 g, 105 mmol) in CH_2Cl_2 (100 mL) at 0 ºC was added triethylamine (21.9 mL, 157 mmol) and followed by the addition of methanesulfonyl chloride (17.98 g, 157 mmol). The reaction mixture was then stirred at 25 ºC for 4 h. After completion of reaction (monitored by TLC), solvents were removed *in vaccuo*. The residue was extracted with EtOAc (3 × 100 mL), the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (pet ether: EtOAc = 95:5) to give mesylate, **30.**

Yield: 25.77 g, 95 %, colorless oil; $[\alpha]_D^{25}$ -5.1º (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 927, 1103, 1351, 1454, 1605, 1724, 2940, 2974, 3064, 3650, cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.97-1.04 (t, *J* = 7.4 Hz, 3H), 1.68-1.75 (m, 2H), 2.97 (s, 3H), 3.56-3.61 (m, 2H), 4.53 (s, 2H), 4.69-4.75 (m, 1H), 7.25-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 25.0, 38.6, 71.5, 73.4, 83.3, 127.5, 127.8, 128.6, 137.7; **Analysis: $C_{12}H_{18}O_4S$** requires C, 55.79; H, 7.02; found C, 55.77; H, 6.99%.

(*S*)- 2-Azido-1-(benzyloxy)butane (31)

To a solution of **30** (24.54 g, 95 mmol) in DMF (100 mL) was added sodium azide (6.17 g, 95 mmol) and the reaction mixture was allowed to stir at 60 ºC for 30 h. After completion of reaction (monitored by TLC) the reaction mixture was poured into 50 mL of water and extracted with diethyl ether (3 × 100 mL) to give the crude product, which was purified, by column chromatography over silica gel (pet ether: EtOAc = 95:5) to give the pure azido compound, **31.**

Yield: 14.03 g, 72 %, colorless oil; $[\alpha]_D^{25}$ + 7.31 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 757 1022, 1216, 1450, 1515, 1616, 2100, 3017, 3370, cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90-0.97 (t, *J* = 7.3 Hz, 3H), 1.61-1.68 (m, 2H), 3.15-3.24 (m, 1H), 3.50-3.54 (m, 2H), 4.46 (s, 2H), 7.23-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$):

δ 9.3, 24.7, 65.6, 71.1, 73.1, 127.5, 128.3, 128.6, 137.3; **Analysis: $C_{11}H_{15}N_3O$** requires C, 64.37; H, 7.37; N, 20.47; found C, 64.39; H, 7.35; N, 20.41%.

(*S*)-2-Aminobutan-1-ol (23)

To a solution of azide **31** (13.9 g, 68 mmol) in MeOH (15 mL) was added 10% Pd/C (1.3 g) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 24 h. After completion of reaction (monitored by TLC), it was filtered through a celite pad, concentrated to near dryness to get the amine **23**, which was purified by column chromatography with neutral Al_2O_3 (pet ether: EtOAc = 60:40) to give pure amino alcohol **23.**

Yield: 3.9 g, 64%, colorless oil; **$[\alpha]^{25}_D$** +12.2 (*c* 2, EtOH) {lit[15] $[\alpha]^{25}_D$ +12.5 (*c* 2, EtOH)}; **IR** ($CHCl_3$): 1060, 1420, 1650, 2960, 3560, 3450 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95-0.99 (t, *J* = 7.58 Hz, 3H), 1.47-1.51 (m, 2H), 2.89-2.91 (m, 1H), 3.36-3.42 (m, 1H), 3.65-3.69 (m, 1H), 4.38 (brs, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.9, 25.8, 54.0, 66.1; **Analysis: $C_4H_{11}NO$** requires C, 53.90; H, 12.44; N, 15.71; found C, 53.97; H, 12.49; N, 15.75%.

((*S*)-2-Aminobutoxy) (*tert*-butyl)dimethyl silane (20)

To a stirred solution of amino alcohol **23** (3.8 g, 43 mmol) in dry CH_2Cl_2 (75 mL) was added imidazole (4.39 g, 64.5 mmol, 1.5 equiv.) at 0 ºC. After stirring for 10 min., TBDMSCl (9.72 g, 64.5 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of reaction (monitored by TLC), the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was then purified by column chromatography over silica gel (pet ether: EtOAc = 80: 20) to give **20**.

Yield: 8.05 g, 92 %, Colorless oil; **$[\alpha]_D^{25}$** +9.5º (*c* 1, $CHCl_3$) {lit.[15] $[\alpha]^{25}_D$ +9.7º (*c* 1, $CHCl_3$); **IR** (neat) ν_{max}: 667, 775, 837, 1103, 1471, 1589, 1739, 2856, 2927, 2952 3355 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 1.28-1.34 (m, 2H), 1.78 (brs, 2H), 2.70 (m, 1H), 3.27-3.35 (m, 1H), 3.54-3.59 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -3.5, 10.4, 18.2, 25.8, 54.3. **Analysis: $C_{10}H_{25}NOSi$** required C, 59.03; H, 12.39; N, 6.89; found C, 59.05; H, 12.44; N, 6.88%.

(*S,S*)-*N*^{1},*N*^{2}-Bis(1-*tert*-butyldimethylsilyloxybutan-3-yl)oxamide (24)

To a solution of amine **20** (7.5 g, 37 mmol) in dry CH_2Cl_2 (100 mL) was added pyridine (3.0 mL, 37 mmol) at 0 ºC, followed by dropwise addition of oxalyl chloride (1.76 mL, 18.5 mmol, 0.5 equiv. dissolved in CH_2Cl_2). After stirring the reaction mixture at 25 ºC overnight, it was quenched with water (10 mL) and extracted with EtOAc (3 × 100 mL). The crude product was purified by column chromatography over silica gel (CH_2Cl_2: MeOH 80:20) to give diamide **24**.

Yield: 15.86 g, 93 %, colorless solid; **mp:** 85 ºC {lit.[15] mp: 86 ºC}; **$[\alpha]_D^{25}$** -59.01º (*c* 1, $CHCl_3$) {lit[15] $[\alpha]^{25}_D$ -60.3º (*c* 1, $CHCl_3$)} (*c* 1, $CHCl_3$) **IR** ($CHCl_3$): 607 846, 917, 1047, 1241, 1374, 1458, 1507, 1739, 1888, 2086, 3547, 3629, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 12H), 0.88 (s, 18 H), 0.90 (t, *J* = 7.3 Hz, 6 H), 1.57-1.63 (m, 6H), 3.61-3.82 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.6, 10.4, 18.1, 24.1, 25.7, 52.7, 63.7, 159.4; **Analysis: $C_{22}H_{48}N_2O_4Si_2$** required C, 57.34; H, 10.50; N, 6.08; found C, 57.48; H, 10.66; N, 6.24%.

(*S,S*)-2,2'-(ethylenediimino)-di-butanol (1)

To a stirred solution of lithium aluminium hydride (114 mg, 3.0 mmol) in dry THF at 0 ºC was added diamide **24** in THF (1.3 g, 2.8 mmol) carefully. The reaction mixture was refluxed for 24 h. After completion (monitored by TLC), It

was quenched by 10 % aq. NaOH (8 mL) and water (5 mL). The precipitate formed was filtered off and washed with EtOAc (3 × 50 mL). The combined organic layers were concentrated to get the crude product, which was purified by column chromatography over silica gel (CH_2Cl_2: MeOH 90:10) to furnish ethambutol (**1**).

Yield: 408 mg, 71 %; colorless solid; **mp:** 85 ºC {lit.[15] mp: 88 ºC}; **$[\alpha]_D^{25}$** +13.4 (*c* 2, H_2O) {lit.[15] $[\alpha]^{25}_D$ +13.7 (*c* 2, H_2O)}; **IR** ($CHCl_3$): 758 1047, 1242 1374, 1447, 1567, 2984, 3465 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88-0.96 (t, *J* = 7.5 Hz, 6 H), 1.38-1.49 (m, 4H), 2.52-2.86 (m, 10H), 3.31-3.40 (dd, *J* = 7.2, 10.8 Hz, 2H), 3.59-3.67 (dd, *J* = 3.7, 10.9, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.3, 23.9, 46.5, 60.4, 62.9; **Analysis: $C_{10}H_{24}N_2O_2$** required C, 58.79; H, 11.84; N, 13.71; found C, 58.81; H, 11.76; N, 13.76%.

Section 2:

Asymmetric Synthesis of Enalaprilat, an Angiotensin Converting Enzyme Inhibitor

1.2.1. Introduction: Angiotensin Converting Enzyme Inhibitor[23-26]

A central role in maintaining the blood pressure is played by a chain of key hormonal reactions. The first step in the chain is the production of renin in the kidneys when the kidneys detect lower blood pressure. The renin stimulates the formation of a protein called angiotensin I, which is then converted to angiotensin II by the angiotensin- converting enzyme in the lungs. Angiotensin II is the most powerful constrictor of blood vessels known. This effect of constricting blood vessels tends to elevate the blood pressure. Angiotensin II also causes the secretion of an additional blood pressure elevating hormone in the adrenal glands, called aldosterone. This chain of blood pressure regulating hormones is referred to as the renin-angiotensin-aldosterone (RAA) hormonal system. The RAA system has long been known to be important in regulating the blood pressure in the body. Many factors affect the functioning of this system including genetics (i.e., heredity, including race), diet, weight, activity, and certain medications. Several classes of blood pressure lowering (anti-hypertensive) medications may have some effects on this hormonal system. However, two classes of drugs have the most substantial effects on the RAA system. These two classes are the angiotensin receptor blockers (ARB drugs) and the angiotensin converting enzyme inhibitors (ACE inhibitors **Fig 6**). Both of these classes of drugs lower blood pressure by blocking certain specific steps in the RAA chain. The ARB drugs block the chemical receptors for angiotensin II on the small arteries (arterioles). Therefore,

the angiotensin cannot cause these arteries to constrict, which lowers the blood pressure.

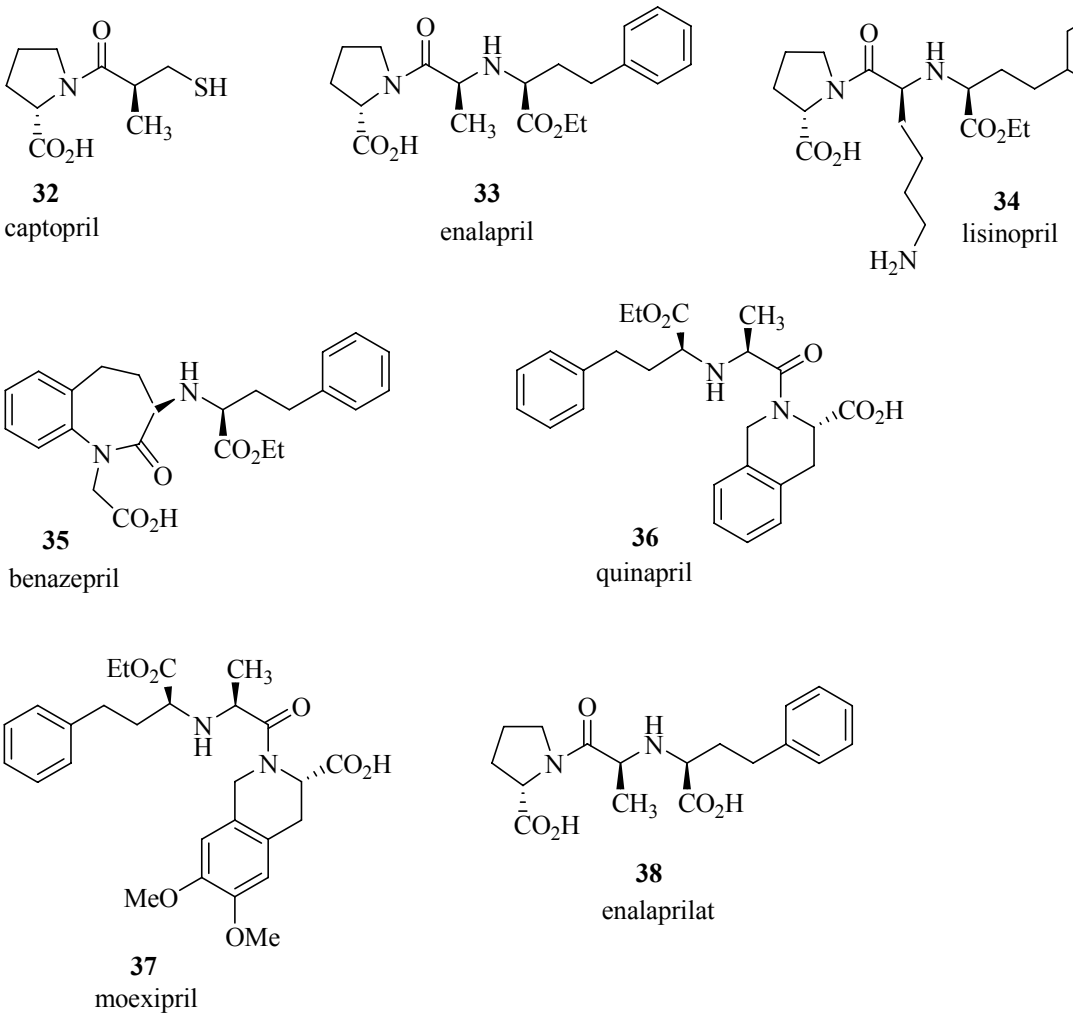


Fig 6: Representative ACE inhibitors

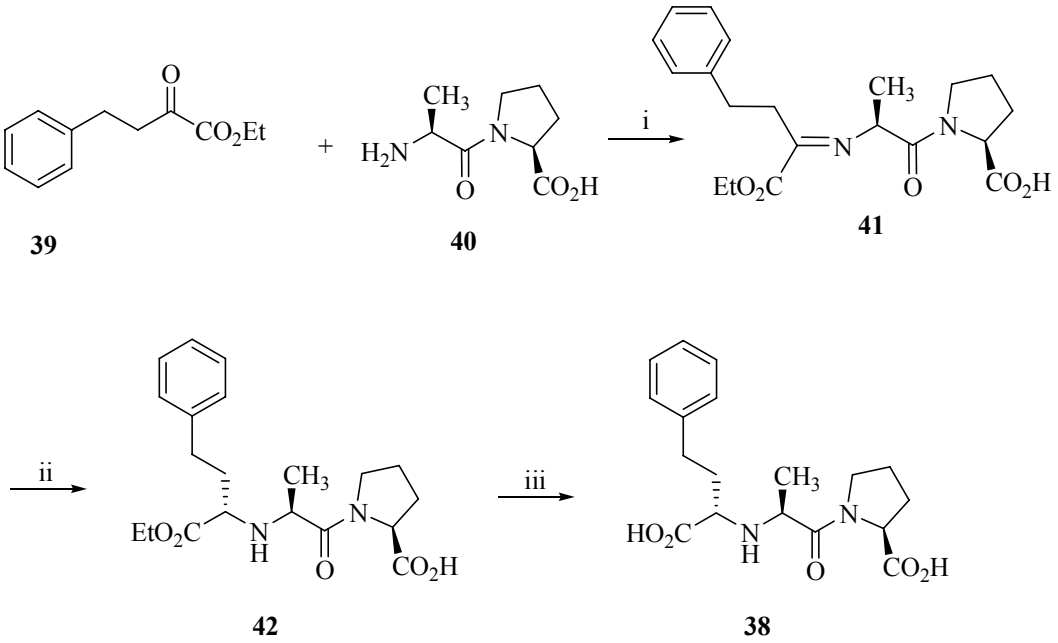
When the small arteries are constricted, they become stiff and narrow, which elevate the blood pressure. By blocking the action of angiotensin II on the small arteries, the ARB drugs prevent them from narrowing (constricting). The effect is to widen the arteries, which lower the blood pressure. The ACE inhibitors block the action of the angiotensin-converting enzyme in the lungs so that angiotensin I is not converted into angiotensin II. The production of this powerful blood vessel constrictor is thereby prevented. The blood vessels thus remain widened, which result in lowering of the blood pressure.

1. 2. 2. Review of Literature

Literature search revealed that there are few methods available for the asymmetric synthesis of enalaprilat **38**, which are described below.

Wyvratt's approach (1983)[27]

Wyvratt *et al.* have synthesized enalaprilat **38** using reductive amination of 2-oxa-4-phenylbutanoate (**39)** with L-alanine-L-proline (**40**).



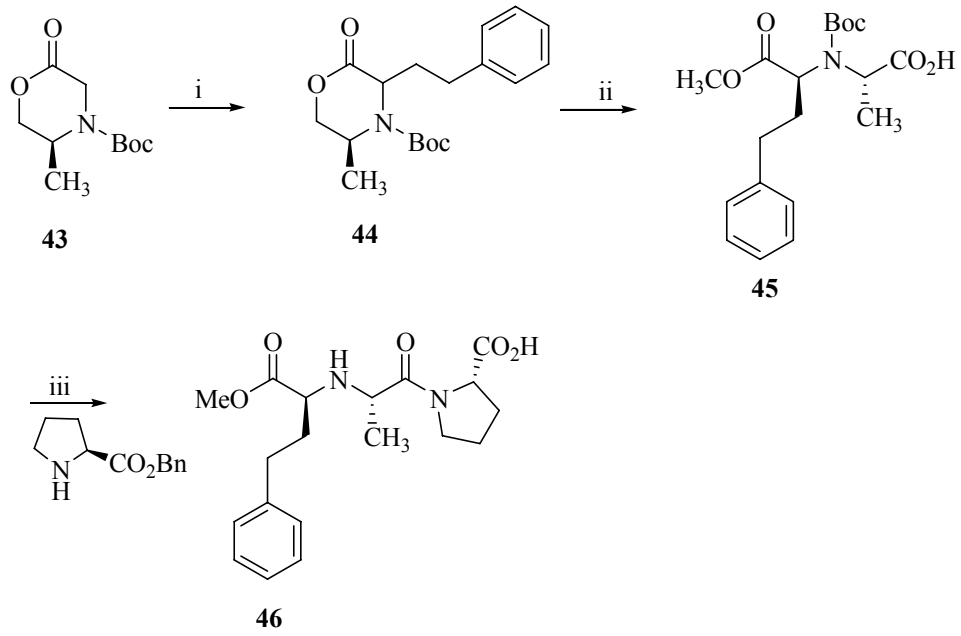
39 **40** **41** **42** **38**

Scheme 11: (i) absolute EtOH, 4 A molecular sieves. (ii) 10% Pd, H_2 (40 psi), 15 h, 60% (iii) 1N NaOH (500 mL), Dowex 50W-2X, 80%

Ethyl 2-oxo-4-phenylbutanoate **39** was condensed with L-alanine-L-proline **40** to give Schiff base **41**. Catalytic hydrogenation of the imine bond in **41** over 10% palladium on carbon resulted in the formation of **42** in 60%. Under these conditions the formation of desired *SSS* diastereomer was favored by a 62:38 margin. Finally alkaline hydrolysis of **42** afforded enalaprilat **38** in 80% yield.

Codon' s approach (1992)[28]

Condon have achieved the synthesis of methyl enalaprilat **46** in seven steps starting from oxazine-2-one, **43**. Alkylation of **43** with phenethyl iodide using NaHMDS gave lactone **44** in 29 % yield.

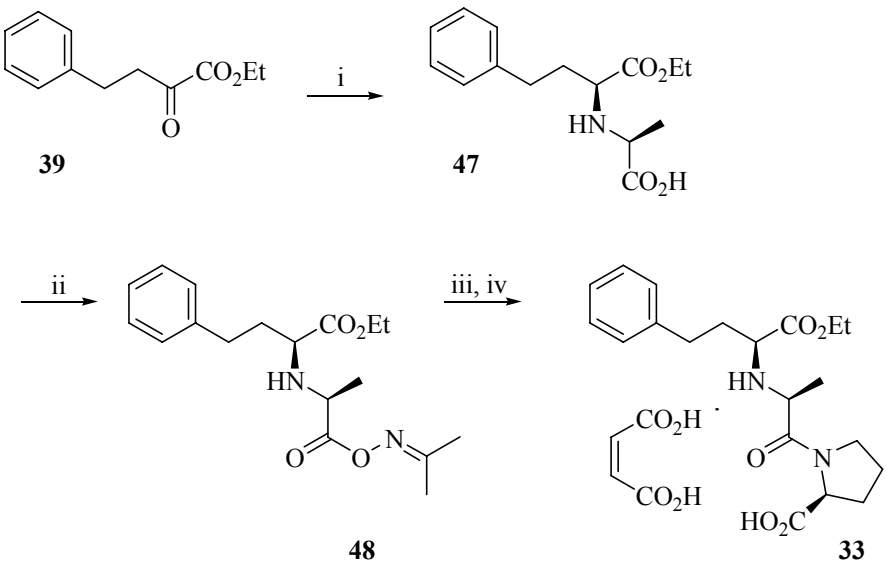


Scheme 12: (i) NaHMDS, $PhCH_2CH_2I$, HMPA, -60 ^oC, (ii) (a) LiOH, H_3O^+, (b) CH_2N_2, (c) $(COCl)_2$, DMSO, Et_3N, -78 ^oC. (d) $KMnO_4$. (iii) $(COCl)_2$, Pd/C, H_2

The lactone was converted into acid **45** using series of reactions as shown in the **Scheme12**. Finally, the coupling of acid **45** with L-proline benzyl ester followed by reductive cleavage of the benzyl ester by hydogenolysis afforded methyl enalaprilat (**46)** in 29% yield.

Palomo's approach (2002)[29]

In this approach synthesis of ethyl enalaprilat was achieved starting from compound **47** which is readily accessible in bulk by the way of reductive amination of ethyl 2-oxo-4-phenylbutyrate (**39)** with L-alanine (**Scheme 13).** The acid, **47** was converted into acetoxime ester, **48** over three steps in 95% yield which upon treatment with a solution of DBU salt of L-proline in acetonitrile gave ethyl enalaprilat, which was isolated as maleate salt **33** in 92% yield over two steps.



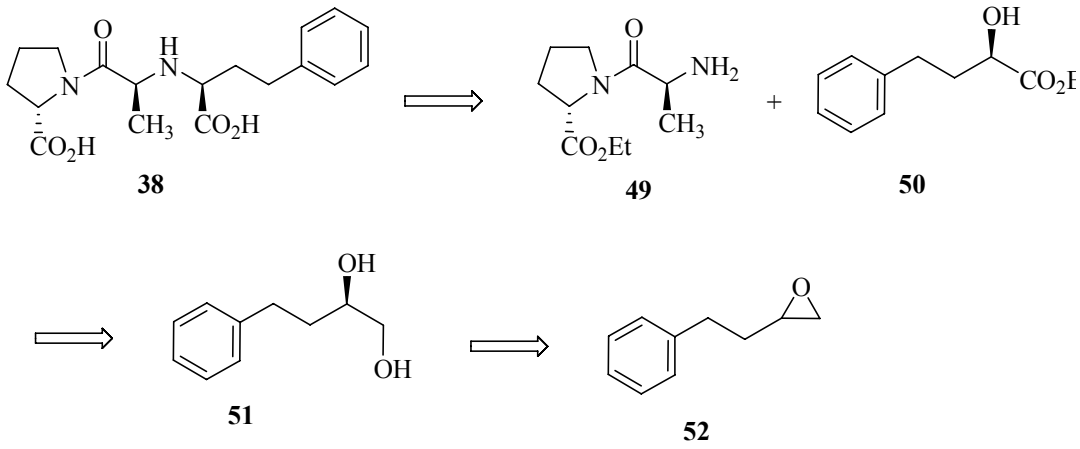
Scheme 13: (i) L-alanine, absolute EtOH, 4 A molecular sieves, Pd/C (40*psi*) (b) HCl(g), CH_2Cl_2,-dioxane. (b) ClCOCOCl-DMF. (c) acetoxime, 0 ^oC, 1h then K_2CO_3 ,95% (over 3 steps). (iii) (a) H-L-pro-OH, DBU, CH_3CN. (b) maleic acid, 92%

1. 2. 3. Present Work:

1. 2. 3.1. Objective

All the literature methods for the synthesis of enalaprilat, **38** make use of chiral starting materials. However, the synthesis of enalaprilate, **38** starting from prochiral substrates using catalytic enantioselective reactions has not been reported and is highly desirable.

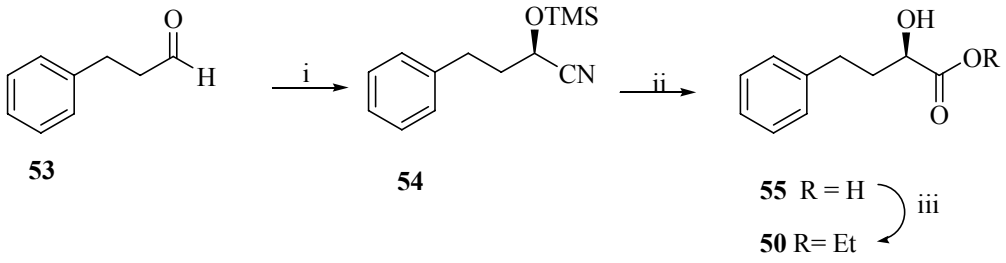
In this section, we describe a highly efficient synthesis of (*S,S,S*)-enalaprilat (**38**) *via* hydrolytic kinetic resolution approach of epoxide **52** and asymmetric hydrocyanation of 3-phenylpropanal. The retrosynthetic analysis of enalaprilat is shown in **Scheme 14,** which reveals that (*R*)-ethyl 2-hydroxy-4-phenylbutanoate **(50)** becomes the key intermediate for its synthesis. The hydoxy ester, **50** could be obtained from either diol **51** or from 3-phenylpropanal **53**. The diol **51** in turn could be obtained from the hydrolytic kinetic resolution of racemic 2-phenethyloxirane (**52)**.



Scheme 14 Retrosynthetic analysis of enalaprilat **38**

1.2.4. Results and Discussions:

(*R*)-Ethyl 2-hydroxy-4-phenylbutanoate (**50**), the main precursor for the synthesis of enalaprilat, was prepared by employing both asymmetric hydrocyanation of aldehyde **53** and hydrolytic kinetic resolution (HKR) of epoxide **52** as the key reactions (**Scheme 15 and 16)**.



Scheme 15: Reagents and conditions: (i) TMSCN, (*S*)-BINOL (1 mol%), *n*-BuLi (1 mol%), H_2O (10 mol%), toluene, -78 °C, 1 h, 89%; (ii) conc. HCl, 25 °C 12 h, 71%; (iii) boric acid (2 mol%), C_2H_5OH, 25 °C, 12 h, 68%.

Thus, asymmetric hydrocyanation of 3-phenylpropanal **53,** was carried out using TMSCN as the cyanide source and (*S*)-BINOL as the chiral ligand catalyzed by *n*-BuLi to obtain silylated cyanohydrin **54** in 89% yield.[30] The ^{1}H NMR spectrum of **54** displayed a signal at δ 5.90 (t) corresponding to the proton at the functionalized carbon (**C**HOTMS). Its ^{13}C NMR spectrum showed signals at δ 64.2 and 118.6

corresponding to the methine (**C**HOTMS) and nitrile carbons (**C**N) respectively (**Fig. 7**).

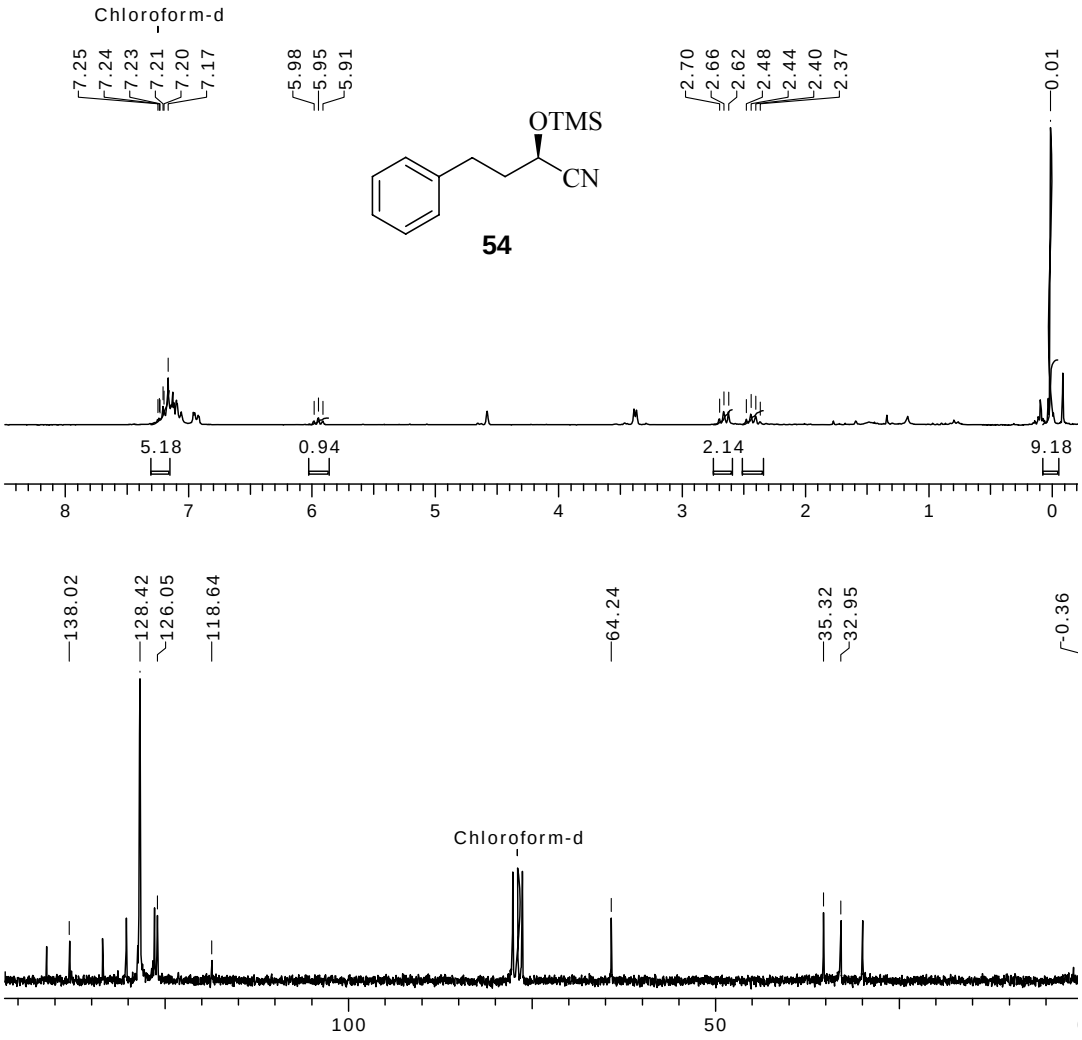


Fig. 7: ^{1}H and ^{13}C NMR spectra of silyalated cyanohydrin 54

Hydrolysis of nitrile group and subsequent deprotection of silyl group in **54** was achieved with conc. HCl, which gave the hydroxy acid **55** in 71% yield. The formation of hydoxy acid **55** was confirmed by the ^{1}H NMR signals at δ 3.53 (b) and 4.34 (t) corresponding to hydroxy and methine (**CH**OH) protons respectively. Its ^{13}C NMR spectra showed peaks at δ 68.8 and 179.0 corresponding to the methine and carbonyl carbon of the carboxylic acid group respectively. A strong band at 1732 cm^{-1} in its IR spectrum confirms the formation of hydroxy acid, **55** (**Fig. 8**).

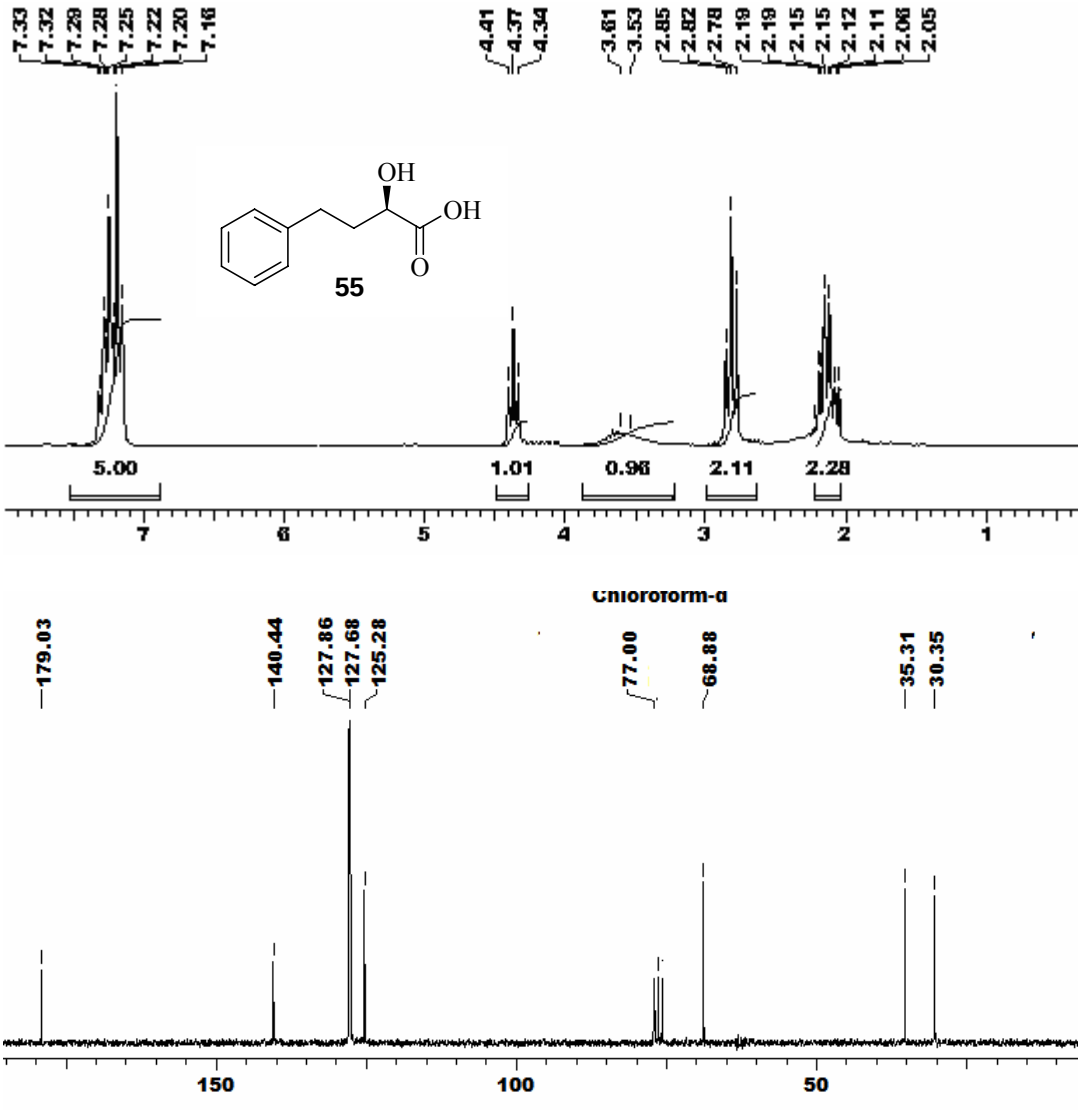


Fig. 8: ^{1}H and ^{13}C NMR spectra of (*R*)-2-hydroxy-4-phenylbutanoic acid (55)

Finally, selective esterification of hydroxy acid **55** was carried out in the presence of catalytic amount of boric acid[31] (2.0 mol %) to give the hydroxy ester **50** in 68 % yield. The ee of the hydroxy ester **50** was determined to be 81% based on comparison of its optical rotation $[\alpha]_D^{25}$ -16.92 (*c* 1, $CHCl_3$) with the reported value{ lit.[32] $[\alpha]^{25}_D$ -20.8 (*c* 1, $CHCl_3$)}. The ^{1}H NMR spectrum of hydroxy ester **50** showed signals at δ 4.19 (q) and 1.29 (t) corresponding to the ester protons respectively. Its ^{13}C NMR spectrum showed carbon signals at δ 69.5 and 175.0 corresponding to methine (**C**HOH) and ester carbonyl carbons respectively.

Moreover, a strong band at 1731 cm^{-1} in its IR spectrum confirms the formation of ester carbonyl in compound **50** (**Fig. 9**).

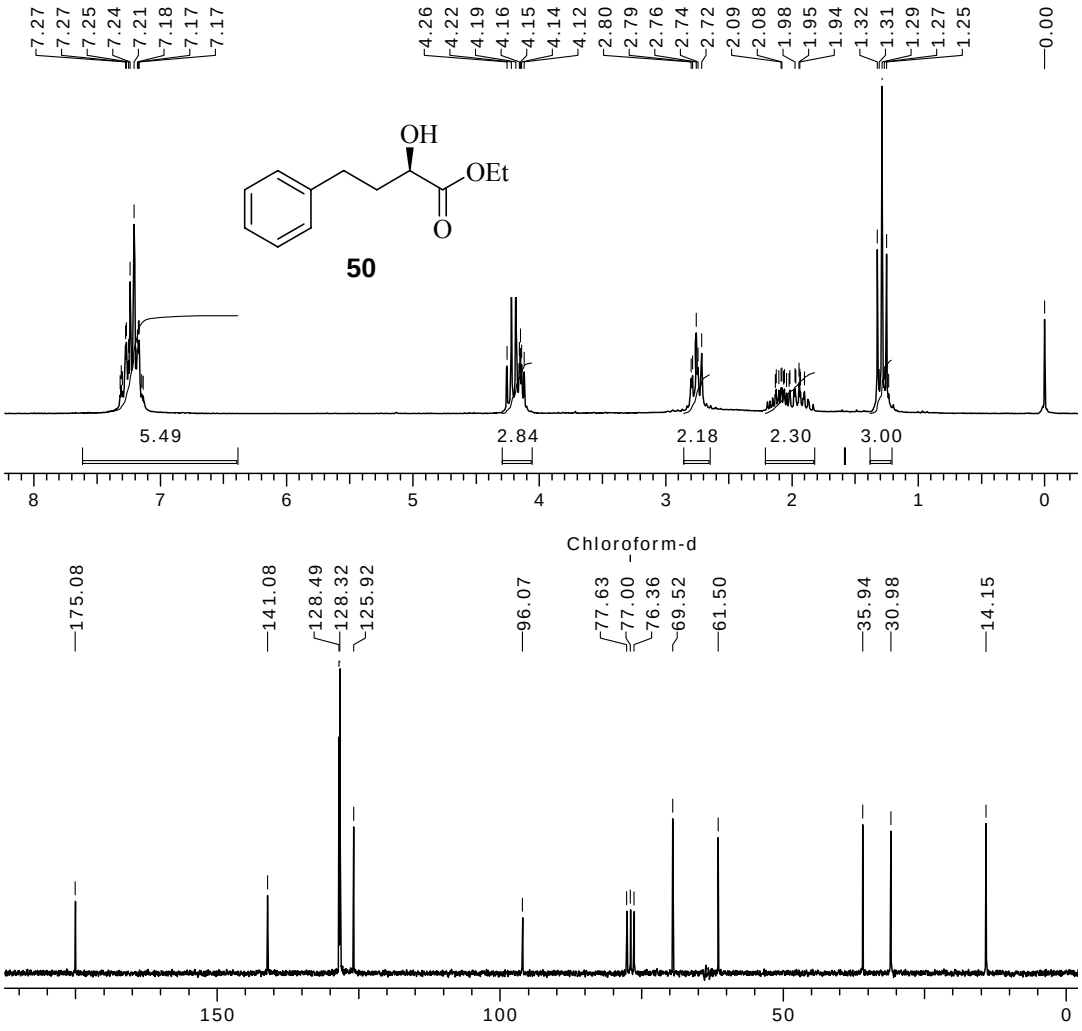
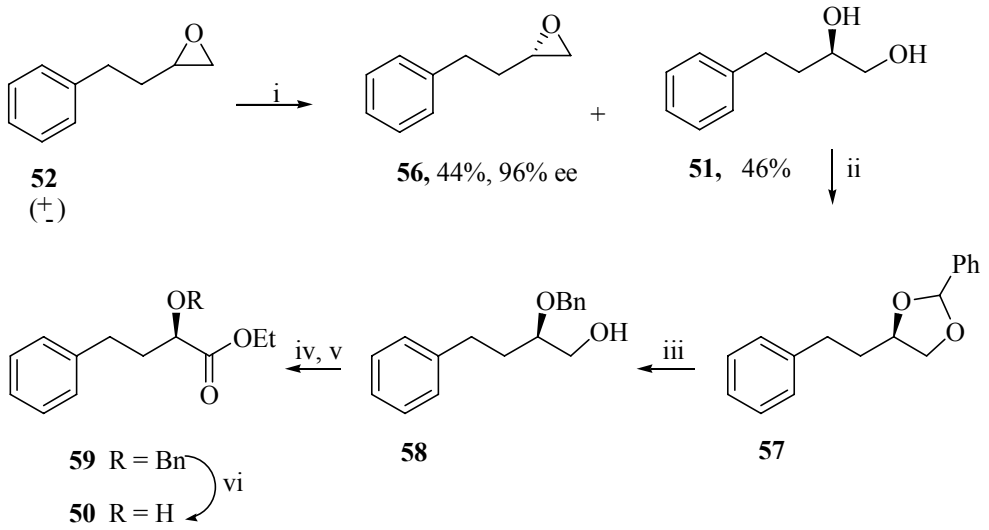


Fig. 9: ^{1}H and ^{13}C NMR spectra of(*R*) –ethyl 2-hydroxy-4-phenylbutanoate (50)

As we obtained a moderate enantiomeric excess of 81% for asymmetric hydrocyanation route, we turned our attention to the hydrolytic kinetic resolution of recemic epoxide **52** (**Scheme 16**). The racemic epoxide **52** was prepared in a single step directly from 3-phenylpropanal, in 76% on the addition of sulfoxonium ylide generated *in situ* from $(CH_3)_3S^+OI^-$ and sodium hydride.



Scheme 16: Reagents and conditions: (i) (*S,S*)-Co(II)-salen, AcOH (0.01 eq), H_2O (0.5 eq), 25 °C; (ii) $C_6H_5CH(OMe)_2$, PPTS (0.5 mol%), CH_2Cl_2 25 °C; (iii) DIBAL-H, CH_2Cl_2, -78°C, 61%; (iv) IBX, DMSO, 87%; (v) oxone, C_2H_5OH, 25 °C, 72%; (vi) H_2 (1 atm), 10% Pd/C 90%.

The formation of epoxide **52** was confirmed by the appearance of multiplets at δ 2.48 and 2.94 due to methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 47.0 and 51.5 due to the two carbons of epoxy ring (**Fig. 10**). Racemic epoxide **52** was then subjected to HKR[20] reaction using catalytic amount of (*S,S)*-salen-Co(III)OAc complex **28** to give chiral epoxide **56** in 44% yield and 96% ee (enantiomeric excess was determined by chiral HPLC analysis; Chiracel OD-H) and chiral diol **51** in 46% yield; $[\alpha]^{25}_D$ +34.0 (*c* 1.0, EtOH); {lit.[33] $[\alpha]^{25}_D$ +32.3 (*c* 1.33, EtOH)}. The formation of diol **51** was confirmed by the appearance of signal at δ 2.47 (dd), 2.69 (dd) and a multiplet at δ 4.05 for methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 65.7 and 75.3 due to the two carbons attached to the alcohol groups (**Fig. 11**) Diol **51** was then protected as benzylidine acetal using benzaldehyde dimethyl acetal and PPTS (0.1 eq) to afford **57** in 91 % yield. The protection of diol **51** as benzylidine

acetal gave both the diastereomers in 1:1 mixture, which was subjected to the next reaction without the separation of the diastereomers.

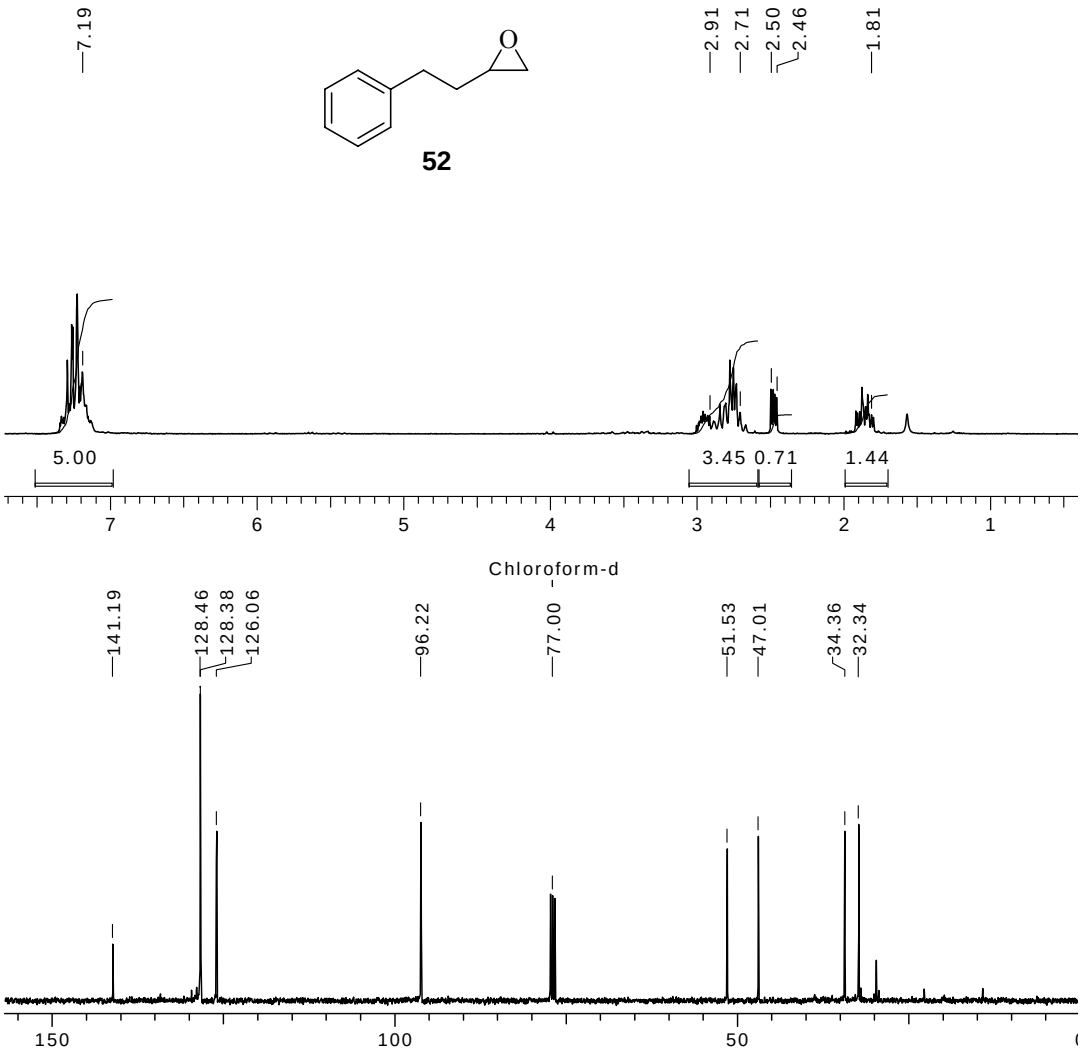


Fig. 10: ^{1}H and ^{13}C NMR spectra of 2-phenethyloxirane (52)

The formation of acetal **57** was confirmed by the appearance of a singlet at δ 5.96 for methine proton of acetal carbon in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed a typical signal at δ 103.0 due to the acetal carbon of **57.** The reductive cleavage of acetal moiety in **57** was achieved using DIBAL-H at -78 ^{o}C to give the primary alcohol **58** in 61% yield.[34] The disappearance of signal at δ 5.96 confirms the reductive cleavage of acetal moiety, moreover the signals at δ 3.71 (m) corresponds to the methine (C**H**OBn)

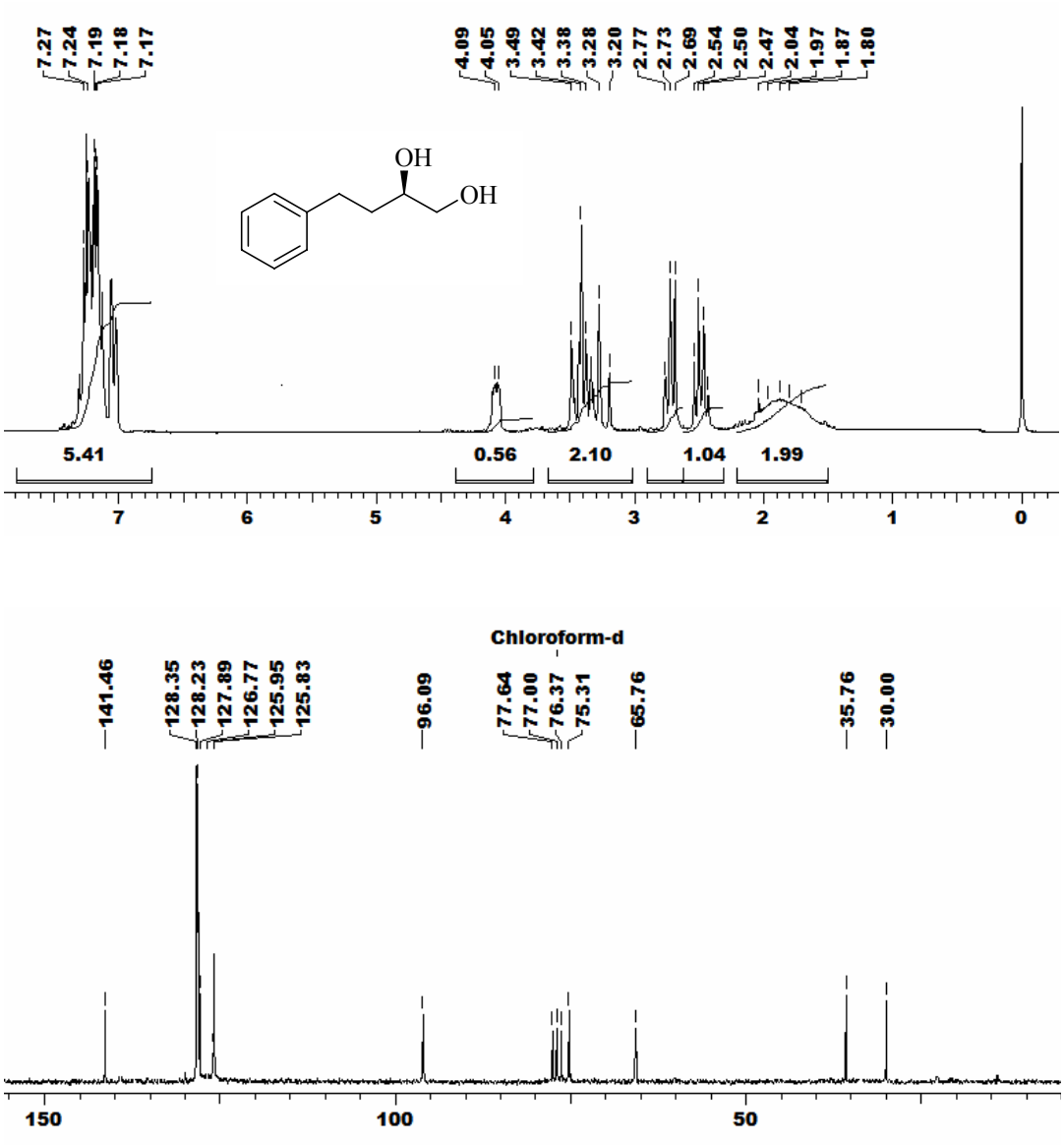


Fig. 11: ^{1}H and ^{13}C NMR spectra of 4-phenylbutan-1,2-diol (51)

proton. Its ^{13}C NMR spectrum showed carbon signals at δ 79.6 and 65.9 corresponding to the methine (**C**HOBn) and methylene (**C**H_2OH) carbons respectively.

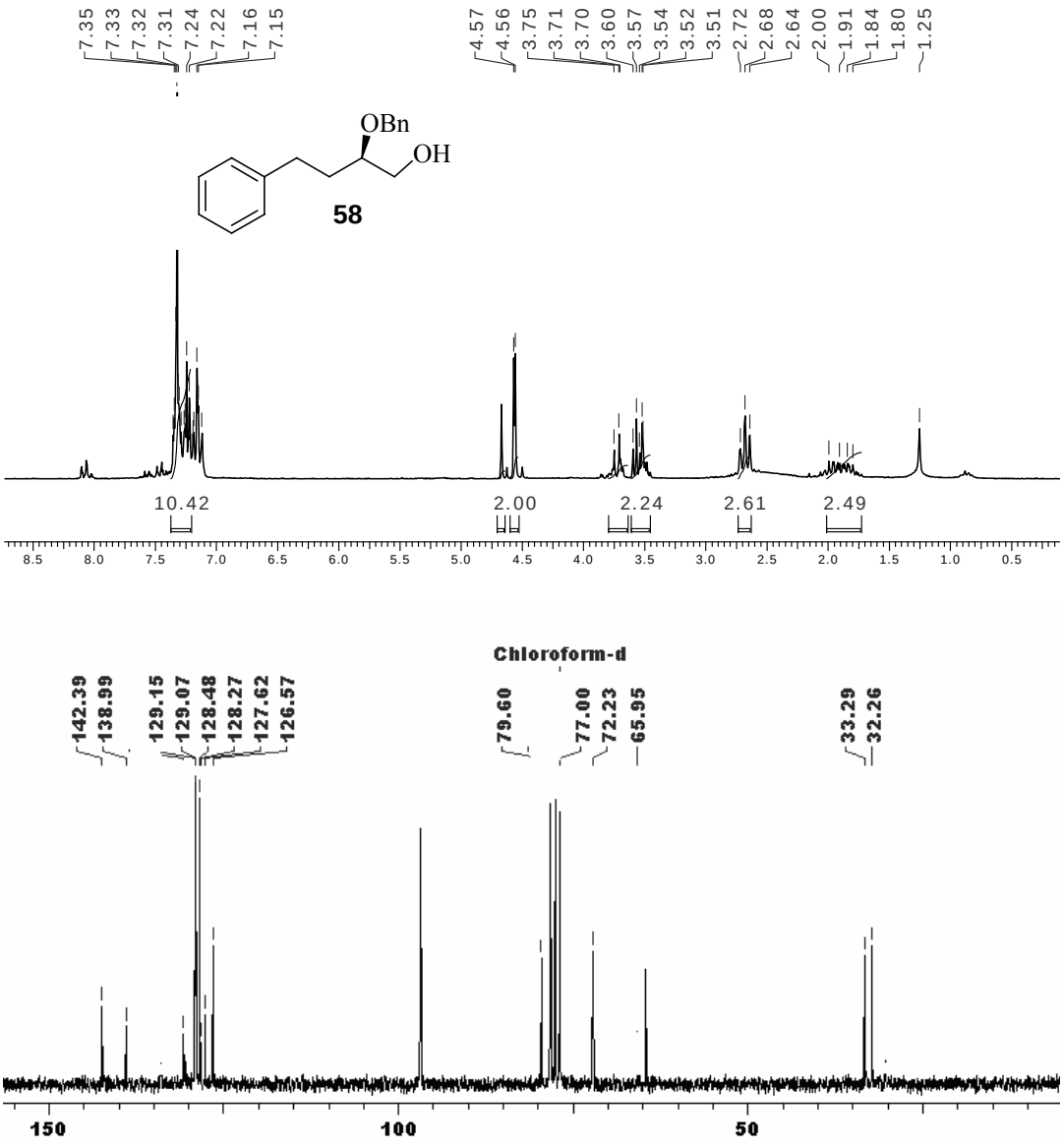


Fig. 12: ^{1}H and ^{13}C NMR spectra of (*R*)-2-(benzyloxy)-4-phenylbutan-1-ol (58)

The alcohol **58** was oxidized using IBX in DMSO at 25 ^{o}C to afford the corresponding aldehyde which, without any further purification, was subjected to esterification mediated by oxone[35] in ethanol to provide the hydroxy ester **59** in 72% yield. The esterification was confirmed by the appearance of signals at δ 1.30 (t) and 4.17 (q) corresponding to methyl and methylene protons of the ester group. Its ^{13}C spectrum showed typical signals at δ 14.1, 61.0 and 172.2 corresponding to the methyl, methylene and carbonyl carbons respectively (**Fig. 13)**. Finally, the deprotection of benzyl group using 10% Pd/C, H_2(1 atm.) afforded hydroxy ester

50 in 90% yield and 98 % ee based on the comparison of its optical rotation with that of reported value; $[\alpha]_D^{25}$ -19.8 (*c* 1, $CHCl_3$) { lit.[32] $[\alpha]^{25}{}_D$ -20.8 (*c* 1, $CHCl_3$)}. The disappearance of signal at δ 4.61 in the ^1H NMR confirms the deprotection of benzyl group. Its ^{13}C NMR spectrum showed typical carbon signals at δ 69.5 and 175.0 corresponding to methine (**C**HOH) and ester carbonyl carbons respectively.

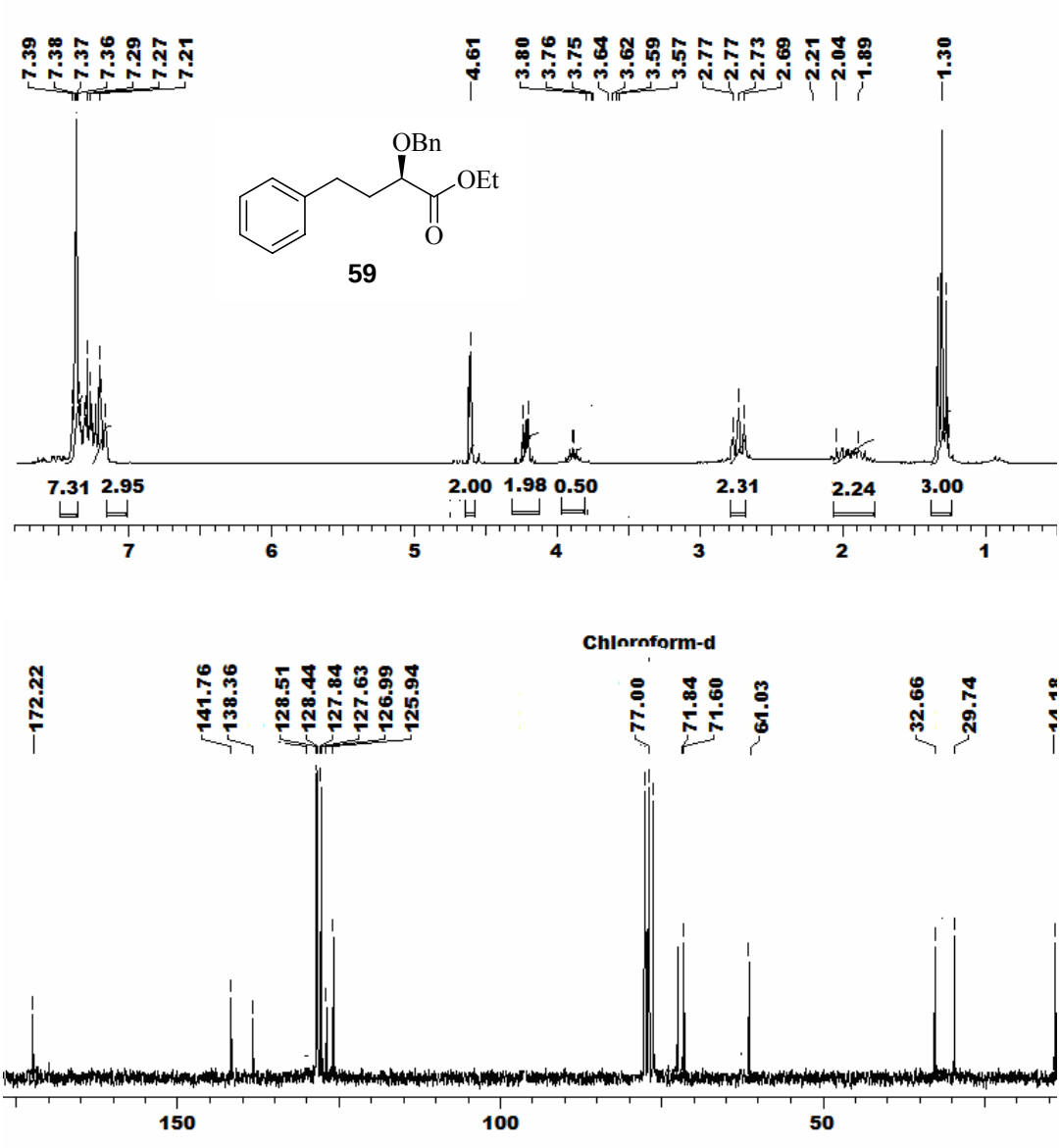
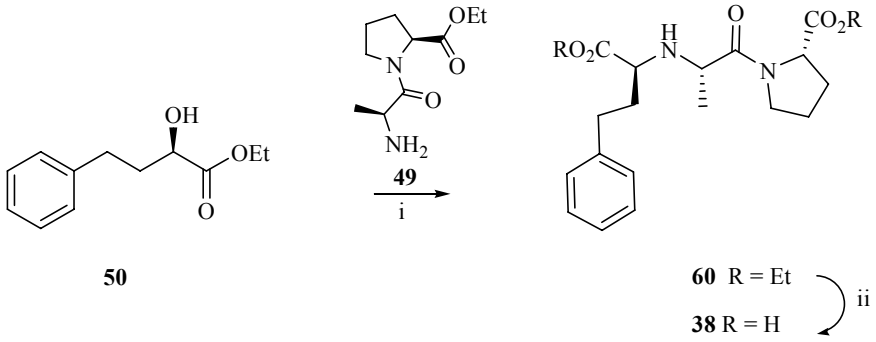


Fig. 13: ^1H and ^{13}C NMR spectra of (*R*)-ethyl-2-(benzyloxy)-4-phenylbutanoate (59)

The hydroxy ester **50** was subjected to amination under Mitsunobu condition[36] (DIAD, Ph_3P) with amine **49** in THF at 25 °C to give diester **60** in 56% yield

(**Scheme 17**). The formation of diester **60** was confirmed by the signals at δ 3.61(m) corresponding to methine (C**H**NH) and at δ 1.94 (bm) corresponding to methylene protons of proline moiety. Its ^{13}C NMR spectrum displayed peaks at δ 29.6, 47.9 and 166.7 due to the methylene carbons of proline moiety and amide carbonyl carbon respectively.



Scheme 17: Reagents and conditions: (i) DIAD, Ph_3P, THF, 25 °C, 56%; (ii) LiOH, THF:H_2O (1:1), 25 °C, 4 h, 54% .

Finally, the diester **60** underwent mild hydrolysis using LiOH in aqueous THF at 25 °C to afford enalaprilat **38** in 54% yield and 85% ee. The ee of enalaprilat was based on comparison of its optical rotation with that of reported value $[\alpha]^{25}_D$ -45.9 (*c* 1, CH_3OH); {lit.[27] $[\alpha]^{25}_D$ -53.5 (*c* 1, CH_3OH)}. The formation of enalaprilat was confirmed by disappearance of signals at δ 4.18 (bm) corresponding to methylene (C**H**$_2$CO$_2$-) of ester groups in the ^1H NMR and its ^{13}C showed typical signal at δ 179.4 and 179.9 corresponding to carbonyl carbons of dicarboxylic acid group (**Fig. 14)**. Its IR spectrum showed bands at 1730 and 1735 cm^{-1} for the ester and amide groups respectively.

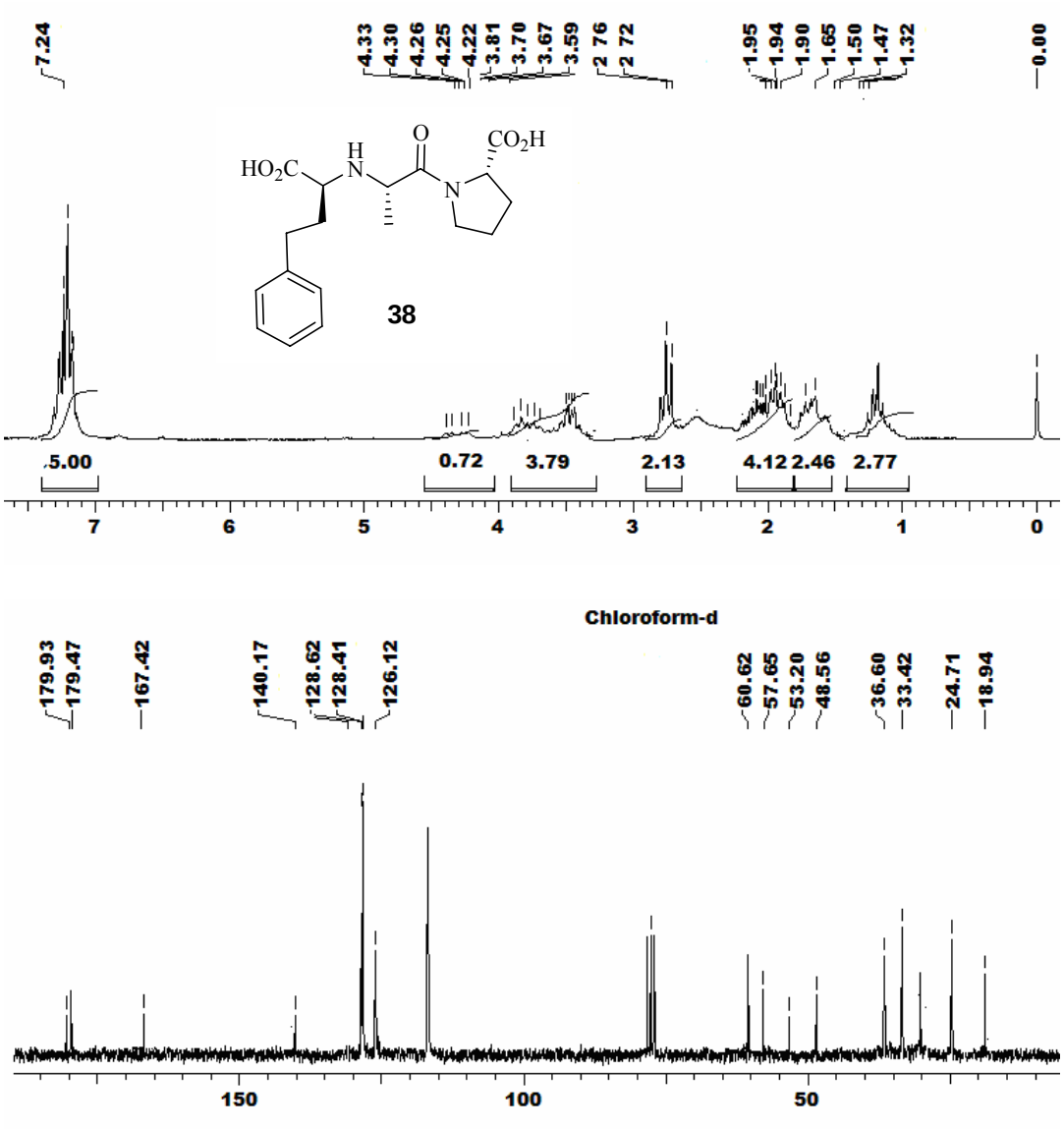


Fig. 14: ^{1}H and ^{13}C NMR spectra of Enalaprilat (38)

1.2.5 Conclusion

In conclusion, we have achieved the synthesis of enalaprilat **38**, a potent ace inhibitor drug, *via* hydrolytic kinetic resolution approach. Good yields, simple and environment friendly procedures, easy availability of starting materials and use of Co-salen **28** as catalyst renders our approach a good alternative to known methods.

1.2.6. Experimental Section

4-Phenyl-2-(trimethylsilyloxy)butanenitrile (54)

To a stirred solution of (*R*)-BINOL (13.12 mg, 0.5 mmol) in 20 mL of toluene was added dropwise *n*-BuLi (1.6 M in hexane, 0.58 mL, 0.5 mmol) at room temperature under nitrogen atmosphere, and the mixture was stirred for 10 min. 3-Phenylpropanal (6.7 g, 50 mmol) was added to the reaction mixture and stirred for 20 min at room temperature. The resulting yellow solution was cooled to -78 °C and stirred for 10 min at that temperature. Trimethylsilylcyanide (10 mL, 75 mmol) was added dropwise, and after stirring for 1 h the reaction mixture was diluted with MeOH (15 mL) at – 78 °C. After 10 min, water (50 mL) was added and the product was extracted with ethyl acetate (100 mL × 2) and washed with brine (100 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the pure cyanohydrin **54** as colorless oil.

Yield: 10.38 g, 89 %; **IR** ($CHCl_3$): 909, 1071, 1137, 1276, 1466, 2254, 3326 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.01 (s, 9H), 2.37-2.48 (m, 2H), 2.62-2.70 (t, *J* = 7.7 Hz, 2H), 5.91-5.98 (t, *J* = 7.0 Hz, 1H), 7.17-7.24 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ

-0.5, 32.9, 35.3, 64.2, 118.6, 126.0, 128.4, 128.5, 138.0; **Analysis**: **$C_{13}H_{19}NOSi$** requires C, 60.90; H, 8.21; N, 6.00 found C, 60.93; H, 8.26; N, 6.03%

(*R*)-2-Hydroxy-4-phenylbutanoic acid (55)

A mixture of silylated cyanohydrin **54 (**7g, 30 mmol**)** and 25 ml of conc. HCl solution was heated 60 °C and stirred for 24 hours. After completion of the reaction (monitored by TLC), water was evaporated *in vacuo* and the residue was purified for column chromatography (silica gel with petroleum ether: EtOAc (70: 30) as eluent) to afford hydroxy acid **55** as a colourless solid.

Yield: 3.8 g, 71 %; colorless solid; **mp** 117 ºC; {lit.[37] mp 116-118 ºC}; **$[\alpha]_D^{25}$** -8.3 (*c* 3, EtOH) { lit.[37] $[\alpha]^{25}_D$ -9.12 (*c* 2.7, EtOH)}; **IR** (KBr): 696, 743, 864, 1097, 1173, 1240, 1454, 1497, 1732, 2582, 2928, 3460 cm^{-1}**;** **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05-2.15 (m, 2H), 2.78-2.85 (t, *J* = 7.7 Hz, 2H), 3.53 (brs, 1H), 4.34-4.41 (t, *J* = 7.0 Hz, 1H), 7.16-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.3, 35.3, 68.8, 125.2, 127.6, 127.8, 140.4, 179.0; **Analysis**: **$C_{10}H_{12}O_3$** requires C, 66.65; H, 6.71; found C, 66.63; H, 6.71 %.

(*R*)-Ethyl 2-hydroxy-4-phenylbutanoate (50)

To a stirred solution of hydroxy acid **55** (2.7 g, 15 mmol) in dry ethanol (30 mL) was added boric acid (19 mg, 0.3 mmol) in one-portion. The mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* with mild heating (40- 45°C) to afford a crude residue that was extracted with CH_2Cl_2 (75 mL) and then washed with 1N $NaHCO_3$ (100 ml) followed by water (50 ml). The organic fraction was dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure to afford ethyl ester **50** as clear oil.

Yield: 2.1 g, 68%; **$[\alpha]_D^{25}$** -16.9 (*c* 1, $CHCl_3$) { lit.[32] $[\alpha]^{25}_D$ -20.8 (*c* 1, $CHCl_3$)}; IR ($CHCl_3$): 909, 1099, 1218, 1248, 1455, 1496, 1603, 1731, 2252, 3515 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25-1.32 (t, *J* = 7.3 Hz, 3H), 1.94-2.09 (m, 2H), 2.72-2.79 (t, *J* = 6.4 Hz, 2H), 4.12-4.16 (m, 1H), 4.19-4.26 (q, *J* = 6.4 Hz, 2H), 7.17-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 30.9, 35.9, 61.5, 69.5, 125.9, 128.3, 128.4, 141.0, 175.0; **Analysis**: **$C_{12}H_{16}O_3$** requires C, 69.21; H, 7.74 found C, 69.23; H, 7.71%.

2-Phenethyloxirane (52)

To a stirred suspension of NaH (60% dispersion in oil, 9.0 g, 375 mmol) in dry DMSO (150 mL) was added trimethylsulfoxonium iodide (82.1 g, 375 mmol).

After 15 min, 3-phenylpropanal (33.5 g, 250 mmol) in DMSO (50 mL) was introduced. The reaction was stirred for 4 h at room temperature. After completion of the reaction (monitored by TLC), it was washed with water (100 mL) and extracted with ethyl acetate (2x100 mL), the organic layer was washed with brine (100 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography (silica gel using petroleum ether: EtOAc (9:1) as eluent) to furnish **52** as a colorless liquid.

Yield: 25.15 g, 68%; colorless liquid; **IR** ($CHCl_3$**)**: 821, 1035, 1247, 1514**,** 1614, 1714, 2339, 2856 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.84-1.92 (m, 2H), 2.47-2.50 (m, 1H), 2.73-2.78 (m, 3H), 2.81-2.94 (m, 1H), 7.15-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.3, 34.3, 47.0, 51.5, 126.06, 128.38, 128.46, 141.19; **Analysis**: **$C_{10}H_{12}O$** requires C, 18.04; H, 8.16 found C, 18.01; H, 8.19%.

(*R*)-4-Phenylbutan-1,2-diol (51)

A 100 mL flask was charged with (*S,S*)-cobalt salen (452 mg, 0.75 mmol, 0.5 mol%), which was dissolved in 5 mL of toluene followed by the addition of glacial AcOH (280 μL, 5 mmol). The entire solution was allowed to stir at 25 ^oC open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated *in vacuo* to leave a crude brown solid. The resulting catalyst residue was dissolved in epoxide **52** (22.2 g, 150 mmol) and H_2O (1.2 mL, 67.5 mmol, 0.45 equiv) was added drop-wise over 5 min at 0 °C. The reaction was allowed to warm to 25 ^oC and stirred for 14 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 and extracted (3 X 100 mL) and concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (silica gel using petroleum ether: EtOAc (7:3) as eluent) to furnish **51** as gum.

Yield: 11.46 g, 46%; **[α]$^{25}_{D}$**: -34 (*c* 1.33, EtOH) {lit [α]$^{25}_{D}$: -32.3 (*c* 1.02, EtOH)}; **IR** (KBr) cm^{-1} 1454, 1496, 1602, 1646, 2929, 3025, 3384 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.80-2.04 (m, 2H), 2.50-2.54 (m, 1H), 2.69-2.77 (m, 1H), 3.20-3.49 (m, 2H), 4.05-4.09 (m, 1H), 7.17-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.0, 35.7, 65.7, 75.3, 125.9, 128.2, 128.3, 141.4; **Analysis**: **$C_{10}H_{14}O_2$** requires C, 72.26; H, 8.49 found C, 72.23, 8.45%.

(4*R*)-4-Phenethyl-2-phenyl-1, 3-dioxolane (57)

To a 250 mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar was added diol **51** (8.3 g, 50 mmol). The flask was placed under an argon atmosphere, and dry CH_2Cl_2 (150 mL) was added *via* syringe. The mixture was cooled to 0 ºC and benzaldehyde dimethyl acetal (7.6 g, 7.5 mL, 50 mmol) was added *via* syringe, PPTS (1.2 g, 5 mmol) was added and the reaction mixture slowly warmed to 25 ºC, then stirred for another 5 h. The solution was filtered through a short silica pad and the solvent was distilled off. The resulting yellow oil was purified by column chromatography (petroleum ether: EtOAc 9:1) to yield the two unsaparable diastereomers, as colorless oil.

Yield: 11.6 g, 91%; **[α]$^{25}_{D}$**: +7.31 (*c* 1.08, $CHCl_3$); **IR** (KBr); 669, 759, 1215, 1702, 2400, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.02-2.06 (m, 5H), 2.70-2.81 (m, 4H), 3.61-3.63 (m, 1H), 3.65-3.72 (m, 1H), 4.06-4.10 (d, *J* = 6.8 Hz, 1H), 4.19-4.24 (m, 3H), 5.79 (s, 1H), 5.94 (s, 1H), 7.18-7.47 (m, 20H); **^{13}C NMR (**50 MHz, $CDCl_3$): δ 32.0, 32.1, 35.3, 69.9, 70.4, 76.3, 103.0, 103.9, 126.0, 126.3, 126.6, 128.2, 128.3, 128.4, 138.4, 141.2; **Analysis**: **$C_{17}H_{18}O_2$** requires C, 80.28; H, 7.13 found C, 80.21; H, 7.16%.

(*R*)-2-(benzyloxy)-4-phenylbutan-1-ol (58)

To a solution of acetal **57** (7.6 mg, 30 mmol) in toluene (50 mL) at -78 ^{o}C, was added DIBAL-H (12 mL, 30 mmol, 2.5 M) dropwise and warmed to -10 ^{o}C. The reaction mixture was stirred for 15 minutes then immediately quenched with saturated aqueous Rochelles salt (30 mL). The resultant mixture was stirred vigorously until two clear layers were obtained. The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (75 mL), dried over anhyd. Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (silica gel using petroleum ether: EtOAc (7:3) as eluent) to furnish **58** as gum.

Yield: 4.7g, 61%; $\alpha]^{25}_{D}$: + 25.6 (*c* 1.0, $CHCl_3$); **IR** (KBr) 879, 1029, 1215, 1591, 2360, 3018, 3369 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.80-2.00 (m, 2H), 2.64-2.72 (t, *J* = 2.4 Hz, 2H), 3.51-3.57 (m, 2H), 3.70-3.75 (m, 1H), 4.56 (s, 2H), 7.15-7.19 (m, 3H), 7.22-7.33 (m, 7H); **^{13}C NMR (**50 MHz, $CDCl_3$): δ 32.2, 33.2, 65.9, 72.2, 79.6, 126.5, 127.6, 128.2, 128.4, 129.0, 130.8, 138.9, 142.3; **Analysis**: **$C_{17}H_{20}O_2$** requires C, 79.65.28; H, 7.13; found C, 79.65, H, 7.86%.

(*R*)-Ethyl-2-(benzyloxy)-4-phenylbutanoate (59)

To a solution of IBX (6.3 g, 2.5 mmol, 1.5 equiv) in 100 mL of dry DMSO was added a solution of alcohol **58** (3.8 g, 15 mmol) in 20 mL of THF. The resulting mixture was stirred for 3 h at 25 °C. The same amount of IBX was added and the reaction mixture was stirred for an additional 3 h. It was then diluted with 10 mL of water and the white precipitate was filtered rinsed several times with ether. The aqueous phase was extracted with 3x100 mL of ether. The combined organic layers were washed with brine, dried over anhyd. MgSO4, filtered and

concentrated *in vacuo* afforded the crude aldehyde, which was immediately subjected to esterification without purification.

Thus, aldehyde (3.0 g, 12 mmol) was dissolved in the EtOH (100 mL), oxone (11.0 g, 18 mmol) was added and stirred at 25 ^{o}C for 18 h. After completion of the reaction (monitored by TLC), 1N HCl (25 mL) was added to dissolve the salts and EtOAc was added to extract the products. The organic extract was again washed with 1N HCl and brine, dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product, which was purified by column chromatography (silica gel using pet. ether: EtOAc 8:2) to afford the pure product **59** (2.6 g) as a colourless liquid.

Yield: 2.6 g, 72%; **[α]$^{25}_{D}$**: -1.72 (c 2.5, $CHCl_3$); **IR** (KBr) 769, 1215, 1373, 1417, 1514, 1730, 2358, 2401, 2927, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27-1.31 (t, *J* = 7.2 Hz, 3H), 1.89- 2.21 (m, 2H), 2.69-2.77 (t, *J* = 6.3 Hz, 2H) 3.57-3.80 (m, 1H), 4.15-4.18 (m, 2H), 4.61 (s, 2H), 7.21-7.39 (m, 10H); **^{13}C NMR (**50 MHz, $CDCl_3$): δ 14.1, 29.7, 32.6, 61.0, 71.6, 72.8, 126.9, 127.6, 127.8, 128.4, 128.5, 130.1, 138.3, 141.7, 172.2; **Analysis**: **$C_{19}H_{22}O_3$** requires C, 76.48; H, 7.43 found C, 76.41; H, 7.42%.

Ethyl-(*R*)-2-hydroxy-4-phenylbutanoate (50)

To a solution of hydroxy ester **59** (2.3 g, 8.0 mmol) in EtOH (25 mL) was added 10% Pd/C (119 mg) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm) for 36 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness to get the hydroxyester **50,** which was purified by column chromatography with neutral Al_2O_3 (pet roleum ether: EtOAc = 90:10) to afford pure hydroxy ester **50** as yellow oil

Yield: 1.5 g, 90%; **$[\alpha]_D^{25}$** -19.8 (*c* 1, $CHCl_3$) { lit.[32] $[\alpha]^{25}_D$ -20.8 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$): 789, 909, 1099, 1218, 1248, 1455, 1496, 1603, 1731, 2252, 3086, 3515 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25-1.32 (t, *J* = 7.3 Hz, 3H), 1.90-2.13 (m, 2H), 2.72-2.79 (t, *J* = 6.4 Hz, 2H), 4.12-4.16 (m, 1H), 4.19-4.26 (q, *J* = 7.3 Hz, 2H), 7.17-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 30.9, 35.9, 61.5, 69.5, 125.9, 128.3, 128.4, 141.0, 175.0; **Analysis**: **$C_{12}H_{16}O_3$** requires C, 69.21; H, 7.74; found C, 69.20; H, 7.79%.

Diethyl 1-[*N*-[1(S)-carboxy-3-phenylpropyl]-L-alanyl]-L-proline diester (60)

To a solution of dry THF containing PPh_3 (1.6 g, 6 mmol), hydroxy ester **50** (833 mg, 4 mmol) and amine **49** (857 mg, 4 mmol) was added DIAD (1.2 g, 6 mmol) dropwise, under nitrogen at 0 ^oC. The reaction mixture was stirred for 2 h at room temperature. After completion of reaction (monitored by TLC), it was concentrated to near dryness and the residue was dissolved in EtOAc (100 mL), washed with $NaHCO_3$ solution and brine, and dried with anhyd. Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by flash chromatography on a column of silica gel eluting with CH_2Cl_2/MeOH (1:1) to afford the diester **60**.

Yield: 906 mg, 56%; **mp** 110 ºC ; **$[\alpha]^{25}_D$**: -38.10 (*c* 1.1, MeOH); **IR** (KBr): 668, 762, 909, 1098, 1216, 1271, 1454, 1663, 1724, 2930, 3677 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29-1.47 (m, 9H), 1.52-1.65 (m, 2H), 1.90-2.02 (m, 4H), 2.72-2.79 (t, *J* = 9.2 Hz, 2H), 3.48-3.83 (m, 4H), 4.12-4.30 (m, 5H), 7.15-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ; 14.0, 18.2, 24.0, 29.6, 32.7, 35.9, 47.9, 53.4, 57.6, 59.09, 61.04, 125.4, 127.6, 127.9, 139.5, 166.7, 172.9, 174.5; **Analysis**: **$C_{22}H_{32}O_5$** requires C, 65.32; H, 7.97; N, 6.93 found C, 65.34; H, 7.91; N, 6.96%

1-[*N*-[1(S)-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline (38)

To a stirred solution of diester **60** (606.7 mg, 1.5 mmol) in THF (20 mL) and MeOH (5 mL) was added LiOH (107.8 mg, 4.5 mmol, 3 equiv) at 0 °C. The reaction mixture was allowed to warm to 25 ^{o}C, and, after 20 h, diluted with diethyl ether (100 mL) and washed with water (50 mL) and brine (50 mL). The combined aqueous layers were washed with diethyl ether (50 mL) and the combined organic extracts were dried anhyd. Na_2SO_4, filtered and concentrated. Purified by column chromatography (silica gel using $CHCl_3$: MeOH 8:2) to afford the pure product **36** (2.6 g) as a colourless liquid.

Yield: 282 mg, 54%; colorless solid; **mp** 147 ºC ; lit.[27] mp 149-151 ºC; **$[\alpha]_D^{25}$** -45.93 (*c* 2, MeOH) { lit.[27] $[\alpha]^{25}_D$ -53.5 (*c* 2, MeOH)}; **IR** (KBr)**:** 757, 1022, 1145, 1307, 1373, 1404, 1730, 1735, 2349, 2977, 3020, 3498 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3/CD_3CN$): δ 1.32-1.47 (m, 3H), 1.50-1.65 (m, 2H), 1.90-1.95 (m, 4H), 2.72-2.80 (t, *J* = 8.9 Hz, 2H), 3.43-3.81 (m, 4H), 4.22-4.33 (m, 1H), 7.24-7.30 (m, 5H) ; **^{13}C NMR** (50 MHz, $CDCl_3/CD_3CN$): δ 18.9, 24.7, 30.03, 33.4, 36.6, 48.5, 53.2, 57.6, 60.62, 126.1, 128.3, 128.6, 140.1, 167.4, 179.4, 179.9; **Analysis**: **$C_{18}H_{24}N_2O_5$** requires C, 62.05; H, 6.94; N, 8.04 found C, 62.06; H, 6.91; N, 8.03%.

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CHAPTER 2

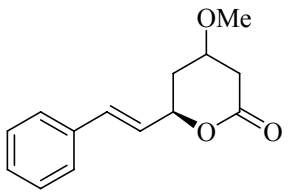
Asymmetric Synthesis of (S)-Dihydrokavain and (S)-Vigabatrin® via Stereoselective Opening of Epoxide with Dimethylsulfonium Methylide

Section I:

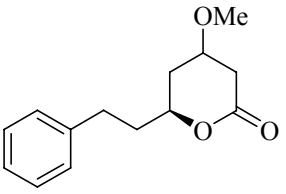
Asymmetric Synthesis of Dihydrokavain

2.1.1 Introduction

(*S*)-7,8-Dihydrokavain (**1**) was isolated from the kava plant. Kava[1-10] is a perennial pepper plant found in the Oceanic Islands of the South Pacific. Kava root is the source of perhaps the most important traditional beverage for many South Pacific Island people. Aqueous extracts of kava roots have been consumed over the past 2000 years without serious effects on health.



1
(+)-kavain



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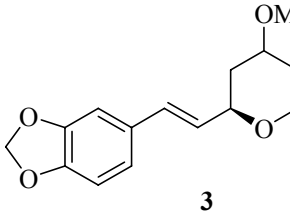
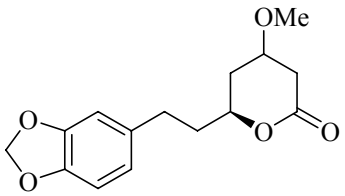


3
(+)-methysticin



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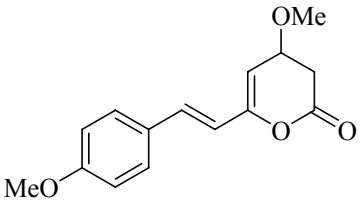
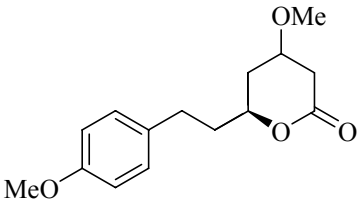
(+)-7,8-dihydromethysticin



5
yangonin



6
(+)-5,6,7,8-terahydroyangonin

Fig. 1. Representative kava lactones from *Pipermethysticum*

Historically, kava has been a popular remedy due to its anxiolytic properties. Many pharmaceutical products prepared from the lipophilic extracts have been widely available as non-prescriptive botanical dietary supplements. The psycho active principals are a family of 15-pyrone derivatives known as the kavalactones

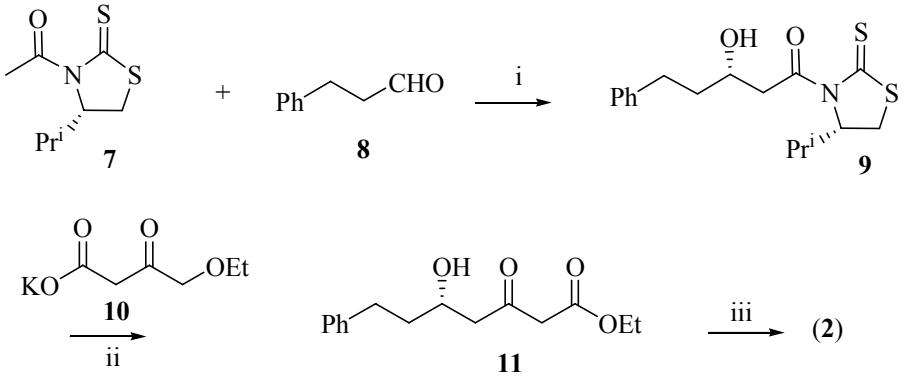
(**Fig. 1**) that comprise roughly 15% of the dried root stock. The more prevalent of these include kavain (**1**), dihydrokavain (**2**) and methysticin (**3**). Structurally, the kava lactones differ chiefly with respect to their arene substitution patterns and the presence or absence of double bonds along their carbon backbones. Although a few of the kavalactones, such as yangonin (**5**), are achiral, the majority have a single stereogenic center at C_6.

2.1.2 Literature Survey

Several asymmetric syntheses of (*S*)-7,8-dihydrokavain **(2)** have been reported, which include (i) aldol reaction using chiral auxillary (ii) stereospecific synthesis from chiral building blocks and (iii) Cosford cross-coupling. These methods are described below.

Smith's approach (2004)[11]

Smith *et al*. have used Evan's aldol approach as the key reaction for the synthesis of (*S*)-dihydrokavain **2**.



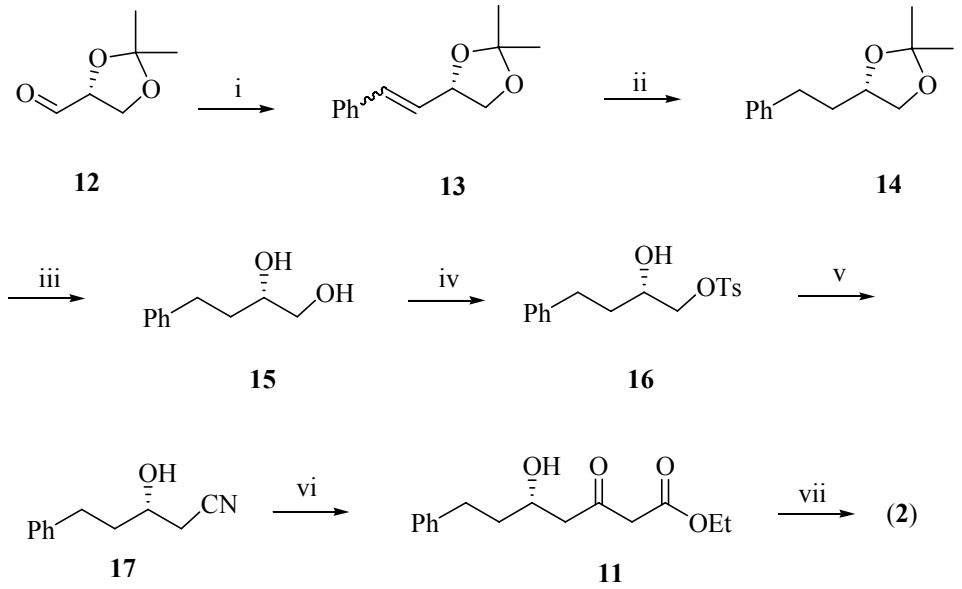
Scheme 1: Reagents and conditions: (i) $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, -78 ^oC, 84%. (ii) $MgCl_2$, imid, THF, 25 ^oC, 89%. (iii) a. K_2CO_3, MeOH. b. $(CH_3)_3SO_4$, acetone, 75%.

The titanium enolate of valine-derived *N*-acetyl thiazolidinethione (**7)** was reacted with 3-phenylpropanal (**8)** to give aldol adduct **9** which on treatment with the potassium salt of mono ethyl malonate **10** and $MgCl_2$ in the presence of imidazole

gave ketoester **11.** Lactonisation of ketoester **11** was smoothly accomplished under basic conditions (K_2CO_3, MeOH) followed by the methylation of its enol with dimethyl sulfate afforded dihydrokavain **2** in 75 % yield (**Scheme 1**).

Yue's approach (2005)[12]

The synthesis of (+)-dihydrokavain (**2**) is shown in **Scheme 2**.The chiral aldehyde **12**, obtained from d- mannitol was subjected to Wittig reaction to give olefin **13** in 80% yield which on hydrogenation (10% Pd/C, H_2) afforded protected diol **14** in 98% yield.



12 **13** **14**

15 **16**

17 **11**

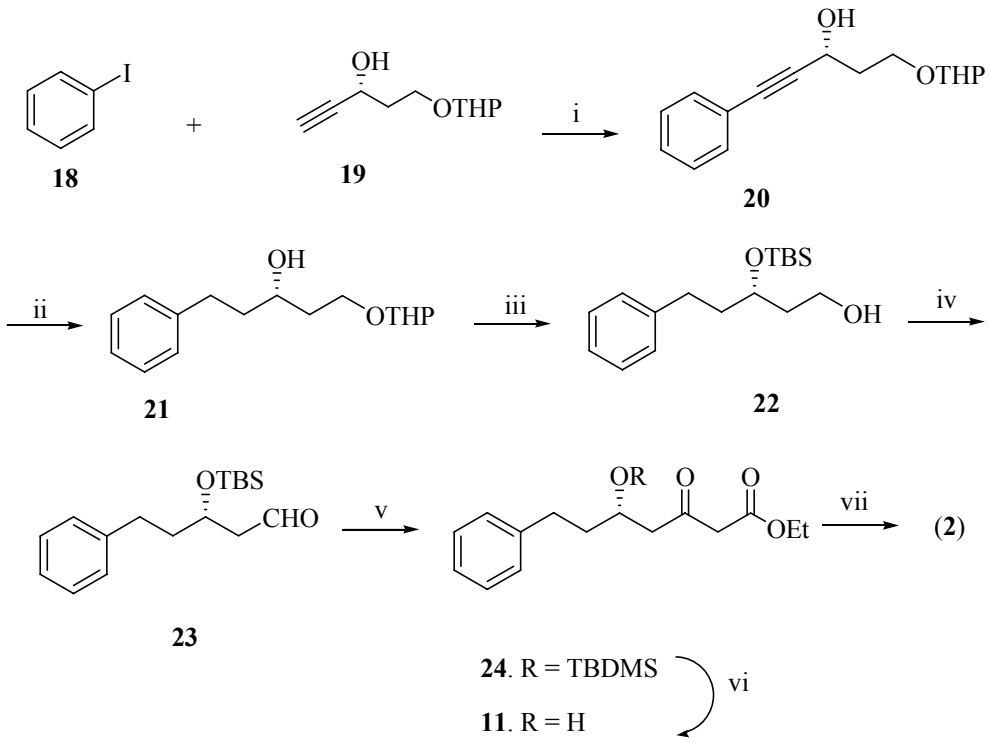
Scheme 2: Reagents and conditions: (i) [$PhCH_2Ph_3P$], nBuLi, THF, 80%. (ii) H_2, Pd/C, MeOH, 98%. (iii) 2M HCl, MeOH, 97%. (iv) TsCl, pyridine, CH_2Cl_2, 75% (v) KCN, DMF, 12 h, 89 % (vi) a. $BrCH_2CO_2Me$, Zn, ultra sound, THF, 69%, *p*TSA, CH_2Cl_2, 84% b. Me_2SO_4, K_2CO_3, acetone, 86%.

Hydrolysis of acetonide **14** furnished diol **15** in 97% yield followed by selective tosylation (TsCl, pyridine) gave tosylate **16** in 75% yield. Reaction of tosylate **16** with KCN in a mixture of EtOH and H_2O (3:2) at room temperature gave nitrile **17** which was subsequently subjected to sonochemical Blaise reaction with $BrCH_2CO_2Me$ in THF in the presence of activated Zn powder to furnish δ-hydroxy-β-oxo ester **11.** Lactonisation of ketoester **11** was smoothly accomplished

under acidic conditions (pTSA, CH_2Cl_2) followed by the methylation of its enol with dimethyl sulfate afforded dihydrokavain **2** in 86% yield.

Yadav's approach (2007)[13]

Yadav *et al* have made use of Cosford cross-coupling as a key step for the synthesis of dihydrokavain. Thus, coupling of iodobenzene with acetylenic alcohol **19,** gave the key intermediate **20** which was reduced (10% Pd/C, H_2) to saturated alcohol **21** in 90% yield.



18 19 20 21 22 23

Scheme 3: Reagents and conditions: (i) Pd/C, CuI, Ph_3P, K_2CO_3, H_2O/DME, 80 ^oC, 2 h, 90%, (ii)H_2, Pd/C, EtOH, 90% (iii) a.TBSCl, Imd, CH_2Cl_2, 0 ^oC, 95%, b. PPTS, MeOH, 90%, (iv) IBX, DMSO, 90% (v) $SnCl_2$, N_2CHCO_2Et, 80% (vi) TBAF, THF, 85% (vii) a. K_2CO_3, MeOH. b. $(CH_3)_3SO_4$, acetone, 75%.

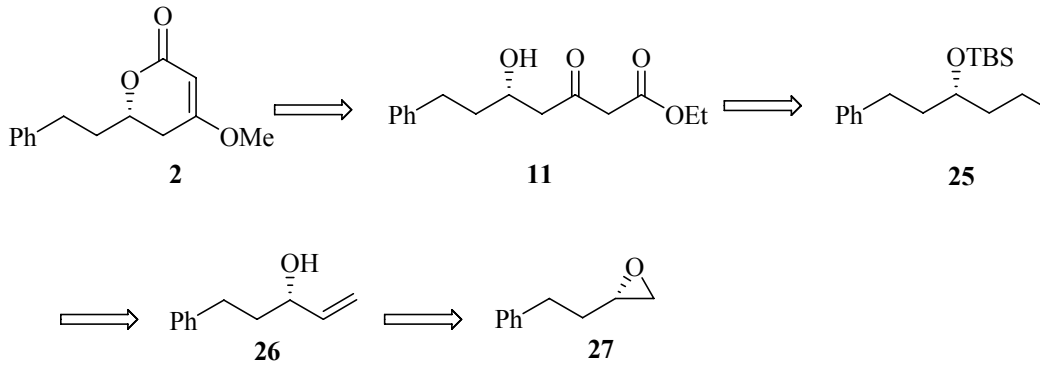
The secondary hydroxy group was protected (TBSCl, imidazole) and subsequent deprotection of THP group was done using PPTS in MeOH to give primary alcohol **22.** The primary alcohol on oxidation (IBX) gave aldehyde **23** in 90% yield which was converted into δ-hydroxy-β-oxo ester **11,** followed by its

lactonisation under basic conditions (K_2CO_3, MeOH) and methylation of its enol with dimethyl sulfate afforded dihydrokavain in 75 % yield (**Scheme 3**).

2.1.3 Present Work

2.1.3.1 Objective

So far, the methods described in the literature for the synthesis of dihydrokavain (**2**) make use of chiral starting materials (chiral pool approaches). However, enantioselective catalytic synthesis of (*S*)-dihydrokavain **(2)** has not been reported and is highly desirable. Retrosynthetic analysis of **2** shows that synthesis of (*S*)-dihydrokavain could be achieved by employing reactions such as HKR of racemic epoxide **40** coupled with regiospecific ring opening of chiral epoxide **27** with dimethylsulfonium methylide constituting the key steps.

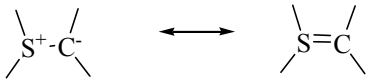


Scheme 4: Retrosynthetic analysis for (S)-dihydrokavain

Thus, dihydrokavain (**2**) could be accessible by the lactonization of δ-hydroxy-β-oxo ester **11,** which could be readily obtained from protected diol **25** by simple group transformations. The diol **25** could be obtained from allyl alcohol **26,** which in turn could be obtained from regioselective opening of epoxide **27** with dimethylsulfonium methylide.

2.1.3.2 Chemistry of sulfur ylides

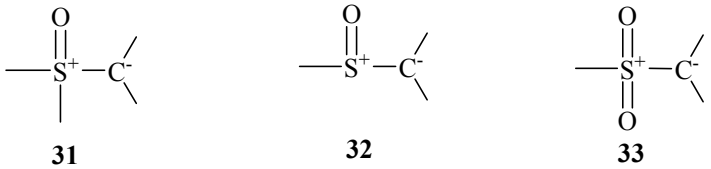
The chemistry of ylides attracted considerable interest in the early 1950s after Wittig has discovered the reaction of phosphonium ylides with carbonyl compounds giving rise to alkenes. Investigations carried out by Corey and Franzen extended the Wittig reaction to sulfur ylides and initiated extensive studies of sulfonium ylides.[15] The further development of the chemistry of these compounds demonstrated that they could be widely used in organic synthesis. Sulfur ylides contain a negatively charged carbon atom directly bound to a positively charged sulfur atom. In the general form, these compounds can be represented by two resonance structures, **viz**., ylide **29** and ylene **30** (**Scheme 5**).



29 ylide ⟷ **30** ylene

Scheme 5: Resonance structures of sulfonium ylides

Sulfonium (**29**) and sulfoxonium (**31**) ylides containing two organic substituents at the sulfur atoms are most often used in organic synthesis. Sulfinyl ylides (**32**), sulfonyl ylides (**33**), thiocarbonyl ylides (**34**) and iminosulfuranes (**35**) are also well known. Sulfur ylides act as nucleophilic reagents, their reactivities being inversely proportional to their stability.

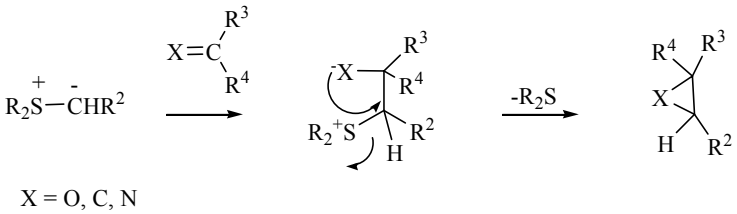


31 **32** **33**

34 **35**

Fig 2: Commonly used sulfur ylides

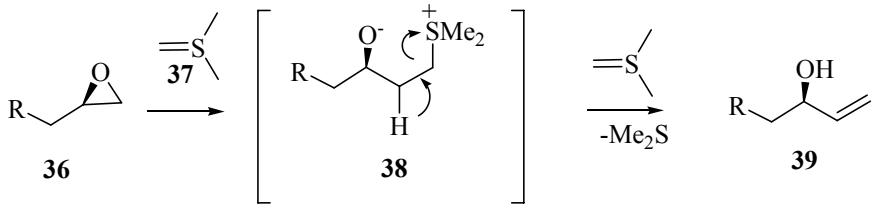
Ylides are stabilized through the electron density delocalisation under the action of electron-withdrawing substituents at the carbanionic centre. The reactions of sulfur ylides with compounds containing C=X bonds (X=O, C or N) gained wide acceptance in organic synthesis. These reactions proceed as the nucleophilic addition followed by 1,3-elimination of a sulfur-containing group to form epoxide, cyclopropane or aziridine, respectively (**Scheme 6**).[16]



Scheme 6: Nucleophilic addition of sulfur ylides

Due to their zwitterionic character, sulfonium ylides are also widely used in rearrangements generating new C-C bonds (often with high stereo- and regioselectivity).

Terminal, allylic and benzylic epoxides are smoothly converted directly to one carbon homologated allylic alcohols in good yields when treated with excess of dimethylsulfonium methylide.[17, 18] In these cases, reaction appears as an interesting stereochemical alternative to the less selective addition of vinyl Grignard to a carbonyl (**Scheme 7**).



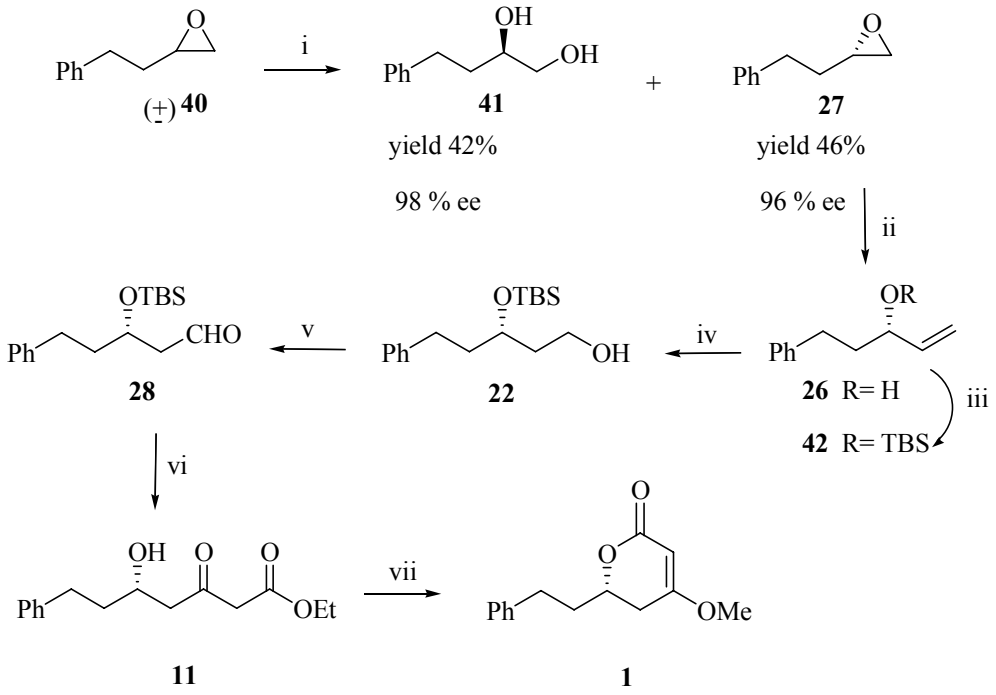
Scheme 7: Stereoselective opening of epoxide with dimethylsulfonium methylide

In the last decade, interest in sulfur ylides was quickened owing to their successful use in asymmetric synthesis. A one-stage procedure, which has been developed

recently for the synthesis of optically active epoxides and aziridines, represent a considerable achievement in this field.

2.1.4 Results and Discussions

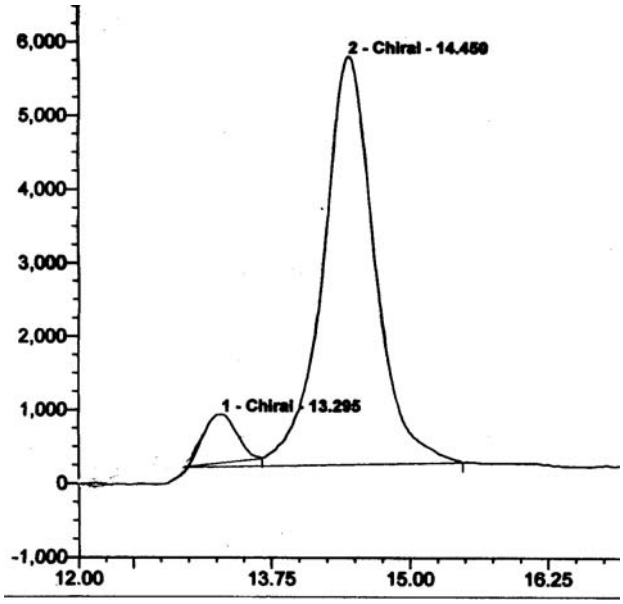
The present synthetic route employed for the synthesis of (*S*)-dihydrokavain (**2**) was synthesized by employing hydrolytic kinetic resolution (HKR) of racemic epoxide **40**



Scheme 8: Reagents and conditions: (i) (*S,S*)-Co(III)-salen.OAc (0.1mol %), H_2O, 25 °C; (ii) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, -10 °C 82%; (iii) TBSCl, Imd, CH_2Cl_2, 97%; (iv) a. $Me_2S.BH_3$, THF b. 3N NaOH, 30% H_2O_2, 73%; (v) IBX, DMSO, 0 °C, 96%; (vi) $BF_3.OEt_2$, N_2CHCO_2Et, CH_2Cl_2, -10 °C, 77%; (vii) a. K_2CO_3, MeOH; b. $(CH_3)_2SO_4$, acetone, 81%.

(**Scheme 8**). Thus, Hydrolytic Kinetic Resolution of recemic epoxide **40** was carried out using catalytic amount of (*S,S)*-salen-Co(III)OAc complex to obtain chiral epoxide **27** in 46% yield and 96% ee (enantiomeric excess was determined by chiral HPLC analysis; Chiracel OD-H, **Fig.2**) and chiral diol **41** in 42% yield and 98% ee. The formation of epoxide **27** was confirmed by the appearance of multiplets at δ 2.48 and 2.94 due to methylene and methine protons respectively in

its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 47.0 and 51.5 due to the two carbons (**C**H_2 and **C**H) of epoxy ring.



Peak No.	R.T (min)	Area (μAU*s)	Area (%)
1	13.295	60.379	1.95
2	14.450	3036.763	98.05

Fig 2: HPLC chromatogram of epoxide 27

Regiospecific opening of epoxide **27** with dimethylsulfonium methylide generated *in situ* by treating $(CH_3)_3S^+I^-$ with *n*-BuLi gave allyl alcohol **26** in 82% yield. The ^{1}H NMR spectrum of **26** displayed signals at δ 5.09 (m) and 5.80 (m) corresponding to the olefinic protons. Its ^{13}C NMR spectrum showed peaks at δ 114.8 and 141.8 and 72.3 corresponding to olefinic and methine carbons respectively (**Fig. 2**). The alcohol **26** was protected (TBSCl, imidazole) to give the corresponding silyl ether **42** in 90% yield. The appearance of signals at δ 0.00 (s) and 0.85 (s) in the ^{1}H NMR spectrum of **42** confirms the TBS protection. Its ^{13}C NMR spectrum showed signals at δ -4.7 and 18.3 corresponding to the methyl and quaternary carbons in the silyl protecting group respectively. The TBS protected allyl alcohol **42** was subjected to hydroboration-oxidation ($Me_2S.BH_3$, 3N NaOH and 30% H_2O_2) to give the TBS protected diol **25** in 73% yield. The ^{1}H NMR spectrum of alcohol **25** displayed signals at δ 3.64 (m) and 3.88 (m) corresponding

to the methylene and methine protons. Its ^{13}C NMR spectrum showed a typical signal at δ 60.0 corresponding to the methylene carbon (**C**H_2OH) adjacent to OH group (**Fig. 4**).

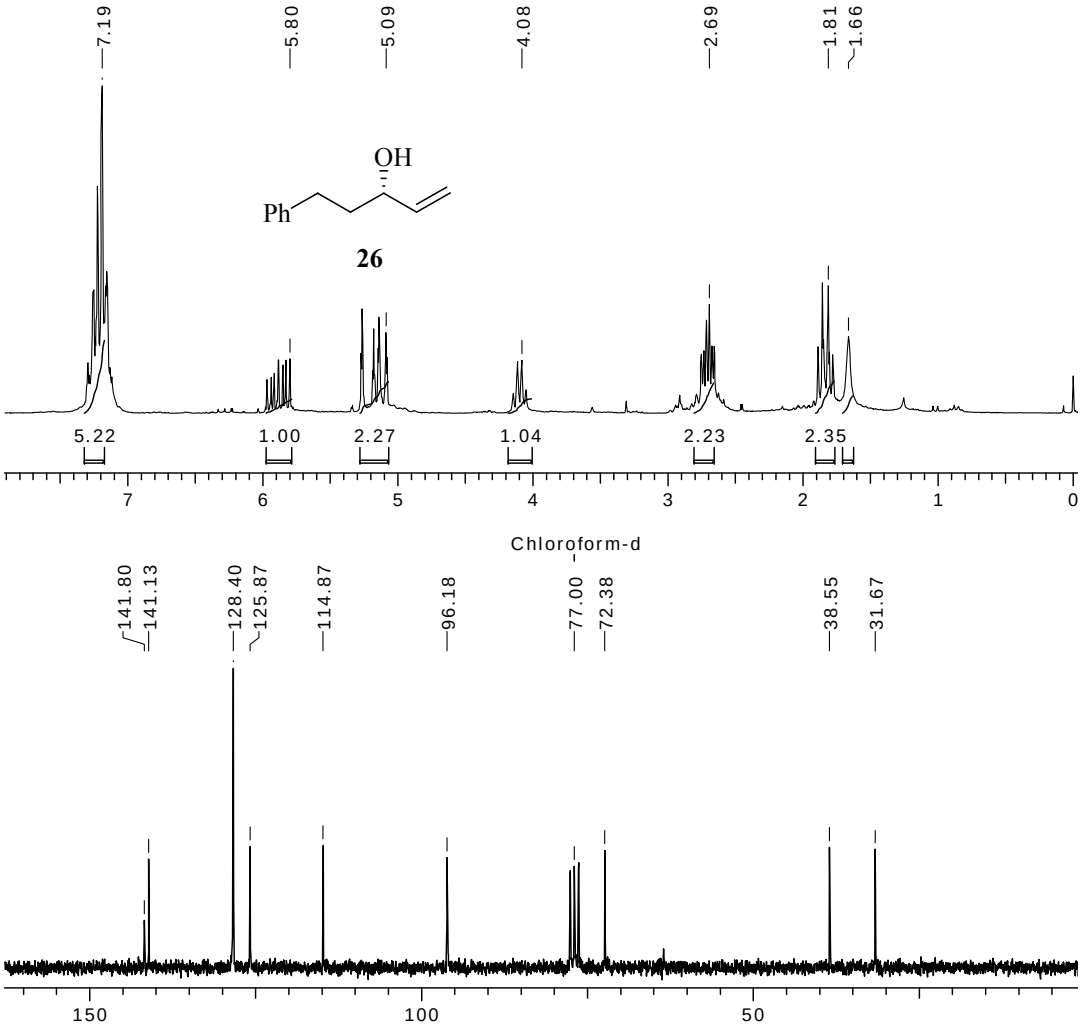


Fig 3: ^{1}H and ^{13}C NMR of (*S*)-5-phenylpent-1-en-3-ol (26)

The alcohol **25** was oxidized using IBX in DMSO at 25 ^{o}C to afford the corresponding aldehyde **28** in 96% yield. The ^{1}H NMR spectrum of aldehyde **28** displayed a characteristic signal at δ 9.71 corresponding to the aldehydic proton**.** Its ^{13}C NMR spectrum showed a typical signal at δ 201.2 corresponding to carbonyl carbon of

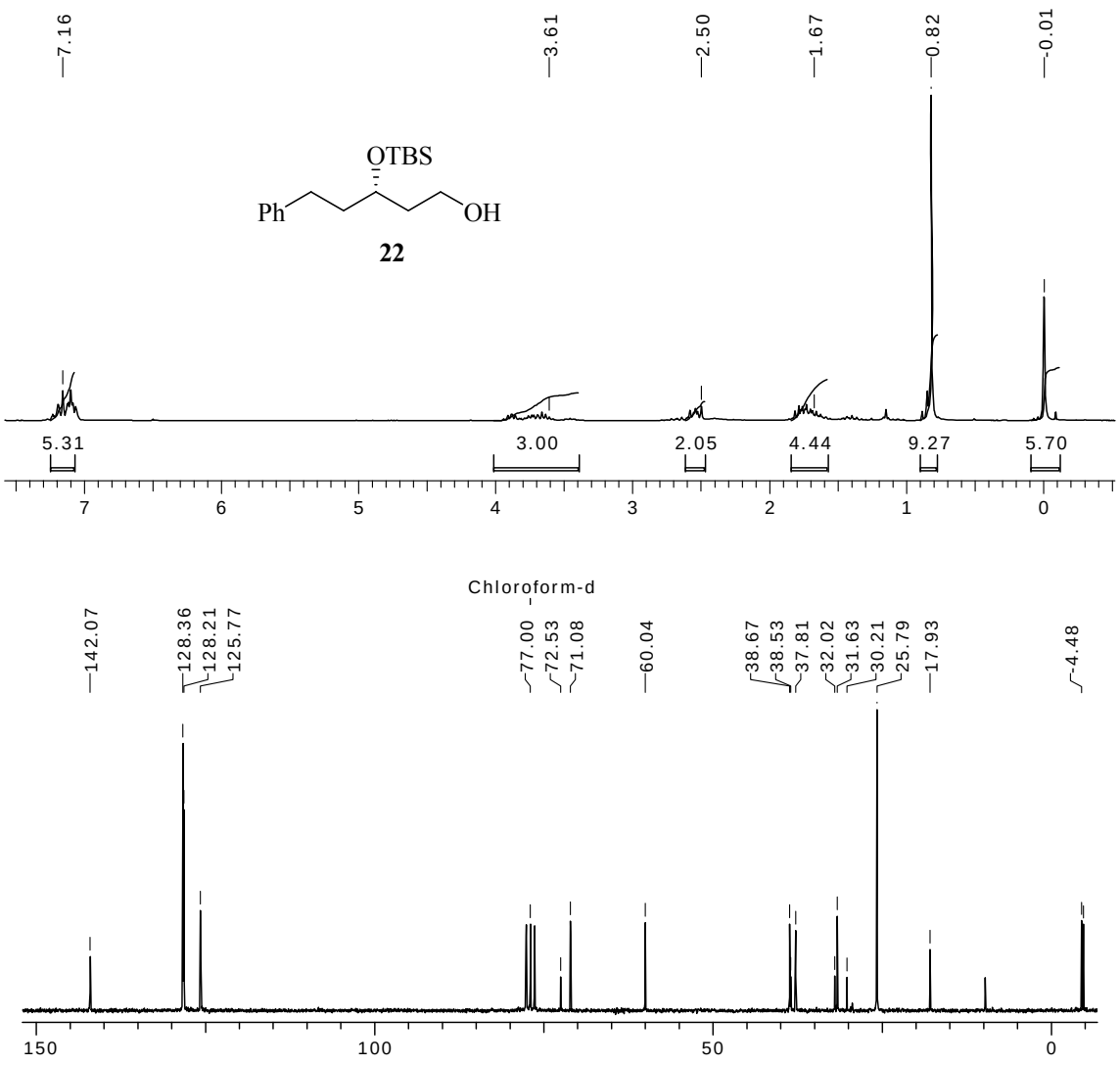


Fig 4: ^{1}H and ^{13}C NMR spectra of ((*S*))-5-phenylpent-1-ol-3-yloxy)(*tert*-butyl)dimethylsilane (25)

aldehyde **28**. Moreover, a strong band at 1718 cm^{-1} (C = O streching) in its IR spectrum confirms the aldehyde group. Treatment of aldehyde **27** with ethyl diazoacetate in the presence of $BF_3.Et_2O$ gave *β*-keto ester **11**. During this reaction, we observed that silyl group in **28** was simultaneously deprotected resulting in *δ*-hydroxy *β*-keto ester **11** in 77% overall yield. The formation of *δ*-hydroxy *β*-keto ester **11** was confirmed by the appearance of a signal at δ 3.46 (s) due to active methylene proton. Its ^{13}C NMR spectrum showed signals at δ 203.2 and 166.6 due to ketone and ester groups. Its IR absorptions at 1712 and 1735 cm^{-1} confirms the presence of ketone and ester groups respectively (**Fig. 5**).

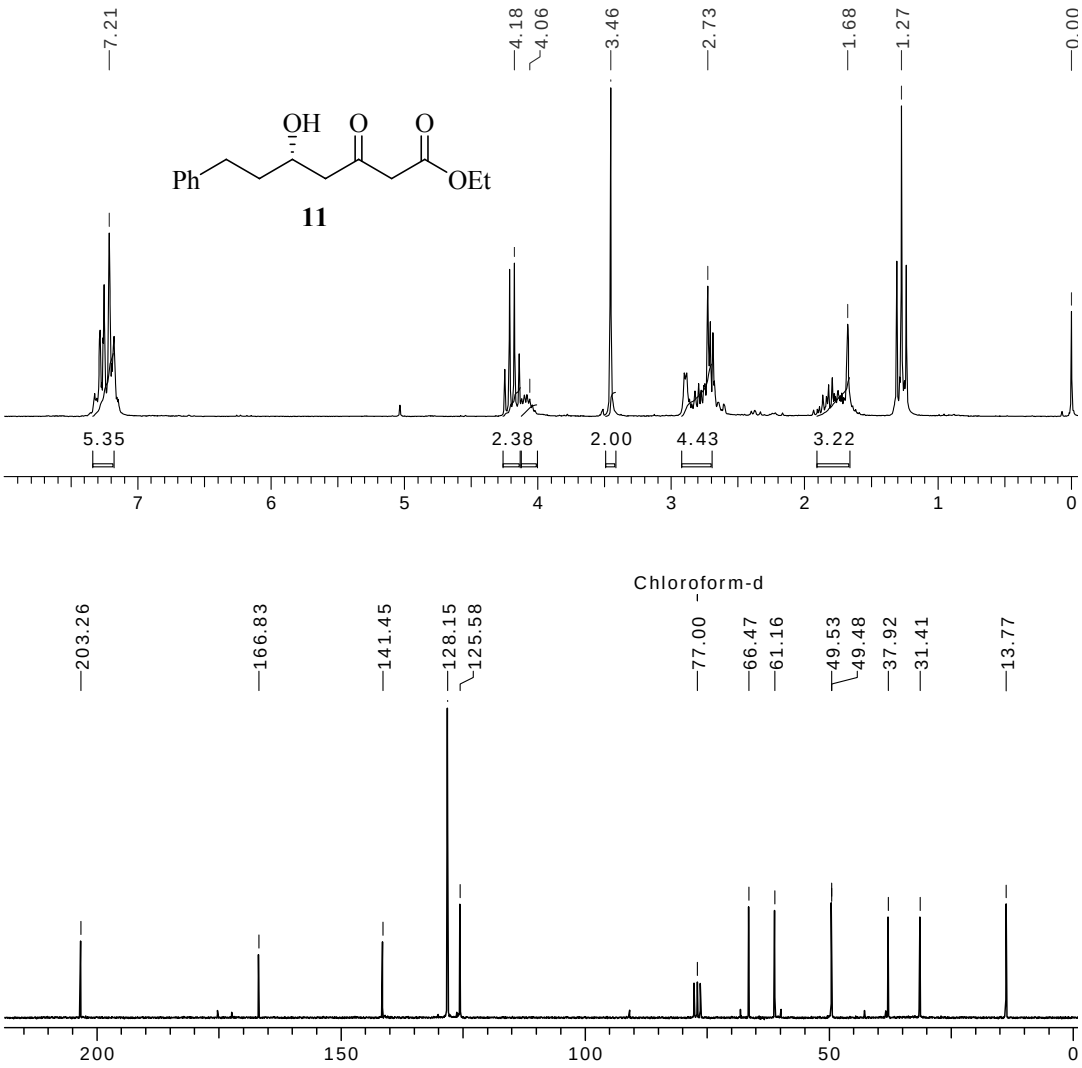


Fig 5: ^{1}H and ^{13}C NMR spectra of (*S*)-ethyl-5-hydroxy-3-oxo-7-phenylheptanoate (11)

Lactonisation of **11** followed by the methylation of its enol with dimethyl sulfate were smoothly accomplished under basic conditions (K_2CO_3, MeOH) to produce (*S*)-dihydrokavain **2** in 81% yield and 94% ee. The ee of dihydrokavain **2** was based on comparison of its optical rotation $[\alpha]^{25}_{D}$ + 29.5 (*c* 1, MeOH) with that reported value {lit.[11] $[\alpha]^{25}_{D}$ + 31.1 (*c* 1, MeOH). The spectral data obtained for dihydrokavain (**2**) were in full agreement with the values reported in the literature.[11, 12]

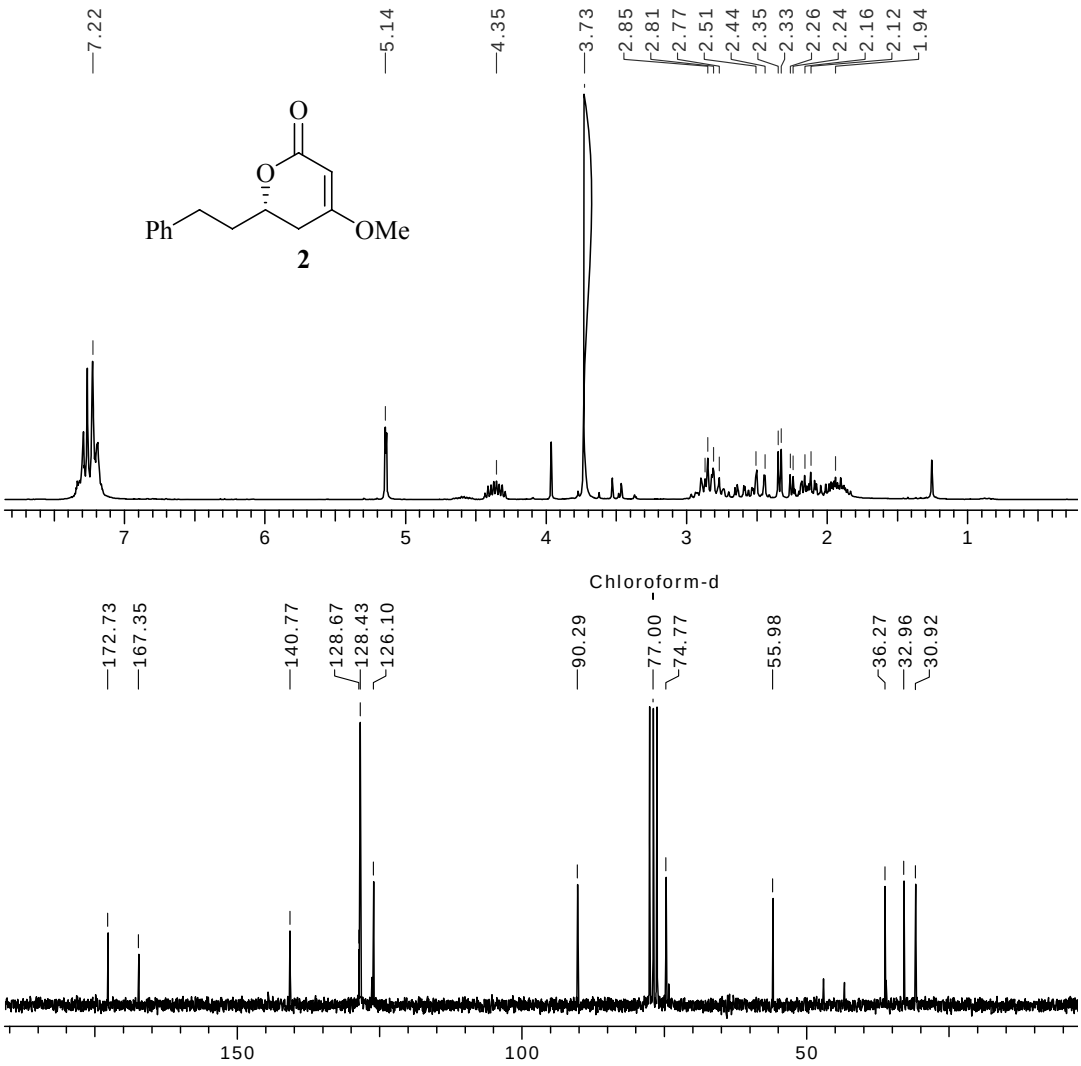


Fig 6: ^{1}H and ^{13}C NMR spectra of dihydokavain (2)

2.1.5 Conclusion

In conclusion, we have achieved the synthesis of dihydrokavain (**2**), *via*, hydrolytic kinetic resolution and regiospecific opening of epoxide **27** with dimethylsulfonium methylide. The reactions are rapid and require a relatively low amount of less expensive Co-salen as catalyst, which is available in both enantiomeric forms. The merit of the synthesis is that (*S*)-dihydrokavain **2** has been obtained with high enantioselectivity (94% ee) and in good overall yield.

2.1.6 Experimental Section

(*S*)-2-Phenethyloxirane (27)

A 100 mL flask was charged with (*S,S*)-Co-salen (452 mg, 0.75 mmol, 0.5 mol%), which was dissolved in 5 mL toluene followed by the addition of AcOH (280 μL, 5 mmol). The entire solution was allowed to stir at 25 ^{o}C open to air for 30 min over which the color of the catalyst changed from orange-red to a dark brown. The solution was concentrated *in vacuo* to leave a crude brown solid. The resulting residue was dissolved in epoxide **40** (22.23 g, 150 mmol) followed by the drop-wise addition of water (1.49 mL, 82.5 mmol, 0.55 equiv) over 5 min at 0 °C. The reaction was allowed to warm to 25 ^{o}C and stirred for 14 h. After completion of the reaction (as monitored by TLC), it was diluted with CH_2Cl_2 and extracted (3 X 100 mL) and concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (silica gel using pet.ether: EtOAc 9:1 as eluent) to furnish **27**.

Yield: 10.22 g**,** 46%**;** colorless liquid; **$[\alpha]^{25}_{D}$**: -4.65 (*c* 1, $CHCl_3$); **IR** (KBr): 821, 1035, 1247, 1514, 1614, 2339, 2856 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.84-1.88 (m, 2H), 2.46-2.50 (m, 1H), 2.73-2.81 (m, 4H), 7.19-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.3, 34.3, 47.0, 51.5, 126.0, 128.3, 128.4, 141.1; **Analysis**: $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found C, 81.07; H, 8.13%.

(*S*)- 5-Phenylpent-1-en 3-ol (26)

To a stirred suspension of trimethylsulfonium iodide (22.45 g, 110 mmol,) in dry THF (150 mL) was added *n*-BuLi (2 equiv, 110 mmol, 68.75 mL of 1.6 M hexane solution) at -10 ^{o}C. After 30 min, chiral epoxide **27** (8.1 g, 55 mmol) in dry THF (30 mL) was introduced drop-wise and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 X 100 mL). The combined extracts were washed with brine, dried over anhyd.

Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel using pet ether: EtOAc = 90:10 as eluent) to give allyl alcohol **26.**

Yield: 7.3g, 82%; colorless oil; **$[\alpha]^{25}_D$**: -8.56 (*c* 1.5, $CHCl_3$); **IR** (KBr): 756, 1215, 1404, 2345, 2306, 2401, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2H), 2.66-2.75 (m, 2H), 4.05-4.14 (m, 1H), 5.08-5.27 (m, 2H), 5.80-5.92 (m, 1H), 7.15-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.6, 38.5, 72.3, 114.8, 125.8, 128.4, 128.4, 141.1, 141.8; **Analysis**: $C_{11}H_{14}O$ requires C, 81.44; H, 8.69; found C, 81.41; H, 8.73 %.

((*S*)-5-Phenylpent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (42)

To a stirred solution of allyl alcohol **26** (6.5 g, 40 mmol) in dry CH_2Cl_2 (75 mL) was added imidazole (4.08 g, 60 mmol, 1.5 equiv.) at 0 ºC. After stirring for 10 min., TBDMSCl (9.04 g, 60 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of reaction (as monitored by TLC), it was poured into water and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give **42.**

Yield: 10.73g, 97%; colorless oil; **$[\alpha]^{25}_D$**: - 7.6 (*c* 1, $CHCl_3$); **IR** (KBr): 759, 837, 1217, 1255, 1417, 1496, 1602, 2403, 2856, 2929, 2954, 3026, 3064 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ –0.02-.0.00 (m, 6H), 0.85 (m, 9H), 1.69-1.80 (m, 2H), 2.54-2.64 (m, 2H), 4.05-4.14 (m, 1H), 4.97-5.16 (m, 2H), 5.73-5.87 (m, 1H), 7.10-7.21 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, 18.3, 25.9, 31.5, 39.8,

73.8, 114.0, 125.6, 128.3, 128.5, 141.4, 142.5; **Analysis**: $C_{17}H_{28}OSi$ requires C, 73.85; H, 10.21; found C, 73.81; H, 10.23 %.

((S)-5-Phenylpentane-1-ol-3-yloxy)(*tert*-butyl)dimethylsilane (25)

To a stirred solution of alcohol **42** (8.3 g , 30 mmol) in 100 mL of dry THF at 0 ^oC was added $BH_3.Me_2S$ (22.59 mL**,** 45 mmol, 2.0 M in THF). The reaction mixture was warmed to 25 ^oC with continued stirring for 4 h. The mixture was re-cooled to 0 ^oC and added 3N NaOH solution (15 mL) followed by the addition of 30% aqueous hydrogen peroxide (15 mL). After 30 min, the solution was again warmed to 25 ^oC and stirred for another 3 h. After completion of the reaction (as monitored by TLC), saturated aqueous Na_2SO_3 (20 mL) was added, and the aqueous layer was extracted with CH_2C1_2 (3 x 40 mL). The combined organic layers were dried over anhyd. Na_2S0_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel with pet ether: EtOAc = 80: 20 as eluent) to give primary alcohol **25**.

Yield: 6.4 g**,** 73%; colorless oil; $[\alpha]^{25}_D$: -26.4 (*c* 1, $CHCl_3$); **IR**(KBr): 757, 1215, 1255, 1996, 1602, 2401, 2856, 2952, 3018, 3409 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ –0.01 (s, 6H), 0.82 (m, 9H), 1.63-1.82 (m, 4H), 2.50-2.58 (m, 2H), 3.61-3.91 (m, 3H), 7.07-7.24 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ; -4.4, 17.9, 25.7, 37.8, 38.6, 60.0, 71.0, 72.5, 125.77, 128.2, 128.3, 142.0: **Analysis**: $C_{17}H_{30}O_2Si$ requires C, 69.33; H, 10.27; found C, 69.34; H, 10.21 %.

((*S*))-5-Phenylpent-1-al-3-yloxy)(*tert*-butyl)dimethylsilane (28)

To a solution of (6.3 g, 22.5 mmol, 1.5 equiv) of IBX in 100 mL of dry DMSO was added a solution of alcohol **25** (4.4 g, 15 mmol) in 20 mL of THF. The

resulting mixture was stirred for 3 h at 25 °C. After completion of the reaction (as monitored by TLC), reaction mixture was diluted with 10 mL of water, and the white precipitate was filtered rinsed several times with ether. The aqueous phase was extracted with ether (3x100 mL). The combined organic layers were washed with brine, dried over anhyd $MgSO_4$, filtered and concentrated *in vacuo*. The crude aldehyde was then purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give aldehyde **28**.

Yield: 4.21 g, colorless oil. 96%; **[α]$^{25}_{D}$**: +3.8 (*c* 1, $CHCl_3$); **IR**(KBr) 790, 909, 1260, 1382, 1403. 1603, 1718, 2252, 2929 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.824 (m, 9H), 1.78-1.89 (m, 2H), 2.52-2.66 (m, 4H), 3.71 (m, 1H), 7.05-7.18 (m, 5H), 9.71 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ; -3.6, 18.2, 25.9, 29.7, 33.2, 63.9, 69.1, 125.7, 128.2, 128.4, 141.7, 201.2; **Analysis**: $C_{17}H_{28}O_2Si$ requires C, 69.81; H, 9.65; found C, 69.89; H, 9.60 %.

(*S*)-Ethyl-5-hydroxy-3-oxo-7-phenylheptanoate (11)

To the stirred solution of $BF_3.OEt_2$ (2.13 g, 1.9 mL, 15 mmol) in dry THF was added ethyl diazoacetate **(**1.7 g, 15 mmol) and aldehyde **28** (2.9 g, 10 mmol) at 0 °C for 4 h. After completion of the reaction (as monitored by TLC), it was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give hydroxyl ester **11.**

Yield: 2.04 g, 77%; colorless oil; **[α]$^{25}_{D}$**: +12.3 (*c* 1, CH_2Cl_2) {lit[11] $[\alpha]^{25}_{D}$: +13.0 (*c* 1, CH_2Cl_2)}; **IR** (KBr): 734, 910, 1712, 1737, 2252, 2856, 2983, 3028, 3548 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24-1.31 (t, *J* = 7.3 Hz, 3H), 1.68-1.86 (m, 3H),

2.68-2.90 (m, 4H), 3.46 (s, 2H), 4.06–4.25 (m, 2H), 7.15-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 31.4, 37.9, 49.4, 49.5, 61.1, 66.4, 125.5, 128.15, 128.16, 41.4, 166.8, 203.2; **Analysis**: $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63; found C, 68.12; H, 7.61 %.

(*S*)-5,6-Dihydro-4-methoxy-6-phenethylpyran-2-one (2)

To a solution of δ-hydroxy-β-ketoester **11** (288 mg, 1.09 mmol) in dry methanol was added anhydrous K_2CO_3 (301 mg, 2.18 mmol) at 25 ^oC and stirred for 2 h. After completion of the reaction (as monitored by TLC), methanol solvent was removed *in vacuo* and was replaced with acetone (3.3 mL). Me_2SO_4 (206 μL, 2.18 mmol) was added to it and the suspension was stirred overnight. The reaction mixture was diluted with EtOAc (20 mL) and was washed with 0.5 M HCl (20 mL). The aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give dihydrokavain **2** as colorless solid**.**

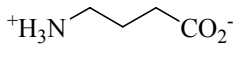
Yield: 210 mg, 83%; colorless solid**; mp**: 57°C {lit.[11] mp: 57.3-58.0}; **$[\alpha]_D^{25}$** +29.0 (*c* 1, MeOH) {lit.[11] **$[\alpha]_D^{25}$** +31.1 (*c* 1, MeOH)}; **IR**(KBr): 730, 910, 1224, 1247, 1396, 1454, 1496, 1625, 1693, 1697, 1703, 2252, 2856, 2941, 3028 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.90-2.12 (m, 1H), 2.16-2.35 (dd, *J* = 17.0, 3.9 Hz, 1H), 2.44-2.51 (dd, *J* = 17.0, 11.9 Hz, 2H), 2.81-2.90 (m, 2H), 3.73 (s, 3H), 4.31-4.41 (m, 1H), 5.14 (s, 1H), 7.19-7.79 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 30.9, 32.9, 36.2, 55.9, 74.7, 90.2, 126.1, 128.4, 128.6, 140.7, 167.3, 172.7; **Analysis**: $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94 ; found C, 72.33; H, 6.93 %

Section II

Asymmetric synthsis of (*S*)-Vigabatrin

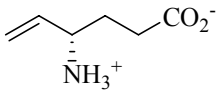
2.2.1 Introduction[19, 20]

The brain and nerves are made up of many nerve cells that communicate with each other through electrical signals. These signals must be carefully regulated for the brain and nerves to function properly. When abnormally rapid and repetitive electrical signals are released in the brain, it becomes over-stimulated and normal function is disturbed. This results in fits or seizures.



43

GABA



44

(*S*)-vigabatrin

4-Aminobutanoic acid (ν-aminobutyric acid, GABA, 1) is an important neurotransmitter in mammalian systems. GABA deficiency has been associated with a variety of neurological disorders including Parkinson's disease, epilepsy and Huntington's chorea. GABA is metabolized by 4-aminobutyrate-2-oxoglutarate aminotransferase (GABA aminotransferase, GABA-T), a mitochondrial enzyme found in synaptic neurons, to succinic semialdehyde. This is further metabolized to succinimide and ν-hydroxybutyrate. Inhibitors of GABA-T are of interest as anticonvulsant agents Treatment of neurological disorders with GABA is severely limited due to the in ability of GABA to efficiently cross the blood-brain barrier (BBB) and the poor synaptic uptake of synthetic GABA. Attempts to circumvent this problem have focused on development of GABA mimics such as baclofen and muscimol, which have had some success. A highly attractive altemative focuses on irreversible inactivation of the enzyme GABA-T, a pyridoxal phosphate-dependent enzyme which operates *via* tautomerism of the Schiff base formed between GABA and pyridoxal phophate. It has been shown

that (*S*)-4-aminohex-5-enoic acid (vinyl GABA, **44**) inactivates GABA-T by selective reaction with the pyridoxal aldehyde moiety. The net result of GABA-T inhibition by **44** (or by other related inhibitors) is an increase in the levels of GABA in the central nervous system (CNS) and the brain. (*S*)-4-Aminohex-5-enoic acid (2) therefore functions as a selective catalytic inhibitor of GABA-T. Vigabatrin® is used to treat epilepsy in those who are not well controlled by or are unable to take other anti-epileptic medicines. It is also used to treat West's syndrome. The biological and pharmacological effects of 4-amino-5-hexenoic acid have been studied extensively. It was found that the biological activity of γ-vinyl GABA is highly dependent upon its absolute configuration. Although racemic vigabatrin is used in clinical practice, (*S*)-γ vinyl GABA is the pharmacologically active enantiomer, whereas (*R*)-γ-vinyl GABA is inactive.

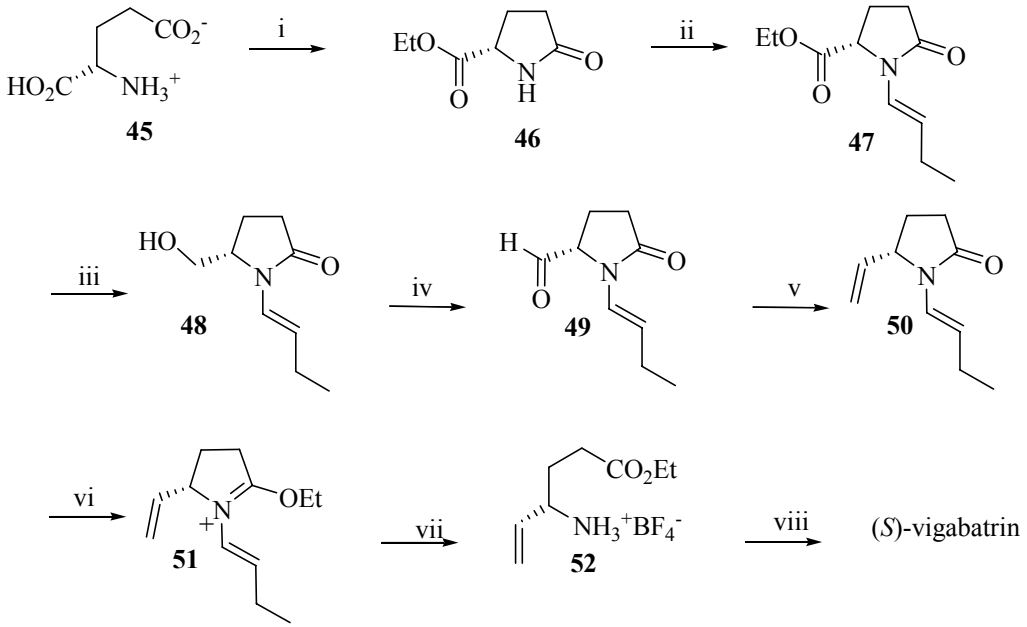
2.2.2 Review of Literature

The literature methods so far known for the synthesis of (*S*)-vigabatrin (**44**) are described below.

Smith's approach (1992)[21]

Smith *el .al*. have used L- glutamic acid (**45**) as a chiral precursor for the synthesis of (*S*)-vigabatrin (**44**). Thus, L- glutamic acid was converted into (*S*)-ethyl pyroglutamate **46** using thionyl chloride and EtOH which on treatment with butanal in the presence of P_2O_5 gave **47** in 83% yield. Reduction ($NaBH_4$) of ester group in **47** produced alcohol **48** in 80% yield followed by oxidation (DMSO:DCC) gave 5-carboxaldehyde derivative, **49** further, olefination of **49** provided 5-ethenyl-l-(l-butenyl)-2-pyrrolidinone, **50,** its treatment with triethyloxonium tetrafluoroborate gave **51** in 97% yield. Subsequent dissolution of

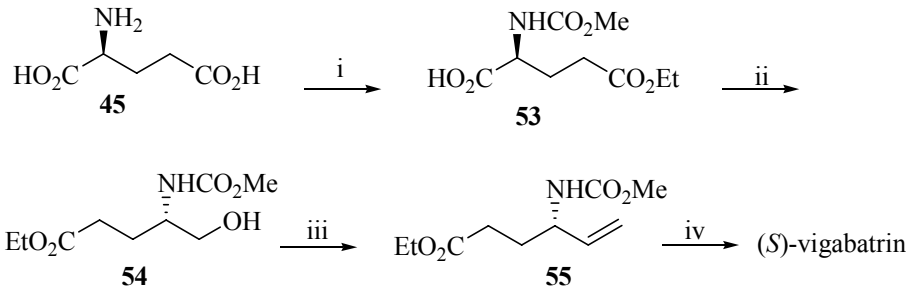
51 in water provided the ethyl ester of vinyl GABA **52** in 87% yield which on saponification yielded 82 % of (*S*)-vigabatrin (**44**).



Scheme 9: Reagents and conditions: (i) $S0Cl_2$, EtOH, 87% (ii) butanal, P_20_5, PhMe, reflux, 83% (iii) $NaBH_4$, EtOH, 0 ^oC - rt, 18 h, 80% (iv) DMSO/DCC, py, cat. TFA, 77% (v) $Ph_3P^+CH_3Br^-$, ^{t}-BuOK, THF, 77% (vi) $Et_3O^+BF^-$, ether; 97%. (vii) H_2O, 25 ^oC, 87%. . (vii) 5% aqueous HCl, 82%.

Knaus approach (1993)[22]

In this approach L-Glutamic acid (**45**) was selectively esterified using concentrated sulfuric acid in EtOH followed by subsequent protection of the amino group (methyl

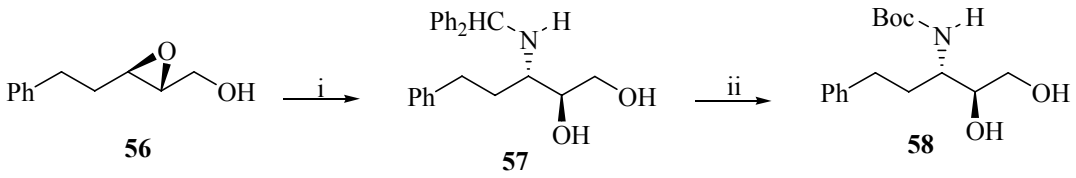


Scheme 10: Reagents and conditions: (i) a. EtOH, H_2SO_4. 93%. b. MeOCOCl. (ii) a. *i*-BuOCOCl, Et_3N b. $NaBH_4$, 73% (iii) ClCOCOCl, DMSO. b. $Ph_3P^+MeBr^-$, TMS_2NNa, 64 % (iv) TMSI, 3N HCl, 89%.

chloroformate) in one pot gave (*S*)-ethyl-*N*-(methoxy carbonyl)glutamate (**53)** in 93% yield. Treatment of **53** with i-BuOCOCl provides mixed anhydride which on reduction with $NaBH_4$ furnished alcohol **54**. Swern oxidation of alcohol **54** and subsequent olefination ($Ph_3P^+Me\ Br^-/TMS_2NNa$) afforded vinyl analog **55** in 64% yield. Removal of amino protective group using TMSI and hydrolysis of the ester group (3N HCl) afforded the target molecule (*S*)-vigabatrin in 89% yield.

Riera's approach (1997)[23]

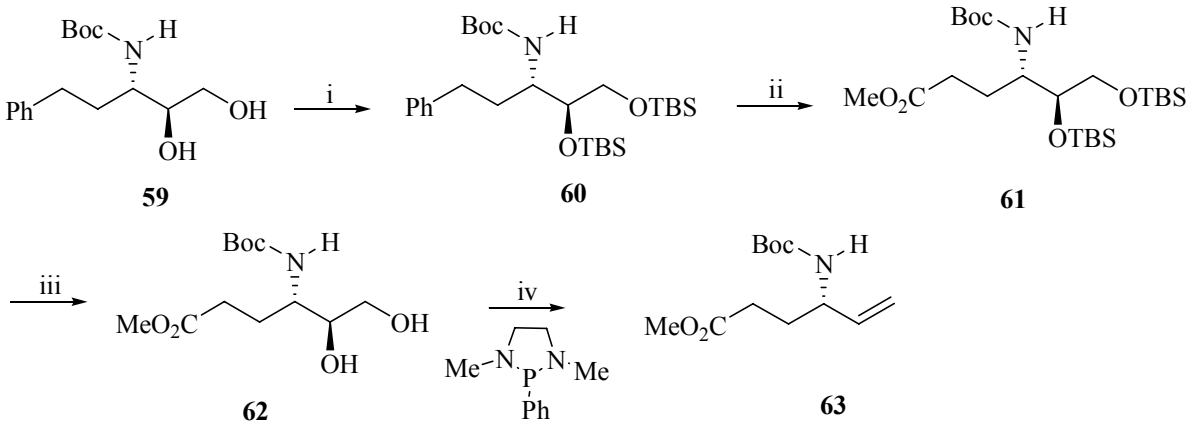
Riera *et al* have synthesized (*S*)- vigabatrin (**44**) from the epoxy alcohol **56** which was was prepared in 77% yield and 98% ee by Sharpless epoxidation. The regioselective ring opening by benzhydrylamine in the presence of Ti(O $^iPr)_4$, gave the crystalline aminodiol **57** in 87 % yield. A subsequent hydrogenolysis of the benzhydryl group followed by simultaneous protection (Boc_2O) led to *N*-Boc amino-diol in 93% yield (**Scheme 10**).



56 **57** **58**

Scheme 10: Reagents and conditions: (i) Ph_2CHNH_2, Ti(O $^iPr)_4$, 70 %, (ii) H_2, $Pd(OH)_2/C$, Boc_2O, 93%.

The diol **59** was protected as *bis*-silyl ether followed by subsequent oxidation ($RuCl_3$, $NaIO_4$) and esterification afforded, ester **61** which on deprotection (TBAF) gave **62** in 40% yield. Finally the diol was subjected to Corey-Hopkins deoxygenating protocol to give the target *N*-Boc-vigabatrin methyl ester **63** in 60% yield.

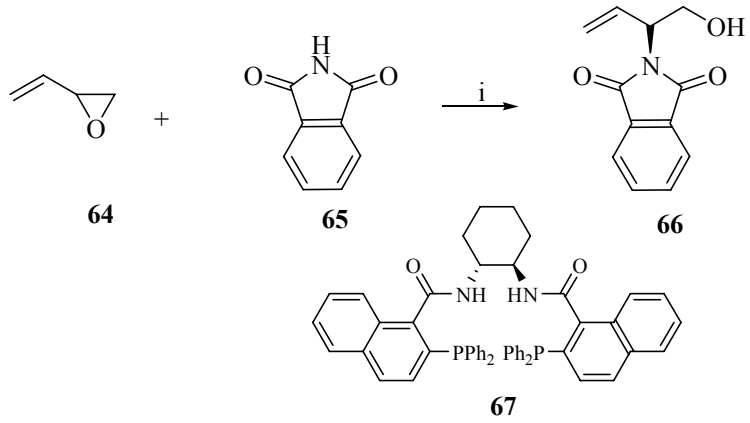


59 **60** **61** **62** **63**

Scheme 11: Reagents and conditions: (i) TBDMSCl, DMF, Imid, 96%. (ii) a. $RuCl_3$ (cat.), $NaIO_4$, $NaHCO_3$, b. MeI, DMF, $KHCO_3$, 63%. (iii) TBAF, 40%. (iv) a. Cl_2CS, 4-DMAP, 60%,

Trost's approach (2000)[24]

Troast *et al* have employed dynamic kinetic asymmetric transformation (DYKAT) of butadiene monoepoxide **64** with phthalimide using palladium-catalyzed asymmetric

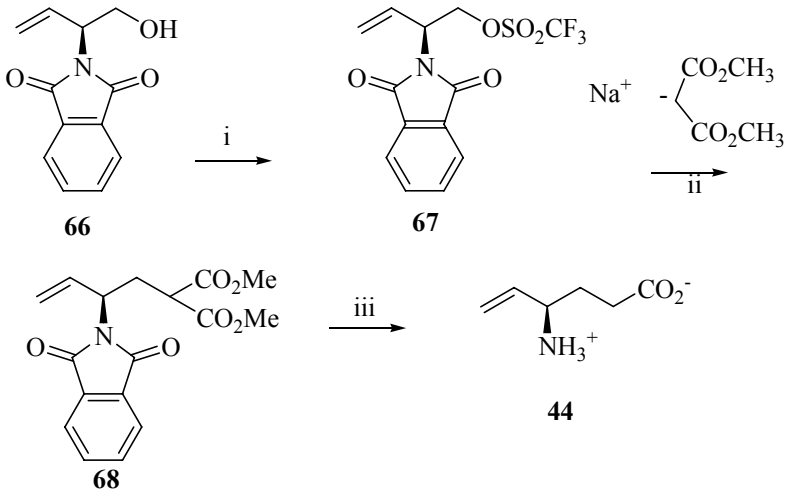


64 **65** **66** **67**

Scheme 12: Reagents and condition: (i) $[\eta^3\text{-}C_3H_5PdCl]_2$, Ligand **67**, rt, 14 h, 98%, 99%ee (after recrysatllization).

allylic alkylation (AAA) for the synthesis of (*S*)-vigabatrin (**44**). Accordingly, exposing a mixture of butadiene monoepoxide **64** and phthalimide to a catalyst formed *in situ* from π-allylpalladium chloride dimer and ligand **67** led to the formation corresponding alcohol **52** in 99% ee (**Scheme 2**). The alcohol **66** was readily converted into sulfonate ester **67** which on treatment with dimethyl sodiomalonate, gave alkylated product **68** in 64 % yield. Global deprotection (6N

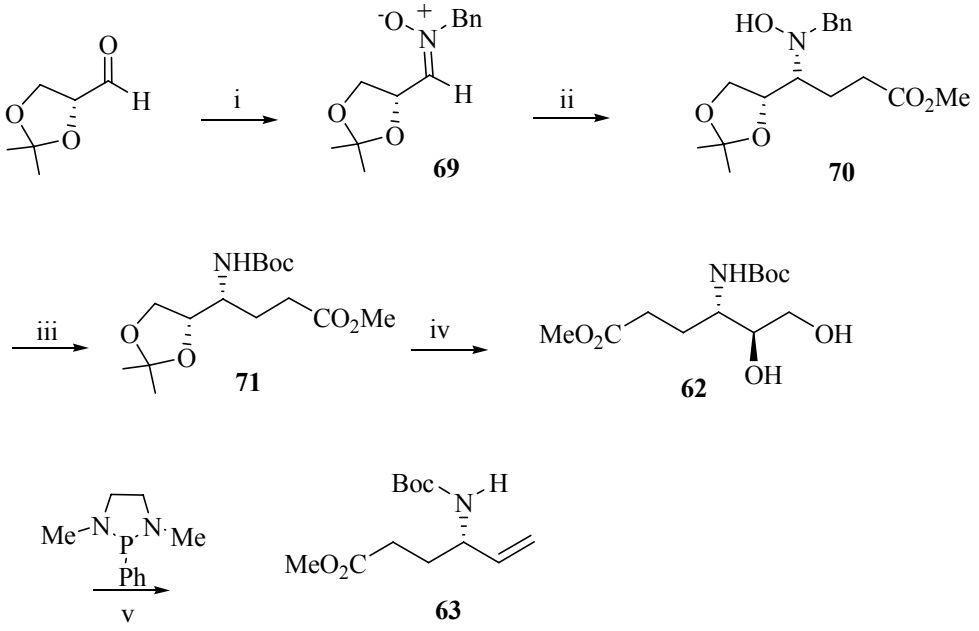
aqueous hydrochloric acid) gave hydrochloride salt of (*R*)-vigabatrin from which free (*R*)-vigabatrin **44** was liberated using a basic-ion exchange column in 96% yield.



Scheme 13: Reagents and conditions: (i) $(CF_3SO_2)_2O$, C_5H_5N, CH_2Cl_2, 0 °C, 89%. (ii) THF, 0 °C, 64%. (iii) 6N, HCl, ion exchange resin, 100 °C, 96%.

Vallée's approach (2003)[25]

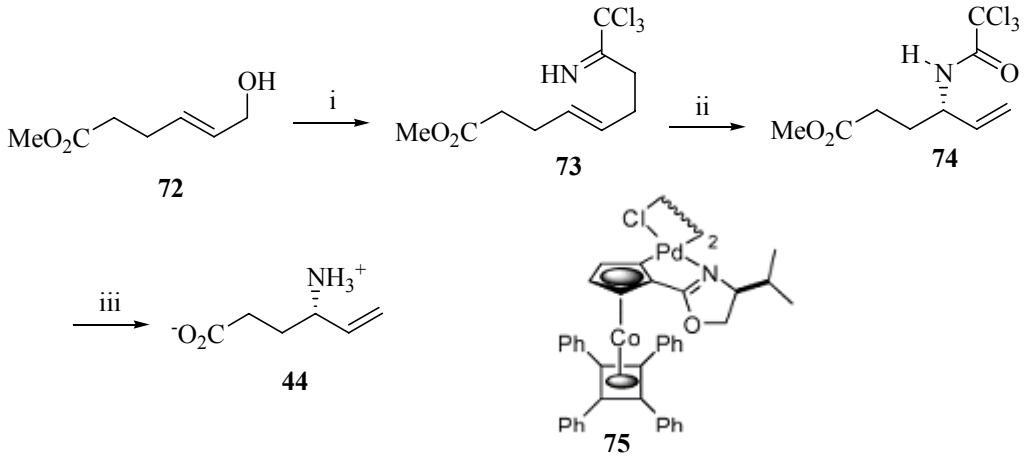
Vallee *et al* have described a short, formal synthesis of (*S*)-vigabatrin from readily available 2,3-diprotected D-glyceraldehyde. The key step of this synthesis involves a samarium diiodide-induced reductive coupling of the corresponding nitrone **69** with methyl acrylate to give γ-*N*-hydroxyamino ester **70** in 90:10 diastereomeric ratio. A subsequent hydrogenation and *in situ* carbamoylation (Boc_2O) gave *N*-Boc aminoester **71** in 82% yield. The deprotection with HCl afforded diol **62** in 40% yield. Finally the diol was subjected to Corey-Hopkins deoxygenating protocol to give *N*-Boc-vigabatrin methyl ester **63** in 60% yield.



Scheme 14: Reagents and conditions: (i) BnNHOH, CH_2Cl_2, $MgSO_4$, 2 h, 95% (ii) methyl acrylate, SmI_2, THF, -78 ^oC. (iii) H_2, Raney Ni, 60 ^oC, THF, Boc_2O, 82%. (iv) H^+, MeOH, 37%. (v) a. Cl_2CS, 4-DMAP, 60%,

Overman's approach (2003)[26]

Overman's approach describes the synthesis of (*S*)-vigabatrin (**44)** using asymmetric allylic imidate rearrangement catalyzed by **75**.



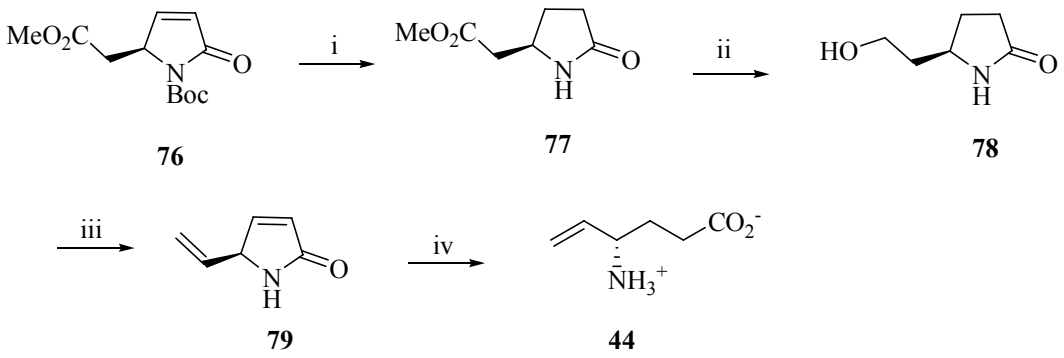
Scheme 15: Reagents and conditions: (i) DBU, 25 ^oC, 68%. (ii) cat. **5**, CH_2Cl_2, 73%, 95% ee. (iii) 6N, HCl, 100 ^oC, 75. %

The trichloroacetimidate **73** was prepared in 68% yield from the addition of allyl alcohol **72** to trichloroacetonitrile catalysed by DBU. The trichloroacetimidate was treated with Pd complex **75** to afford the trichloroacetamido ethyl ester of

vigabatrin **74** in 73% yield and 95% ee which on hydrolysis (6N HCl) afforded the free amino acid (*S*)-vigabatrin **44**.

Reiser's approach (2006)[27]

Reiser *et al*. have employed 3-pyrrolin-2-one **76** as a key intermediate for the synthesis of (*S*)-vigabatrin (**44**). Thus, 3-pyrrolin-2-one **76** on enone reduction with $NiCl_2.H_2O$ followed by *N*-Boc deprotection ($AlCl_3$) afforded **77** in 43% yield**.** Subsequent reduction of methyl ester in **77** ($LiBH_4$) gave alcohol **78**. Final transformation of **78** to (*S*)-vigabatrin (**44**) was carried out by a three-step protocol. Thus, the alcohol **78** on treatment PBr_3 followed by dehydrobromination with KO^t-Bu, gave vinyl pyrrolidinone **79**, which on hydrolysis with KOH, afforded vigabatrin (**44**) in 34% yield.



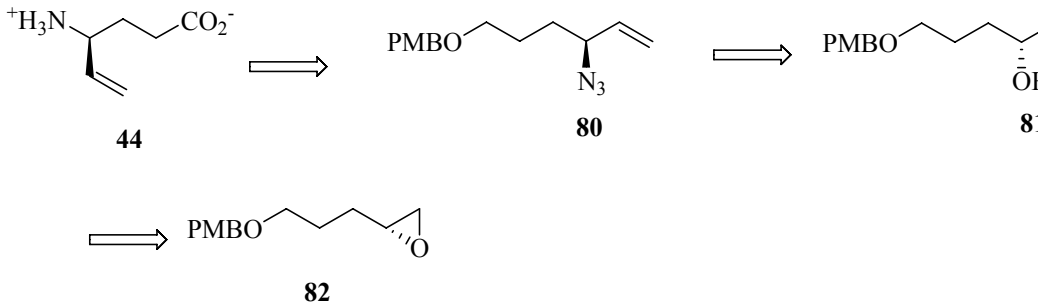
Scheme 16: Reagents and conditions: (i) a. $NiCl_2.H_2O$, $NaBH_4$, MeOH, 0 ^oC - rt, 1h. b. $AlCl_3$, CH_2Cl_2, 0 ^oC - rt, 1 h, 43%. (ii) $LiBH_4$, THF, 4 ^oC, 15 min then rt, 3h, 93% (iii) a. PBr_3, THF, -20 ^oC to rt, 1 h. b. KO^{t}Bu, THF, reflux, 15 min. (iv) KOH, H_2O, 2-propanol, reflux, 24 h, 34 %.

2.2.3 Present Work:

2.2.3.1 Objective

Literature search revealed that several methods such as resolution, chiral pool approach or enantioselective synthesis have been reported for the synthesis of (*S*)-vigabatrin (**44**). However, these methods suffer from many disadvantages such as low over all yields, and use of expensive chiral reagents. In this context, a more

practical method for the synthesis of (*S*)-vigabatrin is highly desirable. Retrosynthetic analysis for (*S*)-vigabatrin (**44**) reveals that chiral azide **80** turns out to be the key intermediate for the synthesis of (*S*)-vigabatrin (**44**) which could be prepared by the displacement of alcohol **81** by azide (N_3^-) ion. The regioselective ring opening of the chiral epoxide **82** using dimethylsulfonium methylide should provide the required allyl alcohol **81**.



44 **80** **81**

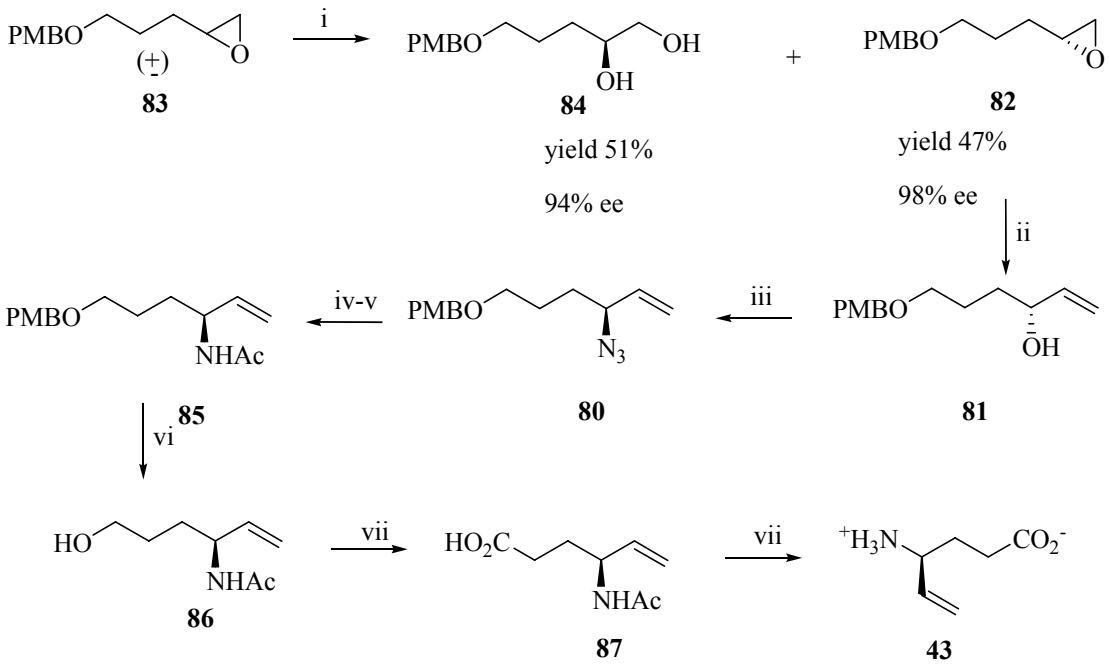
82

Scheme 17: Retrosynthetic analysis of (*S*)-vigabatrin (**44**)

2.2.4 Results and Discussion

The present synthetic route employed for the synthesis of (*S*)-vigabatrin **44** is shown in **Scheme 18**. Racemic epoxide **83** was subjected to hydrolytic kinetic resolution using catalytic amount of (*R,R)*-salen-Co(III)OAc complex to give chiral epoxide **82** in 47 % yield and 98% ee (enantiomeric excess was determined by chiral HPLC analysis; Chiracel OD-H) and chiral diol in 51% yield and 94% ee. The formation of epoxide **82** was confirmed by the appearance of multiplets at δ 2.45 and 2.74 due to methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed characteristic signals at δ 46.0 and 51.9 due to the two carbons of epoxy ring (**Fig. 8**). Regiospecific ring opening of epoxide **82** with dimethylsulfonium methylide generated *in situ* by treatment of $(CH_3)_3S^+I^-$ with *n*-BuLi at -10 ^{o}C gave allyl alcohol **81** in 89% yield. ^{1}H NMR spectrum of **81** showed signals at δ 5.03 (m) and 6.82 corresponding to the olefin

protons. Further, its ^{13}C NMR showed signals at δ 114.2 and 141.1 corresponding to the olefinic carbons **(Fig. 9)**.



Scheme 18: Reagents and conditions: (i) (*R,R*)-Co(III)-salen.OAc, H_2O, 25 °C; (ii) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, -10 °C, 89%; (iii) NaN_3, PPh_3, DMF, CCl_4, 60 °C 79%; (iv) PPh_3, THF, H_2O, 89%; (v) Ac_2O, CH_2Cl_2, pyridine, 97%; (vi) DDQ, CH_2Cl_2, 25 °C, 93%; (vii) a. IBX, DMSO, 25 °C b. $NaClO_2$, $NaClO_4$, TEMPO, CH_3CN 77%; (viii) N_2H_4, THF, MeOH, 87%.

Nucleophilic displacement of alcoholic group in **81** with N_3 was achieved with NaN_3/Ph_3P to give azide **80** in 79% yield with complete inversion of configuration. The IR spectrum of **80** exhibited a characteristic strong band at 2100 cm^{-1} indicating the presence of azide moiety. Its ^1H NMR spectrum showed a signal at δ 4.09 corresponding to the methine proton (C**H**N_3). A characteristic carbon signal at δ 72.6 (-**C**-N_3) in the ^{13}C NMR spectrum of the azide **80** confirmed the presence of the azide group (**Fig. 10**).

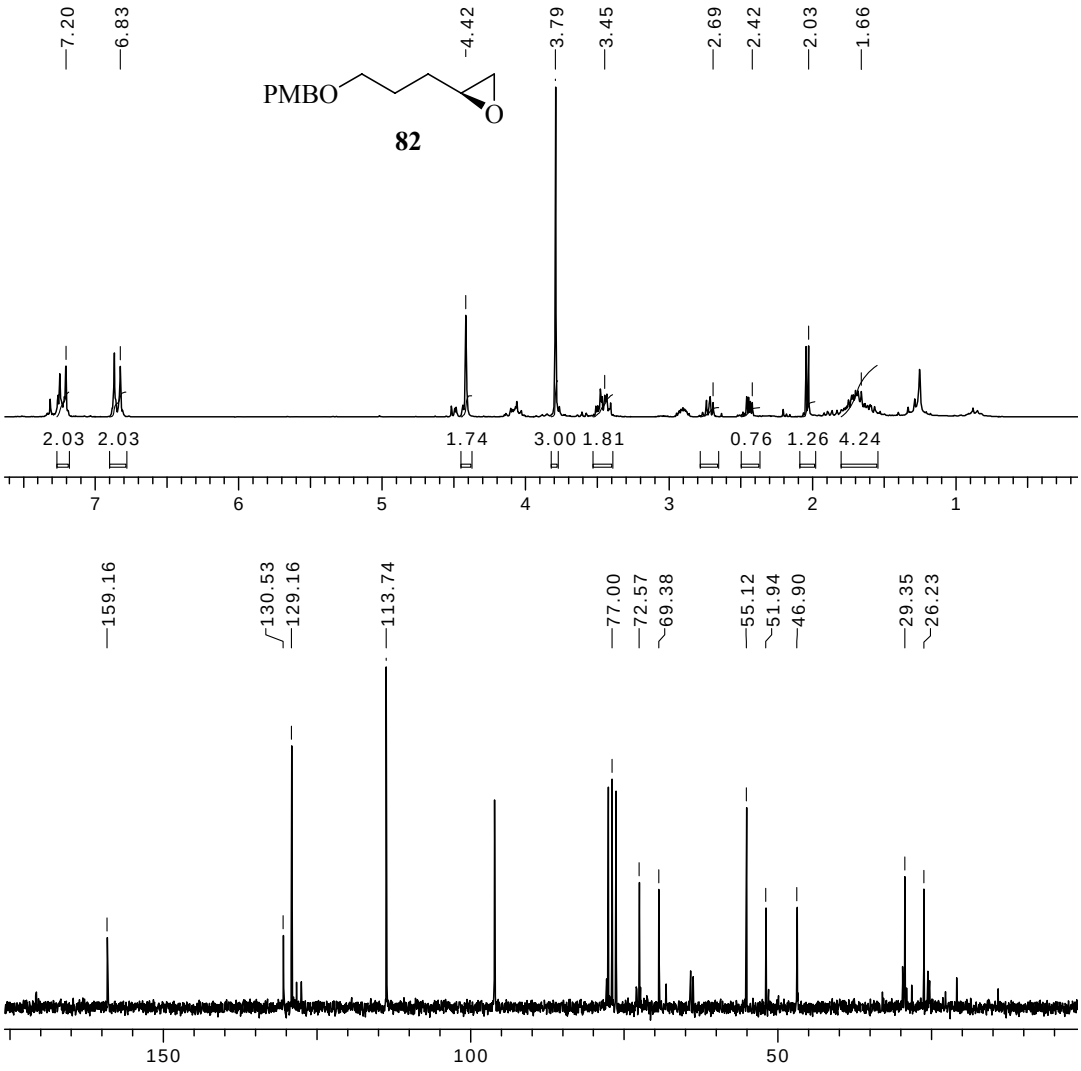


Fig 8: ^{1}H and ^{13}C NMR spectra of 2-(3-(4-methoxybenzyloxy)propyl)oxirane (83)

The azide function in **80** was then reduced with triphenylphosphine in THF-H_2O to furnish the crude amine, which was acylated (Ac_2O, pyridine) *in situ* to give *N*-acetate **85** in 97% yield. The ^{1}H NMR spectrum **85** showed a characteristic signal at δ 2.04 (s) corresponding to the methyl (COC**H$_3$**) proton. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 170.3 due to the carbonyl carbon of the amide group.

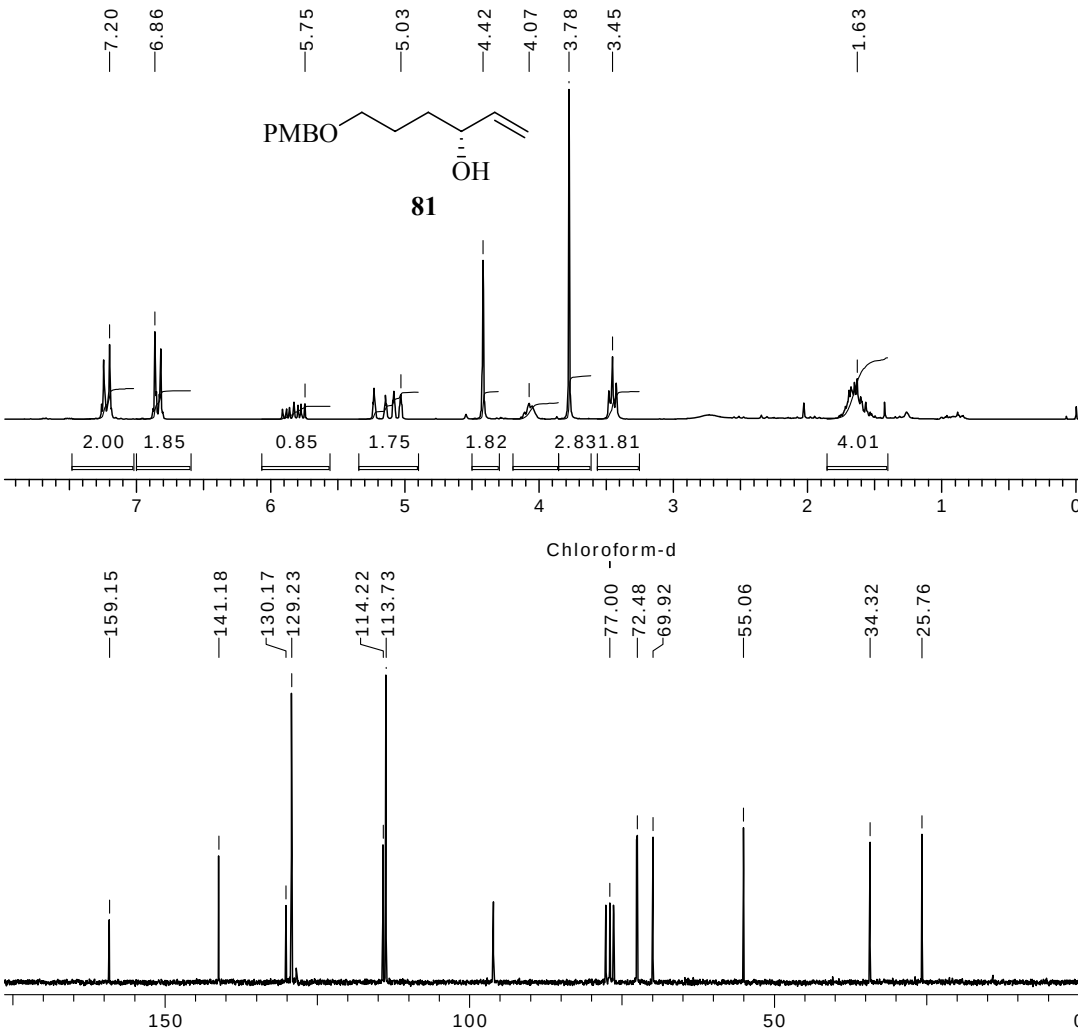


Fig 9: ^{1}H and ^{13}C NMR spectra of (*R*)-6-(4-methoxybenzyloxy)hex-1-en-3-ol (81)

Deprotection of PMB group in **85** was carried out by oxidation with DDQ in CH_2Cl_2-H_2O to give the corresponding alcohol **86** in 93 % yield. The disappearance of a signal at δ 4.42 (s) in the ^{1}H NMR spectrum of alcohol **86** confirmed the deprotection of the benzyl group. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 62.9 corresponding to the methylene carbon (**C**H_2OH) adjacent to OH group (**Fig. 12**). Oxidation of the resulting alcohol **86** with sodium hypochlorite-sodium chlorite mixture in the presence of a catalytic amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) in acetonitrile-phosphate buffer (pH 6.8) afforded the corresponding acid **87** in 87% yield. The ^{1}H NMR spectrum

of acid **87** showed a signal at δ 2.34 (t) for methylene proton adjacent to carboxylic acid group. Also its ^{13}C NMR spectrum displayed a typical peak at 175.4 (acid carbon), thus confirming the presence of acid carbonyl group.

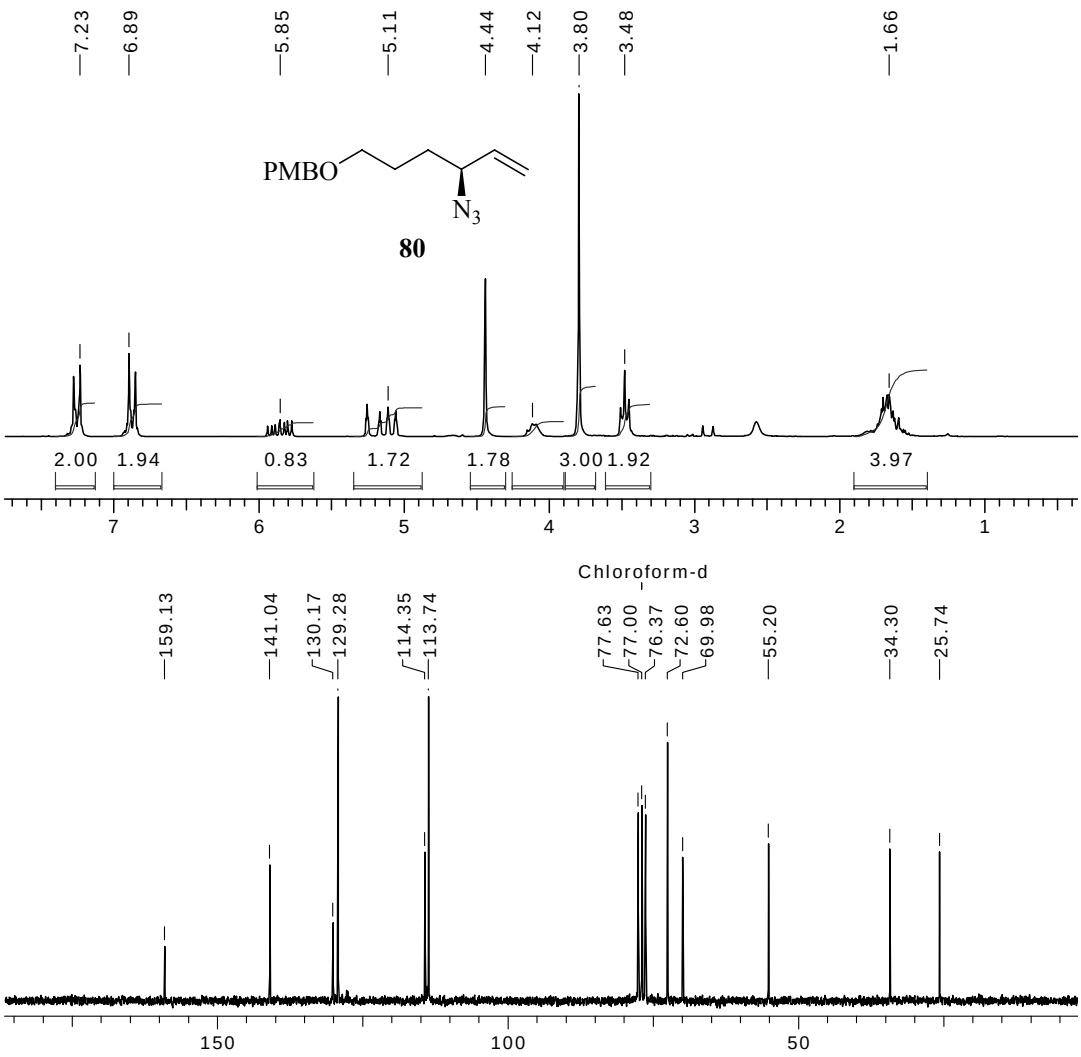


Fig 10: ^{1}H and ^{13}C NMR spectra of 1-(((*S*)-4-azidohex-5-enyloxy)methyl)-4-methoxybenzene (80)

Finally, the *N*-acetyl moiety was deprotected using $N_2H_4.H_2O$ to provide (*S*)-vigabatrin **(44)** in 87% yield. The ee of (*S*)-vigabatrin was found to be 98% based on comparison of its optical rotation $[\alpha]_D^{25}$ +11.8 (*c* 2.5, H_2O) with the reported value lit.[21] $\{[\alpha]^{25}_D$ +12.0 (*c* 2.5, H_2O)$\}$. The physical and spectroscopic data were in full agreement with the literature values.[24]

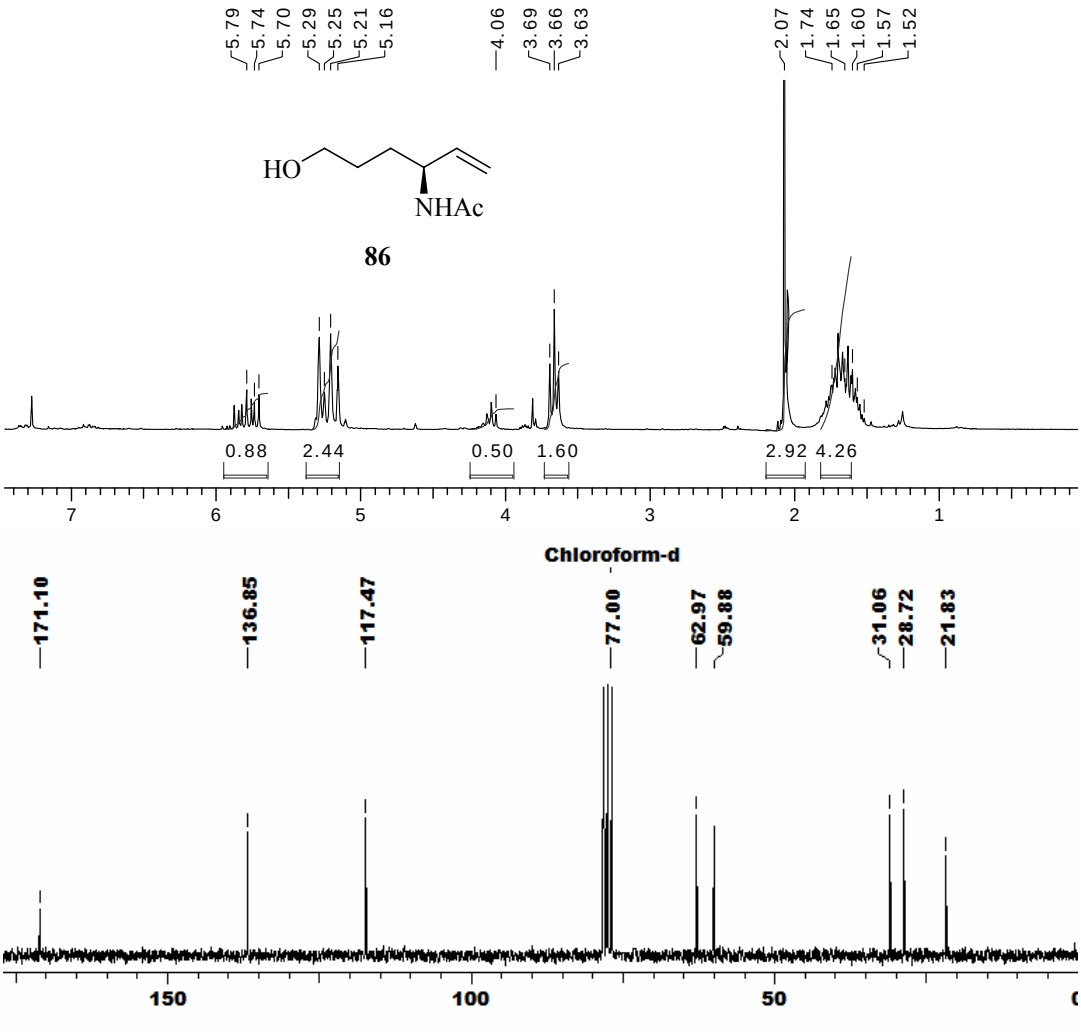


Fig 12: ^{1}H and ^{13}C NMR spectra of *N*-[(*S*)-6-(hydroxy)hex-1-en-3-yl]acetamide (86)

2.2.5 Conclusion:

In conclusion, we have successfully applied the cobalt-catalyst hydrolytic kinetic resolution and regiospecific epoxide opening strategies towards the synthesis of (*S*)-vigabatrin (**44**), which was obtained in 98% ee. It requires a relatively low amount of an inexpensive and nontoxic Co-salen catalyst that is available in both enantiomeric forms. The good overall yield (12%) and less-number of steps render our approach a good alternative to the known methods.

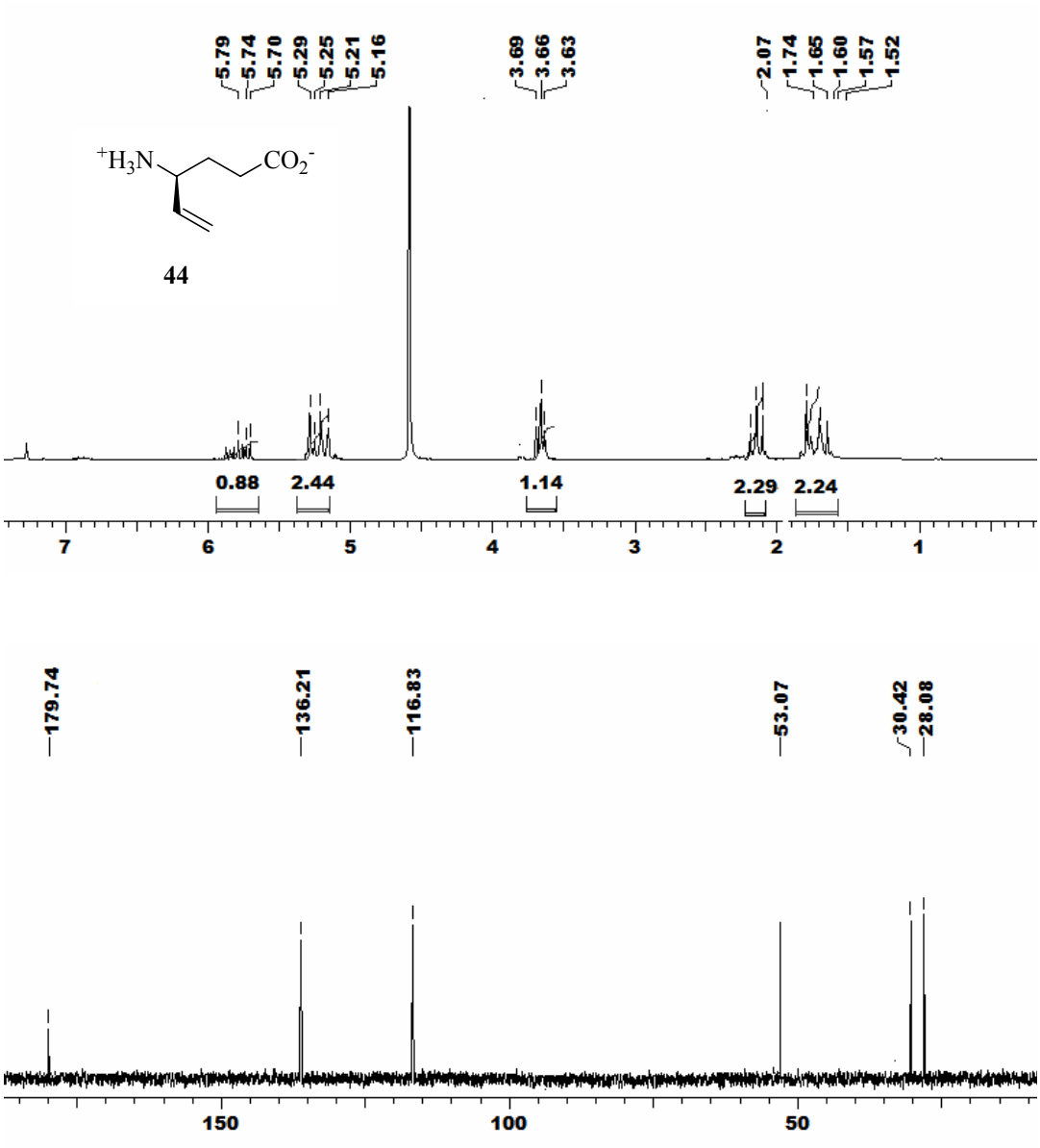


Fig 13: ^{1}H and ^{13}C NMR spectra of (*S*)-4-aminohex-5-enoic acid (44)

2.2.6 Experimental Section:

(*R*)-2-[3-(4-Methoxybenzyloxy)propyl]oxirane (82)

A 100 mL flask was charged with (*S,S*)-Co-salen (452 mg, 0.75 mmol, 0.5 mol%), which was dissolved in 5 mL toluene followed by addition of AcOH (280 μL, 5 mmol). The entire solution was allowed to stir at 25 ^{o}C open to air for 30 min over which the color changed from orange-red to a dark brown. The solution was

concentrated *in vacuo* to leave a crude brown solid. The resulting residue was dissolved in epoxide **80** (33.3 g, 150 mmol) followed by dropwise addition of water (1.49 mL, 82.5 mmol, 0.55 equiv) over 5 min at 0 °C. The reaction was allowed to warm to 25 ^{o}C and stirred for 14 h. After completion of the reaction (as monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 and extracted (3 X 100 mL) and concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (silica gel using pet.ether: EtOAc = 9:1 as eluent) to furnish **82**.

Yield: 15.7 g, 47%; colorless oil; $\mathbf{[\alpha]_D^{25}}$ -5.5 (*c* 1, MeOH); **IR**(KBr) 698, 877, 985, 1216, 1387, 1452, 1607, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.66-1.75 (m, 4H), 2.03-2.05 (d, *J* = 3.3 Hz, 1H), 2.42-2.46 (m, 1H), 2.69-2.74 (t, *J* = 5.2 Hz, 1H), 3.41-3.45 (m, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 6.83-6.87(d *J* = 8.3 Hz, 2H), 7.20-7.25 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.2, 29.3, 46.9, 51.9, 55.1, 69.3, 72.5, 113.7, 129.1, 130.5, 159.1; **Analysis**: $\mathbf{C_{13}H_{18}O_3}$ requires C, 70.24; H, 8.16 %; found C, 70.27; H, 8.13 %.

(*R*)-6-(4-Methoxybenzyloxy)hex-1-en-3-ol (81)

To a stirred suspension of trimethylsulfonium iodide (2 equiv, 110 mmol, 22.45 g) in dry THF (150 mL) was added *n*-BuLi (2 equiv, 110 mmol, 68.75 mL of 2 M hexane solution) at -10 ^{o}C. After 30 min, epoxide (12.22 g, 55 mmol) in dry THF (30 mL) was introduced dropwise and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 X 100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then

purified by column chromatography (silica gel using pet ether: EtOAc = 90:10 as eluent) to give allyl alcohol **81**

Yield: 11.57 g, 89%; colorless oil; $[\alpha]_D^{25}$ -7.8 (*c* 1, MeOH); **IR** (KBr): 669, 859, 1032, 1215, 1473, 1590, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.57-1.70 (m, 4H), 3.42-3.48 (t, *J* = 5.4 Hz, 2H), 3.78 (s, 3H), 4.05-4.11 (m, 1H), 4.42 (s, 2H), 5.03-5.23 (m, 2H), 5.75-5.91 (m, 1H), 6.82-6.86 (d, *J* = 8.7 Hz, 2H), 7.20-7.24 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.7, 34.3, 55.0, 69.9, 72.4, 72.5, 113.7, 114.2, 129.2, 130.1, 141.1, 159.1; **Analysis**: **$C_{14}H_{20}O_3$** requires C, 71.16; H, 8.53 ; found C, 71.27; H, 8.53 %.

1-[((*S*)-4-Azidohex-5-enyloxy)methyl]-4-methoxybenzene (80)

A mixture of alcohol **81** (7.09 g, 30 mmol), sodium azide (2.93 g, 45 mmol) and PPh_3 (7.87 g, 30 mmol) in 50 ml of CCl_4-DMF (1:4) was warmed at 60°C with stirring. After completion of reaction (monitored by TLC), it was brought to 25 °C and quenched by adding 5 ml of water. After stirring for 10 min., reaction mixture was diluted with diethylether (25 ml) and washed thoroughly with water. The combined extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel using pet ether: EtOAc = 90:10 as eluent) to give azide **80**.

Yield: 6.19 g, 79%; colorless oil; $[\alpha]_D^{25}$ +13.7 (*c* 1, MeOH); **IR** (KBr): 804, 1022, 1117, 1254, 1343, 1450, 1515, 2100, 2926, 3017 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.59-1.71 (m, 4H), 3.45-3.51 (t, *J* = 4.8 Hz, 2H), 3.80 (s, 3H), 4.09-4.15 (m, 1H), 4.44 (s, 2H), 5.06-5.26 (m, 2H), 5.77-5.94 (m, 1H), 6.85-6.89 (d, *J* = 8.6 Hz, 2H), 7.23-7.27 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.7, 34.3, 55.2, 69.9, 72.6, 72.5, 113.7, 114.3, 129.2, 130.1, 141.0, 159.1; **Analysis**:

$C_{14}H_{19}N_3O_2$ requires C, 64.35; H, 7.33; N, 16.08; found 64.30; H, 7.38; N, 16.01 %.

***N*-[(*S*)-6-(4-Methoxybenzyloxy)hex-1-en-3-yl)acetamide (85)**

A mixture of azide **80** (5.2 g, 20 mmol), and PPh_3 (7.87 g, 30 mmol) in 50 ml of THF: H_2O (1:3) was warmed at 60 °C with stirring. After completion of reaction (monitored by TLC), it was brought to 25 °C and quenched by adding 5 ml of water. After stirring for 10 min., reaction mixture was diluted with diethylether (25 ml) and washed thoroughly with water. The combined extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then treated with Ac_2O (1.89 mL, 20 mmol) and Et_3N (2.78 mL, 20 mmol) in CH_2Cl_2 and stirred for 3 h at 0 °C. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 X 100 mL). The combined extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel using pet ether: EtOAc = 90:10 as eluent) to give acetamide **84**.

Yield: 5.3 g, 97%; colorless oil; **$[\alpha]_D^{25}$** -16.3 (*c* 1, MeOH); **IR** (KBr) 712, 882, 1029, 1216, 1430, 1660, 1742, 3019, 3437 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60-1.77 (m, 4H), 2.04 (s, 3H), 3.42-3.47 (m, 2H), 3.80 (s, 3H), 4.04-4.10 (m, 1H), 4.42 (s, 2H), 5.13-5.28 (m, 2H), 5.72-5.77 (m, 1H), 6.85-6.90 (d, *J* = 8.6 Hz, 2H), 7.23-7.28 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 25.3, 30.8, 55.2, 60.1, 69.4, 72.5, 113.7, 116.6, 129.2, 130.4, 136.3, 159.1, 170.3; **Analysis**: **$C_{16}H_{23}NO_3$** requires C, 69.29; H, 8.36; N, 5.05 %; found 69.20; H, 8.27; N, 5.09 %.

***N*-((*S*)-6-hydroxyhex-1-en-3-yl)acetamide (86)**

To a solution of acetamide **85** (2.7 g, 10 mmol) in 50 mL CH_2Cl_2 was added DDQ (6.8 g, 30 mmol) and stirred for 1 h. After completion of reaction (monitored by TLC), it was quenched with 15 mL of saturated $NaHCO_3$ solution followed by water and extracted with diethyl ether (3 X 100 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel using pet ether: EtOAc = 80:20 as eluent) to give alcohol **86**.

Yield: 1.5 g, 93%; colorless oil; $[\alpha]_D^{25}$ -6.3 (*c* 1, MeOH); **IR** (KBr): 757, 1022, 1217, 1245, 1307, 1404, 1730, 2349, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52-1.74 (m, 4H), 2.07 (s, 3H), 3.63-3.69 (t, *J* = 6.1 Hz, 2H), 4.06-4.13 (m, 1H), 5.16-5.29 (m, 2H), 5.70-5.79 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 28.7, 31.0, 59.8, 62.9, 117.4, 136.8, 171.1; **Analysis**: **$C_8H_{15}NO_2$** requires C, 61.12; H, 9.62; N, 8.91; found 61.11; H, 9.67; N, 8.92 %.

(*S*)-4-Acetamidohex-5-enoic acid (87)

To a stirred solution of alcohol **86** (943 mg, 6 mmol), TEMPO (65.6 mg, 0.42 mmol), $NaClO_2$ (1 g, 12 mmol) in CH_3CN (30 mL) and phosphate buffer (22.5 mL) at 25 ºC was added NaClO (5%, 0.15 mL) after stirring the reaction mixture for 5 h at 35 ºC, 7.2 mL of 2N NaOH was added and the mixture was added to ice-cold solution of sodium sulfite solution (183 mg in 30 mL) . After stirring for 30 min, the reaction mixture was acidified with 2N HCl to pH 3-4 and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give acid **87**.

Yield: 855 mg, 77%; gum; $[\alpha]_D^{25}$ -2.26 (*c* 0.6, $CHCl_3$); **IR**(KBr): 821, 1035, 1097, 1247, 1514, 1731, 1737, 2061, 2339, 2856, 2927 cm^{-1}; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 1.91-2.02 (m, 2H), 2.07 (s, 3H), 2.23- 2.29 (m, 2H), 4.07-4.12 (m, 1H), 5.18-5.13 (m, 2H), 5.69-5.86 (m, 1H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 28.7, 29.3, 58.4, 116.8, 135.4, 170.1, 175.4; **Analysis**: **$C_8H_{13}NO_3$** requires C, 56.13; H, 7.65, N, 8.18; found 56.10; H, 7.69, N, 8.23 %.

(*S*)-4-Aminohex-5-enoic acid (44)

To a stirred solution of acetamide **87** (171 mg, 1 mmol) as added hydrazine hydrate (0.14 mL, 4.6 mmol) in methanol at 25 °C for 4 h. After completion of reaction (as monitored by TLC), the reaction mixture was poured into CH_2Cl_2, washed with 1N HCl, $CuSO_4$ and dried over anhyd. Na_2SO_4 and concentrated in vacuo to give acid **44**.

Yield: 98 mg**,** 87%; **mp**: 167 ºC {lit.[24] mp: 164-165 ºC; **$[\alpha]_D^{25}$** + 11.8 (*c*, 2.5, H_2O) {lit.[24] **$[\alpha]_D^{25}$** + 12.0 (*c*, 2.5, H_2O)}; **IR**(KBr): 991, 1122, 1393, 1524, 1573, 1639, 2935; **^{1}H NMR** (200 MHz, D_2O): δ 1.52-1.74 (m, 2H), 2.07-2.15 (m, 2H), 3.63-3.69 (m, 1H), 5.16-5.29 (m, 2H), 5.70-5.79 (m, 1H); **^{13}C NMR** (50 MHz, D_2O): δ 28.0, 30.4, 53.07, 116.8, 136.2, 179.7; **Analysis**: **$C_6H_{11}NO_2$** requires C, 55.80; H, 8.58, N, 10.84; found 55.90; H, 8.59, N, 10.89 %.

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CHAPTER 3

Synthetic methodologies involving Cyanation and Esterification

Section 1: Organocatalytic Activation of TMSCN by Ammonium Salts for Efficient Cyanation of Aldehydes and Imines

3.1.1 Introduction

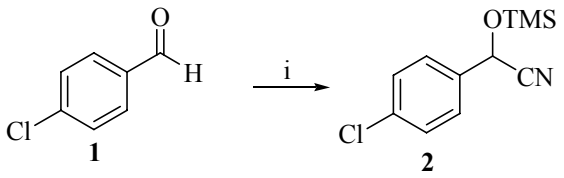
Hydrocyanation and cyanosilylation of aldehydes are important C-C bond-forming reactions[1] in organic synthesis, as they provide versatile intermediates such as cyanohydrins and cyanohydrin silyl ethers, respectively. In particular, cyanohydrin silyl ethers are industrially valuable and important intermediates for the synthesis of α-hydroxy acids and esters, acyloins, vicinal diols, β-amino alcohols and other biologically active compounds.[2]

3.1.2 Review of Literature

Literature search revealed that there are various catalysts available for the cyanation of aldehydes and imines and the chemistry has been reviewed.. These methods involve the addition of trimethylsilyl cyanide (TMSCN), to carbonyl compounds in the presence of Lewis acids,[3] Lewis bases,[4] metal alkoxides,[5] bifunctional catalysts[6] and inorganic salts.[7] Some of the recent developments on this reaction are discussed below.

Bandger's approach (2001)[3c]

Bandger *et al*. have reported the addition of TMSCN to various aldehydes in water using FeF_3 as a new catalyst giving the corresponding cyanohydrins in good yields (**Scheme 1**).

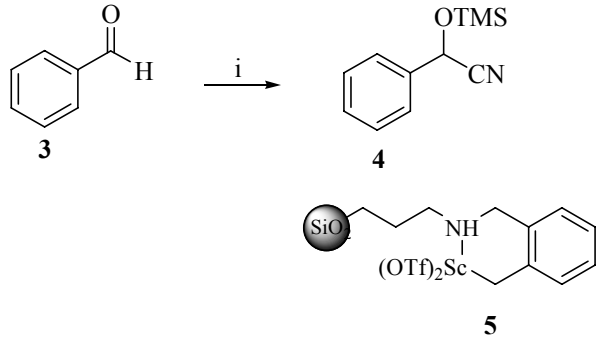


1 **2**

Scheme 1: TMSCN (1.5 equiv.), FeF_3 (0.3 eqiv), H_20, 80 %

Mani's approach (2002)[3d]

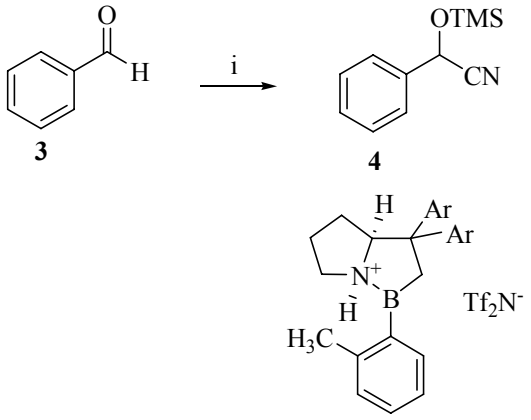
Mani *et al* have reported a new active silica-based scandium (III) interphase catalyst **5** for the conversion of aldehydes into corresponding cyanohydrin trimethylsilyl ethers. The catalyst **5** could be recovered and recycled for atleast 10 reaction cycles without considerable loss of activity (**Scheme 2)**.



Scheme 2: (i) TMSCN (1.2 equiv), CH_2Cl_2, 25 ^oC, catalyst **5** (4.6 mol%), 3 h, 98%.

Corey's approach (2004)[3f]

Corey *et al*. have reported the enantioselective synthesis of trimethylsilylated cyanohydrins using oxazaborolidinium bistriflimidate **(6)**, a powerful chiral Lewis acid. A variety of aldehydes, aromatic and aliphatic, have been transformed into cyanohydrins with > 90% enantiomeric purity under standardized conditions (**Scheme 3)**.

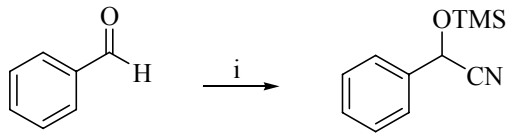


6. Ar = 3,5-dimethylphenyl

Scheme 3: (i) TMSCN (1.2 equiv), CH_2Cl_2, 25 ^oC, catalyst **6** (4.6 mol%), 3 h, 98%.

Iranpoor's approach (2005)[3g]

Iranpoor *et al.* have reported the addition of TMSCN to carbonyl compounds employing dodecatungestophosphoric acid ($H_3PW_{12}O_{40}$) as a heterogeneous and environmentally benign catalyst. By this method aromatic, aliphatic, cyclic and heterocyclic aldehydes are converted into their corresponding cyanotrimethylsilyl ethers in excellent yields in short reaction times **(Scheme 4)**.

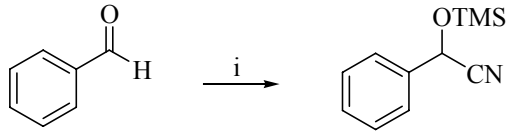


3 **4**

Scheme 4: (i) TMSCN (1.2 equiv), neat condition, 25 ^oC, $H_3PW_{12}O_{40}$ (0.1 mol%), 5 min, 92%.

Ohkuma's approach (2005)[7]

In this approach Ohkuma *et al* have reported LiCl as a highly effective catalyst for cyanosilylation of various aldehydes and ketones to the corresponding silylated cyanohydrins. The reaction proceeds smoothly with a substrate/catalyst molar ratio of 100-100,000 at 20-25 ^oC under solvent-free conditions (**Scheme 5)**.

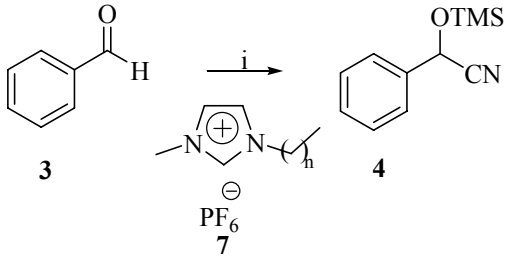


3 **4**

Scheme 5: (i) TMSCN (1.2 equiv), neat condition, 25 ^oC, LiCl (1×10^{-5}),1 h , 100%.

Loh's approach (2005)

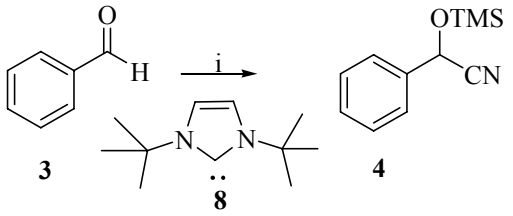
In this approach Loh *at el*. have reported ionic liquid [omom][PF_6] as an efficient and environmentally friendly reaction medium as well as a promoter for the cyanosilylation of aldehydes under mild conditions. In addition, the recovered ionic liquid could be reused for subsequent runs with only a gradual decrease in activity (**Scheme 6)**.



Scheme 6: TMSCN (2 equiv), [omim][PF_6] $_{n=7}$ (0.5 mL), 25 ^oC, 2 h , 99 %.

Song's approach (2006)[4d]

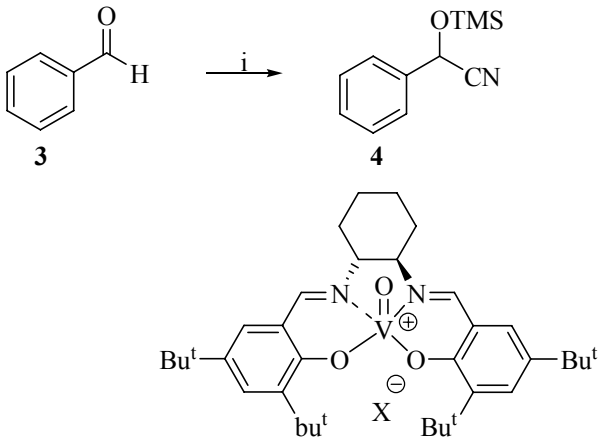
Song's approach describes N- heterocyclic carbenes as organocatalysts in activating TMSCN for facile cyanosilylation of carbonyl compounds. Cyano transfer from TMSCN to carbonyl compounds proceeds at room temperature in the presence of only 0.5 mol % of N-heterocyclic carbene **(8)**, leading to a range of trimethylsilylated cyanohydrins in very good to excellent yields (**Scheme 7)**.



Scheme 7: (i) TMSCN (1.1 equiv), THF, 25 ^oC, catalyst **4** (0.5 mol%), 10 min, 91%.

Belokon's approach (2006)[3h]

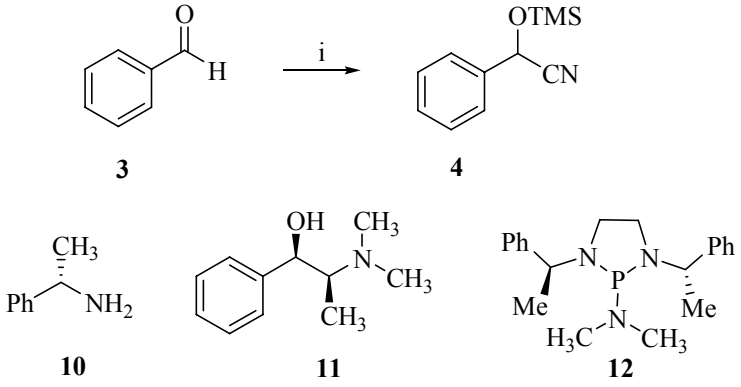
Belokon have reported the synthesis and application of new vanadium (V) salen complexes (**9**) for the asymmetric trimethylsilyl cyanation. The chiral cyanohydrins were obtained in good ee (60-95%) (**Scheme 8)**.



Scheme 8: (i) TMSCN (1.1 equiv), CH_2Cl_2, 25 ^oC, Catalyst **9** (0.5 mol%), 5 min, 92%.

Denmark's approach (2006)[4a]

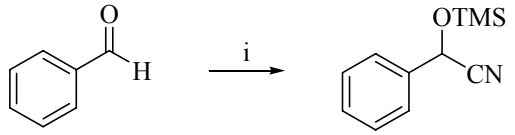
In this approach a variety of chiral amines, (*S*)-α-methylbenzylamine, (**10**), (1*S*, 2*R*)-*N*-methylephedrine (**11**), and chiral aminophosphines **12** were used as catalysts for addition of TMSCN to aldehydes but afforded only racemic products (**Scheme 9)**.



Scheme 9: (i) TMSCN (1.05 equiv), $CHCl_3$, -78 ^oC, Catalyst (0.5 mol%), 15 h, 73 %.

Khan's approach (2007)[3i]

In this approach, $Fe(Cp)_2PF_6$ is used as an efficient catalyst for the addition of trimethylsilyl cyanide (TMSCN) to various aldehydes and ketones under solvent free condition. Excellent yields of trimethylsilylether of cyanohydrins up to (94 %) were achieved within 10 min (**Scheme 10)**.

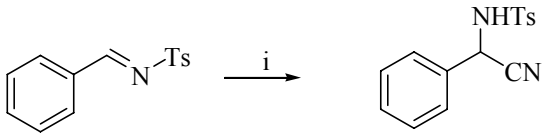


3 **4**

Scheme 10: (i) TMSCN (1.3 equiv), solvent free, 25 ^{o}C, $Fe(Cp)_2PF_6$ (2.5 mol %), 10 min, 94 %.

Singh's approach (2004)[8d]

Singh, *at el*. have reported addition of TMSCN to a variety of arylaldimines (Strecker reaction) in the presence of $LiClO_4$ in acetonitrile as solvent. The reaction provided the addition products in very high yields (**Scheme 11)**.

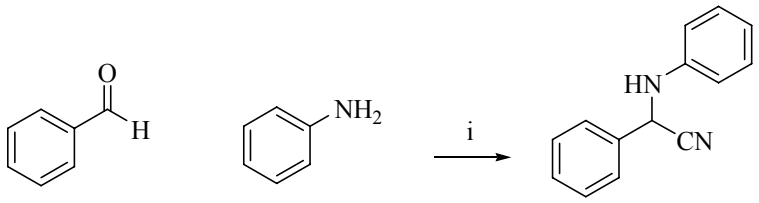


13 **14**

Scheme 11: (i) TMSCN (1.1 equiv), CH_3CN, 25 ^{o}C, $LiClO_4$ (10 mol%), 6 h, 92 %.

Yadav's approach (2003)[8l]

In this approach, Yadav *et al* have reported the addition of trimethylsilyl cyanide addition onto aryl imines derived *in situ* from aldehydes and amines in 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquids under mild and neutral conditions to afford the corresponding α-aminonitriles in excellent yields. The ionic liquids can be recycled in five to six runs without any apparent loss of activity (**Scheme 12)**.

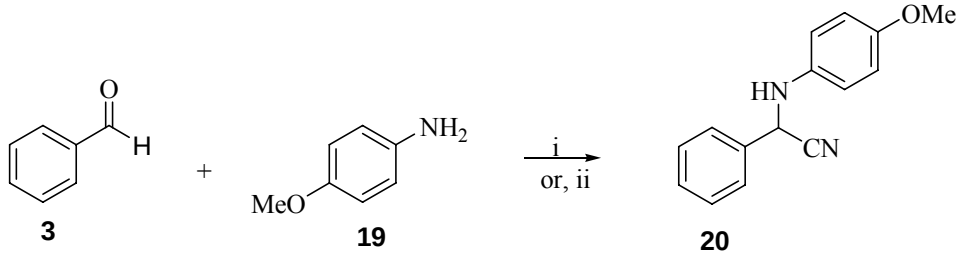


3 **17** **18**

Scheme 12: (i) TMSCN (1.2 eqiv), 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL), 25 ^{o}C, 6 h, 87%

Sudalai's Approach (2006)[8f]

Sudalai *et al*. have reported the addition of cyanide anion such as trimethylsilyl cyanide or acetone cyanohydrin onto *in situ* generated imines using $Cu(OTf)_2$ or Et_3N as catalyst, furnishing α-aminonitriles in excellent yields under ambient conditions **(Scheme 13)**.

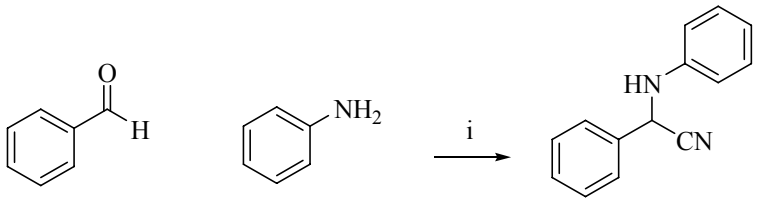


3 **19** **20**

Scheme 13: (i) TMSCN (2 equiv), $Cu(OTf)_2$ (1 mol %), MgSO4, CH_3CN, 25 ^oC, 6 h, 95 %.
(ii) acetone cyanohydrin (2 equiv), Et_3N (5 mol %) , CH_3CN, 25 ^oC, 6 h, 95 %.

Li's approach (2007)[8a]

n this approach, Li *et al* have developed a convenient one pot process for the synthesis of α-aminonitriles using sulfamic acid as catalyst at ambient temperature **(Scheme 14)**.



3 **17** **18**

Scheme 14: (i) TMSCN (1.2 eqiv), $H_2N\text{-}SO_3H$ (10 mol %), CH_3CN, 25 ^oC, 6 h, 87%.

3.1.3 Present work

3.1.3.1 Objective

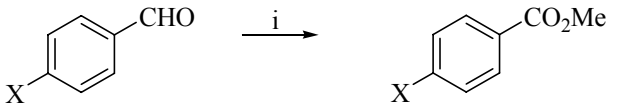
Although there are many methods available in the literature for the cyanation of aldehydes and imines, many of these methods suffer from several disadvantages such as prolonged reaction times, use of heavy metal catalysts and poor yields of

the corresponding cyano trimethylsilyl ethers. Our objective is to use metal-free organocatalysts for the cyanation of aldehydes and imines with TMSCN.

Even though ammonium salts are well known catalyst in many of the organic reactions, but still its use in hydrocyanation reactions using TMSCN, a safe and easily handled reagent compared to HCN or KCN,[10] has not been reported. Therefore, we have decided to explore the use of ammonium salts for effecting cyanosilylation of aldehydes and Strecker-type aminonitrile synthesis using TMSCN as cyanide source.

3.1.2 Results and discussion

4-nitro-and 4-cyanobenzaldehydes were treated with TMSCN (1.5 equiv.) in the presence of several Lewis bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DABCO (1,4-diazabicyclo[2.2.2]octane), or (-)-sparteine, in catalytic amounts, with a view to obtain the corresponding silylated cyanohydrin derivatives. However, the reaction took a different course to furnish their respective methyl esters **21** and **22,** instead of the cyanohydrins, when the reaction was carried out in methanol (**Scheme 15**).



21. X = 4- NO_2

22. X = 4-CN

Scheme 15: (i). TMSCN (1.5 equiv.), DBU or DABCO or sparteine (0.5 mol%), MeOH, 3 h, 25°C.

This observation led us to modify the Lewis basicity in DBU by quaternizing one of the nitrogen atoms with benzyl bromide. Thus, quaternary basic ammonium salt **24** was prepared and, when employed for cyanation of aldehydes, gave exclusively the respective cyanohydrin silyl ethers. Similarly, mono ammonium salts **23** and **25** were prepared from the corresponding diamines by quaternizing

with 1 mole of benzyl bromide and methyl iodide respectively, in toluene as solvent.

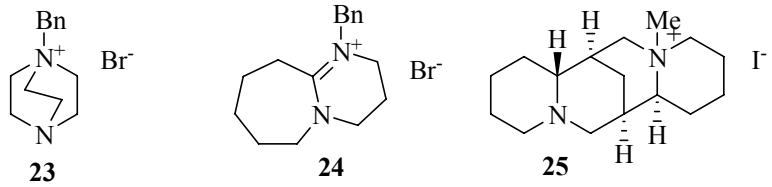


Fig. 1: Quaternized organocatalysts for TMSCN addition to aldehydes and imines

Organocatalysts **23**, **24** and **25** were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy and by single crystal XRD and elemental analysis. **Figure 2** shows the ORTEP diagram of

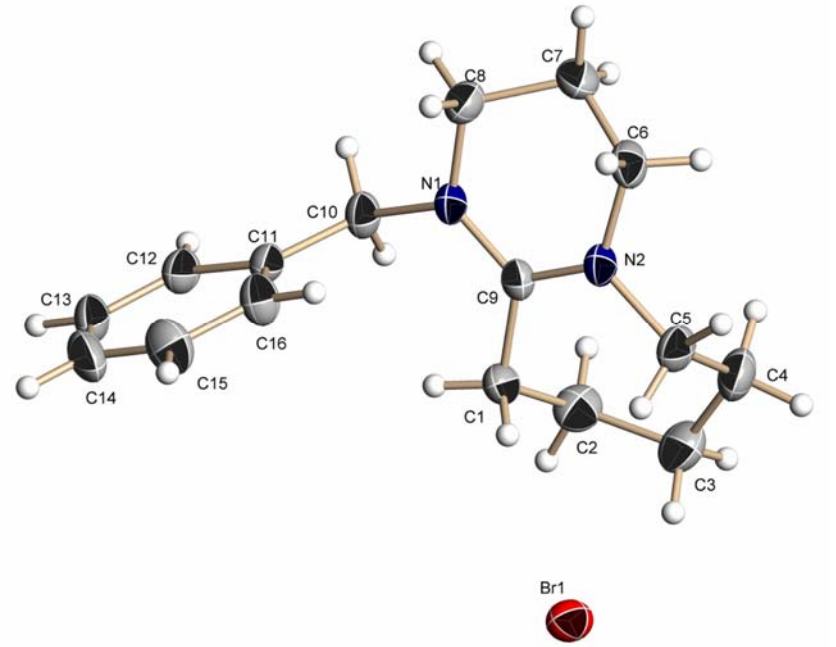


Fig. 2: ORTEP diagram of catalyst **24**

catalyst **24,** which confirms the quaternization at the iminium nitrogen atom with benzyl bromide. The ^{1}H NMR spectrum of catalyst **24** showed typical signal at δ 4.91(s) corresponding to the methylene (C**H**$_2$Ph) proton of benzyl group. Further, its ^{13}C NMR spectrum showed carbon signals at δ 56.7 and 167.0 corresponding to the benzyl methylene and iminium carbons respectively.

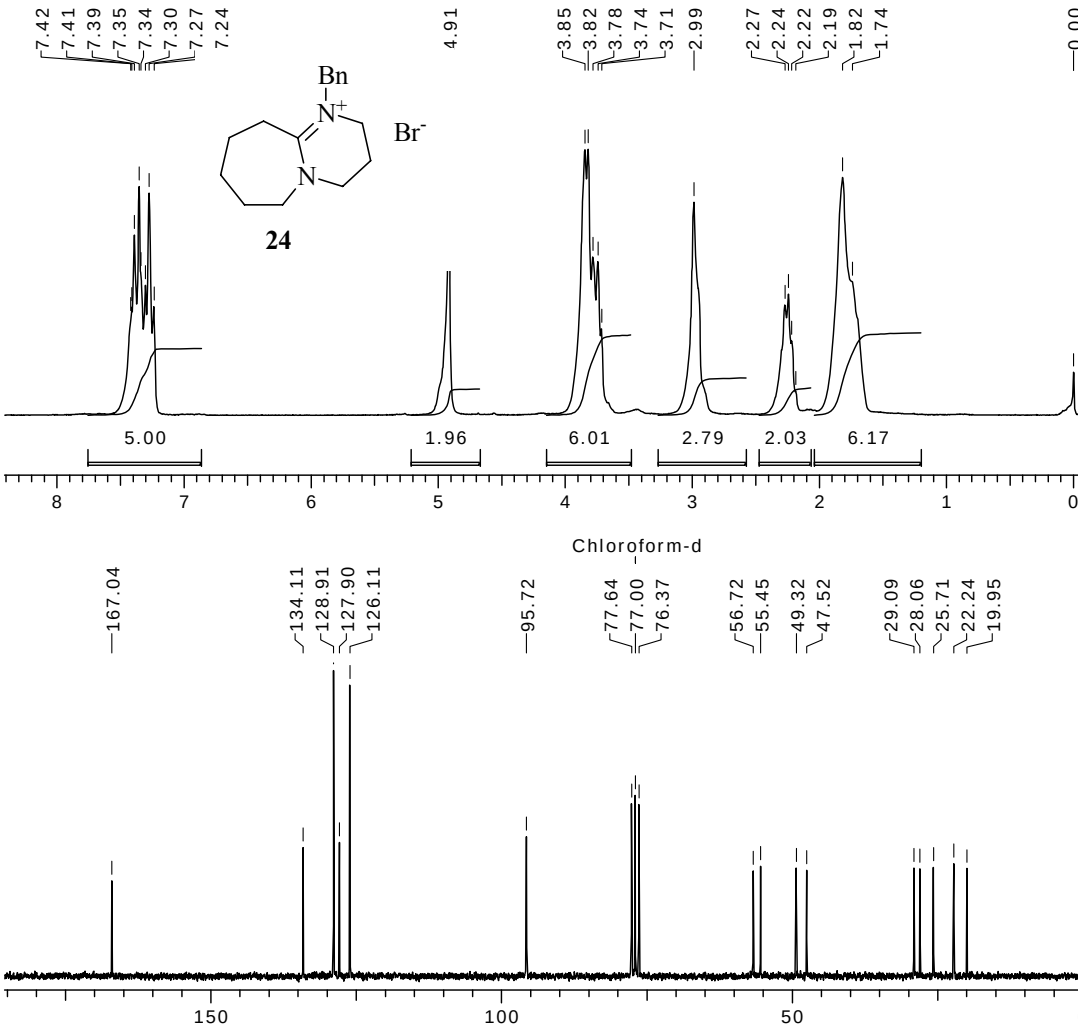
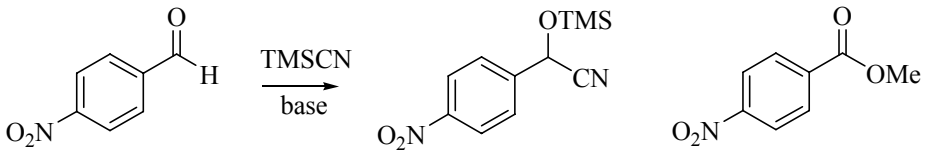


Fig. 3: ^{1}H and ^{13}C NMR spectra of ammonium salt 24

A systematic study on the hydrocyanation of 4-nitrobenzaldehyde as a test substrate in various solvents was carried out using catalytic amount of either DBU, DABCO, (-)-sparteine or their ammonium salts **23**, **24** and **25** and the results are summarized in **Table 1.** Ammonium salt **24** was found to be the best catalyst for the hydrocyanation of 4-nitrobenzaldehyde with TMSCN as cyanide source. Encouraged by this result, a wide range of aldehydes were subjected to cyanosilylation using a catalytic quantity of **24** (0.5mol%) under optimized reaction Conditions (1 equivalent of TMSCN, 25 ^{o}C, CH_2Cl_2). **Table 2** shows the scope of the reaction wherein moderate to high yields of **27**

Table 1: Cyanation of aldehyde: Screening of bases for product selectivity[a]



26 **27g** **21**

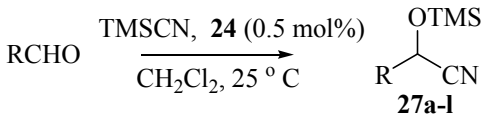
Entry	Base	Solvent	Product (% Yield)[b]	
			21	**27g**
1	DBU	MeOH	93	-
2	DABCO	MeOH	92	-
3	Et_3N	MeOH	81	-
4	**23**	MeOH	-	57
5	**24**	CH_2Cl_2	-	92
6	**24**	MeOH	-	64
7	**25**	MeOH	-	61

[a]Reaction conditions: 4-nitrobenzaldehyde (5.0 mmol), TMSCN (6.0 mmol), base (0.5 mol%), solvent, 25 ^{o} C, 3 h.

[b]Isolated yield after column chromatographic purification.

were obtained in all the cases studied. For aromatic substrates with electron-donating substituents, the reaction time was longer giving moderate yields of **27a-l**. Notably, the cyanosilylation of (*E*)-cinnamaldehyde afforded exclusively the corresponding 1,2-addition product (entry **i**). However, the reaction failed in the case of ketones, probably due to steric reasons.

Table 2: Cyanosilylation of various aldehydes using organocatalyst 24[a]



27a-l

Entry	R	t/h	Yield (%)[b]
a	C_6H_5	24	51
b	4-$MeOC_6H_4$	24	52
c	4-MeC_6H_4	24	62
d	4-HOC_6H_4	24	57
e	4-FC_6H_4	10	73
f	4-NCC_6H_4	3	72
g	4-$O_2NC_6H_4$	3	92
h	$Ph(CH_2)_2$	10	80
i	Ph-CH=CH	10	60
j	$BnO(CH_2)_4$	10	83
k	$BnO(CH_2)_5$	10	83
l	$(CH_3)_2CH$	10	90

[a]Reaction conditions: aldehyde (5.0 mmol), TMSCN (6.0 mmol), organocatalyst **24** (0.5 mol%), CH_2Cl_2, 25° C. [b]Isolated yield after column chromatographic purification.

The formation of cyanohydrin silyl ethers **27a-l** was confirmed by ^1H, ^{13}C-NMR and IR spectroscopy. For example, the ^1H NMR spectrum of **27f** showed signals at δ 0.28 (s) and 5.57 (m) for methyl (TMS) and methine (C**H**OTMS) protons respectively. Its ^{13}C NMR spectrum showed a typical signal at δ 117.9 for the nitrile (CN) carbon (**Fig.4**).

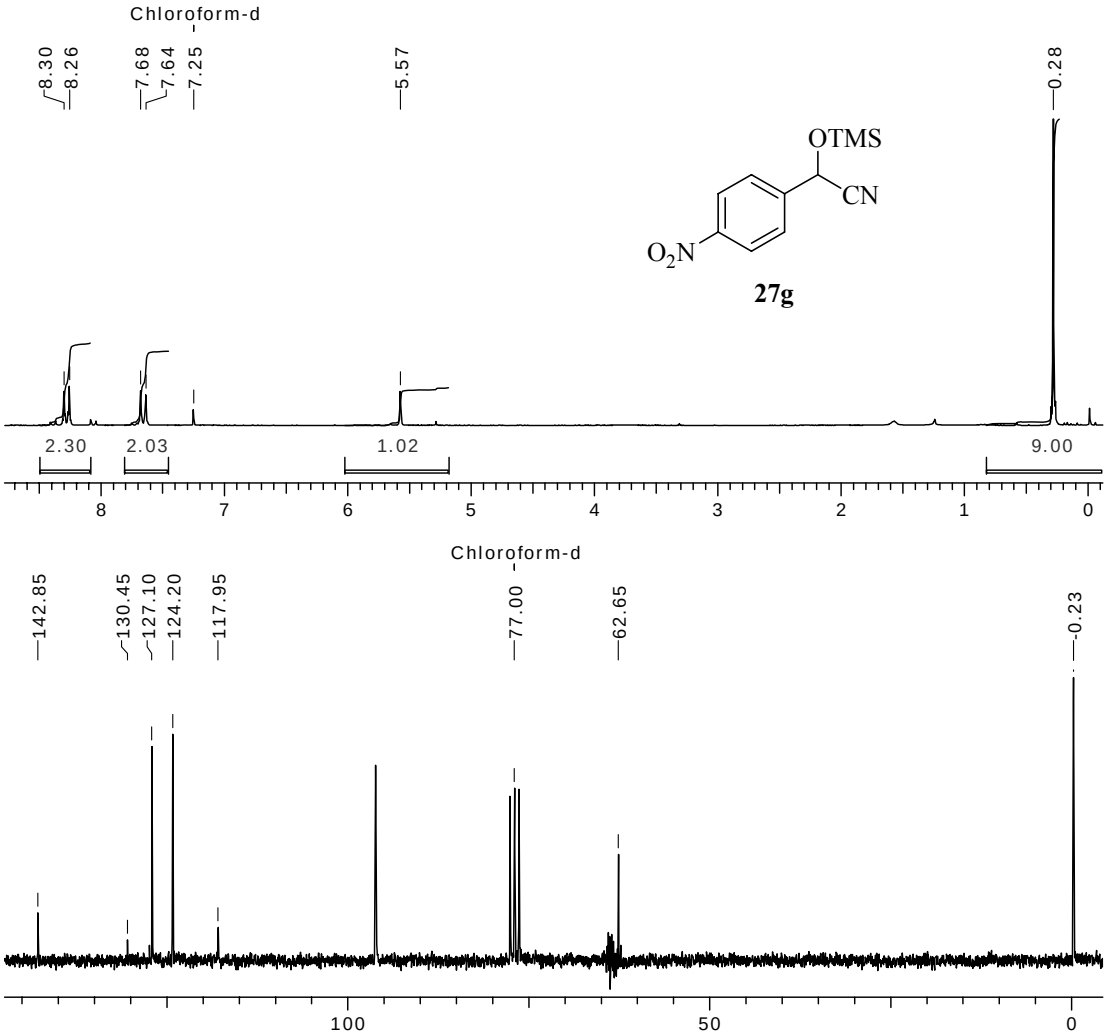


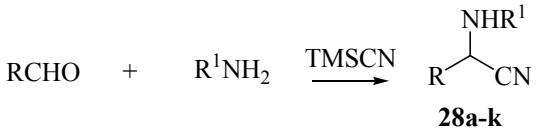
Fig. 4: ^{1}H and ^{13}C NMR spectra of 2-(4-nitrophenyl)-2 trimethylsilyloxy) (acetonitrile (27g)

The Strecker reaction between an aldehyde, an amine and hydrogen cyanide is widely regarded as the first multi-component reaction. α-Aminonitriles **28** are the precursors for several amino acids and also for popular bifunctional synthons that have found numerous synthetic applications.[9] We have extended the present catalytic system to Strecker-type α-aminonitrile synthesis, the results of which are presented in **Table 3**.

After initial experimentation, again catalyst **24** was found to be the most effective for the strecker type three-component reaction. Many aldehydes possessing both

electron-donating as well as electron-withdrawing groups underwent this condensation to afford the corresponding α-aminonitriles **6** in good yields.

Table 3: Strecker-type α-aminonitrile synthesis using 24 as catalyst and TMSCN as cyanide source[a]



28a-k

Entry	R	R^1	Yield (%)[b]
a	C_6H_5	4-$MeOC_6H_4$	77
b	4-$MeOC_6H_4$	4-$MeOC_6H_4$	79
c	3,4-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	67
d	$Ph(CH_2)_2$	4-$MeOC_6H_4$	81
e	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	81
f	4-ClC_6H_4	4-$MeOC_6H_4$	69
g	3- $O_2NC_6H_4$	4-$MeOC_6H_4$	72
h	3,4-methylenedioxyphenyl	4-$MeOC_6H_4$	68
i	CH_3-$(CH_2)_3$	4-$MeOC_6H_4$	73
j	CH_3-$(CH_2)_3$	morpholine	83
k	CH_3-$(CH_2)_3$	*n*-butyl	90

[a] Reaction conditions: aldehyde (5.0 mmol), TMSCN (6.0 mmol), amine (5.0 mmol), **24** (0.5 mol%), anhyd. $MgSO_4$,, CH_2Cl_2 (25 mL), 25 °C, 12 h.
[b] Isolated yield after column chromatographic purification.

The formation of α-aminonitrile **28** was confirmed by ^1H, ^{13}C-NMR and IR spectroscopy. For example, the ^1H spectrum of **28k** showed signals δ 3.47 (t) corresponding to methine proton. Its ^{13}C spectrum showed typical signal at δ 120 for the nitrile (CN) carbon. Moreover a sharp band at 2254 cm^{-1} in its IR spectrum confirms the formation of α-aminonitrile, **28k.**

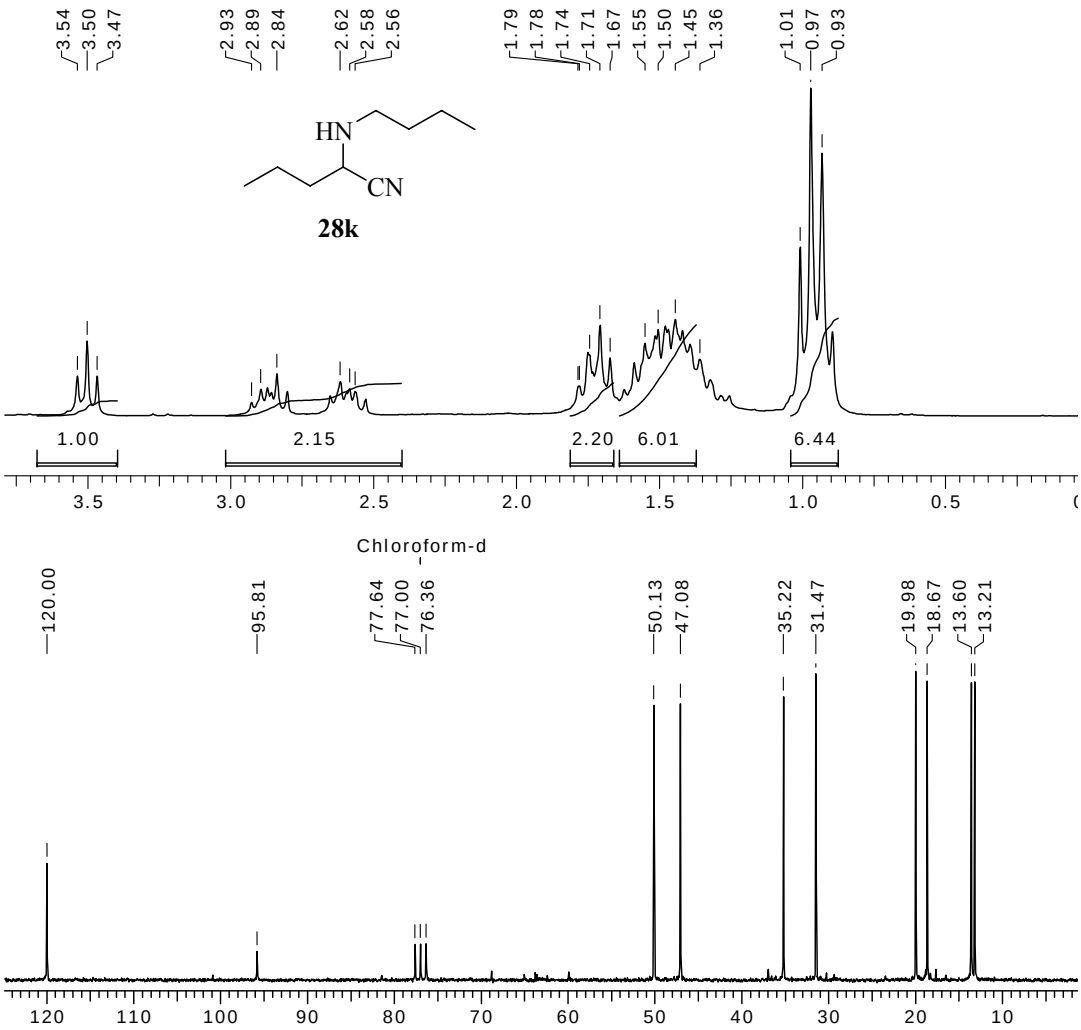
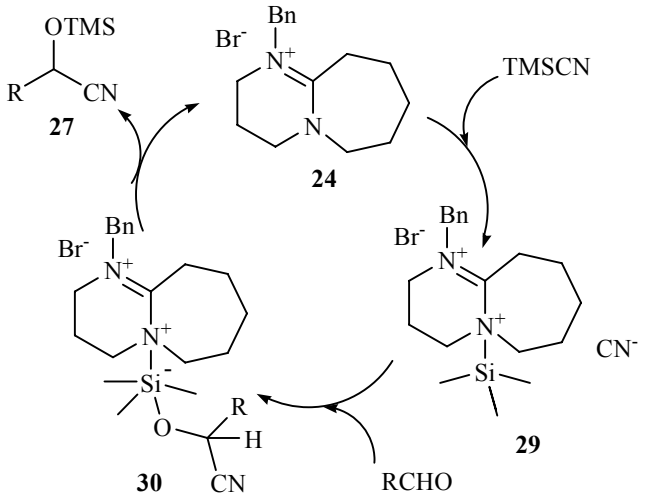


Fig. 5: ^{1}H and ^{13}C NMR spectra of 2-(butylamino)pentanenitrile

Mechanism

Scheme 16 shows the probable mechanistic pathway in which activation of the silyl group in TMSCN by the catalyst **24** leads to the formation of ion-pair **29**. Reaction of **29** with aldehydes gave the intermediate **30,** which subsequently dissociates into silylated cyanohydrin **27** with the regeneration of catalyst **24**.



Scheme 16: Possible pathway for the cyanosilylation of aldehydes

3.1.4 Conclusion

In conclusion, we have shown, for the first time, the use of ammonium salts as new Lewis base catalysts for cyanosilylation of aldehydes and the three-component Strecker- type α-aminonitrile synthesis under ambient conditions. Both the methods are effective and utilize the readily available cyanide source TMSCN.[10] These catalysts have also shown advantages in terms of chemical stability and high solubility in organic solvents.

3.1.5 Experiment Section

Preparation of catalysts (23-25)

To a stirred mixture of DBU (761 mg, 5 mmol) in toluene (2 mL) was added benzyl bromide (855 mg, 0.6 mL, 5 mmol) at 25 °C. After 2.5 h, diethylether (8 mL) was added to the reaction mixture, which resulted in precipitation of colorless solid. The solid was filtered on a sintered funnel, washed with diethyl ether and dried under reduced pressure (5 mm) for 3 h to afford catalyst **24** as colorless solid**.** In a similar manner catalyst **23** and **25** were prepared in high yields by reacting the respective amines with the corresponding alkyl halides.

Catalyst 23: Yield: 92%**;** colorless solid; **mp**: 259 °C (crystallized from CH_2Cl_2); **IR (neat)**: 822, 1037, 1180, 1292, 1443, 1849, 2962, 3355 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.14-3.30 (m, 8H), 3.70-3.77 (m, 6H), 5.02 (s, 2H), 7.41-7.43 (m, 3H), 7.64-7.67 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 43.9, 50.6, 70.5, 73.0, 126.6, 127.5, 128.2, 137.7; **Analysis**: **$C_{13}H_9BrN_2$** requires C, 55.13; H, 6.76; N, 9.89; found C, 55.18; H, 6.75; N, 9.81 %.

Catalyst 24: Yield: 98%; colorless solid; **mp**: 169 °C (crystallized from CH_2Cl_2); **IR** ($CHCl_3$,): 3417, 2936, 2176, 1621, 1525, 1453, 1327, 1200, 924, 733 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.68-1.71 (m, 6H), 2.18-2.29 (m, 2H), 2.94-3.0 (m, 3H), 3.71-3.84 (m, 6H), 4.91 (s, 2H), 7.23–7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.95, 22.24, 25.71, 28.06, 29.09, 47.52, 49.32, 55.45, 56.72, 126.11, 127.90, 128.91, 134.11, 167.04. **Analysis: $C_{16}H_{23}BrN_2$** requires C, 59.45; H, 7.17; N, 8.67; Br, 24.72%; found C, 59.41; H, 7.19; N, 8.69; Br, 24.70%.

Catalyst 25: Yield: 89%; colorless solid; **mp**: 201 °C (crystallized from CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52-2.68 (m, 21H), 3.16-3.22 (m, 3H), 3.43 (s, 3H), 4.15-4.40 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.2, 22.2, 23.7, 25.3, 27.5, 29.2, 31.0, 33.0, 47.1, 55.1, 61.0, 64.9, 66.0, 69.3, 72.5; **Analysis**: **$C_{16}H_{29}IN_2$** requires C, 51.07; H, 7.77; N, 7.44; found C, 51.03; H, 7.79; N, 7.43%.

General experimental procedure for cyanosilylation:

To a solution of catalyst **23**, **24** or **25** as the case may be (0.5 mol %) in dichloromethane (25 mL) under an argon atmosphere at 25 °C was added aldehyde (5.0 mmol) followed by TMSCN (6.0 mmol). The resulting mixture was stirred at 25 °C and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuum. The crude product was purified by

column chromatography on silica gel using 5% ethyl acetate in petroleum ether as eluent to afford the pure product.

2-Phenyl-2-(trimethylsilyloxy)acetonitrile (27a)

Yield: 51%; colourless oil; **IR** (KBr): 560, 665, 783, 1014, 1108, 1252, 1390, 1470, 1490, 1600, 1660, 1800, 1883, 1955, 2230, 2856, 2932, 2976, 3233, 3339 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.25 (s, 9 H), 5.80 (s, 1 H), 7.39-7.48 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ –0.27, 63.6, 119.1, 126.3, 129.0, 129.3, 136.2; **Analysis**: **$C_{11}H_{15}NOSi$** requires C, 64.34; H, 7.36; N, 6.82; found C, 64.31; H, 7.38; N, 6.89 %.

2-(4-Methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (27b)

Yield: 52%; Colourless oil; **IR** (KBr): 791, 1023, 1094, 1217, 1329, 1472, 1493, 1641, 1796, 2221, 2871, 2927, 3331 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.21 (s, 9 H) 3.82 (s, 3 H), 5.44 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 2 H), 7.93 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ –0.2, 55.3,, 63.3, 119.3, 114.2, 127.9, 128.4, 160.3 **Analysis**: **$C_{12}H_{17}NO_2Si$** requires C, 61.24; H, 7.28; N, 5.95; found C, C, 61.23; H, 7.22; N, 5.91 %.

2-(4-Methylphenyl)-2-trimethylsilyloxyacetonitrile (27c)

Yield: 62%; colorless oil; **IR** (KBr): 1042, 1206, 1455, 1583, 1598, 2248, 2821, 3065 cm^{-1}; **^{1}H NMR** (200 MHz, CDCl3,): δ 0.21 (s, 9H), 2.36 (s, 3H), 5.42 (s, 1H), 7.18-7.22 (d, *J* = 8.3 Hz, 2H) 7.34-7.38 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$,): 0.26, 21.1, 63.0, 119.0, 126.6, 129.1, 130.1, 139.5; **Analysis**: **$C_{12}H_{17}NOSi$** requires C, 65.71; H, 7.81; N, 6.39; found C, 65.72; H, 7.87; N, 6.30 %.

2-(4-Hydroxyphenyl)-2-(trimethylsilyloxy)acetonitrile (27d)

Yield: 57%; colorless liquid; **IR** (Neat): 693, 788, 1013, 1088, 1260, 1377, 1473, 1600, 1666, 1812, 1880, 1955, 2233, 2868, 2934, 2969, 3249, 3331cm^{-1}; **^{1}H-NMR** (200Mz, $CDCl_3$): 0.31 (s, 9H), 5.19 (brs, 1H), 5.34 (s, 1H), 6.70-6.85 (d, *J* = 9.00 Hz, 2H), 7.13-7.30 (d, *J* = 9.00 Hz, 2H); **^{13}C-NMR** (50Mz, $CDCl_3$): 0.3, 63.8, 116.0, 119.5, 120.7, 128.2, 151.2; **Analysis**: **$C_{11}H_{15}NO_2Si$** requires C, 59.69; H, 6.83; N, 6.33; found C, 59.60; H, 6.89; N, 6.38%.

2-(4-Flurophenyl)-2-(trimethylsilyloxy)acetonitrile (27e)

Yield: 73%; colorless liquid; **IR** (KBr): 1011, 1078, 1239, 1367, 1454, 1480, 1546, 1612, 1663, 1814, 1890, 1944, 2239, 2914, 2963, 2981, 3245, 3330 cm^{-1}; **^{1}H-NMR** (200 Mz, $CDCl_3$): 0.21 (s, 9H), 5.51 (s, 1H), 7.08-7.16 (m, 2H), 7.47-7.54 (m, 2H); **^{13}C-NMR** (50 Mz, $CDCl_3$): **Analysis**: **$C_{11}H_{14}FNOSi$** requires C, 59.16; H, 6.32; N, 6.27; found C, 59.16; H, 6.32; N, 6.27%

2-(4-cyanophenyl)-2-(trimethylsilyloxy)acetonitrile (27f)

Yield: 72%; colorless liquid; **IR** (Neat): 718, 1057, 1233, 1456, 1487, 1542, 1610, 1651, 1819, 1883, 1940, 2215, 2232, 2912, 2957, 2990, 3240, 3325 cm^{-1}; **^{1}H-NMR** (200 Mz, $CDCl_3$): 0.21 (s, 9H), 5.57 (s, 1H), 7.74-7.77 (d, *J* = 6.0 Hz, 2H), 8.13-8.16 ((d, *J* = 6.0 Hz, 2H); **^{13}C-NMR** (50 Mz, $CDCl_3$): 0.2, 63.1, 116.5, 117.4, 119.2, 129.9, 132.1, 133.3; **Analysis**: **$C_{12}H_{14}N_2OSi$** requires C, 62.57; H, 6.13; N, 12.16; found C, 62.59; H, 6.11; N, 12.13 %.

2-(4-Nitrophenyl)-2-(trimethylsilyloxy)acetonitrile (27g)

Yield: 92%; colorless liquid; **IR** (KBr): 790, 1011, 1080, 1256, 1377, 1465, 1484, 1612, 1658, 1807, 1890, 1955, 2232, 2855, 2935, 2988, 3243 cm^{-1}; **^{1}H-NMR** (200 Mz, $CDCl_3$): 0.29 (s, 9H), 5.59 (s, 1H), 7.67-7.69 (d, *J* = 8.2 Hz, 2H), 8.27-8.31 (d, *J* = 8.2 Hz, 2H); **^{13}C-NMR** (50 Mz, $CDCl_3$): 0.23, 62.6, 117.9, 124.2,

127.1, 130.4, 142.8; **Analysis**: $\mathbf{C_{11}H_{14}N_2O_3Si}$ requires C, 52.78; H; 5.64, N, 11.19; found C, 52.73; H; 5.61, N, 11.18%.

4-Phenyl-2-(trimethylsilyloxy)butanenitrile (27h)

Yield: 80%; colourless oil; **IR** (KBr): 700, 748, 1071, 1455, 1498, 2243, 2930, 3029, 3446 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.20 (s, 9 H), 2.13 (m, 2 H), 2.79 (t, *J* = 7.7 Hz, 2 H), 4.36 (t, *J* = 6.5Hz, 1 H), 7.17–7.24 (m, 3 H), 7.28–7.33 (m, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ –0.4, 30.6, 37.6, 60.6, 119.8, 126.3, 128.3, 128.4, 139.8; **Analysis**: $\mathbf{C_{13}H_{19}NOSi}$ requires C, 66.90; H; 8.21, N, 6.00; found C, 66.58; H; 8.26, N, 6.05%.

(*E*)-4-Phenyl-2-(trimethylsilyloxy)but-3-enenitrile (27i)

Yield: 60%; colourless oil; **IR** (KBr): 701, 761, 1015, 1049, 1455, 2243, 2974, 3031 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.25 (s, 9 H), 5.12 (d, *J* = 6.0 Hz, 1 H), 6.19 (dd, *J* = 15.9, 6.0 Hz, 1 H), 6.81 (d, *J* = 15.9 Hz, 1 H), 7.31–7.43 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ –0.2, 62.2, 118.3, 123.5, 126.9, 128.7, 128.7, 133.9, 134.9; $\mathbf{C_{13}H_{17}NOSi}$ requires C, 67.49; H; 7.41, N, 6.05; found C, 67.51; H; 7.47; N, 6.00%.

5-Benzyloxy-2-(trimethylsilyloxy)pentanenitrile (27j)

Yield: 83%; colorless liquid; **IR**(KBr) 720, 1049, 1238, 1451, 1487, 1523, 1618, 1647, 1820, 1883, 1940, 2213, 3240, 3325 $cm^{-1}cm^{-1}$; **^{1}H-NMR** (200Mz, $CDCl_3$): 0.06 (s, 9H), 1.55-1.89 (m, 4H), 3.33-3.90 (t, *J* = 5.9 Hz, 2H), 4.21-4.26 (m, 1H), 4.35 (s, 2H), 7.15-7.20 (m, 5H); **^{13}C-NMR** (50 Mz, $CDCl_3$): 0.3, 21.4, 29.0, 35.9, 61.2, 69.5, 72.8, 119.7, 127.5, 128.3, 138.3; **Analysis**: $\mathbf{C_{15}H_{23}NO_2Si}$ requires C, 64.94; H, 8.36; N, 5.05; found C, 64.91; H, 8.38; N, 5.09%

6-Benzyloxy-2-(trimethylsilyloxy)hexanenitrile (27k)

Yield: 83%; colorless liquid; **IR** (KBr) 723, 1021, 1213, 1451, 1601, 2213, 1819, 2278, 3029, 3341 cm^{-1}; **^{1}H-NMR** (200 Mz, $CDCl_3$): 0.10 (s, 9H), 1.44-1.75 (m, 6H), 3.40-3.44 (t, *J* = 6.7 Hz, 2H), 4.24-4.30 (t, *J* = 6.2 Hz, 1H), 4.39 (s, 2H), 7.14-7.24 (m, 5H); **^{13}C-NMR** (50Mz, $CDCl_3$): 0.40, 24.8, 33.3, 61.2, 69.1, 72.9, 119.7, 127.5, 127.7, 128.3, 128.4, 138.2; **Analysis**: **$C_{16}H_{25}NO_2Si$**: C, 65.93; H, 8.65; N, 4.81; found C, 65.92; H, 8.61; N, 4.82%.

3-Methyl-2-trimethylsilyloxybutanenitrile (27l)

Yield: 90%**;** colorless liquid; **IR** (KBr): 1075, 1469, 1637, 2248, 2966, 3447 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.2 (s, 9H), 0.88-1.05 (m, 6H), 1.94-1.96 (m, 1H), 4.16 (d, *J* = 6.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$,): δ -0.3, 17.6, 33.9, 67.2, 119.9; **Analysis**: **$C_8H_{17}NOSi$** requires C, 56.09; H, 10.00; N, 8.18; found C, 56.02; H, 10.13; N, 8.12%.

(4-Methoxy-phenylamino)phenylacetonitrile (28a)

Yield: 77%; yellow colored solid; **mp:** 72-73^{0}C (crystallized from $CHCl_3$); **IR** (Neat): 682, 788, 1030, 1092, 1257, 1385, 1457, 1604, 2235, 2862, 2931, 2958, 3342 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 5.34 (s, 1H), 6.72–6.79 (d, *J* = 9.4 Hz, 2H), 6.93-6.94 (d, *J* = 9.4 Hz, 2H), 7.43-7.48 (m, 3H), 7.58-7.63 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.7, 55.0, 114.5, 115.8, 118.3, 126.8, 128.7, 129.3, 133.9, 138.3, 153.4; **Analysis: $C_{15}H_{14}N_2O$** requires C, 75.61; H, 5.92; N, 11.76; found C, 75.63; H, 5.96; N, 11.79%.

(4-Methoxyphenyl)(4-methoxyphenylamino)acetonitrile (28b)

Yield: 79%; red colored solid; **mp:** 69-71^{0}C (crystallized from $CHCl_3$); **IR** (Neat): 685, 791, 1021, 1084, 1237, 1383, 1464, 1486, 1604, 1649, 1796, 1881, 1951, 2226, 2849, 2927, 2968, 3232, 3331 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ

3.76 (s, 3H), 3.83 (s, 3H), 5.25 (s, 1H), 6.70-6.84 (d, *J* = 9.0 Hz, 4H), 6.91-6.95 (d, *J* = 8.6 Hz, 2H), 7.46-7.50 (d, *J* = 8.6 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.4, 55.4, 114.7, 115.0, 116.3, 129.1, 140.1, 153.9, 160.6; **Analysis: $C_{16}H_{16}N_2O_2$** requires C, 71.62; H, 6.01; N, 10.44; found C, 71.63; H, 6.00; N, 10.39%.

(3,4-Dimethoxyphenyl)(4-methoxyphenylamino)acetonitrile (28c)

Yield: 67%; **IR** (Neat): 1015, 1090, 1250, 1390, 1494, 1600, 1650, 1882, 2228, 2857, 2933, 2974, 3235, 3337 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.78 (d, 6H), 3.87(s, 3H), 5.32 (s, 1H), 6.67-7.52 (m, 7H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.4, 55.0, 55.4, 114.7, 115.0, 116.3, 129.1, 140.1, 141.2, 153.9, 160.6; **Analysis: $C_{17}H_{18}N_2O_3$** requires C, 68.44; H, 6.08; N, 9.39; found C, 68.47; H, 6.10; N, 9.40%.

2-(4-Methoxyphenylamino) 4-phenylbutanenitrile (28d)

Yield:81%; **IR** (Neat): 763, 811, 1223, 1372, 1491, 1600, 1629, 2226, 2923, 2994, 3215, 3340 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.21-2.28 (t, *J* = 9.1 Hz, 2H), 2.87-2.96 (m, 2H), 3.74 (s, 3H), 4.01-4.23 (m, 1H), 6.58–6.62 (d, *J* = 8.1 Hz, 2H), 6.76-6.80 (d, *J* = 8.1 Hz, 2H), 7.22-7.32 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 31.6, 34.8, 46.3, 55.4, 114.9, 116.1, 119.6, 126.5, 128.4, 128.6, 138.7, 139.4, 153.9; **Analysis: $C_{17}H_{18}N_2O$** requires C, 76.66; H, 6.81; N, 10.52; found C, 76.68; H, 6.83; N, 10.51%.

(4-Methoxyphenylamino)(4-nitrophenyl)acetonitrile (28e)

Yield: 81%; brown colored solid; **mp:** 104-107 ^{0}C; **IR** (Neat): 684, 780, 1014, 1090, 1251, 1390, 1472, 1500, 1605, 1656, 1807, 1890, 1953, 2160, 2240, 2850, 2935, 2973, 3231, 3344 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.42 (s, 1H), 6.71-6.85 (d, *J* = 9.0 Hz, 2H), 6.90-6.94 (d, *J* = 8.6 Hz, 2H), 7.31-7.42 (d, *J* = 8.4 Hz, 2H), 8.06-8.17 (d, *J* = 8.1 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ

50.4, 55.2, 114.7, 115.0, 122.1, 129.9, 135.8, 140.1, 148.8, 156.1, 160.6; **Analysis:** $C_{15}H_{13}N_3O_3$ requires C, 63.60; H, 4.63; N, 14.83; found C, 63.60; H, 4.60; N, 14.57%.

(4-Chlorophenyl)(4-methoxyphenylamino)acetonitrile (28f)

Yield: 69%; **IR** (Neat): 1011, 1078, 1239, 1367, 1454, 1480, 1546, 1612, 1663, 1814, 1890, 1944, 2239, 2914, 2963, 2981, 3245, 3330 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.41 (s, 1H), 6.81-7.21 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 50.3, 55.3, 114.9, 116.3, 118.7, 129.2, 134.1, 139.4, 153.9 cm^{-1}; **Analysis:** $C_{15}H_{13}ClN_2O$ requires C, 66.06; H, 4.80; Cl, 13.00; N, 10.27; found C, 66.00; H, 4.78; Cl, 13.00; N, 10.22%.

(4-Methoxyphenylamino)(3-nitrophenyl)acetonitrile (28g)

Yield: 72%; yellow colored solid; **mp:** 95–98^{0}C (crystallized from MeOH); **IR** (Neat): 790, 1011, 1080, 1256, 1377, 1465, 1484, 1612, 1658, 1807, 1890, 1955, 2232, 2855, 2935, 2988, 3243, 3329 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 5.30 (s, 1H), 6.68-6.84 (dd, J = 9.40 Hz, 2H), 7.45-8.16 (m, 6H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.8, 55.3, 113.2, 114.5, 115.8, 118.3, 122.3, 126.8, 128.7, 133.9, 138.39, 147.7, 153.4; **Analysis:** $C_{15}H_{13}N_3O_3$ requires C, 63.60; H, 4.63; N, 14.83; found C, 63.55; H, 4.61; N, 14.88%.

Benzo[1,3]dioxol-5-yl-(4-methoxyphenylamino)acetonitrile (28h)

Yield: 68%; brown colored solid; **mp:** 112-114^{0}C (crystallized from EtOAc); **IR** (Neat): 692, 769, 1009, 1090, 1251, 1393, 1470, 1488, 1604, 1655, 1800, 1888, 1952, 2232, 2840, 2935, 2973, 3228, 3334 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.82 (s, 2H), 5.20 (s, 1H), 6.00 (s, 2H), 6.66-6.84 (m, 3H), 7.01-7.09 (m, 2H); **^{13}C-NMR** (200 MHz, CD_3COCD_3): δ 50.6, 55.4, 101.9, 107.9, 108.5,

114.9, 116.2, 119.2, 121.1, 129.1, 139.7, 148.5, 153.8; **Analysis: $C_{16}H_{14}N_2O_3$** requires C, 68.07; H, 5.00; N, 9.92; found C, 68.00; H, 5.00; N, 10.00%.

2-(4-Methoxyphenylamino)pentanenitrile (28i):

Yield: 73%**;** colorless liquid; **IR** (Neat): 923, 1101, 1326, 1453, 1618, 2181, 2937, 3409 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.97-1.04 (t, *J* = 6.2 Hz, 3H), 1.59-1.04 (m, 2H), 1.88-1.92 (m, 2H), 3.75 (s, 3H), 4.12 (t, *J* = 6.9 Hz, 1H), 6.67-6.71 (d, *J* = 8.3 Hz, 2H), 6.81-6.85 (d, *J* = 8.3 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.3, 18.8, 35.3, 46.9, 55.5, 114.9, 116.0, 119.8, 138.8, 153.7; **Analysis: $C_{12}H_{16}N_2O$** requires C, 70.56; H, 7.90; N, 13.71; found C, 70.59; H, 7.91; N, 13.78%.

2-Morpholinopentanenitrile (28j):

Yield: 83%**;** colorless liquid; **IR** (Neat): 913, 1118, 1253, 1382, 1455, 1721, 2253, 2964, 3481 , 3674 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.94-1.01 (t, *J* = 8.3 Hz, 3H), 1.45-1.54 (m, 2H), 1.67-1.78 (m, 2H), 2.42-2.42 (m, 2H), 2.63-2.73 (m, 2H), 3.41-3.49 (t, *J* = 8.1 Hz, 1H), 3.71-3.79 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.2, 18.9, 32.2, 49.7, 57.5, 66.3, 116.4; **Analysis: $C_9H_{16}N_2O$** requires C, 64.25; H, 9.59; N, 16.65; found 64.21; H, 9.55; N, 16.62%.

2-(Butylamino)pentanenitrile (28k)

Yield: 90%; colorless liquid; **IR** (Neat): 909, 1137, 1276, 1154, 2962, 3326 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.93-1.01 (t, *J* = 8.3 Hz, 6H), 1.45-1.79 (m, 6H), 1.67-1.79 (m, 2H), 2.53-2.65 (m, 1H), 2.80-2.89 (m, 1H), 3.47 -3.54 (t, *J* = 6.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 13.2, 13.6, 18.6, 19.8, 31.4, 35.2, 47.0, 50.1, 120.0; **Analysis: $C_9H_{18}N_2$** requires C, 70.08; H, 11.76; N, 18.16; found C, 70.03; H, 11.71; N, 18.19%.

Section 2: A facile direct conversion of aldehydes to esters and amides using acetone cyanohydrin

3.2.1 Introduction

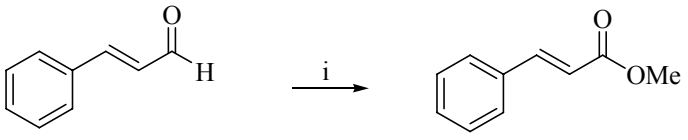
The direct transformation of aldehydes into the corresponding esters[11] and amides[12] under mild conditions is often required in organic synthesis especially in the synthesis of natural products.[13] Esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers etc., many of which are classed as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity.

3.2.2 Literature Survey

Literature Survey revealed that there are various methods available for the direct transformation of aldehydes into the corresponding esters and amids. Recently, Several new procedures involving oxone,[14a] SnO_2/SBA-1-H_2O_2[14b] and pyridinium hydrobromide perbromide[14c] have been employed for the direct oxidative conversion of aldehydes to esters. Some of the recent developments on this reaction are discussed below.

Gopinath's approach (2000)[15]

In Gopinath's approach, aldehydes, in the presence of methanol, undergo oxidative transformation to the corresponding esters upon treatment with catalytic amounts of



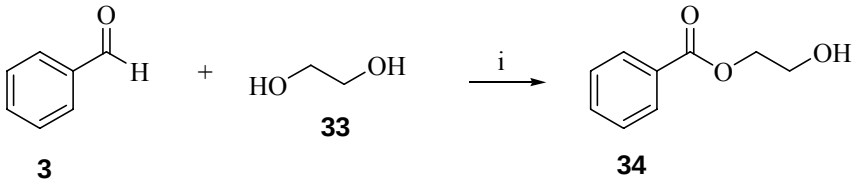
31 **32**

Scheme 17: (i) V_2O_5 (cat.), MeOH, H_2O_2, 80 °C, 100%.

vanadium pentoxide in combination with oxidant 30% hydrogen peroxide (**Scheme 17**).

Sarvari's approach (2003)[14k]

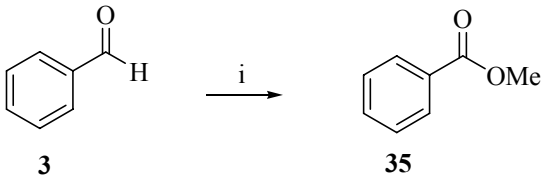
Sarvari' *et al* have found $Al_2O_3/MeSO_3H$ (AMA) as an extremely efficient reagent for the conversion of aromatic aldehydes and diols to glycol monoesters **34**. The remarkable selectivity achieved with this reagent is an attractive feature of this method (**Scheme 18**).



Scheme 18: (i) Al_2O_3, $MeSO_3H$, 80 °C, 4 h, 80%

Traivs's approach (2003)[16]

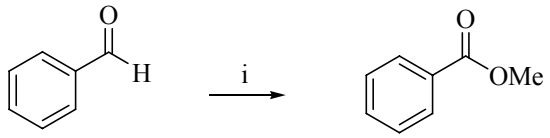
Travis *et al*. have developed a highly efficient, mild, and simple protocol for the oxidation of aldehydes to carboxylic acids utilizing oxone as the sole oxidant. Direct conversion of aldehydes in alcoholic solvents to their corresponding ester products is also reported. These reactions may prove to be valuable alternatives to traditional metal-mediated oxidations but it uses more than stoichiometric amounts of oxone (**Scheme 19**).



Scheme 19: (i) Oxone, MeOH, 18 h, 25 °C, 96%.

Onami's approach (2004)[18]

In this approach, the direct esterification of aldehydes and alcohols was carried out with pyridinium hydrobromide perbromide (PHPB) in water at room temperature. A variety of aldehydes were converted to respective ester derivatives with alcohols such as methanol, 1,2-ethanediol, 1,3-propanediol. Further, a variety of aliphatic alcohols were also converted to the corresponding Tishchenko-like dimeric esters in good yields under the same reaction conditions (**Scheme 20**.

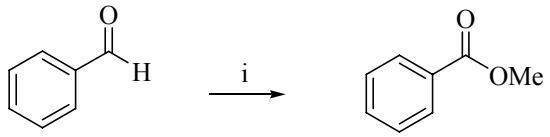


3 **35**

Scheme 20: PHPB, MeOH, H_2O, 25 °C, 87 h, 94%.

Budhewar's approach (2006)[14l]

Budhewar *et al* have developed a simple and mild procedure for the facile direct oxidative methyl esterification of aldehydes using molecular iodine in combination with (diacetoxyiodo)benzene in methanol. Oxidative esterification is induced by iodonium ion generated *in situ* by the chemical oxidation of molecular iodine with (diacetoxyiodo)benzene (**Scheme 21**).



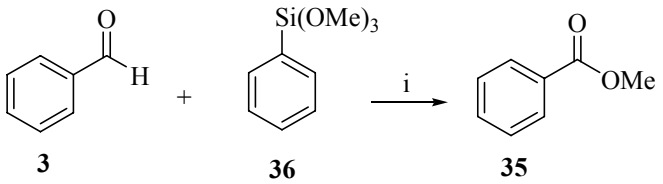
3 **35**

Scheme 21: (i) I_2, $PhI(OAc)_2$, MeOH, 25 °C, 87%.

Wolf's approach (2006)[14m]

In this approach, aldehydes and siloxanes **36** form methyl esters in a single step through mild oxidative esterification in the presence of a palladium catalyst or,

alternatively, afford secondary alcohols *via* TBAF-promoted arylation (**Scheme 22**).

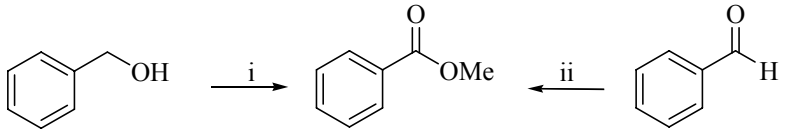


3 **36** **35**

Scheme 22: (i) POPd (cat.), TBAF, CH_3CN, 25 °C, 97%.

Sudalai's approach (2007)[14n]

In this method, aromatic aldehydes or benzylic alcohols **37** are directly converted to the corresponding aromatic esters in high yields on treatment with methanol or ethanol using sodium metaperiodate ($NaIO_4$)/LiBr as oxidant in an acidic medium (**Scheme 23**).

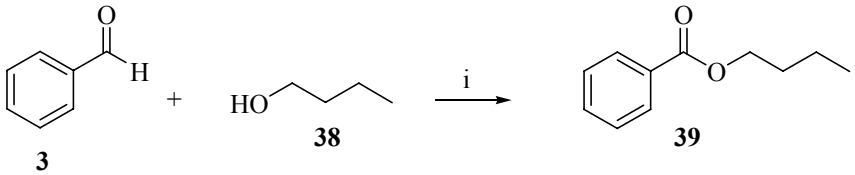


37 **35** **3**

Scheme 23: (i) LiBr, $NaIO_4$, H_2SO_4, MeOH, 25 °C , 89% (ii) LiBr, $NaIO_4$, H_2SO_4, MeOH, 25 °C , 98%.

Li's approach (2007)[14n]

Li *et al* have developed an oxidative esterification reaction between aldehydes and alcohols **38** catalyzed by a combination of $Cu(ClO_4)_2.6H_2O$ and $InBr_3$ using TBHP as an oxidant (**Scheme 24**).

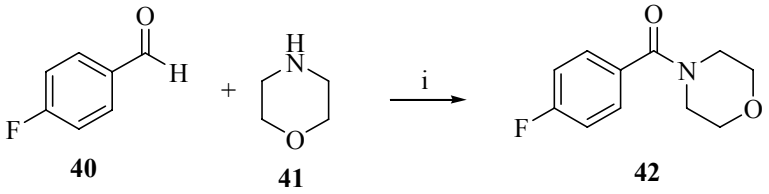


3 **38** **39**

Scheme 24: (i) $Cu(ClO_4)_2$ $6H_2O$, $InBr_3$, TBHP, 100 ^oC, 16 h, 91%.

Beller's approach (2001)[21a]

Beller's approach make use of *N*-methylmorpholine *N*-oxide as an oxidant in the presence of catalytic amounts of rhodium for the oxidative amination of aldehydes to give the corresponding amide **42**. Both aliphatic and aromatic aldehydes react with secondary amines to yield carboxylic acid amides in good to excellent yields (**Scheme 25**).

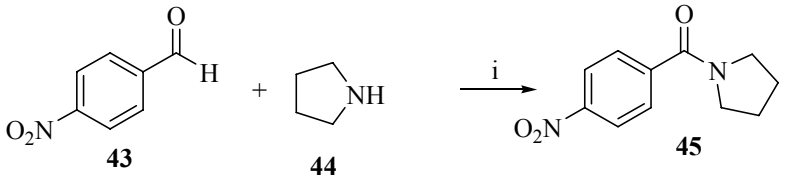


40 **41** **42**

Scheme 25: (i) $[Rh(COD)_2]BF_4$, PPh3, toluene, THF, 100 °C, 29%.

Wolf's approach (2007)[21b]

This approach describes metal-free oxidative amination of aromatic aldehydes in the presence of TBHP to provide amides **45** in 85-99% under mild reaction conditions. This method avoids free carboxylic acid intermediates and integrates aldehyde oxidation and amide bond formation, which are usually accomplished separately, into a single operation (**Scheme 26**).



43 **44** **45**

Scheme 26 (i) TBHP, CH_3CN, 80 °C.

3.2.3 Present Work

3.2.3.1 Objective

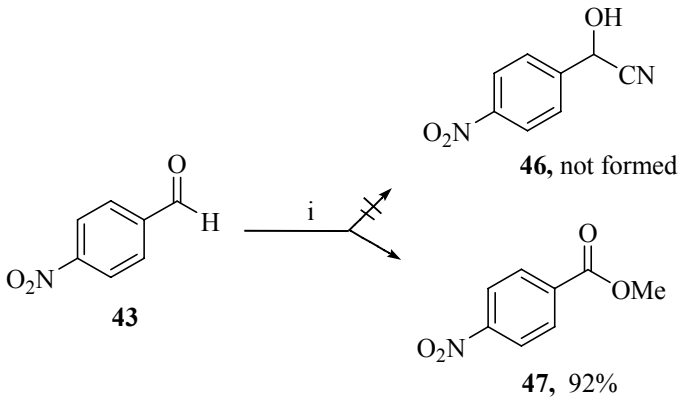
Although several reports of transformation of aldehydes into esters in the presence of alcohols has been reported, these methods usually require harsh conditions and are effective for a limited range of substrates (electron-rich aldehydes and primary alcohols). All these transformation generally involves an oxidative pathway and

requires more than stoichiometric amount of oxidants and long reaction times. Also these reagents are unsatisfactory for aldehydes containing electron-withdrawing groups. Moreover, formation of minor amounts of acids often complicates the oxidative process.

Direct transformation of aldehydes into amides is also an important method in organic synthesis and usually requires transition metal catalysts such as palladium,[19] ruthenium[20] and rhodium.[21a] However, these systems suffer from use of stoichiometric amount of oxidants coupled with low yields of the products. This section describes a facile method for the direct conversion of electron deficient aldehydes to esters and amides mediated by acetone cyanohydrin in the presence of base.

3.2.4 Results and Discussion

During our investigation of the hydrocyanation of 4-nitrobenzaldehyde (**43**) with acetone cyanohydrin in the presence of Et_3N in methanol as solvent, we found surprisingly that the corresponding methyl ester **47**, was obtained in 92% yield instead of the expected cyanohydrin **46** (**Scheme 24**).



Scheme 27: Reaction conditions: (i) 4-nitrobenzaldehyde (5 mmol), acetone cyanohydrin (5 mmol), Et_3N (7.5 mmol), MeOH (5 mL), 25 ^{0}C, 2 h.

Control experiments indicated that no reaction took place in the absence of either the acetone cyanohydrin or Et_3N. Both KOH and Et_3N could be used as the base for this transformation although *t*-BuOK and DABCO were found to be less effective. The results in **Table 4** show that a variety of solvents could be employed successfully for the reaction of 4-nitrobenzaldehyde with methanol. Although most of the polar solvents displayed comparable activity, methanol was found to give the best yield. However, when water was employed as solvent, the only product obtained was the corresponding carboxylic acid.

Table 4: Esterification of 4-nitrobenzaldehyde with methanol using acetone cyanohydrin: effect of solvents

Entry	Solvent	Yield (%)[a]
1	CH_3OH	92
2	CH_3CN	70
3	THF	54
4	benzene	20
5	CH_2Cl_2	23
6	DMF	57
7	acetone	83
8	H_2O	81[b]

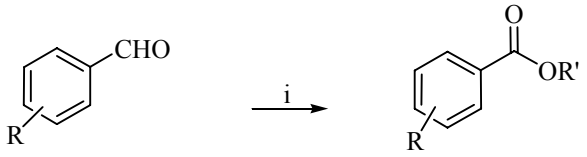
[a] Isolated yield after column chromatographic purification.
[b] 4-nitrobenzoic acid was obtained.

In order to understand the scope and generality of the reaction, a wide range of aldehydes was subjected to the reaction with a variety of alcohols under these reaction conditions. As can be seen, the method worked exceedingly well in the

case of aromatic aldehydes with electron-withdrawing groups such as halo, nitro, CF_3, cyano, etc. (**Table 5**).

Unfortunately, the reaction failed for electron-rich benzaldehydes as well as aliphatic aldehydes perhaps because the nucleophilic addition of cyanide ion onto electron-rich aromatic substrates is more difficult. The formation of esters **47a-j** was confirmed by ^1H, ^{13}C-NMR and IR spectroscopy. For example, the ^1H NMR spectrum of **47e** showed signals at δ 2.53 (t) and 4.94 (d) for propargyl group of **47e**. Its ^{13}C NMR spectrum showed a typical signal at δ 163.8 for the ester group (**Fig. 6**).

Table 5: Acetone cyanohydrin-mediated esterification of deactivated aromatic aldehydes with alcohols[a]



47a-j

Entry	R	Base	Yield of **47** (%)[a]		
			R'= methyl I	allyl[b] II	Propargyl[b] III
a	3-NO_2	Et_3N	78	64	75
b	4- NO_2	Et_3N	92	70	63
c	4-Cl	KOH	82	78	75
d	4-Br	KOH	73	62	85
e	4-CN	Et_3N	80	76	83
f	3-CF_3	KOH	70	62	85
g	4-F	KOH	60	62	-
h	2-CN	Et_3N	61	-	-

Reaction conditions: (i) acetone cyanohydrin (5 mmol), base (7.5 mmol), alcohol (5 mL), 25 ^{0}C, 2 h.
[b] Isolated yield after column chromatographic purification.

[c] Acetonitrile was used as solvent.

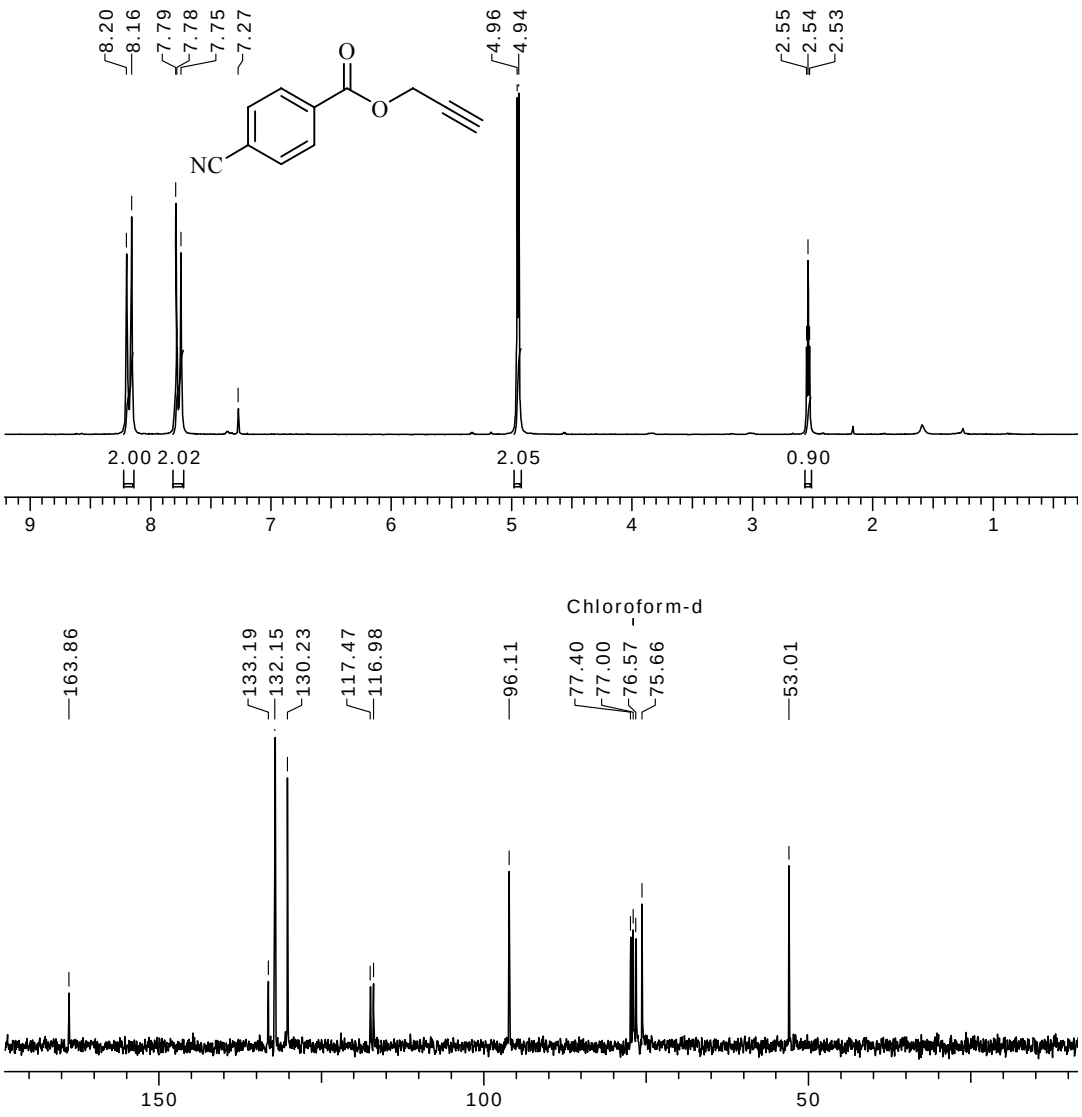
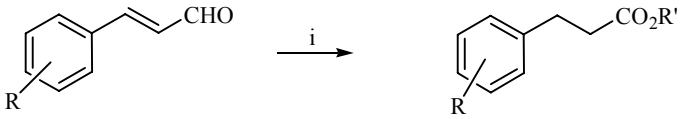


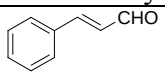
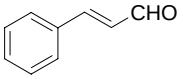
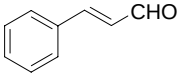
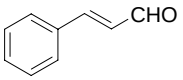
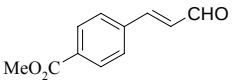
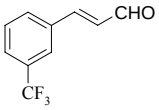
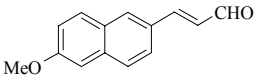
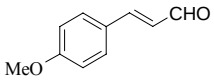
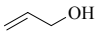
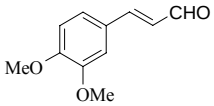
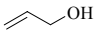
Fig. 6: ^{1}H and ^{13}C-NMR spectra of propargyl 4-cyanobenzoate (47e)

A noteworthy feature of this protocol is that α,β-unsaturated aldehydes when subjected to these reaction conditions gave the corresponding saturated esters[22-23] (**Table 6**). Thus both ester formation and reduction of the C=C bond were achieved in a single step for α,β-unsaturated aldehydes when treated with NaCN or acetone cyanohydrin in the presence

Table 6: Cyanide mediated esterification and reduction of α, β-unsaturated aldehydes with alcohols



48a-i

Entry	Aldehyde	Alcohol	Yield of **48** (%)[b]
a		CH_3OH	93
b			86
c			89
d			88
e			76
f			66
g			61
h			64
i			57

[a] Reaction conditions: (i) acetone cyanohydrin (5 mmol), Et_3N (7.5 mmol), alcohol (5 mL), 25 ^{0}C, 2 h. [b] Isolated yield after column chromatographic purification.

of an alcohol. A wide range of substituted cinnamaldehydes (**48a-i**) can be converted into saturated esters when subjected to these conditions (**Fig. 7**).

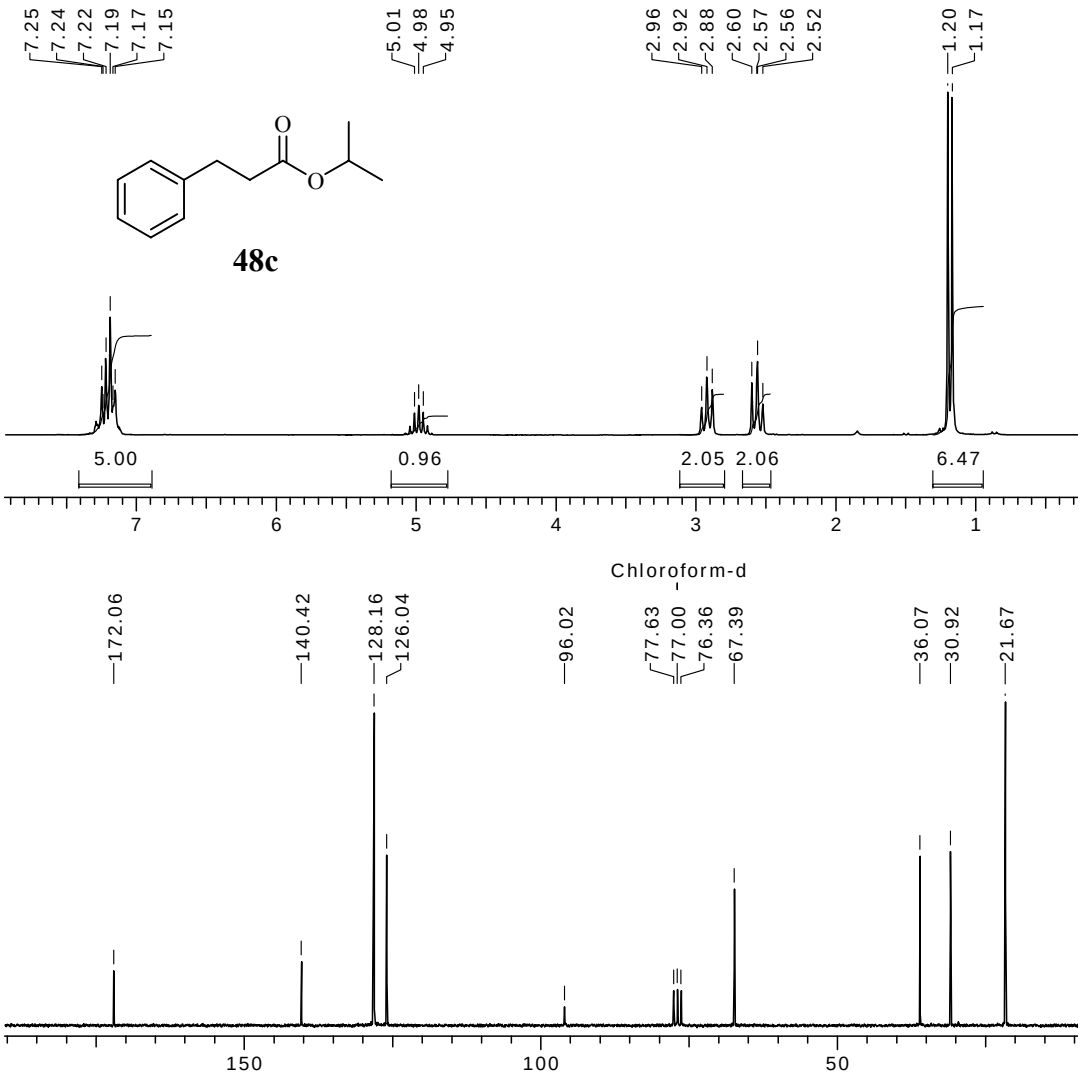


Fig. 7: ^{1}H and ^{13}C-NMR spectra of isopropyl 3-phenylpropanoate (48c)

We have applied the ester formation–reduction strategy to the synthesis of Nabumetone 52, a non-steroidal anti-inflammatory drug[24-25] (Scheme 28). Thus, alcohol 49 on Vilsmeier-Haack reaction, gave the unsaturated aldehyde 50, in 47% yield. The ^{1}H-NMR spectrum of α,β-unsaturated aldehyde 50, showed typical signal at δ 9.72 corresponding

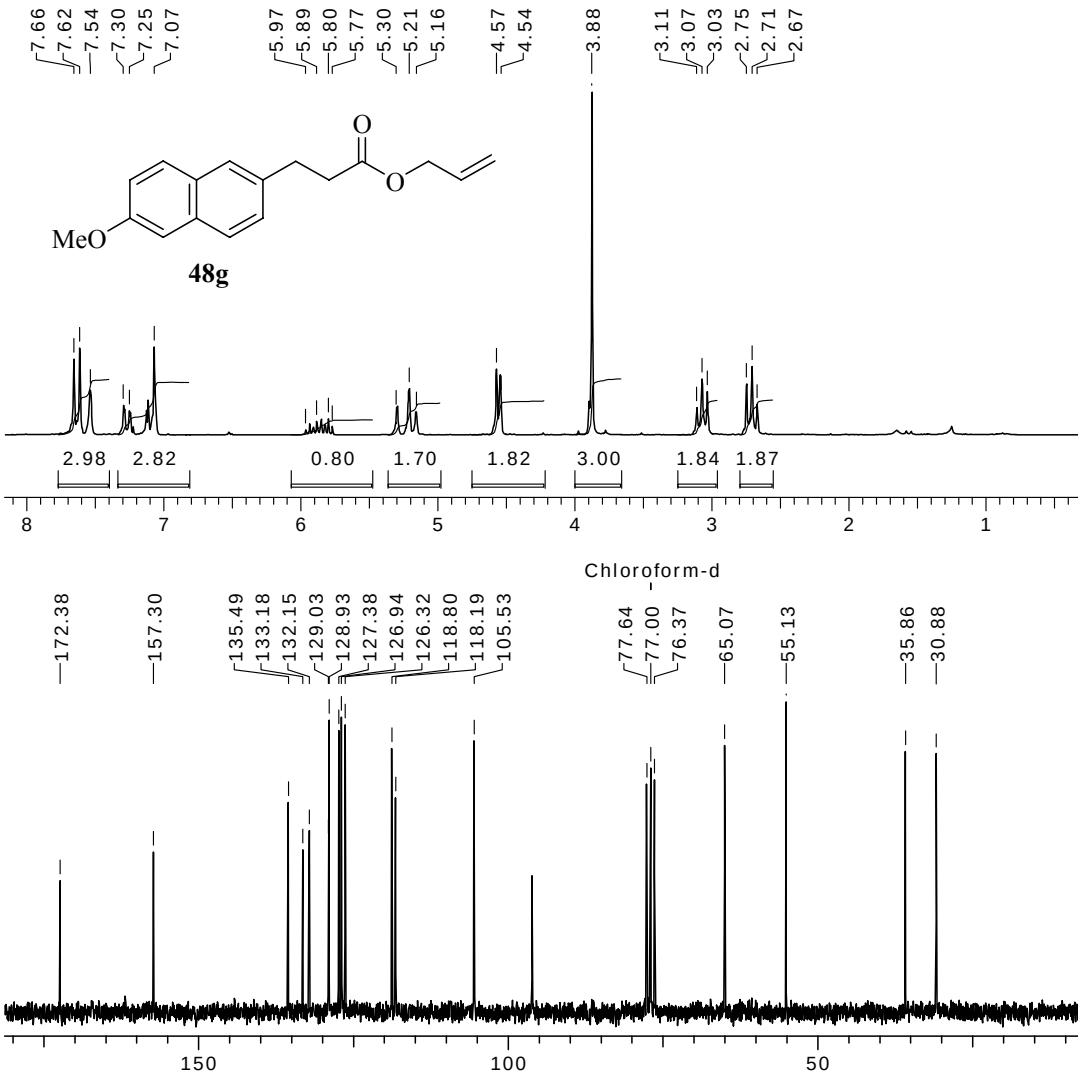
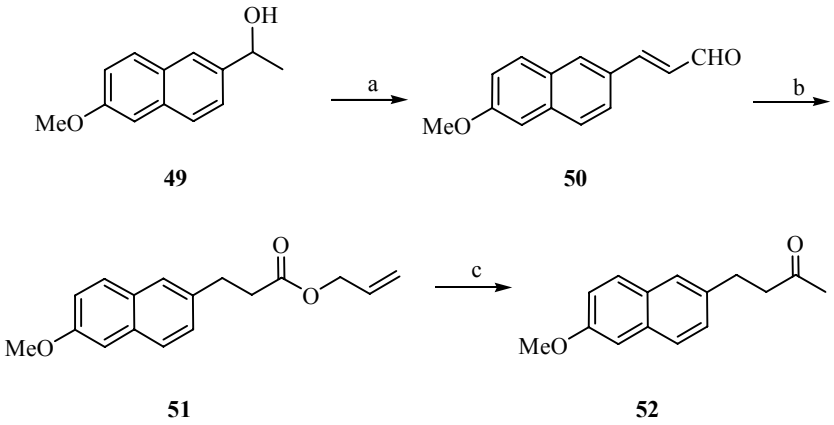


Fig. 8: ^{1}H and ^{13}C NMR allyl 3-(2-methoxynaphthalen-6-yl) propanoate

to the aldehydic proton. Its ^{13}C NMR showed characteristic signal at δ 193.6 corresponding to the carbonyl carbon. Moreover a sharp band at 1683 cm^{-1} in its IR spectra confirms the α,β-unsaturated aldehyde**.**



49 **50**

51 **52**

Scheme 28: Reagents and conditions: (a) $POCl_3$, DMF, 100 °C, 47 %; (b) acetone cyanohydrin, Et_3N, CH_2Cl_2, allyl alcohol, 25 °C, 2h, 61 %; (c) MeMgI, THF, -55 °C, 51%.

α,β-unsaturated aldehyde was then, subjected to the cyanide-mediated ester formation–reduction protocol to afford the saturated ester **51** in 61% yield. The ^{1}H-NMR spectrum of saturated ester **51**, showed typical signals at δ 2.67 (t) and 3.03 (t) corresponding to the methylene groups. Its ^{13}C NMR showed a characteristic signal at δ 172.3 corresponding to the ester carbonyl group (**Fig. 8**). Treatment of ester with one mole of Grignard reagent afforded nabumetone **52** in 51% yield (**Scheme 28**). The ^{1}H NMR spectrum of nabumetone (**52**) showed singlet δ 2.13 corresponding to methylene proton. Its ^{13}C-NMR spectrum showed a signal at δ 207.5 due to the carbonyl carbon. Its MS spectra showed m/z at 228, thus confirming the formation of ketone **52** (**Fig. 9**).

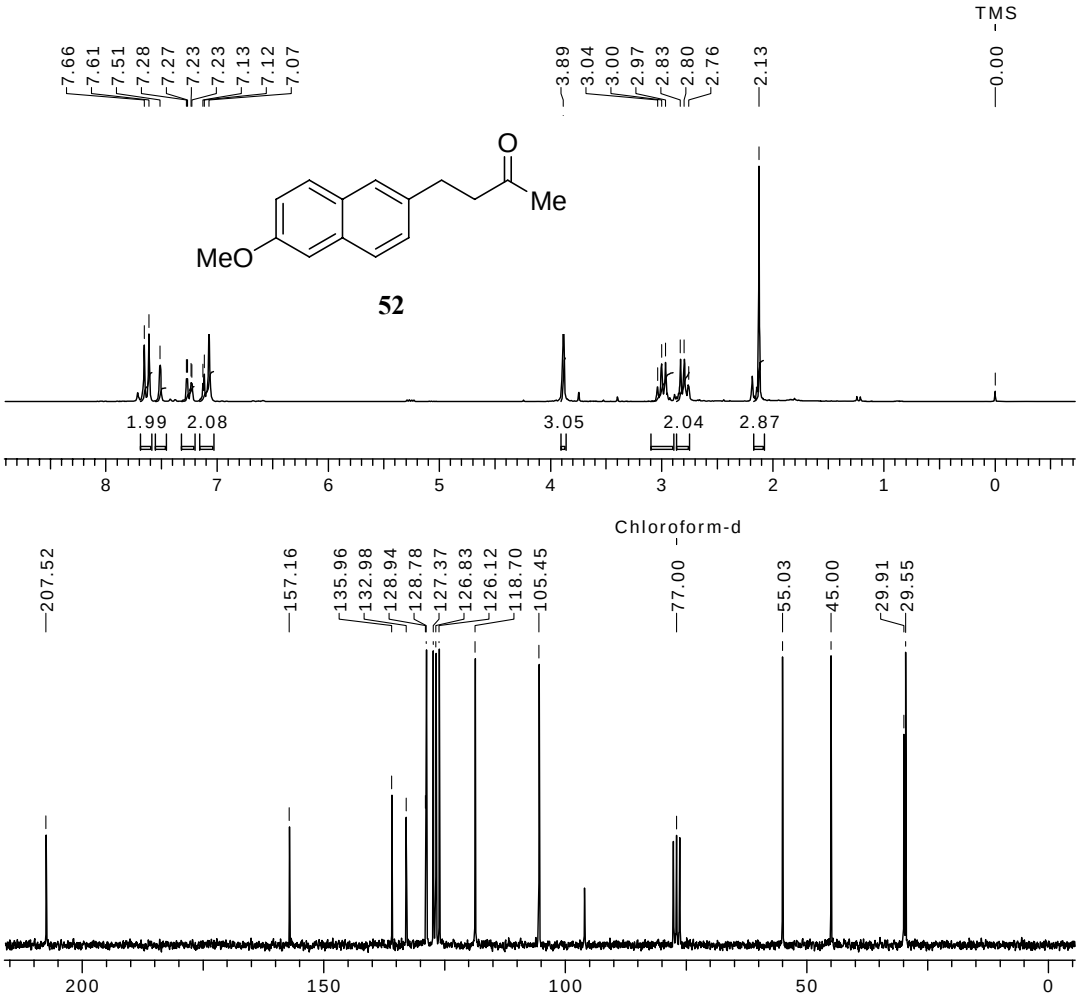
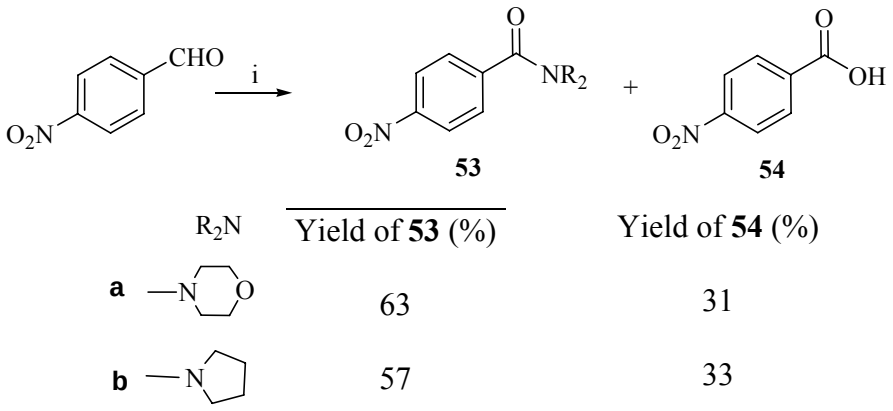


Fig. 9: ^{1}H and ^{13}C NMR spectra of nabumetone (52)

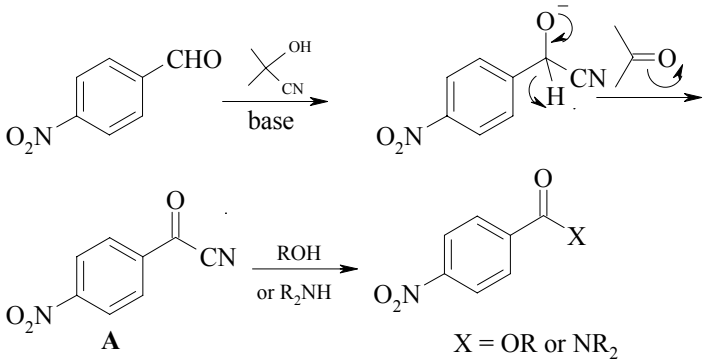
The methodology also worked very well for the direct conversion of aldehydes into amides. When 4-nitrobenzaldehyde was treated with cyclic secondary amine such as morpholine pyrrolidine, piperidine, etc., under the same reaction conditions, the corresponding carboxylic amides were obtained in good yields (54-63%) (**Scheme 29**).



Scheme 29: Reaction conditions: (i) 4-nitrobenzaldehyde (5 mmol), acetone cyanohydrin (5 mmol), Et_3N (7.5 mmol), amine (5 mmol), MeOH (5 mL), 25 ^{0}C, 2 h.

Mechanism

Mechanistically, we believe that the transformation of the aldehydes into esters or amides proceeds through an acyl cyanide intermediate **A,** as confirmed by its isolation and characterization. The first step may involve the formation of cyanohydrins. Subsequently, the cyanohydrins are converted to the acyl cyanides **A** by the way of hydride transfer to acetone (**Scheme 30**).



Scheme 30: Proposed mechanism for the conversion of aldehydes into esters and amides.

3.2.5 Conclusion

In conclusion, this methodology provides a simple procedure for the single-step conversion of electron-deficient aldehydes into the corresponding esters and amides on reaction with either an alcohol or a secondary amine in excellent yields mediated by acetone cyanohydrin or NaCN and base. This protocol is complementary to existing methods of ester formation, which fail in the case of electron-deficient aldehydes.

3.2.6 Experiment Section

General Procedure for the Esterification reactions

A mixture of aldehyde (5.0 mmol), base (7.5 mmol), alcohol (7.5mmol) acetone cyanohydrin (5.0 mmol) in 5 ml of solvent was stirred to appropriate time under argon at 25 °C. After completion of reaction (monitored by TLC), solvent was removed from reaction mixture under reduced pressure. The crude product obtained was further purified by column chromatography through a column of silica-gel using appropriate mixture of petroleum ether and ethyl acetate as eluent to afford pure products.

Methyl 3-nitrobenzoate (47aI)

Yield: 78%; yellow solid; mp:121 ^{o}C; **IR** ($CHCl_3$): 715, 750, 1140, 134, 1510, 1600, 1735, 2940, 3060 cm-1; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.48-7.56 (t, *J* = 8.6 Hz, 1H), 8.19-8.30 (m, 2H), 8.75 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.3, 124.3, 127.7, 129.7, 129.9, 131.9, 133.1, 164.9; **Analysis**: **$C_8H_7NO_4$** requires C, 53.04; H, 3.89; N, 7.73; found C, 53.03; H, 3.93; N, 7.78%.

Allyl 3-nitrobenzoate (47a)

Yield: 64%; yellow solid; **mp**:94 ^{o}C; **IR** ($CHCl_3$): 780, 1156, 1647, 1729, 3021, 3050 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 4.81-4.84 (d, *J* = 5.9 Hz, 2H), 5.21-5.59

(m, 2H), 5.91-6.09 (m, 1H), 7.55-7.63 (t, J = 8.5 Hz, 1H), 8.27-8.36 (m, 2H), 8.75 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 65.9, 119.3, 124.5, 127.1, 129.4, 129.8, 132.6, 133.1, 135.7, 163.7; **Analysis:** $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38; N, 6.76; found C, 57.99; H, 4.38; N, 6.72%**.**

Propargyl 3-nitrobenzoate (47a)

Yield:75%**;** yellow solid; **mp**:121^{o}C; **IR** ($CHCl_3$): 716, 1000, 1144, 1273, 1400, 1533, 1612, 1711, 1776, 1953, 2924, 3263 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.52-2.54 (t, J = 2.3 Hz, 1H), 4.96- 4.97 (d, J = 2.3 Hz, 2H), 7.63-7.71 (t, J = 8.1 Hz, 1H), 8.37-8.46 (m, 2H), 8.88 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.8, 75.5, 77.2, 126.7, 129.1, 129.7, 130.4, 131.6, 133.0, 164.2; **Analysis** $C_{10}H_7NO_4$ Requires C, 58.54; H, 3.44; N, 6.83; found C, 58.58; H, 3.40; N, 6.59%.

Methyl 4-nitrobenzoate (47b)

Yield: 92%**;** yellow solid; **mp:**93 ^{o}C; **IR** ($CHCl_3$): 1112, 1253, 1440, 1612, 1728, 3038 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 8.16-8.30 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.5, 123.4, 130.6, 135.4, 150.8, 164.8; **Analysis:** $C_8H_7NO_4$ requires C, 53.04; H, 3.89; N, 7.73; found C, 53.09; H, 3.83; N, 7.71%.

Allyl 4-nitrobenzoate (47b)

Yield: 70%; white solid; **mp:** 89 ^{o}C; **IR** ($CHCl_3$) 689, 1276, 1371, 1449, 1730, 3029 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.86-4.89 (d, J = 5.7 Hz, 2H), 5.32-5.48 (m, 2H), 5.95-6.12 (m, 1H), 8.16-8.38 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 66.4, 119.2, 123.5, 130.7, 131.5, 135.5, 150.6, 164.1; **Analysis:** $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38; N, 6.76; found C, 57.93; H, 4.33; N, 6.78%.

Propargyl 4-nitrobenzoate (47b)

Yield: 63%; white solid; **mp:** 91 ^{o}C; **IR** ($CHCl_3$) 1113, 1222, 1590, 1713, 1727, 2927, 3305 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.56-2.53 (t, J = 2.0 Hz, 1H),

4.98-4.95 (d, *J* = 2.0 Hz, 2H), 8.35-8.23 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 53.1, 75.8, 77.1, 125.3, 130.8, 134.6, 150.7, 163.5; **Analysis $C_{10}H_7NO_4$** Requires C, 58.54; H, 3.44; N, 6.83; found C, 58.58; H, 3.40; N, 6.81%.

Methyl 4-chlorobenzoate (47c)

Yield: 82%**;** colorless liquid; **IR** ($CHCl_3$):1127, 1265, 1146, 1510, 1510, 1733, 2304, 2971, 3049 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.80-7.85 (d, *J* = 8.6 Hz, 2H), 7.91-7.96 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 51.9, 128.6, 129.5, 130.9, 139.2, 165.6; **Analysis: $C_8H_7ClO_2$** requires C, 56.32; H, 4.14; found C, 56.28; H, 4.19%.

Allyl 4-chlorobenzoate (47c)

Yield: 78%; colorless liquid; **IR** ($CHCl_3$): 1124, 1209, 1241, 1312, 1468, 1521, 1736, 2872, 3063 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.79-4.82 (t, *J* = 6.3 Hz, 2H), 5.27-5.45 (m, 2H), 5.93-6.12 (m, 1H), 7.80-7.84 (d, *J* = 8.1 Hz, 2H), 7.94-7.99, (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 65.3, 119.1, 128.3, 129.3, 132.0, 131.3, 139.4, 165.0; **Analysis: $C_{10}H_9ClO_2$** requires C, 61.08; H, 4.61; found C, 61.08; H, 4.61%.

Propargyl 4-chlorobenzoate (**47d**)

Yield: 75%; colorless liquid; **IR** (Neat): 733, 889, 1111, 1223, 1281, 1363, 1571, 1628, 1751, 3028, 3299; cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.53-2.54 (t, *J* = 2.0 Hz 1H), 4.81-4.82 (d, *J* = 2.0 Hz, 2H), 7.81-7.85 (d, *J* = 7.9 Hz, 2H), 7.93-7.97, (d, *J* = 7.9 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_{3,}$): δ 52.3, 75.2, 77.2, 128.3, 129.5, 131.1, 139.2, 164.9; **Analysis: $C_{10}H_7ClO_2$** requires C, 61.72; H, 3.63; Cl, 18.22; found C, 61.75; H, 3.69; Cl, 18.21.

Methyl 4-bromobenzoate (47d)

Yield: 73%; colorless liquid; **IR** (Neat): 712, 1236, 1413, 1651, 1739, 2118, 2876, 3062 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 3.91 (s, 3H), 7.55-7.59 (d, *J*= 8.6 Hz, 2H), 7.87-7.91 (d, *J* =8.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 52.1, 127.9, 129.0, 131.0, 131.6, 165.9; **Analysis: $C_8H_7BrO_2$** requires C, 44.68; H, 3.28; found C, 44.62; H, 3.24%.

Allyl 4-bromobenzoate (47d)

Yield: 62%; colorless liquid; **IR** (Neat): 860, 1090, 1220, 1270, 1290, 1370, 1490, 1620, 1732, 3100, 3130 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 4.55-4.57 (d, *J* = 4.1 H, 2H), 5.13-5.27 (m, 2H), 5.58-5.94 (m, 1H), 7.51-7.55 (d, *J*= 8.2 Hz, 2H), 7.83-7.87 (d, *J* =8.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 65.7, 118.5, 128.7, 131.0, 132.0, 132.3, 139.4, 165.0; **Analysis: $C_{10}H_9BrO_2$** requires C, 49.82; H, 3.76; found C, 49.87; H, 3.71%.

Propargyl 4-bromobenzoate (47d)

Yield: 85%; colorless liquid; **IR** (Neat): 720, 873, 1101, 1216, 1270, 1349, 1531, 1608, 1753, 3021, 3306; cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.50-2.53 (t, *J* = 2.0 Hz 1H), 4.88-4.90 (d, *J* = 2.0 Hz, 2H), 7.54-7.58 (d, *J*= 8.0 Hz 2H), 7.89-7.94 (d, *J* =8.0 Hz, 2H) **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 52.5, 75.3, 77.0, 128.3, 130.8, 131.7, 132.3, 164.6; **Analysis:** $C_{10}H_7BrO_2$ requires C, 50.24; H, 2.95; found C, 50.29; H, 2.91%.

Methyl 4-cyanobenzoate (47e)

Y**ield**: 80%; white solid; **mp**: 82 °C; **IR** ($CHCl_3$) 1108, 1281, 439, 1605, 1729, 1951, 2229, 2957 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 7.74-7.77 (d, *J* = 6.0 Hz, 2H), 8.16-8.13 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.4, 116.5, 117.4, 129.9, 132.0, 133.7, 164.8; **Analysis $C_9H_7NO_2$** requires C, 67.06; H, 4.38; N, 8.69; found C, 67.29; H, 4.66 ; N, 8.31%.

Allyl 4-cyanobenzoate (47e)

Y**ield**: 76%; white solid; **mp**: 69 °C; **IR** ($CHCl_3$): 1175, 1371, 1445, 1611, 1738, 2203, 3071 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.81-4.84(d, *J* = 5.8 Hz, 2H), 5.34-5.55 (m, 2H), 5.99-6.09 (m, 1H), 7.72-7.76 (d, *J* = 8.0 Hz, 2H), 8.11-8.15 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 66.1, 116.2, 117.4, 118.9, 129.4, 131.9, 132.0, 133.7, 165.8; **Analysis: $C_{11}H_9NO_2$** requires C, 70.58; H, 4.85; N, 7.48; found C, 70.51; H, 4.81; N, 7.49%.

Propargyl 4-cyanobenzoate: (47e)

Yield: 83%; colorless solid **mp**: 82 °C; **IR** ($CHCl_3$) 860, 980, 1019, 1102, 1216, 1733, 2132, 2233, 2401, 3021, 3306 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.53-2.55 (t, *J* = 2.0 Hz, 1H), 4.94-4.95 (d, *J* = 2.0 Hz, 2H), 7.75-7.79 (d, *J* = 8.6 Hz, 2H), 8.20-8.16 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (75MHz, $CDCl_3$,): δ 53.0, 75.6, 77.0, 116.9, 117.4, 130.2, 132.1, 133.1, 163.8; **Analysis**: **$C_{11}H_7NO_2$** requires C, 71.35; H, 3.81; N, 7.56; found C, 71.20; H, 3.86; N, 7.51 %.

Methyl 3-triflurobenzoate (47f)

Yield: 70%; colorless liquid; **IR** (neat); 798, 989, 1078, 1250, 1439, 1617, 1736, 3122 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.94 (m, 3H), 7.56-7.61 (t, *J*= 8.1 Hz, 1H), 7.77-7.92 (d, *J*= 8.1 Hz, 1H), 8.18-8.28 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.4, 124.7, 126.4, 126.5, 129.0, 129.3, 131.0, 132.8, 165.5; **Analysis: $C_9H_7F_3O_2$** requires C, 52.95; H, 3.46; found C, 52.99; H, 3.49%.

Allyl 3-triflurobenzoate (47f)

Yield: 62%; colorless liquid; **IR** (neat); 759, 925, 985, 1072, 1249, 1334, 1436, 1618, 1731, 2927, 3022, 3077 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.82-4.85 (d, *J* = 6.2 Hz, 2H), 5.28-5.46 (m, 2H), 5.93- 6.13 (m, 1H), 7.53-7.61 (m, 1H), 7.78-

7.82 (d, *J* = 8.3 Hz, 1H), 8.21-8.30 (m, 2H); **Analysis: $C_{11}H_9F_3O_2$** requires C, 57.40; H, 3.94; found C, 57.49; H, 3.99%.

Propargyl 3-triflurobenzoate (47f)

Yield: 85%; colorless liquid; **IR** (neat); 649, 759, 925, 1072, 1134, 1436, 1618, 1731, 2854, 3022, 3307 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.52-2.54 (t, *J* = 2.6 Hz, 1H), 4.93-4.94 (d, *J* = 2.6 Hz, 2H), 7.54-7.64 (m, 1H), 7.82-7.86 (d, *J*= 8.3 Hz, 1H), 8.33-8.24 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 53.2, 75.8, 77.2, 124.8, 126.6 127.7, 129.6, 131.2, 132.8, 135.3, 163.5; **Analysis: $C_{11}H_7F_3O_2$** requires C, 57.90; H, 3.09; found C, 57.99; H, 3.91%.

Methyl 4-fluorobenzoate (47g)

Yield: 60%; colorless liquid; **IR** ($CHCl_3$): 720, 937, 1172, 1270, 1431, 1619, 1737, 2989, 3079 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.06-7.15 (d, *J* = 8.1 Hz, 2H), 8.05-8.09 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.1, 116.2, 129.8, 131.7, 165.2, 163.9; **Analysis:** $C_8H_7FO_2$ requires C, 62.34; H, 4.58; found C,62.39; H, 4.55%.

Allyl 4-fluorobenzoate (47g)

Yield: 62%; colorless liquid; **IR** ($CHCl_3$): 930, 1172, 1139, 1470, 1618, 1739, 2830, 3021, 3307 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.79-4.83 (d, *J* = 6.2 Hz, 2H), 5.21-5.46 (m, 2H), 5.93-6.12 (m, 1H), 7.80-7.84 (d, *J* = 8.3 Hz, 2H), 7.97-8.01 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 65.1, 116.2, 119.3, 129.9, 131.7, 132.1, 164.8, 165.3; **Analysis: $C_{10}H_9FO_2$** requires C,66.66; H, 5.03; found C,66.61; H, 5.08%.

Allyl 2-cyanobenzoate (47h)

Yield: 61%; gum; **IR** ($CHCl_3$): 821, 990, 1017, 1378, 1731, 2132, 2237, 2511, 3017, 3319 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 4.89-4.92 (d, *J* = 6.7 Hz, 2H),

5.31-5.52 (m, 2H), 6.01-6.17 (m, 1H), 7.67-7.71 (d, *J* = 8.3 Hz, 2H), 8.15-8.19 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (75MHz, $CDCl_3$,): δ 66.5, 113.0, 117.2, 119.3, 123.9, 131.1, 131.3, 132.3, 132.6, 134.7, 163.5; **Analysis: $C_{11}H_9NO_2$** requires C, 70.58; H, 4.85; N, 7.48; found C, 70.51; H, 4.81; N, 7.49%.

Methyl 3-phenylpropanoate (48a)

Yield: 93%; colorless liquid; **IR** ($CHCl_3$): 700, 1163, 1257, 1496, 1739, 2360, 2950, 3028 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.57-2.65 (t, *J* = 8.1 Hz, 2H), 2.90-2.98 (t, *J* = 8.2 Hz, 2H), 3.65 (m, 3H), 7.15-7.26 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 30.8, 35.6, 51.4, 126.1, 128.3, 128.4, 140.3, 172.9; **Analysis**: **$C_{10}H_{12}O_2$** requires C, 73.15; H, 7.37; found C, 73.17; H, 7.42%.

Allyl 3-phenylpropanoate (48b)

Yield: 86%; colorless liquid; **IR** ($CHCl_3$): 1153, 1496, 1649, 1735, 3028, 3047 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.62-2.66 (t, *J* = 8.2 Hz, 2H) 2.92-2.96 (t, *J* = 8.2 Hz, 2H), 4.58-4.54 (d, *J* = 8.0 Hz, 2H), 5.19-5.35 (m, 2H), 5.58-5.93 (m, 1H), 7.31-7.17 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 30.9, 35.8, 65.1, 118.2, 126.3, 128.3, 128.5, 132.2, 140.4, 172.5; **Analysis**: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42 found C, 73.77; H, 7.48%.

Isopropyl 3-phenylpropanoate (48c)

Yield: 89%; colorless liquid; **IR** ($CHCl_3$) 697, 752, 1029, 1233, 1634, 1731, 2983,3201 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 0.17-0.22 (d, *J* = 6.2 Hz, 6H), 2.52-2.60 (t, *J* = 8.2 Hz, 2H), 2.80-2.96 (t, *J* = 8.2 Hz, 2H), 4.95-5.01 (m, 1H), 7.17- 7.25 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 21.6, 30.9, 36.0, 67.3, 126.0, 128.1, 128.2, 140.4, 172.0; **Analysis**: **$C_{12}H_{16}O_2$** requires C, 74.97; H, 8.39; found C, 74.92; H, 8.35%.

Propargyl 3-phenylpropanoate (48d)

Yield: 88%; colorless liquid; **IR** ($CHCl_3$): 699, 1149, 1454, 1604, 1743, 2129, 3029, 3291cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.42-2.45 (t, *J* = 4.1, 1H), 2.62-2.68 (t, *J* = 8.2 Hz, 2H), 2.92-3.00 (t, *J* = 8.2 Hz, 2H), 4.65-4.66 (d, *J* = 4.1 Hz, 2H), 7.16- 7.31 (m, 5H); **Analysis**: **$C_{12}H_{12}O_2$** requires C, 76.57; H, 6.43; found C, 76.57; H, 6.43%.

Allyl 3-(4-methylbenzoate)propanoate (48e)

Yield: 76%; colorless liquid; **IR** ($CHCl_3$): 698, 755, 1105, 1259, 1315, 1466, 1610, 1734, 2139, 2222, 3022 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.64-2.71 (t, *J* = 6.2 Hz, 2H), 2.97-3.05 (t, *J* = 6.2 Hz, 2H), 3.91 (s, 3H), 4.55-4.58 (d, *J* = 6.3 Hz, 2H), 5.20-5.40 (m, 2H), 6.01-6.31 (m, 1H), 7.25-7.29 (d, *J* = 8.6 Hz, 2H), 7.93- 7.97 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 30.5, 35.3, 51.9, 65.2, 118.3, 127.4, 128.3, 129.8, 132.0, 145.8, 166.0, 172.0; **Analysis**: **$C_{14}H_{16}O_4$** requires C, 67.73; H, 6.50; found 67.78; H, 6.52%.

Allyl 3-(3-(trifluoromethyl)phenyl)propanoate (48f)

Yield: 66%; colorless liquid; **IR** (neat); 759, 925, 985, 1072, 1249, 1334, 1436, 1618, 1731, 2927, 3022, 3077 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.58-2.62 (t, *J* = 8.1 Hz, 2H), 2.81-2.89 (t, *J* = 8.1 Hz, 2H), 4.51-4.54 (d, *J* = 6.5 Hz, 2H), 5.18-5.31 (m, 2H), 5.57-5.98 (m,1H), 7.56-7.61 (t, *J*= 8.1 Hz, 1H), 7.77-7.92 (d, *J*= 8.1 Hz, 1H), 8.18-8.28 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 30.5, 35.3, 65.1, 118.1, 123.0, 124.1, 126.7, 129.0, 129.3, 131.1, 131.9, 141.3, 171.7; **Analysis**: **$C_{13}H_{13}F_3O_2$** requires C, 60.46; H, 5.07; found C, 60.41; H, 5.09%.

Allyl 3-(2-methoxynaphthalen-6-yl)propanoate (48g)

Yield: 61% colorless liquid; **IR** ($CHCl_3$): 754, 1103, 1314, 1614, 1736, 214, 2224, 2854, 2954 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.67-2.75 (t, *J* = 8.2 Hz, 2H), 3.03-3.11 (t, *J* = 8.2 Hz, 2H), 3.86 (s, 3H), 4.55-4.57 (d, *J* = 4.7 Hz, 2H), 5.16-

5.30 (m, 2H), 5.55-5.91 (m, 1H), 7.07-7.12 (m, 2H), 7.25-7.30 (d, *J* = 8.7 Hz, 1H), 7.54- 7.66 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 30.8, 35.8, 51.1, 65.0, 105.5, 118.1, 118.8, 126.3, 126.9, 127.3, 128.9, 129.0, 132.1, 133.1, 135.4, 157.3, 172.3; **Analysis**: **$C_{17}H_{18}O_3$** requires C, 75.53; H, 6.71; found C, 75.55; H, 6.79%.

Allyl 3-(4-methoxyphenyl)propanoate (48h)

Yield: 64%; yellow solid; **mp**: 89 °C; **IR** ($CHCl_3$): 697, 752, 1131, 1187, 1248, 1367, 1419, 1737, 2987 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.60-2.64 (t, *J* = 7.7, 2H), 2.90-2.94 (t, *J* = 7.7, 2H), 3.80 (s, 3H), 4.82-4.85 (d, *J* = 6.2 Hz, 2H), 5.16- 5.34 (m, 2H), 5.55- 5.89 (m, 1H), 6.84-6.89 (d, *J* = 8.3, 2H), 7.13-7.17 (d, *J* = 8.3, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 31.5, 35.8, 55.9, 65.2, 113.3, 118.3, 129.1, 132.0, 132.2, 158.1, 172.2; **Analysis**: **$C_{13}H_{16}O_3$** requires C, 70.89; H, 7.32; found C, 70.84; H, 7.33%.

Allyl 3-(3, 4-dimethoxyphenyl)propanoate (48i)

Yield: 57%; gum; **IR** ($CHCl_3$): 1018, 1107, 1290, 1373, 1466, 1733, 2858, 2931, 3016 cm-1; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.59-2.67 (t, *J* = 8.1 Hz, 2H), 2.87-2.94 (t, *J* = 8.1 Hz, 2H), 3.91 (s, 6H), 4.55-4.58 (d, *J* = 6.5 Hz, 2H), 5.19-5.32 (m, 2H), 5.57-5.98 (m,1H), 6.70-6.80 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): 30.1, 35.7, 55.3, 64.6, 111.4, 115.2, 119.3, 120.0, 131.8, 132.7, 138.3, 140.5, 148.6, 172.0; **Analysis**: **$C_{14}H_{18}O_4$** requires C, 67.18; H, 7.25; found C, 67.19; H, 7.21%.

(*E*)-3-(2-Methoxynaphthalen-6-yl)propenal (50)

The Vilsmeier reagent was prepared by the dropwise addition of $POCl_3$ (2.8 mL, 30 mmol) to a cold DMF (5 mL) under constant stirring. Alcohol **49** (1.01 g, 5 mmol) was dissolved in 5 mL of DMF and added dropwise to the Vilsmeier reagent. The reaction mixture was gradually allowed to attain room temperature, stirred for further 30 min and then refluxed for 4-6 h. After the completion of the

reaction (monitored by TLC), the reaction mixture was quenched with ice and extracted with ether. The organic layer was washed with brine and dried over anhyd. Na_2SO_4, evaporated under reduced pressure and the crude product purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give aldehyde **51,** as colorless solid.

Yield: 47%; colorless solid; **mp:** 61^{o} C**; IR** ($CHCl_3$): 690, 929, 1030, 1216, 1450, 1687, 3021**; ^{1}H NMR** (200 MHz, $CDCl_3$,): δ 3.91 (s, 3H), 6.77-8.85 (m, 1H), 7.21-7.56 (m, 3H), 7.63-7.91 (m, 4H), 9.72-9.75 (d, *J* = 6.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 53.3, 105.9, 119.9, 127.6, 128.4, 129.3, 130.2, 130.5, 136.1, 153.0, 159.9, 193.6; **Analysis**: **$C_{14}H_{12}O_2$** requires C, 79.22; H, 5.70; found 79.28; H, 5.75%.

4-(6-Methoxy-2-napthyl)butan-2-one (Nabumetone) (52):

To a stirred mixture of saturated ester (212 mg, 1mmol) in THF (10 mL) was added methyl magnesium iodide (prepared by addition of methyl iodide (0.142 g of 1 mmol) to magnesium (0.024 g) in 10 mL of THF) at -55 ^{o}C. After completion of the reaction (as monitored by TLC), the reaction mixture was quenched with 2 M HCl (20 mL) and extracted with ether. The organic layer was washed with brine and dried over anhyd. Na_2SO_4, evaporated under reduced pressure and the crude product purified by column chromatography (silica gel with pet ether: EtOAc = 90: 10 as eluent) to give **52**

Yield: 0.148 g, 65%; **mp**: 80 °C; **IR** ($CHCl_3$): 757, 850, 1031, 1770, 1221, 1266, 1363, 1390, 1485, 1605, 1633, 1712, 2360, 2840, 2937, 2966, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 3.89 (m, 3H), 7.07-7.13 (m, 2H), 7.23-7.28 (m, 1H), 7.51 (s, 1H), 7.61-7.66 (m, 2H)**;** **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.5, 29.9, 45.0, 55.0, 105.4,

118.7, 126.1, 126.8, 127.3, 128.7, 132.9, 135.9, 157.1, 207.5. **MS** (m/z, % relative intensity); 228 (34), 185 (11), 171 (100), 158 (5), 141 (9), 128 (23), 115 (14), 63 (7), 43 (64); **Analysis: $C_{15}H_{16}O_2$** requires C, 78.92; H, 7.06; found C, 78.81, H, 7.24%.

***N*-(4-Nitrobenzoyl)morpholine (53a)**

Yield:63%; colorless solid; **mp**:121^{o}C; **IR** ($CHCl_3$): 635, 1288, 1512, 1632, 3071 cm^{-1}: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.36-3.43 (t, *J* = 14 Hz, 4H), 3.62-3.69 (t, *J* = 14 Hz, 4H) 7.66-7.72 (d, *J* = 12 Hz, 2H), 8.23-8.29 (d, *J* = 12 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.1, 26.2, 46.0, 49.0, 123.2, 127.9, 142.9, 148.2, 166.7; **Analysis: $C_{11}H_{12}N_2O_3$** requires C, 59.99; H, 5.49; N, 12.72; found C, 59.19; 5.45, 12.69%.

***N*-(4-Nitrobenzoyl)pyrolidine (53b)**

Yield: 57%; yellow solid; **mp**: 118^{o}C; **IR** ($CHCl_3$): 621, 1278, 1502 1634, 3094 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.72 (bs, 8H), 7.56-7.61 (d, *J*=10 Hz, 2H), 8.25-8.31 (d, *J*= 12.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 300 MHz): δ 42.5, 47.8, 65.5, 123.7, 128.1, 128.1, 141.3, 140.3, 167.6; **Analysis: $C_{11}H_{12}N_2O_4$** requires C,55.93; H, 5.12; N, 11.86; found C, 55.92; H, 5.10; N, 11.63%.

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CHAPTER 4

Synthesis of Novel Phenylhydrazine based Palladacycles and H-β Zeolite Mediated Synthesis of Isatins

Section 1:

Synthesis of Novel Phenyl Hydrazine based Palladacycles: Its Application in Arylation Reactions in Aqueous Medium

4.1.1 Introduction

Palladacycles have recently emerged as one of the most promising classes of catalysts or catalyst precursors in the Pd- catalyzed C–C bond forming reactions such as Heck-Mizoroki,[1] Suzuki-Miyaura,[2] Sonogashira,[3] etc. In the last decade, a number of new types of ligands such as heterocyclic carbenes,[4] thiourea,[5] oxime palladaycles,[6] diazabutadienes,[7] and 2-aryl-2-oxazolines[8] were employed in these cross-coupling reactions. However, a high loading of catalysts and an inert atmosphere in most reactions especially involving phosphapalladacycles[9] and phosphines-free *N*-heterocyclic carbenes are generally required for achieving better conversions. Thus, search for new palladium catalysts has received much attention particularly for the use of less reactive aryl chlorides as substrates, under aerobic conditions or even in aqueous solutions. Aqueous-phase palladium catalyzed reactions are of much interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify the catalyst recovery.

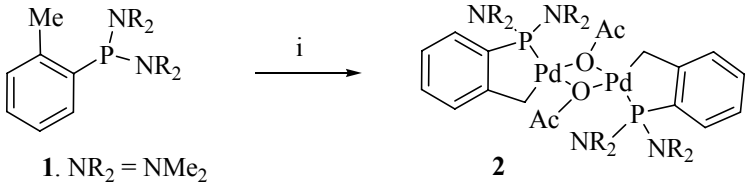
4.1.2 Review of Literature

Literature search revealed that there are several reports on use of pallacycles with ligands such as phosphorous and nitrogen for C-C bond formation reactions like Heck reaction, Suzuki coupling, *etc*. Some of the recent reports on the

palladacycles synthesis and their application in C-C bond formation reactions are discussed below.

Brunel's approach (2000)[10]

Brunel *et al*. have synthesized palladacycle **2**, and used it as a catalyst for the hydroarylation of norbornene. Very high TON upto 196 x 10^6 was observed in presence of hydrogen donor like NEt_3/HCO_2H (**Scheme 1**).

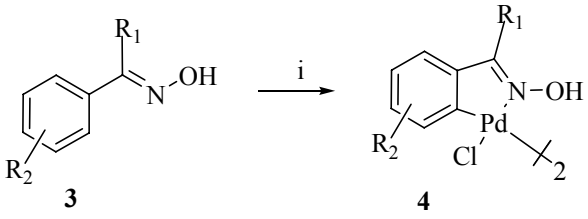


1. $NR_2 = NMe_2$ **2**

Scheme 1: (i) $Pd(OAc)_2$, toluene, 110 °C, 2 h, 90%.

Alonso's approach (2000)[11]

Several oxime palladacycles **4-10** were prepared from very cheap starting materials such as corresponding oximes and these were used as versatile catalysts for different C-C bond forming reactions (**Scheme 2**).



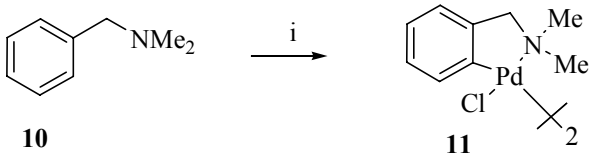
3 **4**

5. R_1= Ph, R_2= H
6. R_1= p-Cl-C_6H_4, R_2= Cl
7. R_1= p-OMe-C_6H_4, R_2= OMe
9. R_1= Me, R_2= H
10. R_1=R_2= fluorenone

Scheme 2: (i) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 72 h, 90%.

Iyer's approach (2000)[12]

Iyer *et al* have reported amine based palladacycle **11,** which was found to be an excellent catalyst for the Heck reaction. High TON upto 1, 45,454 were obtained (**Scheme 3**).

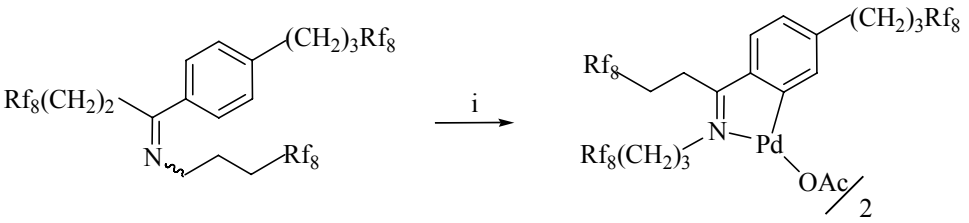


10 **11**

Scheme 3: (i) Li_2PdCl_4, MeOH, 25 °C, 93%.

Gladysz's approach (2002)[13]

The fluorous Schiff base **12** was prepared and cyclopalladated to afford highly effective catalyst precursor **13.** TON up to 14,61,000 was obtained for the Heck reaction (**Scheme 4**).

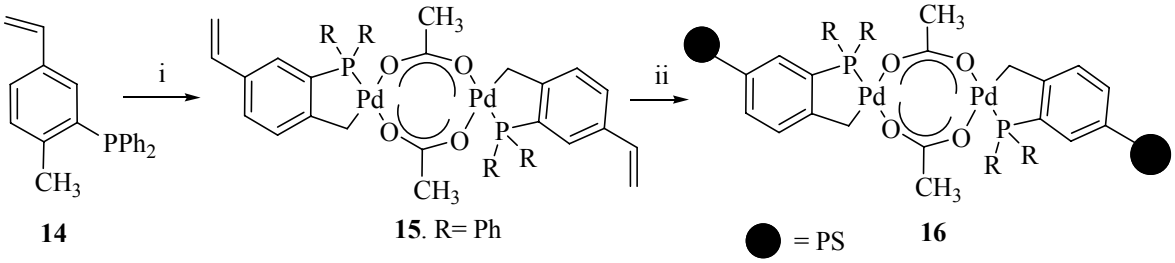


12 $Rf_8 = CF_3(CF_2)_7$ **13**

Scheme 4: (i) $Pd(OAc)_2$, AcOH, 95 °C, 87%.

Lin's approach (2003)[14]

Lin *et al* have reported a new type of soluble polystyrene-supported palladacycle **16** for Heck, Suzuki and Sonogashira reactions (**Scheme 5**).

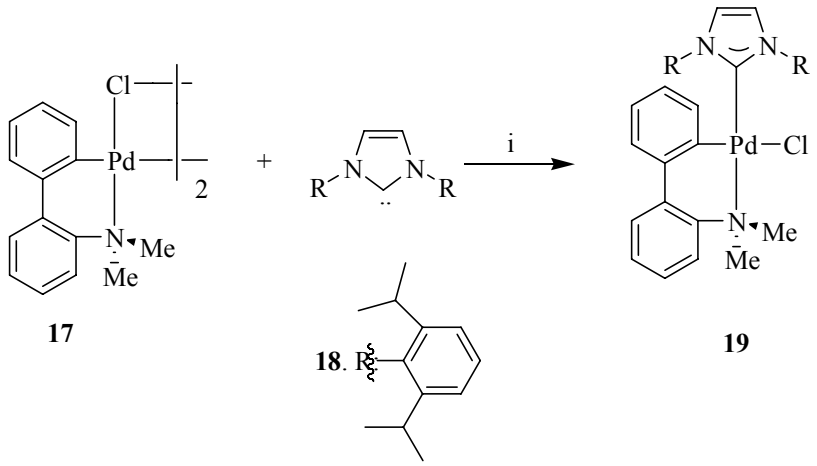


14 **15**. R= Ph **16**

Scheme 5: (i) $Pd(OAc)_2$, toluene, 50 °C, 74%; (ii) styrene, benzene, 70 °C, 40 h, 66%.

Navarro's approach (2006)[15]

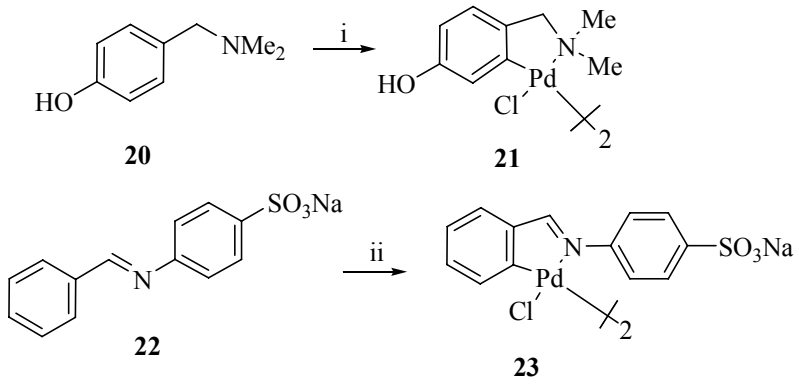
Navarro *et al* have used *N*-Heterocyclic carbene palladacycles **19.** This complex also displays very high activity for α-arylation of ketones with activated and unactivated aryl chlorides (**Scheme 6**).



Scheme 6: (i) THF, 25 °C, 2 h, 67%.

Huang's approach (2006)[16]

Huang *et al* have prepared a family of water-soluble palladacycles (**21** and **23**) from *N,N*-dimethyl-*p*- hydroybenzyl amine **20**, 4-(*N*-benzylideneamino)benzenesulfonate (**22**). They exhibit high activity for the Suzuki coupling of aryl bromides and activated aryl



Scheme 7: (i) $PdCl_2$, NaOAc, MeOH, 25 °C, 81%; (ii) $PdCl_2$, NaOAc, MeOH, 25 °C, 52%.

chlorides in combination with (2-di-*tert*-butylphosphinoethyl)trimethylammonium chloride (*tert*-Bu-Amphos) (**Scheme 7**).

4.1.3 Present Work

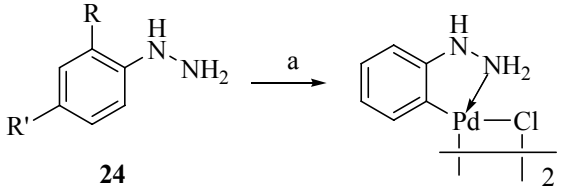
4.1.3.1 Objective

Although there are several palladacycles reported for the C-C bond forming reactions namely Heck, Suzuki and Sonogashira coupling reactions, some of them suffer from several drawbacks: low turn over number (TON), multi-step synthesis of Pd- complexes, use of highly moisture and air-sensitive phosphine ligands, etc. In this context, the nitrogen-containing palladacycles are superior to phosphine-based Palladacycles due to their high stability towards moisture, air and high temperature. Our aim has been to develop methods for synthesizing novel palladcycles from readily accessible air-stable ligand phenyl hydrazine. This section describes, the synthesis, characterization and catalytic activity studies of some of the novel palladacycles in several C-C bond forming cross-coupling reactions, particularly in water as the solvent.

4.1.4 Results and Discussion

4.1.4.1 Synthesis of palladacycles (25-28)

Palladacycles **25-28** were prepared in high yields (64-68%) when phenylhydrazine precursor was treated with Li_2PdCl_4 at 60 °C *via* carbopalladation reaction, (**Schemes 8)**.



24

25 R= C_2H_5 R'= H; 67%, yield
26 R= H; R' = OMe; 68%, yield
27 R= H; R'= Cl; 66%, yield
28 R= H; R' = Me 64%, yield

Scheme 8: (a) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 24 h.

4.1.4.2 Characterization of palladacycles (25-28)

These palladacycles, **25-28** were fully characterized by elemental C, H, N, S analysis, IR, ^1H & ^{13}C NMR spectroscopy and atomic absorption spectroscopy (AAS). The IR spectrum of all palladacycles, **25-28** showed a shift of lower

frequency of 40-60 cm^{-1} in the C-N stretching frequency compared to the parent phenylhydrazine ligands. For example, in the case of palladacycle **26**, the C-N stretching frequency was observed at 1215 cm^{-1} while for the parent phenylhydrazine, it was observed at 1265 cm^{-1}. The percentage of palladium content in the palladacycles **25-28** was analyzed from atomic absorption spectroscopy (AAS). For example, the palladium percentage in the palladium complex **26** was found to be 38.42% (requires theoretically 38.87%). The ^{1}H NMR spectrum of palladacycle **26** showed typical signals at δ 6.81 (d), 7.80 (s), 7.84 (d) for the aromatic protons (**Fig. 1**). Disappearance of three aromatic carbon signals at δ 135.8, 143.8, 144.0 in its DEPT-NMR, confirms the formation of palladacycle **26.**

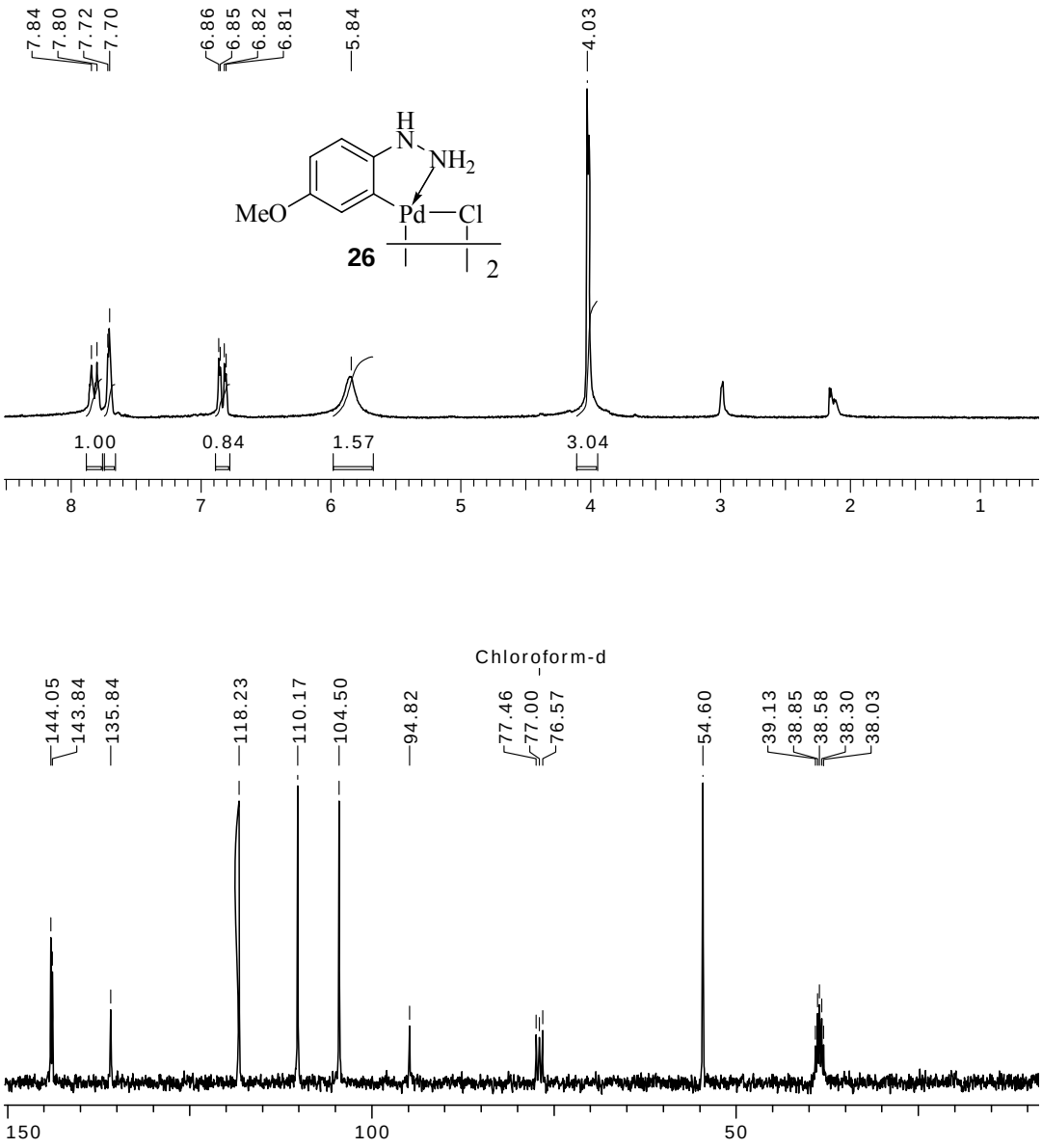


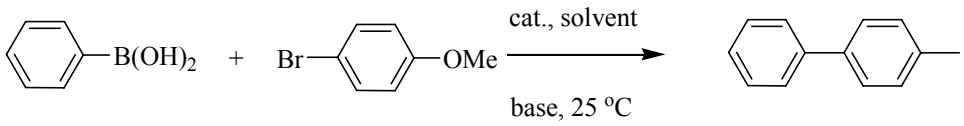
Fig. 1: ^{1}H and ^{13}C NMR spectra of palladacycle 26

4.1.4.3 Catalytic activity studies of palladacycles (25-28)

A. Catalytic Suzuki cross-coupling reactions

The catalytic activity of palladacycles, **25-28** for C-C bond forming reactions was evaluated systematically. Initially, we have conducted experiments for Suzuki coupling of 4-bromotoluene with phenylboronic acid using palladacycles **25-28** and the results are

Table 1: Suzuki coupling of 4-bromotoluene with phenylboronic acid: Screening of palladium complexes[a]



31c

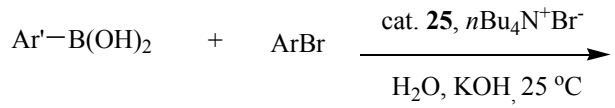
Entry	Palladium catalyst	Solvent	Base	Yield of **31c** (%)[b]	TON[c]
a	**25**	toluene	KOH	89	356000
b	**26**	toluene	KOH	82	328000
c	**28**	water	K_2CO_3	88	352000
d	**25**	water	K_2CO_3	93	372000
e	**26**	water	K_2CO_3	91	364000
f	**26**	DMF	Cs_2CO_3	71	344000
g	**27**	water	K_2CO_3	85	340000
h	**27**	DMF	K_2CO_3	86	344000
i	**28**	water	KO^tBu	51	13000

[a] Reaction conditions: 4-bromoanisole (2 mmol), phenylboronic acid (3 mmol), base (4 mmol), palladacyle ($5x10^{-6}$ mmol), tetrabutylammonium bromide (2 mmol), solvent (6 mL) , 6 h.
[b] Isolated yields after chromatographic purification;
[c] TON = turn over number, defined as mmol of product / mmol of Pd.

summarized in **Table 1**. Among the bases (K_2CO_3, KO^tBu, KOH and Cs_2CO_3) screened, KOH gave the best yield. Palladacycle **25** was found to be the best catalyst and showed highest catalytic activity in terms of yield (93%) and TON (372000). Encouraged by this result, wide range aryl bromides were subjected to Suzuki cross-coupling reaction using palladacycle **25 (**$5x10^{-6}$ mmol) with various phenylboronic acids as coupling partners under optimized reaction conditions (KOH, TBAB, 25 °C, H_2O), **Table 2** shows the scope of the reaction wherein moderate to high yields of **31a-l** were obtained in all the cases studied. The formation of biphenyls **31a-l** was confirmed by ^1H, ^{13}C-NMR and IR

spectroscopy. For example the ^{1}H NMR spectrum of biphenyl **31a** showed a characteristic signal at δ 3.72 for the OCH_3 proton. Its ^{13}C NMR spectrum showed signal at δ 55.1 due to O**C**H_3 carbon (**Fig. 2**).

Table 2: Suzuki coupling of aryl halides with arylboronic acids catalyzed by 30[a]



Entry	Ar'	ArBr	Yield (%)[b]
a	Ph	4-Bromoanisole	78
b	Ph	2-Bromoanisole	72
c	Ph	4-Bromotoluene	83
d	Ph	1-Bromo-4-fluorobenzene	98
e	Ph	Bromobenzene	82
f	Ph	2-Bromonaphthalene	85
g	Ph	3-Bromobenzotrifluoride	70
h	4-Acetyl Ph	Bromobenzene	90
i	2-Naphthyl	Bromobenzene	78

[a] Reaction conditions: aryl halide (5 mmol), phenylboronic acid (7.5 mmol), KOH (10 mmol), palladium catalyst **25**($5x10^{-5}$ mmol), tetrabutylammonium bromide (5 mmol), water (15 mL), 25 °C , 3 h. [b] Isolated yields after chromatographic purification. [c] Reaction was carried out at 100 °C

B. Catalytic Heck Arylation Reaction

A variety of aryl bromides and olefins were subjected to the Heck reaction using palladacycles **25-28** and the results are summarized **Table 3**. For both activated and unactivated aryl bromides, excellent conversions were obtained within 6 h. The formation of product **32a-l** was confirmed by ^{1}H, ^{13}C-NMR and IR spectroscopy. For example, the ^{1}H NMR spectrum of **32a** showed a singlet at δ 2.5

for Ar-$\mathbf{CH_3}$ protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 127.3 and 127.8 due to olefinic carbons.

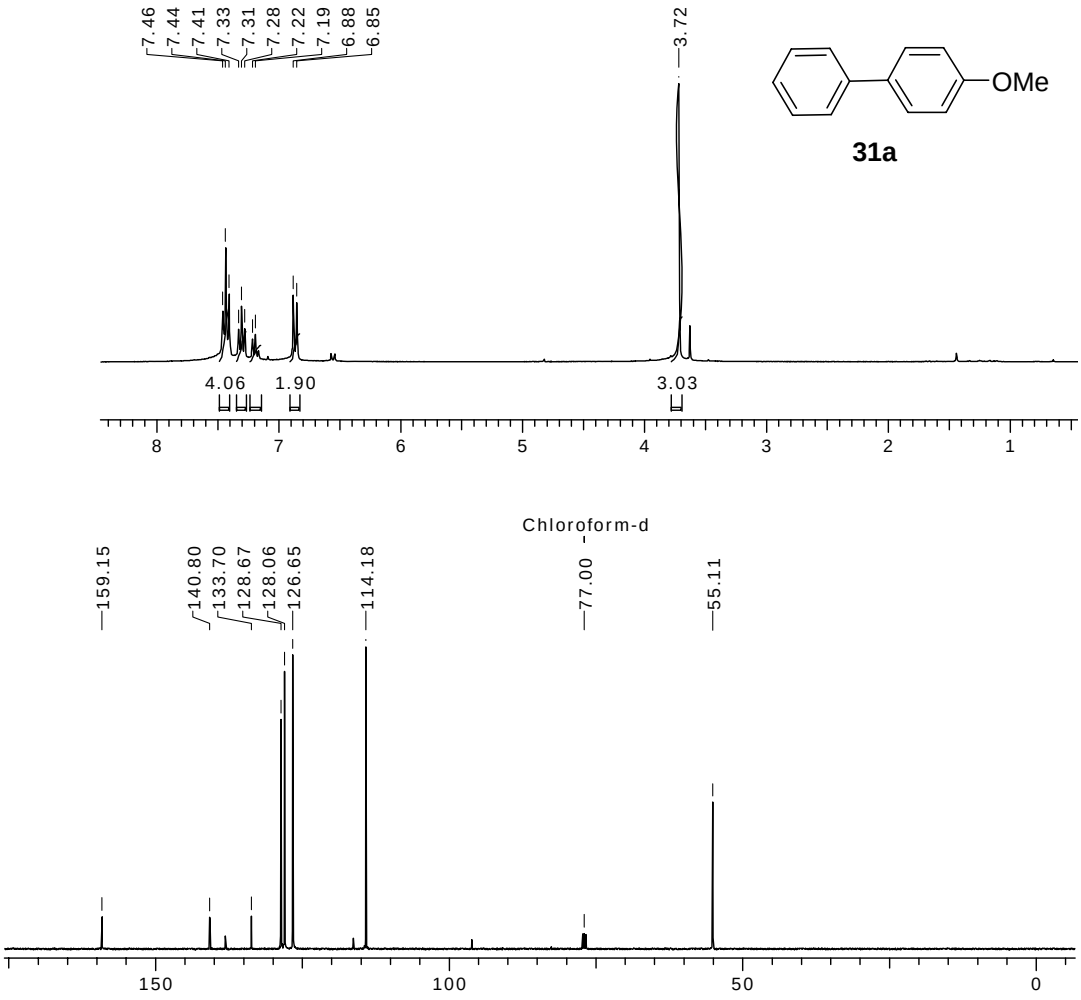
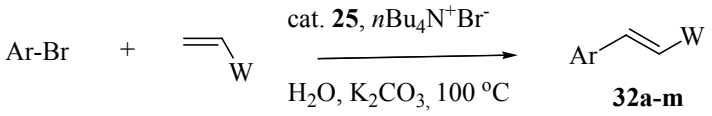


Fig. 2: ^{1}H and ^{13}C NMR spectra of 4-methoxybiphenyl (31a)

Table 3: Heck reaction between aryl halides and olefinic substrates catalyzed by 25[a]



Entry	ArBr	W	Yield (%)[b]
a	4-Bromotoluene	Ph	91
b	1-Bromonaphthalene	CO_2Me	83
c	1-Bromonaphthalene	$CO_2{}^nBu$	95
d	3-Bromobenzotrifluoride	$CO_2{}^nBu$	82
e	3-Bromobenzotrifluoride	CO_2Et	80
f	Bromobenzene	$CO_2{}^nBu$	86
g	Bromobenzene	CO_2Me	84
h	Bromobenzene	Ph	89
i	Bromobenzene	CN	94
j	1-Bromo-4-nitrobenzene	CO_2Et	80
k	4-Bromoanisole	CO_2Et	79
l	4-Bromoanisole	Ph	81
m	2-Bromo-6-methoxynaphthalene	$CO_2{}^nBu$	87

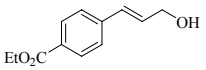
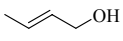
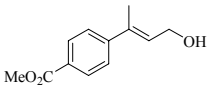
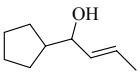
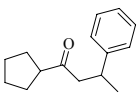
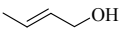
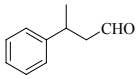
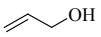
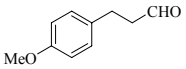
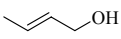
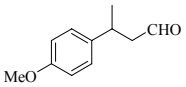
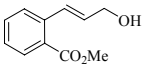
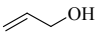
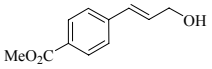
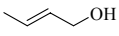
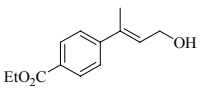
[a] Reaction conditions: aryl halide (2 mmol), olefin (3 mmol), K_2CO_3 (4 mmol), palladium complex **25** ($5x10^{-6}$ mmol), tetrabutylammonium bromide (2 mmol), water (6 mL), 100 °C, 6 h. [b] Isolated yields after chromatographic purification.

C. Catalytic Arylation of allylic alcohols

Arylation of allylic alcohols constitutes a powerful method in organic synthesis for the generation of a three-carbon unit with an aldehydic group.[17] We have carried out arylation of allylic alcohols with aryl halides either with K_2CO_3 or

diisopropylamine (DIPA) as base using phenylhydrazine-based palladacycles (**25-28**) as catalysts in water at 80 ^{o}C.

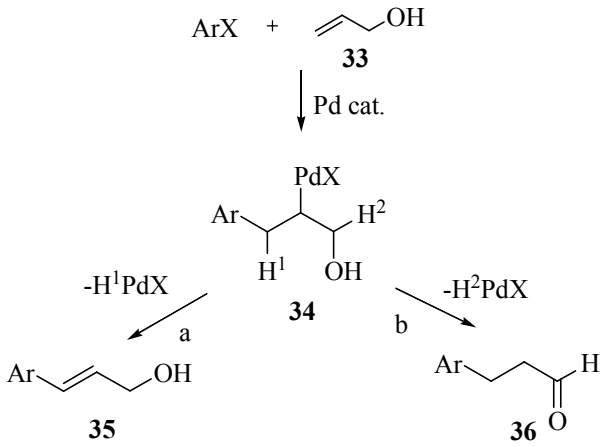
Table 4: Arylation of aryl halides with (Ar-X) allylic alcohols catalyzed by a palladacycle 25 [a]

Entry	Ar-X	Alcohol	Base	Product	Yield (%)[b]
a	Ethyl 4-bromobenzoate		DIPA [c]		82
b	Methyl 4-bromobenzoate		DIPA		88
c	Iodobenzene		K_2CO_3		63
d	Iodobenzene		K_2CO_3		73
e	4-Iodoanisole		K_2CO_3		88
f	4-Iodoanisole		DIPA		92
g	Methyl 2-iodobenzoate		DIPA		90
h	Methyl 4-iodobenzoate		DIPA		81
i	Ethyl 4-bromobenzoate		DIPA		88

[a] Reaction conditions: aryl halide (5 mmol), allyl alcohol (7.5 mmol), base (10 mmol), tetrabutylammonium bromide (5 mmol), water (15 mL), catalyst **6** ($5x10^{-4}$ mmol), 80 °C, 12 h. [b] Isolated yields after chromatographic purification. DIPA =Diisopropylamine.

The novel feature of our system is the selective formation of either α,β-unsaturated alcohols or saturated carbonyl compounds. Selective formation of

aromatic conjugated alcohols was observed in the case of aryl halides with electron- withdrawing groups whereas saturated aldehydes were formed when aryl halides with electron- donating



Scheme 8: Plausible mechanism for arylation with allylic alcohols

groups were used. Good yields of ketones were obtained when secondary allylic alcohol was subjected for arylation reaction (entry c; Table **4**). This selectivity can be explained by the fact that the β hydride elimination from the carbopalladation intermediate **34** can take place from both the available β-hydrogens. Electron-withdrawing group on the aromatic ring makes the H^1- β hydrogen more acidic, thus facilitating its removal readily as palladium hydride species resulting in the formation of aromatic conjugated alcohols **35** (route a) while formation of aldehydes **36** takes place by the elimination of H^2- β hydrogen[18] (route b) (Scheme **8**).

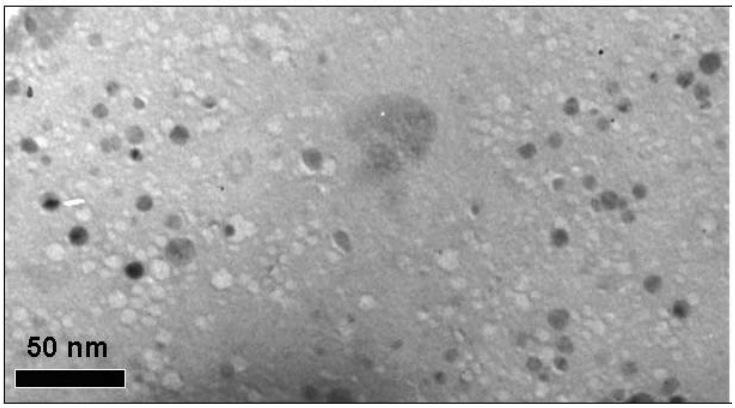


Fig. 4: TEM image of Pd nanoparticles of Pd-catalyst **25** in aqueous medium.

The transmission electron microscope (TEM) measurement for the aqueous medium of the Suzuki reaction (**Fig. 4**) confirmed the presence of Pd(0) nanoparticles of spherical morphology varying in diameter from 10 to 12 nm.

4.1.5 Conclusion

In summary, syntheses of novel family of phenylhydrazine-based palladacycles **25-30** have been achieved from easily available precursors. Several C-C bond forming cross coupling reactions, particularly in aqueous media and totally phosphine-free conditions are some of the salient features of this study. The stability of these palladium catalysts against air, moisture, temperature and the fact that they can be synthesized from inexpensive starting materials render them as promising catalysts.

4.1.6. Experimental Section

Preparation of Palladacycles (25-28)

Two-necked 25 mL RB flask was charged with $PdCl_2$ (177 mg, 1 mmol), LiCl (100 mg, 2.4 mmol) and MeOH (2 mL); the resulting reaction mixture was refluxed under argon atmosphere for 2.5 h. Then to the same reaction mixture was

added a solution of 2-ethylphenylhydrazine (136 mg, 1 mmol) in MeOH (2 mL). The resulting reaction mixture was refluxed for 3 h. After completion of reaction (as monitored by TLC), the resulting solid was filtered on a sintered funnel, dried under reduced pressure for 3 h to afford palladacycles **25** as yellow colored solid. Same procedure was followed for the preparation of palladacycles **26-28** from the corresponding phenylhydrazines.

2.4.1. Characterization of Palladacycles (25-28)

Palladacycle 25

Yield: 67 %; brown solid; **mp**: 310-312 ^{o}C (dec.); **IR** (KBr): 769, 1215, 1490, 2399, 3018, 3301 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.27-1.19 (t, *J* = 8.0 Hz, 3H), 2.62-2.47 (q, *J* = 8.0 Hz, 2H), 7.13-6.96 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 12.92, 23.35, 121.90, 125.99, 127.43, 127.79, 127.89, 136.21; **Analysis**: **$C_8H_{11}N_2PdCl$** requires C, 34.68; H, 4.00; N, 10.11; Cl, 12.80; found C, 34.68; H, 4.06; N, 10.15; Cl, 12.76%.

Palladacycle 26

Yield: 68%; brown solid; **mp**: 291-294 ^{o}C (dec.); **IR** (KBr): 433, 769, 1215, 1504, 2352, 3232 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.03 (s, 1H,), 5.85 (bs, 2H), 6.85 (d, *J* = 8.9 Hz, 1H), 7.70 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 54.50, 122.50, 125.17, 127.23, 127.84, 135.84, 144.05; **Analysis**: **$C_7H_9N_2OPdCl$** requires C, 30.13; H, 3.25; N, 10.04; Cl, 12.71; found: C, 30.08; H, 3.27; N, 10.07; Cl, 12.75%.

Palladacycle 27

Yield: 66%; brown solid, **mp**: 308-311 ^{o}C (dec.); **IR** (KBr); 741, 836, 925, 1060, 1126, 1287, 1418, 1508, 1606, 1818, 2565, 2760, 2858, 3772 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.9 Hz, 1H), 8.35 (d, *J* = 9.9 Hz, 1H), 8.97 (s, 1H);

^{13}C-NMR (50 MHz, $CDCl_3$): 116.35, 117.95, 129.02, 129.17, 129.64, 141.73; **Analysis**: **$C_6H_6N_2PdCl_2$** requires C, 25.42; H, 2.13; N, 9.88; Cl, 25.02; found C, 25.45; H, 2.18; N, 9.89; Cl, 25.08 %.

Palladacycle 28

Yield: 64 %; brown solid; **mp**: 336-340 ^{o}C (dec.); **IR** (KBr); 653, 910, 1030, 1197, 1244, 1350, 1514, 1633, 1866, 2061, 2279, 2472, 3001, 3234 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.22 (s, 1H), 6.92 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 24.90, 120.99, 124.21, 125.09, 126.35, 127.04, 136.49; **Analysis**: **$C_7H_9N_2PdCl$** requires C, 31.96; H, 3.45; N, 10.65; Cl, 13.48; C, 31.98; H, 3.47; N, 10.63; Cl, 13.45 %.

General Procedure for Suzuki Coupling:

To a stirred mixture aryl bromide (5.0 mmol), arylboronic acid (7.5 mmol), KOH (0.58 g, 10 mmol), tetrabutylammonium bromide (1.612 g, 5 mmol) in water (15 mL) was added palladacycles **25,** ($5x10^{-5}$ mmol) at 25 °C for specified time (**Table 2**). After completion of reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude products. The crude product was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to afford biphenyls (**31a-l**).

4-Methoxybiphenyl (31a)

Yield: 78%; colorless solid; **mp**: 87 °C [lit.[19] 86-87 °C]; **IR** ($CHCl_3$): 566, 703, 776, 845, 1051, 1130, 1198, 1304, 1414, 1462, 1530, 1615, 2917, 2970, 3065 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 6.85-7.46 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 114.1, 126.6, 128.0, 128.6, 133.7, 140.8, 159.1; **MS** (m/z,

% relative intensity): 184 (M^+**,** 100), 169 (44), 141 (38), 115 (26), 63 (4); **Analysis: $C_{13}H_{12}O$** requires C, 84.75; H, 6.56; found C, 84.55; H, 6.81%.

2-Methoxybiphenyl (31b)

Yield: 72%; viscous liquid; **IR** ($CHCl_3$): 565, 612, 667, 698, 732, 753, 800, 1028, 1055, 1122, 1236, 1259, 1463, 1504, 1597, 2834, 2956, 3011, 3061 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.71 (s, 3H), 6.75-7.49 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 111.3, 120.8, 121.6, 126.6, 127.7, 128.4, 128.5, 129.4, 130.7, 133.2, 138.6, 156.4; **Analysis: $C_{13}H_{12}O$** requires C, 84.75; H, 6.57; found C, 84.85; H, 6.49%.

4-Methylbiphenyl (31c)

Yield: 83%; viscous liquid; **IR** ($CHCl_3$): 546, 667, 760, 822, 1038, 1352, 1598, 1907, 2589, 3065 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), δ 7.20-7.57 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 126.8, 126.9, 127.1, 128.7, 129.4, 136.8, 138.4, 141.2; **MS** (m/z, % relative intensity): 168 (M^+**,** 100), 167 (68), 165 (22), 152 (20), 115 (6); **Analysis: $C_{13}H_{12}$** requires C, 92.81; H, 7.19; found C, 92.64; H, 7.40%.

4-Fluorobiphenyl (31d)

Yield: 98%; **mp:** 76 ºC; **IR** (nujol): 667, 761, 836, 907, 1007, 1105, 1164, 1264, 1351, 1394, 1451, 1594, 1893, 2559, 2853, 2923, 3062 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.15-7.59 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.4, 115.6, 126.9, 127.2, 128.6, 128.6, 128.7, 137.3, 140.2, 161.5, 163.4; **Analysis**: **$C_{12}H_9F$** requires C, 83.70; H, 5.27; found C, 83.52; H, 5.55%.

Biphenyl (31e)

Yield: 82%; **mp**: 71-72 °C; **IR** (Nujol): 698, 734, 1008, 1074, 1261, 1377, 1431, 1463, 1481, 1568, 2854, 2923, 2954 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.37-

7.47 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 126.7, 126.8, 128.3, 140.8; **Analysis**: **$C_{12}H_{10}$** requires C, 93.46; H, 6.54; found C, 93.43; H, 6.52%.

2-Phenylnaphthalene (31f)

Yield: 85%; colorless solid; **mp**: 105 °C; **IR** ($CHCl_3$): 668, 688, 758, 770, 820, 860, 892, 1076, 1216, 1452, 1496, 1598, 1948, 3106, 3058 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40-8.27 (m, 12H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 125.3, 125.7, 125.9, 126.0, 126.9, 127.1, 127.6, 128.2, 130.0, 131.6, 133.8, 140.2, 140.8; **Analysis: $C_{16}H_{12}$** requires C, 94.08; H, 5.92; found C, 94.29; H, 5.70%.

3-Trifluoromethylbiphenyl (31g)

Yield: 70%; viscous liquid; **IR** ($CHCl_3$): 615, 659, 701, 758, 805, 899, 1022, 1097, 1166, 1261, 1424, 1456, 1483, 1593, 2927, 3037, 3063 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.57-8.01 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 123.9, 127.2, 128.0, 129.2, 130.3, 139.8, 142.2; **Analysis: $C_{13}H_9F_3$** requires C, 70.27; H, 4.08; found C, 70.15; H, 3.95%.

1-Biphenyl-4-yl-ethanone (31h)

Yield: 90%; colorless solid; **mp**: 118 °C; **IR** ($CHCl_3$): 595, 668, 697, 756, 1007, 1216, 1267, 1358, 1604, 1680, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.40-7.47 (m, 3H), 7.56-7.65 (m, 4H), 7.97-8.01 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.3, 127.0, 128.0, 128.7, 135.6, 139.6, 145.4, 196.8; **MS** (m/z, % relative intensity): 196 (M^+, 51), 181 (100), 153 (33), 152 (51), 76 (13), 43 (4); **Analysis: $C_{14}H_{12}O$** requires C, 85.68; H, 6.16; found C, 85.59; H, 6.42%.

General Experimental Procedure for the Heck Reaction:

To a stirred mixture of aryl halide (2.0 mmol), K_2CO_3 (0.552 g, 4.0 mmol), olefin (3.0 mmol), tetrabutylammonium bromide (0.644 g, 2 mmol) in water (6 mL) was added palladacycles **25** (5x 10^{-6} mmol). The reaction mixture was then refluxed

for 6 h. (**Table 3**). After completion of reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude products. The crude product was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to afford arylated products (**32a-i**).

1-(4-Methylphenyl)-2-phenylethylene (32a):

Yield: 91%; viscous liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.00 (s, 3H), 6.68-7.30 (m, 11H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 126.5, 127.4, 127.8, 129.4, 134.6, 137.3, 137.6; **Analysis:** $C_{15}H_{14}$ requires C, 92.74; H, 7.26; found C, 92.79; H, 7.27%.

Methyl *(E)*-3-(1-naphthyl)propenoate (32b)

Yield: 83%; viscous liquid; **IR** ($CHCl_3$): 1023, 1219, 1632, 1704, 2833, 2945, 3010, 3368, 3630 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.87 (s, 3H), 6.56 (d, *J* = 8.0 Hz, 2H), 7.48-7.54 (m, 3H), 7.88 (d, *J* = 8.1 Hz, 2H), 8.21 (d, *J* = 6.2 Hz, 1H), 8.57 (d, *J* = 12.1 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.5, 120.3, 123.3, 124.8, 125.2, 126.0, 126.7, 128.6, 130.3, 131.3, 131.6, 133.6, 141.7, 166.8; **MS** (m/z, % relative intensity): 212 (M^+, 23), 181 (12), 153 (100), 151(71), 76 (58); **Analysis:** $C_{14}H_{12}O_2$ requires C, 79.22; H, 5.70; found C, 79.27; H, 5.79%.

Butyl (*E*) -3-(1-naphthyl)propenoate (32c)

Yield: 95%; viscous liquid; **IR** ($CHCl_3$): 698, 759, 799, 855, 977, 1038, 1087, 1175, 1346, 1464, 1634, 1707, 2933, 2960, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.6 Hz, 3H), 1.36-1.41 (m, 2H), 162-1.67 (m, 2H), 4.16 (t, *J* = 6.5, 2H), 6.41 (d, *J* = 15.5, 1H), 7.34-7.44 (m, 3H) 7.62 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.41 (d, *J* = 16.4, 1H); **^{13}C NMR** (50

MHz, $CDCl_3$): δ 13.7, 19.0, 30.7, 64.1, 120.7, 123.2, 124.7, 125.2, 125.9, 126.6, 128.5, 130.0, 130.2, 131.7, 133.5, 141.3, 166.3; **Analysis: $C_{17}H_{18}O_2$** requires C, 80.28; H, 7.13; found C, 80.29; H, 7.17%.

Butyl *(E)*-3-[(3-trifluoromethyl)-phenyl]propenoate (32d)

Yield: 82%; viscous liquid; **IR** ($CHCl_3$): 803, 865, 902, 984, 1076, 1096, 1134, 1177, 1196, 1219, 1270, 1311, 1335, 1387, 1439, 1643, 1709, 2963 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.33-1.48 (m, 2H), 1.60-1.74 (m, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 7.44-7.74 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.4, 19.0, 30.7, 64.2, 120.3, 124.4, 126.2, 129.1, 130.7, 131.2, 131.6, 135.3, 142.2, 165.8; **MS** (m/z, % relative intensity): 272 (M^+, 9), 253 (7), 216 (57), 199 (100), 171 (31), 151 (59), 102 (14), 56 (47), 41 (50); **Analysis: $C_{14}H_{15}F_3O_2$** requires C, 61.76; H, 5.55; found C, 61.55; H, 5.81%.

Ethyl *(E)*-3-[(3-trifluoromethyl)phenyl]propenoate (32e)

Yield: 80%; viscous liquid; **IR** ($CHCl_3$): 1041, 1077, 1096, 1134, 1169, 1178, 1196, 1219, 1263, 1311, 1335, 1369, 1440, 1643, 1709, 2985 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H); 4.24 (q, *J* = 7.1 Hz, 2H); 6.45 (d, *J* = 16.1 Hz, 1H); 7.25-7.73 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 60.2, 120.3, 124.4, 126.2, 129.1, 130.7, 135.3, 142.2, 165.6; **MS** (m/z, % relative intensity): 244 (M^+, 34), 225 (16), 216 (45), 199 (100), 171 (60), 151 (97), 131 (12), 102 (24), 75 (22), 45 (26); **Analysis: $C_{12}H_{11}F_3O_2$** requires C, 59.02; H, 4.54; found C, 59.31; H, 4.25%.

***(E)*-^{n}Butyl 3-phenyl-2-propenoate (32f)**

Yield: 86%; viscous liquid; **IR** (Nujol): 572, 684, 711, 979, 1026, 1172, 1201, 1255, 1280, 1311, 1326, 1384, 1450, 1496, 1577, 1639, 1712, 2873, 2933, 2960 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.27-1.42 (m, 2H),

1.54-1.68 (m, 2H), 4.12 (t, J = 7.1 Hz, 2H), 6.33 (d, J = 16.1 Hz, 1H), 7.25-7.45 (m, 5H), 7.57 (d, J = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 18.8, 30.5, 63.7, 118.1, 127.6, 128.4, 129.7, 134.2, 144.0, 166.1; **MS** (m/z, % relative intensity): 204 (12, M^+), 148 (57), 131 (93), 103 (80), 77 (100); **Analysis**: $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90; found C, 76.41; H, 7.86%.

***(E)*-Methyl 3-phenyl-2-propenoate (32g)**

Yield: 84%; **IR** (Nujol): 689, 716, 776, 986, 1014, 1030, 1169, 1183, 1202, 1514, 1531, 1722, 2863, 2946, 3029 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.45 (d, J = 16.1 Hz, 1H), 7.29-7.64 (m, 5H), 7.73 (d, J = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.5, 117.9, 128.0, 128.8, 130.2, 134.4, 144.7, 167.2; **MS** m/z (% relative intensity): 162 (M^+, 100), 131 (52), 103 (28), 77 (17); **Analysis**: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.12; H, 6.18%.

***trans*-Stilbene (32h)**

Yield: 89%; **mp**: 123-124 °C; **IR** (Nujol): 766, 962, 1378, 1452, 1464, 1496, 1598, 2866, 2869, 2926, 2966 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.07 (s, 2H), 7.22-7.36 (m, 6H), 7.48 (d, J = 8.0 Hz, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 126.5, 127.6, 128.6, 137.3; **MS** (m/z, % relative intensity): 180 (M^+, 100), 165 (31), 152 (6), 89 (14), 76 (10); **Analysis**: $C_{14}H_{12}$ requires C, 93.29; H, 6.71; found C, 93.24; H, 6.67%.

***(E)*-2-Phenylacrylonitrile (32i)**

Yield: 94%; viscous liquid; **IR** (Neat): 690, 749, 967, 1206, 1449, 1578, 1622, 2218, 3020, 3062 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.86 (d, J = 17.1 Hz, 1H), 7.32-7.40 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 94.8, 95.8, 117.5, 127.0, 128.7,

130.8, 133.3, 149.9; **MS** (m/z, % relative intensity): 129 (100, M^+), 102 (47), 76 (23), 63 (20); **Analysis:** C_9H_7N requires C, 83.69; H, 5.46; N, 10.85; found C, 83.69; H, 5.26; N, 10.78%.

Ethyl *(E)*-3-(4-nitrophenyl)propenoate (32j)

Yield: 80%; yellow solid; **mp**: 139-140 °C; **IR** ($CHCl_3$): 873, 1000, 1166, 1211, 1356, 1525, 1644, 1720, 2855, 2956, 3075 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 6.3 Hz, 3H), 4.21 (q, *J* = 6.3 Hz, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 7.72 (d, *J* = 16.2 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 2H), 8.22 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 60.2, 122.3, 123.7, 129.2, 140.3, 141.5, 147.9, 165.4; **MS** (m/z, % relative intensity): 221 (M^+, 31), 193 (32), 177 (12), 176 (100), 160 (16), 129 (19), 102 (33), 76 (10); **Analysis: $C_{11}H_{11}NO_4$** requires C, 59.73; H, 5.01; N, 6.33; found C, 59.68; H, 5.21; N, 6.25%.

***(E)*-Ethyl 3-(4-methoxyphenyl)-2-propenoate (32k)**

Yield: 79%; viscous liquid; **IR** (Neat): 820, 844, 970, 1020, 1177, 1298, 1340, 1435, 1510, 1580, 1620, 1722, 2998, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6.2 Hz, 3H), 3.82 (s, 3H), 4.24 (q, *J* = 6.2 Hz, 2H), 6.30 (d, *J* = 16.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 54.8, 59.8, 113.9, 115.4, 126.8, 129.3, 143.8, 161.0, 166.8; **MS** (m/z, % relative intensity): 206 (100, M^+), 178 (19), 161 (99), 134 (57), 118 (20), 89 (44), 77 (38), 63 (51); **Analysis**: $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.85; found C, 69.79; H, 6.82%.

1-(4-Methoxyphenyl)-2-phenylethylene (32l)

Yield: 81%; colorless solid; **mp**: 138 °C ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.89 (d, *J* = 10.2 Hz, 2H), 7.02 (d, *J* = 10.2 Hz, 2H), 7.24-7.51 (m, 7H); **^{13}C**

NMR (50 MHz, $CDCl_3$): δ 55.1, 114.1, 126.3, 126.7, 127.2, 127.7, 128.3, 128.6, 130.2, 137.7, 159.3; **Analysis: $C_{15}H_{14}O$** requires C, 85.68; H, 6.71; found C, 85.61; H, 6.79%.

***(E)*-Butyl 3-[(6-methoxy)-2-naphthyl]propenoate (32m)**

Yield: 87 %; viscous liquid; **IR** ($CHCl_3$): 852, 981, 1031, 1168, 1251, 1309, 1344, 1392, 1483, 1600, 1623, 1704, 2873, 2950, 3108 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.36-1.55 (m, 2H), 1.64-1.78 (m, 2H), 3.92 (s, 3H), 4.22 (t, *J* = 6.3 Hz, 2H), 6.48 (d, *J* = 16.1 Hz 1H), 7.09-7.17 (m, 2H), 7.60-7.83 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 19.1, 30.6, 55.1, 64.2, 105.7, 119.2, 124.0, 127.3, 128.4, 129.4, 129.5, 129.9, 135.4, 135.4, 144.6, 158.6, 167.1; **Analysis: $C_{18}H_{20}O_3$** requires C, 76.03; H, 7.09; found C, 76.18; H, 7.19%.

General Procedure for arylation of allylic alcohol

A two-necked 25 mL RB flask was charged with aryl halide (5 mmol), allyl alcohol (7.5 mmol), palladium complex **25** (0.277 mg, $5x10^{-4}$ mmol), K_2CO_3 (1380 mg, 10 mmol), tetrabutylammonium bromide (1610 mg, 5 mmol) and water (15 mL). The resulting mixture was stirred at 80 °C for 6 h. After completion of reaction (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude products. The crude product was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent.

Ethyl 4-(*E*-3-hydroxyprop-1-enyl)benzoate (35a)

Yield: 82 %; **mp**: 88 °C; **^{1}HNMR** (200 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.3 Hz, 3H), 4.34 (q, *J* = 7.3 Hz, 2H), 4.77 (d, *J* = 6.5 Hz, 2H), 5.25-5.40 (m, 1H), 5.94- 6.04 (m, 1H), 7.69-7.78 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 60.8, 65.4,

100.6, 118.3, 129.5, 130.9, 131.9, 137.4, 164.9; **Analysis**: $C_{12}H_{14}O_3$ required C, 69.88; H, 6.84; found: C, 69.87; H, 6.89%.

Methyl 4-(*E*-4-hydroxybut-2-en-2-yl)benzoate (35b)

Yield: 88%; **mp**: 64 °C; **IR** ($CHCl_3$): 626, 682, 756, 846, 933, 940, 1012, 1068, 1108, 1172, 1269, 1361, 1483, 1591, 1722, 1922, 1922, 2950, 3087 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.78 (s, 3H), 3.95 (s, 3H), 4.71-4.89 (m, 2H) 5.65-5.93 (m, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.3, 51.8, 58.9, 126.1, 127.2, 129.4, 129.8, 134.2, 143.7, 166.0; **Analysis**: $C_{12}H_{14}O_3$ required C, 69.89; H, 6.84; found: C, 69.87; H, 6.89%.

Cyclopentyl-3-phenylbutan-1-one (36c)

Yield: 63 %; colorless liquid; **IR** ($CHCl_3$): 700, 761, 910, 956, 1010, 1116, 1176, 1274, 1371, 1452, 1494, 1602, 1708, 2869, 2958, 3028, 3028,3060, 3479 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.43 (d, *J* = 8.0 Hz, 3H), 1.73-1.76 (bm, 9H), 2.88 (d, *J* = 6.0 Hz, 2H), 3.45-3.52 (m, 1H), 7.27-7.56 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.8, 25.9, 28.7, 35.2, 50.3, 51.8, 126.1, 126.8, 128.4, 146.5, 210.8; **MS** (m/z, % relative intensity): 216 (M+**,** 17), 201 (8), 147 (42), 105 (100), 91(33), 69 (100); **Analysis**: $C_{15}H_{20}O$ required C, 83.28; H, 9.32; found: C, 83.36; H, 9.35%.

3-Phenylbutanal (36d)

Yield: 73%; colorless liquid; **IR** ($CHCl_3$): 700, 761, 910, 1020, 1278, 1375, 1452, 1494, 1600, 1704, 2875, 2931, 2964, 3028, 3060, 3083 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (d, *J* = 6.9 Hz, 3H), 2.91 (t, *J* = 5.4 Hz, 2H), 3.56 (m, 1H), 7.44 (m, 5H), 9.90 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.7, 39.0, 52,9, 126.0, 126.0, 128.5, 148.6, 202.1; **MS** (m/z, % relative intensity): 148 (M+**,** 38) 133 (38),

115 (11), 105 (100), 91 (55), 77 (42), 51 (37); **Analysis**: $C_{10}H_{12}O$ required C, 81.04; H, 8.16; found: C, 81.07; H, 8.14%.

3-(4-Methoxyphenyl)propanal (36e)

Yield: 88%; colorless liquid; **IR** ($CHCl_3$): 757, 831, 1033, 1178, 1247, 1308, 1463, 1514, 1612, 1681, 1712, 2057, 2362, 2837, 2933, 3006 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.94 (d, *J* = 7.1 Hz, 2H), 3.10 (d, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 6.92 (d, *J* = 10.2 Hz, 2H), 7.30 (d, *J* = 10.2 Hz, 2H), 9.9 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 27.3, 45.5, 55.0, 113.9, 129.1, 132.2, 158.1, 200.8; **Analysis**: $C_{10}H_{12}O_2$ required C, 73.15; H, 7.37; found: C, 73.31; H, 7.39%.

3-(4-Methoxyphenyl)butanal (36f)

Yield: 92%; colorless liquid; **IR** ($CHCl_3$): 831, 1033, 114, 1178, 1249, 1301, 1375, 1461, 1541, 1608, 1714, 1886, 2054, 2837, 2935, 2962, 3328, 3488 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.67 (d, *J* = 7.0 Hz, 3H), 3.02- 3.06 (m, 2H), 3.63-3.73 (m, 1H), 4.15 (s, 3H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 10.07 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.4, 33.5, 51.9, 54.9, 113.9, 127.7, 130.1, 158.1, 201.2; **Analysis**: $C_{11}H_{14}O_2$ required C, 74.13; H, 7.92; found: C, 74.17; H, 7.96%.

Methyl 2-((*E*)-3-hydroxyprop-1-enyl)-benzoate (35g)

Yield: 90%; **IR** ($CHCl_3$): 669, 769, 929, 1016, 1134, 1251, 1294, 1434, 1728, 2399, 3018 cm^{-1}; **mp**: 77 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.79 (d, *J* = 6.0 Hz, 2H), 5.24-5.44 (m, 2H), 5.92- 6.08 (m, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.0, 65.7, 123.9, 127.5, 129.7, 130.6, 131.5, 132.3, 134.6, 140.9, 165.4; **Analysis**: $C_{11}H_{12}O_3$ required C, 68.74; H, 6.29; found: C, 68.79; H, 6.30%.

Methyl 4-(*E*-3-hydroxyprop-1-enyl)benzoate (35h)

Yield: 81%; **mp**: 76 °C; **IR** ($CHCl_3$): 626, 682, 846, 892, 1012, 1068, 1172, 1269, 1375, 1454, 1591, 1722, 1924, 2914, 2968, 3076 cm^{-1} ; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.77 (d, *J* = 4.6 Hz, 2H), 5.23-5.41 (m, 2H), 6.08-6.97 (m, 1H), 7.53 (d, *J*= 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H); **^{13}C-NMR** (50 MHz, CDCl3): δ 52.0, 65.6, 123.2, 128.0, 129.0, 131.1, 132.0, 140.6, 165.0; **Analysis**: $C_{11}H_{12}O_3$ required C, 68.74; H, 6.29; found: C, 68.71; H, 6.26%.

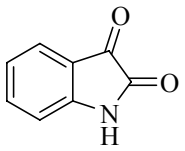
Ethyl 4-(*E*-4-hydroxybut-2-en-2yl)benzoate (35i)

Yield: 88%; **mp**: 83 °C; **IR** ($CHCl_3$): 669, 771, 850, 927, 1012, 1068, 1178, 1217, 1278, 1296, 1319, 1398, 1429, 1589, 1721, 2401, 2563, 2682, 3020 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39 (t, *J* = 6.0 Hz, 3H), 1.77 (s, 3H), 4.31-4.41 (q, *J* = 6.0 Hz 2H), 4.70-4.74 (m, 2H), 5.68-5.64 (m, 1H), 7.69-7.78 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 15.8, 58.6, 60.9, 126.3, 127.2, 129.4, 129.8, 134.2, 143.7, 166.1; **Analysis**: $C_{13}H_{16}O_3$ required C, 70.89; H, 7.32; found: C, 70.85; H, 7.36%.

Section II: H-β Zeolite mediated synthesis of Isatins

4.2.1 Introduction

Isatin (1*H*-indole-2,3-dione, **37**) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids.



37

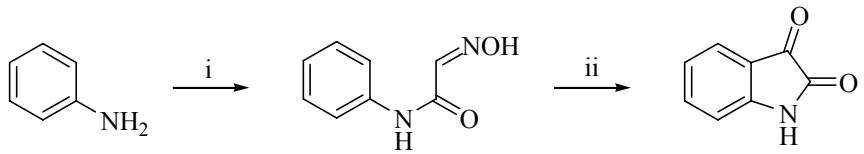
In nature, isatin is found in plants of the genus *Isatis*[20a] and has also been found as a component of secretion from parotid gland of *Bufo* frogs,[20b] and in humans as a metabolic derivative of adrenaline.[21-23] Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa*.[24-26] 6-(3'-methylbuten-2'-yl)isatin was isolated from *Streptomyces albus*[27] and 5-(3'-Methylbuten-2'-yl)isatin from *Chaetomium globosum*[28]. Isatin has also been found to be a component of coal tar.[29]

Litrature survey

Literature search revealed that there are various methods available for the preparation of isatins and chemistry has been reviewed. Some of the important developments for the synthesis of isatins are discussed below.

Sandmeyer's approach[30]

Sandmeyer *et al* have prepared isatins from the reaction of aniline **38** with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form isonitrosoacetanilide **39**, which on treatment with concentrated sulfuric acid, furnished isatin in >75% overall yield (**Scheme 9)**.

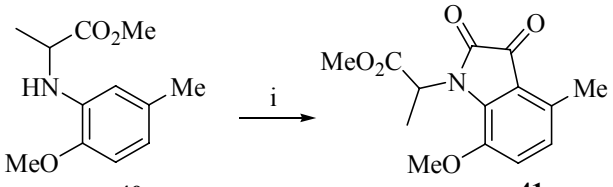


38 **39** **37**

Scheme 9: (i). $Cl_3CCH(OH)_2$, $NH_2OH.HCl$, Na_2SO_4, (ii) H_2SO_4, H_2O.

Terashima's approach[31]

In this method anilines are reacted with oxalyl chloride to form an intermediate chlorooxalylanilide which underwent cyclization in the presence of a Lewis acids, usually aluminum chloride or $BF_3.Et_2O$ and $TiCl_4$ has also been used to give the corresponding isatin in good yields (**Scheme 10)**.



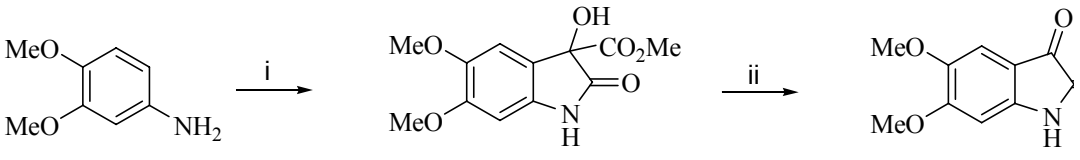
40 **41**

Scheme 10: (i) $(COCl)_2$ (ii) $TiCl_4$, CH_2Cl_2.

Martinet's approach[32]

The Martinet procedure for the synthesis of indole-2,3-diones involves the reaction of

anilines **42,** with oxomalonate ester in the presence of an acid to yield 3-(3-hydroxy-2-oxindole)carboxylic acid derivative **43** which on oxidative decarboxylation yields the respective isatin **44** (**Scheme 11**).

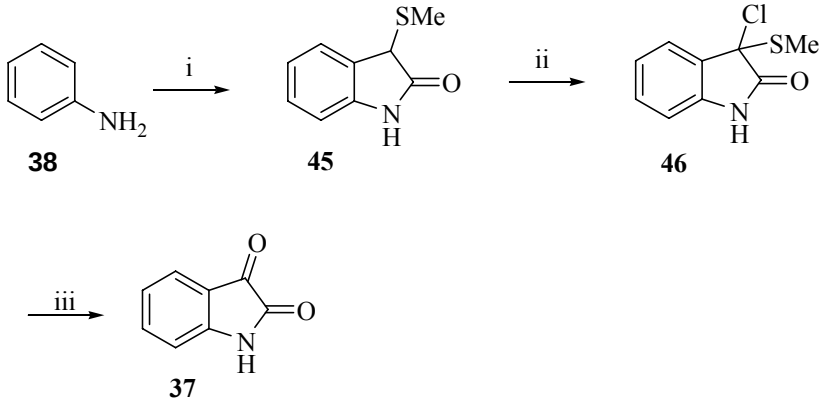


42 **43** **44**

Scheme 11: Diethyl ketomalonate hydrate, AcOH, KOH, reflux. (ii) 37% HCl (pH 1.0).

Gassman procedure[33]

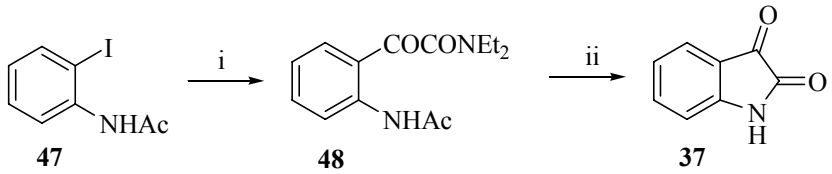
A fundamentally different and general procedure developed by Gassman is another option for the synthesis of isatins. This methodology involves formation and subsequent oxidation of an intermediate 3-methylthio-2-oxindole **45,** to give the corresponding substituted isatins in 40-81% yield (**Scheme 12**).



Scheme 12: (i) a. ^{t}BuOCl. b. $MeSCH_2CO_2Et$. c. Et_3N. d. H_3O^+. (ii) *N*-Chlorosuccinimide. (iii) HgO/BF_3 or H_2O/THF/reflux.

Yamamoto's approach[34]

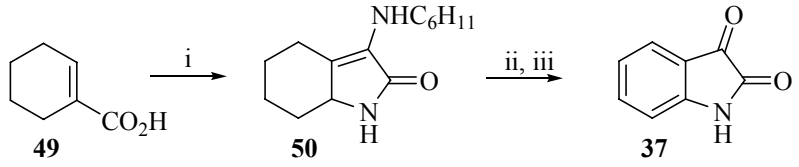
Yamamoto and co-workers have synthesized isatins from palladium catalysed double carbonylation of *ortho*-haloacetanilides **47**, in the presence of Et_2NH to yield the corresponding glyoxylic acid amide **48**. Hydrolysis of this amide yielded the respective isatin in good yields (**Scheme 13**).



Scheme 13: (i) CO, Et_2NH, Pd, 77%, (ii) 3NHCl, 93%.

Rigby's approach[35]

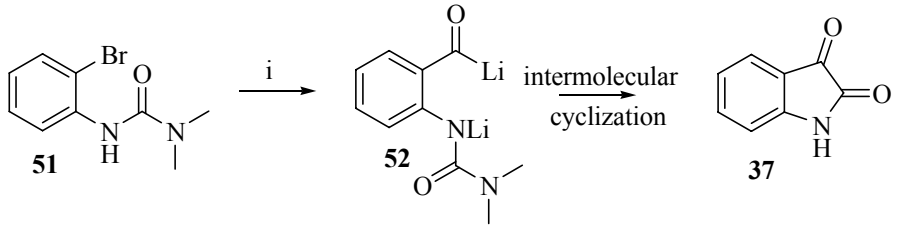
Rigby approach involves [1+4] cycloaddition of vinyl isocyanates and isocyanides to give dienamides **50,** which on hydrolysis and subsequent oxidation by DDQ yielded isatin in good yield (**Scheme 14**).



Scheme 14: (i) DPPA, $C_6H_{11}NC$ (ii) $(CO_2H)_2$, MeOH (iii) DDQ

Parrick' s approach[36]

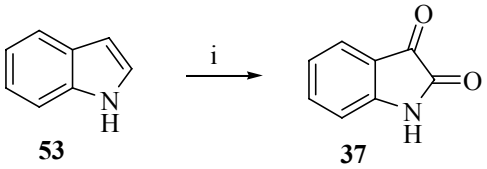
Parric's approach uses metal-halogen exchange method for the synthesis of isatins. It involves lithiation of *ortho*-bromophenylureas **51**, and subsequent intramolecular cyclisation afforded isatins in 71-79% yield (**Scheme 15**).



Scheme 15: (i) a. MeLi, 0 ^oC; b. *t*-BuLi, 0 ^oC; c. CO; d. H_3O^+; 77%.

Yadav's approach[37]

In this approach indoles **53,** and azaindoles undergo smooth oxidation with 2-iodoxybenzoic acid (IBX) in the presence of indium (III) chloride at 80 °C to afford the corresponding isatins in excellent yields. This method is very useful for the direct preparation of isatins from indoles. The reaction proceeds smoothly in aqueous media and the products are obtained in excellent yields (**Scheme 16**).



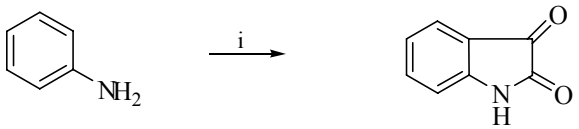
53 37

Scheme 16: (i) $InCl_3$, IBX, MeCN-H_2O, 80 ^oC, 2 h, 85%.

4.2.3 Present Work

4.2.3.1 Objective

Although there are several methods for the synthesis of isatins are known in the literature, these methods suffer from several drawbacks such as use of highly moisture and air-sensitive reagents and use of heavy metal catalysts. All these methods generally involve multistep reactions and require very harsh conditions. This section describes a new, one pot method for the synthesis of isatins starting from the respective anilines using oxalyl chloride as the acylating agent and H-β zeolite as a reusable catalyst, under truly heterogenous conditions (**Scheme 17**).



37, 71%

Scheme 17: (i) $(COCl)_2$, H-β zeolite, (10% w/w), EDC, 90 °C, 12h.

4.2.3.2 Zeolites: A brief introduction

Zeolites[38] are hydrated, crystalline, microporous aluminosilicates. The general formula of zeolites can be represented as

$$Mx/n\ [(AlO_2)x\ (SiO_2)_y]zH_2O$$

The net negative charge on the framework is same as the number of aluminum atoms and is balanced by exchangeable charge compensating cations. x+y

represents the total number of tetrahedra in the unit cell of zeolite. The ratio of y/x > 1 controls the acidity and the morphology of the zeolites. Based on the morphological characteristics,[39-41] crystal structure, chemical composition, effective pore diameter and natural occurrences, zeolites have been classified into several groups. According to IUPAC nomenclature system[42] the naming is based on their framework density and number of T atoms per 1000 Å, irrespective of their composition, distribution of T-atoms, cell dimensions or symmetry parameters. Based on the pore size they can be classified as follows.

Pore Size	Number of T in pore opening	Max. Free diameter Å	Example
Small	6 and 8	4.3	Erionite
Medium	10	6.3	ZSM-5
Large	12	7.5	Y, Beta, ZSM-12
Extra large	18	12	VPI-5

Zeolites[43] and related microporous (**Fig. 5**) materials have attracted considerable international importance due to their versatility. After the development of molecular modeling of zeolites structures, the depth of understanding the catalytic chemistry and structure activity relationship has shown a dramatic growth. Application of zeolites in the synthesis of organic fine chemicals is a relatively underdeveloped area,[43] when compared to the successful use of zeolites in hydrocarbon processing or petroleum refining. Zeolites have gained importance in not only in the field of organic or inorganic synthesis but also in the pharmaceutical field.[44]

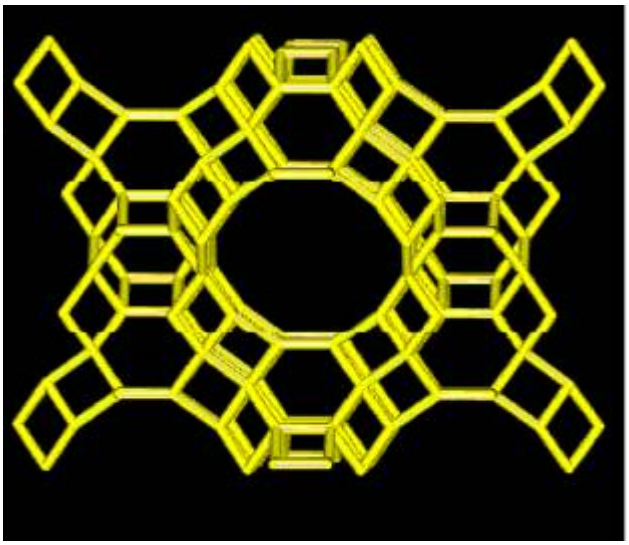
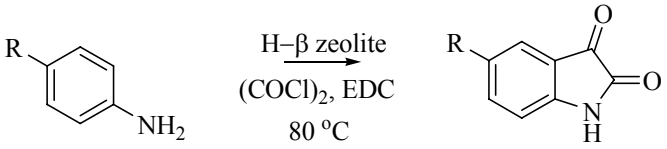


Fig. 5: Structure of Zeolite Y

4.2.4 Results and Discussion

H-β zeolite mediated synthesis of isatin is depicted in **Scheme 17.** When aniline was treated with oxalyl chloride in the presence of H-β zeolite (10% w/w) in dichloroethane (EDC) as solvent at 90°C, the corresponding isatin was obtained in good yield (71%). Control experiments indicated that no reaction took place in the absence of H-β zeolite; lowering of of H-β zeolite (wt %) also resulted in the reduced yield. Dichloroethane could be used as the solvent for this transformation although CH_3CN and nitrobenzene were found to be less effective. In order to understand the scope and generality of the reaction, a wide range of anilines were treated with oxalyl chloride using H-β zeolite (10% w/w) under optimized reaction conditions (1 equivalent of oxalyl chloride, 90°C, EDC). **Table 5** shows the scope of the reaction wherein moderate to high yields of **37a-h**

Table 5: H-β zeolite mediated synthesis of isatins[a]



37a-j

Entry	R	T/h	Yield (%)[b]
a	H	24	71
b	CH_3	24	76
c	$(CH_3)_2CH$	24	61
d	Cl	30	59
e	F	36	51
f	OMe	12	79
g	NO_2	30	48
h	CO_2Me	30	69

[a] Reaction conditions: Aniline (2 mmol), $(COCl)_2$ (2 mmol), Hβ-zeolite (10 % w/wt), dichloroethane (30 mL), 90 ^oC.
[b] Isolated yields after chromatographic purification.

were obtained in all cases studied. For aromatic substrates with electron-withdrawing substituents, the reaction time was longer giving moderate yields. The catalyst could be activated once again by heating at 400 °C and resued for atleast 5 reaction cycles without considerable loss of activity. The formation of isatins was confirmed by ^1H, ^{13}C and IR spectroscopy. For example, the ^1H NMR spectrum of 5-methylisatin showed typical signals at δ 6.76 (d), 7.29(s) and 7.37 (d) for the aromatic protons. Its ^{13}C NMR showed typical carbon signals at δ 159.5 and 184.6 for the amide and ketone carbonyl groups

respectively. Its IR spectrum showed two strong bands at 1750 and 1622 cm^{-1} corresponding to the carbonyl stretching of isatin, **37b**.

4.2.5. Conclusion

In conclusion, this methodology provides a simple and efficient procedure for the single step preparation of isatins from the commercially available anilines using zeolite as the catalyst. The catalysts are easy to separate by simple filtration and are recycled at least three times without much loss in their activity. It has been demonstrated that H-β zeolites are excellent catalyst that are alternatives to Lewis acids like $SnCl_4$, $BF_3.Et_2O$.

4.2.6. Experiment Section

General Procedure for the synthesis of isatins

To a mixture of aniline (2.0 mmol) and H-β zeolite (50 mg, 10 % wt/wt) in dichloroethane was added oxalyl chloride (2.0 mmol) and refluxed under nitrogen atmosphere. After completion of the reaction (as monitored by TLC), it was filtered and the catalyst was recovered, distillation of solvent under reduced pressure furnished the crude material. The crude product was purified by column chromatography on silica gel using $CHCl_3$ and MeOH (1:1) as eluent to afford pure isatins.

Isatin (37a)

Yield: 71%; colorless solid; **mp**: 207°C (recrystallized from benzene){lit.[33] mp: 200-202 °C}; IR (KBr): 620, 780, 950, 1120, 1200, 1310, 1450, 1610, 1710, 3210 cm^{-1}; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 6.91 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 11.02 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 112.2, 117.8, 122.8, 124.7, 138.4, 150.7, 159.4, 184.4; **Analysis**: **$C_8H_5NO_2$** requires C, 65.31; H, 3.43; N, 9.52; found C, 65.36; H, 3.48; N, 9.55%.

5-Methylisatin (37b)

Yield: 76%; red needles; **mp**: 187°C (recrystallized from ethanol) {lit.[33] mp: 185-187 °C}; **IR** (KBr): 752, 839, 1044, 1150, 1151, 1226, 1433, 1527, 1622, 1750, 3322; cm^{-1}; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 2.24 (s, 3H), 6.76 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.37 (d, *J* = 8.0, Hz, 1H), 10.93 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 20.1, 112.0, 117.8, 124.8, 132.0, 138.8, 148.5, 159.5, 184.6; **Analysis**: **$C_9H_7NO_2$** requires C, 67.07; H, 4.38; N, 8.69; found C, 67.09; H, 4.33; N, 8.61%.

5-*iso*-Propylisatin (37c)

Yield: 61%**;** yellow solid; **mp**: 166°C; **IR** (KBr): 706, 770, 848, 1041, 1046, 1149, 1431, 1522, 1620, 1752, 3351; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.16 (d, *J* = 6.9 Hz, 1H), 2.86 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 7.47 (dd, *J* = 8.0, 2.8 Hz , 1H), 10.95 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 23.7, 32.7, 112.1, 117.8, 122.3, 136.6, 143.2, 148.9, 159.6, 184.6; **Analysis**: **$C_{11}H_{11}NO_2$** requires C, 69.83; H, 5.86; N, 7.40; found C, 69.89; H, 5.81; N, 7.49%.

5-Chloroisatin (37d)

Yield: 59%**;** red solid; **mp**: 249°C (recrystallized from ethanol) {lit.[37] mp: 248-251 °C}; **IR** (KBr): 770, 842, 1041, 1132, 1205, 1240, 1430, 1610, 1710, 1780, 2390, 2950, 3190; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 6.91 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.60 (dd, *J* = 8.3, 2.3 Hz , 1H), 11.15 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 113.9, 119.2, 124.2, 126.8, 137.3, 149.2, 159.2, 183.4; **Analysis**: $C_8H_4ClNO_2$ requires C, 52.92; H, 2.22; N, 7.71; found C, 52.97; H, 2.21; N, 7.79%.

5-Fluoroisatin (37e)

Yield: 51%**;** yellow solid; **mp**: 223 °C (recrystallized from ethanol); **IR** (KBr): 771, 845, 1041, 1156, 1434, 1521, 1625, 1750, 3341; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 6.91 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.38 (dd, *J* = 7.2, 2.7 Hz, 1H), 7.44 (m, 1H), 11.02 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 111.3, 113.4, 118.4, 124.4, 147.0, 146.9, 159.3, 183.9; **Analysis**: **$C_8H_4FNO_2$** requires C, 58.19; H, 2.24; N, 8.48; found C, 58.16; H, 2.21; N, 8.44%.

5-Methoxyisatin (37f)

Yield: 79%**;** yellow solid; **mp**: 201°C (recrystallized from ethanol) {lit.[33] mp: 202-203 °C}; **IR** (KBr): 709, 820, 904, 1104, 1171, 1253, 1318, 1468, 1602, 1735, 2922, 3045 cm^{-1}; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 3.75 (s, 3H), 6.87 (d, *J* = 9.6 Hz, 1H), 7.1 (d, *J* = 9.6 Hz, 1H), 7.17 (m, 1H), 10.86 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 55.8, 108.8, 113.3, 118.1, 124.9, 144.7, 155.4, 159.6, 184.1; **Analysis**: **$C_9H_7NO_3$** requires C, 61.02; H, 3.98; N, 7.91; found C, 61.04; H, 3.93; N, 7.97%.

5-Nitroisatin (37g)

Yield: 48%**;** yellow solid; **mp**: 256°C (recrystallized from ethanol) {lit.[33] mp: 252-254 °C}; **IR** (KBr): 700, 745, 826, 885, 1020, 1074, 1123, 1168, 1331, 1467, 1518, 1611, 1749, 2925, 3101 cm^{-1}; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 6.98 (d, *J* = 8.6, Hz, 1H), 8.30 (s, 1H), 8.36 (d, *J* = 8.6, Hz, 1H), 10.52 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 112.6, 118.2, 119.6, 133.2, 142.7, 155.3, 159.9, 182.4; **Analysis**: **$C_8H_4N_2O_4$** requires C, 50.01; H, 2.10; N, 14.58; found C, 50.06; H, 2.13; N, 14.55%.

Methyl 2,3-dioxo-2,3-dihydro-1*H*-indole-5-carboxylate (37h)

Yield: 69%**;** yellow solid; **mp**: 258°C (recrystallized from ethanol) {lit.[33] mp: 258-259 °C}; **IR** (KBr): 698, 1070, 1193, 1285, 1323, 1378, 1440, 1537, 1609, 1739, 2852, 2923; cm^{-1}; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 3.89 (s, 3H), 6.99 (d, *J* = 8.1, Hz, 1H), 8.09 (s, 1H), 8.17 (d, *J* = 8.1, Hz, 1H), 11.37 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 52.3, 112.3, 117.8, 124.6, 125.0, 139.0, 154.1, 159.4, 164.3, 183.4; **Analysis**: **$C_{10}H_7NO_4$** requires C, 58.54; H, 3.44; N, 6.83; found C, 58.58; H, 3.49; N, 6.81%.

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List of Publications

1. Organocatalytic activation of TMSCN by basic ammonium salts for efficient cyanation of aldehydes and imines. **Raj**, **I. V. P**.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett*. **2007**, *48*, 7211.
2. Hydrolytic Kinetic Resolution approach for the asymmetric synthesis of (*S*)-dihydrokavain and (*S*)-vigabatrin. **Raj**, **I. V. P**.; Sudalai, A. *Tetrahedron Lett*. **2007** (communicated).
3. Sulfonamide-and hydrazine-based palladium catalysts: Stable and efficient catalysts for C–C coupling reactions in aqueous medium. Kumar, N. S. C. R.; **Raj**, **I. V. P**.; Sudalai, A. *J. Mol. Cat*. **2007**, *269*, 218.
4. Asymmetric synthesis of (S,S)-Ethambutol using Hydrolytic Kinetic resolution. **Raj**, **I. V. P**.; Sudalai, A. *Tetrahedron Lett*. **2007** (communicated).
5. A facile direct conversion of aldehydes to esters and amides using acetone cyanohydrin. **Raj**, **I. V. P**.; Sudalai, A. *Tetrahedron Lett*. **2005**, *46*, 8303.