ASYMMETRIC DIHYDROXYLATION AND WITTIG-HORNER APPROACH TO THE SYNTHESIS OF BIOACTIVE MOLECULES AND HETEROGENEOUS CATALYSIS FOR ORGANIC TRANSFORMATIONS

A THESIS SUBMITTED TO THE

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IN

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"ASYMMETRIC DIHYDROXYLATION AND WITTIG-HORNER APPROACH TO THE SYNTHESIS OF BIOACTIVE MOLECULES AND HETEROGENEOUS CATALYSIS FOR ORGANIC TRANSFORMATIONS"** submitted by **Rajesh Kumar Pandey** was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been only acknowledged in the thesis.

(Dr. Pradeep Kumar)
Research Guide

March 2003

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CANDIDATE DECLRATION

I hereby declare that the thesis entitled **"ASYMMETRIC DIHYDROXYLATION AND WITTIG-HORNER APPROACH TO THE SYNTHESIS OF BIOACTIVE MOLECULES AND HETEROGENEOUS CATALYSIS FOR ORGANIC TRANSFORMATIONS"** 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.

Rajesh Kumar Pandey

March 2003

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Rajesh Kumar Pandey

Memory of My Father

Late Kailash Nath Pandey

CONTENTS

GENERAL REMARKS

1. All melting points and boiling points temperature are in centigrade scale.

2. The compound numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

3. All solvents were distilled prior to use. Petroleum ether refers to the fraction collected in boiling range 60-80^{o}C.

4. Organic layers were dried over anhydrous sodium sulfate.

5. TLC analyses were carried out on glass plate using silica gel; GF-254 and the plates were developed in iodine stain.

6. In case where chromatographic separations were done, SiO_2 was used as the stationay phase.

7. The IR spectra were recorded on Perkin-Elmer spectrophotometer 683 B or 1605 FT-IR and adsorptions are expressed in cm^{-1}.

8. The ^{1}H and 13C NMR spectra were recorded on Bruker AC-200 or MSL-300 instruments using trimethylsilane as the internal standard. The follwing abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet and dd = double doublet.

9. The mass spectra were recorded on Finingan MAT-1020-B-70eV mass spectrometer.

10. The optical rotations were done in Carlo ERBA EA110B instrument.

GLOSSARY

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
AD	Asymmetric dihydroxylation
Ar	Aryl
BP	Boiling point
Boc_2O	*Di-tert*-butyl dicarbonate
t-Bu	*tert*-Butyl
Bn	Benzyl
$CDCl_3$	Deuterated chloroform
D_2O	Deuterium oxide
$(DHQ)_2$-PHAL	1,4-Bis(dihydroquinin-9-*O*-yl)-phthalazine
$(DHQD)_2$-PHAL	1,4-Bis(dihydroquinidin-9-*O*-yl)-phthalazine
DMAP	N,N-(Dimethylamino)pyridine
DMSO	Dimethyl sulfoxide
DMF	N,N-Dimethylformamide
ee	Enantiomeric excess
EIMS	Electron impact mass spectrum
eq.	Equivalent
Et	Ethyl
EtOH	Ethyl alcohol
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
gm	Grams
h	Hours
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide
ml	Milliliter
Me	Methyl
MeCN	Acetonitrile

MeOH	Methanol
mg	Milligram
mmol	Millimol
min.	Minutes
M.P.	Melting point
M^+	Molecular ion
MS	Mass spectrum
NMR	Nuclear magnetic resonance
Pet. ether	Petroleum ether
Ph	Phenyl
Piv	Pivaloyl
Py	Pyridine
p-TSA	*p*-Toluene sulfonic acid
rt	Room temparature
SAD	Sharpless asymmetric dihydroxylation
TBDMS	*Tert*-Butyl dimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluene sulfonyl

ABSTRACT OF THE THESIS

Thesis entitled **"Asymmetric Dihydroxylation and Wittig-Horner approach to the Synthesis of Bioactive Molecules and Heterogeneous Catalysis for Organic Transformations"** is divided into five chapters.

Chapter 1: describes a brief introduction to the Sharpless Asymmetric dihydroxylation (SAD) and its application to the synthesis of enantiomerically pure fluoxetine, phenylephrine and related analogs and is divided into two sections.

Chapter 2: deals with the application of Wittig-Horner approach/Heck coupling reaction towards the synthesis of tamoxifen and mintlactone and is divided into three sections.

Chapter 3: includes the synthesis, characterization and catalytic properties of sulfated yttrium based strong Lewis acid catalyst and is divided into two sections.

Chapter 4: covers the application of zeolites in organic synthesis and is divided into three sections.

Chapter 5: constitutes the synthesis, characterization and catalytic activity of sulfated cerium based new solid super acid catalyst and is divided into two sections.

Chapter 1

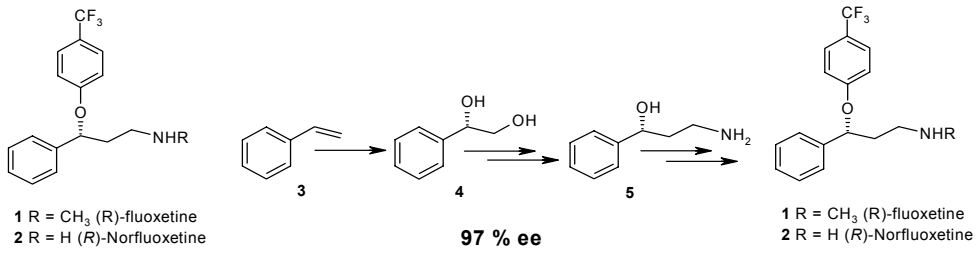
Asymmetric dihydroxylation route towards synthesis of bioactive molecules

This chapter gives a brief introduction to Sharpless asymmetric dihydroxylation (SAD) reaction. A catalytic asymmetric reaction provides an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. The SAD reaction is one such reaction developed in early 1990.[1] It has evolved as one of the most powerful methods for enantioselective oxidation of olefins to optically active vicinal diols that are versatile and convenient building blocks in the synthesis of bioactive compounds.

In our synthetic endeavors we have employed the chiral diol compounds obtained by SAD reaction towards the synthesis of fluoxetine, phenylephrine and related analogs. The chapter is further divided into two sections.

Section A: Enantioselective synthesis of norfluoxetine, fluoxetine and related analogs

Fluoxetine **1**, and its metabolite norfluoxetine **2** are among the most important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity and bulimia).[2] We have employed a short and efficient route for the synthesis of (*R*)-fluoxetine (Scheme 1).



Scheme 1

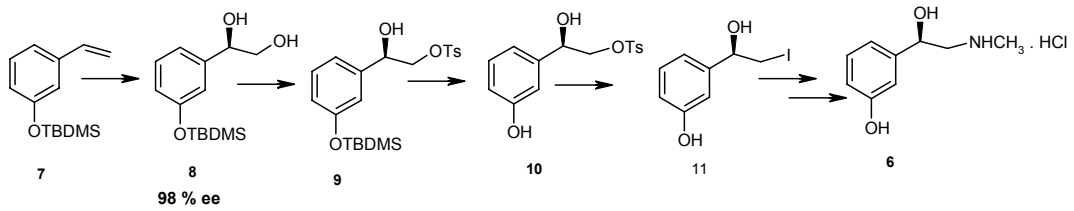
The synthetic strategy features a Sharpless asymmetric dihydroxylation (SAD) route to the common building block 1,3-amino alcohol **5** from which (*R*)-norfluoxetine, (*R*)-fluoxetine were synthesized. Thus the asymmetric dihydroxylation of styrene **3** to the diol **4** followed by selective conversion of OH group into tosylate, nucleophilic displacement with cyanide and subsequent reduction provided the 1,3-amino alcohol **5**. This key intermediate was then used to prepare the optically active (*R*)-norfluoxetine and (*R*)-fluoxetine by arylation with 4-chlorobenzotrifluoride. Conversion of (*R*)-norfluoxetine **2** to (*R*)-fluoxetine **1** was achieved *via* carbamate formation.

Thus, a practical and highly enantioselective synthesis of (*R*)-fluoxetine **1** and (*R*)-norfluoxetine **2** has been achieved for the first time using SAD as the source of chirality.

Section B: Enantioselective synthesis of (*R*)-phenylephrine hydrochloride

Phenylephrine hydrochloride **6** is a potent adrenergic agent and ß-receptor sympathomemitic drug.[3] So far only two chiral synthesis of this molecule is reported in literature. We have employed high yielding, enantioselective route for the synthesis of (*R*)-phenylephrine hydrochloride. The synthetic route is depicted in Scheme 2. The selective tosylation of **8** to **9** and subsequent deprotection of TBDMS group followed by

nucleophilic displacement of OTs group with NaI gave iodo alcohol **11**. Replacement of iodo group with methylamine followed by treatment with hydrochloric acid resulted in (*R*)-phenylephrine hydrochloride (Scheme 2).



Scheme 2

Thus, a short and efficient asymmetric synthesis of (*R*)-phenylephrine hydrochloride is achieved.

Chapter 2

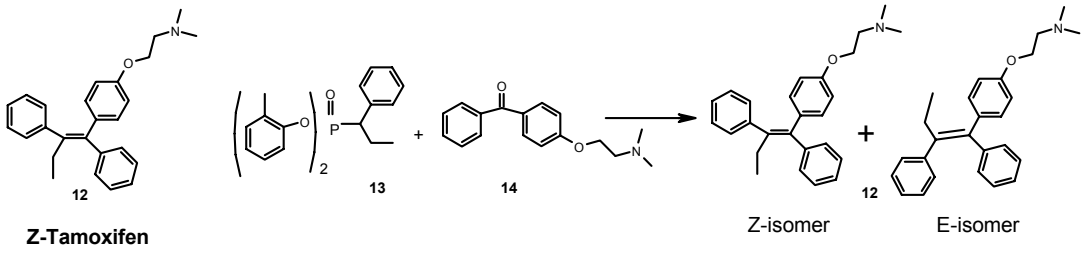
Wittig - Horner approach and Heck coupling reaction towards the synthesis of Z-tamoxifen and mintlactone

This chapter summarizes our studies on the Wittig-Horner approach and Heck coupling reaction towards the synthesis of tamoxifen and mintlactone and is further divided into three sections.

Section A: A Wittig - Horner approach towards the synthesis of anticancer drug "tamoxifen"

(Z) – Tamoxifen[4] **12** (ICI – 46, 474, Nolvadex), a clinically useful triaryl ethylene, is a synthetic antiestrogenic drug that elicits varied endrogenic effects. It is a powerful non-steroidal drug useful for the treatment of hormone responsive human metastatic breast cancer as well as uterine, ovarian and prostatic neoplasm. Tamoxifen was first synthesized[4] in 1966 by Harper and Walpole, which resulted in a mixture of E and Z isomers, the E–tamoxifen, has no clinical uses.

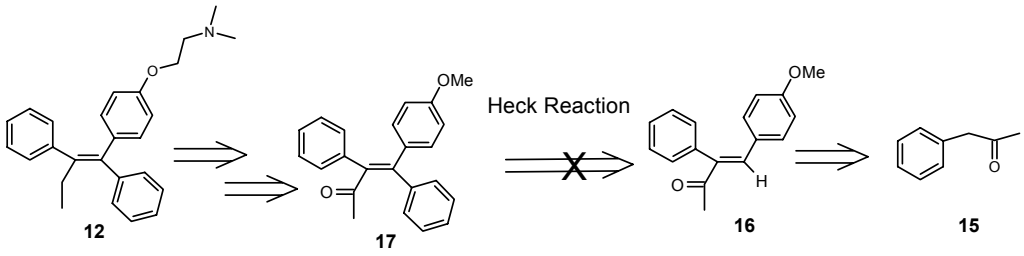
Our initial attempt to synthesize the target compound **12** by the normal Wittig reaction under varied reaction conditions failed. Therefore, a recent report by Ando[5] for the highly selective synthesis of Z-olefin using the Horner-Emmons reagent, ethyl (diarylphosphono) acetate was employed towards the tamoxifen synthesis. However, the Wittig-Horner reaction between the phosphonate **13** and ketone **14** gave tamoxifen **12** as a mixture of E and Z-isomers in 35: 65 ratio (Scheme 3).



Scheme 3

Section B: Heck coupling reaction towards the synthesis of Z-tamoxifen

We further employed the Heck process for the synthesis of Z-tamoxifen **12** as shown in Scheme 4. Condensation of phenyl acetone **15** with *p*-anisaldehyde gave olefin **16**. The olefin **16** was subjected for Heck reaction with halobenzene in presence of catalytic amount of Pd (0) complex. Unfortunately, the Heck coupling reaction did not work under different reaction conditions.

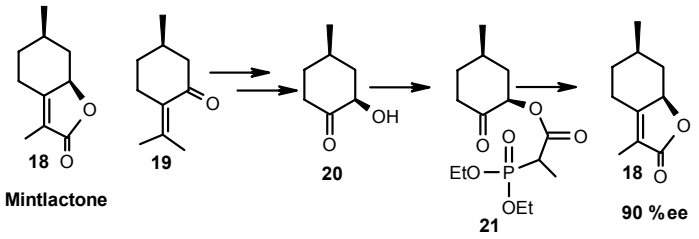


Scheme 4

Thus, Z-tamoxifen could not be synthesized employing Heck coupling reaction.

Section C: A Wittig - Horner approach towards the synthesis of mintlactone

Mintlactone **18** is a biologically useful compound.[6] This section describes the asymmetric synthesis of **18**. The synthetic route is depicted in Scheme 5. Thus, the reduction of cis-pulegone **19** and subsequent ozonolysis gave the keto alcohol **20,** which on treatment with $(EtO)_2P(O)CH(CH_3)COOH$ gave phosphonate **21**. Intramolecular Wittig-Horner reaction of phosphonate **21** gave (-)-mintlactone.



Scheme 5

Thus, a short and stereoselective synthesis of mintlactone has been achieved.

Chapter 3
Synthesis and characterization of sulfated yttria-zirconia based Lewis acid catalyst and its applications for organic transformations

Yttria-zirconia based strong Lewis acid catalyst was recently developed in our group and application of this catalyst was explored for Diels-Alder reaction.[7] This chapter deals with the synthesis and physicochemical characterization of sulfated yttrium based strong Lewis acid catalyst and its applications for various organic transformations. This is further divided into two sections.

Section A: Synthesis and physicochemical characterization of sulfated yttrium based strong Lewis acid

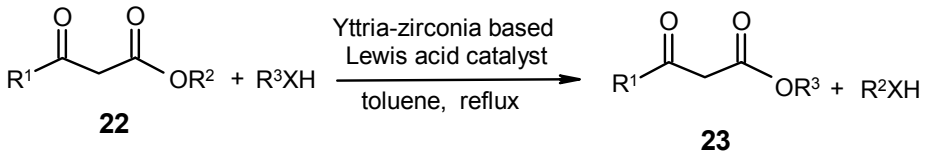
The catalyst was prepared by mixing aq. solutions of yttrium nitrate and zirconium nitrate to which aqueous ammonia was added under vigorous stirring until a pH of 8.5 was achieved and precipitate was formed. Washing, drying and treating with sulfuric acid, further drying and subsequent calcination resulted in a highly acidic material. The chemical composition of the final catalyst was determined by XRF technique. The physicochemical characterization of catalyst was carried out by x-ray powder diffraction, FT-IR, potentiometric titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

Section B: Application of sulfated yttria-zirconia based Lewis acid catalyst for organic transformations

This section describes the application of yttrium based strong Lewis acid catalyst for various organic transformations and is further divided into five sub-sections.

Section I: A facile and selective transesterification of β-keto esters by yttria–zirconia based Lewis acid

Transesterification is an important reaction, which has wide application both in academic and industrial research.[8] In general, the transesterification is accelerated by protic acid, Lewis acids and basic catalyst such as 4-(dimethylamino)pyridine, metal alkoxide and metal carbonate. [9]



22 **23**

X = NH, O and S
R^1 = Me, Cyclopntyl and phenyl; R^2 = Me or Et
R^3 = alkyl, cyclic, benzyl, allylic etc

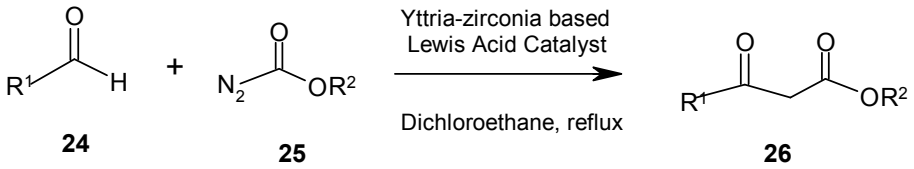
Scheme 6

During our recent endeavor with yttria-zirconia based Lewis acid mediated synthesis of acetals[10] from carbonyl compounds, interestingly we observed an efficient trasesterification instead of carbonyl protection when the reaction was applied to β-keto esters. This prompted us to initiate a systematic investigation on yttria-zirconia based Lewis acid catalyzed transesterification of β-keto ester. The method developed by us is quite general as a wide range of structurally varied β-keto esters such as open chain, cyclic and aromatic ones underwent transesterification with a variety of alcohols. The noteworthy feature of this method is that synthesis of β-keto esters with an aromatic moiety can be achieved in excellent yield. The reaction is also selective for the primary alcohol over secondary in the case of 1,2-diol. Similarly OH group of 2-mercaptoethanol reacts preferentially over thiol and amine reacts faster than alcohol in the case of aliphatic amino alcohol.

Thus, an efficient and selective method to effect transesterification of β-keto esters by a variety of alcohol is developed.

Section II: Synthesis of of β-keto esters via condensation of methyl/ethyl diazoacetate with aldehydes catalyzed by yttria–zirconia based Lewis Acid

There are several methods reported in the literature[11] for the synthesis β-keto esters by the condensation of aldehydes with ethyl diazoacetate using Lewis acid catalyst. The main drawback of all the earlier methods was the low yield of the corresponding β-keto esters when aromatic aldehydes were used as one of the substrate.



24 **25** **26**

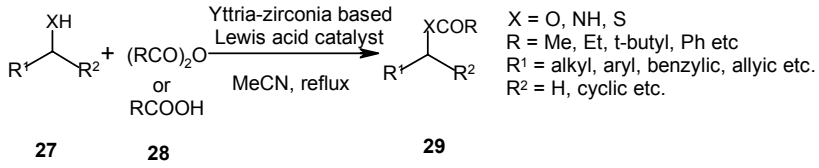
R^1 = aliphatic, aromatic; R^2 = Me, Et

Scheme 7

We applied yttria-zircona based Lewis acid catalyst for the synthesis of β-keto esters by the condensation of aldehydes with methyl/ethyl diazoacetate. The reaction is general as a wide range of structurally varied aldehydes underwent condensation with methyl/ethyl diazoacetate to afford β-keto esters in moderate to excellent yields (Scheme 7).

Section III: Efficient and chemoselective acylation of alcohols, amines and thiols with acid anhydride and carboxylic acids promoted by Yttria–Zirconia based Lewis acid

The acylation of alcohols, amines and thiols by acyl chloride or acid anhydrides under basic conditions is well established reactions in organic synthesis.[12] Most commonly employed basic catalysts for this purpose are 4-(dimethylamino)pyridine and 4-pyrolidinopyridine (ppy).[13] The Lewis acid catalyzed acylation of alcohols and amines is a mild strategic alternative to basic and nucleophilic catalysts. We have further extrapolated the catalytic potential of yttria-zirconia Lewis acid for acylation of alcohols, amine and thiols using acid anhydride or carboxylic acid as acylating agent.



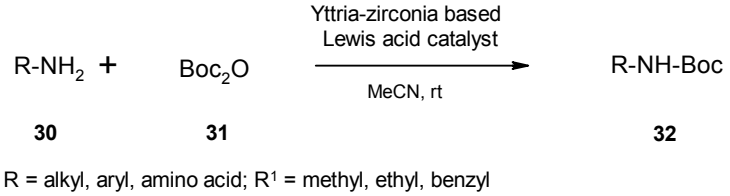
Scheme 8

The present procedure for acylation is quite general as a wide range of structurally varied alcohols such as open chain, cyclic and aromatic ones underwent acylation with carboxylic acid or anhydride. The reaction was found to be chemoselective for the amino alcohol, 2-mercapto ethanol and 1,2-diol. Thus, using this method, acylation of an amino group in the presence of OH group, of OH group in the presence of SH and of a primary OH group in the presence of secondary OH group has been achieved with excellent selectivity. Another notable feature of this methodology is that even hindered substrates can be acylated in high yields under mild conditions.

Thus, we have developed a simple and efficient method for the acylation of alcohols, amines and thiols using yttria-zirconia based Lewis acid as catalyst and carboxylic acids and anhydrides as acylating agents.

Section IV: A facile procedure for *tert*-butoxycarbonylation of amines promoted by yttria-zirconia based strong Lewis acid catalyst

The *tert*-butoxycarbonyl (Boc) is extensively used an amino protecting group in organic synthesis.[12, 14] Although there has been several examples with regards to protection of amines as N-Boc group, the use of Lewis acid catalyst to effect the above transformation is rather scarce. The only method reported by Porta[15] used aliphatic amines with diethyl carbonate and catalyzed the transformation with different Lewis acid. However this method could not be extended to the synthesis of *N*-aryl derivatives. Thus, when a variety of amines were treated with Boc_2O in the presence of catalytic amount of the new yttria-zirconia based catalyst, the corresponding *N*-Boc protected amines were obtained in excellent yields (Scheme 9).



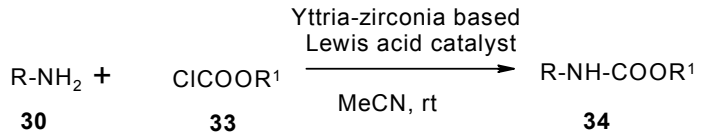
Scheme 9

The present protocol offers mild reaction conditions, selectivity and short reaction time. The noteworthy feature of this methodology is that the chiral substrate is resistant to racemization and labile functionalities such as esters is compatible with reaction condition. This is the first report of use of Lewis acid catalyst for amino group protection using Boc anhydride.

Thus a new and facile procedure for *tert*-butoxycarbonylation of amines is developed.

Section V: An expeditious synthesis of carbamates using yttria-zirconia based Lewis acid catalyst

Carbamates are endowed with an array of biological activities. They are known to have pesticide,[16a] insecticide,[16b] antibiotic[16c] and other pharmacological properties. They also serve as useful protecting groups in organic synthesis, particularly in peptide synthesis. A number of methods have been employed to prepare carbamates. However, the scope of existing methodologies for carbamate formation are limited by the operational complexity, need for specialized reagents and due to the lack of generality of the reaction. In continuation of our interest on the application of yttria-zirconia catalyst for organic transformation, we have further explored its catalytic potential for carbamate synthesis.



R = alkyl, aryl, amino acid; R^1 = methyl, ethyl, benzyl

Scheme 10

The present procedure for carbamate synthesis is quite general. The reaction is remarkable fast and leads to high yields of product. The reaction is chemoselective in case of 2-amino phenol. Another noteworthy feature of this methodology is that amino group in amino acid could be protected easily demonstrating the practical utility of this protocol particularly in peptide synthesis. Under the reaction condition employed, the ester and silyl ether groups remain unaffected and there is no racemization of the chiral substrate encompassing amino acid.

Thus, an expeditious synthesis of carbamates using yttria-zirconia based Lewis acid as a catalyst has been achieved.

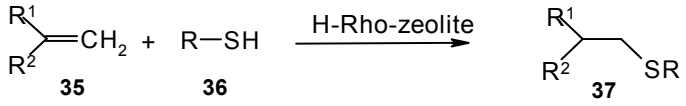
Chapter 4
Application of zeolites for organic transformations

Zeolites are porous, crystalline, hydrated aluminosilicates, molecular sieves having highly ordered rigid three dimensional infinite frame work. These structures are built by the sharing of SiO_4 and AlO_4, tetrahedra, linked through common oxygen atoms. They are thermally stable, shape selective and acidic or basic in nature having void and channels. This chapter deals with the application of zeolites in organic synthesis. This is further divided into three sections. Section A covers the application of Rho-zeolite for Anti-Morkovnikov addition of thiols across the double bond. Section B describes the utility of H-β zeolite for deprotection of allyl esters. The last section includes the results of oxidation of furan and allyl chloride over TS-1/H_2O_2 system.

Section A: Anti-Markovnikov addition of thiols across double bonds catalyzed by H-Rho-zeolite

In general, the protic acid or Lewis acid catalyzed addition of thiols across double bonds is known to give thioethers having structure which are accordance with Markovnikov's rule. However, in the presence of free radical initiator, thiols have been reported to add to double or triple bonds in anti-Markovnikov fashion by a free radical mechanism.[17]

We have developed a new and catalytic method for the thiol addition across double bond using H-Rho-zeolite (Scheme 11).



R = Et, n-Pr, Ph etc
R^1 = H, Me; R^2 = alkyl, cyclic and Ph

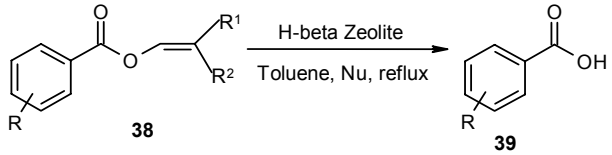
Scheme 11

The reaction is quite general as a wide range of olefins can be reacted with thiols easily under mild conditions affording exclusively anti-Markovnikov products. Interestingly, due to steric constraints on the diffusional path of the molecules imposed by the different structural feature of the zeolite, the more bulkier Markovnikov adduct could not be retained in the zeolite pore and presumably for this reason only anti-Markovnikov product was obtained.

Thus a facile, heterogeneous catalytic method for the anti-Markovnikov addition of thiols to a variety of olefinic compounds has been established.

Section B: Facile and selective deprotection of allyl esters catalyzed by H-β zeolite

Functional group protection and deprotection strategies are quite often a necessary requirement in the manipulation of multifunctional organic molecules.[12, 18] The carboxyl function is one of the most important groups in organic molecules and its controlled manipulation during the synthesis is of great value to synthetic organic chemistry. We have developed an unprecedented, convenient and heterogeneous catalytic methodology for deprotection of allyl ester using H-β zeolite (Scheme 12).



R = Me, OMe, halo, NO_2 etc.

R^1 = H, Me; R^2 = allyl, benzyl, cinnamyl etc.

Scheme 12

When allyl esters were refluxed in toluene in the presence of catalytic amount of H-β zeolite, the corresponding acids were obtained in excellent yields. The allyl esters were deprotected selectively in the presence of methyl ester in mixed ester. The method was also found selective for the deprotection of aromatic allyl esters. Allyl esters derived from aliphatic acid failed to undergo reaction.

Thus, a method for regeneration of carboxylic acids from their corresponding allyl or cinnamyl esters by H-β zeolite under environmentally safe, heterogeneous reaction conditions has been developed.

Section C: Oxidation reaction over TS-1/ H_2O_2 system

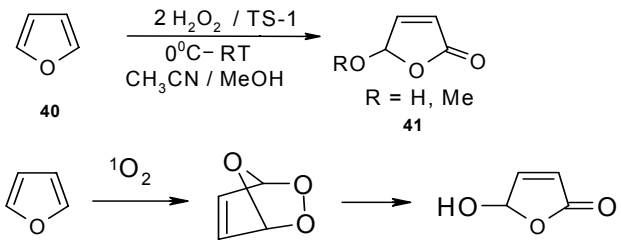
Titanium silicate molecular sieve, having MFI (TS-1) topology, efficiently catalyzes the oxidation reaction using dilute hydrogen peroxide as an oxidizing agent. This section

deals with the oxidation of furan and allyl chloride with aq. H_2O_2 over titanium silicate (TS-1) molecular sieve and is further divided into two sub-sections.

Section I: An efficient synthesis of 5-Hydroxy-2(5*H*)-furanone using titanium silicate molecular sieve catalyst

This part describes the application of TS-1 catalyst for the oxidation of furan to 5-hydroxy-2(5*H*)-furanone. 5-Hydroxy-2(5*H*)-furanone is a key constituent in a number of biologically active compounds such as manoalide (a nonsteroidal anti-inflammatory agent), secomanolide, luffariellin, thoreotolide and cacospongiolide.[19] It has been also used as a useful synthon in the total synthesis of portulal, (d,l)-strigol and camptothecin.

Titanium silicate molecular sieve, efficiently catalyzes the oxidation of furan to the corresponding 5-hydroxy-2(5H)-furanone in excellent yields, using dilute hydrogen peroxide (25%) as an oxidizing agent; mechanistically the intermediacy of $^1O_2$ has been proposed (Scheme 13).



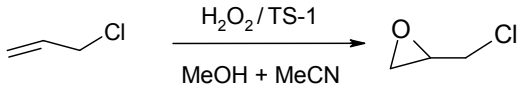
Scheme 13

Thus, a facile heterogeneous catalytic method for the oxidation of furan to the corresponding hydroxylactone has been developed. The method offers a practical alternative to conventional methods and the process itself is environmentally friendly with minimal waste.

Section II: Synthesis of epichlorohydrin using titanium silicate (TS-1) molecular sieve and hydrogen peroxide system

This part describes the epoxidation of allyl chloride to epichlorohydrin (Scheme 14). We have developed an efficient, high yielding synthesis of epichlorohydrin by the epoxidation of allyl chloride over TS-1 / H_2O_2 in a mixed solvent systems. In this system solvent plays very significant role in the conversion of allyl chloride to epichlorohydrin

selectively. Protic solvent like methanol is found to be good for higher allyl chloride conversion while aprotic solvents was useful particularly for higher selectivity. Mixed solvent systems using acetonitrile and methanol in various proportions are systematically studied with the aim to maximize the H_2O_2 utilization towards the epichlorohydrin formation.



42 43

Scheme 14

Thus, a method for the epoxidation of allyl chloride to epichlorohydrin under mixed solvent systems has been developed.

Chapter 5
Synthesis, characterization and catalytic properties of new cerium based strong Lewis acid

Yttria-zirconia based strong Lewis acid catalyst was recently developed in our group and application of this catalyst was explored for a variety of organic transformations. This prompted us to develop a new solid catalyst with enhanced and better catalytic activity. This chapter deals with the synthesis and physicochemical characterization of sulfated cerium based strong Lewis acid catalyst and its applications for organic transformations. This is further divided into two sections.

Section A: Synthesis and physicochemical characterization of sulfated cerium based strong Lewis acid

The catalyst was prepared by mixing aq. solutions of yttrium nitrate and cerium nitrate to which aqueous ammonia was added until pH of 8.5 was achieved and precipitate was formed. Washing, drying, treating with sulfuric acid (2N), and again drying at 120°C and subsequent calcinations at 500°C resulted in a highly acidic material. The chemical composition of the final catalyst was determined by XRF technique. The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

Section B: Application of sulfated ceria-zirconia based Lewis acid catalyst for organic transformations

This section describes the application of cerium based strong Lewis acid catalyst for various organic transformations and is further divided into three parts. Part I covers the application of cerium based strong Lewis acid catalyst for the intramolecular ene reaction; for example the conversion of citronellal to isopulegol has been investigated. Second part deals with the catalytic potential of this catalyst for acylation of alcohols with acid anhydrides and carboxylic acids. Last and third part includes the application of cerium based Lewis acid catalyst for transesterification of β-keto esters.

Thus we have developed a new cerium based strong Lewis acid catalyst and its application was explored for the intramolecular ene reaction, acylation reaction of alcohols and tranesterification of β-keto esters.

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CHAPTER 1

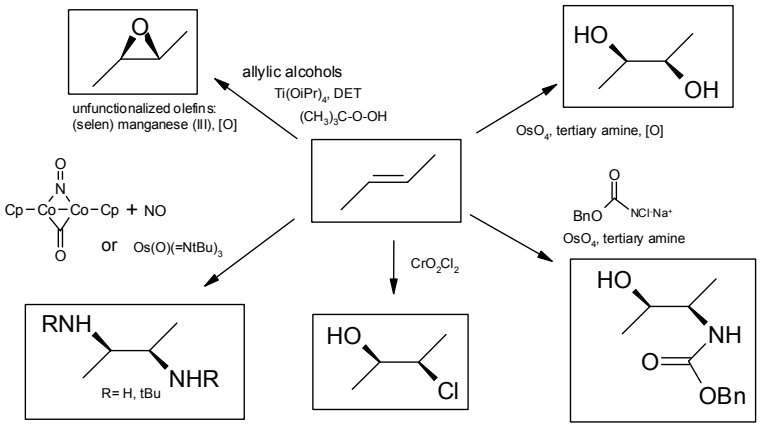
ASYMMETRIC DIHYDROXYLATION ROUTE TOWARDS SYNTHESIS OF BIOACTIVE MOLECULES

1.1 SECTION A

General Introduction about Asymmetric Dihydroxylation

1.1.1. Introduction

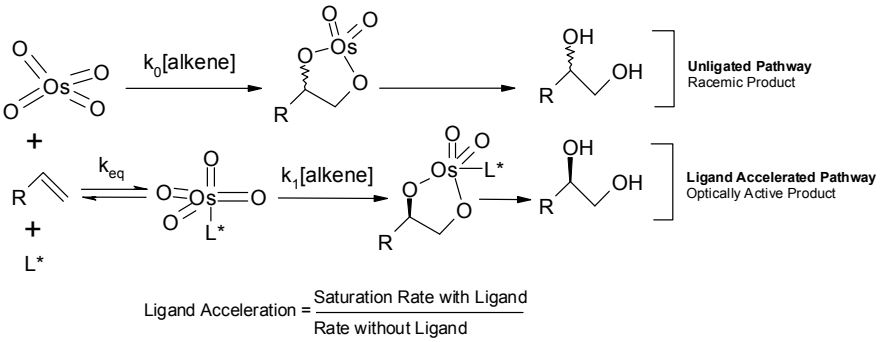
Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to various applications in drug and pharmaceutical industries and biotechnology. During the last two decades a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (Scheme 1).



Scheme 1. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

A number of transition metal mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand*

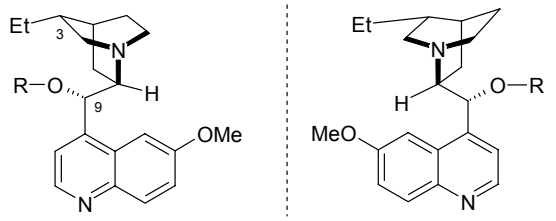
acceleration,[7] wherein a metal-catalyzed process turns over faster in the presence of a coordinating ligand (Scheme 2). This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way.



Scheme 2: Ligand accelerated catalysis-dihydroxylation of olefins.[7]

The osmium tetroxide catalyzed asymmetric dihydroxylation of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry. Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[8] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[9] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[8] Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate ligands[11] and bidented diamine ligands. [11]

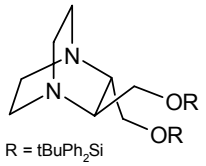
(a) Cinchona Alkaloid Ligands for AD under *Catalytic* Conditions[8,12,14,15]



Dihydroquinidine (R = H)
DHQD

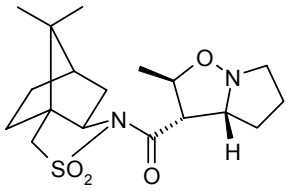
Dihydroquinine (R = H)
DHQ

(b) Recent Monodentate Ligands for AD under *Catalytic* Conditions



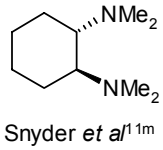
R = $tBuPh_2Si$

Hirama *et al*[10]

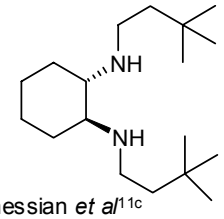


Murahashi *et al*[11n]

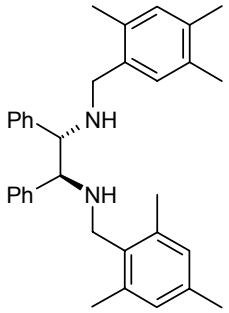
(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions.



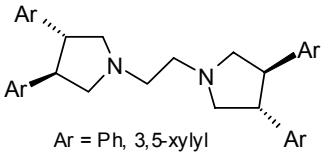
Snyder *et al*[11m]



Hanessian *et al*[11c]

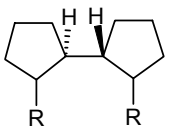


Corey *et al*[11d]



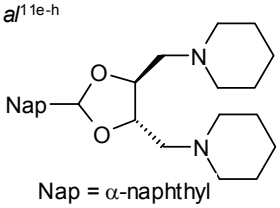
Ar = Ph, 3,5-xylyl

Tomioka *et al*[11e-h]



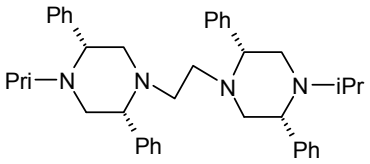
R = neohexyl

Hirama *et al*[11j,k]



Nap = α-naphthyl

Narasaka *et al*[11l]



Fuji *et al*[11i]

Figure 1: Some ligands for AD reaction[8,11]

Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os (VI) glycolate products and as a consequence prevent in situ recycling of the Os and the ligand. Thus all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[11] (Figure 1). Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless found that the process became catalytic when NMO was employed as the cooxidant.[12] However the enantiomeric excess of the diol products obtained under these catalytic conditions were initially lower than those produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be due to the presence of a second catalytic cycle,[13] which exhibited only low or no enantioselectivity (Figure 2).

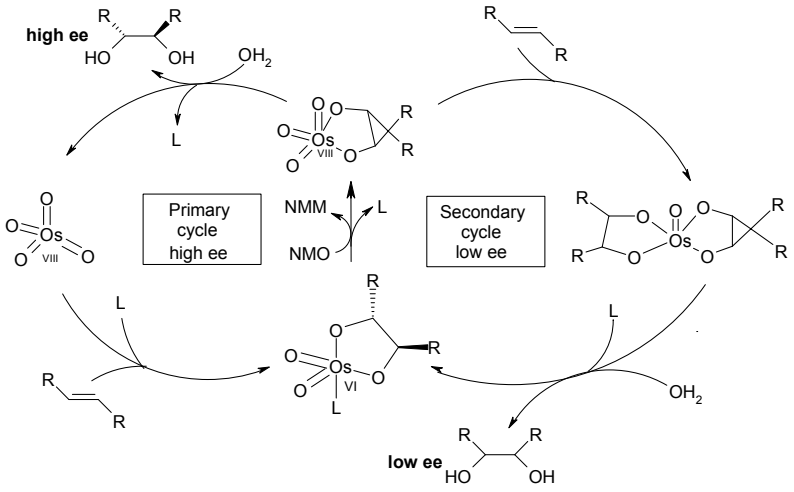


Figure 2: Two Catalytic Cycles for the AD Reaction using NMO as Cooxidant.[8]

Wai discovered a partial remedy in slow addition of the olefin.[13] Kwong found that the participation of second catalytic cycle can be virtually eliminated by performing the

reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric reoxidant.[14] Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting Osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (Figure 3).

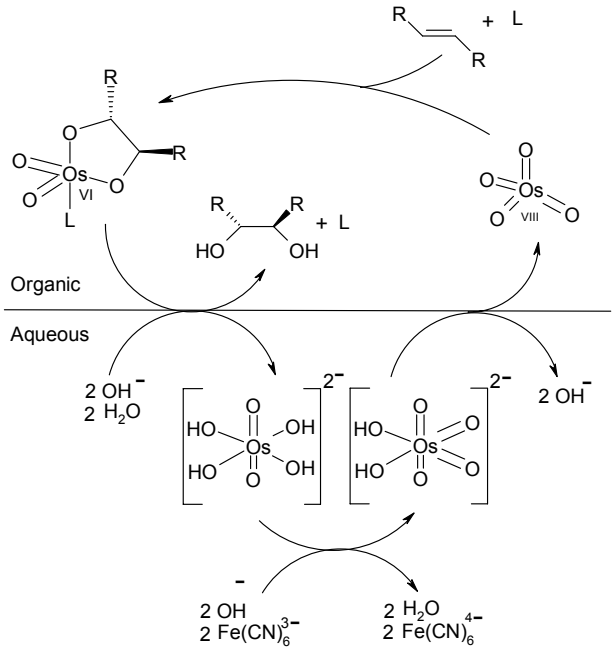


Figure 3: Catalytic Cycle of the AD Reaction with $K_3Fe(CN)_6$ as the Cooxidant.[14]

Sharpless et al. found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive.[15] This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather

than at room temperature, which may have beneficial influence on the selectivity.[16] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

The discovery of ligands with two independent cinchona alkaloid units by Hartung[15] (phthalazine core) and Crispino[17] (diphenylpyrimidine core) attached to a heterocylic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (Figure 4).

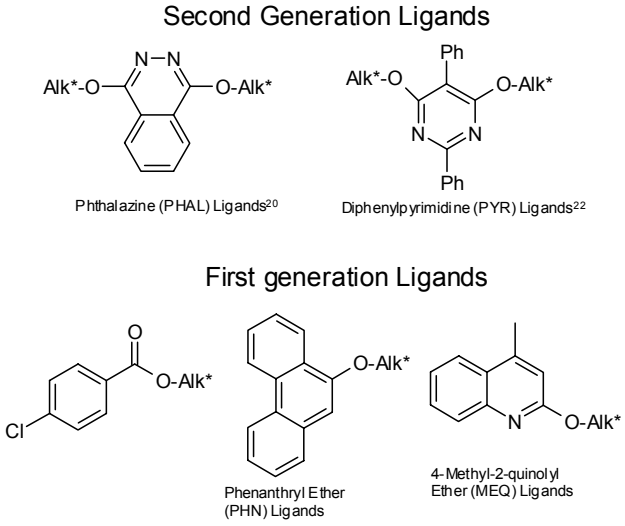
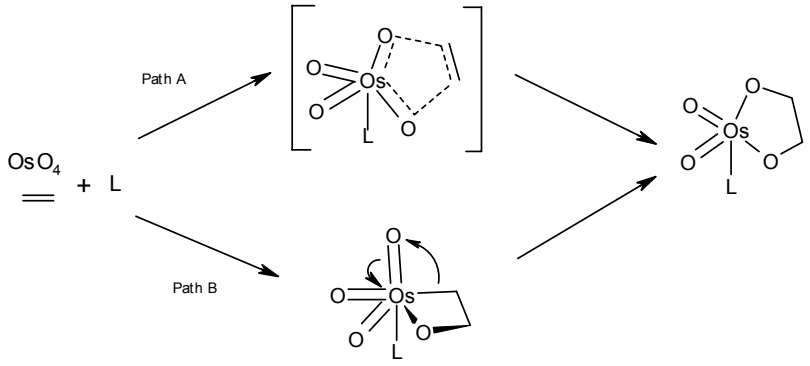


Figure 4: The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1a)

1.1.2 The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken and Criegee originally proposed a concerted [3+2] pathway,[18, 19a] (Scheme 3, Path A) while Sharpless et al. suggested a stepwise reaction[19b,c] which is initiated by a [2+2] like

addition of the olefin across an Os=O bond (Path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.



Scheme 3: Schematic presentation of the concerted [3+2] mechanism[23a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[23b, c]

1.1.3 Reaction conditions

Catalytic asymmetric dihydroxylation is performed in a solvent mixture containing 50% water, and is best carried out under heterogeneous conditions with 3 equiv of both $K_3Fe(CN)_6$ and K_2CO_3 in order to avoid the second catalytic cycle. Optimization studies have revealed that a 1:1 mixture of water and *t*-BuOH is the solvent of choice. The olefin concentration in the *t*-BuOH/water mixture is usually 0.1 M.[15] While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aq layer),[20] it is possible to buffer the system with 3 eq of $NaHCO_3$ (pH 10.3, aq layer). Buffering of the reaction has a beneficial effect on the yield when base sensitive substrates are used or base sensitive products are formed.

Normally the reaction is performed with 3eq of $K_3Fe(CN)_6$ as the reoxidant. The key reagents used are the Os reagent and the ligands. Only 0.2 to 0.4 mol% of Os reagent either OsO_4 or the nonvolatile $K_2OsO_2(OH)_4$ is added. The ligand concentration is 1 mol %. However it can be dropped in some cases without much loss in enantioselectivity. For

example, stilbene still gives 96% ee when 1/100 of 1 mol% of $(DHQD)_2$-PHAL is used as compared to the 99.8% ee obtained under normal conditions.[15] Alternatively the amount of OsO_4 can be increased to 1 mol % for accelerating the reaction rate of relatively unreactive olefins.

Additionally, the ligand can be recovered especially when large-scale reactions are carried. For the PHAL ligands, the combined organic layers are extracted with 3% aq H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1 g of ligand), followed by a second extraction of the organic solution with saturated K_2SO_4 (ca. 40 mL/1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture.

Since most substrates require very similar reaction condition, it is possible to use premix of all reactants. These are available commercially as 'AD-mixes' as AD-mix-β [$(DHQD)_2$PHAL] and AD-mix-α [$(DHQ)_2$PHAL]. 1 kg of AD-mix contains $K_3Fe(CN)_6$ (699.6 g), K_2CO_3 (293.9 g), ligand (5.52 g) and $K_2OsO_2(OH)_4$ (1.04 g). The standard AD procedure calls for 1.4 g of this AD-mix per mmol of olefin. 1 equiv of $MeSO_2NH_2$ should be added for all substrates other than terminal olefins to enhance hydrolysis of the osmate (VI) ester and hence the rate of catalytic turn over.

1.1.4 The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands

The phthalazine ligands are most widely used, due to their ready availability and their broad substrate scope.[21b] This ligand class is used in the AD-mix formulation. PHAL

ligands react especially well when aromatic groups are present, and remarkably high enantioselectivities are observed when the aromatic substituents appear in certain optimal locations/patterns[21a] inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents[22] except for olefins with aromatic or sterically demanding substituents. Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[17]

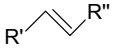
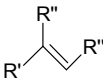
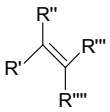
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL)ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[23] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[24] However, in certain cases better results are obtained with the new second generation ligands.[22, 23, 25]

Table 1. Recommended ligands for each olefin class.

Olefin Class						
Preferred Ligands	<u>R = Aromatic</u> DPP, PHAL <u>R = Aliphatic</u> AQN <u>R= Branched</u> PYR	<u>R^1, R^2 = Aromatic</u> DPP, PHAL <u>R^1, R^2 = Aliphatic</u> AQN <u>R^1, R^2 = Branched</u> PYR	<u>Acyclic</u> IND <u>Cyclic</u> PYR, DPP, AQN	<u>R^1, R^2 = Aromatic</u> DPP, PHAL <u>R^1, R^2 = Aliphatic</u> AQN	PHAL, DPP, AQN	PYR, PHAL

1.1.5 Conclusion

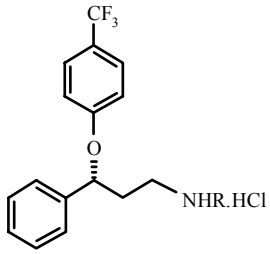
Thus, AD has become a powerful catalytic oxidation reaction. With the optimization of ligands and amount of primary oxidant this catalytic oxidation reaction of olefins to chiral diols proved very promising in both yields and enantioselectivity. It has contributed to synthetic organic chemistry giving access to new molecules needed to investigate hitherto unexplained and undiscovered phenomenon in the molecular world.

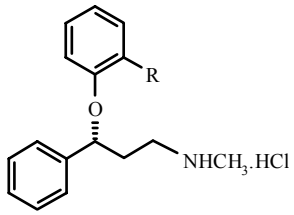
1.2 SECTION B

Synthesis of Enantiomerically Pure Norfluoxetine and Fluoxetine

1.2.1 Introduction

Fluoxetine, tomoxetine and nisoxetine (**2-4**) are among the most important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity and bulimia) [26] (Figure 5). Fluoxetine, marketed under the trade name Prozac®, has recently surpassed the $2 billion mark in annual sales. In view of different pharmacological activities displayed by the individual enantiomer and differences in metabolic behaviour, the asymmetric synthesis of both enantiomers of fluoxetine and related compounds has received growing interest in recent years.





1 R = H, (*R*) - Norfluoxetine hydrochloride
2 R = CH_3, (*R*)- Fluoxetine hydrochloride
3 R = CH_3, (*R*)- Tomoxetine hydrochloride
4 R = OCH_3, (*R*) - Nisoxetinehydrochloride

Figure 5: Some important oxetine drugs

Most of these approaches start with a three-carbon-chain segment and establish the chirality by enzymatic resolution,[27] asymmetric reduction,[28] asymmetric epoxidation,[29] chemical resolution[30] and an asymmetric carbonyl-ene reaction.[31] Recently a four-

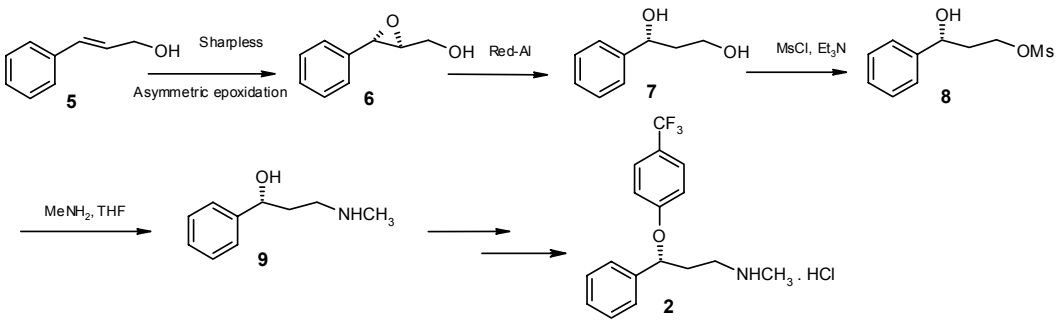
carbon-chain segment has been employed to make fluoxetine and its analogs by incorporating asymmetric reduction and Hofmann rearrangement.[32] Surprisingly there has been no report in the literature about the asymmetric synthesis of fluoxetine and its analogs employing the Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones,[33a-b] amino alcohols,[33c-e] and diolmycins,[33f] the Sharpless asymmetric dihydroxylation[5a, 22] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. Herein a new and highly enantioselective synthesis of fluoxetine and norfluoxetine is described through a common intermediate by employing the Sharpless asymmetric dihydroxylation.

1.2.2 Review of Literature

Various Synthetic methods for the optically pure oxetine drugs have been reported. Most of these approaches start with a three-carbon-chain segment and establish the chirality by enzymatic resolution, asymmetric reduction, asymmetric epoxidation or resolution. Some of the important asymmetric synthetic routes reported are discussed below.

Sharpless *et al.* (1988)[29a] Scheme 4

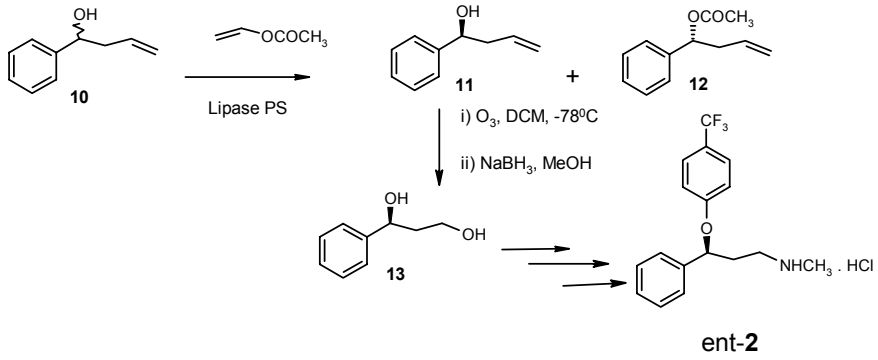
Both enantiomers of tomoxetine and fluoxetine have been synthesized from cinnamyl alcohol **5**. Thus the asymmetric epoxidation of **5** and regioselective Red-Al reduction gave the diol **7**. The selective mesylation of primary hydroxy group and subsequent nucleophilic displacement with methyl amine followed by arylation furnished (*R*)-fluoxetine hydrochloride **2** (Scheme 4).



Scheme 4

Kumar *et al.* (1996)[27i] Scheme 5

Kumar *et al.* carried out enzymatic resolution of homoallylic alcohol **10** by *Lipase PS* to give the optically pure compound **11** which was subjected to ozonolysis and subsequent sodium borohydride reduction to furnish 3-phenyl-1,3-propanediol **13** which is known precursor for oxetines (Scheme 5).

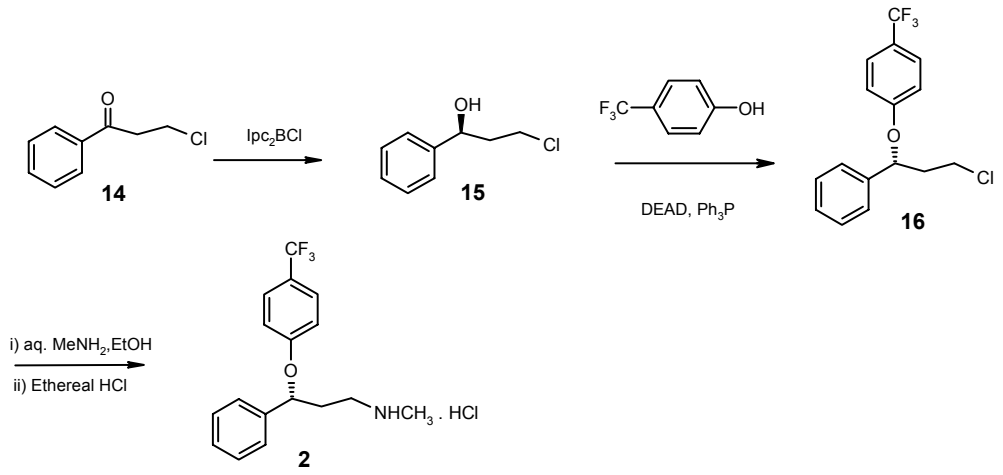


Scheme 5

Brown *et al.* (1988)[28d] Scheme 6

Brown *et al.* have utilized enantioselective reduction of 3-chloropropiophenone **14** by diisopinocamphenylchloroborane (Ipc_2BCl) to give (+) or (-)-3-chloro-1-phenyl-propanol **15** as a highly versatile intermediate. *O*-Alkylation of chloroalcohol **15** followed by

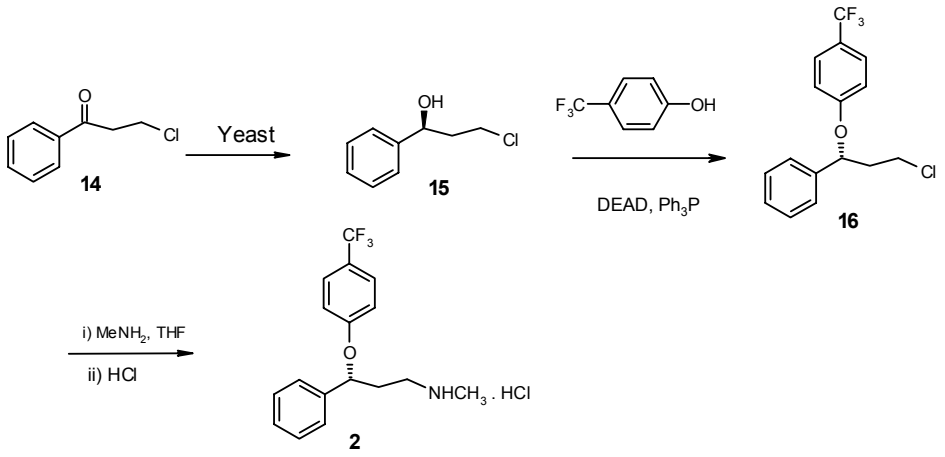
displacement with methylamine and subsequent treatment with ethereal HCl afforded fluoxetine **2** (Scheme 6).



Scheme 6

Fronza *et al.* (1991)[27h] Scheme 7

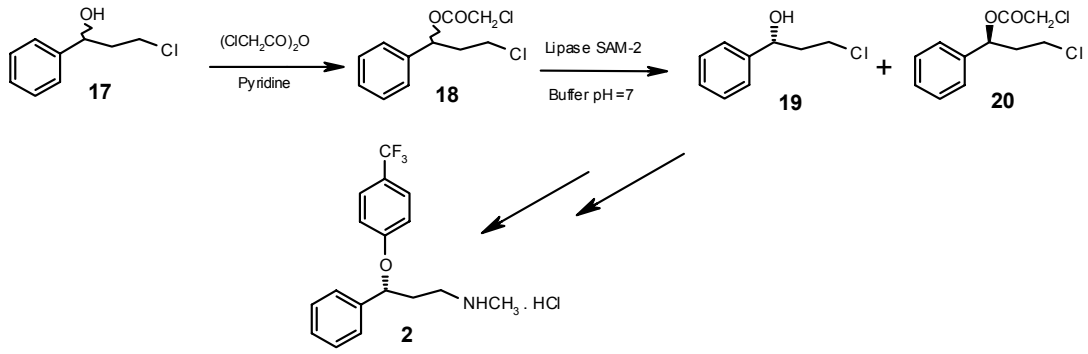
Fronza *et al*. have employed the yeast mediated enantioselective reduction of 3-chloropropiophenone **14** to give (1*S*)-3-chloro-1-phenyl-propan-1-ol **15** in 58 % yield which was smoothly converted into (*R*)-fluoxetine **2** following Brown's synthetic pathway which proceeds under Mitsunobu conditions with inversion of chiral center present in **15** (Scheme7).



Scheme 7

Schneider *et al.* (1992)[27d] Scheme 8

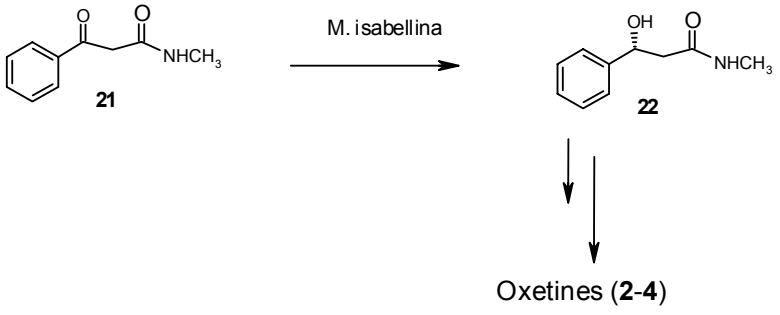
Schneider has employed the enzymatic resolution method to resolve both the enantiomers of 3-chloro-1-phenylpropan-1-ol. They were subsequently converted via enantioconvergent routes into all enantiomers of the important antidepressants (*R*)- and (*S*)-tomoxetine, fluoxetine **2** and nisoxetine (Scheme 8).



Scheme 8

Gotor *et al.* (1997)[27a] Scheme 9

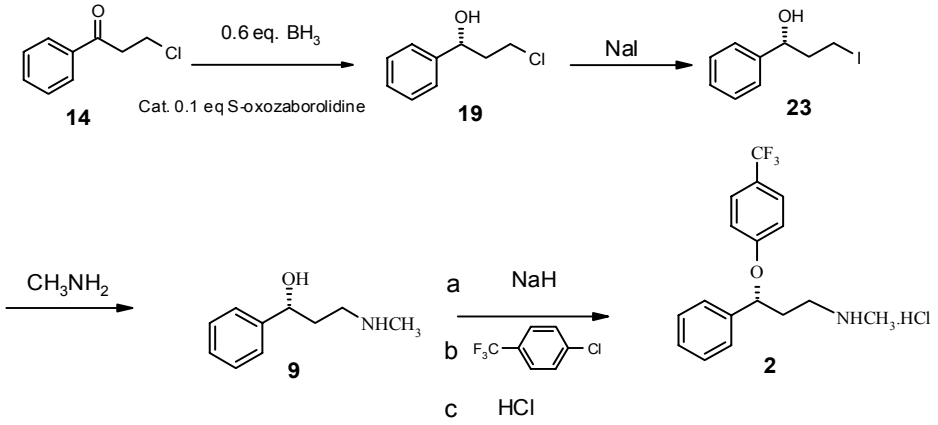
Gotor *et al.* have employed incubation of the fungus *Mortierella isabellina* NRRL 1757 with N-methyl-3-oxo-3-phenylpropanamide **21** to afford *N*-methyl-(*S*)-3-hydroxyamide **22** in high chemical yields and enantiomeric excess. Compound **22** serves as suitable precursor for the chemical synthesis of the antidepressants tomoxetine, fluoxetine and nisoxetine or their *N*-alkyl analogs in optically active forms (Scheme 9).



Scheme 9

Corey *et al.* (1989)[28a] Scheme 10

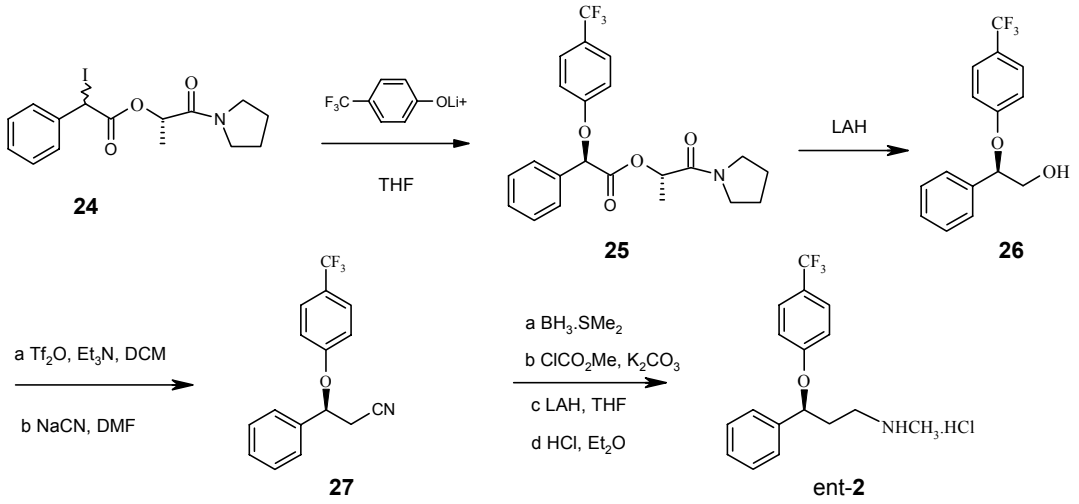
An efficient asymmetric route to (*R*)- and (*S*)- fluoxetine is reported by Corey using a chiral, enzyme like catalyst (chemzyme) to establish the stereocenter which made these important therapeutic agents readily available in enantiomerically pure form. Thus 3-chloropropiophenone **14** was first converted into 3-chloro-1-phenyl-1-propanol **19** in quantitative yield with 94 % ee in the presence of borane as reductant and 0.1 eq. of *S*-oxazaborolidine as catalyst. The subsequent treatment of **19** with NaI and methylamine afforded the aminoalcohol **9**. *O*-Arylation followed by treatment with HCl afforded fluoxetine hydrochloride **2** (Scheme10).



Scheme 10

Devine *et al.* (1997)[34] Scheme 11

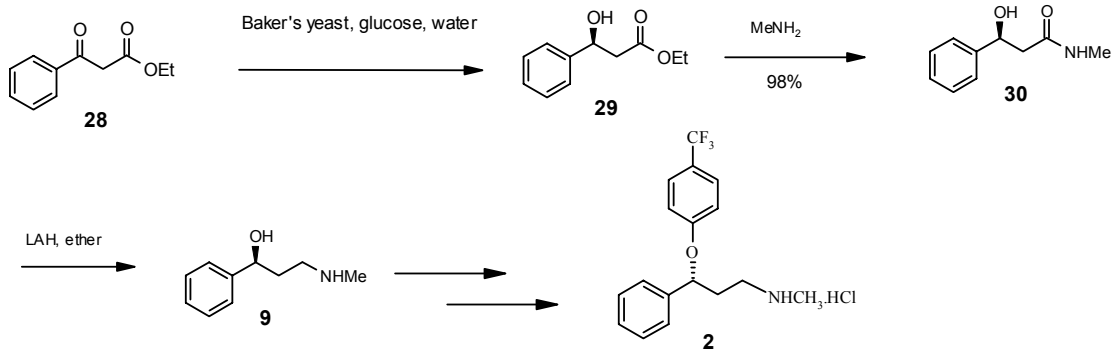
Devine *et al.* have utilized the stereoselective coupling reaction between racemic α-haloacids and aryloxides mediated by a pyrrolidine derived (*S*)-lactamide auxiliary to the enantiopure preparation of (*S*)-fluoxetine (Scheme 11).



Scheme 11

Kumar *et al.* (1991) [27f] Scheme 12

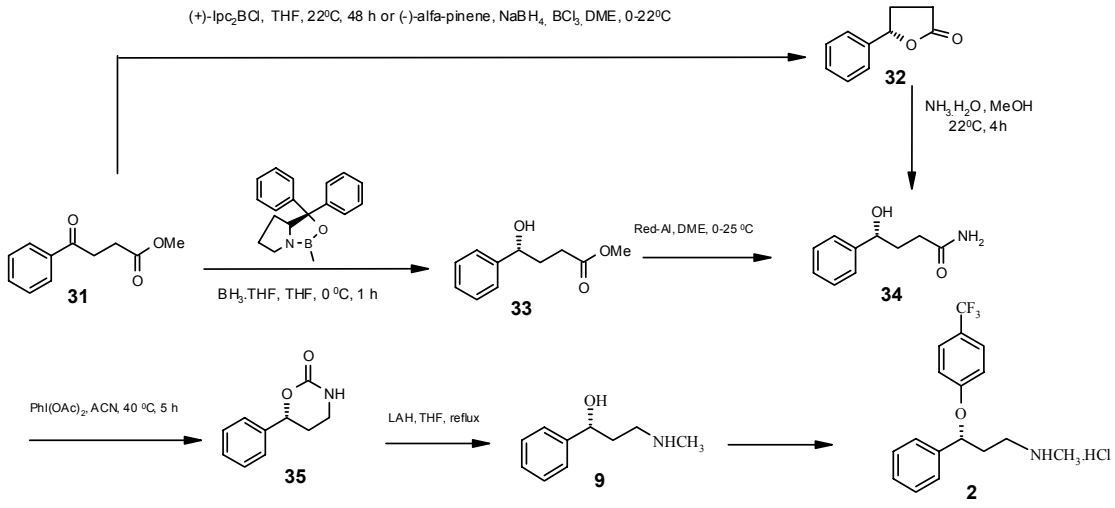
Baker's yeast reduction of ethyl benzoyl acetate **28** to give the corresponding alcohol **29** (85 % ee) is the key step in this approach. The latter was reacted with aq. methylamine to furnish the amide **30** which on LAH reduction yielded (-)-*N*-methyl-3-phenyl-3-hydroxypropylamine **9** in quantitative yield. Compound **9** was smoothly converted into (*R*)-fluoxetine hydrochloride by reacting with 4-trifluoromethylphenol under Mitsunobu conditions followed by treatment with ethanolic HCl (Scheme 12).



Scheme 12

Senanayake *et al.* (2001)[32] Scheme 13

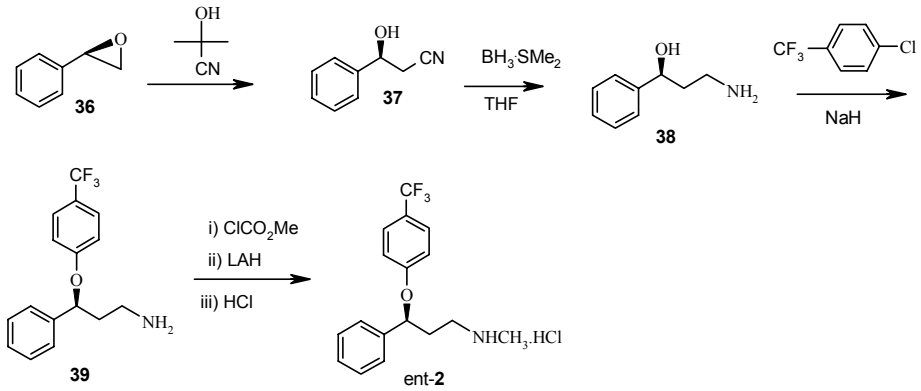
In this approach, synthetic strategy adopted relied on use of CBS reduction of γ-keto ester **31** and Hoffmann rearrangement of ketoamide **34** to establish the key intermediate **9** which was smoothly converted to (*R*)-fluoxetine **2** using known standard procedures (Scheme 13).



Scheme 13

Mitchell *et al.* (1995)[29b] Scheme 14

A key feature of this approach is the opening of styrene epoxide **36** by cyanohydrin and subsequent reduction of nitrile **37** to the corresponding amino alcohol **38**. The subsequent arylation and *N*-methylation first by carbamate followed by reduction furnished (*S*)-fluoxetine hydrochloride (ent-2) in excellent yield (Scheme 14).

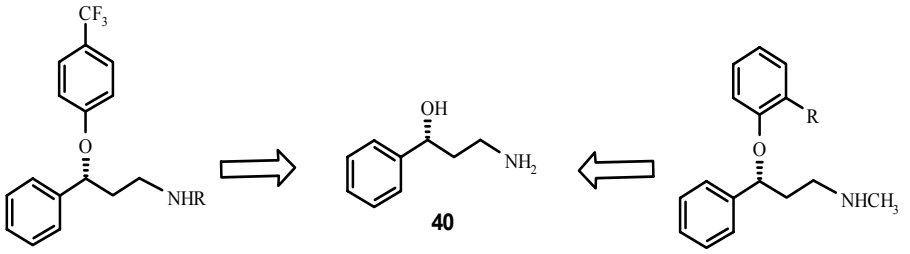


Scheme 14

1.2.3 Present Work

Objective

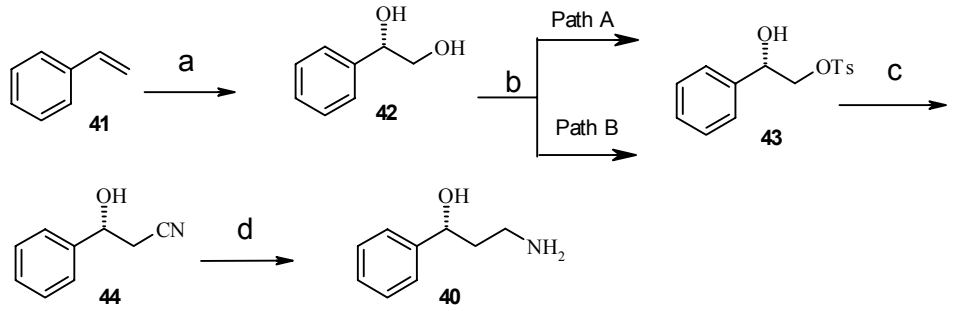
Most of the syntheses of fluoxetine and norfluoxetine as described above are multi-step in nature; suffer from poor enantio-selectivity, involve expensive resolving and chiral inducing reagents, high cost of materials and sometimes giving overall low yield of the desired compounds. A more practical approach with lesser number of steps for the synthesis of norfluoxetine and fluoxetine is highly desirable for further studies. Sharpless asymmetric dihydroxylation (SAD) is the most efficacious method in recent years for the synthesis of vicinal diols. Surprisingly the dihydroxylation approach has not been extrapolated for the synthesis of this class of compounds. The objective of present invention is to devise a practical, flexible and high yielding route to the synthesis of norfluoxetine and fluoxetine employing SAD as the source of chirality (Scheme 16 and 17).



1 R= H, (*R*) - Norfluoxetine hydrochloride
2 R = CH_3, (*R*) - Fluoxetine hydrochloride

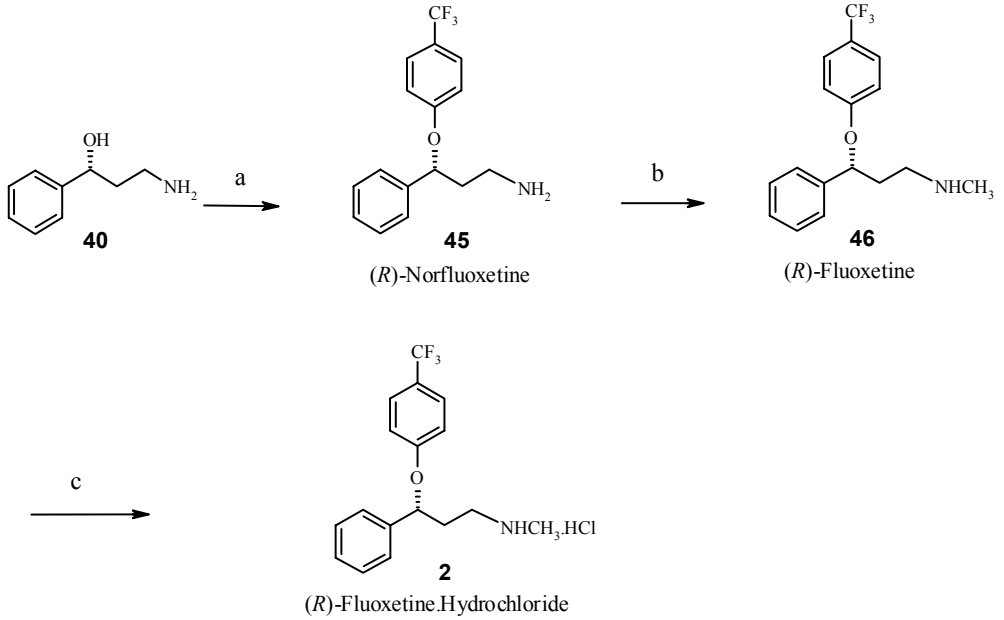
3 R = CH_3, (*R*)- Tomoxetine hydrochloride
4 R = OCH_3, (*R*) - Nisoxetine hydrochloride

Scheme 15



Reagents and conditions: (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2$-PHAL, OsO_4 (cat), *t*-BuOH:H_2O (1:1), 0^0C, 24 h, 100%; (b) **Path A:** *p*-TsCl, pyridine, CH_2Cl_2, -15^0C, 24 h, 78 %; **Path B:** Bu_2SnO, *p*-TsCl, TEA, rt, 45 min. 99%; (c) NaCN, EtOH:H_2O (4:1), rt, 24 h, 90%; (d) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h, 96 %.

Scheme 16



Reagents and conditions: (a) NaH, DMSO, 55^0C, 30 min, then 4-chlorobenzotrifluoride, 90^0C, 1 h, 90%; (b) (i) $ClCO_2Me$, CH_2Cl_2, aq. K_2CO_3, 30 min, (ii) $LiAlH_4$, THF, 65^0C, 2 h, 90%; (c) HCl gas, ether, 95%.

Scheme 17

1.2.4 Results and discussion

The 1,3-amino alcohol **40** is envisaged as a common building block from which (*R*)-fluoxetine and related analogs can be synthesized (Scheme 15). The synthesis of intermediate starts from styrene **41** a readily available starting material as illustrated in Scheme 16. We planned to incorporate the amine functionality early in the synthesis *via* cyanide addition. Towards this end, the asymmetric dihydroxylation of styrene using osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(dihydroquinin-9-*O*-yl)-phthalazine [$(DHQ)_2$–PHAL] gave the diol **42** essentially in quantitative yield with 97% ee having $[\alpha]_D^{20}$ + 54.93 (*c* = 1, $CHCl_3$) [lit.[35] $[\alpha]_D^{21}$ + 38.1 (*c* = 1.25, EtOH)]. IR spectrum of **42** showed a strong peak at 3376 cm^{-1}corresponding to the hydroxyl functionality. In ^1H NMR spectrum the CH_2 protons appeared at 3.73 δ as multiplet and benzylic proton as double doublet at 4.82 δ. The aromatic proton appeared as a multiplet at 7.37 δ for five protons. The mass spectrum of **42** showed the M^+ peak at 138. Selective conversion of the primary hydroxyl group of **42** into a tosylate **43** was carried out using tosyl chloride in pyridine at –15°C in 78% yield (Scheme 16 path A). In order to further improve the yield at this step, we followed a method recently reported by M. J. Martinelli *et al*.[36] for the selective mono-tosylation of primary hydroxyl group in a 1,2-vicinal diol using dibutyltin oxide as a catalyst. Towards this end the diol **42** was first treated with dibutyltin oxide (0.02 mol %) followed by addition of tosyl chloride and triethylamine in dichloromethane to get monotosyl compound **43** in 99 % yield (Scheme 16 path B). The IR spectrum of monotosylate **43** showed a band at 3529 cm^{-1} confirming the presence of OH functionality. The ^1H NMR spectrum of **43** showed CH_3 protons at 2.45 δ and the OH proton at 2.75 δ as broad singlet. While the CH_2 protons attached to OTs group appeared at 4.20 δ; the CH proton attached to –OH group was seen at 5.00 δ

as double doublet (Figure 6). Further the structure was proved by mass spectrum showing M^+ peak at 292. The nucleophilic displacement of tosylate **43** with sodium cyanide in aqueous ethanol furnished cyano compound **44** in 90% yield having $[\alpha]_D^{20}$ +60.2 (*c* = 1, $CHCl_3$). The IR spectrum of **44** showed a strong band at 3500 cm^{-1} confirming the presence of hydroxyl group and a strong band at 2250 cm^{-1} proved the presence of nitrile functionality. Absence of a singlet at 2.45 δ corresponding to CH_3 of tosyl group and two doublets in aromatic region showed the introduction of cyano group by displacement of OTs group. The CH_2 protons attached to cyanide functionality appeared at 2.71 δ (Figure 7). ^{13}C NMR spectrum indicated the presence of carbon attached to –CN functionality at 38.08 δ (Figure 8). Further structure was proved by mass spectrum showing the M^+ peak at 147. While the reduction of nitrile **44** with lithium aluminium hydride was not very satisfactory, the reaction proceeded smoothly with the use of borane-dimethyl sulfide as reducing agent providing the 1,3-amino alcohol **40** in 96 % yield having $[\alpha]_D^{20}$ + 40.5 (*c* = 1, $CHCl_3$) [Lit.[29b] $[\alpha]_D^{25}$ – 43.65 (*c* = 1, MeOH) for (*S*)-enantiomer]. The IR spectrum of **40** showed a band at 3400 cm^{-1} confirming the presence of OH and NH functionalities. In ^1H NMR spectrum the CH_2 protons attached to $–CH_2NH_2$ group appeared at 1.70 δ as a multiplet and other CH_2 protons were observed at 2.90 δ as a multiplet together with NH_2 and OH protons. A double doublet appeared at 4.85 δ for the CH proton attached to –OH functionality (Figure 9). Further, the structure was confirmed by mass spectrum showing the M^+ peak at 151.

The key intermediate, 1,3-amino alcohol **40** was then used to prepare the optically active (*R*)-norfluoxetine **45** and (*R*)-fluoxetine **46** (Scheme 17). Thus, the arylation of **40** was carried out by nucleophilic aromatic substitution employing NaH as a base and 4-chlorobenzotrifluoride as an electrophile in DMSO to afford (*R*)-norfluoxetine **45** in 90% yield as viscous liquid. The IR spectrum of **45** showed a band at 3298 cm^{-1} indicating the

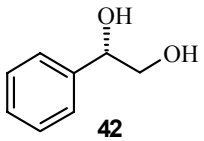
presence of NH_2 group. ^1H NMR spectrum showed multiplet at 2.00 δ for CH_2 protons attached to $–CH_2NH_2$ functionality. The NH_2 protons appeared at 2.10 δ as a broad singlet, whereas a triplet at δ 2.90 indicated the presence of CH_2 protons attached to NH_2 group. Two doublets in aromatic region at 6.90 δ and 7.45 δ confirmed the presence of aromatic ring having *p*-substitution of CF_3 group (Figure 10). Conversion of (*R*)-norfluoxetine **45** to (*R*)-fluoxetine **46** was achieved *via* carbamate formation. Thus, the treatment of **45** with methylchloroformate in aq. K_2CO_3 afforded the carbamate which on subsequent reduction with lithium aluminium hydride furnished (*R*)-fluoxetine **45**. IR spectrum showed a band at 3298 cm^{-1} indicating the presence of NH group. ^1H NMR spectrum showed CH_2 protons attached to $–CH_2NH_2$ functionality at 2.15 δ as a multiplet. The CH_3 protons appeared as a singlet at 2.36 δ and CH_2 protons attached to NH group appeared at 2.60 δ as a multiplet along with NH proton (Figure 11). (*R*)-Fluoxetine **45** was treated with hydrogen chloride to form the colorless, crystalline hydrochloride **2** of **45** in 95% yield. $[\alpha]_D^{20}$ –13.6 (*c* = 1, $CHCl_3$) [lit. [28a] $[\alpha]_D$ –13.8 (*c* = 1, $CHCl_3$)]. The physical and spectroscopic data were in full agreement with the literature data.[28d, 29a]

1.2.5 Conclusion

In summary, a practical and highly enantioselective synthesis of norfluoxetine and fluoxetine was achieved for the first time using the Sharpless asymmetric dihydroxylation as the source of chirality. Thus, the results described herein constitute a short and efficient route to enantiopure norfluoxetine and fluoxetine. The synthesis of other analogs, tomoxetine and nisoxetine can be achieved by arylation of the intermediate **40** with *o*-chlorotoluene and *o*-chloroanisole respectively.

1.2.6 Experimental

Synthesis of (*R*)-1-phenylethane-1,2-diol (42): To a mixture of $K_3Fe(CN)_6$ (47gm, 144 mmol), K_2CO_3 (19.888 gm, 144 mmol) and $(DHQ)_2PHAL$ (0.378 gm, 0.48 mmol) in t-BuOH-H_2O (1:1, 240 ml : 240 ml) cooled to 0^oC was added OsO_4 (1.943 ml, 0.4 mol %, 0.1 M solution in toluene). After stirring for 5 minutes at 0^oC, styrene **41** (5.0 gm, 48.0 mmol) was added in one portion. The reaction mixture was stirred at 0^oC for 24h and then quenched with solid sodium sulfite. The stirring was continued for 1h and the solution was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (3.5: 1.5) as eluent gave (*R*)-phenylethylene glycol **42** (6.596 gm) as a white solid.



42

Yield: 99 %

White solid: M.P. 59-60^oC

$[\alpha]_D^{25}$ = +54.93 (*c* = 1, $CHCl_3$) [lit.[35] $[\alpha]_D^{21}$ + 38.1 (*c* = 1.25, EtOH)].

IR ($CHCl_3$): cm^{-1} 3376,1640,1800, 1214.

^1H NMR (200 MHz, $CDCl_3$): δ 2.49 (bs, 1H), 2.89 (bs, 1H), 3.61-3.79 (m, 2H), 4.82 (dd, J = 4.65 and 8.55 Hz, 1H), 7.37 (s, 5H).

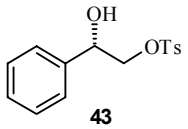
MS (m/z, rel. int. %): M^+ 138 (7), 107 (85), 91 (6), 79 (100), 77 (74).

(*S*)-1-phenylethane-1,2-diol was prepared according to the above procedure with 2.5 gm of styrene as the starting materials using $(DHQD)_2PHAL$ ligand to provide (*S*)-phenyl-ethane-1,2-diol (3.24 gm) as a white solid.

Yield: 99.6 %; M. P. 59-60^{o}C

$[\alpha]_D^{25}$ = -55.50 (*c* = 1, $CHCl_3$)

Synthesis of (*R*)-toluene-4-sulfonic acid 2-hydroxy-2-phenylethyl ester (43): To a mixture of (*R*)-phenylethane-1,2-diol **42** (4.42 gm, 32.02 mmol), in dry dichloromethane (65 ml) was added dibutyltin oxide (15 mg, 0.2 mol % of diol) followed by the addition of *p*-toluenesulfonyl chloride (6.17 gm, 32.02 mmol) and triethylamine (4.4 ml, 32.02 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC after completion of reaction (45 min) and quenched by adding water. The solution was extracted with dichloromethane (3 x 25 ml) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (4: 1) as eluent gave monotosyl compound **43** (9.27 gm) as a white solid.



43

Yield: 99 %

White solid: M.P. 60-61^{o}C

$[\alpha]_D^{25}$ = + 49.95 (*c* = 1, $CHCl_3$)

IR ($CHCl_3$): cm^{-1} 3529, 1598, 1360, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.75 (bs, 1H), 4.00-4.25 (m, 2H), 5.00 (dd, J = 3.45 and 8.00 Hz, 1H), 7.30 (s, 5H), 7.31(d, J = 8.15 Hz, 2H), 7.75 (d, J = 8.15 Hz, 2H).

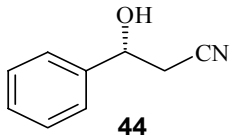
MS (m/z, rel. int. %): M^+ 292 (0.2), 262 (4), 155 (3), 107 (100), 91 (38), 79 (45), 77 (31).

(*S*)-Toluene-4-sulfonic acid 2-hydroxy-2-phenylethyl ester was prepared from 3.0 gm (*S*)-diol by the above procedure in 99 % yield as a white solid.

M. P. 60-61^{o}C

$[\alpha]_D^{25}$ = -51.50 (*c* = 1, $CHCl_3$)

Synthesis of (*R*)-3-hydroxy-3-phenylpropionitrile (44): To stirring mixture of monotosyl compound **43** (3.0 gm, 10.26 mmol) in ethanol-H_2O (35 ml: 25 ml) at 0^0C was added NaCN (1.76 gm, 35.92 mmol) in one portion. The reaction mixture was stirred at room temperature for 24h. The reaction mixture was concentrated at 50^0C on rotatory evaporator and extracted with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (3: 1) as eluent gave (*S*)-3-phenyl-3-hydroxypropanenitrile **44** (1.351 gm) as a pale yellow oil.



44

Yield: 90 %

Pale yellow oil.

$[\alpha]_D^{25}$ = + 60.21 (*c* = 1, $CHCl_3$)

IR ($CHCl_3$): cm^{-1} 3500, 2250, 1660,1 540.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.71-2.77 (m, 2H), 2.98 (bs, 1H), 5.01 (m, 1H), 7.38 (m, 5 H).

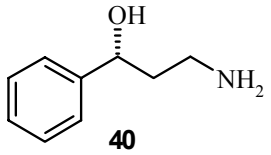
^{13}C NMR (200 MHz, $CDCl_3$): δ 38.08, 79.89, 128.02, 135.93, 138.89, 139.10, 151.49

MS (m/z, rel. int. %): M^+ 147 (3.8), 116 (8), 107 (76), 79 (100), 77 (83).

(*S*)-3-Hydroxy-3-phenylpropionitrile was prepared in 91 % yield from (*S*)-monotosyl compound by the above method as a pale yellow oil.

$[\alpha]_D^{25}$ = - 60.21 (*c* = 1, $CHCl_3$)

Synthesis of (*R*)-3-amino-1-phenylpropan-1-ol (40): To a THF (10.0 ml) solution of (*R*)-3-phenyl-3-hydroxypropanenitrile **44** (1.25 gm, 8.5 mol) was slowly added borane dimethyl sulfide complex (0.84 gm, 11.0 mmol) at room temperature. Methyl sulfide was then distilled from the reaction vessel and the resulting THF solution refluxed for 2.5h. After cooling to room temperature methanolic HCl (6.25 ml, 1.0 M) was added to the reaction mixture. Methanol and methyl borate were removed by distillation and the reaction mixture neutralized with sodium hydroxide (6.0 ml, 5N). Extraction of the mixture with dichloromethane followed by concentration provided the crystalline (*R*)-3-phenyl-3-hydroxypropylamine **40** (1.23 gm).



40

Yield: 96 %

$[\alpha]_D^{25}$ = + 40.50 (*c* = 1, $CHCl_3$) [lit.[29b] $[\alpha]_D^{25}$ – 43.65 (*c* = 1, MeOH) for (*S*)-enantiomer].

IR ($CHCl_3$): cm^{-1} 3400, 1620, 1598, 1540.

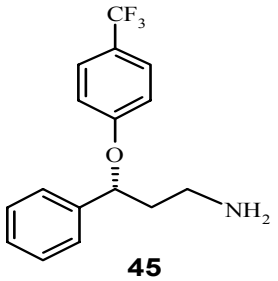
^1H NMR (200 MHz, $CDCl_3$): δ 1.61-1.88 (m, 2H), 2.80-3.05 (m, 5H), 4.85 (dd, J = 3.4, 8.0 Hz, 1H), 7.12 -7.32 (m, 5H).

MS (m/z, rel. int. %): M^+ 151 (4), 134 (43), 104 (67), 79 (66), 77 (100).

(*S*)-3-Amino-1-phenylpropan-1-ol was synthesized from (*S*)-cyano alcohol by the above method in 96 % yield.

$[\alpha]_D^{25}$ = - 41.50 (*c* = 1, $CHCl_3$)

Synthesis of (*R*)-norfluoxetine (45): The alkoxide of (*R*)-3-phenyl-3-hydroxypropylamine **40** (1.0 gm, 6.6 mmol) was generated with sodium hydride (0.47 gm, 9.9 mmol 50 % in oil) in DMSO (2.0 ml) at 55^0C for 30 minute under nitrogen atmosphere. 4-Chlorobenzotrifluoride (1.8 gm, 9.9 mmol) in 1.0 ml DMSO was then slowly added to the reaction mixture and the resulting solution heated to 90^oC for 1h. The resulting mixture was cooled to room temperature and diluted with NaOH (10.0 ml, 2N aq. solution). Toluene (4x 3 ml) was used to extract the product from the hydroxide solution (1.96 gm).



45

Yield: 90 %

Viscous Liquid

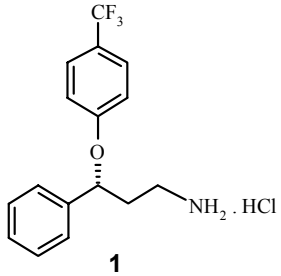
$[\alpha]_D^{25}$ = + 10.27 (*c* = 0.62, $CHCl_3$)

IR ($CHCl_3$): cm^{-1} 3369, 3298, 1613, 1500, 1327, 1232.

^{1}H NMR (200MHz, $CDCl_3$): δ 1.90-2.20 (m, 2H), 2.1(bs, 2H), 2.90 (t, J = 7.35 Hz, 2H), 5.35 (dd, J = 3.45 and 8.55 Hz, 1H), 6. 90 (d, J = 8.55 Hz, 2H), 7.20-7.35 (m, 5H), 7.45 (d, J = 8.55 Hz, 2H).

MS (m/z, rel. int. %): (M^+-2) 295 (0.4), 278 (0.2), 251 (1), 197 (18), 162 (15), 134 (100), 104 (85), 91 (40), 77 (67).

Synthesis of (*R*)-norfluoxetine hydrochloride (1): (*R*)-Norfluoxetine (1.9 gm) was dissolved in toluene (4.0 ml) and heptane (10.0 ml) was added, HCl gas was passed to form (*R*)-Norfluoxetine hydrochloride **1** (1.92 gm).



1

Yield: 90 %

Solid; M. P. 129-130°C [Lit. [29b] 131^{0}C]

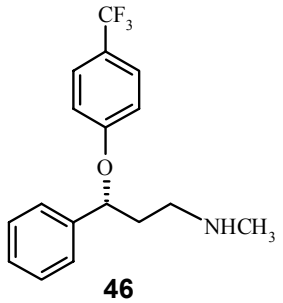
$[\alpha]_D^{25}$ = - 36.0 (*c* = 1.5, MeOH) [lit.[29b] $[\alpha]_D^{25}$ +36.3 (*c* = 2, MeOH) for (*S*)-enantiomer].

(*S*)-Norfluoxetine hydrochloride was prepared by the above method in 85 % overall yield starting from (*S*)-aminoalcohol.

$[\alpha]_D^{25}$ = + 36.0 (*c* = 1.5, MeOH)

Synthesis of (*R*)-fluoxetine (46): To a solution of norfluoxetine **45** (1.0 gm, 3.378 mmol) and methyl chloroformate (0.287 ml, 3.72 mmol) in dichloromethane (15.0 ml) was added aqueous K_2CO_3 (2.33 gm, 16.89 mol in 30 ml water). The reaction was rapidly stirred for 20 minutes and was diluted with H_2O. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase were dried (Na_2SO_4) and concentrated to give carbamate as a pale yellow oil. To a stirring suspension of lithium aluminum hydride (0.25 gm) in dry THF (15.0 ml) at 0^{0}C was added a solution of carbamate in dry THF (5.0 ml) under nitrogen. The ice bath was removed and then the reaction mixture was refluxed for 2h. Excess lithium aluminium hydride was destroyed by adding H_2O and EtOAc. The white precipitate

obtained was filtered and washed with MeOH. The combined filtrate was concentrated to give (*R*)-fluoxetine **46** (0.942 gm) as an oil.



46

Yield = 90 %

Viscous Liquid

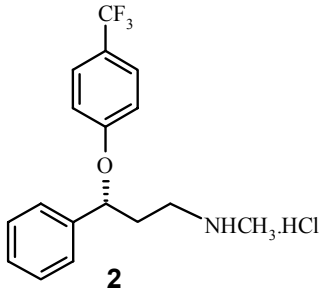
$[\alpha]_D^{25}$ = + 5.00 (*c* = 1 in $CHCl_3$)

IR (Neat): cm^{-1} 3298,1620,1595,1520,1360

^1H NMR (200MHz, $CDCl_3$): δ 2.08-2.30 (m, 2H), 2.36 (s, 3H), 2.55-2.75 (m, 3H), 5.34 (dd, J = 4.00 and 8.55 Hz, 1H), 6.30 (d, J = 8.55 Hz, 2H), 7.29-7.37 (m, 5H) 7.44 (d, J = 8.55 Hz, 2H).

(*S*)-Fluoxetine was synthesized according to the above procedure from (*S*)-norfluoxetine in 88 % yield.

Synthesis of (*R*)-fluoxetine hydrochloride (2): Fluoxetine (0.90 gm) was dissolved in ether (15 ml) and acidified with HCl gas (pH 3-4) to give an acidic ethereal solution (no precipitate formed). The solution was concentrated at room temperature to give a yellow solid, which was washed with ether. After recrystallization was obtained pure (*R*)-fluoxetine hydrochloride **2** (0.91 gm).



2

Yield: 90 %

Solid; M P. 139-140°C [lit.[28d] 142-143°C]

$[\alpha]_D^{25}$ = -13.6 (*c* = 1, $CHCl_3$) [lit.[28a, b] $[\alpha]_D^{25}$ – 13.8 (*c* = 1, $CHCl_3$)].

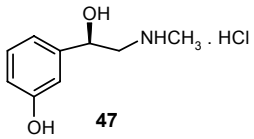
(*S*)-Fluoxetine hydrochloride was prepared by the above method using (*S*)-fluoxetine in 89 % yield.

$[\alpha]_D^{25}$ = +13.4 (*c* = 1,$CHCl_3$)

1.3 SECTION C

1.3.1 Introduction

The growing awareness of chirality in the context of biological activity has led to the discovery of many new asymmetric reaction in order to produce drugs and drug intermediates in enantiomerically pure forms. Catalytic asymmetric reactions have distinct advantages over stoichiometric versions for economic and environmental reasons. Due to growing concern about chiral drugs being sold as racemates, many pharmaceutical industries are switching over to produce enantiomerically pure forms of the chiral drugs. Since its discovery, (*R*)-phenylephrine hydrochloride[37] is a clinical potent adrenergic agent and β-receptor sympathomimetic drug, exclusively marketed in the optically active (*R*)-form.



47

Figure 12: (*R*)-Phenylephrine hydrochloride

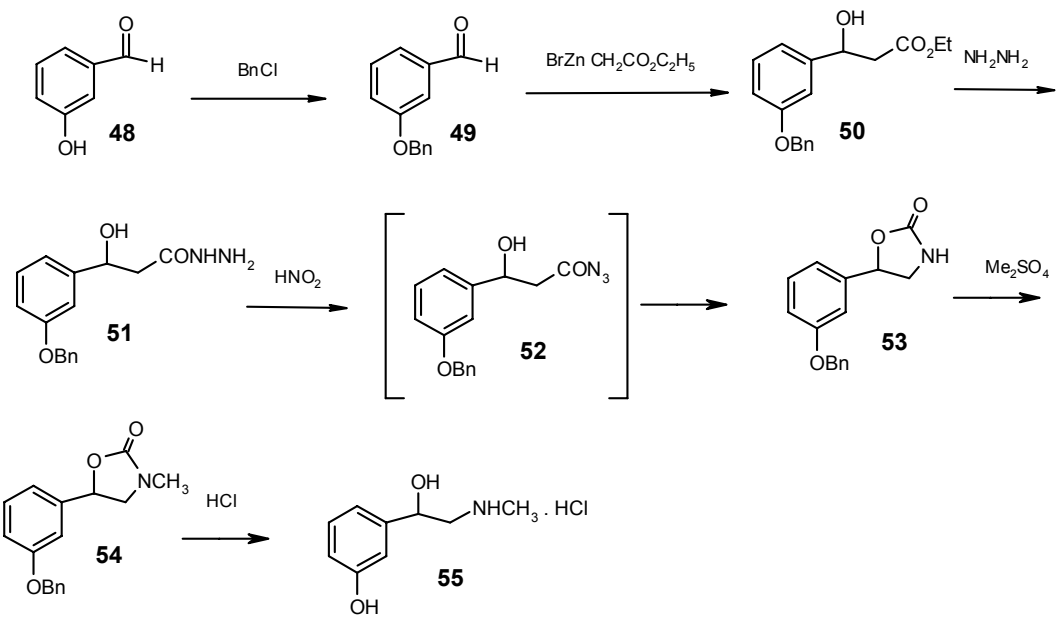
Although many nonchiral synthesis of phenylephrine hydrochloride have been reported,[38-41] the asymmetric synthesis of (*R*)-form has been largely neglected.[42] There has been no report in the literature about the asymmetric synthesis of (*R*)-form employing the Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones,[33a-b] amino alcohols,[33c-e] diolmycins,[33f] fluoxetine and norfluoxetine,[43] the Sharpless asymmetric dihydroxylation[5a, 22] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. We have further extrapolated the SAD reaction for the enantioselective synthesis of (*R*)-phenylephrine hydrochloride and results of such study are described below.

1.3.2 Review of Literature

There are few reports on the synthesis of phenylephrine hydrochloride. Most of the syntheses reported in literature are nonchiral. The methods reported in literature are described below.

Bergmann (1951)[38] Scheme 18

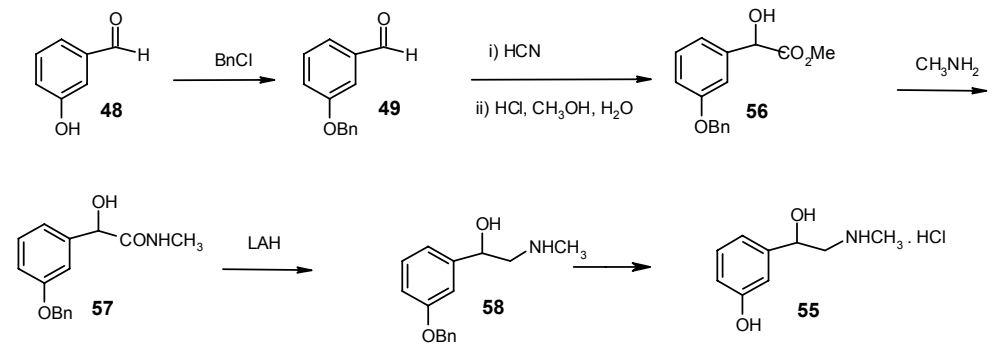
The Curtius rearrangement of β-hydroxy acid azide **52** to oxazolidones **53** was utilized as key step in the synthesis of (±)-phenylephrine (Scheme 18).



Scheme 18

Russell (1961)[41] Scheme 19

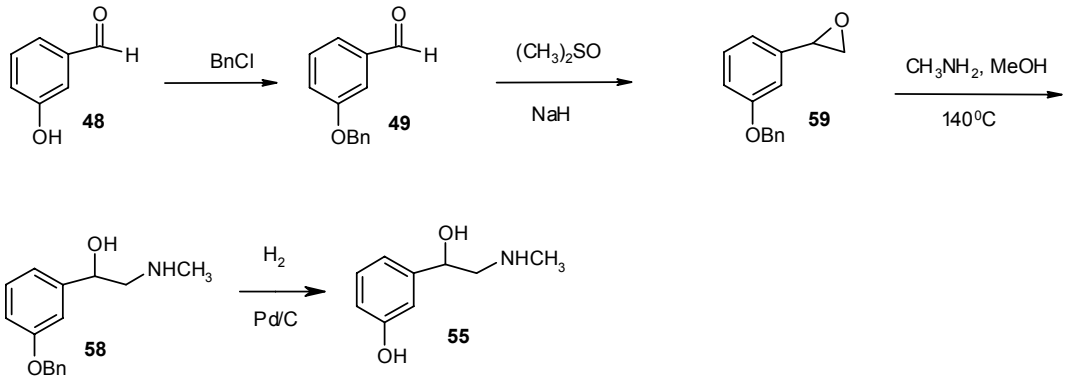
Lithium aluminium hydride reduction of 3-benzyloxy-*N*-methylmandelamide **57** followed by debenzylation has furnished (±)-phenylephrine (Scheme 19).



Scheme 19

Britten (1968)[40] Scheme 20

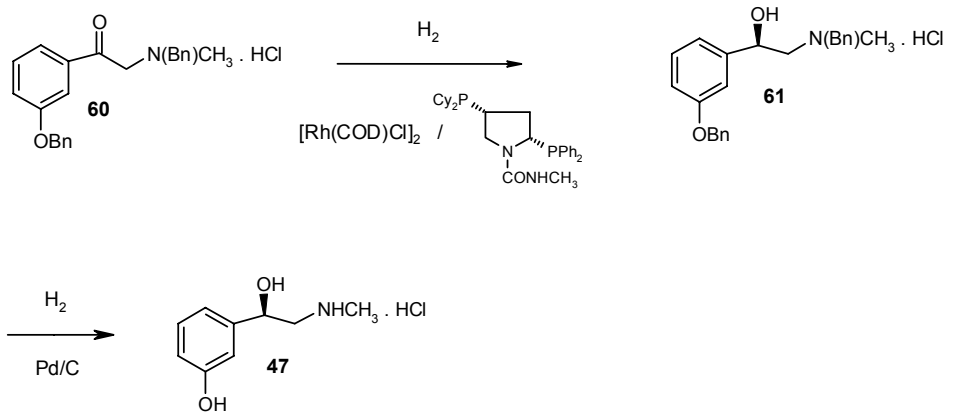
The ring opening of 3-benzyloxystyrene epoxide **59** by methylamine has been employed as key step to synthesize (±)-phenylephrine **55** (Scheme 20).



Scheme 20

Takeda (1989)[42] Scheme 21

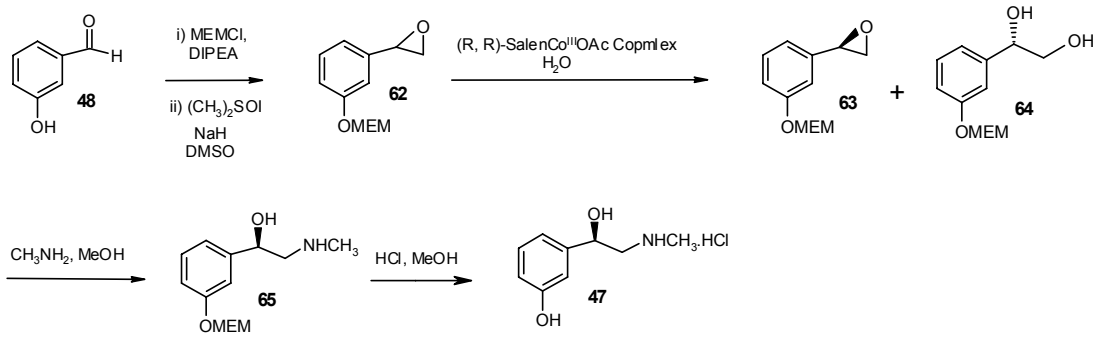
The key step involved in this approach has been the asymmetric hydrogenation of 3-benzyloxy-2-(*N*-benzyl-*N*-methyl)aminoacetophenone hydrochloride **60** using (2*R*, 4*R*)-MCCPM-rhodium complex as a catalyst (Scheme 21).



Scheme 21

Gurjar (1998)[44] Scheme 22

Gurjar employed the asymmetric kinetic resolution of styrene oxide derivative **63** using (*R*, *R*)-salen $Co^{III}OAc$ complex as a catalyst which eventually led to the optically pure phenylephrine **47** (Scheme 22).

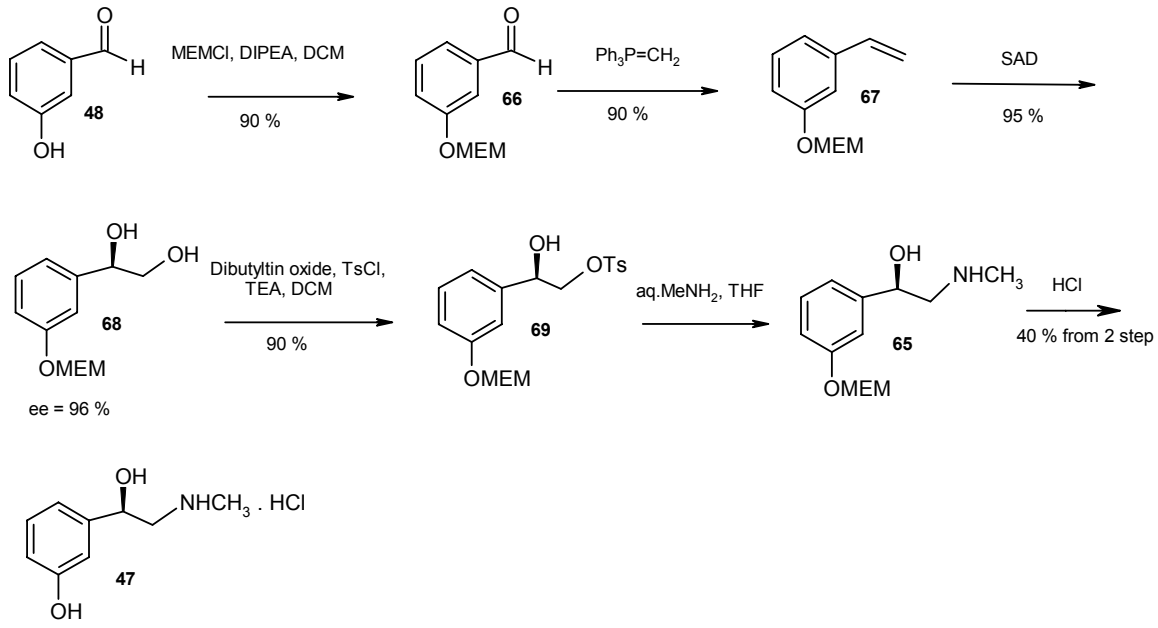


Scheme 22

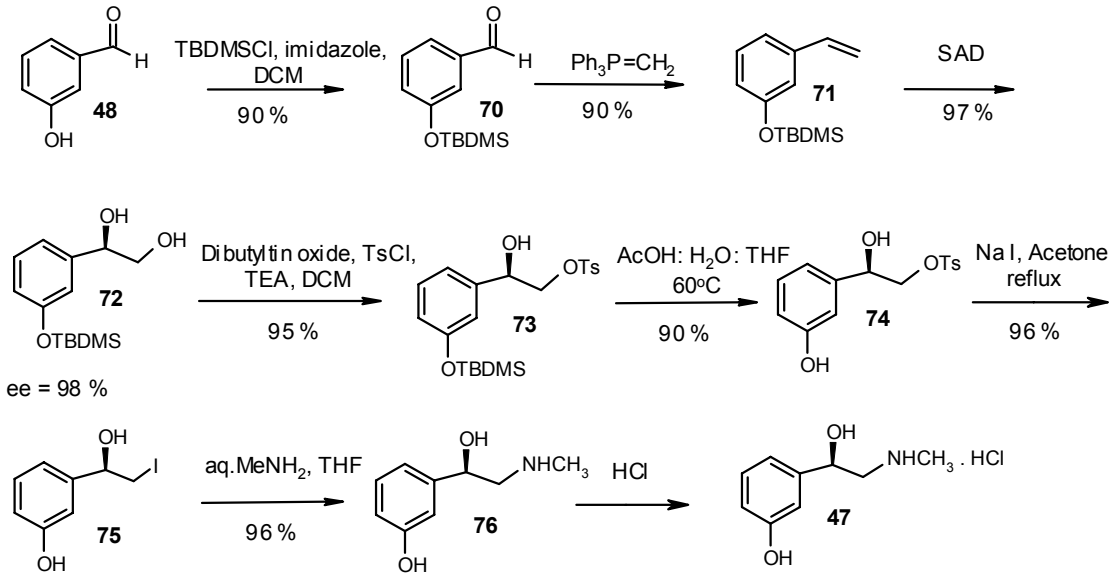
1.3.3 Present work

Objective

Although racemic β-blockers have been used over two decades, there is now a great deal of concern about enantiomerically pure isomer having affinity to β-receptors. As described in introduction section, a few reports are available in the literature for the synthesis of phenylephrine hydrochloride. Most of the syntheses of phenylephrine hydrochloride as described above are not stereoselective. Most of the methods reported involved the use of substituted styrene oxide as the key intermediate in the synthesis. The objective of our work was to explore the chemistry of SAD and to develop an enantiomerically pure and high yielding new route for the synthesis of (*R*)-phenylephrine hydrochloride.



Scheme 23



Scheme 24

1.3.4 Results and discussion

The present strategy for the synthesis of (*R*)-phenylephrine hydrochloride **47** is depicted in Scheme 23 and 24. 3-Hydroxybenzaldehyde **48** was reacted with methoxyethoxy-methylchloride (MEM-Cl) using diisopropylethylamine (DIPEA) as a base in dichloromethane to give the corresponding ether **66** in 90 % yield. The CH_3 protons of MEM group appeared at 3.30 δ in ^{1}H NMR spectrum. The two CH_2 protons appeared as a multiplet at 3.56 δ and 3.80 δ. One singlet appeared at 5.29 δ for the -OCH_2O- protons of OMEM group. The *m*-methoxyethoxymethoxystyrene **67** was obtained by the Wittig reaction between protected aldehyde **66** and ylide generated by the reaction of triphenylphosphinemethyl iodide salt and n-butyllithium in 90 % yield. ^{1}H NMR spectrum of styrene compound showed the characteristic signal of styrene at 5.24 δ

(doublet), 5.80 δ (doublet) and 6.7 δ (double doublet). Compound **67** was subjected to asymmetric dihydroxylation using (DHQD)-PHAL as chiral ligand to furnish the diol **68** in 95 % yield and 96 % ee. The IR spectrum of **68** showed a band at 3401 cm^{-1} indicating the presence of hydroxyl functionality. The CH_2 protons attached to –OH group appeared at 3.7 δ in ^1H NMR spectrum. The CH proton appeared at 4.74 δ as double doublet (Figure 13). The ee of diol **68** was estimated to be 96 % as determined by HPLC. When TBDMS protected styrene was subjected to SAD reaction, we observed a marginal improvement in ee (98 %) that may be attributed to the effect of substitution. The diol **68** was transformed into corresponding monotosyl compound **69** using dibutyltin oxide catalyst in triethylamine in 90 % yield. The IR spectrum of compound **69** showed a band at 3320 cm^{-1} characteristic of –OH group. ^1H NMR spectrum of **69** showed a singlet at 2.45 δ characteristic of CH_3 protons of tosyl group including hydroxy proton. Two doublet appeared in aromatic region at 7.32 δ and 7.78 δ for the aromatic protons of tosyl group (Figure 14). ^{13}C NMR spectrum of tosyl compound **69** showed a signal at 21.32 δ for the CH_3 carbon of tosyl group (Figure 15). When **69** was treated with 40 % aqueous methylamine in THF at room temperature it furnished (*R*)-phenylephrine **65** which on subsequent treatment with HCl at reflux temperature gave (*R*)-phenylephrine hydrochloride **47** in 40 % yield.

In order to synthesize **47** in high yield with high enantiomeric excess the following protocol was used. 3-Hydroxybenzaldehyde **48** was reacted with *t*-butyldimethylsilyl chloride (TBDMS-Cl) using imidazole to give the corresponding silyl compound **70** in 90 % yield. The CH_3 protons of TBDMS group appeared at 0.23 δ in ^1H NMR spectrum and one singlet appeared at 1.05 δ for nine protons of *t*-butyl group of TBDMS group. The styrene compound **71** was obtained by the Wittig reaction between the protected aldehyde **70** and the ylide generated by the reaction of triphenylphosphinemethyl iodide salt and n-

BuLi in 90 % yield. ^{1}H NMR spectrum of compound **71** showed the doublet at 5.29 δ, 5.72 δ and 6.75 δ characteristic of styrene. The substituted styrene **71** was subjected to asymmetric dihydroxylation using (DHQD)-PHAL as chiral ligand to furnish the diol **72** in 97 % yield and with 98 % ee. The ee was determined by HPLC (Figure 16). The IR spectrum of **72** showed a band at 3401 cm^{-1} indicating the presence of hydroxyl functionality. NMR spectrum showed CH_2 protons at 3.70 δ and CH proton at 4.75 δ as double doublet (Figure 17). Similarly, ^{13}C NMR spectrum showed two signal at 78.31 δ and 84.78 δ corresponding to CH_2 and CH carbon attached to –OH group respectively (Figure 18).

The diol **72** was transformed into monotosyl compound **73** using dibutyltin oxide catalyst in triethylamine in 95 % yield. The IR spectrum of compound **73** showed a band at 3329 cm^{-1} characteristic of –OH group. ^{1}H NMR spectrum of **73** showed a singlet at 2.45 δ characteristic of CH_3 protons of tosyl group. Two doublet appeared in aromatic region at 7.30 δ and 7.76 δ for the aromatic protons of tosyl group (Figure 19). ^{13}C NMR spectrum of tosyl compound **73** showed a signal at 21.56 δ for the CH_3 carbon of tosyl group (Figure 20).

When tosyl compound **73** was treated with acetic acid in THF and water in the ratio (3:1:1) at 60^{0}C for 10 h, the TBDMS group was deprotected to give **74** in 90 % yield. The IR spectra of **74** showed two strong bands at 3321 cm^{-1} and 3100 cm^{-1} indicating the presence of aliphatic and aromatic hydroxyl functionality. The ^{1}H NMR of **74** showed the absence of two singlet at 0.20 δ and 1.00 δ indicating the deprotection of TBDMS group (Figure 21). When **74** was treated with sodium iodide in acetone at reflux temperature, the iodo compound **75** was obtained in almost quantitative yield. The IR spectrum of **75** showed two bands at 3320 and 3100 cm^{-1} characteristics of –OH group. In ^{1}H NMR spectrum of compound **75**, absence of one singlet at 2.55 δ and two doublet in aromatic

region corresponding to tosyl group and appearance of a multiplet at 3.40 δ indicated the substitution of iodo group (Figure 22).

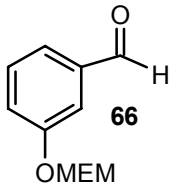
When compound **75** was treated with 40 % methylamine in THF at room temperature it furnished (*R*)-phenylephrine **76** in 98 % yield. (*R*)-Phenylephrine was dissolved in methanol and treated with methanolic HCl to furnish (*R*)-phenylephrine hydrochloride **47** in 90 % yield (Figure 23).

1.3.5 Conclusion

A practical and highly enantioselective synthesis of (*R*)-phenylephrine hydrochloride (98 % ee) has been achieved for the first time using the Sharpless asymmetric dihydroxylation as the source of chirality.

1.3.6 Experimental

Synthesis of (3-methoxyethoxymethoxy)benzaldehyde (66): To a stirred solution of 3-hydroxybenzaldehyde **48** (5.0 gm, 40.975 mmol) in dry dichloromethane (50 ml) at 0^oC were added diisopropylethylamine (10.6 ml, 81.95 mmol) and MEM-Cl (5.6 ml, 49.15 mmol). After 3.5 h, the reaction mixture was washed with water (25 ml). The organic layer was dried (Na_2SO_4) and concentrated, and residue was purified on silica gel by eluting with EtOAc-light petroleum ether (1:9) to furnish **66** (7.74 gm) as a colorless liquid.



66

Yield: 90 %

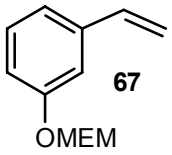
Colorless liquid

IR (Neat): cm^{-1} 2924, 2821, 1706, 1586.

^1H NMR (200 MHz, $CDCl_3$): δ 3.33 (s, 3H), 3.50-3.55 (m, 2H), 3.78-3.83 (m, 2H), 5.29 (s, 2H), 7.26-7.50 (m, 4H), 9.93 (s, 1H).

Synthesis of (3-methoxyethoxymethoxy)styrene (67): Methyltriphenylphosphosphonium iodide salt (20.27 gm, 50 mmol) was taken in dry benzene (200 ml) and n-butyllithium (21.33 ml, 15 % solution in THF, 50 mmol) was added drop-wise and mixture was stirred for 6 h under nitrogen. The reaction mixture was filtered under nitrogen through sintered funnel. To the above solution was added the aldehyde **66** (7. 0 gm, 33.33 mmol in 50 ml benzene) drop-wise under vigorous stirring under nitrogen at room temperature. After completion of reaction (8 h), saturated ammonium chloride solution (50 ml) was added and organic layer separated and aqueous solution extracted with benzene (2 x 50 ml). The combined organic phase were dried over Na_2SO_4,

concentrated and residue was purified on silica gel by eluting with light petroleum ether to furnish substituted styrene **67** (6.24 gm) as a colorless liquid.



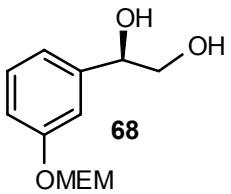
Yield: 90 %

Colorless liquid

IR (Neat): cm^{-1} 2924, 2818, 1599, 1579, 1484, 1248.

^1H NMR (200 MHz, $CDCl_3$): δ 3.40 (s, 3H), 3.57 (t, J = 5.0 Hz, 2H), 3.85 (t, J = 5 Hz, 2H), 5.24 (d, J = 10.0 Hz, 1H), 5.30 (s, 2H), 5.80 (d, J = 16.9, Hz, 1H), 6.70 (dd, J = 6.7, 10.87 Hz, 1H), 6.95-7.25 (m 4H).

Synthesis of (*R*)-1-(3-methoxyethoxymethoxy)phenylethane-1,2-diol (68): To a mixture of $K_3Fe(CN)_6$ (11.825 gm, 36.0 mmol), K_2CO_3 (4.975 gm, 36.0 mmol) and $(DHQ)_2PHAL$ (0.095 gm, 0.12 mmol) in t-BuOH-H_2O (1:1, 60 ml: 60 ml) cooled to 0^0C was added OsO_4 (0.50 ml, 0.4 mol % of styrene, 0.1 M solution in toluene). After stirring for 5 minutes at 0^oC, substituted styrene **67** (2.50 gm, 12.0 mmol) was added in one portion. The reaction mixture was stirred at 0^oC for 24h and then quenched with solid sodium sulfite. The stirring was continued for 1h and the solution was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (6: 4) as eluent gave (*R*)-phenylethylene glycol **68** (2.85 gm) as a viscous liquid with 96 % ee.



Yield: 98.3 %

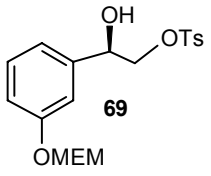
Viscous liquid

$[\alpha]_D^{25}$ = -34.65 (*c* = 1.12, $CHCl_3$) [lit.[44] $[\alpha]_D$ +34.4 (*c* = 1.49, $CHCl_3$) for (*S*)-enantiomer].

IR (Neat): cm^{-1} 3401, 2924, 2818, 1604, 1586, 1451, 1248.

^1H NMR (200 MHz, $CDCl_3$): δ 3.12 (bs, 2H), 3.35 (s, 3H), 3.50 (t, J = 5.0 Hz, 2H), 3.36-3.79 (m, 2H), 3.80 (t, J = 5 Hz, 2H), 4.74 (dd, J = 3.40 and 7.00 Hz, 1H), 5.27 (s, 2H), 6.95-7.25 (m, 4H).

Synthesis of (*R*)-toluene-4-sulfonic acid 2-hydroxy-2-(3-methoxyethoxymethoxy)-phenylethyl ester (69): To a mixture of diol **68** (0.866 gm, 3.58 mmol), in dry dichloromethane (7.0 ml) was added dibutyltin oxide (2.0 mg, 0.2 mol % of diol) followed by the addition of *p*-toluenesulfonyl chloride (0.678 gm, 3.58 mmol) and triethylamine (0.5 ml, 3.58 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC; after completion of reaction (45 min) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 10 ml) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (7: 3) as eluent afforded monotosyl compound **69** (1.275 gm) as a viscous liquid.



69

Yield: 90 %

Viscous liquid

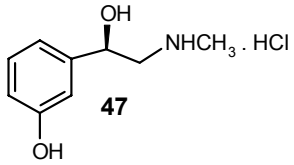
$[\alpha]_D^{25}$ = -34.65 (*c* = 1.00, $CHCl_3$)

IR (Neat): cm^{-1} 3320, 2924, 2818, 1620, 1580, 1450.

^1H NMR (200 MHz, $CDCl_3$): δ 2.41(bs, 1H), 2.45 (s, 3H), 3.36 (s, 3H), 3.55 (t, J = 5.0 Hz, 2H), 3.81 (t, J = 5 Hz, 2H), 3.97-4.16 (m, 2H), 4.52 (dd, J = 3.40 and 7.00 Hz, 1H), 5.2 4 (s, 2H), 6.92-7.01 (m, 3H), 7.21-7.29 (m, 1H), 7.35 (d, J = 8.2 Hz, 2), 7.77 (d, J = 8.2 Hz, 2H).

^{13}C NMR (200 MHz, $CDCl_3$): δ 21.32, 58.60, 67.31, 71.24, 74.00. 93.07, 113.95, 115.70, 119.43, 127.63, 129.39, 129.65,132.29, 140.23, 144.72, 157.11.

Synthesis of (*R*)-phenylephrine hydrochloride (47): Monotosylate compound **69** (0.80 gm, 2.0 mmol) was dissolved in THF (5.0 ml) and methylamine (5.0 ml, 40 % aqueous solution) was added and stirred at room temperature for 4 h. Solvent was evaporated in rotatory evaporator and crude product was dissolved in methanol (5.0 ml) and one drop conc. HCl was added and refluxed for 2 h, cooled to room temperature. Evaporation of solvent gave the crude product which was purified by crystallization in isopropanol to yield **47** (0.164 gm) in 40 % yield.



47

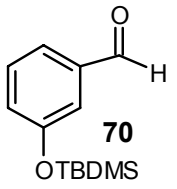
Yield = 40 %

White solid: M.P. 141-143°C [Lit.[39] 141-145°C]

$[\alpha]_D^{25}$ = - 43.0 (*c* = 2.0, H_2O) [Lit.[44] – 44.0 (*c* = 2.16, H_2O)]

^1H NMR (200 MHz, D_2O): δ 2.65 (s, 3H), 3.25 (m, 2H), 5.10 (m, 1H), 6.80-7.32 (m, 4H).

Synthesis of (3-*t*-butyldimethylsilyloxyl)benzaldehyde(70): To a stirred solution of 3-hydroxybenzaldehyde **48** (5.0 gm, 40.975 mmol) in dry dichloromethane (50 ml) at 0^oC were added imidazole (5.58 gm, 81.95 mmol) and solution was stirred for 30 min and TBDMS-Cl (7.41 gm, 49.15 mmol) was added and stirred for 5 h, the reaction mixture was washed with water (25 ml). The organic layer was dried (Na_2SO_4) and concentrated, and residue was purified on silica gel by eluting with EtOAc: light petroleum ether (0.5: 9.5) to furnish compound **70** (8.70 gm) as a colorless liquid.



70

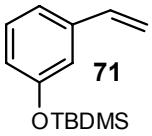
Yield: 90 %

Colorless liquid

IR (Neat): cm^{-1} 2924, 2821, 1703, 1586.

^1H NMR (200 MHz, $CDCl_3$): δ 0.23 (s, 6H), 1.00 (s, 9H), 7.11-7.47 (m, 4H), 9.96 (s, 1H).

Synthesis of (3-*t*-butyldimethylsilyloxyl)styrene (71): Methyltriphenylphosphosphonium iodide salt (12.87 gm, 31.779 mmol) was taken in dry benzene (120 ml) and n-butyllithium (13.60 ml, 15 % solution in THF, 31.779 mmol) was added drop-wise and mixture was stirred for 6 h under nitrogen. Solid was filtered under nitrogen from reaction mixture and benzene solution of the aldehyde **70** (5.0 gm, 21.186 mmol in 25 ml benzene) was added drop-wise under vigorous stirring under nitrogen at room temperature. After completion of reaction (10 h), saturated ammonium chloride solution (50 ml) was added and organic layer was separated and aqueous solution was extracted with benzene (2 x 50 ml). The combined organic phase were dried over Na_2SO_4, concentrated and residue was purified on silica gel by eluting with light petroleum ether to furnish substituted styrene **71** (4.46 gm) as a colorless liquid.



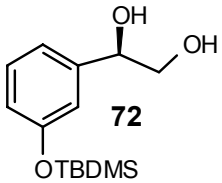
Yield: 90 %

Colorless liquid

IR (Neat): cm^{-1} 2924, 2818, 1600, 1579, 1486, 1250.

^1H NMR (200 MHz, $CDCl_3$): δ 0.23 (s, 6H), 1.00 (s, 9H), 5.24 (d, J = 15.7 Hz, 1H), 5.70 (d, J = 23.0, Hz, 1H), 6.75 (d, J = 15.7 Hz, 1H), 6.95-7.35 (m 4H).

Synthesis of (*R*)-1-(3-*t*-butyldimethylsilyloxyl)phenylethane-1,2-diol (72): To a mixture of $K_3Fe(CN)_6$ (6.30 gm, 19.2 mmol), K_2CO_3 (2.70 gm, 19.2 mmol) and $(DHQ)_2PHAL$ (0.050 gm, 0.064 mmol) in *t*-BuOH-H_2O (1:1, 30 ml: 30 ml) cooled to 0^0C was added OsO_4 (0.25 ml, 0.4 mol % of styrene, 0.1 M solution in toluene). After stirring for 5 minutes at 0^oC, substituted styrene **71** (1.50 gm, 6.4 mmol) was added in one portion. The reaction mixture was stirred at 0^0C for 24 h and then quenched with solid sodium sulfite. The stirring was continued for 1h and the solution was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (3.5: 1.5) as eluent gave (*R*)-phenylethylene glycol **72** (1.68 gm) as a viscous liquid with 98 % ee.



Yield: 98.0 %

Viscous liquid

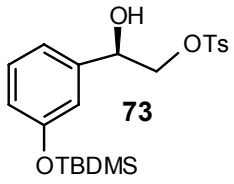
$[\alpha]_D^{25}$ = -34.33 (*c* = 1.2, $CHCl_3$).

IR (Neat): cm^{-1} 3401, 2924, 2818, 11604, 1586, 1451, 1248.

^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 2.26 (bs, 2H), 3.60-3.80 (m, 2H), 4.75 (dd, J = 4.50 and 8.50 Hz, 1H), 6.96-7.25 (m, 4H).

^{13}C NMR (200 MHz, $CDCl_3$): δ -4.67, 17.88, 25.45, 67.78, 74.25, 117.62, 118.84, 129.04, 142.31, 155.44.

Synthesis of (*R*)-toluene-4-sulfonic acid 2-hydroxy-2-(3-*t*-butyldimethylsilyloxyl)-phenylethyl ester (73): To a mixture of diol **72** (0.96 gm, 3.58 mmol), in dry dichloromethane (7.0 ml) was added dibutyltin oxide (2.0 mg, 0.2 mol % of diol) followed by the addition of *p*-toluenesulfonyl chloride (0.678 gm, 3.58 mmol) and triethylamine (0.5 ml, 3.58 mmol) and reaction mixture was stirred at room temperature under nitrogen. The reaction was monitored by TLC; after completion of reaction the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 10 ml) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (4: 1) as eluent afforded monotosyl compound **73** (1.436 gm) as a viscous liquid.



73

Yield: 95 %

Viscous liquid

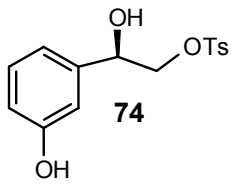
$[\alpha]_D^{25}$ = - 46.62 (*c* = 0.6, $CHCl_3$)

IR ($CHCl_3$): cm^{-1} 3529, 1599, 1485, 1359, 1277.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 2.45 (s, 3H), 2.63 (bs, 1H), 3.95-4.15 (m, 2H), 4.91 (dd, J= 3.50 and 8.00 Hz, 1H), 6.75-7.22 (m, 4H), 7.34 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H).

^{13}C NMR (200 MHz, $CDCl_3$): δ -5.10, 17.60, 20.94,25.17, 70.77, 73.79, 117.51, 118.76, 119.2, 127.36, 129.38, 140.33, 144.30, 155.22.

Synthesis of (*R*)-toluene-4-sulfonic acid 2-hydroxy-2-(3-hydroxy)phenylethyl ester (74): In a single neck round bottom flask was added compound **73** and a mixture of acetic acid: water: THF in the ratio 3: 1: 1 (10 ml: 5 ml : 5 ml) and heated at 55^{o}C for 15 h and reaction mixture was cooled to room temperature. About ¼ amount of solvent was evaporated in rotatory evaporator at 40^{o}C. Reaction mixture was neutralized by $NaHSO_4$ and extracted with ethyl acetate (3 x 25 ml). The combined layer were washed with brine and dried over Na_2SO_4 and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (7: 3) as eluent gave compound **74** (0.826 gm) as a white solid.



74

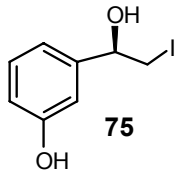
Yield: 90 %

White solid: M.P. 105-106^{o}C

IR (Nujol): cm^{-1} 3329, 3100, 1590, 1485, 1270.

^{1}H NMR (200 MHz, $CDCl_3$ one drop DMSO-d_6): δ 2.40 (s, 3H), 3.90-4.15 (m, 3H), 4.90 (dd, J= 4.00 and 8.50 Hz, 1H), 6.80-7.21 (m, 4H), 7.40 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H).

Synthesis of (*R*)-3-(1-hydroxy-2-iodoethyl)-phenol (75): To a solution of tosyl compound **74** (0.75 gm, 2.4 mmol) in acetone (10.0 ml) was added sodium iodide (3.626 gm, 24.0 mmol) and reaction mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature and solvent was evaporated and water (5.0 ml) was added and extracted with ethyl acetate (3 x 20 ml); the combined layer were washed with water and dried over sodium sulfate (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (4: 1) as eluent gave the iodo compound **75** (0.63 gm) as a white solid (decomposes at room temperature).



75

Yield: 98 %

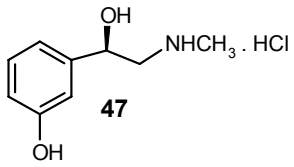
White solid: M.P. 122-124^oC

$[\alpha]_D^{25}$ = -16 (*c* = 0.16, $CHCl_3$)

IR (Nujol): cm^{-1} 3320, 3100, 1590, 1480, 1270.

^1H NMR (200 MHz, $CDCl_3$ + two drop DMSO-d_6): δ 2.25 (bs, 1H), 3.34-3.53 (m, 2H), 4.80 (dd, J= 4.00 and 8.50 Hz, 1H), 6.80-7.21 (m, 4H).

Synthesis of (*R*)-phenylephrine hydrochloride (47): To a solution of iodo alcohol **75** (0.60 gm, 2.227 mmol) in THF (8.7 ml) was added methylamine (8.7 ml, 40 % aqueous solution, 112.53 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated in rotatory evaporator at 40^oC to give (*R*)-phenylephrine **76** (0.371 gm) in 98 % yield. (*R*)-Phenylephrine **76** (0.35 gm) was dissolved in methanol (2.5 ml) and methanolic HCl was added and solution was refluxed for 1 h. The evaporation of solvent gave viscous liquid which was recrystallized with isopropanol to furnish (*R*)-phenylephrine hydrochloride **47** (0.405 gm) in excellent yield.



47

Yield = 90 %

White solid: M.P. 141-142°C [Lit.[39] 141-145°C]

$[\alpha]_D^{25}$ = - 45.0 (*c* = 0.75, H_2O) [Lit.[44] - 44 (*c* = 2.16, H_2O)]

^{1}H NMR (200 MHz, D_2O): δ 2.65 (s, 3H), 3.25 (m, 2H), 5.10 (m, 1H), 6.80-7.32 (m, 4H).

1.4 Spectra

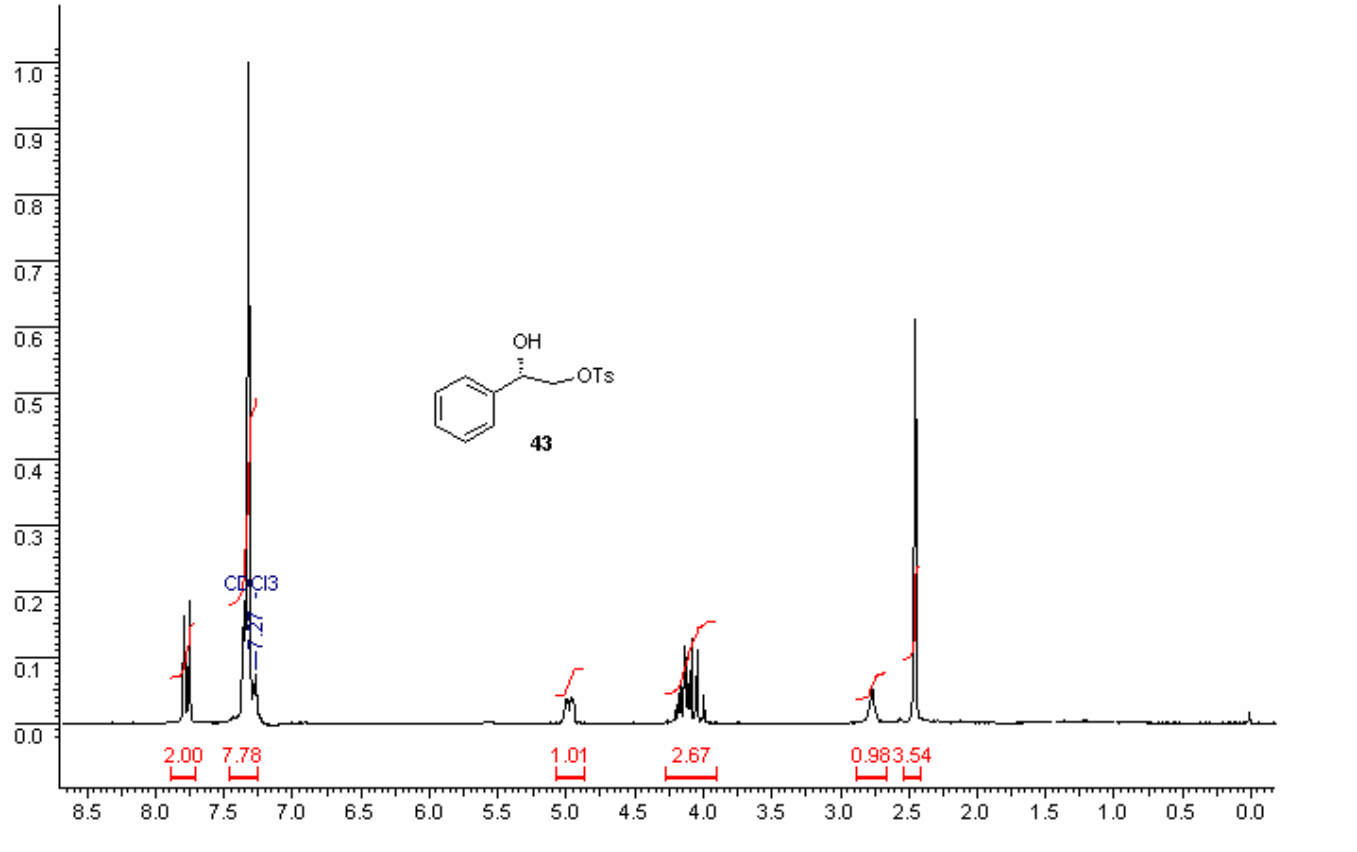


Figure 6: ^{1}H NMR Spectrum of **43**

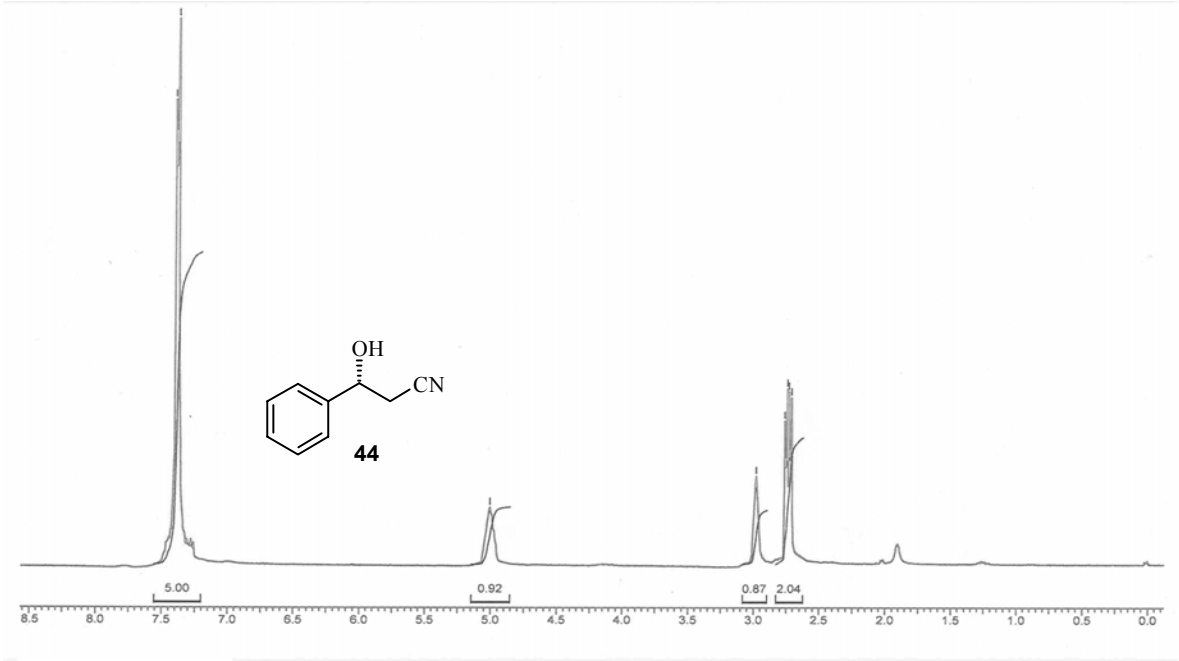


Figure 7: ^{1}H NMR Spectrum of **44**

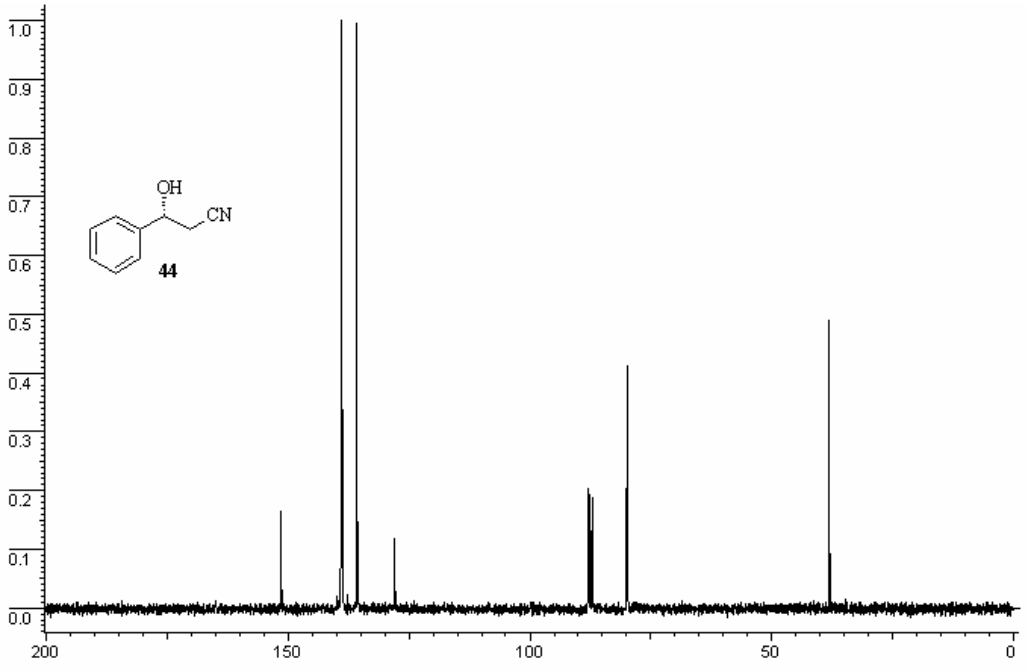


Figure 8: ^{13}C NMR Spectrum of **44**

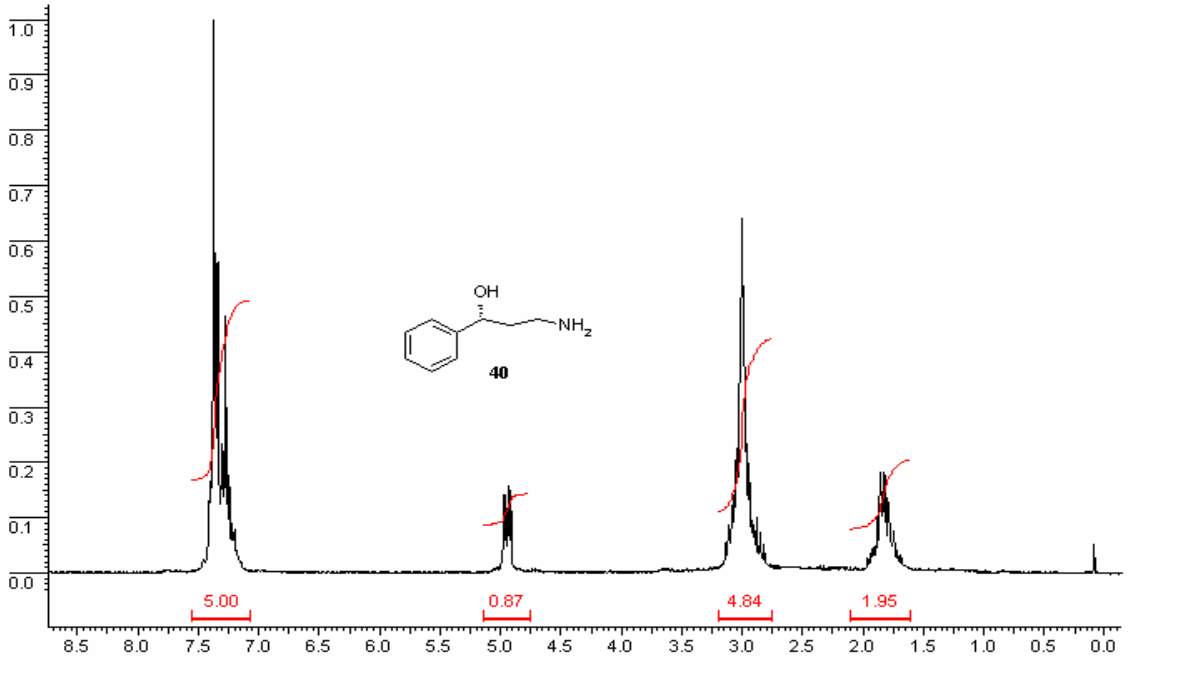


Figure 9: ^{1}H NMR Spectrum of **40**

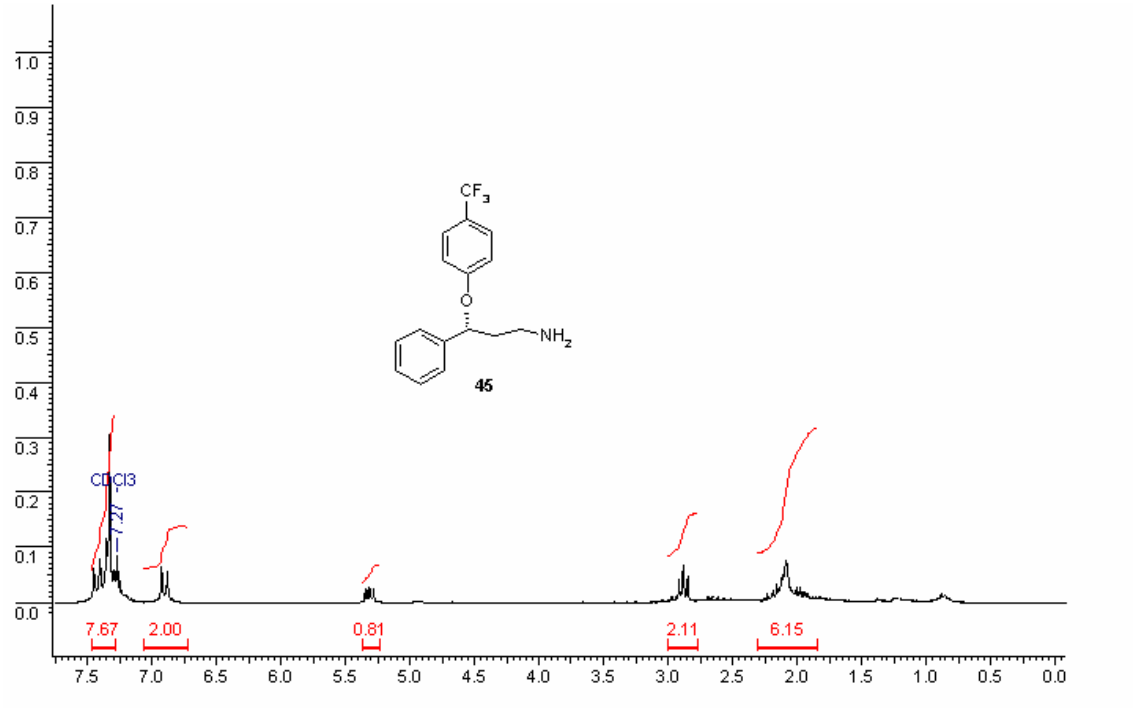


Figure 10: ^{1}H NMR Spectrum of **45**

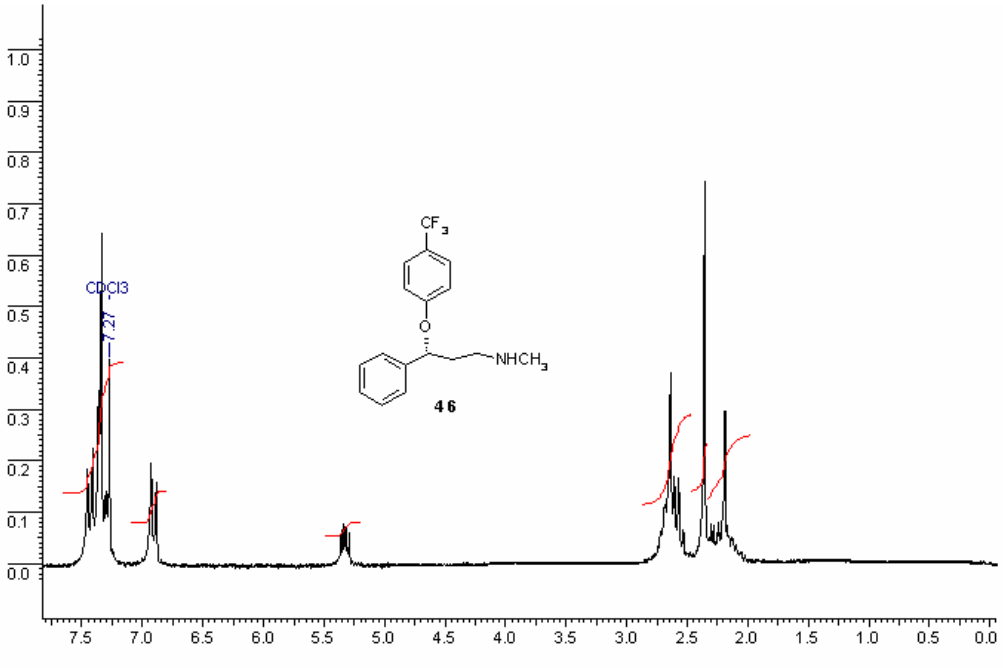


Figure 11: ^{1}H NMR Spectrum of **46**

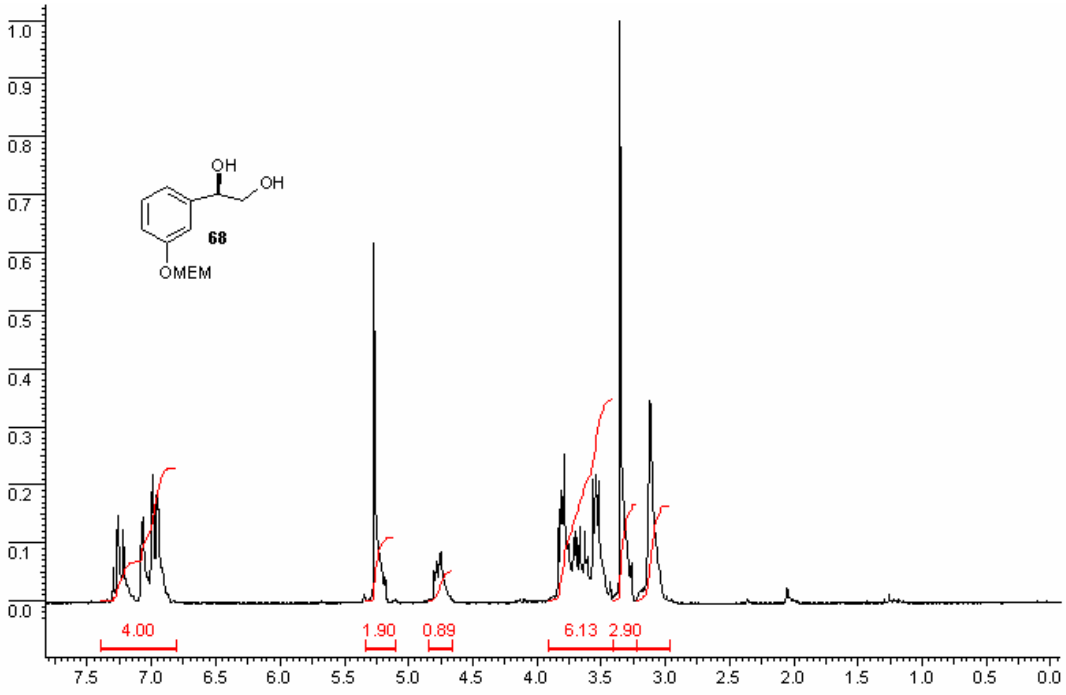


Figure 13: ^{1}H NMR Spectrum of **68**

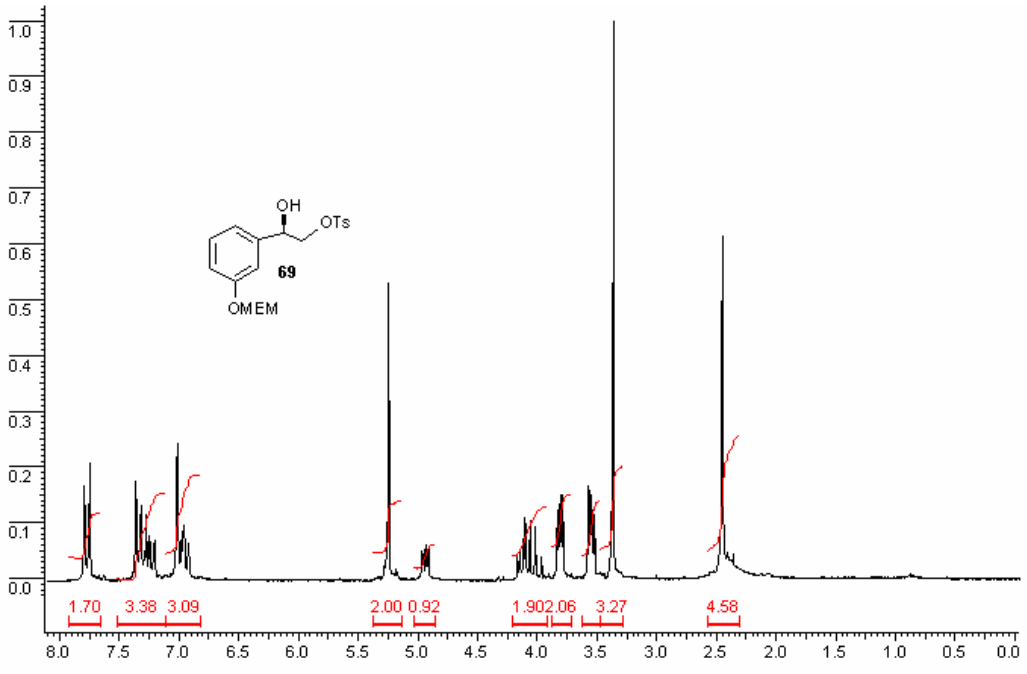


Figure 14: ^{1}H NMR Spectrum of **69**

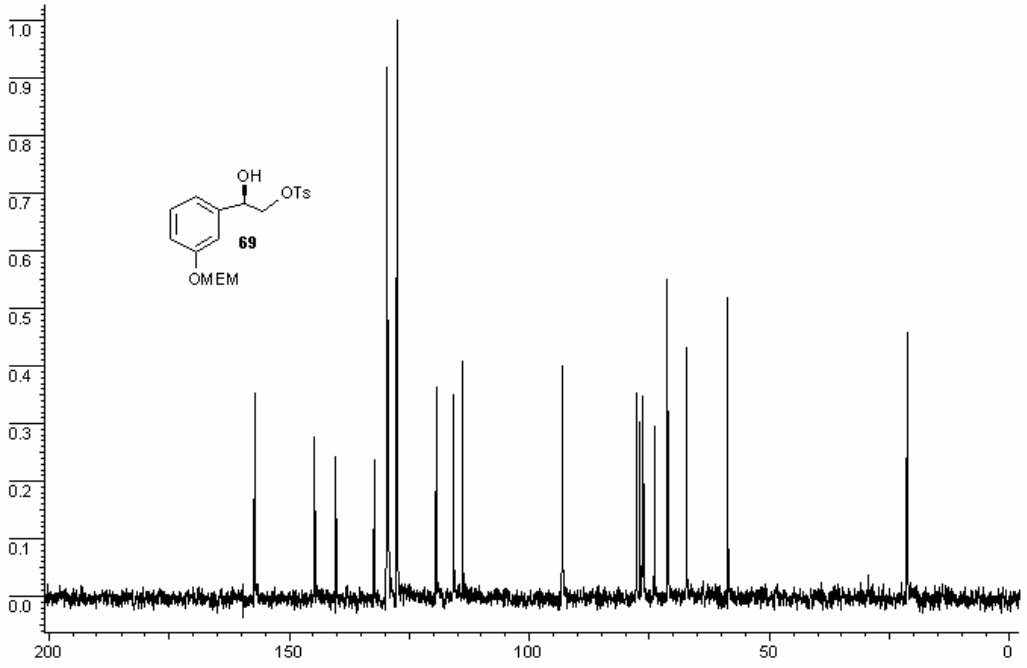
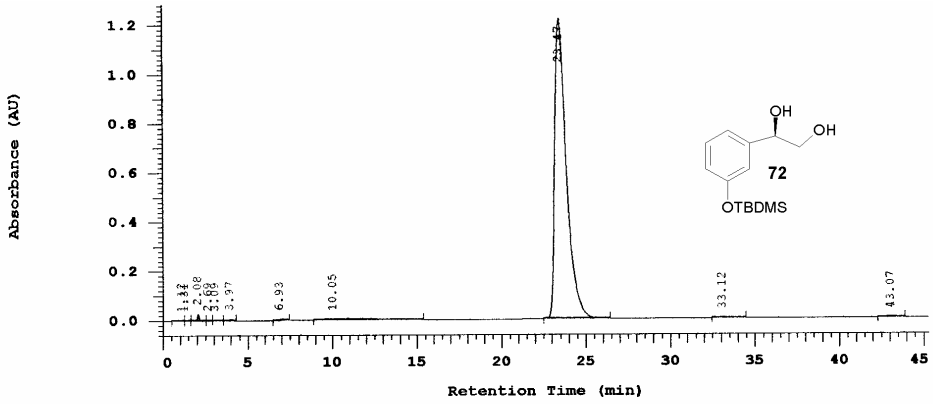


Figure 15: ^{13}C NMR Spectrum of **69**



Chrom Type: Fixed WL Chromatogram, 210 nm
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	1.12	1391	10515	0.036
2	1.31	226	2362	0.008
3	2.08	14582	94133	0.318
4	2.69	1894	12204	0.041
5	3.09	1509	12893	0.044
6	3.97	3306	36892	0.125
7	6.93	2725	41628	0.141
8	10.05	1550	239242	0.809
9	23.47	610321	29084985	98.359
10	33.12	295	14428	0.049
11	43.07	405	20962	0.071
		638204	29570244	100.000

Figure 16: HPLC of **72**, HPLC model: Merck-Hitachi Lachrom PDA system D-7000 series; Column: Lichrospher RP-18 (125 x 4); Mobile Phase: Methanol:Water: (65: 35); Flow: 1 ml/min; λ: 210 nm.

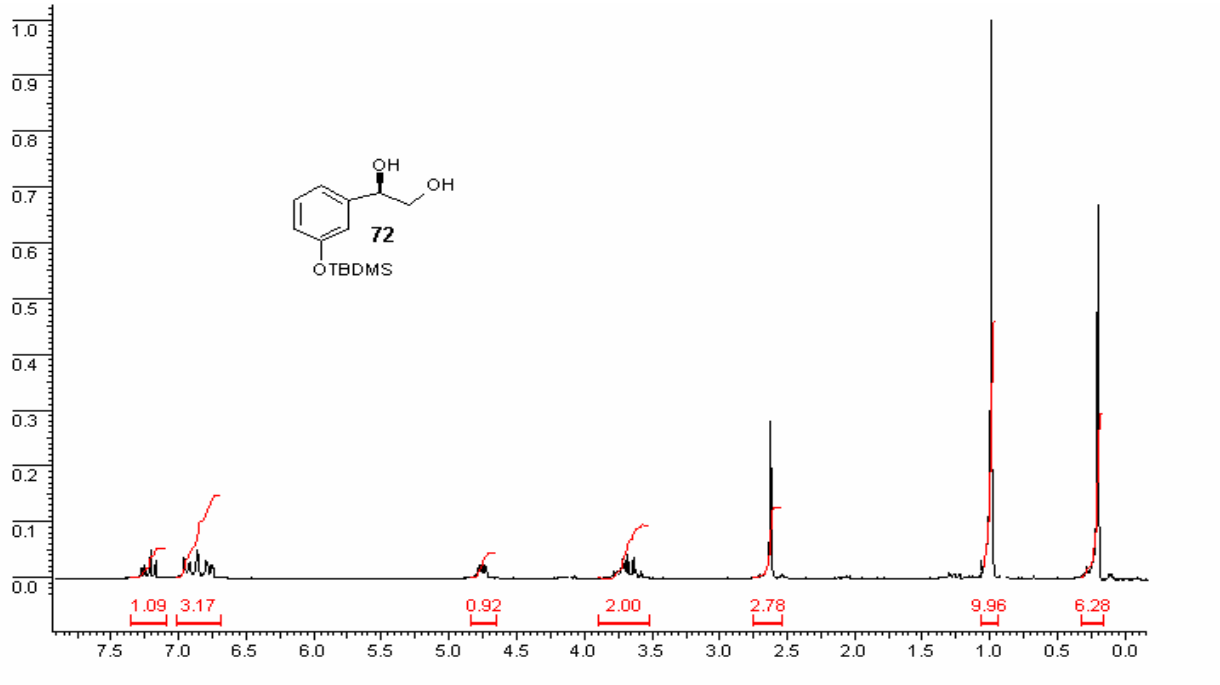


Figure 17: ^{1}H NMR Spectrum of **72**

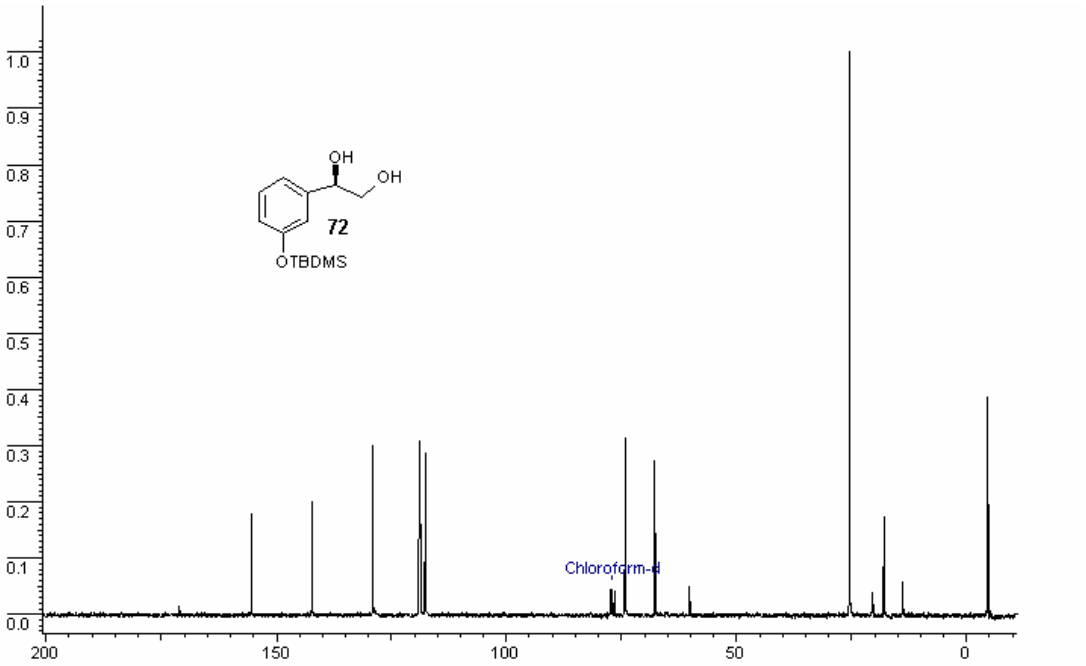


Figure 18: ^{13}C NMR Spectrum of **72**

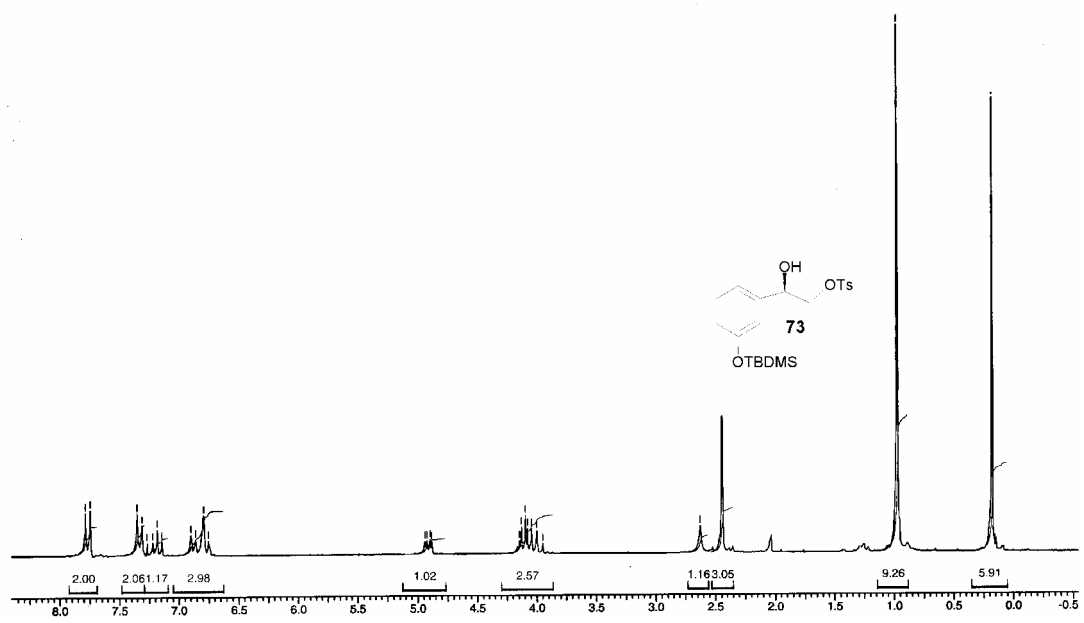


Figure 19: ^{1}H NMR Spectrum of **73**

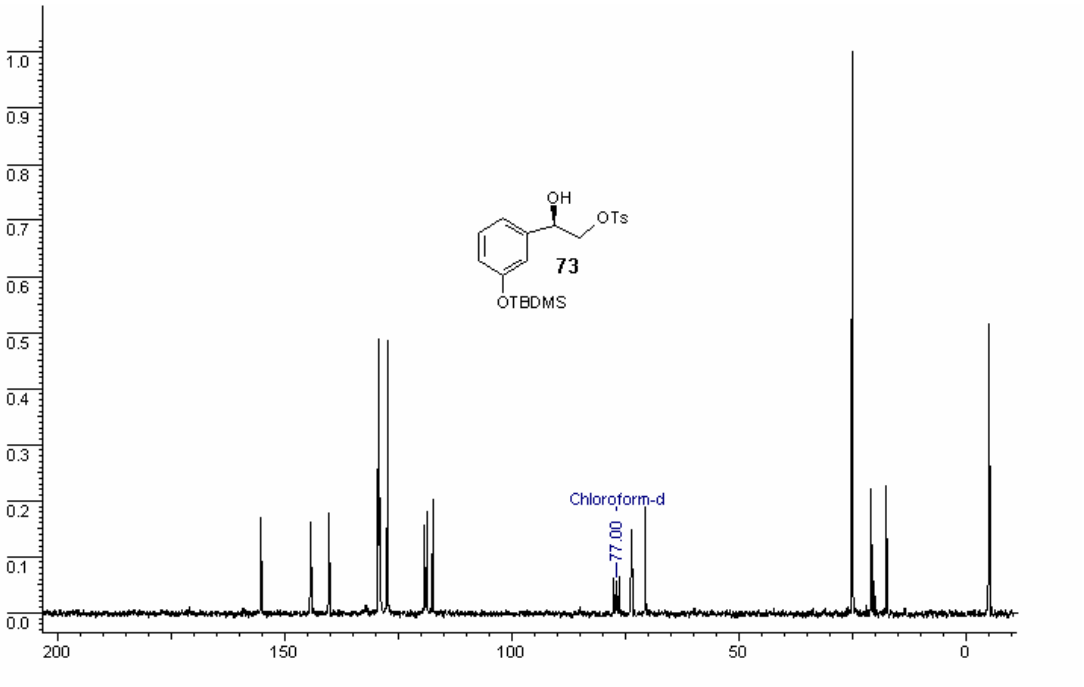


Figure 20: ^{13}C NMR Spectrum of **73**

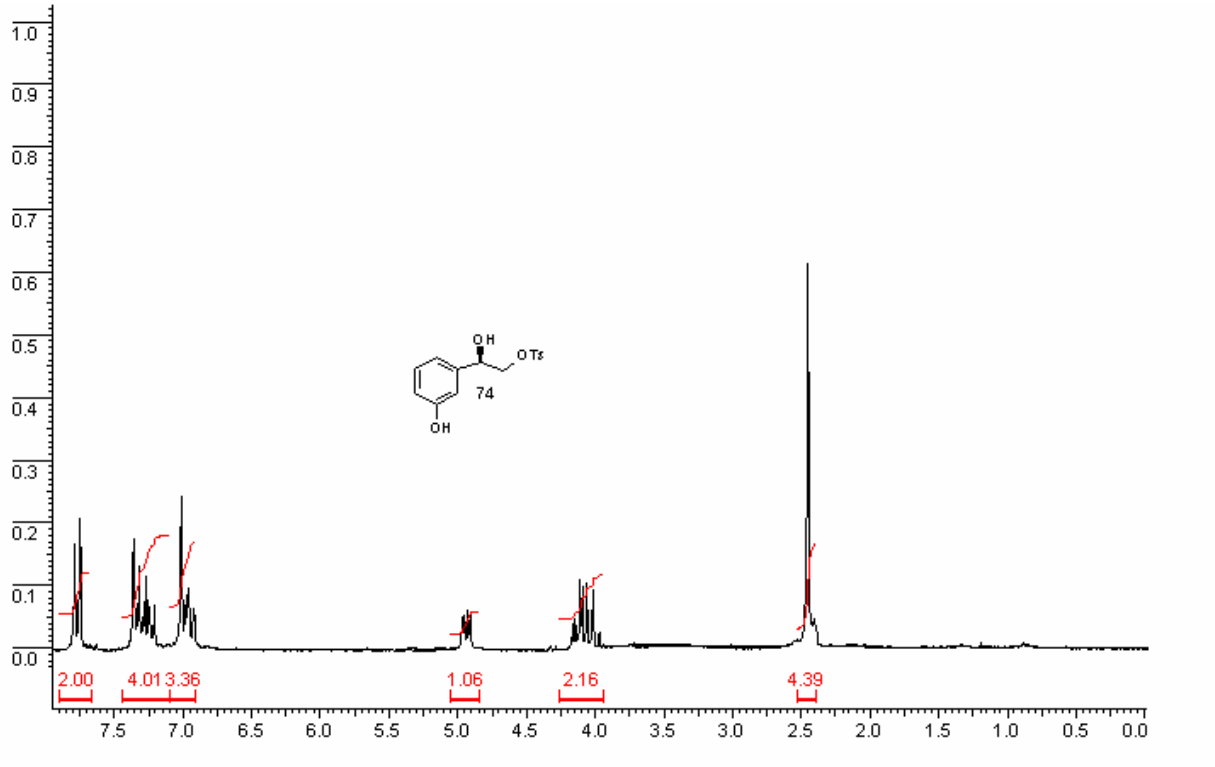


Figure 21: ^{1}H NMR Spectrum of **74**

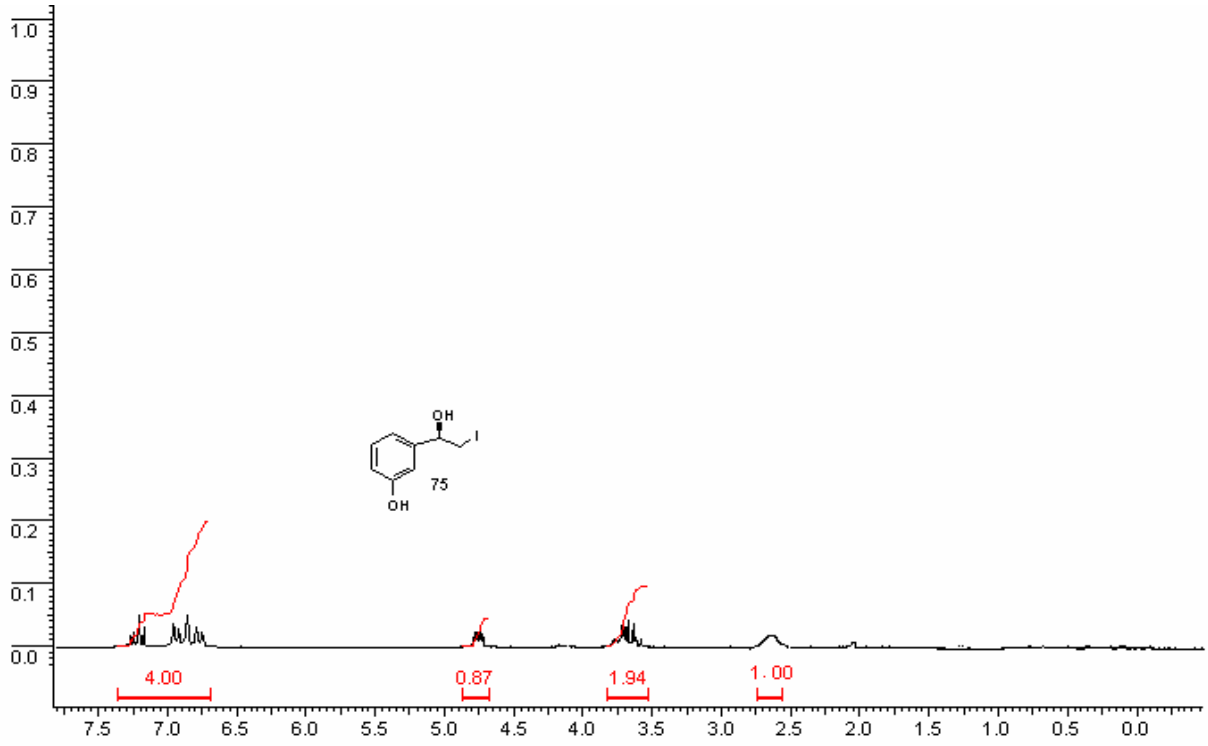


Figure 22: ^{1}H NMR Spectrum of **75**

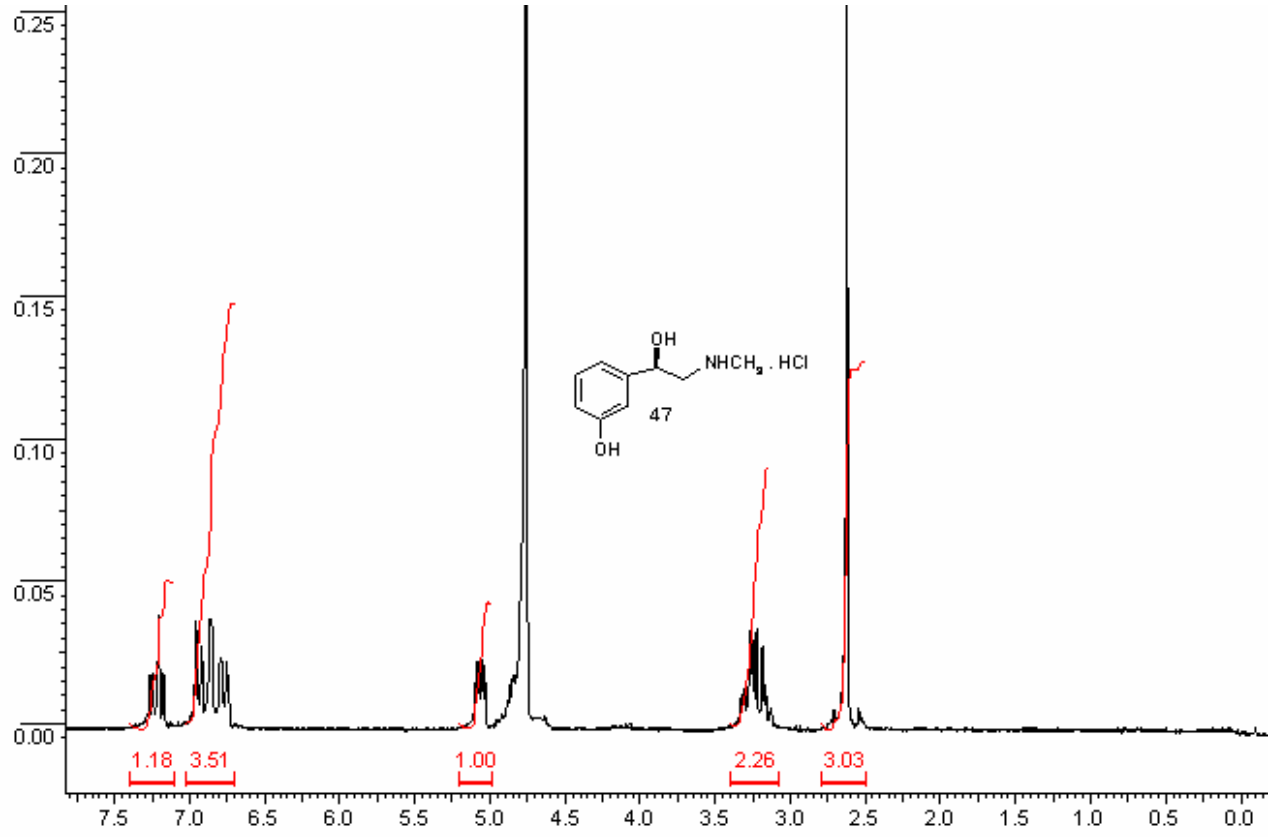


Figure 23: ^{1}H NMR Spectrum of **47**

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CHAPTER 2

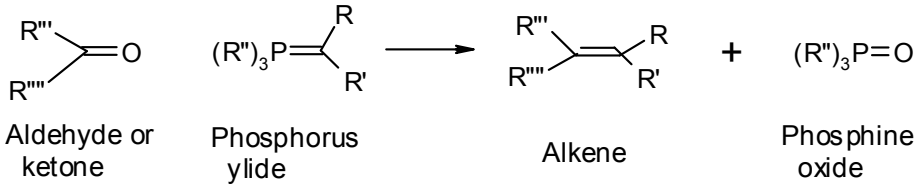
WITTIG - HORNER APPROACH AND HECK COUPLING REACTION TOWARDS THE SYNTHESIS OF Z-TAMOXIFEN AND MINTLACTONE

2.1 SECTION A

General Introduction about Wittig Reaction

2.1.1 Introduction

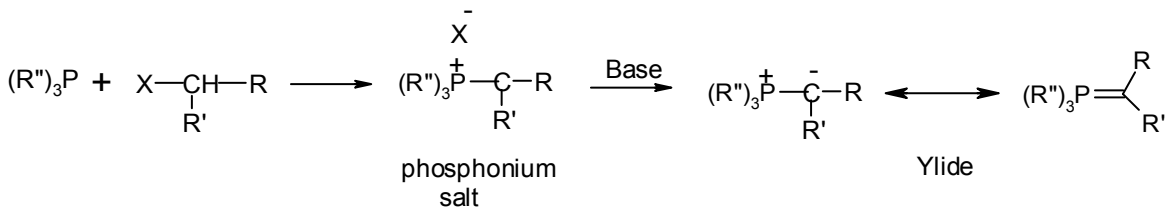
There was a time in organic chemistry when the olefination of ketones and aldehydes was faced with some trepidation. Because of limited synthetic methods, 30 years ago, the chemist had to contend with two isomer problems, that of double bond position and geometry. Landmark papers[1, 2] published by Wittig and co-workers in the early 1950s disclosed a means for the preparation of alkenes with unambiguous positioning of the double bond, based on the reaction of aldehydes or ketones with phosphonium ylides (Scheme 1). Because of its effectiveness and generality, the Wittig reaction became widely used and there by changed the course of olefin synthesis for all time.[3] Indeed, the development of the Wittig reaction helped to usher into modern era of organic synthesis. Using Wittig reaction, the problem of positional selectivity, stereoselectivity and chemoselectivity faced by synthetic organic chemist, which are of paramount importance could be solved.[4]



Scheme 1

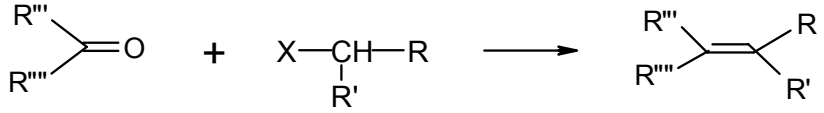
In the Wittig reaction an aldehyde or ketone is treated with a phosphorus ylide (also called a phosphorane) to give an olefin (Scheme 1). According to general reactivity there are three types of ylides (i) stabilized ylides strongly conjugated with electron-withdrawing

substituent at α-position, is more stable, usually favor E-alkenes (ii) semistabilized (moderate) ylides have mild conjugating substituents and (iii) nonstabilized ylides lack such functionality and usually favor Z-alkenes. Phosphorus ylides, which are hybrids of two canonical forms, are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salt are usually prepared from the phosphine and an alkyl halide (Scheme 2).



Scheme 2

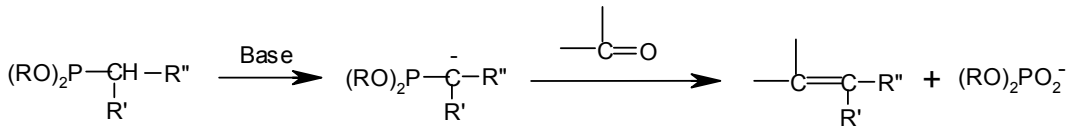
The overall sequence of three steps may be called the Wittig reaction, or only the final step. The phosphonium salt are most often converted to the ylides by the treatment with a strong base such as butyllithium, sodium amide, sodium hydride, or a sodium alkoxide and weak base may be used if the salt is acidic enough. The conversion of phosphonium salts to ylides is apparently a simple acid-base reaction but at least with alkyllithiums, it must be more complicated than that, since, in addition to a simple proton abstraction, exchange group can occur. The $Ph_3P^+CH_3\ Br^-$ with methyllithium gave 26 % benzene.[5]



Scheme 3

The Wittig reaction is very general in the sense that it tolerates variety of functional groups. Though it readily reacts with aldehydes and ketones in some cases it also react with esters but at a very slow rate when compared to aldehydes and ketones.[6]

The Wittig reaction has also been carried out with other types of ylides, the most important being prepared from phosphonates[7] (Scheme 4).



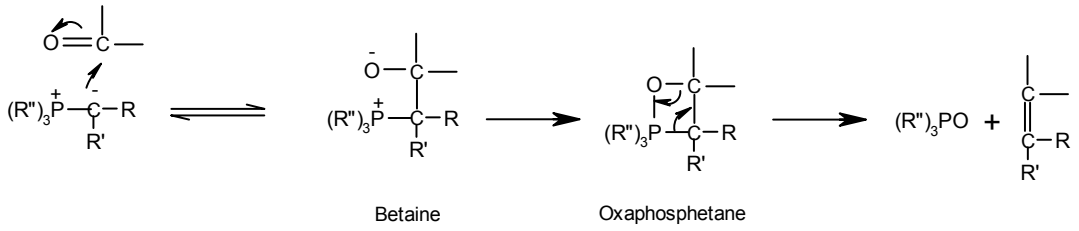
Scheme 4

This method, is known as the Horner-Emmons reaction[8] and it has several advantages over the use of phosphoranes. These ylides are more reactive than the corresponding phosphoranes and often react with ketones which are inert to phosphoranes when R` is an electron-withdrawing group. In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the olefin product. Phosphonates are also cheaper than phosphonium salts and can be easily prepared by the Arbuzov reaction.[9]

2.1.2 Phosphonium Ylides

2.1.2.1 Stereochemistry and Mechanism

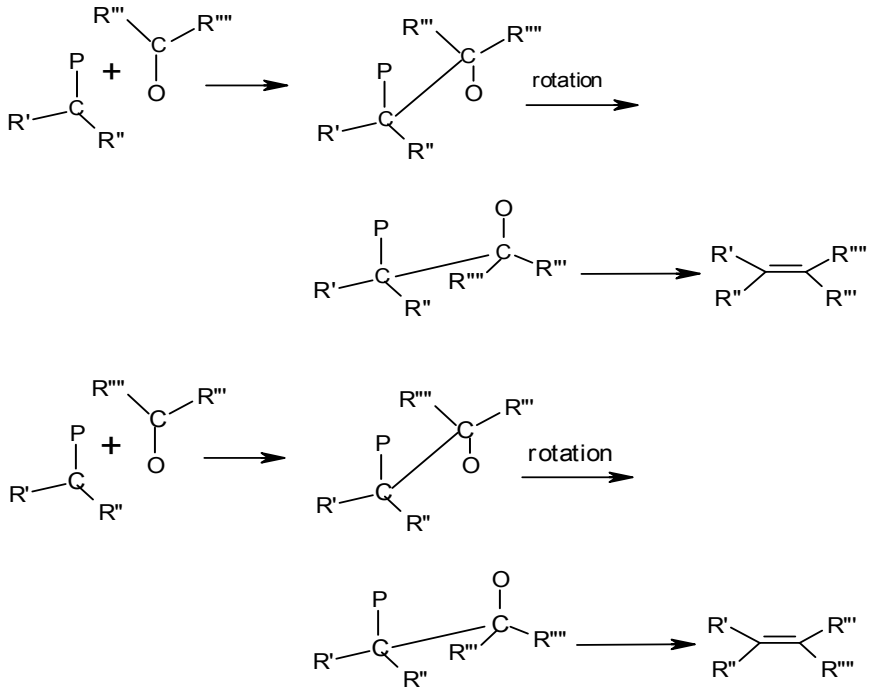
The mechanism of the key step of the Wittig reaction consists of at least two to three steps (Scheme 5).



Scheme 5

In reactions in which there is a betaine intermediate, it would be interesting to examine whether step 1 is faster than steps 2 and 3 and vice versa. It is established that the ylide is increased in stability (and decreased in reactivity) by the presence of electron-withdrawing groups on the carbon. Another factor is the presence of electron donating groups on the phosphorus. These groups stabilized the ylide canonical form (of the resonance hybrid) at the expense of C=P form by decreasing the positive charge on the phosphorus. This increases the reactivity of the ylide and explains, for example, why trialkyl phosphorus ylides are more reactive than the triaryl variety. On the other hand, once the betaine is formed, these factor work in precisely the opposite direction. Electron-withdrawing groups on the carbon increase the reactivity of the betaine because they stabilize (by conjugation) the newly forming double bond; and electron donating substituents on the phosphorus decrease the reactivity of the betaine since they decrease the positive charge on the phosphorus and make it less attractive to the negative oxygen. We can see from all this that with ylides containing electron donating groups on the phosphorus, the first step will be faster than the subsequent ones. In some cases, indeed, it has proved possible to isolate the betaine. However, if there is electron-withdrawing groups on the carbon, the first step will be slower than the subsequent ones and it should be much more difficult to isolate the

betaine. Till today no such betaine has been isolated. Thus, it may be difficult to isolate a betaine in cases where steps 2 and 3 are simultaneous.



Scheme 6

The cis-trans ratio of the product can often be changed by a change in solvent or by the addition of salts. It has been found possible to control the reaction so that the cis or the trans olefin is the main product.[10 a-f] Factors responsible for governing cis and trans products are described in Table 1. Another way of controlling the stereochemistry of the product is by use of the phosphonic acid bisamides. In this case the betaine does not undergo spontaneous elimination but when treated with water gives the β-hydroxyphosphonic acid bisamide, which can be crystallized and then cleaved to olefin.[10g-h] In reactions where the betaine intermediate is present in the solution, it is possible to extend the chain further if hydrogen is present α to the phosphorus.

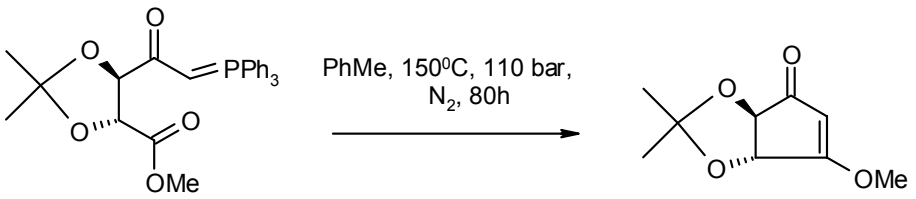
Table 1: Factors responsible for E- and Z-Products in the Wittig reaction

Entry	Thermodynamic control (E-product)	Kinetic control (Z-product)
1	Elevated temperature	Low temperature
2	Nonpolar, protic solvent	Polar, aprotic solvent
3	Betain stabilizing salts e.g.	Lewis base
	$Li^{+}BPh_4^{-}$	Salt free solvents
4	Carbanion stabilization	No carbanion stabilization
5	Electron rich phosphorus atom	Electrophilic phosphorus atom
6	Excess base	

2.1.2.2 Selected Synthetic Applications

Wittig reaction offers some important advantages over the stereoselective synthesis of olefins by other methods. Herein a few recent applications are documented below.

The Wittig reaction with esters are reported for intra- and intermolecular processes and that forms heterocyclic or carbocyclic products.[11] Bestmann and co-workers reported the cyclization of tartrate-derived phosphorane **1** into cyclopentenone **2**, the starting material for the nucleoside (-)-neplanocine A (Scheme 7).[12]

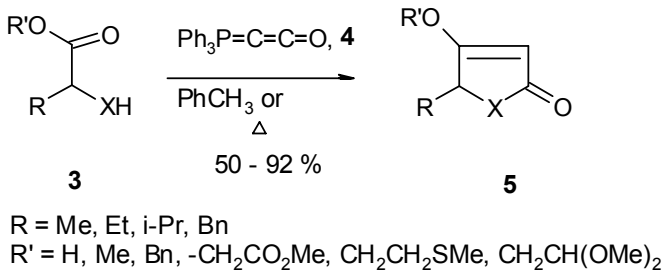


1 **2**

Scheme 7

Schobert[13a, b] developed a method for the synthesis of tetronates **5** (X = O), tetramates (X = NH) and thiotetronates (X = S) by the reaction of α-hydroxy, α-amino or α-sulfanyl

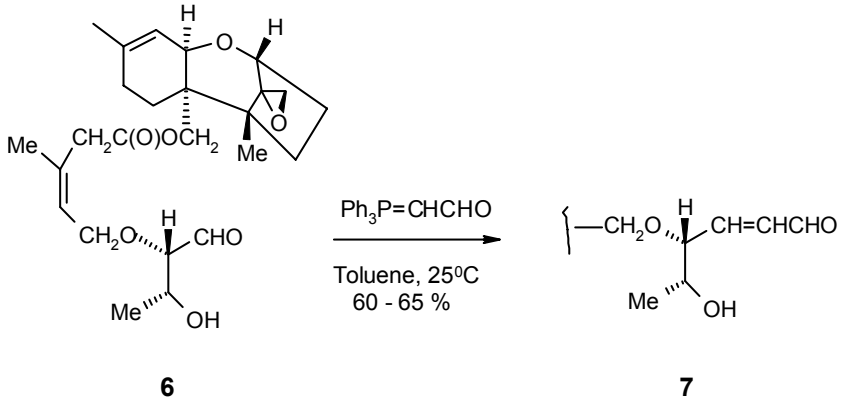
carboxylate **3** with ketenylidene(triphenyl)phosphorane **4** for the formation of unsaturated lactone **5** (Scheme 8). This reaction was then extended to the synthesis of δ-lactam, quinolone, thiocoumarin and coumarin.



Scheme 8

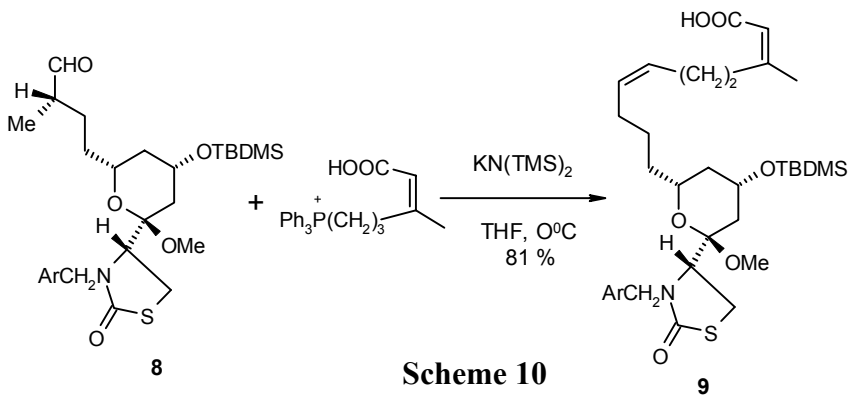
Similarly Wittig reaction was carried out with lactones, thiol ethers, amides, anhydride, imides and carbonates.[11]

In the synthesis of two macrocyclic trichothecaniods, baccharin B5 and roridin E, Still et al.[14] performed a Wittig reaction on **6** with Ph_3P=CHCHO to get **7**, the E-isomer of which was a precursor for a phosphonate-based macrocyclization (Scheme 9).



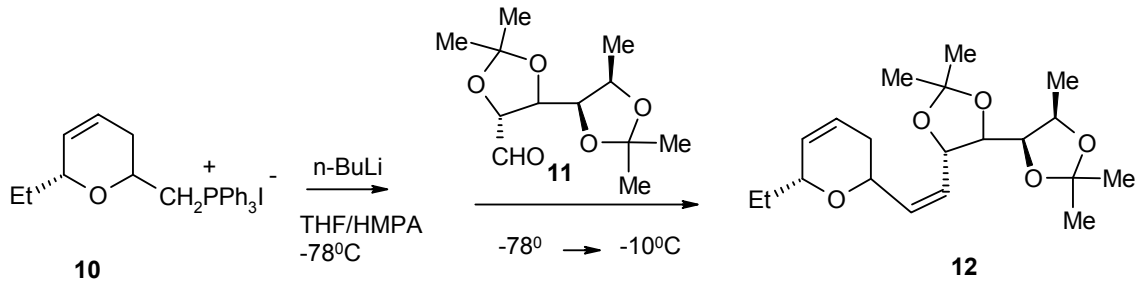
Scheme 9

The synthesis of latrunculin B relied on Z- selective coupling of **8** and **9** as a key step (Scheme 10).[15]



Scheme 10

A convergent synthesis of (-)-anamarine, **12** from D-glucose relied on linkage of the ylide **10** with **11** (Scheme 11).[16] Since ylide formation with β-alkoxyphosphonium salt is proven to elimination chemistry[17] care must be exercised in the choice of reaction conditions.



Scheme 11

2.1.3 Phosphonate Carbanions

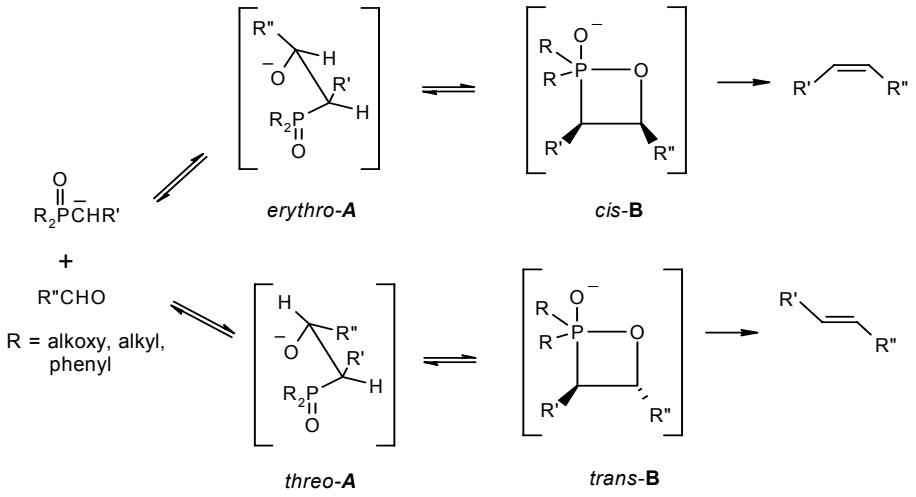
Horner and co-worker were the first to react phosphoryl-stabilized carbanions with aldehydes and ketones to produce olefins.[8a, b, 7a, b] The carbanions used were derived from either diphenylphosphine oxides or diethylbenzylphosphonate. In these studies, benzylic carbanions were found to combine with benzophenone to give olefin in good yields. However, the advantages of phosphonates in alkene synthesis were not demonstrated until later. Indeed, the 1961 paper by Wadsworth and Emmons served to popularize this method in the organic synthetic community.[18] In the ensuing years, there has been confusion about

whom to credit for this class of reaction, as the names "Horner" Wadsworth", Emmons", "Wadsworth-Emmons", and "Horner-Wittig" have appeared as descriptors with regularity. For the purpose of our current discussion, phosphonate-mediated olefinations will be referred as the "Horner-Wadsworth-Emmons" (more concisely "HWE") reaction.

Several types of phosphonates have been used in the synthesis[19] such as nonstabilized phosphonates, phosphonate bearing an α-carbonyl or cyano group, phosphonate bearing both α- and γ-carbonyl groups, vinyl and aryl stabilized phosphonates, bisphosphonate and related reagents and heteroatom-stabilized phosphonates.

2.1.3.1 Mechanistic Aspects

The mechanism for the HWE reaction, related to that of the Wittig reaction (2.1.2.1) is shown in Scheme 7 for an aldehyde condensation (Scheme 12).



Scheme 12

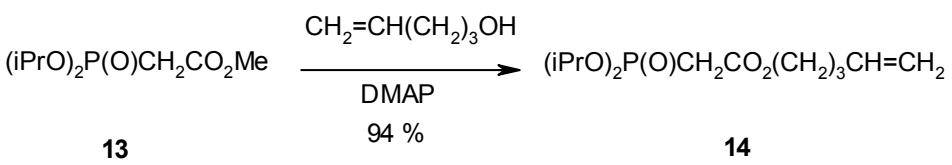
The phosphoryl-stabilized carbanion attacks the carbonyl in a step-wise manner, to give oxyanion intermediate **A**, which then decomposes via a transient four-centered intermediate,

B, to yield olefin. The stereochemistry is determined by a combination of the stereoselectivity in the initial carbon-carbon bond forming step and perhaps, reversibility of intermediates (e.g., **A** and **B**). Although direct observation of intermediates in the HWE reaction has not been generally possible, there are several kinetic and spectroscopic studies that shed light on the course of this process. There are also several reports that demonstrate the reversible dissociation of originally formed HWE aldolates. In reaction of phosphine oxides, investigated in detail by Warren and colleagues,[20] erythro-**A** and threo-**A** can be captured by protonation and isolated as stable β-hydroxy phosphine oxides examples of which have been independently and stereospecifically converted to the respective (Z)- and (E)-alkenes.

2.1.3.2 Preparation of Phosphonate Reagent

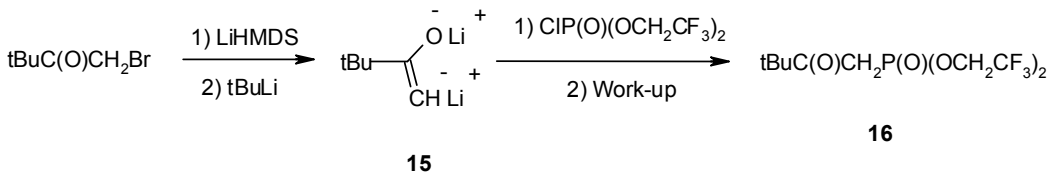
Phosphonate can be readily prepared by Arbuzov[21] or Micharlis-Becker[22] reactions. Several efficient methods have appeared in the last 20 years. Only references that bear on the preparation of HWE reaction are included.

An efficient ester-exchange reaction has been developed by Takano and associates for the preparation of differentially substituted phosphonoacetates.[23] For example heating of phosphonate, **13** and 4-penten-1-ol with a catalytic amount of DMAP resulted in transesterification to give **14** (Scheme 13).



Scheme 13

Alternatively, different ester groups can be incorporated by reaction of $(MeO)_2P(O)CH_2Cl$ with alcohols. A DCC coupling was employed to place a complex carbon skeleton in the carboxylic ester of a phosphonoacetate in 86 % yield enroute to brefeldin A.[24] The Arbuzov synthesis of β-keto phosphonates does not work well, so several other methods have been developed to access these compounds such as the reaction of $(EtO)_2P(O)COCl$ with cuprate[25a] and $(RO)_2P(O)CH_2Cu$ with acid chlorides.[25b] β-Keto phosphonates, **16** can also be prepared by the combination of dianions, **15** derived from β-bromo ketones with dialkyl chlorophosphonates (Scheme 14).[26]



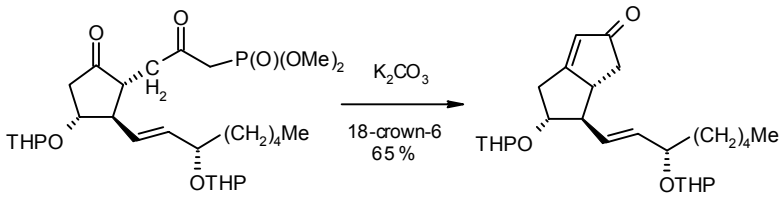
Scheme 14

2.1.3.3 Intramolecular Reactions

The intramolecular HWE reaction has become an indispensable means of cyclization, particularly for macrocyclic ring systems. A review covering intramolecular Wittig reactions, including those of phosphorane and phosphoryl-stabilized carbanions, appeared in 1980.[27] Although the HWE reaction had been used to prepare five- and six-membered rings early on,[27, 28] the first application to macrolide construction (a 16-membered-ring) appeared only as recently as 1978,[29] in a synthesis of vermiculine.

The use of lithium bases in THF with ca. 1 % HMPA was advanced as a reliable method for macrolide synthesis.[30] Cyclization has also been effected by mild base (DBU and LiCl)[31-35] or crown ether catalysis.[12, 36-39] The crown ether catalysis is an important discovery, which has proven crucial in some macrocyclizations.[36a, b] For example, the use of 18-crown-6,

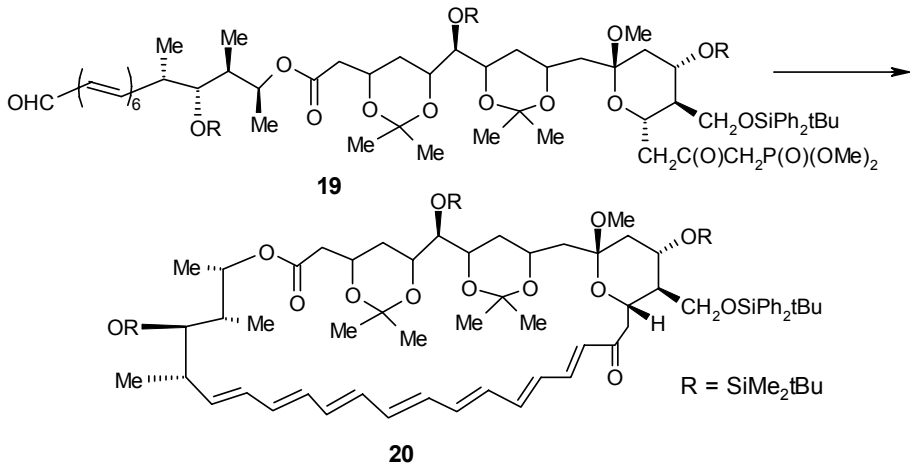
introduced for intramolecular reactions by Aristoff et al.,[40] played an essential role in the conversion of ketone **17** to bicyclic, **18**, an intermediate in the synthesis of 6α-carbaprostaglandin I_2 (Scheme 15).



17 **18**

Scheme 15

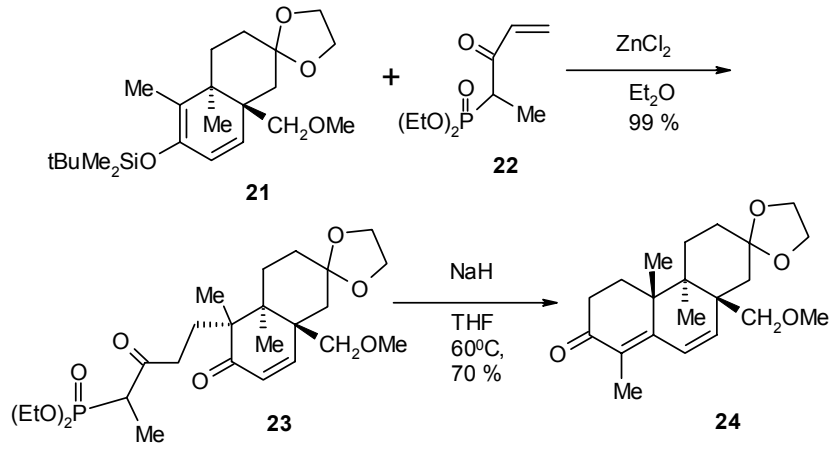
The geometry of the new double bond in intramolecular HWE reactions is usually E. However, in cases where large rings are being formed, one can often find considerable amounts of the Z isomer.[18] Polyene precursor **19** was smoothly cyclized to 38-membered product **20** (70-80 % yield) in Nicolaou's synthesis of amphotericin B (Scheme 16).[35, 41] This reaction was performed by using either K_2CO_3 / 18-crown-6 (in toluene at 0.001 M) or DBU / LiCl (in acetonitrile at 0.01 M).



Scheme 16

Nicolaou concluded that "the intramolecular keto phosphonate-aldehyde condensation reaction is a most powerful method for constructing macro rings".[41c]

As an alternative to the Robinson annulation, **22** was condensed with silyl enol ether **21** to yield **23**, which underwent intramolecular HWE reaction to **24** (Scheme 17).[42]



Scheme 17

2.1.4 Conclusion

Thus, the Wittig olefination and HWE reaction have found widespread prominence in organic synthesis. They have become a powerful technique for the olefination reaction. With the optimization of reaction conditions, we can fix the geometry of olefins. It has novel contribution to synthetic organic chemistry giving rise to new molecules.

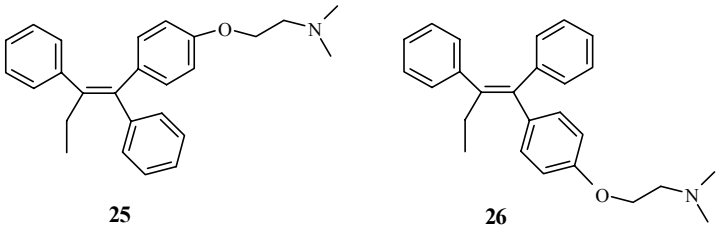
2.2 SECTION B

Synthesis of Anticancer Drug "Tamoxifen"

2.2.1 Introduction

Antiestrogens are a group of compounds, which block at least in part the action of estrogen target tissues. They inhibit uterine growth and the development and growth of estrogen dependent mammary tumors[43] and are effective in the control of other diverse neoplastic diseases as well as controlling and correcting various endocrine disorders.

(Z)–Tamoxifen[44, 45] (ICI –46, 474, Nolvadex), a clinically useful triaryl ethylene, is a synthetic antiestrogenic drug that elicits varied endrogenic effects (Scheme 18). It is powerful non steroidal agonist useful for the treatment of hormone responsive human metastatic breast cancer as well as uterine, ovarian and prostatic neoplasm.[46]



25 **26**

Z-Tamoxifen **E-Tamoxifen**

Scheme 18

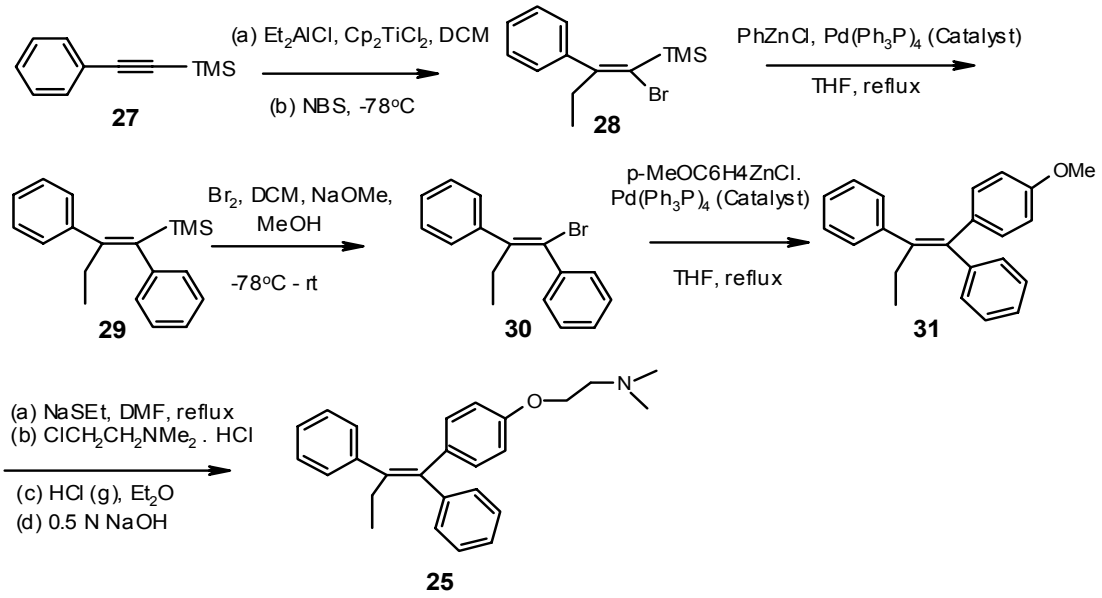
Tamoxifen first synthesized[44] in 1966 by Harper et al. resulted in a mixture of E and Z isomers. Since then several methods of synthesis of this drug have been reported.[47-56] The (E) – tamoxifen, usually referred to as cis – tamoxifen (ICI - 47,699) has no clinical uses and is an estrogen agonist. Since, majority of the synthetic approaches to tamoxifen have been nonstereospecific[47] producing a mixture of Z- and E - isomers which were separated by fractional crystallization techniques or by column chromatography, therefore, an efficient highly stereospecific large scale synthesis of this drug is still desirable.

2.2.2 Review of Literature

Various preparative methods of tamoxifen have been reported. Majority of them suffer with one or other drawbacks providing only the low selectivity for Z-isomer. Some of the important synthetic routes are discussed below.

Miller's et al. (1985)[49] Scheme 19

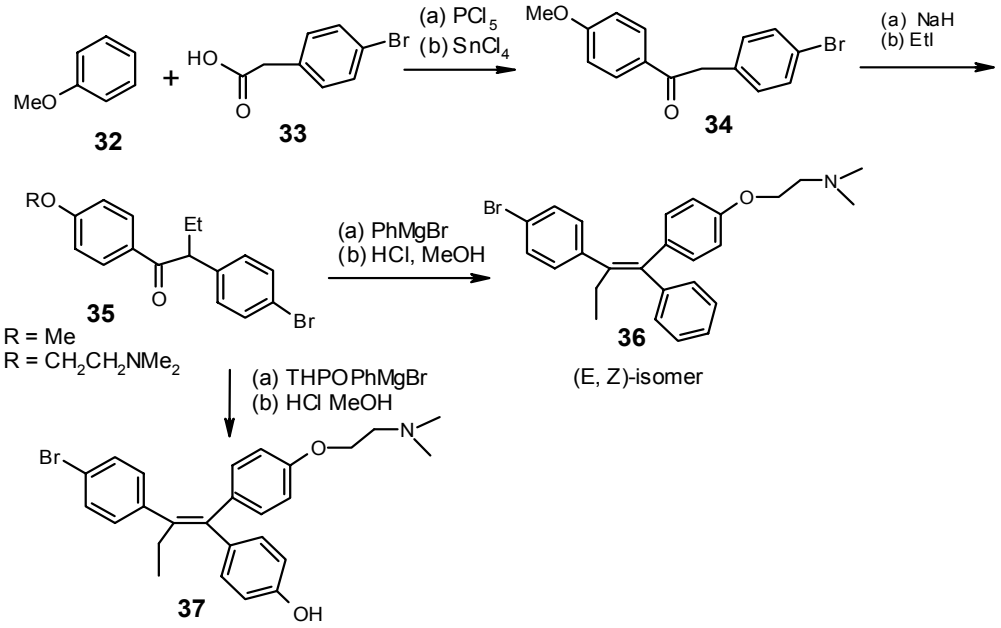
Miller et al. synthesized compound **31** by the carbonylation of phenyl(trimethylsilyl)acetylene **27** with diethylaluminium-chloride-titanocene dichloride followed by two times bromination and subsequent Heck coupling reaction. **31** was transformed into Z-tamoxifen by demethylation and subsequent protection of hydroxyl group (Scheme 19).



Scheme 19

Robertsons et al. (1982)[50] Scheme 20

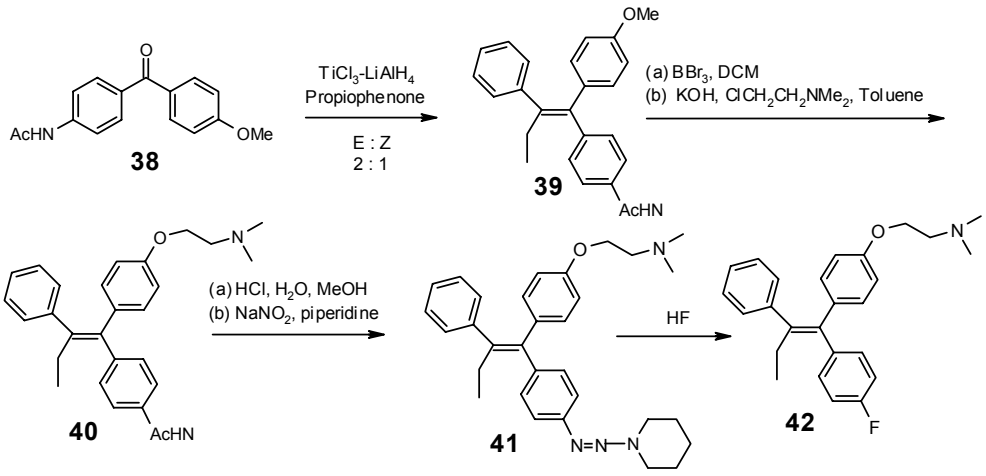
E, Z-Tamoxifen **36** and hydroxytamoxifen **37** were synthesized in a high specific acivity, tritium labeled form by catalytic tritiumhalogen exchange performed on bromate precursor. Acylation of anisole **32** by **33** gave **34**, which on alkylation furnished **35**. The ketone **35** was used as a precursor for the synthesis of derivatives of tamoxifen **36** and **37** (Scheme 20).



Scheme 20

Shani et al. (1985)[51] Scheme 21

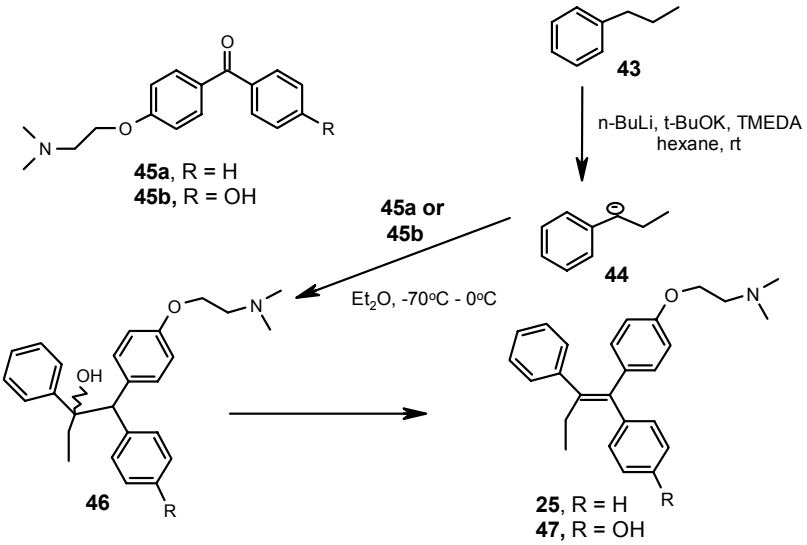
Fluorotamoxifen **42** was prepared by the reaction of ketone **38** and propiophenone using McMurry reagent ($TiCl_3$-$LiAlH_4$) as the key step. The intermediate **39** was converted into **40** by the demethylation and subsequent protection. **40** was transformed into diazo compound **41** which on treatment with HF furnished **42** (Scheme 21).



Scheme 21

Aitken et al. (1995)[52] (Scheme 22)

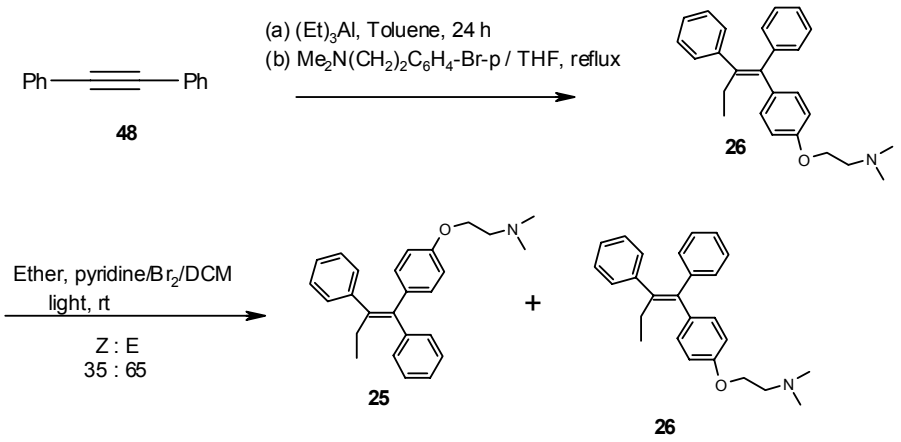
Tamoxifen **25**, and hydroxytamoxifen **47** were synthesized by the regioselective metalation of propylbenzene **43** using n-BuLi-t-BuOK-TMEDA super base combination. The resulting carbanion **44** was condensed with functionalized benzophenone **45** to provide **46** which on dehydration furnished tamoxifen **25** and hydroxytamoxifen **47** (Scheme 22).



Scheme 22

Al-Hassan (1987)[53] Scheme 23

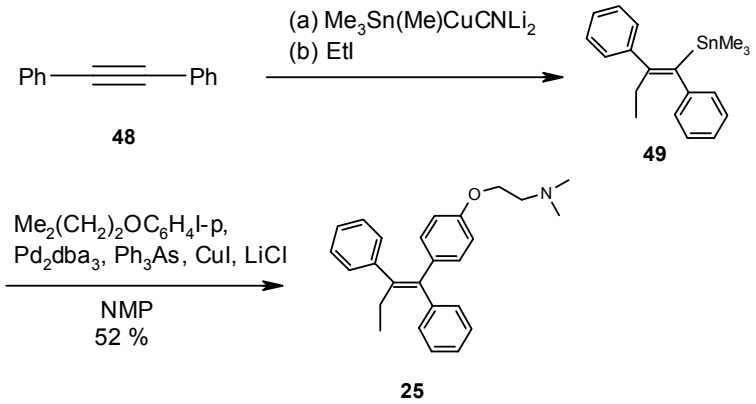
E-Tamoxifen **26** was synthesized from **48** via palladium catalyzed cross-coupling reaction of vinylmetal with 2-(4-bromophenoxy)-1-dimethylaminoethanol (Scheme 23). **26** was converted into **25** via photochemical reaction.



Scheme 23

Cummins (1995)[54] Scheme 24

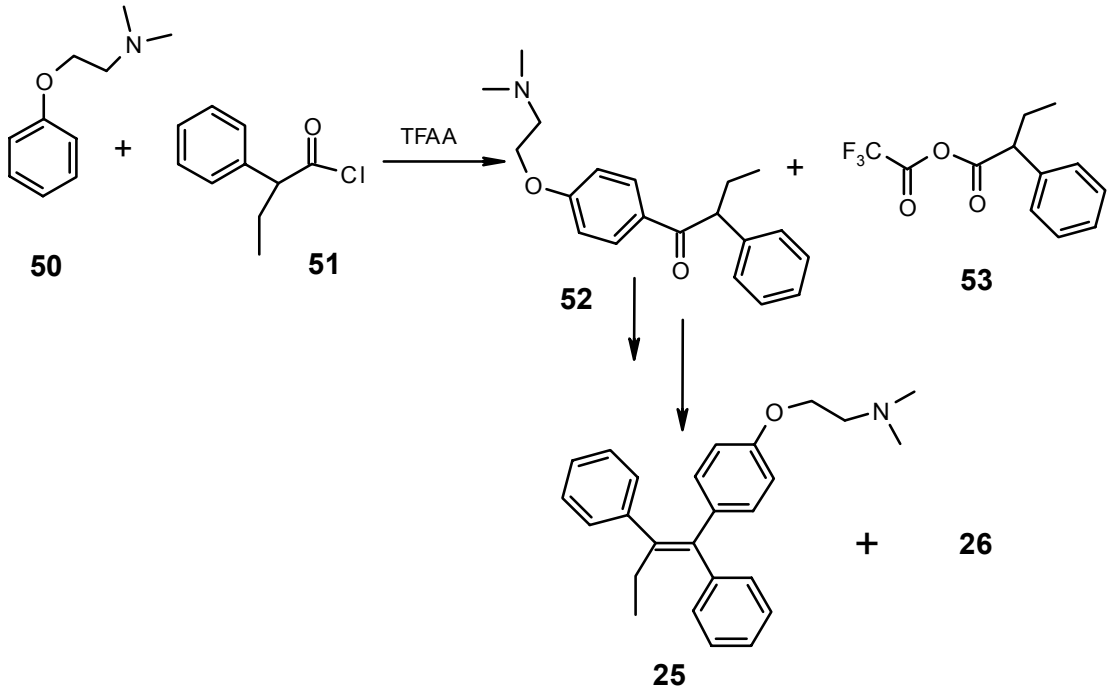
This method described the *trans*-stannylcupration of diphenyl acetylene to 1,2-dimetalstilbene which was elaborated into tamoxifen via palladium catalyzed coupling reaction (Scheme 24).



Scheme 24

Smyth et al. (1997)[55] (Scheme 25)

This approach described the synthesis of tamoxifen by the Friedel-Craft acylation (Scheme 25). A mixed anhydride is used as acylating agent. Compound **50** was converted into **52** by acylation using TFAA and **51** as an acylating agent. **52** was subjected to Grignard reaction followed by dehydration to furnish the target compound **25** and **26**.

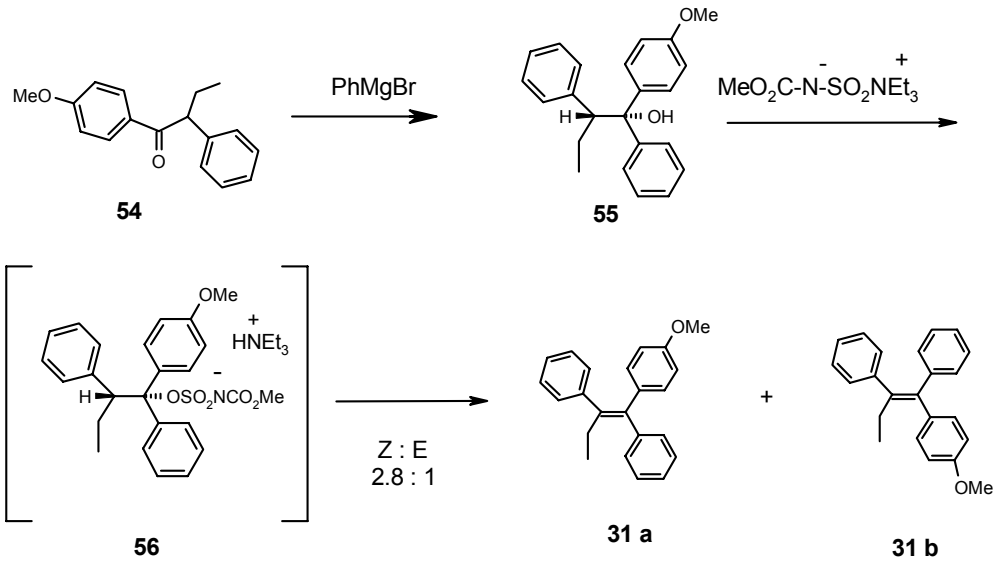


Scheme 25

McCague (1987)[56] Scheme 26

McCague used the acid catalyzed dehydration of triaryl compound **55** to give mainly the Z-isomer **31a** (Scheme 26) by the use of *N,N,N*-triethylammonio-*N*'-methoxycarbonylsulphamidate as a dehydrating reagent. The triaryl compound was

synthesized by the reaction of ketone **54** and phenylmagnesium bromide. **31** is known precursor for tamoxifen, **25** and **26**.



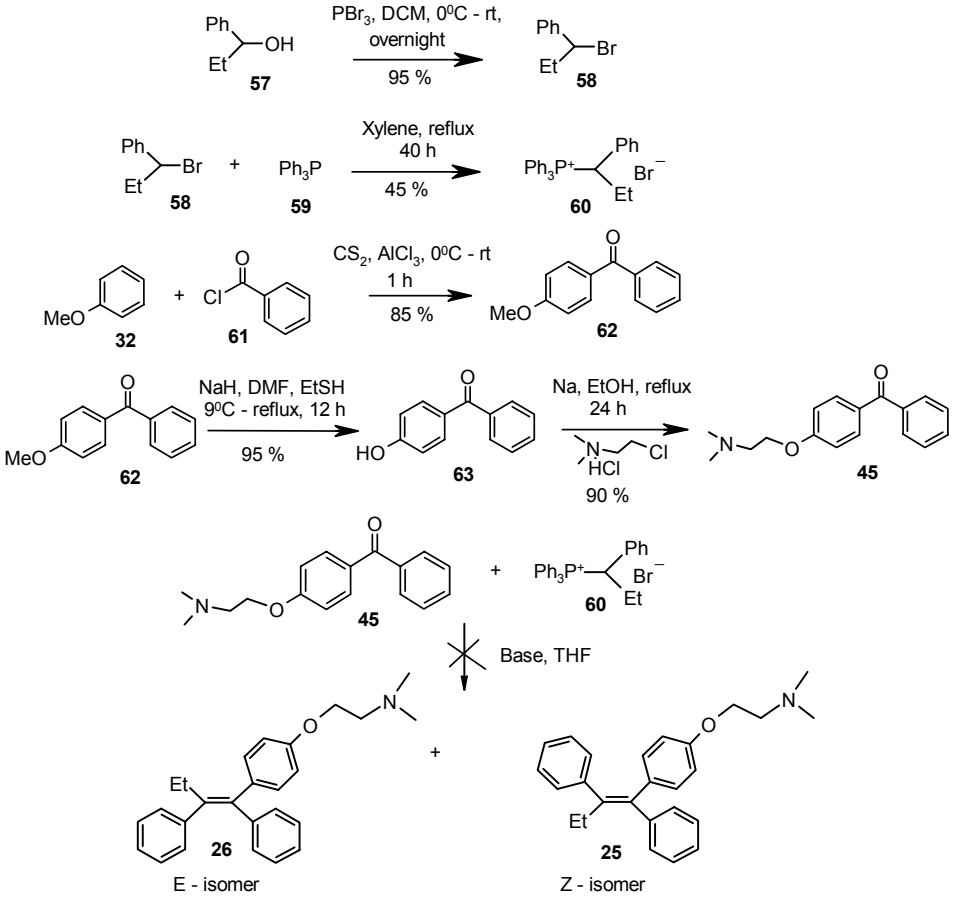
Scheme 26

2.2.3 Section I

Wittig Approach

2.2.3.1 Present Work

With the advancement in synthetic strategies proper tailoring of stereo, regioselectivity of biologically active compounds is possible. We have made an attempt to the stereoselective synthesis of tamoxifen i.e. synthesis of Z–isomer TAM, 1 (Nolvadex) exclusively by using simple and well established techniques and readily available starting materials and reagents as well. We employed Wittig approach for the synthesis of tamoxifen as shown in Scheme 27.



Scheme 27

2.2.3.2 Results and discussion

The synthetic route for the synthesis of Z-tamoxifen is depicted in Scheme 27. 1-Phenyl-1-bromopropane **58** was prepared by the reaction of 1-phenyl-1-propanol **57** with PBr_3 in dichloromethane at room temperature. In ^1H NMR spectrum of compound **58**, the signal corresponding to CH_3 protons appeared at 0.91 δ as triplet and CH proton attached to bromine appeared at 4.73 δ as a triplet. 1-Phenyl-1-bromopropane **58** was reacted with triphenyl phosphine in xylene at reflux temperature to give triphenyl-(1-phenyl-propyl)phosphonium bromide salt **60**. The ^1H NMR spectrum showed signal corresponding to CH proton attached to phosphorus atom at 6.15 δ as a multiplet and CH_3 protons at 1.06 δ as a triplet. The *p*-methoxybenzophenone **62** was prepared by the Friedel-Crafts acylation of anisole **32** by benzoyl chloride **61** in the presence of $AlCl_3$ as a Lewis acid. The IR spectrum of compound **62** showed a sharp peak at 1720 cm^{-1} corresponding to ketone functionality. In ^1H NMR spectrum of **62**, the signal corresponding to CH_3 protons appeared as a singlet at 3.90 δ. The aromatic protons of *p*-substituted benzene ring appeared as a two set of doublet at 6.96 δ and 8.20 δ. Finally the assigned structure was confirmed by mass spectrum analysis which showed M^+ peak at 212. The ketone **62** was demethylated to 4-hydroxybenzophenone **63** by the use of NaSEt in DMF solvent. The demethylated product **63** in IR spectrum showed two strong bands at 3200 and 1710 cm^{-1} corresponding to hydroxyl and ketone functionality respectively. In ^1H NMR spectrum of **63** disappearance of one singlet at 3.90 δ confirmed the demethylation of 4-methoxybenzophenone. Further structure was proved by mass spectrum, showing M^+ peak at 198. The hydroxyl group of compound **63** was protected using 2-(N, N-dimethyl amino)ethylchloride hydrochloride in the presence of sodium ethoxide to furnish [4-(2-dimethylamino-ethoxy)-phenyl]-phenyl-

methanone **45**. The hydroxy protected ketone **45** showed a strong band in IR spectrum at 1720 cm^{-1} corresponding to ketone functionality. In ^1H NMR spectrum of **45** both signal for CH_3 protons attached to nitrogen atom appeared as a singlet at 2.49 δ. The signal corresponding to CH_2 protons attached to amine functionality appeared as triplet at 2.95 δ and the CH_2 protons of OCH_2 group appeared as a triplet as 4.25 δ (Figure 1). Further the assigned structure was confirmed by mass spectrum showing M^+ peak at 269. When phosphonium salt **60** was subjected to the Wittig reaction using ketone **45** the desired compound **25** could not be obtained. We screened different kind of bases such as NaHMDS, NaH, n-BuLi, LDA etc and carried out reaction in various types of solvents like THF, DMSO, dioxane etc. at different temperature. However, under all these conditions, the reaction was a failure and thus the synthesis of target compound could not be achieved. The reason for this could perhaps be attributed to the steric factor in the Wittig reaction.

2.2.3.3 Conclusion

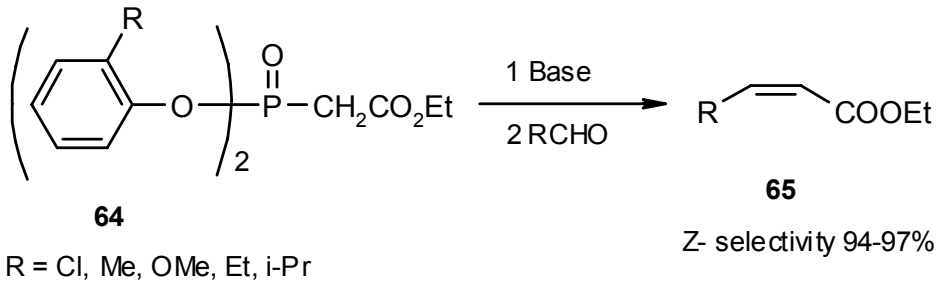
Under the various reaction conditions employed, the Wittig reaction did not work probably due to the steric hindrance caused by the phenyl group in the substrate and low reactivity of the carbonyl compound.

2.2.4 Section II

Wittig - Horner Approach

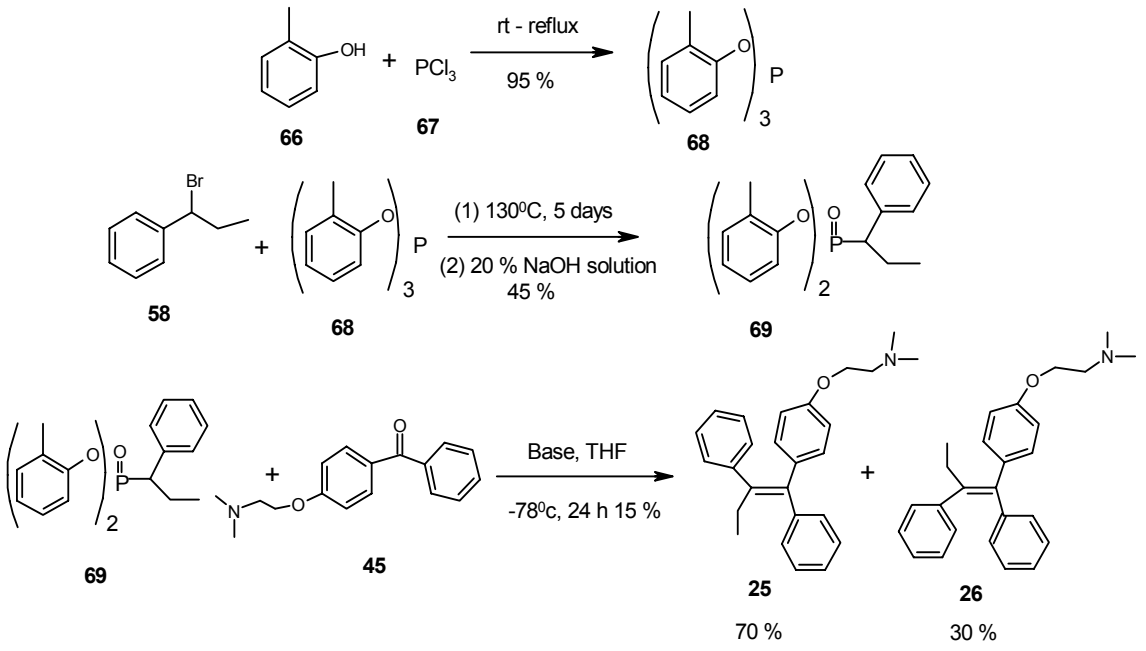
2.2.4.1 Present Work

Our initial attempt to synthesize the target compound by normal Wittig reaction under varied reaction conditions failed (Section B). The Wittig-Horner-Emmons reaction is one of the most important reactions for the synthesis of olefins by the reaction of aldehyde/ketone and phosphonate. To our knowledge the Wittig-Horner approach has not been extrapolated for the synthesis of tamoxifen and related analogs. A recent report by Ando[57] about the highly selective synthesis of Z-olefin using the Horner-Emmons reagent prompted us to use this methodology for the stereoselective synthesis of Z-tamoxifen. Accordingly a variety of substituted aryl phosphonates having *o*-substitution such as chloro, methyl or ethyl group were known to react with variety of aldehydes to give predominantly Z-isomer (Scheme 28).



Scheme 28

We have made an attempt to synthesize Z-tamoxifen using the above protocol. The details of the proposed synthesis are depicted in Scheme 29.



Scheme 29

2.2.4.2 Results and discussions

The proposed synthesis began with o-cresol **66** which was treated with PCl_3 **67** under reflux condition to give tritolylphosphite **68**. The phosphite **68** on treatment with bromo compound **58** at 130^{o}C for five days furnished the desired phosphonate **69** in 45 % yield. In ^{1}H NMR spectrum, the signal corresponding to CH_3 protons of propyl group of phosphonate **69** appeared at 0.95 δ as a triplet and CH_3 protons of tolyl group appeared as a singlet at 2.55 δ. The signal for aromatic protons appeared as a multiplet at 6.50 to 7.40 δ (Figure 2). ^{13}C NMR spectrum showed the signal for CH carbon attached to phosphorus at 56.91 δ (Figure 3). Further assigned structure was confirmed by mass spectral analysis which showed M^{+} peak at 380 (Figure 4).

The synthesis of *Z*-tamoxifen **25** was carried out employing Wittig-Horner reaction between ketone **45** and phosphonate **69** in the presence of n-BuLi or NaHMDS at –78°C as shown in Scheme 29. However a mixture of *Z* and *E*-isomer (2.33:1) was obtained in low yield, which was separated by column chromatography. The ^{1}H NMR spectrum showed peak for CH_3 protons of at 0.92 δ as a triplet. Both CH_3 protons attached to nitrogen came together as a singlet at 2.25 δ. The signal for CH_2 protons of butene group appeared at 2.5 δ as a quadrate and both CH_2 attached to nitrogen and oxygen appeared as a triplet at 2.75 δ and 3.90 δ respectively. The aromatic protons of *p*-substituted benzene ring appeared as a two doublets at 6.50 δ and 6.75 δ for Z-isomer (Figure 5). Finally the assigned structure was confirmed by ^{13}C NMR spectrum (Figure 6), melting point (95-96^{o}C) and by comparing the other physical and spectroscopic data reported in literature.[49]

2.2.4.3 Conclusion

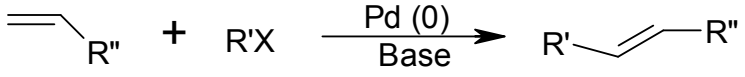
In conclusion, we have synthesized Z-tamoxifen though in poor yield via Wittig-Horner approach in a stereoselective manner.

2.2.5 Section II

Heck Coupling Reaction Towards the Synthesis of Z-Tamoxifen

2.2.5.1 General introduction about Heck reaction

The synthesis of arylated and vinylated olefins is of fundamental importance in organic synthetic chemistry. The palladium catalyzed coupling reactions of haloalkenes and haloarenes with alkenes, generally known as the Heck reaction, provides an efficient gateway into such compounds.[58] As shown in Scheme 30, styrenes and dienes can be prepared from the corresponding alkene and aryl or vinyl compounds substituted with a leaving group X = Cl, Br, I, N_2BF_4, OTf and COCl. This reaction is important owing to the possibility to preparation of not only simple terminal or 1,2-disubstituted olefins but also numerous complex molecular frameworks, e.g. tertiary and quaternary stereocenters. Dienes and alkynes can also be used as unsaturated compounds to get the corresponding coupled products. The reaction was discovered by R. F. Heck in late sixties. Initially, the reaction received much attention for forming new carbon-carbon bond in a single step.



R' = aryl, alkenyl
R" = aryl, alenyl, COOEt, etc
X = I, Br, OSO_2CF_3

Scheme 30

Mechanism of Heck reaction

The most acceptable mechanism of this reaction goes through the following organometallic intermediates. These are two major steps involved in the reaction mechanism, oxidative addition and reductive elimination as shown in Figure7.

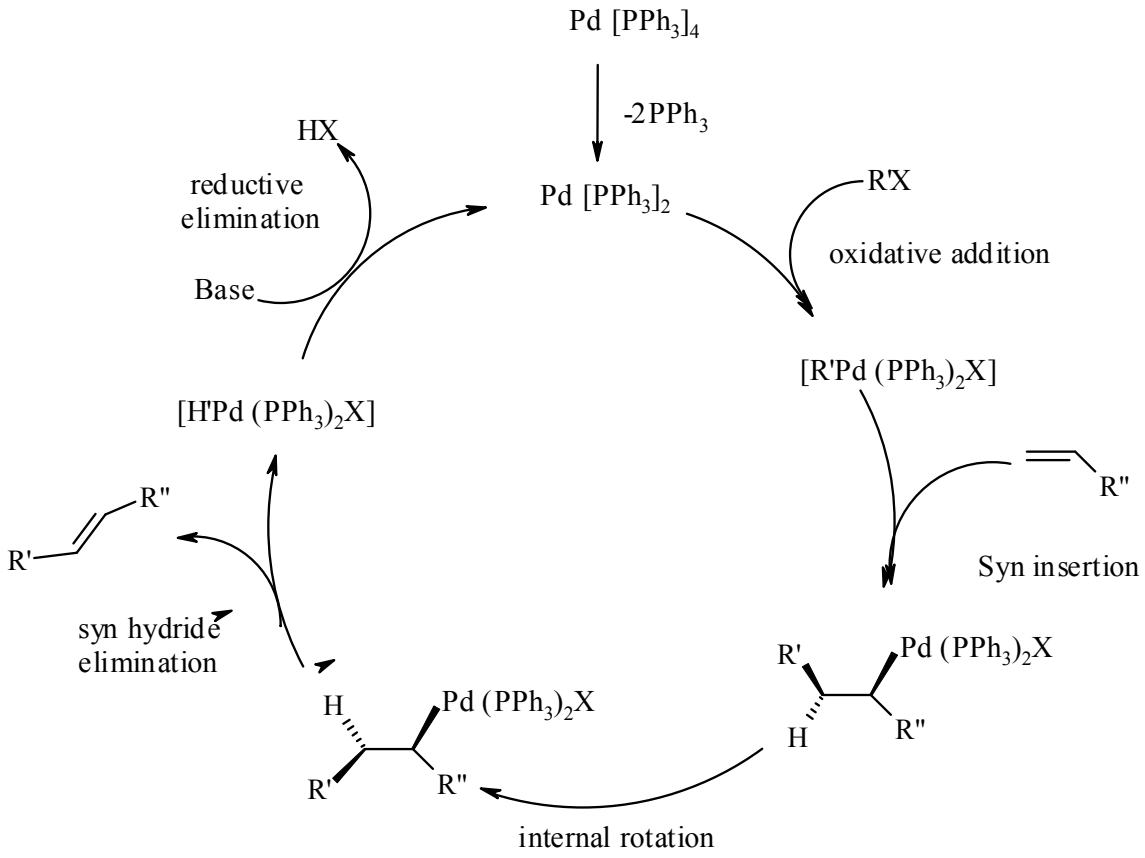


Figure 7: Mechanism of Heck reaction

Synthetic usefulness of the Heck reaction is explained by the following facts:

1. The Heck methodology is amenable to a variety of easily available starting materials.

2. It has remarkable chemoselectivity, hence educts containing most functional groups may be used.
3. The palladium catalysts typically employed are water and air stable.

Much progress has been made over the past ten years and several reviews have appeared.[59] Since it's discovery in the late sixties, most particularly in the last few years, several exciting breakthroughs have been made in the reaction including

(i) Development of more active and thermally stable catalyst system

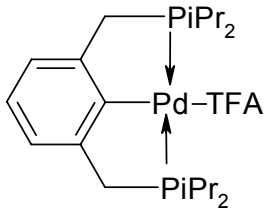
(ii) New more efficient enantioselective variant and

(iii) Expanded application in organic synthesis.

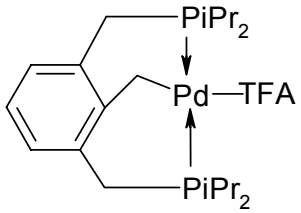
Catalysts

Palladium (0) phosphine complexs, such as $Pd(PPh_3)_4$ are generally used as Heck reaction catalyst. However, Pd(II) salt in the presence of phosphine ligands are more often employed as in situ catalyst.

In recent years, new and efficient catalyst (palladacycle) have been synthesized (Scheme 31) and applied for Heck reaction to achieve high turnover numbers and turnover frequencies and to activate less reactive chloride.[60]



70

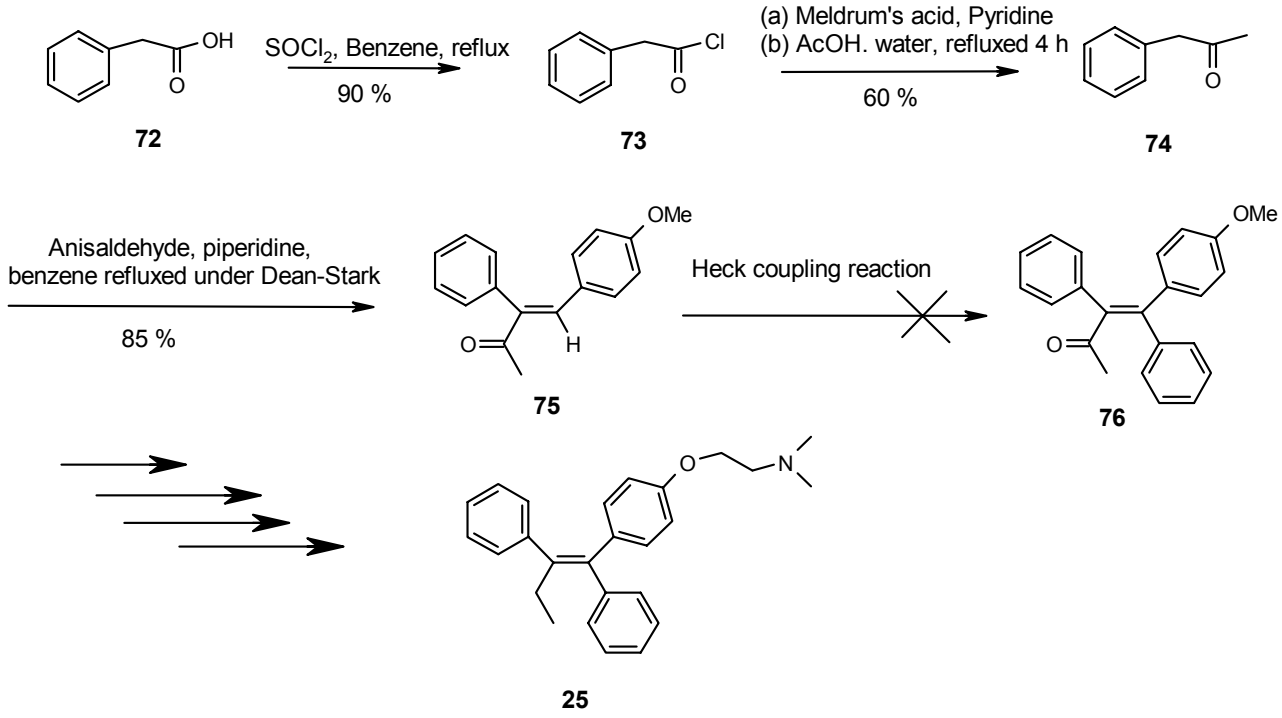


71

Scheme 31

2.2.5.2 Present work

As Heck reaction is a well known reaction for the arylation of olefins it was planned to synthesize Z-tamoxifen by employing Heck coupling reaction and the details of synthetic strategy are illustrated in Scheme 32.



Scheme 32

2.2.5.3 Results and discussion

In order to synthesize the target molecule **25**, the synthetic sequence was worked out as depicted in Scheme 32. Phenylacetyl chloride **73** was prepared by the treatment of phenylacetic acid **72** with thionyl chloride in benzene at reflux temperature for 10 h, as a

rosy color liquid in 90 % yield. The acid chloride **73** was treated with Meldrum's acid in pyridine at 0^oC to room temperature in dichloromethane to give phenyl acyl Meldrum's acid as a solid which was refluxed with acetic acid and water to furnish phenyl acetone **74** in 60 % yield. The IR spectrum of phenyl acetone **74** showed a strong band at 1712 cm^{-1} indicating the presence of ketone functionality. In ^1H NMR, the signal corresponding to CH_3 protons appeared as a singlet at 2.10 δ and another singlet shown at 3.65 δ for benzylic CH_2 protons. The signal corresponding to aromatic protons appeared as two multiplets one at 7.15 δ for three protons and another at 7.35 δ for two protons.

When phenyl acetone was reacted with anisaldehyde in presence of piperidine using Dean-Stark apparatus in benzene, the condensed product *trans*-4-(4-methoxyphenyl)-3-phenyl-but-3-en-2-one, **75** was obtained in 85 % yield. The IR spectrum of condensed product **75** showed a strong band at 1720 cm^{-1} for the ketone functionality. ^1H NMR spectrum of **75** showed a singlet at 2.27 δ for CH_3 protons attached to ketone functionality and another singlet appeared at 3.71 δ for CH_3 protons attached to oxygen. Two doublets appeared at 6.68 δ and 6.95 δ for the para substituted aromatic protons. Olefinic proton appeared as a singlet at 7.60 δ (Figure 8). Further, the assigned structure was confirmed by mass spectrum showing M^+ peak at 252.

The Heck coupling reaction was carried out by the use of palladium acetate as a catalyst under varied reaction conditions. The details of reaction conditions are described in Table 1. Unfortunately, the Heck coupling reaction did not work even with use of various bases, solvents, halobenzene and additive under different conditions.

Table 1: Heck coupling reaction between *trans*-4-(4-methoxyphenyl)-3-phenyl-but-3-en-2-one and halobenzene[a]

Entry	Solvent	Base	Reaction temp.	Reaction time (h)	Additive	Halide	Product
1	Acetonitrile	K_2CO_3	Reflux	24	-	PhI	Nil
2	Acetonitrile	TEA	Reflux	24	-	PhI	Nil
3	TEA	-	Reflux	24	-	PhI	Nil
4	Acetonitrile	K_2CO_3	Reflux	24	CuI	PhBr	Nil
5	TEA	K_2CO_3	Reflux	24	-	PhI	Nil
6	Pyridine	K_2CO_3	100^oC	20	-	PhI	Nil
7	DMF	K_2CO_3	110^oC	20	-	PhI	Nil

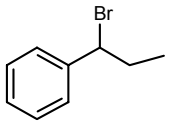
[a]Reaction condition: Ratio in mol of olefin: halobenzene 1.2:1.0; palladium acetate (10 mol %); triphenyl phosphine (40 mol %); K_2CO_3, 2 mol with respect to olefin.

2.2.5.4 Conclusion

Z-Tamoxifen could not be synthesized employing Heck coupling reaction. The change of different parameter of reactions such as temperature, solvent, bases, halo-benzene and use of additive has no effect on the course of reaction.

2.2.6 Experimental

Synthesis of 1-phenyl-1-bromopropane 58: To a solution of 30 gm (0.22 M) of 1-phenylpropanol in dichloromethane (100 ml) was added PBr_3 (15 ml) at 0^oC dropwise. After complete addition, the reaction mixture was stirred overnight at room temperature and water was added to reaction mixture. The reaction mixture was extracted with dichloromethane (2 x 100 ml), combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude compound which was distilled at 84^oC (4 mm) to obtain 41.5 gm of colorless liquid. On standing it turns brown due to HBr evolution.



58

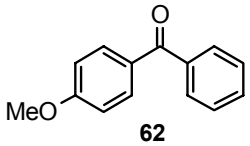
Yield 95 %

Colorless liquid

^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, J = 6.6 Hz, 3H), 2.15 (m, 2H), 4.79 (t, J = 7.0 Hz, 1H), 7.10-7.25 (m, 5H).

Synthesis of 4-methoxybenzophenone 62: Dry $AlCl_3$ (24 gm, 0.185 M) was added in portion to the mixture of benzoyl chloride (26.03 gm, 0.1852 M) and anisole (20 gm, 0.1852 M) in CS_2 (100 ml) at 0^oC under vigorous stirring. Towards the end of the addition, a red complex precipitated. After 1 h at room temperature the reaction was treated with concentrated HCl (75 ml) and ice and reaction mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated. Silica gel column chromatography of crude product

using petroleum ether: EtOAc (9.5: 0.5) as eluent afforded acylated compound (46.1 gm) as a white solid.



62

Yield: 85 %

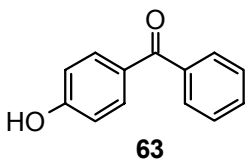
White solid, M.P. 60-62^{o}C

IR (Nujol): cm^{-1} 2935, 1720,1620,1586.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.9 (s, 3H), 6.96 (d, J = 10.40 Hz, 2H), 7.45-7.59 (m, 3H), 7.75-7.87 (m, 2H), 8.20 (d, J = 10.4 Hz, 2H).

EIMS (m/z): M^{+}212 (35.3), 181 (2), 169 (3), 135 (100), 107 (26), 92 (10).

Synthesis of 4-hydroxybenzophenone 63: To the slurry of sodium hydride [(7.92 gm, 165 mmol) 50 % mineral oil suspension washed twice with dry hexane (75 ml)] in dry DMF (350 ml) cooled to 9^{o}C was added ethanethiol (12.28 gm, 198 mol) dropwise at such a rate as to prevent foaming. After completion of addition at 9^{o}C, the mixture was stirred for 15 minutes. Then 4-methoxybenzophenone (10 gm, 47 mmol) in dry DMF (100 ml) was added to the reaction mixture in one portion. The resultant mixture was refluxed for 10 h, cooled to room temperature, poured into 3N HCl and extracted with ether. The combined organic layers were washed with 3 N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (9: 1) as eluent provided demethylated compound **63** (8.87 gm) as a white solid.



63

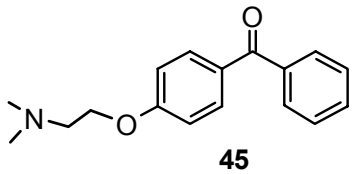
Yield: 95 %

M.P. 132-134^{o}C

IR (Nujol): cm^{-1} 3200, 2980, 1716,1625,1580.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (d, J = 8.3 Hz, 2H), 7.40-7.65 (m, 4H), 7.65-7.82 (m, 2H), 8.85 (d, J = 8.3 Hz, 2H).

Synthesis of 4-(2-Dimethylaminoethoxy)benzophenone 45: To a solution of sodium ethoxide in ethanol [prepared by adding sodium metal (3.04 gm, 132 mmol) to absolute ethanol (150 ml)] was added 4-hydroxybenzophenone **63** (7.5 gm, 37.87 mmol) in absolute ethanol (150 ml). To this mixture was then added in one portion a solution of 2-(dimethylamino)ethyl chloride hydrochloride (10.833 gm, 75.75 mmol) in warm absolute ethanol (150 ml). The resultant mixture was then refluxed for 24 h, cooled to room temperature, poured into water and extracted with ether (3 x 100 ml). The combined organic layers were washed with 5 % sodium hydroxide solution, brine, dried over anhydrous Na_2SO_4 and concentrated. Silica gel column chromatography of crude product using chloroform: methanol (9.5: 0.5) as eluent gave protected compound **45** (9.17 gm) as a viscous pale yellow liquid.



45

Yield: 90 %

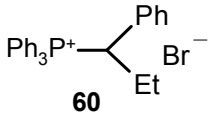
Viscous pale yellow liquid

IR (Neat): cm^{-1} 2930, 1720,1620,1540.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.49 (s, 6H), 2.95 (t, J = 6.6 Hz, 2H), 4.25 (t, J = 6.6 Hz, 2H), 6.98 (d, J = 9.3 Hz, 2H), 7.35-7.65 (m, 3H), 7.75-7.80 (m, 2H), 8.85 (d, J = 9.3 Hz, 2H).

EIMS (m/z): M^+269 (3), 152 (2), 105 (7), 77 (14), 58 (100).

Synthesis of triphenyl-(1-phenylpropyl)phosphonium bromide 60: A mixture of triphenylphosphine (2.62 gm, 10 mmol), 1-phenyl-1-bromopropane (1.99 gm, 10 mmol) in xylene (15 ml) was refluxed for 48 h. Xylene was evaporated and viscous solid thus obtained was washed with benzene to remove unreacted starting materials and dried in vaccuo to give salt **60** (2.075 gm).



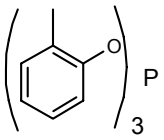
60

Yield: 45 %

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, J = 6.7 Hz, 3H), 1.90-2.30 (m, 2H), 6.15 (m, 1H), 7.18-7.90 (m, 20H).

Wittig reaction between phosphonium salt 60 and ketone 45: In a two neck round bottom flask charged with phosphonium salt **60** (2.0 mmol) under nitrogen environment was added THF (5.0 ml) and base (2 mmol) and mixture was cooled to -78^{o}C. The stirring was continued for 1 h followed by the addition of ketone (2.0 mmol in 2.5 ml THF). The reaction mixture was stirred at –78^{o}C to room temperature and subsequently refluxed for 24 h. The mixture was cooled to room temperature and treated with saturated ammonium chloride solution and extracted with ethyl acetate, dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure provided starting material back.

Synthesis of tritolylphosphite 68: A mixture of o-cresol (20 gm, 195.18 mmol) and PCl_3 (8.10 gm, 59.14 mmol) was slowly heated to 180^oC, when temperature became constant and evolution of HCl was very slow after 10 h. The excess o-cresol was distilled out at reduced pressure and tritolyl phosphite (19.77 gm) was obtained at 200^oC at 0.10 mm pressure.

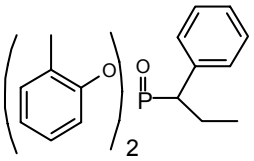


68

Yield: 95 %

B. P. 200^oC / 0.1 mm

Synthesis of (1-Phenylpropyl)phosphonic acid di-*o*-tolyl ester 69: Tritolyl phosphite-1-phenyl-1-bromopropane adduct was formed by the heating a mixture of tritolyl phosphite **68** (10 gm, 28.4 mmol) and 1-phenyl-1-bromopropane **58** (5.65 gm, 28.4 mmol) at 130^oC for five days. Hydrolysis of the adduct with aqueous NaOH (2 M solution) at room temperature, followed by the extraction with ethyl acetate and drying over Na_2SO_4 of the organic layer afforded crude product. Silica gel column chromatography of crude product using petroleum ether as eluent gave phosphonate **69** (4.58 gm) as a viscous liquid.



69

Yield: 45 %

Colorless viscous oil

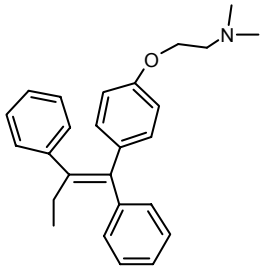
IR (Neat): cm^{-1} 2930, 1620, 1550, 1450.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, J = 6.6 Hz, 3H), 2.00-215 (m, 2H), 2.55 (s, 6H), 4.15 (t, J = 6.6 Hz, 1H), 6.50-7.40 (m, 13H).

^{13}C NMR (200 MHz, $CDCl_3$): δ 23.13, 26.36, 56.91, 130.43, 130.74, 134.49, 136.08, 136.72, 137.58, 138.28, 138.95, 139.22, 141.18, 154.88, 162.45.

EIMS (m/z): M^{+}380 (4), 344 (5), 315 (23), 226 (29), 197 (100), 165 (28), 152 (20), 115 (22), 91 (32).

Synthesis of Z-tamoxifen 25: A solution of phosphonate **69** (0.5 gm, 1.316 mmol) in THF (20 ml) was treated with n-butyllithium (0.561 ml 15 % solution in hexane, 1.316 mmol) at –78^{o}C for 1 h. A solution of ketone in THF (0.345 gm dissolved in 5 ml THF, 1.316 mmol) was then added and the resulting mixture was stirred at –78^{o}C for 48 h. The reaction was then quenched with saturated NH_4Cl, extracted with ethyl acetate (3 x 20 ml). The combined extracts were washed with water (2 x 20 ml) followed by brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash silica gel column chromatography using chloroform: methanol (9.5: 0.5) eluent to furnish Z-tamoxifen **25** (0.073 gm) along with some unreacted starting material.



25

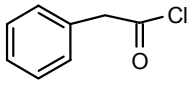
Yield: 15 %

White solid; M.P.: 95-96^{o}C (Lit.[49] M. P. 95-97^{o}C)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, J = 6.6 Hz, 3H), 2.25 (s, 6H), 2.40-2.55 (q, J = 6.5 Hz and 12.6 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 3.90 (t, J = 6.0 Hz, 1H), 6.50 (d, J = 10.0 Hz, 2H), 6.75 (d, J = 10.0 Hz, 2H), 7.15-7.40 (m, 10H).

^{13}C NMR (200 MHz, $CDCl_3$): δ 13.38, 28.78, 45.66, 58.08, 65.54, 113.22, 125.83, 126.30, 127.66, 127.88, 129.24, 142.22, 143.62, 156.59.

Synthesis of phenylacetyl chloride 73: Thionyl chloride (47.6 gm, 0.4 mol) was added to the solution of phenylacetic acid (27.2 gm, 0.2 mol) in benzene (100 ml). The reaction mixture was refluxed for 15 h, then cooled to room temperature, benzene was removed on rotatory evaporator. Phenylacetyl chloride was distilled out at 94-96^{o}C/12 mm as a pink colored liquid (28.0 gm) in 90 % yield.



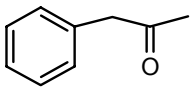
73

Yield: 90 %

Pink color liquid

Synthesis of phenyl acetone 74: Dry pyridine (41.8 ml, 0.52 mol) was added into a solution of Meldrum's acid (29.7 gm, 0.2 mmol) in dry dichloromethane (80 ml) at 0^{o}C under argon. To the resulting colorless solution phenylacetyl chloride **73** (20.1 gm) in dry dichloromethane (50 ml) was added over a period of 2 h. The resulting orange cloudy mixture was stirred for 1 h at 0^{o}C then for additional 1 h at room temperature. The reaction mixture was diluted with dichloromethane (30 ml) and then poured into crushed ice

containing HCl (2N, 100 ml). The organic phase was separated and aqueous layer was extracted with dichloromethane (2 x 100 ml). The combined organic phase was washed with HCl (2N, 100 ml) and then with brine, dried over anhydrous Na_2SO_4. Evaporation of solvent gave orange color solid of phenyl acyl Meldrum's acid. The isolated acid was refluxed in acetic acid: water (1: 2) until complete consumption of starting material as indicated by TLC (4h). The reaction mixture was diluted with water, extracted twice with petroleum ether (100 ml) and combined organic layer was washed with dil. $NaHCO_3$ and dried over anhydrous Na_2SO_4. The organic layer was concentrated to afford the crude product, which on distillation gave 10.45 gm of phenyl acetone **74** as a yellow oil.



74

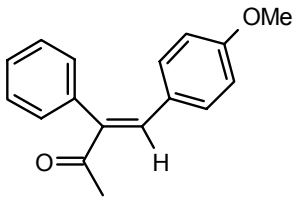
Yield: 60 %

Yellow oil

IR (Neat): cm^{-1} 2924,1713, 1652, 1495, 1450.

^1H NMR (200 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.71 (s, 2H), 7.20-7.36 (m, 5H).

Synthesis of *trans*-4-(4-methoxyphenyl)-3-phenyl-but-3-en-2-one 75: A mixture of anisaldehyde (10.8 gm, 0.1 mol), phenyl acetone **74** (13.4 gm, 0.1 mol), and piperidine (0.2 gm) in dry benzene (100 ml) was refluxed under Dean-Stark condition. After 15 h the reaction mixture was cooled to room temperature and concentrated in vacuo to give the crude product which on distillation at 200^oC at 0.1 mm pressure furnished the pure ketone **75** (21.42 gm).



75

Yield: 85 %

Yellow solid; M.P. 54-56^{o}C

IR (Nujol): cm^{-1} 2923, 1720, 1640, 1540.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.71 (s, 3H), 6.65 (d, J = 10.0 Hz, 2H), 6.95 (d, J = 10.0 Hz, 2H), 7.14-7.40 (m, 5H), 7.60 (s, 1H).

EIMS (m/z): 252 (M^{+}).

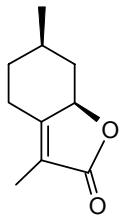
Heck reaction between 75 and aryl halide: A mixture of aryl halide (2.0 mmol), olefin **75** (2.4 mmol), base (2.0 mmol), palladium acetate (10 mol %), triphenylphosphine (40 mol %) in solvent (4.0 ml) was heated at given temperature and indicated length of time (see Table 1) under nitrogen environment. Reaction mixture was cooled to room temperature, then 10 % HCl was added and extracted with ethyl acetate, dried over anhydrous Na_2SO_4. Evaporation of solvent at reduced pressure provided starting material back.

2.3 SECTION C

A Wittig - Horner Approach towards the Synthesis of Mintlactone

2.3.1 Introduction

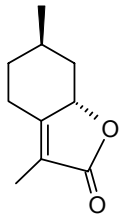
(-)-Mintlactone **77** and (+)-isomintlactone **78** (Scheme 33) are monoterpenic compounds found as minor components in the essential oil of several *Mentha* species.



77

Mintlactone

(6*R*, 7a*R*)-3,6-Dimethyl-5,6,7,7a-tetrahydro-2-(4*H*)-benzofuranone



78

Isomintlactone

(6*R*, 7a*S*)-3,6-Dimethyl-5,6,7,7a-tetrahydro-2-(4*H*)-benzofuranone

Scheme 33

The mint oil is produced on a large scale throughout the world, being used as flavoring agent for cosmetics, medicines and foods. The major constituents (ca. 70 %) of this oil are (-)-menthol and (-)-menthone, besides approximately 300 other minor volatile compounds.[61]

The presence of (-)-mintlactone in the oil of *M. cardiaca G.* (Spearmint oil), *M. arvensis* (Japanese peppermint) and *M. piperita L.* (Mitcham peppermint) was noticed for the first time in 1968 during a symposium in Japan.[62] Some years later, (-)mintlactone was isolated from *M. pulegium L.*[63] and from a variety of *M. arvensis* known as Shubi.[64]

In 1980, Takahashi et al.[65] identified an isomer of **77**, the (+)-isomintlactone **78**, in the oil of *M. piperita L.,* and determined their relative configuration from spectral data. They were

also able to assign the absolute configuration of the two lactones, by synthesizing them from menthofuran.

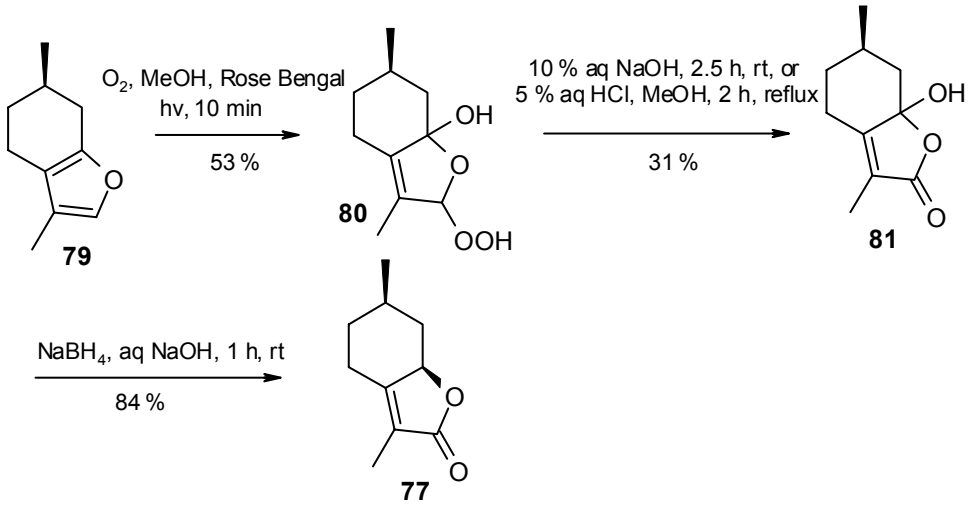
More recently, Iwabuchi reported the isolation of the enantiomers (+)-mintlactone and (-)-mintlactone from the oil of the wood of *Bursera graveolens*.[66] In 1998, these lactones were reported to be present in the oil of *M. piperita L.* cultivated in Italy.[67] Although the lactones **77** and **78** are present in small quantities in the mint oils, they are important from a biosynthetic and phylogenetic point of view,[68] and seem to be significant flavor components in the oil.[69]

2.3.2 Review of literature

Various synthetic methods for the mintlactone have been reported. Most of these approaches start with transformation of monoterpenes such as (+)-menthofuran, (+)-citronellal, (-)-isopulegol etc. and cyclohexanone derivatives. Some of the important asymmetric synthetic routes reported are discussed below.

Foote et al (1967)[70] Scheme 34

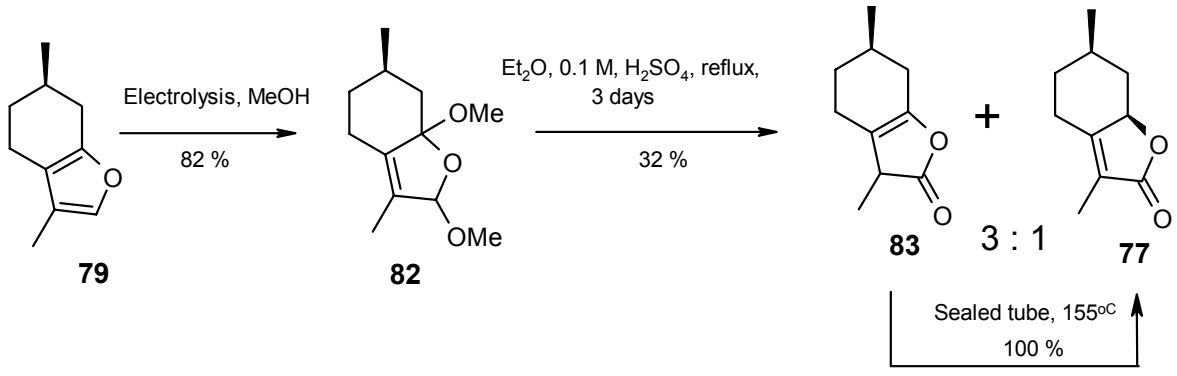
During a study about photosensitized oxygenation of furans, Foote et al. reported the first preparation of optically active mintlactone **77,** starting from natural (+)-menthofuran **79**. Thus, irradiation of **79** with visible light afforded the peroxide **80**, which rearranged to pseudo acid under acidic or basic conditions. The lactone **77** was obtained in high purity and good yield by sodium borohydride reduction of **81**(Scheme 34).



Scheme 34

Hirsch et al. (1967)[71] Scheme 35

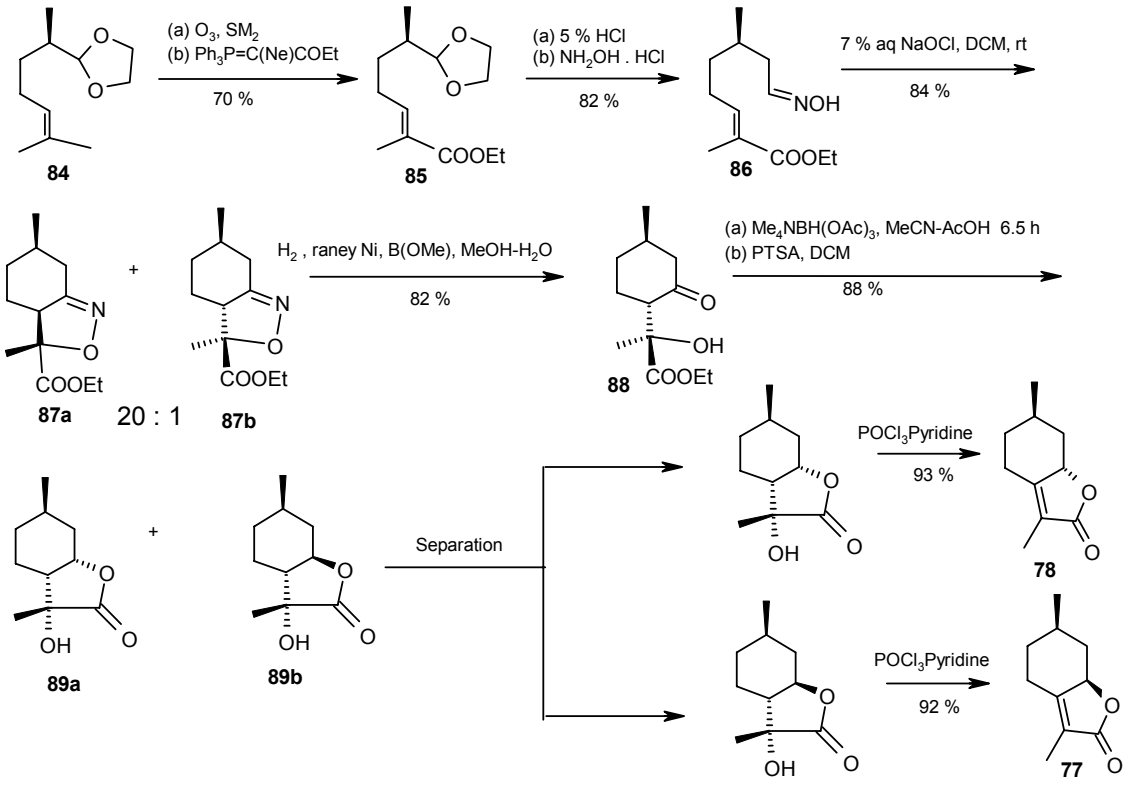
Hirsch et al. also obtained lactone **77** from (+)-menthofuran **79** employing an electrolytic methoxylation followed by hydrolysis. The β, γ-unsaturated lactone **83** thus obtained was converted into lactone **77** by thermal equlibration (Scheme 35).



Scheme 35

Shishido et al. (1992)[72] Scheme 36

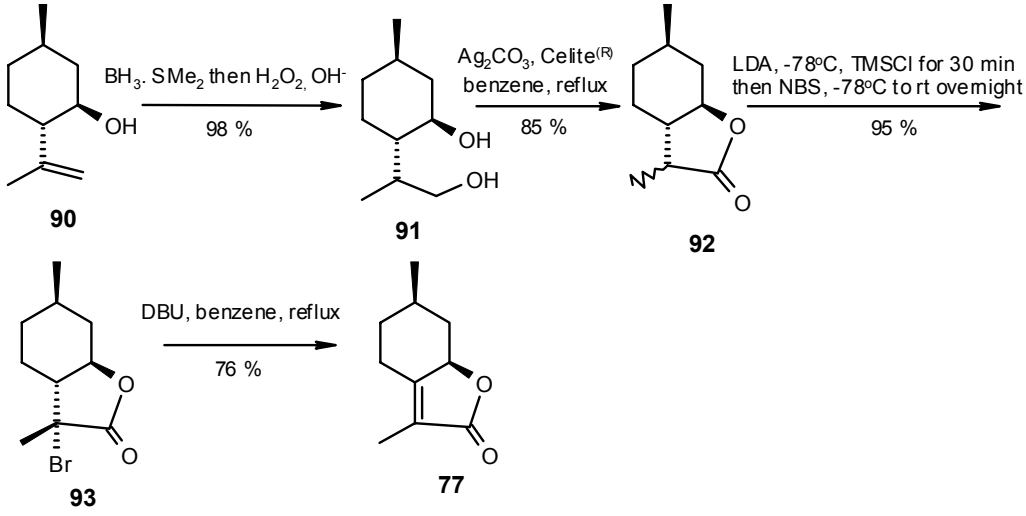
The synthesis of (-)-mintlactone **77** and (+)-isomintlactone **78**, was reported by these authors starting from the acetal of (+)-citronellal **84**. The key step of the sequence consisted of the intramolecular [3 + 2] cycloaddition of the nitrile oxide **86** to isoxazolines **87a** and **87b**. The pure isoxazolines were separated by column chromatography. Reductive hydrolysis of isoxazolines **87a** followed by hydride reduction of **88** and lactonization, provided **89a** together with minor amont of its isomer **89b**. It was possible to get **87a** and **87b** in 1:6 ratio by changing the base to zinc borohydride. Separation and dehydration provided the mintlactone **77** and isomintlactone **78** (Scheme 36).



Scheme 36

Chavan et al. (1993)[73] Scheme 37

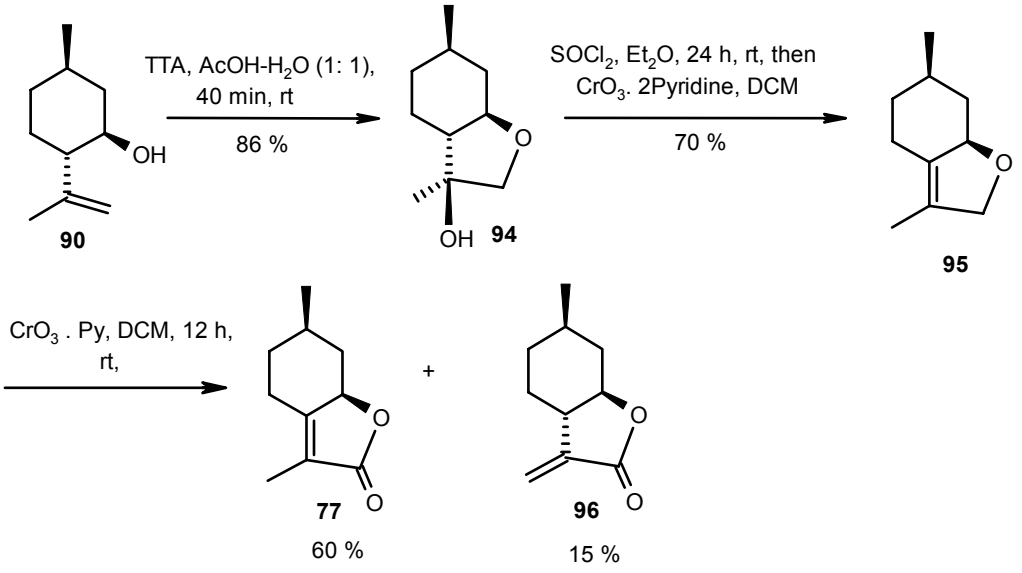
Chavan et al. synthesized (-)-mintlactone **77** from (-)-isopulegol **90**. The sequence described by the authors consists of an anti-Markovnikov addition of water to **90**, followed by oxidation of the primary alcohol and in situ lactonization. The α-methyl lactone **92** was selectively brominated to give bromolactone **93** followed by stereoselective anti-dehydrobromination of **93** to the lactone **77** (Scheme 37).



Scheme 37

Ferraz et al. (2000)[74] Scheme 38

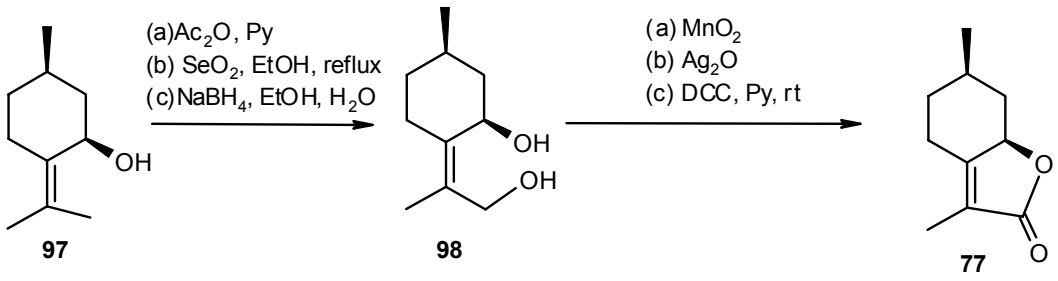
Ferraz et al. also synthesized mintlactone **77** by employing the (-)-isopulegol **90** as starting material. The key step consists of a highly stereoselective thallium triacetate (TTA) mediated cyclization of (-)-isopulegol leading to the β-hydroxy ether **94** which gave the target molecule **77** by dehydration followed by allylic oxidation (Scheme 38).



Scheme 38

Rao et al. (1971)[75] Scheme 39

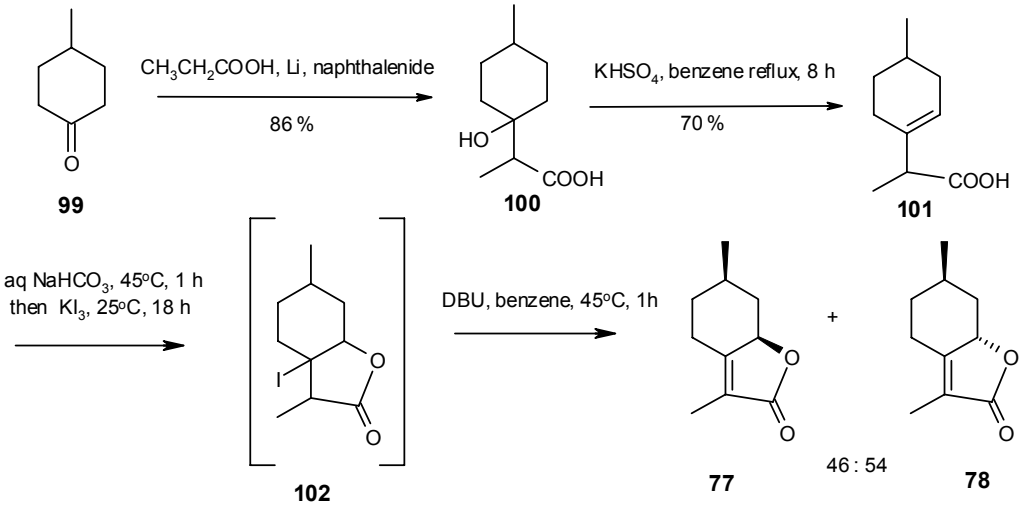
Rao et al. synthesized the (-)-mintlactone **77** by employing a sequence of oxidation reactions of cis-pulegol **97** as illustrated in Scheme 39.



Scheme 39

Fujita et al. (1985)[76] Scheme 40

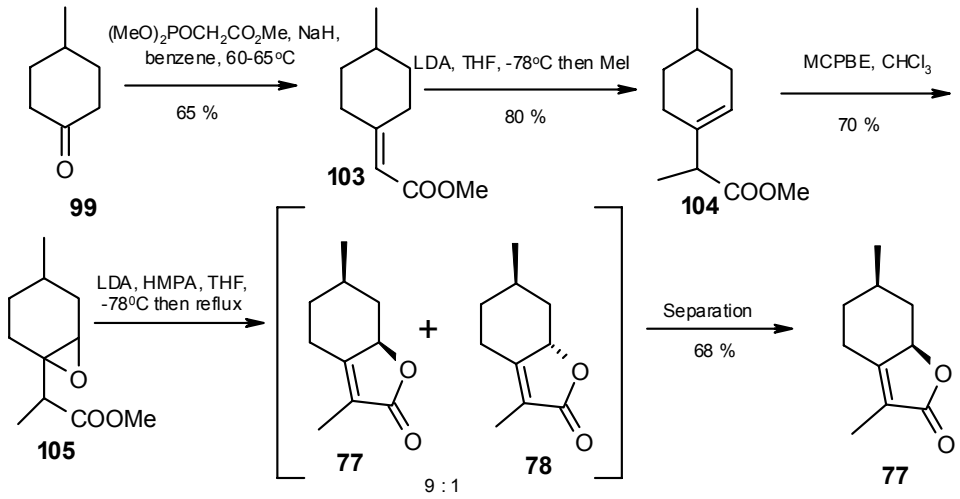
Fujita et al. utilized 4-methyl cyclohexanone **99** as starting material for the synthesis of (±)-mintlactone **77** and (±)-isomintlactone **78**. In this approach, the acid **101** was prepared in two steps from **99** and subsequently converted into a mixture of **77** and **78** in the ratio (46: 54) by iodolactonization followed by in situ dehydroiodination (Scheme 40).



Scheme 40

Cory et al. (1990)[77] Scheme 41

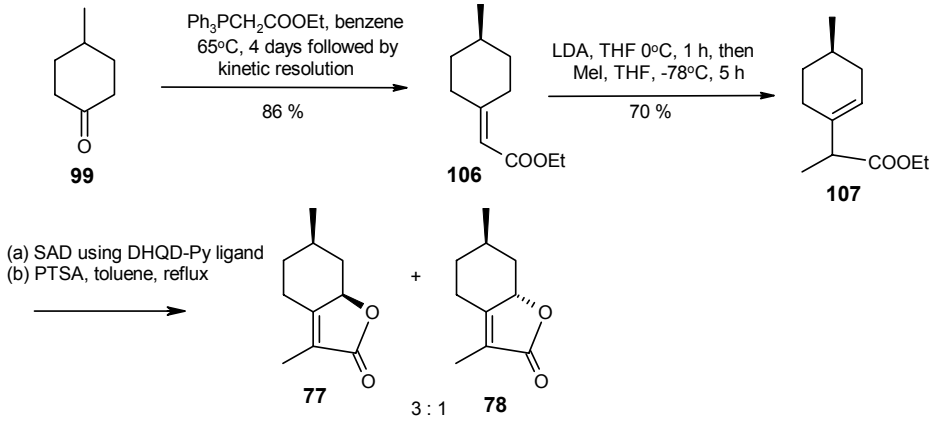
In 1990, Cory et al. obtained mintlactone **77** in a highly stereoselective manner. The β, γ-unsaturated methyl ester **104** was prepared by olefination of 4-methyl cyclohexanone **99** followed by deconjugative alkylation. Epoxidation of **104** gave **105**, which on rearrangement led to a 9: 1 mixture of **77** and **78** from which **77** could be obtained in pure form in 68 % yield (Scheme 41).



Scheme 41

Lohray et al. (1997)[78] Scheme 42

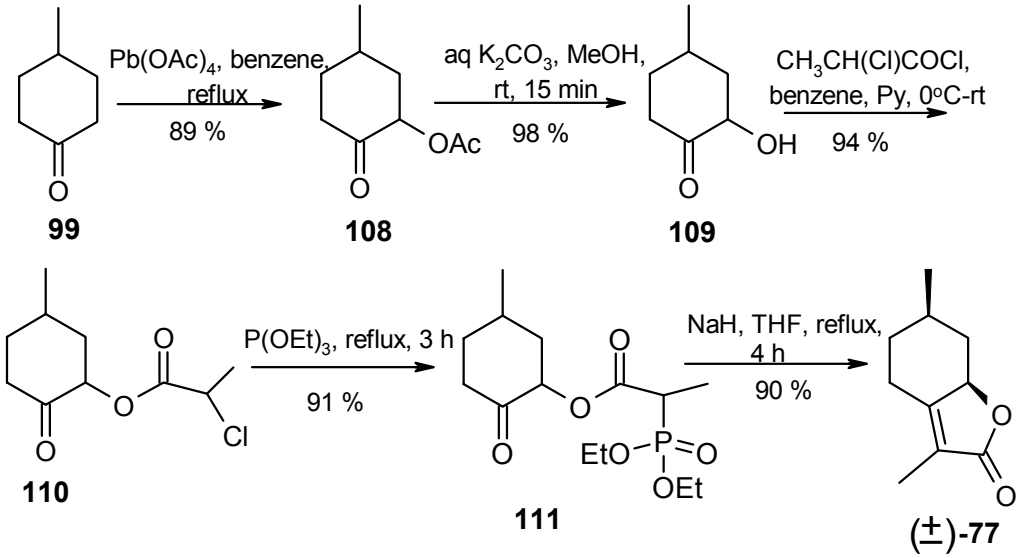
The author performed the kinetic resolution of the olefin, prepared from 4-methyl cyclohexanone **99** and obtained (*R*)-isomer of **106** in 85 % ee. Deconjugative alkylation of olefin **106** was accompanied by racemization, affording the β, γ-unsaturated ethyl ester **107**. Asymmetric dihydroxylation of ethyl ester **107** followed by dehydration furnished mintlactone **77** and isomintlactone **78** in different ratios (Scheme 42).



Scheme 42

Tanyeli et al. (1997)[79] Scheme 43

Tanyeli et al. have used a different approach to (±)-mintlactone starting from **99**. The α-acetoxylation of **99** with lead tetraacetate, followed by transesterification afforded the derivative **110,** which was treated with triethylphosphite to give corresponding phosphonate **111**. A Horner-Emmons intramolecular reaction led directly to the target molecule **77**.

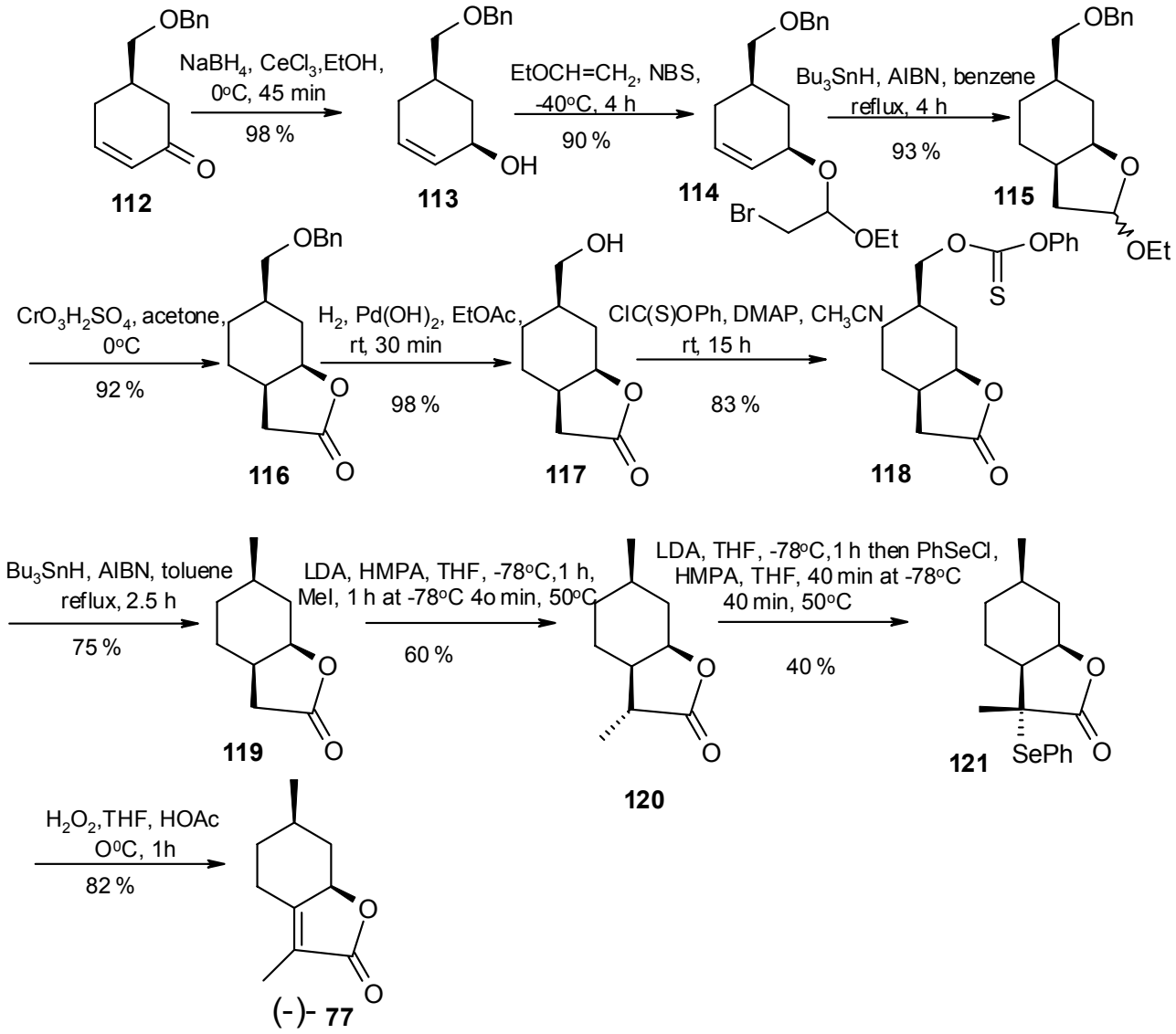


Scheme 43

Carda et al. (1991)[80] Scheme 44

In 1991, Carda et al. reported the first total synthesis of (-)-mintlactone **77** using the chiral enone **112** as starting material. The key step of this synthesis is the stereoselective ring closure of the bromoacetal **114** employing a well established homolytic protocol. Oxidation of lactol **115** with Jones reagent, followed by a three step reductive elimination of the

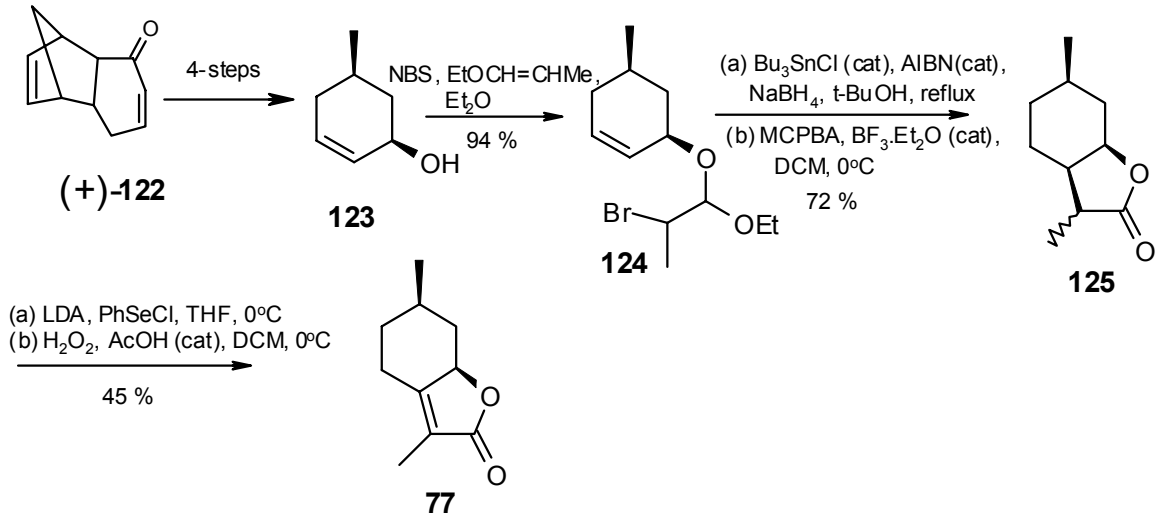
protected hydroxyl group of **118** led to the lactone **119** in a good yield. Finally lactone **119** was transformed into (-)-mintlactone **77** (Scheme 44).



Scheme 44

Ogasawara et al. (1998)[81] Scheme 45

Ogasawara et al. described an efficient approach to (-)-mintlactone **77** starting from chiral tricyclic dienone **122**. The transformation of dienone **122** into allylic alcohol **123** was completed in three steps. The chiral allylic alcohol **123** was transformed into (-)-mintlactone **77** in five steps (Scheme 45).

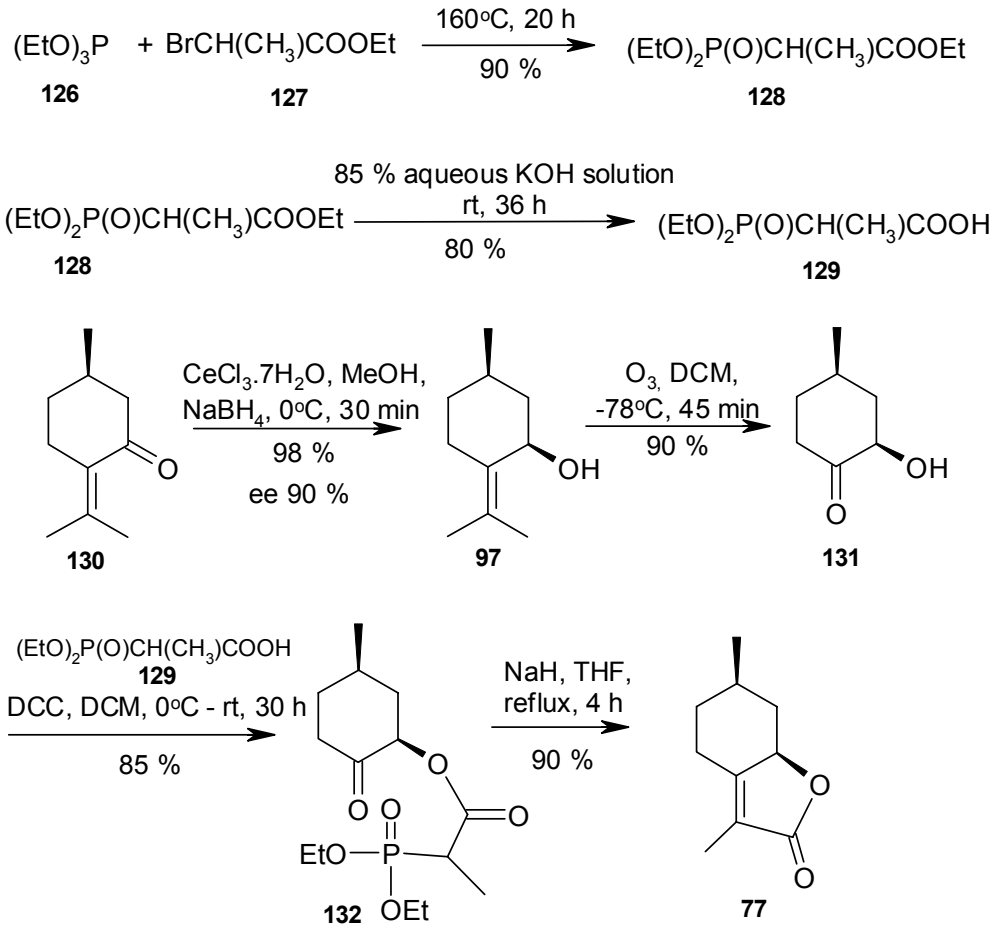


Scheme 45

2.3.3 Present work

Objective

Most of the syntheses of (-)-mintlactone **77** as described above are either not very stereoselective or low yielding. The objective of the present study is to explore the chemistry of intramolecular Wittig-Horner reaction and to develop a new protocol which will be more practical and flexible for the optically pure synthesis of (-)-mintlactone **77**. The detailed strategy is depicted in Scheme 46.



Scheme 46

2.3.4 Results and discussion

As illustrated in Scheme 46, the phosphonate **132** required for the intramolecular Wittig-Horner reaction was prepared by DCC coupling of the acid **129** and alcohol **131**. The acid **129** was prepared in following manner. The triethylphosphite **126** and ethyl 2-bromopropionate **127** were mixed and heated at 160^{o}C to afford the phosphonate (triethyl 2-phosphonopropionate) **128** in 90 % yield (Arbuzov reaction). The IR spectrum of phosphonate **128** showed a band at 1720 cm^{-1} corresponding to ester functionality. ^{1}H NMR showed CH_3 protons as a multiplet at 1.07 – 1.43 δ and CH proton attached to phosphorus also as a multiplet at 3.00 δ. The CH_2 protons appeared at 4.1 δ. 2-(Diethoxyphosphoryl)propionic acid **129** was prepared by the hydrolysis of **128** using 85 % aqueous solution of potassium hydroxide in ethanol. The IR spectrum of compound **129** showed two strong bands at 3400 and 1710 cm^{-1} corresponding to hydroxyl and carbonyl functionality respectively of the carboxylic group. In ^{1}H NMR spectrum the CH_3 protons appeared at 1.25-1.47 δ as a multiplet, while the acid proton was seen at 9.73 δ as a broad singlet. The (+)-pulegone **130** was reduced to cis-pulegol **97** using sodium borohydride and cerium chloride in methanol at 0^{o}C in 98 % yield with 90 % ee, having $[\alpha]_D^{25}$ – 103.0 (*c* = 1, MeOH) [lit. $[\alpha]_D^{25}$ - 105.0 (*c* = 1, MeOH)]. The IR spectrum of cis-pulegol **97** showed a band at 3400 cm^{-1} for the hydroxyl functionality. The CH_3 protons attached to cyclohexane ring appeared as a doublet at 0.97 δ in ^{1}H NMR spectrum. Compound **97** was converted into 2-hydroxy-4-methyl-cyclohexanone **131** by ozonolysis in dichloromethane in excellent yield. The IR spectrum of **131** showed a strong band at 3443 cm^{-1} for the hydroxyl group and a band at 1719 cm^{-1} for ketone functionality. The ^{1}H NMR spectrum showed CH_3 protons as a doublet at 1.00 δ. The signal for CH proton attached to hydroxyl group

appeared at 4.20 δ. Further structure was proved by mass spectrum, showing M^+ peak at 128. 2-Hydroxy-4-methylcyclohexanone **131** was treated with 2-(diethoxy-phosphoryl)propionic acid **129** under neutral condition using DCC in dichloromethane to afford 2-(diethoxyphosphoryl)propionic acid 5-methyl-2-oxo-cyclohexyl ester **132** in 85 % yield having $[\alpha]_D^{25}$ + 39.0 (*c* = 2, $CHCl_3$). The IR spectrum of phosphonate **132** showed a strong band at 1727 cm^{-1} corresponding to ester functionality. In ^1H NMR spectrum, the signal corresponding to CH_3 protons attached to ring appeared at 1.02 δ as a doublet. The CH_3 protons of phosphonate appeared as a multiplet at 1.40 δ, and CH_2 protons attached to ketone functionality was seen at 2.44 δ. The CH_2 protons of OCH_2CH_3 group appeared as multiplet at 4.15 δ and CH proton attached to ester group also appeared as a multiplet at 5.25 δ (Figure 9). In ^{13}C NMR the carbon attached to phosphorus appeared at 61.81 δ (Figure 10). Further the structure was confirmed by mass spectrum showing M^+ peak at 320. Compound **132** was treated with sodium hydride in THF to afford (-)-mintlactone **77** in 90 % yield having $[\alpha]_D^{25}$ - 57.0 (*c* = 1, $CHCl_3$) [lit. $[\alpha]_D^{25}$ -57.0 (*c* = 1, $CHCl_3$)]. The IR spectrum of (-)-mintlactone **77** showed a strong band at 1754 cm^{-1}corresponding to the 5-membered lactone. In ^1H NMR spectrum the CH_3 protons attached to cyclohexane ring appeared as a doublet at 1.00 δ. Further, the ^1H NMR spectrum indicated the CH_3 proton attached to lactone ring as a triplet at 1.80 δ and the CH proton attached to ester functionality as a multiplet at 4.61 δ (Figure 11).

2.3.5 Conclusion

In conclusion, the synthesis of (-)-mintlactone has been achieved in high yield with 90 % ee starting from (+)-pulegone and using intramolecular Wittig-Horner reaction as the key step.

2.3.6 Experimental

Synthesis of triethyl 2-phosphonopropionate 128: A mixture of triethyl phosphite (10gm, 60.24 mmol) and ethyl 2-bromopropionate (10.90 gm, 60.24 mmol) heated at 160^{o}C using reflux condenser. After 20 h, the unreacted starting material was distilled out followed by further distillation at reduced pressure at 145^{o}C/14 mm to afford the product **128** (12.90 gm).

$(EtO)_2P(O)CH(CH_3)COOEt$

128

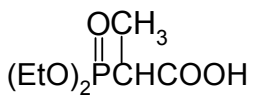
Yield: 90 %

Colorless liquid

IR (Neat): cm^{-1} 2930, 1720, 1455.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 –1.48 (m, 12H), 2.92-3.07 (m, 1H), 4.05-4.19 (m, 6H).

Synthesis of 2-(diethoxyphosphoryl)propionic acid 129: Aqueous solution of potassium hydroxide (15 ml, 85 %) was added to the solution of triethyl 2-phosphonopropionate **128** (10 gm, 42.02 mmol) in ethanol (15 ml) under stirring over a period of 5 min. The reaction mixture was stirred at room temperature. After 30 h the reaction mixture was concentrated to thick liquid and treated with ether (3 x 100 ml), ether layers were discarded, thick liquid was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. Evaporation of solvent gave 7.059 gm of hydrolyzed product **129** as a viscous liquid.



129

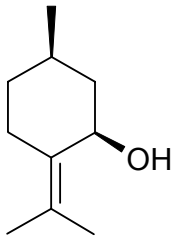
Yield: 80 %

Viscous liquid

IR (Neat): cm^{-1} 3400, 2930, 1720, 1455.

^1H NMR (200 MHz, $CDCl_3$): δ 1.25 –1.47 (m, 9H), 2.98-3.13 (m, 1H), 3.76-4.21 (m, 4H), 9.73 (bs, 1H).

Synthesis of cis-Pulegol 97: Sodium borohydride (1.9 gm, 0.05 mol) was added to a mixture of (+)-pulegone (7.6 gm, 0.05 mol) and cerium chloride heptahydrate (18.625 gm, 0.05 mol) in methanol (125 ml) over a period of 5 min under vigorous stirring under nitrogen at 0^oC. Reaction mixture was stirred for 30 min, then water was added. The mixture was extracted with ether (3 x 100 ml). Combined organic layers were washed with brine, dried over anhydrous potassium carbonate. Evaporation of solvent gave 7.546 gm of cis-pulegol as a viscous liquid.



97

Yield: 98 %

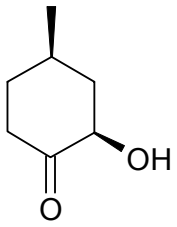
Viscous liquid

$[\alpha]_D^{25}$ – 103.00 (c = 1, MeOH) [lit.[82] $[\alpha]_D^{25}$ –80].

IR (Neat): cm^{-1} 3400, 1670, 1550, 1455..

^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 3H), 1.00-2.5 (m, 13 H), 4.69 (t, J = 6 Hz, 1H), 5.69 (bs, 1H).

Synthesis of 2-hydroxy-4-methylcyclohexanone 131: *cis*-Pulegol (7.0 gm, 45.45 mmol) was dissolved in dichloromethane (75 ml) and cooled to –78^{o}C and ozone was bubbled, after 45 min the color of reaction mixture became blue-green. Then oxygen was passed for 15 min and dimethyl sulfide (2 ml) was added, reaction mixture was stirred at 0^{o}C for 15 min and then at room temperature for 15 min. The evaporation of solvent gave crude ozonolysis product (5.23 gm) as a viscous liquid.



131

Yield: 90 %

Viscous liquid

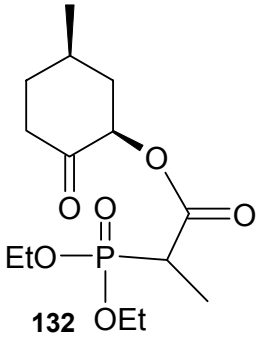
IR (Neat): cm^{-1} 3443, 2930, 1719, 1672, 1455.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00 (d, J = 7.4 Hz, 3H), 1.11-2.6 (m, 7H), 3.85 (bs, 1H), 4.20 (m, 1H).

EIMS (m/z): M^{+}128 (24), 112 (12), 84 (100), 71 (57).

Synthesis of 2-(diethoxyphosphoryl)propionic acid 5-methyl-2-oxo-cyclohexyl ester 132: 1,3-Dicyclohexylcarbodiimide (4.82 gm, 23.43 mmol) was added to a mixture of 2-hydroxy-4-methyl-cyclohexanone **131** (2.5 gm, 19.53 mmol), 2-(diethoxyphosphoryl)propionic acid **129** (4.10 gm, 19.53 mmol) in dry dichloromethane (25 ml) and cooled to 0^{o}C under vigorous stirring. The reaction was stirred at room temperature for 24 h under nitrogen. Solid was separated by filtration, water was added to the filtrate and

extracted with dichloromethane (2 x 50 ml). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The evaporation of organic layer gave the crude product. Silica gel column chromatography of crude product using petroleum ether: ethyl acetate (4:6) as eluent afforded phosphonate **132** (5.31 gm) as a viscous liquid.



132

Yield: 85 %

Colorless viscous liquid

$[\alpha]_D^{25}$ + 39 (c = 2, $CHCl_3$)

IR (Neat): cm^{-1} 2930, 1727, 1455.

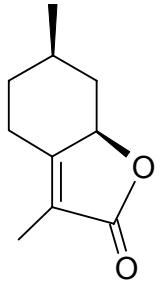
^1H NMR (200 MHz, $CDCl_3$): δ 1.02 (d, J = 7.0 Hz, 3H), 1.27-1.55 (m, 12H), 2.04-2.29 (m, 2H), 2.42 (m, 2H), 3.09-3.24 (m, 1H), 4.08-4.21 (m, 4H), 5.20-5.30 (m, 1H).

^{13}C NMR (200 MHz, $CDCl_3$): δ 10.73, 15.28, 19.88, 29.58, 33.99, 36.49, 37.04, 38.33, 39.00, 39.66, 61.81, 75.20, 167.57, 202.60.

EIMS (m/z): M^+320 (2), 261 (5), 219 (5), 179 (27), 151 (44), 123 (100), 81 (95), 65 (54).

Synthesis of (-)-mintlactone 77: Phosphonate **132** (0.75 gm, 2.344 mmol) was dissolved in dry THF and sodium hydride [(0.225 gm, 4.688 mmol) 50 % in mineral oil washed with THF] was added. The reaction mixture was refluxed for 6 h, cooled to room temperature and

then water was added. The reaction mixture was extracted with ethyl acetate (3 x 25 ml). The organic layer was separated washed with brine and dried over anhydrous Na_2SO_4. Evaporation of organic layer gave the crude product which on silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent afforded (-)-mintlactone **77** (0.350 gm) as an oil.



77

Yield: 90 %

Colorless oil

Yield: 98 %

$[\alpha]_D^{25}$ – 57 (*c* = 2, $CHCl_3$) [lit.[73] $[\alpha]_D^{25}$ – 57 (*c* = 2.4, $CHCl_3$].

IR (Neat): cm^{-1} 2929, 2870, 1754, 1688, 1455.

^1H NMR (200 MHz, $CDCl_3$): δ 1.00 (d, J = 6.6 Hz, 3H), 1.10-1.50 (m, 2H), 1.75 (m, 1H), 1.80 (t, J = 1.4 Hz, 3H). 1.95-2.25 (m, 2H), 2.41 (m, 1H), 2.82 (m, 1H), 4.61 (m, 1).

2.4 Spectra

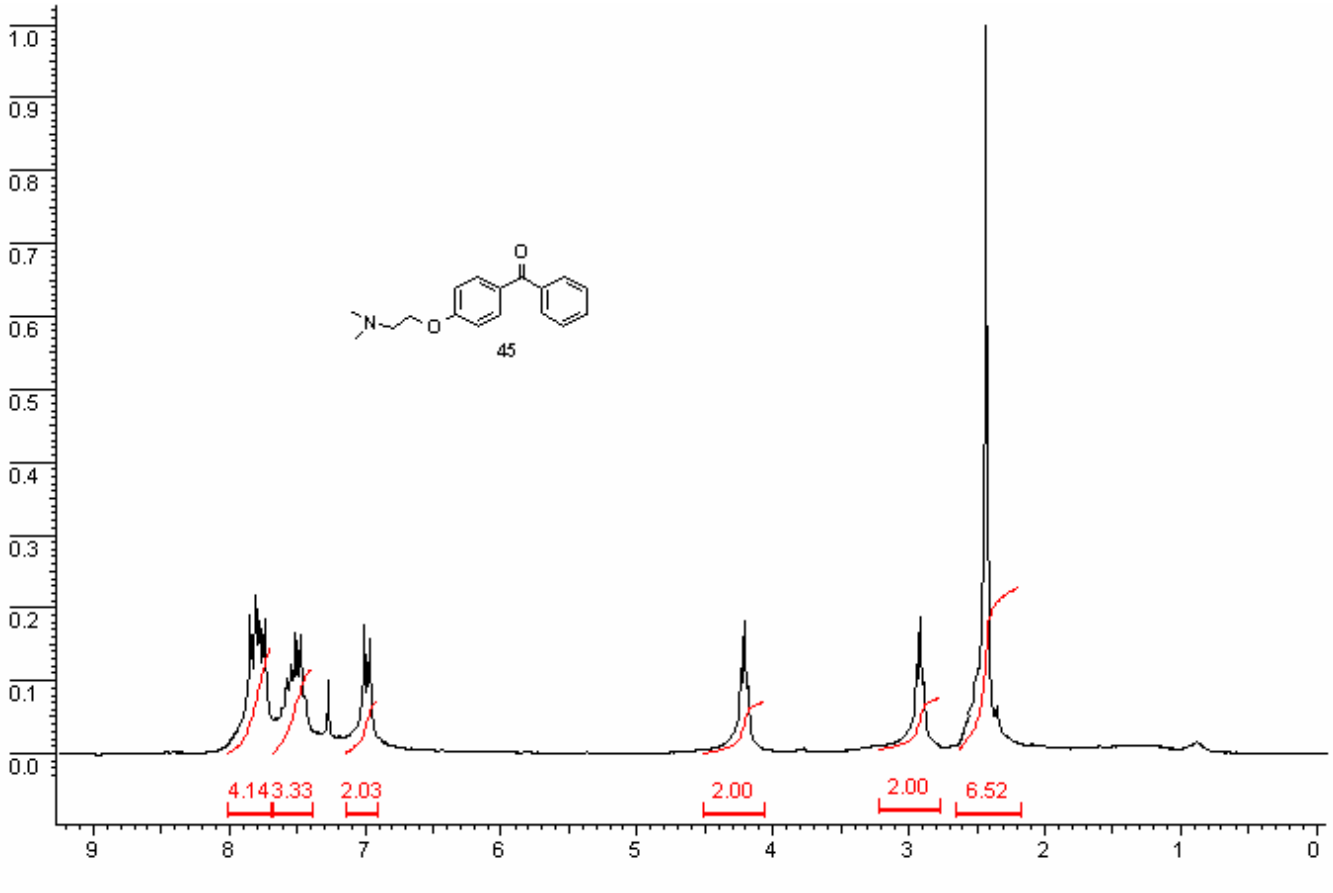


Figure 1: ^{1}H NMR spectrum of **45**

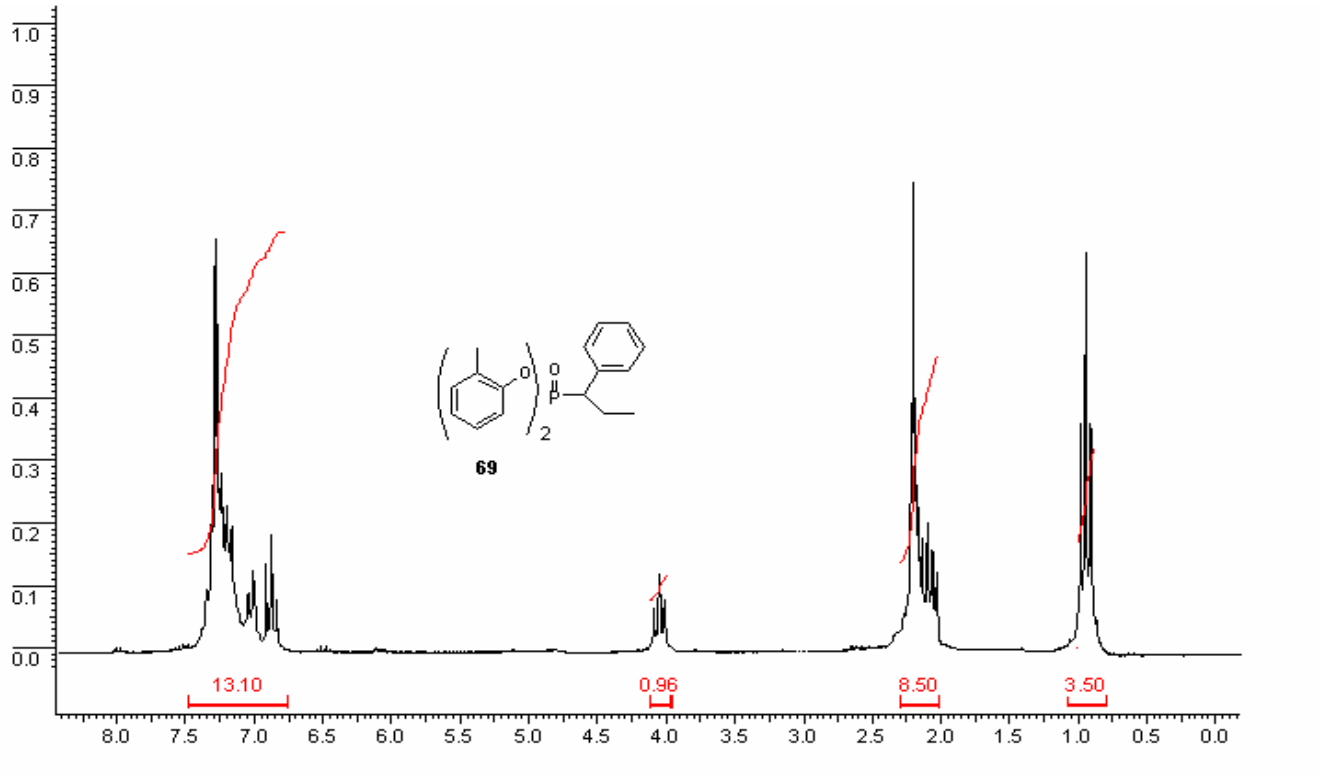


Figure 2: ^{1}H NMR spectrum of **69**

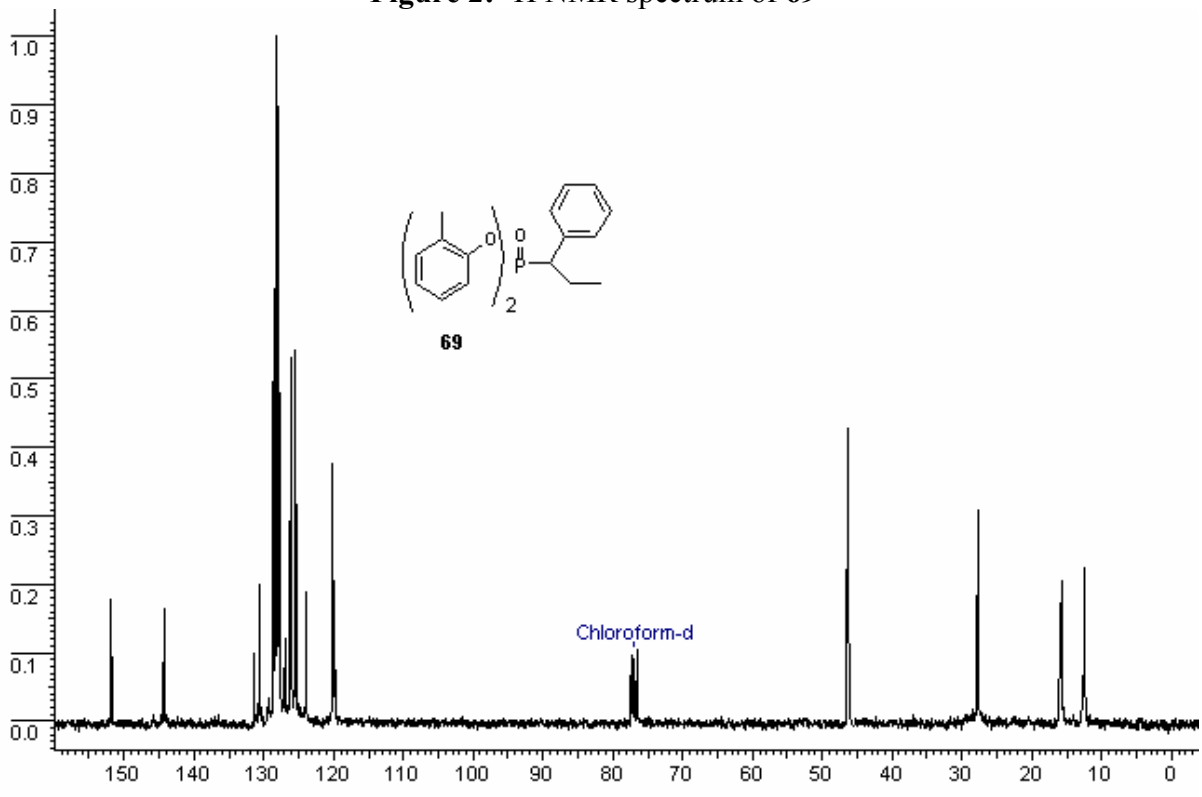


Figure 3: ^{13}C NMR spectrum of **69**

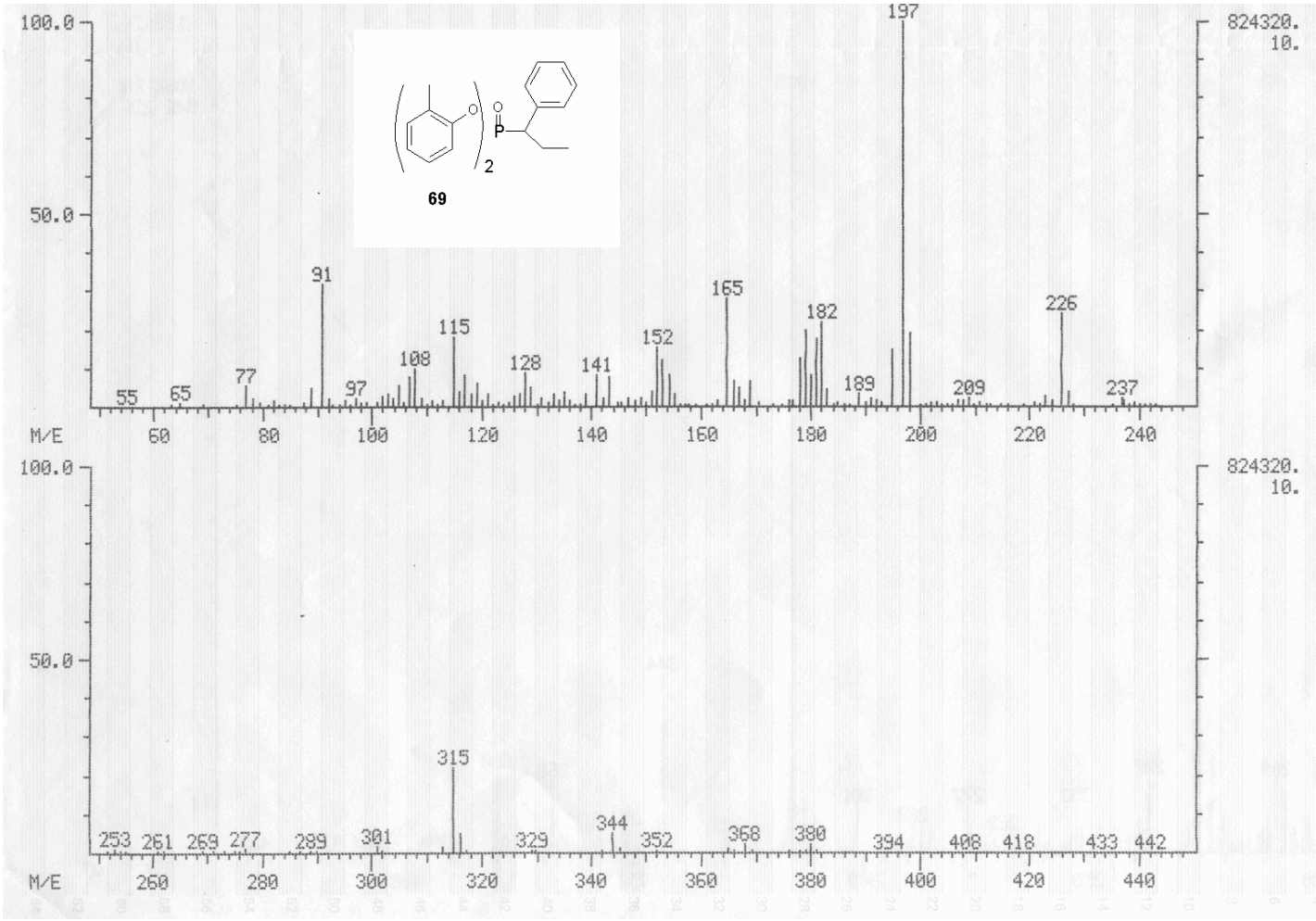


Figure 4: Mass spectrum of **69**

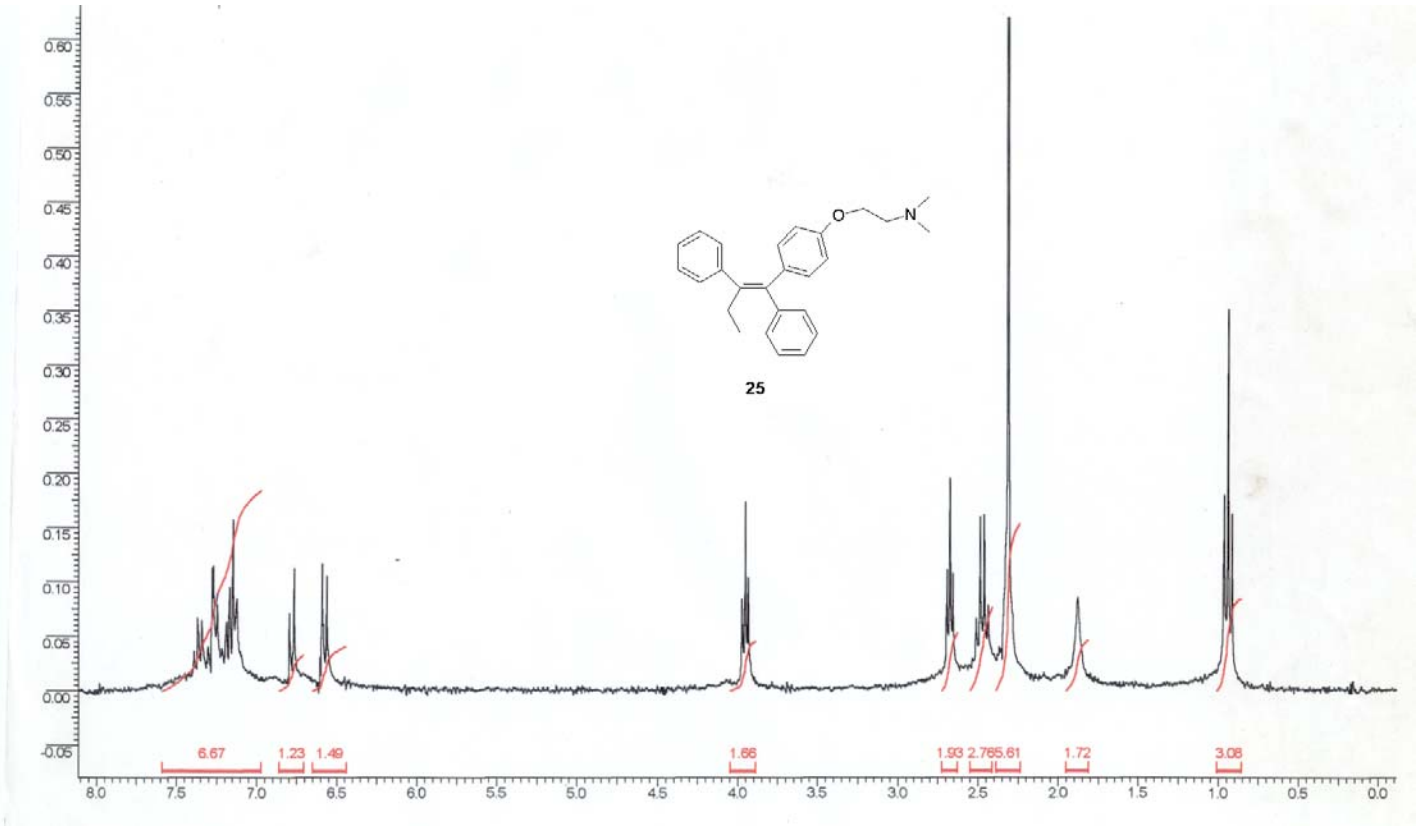


Figure 5: ^{1}H NMR spectrum of **25**

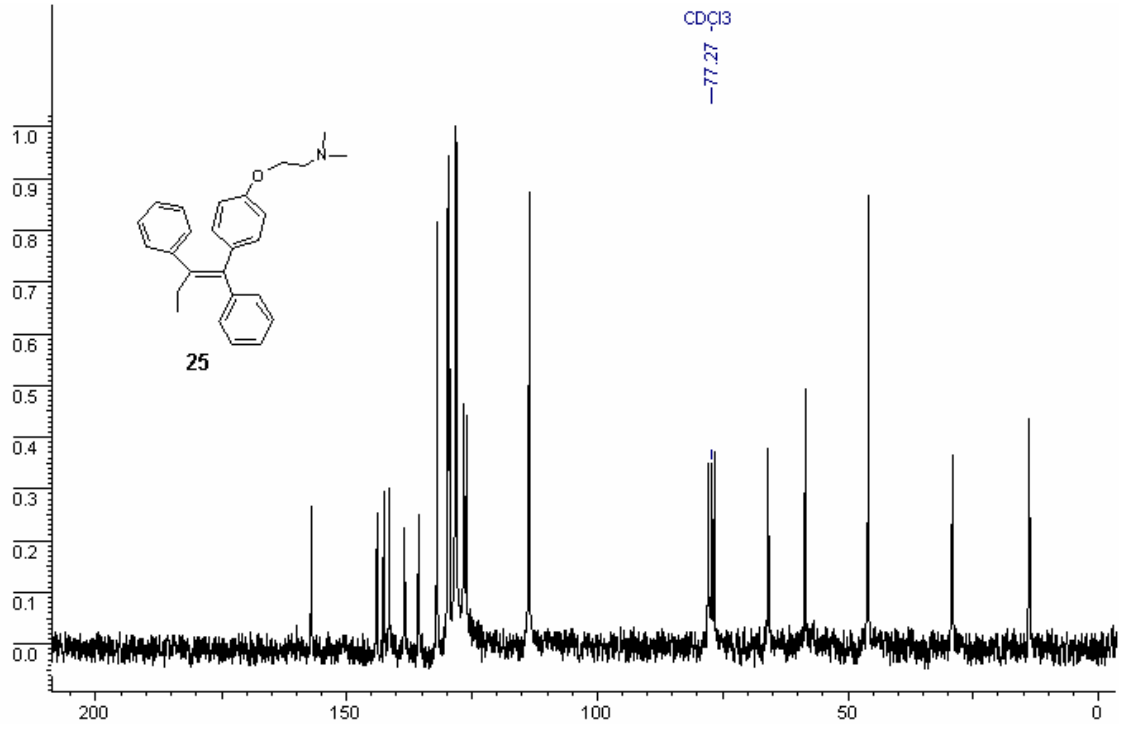


Figure 6: ^{13}C NMR spectrum of **25**

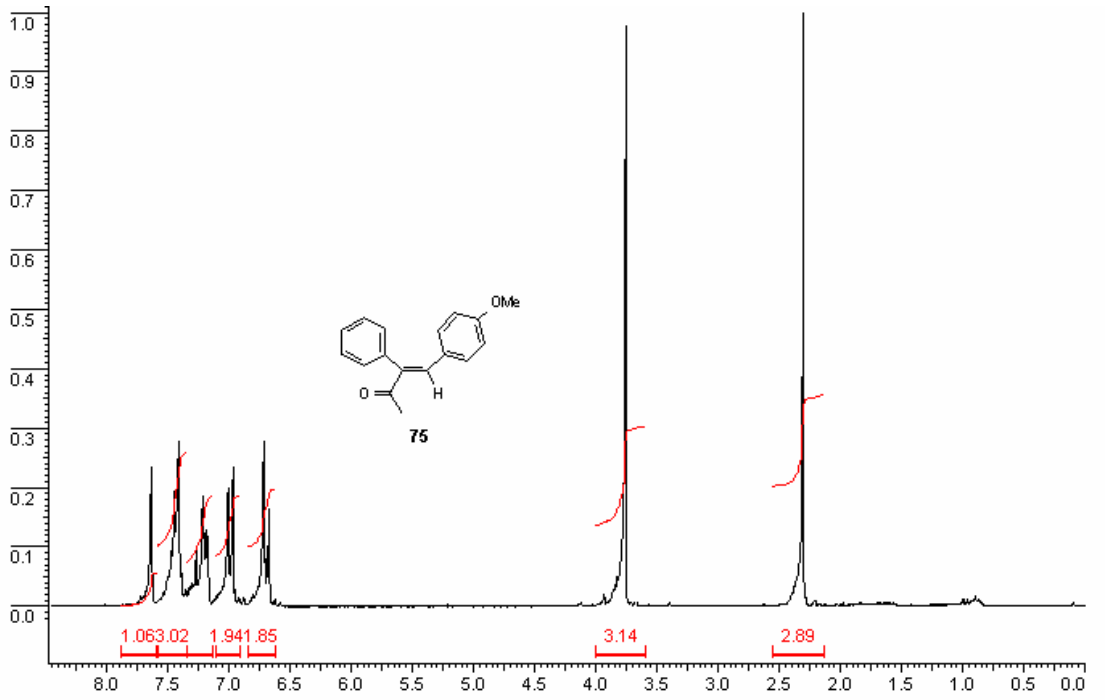


Figure 8: ^{1}H NMR spectrum of **75**

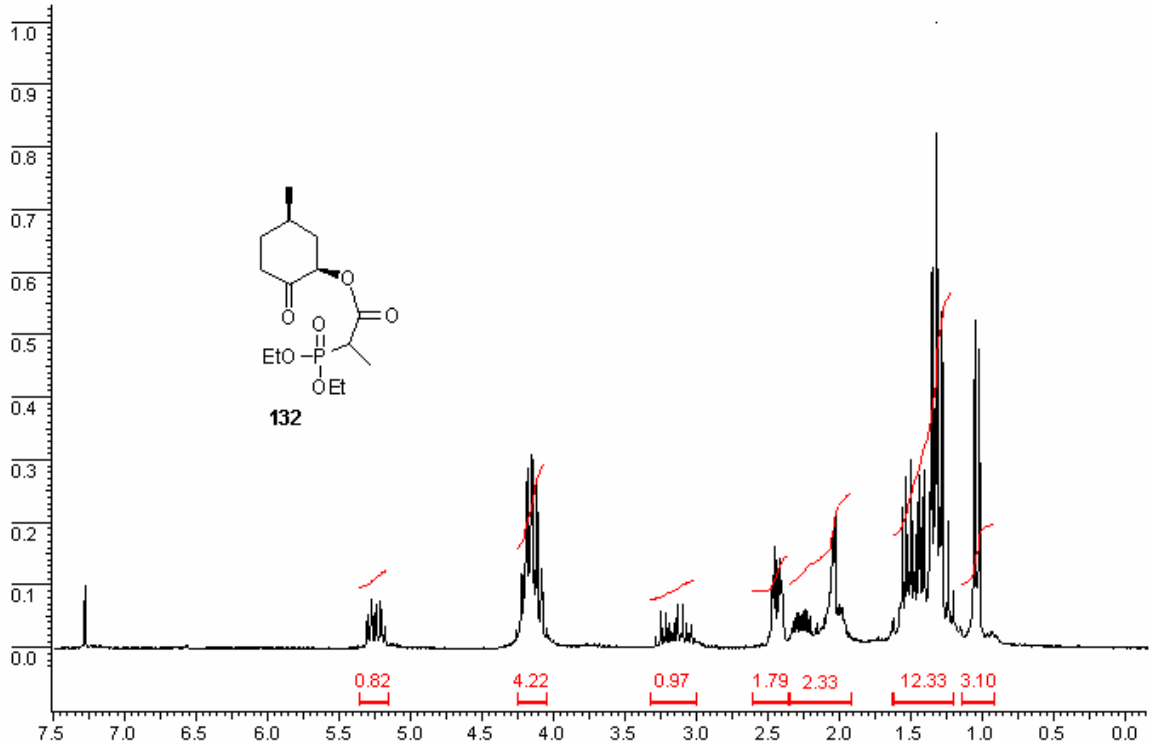


Figure 9: ^{1}H NMR spectrum of **132**

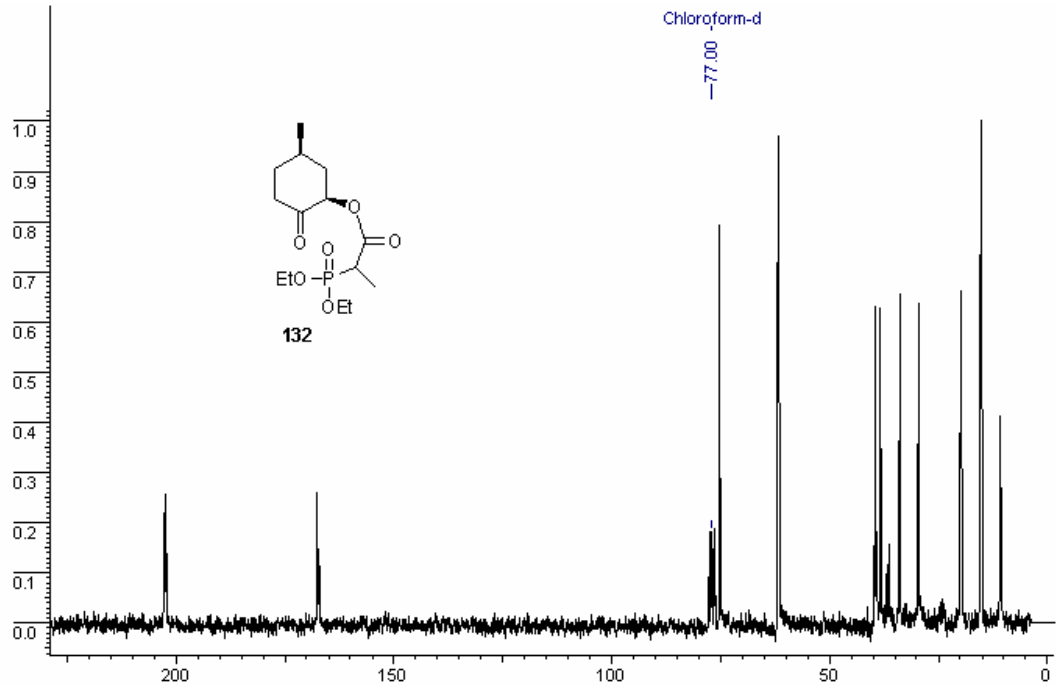


Figure 10: ^{13}C NMR spectrum of **132**

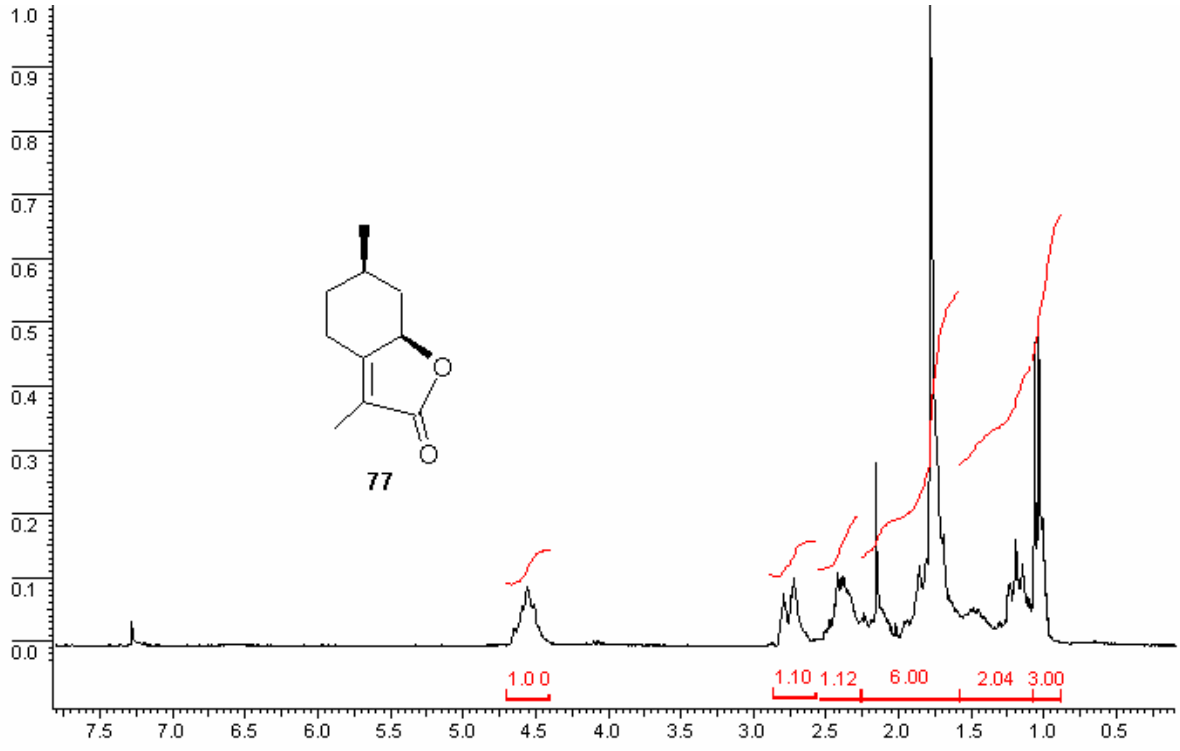


Figure 11: ^{1}H NMR spectrum of **77**

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CHAPTER 3

SYNTHESIS, CHARACTERIZATION AND CATALYTIC PROPERTIES OF YTTRIA-ZIRCONIA BASED STRONG LEWIS ACID CATALYST

3.1 Introduction

Heterogeneous catalysis is crucial to chemical technology. Innumerable chemical reactions are facilitated by catalysis. Chemical bonds are broken and new chemical bonds are formed during the catalytic process. These events occur repeatedly usually without a significant change of the catalyst. In the absence of the catalysts, this chemical transformation would either not occur or would take place with lower efficiencies of slower rates. The study of heterogeneous catalysis dates back to the early 1800s. Faraday was one of the first scientists to examine the ability of platinum to facilitate oxidation reactions. Many other catalytic processes were subsequently developed that facilitated hydrogenation, dehydrogenation, isomerization and polymerization reactions. These catalytic reactions played a key role in the development of industrial revolution.

The ability of catalyst to crack long-chain hydrocarbons was critical for the emerging automobile industry. As we are now in 21st century, we would have difficulty in imagining the world without fruits of heterogeneous catalysis. The needs for the better catalysis will only increase as environmental and economic concerns motivate the development of more efficient catalysts.

Inorganic oxides and zeolites play an extremely important role in heterogeneous catalysis. We have been involved in the development of new heterogeneous catalysis and syntheses of new catalysts viz. zeolites and some metal oxides and its utility for some organic transformations and for auto exhaust emission control etc. In continuation of these efforts, we synthesized first time an yttria-zirconia based strong Lewis acid catalyst and its Lewis-acidity has been successfully exploited for the acceleration of Diels-Alder reaction (C-C bond forming reaction) under mild conditions.[1] The possibility of using it for the other organic synthetic transformations has been investigated.

3.2 SECTION A

Synthesis and Physicochemical Characterization of Yttria-Zirconia based Lewis acid Catalyst

3.2.1 Synthesis of Catalyst

The catalyst was prepared by mixing aq. solutions of yttrium nitrate and zirconyl nitrate in the mole ratio 16:84, to which aqueous ammonia (28%) was added under vigorous stirring until a pH of 8.5 was achieved and precipitate was formed. Washing with deionized water, drying at 110°C for 24 hours, treating with sulfuric acid (4M), drying at 120°C and subsequent programmed calcination at 500°C for 3 hours at a heating rate of 2°C min^{-1} resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mol% Zr, 15.6 mole% Y and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

3.2.2 Physicochemical Characterization

The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with N-filtered Cu-Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile (ammonia) of the cerium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner-Emmett-Teller) N_2 adsorption using a Omnisorp 100CX apparatus.

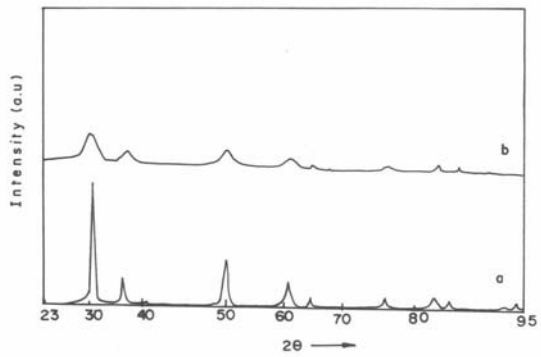


Figure 1. X- ray powder diffraction pattern of the yttrium based catalyst prior to (a) and after (b) sulfation. The diffractogram was recorded on a Rigaku diffractometer, model D/Max. IIIVC, with Ni-filtered $Ca_{k\alpha}$ radiation. I = intensity (arbitrary units).

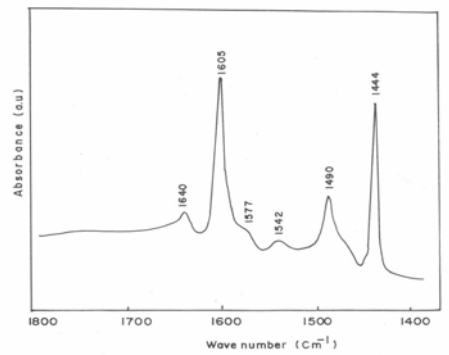


Figure 2. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst, recorded on a Nicolet 60 SXB FTIR spectrometer. A = absorption (arbitrary units).

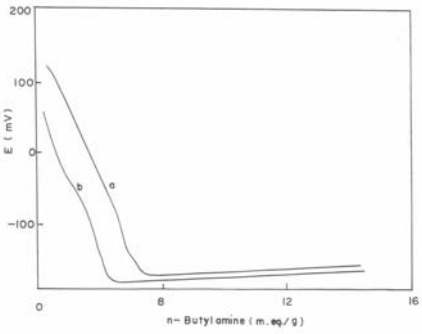


Figure 3. Potentiometric titration curves of the sulphated catalyst with yttrium (curve a) and without yttrium (curve b) in CH_3CN. For details see ref, [19]. n = number of molar equivalents of n-butylamine per g.

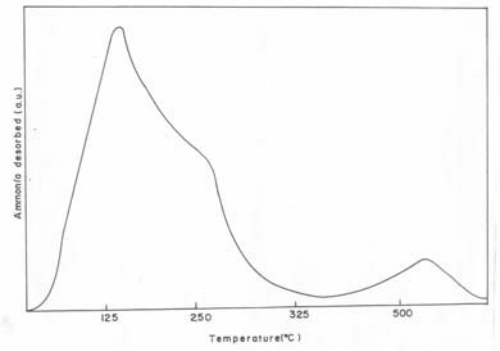


Figure 4. TPD profile (ammonia) of the yttrium-based catalyst, recorded on a Sorbstar apparatus, Institute of Isotopes, Hungary, with He as the carrier gas, a flow rate of 50 mL min^{-1}, and a heating rate of 10 K min^{-1} from room temperature to 625°C. NH_3 = amount of ammonia desorbed (arbitrary units).

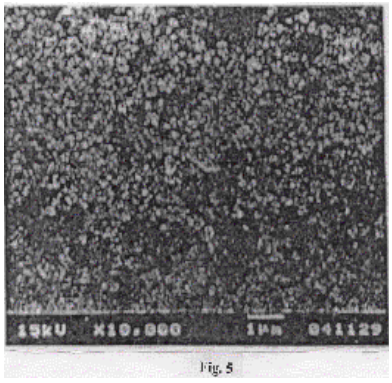


Figure 5. Scanning electron micrograph of the catalyst

3.2.3 Results and discussion

The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques. The X-ray powder diffraction profile of the catalyst shows the formation of a cubic phase (Figure 1). The IR spectra of pyridine adsorbed on the catalyst show absorption bands at 1640, 1605, 1577, 1542, 1490 and 1444 cm^{-1} (Figure 2).The strong absorption bands at 1605 and 1444 cm^{-1} indicate the presence of coordinated pyridine at the Lewis acid sites of the catalyst. The weak absorption at 1542 cm^{-1}, attributed to the pyridinium ion[2] indicates the presence of a few Brönsted acid sites. The potentiometric titration of the acid sites with n-butylamine in nonaqueous medium (Figure 3) shows the influence of yttrium in enhancing the number of acid sites.[3] The amount of n-butylamine consumed was 7.7 mol equiv g^{-1} for the yttrium-based catalyst compared to 5.8 mol equiv g^{-1} for the yttrium-free catalyst. The presence of very strong acid sites in the catalyst is indicated by the peak maxima at 530°C in the TPD profile (Figure 4).[4] The scanning electron micrograph of the sample shows the presence of uniform-sized (around 0.3 μm) particles (Figure 5). The surface area of the sample determined by the BET method was 150 m^2g^{-1} The lattice defects caused by the incorporation of yttrium in the Zr^{4+} sites appear to enhance the number and strength of the Lewis acid sites of the catalyst.

3.2.4 Conclusion

In conclusion we have synthesized sulfated yttria-zirconia based strong Lewis acid catalyst for the first time which was fully characterized by physicochemical characterization methods such as XRD, SEM, TPD, and FT-IR.

3.3 SECTION B

Organic Transformations Catalyzed by Yttria-Zirconia Based Strong Lewis Acid Catalyst

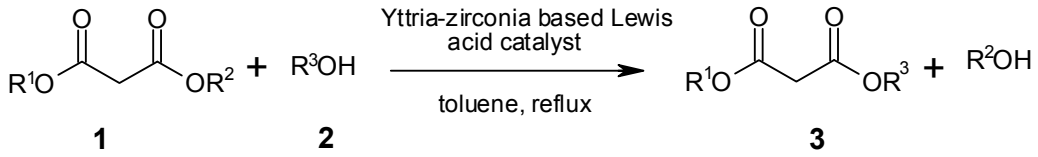
3.3.1 SECTION I

Transesterification of β-Keto Esters

3.3.1.1 Introduction

Transesterification is an important reaction which has wide applications both in academic and industrial research.[5] In general, the transesterification reaction is accelerated by the protic acid,[6] Lewis acid[7] catalysts such as boron tribromide,[6] anhydrous aluminium trichloride embedded in polystyrene divinyl benzene,[7] Brönsted acid catalysts e.g. hydrochloric, phosphoric, sulfonic, sulfuric or *p*-toluenesulfonic acid[8] and basic catalysts such as metal alkoxides,[9] metal carbonates[10] etc. Transesterification of β-keto esters catalyzed by DMAP has been also reported in good to excellent yields.[11] Another publication[12] describes an efficient method of transesterification which is restricted only to tertiary butyl esters thus lacking generality. Otera et. al.[13] has shown that ketoesters can be smoothly transesterified by tetrabutyldistannoxanes as catalyst under mild condition. More recently use of sulfated tin oxide,[14] zeolites[15] kaolinitic clay,[16] NBS[17] and polymer supported lipase catalyst[18] has been reported for transesterification. Nevertheless there are sufficient drawbacks to most of these procedures to justify the need for a general, selective and practical method of transesterification. During our recent endeavor with yttria-zirconia based Lewis acid mediated synthesis of acetals[19] from carbonyl compounds, interestingly we observed an efficient transesterification instead of carbonyl protection when the reaction was applied to β-keto esters. This prompted us to initiate a

systematic investigation on yttria-zirconia based Lewis acid catalyzed transesterification of β-keto ester and herein results of this study are described (Scheme 1).



Scheme 1

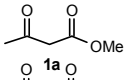
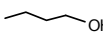
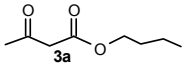
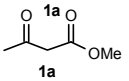
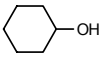
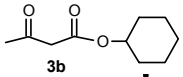
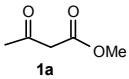
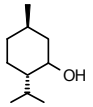
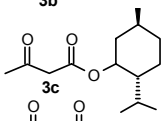
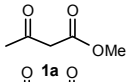
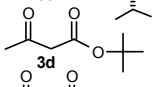
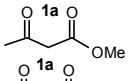
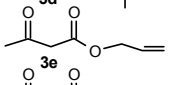
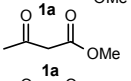
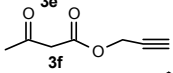
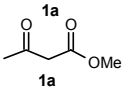
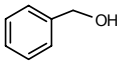
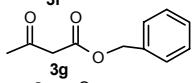
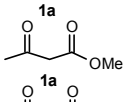
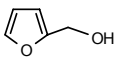
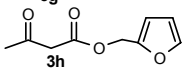
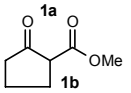
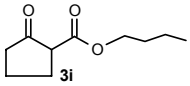
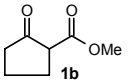
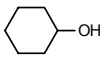
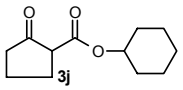
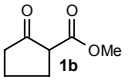
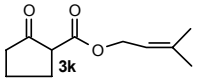
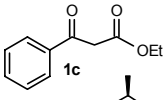
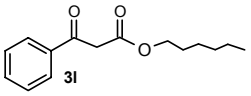
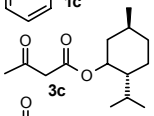
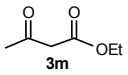
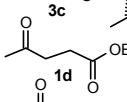
3.3.1.2 Results and discussion

In a typical experimental procedure, when the β-keto esters were treated with alcohols in the presence of catalytic amount of yttria-zirconia catalyst, the corresponding transesterified products were obtained in good to excellent yields (Table 1). Thus, methyl acetoacetate on reaction with butanol in the presence of yttria-zirconia as catalyst, furnished product **3a** in 67 % yields (Table 1, entry 1). The IR spectrum of **3a** showed two bands at 1740, 1710 cm^{-1} corresponding to ester and ketone respectively. In ^1H NMR spectrum the CH_3 protons of butyl group appeared at δ 0.9 as a triplet and methyl at C-3 position appeared as a singlet at δ 2.20. While C-2 methylene protons appeared as a singlet at 3.45, 4.98 and 12.2 δ due to the presence of keto-enol form, the CH_2-O protons was observed at 4.1 δ as a triplet. Further structure was proved by mass spectrum which showed M^+ peak at 158. The present procedure is quite general as a wide range of structurally varied β-keto esters such as open chain, cyclic and aromatic ones underwent transesterification with a variety of alcohols. The reaction proceeds smoothly with primary and secondary alcohols in excellent yields; whereas transesterification of t-butyl esters (Table 1, entry 4) which is often problematic in acid catalyzed reaction, is also

realized by this reagent though in moderate yield. Another noteworthy feature of this methodology is that unsaturated alcohols like allylic and propargyl alcohols underwent transesterification reaction smoothly affording the corresponding products in excellent yields (Table1, entries 5, 6) although it should be noted that transesterification with unsaturated alcohols is rather difficult as it is offset by facile decarboxylated rearrangement.[20-21] The superiority of this procedure can be clearly visualized in transesterification reactions which led to the synthesis of β-keto esters with an aromatic moiety in excellent yields (Table 1, entries 7, 8). In this connection it should be mentioned that a recent report employing a tin based superacid catalyst though efficient for the synthesis of alkyl β-keto esters but failed with aromatic substrates.[14] It is important to mention that the reaction appears to be specific only for the transesterification of β-keto esters. Other esters like α-keto esters, γ-keto esters unsaturated esters as well as normal esters failed to undergo the reaction. The difference in the reactivity of β-keto esters from other esters in transesterification may probably be due to the formation of acyl ketene intermediate in the former as proposed by Campbell and Lawrie.[22] It is clear from Table 1 that while conversion from methyl / ethyl ester to higher homologues appears to be efficient by this procedure, the reverse transformations as in the case of menthyl ester to ethyl alcohol (Table 1, entry 13) could be achieved only in moderate yields.

In order to explore the generality and scope of yttria-zirconia based Lewis acid catalyzed transesterification reaction, the procedure has been extended to a variety of other nucleophiles such as thiols and amines. The conversion of β-keto ester to its thio analogue which is often problematic due to its facile decarboxylation upon hydrolysis, was achieved by this procedure though in moderate yield (Table 2, entries 1-3).

Table 1: Transesterification of various β-keto esters with different alcohols catalyzed by yttria-zirconia based Lewis acid catalyst

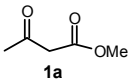
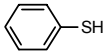
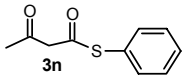
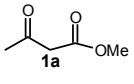
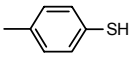
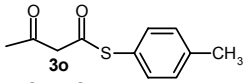
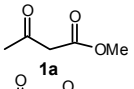
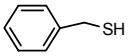
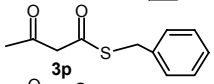
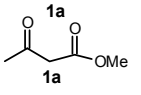
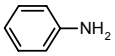
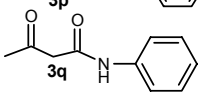
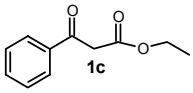
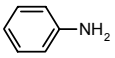
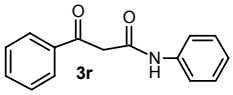
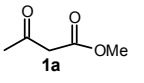
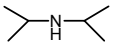
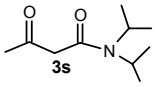
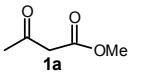
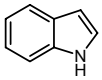
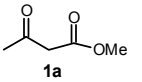
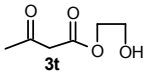
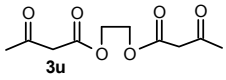
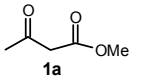
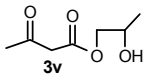
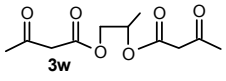
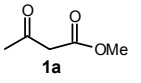
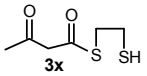
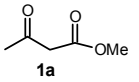
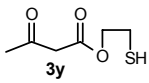
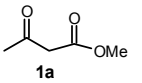
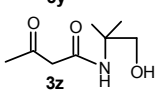
Entry	Keto ester **1**	Alcohol **2**	Time (h)	Product[a] **3**	Yield (%)[b]
1			10		67
2			13		92
3			18		98
4			15		39
5			18		66
6			15		67
7			14		99
8			13		95
9			10		62
10			6		94
11			8		82
12			10		93
13		EtOH	18		35[b]
14			9	no reaction	
15			15	no reaction	
16			15	no reaction	

[a]Yields refer to isolated pure products. [b]As the reaction did not proceed in toluene as solvent, excess of ethanol was used to effect reverse transesterification.

In a similar manner aniline underwent reaction with a variety of β-keto esters smoothly to give the corresponding amidation products (Table 2, entries 4-5). Even the hindered

amine such as diisopropyl amine furnished the desired product in repeatable yield (Table 2, entry 6).

Table 2: Selective transesterification of β-keto ester with thiol, amine, diol, mercapto alcohol and amino alcohol catalyzed by yttria-zirconia based Lewis acid catalyst

Entry	Keto ester **1**	Alcohol **2**	Time (h)	Product **3**	Yield (%)[a]
1	 **1a**		10	 **3n**	42[b]
2	 **1a**		15	 **3o**	55
3	 **1a**		16	 **3p**	50
4	 **1a**		6	 **3q**	59[c]
5	 **1c**		8	 **3r**	95[c]
6	 **1a**		8	 **3s**	60[c]
7	 **1a**		24	no reaction	
8	 **1a**		8	 **3t**	62
				 **3u**	30
9	 **1a**		8	 **3v**	68
				 **3w**	15
10	 **1a**		9	 **3x**	59[b]
11	 **1a**		9.5	 **3y**	86[b]
12	 **1a**		10	 **3z**	91[c]

[a]Yields refer to isolated pure products. [b]The formation of ketone protected product was not observed. [c]Only the transaminated product was isolated.

Encouraged by this results, it was felt worthwhile to study the reactivity pattern of different kind of thiols, mercapto alcohols and amino alcohols towards β-keto ester over yttria-zirconia based Lewis acid catalyst and results of such study are presented in Table 2. Thus it was observed that the reaction is selective for the primary alcohol over secondary in the case of 1,2-diol; however a mixture of mono- and di-transesterified products were obtained (Table 2, entry 9). Similarly hydroxyl group of 2-mercapto ethanol reacts preferentially over thiol (Table 2, entry 11). In the case of aliphatic amino alcohols, amine being more nucleophilic than alcohol, it reacts faster with ester giving the corresponding amidation product in excellent yield (Table 2, entry 12), which is in agreement with Mukaiyama procedure.[23]

3.3.1.3 Conclusion

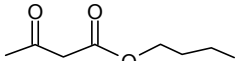
In conclusion, we have demonstrated that yttria-zirconia based Lewis acid catalyst serves as an efficient catalyst to effect transesterification of β-ketoesters by a variety of alcohols. Besides, the high selectivity and reactivity exhibited by the catalyst will present a better and more practical alternative to the existing methodologies and should find widespread applications in organic synthesis.

3.3.1.4 Experimental

General procedure for transesterification: A mixture of ketoester (1 eq), alcohol (1 eq), and catalyst (20 % by weight) in toluene was refluxed in a two-necked round bottomed flask. The reaction was monitored by T. L. C. After completion of the reaction, the catalyst was filtered and the filtrate was concentrated. The residue was chromatographed on a silica gel column using pet-ether: ethyl acetate (9.5: 0.5) to afford the ester in good to excellent yields.

3-Oxobutyric acid butyl ester (3a):

Colorless liquid.



3 a

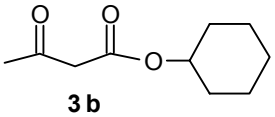
IRν_{max} / cm^{-1} (Neat): 2920, 1740, 1710, 1620, 1140, 1040.

^{1}H NMR ($CDCl_3$) δ: 0.9 (t, *J* = 6.8 Hz, 3H), 1.3 (m, 2H), 1.6 (m, 2H), 2.2 (s, 3H), [3.45, 4.98, 12.2] (s, 2H), 4.1 (t, *J* = 6.8 Hz, 2H).

MS (m/z, rel. int %): M^+158 (25.75), 143 (2.99), 116 (4.79), 103 (100), 85 (80.84), 73 (2.4), 69 (5.99), 55 (10.18).

3-Oxobutyric acid cyclohexyl ester (3b):

Colorless liquid.



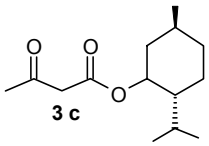
3 b

IRν_{max} / cm^{-1} (Neat): 2910, 1740, 1720, 1644, 1149, 1031.

^{1}H NMR ($CDCl_3$) δ: 1.1-2.0 (m, 10H), 2.25 (s, 3H), [3.4, 4.9, 12.25] (s, 2H), 4.7-4.9 (m, 1H).

MS (m/z, rel. int %): M^+184 (1.79), 103 (100), 99 (22.16), 85 (55.09), 82 (62.28), 76 (19.16), 55 (3.59).

3-Oxobutyric acid 5-methyl-2-(1-methylethyl) cyclohexyl ester (3c):

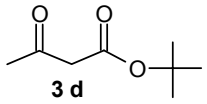
Colorless liquid 

IRν_{max} / cm^{-1} (Neat): 3320, 2927, 1740, 1720, 1644, 1149, 1031.

^{1}H NMR ($CDCl_3$) δ: 0.85 (d, *J* = 6 Hz, 3H), 0.9-1.2 (m, 8H), 1.4-1.5 (m, 2H), 1.65-1.75 (m, 2H), 1.9-2.1 (m, 3H), 2.25 (s, 3H), [3.45, 4.9, 12.2] (s, 2H), 4.75 (dt, *J* = 12 and 6 Hz, 1H).

MS (m/z, rel. int %): M^+240 (7.8), 179 (2.99), 155 (42.51), 138 (100), 123 (47.30), 103 (8.38), 95 (70.66), 81 (38.92), 69 (6.59), 55 (3.4).

3-Oxobutyric acid *t*-butyl ester (3d):

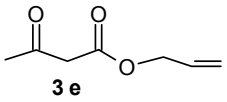
Colorless liquid. 

IRν_{max} / cm^{-1} (Neat): 2920, 2890, 1735, 1690, 1640, 1150, 1075, 1040.

^{1}H NMR ($CDCl_3$) δ: 1.5 (s, 9H), 2.2 (s, 3H), [3.35, 4.98, 12.22] (s, 2H).

MS (m/z, rel. int %): M^+158 (2.7), 131 (14.97), 123 (17.96), 103 (18.56), 97 (48.50), 91 (31.98), 85 (59.28), 69 (78.44), 57 (100).

3-Oxobutyric acid allyl ester (3e):

Colorless liquid 

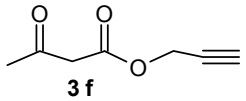
IRν_{max} / cm^{-1} (Neat) : 2920, 1738, 1710, 1640, 1130, 1080, 1040.

^{1}H NMR ($CDCl_3$) δ: 2.2 (s, 3H), [3.45, 4.95, 12.25], (s, 2H), 4.6 (d, *J* = 5.6 Hz, 2H), 5.25 (dd, *J* = 8.9 Hz, *J* = 4.4 HZ, 2H), 5.7-6.0 (m, 1H).

MS (m/z, rel. int %): M^+142 (2.99), 124 (2.4), 114 (2.7), 100 (24.55), 96 (2.99), 85 (100), 69 (13.77), 58 (14.37).

3-Oxobutyric acid prop-2-ynyl ester (3f):

Colorless liquid



3 f

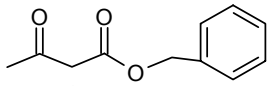
IRν_{max} / cm^{-1} (Neat): 2950, 2926, 2260, 1744, 1719, 1404, 1148, 1028.

^{1}H NMR ($CDCl_3$) δ: 2.28, (s, 3H), 2.5 (t, J = 2.5 Hz, 1H), [3.51, 4.95, 12.5] (s, 2H), 4.65 (d, J = 2.5 Hz, 2H).

MS (m/z, rel. int %): M^+ 140 (5), 125 (5), 107 (15), 98 (88), 85 (100), 69 (72), 57 (9), 55 (52), 53 (49).

3-Oxobutyric acid benzyl ester (3g):

Colorless liquid



3 g

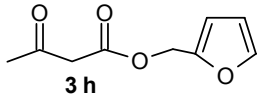
IRν_{max} / cm^{-1} (Neat): 2920, 1735, 1710, 1640, 1140, 1030.

^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H), [3.45, 4.95, 12.25] (s, 2H), 5.2 (s, 2H), 7.4 (s, 5H).

MS (m/z, rel. int %): M^+192 (2.39), 164 (5.99), 107 (64.07), 98 (20.36), 91 (100), 79 (29.95), 65 (15.57), 58 (2.99).

3-Oxobutyric acid furan-2-yl methyl ester (3h):

Colorless liquid



3 h

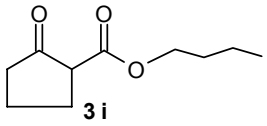
IRν_{max} / cm^{-1} (Neat): 2926, 1743, 1717, 1640, 1403, 1148, 1018.

^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H), [3.48, 5.01, 11.96] (s, 2H), 5.15 (s, 2H), 6.3-6.45 (m, 2H), 7.43 (m, 1H).

MS (m/z, rel. int %): M^+ 182 (5.99), 154 (2.99), 97 (59.28), 85 (6.59), 81 (100), 69 (8.38), 58 (5.39), 53 (15.56).

2-Oxocyclopentanecarboxylic acid butyl ester (3i):

Colorless liquid



3 i

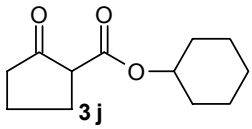
IRν_{max} / cm^{-1} (Neat): 2930, 1740, 1710, 1640, 1110, 1070.

^{1}H NMR ($CDCl_3$) δ: 0.9 (t, *J* = 6.8 Hz, 3H), 1.2-2.2 (m, 10H), 3.15 (t, *J* = 8.3 Hz, 1H), 4.1 (t, *J* = 6.8 Hz, 2H).

MS (m/z, rel. int %): M^+184 (2.99), 156 (8.38), 142 (3.59), 128 (11.38), 111 (100), 100 (35.33), 82 (43.11), 73 (86.83), 68 (11.38), 55 (44.31).

2-Oxocyclopentanecarboxylic acid cyclohexyl ester (3j):

Colorless liquid



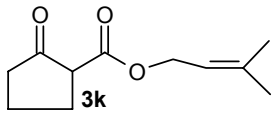
3 j

IRν_{max} / cm^{-1} (Neat): 2920, 1740, 1710, 1650, 1110, 1040.

^{1}H NMR ($CDCl_3$) δ: 1.15-2.5 (m, 16H), 3.15 (t, *J* = 8.3 Hz, 1H), 4.65-4.95 (m, 1H).

MS (m/z, rel. int %): M^+210 (7.78), 182 (2.69), 143 (23.05), 128 (67.66), 111 (53.59), 100 (100), 88 (8.98), 83 (44.61), 73 (10.78), 67 (14.37), 55 (17.96).

2-Oxocyclopentanecarboxylic acid 3-methyl-but-2-enyl ester (3k):



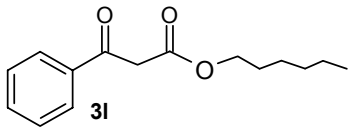
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 2900, 2680, 2325, 1740, 1710, 1670, 1640, 1120, 1020.

^{1}H NMR ($CDCl_3$) δ: 1.65 (s, 3H), 1.75 (s, 3H), 1.8-2.24 (m, 6H), 3.15 (t, *J* = 8.3 Hz, 1H), 4.65 (d, *J* = 8.3 Hz, 2H), 5.35 (t, *J* = 8.3 Hz, 1H).

MS (m/z, rel. int %): M^+196 (1.49), 178 (2.09), 168 (2.99), 143 (6.88), 129 (19.76), 111 (46.70), 85 (76.65), 69 (100), 59 (9.88), 55 (32.34).

3-Oxo-3-phenylpropionic acid *n*-hexyl ester (3l):



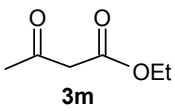
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 2929, 2861, 1737, 1686, 1636, 1148, 1020.

^{1}H NMR ($CDCl_3$) δ: 0.87 (t, *J* = 6.8 Hz, 3H), 1.15-1.7 (m, 8H), [4.01, 5.69, 12.60] (s, 2H), 4.2 (t, *J* = 6.8Hz, 2H), 7.4-7.8 (m, 5H).

MS (m/z, rel. int %): M^+ 248 (3.59), 189 (1.8), 165 (40.12), 147 (15.57), 120 (3.29), 105 (100), 77 (14.67), 69 (2.39), 56 (1.80).

3-Oxobutyric acid ethyl ester (3m):



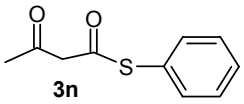
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 2933, 1740, 1717, 1638, 1408, 1150, 1032.

^{1}H NMR ($CDCl_3$) δ: 1.25 (t, *J* = 6.8 Hz, 3H), 2.2 (s, 3H), [3.4, 4.9, 12.3] (s, 2H), 4.15 (q, *J* = 6.8 Hz, 2H).

MS (m/z, rel. int %): M^+ 130 (17.37), 115 (6.89), 102 (32.63), 85 (100), 69 (32.64), 60 (11.98).

3-Oxothiobutyric acid *S*-phenyl ester (3n):



3n

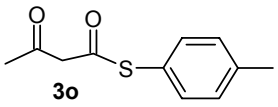
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3060, 2923, 1720, 1698, 1620, 1072.

^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), [3.74, 5.5, 12.65] (s, 2H), 7.35-7.7 (m, 5H).

MS (m/z, rel. int %): M^+ 194 (14.37), 135 (2.99), 110 (100), 85 (62.57), 77 (3.29), 65 (4.19).

3-Oxothiobutyric acid *S*-*p*-tolyl ester (3o):



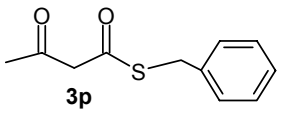
3o

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3050, 2923, 1725, 1695, 1625, 1070.

^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 2.4 (s, 3H), [3.8, 5.5, 12.6] (s, 2H), 7.2-7.5 (m, 4H).

3-Oxothiobutyric acid *S*-benzyl ester (3p):



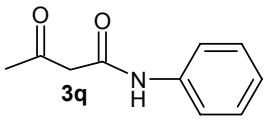
3p

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3060, 2920, 1730, 1698, 1640, 1060.

^{1}H NMR ($CDCl_3$) δ : 2.23 (s, 3H), [3.8, 5.5, 12.6] (s, 2H), 5.8 (s, 2H), 7.2 (s, 5H).

3-Oxo-*N*-phenylbutyramide (3q):



3q

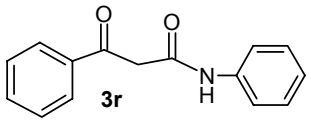
White solid, M.P. 82^{o}C

IRν_{max} / cm^{-1} (Neat): 3310, 1718, 1665, 1597, 1543, 1170.

^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 3H), 3.58 (s, 2H), 7.08-7.55 (m, 5H), 9.12 (bs, 1H).

MS (m/z, rel. int %): M^+ 177 (65.87), 144 (2.99), 134 (4.19), 119 (19.76), 106 (2.99), 93 (100), 85 (7.18), 77 (8.38), 65 (7.78), 58 (2.39).

***N*-Phenyl-3-oxo-3-phenylpropionamide (3r):**



3r

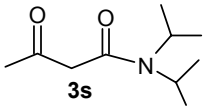
White solid, M.P. 98-100^{o}C

IRν_{max} / cm^{-1} (Neat): 3256, 3089, 1710, 1665, 1557.

^{1}H NMR ($CDCl_3$) δ: 4.1 (S, 2H), 7.05 – 8.1 (m, 10H).

MS (m/z, rel. int %): M^+ 239 (42.51), 147 (4.49), 120 (53.89), 105 (95.80), 93 (98.80), 83 (73.05), 77 (100), 65 (28.44), 57 (15.57).

***N, N*-Diisopropyl-3-oxo-butyramide (3s):**



3s

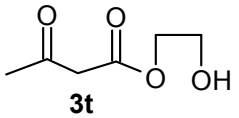
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 1962, 1713, 1635, 1445.

^{1}H NMR ($CDCl_3$) δ: 1.17 (d, J = 6.25, 6H), 1.38 (d, J = 6.25, 6H), 2.2 (s, 3H), 3.5 (s, 2H), 3.8 (m, 2H).

MS (m/z, rel. int %): M^+ 185 (23.35), 170 (17.06), 142 (41.90), 128 (8.08), 100 (29.94), 86 (100), 70 (24.85), 58 (64.67).

3-Oxobutyric acid 2-hydroxyethyl ester (3t):



3t

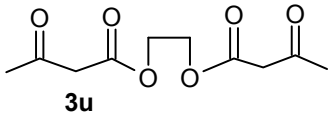
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3415, 2932, 1740, 1712, 1640, 1403, 1154, 1039.

^{1}H NMR ($CDCl_3$) δ: 1.75 (bs, 1H), 2.2 (s, 3H), [3.5, 5.0, 12.58] (s, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 4.65 (t, *J* =5.9 Hz, 2H);

MS (m/z, rel. int %): M^+ 146 (7.78), 128 (6.59), 116 (52.69), 103 (40.70), 85 (100), 69 (8.08), 58 (3.59).

Bis-(3-oxobutyric acid)ethyl-1,2-diester (3u):



3u

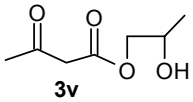
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 2928, 1744, 1715, 1630, 1404, 1148, 1046.

^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 6H), [3.5, 5.02, 11.95] (s, 4H), 4.38 (s, 4H).

MS (m/z, rel. int %): M^+ 230 (1.8), 188 (12.58), 146 (3.89), 129 (46.7), 113 (30.84), 103 (11.68), 85 (100), 69 (14.97), 58 (1.8).

3-Oxobutyric acid-2-hydroxypropyl ester (3v):



3v

Colorless liquid

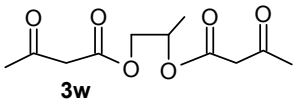
IRν_{max} / cm^{-1} (Neat): 3410, 2920, 2854, 1725, 1710, 1640, 1046.

^{1}H NMR ($CDCl_3$) δ: 1.23 (d, *J* = 6.8 Hz, 3H), 2.2 (s, 3H), 2.33 (bs, 1H), [3.54, 5.05, 12.25] (s, 2H), 3.59-3.7 (m, 1H), 4.0-4.21 (m, 2H).

MS (m/z, rel. int %): M^+ 160 (2.99), 142 (2.69), 130 (7.49), 116 (37.13), 102 (12.87), 85 (100), 74 (4.79), 69 (29.34), 58 (42.51).

Bis-(3-oxobutyric acid)-1,2-propyl ester (3w):

Colorless liquid



3w

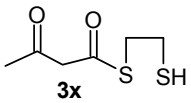
IRν_{max} / cm^{-1} (Neat): 2927, 1729, 1710, 1638, 1142, 1028.

^{1}H NMR ($CDCl_3$) δ: 1.25 (d, *J* = 6.8 Hz, 3H), 2.2 (s, 6H), [3.40, 3.45, 5.0, 12.25] (s, 4H), 4.1-4.3 (m, 2H), 5.2 (m, 1H).

MS (m/z, rel. int %): M^+ 244 (1.20), 202 (4.79), 158 (2.39), 143 (36.83), 127 (19.16), 116 (15.57), 101 (58.38), 85 (100), 69 (23.95), 58 (14.07).

3-Oxothiobutyric acid *S*-(2-mercaptoethyl) ester (3x):

Colorless liquid



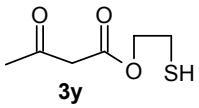
3x

IRν_{max} / cm^{-1} (Neat): 3441, 2926, 2868, 1729, 1680, 1618, 1403, 1189, 1085, 831.

^{1}H NMR ($CDCl_3$) δ: 1.63 (t, *J* = 7.6 Hz, 1H), 2.25 (s, 3H), 2.72 (m, 2H), 3.13 (m, 2H), [3.67, 5.42, 12.58] (s, 2H).

MS (m/z, rel. int %): M^+ 178 (4.79), 160 (3.59), 119 (63.47), 85 (100), 77 (2.9), 69 (8.08), 61 (8.98).

3-Oxobutyric acid 2-mercaptoethyl ester (3y):



3y

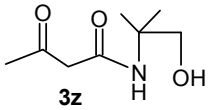
Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3300, 3019, 2950, 1743, 1717, 1648, 1150, 1034, 757.

^{1}H NMR ($CDCl_3$) δ: 1.55 (t, *J* = 7.6 Hz, 1H), 2.2 (s, 3H), 2.79 (m, 2H), [3.5, 5.02, 11.96] (s, 2H), 4.26 (t, *J* = 7.6 Hz, 2H).

MS (m/z, rel. int %): M^+ 162 (17.37), 144 (3.29), 134 (7.78), 116 (14.37), 102 (100). 85 (88.62), 77 (2.99), 69 (4.19), 60 (19.46).

***N*-(2-Hydroxy-1,1-dimethyl ethyl)-3-oxobutyramide (3z):**



3z

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3352, 3317, 1713, 1651, 1551, 1458, 1055.

^{1}H NMR ($CDCl_3$) δ: 1.3 (s, 6H), 2.26 (s, 3H), 3.39 (s, 2H), 3.58 (s, 2H), 4.5 (bs, 1H), 7.15 (bs, 1H).

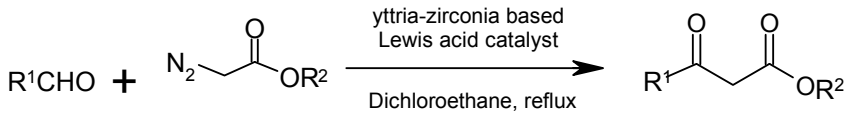
MS (m/z, rel. int %): M^+ 173 (2.39), 143 (100), 135 (1.8), 100 (8.38), 85 (14.97), 74 (6.59), 74 (6.29), 58 (40.72).

3.3.2 SECTION II

Synthesis of β-Keto Esters via Condensation of Aldehyde and Methyl/Ethyl Diazoacetate

3.3.2.1 Introduction

β-Keto esters, a class of versatile intermediates, are extensively used in the agrochemical, pharmaceutical and dyestuff industries. Numerous methods have been reported for their preparations, mostly involving ester derivatives as main starting materials.[24] In view of this, several methods have been developed for their synthesis. Apart from the classical Claisen condensation[25] and related reactions[26] the most direct methods involve the condensation of aldehydes with ethyl diazoacetate. This transformation is achieved either thermally[27] or in the presence of Lewis acids.[28-30] The earlier works date back to 1980s when Fernandez et al.[28a] and Pellicciari et al.[28b] reported the condensation of aldehydes with ethyl diazoacetate. However, an improved method using a variety of Lewis acid was later reported by Roskamp and Holmquist.[29a] Similarily Mali et al.[29b] reported a simple route to β-keto esters using activated alumina and more recently H-beta zeolites and montmorillonite K-10 catalyst have been employed to effect the above transformation.[30a,b] The main drawback of all the earlier methods was the low yield of the corresponding β-keto esters when aromatic aldehydes were used as one of the substrates. In continuation we have further explored the efficacy of yttria-zirconia based Lewis acid catalyst for the synthesis of β-keto esters by the condensation of aldehyde and methyl/ethyl diazoacetate (Scheme 2).



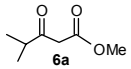
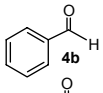
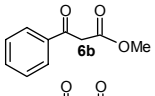
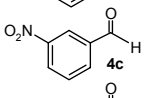
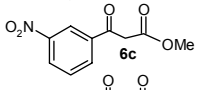
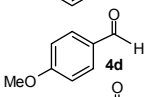
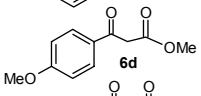
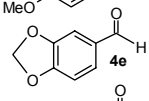
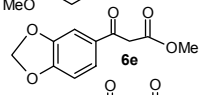
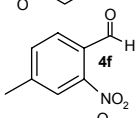
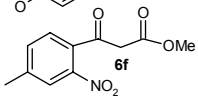
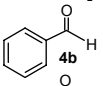
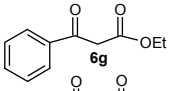
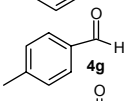
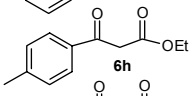
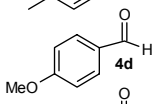
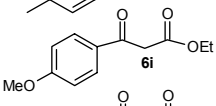
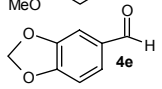
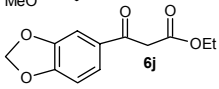
4 **5** **6**

Scheme 2

3.3.2.2 Results and discussion

A variety of aldehydes were treated with methyl/ethyl diazoacetate in presence of catalytic amount of yttria-zirconia based Lewis acid catalyst to afford the corresponding β-keto esters in good to excellent yields, the results obtained are summarized in Table 3. Thus, when anisaldehyde was reacted with ethyl diazoacetate in the presence of yttria-zirconia catalyst, the corresponding β-keto ester **6i** was obtained in 75 % yield. The IR spectrum of **6i** showed two bands at 1725 and 1698 cm^{-1} indicating the presence of β-keto ester functionality and another band at 3300 cm^{-1} showed the presence of hydroxyl functionality due to the presence of keto-enol form. The ^{1}H NMR spectrum showed the CH_3 protons of ester group at 1.15 δ as a multiplet while the -OCH_3 protons appeared at 3.8 δ as singlet and methylene protons flanked by two keto group appeared as three singlet at 4.0, 5.7 and 12.6 δ due to the presence of keto-enol form. Aromatic protons appeared as a multiplet at 7.0-7.5 δ due to the keto and enol forms. The aliphatic aldehyde reacted faster than aromatic one (Table 3 entry 1). The noteworthy feature of this protocol is that yttria-zirconia based Lewis acid catalyzed the condensation of aromatic aldehyde with methyl/ethyl diazoacetate in high yields. The substitution pattern in the aromatic ring has the marked influence on the rate of reaction. Thus the aromatic aldehyde with electron donating substituents accelerated the reaction (Table 3, entries 4-6) whereas an electron withdrawing substituent retarded the rate of reaction (Table 3, entries 3 and 6), therefore it took little longer time to complete the reaction; however yields obtained were comparable. If aromatic aldehyde is substituted by both electron donating group as well as electron withdrawing group then reaction became slow (Table 3, entry 6) although yield was very high. A longer reaction time was also observed for the reaction of methyl/ethyl diazoacetate with prenal compared to other aromatic aldehydes (Table 3, entries 5 and 10); that may be due to the difference in reactivity pattern.

Table 3: condensation of aldehyde with diazoacetate in the presence of catalytic amount of yttria-zirconia based Lewis acid catalyst

Entry	Aldehyde	Diazoacetate	Reaction time (h)	Product[a]	Yield[b] (%)
1	 4a	Methyl	10	 6a	85
2	 4b	Methyl	12	 6b	83
3	 4c	Methyl	20	 6c	85
4	 4d	Methyl	12	 6d	86
5	 4e	Methyl	20	 6e	83
6	 4f	Methyl	18	 6f	80
7	 4b	Ethyl	13	 6g	80
8	 4g	Ethyl	12	 6h	85
9	 4d	Ethyl	12	 6i	75
10	 4e	Ethyl	22	 6j	80

[a]All products were characterized by their IR, [1]HNMR. [b]Yields refer to isolated pure products.

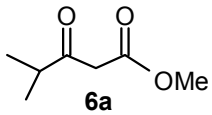
3.3.2.3 Conclusion

In conclusion we have developed a method for the synthesis of β-keto esters catalyzed by yttria-zirconia based Lewis acid by the condensation of aldehyde and diazoacetate. Thus, a variety of aromatic aldehydes can be smoothly converted to the corresponding β-keto esters in high yields.

3.3.2.4 Experimental

General procedure for condensation of diazoacetate with aldehydes: A solution of the aldehyde (5.0 mmol) and diazoacetate (7.5 mmol) in dichloroethane (10 ml) containing yttria-zirconia based Lewis acid catalyst (50 mg; 10 % w/w) was refluxed for the indicated length of time (Table 3) under N_2 atmosphere. The catalyst was recovered by filtration, evaporation of solvent under reduced pressure furnished the crude material. Purification by silica gel column chromatography using pet ether: ethylacetate (9.8: 0.2) afforded the pure products.

4-Methyl-3-oxopentanoic acid methyl ester (6a):



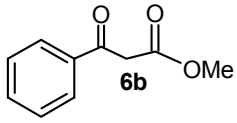
6a

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 1732, 1695, 1456.

^{1}H NMR ($CDCl_3$) δ: 1.3 (d, J = 6.25 Hz, 6H), 2.1-2.28 (m, 1H), 3.5 (s, 2H), 3.9 (s, 3H).

3-Oxo-3-phenylpropionic acid methyl ester (6b):



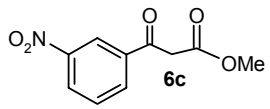
6b

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 1735, 1695,1450.

^{1}H NMR ($CDCl_3$) δ: [4.0,5.7,12.3] (s, 2H), 4.1 (s, 3H), 7.8-7.4 (m, 3H), 8.1-7.9 (m, 2H).

3-(3-Nitrophenyl)-3-oxopropionic acid methyl ester (6c):



6c

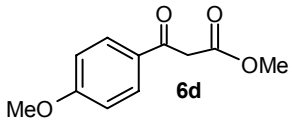
White solid

IRν_{max} / cm^{-1} (Neat): 3310, 1740, 1700, 1595, 1540.

^{1}H NMR ($CDCl_3$) δ: [3.9,5.8,12.6] (s, 2H), 4.1(s, 3H), 7.6-7.3 (m, 2H), 8.1-7.9 (m, 2H).

3-(4-Methoxyphenyl)-3-oxopropionic acid methyl ester (6d):

White solid: M.P. 70^{o}C



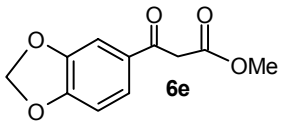
6d

IRν_{max} / cm^{-1} (Neat): 3300, 1725, 1695,1590.

^{1}H NMR ($CDCl_3$) δ: 3.7 (s, 3H) 3.8 (s, 3H), [4.1,5.5,12.6] (s, 2H), 7.8-6.9 (m, 4H).

3-Benzo[1,3]-dioxol-5-yl-3-oxopropionic acid methyl ester (6e):

Colorless liquid

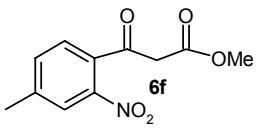


6e

IRν_{max} / cm^{-1} (Neat): 3300, 1727, 1698, 1593.

^{1}H NMR ($CDCl_3$) δ: [4.0, 5.6, 12.6] (s, 2H), 4.1(s, 3H), 6.05 (s, 2H), 6.95 (d, J=7Hz, 1H), 7.45 (d, J=7Hz, 1H), 7.6-7.55 (m, 1H).

3-(2-Chloro-4-methylphenyl)-3-oxopropionic acid methyl ester (6f):



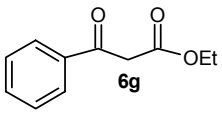
6f

White solid: M.P. 110^{o}C

IRν_{max} / cm^{-1} (Neat): 1746, 1698, 1557, 1447.

^{1}H NMR ($CDCl_3$) δ: 2.6 (s, 3H), [3.9, 5.7, 12.3] (s, 2H), 4.1 (s, 3H), 7.2 (s 1H), 8.0 (d, J = 7 Hz, 1H), 8.4 (d, J = 7 Hz, 1H).

3-Phenyl-3-oxopropionic acid ethyl ester (6g):



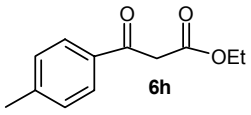
6g

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3345, 1738, 1695, 1592, 1447.

^{1}H NMR ($CDCl_3$) δ: 1.18-1.3 (m, 3H), [3.9, 5.7, 12.3] (s, 2H), 4.1-4.2 (m, 2H), 7.4-7.8 (m, 3H), 8.0-8.1 (m, 2H).

3-(4-Methylphenyl)-3-oxopropionic acid ethyl ester (6h):



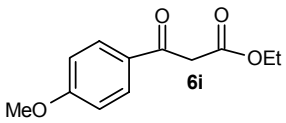
6h

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3300, 1740, 1700, 1560, 1450.

^{1}H NMR ($CDCl_3$) δ: 1.15-1.28 (m, 3H), 2.4 (s, 3H), [4.0, 5.7, 12.5] (s, 2H), 4.1-4.2 (m, 2H), 7.2-7.8 (m, 4H).

3-(4-Methoxyphenyl)-3-oxopropionic acid ethyl ester (6i):



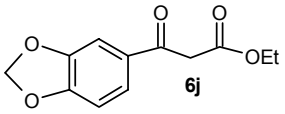
6i

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 3300, 1725, 1698, 1557, 1447.

^{1}H NMR ($CDCl_3$) δ: 1.1-1.22 (m, 3H), 3.8 (s, 3H), [4.0, 5.7, 12.6] (s, 2H), 4.1-4.2 (m, 2H), 7.0-7.5 (m, 4H).

3-(3,4-Methylenedioxyphenyl)-3-oxopropionic acid ethyl ester (6j):



6j

Solid: M.P. 40°C (lit. 41°C)[30a]

IRν_{max} / cm^{-1} (Neat): 1740, 1685, 1640, 1447.

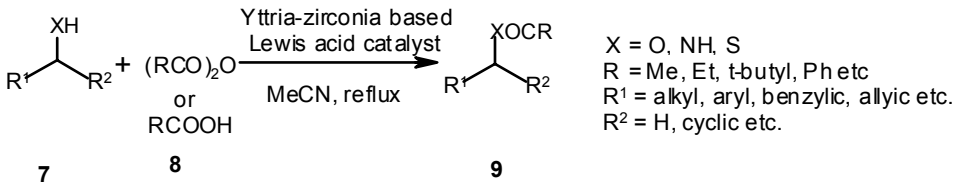
^{1}H NMR ($CDCl_3$) δ: 1.22 (t, J=7.4Hz, 3H), [4.0, 5.65, 12.6] (s, 2H), 4.2 (q, J=7.4Hz, 2H), 6.1 (s, 2H), 6.95 (d, J=7Hz, 1H), 7.4 (d, J=7Hz, 1H), 7.5-7.6 (m, 1H).

3.3.3 SECTION III

Acylation of Alcohols, Amines and Thiols by Carboxylic Anhydrides/Acids

3.3.3.1 Introduction

The acylation of alcohols, amines, and thiols by acyl chloride or acid anhydride under basic conditions is a well established reaction in organic synthesis.[31] The most commonly employed basic catalysts for this purpose are 4-(dimethylamino)pyridine and 4-pyrrollidinopyridine (PPY).[32] The Lewis acid catalyzed acylation of alcohols and amines with acid anhydride is a mild, strategic alternative to basic and nucleophilic catalysts. Some procedures have been developed wherein Lewis acid catalysts such as $Cu(OTf)_2$,[33] $TaCl_5$,[34] TMSOTf,[35] $Sc(OTf)_3$,[36] $In(OTf)_3$,[37] $CoCl_2$,[38] Bu_3P[39] have been used for acyl transfer reactions in alcohols. More recently, use of montmorillonite K-10, KSF,[40] $Bi(OTf)_3$ [41a] and H-FER.[41b] as heterogeneous catalysts has been reported to effect acylation reactions. As part of a research program aimed at developing a new solid catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid was found to be an extremely efficient catalyst for the Diels-Alder reaction[1] and transesterification of β-keto esters.[42] This prompted us to use this catalyst for acylation reactions and herein the results of yttria-zirconia based Lewis acid catalyzed acylation of alcohols, thiols and amines are described (Scheme 3).



Scheme 3

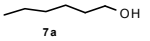
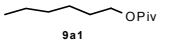
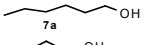
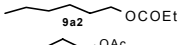
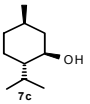
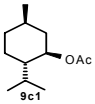
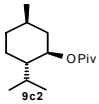
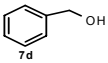
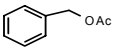
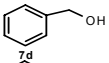
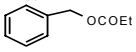
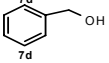
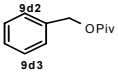
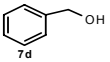
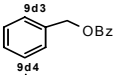
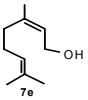
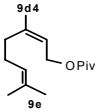
3.3.3.2 PART I

Acylation by Carboxylic Anhydrides

3.3.3.2.1 Results and discussion

A variety of alcohols were treated with acid anhydrides in the presence of a catalytic amount of the new yttria-zirconia based catalyst to afford the corresponding acetates in excellent yields Thus, when hexanol was reacted with pivalic anhydride in the presence of catalytic amount of yttria-zirconia catalyst, the corresponding ester **9a1** was obtained in 85 % yield. The IR spectrum of **9a1** showed a band at 1730 cm^{-1} corresponding to ester functionality. The CH_3 proton of hexyl group appeared as triplet at 0.89 δ. All the nine protons of pivalic group appeared as a singlet at 1.23 δ. The CH_2 protons attached to ester functionality appeared at 4.10 δ. A similar spectral pattern was obtained for the other acylated products on the basis of which those compounds were characterized. The substrates examined in our studies and the results obtained are summarized in Table 4-6. Thus the present procedure for acylation is quite general as a wide range of structurally varied alcohols such as open chain, cyclic and aromatic ones underwent acylation with acid anhydrides. However, the reaction of alcohols with benzoic anhydride is found to be sluggish and hence a little longer time is required to complete the reaction affording relatively low yield of the products (Table 4, entries 5 & 11). The efficacy of the yttria-zirconia based catalyst can be clearly visualized in the acetylation of polyhydroxy compounds under similar conditions. For example, both aliphatic and aromatic polyols were acylated in very high yield (Table 4, entries 16-20). Another noteworthy feature of this methodology is that polyol such as D-mannitol underwent exhaustive acetylation smoothly demonstrating the practical utility of this method (Table 4, entry 20).

Table 4: The yttria – zirconia based Lewis acid catalyzed acylation of alcohols and polyols

Entry	Alcohol	Anhydride	Reaction Time (h)	Product	Yield[a] (%)
1	 7a	Pivalic	7	 9a1	85
2	 7a	Propionic	4	 9a2	88
3	 7b	Acetic	4	 9b1	99
4	 7b	Pivalic	9	 9b2	91
5	 7b	Benzoic	6	 9b3	71
6	 7c	Acetic	6	 9c1	96
7	 7c	Pivalic	10	 9c2	85
8	 7d	Acetic	6	 9d1	94
9	 7d	Propionic	4	 9d2	87
10	 7d	Pivalic	10	 9d3	85
11	 7d	Benzoic	15	 9d4	71
12	 7e	Pivalic	11	 9e	85
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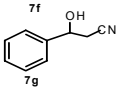
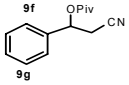
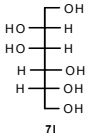
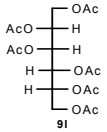
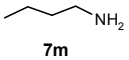
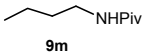
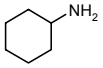
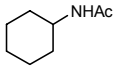
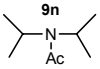
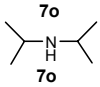
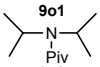
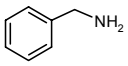
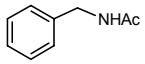
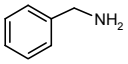
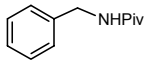
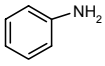
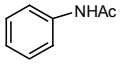
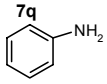
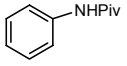
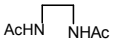
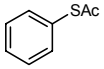
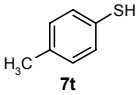
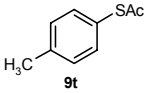
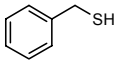
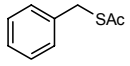
14	 7g	Pivalic	9	 9g	80
15	 7h	Acetic	12	 9h	97[b]
16	 7i	Acetic	5	 9i	98
17	 7j	Acetic	6	 9j	96
18	 7k	Acetic	8	 9k1	99
19	 7k	Pivalic	15	 9k2	75
20	 7l	Acetic	10	 9l	94

[a]Yields refer to isolated pure products. [b]1.5 eq. of Acetic anhydride with respect to the substrate was used for the completion of reaction.

Table 5: The yttria – zirconia based Lewis acid catalyzed acetylation of amines and thiols

Entry	Substrate	Reaction Time (h)	Product[a]	Yield[b] (%)
1	 **7m**	2.5	 **9m**	90
2	 **7n**	3.5	 **9n**	97
3	 **7o**	2	 **9o1**	91
4	 **7o**	2.5	 **9o2**	90
5	 **7p**	2.5	 **9p1**	95
6	 **7p**	3	 **9p2**	94
7	 **7q**	2.5	 **9q1**	99
8	 **7q**	3	 **9q2**	98
9	 **7r**	2.5	 **9r**	99
10	 **7s**	10	 **9s**	97
11	 **7t**	6	 **9t**	94
12	 **7u**	6	 **9u**	97

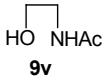
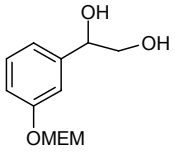
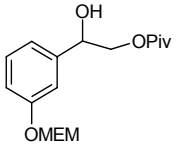
[a]Products were characterized by spectroscopic data and also by comparison with the authentic sample.
[b]Yields refer to isolated pure products.

A wide range of structurally varied alcohols such as cyclic, acylic, benzylic, allylic and tertiary alcohols underwent pivalation in the presence of yttria-zirconia Lewis acid catalyst, though the reaction was found to be sluggish compared to acetylation (Table 4, entries 1, 4, 7, 10, 12-14).

In order to explore the generality and scope of the yttria-zirconia based Lewis acid catalyzed reaction, the procedure has been extended to a variety of other substrates such as amines and thiols. Thus, the aromatic and aliphatic amines were successfully acylated

in the presence of a yttria-zirconia based Lewis acid catalyst (Table 5). Another notable feature of the reaction is that even a hindered amine was acylated in very high yield (Table 5, entry 3-4). In a similar manner acylation of thiols was also achieved by this procedure in excellent yields (Table 5, entries 10-12).

Table 6: Chemoselective acylation of amino alcohol, mercapto alcohol and diol catalyzed by yttria – zirconia based Lewis acid catalyst

Entry	Substrate	Reaction Time (h)	Product[a]	Yield[b] (%)
1	 **7v**	4[c]	 **9v**	98
2	 **7w**	12[d]	 **9w**	84
3	 **7x**	10[d]	 **9x1**  **9x2**	10 76
4	 **7y**	12	 **7y**	74

[a]Products were characterized by spectroscopic data and also by comparison with the authentic sample. [b]Yields refer to isolated pure products. [c]Reaction was performed at room temperature. [d]Reaction was carried out at 40°C.

Encouraged by this finding, it was felt worthwhile to study the reactivity pattern of different kind of amino alcohols, mercapto alcohols and diols for acylation reaction over yttria-zirconia Lewis acid catalyst and results of such study are presented in Table 6. More significantly, it was observed that the reaction is chemoselective for the amino alcohols, mercapto alcohols and diols. The acylation of amino alcohol produced the corresponding acetamide only (Table 6, entry 1); the hydroxy moiety remained untouched. The selective acylation of a primary NH_2 over a primary OH by this process is

of considerable synthetic importance and is difficult to achieve with many other reagents.[31, 36a, 38, 39a] Similarly, the hydroxyl group of 2-mercapto ethanol reacted preferentially over the thiol affording the corresponding acetate in high yield (Table 6, entry 2). In the case of 1,2-diol, we observed preference in the acylation for primary alcohol over secondary; however a mixture of mono and di-acylated products was obtained (Table 6, entry 3) but in case of pivalation only primary hydroxyl group reacted over secondary hydroxyl group (Table 6, entry 4) The chemoselectivity in acylation reaction with respect to different functional groups is in accordance with those observed by us in the transesterification reaction.[42]

3.3.3.2.2 Conclusion

In conclusion, we have shown that yttria-zirconia based Lewis acid serves as an efficient and chemoselective catalyst for acylation of alcohols, amines and thiols. The notable feature of this methodology is that even hindered substrates can be acylated in high yields under mild conditions. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of work-up and recyclability of the catalyst are noteworthy.

3.3.3.2 PART II

Acylation by Carboxylic Acids

The acylation of alcohols, thiols and amines is one of the most frequently used transformations in organic synthesis as it provides an efficient and inexpensive means for protecting hydroxy, thiol and amino groups in a multi-step synthetic process.[31] Acylation is usually performed employing acid anhydrides or acid chlorides in the presence of stoichiometric amounts of bases[32, 39a] The Lewis acid catalyzed acylation of alcohols and amines is a mild, strategic alternative to basic and nucleophilic catalysts.[33-42] However, most of these methods either suffer from problem in recovery of the large amount of soluble bases or acids or from the excessive use of acetic anhydride or acid chloride as acylating agent. These drawbacks have a negative impact on the environment. Therefore, there is a genuine need to develop a reusable solid catalyst for acylation reaction using carboxylic acids so as to achieve high atom efficiency. More recently, the use of montmorillonite K-10 and KSF[40] and zeolite[41b, c] as heterogeneous catalysts has been reported to effect acylation reaction. We have now developed a method for the acylation of alcohols, amines and thiols by the use of carboxylic acid as an acylating reagent using yttria-zirconia based Lewis acid catalyst. The results of such study are described in the following section.

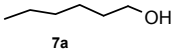
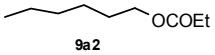
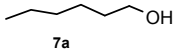
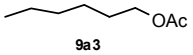
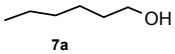
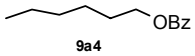
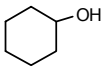
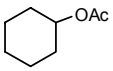
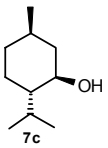
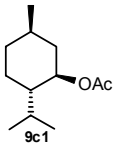
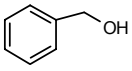
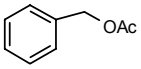
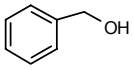
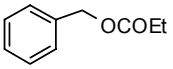
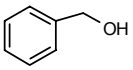
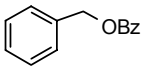
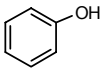
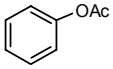
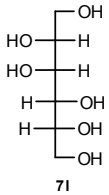
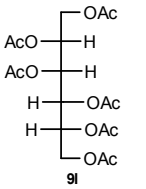
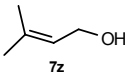
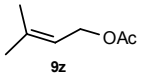
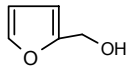
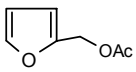
3.3.3.3.1 Results and discussion

A wide range of structurally varied alcohols, amines and thiols were subjected to acylation with carboxylic acid by this procedure and the desired products were obtained in good to excellent yield. Thus, when hexanol was treated with benzoic acid in the

presence of catalytic amount of yttria-zirconia catalyst, the corresponding ester 9a4 was obtained in 83 % yield. The IR spectrum of 9a4 showed a band at 1721 cm^{-1} indicating the presence of ester functionality. In ^1H NMR CH_3 protons of hexyl group and CH_2 protons attached to the ester functionality appeared as triplet at 0.90 δ and 4.10 δ respectively. The aromatic protons appeared as two sets one at 7.3-7.5 δ multiplet for three protons and another multiplet at 8.0-8.1 δ for two protons. The present methodology demonstrates a simple acylation procedure under environmentally safe, heterogeneous reaction conditions and has wide applicability, extending the scope to primary, secondary, allylic, cyclic and heterocyclic alcohols (Table 7). However, the acylation reaction with phenol is found to be sluggish and hence a little longer time is required to complete the reaction affording relatively low yield of the products (Table 7, entry 9). The reaction conditions are mild enough not to induce any isomerisation of the double bond in allylic alcohol (Table 7, entry 12). Another notable feature of this method is that optically active alcohol underwent acylation without any racemisation (Table 7, entry 5) and also the polyhydroxy compounds such as ethylene glycol and D-mannitol underwent exhaustive acylation to afford the corresponding products in excellent yields (Table 7, entries 10, 11). Even a wide variety of other alcohols could be acylated using propionic or benzoic acid as acylating agent under the present reaction conditions (Table 7, entries 2, 3, 7, 8).

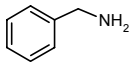
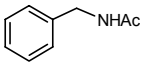
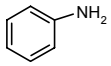
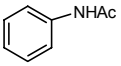
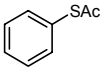
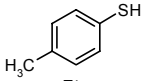
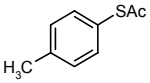
In order to explore the generality and scope of the yttria-zirconia based Lewis acid catalyzed reaction, the procedure has been extended to a variety of other substrates such as amines and thiols. Thus aromatic and benzylic amines were successfully acylated in the presence of a yttria-zirconia based Lewis acid catalyst (Table 8, entries 1-2). Similarly, acylation of thiols was also achieved by this procedure in excellent yields (Table 8, entries 3-4).

Table 7: The yttria – zirconia based Lewis acid catalyzed acylation of alcohols by carboxylic acids

Entry	Alcohol	Acid	Reaction Time (h)	Product[a]	Yield[b] %
1	 7a	AcOH	3	 9a2	90
2	 7a	EtCOOH	3.5	 9a3	89
3	 7a	C_6H_5COOH	9	 9a4	83
4	 7b	AcOH	4.5	 9b1	94
5	 7c	AcOH	3	 9c1	91
6	 7d	AcOH	4	 9d1	94
7	 7d	EtCOOH	3.5	 9d2	90
8	 7d	C_6H_5COOH [d]	13.5	 9d4	79
9	 7h	AcOH	15	 9h	77
10	 7j	AcOH	8	 9j	92
11	 7l	AcOH	9	 9l	92
12	 7z	AcOH	8	 9z	85
13	 7za	AcOH	7	 9za	88

[a] Products were characterized by usual spectral analyses. [b] Isolated yield. [c] 10 equivalents of acid was used. [d] 1.1 equivalent of acid was used.

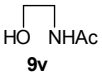
Table 8: The yttria – zirconia based Lewis acid catalyzed acetylation of amines and thiols by acetic acid

Entry	Substrate	Reaction Time (h)	Product[a]	Yield[b] %
1	 **7p**	2	 **9p1**	93
2	 **7q**	2	 **9q1**	92
3	 **7s**	8	 **9s**	94
4	 **7t**	4	 **9t**	92

[a] Products were characterized by usual spectral analyses. [b] Isolated yield

More significantly, it was observed that the reaction is chemoselective for the amino alcohols, mercapto alcohols and diols. The acylation of amino alcohol produced the corresponding acetamide only (Table 9, entry 1); the hydroxy moiety remained untouched. The selective acylation of a primary NH_2 over a primary OH by this process is of considerable synthetic importance and is difficult to achieve with many other reagents.[31, 36a, 38, 39a] Similarly, the hydroxyl group of 2-mercapto ethanol reacted preferentially over the thiol affording the corresponding acetate in high yield (Table 9, entry 2). In the case of 1,2-diol, we observed preference in the acylation for primary alcohol over secondary; however a mixture of mono and di-acylated products was obtained (Table 9, entry 3). The chemoselectivity in acylation reaction with respect to different functional groups is in accordance with those observed by us in the transesterification reaction.[42]

Table 9: Chemoselective acetylation of amino alcohol, mercapto alcohol and diol catalyzed by yttria – zirconia based Lewis acid catalyst

Entry	Substrate	Reaction Time (h)	Product[a]	Yield[b] (%)
1	 **7v**	24[c]	 **9v**	94
2	 **7w**	24[d]	 **9w**	65
3	 **7x**	20[e]	 **9x1**  **9x2**	72 8

[a] Products were characterized by usual spectral analyses.[b] Isolated yield. [c] Reaction was performed at 60°C. [d] Reaction was carried out at 85°C. [e] Reaction was performed at 75°C

3.3.3.3.2 Conclusion

We have described a mild, highly efficient and selective procedure for acylation of alcohols, thiols and amines using various carboxylic acids as an acylating agent in the presence of catalytic amount of yttria-zirconia base Lewis acid catalyst. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of work-up and recyclability of the catalyst are noteworthy. We believe this will present a better, more practical and environmentally safer alternative to the existing methodologies and should find widespread applications in organic synthesis.

3.3.3.4 Experimental

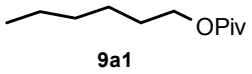
General Experimental Procedure for the Acylation with Acid Anhydride: Acid anhydride (benzoic, propionic, and acetic) (11 mmol; 1.1 equiv. per OH, NH_2 or SH) was added dropwise to a solution of alcohol, amine, or thiol (10 mmol) in dry acetonitrile (5ml) containing catalyst (20% by weight) and the mixture was refluxed for the indicated length of time (Table 4-6). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the filtrate was concentrated, diluted with water (15 ml) and extracted with CH_2Cl_2 (2x20 ml). The organic layer was separated, washed with 10 % aq. $NaHCO_3$, brine, water and dried over Na_2SO_4. The solvent was removed and the crude product was chromatographed on a silica gel column to afford the pure product. After the reaction, the catalyst is recovered with retention of its catalytic activity. It can be further reactivated for reuse by heating it at 500^oC in the presence of air.

General Experimental Procedure for the Pivalation with Pivalic Anhydride: Pivalic anhydride (15 mmol; 1.5 equiv. per OH, NH_2) was added to a solution of alcohol (10 mmol) in dry acetonitrile (5ml) containing catalyst (20% by weight) and the mixture was refluxed for the indicated length of time (Table 4-6). The reaction was monitored by TLC. After completion of reaction, 5 ml methanol was added and the mixture was again refluxed for 10 h and then allowed to come to room temperature, the catalyst was filtered and the filtrate was concentrated, diluted with water (15 ml) and extracted with CH_2Cl_2 (2x20 ml). The organic layer was separated, washed with 10 % aq. $NaHCO_3$, brine, water and dried over Na_2SO_4. The solvent was removed and the crude product was chromatographed on a silica gel column to afford the pure product.

General Experimental Procedure for the Acylation with Carboxylic Acid: Alcohol/amine/thiol (10 mmol) was added to acid (50 mmol) containing catalyst (20 %

w/w with respect to substrate) and mixture was heated to 110°C (125°C in the case of benzoic acid) for the indicated length of time (Table 7-9). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered; filtrate was concentrated, diluted with water (15 ml) and extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was separated, washed with 10% aq. $NaHCO_3$, brine, water and dried over Na_2SO_4. The solvent was removed and the crude product was chromatographed on silica gel column (3% EtOAc in light petroleum ether) to afford the product in high yield.

2, 2-Dimethylpropionic acid hexyl ester (9a1):



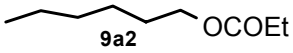
9a1

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2931, 1730, 1159.

^1H NMR (200 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.6 Hz, 3H), 1.23 (s, 9H), 1.25-1.75 (m, 8H), 4.10 (t, J = 6.6 Hz, 2H).

Propionic acid hexyl ester (9a2):



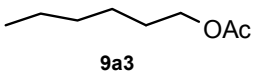
9a2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3020, 2980, 1727, 1500, 1215.

^1H NMR (200 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.3 Hz, 3H), 1.15 (t, *J* = 6.3, 3H), 1.17-1.7 (m, 8H), 2.4 (q, *J* = 6.3 Hz, 2H), 4.1 (t, *J* = 6.3 Hz, 2H).

Acetic acid hexyl ester (9a3):



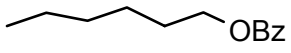
9a3

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3020, 2956, 1721, 1252.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.9 (t, *J* = 6.6 Hz, 3H), 1.25-1.45 (m, 6H), 1.5-1.7 (m, 2H), 2.1 (s, 3H), 4.1 (t, *J* = 6.6 Hz, 2H).

Benzoic acid hexyl ester (9a4):



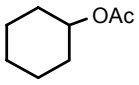
9a4

Viscous liquid

IR ν_{max} /cm^{-1} (Neat): 2956, 1721, 1273.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.9 (t, *J* = 6.67 Hz, 3H), 1.25-1.45 (m, 6H), 1.5-1.7 (m, 2H), 4.1 (t, *J* = 6.6 Hz, 2H), 7.3-7.5 (m, 3H), 8.0-8.1 (m, 2H).

Acetic acid cyclohexyl ester (9b1):



9b1

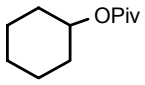
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2980, 1740, 1464, 1215.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.45-2.0 (m, 10H), 2.1 (s, 3H) 5.03 (m, 1H).

MS (m/z, rel. int. %): M^+ 142 (5), 99 (10), 82 (100), 67 (50).

2, 2-Dimethylpropionic acid cyclohexyl ester (9b2):



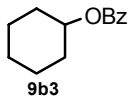
9b2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2937, 1727, 1480, 1283.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19 (s, 9H), 1.36-1.52 (m, 6H), 1.68-1.79 (m, 4H), 4.75 (m, 1H).

Benzoic acid cyclohexyl ester 9b3:



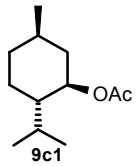
9b3

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2980, 1740, 1464, 1215.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25-2.1 (m, 10H), 5.03 (m, 1H), 7.47 (m, 3H), 8.03 (m, 2H).

Acetic acid menthyl ester (9c1):



9c1

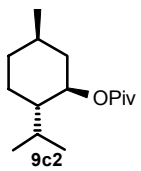
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2926, 1715, 1225, 1007.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.75 (d, *J* = 6.5 Hz, 3H), 0.85 (s, 3H), 0.9 (s, 3H), 0.95-2.1 (m, 9H), 2.2 (s, 3H), 4.7 (m, 1H).

MS (m/z, rel. int. %): M^+ 198 (3), 150 (5), 138 (100), 123 (20), 95 (32).

2, 2-Dimethylpropionic acid menthyl ester (9c2):



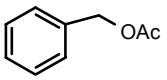
9c2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3432, 2953, 1725, 1425, 1369, 1285.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.75 (d, *J* = 6.6 Hz, 3H), 0.80-1.00(m, 9H), 1.20 (s, 9H), 1.25-1.55 (m, 2H), 1.58-1.75 (, 2H), 1.75 –2.00 (m, 2H), 4.7 (m, 1H).

Acetic acid benzyl ester (9d1):



9d1

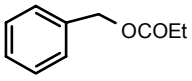
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2936, 1727, 1357, 1240.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.1 (s, 3H), 5.11 (s, 2H), 7.36 (s, 5H).

MS (m/z, rel. int. %): M^+ 150 (31), 107 (100), 91 (57), 79 (22).

Propionic acid benzyl ester (9d2):



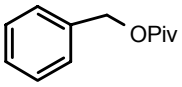
9d2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2943, 1740, 1357, 1240.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.9 (t, J = 6.1 Hz, 3H), 2.4 (q, J = 6.1 Hz, 2H), 5.15 (s, 2H), 7.36 (s, 5H).

2, 2-Dimethylpropionic acid benzyl ester (9d3):



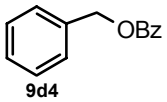
9d3

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2972, 1730, 1357, 1216.

^{1}H NMR (200 MHz $CDCl_3$) δ: 1.25 (s, 9H), 5.13 (s, 2H), 7.36 (s, 5H).

Benzoic acid benzyl ester (9d4):



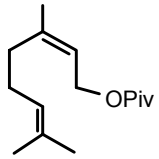
9d4

Viscous liquid

IR ν_{max} /cm^{-1} (Neat): 3065, 2943, 1720, 1272, 1110.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.94 (s, 2H), 7.4-7.9 (m, 10).

2, 2-Dimethylpropionic acid geranyl ester (9e):



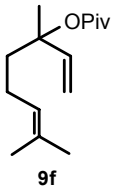
9e

Viscous liquid

IR ν_{max} /cm^{-1} (Neat): 2966, 1729, 1450, 1281, 1151.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.17 (s, 9H), 1.58 (s, 3H), 1.65 (s, 3H), 1.67 (s, 3H), 1.90-2.22 (m, 4H), 4.53 (d, J = 6.5 Hz, 2H), 5.06 (t, J = 6.5 Hz, 1H), 5.30 (t, J = 6.5 Hz, 1H).

2, 2-Dimethylpropionic acid linaloolic ester (9f):



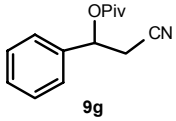
9f

Viscous liquid

IR ν_{max} /cm^{-1} (Neat): 2929, 1727, 1459, 1286, 1159.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.17 (s, 9H), 1.55 (s, 3H), 1.65 (s, 3H), 1.75 (s, 3H), 1.90-2.20 (m, 4H), 5.15 (t, J = 6.6 Hz, 2H), 5.30 (t, J = 6.6 Hz, 1H), 6.00 (t, J = 6.6 Hz, 1H).

2, 2-Dimethylpropionic acid 2-cyano-1-phenylethyl ester (9g):



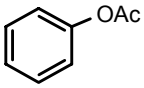
9g

Viscous liquid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3020, 2255, 1734, 1216.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.24 (s, 9H), 2.85 (m, 2H), 5.93 (m, 1H), 7.28-7.80 (m, 5H).

Acetic acid phenyl ester (9h):



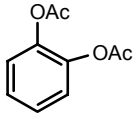
9h

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3058, 2932,1756, 1194.

^1H NMR (200 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 7.1-7.5 (m, 5H).

Acetic acid 2-acetoxyphenyl ester (9i):



9i

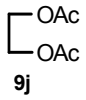
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3433, 1759, 1200, 1161.

^1H NMR (200 MHz, $CDCl_3$) δ: 2.34 (s, 6H), 7.2-7.33 (m, 4H).

MS (m/z, rel. int. %): M^+ 194 (3), 152 (14), 110 (100), 81 (16).

Acetic acid 2-acetoxyethyl ester (9j):



9j

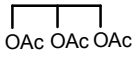
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3065, 2948, 1734, 1366, 1217, 1040.

^1H NMR (200 MHz, $CDCl_3$) δ: 2.1 (s, 6H), 4.5 (s, 4H).

MS (m/z, rel. int. %): M^+ 146 (2), 116 (34), 86 (100), 72 (40).

Acetic acid 2,3-diacetoxypropyl ester (9k1):



9k1

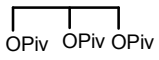
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3065, 2955, 1739, 1367, 1222, 1045.

^1H NMR (200 MHz, $CDCl_3$) δ: 2.05 (s, 6H), 2.06 (s, 3H), 4.0-4.32 (m, 4H), 5.25 (m, 1H).

MS (m/z, rel. int. %): M^+ 218 (2), 158 (10), 144 (100), 115 (81), 103 (70).

2, 2-Dimethylpropionic acid 2,3-bis-(2, 2-dimethylpropionyloxy)propyl ester (9k2):



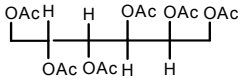
9k2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3065, 2930, 1730, 1150.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.17 (s, 18H), 1.20 (s, 9H), 4.15 (d, J = 4.38 Hz, 4H), 4.33 (m, 1H).

***D*-Manitol hexaacetate (9l):**



9l

White solid; M.P. 116-123°C (Lit.[37] 120-127 °C)

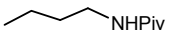
IR ν_{max} /cm^{-1} (Neat): 3065, 1759, 1363, 1200.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.07 (s, 6H), 2.08 (s, 6H), 2.09 (s, 6H), 4.14 (m, 4H), 5.07 (m, 2H), 5.44 (m, 2H).

MS (m/z, rel. int. %): $[M^+$-59] 375 (4), 289 (20), 187 (56), 139 (77), 115 (100), 103 (31).

***N*-Butyl-2,2-dimethylpropionamide (9m):**

Colorless liquid



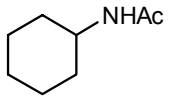
9m

IR ν_{max} /cm^{-1} ($CHCl_3$): 3371, 1644, 1518, 1365, 1215.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.2 Hz, 3H), 1.15 (s, 9H), 1.27-1.48 (m, 4H), 3.20(q, *J* = 6.2 Hz, 2H), 5.80 (bs, 1H).

***N*-Cyclohexylacetamide (9n):**

White solid: M.P. 80°C



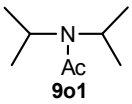
9n

IR ν_{max}/cm^{-1} (Neat): 3277, 2913, 1630, 1545, 1437, 1241.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1-1.95 (m, 10H), 2.05 (s, 3H), 3.75 (m, 1H), 3.95 (s, 1H).

MS (m/z, rel. int. %): M^+ 141 (67), 98 (42), 60 (88), 56 (100).

***N*, *N*-Diisopropylacetamide (9o1):**



9o1

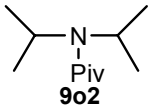
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3453, 2961, 1627, 1437, 1365, 1323.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 4.5 Hz, 6H), 1.34 (d, *J* = 4.5 Hz, 6H), 2.07 (s, 3H), 3.49 (m, 1H), 3.88 (m, 1H).

MS (m/z, rel. int. %): M^+ 143 (18), 100 (29), 86 (100), 58 (20).

***N*, *N*-Diisopropyl-2,2-dimethylpropionamide (9o2):**



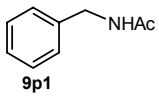
9o2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3453, 2959, 1640, 1450, 1366.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 4.5 Hz, 6H), 1.20 (S, 9H), 1.35 (d, *J* = 4.5 Hz, 6H), 3.50 (m, 1H), 3.89 (m, 1H).

***N*-Benzylacetamide (9p1):**



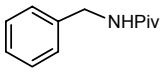
9p1

White solid: M.P. 93-95^{0}C

IR ν_{max}/cm^{-1} (Neat): 272, 2913, 1619, 1533, 1422, 1252.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.1 (s, 3H), 4.5 (d, *J* = 6.25 Hz, 2H), 6.28 (bs, 1H), 7.5 (m, 5H).

***N*-Benzyl-2,2-dimethylpropionamide (9p2):**



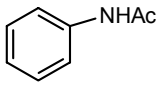
9p2

White solid: M.P. 110^{0}C

IR ν_{max}/cm^{-1} (Neat): 3320, 1643, 1531, 1454, 1366.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.23 (s, 9H), 4.5 (d, *J* = 6.5 Hz, 2H), 5.96 (bs, 1H), 7.25-7.36 (m, 5H).

***N*-Phenylacetamide (9q1):**



9q1

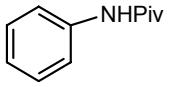
White solid: M.P. 100^{o}C

IR ν_{max}/cm^{-1} (Neat): 3268, 2907, 1638, 1585, 1470, 1357.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.1 (s, 3H), 7.1-7.6 (m, 5H), 7.75 (bs, 1H).

MS (m/z, rel. int. %): M^+ 135 (62), 106 (100), 91 (23), 79 (24).

***N*-Phenyl-2,2-dimethylpropionamide (9q2):**



9q2

White solid: M.P. 142-145^{o}C

IR ν_{max}/cm^{-1} (Neat): 3298, 1654, 1595, 1462, 1377.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.33 (s, 9H), 1.66(bs, 1H) 7.07-7.56 (m, 5H).

***N*-(2-Acetylaminoethyl)acetamide (9r):**

9r

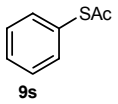
White solid: M.P. 200^{o}C

IR ν_{max} /cm^{-1} (Neat): 3286, 2919, 1642, 1554, 1450, 1365

^{1}H NMR (200 MHz, D_2O): 2.1 (s, 6H), 3.41 (s, 4H), 5.0 (bs, 2H).

MS (m/z, rel. int. %): M^+ 144 (2), 85 (100), 73 (60).

Thioacetic acid *S*-phenyl ester (9s):



9s

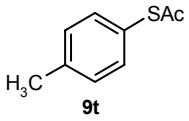
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3060, 2923, 1720.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.4 (s, 3H), 7.4 (s, 5H).

MS (m/z, rel. int. %): M^+ 152 (5), 109 (100), 77 (6).

Thioacetic acid *S*-*p*-tolyl ester (9t):



9t

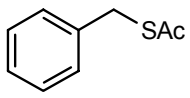
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3060, 2925, 1720.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.4 (s, 3H), 2.43 (s, 3H), 7.3-7.5 (m, 4H).

MS (m/z, rel. int. %): M^+ 166 (4), 122 (17), 91 (100), 77 (60).

Thioacetic acid *S*-benzyl ester (9u):



9u

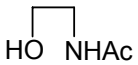
Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3060, 2925, 1721.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.4 (s, 3H), 4.2 (s, 2H), 7.25 (s, 5H).

MS (m/z, rel. int. %): M^+ 166 (3), 124 (90), 91 (100), 77 (60).

***N*-(2-Hydroxyethyl)acetamide (9v):**



9v

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3303, 3097, 2935, 1655, 1558, 1431, 1066.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.93-2.03 (d, 3H), 3.35 (m, 2H), 3.7 (m, 2H), 5.18 (bs, 1H), 6.67 (s,1H).

Acetic acid 2-mercaptoethyl ester (9w):

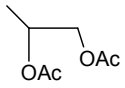
9w

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3441, 2926, 1729, 1403

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.7 (s, 1H), 2.06 (s, 3H), 2.9 (t, *J* = 4.8 Hz, 2H), 4.3 (t, *J* = 4.8 Hz, 2H).

Acetic acid 2-acetoxypropyl ester (9x1):



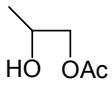
9x2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2987, 1743, 1440, 1373, 1228, 1049.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (d, *J* = 4.5 Hz, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 4,0-4.2 (m, 2H), 5.1 (m, 1H).

Acetic acid 2-hydroxypropyl ester (9x2):



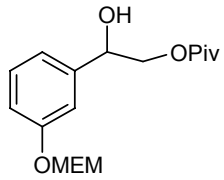
9x2

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3441, 2926, 1740, 1403.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (t, *J* = 5.7 Hz, 3H), 2.05 (bs, 1H), 2.1 (s, 3H), 3.05-3.32, 4.9 (m, 1H), 3.85-4.1 (m, 2H).

2, 2-Dimethylpropionic acid 2-hydroxy-2-[3-(2-methoxyethoxymethoxy)phenyl]-ethyl ester(9y):



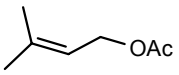
9y

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3442, 2969, 1727, 11587.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.20 (s, 9H), 1.90 (bs, 1H), 3.37 (s, 3H), 3.53-3.84 (m, 4H), 4.17-4.24 (m, 2H), 4.85 (m, 1H), 5.27 (s, 2H), 6.99-7.30 (m, 4H).

Acetic acid 3-methylbutenyl ester (9z):



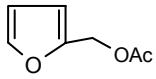
9z

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2926, 1715, 1225, 1007.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.55 (s, 6H), 2.10 (s, 3H), 4.85 (d, J = 9.75 Hz, 2H), 5.52 (t, J = 9.75 Hz, 1H).

Acetic acid furan 2-ylmethyl ester (9za):



9za

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 3060, 1720, 1270.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 3.9 (t, *J* = 6.5 Hz, 1H), 5.05 (s, 2H), 6.37 (d, *J* = 6.8 Hz, 1H), 6.4 (d, *J* = 6.7 Hz, 1H).

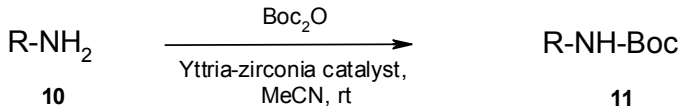
3.3.4 SECTION IV

tert-Butoxycarbonylation of Amines

3.3.4.1 Introduction

The *tert*-butoxycarbonyl (Boc) is extensively used as amino protecting group in organic synthesis.[43] The instability of *tert*-butyl chloroformate precludes its use for preparing Boc derivatives and so a large number of alternative reagents and methods have been developed of which Boc_2O[44] is one of the most commonly reagents used for this purpose. Being inert towards catalytic hydrogenation and extremely resistant towards basic and nucleophilic reagent makes it an ideal orthogonal partner to benzyl esters and carbamates used in peptide synthesis.[45] In some cases Boc_2O is also used as an apparent dehydrating agent when it reacts with carboxylic acid,[46] certain hydroxyl group[47] or with primary nitro alkanes.[48] Although there has been several examples with regards to protection of amines as *N*-Boc group, the use of Lewis acid catalyst to effect the above transformation is rather scarce. One of the method reported by Porta et al.[49] used aliphatic amine with diethyl carbonate and catalyzed the transformation with different Lewis acids. However this method could not be extended to the synthesis of *N*-aryl derivatives.

As part of a research program aimed at developing a new catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid[1] was found to be an extremely efficient catalyst for the Diels-Alder reaction,[1] transesterification of ß-keto esters[42] and acylation reaction.[50] This prompted us to use this catalyst for the synthesis *N*-Boc protected amines and herein the results of that yttria-zirconia based Lewis acid catalyzed *t*-butoxycarbonylation of amines are described (Scheme 4).



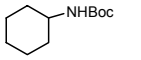
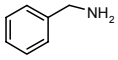
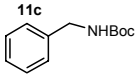
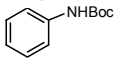
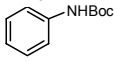
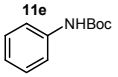
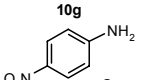
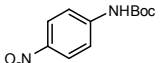
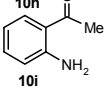
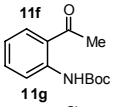
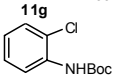
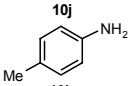
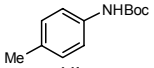
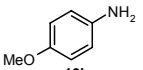
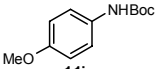
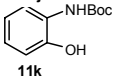
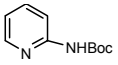
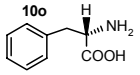
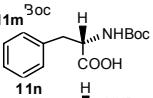
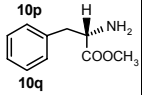
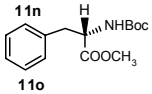
R = alkyl, aryl, benzyl, heterocyclic, amino acid

Scheme 4

3.3.4.2 Results and discussion

A variety of amines were treated with Boc_2O in the presence of catalytic amount of the yttria-zirconia based catalyst to afford the corresponding *N*-Boc protected amines in excellent yields. Thus, when benzyl amine was treated with Boc_2O in the presence of yttria-zirconia Lewis acid, the corresponding Boc protected compound **11d** was obtained in 95 % yield. The IR spectrum of **11d** showed a band at 3348 cm^{-1} indicating the presence of –NH group and another band at 1712 cm^{-1} showed the presence of urethane group. In ^1H NMR spectrum methyl protons of Boc group appeared at 1.50 δ as a singlet. The CH_2 protons of benzyl group showed a singlet at 4.50 δ. The aromatic protons appeared as multiplet at 7.20-7.50 δ. Further structure was proved by mass spectrum showing M^+ peak at 207. Similarly other products obtained were characterized based on their spectral data. The substrates examined in our studies and the results obtained are summarized in Table 10. Thus, the present procedure to introduce the *tert*-butoxycarbonyl (Boc) protecting group is quite general as a wide range of structurally varied amines such as open chain, cyclic, aromatic, heteroaromatic, amino acid underwent reaction smoothly with Boc_2O. While the conversion of aniline to the corresponding Boc-derivative appears to be sluggish at room temperature with or without catalyst (Table 10, entries 5, 6), the reaction could be completed within a short span of time (3h) under reflux condition (Table 10, entry7).

Table 10: Conversion of amines to *N*-Boc derivatives catalyzed by yttria-zirconia based Lewis acid

Entry	Amine	Reaction time (h)	Product[a]	Yield[b] %
1	**10a**	3	 **11a**	90
2	 **10b**	4	**11b**	60
3	 **10c**	5	 **11c**	90
4	 **10d**	10	 **11d**	95
5	 **10e**	14	 **11e**	90
6	 **10f**	48	 **11e**	60[c]
7	 **10g**	3	 **11e**	96[d]
8	 **10h**	8	 **11f**	91[d]
9	 **10i**	8	 **11g**	85[d]
10	 **10j**	8	 **11h**	90
11	 **10k**	8	 **11i**	90
12	 **10l**	6	 **11j**	94
13	 **10m**	6	 **11k**	89
14	 **10n**	8	 **11l**	90
15	 **10o**	4	 **11m**	85
16	 **10p**	6	 **11n**	87
17	 **10q**	5	 **11o**	90
18	 **10r**	3	 **11p**	80

[a]product was characterized by spectroscopic data. [b]yields refer to isolated pure products. [c]reaction carried out at room temparature without catalyst. [d]reaction performed under reflux condition.

Subsequently, with the introduction of an electron withdrawing substituent on the aromatic ring (i.e. carbonyl or nitro group), the amine was rendered less nucleophilic; hence the reactions were sluggish; however excellent yields of product were obtained (Table 10, entries 8, 9). It is noteworthy that the reaction is chemo selective in case of 2-aminophenol as the amine, being more nucleophilic than alcohol, underwent reaction faster giving the corresponding *N*-Boc product in high yield (Table 10, entry 13). Similar is the case with 2-aminoethanol where the *N*- Boc protected product was obtained in reasonably good yield (Table 10, entry 18). Another notable feature of the reaction is that even a secondary amine reacted smoothly to afford the product in high yield (Table 10, entries 2 & 15). Mention must be made here that amino group in amino acid could be protected easily demonstrating the practical utility of this protocol particularly in peptide synthesis. Thus *L*-phenylalanine acid/ester was smoothly converted to the corresponding carbamate in excellent yield (Table 10, entries 16 & 17). Under the reaction conditions employed, the ester remains unaffected and there is no racemization of the chiral substrate encompassing amino acid. So this protocol could be useful and further be extended to the peptidomimetic synthesis. It should be pointed out here that although the reactions of amines with Boc_2O in the presence of DMAP are well studied, the formation of side products in large amounts has recently been observed by Hassner et al. [51] during the course of their revisit into this reaction. However, the same reaction in the presence of yttria-zirconia based Lewis acid catalyst under the reaction condition employed did not lead to any side products. In this connection, our methodology for *N*- Boc protection is noteworthy. A time dependent study of reaction of aniline with Boc_2O in the absence and in the presence of varying concentration of yttria-zirconia catalyst indicated that even small amount of catalyst (10 wt %) can catalyze and accelerate the reaction, however, high yields of *N*-Boc derivatives and high efficiency of the reaction are found only using

catalyst (20 wt %). In the absence of the catalyst, the limited carbamation occurred very slowly even when the reaction was continued for 48h (Table 10, entry 6) The plausible mechanism can be visualized as the activation of carbonyl group of Boc anhydride by the Lewis acid sites of the catalyst followed by nucleophilic attack of amine to the Boc anhydride. This facilitates the extrusion of *t*-butanol and carbon dioxide as leaving entities eventually leading to the formation of *N*-Boc protected amines.

The heterogeneous catalytic method described here is profitable as it provides high yields of the product and does not involve the use of stoichiometric amount of reagent such as base for *N*-Boc protection. In addition, the reaction conditions are particularly mild and the work-up procedure is exceedingly simple and reduced to a mere filtration. Another significant advantage of the present method lies in the simplicity involved in the preparation of the catalyst.

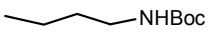
3.3.4.3 Conclusion

In summary, a facile heterogeneous catalytic method for the protection of amine as *N*-Boc group employing a novel yttria-zirconia based Lewis acid catalyst has been developed. To the best of our knowledge this is the first report of use of Lewis acid catalyst for amino group protection using Boc anhydride. Furthermore, the present protocol offers mild reaction conditions, selectivity and short reaction times. The noteworthy feature of this methodology is that chiral substrate is resistant to racemization and labile functionalities such as an ester are compatible with the reaction condition.

3.3.4.4 Experimental

General experimental procedure for the reaction of amines with Boc_2O: Formation of *N*-Boc products: In a typical experimental procedure, Boc_2O (2 mmol) in dry acetonitrile (1.5 mL) was added drop wise to a solution of amine (2 mmol) in dry acetonitrile (2.5 mL) containing catalyst (20 % by weight) with constant stirring and the mixture was stirred at room temperature for the indicated length of time (Table 10). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and washed thoroughly with ether (50 ml). The filtrate was washed with 10% sodium bicarbonate solution, then water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave the crude product, which was purified by neutral alumina column using petroleum ether: ethyl acetate (97:03) as eluent to give the pure product.

Butylcarbamic acid *tert*-butyl ester (11a):



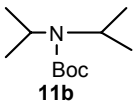
11a

Colorless liquid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3371, 1705, 1518, 1365, 1215.

^1H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.2 Hz, 3H), 1.27-1.48 (m, 4H), 1.51 (s, 9H), 3.20(q, *J* = 6.2 Hz, 2H), 5.80 (bs, 1H).

Diisopropylcarbamic acid *tert*-butyl ester (11b):



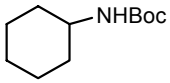
11b

Colorless liquid

IR ν_{max} /cm^{-1} (Neat): 2984, 1735, 1393, 1172.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.15 (d, *J* = 8.8, 12H), 1.45 (m, 2H), 1.5 (s, 9H).

Cyclohexylcarbamic acid *tert*-butyl ester (11c):



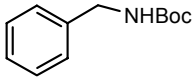
11c

White solid: M.P. 45°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3345, 2979, 1705, 1504, 1393, 1169.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.00-2.00 (m, 11H), 1.5 (s, 9H), 3.15 (m, 1H).

Benzylcarbamic acid *tert*-butyl ester (11d):



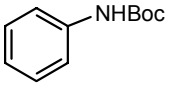
11d

White solid: M.P. 75°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3348, 2978, 1712, 1525, 1368, 1169.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 4.5 (s, 2H), 5.5 (s, 1H), 7.2-7.5 (m 5H).

Phenylcarbamic acid *tert*-butyl ester (11e):



11e

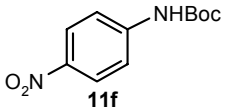
White solid: M.P. 64°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3437, 3019, 1723, 1518, 1215, 1159.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 6.5 (bs, 1H), 7.15-7.65 (m, 5H).

MS (m/z, rel. int %): M^+ 193 (9), 137 (67), 93 (100), 65 (56), 57 (95).

(4-Nitrophenyl)carbamic acid *tert*-butyl ester (11f):



11f

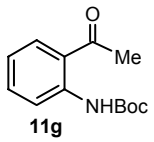
Pale yellow solid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3430, 3020, 1731, 1215, 1159.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 6.5 (bs, 1H), 7.8 (d, *J* = 8.9, 2H), 8.2 (d, *J* = 8.9, 2H).

(2-Acetylphenyl)carbamic acid *tert*-butyl ester (11g):

White solid: M.P. 149°C



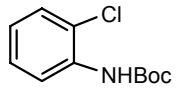
11g

IR ν_{max} /cm^{-1} ($CHCl_3$): 3430, 3018, 1726, 1703, 1651, 1582, 1522, 1313, 1220.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 9H), 2.64 (s, 3H), 6.64-7.8 (m, 4H)), 10.96 (bs, 1H).

(2-Chlorophenyl)carbamic acid *tert*-butyl ester (11h):

Colorless liquid



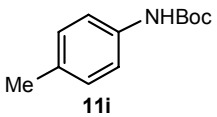
11h

IR ν_{max} /cm^{-1} ($CHCl_3$): 3425, 2980, 1729, 1596, 1522, 1393, 11304, 1160.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.59 (s, 9H), 6.9 (t, *J* = 7.14, 1H), 7.0 (bs, 1H), 7.22 (t, *J* = 7.14, 1H), 7.32 (d, *J* = 7.5, 1H), 8.15 (d, *J* = 7.14, 1H).

***p*-Tolylcarbamic acid *tert*-butyl ester (11i):**

White solid: M.P. 95°C

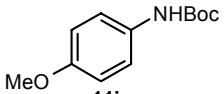


11i

IR ν_{max} /cm^{-1} ($CHCl_3$): 3438, 2980, 1721, 1593, 1522, 1314, 1160.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 9H), 2.30 (s, 3H), 6.41 (bs, 1H), 7.1 (d, *J* = 7.35, 2H), 7.24 (d, *J* = 7.35, 2H)

(4-Methoxyphenyl)carbamic acid *tert*-butyl ester (11j):



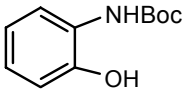
11j

White solid: M.P. 105-110°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3440, 2981, 1717, 1520, 1368, 1242.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 3.77 (s, 3H), 6.36 (bs, 1H), 6.88 (d, *J* = 7.5, 2H), 7.26 (d, *J* = 7.5, 2H).

(2-Hydroxyphenyl)carbamic acid *tert*-butyl ester (11k):



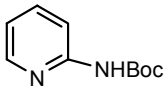
11k

White solid: M.P. 170°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3224, 2921, 1705, 1455, 1231.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 5.5 (bs, 1H), 6.5 (bs, 1H), 6.90-7.25 (m, 4H).

Pyridin-2-yl-carbamic acid *tert*-butyl ester (11l):



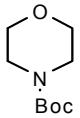
11l

White solid: M.P. 125°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3400, 3018, 1720, 1513, 1308.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 7.0 (m, 1H), 7.25-8.4 (3H), 8.5 (bs, 1H).

Marpholine-4-carboxylic acid *tert*-butyl ester (11m):



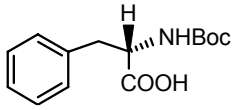
11m

White solid: M.P. 40°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 2979, 1690, 1421, 1249.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.5 (s, 9H), 3.7 (t, *J* = 6.3, 4H), 3.8 (t, *J* = 6.5, 4H).

2-*tert*-Butoxycarbonylamino-3-phenylpropionic acid (11n):



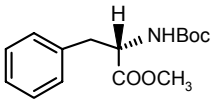
11n

White solid: M.P. 88°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3435, 2980, 1703, 1583, 1498, 1216.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 3.0 (m, 2H), 4.4 (m, 1H), 5.3 (m, 1H), 7.2-7.5 (m, 5H), 11.50 (bs, 1H).

2-*tert*-Butoxycarbonylamino-3-phenylpropionic acid methyl ester (11o):



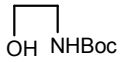
11o

White solid: M.P. 46°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3381, 2954, 1732, 1708, 1520, 1222.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 3.1 (m, 2H), 3.80 (s, 3H), 4.74 (s, 1H), 5.2 (m, 1H), 7.05-75 (m, 5H).

(2-Hydroxyethyl)carbamic acid *tert*-butyl ester (11p):



11p

Viscous liquid

IR ν_{max} /cm^{-1} (Neat): 3303, 3097, 2935, 1705, 1528, 1430, 1060.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 3.35 (m, 2H), 3.72 (m, 2H), 5.00 (bs, 1H), 6.60 (s, 1H).

3.3.5 SECTION V

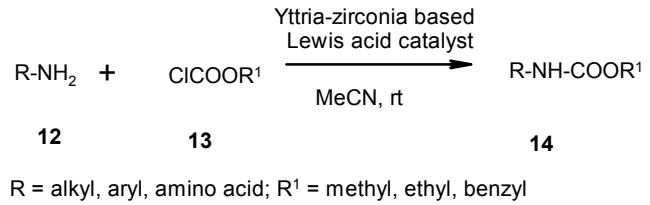
Synthesis of Carbamates using Chloroformates

3.3.5.1 Introduction

Carbamates are endowed with an array of biological activities.[52] They are known to have pesticide,[53a] insecticide,[53b] antibiotic[53c] and other pharmacological properties. They also serve as useful protecting groups in organic synthesis, particularly in peptide synthesis.[43] Due to their high demand, there has been a considerable resurgence of interest in the synthesis and biological evaluation of carbamates.[54] The carbamate synthesis is generally performed by the reaction of an amine with chloroformate in the presence of bases such as sodium hydroxide, sodium bicarbonate, triethyl amine or pyridine.[43a] A number of other methods employed to prepare carbamates are the reaction of diethyl carbonate with amine,[55] from amides,[56] reductive carbonylation of aromatic nitro compounds with $Ru_3(CO)_{12}$ or $Ru(CO)_3(PPh_3)_2$ and methanol,[57] enzymatic oxidative conversion of thio to oxo by Baker's yeast,[58] reaction of alcohol with trichloroacetyl isocyanate.[59] More recently, the reaction of amine with chloroformate using stoichiometric amount of activated zinc[60] and a three-component coupling reaction of amine, CO_2 and alkyl halide in the presence of cesium carbonate and tetrabutylammonium iodide[61] have been reported for carbamate synthesis. Although there has been several examples with regards to carbamate formation, the use of Lewis acid catalyst to effect the above transformation is rather scarce. One of the method reported by Porta et al[49] used aliphatic amine with diethyl carbonate and catalysed the transformation with different Lewis acids. However this method could not be extended to the synthesis of *N*-arylcarbamate.

As part of our research program aimed at developing new catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid was found to be an extremely efficient catalyst for the Diels-Alder reaction,[1]

transesterification of β-keto esters,[42] acylation reaction[50] and *tert*-butoxycarbonylation of amine.[62] This prompted us to use this catalyst for carbamate synthesis and herein a detailed study of alkoxycarbonylation of amines by yttria-zirconia based Lewis acid is presented.

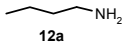
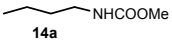
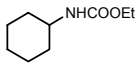
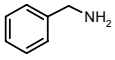
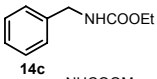
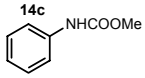
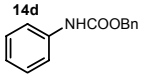
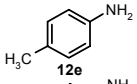
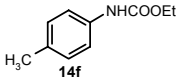
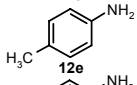
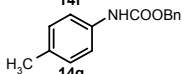
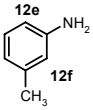
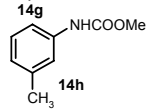
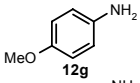
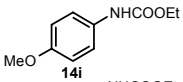
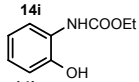
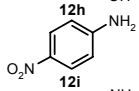
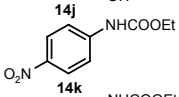
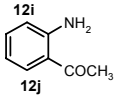
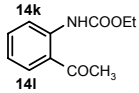
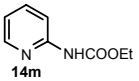
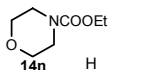
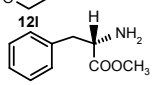
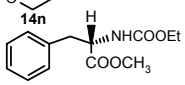
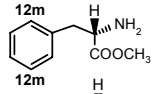
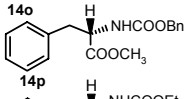
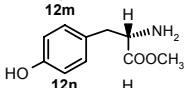
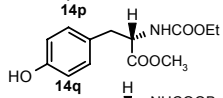
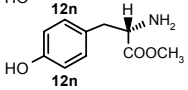
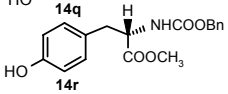


Scheme 5

3.3.5.2 Results and discussion

A variety of amines were treated with chloroformates in the presence of catalytic amount of yttria-zirconia based catalyst to afford the corresponding carbamates in excellent yields. Thus, when aniline was treated with benzyl chloroformate in the presence of sulfated yttria-zirconia Lewis acid, the corresponding phenylcarbamic acid benzyl ester **14e** was obtained in 95 % yield. The IR spectrum of **14e** showed a band at 3431 cm^{-1} indicating the presence of NH group and another band at 1731 cm^{-1} showed the presence of urethane functionality. The ^1H NMR spectrum showed CH_2 protons of benzyl group at 5.07 δ as a singlet. The aromatic protons appeared as a multiplet at 6.85-7.38 δ. The substrates examined in our studies and the results obtained are summarized in Table 11. Thus, the present procedure for carbamate synthesis is quite general as a wide range of structurally varied amines such as open chain, cyclic, aromatic, heteroaromatic, amino acid underwent reaction smoothly with chloroformates. The reaction is remarkably fast and leads to high yields of the products.

Table 11: Preparation of carbamates by yttria-zirconia based Lewis acid catalyst

Entry	Amines	Reaction times (min)	Products	Yields[a]
1	 **12a**	5	 **14a**	94
2	 **12b**	5	 **14b**	88
3	 **12c**	8	 **14c**	90
4	 **12d**	7	 **14d**	96
5	 **12d**	15	 **14e**	95
6	 **12e**	7	 **14f**	90
7	 **12e**	15	 **14g**	95
8	 **12f**	8	 **14h**	90
9	 **12g**	5	 **14i**	94
10	 **12h**	5	 **14j**	94
11	 **12i**	360	 **14k**	90
12	 **12j**	355	 **14l**	90
13	 **12k**	15	 **14m**	94
14	 **12l**	10	 **14n**	91
15	 **12m**	12	 **14o**	93
16	 **12m**	18	 **14p**	92
17	 **12n**	15	 **14q**	92
18	 **12n**	20	 **14r**	91

[a]All the product exhibited physical and spectral (NMR and IR) properties in accord with the assigned structure

As summarized in Table 11, aromatic amines underwent facile carbamation with a variety of chloroformates in excellent yields. Subsequently, with the introduction of an electron withdrawing substituent on the aromatic ring (i.e. carbonyl or nitro group), the amine was rendered less nucleophilic; hence the reactions were sluggish; however an excellent yields of product were obtained (Table 11, entries 11-12). Similarly the reaction of various amines with benzyl chloroformate was found to be relatively slow and hence a little longer time was required to complete the reaction; affording excellent yields of the products (Table 11, entries 5,7, 16, 18). It is noteworthy that the reaction is chemoselective in case of 2-aminophenol as the amine, being more nucleophilic than alcohol, underwent reaction faster giving the corresponding *N*-carbamate product in excellent yield (Table 11, entry 10). Another notable feature of the reaction is that even a secondary amine reacted smoothly to afford the carbamate in high yield (Table 11, entry 14). Mention must be made here that amino group in amino acid could be protected easily demonstrating the practical utility of this protocol particularly in peptide synthesis. Thus L-phenylalanine ester was smoothly converted to the corresponding carbamate in excellent yield (Table 11, entry 15). Similarly in case of L-tyrosine ester, the amino group is protected selectively in the presence of hydroxyl group (Table 11, entries 17, 18). Under the reaction conditions employed, the ester groups remain unaffected and there is no racemization of the chiral substrate encompassing amino acid. So this protocol could be useful and further be extended to the peptidomimetic synthesis. A time dependent study of carbamation of aniline with methyl chloroformate in the absence and in the presence of varying concentration of yttria-zirconia catalyst indicated that even small amount of catalyst (10 wt %) can catalyze and accelarate the reaction, however, high yields of carbamates and high efficiency of the reaction are found only using catalyst (20 wt %). In the absence of the catalyst, the limited carbamation occurred very slowly even

when the reaction was continued for 20h. The reaction was performed even on large scale in the presence of catalyst and the results could be reproduced. The anhydrous HCl generated during reaction evolves in the form of gas which has been experimentally detected by trapping it into the ammonia solution. Thus, the HCl gas evolved was driven away in order to avoid the formation of any amine hydrochloride.

The heterogenous catalytic method described here is profitable as it provides high yields of the product and does not involve the use of stoichiometric amount of reagent such as base for carbamate synthesis. Thus, the present protocol could be useful particularly for those substrates containing base sensitive functionalities. In addition, the reaction conditions are particularly mild and the work-up procedure is exceedingly simple and reduced to a mere filtration. Another significant advantage of the present method lies in the simplicity involved in the preparation of the catalyst.

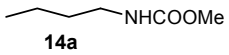
3.3.5.3 Conclusion

In summary, a facile heterogeneous catalytic method for the preparation of a variety of carbamates employing a novel yttria-zirconia based Lewis acid catalyst has been developed. To the best of our knowledge this is the first report of use of Lewis acid catalyst for carbamate synthesis from amine using chloroformate. Furthermore, the present protocol offers mild reaction conditions, selectivity and short reaction times. The noteworthy feature of this methodology is that chiral substrate is resistant to racemization and labile functionalities such as an ester are compatible with the reaction condition. Thus the present catalytic method should offer a general synthetic method for various carbamates offering a wide variety of application.

3.3.5.4 Experimental

Typical experimental procedure for the preparation of carbamate: In a typical experimental procedure, chloroformate (20 mmol) in dry acetonitrile (15 mL) was added dropwise to a solution of amine (20 mmol) in dry acetonitrile (25 mL) containing catalyst (20 % by weight) with constant stirring and the mixture was stirred at room temperature for the indicated length of time (Table 11). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the solid was washed thoroughly with ether (100 ml). The combined filtrate was washed with 10 % sodium bicarbonate solution, then water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave the crude product which was purified by silica gel chromatography using petroleum ether: ethyl acetate (97:03) as eluent to give the pure product.

Butylcarbamic acid methyl ester (14a):

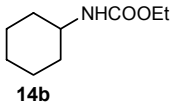
Yellow oil 

14a

IR ν_{max} /cm^{-1} (Neat): 3323, 2964, 1710, 1520, 1216.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 6.5, 3H), 1.25-1.50 (m, 4H), 1.75 (bs, 1H), 3.20 (t, *J* = 6.5, 2H), 3.15 (s, 3H).

Cyclohexylcarbamic acid ethyl ester (14b):

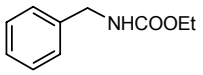
White solid, M. P. 60°C 

14b

IR ν_{max} /cm^{-1} (Neat): 3323, 2962, 1730, 1546, 1235.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.11 (t, *J* = 7.5, 3H), 1.15-2.25 (m, 10H), 3.15 (m, 1H), 3.45 (bs, 1H), 4.10 (q, *J* = 5.6, 2H).

Benzylcarbamic acid ethyl ester (14c):



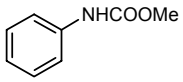
14c

White solid: M. P. 55°C

IR ν_{max} /cm^{-1} (Nujol): 3450, 3018, 1711, 1516, 1216.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.10 (t, *J* = 7.5, 3H), 3.90 (q, *J* = 5.6, 2H), 4.15 (d, *J* = 5.3, 2H), 7.05-7.50 (m, 5H), 8.50 (bs, 1H).

Phenylcarbamic acid methyl ester (14d):



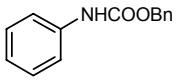
14d

White solid: M. P. 50°C

IR ν_{max} /cm^{-1} (Nujol): 3291, 2950, 1730, 1543, 1216.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 6.70 (bs, 1H), 7.10-7.40 (m, 5H).

Phenylcarbamic acid benzyl ester (14e):



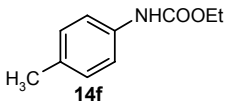
14e

White solid: M.P. 80°C

IR ν_{max} /cm^{-1} (Nujol): 3431, 3019, 1731, 1525, 1214.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.07 (s, 2H), 6.85-7.38 (m, 10H), 8.31 (bs, 1H).

***p*-Tolylcarbamic acid ethyl ester (14f):**



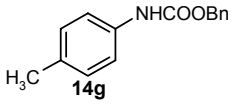
14f

White solid: M.P. 63°C

IR ν_{max} /cm^{-1} (Nujol): 3318, 2981, 3019, 1706, 1529, 1229.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.2, 3H), 2.60 (s, 3H), 4.20 (q, *J* = 5.6, 2H) 6.60 bs, 1H), 7.10 (d, *J* = 5.45, 2H), 7.25 (d, *J* = 5.45, 2H).

_p_-Tolylcarbamic acid benzyl ester (14g):



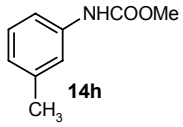
14g

White solid: M.P. 140°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3431, 3018, 1724, 1526, 1217.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 5.21 (s, 2H), 6.68 (bs, 1H), 7.1-7.5 (m, 9H).

_m_-Tolylcarbamic acid methyl ester (14h):



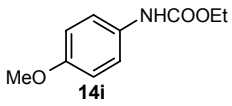
14h

White solid: M.P. 50°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3430, 2922, 1713, 1457, 1226.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 3.15 (s, 3H), 6.68 (bs, 1H), 7.1-70.80 (m, 4H).

(4-Methoxyphenyl)carbamic acid ethyl ester (14i):



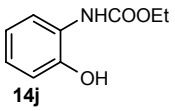
14i

White solid: M.P. 85-86°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3313, 2921, 1697, 1458, 1241.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.20 (t, *J* = 7.25, 3H), 3.60 (s, 3H), 4.10 (q, *J* = 5.9, 2H), 6.70 (bs, 1H), 6.91 (d, *J* = 6, 2H), 7.20 (d, *J* = 6, 2H).

(2-Hydroxyphenyl)carbamic acid ethyl ester (14j):



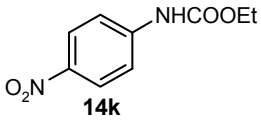
14j

White solid: M.P. 80°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3224, 2921, 1700, 1456, 1231.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 71.6, 3H), 4.28 (q, J = 5.9, 2H), 6.80 (bs, 2H), 6.90-7.25 (m, 4H).

(4-Nitrophenyl)carbamic acid ethyl ester (14k):



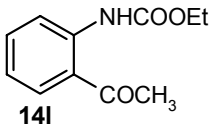
14k

Yellow solid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3221, 2921, 1730, 1458, 1230.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (t, *J* = 7.2, 3H), 4.28 (q, *J* = 59, 2H), 7.06 (s, 1H), 7.80 (d, *J* = 8.9, 2H), 8.20 (d, *J* = 8.9, 2H).

(2-Acetoxyphenyl)carbamic acid ethyl ester (14l):



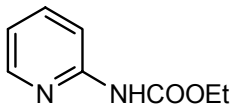
14l

Yellow oil

IR ν_{max} /cm^{-1} ($CHCl_3$): 3446, 3018, 1726, 1705, 1582, 1220.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (t, *J* = 7.25, 3H), 2.64 (s, 3H), 4.28 (q, *J* = 5.9, 2H), 6.80 (bs, 1H), 7.10-7.88 (m, 4H).

Pyridin-2-yl-carbamic acid ethyl ester (14m):



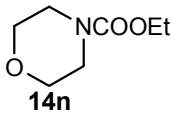
14m

White solid: M.P. 100°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3446, 3220, 3019, 1726, 1705, 1585, 1217.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.25, 3H), 4.25 (q, *J* = 5.9, 2H), 6.60 (bs, 1H), 7.0 (t, *J* = 6.6, 1H), 7.75 (t, *J* = 6.6, 1H), 8.05 (d, *J* = 6.8, 1H), 8.5 (d, *J* = 5.3, 1H).

Marpholine-4-carboxylic acid ethyl ester (14n):



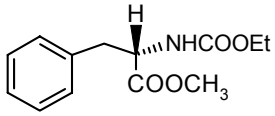
14n

Colorless oil

IR ν_{max} /cm^{-1} ($CHCl_3$): 2927, 1695, 1454, 1103.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (t, *J* = 7.25, 3H), 3.25 (m, 4H) 3.5 (m, 4H), 4.25 (q, *J* = 5.9, 2H);

2-Ethoxycabonylamino-3-phenylpropionic acid methyl ester (14o):



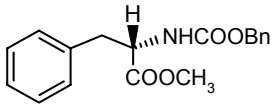
14o

White solid: M.P. 110°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3381, 2954, 1742, 1708, 1526, 1225.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.25, 3H), 3.10 (m, 2H) 3.75 (s, 3H), 4.20 (q, *J* = 5.9, 2H), 4.74 (s, 1H), 5.20 (m, 1H), 7.05-7.50 (m, 5H).

2-Benzyloxycabonylamino-3-phenylpropionic acid methyl ester (14p):



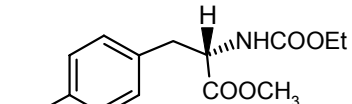
14p

White solid: M.P. 190°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3381, 2954, 1742, 1708, 1526, 1225.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.10 (m, 2H) 3.75 (s, 3H), 4.74 (s, 1H), 5.20 (s, 2H), 5.25 (m, 1H), 7.05-7.50 (m, 10H).

2-Ethoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (14q):



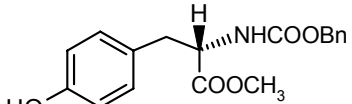
14q

White solid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3381, 2954, 1745, 1708, 1528, 1220.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.25, 3H), 3.10 (m, 2H) 3.75 (s, 3H), 4.20 (q, *J* = 5.9, 2H), 4.74 (s, 1H), 5.20 (m, 1H), 6.90 (s, 1H), 7.01-7.50 (m, 4H).

2-Benzyloxycabonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (14r):



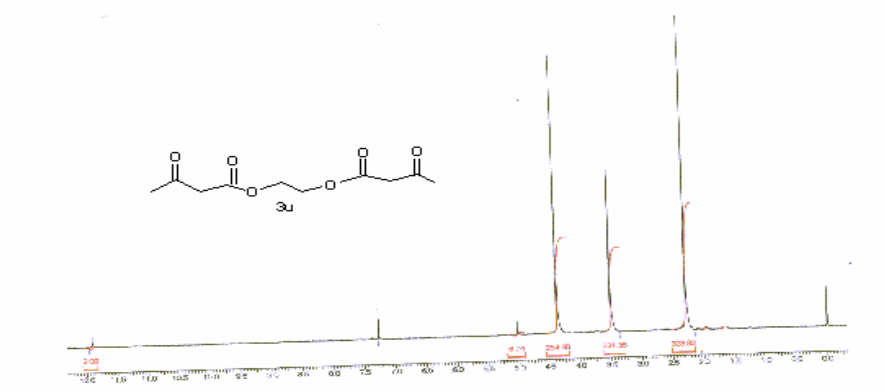
14r

White solid: M.P. 200°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3380, 2950, 1740, 1702, 1522, 1220.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.10 (m, 2H) 3.75 (s, 3H), 4.74 (m, 1H), 5.10 (s, 2H), 5.25-5.56 (m, 1H), 7.10-7.53 (m, 10H).

3.4 Spectra



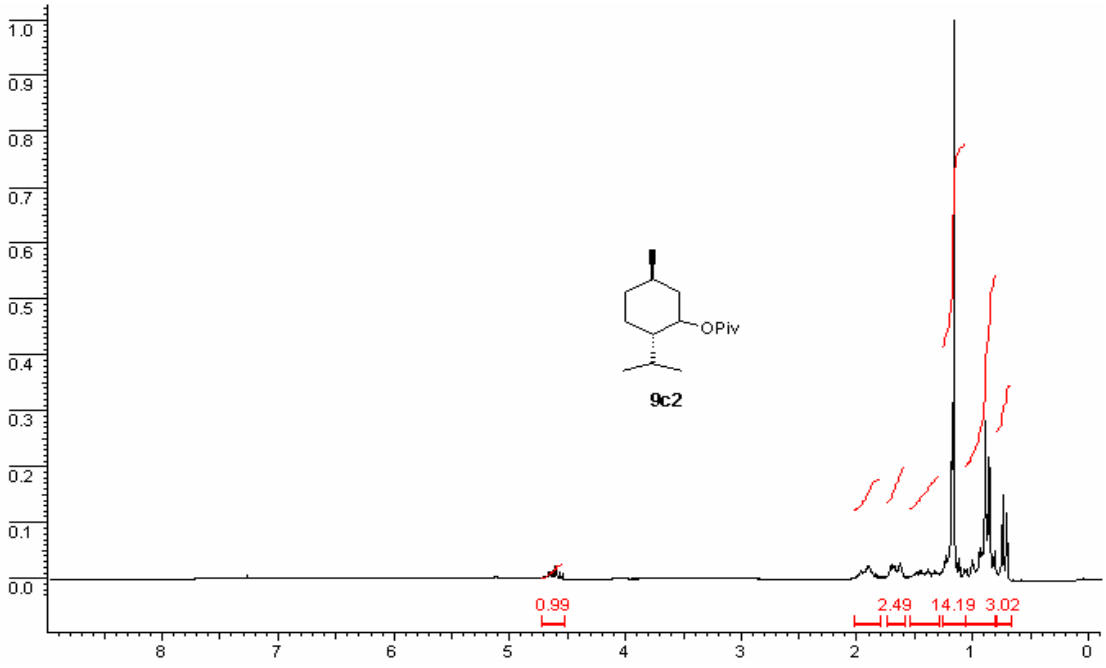


Figure 9: ^{1}H NMR spectrum of **9c2**

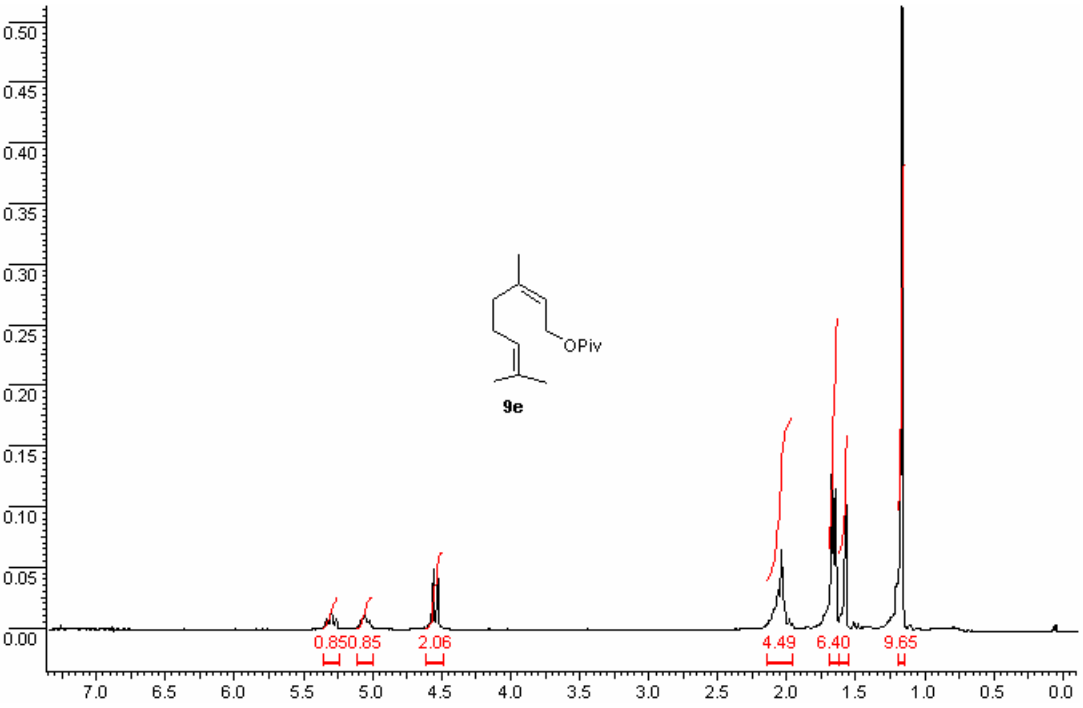


Figure 10: ^{1}H NMR spectrum of **9e**

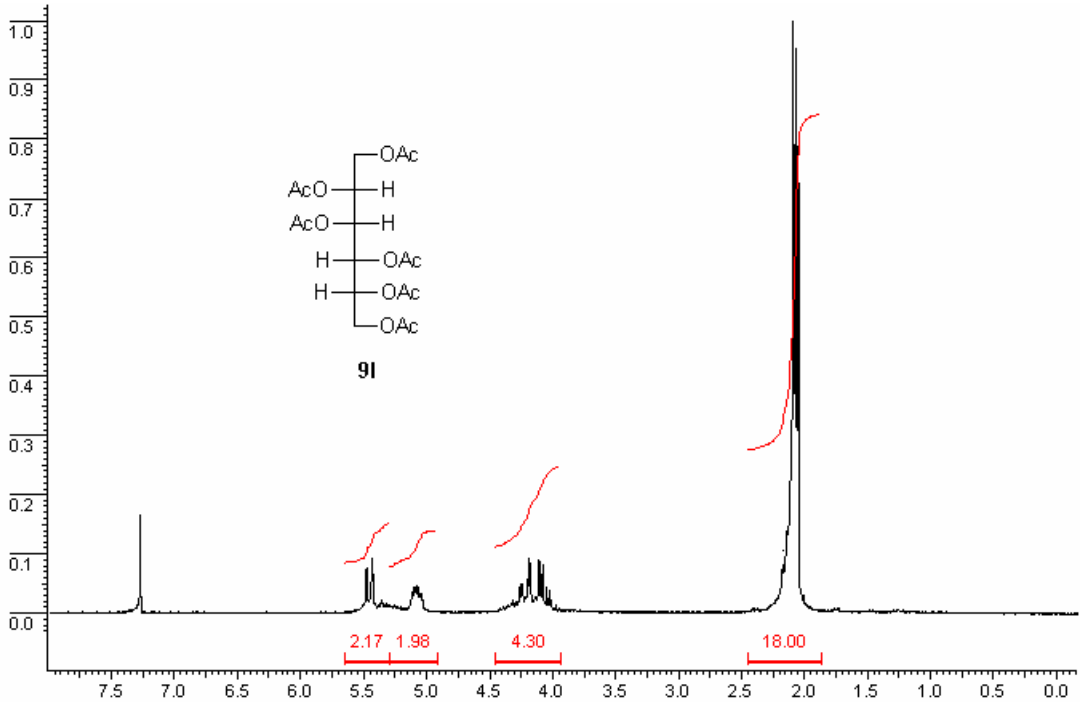


Figure 11: ^{1}H NMR spectrum of **9l**

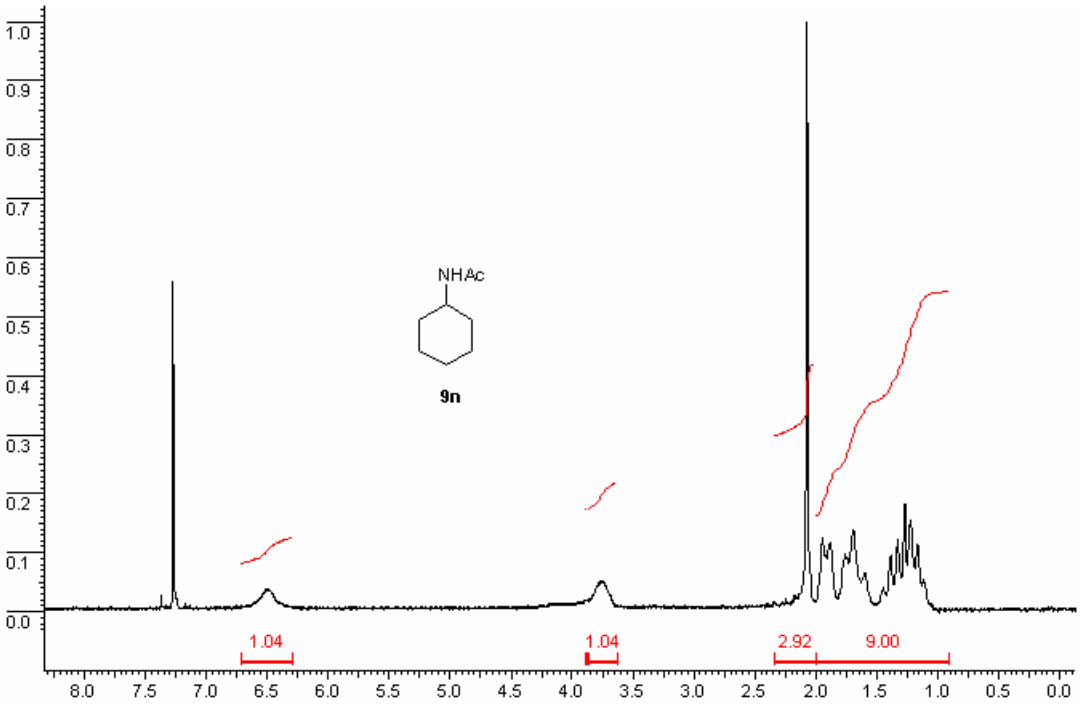


Figure 12: ^{1}H NMR spectrum of **9n**

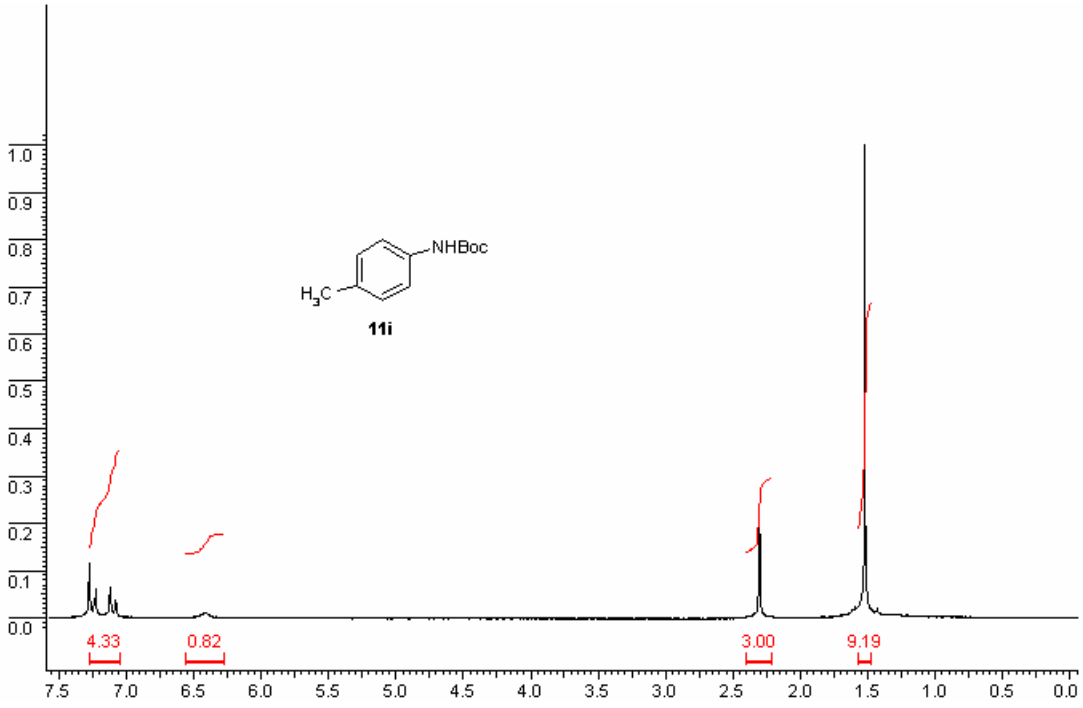


Figure 13: ^{1}H NMR spectrum of **11i**

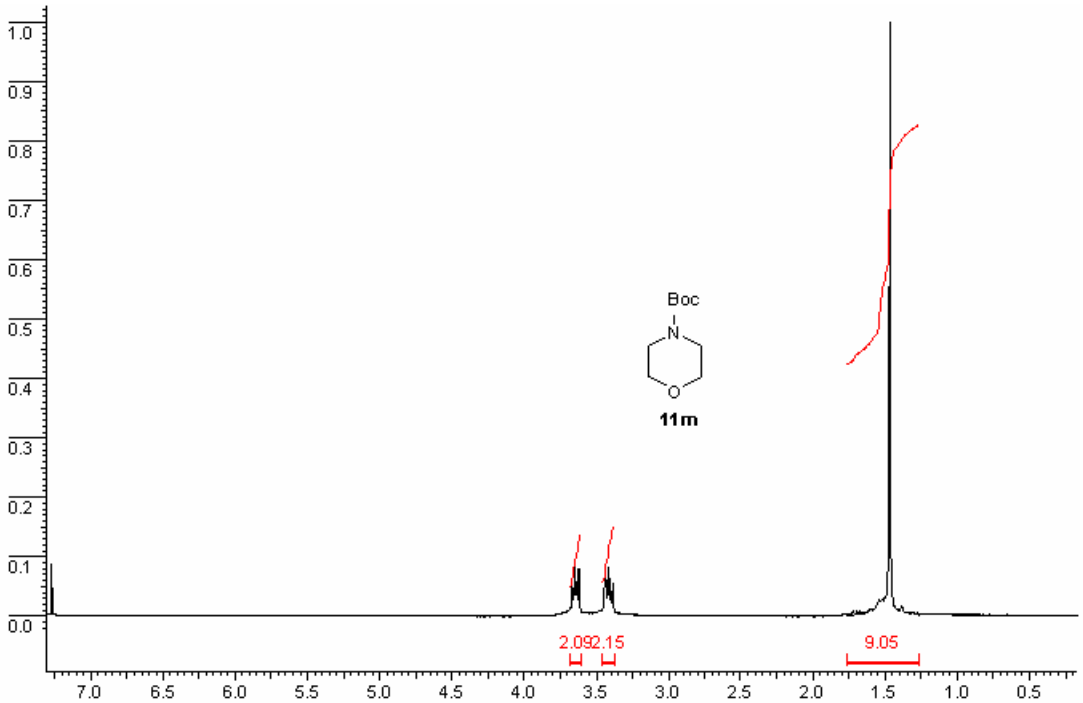


Figure 14: ^{1}H NMR spectrum of **11m**

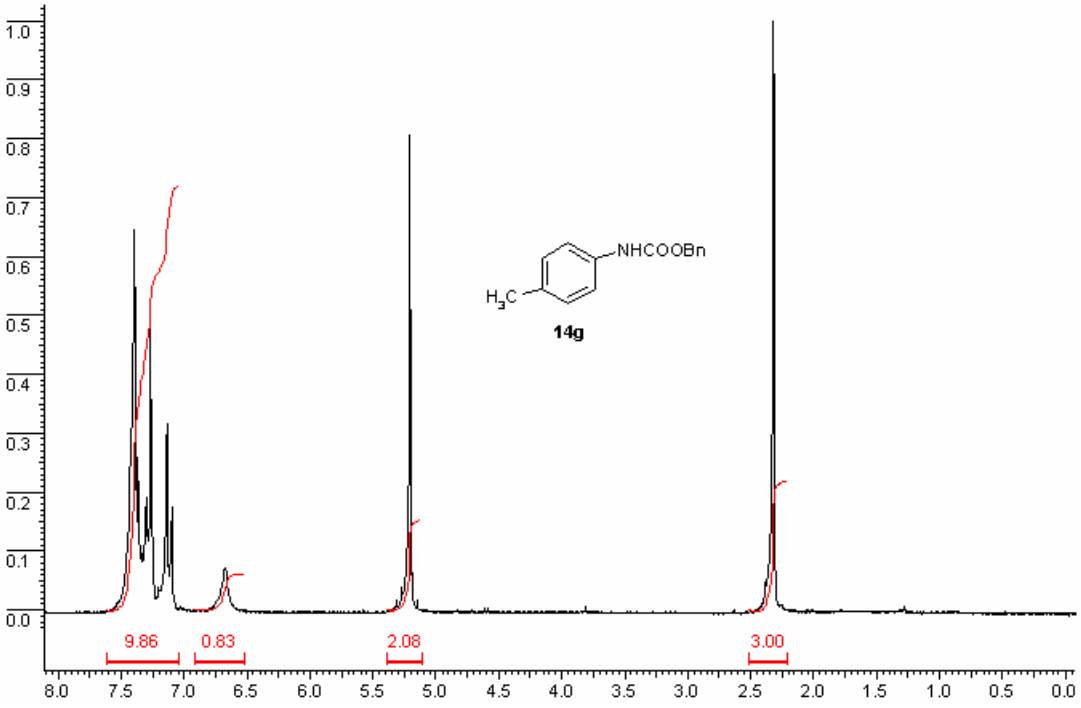


Figure 15: ^{1}H NMR spectrum of **14g**

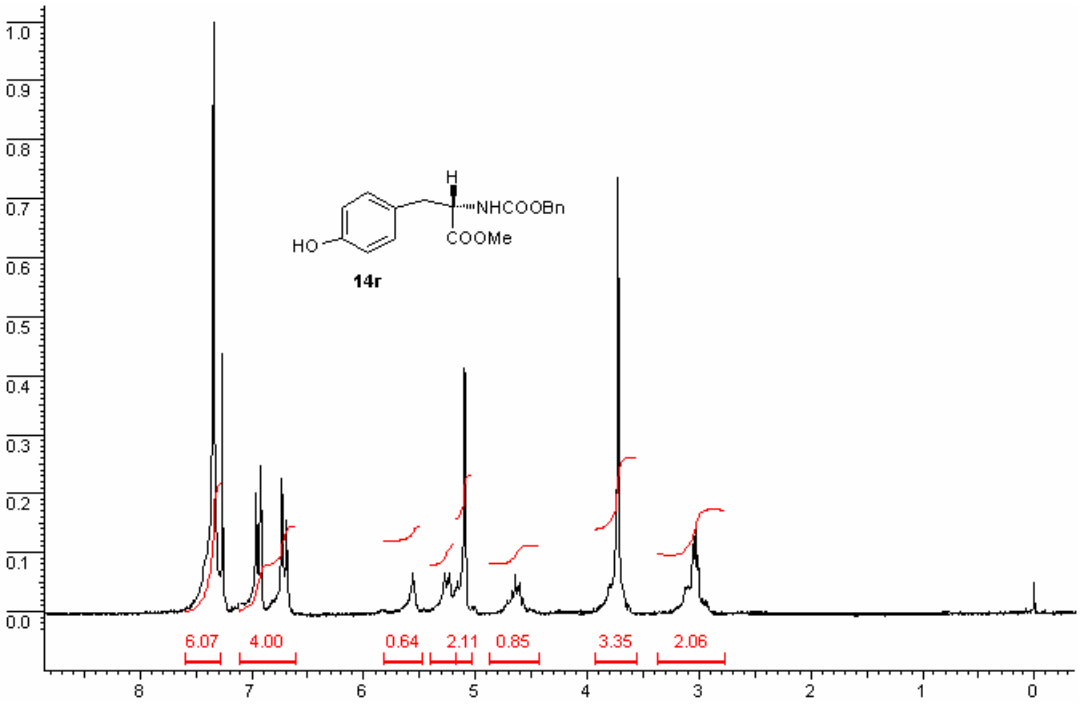


Figure 16: ^{1}H NMR spectrum of **14r**

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CHAPTER 4

ZEOLITE FOR ORGANIC TRANSFORMATIONS

4.1 SECTION A
General Introduction about Zeolite

4.1.1 Introduction

Zeolites are porous crystalline, hydrated aluminosilicates, having highly ordered rigid three dimensional infinite framework. These structures are built by sharing SiO_4 and AlO_4 tetrahedra linked through common oxygen atoms. Zeolite may be represented by the general formula[1] $M_{x/n}[(AlO_2)_x(SiO_4)_y]ZH_2O$ where 'M' is a cation of valence 'n,' Z is the number of water molecules and the ratio y/x usually has the value of 1-5 depending upon the structure, the sum (x+y) is total number of tetrahedral in the unit cell. The cations (M) are often from group I or II or rare earth ions, or organic species. Moreover, the cations are mobile and may be usually exchanged.

Zeolites are endowed with unique physical and chemical characteristics, which offer opportunities to manipulate active site micro-environment, similar to catalytic antibodies[2] and metalloenzymes.[3] Some of physical characteristics of zeolites are its ruggedness to temperature and pressure and its ability to recognize, discriminate and organize molecules with less than 1 Å level precision at the active site, whereas the noteworthy chemical characteristics are the possibility of manipulating framework metal ion properties e.g. acidic and basic (either Lewis or Brönsted), oxidizing and reducing etc.[4, 5] Indeed, their useful and versatile properties make zeolite as a super candidate for developing highly desirable environmentally friendly and cost effective heterogeneous catalytic technologies.[4, 5] Consequently, the interface of synthetic organic chemistry and zeolite induced transformations have acquired an enhanced degree of attraction and activity in the last decade.[4, 5]

4.1.2 Why use Zeolites?

There are several reasons for using zeolites over other possible reagent/catalysts. From an industrial standpoint, zeolites offer the advantages of (i) having high thermal stability, (ii) being insoluble version of noxious Brönsted and Lewis acids, and (iii) providing shape selectivity by possessing identical, well-defined reaction cavities. Figure 1 summarizes the advantage of zeolite type materials for potential industrial processing of organic chemicals. These features are of utility to the synthetic organic chemist continuously dealing with issues of reagent compatibility and reaction selectivity. However, the less obvious benefit to using zeolites involves their (controlled) variability. Through the process of cation exchange, metal framework substitution, covalent modification, and organic templating, the chemist can fine-tune zeolite dimensions, acidity and electrostatics. The latter is particularly important for electron and energy transfer processes, or for stabilizing reactive cationic intermediates.

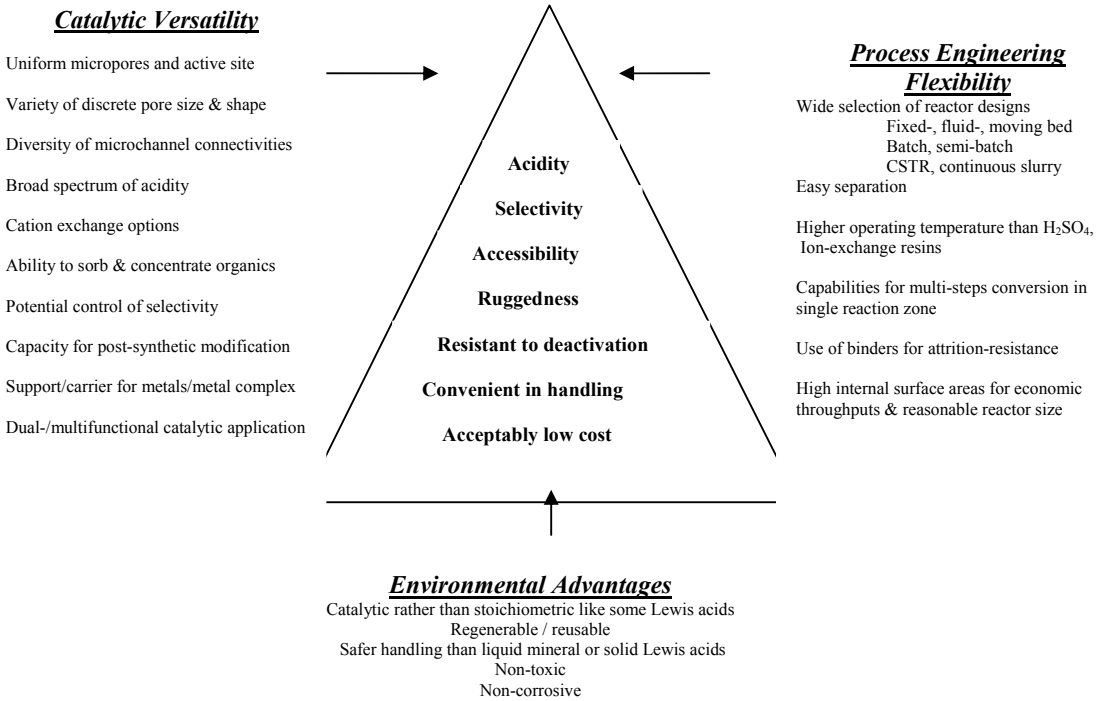


Figure 1: Zeolites and molecular sieves meet the requirement for industrial processing of organic chemicals. They also offer significant opportunity for "molecular engineering" or "tailor-making" of desired products.

The shape selectivity observed for zeolite catalysis has been categorized into three different types:[6]

1. **Reactant selectivity:** From a mixture of reactants, only those of the appropriate dimensions will enter the zeolite cavity and undergo chemical transformation. A classic example is the selective cracking and adsorption of n-alkanes from paraffin mixture.
2. **Product selectivity or molecular trafficking:**[7] From a mixture of products formed during the zeolite-catalyzed reaction, only those of the appropriate dimensions may diffuse out of the pores. An important application of this process is seen in zeolite-mediated electrophilic aromatic substitutions, examplified by the *para*-selectivity Friedel-Crafts monoalkylation of toluene usig zeolite ZSM-5.
3. **Transition state shape selectivity:** This last type of selectivity, also termed as *restricted transition state selectivity*, requires the reaction to occur either at or within the zeolite pore.[8] Similar to enzyme catalysis, zeolite will stabilize one transition state over another, either by size or shape effects.

Thus by one or more of the above methods, zeolites can control the selectivity of chemical transformations, by changing either the products formed or the ratio of the product(s) formed. The extent of reactant and transition state shape selectivity have been qualified by examining the zeolite-mediated dehydration of 1-*versus* 2-butanol. Using this as a benchmark, it would appear that zeolite can discriminate between differences in structure of less than 1 Å.[4a]

4.1.3 Classification of Zeolites

Until today, 40 species of natural zeolites and more than 260 synthetic zeolites have been identified. Classification of zeolites has been done on the basis of different factors. The

zeolite lattice contains cavities of varying diameters depending on the type of zeolite. The frame work of zeolite contains channels and interconnected voids, which are occupied by the cation and water molecules. These cations are quite mobile and may usually be exchanged to varying degree by other cations. Classification based on pore diameter[9] as discussed here in detail, is more pertinent to organic chemistry. However, different classifications reported in the literature are based on natural occurrence and morphological characters, crystal structure or chemical composition. Barrer[10] and Sand [9a] have classified zeolite into three groups based on their effective diameter viz. small-pore, medium-pore and large-pore zeolites (Table 1, Figure 2). In the case of small-pore zeolites, the diameter of the cavity is 4.1Å. This is formed by eight SiO_4 tetrahedra. All medium-pore zeolites are called pentasil zeolites, having a ten atom ring system with a tubular diameter of 5.6 Å. The third category is the large pore zeolites having 12 atom rings of cavities with a diameter 7.4 Å. Recently, a vary large-pore zeolites aluminophosphate molecular sieve (UPI-5), containing a 18-membered ring has been synthesized.[11] Very recently an extra-large 20-membered ring pore openings called Cloverity has been discovered.[12]

Table 1: Classification of zeolites based on their pore-diameter

Small Pore	Medium Pore	Large Pore	Meso-porous
A	ZSM-5	Faujasite	MCM-41
Erionite	ZSM-11	X, Y	MCM-48
Chabazite	ZSM-22	Beta	MCM-22
Rho	ZSM-23	Mordenite	FBA-15
	ZSM-48	L	
	TS-1, VS-2	Omega	
	TS-2, VS-2	ZSM-12	
	Silicalite	Offretite	
	Theta-1		

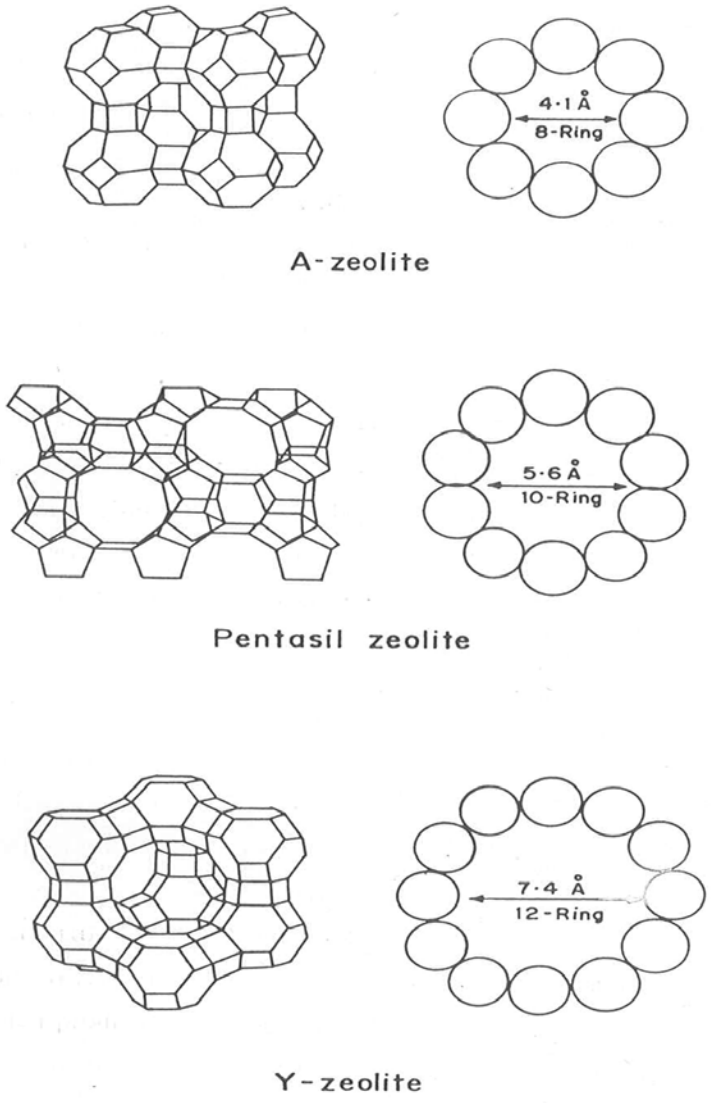


Figure 2: Zeolite Structures

4.1.4 Zeolite Catalysts in Organic Synthesis

The physical and chemical properties of zeolites offer a vast number of options for the tailoring of catalysts of specific reaction within the constraints that the structure must be accommodating the reactants. In addition, the combination of activity and shape selectivity in the zeolite catalysts is an important factor in organic synthesis. The acid strength and the number of acidic sites can be adjusted in a controlled manner during

synthesis and / or by subsequent metal (cation) exchange. Application of zeolites in organic synthesis includes catalytic and non-catalytic uses. The non-catalytic[13] uses of zeolites are the following:

i) Drying and purification of reactants and media.

ii) Separation of products.

iii) Use as scavenger e.g. in shifting equilibria.

iv) Zeolites serve as hosts to organize guest atoms and molecules that provide composite material with optoelectronics e.g. non-linear optical properties and electrochemical properties.

The most important application of zeolites is in reactions catalyzed by protic acids and Lewis acids where the change from a homogeneous to heterogeneous procedures brings advantages in respect of easy separation and disposal of catalyst, avoidance of corrosivity etc. As evident by the number of reviews,[5, 13] the application of zeolites in organic synthesis is a blossoming field, and there is enormous scope for using them in various synthetic organic transformations.

A) Aromatic Substitution Reactions:[5, 13]

Zeolite catalyzed alkylation of benzene, its derivatives and naphthalene has been studied. Methylation, ethylation and lower alkylation reactions, ideally take place in gaseous phase. In many alkylation reactions with long-chain alkenes, it is necessary to revert to the liquid phase. As the chain length increases, cracking reactions must be expected in the gas phase. The alkylation of aniline with olefin, provides C-alkylated aniline (ortho position) in contrast to N-alkylated products. The alkylation of pyridine has been studied. Another type of aromatic substitution is the direct hydroxylation of phenol with H_2O_2 in the presence of H-ZSM-5. Taramasso et. al.[14] have reported that Ti containing zeolites are more reactive in the hydroxylation of phenol with H_2O_2 than any other catalyst. Like

alkylation, the acylation of amines can also be carried out using zeolites. The acylation of toluene with C_1-C_2 carboxylic acids using Ce-Y zeolite in the liquid phase has been reported.[15] A surprising part in the chlorination of benzene is that the substitution product chlorobenzene is obtained on Y-zeolite whereas on ZSM-5 the addition product hexachlorocyclohexane (Gammaxane or Lindane) is formed.[16]

B) Isomerization and Rearrangements:[4, 13]

Isomerization of alkyl substituted arenes, 2,4-dichlorophenol to 2,5-dichlorophenol, 2-chlorothiophene to 3-chlorothiophene[17] and 3,4-dichlorotoluene to 2,5-dichlorotoluene over ZSM-5 zeolites has been reported. Double bond isomerization in olefins, isomerization of aniline to 2-methyl pyridine, aldehyde to ketone skeletal rearrangements of paraffins, the pinacol-pinacolone rearrangement, Beckmann-rearrangement, Wagner-Meerwein rearrangements and rearrangement of epoxides have also been reported over many pentasil type zeolites.

C) Condensation Reactions:[4, 13]

Generally, condensation reactions are catalyzed by acids and bases. Over acid aluminium zeolites, acetone is converted into mesityl oxide, isobutene, mesitylene and alkyl phenols. Synthesis of isoprene from the reaction of isobutene with formaldehyde is a well known strategy. Another class of condensation reaction with NH_3 is the synthesis of *N*-heterocyclic compounds. Picolines are obtained by the condensation of acetaldehyde with NH_3 over ZSM-5 and Cd-ZSM-5 zeolite.[18a] Condensation of acetone, methanol and ammonia on H-ZSM-5 yields selectively 2,6-lutidine.[18b]

D) Oxidation reactions:[4, 13]

Many straight chain organic molecules with low molecular weight have been oxidized with zeolite catalysts, in the presence of either molecular oxygen or hydrogen peroxide. One of the latest arrival on the zeolite scene is crystalline microporous titanium silicate

molecular sieves TS-1[14] and TS-2[19] which has led to the remarkable progress in the field of oxidation with H_2O_2. The direct hydroxylation of aromatic hydrocarbons (phenol, anisole, toluene, ethyl benzene, cresols) with H_2O_2 can be preformed using TS-1/TS-2 as catalyst.[20] Another important part of reaction of titanium silicate zeolite is the liquid phase conversion of cyclohexanone to its oxime in the presence of NH_3 and H_2O_2[21] also cleavage of "C=C" double bond[22] and oxidation of thioethers.[23]

E) Cyclization Reaction:[13]

Cyclization/aromatization of hexane and higher n-alkanes is selectively attained using Pt-loaded neutral L-zeolites. For instance, n-hexane is converted over 0.6% Pt/K-L at 460^0C in 80% selectivity to benzene. Zeolites are known to catalyze Diels-Alder cycloadditions, the conversion of cyclopropane towards tricycle [3.1.0.0] hexane, cyclopropanation of various olefins, anthracene formation of benzyl alcohol and ring closure towards heterocyclic compounds etc.

4.1.5 Conclusion

In conclusion, we discussed about the definition, classification of zeolites and its application for organic transformations. It is clear from the above point that the zeolites are very important for organic synthesis in multipurpose value such as drying and purification of reactants and media, separation of products, use as scavenger e.g. in shifting equilibria and beside this catalyses the several organic transformations in chemoselective and eco-friendly manner.

4.2 SECTION B

Anti-Markovnikov Addition of Thiols Across Double Bond Catalyzed by H-Rho-Zeolite

4.2.1 Introduction

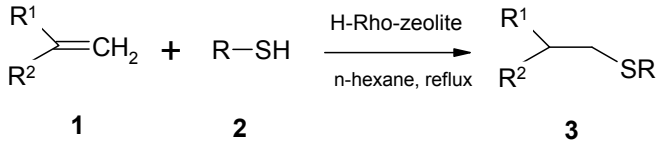
Rho-zeolite is a small pore (micro-porous aluminosilicate) molecular sieve composed of a body centered cubic arrangement of truncated cubo-octahedra or cages linked via double 8-membered rings. Structural studies[24] have shown that zeolites H-Rho undergo an appreciable distortion and loss of symmetry upon dehydration. This change in symmetry is directly related to an enormous 8.9% decrease in the lattice volume.

For many zeolites, control over the ring aperture dimension is achieved typically using different sized cations. However, for Rho-zeolite, it is the framework itself which destracts to modify the openings. The distortion showed to vary from 0 to about 1.9Å.[25]

The framework of this zeolites can be manipulated from 15.098 to 13.965Å by suitable ion exchange and calcination procedures.[26]

The last few years have witnessed considerable upsurge of interest in the area of zeolite induced organic transformations.[4a,b, 27] In a series of publications from our group,[23, 28] we have exploited the catalytic potential of zeolites for various organic synthetic transformations, e.g. thioacetalization of carbonyl compounds, sulfoxidation of thioethers, deketalization, tetrahydropyranylation of alcohols, oxidative cleavage of tosylhydrazones, methoxymethylation of alcohols, chemo- and stereoselective epoxidation and acetylation of aldehydes etc. In continuation, we have developed a mild, convenient and heterogeneous catalytic methodology for the synthesis of anti-Markovnikov addition products by the reaction of thiols and olefins using Rho-zeolite.

In general, the protic acid[29] or Lewis acid[30] catalyzed addition of thiols across double bonds is known to give thioethers having structures which are in accordance with Markovnikov's rule. However, in the presence of free-radical initiator, thiols have been reported to add to double or triple bonds in anti-Markovnikov's fashion by a free-radical mechanism.[31] A variety of hydroboration reagents developed for this reaction are also reported to give the anti-Markovnikov product.[32] However, the use of conventional protic or Lewis acid catalysts entails the problem of corrosivity, work-up and effluent pollution. Consequently, there is genuine need for an efficient and heterogeneous catalytic method for this reaction using inexpensive and nonpolluting reagents. We have now exploited the catalytic potential of H-Rho-zeolite for the thiol addition to olefins in an anti-Markovnikov fashion as depicted in Scheme 1.



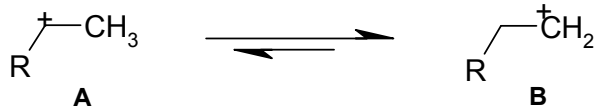
Scheme 1

4.2.2 Results and Discussion

Thus, when the olefins were treated with thiols in the presence of catalytic amount of H-Rho-zeolite, the corresponding anti-Markovnikov products were obtained in good to excellent yields (Table 2). In a typical reaction procedure, to a stirred solution of olefin **1** (20 mmol) in n-hexane (25 ml) were added H-Rho-zeolite (0.5 equivalent by wt. of olefin) and thiol **2** (25 mmol) and the mixture was refluxed with stirring for the indicated length of time (Table 2). The reaction was monitored by TLC and GC. After the completion of reaction, zeolite was filtered off and washed with n-hexane; the filtrate was

then washed with 10% aq. NaOH solution to remove excess thiol and then further washed with water, brine and dried over Na_2SO_4. Removal of solvent and subsequent silica gel column chromatography afforded the pure product **3**, which was analyzed by ^{1}HNMR, IR and mass. Much to our surprise, an anti-Markovnikov addition product was obtained which otherwise formed in the presence of peroxide. Due to steric constraints on the diffusional path of the molecules imposed by the different structural feature of the zeolite, the more bulkier Markovnikov adduct could not be retained in the zeolite pore and presumably for this reason only the anti-Markovnikov product was obtained.

The mechanism of anti-Markovnikov addition could be compared with those mediated by the free-radical initiators where the main effect also seems to be steric and thus the only compound obtained is the sterically preferred anti-Markovnikov product. The observation could be explained as the two carbocations **A** and **B** are being formed in the zeolites pore, which are in equilibrium (Scheme 2). Out of which **B** seems to be in major amount probably due to the shift of equilibrium to R. H. S. After the attack of $RS^{(-)}$ ion which gives rise to linear product, which can easily be accommodated in the zeolites pore due to steric constraints on the diffusioned path of the molecules imposed by the different structural feature of the zeolites, which may not allow the more bulkier Markovnikov's adduct to retain in the pore.

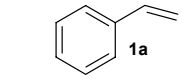
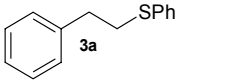
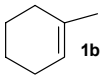
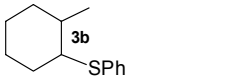
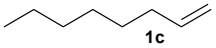
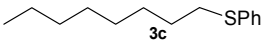
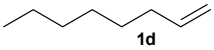
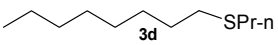
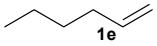
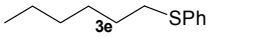
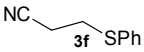
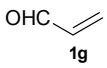
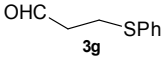


Scheme 2

The present procedure for thiol addition to an olefin is quite general as a wide range of olefins such as terminal, internal, cyclic, acyclic and branched olefins can be reacted with thiols easily under mild conditions. Under the reactions conditions employed, styrene reacted smoothly with a variety of thiols to afford the anti-Markovnikov product (Table 2,

entry 1) and no polymerization of styrene could be observed. Cyano and aldehyde groups are also compatible under the reaction conditions (Table 2, entries 6-7). Its noteworthy that the reaction of thiophenol with olefin did not yield any Friedel-Crafts addition product and ethanethiol also reacted smoothly under the reaction conditions.[29c]

Table 2: Addition of Thiols across Double Bonds using H-Rho–Zeolite

Entry	Substrate	Thiol	Time (h)	Product[a]	Yield %[b]
1	 1a	PhSH	5	 3a	69
2	 1b	PhSH	5	 3b	63
3	 1c	PhSH	10	 3c	54
4	 1d	n-PrSH	10	 3d	69
5	 1e	PhSH	8	 3e	50
6	 1f	PhSH	10	 3f	55
7	 1g	PhSH	12	 3g	53

[a]All products were characterized by their IR, ^{1}H-NMR and Mass spectroscopic data. [b]Yields refer to isolated pure products.

4.2.3 Conclusion

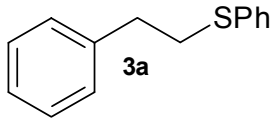
In conclusion, we have established a facile, heterogeneous catalytic method for the anti-Markovnikov addition of thiols to a variety of olefinic compounds. The obvious advantages of heterogeneous catalysis in terms of ease of separation, consistent yields and recyclability of the catalyst are noteworthy. Thus, the present catalytic method should serve as a useful addition to synthetic organic chemistry.

4.2.4 Experimental

Rho-zeolite was calcined at 500^0C in the presence of air prior to use. H-Rho-zeolite was procured as a gift sample from Catalysis Division, NCL, Pune. The olefins, thiols and solvents used were freshly distilled.

Addition of thiols to olefins: General procedure: To a stirred solution of olefin **1** (20 mmol) in n-hexane (25 ml) were added H-Rho-zeolite (0.5 equivalent by wt. of olefin) and thiol **2** (25 mmol) and the mixture was refluxed with stirring for the indicated length of time (**Table 2**). The reaction was monitored by TLC and GC. After the completion of reaction, zeolite was filtered off and washed with n-hexane; the filtrate was then washed with 10% aq. NaOH solution to remove excess thiol and subsequently washed with water, brine and dried over Na_2SO_4. Removal of solvent followed by silica gel column chromatography afforded the pure product **3**, which was analyzed by IR, ^{1}H NMR, and mass spectra.

2-Benzenesulfanylethylbenzene: Colorless liquid



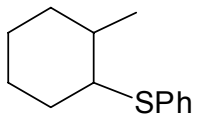
3a

IRν_{max}/ cm^{-1} (Neat): 693, 748, 1080, 1439, 1475, 1578, 2850, 2920.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.90 (t, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 6.8 Hz, 2H), 7.20 – 7.55 (m, 10H).

M. S. (m/z, rel.int %): M^+ 214 (60), 185 (5),154 (6), 123 (6), 110 (100), 109 (40), 91 (18), 77 (35), 69 (10), 65 (30).

(2-Methylcyclohexylsulfanyl)benzene: Colorless liquid



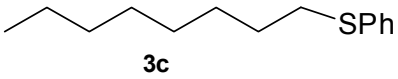
3b

IRν_{max} /cm^{-1}(Neat): 686, 732, 1021, 1083, 1371, 1464, 1577, 2851, 2919.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.20 (d, *J* = 6.8 Hz, 3H), 1.30 – 2.00 (m, 9H), 3.50 (m, 1H), 7.20 – 7.40 (m, 5H).

MS (*m/z*, rel. int %): (206 M^+5 % less) 192 (2), 135 (4), 110 (58), 97 (25), 81 (18), 67 (18), 55 (100).

Octylsulfanylbenzene: Colorless liquid



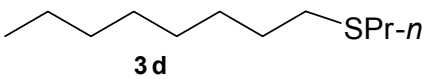
3c

IRν_{max} /cm^{-1}(Neat): 686, 732, 1021, 1083, 1371, 1464, 1577, 2851, 2919.

^{1}HNMR ($CDCl_3$, 200 MHz) δ: 0.90 (t, *J* = 6.8 Hz, 3H), 1.20 – 1.50 (m, 8H), 1.67 (m, 4H), 2.93 (t, *J* = 6.8 Hz, 2H), 7.20 – 7.40 (m, 5H).

MS (*m/z*, rel. int %): M^+ 222 (55), 165 (2), 135 (5), 123 (56), 110 (100), 91 (9), 77 (20), 65 (13), 57 (2).

1-Propylsulfanyloctane: Colorless liquid



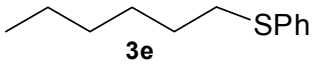
3 d

IRν_{max} /cm^{-1}(Neat): 753, 1214, 1453, 2854, 2920.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (t, *J* = 5.88 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H), 1.20 – 1.45 (m, 10H), 1.62 (m, 4H), 2.50 (t, 4H).

MS (*m/z*, rel. int %): M^+ 188 (36), 159 (6), 145 (64), 131 (5), 117 (4), 112 (51), 103 (18), 97 (5), 89 (52), 83 (38), 76 (73), 69 (100), 61 (42), 55 (15).

Hexylsulfanylbenzene: Colorless liquid



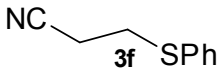
3e

IRν_{max} /cm^{-1}(Neat): 685, 733, 1020, 1080, 1466, 1577, 2853, 2921.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.91 (t, *J* = 6.8 Hz, 3H), 1.20 – 1.50 (m, 6H), 1.55-175 (m, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 7.10 – 7.70 (m, 5H).

MS (*m/z*, rel. int %): M^+ 194 (30), 163 (63), 135 (3), 123 (100), 109 (36), 91 (8), 77 (42), 69 (30), 65 (49), 59 (3).

3-Phenylsulfanylpropionitrile: Colorless liquid



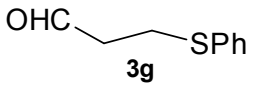
3f

IRν_{max}/ cm^{-1}(Neat): 667, 691, 747, 903, 1023, 1088, 1429, 1477, 1581, 2249, 2930.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.65 (t, *J* = 6.8 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 7.20 – 7.70 (m, 5H).

MS: (*m/z*, rel.int %): M^+163 (64), 135 (3), 123 (100), 109 (36), 91 (8), 77 (42), 69 (30), 65 (49), 59 (3).

3-Phenylsulfanylpropionaldehyde: Colorless liquid



3g

IRν_{max}/ cm^{-1}(Neat): 685, 741, 1213, 1422, 1470, 1578, 1632, 1717, 2824, 2922.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.78 (t, *J* = 6.8 Hz, 2H), 3.2 (t, *J* = 6.8 Hz, 2H), 7.2 – 7.45 (m, 5H), 9.78 (s, 1H).

MS: (*m/z*, rel.int %): M^+ 166 (20), 135 (2), 123 (4), 110 (100), 97 (3), 91 (5), 84 (9), 77 (16), 66 (13).

4.3 SECTION C

Deprotection of Allyl Esters over H-β Zeolite

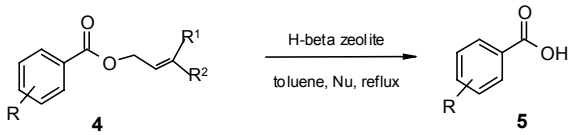
4.3.1 Introduction

Functional group protection and deprotection strategies are quite often a necessary requirement in the manipulation of multifunctional organic molecules.[33] The carboxyl function is one of the most important groups in organic molecules and its controlled manipulation during the synthesis is of great value to synthetic organic chemistry. In general, carboxylic acids can be protected as anhydrides,[34] amides[35] or esters.[36] Allyl esters serve as important protecting groups for carboxylic acids due to their outstanding stability under a variety of reaction conditions and ease of preparations either by the treatment of corresponding alcohol with acid chloride or alkylation of acid with the corresponding allyl halide under base catalyzed conditions.[37]

A number of methods employed for the deprotection of allyl esters include the use of $Pd(OAc)_2$,[38] $PdCl_2(Ph_3P)_2$,[39] $Pd(Ph_3P)_4$,[40] $(Ph_3P)_3$ RhCl,[41] Me_2CuLi,[42] formic acid[43] and excess of iodine.[44] More recently, sulphated SnO_2,[45] natural kaolinitic clay and EPZG,[46] montmorillonite K-10[47] have been developed for this purpose. Some carboxylic acids protected as 3-buten-1-yl esters have been deprotected via ozonolysis[48a] and β-elimination.[48b] Nevertheless there are sufficient drawbacks to most of these procedures to justify the need for a general, selective and practical method for deprotection of allyl esters.

Owing to the environmental and economic concerns in recent years, there has been considerable upsurge of interest in the area of zeolite induced organic transformations.[4a,b 27] In a series of publications from our group,[28, 49] we have exploited the catalytic potential of zeolites for various organic synthetic transformations e.g. thioacetalization of carbonyl

compounds, sulfoxidation of thioethers, tetrahydropyranylation of alcohols, oxidative cleavage of tosylhydrazones, methoxymethylation of alcohols, acetylation of aldehydes, addition of thiols across double bonds, chemo-and stereo selective epoxidation and oxidation of furan etc. In continuation, we have further exploited the catalytic potential of H-β zeolites for deprotection of allyl ester as illustrated in Scheme 3.

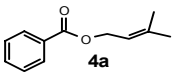
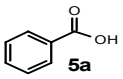
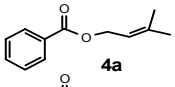
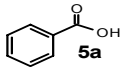
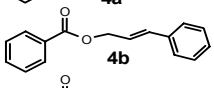
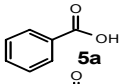
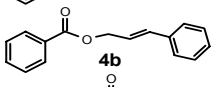
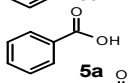
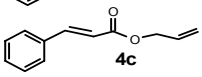
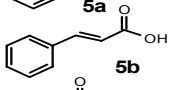
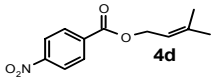
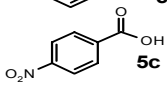
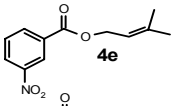
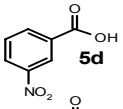
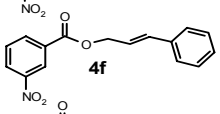
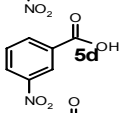
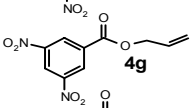
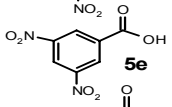
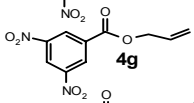
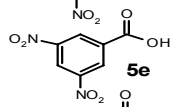
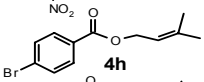
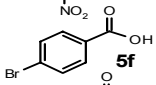
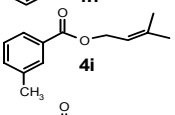
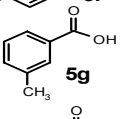
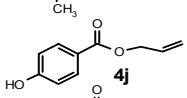
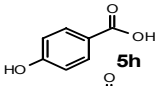
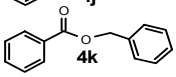
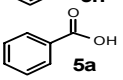
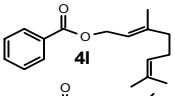
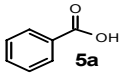
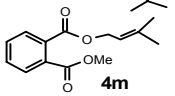
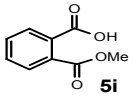
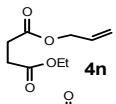
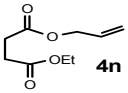
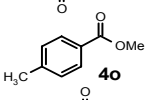
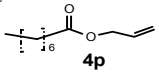
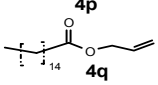


Scheme 3

4.3.2 Results and Discussion

In a typical experimental procedure, when allyl esters were refluxed in toluene in the presence of catalytic amount of H-β zeolite, the corresponding acids were obtained in excellent yields (Table 3). The present procedure is quite general as a wide range of structurally varied allyl esters underwent deprotection smoothly under the reaction conditions employed. The noteworthy feature of this methodology is that the reaction is performed under anhydrous conditions and the formation of allyl cations by zeolite is followed by the alkylation by aromatic nucleus, toluene or anisole. It is evident from Table 3 that the presence of nucleophile (anisole) facilitates the reaction whereas its absence requires a little longer time to complete the reaction affording relatively low yield of the corresponding acid. It is noted that the prenyl or allyl esters are easily deprotected as compared to cinnamyl esters. Even though cinnamyl esters took little longer time, the corresponding acids were obtained in excellent yields (Table 3, entries 3, 8). It is important to note that allyl ester could be selectively deprotected in the presence of methyl ester in mixed ester (Table 3, entry 16). Interestingly, the benzyl ester could be deprotected smoothly (Table 3, entry 14) while the normal esters remained unaffected under the reaction conditions (Table 3, entries 16, 18).

Table 3: Selective deprotection of allyl esters using H-β zeolite

Entry	Allyl esters	Reaction time (h)	Nucleophile Anisole (eq)	Product	Yield (%)
1	 **4a**	2	2	 **5a**	90
2	 **4a**	6.5	-	 **5a**	80
3	 **4b**	3	2	 **5a**	96
4	 **4b**	8	-	 **5a**	76
5	 **4c**	2	2	 **5b**	90
6	 **4d**	1.5	2	 **5c**	80
7	 **4e**	5	-	 **5d**	70
8	 **4f**	3	2	 **5d**	90
9	 **4g**	1.5	2	 **5e**	87
10	 **4g**	6	-	 **5e**	70
11	 **4h**	2	2	 **5f**	89
12	 **4i**	2.5	2	 **5g**	93
13	 **4j**	3	2	 **5h**	90
14	 **4k**	8	2	 **5a**	95
15	 **4l**	6	2	 **5a**	90
16	 **4m**	1.5	2	 **5i**	85
17	 **4n**	8	2	 **4n**	0
18	 **4o**	10	2	–	0
19	 **4p**	10	2	–	0
20	 **4q**	10	2	–	0

The superiority of this procedure can be clearly visualized in deprotection of a variety of substituted aromatic allyl esters leading to the corresponding acids in excellent yields (Table 3, entries 6-13). In this connection it should be mentioned that a recent literature report[46] which describes the selective regeneration of carboxylic acids from their corresponding allyl or cinnamyl esters employing a natural kaolinitic clay and EPZG failed with para substituted esters.

The effectiveness of this protocol is further manifested in its selectivity for the deprotection of aromatic allyl esters whereas allyl esters derived from aliphatic acids failed to undergo reaction (Table 3, entries 17, 19, 20). It should be pointed out that these results are in contrast with those observed by the other solid catalysts already reported in literature.[45-47] The difference in the reactivity pattern of aromatic allyl esters from aliphatic ones could probably be utilized in the selective manipulation of esters in a synthetic sequence. As a control experiment, the use of other zeolites such as H-ZSM-5, mordenite, 4Å and 5Å molecular sieves failed to accomplish above transformation. However, H-Y gave desired products in low yields after prolonged heating compared to H-β zeolite. The observed efficient performance of H-β zeolite may be attributed to its large pore opening, three dimensional channel system and higher concentration of acid sites.[50] The recovered catalyst was reactivated for reuse by heating at 500°C in the presence of air. The same catalyst was recycled for all the reactions without loss of activity and selectivity.

4.3.3 Conclusion

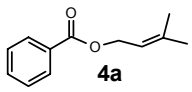
We have established a facile, heterogeneous catalytic method for selective regeneration of carboxylic acids from their corresponding allyl esters. While the aromatic allyl ester could be deprotected easily, allyl esters derived from aliphatic acids failed to undergo reaction.

4.3.4 Experimental

Solvents were purified and dried by standard procedures before use. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker AC-200 spectrometer. H-β zeolite was procured as a gift from United Catalyst India Ltd. (UCIL) Mumbai; SiO_2/Al_2O_3 = 30, Surface area = 700 m^2/g, Pore diameter =7.6x 6.4 Å. Prior to use it was calcined at 550 ^oC for 5h in air.

General procedure for preparation of allyl esters 4: To a stirred solution of allyl alchol (10 mmol) in dichloromethane (15 ml) at 0^{o}C was added triethylamine (10 mmol) dropwise and stirred for 10-15 min. Acid chloride (10 mmol) was added slowly with vigorous stirring at low temperature for 10 min. The reaction mixture was stirred at 0^{o}C for 2 h and then at room temperature for another 2 h. After completion of reaction (TLC), dil HCl was added and the aqueous layer was extracted with dichloromethane. Organic layer was washed once with water and brine, dried over anhydrous sodium sulphate. Solvent evaporation under reduced pressure gave the crude allyl ester, which was purified by flash chromatography using light petroleum ether-ethyl acetate as eluent.

Benzoic acid 3-methylbut-2-enyl ester: Colorless liquid



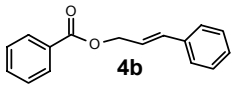
4a

Yield: 85 %

IRν_{max} / cm^{-1} (Neat): 1000, 1620, 1720, 2350.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 4.85 (d, J = 9.75 Hz, 2H), 5.52 (t, J = 9.75 Hz, 1H), 7.50 (m, 3H), 8.10 (m, 2H).

Benzoic acid 3-phenylallyl ester: Colorless liquid



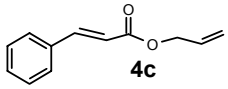
4b

Yield: 84 %

IRν_{max} / cm^{-1} (Neat): 1500, 1600, 1720, 1800, 3020.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.8 (d, J = 6.5 Hz, 2H), 6.5 (m, 1H), 6.85 (d, J = 16 Hz, 1H), 7.50-8.15 (m, 10H).

3-Phenylacrylic acid allyl ester: Colorless liquid



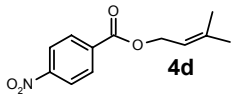
4c

Yield: 70 %

IRν_{max} / cm^{-1} (Neat): 1500, 1640, 1718, 3050.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.63 (d, J = 5.71 Hz, 2H), 5.30 (t, J = 11.43 Hz, 2H), 5.93 (m, 1H), 6.50 (d, J = 16 Hz, 1H), 6.80 (d, J = 16 Hz, 1H), 7.50-8.00 (m, 5H).

4-Nitrobenzoic acid 3-methylbut-2-enyl ester: Pale yellow solid; MP: 63^{o}C



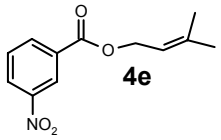
4d

Yield: 85 %

IRν_{max} / cm^{-1} (Neat): 1350, 1550, 1622, 1725, 3000.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.80 (s, 6H), 4.85 (d, J = 9.5 Hz, 2H), 5.51 (t, J = 9.5 Hz, 1H), 8.10-8.50 (m, 4H).

3-Nitrobenzoic acid 3-methylbut-2-enyl ester: Viscous liquid



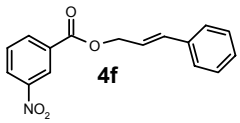
4e

Yield: 70 %

IRν_{max} / cm^{-1} (Neat): 1345, 1500, 1640, 1720, 3020.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.80 (s, 6H), 4.80 (d, J = 9.0 Hz, 2H), 5.51 (t, J = 9.0 Hz, 1H), 8.20-8.55 (m, 4H).

3-Nitrobenzoic acid 3-phenylallyl ester: Viscous liquid



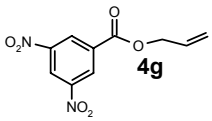
4f

Yield: 75 %

IRν_{max} / cm^{-1} (Neat): 1340, 1490, 1620, 1722, 3010.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.60 (d, J = 6.5 Hz, 2H), 6.77 (m, 1H), 7.14 (d, J = 16 Hz, 1H), 8.60-8.50 (m, 7H), 9.62-9.71 (m, 2H).

3,5-Dinitrobenzoic acid allyl ester: Pale yellow solid



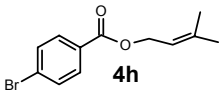
4g

Yield: 74 %

IRν_{max} / cm^{-1} (Neat): 1350, 1490, 1640, 1720, 3020.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.70 (d, J = 5.71 Hz, 2H), 5.5 (t, J = 11.43 Hz, 2H), 6.10 (m, 1H), 8.95-9.25 (m, 3H).

3-Bromobenzoic acid 3-methylbut-2-enyl ester: Viscous liquid



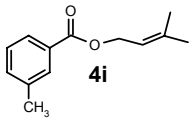
4h

Yield: 65 %

IRν_{max} / cm^{-1} (Neat): 1450, 1500, 1640, 1720, 3030.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.80 (s, 6H), 4.80 (d, J = 8.5 Hz, 2H), 5.51 (t, J = 8.5 Hz, 1H), 7.33 (d, J = 5.0 Hz, 2H), 7.84 (d, J = 5.0 Hz, 2H).

3-Methylbenzoic acid 3-methylbut-2-enyl ester: Colorless liquid



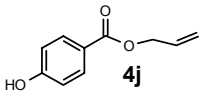
4i

Yield: 80 %

IRν_{max} / cm^{-1} (Neat): 1640, 1720, 3050.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.81 (s, 6H), 2.41 (s, 3H), 4.80 (d, J = 7.5 Hz, 2H), 5.48 (t, J = 7.5 Hz, 1H), 7.32 (m, 3H), 7.84 (m, 1H).

4-Hydroxybenzoic acid allyl ester: Colorless liquid



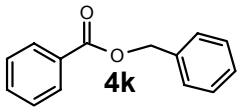
4j

Yield: 70 %

IRν_{max} / cm^{-1} (Neat): 1500, 1640, 1720, 3300.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.70 (d, J = 5.71 Hz, 2H), 5.5 (t, J = 11.43 Hz, 2H), 6.10 (m, 1H), 7.40 (d, J = 6.0 Hz, 2H), 7.85 (d, J = 6.0 Hz, 2H).

Benzoic acid benzyl ester: Colorless liquid



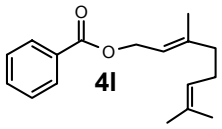
4k

Yield: 85 %

IRν_{max} / cm^{-1} (Neat): 1500, 1640, 1722, 3020.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.45 (s, 2H), 7.44-7.63 (m, 8H), 8.16 (d, J = 7.2 Hz, 2H).

Benzoic acid geranyl ester: Colorless liquid



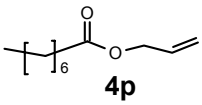
4l

Yield: 75 %

IRν_{max} / cm^{-1} (Neat): 1490, 1642, 1718, 3020,

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.62 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 2.1 (s, 4H), 4.85 (d, J = 7.5 Hz, 2H), 5.11 (t, J = 5.6 Hz, 1H), 5.49 (t, J = 7.5 Hz, 1H), 7.40-7.56 (m 3H), 8.05 (d, J = 7.5 Hz, 2H).

Octanoic acid allyl ester: Colorless liquid



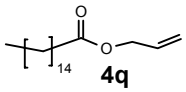
4p

Yield: 60 %

IRν_{max} / cm^{-1} (Neat): 1450, 1715, 2950.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.91 (t, *J* = 6.8 Hz, 3H), 1.31-2.20 (m, 10H), 2.62 (t, J = 6.8 Hz, 2H), 4.62 (d, J = 5.7 Hz, 2H), 5.30 (t, J = 11.4 Hz, 2H), 5.93 (m, 1H).

Hexadecanoic acid allyl ester: Colorless liquid



4q

Yield: 65 %

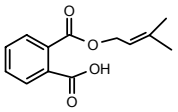
IRν_{max} / cm^{-1} (Neat): 1450, 1712, 2950.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 7.0 Hz, 3H), 1.25-3.05 (m, 26H), 2.65 (t, J = 7.0 Hz, 2H), 4.65 (d, J = 5.5 Hz, 2H), 5.30 (t, J = 11.2 Hz, 2H), 5.91 (m, 1H).

General procedure for preparation of diesteres: To a stirred solution of allyl alchol (10 mmol) and triethylamine (10 mmol) in dichloromethane (15 ml) at 0^{o}C was added acid anhydride (10 mmol). The mixture was stirred at 0^{o}C for 2 h and the reaction mixture was allowed to stir at room temperature for another 2 hrs. After completion of reaction (TLC), dil HCl was added and the aqueous layer was extracted with dichloromethane. Organic layer was washed with water and brine, dried over anhydrous sodium sulphate. Solvent evaporation under reduced pressure gave the crude allyl ester, which was purified by flash chromatography using pet-ether: ethyl acetate (8: 2) as eluent.

A mixture of half ester (10 mmol), dimethyl sulfate (10 mmol) and anhydrous potassium carbonate (4 eq) in acetone was refluxed with stirring for 5-8 hrs. After filtration and concentration under reduced pressure, the residue (diester) was purified by column chromatography to give pure diester.

Phthalic acid mono-(3-methylbut-2-enyl) ester: Colorless liquid

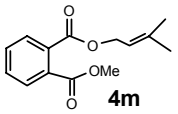


Yield: 75 %

IRν_{max} / cm^{-1} (Neat): 1490, 1642, 1700, 1718, 3020, 3500.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.71 (s, 6H), 4.83 (d, J = 7.2 Hz, 2H), 5.46 (t, J = 7.2 Hz, 1H), 7.64 (m, 2H), 7.89 (m, 2H).

Phthalic acid 1-methyl ester 2-(3-methylbut-2-enyl) ester: Colorless liquid



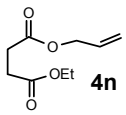
4m

Yield: 65 %

IRν_{max} / cm^{-1} (Neat): 1580, 1600, 1700, 2950.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.77 s, 6H), 3.90 (s, 3H), 4.80 (d, J = 7.7 Hz, 2H), 5.45 (t, J = 7.7 Hz, 1H), 7.40-7.78 (m, 4H).

Succinic acid allyl ester ethyl ester: Colorless liquid



4n

Yield: 65 %

IRν_{max} / cm^{-1} (Neat): 1450, 1720, 1750, 2950.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, J = 7.2 Hz, 3H), 2.67 (s, 4H), 4.20 (q, J = 7.2 Hz, 2H), 4.62 (d, J = 5.7 Hz, 2H), 5.30 (t, J = 11.4 Hz, 2H), 5.93 (m, 1H).

General procedure for deprotection of allyl esters: A mixture of allyl ester (10 mmol), anisole (20 mmol) and catalyst H-β zeolite (10 % by wt) in dry toluene (20 ml) was refluxed for the indicated length of time (Table 3). The reaction was monitored by TLC. After completion of the reaction, the catalyst was separated from the reaction mixture by filtration. Filtrate was treated with aq. NaOH solution and then extracted with ethyl acetate (3 x 50 ml). The aq. layer was neutralized with dil. HCl, saturated with NaCl and extracted with ethyl acetate. The organic layer was separated, dried over anhyd. Na_2SO_4 and concentrated to give the corresponding pure acid in high yields. The acids prepared were compared with the authentic samples.

4.4. SECTION D

Oxidation Over TS-1/H_2O_2 System

4.4.1 Introduction

As discussed in the introductory section of this chapter, one of the advantages of zeolite chemistry is the possibility to manipulate frame work metal ions with the introduction of titanium in the frame. The crystalline microporous, titanium silicate molecular sieves, TS-1 (MFI) and TS-2[19] (MFL) exhibit unique catalytic properties in the area of selective oxidation catalysis. In TS-1 and TS-2, Ti^{4+}ions are present in the lattice along with Si^{4+} ions. The pure titanium analogs do not possess the strong acidity characteristics of the aluminosilicates (zeolites). These molecular sieves have been found to catalyze the oxidation of n-alkenes, alkylbenzenes, phenol, anisole, cresol, benzyl alcohol, cyclohexanol and olefins with H_2O_2 under very mild conditions.[19, 20] Alcohols and ketones are formed at secondary and tertiary sites of the alkyl chain. Recently, Jacobs et.al.[20a] have reported a biomimetic type of C-H functionalization with TS-1/H_2O_2 and are able to activate secondary and tertiary carbon atoms in alkenes to alcohols and subsequently to ketones. The catalyst has low regioselectivity for alcohol formation but high reactant selectivity on the formation of ketones. Indeed, above developments are not only fascinating from the industrial application point of view, but the nature of the proposed reactive species involved in the catalytic cycle are also unique and interesting. We have also exploited the catalytic potential of zeolites mainly titanium silicate molecular sieve (TS-1) for various organic synthetic transformations.[22, 23a, 28]

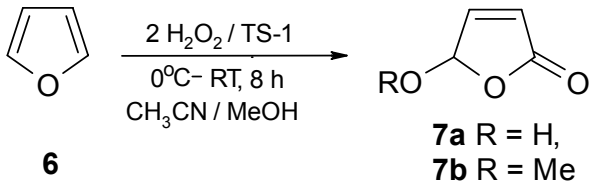
4.4.2 Section I

Oxidation of Furan to 5-Hydroxy-(2*H*)-Furanone

4.4.2.1 Introduction

5-Hydroxy-2-(5H)-furanone, **7a** is a key constituent in a number of biologically active compounds such as manoalide; a nonsteroidal anti-inflammatory agents, secomanolide, luffariellin, thoreotolide and cacospongiolide[51] etc. Besides, it has been applied as useful synthon in the total synthesis of portulal,[52] (d, l)–pyrenophorin, d, l–strigol[53] and camptothecin.[54]

Various methods for the synthesis of 5-hydroxy-2(5H)-furanone have been reported in the literature. The dye-sensitised oxygenation of furfural in ethanol followed by acid hydrolysis of 5-ethoxy analogue is known to give 5-hydroxy-2(5H)-furanone.[55] The hydroxy furanone and its derivatives have also been prepared by the oxidation of 2-furoic acid via singlet oxygenation generated by photochemical method[56] or by the reaction of furfural and hydrogen peroxide in the presence of catalyst consisting of metal group V and VI of the periodic table.[57] The photoinduced oxidation of furan / furfural in ethanol in the presence of eosin for 9-18 days is reported to give 5-hydroxy-2(5H)-furanone in reasonably good yield.[58] However, many of these methods have several limitations : expensive and stoichiometric amount of the reagent, tedious workup procedures, high temperature, multistep synthesis, low substrate concentration and longer reaction time. Consequently, there is need to develop alternative reagents for this reaction. We have now developed a simple, efficient, high-yielding, and one-pot synthesis of 5-hydroxy-2(5H)-furanone by oxidation of furan over a TS-1/ H_2O_2 system, the results of this study are presented below.



Scheme 4

4.4.2.2 Results and Discussion

When furan **6** was treated with aq. hydrogen peroxide in acetonitrile in the presence of TS-1, the corresponding hydroxy lactone **7a** was obtained in excellent yield (Scheme 4). Thus, furan reacted smoothly with TS-1/H_2O_2 system and this transformation is first of its kind in the literature. Under similar conditions, cyclic 1,3 - dienes containing other heteroatom e.g. thiophene mainly gave the sulfoxide and sulfone as major products and the formation of hydroxy enones could not be observed. The reaction with 1,3–acyclic and cyclic dienes was a failure due to possibility of consecutive and multiple reaction pathways open to these dienes.

The effect of time on stream (TOS) was also studied which is shown in Table 4. It is clear from Table 5 that for oxidation of 1 mole of furan 2 mole of hydrogen peroxide is required. The influence of furan / H_2O_2 mole ratio on the conversion and product selectivity is presented in Table 5. With the increase in H_2O_2 / furan ratio from 0.6 to 2.4, there was a significant increase in the product yield. Thus, the reaction gave almost quantitative yield of the desired hydroxyl lactone **7a** with the use of excess of hydrogen peroxide (ca 2.4 eq).

Similarly, the effect of different solvent on furan conversion and product selectivity was studied. Aprotic solvents like acetone and acetonitrile seem to favor the formation of the hydroxy lactone vis-à-vis protic solvent like methanol. It was observed that when methanol was used as solvent, apart from hydroxy lactone **7a** (25%), another major

product 5-methoxy-2(5H)-furanone **7b** (75% yield) characterised by spectroscopic data was formed due to the subsequent methylation of the corresponding hydroxy compound (Table 6).

Table 4: Oxidation of furan with H_2O_2 over TS-1: Effect of time on stream (TOS)

Entry	TOS (h)	TON (h^{-1})[a]	H_2O_2 Conv. (%)	Product Yeild[b] (%)
1	2	104	57	34.4
2	4	286	78	47.0
3	6	507	93	55.8
4	8	717	99	59.2

Reaction condition: Solvent: acetonitrile; temperature: 0°C to room temperature; furan: H_2O_2: 1: 1.2, catalyst: 20% w.r.t. furan. [a]TON: mol of furan converted per mol of Ti in the catalyst per hour. 0.4 gm TS-1 (Si/Ti molar ratio 33) contains 1.94×10^{-4} mol of Ti. [b]Pure and isolated product.

Table 5: Oxidation of furan with H_2O_2 over TS-1: Effect of furan: H_2O_2 mol ratio

Entry	H_2O_2 / Furan (mol ratio)	Substrate		Product Yield[a]
		Furan	H_2O_2 (25 %)	
1	0.6	2 g (29.4 mmol)	2.4 g (17.647 mmol)	0.876 g (29.8 %)
2	1.2	2 g (29.4 mmol)	4.8 g (35.29 mmol)	1.74 g (59.2 %)
3	2.4	2 g (29.4 mmol)	9.6 g (70.58 mmol)	2.89 g (98.3 %)

Reaction condition: solvent: acetonitrile (10ml), temperature 0°C to room temperature, reaction time 8 h, catalyst wt % with respect to furan = 20. [a]Yields refer to isolated pure product.

The effect of time for the conversion of furan in acetonitrile solvent was also studied. The results obtained has been summarized in Table 7. A time dependent study of oxidation of furan with H_2O_2 in the presence of varying concentration of TS-1 catalyst indicated that

even a small amount of catalyst (7.5 wt%) can significantly catalyze and accelerate the rate of reaction (Table 8). As the concentration of the catalyst was increased, the reaction became faster. Thus 20 wt% (on the basis of furan) catalyst was sufficient to oxidize furan completely affording the corresponding hydroxy lactone. The use of other catalyst such as Sn-silicalite-1, vanadium silicate, VS-1 or VS-2 and Cr-silicalite-1 failed to accomplish the above transformation.

Table 6: Oxidation of furan with H_2O_2 over TS-1: Effect of solvents

Entry	Solvent	Product	% Yield[a]	Selectivity
1	Acteone	5-hydroxy-2(5H)-furanone	90	100%
2	Acetonitrile	5-hydroxy-2(5H)-furanone	98.5	100 %
3	Methanol	5-hydroxy-2(5H)-furanone	99	25 %
		5-methoxy-2(5H)-furanone		75 %

Reaction condition: Furan 2.0g, H_2O_2 4.8 g (25 %), solvent 10ml, temperature 0^oC to room temperature, reaction time 8 h, catalyst wt % w. r. t. furan = 20. [a]Yields refer to isolated pure product.

Table 7: Oxidation of furan with H_2O_2 over TS-1: Effect of ratio of solvent (v/v)

Entry	Solvent / Furan	4 h		8 h	
		Yield[a] (%)	H_2O_2 conv. (%)	Yield[a] (%)	H_2O_2 conv. (%)
1	2	57	95	59.5	99.2
2	3	53	89	59.4	99.0
3	5	47	79	59.2	98.5

Reaction condition: Furan 2.0g, H_2O_2 4.8 g (25 %), solvent 10ml, temperature 0^oC to room temperature, reaction time 8 h, catalyst wt % w. r. t. furan = 20. [a]Yields refer to isolated pure product.

Table 8: Oxidation of furan with H_2O_2 over TS-1: Effect of amount of catalyst

Entry	Catalyst (wt %)	H_2O_2 conversion (%)	Yield[a] (%)
1	7.5	90.0	54.4
2	10	96.0	57.5
3	15	97.8	58.6
4	20	98.5	59.2

Reaction condition: solvent: acetonitrile; temperature: 0°C–room temperature; acetonitrile / furan = 5 (V/V); furan: H_2O_2 (mol ratio) = 1: 1.2; [a]Yields refer to isolated pure product.

Regarding possible mechanism, some of the reactive species e.g. hydroxyperoxy, peroxy in the presence of H_2O_2 (Figure 3) are routinely being proposed for oxidation processes involving TS-1.[28, 59,22]

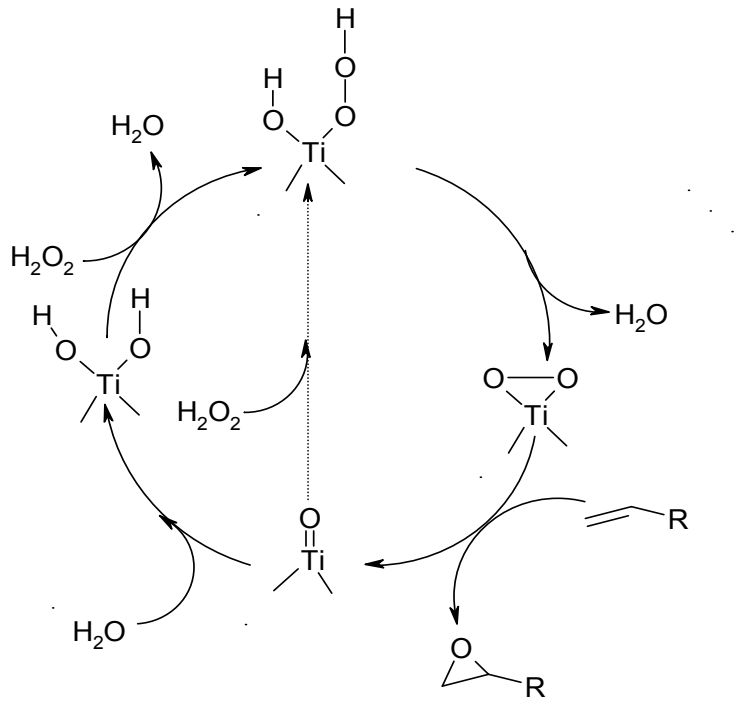
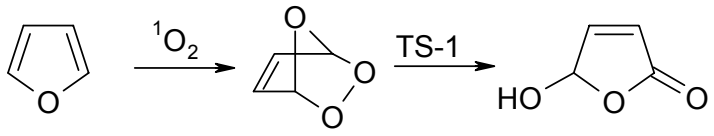


Figure 3

Alternatively, one could invoke the intermediacy of singlet oxygen[60] in the oxidation of furan.[21] Presumably, the generation of singlet oxygen could be visualised from the hydroperoxo or peroxo titanium species. Indeed, when the endoperoxide of furan was treated under TS-1 conditions, the formation of hydroxy lactone **7a** was observed indicating the intermediacy of $^1O_2$ in TS-1 / H_2O_2 chemistry (Scheme 5).



Scheme 5

It should be mentioned here that the oxidation of furan by singlet oxygen generated via the nonphotolytic method e.g. by the reaction of sodium hypochlorite and hydrogen peroxide has also been widely investigated.[61]

4.4.2.3 Conclusion

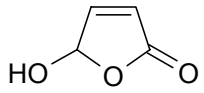
In summary, a facile heterogeneous catalytic method for the oxidative conversion of furan to the corresponding hydroxy lactone has been developed. This method thus offers a practical alternative to conventional methods and the process itself is environmentally friendly with minimal waste.

4.4.2.4 Experimental

Titanium silicate molecular sieve (TS-1) was prepared by employing recently developed concept of promoter induced synthesis of zeolite[62] materials from tetraethylorthosilicate, tetrabutylorthotitanate, tetrapropylammonium hydroxide, orthophosphoric acid and water. The Si : Ti molar ratio of the sample was 33. The X-rays powder pattern of the calcinated sample of TS-1 is characteristic of the MFI structure. The Al –free titanium silicate (TS-1) retained its orthorhombic symmetry after calcination. The scanning electron micrograph of the TS-1 sample exhibited the absence of any amorphous material. The particle size of the cuboid - shaped crystallites range from 0.1 to 0.2 μm. The UV – VIS spectrum of TS-1 showed a band at 209 nm, and the IR spectrum showed a characteristic absorption at 960 cm^{-1}.

Typical experimental procedure for oxidation of furan: In a typical experimental procedure, to a cooled solution (0^oC) of furan **6** (2g, 29.4 mmol) in acetonitrile (10 ml) were added TS-1 catalyst (0.4 g) and 25% H_2O_2 (9.6 g, 71 mmol) and the mixture was stirred for 8h as it was allowed to attain room temperature gradually. The catalyst was filtered off and the filtrate was concentrated and extracted with ethyl acetate, washed with aq. Na_2SO_3 solution and brine. The organic layer was separated and dried over anhydrous Na_2SO_4. Removal of solvent and subsequent silica gel column chromatography using pet ether: ethyl acetate (3: 2) gave colorless viscous oil which solidified on cooling. The solid was recrystallised from ether-petroleum ether solvent mixture to afford 2.98 g (98.3%) of 5-hydroxy-2(5H)-furanone **7a**. The compound was fully characterised by the physical and spectroscopic data and also by comparison with authentic sample. However, the ^1H NMR of compound **7a** (R=H) showed the presence of very minor amount of hydrolysed product

i.e. fumaraldehydic acid. The physical and spectroscopic data were in full agreement with the literature data.[64]



7a

Cream color solid: M.P. 56 – 58°C (lit.[63] 58 – 59°C).

IRν_{max} / cm^{-1} (Nujol): 1640, 1760, 1790, 3020, 3560.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.80 (bs, 1H), 6.20 (s, 1H), 6.25 (s, 1H), 7.40 (d, J = 5.7 Hz, 1H).

4.4.3 Section II

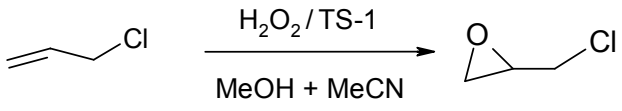
Epoxidation of Allyl Chloride to Epichlorohydrin

4.4.3.1 Introduction

Epichlorohydrin, ECH, is a readily available three carbon unit functionalized on every carbon making it an industrially important chemical mainly used as raw materials in polymer chemistry.[65] Other common uses include in situ trapping agent for HCl, HBr[66] or the alcohol generated during formation of Meerwein's reagent,[67] and preparation of heterocycles.[68] ECH is also used as a synthetic intermediate for the synthesis of pheromone *S*-(-)-ipsenol,[69] anisomycin,[70] propranolol analog and a whole class of medicinally important compound called β-blockers.[71] Commercially ECH is manufactured by reacting allyl chloride (ALC) chlorine-water to give a mixture of chlorohydrine, which are then treated with lime water to produce ECH. In this way large quantity of sluge is co-produced which causes severe technical and environmental problems. Although, ECH can also be produced via liquid phase epoxidation of allyl chloride catalysed by solid TS-1 using dilute hydrogen peroxide as oxidant,[72] the selectivity for ECH needs to be improved. Owing to environmental and economic concerns in recent years, the development of alternative environmentally benign synthetic route is of primary concern. In the context of developing processes with low E-factor and high atom efficiencies, the use of environmentally friendly heterogeneous catalyst assumes significance as it results in waste minimization, safe and simple operations and easy work-up. The use of solid catalysts such as clay and zeolites as 'green' catalyst has been well established.[73, 74]

The catalytic potential of titanium silicate molecular sieve for various organic synthetic transformation has been exploited by us.[28] In continuation we have further utilized the catalytic properties of TS-1 catalyst for the synthesis of ECH by the epoxidation of allyl

chloride in a mixed solvent systems. In this system solvent plays very significant role in the conversion of allyl chloride and epichlorohydrin selectivity. Protic solvent like methanol is found to be good for higher allyl chloride conversion while aprotic solvents are particularly useful for higher selectivity. Mixed solvent system using acetonitrile and methanol in various proportion are systematically studied with the aim to maximize the H_2O_2 utilization towards the ECH formation.



8 **9**

Scheme 6

4.4.3.2 Results and Discussion

The epoxidation of allyl chloride using TS-1/H_2O_2 has been studied in a mixed solvent system. Table 9 shows the effect of different solvents such as methanol, acetonitrile (biphase) and water (triphase). The conversion of allyl chloride in acetonitrile is rather slow but the selectivity towards epoxide is quite high. While the protic solvents like methanol and water are good reaction medium for the conversion of allyl chloride, the selectivity towards ECH is rather low. However in the case of methanol, the ECH selectivity decreased slowly compared to that in the presence of water, where the concentration of epichlorohydrin sharply decreases with the reaction time.

When solvent to substrate ratio was increased from 3 to 5, it was found that the selectivity for ECH increased. However, this difference was more pronounced mainly in the case of water and to a lesser extent in the case of methanol. As the dilution increases with increasing solvent / allyl chloride ratio, the ECH selectivity is slightly increased due to decreased cleavage of oxirane ring. From the above discussion it is clear that the

acetonitrile, methanol and water independently are not quite suitable because in acetonitrile the reaction is very slow with less conversion vis-a-vis methanol and water. In protic solvents like methanol and water, the selectivity of epoxide decreases significantly and sharply with conversion and reaction time. Since one would like to maximize the selectivity of epichlorohydrin at maximum conversion of allyl chloride and also epoxide selectivity should not decrease sharply with increasing reaction time. Hence the present work was carried out keeping this aim in the mind.

Table 9: Epoxidation of allyl chloride in different solvents[a]

Solvent	Solvent / allyl chloride ratio	Reaction time (h)	Allyl chloride % conversion	Epichlorohydin % selectivity[b]
Acetonitrile	3	6	45	100
		8	65	97.6
		10	67	97
	5	6	40	100
		8	60	99.5
		10	61	98
Methanol	3	1	90	99.5
		1.5	95.5	91.5
		2	99	85.2
	5	1	89	95
		1.5	95	93
		2	99	91
Water	3	1	90	99.9
		1.5	99	22
		2	100	8
	5	1	99	90.6
		1.5	99.9	62.9
		2	100	22

[a] Reaction conditions: allyl chloride: H_2O_2 = 1: 1 (molar ratio); temperature = 60^oC; catalyst = 15 % (w/w) wrt allyl chloride. [b] Remaining are high boiling side product.

Effect of the ratio of methanol and acetonitrile in a mixed solvent system

Table 10, (entries 1-7) shows the effect of mixed solvent system methanol / acetonitrile weight ratio on the allyl chloride conversion and ECH selectivity. As expected, with increasing methanol / acetonitrile ratio in the mixed solvent, allyl chloride conversion increased considerably from 54 % (entry 1) to 95 % (entry 6). However, the ECH selectivity decreased from 97 % to 89 %. Entries 5-7 (Table 10) indicate the effect of reaction temperature at methanol: acetonitrile ratio 3: 1. At 318 K, both the conversion and ECH selectivity were quite high (95-96 %). It is quite expected that at higher temperature change of ECH to diol will be facilitated thereby decreasing ECH selectivity.

Table 10: Effect of proportion of methanol and acetonitrile[a]

Entry	MeOH: MeCN (w/w)	Temp.(K)	ALC Conversion	ECH selectivity[b]
1	1: 3	333	54	96
2	1: 2	333	70	93
3	1: 1	333	75	93
4	2: 1	333	92	90
5	3: 1	333	96	89
6	3: 1	318	95	96
7	3: 1	303	92	97

[a] Reaction conditions: allyl chloride: total solvent (w/w) = 1: 3; reaction time (h) = 3; catalyst = 15 % (w/w) wrt allyl chloride. [b] Remaining are high boiling side product.

Table 11, compares the data obtained at three different total solvent / allyl chloride ratios (2: 1; 3: 1 and 5: 1) at 303 K, 318 K and 333 K keeping 3: 1 MeOH: MeCN ratio same in mixed solvent system. It is clear from Table that both, the conversion and the selectivity of epoxide are quite high at 318 K for solvent / allyl chloride (weight ratio) of 2: 1 and 3:

1. As have been mentioned earlier that the epichlorohydrin selectivity can be increased by using larger amount of solvents that is by diluting the system. However, approach is not quite suitable for practical point view mainly because of less throughput involving larger amount of solvent removal and recycle which is energy intensive.

Table 11: Effect of total solvent / allyl chloride (ALC) ratio at different temperature[a]

Reaction temp. (K)	Reaction time (h)	Total solvent / allyl chloride (w/w)					
		2: 1		3: 1		5: 1	
		ALC % conv.	ECH % selectivity	ALC % conv.	ECH % selectivity	ALC % conv.	ECH % selectivity
303	1	90	98	87	98	60	99
	2	92	96	89	97	70	98
	3	95	94	92	96	75	98
	4	98	93	94	94	78	97
318	1	90	95.5	87.6	97.5	65.5	99
	2	97	95	90.9	96.7	76.5	98.7
	3	97	94	95	96	78	98
	4	98.6	93	97.5	95	80	95
333	1	93	93	88	95	86	96
	2	97	90	90	93	91	94
	3	98	87	96	89	94	92
	4	99	84	98	86	97	89

[a] Reaction condition: allyl chloride: catalyst (w/w) = 1: 0.15; allyl chloride: H_2O_2 (molar ratio) = 1: 1; mixed solvent = methanol + acetonitrile (3: 1 w/w). [b]Remaining are high boiling side product.

Hence, it is desirable to maximize the epichlorohydrin yield per batch by minimizing the solvent amount without any significant loss on ECH selectivity. Since our present efforts were aimed at these problems, we have tried to optimise the reaction conditions accordingly.

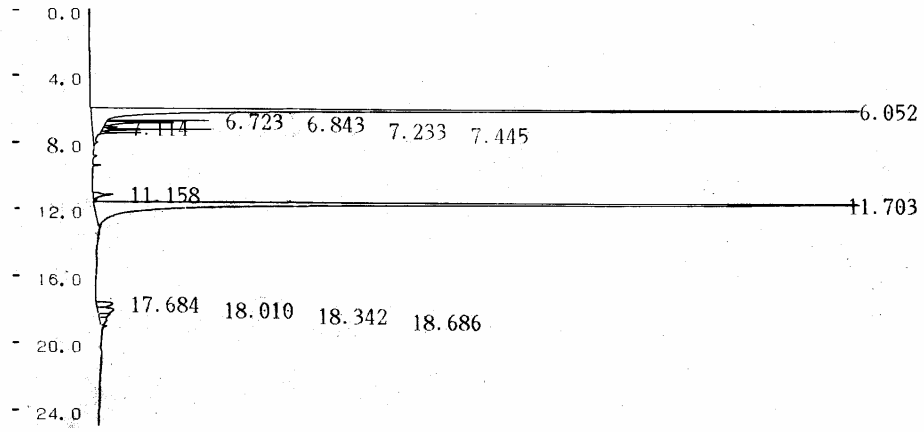
4.4.3.3 CONCLUSION

A catalytic method for the epoxidation of allyl chloride to epichlorohydrin under mixed solvent conditions has been developed. We do believe that this method is practical alternative to the conventional existing methods and the process is environmentally friendly with minimal waste with high potential for commercial production of epichlorohydrin.

4.4.3.4 Experimental

Liquid phase catalytic experiment for epoxidation of allyl chloride: In liquid phase, catalytic experiments were conducted in glass batch reactor (200 mL capacity). In a typical run 0.1 mol of allyl chloride along with solvent (acetonitrile and / or methnol) and catalyst (15 % by weight wrt. allyl chloride) were stirred and dilute hydrogen peroxide 0.1 mol (45 % aq.) was added in one portion. The products were analyzed by high resolution capillary gas chromatograph (Shimazu R-17 using flame ionization detector) (Figure 4).

4.5 Spectra



** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	6.052	1430181	384983	S		74.9207	
	2	6.723	9670	2129	T		0.5065	
	3	6.843	7148	1418	TV		0.3744	
	4	7.114	1234	310	TV		0.0647	
	5	7.233	8939	2300	TV		0.4683	
	6	7.445	3500	888	TV		0.1833	
	11	11.158	4720	442			0.2473	
	13	11.703	426107	60914	S		22.3218	
	16	17.684	5701	353			0.2986	
	17	18.01	6676	345	V		0.3497	
	18	18.342	2337	226	V		0.1224	
	19	18.686	2714	146	V		0.1422	
		TOTAL	1908927	454453			100	

Figure 4: Gas Chromatograph: formation of ECH by epoxidation of ALC with H_2O_2

The products were analysed by high resolution capillary gas chromatograph

(Shimadzu R-17 using flame ionisation detector)

Temperature Program: 40^{o}C, 5 min; 2^{o}C/min 110^{o}C 10 min; 10^{o}C/min 240^{o}C 30 min.

RT: 6.052 corresponding to solvents; 7.233 corresponding to ALC; 11.703 corresponding to ECH;

17.684-18.686 corresponding to side products;
ALC conversion: 98.02 %; ECH selectivity: 96.7%

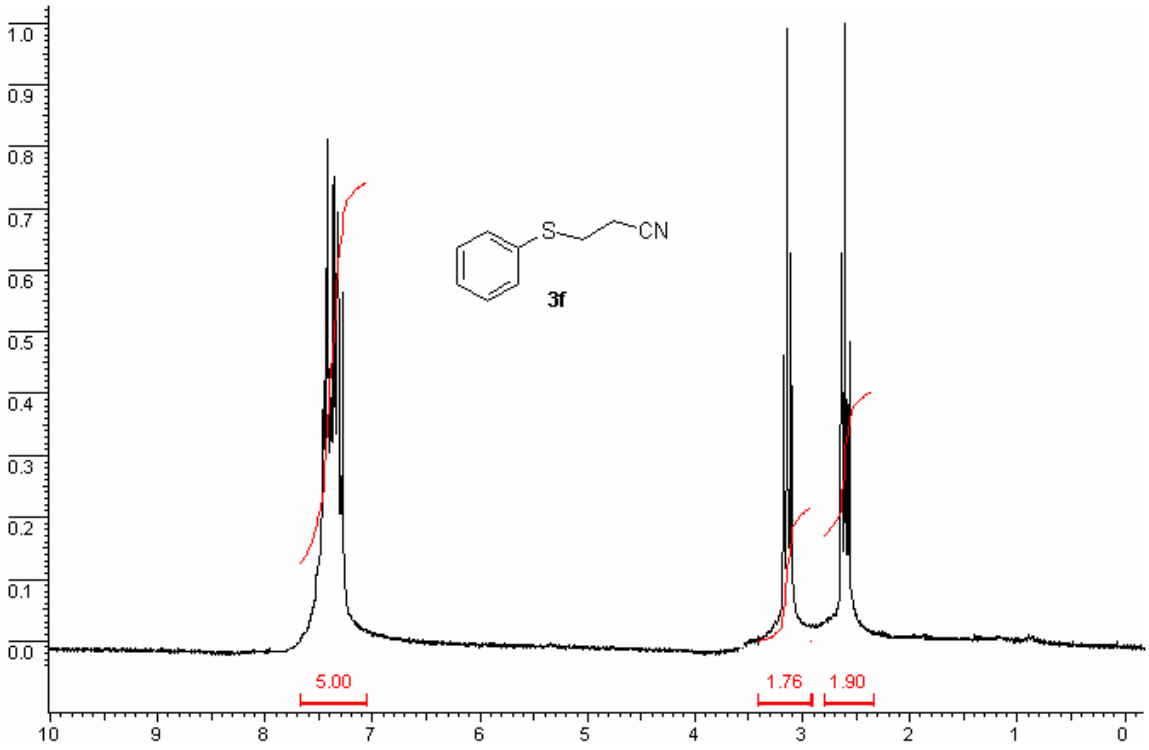


Figure 5: ^{1}H NMR spectrum of **3f**

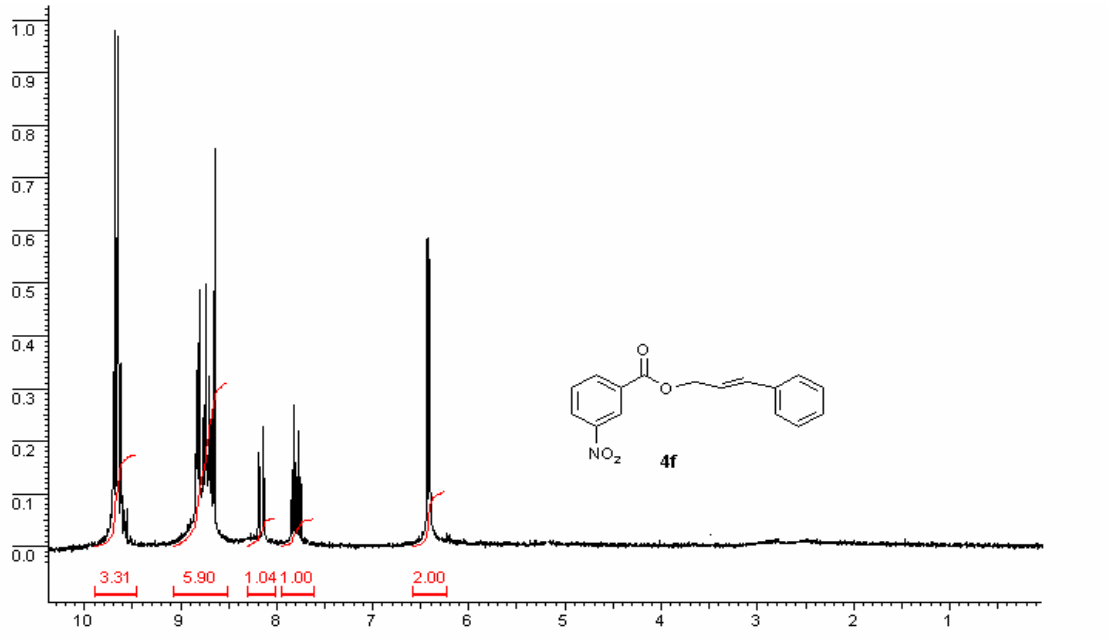


Figure 6: ^{1}H NMR spectrum of **4f**

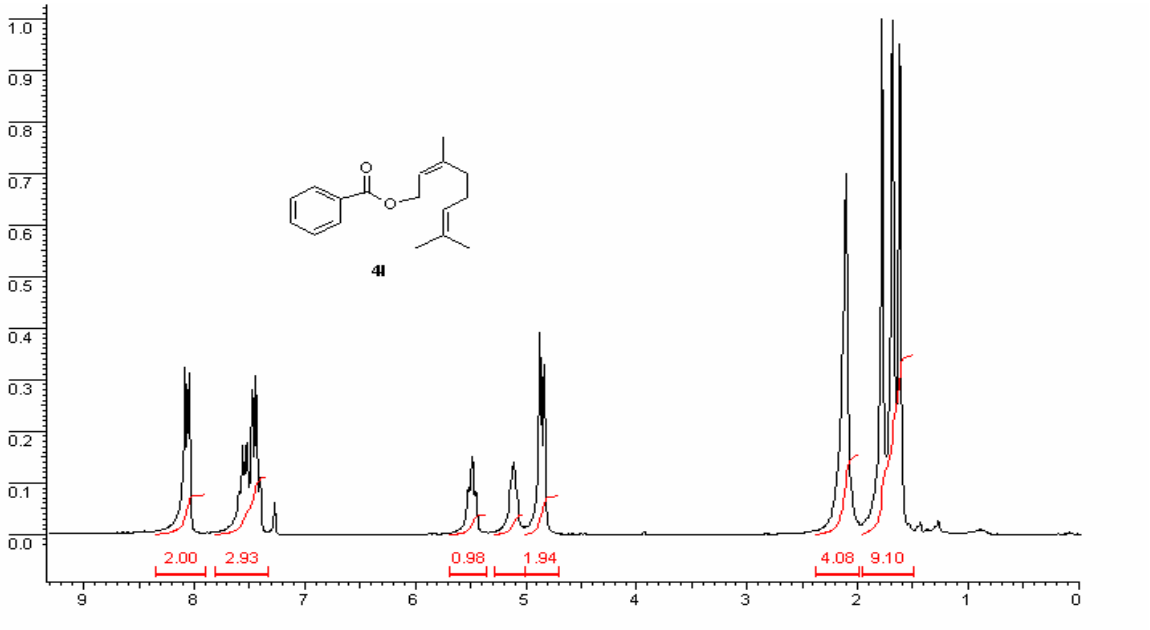


Figure 7: ^{1}H NMR spectrum of **4l**

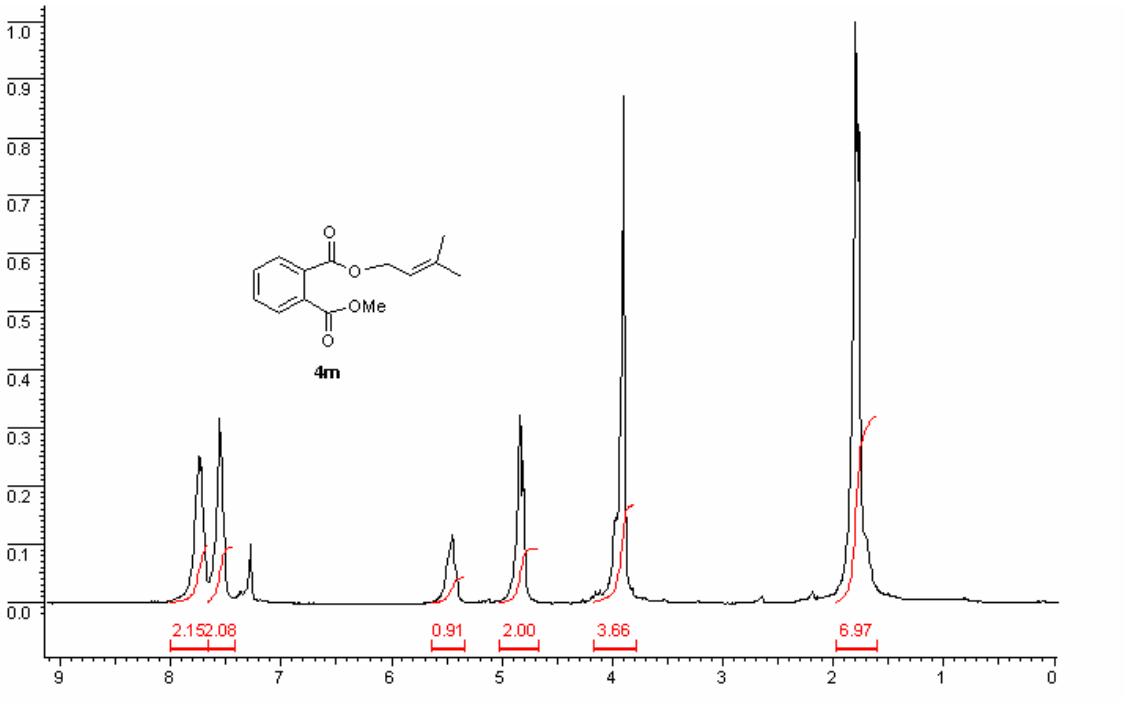


Figure 8: ^{1}H NMR spectrum of **4m**

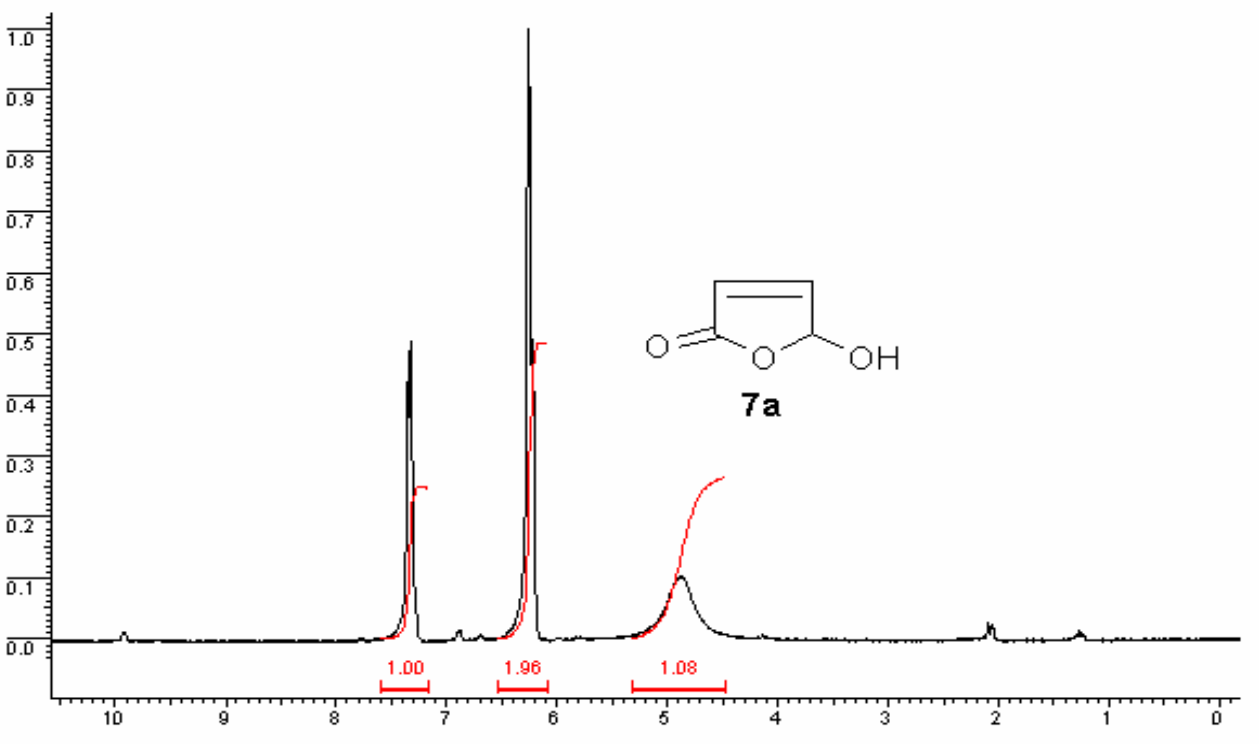


Figure 9: ^{1}H NMR spectrum of **7a**

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CHAPTER 5

SYNTHESIS, CHARACTERIZATION AND CATALYTIC PROPERTIES OF SULFATED CERIUM BASED STRONG LEWIS ACID CATALYST

5.1 Introduction

Yttria-zirconia based strong Lewis acid[1] catalyst was recently developed in our group and application of this catalyst was explored for a variety of organic transformations.[2] That prompted us to develop a new solid catalyst with enhanced and better catalytic activity. Some of the cerium based reagents / catalysts described in literature involved cerium metal either in powder form or chips which has been used in Barbier reaction between alkyl halide and carbonyl compounds,[3, 4] Reformatsky reaction with carbonyl compounds.[5] In combination with iodine this is used for reductive coupling of carbonyl compound.[6] Ceric ammonium nitrate is used as a volumetric standard oxidant[7] and oxidant for many functional groups.[8] Some of the other cerium based oxidizing reagents are cerium^{III}ammoniumnitrate-sodiumbromate $[(NH_4)_2Ce(NO_2)_6]$,[9a] cerium^{III}ammonium sulfate $[Ce(NH_4)_4SO_4]$,[9b] cerium^{IV}Nafion511,[9b] cerium^{IV}pyridinium chloride $[(C_5H_6N)CeCl_6]$,[9c] cerium^{IV}trifluoroacetate $[Ce(O_2CCF_3)_4]$,[9d] cerium^{IV}trifluoromethanesulfonate $[Ce(OSO_2CF_3)_4]$,[9d] cerium^{IV}trihydroperoxide $[Ce(OH)_3OOH]$.[9e] Some of the cerium based reagents used as a Lewis acid are cerium^{IV}acetate borontrifluoride etherate $[Ce(OAc)_3\text{-}BF_3.OEt]$ for the cyclocondensation of aldehyde with siloxydienes.[10a, b, c] Cerium chloride as a mild Lewis acid is capable of selective acetalization.[11] Organocerium reagents have increased oxo-[12] and azaphilicity[13] and greatly reduced basicity,[14a] in combination with $NaBH_4$ in selective 1,2-reducing reagent.[14b] Recently we used cerium based MCM-41 catalyst for the acylation of alcohols and amines.[15] From the above discussion it is clear that very few reports are available in literature about the Lewis acidic properties of cerium based reagent. This prompted us to explore the Lewis acidic properties of cerium containing heterogeneous catalyst. This chapter deals with the synthesis and physicochemical characterization of sulfated cerium based strong Lewis acid catalyst and its applications for organic transformations.

5.2 SECTION A

Synthesis and Physicochemical Characterization of Sulfated Ceria-Yttria Lewis Acid Catalyst

5.2.1 Synthesis of Ceria-Yttria Based Lewis acid Catalyst

Sulfated CeO_2/ Y_2O_3 was prepared by employing the sol-gel technique. A solution of cerium nitrate (2.48 gm, AR grade, Loba make) in isopropyl alcohol (50 ml) was added under constant stirring to the solution of yttrium nitrate (17.5 gm, AR grade, Merck) in isopropyl alcohol (150 ml). The final homogeneous solution thus formed was allowed to stand overnight. A yellowish gel was formed which was air-dried and then dried at 110 °C, ground to fine powder. The powder thus formed was added to H_2SO_4 (100 ml of 2N), stirred and dried on a water bath and then in oven at 110°C for 24 h. Subsequent programmed calcination at 500°C for 3 hours at a heating rate of 2°C min^{-1} resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 79.5 mole % Y, 19 mole % Ce and 1.5 mole % S.

5.2.2 Physicochemical Characterization of Ceria- Yttria Based Lewis Acid Catalyst

The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with N-filtered Cu-Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile (ammonia) of the cerium-based catalyst was recorded on a Micromeritics Autochem 2910 apparatus. Determination of specific surface area was carried out by BET (Brunner-Emmett-Teller) N_2 adsorption using a Omnisorp 100CX apparatus.

5.2.3 Results and discussion

The X- ray powder diffraction, XRD pattern of the calcined catalyst (Figure1) shows the presence of both CeO_2 and Y_2O_3 reflections indicating the product as a two-phase mixed oxide.

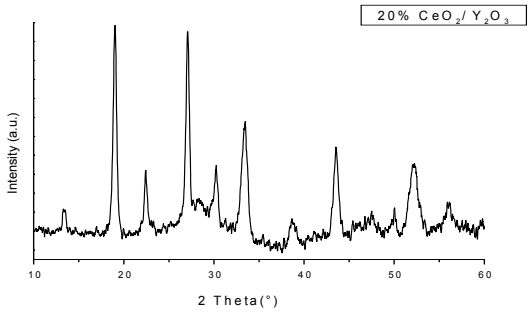


Figure 1: X- ray powder diffraction pattern of the sulfated CeO_2/ Y_2O_3

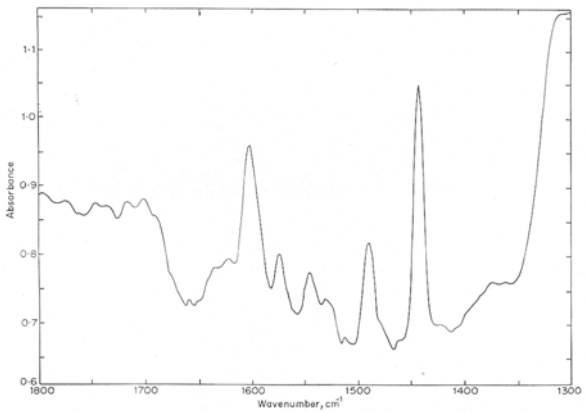


Figure 2: FTIR spectrum of pyridine adsorbed on the cerium-based catalyst

The IR spectra of pyridine adsorbed on the catalyst show absorption bands at 1640, 1605, 1577, 1542, 1490 and 1444 cm^{-1} (Figure 2). The strong absorption bands at 1605 and 1444 cm^{-1} indicate the presence of coordinated pyridine at the Lewis acid sites of the catalyst. The weak absorption at 1542 cm,$^{-1}$ attributed to the pyridinium ion[16a] indicates the presence of a few Brönsted acid sites. Temperature programmed desorption of the

catalyst shows the presence of strong acid sites as well as weak acid sites. The presence of strong acid sites in the catalyst is indicated by the peak maxima at 470°C in the TPD profile (Figure 3).[16b] These results are in good agreement with the ones obtained by FTIR. The scanning electron micrograph of the sample shows the presence of uniform-sized (around 0.1-0.2 μm) particles (Figure 4). Thermal analysis (TG-DTA) of sulfated CeO_2/ Y_2O_3 is shown in Figure 5. It indicates that up to 200°C there is an endothermic weight loss of 4.5 % due to the adsorbed water from the surface of the catalyst. From 200-760°C, the weight loss of only 2.3 % suggests that the catalyst is thermally stable in the temperature range 200-760. Final weight loss of 10 % above 760°C indicates that the catalyst is not stable above that temperature because of the structural breakdown.

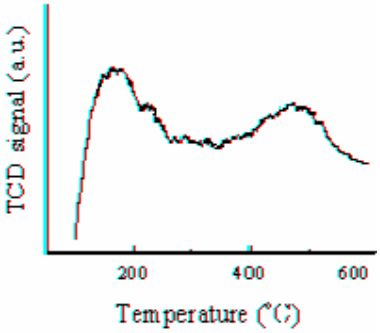


Figure 3: TPD profile (ammonia) of the cerium-based catalyst 0.5 mmol/gm of catalyst ammonia desorbed

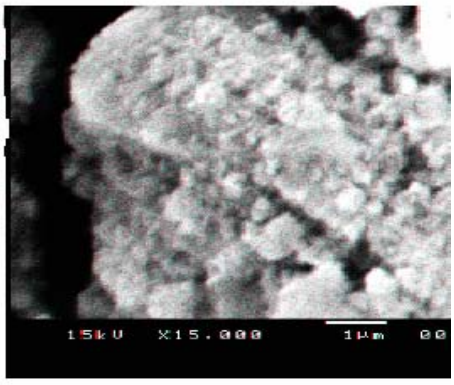


Figure 4: Scanning electron micrograph of the catalyst

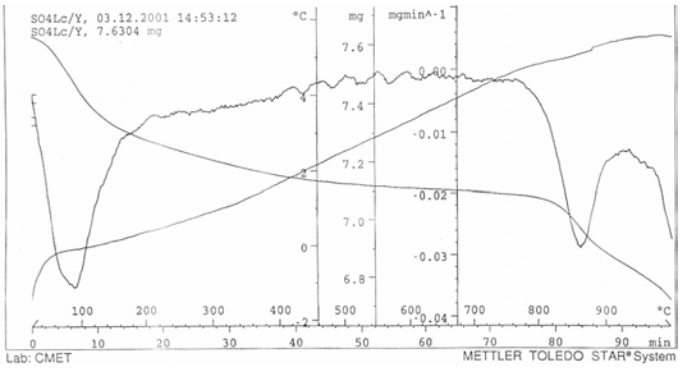


Figure 5: Thermal analysis (TG-DTA) of sulfated CeO_2/ Y_2O_3

The surface area of the sample determined by the BET method was 100 $m^2g.^{-1}$ The lattice defects caused by the incorporation of cerium in the yttrium sites appear to enhance the number and strength of the Lewis acid sites of the catalyst.

5.2.4 Conclusion

In conclusion we have synthesized sulfated ceria-yttria based strong Lewis acid catalyst for the first time, which was fully characterized by physicochemical characterization methods like XRD, SEM, TPD, thermal analysis, and FT-IR. Pyridine absorption FT-IR shows the presence of strong Lewis acidic sites on the sulfated ceria-yttria based catalyst.

5.3 SECTION B

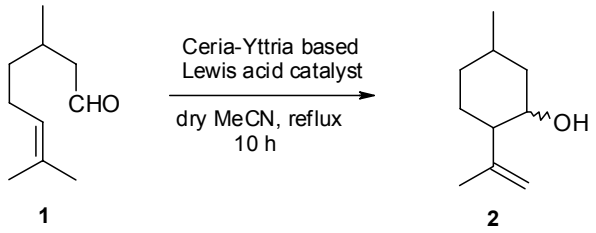
Organic Transformations Over Sulfated Cerium Based Strong Lewis Acid Catalyst

5.3.1 SECTION I

Synthesis of Isopulegol from Citronellal via Intramolecular Ene Reaction

5.3.1.1 Introduction

The ene reaction is defined as the direct substitution addition of a carbonyl compound with a double bond (enophile). It is also shown that the ene-reaction possesses wide scope and applicability ranging from industrial to biosynthetic processes.[17] Solid super acids have been employed in petrochemical industries. However, their potential in organic synthesis has not been fully realized. The very first application of ceria-yttria based strong Lewis acid catalyst was for the ene reaction and this study revealed that isopulegol **2** can be conveniently prepared from citronellal **1** by intramolecular ene reaction using ceria-yttria Lewis acid catalyst.



Scheme 1

5.3.1.2 Results and discussion

When citronellal was treated with catalytic amount of cerium based Lewis acid catalyst in dry acetonitrile, isopulegol was obtained in good yield. The other catalysts for this reaction were also screened and the results of such study are summarized in Table 1. Thus

ceria-yttria based Lewis acid catalyst was found to be the best catalyst for the conversion of citronellal to isopulegol compared to H-mordenite and H-beta zeolite.

Table1: Effect of different catalyst for the conversion of citronellal to isopulegol[a] in acetonitrile[a]

Entry	Catalyst	Reaction time (h)	Yield (%)[b]
1.	Ceria-yttria based Lewis acid	10	60
2.	H-Beta	14	35
3.	H- Mordenite	30	25[c]

[a] product was characterized by spectroscopic data and also by comparison with authentic sample. [b] yields refer to pure and isolated product. [c] 50 % catalyst was used.

We also studied the effect of different solvents such as hexane, tetrahydrofuran, acetone and acetonitrile for the conversion of citronellal to isopulegol. The results are summarized in Table 2. It is clear from the Table 2 that polar solvents were proved to be better than nonpolar solvent.

Table 2: Effect of various solvent for the synthesis of isopulegol[a]

Entry	Solvent	Reaction time (h)	Yield (%)[b]
1.	Hexane	20	40
2.	Acetonitrile	10	65
3.	Acetone	11	60
4.	Tetrahydrofuran	14	55

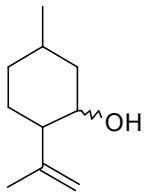
[a] Product was characterized by spectroscopic data and also by comparison with authentic sample. [b] Yields refer to pure and isolated product.

5.3.1.3 Conclusion

In conclusion, sulfated ceria-yttria based Lewis acid catalyst catalyzes the intramolecular ene reaction in the synthesis of isopulegol from citronellal under mild conditions.

5.3.1.4 Experimental

General procedure for the ene-reaction: Citronellal (1.54 gm, 10 mmol) was added to dry acetonitrile (10 ml) containing cerium based Lewis acid catalyst (0.308 gm, 20 % w/w with respect to citronellal) under nitrogen and mixture was refluxed for 10 h. The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the filtrate was concentrated to get the crude product which was purified by column chromatography using pet ether: ethyl acetate (8.5:1.5) as eluent to afford the product in good yield.



2

Yield: 65 %

Colorless liquid

IR (Neat) cm^{-1}: 3300, 1560, 1450.

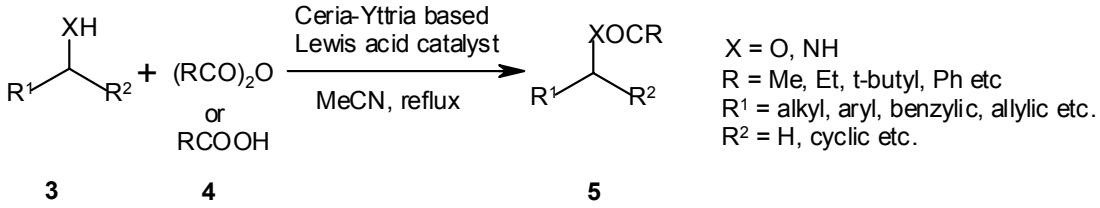
^1H NMR (200 MHz, $CDCl_3$): δ 0.98 (d, J = 6.0 Hz, 3H), 1.20-2.16 (m, 12H), 3.42 (m, 1H), 4.85 (m, 2H).

5.3.2 SECTION II

Acylation of Alcohols and Amines

5.3.2.1 Introduction

The acylation of alcohols and amines, by acyl chloride or acid anhydride under basic conditions is a well established reaction in organic synthesis.[18] The most commonly employed basic catalysts for this purpose are 4-(dimethylamino)pyridine and 4-pyrrolidinopyridine (PPY).[19] The Lewis acid catalyzed acylation of alcohols and amines with acid anhydride is a mild, strategic alternative to basic and nucleophilic catalysts. Some procedures have been developed wherein Lewis acid catalysts such as $Cu(OTf)_2$,[20a] $TaCl_5$,[20b] TMSOTf,[20c] $Sc(OTf)_3$,[20d-g] $In(OTf)_3$,[20h] $CoCl_2$,[20i] Bu_3P[20j,k] have been used for acyl transfer reactions in alcohols. More recently, use of montmorillonite K-10, KSF,[21] $Bi(OTf)_3$,[22a] H-FER.,[22b] yttria-zirconia based Lewis acid[2b,c] as heterogeneous catalysts has been reported to effect acylation reactions. As part of a research program aimed at developing new solid catalyst and its subsequent application for various organic transformations, the ceria-yttria based Lewis acid was found to be an extremely efficient catalyst for the ene reaction. This prompted us to use this catalyst for acylation reactions of alcohols and amines (Scheme 2), and the results of such study are described below.



Scheme 2

5.3.2.2 Results and discussion

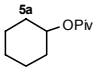
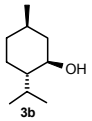
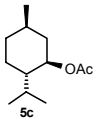
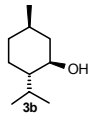
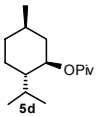
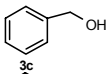
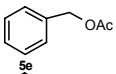
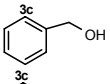
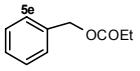
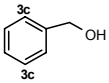
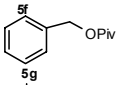
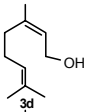
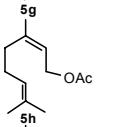
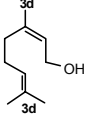
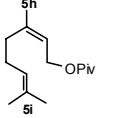
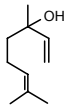
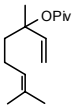
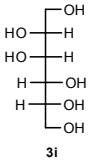
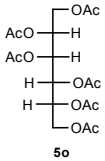
Thus, when n-hexanol was treated with acetic anhydrides in the presence of a catalytic amount of the new ceria-yttria based catalyst, the corresponding hexyl acetate was obtained in 94 % yields (Table 3, entry 1). The IR spectrum of n-hexyl acetate showed a band at 1727 cm^{-1} indicating the presence of ester group. The CH_3 protons of hexyl group appeared at 0.98 δ as a triplet in ^1H NMR spectrum. The CH_3 protons of acetate group appeared as a singlet at 2.10 δ, while a triplet at 4.10 δ indicated the presence of CH_2 protons attached to $–OCOCH_3$ group. Further structure was proved by mass spectrum showing M^+ peak at 143. The substrates examined in our studies and the results obtained are summarized in Table 3-6. Thus the present procedure for acylation is quite general as a wide range of structurally varied alcohols such as open chain, cyclic and aromatic ones underwent acylation with acid anhydrides in excellent yields.

Table 3: Acylation of hexanol with different acylating agent[a]

Entry	Acylating agent	Reaction time (h)	Yield (%)[b]
1	Acetic anhydride	3.0	94
2	Propionic anhydride	3.5	90
3	Pivalic anhydride	5.0	90
4	Benzoic anhydride	8.0	80
5	Acetic acid	4.0	92[c]
6	Propionic acid	5.0	90[c]
7	Benzoic acid	10.0	78[c]
8	Acetyl chloride	2.5	94
9	Benzoyl chloride	4.0	85

[a] **Reaction condition:** Hexanol (2.5 mmol), dry acetonitrile (5.0 ml), catalyst (20 % w/w w.r.t. hexanol) acylating agent (3.75 mmol). [b] Yields refer to pure and isolated product. [c] Reaction carried with 12.5 mmol acid at 130°C without any solvent.

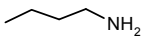
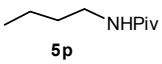
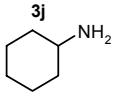
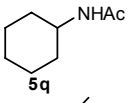
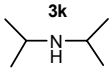
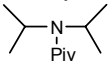
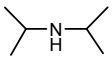
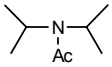
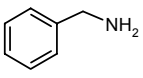
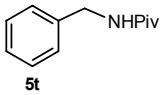
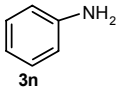
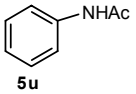
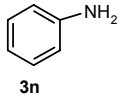
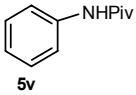
Table 4: The ceria-yttria based Lewis acid catalyzed acylation of alcohols and polyols

Entry	Alcohol	Anhydride	Reaction Time (h)	Product	Yield[a] (%)
1	 3a	Acetic	5	 5a	95
2	 3a	Pivalic	4	 5b	91
3	 3b	Acetic	4	 5c	96
4	 3b	Pivalic	5	 5d	86
5	 3c	Acetic	4	 5e	94
6	 3c	Propionic	4.5	 5f	90
7	 3c	Pivalic	6	 5g	85
8	 3d	Acetic	5	 5h	90
9	 3d	Pivalic	6	 5i	87
10	 3e	Pivalic	15	 5j	40
11	 3f	Acetic	10	 5k	85[b]
12	 3g	Acetic	9	 5l	98
13	 3h	Acetic	6	 5m	96
14	 3h	Pivalic	8	 5n	75
15	 3i	Acetic	10	 5o	94

[a]Yields refer to the pure and isolated product.

However, the reaction of alcohols with benzoic acid/anhydride was found to be sluggish and hence a little longer time is required to complete the reaction affording relatively low yield of the products (Table 3, entries 4 and 7). The efficacy of ceria-yttria based catalyst can be clearly visualized in the acetylation of polyhydroxy compounds under similar conditions. For example, both aliphatic and aromatic polyols were acylated in very high yields (Table 4, entries 12-15). Another noteworthy feature of this methodology is that polyol such as D-mannitol underwent exhaustive acetylation smoothly demonstrating the practical utility of this method (Table 4, entry 15). Another noteworthy feature of this methodology is that wide range of structurally varied such as cyclic, acylic, benzylic, allylic and tertiary alcohols underwent pivalation reaction in the presence of catalytic amount of new ceria-yttria Lewis acid (Table 4, entries 2, 4, 7, 9, 10, 14). However, the reaction of pivalation was found slower compared to acetylation but yields were high.

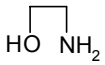
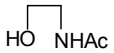
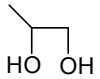
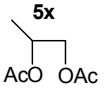
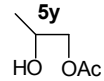
Table 5: The ceria – yttria based Lewis acid catalyzed acylation of amines and thiols[a]

Entry	Substrate	Reaction Time (h)	Product[a]	Yield[b] (%)
1	 **3j**	5.0	 **5p**	90
2	 **3k**	3.5	 **5q**	97
3	 **3l**	2	 **5r**	91
4	 **3l**	2.5	 **5s**	90
5	 **3m**	4.5	 **5t**	95
6	 **3n**	3	 **5u**	99
7	 **3n**	5	 **5v**	95

[a] Reaction was performed at room temperature. [b]Yields refer to isolated pure products.

In order to explore the generality and scope of the ceria-yttria based Lewis acid catalyzed reaction, the procedure has been extended to a variety of other substrates such as amines. Thus, the aromatic and aliphatic amines were successfully acylated in the presence of a ceria-yttria based Lewis acid catalyst (Table 5). Another notable feature of the reaction is that even a hindered amine was acylated in very high yield (Table 5, entry 3-4).

Table 6: Chemoselective acetylation of amino alcohol, mercapto alcohol and diol catalyzed by Ceria-yttria based Lewis acid catalyst

Entry	Substrate	Reaction Time (h)	Product	Yield[a] (%)
1	 **3o**	4[b]	 **5w**	98
2	 **3p**	12[c]	 **5x**	84
3	 **3q**	10[c]	 **5y**  **5z**	10 80

[a]Yields refer to isolated pure products. [b]Reaction was performed at room temperature. [c]Reaction was carried out at 40 ^{0}C.

Encouraged by this finding, it was felt worthwhile to study the reactivity pattern of different kind of amino alcohols, mercapto alcohols and diols for acylation reaction over ceria-yttria Lewis acid catalyst and results of such study are presented in Table 6. Thus it was observed that the reaction is chemoselective for the amino alcohols as the amine, being more nucleophilic than the alcohol, was acylated faster giving the corresponding *N*-acetate product in excellent yield (Table 6, entry 1). Similarly the hydroxyl group of 2-mercapto ethanol reacted preferentially over the thiol affording the corresponding acetate in very high yield (Table 6, entry 2). In the case of 1,2-diol, we observed preference in the acylation for primary alcohol over secondary; however a mixture of mono and di-acylated products was obtained (Table 6, entry 3).

5.3.2.3 Conclusion

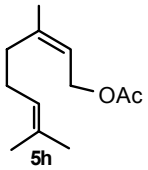
We have developed a mild, highly efficient and chemoselective procedure for acylation of alcohols, thiols and amines using varieties of acylating agents in the presence of catalytic amount of ceria-yttria base Lewis acid catalyst. The notable feature of this methodology is that reaction is chemoselective even the hindered substrates can be acylated in high yields under mild conditions. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of work-up and recyclability of the catalyst are noteworthy.

5.3.2.4 Experimental

General experimental procedure for the acylation with acid anhydride: Acid anhydride (benzoic, propionic and acetic) (3.75 mmol; 1.5 equiv. per OH or NH_2) was added dropwise to a solution of alcohol, amine, or thiol (2.5 mmol) in dry acetonitrile (5.0 ml) containing catalyst (20% by weight) and the mixture was refluxed for the indicated length of time (Table 3-6). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the filtrate was concentrated, diluted with water (5.0 ml) and extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was separated, washed with 10 % aq. $NaHCO_3$, brine, water and dried over Na_2SO_4. The solvent was removed and the crude product was chromatographed on a silica gel column to afford the pure product. After the reaction, the catalyst is recovered with retention of its catalytic activity. It can be further reactivated for reuse by heating it at 500 ^{0}C in the presence of air.

General experimental procedure for the pivalation with pivalic anhydride: Pivalic anhydride (10 mmol; 2.0 equiv. per OH or NH_2) was added to a solution of alcohol (5.0 mmol) in dry acetonitrile (5.0 ml) containing catalyst (20% by weight) and the mixture was refluxed for the indicated length of time (Table 4-5). The reaction was monitored by TLC. After completion of reaction, methanol (5.0 ml) was added and mixture again refluxed for 10 h and then allowed to come to room temperature, the catalyst was filtered and the filtrate was concentrated, diluted with water (5.0 ml) and extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was separated, washed with 10 % aq. $NaHCO_3$, brine, water and dried over Na_2SO_4. The solvent was removed and the crude product was chromatographed on a silica gel column to afford the pure product.

Geranyl Acetate (5h):



Colorless liquid

IR (Neat) cm^{-1}: 2923, 1720,1560, 1450.

^1H NMR (200 MHz, $CDCl_3$): δ 1.58 (s, 3H), 1.65 (s, 3H), 1.67 (s, 3H), 1.90-2.13 (m, 4H), 2.15 (s, 3H), 4.53 (d, J = 6.5 Hz, 2H), 5.10 (t, J = 6.5 Hz, 1H), 5.31 (t, J = 6.5 Hz, 1H).

The spectroscopic data of other compounds prepared were identical with those reported in foregoing section (Chapter 3, Section B).

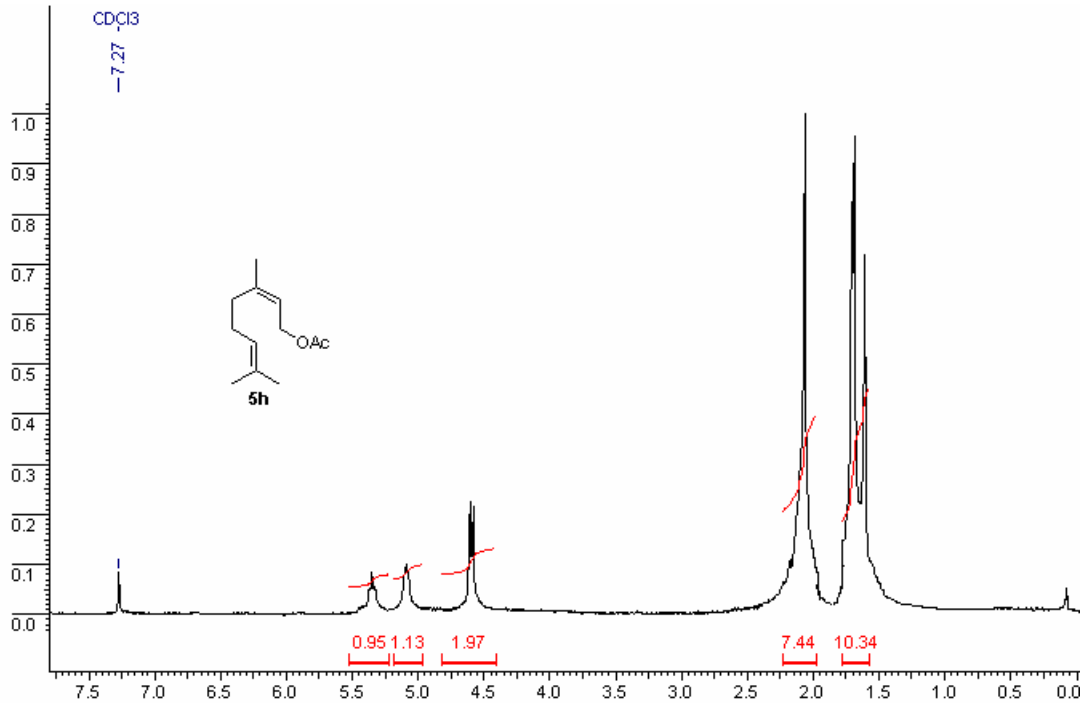


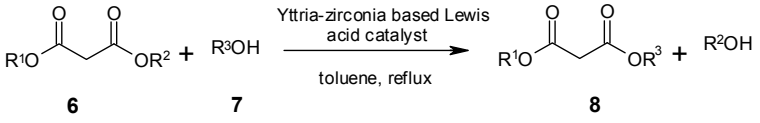
Figure 6: ^1H NMR spectrum of **5h**

5.3.3 SECTION III

Transesterification of β-Keto Esters

5.3.3.1 Introduction

Transesterification is an important reaction which has wide applications both in academic and industrial research.[23] In general, the transesterification reaction is accelerated by the protic acid, Lewis acid catalysts such as boron tribromide,[24] anhydrous aluminium trichloride embedded in polystyrene divinyl benzene,[25] Brönsted acid catalysts e.g. hydrochloric, phosphoric, sulfonic, sulfuric or *p*-toluenesulfonic acid[26] or basic catalysts such as metal alkoxides,[27] metal carbonates[28] etc. Recently, DMAP catalyzed transesterification of β-keto esters with good to excellent yields has been reported.[29] Another publication[30] describes an efficient method of transesterification which is restricted only to tertiary butyl esters thus lacking generality. Otera et. al.[31] has shown that ketoesters can be smoothly transesterified by tetrabutyldistannoxanes as catalyst under mild condition. More recently use of sulfated tin oxide SnO_2,[32] zeolites,[33] kaolinitic clay,[34] NBS,[35] sulfated yttria-zirconia[2a] and polymer supported lipase catalyst[36] has been reported for transesterification. Nevertheless there are sufficient drawbacks to most of these procedures to justify the need for a general, selective and practical method of transesterification. The ceria-yttria based Lewis acid was found to be an extremely efficient catalyst for the ene reaction, acylation of alcohols and amines. This prompted us to use this catalyst for transesterification and herein sulfated ceria-yttria Lewis acid catalyzed transesterification of β-keto ester (Scheme 3) is described.



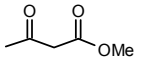
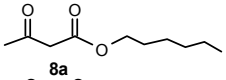
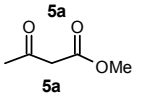
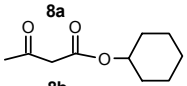
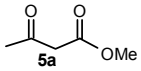
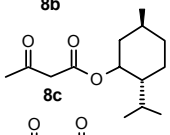
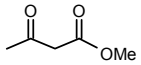
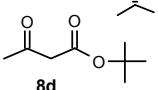
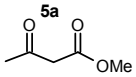
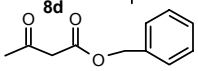
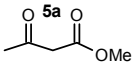
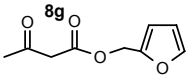
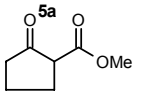
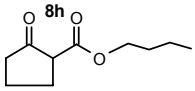
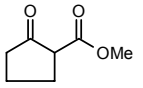
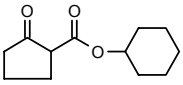
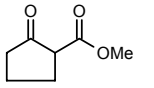
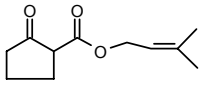
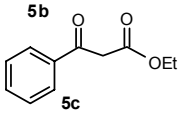
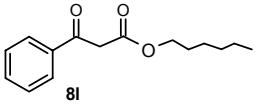
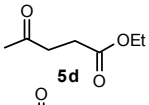
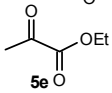
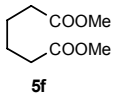
Scheme 3

5.3.3.2 Results and discussion

When methyl acetoacetate was treated with cyclohexyl alcohol in the presence of catalytic amount of ceria-yttria based strong Lewis acid catalyst, the corresponding transesterified product **8b** was obtained in 95 % yields (Table 7, entry 2). The IR spectrum of **8b** showed a strong band at 1740 and 1720 cm^{-1} indicating the presence of β-keto ester group and another band obtained at 3040 cm^{-1} indicates the presence of hydroxyl group of the enolic form of cyclohexyl actoacetate. The ^1H NMR spectrum showed a multiplet at 1.10-2.00 δ for CH_2 protons of cyclohexyl group, and a singlet at 2.25 δ for CH_3 protons. The CH_2 protons of acetoacetate appeared at 3.40 δ as a singlet. The enolic form of cyclohexylacetoacetate showed two singlet at 4.90 δ and 12.5 δ. Further the structure was proved by mass spectrum showing M^+ peak at 184. The present procedure is quite general as a wide range of structurally varied β-keto esters such as open chain, cyclic and aromatic ones underwent transesterification with a variety of alcohols. The reaction proceeds smoothly with primary and secondary alcohols in excellent yields; whereas transesterification of t-butyl esters (Table 7, entry 4) which is often problematic in acid catalyzed reaction, is also realized by this reagent though in moderate yield. Another noteworthy feature of this methodology is that unsaturated alcohols like prenyl alcohol underwent transesterification reaction smoothly affording the corresponding products in excellent yields (Table 7, entry 9) although it should be noted that transesterification with unsaturated alcohols is rather difficult as it is offset by facile decarboxylated rearrangement.[37] The superiority of this procedure can be clearly

visualized in transesterification reactions which led to the synthesis of β-keto esters with an aromatic moiety in excellent yields (Table 7, entry 10).

Table 7: Transesterification of β-keto esters with different alcohols catalyzed by cerium base strong Lewis acid catalyst

Entry	Keto ester **6**	Alcohol **7**	Time (h)	Product[a] **8**	Yield (%)[b]
1	 **5a**	Butyl	10	 **8a**	90
2	 **5a**	Cyclohexyl	8	 **8b**	95
3	 **5a**	Menthyl	9	 **8c**	98
4	 **5a**	*t*-Butyl	15	 **8d**	30
5	 **5a**	Benzyl	10	 **8g**	95
6	 **5a**	Furfuryl	15	 **8h**	65
7	 **5b**	*n*-Butyl	9	 **8i**	82
8	 **5b**	Cyclohexyl	8	 **8j**	97
9	 **5b**	Prenyl	10	 **8k**	85
10	 **5c**	*n*-Hexyl	8	 **8l**	93
11	 **5d**	*n*-Hexyl	15	no reaction	
12	 **5e**	*n*-Hexyl	15	no reaction	
13	 **5f**	*n*-Hexyl	15	no reaction	

[a]Yields refer to isolated pure products.

It is important to mention that the reaction appears to be specific only for the transesterification of β-keto esters. Other esters like α-keto esters, γ-keto esters as well as normal esters failed to undergo reaction. The difference in the reactivity of β-keto esters from other esters in transesterification may probably be due to the formation of acyl ketene intermediate in the former as proposed by Campbell and Lawrie.[38]

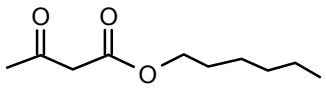
5.3.3.3 Conclusion

In conclusion, we have demonstrated that ceria-yttria based Lewis acid catalyst serves as an efficient catalyst for transesterification of β-keto esters by a variety of alcohols. Besides, the high selectivity and reactivity exhibited by the catalyst will present a better and more practical alternative to the existing methodologies. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of work-up and recyclability of the catalyst are noteworthy.

5.3.3.4 Experimental

General procedure for transesterification: A mixture of β-keto ester (10 mmol), alcohol (10 mmol), and catalyst (20 % by weight) in toluene (15 ml) was refluxed using Dean-Stark apparatus. The reaction was monitored by T. L. C. After completion of the reaction, the catalyst was filtered and the filtrate was concentrated. The residue was chromatographed on a silica gel column using pet-ether: ethyl acetate (9.75: 0.25) to afford the ester in good to excellent yields.

3-Oxo-butyric acid hexyl ester (8b):



8a

Colorless liquid

IRν_{max} / cm^{-1} (Neat): 2920, 1740, 1720, 1620, 1140, 1040;

^{1}HNMR (200MHz, $CDCl_3$) δ: 0.90 (t, J = 6.6 Hz, 3H), 1.25-1.75 (m, 8H), 2.2 (s, 3H), [3.44, 5.00, 12.20] (s, 2H), 4.15 (t, *J* = 6.6 Hz, 2H).

The spectrospopic data of other compounds prepared were in accord with those mentioned in Chapter 3, Section A.

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