FACILE SYNTHESIS OF AZIRIDINES USING COPPER HYDROTALCITE UNDER MICROWAVE IRRADIATION; SYNTHESIS OF 3-SUBSTITUTED-2(1*H*)-QUINOLINONES CATALYZED BY HYDROTALCITE LIKE ANIONIC CLAYS; REARRANGEMENT OF α-PINENE EPOXIDE TO CAMPHOLENIC ALDEHYDE WITH MODIFIED BETA ZEOLITE CATALYST AND REGIOSELECTIVE NITRATION OF PHENOLS WITH NEW PHOSPHORUS BASED IONIC LIQUIDS

A THESIS
SUBMITTED TO THE
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FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

IN
CHEMISTRY

BY
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UNDER THE GUIDANCE OF
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PUNE 411 008, INDIA

[MARCH, 2008]

DEDICATED

TO

MY PARENTS

DECLARATION

I hereby declare that the work presented in the thesis entitled **"Facile Synthesis of Aziridines using Copper Hydrotalcite under Microwave Irradiation; Synthesis of 3-substituted-2(1*H*)-Quinolinones Catalyzed by Hydrotalcite like Anionic Clays; Rearrangement of α-Pinene Epoxide to Campholenic Aldehyde with Modified Beta Zeolite Catalyst and Regioselective Nitration of Phenols with New Phosphorus Based Ionic Liquids"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune, India under the guidance of **Dr. (Mrs.) Bhanu. M. Chanda.** The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

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CERTIFICATE

CERTIFIED that the work incorporated in the thesis entitled **"Facile Synthesis of Aziridines using Copper Hydrotalcite under Microwave Irradiation; Synthesis of 3-substituted-2(1*H*)-Quinolinones Catalyzed by Hydrotalcite like Anionic Clays; Rearrangement of α-Pinene Epoxide to Campholenic Aldehyde with Modified Beta Zeolite Catalyst and Regioselective Nitration of Phenols with New Phosphorus Based Ionic Liquids"** submitted by Mr. **Yashawant Vasudeo Dharap** was carried out by the candidate under my guidance. Such material as obtained from other sources has been duly acknowledged in the thesis.

Bhanu
(B. CHANDA)

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March 2008

Dr. (Mrs.) B. M. Chanda

(Research Guide)

CONTENTS

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Yashawant V. Dharap

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
AIBN	2, 2'-Azobisisobutyronitrile
bp	Boiling point
$BF_3.OEt_2$	Borontrifluoride diethyl etherate
b	Broad (signal)
Boc	*tert* – butyloxycarbonyl
$CDCl_3$	Deuterated chloroform
CHT	Calcined hydrotalcite
d	Doublet
DIBAL	Diisobutyl aluminium hydride
DMAP	*N, N'*-Dimethylaminopyridine
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
EDC	Ethylene dichloride
ee	Enantiomeric excess
g	Grams
GC	Gas chromatography
h	Hours
HMPA	Hexamethyl phosphoric triamide
HTs	Hydrotalcites
IR	Infra red
LTA	Lead tetraacetate
m	Multiplet
M^+	Molecular ion
Me	Methyl
mg	Milligrams

min	Minutes
ml	Millilitre
mmol	Millimole
mol	Mole
mp	Melting point
n-BuLi	*n*-Butyllithium
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
$Pd(dba)_2$	Palladium di-benzylidine acetone
Ph	Phenyl
PPA	Polyphosphoric acid
p-TSA	*p*-Toluene sulfonic acid
q	Quartet
r. t.	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TBDMS	*tert*-Butyldimethyl silyl
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
$ZnCl_2$	Zinc chloride
$ZnBr_2$	Zinc bromide

General remarks

1. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware.

2. Progress of the reaction was monitored by TLC and was visualized by UV absorption by florescence quenching or I_2 staining or by both.

3. Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi rotary evaporator. Silica gel for column chromatography was 60-120 mesh and 100-200 mesh.

4. All the temperatures are in °C. All the melting points and boiling points are in °C and are uncorrected. Melting points were recorded on Buchi B-540 melting point apparatus.

5. IR spectra were recorded on a Perkin-Elmer infra-red spectrometer model 599-B and model 1620 FT-IR (ν-max in cm^{-1}).

6. Unless otherwise stated, ^1H NMR spectra were recorded using TMS as internal reference on Bruker AC-200, AC-400 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million downfield from TMS. The coupling constants (*J* values) are reported in Hertz.

7. ^{13}C NMR spectra were recorded on Bruker AC-200 and AC-400 instruments operating at 50 MHz and 100 MHz.

8. Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.

9. GC analysis was carried out on Chemito 1000, and Hewlett Packard 5890 instruments.

10. Microanalysis was carried out in the microanalytical section of NCL.

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

12. Microwave irradiations were carried out in a LG convection domestic microwave oven model MC-808WAR operating at 2450 MHz and reactions were performed at 30% of its full power.

ABSTRACT

The thesis titled "Facile Synthesis of Aziridines using Copper Hydrotalcite under Microwave Irradiation; Synthesis of 3-Substituted 2(1*H*)–Quinolinones Catalyzed by Hydrotalcite like Anionic Clays; Rearrangement of α-Pinene Epoxide to Campholenic Aldehyde with a Modified Beta Zeolite Catalyst and Regioselective Nitration of Phenols with New Phosphorus Based Ionic Liquids"

The thesis is divided into three chapters.

Chapter 1: This chapter titled "Copper Hydrotalcite Catalyzed Synthesis of Aziridines under Microwave Irradiation" has two parts. Part I: Aziridination, A Brief Review on Aziridination and Part II: Synthesis of Aziridines using Copper Hydrotalcite under Microwave Irradiation.

Chapter 2: Synthesis of 3-Substituted 2(1*H*)-Quinolinones Catalyzed by Hydrotalcite like Anionic Clays.

Chapter 3: This chapter is sub-divided into two sections.

Section I: Application of Modified Zeolite Beta Catalyst in the Rearrangement of α-Pinene oxide to Campholenic Aldehyde.

Section II: Regioselective Nitration of Phenols with new Phosphorus Based Ionic Liquids.

Chapter 1: Copper Hydrotalcite Catalyzed Synthesis of Aziridines under Microwave Irradiation

Part I: Aziridination, A Brief Review

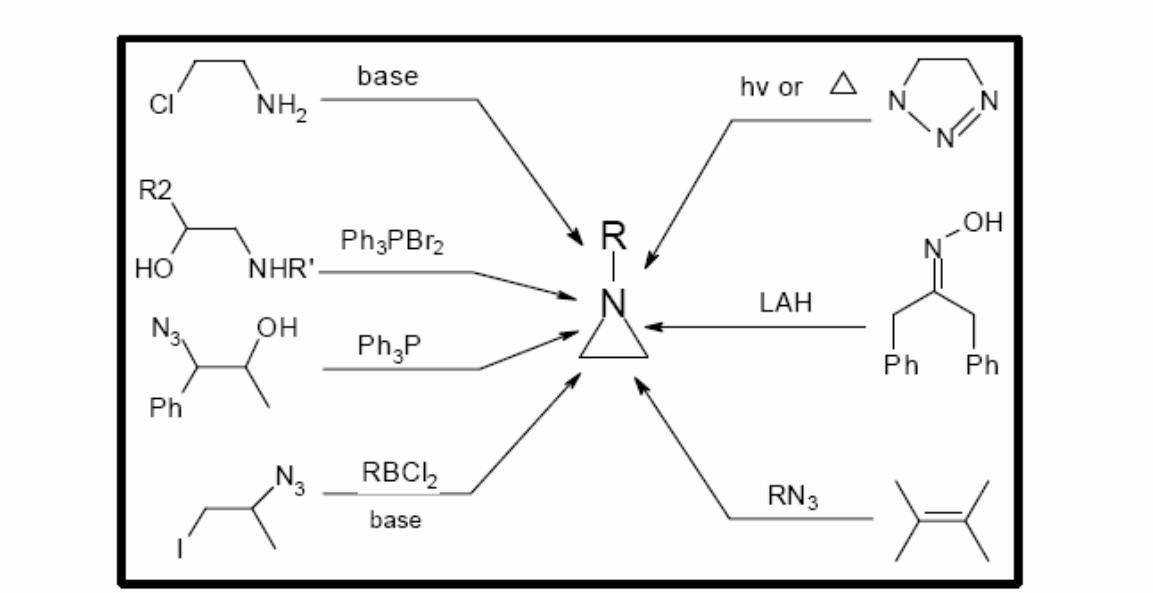
Significance of aziridines is due to their presence in several natural products which are potent biologically active agents. Chiral aziridines are attractive building blocks and have been applied to the total synthesis of several natural products. In addition, aziridines are also important industrial intermediates in the synthesis of drugs.

The recent years have witnessed an overwhelming importance in the catalytic aziridination reactions. Though various reviews were written in the past on catalytic aziridination, it is worthwhile to highlight the recent developments in this area since

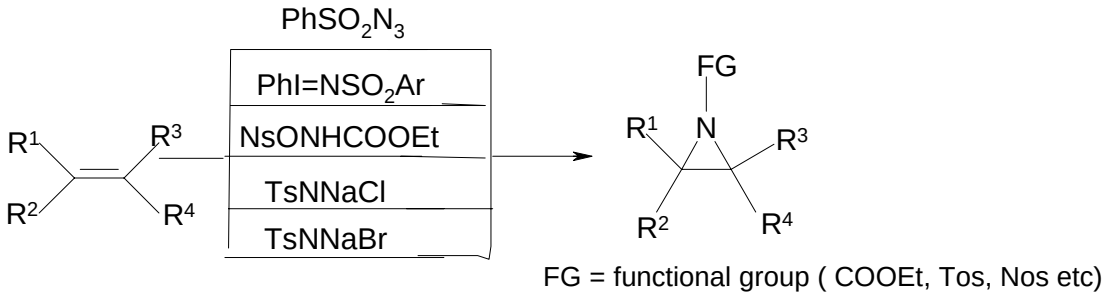
2002. This review has been presented giving emphasis on various recent aspects such as, heterogeneous catalytic methods along with their reaction profiles, novel reagents as nitrogen source and the application of aziridination reaction in organic chemistry.

Part II: Synthesis of Aziridines using Copper Hydrotalcite under Microwave Irradiation

Aziridines can be synthesized by various indirect methods as follows.

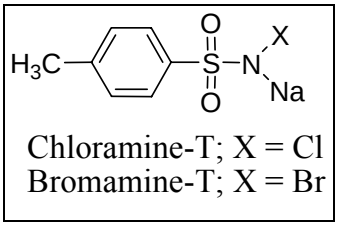


All the above methods involve laborious work up and low yields of aziridines. Recently developed approaches towards one step route to aziridines from olefins are summarized below.



Most of these methods suffer from major drawbacks like drastic reaction conditions, cumbersome preparation of reagents, expensive starting materials and low yields.

Halo derivatives of *p*-toluene sulfonamide are used as nitrene sources for aziridination of various olefins. Bromamine-T has been reported to be superior to chloramine-T as nitrene source. Use of bromamine-T for aziridination of olefins under homogenous conditions in the presence of Cu (I) and Cu (II) salts has been already demonstrated.

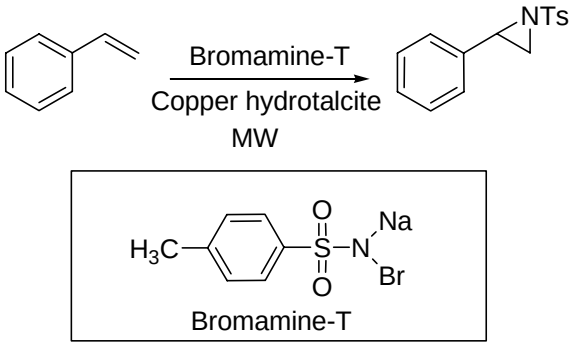


Chloramine-T; X = Cl
Bromamine-T; X = Br

Use of heterogeneous catalysts brings advantages in respect of easy separation, environmental safeguard, high turnover number, better selectivity, catalytic amount and avoidance of corrosion. Several metal-exchanged zeolite Y (Zn^{2+}, Ni^{2+}, Fe^{3+}, Mn^{2+}, Co^{2+}, Cu^{2+}) as heterogeneous catalysts have been studied for aziridination of olefins. Chelated manganese and iron metal complexes on a polymer support and bromamine-T as a source of nitrene are reported for aziridination of olefins. Use of microencapsulated copper (II) acetylacetonate [$MCCu(acac)_2$] and heterogeneous alumina supported copper nano particles as heterogeneous catalyst are also reported in the literature. Copper hydrotalcite has found applications as catalyst in reactions like hydroxylation and amination etc. However it has not been used for aziridination of olefins.

Microwave assisted chemical transformations have gained importance in recent years. The main advantages of using microwaves in organic synthesis are to shorten the reaction time dramatically and suitability on small to medium scale. These reactions are conducted in few minutes with complete safety in open vessel at ambient pressure in domestic microwave oven. Although there are a number of reports about various reactions under microwave conditions, aziridination under microwave irradiation in the presence of heterogeneous catalyst has not found mention in the literature.

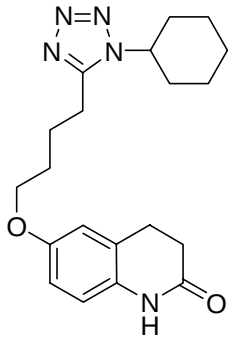
The thesis reports development of a methodology where copper hydrotalcite was used as heterogeneous catalyst and bromamine-T as a nitrogen source for aziridination of olefins under microwave irradiation.



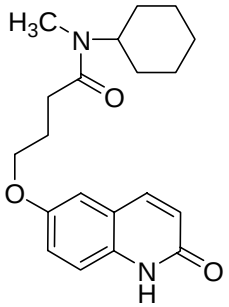
The yields were found to be comparable to normal aziridination conditions and at times better than those with other heterogeneous catalysts used for aziridination. A detailed study was carried out with respect to reaction conditions and substrate scope. Catalyst recycle study was also carried out with practically consistent yields of aziridines.

Chapter 2: Synthesis of 3-Substituted 2(1*H*)-Quinolinones Catalyzed by Hydrotalcite like Anionic Clays

2(1*H*)-Quinolinone moiety is an important structural unit present in many biologically active molecules such as cilostazol, cilostamide, aza-calanolide, etc. Ischemic diseases such as myocardial infarction, unstable angina and cerebral infarction are caused by an arteriostenosis which is led by chronically formed vascular intimal thickening and acutely formed thrombus in the vessels. Both Cilostazol, an anti-thrombotic agent, and**,** Cilostamide a potent platelet aggregation inhibitor and anti-hyperplastic agent, possess 2(1*H*)-quinolinone as core moiety and drugs like Repirinast (antiallergic), Procaterol and Rebamipide (ulcer therapeutic) also possess quinolinone in their core structure.

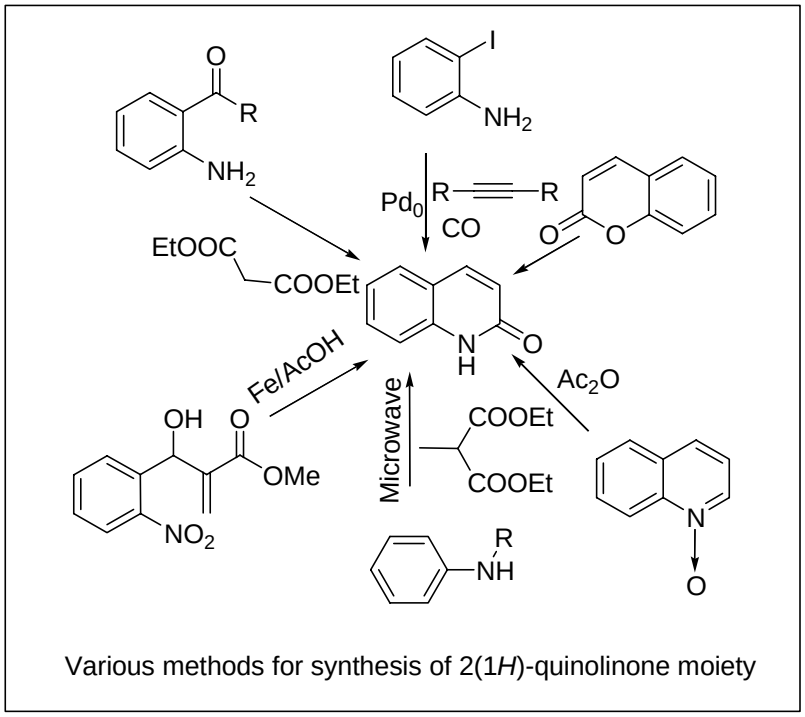


Cilostazol



Cilostamide

Some of the methods reported for synthesis of 2(1*H*)-quinolinones are schematically depicted below.

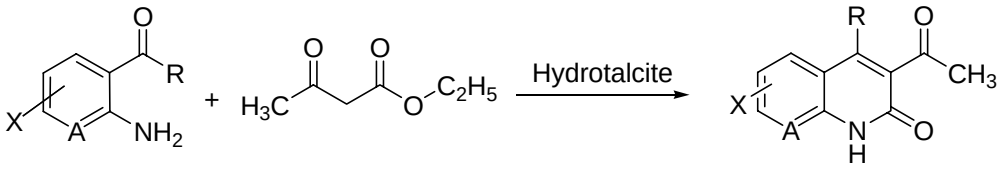


Various methods for synthesis of 2(1*H*)-quinolinone moiety

The classical methods of synthesis of 2(1*H*)-quinolinones include a base-catalyzed intramolecular aldol condensation, Friedlander synthesis, Camps modification of the Friedlander synthesis and an acid catalyzed cyclization of 3-ketoanilides i.e. Knorr synthesis. Recent methods include use of Baylis Hillman adduct and various palladium catalysed routes for wide variety of substituted 2-quinolinones. These synthetic methods have limited utility and drawbacks of low yield and laborious work up. Several other

methods for synthesis of 3,4-disubstituted 2(1*H*)-quinolinones such as the titanium-promoted intermolecular reductive cyclization of *N*-(2-acylphenyl) alpha ketoamides, the $AlCl_3$ promoted annulation of terminal and internal alkynes and the oxidation of 2-cyanostyrene with *m*-CPBA have also been reported in the literature. The yields of these processes however are often low.

In present work, hydrotalcites, which are extremely useful as base catalysts in synthetic organic chemistry, have been successfully used for synthesis of 3-substituted-2(1*H*)-quinolinones with high and consistent yields. The catalysts were recycled with practically consistent yields of 2(1*H*)-quinolinones.



X = Cl, Br, OCH_3

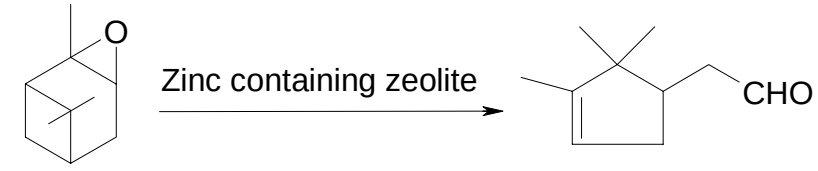
A = CH, N

R = CH_3, OCH_3

Chapter 3

Section I: Application of Modified Zeolite Beta Catalyst in the Rearrangement of α-Pinene Oxide to Campholenic Aldehyde

This section of Chapter 3 reports study towards synthesis of campholenic aldehyde by rearrangement of α-pinene oxide, using a new modified zinc containing zeolites (Y-type and β-type).



Pinene oxide Campholenic aldehyde

Following parameters were studied for optimum results using both the catalysts.

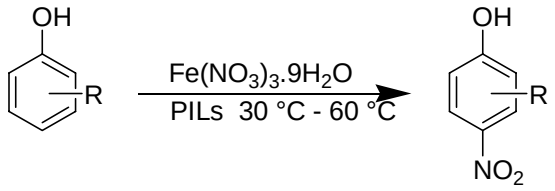
1) Effect of catalyst load (Y-type and β-type zinc containing zeolites) on conversion of pinene epoxide and selectivity towards campholenic aldehyde.
2) Optimum temperature required for maximum conversion and selectivity.
3) Effect of catalyst load (β-type) on conversion and selectivity when reactions were carried out under pressure with constant RPM.
4) Optimum catalyst loading required for maximum conversion and selectivity at atmospheric pressure and under pressure.

Campholenic aldehyde is an important and useful industrially fragrance intermediate used in particular for preparation of sandalwood like fragrances. Industrially synthesis of campholenic aldehyde is carried out by employing zinc halides as homogeneous catalysts. This method has severe drawbacks like poisoning of bacteria in sludge treatment by metal catalysts and contamination of water by the zinc salts etc. In addition, the workup procedures are generally difficult and more expensive. Various heterogeneous catalysts are also reported for rearrangement of α-pinene oxide to campholenic aldehyde. Following are different catalysts reported in literature for rearrangement of α-pinene oxide to campholenic aldehyde.

Catalyst	**Conversion**	**Selectivity**
$ZnBr_2$	>95%	80%
$ZnCl_2$	>95%	70%
p-TSA	70%	24%
$BF_3.Et_2O$	>90%	73%
$H_3PW_{12}O_{40}$	86%	62%
$Zn(CF_3SO_3)_2$	85%	75%
B_2O_3/SiO_2	>85%	69%
$ZnCl_2$/MCM-41	26%	85%
HY Zeolite	>95%	75%
Ti molecular sieves	96%	82%
Ti β-zeolite: Liq. Phase Vap. phase	29% 95%	81% 65%
H-US-Y	>90%	75%

The present work demonstrates application of Zinc containing zeolites for the first time in the rearrangement of α-pinene oxide to campholenic aldehyde with high yield and excellent selectivity.

Section II: Regioselective Nitration of Phenols with New Phosphorus Based Ionic Liquids



Nitration of aromatic compounds is an important unit process in industry and the nitro compounds find wide use in dyes, pharmaceuticals, perfumes and plastics. Conventional nitration process requires concentrated acids, which make downstream process expensive and tedious. Survey of literature provided light to various eco-friendly processes and researchers came up with different nitrating species and conditions. A wide variety of homogeneous and heterogeneous catalysts were invented in last decade for the development of green and clean processes.

Nitration of phenols has always been challenging as it lacks selectivity in the conventional processes. Among the nitrating agents employed, metal nitrates either alone or supported on solid matrices enjoyed considerable importance. Nitration of phenol using hydrated ferric nitrate as nitrating agent with imidazolium based ionic liquids is reported recently. Excellent regio-selectivities were found to be obtained when the reaction was carried out at ambient conditions.

Phosphonium ionic liquids are much more thermally stable than the corresponding imidazolium salts and even have an edge over imidazolium salts. Imidazolium ionic liquids contain C-2 proton which is reactive and acidic resulting in carbene formation. Phosphonium salts, on the other hand, have no such acidic protons. Also alkylphosphonium salts are, in general, less dense than water and can be beneficial in

product work-up steps. Imidazolium salts, on the other hand are denser than water. Thus phosphonium ionic liquids are good candidates in the nitration of phenols.

Nitration of aromatics using nitric acid in phosphonium ionic liquids is already demonstrated with excellent results. Nitration of phenols using hydrated ferric nitrate as nitrating agent in phosphorous based ionic liquids in particular phosphonium ionic liquids (PILs) was studied. Excellent *p*-selectivity was observed making this method a very convenient one for *p*-nitrophenols. The section demonstrates utility of phosphonium ionic liquids in nitration of phenol with excellent *para* selectivity.

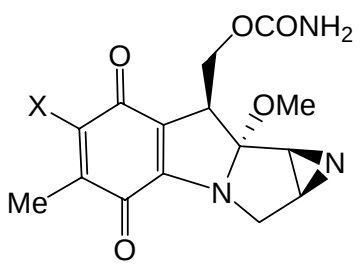
CHAPTER 1

COPPER HYDROTALCITE CATALYZED SYNTHESIS OF AZIRIDINES UNDER MICROWAVE IRRADIATION

Part I: Aziridination: A Brief Review

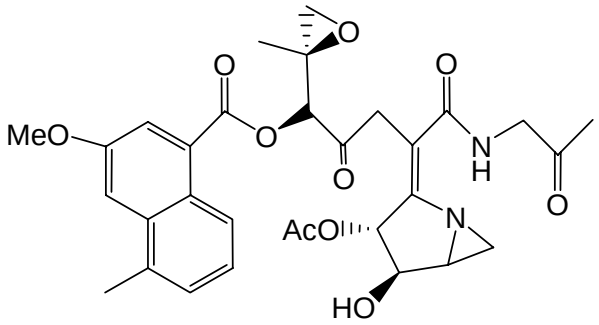
Introduction

Aziridines are three-member nitrogen containing heterocycles. The inherent reactivity of aziridine is due to its ring strain energy (SE), which is 26.7 Kcal/mole for unsubstituted aziridines.[1] Significance of this nitrogen containing heterocycle is due to its presence in several natural products such as mitomycin (**1**), porfiromycin (**2**) and azinomycin (**3**) which are potent antitumor and antibiotic agents.[2-6]



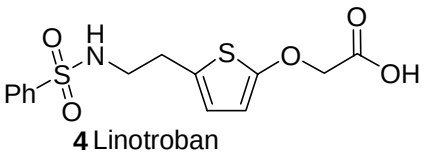
1 X= OMe, Mitomycin A

2 X = NH_2, Porfiromycin

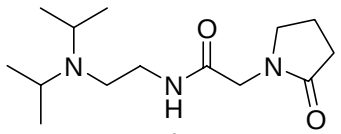


3 Azinomycin A

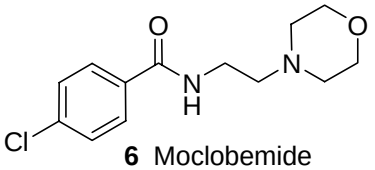
In addition to their utility as synthetic end products, aziridines are also important as intermediates in the synthesis of drugs such as linotroban (**4**), pramiracetem (**5**), moclobemide (**6**) etc.



4 Linotroban

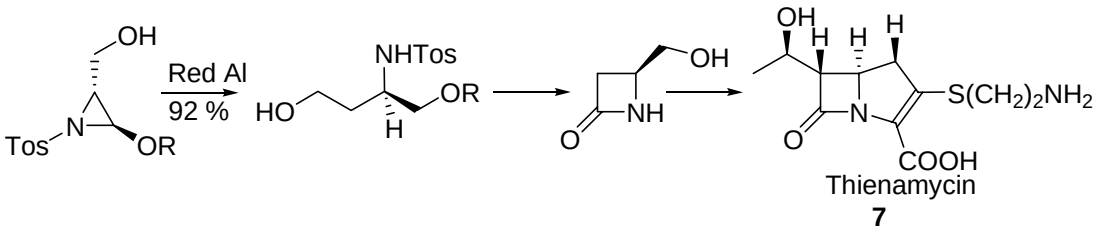


5 Pramiracetem



6 Moclobemide

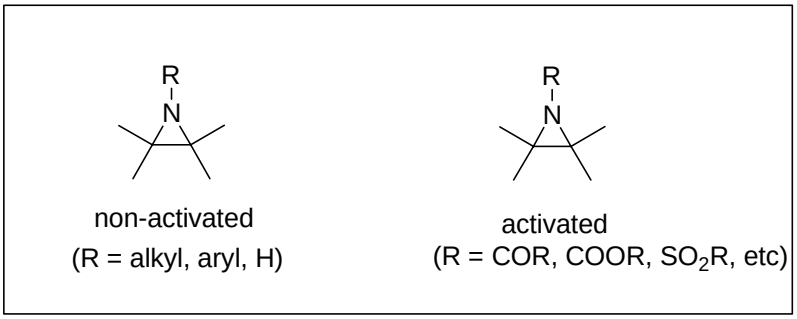
Aziridines have been synthetic targets as well as building blocks in synthesis since Gabriel's discovery (1888) of this smallest nitrogen containing heterocycle. Chiral aziridines are also attractive building blocks in organic synthesis and have been applied to the total synthesis of several natural products including alkaloids, amino acids, amino sugars and their derivatives and β-lactam antibiotics. For example Oppolzer and Flaskamp[7] used chiral aziridne in an enantioselective synthesis of alkaloid pumilotoxin-C, whereas thienamycin **7,** a carbapenem antibiotic, has been synthesized from aziridinyl alcohol *via* regio- and stereoselective ring opening using Red-Al ([$(CH_3OCH_2CH_2O)_2$ AlH_2]Na) as the hydride donating agent[8] (**Scheme 1**).



Scheme 1

Ring opening reactions of aziridines

In considering the ring opening reactions, aziridines may be divided into two main groups, according to nature of substituent present on the nitrogen atom. Non-activated or simple aziridines are generally unsubstituted or possess alkyl or aryl N-substituent and usually undergo ring opening reactions after protonation, quaternisation or formation of Lewis acid adduct. Activated aziridines contain substituents which are capable of stabilizing the developing negative charge on the nitrogen atom during nucleophilic ring opening.



In terms of synthetic transformations their utility comes from selective ring opening reactions.[9] Various nucleophiles such as carbon, sulfur, nitrogen, oxygen and halogens can be used for ring opening reactions of aziridines, whereas hydrogenation of aziridines in presence of palladium catalyst is widely used to cleave C-N bond.[10]

Chiral aziridines readily undergo regio and stereoselective ring opening to relieve ring strain, allowing access to a predictable α or β products. The increase in synthetic accessibility of chiral aziridines has propelled their use in ring opening reactions in organic synthesis.[2,11,12]

In addition, aziridines can function as sources of chirality in stereocontrolled reactions and have found use both as ligands and auxiliaries in asymmetric synthesis.[13,14] Metallation at a ring carbon atom allows aziridines to be used as chiral reagents for asymmetric synthesis. Enantiopure aziridines have found a new role as chiral ligands in enantioselective dihydroxylation and cyclopropanation reactions and for palladium catalyzed allylic substitution reactions.

Literature on chemistry of aziridines is extensive; however, catalytic aziridination reaction has so far received little attention. Comprehensive reviews by Tanner[3] and Sweeney and Osborn[2] deal mainly with non-racemic aziridines along with their use in stereoselective transformations. Another review by Ibuka[15] describes the aza-Payne rearrangement of N-activated 2-aziridinemethanols, to give the corresponding epoxy sulfonamides in high yields.

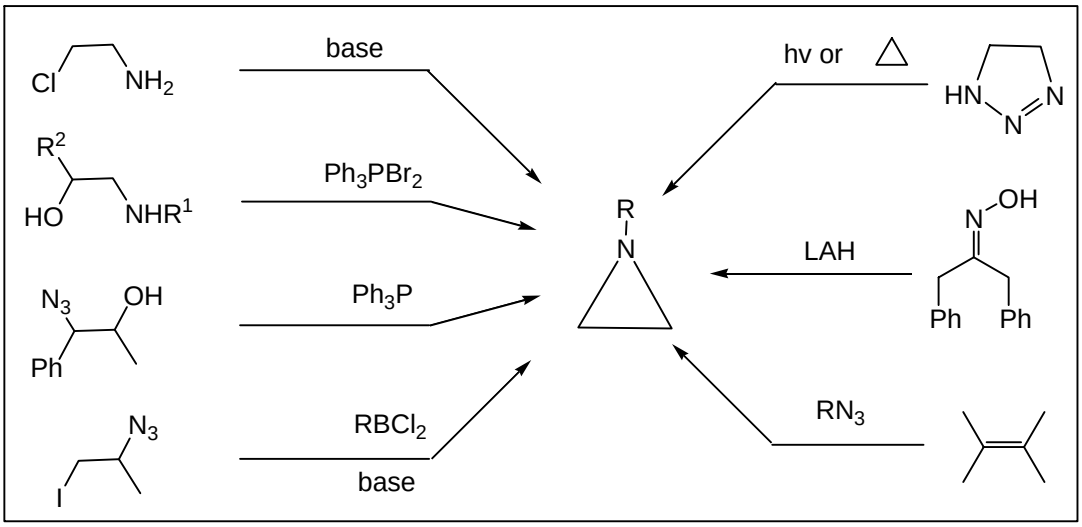
A recent review by Muller *et al.*[14] mainly focused on catalytic asymmetric methods for synthesis of aziridines based on formal nitrene transfer to olefins and carbene transfer to imines. This review is, therefore, intended to serve as an update to the previous reviews. In this review an attempt has been made to present and analyze the

reports of catalytic aziridine synthesis developed by several workers with respect to choice of reagents, metal catalyst variation, mechanistic consideration, stereochemical outcome and various heterogeneous methods useful as green technology for future development of synthesis of aziridines.

Synthesis of aziridine by indirect methods

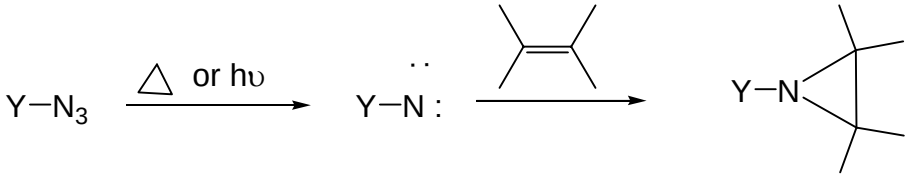
For a better understanding of the subject, a brief overview of the conventional methods of synthesis of aziridines and their intrinsic disadvantages is provided in the following section. **Scheme 2** depicts the known methods in literature for preparation of aziridines[2]. 2-Chloroethylamine when treated with base gives aziridines. β-Amino alcohols give aziridines when treated with triphenylphosphine dibromide in the presence of triethylamine with inversion at the OH carbon indicating that an S_N2 mechanism is involved. Epoxides react with sodium azide to give β-azido alcohols, which are readily converted to aziridines in the presence of triphenyl phosphine. β-Iodo azides can be reduced to aziridines with LAH or converted to *N*-alkyl or *N*-arylaziridines by treatment with an alkyl or aryl dichloroborane followed by treatment with a base. In both the cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure follows. Darzens glycidic ester condensation has been extended to the formation of analogous aziridines by treatment of an imine with α-halo ester or α-halo-*N*,*N*-disubstituted amide in the presence of *t*-BuOK and 1,2-dimethoxyethane. Aziridines can also be prepared by the extrusion of nitrogen from triazolines.

In this process, side reactions are very frequent and some substrates do not undergo the reaction at all. In general photolysis gives better yield. Both aldoximes and ketoximes can be reduced to primary amines with LAH. With certain oximes (e.g. those of type $ArCH_2CR$= NOH), treatment with LAH gives aziridines.



Scheme 2: Synthesis of aziridines by indirect methods

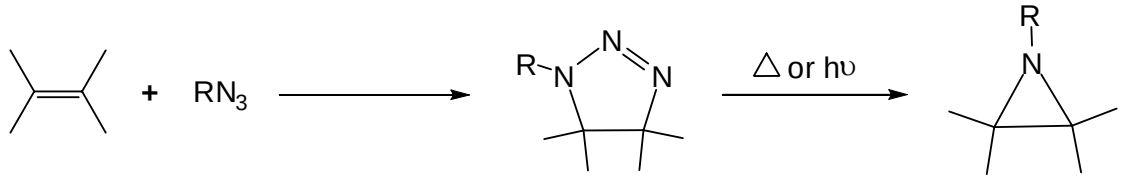
A single step route to synthesis of aziridines *via* a single metal atom transfer to olefins is the most atom efficient method of their preparation. While this process is well established in the case of epoxides, it is relatively less known and less developed for the nitrogen counterpart. The classical one-step approach to their preparation is *via* the thermal or photochemical decomposition of a mixture of the substrate and azides. The reaction can take place by at least two pathways. In one, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition. When the decomposition is carried out in the presence of an alkene, the corresponding aziridine is obtained (**Scheme 3**).



Scheme 3

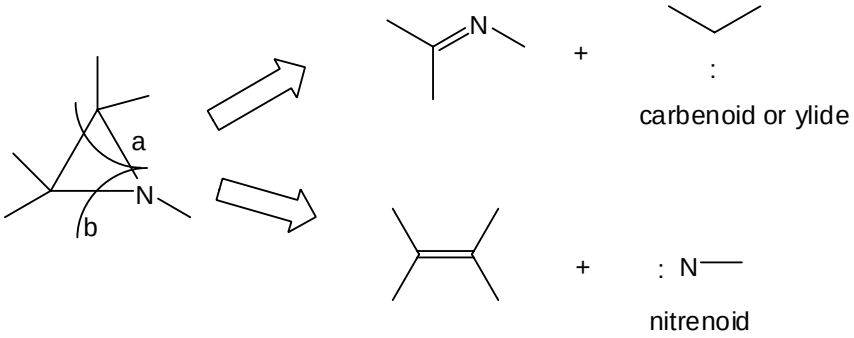
In the other pathway depending upon the nature of the organic azide and of the alkene, as well as reaction conditions, a 1,3 dipolar cycloaddition can occur to give 4,5-dihydro-1,2,3- triazoles. Most of the dihydrotriazoles are isolated and successively

decomposed to aziridines either thermally or photochemically. However sometimes the dihydrotriazoles are unstable and the aziridines are obtained directly (**Scheme 4**).



Scheme 4

All the above-mentioned methods, being indirect methods, involve laborious multi-step reactions with inherent drawbacks like side reactions and low yields. The simplest one step route to aziridine synthesis is the transition metal catalyzed single atom transfer to olefins. There are two general approaches to this, (a) addition of a carbene moiety to imine and (b) nitrene addition to olefins.



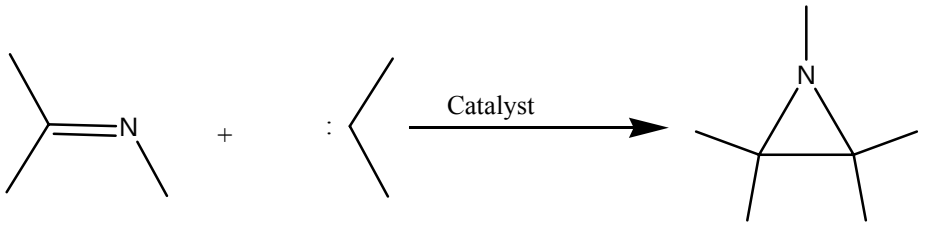
Thus a simple and straightforward approach to the synthesis of aziridines can be accomplished by either the modification of the carbon-nitrogen bond or the carbon-carbon double bond.

Modification of carbon-nitrogen bond

Comprehensive literature survey revealed that there are four methods for direct aziridination with C=N bond *viz*. the carbene approach, the aza-Darzen reaction, Lewis acid catalysis and the recent ylide approach.

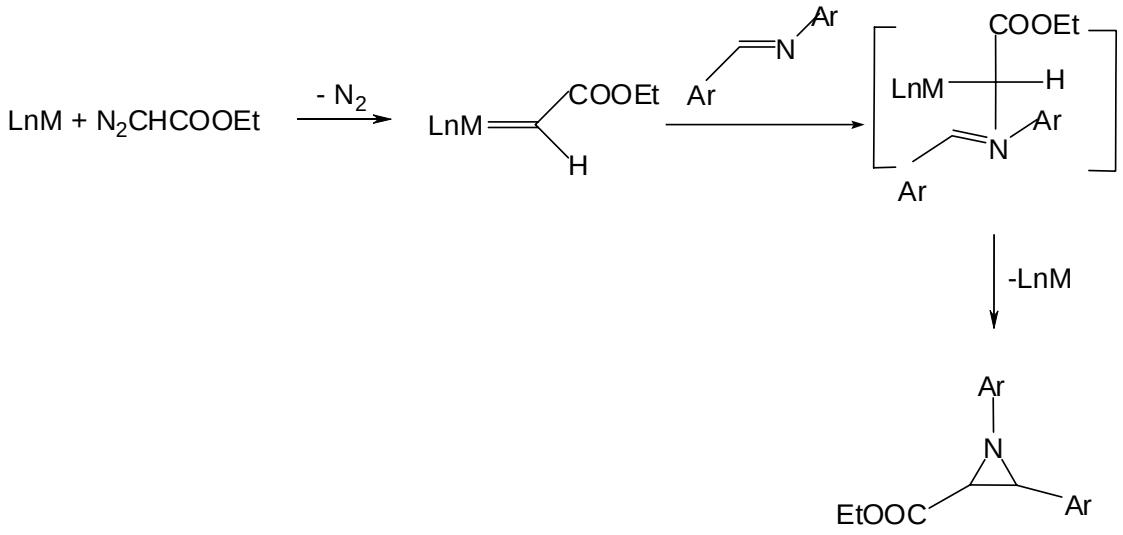
Synthesis of aziridines *via* carbene addition

The reaction of imines with a carbene donor in the presence of a metal complex as a catalyst is a new entry for the formation of aziridines (**Scheme 5**).



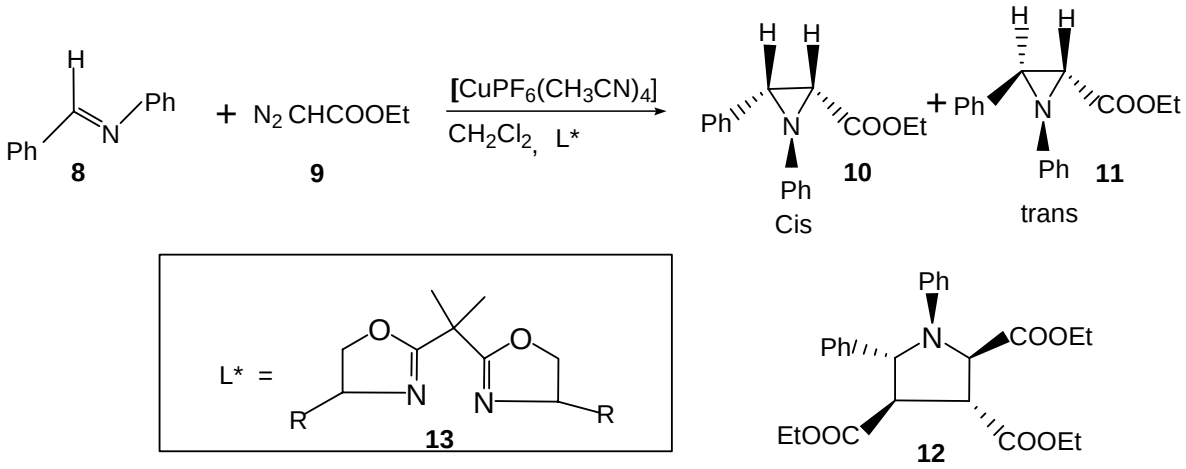
Scheme 5

Aziridine formation by the reaction of imines with diazo compounds, such as ethyl diazoacetate (EDA), as the carbene donor fragment in the presence of a metal complex can take place by two different reaction paths. The metal complex first reacts with EDA followed by elimination of N_2 resulting in metal carbene complex, which in turn transfers the carbene fragment to the imine to form the corresponding aziridines (**Scheme 6**).



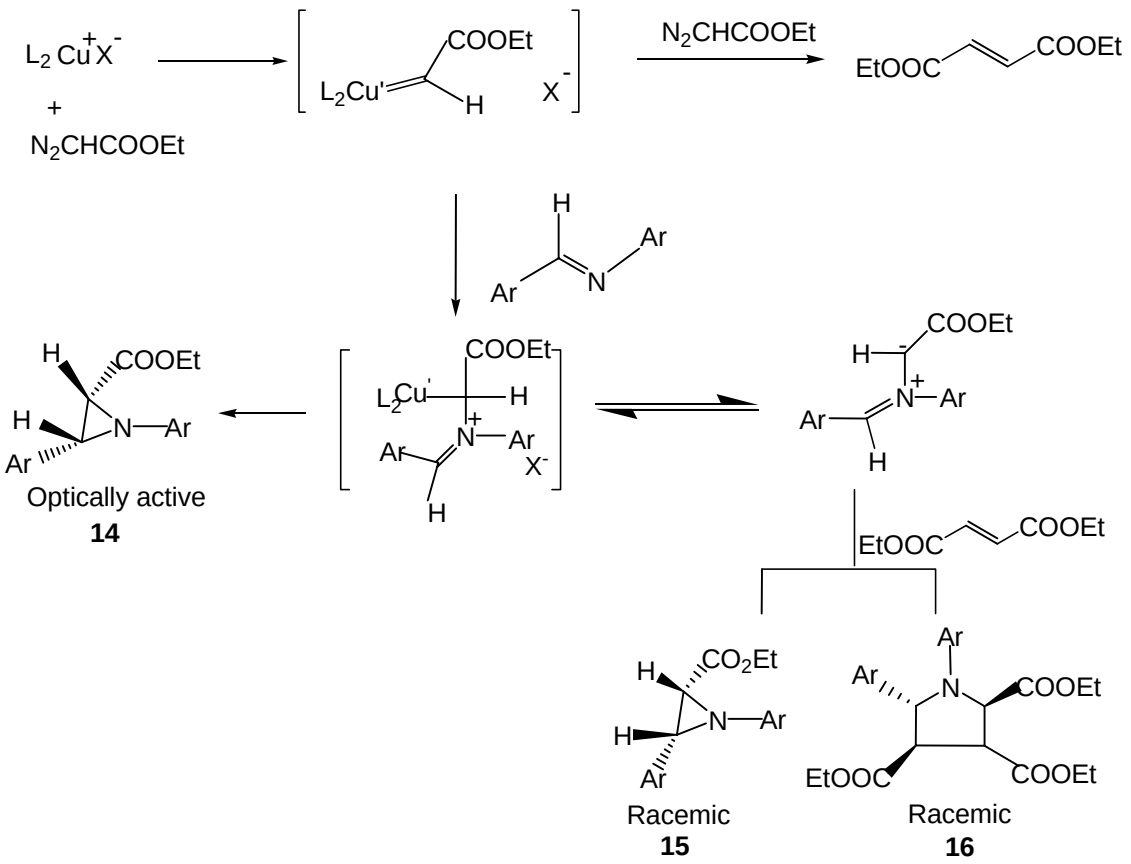
Scheme 6

The route involving carbene transfer to imines to form optically pure aziridines was first reported by Jacobsen.[16] Reaction of imines with EDA catalyzed by chiral Cu (I) bis (dihydroxazole) **13** complexes produces aziridines in moderate yields and ee's. Thus treatment of *N*-benzylidene aniline **8** with ethyl diazoacetate **9** in the presence of copper (I) hexafluorophosphate {$Cu(PF_6)(CH_3CN)_4$} and ligand resulted in the formation of enantiomerically enriched aziridine as a mixture of two diastereomers, **10**, **11** and racemic pyrrolidine **12** (**Scheme 7**).



Scheme 7

The reaction was studied further and a plausible mechanism was also given. A transient bis (hydroxazole) copper carbene complex was proposed which reacts either with diazoester to form a mixture of diethyl maleate and fumarate or with imine nitrogen lone pair to form a metal complexed azomethine ylide. The complexed ylide may undergo intramolecular ring closure to form the aziridine **14** enantioselectively (**Scheme 8**).



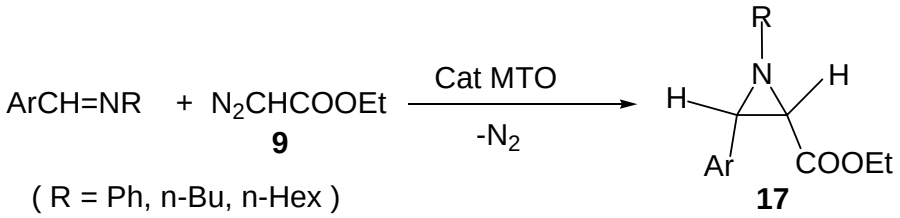
Scheme 8

Alternately, it can reversibly dissociate from the metal-ligand complex. The free azomethine ylide can then undergo either dipolar cycloaddition with diethyl fumarate to generate racemic pyrrolidine **16** or intramolecular cyclization to form racemic aziridine **15**.

This method thus outlined offers an extremely direct strategy for the synthesis of enantiomerically enriched *N*-aryl aziridines and consequently *N*-aryl amino acids, albeit in moderate yields. Jorgenson and Rasmussen were able to increase the yield of aziridine to 80-90 %, using $Cu(OTf)_2$ in combination with (-)-menthyl diazoacetate or (R)-(+)-2,2'-isopropylidene bis(4-phenyl-2-oxazoline), but enantioselectivities were moderate.

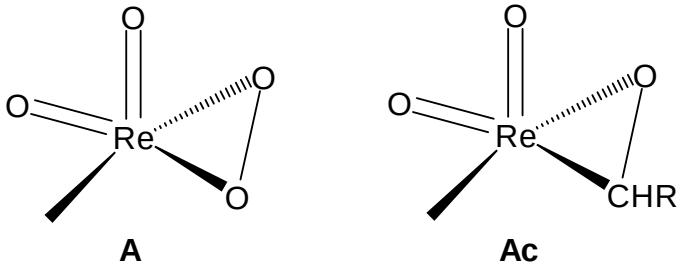
Espenson[17] reported reaction of imines with EDA catalyzed by methyl rhenium trioxide MTO or CH_3ReO_3. MTO has wide applications in catalysis, including epoxidation, metathesis of olefins, aldehyde olefination and oxygen transfer. A catalytic

amount of MTO with ethyl diazoacetate (EDA) converted aromatic imines to aziridines **17** (**Scheme 9**).



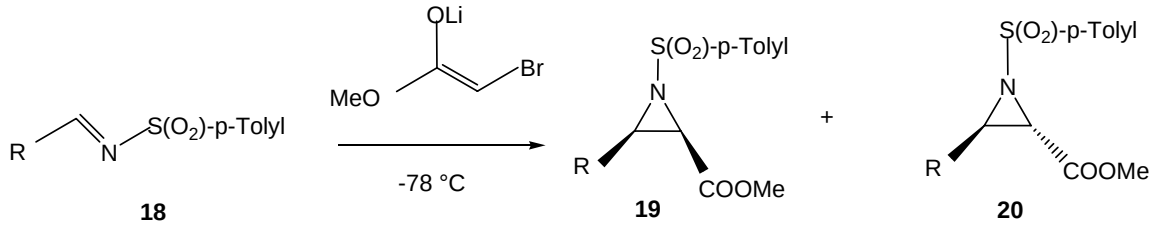
Scheme 9

Synthesis of aziridine proceeded conveniently and in high yields under anaerobic conditions and the only by-product observed was diethyl maleate (5%). The mechanism for the transformation was not given in detail but a metal carbene intermediate **Ac**, similar to the well studied peroxide system **A**, was thought to be involved.



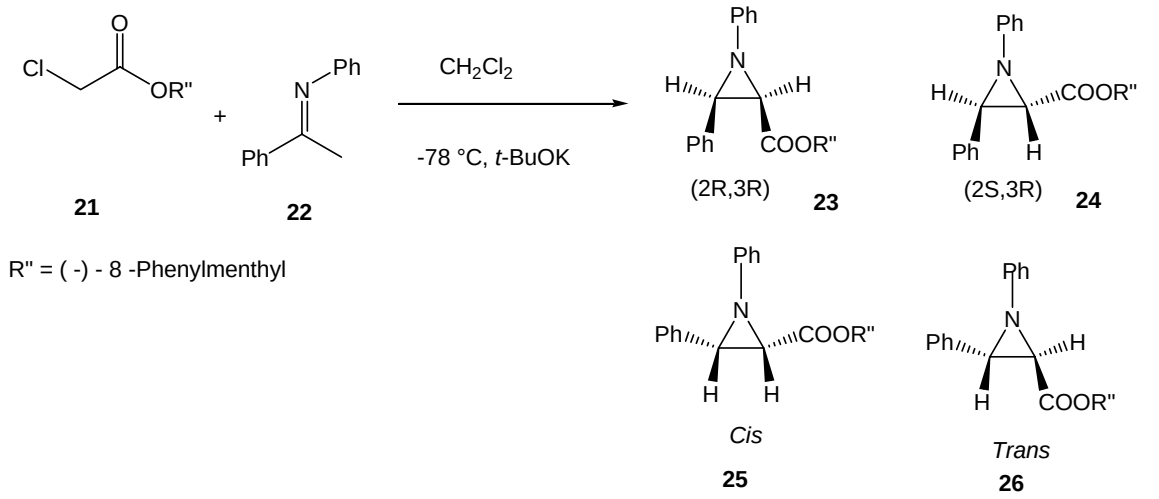
***Aza*-Darzen's approach**

Darzen type synthesis of racemic aziridines is known in the literature[11] and has been reviewed earlier. However asymmetric synthesis of aziridines *via* Darzen's reaction has been recently reported by Davis *et al.*[18] who developed a one pot asymmetric synthesis of *N*-(*p*-toluenesulfinyl)-2-carbomethoxy aziridines **19, 20** *via* Darzen's reaction of lithium enolate of methyl bromoacetate with enantiopure sulfinimines **18** (**Scheme 10**). In each case the *cis*-aziridine **19** was formed exclusively and this *cis* selectivity was explained by the transition state geometries of the enolate and sulfinimine.



Scheme 10

In a recent report by Ohkata *et al.*[19] asymmetric Darzens condensation of benzaldehyde and various ketones has been investigated using chiral auxiliaries such as (-)-menthyl and (-)-8-phenylmenthyl groups as the ester moiety. The aza-Darzens reaction of (-)-8-phenylmenthyl α-chloroacetate **21** with *N*-benzylideneaniline **22** afforded aziridine in 40 % yield as a stereoisomeric mixture **23-26**. The *cis*/*trans* selectivity was 1.5:1 and the diastereoselectivity of the *trans* aziridine was high (>80 % e.e) as shown in **Scheme 11**.

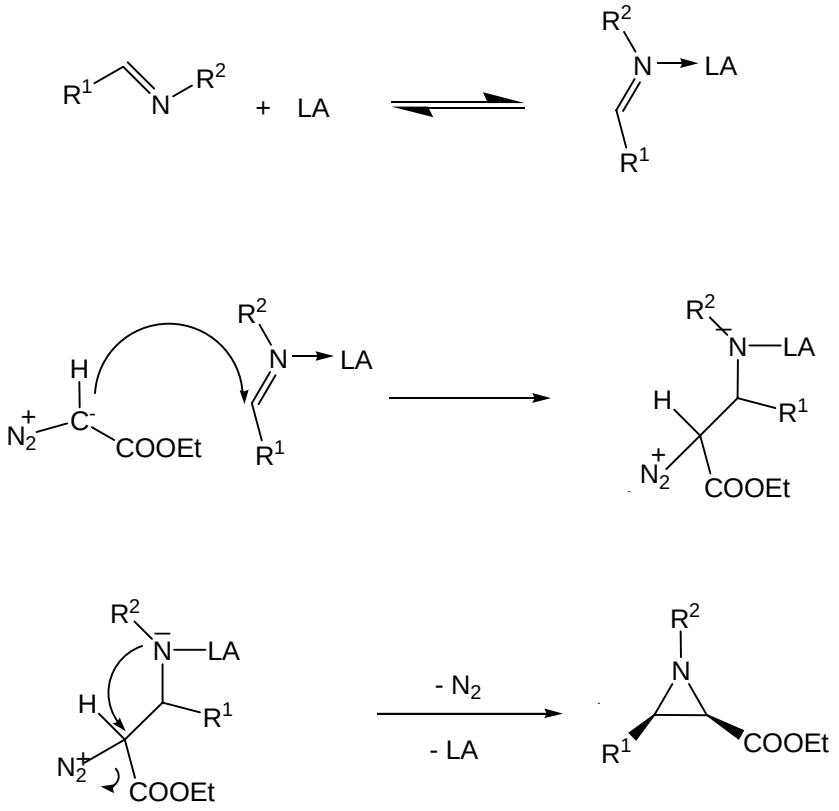


Scheme 11

Lewis acid approach

This approach involves the "activation of the imine by the metal", the latter now acting as the Lewis acid. The co-ordination of the imine to the Lewis acid, activates the imine for a nucleophilic attack by EDA at the carbon atom leading to an intermediate,

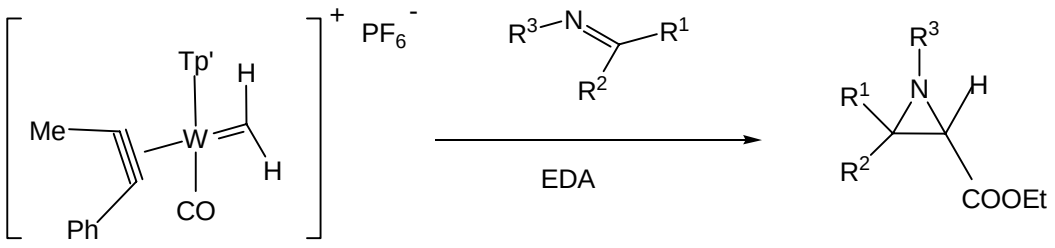
which undergoes subsequent ring closure and loss of nitrogen to provide aziridines (**Scheme 12**).



Scheme 12

A wide range of Lewis acids was found to be effective as catalysts for aziridination of imines, such as $SnCl_4$,[20] methylrhenium trioxide,[21,22] tungsten (II) methylene complex,[23] iron Lewis acid $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]^+[BF_4]^-$,[24] lanthanide triflates,[25] $[InCl_3]$[26] and $[Mo(OTf)(\eta^3\text{-}C_3H_5)(CO)_2(phen)]$.[27]

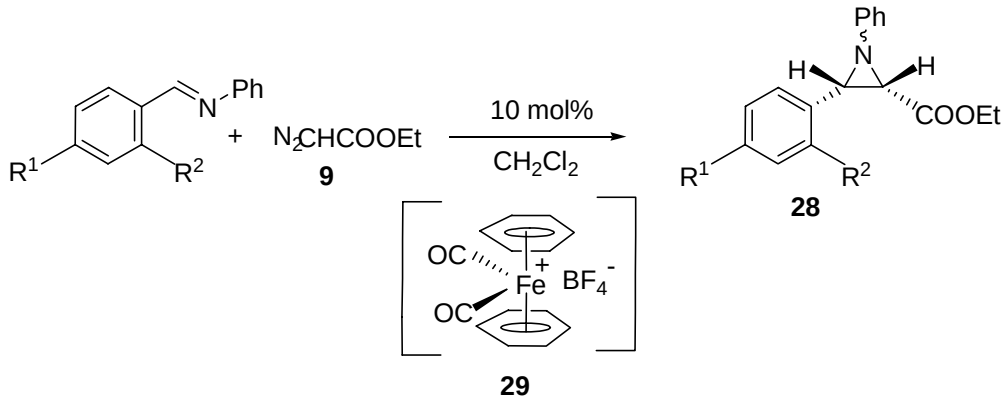
Templeton and co-workers also synthesized[28] [Tp′ (CO) (PhC_2Me) $W{=}CH_2$] $[PF_6]$ (Tp′= hydrotris (3,5-dimethylpyrazolyl)borate) an electrophilic carbene complex **27** that binds nucleophiles and acts as a Lewis acid to activate imines towards nucleophilic attack by EDA (**Scheme 13**).



27

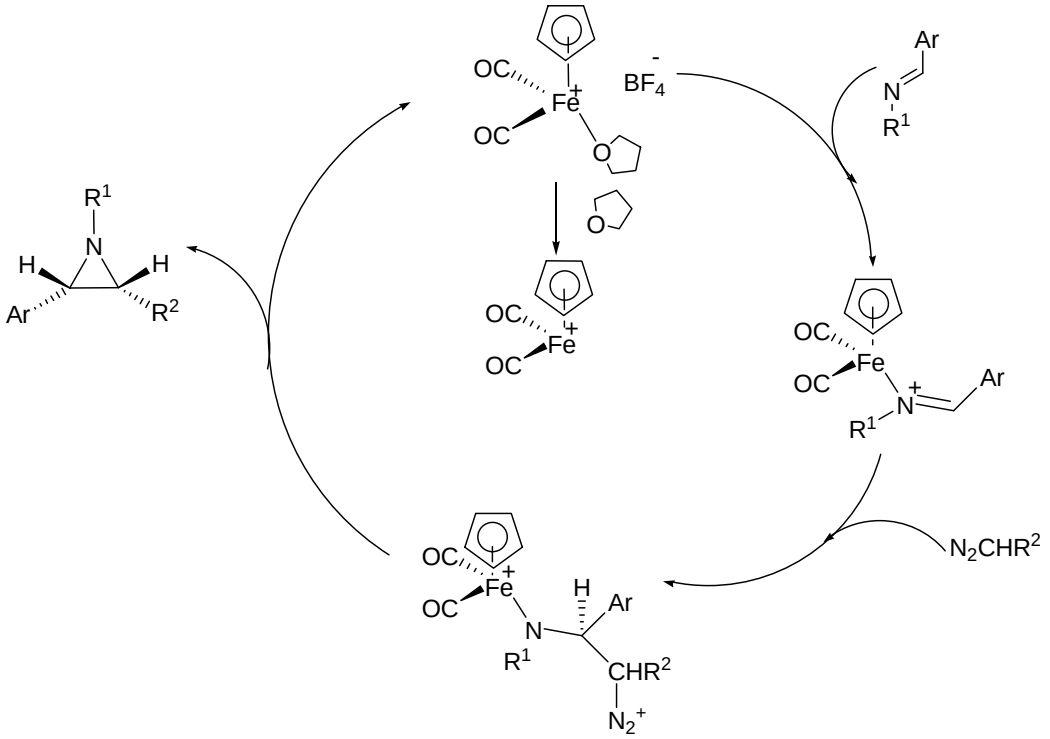
Scheme 13

Mayer and Hossain[29] developed a facile one step route to predominantly *cis* aziridines **28** using iron lewis acid $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)^+(BF_4)^-]^-$ **29** with yields upto 95 %, from compounds with a diazo functionality and a variety of substituted *N*-benzylidene imines with *N*-ayrl or *N*-alkyl groups (**Scheme 14**).



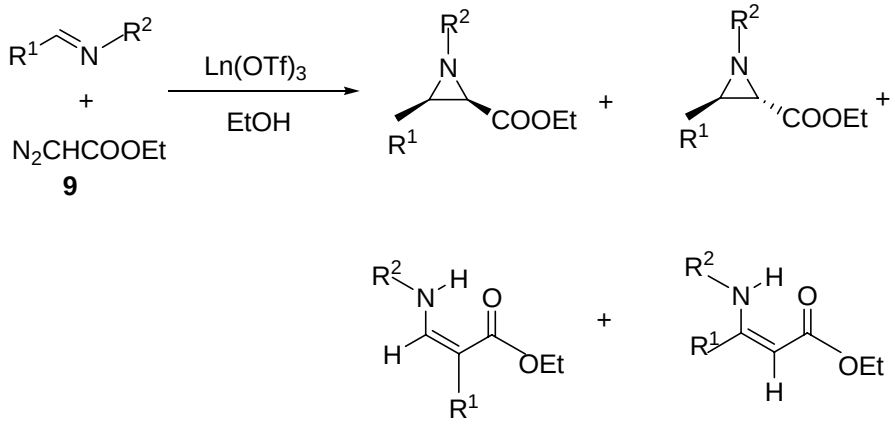
Scheme 14

The reaction mechanism is believed to proceed through an electophilic iminium ion intermediate. This mechanism was further corroborated by synthesis of iron Lewis acid-imine complex $(\eta^5(C_5H_5)Fe\ (CO)_2\ (PhCH{=}NPh)^+$ $[BF4]^-$ and its reaction with different diazo compounds to provide *cis*-aziridines (**Scheme 15).**



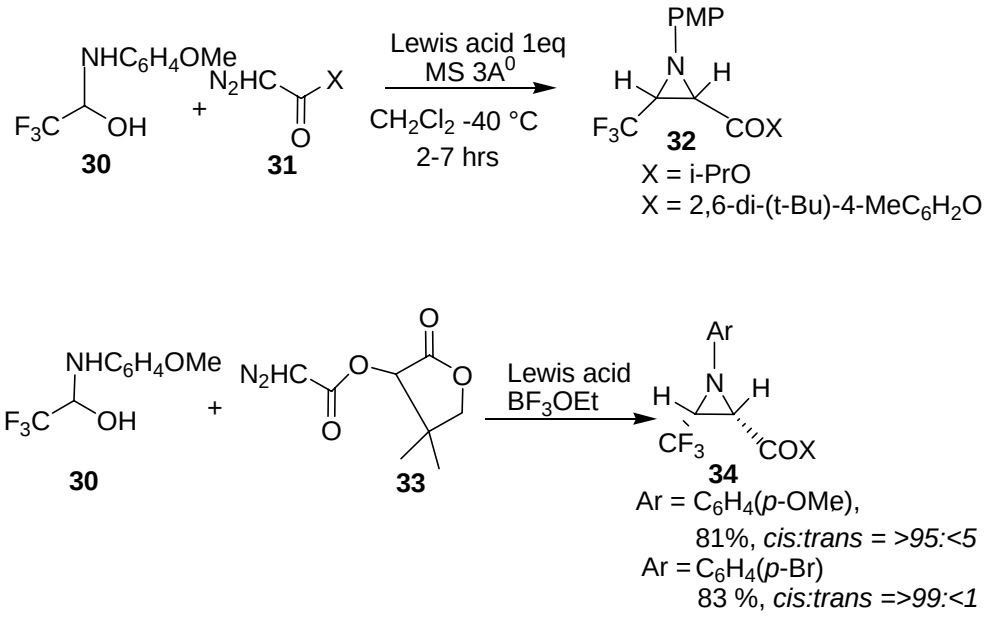
Scheme 15

Wang *et al*.[30] reported $Ln(OTf)_3$ catalyzed aziridination from imines and diazo compound in protic media. Use of protic solvents allowed for the use of $Ln(OTf)_3$ hydrates which are much less expensive than the anhydrous lanthanum salts. Reaction conditions were mild and selectively *cis*-aziridines were formed (**Scheme 16**).



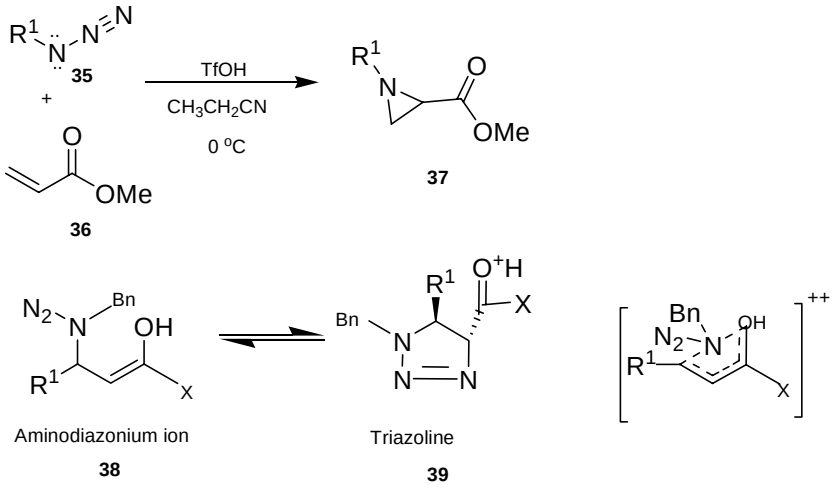
Scheme 16

In 2003, Akiyama *et al*.[31] reported streoselective synthesis of CF_3 substituted aziridine carboxylates **32** by treatment of trifluroacetaldehyde N,O acetal **30** in presence of $BF_3{\cdot}OEt_2$ or $SnCl_4$ as Lewis acids. Various substituted (X = i-Pro, *t*-BuO, 2, 4, 6-trimethyl phenoxy, phenyl) diazoacetates **31** were used for synthesis of aziridines **32**. Although lewis acid catalyzed aziridination of imine with diazoacetate generally gave enamines as side products, the N,O acetal **30** did not generate corresponding products and furnished cis aziridines in high yields. Use of 2,6-di-*t*-butyl-4-methylphenyl diazoacetate for aziridination was reported first time for *trans*-selective aziridination**.** Chiral synthesis of CF_3 substituted aziridines **34** was achieved with excellent diastereoselectivity by use of (R)-pantolactone **33** as chiral auxiliary (**Scheme 17**).



Scheme 17

Johnston *et al*.[32] reported new Bronsted acid promoting addition of azides **35** to activated olefins **36** to give corresponding aziridines **37** in good yields under mild and non-redox conditions. The addition of electron rich azides to electron deficient olefins may be promoted by aminodiazonium ion **38** intermediate by either direct conjugate addition or fragmentation of triazoline **39** (**Scheme 18**).



35 **36** **37** **38** **39**

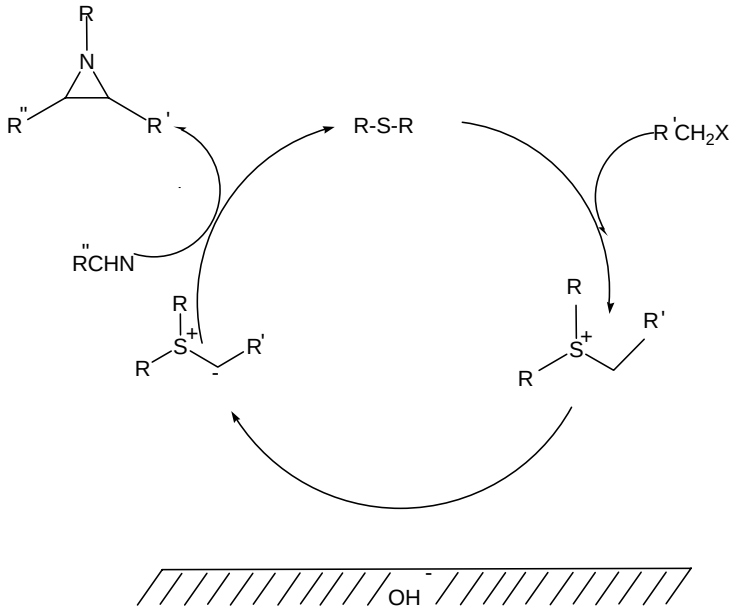
Scheme 18

Acetonitrile was identified as the most effective medium for aziridination and the yield was in the range of 79-92 %.

Ylide approach

Among various strategies starting from prochiral C=C and C=N bonds, aziridination through the reaction of an imine with a ylide i.e. ylide aziridination has recently shown great promise in obtaining various functionalized aziridines. Compared with other direct aziridinating reactions with a C=N bond, e.g., the carbene approach, the aza-Darzens reaction, and the Lewis acid method, the present ylide approach has several advantages. (a) There are a wide range of ylide reagents to choose from and most of them are easily accessible. (b) A variety of substrates, either aromatic or aliphatic aldimines or ketimines can be used. (c) The reaction conditions are generally mild, and the operations are simple. (d) The ylide precursor reagents are recyclable.

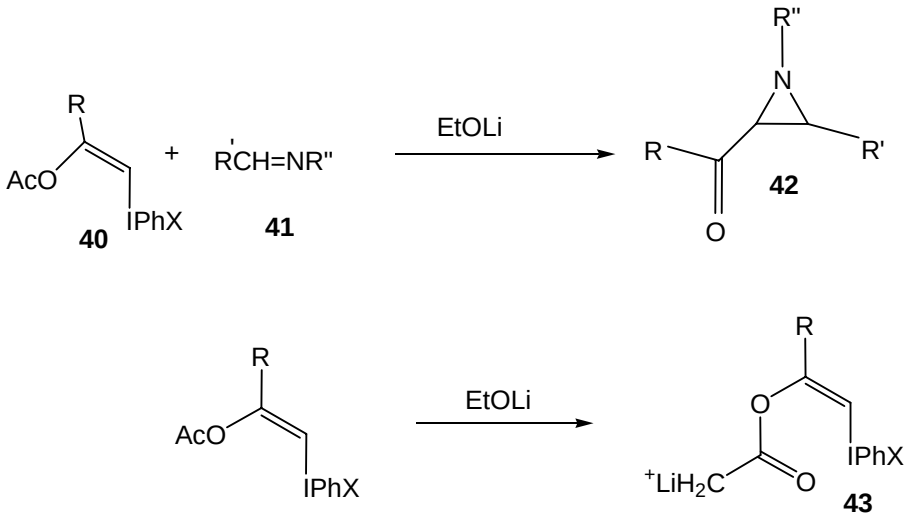
Aggarwal[33] developed a process for aziridination of imines utilizing diazo compounds and mediated by catalytic quantities of transition metals and sulfides. In the catalytic cycle, the diazo compound is decomposed by the metal, to give a metal carbenoid species, which reacts further with sulfur to give a sulfur ylide. This in turn reacts with the imine furnishing aziridine in high yield and returns the sulfide back to the catalytic cycle (**Scheme 19**).



Scheme 19

The process could be rendered asymmetric by the use of chiral sulfides in the catalytic process.

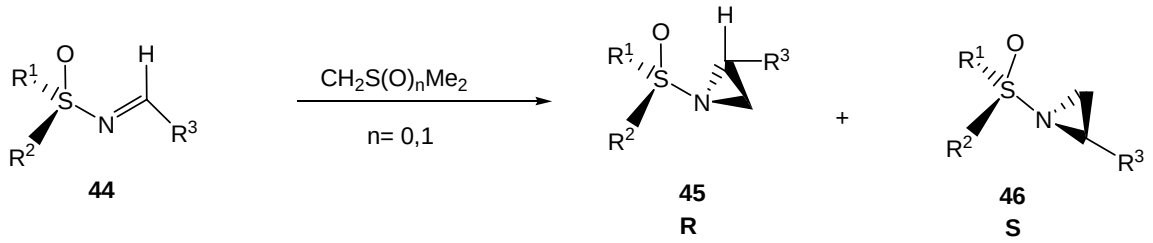
Ochiai and Kitagawa[34] generated monocarbonyl iodonium ylides **43** *in situ* from (Z)-2- (acetoxyvinyl) iodonium salts **40** *via* an ester exchange reaction with LiOEt. These ylides **43** undergo alkylidene transfer reaction to activated imines **41** yielding 2-acylaziridines **42** in good yields (**Scheme 20**).



Scheme 20

They demonstrated that the stereochemical outcome of this aziridination reaction was dependent on both the activating groups of the imines and the reaction solvents. Aziridination of *N*-(2,4,6-trimethylbenzene sulfonyl) imines in THF affords the *cis*-aziridines as a major product while that of *N*-benzoylimines in THF-DMSO or THF gives the *trans*-isomer stereoselectively.

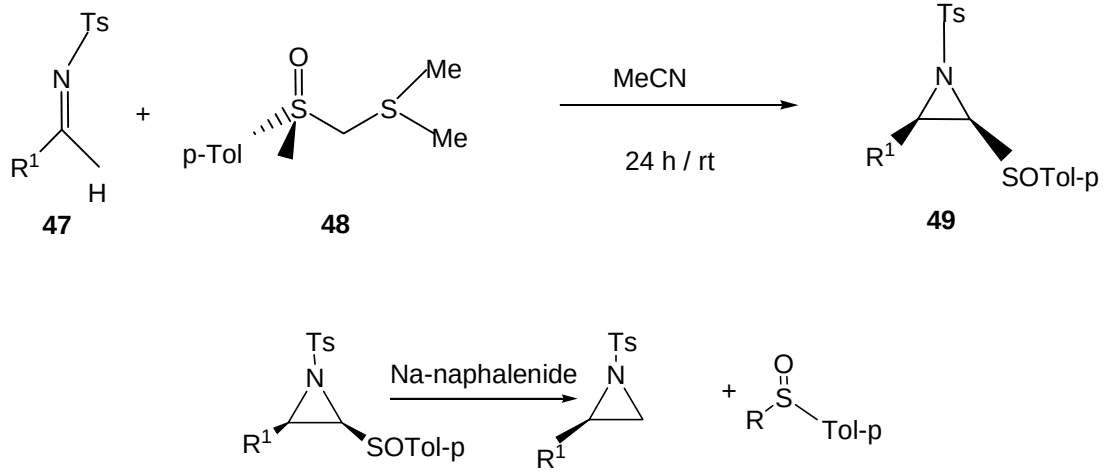
Ruano and co-workers[35] have recently described a simple method to prepare both enantiomers of chiral non-racemic aziridines based on reactions of *N*-*p*-tolylsulfinylimines **44** and sulfur ylides. The stereochemical outcome of the reaction could be inverted by using dimethyloxosulfonium methylide instead of dimethylsulfonium methylide. Asymmetric aziridination of *N*-sulfinylimines by use of *tert*-butyl sulfinyl group as the chiral auxiliary was also carried out by them. The asymmetric induction could be achieved in two ways depending upon a) chirality at the *tert*-butyl sulfinyl sulfur or b) nature of the methylene transfer reagent used. Both (R) **45** and (S)-aziridines **46** at C-2 were obtained in enantiomerically pure form in 75% yield after a single crystallization (**Scheme 21**).



Scheme 21

The effect of the increase of steric hindrance of the substituent, at the sulfinyl sulfur in the N-sulfinylimines on the diastereoselectivity of the aziridination reaction was evaluated. The tert-butylsulfinyl group was shown to be the best chiral auxiliary.

Midura[36] used (S)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide **48** for aziridination of *N*-tosyl imines **47**. For all the substituted *N*-tosyl imines studied the reaction afforded the desired *cis*-aziridines **49** as single diastereomers. The chiral sulfinyl substituent can be removed without ring opening using sodium naphthalenide (**Scheme 22**).



Scheme 22

Transformation of carbon-carbon double bond

Aziridines can be synthesized by a single nitrogen atom transfer to the olefin double bond, catalyzed by either transformation metal complexes or Lewis acids. Both metal nitrenoid or carbocation mechanism has been found to operate in these reactions.

Aziridination *via* nitrene transfer to olefins

Synthesis of aziridines by direct addition of nitrene moiety to alkenes is conceptually closest to the peracid epoxidation of alkenes and has been improved over recent years by the development of new, mild conditions for nitrene generation. The possibility of transferring nitrenes to olefins by means of transition metal catalyst was recongnized well before asymmetric catalysis was established. Early attempts using tosyl azide in conjugation with Cu(I) catalyst met only limited success. Gillmann *et al*.[37] reported inter and intramolecular C-H insertions by tosyliminophenyliodinane (TsN=I Ph) in presence of Mn (III) or Fe (III) porphyrins or $[Rh_2(OAc)_4]$.[38] Aziridination of olefins by TsN=IPh as nitrenes donor using Fe-Mn-porphyrins was developed by Mansuy *et al.*[39], while Graves and Takahashi[40] described the stoichiometric aziridination of olefins with an *in situ* generated (porphyrine) manganese-imido complex. These investigations prepared the grounds for synthetic catalytic transfer of nitrenes.

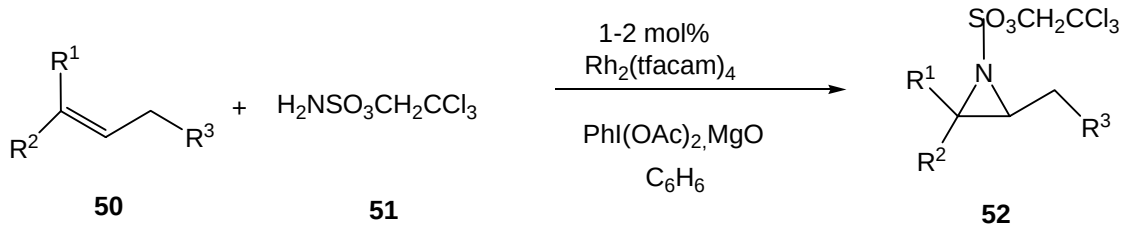
Since the development of copper catalyzed aziridination reaction employing [*N*-(*p*-tolylsulfonyl imino)] phenyl iodinane as nitrenes precursor by Evans *et al*.[41], numerous reports have appeared in this area. Dauban and Dodd[42] reported preparation and synthetic application of the [(*N*-(trimethylsilyl) ethane sulfonyl) imino] phenyl iodinane (PhI=NSes), for copper catalyzed aziridination of olefins. Ses protected aziridines were synthesized and the yields are comparable to those of PhI=NTs. Anderson *et al.*[43] found that the performance of copper catalyzed asymmetric aziridination is highly dependent on the properties of nitrene precursor.

The most widely used nitrene sources for aziridination are [*N*-(*p*-tolylsulfonyl)imino] phenyliodinane commonly called PhI=NTs and related derivatives. To overcome several limitations associated with the use of PhI=NTs, alternative nitrene

sources such as chloramine-T, bromamine-T and tosyl azide, tosyl carbamates have been actively pursued and with these nitrene sources, complexes of Mn, Fe, Ru, Rh and Cu that are supported by different ligands, have been identified to catalyze aziridination.

Following part of the chapter is dedicated to all these alternative methods along with the mechanistic, stereoselectivity and yield considerations.

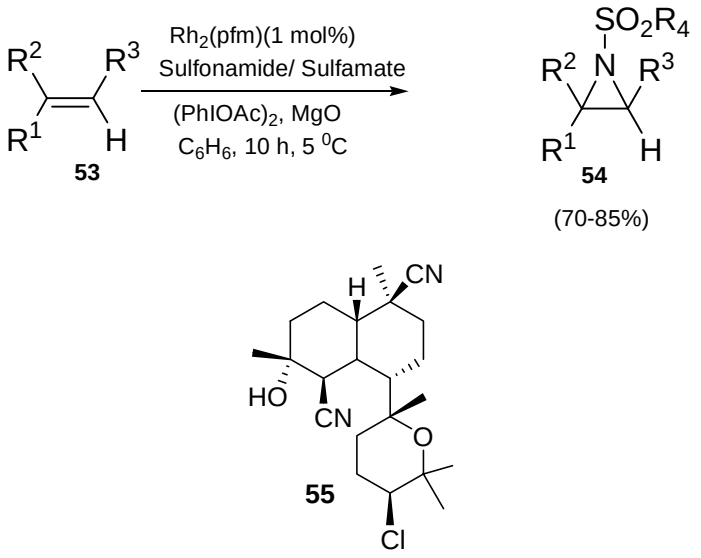
Bois *et al*.[44] decribed preparation of aziridines using sulfamate ester and $Rh_2(tfacam)_4$, (tfacam = CF_3CONH), as catalyst. Although rhodium based aziridination is known, this method provides a wider range of substrate for aziridination. Crystalline trichloroethylsulfamate ester **51** was used as nitrogen source because of its ease of preparation and its inability to undergo intramolecular C-H insertion. They found that using $Rh_2(tfacam)_4$ as catalyst, aziridination is stereospecific with trans and *cis*-β-methyl styrene. Various aliphatic and aromatic olefins **50** were aziridinated to give aziridines **52** in moderate to good yields (**Scheme 23**).



50 **51** **52**

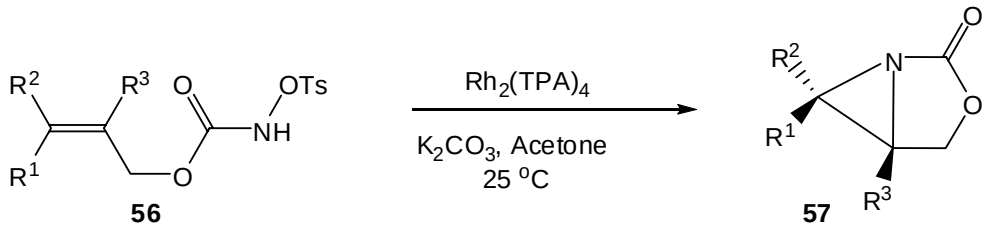
Scheme 23

Wood *et al.*[45] used rhodium perfluorobutyramide ($Rh_2(pfm)_4$) to catalyze the conversion of olefins **53** to trichloroethoxy, sulfonyl, nosyl and tosyl aziridines **54**. Preparation of catalyst ($Rh_2(pfm)_4$) was carried out under microwave conditions and various alkenes were aziridinated in moderate to good yields (**Scheme 24**). Application of this methodology was further extended for total synthesis of (+)-kalihinol A **55**.



Scheme 24

Helenebel *et al.*[46] converted *N*-tosyloxycarbamates into metal nitrene species, which can undergo intramolecular reaction to give aziridination, using $Rh_2(TPA)_4$ as catalyst. Various allyl *N*-tosyloxycarbamates **56** as a source of nitrenes were used for preparation of aziridines **57** using $Rh_2(TPA)_4$ as a catalyst. Both C-H insertion and aziridination reactions were observed when aromatic substituted allylic substrates were used (**Scheme 25**).

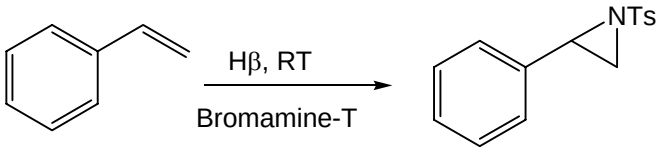


Scheme 25

Catalytic and asymmetric Mn-catalyzed aziridination using an optimized salen complex has been developed by Katsuki,[47] who reached up to 94% ee for aziridination of styrene with TsN=IPh. A chiral Mn (III) porphyrin complex, Mn in conjugation with TsN=Iph provided aziridination products in moderate yields and enantioselectivity.[48]

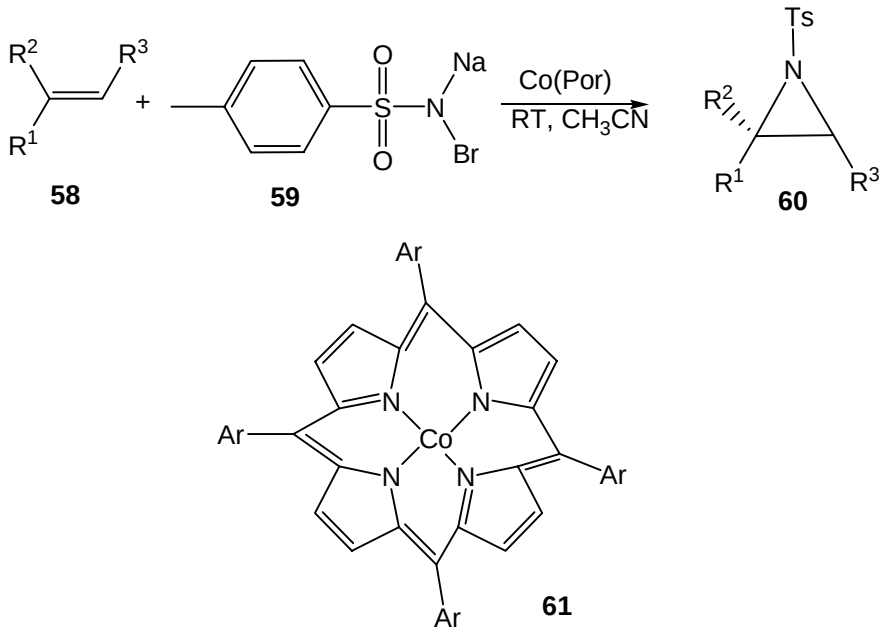
A new, polymer supported manganese (II) complex was developed by Chanda *et al.*[49] and applied in the aziridination of olefins. The catalytic activity of this polymer

supported Mn (II) complex for aziridination of olefins using bromamine-T as nitrene source gives good to moderate yields of aziridines. Bromamine-T as nitrene source for copper catalyzed aziridination of olefins under homogeneous conditions was demonstrated and in comparison with chloramine-T as nitrene source, bromamine-T was found to be superior nitrene source. In 2004, Chanda *et al*.[50] further demonstrated the aziridination using two new polymer based catalysts, one manganese derived and another iron derived, for aziridination of olefins. The same group also demonstrated aziridination of olefins carried out using Hβ-zeolite and in the absence of any metal catalyst. The latter reaction is shown to give selectively the *trans*-product in the case of substituted olefins (**Scheme 26**).



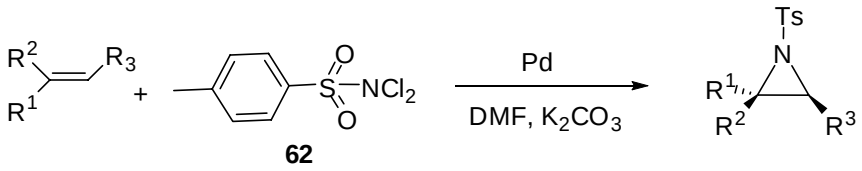
Scheme 26

Zhang *et al.*[51] introduced cobalt porphyrins as the new entry, for aziridination of various alkyl and halogen substituted styrene derivatives using bromamine-T **59** as source of nitrene. Among different porphyrins used Co(TDCIPP) **61**is found to be an effective catalyst that can take part in aziridination of different alkenes **58** (**Scheme 27**).



Scheme 27

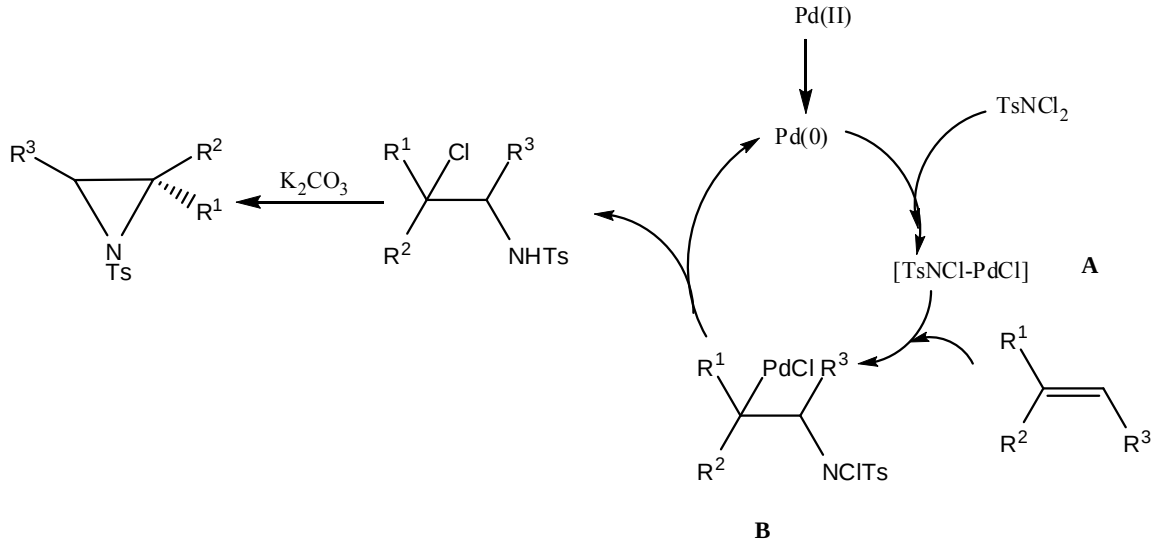
Yufeng Li *et al.*[52] reported palladium-catalyzed aziridination of alkenes using *N*, *N*-dichloro-*p*-toluene sulfonamide **62** as nitrogen source. Substrate scope was studied for different substituted styrene derivatives, cyclooctene and diphenyl substituted alkenes. Good to moderate yields of aziridines were observed. Methyl cinnamate failed to react under these conditions (**Scheme 28**).



62

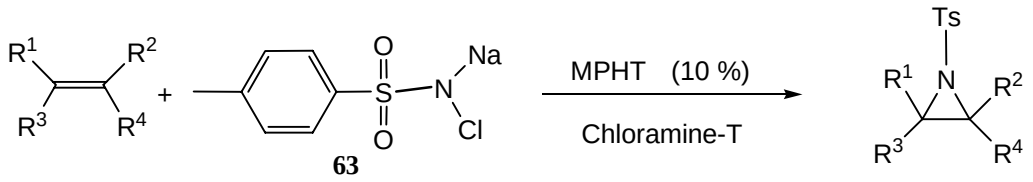
Scheme 28

Palladium (0) is assumed to be the catalytic species produced by reduction of Pd (II) with olefin. The first step of catalytic cycle involves the formation of Pd-nitrogen intermediate **A**, which reacts with olefin to form intermediate **B**. It decomposes further to give the aminochlorination product and to regenerate Pd (0) species (**Scheme 29).**



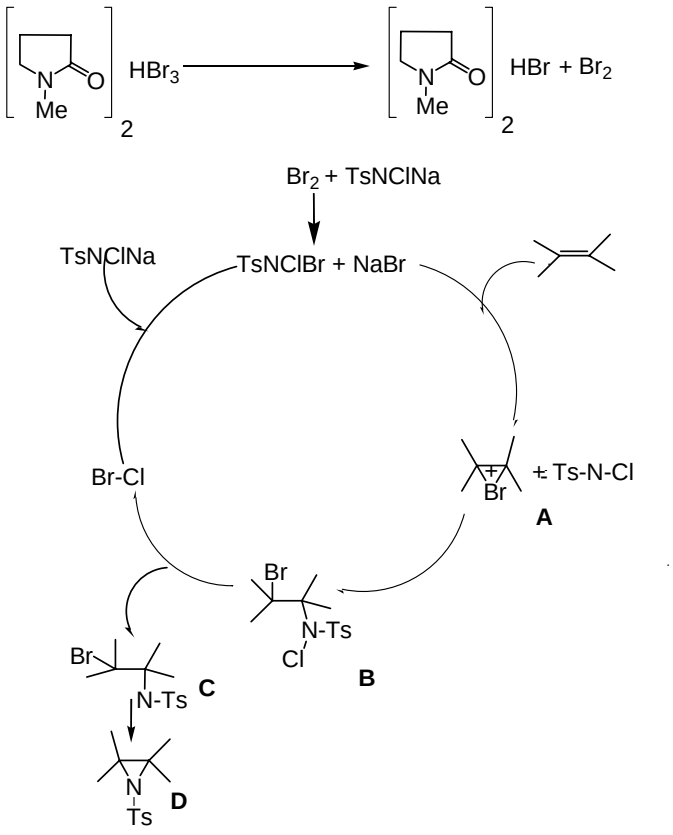
Scheme 29

Sain *et al.*[53] reported N-methyl pyrrolidine-2-one hydrotribromide catalyst for aziridination of alkenes using chloramines-T **63** as nitrene source (**Scheme30**).



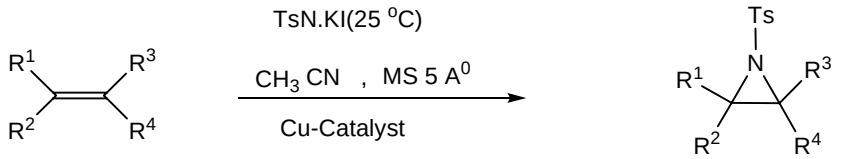
Scheme 30

Although the mechanism of the reaction is not clear, the reaction is probably initiated *via* the generation of bromonium ion (Br^+) from MPHT regent, as depicted in the **Scheme 31.** The generated bromonium ion initially reacts with olefin to afford intermediate **A**, which undergoes ring opening by $Ts(Cl)N^-$ to give bromo-*N*-chloro-*p*-toluene sulfonamide **B**. Attack of Br^- on *N*-chloro group of presumed intermediate **B** generates the anion **C**, which on subsequent cyclization yields corresponding aziridine **D** and the regenerated Br^- species again reacts with chloramine-T to initiate another catalytic cycle (**Scheme 31**).



Scheme 31

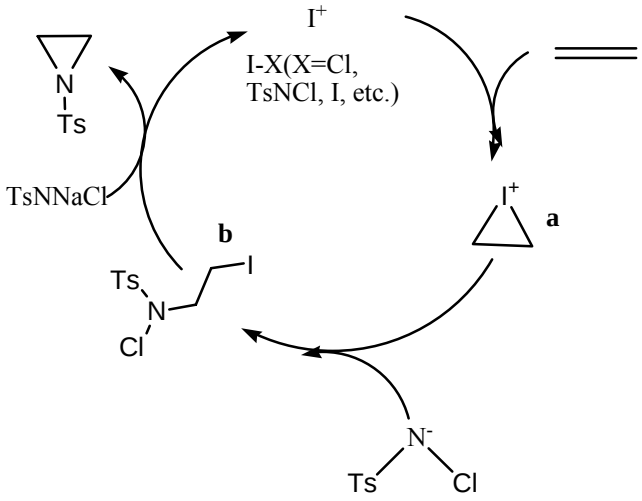
Among the various alkenes studied, *trans*-methyl cinnamate was found to be least reactive. This group also demonstrated *N*-iodo-*N*-potassio-*p*-toluenesulfonamide as a source of nitrene for aziridination of olefins using CuCl as catalyst**.** *N*-iodo-*N*-potassio *p*-toluene sulfonamide is found to be better nitrene source than chloramine-T and bromamine-T. This may be due to weak bonding between nitrogen and iodine which facilitates the formation of copper-nitrenoid complex (**Scheme 32)**.



Scheme 32

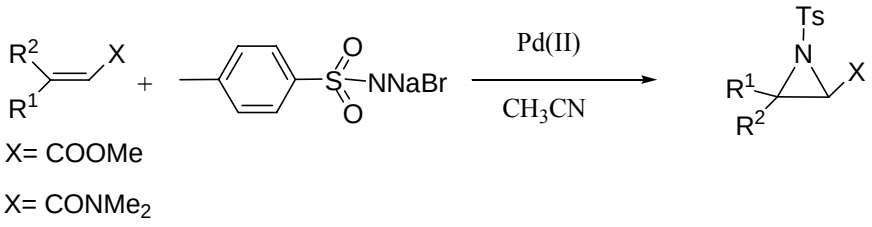
Jain *et al*[54]. further modified the system by using H_2O_2 and HBr, without using metal catalyst and chloramine-T as nitrene source. The mechanism of this reaction is not clear but the reaction probably involves the formation of hypobromous acid by the reaction of hydrogen peroxide with hydrobromic acid, which acts as a source of bromonium ions. The bromonium ion reacts with olefin which undergoes ring opening by $Ts(Cl)N^-$ to give β-bromo-*N*-chloro-*p*-toluenesulfonamide. Attack of OH^- on the N-Cl group of presumed intermediate generates the anion which on subsequent cyclization yields the aziridine. The mechanism of reaction is similar to that explained earlier for *N*-methyl pyrrolidine-2-one hydrotribromide as catalyst. (**Scheme 31**).

Xia *et al.*[55] reported aziridination of olefins using hydrated chloramine-T as nitrene donor and copper iodide as catalyst in water as solvent. Tetrabutyl ammonium bromide is used as phase transfer catalyst. Various metal halides of Mn and Cu were studied for aziridination, when copper iodide was found to be the best. The combination of chloramine-T and iodide is an efficient iodination reagent. The reaction probably involves the formation of I^+ species by the reaction of chloramine-T with copper iodide. The proposed pathway for aziridination of olefin in water solvent is due to reaction of iodine with I^+ source (I-X) to give iodonium ion **a**. The iodoaminated intermediate **b** leads to the aziridine and the generated I-X species is available to initiate another turn of catalytic cycle (**Scheme 33**).



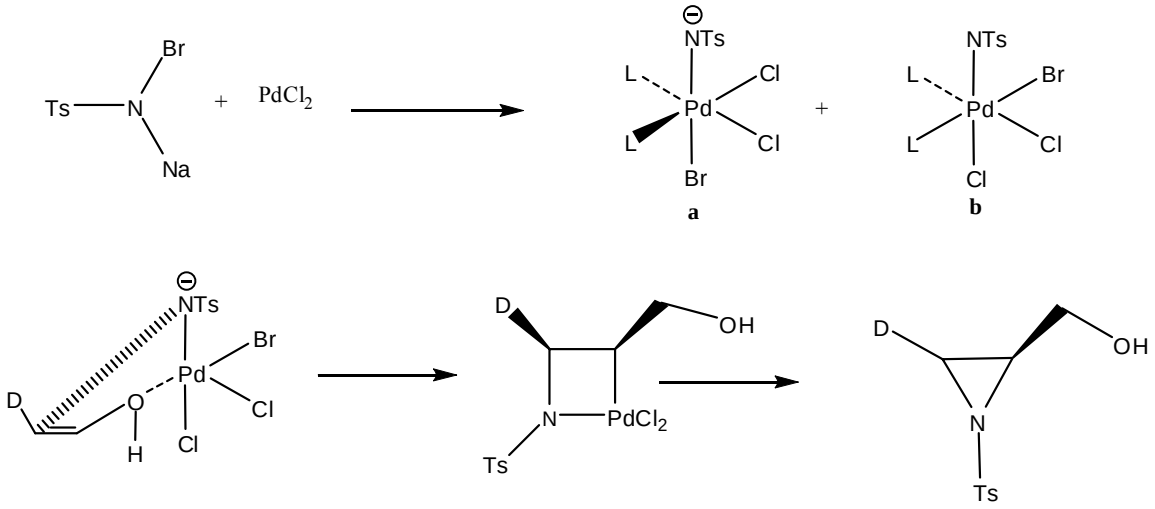
Scheme 33

Branco *et al*.[56] reported Pd (II) promoted reaction of a variety of olefins and bromamine-T under mild conditions (**Scheme 34**).



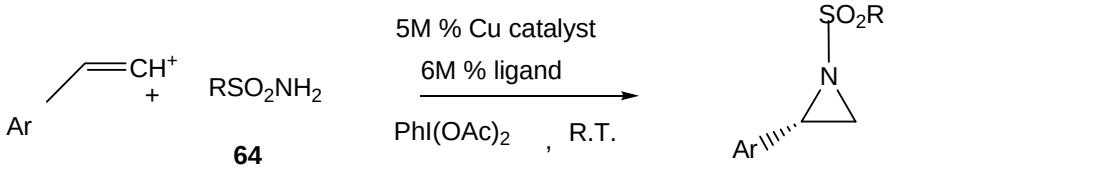
Scheme 34

Synthetically useful *N*-tosyl-2-substituted aziridine can be obtained in good to moderate yield. It is suggested that an oxidative addition of bromamine-T to $PdCl_2$ results in the formation of two organo Pd^{4+} complexes **a** and **b** in equilibrium. The palladocycle thus formed gives aziridine, regenerating Pd^{2+} species (**Scheme 35**).



Scheme 35

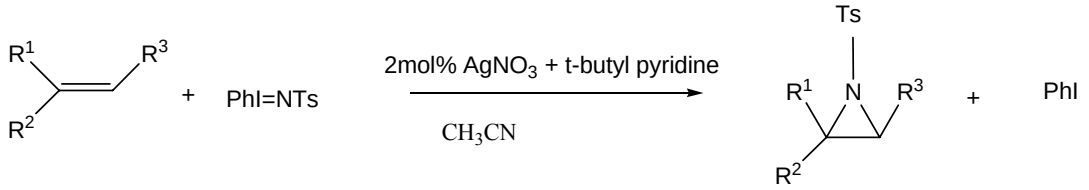
Kwong *et al.*[57]demonstrated one pot synthesis of aziridine, using $PhI(OAc)_2$ and copper as catalyst. Benzene sulfonamide and various 4-substituted benzene sulfonamides **64** are used as a source of nitrenes. Among all the copper catalysts studied, Cu $(CH_3CN)_4$ ClO_4 gave best results with 55% yield. To develop chiral version of this procedure, Evan's chiral bis(oxazoline) ligand was used in presence of CH_2Cl_2 as solvent, when aziridination was effected with 29 % ee (**Scheme 36**).



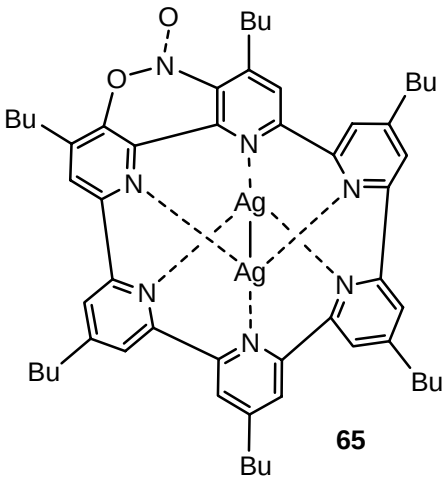
Upto 94 % isolated yield with 75 %ee

Scheme 36

He *et al.*[58] studied aziridination of various substituted styrene derivatives and terminal alkenes using $[Ag_2$ (*t*-Bu_3tpy$)_2(NO_3)](NO_3)$ **65** and PhI=NTs as nitrene donor in acetonitrile solvent. Disilver catalyst was prepared by reaction of silver nitrate with 4,4',4"-tri-*tert*-butyl- 2,2',6',2"-terpyridine (*t*-Bu_3t-py) (**Scheme 37**).

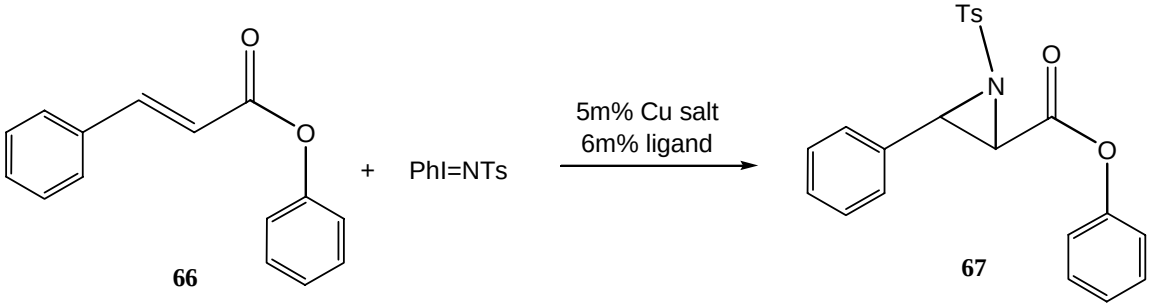


Following structure was assigned for disilver complex.



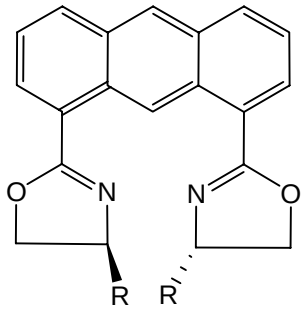
65

Ma *et al.*[59] prepared 1,8-anthracene linked bis-oxazolines (AnBOX) **68** and evaluated in the catalystic aziridination with PhI=NTs as nitrene source. The results indicate highly enantioselective aziridination of chalcones catalyzed by AnBOX and CuOTf complex with >99 % ee whereas phenyl trans-cinnamate **66** afforded the corresponding aziridine **67** with 44 % ee (2S,3R) and 61 % yield (**Scheme 38**).



66 **67**

Scheme 38



ANBOX **68**

Jain *et al*.[54] used metallophthalocyanin as catalyst for aziridination of olefins using [*N*-(*p*-tolylsulfonyl) imino] phenyliodinane, chloramine-T and bromamine-T as nitrene precursors. Good to moderate yields of aziridines are observed. Aromatic substituted olefins are found to be more reactive than aliphatic alkenes.

Conclusion

The illustrations discussed above distinctly bring out the importance of aziridination strategy in synthetic chemistry. Even though the quantum of work reported in this field is enormous, the examples cited in this review were selected exclusively in correlation with our interest in this area. In the light of above discussions and the importance of aziridine chemistry, the results of our successful studies using heterogeneous catalyst in the synthesis of substituted aziridines are presented in detail in the following section.

Part II: Synthesis of aziridines using copper hydrotalcite under microwave irradiation

Introduction

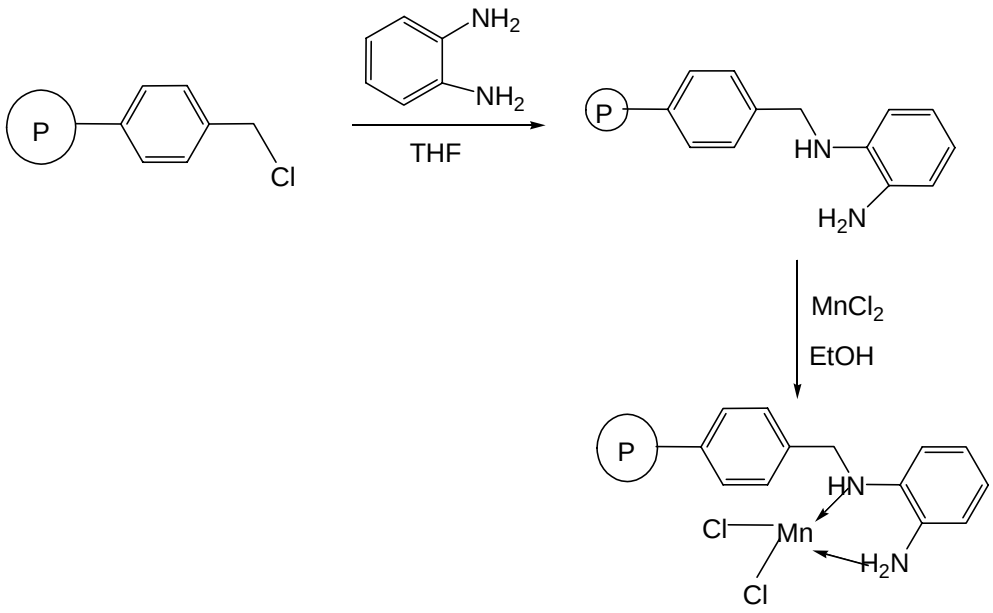
A recent trend is for renewed interest in the use of heterogeneous catalysts in replacing the conventional homogeneous catalyst systems. Though homogeneous catalysts are well established, individually optimized and commercially pronounced based on statistical data, the future trend of R & D is on the development of new and potential heterogeneous catalyst systems practiced for industrial applications. The green synthesis of organic compounds is an area of growing importance in industry. Any modification in the existing organic process that removes environmentally harmful solvents and reagents, reduces waste, or involves recycling of materials can be considered a green adaptation. Use of heterogeneous catalyst brings advantages in respect of easy separation, environmental safeguard, high turnover number and hence low cost of process, better selectivity, catalytic amount and avoidance of corrosion. Following is the brief introduction of various heterogeneous methods reported in the literature for aziridination of olefins using heterogeneous catalysts.

Hutchings *et al*.[60,61] first introduced CuHY zeolite as a heterogeneous catalyst for aziridination and [*N*-(tolyl-*p*-sulfonyl) imino] phenyliodinane (PhI=NTs) as nitrene source. After exchange of several cations in Y type zeolite, CuHY was observed to be the best catalyst. This group also designed a catalyst for the enantioselective aziridination of alkenes based on copper-exchanged zeolite HY. One additional and interesting fact in this work was the absence of aziridination reaction of *trans*-stilbene. The non-activity of the other exchanged-metal zeolites can be due to the ability of those metals to catalyze the breakdown of the PhI=NTs yielding iodobenzene and sulfonamide. They also studied the water effect as a reaction inhibitor, concluding that the reaction rate drastically decreases even with low water quantity and demonstrated the need to use dry solvents. To study the effect of nitrene donor on enantioselectivity, the same research group compared both catalytic systems (homogeneous and heterogeneous) with two possible nitrene donors ([*N*-(*p*-tolylsulfonyl)-imino)]phenyliodinane (PhI=NTs) and [*N*-(*p*-

nitrophenylsulfonyl)-imino]phenyliodinane (PhI=NNs)) with several chiral modifiers, with several metal-exchanged zeolite Y (Zn^{2+}, Ni^{2+},Fe^{3+}, Mn^{2+}, Co^{2+}, Cu^{2+}), and styrene as the main substrate. In relation to the use of these other metals it was observed that, using PhI=NNS and PhI=NTS as the nitrene donors, CuHY showed to be the most efficient catalyst, minimizing the formation of side products such as benzaldehyde. Optimizing the reaction conditions, the best enantioselectivity was obtained when a slight excess of nitrene donor (nitrene donor:styrene = 1.5:1) was used, and when the nitrene donor concentration was increased there was a drop in aziridine yield, probably because of the formation of benzaldehyde as by-product. A patent by same inventors[62] discloses the art of aziridination by using CuHY zeolite. Aziridination of various olefins using PhI=NTs as nitrene donors indicated moderate yields of aziridines. Aziridination of methylcinnamate using 5 mol / m PhI=NTs and 0.25 g atom of Cu gives about 84 % aziridinated product. The yield of cyclic olefins like cyclohexene was in the range of 50 %. Asymmetric aziridination of olefins using 4,4'-disubstituted bis(oxazoline) before contact of the nitrene donor gave about 30-40 % ee in acetonitrile as solvent.

In 2002, Hutchings *et al*.[63] further demonstrated Cu^{2+} ion exchanged in zeolite HY for aziridination of olefins. By careful control of (styrene: nitrene donor) molar ratio and the solvent, 90-95 % *ee* was obtained for the heterogeneous catalyzed bis(oxazoline) modified zeolite CuHY.

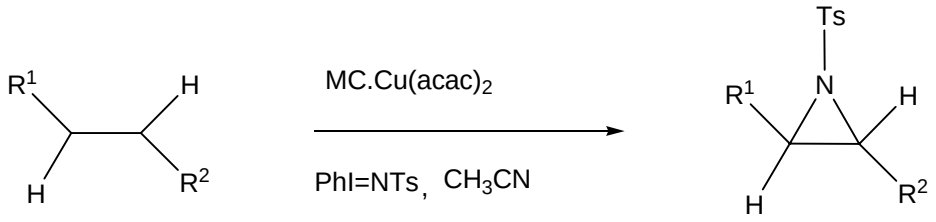
In 2000, Chanda *et al.*[64] prepared the chelated manganese metal complex on a polymer support and used it as catalyst in the aziridination of olefins using bromamine-T as a source of nitrene. Chloromethylated styrene-divinyl benzene of 8 % cross-link was functionalized using *o*-phenylene diamine and finally it was treated with Mn II for the formation of metal complex on the surface (**Scheme 39**). Good to moderate yields of aziridines were obtained using acetonitrile as solvent.



Scheme 39

This group also reported first time the aziridination using Hβ-zeolite and in the absence of metal catalyst with bromamine-T as nitrene source, moderate to good yields of aziridines were observed. *Trans* selectivity to aziridination was also one of the key feature of using Hβ-zeolite as catalyst.

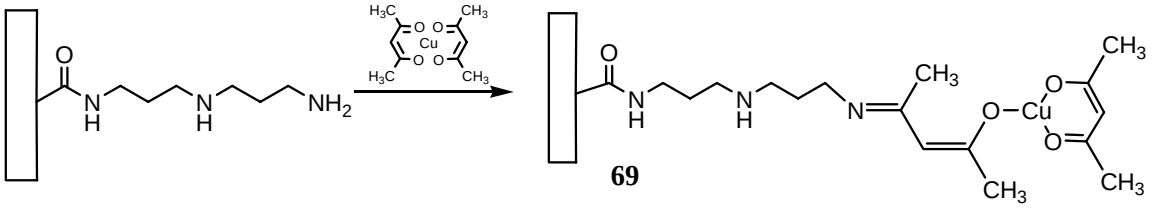
In 2003, Lakshmi Kantam *et al*.[65] reported microencapsulated copper (II) acetylacetonate [MCCu(acac)$_2$] catalyst for aziridination of olefins using [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrogen source. Microencapsulation is a new method of immobilizing catalysts onto polymers accomplished by physical envelopment by the polymers. Catalyst was found to be recyclable several times and was found to be more effective than CuHY zeolite catalyst (**Scheme 40**).



Scheme 40

In 2004, Huang *et al.*[66] demonstrated use of PbO*x*-modified zeolite for aziridination. When *N*-aminophthalimide and 3-cinnamoyl-2-oxazolidinone were photolyzed with NaY/PbO*x*, (2R,3S)- and (2S,3R)-*N*-phthalimidoaziridines were observed as the major products.

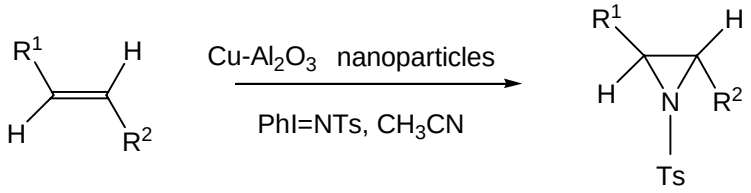
Silva *et al.*[67] in 2005, demonstrated copper (II) acetyl acetonate anchored onto activated carbon as a heterogeneous catalyst for the aziridination of styrene. Copper (II) acetyl acetonate immobilized onto an amine functionalized carbon **69** acted as heterogeneous catalyst in the aziridination of styrene, with the similar parameters as the one obtained with the homogeneous phase reaction using $[Cu(acac)_2]$ as catalyst.



69

In the same year Kuhn *et al.*[68] used $[Cu(NCCH_3)_6][B(C_6F_5)_4]_2$ as catalyst, heterogenized by ion exchange on NaAlMCM-41 and NaAl MCM-48 and used for aziridination of olefins. Good to moderate yields are observed for non-bulky olefins.

Lakshmi Kantam *et al.*[69] demonstrated the use of alumina supported copper nanoparticles catalyzed aziridination of olefins using [*N*-(*p*-tolyl sulfonyl) imino] phenyl iodinane as nitrene source (**Scheme 41**). The Cu-Al_2O_3 nanoparticles heterogeneity and recyclability was found to be well established.



Scheme 41

Thus, various homogeneous and heterogeneous catalytic methods are reported in the literature. After reviewing the literature, copper was the best transition metal for the catalyst observed for both homogeneous and heterogeneous aziridination.

Applications of copper hydrotalcites

Hydrotalcites (HTs) are potentially useful as catalysts and catalyst precursors due to their high surface area and metal exchange ability. They have been employed as catalysts or catalyst supports for incorporating transition metals in the interlayers. Various catalytic processes using hydrotalcites type of anionic clays along or incorporated with transition metals in the interlayer have been developed for synthesis of organic moieties.

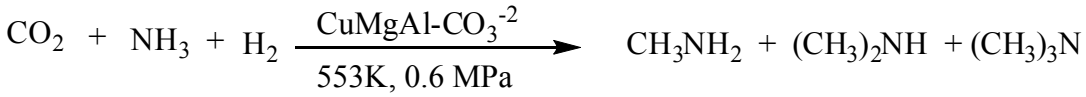
Hydrotalcite like anionic clays constitute a class of extremely useful materials for research in the field of catalysis. These clays are synthetic or natural crystalline materials constituting positively charged two dimentional sheets with water and exchangeable charged compensating anions in the interlayer region.

Their general formula is $[M^{2+}_{1-x}Mx^{3+}(OH)_2]X^{+}\text{-}(A^{n-}_{x/n}).mH_2O$ where M^{2+} and M^{3+} represent divalent and trivalent cations in the brucite type layer. A is the interlayer anion with charge n, x is the fraction of trivalent cations. (x values in the general formula are in the range of 0.2-0.5, and m is the water of crystallization.

Hydrotalcites, both natural and synthetic can be successfully applied in a broad spectrum of organic reactions with advantages such as improved activity, improved selectivity, metal dispersion, less waste production and an improved recuperation of immobilized catalysts.

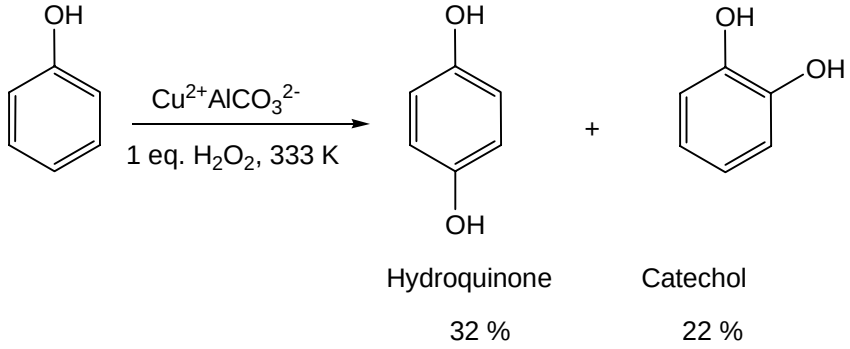
A particular advantage of hydrotalcites is that numerous transition metals can be easily introduced into brucite like layer-interlayer space. In processes for manufacture of methanol, acetic acid, higher branched alcohols and hydrocarbons, catalysts derived from hydrotalcite like structures are extensively adopted. Hydrotalcites containing copper is already known in literature and has been found to be explored for various catalytic applications. Following are some of the catalytic applications demonstrated for industrial utility of this catalyst.

Oxidative transformation of methanol into hydrogen in presence or absence of steam has been performed with CuZnAl(Zr) HTs. Cobalt and copper containing HT precursors can be applied to Fisher-Tropsch synthesis. Metal oxides form $CuMgAlCO_3^{-2}$ HTs have been recognized for selective synthesis of highly demanded mono-methylamine using CO_2, H_2 and NH_3 (**Scheme 42**).



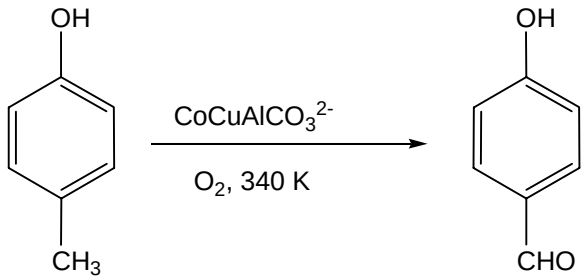
Scheme 42

Cu (II) HT has been tested for liquid phase hydroxylation of phenol using H_2O_2 as the oxygen source[70] (**Scheme 43**).



Scheme 43

Liquid phase oxidation of *p*-cresol using cobalt hydrotalcites can yield *p*-hydroxy bezaldehyde[71] (**Scheme 44)**.



Scheme 44

Hydrotalcites can be used in synthesis of heterocyclic compounds, processes involving alkylation, acylations, reductions, polymerization and dehydrogenation. Thus, hydrotalcites can provide a technically attractive zero waste alternatives to normal homogeneous catalytic processes. Apart from simple base catalysis, metal functions can co-operate with the base function or synergism may exist between several metal ions or metals within the HTs catalysts. Interaction between the metals may be the key step towards high activity and selectivity. The main advantage of HTs is that, they are purely inorganic materials except that metallo-organic hosts are introduced.

Advantages of microwave technique in synthetic organic chemistry

Microwave assisted chemical transformations have gained importance in recent years. Although microwave technology has been used in inorganic chemistry since 1970, Gedye[72,73] and Giguere[74] first implemented it to accelerate the organic reaction in 1986. Microwave assisted organic chemistry has experienced exponential growth since mid-1990s. There are two mechanisms associated with microwave heating, dipole rotation and ionic conduction. When molecule is irradiated with microwave it will attempt to align itself with the electric field by rotation. If the frequency of the molecular rotation is similar to the frequency of the microwave radiation, the molecule will continually align and realign itself with an oscillating field; therefore the electrical energy is absorbed by the molecule.

In case of ionic conduction, ions move through the solution under applied field and heat is generated by friction. Microwave technique is suitable for a variety of preparative reactions on small scale to medium scale. These reactions are conducted in few minutes with complete safety in open vessel at ambient temperature in domestic microwave oven. The strategy is to heat rapidly the reactants with minimal vaporization. When the reactions can not be performed neat, a high boiling solvent with high dielectric constant is employed. Microwave irradiation can be used as an efficient source for thermal energy. Performing reactions under these conditions leads to faster and cleaner reactions which may be attributed to less thermal decomposition of product and minimization of unwanted side reactions. Many reactions are known in recent literature

where microwave reactions gave excellent results. Some of the important reactions are Diels-Alder reaction, Claisen rearrangement and Fischer cyclisations.

The main advantages are

1) Reaction time can be dramatically shortened than with conventional heating.
2) Energy can be introduced remotely, without contact between the source and the reactants.
3) Energy input to the sample starts and stops immediately when the power is turned on or off.
4) Thermal inertia is lower than with conventional conductive heating.
5) Energy is delivered throughout the mass of the product and not at only surfaces.
6) Heating rate is higher than that can be achieved conventionally if at least one of the components can couple strongly with microwaves.
7) The technique can be readily employed for sequential or parallel microwave synthesis.
8) The outcome of an organic reaction is completely dependent on the delivery of energy and the timing of its introduction into the reaction system.

Among the sources available, microwave irradiation has huge potential to provide controlled energy directly to the molecules of interest.

Accordingly, since the mid-1980s, a vast number of research reports have demonstrated that accelerated chemical rates can be achieved when reactions are heated with microwave irradiation instead of using traditional sources of heat. Metal catalysis is one of the steps present in nearly all novel target synthesis reported in this period. Palladium, copper and nickel catalyzed reactions proceed *via* aryl or vinyl metal intermediates.

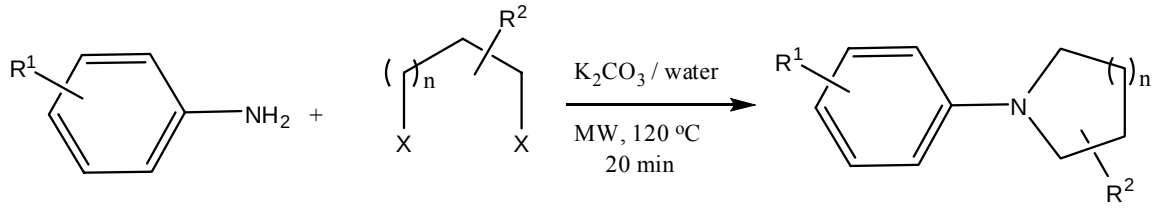
Metal-mediated transformations have proven to be especially valuable for introducing substituents on to aromatic core structures, and they are performed equally well in both inter and intramolecular applications. An important advantage is that hydroxyl, carboxylic acid and amine groups usually do not need protection. However, the long reaction time required for complete conversion have limited exploitation of full

potential of homogeneous catalysis in fine chemical, high-throughput and medicinal synthesis. Rapid and reliable microwave methods are therefore highly desirable.

The advantages of microwave technology enabled organic and medicinal chemists to reduce the time of synthesis of heterocycles and other molecules from days and hours to minutes and even seconds. In addition, formation of side-products at low level and improved yields has been frequently observed under microwave heating conditions. Moreover, the extremely fast and efficient dielectric heating mode has sometimes identified unusual reactivities that could not be achieved by conventional heating.

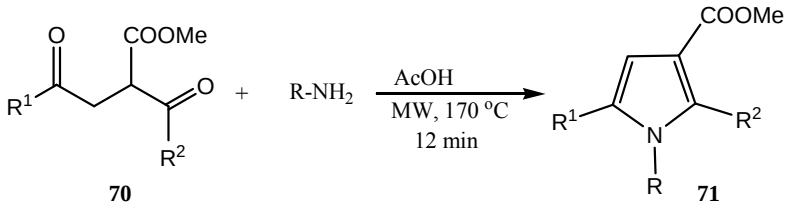
Microwave assisted reactions for the synthesis of nitrogen heterocycles

A series of substituted pyrrolidines were conveniently prepared in a microwave-assisted double alkylation of aniline derivatives with alkyl dihalides in water in the presence of K_2CO_3 as a base.[75,76] The reaction conditions were sufficiently mild to tolerate a variety of functional groups in anilines such as hydroxyls, ketones and esters. Alkyl bromides and tosylates were equally efficient as alkylating agents (**Scheme 45**).



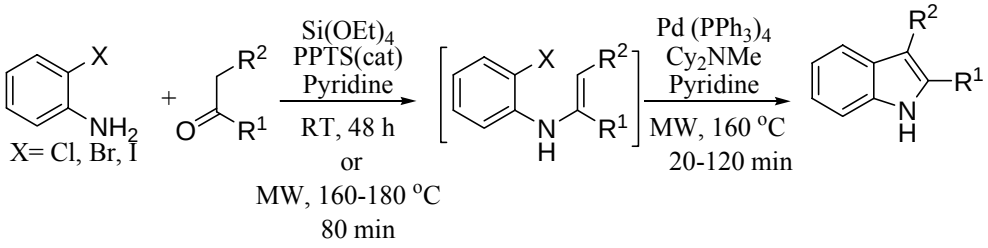
Scheme 45

One of the most common approaches to pyrrole synthesis is the Paal–Knorr reaction. The microwave-assisted Paal–Knorr cyclization was successfully carried out on various 1,4-diketoesters **70** in the presence of amines, affording the desired pyrroles **71** in good yields[77] (**Scheme 46**).



Scheme 46

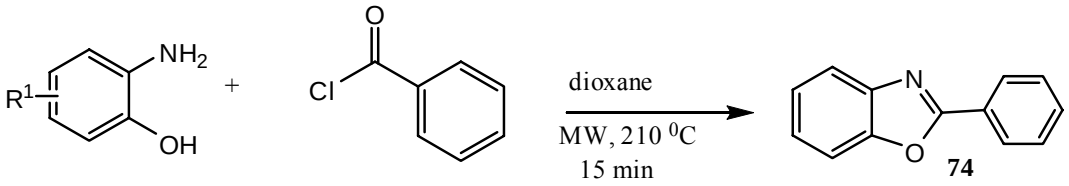
The widely employed Leimgruber–Batcho protocol for indole **73** synthesis comprises two consecutive steps, formation of enamines **72** followed by a reductive cyclization. Use of microwave irradiation at 180 °C reduced the time of formation of enamines from 22 h (at 110 °C) to 4.5 h[87](**Scheme 47**).



Scheme 47

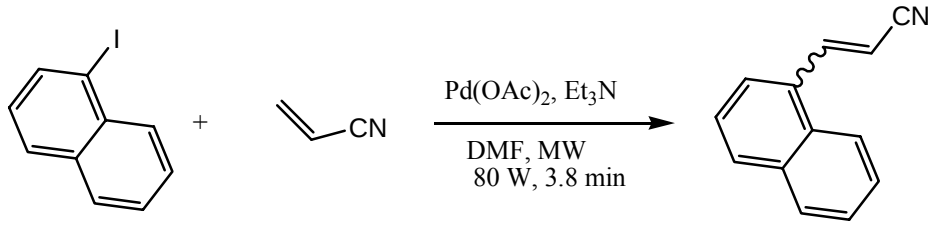
Multi-component condensation of ketones (or aldehydes), *α*-activemethylene nitriles and elementary sulfur (Gewald reaction) is an efficient methodology to access diverse 2-aminothiophenes. The Gewald reaction, however, suffers from long reaction times (8 - 48 hours) and laborious purification of the desired products. When the reaction was performed on solid support under microwave dielectric heating conditions, it furnished 2-aminothiophenes within 20 min.[79] Imidazolidine-2-ones were synthesized by microwave-accelerated coupling of urea with aliphatic and aromatic diamines in the presence of ZnO as a catalyst.[80] Benzoxazoles are routinely prepared in a two-step sequence comprising base-catalyzed bis-acylation of *o*-aminophenols followed by a Lewis-acid assisted cyclization-dehydration reaction. Microwave flash heating of readily available acid chlorides and *o*-aminophenols in sealed reaction vessels delivered

benzoxazoles **74** in a one-pot process without aid of any additive such as base or Lewis acids[81] (**Scheme 48**).



Scheme 48

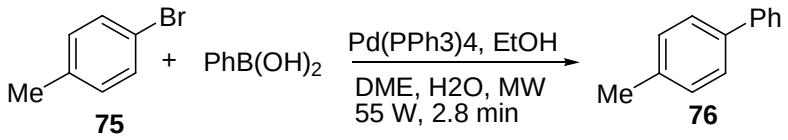
In the late 1960s, the research teams of Moritani–Fujiwara and Heck independently discovered the palladium-mediated arylation and alkenylation of alkenes.[82] During the last thirty five years, this selective palladium catalyzed transformation, generally known as Heck reaction, has been extensively explored and used in several diverse areas such as the preparation of natural products, pharmaceuticals, agrochemicals and dyes, because of the mildness and high selectivity of the reaction.[83,84] Heck arylation was reported in 1996 and constitutes the first example of palladium catalyzed microwave-promoted, C – C bond formation[85] (**Scheme 49**).



Scheme 49

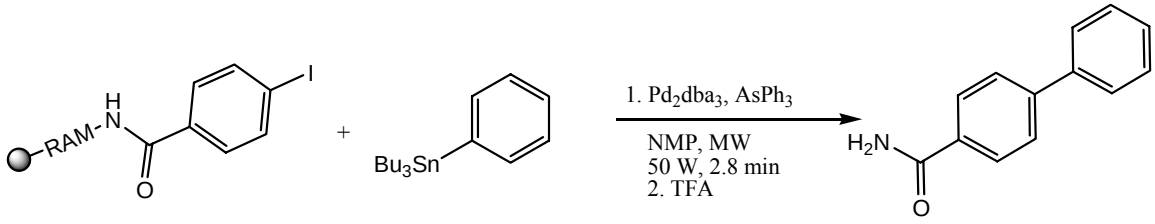
Sonogashira reaction, using copper and palladium catalysts, is a general and reliable protocol used to cross-couple terminal alkynes with aryl/vinyl halides, forming aryl alkynes in an easy manner.[86] The option to perform Sonogashira and similar reactions while avoiding the use of transition-metals is indisputably very attractive, mainly due to cost and environmental issues. Erik van der Eycken and his group have exemplified the omission of transition metals in the coupling of phenyl acetylene with different aryl halides, employing microwave heating at 175 °C with a carbonate base and TBAB in water.[87]

The first microwave-promoted Suzuki couplings were published in 1996.[88] Phenyl boronic acid was coupled with 4-methylphenyl bromide **75** to give a fair yield of product **76** after a reaction time of less than four minutes under single-mode irradiation (**Scheme 50**).



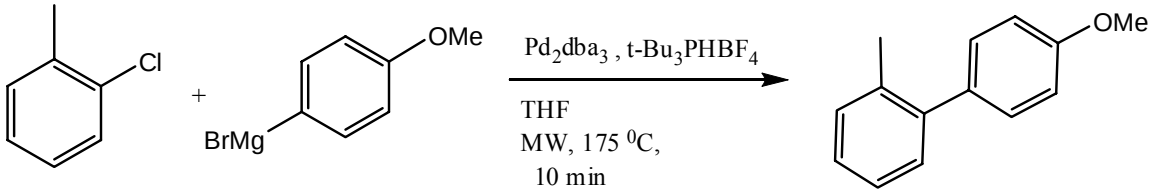
Scheme 50

Stille reaction was one of the earliest transition metal-catalyzed reactions to be accelerated with microwave-heating. Single-mode irradiation with very short reaction time was easily applied to Stille reactions in solution as well as on resin support[89] **(Scheme 51**).



Scheme 51

Microwaves were utilized both in the preparation of the Grignard reagent and in the Kumada couplings[90] with aryl chlorides (**Scheme 52**).



Scheme 52

Microwave-promoted chemistry is indeed an emerging and vibrant field for research and development. Nevertheless, the synthetic chemist can now take advantage of

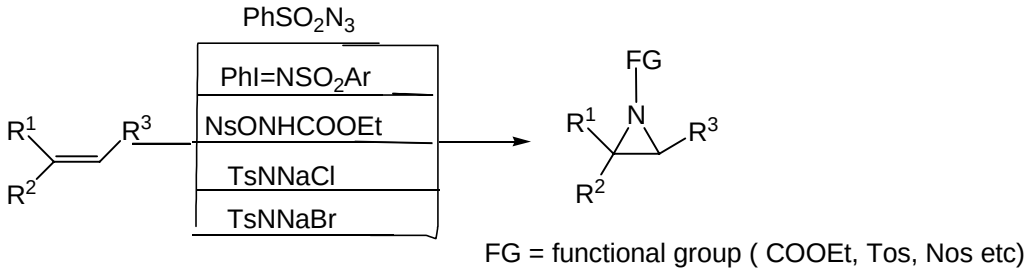
the unique carbon–carbon and carbon–heteroatom bond formations offered by transition metal activation and make the reaction happen in minutes, instead of hours, by microwave flash heating, a feat that is of high importance since many transition metal-catalyzed reactions are known to be time-consuming.

Synthesis of aziridines using homogeneous Cu (II) catalyst and bromamine-T as source of nitrene using microwave irradiation is already known.[91] Enhancement in the aziridination yield with less reaction time has been observed when bromamine-T was used as a source of nitrene instead of chloramine-T. Good to moderate yields of aziridines have been also observed for different olefins. Aziridination of less reactive substrates such as methyl and *tert*-butyl cinnamates does not yield aziridines using homogeneous catalysts like $CuCl_2$ and $CuBr_2$ under normal reactions but under microwave assisted reaction, aziridination of cinnamates is observed with low yield. Various metal catalysts have been previously scanned[91] for aziridination of olefins and copper halides found to be the ideal catalyst for these types of reactions.

Present Work

Thus aziridines are synthesized with or without catalyst. Both homogeneous and heterogeneous catalysis have been reported in the literature. Though copper hydrotalcite has been used as catalyst for hydroxylation, amination, etc, to our knowledge, no such reports are available for aziridination of alkenes. Further, though heterocyclic compounds have been synthesized using microwave irradiation, no such reports are available for aziridination under heterogeneous catalysis conditions and microwave irradiation conditions. However, microwave assisted homogeneous catalyzed aziridination with accelerated rate has been reported earlier.[91]

Some of the recent approaches to the synthesis of aziridines can be summarized as shown in **Scheme 53**.



Scheme 53

Most of these methods suffer from major drawbacks. Syntheses of aziridines *via* decomposition of benzenesulfonyl azide requires drastic reaction conditions, and gives a mixture of products. PhI=NTs requires a cumbersome two step preparation, expensive starting materials and gives iodobenzene as the side product. Nosyl oxycarbamates, the precursors of (ethoxy carbonyl) nitrene are not very stable reagent and moreover their preparation is cumbersome.

It was therefore reasoned that of study of aziridination of various olefins using heterogeneous catalyst under microwave irradiation would yield interesting results. Since copper salts are reported to be the best catalysts for aziridination from various metal catalysts, copper hydrotalcite was selected as the heterogeneous catalyst for aziridination of different olefins. Comparative study earlier reported indicates bromamine-T is a better source of nitrene than chloriamine-T. All the work carried out in this direction uses bromamine-T as the nitrene source.

Results and Discussion

Preparation of copper hydrotalcite catalyst

Literature survey revealed that copper hydrotalcite can be synthesized by co-precipitation method. Jiang *et al.*[92] prepared various proportions of copper containing hydrotalcite clays by co-precipitation method and their performance in catalytic combustion of methane was studied. In this method of preparation of copper hydrotalcite,

solution of magnesium nitrate, aluminium nitrate and copper nitrate was added to a solution of potassium hydroxide to co-precipitate copper hydrotalcite.

Baiker *et al.*[93] used Cu-Mg-Al hydrotalcite, prepared from corresponding nitrates and sodium carbonate and used for preparation of methyl amines from methanol and ammonia. X-ray diffraction pattern indicates hydrotalcite phase along with CuO phase in the catalyst.

Koovanda *et al.*[94] prepared copper hydrotalcite with various ratios of Cu, Mg and Al by co-precipitation method from their sulphate salts. These different copper containing hydrotalcites were characterized by XRD. The oxidation activity of these hydrotacites for toluene combustion was found to increase with increasing amount of Cu^{2+}. They found that the acidity of copper hydrotalcite is directly proportional to the amount of copper in hydrotalcite. Acidity of copper hydrotalcite was found to increases along with acidic sites in the copper hydrotalcite, as copper content in the hydrotalcite increases. Copper hydrotalcite prepared by equimolar proportion from the sulphates of Cu, Mg and Al indicates acidity of 0.19 mmol/g by ammonia uptake value.

Crivello *et al*.[95] prepared copper hydrotalcites to study the dehydrogenation of 2-octanol using nitrates of copper, magnesium and aluminium. Catalytic performances of these mixed oxides was studied at 450 °C in dehydrogenation of 2-octanol. From XRD analysis they found that, in all cases the hydrotalcite phase was detected. Decrease in sharpness of the peaks indicates decrease in crystallinity and increase in copper content in hydrotalcite. X-ray photoelectron spectroscopy (XPS) indicates presence of Cu^{2+} species in the catalyst. The presence of Cu^{2+} species is advantageous for use as catalyst for aziridination.

Fig 9: XRD of copper hydrotalcite reported by Crivello *et al*.

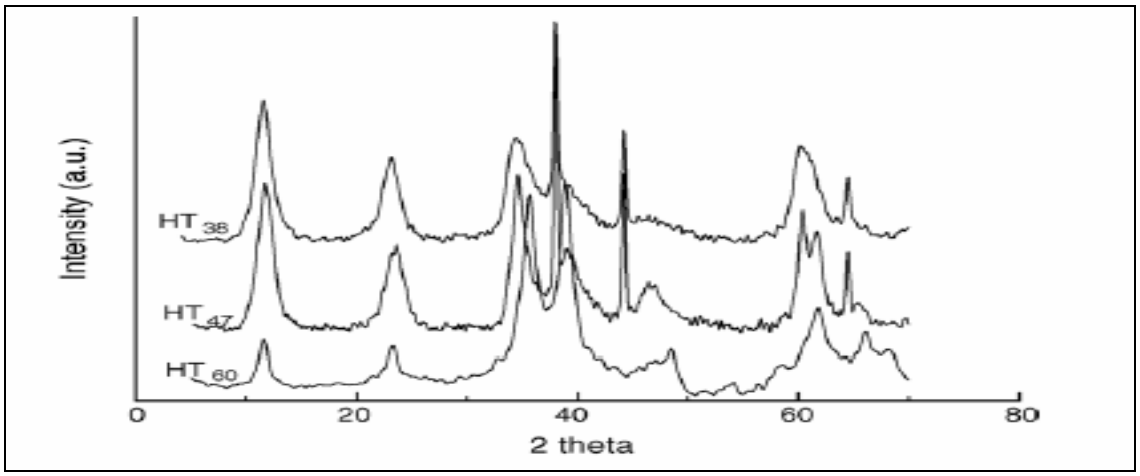
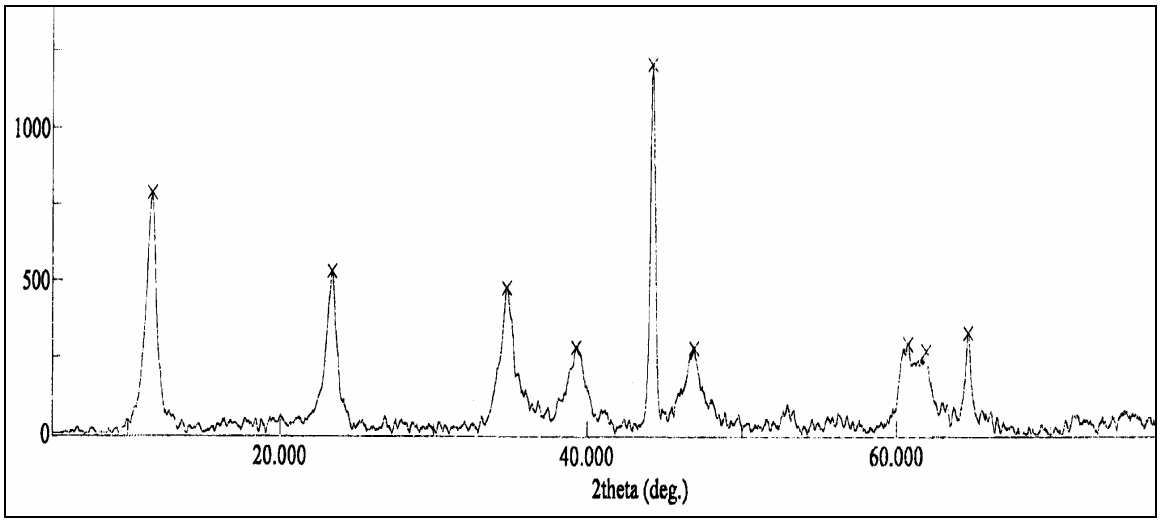


Fig 10: XRD of copper hydrotalcite prepared



For the present study, copper hydrotalcite catalyst was prepared by simultaneous addition of a solution of magnesium nitrate, aluminum nitrate and copper nitrate in distilled demineralized water along with solution of sodium hydroxide and sodium carbonate in distilled water and maintaining the pH at 10-10.2 as per the procedure reported by Crivello *et al.*[95] The precipitate formed was heated to 60° for 30 min, cooled to room temperature and filtered. Precipitate was washed with water to neutral and then dried first at 100 °C and then at 150 °C.

X-ray diffraction pattern of copper hydrotalcite prepared thus was comparable with that of hydrotalcite HT_{47} prepared by Crivello *et al.*[95] 2 Theta values were also found to be comparable.

Copper and magnesium content in copper hydrotalcite

The contents were determined by classical analysis methods.

A known weight of catalyst was dissolved in concentrated hydrochloric acid and diluted to a known volume. To a measured volume of this solution, standard KI solution was added and the liberated iodine was titrated with sodium thiosulphate solution. The copper content in copper hydrotalcite prepared was found to be 19.8% according to following formula.

$$\% \text{ of Cu} = \frac{\text{Reading} \times \text{N(thiosulphate solution)} \times \text{Eq.Wt. of copper} \times \text{Dilution factor}}{\text{Wt. of sample} \times 10}$$

To a known volume of above diluted solution aqueous ammonia solution was added to make it highly alkaline and titrated it with standard EDTA solution with Erichrome Black-T as indicator. End point was wine red to blue. The magnesium content in copper hydrotalcite was found to be 45% according to following formula.

$$\% \text{ of Mg} = \frac{\text{Reading} \times \text{N(EDTA solution)} \times \text{Mol.Wt. of Mg} \times \text{Dilution factor}}{\text{Wt. of sample} \times 10}$$

Acidity studies by ammonia uptake

Copper hydrotalcite powder was analyzed for ammonia uptake to calculate the acidity of catalyst. Ammonia uptake was found to be 0.1632 mmol/g of catalyst.

Bromamine-T

Chloramine-T was treated according to literature procedure with bromine to give the intermediate dibromamine-T which on further treatment with sodium hydroxide gave bromamine-T.

Aziridination of olefins using copper hydrotalcite under microwave irradiation

Aziridination of different olefins *viz.* styrene **77**, α-methyl styrene **78**, β-methyl styrene **79**, methyl cinnamate **80**, cyclohexene **81**, cyclooctene **82** and n-decene **83** were carried out heterogeneously using cooper hydrotalcite under microwave irradiation. In a general procedure a mixture of olefin (2 mmol), bromamine-T (4 mmol) and 10 % by wt of copper hydrotalcite catalyst in 15 ml of acetonitrile was irradiated in domestic microwave oven for 7-10 min. After work up, the crude product was purified by column chromatography to afford aziridines (72 – 81 %).

In **Table 1** yields of aziridines obtained using copper hydrotalcite catalyst under microwave conditions are compared with those of aziridines obtained using homogeneous copper catalyst[57]. Yields of all the aziridines obtained using copper hydrotalcite catalyst under microwave conditions were better than those obtained under homogeneous conditions except in case of α-methyl styrene where the yield was almost comparable. No data was available for β-methyl styrene and methyl cinnamate under homogeneous conditions. However both olefins give good yields of aziridines using copper hydrotalcite as catalyst under microwave conditions (72 – 73 %).

While comparing the yield of aziridines with other heterogeneous copper catalysts **(Table II)**, the main difference was reaction condition; in the present studies microwave as energy source was used whereas conventional heating was used earlier. Secondly, bromimine-T as nitrene source in the present studies where as other groups used different nitrene sources such as PhI=NTs and $PhIN(OAc)_2$.

Thus the yield of styrene aziridination was 75% using copper hydrotalcite, where as using copper nanoparticles and microencapsulated $Cu(acac)_2$ resulted in greater than 90 % yield. Using $[Cu(NCCH_3)_6][B(C_6F_5)_4]_2$ and CuHY zeolite the yields were found to

be 65-80 %. The reaction period in all cases was in hours, where as the present study yielded results in just seven minutes. In case of α-methyl and β-methyl styrene aziridination, yields were found to be comparable with microencapsulated $Cu(acac)_2$ catalyst, and all other catalysts were found to give less yields.

Cyclohexene aziridination yield (71%) using copper hydrotalcite under microwave conditions was found to be better than with other heterogeneous catalysts (40-52 %). In case of methyl cinnaminate yield of aziridine using CuHY zeolite was found to be 85% with copper nanoparticles it was only 30%, whereas when copper hydrotalcite catalyst was used, yield was 72%. In case of cyclooctene, use of $[Cu(NCCH_3)_6][B(C_6F_5)_4]_2$ as catalyst gives less yield whereas the yield of aziridine was found to be comparable with CuHY zeolite. During aziridination of above mentioned olefins the reaction time in all cases was very less as compared to reactions carried out using other catalysts.

Earlier,[50] polymer supported Mn and Fe catalysts were used for aziridination of olefins. It was observed that styrene aziridination using bromamine-T, Mn and Fe-catalyst, gave low aziridination of styrene. Iron catalyzed aziridination of α-methyl styrene gave comparatively better aziridination, whereas no aziridination was observed in case of β-methyl styrene. Both the catalysts fail to aziridinate methyl cinnamate, whereas Fe-catalyst gave low yield of aziridine under microwave conditions. Aziridination of different olefins using Hβ zeolite and broamine-T as nitrene source resulted in low to moderate yields. Aziridination of methyl cinnamate was found to result low yield even at 45 °C when Hβ zeolite was used as catalyst.

Table I: Comparative data for aziridination of olefins with homogeneous copper catalysts.

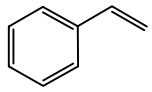
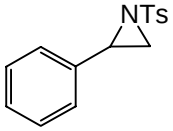
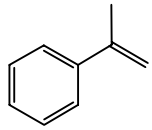
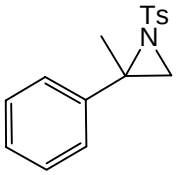
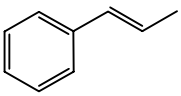
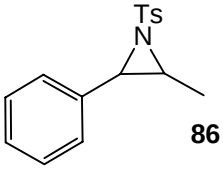
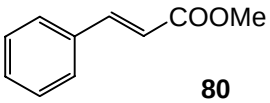
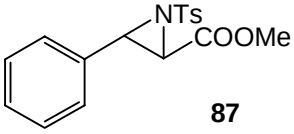
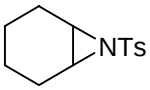
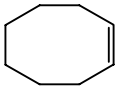
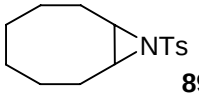
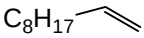
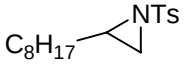
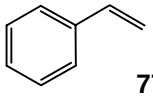
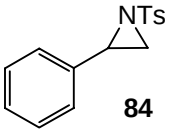
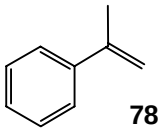
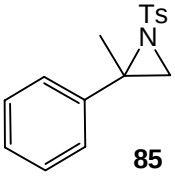
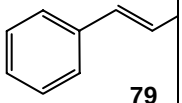
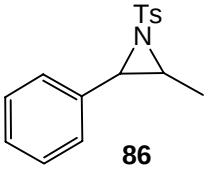
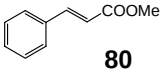
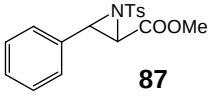
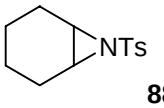
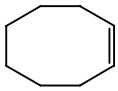
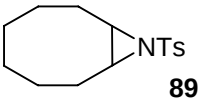
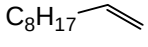
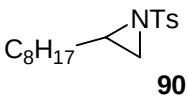
Substrate	Product	Homogeneous catalysis and bromamine-T	Copper hydrotalcite and Bromamine-T under microwave conditions
 **77**	 **84**	48 %	75 % (7 min)
 **78**	 **85**	81 %	78 % (7 min)
 **79**	 **86**	Not reported	73 % (10 min)
 **80**	 **87**	Not reported	72 % (7 min)
 **81**	 **88**	55 %	71 % (8 min)
 **82**	 **89**	72 %	81 % (8 min)
 **83**	 **90**	20 %	75 % (8 min)

Table II: Comparative data for aziridination of olefins with other heterogeneous copper catalysts

Substrate	Product	Heterogeneous catalysis using Cu-hydrotalcite and Bromamine - T	Heterogeneous copper nanoparticles and PhI=NTs as nitrene donor[#]	$[Cu(NCCH_3)_6][B(C_6F_5)_4]_2$ and(PhI= NTs) as nitrene donor[ψ]	(*)Using Cu exchanged Y-type Zeolite[ϕ]	Micro encapsulat-ed Cu(acac)2 PhI=NTs[$]
 **77**	 **84**	75 % 7 min	92 % (3 hrs)	65 %	62 %	90 %
 **78**	 **85**	78 % 7 min	64 % (3 hrs)	49 %	33 %	82 %
 **79**	 **86**	73 % 10 min	74 % (3 hrs)	32 %	Not available	80 %
 **80**	 **87**	72 % 7 min	30 % (7 hrs)	Not available	84 %	Not reported
 **81**	 **88**	71 % 8 min	40 % (5 hrs)	Not available	50 %	52 %
 **82**	 **89**	81 % 8 min	Not available	47 %	Not available	88 %
 **83**	 **90**	75 % 8 min	Not available	Not available	Not available	Not reported

- Reference 78

$ - Reference 73

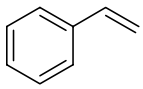
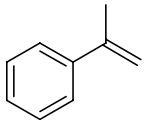
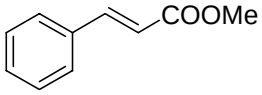
ψ - Reference 77

ϕ -Reference 96

Recyclability of copper hydrotalcite

Heterogenecity of copper hydrotalcite was evaluated by recycling the catalyst. After reaction, catalyst was separated by centrifuging. The catalyst was washed thrice by 10 ml acetonitrile each time. Aziridination was carried out using the same catalyst and same molar ratios of olefin and bromamine-T. The yield of each cycle is depicted in table III. Catalyst was successfully recycled two or three times without hampering the yields. Further recycling of catalyst was not carried out; however, we believe that it could be used many more times without much loss of activity.

Table III: Recyclability study

Entry	Olefin	Yield
1		75 % (1st recycle) 75 % (2nd recycle) 74 % (3rd recycle)
2		77 % (1st recycle) 75 % (2nd recycle)
3		70 % (1st recycle) 68 % (2nd recycle)
4		71 %(1st recycle) 70 % (2nd recycle)

Conclusion

Microwave assisted aziridination of olefins has been demonstrated for the first time using copper hydrotalcite as heterogeneous catalyst and bromamine-T as source of nitrene.The reagent can be easily prepared from chloramine-T at room temperature. Copper hydrotalcite is prepared and used as catalyst for aziridination of olefins. There is an appreciable increase in the yield in all cases. Aziridination of less reactive methyl cinnamate resulted in good yield with heterogeneous copper hydrotalcite. Yields of aziridination in the presence of heterogeneous copper hydrotalcite have been found to be comparable and many times better than copper exchanged Y- type zeolite. Finally it can be concluded that the present methodology has vast potential in aziridination of olefins and studies with other nitrene sources like chloramine-T, PhI=NTs etc. should yield comparative results. Further work on these lines is in progress.

Experimental

Preparation of copper hydrotalcite catalyst

The hydrotalcite clay containing copper was prepared by co-precipitation method. Magnesium nitrate (113.38 g, 0.45 mol), aluminum nitrate (56.27g, 0.15 mol) and copper nitrate (37.35 g, 0.15 mol) were dissolved in 400 ml distilled and demineralized water. The magnesium nitrate, aluminum nitrate and copper nitrate mixture was labeled as solution B. Sodium hydroxide (30.0 g, 0.75 mol) and sodium carbonate (25.0 g, 0.227 mol) were dissolved in 200 ml distilled and demineralized water and labeled as solution A.

To an open flanged reactor equipped with double turbo and a bottom anchor stirrer was charged 300 ml double distilled water. A pH electrode was attached in such a way that it immersed almost ¼ into the water charged. Both the solutions were added simultaneously in such a way that pH of reaction mixture was maintained at about 10-10.2.

After completion of addition the precipitate obtained was aged at 65°C for 30 minutes. Then reaction mass was cooled to room temperature. The precipitate was filtered and washed several times with distilled water till the filtrate pH was found to be neutral. The precipitate was dried initially at 100 ^{o}C and this dry powder was then again dried at 150 °C in muffle furnace. The light green colored catalyst thus obtained was analyzed for copper content by classical method of analysis. The X-ray diffraction study of prepared catalyst matched with the published information.

Preparation of Bromamine-T

Step I: Preparation of dibromamine-T

Recrytsallized chloramine-T (1.0 g, 4 mmol) was dissolved in water (20 ml) and liquid bromine (2 ml, 12 mmol) was added dropwise from a burette with constant stirring

of the solution. The golden yellow precipitate of the dibromamine-T was thoroughly washed with water, filtered under suction and dried in a vacuum desiccator for 24 hours.

mp 92 °C (lit[97] mp 92-93 °C).

Anal. Calcd for $C_7H_7NO_2SBr_2$ N, 4.26; S, 9.75; Br, 48.57 %.

Found N, 4.23; S, 9.71; Br, 48.54 %.

Step II: Preparation of bromamine-T

Dibromamine-T (3.3 g, 11 mmol) was dissolved in small lots at a time with stirring, in aqueous solution of sodium hydroxide (0.8 g, 20 mmol) in 50 ml of water, and the solution was cooled in ice. Pale yellow crystals of bromamine-T separated out. The solid was filtered under suction, washed quickly with minimum quantity of water and dried over P_2O_5 in a desiccator. The bromamine-T trihydrate obtained in the above step was dried to constant weight at 80 °C under vacuum.Yield: 2.8 g (86%)

^{1}H NMR (200 MHz, D_2O): δ 2.40 (s, 3H), 7.40 (2H, d, J = 1.9 Hz), 7.70 (2H, d, J = 1.9 Hz).

^{13}C NMR (50 MHz, D_2O): δ 25.45, 143.38, 134.30, 131.26, 129.31.

MS m/z: 274 (M^{2+}, 21), 272 (M^+, 7), 185 (5), 171 (18), 155 (22), 107 (17), 91(100), 77 (4).

Anal. Calcd for $C_7H_7NO_2SBrNa$ N, 5.15; S, 11.78; Br, 29.37 %.

Found N, 4.10; S, 11.75; Br, 29.32 %.

Typical experimental procedure for aziridination

To a solution of styrene (0.208 g, 2 mmol) in 15 ml acetonitrile, bromamine-T (1.088 g, 4mmol) and copper hydrotalcite (21 mg) were added and the mixture was kept in domestic microwave oven and irradiated for 7 min. After completion of reaction, the mixture was filtered. Residue was thoroughly washed with 15 ml more acetonitrile. The filtrate was evaporated under vacuum to afford crude product, which was further purified by column chromatography over silica gel using hexane: ethyl acetate as eluent to afford *N*-(*p*-tolylsulfonyl)-2-phenyl aziridine (394 mg, 75 %).

Spectral data

1) *N*-(*p*-Tolylsulphonyl)-2-phenyl aziridine (84)

mp	86-87 °C (lit[53] mp 87-88 °C).
IR (Nujol):	ν_{max} 3017, 1327, 1217, 1161 cm^{-1}.
^{1}H NMR (200 MHz):	δ 8.20 (2H, d, *J* = 10.8 Hz,), 7.7-7.5 (7H, m), 4.18 (1H, dd, *J* = 9.7, 6.5 Hz,), 3.39 (1H, d, *J* = 9.8 Hz), 2.82 (3H, s), 2.72 (1H, d, *J* = 6.3 Hz).
MS (m/z):	273 (M^+, 5), 155 (4), 118 (83), 91 (100).

2) *N*-(*p*-Tolylsulphonyl)-2-phenyl-2-methyl aziridine (85)

mp	80-81 °C (lit[53] mp 82-83 °C).
IR (Nujol):	ν_{max} 3060, 3028, 2992, 1440, 930 cm^{-1}.
^{1}H NMR (200 MHz):	δ 7.80 (2H, d, *J* = 8 Hz), 7.55 – 7.15 (7H, m), 2.81 (3H, s), 2.16 (3H, s).
MS (m/z):	287 (M^+, 1), 256 (1), 222 (10), 188 (40), 171 (65), 155 (100).

3) *N*-(*p*-Tolylsulphonyl)-2-phenyl-1-methyl aziridine (86)

IR (Nujol):	ν_{max} 3060, 3028, 2992, 1440, 930 cm^{-1}.
^{1}H NMR (200 MHz):	δ 7.84 (2H, d, *J* = 8 Hz), 7.18 – 7.29 (7H, m), 3.82 (1H, d, *J* = 7 Hz), 2.97 (1H, m), 2.47 (3H, s), 1.86 (3H, d, J = 7 Hz).
MS (m/z):	287 (M^+, 1), 271 (1), 155 (10), 118 (30), 91 (100),

4) *N*-(*p*-Tolylsulphonyl)-2-carbomethoxy-3-phenylaziridine (87)

IR (Nujol):	ν_{max} 3068, 3021, 2960, 1750, 1600, 1412 cm^{-1}.
^{1}H NMR (200 MHz):	δ 7.62 (2H, d, *J* = 8.3 Hz), 7.27-7.30 (7H, m), 5.11 (1H, d, *J* = 4.0 Hz), 4.44 (1H, s), 3.58 (1H, d, *J* = 4.0 Hz), 2.42 (3H, s).

5) *N*-(*p*-Tolylsulphonyl)-7-aza bicyclo [4.1.0] heptane (88)

mp 87-88 °C (lit[53] mp 88-89 °C).

IR (Nujol): ν_{max} 3020, 1600, 1440, 1395, 965, 920 cm^{-1}.

^{1}H NMR (200 MHz): δ 7.81 (2H, d, *J* = 9.8 Hz), 7.40 (2H, d, *J* =9.8 Hz), 3.10 (2H, t, *J* = 1.2 Hz), 2.49 (3H, s),1.80 -1.70 (4H, m), δ 1.50-1.40 (4H, m).

MS (m/z): 252 (M^{+1}, 1), 210 (2), 155 (6), 96 (100), 91 (40), 69 (40), 65 (17).

6) *N*-(*p*-Tolylsulphonyl)-9-aza-bicyclo [6.1.0] nonane (89)

IR (Nujol): ν_{max} 3028, 2982, 2936, 1600, 1498, 1160, 610 cm^{-1}.

^{1}H NMR (200 MHz): δ 7.77 (2H, d, *J* = 8.3 Hz,), 7.31-7.24 (2H, d, *J* = 8.3 Hz), 4.44 (1H, d, *J* =3.9 Hz), 3.53 (1H, d, *J* = 4 Hz), 2.41 (3H, s), 1.59- 1.20 (12H, m).

MS (m/z): 278 (2), 259 (M^+, 3), 210 (12), 125 (100), 91 (45), 55 (58).

7) *N*-(*p*-Tolylsulphonyl)-2-octylaziridine (90)

IR (Nujol): ν_{max} 3017, 1327, 1217, 1161, 916, 783 cm^{-1}.

^{1}H NMR (200 MHz): δ 7.8 (2H, d, *J* = 8 Hz), 7.4 (2H, d, *J* = 8 Hz), 2.56 (2H, d, *J* = 6 Hz), 2.46 (1H, m), 2.40 (s, 3H), 1.56 (14 H, m), 1.02 (3H, t, *J* = 4.8 Hz).

MS (m/z): 273 (M^+, 5), 155 (4), 118 (83), 91 (100), 65 (21).

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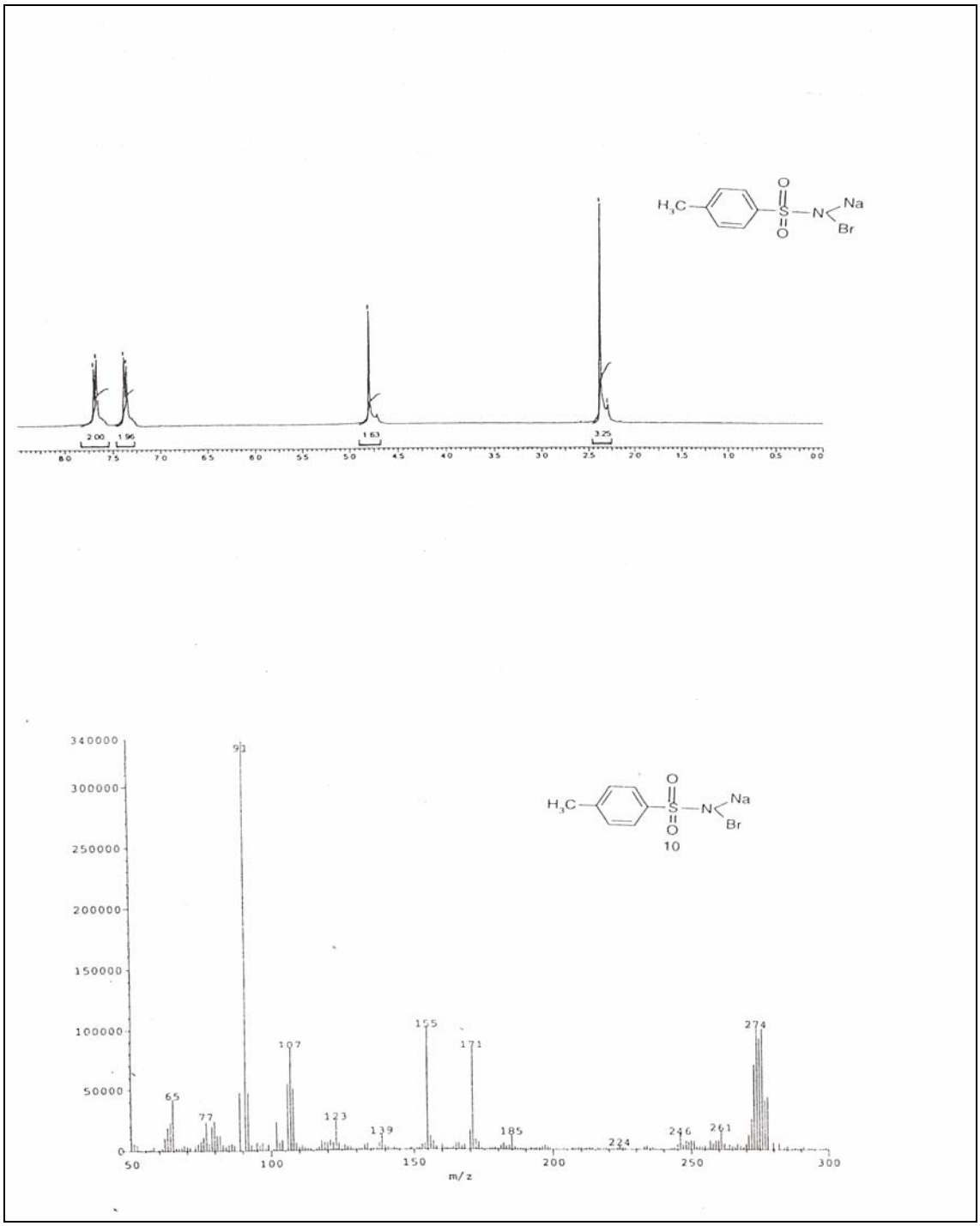
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N
Na
Br
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1.96
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3.25
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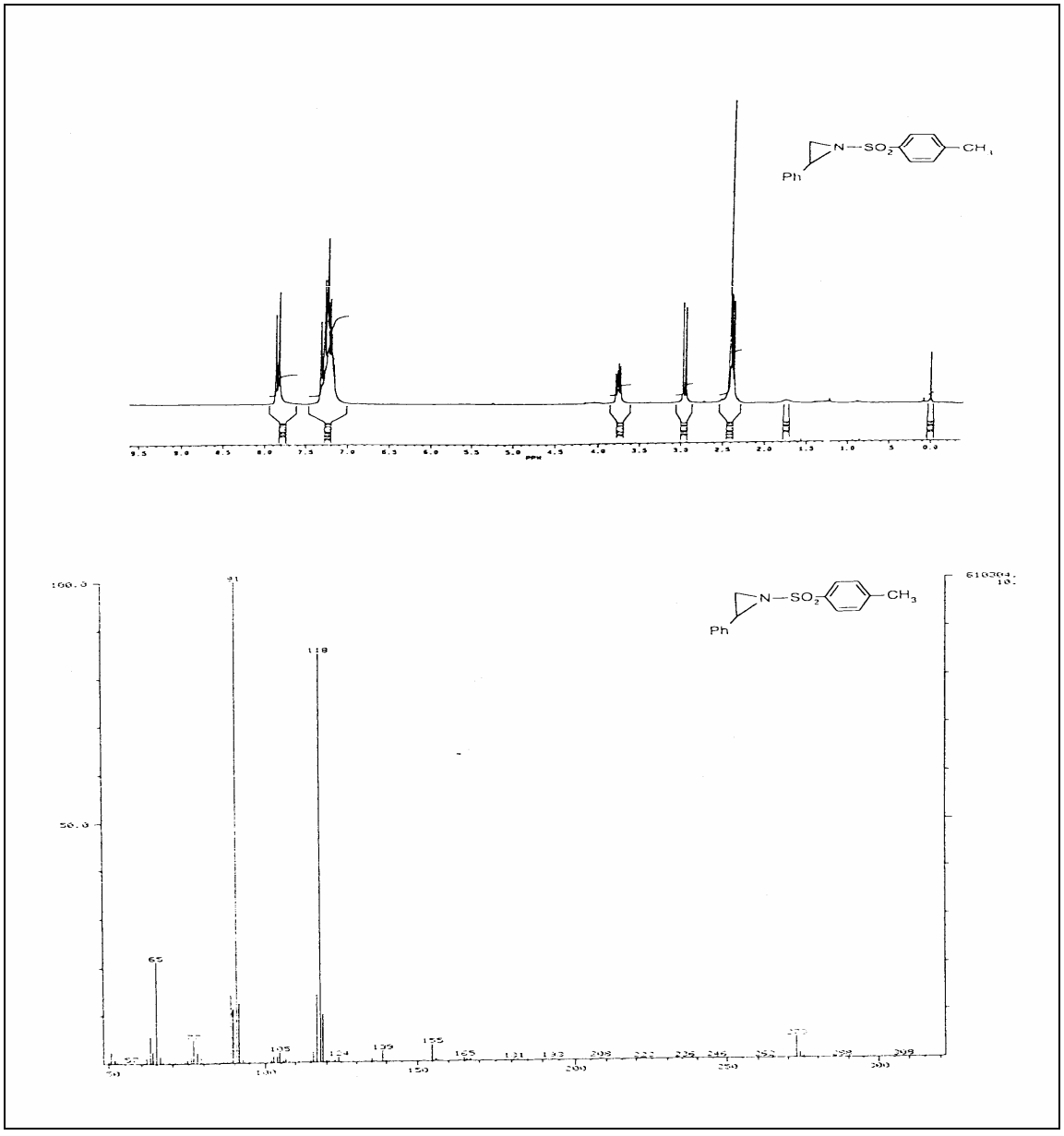
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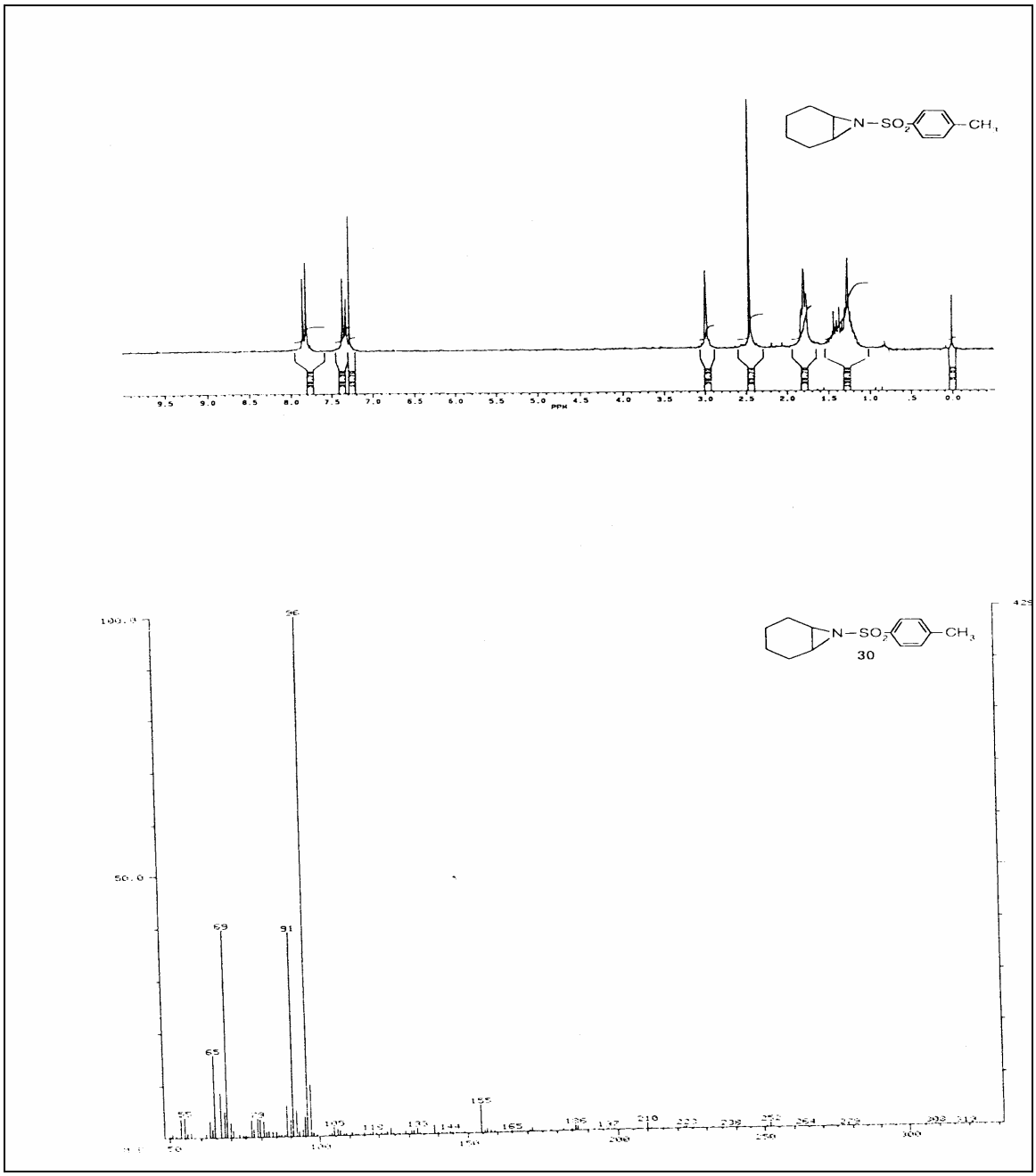
SO2
CH3
100.0
50.0
91
118
65
155
610364:
10: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PPM
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
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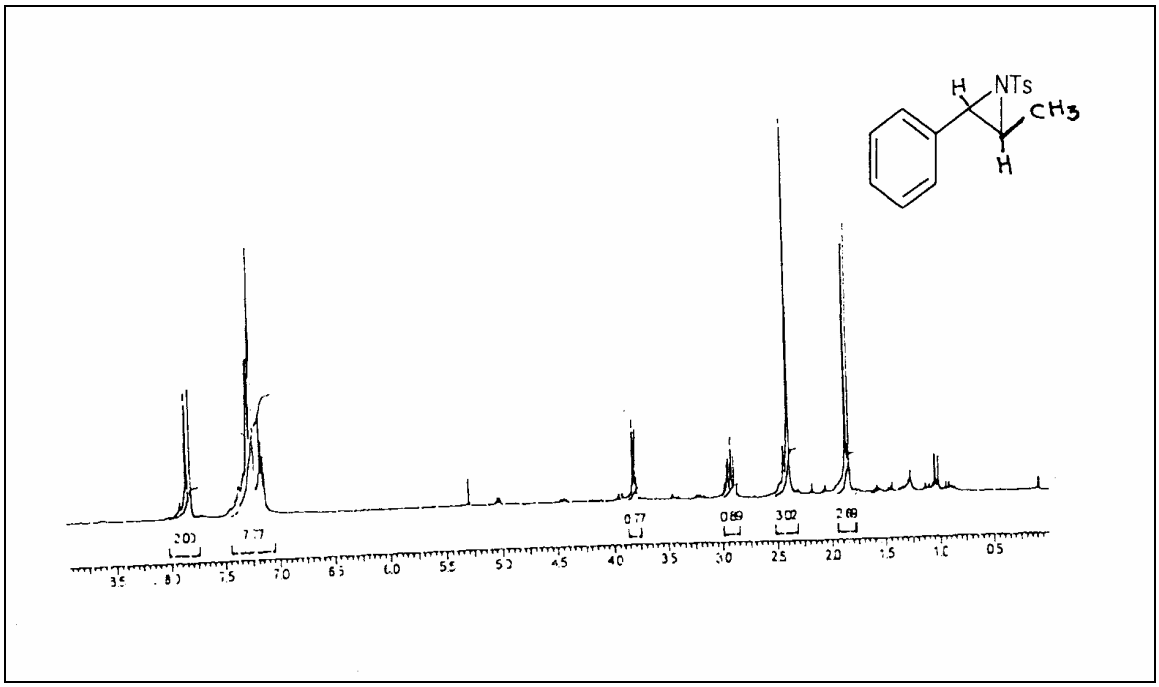
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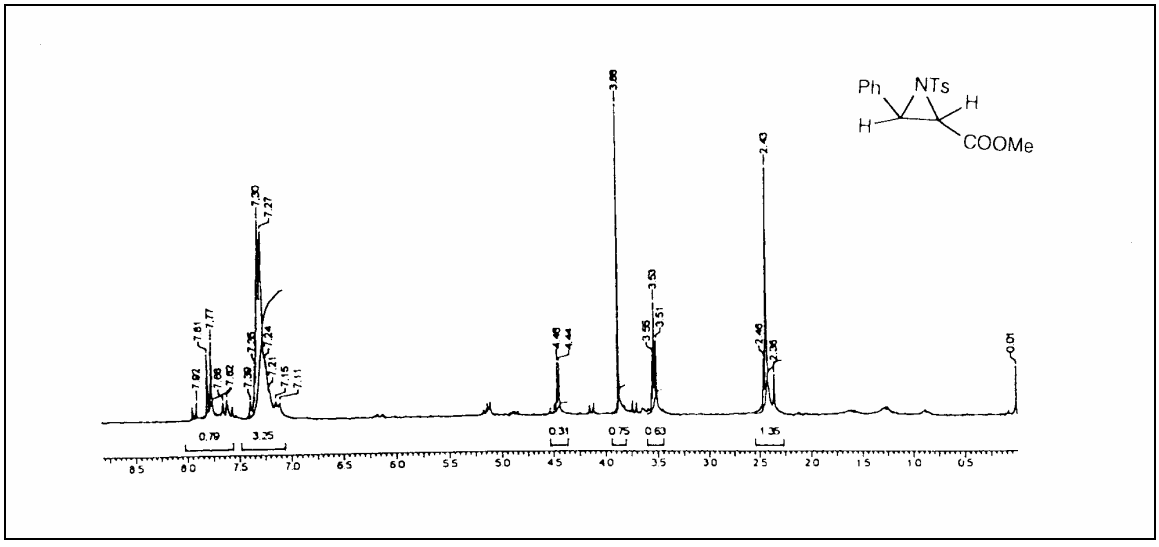
CH3
H


Ph
NTs
H
H
COOMe

CHAPTER 2

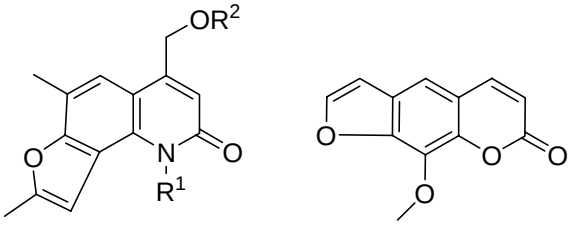
SYNTHESIS OF 3-SUBSTITUTED 2(1*H*)-QUINOLINONES CATALYZED BY HYDROTALCITE LIKE ANIONIC CLAYS

Part I: Synthesis of 2(1*H*)-Quinolinones: A Brief Review

Introduction

The 2(1*H*)-quinolinone moiety, often referred to as carbostyril moiety, is an important structural unit present in many biologically active molecules.[1-5] 4-Hydroxy-2(1*H*)-quinolinones and their derivatives represent a class of heterocyclic compounds that have been associated with several pharmacological,[6] medicinal and industrial applications;[7] platinum-containing derivatives were found to be useful for the treatment of a malignant tumor,[8] some *N*-benzyl derivatives were useful against HSV-1 and HSV-2 viruses[9] and 1-benzyl-3-formyl-4-hydroxy-2(1*H*)-quinolinone inhibited, *in vitro*, herpes simplex 2 virus.[10]

Recently, 4-hydroxymethyl -1, 6, 8-trimethylfuro[2, 3-h] – quinolin – 2 (1*H*) - one (HOFQ) **1** and its analogues **2** (MOFQ) and **3** (HOHFQ) were prepared.[11] These compounds show strong photoantiproliferative activity, higher than that of 8-methoxypsoralen (8-MOP) **4,** the most widely employed drug for photochemotherapy. Moreover, their activity is devoid of mutagenicity and skin phototoxicity.[12] Due to these features, furoquinolinones and other analogues appear to be very promising photochemotherapeutic agents.

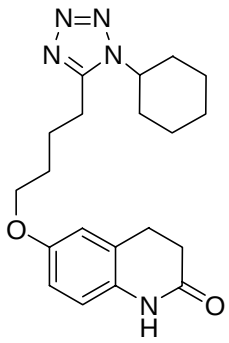


1 HOFQ R^1= Me, R^2=H
2 MOFQ R^1= Me, R^2=Me
3 HOHFQ R^1= H, R^2=Me

4 8-MOP

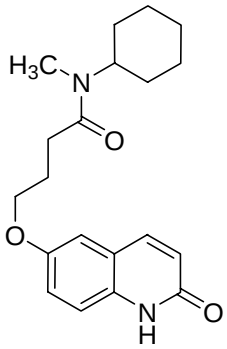
Ischemic diseases such as myocardial infarction, unstable angina and cerebral infarction are caused by an arteriostenosis which is led by chronically formed vascular intimal thickening and acutely formed thrombus in the vessels. Cilostazol[13] **5**, an anti-thrombotic agent, and cilostamide[14] **6,** a potent platelet aggregation inhibitor and anti-

hyperplastic agent, both have 2(1*H*)-quinolinone as core moiety. Drugs like repirinast (antiallergic) **7**, procaterol **8** and rebamipide (ulcer therapeutic) **9** possess quinolinone as core structure.



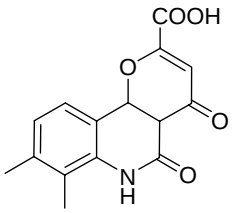
Cilostazol

5



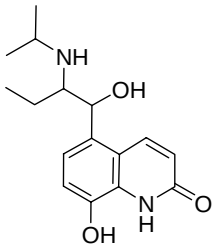
Cilostamide

6



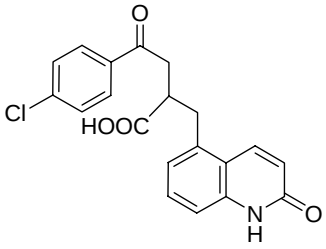
Repirinast (Antiallgeric)

7



Procaterol (Bronchodilator)

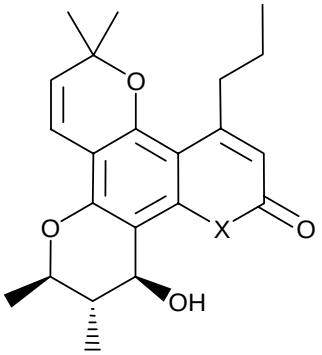
8



Rebamipide (Ulcer therapeutic)

9

Substituted 2(1*H*)-quinolinones bearing an electron withdrawing group and alkyl substituents have attracted considerable attention in recent years because of their pharmacological properties. Human immunodeficiency virus type I (HIV-1) is the causative agent for the transmission and development of the acquired immunodeficiency syndrome (AIDS).[15] Some 2(1*H*)-quinolinones have been used as intermediates in the synthesis of HIV-1 reverse transcriptase inhibitors.[16] Both naturally occurring (+)-calanolide A (**10a**) and its synthetic analogue aza-calanolide A (**10b**) belong to this class of NNRTI (Non-Nucleosidic Reverse Transcriptase Inhibitor) compounds. In fact, **10b** has been demonstrated to be more active than **10a**.[17]



10a X = O, (+)-Calanolide A

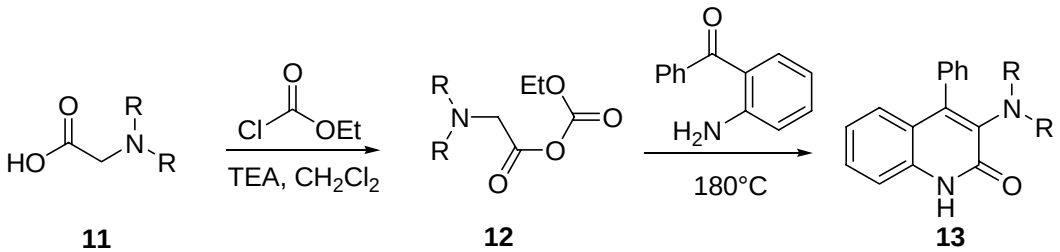
10b X = N, (+)-Aza-Calanolide A

Functionalized 4-arylquinolin-2(1*H*)-ones possess promising biological properties and a number of analogues of this class of heterocyclic structure have been reported as lead compounds or are currently undergoing clinical trials.[18-22]

Due to their interesting and important biological properties, a number of methods are reported in literature for the synthesis of 2(1*H*)-quinolinone moiety and quinoline derivatives with different substitution profiles and in fact, development of new and efficient methods for the preparation of these important molecules still continues to be an interesting and attractive area of research in synthetic organic chemistry. In the following pages, important approaches for the synthesis of 2(1*H*)-quinolinone will be highlighted.

Synthesis of 2(1*H*)-quinolinone moiety

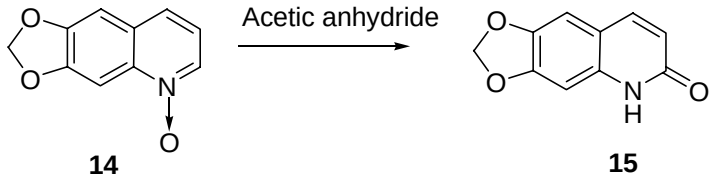
More than two dozen methods for the synthesis of 2(1*H*)-quinolinone moiety are reported. Soloshonok *et al*.[23] synthesized 3-amino substituted quinolinones by condensation of commercially available amino acid **11** with ethyl chloroformate to form an intermediate, mixed anhydride **12**, which on further treatment with *o*-amino benzophenone at high temperature gives 2(1*H*)-quinolinone **13** (**Scheme 1**).



11 **12** **13**

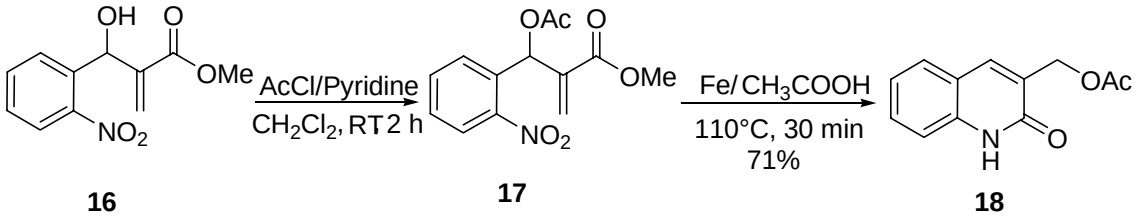
Scheme 1

Pettit *et al*.[24] synthesized 6,7-methylenedioxy carbostyril **15** from corresponding quinoline *N*-oxide **14** by heating the latter with acetic anhydride and evaluated the product for antitumor activity (**Scheme 2**). Benzoic anhydride, trifluroacetic anhydride and sodium acetate also can be used in place of acetic anhydride to synthesize such carbostyril derivatives.



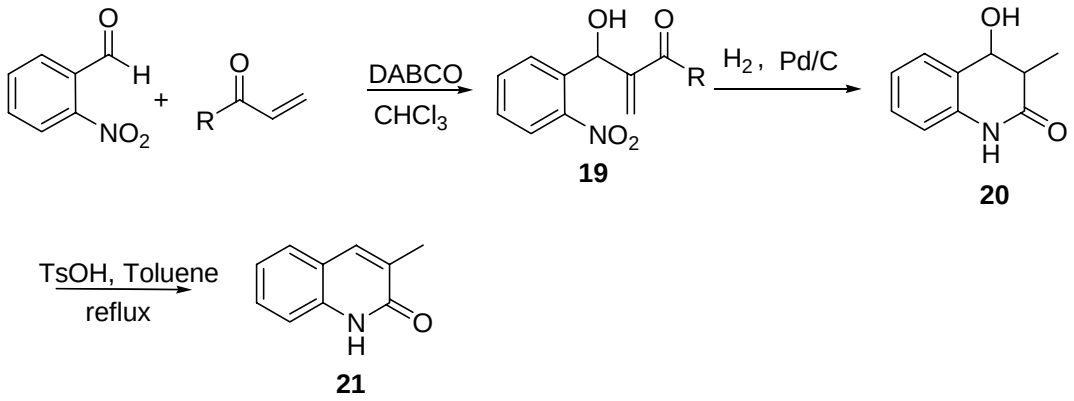
Scheme 2

Baylis-Hillman carbon-carbon bond forming reaction has become increasingly important because it is an atom economic reaction and provides various functionalized molecules. Basavaiah *et al*.[25] synthesized various 3-substituted quinolinones from Baylis-Hillman adduct derived from 2-nitrobenzaldehydes. 3-Hydroxy-3-(2-nitrophenyl)-2-methylene propanoate **16** on treatment with acetyl chloride in presence of pyridine as an acid binder gives **17,** further treatment of **17** with Fe/acetic acid at 110 °C gives 3-acetoxymethyl-(1*H*)-quinolin-2-one **18** in almost 70% yield (**Scheme 3**).



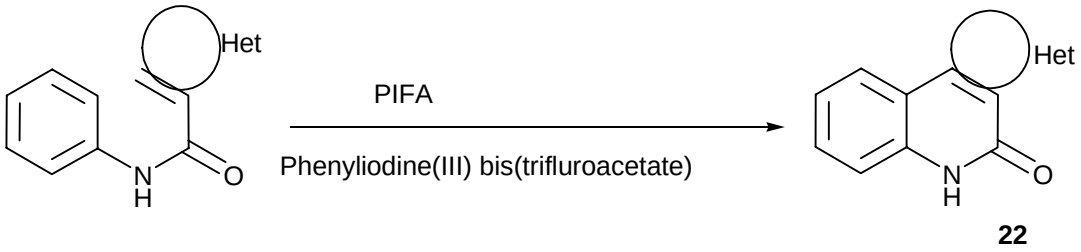
Scheme 3

Another application of Baylis-Hillman reaction was reported by Kaye *et al*.[26] They synthesized quinoline derivatives by reaction of 2-nitrobenzaldehyde with methyl vinyl ketones or ethyl acrylates in presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) below room temperature to give Baylis-Hillman adduct **19**, which on hydrogenation over palladium on charcoal and further dehydration gives substituted carbostyril derivatives **21** (**Scheme 4**).



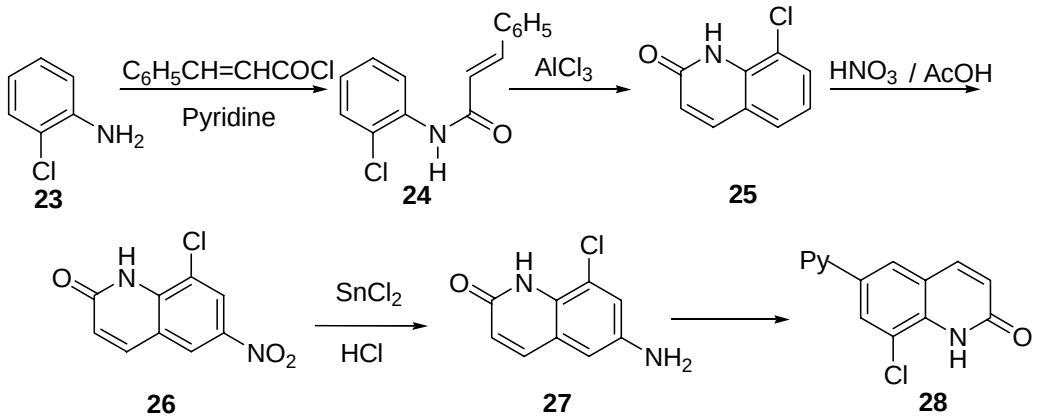
Scheme 4

Tellitu *et al*.[27] reported synthesis of heterocycle-fused quinolinone (**22**) derivatives by using phenyliodine (III) bis (trifluroacetate) (PIFA) mediated aryl-heteroaryl coupling reaction (**Scheme 5**).



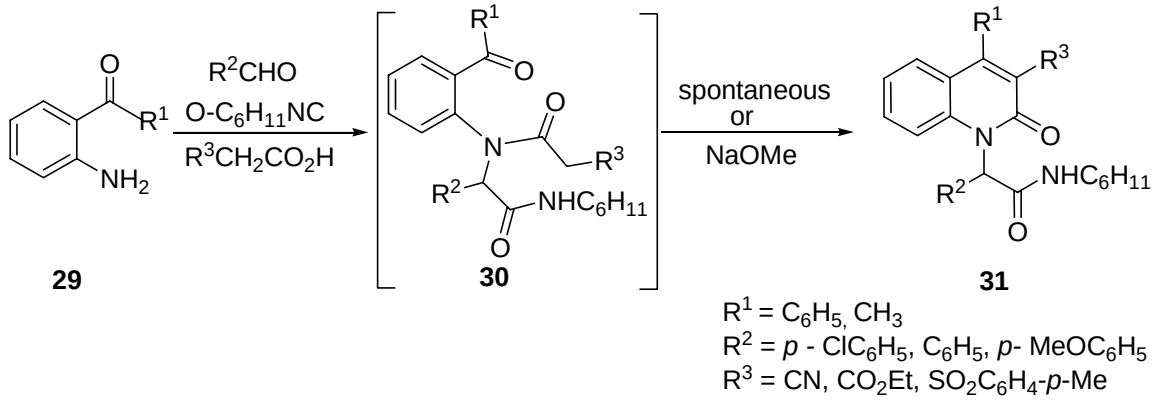
Scheme 5

Synthesis of a series of 6,7 and 8-pyridyl-2(1*H*)-quinolinone derivatives with various substituents like methyl, chloro, hydroxy and methoxy was reported by Leclerc *et al*.[2] For example, *o*-chloro aniline (**23**) was *N*-acylated with cinnamoyl chloride to give **24** and the latter on cyclization in the presence of $AlCl_3$ yielded 2(1*H*)-quinolinone **25**. This quinolinone was nitrated using nitric acid to give nitrate **26**, which on further reduction gave the amino derivative **27**. The latter was then converted into pyridyl derivative **28** (**Scheme 6**). Several such derivatives thus synthesized using different acid chlorides were found to possess cardiotonic properties.



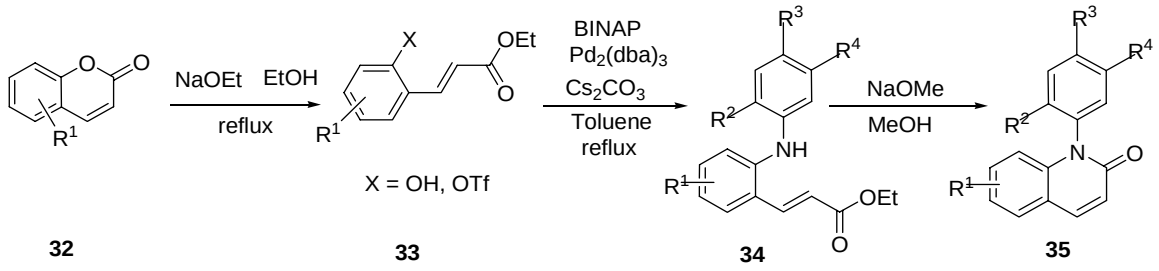
Scheme 6

Marcaccini *et al*.[28] synthesized various 3-substituted quinolin-2(1*H*)-ones bearing electron withdrawing groups by application of Ugi reaction. A four-component, one-pot sequential Ugi condensation of *o*-acylanilines **29** with aldehydes, malonic or tosylacetic acids and cyclohexyl isocyanide followed by cyclization resulted in the formation of substituted 2(1*H*)-quinolinones **31**(**Scheme 7**).



Scheme 7

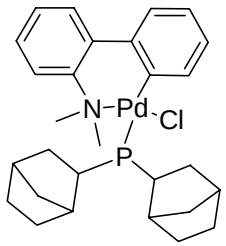
N-phenyl-2(1*H*)-quinolinones were synthesized by Ullrich *et al*.[29] from variety of commercially available coumarins using Buchwald-Hartwig amination protocol in the key reaction. Base catalyzed ring opening of coumarins **32** followed by amination with substituted aniline gave the aminoester **34,** further cyclization of **34** yielded *N*-phenyl-2(1*H*)-quinolinones **35** (**Scheme 8**).



R^1 = H, 6-Me, 6-NO_2, 7-Me, 7-OMe
R^2 = R^3 = R^4 = H
R^2 = R^3 = H, R^4= OMe
R^2 = Cl, R^3 = COOMe, R^4= OMe

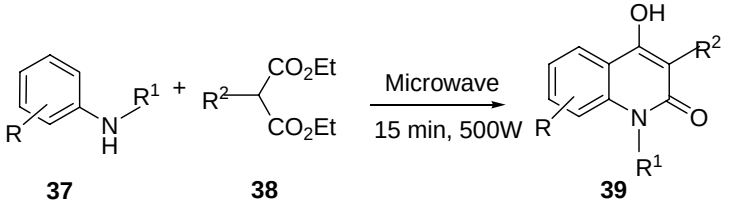
Scheme 8

Microwave assisted amination of **33** was also attempted by the same group to give 47% yield of aminated product **34**. By using catalyst **36** [bis(bicyclo[2.2.1]hept-2-yl)phosphine]chloro[2'-(dimethylamino-κN)-[1,1'-biphenyl]-2-yl-κC]palladium (SK-CC01-A), they observed that the reaction proceeded at a faster rate to give 80% yield of aminated product **34**.



36

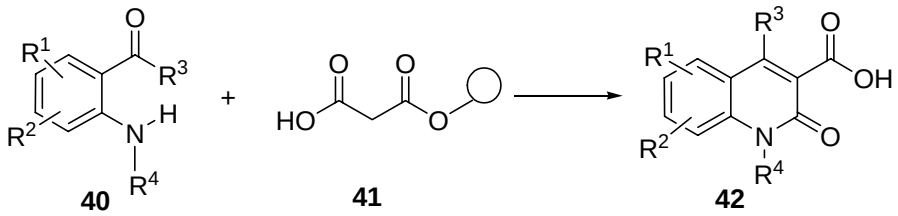
3-Aryl-4-hydroxyquinolin-2(1*H*)-ones are potent NMDA receptor antagonists. Microwave assisted synthesis of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones under solvent free condition was developed by Lange *et al*.[30] The quinolinones **39** were thus obtained by formal amidation of malonic ester derivatives **38** with anilines **37** and subsequent cyclization of intermediate malonadianilides (**Scheme 9**).



R = H, 2-Cl, 2-MeO, 2-CF_3, R^1 = H, CH_3, Cyclohexyl, R^2 = Ph, 4-MeO-C_6H_5

Scheme 9

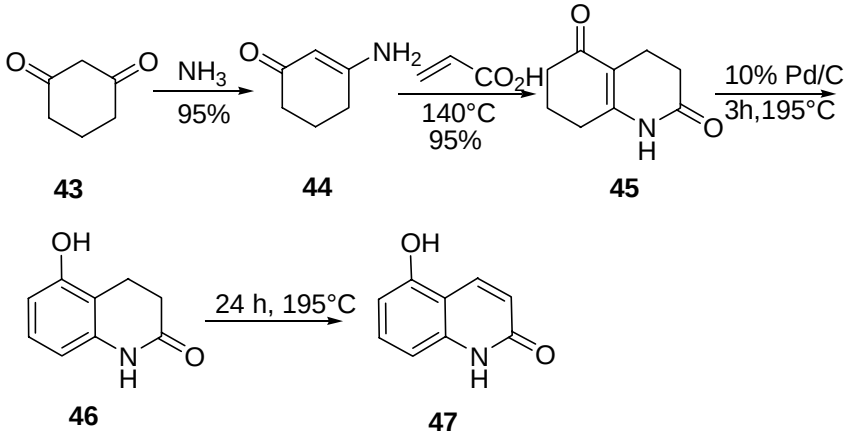
Watson *et al.*[31] synthesized 3-substituted 2(1*H*)-quinolinones **42** by two-step synthesis in which *o*-aminophenones **40** are coupled with malonic acid **41** bound to the Wang resin followed by ring closure *via* an intramolecular Knoevenagel condensation (**Scheme 10**).



$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = H$
R^1 = 4-MeO, R^2 = 5-MeO, R^3= Me, $R^4 = H$

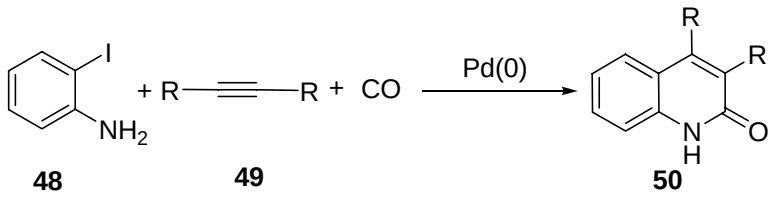
Scheme 10

Shono *et al.*[32] synthesized 5-hydroxy carbostyril by reaction of 1,3-cyclohexanedione **43** with ammonia to give 3-amino-2-cyclohexen-1-one **44**. Heating **44** with acrylic acid at 140 °C gave **45** which on heating with 10% Pd/C gives tetrahydro derivative **46** and on continued heating for 24 hrs gives desired 5-hydroxy quinolinone **47** was obtained (**Scheme 11**).



Scheme 11

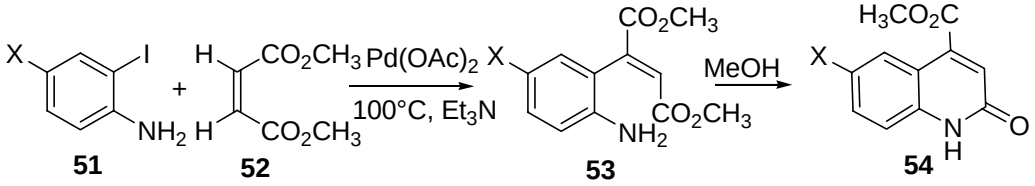
Synthesis of 3,4-disubstituted 2(1*H*)-quinolones **50** was reported by Larock *et al.*[33] by palladium catalyzed annulation of alkynes **49** with *o*-iodoaniline **48** (**Scheme 12**).



48 **49** **50**

Scheme 12

Heck *et al*.[34] reported Pd catalyzed synthesis of 2(1*H*)-quinolones by reaction of 2-iodo anilines **51** with acrylic acid derivative **52** to obtain 2(1*H*)-quinolones **54** in moderate to good yields (**Scheme 13**).

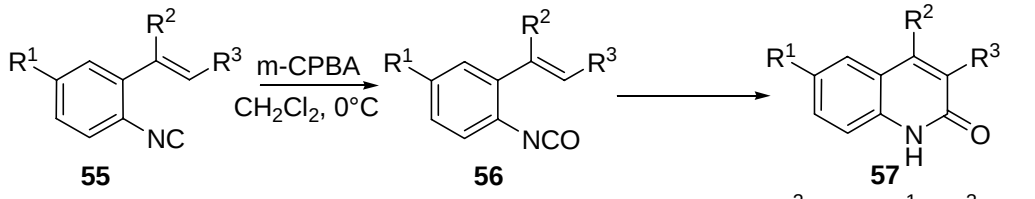


51 **52** **53** **54**

X= H, Br, OH

Scheme 13

Kobayashi *et al*.[35] prepared substituted 2(1*H*)-quinolones **57** *via* electrocyclic reaction of isocyanatostyrenes **56** generated *in situ* from *m*CPBA oxidation of *o*-isocyanostyrenes (**55**) (**Scheme 14**).



55 **56** **57**

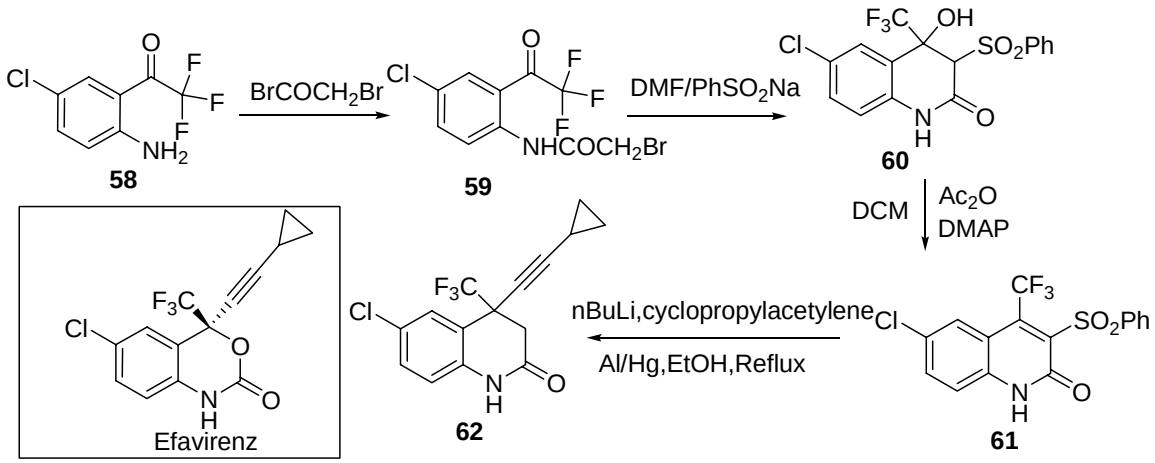
R^2 = Me, R^1 = R^3 = H

R^2 = Ph, R^1 = R^3 = H

Scheme 14

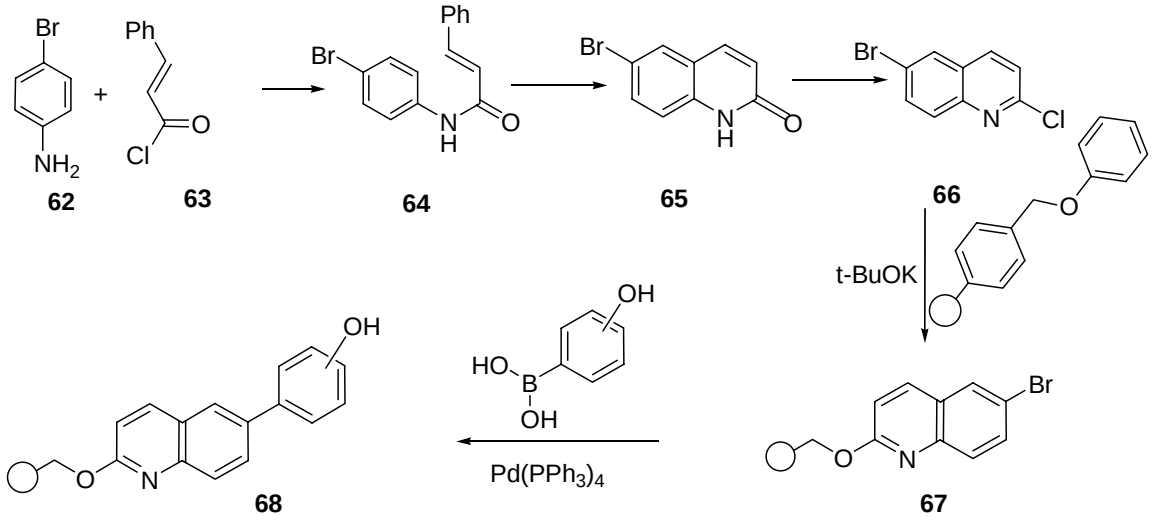
Patel *et al*.[16] prepared amide **59** from trifluro derivative of amino acetophenone **58** which was subjected to intramolecular cyclization to give dihydroquinolinone **60**. The latter was dehydrated with acetic anhydride to yield 2(1*H*)-quinolinone **61**. C-alkylation

with cyclopropylacetylene in presence of n-BuLi yielded the HIV-1 reverse transcriptase inhibitor **62** (**Scheme 15**). It showed enhanced activity than known anti HIV drug efavirenz.



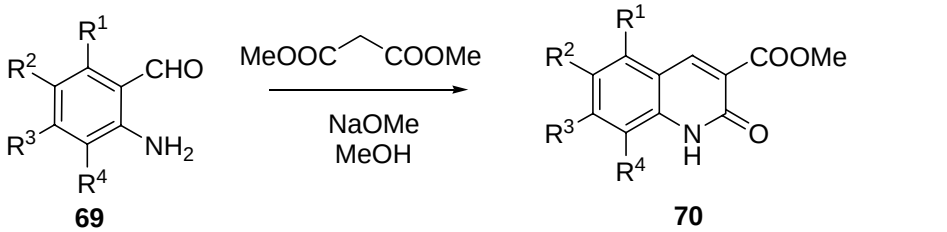
Scheme 15

Ruda *et al*.[36] synthesized solid phase linked various 6-substituted quinolinones **68** starting from substituted anilines **62** and acrylic acid derivative **63.** The intramolecular cyclization of **64** was carried out with done using $AlCl_3$ as catalyst to yield **65**. Further conversion to its chloro derivative was achieved using $POCl_3$. Pd catalyzed Suzuki coupling after solid phase linking to achieve 6-substitution gave the required product **68** (**Scheme 16**).



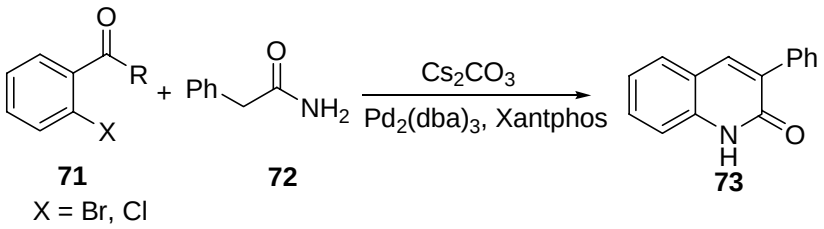
Scheme 16

Cordi *et al*.[37] synthesized various 3-substituted quinolinones **70** by base catalyzed reaction of substituted *o*-amino benzaldehyde **69** with dimethyl malonate in presence of NaOMe (**Scheme 17**).



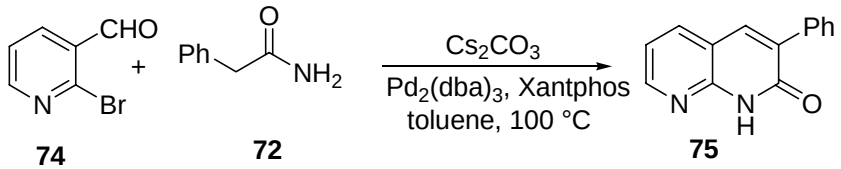
Scheme 17

Manley *et al*.[38] synthesized 2(1*H*)-quinolinones **73** by palladium catalyzed amidation of **71** by substituted amides **72** in presence of xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), as an alternative to Friedlander condensation in about 32-94% yield (**Scheme 18**).



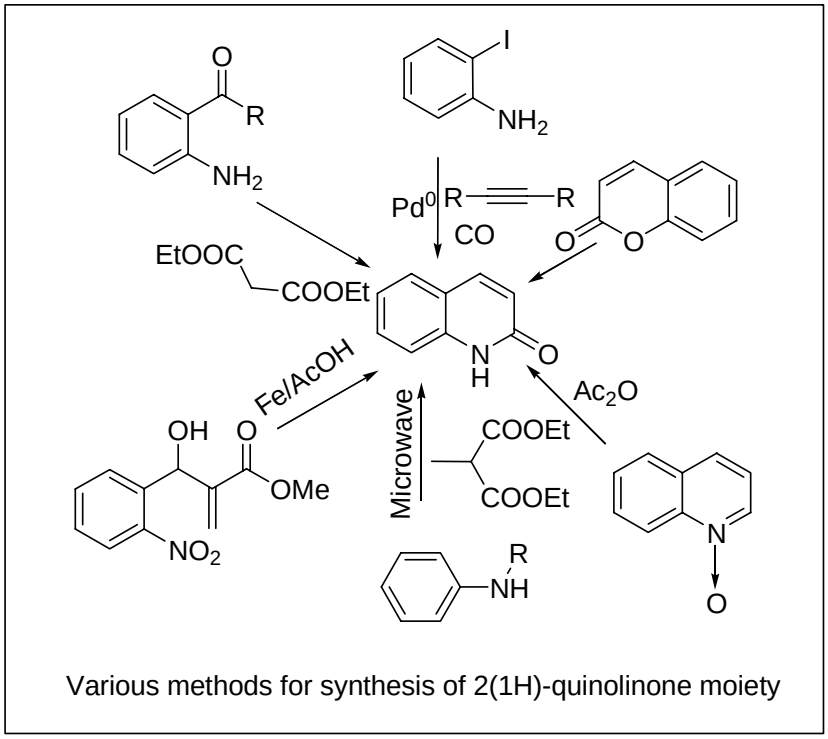
Scheme 18

They further extended the scheme for synthesis of 1,8-naphthyridinones **75** by using halo substituted pyridine carboxaldehyde **74** (**Scheme 19**).



Scheme 19

Thus various methods reported here for the synthesis of 2(1*H*)-quinolinone can be summarised as follows.



Various methods for synthesis of 2(1H)-quinolinone moiety

The schemes depicted so far distinctly bring out the importance of 2(1*H*)-quinolinone moiety in synthetic organic chemistry. These substituted quinolinones exhibit anti-HIV, anti-cancer, anti-ulcer, cardiotonic and antidepressant activities. The classical methods of synthesis of 2(1*H*)-quinolinones include a base-catalyzed intramolecular aldol condensation, Friedlander synthesis, Camps modification of the Friedlander synthesis, and an acid catalyzed cyclization of 3-ketoanilides i.e. Knorr synthesis. Recent methods include synthesis of 2(1*H*)-quinolinones using Baylis Hillman adduct and various palladium catalysed routes for wide variety of substituted 2-quinolinones. These synthetic methods have limited utility and drawbacks of low yield and laborious work up. Several other methods for synthesis of 3,4-disubstituted 2(1*H*)-quinolinones such as the titanium-promoted intermolecular reductive cyclization of *N*-(2-acylphenyl) alpha ketoamides, the $AlCl_3$ promoted annulation of terminal and internal alkynes and the oxidation of 2-cyanostyrene with *m*-CPBA have also been reported in the

literature. The yields of these processes however are often low and the variety of substrates is also found to be limited. The alternate method for Friedlander condenstion includes the use of expensive palladium catalyst. Syntheses of 2(1*H*)-quinolinone involve intramolecular cyclization of *o*-substituted amino moiety with the compounds having active methylene group in presence of a basic catalyst like sodium methoxide or cyclization using Lewis acid like $AlCl_3$ or H_2SO_4. Carbostyril derivatives require either substituted o-nitro benzaldehyde or amino aldehyde. It is apparent from the various synthetic methods presented above that future strategies should be chosen effectively for catalytic synthesis of 2(1*H*)-quinolinone as core moiety with different substitutents. It is with this view in mind that the present work was undertaken and the same is elaborated in Part II.

Part II: Synthesis of 3-substituted 2(1*H*)-quinolinones catalyzed by hydrotalcite like anionic clays

Introduction

Green and Sustainable Chemistry (GSC) is a revolutionary concept which aims at safety and environmental aspects of chemical processes and reduction of the risks of chemical products to people and the environment. In recent years, there has been increasing emphasis on the use and design of environment-friendly solid acid–base catalysts to reduce the amount of toxic waste and by-products arising from the chemical processes prompted by stringent environment protection laws. Many of the steps involved in the synthesis of fine chemicals and pharmaceuticals make use of large quantities of reagents such as mineral acids, bases and functionalizing agents. As a result, the *E*-factor (weight of by-product per unit weight of product) is large; being in the range 5 - 100. The large yields of the by-products lower the atom efficiencies of the processes, waste valuable raw materials and necessitate expensive waste treatments lowering their overall economics. Development of alternative environmentally benign synthetic routes is thus of primary concern. In this connection, use of environmentally friendly heterogeneous catalysts assume significance as it results in waste minimization, safer operating

conditions and easier product work-up. Though the use of solid acids such as clays and zeolites as 'green' catalysts has been well established,[39,40] the use of solid bases is much less developed.[41,42]

Hydrotalcite (a mineral that can be easily crushed into white powder similar to talc, discovered in Sweden at around 1842), is hydroxycarbonate of magnesium and aluminium and occurs in nature in foliated and contorted plates or fibrous masses. Synthetically prepared hydrotalcites have been used as such or mainly after calcination for various catalytic reactions.

The most interesting properties of the oxides obtained by calcination are as follows:

1) High surface area
2) Basic properties.
3) Formation of homogeneous mixtures of oxides with very small crystal size, stable to thermal treatment, which by reduction form small and thermally stable metal crystallites.
4) "Memory effect", which allows the reconstruction, under mild conditions, of the original hydrotalcite structure when contacting the product of the thermal treatment with water solutions containing various anions.

Properties 1, 2 and 3 have found application in the field of heterogeneous catalysis whereas properties 1, 2 and 4 are found to be utilized in the application such as chloride ions removal and purification of water or gases.

To understand the structure of these compounds it is necessary to start from the structure of brucite, $Mg(OH)_2$, where octahedra of Mg^{2+} (6-fold coordinated to OH^-) share edges to form infinite sheets. These sheets are stacked on top of each other and are held together by hydrogen bonding (**Fig A**). When Mg^{2+} ions are substituted by a trivalent ion having not too different radius (such as Fe^{3+} for pyroaurite and Al^{3+} for hydrotalcite, respectively) a positive charge is generated in the hydroxyl sheet. This net positive charge is compensated by $(CO_3)^{2-}$ anions, which lie in the interlayer region between the two brucite-like sheets (**Fig B**). In the free space of this interlayer, the water of crystallization also finds a place (**Fig C**). The main features of HTc structures

therefore are determined by the nature of the brucite-like sheet, by the position of anions and water in the interlayer region and by the type of stacking of the brucite-like sheets.

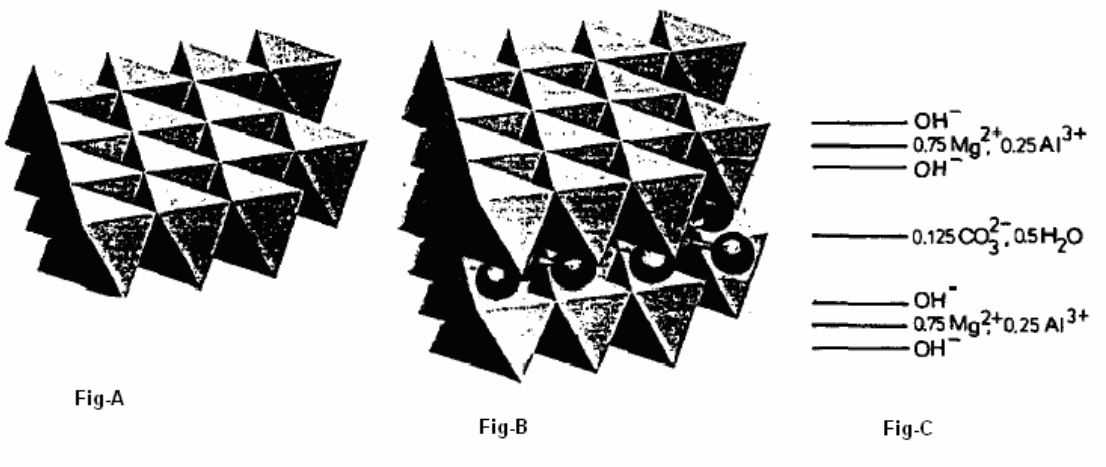


Fig-A Fig-B Fig-C

Hydrotalcite may be represented by the general formula

$[M^{2+}_{1-x}M^{3+}_{x}(OH)_2]^{x+}$ $(A^{n-})_{x/n} \cdot mH_2O]$, where M^{2+} (M = Mg, Fe, Co, Cu, Ni, or Zn) and M^{3+} (M = Al, Cr, Ga, Mn or Fe) are di- and trivalent cations respectively; the value of x is equal to the molar ratio of $M^{2+}/(M^{2+} + M^{3+})$ and is generally in the range 0.2–0.33; A^{n-} is an anion.

Thus hydrotalcite can be considered complementary to aluminosilicate clays, with widely varied physicochemical properties that can be obtained by changing the nature of the metal cations, the molar ratios of M^{2+}/M^{3+} as well as the type of interlayer anions.

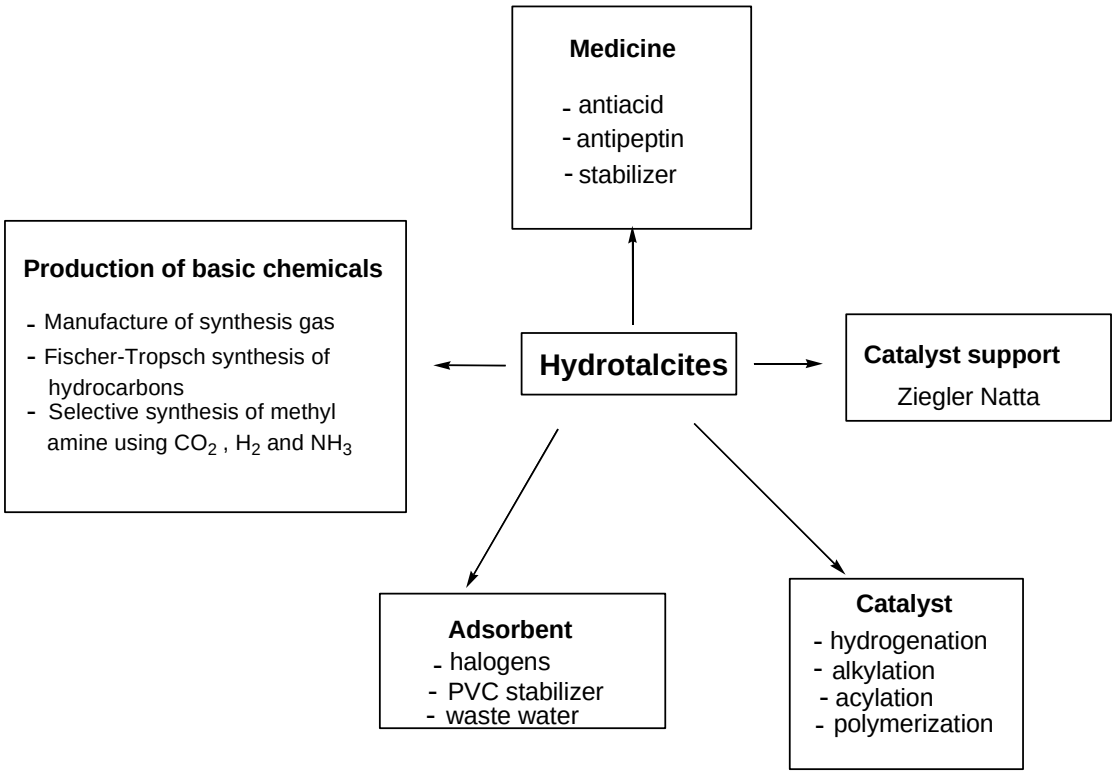
Due to their high versatility, easily tailored properties and low cost, LDHs (Layered double hydroxides) prepared directly or after thermal treatment, are promising materials for a large number of practical applications in catalysis, adsorption, pharmaceutics, photochemistry, electrochemistry and other areas.

Catalytic applications of hydrotalcites

Many workers have reported the use of non-calcined LDHs in a large number of catalytic reactions, including epoxidation reactions of styrene using Mg/Al LDHs,[43] Knoevenagel condensation using Ni/Al LDHs,[44] hydroxylation of phenol over Co/Ni/Al

LDHs[45] and liquid phase carbonylation of methanol to methyl acetate over Ni/Al LDHs.[46] Choudary *et al*.[47] have reported a catalyst derived from calcined-rehydrated Mg/Al LDH (Mg/Al= 2.5:1), which was used for selective Michael addition reactions on methyl vinyl ketone, methyl acrylate, and simple and substituted chalcones by donors such as nitroalkanes, malononitrile, diethyl malonate, cyanoacetamide and thiols, with quantitative yields obtained under mild reaction conditions.

Many reports have focused on the use of mixed oxide catalysts formed by thermal treatment on LDHs. Such metal oxides are known to promote a wide variety of industrially important base-catalyzed reactions.[47]



Hydrotalcites applications

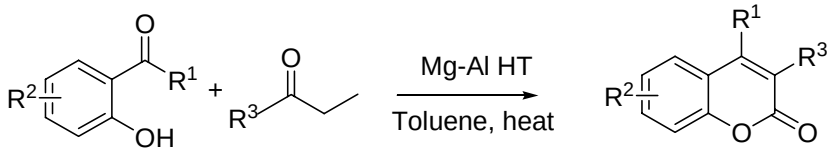
High activity and selectivity with calcined Mg/Al LDH catalysts have been reported in a wide variety of reactions, such as aldol,[48-53] Claisen-Schmidt,[54] and Knoevenagel condensations,[55,56] Meerwein-Ponndorf-Verley (MPV) reduction,[57-59] Henry reaction of aldehydes,[60] isomerizations[61,62] and the polymerization of propylene oxide.[63] Kumbhar *et al*.[64] found that Mg/Al-CO_3 LDHs heated in N_2 up to 550 °C are

highly active and selective catalysts for the liquid phase MPV reduction of carbonyl compounds using 2-propanol as the hydrogen donor; the catalysts can also readily be regenerated.

Present work

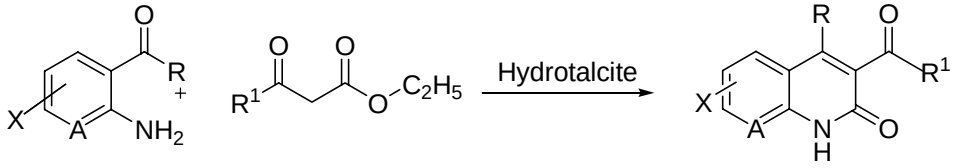
Most of the methods mentioned earlier for the synthesis of 2(1*H*)-quinolinones involve intramolecular cyclization of *o*-substituted amino moiety with the compounds having active methylene group in presence of basic catalyst such as sodium methoxide. In the present work, hydrotalcites, which are extremely useful as base catalysts in synthetic organic chemistry, have been used for synthesis of 2(1*H*)-quinolinone successfully with high and consistent yield.

Chanda *et al*.[65] already demonstrated synthesis of 2(*H*)-benzopyran-2-ones using hydrotalcite like anionic clay as catalyst for Knoevenagel condensation (**Scheme 20**). Various hydrotalcites were synthesized with different ratios of Mg:Al and investigated for synthesis of coumarins. They found that Mg-Al 3.0 CHT (Calcined hydrotalcite) was more active than Mg-Al 2.0 CHT and Mg-Al 4.0 CHT.



Scheme 20

Hence, it was decided to utilize Mg-Al 3.0 CHT as catalyst for the synthesis of various 2(1*H*)-quinolinones by reacting substituted *o*-amino arylaldehydes or *o*-aminoarylcarbonyl compounds with ethyl acetoacetate or diethyl malonate (**Scheme 21**).



Scheme 21

Synthesis of Mg: Al hydrotalcite Clay

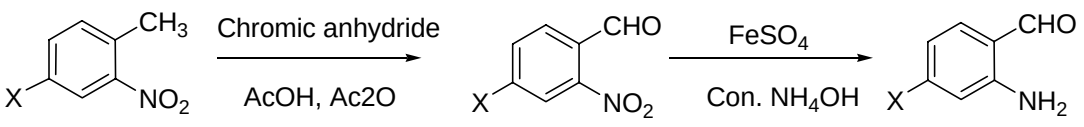
Various methods for preparation of hydrotalcites are reported in the literature. Most of the methods involve precipitation at increasing pH or co-precipitation at low or high concentration with hydrothermal treatment or aging during synthesis of hydrotalcites. Co-precipitation at low saturation and at constant pH is the method frequently used for synthesis of hydrotalcites. Low saturation is usually preferred for more crystalline precipitate due to slow rate of nucleation than the crystal growth rate.

Thus, the aqueous solution of magnesium nitrate and aluminium nitrate was mixed with aqueous solution of sodium hydroxide and sodium carbonate keeping reaction pH 10 to precipitate out hydrotalcite clay with the composition of Mg/Al = 3. The clay was filtered, washed with water and calcinated at 250 °C before use.

Synthesis of *o*-aminocarbonyl compounds

Various 2-amino substituted carbonyl compounds were synthesized by multistep synthesis reported in literature.

2-Aminobenzaldehyde (**76**) was synthesized by reducing 2-nitrobezaldehyde using ferrous sulfate and ammonium hydroxide.[66] The product was isolated by steam distillation. 4-Chloro-2-aminobenzaldehyde (**81**) and 4-bromo-2-aminobenzaldehyde (**82**) were synthesized by reduction of 4-chloro-2-nitrobenzaldehyde (**79**) and 4-bromo-2-nitrobenzaldehyde (**80**) respectively by treatment with ferrous sulfate and ammonium hydroxide. Starting nitro compounds were in turn synthesized by oxidation of 2-nitro-4-chlorotoluene (**77**) and 2-nitro-4-bromotoluene (**78**) respectively with chromic acid by reported method[67] (**Scheme 22**).



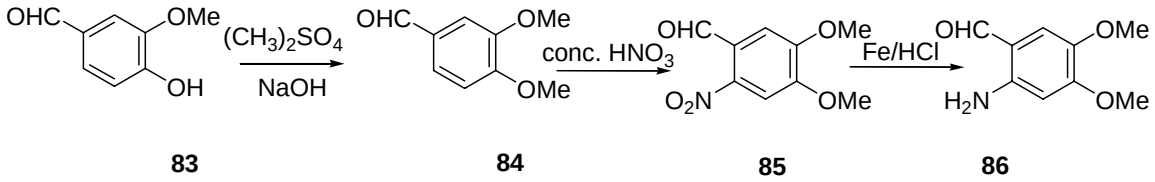
77 X = Cl
78 X = Br

79 X = Cl
80 X = Br

81 X = Cl
82 X = Br

Scheme 22

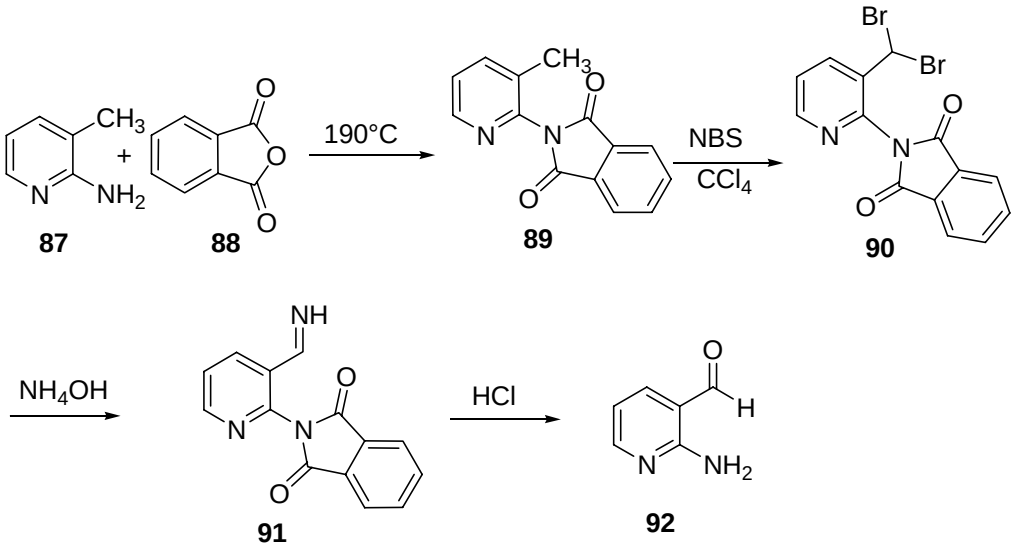
2-Amino-4,5-dimethoxybenzaldehyde (**86**) was prepared from 2-nitro-4,5-dimethoxy benzaldehyde (**85**). The latter compound itself was synthesized from commercially available vanillin (**83**), first by converting it to 4,5-dimethoxybenzaldeyde (**84**) followed by nitration using concentrated nitric acid.[69] The nitro compound (**85**) was subsequently reduced using Fe/HCl to get corresponding amino compound (**86**) (**Scheme 23**).



83 **84** **85** **86**

Scheme 23

2-Amino-3-picoline (**87**) was reacted with phthalic anhydride (**88**) at high temperature to convert into phthalimide (**89**), which was brominated using *N*-bromosuccinimide. Dibromo derivative (**90**) thus obtained was converted into imine (**91**) using concentrated ammonia solution which was further treated with hydrochloric acid to give 2-amino nicotinaldehyde (**92**)[70] (**Scheme 24**).

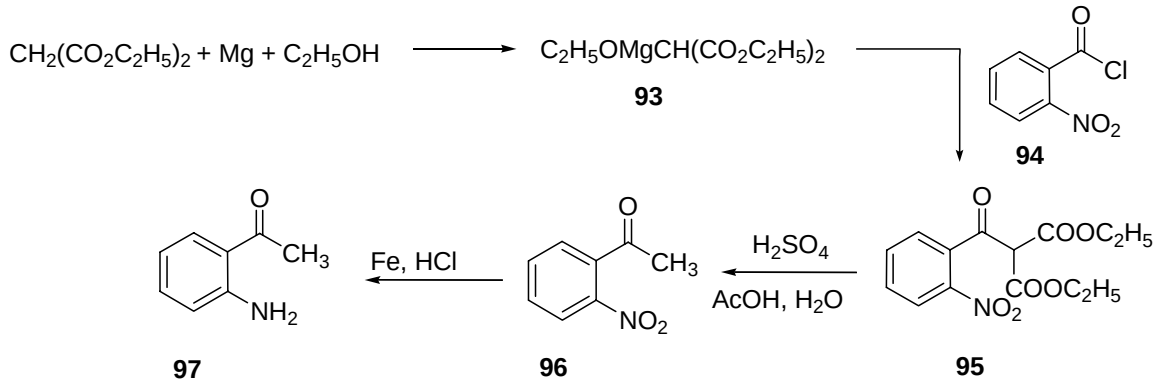


87 **88** **89** **90**

91 **92**

Scheme 24

o-Amino acetophenone (**97**) was obtained from *o*-nitrobenzoyl chloride (**94**) by reported procedure.[68] Thus **94** was reacted with magnesium-ethoxide salt of diethyl malonate (**93**) to get diethyl *o*-nitrobenzoyl malonate (**95**). The malonate (**95**) was further treated with a mixture of acetic acid-sulfuric acid-water to yield *o*-nitroacetophenone (**96**) which in turn was reduced using iron and hydrochloric acid to yield *o*-aminoacetophenone **97** (**Scheme 25**).

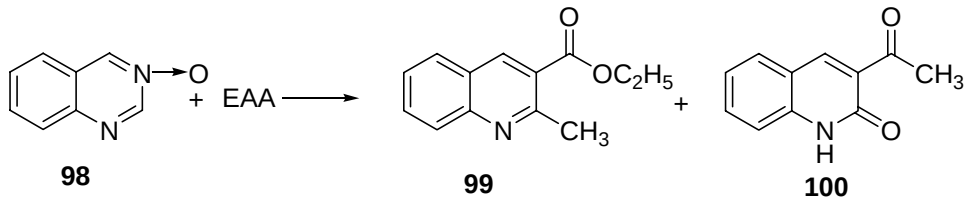


Scheme 25

Synthesis of 2(1*H*)-quinolinones catalyzed by hydrotalcite

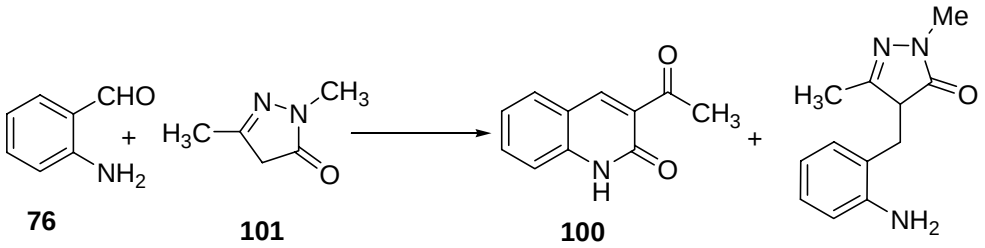
To a solution of 2-aminobenzaldehydes (1 part) in toluene, ethyl acetoacetate (1.2 part) and hydrotalcite (20% w/w) were added and the reaction mixture was refluxed with stirring till completion of reaction. Reaction mixture was filtered when hot to isolate the catalyst. The filtrate was concentrated to small volume and diluted with n-hexane. The precipitated 2(1*H*)-quinolinones were isolated by filtration. The yields of 2(1*H*)-quinolinones were in the range of 75 – 84% (**Table 1**).

Thus when 2-aminobenzaldehyde (**76**) was reacted with ethyl acetoacetate, 3-acetyl-2(1*H*)-quinolinone (**100**) was obtained in 82% yield. Compound **100** was earlier[71] synthesized along with 3-carboethoxy-2-methyl quinoline (**99**) by reacting quinazoline *N*-oxide (**98**) with ethyl acetoacetate at 100 °C for 1 hour **(Scheme 26**).



Scheme 26

100 was also obtained as a by-product[72] in 8% yield during reaction of *o*-aminobenzaldehyde (**76**) with 3-methyl-1-methylpyrazolin-5-one (**101**) (**Scheme 27**).

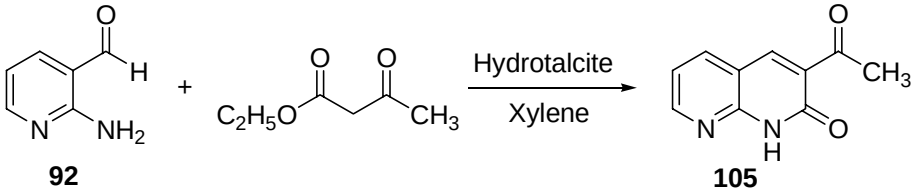


Scheme 27

Similarly 4-chloro-2-aminobenzaldehyde (**81**) and 4-bromo-2-aminobenzaldehyde (**82**) were reacted with ethyl acetoacetate in presence of hydrotalcite in toluene to obtain 3-acetyl-7-chloro-2(1*H*)-quinolinone (**102**) and 3-acetyl-7-bromo-2(1*H*)-quinolinone (**103**) in 84 and 80% yield respectively.

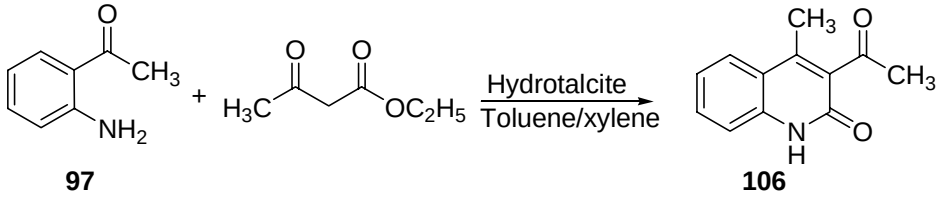
4,5-Dimethoxy-2-aminobenzaldehyde (**86**) was reacted with ethyl acetoacetate in presence of hydrotalcite in *o*-xylene to obtain 3-acetyl-6,7-dimethoxy-2(1*H*)-quinolinone (**104**) in 78% yield.

2-Aminonicotinaldehyde (**92**) when reacted with ethyl acetoacetate in presence of hydrotalcite and *o*-xylene as solvent, 3-acetyl-1,8-nathpharidin-2-one (**105**) was obtained in 75% yield (**Scheme 28**).



Scheme 28

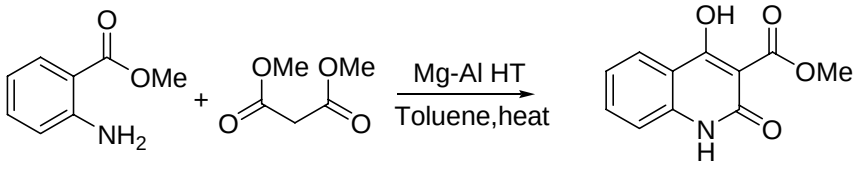
Hydrotalcite like anionic clay (Mg/Al = 3, CHT) was used further for synthesis of 3-acetyl-4-methyl-2(1*H*)-quinolinone (**106**) by reacting *o*-amino acetophenone (**97**) with ethyl acetoacetate in toluene (**Scheme 29**).



97 **106**

Scheme 29

Synthesis of 2(1*H*)-quinolinone was also carried out from *o*-amino methylbenzoate (**107**). Thus **107** was refluxed with dimethyl malonate using hydrotalcite as catalyst in toluene to obtain 3-carbomethoxy-4-hydroxy-2-(1*H*)-quinolinone (**108**) in 78% yield (**Scheme 30**).



107 **108**

Scheme 30

Thus hydrotalcite was used as heterogeneous catalyst for synthesis of various 3-acetyl-2(1*H*)-quinolinones in 75 to 84% yield. Its utility as heterogeneous catalyst was further studied by recycling the catalyst for consecutively three times. The yields are found to be practically consistent while recycling the catalyst (**Table 2**). While catalyst can be reused as such after filtration of reaction mixture in all cases, catalyst recovered after *o*-amino acetophenone reaction with EAA, had to be dehydrated before next cycle. It was carried out by refluxing the catalyst in *o*-xylene followed by distillation to remove water azeotropically.

Table 1: Synthesis of 3-acetyl-2(1*H*)-quinolinones using Mg-Al 3 CHT as catalyst

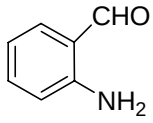
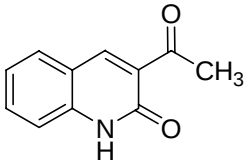
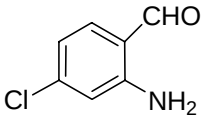
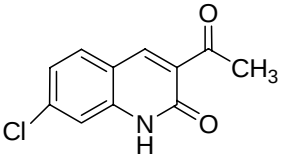
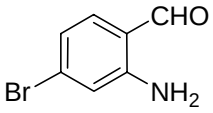
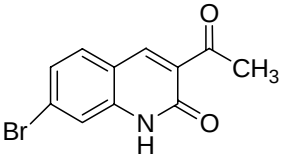
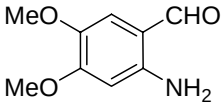
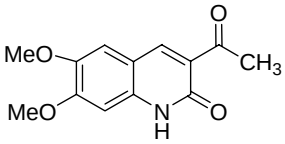
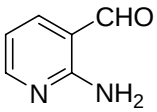
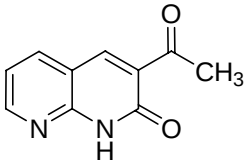
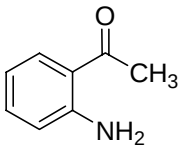
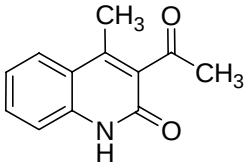
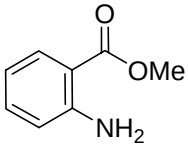
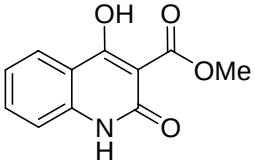
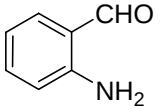
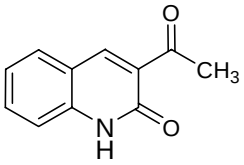
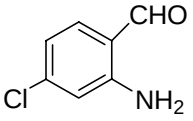
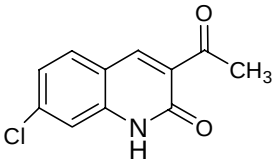
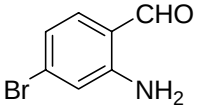
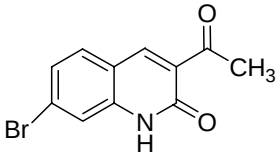
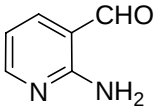
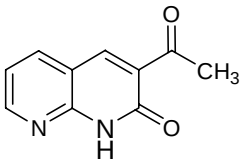
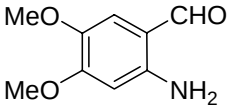
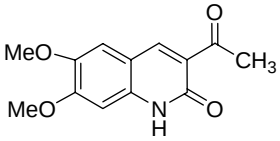
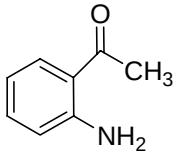
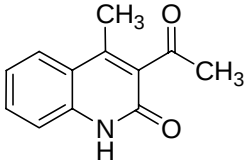
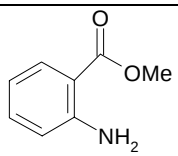
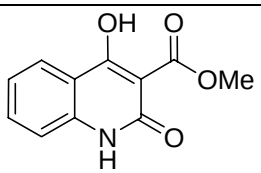
S. No.	Substrate 1	Substrate 2	Reaction conditions	Product	Yield
1	 **76**	EAA	Toluene/ 110 °C/ 4 h	 **100**	82 %
2	 **81**	EAA	Toluene/ 110 °C/ 6 h	 **102**	84 %
3	 **82**	EAA	Toluene/ 110 °C/ 6 h	 **103**	80 %
4	 **86**	EAA	Xylene/ 140 °C/ 8 h	 **104**	78 %
5	 **92**	EAA	Xylene/ 140 °C/ 8 h	 **105**	75 %
6	 **97**	EAA	Xylene/ 140 °C/ 12 h	 **106**	82 %
7	 **107**	Diethyl malonate	Toluene/ 110 °C/ 3 h	 **108**	78 %

Table 2: Recyclability studies of Mg-Al 3 CHT for different substrates.

S. No	Substrate	Reactant	Product	Recycle Yield
1		EAA		1st 82 % 2nd 80 % 3rd 80 %
2		EAA		1st 84 % 2nd 82 % 3rd 78 %
3		EAA		1st 80 % 2nd 78 % 3rd 76 %
4		EAA		1st 75 % 2nd 73 % 3rd 72 %
5		EAA		1st 78 % 2nd 76 % 3rd 75 %
6		EAA		1st 82 % 2nd 78 % 3rd 78 %
7		Diethyl malonate		1st 78 % 2nd 76 % 3rd 76 %

Conclusion

Thus pharmaceutically useful 3-acetyl-2(1*H*)-quinolinone moiety was synthesized in high yields by reacting *o*-amino benzaldehydes or *o*-amino acetophenones with ethyl acetoacetate catalyzed by Mg Al 3 CHT type anionic clays. 2(1*H*)-quinolinones are also synthesized by reacting *o*-amino carboxylates with diethyl malonate in presence of Mg-Al 3 CHT as catalyst. The catalyst was easily separable from reaction mixture and could be recycled several times without affecting its efficiency. The process is environmentally friendly with minimal waste. The method thus offers a practical alternative to conventional bases since carbonyl compounds are sensitive to strong base catalyzed reactions resulting in several by-products. Formation of dimer, a common product in the reaction of *o*-amino carboxylates with bases, can be avoided when Mg-Al 3 CHT is used as the base catalyst. The methodology can also be extended to synthesis of different 3 and 4 substituted 2(1*H*)-quinolinones.

Experimental

Preparation of Mg-Al 3 CHT

A solution of magnesium nitrate (115.38 g, 0.45 mol) and aluminium nitrate (56.27 g, 0.15 mol) in 300 ml distilled and demineralized water and a solution of sodium hydroxide (25 g, 0.63 mol) and sodium carbonate (15 g, 0.15 mol) in 150 ml of distilled and demineralized water were added simultaneously in 300 ml distilled water keeping pH of reaction mixture at 10. After addition precipitate obtained was aged at 65 °C for 30 minutes. The mixture was cooled to room temperature and filtered. Precipitate was washed several times with distilled water till neutral. Precipitate was then dried at 100 °C and calcined at 250 °C. This dried powder was used as catalyst for the reactions.

Preparation of *o*-aminobenzaldehyde (**76**)

To a solution of ferrous sulfate (210 g, 0.76 mol) in 250 ml water and 1 ml HCl, *o*-nitrobenzaldehyde (20 g, 0.13 mol) was added and reaction mass was heated as early as possible to 90 °C under vigorous stirring and 50 ml of concentrated ammonia solution was added in one lot. Stirring and heating was continued with continuous addition of concentrated ammonia solution (60 ml) over a period of 15 min. After completion of addition the reaction mixture was heated to reflux and the product **76** was steam distilled. (Yield 12.8 g, 80%). mp 38 – 39 °C.

Preparation of 2-amino-4-chlorobenzaldehyde (81)

Step I: Preparation of 2-nitro-4-chlorobenzaldehyde (79)

To a mixture of 2-nitro-4-chlorotoluene (3.7 g, 21.6 mmol), glacial acetic acid (35 ml) and acetic anhydride (34 ml), was added conc. sulfuric acid (5 ml) with stirring at 5 - 10 °C. To this reaction mixture, chromic anhydride (6 g) was added over a period of 10 min. at 5 – 10 °C. The mixture was stirred for an additional hour. The reaction mixture was poured with stirring into 100 ml of ice water and allowed to stand overnight. The

white solid obtained was separated by filtration, washed with water. The cake was further stirred with aqueous sodium carbonate solution (20 ml) for three hours, filtered, and the crude product was refluxed with 10 ml of petroleum ether, cooled, filtered and dried to yield 2.8 g of aldehyde diacetate.

Aldehyde diacetate (2.8 g) was heated on the steam-bath with 5 N hydrochloric acid (35 ml) and ethanol (5 ml) for six hours. The mixture was cooled and the precipitate obtained was filtered and dried to yield crude aldehyde (1.96 g, 48% yield). The crude product (**79**) was crystallized from petroleum ether. (Yield 1.76 g). mp 67-68 °C.

Step II: Reduction of 2-nitro-4-chlorobenzaldehyde (79)

2-Nitro-4-chlorobenzaldehyde (20 g, 0.11 mol) was added to a solution of ferrous sulfate (210 g, 0.76 mol) in 250 ml water and 1 ml HCl and reaction mass was heated to 90 °C under vigorous stirring and 50 ml of concentrated ammonia solution was added in a one lot. Stirring and heating was continued with continuous addition of concentrated ammonia solution (60 ml) over a period of 15 min. Reaction mixture was refluxed further for one hour, cooled and filtered. The filtrate was extracted with dichloromethane. The organic layer was washed with brine, dried over anhy. sodium sulphate and concentrated under reduced pressure to obtain 2-amino-4-chlorobenzaldehyde (**81**). It was purified by column chromatography (Yield 12.18 g, 73%). mp 85 - 86 °C.

Preparation of 2-amino-4-bromobenzaldehyde (82)

2-Amino-4-bromobenzaldehyde was synthesized by a similar procedure from 2-nitro-4-bromotoluene in two steps as that of 2-amino-4-chlorobenzaldehyde (**81**). (Yield 75%). Mp 87-88 °C

Preparation of 2-amino-4, 5-dimethoxy benzaldehyde (86)

Step I: Preparation of veratraldehyde (84)

Vanillin (18.2 g, 0.12 mol) was dissolved in hot 120 ml of 1.5 N NaOH solution. To this solution, dimethyl sulfate (22.8 g, 0.18 mol)) was added under stirring at 95 – 98

°C. Stirring was continued for 30 min and 1.5 N NaOH solution was added to make pH highly alkaline. Another lot of dimethyl sulfate (4.0 g, 0.03 mol) was added and stirred further for 30 min. more. Reaction mixture was cooled and made alkaline using 1.5 N NaOH solution and extracted with diethyl ether. Organic layer was dried over anhy. Na_2SO_4 and concentrated to yield veratraldehyde. (Yield 16.3 g, 82%) mp 44 - 45 °C.

Step II: Preparation of 6-nitroveratraldehyde (85)

Veratraldehyde (15.0 g) was added to concentrated nitric acid (150 ml) at 0-5 °C slowly over a period of 1.5 hr while stirring. The reaction mixture was stirred further for 2 h and poured over 800 ml of ice-water under stirring. The yellow precipitate obtained was filtered and washed with cold water. Crude product was crystallized using ethanol. (Yield 12.77 g, 67%). mp 133 -134 °C.

Step III: **Reduction of 6-nitroveratraldehyde (85)**

Reduction of 6-nitroveratraldehyde was carried out similar to that of 2-nitro-4-chlorobenzaldehyde to yield 2-amino-4,5-dimethoxy benzaldehyde (**86**). (Yield 80%).

Preparation of 2-aminonicotinaldehyde (92)

Step I: Preparation of 2-(3-methyl-2-pyridinyl)-1*H*-isoindole-1,3(2*H*)-dione (**89**)

A mixture of 2-amino-3-picoline (**87**) (20.0 g, 0.185 mol) and phthalic anhydride (**88**) (27.4 g, 0.185 mol) was heated to 190°C, with continuous distillation of water formed during reaction. When water removal was completed the reaction mass was cooled and then dissolved in dichlromethane. Dichloromethane solution was washed with water, dried and concentrated to isolate the product **89**. (Yield 42.7 g, 97%)

Step II: **2-(3-(Dibromomethyl)-2-pyridinyl)-1*H*-isoindole-1, 3(2*H*)-dione** (**90**)

Phthalimide **89** (25 g, 0.105 mol) was suspended in 300 ml of CCl_4 and *N*-bromosuccinimide (30.8 g, 0.17 mol) and AIBN (0.2 g) were added. The reaction mixture was irradiated with 100 W lamp till completion of reaction The reaction mixture was

diluted with dichloromethane and washed with sodium thiosulphate solution. The organic layer was dried and concentrated under vacuum. (Yield 35.34 g, 84%)

Step III: **2-Aminonicotinaldehyde** (**92**)

Dibromide **90** (20.0 g, 0.05 mol) obtained from step II was suspended in ethanol (100 ml) and concentrated ammonium hydroxide (50 ml) was added and stirred for 1.5 h. Ethanol was removed by distillation and 100 ml conc. HCl was added and refluxed for 5 h. Reaction mixture was diluted with water, basified with aq. Na_2CO_3 solution and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and concentrated to give 2-aminonicotinaldehyde (**92**). (Yield 4.0 g, 64%).

1) Preparation of 3-acetyl-2(1*H*)-quinolinone (**100**)

To a solution of 2 g (16.5 mmol) 2-aminobenzaldehyde in 25 ml of dry toluene was added 2.58 g (19.8 mmol) ethyl acetoacetate and 0.4 g of Mg-Al 3 CHT (catalyst). The mixture was stirred magnetically for five minutes. If the catalyst turns immediately in to faint pale yellow color, it indicates that the catalyst is active. The mixture was heated to reflux (110 °C) for 4 h, cooled to 90 °C and filtered to remove the catalyst. Catalyst was washed with 20 ml hot toluene. Filtrate was concentrated. To the residue, 20 ml of n-hexane was added and solid obtained was filtered. It was crystallized from ethyl acetate. Yield (2.53 g, 85%). mp 236 - 237 °C.

^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 7.19 (t, 1H, J = 7.5 Hz), 7.31 (d, 1H, J = 8.4 Hz), 7.57 (t, 1H, J = 7.1 Hz), 7.83 (d, 1H, J = 7.9 Hz), 8.42 (s, 1H), 12.08 (br s, 1H).

^{13}C NMR (DMSO-d_6): δ 30.87, 116.11, 118.31, 122.29, 128.88, 129.40, 132.47, 140.21, 143.53, 161.10, 197.73.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48 %.

Found: C, 70.23; H, 4.78; N, 7.40 %.

2) 3-Acetyl-7-chloro-2(1*H*)-quinolinone (**102**)

To a solution of 2 g (12.8 mmol) 2-amino-4-chloro benzaldehyde in 25 ml of toluene was added 2 g (15.44 mmol) ethyl acetoacetate and 0.4 g of catalyst. The mixture was heated at 110 °C for 6 h, cooled to 90 °C and filtered when hot. Catalyst was washed with hot toluene. Filtrate was concentrated and worked up as usual to give crude 2(1*H*)-quinolinone (**102**). It was purified by column chromatography. Yield 2.38 g (84%).

^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3H), 7.27-7.32 (m, 2H), 7.94 (d, 1H, J = 8.44 Hz), 8.49 (s, 1H), 12.18 (br s, 1H).

Anal. Calcd. for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32 %.

Found C, 59.58; H, 3.63; N, 6.31 %.

3) 3-Acetyl-7-bromo-2(1*H*)-quinolinone (103)

To a solution of 2 g (12.5 mmol) 2-amino-4-bromo benzaldehyde in 25 ml of toluene was added 1.95 g (15.4 mmol) ethyl acetoacetate and 0.4 g of catalyst. The mixture was heated to reflux for 6 h, cooled to 90 °C and filtered hot. Catalyst was washed with hot toluene. Filtrate was concentrated and worked up as usual to give crude 2(1*H*)-quinolinone (**103**). It was purified by column chromatography using hexane: ethyl acetate (1:3). (Yield 2.66 g, 80%).

^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3H), 7.39-7.42 (m, 2H), 8.04 (d, 1H, J = 8.44 Hz), 8.49 (s, 1H), 12.18 (br s, 1H).

Anal. Calcd. for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.03; N, 5.26 %.

Found C, 49.58; H, 3.05; N, 5.23 %.

4) 3-Acetyl-6, 7-dimethoxy-2(1*H*)-quinolinone (**104**)

To a solution of 2 g (11.0 mmol) 2-amino- 4,5-dimethoxy benzaldehyde in 25 ml of *o*-xylene, 1.8 g (13.2 mmol) ethyl acetoacetate and 0.4 g of catalyst were added. The mixture was refluxed for 8 h, cooled to 110 °C and filtered when hot. Catalyst was

washed with 30 ml 110 °C hot *o*-xylene. Filtrate was concentrated and worked up as usual to give crude 2(1*H*)-quinolinone (**104**). It was purified by column chromatography using ethyl acetate:n-hexane (4:1). Yield 2.12 g (78%).

^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 6.85 (s, 1H), 7.30 (s, 1H), 8.39 (s, 1H), 11.89 (br s, 1H)

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67 %.

Found C, 63.05; H, 5.12; N, 5.63 %.

5) 3-Acetyl-1, 8-naphthyridin-2-one (**105**)

A mixture of 2-amino nicotinaldehyde (2 g, 16.4 mmol), 0.4 g catalyst and ethyl acetoacetate (2.34 g, 18 mmol) in 25 ml of *o*-xylene was refluxed for 8 h. After completion of reaction, it was worked up as usual. The crude product was purified by column chromatography. (Yield 2.15 g, 75 %).

^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H), 7.28-7.30 (m, 1H) 8.31-8.32 (m, 1H), 8.44 (s, 1H), 8.60-8.62 (m, 1H), 12.48 (br s, 1H).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.26; N, 14.89 %.

Found C, 63.64; H, 4.31; N, 14.82 %.

6) 3-Acetyl-4-methyl- 2(1*H*)-quinolinone (106)

A mixture of 2-aminoacetophenone (2 g, 14.8 mmol), 0.4 g catalyst and ethyl acetoacetate. (1.8 g, 17.7 mmol) in 25 ml of *o*-xylene was refluxed for 12 h. After completion of reaction it was worked up as usual. The crude product was purified by column chromatography. Yield 2.43 g (82 %).

^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H), 2.43 (s, 3H), 7.21-7.33 (m, 2H), 7.49-7.53 (m, 1H), 7.75-7.80 (m, 1H), 11.96 (br s, 1H)

^{1}C NMR (DMSO-d_6): δ 15.10, 31.18, 115.82, 119.41, 122.09, 124.81 (2 C), 130.64 (2 C), 137.77, 160.14, 203.54.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96 %.

Found C, 71.59; H, 5.32; N, 6.94 %.

7) 3-Carbomethoxy-4-hydroxy-2(1*H*)-quinolinone (108)

To a solution of methyl anthranilate (2 g, 13.24 mmol) in 25 ml of toluene, diethyl malonate (2.52 g, 15.5 mmol) and catalyst (0.4 g) were added. The mixture was refluxed for 3 hours and worked up further as usual. The crude product obtained was purified by column chromatography. Yield 2.26 g (78 %).

^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H), 7.08-7.15 (m, 1H), 7.51 (ddd, 1H, J = 1.69, 7.57, 8.85 Hz), 8.04 (dd, 1H, J = 1.69, 8.07 Hz), 8.72 (dd, 1H, J = 1.13, 8.45 Hz) 11.54 (br s, 1H).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39 %.

Found C, 60.19; H, 4.41; N, 6.65 %.

Typical experiment for recycle of catalyst

To a solution of 2 g (16.5 mmol) 2-aminobenzaldehyde (**76**) in 25 ml of dry toluene was added 2.58 g (19.8 mmol) ethyl acetoacetate and 0.4 g of Mg-Al 3 CHT (catalyst). The mixture was heated to reflux for 4 h, cooled to 90 °C and filtered to remove the catalyst. Catalyst was washed with 20 ml hot toluene. Filtrate was concentrated and worked up further as usual to yield 3-acetyl-2(1*H*)-quinolinone (**100**) (2.53 g, 82%). The filtered catalyst was again taken in 25 ml toluene and 2 g of 2-aminobenzaldehyde (**76**) and 2.58 g of ethyl acetoacetate were added and heated to reflux for 4 h. The reaction mixture was further worked up to yield 2.46 g (80%). The catalyst was filtered and recycled for third batch. The yields were found to be consistent.

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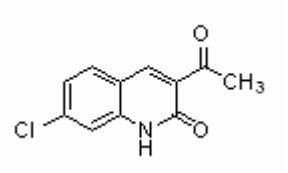
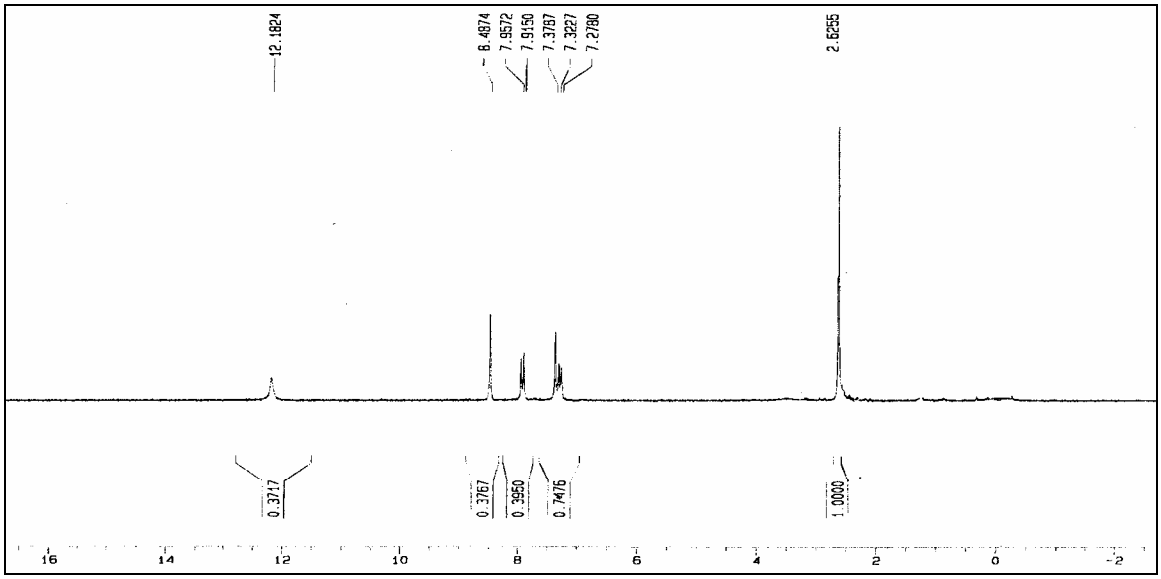
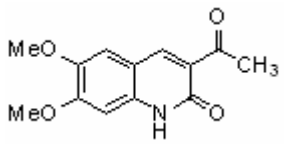


^{1}H NMR of compound **102** in DMSO-d_6





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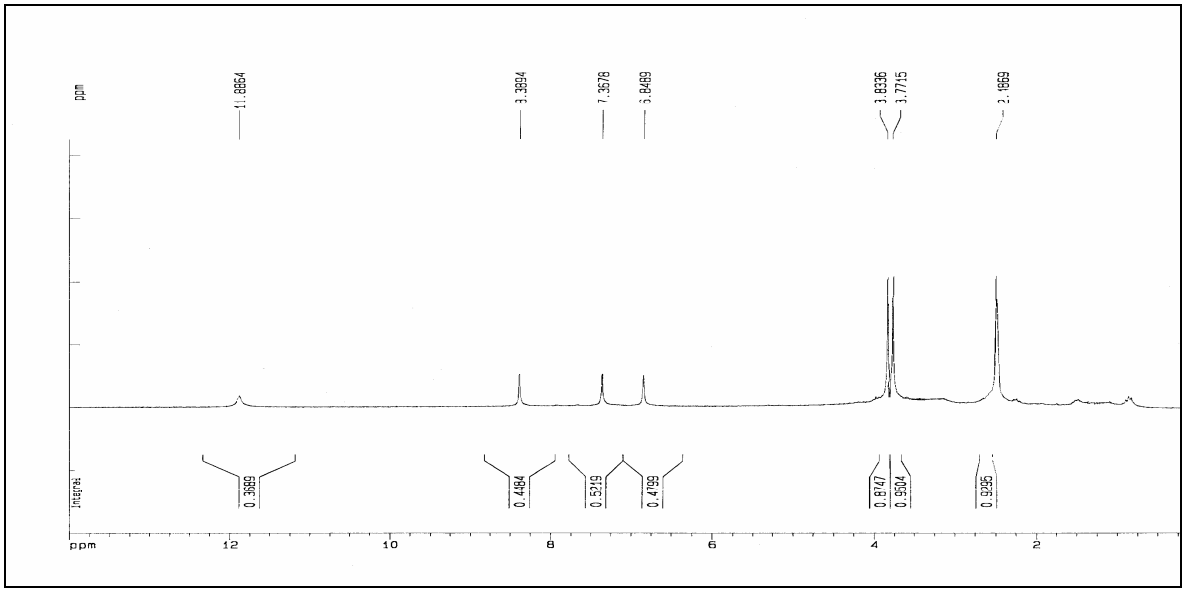

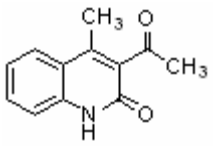

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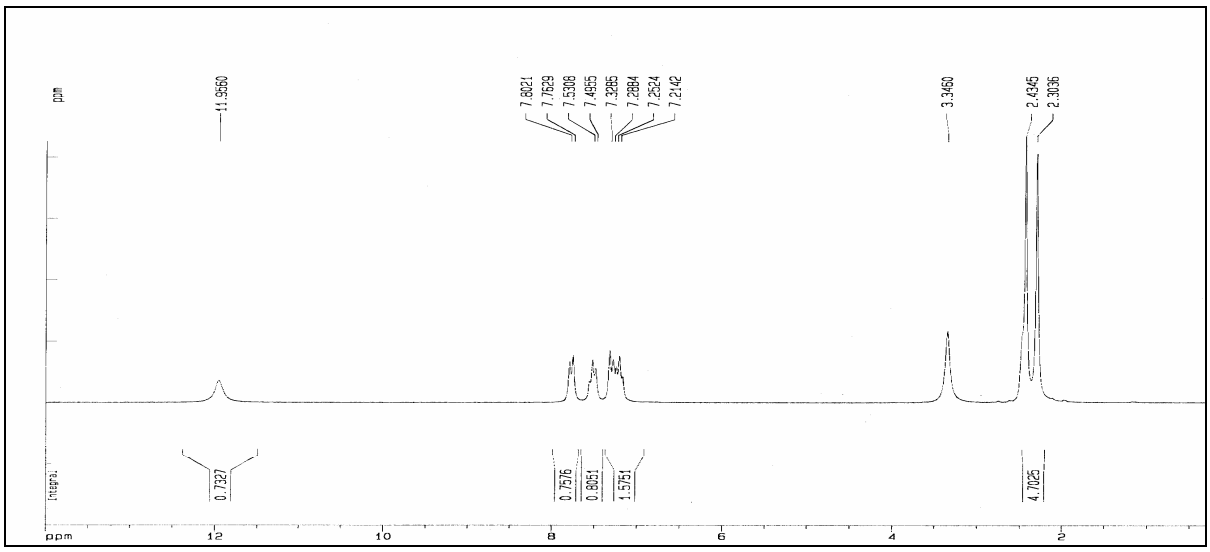
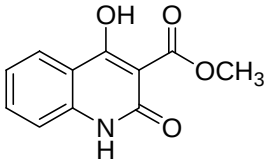
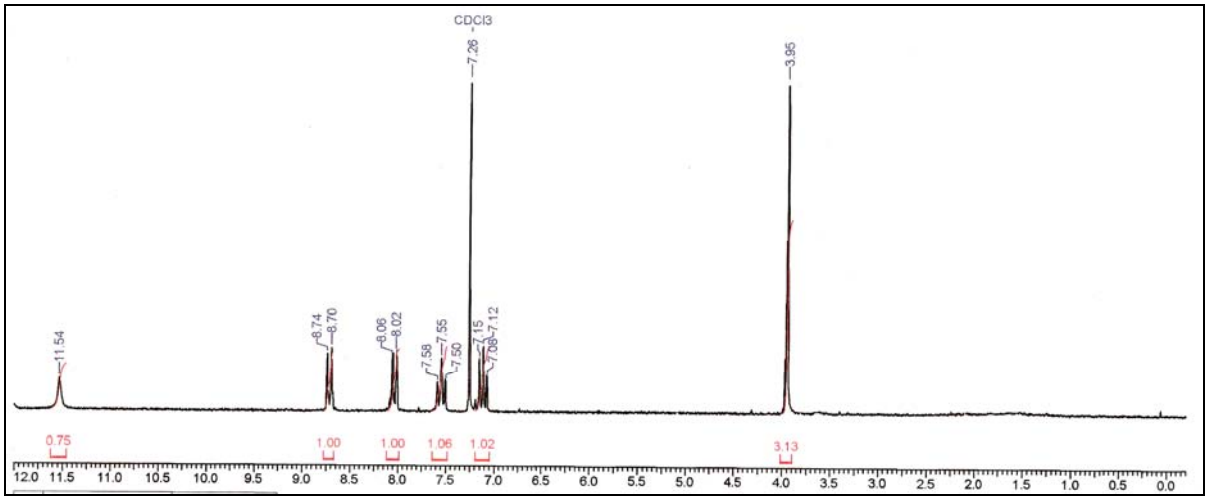
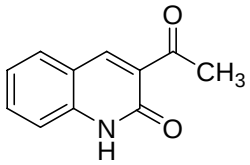


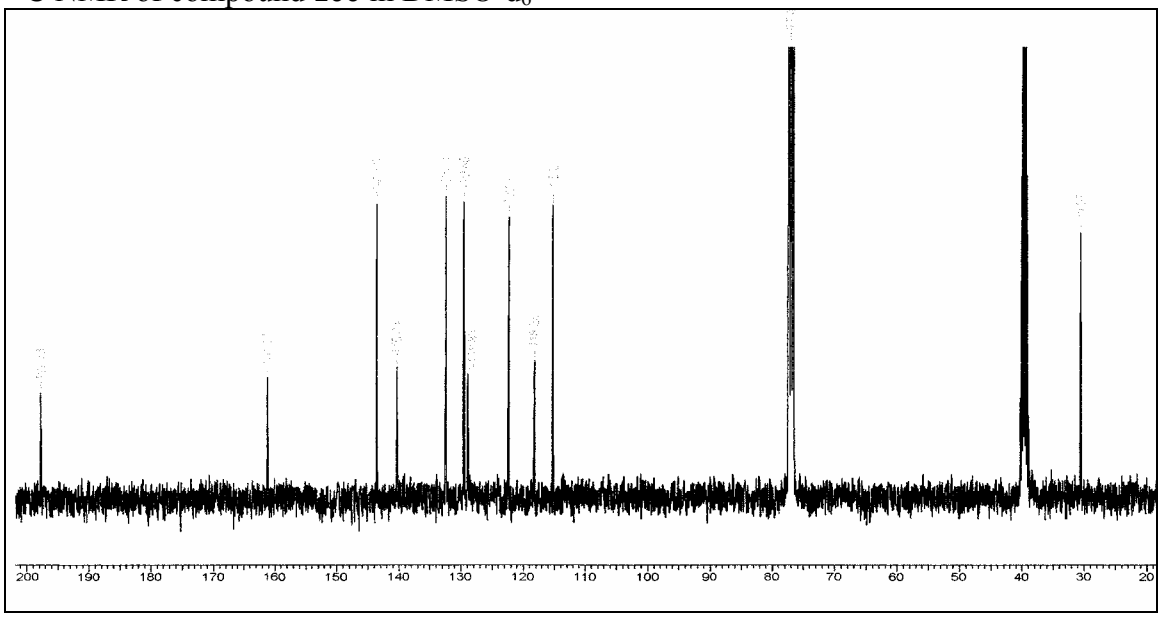


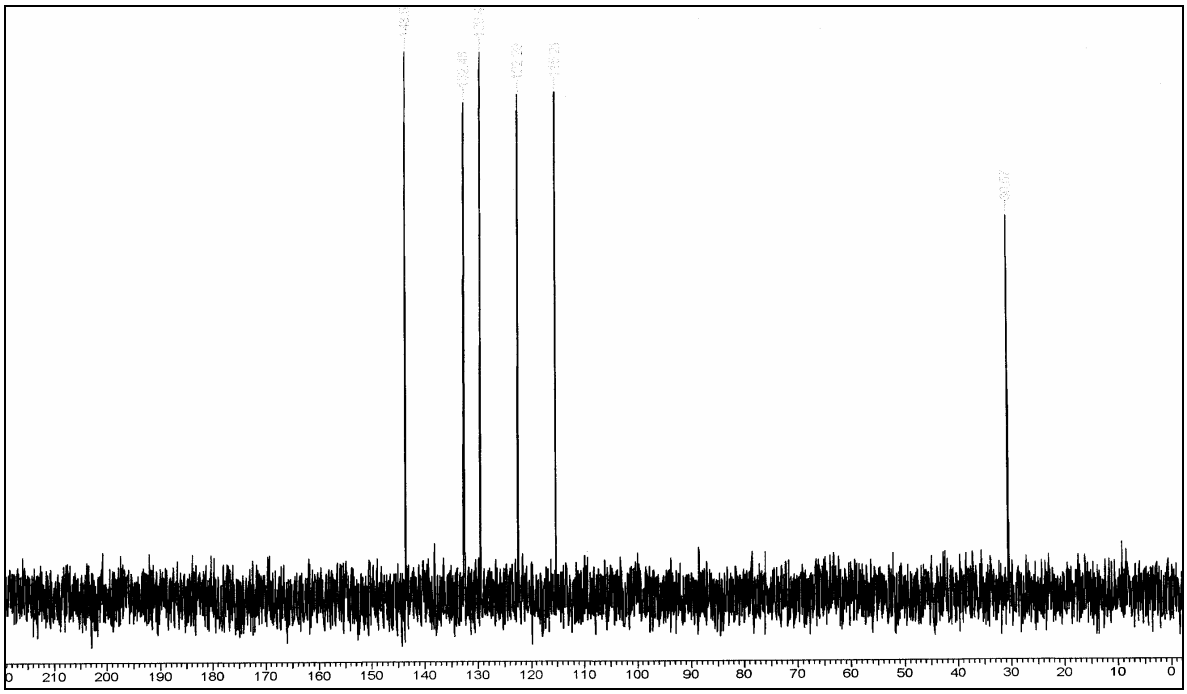
^{1}H NMR of compound **108** in DMSO-d_6





^{13}C NMR of compound **100** in DMSO-d_6





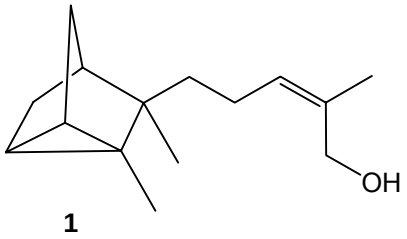
CHAPTER 3

SECTION I

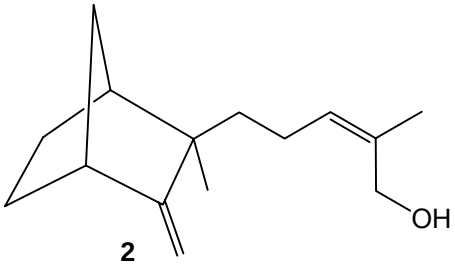
APPLICATION OF MODIFIED ZEOLITE BETA CATALYST IN THE REARRANGEMENT OF α-PINENE OXIDE TO CAMPHOLENIC ALDEHYDE

INTRODUCTION

The powerful, sweet, woody fragrance of East Indian sandalwood oil is a valuable constituent of perfume compositions and most prized of the oil essential in the formulation of soaps and cosmetic perfumes. According to Guenther[1] East Indian sandalwood oil has been perhaps one of the most precious perfumery materials from antiquity down to modern times and its popularity has shown no signs of waning. East Indian Sandalwood oil obtained from the tree *Santalum album* (L. Santalaceae) is a complex mixture of ingredients. (Z)-(+)-α-Santalol **(1)** (45-47%) and (Z)-(-)-β-santalol (**2**) (approximately 25%) are considered to be the main components. It is difficult to establish the contribution of each component to the overall odor profile.[2]



1

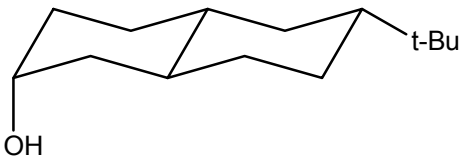


2

(Z)-(+)-α-Santalol

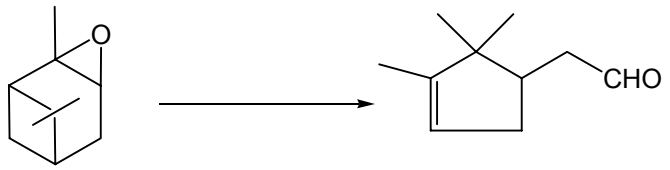
(Z)-(-)-β-Santalol

As resources conservation process the production of sandalwood oil is limited. Hence a large number of compounds have been synthesized with this typical odor tonality. 3α-Hydroxy-7α-*t*-butyldecaline, a synthetic compound showing typical sandalwood fragrance, is usually employed as a standard for molecular calculations and surface comparisons of sandalwood odour molecules.[3]



3α-Hydroxy-7α-*t*-butyldecaline

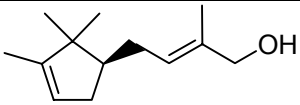
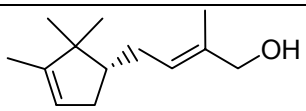
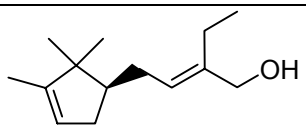
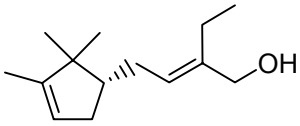
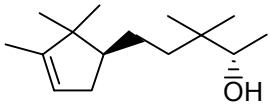
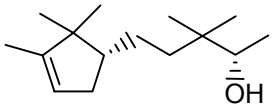
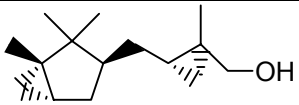
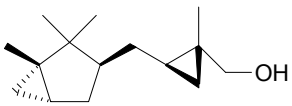
Among the synthetic chemicals developed to satisfy the demand of sandalwood odour, the derivatives of campholenic aldehyde (**4**) which in turn is synthesized from pinene oxide (**3**) have great demand in fragrance industry.



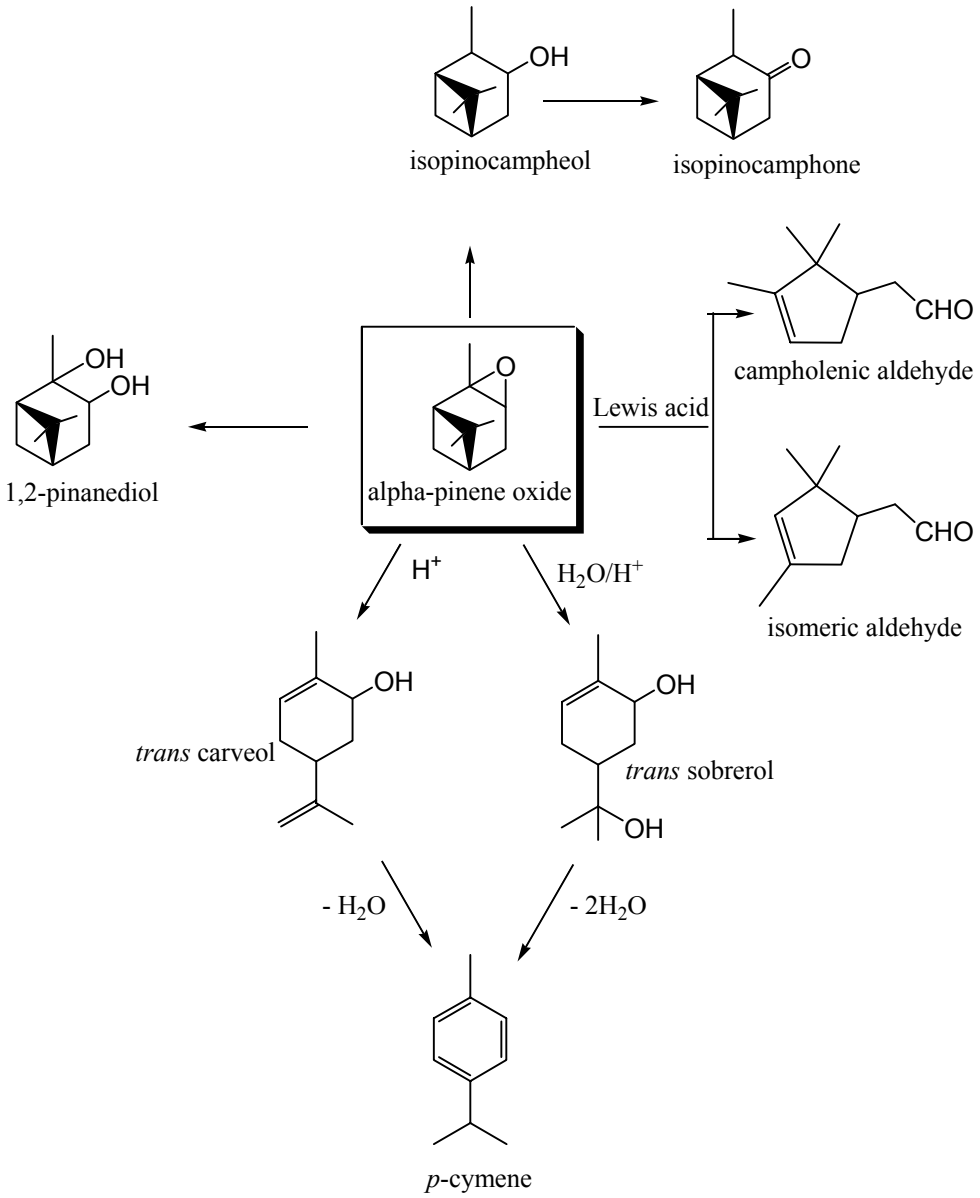
3 **4**

Some of the important derivatives of campholenic aldehyde having comparable sandalwood and other odours are depicted in Table 1.

Table 1: Derivatives of campholenic aldehyde

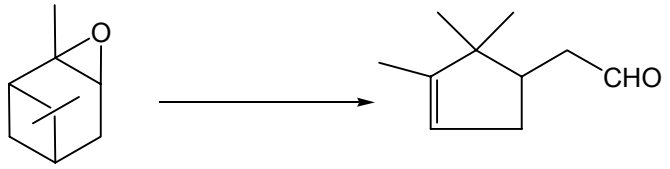
S. No.	Structure	Odour discription
1		Fresh and strong sandalwood oil associated with green trees
2		Dry and weak sandalwood oil odour
3		Clean, bright and strong sandalwood oil with richness and woody note
4		Milky sandalwood oil with cedar note
5		Mild sandalwood odour
6		Remarkably powerful and elegant, with a prized sandalwood milky character
7		Sandalwood, creamy, warm
8		Sandalwood, creamy, lactonic

α-Pinene oxide is a reactive molecule which is readily rearranged under acidic conditions, affording several different products. In every acid - catalyzed reaction for rearrangement of α-pinene oxide various side products are formed and more than 200 different compounds are detected. Some of the major products formed during acid catalyzed rearrangement of α-pinene oxide are as denoted in **Scheme 1**.



Scheme 1

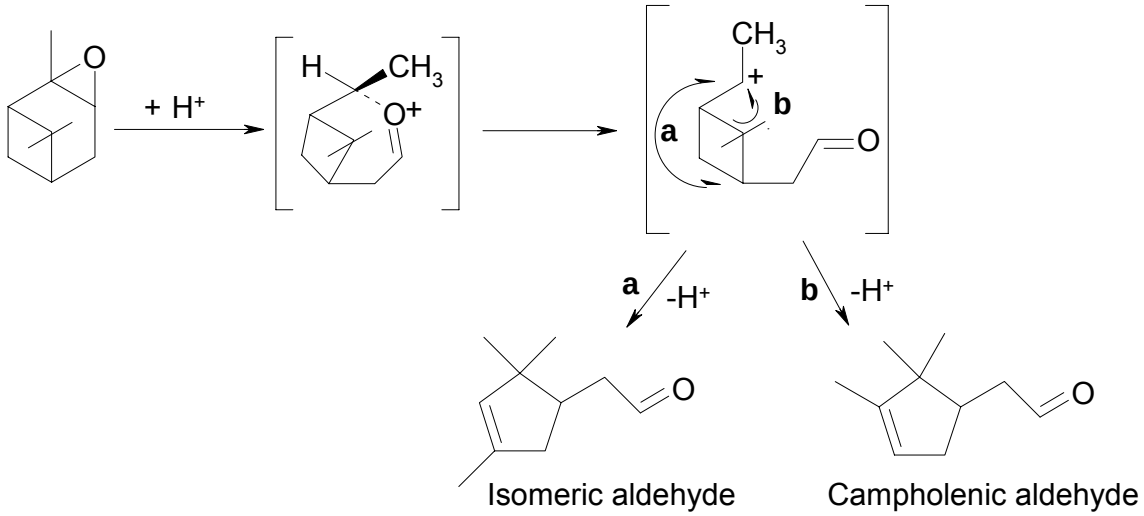
According to literature campholenic aldehyde (**4**) has been synthesized starting from α-pinene oxide (**3**) (also called pinene epoxide, pinene oxide) (**Scheme 2**). Various synthetic methods are available for conversion of α-pinene oxide to campholenic aldehyde.



3 **4**

Scheme 2

Whittaker *et al*.[4] postulated the reaction mechanism for the rearrangement of α-pinene oxide. The first step is the cleavage of the C-C bond in the oxirane ring, followed by hydride shift. The resulting seven-membered heterocyclic ring undergoes C-O cleavage, the carbocation formed rearranges to the two isomeric aldehydes depending on whether the isopropyl or methylene bridge is shifted. Because of this type of mechanism many homogeneous acidic catalysts do not differentiate between these isomers (**Scheme 3**).

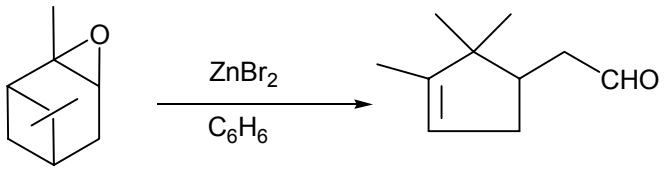


Scheme 3

When $ZnBr_2$ is used as catalyst, the intermediate gets stabilized by forming a complex with zinc, and hence the selectivity towards campholenic aldehyde is up to 85%.

Various approaches to the synthesis of campholenic aldehyde from pinene oxide

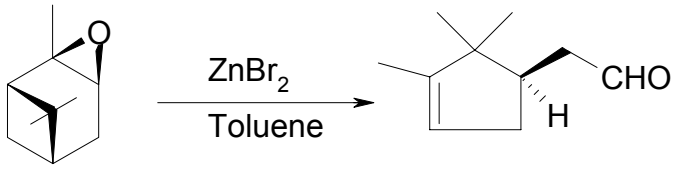
A practically sound method for obtaining campholenic aldehyde **(4)** was described by Arbuzow[5] in 1935. According to this method, α-pinene oxide (**3**) undergoes rearrangement exothermically in presence of zinc bromide as catalyst in benzene to give **3** in 80% yield (**Scheme 4**).



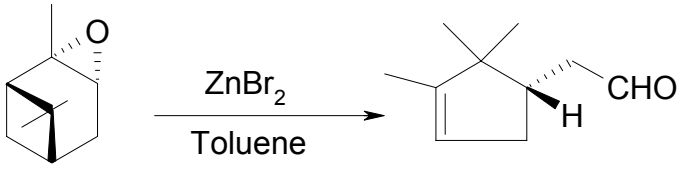
3 **4**

Scheme 4

It was also observed that rearrangement of α-pinene oxide into α-campholenic aldehyde is stereospecific. Chapuis *et al*.[6] observed that (-)-α-pinene oxide (**5**) was converted into (+)-R-α-campholenic aldehyde (**6**) in presence of zinc bromide in refluxing toluene with 75% yield and (+)-α- pinene oxide (**7**) gets converted into (-)-S-α-campholenic aldehyde (**8**) (**Scheme 5**).



(-)-α-Pinene oxide (**5**) (+)-R-α-Campholenic aldehyde (**6**)



(+)-α-Pinene oxide (**7**) (-)-S-α-Campholenic aldehyde (**8**)

Scheme 5

Rearrangement of α-pinene epoxide was further studied[7] to check zinc bromide activation and reaction conditions, which was not described by Arbuzow. To get consistent yield of campholenic aldehyde, the main factor responsible was the activation of zinc bromide. When dehydrated and molten zinc bromide was added to solution of α-pinene epoxide in benzene at 60-65 °C, an exothermic reaction ensued to yield campholenic aldehyde in 80% yield, confirming results reported by Arbuzow. Zinc chloride in benzene was also used as an alternate catalyst system to effect the rearrangement in 70% isolated yield of campholenic aldehyde.[8]

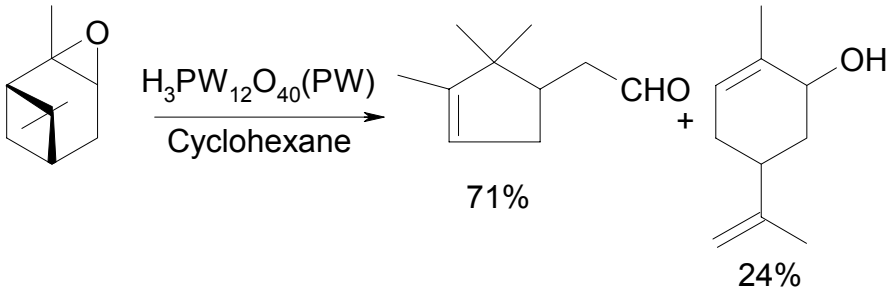
Treatment of quinaldine solution of α-pinene epoxide with *p*-toluene sulfonic acid as catalyst yielded[9] mixture of aldehydes in overall 30% yield; 70% α-pinene epoxide was found to get converted into hydrocarbons. The aldehyde fraction was converted into sodium bisulphite adduct and separated from reaction mixture. Aldehyde fraction as bisulphite adduct was then treated with sodium hydroxide to regenerate the aldehydes. From the mixture of aldehydes, campholenic aldehyde was found to be only 85% i.e. 24 to 25% overall selectivity. Vialemaringe *et al*.[10] used BF_3-etherate as an acid catalyst to give 73% campholenic aldehyde at -50 °C. Due to rearrangement at low temperature, this method was found to be less applicable industrially. Recycling of zinc bromide catalyst solution for the rearrangement of α-pinene epoxide was demonstrated by Davey *et al*.[11] Zinc bromide solution was reused after azeotropic removal of water in batch process system; however, the azeotropic removal of water is laborious and energy consuming.

Rearrangement of α-pinene epoxide was carried out using zinc bromide in high boiling solvents such as diphenyl ether, diethylene glycol or dibutyl ether.[12] The entire system operated under reduced pressure and campholenic aldehyde was distilled from reaction mixture continuously. The distilled campholenic aldehyde was always found to be contaminated with solvent necessitating further purification.

Thus various drawbacks of homogeneous catalysis in rearrangement of pinene epoxide diverted further research into the use of heterogeneous catalysis such as solid acid catalysts and zeolites.

Silica supported heteropoly acid $H_3PW_{12}O_{40}$ (PW) for rearrangement of α-pinene epoxide was used by Kelly *et al*.[13] The reaction was performed in liquid phase using cyclohexane as solvent. 86% Conversion at 0.15 wt percentages loading of catalyst

containing 20% of heteropoly acid was observed. The selectivity towards campholenic aldehyde was found to be 62% with 86% conversion. When reaction was carried out at 0.30% loading, conversion of 98% was observed with 71% selectivity for campholenic aldehyde. At higher temperature (40 °C) even though the conversion was 100% selectivity of 59% was observed. The other product was found to be *trans* carveol (**9**) (**Scheme 6**).



trans Carveol (**9**)

Scheme 6

Zinc triflate (Zn $(CF_3SO_3)_2$) promoted rearrangement of α-pinene epoxide to campholenic aldehyde using dichloromethane as solvent in liquid phase was studied by Vicevic *et al*.[14] Various kinetic data was collected and it was observed that the reaction followed zero order kinetics. Performance of zinc triflate ($Zn(CF_3SO_3)_2$) catalyst was further enhanced using spinning disc reactor (SDR).[15] They tested different catalyst loadings and supports *viz* 0.05 mmol/g Zn-triflate / K60, 0.01 mmol/g Zn-triflate/K100 and 0.05 mmol/g Zn-triflate/HMS24. Maximum conversion of 85% with 75% selectivity towards campholenic aldehyde at 45 °C with 1500 RPM and feed rate of 6 ml/sec was obtained. The overall rate of reaction was double than that of the experiments carried out in normal batch reactor. Spinning disk reactor consists of a spinning disc coated with catalyst and equipped with excellent heating and cooling facilities which rotates at high RPM. Reactant was fed through a tube over a disk for catalytic conversion (**Fig 1**).

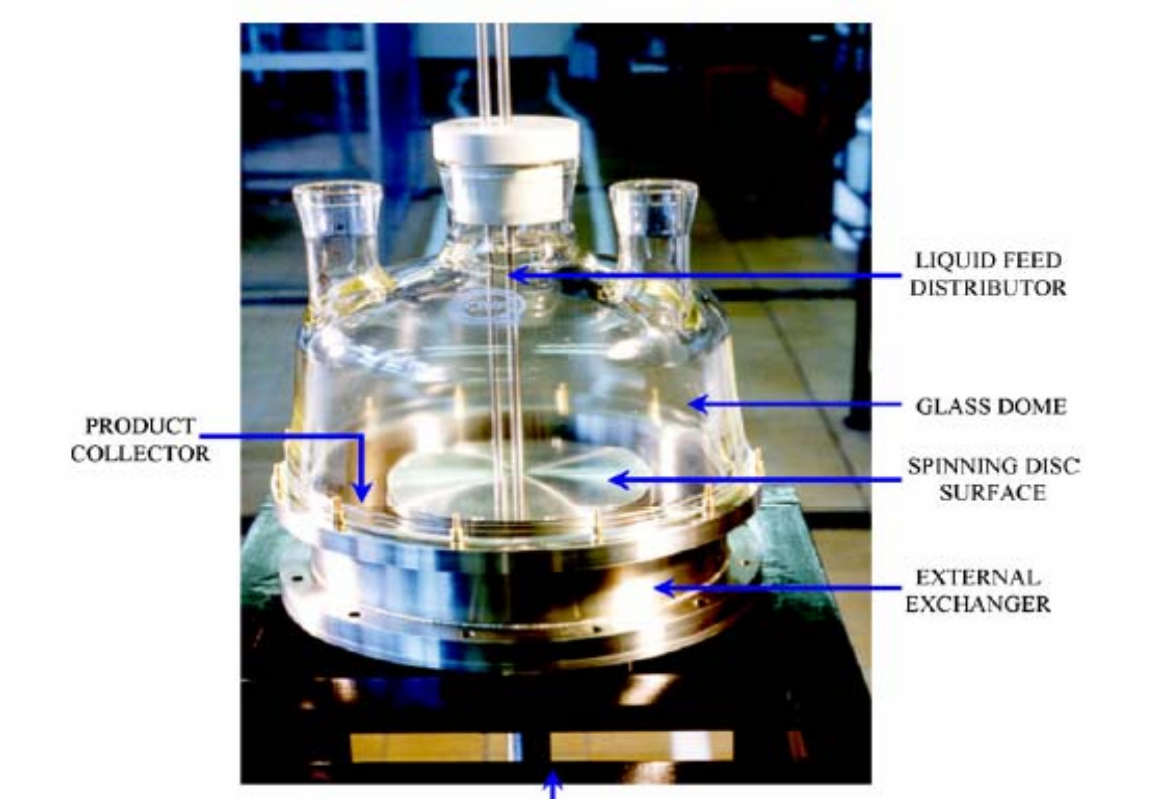
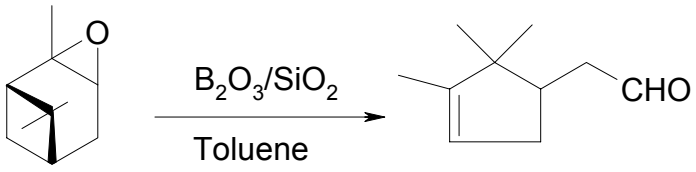


Fig 1: Spinning disk reactor

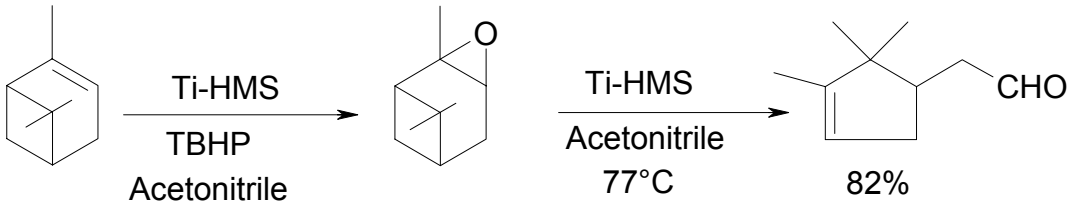
Various other solid acid catalysts l9ike B_2O_3/SiO_2, $ZnCl_2$/MCM-41, Al-MCM-41 and HY zeolites were investigated for isomerisation of α-pinene epoxide by Ravindra *et al.*[16] It was found that irrespective of loading, the selectivity over B_2O_3/SiO_2 was 69% for campholenic aldehyde whereas in case of $ZnCl_2$/MCM-41, the selectivity towards campholenic aldehyde was 85% at 26% conversion. When HY zeolites were used high conversion was observed but selectivity towards campholenic aldehyde was found to be in the range of 75% only (**Scheme 7**).



Scheme 7

Rearrangement of α-pinene oxide was also carried out in the presence of other solid acid and base catalysts like SiO_2-Al_2O_3, SiO_2-TiO_2, solid H_3PO_4 and $FeSO_4$.[17]

A one pot procedure for synthesis of campholenic aldehyde using Ti containing molecular sieves as bifunctional catalyst for catalytic epoxidation of α-pinene using TBHP and further rearrangement to convert α-pinene epoxide into campholenic aldehyde was developed by Suh *et al*.[18] It was observed that due to presence of water, both non radical and radical oxidation reactions gave various side products like isomeric aldehyde, verbenone and 1,2-pinene diol. Maximum conversion was found to be 95% with 22.8% selectivity. When TBHP was dried over $MgSO_4$ and used under inert atmosphere the selectivity towards campholenic aldehyde was found to be 82% with 96% conversion (**Scheme 8**).



Scheme 8

Titanosilicate with zeolite beta structure as an effective Lewis acid catalyst was employed[19] in the rearrangement of α-pinene epoxide to campholenic aldehyde, both in liquid and vapor phases. In the liquid phase using acetonitrile as solvent selectivity to campholenic aldehyde was found to be 89% at 7% conversion whereas in dichloroethane 81% selectivity was observed at 29% conversion. In isopropanol even though the conversion was 100%, selectivity to campholenic aldehyde was found to be only 33%. However, in vapor phase, in absence of solvent 95% conversion with 65% selectivity was observed. When solvent was used in vapor phase experiments both selectivity and conversion were more than 90% at low concentration (about 1% solution) of epoxide. Among the various solvents scanned, 1,2-dichlroethane was found to be the best solvent for vapor-phase reaction.

H-US-Y zeolite, a new highly dealuminated zeolite, was used for rearrangement of α-pinene epoxide.[20] At 13.3% of catalyst loading 75% selectivity to campholenic aldehyde was observed.

The various methods discussed in the earlier pages have been summarized in a tabular form below:

Table 2 Rearrangement of pinene oxide to campholenic aldehyde using various catalysts

Catalyst	Conversion	Selectivity	Reference
$ZnBr_2$	>95%	80%	5
$ZnCl_2$	>95%	70%	8
p-TSA	70%	24%	9
$BF_3.Et_2O$	>90%	73%	10
$H_3PW_{12}O_{40}$	86%	62%	13
$Zn(CF_3SO_3)_2$	85%	75%	15
B_2O_3/SiO_2	>85%	69%	16
$ZnCl_2$/MCM-41	26%	85%	16
HY Zeolite	>95%	75%	16
Ti molecular sieves	96%	82%	18
Ti β-zeolite Liquid phase Vapour phase	 29% 95%	 81% 65%	19
H-US-Y	>90%	75%	20

From the table it is clear that acid-catalyzed rearrangement of α-pinene epoxide demonstrated the potential towards solid Lewis acids in promoting the selective formation of campholenic aldehyde. In general Brönsted acids gave maximum conversion, while Lewis acids, especially zinc halides gave selectivities upto 85%. However, the industrial process for production of campholenic aldehyde with zinc halides giving a maximum conversion of 98-100% with 85% selectivity, has drawbacks like corrosion of the reactor vessels, poisoning of bacteria in sludge treatment by metal

catalysts and contamination of water by the zinc salts etc. In addition, the workup procedures are generally difficult and more expensive. Tightening of the environmental legislation has led to a drive in developing new, more efficient and selective heterogeneous systems that offer ease of catalyst separation combined with high activities and selectivities, thus reducing the waste.

Use of Ti-β zeolite gives acceptable selectivity in vapor phase as compared to other heterogeneous catalysts; however, due to use of co-absorbent or solvent, throughput has been found to be significantly reduced. Hence selectivity to campholenic aldehyde is found to be almost comparable to that of zinc halide catalyzed reactions. But its application as an industrial process is not acceptable and not recommended. Drawbacks as highlighted above bring out the necessity to develop efficient catalyst systems leading to higher conversion and higher selectivities in both liquid and vapor phase. This issue has laid the foundation for the present work.

Present Work

The drawbacks discussed above clearly bring out the need for further development of heterogeneous catalysts which will provide better conversion, selectivity and have a potential use as an industrial catalyst. A literature survey demonstrated that zinc halides are the only catalysts which have an ability to give both selectivity and conversion when used in liquid phase. Among the various heterogeneous catalysts tried in past, large pore size zeolites are found to give better selectivity in vapor phase. With a purpose to combine both liquid and vapour phase reactions *via* single catalyst, we developed modified Y type and beta type zeolites containing zinc for the rearrangement of α-pinene epoxide. With this endeavour, the work was carried out and the results obtained are presented here. Before the actual work is described, it is of relevance to discuss at length about zeolites as catalysts and briefly highlight some of their applications.

Zeolites as catalysts

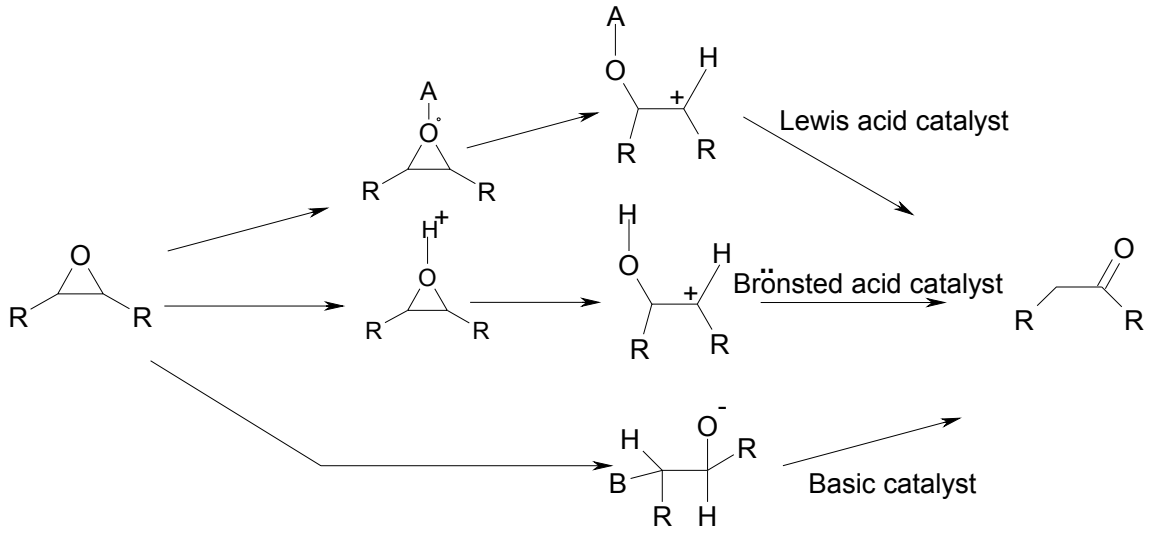
During the last four decades, there has been renewed interest in the use of heterogeneous catalysts in replacing the conventional homogeneous acid catalyst reaction systems. Though homogeneous catalysts are well established, individually optimized and commercially pronounced, based on statistical data, the future trend of R & D is on the development of new and potential catalyst systems practiced for industrial applications.

Zeolites and zeotype can be defined as microporous crystalline structures in which the frame work is formed by tetrahedral of silica, in which there is isomorphic substitution with trivalent or tetravalent elements such as for instance Al, Ga, B, Fe, Cr, Ge, Ti etc[21]. (Similar types of structures can also be achieved with the framework formed by Al and P, with or without transition metal elements).[22] These types of structures are denoted as AIPOs, SAPOs, and MEAPOs depending on the composition of the frame work. Acidic, basic and redox active sites can be introduced either in frame work or in the extra framework. Zeolites have also transformed the field of chiral catalysis, because of the possibility of introducing extra frame work active sites in the pores of these materials. The main characteristic of microporous molecular sieves is that they contain uniform distribution of micropores with dimentions between 0.4 to 1.4 nm. Zeolites are attractive as heterogeneous catalysts due to properties such as well defined crystalline structure, high internal surface area, uniform pores of one or more discrete sizes, good thermal stability, ability to adsorb and concentrate hydrocarbons and highly acidic sites in the protonated form.

There are many types of solid acids such as zeolites, heteropolyacids, sulfated metal oxides and organic-inorganic composites that possess different acidities. Porous solids like zeolites have extensive applications as adsorbents, catalysts and catalyst supports due to their high surface area. According to the IUPAC definition, porous materials may be divided into three types based on their pore sizes, microporous: < 20 Å, mesoporous: 20-500 Å and macroporous: >500 Å. Well known microporous materials are zeolites and aluminophosphate molecular sieves, which are inorganic composites having a crystalline three-dimensional framework woven with tetrahedral atoms (T atom) like Al, Si, P etc. that are bridged by oxygen atoms. Modification of the framework and extra-

framework composition renders these materials useful for catalyzing organic reactions. The most important application of zeolites is in reactions normally catalyzed by Brönsted and Lewis acids.

Catalytic rearrangements of epoxides can be performed over Lewis and Brönsted acidic and basic catalysts (**Scheme 9**). The ring opening mechanism[23] in basic medium is clearly S_N2, whereas in the acid catalyzed reactions it is often termed borderline S_N2 and usually proceeds faster. The pathways to carbonyl compounds are as follows.



Scheme 9

From above reaction pathways regarding opening of epoxide, only acid catalyzed ring opening leads to an intermediate carbocation which can easily result in migration of substituents.

Zeolite beta (**Fig 2**) was first reported in late 1960s. It is a multidimensional, large-pore zeolite that has found industrial use as well as being the object of much scientific investigation. The structure of zeolite beta is known and contains an intergrowth of two polymorphs. Since one of the polymorphs can form an enantiomorphic pair, the possibility of synthesizing a chiral zeolite based on this structure has been openly discussed. Because of the great scientific and industrial interest in zeolite beta, new varieties of this material are currently being investigated.

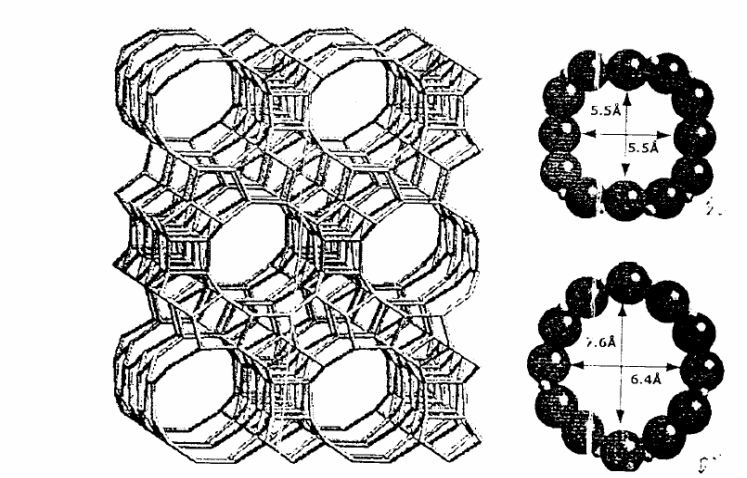


Fig 2: Structure and pore size of beta zeolite

Zinc-loaded zeolites[24], in particular, are suitable catalysts for the Heck reaction, propane aromatization, dehydrogenation of small paraffins, hydroamination, aromatization of *in situ* generated ethylene, and the hydration of acetylene. Understanding the nature and the location of Zn cations at specific sites is required for controlling activity and selectivity of such catalysts. Therefore, controlled preparation and detailed characterization, in particular the identification of ion exchange positions for Zn^{2+}, is crucial.

Zinc containing zeolite catalyst was disclosed in 1972 by Shell oil company[24] for hydrocracking and hydrorearrangement. Biscardi *et al*.[25] used Zn/HZSM5 for propane aromatization. In 2004, Penzien[26] prepared zinc zeolite beta and characterized the same using various techniques. At low concentration of zinc, the cations are found to be incorporated in the vicinity of two framework aluminum atoms. With increasing zinc loading, additional cation sites are found to be generated in which two zinc cations are bridged by an oxygen atom (**Fig 3**).

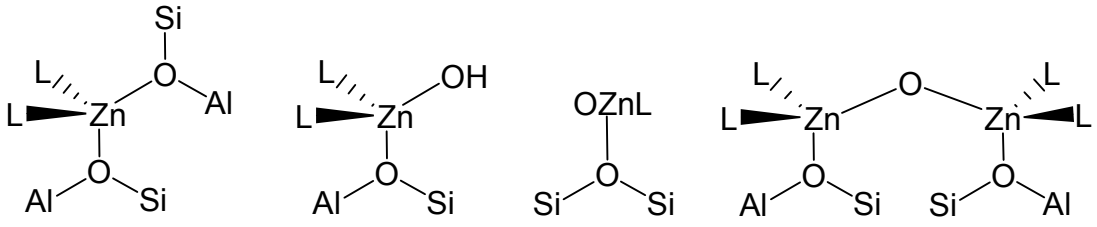


Fig 3: Possible Zn sites in Zn/H-BEA (L= framework oxygen or neutral ligand)

Seff[27] in 2005 proved the cationic zinc clusters in the zeolite Y (FAU). Davis *et al*.[28] reported the preparation of a new family of molecular sieve materials that possess the beta type zeolite structure containing zinc known as BEA (the three letter code has been assigned by the Structure Commission of the International Zeolite Association (IZA) topology. These materials are the basis of a new zincosilicate molecular sieve denoted as CIT-6 (CIT stands of California Institute of Technology). They also reported the presence of Zn^{2+} cations, thus presence of Lewis acid sites in the catalyst.

Although zinc containing zeolites had been tried for many reactions, as per our knowledge these zeolites have not been used for epoxide rearrangement reactions. We thus attempted to synthesize the commercially useful campholenic aldehyde using synthesized zinc Y and beta type zeolites. The catalysts were modified and prepared at the catalysis division of National Chemical Laboratory, Pune and are under investigation for scope in various catalytic conversions. Even though the similar Y and beta type catalysts were found to be reported in the literature, use of these catalysts for rearrangement of α-pinene oxide was not reported in the literature. Hence, the rearrangement of α-pinene oxide to campholenic aldehyde for conversion and selectivity using both the zinc containing zeolites was studied. As expected, the reactions were found to be very selective towards formation of campholenic aldehyde.

XRD of zinc beta zeolite

The XRD of zinc beta zeolite prepared for the present work (**Fig 5**) was found to be matching with that of XRD prepared by Davis *et al*.[28] (**Fig 6**). The XRD data clearly indicates that the sample does not collapse after calcinations.

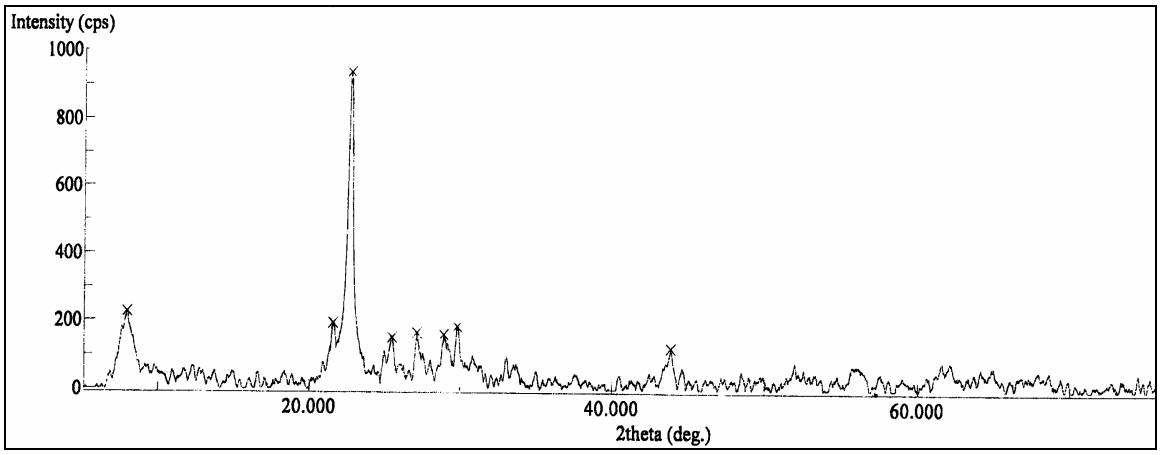


Fig 5: XRD of zinc beta zeolite prepared

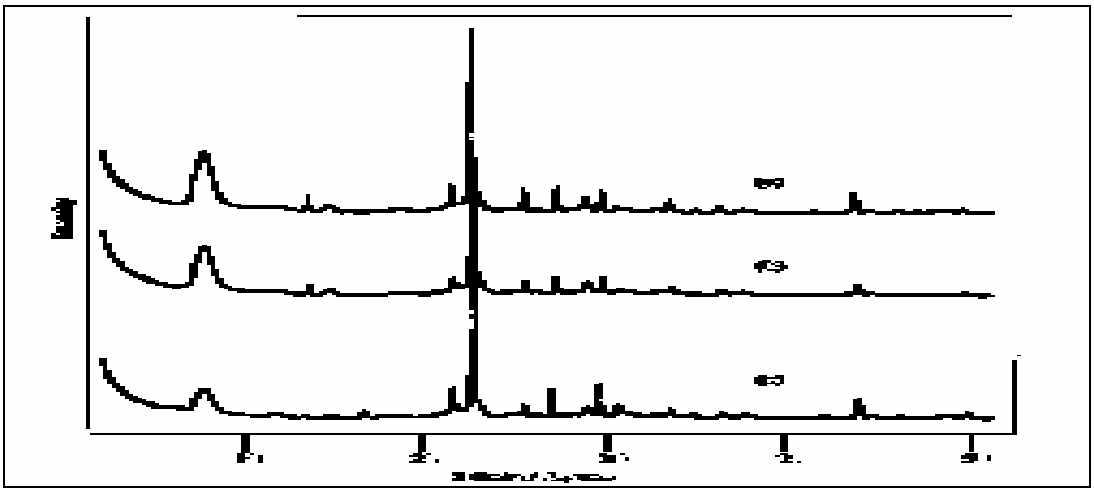


Fig 6: Reported XRD data prepared by Davis *et al*.

Results and Discussion

Kunkeler *et al.*[19] have used acetonitrile and dichloroethane as solvent for rearrangement of α-pinene oxide to campholenic aldehyde using Ti-beta zeolite and achieved 81% selectivity. In the present study, acetonitrile and dichloromethane having different dielectric constants and boiling points (**Table 2**), have been used as solvents for rearrangement of pinene epoxide with both zinc Y and zinc beta type zeolites.

Table 2: Solvents used for rearrangement of α-pinene epoxide

Solvent	Dipole moment	Dielectric constant	Boiling point
Acetonitrile	3.44	37.50	81 - 82 °C
Dichloromethane	1.14	8.93	39.8-40 °C

A solution of α-pinene epoxide in either solvent was refluxed with 5 – 30 wt% of catalyst. The reaction was monitored by periodically analyzing the samples by gas chromatography. Reaction mass volume was kept constant in order to get similar conditions, while studying optimization of catalyst quantity.

Following parameters were studied for optimum results.

1) Effect of catalyst load (Y- type and β-type zinc containing zeolites), on conversion of pinene epoxide and selectivity towards campholenic aldehyde.
2) Optimum temperature required for maximum conversion and selectivity.
3) Effect of catalyst load (β-type) on conversion and selectivity when reactions were carried out under pressure with constant RPM.
4) Optimum catalyst loading required for maximum conversion and selectivity at atmospheric pressure and under pressure.

Rearrangement of α-pinene epoxide using zinc Y type catalyst

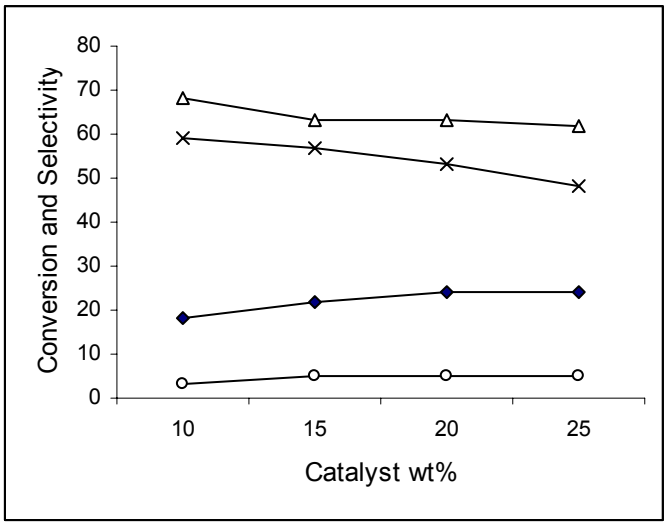
The reactions were carried out at reflux temperature of both solvents under inert atmosphere. Rearrangement of pinene epoxide was observed to give desired campholenic aldehyde in both the solvents. The conversions were low even after 10 h (**Table 3**). However, in acetonitrile, the conversions and selectivities were found to be better than in dichloromethane.

Table 3: Conversion and selectivity of α-pinene epoxide to campholenic aldehyde using Y type zeolite over a period of 10 h

Catalyst Wt%	Solvent	Conversion	Selectivity
10%	Acetonitrile	18 %	68%
	Dichloromethane	3%	59%
15%	Acetonitrile	22%	63%
	Dichloromethane	5%	57%
20%	Acetonitrile	24%	63%
	Dichloromethane	5%	53%
25%	Acetonitrile	24%	62%
	Dichloromethane	5%	48%

Using acetonitrile as solvent at 81 °C (reflux), the change in conversion was observed from 8% to 15%, when catalyst load was increased from 10 wt% to 25 wt%. The selectivity was found to decrease due to side reactions, when catalyst load was increased from 10-25%. No change in conversion was observed even if catalyst load was increased. In case of dichloromethane as a solvent at 40 °C (reflux) the conversion and selectivity was very low. At 15 wt% of catalyst, maximum conversion and selectivity was obtained. Thus acetonitrile was found to be a better solvent than dichloromethane.

Fig 7: Conversion and selectivity against zinc Y catalyst wt%



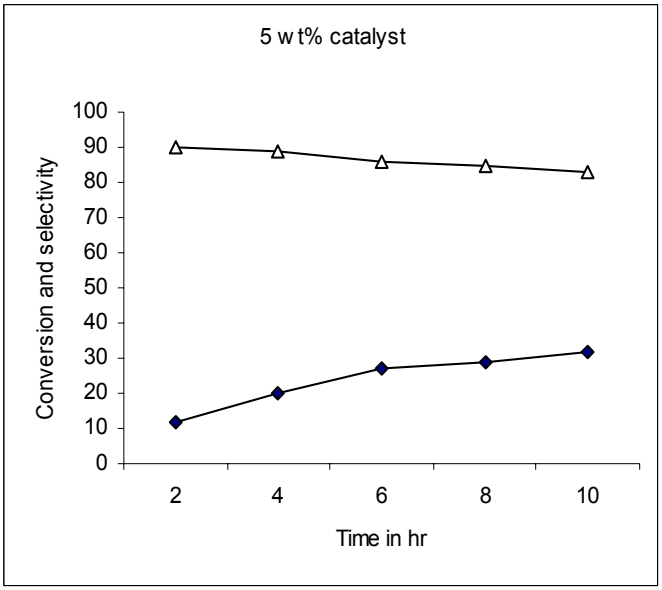
▪ = Conversion in acetonitrile ◦ = Conversion in dichloromethane

Δ = Selectivity in acetonitrile × = Selectivity in dichloromethane

Rearrangement of α-pinene epoxide catalyzed by zinc beta

Further study was conducted using zinc beta zeolite as the catalyst. At 5 wt% zinc beta zeolite catalyst in acetonitrile, initial result of conversion of pinene epoxide to aldehyde was encouraging. Though after one hour, conversion was very low; at second hour the conversion was 12% whereas selectivity was 90%. The reaction was monitored after every 2 hours. At 8 hours 30% conversion with 83 % selectivity to campholenic aldehyde was observed. After 10 hours there was little increase in conversion whereas selectivity still reduced (**Fig 8**).

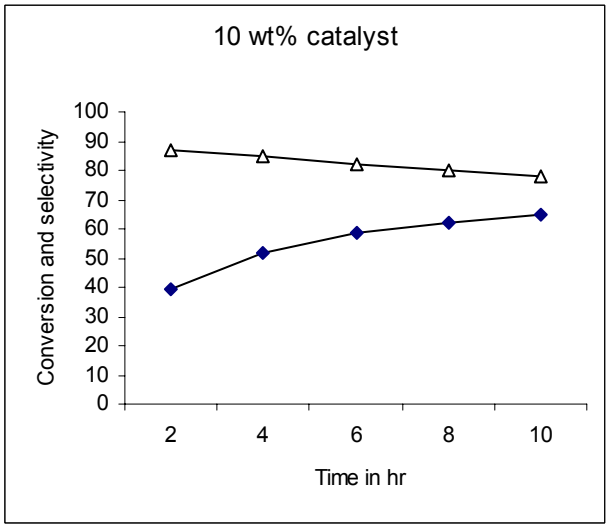
Fig 8: Rearrangement with 5 wt% catalyst in acetonitrile



Δ = Selectivity, ▪ = Conversion

Using 10% catalyst, even though the conversion was gradual over a period of time, it was maximum 65% after 10 h with 79% selectivity. During first four hours of reaction, the conversion was 52% with 85% selectivity (**Fig 9**).

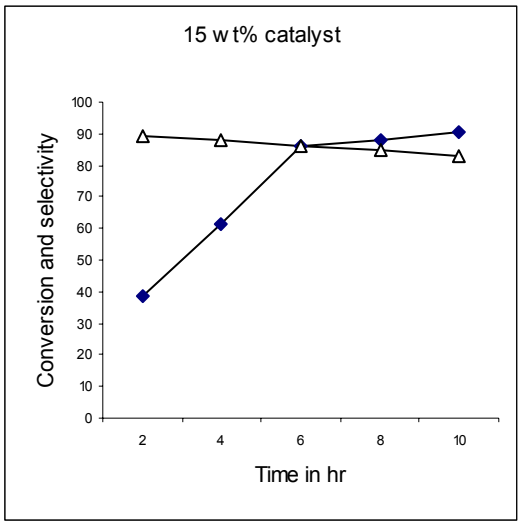
Fig 9: Rearrangement with 10 wt% catalyst in acetonitrile



Δ = Selectivity, ▪ = Conversion

When 15 wt% catalyst was employed, there was no change in selectivity and conversion during the first 2 h as compared to rearrangement using 10 wt% catalyst. After 6 h, selectivity was 86% with 85% conversion. After 10 h, conversion increased up to 92% but selectivity decreased to 83% (**Fig 10**).

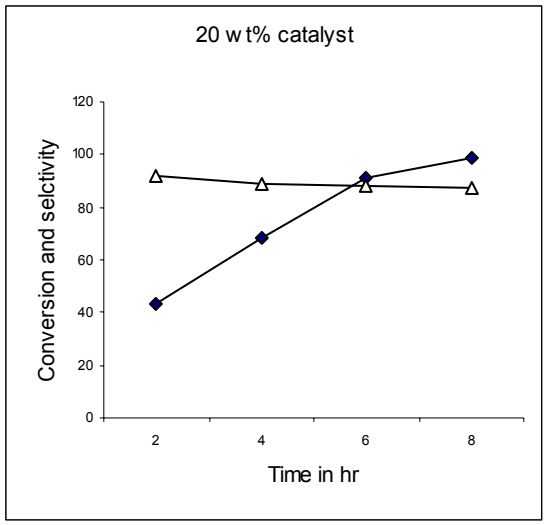
Fig 10: Rearrangement using 15 wt% catalyst in acetonitrile



Δ = Selectivity, ▪ = Conversion

Further conversion and selectivity were 98% and 87% respectively after 8 h when 20 wt% catalyst was used. Both conversion and selectivity were obtained maximum (42% and 92% respectively) after first 2 h of reaction among all the reactions carried out (**Fig 11**).

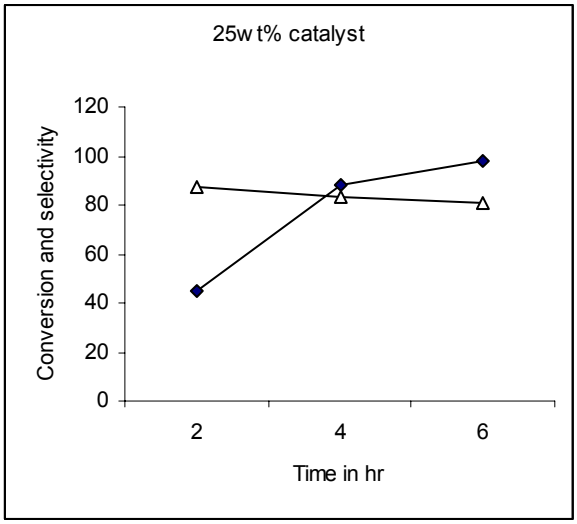
Fig 11: Rearrangement in the presence of 20 wt% catalyst in acetonitrile



Δ = Selectivity, ▪ = Conversion

The catalyst load was further increased to 25 wt% when 98% conversion was observed in six hours, but the selectivity was only 78%. The trend of decrease in selectivity even after two hours was found to be much higher and the selectivity continued to decrease with longer time.

Fig 12: Rearrangement in the presence of 25 wt% catalyst in acetonitrile

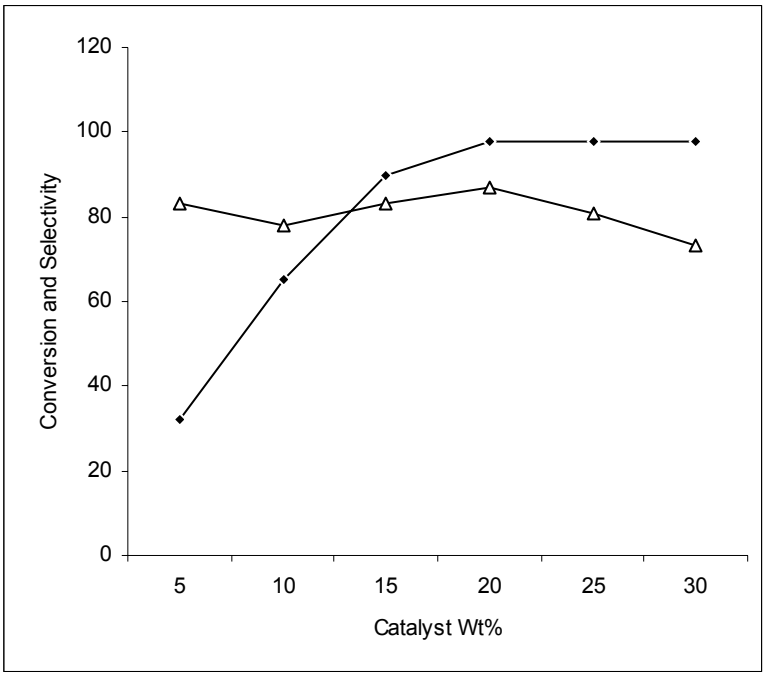


Δ = Selectivity, ▪ = Conversion

In case of 30 wt% catalyst, 98% conversion was found in 6 hrs but the selectivity was found to be only 73%.

Comparison of various weight proportions of catalyst for selectivity and conversion showed that 20 wt% of zinc beta zeolite catalyst was the ideal proportion for rearrangement (**Fig 13**). Practically complete conversion was achieved over 6 hrs when 20 wt% catalyst was used with 87% selectivity. The results were almost matching with liquid phase reaction when zinc bromide was used as catalyst. Control of reaction at desired conversion is the main advantage of heterogeneous zinc beta zeolite. The catalyst quantity was found to be very low as compared with liquid phase reactions. The present industrial method uses zinc bromide as catalyst and for which special techniques are required to maintain an anhydrous condition. While using heterogenous zinc beta zeolite no such special techniques will be required.

Fig 13: Catalyst optimization



Δ = Selectivity, ▪ = Conversion

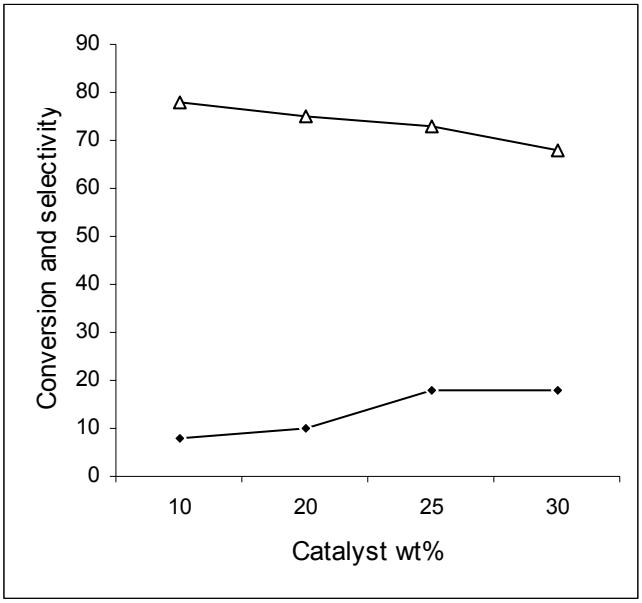
The reactions were then conducted using dichloromethane as solvent at atmospheric pressure. The catalyst proportions used were 10 wt%, 20 wt%, 25 wt% and

30 wt%. The rearrangement was monitored periodically by gas chromatography. The conversion rate was found to be low at 2 hours, 4 hours and 6 hours as compared with that of reactions carried out in acetonitrile. All the reactions were carried out for 10 hours (**Table 4, Fig 14**). When 10 wt% catalyst was used, the conversion was found to be only 8% after 10 hours, whereas at 20 wt% catalyst the conversion was 10%, but in both the cases the selectivity was found to be more than 74%. At 30 wt% of catalyst the decrease in selectivity to 68% was observed.

Table 4: Rearrangement in dichloromethane using zinc beta zeolite at atmospheric pressure

Sr. No.	Wt % of catalyst	Conversion %	Selectivity %
1	10	8	78
2	20	10	75
3	25	18	73
4	30	18	68

Fig 14: Rearrangement in dichloromethane using zinc beta zeolite

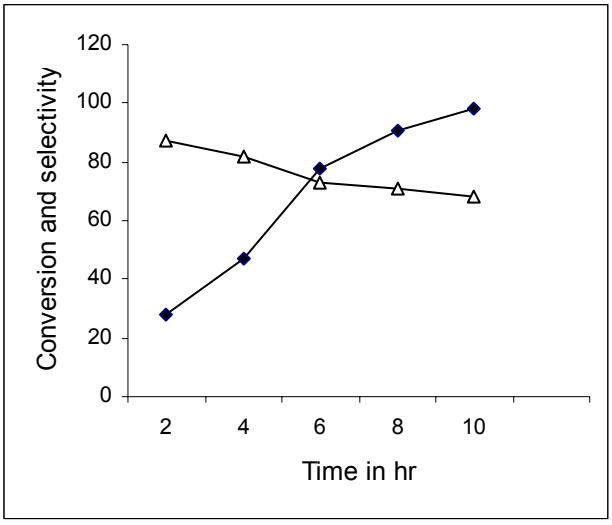


Δ = Selectivity, ▪ = Conversion

The low conversion may be due to difference in dielectric constant of the solventsas observed by Kunkeler *et al.*[18] or due to reaction temperatures.

To check the effect of temperature, rearrangement of α-pinene epoxide was carried out in dichloromethane at 81-82 °C under pressure. The reactions were carried out in 50 ml Parr autoclave. The concentration of reaction solution was same as that of the reaction carried out at atmosphere pressure. Since at 25 wt% of catalyst, conversion and selectivity was optimum at atmospheric pressure, the first reaction was conducted using same percentage of catalyst. The conversion was found to be 98% with 68% selectivity over a period of 10 hours.

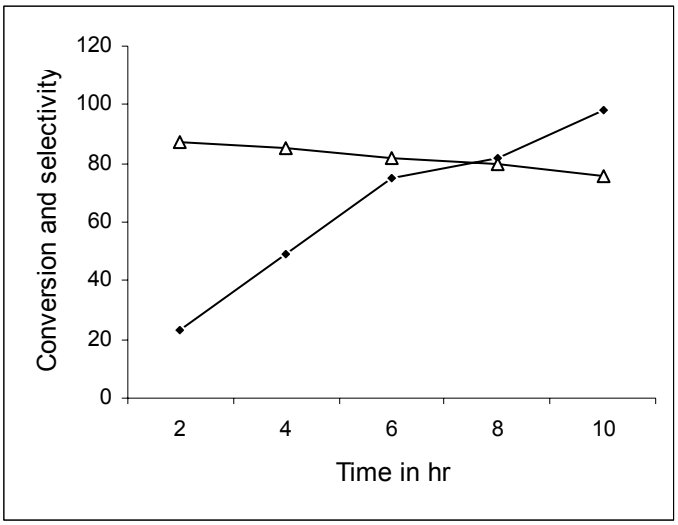
Fig 15: Rearrangement in dichloromethane under pressure with 25 wt% catalyst



Δ = Selectivity, ▪ = Conversion

Using 20 wt% catalyst the conversion was 98% with 73% selectivity over a period of 10 hours whereas conversion and selectivity were 98% and 76% over 10 hours when 15 wt% catalyst was used.

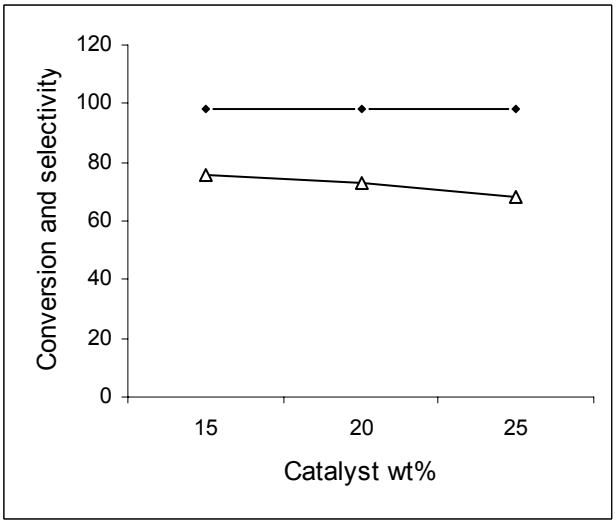
Fig 16: Rearrangement in dichloromethane under pressure in the presence of 15 wt% catalyst



Δ = Selectivity, ▪ = Conversion

Thus under pressure and at 81 °C in dichloromethane, conversion was almost 98% at all concentrations of catalyst tried, whereas selectivity reduced from 76% to 68% as catalyst proportion increased (**Fig 17**).

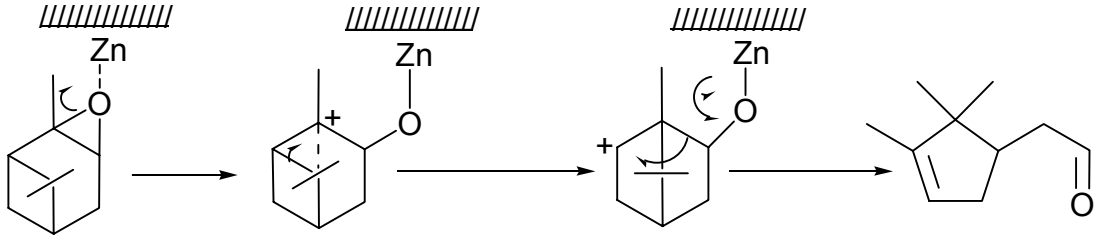
Fig 17: The study of optimum wt% of catalyst



Δ = Selectivity, ▪ = Conversion

The rearrangement of α-pinene oxide to campholenic aldehyde is proposed to be effected by the coordination of epoxide oxygen atom to a Lewis acid center, thereby inducing ring opening of the epoxide, followed by subsequent or concerted alkyl shifts.[28] This mechanism may also hold good in the case of modified zinc beta as the Lewis acid catalyst.

Fig 18: Plausible mechanism



Recyclability studies of catalyst were carried out for three consecutive reactions in acetonitrile at atmospheric pressure and in dichloromethane under pressure using optimum ratio of catalyst. The deactivation of catalyst was observed during recycle study under pressure. This may be due to blocking of pores by some organic material. In case of atmospheric reactions, almost consistent results were obtained indicating practically no loss of activity.

Table 5: Recyclability studies at atmospheric pressure in acetonitrile

	Conversion	Selectivity
1st recycle	98	87
2nd recycle	96	85
3rd recycle	95	83

Table 6: Recyclability studies under pressure with dichloromethane as solvent

	Conversion	Selectivity
1st recycle	98	73
2nd recycle	96	70
3rd recycle	95	68

Thus, effect of catalyst load (both Y-type and β-type) on conversion and selectivity was studied in the above mentioned solvents, keeping parameters like temperature, pressure and mixing unchanged. The effect of temperature was also studied as different set of experiments, by carrying out reactions under pressure with dichloromethane as solvent. Optimum catalyst loading required was also studied for reactions carried out under pressure. The optimum quantity of catalyst required both at atmospheric pressure and under pressure to get optimum and acceptable conversion and selectivity was thus established.

Epoxidation of α-pinene and further conversion to campholenic aldehyde

A one pot synthesis of campholenic aldehyde from α-pinene in the presence of Ti-HMS as the catalyst was reported recently.[17] The catalyst Zn-beta, used in the present study, was applied in the second step of the 2-step operation as described here. Epoxidation of α-pinene was carried out using hydrogen peroxide-urea (UHP) complex in dichloromethane as solvent. After isolating epoxide in dichloromethane, dichloromethane solution was dried and the mixture was subjected to rearrangement using zinc beta zeolite under pressure. Using optimum quantity of zinc beta zeolite (15 wt%), 98% conversion with 76% selectivity was obtained. The overall yield of campholenic aldehyde was 58% from α-pinene over two steps.

Conclusion

Thus rearrangement of α-pinene epoxide to campholenic aldehyde was studied with two zinc containing zeolites in acetonitrile and dichloromethane. Zeolite Y-type and beta type were used for rearrangement of α-pinene epoxide. Both the catalysts were found to isomerize α-pinene epoxide at atmospheric pressure. Upto 98% conversion with 87% selectivity was observed in acetonitrile at atmospheric pressure using zinc beta catalyst. In dichloromethane, 98% conversion with 76% selectivity was achieved by conducting the reaction under pressure. Temperature effect on conversion was established. Practically no loss of activity was observed during recyclability studies of catalysts.

Campholenic aldehyde was also synthesized in two stage operations. α-Pinene epoxide was prepared in 77% yield, using UHP in dichloromethane and was further converted in to campholenic aldehyde by carrying out reaction under pressure. The overall yield of campholenic aldehyde was found to be 58% from α-pinene (2 steps).

Thus the heterogeneous catalyzed green method for the synthesis of campholenic aldehyde was thoroughly studied with various parameters and optimization of catalyst. These catalysts can be scanned for various other chemical transformations. Work on these lines is underway in our laboratories.

Experimental

Synthesis of α-pinene epoxide from α-pinene

To a mixture of α-pinene (6.5 g, 47 mmol) UHP (18.14 g, 193 mmol) and disodium hydrogen orthophosphate (4.7 g, 26 mmol) in dichloromethane (80 ml), acetic anhydride (9.7 g, 95 mmol) was added at 10 °C over a period of 1.5 h while stirring. The reaction mixture was stirred further for one more hour at same temperature and allowed to come to room temperature and stirred further for six hours. The reaction mixture was diluted with dichloromethane (20 ml) and washed with water (2 X 20 ml). The dichloromethane solution was dried and concentrated. The crude product was purified by column chromatography to afford pure α-pinene epoxide (5.59 g, 77%).

Rearrangement of α-pinene epoxide to campholenic aldehyde in the presence of Y type zeolite

a) Catalyst 10 wt%

α-Pinene epoxide (5 g, 32.9 mmol), acetonitrile (25 ml), tetradecane, as internal standard and zinc Y type zeolite (0.5 g, 10 wt%) were charged in a three neck 50 ml R. B. flask equipped with condenser, thermometer pocket and magnetic stirrer. The reaction vessel was placed in pre-heated (95 °C) oil bath to reflux the reaction mixture.

Progress of the reaction was followed by gas chromatography (GC) using a Chemito 1000 instrument fitted with a Carbowax 30 M capillary column and a flame ionization detector. At appropriate time intervals, stirring was stopped and after, allowing the catalyst to settle, aliquots were drawn and analyzed by GC. The GC mass balance was calculated on substrate charged. After 10 hours, reaction mass was cooled to 30°C and filtered. Filtrate was concentrated and the crude product was purified by flash column chromatography to get campholenic aldehyde (0.89 g, 18%).

The above experiment was repeated with dichloromethane as solvent at reflux temperature. The yield of campholenic aldehyde obtained was (0.15 g, 3 %).

b) Catalyst 15 wt%

α-Pinene epoxide (5 g, 32.9 mmol), acetonitrile (25 ml), tetradecane, as internal standard and zinc Y type zeolite (0.75 g, 15 wt%) were charged in a three neck 50 ml R. B. flask equipped with condenser, thermometer pocket and magnetic stirrer. The reaction vessel was placed in pre-heated (95 °C) oil bath to reflux the reaction mixture.

Progress of the reaction was followed by gas chromatography (GC) using a Chemito 1000 instrument fitted with a Carbowax 30 M capillary column and a flame ionization detector. At appropriate time intervals, stirring was stopped and after the catalyst settled, aliquots were drawn and analyzed by GC. The GC mass balance was calculated on substrate charged. After 10 hours reaction mass was cooled to 30°C and filtered. Filtrate was concentrated and the crude product was purified by flash column chromatography. (Yield 1.1 g, 22%).

The above experiment was repeated with dichloromethane as solvent at reflux temperature. The yield of campholenic aldehyde obtained was (0.25 g, 5%)

c) Catalyst 20 wt%

α-Pinene epoxide (5 g, 32.9mmol), acetonitrile (25 ml), tetradecane as internal standard and zinc Y type zeolite (1.0 g, 20 wt%) were charged in a three neck 50 ml R. B. flask, equipped with condenser, thermometer pocket and magnetic stirrer. The reaction vessel was placed in pre-heated (95 °C) oil bath to reflux the reaction mixture.

The reaction progress was followed by gas chromatography (GC) using a Chemito 1000 instrument fitted with a Carbowax 30 M capillary column and a flame ionization detector. At appropriate time intervals, stirring was stopped and after allowing the catalyst to settle, catalyst settling aliquots were taken and analyzed by GC. The GC mass balance was calculated on substrate charged. After stipulated period, reaction mass was cooled to 30°C and filtered. Filtrate was concentrated and crude product was purified by flash column chromatography. (Yield 1.2 g, 24%).

The above experiment was repeated using dichloromethane as solvent at reflux temperature. The yield of campholenic aldehyde obtained was (0.25g, 5%).

d) Catalyst 25 wt %)

α-Pinene epoxide (5 g, 32.9mmol), acetonitrile (25 ml), tetradecane as internal standard and zinc Y type zeolite (1.25 g, 20 wt%) were charged in a three neck 50 ml R. B. flask, equipped with condenser, thermometer pocket and magnetic stirrer. The reaction vessel was placed in pre-heated (95 °C) oil bath to reflux the reaction mixture.

The reaction progress was followed by gas chromatography (GC) using a Chemito 1000 instrument fitted with a Carbowax 30 M capillary column and a flame ionization detector. At appropriate time intervals, stirring was stopped and after catalyst settling aliquots were taken and analyzed by GC. The GC mass balance was calculated on substrate charged. After stipulated period, reaction mass was cooled to 30°C and filtered. Filtrate was concentrated and crude product was purified by flash column chromatography. (Yield 1.2 g, 24%).

The above experiment was repeated using dichloromethane as solvent at reflux temperature. The yield of campholenic aldehyde obtained was (0.25 g, 5%)

Typical experiment for rearrangement of α-pinene epoxide to campholenic aldehyde at atmospheric pressure using zinc beta zeolite

In a typical experiment α-pinene epoxide (5 g, 32.9 mmol), solvent (25 ml) (acetonitrile or dichloromethane), tetradecane as internal standard and zinc beta zeolite were charged in a three neck 50 ml R. B. flask, equipped with condenser, thermometer pocket and magnetic stirrer. The reaction vessel was placed in pre-heated (95 °C for acetonitrile and 50 °C for dichloromethane) oil bath to reflux the reaction mixture.

The reaction progress was followed by gas chromatography (GC) using a Chemito 1000 instrument fitted with a Carbowax 30 M capillary column and a flame ionization detector. At appropriate time intervals, stirring was stopped and after catalyst settling aliquots were taken and analyzed by GC. The GC mass balance was calculated on substrate charged. After stipulated period, reaction mass was cooled to 30 °C and filtered. Filtrate was concentrated and crude product was purified by flash column chromatography.

Catalyst recyclability studies

Catalyst recycling was performed as follows. After completion of reaction, the mixture was centrifuged to settle the catalyst. The upper clear solution was removed by a pipette. Catalyst was washed with solvent (2 X 20 ml) and the organic solution was removed after centrifuging the catalyst. Catalyst was transferred using 25 ml of solvent into the reaction assembly for further recycle study using fresh substrate.

Typical experiment for rearrangement of α-pinene epoxide to campholenic aldehyde under pressure

In a typical experiment α-pinene epoxide (5 g, 32.9 mmol), dichloromethane (25 ml), tetradecane as internal standard and zinc beta zeolite catalyst were charged in a 50 ml Parr autoclave under nitrogen atmosphere. The reaction mixture was heated at 81-83 °C (2.8-3.2 Kg/cm^2) while stirring. Aliquots were removed under pressure and analyzed by GC.

For recyclability studies, after completion of reaction, the reaction mass was removed from reactor and centrifuged to settle the catalyst. The upper clear solution was removed by a pipette. Catalyst was washed with solvent (2 X 20 ml) and the organic solution removed after centrifuging the catalyst. Catalyst was transferred using 25 ml of solvent in to Parr reactor for further recycle study using fresh substrate.

^{1}H NMR ($CDCl_3$, 200MHz): δ 0.83 (s, 3H), 1.04 (s, 3H), 1.66 (s, 3H), 1.97 (m, 1H), 2.37-2.54 (m, 4H), 5.28 (s, 1H), 9.84 (d, J = 1 Hz, 1H).

^{1}C NMR ($CDCl_3$, 50MHz): δ 12.6, 20.0, 25.7, 35.6, 44.3, 45.1, 47.0, 121.6, 148.6, 202.4.

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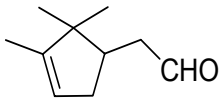
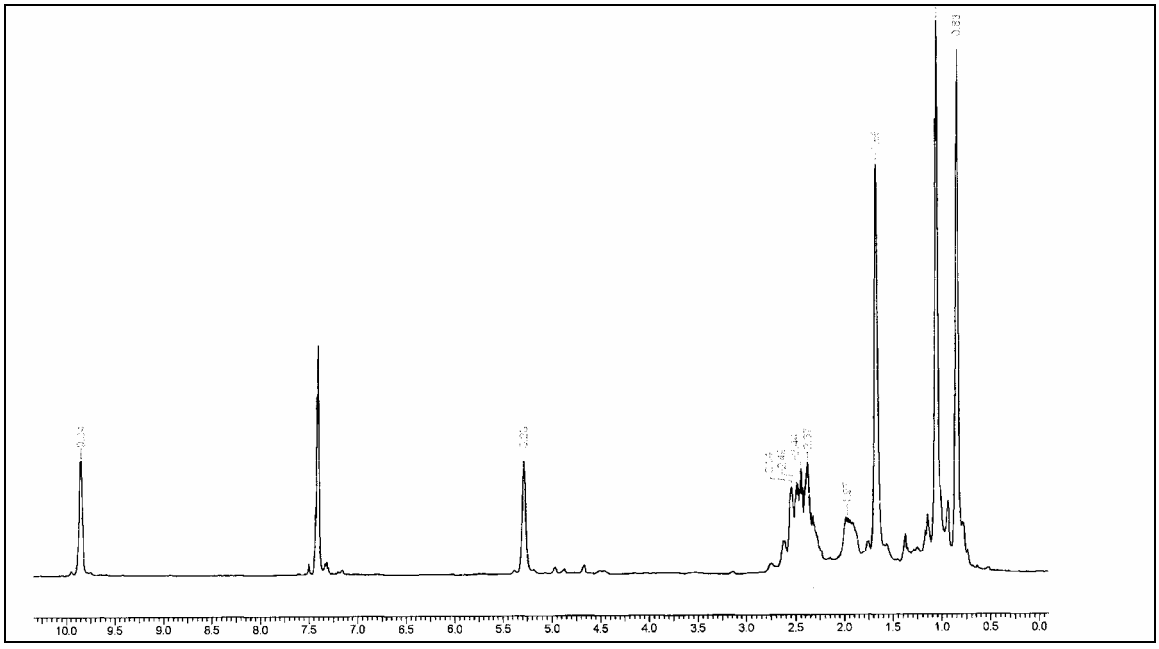


Campholenic aldehyde

^{1}H NMR of Campholenic aldehyde in $CDCl_3$



CHAPTER 3

SECTION II

REGIOSELECTIVE NITRATION OF PHENOLS WITH NEW PHOSPHORUS BASED IONIC LIQUIDS

Introduction

Nitration is a unit process of great industrial importance generating commercially valuable intermediates. The nitration reaction serves to introduce one or more nitro groups into reacting molecules. Nitroparaffins and aliphatic nitro compounds are useful solvents, additives and fuels. These nitro compounds are useful as heat sensitizers for latex and as hardening agents. Nitration of aromatic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature with extensive and well documented reviews.[1-5] Nitration of aromatic compounds is of considerable commercial importance, as nitrated aromatic compounds find utility as dyes, explosives, pharmaceuticals, perfumes, plastics and solvents. These nitro intermediates can further be processed for introduction of amino group, hydroxy group and for azo and azoxy compounds.

In the nitration process, the entering nitro group may replace a number of different monovalent atoms or groups of atoms. A variety of reagents can be used to effect nitration. These include fuming nitric acid, aqueous nitric acid and mixture of nitric acid with sulfuric acid, acetic anhydride, acetic acid, phosphoric acid etc. Nitrogen pentoxide (N_2O_5) and nitrogen tetroxide (N_2O_4) are also used in certain cases.

The system nitric acid-sulfuric acid, commonly known as mix acid, is the most important nitrating medium and is probably also the best understood. It is known that nitric acid exists in presence of strong sulfuric acid as the nitryl ion, NO_2^+. The Van't Hoff (i) factor of various nitrating agents can be represented by following equations.

$$HNO_3 + 2H_2SO_4 \dashrightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$$

$$C_2H_5ONO_2 + 3H_2SO_4 \dashrightarrow NO_2^+ + H_3O^+ + 2HSO_4^- + C_2H_5OSO_3H$$

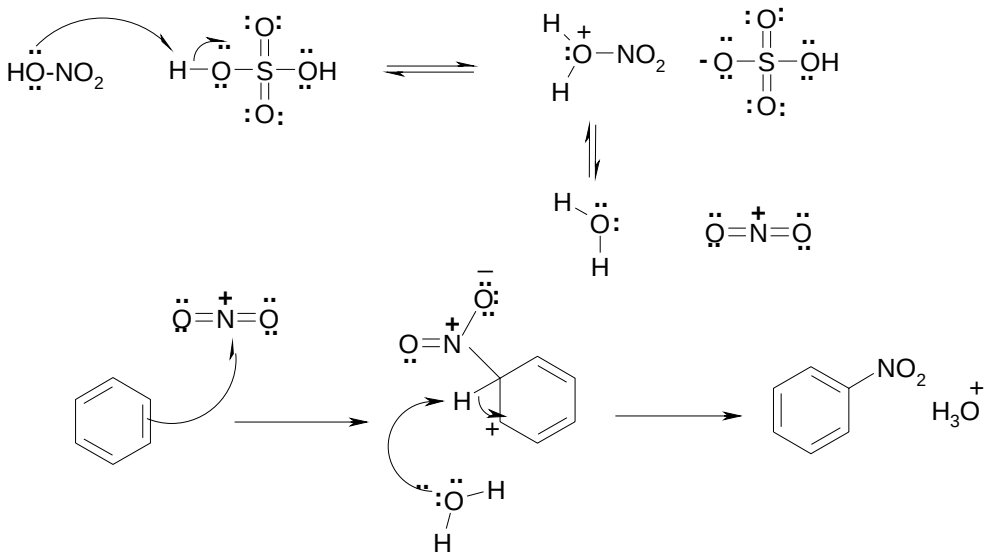
$$N_2O_5 + 3H_2SO_4 \dashrightarrow 2NO_2^+ + H_3O^+ + 3HSO_4^-$$

$$N_2O_4 + 3H_2SO_4 \dashrightarrow NO^+ + NO_2^+ + H_3O^+ + 3HSO_4^-$$

In a solution weaker than 86% sulfuric acid, the ionization of nitric acid is very little, but rapidly rises as the sulfuric acid concentration increases. In about 94% sulfuric acid, the nitric acid is practically completely ionized to nitryl ion.

Nitration of aromatic compounds

The electrophilic nitration of aromatic compounds can be represented by the following scheme.

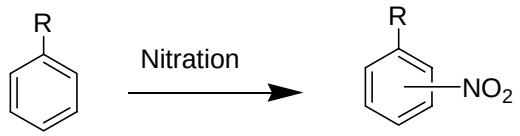


In most of the commercial manufacturing nitration processes, a mixture of nitric acid and sulfuric acid is used as nitrating mixture. During nitration, sulfuric acid gradually gets deactivated due to formation of water. Disposal of this spent acid is a key effluent treatment. Another important factor is the temperature during nitration. Due to highly exothermic nature of the process, temperature is to be maintained during nitration reactions and chilling facilities are required. Commercially, preparation of mix acid is carried out at low temperature (< 5 °C). All these factors add to the economics of the process.

Nitration is an electrophilic process and hence reaction will be favored at the carbon atom of the aromatic ring where the electron density is greatest. When monosubstituted aromatic compounds are nitrated, the nitration can occur at the *ortho*, *meta* or *para* positions. The relative amounts of these isomers formed will depend upon the substitutents, since the substitutents have profound effect on electron densities around the various carbon atoms. The substituents present on ring influence the electron density, by two ways: 1) inductive effect (+I or –I) 2) mesomeric effect. The +I effect causes all

the positions in the ring to be more reactive than unsubstituted benzene and *ortho* and *para* positions are more reactive than *meta*, whereas –I effect reduces the reactivity of all the positions but the effect is more at *ortho* and *para* positions. Thus toluene nitration produces *ortho* and *para* nitro toluenes whereas nitrobenzene produces meta-dinitrobenzene.

Substituents which have an unshared pair of electron can increase the electron density in the ring by mesomeric effect. Substituents like COOR (ester), SMe_2 (dimethylthio) produce predominantly *meta* derivatives due to (-M) effect (**Scheme 1**).



o-, *p-* directing = F, Cl, Br, I, CH_3, OCH_3, OH
m-directing = COOR, COOH, NO_2, CCl_3

Scheme 1

The obvious disadvantages of conventional processes have led to a substantial effort to develop viable alternatives like solid acid catalysis, other sources of NO_2^+, organic nitrating agents, other acids replacing sulfuric acid etc. Various solid acid catalysts such as sulfonic ion-exchange resins (Amberlite IR-120),[6] claycop, cupric nitrate-impregnated on acidic montmorillonite clay K-10,[7] Fe^{+3}-exchanged montmorillonite,[8] H-ZSM-5[9] are reported for nitration of aromatic compounds. Although economically competitive nitration processes for aromatic compounds based on solid acid catalysis are available, the technology is yet to be improved to become much competitive to traditional ways of nitration.

The drawbacks enumerated above have put the chemical industry under considerable pressure to perform atom economic processes, creating minimal or no environmentally hazardous by- products and to develop novel catalytic systems that facilitate aromatic nitration. The “no effluent” processes are generally termed as green processes. Due to environmental hazards there is an urgent need for good and appropriate solvents which can be used for nitration reactions under highly acidic conditions and which are almost non-volatile.

Nitration of phenols

Phenol can be nitrated with aqueous nitric acid in the presence of catalytic nitrous acid to give mixture of 2- and 4- nitro phenols.[10] Although these can be separated (*o*-isomer is steam volatile), the process for regioselective formation of *para* isomer is always appreciated. A survey of literature shows nitration of phenol lacks position selectivity for *para* isomer with majority of processes giving rise to *o*-isomer (~67%) as the major product with minor *p*- isomer (~33%).[11-13] A variety of nitrating agents under different conditions have been reported recently for the nitration of phenols. Indeed metal nitrates and supported metal nitrates on various supports are reported to effect *para* selectivity.

Very recently, Rodrigues *et al*.[12] reported that phenol can be nitrated by silica-gel supported acetyl nitrate with excellent *ortho* selectivity. A large volume of literature is available for *ortho* selective nitration of phenols. Nitration of phenol with N_2O_4[13] and pyridine derivatives carrying transferable nitro group or silica gel supported acetyl nitrate gave exclusively *ortho* product. Poierier *et al.*[14] compared the nitrating effect of various commercially available metal nitrates in the nitration of phenol. They found that ferric nitrate in ethanol gave a 1:1 mixture of *o*- and *p*- isomers. The same reaction in chloroform resulted in a slight increase in *para* selectivity whereas chromium nitrate gave high *para* selectivity. Various reagents and conditions have been reported recently (**Table 1**) for the nitration of phenol and the results are depicted below

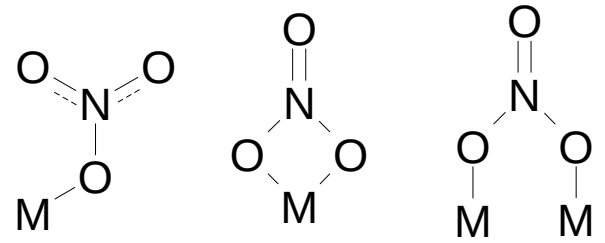
Table 1: Various reagents used for nitration for phenol

S. No.	Reagent/solvent/conditions	Ortho %	Para %	Reference
1	HNO_3/H_2SO_4	36	25	12,13
2	CLAYFEN/THF/r. t./ 20 h	40	50	104
3	$HNO_3/SiO_2/CH_2Cl_2$	40	42	10
4	CLAYCOP/acetic anhydride/CCl_4	86	6	11
5	$Fe(NO_3)_3.9H_2O$/EtOH/50 °C/3 h	50	50	14
6	$Fe(NO_3)_3.9H_2O/CHCl_3$/50 °C/3 h	49	47	12
7	$Cr(NO_3)_3.9H_2O$/EtOH/65 °C/4 h	24	76	13
8	$Cr(NO_3)_3.9H_2O$/THF/r. t./24 h	37	60	13
9	$Cr(NO_3)_3.2N_2O_4$/THF/r. t.	40	59	15

Nitration of phenols using metal nitrates

Metal nitrates have been extensively used in the nitration of phenol as can be seen from the literature available. In this, transition metal nitrates on suitable supports have enjoyed more attention being more selective and eco-friendly.[15] Mechanistically, the classical Hughes-Ingold (ionic) and Perrin (radical) pathways compete in nitration reaction.[16] The latter gives a product distribution stemming from unpaired spin density in the radical cation intermediate.[17] This unpaired spin density is greater in the *para* than in the *ortho* position. Therefore, for more *para* selectivity, the logical way is to make the reaction proceed through radical instead of ionic pathway.

It is well documented that in many (anhydrous) transition metal nitrates,[18,19] the bond between the metal and the nitrate group is covalent and hence they can be considered as coordination complexes.[20,21] Examples are bivalent metals like $Mn(NO_3)_2$, $Ni(NO_3)_2$, $Cu(NO_3)_2$, trivalent metals like $Cr(NO_3)_3$ and tetravalent metals like $Ti(NO_3)_4$ and $Sn(NO_3)_4$. The nitrato group is unique as its chemical reactivity varies widely with the multiplicity of the metal-nitrate bond; also the more multiple the bond becomes, the more reactive is the nitrate group. Three types of covalent bonds are possible as shown below.



Unidentate Bidentate Bridging

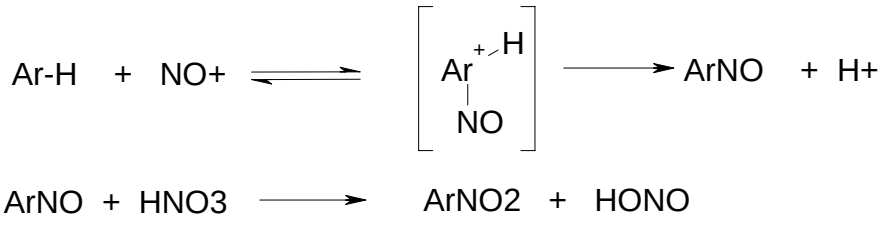
It has been found that the unidentate nitrates are not reactive whereas bidentate species possess strong oxidizing powers towards many organic substances.[21]

Depending on the strength of the sigma bond by which oxygen atom is bonded to the metal, either a nitrate ion or NO_2 radical is produced. The metallic center then achieves abnormally large coordination numbers: 8 with tetranitrato derivatives of titanium (IV), manganese (II), iron (III), cobalt (II), tin (IV) and up to 12 with hexanitrato derivatives of cerium (III), cerium (IV), thorium (IV). The exceptional reactivity of these substances, coupled with their inter-relationship with other oxygenated derivatives of nitrogen,[20] allows one to direct formation of either neutral or charged, radical, or electrophilic or nucleophilic species, depending upon the substrate. The dual condition for the reactivity of a metallic nitrate is the coexistence of a bidentate covalent coordination by the nitrato group to the metal, with the availability of lower intermediate oxidation states for the metal.[21] Cornelis *et al*.[22] studied activity of the cheap and non-toxic ferric nitrate nonahydrate towards organic substrates. Apparently, this ionic mode of existence precludes the required covalent bonding of the nitrato group. They obtained a dark red oil when an acetone solution of ferric nitrate nonahydrate was subjected to high vacuum which was confirmed by IR spectral data to be a bidentate nitrate group on iron.

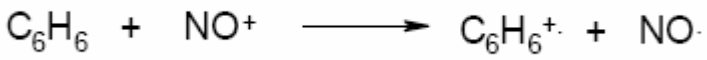
Mechanism

The classical nitration of phenol is the nitrous acid catalyzed nitration.[23] The electrophilic attack prompted by the nitrosonium ion (NO^+), arising from a catalytic

amount of nitrous acid, forms an intermediate nitroso compound, which is oxidized by nitric acid to the nitro derivative with the regeneration of nitrous acid.



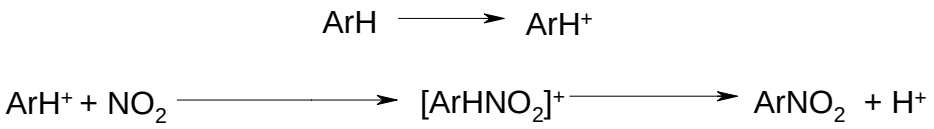
The nitrosonium ion (NO^+) is an interesting chemical species. As a Lewis acid, it is unique. Other acids either have a very high electron affinity (H^+) or a very low electron affinity (alkali ions), relative to the standard bases. Hence, location of the charge in acid-base salts or complexes is not in doubt. For the nitrosonium ion, however, its electron affinity (9.2 eV) is of comparable magnitude as for typical bases.



To give an example, which will be further elaborated upon in the section on nitration of phenols, the reaction leads to the formation of an aromatic radical cation, with an equilibrium constant K=119 in the gas phase. This is due to the matching between the ionization potentials of benzene (9.24 eV) and the electron affinity of NO^+ (9.26). This mid-range electron affinity makes nitrosonium ions highly reactive species because of their charge and, at the same time, renders them relatively mild and finely tunable oxidants.

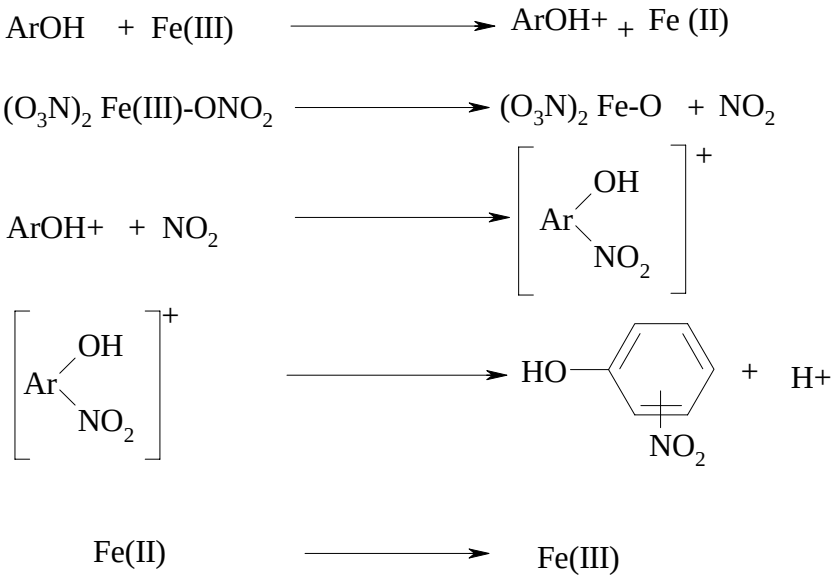
The classical Hughes-Ingold mechanism for aromatic substitution is a two-step sequence. The Wheland intermediate formed in the first step deprotonates to the final product in the second step.[16] Kenner[24] proposed transfer of a single π electron from the aromatic substrate to the electrophile, as the initial step. Nagakira[25] showed operation of strong driving force for such single electron transfer (SET) whenever the electron affinity of electrophiles exceeds the ionization potential of the aromatic substrate. The interventions of charge-transfer complexes as intermediates have been postulated by Brown.[26] But it was Perrin[27] who threw light into actual SET mechanism. The initial SET

between aromatic donor and the nitronium or nitrosonium ion acceptors leads to an ion radical pair, [$ArH^{+\cdot}$, $NO_2^{\cdot}$] or [$ArH^{+\cdot}$, $NO^{\cdot}$], which collapses in a fast step to Wheland intermediate. Accordingly, nitration occurs preferentially at the sites of the $ArH^{+\cdot}$, radical cation, with the greatest potential for new bond formation. Since collapse of a radical pair is involved, positions with the greatest unpaired spin density will be attacked preferably. This unpaired spin density is greater in *para* than in *ortho* position. This can be summarized as shown in **scheme 2**.



Scheme 2

Another plausible mechanism suggested for nitration by ferric nitrate is as shown in **scheme 3**.[28]



Scheme 3

History of Ionic liquids (ILs)

The earliest material that can be classified as ionic liquid was a red oil, which was obtained in Freidel-Crafts reactions reported in mid-19th century. The first report of a

room temperature molten salt was made by Walden[29] in 1914, who noted the physical properties of ethylammonium nitrate (Mp 12-14 °C) formed by reaction of ethylamine with concentrated nitric acid. This early study on liquid salt did not lead to an explosion of interest in ionic liquids and it was not before the late 1940's that the next ionic liquid was discovered by Hurley *et al.*[30] While looking for an inexpensive method for aluminium electroplating they noted that mixing powdered alkylpyridinium chlorides with $AlCl_3$ resulted in formation of liquid. These liquids incorporate organic cations and chloroaluminate anions which form the basis of modern synthetic ionic liquids. While such anions are still being used in synthesis and catalysis, they have become less popular than other more inert anions. This is mainly due to their sensitivity towards air and moisture and the fact that extraction of certain organic products may result in the destruction of these particular ionic liquids.

Robinson,[31] Wiikes,[32] Appleby[33] and Boon[34] working on electrochemical aspects of the chloroaluminates were largely responsible for bringing ionic liquids to the attention of a wider scientific community. They used chloroaluminates as solvents for transition metal complexes and as reaction media for organic synthesis. Carlin[35] used Ziegler-Natta catalyst in acidic chloroaluminates to polymerize ethylene whereas Wilkes[36] synthesized water-soluble ionic liquids that contain tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate anions.

Ionic liquids were then used for many applications such as for separation processes,[37,38] as lubricants,[39] matrices in MALDI mass spectrometry[40] and industrial chemical synthesis.[41]

The working definition of ionic liquid is that it is a salt with melting temperature below the boiling point of water. Most salts identified in the literature as ionic liquids, are liquids at room temperature, and hence termed also as room temperature ionic liquids. Most of the ionic liquids have organic cations and inorganic anions. In practice, ionic liquids can be handled like ordinary solvents. In recent years the term **'neoteric solvent'** has been used for ionic liquids and supercritical fluids.

Properties of ionic liquids

Some simple physical properties of the ionic liquids which make them interesting as potential solvents for organic transformations are:

1) Ionic liquids do not evaporate as they have no detectable vapour pressure. Since reducing the emissions of volatile organic compounds is viewed as one of the most important ways of reducing pollution from the chemical industry, it is perhaps this property of ionic liquids that makes them so attractive as potentially benign replacement to organic solvents.

2) Many metal catalysts (notably salts), organic compounds (especially polar compounds), gases and biocatalysts dissolve in ionic liquids, allowing homogeneously catalyzed reactions to be performed.

3) Ionic liquids are immiscible with many organic solvents and compounds, which lends themselves to biphasic or multiphasic catalytic reactions. Most are also immiscible with fluorous phases and some are immiscible with water.

4) Ionic liquids have polarities comparable to alcohols, which are amongst the most widely used solvents. In contrast to alcohols, however ionic liquids are non-nucleophilic and hence can be used for catalytic reactions.

5) Ionic liquids have favorable thermal stabilities and operate over large temperature ranges. Many of the commonly used ionic liquids melt below room temperature. On the other hand they often start decomposing above 350 °C, providing a large temperature range compared to molecular solvents.

6) It is not always necessary to modify a catalyst for use in ionic liquids since many catalysts are salts and in general these are very well retained in ionic liquids.

7) They are composed of poorly coordinating ions, so that they have the potential to be highly polar.

Above solvent properties thus gives the indication that they can be used as green solvents for various chemical transformations with variety of reagents. The link between ionic liquids and green chemistry is clearly related to the solvent properties due to huge liquidious range. Liquidious range is the span of temperatures between the freezing point and boiling point of a liquid.

Melting point

The most interesting and most debated property of the ionic liquid is the melting point. The melting point of the salt is related to its lattice energy. The relationship was first studied by Kapustinskii,[41] who coined the equation known as Kapustinskii equation.

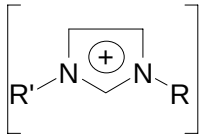
$$U = \frac{287.2vZ^{+}Z^{-}}{r_o} \left(1 - \frac{0.345}{r_o}\right)$$

Where U = lattice energy; v = no. of ions per molecule, r_o= sum of ionic radii, Z^{+},Z^{-} = Charge of the ionic species.

From above equation it is clear that as we increase both the size of the anions as well as cations, the melting point decreases. However the effect on the melting point is complicated since as covalency increases it affects on melting point. Following are some of the examples of ionic liquids with melting points.

In case of imidazolium chloride salts as the alkyl group size increases melting point decreases whereas as cation and anion size increases the sharp decrease in the melting point is observed (**Table 2**).

Table 2: Melting points of different ionic liquids

Imidazolium salt	Melting Point °C
 R = R' = methyl ([MMIM]Cl R = methyl, R' = ethyl ([EMIM]Cl) R = methyl, R' = n-butyl([BMIM]Cl)	125 87 65
[EMIM]NO_2	55
[EMIM]NO_3	38
[EMIM]$AlCl_4$	7
[EMIM]BF_4	6
[EMIM]CF_3SO_3	-9
[EMIM]CF_3CO_2	-14

Density

Density is an important property used in fluid flow calculations. It can be generalized that the density of ILs depends on the bulkiness of anions. It has been observed that changes in the structure of cation also can have slight changes in the density.

Viscosity

The viscosity of ILs is essentially governed by their tendency to form hydrogen bonding and by the strength of their van der Walls interactions. The structure of cations also influences viscosity of ILs. Increasing the chain length or fluorinating the alkyl chains will result in higher viscosity.

Polarity and solvent properties

Solvent polarity is the most commonly used criterion for solvent classification. The terms such as polar, non-polar and apolar are used indiscriminately to values of dielectric constants, dipole moments, and polarizabilities, even though none of these are directly correlated. The simplest qualitative definition is that a polar solvent is one that will dissolve and stabilize dipolar or charged solutes. Ionic liquids have abilities to form homogeneous mixture with various metal salts and have ability to dissolve many organic and inorganic molecules so they can be considered as polar solvents.

Table 3: Physical properties and solubilities of commonly used ionic liquids.

Ionic liquid	Al - Cl_3	MW	Density g/ml	Liquidious range °C		Solubility in common solvents				
				Lowest	Highest	H_2O	CH_3OH	$CHCl_3$	Hexane	Toluene
[bmim] BF_4		226.02	1.32	-48.96	399.20	s	s	s	i	i
[bmim] PF_6		284.18	1.51	13.2	388.34	i	s	s	i	i
[bmim] Cl/$AlCl_3$	0.5 0.55 0.60	154.01 151.94 149.87	1.421 1.456 1.481	-88.69 -94.44 -95.87	263.1 286.59 316.34	r r r	r r r	s s s	i i i	s s s
[emim] PF_6		256.13	1.426	2.71	304.65	i	i	s	i	i
N-Butyl pyridine/$AlCl_3$	0.50 0.55 0.60	152.59 150.59 148.67	1.412 1.430 1.497	18.8 33.73 18.11	240 245.39 260.24	r r r	r r r	i i i	i i i	s s s

s = soluble, i = insoluble, r = rarely or very less soluble

Toxicological and Environmental Concerns

The toxicological and environmental properties of ionic liquids are slowly emerging, but are becoming increasingly needed, as ionic liquids are beginning to be employed in larger quantities. While ionic liquids are classified as non-toxic and green solvents this is not necessarily the case and such generalization must be taken with extreme caution. It would appear that many ionic liquids are more toxic than commonly used organic solvents. A strategy for the risk-assessment of ionic liquids has been developed and the biodegradation of both imidazolium cations and a range of anions have been investigated. It was found that 1-butyl-3-methylimidazolium based ionic liquids with a range of different anions are essentially poorly degradable. The latest report[42] indicated that some ionic liquids are found to be toxic to fish. The release of HF by hydrolysis of PF_6 and BF_4 containing ionic liquids is one of other issues of toxicological concern.[43,44,45] The latest toxicological study by Cho *et al.*[46]evaluated 1-butyl-3-

methylimidazolium [BMIM], incorporated with tetrafluoroborate, hexafluorophosphate and hexafluoroantimonate, in which SbF_6^- and PF_6^- anions were found to be more toxic.

Classification of ionic liquids

Ionic liquids (ILs) are classified into two categories.

1) Binary ionic liquids-salts, where equilibrium is involved.

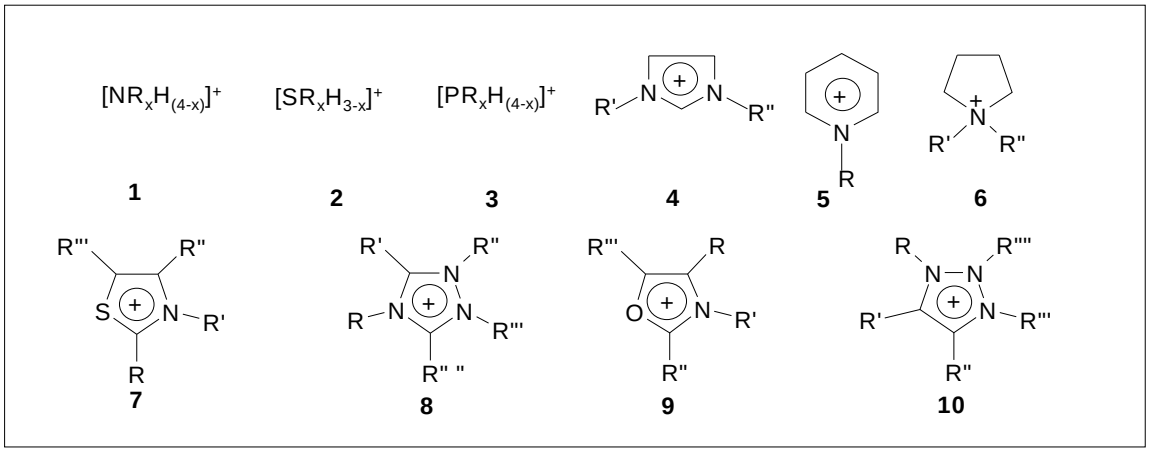
2) Simple salts-made of single anions and cations.

In the first category, the first generation ILs, contain a mixture of metal halide and dialkylimidazolium chloride. These contain several ionic species and their melting point and other properties depend on mole fractions of the individual components.

The second class, generally termed as second generation ILs, consists of simple cation and anion. e. g. ethyl ammonium nitrate ($[EtNH_3]^+[NO_3]^-$), dialkylimidazolium ILs [bmim]Br etc. The third generation ILs consists of chiral ILs made from either chiral cations or anions.

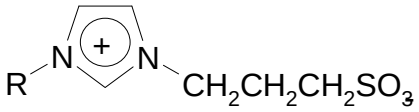
Recent development in cations and anions

The cations are generally organic components with low symmetry and bulk in size. Those described until now are based on ammonium **1**, sulfonium **2**, phosphonium **3,** imidazolium **4**, pyridinium **5**, pyrrolidinium **6**, thiazolium **7**, triazolium **8**, oxazolium **9** and pyrazolium **10** cations.

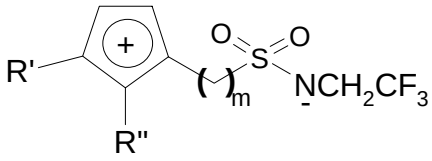


Cations described in different ionic liquids

Concerning the anions, they can be classified in two categories, those which give polynuclear anions, e.g. Al_2Cl_7, Al_3Cl_{10}, Fe_2Cl_7, Sb_2F_{11} and mononuclear anions which gives neutral stoichiometric ionic liquids like Cl, Br, ClO_4, CF_3SO_3, CH_3SO_3, CF_3CO_2, etc. The series of zwitterionic type ionic liquids consisting of imidazolium cations containing covalently bound counter anionic sites, such as sulfonate or a sulfonamide group have been prepared.



R = Et, CH_2=CH-

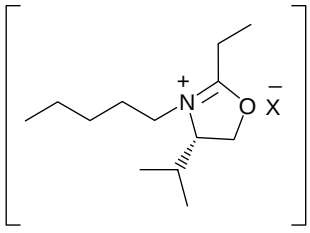


R' = Et, R'' = H, m = 3

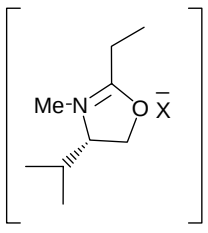
R' = Me, R'' = Me, m = 2

Zwitterionic salts

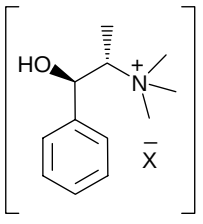
Chiral ionic liquids are quite attractive for their potential application to chiral discrimination including asymmetric synthesis and optical resolution of racemates. New chiral ionic liquids, directly derived from the 'chiral pool', have been synthesized and are interesting solvents for enantioselective reactions and useful in chiral separation techniques.[47]



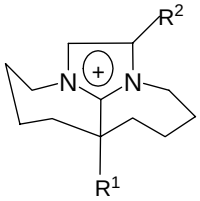
X = PF_6^-



X = PF_6^-



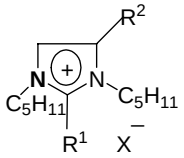
X = $[(CF_3SO_2)_2N]^-$



R^1= R^2 = H

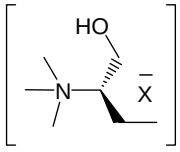
R^1=Me, R^2=H

R^1=Me, R^2=Me



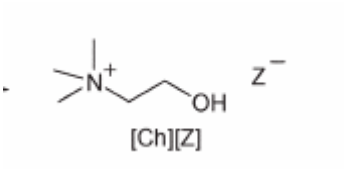
R^1= R^2 = H

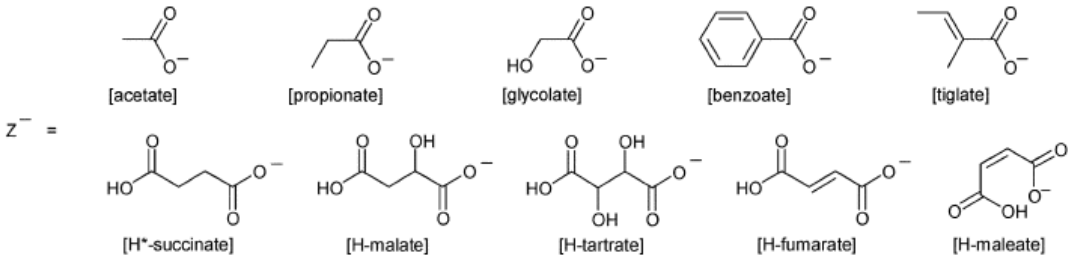
R^1=Me, R^2=Me



X = $[(CF_3SO_2)_2N]^-$

Recently Ohno *et al.*[48] introduced ionic liquids composed of solely biomass, in particular a choline cation combined with propionate, tiglate, hydrogen maleate, succinate, etc as alternative green solvents. Choline is an organic compound and usually grouped with a vitamin B complex. Choline is a quaternary saturated amine where the counterion may be chloride, hydroxide or tartarate. The eutectic mixture of chloline chloride with urea is known ionic liquid (DES) having melting point less than 12 °C.





Applications of ionic liquids

Large volume of literature is available which shows the importance of ILs which is covered in a number of excellent books,[49] recent general reviews[50] as well as those covering specific topics such as catalysis,[51] synthesis of organometallic complexes[52] in ionic liquids, biphasic systems and supported ionic liquids,[53] analytical applications of ionic liquids,[54] electrochemistry[55] in ionic liquids. In addition, a number of special issues have appeared covering a range of topics including ionic liquids as green solvents, physical and thermodynamic data and organometallic chemistry in ionic liquid.

Industrial applications of ionic liquids

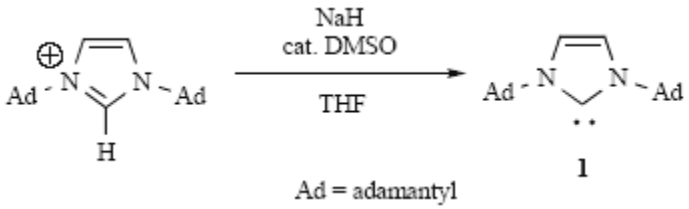
BASF recently[56] patented a procedure for conversion of nitriles to amines in presence of ionic liquids like ethylimidazolium chloride using Ru/Carbon as catalyst. Similarly Clariant Corporation patented [57] the applications of various ionic liquids for

final finishing treatment of pigments. Recently, a review[58] appeared explaining various industrial applications of ionic liquids such as process for the production of generic photoinitiator precursor, alkoxy phenylphosphines, preparation of haloalkane from alcohol in presence of ionic liquids and isomerization of 3,4-epoxybut-1-en to 2,5-dihydrofuran using Lewis basic ionic liquid [$P_{888\ 18}$] manufactured by **Cytec**.

Reactivity of imidazolium ionic liquids

The most extensively studied class of ILs is based upon the imidazolium ion and the most common examples are the ethylmethylimidazolium ion with anions such as $[BF_4]^-$ and $[AlCl_4]^-$. Notwithstanding the sensitivity of the anions, ILs of this class have garnered attention since they facilitate many important chemical reactions. However, imidazolium-based solvent systems are unsuitable for reactions involving either active metals (e. g. Na or K) or in reactions those involve strong bases (e. g. Grignard, organolithium, and amide) since these reagents react with the imidazolium-based solvents. For instance, imidazolium ions react with potassium metal to produce imidazol-2-ylidenes (N-heterocyclic carbenes, NHCs), or reaction with lithium di-iso-propylamide or potassium t*ert*-butoxide, to generate NHCs. Aggarwal *et al*.[59] have shown that imidazolium-based ionic liquid in Baylis-Hillman reaction resulted in the addition of deprotonated imidazolium cation to an aldehyde in presence of weak bases.

Reactivity of imidazolium cations mainly stems from the relatively high acidity (pKa = 22-24) of the C-2 hydrogen of imidazolium ion. It is well known by the work of Arduengo *et al*.[60] that deprotonation at C-2 position of the imidazolium salts generate N-heterocyclic carbene ligands. The imidazolium salt with two larger groups on two nitrogens gives more isolable N-heterocyclic carbene ligand.



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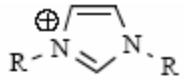
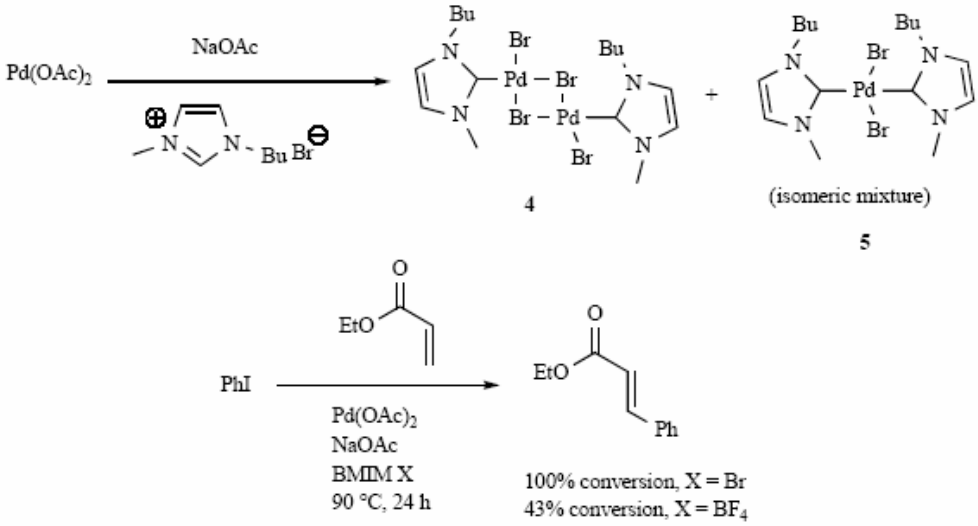
Ad = adamantyl

pKa values of imidazolium salts due to C-2 acidity



Entry	R	Solvent	pKa Value
1[9]	*t*Bu	DMSO	22.7
2[11]	Me	H_2O	23.0
3[11]	Me	DMSO	21.1
4[12]	*t*Bu	DMSO	22.6
5[12]	Ph	DMSO	16.1
6[10]	*i*Pr (4,5-dimethyl)	DMSO	24.0

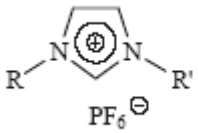
Handy *et al.*[61] studied the deuterium exchange on substituted imidazolium and investigated that under more basic conditions the exchange is possible. They found that the bmim BF_4 does not give any deuterium exchange. The N-heterocyclic carbene ligand formed, gets complexed with a metal ion which is found to be useful for various catalytic reactions like Heck reaction, Suzuki coupling etc. Xiao *et al.*[62] noted that palladium-NHC complexes were formed by stirring palladium acetate in bmim bromide in the presence of sodium acetate which act as a catalyst for various transformations like Heck reaction.



Phosphorus containing ionic liquids

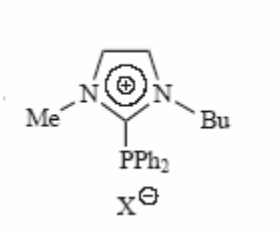
Phosphorus containing ionic liquids can be classified in to two groups; a) ionic liquids where phosphorus is an **anion** (dialkylimidazolium hexafluorophosphate) and b) where phosphorus acts as a **cation** (quaternary phosphonium salts).

The first group of ionic liquids (phosphorus containing imidazolium based ionic liquids) was introduced[63a] and thoroughly studied and lot of literature is available regarding properties, synthesis and applications. A review article by Keglevich[63b] explains various green chemistry aspects of both phosphorus based ionic liquids along with their applications. Various applications of 1-alkyl-3-methylimidazolium hexafluorophosphates as alternative reaction media are found in the literature.[64,65] Dzyuba *et al.*[66] reported the synthesis and properties of 1,3-dialkylimidazolium hexafluorophosphates. All these 1,3-dialkylimidazolium hexafluorophosphates with dibutyl, dioctyl, dinonyl, and didecyl substitutents have melting points less than 100°C.



R = C_1–C_{10} alkyl
R' = C_1–C_{10} alkyl

Imidazolium phosphine type ionic liquids were introduced for reactions involving metal complexes as catalyst.[67-71]



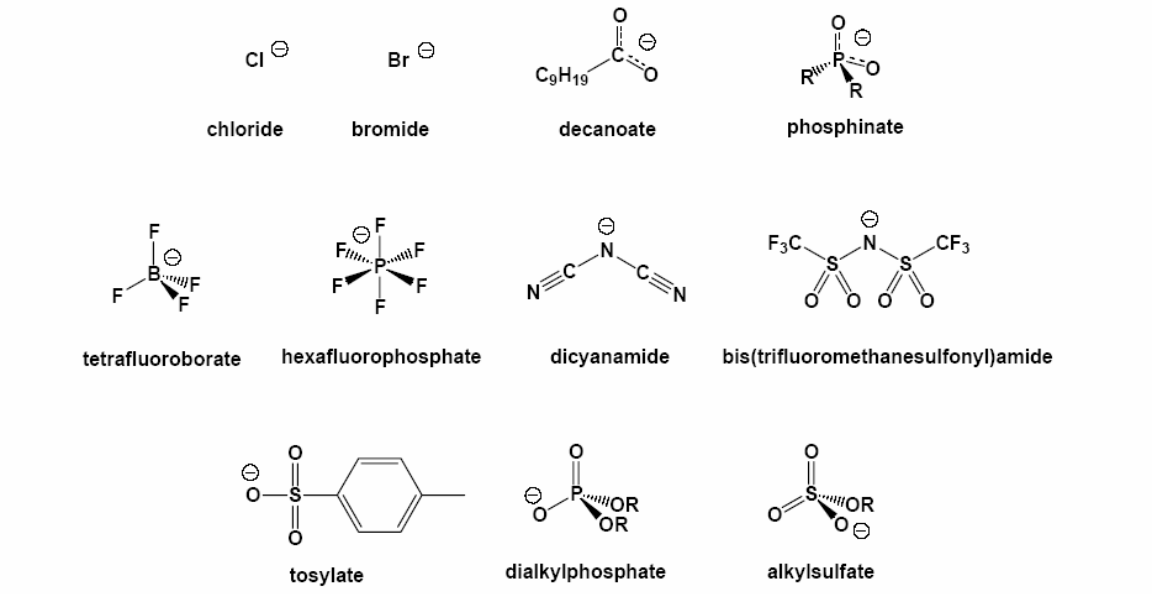
X = Cl^-, PF_6^-

Gathergood *et al.*[72] synthesized diimidazolium hexafluorophosphate salts with biodegradable substitutents.

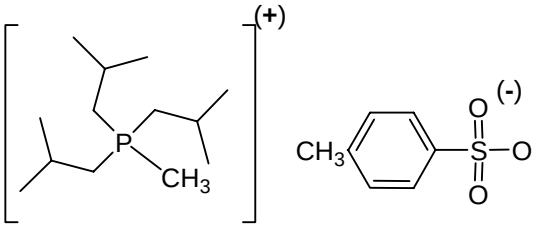
Phosphonium-based ionic liquids (PILs)

Very recently, a new class of ionic liquids has been introduced in organic reactions. They are phosphonium based ionic liquids, which differ from the well known imidazolium ILs.

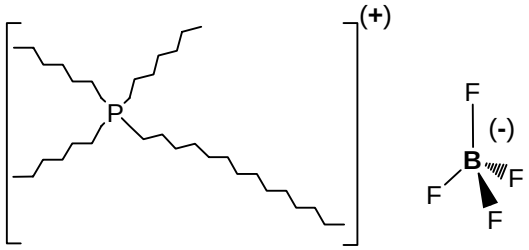
The other group of phosphorus containing ionic liquid is where phosphorus acts as a cation (quaternary phosphonium salts). These are popularly known as phosphonium ionic liquids (PILs). Following are some anions that can be paired with phosphorus cation, and structures of some phosphonium ionic liquids are depicted below.



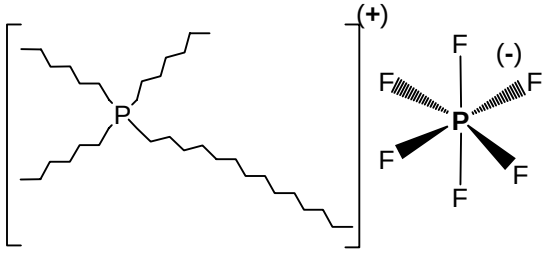
Structures of various phosphonium ionic liquids



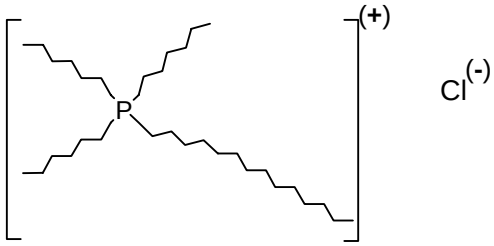
Triisobutyl (methyl) phosphonium tosylate



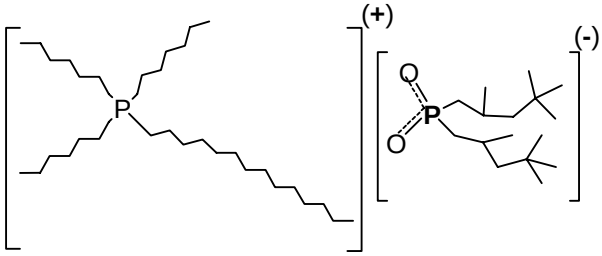
Trihexyl (tetradecyl) phosphonium tetrafluoroborate



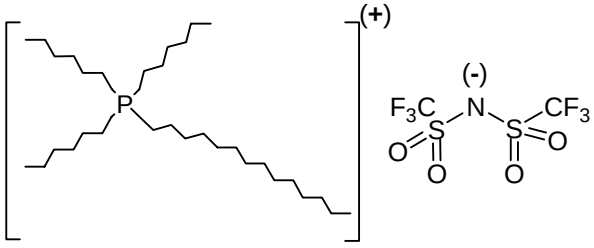
Trihexyl (tetradecyl) phosphoniumhexafluoro phosphate



Trihexyl (tetradecyl) phosphonium chloride



Trihexyl (tetradecyl) phosphonium bis (2,4,4 -trimethylpentyl) phosphinate



Trihexyl (tetradecyl) phosphonium bis(trifluoromethane)sulphonylamide

Advantages of phosphonium ionic liquids

Phosphonium salts are much more thermally stable than the corresponding ammonium salts and even have an edge on imidazolium salts. This is beneficial for various chemical transformations carried out at greater than 100 °C. Imidazolium-based ILs are known to be unsuitable for reactions involving active metals such as sodium, potassium and strong bases such as organolithium and organomagnesium to produce imidazol-2-ylidenes (N-heterocyclic carbenes, NHCs). N-heterocyclic carbene ligands are generated in imidazolium ionic liquids due to high acidity (pKa = 22-24) of the C-2 hydrogen. Phosphonium salts, on the other hand have no such acidic protons and hence found applications in various nucleophilic reactions. Alkylphosphonium ionic liquids are less dense than water, the property which can be beneficial in product work-up involving separation methods. Some unsymmetrical alkyl substituted phosphonium ionic liquids are depicted in table 4.

Table 4: Alkyl substituted phosphonium ionic liquids

S. No	Phosphonium ionic liquid
1	Tetradecyl(trihexyl) phosphonium chloride
2	Tetradecyl(trihexyl) phosphonium bromide
3	Tetradecyl(trihexyl) phosphonium decanoate
4	Tetradecyl(trihexyl) phosphonium dicyanamide
5	Tetradecyl(trihexyl) phosphonium bistriflamide
6	Tetradecyl(trihexyl) phosphonium hexafluorophosphate
7	Tetradecyl(trihexyl) phosphonium tetrafluoroborate
8	Tetradecyl(trihexyl) phosphonium dodecylsulfonate

Applications of phosphonium ionic liquids

Phosphonium ionic liquids have been used as reaction medium for various chemical transformations. Trihexyl(tetradecyl)phosphonium chloride, has been used[73] for

the enhancement of the enantioselectivity and the stability of Ru-BINAP during hydrogenation of dimethyl itaconate to (S)-dimethyl methylsuccinate. The catalyst and ionic liquid were efficiently separated by nanofiltration from the product, followed by simultaneous recycling of the catalyst and ionic liquid. Palladium catalyzed Suzuki cross-coupling of aryl boronic acids with aryl halides under mild conditions was demonstrated in same ionic liquid with 76-100% yields.[74] It was also demonstrated by Wong *et al*.[75] for 4-bromo acetophenone in three different PILs. Catalyst and ionic liquid were efficiently separated by nanofiltration from the product for further recylization.

Buchwald–Hartwig amination[76]of aryl halides using palladium as catalyst was studied in phosphonium ionic liquids containing trihexyl(tetradecyl)phosphonium cation with a range of anions. Trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide was found to be better among used ionic liquids.

The Heck cross-coupling[77] of aryl iodides and bromides with methyl acrylate was reported in trihexyl(tetradecyl)phosphonium chloride and trihexyl(tetradecyl) phosphonium decanoate in 78% and 75% yields respectively. Trihexyl(tetradecyl)phosphonium chloride was easier to separate during the purification stage. Addition of hexane and brine to the reaction mixture gave three distinct phases with the palladium remaining in the middle ionic liquid layer, the coupled product in the organic layer and salts in the aqueous layer. Tetrabutylphosphonium bromide was used for thiolyzation of epoxides with aryl disulfides catalyzed by cerium(III) chloride heptahydrate.[78]

Comyns *et al.*[79] demonstrated hydrogen transfer to acetophenone using ethyltrioctylphosphonium tosylate and Ru as catalyst. The product was separated by simply decantation as PIL is solid at ambient temperature. Similarly selective hydrogenation of 1,3-butadiene to 1-butene[80] and the hydroformylation of 1-hexene to C-7- aldehyde[81] are described in phosphonium ionic liquids.

The conversion of methanol to acetic acid was reported in presence of phosphonium ionic liquids with tetrafluoroborate as anion and Ru and Co as catalyst.[82] Highly regioselective O-alkylation of β-naphthol with benzyl bromide was demonstrated in tetraalkylphosphonium halides.[83]

Design of novel phosphonium ionic liquids that are compatible with Grignard reagents have been investigated.[84] It has been established that even basic aliphatic Grignard reagent-mediated reactions are possible when methoxyethyl(tri-n-butyl)phosphonium bis(trifluoromethanesulfonyl)imide is used as the solvent.

Ramnial *et al*.[85] reported in 2005 that Grignard reagents are persistent in tetradecyl(trihexyl)phosphonium chloride and may be more suitable for reactions involving strong bases. They further suggested[86] that Grignard reagents in phosphonium ionic liquids possessing *O*-donor anions are excellent reaction media for electron transfer processes and transmetallation reactions.

Itoh *et al*.[84] in 2007 further demonstrated that Grignard reagent-mediated reactions are possible when methoxyethyl (tri-*n*-butyl) phosphonium bis (trifluoromethanesulfonyl) imide is used as the solvent. Reactions of saturated chlorides with hydrogen fluoride in PIL were also reported.[87] This method may be suitable for the preparation of industrially useful fluorine derivatives such as freons.

Phosphonium tosylates were used in Diels-Alder reactions of isoprene with methyl acrylate, but-2-en-2-one and acrylonitrile; demonstrating a high regioselectivity (>99%) of 1,4-isomer with oxygen-containing dienophiles even without Lewis acids as catalysts.[88]

Forbes *et al*. demonstrated esterification of acetic acid using ethanol and phosphonium ionic liquid bearing sulfopropyl moiety which act as an acid catalyst for esterification reaction.[89]

Friedel-Crafts acylation of substituted benzene with benzoyl chloride was also reported by Earle *et al*,[90-93] in presence of $(C_6H_{13})_3P^+C_{14}H_{29}\ X^-$.

Ionic liquids $[C_4bmim]BF_4$ and $[C_4bmim]PF_6$ have been used for biocatalytic resolution of phenethyl alcohol using *Candida antarctica* lipase[94] and enzymatic catalysis of formation of *Z*-aspartame[95]. Chanda *et al*.[96] demonstrated kinetic resolution of racemic 1-phenylethanol by transesterification with vinyl acetate in phosphonium ionic liquids.

Phosphonium ionic liquids are also found to be suitable solvents for electrophilic reactions such as nitration and sulfonation. The nitration of benzene derivatives by nitric acid[97, 98] and the sulfonation of substituted benzenes by sulphur trioxide[99] were found to be reported in literature.

Thus, above literature indicates utility of phosphonium-based ionic liquids for various catalytic reactions along with nucleophilic and electrophilic reactions.

Ionic liquids in nitration reactions: A recent study

Ionic liquids are known to be non-volatile and withstand under highly acidic conditions. These solvents are generally termed as green solvents. There are very few reports of use of ionic liquids as solvents for nitration.

Lalli *et al*.[100] demonstrated nitration of aromatics using ammonium nitrate/TFAA and isoamyl nitrate/TfOH in various ionic liquids. They found that [emim]OTf and [emim][CF_3COO]$^-$ were promising ionic liquids for nitration. The good yields were observed for both activating and deactivating substrates.

Srinivasan *et al*.[101] demonstrated regio-selective nitration of phenols in 1,3-di-n-butylimidazolium tetrafluoroborate [bbim]BF_4 as the solvent. They used ferric nitrate as a nitrating agent for nitration of phenols. They found complete conversion in all the reactions with mono nitration of phenols. Ionic liquid was recovered and recycled successfully. Phenols and activated phenols can be completely nitrated at 30 °C in 1-1.5 hours whereas deactivated phenols required elevated temperature. For phenol almost 90% selectivity was observed for *p*-nitro phenol. Srinivasan *et al*.[102] further demonstrated ultrasound promoted *p*-selective nitration of phenols using ferric nitrate in ethyl ammonium nitrate. In all cases almost 100% conversion was observed with selectivity towards *p*-isomer. Lancaster *et al*.[103] studied the nitration of various aromatic compounds using [bmim]BF_4, [bm_2im][$N(Tf)_2$] and [bmpy][NTf_2] at 25°C. The nitrating agent used was nitric acid in presence of acetic anhydride, thus giving acyl nitrate *in situ*. They compared nitration of various aromatics in dichloromethane with nitration done in ionic liquids. They observed that in activated system there was little difference between the ionic liquid and the molecular solvent.

Earle *et al*.[104] demonstrated nitration of various aromatic compounds using 67% nitric acid in IILs, 1-decyl-3-methylimidazolium trifluoromethane sulfonate and 1-butyl-3-methyl imidazolium trifluoromethane sulfonate. They found almost quantitative

conversion for various substrates. Dinitration was also studied and found to be feasible at higher temperature.

In all above examples of aromatic nitration, imidazolium ionic liquids are used as solvent (**Table 5**). Nitration of aromatic compounds like benzene, alkylbenzene, naphthalene, anisole, nitrobenzene with nitric acid in phosphonium ionic liquids (CYTEC) have been reported in high yield and selectivity by Ramani *et al*. only.[93] These phosphonium ionic liquids were recycled many times without loss of activity or selectivity. The PILs used were unsymmetrical alkyl substituted phosphonium cations paired with anions like, chloride, bromide, triflate, sulfate, tosylate, tetrafluoroborate, etc. However, they did not perform nitration of phenols.

Table 5: Nitration of aromatic compounds in ionic liquids

Ionic liquid	Nitrating agent	Substrates	Yield
[emim][OTf] [emim][CF_3COO]	Isoamyl nitrate, NH_4NO_3	Aromatic compounds with Me,OMe, Halo substituents	24-95%
[bbim] BF_4 [bbim] Br	Ferric nitrate Ferric nitrate	Phenols	100% 60%
[bbim] BF_4 [bbim][$N(Tf)_2$] [bmpy][$N(Tf)_2$]	HNO_3-Ac_2O NH_4NO_3-TFAA Ferric nitrate- TFAA	Toluene	35% 4% 25%
Trihexyl(tetradecyl) phosphonium bistriflate	Nitric acid	Benzene, Toluene, Xylene isomers, Napthalene	80% to 100%
Trihexyl(tetradecyl) phosphonium bistriflamide	Nitric acid	Benzene	100%

Present work

The utility of phosphonium ionic liquids for nitration of aromatic compounds and the absence of reports about their exploration for nitration of phenols prompted us to undertake the present work. In traditional nitration methods several nitrating agents are employed, such as mixed acid, super acids, acyl nitrates and metal nitrates like ceric ammonium nitrate, copper nitrate, ferric nitrate, etc. under different conditions. Among

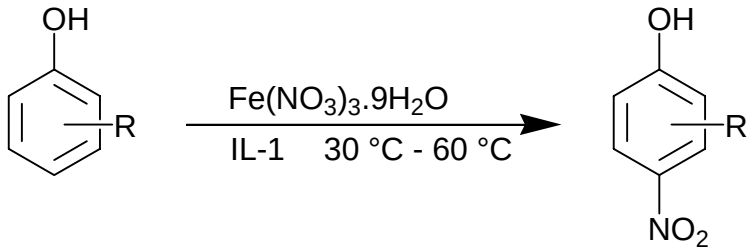
metal nitrates, ferric nitrate either alone or supported on solid clays has been extensively studied. Srinivasan *et al*.[101] also studied nitration of phenols in imidazolium ionic liquids using ferric nitrate. Hence, ferric nitrate was selected as nitrating agent in present study and the same is elaborated below.

In a typical experiment 0.6 equivalent of ferric nitrate was added in one lot to a mixture of 1.0 equivalent of phenol and ionic liquid at 30 °C and reaction was periodically monitored by TLC. The crude mixture was separated by column chromatography. The products were identified by ^{1}H NMR, GCMS, TLC and melting point.

Results and discussion

Nitration of phenols was studied in two different ionic liquids 1) trihexyl (tetradecyl) phosphonium tetrafluroborate, (IL-1) 2) trihexyl (tetradecyl) phosphonium chloride (IL-2). These ionic liquids were obtained from **Cytec**, Canada.

Nitration using trihexyl (tetradecyl) phosphonium tetrafluroborate (IL-1)



Nitration of phenol using traditional nitration methods gives both the isomers depending on conditions, along with some dinitration and oxidation products. In present study also nitration of phenol in IL-1 yielded both the isomers; *p*-nitrophenol was 75% whereas ortho isomer was 18%. Conversion was quantitative. In *para* substituated phenols, such as, *p*-chlorophenol, *p*-methoxyphenol, *p*-nitrophenol, *p*-acetylphenol, *p*-carbomethoxyphenol, *p*-cresol, as expected only *ortho* isomer was obtained in 79% to 91% yield (**Table 6**). These yields were comparable (82 – 92%) with those of reported[87] for various *para* substituated phenols in imidazolium ionic liquid [bbim][BF_4] (1,3-di-*n*-

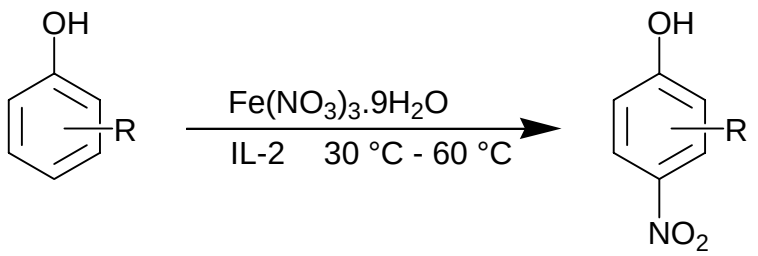
butylimidazolium tetraflouroborate). In *ortho* substituted phenols, such as, *o*-chlorophenol, *o*-acetylphenol, *o*-carbomethoxyphenol, *o*-nitrophenol and *o*-methoxyphenol, the yields were again quantitative. Nitration of *o*-acetylphenol, *o*-carbomethoxyphenol and *o*-nitrophenol yielded only *para* isomers, however *o*-chlorophenol and *o*-methoxyphenol yielded mixture of both *ortho* and *para* isomers where the *para* isomers were in the range of 72-76% and *ortho* isomers were in the range of 14-15%. Regioselectivity of these nitrates was again similar to that obtained in imidazolium ionic liquid[101] with comparable yields. In case of *m*-cresol, nitration gave mixture of both isomers in quatitative yield. Again the regioselectivity was found to be comparable i. e. *o*-isomer 11% and *p*-isomer 73%, with that of reported literature.[101] Though, yields and regioselectivity of nitration of various phenols were comparable for both ionic liquids, reaction period for completion of reactions was little more in this phosphonium ionic liquid than that of imidazolium ionic liquid used by Srinivasan.[101]

Nitration reactions of substituted nitro phenols and acetophenone went to completion at 60 °C whereas all other nitrations went smoothly at 30 °C.

Table 6: **Nitration of phenols using trihexyl (tetradecyl) phosphonium tetrafluroborate (IL-1)**

S. No.	Substrate Phenol	Time	Conversion	Product Distribution (%)		
				Ortho	*Para*	others
1	H	3.0 h	quantitative	18 %	75 %	7%
2	*p*-Cl	3.0 h	quantitative	91%	n/a	9%
3	*o*-Cl	2.5 h	quantitative	15%	76%	9%
4	*p*-CH_3	3.0 h	quantitative	86%	n/a	14%
5	*m*-CH_3	3.0 h	quantitative	11%	73%	16%
6	*p*-$COCH_3$	2.5 h	>90%	83%	-----	17%
7	*o*-$COCH_3$	3.0 h	>90%	-----	82%	18%
8	*o*- NO_2	6.0 h	>90%	-----	83%	17%
9	*p*-NO_2	6.0 h	>90%	82%	-----	18%
10	*o*-COOMe	5.0 h	quantitative	-----	83%	17%
11	*p*-COOMe	5.0 h	quantitative	82%	-----	18%
12	*o*-OCH_3	4.0 h	quantitative	14%	72%.	14%
13	*p*-OCH_3	4.0 h	quantitative	79%	-----	19%

Nitration of phenols using trihexyl (tetradecyl) phosphonium chloride (IL-2)



Nitration was then studied using IL-2 for all above phenols. In this study nitration of phenol yielded both the isomers as expected, however ratio of ortho:para was different than that of IL-1. *Para* isomer was obtained more (58%) whereas *ortho* isomer was 42%. In *para* substituated phenols like *p*-chlorophenol, *p*-methoxyphenol, *p*-nitrophenol, *p*-acetylphenol, *p*-carbomethoxyphenol and *p*-cresol, *ortho* isomer was obtained in 82% to 97% yield (**Table 7**). In *ortho* substituted phenols i.e. *o*-chlorophenol, *o*-acetylphenol, *o*-carbomethoxyphenol, *o*-nitrophenol and *o*-methoxyphenol, the yields were again quantitative. Nitration of *o*-acetylphenol, *o*-carbomethoxyphenol and *o*-nitrophenol yielded only *para* isomers, however *o*-chlorophenol and *o*-methoxyphenol yielded mixture of both *ortho* and *para* isomers where the *para* isomers were in the range of 73-80% and *ortho* isomers in the range of 9-11%. In case of *m*-cresol, nitration gave mixture of both isomers in quantitative yield. The *o*-isomer was 14% and *p*-isomer was 71%. Though in this ionic liquid, regioselectivity of *ortho* and *para* isomers were same as that of obtained in IL-1 and also in [bbim][BF_4], the ratios of *ortho* **:** *para* were different. In IL-2 in all reactions yields of *para* isomer were marginally less, only in case of phenol, ortho selectivity was much more in comparison with IL-1. Further regioselectivity of nitration of phenols was comparable with [bbim][BF_4].[101] However reaction temperature for individual phenols for nitration was same as it was in IL-1. Conversion in all the reactions was quantitative. The nitration of phenols in IL-2 required less hours than it required for reactions in IL-1. However, it was more than that of [bbim][BF_4].[101]

During nitration of *o*-carbomethoxyphenol and *p*-carbomethoxyphenol the carbomethoxy group partially hydrolyzed to yield corresponding carboxylic acids in 5-6% yield. This may be due to the presence of HCl in IL-2.

Table 7: Nitration of phenols using trihexyl (tetradecyl) phosphonium chloride (IL-2)

S. No.	Substrate	Time	Conversion	Yields (%)		
				Ortho	*Para*	Others
1	Phenol	1.5 h	quantitative	42%	58%	Nil
2	*p*- Cl	2.5 h	quantitative	92%	Nil	8%
3	*o*-Cl	2.5 h	quantitative	11.01%	80%	9%
4	*p*-CH_3	2.5 h	quantitative	97%	Nil	3%
5	*m*- CH_3	2.5 h	quantitative	14.3%	71%	14.7%
6	*p*-$COCH_3$	3.0 h	quantitative	87%	------	13%
7	*p*-NO_2	4.0 h	quantitative	87%	-------	13%
8	*o*- NO_2	4.0 h	quantitative	---------	78%	22%
9	*o*-$COCH_3$	6.0 h	quantitative	---------	75%	25%
10	*o*-COOMe	4.0 h	quantitative	-------	78%	22%
11	*p*-COOMe	3.5 h	quantitative	82%	------	18%
12	*o*-OCH_3	5.0 h	quantitative	9%	73%	18%
13	*p*-OCH_3	5.0 h	quantitative	82%	--------	18%

The reaction mixtures were homogeneous during nitration in both i.e. trihexyl (tetradecyl) phosphonium chloride and trihexyl (tetradecyl) phosphonium tetrafluroborate ionic liquids. The conversion was found to be complete at 30 °C for all substituted phenols except nitro and acetyl substituted phenols where conversion was carried out at 60 °C. Addtion of ferric nitrate in ionic liquids was mild exothermic process, which may be due to heat of dissolution of ferric nitrate. Hence addition of ferric nitrate was done maintaining temperature at 30 °C. Trihexyl (tetradecyl) phosphonium chloride was recovered and recycled for nitration of phenol to check the recyclibilty of this ionic liquid. Trihexyl (tetradecyl) phosphonium chloride is highly acidic which may be due to presence of HCl.

Conclusion

Applying both the ionic liquids nitration of phenols is possible and found to be regio-selective. The time of reaction was also observed to be in the range of 3-6 hrs. Trihexyl (tetradecyl) phosphonium tetrafluroborate was found to be more suitable even though the nitration rate was low. The higher rate of nitration in case of trihexyl (tetradecyl) phosphonium chloride may be due to high acidity.

Mononitration of phenols with ferric nitrate has been achieved for the first time in high regio-selectivities and in excellent yields with phosphonium ionic liquids as solvent. In particular, excellent *para* selectivities were observed for the unsubstituted, *ortho* and *meta* substituted phenols. The quantitative conversion was observed during all reactions making this methodology attractive for synthetic and commercial utility.

Experimental

Typical procedure for nitration of phenols using trihexyl (tetradecyl) phosphonium tetrafluroborate

To a solution of phenol (1.92 g, 20 mmol) in trihexyl (tetradecyl) phosphonium tetrafluroborate (5.0 g), $Fe(NO_3)_3{\cdot}9H_2O$ (4.85 g, 12 mmol) was added in single lot and was stirred vigorously at 30 °C under nitrogen atmosphere. Reaction was monitored by TLC. After completion of reaction (absence of starting phenol), reaction mixture was extracted with n-hexane (3 X 20 ml). Organic layer was washed with brine (10 ml), dried over anhydr. sodium sulphate and concentrated under vacuum. Crude reaction mixture was chromatographed over silica gel to isolate *o*-nitrophenol (0.5 g, 18%) and *p*-nitrophenol (2.08 g, 74.8%).

Typical procedure for nitration of phenols using trihexyl (tetradecyl) phosphonium chloride.

To a solution of phenol (1.92 g, 20 mmol) in trihexyl (tetradecyl) phosphonium chloride (5.0 g), $Fe(NO_3)_3{\cdot}9H_2O$ (4.85 g, 12 mmol) was added in single lot and was stirred vigorously at 30 °C under nitrogen atmosphere. Reaction was monitored by TLC. After completion of reaction (absence of starting phenol), reaction mixture was extracted with n-hexane (3 X 20 ml). Organic layer was washed with brine (10 ml), dried over anhydr. sodium sulphate and concentrated under vacuum. Crude reaction mixture was chromatographed over silica gel to isolate *o*-nitrophenol (1.17 g, 42%) and *p*-nitrophenol (1.61 g, 58%).

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List of publications:

1. Copper Hydrotalcite Catalyzed Synthesis of Aziridines under Microwave Irradiation.
   Bhanu. M. Chanda and **Yashawant V. Dharap**
   (**Manuscript under preparation for** *Green Chemistry*)
2. Synthesis of 3-Substituted 2(1*H*)- Quinolinones Catalyzed by Hydrotalcite like Anionic clays.
   Bhany. M.Chanda and **Yashawant V. Dharap**
   (**To be communicated to** *Green Chemistry***, 2008**)
3. Application of Modified Zeolite Beta in the Rearrangement of α-Pinene Oxide to Campholenic Aldehyde.
   Bhanu. M. Chanda. **Yashawant V. Dharap**, M. W. Kasture, A. N. Niphadkar and P. N. Joshi
   (**Communicated to** *J. Mol. Cat. (A)**, 2008***)
4. Regioselective Nitration of Phenols with New Phosphorous Based Ionic Liquids.
   Bhanu. M. Chanda, A. Ramani, Yashawant V. Dharap and A. J. Robertson
   (**Targetted for** *Green Chemistry*, **2008**)

PATENTS:

1. A Process for Campholenic Aldehyde with an Improved Zinc Beta Zeolite.
   Bhanu. M. Chanda. **Yashawant V. Dharap**, M. W. Kasture, A. N. Niphadkar and P.N. Joshi
   Indian Patent (To be filed)
   US Patent (To be filed)
2. A Process for the Preparation of an Improved zinc Beta zeolite.
   Indian Patent (To be filed)
   US Patent (To be filed)

PAPER PRESENTATION

1. Studies in Nitration in Ionic Liquids and Biocatalysis in Ionic Liquids.
   Bhanu. M. Chanda, **Yashawant V. Dharap**, Dilip D. Sawaikar and Rohidas S. Sulke.
   Oral presentation at ICOB-4 and ISCNP-24, January 2004, New Delhi, India.
2. Development of Environmentally Benign Green Processes and Synthesis
   Bhanu. M.Chanda, **Yashawant V. Dharap**, A. Ramani and Rohidas S.Sulke.
   Oral presentation at National Seminar on “Green Chemistry and Natural Products”, November 2007, New Delhi, India.