# APPLICATION OF CHIRAL LIGANDS IN TRANSITION METAL CATALYZED AZIRIDINATION, REDUCTION, OXIDATION AND CYCLOPROPANATION REACTIONS

A THESIS

SUBMITTED TO THE

**UNIVERSITY OF PUNE**

FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

IN CHEMISTRY

**RENU VYAS**

DIVISION OF ORGANIC CHEMISTRY (TECHNOLOGY)

NATIONAL CHEMICAL LABORATORY

PUNE – 411 008

JUNE 2001

# CERTIFICATE

Certified that the work incorporated in the thesis entitled **"APPLICATION OF CHIRAL LIGANDS IN TRANSITION METAL CATALYZED AZIRIDINATION, REDUCTION, OXIDATION AND CYCLOPROPANATION REACTIONS"** by Mrs Renu Vyas was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

Date:

**Dr. (Mrs). Bhanu Chanda**
(Research Supervisor)

## DECLARATION

I hereby declare that the thesis entitled " **Application of Chiral Ligands in Transition Metal Catalyzed Aziridination, Reduction, Oxidation and Cyclopropanation reactions**" submitted for Ph.D. degree to the University of Poona has been carried out at National Chemical Laboratory, under the supervision of Dr. Bhanu Chanda . The works is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date: (Renu Vyas)

Division of Organic Chemistry (Technology)
Nationa Chemical Laboratory
Pune - 411 008.

**DEDICATED**

**TO**

**MY PARENTS**

**Acknowledgements**

It gives me a great pleasure to acknowledge my research supervisor **Dr. (Mrs.) Bhanu Chanda** for her constant encouragement and support throughout my research career. I am greatly indebted to her for empathizing with me during times of distress and despair. Her accommodative nature helped me to reach my research goals successfully.

My sincere thanks and reverence to **Dr. Ravindranathan**, former head, OCT Division for giving me a career. I also wish to thank Dr A.V. Bedekar for his immense help and valuable discussions during major part of my research work. I owe sincere gratitude to Dr. H. B. Borate for painstakingly correcting my thesis manuscript in minute detail.

I am grateful to all the scientists and students of OCT division from whom I have always taken some help. I am especially grateful to Mrs. Latha Sivadasan and Mrs. Kamalam Balakrishnan for creating a congenial atmosphere in the lab and for their help and affection. I thank my seniors Dr. Reni Joseph, Dr. B.S. Balaji, Dr. A Ramani, Dr. Anil Gajare for their useful suggestions during my research work. Thanks are due to my colleagues - Bulbule, Patil, Sandeep, Shivappa, Shiv Shankar, Vasudha, Anil Sharma and Bennur for unconditional help I thank my juniors Mary Sarita and Santosh Bhor for their assistance during the thesis writing stage.

I take this opportunity to thank some of the scientists at NCL for their good wishes and timely help- Dr. Paul Ratnasamy, Dr. Sivasanker, Dr. Vetrivel, Dr. Pinak Chakrborthy, Dr. Anil Kumar, Dr.A Sudalai, Dr. S. Krishnan, Shri Prabhakaran and Dr. K.N. Ganesh.

Words are not enough to express my gratitude to my parents for encouraging and inspiring me to have a successful academic career. The values I imbibed from them stood me in good stead under challenging circumstances. I thank my sisters Anju and Pinky for their affection and deep concern for my research career. I thank my uncle and auntie Drs. N.K. Vyas and Meenakshi N Vyas for their guidance on scientific research. I cannot forget my uncle, late Prof. B.D. Vyas (IIT, Bombay) whose life was a model of academic excellence through honesty and dedication. My heartfelt thanks are due to my husband Dr. M. Karthikeyan for all the personal and professional help during my research work. He was like a strong pillar to rely on in times of need. I am indeed grateful to my son Vineet for giving me a happy motherhood. I am obliged to my in-laws for their good wishes and blessings.

Thanks are due to the analytical staff of NMR, IR, Mass. I am thankful to Mrs. Behlekar for help in characterizing my samples. The help rendered by library staff cannot be forgotten

.

My sincere thanks to Dr. M.K. Gurjar, head, OCT Division for providing infrastructural facilities and allowing me to complete my work towards submission of thesis. I am thankful to Director, NCL for permitting me to work in NCL and submit the work in the form of a thesis. Finally, thanks are due to CSIR, New Delhi for financial assistance in the form of fellowship.

# CONTENTS

## EXPERIMENTAL SECTION

### General Remarks

The chemicals and reagents used in this study were of commercial grade and some of them were synthesized in the laboratory. Bromamine-T was made from commercially available Chloramine-T hydrate by following literature procedure. PhI=NTs was also synthesized in the laboratory by standard procedure Molecular sieves used were of $5^{o}$. Column chromatography was performed over ordinary silica gel (60-120 mesh) and flash silica gel (100-200 mesh). TLC analysis were carried out on glass plates using silica gel; GF-254 and the plates were developed by iodine stain. The solvents used during experiments were purified, unless otherwise stated, by standard literature procedure. Slow addition of the compounds was performed using syringe addition pump Orion make model 341 B SAGE PUMPS.

All compounds were characterized by IR, $^{1}H$ NMR, $^{13}$ C NMR and Mass Spectroscopy. Infrared spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR and values are reported in $cm^{-1}$. Nuclear Magnetic Resonance spectra obtained for $^{1}H$ and $^{13}C$ are recorded on BRUKER MSL-300 and BRUKER AC-200FT MHz spectrometers using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million down field from TMS. The coupling constants (J values) are reported in Hertz. Mass spectra were obtained at a voltage of 70 eV on Finnigan MAT-1020 B instrument. Sonication experiments were carried out using an ultrasonic bath (Sheishin model) operating at 36 KHz. Bulk temperature during sonication was kept at 25 $^{o}$C. Microwave irradiations were carried out in a Batliboi Eddy domestic microwave oven model No. ER 5054D operating at 2450 MHz and reactions were performed at 30% of its full power. Optical measurements were recorded on a JASCO polarimeter. ESR was recorded in the granular form on ESR, Bruker EMX instrument.

# ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| AcOMs | Acetyl methanesulphonate |
| bp | Boiling Point |
| DMSO | Dimethyl Sulfoxide |
| DMF | Dimethyl Formamide |
| g | Grams |
| h | Hours |
| ml | Milli litre |
| NMR | Nuclear Magnetic Resonance |
| IR | Infra Red |
| LTA | Lead tetraacetate |
| Me | Methyl |
| mg | Milligrams |
| min | Minutes |
| mp | Melting Point |
| M+ | Molecular Ion |
| MS | Mass Spectrum |
| Pet.ether | Petroleum ether |
| Ph | Phenyl |
| PPA | Poly Phosphoric acid |
| pTSA | p-Toluene Sulfonic Acid |
| RBF or rbf | Round Bottom flask |
| r.t. | Room Temperature |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |

## ABSTRACT

**Title: "Application of chiral ligands in Transition metal catalyzed aziridination, reduction, oxidation and cyclopropanation reactions"**

Thesis is divided into five chapters. Chapter I presents a brief review on Aziridination chemistry and highlights the recent developments in this area. Chapter II deals with studies in BromamineT catalyzed aziridination reactions .It is further divided into three sub-sections. Section A describes the detailed study of transition metal catalyzed aziridination of olefins with Bromamine-T as a source of nitrogen. Section B deals with the heterogeneous synthesis of aziridines using a novel polymer supported Mn complex and its application to aziridination of olefins.. Section C describes the Hβ catalyzed heterogeneous synthesis of aziridines. Chapter III includes the asymmetric synthesis of aziridines of olefins with Bromamine-T. Various chiral ligands employed in reaction are described. Chapter IV deals with the asymmetric synthesis of cyclopropanes using a novel Rh catalyst.

Chapter V deals with various catalytic redox reactions.. It is divided into two sections. Section A describes the catalytic oxidation reaction. It is further divided into three parts. Part I includes asymmetric Baeyer-Villiger Oxidation of ketones with Cu imine complex. Synthesis of a new iron based polymer supported complex and its application to oxidation reactions is dealt with in Part II. Part III deals with the sulphurylation of aromatics to Disulphides and Persulphides. Section B consists of three parts. Part I include cobalt catalyzed transfer hydrogenation reaction of ketones. Part II and III describe Rh based catalyst for transfer hydrogenation of prochiral ketones.

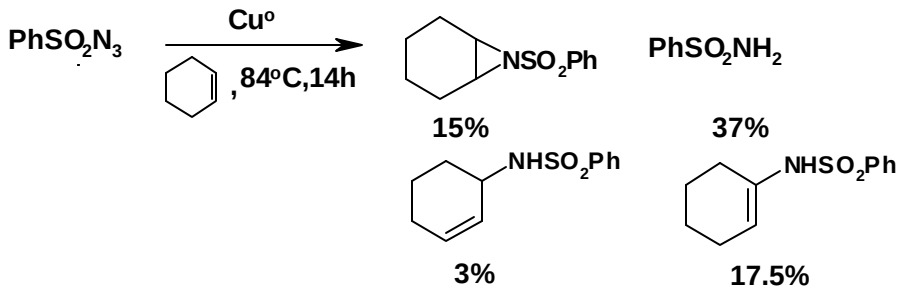
***Chapter I :*** **Aziridination: A Short review**

The recent years have witnessed an overwhelming importance in he catalytic aziridination reactions. Though various reviews were written in the past on the aziridination chemistry, it is worth to highlight the recent developments in this area. The present review highlights the latest developments in this area since 1995. This includes reaction mechanisms, reaction profiles, catalytic methods, substrate selection novel reagents as nitrogen source and the application of aziridination reaction in organic chemistry for developing strategy to synthesize natural products and their analogs.

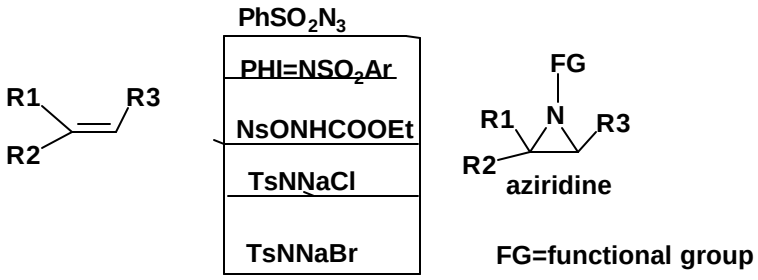
***Chapter- II: Studies in BromamineT - catalyzed aziridination reactions.***

***Section A***

It presents the investigations in the transition metal catalyzed aziridination of olefins with Bromamine-T as source of nitrogen. Conventionally aziridines were prepared by thermal or photochemical decomposition of azides. It had severe drawbacks viz., side reactions like insertion and hydrogen abstraction reactions coupled with drastic reaction conditions.

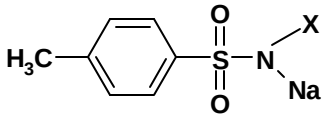



The recently developed approaches towards single one step route to aziridines from olefins are described in Scheme I below:



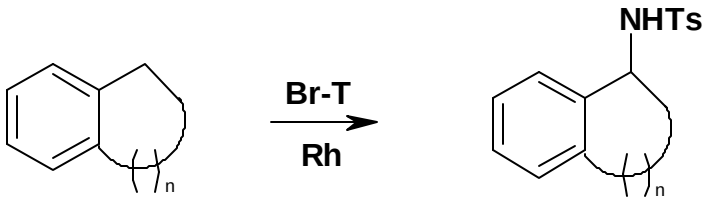

The above mentioned reagents suffer from drawbacks like cumbersome preparation, instability, narrow substrate scope, low yields, hazardous side products etc.

We have developed a methodology employing Bromamine-T as nitrogen source for the aziridination of olefins. The reaction proceeds well with Cu (I) and Cu (II) salts.




**CHLORAMINE-T; X=Cl**
**BROMAMINE-T; X=Br**

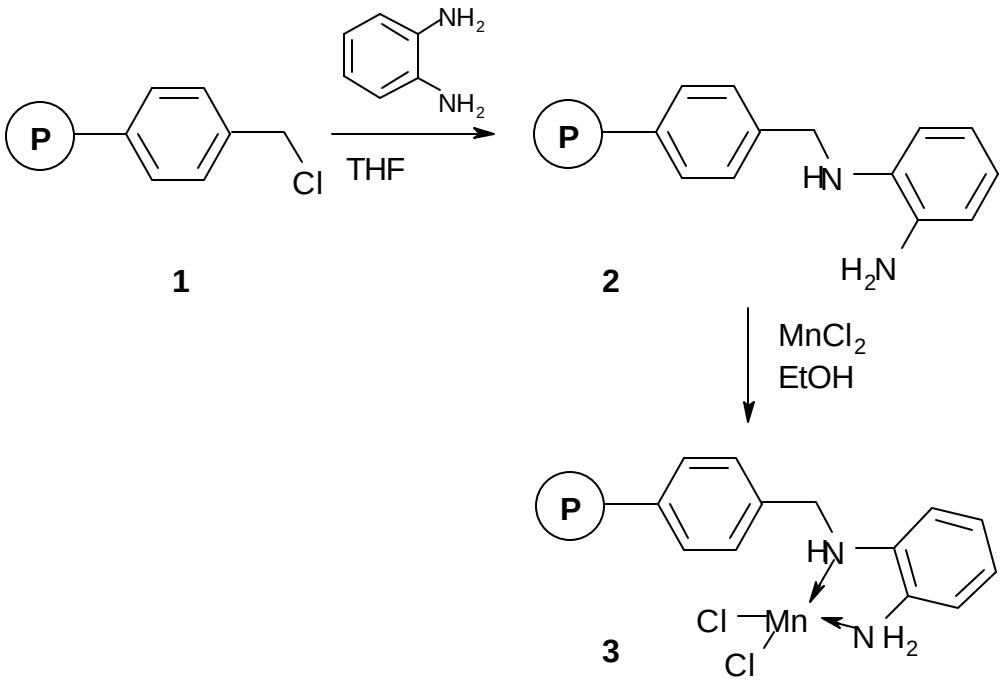
A further detailed study of the reaction was done with respect to catalyst variation, reaction conditions, substrate scope etc. The effect of ultrasound and microwave in the product formation is also studied. As a part of study bleaching powder as a positive source of chlorine effectively catalyses the reaction even in he absence of a metal catalyst. The methodology is extended to benzylic amination reaction.



***SECTION B***

***Synthesis of novel polymer supported Mn complex and its application to Aziridination of olefins***

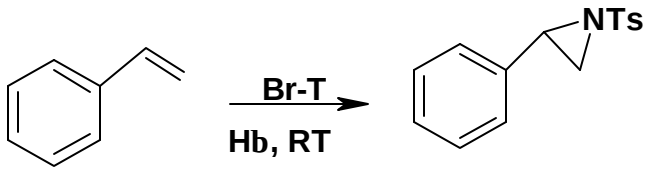
A novel Manganese based metal complex on PZ-DVB of 8 % cross-link has been synthesized. The synthesis, characterization and application of this polymer complex for the aziridination reaction were studied in detail. The synthetic steps are outlined in the scheme.




***Section C***

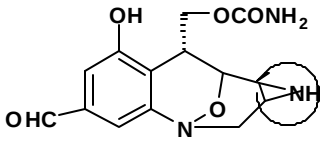
***Hb catalyzed heterogeneous synthesis of aziridines***

Heterogeneous catalysts are found to be very effective in many organic transformations. He heterogeneous version of aziridination reaction was studied using Hβ a zeolite catalyst for atom efficiency and reusability of the catalyst. It was found that the reaction proceeded without any metal catalyst. Various substrates and different reaction conditions such as effect of temperature, solvent etc ere studied. The stereochemistry of the product n relation to the catalyst pore size was also studied. The mechanistic aspect of the reaction was evaluated with the help of computational tools.

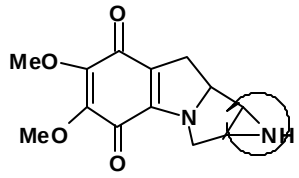


## *CHAPTER III: Application of chiral ligands in the aziridination of olefins with Bromamine-T*

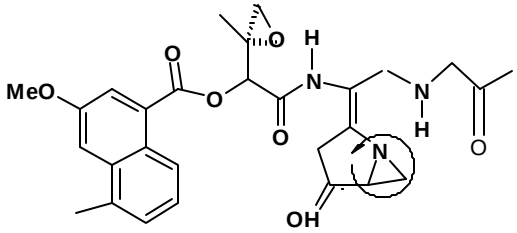
Ch*ir*al aziridines are an attractive class of compounds. They are present in many biologically active natural products such as azinomycin, mitomycin, porfiromycin etc. The structure activity studies of these molecules show aziridine moiety to be responsible for the activity




FR 900482

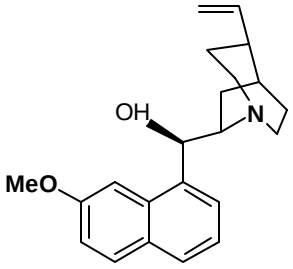



MITOMYCIN A

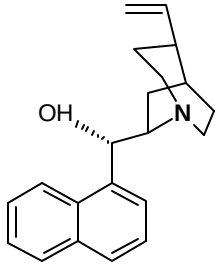



In continuation of the previous study and the encouraging results obtained for aziridination reactions using Bromamine-T as the nitrene source, attempt has been made for the exploitation of the regent for chiral substrates. Enantioselective synthesis of aziridines was studied using both naturally available alkaloid ligands and synthetically derived ligands from tartaric acid, imines oxazolines etc.

**Naturally available chiral pool (alkaloids**)

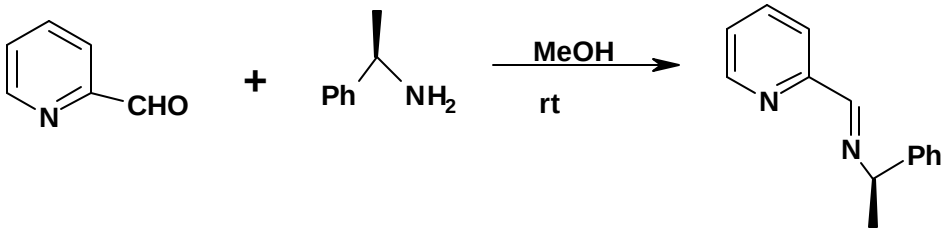


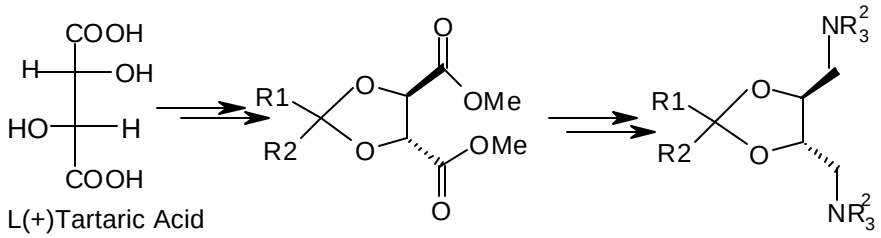

QUININE




CINCHONINE

***Synthetically derived ligands:***



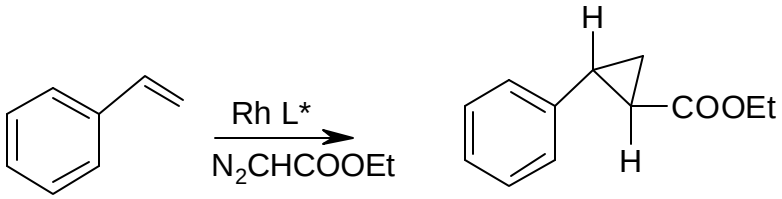


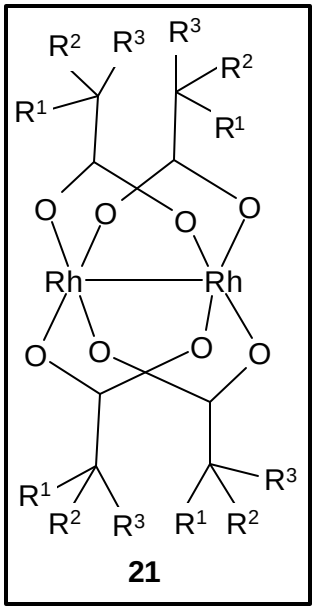

Additionally chiral benzylic amination with Rh based ligands was studied.

***Chapter IV: A Novel aqueous Rh catalyst for asymmetric cyclopropanation reactions***

As a part of three membered strained ring systems, and an important carbocyclic framework, cyclopropanation reactions were studied using Rh catalyst. The results obtained these reactions were compared with similar type of reaction using various other metal catalysts. A new water-soluble phosphorus free di-rhodium catalyst was synthesized and characterized.

The application of this catalyst for cyclopropanation reaction was demonstrated. The exclusive *trans* product obtained for these reactions were explained with mechanistic details.



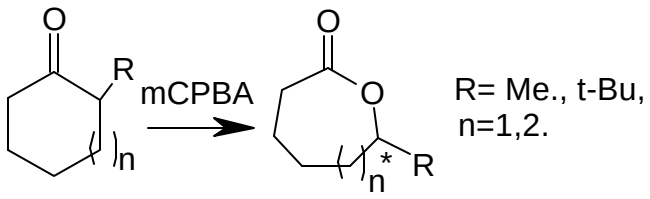




**21**

***Chapter V: Catalytic Redox Reactions***

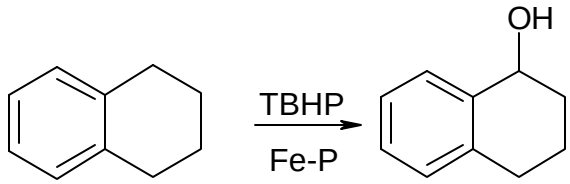
***Part I. Asymmetric Baeyer Villiger Oxidation of prochiral ketones with a Cu-imine complex.***

A range of substituted cyclic ketones was oxidized using Cu-imine complex in an asymmetric manner. The ee's and yields obtained were encouraging.




***Part II. Synthesis of a novel polyaniline supported iron complex. A versatile oxidation catalyst.***

A new Fe based polymer supported complex was synthesized and its various applications in oxidation of saturated hydrocarbons, lactonisation of cyclic ketones and oxidation of ketones to esters were studied.

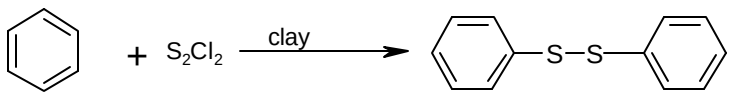



***Part III. Sulphurylation of aromatics to disulfides and Persulphides***

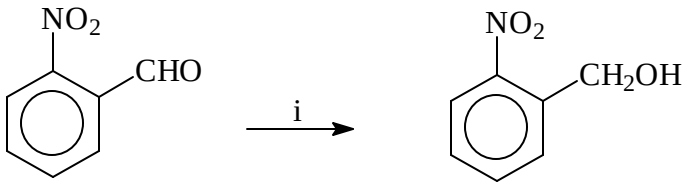
Disulfides are a class of sulfur compound possessing unique and rich chemistry in synthetic and biochemical area. They are prevalent in proteins and many other bioactive molecules. Industrially they are vulcanizing agents for rubbers and elastomers. Preparation of disulfides generally involves the photochemical an electrochemical oxidation of thiols. These methods lead to over oxidation and not used for preparative purposes. Other catalytic methods known in literature being indirect are not viable. Currently acid catalysis of organic transformations is an area of high potential interest. We found that Kaolinitic Clay efficiently catalyses the reaction of sulfur monochloride with arenes to yields symmetrical 4,4' arene disulfides in a single step under heterogeneous phase.

***Section B***

***$Co(OAc)_2$ assisted transfer hydrogenation Reaction***



Chemoselective transfer hydrogenation of ketones, nitro compounds, alkenes, aldehydes etc in propanol using $Co(OAc)_2$ as the catalyst was studied. The selectivity of reduction in presence of other functional groups was studied. The mechanistic aspects of the chemoselectivity and reaction profiles are described.




i) $Co(OAc)_2$, propan-2-ol, KOH, reflux, 3h

***Part II. New Rh based monocyano oxazoline ligands for transfer hydrogenation of prochiral ketones.***

Modified oxazoline ligands were synthesised and Rh complex of these ligands was utilised for the transfer hydrogenation of acetophenone, ibuprofen, and naproxen precursors. The results obtained in term of yields and ee are presented.

***Part III***
***A novel Rh catalyst for transfer hydrogenation of ketones***

A new dirhodium chiral catalyst was prepared and used for asymmetric transfer hydrogenation of ketones. The yields and ee's obtained are described.

**List of Publications**

1) *Chem. Lett*. (**1998**), *1*, 43. **Renu Vyas**, Bhanu Chanda and A. Sudalai
2) *Tet Lett* (**1998**), 4715-4716. **Renu Vyas**, Bhanu Chanda and AV. Bedekar
3) *J Mol Cat* (**2000**), 160, 237-241**.Renu Vyas**, Bhanu Chanda, A.A. Belhekar, D.R. Patel and A. V. Bedekar.
4) *J Org Chem* (**2001**), 61, 30. Bhanu Chanda**, Renu Vyas** and A.V. Bedekar
5) A novel polyaniline supported iron complex: A versatile oxidation catalyst., **Renu Vyas**, Bhanu Chanda, A.V. Bedekar and H. S. Rama.(to be communicated).

**Patents**

An improved process for the aziridination of olefins using Bromamine-T and Chloramine-T . (NF 33, 2000)

.

**Abstracts/Posters**

1. $Co(OAc)_2$ catalyzed chemoselective transfer hydrogenation of aldehydes and ketones with propane-2-ol, **Renu Vyas**, Bhanu Chanda and A. Sudalai in National symposium on Newer Concepts in Organic Chemistry, Aurangabad University, 1998
2. Investigations in the transition metal catalyzed aziridination of olefins with BromanineT as the source of nitrene. **Renu Vyas**, Bhanu Chanda and A.V. Bedekar, (Abstract published in National Symposium in Organic Chemistry at IISc, Bangalore) p-112.
3. Synthesis of polymer anchored Mn complex and its application in the aziridination of olefins. **Renu Vyas**, Bhanu Chanda and A.V. Bedekar, p 1. National Seminar on Trends in Industrial Catalysis, Baroda.
4. Hβ catalyzed aziridination of olefins**, Renu Vyas**, Bhanu Chanda, A.V. Bedekar, P.N. Joshi and W.B. Kasture. (Paper accepted at International Zeolite Conference, Montpellier, France for oral presentation)

# Chapter-1

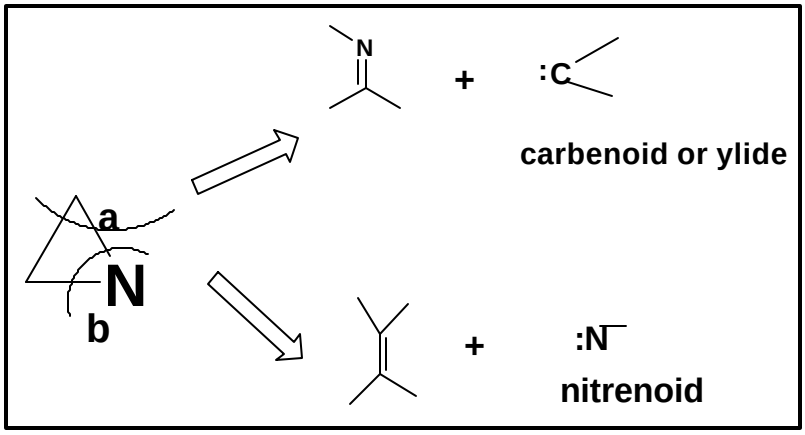
# Aziridination: A Brief Review

# INTRODUCTION

Aziridines pertain to an important class of organic compounds with three membered nitrogen containing heterocycles, which is an important subunit in several natural products. The aziridine moiety is successfully used in the synthesis of various alkaloids, amino acids, amino sugars, polymers, pyrrolidines and β-lactam antibiotics.[1] In addition, substrate controlled diastereoselective synthesis is also possible by the use of aziridines as removable chiral auxiliaries for asymmetric alkylation and aldol transformations. Metalation 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.[2] Chiral aziridines are also currently of interest as enzyme substrates and enzyme inhibitors. Like other three membered rings such as cyclopropanes and epoxides, aziridines are highly strained and this ring strain renders them susceptible to the ring opening reactions that dominate their chemistry and makes them useful synthetic intermediates that deserve a prominent place in organic chemistry. Ring opening can be effected by various carbon and heteroatom nucleophiles often with regiocontrol to produce a variety of functionalized amino compounds.[3] The exocyclic N-substituent in the ring modulates the properties and reactivity of the three membered ring.[4]

Literature on aziridine chemistry is extensive; however catalytic aziridination reaction has so far received little attention. Comprehensive reviews by Tanner[5], and Sweeney and Osborn[2] deal mainly with non-racemic aziridines along with their use in stereoselective transformations. Another review by Ibuka[6] describes the aza-Payne rearrangement of N-activated 2-aziridinemethanols, to give the corresponding epoxy sulfonamides in high yields. Since 1994, there has been a tremendous progress in the field of aziridine synthesis with a spate of publications from various groups, necessitating a need to update the literature in this field. 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 considerations and stereochemical outcome.

Conventionally, aziridines have been synthesized *via* the thermal or photochemical decomposition of azides with inherent drawbacks.[7] 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 carbon carbon bond **(Scheme-1)**.




**Scheme-1**

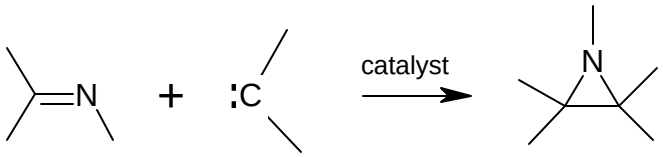
Thus a simple and straightforward approach to the synthesis of aziridines can be accomplished by either the modification of the carbon-nitrogen bond or the carbon-carbon double bond. Both the approaches are discussed in this review.

**Transformation of the C=N bond**

A comprehensive literature survey revealed that there are four methods for direct aziridinating reactions with a C=N bond, viz., the carbene approach, the aza-Darzens reaction, Lewis acid catalysis and the recent ylide approach. These approaches with recent examples are described in detail.

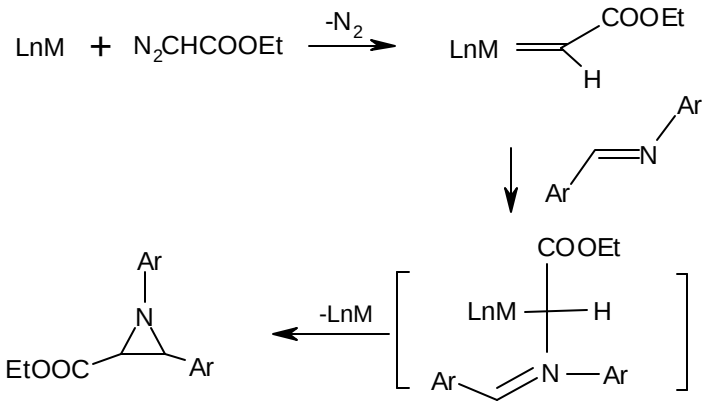
**Aziridine synthesis *via* carbene addition**

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-2)**.



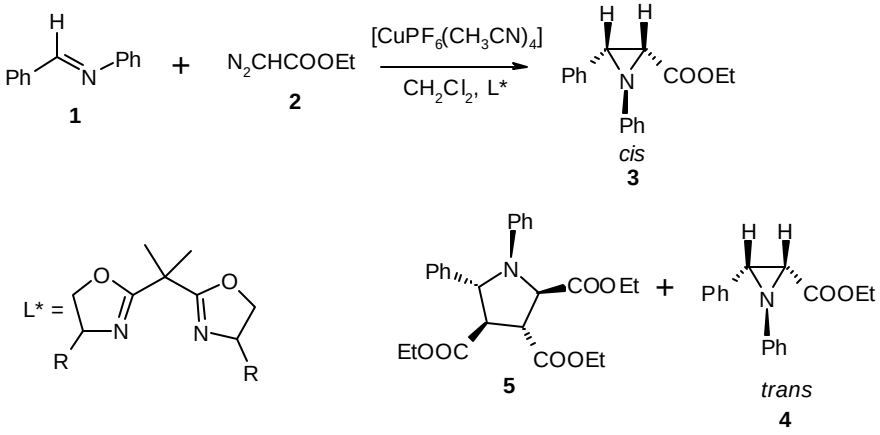

**Scheme-2**

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 aziridine **(Scheme-3)**. The other pathway is discussed under the 'Lewis acid approach'.



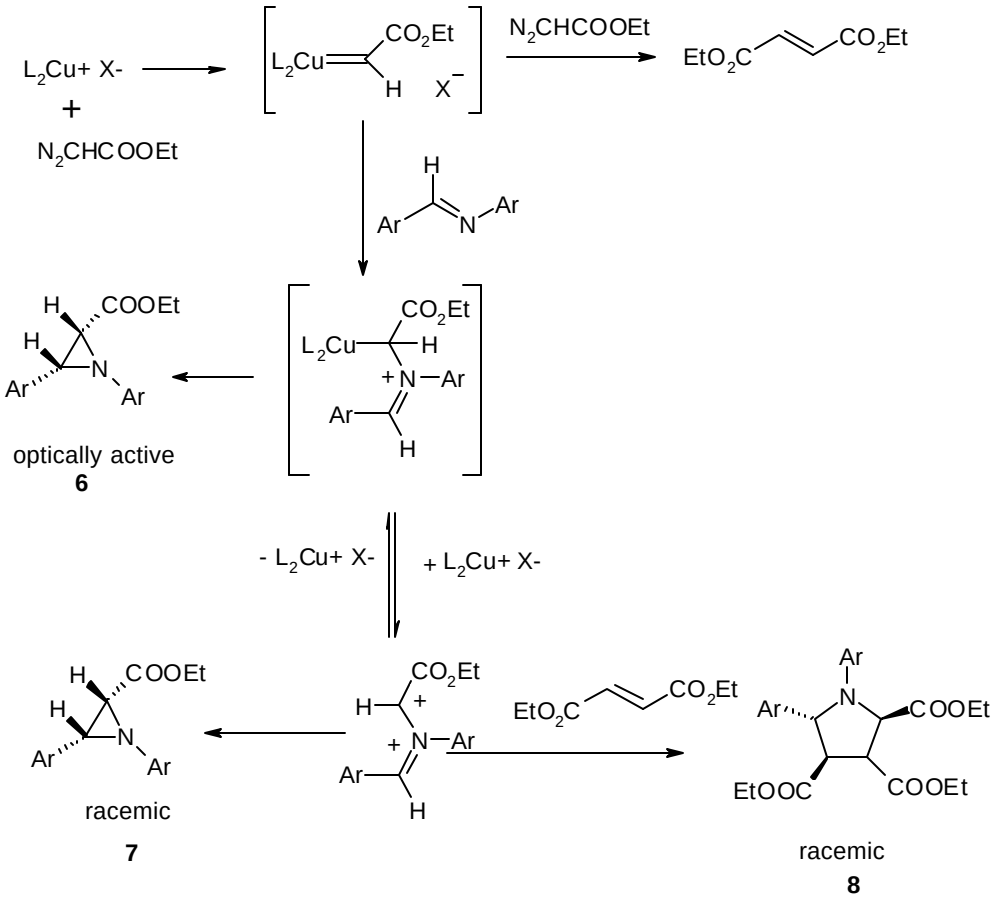

**Scheme-3**

The route involving carbene transfer to imines to form optically pure aziridines was first reported by Jacobsen.[8] Reaction of imines with EDA catalyzed by chiral Cu (I) bis (dihydroxazole) complexes produces aziridines in moderate yields and ee's. Thus treatment of N-benzylidene aniline with ethyl diazoacetate in the presence of copper (I) hexafluorophosphate $\{Cu(PF_6)(CH_3CN)_4\}$ and ligands resulted in the formation of enantiomerically enriched aziridine as a mixture of two diastereomers, **3, 4** and racemic pyrrolidine **5 (Scheme-4)**.




**Scheme -4**

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 **6** enantioselectively **(Scheme -5)**.

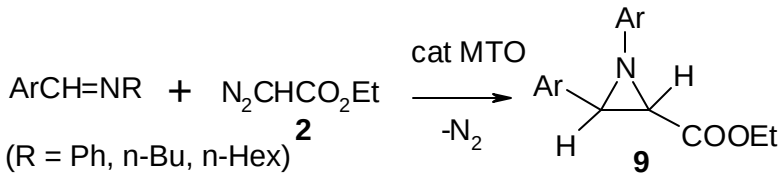



**Scheme -5**

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 **8** or intramolecular cyclization to form racemic aziridine **7.**

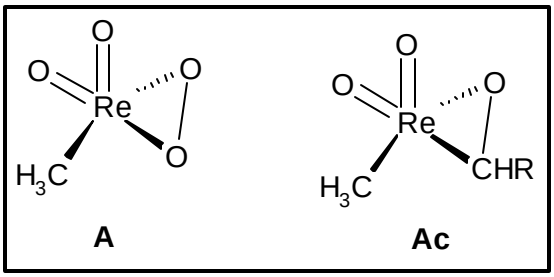
This method thus outlined offers an extremely direct strategy for the synthesis of enantiomerically enriched N-aryl aziridines and consequently N-aryl amino acids, albeit in moderate yields. Jorgenson and Rasmussen [9] were able to increase the aziridine yield to 80-90 %, using $Cu(OTf)_2$ in combination with (-) menthyl diazoacetate or (R) (+) 2,2' isopropylidene bis (4-phenyl-2-oxazoline), but enantioselectivities were moderate.

Espenson[10] 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 **(Scheme-6)**.




**Scheme-6**

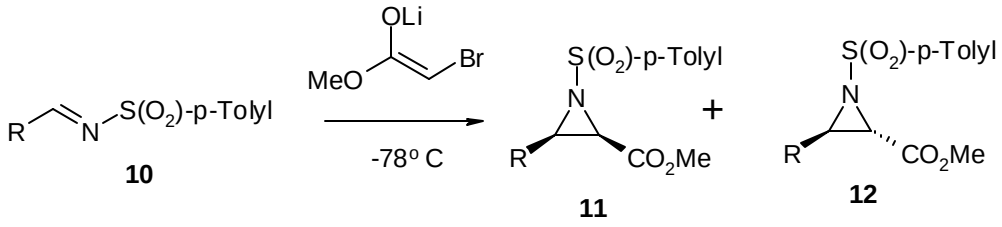
The aziridine preparation proceeded conveniently and in high yields under anaerobic conditions and the only by-product observed was diethyl maleate (5 %). The mechanism for the transformation was not given in detail but a metal carbene intermediate **Ac**, similar to the well studied peroxide system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



An electron rich double bond may attack the -CHCOOEt group of **Ac** just like other electron rich centres attack the peroxide oxygen of **A**.

**Aza-Darzens approach**

Darzen type synthesis of racemic aziridines is known in the literature[11] and has been reviewed earlier. However asymmetric synthesis of aziridines *via* Darzens reaction has been recently reported by Davis *et al.*[12] who developed a one pot asymmetric synthesis of N- (p-toluenesulfinyl)- 2-carbomethoxy aziridines *via* Darzen reaction of lithium enolate of methyl bromoacetate with enantiopure sulfinimines **(Scheme-7)**.

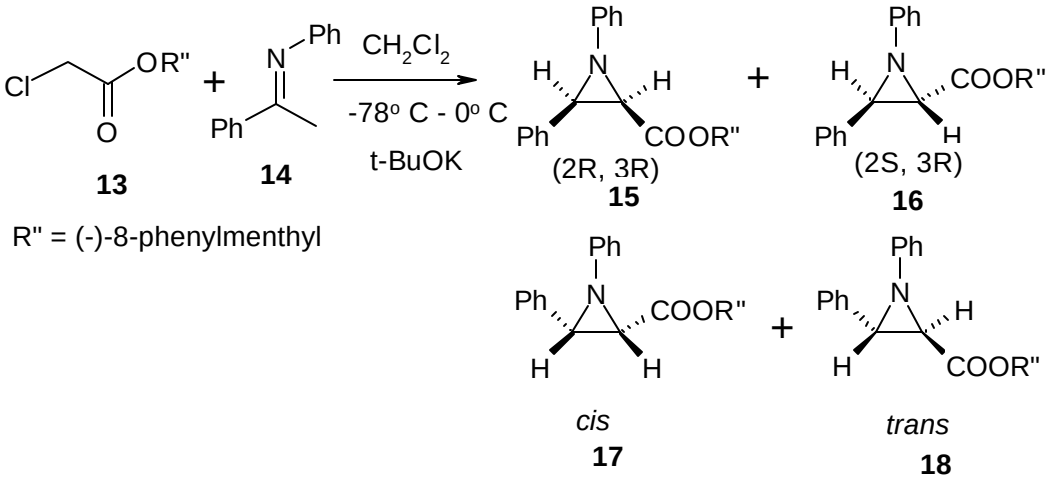



**10** **11** **12**

**Scheme-7**

In each case the *cis* aziridine was formed exclusively and this *cis* selectivity was explained by the transition state geometries of the enolate and sulfinimine. These *cis* N-sulfinyl aziridine-2 carboxylates have found applications in synthesis of amino acids, β-hydroxy amino acids, the antibiotic thiamphenicol, the antitumour agent dysidazrine and sphingosine. An extension of the protocol was published later by the same workers[13] and 2-substituted aziridine-2-carboxylic acids were prepared *via* a highly diastereoselective Darzen type reaction of α-bromo enolates to enantiopure sulfinimines. Regio- and stereochemical opening of the aziridines obtained afforded α-methylphenyl serine in high enantiomeric purity. In a recent report by Ohkata *et al.*[14] asymmetric Darzens condensation of benzaldehyde and various ketones has been investigated using chiral auxiliaries such as (-) menthyl and (-) 8-phenylmenthyl groups at the ester moiety. The aza-Darzens reaction of (-)-8-phenylmenthyl α-chloroacetate with N-benzylideneaniline afforded aziridine in 40

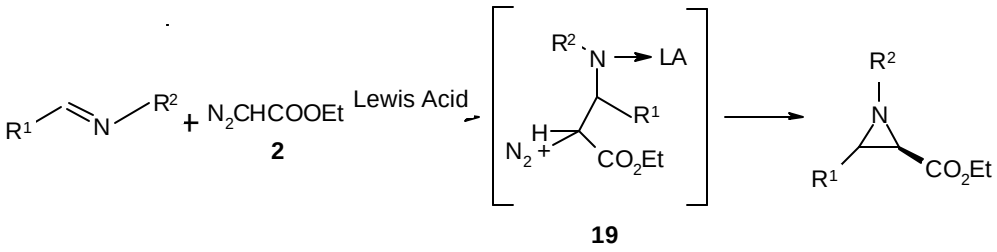
% yield as a stereoisomeric mixture. The *cis / trans* selectivity was 1.5:1 and the diastereoselectivity of the *trans* aziridine was high (>80 % de) as shown in **Scheme - 8**.




**Scheme-8**

**Lewis acid approach**

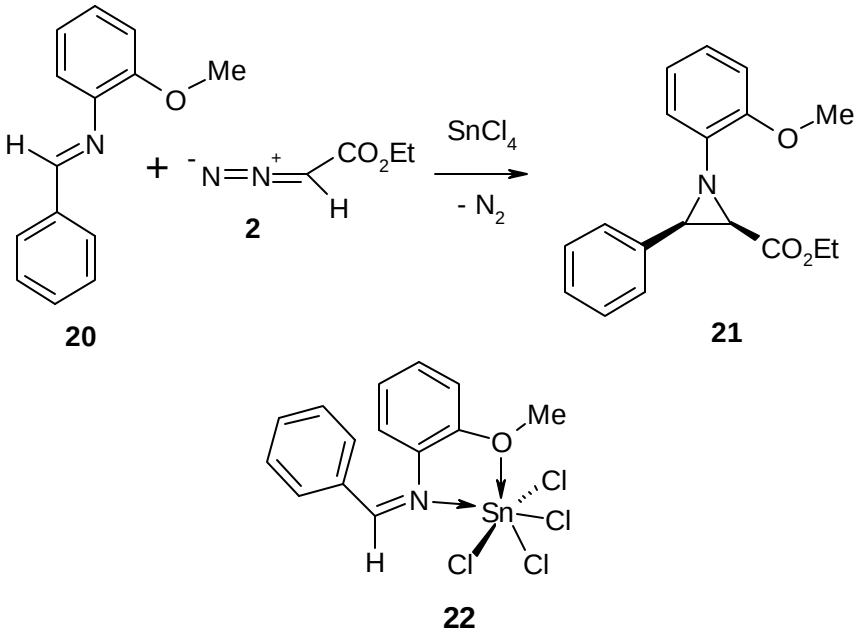
This approach involves the "activation of the imine by the metal", the latter now acting as the Lewis acid. The coordination of the imine to the Lewis acid activates the imine for a nucleophilic attack by EDA (**2**) at the carbon atom leading to an intermediate **19**, which undergoes subsequent ring closure and loss of nitrogen to provide aziridines **(Scheme-9)**.




**Scheme-9**

Various Lewis acid complexes such as titanium (IV), zinc (II), ytterbium (III), tin (IV), silicon (IV), boron (III), methyl rhenium trioxide, and $K_{10}$ clays can catalyze the formation of aziridines from imines. Jorgensen *et al.*[15] performed tin (IV) catalyzed aziridination of alkenes using ethyl diazoacetate as carbene fragment donor, giving *cis* aziridines as the major product. The intermediate

**22** has been isolated and characterized by X-ray diffraction. The intermediate was formed in the aziridination reaction of N-benzylidene-o-anisidine (**20**) with EDA (**2**) in the presence of $SnCl_4$ as the catalyst. The imine utilizes both the nitrogen and oxygen lone-pair electrons for a bidentate coordination to the metal. Further, the imine isomerises from a *trans* geometry to a *cis* geometry by coordination to $SnCl_4$.The mechanism was deduced based on a series of competition experiments, to be a Lewis acid activation of the imine for a nucleophilic attack of ethyl diazoacetate **(Scheme-10)**.

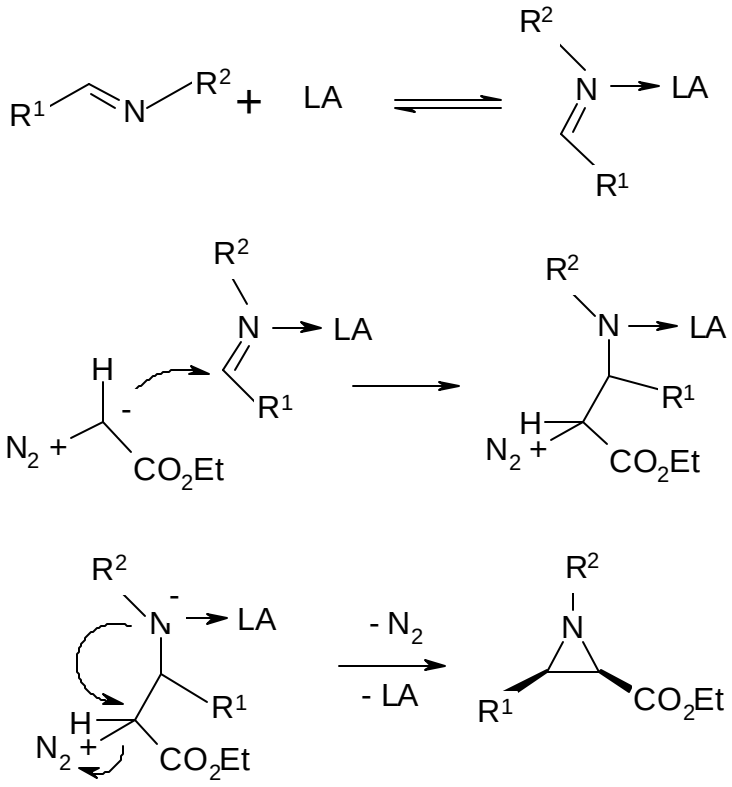



**20** **2** **21**

**22**

**Scheme-10**

In another report by Jorgenson *et al.*[16] the metal catalyzed aziridination of imines with ethyl diazoacetate as the carbene fragment donor using various Lewis acids was carried out and the catalytic properties of various Lewis acids were tested. Both main group complexes such as $BF_3$-$OEt_2$, early and late transition metal complexes, such as $TiCl_2(O\text{-}Pr^i)_2$, Cu $(OTf)_2$, Zn $(OTf)_2$, and rare earth complexes $Yb(OTf)_3$ catalyzed the formation of aziridines yielding *cis* aziridine as the major diastereomer. $Zn(OTf)_2$ and $Yb(OTf)_3$, in combination with chiral ligands catalyzed the formation of optically active aziridines. Based on the trapping and reaction rate experiments, a reaction mechanism was proposed as shown in **Scheme-11**.

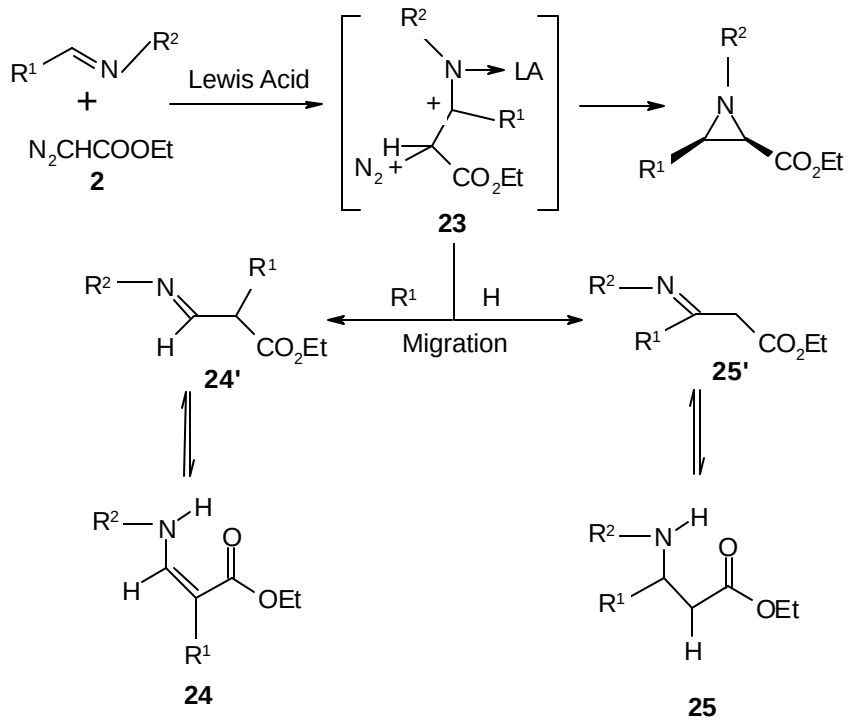



**Scheme -11**

The first step in the mechanism is the coordination of the Lewis acid to the nitrogen atom in the imine. The next step which is the rate determining step is a nucleophilic attack of EDA on the C=N bond followed by a nucleophilic attack of the nitrogen atom on the carbon atom with $N_2$ as the leaving group. The mechanism proposed is very different from the one proposed by Jacobsen discussed above, as the Lewis acid activates the imine in the present aziridination, while in the former the metal complex reacts with EDA with elimination of $N_2$ and the formation of a metal carbene species.

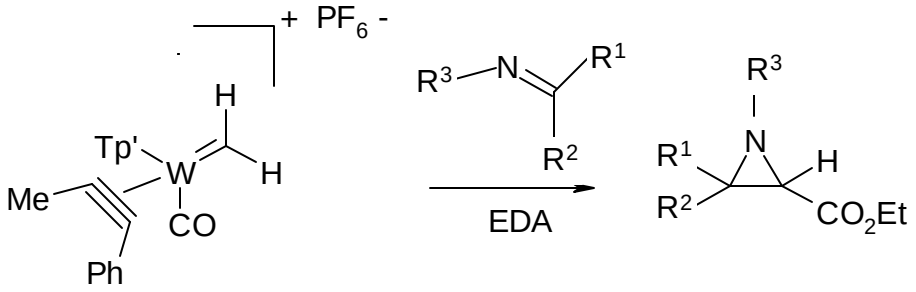
Ravindranathan *et al.*[17] used K10 clays to catalyze the reaction of EDA with imines to give aziridines. Further substantial work in this area was carried out by Templeton *et al.*[18] who developed a convenient synthesis of aziridines from various imines and ethyl diazoacetate catalyzed by readily available Lewis acids e.g., $BF_3$-$Et_2O$, $AlCl_3$, $TiCl_4$ etc. In no case products derived from carbene coupling viz. diethyl fumarate or maleate were detected. The absence of carbene coupling

products suggests that no metal carbenoid species are involved in the transfer process. The formation of **24** and **25** could be minimized by use of hexane as solvent. The mechanism involves activation of the imine by complexation with the Lewis acid followed by nucleophilic addition of EDA (**2**) resulting in the formation of an intermediate **23**. Subsequent ring closure and loss of $N_2$ provides aziridines. By-products **24** and **25** result from 1,2 migration of either the $R^1$ substituent or H to the incipient carbocation to yield initially **24'** and **25'**. The ratio of aziridines to migration products is dependent on the nature of the aryl ring **(Scheme-12)**.




**Scheme-12**

Templeton and co-workers also synthesized [Tp'(CO) ($PhC_2Me$) $W{=}CH_2$][$PF_6$] (Tp'= hydrotris (3,5-dimethyl pyrazolyl borate) (**26**) an electrophilic carbene complex that binds nucleophiles and acts as a Lewis acid to activate imines towards nucleophilic attack by EDA[19] **(Scheme-13)**.

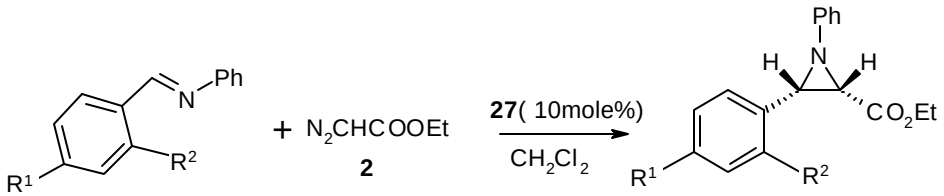


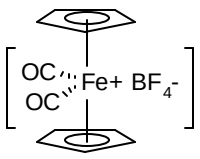

**26**

**Scheme-13**

The two major products were aziridines and enamines. This discovery suggested another possible mechanistic pathway in transition metal mediated carbene transfer reactions.

Mayer and Hossain[20] developed a facile one step route to predominantly *cis* aziridines using an iron Lewis acid $[(\eta^5\text{-}C_5H_5)\ Fe\ (CO)_2\ (THF)^+\ (BF4^-)]^-$ (**27**) , with yields upto 95 %, from compounds with a diazo functionality and a variety of substituted N-benzylidene imines with N-aryl or N-alkyl groups **(Scheme-14)**.



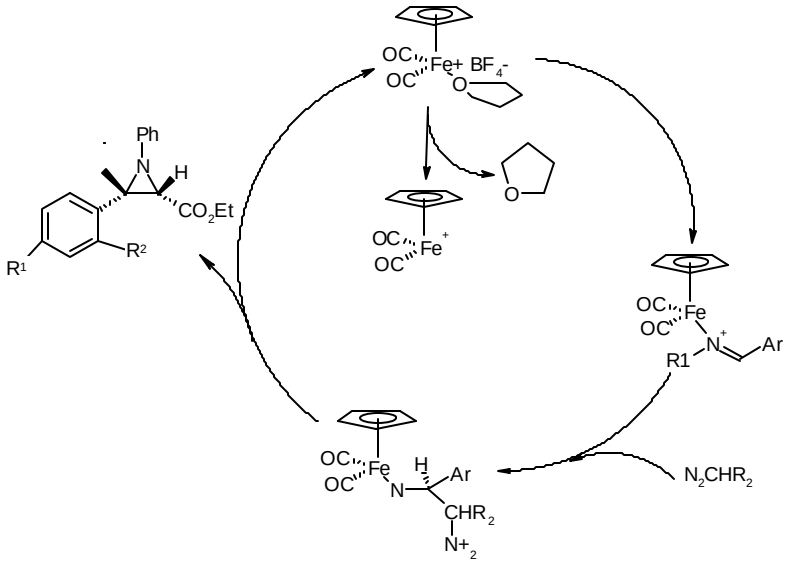




**27**

**Scheme-14**

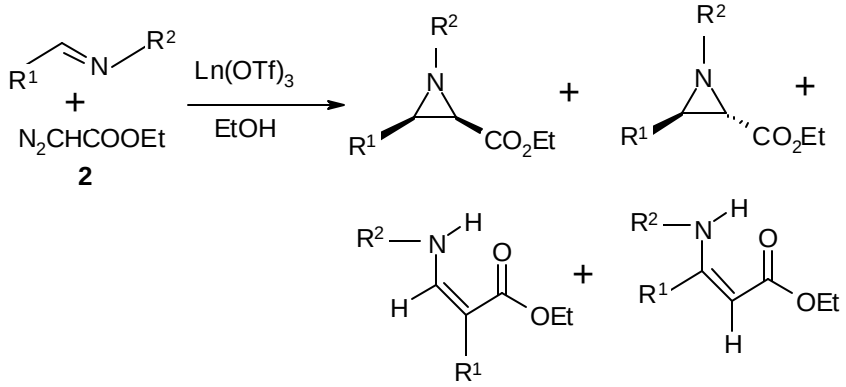
The reaction mechanism is believed to proceed through an electrophilic iminium ion intermediate **(Scheme -15)**. This mechanism was further corroborated by synthesis of the iron Lewis acid-imine

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**

Very recently, Wang *et al.*[21] reported Ln (OTf) $_3$ catalyzed aziridine synthesis from imines and diazo compounds 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)**.



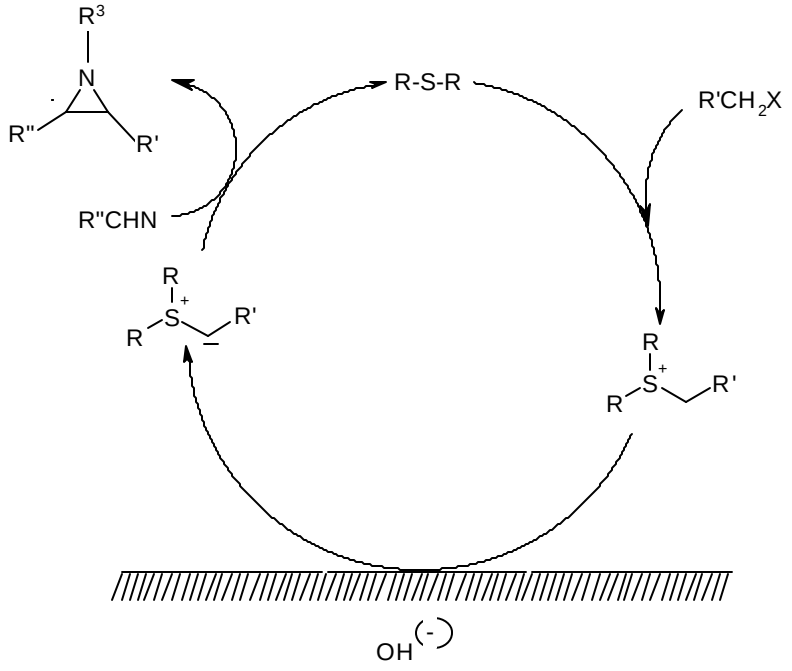
**Scheme-16**

The imines used were mainly those derived from aromatic aldehydes and aromatic amines with either electron donating or electron withdrawing substituents. Six lanthanide triflates as well as Sc (OTf) $_3$ and $Y(OTf)_3$ were tested as catalysts for aziridination reactions.

**Ylide approach**

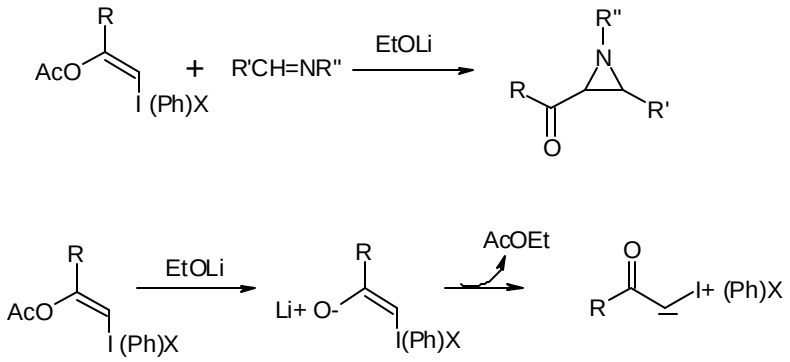
Among various strategies starting from prochiral C=C and C=N bonds, the aziridination through the reaction of an imine with a ylide i.e. ylide aziridination has recently shown great promise in obtaining various functionalized aziridines. Compared with other direct aziridinating reactions with a C=N bond, 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. The results of various groups in this area, which have been reported recently, are discussed in detail.

Aggarwal [22] 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-17)**.




**Scheme-17**

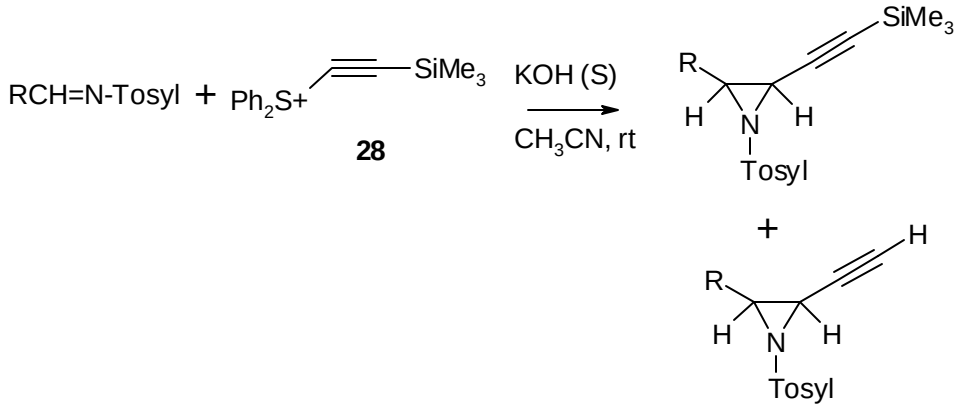
The process could be rendered asymmetric by the use of chiral sulfides in the catalytic process. Ochiai and Kitagawa[23] generated monocarbonyl iodonium ylides *insitu* from (Z)-2 (acetoxyvinyl) iodonium salts *via* an ester exchange reaction with LiOEt. These ylides undergo alkylidene transfer reaction to activated imines yielding 2-acylaziridines in good yields **(Scheme-18)**.




**Scheme-18**

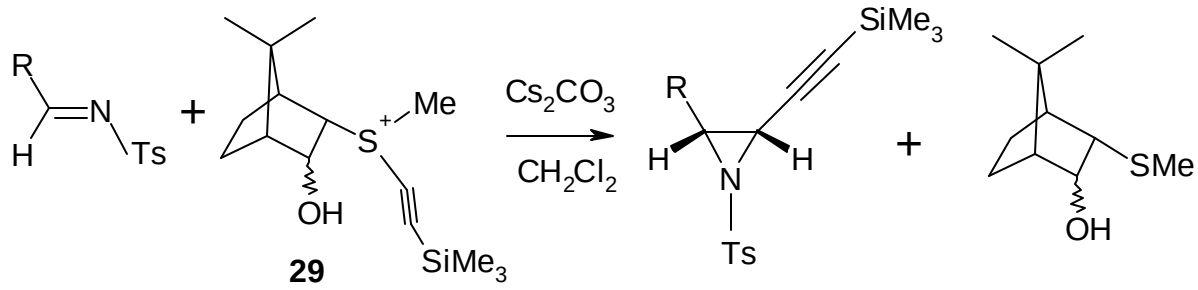
They demonstrated the stereochemical outcome of this aziridination reaction to be dependent on both the activating groups of the imines and the reaction solvents. The aziridination of N- (2,4,6-trimethylbenzene sulfonyl) imines in THF affords the *cis* aziridines as a major product while that of N-benzoylimines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

Dai and co-workers[24] synthesized acetylenyl aziridines in good yields under phase transfer or low temperature conditions. The ylide generated from diphenylsulfonium salt **28** reacts with N- sulfonyl imines to give acetylenyl aziridines **(Scheme-19)**.




**Scheme-19**

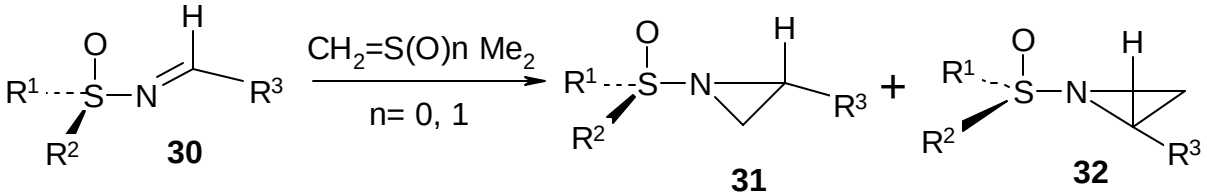
The *cis / trans* selectivities were moderate to low. With $Cs_2CO_3$ as the base dimethyl sulfonium salts showed much better *cis / trans* selectivity (98:2). The asymmetric version of this reaction using camphor derived sulfonium salt **29** gave chiral aziridines with ee values upto 85 % **(Scheme-20)**.




**Scheme-20**

3-Phenyl or 3-alkyl substituted propargyl sulfonium salts can also be used to perform the above aziridination. Among telluronium, sulfonium and arsonium salts, the sulfonium ylides were found to be the most efficient reagents to effect aziridination.

Ruano and co-workers[25] have recently described a simple method to prepare both enantiomers of chiral non-racemic aziridines based on reactions of N-p-tolylsulfinylimines 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 S, S and R, R aziridines, **31** and **32** epimers 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.

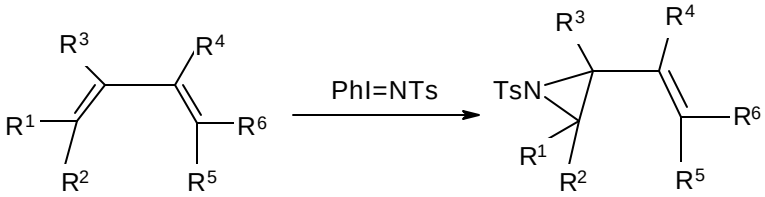
**Transformation of the carbon- carbon bond**

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

**Synthesis *via* nitrene addition to carbon- carbon double bond**

Since the development of the copper catalyzed aziridination reaction employing [N- (p-tolylsulfonylimino)] phenyl iodinane as nitrene precursor by Evans *et al.*,[26] numerous reports have appeared in this area. The significance of this reaction has been recently demonstrated in the total synthesis of natural products and dipeptide isosters. This process catalyzed by $Cu(acac)_2$ was recently incorporated into the total synthesis of pancratistatin.[27]

Knight and co-workers have developed a copper catalyzed regioselective aziridination of 1,3 dienes using PhI=NTs as nitrene donor.[28] Aziridination could be carried out successfully on a range of dienes with different steric and electronic properties with moderate to high yields. There is a preference for reaction on the more electron rich double bond as expected since it is an electrophilic system **(Scheme-22)**.

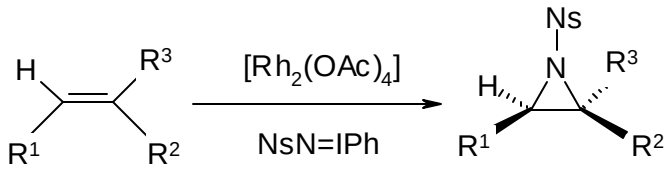



**Scheme-22**

Dauban and Dodd[29] reported the 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 were comparable to those of PhI=NTs.

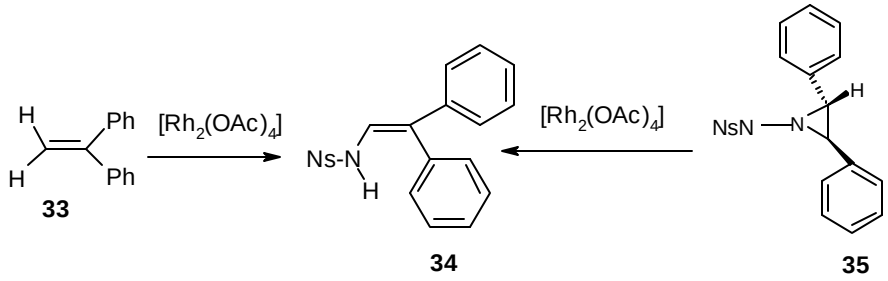
N-(Ses) aziridines have been successfully used for the preparation of substituted α-amino acids and oligosaccharides. The reaction proceeded in a stereospecific manner giving only *trans* aziridines. N -(Ses) aziridines are sufficiently activated to allow ring opening by nucleophiles. Significantly the N- (Ses) aziridines themselves could be deprotected without provoking opening of the aziridine ring. TASF [tris(dimethyl amino) sulfonium trifluorodimethyl silicate] was found effective for deprotection of the Ses group.

Mueller *et al.*[30] attempted to optimize nitrene transfer from PhI=NTs to olefins under $[Rh_2(OAc)_4]$ catalysis. Even under best conditions, the yield of aziridine from styrene never exceeded 59 %. However it was found that the reaction proceeded well with N - (p -nitro benzene sulfonyl) imino phenyl iodinane (PhI=NNs) as shown in **Scheme-23**.




**Scheme-23**

Aziridination of *cis*-methyl styrene and *cis*-hex-2-ene was stereospecific. However with *cis*-stilbene a mixture of *cis* and *trans* aziridines was obtained. The *trans* isomer **35** underwent phenyl migration upon exposure to $[Rh_2(OAc)_4]$ and rearranged to enamine **34** which was also observed as a side product upon aziridination of 1,1-diphenyl ethene (**33**) **(Scheme-24)**.

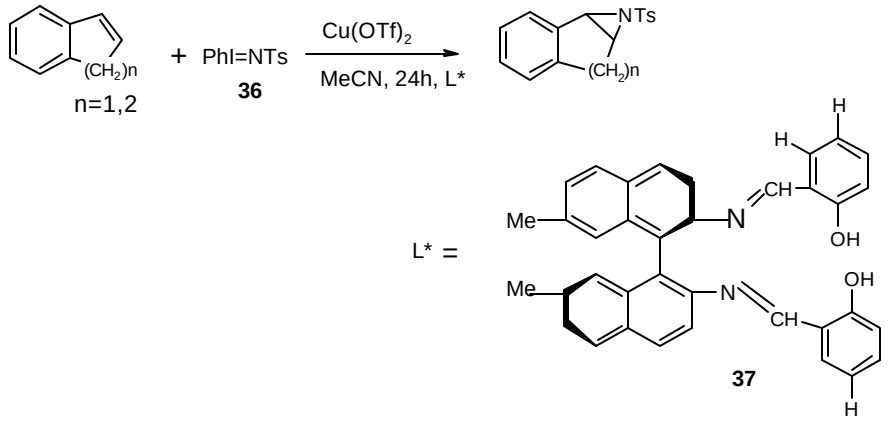



**Scheme-24**

Cyclohexene afforded only trace amounts of aziridine (4 %) and the main product was derived from nitrene insertion into the allylic CH bond. Aziridines derived from electron rich olefins undergo ring opening under the conditions of aziridination and afford rearrangement products or pyrrolidines. In the presence of chiral Rh (II) catalysts, the aziridination was enantioselective, affording an ee of 73 % with *cis*-methyl styrene and Pirrungs catalyst [$Rh_2${(-)(R)-bnp}$_4$].

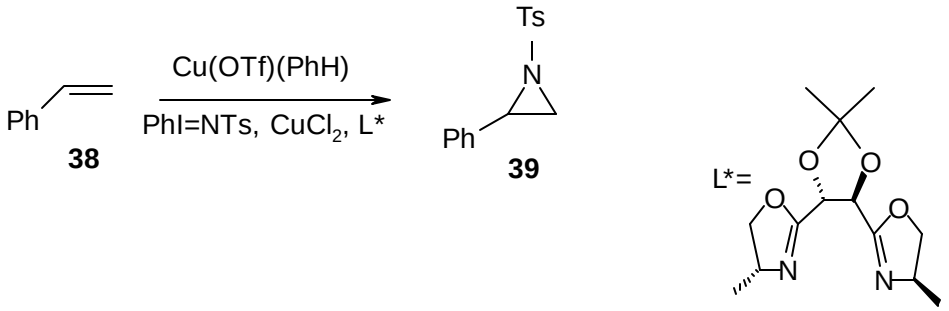
**Asymmetric nitrene transfer to olefins**

The development of systems capable of asymmetric nitrene transfer to olefins is in progress in several research groups. Anderson *et al.*[31] increased the scope of the Evans asymmetric aziridination reaction by modifying the nitrene precursor PhI=NTs. They found that the performance of the copper catalyzed asymmetric aziridination is highly dependent on the properties of the nitrene precursor. There was indeed a significant improvement in the enantioselectivity and chemical yields when [N-(4-nitrobenzenesulfonyl)imino phenyl iodinane] (p-$NO_2C_6H_4SO_2N$=IPh) was employed instead of the commonly used p-tosyl analog PhI=NTs. Shi *et al.*[32] used diimine ligands (**37**) and copper reagent to catalyze the asymmetric aziridination of some aryl alkenes with PhI=NTs (**36**) with low enantioselectivities **(Scheme-25)**.




**Scheme-25**

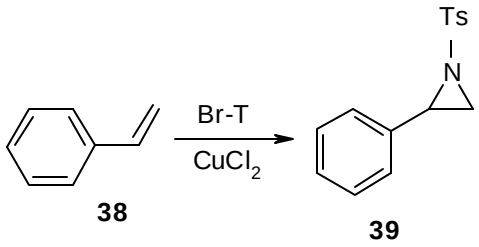
Knight *et al.*[33] performed asymmetric aziridination of styrene (**38**) using chiral tartarate derived bis-oxazoline ligands with PhI=NTs as nitrogen source **(Scheme-26)**.




**Scheme-26**

The effects of variation in the size of the oxazoline substituent and in the size of the diazoacetate ester substituent $R_2$ on the level and sense of enantioselection were described. The ee's obtained were low. Catalytic asymmetric aziridination of styrene by PhI=NTs was also achieved by manganese and iron tetramethyl chiroporphyrins[34]. Komatsu and co-workers[35] have reported an alternate nitrogen source, Chloramine-T (N-chloro-N-sodio-p-toluensulfonamide) for the aziridination of olefins. When anhydrous Chloramine-T was added to acetonitrile solution of alkenes in presence of various copper catalysts and molecular sieves (5 $A^o$) the corresponding aziridines were obtained in moderate to good yields. This process was vastly improved by utilizing Bromamine-T as the source of nitrogen[36] **(Scheme-27)**.

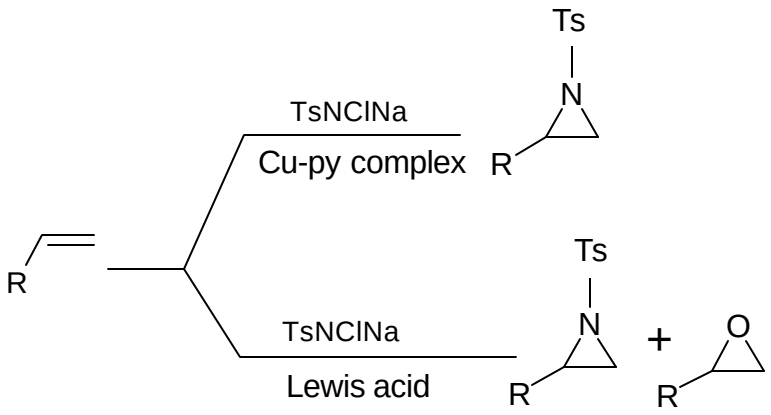
A detailed study of this reaction with respect to substrate scope, reaction conditions, mechanistic consideration etc. is presented in the following chapter (Chapter II).




**Scheme-27**

Since Komatsu's report, several other groups have also reported aziridination of olefins with various catalysts utilizing Chloramine-T as nitrogen source. Taylor and coworkers[37] employed hydrated Chloramine-T and a nitrogen complex to catalyze aziridination of activated olefins. They described a mechanism based approach to selection of an efficient catalyst for nitrene transfer from Chloramine-T. It was concluded that in reactions where no nitrogen ligands are present, the reaction follows Lewis acid mechanism whereby both styrene oxide and aziridine products are obtained and

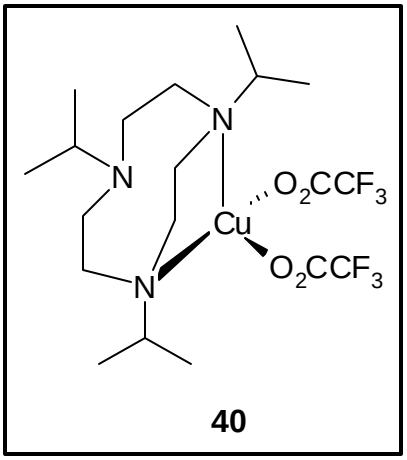
in the presence of pyridine or bipyridine ligands a nitrene transfer mechanism operates yielding only the aziridine product **(Scheme-28)**.




**Scheme-28**

The intermediacy of nitrene species in aziridination reaction was also probed by Halfen *et al.*[38] who stabilized the nitrene intermediate with an electron rich, sterically hindered ancillary ligand **40**.

Tosylaziridines were prepared in moderate to good yields by the reaction of PhI=NTs and olefins in the presence of **40**.

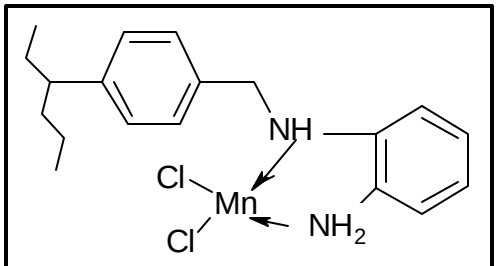



**40**

Recently the first report of catalytic heterogeneous aziridination was published by Hutchings *et al.*[39] with PhI=NTs as nitrene donor. Copper exchanged zeolite (CuHY) was found to be a highly

effective catalyst for a range of olefins. Modification of the CuHY catalyst with a pyridine based bis oxazoline led to chiral aziridines. The highest enantioselectivities of 61 % was observed in aziridination of styrene using acetonitrile as solvent at -10 $^{o}$C.

A synthesis of aziridines using a novel polymer supported Mn complex **41** has been reported with Bromamine-T as source of nitrogen.[40] The detailed study is presented in subsequent chapter (Chapter -II).

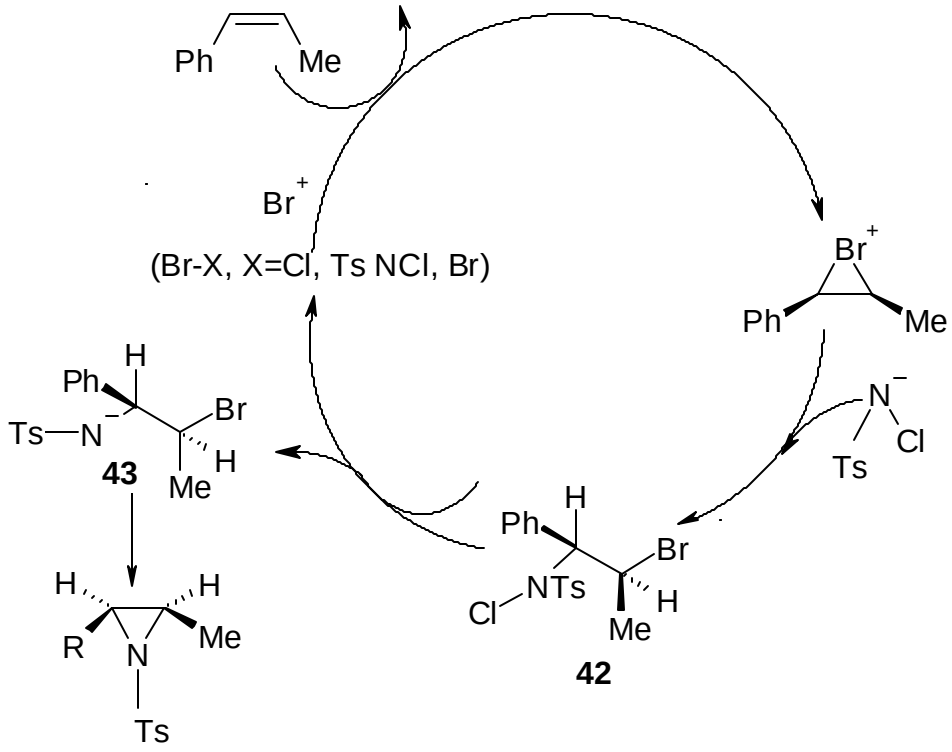



**41**

This system works better than its homogeneous counterpart developed by Evans using PhI=NTs. By suitable choice of chiral amine ligands an asymmetric version of the reaction is feasible. Currently work is in progress on these lines.

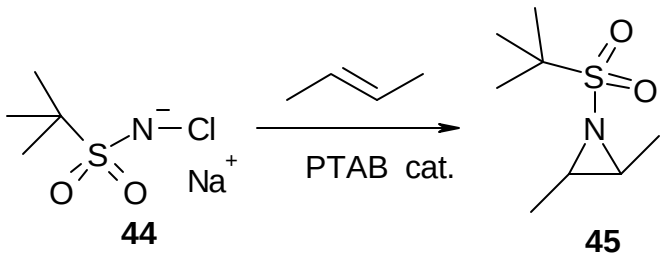
**Aziridination *via* Ionic mechanism**

There are several reports in the literature of aziridine synthesis *via* ionic mechanism. For the sake of brevity a few examples are described here. Komatsu and coworkers[41] found iodine to be an efficient catalyst for the aziridination of alkenes using Chloramine-T as nitrogen source. This reaction was found to proceed through the intermediacy of iodonium ion. Sharpless *et al.*[42] reported a number of screening experiments and identified a bromine based catalyst system: phenyl trimethyl ammonium tribromide also known as PTAB. This catalyst provides good to excellent yields of aziridines in presence of anhydrous Chloramine- T. The mechanism involves reaction of olefin with a positive bromine source to form bromonium ion, which undergoes benzylic opening to give **42** which is the key intermediate. The latter undergoes attack of Br- on N-Cl group generating anion **43**. Expulsion of bromine from anion **43** yields the final aziridine **(Scheme-29)**.




**Scheme-29**

In a later report by the same workers, N-Chloramine salt of tert-butylsulfonamide (**44**) was shown to be an efficient nitrogen source and terminal oxidant for the catalytic aziridination of olefins[43] **(Scheme-30)**. This nitrogen source resembles Chloramine-T in its behaviour. The advantage of this method is that the sulphonyl nitrogen bond can be cleaved under mild acidic conditions.

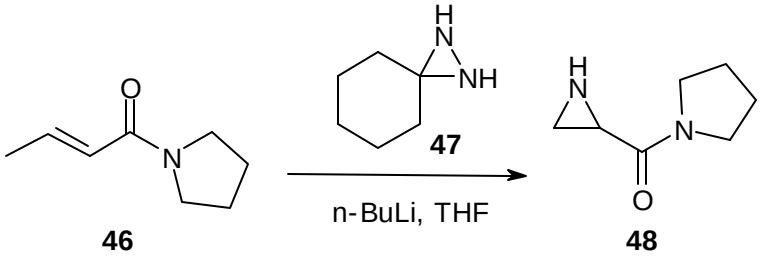



**Scheme-30**

Sudalai and co-workers[44] used py-$HBr_3$ (pyridinium hydrobromide perbromide), which being more electrophilic in nature than $PhNMe_3$-$Br_3$(PTAB) dissociates in presence of olefin to give py-$Br_2$ which reacts with olefins to form the bromonium ion. This bromonium ion undergoes nucleophilic

opening with Chloramine-T, followed by its cyclization to give the aziridine. Commercially available bleaching powder was found to catalyze the formation of aziridines from olefins with Bromamine-T.[45] The reaction proceeded even in the absence of metal catalysis. Bleaching powder (calcium oxychloride) is known to be a source of positive chlorine. It is the chloronium ion, which initiates the catalytic cycle. The details regarding results are enumerated in the succeeding chapter (Chapter-II).

Very recently, Katsuki and co-workers[46] carried out aziridination of α,β-unsaturated amides (**46**) by treatment with lithiated 3,3-pentamethylene diaziridine (**47**) in high diastereoselectivity **(Scheme-31)**.




**Scheme-31**

A stepwise mechanism involving 1,4- addition of a lithiated diaziridine to α, β-unsaturated amides and subsequent ring closure at the nitrogen atom was proposed to explain the exclusive formation of *cis* isomer.

**Conclusion**

The above illustrations distinctly bring out the importance of aziridination strategy in synthetic organic chemistry. It is apparent from this review that future strategies should be chosen effectively for accomplishing catalytic aziridination reactions. 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 the above discussions, and the importance of aziridine chemistry our success in the synthesis of substituted aziridines is presented in detail in the following chapters (Chapters II and III).

## References


1. a) Padwa, A. and Woolhouse, A.D., *Comprehensive Heterocyclic Chemistry*, Lwowski, W., Ed. Pergamon Oxford, **1983,** 7, 47. b) Kemp, J.E.G., *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I., Eds. Pergamon Oxford, **1991,** 7, p 469.
2. Osborn, H.M.I. and Sweeney, J., *Tetrahedron Asymmetry*, **1997,** 8, 1693.
3. a) Tanner, D., Andersson, P.G. and Somfai, A.P., *Tetrahedron Lett.*, **1994,** 35, 4631. b) Andersson, P.G., Harden, A., Tanner, D. and Norby, P.O., *Eur. J. Chem.*, **1995,** 1,12.
4. Pearson, W.H., Lean, B.W. and Bergmeir, S.C., In *Comprehensive Heterocyclic Chemistry*, II, Padwa A. Ed, Pergamon Press, New York, **1996,** Vol A, 1-60.
5. Tanner, D., *Angew. Chem. Int. Ed. Engl.*, **1994**, 33, 599.
6. Ibuka, T. *Chem. Soc. Rev*., **1998**, 27, 145.
7. For reviews see, a) Lwowski, W. "Carbonylnitrenes". In *Nitrenes* Lwowski, W, Ed Interscience, New York, **1970,** 185-224. b) Edwards, O.E. Acylnitrenes. In *Nitrenes*, Lwowski, W, Ed Interscience, New York, **1970,** 225-247.
8. Hansen, K.B., Finney, N.S. and Jacobsen, E.N., *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 676.
9. Rasmussen, K.G. and Jorgenson, K.A., *J. Chem. Soc. Chem. Com.*, **1995**, 1401.
10. Zhu, Z. and Espenson, J.H., *J. Org. Chem.*, **1995**, 60, 7090.
11. Rosen, T., In *Comprehensive Organic Synthesis*, Heathcock, C.H, Ed Pergamon Press Oxford, **1991**, Vol 2, p 409. b) Cainelli, G Panunzio, M. and Giacomini, D., *Tetrahedron Lett*., **1991**, 32, 121.
12. Davis, F. A., Zhou, P. and Reddy, G.V., *J. Org. Chem.*, **1994,** 59, 3243.
13. Davis, F.A., Liu H. and Reddy, G.V., *Tetrahedron Lett.*, **1996,** 37, 5473.
14. Takagi, R., Kimura, J., Shinohara, Y., Ohba, Y., Takenono, K., Hiraga, Y., Kojima, S. and Ohkata, K., *J. Chem. Soc. Perkin. Trans 1.*, **1997**, 689.
15. Rasmussen, K.G., Juhl, K., Hazell, R.G. and Jorgensen, K.A., *J. Chem. Soc. Perkin. Trans 2.*, **1998**, 6, 1347.
16. Rasmussen, K.G. and Jorgenson, K.A., *J. Chem. Soc. Perkin. Trans 1.*, **1997**, 1287.
17. Madan Mohan, J., Uphade, B.S., Choudhary, V.R., Ravindranathan, T. and Sudalai, A., *J. Chem. Chem. Commun.*, **1997**, 15, 1429.
18. Casarrubios, L., Perez, J.A., Brookhart, and Templeton, J. L., *J. Org. Chem.*, **1996**, 61, 8358.

19. Gunnoe, B.T., White, P.S., Templeton, J.L. and Casarrubios, L ., *J. Am. Chem. Soc.*, **1997,** 119, 3171.
20. Mayer, M.F. and Hossain, M.M. *J. Org. Chem.*, **1998**, 63, 6839.
21. Xie, W. Fang, J, Li, J. and Wang, P.G., *Tetrahedron*, **1999**, 55, 12929.
22. Aggarwal, V.K., *Syn Lett*., **1998**, 329.
23. Ochiai, M. and Kitagawa, Y., *J. Org. Chem.*, **1999**, 64, 3181.
24. Li, A-H., Zhou, Y-G., Dai ,L-X., Hou, X-L., Xia, L-J. and Lin, L., *J. Org. Chem.* ,**1998**, 63, 4338.
25. Ruano, J.J.G., Fernandez, I., Catalina, M.P. and Cruz, A.A., *Tetrahedron Asymmetry*, **1996**, 7. 3407.
26. Evans, D.A., Faul, M. M. and Bilodeau, M.T., .*J. Am. Chem. Soc.*, **1994**, 116, 2742.
27. Tian, X., Hudlicky, T. and Konigsberger, K., *J. Am. Chem. Soc.*, **1995,** 117, 3643.
28. Knight, J.G. and Muldowney, M.P., *Synlett*., **1995**, 949.
29. Dauban, P. and Dodd, R.H., *J. Org. Chem.*, **1999**, 64, 5304.
30. Mueller, P., Baud,C. and Jacquier, Y., *Tetrahedron*, **1996**, 52, 1543.
31. Sodergren, M.J., Alonso, D.A., Bedekar, A.V. and Andersson, P.G., *Tetrahedron Lett*., **1997**, 38, 6897.
32. Shi, M., Itoh, N. and Masaki, Y. *J. Chem. Res. Miniprint*., **1996,** 8, 1946.
33. Harm, A.M., Knight, J.G. and Stemp, G., *Tetrahedron Lett*, **1996**, 37, 6189.
34. Simonato, J-P., Peacut, J., Scheidt, R. and Marchon, J-C., *J. Chem. Soc. Chem. Com.*, **1999**, 11, 989.
35. Ando, T., Minakata, S., Ryu, I. and Komatsu, M., *Tetrahedron Lett.*, **1998,** 39, 309.
36. Vyas, R., Chanda, B.M. and Bedekar, A.V., *Tetrahedron Lett.*, **1998,** 39, 4715.
37. Albone, D.P., Aujla, P.S., Taylor, P.C., Challenger, S. and Derrick, A.M., *J. Org. Chem.*, **1998**, 63, 9569.
38. Halfen, J.A., Hallman, J.K., Schultz, J.A. and Emerson, J.P., *Organometallics***, 1999**, 18, 5435.
39. Langham, C., Taylor, S., Bethell, D., Mcmorn, P., Page P.C.B., Willock, J.D., Sly,C., Hancock, F.E., King, F. and Hutchings, G.J., *J. Chem. Soc. Perkin. Trans 2*.**, 1999,** 1043-1049.
40. Vyas, R., Chanda, B.M., Belhekar, A.A., Patel, D.R., Ram, R.N. and Bedekar, A.V., *J. Mol. Catal. A.*, **2000**, 160, 237.
41. Ando, T., Kano, D., Minakata, S., Ryu, I., Komatsu, M., *Tetrahedron*, **1998,** 54, 13485.

42. Jeong, J.U., Tao, B., Sagasser, I., Henniges, H. and Sharpless, K.B., *J. Am. Chem. Soc.*, **1998**, *120*, 6844.
43. Gontcharov, A.V., Liu, H. and Sharpless, K.B., *Org. Lett*., **1999**, 1, 783.
44. Iliyas, Ali, S., Nikalje, M.D. and Sudalai, A., *Org. Lett.*, **1999**, 1, 705.
45. Vyas, R., Chanda, B. M. and Bedekar, A.V., "An improved process for the aziridination of olefins". Indian Patent No. NF 33, **2000.**
46. Hori, K., Sugihara, H., Ito, Y.N. and Katsuki, T., *Tetrahedron Lett*., **1999,** 40, 5207.

# Chapter-2

# Studies in Bromamine-T catalyzed aziridination reactions

# INTRODUCTION

The importance of aziridine chemistry is highlighted in the introductory review chapter. In the present chapter the emphasis is mainly on catalytic aziridination reactions. The chapter is divided into three sections A, B and C. Section A deals with catalytic aziridination reactions under various reaction conditions with Bromamine-T as source of nitrogen. Section B describes the synthesis and application of a novel polymer supported Mn complex to aziridination reactions while Section C discusses the heterogeneous synthesis of aziridines using H β zeolite with Bromamine-T as source of nitrogen.

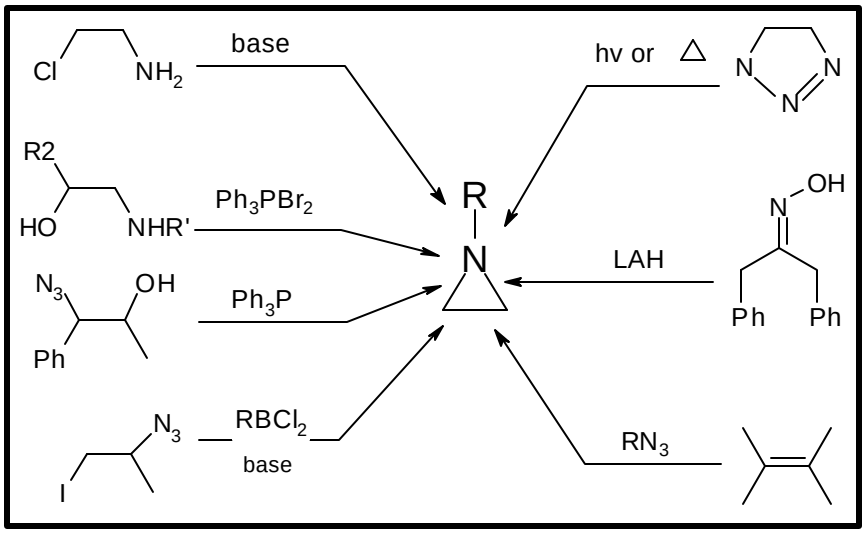
Throughout the last decade metals have had a revolutionary impact on organic synthesis.[1] Metal species may by acting as efficient catalysts, allow reactions to take place very selectively and under mild conditions. Numerous efficient catalytic systems based on this principle have been developed for a wide range of different synthetic transformations. Until now the formation of epoxides from alkenes and oxygen donor has received considerable attention, whereas the catalytic formation of the nitrogen analogue, i.e. aziridines has been less examined. Despite some recent progress, there is still a need for a more general one-step route to aziridines from very simple substrates. With this objective in mind, efforts were directed towards the preparation of some new nitrene precursors along with assessment of efficient reaction conditions for enhanced yields. An investigation in Bromamine-T catalyzed aziridination is discussed in length in this chapter and the succeeding chapter evaluates its efficiency in the asymmetric version of the reaction.

## Section A

### Catalytic aziridination reactions using Bromamine-T as the source of nitrogen

For a better understanding of the subject, a brief overview of the conventional methods of aziridine synthesis and their intrinsic disadvantages is provided in the following section. **Scheme-1** 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 $SN_2$ 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

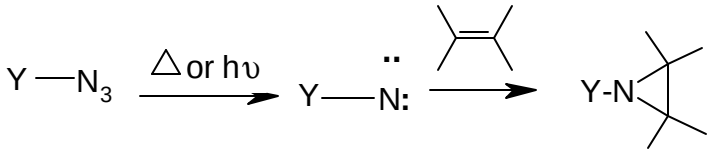



**Scheme-1Conventional routes to aziridine synthesis**

with an α-halo ester or an α-halo N,N-disubstituted amide in the presence of t-BuOK 1,2-dimethoxyethane. The 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 $LiAlH_4$. With certain oximes (e.g. those of type $ArCH_2CR$= NOH), treatment with LAH gives aziridines.

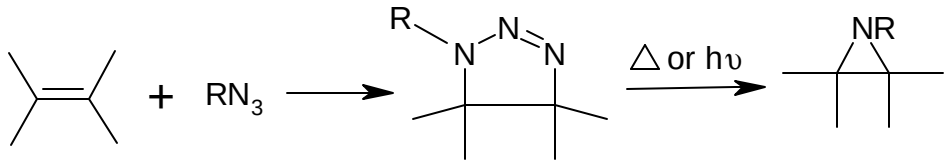
All the above-mentioned methods being indirect methods involving laborious multi-step reactions, are not synthetically viable. A single step route to aziridines synthesis *via* a single metal

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.[3] 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-2)**.




**Scheme-2**

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.[4] 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-3)**.

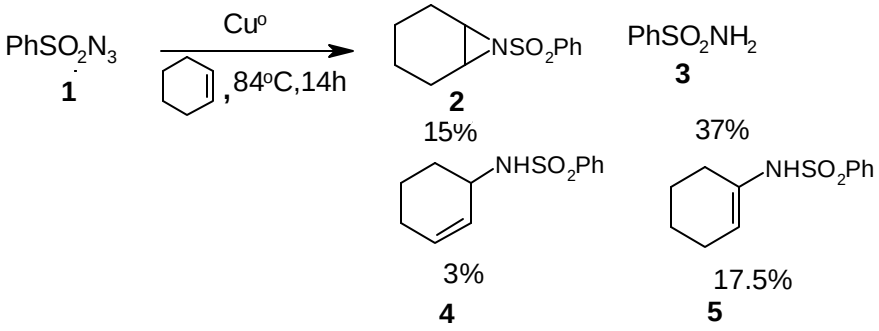



**Scheme-3**

Evidence for nitrene pathway is most compelling for R= acyl groups. However the synthetic utility of this process is limited due to poor conversion and formation of side products viz. insertion reactions, hydrogen abstraction etc.[5]

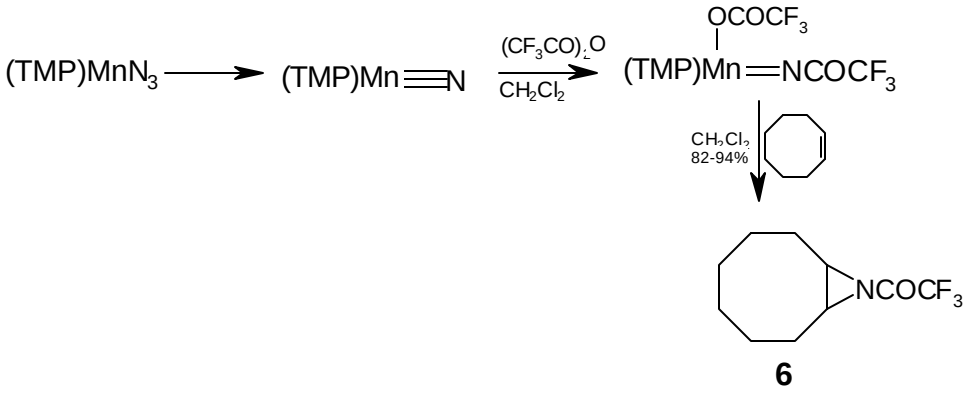
**Catalytic Synthetic Methods**

Kwart and Kahn[6] reported the first metal catalyzed atom transfer process in 1967, when they demonstrated that copper powder promoted the decomposition of benzensulfonyl azide (**1**) when heated in cyclohexene. The resulting distribution of products is consistent with the intervention of nitrene (metal nitrenoid) intermediate (**Scheme-4)**.



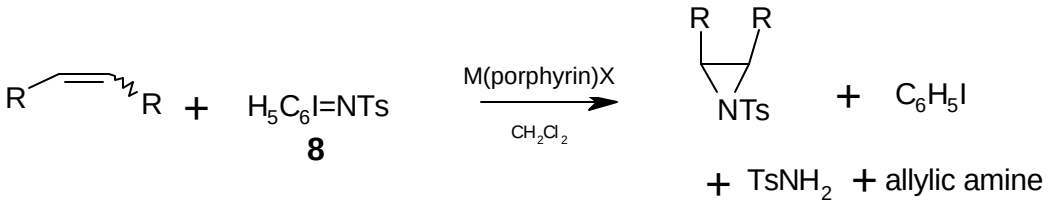

**Scheme-4**

In 1983, Groves[7] reported manganese-catalyzed aziridination of olefins. The reaction of nitrido (5,10,15,20-tetramesityl porphyrinato) manganese $^{(V)}$ (TMP-MnN), obtained by photolysis of the azide ($TMPMnN_3$) with excess trifluoroacetic anhydride, afforded in situ, the trifluoroacetylimido manganese (V) trifluoroacetate which reacted with cyclooctene to give the corresponding N-trifluoroacetyl aziridine **6 (Scheme-5)**.



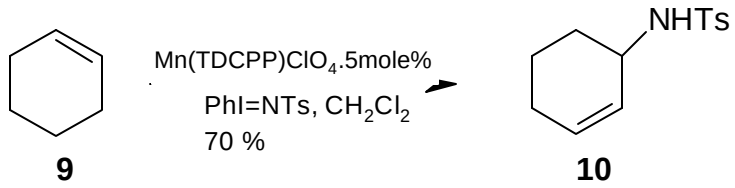

**Scheme-5**

A year later, Mansuy and workers[8] carried out a seminal study on the scope of metal catalyzed nitrogen atom transfer to olefins. The aziridination of alkenes, catalytic in porphyrinato iron and manganese salts has been developed where the nitrene moiety is supplied by N-(4-methylphenylsulfonyl) imino phenyl iodinane ($C_6H_5I$=NTs) (**8**). This reaction intermediate is a high valent tosylimidometal species. It may undergo addition to an alkene bond by a free radical mechanism or via a four membered metallocycle **(Scheme-6)**.




**Scheme-6**

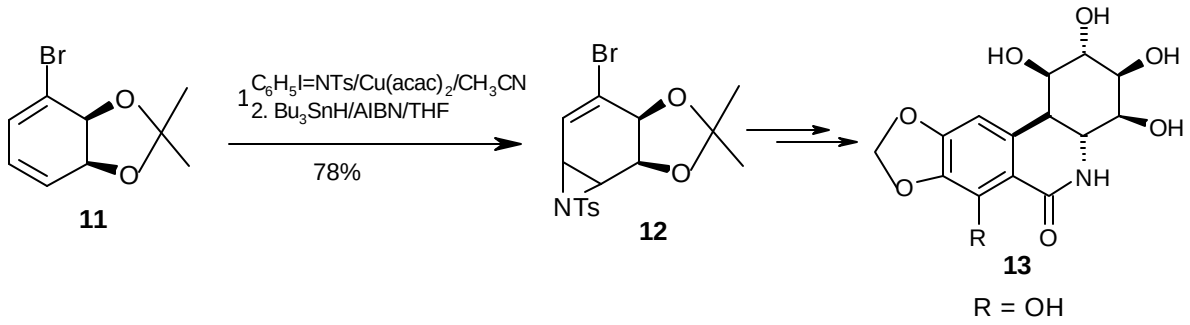
Although the Mn (TPP) Cl catalyzed reaction of PhI=NTs with styrene afforded the desired aziridine in 80 % yield, significantly lower yields were obtained with other olefins, even with optimized catalysts. Another drawback was the side reactions, viz., hydrolysis of the imido metal intermediates by traces of water, leading to an oxo metal species and ultimately to epoxides and the allylic amination of olefins, viz. cyclohexene (**9**) as shown in **Scheme-7**.




**Scheme-7**

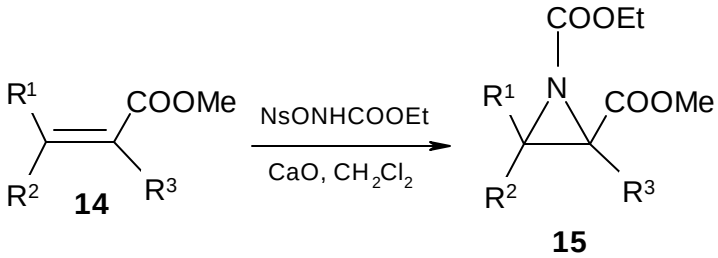
The above process was improved by use of copper (I) and copper (II) salts and using N- (4-methylphenylsulfonyl) imino phenyl iodinane as the nitrene precursor by Evans *et al*.[9] The copper catalysts were unique in the sense that there was no competing allylic insertion with aliphatic alkenes. In view of the fact that the iodinane reagent is an oxidant, it has been assumed that the true catalysts are the copper $^{(II)}$ species even in copper $^{(I)}$ catalyzed reactions. E disubstituted alkenes

gave the *trans* aziridine and (Z)-2-octene gave the *cis* aziridines in good yields, providing support for the concerted mechanism. Lewis acid catalysts gave generally low yields of aziridine from (E) -1-phenylpropene with the exception of $SmI_2$ (O-$^t$Bu), which however caused the partial isomerisation of the *trans* aziridine to the *cis* isomer and was not useful with other substrates. Copper $^{(II)}$ acetylacetonate was used as catalyst in the diastereoselective aziridination of homochiral protected *cis* diol **11 (Scheme-8)**. The N-tosyl aziridine **12** obtained was converted to (+) pancrastatin (**13**),[10] which is known to possess antimitotic properties.



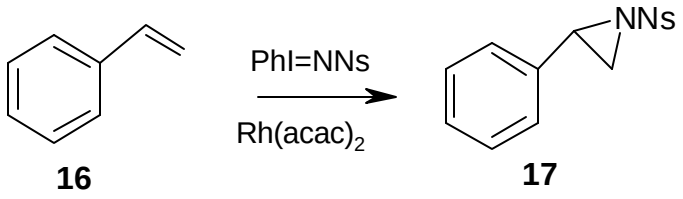

**Scheme-8**

In another approach aziridine 2-carboxylates (**15**) were prepared by reaction of (ethoxycarbonyl) nitrene generated by α-elimination of ethyl N-[(4-nitrobenzenesulfonyl) oxy]carbamate($NsONHCO_2Et$) with **14** using calcium oxide as a base in heterogeneous phase [11] **(Scheme-9)**.




**Scheme-9**

Mueller *et al*.[12] synthesized aziridines using rhodium catalysts and (4-nitrobenzenesulfonyl)iminophenyl iodinane (PhI=NNs) **(Scheme-10)**.



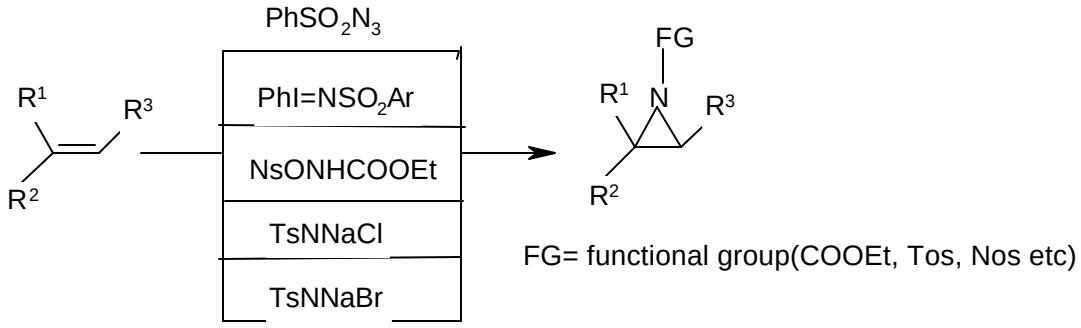

**Scheme-10**

Recently, Chloramine-T (TsNNaCl) has been introduced as a source of nitrogen in the copper (I) catalyzed aziridination of olefins.[13]

**Present Work**

In a preliminary communication[14] the use of Bromamine-T as a superior source of nitrene for the copper (I) or copper (II) catalyzed aziridination of olefins has been demonstrated. Bromamine-T is known in the literature to be a titrant for oxidimetric estimations[15] and oxidation of dimethylsulfoxide[16] but there is no report of its use as a reagent in any organic transformations. In this chapter the details of the aziridination reaction with Bromamine-T as source of nitrogen and further applications of this versatile reagent are presented.

The recent popular approaches to the synthesis of aziridines can be summarized as shown in **Scheme-11**.



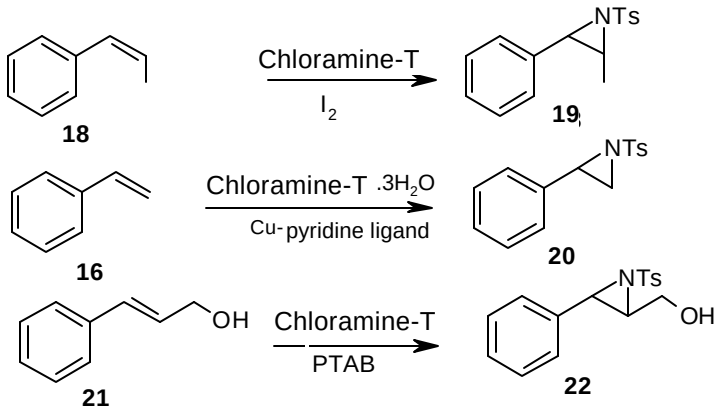

**Scheme-11**

Most of these methods suffer from major drawbacks. The synthesis 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 reagents and moreover their preparation is cumbersome.

Komatsu and co-workers[13] have recently reported copper catalyzed aziridination of olefins with Chloramine-T as source of nitrogen. A range of olefins was subjected to this reaction and aziridines were isolated in low to moderate yields. Aziridination with some substrates was not so facile with Chloramine-T. For example, cyclohexene and 1-decene gave unwanted products probably of allylic amination and 1-decene yielded the corresponding aziridine in only 12 % yield. In view of these limitations, these reactions were investigated with Bromamine-T, **23** as the source of nitrogen.

During this period, three more accounts were published dealing with aziridination of olefins with Chloramine-T **(Scheme-12)**.

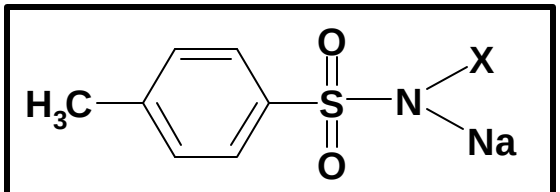



**Scheme-12**

Taylor *et al.*[17] carried out aziridination using hydrated Chloramine-T with a Cu-pyridine ligand, Komatsu *et al.*[18] reported iodine as catalyst for aziridination of olefins, while Sharpless *et al.*[19] used phenyl trimethylammonium tribromide (PTAB) as activator as well as phase transfer catalyst for synthesis of aziridines from olefins with anhydrous Chloramine-T.

**Results and Discussion**

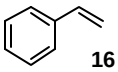
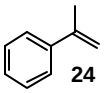
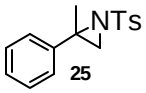
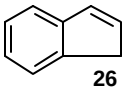
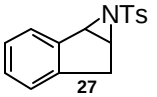
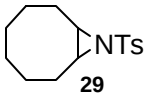
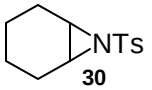
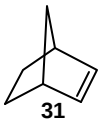
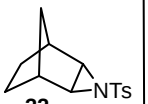
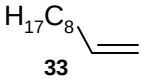
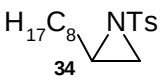
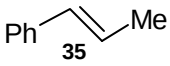
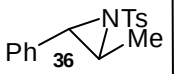
Bromamine-T (**23**) was prepared according to the literature procedure from Chloramine-T (**22**) at room temperature.[20] Preliminary experiments for the comparison of Chloramine-T and Bromamine-T were carried out with CuCl as the catalyst for the aziridination of styrene as substrate. Under identical conditions **23** furnished the aziridine in 48 % yield as compared to that 31 % yield with **22** as the nitrogen source.




**22 X=Cl, Chloramine-T**
**23 X=Br, Bromamine-T**

The aziridine product was characterized by $^1$H NMR, Mass and IR spectra as well as elemental analysis In the $^1$H NMR of N (p-tolylsulfonyl) 2-phenyl aziridine the aziridine protons appeared at δ 4.18 as a doublet of doublet, at δ 3.39 as a doublet and at δ 2.72 as another doublet. The rest of the peaks in the spectrum corresponded to phenyl and tosyl moieties. The structure of the product aziridine was further confirmed by its mass spectrum and elemental analysis. As the results were encouraging, a complete study was carried out and other olefins were subjected to identical reaction conditions **(Table-1)**.

**Table-1: A comparative study of aziridination of olefins using Chloramine-T and Bromamine-T as source of nitrogen.**

| Entry | Substrate | Product | % yield of aziridine [a] | |
|---|---|---|---|---|
| | | | **22** | **23** |
| a |  **16** |  **20** | 31 | 48 |
| b |  **24** |  **25** | 75 | 81 |
| c |  **26** |  **27** | 30 | 45 |
| d |  **28** |  **29** | 38 | 70<br>72[b] |
| e |  **9** |  **30** | <5 | 55 |
| f |  **31** |  **32** | 45 | 73 |
| g |  **33** |  **34** | 12 | 20 |
| h |  **35** |  **36** | 64 | 76 |

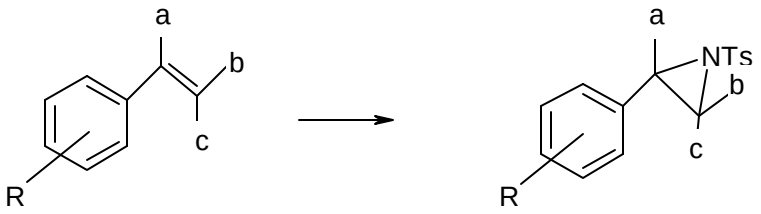
[a] isolated yield [b] with $CuCl_2$

Improvement in the efficiency of aziridination with **23** was more evident in the case of cyclooctene (entry d), where the yield was almost doubled compared to that with **22**. Aziridination of cyclooctene with **23** performed with $CuCl._2$ proceeds with almost the same efficiency as copper (I), because Bromamine-T (**23**) oxidizes cuprous chloride to cupric chloride. The actual catalytic species could be Cu(II) as observed by Evans for aziridination of olefins with PhI=NTs. [9] The yield enhancement could be attributed to the fact that N-Br bond in **23** is much weaker than N-Cl bond.

After establishing this methodology, a detailed study of this reaction with respect to substrate scope, catalyst variation, varied reaction conditions, mechanistic considerations, stereospecific outcome etc was carried out.

**Substrate scope**

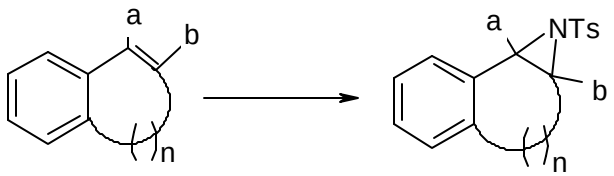
As is evident from **Table 1** the reaction proceeded with a wide variety of substrates. Aromatic, aliphatic and alicyclic olefins all undergo this reaction with ease. Styrene and α,β-substituted styrenes underwent this reaction in a facile manner giving the desired product aziridines in good yields. However it is to be noted that β-nitro styrene did not undergo the reaction even under microwave conditions. So the present system does not work well with electron deficient systems **(Scheme-13)**.




R=H a=b=c=H
a=Me; b=c=H
a=H; b=Me; c=H
a=H; b=$NO_2$; c=H

**Scheme-13**

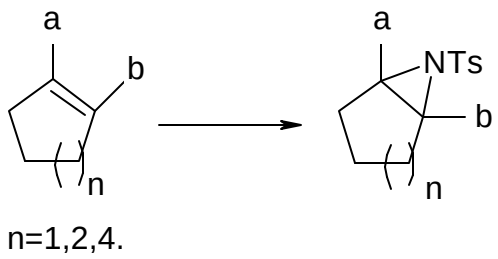
Substrates possessing cyclic systems conjugated with a phenyl ring gave the corresponding aziridines in good yields. For instance, dihydronapthalene and indene produced the desired aziridines at room temperatures and in good yields **(Scheme-14)**.




n=1 a,b=H
n=2 a,b=H

**Scheme-14**

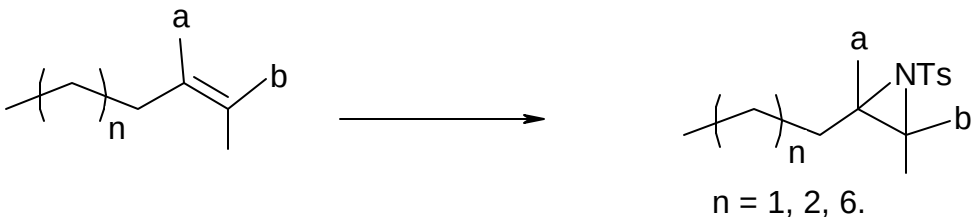
Alicyclic compounds viz. cyclooctene, cyclopentene and cyclohexene gave the desired aziridines even at room temperatures **(Scheme-15)**. These results are to be contrasted with the results from previous methodologies where the major product is due to allylic amination.




n=1,2,4.

**Scheme-15**

Aliphatic linear chain olefins like hexene and 1-decene underwent the reaction to give the aziridines in moderate to good yields **(Scheme-16)**.




n = 1, 2, 6.

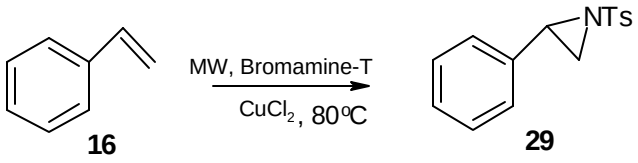
**Scheme-16**

Thus the present methodology encompasses a wide range of substrates.

**Microwave Assisted Aziridination of Olefins**

One of the objectives of the current work was to establish the most suitable metal catalyst and ideal reaction conditions for high yield synthesis of aziridines with **23** as a source of nitrogen. Microwave assisted reactions have gained importance in recent years.[21] They are suitable for a variety of preparative reactions on small to medium scale. These reactions are conducted in a few minutes with complete safety in open vessels at ambient pressure in domestic microwave oven. The strategy is to heat rapidly the reactants with minimal vaporization. When the reaction cannot be

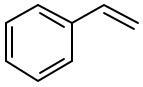
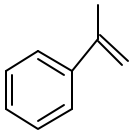
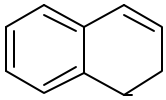
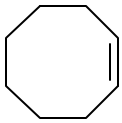
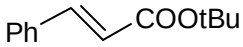
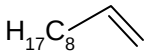
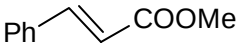
performed neat, a high boiling solvent with high dielectric constant is employed. Microwave irradiation can be used as an efficient source for thermal energy. Performing reactions under this condition leads to faster and cleaner reactions which may be attributed to less thermal decomposition of product and minimization of secondary processes (unwanted side reactions). Many reactions are known in the recent literature where microwave irradiation has given excellent results. Some of the important ones are α-amino β-lactam synthesis,[21] Diels-Alder[22], Claisen rearrangements[22] and Fischer cyclisations.[23] With an objective to enhance the yields and expedite the reaction time, the reactions were performed under microwave irradiation. The reactions were carried out in a small pear shaped flask placed in an appropriate sized beaker. The flask was charged with olefin, Bromamine-T and $CuCl_2$ in few drops of anhydrous acetonitrile. The whole system was irradiated for 12 minutes, the flask was then cooled to room temperature and workup done in the usual manner to give aziridines **(Scheme-17)**.




**Scheme-17**

This is probably the first report of microwave assisted aziridination of olefins. Standard reaction of styrene with **23** and $CuCl_2$ as catalyst led to a marked improvement in the yield (**Table-2**).

**Table-2: A comparative study of room temperature and microwave assisted aziridination reactions with 23.**

| Entry | Substrate | % yield of aziridine [a] RT | MW[b] |
|---|---|---|---|
| a |  | 48 | 70 |
| b |  | 81 | 88 |
| c |  | 60 | 70 |
| d |  | 70 | 81 |
| e |  | NR | 36 |
| f |  | 20 | 80 |
| g |  | NR | 38[c] |

[a] isolated yield [b] irradiated for 12 minutes [c] with $CuBr_2$

It is interesting to note that there was no aziridination with less reactive substrates such as cinnamates with **22** as well as with **23** in presence of $CuCl_2$ and $CuBr_2$ at room temperature. However the reaction proceeded under microwave irradiation with $CuBr_2$ to yield the aziridine, albeit in moderate yields.

**Catalyst Variation**

One of the objectives of the current work was to establish the most suitable catalyst for the aziridination of olefins with **23** as source of nitrogen**.** With this view, styrene was subjected to aziridination with **23** under the catalysis of different metal salts under microwave irradiation (**Table-3**).

**Table-3: Catalyst variation**

| Entry | Metal halide[a] | % Yield[b] |
|---|---|---|
| (a) | $CuCl_2$ | 70 |
| (b) | $NiCl_2$ | 60 |
| (c) | $CoCl_2$ | 56 |
| (d) | $FeCl_3$ | 63 |
| (e) | $MgCl_2$ | 57 |
| (f) | $MnCl_3$ | 54 |
| (g) | $SrCl_2$ | 40 |
| (h) | $CuBr_2$ | 88 |
| (i) | $Rh_2(OAc)_4$ | 30 |
| (j) | No catalyst | No reaction |

*[a]A mixture of the catalyst (5 mol %) , Bromamine-T (1 eq.) , styrene (5 eq.) in acetonitrile was exposed under microwave for 12 min. [b]Isolated yield*

It is evident from this study that the halides of copper (entries a and h) are ideal candidates as catalyst for this reaction.

**Ultrasound mediated aziridination**

Reactions characteristic of ultrasound irradiation have been named sonochemical transformations and have become topical in recent years with applicability across the breadth of chemistry from polymer science to chemical physics.[24a] The use of ultrasound in chemistry is not a new topic. However the subject is gaining importance due to current wide availability of laboratory ultrasonic equipments in the form of cleaning baths and ultrasonic bath.

It will be appropriate here to have a brief introduction to this technique.[24b] Ultrasound is the name given to sound waves having frequencies higher than those which human ear can respond to (i.e. >16 kHz). The upper limit is usually 5 MHz for gases and 500 MHz for liquids and solids. The types of ultrasound which are used in chemistry can be broadly categorized into power ultrasound, between 20 and 100 kHz, and high frequency ultrasound, in 2-10 MHz range. Majority of synthetic chemists are interested in power ultrasound because it provides a form of energy for the modification of chemical reactivity which is different from that normally used i.e., heat, light and pressure. Power ultrasound produces its effects *via* cavitation bubbles, which are generated during the process. The synthetic chemist is mainly concerned with the effect of ultrasound on reactions in solutions. This can be studied under four headings:

a) Reactions involving metal surfaces
b) Reactions involving powder or other particulate matter
c) Emulsion reaction
d) Homogeneous reactions

In the current work, only the first type of effect was of interest. Hence, a description of other types is not given here. There are two types of ultrasound mediated reactions involving metals

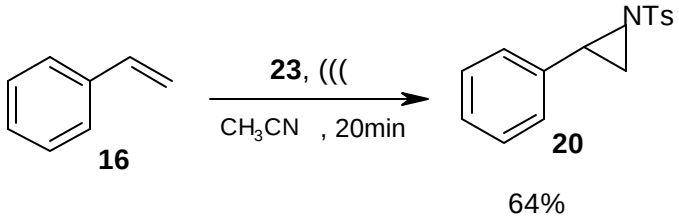
(i) those in which metal is a reagent and is consumed in the process and
(ii) those in which the metal functions as a catalyst.

In the latter case the sonication serves a simple purpose- it exposes clean or reactive surface to the reagents involved and to increase the effective surface area available for reaction. In many cases however it is found that cleaning effect alone is not sufficient to explain extent of sonochemically enhanced reactivity. In such cases it is conjectured that sonication serves to sweep reactive intermediates, or products, clear of the metal surface. This presents renewed clean surface for reaction which would not be possible by means of normal mechanical agitation.

To sum up ultrasound has a wide range of applications and the organic chemist can achieve one or more of the following benefits:

1) To accelerate a reaction or permit use of less forcing conditions.
2) To reduce the number of steps which are required using normal methodology.
3) To make use of cruder reagents.
4) To initiate reactions, often without the need of additives.
5) To reduce any induction period involved.
6) To drive a reaction through alternate pathway.

Sonication induces a specific chemical reactivity although the detailed mechanism of the sonochemical excitation is still unclear. To study the effect of sonication on aziridination and to compare the results with those of room temperature reactions, the standard reaction of styrene with **23** under ultrasound irradiation was performed. There was a considerable enhancement in yields coupled with short reaction times **(Scheme-18)**.

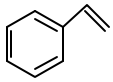
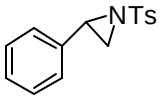
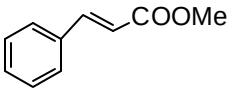
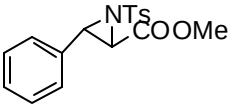
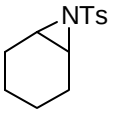
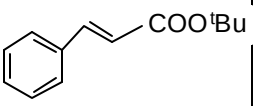
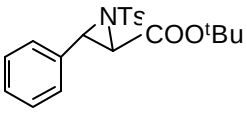



**Scheme-18**

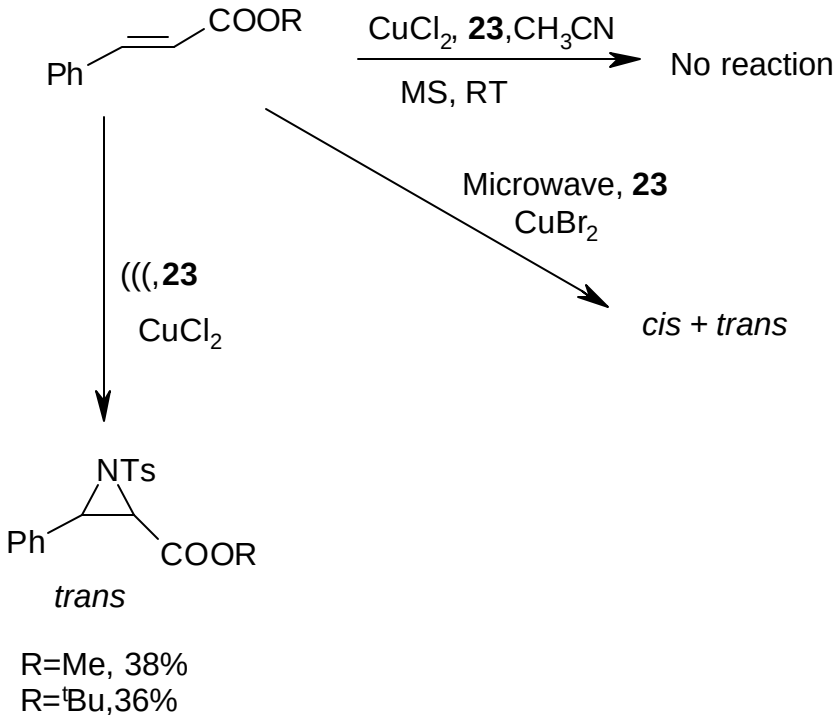
In the case of cinnamates (entries b and d) it was observed that ultrasound has changed the product distribution. Under stirring and refluxing alone no aziridine products were obtained and under

microwave irradiation, a *cis-trans* mixture was obtained. In contrast sonication has changed the stereochemical course of the reaction and given only the *trans* isomer. An in-depth analysis of the activation mechanism needs to be carried out in order to explain the different product distribution of the two processes.

**Table-4: Ultrasound mediated aziridination reactions**

| ENTRY | SUBSTRATE | PRODUCT | YIELD | |
|---|---|---|---|---|
| | | | RT | ((( |
| a. |  **16** |  **20** | 48 | 64 |
| b |  **39** |  **40** | NR | 34 (trans) |
| c |  **9** |  **30** | 48 | 58 |
| d |  **38** |  **41** | NR | 36 (trans) |

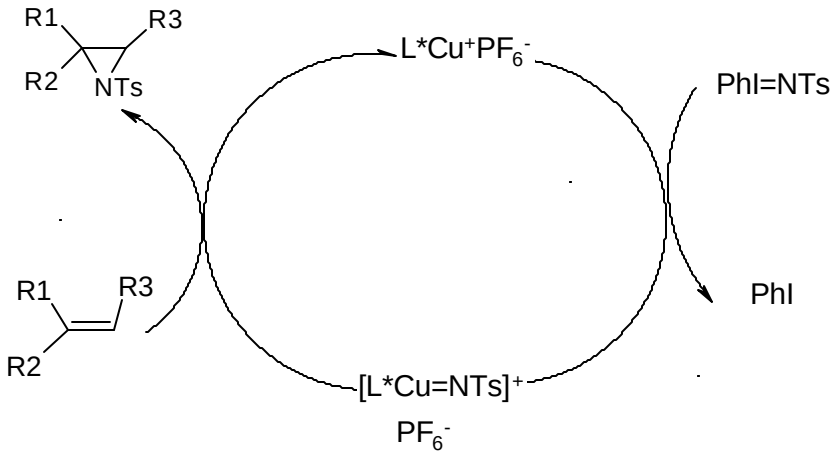
This is beyond the scope of this work, however it will be worth mentioning here that the process of cavitation in ultrasound is probably producing a structural change in the catalytic sites **(Scheme-19)**.




**Scheme-19**

**Mechanistic considerations in the aziridination reactions**

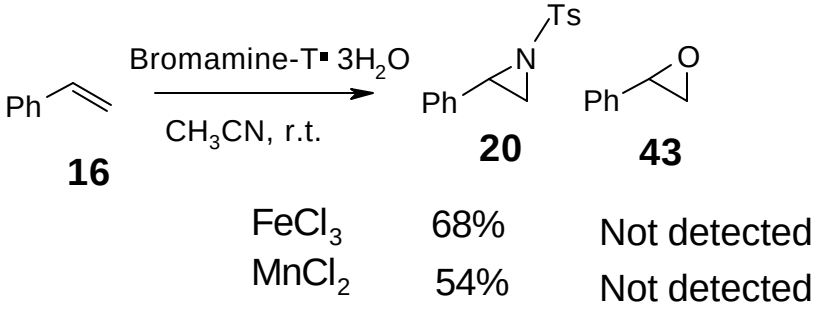
After optimizing the reaction conditions, ascertaining the mechanism of this conversion was the next logical step. By analogy with a well-established mechanism of metal catalyzed cyclopropanation of olefins, there is a probability of transfer of nitrene generated from **22** or **23** in presence of Cu catalyst via Cu nitrenoid intermediate. Experimental evidence for this possibility was given by Jacobsen *et al*[25] in their work on the asymmetric aziridination with PhI=NTs as nitrene precursor as shown in **Scheme-20.**




**Scheme-20**

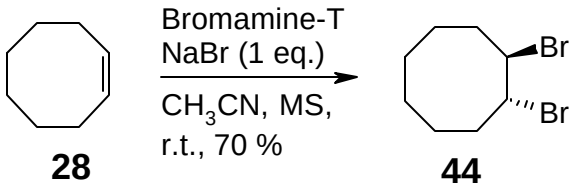
Komatsu and co-workers[18] employed iodine to initiate the reaction and suggested the formation of a cyclic iodonium intermediate, followed by nucleophilic addition of nitrogen part to give aziridine. Sharplesset al [19] performed the same reaction with PTAB (phenyl triethyl ammonium tribromide), a phase transfer catalyst which supplies bromonium ion to catalyze the reaction in more or less the same fashion. Alternatively the Cu catalyzed aziridination of olefins could follow a Lewis acid mechanism. Support for this consideration is available in the literature in the form of examples of epoxidation and aziridination with PhI=NTs catalyzed by simple Lewis acids.[9]

Taylor and co-workers [26] have investigated whether Chloramine-T can be a nitrene transfer agent in sulfimidation reactions. In a later publication they proposed the mechanism of reported Cu catalyzed aziridination and amination of alkenes with hydrated Chloramine-T.[17] Aziridination of styrene with commercial Chloramine-T did not give epoxide even in the absence of molecular sieves suggesting a possible Cu nitrenoid mechanism. On similar lines the reaction of styrene with Bromamine-T hydrate in presence of $CuCl_2$ as catalyst without any molecular sieves was carried out. Although aziridine **20** was isolated, no styrene oxide (**43**) could be detected in the reaction mixture lending support to the Cu-nitrenoid mechanism **(Scheme-21)**.



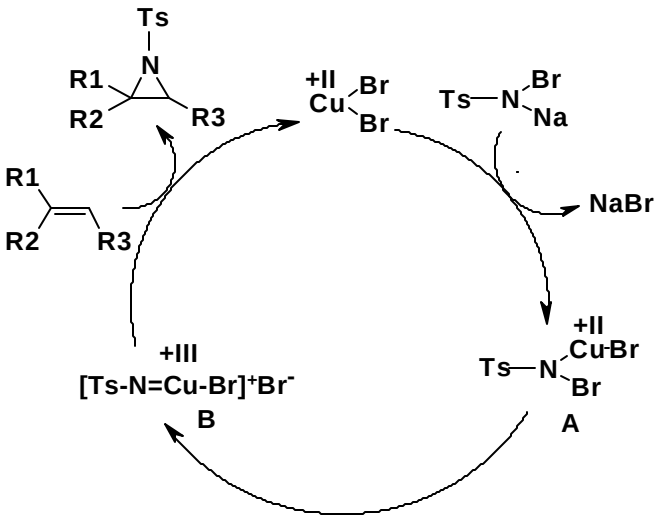

**Scheme-21**

In another experiment, aziridination of **28** with CuCl and $CuCl_2$ proceeded in good yield, with one equivalent of NaBr and without Cu catalyst, *trans*-1, 2-dibromocyclooctane (**44**) was obtained as the sole product **(Scheme-22)**.




**Scheme-22**

It was therefore concurred that Bromamine-T here served as the source of bromonium ion in the absence of copper halide. On the basis of the above experiments it was concluded that the reaction mechanism involved a Cu nitrenoid species similar to generally accepted copper carbenoid intermediate for cyclopropanation. A probable mechanistic pathway was proposed. Initially Bromamine-T, (**23**) reacts with copper halide giving intermediate **A** with elimination of sodium bromide. The intermediate **A** gives **B,** which is similar to the one suggested by Jacobsen in the redox mechanism, having a discrete Cu (III) nitrene reactive species capable of transferring the nitrogen center to alkene to give aziridine **(Scheme -23)**.




**Scheme -23**

To verify the mechanism further, *trans* β-methyl styrene (**35**) was subjected to aziridination under the usual room temperature conditions with $CuCl_2$ as catalyst. The formation of the corresponding *trans* aziridine **36** selectively was observed as confirmed by an analysis of its $^1H$ NMR spectrum which showed a doublet at δ 7.83 corresponding to two aromatic protons and a multiplet at δ 7.1 of seven aromatic protons, a doublet at δ 3.79 of one CH aziridine proton and a doublet of quartet at δ 2.9 corresponding to another CH aziridine proton along with peaks at δ 2.4 for methyl protons of the tosyl group and at δ 1.85 for three methyl protons of methyl styrene confirming the *trans* product, the exclusive formation of which was in agreement with the proposed redox mechanism.

**Bleaching Powder Assisted Aziridination of Olefins**

Recently three independent groups led by Komatsu[18], Sharpless[19] and Sudalai [27]reported aziridination of olefins catalyzed by iodine, phenyltrimetyl ammonium tribromide (PTAB) and pyridinium hydrobromide perbromide respectively. All the three reactions proceeded with **22** *via* an ionic mechanism. In the present work application of a cheap and commercially available inexpensive reagent for aziridination of olefins is described.[28] Calcium hypochlorite commonly

known as bleaching powder was used to initiate aziridination of olefins. It is an industrially useful reagent, well known for its algicidal, bactericidal, deodorizing, disinfecting, oxidizing, sugar refining and bleaching properties.[29] Bleaching powder is known in the literature to be a source of positive chlorine and is generally used for the oxidation of secondary ketones and for oxidation of aliphatic aldehydes to the corresponding acids. The reagent is also effective for oxidative cleavage of α-glycols to aldehydes, α-hydroxy ketones to aldehydes and carboxylic acids and α-diketones to acids.[30] Preliminary experiments with both Bromamine-T and Chloramine-T as nitrogen source gave good yields under mild reaction conditions with 10 mole % of bleaching powder. This methodology obviates the need for a metal catalyst for aziridination of olefins. Several substrates were screened under similar conditions and it can be seen from **Table-5** that the yields are comparable to those where metal catalysts are employed.

**Table-5: Bleaching Powder assisted aziridination of olefins**

| Entry | Substrate | Mole Ratio(%) | Yield(%) [a] |
|---|---|---|---|
| 1 | Styrene | 10 mol | 59 |
| 2 | Styrene | 20 mol | 68 |
| 3 | Cyclooctene | 20 mol | 73 |
| 4 | 1-Decene | 20 mol | 28 |
| 5 | 1,2-Dihydronaphthalene | 20 mol | 80 |

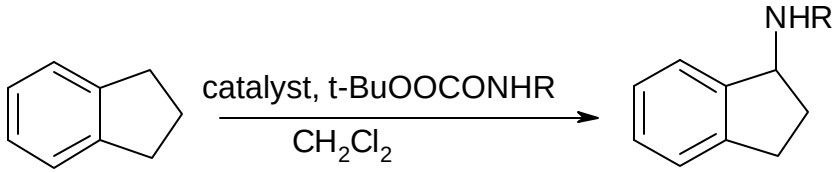
[a] Isolated yields

The mechanism operating here is an ionic one. The reaction is believed to proceed through the intermediacy of a chloronium ion in the catalytic cycle. The products were characterized by their IR, NMR and mass spectra. The yield of dihydronapthalene aziridine is very good (entry 5) compared to previous methodology using metal catalysis. The structure of the dihydronapthalene aziridine (**37**) was confirmed by its $^1$H NMR, in which a doublet for two protons appeared at δ 7.85 and a multiplet of six protons at δ 7.25, corresponding to the aromatic region. A doublet of one proton appeared at δ 3.55 and another at δ 3.8, a doublet of a triplet appears at δ 2.7. A doublet of

doublet at δ 2.6, a singlet for three protons at δ 2.49 corresponding to methyl of the tosyl group, a doublet of doublet at δ 3.32 corresponding to one proton and a doublet of triplet at δ 1.71 confirmed the structure. The structure was further confirmed by its mass spectrum, which showed molecular ion peak at m/z 299.

**Benzylic Amination of Olefins**

Substitution of benzyl halides or alcohol derivatives by an amine or its equivalent is the general method for the preparation of benzylic amines.[31] Till recently there were a few reports of direct amination of olefins. Insertion products were often obtained upon aziridination of olefins with TsN=IPh under catalysis with $Mn^{III}$ or less efficiently with $Fe^{III}$ porphyrinates.[32] Cyclohexane and admantane (at bridge head) were aminated with PhI=NTs in 15 and 56 % yields respectively in the presence of {Mn (tdcpp) (tdcpp=tetrakis(2,6-dichlorophenyl) porphyrinato}. A radical mechanism initiated by hydrogen abstraction by a high valent Mn-nitrene intermediate was proposed for the Mn catalyzed insertions.[33] However catalytic amidation has not been used for synthetic applications. The $Rh_2(OAc)_4$ catalyzed decomposition of NsN=IPh resulted in formal insertion into CH bonds, activated by phenyl or vinyl groups, or by O-substituents [34] in presence of 20 fold excess of the substrate. Katsuki *et al.* [35] directly introduced a N- (p-toluenesulfonyl) amino group at benzylic or allylic carbon by treating alkenes with t-butyl N- (p-toluensulfonyl) peroxycarbamate in the presence of Cu(II) triflate (**Scheme-24)**.



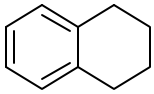
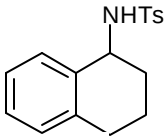
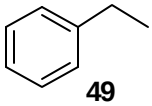
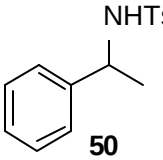
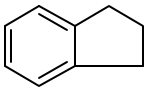
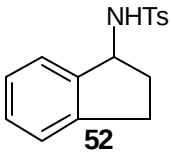

**45** **46**

**Scheme-24**

However in the above reaction with indane (**45**), p-toluene sulfonamide was obtained as the major side product with a trace amount of 1-(t-butoxy) indane and **46** was obtained as a minor product after stirring the alkene and the reagent in the presence of copper triflate for 60 hours. Recently Sharpless and Taylor have reported benzylic and allylic aminations with Chloramine-T. In

our continuing efforts towards application of Bromamine-T towards such reactions, benzylic amination reaction was studied. The results obtained are good and are presented in **Table-6.**

**Table-6: Rhodium catalyzed benzylic amination of olefins**

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| a |  **47** |  **48** | 70 |
| b |  **49** |  **50** | 60 |
| c |  **51** |  **52** | 33 |

Tetralin (**47**) was subjected to benzylic amination with **23** in presence of catalytic amount of $Rh_2(OAc)_4$. The expected insertion product was obtained albeit in low yields. Subjecting the same reaction under ultrasound conditions resulted in enhanced yields of the desired product. Reaction of cyclohexene with this catalyst gave a mixture of aziridine and allylic amine. The reactions were run in acetonitrile at room temperature under ultrasound conditions in the presence of **23** and 2.5 mole % of [$Rh_2(OAc)_4$]. Insertion into benzylic groups occurred in 70, 33 and 60 % for tetralin, indane and ethyl benzene respectively. Toluene and isopropyl benzene were inert under these conditions.

Here a mechanism involving direct insertion by a Rh-complexed nitrene into the CH bond is proposed. The successful benzylic amination with Bromamine-T in the presence of $Rh_2(OAc)_4$ has opened up several possibilities. This can be a practical approach towards preparation of benzylic

amines, in particular the chiral amines. An enantioselective version of the reaction is envisaged using chiral ligands.

**Conclusions**

Aziridination of olefins is demonstrated for the first time with Bromamine-T as the nitrene source. This reagent has so far been used only for oxidimetric titration and estimations. The reagent can be easily prepared from Chloramine-T at room temperature. The superiority of Bromamine-T over Chloramine-T in the aziridination of olefins has been demonstrated. (Cited in ***Methods in Organic Synthesis)***. The reagent works well with both CuCl and $CuCl_2$, unlike Chloramine-T which works only with CuCl which is unstable and has to be freshly prepared each time There is an appreciable increase in yields in all cases and a drastic increase in case of cyclohexene. For the first time microwave and ultrasound assisted aziridinations are reported. The reaction has a wide scope-.aromatic alkenes, aliphatic, cyclic and linear chain alkenes undergo this reaction. Less reactive substrates viz. methyl cinnamate and t-butyl cinnamate gave aziridines under microwave and ultrasound conditions. A cheap and readily available reagent bleaching powder catalyzes the reaction efficiently at ambient temperatures. Due to the wide scope offered by this method , an Indian Patent has been filed.**(Indian Patent** No. NF 33, 2000). The aziridination methodology has been successfully extended to benzylic amination with good yields. Results of rhodium catalyzed benzylic amination in presence of Bromamine-T have opened up avenues in chiral amine chemistry. Finally it can be inferred that the present methodology has vast potential and the new nitrene precursor will most likely find use in other reactions that utilize the same type of reagents, viz. imidation of sulfides, aminohydroxylation of olefins and amination of allylsilanes.

## Section- B

## Bromamine-T Mediated Aziridination of Olefins With a New Polymer Supported Manganese (II) Complex as Catalyst

### Introduction

Polymer-supported metal complexes have found an important place in synthetic organic chemistry . The breadth of synthetic chemistry applied to solid phase synthesis has widened owing to the emergence of combinatorial chemistry in pharmaceutical and agrochemical research. This is evidenced from the current interest in the synthesis of drug like compounds for drug discovery programmes such as hydroxamic acids, polyamines, biotinylated probes, pepetidomimetics and benzodiazepines.[36] Compared to analogous homogeneous reaction systems, polymer supported reactions show substrate selectivity, are slower or faster, follow a different reaction course or give a significantly different stereochemical result. Pioneering work in this field was done by Merrifield[37] on 'solid phase' peptide synthesis, which induced the study of a wide range of synthetic organic reactions. These reactions exhibit well-documented advantages over the homogeneous systems.[38] They are found to be very attractive because not every site needs to react, low loadings are often acceptable, they do not contaminate the product solution, they are odorless, amenable to large scale synthesis, are non-toxic and the crosslinked polymeric species is often available for immediate reuse.[39] The major differences between reactions on polymer supports and their low molecular mass analogues, from a synthetic chemist's point of view, can be grouped loosely into three main types of effects.

1) Effects resulting from the need for the soluble reactants to gain access to the supported reactants.
2) Microenvironmental effects, and
3) Site-site interactions.

Although a detailed discussion of each effect is beyond the scope of this work, a brief idea about each will be useful for a clear understanding of the concept of polymer supported reactions.

**Access of soluble reactants to supported reactants**

The supports which have been used extensively for polymer supported synthesis are microporous beads crosslinked at 1 or 2 position of divinylbenzene, which allow the easy detachment of the products when required. For reactive species in solution to gain access to the reactive sites in beads, these beads must be swollen by the reaction solvent. The reactions in the swollen beads take place in a gel phase and are not as commonly described 'solid phase'.

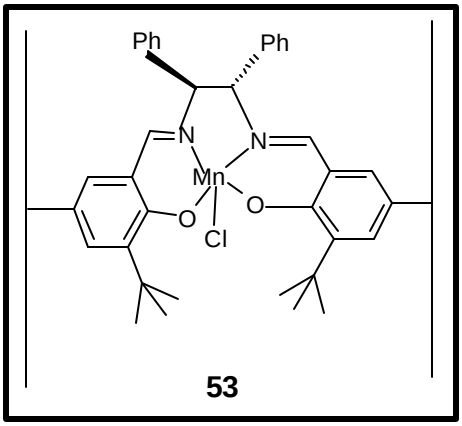
**Microenvironmental effects**

The microenvironment in a bead may alter the concentration of low molecular mass reactants present relative to those in the solution. The microenvironment in the vicinity of the polymer backbone can be expected to be sterically crowded. This is the reason why chlorination of polymer containing residues occurs mainly at the side position rather than the backbone position. This reaction forms convenient route for the preparation of chloromethylated polystyrene.[40] In general steric effects will be greatest when a reactive functional group is directly attached to the polymer backbone by 'spacer groups' but as the functional groups are separated from the backbone by 'spacer groups', steric effects will disappear quickly and functional groups accessibility and mobility increases. Most polymer-supported reactants are prepared from polystyrene and here the benzene ring itself acts as a small rigid spacer group.

**Site-site interactions**

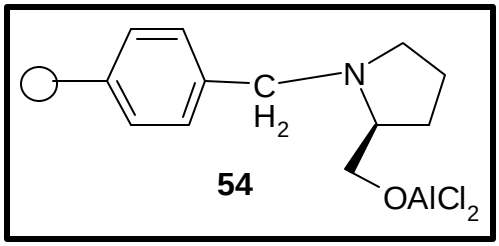
The ease with which the polymer supported reactive groups can react together has long been a topic of debate. In most of the polymer-supported systems studied the overall concentration of the reactive groups in the beads is reasonably high. Site-site interactions are possible between a large fraction of the reactive sites on both highly crosslinked polystyrene beads and macroporous polystyrene beads. While crosslinking will reduce mobility it will have to be very extensive to

achieve permanent site isolation. Some of the general organic syntheses using polymer-supported catalysts are illustrated in this section. Chiral (salen) Mn(II) complexes are useful compounds for organic synthesis,[41] consequently several researchers have investigated the immobilization of these catalysts on polymer supports. Sivaram et al[42] have reported the preparation and application of a polymer supported chiral (salen) Mn(II) complex (**53**).



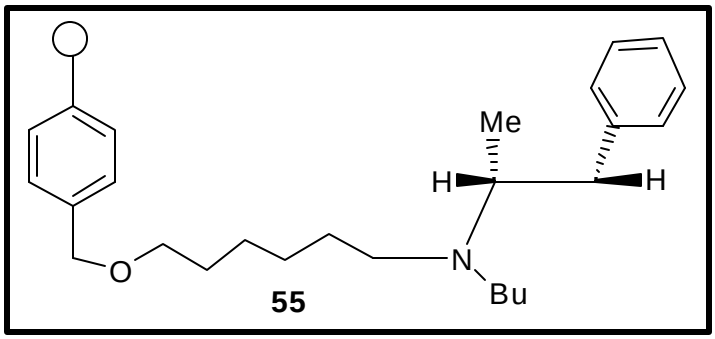

**53**

However the enantioselectivities obtained were low. Diels-Alder reactions[43] have been studied using polymer bound amino alcohols complexed to aluminum and titanium (**54)**. These catalysts displayed superior activity to their homogeneous counterparts**.**



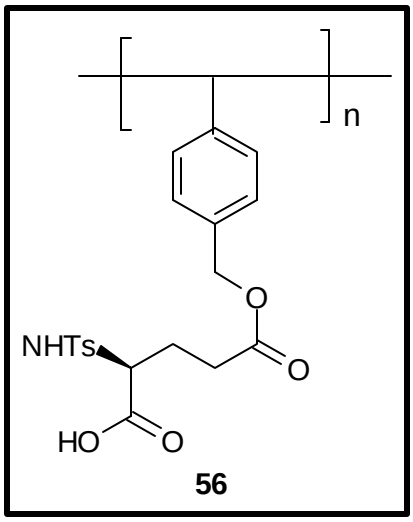

**54**

Soai *et al.*[44] have reported the immobilization of N-butylnorephedrine onto polystyrene **(55)** for use as a catalyst in enantioselective addition of diethyl zinc to aldehydes producing secondary alcohols in high yields and ee's.




**55**

Chiral borane complex **56** has been used by Kiyookas[45] as a catalyst for aldol reaction involving benzaldehyde and silyl ketene acetals. The aldol product was obtained in high ee (90 %) but low chemical yield (28 %).




**56**

**Present Work**

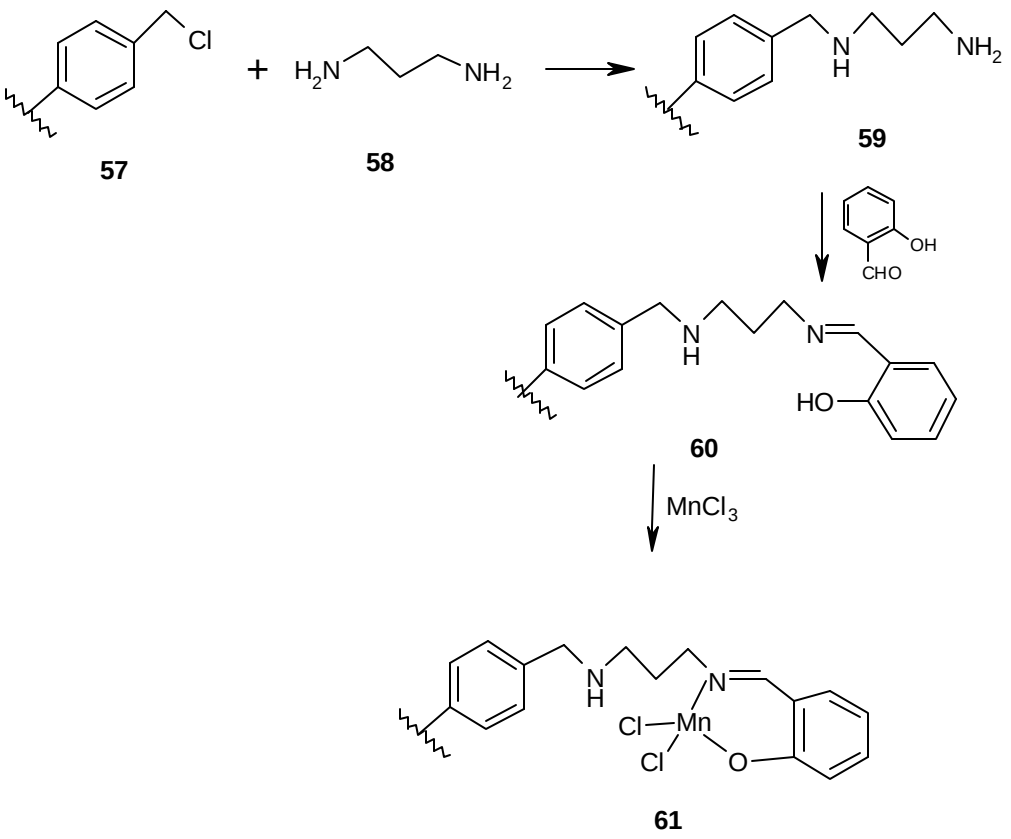
Synthesis of aziridines is a subject of intensive research over the last few years. The most atom efficient method of preparation of aziridines lies in the direct aziridination of olefins with suitable nitrenes.[46] In the previous section the use of Bromamine-T, **23** (TsNNaBr) as a superior source of nitrogen in the copper catalyzed aziridination of different olefins has been demonstrated. The present study deals with the preparation of chelated manganese metal complexes on a polymer

support and investigations of their catalytic behavior in the aziridination of olefins with Bromamine-T. The synthesis of the catalyst and its application to the aziridination reaction are described.

**Synthesis of the Polymer Supported Catalyst**

The first step in the synthesis of the catalyst is the introduction of the amine onto the polymer support. As mentioned in the introduction the most common polymer supports are crosslinked polydivinyl benzenes. Chloromethylated PS-DVB of 8 % cross-link (**57**) was chosen as the support, it was washed with water, water-ethanol mixture (1:1) and finally with ethanol. Any adsorbed material was removed by extracting the polymer in a soxhlet using ethanol-benzene mixture for 10 h. Chlorine content of the polymer beads was estimated using standard method and found to be 17.5 %. The chloromethylated PS-DVB was kept in contact with NaI in acetone-dioxane mixture for 4 days. It was purified by soxhlet extraction using acetone as solvent and dried at 60-70 °C for 8 h. The polymer beads thus processed were refluxed with n-propyl diamine in THF (2 %) for 2 days and finally it was filtered and washed with THF. The loading of n-propyl diamine on the polymer was confirmed by the estimation of nitrogen.

The second step in the catalyst synthesis includes attachment of the metal ion to the polymer-anchored ligand. In a round bottom flask 10.0 g of polymer anchored diamine was taken in ethanol (60 mL) and left for about 30 min. To this mixture ethanolic solution of $MnCl_2 \cdot 4H_2O$ (0.25 % 100 mL) was added via an addition funnel over 30 min. The reaction was continued for seven days at ambient temperature after which the beads of polymer acquired light pink colour indicating the formation of metal complex on the surface of the polymeric material **(Scheme-25)**.

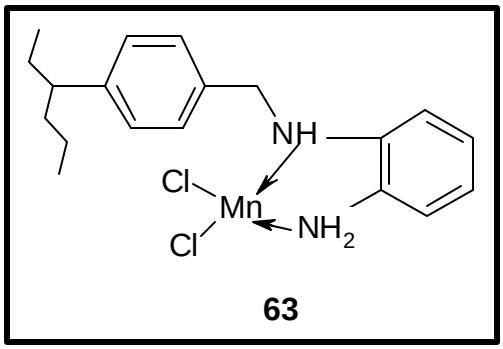



**57** **58** **59** **60** **61**

.

**Scheme -25**

Preliminary experiments were carried out with styrene as the substrate and 10 % of the catalyst (**61**) in acetonitrile at room temperature. The reaction proceeded smoothly to give the desired aziridine as the sole product. However when the recovered catalyst was recycled and reused there was no reaction. Apparently there was some leaching of the metal ion. It was felt that since the Mn-O bond is weak, the metal leaches out of the system after work up in the second catalytic cycle. To prevent leaching an efficient heterogeneous system was designed, where Mn is coordinated to two nitrogen atoms in close vicinity. Towards this end the catalyst **63** was synthesized.




**63**

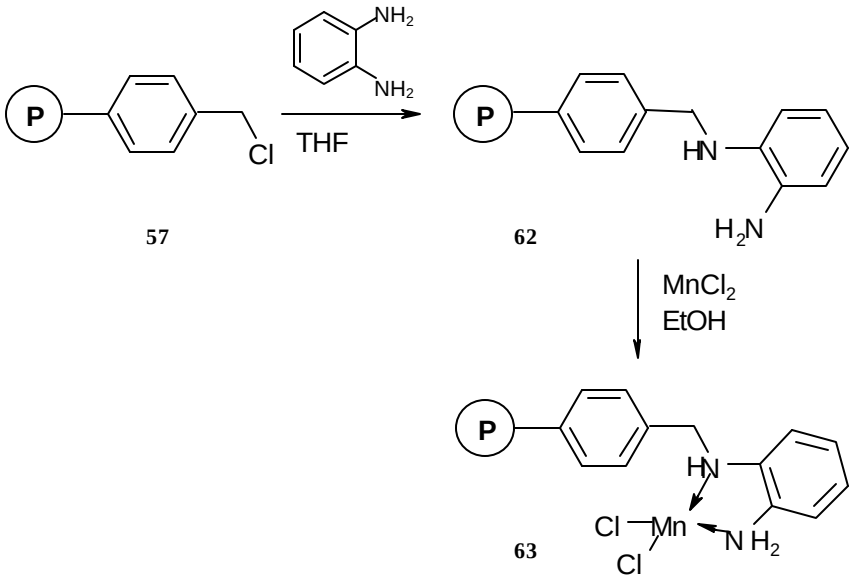
Here the metal-heteroatom bond is present in a five membered ring system unlike the previous catalyst where the metal heteroatom bonds were part of a six membered ring system.

The catalyst **63** was synthesized by a similar type of procedure as previous one, using the same polymer support. Chloromethylated PS-DVB of 8 % cross-link was washed with water, water-ethanol mixture (1:1) and finally with ethanol. Any adsorbed material was removed by extracting the polymer in a soxhlet using ethanol-benzene mixture for 10 h. Chlorine content of the polymer beads was estimated using standard method and found to be 17.5 %. The chloromethylated PS-DVB was kept in contact with NaI in acetone-dioxane mixture for 4 days. It was purified by soxhlet extraction using acetone as solvent and dried at 60-70 °C for 8 h. The polymer beads thus processed were refluxed with *o*-phenylene diamine in THF (2 %) for 2 days and finally it was filtered and washed with THF. The loading of *o*-phenylene diamine on the polymer was confirmed by the presence of N, which was found to be 3.32 %.

**Attachment of metal ion on to the polymer anchored ligand**

In a round bottom flask 10 g of polymer anchored diamine **62** was taken in ethanol (60 ml) and left for about 30 min. To this mixture ethanolic solution of $MnCl_2.4H_2O$ (0.25 %; 100 ml) was added *via* an addition funnel over 30 min. The reaction was continued for seven days at ambient temperature after which the beads of polymer **63** acquired light pink colour indicating the formation of metal complex on the surface of the polymeric material. In order to estimate the metal content 99 mg of the catalyst **63** was treated with 1:1 HCl for thrice for the total extraction of the metal ions

and determined by the atomic absorption spectroscopy. The quantity of Mn present was found to be 2.73 X $10^{-2}$ %g **(Scheme-26)**.




**Scheme-26**

**Characterization of the Catalyst**

Elemental analyses at different stages of preparation of catalyst are given in **Table-7.** Elemental analysis and metal estimation of the catalyst indicate a low level of anchoring of the metal ion on to the aminated polymer. This might be due to the lack of access of ligands to the metal ions. Similar observations were made by workers while loading ruthenium, palladium and rhodium on styrene-DVB cross linked polymer.[47]

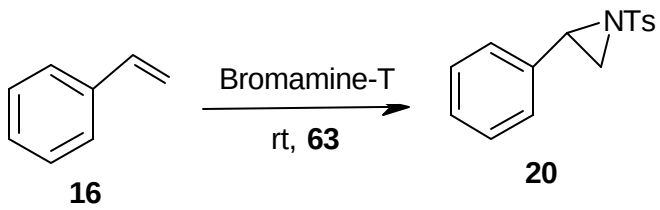
**Table-7**: **Elemental analysis at different stages of polymer catalyst preparation.**

| Polym. **57** | | | Polym. **62** | | | | Polym. **63** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 72.95 | 5.93 | 17.50 | 54.27 | 4.85 | 3.45 | 11.18 | 61.76 | 5.69 | 2.98 | 10.47 |
| % C | % H | % Cl | % C | % H | % N | % Cl | % C | % H | % N | % Cl |

However, anchoring of the metal complex on to the polymer was confirmed by comparative spectral studies of polymer bound complex. The various IR frequencies assigned for N-H, metal-N and $CH_2$-Cl groups are 3438, 532 and 1699 $cm^{-1}$ respectively. ESR was recorded in the granular form on ESR, Bruker EMX instrument. The main peak at 3440 G was due to C˙ radical while other small signals with g value 2 was due to $Mn^{++}$ species which indicated that Mn is present in +2 oxidation state. In DTA-TG analysis, it was found that polymer degradation starts above 125 °C. A weight loss of about 5 % below this temperature may be due to moisture content. Hence it was ensured that the polymer-anchored catalyst may be used in catalytic studies below 125 °C. The surface area of the support **57** was found to be 37.37 $m^2/g$ while that of the catalyst **63** was 24.00 $m^2/g$. The decrease in the surface area observed after loading the metal ions on to the polymer support might be due to blocking of pores of the polymer support after introducing the ligand and the metal ions and was in accordance with previous observations.

**Results and discussion**

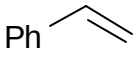
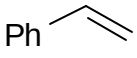
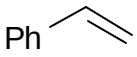
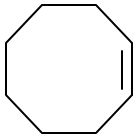
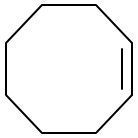
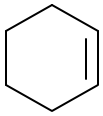
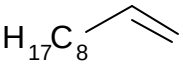
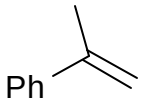
Several methods are reported for the direct aziridination of olefins with a variety of reagents used as source of the nitrogen component. Recently {*N*- (arenesulfonyl) imino}-phenyliodinanes have been widely used for the aziridination of olefins. However, their preparation is difficult and gives iodobenzene as a byproduct in the reaction. Recently few groups have reported **22** as an alternative source of nitrogen for this transformation. For the first time **23** was used for this purpose and found to be superior in this reaction. The polymer-anchored Mn-complex was now screened as heterogeneous catalyst for the aziridination of olefins with **23** as the source of nitrogen. A standard reaction was run with styrene as the test substrate. The aziridine was isolated in 42 % yield after the reaction was left stirring for 15 h at ambient temperature **(Scheme-27)**.




**Scheme-27**

The catalyst was physically separated and recycled for twice with very little loss of activity indicating its reusability. There was no leaching of the metal into the solution. A variety of olefins were successfully examined for this useful transformation and the results are presented in **Table 8.**

**Table 8: Catalytic aziridination of olefins using polymer supported catalyst**

| Entry | Olefin | % Yield[a] of the Aziridine |
|---|---|---|
| a. |  | 42 (1st cycle) |
| b. |  | 39 (2nd cycle) |
| c. |  | 38 (3rd cycle) |
| d. |  | 70 (1st cycle) |
| e. |  | 67 (2nd cycle) |
| f. |  | 28 |
| g. |  | 60 |
| h |  | 73 |

[a]*Isolated yield. The aziridines were characterized by usual spectral analyses.*

Catalytic aziridination of nitrene source with cyclohexene has been a peculiar case due to the formation of undesired insertion products. However, in this procedure, required aziridine of

cyclohexene was isolated, albeit in moderate yields (entry f). The structure of the cyclohexene aziridine product was confirmed by its $^1$H NMR spectrum which showed a doublet at δ 7.81 corresponding to two aromatic protons and another doublet at δ 7.40 corresponding to the other two aromatic protons of the tosyl group a typical $A_2B_2$ pattern, a triplet of three protons at δ 3.10 corresponding to CH aziridine protons, a singlet of three protons at δ 2.49 which could be assigned to the aromatic methyl of the tosyl group and finally two multiplets of four protons each at δ 1.81 and δ 1.5 respectively corresponding to the ring CH protons. There was absence of any allylic insertion products which are generally obtained with other Mn based homogenous systems. This catalyst has worked better than Mn based homogeneous system investigated for {*N*-(*p*-tolylsulfonyl)imino}phenyliodinane by Evans.[48] (The catalyst was synthesized at Department of Chemistry, Faculty of Science, MS University of Baroda, Baroda. It was subsequently characterized by Catalysis Division at National Chemical Laboratory, Pune.)

**Conclusion**

A novel polymer supported manganese complex has been synthesized and successfully applied to aziridination reaction with Bromamine-T in good yields. The catalyst can be recovered after a simple work up and was used three times without loss in activity. The complex can be prepared by simple synthetic manipulations from commercially available chloromethylated resin. Catalytic aziridination of cyclohexene generally gives undesired allylic side products, however in the present work we obtained the desired aziridine as the sole product. The present catalytic system works better than Mn based homogeneous system investigated for {N- (p-tolyl sulfonyl) imino} phenyl iodinane by Evans. The methodology can be easily extended to the synthesis of chiral aziridines by anchoring a chiral diamine to the polymer matrix.

## Section C

### Hb Catalyzed Heterogeneous Aziridination of Olefins

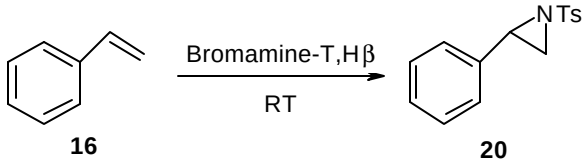
Aziridines are important heterocyclic compounds as they form part of several natural products and their utility as reaction intermediates towards functionalized molecules is well documented. Although several methods are available for the preparation of aziridines, the shortest route to the aziridine is its direct preparation from olefin, which involves transition metal catalyzed transfer of nitrogen atom. Different precursors of nitrogen for this catalytic transformation known in the literature suffer from severe drawbacks. Recently Chloramine-T (TsNNaCl) has been used as a nitrogen source for aziridination of olefins.[17] In this case also, the yields are low and it works well only with limited substrates. An improved process for aziridination of olefins with Bromamine-T [18] described earlier in many cases works better than the other nitrene sources in many cases. All these sources require transition metal based catalysts to run the reaction, which is a main drawback of this method of aziridination. Catalysts derived from transition metals like rhodium, copper, manganese, iron are either expensive, difficult to access or give poor yields in the aziridination reaction. It is therefore necessary and desirable to furnish a process for an improved aziridination of olefins with Bromamine-T as the source of nitrogen, using a suitable catalyst, which obviates the use of any metal.

### Present Work

Zeolites have proved to be valuable technical catalysts. Numerous types of aluminosilicates, metallosilicates and aluminophosphates have been synthesized by hydrothermal crystallization at autogenous pressure.[49] High silica zeolites are important and attractive catalysts by virtue of their hydrophobicity and potential thermal, hydrothermal and acidic properties with resistance to coke formation.[50] Zeolite Beta is high silica, large-pore crystalline aluminosilicate material. The framework structure of zeolite beta possesses three dimensional 12-membered ring pores with an interconnected channel system.[52] Zeolites of type BEA have proved to be the potential catalysts in various hydrocarbon conversion processes. Their characteristic properties such as acidity, shape

selectivity and thermal stability enable them to be used for highly selective synthesis in the field of chemical intermediates and fine chemicals.[53] This interesting area of application has grown continuously in recent years. The most important application of zeolite is in reaction catalyzed by proton acids and Lewis acids, where the change from a homogeneous to heterogeneous procedure brings advantages in respect of easy separation, environmental safeguard, disposal of the catalyst, avoidance of corrosion, etc. So far there is only a single report of aziridination using heterogeneous catalysts where the authors have used Cu exchanged HY zeolite with PhI=NTs as the source of nitrogen.[54] Exchange of zeolite Y with other cations ($Ag^{+}$, $Co^{2+}$, $Fe^{3+}$, $Mg^{2+}$, $Ni^{2+}$, $Zn^{2+}$) was found to be ineffective.

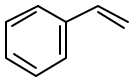
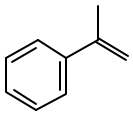
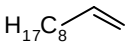
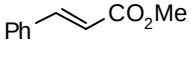
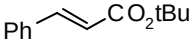
In the current work an improved procedure for the preparation of aziridines from olefins utilizing commonly available, inexpensive H β with Bromamine-T as the source of nitrogen has been developed. The aziridination reaction with styrene using H β (500 mg) was therefore explored[55] **(Scheme-28)**.




**Scheme-28**

The reaction proceeded well at room temperature to give the corresponding aziridine in 54 % yield. Next the catalyst substrate ratio was brought down to 10 % w/w without affecting the yields by modifying the drying procedure of H β. Encouraged by these results other olefins like α-methyl styrene, 1-decene, cis-cyclooctene, cyclohexene etc were subjected to identical conditions in acetonitrile for a period of 12 hours with **23** in the presence of H β under argon or nitrogen. The results are summarized below in **Table-9.**

**Table 9: Hb catalyzed heterogeneous synthesis of aziridines**

| Entry | Substrate | % Yield[a] | Temperature(°C) |
|---|---|---|---|
| a |  | 54 | RT |
| b |  | 52 | RT |
| c. |  | 43<br>60 | RT<br>45 |
| d |  | 60 | RT |
| e |  | 26 | RT |
| f. |  | 28<br>40 | RT<br>45 |
| g |  | 35<br>44 | RT<br>45 |

[a].isolated yields

The yields were good to moderate at room temperature. Less reactive substrates such as cinnamates underwent the reaction smoothly to give the corresponding aziridines. Same substrates did not undergo aziridination even at reflux temperatures in the homogenous version with $CuCl_2$ as the catalyst. Increasing the temperature to 40°C enhanced the yields, but further increase had no appreciable effect on the yields. An interesting feature of this conversion is the selectivity in the case of substituted olefins *viz*. cinnamates (entries f and g) where exclusively the *trans* aziridine product was obtained. The products were characterized by $^1$H NMR and Mass spectra. An analysis of the $^1$H NMR spectrum of aziridine from methyl cinnamate showed a doublet at δ 3.53 (J = 4 Hz) corresponding to one aziridine proton and another doublet at δ 4.4 (J = 4 Hz) which can be assigned to another aziridine proton, a singlet at δ 3.85 corresponding to three methoxy protons, a singlet of

three protons at δ 2.41 corresponding to tosyl protons, the peaks for aromatic protons appeared as a doublet for two protons at δ 7.7(8.3 Hz) and a multiplet of seven protons at δ 7.31 thus confirming the exclusive formation of the *trans* isomer. This is to be contrasted with previous results with the same substrates under metal catalyzed conditions[56] where a 50:50 *cis*/*trans* mixture was obtained. The exclusive formation of the *trans* isomer can be attributed to the shape selectivity of the zeolite, which is explained later in the text.

Some of the mechanistic aspects of this conversion were looked into. A metal nitrenoid mechanism does not operate here as the reaction proceeds without any metal catalyst. It was therefore expected to be a protonic form of mechanism as Hβ zeolite is known to possess high acid strength. To confirm this, other known proton sources were evaluated under similar reaction conditions with styrene as the substrate as shown in **Table-10**.

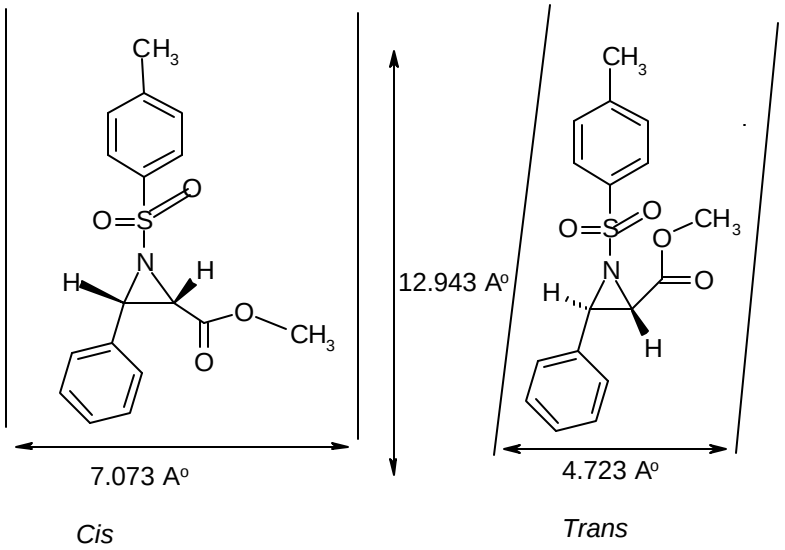
**Table-10: Aziridination of styrene with various proton sources**

| **Entry** | **Proton Source** | **Yield(%)** |
|---|---|---|
| a) | Amberlyst-15 | NR |
| b) | PTSA | NR |
| c) | HZSM-5 | NR |
| d) | Conc.$H_2SO_4$ | NR |
| e) | Hβ | 54% |

However all of the acidic catalysts listed in **Table-10,** except Hβ failed to give the desired aziridine product thereby ruling out a protonic mechanism. The failure of HZSM-5 to catalyze this reaction can be attributed to the fact that the pore size and void space of this zeolite is too small in comparison with H β for the aziridine molecule to diffuse out through zeolite channels. It is therefore suggested that the reaction takes place in the intracrystalline space of the zeolite. The reaction occurs within the zeolite pore in an environment in which trapping to form aziridines takes

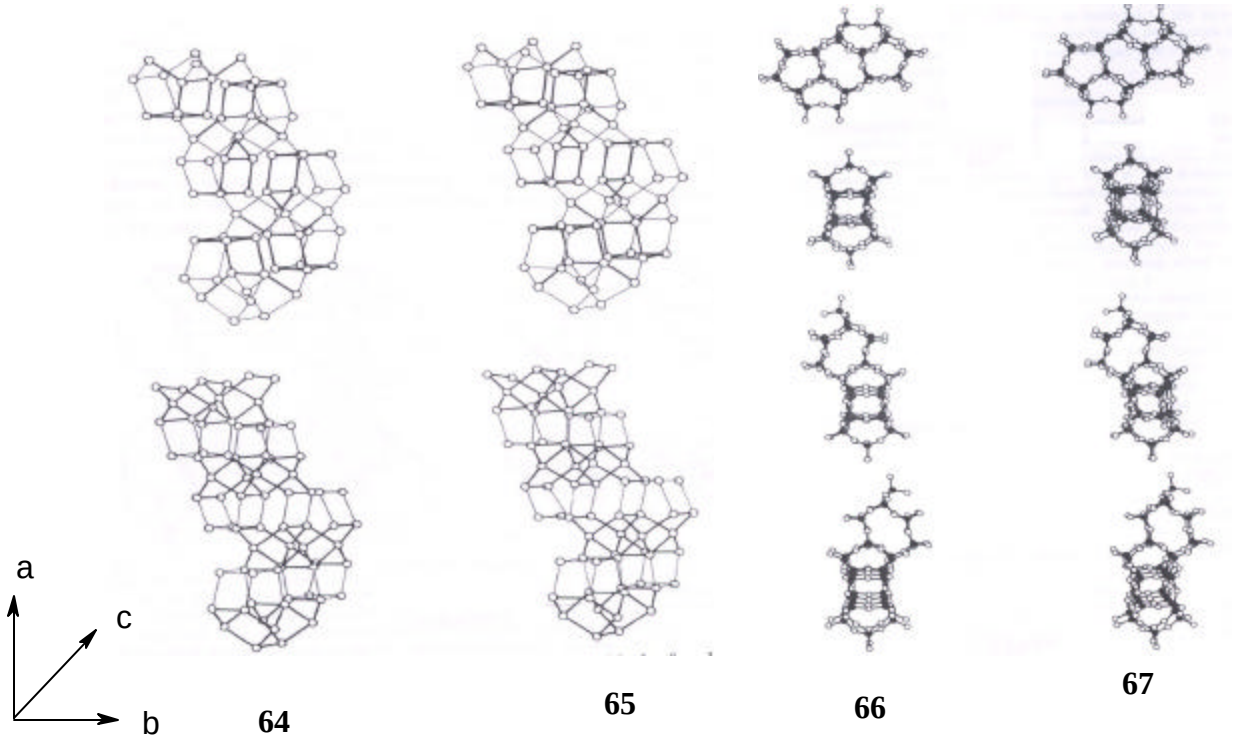
place due to the presence of the alkene in the close vicinity of Bromamine-T. There is further evidence for this as (E) Stilbene fails to undergo this reaction in the presence of the zeolite although the reaction occurs with similarly sized methyl cinnamate in good yields. The E-stilbene aziridine can be theoretically constructed within the pores of the zeolite but it is too bulky to diffuse out through the interconnecting channels in the structure. A similar observation was made by Hutchings *et al.* [54] in their work on CuHY catalyzed aziridination reaction where they concluded that the active catalytic sites are within the zeolite pores.

The mechanistic aspects of this conversion were further studied with the aid of computational tools using the PCMODEL[57] software. Both the *cis* and *trans* conformations of methyl cinnamate aziridine product were modeled. The minimum energy, surface area, volume, diameter and molecule length of both the isomers were determined using MMX calculations. The volumes of both the isomers were similar. The minimum energy of the *cis* isomer was shown to be higher than the *trans*, thus thermodynamically *trans* is the more stable form. The height and length calculations of the isomers led to an interesting observation, which throws light on the exclusive formation of *trans* isomer. The length of both the isomers is same (12.943 $A^o$), but the diameter or the width of the molecule showed a significant difference of 2.35 $A^o$ (**64**). The *cis* conformation requires a lager pore size to fit into the zeolite cavity.




**64**

A brief look at the zeolite beta pore size, structure and shape will be appropriate here. In both the polymorphs A and B of zeolite beta, the pore systems are three-dimensional, with straight 12-ring channels parallel to **a** and **b** and 12-ring paths along the respective **c** directions as shown in the figures **64, 65**,**66 and 67.**




**Stereoviews of the tertiary building block of zeolite beta**

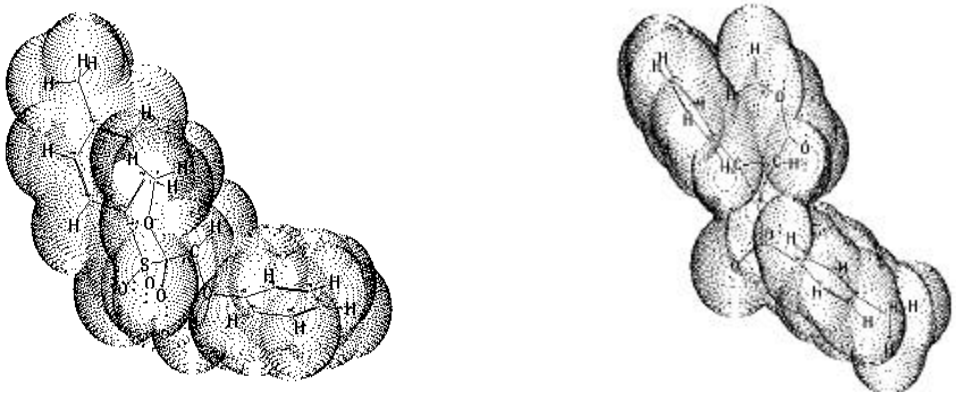
The figures **64** and **65** show the stereoviews illustrating how the secondary building blocks can be interconnected to form the polymorph A framework. Figures **66** and **67** depict the stereoviews of the tertiary building block of zeolite beta and how the structure grows from this building block. The cross sectional aperture dimension for the polymorph A structure is 0.73 x 0.60 nm (for the straight channels along a and b) and 0.56 x 0.56 nm (along c) assuming a framework oxygen atom radius of 0.135nm [58] Hence it can be concluded that the dimension of the *cis* isomer does not permit it to be formed within the supercages of the zeolite. Even if it is theoretically formed it will be difficult for it to diffuse out of the zeolite channels. **Table -11** shows the computed data for various parameters for both the *cis* and *trans* isomers calculated using

PCMODEL. Space filling models of both the isomers were drawn which corroborate this explanation that is suggested here.

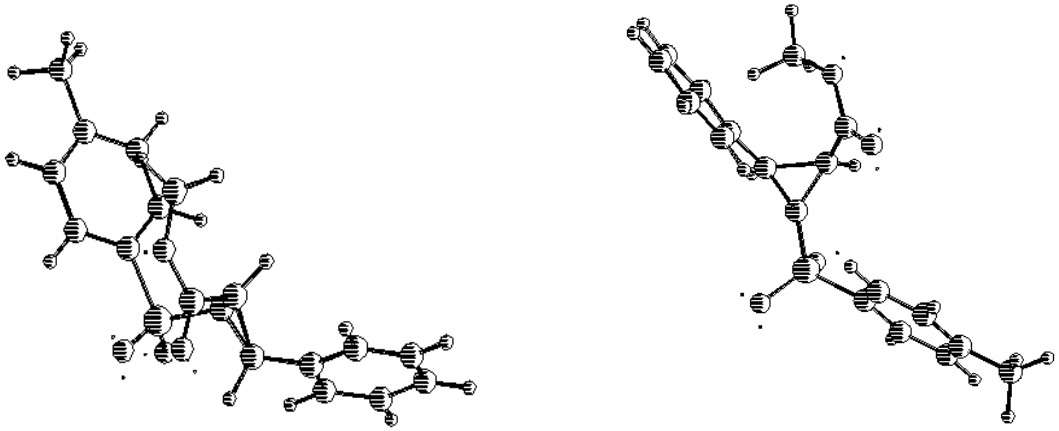
**Table-11: Computed data for various parameters generated using the PCMODEL program**

| **Computed Data** | ***Cis*** | ***Trans*** |
|---|---|---|
| Width ($A^o$) | 7.073 | 4.723 |
| Length ($A^o$) | 12.811 | 12.943 |
| Molecular Volume ($A^{o3}$) | 441 | 450 |
| Molar Volume ($cm^3$) | 264 | 270 |
| Energy (MMX) | 48.296 | 45.477 |
| Heat of Formation (Hf) | 9.74 | 6.81 |

**Space filled models of cis and *trans* conformers**



**Ball and stick models of cis and *trans* conformers**



## Conclusions

This is the first report of a non-metal catalyzed heterogeneous synthesis of aziridines .The catalytic system has all the advantages of a heterogeneous reaction- reusability of catalyst, environmental friendly etc. Less reactive substrates viz. methyl cinnamate, t-butyl cinnamate give aziridine products even at room temperatures (the aziridine products were not obtained even at reflux temperatures in the Bromamine-T catalyzed homogeneous counterpart). The catalyst can be recovered by filtration and reused. The reaction selectively gives the *trans* aziridine products, which can be attributed to the pore size and shape selectivity of the zeolite, which was further rationalized with the aid of molecular modeling tools.

## Experimental

### Synthesis of Amidogen, bromo [(4-methyl phenyl) sulfonyl] (23)[24]

### 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 dessicator for 24 hours.

**M.P.** 92°C (Lit[15] M.P. 92-93° C)

**Analysis** Calculated for $C_7H_7NO_2S\,Br_2$ ; N = 4.20 %, S = 9.70%, Br = 48.6
Observed N = 4.26 %, S = 9.73 %, Br = 48.56 %

### Preparation of Bromamine-T

Dibromamine-T (3.3 g, 11 mmol) was dissolved in small lots at a time with stirring, in aqueous solutions of sodium hydroxide (0.8 g, 20 mmol) in 50 mL of water, and the solution was cooled in ice. Pale yellow crystals of BromamineT separated out. The solid was filtered under suction, washed quickly with minimum quantity of water and dried over $P_2O_5$ in a dessicator.

**Yield** 2.8 g (86 %)

**$^1$H NMR** ($D_2O$) δ 2.4 (s, 3H), 7.4(d , *J* = 1.9 Hz, 2H), 7.7(d, *J* = 1.9 Hz, 2H).

**$^{13}$C NMR** ($D_2O$) δ 143.38, 134.30, 131.26 and 129.31

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

**Analysis** Calculated for $C_7H_7NO_2SBrNa$ ; Br =24.4 %, N = 4.4 %, S = 9.5 %
Found Br = 24.0 %, N = 4.1 %, S = 9.4 %

**Drying of Bromamine-T**

The Bromamine-T trihydrate obtained in the above step was dried to constant weight at 80°C under vacuum. Accurate control of temperature is essential for effective drying.

**General Procedure for aziridination**

A two necked 25 mL round bottomed flask was charged with Bromamine-T (100 mg, 0.4 mmol), 5A° powdered molecular sieves (10 mg) and anhydrous $CuCl_2$ (5 mg, 0.4 mmol). Anhydrous acetonitrile (5 mL) and styrene (0.23 mL, 2 mmol) were then added and the suspension was stirred for 12 hours at room temperature under inert atmosphere. It was diluted with dichloromethane and passed through a short plug of silica gel. The crude reaction mixture was purified by silica gel column chromatography to yield 49 mg (45%) of the pure aziridine product.

**General procedure for aziridination using bleaching powder**

A two necked 25 mL round bottomed flask was charged with Bromamine-T (100 mg, 0.4mmol), 5A° powdered molecular sieves (10 mg) and commercial calcium hypochlorite (5 mg, 10 mole %). Anhydrous acetonitrile (5 mL) was then added and after 5 min. styrene (0.23 mL, 2 mmol) was added and the suspension was stirred at room temperature for 12 h under inert atmosphere. The crude reaction mixture was passed through a short pad of silica gel and the solvent concentrated in vacuum. Crude product was purified by chromatography on silica gel to yield 64 mg (59 %) of the pure aziridine.

**Typical Procedure for aziridination using ultrasound**

Styrene (0.23 mL, 2 mmol), Bromamine-T (100 mg, 0.4 mmol) and $CuCl_2$ (5 mg, 10 mole %) in anhydrous acetonitrile (5 mL) were taken in a glass tube which was then irradiated in the sonication bath for 20 minutes under dry atmosphere. The catalyst was filtered and the crude reaction mixture was purified using silica gel column chromatography to yield 69 mg (64 %) of the aziridine.

**Typical procedure of aziridination under microwave conditions**:

A 25-mL pear shaped round flask was charged with Bromamine-T (50 mg, 2 mmol), $5^{o}$A powdered molecular sieves (5 mg) and $CuBr_2$ (5.0 mg, 10 mole %). Dry acetonitrile (2 mL) and styrene (0.12 mL, 1 mmol) were then added and the reaction mixture was irradiated for 12 minutes in domestic microwave oven. After cooling, the contents of the flask were passed through a short plug of silica gel. The pure aziridine (90mg, 88 %) was obtained by column chromatography.

**Typical procedure for benzylic amination in ultrasound:**

To a mixture of $Rh_2(OAc)_4$ (4.0 mg, 2.5 mole %), molecular sieves (40 mg) and tetralin (0.19 mL, 1 mmol) in dry acetonitrile (2 mL) was added Bromamine-T (100 mg, 0.4 mmol). The reaction mixture was subjected to ultrasound radiation for 20 minutes. After filtration the reaction mixture was subjected to column chromatography to give the aziridine 74 mg (70 %).

**Aziridination with polymer supported Mn (II) catalyst 25**

Bromamine-T (0.10 g, 0.4 mmol) and Mn catalyst **25** (100 mg) along with activated powdered molecular sieves (500 mg) were charged in a 25 ml 2 neck round bottomed flask. Styrene (0.12 mL), 1 mmol) in dry acetonitrile (5 mL) was added via syringe and the reaction mixture was stirred for 15 hours at ambient temperature under argon atmosphere. After completion of the reaction (TLC), the catalyst was filtered off and washed with dichloromethane and the product was purified by column chromatography on silica gel (10 % EtOAc in light petroleum ether) to afford *N-p*-toluenesulfonyl-2-phenylaziridine (46 mg , 42 %). The structure was confirmed by proton NMR and Mass spectroscopy.

**Heterogeneous synthesis of aziridines using H b**

A two neck 25-mL round-bottomed flask was charged with of Bromamine-T(100 mg, 0.4 mmol) and 10 % w/w dehydrated H β. Anhydrous acetonitrile (5 mL) was added to the reaction

mixture at room temperature. Styrene (0.12 mL, 1 mmol) was added via syringe to the reaction mixture and it was stirred for 48 hours under argon atmosphere. The crude reaction mixture was filtered through Whatman paper and the filtrate concentrated in vacuum. It was then chromatographed on silica gel to yield 59.2 mg (54 %) of the pure aziridine product.

**Spectral data**

***N*- (*p*-Tolylsulphonyl)-2-phenyl aziridine (20)**

**IR(**nujol**)** 3017, 1327, 1217, 1161, 916, 783, 769, 713, 696, 665 $cm^{-1}$.

**$^1$H NMR** δ 8.20 (d, *J* = 10.8 Hz, 2H), 7.7-7.5 (m, 7H), 4.18 (dd, *J* = 9.7 Hz, 6.5 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 2.82 (s, 3H), 2.72 (d, *J* = 6.3 Hz, 1H).

**MS** m/z (%) 273 ($M^+$, 5), 155 (4), 118 (83), 91 (100).

***N*- (*p*-Tolylsulphonyl)-2-phenyl-2-methyl aziridine (25)**

**IR** (nujol) 3060, 3028, 2992, 1440, 930 $cm.^{-1}$

**$^1$H NMR** δ 7.80 (d, *J* = 8 Hz, 2H), 7.55 – 7.15 (m, 7H), 2.81 (s, 3H), 2.16 (s, 3H).

**MS** m/z (%) 287 ($M^+$, 1), 256 (1), 222 (10), 188 (40), 171 (65), 155 (100).

***N*- (*p*-Tolylsulphonyl)-9-aza-bicyclo [6.1.0] nonane (29)**

**IR** (nujol) 3028, 2982, 2936, 1600, 1498, 1160, 610 $cm^{-1}$

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

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

***N*- (*p*-Tolylsulphonyl)-7-aza bicyclo [4.1.0] heptane (30)**

**IR** (nujol) 3020, 1600, 1440, 1395, 965, 920 $cm^{-1}$

**$^{1}$H NMR** δ 7.81 (d, *J* = 9.8 Hz, 2H), 7.40 (d, *J* =9.8 Hz, 2H), 3.10 (t, *J* = 1.2 Hz, 2H), 2.49 (s, 3H), 1.8 -1.7 (m, 4H), 1.5-1.4 (m, 4H).

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

***N*- (*p*-Tolylsulphonyl)-2-octylaziridine (34)**

**IR** (nujol) 3017, 1327, 1217, 1161, 916, 783, 769, 713, 696, 665 $cm.^{-1}$

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

**MS** m/z (%) 273 ($M^{+}$, 5), 155 (4), 118 (83), 91 (100), 65 (21).

***N*- (*p*-Tolylsulphonyl)-2-carbomethoxy-3-phenylaziridine (40)**

**IR** (nujol) 3068, 3021, 2960, 1750, 1600, 1412, 1167, 906 $cm.^{-1}$

**$^{1}$H NMR** (*trans* isomer) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31-7.24 (m, 7H), 4.44 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 3H), 3.53 (d, *J* = 4.0 Hz, 1H), 2.41 (s, 3H).

**$^{1}$H NMR** (*cis* isomer) δ 7.90 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.25 (m, 5H), 4.10 (d, *J* = 7.8 Hz, 1H), 3.70 (d, *J* = 7.8 Hz, 1H), 3.50 (s, 3H), 2.49 (s, 3H).

**MS** m/z (%) 332 ($M^{+1}$, 5), 331 ($M^{+}$, 8), 300 (10), 176 (75), 144 (25), 116 (100), 91 (70), 65 (30).

***N*- (*p*-Tolylsulphonyl)-2-carbo- (2-methyl-2-propoxy)-3-phenylaziridine (41)**

**IR** ($CHCl_3$) 3028, 1740, 1085, 910 $cm.^{-1}$

**$^{1}$H NMR** δ 7.80 (d, *J* = 8 Hz, 2H), 7.4 - 7.0 (m, 7H), 4.44 (d, *J* = 2 Hz, 1H), 3.40 (d, *J* = 2 Hz, 1H), 2.49 (s, 3 H), 1.5 (s, 9H).

**MS** m/z (%) 373 ($M^{+}$, 0.5), 300 (18), 273 (18), 162 (70), 91(100).

***N*- (*p*-Tolylsulphonyl) amino)-1,2,3,4- tetrahydronapthalene -1, 2-imine (37)**

**IR** (nujol) 1599, 1150, 1092, 990, 665 $cm.^{-1}$

**$^1$H NMR** δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.25-7.15 (m, 6H), 3.8 (d, *J* = 7.7 Hz, 1H), 3.55 (d, *J* = 6.9 Hz, 1H), 2.70 (dt, *J* = 15.5 and 5.2 Hz, 1H), 2.60 (dd, *J* = 15.5 and 6.2 Hz, 1H), 2.49 (s, 3H), 2.32 (dd, *J* = 15.2 and 5.3 Hz, 1H), 1.71 (dt, *J* = 13.7 and 5.4 Hz, 1H).

**MS** m/z (%) 299($M^+$, 1), 226 (1.5), 144 (100), 117 (67), 91(32).

**1,1a, 6,6a-Tetrahydroindeno[1,2-b] aziren-1--yl-4-methyl phenyl sulfone (27)**

**IR** (nujol) 3072, 2735, 2025, 1115, 960 $cm.^{-1}$

**$^1$H NMR** δ 7.7-7.5 (m, 4H), 6.9- 6.7(m, 4H), 5.4 -5.3(m, 3H), 3.10 (m, 1H), 2.7 (s, 3H).

**MS** m/z (%) 285($M^+$, 10), 252 (40), 221 (35), 167(60), 91 (100).

**3-(4- Methyl phenyl sulfonyl)-3-azatricyclo [3.2.1.0} octane (32)**

**IR** (nujol) 3016, 1300, 1280, 1008, 960 $cm.^{-1}$

**$^1$H NMR** δ 7.97(d, *J* = 8 Hz, 2H), 6.77(d, *J* = 8 Hz, 2H), 2.8(s, 2H), 1.9(s, 2H), 1.8(s, 3H), 1.45(dt, *J* = 2, 9 Hz, 1H), 0.97-0/92(m, 2H), 0.77-0.7 (m,2H), 0.3(d, *J* = 9 Hz, 1H).

**MS** m/z (%) 263 ($M^{+1}$,1), 155 (30), 91(100), 60(35).

***Trans*-N- (p-Tolylsulfonyl)-2-methyl-3-phenyl aziridine (36)**

**IR** (nujol) 3030, 1327, 1281, 1037, 870, 740, 660 $cm.^{-1}$

**$^1$H NMR** δ 7.83 (d, *J* = 8.8Hz, 2H), 71-7.4 (m, 7H), 3.78 (d, *J* = 4.3Hz, 1H), 2.9(dq, *J* = 6.2Hz, 4.3 Hz, 1H,), 2.4 (s, 3H), 1.85 (d, *J* = 6.2 Hz, 3H).

**MS** m/z (%) 263 ($M^{+1}$, 1) 19(18), 155(30), 91(100), 60(35).

**1-{N- (p-Tolylsulfonyl) amino}-1,2,3,4-tetrahydronaphthalen-1-yl sulfone (48)**

**IR** (nujol) 3361, 3236, 3000, 2847, 1140, 742 $cm.^{-1}$

**$^1$H NMR** δ 7.90 (d, *J* = 8 Hz, 2H), 7.30-6.85 (m, 6H), 4.85(d, *J* = 6 Hz, 1H), 4.5-4.4 (m, 1H), 2.9-2.6 (m, 2H), 2.45(s, 3H), 1.9-1.6(m, 4H).

**MS** m/z (%) 301 ($M^+$, 2), 235 (20), 155 (40), 146 (90), 130 (100), 91 (80).

**1-{N-(p-Tolylsulfonyl)amino}indane (52)**

**IR** (nujol) 3246, 3047, 2968, 1730, 1400, 1125 $cm.^{-1}$

**$^1$H NMR** δ 7.80 (d, *J* = 8 Hz, 2H), 7.4-7.1 (m, 6H), 5.0 (d, *J* = 6 Hz, 1H), 1H), 4.62 (m, 1H), 3.2-3.1(m, 1H), 3.15 (m, 1H), 2.42 (s, 3H), 2.30-1.60 (m, 2H).

**MS** m/z (%) 287($M^+$, 0.3), 149 (15), 133 (100), 115 (50), 91 (12), 77 (35) 235 (20), 155 (40), 146 (90), 130 (100), 91 (80).

**1-{N- (p-Tolylsulfonyl) amino}-1phenylethyl (50)**

**IR**(nujol) 3368, 3319, 2970, 1360, 752 $cm.^{-1}$

**$^1$H NMR** δ 7.65 (d, *J* = 8 Hz, 2H), 7.5-7.0 (m, 7H), 4.75 (d, *J* = 6 Hz, 1H), 4.50 (m, 1H), 2.46 (s, 3H), 1.48 (d, *J* = 4Hz, 3H).

**MS** m/z (%) 275 ($M^+$ 0.5), 260 (95), 210 (1), 165 (1), 155 (48), 120 (50), 104 (30), 91 (100), 77 (22).

**References**


1. Seebach, D. *Angew. Chem. Int. Ed. Engl.,* **1990**, 29, 1320.
2. Deyrup, J.A. In *The Chemistry of Heterocyclic Compounds*, Hassner, A, Ed, Wiley, New York, **1983,** Vol 42, Part I, Chapter I.
3. Houben-Weyl, Vol 5/1b, **1972,** p1068.
4. Scriven, E.F.V. and Turnbull, K., *Chem. Rev.,* **1988,** 88, 297.
5. For reviews see, a) Lwowski, W. "Cabonylnitrenes". In *Nitrenes* Lwowski, W, Ed Interscience, New York, **1970,** pp 185-224. b) Edwards, O.E. Acylnitrenes. In *Nitrenes* Lwowski, W, Ed Interscience, New York, **1970** pp 225-247.
6. Kwart, H. and Kahn, A. A., *J. Am. Chem. Soc.,* **1967,** 89, 1951.
7. Groves, J.T and Takahashi, T., *J. Am. Chem. Soc*., **1983**, 105, 2073.
8. Mansuy, D., Mahy, J.P., Dureault, A., Bedi, G. and Battioni, P., *J. Chem. Soc. Chem. Commun*, **1984,** 1161.
9. Evans, D.A., Faul, M. M. and Bilodeau, M.T., *J. Am. Chem. Soc*., **1994**, 116, 2742.
10. Tian, X., Hudlicky T. and Konigsberger K., *J. Am. Chem*. *Soc*., **1995**, 117, 3643.
11. Carducci, M., Fioravanti, S., Loreto, M.A., Pellacani, L. and Tardella, P.A., *Tetrahedron Lett.*, **1996**, 37, 3777.
12. Mueller, P., Baud, C. and Jacquier, Y., *Tetrahedron*, **1996,** 52, 1543.
13. Ando, T., Minakata, S., Ryu, I. and Komatsu, M., *Tetrahedron Lett.,* **1998,** 39, 309.
14. Vyas, R., Chanda, B.M. and Bedekar, A.V., *Tetrahedron Lett.,* **1998**, 39, 4715.
15. Nair, C.G. R. and Indrasenan, P., *Talanta,* **1976,** 23, 239.
16. Mahadevappa, D.S., Nanda S., Murthy A.S.A. and Rangappa, K.S., *Tetrahedron*, **1984**, 40, 1673.
17. Albone, D.P., Aujla, P.S., Taylor, P.C., Challenger, S. and Derrick, A.M., *J. Org. Chem.,* **1998**, 63, 9569.
18. Ando, T., Kano, D., Minakata, S., Ryu, I. and Komatsu, M., *Tetrahedron*, **1998**, 54, 13485.
19. Jeong, J.U., Tao, B., Sagasser, I., Henniges, H. and Sharpless, K.B., *J. Am. Chem. Soc.,* **1998**, 120, 6844.
20. Nair, C.G.R., Lalithakumari, R. and Senan, P.I., *Talanta,* **1978**, 25, 525.

21. Bose, A.K., Jayraman, J., Okawa, A., Bari S.S., Robb, E.W. and Manhas M.S, *Tetrahedron Lett*., **1996,** 37, 6989 and references cited therein.
22. Giguere, R.J., Bray, T.L., Duncan, S.M. and Majetich, G., *Tetrahedron Lett.*, **1986**, 27, 4945.
23. Abramovitch, R.A. and Bulman, A., *Synlett.*, **1992,** 795.
24. a) Lindley, J. and Mason, T.J., *Chem. Soc. Rev*., **1987,** 16, 275.b) Einhorn, C., Einhorn, J and Luche, J-L., *Synthesis*, **1989**, 787.
25. Li, Z., Quan, R.W. and Jacobsen, E.N., *J. Am. Chem. Soc.*, **1995**, *117*, 5889.
26. Aujla, P.S., Baird, C.P. and Taylor, P.C., *Tetrahedron Lett.,* **1997,** 38, 7453.
27. Iliyas, A. S., Nikalje, M.D. and Sudalai, A., *Org. Lett.*, **1999**, 1, 705.
28. Vyas, R., Chanda, B.M. and Bedekar A.V., "An improved process for the aziridination of olefins", Indian Patent No. NF 33, **2000.**
29. Cady, P., *Inorganic Synthesis*, **1957,** 5, 161.
30. Nwaukwa, S.O. and Keehn, P.M., *Tetrahedron Lett*., **1982, 2**3, 35.
31. a) Gibson, M.S. and Bradshaw, R.W. *Angew. Chem. Int. Ed. Engl.*, **1968**, 7, 919. b) Trost, B.M. and van Vranken, D.L., *Chem. Rev*., **1996**, 96, 395.
32. Evans, D.A., Faul, M.M. and Bilodeau, M.T., *J. Org. Chem.*, **1991,** 56, 6744; Evans, D.A., Faul, M.M., Bilodeau, M.T., Andersson, B.A. and Barnes, D.M., *J. Am. Chem. Soc.*, **1993,** 115, 5328.
33. Mahy, J.P., Bedi, G., Battioni, P. and Mansuy, D., *New J. Chem.*, **1989**, 13, 651.
34. Nageli, I., Baud, C., Bernardinelli, G., Jacquier, Y., Moran, M. and Muller, P., *Helv. Chim. Acta.*, **1997**, 80, 1087.
35. Kohmura, J. Y., Kawasaki, K. and Katsuki, T., *Synlett*., **1997**, 12,1456.
36. Shuttleworth, S.J., Allin, S.M. and Sharma, P.K., *Synthesis*, **1997,** 1217.
37. Merrifield, R.B., *Science*, **1986**, 232, 341.
38. Merrifield, R.B., *J. Am. Chem. Soc.*, **1963**, 85, 2149.
39. a) Pitman, C.U., Jr, Hodge, P. and Sherrington D.C. (Eds.), in *Polymer Supported Complexes*, Elsevier, Amsterdam, **1981**. b) Kaneda, K. and Imanaka, T., *Trends Org. Chem*., **1991,** 2, 109.
40. Hodge, P., *Chem. Soc. Rev.*, **1997,** 417.
41. Mohanraj, S. and Ford, W.T., *Macromolecules*, **1986,** 19, 2470.
42. De, Binod, B., Lohray, B.B., Sivaram, S. and Dhal, P.K., *Tetrahedron Asymmetry*, 9**, 1995**, 2105.

43. Fraile, J.M., Mayoral, J.A., Royo, A.J., Savador, R.V., Altava, B.S. and Burgette, M.I., *Tetrahedron*, **1996**, 52, 9853.
44. Soai, K., Niwa, S., Watanabe, M., *J. Org. Chem.*, **1988**, 53, 927.
45. Kiyookas, S., Kido, Y. and Kaneko, Y., *Tetrahedron Lett*., **1994**, 35, 5243.
46. a) Mansuy, D., Mahy, J-P., Dureault, A., Bedi, G. and Battioni, P., *J. Chem. Soc. Chem. Commun*., **1984,** 1161. b) Sodergren, M.J., Alonso, D., Bedekar, A.V. and Andersson, P.G., *Tetrahedron Lett*., **1997,** 38, 6897.
47. a) Patel, D.R., Dalal, M.K. and Ram, R.N., *J. Mol. Catal*., **1996,** 109, 141. b) Patel, D.R. and Ram R.N., *J. Mol. Catal.*, **1998,** 130, 57. c) Gokak, Kamath, B.V. and Ram, R.N., *React. Polym*., **1989,** 10, 37.
48. Evans, D. A., Faul, M.M. and Bilodeau, M.T., *J. Am. Chem. Soc*., **1994,** 116, 2742.
49. Szostak, R., Handbook of Molecular Sieves, Van Nostrand Reinhold, New York, **1992**.
50. Scherzer, J., *Catalytic Materials: Relationship Between Structure and Reactivity*, Ed. Baker, R.T., Deronane, E.G., Dalla Bett R.A. and Whyte, T.E., American Chemical Society, Washington, DC, **1984**, p157.
51. Wadlinger, R.L., Keer, G.T. and Rosinki, E.J., US Pat. 3 308 069, **1964.**
52. a)Traey, M.M.J. and Newsam, J.M., *Nature*, **1988,** 332, 24. b)Tomlinson, S.M., Jackson, R.A and Cathlow, R.A., *J. Chem. Soc. Chem. Commuun.*, **1990,** 813.
53. La Pierre, R.B., Patridge, R.D., Chen, N.V. and Wond, S.S., Eur. Pat, 95 **1983** 303. b) Perez-Pariente, J., Martens, J.A and Jacobs, P.A., *Appl. Catal.*, **1987**, 31, 35. c) Camblor, M.A. and Perez-Pariente, J., *Zeolite*s, **1991**, 11, 202.
54. Langham, C., Taylor, S., Bethell, D., Mcmorn, P., Page, P.C.B., Willock, J.D., Sly, C., Hancock, F.E., King, F. and Hutchings, G.J., *J. Chem. Soc. Perkin. Trans 2*.**, 1999,** 1043.
55. The framework structure of the BEA zeolite used in the reaction may be selected from framework Si/Al ratio ranging from 15 to 375 in any form wherein non-framework cations may be mono-, di or trivalent.
56. Chanda, B. M., Vyas, R. and Bedekar, A.V., *J. Org. Chem.*, **2001**, 61, 30.
57. Serena software, version 5.1 for Windows.
58. Newsam, J.M., Treacy, M.M.J., Koestsier, W.T. and de Gruyter**,** *Proc. R. Soc. Lond*. A., **1988,** 420, 375.

# Chapter-3

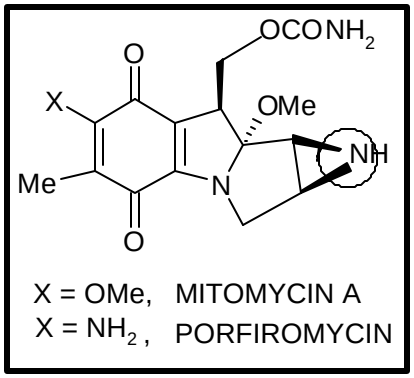
## Asymmetric Synthesis of Aziridines From Olefins With Bromamine-T As Nitrene Source

# INTRODUCTION

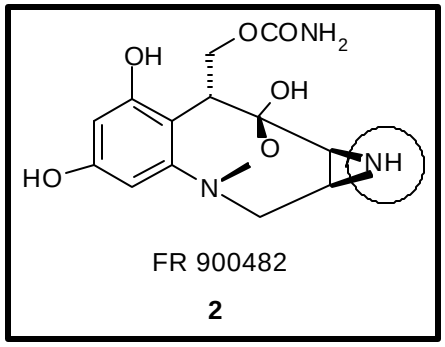
The present chapter deals with the application of chiral ligands, both natural and synthetic, to asymmetric aziridination reactions. The ability of aziridines to undergo regio- and stereoselective ring opening reactions makes them useful synthons in organic synthesis.[1] Chiral aziridines and aziridinium ions have profound use in total synthesis with a plethora of applications viz. synthesis of alkaloids, amino sugars, amino acids, β-lactam antibiotics, polymers, pyrrolidines etc.[2] $C_2$-symmetric chiral aziridines can be used as chiral auxiliaries for diastereoselective alkylation and aldol transformations.[3] Aziridines have also found use as chiral reagents in organic synthesis. Moreover aziridines themselves can be used as chiral ligands e.g. enantioselective dihydroxylation, cyclopropanation, aziridination and for palladium catalyzed allylic substitution reactions.[4] Enantiopure aziridines also find applications as enzyme substrates[5] and enzyme inhibitors.[6]

Aziridine moiety is present in many biologically active natural products such as mitomycin (**1**), azinomycin (**3**), porfiromycin etc.[7] Mitomycins represent an important class of naturally occurring mitosanes which exhibit both antitumour and antibiotic activity.[8] Their antitumour property results from their ability to cross-link DNA. Structure-activity studies have demonstrated the aziridine moiety as essential for their antitumour activity and therefore lot of attention has been given to the synthesis of these compounds and their derivatives.[9] Azinomycins are naturally occurring metabolites, which demonstrate activity against a wide range of tumors. Many synthetic aziridines like **4** also exhibit biological properties e.g. 4, 2-(4-amino-4-carboxybutyl) aziridine-2-carboxylic acid (**5)** is a potent irreversible inhibitor of bacterial enzyme diaminopimelic acid epimerase, while 2-(3-carboxypropyl) aziridine-2-carboxylic acid (**6**) is an irreversible inhibitor of glutamate racemase.[10] Azirdines are therefore worthy targets for synthetic organic chemists. Consequently frantic efforts are being directed to develop efficient methods for their facile synthesis by various groups. While racemic aziridines are readily available, procedures for their synthesis in enantiopure form are limited. This chapter attempts to highlight the importance and use of chiral aziridines in general and describes the work carried out in the field of enantioselective transition metal catalyzed synthesis of aziridines.

**Naturally occurring aziridines**

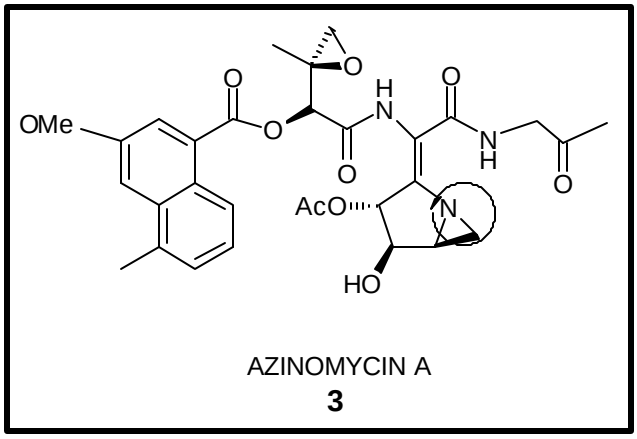



X = OMe, MITOMYCIN A
X = $NH_2$, PORFIROMYCIN




FR 900482

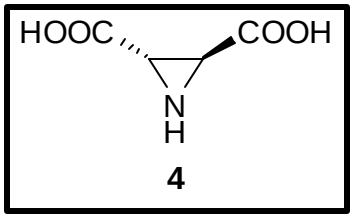
**2**



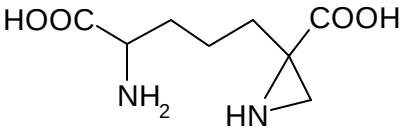

AZINOMYCIN A

**3**

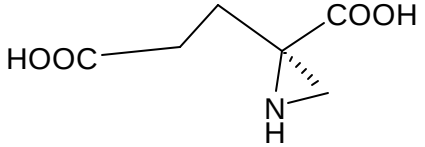
**Biologically active synthetic aziridines**




**4**

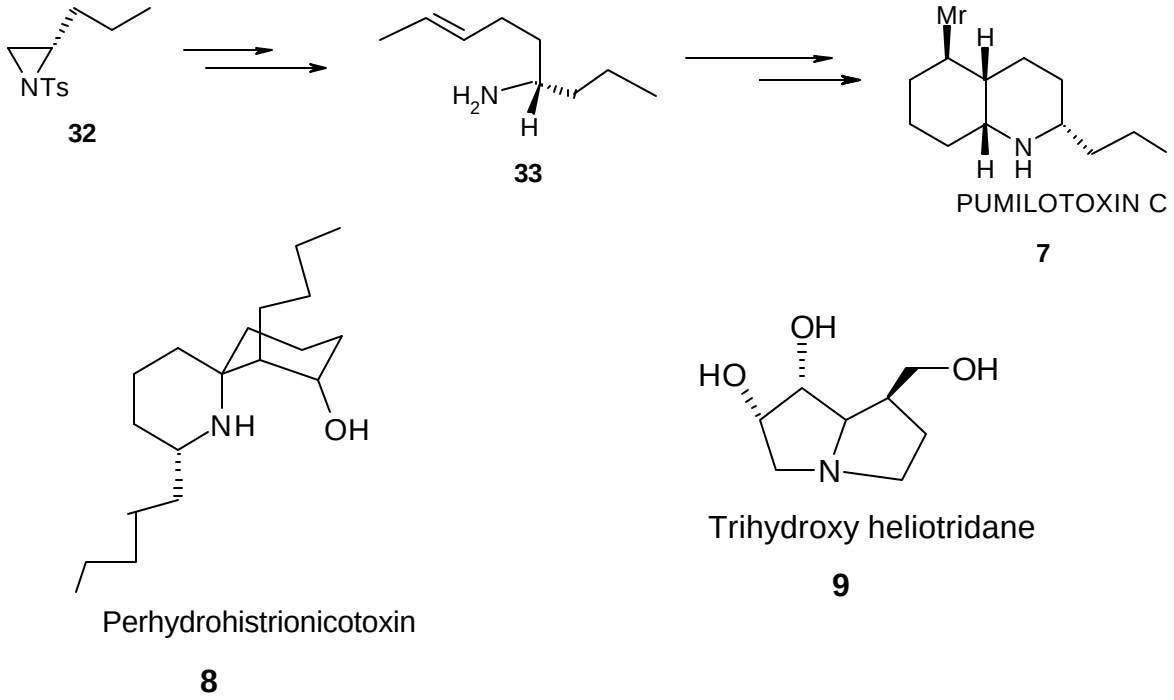



**5**



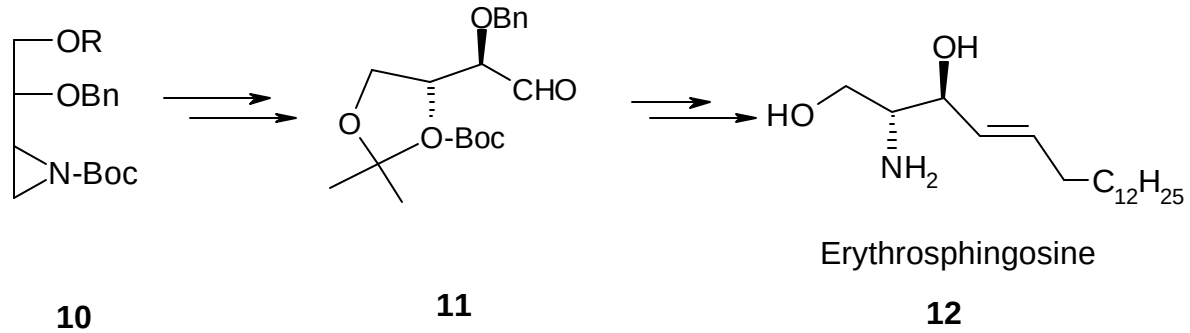

**6**

A few examples demonstrating the use of chiral aziridines as versatile building blocks in organic synthesis are worth mentioning. Chiral aziridines find important place in the total synthesis of important members of alkaloid group. They have been used for the total synthesis of Pumilotoxin C (**7**),[11] trihydroxyheliotridane (**9**)[12] and the challenging synthesis of histrionicotoxin family of spirocyclic alkaloids (**8**) [13] **(Scheme-1)**.



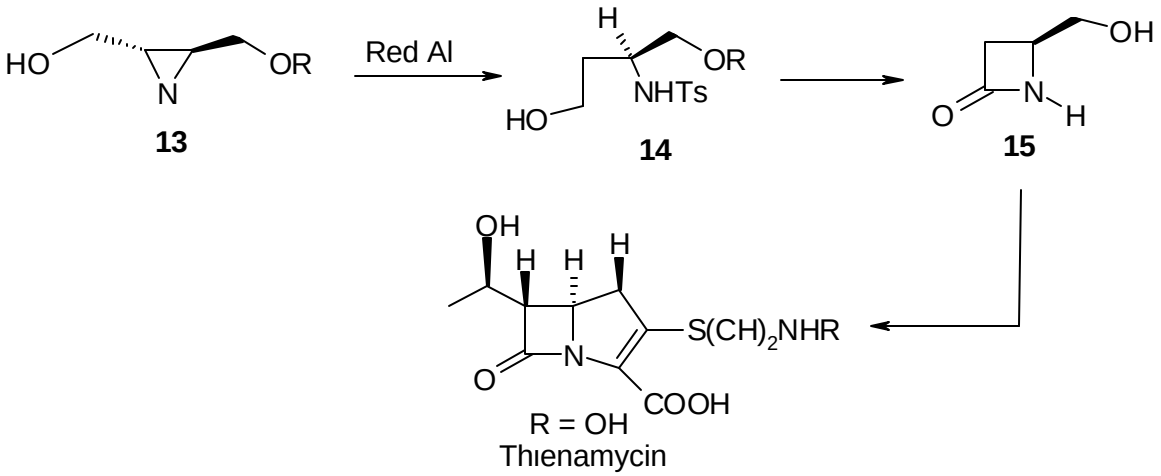

**Scheme - 1**

Amino sugars and amino acids can be synthesized via aziridine ring opening reactions. The scheme below shows the synthesis of erythrosphingosine from chiral aziridine **10** [14]**(Scheme-2)**.




**Scheme - 2**

Ring opening of optically pure aziridino alcohols has been exploited as the key step in the synthesis of important members of the class of carbapenem antibiotics.[15] For instance thienamycin was synthesized from key intermediate **15** obtained by regio and stereoselective ring opening of aziridino alcohol **13** (**Scheme-3)**.



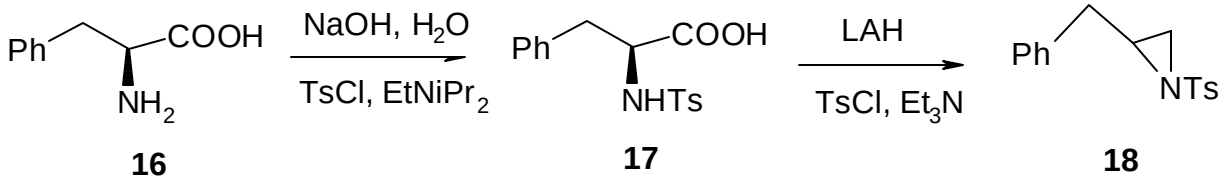

**Scheme-3**

**General routes to chiral aziridine synthesis**

The known synthetic routes to chiral aziridines either rely on the availability of enantiomerically pure starting materials or on asymmetric transformations of the C-C or C-N double bonds. These general routes are described in detail in this section.

**Synthesis from amino acids**

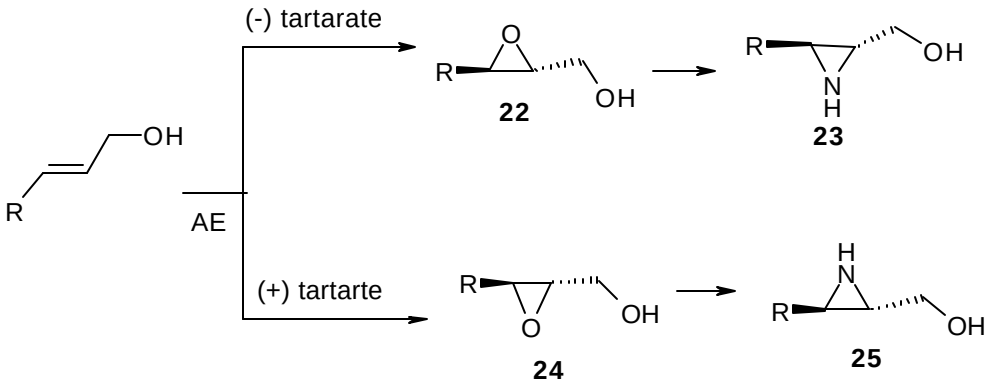
The ring closure of 1, 2-amino alcohols or suitable derivatives is a general synthetic method for aziridines, therefore amino acids are widely used as chiral starting materials[16] **(Scheme-4)**.




**Scheme - 4**

**Synthesis from carbohydrates**

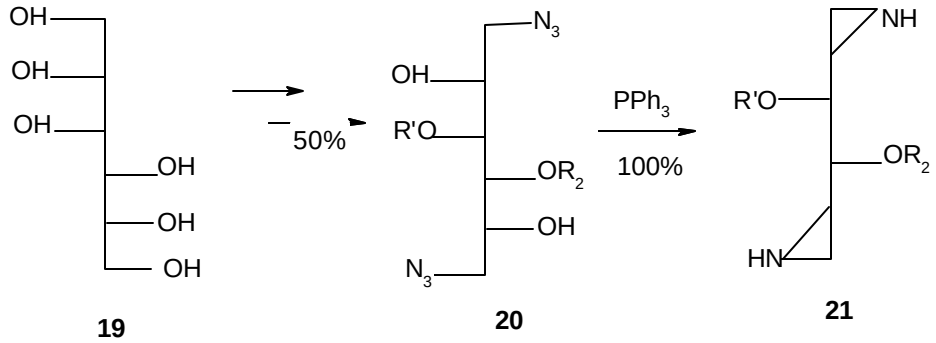
Sugar derivatives are attractive chiral starting materials because of the easy regio and stereoselective manipulation of the various hydroxyl groups.[17] A severe drawback of this method is that only one enantiomer of the starting materials is cheap or readily available **(Scheme-5)**.




**Scheme-5**

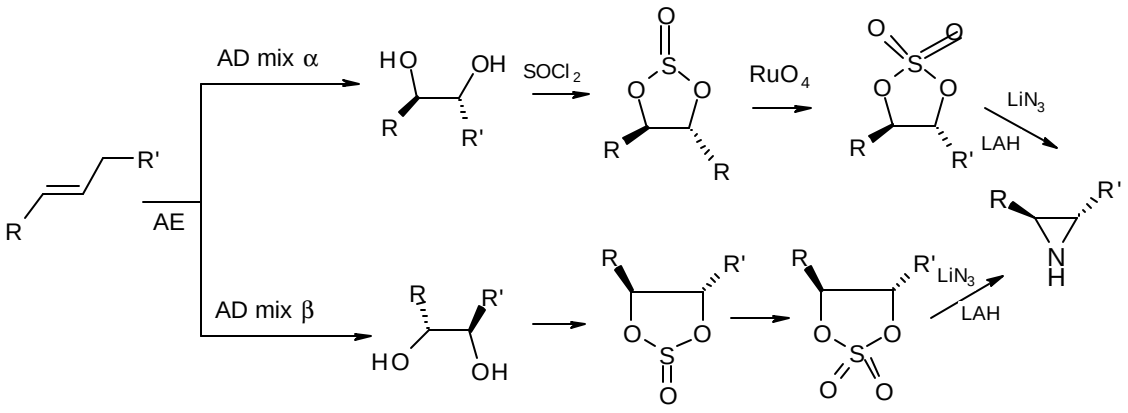
**Synthesis from alkenes via chiral epoxides and 1,2 diols**

Sharpless asymmetric epoxidation of allylic alcohols mediated by titanium (IV) alkoxide and tert-butyl hydroperoxide in the presence of tartarate ester provides a general route to synthesis of hydroxymethylaziridines via epoxide formation.[18] These aziridino alcohols like **23** and **25** are very useful chiral intermediates. The advantage of this synthetic route is that both the enantiomers of the product are available easily from a common starting material **(Scheme-6)**.



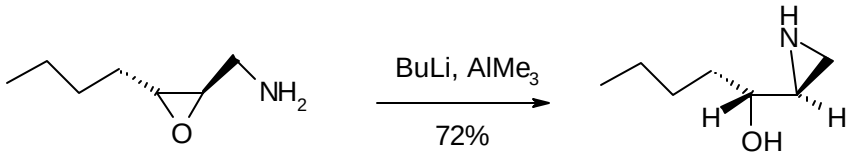

**Scheme-6**

However there is a limitation that the substrate must always contain an allylic alcohol in the form of a handle, thus nonfunctionalized olefins cannot undergo epoxidation.[19] Recently Sharpless[20] has come up with a solution which relies on cyclic sulfates of chiral 1,2 diols, by osmium catalyzed asymmetric dihydroxylation (AD) as shown in **Scheme-7**.




**Scheme- 7**

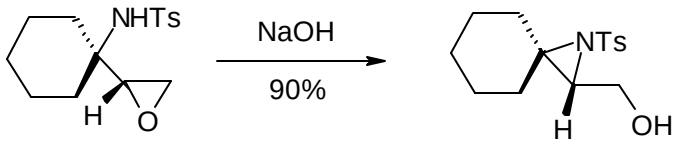
Payne rearrangement[21] is a very useful method in epoxy alcohol chemistry involving isomerisation of oxiranemethanols in aqueous alkaline media. Amino epoxides can perform similarly in the presence of complexes of titanium or aluminum **(Scheme-8)**.




**26**

**Scheme -8**

N-Tosyl amino epoxides like **27** undergo the rearrangement on treatment with a base [22] **(Scheme-9)**.

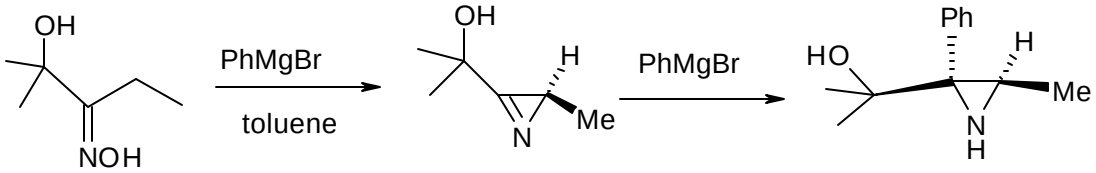



**27** **28**

**Scheme-9**

**Asymmetric transformation of C-N double bonds**

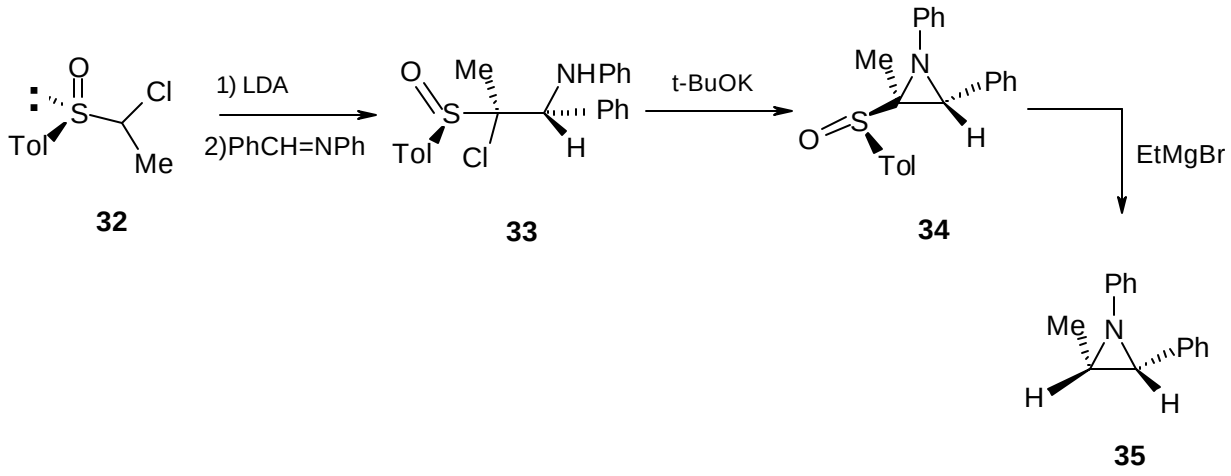
Aziridines are readily available by reaction of hydroxy oximes with Grignard reagents via azirine intermediate **30**[23] **(Scheme-10)**.




**29** **30** **31**

**Scheme-10**

Another example under this category is an analogue of aza Darzens reaction where an N-tosylsulfoxime was used as a chiral nucleophilic alkylidene transfer reagent, but the enantiomeric purity of the aziridine could not be determined.[24] An efficient asymmetric synthesis of aziridines involving chiral sulfoxides is shown in **Scheme-11.**




**32** **33** **34** **35**

**Scheme-11**

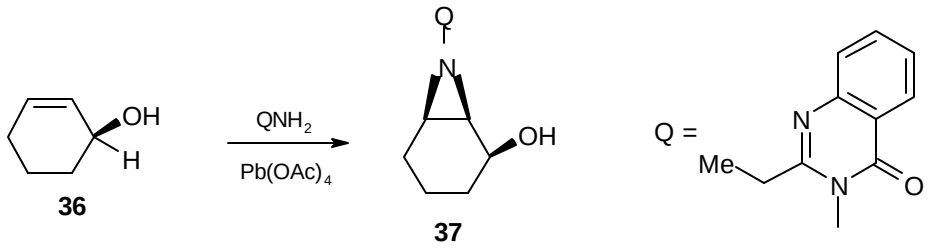
Here a stereospecific desulfinylation reaction takes place to give aziridine **35.**[25] A chiral metalated aziridine is supposed to be the intermediate.

**Asymmetric transformation of C-C double bonds**

A comprehensive literature search revealed that there are some commonly used routes for the synthesis of aziridines from olefins. They can be categorized under the following subheadings;

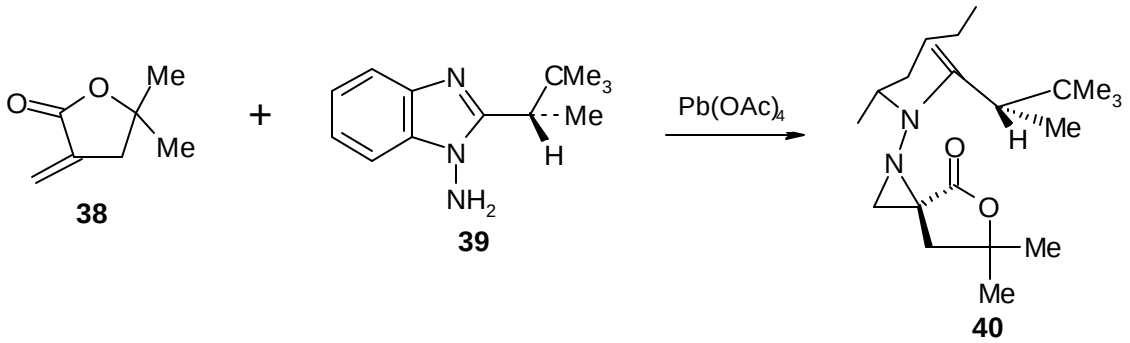
1) Addition of $IN_3$ or INCO followed by reductive or hydrolytic ring closure.
2) Addition of a primary amine to a suitably substituted acrylic acid derivative.
3) Michael addition of a nitrogen nucleophile followed by expulsion of a leaving group at nitrogen.
4) 1,3-Dipolar cycloaddition of azides and subsequent decomposition of the triazole intermediate.
5) Direct addition of nitrene species.

There are many examples for these general methods for aziridine synthesis which range from substrate control through reagent control to enantioselective catalysis .For the sake of brevity only a few examples are shown here. An example of substrate control is given in **Scheme-12** where the starting material **36** was racemic but optically pure 2-cyclohexen-1-ol (**37**) was obtained.[26]




**Scheme -12**

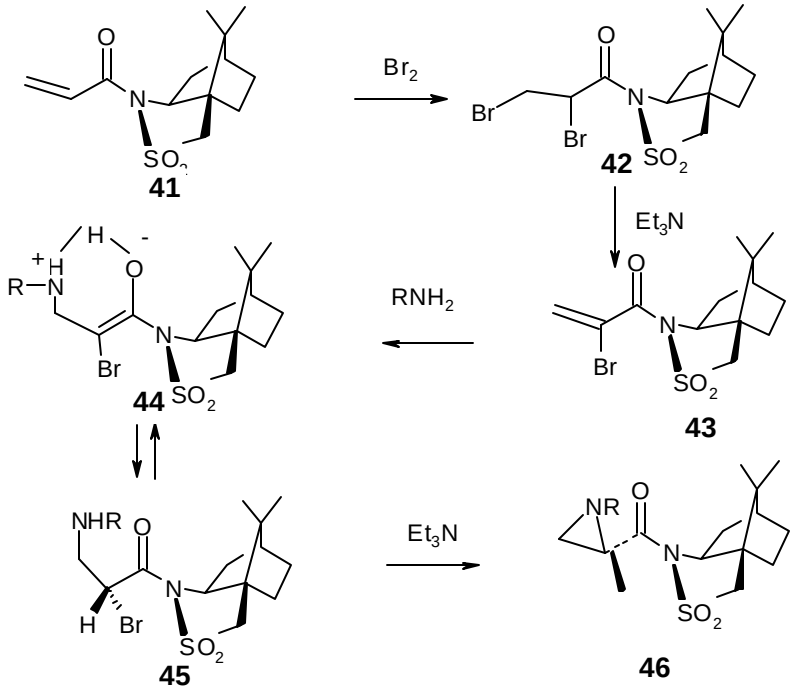
The nitrene reaction of alkene **38** to yield aziridine **40** can serve as an example of reagent control[27] as high asymmetric induction is observed in this case **(Scheme-13)**.




**Scheme -13**

**Gabriel Cromwell reaction**

1,2-Dibromo alkanes prepared via addition of bromine to alkenes can be elaborated to yield racemic aziridine on treatment with amines.[28] An asymmetric version of the same reaction with optically pure 2-bromocarboxylates leads to chiral N-alkyl aziridines **(Scheme-14)**.

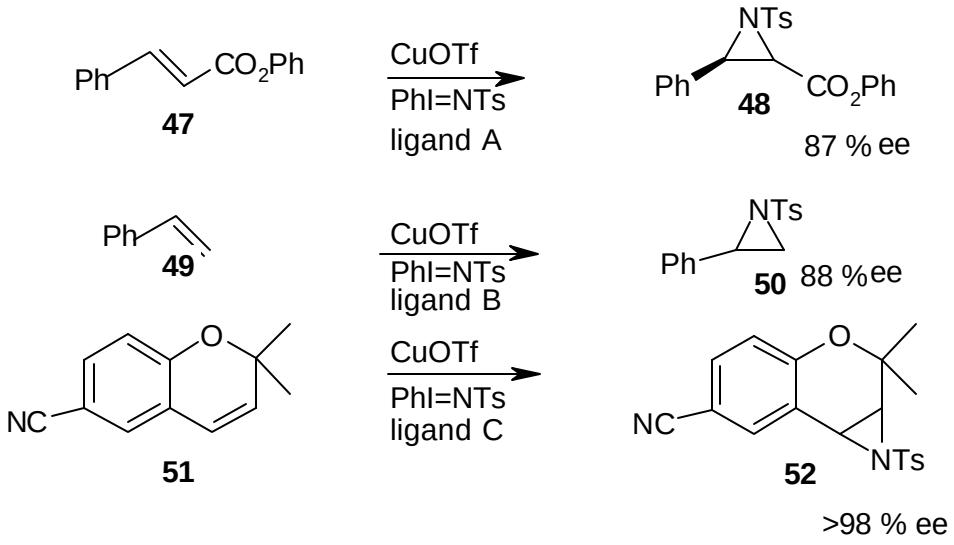


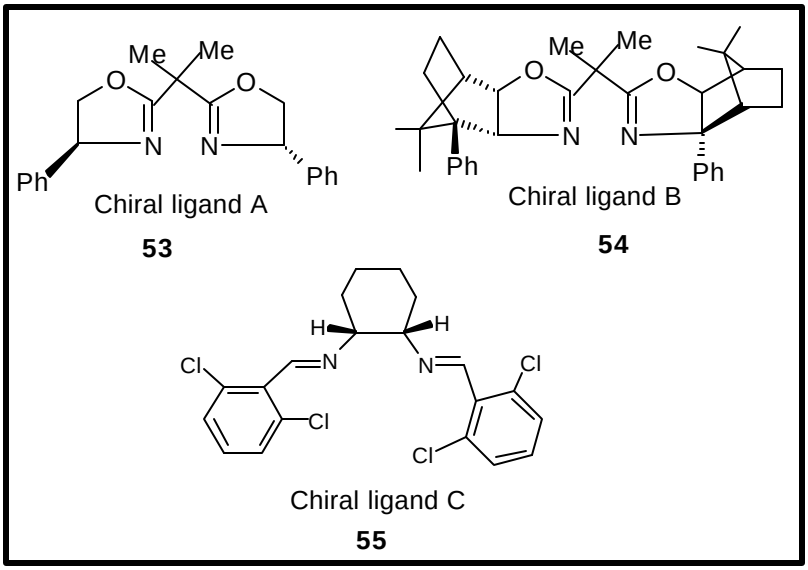

**Scheme -14**

Camphor sultam is used here as a stoichiometric chiral controller.[29]

**Enantioselective catalysis**

In the field of asymmetric synthesis, presently enantioselective catalysis occupies the top position. Many recent reports of catalytic asymmetric synthesis of aziridines have been discussed in the first review chapter on aziridination. Three pioneering developments in catalytic asymmetric aziridination are summarized in the **Scheme-15.**

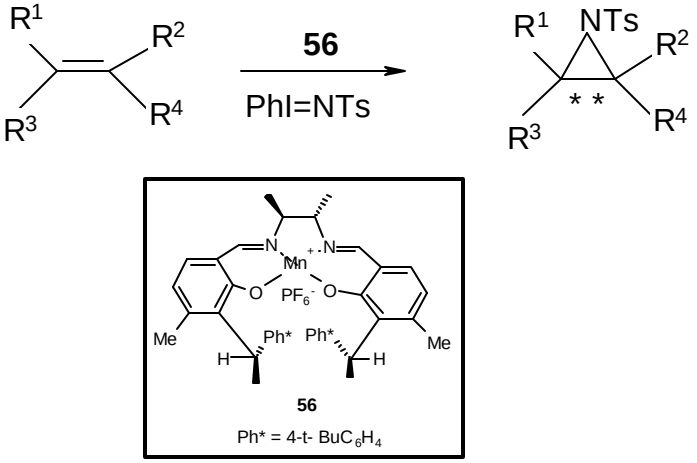



**Scheme-15**

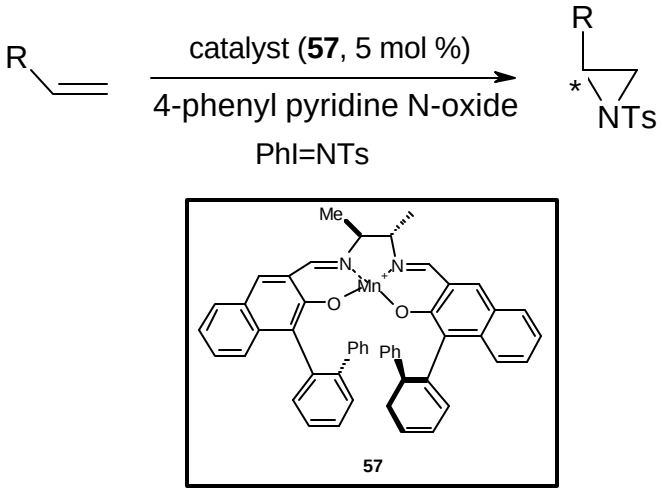
Evans *et al*. [30] have described the use of bis (oxazoline)-copper complex (**53**) as chiral catalyst for the enantioselective aziridination of olefins. They carried out a complete study of the effects of ligand architecture, medium effects and metal sources to develop an efficient process. Cinnamate ester substrates gave high enantioselectivities in non-polar solvents than in polar or Lewis basic media. In the case of β-methyl styrene the enantioselectivity increased with increasing solvent polarity. Jacobsen *et al.*[31] performed asymmetric aziridination of styrene with (diimine) copper (I) Schiff bases (**55**) as catalysts. Masamune and Lowenthal [32] used modified bisoxazoline ligand **54** to achieve enantioselective aziridination.

Since then, numerous reports of metal catalyzed asymmetric aziridination reactions using PhI=NTs as nitrene source have appeared. Mainly Cu(I) dinitrogen ligand complexes or salen manganese(I) complex as catalysts and PhI=NTs as aziridinating agent have been utilized in these reactions. But in most of these reports either the enantioselectivities are moderate or substrate specific or the chemical yields are low. For instance, aziridination of styrene with salen manganese (II) complex **56** gives a moderate ee of 61 % but with a very low chemical yield **(Scheme-16)**.



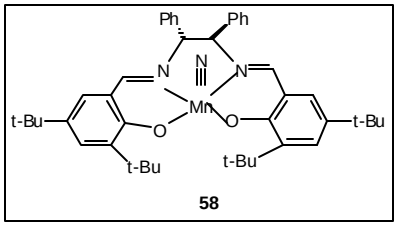

**Scheme -16**

Katsuki *et al*. [33] could increase the enantioselectivity to 94 % by introducing binapthyl moieties into the complex. **57** (**Scheme-17)**.

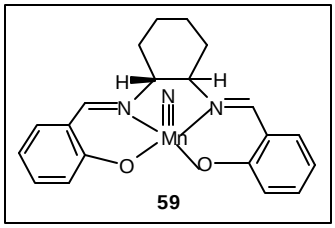



**Scheme - 17**

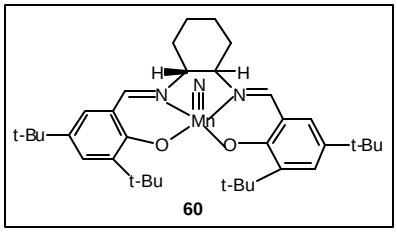
The reactions were carried out with 5 mole % of the catalyst in presence of 4-phenyl-N-oxide. In a recent report by Lau *et al.* [34] asymmetric aziridination using chiral salen manganese (V) nitrido complexes is described. They prepared various complexes and determined their crystal structures and screened them for asymmetric aziridination in presence of Bronsted or Lewis acids such as $F_3CCO_2H$ or $BF_3$- $Et_2O$. Aziridination with complex **58** with styrene and (E)-β-methyl styrene gave a high ee. However, very low ee was obtained for (Z)-β-methyl styrene. Complex **59** gave low yields and low ee (35 %, 30 % ee), while complex **60** gave low chemical yield of 7 %.



**58**

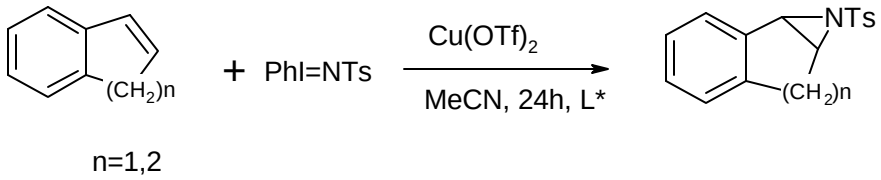


**59**



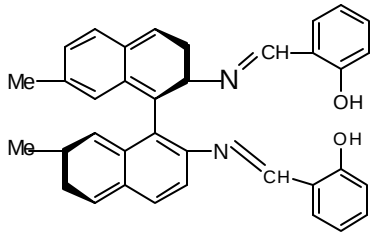
**60**

Shi *et al.*[35] prepared axially dissymmetric chiral diamine and diimine ligands having a 1, 1' -binaphthyl or 1,1'-biphenyl moieties and used their copper complexes to catalyze asymmetric aziridination of alkenes using PhI=NTs as the nitrene source **(Scheme - 18)**.



n=1,2

L* =




**Scheme-18**

The enantioselectivities achieved were dismally low. Clearly there is still a dearth of an effective general asymmetric synthetic scheme for aziridination of olefins.

**Present Work**

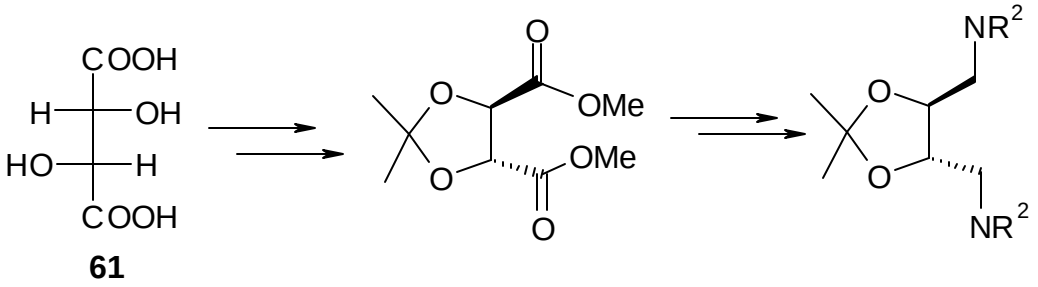
Transition metal catalysis is a highly attractive method to obtain chiral compounds since the chirality can be transferred from a small amount of chiral compound to a large amount of the product. Many of the exciting recent developments in stereoselective organic synthesis are based on transition metal catalyzed processes. To achieve this, efficient chiral ligands are required and hence current interest is devoted to them. The rational design of chiral ligands for enantioselective catalysis presents a formidable challenge. Although the preliminary reports discussed above include some impressive results, with application to *cis* as well as *trans* disubstituted olefins, the methods have not yet found much use for preparative purposes. All olefins undergoing enantioselective aziridination remain within a narrow branch of styrene derivatives. Moreover all the reports of successful chiral aziridination carried out so far have used only PhI=NTs as the nitrene source. The preparation of PhI=NTs is cumbersome, requires costly staring materials and leads to iodobenzene as the side product. Due to these considerations, it was decided to use Bromamine-T as a source of nitrene[36] and develop an enantioselective version of the aziridination methodology discussed in the previous chapter (Chapter-II). In the present work asymmetric synthesis of aziridines was studied using both naturally available chiral ligands and synthetically derived chiral ligands using transition metal complexes with Bromamine-T as aziridinating agent.

**$C_2$ symmetric diamine ligands derived from tartaric acid**

Chiral amines have proven to be versatile ligands in a variety of catalytic applications, in many cases inducing high stereoselectivity. Therefore they are gaining tremendous importance in asymmetric synthesis. They serve as chiral reagents [36], chiral auxiliaries [37] and also as ligands and ligand building blocks [38] in transition metal catalyzed asymmetric synthesis.

In the quest of getting enantiopure aziridines, synthesis of efficient chiral diamine ligands, which can be synthesized in few steps by using cost-effective materials, was planned. This led to selection of L(+)-tartaric acid as the starting chiral source, due to its low cost and wide availability in optically pure form. A series of $C_2$ symmetric diamines were synthesized [39] and screened for asymmetric aziridination reaction using Bromamine-T as the source of nitrogen. Some of these

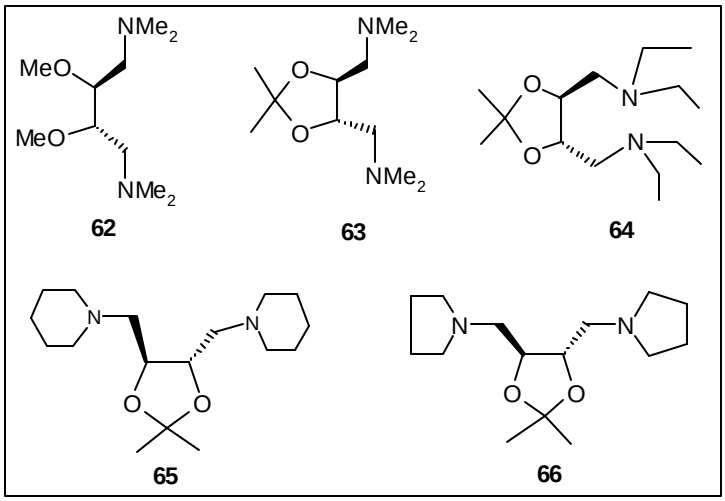
diamines have been used for asymmetric oxidation of olefins with osmium tetraoxide.[40] The synthetic steps starting from L- tartaric acid (**61**) are outlined below **(Scheme -19)**.




**61**

**Scheme -19**

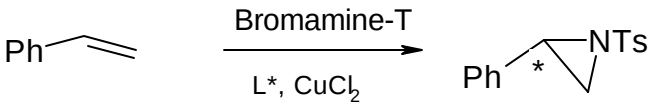
The following series of ligands (**62-66)** were synthesized using reported procedures [39, 40] and characterized.




**62** **63** **64**

**65** **66**

They were screened for asymmetric aziridination with Bromamine-T as nitrogen source and $CuCl_2$ as catalyst **(Scheme -20)**.



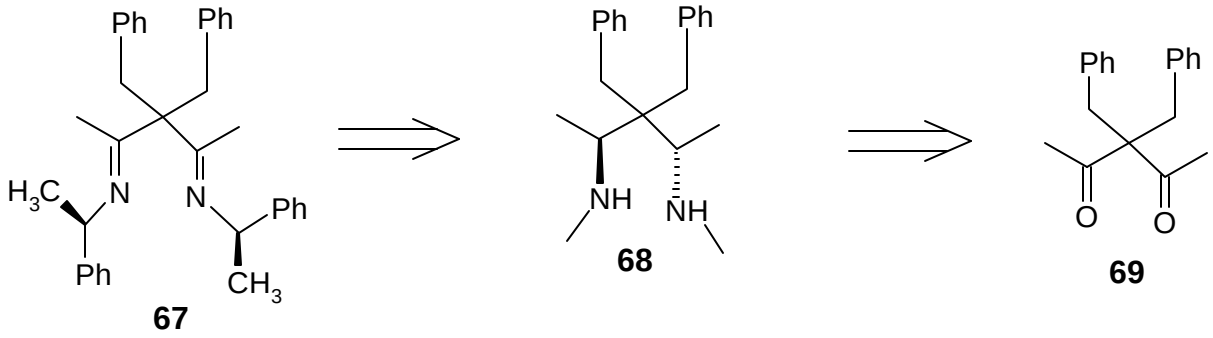

**49** **50**

**Scheme -20**

The reactions were performed at room temperature. First the metal-ligand complex was formed by stirring a solution of $CuCl_2$ and the ligand in dry acetonitrile for 2 hours at 60°C. Styrene was added and finally freshly prepared anhydrous Bromamine-T was added to the reaction mixture. There was no chiral induction with ligands **62, 63** and **66**. Ligand **64** gave a slight induction of 9 %. The highest ee of around 11 % was obtained with ligand **65.** As the enantiomeric excess seemed to increase with increasing steric bulk around nitrogen atom, synthesis of bulkier ligands with increased steric hindrance were planned.

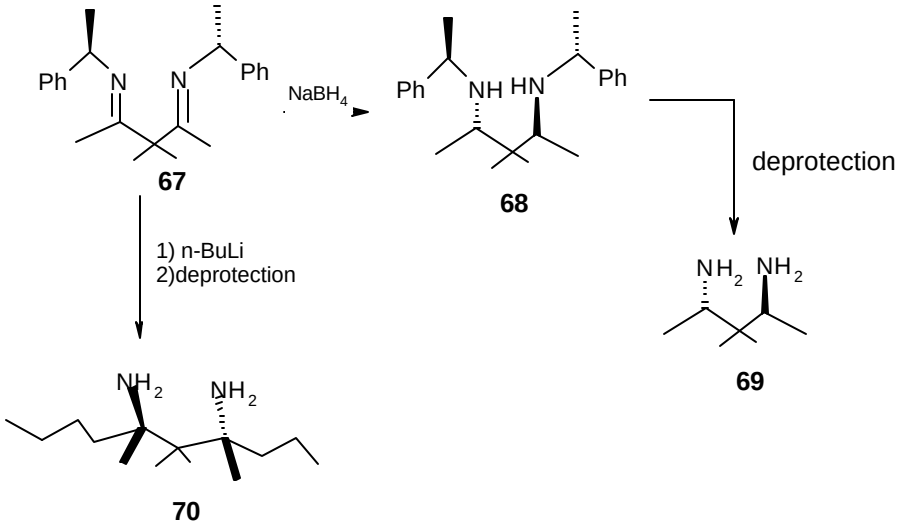
**Synthesis of sterically hindered imines**

A class of $C_2$-symmetric molecules that has been found to inhibit HIV protease contains 1, n-diamino functions (n = 3 - 5) as a structural feature.[41] In continuing efforts towards synthesis of $C_2$ symmetric diamines the sterically hindered 1, 3-bisimine (**67)** was designed. The retrosynthetic approach planned for its synthesis is shown below **(Scheme - 21)**.



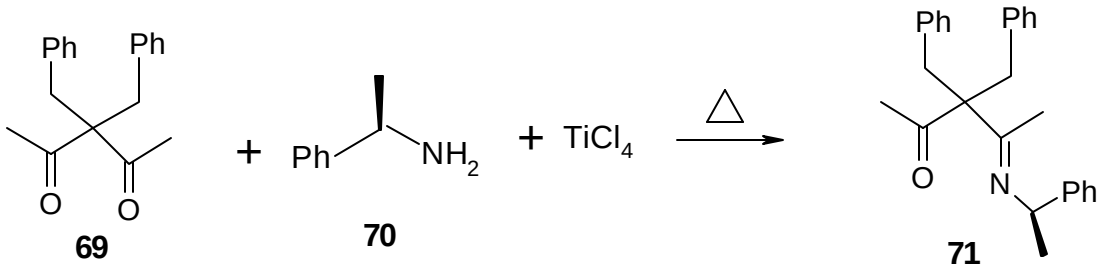

**Scheme -21**

The bisimine would undergo borohydride reduction to yield desired bisamine, which on deprotection under suitable conditions would yield the final 1, 3-diamine **69**. Alternately the bis imine could be lithiated with n-butyl lithium and deprotected to get the 1,3 diamine **70 (Scheme - 22)**.




**Scheme -22**

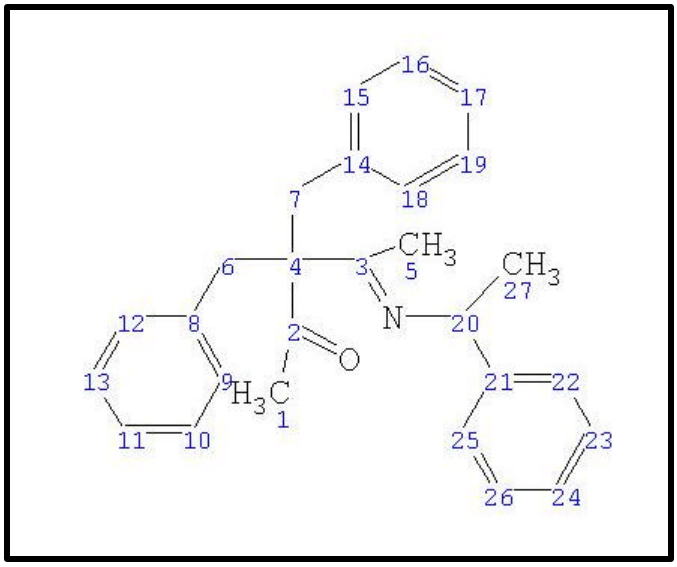
Towards this objective the corresponding diketone was prepared and then reacted with (R)-α- methyl benzyl amine in presence of $TiCl_4$ in anhydrous dichloromethane for 12 hours **(Scheme - 23)**.




**Scheme -23**

The desired bisimine **67** was not obtained. The product obtained was characterized to be the monoimine **71** from its nmr and mass spectra. An analysis of its $^1H$ nmr spectrum showed a doublet at δ 1.45 (J = 10.5Hz) corresponding to three protons which could be assigned to three methyl protons of α-methyl benzyl amine, a singlet of three protons at δ 1.8 arising due to methyl protons of the diketone part, another singlet of three protons at δ 2.1 corresponding to the other methyl group adjacent to nitrogen, a multiplet of four protons at δ 3.4 confirming the presence of benzylic protons, a quartet at δ 4.7 integrating for one proton adjacent to phenyl and methyl groups of the amine part and a multiplet at δ 7.2 region integrating for 15 aromatic protons .The structure was

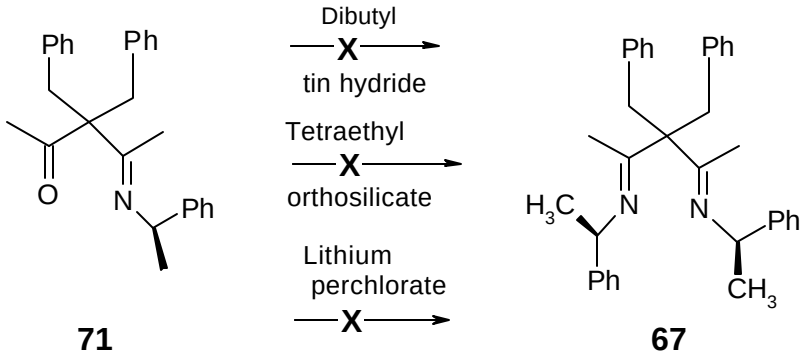
further confirmed by its $^{13}C$ NMR spectrum. The peaks were assigned for the corresponding carbon atoms of **71** as shown below.




In the $^{13}C$ NMR spectrum, the ketonic carbon C-2 appeared at 209.27 ppm and the phenyl carbon C-1 appeared at 145.2 ppm. The aryl carbons of the other two benzene rings i.e., C-18 and C-14 appeared at 137.6 ppm. Peaks in the region 120-130 ppm corresponded to the remaining 15 aromatic carbons. The characteristic C=N peak of C-3 appeared at 165.72 ppm. The quaternary carbon C-4 appeared at 67 ppm while the other quaternary carbon adjacent to nitrogen C-20 appeared at 59 ppm. The methylene carbons C-6 and C-7 appeared at 38 ppm. The methyl carbon C-2 of the acetyl group appeared at 27.2 ppm and the methyl carbon C-27 appeared at 24.2 ppm. . The methyl carbon C-5 of the imine part appeared at 16 ppm in the spectrum. The mass spectrum showed molecular ion peak at m/z 383 and a $M^{+1}$ peak at m/z 384 further corroborating the structure of **71**.

A comprehensive literature search was carried out to find other suitable methods for preparation of bisimines. Although the preparation of imines from ketones is well documented, many conventional methods i.e. KOH or azeotropic distillations do not apply to very hindered ketones. The use of $TiCl_4$ is recommended for such cases, however it has severe drawbacks viz. large excess of amine is required, HCl is obtained as the byproduct, sensitivity to substrate and reaction conditions and often loss in optical activity. There are a few reports of synthesis of bulky imine systems using reagents such as tetraethyl orthosilicate,[42] lithium perchlorate,[43] dibutyl tin

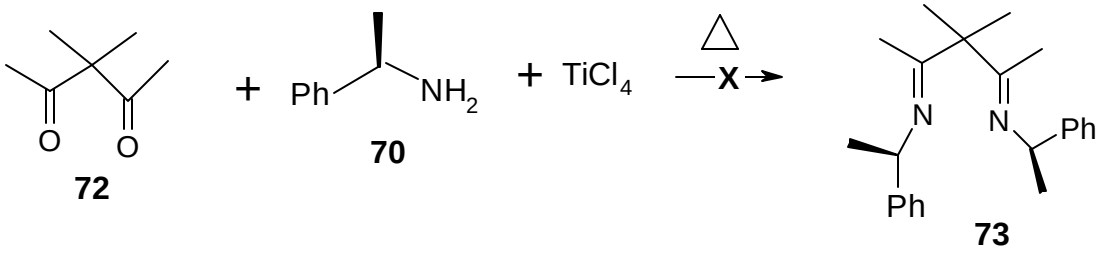
hydride[44] etc. The monoimine **71** was subjected to the conditions reported in the literature with the above mentioned reagents to obtain the desired bis imine. However all the attempts to synthesize bis imine were unsuccessful **(Scheme-24)**.




**71** **67**

**Scheme -24**

It was felt that the ligand was too bulky and the non-bonded interactions between the two phenyl groups were generating steric hindrance for the molecule to be synthesized. To minimize this effect, methyl groups were placed instead of the bulky phenyl groups in the target molecule. Dimethylation of the corresponding 1,3 diketone seemed an attractive strategy for this approach. Alkylation of 1,3-diketone is extensively investigated and many methods exist for it using DBU, TBAB etc. However none of the methods gave the desired diketone. Finally it was prepared by stirring 2,4-pentanedione in acetonitrile with methyl iodide in presence of potassium carbonate at room temperature .The dimethylated diketone was subjected to all the previous reaction conditions mentioned but unfortunately the desired bisimine was not obtained **(Scheme-25)**.

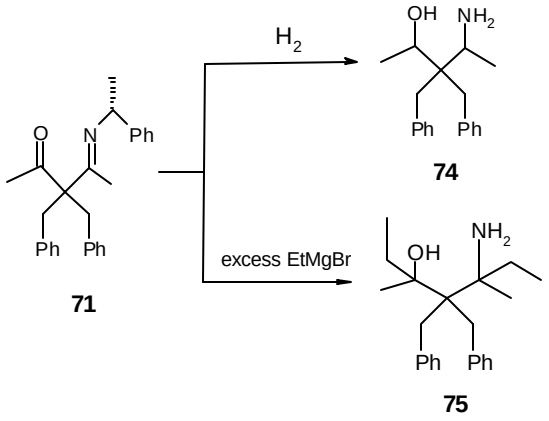



**72** **70** **73**

**Scheme -25**

Due to non-formation of the bis-imine, the above scheme was discontinued. Therefore the scheme was discontinued. However the monoimine **71** obtained can be reduced under suitable

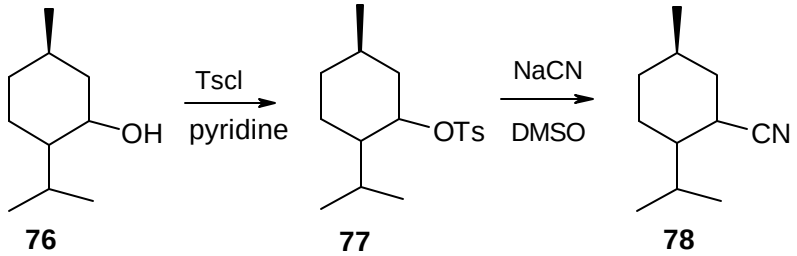
conditions to yield a chiral amino alcohol **74** which is also very useful compound in asymmetric synthesis. It has potential for application in diethylzinc addition to aldehydes, Diels Alder reaction etc. Alternately a Grignard reaction can be carried out on the monoimine with excess of the reagent to yield another chiral amino alcohol **75** as shown in **Scheme-26**.Work on these lines is in progress.




**Scheme-26**

**Menthol based ligands**

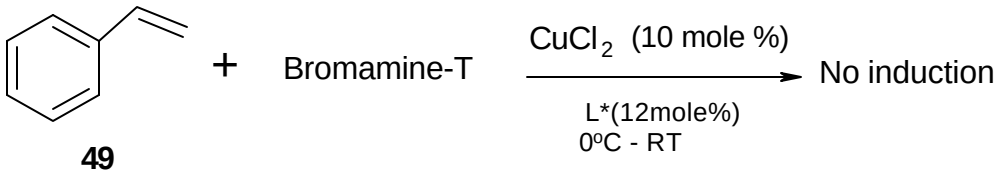
Menthol is a cheap and readily available chiral compound from the existing natural chiral pool. As the cyano group is known to be a good coordinating ligand and can complex with copper chloride readily, it was decided to synthesize cyano menthol and use it as a ligand for the present work. Cyano menthol (**78**) was prepared via menthyl tosylate[45] using the following steps[46] **(Scheme-27)**.




**Scheme -27**

Using this ligand, styrene was subjected to asymmetric aziridination reaction using Bromamine-T as nitrogen source at room temperature. However there was no asymmetric

induction. To achieve some enantioselectivity the temperature was lowered to 0°C, however there was still no effect on enantioselectivity and only racemic aziridine was obtained **(Scheme-28)**.

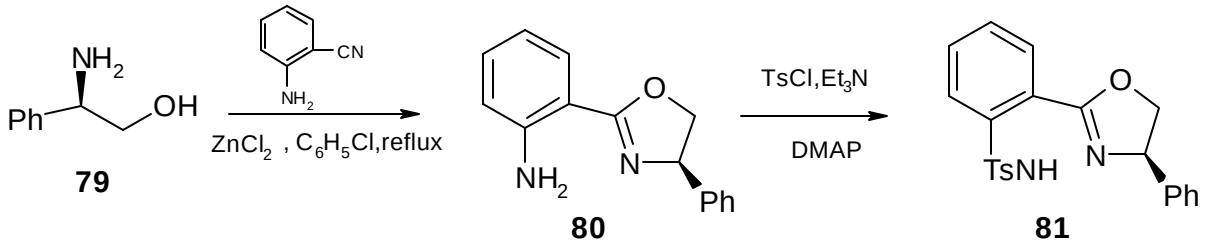



**Scheme -28**

**Enantioselective aziridination reaction of olefins using chiral oxazolines**

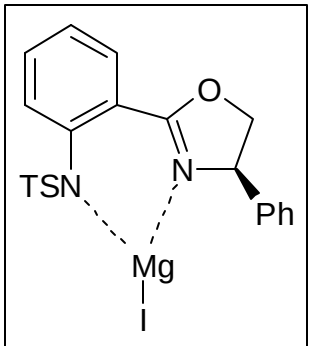
Oxazolines are an important functionality in synthetic organic chemistry. They Oxazolines have been extensively used as protecting groups[49], and optically active oxazolines are valuable auxiliaries in organic synthesis.[50] Recently developed oxazoline systems include semicorrin[51], aryl monooxazoline as well as bis oxazolines[52], and pybox.[53] These have been successfully employed in efficient transition metal catalyzed transformations.

In a recent report by Fujisawa *et al.* [54] a new chiral 2-(2p-Tolylsulfonylamino) phenyl-4-phenyloxazoline was complexed with magnesium (**82**) and found to undergo chiral Diels-Alder reaction with 91 % ee. With this background in mind the ligand **81** was synthesized using the reported procedure and screened for asymmetric aziridination reaction using Bromamine-T **(Scheme-29)**.



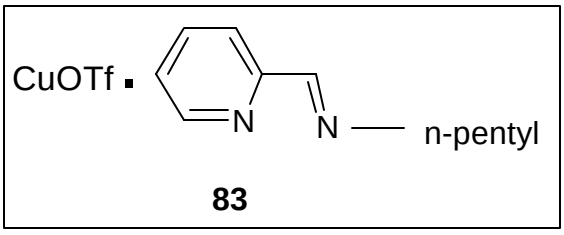

**Scheme-29**

However there was no asymmetric induction. This reaction was further tried in presence of sodium hydride, which would abstract the proton and make the nitrogen lone pair available for coordination with copper to obtain a ligand metal complex similar to magnesium oxazoline complex **82,** but there was still no induction in the product aziridine.



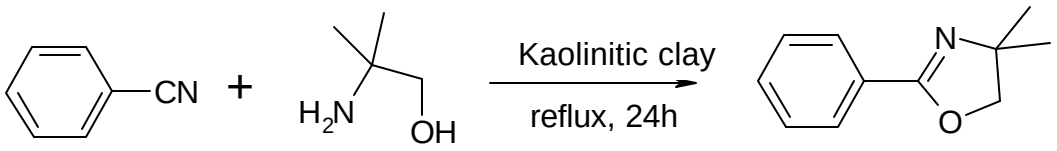

**82**

It was then decided to prepare other modified oxazolines. In a recent report by Taylor *et al.*[55] aziridination of olefins was carried out with hydrated Chloramine-T to explain the mechanism of the reaction. They selected the catalyst n-alkyl imine of pyridyl 2-carboxylate (**83**), which gave aziridine exclusively even without added molecular sieves. There was no trace of epoxide, which would have formed if it were an ionic mechanism. This led them to conclude that nitrene transfer mechanism is operative in the presence of donor ligands.



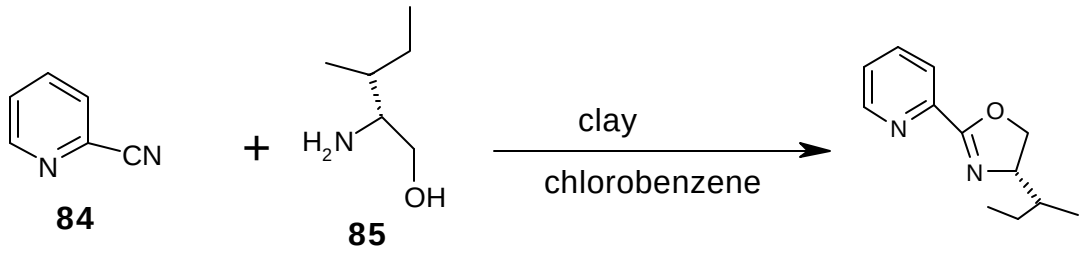

**83**

It was therefore felt that similar type of ligands possessing a 2- pyridyl skeleton would efficiently complex with copper (II) and give high enantioselectivities. A methodology [56] has been recently developed in our laboratory, which provides a convenient one-pot synthesis of 2-oxazolines in good yields under mild conditions **(Scheme-30)**.



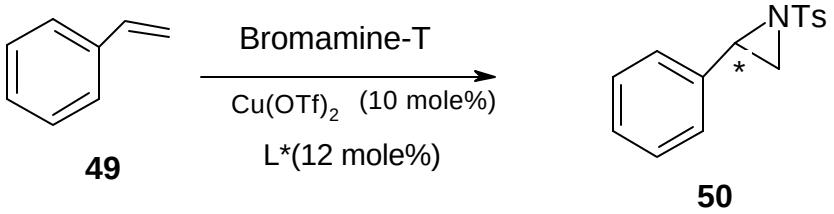

**Scheme-30**

A mixture of benzonitrile and kaolinitic clay (20 % w/w), was refluxed in 2-amino 2-methylpropanol for 24 hours to afford 2-phenyl 4,4- dimethyl -2-oxazoline in good yields. This methodology was applied to synthesize the chiral oxazoline **86** from amino alcohol **85** and 2-cyanopyridine (**84**)**.** The pyridyl oxazoline was obtained in good yield and also gave good ee. This class of pyridyl oxazolines is known to be efficient ligands in several asymmetric transformations[57] **(Scheme-31)**.




**Scheme - 31**

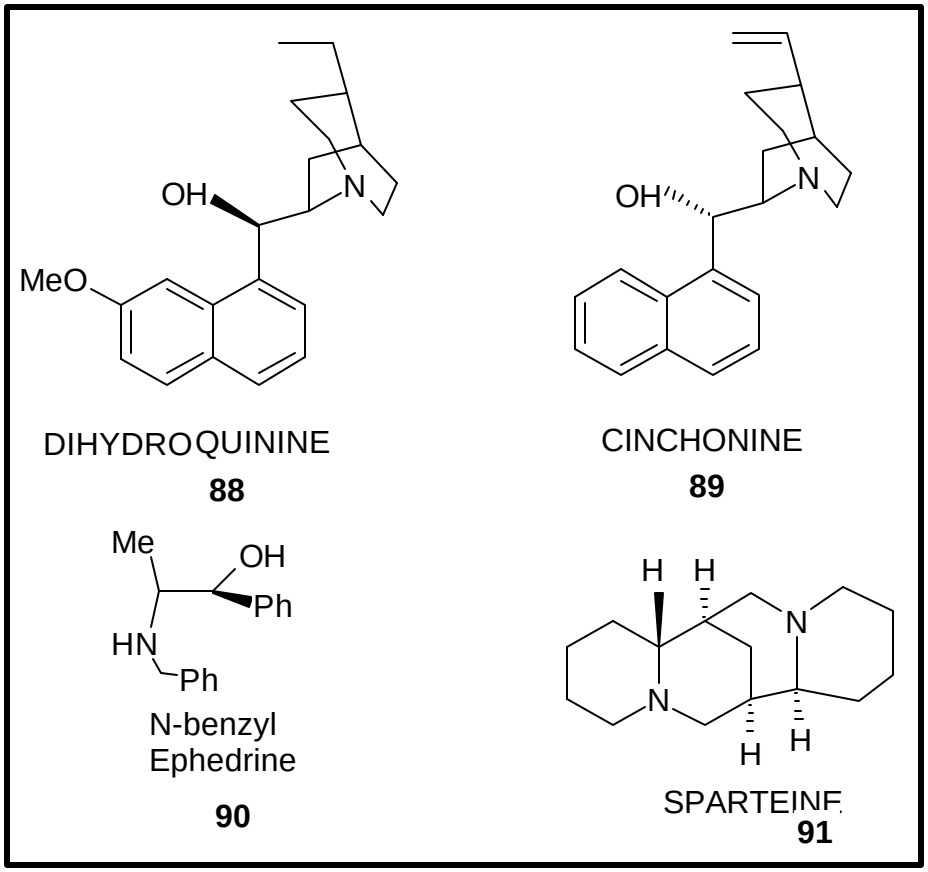
The asymmetric aziridination of styrene was carried out under the usual conditions with this ligand and an enantioselectivity of 17 % was obtained **(Scheme-32)**.




**Scheme - 32**

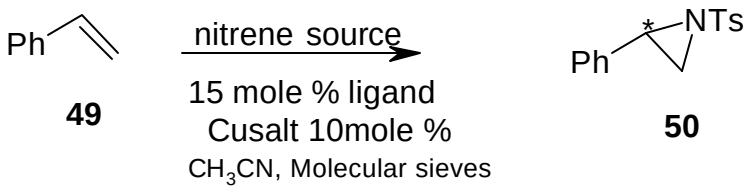
**Enantioselective aziridination with cinchona alkaloids**

Encouraged by the above results, which indicated that ligands with strong carbocyclic framework and steric hindrance around the nitrogen atom are appropriate for the asymmetric induction in aziridines, a literature search was carried out to select such ligands from the existing natural chiral pool. Alkaloids serve as ideal ligands, with strong carbon framework and appropriate position of the nitrogen atom to coordinate with the transition metal. They have been used in various organic transformations. Naturally available cinchona alkaloids viz., quinine (**87**), dihydroquinine (**88**) cinchonine (**89**), N-benzyl ephedrine (**90**) and sparteine (**91**) were chosen as ligands for enantioselective aziridination of olefins.




Dihydroquinine was prepared by reduction of quinine using the standard procedure while other ligands were commercially obtained.At first the metal ligand complex was formed by heating a suspension of anhydrous copper (II) chloride and quinine (12 mole %) in dry acetonitrile at 60 $^{o}$C

for two hours. Then Bromamine-T or PhI=NTs (1 mole) and finally the olefin (5 moles) was added after the reaction mixture was brought to room temperature **(Scheme-33)**. The reaction mixture was stirred for another five hours. The results obtained are summarized in **Table-1.**




**Scheme -33**

**Table-1: Enantioselective aziridination of olefins using copper alkaloid complexes**

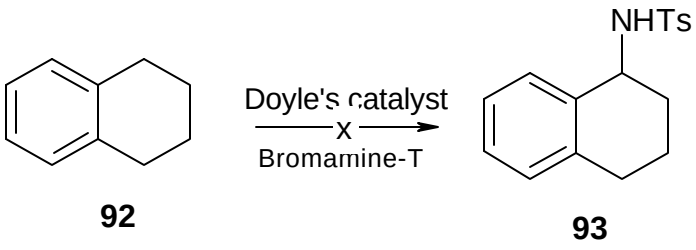
| **Entry** | **Substrate** | **Nitrene source** | **Solvent** | **Metal salt** | **Ligand** | **Yield %** | **ee[a] %** |
|---|---|---|---|---|---|---|---|
| (a) | Styrene | PhI=NTs | EDC | $Cu(acac)_2$ | Quinine | 50 | 28 |
| (b) | Styrene | PhI=NTs | $CH_3CN$ | $CuCl_2$ | Quinine | 43 | 17 |
| (c) | Styrene | Chloramine-T | $CH_3CN$ | CuCl | Quinine | 32 | 7 |
| (d) | Styrene | Bromamine-T | $CH_3CN$ | $CuCl_2$ | Dihydroquinine | 39 | 43 |
| (e) | Styrene | Bromamine-T | $CH_3CN$ | $CuCl_2$ | Cinchonine | 10 | 20 |
| (f) | Styrene | Bromamine-T | $CH_3CN$ | $CuCl_2$ | N-benzyl ephedrine | 60 | 10 |
| (g) | DHN | Bromamine-T | $CH_3CN$ | $CuCl_2$ | Sparteine | 38 | 12 |

[a] the ee's were measured by comparison with known optical rotation values.

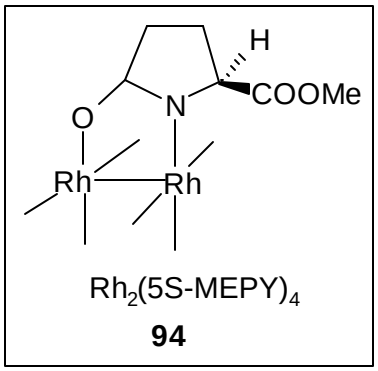
As is evident form **Table-1** the highest enantioselectivity is obtained from the cinchona alkaloids especially dihydroquinine (entry d). The cinchonine ligand gives the opposite enantiomer albeit in low enantioselectivity (entry e).

**Chiral benzylic amination**

A methodology for benzylic amination with Bromamine-T and rhodium acetate has been discussed in the previous chapter (Section A, Chapter II). An enantioselective version of the same using rhodium based chiral ligands was envisaged. Towards this objective, commercially available Doyle's catalyst $Rh_2[MEPY]_4$ (**94**) was chosen as the chiral ligand due to its tremendous success in achieving high enantioselectivities in cyclopropanation reactions. Tetralin (**95)** was subjected to benzylic amination reaction at room temperature under the usual reaction condition with 5 mole % of the catalyst **94**. However surprisingly the product obtained was characterized to be tetralone and not the expected benzylic amination product **93 (Scheme -34)**.




**92** **93**




**94**

**Scheme -34**

Probably there is hydrolysis of the intermediate rhodium nitrene complex under the present reaction conditions and the substrate undergoes some sort of oxidation reaction to give the product. Further study with different nitrene precursors and different substrates is under progress to explicate the present observation.

## Conclusions

The application of various classes of ligands to asymmetric aziridination has been demonstrated. Asymmetric aziridination of alkenes with Bromamine-T as source of nitrogen has been evaluated for the first time. A new sterically hindered chiral imine has been prepared which will also find applications in important organic transformations like Diels-Alder reaction, diethyl zinc addition to aldehydes etc. Even though the enantioselectivities obtained are low, the results suggest that some of the copper ligand complexes described have potential as catalysts for asymmetric aziridination.

## Experimental

### Synthesis of tartaric acid derived ligands (62-66)

**Dimethyl 2,3-O-isopropylidene-L-tartarate**: In a 50 mL round bottomed flask fitted with a reflux condenser and a magnetic bar under argon, a mixture of L-tartaric acid (10.1 g, 0.673 mol), 2,2-dimethoxy propane (19 mL, 16.1 g, 1.54 mol), methanol (4 mL) and p-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) was warmed on a steam bath with occasional swirling until a dark red homogeneous solution was obtained. Additional 2,2-dimethoxypropane (9.5 mL, 8.05 g, 0.77 mol) and cyclohexane (45 mL) were added and the flask was fitted with a 30 cm Vigruex column and a variable reflux distilling head. The mixture was heated to reflux with internal stirring and the acetone-cyclohexane azeotropes were slowly removed. Additional 2,2-dimethoxypropane (0.6 mL, 2.5 g, 49 mmol) was then added and the mixture heated under reflux for 15 min. After the mixture had cooled to room temperature, anhydrous potassium carbonate (0.1 g, 7.2 mmol) was added and the mixture was stirred well until the reddish color had abated. Volatile material was removed under reduced pressure and the residue was fractionally distilled under vacuum to afford the product as pale oil, b.p. 94$^{o}$C(0.5mm), lit. b.p. 94-101$^{o}$C.

| | |
|---|---|
| **Yield** | 13.2 g (91 %). |
| **IR** (neat) | 2957, 1761, 1439, 1213, 859cm.$^{-1}$. |
| **$^{1}$H NMR** | $\delta$ 4.8(s, 2H). 3.7(s, 6H), 1.5(s, 6H). |

**2,3-Di-O-isopropylidene-L-threitol**: In a dry, 2 L, three necked round bottomed flask equipped with a 50 mL pressure equalizing funnel, reflux condenser, thermometer and a magnetic stirring rod was suspended lithium aluminium hydride (3.6 g, 0.95 mol) in distilled ether (60 mL) under argon. The mixture was stirred and heated to reflux for 30 min. Heating was continued while a solution of dimethyl 2,3-O-isoprpylidene-L-tartarate (12.3 g, 0.564 mol) in diethyl ether (30 mL) was added dropwise over 2 h. Heating was resumed and the mixture was refluxed for an additional 3 h. It was cooled to 0$^{o}$C and cautiously treated with water (3.6 mL), and then stirred at room temperature until the grey color of unquenched lithium aluminium hydride had completely disappeared. The mixture

was filtered on a Buchner funnel and the inorganic precipitate was extracted with ether. The combined ethereal extracts were dried over sodium sulfate and filtered and volatile material was removed under reduced pressure. The residue was fractionally distilled under vacuum to afford the product as a colorless to pale yellow oil.

| | |
|---|---|
| **Yield** | 5.47 g (60 %) |
| **B.P**. | 95$^{o}$C(0.4 mm) (Lit [39] B.P. 94-106 $^{o}$ C) |
| **IR(neat)** | 3413,2987, 2930,1455,1372,1057, 801 cm-$^{1}$. |
| **$^{1}$H NMR** | δ 3.9(m, 2H) 3.7(m, 4H), 2.8(bs, 2H), 1.4(s, 6H). |
| **$^{13}$C NMR** | δ 26.7, 62.1, 78.45, 109.13. |

**1,4-Ditosyl-2-3-O-isopropylidene L threitol**

To 1 g (6.2 mmol) of reduced product (alcohol ) in 10 mL of dry pyridine at -10 $^{o}$C, 3 g (5.7 mmol) of finely powdered p-toluensulfonyl chloride was added in one portion. The mixture was stirred until homogeneous and kept at 0$^{o}$C for 12 hours. The product was crystallized by slow addition of water (2-3 h). The product was then washed on filter with 95 % ethanol. It was recrystallized from ethanol.

| | |
|---|---|
| **Yield** | 2.13 g (70 %) |
| **M.P**. | 90$^{o}$C (Lit. M.P. 91$^{o}$C) |
| **IR (neat)** | 2988, 2955, 1724, 1189, 1096, 934, 815, 666 cm$^{-1}$. |
| **$^{1}$H NMR** | δ 7.85(d, *J* = 8.1 Hz, 4H). 7.3(d, *J* = 8.1 Hz, 4H), 4.2 (m, 4H), 3.9(m, 2 H), 2.9(s, 6H), 1.25(s, 6H). |

**General procedure for the last step in the preparation of the ligands 62-66**

The ditosylated product (1 mmol) obtained from the previous step was taken in 2 mmol of the corresponding amine and heated at 60 $^{o}$C for three hours and then stirred at room temperature for 12 h. The reaction mixture was then cooled in an ice bath and brought to room temperature. To it 50 mL water was added and the reaction mixture was extracted twice with ether. It was then dried over sodium sulfate and concentrated *in vacuo* to yield the final diamine ligand.

**General procedure for the asymmetric aziridination reactions using ligands 62-66**

A 25 mL round bottomed flask was charged with the tartarate ligand (12 mole %) and copper chloride (10 mole %). Anhydrous acetonitrile (6 mL) was added via syringe and the resulting mixture was stirred for 2 h at room temperature. This mixture was then transferred via cannula to a septum capped 25 mL round bottomed flask containing suspension of olefin (5 mmol), anhydrous Bromamine-T (1 mmol) and 200 mg activated 5A$^{o}$ powdered molecular sieves at 0$^{o}$C. The reaction mixture was stirred for additional 6 h at room temperature. Then it was diluted with ethyl acetate and filtered though a short plug of silica gel. The silica gel was thoroughly washed with additional portions of ethyl acetate and the filtrate was concentrated by rotary evaporation. The aziridine product was isolated by flash chromatography with elution by pet ether: ethyl acetate (75:25).

**(S,S)- (+)- 2,3-Dimethoxy- N,N,N',N'- tetramethyl-1,4-butandiamine ( 62)**

| | |
|---|---|
| **Yield** | 0.247g (60 %). |
| **IR** ($CCl_4$) | 2970, 2940, 2760, 1455, 1150, 1040, 750 cm$^{-1}$. |
| **$^{1}$H NMR** | δ 3.4-3.0(m, 2H), 3.2(s, 6H), 2.4-1.8(m, 4H), 2.10(s, 12H). |
| **$^{13}$CNMR** | 78.9, 59.3, 58.4, 46.3. |
| **Analysis** | Calculated for $C_{15}H_{32}NO_2$ ; C = 58.78 %, H = 11.84 %, N = 13.7 % |
| | Observed C = 58.94 %, H = 11.88 %, N = 16.6 %. |
| **[ a ]$_D^{25}$** | +.14.7 $^{o}$(neat). |

**(S,S)-(+)- 3,4-Isopropylidenedioxy- N,N,N',N'-tetramethyl-1,4-butandiamine(63)**

| | |
|---|---|
| **Yield** | 0.336 g (77 %). |
| **IR** ($CHCl_3$) | 980, 910, 1110, 1160, 1375, 1470, 2700 cm$^{-1}$. |
| **$^{1}$H NMR** | δ 3.85(m, 4H), 3.5(m, 2H), 3.34(s, 6H), 1.32(s, 12H). |
| **Analysis** | Calculated for $C_{11}H_{20}NO_4$; C = 61.08 %, H = 11.18 % |
| | Observed C = 61.35 %, H = 11.48 %. |
| **[ a ]$_D^{25}$** | +7.78 $^{o}$(neat). |

**(S,S)-(-)- 2,2-Dimethyl-4,5 bis(pyrrolidino methyl)-1,3-dioxolane (64)**

| | |
|---|---|
| **Yield** | 371 mg (68 %). |
| **IR** ($CHCl_3$) | 2968, 2878, 2795, 1630, 1460, 1370, 1106,755 $cm^{-1}$ . |
| **$^1$H NMR** | δ 3.8-3.7(m, 2H). 2.6-2.5(m, 12H), 1.8-1.7(m, 8H), 1.4(s, 6H). |
| **MS** m/z ( %) | 269 (1.2, $M^+$ ), 253 (11), 193 (10.5), 184 (65), 84 (100), 126 (70). |

**(S,S)- (-) 2,2 Dimethyl-4,5 bis(piperidino methyl), 1,3-dioxolane (65)**

| | |
|---|---|
| **Yield** | 359 mg (60 %). |
| **IR** ($CHCl_3$) | 2987, 2785, 1302, 1075, 1121, 1057, 758. |
| **$^1$H NMR** | δ 3.9-3.7 (m, 2H). 2.6-2.3(m, 12H), 1.7-1.3(m, 12H), 1.35 (s, 6H). |
| **$[a]_D^{25}$** | -37.8$^o$(c = 2, MeOH). |

**(S,S)-(-)- 1, 3-dioxolane-4-5-dimethanamine, a , a '-dibutyl-2-2-dimethyl (66)**

| | |
|---|---|
| **Yield** | 327 mg (61 %). |
| **IR** ($CHCl_3$) | 2985, 1671, 1452, 1210, 743 $cm^{-1}$. |
| **$^1$H NMR** | δ 4.3-4.2(m, 6H) 3.0(q, *J* = 5.4 Hz, 8H), 1.5(s, 6H), 1.3(t, *J* = 5.4 Hz, 12H). |

**Synthesis of menthol based ligands**

**(1R,2S, 5R)-Menthotosylate( 77)**

To l-menthol (2.5 g, 15 mmole) in dry pyridine was added recrystallized tosyl chloride (4.5 g, 22 mole) at 0 $^o$C. The reaction mixture was stirred overnight at room temperature. After aqueous work up a white solid was obtained in 90 % yield.

| | |
|---|---|
| **Yield** | 3.06 g (90 %). |
| **IR** (nujol) | 2956, 2913, 1455, 1179, 913, 875 $cm^{-1}$. |
| **$^1$H NMR** | δ 7.88(d, *J* = 8 Hz, 2H), 7.3(d, *J* = 8 Hz, 2H), 2.4(s, 3H), 2.2(d, 11Hz, 3H,), 1.9(m, 1H), 1.6-1.0(m, 7H), 1-0.2 (m, 8 H). |

**Preparation of (1S,2S, 5R)-1-cyano-2-isopropyl-5-methyl cyclohexane (78)**

Menthyl tosylate (2.60 g, 8.44 mmol) and sodium cyanide (830 mg, 16.9 mmol) were stirred in DMSO (50 mL) at 90 $^{o}$C for 5 h. The reaction mixture was diluted with water and extracted using EtOAc. The combined organic phases were dried over $Na_2SO_4$ and vacuum distilled to give the desired nitrile.

**Yield** 1.448 g (90 %).

**$^{1}$H NMR** δ 3.05(m, 1H) 1.9(dq, *J*=13 and 3Hz, 1H), 1.9-1.85 (m, 1H), 1.8-1.6 (m, 2H), 1.63-1.5(m, 1H), 1.3-1.2 (m, 1H), 1.1(ddd, *J* = 13,1,4 Hz, 1H) 0.96(dd, *J* = 6 Hz, 6H), 0.9(d, *J* = 6 Hz, 3H), 1-0.80 (m, 2H).

**MS** m/z (%): 164 (2.5, $M^{+}$), 150 (11), 136 (4), 122 (62), 81 (100), 69 (65).

**Synthesis of oxazoline based ligands**

**Preparation of 2-(2-p-tolylsulfonylamino)phenyl -4-phenyl oxazoline (81)**

A mixture of 2-aminobenzonitrile (1 g, 9 mmol) with D-phenyl glycinol (1.22 g, 9 mmol) in chlorobenzene(10mL) in presence of catalytic amount of zinc chloride was refluxed at 170 $^{o}$C for 4 days to afford 2-(2-aminophenyl)-4-phenyloxazoline (1.45 g, 60 % yield) which was further reacted with toluene sulfonylchloride(1.64 g, 8 mmole), triethylamine( 2.9 g, 29 mmole) and catalytic amount of DMAP at room temperature for 2 days. The product obtained after workup was recrystallized from petether to give oxazoline **81**.

**Yield** 2.68 g (90 %).

**IR** (neat) 3100, 2825, 1601, 1597, 1354, 950 cm.$^{-1}$.

**$^{1}$H NMR** δ 7.77(m, 4H). 7.32(m, 9H), 5.5(dd, *J* = 2.1 Hz and 4.2 Hz, 1H), 4.69(dd, *J* = 2.8 Hz and 3.5Hz, 1H), 4.2(dd, *J* = 2.8Hz and 2.81Hz, 1H), 2.35(s, 3H).

**$^{13}$C NMR** δ 164.5, 143.5, 141.4, 139.3, 36.6, 132.7, 129.5, 129.4, 28.7, 12.9, 127.9, 127, 126, 122.4, 117.9, 113, 73.4, 69.4, 21.2.

**Synthesis of (S)-(-)-4-isobutyl 2-(2-pyridyl) oxazoline (86)**

The amino alcohol was prepared according to the literature procedure using iodine and borohydride from corresponding amino acid.[58]

A mixture of 2-cyanopyridine (1 g, 9 mmol), kaolinitic clay (20 % w/w) and isoleucinol (1.05 g, 9 mmol) was refluxed in chlorobenzene for 10 h. The catalyst was filtered and the filtrate evaporated *in vaccuo*. The resulting reaction mixture was purified by column chromatography to yield the oxazoline **90**.

**Yield** 1.48 g (80 %).

**IR** (neat) 3382, 3019, 1665, 1524.26, 1215, 763, 69 $cm^{-1}$.

**$^1$H NMR** δ 8.6 (m, 1H), 8.3 (m, 1H), 7.9(m, 1H), 7.4(m, 1H), 4-3.8 (m, 3H), 1.8(m, 1H), 1.25 (m, 2H), 0.95(m, 6H) .

**Synthesis of sterically hindered mono imine ligand.**

**Preparation of dimethylated 1,3 diketone (72)**

To a stirred mixture of acetyl acetone (2 g, 19 mmol) and methyl iodide (2.48 mL, 39 mmol) in dry acetonitrile, activated and powdered potassium carbonate (15 g, 11.4 mmol) was added in one portion. The reaction mixture was further stirred at room temperature for two days. The inorganic materials were removed by filtration and the reaction mixture was washed with ether. It was then concentrated *in vacuo* to give a crude product, which was column purified to give the desired diketone.

**Yield** 1.98 g (65 %).

**IR** ($CHCl_3$) 1719, 1701 $cm^{-1}$.

**$^1$H NMR** δ 1.96 (s, 6H), 1.19 (s, 6H).

**MS** m/z (%): 128 ($M^+$, 0.3), 71(100).

**Preparation of dibenzyl 1,3 diketone (69)**

Benzyl bromide (3.38 g, 19 mmol) was added dropwise through syringe to a stirred solution of acetyl acetone (1 g, 9 mmol) under argon. The reaction mixture was refluxed for 6 hours to yield the final product.

**Yield** 2.14 g (68 %).

**IR** ($CHCl_3$) 2922 , 2860, 1696, 1489, 1265, 1080, 700 $cm^{-1}$.

**$^1$H NMR** δ 7.21(m, 6H). 7(m, 4H), 3.21(s, 4H), 2.18(s, 6H).

**MS** m/z (%): 281($M^{+1}$, 4), 280 (5, $M^+$), 237(100), 189 (90), 147 (70), 91(63).

**Synthesis of {(3, 3-dibenzyl)- 4-[phenyl ethyl] imino}-2-pentanone( 71)**

R(-)-α-Methyl benzyl amine (1 g, 8.9 mmol) and triethylamine (5.8 mL, 42 mmol) were taken in dry toluene and stirred at room temperature. The reaction flask was cooled to $0^oC$ and $TiCl_4$ in dichloromethane (0.58 mL, 4.2mmol) was added via syringe to the stirred solution under argon. Finally the diketone, **69** (1 g, 3.5 mmol) was added in small portions to the flask. The reaction mixture was then allowed to reflux for 12 hours. It was then diluted with ether and filtered through celite and concentrated *in vacuo* to give a thick yellow liquid. TLC, Rf =0.5(90:10 petroleum ether: ethyl acetate). Column purification on neutral alumina with 6 % ethyl acetate- pet ether as eluent gave the monoimine product.

| | |
|---|---|
| **Yield** | 0.889 g (65 %). |
| **IR** ($CHCl_3$) | 3022, 2959.4, 2929, 287, 1599 $cm^{-1}$. |
| **$^1$H NMR** | δ 7.4-7.2(m, 15H). 4.7(q, *J* = 5.4 Hz, 1H), 3.3-3.4(m, 4H), 2.1(s, 3H), 1.8(s, 3H), 1.45(d, *J* = 5.4 Hz, 3H). |
| **MS** m/z (%): | 384($M^+$, 0.2), 340(21), 236(12), 188(35), 157(53), 105(100), 91(60). |
| **$^{13}$C NMR** | δ 209.27, 165.72, 145.2, 137.6, 130, 128.6 128.9,128.4, 128.1, 126.8, 126.4, 77.8, 77.2, 76.6, 67.79, 59.6, 38.2, 27.6, 24, 16.7. |
| **Analysis** | Calculated for $C_{27}H_{29}NO$ ; C = 70 %, H = 7.5 %, N = 3.6 %<br>Observed C = 69 %, H = 7.37 %, N = 3.2 %. |

**Procedure for the synthesis of N- benzylated ephedrine (90)**

500 mg (3 mmol) of ephedrine was dissolved in 10 mL of dry THF and stirred at room temperature. To this, 60 mg (3.5 mmol) benzyl bromide and 40 mg anhydrous potassium carbonate were added. The reaction mixture was then refluxed for 5-6 h. The inorganic solid was filtered off and the crude reaction mixture was column chromatographed to give the desired product.

| | |
|---|---|
| **Yield** | 2.6 g (65 %) |
| **$^1$H NMR** | 7.4-7.3(m, 10 H), 4.9(d, *J* = 5.1Hz, 1H), 3.6(s, 2H), 3.0-2.9(m, 1H), 2.2(s, 3H), 1.9(bs, 1H), 1.1(d, *J* = 7.8 Hz, 3H). |

Hydroquinine (**88**) was prepared by hydrogenation of quinine sulfate in presence of $PdCl_2$ as reported in the literature.[60]

**General procedure for the asymmetric aziridination of olefins using alkaloid ligands (91-94)**

Hydroquinine (38 mg, 0.12 mmol) and copper (II) chloride (13 mg, 0.10 mmol) were stirred under argon in anhydrous acetonitrile at 60$^o$C for two hours. To this mixture was added olefin (458 mg, 5 mmol), powdered molecular sieves (500 mg) and dry Bromamine-T (250 mg, 1 mmol). The heterogeneous mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with ethyl acetate and passed through a short plug of silica gel. The solvent was concentrated *in vacuo* and was column purified to give the desired aziridine.

PhI=NTs was prepared by the reported literature procedure from diacetoxy iodo benzene and p-toluenesulfonamide.[59]

***N*- (*p*-Tolylsulphonyl)-2-phenyl aziridine (50)**

| | |
|---|---|
| **Yield** | 38 mg (38 %). |
| **IR** | 3017, 1327, 1217, 1161, 916, 783, 769, 713, 696, 665 cm$^{-1}$. |
| **$^1$H NMR** | δ 8.20 (d, *J* = 10.8 Hz, 2H), 7.59 (m, 7H), 4.18 (dd, *J* = 9.7 Hz and 6.5 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 2.82 (s, 3H), 2.72 (d, *J* = 6.3 Hz, 1H). |
| **MS** m/z (%) | 273 ($M^+$, 5), 155 (4), 118 (83), 91 (100). |
| **$[a]_D^{25}$** | Calculated 97.2 $^o$ (c = 1, $CHCl_3$) |
| | Observed 41.7 $^o$ (c = 1, $CHCl_3$) |
| **Enantiomeric excess** | 43 % |

***N*- (*p*-Tolylsulphonyl)amino-1,2,3,4-- tetrahydronapthalene-1, 2- imine**

| | |
|---|---|
| **Yield** | 41.4 mg (38 %). |
| **IR** | 1599, 1150, 1092, 990, 665 $cm.^{-1}$. |
| **$^1$H NMR** | δ 7.85(d, *J*=8.5Hz, 2H), 7.25-7.15(m, 6H), 3.80(d, *J*= 7.7 Hz, 1H), 3.55(d, *J*= 6.9Hz, 1H), 2.70(dt, *J*=15.5 and 5.2Hz, 1H), 2.60(dd, *J*=16.5 and 6.2Hz, 1H), 2.49(s, 3H), 2.32(dd, *J*=15.2 and 5.3Hz, 1H), 1.71(dt, *J*=13.7 and 5.4Hz, 1H) |
| **MS** m/z (%) | 299($M^+$, 1), 226(1.5), 144(100), 117(67), 91(32). |
| **$[a]_D^{25}$** | Calculated 99 $^o$ (c = 1, $CHCl_3$) |
| | Observed 11.88 $^o$ (c = 1, $CHCl_3$) |
| **Enantiomeric excess** | 12 % |

## References


1. Tanner, D., *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 599.
2. Osborn, H.M.I. and Sweeney, J., *Tetrahedron Asymmetry*, **1997**, 8, 1693.
3. a) Tanner, D., Birgersson, C., *Tetrahedron Lett.*, **1991**, 32, 2533. b) Tanner, D., Birgersson, C., Gogoll, A. and Luthman, K., *Tetrahedron*, **1994**, 50, 9797.
4. a) Tanner, D., Andersson, P.G., Harden, A. and Somfai, P., *Tetrahedron Lett*., **1994**, 35, 4631. b) Anderson, P.G., Harden, A., Tanner, D. and Norby, P.O., *Angew. Chem. Int. Ed. Engl*., **1995**, 34, 12.
5. Murphy, B.P. and Pratt, R.F., *Biochem.*, **1991**, 30, 3640.
6. a) Zhong, Z., Bibbs, J.A., Yuan, W. and Wong, C.H. *J. Am. Chem. Soc*. **1991**, 113, 2259. b) Moroder, L., Musiol, H. J.and Scharf, R., *FEBS Lett*., **1992**, 51, 299.
7. a) For a review see Kasai, M. and Kono, M., *Synlett.*, **1992**, 778. b) Kinoshita, S., Uzu, K., Nakano, K., Shimizu, M. and Takahashi, T., *J. Med. Chem.*, **1971**, 14, 103.
8. Review: W.A. Remers, B.S. Iyengar in *Recent Progress in the Chemical Synthesis of Antibiotics* (Eds. G. Lukaccs, M. Ohno) Springer, Berlin, **1990** p 415.
9. Kunz, K. R., Iyengar, B.S., Dorr, R.T., Alberts, D.S. and Remers, W.A., *J. Med. Chem.*, **1991**, 34, 2281.
10. a) Gerhart, F., Higgins, W., Tardiff, C.and Ducep, J. *J.Med. Chem.*, **1990**, 33, 157. b) Tanner, M.E. and Miao, S. *Tetrahedron Lett*, **1994**, 35, 4073.
11. Oppolzer, W. and Flaskamp, E., *Helv. Chim. Acta*, **1977**, 60, 204.
12. Hudlicky, T., Luna, H., Price, J.D. and Rulin, R., *J. Org. Chem.*, **1990,** 55, 4683.
13. Corey, E. J. and Alanson, R.D., *Heterocycles.*, **1976**, 5, 445.
14. Cardillo, G., Orena, M., Sandri, S. and Tomasini, C., *Tetrahedron*, **1986**, 42, 917.
15. Tanner, D.and Somfai, P., *Tetrahedron Lett*., **1987**, 28, 1211.
16. Kelly, J.V., Eskew, V and Evans, S.A., Jr., *J. Org. Chem.*, **1986**, 51, 95.
17. a) Paulsen, H. and Patt. H., *Liebegs. Ann. Chem.*, **1981**, 1633. b) Brimacombe, J.S. and Rahman, K.M., Carbohydr. *Res*., **1983**, 113, C6.
18. Johnson, R.A. and Sharpless K.B., in *Comprehensive Organic Synthesis,* Vol 7 (Eds. B.M. Trost, I. Fleming) Pergamon Press, Oxford, **1991**, p 389.

19. Jacobsen, E. N., Zhang, W., Muci, A.R., Ecker, J.R. and Deng. L., *J. Am. Chem. Soc*., **1991**, 113, 7063.
20. Sharpless, K.B., Amberg, W., Bennani, Y.L., Crispino, G.A., Hartung. J., Jeong, K.S., Kwong, H-L, Morikawa, K., Wang, Z-M, Xu, D. and Zhang. X-L., *J. Org. Chem.*, **1992**, 57, 2768.
21. Payne, G. B., *J. Org. Chem.*, **1962**, 27, 3819.
22. Moulines, J., Charpentier, P., Bats, J. P., Nuhrich, A. and Lamidey, A-M, *Tetrahedron Lett*, **1992**, 33, 487.
23. Laurent, A., Marsura, A.and Perre, J.L., *J. Heterocyclic. Chem.*, **1980**, 54973.
24. Johnson, C.R., Kirchoff, T.A., Reischer, R.J. and Katekar, G.F., *J. Am. Chem. Soc.*, **1973**, 95, 4287.
25. Satoh, T, Sato, T., Oahara, T. and Yamakawa, K., *J. Org. Chem.* **1989**, 54, 3973.
26. Atkinson, R.S. and Kelly, B.J., *J. Chem. Soc. Perkin. Trans. 1*, **1989,** 1515.
27. Atkinson, R.S., Fawcett, J., Russel, D.R. and Tughan, G., *J. Chem. Soc. Chem. Commun.*, **1986**, 832.
28. Shustov, G.V., Kruitius, O.N., Voznesensky V.N., Chervin, I.I., Eremeev, A.V., Krostyanovsky, R.G. and Polyak, F.D. *Tetrahedron*, **1990**, 46, 6741.
29. Ploux, O., Caruso, M., Chassaing, G. and Marquet, A., *J. Org. Chem.*, **1988**, 53, 3154.
30. Evans, D.A, Faul, M.M., Bilodeau, M.T., Andersson, B.A. and Barnes, D.M., *J. Am. Chem. Soc.*, **1993**, 115, 5328.
31. Li, Z., Conser, K.R. and Jacobsen, E.N., *J. Am. Chem. Soc.*, **1993**, 115, 5326.
32. Lowenthal, R.E. and Masamune, S., *Tetrahedron Lett*.**, 1991**, 32, 7373.
33. Nishikori, H. and Katsuki, T., *Tetrahedron Lett*, **1996,** 37, 9245.
34. Lau, T.C., Kwong, H. L. and Wong W., *J. Chem. Soc., Dalton Trans.*, **1999,** 2411.
35. Shi, M., Itoh, N. and Masaki, Y., *J. Chem. Res.*, **1996**, 352.
36. a) Davies, S.G. and Mortlock, A.A., *Tetrahedron*, **1993**, 49, 4419. b) Alexakis, A., Mangeney P., Lensen, N., Tranchier, J-P, Gosmini, R. and Raussou, S., *Pure. Appl. Chem.*, **1996**, 68, 531.
37. a) Fuji, A., Hashiguchi, S., Uematsu, N., Ikariya, T. and Noyori, R.,. *J. Am. Chem. Soc.*, **1996**, 118, 2521. b) Nishibayasi, Y., Arikawa, Y., Ohe, K. and Uemura, S., *J. Org. Chem*., **1996**, 61, 1172.

38. a) Gao, J-X., Ikariya, T. and Noyori, R., *Organometallics*, **1996**, 15, 1087. b) Trost, B.M. and Shi, Z. *J. Am. Chem. Soc.*, **1996,** 118, 3037. c) Trost, B.M. and Bunt, R. C., *Angew. Chemie.*, **1996**, 108, 70.
39. Mash, E.A., Nelson, K.A., Deusen, S.V. and Hemperly, S.B., *Organic Synthes*is, Vol 68, **1990,** 92.
40. Yamada, T. and Narasaka, K., *Chem. Lett.*, **1986**, 131.
41. Review Erickson, J.W., *Perspectives in Drug Discovery and Design*, **1993**, 1, 109.
42. Love, B.E. and Ren, J., *J. Org. Chem.*, **1993**, 5556.
43. Stetin, C.B., de Jeso and Pommier, J.C., *Syn. Commun.*, **1982**, 495.
44. Desimoni, G., Faita, G., Righetti, P.P. and Tacconi, G., *Tetrahedron*, **1991**, 39, 8399.
45. Cesarotti, E., Kagan, H., Goddard, R. and Kruger, C.J., *J. Organomet. Chem.*, **1978**, 162, 279.
46. Adolfsson, H., Nordstrom, K., Warnmark, K. and Moberg, C., *Tetrahedron Asymmetry*, **1996**, 7, 1967.
47. Kim, B.M. and Sharpless, K.B., *Tetrahedron Lett.*, **1990**, 31, 3003.
48. Vyas, R., Chanda, B.M., Belhekar, A.A., Patel, D.R., Ram, R.N. and Bedekar, A.V., *J. Mol. Catal. A.*, **2000**, 160, 237.
49. a) Frump, J.A., *Chem. Rev.*, **1971**, 71, 483. b) Greene, T.W. and Wuts, P.G.M., *Protecting Groups in Organic Synthesis*, 2nd ed J. Wiley, New York **1991**.
50. a) Lutomski, K.A. and Meyers, A.I., In *Asymmetric Synthesis*, Morisson, J.D. Ed., Academic Press, Orlando FL, **1984**, vol 3 p 213. b) Meyers, A.I., *Tetrahedron*, **1985,** 41, 837.
51. a) Pfaltz, A., *Acc. Chem. Res.*, **1993**, 26, 339. b) Bolm, C., *Angew. Chem. Int. Ed.*, **1991**, 30, 542.
52. a) Evans, D.A. Miller, S.J. Lectka,T *J Am Chem Soc* **1993**, 115, 6460. b) Bedekar, A.V., Koroleva, E.B.and Andersson P.G. *J. Org. Chem.*, **1997**, 62, 2518.
53. a) Nishiyama, H., Itoh, Y., Matsumoto, H., Park, S.B. and Itoh ,K.J., *J. Am. Chem. Soc.*, **1994,** 116, 2223. b) Evans, D.A., Murry, J.A.,. von Matt, P., Norcross, R.D. and Miller, S. J., *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 798.
54. Fujisawa,T., Ichiyanagi, T. and Shimizu, M., *Tetrahedron Lett.*, **1995**, 36, 5031.
55. Albone, D.P., Aujla, P.S., Taylor, P.C., Challenger, S. and Derrick, A.M., *J. Org. Chem.*, **1998**, *63*, 9569.

56. Jnaneshwara, G.K., Deshpande, V.H., Lalithambika, M., Ravindranathan, T. and Bedekar, A.V., *Tetrahedron Lett.*, **1998**, 39, 459.
57. a)Brunner, H. and Obermann, U., *Chem. Ber.*, **1989,** 122, 499. b) Brunner, H., Obermann, U. and Wimmer, P. *J. Organomet. Chem.*, **1986**, 316. c) Brunner, H. and Henrichs, C., *Tetrahedron Asymmetry*, **1995**, 6, 653.
58. Meyers, A.I., *J. Org. Chem.*, **1993**, 58, 3568.
59. Yamada, Y., Yamamoto, T. and Okawara, M., *Chem. Lett.*, **1975,** 361.
60. Heidelberger, J., *J. Am. Chem. Soc*., 41, **1919**, 819.

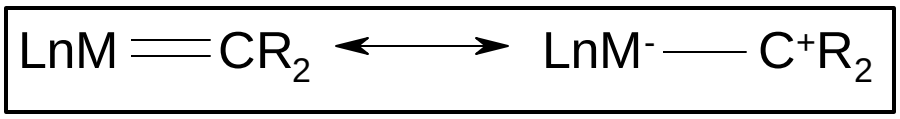
# Chapter-4

## A novel homogeneous Rhodium based catalyst for asymmetric Cyclopropanation reactions

## INTRODUCTION

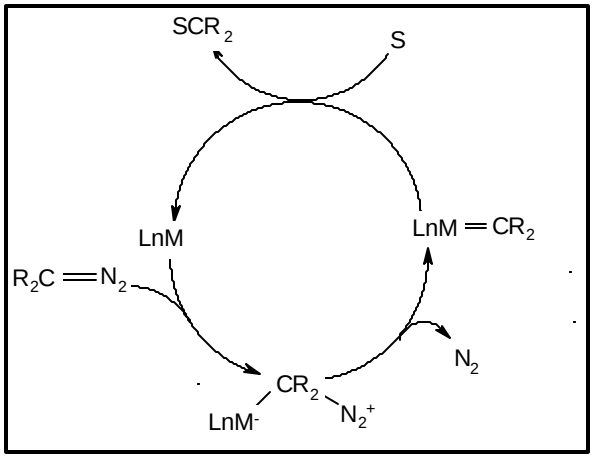
Cyclopropanes, which belong to three membered carbocyclic strained ring systems, constitute an important moiety in organic synthesis. Over the past few years, there has been an increasing interest in developing synthetic methodologies towards the synthesis of organic compounds containing cyclopropanes, due to their natural occurrence, their biological properties and their versatile synthetic utility.[1] As in other fields here too catalytic methods have supplanted thermal and photochemical schemes and efficient procedures for cyclopropanation using these methods have arisen. The present chapter discusses cyclopropanation reactions in general and asymmetric cyclopropanation in particular.

There is now a clear understanding of transition metal catalyzed transformations.[2] Cyclopropane formation occurs from reaction between diazo compounds and alkene catalyzed by a wide variety of transition metal compounds, that involves the addition of carbene moiety to a carbon- carbon bond **(Scheme -1)**.




**Scheme -1**

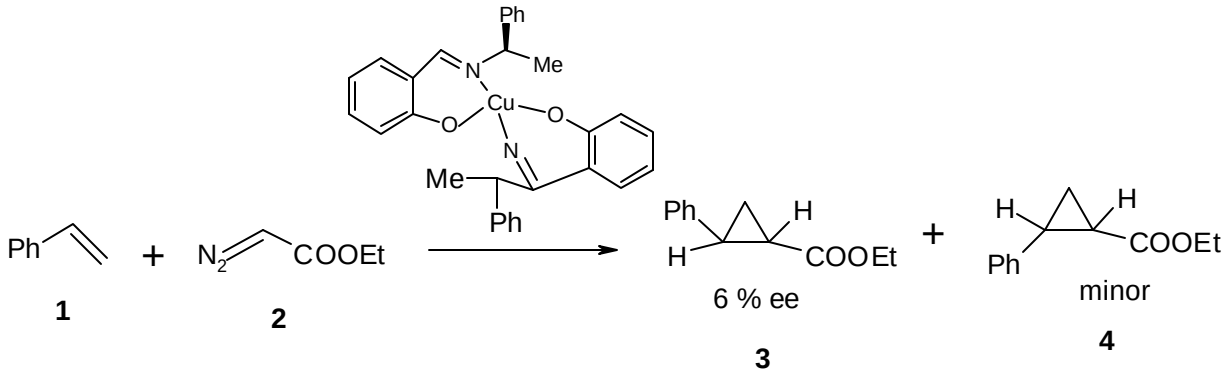
The catalytic activity of transition metal compounds depends on coordination unsaturation at their metal center, which allows them to react as electrophiles with diazo compounds. Electrophilic addition causes the loss of nitrogen and production of a metal stabilized carbene. Transfer of the carbene entity to an electron rich substrate completes the catalytic cycle **(Scheme 2)**.




**Scheme 2**

Among transition metal compounds that are effective for cyclopropanation reactions, those of copper and rhodium have received the greatest attention.[3] Although metal carbene intermediates with catalytically active copper or rhodium compounds have not yet been observed, correlation in relative reactivities and diastereomeric selectivities, suggest their involvement in catalytic reactions.

The development of chiral transition metal catalyst for the asymmetric syntheses of cyclopropanes has taken place during the evolution of mechanistic understanding of metal carbene formation. The first chiral transition metal catalyst designed for an enantioselective transformation was the reaction between a diazo ester and an alkene to form cyclopropane. Noyori and co-workers[4] used chiral ligand derived from α- phenylethylamine and a Schiff base copper complex to effect the cyclopropanation **(Scheme -3)**.

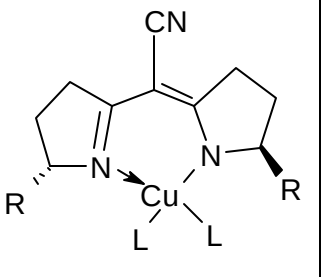



**Scheme -3**

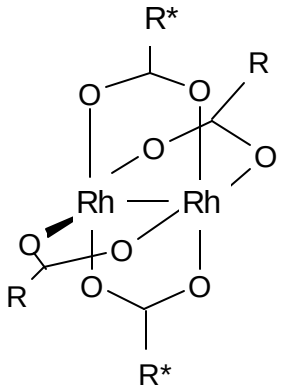
Although enantioselectivities were low, the report laid the foundation for chiral catalyst development for generating and distinguishing between diastereomeric transition states involving transition metals.

In recent years advances in ligand design for transition metals that are effective for cyclopropanation reaction have intensified efforts towards high enantioselectivity and have led to a resurgence of interest in chiral cyclopropane compounds and their synthesis. Today several catalysts are available that provide exceptional enantiocontrol in both intermolecular and intramolecular cyclopropanation reactions. [5,6]

Copper catalysis for reactions of diazo compounds with olefins has been known for more than 80 years[7a] and the most significant recent advance made in this field is by Pfaltz[7b] and co-workers who used semicorrinato complexes such as **5** to achieve enantioselective cyclopropanation. However rhodium catalysis was not reported until the 1970s.[8] Rhodium $^{(II)}$ carboxylates especially $Rh_2(OAc)_4$ has emerged as the most generally effective catalyst for carbenoid formation.[9,10,11] There is a growing interest in design and development of dirhodium $^{(II)}$ catalysts that possess chiral ligands such as **6**. The first of these applied to cyclopropanation reactions was the chiral rhodium (II) carboxylate derivative developed by Brunner[12] who prepared 13 chiral dirhodium tetrakis (carboxylate) derivatives from enantiomerically pure carboxylic acids -$R^1$ $R^2$ $R^3$ CCOOH with various substituents ranging from H, Me, and Ph to NHAc and $CF_3$. However reactions performed between ethyl diazoacetate and styrene yielded cyclopropane products with less than 12 % ee.

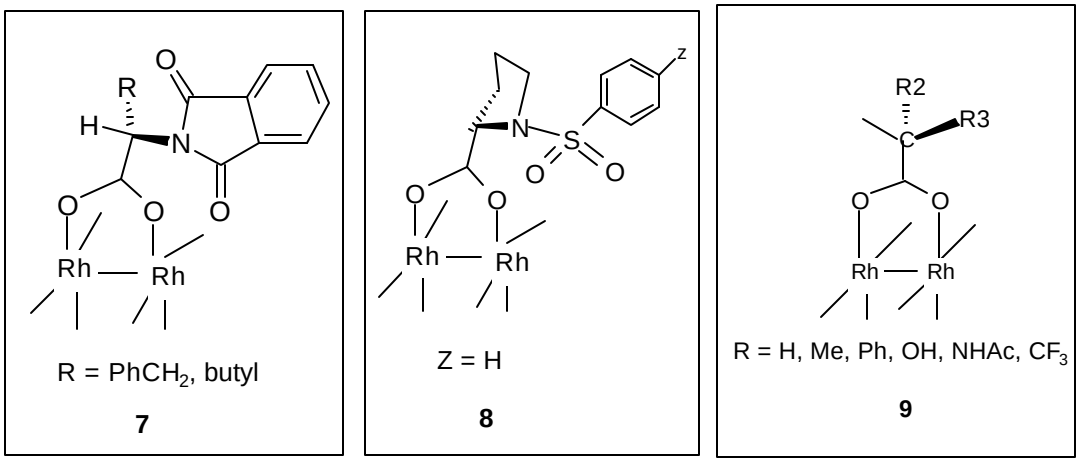



**5**

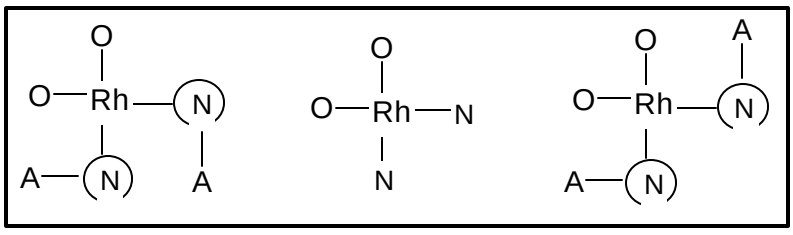



**6**

Rhodium $^{(II)}$ carboxylates are structurally well defined having $D_{2h}$ symmetry[13] with axial coordination sites at which carbene formation occurs in reaction with diazo compounds. With chiral dirhodium $^{(II)}$ carboxylates the chiral center is relatively far from the carbene center in the metal carbene intermediate. Since the initial report of the effective use of $Rh_2[OAc]_4$ for O-H insertion by Teyssie and co-workers,[14] dirhodium $^{(II)}$ carboxylates have become the catalyst of choice for cyclopropanation. Chiral carboxylate ligands **7**, **8** and **9** have been independently reported by Brunner *et al.*[12] , Mc Karvey *et al.*[15] **,** and Hashimoto *et al.*[16] for tetrasubstitution around the dirhodium $^{(II)}$ core but their enantioselectivities in intermolecular reactions with simple alkenes have been marginal.

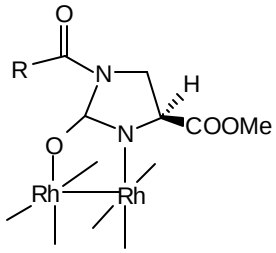



Chiral carboxamidate ligated dirhodium compounds have been designed and developed by Doyle and co-workers.[6] In these compounds the dirhodium $^{(II)}$ core is bound to four carboxamidate ligands so that two nitrogen atoms and two oxygen atoms are bound to each rhodium with a *cis* array .[17] The chiral center is the carbon atom adjacent to the ligated nitrogen [18] where **A** is the attachment to the chiral center **(10)**.



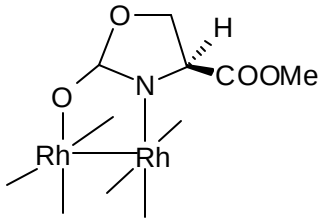
**10**

Four different classes of carboxamidate ligands have been reported, the most effective being those with carboxylate ester attachments **A** to amino acid derived 2-oxopyrrolidines[19] (**11**), 2-oxazolidines[20] (**12**), N-acyl 2-oxoimidazolidine[21] (**13**) and 2-oxoazetidine[22] (**14**).



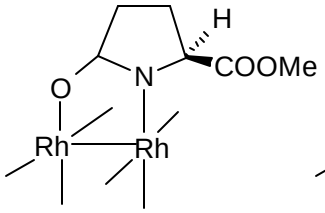

$Rh_2(4S\text{-}MACIN)_4$

**11**



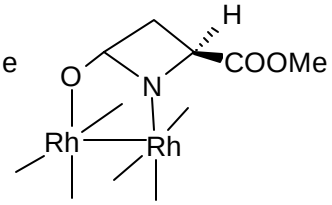

$Rh_2(4S\text{-}MEOX)_4$

**12**




$Rh_2(5S\text{-}MEPY)_4$

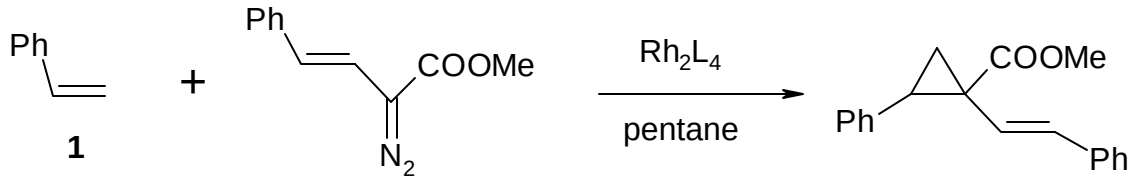
**13**




$Rh_2(4S\text{-}IBAZ)_4$

**14**

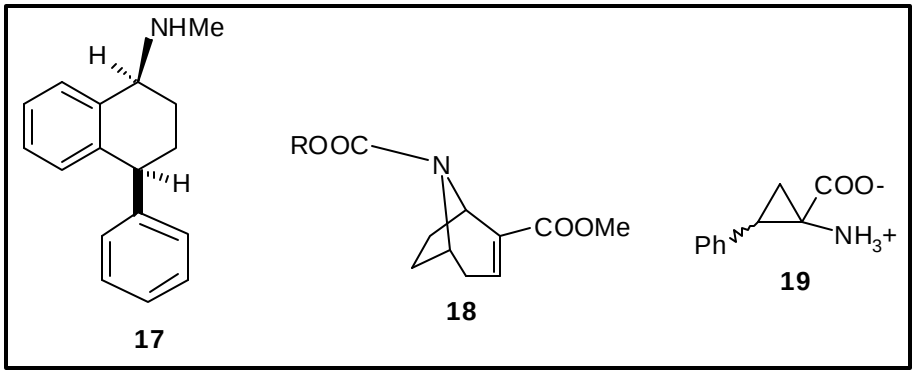
Dirhodium (II) catalysts are not oxygen sensitive and have long shelf lives. However their initial applications with intermolecular cyclopropanation reaction between styrene and *l* or *d* menthyl diazoacetate[17] provided lower stereocontrol than previous catalysts *viz*. Aratani catalysts.[23] Chiral copper catalysts especially those with constructed bisoxazoline ligands were found to be more effective than those of rhodium in producing the highest level of enantiocontrol. However there is a notable exception, high levels of enantiocontrol have been achieved in reactions of aryl diazo acetates and vinyl diazoacetates [24] with a rhodium based ligand **(Scheme-4)**.




**1** **15** **16**

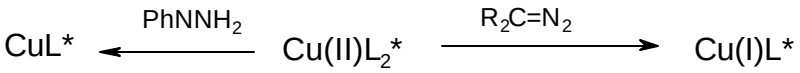
**Scheme -4**

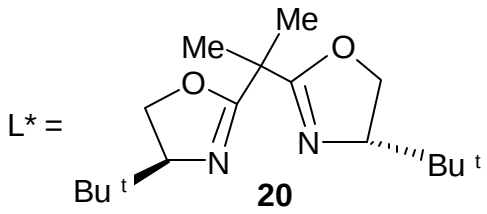
For these substrates the preferred catalyst is the dirhodium (II) N-arenesulfonyl prolinate (**7**), reported by Mc Kervey *et al*.[15] Corey and Grant [25] have employed this methodology for the synthesis of the antidepressant sertalin (**17**) and Davies *et al*.[26] have applied this to enantioselective synthesis of functionalized tropanes (**18**) and to the synthesis of four stereoisomers of 2-phenyl cyclopropane-1-amino acid (**19**).




**17** **18** **19**

In intermolecular cyclopropanation reactions, copper (I) and bisoxazoline **20** have given the highest ee values for cyclopropanation of styrene, [13] isobutylene and 1,1-diphenylethene but the universal applicability of this catalyst system is elusive **(Scheme-5)**.




**20**

**Scheme-5**

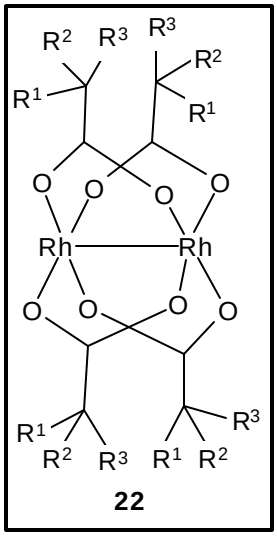
In addition, diastereocontrol is an added complication, except with the use of diazoacetates with bulky ester appendages, that limits the applications of this technology.

**Present Work**

Although a large number of catalysts have been introduced for catalytic asymmetric cyclopropanation only a few copper based ones have high potential to achieve high enantioselectivities. Moreover in intermolecular cyclopropanation reaction, diastereocontrol is a challenging task with the notable exception of Ru-pybox catalyst, [27] where some amount of diastereoselectivity has been achieved. Unlike catalytic asymmetric aziridination reactions discussed in Chapter III where enantiocontrol is the only stereochemical differentiation, synthetically effective intermolecular cyclopropanation reaction requires both diastereocontrol and

enantiocontrol. With an aim to develop efficient chiral catalyst which could solve the problem of diastereoselectivity in addition to giving high enantioselectivities, the present work was taken up .Due to the current interest in dirhodium complexes, attention was focussed on the synthesis of some new rhodium complexes and their application to asymmetric cyclopropanation reactions. New nitrogen based ligands were designed for this purpose. Phosphorus based ligands were not used as they suffer from severe drawbacks. Organophosphorus compounds sometimes are sulphonated to enable better solubility. These ligands are efficient at ambient temperature and pressure, however at higher temperature and pressure, the catalysts do not perform efficiently, as they tend to dissociate or get converted to other unstable materials. Organophosphorus based ligands are air sensitive, moisture sensitive and tend to degrade to phosphine oxide which is difficult to remove and ineffective for catalysis..

α- Methoxy - α- trifluoromethylphenyl acetic acid (MTPA) (**21**) is a well known chiral compound. It is an air stable reagent used for determining the enantiomeric purity of hydroxy compounds and amines.[28] It does not undergo racemisation easily even under harsh conditions of acidity, basicity and temperature. It is readily available and cost effective. It was therefore recognized that it might be ideally suited as a ligand. The following complex **21** was designed in which four molecules of MTPA are bonded with the two rhodium atoms bound to each other to give a $C_2$ symmetric molecule having a structural formula: $Rh_2[(C_6H_5)C(CF_3)(OCH_3)(CO_2)]_4$.

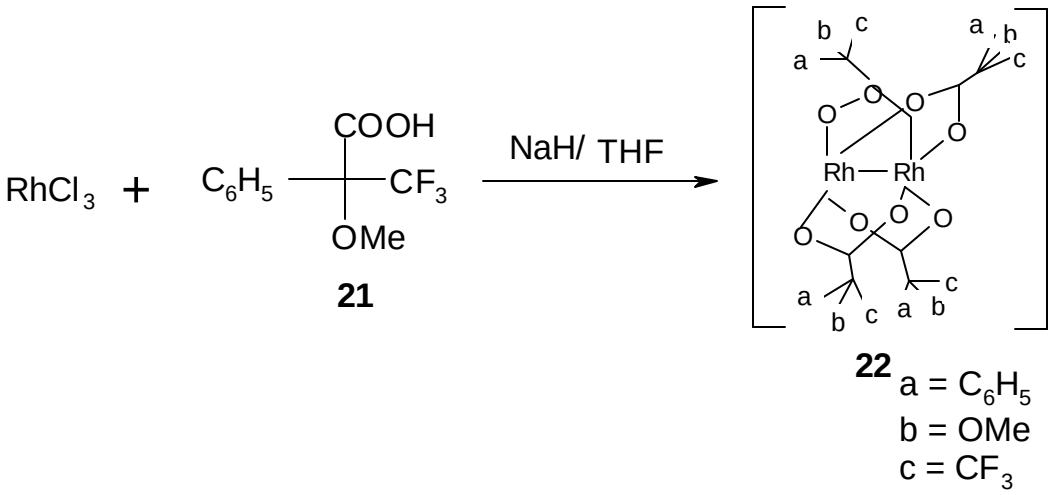



**22**

$R_1 = C_6H_5$, $R_2$ = OMe , $R_3 = CF_3$

**Results and Discussion**

Various reaction conditions were tried for the synthesis of the molecule and finally the desired compound was obtained in good yields by using the following protocol **(Scheme-6)**. At first the sodium salt of MTPA was prepared from MTPA (0.5 mmol) using sodium hydride as the base in dry THF. To the dried salt rhodium chloride (0.25 mmol) was added and the solids were dissolved in dry ethanol. The mixture was refluxed under argon for 6-8 hours. Removal of ethanol under vacuum furnished the catalyst as a brownish red solid.[29]

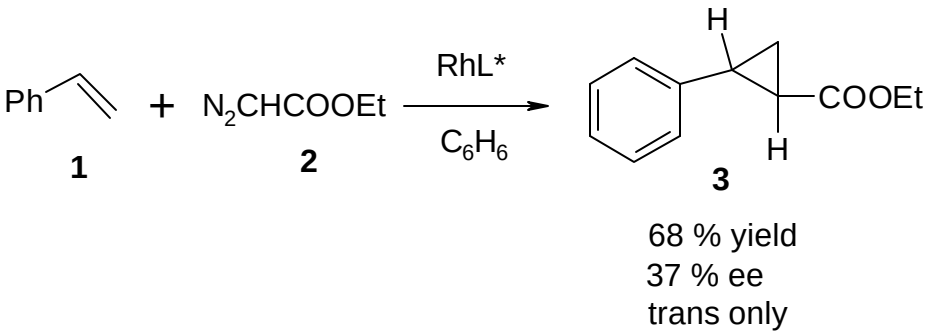



**21**

**22** a = $C_6H_5$
b = OMe
c = $CF_3$

**Scheme-6**

The catalyst was thoroughly characterized by AAS, NMR and C, H, N analysis. The rhodium content was estimated using atomic absorption studies (AAS) and determined to be 97 ppm. The optical rotation of the catalyst was $-0.89^{o}$ in ethanol at the concentration c = 0.08 and C, H analysis of the compound was in good agreement to the assigned structure The catalyst was screened for intermolecular cyclopropanation with styrene as the substrate **(Scheme-7)**.




**Scheme-7**

Ethyl diazoacetate was added slowly *via* a syringe pump dropwise over a period of 10 hours to a refluxing suspension of the catalyst in the olefin under nitrogen atmosphere. The resultant mixture was filtered to give the cyclopropanation product in good yield (68 %). There was no competitive carbenoid dimerization product formation even though an equimolar amount of the alkene was taken. An interesting feature to be noted here is that only the *trans* isomer was obtained indicating high levels of diastereoselectivity. Another example, dihydronapthalene was chosen for the reaction and subjected to similar reaction conditions. The product was characterized to be the *trans* cyclopropane product. The structure of the *trans* styrene cyclopropanation product was confirmed by its $^1$H NMR spectrum which showed a multiplet of 5 protons at $\delta$ 7.6 corresponding to aromatic protons of styrene, a quartet of two protons appearing at $\delta$ 4.2 (J = 9 Hz) corresponding to the two methylene protons of the ester group, a doublet of a doublet at $\delta$ 3.9 ( J = 9.5 Hz) integrating for one proton and another doublet of a doublet at $\delta$ 2.5 (J = 9.5 Hz) for one proton which could be assigned to two cyclopropane ring protons, a multiplet at $\delta$ 1.6-1.8 corresponding to two protons of the cyclopropane ring and a triplet of three protons at $\delta$ 0.97( J = 9 Hz) corresponding to the carboxylate ethyl ester. The product was further characterized to be the cyclopropane product by its mass spectrum in which the molecular ion peak appeared at m/z 190. These results are to be contrasted with rhodium acetate catalyzed transformations where the stereoselectivites are quite low.[30] The catalyst however does not work well with cinnamates and nitriles. This is in accordance with other reports in the literature using dirhodium carboxylate catalysts (**Table-1**).

**Table-1: Diastereoselective cyclopropanation of alkenes with ethyl diazoacetate catalyzed by the rhodium (II) catalyst 21**

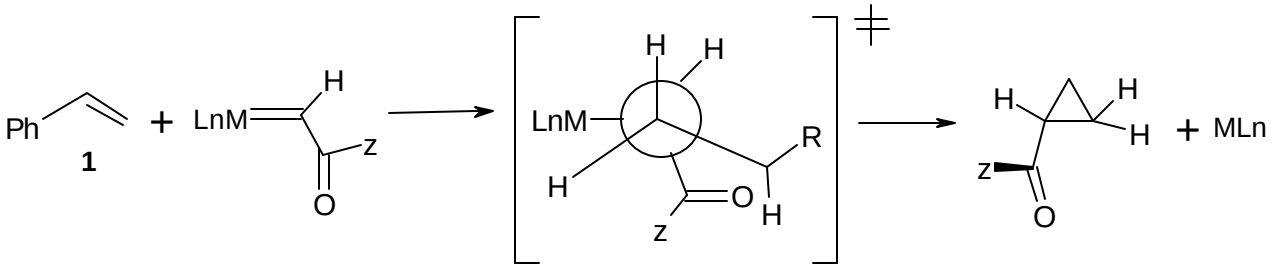
| Entry | Alkene | Catalyst configuration | Trans:cis | Yield[a] (%) | ee[b] % |
|---|---|---|---|---|---|
| a) | Styrene | R | Trans | 68 | 37 |
| b) | Styrene | S | Trans | 55 | 29 |
| c) | 1, 2-Dihydro naphthalene | R | - | 45 | 30 |
| d) | 1, 2-Dihydro naphthalene | S | - | 38 | 19 |
| e) | 1-hexene | S | Trans | 40 | 22 |
| f) | 1- hexene | R | Trans | 48 | 30 |
| g) | Methyl cinnamate | | - | NR[c] | |

[a] Isolated yields [b] By comparison with known optical rotation values. [c] no reaction.

The optical purity of the styrene cyclopropanation product as determined to be 37 % ee's are low but encouraging for initial studies.

The exclusive *trans* formation of the cyclopropane product can be attributed to the electronic influence of the ligand in $Rh_2[L^*]_4$. A detailed mechanistic study is required to probe into the selectivity in product formation. However at this juncture it can be hypothesized that the electronic influence of the ligand is apparently increasing the stability of the metal carbene leading to closer approach of the olefin to the electrophilic carbenoid center This is in agreement with the previous report by Doyle *et al*. [31] who recognized stabilization of the transition state **22** by association of the

ester carbonyl oxygen with the developing electropositive center of the reacting alkene, and this accounts for the preferential formation of the *trans* product **(Scheme-8)**.




**22**

**Scheme -8**

## Conclusions

A new rhodium based chiral catalyst has been synthesized and characterized. The catalyst is stable and has a long shelf life. The catalyst does not undergo racemisation easily even under harsh conditions .It can be synthesized from simple steps with commonly available starting materials. Many other forms of the catalyst can be synthesized by using appropriately substituted chiral phenylacetic acid. The catalyst does not use chiral phosphine ligands, which have a lot of problems of accessibility and recovery. The catalyst is a water-soluble compound, water being a universal solvent increases the scope of its applications tremendously. The catalyst has been successfully applied to asymmetric cyclopropanation reactions. Another important feature of this methodology is that exclusively the *trans* product is obtained, thus solving the problem of diastereoselectivity in intermolecular reactions encountered with previous reports in the literature. The catalyst has been shown to have potential for other organic conversions like transfer hydrogenation, aziridination as well as hydroformylation.

## Experimental

### Preparation of glycine ethyl ester hydrochloride [32]

Thionyl chloride (60 g, 36.8 mL, 50.4 mmol) was added gradually to a stirred and cooled (0 $^{o}$C) suspension of glycine (25.2 g, 3.6 mmol) in absolute ethanol (125 mL). The mixture was allowed to warm to room temperature and stirred for 30 minutes and then refluxed until the solution was clear (four hours). The solvent was removed under vacuum to afford glycine ethyl ester hydrochloride as a white solid which was used as such for the next step.

### Preparation of ethyl diazoacetate [33]

Glycine ethyl ester hydrochloride (96 g, 33 mmol) obtained from the first step was taken in 200 mL of dichloromethane. The suspension was then cooled with ice-salt mixture and NaOAc/AcOH buffer was added to maintain a neutral pH. A solution of sodium nitrite (22.8 g, 33 mmol) in water (30 mL) was added slowly and resultant yellow mixture was stirred at 0 $^{o}$C for half an hour and at room temperature for 2 h. The yellow solution thus obtained was transferred to a separating funnel and the organic layer was washed with sodium carbonate solution till the washings became neutral. The DCM solution thus obtained was passed through a short column of silica gel and stored as such in the refrigerator over sodium sulfate.

### Procedure for the synthesis of novel chiral rhodium complex (22)

Sodium hydride (24 mg, 60 % dispersion in mineral oil) was taken in 2-necked RB flask fitted with 2-way stopcock and septum under argon. It was washed using dry petroleum ether twice and then it was taken in dry THF (5 mL). (R)-(+) -MTPA acid (117 mg, 0.5 mmol) in dry THF was added to the reaction flask while cooling with ice. This cold solution was stirred at 0 $^{o}$C for 15 minutes. The whole addition took place in 5 minutes. The reaction mixture was stirred at room temperature for 30 minutes. The solvent was removed under vacuum while keeping the system at room temperature. The completely dried sodium salt was dissolved in absolute ethanol (5 mL) and $RhCl_3$ (52 mg, 0.25 mmol) was added in portions to the ethanolic solution of the sodium salt under argon. After the addition was over, the septum was replaced with a reflux condenser and a two-way stopcock. The contents of the reaction mixture were heated under reflux for 6-8 h. The brownish red

reaction mixture was filtered and the solvent was removed under reduced pressure to afford a brownish red solid .[30]

| | |
|---|---|
| **Yield** | 272 mg(76 %). |
| **Analysis** | Calculated for $C_{40}H_{36}F_{12}O_{12}Rh_2$ : C= 42 %, H= 3.15 %, |
| | Observed: C= 41.8 %, H= 2.87 %. |
| **AAS** (Rh content): | 97 ppm |
| **[a ]$_D^{25}$** | -0.89 $^o$ (c = 0.8, EtOH). |

**Typical procedure for cyclopropanation reaction using Rh (II) ligand:**

Styrene (115 mg, 1.0 mmol) was taken in dry benzene (8 mL) in a two neck round bottomed flask fitted with a reflux condenser and septum. The Rh catalyst (5 mg, 5 % w/w) was added to the reaction mixture and the whole system was placed under argon. Ethyl diazoacetate (120 mg, 1.2 mmol) was taken in dry benzene (5 mL) and this solution was added to the refluxing solution of the reaction mixture using syringe addition pump. The addition was maintained at a rate of 0.5 mL per hour. The whole addition was over in 10 h. After complete addition the reaction mixture was refluxed for one hour.

After completion of the reaction (TLC) the reaction mixture was passed through a small plug of celite (3-cm diameter). The celite was washed with more solvent and filtrates were combined. The solvent was removed under reduced pressure. The crude reaction mixture was purified using flash chromatography to afford the *trans* substituted product.

**(+) Ethoxy(2-phenyl cyclopropyl)-1-methanone (3 )**

| | |
|---|---|
| **Yield** | 159 mg( 68 %). |
| **$^1$H NMR** | $\delta$ 7.6-7.2 (m, 5H), 4.2(q, *J* = 9 Hz, 2H), 3.9(dd, *J* = 9.5 Hz, 1H), 2.5 |
| | (dd, *J* = 9.5 Hz, 1H), 1.8-1.6 (m, 2H), 0.97(t, *J* = 9 Hz, 3H). |
| **Mass (m/z)** | 190 ($M^+$, 28), 162 (4), 145 (26), 117 (100), 104 (18), 91(42). |
| **[a }$_D^{25}$** | Standard: -290 $^o$ ( c=1, $CHCl_3$) |
| | Observed -107 $^o$(c=1, $CHCl_3$) |
| **Enantiomeric excess** | 37 % |

**(-) Ethoxy(2-phenyl cyclopropyl)-1-methanone (3 )**

| | |
|---|---|
| **Yield** | 159 mg( 55 %). |
| **$^1$H NMR** | δ 7.6-7.2 (m, 5H), 4.2(q, *J* = 9 Hz, 2H), 3.9(dd, *J* = 9.5 Hz, 1H), 2.5 (dd, *J* = 9.5 Hz, 1H), 1.8-1.6 (m, 2H), 0.97(t, *J* = 9 Hz, 3H). |
| **Mass (m/z)** | 190 ($M^+$, 28), 162 (4), 145 (26), 117 (100), 104 (18), 91(42). |
| **[a ]$_D^{25}$** | Standard: -290 $^o$ ( c=1, $CHCl_3$) |
| | Observed -84 $^o$(c=1, $CHCl_3$) |
| **Enantiomeric excess** | 29 % |

**(+) 1a, 2,3,7b-tetrahydro-1H-cyclopropa[a] napthalen 1-yl-ethoxy-1-methanone**

| | |
|---|---|
| **Yield** | 88.6 mg (47 %). |
| **$^1$H NMR** | δ 7.4- 7.3 (m, 2H), 7.0-6.7 (m, 2H), 4.0-3.8 (m, 4H), 3.7-3.3(m, 3H), 1.5-1.3 (m, 2H), 0.9 (t, *J* = 9 Hz, 3H). |
| **Mass (m/z)** | 214 ($M^+$, 0.5), 203 (100), 192 (20), 149 (30), 91 (80). |

**(-) 1a, 2,3,7b-tetrahydro-1H-cyclopropa[a] napthalen 1-yl-ethoxy-1-methanone**

| | |
|---|---|
| **Yield** | 88.6 mg (47 %). |
| **$^1$H NMR** | δ 7.4- 7.3 (m, 2H), 7.0-6.7 (m, 2H), 4.0-3.8 (m, 4H), 3.7-3.3(m, 2H), 1.5-1.3 (m, 3H), 0.9 (t, *J* = 9 Hz, 3H). |
| **Mass (m/z)** | 214 ($M^+$, 0.5), 203 (100), 192 (20), 149 (30), 91 (80). |

**(+) trans-2-(n-Butyl) cyclopropylethoxy -1- methanone**

| | |
|---|---|
| **Yield** | 82 mg (48 %) |
| **$^1$H NMR** | 4.2(q, *J* = 9 Hz, 2H), 1.67(ddd, *J* = 8.2, 4.4, 4.2 Hz, 1H), 1.55-1.15(m, 6H), 0.97(t, *J* = 9Hz, 3H), 0.93-0.92 (m,1H), 0.92 (t, *J* = 7Hz, 3H), 0.83-0.81(m, 2H). |
| **Enantiomeric excess** | 30 % |

**(-)trans-2-(n-Butyl) cyclopropylethoxy -1- methanone**

| | |
|---|---|
| **Yield** | 74 mg (40 %) |
| **$^1$H NMR** | 4.2(q, *J* = 9 Hz, 2H), 1.67(ddd, *J* = 8.2, 4.4, 4.2 Hz, 1H), 1.55-1.15(m, 6H), 0.97(t, *J* = 9Hz, 3H), 0.93-0.92 (m,1H), 0.92(t, *J*= 7Hz, 3H), 0.83-0.81(m, 2H). |
| **Enantiomeric excess** | 22 % |

**References**


1. Cossy, J., Blanchard, B. and Meyer, C., *Synthesis*, **1999**, 1063-1075.
2. Doyle, M.P., in *Catalytic Asymmetric Synthesis,* Ed, Ojima, I., VCH Publishers, New York, **1983**, Chapter 3, 62 p.
3. Doyle, M.P., *Chem. Rev*., **1986**, 86, 919.
4. Noyori, R., *Science*, **1990**, 248, 1194.
5. Fritschi, H., Leuteneggar, U. and Pfaltz, A., Angew. *Chem. Int. Ed. Engl.*, **1986**, 25, 1005.
6. Doyle, M.P., Brandes, B.D., Kazala, A.P., Pieters, R.J., Jarostfer, M.B., Watkins, L.M. and Eagle, C.T., *Tetrahedron Lett*., **1990,** 31, 6613.
7. a) Silberrad, O. and Roy, C.S., *J. Chem. Soc.*, **1906,** 89, 179.b) Pfaltz, A. *Acc. Chem. Res*., **1993**, 26, 339.
8. Hubert, A.J., Noels, A.F., Anciaux, A.J. and Teyssie, P., *Synthesis*, **1976**, 600.
9. Doyle, M.P., *Acc. Chem. Res*., **1986**, 19, 348.
10. Maas, G., *Top. Curr. Chem.,* **1987**, 137, 75.
11. Adams, J. and Spero, D.M., *Tetrahedron,* **1991**, 47, 1765.
12. Brunner, H., Kluschanzoff, H. and Wutz, K., *Bull. Chem. Soc.* Belg., **1989**, 98, 63.
13. a) Cotton, F.A. and Walton, RA., *Multiple Bonds between Metal Atoms,* Wiley New York, **1982,** Chapter 7. b) Felthouse, T.R., *Prog. Inorg. Chem.,* **1982**, 29, 73. c) Boyar, E.B., Robinson, S.D., *Coord. Chem. Rev.*, **1983**, 50, 109.
14. Paulissen, R., Reimlinger, H, Hayez, E., Hubert, A.J. and Teyssie, Ph., *Tetrahedron Lett*., **1973,** 24, 2233.
15. Kennedy, M., Mc Kervey, M.A., Maguire, A.R. and Ross G.H.P., *J. Chem. Soc. Chem. Com.*, **1990**, 361.
16. Hashimoto, S., Watanabe, N. and Ikegami, S., *Tetrahedron Lett*., **1990**, 31, 5173.
17. a) Evans, D.A., Woerpel, K.A., Hinman, M.M., Faul, M.M., *J. Am. Chem. Soc.,* **1991**, 113, 726.B) Evans D.A., Woerpel, K.A. and Scott, M.J., *Angew. Chem. Int. Ed. Engl.*, **1992**, 31, 431.
18. Mueller, D., Umbricht, G., Weber, B. and Pfaltz, A., *Helv. Chim. Acta.*, **1991**, 74, 232.
19. Doyle, M.P., Winchester, W.R., Hoorn, J.A., Lynch, V., Simonsen, S.H. and Ghosh, R., *J. Am. Chem. Soc.,* **1993**, 115, 9968.
20. Doyle, M.P., Dyatkin, A.B., Protopopova, M.N., Yan, C.I., Miertschin, C.S. and Winchester, W.R., Simonsen, S.H. and Ghosh, R., *Recl. Trav. Chim. Pays-Bas.*, **1995**, 114, 163.

21. Doyle, M.P., Zhou, Q-L., Raab, C.E., Roos, G.H.P., Simonsen, S.H. and Lynch, V., *Inorganic. Chem.*, **1996**, 35, 6064.
22. Doyle, M.P., Zhou, Q-L .,Simonsen, S.H , and Lynch, V., *Synlett*, **1996**, 697.
23. Aratani, T., *Pure. Appl. Chem.*, **1985,** 57, 1839.
24. Doyle, M.P., Zhu, Q-L., Charnsangavej, C., Longoria, M.A., Mc Kervey, M.A. and Garcia, C.F., *Tetrahedron Lett*., **1996**, 37, 4129. b) Davies, H.M.L., Bruzinski, P.R. and Fall, M.J., *Tetrahedron Lett*., **1996**, 37, 4133.
25. Corey, E.J. and Gant, T.G., *Tetrahedron Lett*., **1994**, 35, 5373.
26. Davies, H.M.L., Bruzinski, R., Lake, D.H., Kong, N. and Fall M.J., *J. Am. Chem. Soc*., **1996**, 118, 6897.
27. Fritschi, H., Leutenegger, U., Siegmann, K., Pfaltz, A., Keller, W. and Kratky, Ch., *Helv. Chim. Acta.*, **1988**, 71, 1541.
28. Dale, J.A., Dull, D.L. and Mosher, H.S., *J. Org. Chem.*, **1969**, 34, 2543.
29. Chanda, B. M. and Balaji, B.S., **Indian Patent** No. NF/295/98.
30. Doyle, M.P., Van Lesen, D. and Tamblyn, W.H., *Synthesis*, **1981**, 787.
31. Doyle, M.P., Griffin, J.H., Bagheri, V. and Dorow, R.L., *Organometallics* **1984**, 3, 53.
32. Holker, A.G., Ph.D. thesis, Pune University, **1997**, p 84.
33. Serale, N.E., *Organic Syntheses, Collective Vol*., *IV*, John Wiley and Sons. Inc, New York,. **1963,** p 424.

# Chapter-5

# Catalytic Oxidation and Reduction Reactions

# INTRODUCTION

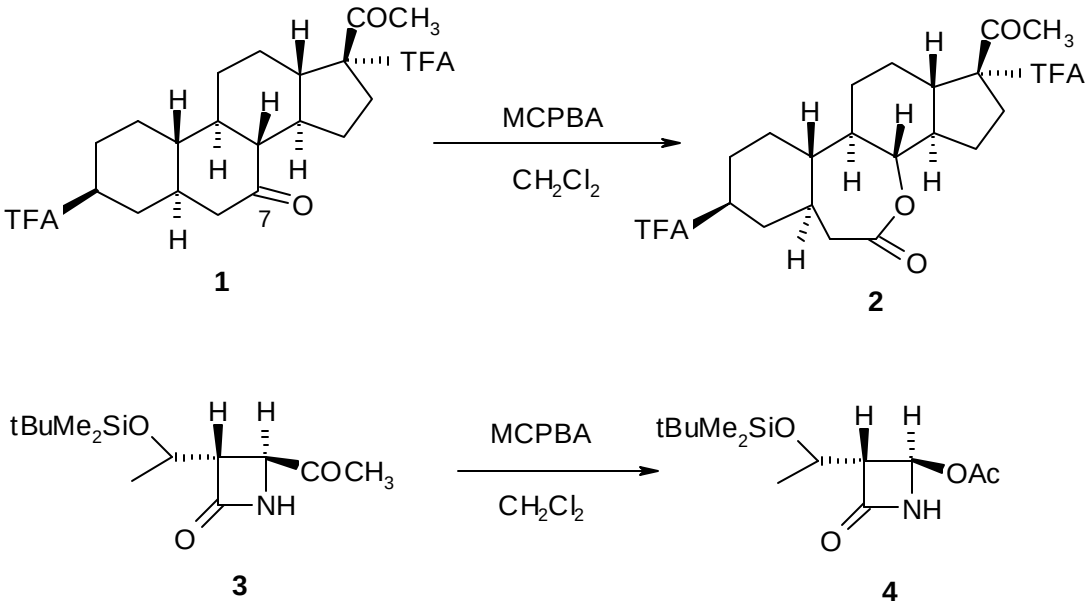
The conventional organic synthetic procedures make use of multistep synthetic methods giving a lot of waste by-products, which outweigh the useful product and are difficult to dispose off. Increased ecological awareness is forcing the chemists to look for alternative benign, environmentally friendly methods. In this context the development of efficient catalytic oxidation and reduction reactions which use simple procedures and cleaner reagents needs to be accorded top priority This chapter is divided into two sections A and B, which deal with catalytic oxidation and reduction reactions respectively. Each section is further subdivided into three parts. In section A, the first part describes asymmetric Baeyer-Villiger oxidation reactions, the second part discusses polymer supported heterogeneous oxidation reactions and the third part describes an efficient methodology for the synthesis of 4, 4' symmetric aromatic disulfides by oxidative sulfurylation of aromatics. Section B discusses catalytic reduction reactions mainly transfer hydrogenation reactions. It is divided into two parts. The first part deals with $Co(OAc)_2$ catalyzed chemoselective transfer hydrogenation reactions, the second part describes asymmetric transfer hydrogenation reactions catalyzed by various ligands.

## Section A: Catalytic Oxidation Reactions

### General Introduction

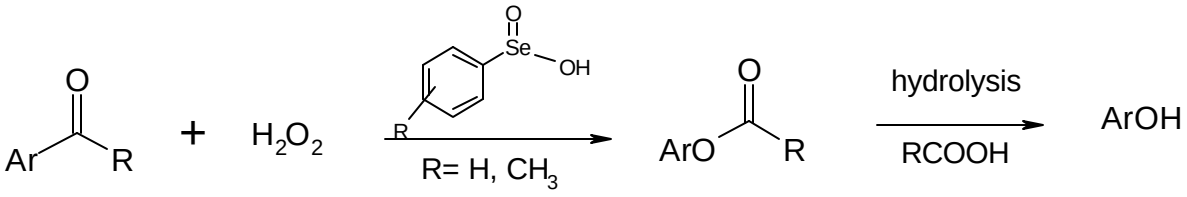
Oxidation reactions are of paramount importance in organic synthesis, important examples include dihydroxylation of olefins, epoxidation of allylic alcohols, aromatization, ozonolysis etc. The first part of this section deals with an important organic reaction-the Baeyer-Villiger oxidation, which has wide synthetic applications.[1] Some examples worth a mention are synthesis of steroids and antibiotics, synthesis of pheromones for agrochemistry, synthesis of monomers for polymerization etc. The versatility of this reaction is obvious by the vast literature available on the subject since its discovery more than a hundred years ago.[2] The reaction has a number of advantages which have been fully exploited by synthetic organic chemists. It tolerates the presence of many functional groups in the molecules. The regiochemisry can be controlled by placing groups with reference to scale of migratory aptitude. It is stereoselective as the migrating carbons retain their configuration in the product ester. Two important examples will suffice to validate the above

mentioned points. Pregnan-7, 20 dione (**1**), a precursor of 7-oxyprogesterone, reacts only at the C-7 carbonyl despite the presence of other oxidizable functional groups.[3] The acyl substituted β-lactam **3** an intermediate in the synthesis of carbapenem antibiotics is converted exclusively into the corresponding acetate[4] **(Scheme-1)**.




**Scheme-1**

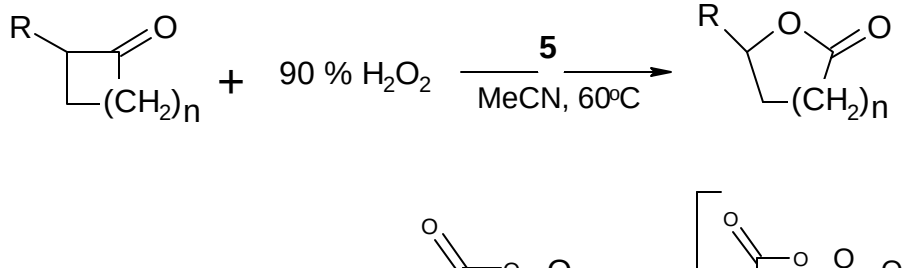
However surprisingly the attempts to apply transition metal catalysts to this important transformation have met with only moderate success. Even though the acid or basic catalysis with hydrogen peroxide in the Baeyer-Villiger oxidation is now known for quite some time [1a] it is limited to strained cyclic ketones such as cyclobutanones or bicyclo [2,2,1] hepten-2-ones. The success of the reaction is more due to the reactivity of the substrate rather than the oxidant. The most widely known catalytic work is the reaction between benzeneselenic acids and 30-90 % hydrogen peroxide to produce the corresponding peracids which convert aromatic aldehydes and ketones into phenols by hydrolysis of corresponding formates or acetates[5] **(Scheme-2)**.

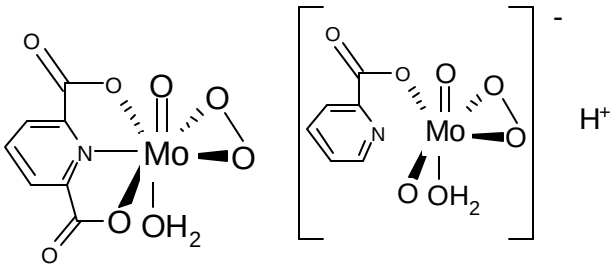



**Scheme -2**

The major drawback of this system is that 30 % $H_2O_2$ can be used only with the easily oxidizable aldehydes, while ketones require the no longer commercially available 90 % $H_2O_2$. Arsenated polystyrene resins catalyze biphasic and triphasic Baeyer-Villiger oxidations of ketones in methanol, dioxane or chloroform with 30 or 90 % $H_2O_2$. However even the use of water miscible solvents could not prevent extensive hydrolysis of the ester formed , especially with 30 % $H_2O_2$. The problem could be partly solved by using 90 % $H_2O_2$ or use of triphasic system with chloroform.

The first report of transition metal catalysis in Baeyer-Villiger oxidation of cyclic ketones is from Mares and co-workers, [6] who used picolinato and dipicolinato peroxo $Mo^{(IV)}$ complexes **5** and **6** as catalysts and 90 % $H_2O_2$ as oxidant. Molar turnovers ranged from poor to moderate **(Scheme-3)**.

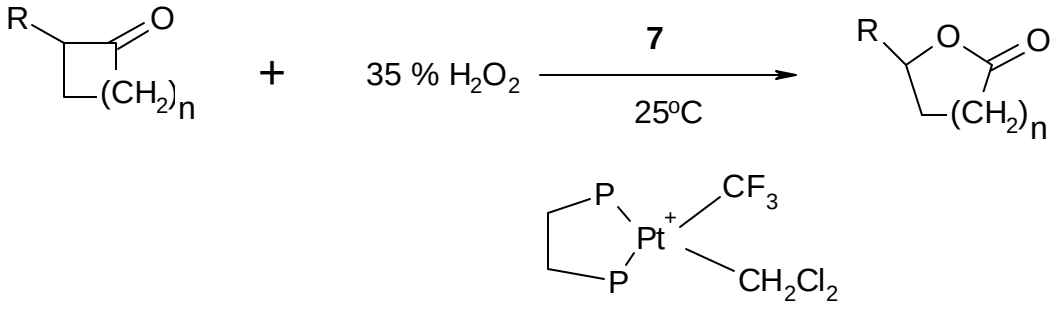



**5** **6**

**Scheme -3**

The system was reinvestigated [7] and interestingly an equivalent amount of sulfuric acid resulted in same catalytic activity, doubting the role of the oxidant. The first unambiguous example of transition metal catalysis applied to BVO is use of [(DPPE) Pt $(CF_3)(CH_2Cl_2)$] $BF_4$ with 35 % $H_2O_2$.[8] It is more efficient than molybdenum system and operates under mild conditions **(Scheme-4)**.

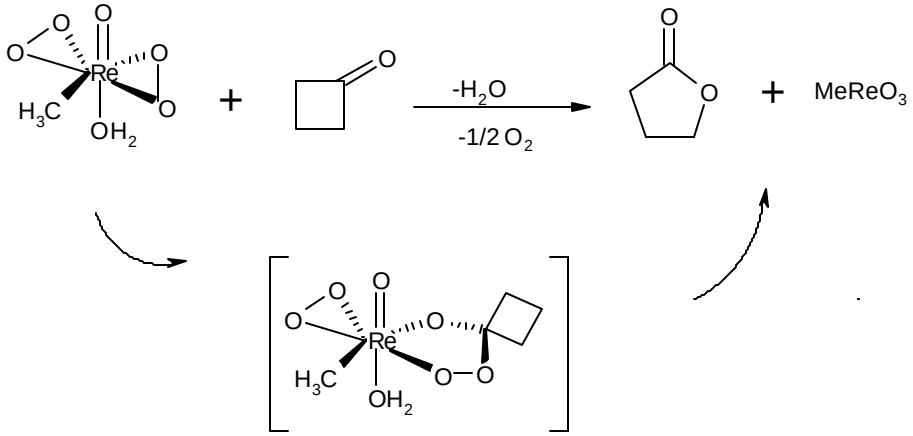



**7**

**Scheme -4**

However the Pt complex **7** was found to be inactive in the oxidation of acyclic ketones, even highly substituted ones such as methyl-tert-butyl ketone. It tends to deactivate as the oxidation proceeds, thereby limiting the maximum achievable turnover. Methyl trioxorhenium (MTO) is also used as catalyst in the Baeyer-Villiger oxidation of cyclic ketones with $H_2O_2$ *via* peroxy intermediates.[9] The reaction was suggested to proceed through the formation of an intermediate peroxometallic species **8** as shown in **Scheme-5**.

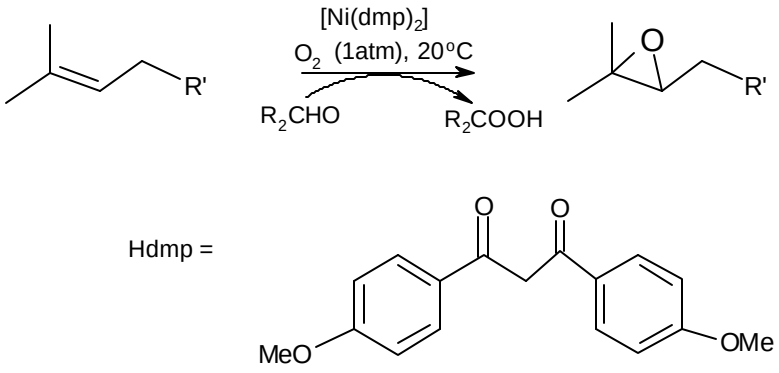
**8**




**Scheme -5**

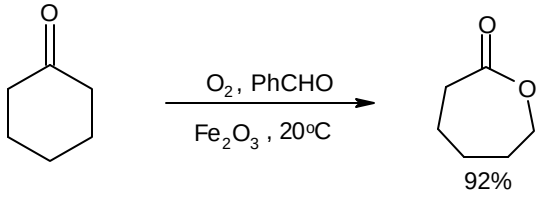
A very recent example is titanium silicalite (TS-1) catalyzed Baeyer-Villiger oxidation.[10] The oxidations of cyclohexanone and acetophenone was accomplished at 80°C with modest

turnovers that increase slightly with addition of a free acid. The modest activity observed is in agreement with the nature of the actual oxidant, which is believed to be a surface Ti(IV) peroxy species. In this respect TS-1 is similar to the old Mo catalyst. Mukaiyama and co-workers[11] reported the use of aldehydes for aerobic epoxidation of olefins in the presence of Ni complexes as catalysts **(Scheme-6)**.




**Scheme-6**

This strategy proved useful for the Baeyer-Villiger oxidation as well. $Fe_2O_3$ catalyses the oxidation of cyclohexanone and other ketones to the corresponding lactones in high yields [12] **(Scheme-7)**.

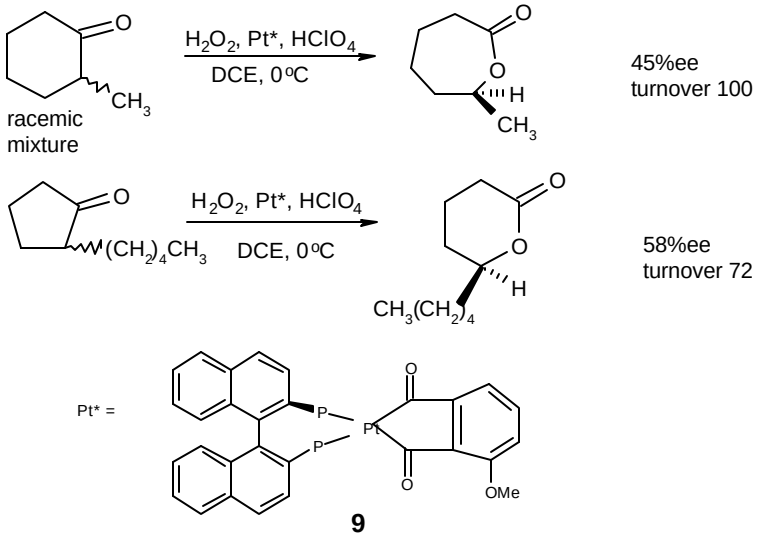



**Scheme-7**

## Part - I

### Asymmetric Baeyer-Villiger Oxidations

The use of microorganisms in the asymmetric Baeyer-Villiger oxidation of ketones has been known for several years and had been recently reviewed.[13] Whole cell cultures or purified enzymes extracted from *Acinobacter* family have allowed the preparation of chiral lactones with optical purity higher than 98 %. However the first two examples of transition metal catalysis for the Baeyer-Villiger oxidation were reported simultaneously by Gusso *et al.*[14] and Bolm *et al.*[15] quite recently. In both the cases the reaction was the kinetic resolution of racemic ketones through enantiospecific conversion into chiral lactones. The former studies were based on the use of platinum complexes modified with chiral diphosphene **9** and hydrogen peroxide as oxidant. Optimization of the catalyst structure led to the conversion of a series of racemic cyclohexanone and cyclopentanones into chiral lactones related to pheromones and fragrances with an *ee* of 58 % **(Scheme-8)**.

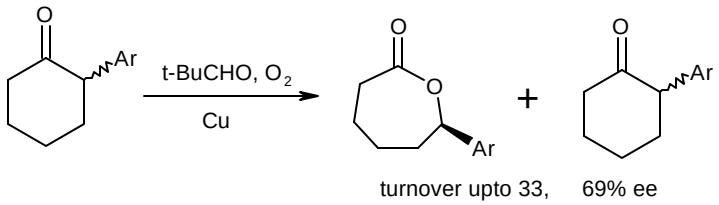



**9**

**Scheme-8**

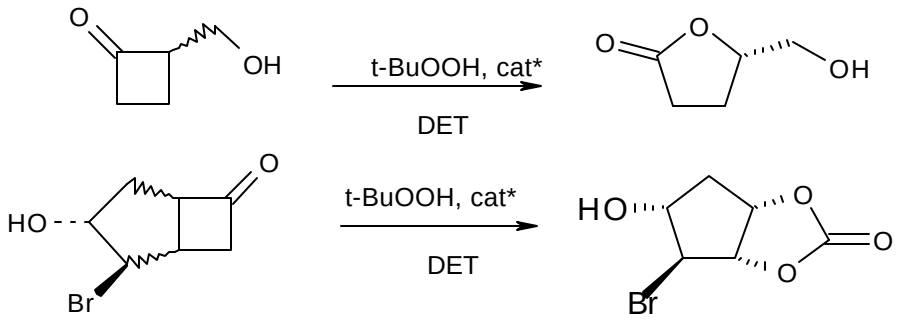
The latter studies were based on a modified Mukaiyama system consisting of a chiral Cu complex, pivaldehyde and oxygen as primary oxidant. Racemic aryl substituted cyclohexanone could be oxidized to the enantiomerically enriched lactones with an enantioselectivity upto 69 %. No enantiospecificity was observed with homologous Ni complexes and the use of other aldehydes

led to lower *ees*. The steric and electronic properties of the ligand influence the activity and enantiospecificity of the catalysts **(Scheme-9)**.




**Scheme-9**

Similar results have been observed by Lopp *et al.*[16] using Sharpless catalyst [Ti(O-iPr)$_4$-diethyl tartarate] and t-BuOOH as oxidant **(Scheme-10)**.




cat* = [Ti(O-iPr)$_4$ } + DET(diethyl tartarate)

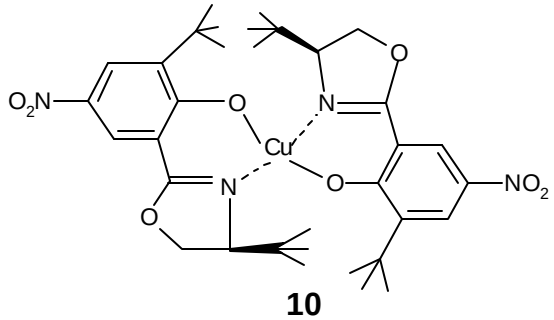
**Scheme-10**

Yields are moderate, but the reaction cannot be considered truly catalytic, as more substrate was present in the reaction mixture. Again only substituted cyclobutanones could be oxidized reflecting the inadequacy of Ti(IV) (a d $^0$ transition metal center) to bring about the reaction.

**Present Work**

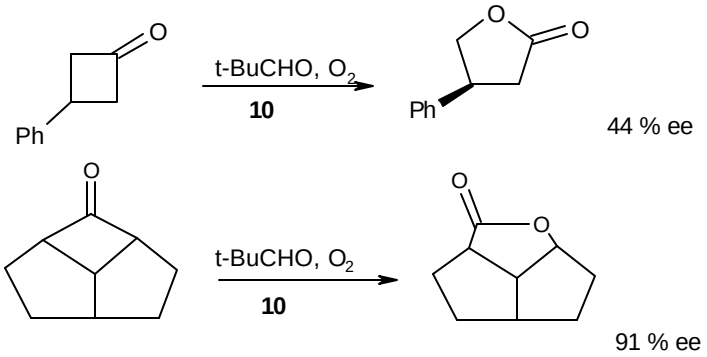
From a synthetic point of view the use of chiral transition metal catalyst appears to be the only promising alternative to catalysis by microbes for the synthesis of esters and lactones with optical purity. Transition metal catalysis in the Baeyer-Villiger oxidation of ketones is still a challenging issue as the reaction mechanism is elusive and the number of transition metal systems capable of efficient catalysis are very limited.

In a recent report by Bolm *et al.*[17] enantiospecific oxidation of ketones using chiral copper complex **10** was carried out and enantiomerically enriched lactones with an ee of upto 69 % were



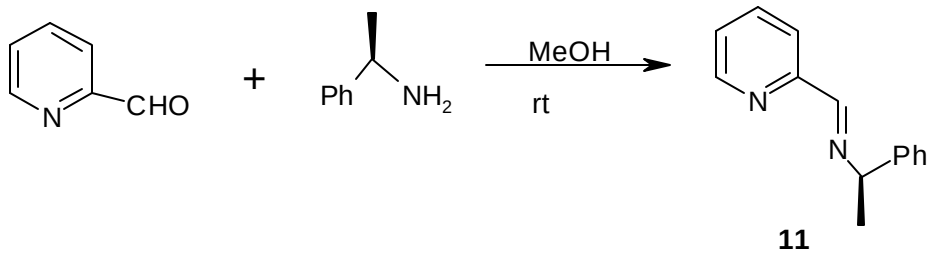
**10**

obtained. Substituted cyclobutanones afforded the corresponding butyrolactones with an asymmetric induction upto 91 % ee. Unfortunately the system is unable to oxidize ketones other than cyclobutanones **(Scheme-11)**.




**Scheme-11**

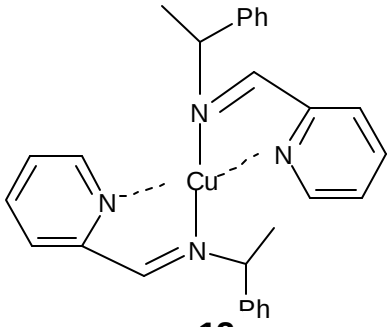
It was decided to design similar Cu based ligands from readily available starting materials. Towards this objective the imine complex **11** was synthesized by condensation of 2- pyridine carboxaldehyde and α-benzylmethylamine[18] **(Scheme-12)**.




**11**

**Scheme -12**

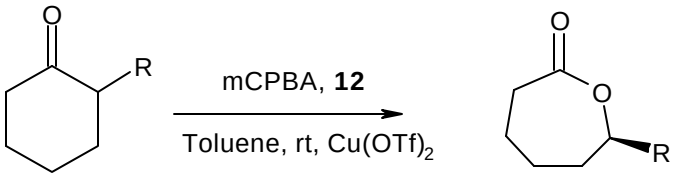
This ligand would complex with Cu (II) triflate to form the complex **12** which would catalyze the enantiospecific oxidation of ketones.




**12**

**Results and Discussion**

The ligand **11** was prepared by stirring a mixture of the chiral amine and aldehyde at room temperature in methanol in the presence of molecular sieves. It was characterized by the usual spectral analysis. Preliminary experiments were carried out with methyl cyclohexanone as the substrate and MCPBA as the oxidant. The reaction proceeded smoothly at room temperature to give the desired lactone in 37 % yield and in 23 % enantioselectivity **(Scheme-13)**.




**Scheme-13**

Encouraged by these results other substrates were subjected to similar reaction conditions and the results are summarized in **Table- 1.**

**Table-1: Asymmetric Baeyer-Villiger oxidation of ketones using MCPBA and 5 mole % ligand.**

| Entry | Substrate | Yield(%)[a] | Ee (%)[b] |
|---|---|---|---|
| a | 2-Methyl cyclohexanone | 43 | 30 |
| b | 4-tert-Butyl cyclohexanone | 77 | 23 |
| c | 4-Phenyl cyclohexanone | 80 | 27 |
| d | 2-Methyl cyclopentanone | 45 | 11 |

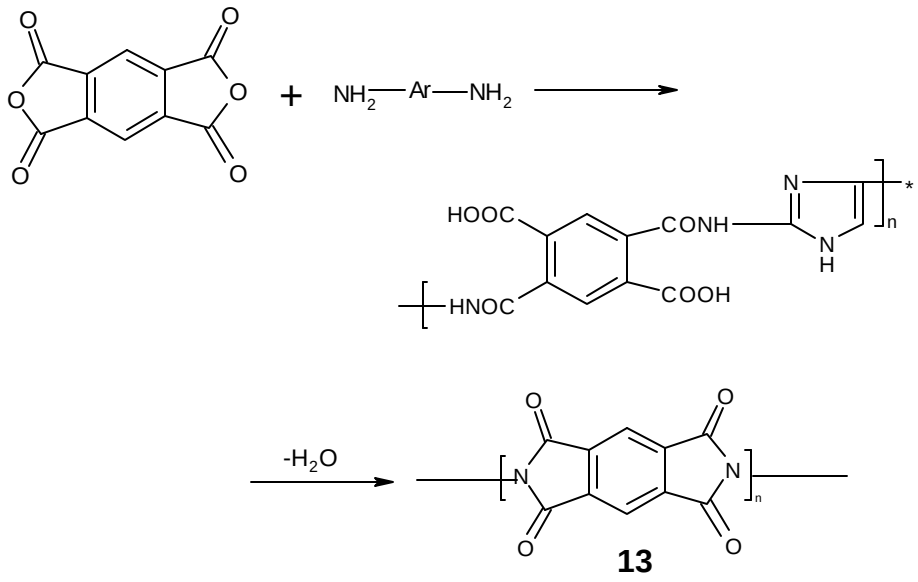
[a] Isolated yields after column chromatography [b] ee's were calculated by comparison with known optical rotation values.

As is evident from the table the highest enantioselectivity is achieved with 2-methyl cyclohexanone as the substrate. Although the enantioselectivities are moderate, this work has some potential and by varying the ligand architecture a higher chiral induction can be achieved. As the synthesis of ligand is trivial, tuning the ligand by introducing different substituents either at the stereocentre or at other positions is an easy task, work on these lines is being planned and executed.

## Part -II

**Synthesis of a novel polyaniline supported iron complex: A versatile oxidation catalyst.**

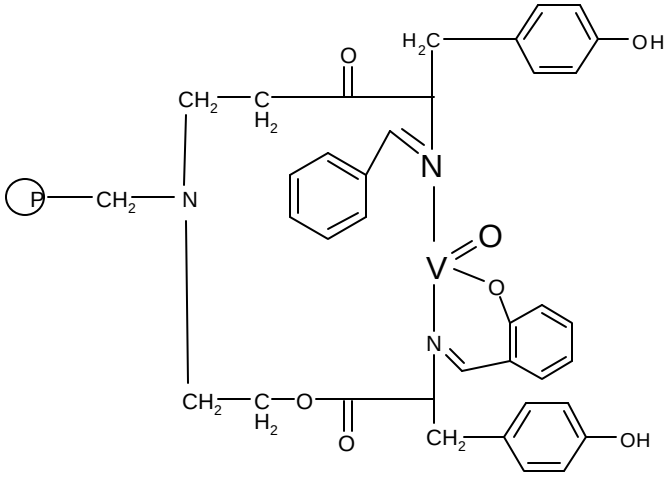
Polymer supported complexes have recently gained importance in organic syntheses.[19] A general introduction to their utility and application is presented in Section B of Chapter II. Due to their non-toxicity and recoverability at the end of the reaction, these catalysts are increasingly being used in a number of organic transformations. There are only a few scattered reports of application of metal-anchored catalysts for oxidation. Successful epoxidation of *trans* hex-2-en-ol was achieved by using a polyimide supported molybdenum (IV) epoxidation catalyst **13**[20] **(Scheme-14)**.



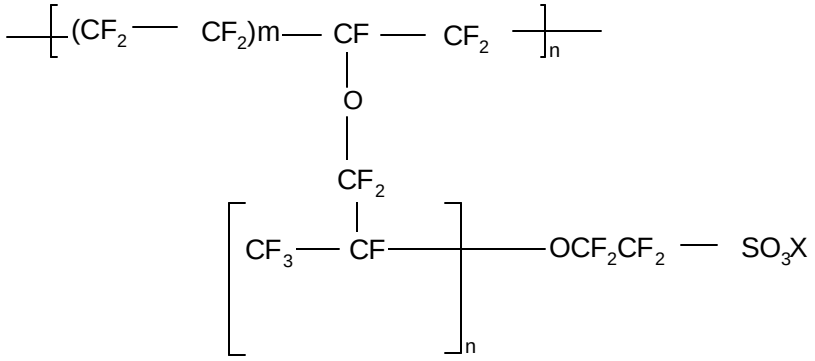

**13**

**Scheme-14**

Kumar and co-workers [21] have prepared and used a polymer supported vanadyl ($VO^{2+}$) complex (**14**), for use in hydroxylation of benzene using 30% hydrogen peroxide. The catalyst was recovered by filtration. The analysis of the beads after the reaction showed that the phenyl residues of the polymer complex did not undergo hydroxylation.



**14**

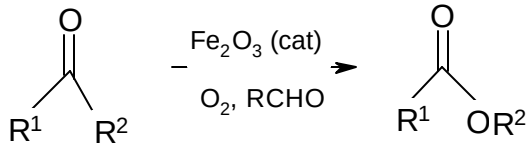



**15**

Another interesting example is the successful oxidation of alcohol by polymer supported chromium and cerium catalyst (**15**) in the presence of TBHP by Nozaki *et al*.[22] The Cr(II) and Ce(IV) catalysts were anchored onto commercially available Nafion 511 and the metal complex was prepared by treating the resin with the metal salts. These catalysts were reported to be superior to others due to ease of manipulation.

**Present Work**

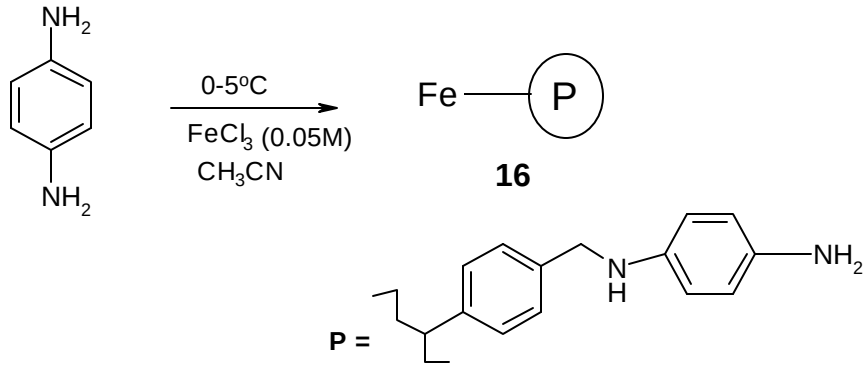
With this background in mind and current interest in polymer supported reactions it was decided to design and prepare a new polymer supported catalyst for oxidation reactions. Murahashi and co-workers [23] have recently reported $Fe_2O_3$ catalyzed Baeyer- Villiger oxidation of ketones with molecular oxygen in the presence of aldehydes **(Scheme-15)**.




56-98 % yield

**Scheme-15**

It was felt that iron was a suitable metal catalyst having potential for oxidation reactions in comparison with other metal salts, hence development of a polymer supported iron complex seemed an attractive strategy to develop an efficient heterogeneous oxidation protocol. Towards this objective, a new iron based polymer supported complex was synthesized in non-aqueous medium using simple synthetic manipulations from *p*- phenylene diamine **(Scheme-16)**. It was synthesized at the Department of Inorganic Chemistry, Baroda University and subsequently characterized at Catalysis Division, NCL, Pune.



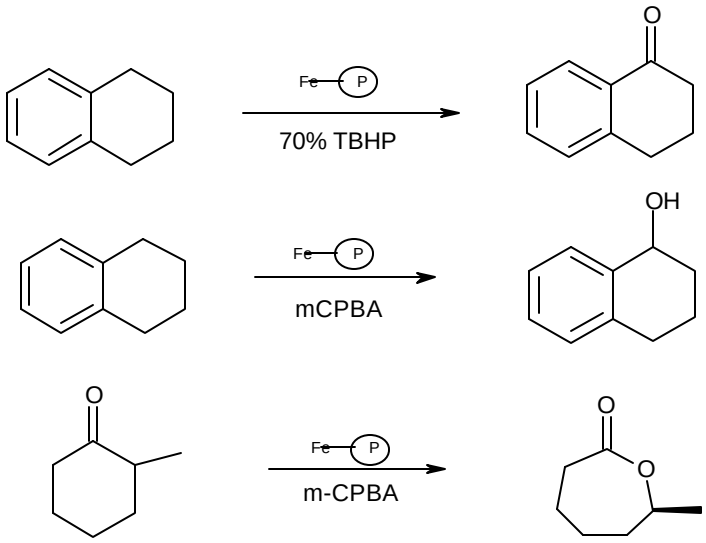

**Scheme-16**

## Characterization

The catalyst was thoroughly characterized using AAS, ESR, FT-IR, DTA-TGA Analysis, surface area measurements and C, H, N analysis. The metal content of the polymer catalyst was estimated using atomic absorption studies and found to be 1.5 ppm. The FT-IR showed N-H stretching frequencies at 3120 $cm^{-1}$. The surface area measurement of the catalyst was 55 $mg^2$. The DTA-TGA analysis showed that the catalyst is stable upto 220 $^oC$. The ESR spectrum appeared as a typical pattern of octahedral iron present in +3 oxidation state.

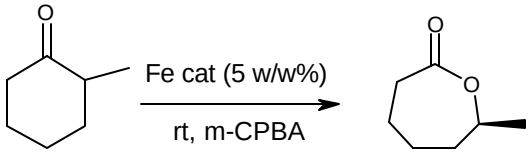
## Results and Discussion

Some initial experiments were performed with the polyaniline supported iron complex. It was found that the catalyst successfully oxidized tetralone to tetralol in presence of 70 % TBHP. Tetralin was converted to tetralone in presence of mCPBA while the methyl cyclohexanone underwent a Baeyer-Villiger oxidation and was converted to the corresponding methyl butyrolactone in high yields. Therefore **16** is a versatile oxidation catalyst working over a range of substrates **(Scheme-17)**.



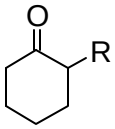
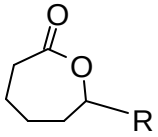
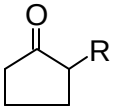
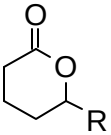
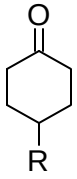
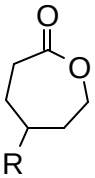
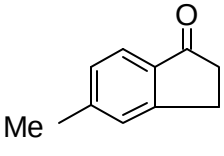
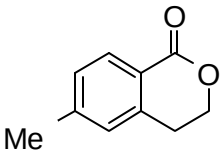

**Scheme-17**

In the quest of finding an efficient Baeyer-Villiger oxidation catalyst a complete study of reaction of **16** with a number of substrates was carried out. The reactions were performed by stirring 5 % w/w of the catalyst, 1.2 equivalent of m-CPBA and ketone at room temperature under argon (**Scheme -18**). The results obtained are very good and are tabulated below (**Table -2)**




**Scheme -18**

**Table-2: Baeyer-Villiger oxidation of various ketones by iron supported polymer complex.**

| Entry | Substrate | Product[b] | | Yield [a](%) |
|---|---|---|---|---|
| a |  |  | 17 R=H<br>18 R=Me | 95<br>90 |
| b |  |  | 21 R=H<br>22 R=Me | 27<br>45 |
| c |  |  | 19 R=t-Bu<br>23 R=Ph | 88<br>76 |
| d |  |  | 20 | 83 |

[a] Isolated yields [b] Products were characerized by IR, NMR and Mass.

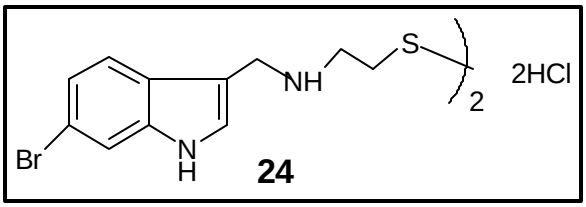
## Conclusions

The methodology is cheap and environment-friendly. The catalyst has all advantages of a heterogeneous synthesis viz. easy workup procedure, recoverability of the catalyst etc. The catalyst works well with a varied number of substrates. The work can be extended further to study the other oxidations viz. epoxidation, hydroxylation etc. The asymmetric Cu imine catalyzed reaction gave moderate enantioselectivities but has demonstrated that such systems can be developed into efficient ligands for asymmetric synthesis of lactones from cyclic ketones.

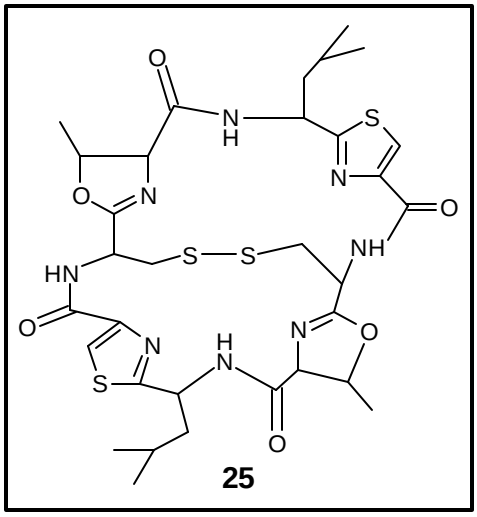
**Part - III : Sulphurylation of aromatics to 4,4' symmetric disulfides using Kaolinitic clay**

**Introduction**

The disulfides are a class of sulfur compounds with a unique and rich chemistry in synthetic and biochemical area. Large disulfide linked aggregates are prevalent in proteins and many other bioactive molecules .[24] Covalent disulfide bonds provide bridges that are believed to be responsible for initial protein folding. Many examples are known of extracellular proteins in which the functional structure is dependent on disulfide bridges. Large disulfide linked aggregates are also found in hair and related animal



**24**



**25**

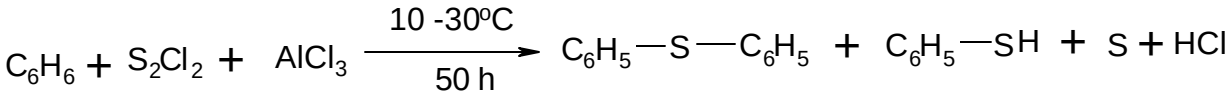
keratins. The disulfide link is found among many marine natural products, [25] for instance citorellamine (**24**), the first indole disulfide dihydrochloride from a marine organism. ulithiacyclamide (**25**), a new small peptide from a marine tunicate also has a disulfide linkage.[26] This molecule is believed to possess antimicrobial and neurophysiological properties.

Industrially, disulfides find wide applications as vulcanizing agents for rubbers and elastomers, giving them excellent tensile strength. Disulfides are much less prone to participate in organic reactions (e.g. oxidation, alkylation, acylation) than the corresponding free thiols and as such serve as protection for the thiol group. The conventional preparation of disulfides generally involves the photochemical and electrochemical oxidation of thiols.[27] However such methods

generally lead to overoxidation and are scarcely used for preparative purposes. Another common method involves the catalytic oxidation of thiols in the presence of various catalysts like tetrazoannulene cobalt, tetrabutyl ammonium ceric nitrate, coenzyme PQQ, diselenide salt, iodosylbenzene, DMSO, poly (vinyl pyridine) supported silver chromate etc.[28] The cleavage of thiol acetates with clayfen[29] and the oxidation of alkyl halide with tetrathiometallates of both molybdenum and tungsten[30] leading to the formation of disulfides have also been well documented. However, these methods, being indirect involving preparation of thiol and subsequent oxidation with catalyst are not viable methods for large-scale synthesis.

**Present Work**

A comprehensive literature search revealed that $S_2Cl_2$ has been known to react with activated substrates such as phenols and alkenes in the presence of a base to yield disulfides in moderate yields. [31] However the method suffers from severe disadvantages such as long reaction times (50 h), use of large excess of substrates etc. Further use of $AlCl_3$ in stoichiometric amounts in order to catalyze the reaction of $S_2Cl_2$ with benzene results in moderate yields of monosulfide along with the formation of thiophenol and thioanthrene [32] **(Scheme-19)**.

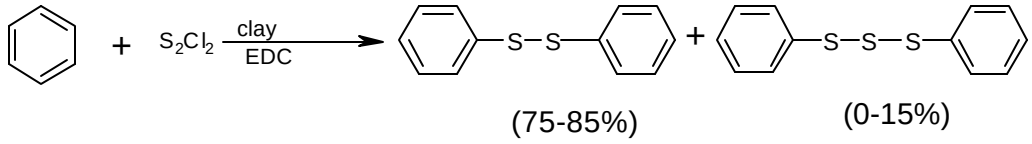



**Scheme-19**

Considering the importance of disulfide bond and impending need for development of heterogeneous catalytic and efficient ecofriendly synthetic methods, the present work was initiated and good results were obtained. Currently acid catalysis in organic transformations is an area of high potential and interest. Due to their Bronsted and Lewis acidities, clays function as efficient catalysts for a variety of organic transformations.[33] With this background in mind a systematic study of reaction of $S_2Cl_2$ with aromatics catalyzed by solid acid catalyst such as clay was undertaken, and the results are described here.

**Results and Discussion**

When sulfur monochloride is reacted with aromatics in the presence of kaolinitic clay catalyst, a high yield of symmetrical 4,4' disulfides is obtained, along with minor amounts of trisulphides **(Scheme-20)**.




**Scheme-20**

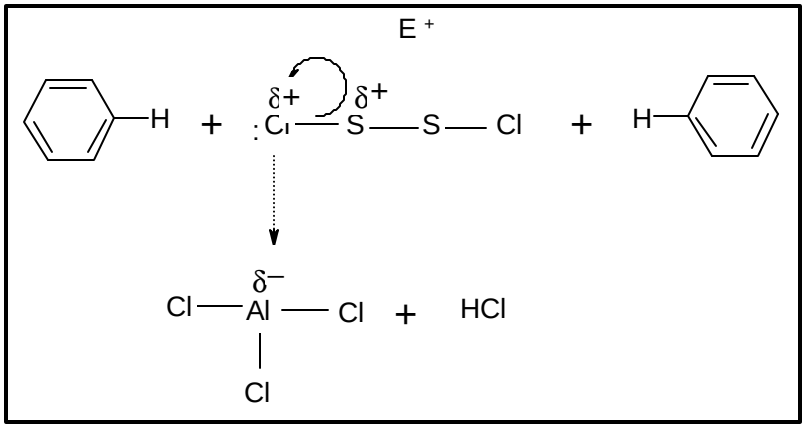
**Table-3: Kaolinitic clay catalyzed synthesis of disulfides**

| Entry | Substrate | Product[a] | Disulfide | Tri-sulphide |
|---|---|---|---|---|
| a) | Benzene | Diphenyl disulfide(**26**) | 70[c] | 15 |
| b) | Toluene | 4,4'-Ditolyl disulfide (**27**) | 65 | 10 |
| c) | Chlorobenzene | 4,4'-Dichlorophenyl disulfide(**28**) | 76 | 10 |
| d) | Naphthalene | 1, 1'-Dinaphthyl disulfide(**29**) | 75 | 15 |
| e) | Anisole | 4,4'-Dimethoxyphenyl disulfide(**30**) | 78[b] | 5 |
| f) | Biphenyl | 4,4'-Bis biphenyl disulfide(**31**) | 68 | 10 |
| g) | Anthracene | 2,2'-Dianthracenyl disulfide(**32**) | 68 | 10 |
| h) | Thiophene | 2,2'-Dithienyl disulfide(**33**) | 80[b] | 10 |
| i) | Cyclohexene | 2,2'-Dichlorodicyclohexyl disulfide(**34**) | 80 | 0 |

[a] Products were characterized by IR, Mass, NMR and microanalysis.
[b] Reaction proceeded at room temperature
[c] The catalyst was recycled thrice without any loss in activity.

From the above table it is evident that the conversions are nearly quantitative in all substrates studied. In the absence of the catalyst no reaction took place. A remarkable feature of the method is that a regiospecific formation of 4,4'-disulfides has been observed (entries b-f) in Table-3. 2,2'-Disulfides are not formed possibly due to steric crowding of the substrates experienced inside the β-intralamellar space of the clay. The reaction proceeds well with unactivated substrates such as benzene and toluene. Interestingly, with cyclohexene as the substrate, a high yield of 2,2'-dichlorocyclohexyl disulfide (80 %) was obtained and no formation of trisulfide was observed.

It may be of interest to note that other solid catalysts such as HZSM-5, H β, HY and $SiO_2$, $Al_2O_3$ have failed to activate $S_2Cl_2$ with aromatic substrates. The catalyst was recovered by filtration and successfully reused at least three times (in the case of benzene) without any loss in activity. The enhanced catalytic activity of acid activated clay could be attributed to the significant amount of acidity derived from $Al^{3+}$, $Fe^{2+}$ and $Ti^{2+}$ ions leached from the octahedral layer of the clay structure during the acid leaching.[5] The mechanism operating here is similar to the conventional Friedl-Crafts reaction, the sulfur monochloride coordinates well with the $Al^{3+}$ present in the clay and thereby getting activated so that the electrophiles attack the aromatic nucleus leading to the formation of disulfides **(Scheme-21)**.




**Scheme-21**

Thus the present methodology offers cheap, mild, neutral and environmentally friendly approach for the preparation of disulfides in a single step and in high yields. The kaolinitic clay was procured from the Padappakara mine of Quilon district Kerala, India. It was subsequently purified, calcined and treated with acid (2M HCl) as reported elsewhere.[34] The clay has been thoroughly characterized by XRD, UV, ESR, SEM, EDX and chemical analysis. The chemical component of the clay was determined by wet chemical analysis (in %) $SiO_2$= 67.45, $Al_2O_3$= 2.20, $TiO_2$= 3.15, $Fe_2O_3$= 6.1 and K= 0.8.

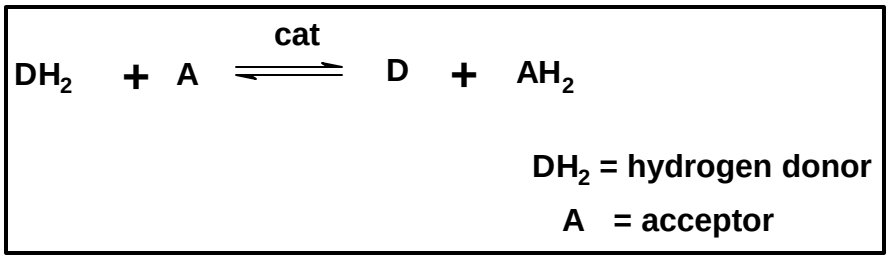
**Conclusions**

This is the first report of use of new heterogeneous catalyst for the preparation of symmetric disulfides by reaction of $S_2Cl_2$ with aromatic substrates .The main advantage is that the catalyst can be recovered and reused without affecting the activity or selectivity of the process. The present method involved a single step process to prepare disulfides as compared to the conventional method in two steps .In all the substrates studied, *para*-selectivity in product formation (regiospecific formation of para product) has been observed, no *ortho* products are formed. Another special feature of the method is that when cyclohexene is subjected to the reaction conditions, the corresponding dichlorodicyclohexyl disulfide is formed in 80% yield. In this case no trisulfide is formed. The clay is a natural one and not modified, it is available in plenty and it is cheap.

## Section-B : Transfer Hydrogenation

### General Introduction

Reduction of organic compounds is important synthetically both in laboratory and industry. Of all the methods available for hydrogenation, catalytic transfer hydrogenation has so far been relatively unutilized. Transfer hydrogenation involves the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst.[35] The process involves hydrogen abstraction from the recipient (hydrogen donor) by means of the catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate hydrogen acceptor **(Scheme-22)**.




**Scheme-22**

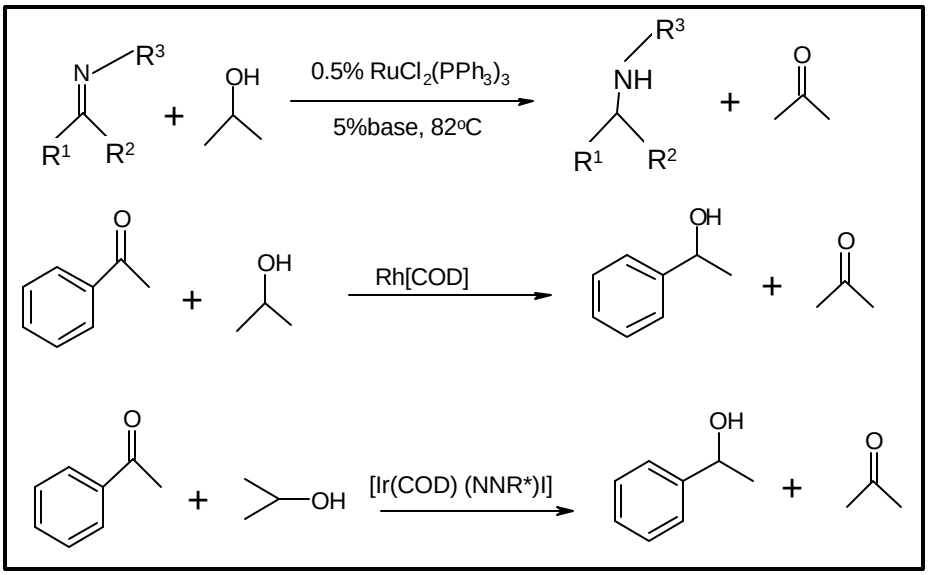
This method has several distinct advantages over the conventional hydrogenation procedure. It obviates the use of hydrogen gas, which is inflammable and does away with the large pressure hydrogenation apparatus requiring only simple reflux techniques. It uses cheap hydrogen donors such as isopropanol, formic acid, formaldehyde, cyclohexene, methanol etc. The main advantage is that the rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donors. Judicious choice of a hydrogen donor can control the rate and specificity of a reaction by its competitive adsorption to a catalyst surface.

A wide variety of homogenous and heterogeneous catalytic systems in combination with various hydrogen donors have been used to reduce most of the functional groups. Homogeneous catalysts with organometallic compounds are extremely efficient compared to their heterogeneous counterparts, [36] as each expensive metal atom is an 'active' site as opposed to just those on the surface. In homogenous catalysis each atom is an identical environment increasing reaction

specificity. The selectivity can be fine-tuned by appropriate choice of ligands, solvents and other variables. Heat is more easily dissipated and reaction conditions are generally mild. While homogenous catalysts can be deactivated by catalyst poisons, this effect seems to be more severe with the heterogeneous catalysts, particularly when they are formed from metals deposited on active carbon as support. The activity of a heterogeneous catalyst can be reduced or inhibited by traces of S, P, N, Hg and even oxygenated compounds. Finally mechanistic studies are easier, allowing better understanding and greater control of reaction under homogeneous conditions.

**Present Work**

The past years have witnessed a tremendous growth in the field of hydrogen transfer reactions. Mainly rhodium, ruthenium and iridium based hydrogen transfer catalyst systems have been developed by workers in this area [37] **(Scheme -23)**.




**Scheme -23**

All the above processes use precious metal and being highly active catalysts are not so selective. It has been observed that controlling the reaction rates is very difficult in these active catalysts. They show no selectivity when the molecule has multiple or labile moieties. Raney nickel is not so expensive but it is pyrophoric and reduces all the functional groups such as C-X, C=O, $NO_2$ simultaneously. Further its use for the reduction of aromatic ketones to benzylic alcohols leads to hydrogenolysis at the benzylic position.[38] Although chemoselective reduction of functional groups

can be achieved with the classical Meerwein- Pondorrf-Verley reductions, the use of stoichiometric amounts of aluminum isopropoxide under the drastic reaction conditions leads to undesired side reactions.[39]

In view of the above observations, it was felt imperative to develop a mild and cheap commercially available catalyst for the selective reduction of functional groups. With this aim in mind a complete study of the potential application of various cheap and commercially available nickel and cobalt based catalyst for transfer hydrogenation was carried out and the results obtained are presented here.

**Results and Discussion**

Various catalysts, which were screened for their activity, are shown in **Table-4**. Propan-2-ol was used as the hydrogen donor because of its simplicity, cost effectiveness, availability and easy removal of its dehydrogenation product, acetone from the system. Acetophenone was the substrate chosen for determining the catalyst selectivity. Its conversion into 1- phenethyl alcohol was observed. The catalyst $Co(OAc)_2$ and $Ni(acac)_2$ are commercially available while Co(SMDPT) [40] and $CoCl(PPh_3)_3$[41] can be easily prepared by the procedures given in the literature.

**Table-4: Transfer hydrogenation of acetophenone to 1-phenethyl alcohol with propan-2-ol over different catalysts**

| Entry | Catalyst | Product Yield (%) | |
|---|---|---|---|
| | | 1-Phenethyl alcohol | Unreacted acetophenone |
| 1. | No Catalyst | 0 | 100 |
| 2. | Co(Oac)2 | 98.0 | 2.0 |
| 3. | CoCl(PPh3)3 | 67.5 | 32.5 |
| 4. | Co(SMDPT) | 66.9 | 33.0 |
| 5. | Ni (acac) | 96.1 | 3.2 |
| 6. | Raney Ni | | |

It is to be noted that $Co(OAc)_2$ has shown excellent activity and selectivity to reduce acetophenone. Hence it was chosen for further study. Raney nickel under similar conditions gives ethyl benzene. In the absence of the catalyst no reaction took place. The reaction also requires the use of solid KOH as a co-catalyst. Potassium hydroxide is believed to be effective by removing a proton from the reacting complex during part of the catalytic cycle. The base promotes the transfer of a hydride ion from an alkoxy radical onto an adjoining coordinated ketone. Other mild bases such as $K_2CO_3$ or $NaHCO_3$ failed to catalyze the reaction. $Co(OAc)_2$ was further studied for the transfer hydrogenation of various functional groups viz., C=O, C=N, $NO_2$, the results of which are presented in **Table 5.**

**Table 5**: **Transfer hydrogenation of aldehydes and ketones with propan-2-ol catalyzed by $Co(OAc)_2$**

| | **Substrate** | **Product** | **Yield (%)** |
|---|---|---|---|
| A | Acetophenone | 1-Phenethyl alcohol | 90 |
| B | Benzophenone | Benzhydrol | 62 |
| C | Cinnamaldehyde | Cinnamyl alcohol **(37)** | 70 |
| D | 2-Octanone | 2-Octanol (38) | 40 |
| E | 1-Tetralone | 1-Tetralol (39) | 91 |
| F | Pyridine-2-carboxaldehyde | 2-Hydroxy methylpyridine (40) | 90 |
| G | Nitrobenzene | Aniline (**41**) | 66 |
| H | 2-Nitrobenzaldehyde | 2-Nitrobenzyl alcohol (**42**) | 72 |
| I | 4-Nitrobenzaldehyde | 4-Nitrobenzyl alcohol (**43**) | 60 |
| J | 4-Nitrobenzophenone | 4-Nitrobenzhydrol (**44**) | 70 |
| K | 4-Chlorobenzaldehyde | 4-Chlorobenzyl alcohol (**45**) | 80 |
| L | Benzophenone + Benzaldehyde (1:1) | Benzyl alcohol(**46**)+ Benzophenone | 90 |

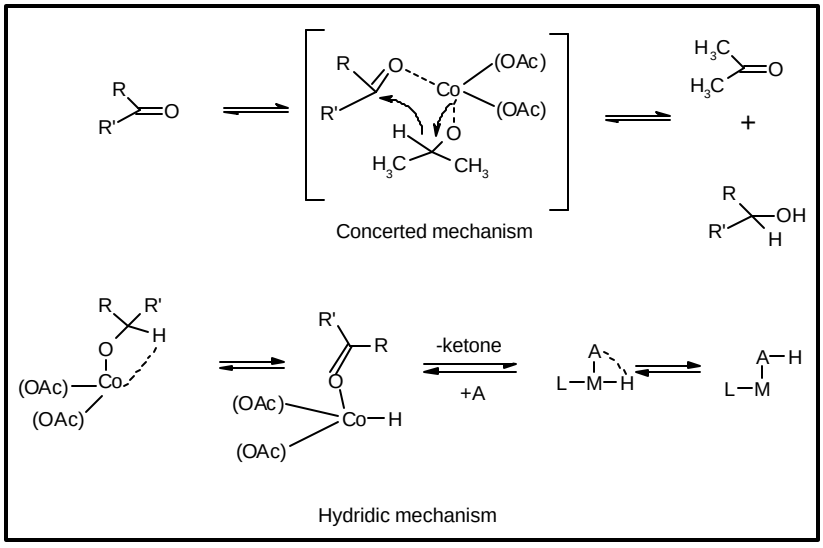
[a]Products were characterized by IR, $^1H$ NMR, $^{13}C$ NMR and MS spectra.

[b]Isolated yields, the rest being essentially unreacted starting materials.

It is interesting to note that the present catalytic system reduces a range of carbonyl compounds- aromatic, aliphatic, heterocyclic to respective alcohols in good yields. A remarkable feature of this catalytic system is that the reduction proceeds in a chemoselective manner (entries c, h, l). For instance when 2-nitrobenzaldeyde was subjected to reduction, the only product obtained was 2-nitrobenzyl alcohol without $NO_2$ group being reduced (GC). However it is to be noted that nitrobenzene could be reduced to aniline in 66% yield when subjected to reduction separately. Similarly, C=C and C-Cl bonds are not hydrogenated at all in the presence of C=O functionality. Also when equimolar amount of benzophenone and benzaldehyde were subjected to reduction with $Co(OAc)_2$ system the reaction proceeded very well furnishing only benzyl alcohol and benzophenone did not undergo any reduction. However the present system failed to reduce ketones such as cyclohexanone, mesityl oxide, chalcone etc.

**Mechanistic Studies**

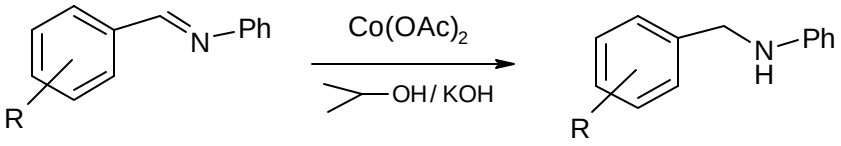
The mechanism of the transfer hydrogenation process from 2-propanol to a ketone substrate has been well studied with the rhodium system $RhCl(PPh_3)_3$[42] so most of the details are clear. Based on the reports, the following mechanism can be proposed on similar lines. Either it can be a hydridic stepwise mechanism or a concerted one with simultaneous bond making and breaking **(Scheme - 24)**.




**Scheme -24**

**Transfer hydrogenation of imines**

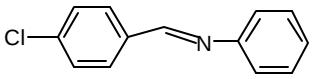
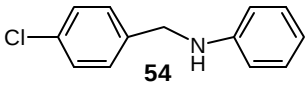
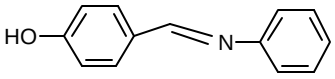
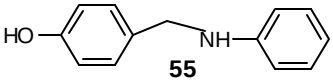
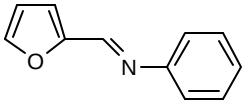
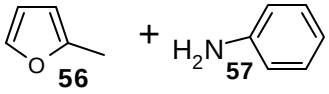
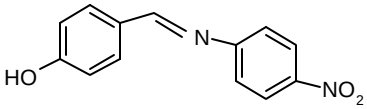
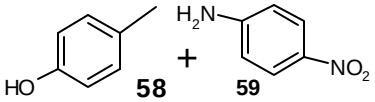
Even though there have been several developments in the field of transfer hydrogenation of ketones and carbon carbon double bonds, there are relatively few reports of transfer hydrogenation of imines.[43] Owing to the synthetic interest in these reactions it was decided to extend the methodology using cobaltic system to transfer hydrogenation of imines. The present catalyst system [ $Co(OAc)_2$, KOH, Isopropanol] was screened for the transfer hydrogenation of imines **(Scheme-25)**.



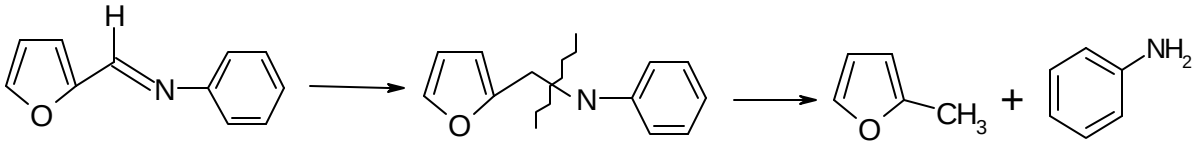

**Scheme-25**

Compared with the cobalt catalyzed transfer hydrogenation of ketones, the reaction rate of imines was much lower. Both steric and electronic factors may lead to a slower hydrogen transfer from propan-2-ol to imines compared to ketones. The presence of a catalytic amount of base such as NaOH or KOH is necessary for the transfer hydrogenation of imines, which is also observed for transfer hydrogenation of ketones. In the absence of a base no reaction occurred even after 20 h. It is important here that isopropanol employed is dry since water reacts reversibly with imines affording amine and an aldehyde or ketone. The present system works well for the reduction of imines to amines (entries 1, 2). Good yields of corresponding amines were obtained (**Table-6**). Interestingly in the case of some of the imine substrates transfer hydrogenolysis products (entries c, d) were detected instead of the expected amines Transfer hydrogenolysis refers to reaction in which σ-bonds of functional groups are cleaved upon addition of hydrogen.

**Table-6: Transfer hydrogenation of imines using cobalt catalyst**

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| a |  |  **54** | 68 |
| b |  |  **55** | 70 |
| c |  |  **56** **57** | 58 |
| d |  |  **58** **59** | 60 |

Significant use has been made of the hydrogenolytic cleavage of C-N bonds in deprotonation of peptides.[44] Transfer hydrogenolysis reactions do not follow a radical chain mechanism. The first step of these reactions complements the bimolecular formation of 1,4-diradicals from alkene or heteroalkenes. They play an important role in coal liquefaction, aromatization reactions with nitroarenes or quinones and possibly biochemical dehydrogenations .In the present case, probably the reduced amine was initially formed and underwent hydrolytic cleavage *in situ* to give the alkylated products under the given reaction conditions **(Scheme - 26)**.



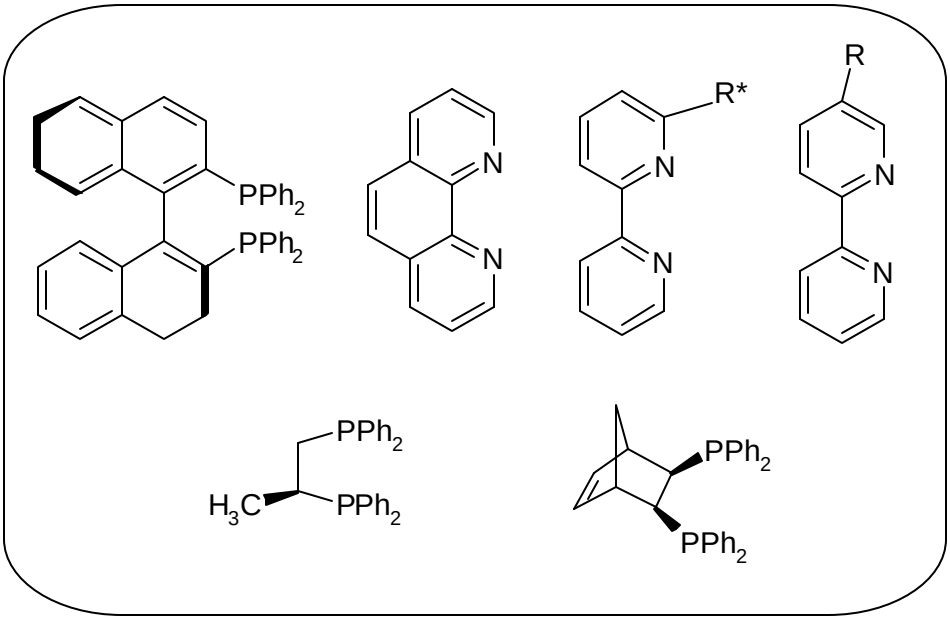
**Scheme - 26**

**Conclusions**

This is the first report of the use of a new homogeneous catalytic system Co $(OAc)_2$-propanol-KOH, for the reduction of a variety of aldehydes and ketones to the corresponding alcohols in high yields. The main advantage of the present method is that the reduction proceeds in a chemoselective manner in the presence of other reducible functional groups. The reactivity order follows: CHO>C=O>>$NO_2$>C-X, C=C bonds. Even benzylic double bond is not affected. This result is to be contrasted with Raney nickel which reduces $NO_2$, CHO, CO and C-X groups simultaneously under the same reaction conditions, thus exhibiting no selectivity. The present catalytic system works well for the reduction of imines also. Some of the imine substrates undergo hydrogenolysis, which is also an important organic transformation. The method does not require hydrogen gas nor any pressure reactor, 2-propanol functions both as a solvent and as hydrogen source. The workup is easy involving merely filtration of the catalyst. Co $(OAc)_2$ is commercial, cheap and no phosphine ligands need to be added to catalyze the reaction.

**Part II : Asymmetric transfer hydrogenation of ketones using rhodium based mono cyanooxazoline ligands**

Chiral non racemic hydrogen donors can be profitably employed as chirality source for inducing enantioselectivity in the product, thus providing new routes to accomplish an asymmetric process. This expands the potential of asymmetric hydrogen transfer and makes it more versatile than asymmetric catalytic hydrogenation.

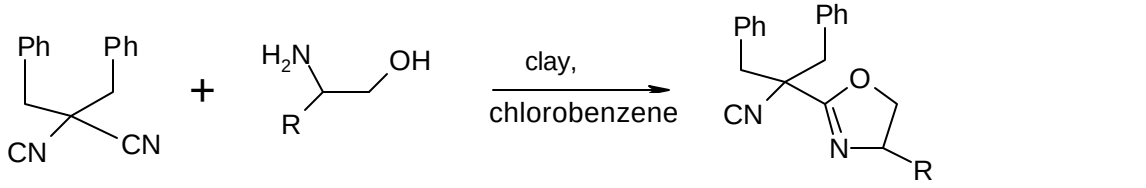



**47**

There are two basic ways by which enantioselective hydrogen transfer can be achieved, enantioface selection by means of a chiral catalyst on achiral substrates or enantiomer selection (kinetic resolution) of a racemic compound.[45] The most efficient and economic way to perform an asymmetric hydrogen transfer is by means of enantiomerically pure catalyst, where a single metal atom promotes the transformation of a great amount of substrate and reagent molecules. In recent years numerous advances have been made in this field. So far mono and polynuclear $Ru^{(II),}$ $Rh^{(I),}$ $Ir^{(I)}$, complexes with chiral phosphorous[46] and nitrogen ligands[47] have been the most successfully employed enantioselective hydrogen transfer reactions (**47**).

**Present Work**

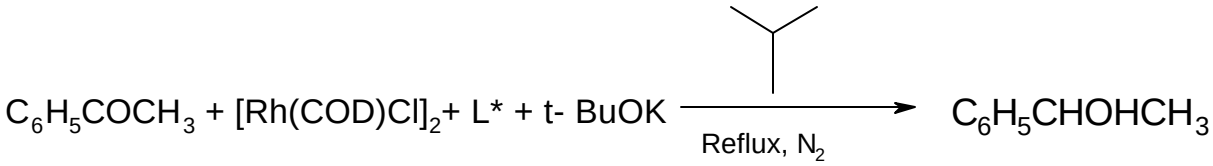
Oxazoline ligands have gained paramount importance in recent years. They can be readily synthesized from easily available chiral amino alcohols. The stereogenic center is quite close to the reactive site of the catalyst. In particular, the oxazoline ligands with $C_2$ symmetry have achieved high enantioselectivities in various catalytic processes.[53] However there are a few reports of catalysts with unsymmetric oxazoline ligands which also have two coordinating nitrogen atoms. In the present work during the studies on the design of new nitrogen containing chiral ligands, new monocyanooxazoline ligands which have similar electronic properties to bisoxazolines were prepared using a methodology recently developed in the laboratory.[49] These ligands have a diffident size chelate in the metal complexes formed in the reaction, which is bound to have some influence on the stability, stereochemistry and enantioselectivities of catalyst. Towards this objective the following series of modified monocyanooxazoline ligands was synthesized. The general formula is written below. The R substituent can be varied by varying the starting amino alcohol. The ligands were synthesized in simple steps from dibenzyl malonoitrile **(Scheme-27)**.




R = isopropyl, ethyl, benzyl

**Scheme-27**

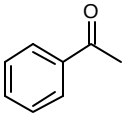
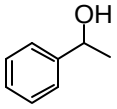
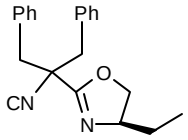
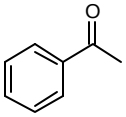
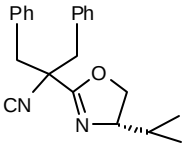
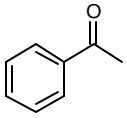
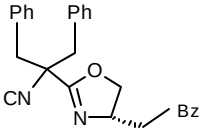
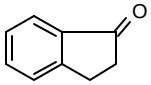
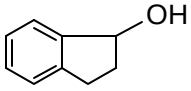
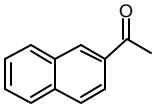
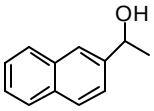
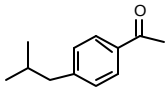
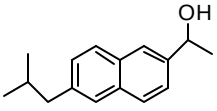
The asymmetric hydrogen transfer reaction was carried out using propan-2-ol as hydrogen source, the usefulness of which has been mentioned in the earlier section. Rhodium was used as the metal center. The rhodium cyclooctadiene complex was prepared as per the reported procedure.[50] At first the metal ligand complex was prepared by stirring the rhodium COD complex (5 mol %) and ligand (6 mole %) at 60°C for 2-3 hours. To this the base potassium t-butoxide was added. Other bases like NaOH and KOH failed to give the product. The reaction was initially screened for asymmetric transfer hydrogenation with acetophenone **(Scheme-28)**.




**Scheme-28**

As there was some chiral induction, different substrates were subjected to transfer hydrogenation to test the efficiency of the present catalytic system using mono cyanooxazolines as ligands. **(Table-7)**

**Table-7: Asymmetric transfer hydrogenation of prochiral ketones with monocyano oxazoline ligands**

| Entry | Substrate | Product | Ligand | Yield [a] (%) | ee [b] (%) |
|---|---|---|---|---|---|
| a |  |  **36** |  **51** | 80 | 18 |
| b |  | **36** |  **52** | 83 | 22 |
| c |  | **36** |  **53** | 90 | 8 |
| d |  |  **48** | **51** | 40 | 20 |
| e |  |  **49** | **52** | 80 | 11 |
| f |  |  **50** | **52** | 87 | 15 |

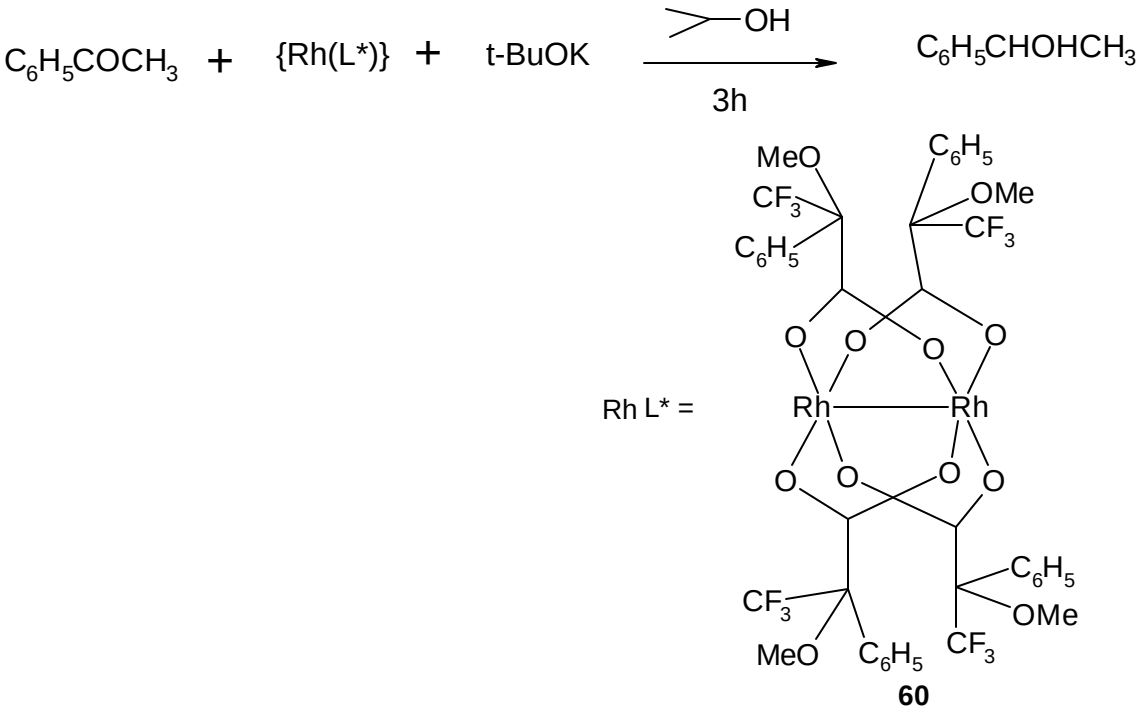
[a] Isolated yields [b] ee's are based on comparison with known optical rotation values.

As is evident from the table, the highest enantioselectivities are obtained with the isopropyl ligand Therefore it was screened further for transfer hydrogenation of naproxen and ibuprofen precursors (entries e and f) which are well known important non-steroidal anti-inflammatory drugs belonging to the class of α aryl propanoic acids.[51] They were prepared by the reported procedures in the literature.[52]

## Part - III

### Transfer hydrogenation of ketones using a novel rhodium based ligand

In continuation of efforts towards development of an asymmetric transfer hydrogenation protocol, a bulky nitrogen based ligand was screened for transfer hydrogenation of ketones. Encouraged by the success of the novel Rh ligand in asymmetric cyclopropanation reactions discussed in the previous chapter (Chapter -IV), the efficacy of the ligand was further tested for asymmetric transfer hydrogenation of prochiral ketones **(Scheme-29)**.




**60**

**Scheme-29**

All the reactants were dried and refluxed for three hours in anhydrous degassed isopropanol. After completion of the reaction as monitored by TLC, the catalyst was filtered through celite and the reaction mixture was concentrated and purified on silica gel chromatography. The sec-phenyl ethyl alcohol obtained in good yields was measured for the enantiomeric excess, which was around 11 % by comparison with known optical rotation value.

## Conclusions

In this study, new monocyanooxazoline ligands have been designed and used successfully for asymmetric transfer hydrogenation reactions. Even though the *ee*'s obtained are moderate chemical modification by varying substituents on the ligand can lead to higher induction. The feasibility of the application of the novel rhodium ligand to asymmetric transfer hydrogenation has been studied and further work is in progress.

## Experimental

### Synthesis of 1-phenyl-N [(E)-2-pyridinyl methylidene]-1-ethanamine (11)

Pyridine-1-carboxaldehyde (200 mg, 1.8 mmol) and (R)-α-methylbenzylamine (248 mg, 1.9 mmol) were stirred in presence of molecular sieves under argon in anhydrous methanol for 12 hours at room temperature. After completion of the reaction (TLC) the molecular sieves were filtered off and the crude reaction mixture was purified to give the desired imine.

| | |
|---|---|
| **Yield** | 352 mg (90 %) |
| **M.P.** | 92.3 $^{o}$ (Lit[18] M.P. 90$^{o}$C) |
| **$^{1}$H NMR** | δ 8.50(s, 1H), 7.7-7.3(m, 8H), 6.9(m, 1H), 4.7-4.6(m, 1H), 1.38(d, *J* = 1.9 Hz, 3H). |
| **Mass (m/z)** | 210 ($M^{+}$, 12), 194 (100), 167 (8), 133 (10), 105 (75), 77 (22). |

### General Procedure for the Baeyer Villiger oxidation of Cyclic Ketones with Chiral Cu-Imine complex.

Chiral imine (252 mg, 0.1 mmol) and copper (II) triflate (18 mg, 0.05 mmol) were stirred in dichloromethane (5mL) under argon at room temperature for two hours. Methyl cyclohexanone (200 mg, 1 mmol) was added *via* syringe to the stirred solution. Finally m-chloroperbenzoic acid (215 mg, 1.25 mmol) was added and the reaction mixture was allowed to stir overnight. After completion of the reaction, it was diluted with ether and given bicarbonate wash. The ethereal extract was concentrated *in vacuo* and column purified to give 110 mg (90 %) of the corresponding lactone.

### Preparation of polyaniline supported iron complex 16

Monomer (poly p-phenylene diamine) was first dissolved in acetonitrile and cooled to 0-5 $^{o}$C. A cooled solution of 0.05 M $FeCl_3$ in $CH_3CN$ was added to it dropwise and the reaction mixture was stirred overnight on a magnetic stirrer for 12-15 h. It was then filtered and washed with the solvent until the filtrate obtained was colourless. The reddish black colored precipitate obtained was

dried at room temperature to give the product. It was characterized by AAS, ESR, FT-IR, DTA-TGA Analysis and surface area measurements.

**Typical Procedure for oxidation reactions using the polymer supported iron complex**

To a stirred solution of 5-methoxy indanone (100 mg, 0.6 mmol) in dry DCM was added 15 mg (5 % w/w) of the iron catalyst, at room temperature. Finally MCPBA (103 mg, 0.6 mmol) was added to the reaction mixture and reaction was stirred further for 12 hours. After completion the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and column purified to give the desired lactone, (91 mg, 83.5 %) yield. Similar procedure was followed for the conversion of tetralin to tetralone and tetralin to tetralol.

**2-Oxepanone (17)**

**Yield** 205 mg (95 %).

**$^1$H NMR** 4.4-4.2(m, 2H), 2.8-2.5(m, 2H), 2.1 -1.5(m, 6H).

**Mass (m/z)** 84 ($M^+$, 70), 67 (15), 55 (100).

**S(-)7-Methyl 2-oxepanone (18)**

**Yield** 110 mg (90 %).

**IR (**neat**)** 3428, 3015, 2861, 1703, 1569, 1215, 923 cm-$^1$.

**$^1$H NMR** δ 4.5 - 4.4 (m, 1H)**,** 2.7 - 2.5 (m, 2H), 2.0 -1.8(m, 3H), 1.7 - 1.5 (m, 3H), 1.35(d, *J* = 2.2 Hz, 3H).

**Mass (m/z)**: 128 ($M^+$,0.9), 55(100).

**[a ]$_D$ $^{25}$** Absolute +25.0 $^o$(c = 1.8, $CHCl_3$).

Observed -7.5 $^o$ (c = 1.8, $CHCl_3$)

**Enantiomeric excess** 30 %

**5-tert-Butyl-2-oxepanone (19)**

**Yield** 193 mg (88 %).

**IR**(nujol) 2960, 1742, 1190, 1181, 1140 cm$^{-1}$

**$^1$H NMR** δ 4.6 - 4.2 (m, 2H), 2.9 - 2.7 (m, 2H), 2.3 - 2.1 (m, 2H), 1.6 - 1.5 (m, 3H), 1.1 (s, 9H).

**Mass (m/z)** 170 ($M^+$, 0.1), 156 (41), 139 (62), 114 (100), 86 (61).

**6-Methoxy-3, 4-dihydro-2H-benzo[c] pyran-1-one (20)**

**Yield** 91 mg (83 %).

**$^1$H NMR** δ 7.3 -7.1 (m, 1H), 7.0- 6.9 (m, 2H), 4.0(s, 3H), 3.3 - 3.2(m, 2H), 3.1-2.9 (m, 2H).

**Mass (m/z)** 178 ($M^+$, 70), 150 (32), 135 (100), 108 (28), 77 (15).

**Analysis** Calculated for $C_{10}H_{10}O_3$ ; C = 67.4 %, H = 5.6 % .
Observed C = 66.6 %, H = 5.1 %.

**perhydro-2-Pyranone (21)**

**Yield** 36 mg (27 %).

**$^1$H NMR** 4.21-4.18(m, 2H), 2.44-2.40(m, 2H), 1.80-1.70(m, 2H), 1.40-1.30(m, 2H).

**6-Methyl perhydro-2-pyranone (22)**

**Yield** 78 mg (45 %).

**IR (**$CHCl_3$**)** 3027, 1735, 1215, 748, 448 $cm^{-1}$.

**$^1$H NMR** δ 4.58 - 4.21 (m, 1H), 2.7-2.3 (m, 2H), 2.0-1.4 (m, 4H), 1.36 (d, *J* = 6Hz, 3H).

**$[a]_D^{25}$** Absolute = +18.4 $^o$ (1.1, MeOH)
Observed = -2.02$^o$ (1.1, MeOH)

**Enantiomeric excess** 11 %

**5- Phenyl 2-oxepanone (23)**

**Yield** 124 mg (76 %).

**IR (**$CHCl_3$) 3020, 1726, 1215, 748, 448 $cm^{-1}$.

**$^1$H NMR** δ 7.4-7.3 (m, 5H), 4.5 - 4.4 (m, 2H), 2.9 - 2.8 (m, 3H), 2.3 - 2.1 (m, 3H), 2.0 - 1.8 (m, 1H).

**Mass (m/z)** 191 ($M^{+1}$, 24), 190 ($M^+$, 23), 162 (4), 148 (45), 117 (100), 104 (20), 91 (17), 77 (8).

**General procedure for the sulfurylation of aromatics to symmetrical disulfides**

To a mixture of substrate (10 mmol), and day catalyst (5 % w/w), in ethylene dichloride (20 mL) was added sulfur monochloride (5 mmol) dropwise. It was then refluxed for 2 h. After the reaction was complete (TLC) the catalyst was filtered off and the solvent removed by distillation. The crude reaction mixture was purified by column chromatography ($SiO_2$) to give the corresponding disulfides.

**Diphenyl disulfide (26)**

**Yield** 2.27 g (70 %)

**M.P**. 56 $^oC$ (Lit M.P. 60 $^oC$)

**$^1$HNMR** $\delta$ 7.7- 7.6 (m, 6H), 7.2 - 7.1. (m, 4H).

**Mass (m/z)** 250 ($M^+$, 30), 218 (70), 185 (20), 154 (20), 141 (62), 109 (100), 77 (40), 69 (32).

**di(4-Methyl phenyl) disulfide (27)**

**Yield** 1.23 g (65 %)

**M.P.** 43.9 $^oC$ (Lit M.P. 45 $^oC$)

**$^1$H NMR** $\delta$ 7.5- 7.4 (m, 4H), 7.2- 7.1 (m, 4H), 2.6 (s, 6H).

**Mass (m/z)** 246 ($M^+$, 35), 214 (12), 155 (28), 139 (35), 123 (85), 91 (100), 77 (60).

**di(4-Chlorophenyl) disulfide (28)**

**Yield** 1.94 g (76 %)

**M.P**. 72 $^oC$ (Lit M.P. 69$^oC$)

**$^1$H NMR** $\delta$ 7.7-7.1 (m, 8H).

**Mass (m/z)** 286 ($M^+$,10), 256 (52), 84 (49), 108 (65), 75 (60), 64 (100).

**di(2-Napthalenyl) disulfide (29)**

**Yield** 1.98 g (75 %)

**M.P.** 71$^oC$ (Lit M.P. 73$^oC$)

**$^1$H NMR** $\delta$ 8.7-8.2 (m, 4H) 7.6-7.2 (m, 10H).

**Mass (m/z)** 318 ($M^+$, 40), 286 (15), 254 (10), 190 (25), 159 (95), 115 (100), 64 (22).

**di (4-Methoxyphenyl) disulfide (30)**

**Yield** 2 g (78 %)

**M.P.** 44.6 $^oC$ (Lit M.P. 46$^oC$)

**IR (neat)** 2900, 1590, 1250, 1100, 820 $cm^{-1}$

**$^1$H NMR** δ 7.4 (d, *J* = 10Hz, 4H) 6.85 (d, *J*= 10Hz, 4H), 3.6 (s, 6H).

**Mass (m/z)** 278($M^+$, 10), 246 (100), 231(95), 171 (20), 139 (30), 63(30).

**di(4-phenyl phenyl)disulfide (31)**

**Yield** 1.63 g (68 %)

**M.P**. 67.6$^oC$ (Lit M.P. 66$^oC$)

**$^1$HNMR** δ 7.6-7.2 (m, 18H).

**Mass (m/z)** 370 ($M^+$, 20), 338 (80), 256 (20), 192 (20), 185 (80), 152 (50), 64 (100).

**Analysis** Calculated for $C_{24}H_{18}S_2$ ; C = 82 %, H = 4.4 %, S =12.2 %.
Observed C = 81.7 %, H = 4 %, S = 11.7 %.

**di(2-anthracenyl) disulfide (32)**

**Yield** 1.59 g (68 %).

**M.P** . 83.4 $^oC$ (Lit M.P. 85 $^oC$).

**$^1$H NMR** δ 8.5 (m, 10 H), 7.6 (m, 8 H).

**Mass (m/z)** 418 ($M^+$, 5), 20 (40), 209 (20), 176 (50), 123 (40), 88 (40).

**2-(2-thiophenyl dithio) thiophene (33)**

**Yield** 2.24 g (80 %)

**M.P.** 49.8 $^oC$ (Lit M.P. 48$^oC$)

**$^1$HNMR** δ 7.6-7.5 (m, 2H) 7.2-7.1 (m, 2H), 7.0-6.9 (m, 2H).

**Mass (m/z)** 230 ($M^+$,42), 198 (30), 166 (10), 147 (17), 71 (100), 64 (5).

**di(2-Chlorocyclohexyl disulfide) (34)**

**Yield** 2.03 g ( 80 %)

**$^1$H NMR** δ 4.1-3.9 (m, 2H). 3.2- 2.9 (m, 2H), 2.10 (s, 4H), 1.5 (s, 8H), 1.10 (s, 4H).

**Mass (m/z)** 298 ($M^+$, 10), 266 (10), 231 (11), 182 (3), 116 (5), 80 (100), 67 (13), 53 (19).

**General Procedure for synthesis of monocyano oxazoline ligands for asymmetric transfer hydrogenation**

A mixture of dibenzyl malononitrile (0.05 mole), 2-aminomethyl propanol (0.04 mole) and 20 mg (10.5 % w/w) of clay catalyst in *o*-dichlorobenzene (10 mL) was refluxed for 10-12 hours. After completion of the reaction (TLC) the reaction mixture was poured into dichloromethane (3x 20 mL) the combined organic layers were washed with water, followed by brine solution and dried over $Na_2SO_4$, the organic layer was concentrated and purified on neutral alumina to give the corresponding monocyano ligands.

**Preparation of di-μ-chloro-bis (η$^4$-1,5-cyclooctadiene) dirhodium**

Rhodium chloride trihydrate (2 g, 7.6 mmole) in ethanol (30 mL) was boiled under reflux with *cis* cyclooctadiene (2 mL, 27.7 mmole) for 3h. The solution was cooled and the orange solid filtered off, washed with ethanol, dried and recrystallized from acetic acid to give orange needles.

**Yield** 1.67 g (94 %).

**M.P**. 254$^o$C (Lit [50] M.P. 256$^o$C).

**$^1$H NMR** δ 5.3 (s, 8H), 2.6 (s, 16H).

**IR** (nujol) 998, 965 and 818 $cm^{-1}$.

**Analysis** Calculated for $C_{16}H_{24}Cl_2Rh_2$ ; C = 38.97 %, H = 4. 81 %, Cl = 14.38 %.

Observed C =39.01 %, H= 4.80 %, Cl = 14.28 %.

**General Procedure for the transfer hydrogenation of prochiral ketones using ligand rhodium complex**

Rh [COD] complex (19 mg, 0.04mmol) and monocyano ligand (47 mg, 0.12 mmol) were stirred under argon for three hours at 60$^{o}$C in dry isopropanol. Potassium t-butoxide (44 mg, 0.4 mmol) was added to the stirred solution at room temperature. Finally acetophenone (200 mg, 1.6 mmol) dissolved in isopropanol was added *via* syringe and the reaction mixture was refluxed for 12 hours. After completion of the reaction the reaction mixture was brought to room temperature and subjected to aqueous workup. The crude reaction mixture was column purified to give 90 % (181 mg) of the desired alcohol.

**Transfer hydrogenation of ketones using a novel Rh based chiral catalyst.**

Acetophenone (200 mg, 0.4 mmol) was stirred in dry isopropanol. To this t-potassium butoxide (44 mg, 0.4 mmol) and finally the rhodium catalyst (5 mg, 0.004 mmol) were added in one portion and the reaction refluxed for three and half-hours. The reaction mixture was passed through celite and the organic solution was concentrated *in vacuo*. The pure product was isolated by column chromatography.

**1-(4-ethyl -(4R)-4,5-dihydro[1,3]oxazol-2-yl)-2-phenyl -1-phenyl methyl cyanide (51)**

| | |
|---|---|
| **Yield** | 0.80 g (67 %) |
| **IR**( nujol ) | 2925, 2864, 1671, 1456, 1374, 704 cm$^{-1}$. |
| **$^{1}$H NMR** | $\delta$ 7.38 (s, 10H). 4.44 (dt, *J* = 1.9 Hz, 1H), 4.0-3.7 (m, 2H), 3.4-3.1 (dd, *J* = 1.9 and 2.5 Hz, 4H), 1.4 (dq, *J* = 1.9Hz, 2H) 0.9 (t, *J* = 2.5 Hz, 3H). |
| **Mass (m/z)** | 294 (M$^{+}$,0.3), 226 (40), 155 (7), 127 (5), 91 (100), 64 (40). |

**1-{4-(1methylethyl)-(4S) 4, 5-dihydro[1,3] oxazol-2-yl)-2-phenyl-1-henylmethylethyl cyanide (52)**

**Yield** 0.93 g (72 %)

**$^1$H NMR** δ 7.35 (s, 10H) 4.2-4.3 (m, 1H), 3.85-3.95 (m, 1H), 3.7-3.8 (m, 1H), 3.2 (dd, *J* = 13.45 and 14 Hz, 4H), 0.85 (d, *J* = 5.4Hz, 3H), 1.5-1.65 (m, 1H), 0.75 (d, *J* = 5.4Hz, 3H).

**Sec-phen ethyl alcohol (35)**

**Yield** 0.91 g (90 %)

**$^1$H NMR** δ 7.4-7.3 (m, 5 H), 4.9 (q, *J* = 2. Hz, 1 H), 1.8 (bs, 1 H), 1.5 (d, *J* = 2 Hz, 3H).

**$[a]_D^{25}$** Absolute 42 $^o$ (neat)

Observed 9.24 $^o$ (neat)

**Enantiomeric excess** 22 %

**1-Indanol (48)**

**Yield** 0.41 g (40 %)

**M.P.** 70.5$^o$C (Lit. M.P. 72$^o$C)

**$^1$H NMR** δ 7.3-7.1(m, 4H), 4.87(dt, *J* = 6Hz, 1H), 3.18(bs, 1H), 2.72(t, *J* = 4Hz, 2H), 2.4-2.3(m, 2H).

**$[a]_D^{25}$** Absolute -34 $^o$ (c =1, $CHCl_3$)

Observed -6.8 $^o$ (c=1, $CHCl_3$)

**Enantiomeric excess** 20 %

The naproxen and ibuprofen precursors were prepared according to the reported procedures.[52]

**1-(4-(2-methylpropyl) phenyl)-1-ethanol (49)**

**Yield** 0.87 g (87 %).

**IR** (neat**)** 3445, 2964, 2920, 2860 cm$^{-1}$.

**$^1$H NMR** δ 7.35 (d, *J* = 2.3 Hz, 2H). 7.1 (d, *J*= 2.3 Hz, 2H), 4.8 (q, *J*= 2.3 Hz, 1H), 2.45 (d, *J*= 1.5 Hz, 2H), 1.9-1.7 (m, 1H), 1.4 (d, *J* = 2.3 Hz, 3H,), 0.9 (d, *J*= 1.5 Hz, 6H).

**1(6-methoxy-2-napthalenyl)-1-ethanol (50)**

**Yield** 0.79 g (80%)

**$^1$H NMR** δ 7.2-7.7 (m, 6H). 5.1 (q, *J* = 4.8 Hz, 1H), 3.9 (s, 3H), 2.2 (bs, 1H), 1.5 (d, *J* = 4.8 Hz, 3H).

**$[a]_D^{25}$** Absolute +25.6$^o$ (c= 0.798, EtOH)

Observed + 2.8$^o$ (c =0.798, EtOH)

**Enantiomeric excess** 11 %

**General Procedure for the transfer hydrogenation of ketones with $Co(OAc)_2$**

In a typical reaction, a mixture of 2-nitrobenzaldehyde (1 g, 6 mmol), $Co(OAc)_2$ $4H_2O$ (100 mg, 0.4 mmol) and KOH pellets (300 mg, 4.7 mmol) in propan-2-ol (20 mL) was refluxed for 3hours.After completion of the reaction (TLC), the solvent was distilled under reduced pressure and the crude reaction mixture was subjected to aqueous work up , followed by extraction with ether,the ether layer as then dried over $Na_2SO_4$. The product obtained after removal of solvent was purified by column chromatography to afford the pure 2-nitrobenzyl alcohol (72 %, 0.72 g).

**Cinnamyl alcohol (37)**

**Yield** 70 % (0.71 g).

**B.P**. 238 $^o$C (Lit. B.P. 240$^o$C).

**$^1$H NMR** δ 7.3-7.2 (m, 5H). 6.6 -6.5(m, 1H) 6.4-6.3 (m, 1H), 4.3 (d, *J* = 7.74 Hz, 2H), 2.6 (s, 1H).

**Mass (m/z)** 135 ($M^+$, 6), 115 (1), 105 (67), 91 (100), 77 (65), 63 (22).

**2-Octanol (38)**

**Yield** 0.40 g (40 %)

**B.P.** 84.7 $^o$C (Lit. B.P. 85 $^o$C)

**$^1$H NMR** δ 3.75 (m, 1H), 1.5-1.4 (m, 10H), 0.9 (t, *J* = 2.5 Hz, 3H), 0.8(d, *J* = 15 Hz, 3H).

**1-Tetralol (39)**

**Yield** 0.92 g (91 %).

**M.P.** 38.$^o$ C (Lit B.P. 39-40 $^o$C).

**$^1$H NMR** δ 7.5-7.4 (m, 2H) 7.2 -7.1(m, 2H), 4.7 (t, *J* = 1.48 Hz, 1H), 2.9-2.7 (m, 2H) 2.0-1.7 (m, 4H).

**Mass (m/z)** 148, ($M^+$, 35), 130 (65), 119 (60), 105 (55), 91 (60), 71 (44), 57 (100).

**2-Hydroxymethyl pyridine (40)**

**Yield** 0.91 g (90 %).

**M.P.** 167 $^o$C (Lit M.P.168-169$^o$C).

**$^1$H NMR** δ 8.5 (s, 1H), 7.6- 7.5 (m, 1H), 7.3-7.2(m, 2H), 4.6 (s, 2H), 3.5 (s, 1H).

**2-Nitrobenzyl alcohol (42)**

**Yield** 0.72 g( 72 %)

**B.P**. 237$^o$C (Lit. B.P. 240$^o$C)

**$^1$H NMR** δ 7.7-7.5(m, 4H), 4.8(s, 2H), 2.3(bs, 1H).

**Mass (m/z)** 152 ($M^+$,1), 135 (8), 121 (5), 105 (21), 91 (27), 77 (100).

. **4-Nitrobenzene methanol (43)**

**Yield** 0.84 g (60 %).

**$^1$H NMR** δ 8.2 (d, *J* =10.81 Hz, 2H). 7.5(d, *J* = 10.81Hz, 2H), 4.9(s, 2H), 2.4(bs, 1H).

**4-Nitro benzhydrol (44)**

**Yield** 0.706 g (70 %)

**M.P.** 70 $^o$C (Lit M.P. 71$^o$C)

**IR** ($CHCl_3$) 3400, 1700, 1219 $cm^{-1}$

**$^1$H NMR** δ 7.5-7.8 (m, 9H) 6.7 (s, 1H) 3.51 (bs, 1H).

**Mass (m/z)** 225 ($M^+$, 0.1), 197 (61), 180 (5), 168 (5), 120 (100).

**4-Chlorobenzyl alcohol (45)**

**Yield** 0.80 g (80 %)

**M.P.** 70 $^oC$ (Lit M.P. 71$^oC$)

**IR** ($CHCl_3$) 3400, 789, 1219, 1700 $cm^{-1}$

**$^1$H NMR** δ 7.3-7.2 (m, 4H), 4.6 (s, 2H), 2.1 (s, 1H).

**Mass (m/z)** 142 ($M^+$, 1), 125 (1), 107 (63), 77 (100).

**N-(4-hydroxybenzyl)-N-phenylamine (55)**

**Yield** 0.76 g (70 %)

**$^1$H NMR** δ 7.3-7.48 (m, 9H), 4.7 (s, 2H), 3.4 (bs, 1H).

**MASS (m/z)** 199 ($M^+$, 0.5), 196 (100), 178 (1), 167 (3), 104 (5), 93 (10), 7 (55).

## References


1. a) Hassall, C.A, *Org. React.*, **1957**, 9, 73. b) House, H.O., *Modern Synthetic Reactions*, Benjamin, New York, **1972**, 327p. c) Hudlicky, M., O*xidations in Organic Chemistry*, American Chemical Society, Washington, **1990**, 186 p. d) Krow, G.C., *Org. React.*, **1993**, 43, 251.
2. Baeyer, A. and Villiger, V., *Ber. Dtsch. Chem. Ges.*, **1899**, 32, 3625.
3. Le Mahieu, R.A., Boris, A., Carson, R., Guthrie, R.W. and Kierstead, R.W., *J. Med. Chem.*, **1973,** 16, 647.
4. Shiozaki, M., Ishida, N., Maruyama, H. and Hiraoka, T., *Tetrahedron*, **1983**, 39, 2399.
5. a) Syper, L., *Synthesis*, **1989**, 167. b) Syper, L. and Mlochowski, J., *Tetrahedron*, **1987**, 43, 207.
6. Jacobsen, S.E., Mares, F. and Tang, R., *J. Chem. Soc. Chem. Commun.*, **1978**, 888.
7. Campestrini, S. and Furia, F.D., *J. Mol. Catal.*, **1993**, 79, 13.
8. Frisone, M.D.T., Pinna, F. and Strukul, G., *Stud. Surf. Sci. Catal.*, **1991**, 66, 405.
9. Herrmann, W.A., Fischer, R.W. and Correia, J.D.G., *J. Mol. Catal.*, **1994,** 94, 213.
10. Yamada, T., Rhode, O., Takai, T. and Mukaiyama, T., *Chem. Lett.*, **1991**, 5.
11. Takai, T., Yamada, T., Rhode, O. and Mukaiyama, T., *Chem. Lett.*, **1991**, 281.
12. a) Murahashi, S-I., Oda, Y. and Naota, T., *Tetrahedron Lett.*, **1992**, 33, 7557. b) Murahashi, S-I., *Angew. Chemie.*, **1995**, 107, 2670.
13. Alphand, V. and Furstoss, R., in *Enzyme Catalysis in Organic Synthesis*, (Eds. K Drauz, H Waldmann) VCH, New York, **1995,** p 745 and references therein.
14. Gusso, A., Baccin, C., Pinna, F. and Strukul, G., *Organometallics*, **1994,** 13, 3442.
15. Bolm, C., Schlingloff, G., Weickhardt, K., *Angew. Chem.*, **1994**, 106, 1944; Angew. *Chem. Int. Ed. Engl.*, **1994**, 33, 1848.
16. Lopp, M., Paju, A., Kanger, T. and Pehk, T., *Tetrahedron Lett.*, **1996**, 37, 7583.
17. Bolm, C., Schlingloff, G., Bienewald, F., *J. Mol. Catal.*, **1997**, 117, 347.
18. Zassinovich, G., Bettella, R., Mestroni, G., B-Pahor, N., Geremia, S. and Randaccio, L., *J. Organomet. Chem.*, **1989**, 370, 187.
19. Pitman, C.U., Jr., in Hodge, P. and Sherrington D.C. (Eds.*), Polymer Supported Complexes*, Elsevier, Amsterdam, **1981.** b) Kaneda, K. and Imanaka, T., *Trends Org. Chem*., **1991,** 2, 109.
20. Miller, M.M. and Sherrington, D.C., *J. Catal.*, **1995**, 152, 368.

21. Das, S.K., Kumar, A. and Nandrajyog, S., *Tetrahedron Lett.*, **1995**, 36, 7909.
22. Kanemoto, S., Saimoto, H., Oshima, K. and Nozaki, H., *Tetrahedron Lett.*, **1984,** 25, 3317.
23. Murahashi, S-I., Yoshiaki, O. and Naota, T., *Tetrahedron Lett.*, **1992**, 33, 7557.
24. Bodzansky, M., in *Principles of Peptide Synthesis,* Springer-Verlag, Berlin, **1984,** Chapter 4.
25. Moriarty, M.R., Roll, D.M., Ku, Y-Y., Nelson, C. and Ireland, C.M., *Tetrahedron Lett*., **1987,** 28**,** 749.
26. Hall, D.G. and Morton, T.H., *J. Am. Chem. Soc.*, **1980,** 102, 5688.
27. Wolmon, Y., in *The Chemistry of the Thiol Group*, Ed by S. Patai, John Wiley and sons, London, **1974,** Chapter 14.
28. Sato, T., Otera, J. and Nozaki, H., *Tetrahedron Lett*., **1990**, 31, 3595 and the references cited therein.
29. Mehsram, H.M., *Tetrahedron Lett.*, **1993**, 34, 2521.
30. Chandrasekaran, S. and Dhar, P., *J. Org. Chem.*, **1989,** 54, 2998.
31. Lautenschlaeger, F., and Schwartz, N.V., *J. Org. Chem.*, **1969**, 34, 3991.
32. Hartman, W.W., Smith, L.A. and Dickey, J.B., *Org. Syn. Coll. Vol.* II, **1943**, 242.
33. Laszlo, P., *Acc. Chem. Res.*, **1986,** 19, 121.
34. For purification of the clay see Sabu, K.R., Sukumar, R. and Lalithambika, M., *Bull. Chem. Soc. Jpn.*, **1993**, 66, 3535.
35. Johnstone, R.A.W., Wilby, A.H. and Entwistle, I.D., *Chem*. *Rev*., **1985,** 85, 129. b) Kabalka, G.W. and Varma, R.S., in *Comprehensive Organic Synthesis*, Ed Trost, B.M. and Fleming, I., Academic Press, Oxford, Vol 8, **1991**, 363.
36. Black, H.T., *Aldrichimica. Acta.*, **1982**, 15, 13.
37. a) Chowdhury, R.L. and Backvall, J.E., *J. Chem. Soc. Chem. Commun*., **1991,** 1063. b) Wang, G.Z. and Backvall, J.E.., *J. Chem. Soc. Chem. Commun.*, **1992,** 980. c) Iyer, S. and Varghese, J.P., *J. Chem. Soc. Chem. Commun.*, **1995**, 465.d) Nose, A. and Kudo, J., *J. Chem. Pharm. Bull.*, **1988**, 36, 1529.
38. Andrews, M.J. and Pillai, C.N., *Ind. J. Chem.*, **1978**, 16B, 46.
39. Wilds, A.L., *Org. React.*, **1944**, 2, 178.
40. Wakatsuki, Y. and Yamazaki, H., *Inorg. Synth.*, **1989**, 26, 190.
41. Drago, R.S., Cannady, J.P. and Leslie, A., *J. Am. Chem. Soc.*, **1980**, 102, 6014.

42. Sharf, V.Z., Freidlin, L. K. and Krutii, V.N., *Akad Nauk* SSSR, Ser Khim, **1977,** 735; *Chem Absr*, **1977**, 87, 38552.
43. Wang, G-Z., and Backvall, Jan-E., *J. Chem. Soc. Chem. Commun.*, **1992**, 14, 980.
44. Entwistle, I.D., Johnstone, R.A. and Povall, T.J., *J. Chem. Soc. Perkin. Trans. 1.*, **1975,** 1300.
45. Zassinovich, G. and Mestroni, G., *Chem. Rev.*, **1992,** 92, 1051.
46. Krause, H.W. and Bhatnagar, A.K., *J. Organomet. Chem.*, **1986**, 302, 265.
47. a) Zassinovich, G., Mestroni, G., Camus, A.J., *J. Organomet. Chem.*, **1979**, 168, C 37. b) Uson, R., Oro, L.A., Sariego, R. and Esteruelas, M.A., *J. Organomet. Chem.*, **1981**, 214, 399.
48. Mestroni, G., Zassinovich, G., del Bianco, C. and Camus, A., *J. Mol. Catal.*, **1983,** 18, 33.
49. Jnaneshwara, G.K., Deshpande, V.H., Lalithambika, M., Ravindranathan, T. and Bedekar, A.V., *Tetrahedron Lett.*, **1998**, 39, 459.
50. Chatt, J. and Venanzi, L.M., *J. Chem. Soc.*, **1957,** 4735.
51. Shen, T.Y., *Angew. Chem. Int. Ed. Engl.*, **1972**, 6, 460.
52. Giordano, C. and Villa, M., *Syn. Commun.*, **1990**, 20, 383.